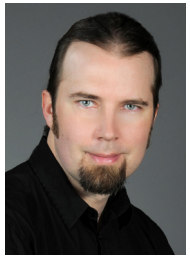

The Valley of Death, the gap between research and clinical practices, is hard to bridge. It becomes impassable when the supervisory medical authority claims that advanced therapies are illegal to use as treatment in patients with incurable cancer.

Internationally leading oncolytic virus researcher *Dr Akseli Hemminki* reveals problems, solutions, hopes and enthusiasms relating to advanced cancer therapies.

**Akseli Hemminki, MD, PhD**

started studying cancer genetics in his second year of medical school at the age of 20. Following graduation, he moved to the US to learn about cancer gene therapy with oncolytic viruses, and then returned to Finland to specialize in clinical oncology and radiotherapy.

He then set up a revolutionary individualized treatment program, the Advanced Therapy Access Program, where cancer patients beyond routine treatments were offered access to an individually tailored oncolytic virus therapy. Despite clinical success, the program was shut down and a legal case followed.

At 41, Dr. Hemminki has more than 2 decades of experience in translational cancer research and is now a professor of oncology at the University of Helsinki in Finland and father of 3 children. He has authored more than 200 scientific papers, founded 2 biotechnology companies and been involved in a dozen clinical trials.

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*Carl June,* MD

Richard W Vague Professor in Immunotherapy, University of Pennsylvania, Philadelphia, PA

AKSELI HEMMINKI CROSSING THE VALLEY OF DEATH

Nomerta

# Akseli Hemminki

# CROSSING THE VALLEY OF DEATH

## With Advanced Cancer Therapy

"This book reads like a thriller and the reader is taken through many surprising events, which - incredibly - are true."

*Eva Galanis*, MD, DSc
Medical Oncologist, Translational Researcher,
Mayo Clinic, Rochester, MN

# CROSSING THE VALLEY OF DEATH

# WITH ADVANCED CANCER THERAPY

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**Akseli Hemminki**

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*Dedicated to my fellow warriors: patients, physicians, nurses and scientists.*

*Although the physicians of all nations, from the times of Hippocrates to the present, have, by numberless researches and experiments, made trials of everything in nature, from the most innocent drug to the most virulent poison, both in the mineral and vegetable kingdoms, yet the disease still baffles the power of physic[ians][1] (William Burrows, 1767).*

*The efforts of those, who are placed in a position fitted for the purpose, should be unceasing for the search after such a medicine; for nothing can be more unphilosophical than to conclude that it does not exist, because it has not yet been found[2] (Walter Hayle Walshe, 1846).*

*At every crossroads on the path that leads to the future, tradition has placed 10,000 men to guard the past (Maurice Maeterlink, 1862-1949) .*

*Cure for cancer possible in 5 to 10 years[3] (Nobel Laureate James Watson, 2011).*

## Contents

## Forewords

Gene therapy offers huge promise but past events have also underlined inherent risks. The field attracts people who think out of the box of whom Dr *Hemmink*i is one. Although the Advanced Therapy Access Program employed by Dr Hemminki has had its critics, many experts in the field have valued the patient-centered approach and the way in which the data have been made available to the scientific community. Dr *Hemminki* tells three intertwining stories; the history of oncolytic viruses; the Advanced Therapy Access Program and other regulatory aspects; and Dr *Hemminki's* own struggles with the competing needs and demands on innovative clinical investigators, from patients, the University, investors, company people, trainee scientists, family etc. It is an awe-inspiring story that also reminds us of how much more society could achieve if "we could all just get along"!

*Malcolm Brenner,* MD, PhD
T-cell therapist and gene therapy innovator
Baylor College of Medicine, Houston, TX

In 2007, Dr *Akseli Hemminki* started in Finland a unique and brave treatment program aiming at individualized treatment of cancer patients with a fascinating novel technology, oncolytic viruses. His goal was to help individual patients who had progressed beyond routine treatments. Although as members of a scientific community passionate about oncolytic viruses, we were very eager to learn how these treatments work, what they can and cannot accomplish,

this program still sparked significant controversy both in Europe and in the US. In his exciting book, Dr *Hemminki* provides also a profound and opinionated review of the history of gene therapy and virotherapy, the approach employing replicating viruses, one of the most destructive forces in nature, but harnessing them to attack cancer. Using this Advanced Therapy Access Program as a backdrop, Dr *Hemminki* discusses many of the problems facing translational scientists today, in their efforts to convert laboratory science into clinical gains. It also highlights some of the hopes, challenges and opportunities that the medical field is facing as we are shaping the evolution of personalized medicine toward becoming a clinical reality.

The book reads like a thriller and the reader is taken through many surprising events, which – incredibly – are true.

*Eva Galanis*, MD, DSc
Medical Oncologist and Translational Researcher, Mayo Clinic, Rochester, MN

The immune system is a complex and powerful defense system whose function extends beyond protection from infection. A large body of evidence, first derived from experiments in mice, indicates that the immune system plays a role in the control and perhaps more importantly, the spread of a variety of cancers. Tumor metastasis accounts for about 90% of cancer mortality. In principle, the trafficking and highly specific tumor recognition of T lymphocytes, coupled with the systemic distribution of antibodies and other immune effector molecules, is a promising approach for treatment of cancer.

Immunotherapy is now established as an essential component





for effective treatment of a wide variety of cancers. The goal of cancer immunotherapy is to generate a potent tumor-specific immune reaction by restoring or enhancing immune function, or by neutralizing or nullifying a suppressive immune environment. Established immunotherapy approaches include bone marrow transplantation, donor leukocyte infusions, immune adjuvants, cytokines, monoclonal antibodies against tumor antigens or immune modulatory proteins, and most recently, vaccines. Stand alone experimental cancer immunotherapies on the near horizon are likely to be more potent, less toxic and more cost-effective than extant therapies. The toolbox for experimental cancer immunotherapy presently includes adoptively transferred gene-modified T cells, and engineered oncolytic viruses, the topic of this book.

The field of cancer immunotherapy is likely to face a major challenge in what is referred to as “Type II translation”, that will enable the new potent immunotherapies to be widely adopted in the community. In this regard, it is instructive to recall the lessons of allogeneic bone marrow transplantation, especially the development of strategies to manage graft versus host disease. From that case, a subspecialty of medical oncologists emerged with specialized training and experience. It is likely that these clinicians will lead the development of potent combination cancer immunotherapies, and that they will in turn develop the best practices to safely implement these powerful treatments with oncolytic viruses into routine clinical practice.

For cancer immunotherapy as a whole, the time from discovery to approval by the health authorities tends to be longer than industry standards for other cancer treatments. For example, monoclonal antibodies were invented in 1975 and first given to patients with lymphoma in 1980, yet *Rituximab* was not commercialized until 1996. Similarly, dendritic cells were observed in the nineteenth century, named in 1973, first tested in cancer trials in the early 1990s, but not commercialized as a cancer therapy until 2010. Reasons for the extended period of clinical development include

the inherent complexity of the immune system and a commercial reluctance by the pharmaceutical industry. In particular, cell based immune therapies and oncolytic viruses have not been thought to fit into a standard business model, and therefore the delay between pilot testing and pivotal trials, often referred to as the "valley of death" as described by *Hemminki*, is longer for cancer immunotherapies than other forms of cancer treatment.

Cancer immunotherapy was first proposed more than a century ago. With rare exceptions, the field has suffered from disappointing results. However, recent progress in translating basic findings into potent therapies has pushed the field past the tipping point. Previous setbacks were caused by a woefully inadequate understanding of cancer biology and immunology. Advances in our understanding of the science of the molecular interactions between tumors and the immune system have led to many novel investigational therapies and continue to inform efforts for devising more potent therapeutics. As a result of major advances in the basic sciences in the past two decades, the development of the next generation of cancer immunotherapy has evolved to include engineering the immune system. While continued understanding in the areas of cancer biology and immunology is inevitable, the principles are sufficiently understood to generate supraphysiologic immune systems that will deliver molecularly targeted cancer immunotherapies.

In this book *Hemminki* provides a rare glimpse into the world of developing novel oncolytic viruses for cancer therapy. He has led their development for nearly two decades and chronicles the history to the initial first commercial approvals. This book reveals many reasons for the slower than expected delivery of these new cancer therapies, from inadequate funding, scientific competition rather than cooperation and over-regulation by various government health authorities. *Hemminki* has a rare talent in reducing complicated and technical science to a readily understandable and compelling story for the lay public. Collectively, the chapters in his book provide a state of the art road map that will lead to the creation of the engineered





oncolytic viruses as "performance enhancing drugs" for cancer therapy.

*Carl June*, MD
Richard W Vague Professor in Immunotherapy, University of Pennsylvania, Philadelphia, PA

## List of abbreviations

| | |
|---|---|
| Ad | adenovirus |
| AIDS | acquired immunodeficiency syndrome |
| ATAP | Advanced Therapy Access program |
| CAR | chimeric antigen receptor modified T-cell therapy |
| CAR | coxsackie-adenovirus receptor |
| CD | cluster of differentiation |
| CEO | chief executive officer |
| CGTG | Cancer Gene Therapy Group |
| CTLA4 | cytotoxic T-lymphocyte-associated protein 4 |
| DNA | deoxyribonucleic acid |
| EGFR | epidermal growth factor receptor |
| EMA | European Medicines Agency |
| EU | European Union |
| FDA | Food and Drug Administration (US) |
| FIMEA | Finnish Medicines Agency |
| GMCSF | granulocyte-macrophage colony stimulating factor |
| GCSF | granulocyte colony stimulating factor |
| GMP | good manufacturing practices |
| Her2 | human epidermal growth factor receptor 2 |
| HUCH | Helsinki University Central Hospital |
| MD | Doctor of Medicine |
| NIH | National Institutes of Health (US) |
| NK | Natural Killer cells |
| PAMP | pathogen associated molecular pattern |
| PhD | Doctor of Philosophy |
| PSA | prostate specific antigen |
| RAID | rapid advancement of innovative disease interven tions (NIH program) |
| RNA | ribonucleic acid |
| SCID | severe combined immunodeficiency syndrome |
| TIL | tumor infiltrating lymphocyte |
| TNF | tumor necrosis factor |
| TUKIJA | the National Committee on Medical Research Eth ics (of Finland) |
| T-Vec | talimogene laherparepvec |





## Timeline of main events described in this book

| | |
|---|---|
| 1896 | Decrease in tumor cells reported in a ”flu” patient. |
| 1896 | Radiation therapy first used in cancer treatment. |
| 1896 | Hormonal therapy first used in cancer treatment. |
| 1910–1930 | West Nile virus, rabies, hepatitis and influenza virus tested in patients. |
| 1940s | Chemotherapy becomes available for cancer therapy. |
| 1950s | Adenoviruses first used in patient treatments. |
| 1991 | Oncolytic viruses are invented again as a promising approach. The leading viruses are adeno-, vaccinia and herpes viruses. |
| 1990s | The first rationally designed tumor selective viruses are constructed. |
| 1999 | First oncolytic adenovirus trial is published. |
| 2000s | Several different oncolytic viruses are being tested in the laboratory and in clinical trials with promising results. Several new types of viruses enter trials: reovirus, parvovirus, coxsackievirus, Newcastle disease virus etc. |
| 2001 | Leading oncolytic virus company Onyx Pharmaceuticals partners with Pfizer but adenovirus program is dropped. Phase 3 never started. |
| 2004 | First adenovirus based drug Gendicine approved in China. |
| 2005 | First oncolytic adenovirus based drug Oncorine aproved in China. |
| 2010 | Randomized phase 3 brain cancer trial with adenoviral gene therapy Cerepro is positive but not approved by EMA. |
| 2010 | First cell therapy product approved in US (*sipuleucel-T*). |
| 2011 | First immunotherapy product approved in Europe and USA (*ipilimumab*). |
| 2012 | First gene therapy product approved in Europe (*Glybera*). |
| 2013 | First randomized global phase 3 trial with an oncolytic virus (*T-Vec*) reports positive results. |
| 2014 | Dozens of oncolytic viruses are in clinical trials. |
| 2014 | Amgen files marketing authorization for T-Vec. |
| 2015 | FDA votes in favor of approving T-Vec. |

# Introduction

Cancer research has taken huge leaps forward in past decades. However, with some notable exceptions, metastatic cancer remains almost as incurable as a century ago. Why is this? While scientists have discovered many promising approaches in the lab, and have deemed it appropriate to proceed to humans, clinical research has become more and more difficult, more and more expensive.

When I completed my PhD on cancer genetics in the late 1990s, I thought we were nearing the cure to cancer. A few years later, when I trained to be an oncologist, I met with the reality of what treatment of cancer continues to be despite seemingly exciting progress reported daily even in lay newspapers. I looked thousands of patients and relatives in the eye and explained their disease and prognosis to them. Then I started toxic therapies which often did little to help, and some patients died because of side effects.

Despite of often close physical proximity, I realized there was a huge organizational, regulatory and mental gap between the lab and the clinic, appropriately called the “Valley of Death”, the place where most translational projects die. Frankly, patients also die in this Valley, in the sense that they might not have, if scientific discoveries would have been implemented into clinical practice sooner.

Many or most of the obstacles in the path of clinical translation of promising technologies are put there by us as society. We elected the politicians who approved the laws and directives or appointed the regulators. This book is my attempt to point out that there are many things which currently hinder the process of medicine, causing and prolonging patient suffering. Most importantly, all of these things could be corrected. Although I have lost much of my naiveté and some of my optimism, I have not completely lost hope that one day science could be helping patients more, and faster, than it is now. However, many changes would be needed to fully harness science to serve patients.

I have always been fascinated by history, and the history of oncology is incredibly intriguing, even if it is rather short. There are many excellent books out there on the topic so I haven't tried to compete with their merits. Instead I have focused on the history of gene therapy and oncolytic viruses, using the Advanced Therapy Access Program, invented by myself, as a concrete example of how science could be helping patients with cancer, and why it doesn't always work out the way any of the interested parties would like. Also, I have provided an introduction to gene therapy, with emphasis on oncolytic virotherapy. These aspects are presented against the backdrop of the societal reasons why it is so difficult taking new cancer drugs from the lab into the clinical arena, in an appeal to make clinical translation of promising new anticancer technologies more feasible.

## Genes -> proteins -> function

The subject that most interested me in medical school was genetics, which was going through an exciting time in the early 90s. Molecular biology had developed rapidly and suddenly there was access to molecular markers that could be utilized for mapping of traits, including those that predispose to disease. Mapping means localization of a genetic defect to a region of one of the chromosomes.

To summarize human genetics: genes are stretches of DNA, which forms chromosomes. Humans have 23 pairs of chromosomes, named from 1–22 and then the X and Y. Taken together, the chromosomes form the genome, which is located in the nucleus of the cell. Nowadays, with the Human Genome Project mostly completed in 2000, the genome is known to contain circa 20 000 genes. All cells except sex cells have the entire genome in their nucleus,





but different genes are expressed in different cell types, resulting in the tremendous variation seen in different tissues. DNA contains both "coding regions", ie. exons, and "non-coding" regions, introns, traditionally thought as having a smaller role in the function of the genome, although this might not be the whole truth. The exonic genetic sequence consists of four bases: A, T, G and C, whose order determines which protein is produced. These bases form groups of three, and each combination corresponds with a certain amino acid. Then there are certain triplets which indicate the start and stop sites for protein production.

Simplistically, one could say that most events and actions in any organism are performed by proteins, and the main reason for genes is to code for proteins. Thus, the basic flow chart of life is quite simple: genes -> proteins -> function. The production of any protein can be either on or off, and the relative expression of each protein in different cell types is the main mechanism for the tremendous variation of structure and function seen in for example the human body. It is amazing that the same 20 000 genes are present in cells as different as the egg cell, the nerve cell or a white blood cell, and that the differences are all due to which genes are on and which off. Of course, since nature is quite devious, reality is a bit more complex. For those who became interested, it is easy to find more information and in this book I won't go deeper into basic genetics.

Genes can have disease causing mutations, which can be acquired during life or inherited from parents. The conventional way to find the latter is to first map them into an area of a chromosome and then zoom in on the actual sequence to show the disease causing mutation, although nowadays the whole process is increasingly automated and done in basically one step by sequencing robots. In 1993, the first monogenic diseases had just been described on the molecular level, which seemed to suggest immediate utility for clinical translation, ie. development of interventions in the laboratory and then taking them into patients.

## Mutation in genes cause cancer

There were several groups studying genetics at our Faculty but the most interesting one was working with hereditary cancer. In addition to finding the location of a gene predisposing to familial colon cancer, they had also studied a phenomenon they called "replication errors" which was characterized by lack of fidelity of DNA replication in tumors. Eventually, this phenotype, nowadays called mismatch repair deficiency, led to identification of the causative genes and uncovered a completely new mechanism of carcinogenesis. It was known before that tumors are genetically unstable resulting in all kinds of rearrangements of the genome, easily seen with a method called karyotyping where the chromosomes, which contain the DNA, are stained with a dye, photographed under a microscope, and evaluated for rearrangements. Some tumor types, especially certain leukemias, can be accurately classified based on their typical chromosome rearrangements.

A tumor can contain hundreds of chromosome-level rearrangements. Even though it initially seems that these mutations would be bad for the tumor, in fact genetic instability is an important motor in the carcinogenic process. The development of tumors is evolution fast-forwarded. Evolution of species takes thousands of years but in tumors it all happens in ten or fifteen years or even less. The mechanism of evolution is changes in genes, called mutations and polymorphisms. The former term is often used when the change causes disease and the latter in other situations. Most changes in genes have no effect on the cell. However, rarely they may yield some benefit to the host, in changing environmental situations for example. For example, when humans moved from Africa into areas with less sun light, genetic changes resulting in pale skin was useful for increased production of vitamin D.

In some cases, changes in genes can be harmful. Recessive monogenic diseases are caused by mutation of both pairs of a gene while





a mutation in just one is sufficient in case of dominant genetic diseases. Lets say a father and mother have one healthy and one mutant version of a xeroderma pigmentosum gene. Each one of their kids would then have a 1 in 4 likelihood of receiving a faulty gene from both parents resulting in clinical xeroderma pigmentosum, a condition predisposing to skin cancers. In recessive syndromes "carriers" with a single mutation don't have any symptoms, but when both gene pairs are mutated, the patient is affected. However, there are many dominant cancer syndromes where inheritance of just one mutated gene is sufficient to predispose to cancer, often at a young age, and in these families children have a 50% likelihood of receiving the faulty gene from their parent. Examples include familial adenomatous polyposis, Li-Fraumeni syndrome, hereditary breast and ovarian cancer, von Hippel-Lindau syndrome and many others.

In contrast, hundreds of mutations are seen in advanced cancers. It all starts with one cell acquiring a genetic change which gives it some growth advantage over other cells. In most cases, such changes are recognized and fixed by the repair machinery of the cell, if this is unsuccessful, the body detects the cell as abnormal and kills it. However, sometimes the change can go undetected and the clone, meaning a group of identical cells originating from the single cell where the change occurred, can acquire further mutations. Again, most of these will be harmful for the clone, and those lines will be eradicated but rare cases can be useful for the clone, although not for the host individual, resulting in further growth advantage. This is the exact same process as seen in evolution, only much faster.

The work by *Albert de la Chapelle* and *Lauri Aaltonen* and colleagues at our Faculty had revealed that in addition to the chromosome level, genome instability can occur on a smaller scale, through the polymerase (a key protein in DNA replication) skidding and slipping in areas where there are repetitive sequences in the genome. "Footing" can be confusing in such areas, much like the lioness can have a hard time grabbing an effective hold of a zebra running in

a herd because of the replicating patterns zigzagging all over. Replication defects occurring through such slippage but not corrected through normal proofreading activity is called "replication errors" or "mismatch repair deficiency" and it is caused by defects in the mismatch repair genes, whose job it would normally be to correct such mistakes. The results of these defects – mutations in cancer causing genes – are similar as with chromosome level instability, although there are some differences in the target genes due to eg. structural issues; genes with repetitive sequences are likely victims of mismatch repair deficiency while genes located at typical chromosomal breakpoints, weak areas of the tertiary structure, are often affected in chromosome level instability. However, at the time it was not known if the mismatch repair genes behave like typical tumor suppressor genes.

Cancer-causing mutations can be grouped into two general categories: activating mutations in oncogenes and loss-of-function mutations in tumor suppressor genes. Generally, one mutation is sufficient to activate an oncogene while both pairs of a tumor suppressor gene – one obtained from the father and one from the mother – need to be damaged for that checkpoint to be inactive. In 1993 it was apparent that at least two different mismatch repair genes, residing in chromosomes 2p and 3p, predispose to colorectal cancer. One morning Lauri had been brushing his teeth in a particularly inventive mode and had come up with the idea to study if Finnish hereditary colon cancers might provide clues if mismatch repair genes resemble tumor suppressor genes. The plan was to study tumor samples from families whose germline carried a hereditary mutation in one of the mismatch repair genes.

## Working towards a PhD

The mismatch repair project was a stellar success. I had visited *Albert's* office in December 1993, started in the lab in January 1994





and in December 1994 the paper was published in *Nature Genetics*, one of the best journals in our field.[4] This more than fulfilled the Faculty's requirements regarding the student thesis I had set out to complete, but I had enjoyed the work and thus I asked *Lauri* if there was something else I could work on. He told me that there were some families with a rare cancer syndrome called Peutz-Jeghers polyposis and that the causative gene was not known. He suggested using a new method called Comparative Genomic Hybridization for evaluating 18 polyps removed from one individual. Although the polyps were not really cancers, *Lauri's* idea was that they would represent premalignant lesions already harboring a loss of both alleles of the critical tumor suppressor gene which was unknown at the time.

I spent some time learning the method and then analyzed the samples. Most of the genome of these pre-tumors was normal but the short arm of chromosome 19 seemed to be lost in a few of the polyps. The finding was not very dramatic and additionally it was known that this area of the genome was difficult to analyze with the method used. Thus, understandably, Lauri and Albert were not very impressed and they suggested that should try to confirm the finding with another method, analysis of "loss of heterozygosity", the same method I had used in my first paper. This phenomenon is a classic indicator of a tumor suppressor gene, first proposed by *Carl O. Nordling* in 1953[5] and developed further by *Alfred G. Knudson* in 1971.[6] The other gene pair has a mutation, which can be a hereditary one in the case of familial cancer syndromes, while the other suffers a larger deletion during life, seen as "loss of heterozygosity" in molecular analyses, since the other gene pair disappears because of the deletion. The result is no functional copies of the tumor suppressor.

Since the polyps did not look fully malignant under the microscope, we hypothesized that only a part of them actually contains genetic alterations, while the rest is normal or reactive. To dig deeper into the different structures within the polyps we contacted

an investigator at the University of Southern California who had developed a method called Selective Ultraviolet Radiation Fractionation (SURF; he was a big fan of surfing) which allowed to isolate DNA from specific parts of the polyp, containing only a few hundred cells. I spent a few weeks in his lab in the East Side of Los Angeles and found that indeed loss of heterozygosity was seen in the polyps with chromosome 19 markers but only in the epithelial part of the polyp. The deletions were also able to more accurately define and limit the location of the critical region where we thought the gene would reside.

Immediately after returning to Finland I did linkage analysis with families with Peutz-Jeghers syndrome. A few days later, I had located my first gene. The paper was published in Nature Genetics the next year but soon I realized that the work had just begun.[7] It was the dawn of the Golden Age of Genetics and the tools for precise identification and characterization of gene defects causative of diseases had become available through rapid development in molecular techniques. Having published the location of the gene in the short arm of chromosome 19, we knew many groups globally would be competing for identification of the actual gene sequence and the mutations in it. Location just indicates the region of the gene in the chromosomes, a bit of like saying someone's house is located in a certain city. But it is a long way to go from that information to the actual street address of the house, and further yet to the other details, such as how many floors it has, how many rooms, how many people live in it and what do these people do.

Identification of the disease causing mutations and the segregation of these mutations with the affected individuals, but not the unaffected individuals, in families, would be the final proof that the mutations were causative of the disorder. Each cell contains 23 pairs of chromosomes which contain the circa 20 000 genes we have. Thus, on an average there are about 1000 genes per chromosome although the size of chromosomes varies quite a lot. Chromosome 1 is the largest one while poor little Y has barely any genes at all,





but makes half of us men nevertheless. Moreover, gene density differs in different areas of the genome and the ends of chromosomes tend to contain more genes than central regions, which have more non-coding sequence, that is, genetic material that is not responsible for production of proteins. The very end of chromosome 19p, p indicating the short arm, where our gene was located, is one of the most gene rich areas in the human genome and thus the hunt was not going to be easy.

The reason why scientists are so interested in the genes causative of relatively rare hereditary cancer syndromes is that the same genes have proven important also in the regular sporadic (=not hereditary) cases which constitute the great majority of cancer cases overall. In fact, a big part of what we know about cancer as a disease has been discovered through genetic and molecular biology studies of hereditary cancer syndromes. The initial thinking was that identification of the causative genes would also immediately lead to drugs that could be used for treatment. This has not proven the case, despite what many preclinical papers claim, for reasons that will be discussed later. However, the understanding gained from studying these syndromes has revealed much more insight into cancer biology than could have been imagined initially. Also, for the families affected with these syndromes, gene discovery has facilitated genetic testing and prophylactic screening to find tumor precursors or early tumors. In some cases, there is evidence that this has reduced the incidence (=new cases) of advanced tumors which are the ones difficult to cure and thus genetic information may have reduced the mortality (=death rate) of carriers of genetic defects. One dramatic but effective embodiment of such knowledge is the ability of hereditary breast cancer mutation carriers being able to prevent breast cancer by having their breast tissue replaced by implants.

Being young and naive, I was not daunted by difficult tasks and fierce competition and thus I continued to spear-head the hunt for the gene in the research group run by *Lauri* and *Albert*. First,

we studied our Peutz-Jeghers syndrome families closely to narrow down the area of interest on chromosome 19p. Then, through collaborations, the region was broken down to smaller artificial pieces which could be more easily studied in the lab for mutations. This is done by yeast or bacterial artificial chromosomes, which sound a bit exotic but just mean fragments of the human genome grown in yeast or bacteria with standard molecular biology techniques. The advantage is that this way you can get a lot of the key materials for analyses, and the artificial chromosomes are easy to manipulate in the lab. Concurrently, a lot of protein coding gene pieces (complementary DNAs) were being deposited into databases and those that were from our region of interest we studied for mutations. The consortium had grown rapidly to 25 people from 6 countries and 3 continents and just coordinating all the actions took a lot of effort; this was *Lauri's* job. Here is where the new method called e-mail, steadily gaining popularity, was proving useful and all information produced by the consortium was openly shared regularly.

During most of my PhD, I was able to keep up in medical school at the usual pace and getting reasonable grades. In fact, I doubt my grades would have been better even if I weren't spending all my nights and weekends in the lab since I never thought that being a good doctor could be learned just from books. This could be true or it could have been a justification for not studying hard enough. It is clear that the basic theoretical things need to be learned to become a physician as medicine is based on science, and in fact even just the basics is quite a lot to learn, but most questions in exams are about small details which tend to change over time or can be easily looked up when needed. Some subjects I really enjoyed and consequently the grades tended to reflect that. I was especially interested in pathology, genetics and during the oncology course I realized that if I am going to do clinical work it must be oncology.

Always enjoying the challenge, it became clear that oncology is the area of medicine where the unmet clinical need is the greatest, therefore the possible impact of a single person is the greatest. As





the Finnish author *Väinö Linna* wrote in his classic "*Unknown Soldier*", which is a must-read for anyone who wants to understand the Finnish mind-set: "show me where the line is weakest, where you need a really good man, for here you have one".[8]

I was astounded by the numbers.[9] With swift declines in death rates due to cardiovascular or infectious disease and a rapid increase in the average life span in both developed and developing countries, cancer was becoming a huge health issue. According to some estimates, up to half of us might get cancer during our lifetime and up to a third of us would die of it.[10] Nevertheless, although this figure has been increasing, in the 1990s less than 5% of the overall expenditure of developed health care systems was spent on cancer treatment and therefore it seemed that in addition to the unmet clinical need, cancer treatment was under-resourced. Even allowing for a large variation in this number in different sources, due to differences in ways of counting the overall total cost of cancer care, and the swift increase in the proportional cost of cancer care, this number continues to be strikingly low compared to other common diseases. To me it would seem fair that the expenditure would be proportional to the morbidity or mortality caused by the disease. And if anything, the more serious the disease, the bigger the effort should be to help the patients. And nothing is more serious than cancer.

## Stop codon

On a personal level, I was pushing myself hard. My typical day would start with medical school lectures, practical training sessions or rounds at the hospital. At some time in the afternoon I would slip into the lab and stay until eight, but sometimes until ten or past midnight. It wasn't rare that it was nearing three when I finally jumped on my bike and cycled home to sleep. On weekends, I tried to attend every medical school party there was, but in those days it

was no problem getting up in the morning and heading for the lab. Often I would go straight from the lab to another party on Saturday and then on Sunday it was back to the lab. At one point I counted more than 300 consecutive days in the lab with the exception of a few trips abroad in between. If there was an exam coming I would try to study a few hours each day of the week, while the experiments were brewing in the lab, but often I had to pull caffeine and glucose powered all-nighters to catch up on my reading and then crash after the test. Eventually, with things heating up in the lab, I took a year off from medical school so I could focus on finding the Peutz-Jeghers gene.

In the Fall of 1997, *Stina Roth*, a colleague of mine who was working in the team, had done some sequencing of some candidate genes located in the critical region. She was away at a meeting in Sestri Levante Italy and *Lauri* noticed a pile of sequence printouts on her table. Some of them seemed looked pretty weird in a very exciting way because they were compatible with a frameshift mutation (= changing the amino acid sequence in a major way) present in that gene. *Lauri* picked up the pile and asked me to take a look. He hovered nearby while I worked out the reading frame, indicating which amino acids are coded by the bases which form the DNA. After decoding the base sequence, I said: “stop codon”. This means a mutation that mixes up the normal sequence of the gene, resulting in an abnormal “stop protein production” signal. Thus, the resulting protein is either abnormal, absent, or both. This is the most severe type of mutation and also the most easy to interpret because it really messes up the protein.

We had found it! After a further few minutes, we realized there were several mutations in that pile of printouts, all of them in a gene called LKB1. It was a previously known kinase, and since this class of molecules mediates signaling inside cells, they are likely culprits for almost anything, and are involved in the carcinogenesis of many types of tumors. Kinases are proteins that facilitate the function of other proteins and typically have a role in signal transduction,





contributing to the “administration” of cellular functions. However, this was the first kinase of this type described to feature hereditary mutations, giving rise to cancer. Subsequently, it didn’t take long to detect mutations in all of our Peutz-Jeghers syndrome families, and the absence of such mutations in normal individuals, and then we were ready to publish our finding.

## Identification of the gene reveals a darker side of the science community

We had excitedly shared the news within the consortium but it turned out dissolution of the hegemony was imminent. One of the consortium members carefully read the e-mails being disseminated and proceeded to publish the finding independently from the rest of us. He had asked another consortium member to be coauthor on his paper but she declined, protesting his plan of publishing independently of the consortium which had worked on the project together, and informed us of the situation. We therefore knew which journal he was submitting his paper to and tried to explain the situation to the Editor, to no avail. At the time I felt outraged but 20 years later it seems conceivable that it was difficult for the Editor to estimate what had actually happened. I’m sure our former colleague had some explanation for the situation, which differed from our view. Thus it became a race of who gets the paper out first. Being second would mean that the best journals would not be interested any more.

There are no statistics on this, but it could be that such incidents are common in publishing on a general level. Theoretically, right or wrong could be relegated to second fiddle when the key thing is to sell as many papers as possible. After all, a point which puritan scientists sometimes forget is the fact that the publishing houses responsible for scientific journals are companies trying to make the biggest profit they can and in that they are no different from any

other publishers or companies in general. However, one could argue that there is a double standard in place since there are quite a lot of requirements placed on scientists who wish to publish their data, while there are few restrictions on the journals and their editors.

Many scientists have long been annoyed with the situation that journals take advantage of the scientific community. For example, the peer-review process is performed by scientists, for no compensation, while most journals operate for a profit. The profit is collected from three different directions: subscription fees, advertising and page charges paid by authors. Isn't there something wrong with the situation that scientists work for the journal by reviewing papers, without compensation, they then provide their own manuscripts to the journal, sign away the copyright, and pay the journal to publish the paper? And yes, there are also submission fees; we pay just to have the journal take a look at the paper, and we pay extra for color figures and longer than usual papers, even if it was the journal asking for additional data. Most of the profit journals make is based on subscription fees, and these are dependent on the "impact factor" of the journal. It is measured by calculating the average number of citations a paper in a journal receives per year in the 2 years following publication. The higher this factor, the more respected the journal. This is reflected in the number of readers and the more readers, the higher the subscription fees can be. These fees are paid mostly by libraries, universities and only rarely individuals, so in fact the profit of the journals comes chiefly from governments or private foundations.

"Open access" is an interesting notion meaning there are no subscription fees and anyone can read the paper free over the internet. While undoubtedly a major step forward with regard to the availability of the data, new problems have emerged. Although some of the first open access journals were not-for profit, just maintaining journal operations seems to require publication charges of 1000–3000 dollars per paper, again paid by the author.





Subsequently, smelling business opportunity, hundreds or thousands of for-profit open-access journals have mushroomed in the first decade of the new millenium. With minimal start-up and operating costs, basically anyone can launch their own journal and start collecting publishing fees, while keeping peer review at a minimum in order to not reduce the number of accepted papers. The trick is to get scientists to submit their work to your new journal, and this is achieved through e-mail campaigns, misleading web sites, and using journal names which are remarkably similar to the names of more established journals. Many scientists have confused a for-profit open access journal of questionable reputation with a more respected and established journal. Nevertheless, while there are issues with open access, it seems likely to rapidly replace conventional subscription-based publishing, just like Napster, iTunes, Spotify and the like changed the way music is sold and distributed over the internet. An interesting character spearheading the critique on "predatory open access publishers" is *Dr Jeffrey Beall*, who has a blog and list of publishers and journals he critiques.[11]

Rewinding back in time to our discovery of the Peutz-Jeghers gene, the race for first publication resulted in a tie. Our former collaborator published in *Nature Genetics*[12] and on the same week we published in *Nature*,[13] both excellent journals. Although we had narrowly escaped a major disappointment, this experience shook me to the core. He had arranged first authorship – the most prestigious position in an author list, typically identifying the person who did the most work – for himself based on data generated by a large consortium which he had joined late, and very nearly ruined several years of extremely hard work for the rest of us. There are few rules or laws in science and thus it would not easy to call this anything worse than opportunism. Also, he might have a different view on the events.

I learned that no-one owns the information generated in science. Thus taking the fruits of a large collaboration and using it independently was not a crime as defined by law, even though it could

have serious consequences regarding careers, grants, salaries and jobs. In essence, stealing information is not much different from stealing money from someone's pocket but it nevertheless seems to happen quite commonly in the scientific community, without repercussions, if coffee-table gossip has any foundation of truth. Again, this has not been studied formally and thus no statistics are available.

I had more than enough papers to write up my PhD so I bade *Lauri* and *Albert* farewell, went back for my last year in medical school and decided that I would become a clinician.

## Trying my hand at clinical work

After defending my thesis, I had my first clinical job over the summer and I enjoyed it a lot. However, I realized I was all the time asking "why" and trying to understand the reasons patients were treated as they were. In clinical work many things are done a certain way because that is the medical tradition passed over generations from master to apprentice. Also, for some questions there are no good scientific answers, just medical praxis. Medicine is only part science, and the rest is art. Thus, I realized internal medicine, where the art plays a particularly big role, was probably not my thing. The last 6 months of medical school are internships and I had a chance to do one month at the oncology clinic and this confirmed that if I was going to do clinical work it would be oncology.

I had now been out of the lab for 6 months, my burn-out had mended, and I was starting to gravitate back. I wanted to try something more clinical so I investigated how patients from some of our hereditary cancer families had responded to chemotherapy. The project was interesting and resulted in a good publication[14] but it didn't feel like I was making enough of a difference just retrospectively studying the results of work done by others.

Then, in some journal I had been browsing through, I came across





the notion of gene therapy. I immediately liked the idea since it was an approach completely different from all the other existing cancer therapy approaches. Since I already knew for a fact, after my "extensive" one month experience working as an intern at the oncology clinic, that most metastatic tumors couldn't be cured with the available approaches, I figured we would need also some completely new approaches.

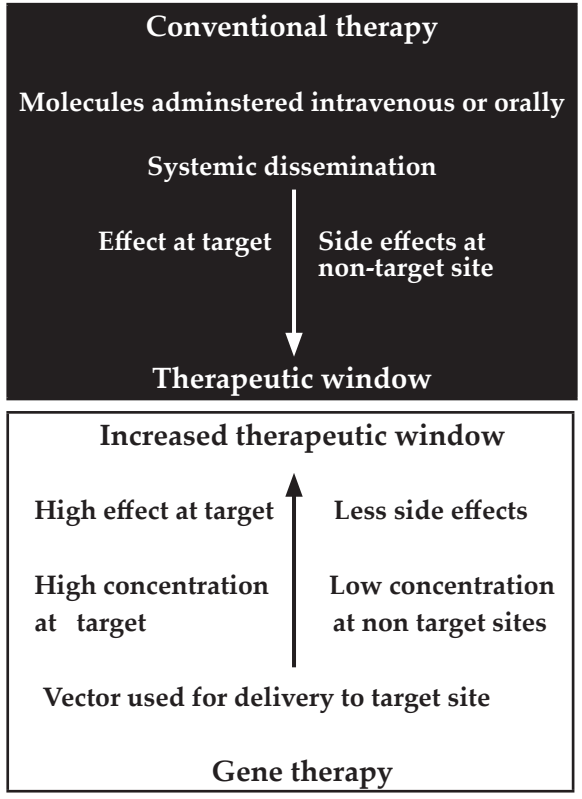
## Gene therapy

Unlike the name implies, the basic idea in gene therapy is usually not to modify the genes of the patient but instead to use gene transfer for therapeutic effect (Figure 1, 2). The function of most genes is to produce proteins and thus at its simplest gene therapy can be considered a form of protein therapy. The only difference to routine protein therapy, for example insulin, interferon, erythropoietin, antibodies, etc, is that to achieve high local and low systemic protein concentrations, the gene coding for the protein product is used (Figure 3). Since the gene is not "spent" but can in fact induce production of unlimited amounts of protein, a lasting effect can result. Kinases – also protein structures – are the master controllers of proceedings inside cells. Mediating both structure and function between cells and organs, proteins and peptides (small proteins) have an even more prominent role. Thus, in fact almost anything in the human body can be controlled or modulated by production of proteins. Therefore, gene therapy can be used for almost anything in medicine (Figure 1).

A critical aspect of the approach is the concept of the gene transfer vehicle or vector. Genes consist of DNA but naked DNA does not enter cells very effectively and it is rapidly degraded in intact organisms including animals and humans. Artificial vectors such as plasmids (=bacterial chromosomes much used in molecular biology) work well in the laboratory but they are rarely effective enough in

**Figure 1. What is gene therapy?**

- Usually, genes are not the target of therapy.
- Instead, genes are used for production of proteins, which mediate therapeutic effect.
- Genetic properties of the patient or are offspring not altered.
- Usually a vector (=transporter) is required for delivery.
- Viral vectors are currently most effective.




humans. Therefore, almost all currently functional gene therapy approaches are based on viral vectors. This is because viruses are nature's own gene delivery device. It is a matter of philosophy if viruses are alive or not since they cannot reproduce on their own. Instead, they need the cells of the host for producing offspring





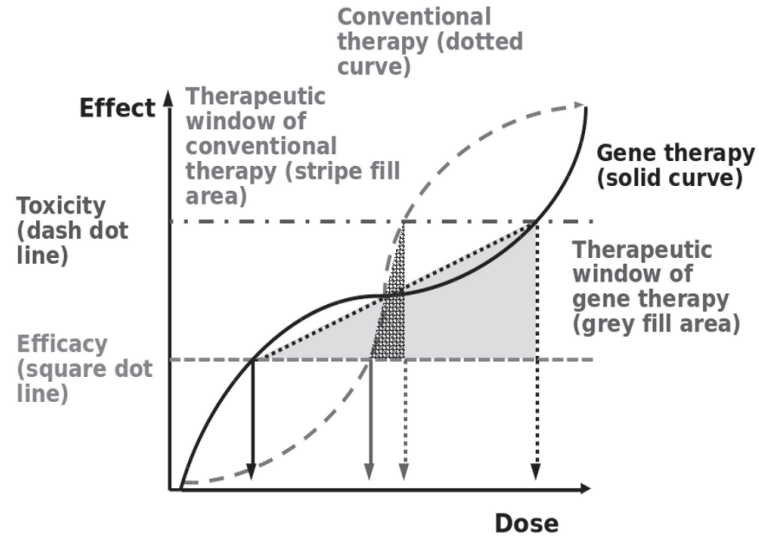
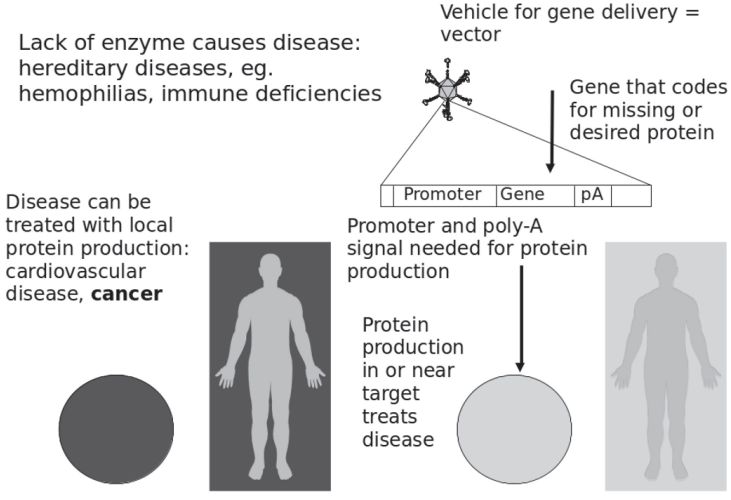



**Figure 2. What is the therapeutic window?**

Gene therapy can simplistically be seen as an approach aiming at increasing the therapeutic window of protein therapy. For basically all drugs and therapies, there is a level (often a concentration) needed for efficacy (square dots). As the dose increases, the effect can increase but ultimately toxicity results (dash dots). By utilization of a vector (=gene delivery vehicle), gene therapy aims at production of transgene products (proteins or peptides) locally, with reduced systemic (=bodywide) levels, resulting in an increase in the therapeutic window (grey fill for gene therapy, blue fill for conventional therapy). Local production also results in a dose-effect curve with a different shape (black solid line) than for conventional therapy (dotted line), resulting in the therapeutic effect starting at a lower dose (black arrow, versus grey arrow for conventional therapy). Also, this can result in safety gains as the dose that causes toxicity is higher with gene therapy (black dotted line, versus grey dotted line for conventional therapy). The levels needed for efficacy and toxicity together determine the therapeutic window of an approach.

**Figure 3. Conventional gene therapy can be seen as a form of protein therapy.**

There are many diseases caused by lack of a single protein (dark circle). Most such diseases are rare however, but a much more common situation is the possibility of disease intervention by local production of a single protein. Key to the approach of gene therapy is the concept of the vector, meaning a gene delivery vehicle. The gene coding for the missing/desired protein is placed into the vector under a promoter which is responsible for regulating expression of the gene. Genes code for proteins. pA=poly-adenosine signal, indicating the end of a transcript.




which are called virions. Typically, viruses enter cells and then deliver their genome into the nucleus ("center") of the cell, which is the location of the host DNA and thus a preferred location to get the viral genome amplified. The virus then proceeds to take over the cell for production of viral proteins and viral genetic material, which is then packaged into virions and released into surrounding tissue.

In the earliest embodiments of gene therapy, viral replication was disabled by replacing critical parts of the virus genome with a transgene, which means a foreign gene coding for a protein





of interest. This way, instead of being able to use the cell for production of new virions, the crippled virus results in high production of the protein product of the transgene. In the late 90s, the most common transgenes used in cancer gene therapy coded for molecules such as p53, a protein which is often mutant in tumor cells. If healthy p53 protein is reintroduced into malignant cells, it can cause death of the cell, or sensitize it to chemotherapy and radiation. A positive randomized trial using this approach has been reported in China, resulting in national approval of a product called Gendicine for the treatment of head and neck cancer.[15] Similar results were obtained in a trial performed in the US but this did not lead to product approval.[16]

Another approach utilizes prodrug converting enzymes. For example, a thymidine kinase gene can be borrowed from *Herpes Simplex* virus and used for arming an adenovirus. Anti-herpetic drugs such as ganciclovir can then be used for killing of transduced cells. Also this approach was successfully tested in a randomized human trial but again not leading to product approval although coming close. *Seppo Ylä-Herttuala* is a global leader in the field of adenoviral gene therapy. He is a Finn based in Kuopio and he co-founded a company called Ark Therapeutics, together with some British investigators. Using an adenovirus coding for thymidine kinase, Ark performed a randomized phase 3 trial in brain cancer, and the trial was positive with regard to its primary endpoint, time to re-intervention or death.[17]

The approach was rational in that the tumor was first operated, to minimize tumor load, and virus was injected into resection margins, where the tumor would typically recur. The endpoint had been agreed with the European Medicines Agency prior to initiation of the trial, and the goal was successfully met in a statistically significant manner, but the drug was not approved.[18]

Certainly the actions of the Agency with regard to the *Glybera* farce, discussed later on, lends support to the notion of questionable judgment with regard to new technologies. My personal opinion

is that it is seems terribly inconsistent to agree on an endpoint, but then not to approve the drug if that endpoint is met. Evidently there was quite a lot of internal discussion about this at EMA, given the amount of documentation on the subject found on EMA webpages.[19] From a medical perspective, glioma, the most common type of brain cancer, is a horrifying disease lacking curative therapeutic options for most patients and thus new approaches would be more than welcome.

The data has been published in *Lancet Oncology* in 2013,[20] but the information not in print is also interesting. Evidently, EMA was concerned with the safety/efficacy profile, given that the number of patients in this trial was smaller than in some previous glioma trials, and that there were more adverse events in the gene therapy group than in the control group. Their recommendation was that an additional trial should be performed. Sound advice, I'm sure, but the venture capitalist community did not agree and the company ran out of money. Fortunately, another company has picked up the intellectual property and perhaps this approach will continue to go forward. With the approval of *Glybera*, perhaps EMA will become less xenophobic with regard to gene therapeutics.

The fact that China is an unequivocal leader in adopting gene-based technologies is an interesting discussion topic in its own right, although with the same country increasingly dominating all areas of global economy by mid 2010s, there is no surprise involved. Comparing [phase 2] trial results with those obtained in the West indicates that there is nothing different in the Chinese patient population or how the trials were done. However, the differentiating factor seems to be that in China they have had the determination to develop gene therapy approaches into randomized phase 3 trials; which are the only mechanism for showing efficacy for a new medical technology. Perhaps the Chinese are less xenophobic about the word "gene" or perhaps they have done the math to realize that once the Chinese cigarette smokers (this habit is more common in China than almost anywhere else in the world) arrive at the age





when cancer appears, they might not be able to afford the non-curative but expensive drugs currently used in the West. Perhaps they figure that gene-based therapies will be competitive with regard to both efficacy and cost.

### Box 1. The three phases of clinical trials. [21]

*Phase I: Safety and toxicity? In non-cancer phase 1 trials healthy volunteers are typically enrolled but in cancer trials the population is typically patients.*

*Phase II: Any evidence of efficacy? A more homogeneous patient population is enrolled and comparison is typically to historical controls.*

*Phase III: Proof of safety and efficacy, typically embodying randomization, meaning random allocation of patients to experimental or standard therapy. More than 90% of the costs of drug development derive from phase 3 trials, because of regulatory requirements and the large number of patients required for statistical significance. The average overall cost of getting a new drug approved in 2013 is getting into the 5 billion USD range.*

Sources disagree but one popular view is that gene therapy as an approach was first suggested by *Friedmann* and colleagues in 1972.[22] However, the idea had been around for a lot longer. For example, *Sinclair Lewis*, in his highly recommendable 1925 book *Arrowsmith*,[23] described using bacteriophages for treatment of plaque, in an approach which could be considered gene transfer. Like many gripping fictional stories, also this one is based on actual clinical tests in the 1920s. Far ahead of his time, *Arrowsmith* attempts to perform a randomized trial to prove the efficacy of his treatments, by treating half of the island's population and not treating the other half. As a side note, the concept of a randomized trial is usually attributed to *Dr James Lind* who allocated seamen to various

treatments for scurvy in 1753.[24]

In our millennium, the most commonly mentioned reasons for failing to complete trials are probably lack of funding and inability to overcome regulatory barriers. However, I would claim that in reality most contemporary trials that are not completed, or even started, because of the fatigue caused by the merciless grind imposed on investigators by bureaucrats, regulators, administrators, lawyers, journalists, grant managers, unhappy post-docs, the tax authorities, grumpy husbands and wives, and biotechnology wannabes whose plans change from week to week, according to the most recent rumor they heard blowing in the wind.

In contrast, *Arrowsmith's* trial failed because of plague (*Yersinia pestis*) overwhelming the entire island before the trial is properly under way and thus he didn't have a chance to treat only half of the island as planned. A bit like a modern version of the plague the sweeping global cancer epidemic kills in all countries, age groups and social classes. There is a tremendous unmet clinical need, plenty of novel approaches, but in between the lab and the clinic the "Valley of Death" claims most projects.

While *Arrowsmith* used a naturally occurring pathogen of bacteria, a bacteriophage, literally meaning a "bacterium eater", genetic engineering was described by *Jack Williamson* in his 1951 book *Dragon's Island*,[25] and I'm sure there are others in the science fiction genre. By the way, both *Williamson's* book and *Lewis' Arrowsmith* are must-reads for anyone interested in gene therapy. As typical for true classics, time has barely touched the language, the excitement of the plot, or the currency of their topic. It will be interesting to see if the *Will Smith* movie "I Am Legend", which popularized oncolytic viruses in 2007, albeit in a controversial manner lacking much scientific rationale, will stand the test of time as successfully. Rise of *the Planet of the Apes (2011)*, also revolves around the idea of gene therapy initially helping patient but then going awry, and there are several others.

Thus, although the idea had been around in fiction before and





since, the actual scientific history (without the fiction) of gene therapy really only begins in 1980, when *Martin J. Cline* and colleagues reported successful gene transfer to bone marrow cells of mice.[26] In true pioneer spirit *Dr Cline* proceeded with the purpose of treating humans suffering from beta-thalassemia. The ethics committee at his own university in California wouldn't approve the trial so he travelled to Italy and Israel to treat two patients. Bone marrow cells were harvested and plasmids coding for the missing beta-globin gene were applied. The data haven't been published as far as I know, but apparently the treatments were safe, and one can surmise they had little of the desired effect, based on what has since been learned about the gene transfer efficacy of plasmids. However, a major controversy emerged when he returned to the US. Regulatory problems were claimed by jealous colleagues, the eternal bane of successful scientists, and he was sanctioned by the National Institutes of Health, a moratorium was placed on his research grants, evidently ending his research career.

This might have cooled the translational enthusiasm of the field for the next decade, and it wasn't until the 1990s, when two important trials were performed at the National Institutes of Health in Bethesda, Maryland. As reported in 1990 in *the New England Journal of Medicine*, *Steve Rosenberg* and colleagues labeled T-cells with a neomycin resistance gene and returned these cells into the body.[27] The labeling was done to be able to see if the cells tracked to the tumor, which they did.

The second important trial, and the first one with therapeutic intent, was performed by *French Anderson, Mike Blaese, Rosenberg* and others.[28] They used a retrovirus to replace a deficient adenosine deaminase gene into white blood cells of two children (*Ashanti DeSilva* being the first)[29] with an immunodeficiency disorder caused by the genetic defect. The treatment appeared successful and the children were alive and well several years later, and there were signs of successful and lasting gene transfer, according to the authors' *Science* publication in 1995.[30] The biggest achievement of these

trials may have been that they were able to overcome some awesome regulatory hurdles.

The career of one of the pioneers of gene therapy ended sadly when *French Anderson* was convicted of abusing an employee's child and was sentenced to 14 years in jail.[31] However, *Mike Blaese* continued to have success in both science and on the lecturer circuit, while the career of *Rosenberg* has proceeded on a stellar trajectory far beyond the dreams of most of us. Not only was he an important part of the starting the field of gene therapy, but he has also almost single-handedly initiated the field of adoptive cell therapy of cancer.[32]

**Figure 4. Steve Rosenberg, a gene therapy pioneer and the founder of the field of cell therapy of cancer, with the author in May 2014.**

Results by *Rosenberg* and other giants such as *Carl June* and *Malcolm Brenner* have launched the exciting field of adoptive cell therapy of cancer into swift progress resulting in many breakthroughs in the mid 2010s.[33] For example, *Carl June* and colleagues have achieved 90% complete response rates in patients with CD19+ leukemia using technology called chimeric antigen receptors, in which gene therapy with a lentivirus is used to assign new specificity to white blood cells collected from the patient's blood.[34] *Rosenberg* and colleagues consistently achieve more than 50% long term responses in melanoma patients with tumor infiltrating lymphocytes (TIL), a technology he has been tweaking and improving for 3 decades.[35] It is amazing there are now many patients alive and well 2 decades after being treated in an immediately life threatening





situation. This form of therapy is not gene therapy, however, because the TIL are not genetically modified. *Brenner* and colleagues have made superb progress by targeting a neuroblastoma associated structure,[36] or proteins of Epstein-Barr virus, which has a role some lymphomas.[37]

However, returning to Bethesda in the 1990s, several trials followed the pioneering work done by *Rosenberg* and colleagues. Because the approach is so logical, and works really well in the laboratory, the entire gene therapy field has been plagued by excessive optimism since its inception. Since the early clinical data wasn't really living up to the promise seen in the lab, because of some very simple biological and clinical obstacles being overlooked in the rush to cure cancer and other diseases, it was just a question of time when people, and especially "experts", the notorious hang-men of academic society, would lose faith. The hype collapsed into meltdown in 1999 with the death of *Jesse Gelsinger,* as will be explained shortly.

## Post-doctoral research

Following my stumbling upon gene therapy as an approach, I decided to give science another try and started looking at possible groups to do a post-doctoral research period in. This was 1999 and it seems amazing in retrospect how fast communication has changed in just over a decade. Science keeps advancing but information technology has gone from a walking pace to the speed of light in just a decade. Internet existed but no-one was really using it much. I remember teaching Medline searches to an older colleague who was amazed by the possibilities it offered to supplement the medical tradition of looking things up in textbooks. E-mail was becoming more common but snail mail and faxes were still the main form of communication. Couriers such as Fedex were an expensive method saved for the most important deliveries. Nowadays, it would be

easy to find groups working in cancer gene therapy by just googling for half an hour, but at the time it took quite a bit of investigative work, snooping around the library, sending faxes to obtain meeting programs, trying to figure out who to ask for help. In the end my best resource was looking at the speaker list at some recent gene therapy meeting that I had obtained somehow, and then studying what the speakers had published, using the "gut-feeling" method to focus on interesting subjects.

With this approach I identified maybe 40 groups that seemed to be working in the field. I wanted to go to the US since I had fond memories from my childhood – my parents had worked several years there when I was 4, 8 and 14 – and the US was still by far the leading country for science. In many European countries the BTA-factor ("Been To America") still plays a big role in career development. I selected the 20 most interesting groups and sent faxes to all of them. Maybe 10 groups replied and after some discussions I had narrowed it down to two: a group in New York City and *David Curiel's* group in Birmingham Alabama. I visited both places and talked with the group leaders and some senior investigators. New York is a fun place to visit once or twice but I wasn't sure if I wanted to live there. I hadn't been to Birmingham before but I found myself liking the vibe of the city and the South. Nevertheless my decision to go there was made more on scientific grounds.

David had introduced the concept of oncolytic viruses to me and I liked it a lot. This technology will be discussed in detail later on. *David's* big group, probably the largest in the world, was fully focused on adenovirus, which – when compared to many other gene therapy vectors out there – sounded to me like a good platform for cancer gene therapy for three simple reasons: ease of production of large amounts of virus, stability of the virus and the high degree of transgene expression that can be obtained in transduced cells (Figure 5). Looking back 14 years later, these issues are still critical, but I could add a fourth which we paid little mind to but which may be critically useful for the treatment of cancer:





immunogenicity.

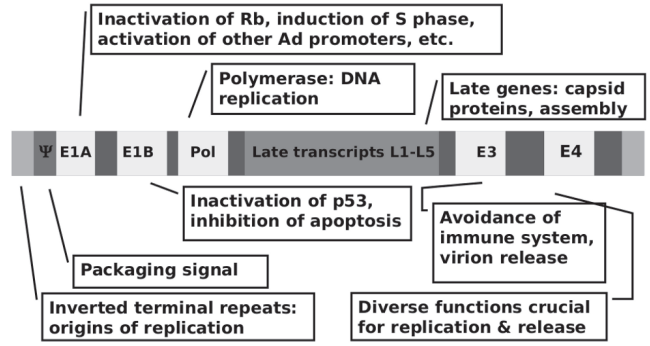



**Figure 5. Some basic features of the adenovirus genome.**

As scientists, we don't often appreciate the importance of drug production or producability. However, having now some company experience, and having seen the entire path from the lab to clinical use, I appreciate the first two items even more than before. With adenovirus, you can produce a trillion ($10^{12}$) particles easily, a quadrillion ($10^{15}$) with some effort, and rumor has it that the process can be scaled up to a quintillion ($10^{18}$) particles.

Lets say we come up with a really effective oncolytic adenovirus, which can be used for treatment of any cancer. There will be circa 15 million cases of cancer globally in 2013, and if one injection of $6.6x10^{10}$ particles would be sufficient, we could treat all cancer patients in the world with virus made in one production run. One run takes a few weeks, and given some preparatory work and quality control, it could probably be done in a few months. This is all just provocative speculation of course but it does indicate that with adenoviral gene therapy production scales up extremely well. If

the four criteria mentioned here (production scaling, stability, transgene expression, immunogenicity) are given the highest priority, adenoviruses are superior to all other current cancer gene therapy approaches. Moreover, from a public health perspective, it is clear that the cost-effectiveness of adenoviral gene therapy is not dependent on actual production costs but regulatory issues. In other words, if adenovirus-based drugs will be expensive, as I'm sure the will be, it is because the regulators made it that way, not because the technology requires it.

## Gene therapy kills

Perhaps as evidence of how communication was different back in 1999 without an ubiquitous Internet, I had missed the *Jesse Gelsinger* episode in September 1999.[38] This incident triggered the end of the first coming of gene therapy. Jesse was an 18-old with a hereditary lack of an enzyme called ornithine transcarbamylase. This defect eventually results in liver failure in all patients. He already had some liver dysfunction but was nevertheless able to take part in a gene therapy trial using a non-replicating adenovirus vector (ie. not oncolytic virus) for delivery of the missing gene into his liver. In those days, the potential for adenovirus mediated liver toxicity was not well appreciated and the trial protocol featured dose escalation into eventually very high amounts of virus. In *Jesse Gelsinger's* case, the high dose resulted in production of large amounts of cytokines by his body, possibly influenced by the already dysfunctional liver, which then triggered disseminated intravascular coagulation leading to multiorgan failure and death.[39] It became clear that the adenovirus treatment had in fact resulted in his death, much before than he would have died from the hereditary defect.

*The New York Times* and *Washington Post*, gene therapy's worst enemies at least in the past, made it into "Gene Therapy Kills Patient"[40] type headline stories, and dozens of other papers





followed, resulting in the US Food and Drug Administration shutting down all gene therapy trials at the University and subsequently reviewing all ongoing gene therapy trials in the country. Further headlines followed subsequent to discovery of the principal investigator's and the University's commercial involvements. Although company involvement is a standard practice encouraged by Universities, and almost required for clinical translation, especially for later stage trials, journalists used this aspect to add spice to their story.

Given the court-oriented nature of US society it inevitably turned nasty when the family filed a law suit against the University. While the personal tragedy in the family deserves all possible empathy, in my opinion the avalanche of bad press seemed a bit unfair since adenovirus had been safe in hundreds of humans before the event and therefore the serious adverse reaction was unexpected, but surely well accounted for in the patient information form. The patient who died was not the one who received the highest dose and therefore the death might have been triggered by an unusual sensitivity to adenovirus, or perhaps the liver of the patient was already too badly damaged due to the disease whose treatment was being attempted. Also, the hereditary defect he had was a severe one and would eventually have led to his death and thus unmet clinical need was present and experimental therapy was ethically and medically indicated. However, this is a trained scientist's and oncologist's view; a different view can be read in Jesse's fathers message posted on the internet.[41]

Obviously it is terrible when a patient dies as a result of treatment but unfortunately this happens in medicine. In fact, each year hundreds of thousands of people globally die due to [routine] treatment related events and in some cases the treatment was prescribed for condition that did not pose serious risk to the patient.[42] For example, most forms of surgery carry a risk for mortality. Fortunately the risk is usually small but thousands of healthy people nevertheless die because of surgery-related complication

but this does not usually result in headlines. However, when one patient dies of gene therapy, it is – or at least was – immediately headline news and resulted in shutting down of almost the entire field, despite the fact that overall gene therapy has been remarkably safe, much safer than surgery or chemotherapy for example.

I only learned of this story after arriving in the US; *David* was surprised that I had decided to come despite all the bad press the field had received.

## Experts declare: gene therapy does not work

One thing that has not changed over the decades – more likely centuries or millennia – is that there are always plenty of experts declaring that a new approach "does not work". One typical motivation for such statements is that they themselves are working on a different (older) approach – which of course has several advantages according to the experts – and for which they are trying channel funding by shooting down competitors; politics as usual I suppose. Another reason is that typically "experts" are older men to whom skepticism and conservatism comes more naturally than to innovators who tend to be younger, not yet crushed by the failure of their hopes and dreams. However, in science "the experts" present a very particular bane since the whole business depends on judgment by peers, meaning "the experts", and the merits of scientists' achievements is a 100% subjective question.

Accordingly, experts were saying that gene therapy does not work. Just like they had said about monoclonal antibodies, anti-angiogenesis approaches and cancer immunotherapy. It is a recurring theme in medicine that "the experts" don't seem to be able to grasp the notion that developing a new therapeutic approach is likely to take some time and initial trials don't usually lead to immediate breakthroughs. For antibodies and anti-angiogenesis it took almost 30 years to go from lab findings to approved products but both





of them are now mainstream. With tumor immunotherapy, a field launched by *William B. Coley* in the late 1800s, the biggest breakthroughs are still probably ahead although two products (*sipuleucel-T and ipilimumab*) were already approved in 2011, and several other checkpoint inhibiting antibodies were approved in 2014.

*Coley's* work represents an extraordinarily exciting passage in medical pioneering. There are several excellent books on his work[43] but his impact is felt also in the genetic immunotherapy field. Taking advantage of case reports on tumors disappearing following bacterial infection, *Coley* purposefully contracted cancer patients which couldn't be cured with surgery. Initially he used *Streptococcus pyogenes* and saw some good results although some patients also died due to fulminant bacterial sepsis ("blood poisoning"). He then proceeded to attempt to purify the anti-tumoral substance from the supernatant (="fluid") used to nurture bacterial cultures in the laboratory cell culture plates. Eventually he combined the filtered supernatants of two different bacteria and injected each patient in an individualized approach, dosing them in increasing amounts until they presented a sepsis like reaction, with high fever, attempting to recreate the actual sepsis seen in the earlier well-responding patients but without the risk of mortality.

A different medical culture existed and at that time series of case reports were the norm. Controlled trials had been conceived but were not common yet, to say nothing about randomized series. However, a thing that has not changed in the 100 years since *Coley* is that his worst nemesis was his close academic colleague *James Ewing*. Initially a collaborator working at the same institution, *Ewing* turned into a bitter enemy and spent much energy undermining *Coley's* work. In a set-up frequently encountered through the centuries, and beautifully exemplified by the story of "*Arrowsmith*", by *Sinclair Lewis*,[44] and more common than ever currently, *Coley* was the pioneering clinician placing himself in the line of fire by attempting to help patients, while *Ewing* was the risk-averse politician operating from the stronghold of the University laboratory. *Ewing* was a pathologist

and therefore, as accepted in medicine then and now, had the final say, despite never seeing patients while they were alive.

From an immunological perspective *Coley's* work is the stuff of legend, with many aspects confirmed only a century later, but his legacy is somewhat tainted by the fact that his results could not be easily reproduced by concurrent and subsequent parties. Some texts propose that this might have been caused in part by lack of consistency in the product, "Coley's toxin", produced by several pharmaceutical companies. However, integral to *Coley's* personalized approach was individually dosing each patient until sepsis-like symptoms. This might have required boldness and experience, and thus this hands-on skill may not have translated optimally to other hospitals. This constitutes another parallel to cancer gene therapy, which often requires intratumoral injection, a procedure not difficult, but needs to be done right. If you stick the virus into the wrong place, it will not work.

Another technique of relevance to this book which hasn't travelled that well between laboratories is adoptive T-cell therapy. Clinical results from the Surgery Branch at the National Cancer Institute in Bethesda Maryland, led by the founder of the T cell therapy field *Steve Rosenberg,* continue to be better than seen in other institutions. Probably the difference is caused by many factors which relate to practical skills. Selecting the right patients is important, growing the cells in the laboratory can be done in several ways, applying preconditioning therapies is important, but possibly the most variation is present in the individualized manner of giving interleukin 2 after therapy. *Rosenberg* doses "until toxicity", and ends up giving a lot more IL2 than many of his colleagues, literally taking his patients to the brink of death.[45]

Given the non-specific immunostimulation delivered by *Coley's* filtered supernatant, consisting of eg. endotoxin and tumor necrosis factor (TNF), low doses are unlikely to be sufficient for breaking immunological tolerance at tumors. Nowadays, some of the mechanisms responsible for the efficacy of Coley's toxin are being uncovered.





TNF is certainly appreciated for its antitumor effects,[46] when given locally to avoid severe systemic adverse effects, while the capacity of endotoxin, a product of the bacterial cell wall, to stimulate pathogen associated molecular pattern (PAMP) receptors is increasingly understood.[47]

PAMPs are among the most potent approaches for breaking tumor associated immunological tolerance. Tolerance means that even though the immune system may be recognizing the tumor as "bad", the tumor actively machinates in the opposite direction and successfully fools the immune system into thinking that nothing is wrong. This is achieved through many mechanisms including production of immune suppressive molecules such as transforming growth factor beta, interleukin 10 and recruitment of suppressive cell types such as regulatory T cells and myeloid derived suppressors. However, the immune system is forever in a precarious balance between immunity and tolerance, and the scales can be tipped into the former direction by increasing danger signals at the tumor, as achieved by *Coley's toxin*, or by other PAMPs, including those present in oncolytic adenoviruses.[48]

## The war on cancer

Being a patient-centered physician at heart, *Coley* wouldn't have had the gall to declare a general war on cancer, given that war is basically a political activity, or at best an extension of politics as *von Clausewitz* worded it. As a practical clinician working with cancer patients, *Coley* was probably humbled every day by the fates of clients. One can speculate if his nemesis *Ewing* was more interested in academic power, which fueled his burgeoning political career, than with helping individual patients.

With regard to war on cancer, it took another 6 decades for an unusual pair to meet and increase the stakes by publicly crying for attention to speed up cancer research. While *Richard Nixon* is often

credited or blamed for the "War on cancer", in fact it was the unlikely team of an aggressive political lobbyist and philanthropist *Mary Lasker* and a pioneering pediatric pathologist *Sidney Farber* who made the wheels move faster. Their methods were criticized, as they brought into play an aggressive and provocative style of advertising, unheard of in medicine at the time, including extra-large billboards and the like, which are not so uncommon today. However, there is little doubt that they contributed in a major way to founding of the National Cancer Institute, which continues to be one of the main funding instruments for cancer research globally. Also, they basically single-handedly initiated the concept of private-public partnerships for cancer research. One of the most concrete examples of this was building of the Children's Cancer Research Foundation hospital, nowadays the Dana-Farber Cancer Institute, one of the world's premier cancer research centers, which was achieved through private donations obtained through media exposure of a young cancer patient "Jimmy". There are many magnificent books on *Lasker* and *Farber's* work, their story is told in for example *Siddharta Mukherjee's* "The Emperor of all Maladies" from 2011, which I highly recommend to anyone interested in the history of oncology.[49]

Following *Lasker's* and *Farber's* crusade, including a full page "Mr Nixon: You can cure cancer" advertisement in *the Washington Post*, *Nixon* signed the National Cancer Act in 1971 and the "War on cancer", was declared. Unlike most diseases, cancer always invokes military terminology. Patients "do battle" or "fight" against the tumor, they are reported to "beat" their cancer, or finally "lose" after a heroic struggle. Advertisements in the US urge patients not to "surrender" to cancer. I'll leave it to psychologists to explain this in scientific terms but my personal opinion is that it is in part a form of rationalization. By turning a frightening disease into an enemy that must be fought, it becomes easier to deal with. Just like the black and white world of comics: cancer is evil, it must be killed and in fact the patient is the hero of the story and being a hero is more





satisfying the being an unlucky victim who developed a horrible disease for no particular reason. Also, since most current cancer treatments do invoke a lot of suffering, it fits well with the hero sustaining some damage while locked in combat with the evil enemy.

*Richard Nixon's* National Cancer Act of 1971 was headlined by the media as a *de facto* "War on Cancer", taking the military phraseology to a different level. Now it was not just the patient doing battle with the tumor but the entire USA. I guess such declarations can be seen useful from the point of view of highlighting important topics, raising funding and perhaps conveying a sense of optimism, but the problem is that journalists, reflecting the needs of their readers, want to have a schedule. Obviously it is not a grabbing message to say "we'll do our best over the next two or three decades and see where we get". No, to make the front page it needs to be "Cancer will be beat in 10 years".[50] Also, the journalists will ask how this will be achieved and they want a concrete answer. "Step-by-step increments", "building our understanding through basic research", or "doing some experiments and lets see where they take us" are not appealing. Instead, it needs to be something simple, new, different and tangible. Such as "tumor viruses are the cause of cancer".[51]

Looking back at the first fifty years of cancer research, until approximately the early 1970s, the aspect most bizarre to me is the absolute conviction many cancer researchers held that most tumors are caused by viruses. Presumably, all that was needed was detection of those viruses, development of anti-viral drugs, treatment with them and cancer would be a beaten disease. After an immense research effort, a number of tumor-causing viruses were eventually identified, and some scientists would postulate that more may be awaiting discovery.

Although it can be concluded that tumor-causing viruses were not the overall simple explanation for cancer, as once hoped for, there are some spectacular exceptions. Human papilloma virus causes almost all cases of cervical cancer.[52] In the past, cervical cancer treatments were surgery, radiation and chemotherapy, but

recently vaccination against the virus has changed the paradigm.[53] In vaccinated women, it seems that almost no malignant lesions develop, and thus immunization against a cancer-causing virus may have eradicated an entire tumor type, if long-term follow-up confirms the initial data.

These developments were recognized by the 2008 Nobel prize in Medicine given to *Harald zur Hausen*. I had the privilege of having dinner with him one night in Copenhagen, where we were both invited speakers at the Danish Nobel Symposium and at another occasion since. If all Nobelists are like him, it gives hope to humankind. He is extremely sharp, opinionated, precise, yet able to see the bigger picture, with a large heart and caring about young researchers. When reviewing his comments on the manuscript for this book, we sat down together and went through his notes page by page and he made several useful comments. For example, he pointed out that hepatitis B and hepatitis C viruses should be mentioned as they are a major cause of cancer globally, with also immediate therapeutic relevance, as both can be treated and there is a vaccine against B.

My impression was that he is a diligent virologist who just wanted to do good science, and this eventually required vaccination trials and the revolution probably leading to eradication of cervical cancer started from there. At 77, he had given up the leadership of the German Cancer Research Center, the premier site for cancer research on the continent, but was still active with his research group, with several interesting hypotheses for further cancer causing viruses.

In addition to these examples, there is some evidence that viruses may play a role in some tumor types such as Burkitt's lymphoma and head and neck cancer, but the causal link is more tenuous than in cervical cancer, and vaccination seems unlikely to produce a similar impact. There is a rare type of leukemia certainly caused by a retrovirus and Kaposi's sarcoma is a tumor common in AIDS patients, caused by Human Herpesvirus 6. Merkel cell tumor seems





to associate with a polyomavirus, and there are other examples, and thus *zur Hausen* and colleagues can be congratulated for their persistence; the hunt for cancer-causing viruses has eventually led to an increasing list of culprits. One can propose that these results have been possible only with effective molecular laboratory methods. Similarly to the technology advances which brought about the Golden Age of Genetics in the 1990s, the level of technology available has determined what has ended up in the net of hunters of cancer causing viruses.

With regard to other microbes and cancer, even less is known. However, there is a certain type of lymphoma of the lining of the stomach, which is associated with a bacterium, *Helicobacter pylori*. In an almost perfect embodiment of the dreams of the virus hunters, eradication of the bacterium with antibiotics cures the lymphoma! The only thing making the story less than perfect is the fact that the causative microbe is a bacterium, not a virus.

However, since many microbes cause inflammation, which is a recognized risk factor for cancer, there could be a larger indirect role for microbes in carcinogenesis (=the development and growth of tumors). If so, this role is likely to be in tumor initiation, and when the tumor becomes clinically apparent, often a decade later, the microbe no longer plays any role. In other words, although inflammation – which can be caused by microbes, chemicals or for example gastric acid - is a known motor in carcinogenesis, microbes are the sole cause of tumors only rarely. Moreover, several years or even decades after tumor initiation, when the tumor is already established as a clinical entity, inflammation is no longer useful for the tumor. This is demonstrated by the strong immunosuppression featured by many or most advanced tumors. It has recently become apparent that induction of inflammation in such tumors can result in anti-tumor consequences. Thus, inflammation is an important motor of early carcinogenesis but with regard to established advanced tumors, approaches able to induce strong inflammation in the immunosuppressive tumor

microenvironment can be useful in induction of anti-tumor immune responses.

Gradually failure was admitted in the hunt for an ubiquitous cancer causing virus, but some good came out of it. Since the empiric approach to cancer treatment – randomly searching for poisons more toxic to tumor than normal cells – seemed to be reaching a plateau, and viruses didn't seem to account for most tumors, the next step was putting a significant effort into basic cancer research. Finally oncologists, cancer researchers and policy makers were admitting that understanding the disease better on a molecular level would be useful for developing better treatments.

It says something about human psychology that since *Paul Ehrlich's* time in early 1900s, almost every decade there seems to be a declaration of a "magic bullet" discovered. *Ehrlich's* initial idea involved the notion of anti-tumor antibodies, but it took nearly a century for this approach to develop into drugs. However, the idea was sound and dozens of monoclonal antibodies are nowadays used in cancer therapy and many other areas of medicine. In particular, they have revolutionized the treatment of autoimmune diseases such as rheumatoid arthritis. Antibodies are among the few treatment modalities that can be curative for some cancer patients, especially when used in adjuvant therapy, meaning treatment given in a minimal disease load situation. In fact adjuvant therapy means treatment given in a situation when there is no direct evidence of tumor cells remaining, just a strong suspicion based on a pathologist's analysis of the tumor. Adjuvant therapy is given to reduce the statistical risk of recurrence, because risk factors suggest that tumor cells might nevertheless be lurking somewhere. Perhaps the best and most effective example of this is use of the monoclonal antibody trastuzumab in adjuvant therapy of breast cancer patients with Her2 positive tumors.[54]

In the 1950s, chemotherapy – as will be discussed later – seemed certain to cure cancer but due to low selectivity, resulting in significant harm to normal tissues, it doesn't really fit the description





of a magic bullet. Monoclonal antibodies, however, are the original magic bullet, replaced a decade later by anti-angiogenesis and after another decade by "targeted therapy", a term which usually refers to small molecular inhibitors of kinases or other enzymes active in cancer cells. "Targeted" is a great marketing slogan because it would seem to refer to drugs that only impact cancer cells. Alas, this is not the case because the term only means that the drug targets a certain cellular crevice perfectly, but these crevices belong to kinases active in both tumor and normal cells and thus often significant side effects result. However, the main issue with "targeted therapies" is not adverse events but lack of long term efficacy with some notable exceptions, but that is another story. In the 1990s it was the turn of gene therapy to be hailed as the magic bullet, not just for cancer but for almost any medical condition. While enthusiasm for new approaches can be applauded the hype tends to become counterproductive when unrealistic expectations are not met (Figure 6). This was exactly where the field of gene therapy was when the millennium was nearing its end.

Admittedly, there was need for introspection in the gene therapy field, since initial approaches in the early nineties had been characterized by excessive optimism, often whipped up by journalists into unrealistic expectations by patients and funders. Scientists are also partially to blame of course, but I think much of the early optimism was just due to passion generated by the extremely simple logic of gene therapy: if there is a faulty gene, lets replace it with a functioning one!

The only problem was with the vector (=gene delivery) systems that were available: they were not understood well enough nor was their use rationally based. This was recognized already before the *Gelsinger* affair. For example, the high-profile *Orkin-Motulsky* report by the NIH in 1995 identified a need for studying vector systems to make gene therapy work in patients.[55] This is exactly what happened over the next decade an now in 2013 we have several clinical gene therapy success stories, even including an approved

product (*Glybera*), despite the reservations that non-Chinese regulatory agencies have toward gene therapy. The critical aspect defining the clinical success of gene therapy continues to be gene delivery. It has been almost surprising how predictably the payloads have performed in the laboratory, in animals and in humans, if they can be delivered. Thus, the basic notion of using genes for production of proteins, for therapeutic effect, remains perfectly viable. Therefore, with further optimization of vectors, gene therapy may yet fulfill many of the expectations it has raised, in cancer and non-cancer fields alike.

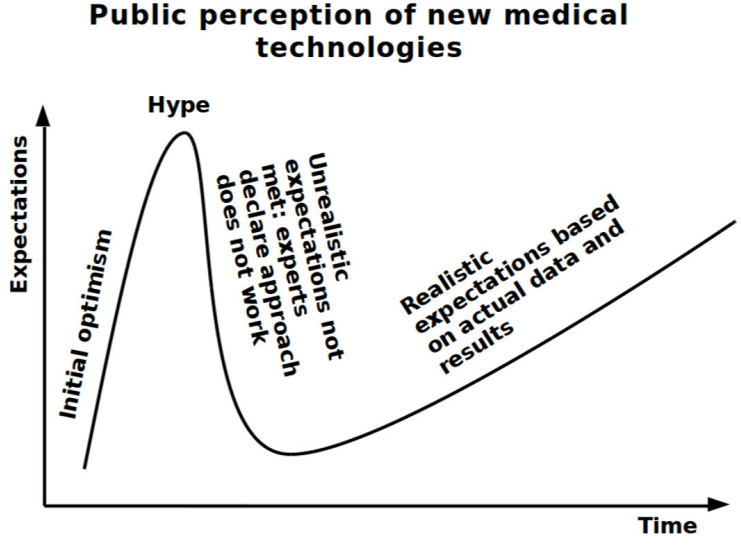



**Figure 6. Public perception of new medical technologies.**

## Cancer-busting colds, oncolysates and other weird classics

Initially, most projects in the ovarian cancer group at University of Alabama in Birmingham related either to adenovirus targeting,





arming or oncolytic adenoviruses, but pretty soon the approaches converged into an advanced generation of oncolytic adenoviruses featuring multiple modifications for enhanced selectivity, retained efficacy and increasingly including an arming device. Once I started digging deeper into the field, I realized that use of viruses for cancer therapy was in fact not a new invention. Already in 1896 a report had been published where a leukemia patient contracted a "flu" and the amount of tumor cells in her blood reduced.[56] In the 1910s and 1920s a number of patient series were reported, where many of the viruses that had been identified at the time were tested in cancer patients. Some examples include Egypt 101, which is a strain of West Nile virus, rabies, hepatitis and influenza.[57]

Adenovirus was tested almost immediately after its identification in the 1950s.[58] In a classic example of translational research, different adenovirus serotypes were cultured in a laboratory at the National Institutes of Health, and culture medium was taken downstairs and injected into cervical cancer patients' tumors. Impressively, many tumors reduced in size following therapy but since they often eventually recurred, the approach was abandoned in favor of chemotherapy, which was just being developed as a new approach and thought to result in the lack of need for other therapeutics.

The development of chemotherapy is an incredibly interesting story in its own right. Although arsenic was tried already in 1500 B.C., evidently with some success when it could be directly applied as a paste, the next 3440 years were a slow period, well summarized in *MacGregor's* entertaining paper from 1966.[59] Incidentally, after having been discredited as a poisonous and ineffective "patent medicine", and replaced by other nearly equally toxic "modern chemotherapies", arsenic trioxide has recently made a comeback in the form of *Trisenox*, an FDA approved drug for a certain subtype of leukemia. Zinc paste was another local anti-tumor agent which has not made a comeback yet; perhaps some young biotechnology oriented reader will pick up on this idea.

The first effective agents following arsenic were developed from

nitrogen mustard, a chemical warfare agent, which was secretly tested in clinical trials in lymphoma and leukemia patients already during World War 2. Then, during the war, an Allied ship loaded with the agent was bombed in the harbor of Bari and thousands of people were accidentally exposed to the gas. Sublethal exposure resulted in skin problems and reduction in white blood cells, while lethal exposure was caused by a more profound destruction of white blood cells, in what oncologists call leukopenia. These findings were taken note of by an army chemical warfare expert *Dr Alexander*,[60] and developed in laboratory animal tests and clinical trials by *Dr Gilman.*[61] By giving the agent intravenously, skin problems could be avoided, and there seemed to be a therapeutic window between the death of cancerous and normal white blood cells. A molecule similar to nitrogen mustard, estramustine, is still in widespread use for treatment of prostate cancer.

Following the World War, battle gas based chemotherapies were spearheading the first skirmishes against cancer; the War on cancer had not been declared yet. Alkylating agents such as cyclophosphamide and ifosfamide, both still used today, are quite similar to the sulfur mustard battle gas. They work by incorporating into dividing DNA, forming abnormal genetic structures. This frustrates the cell which then commits suicide (the fancy name is apoptosis) if it can; suicide resistant clones eventually emerge and predictably feature resistance to this form of chemotherapy. Since cancer cells divide more than normal cells, there is some selectivity to the effects but also regenerating normal tissues suffer. In the human body, the most rapidly dividing normal cells include the bone marrow, intestinal cells and mucous membranes, and these are also the typical organs for toxicities, often including decreases in cells of the blood, nausea, vomiting, diarrhea and sore membranes.

Meanwhile, the aforementioned *Sidney Farber* and colleagues were taking advantage of another dependence of tumors: their increased need for vitamins and minerals. One such vitamin is folic acid, also known as Vitamin B9. *Farber* and colleagues developed and used in





patients the first anti-folates, initiating the class of anti-metabolite cancer therapies. Key members of this class, including methotrexate, are still used in oncology today. Thus began the field of chemotherapy which was thought to cure cancer within the next decade.

With all the waves that chemotherapy was creating, virotherapy was basically abandoned. Again, this direction was partially determined by available technology; virology was far behind chemistry as a science and immunology was lagging even further behind. Recombinant DNA technology had been conceived by novelists but not yet realized by scientists.[62] In contrast, chemists were able to synthesize and study various compounds and much of the relevant chemical sciences that persist today had been worked out. Nature seemed to be full of substances that might be more effective in killing of tumor than normal cells.

In contrast, the only thing that was known about viruses was that they can cause “cytopathic effect” in laboratory cell cultures. Cytopathic effect means the visual effect that virus replication has on cells under a microscope; first they round up, their membrane becomes clearly visible, and then they burst and die. Since most cell cultures used in the laboratory originated from tumors, as tumor cells are naturally immortal and much hardier than normal cells, it was only a short logical step to translate the observation of “cytopathic effect” this into viral treatment of tumors in humans. However, there was no way to actually detect a virus, which is too small to be seen under a light microscope and electron microscopy was still in its infancy. The key to understanding viruses was the realization that their only purpose is to deliver their genetic material, DNA or RNA, into cells, in order to propagate themselves. With regard to this goal, all life on Earth is similar. However, since the structure of DNA wasn’t known until 1953, and RNA a few years later, it was obviously difficult to understand viruses in the fifties. Nevertheless, some hard-core believers continued to study oncolytic viruses instead of focusing on just chemotherapy, or the hunt for the elusive cancer causing viruses, and in the next few decades the most popular approach in this fringe

field was oncolysates.

Oncolysates mean tumor cells collected either from the patient or grown in the laboratory, infected with virus, often irradiated to kill the virus and cells, and then injected back into the patient as a type of cancer vaccine. One of the leaders of that field was *Chester Southam*, who is mostly remembered nowadays for his clinical studies performed in "volunteers", who were in fact prisoners, or senile geriatric patients, which was not completely uncommon at the time.[63] Being a meticulous scientist, while probably not the most profound humanist, he included control groups in his studies, resulting in some prisoners being injected with live viruses while others were injected with live tumor cells. At the time there were no viruses engineered for selectivity for tumor cells and thus side effects were common. I'm sure he was most interested in the main study groups whose tumors had been injected with virus or who received oncolysate, but in fact the ethically controversial control groups (eg. tumor cells only) also provided interesting insights into tumor immunology. Although injected live tumor cells sometimes grew for a while, the tumors eventually disappeared when the adaptive immune system kicked in.[64] In patients with advanced tumors, injected tumor cells often grew a little longer than in healthy prisoners, implying body-wide cancer-mediated immunosuppression, a phenomenon better understood nowadays although much still remains to be learned.

In retrospect, I think it can be concluded that the first decades of tumor immunology were disastrous from an ethical perspective. *Southam's* tumor transplantation experiments had been preceded by Third Reich doctors on concentration camps. They had discovered that limbs or organs cannot be transplanted to other individuals, due to the immune response. Possibly this rationalized *Southam's* transplantation of tumors to "volunteers" as similar rejection was expected, and thus he correctly presumed the experiment would be safe for the convicts. Clearly *Southam's* studies would be profoundly unethical by today's standards and already at the time he faced stark criticism





from his colleagues, although research ethical standards were quite different from today, and the World Medical Association Declaration of Helsinki had not been written yet[65] although it would be soon. Following a recurring theme in medicine, his strongest adversary was from his own department at Memorial Sloan-Kettering in New York and eventually he was forced to leave. In an amazing turn of events he nonetheless re-emerged as the president of the American Association for Cancer Research.

These developments had the side effect of giving the virotherapy/oncolysate field a bad name and things were slow for a few decades, during which combination chemotherapy made slow but sure incremental advances. Nevertheless, it was becoming clear that it was unlikely that chemotherapy would cure metastatic cancer and therefore more experimental approaches lingered. Critical to the development of cancer research as a preclinical science, instead of an empiric clinical approach, was the development of animal models of cancer. Pioneered by none other than the infamous *Dr Southam* and his colleague and co-worker *Dr Moore,*[66] rodent models have taught us a great deal. They have also helped improve the reputation of cancer research as a hard-core scientific approach and well-executed mouse experiments have made thousands of stellar careers. Still, it remains [a rarely spoken] truth that animal models are poorly predictive of human results. There are many reasons for this, including major differences in the immunology, metabolism and genetic make-up of different species.

With regard to oncolytic viruses and in fact most immunotherapeutics, there are severe species incompatibilities which complicate preclinical analyses. For example, human adenoviruses don't replicate in mouse tissues, and mouse adenoviruses have completely different biology from their human counterparts. Before people misunderstand me, however, I should state that preclinical animal work has its uses. Animal experiments are critical for forming hypotheses for human trials. Many things can be tested in animals that could never be done in humans. Also, with regard to our own work with oncolytic

viruses, the emerging human data (immunological pathways etc) is in fact well in line with prior animal work. However, professional scientists sometimes over-emphasize the utility of animal models. The reason is simple, animal experiments are the tool we have available and everything looks like a nail when you have a hammer. Also, since this is the method we have and know how to use, it is the best way to get good publications needed to build a successful career. Thus, mouse experiments allow scientists to provide for their families even if they are not always so helpful in predicting what will happen in cancer patients.

Regulators also believe in animal work. In contrast to scientists who at least have a hypothesis for every experiment, justifying the use of animals, regulators will demand preclinical toxicity and biodistribution assays in hundreds of animals and often in several species because it says so in the Pharmacopeia, even if there is little or no utility to these studies due to species incompatibility issues.

## Rationally designed oncolytic viruses

Following three decades of smouldering on the fringe of the cancer research field, use of viruses for cancer therapy re-emerged with a vengeance in 1991 when a tumor-selective strain of herpes virus was discovered, therefore constituting the first oncolytic virus.[67] Oncolytic viruses are defined as viruses that preferentially infect and lyse (=break) cancer versus normal cells. The viruses used in earlier decades were wild type (=unmodified) strains possessing little selectivity for tumor cells. This can be debated scientifically, of course, given for example differences in anti-viral responses between normal and tumor cells, implying that even unmodified wild type viruses can be tumor selective to some degree. Nevertheless, in most cases the term oncolytic virus is used to indicate viruses rationally modified to replicate more in tumor versus normal





cells (Figure 7). Typically, this is achieved with techniques involving genetic engineering, but serial passage in tumor cells and other forms of bioselection can also be used.[68]

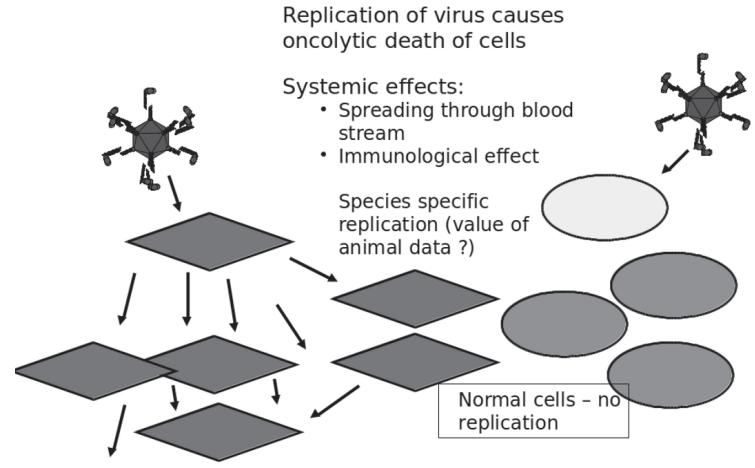



**Figure 7. How oncolytic viruses work.**

Diamonds represent tumor cells, which allow replication of the virus. Each dying cell releases thousands of virions into the surrounding tumor tissue, and in theory the process continues as long as there are cancer cells remaining. Dying tumor cells release virus also into the circulation from which the virus can infect metastases. Systemic effects are mediated by vascular dissemination of virus and the immunological effect resulting from oncolysis. Oncolytic virus means a virus that replicates selectively in tumor cells. Thus, infected normal cells (light ellipse) don't allow virus replication and thus normal tissues (dark ellipses) are spared.

The oncolytic adenovirus field was kick-started a few years later with ONYX-015, also known as dl1520, a virus strain proposed selective for p53 mutant cells.[69] The entire story of this virus is filled with drama, starting from its first description several years earlier

by Barker and Berk as a patient isolate.[70] Thus in fact this virus was not designed, at least not by man, for treatment of cancer, but represented a naturally occurring strain. The slower replication of the virus, caused by mutation of one of the early viral genes, revealed insights into viral biology which were later converted into a theory about tumor selectivity.[71] As often happens in the publication history of successful scientists, several high impact papers were published by the same authors, each disproving their earlier hypothesis why the virus was tumor selective.[72]

These hypotheses were converted into patents and a biotechnology company which executed several clinical trials with the virus. Safety was good and there was some evidence of efficacy, especially when combined with chemotherapy.[73] However, overall the anti-tumor activity of the approach was deemed insufficient, possibly due to extensive focus on tumor size as the main end-point in the trials. The inflammation now well known to associate with oncolysis probably caused a lot of false "pseudo-progression" which may have underestimated the true efficacy of the agent.[74] Another factor probably contributing to efficacy of the virus was that it was severely crippled also in tumor cells, being up to 100-fold less effective than the wild-type (=normal) viruses used in the first adenovirus trials in the 1950s at the NIH.[75] This crippling reduced the efficacy of the virus in killing tumor cells. This virus was never taken into a randomized trial, which would have proven or disproven the efficacy of the virus beyond any doubt. However, in China a very similar virus, H101 or Oncorine, was used in a randomized Phase 3 trial, which was positive, and led to product approval in China, for treatment of head and neck cancer.[76]

Vaccinia, Newcastle disease, respiratory enteric orphan (REO) and other viruses studied earlier also re-emerged and by the turn of the millennium oncolytic viruses had been resuscitated as an anti-tumor approach. A number of clinical trials were completed with excellent safety data and most of them also suggesting anti-tumor activity. However, it was also becoming apparent that





these viruses were not the miraculous cure for cancer that they were hyped up to be in the late 90s. Possibly there were a couple people around who remembered or had read about the work done several decades earlier, and to them the lack of cures probably didn't come as a surprise, since most of these viruses had been first used half a century earlier, albeit as wild type serotypes instead of the newer tumor-selective variants.[77] Nevertheless, the failure of the viruses to cure all treated patients was interpreted by "experts" as the therapy not working.

Most people entering the oncolytic virus field in the early 2000s were trained either in oncology or in molecular biology. This mix resulted in clinically relevant hypotheses and intellectually attractive but complicated virus constructs, respectively, while the middle ground in between or in the left field were not covered at all. As became apparent, the missing links included understanding of the relevant virology and immunology, both critical to the success of gene therapy including oncolytic viruses. Given the excessively hostile post-*Gelsinger* climate, the focus of the field was on safety and many careers were made by reporting double, triple or quadruple controlled viruses all resulting in beautiful bar diagrams and small error bars. In vitro conditions were honed to perfection to demonstrate that small but statistically significant improvement over the previous virus generation. Although clinical data was already becoming available, the need for enhancing efficacy seemed not to penetrate the scientific community, while at Big Pharma headquarters "experts" were saying that "oncolytic viruses don't work". Possibly the single most important factor in this thinking was the fact that inflammation resulted in lack of correlation between anti-tumor effects and tumor size. Take a lay man off the street and they would probably assume that tumor size and therapeutic efficacy would correlate. However, if treatment induces inflammation, resulting in swelling of the tumor, this is not necessarily the case, at least at early time-points after treatment.[78]

Cancer immunology and immunotherapy were fields foreign to

mainstream cancer researchers and oncologists. It was not appreciated that immunotherapy takes time to work, and that rapid tumor size reductions – typical of apoptosis (=cellular suicide) inducing drugs such as chemotherapy – are not the mode of action of immunotherapies. Instead, induction of anti-tumor immunity converts into prolongation of survival, a change in the growth pattern of the tumor, increased chemo- and radiosensitivity (Figure 8).

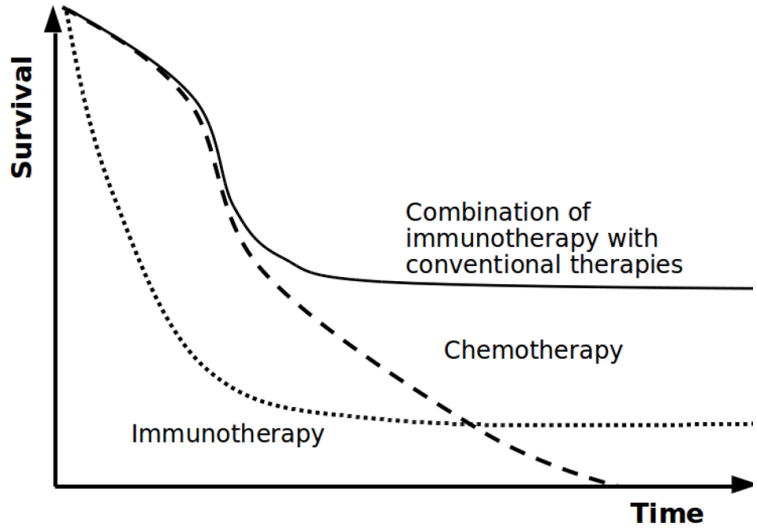



**Figure 8. Chemotherapy and immunotherapy cause different effects on patient survival curves.**

If they can be combined in a rational manner, improved survival could result.

Most importantly, if immunotherapy is used early enough when the tumor load is small, it can cure patients. Only with the breakthroughs of cancer immunotherapy in the first half of 2010s, have these notions become more widely appreciated and there is still a long way to go before the general oncology community understands





these aspects.

Chemotherapy and immunotherapy have different effects on the number of tumor cells and length of survival. Chemotherapy can be effective in reducing the number of tumor cells rapidly, but resistance eventually develops and the tumor regains its former speed of growth or may even grow faster. Thus, the treatment may or may not have an effect on the survival of the patient. Chemotherapy can work in a situation of high tumor load or low tumor load. Due to tumor immunosuppression, which is more pronounced in large tumors, the impact of immunotherapy depends much more on tumor load. If started late, tumor size might not get smaller at all, even if survival is extended. However, the sooner the treatment is started, he more dramatic the impact is on survival, and if started early enough, immunotherapy is among the few anti-tumor approaches that has the potential to cure tumors.

## Oncolytic viruses: a graveyard of failed projects?

Now, upon writing this book, 15 years after my initiation to oncolytic viruses, it is clear to many in our community that major caveats had been ignored. However, my vision was just as clouded as that of other people in the field until I started seeing patients treated with oncolytic viruses. Since scientists work in the laboratory, they mostly utilize cell lines and the respective mouse models. Since most oncolytic viruses are relatively human specific, and our funding is for treatment of human [instead of mouse] cancer, human cell lines are typically used. Consequently, our mouse models need to be immune defective as human tumors will not grow otherwise. Thus, in the Petri dish, we study the number of cells lysed while in our immune deficient mice we look at tumor size. Since the development and approval of chemotherapeutics had been based almost solely on counting “responses” in patients, meaning which proportion of tumors became smaller after therapy, and how long

patients are free from progression, and the same aspect had been studied in mice, naturally initial trials focused on this aspect.

In early trials, tumor size assessment is typically performed at one month or 6 weeks, and if the tumor is larger, the patient is taken off protocol. Unfortunately, it was somehow ignored that most oncolytic viruses cause a lot of inflammation which makes infected tissues swollen. *Rubor, tumor, calor et dolor* (redness, swelling, warmth and pain) wrote *Celsus* to describe inflammation in his book *De Medicina* in 47 before Christ[79] but this was not taken into account when planning oncolytic virus trials. Obviously, these signs would not be seen in the Petri dish or in "nude" (=athymic, lacking a thymus where T-cells develop) mouse lacking the cells that cause inflammation. In contrast, these symptoms are very much seen in humans. When I saw with my own eyes what was happening in patients, the veil obstructing my vision was rapidly lifted.

The second caveat that was not understood is the heterogeneity of tumors. Unfortunately they do not consist of collections of identical malignant cells. Instead, there are blood vessels, cells of the immune system, supportive structures (=stroma), dead areas (=necrosis), areas with high pressure or lack of oxygen. All of these are major problems for dissemination of any drug within tumors and especially so for large agents such as oncolytic viruses. Moreover, due to their tumor selectivity, oncolytic viruses can only propagate in malignant cells and if they hit a stromal area they won't be able to proceed. Considering that some tumors only have 5% malignant cells while the rest are other cells, and injected virus only infects the needle tract, or perivascular areas in the case of intravenous delivery, comprising perhaps a percent or less of the overall tumor cell number, it is an impressive demonstration of the potency of the approach that any activity was seen in initial trials. Even in tumors with a high proportion of tumor cells, the tumor often resembles the tissue of origin in a perversely altered way, trying to form for example gland-like structures consisting of cancer cells and surrounded by non-malignant stromal areas. Hitting the stromal barrier would be





expected to stop the wave of oncolysis.

Third, due to the co-evolution of humans with microbes, the body has many ways to protect itself against viruses. One key defense mechanism is the interferon response. Classically, tumor cells have been thought defective in this regard, and this may be true for most cell lines growing on the dish in the lab, but perhaps not so for the intact human tumor, where the non-cancerous stromal cells are capable of an interferon response, which then affects the entire tumor.[80] In 2000, none of these issues were understood.

## Gene therapy causes cancer

When we returned home to Finland in the end of 2002, it was again a most testing time for gene therapy. The field hadn't gotten over the Gelsinger-affair slump yet and more bad news followed from clinical trials using retrovirus to treat severe combined immunodeficiency syndrome (SCID). There are many forms of SCID, some of which can be treated with enzyme replacement therapy, while for some the only treatment is a bone marrow transplant from another person (=allogeneic transplant), which has a high risk for adverse events and up to half of the patients die because of the procedure.[81] And not all patients can even be transplanted and they live their lives in isolators ("bubbles") which attempt to protect them from microbes against which they have no immunological defense.

Gene therapy had been used to replace the defective gene into the blood stem cells which were then returned into the patient. Even a small amount of repaired stem cells would lead to proliferation of the missing cell types and re-constitution of the immune system. Because of this positive selection the approach was really efficient and nearly all treated patients were completely cured with a single treatment without exposing them to the dangers of bone marrow transplantation.[82]

In subsequent trials the approach was improved in efficacy and dozens of patients had been treated successfully, and in fact most patients treated were cured, which in my mind constitutes a solid proof-of-concept for the technology and a genuine breakthrough for gene therapy as a field. However, in longer follow-up it became apparent that in some of the patients introduction of the missing gene had occurred a bit too well and there ended up being too many white blood cells in the blood. In fact, a leukemia-type lymphoproliferative disorder was diagnosed in a few patients and it was discovered that the gene therapy had caused it.[83] Some patients died. The vector used was a mouse retrovirus which permanently integrates into the target cell. Depending on the integration site it was known that there is a theoretical risk of mutagenesis through inactivation of tumor suppressor genes or activation of oncogenes. In fact, the name of virus used was Moloney murine leukemia virus which immediately suggests oncogenic potential but this had nonetheless not been seen in most model systems, or in previous trials, so the risk was viewed as theoretical.

Nevertheless, the human data proved that it was a real risk. But the other side of the coin is that the kids were able to leave the isolation of the bubble and join their families. Most patients were completely cured of their disorder with a single treatment and didn't die because of their immunodeficiency or acute treatment related effects. Without the gene therapy treatment, all of these children would have eventually died of an infection caused by their genetic defect.

Further study of the patients' cells revealed that in fact in humans integration of the mouse retrovirus is not random as in mice but instead there are preferential integration sites, one of which is near a previously known oncogene LMO2.[84] In the patients who developed the lymphoproliferative disease, it was discovered that virus integration activates LMO2 which gives a growth advantage and leukemia can eventually result subsequent to additional mutations in the same cell.





My own interpretation was that the trials were still a success since although leukemia is obviously a very nasty side effect to have, the overall safety of the approach was still much better than with the alternative, bone marrow transplantation, for which mortality rates can approach 50%, even if a matching donor can be found, and graft-versus-host disease can be horrid even in surviving patients. In fact the children in the fateful trial were not treatable with transplantation due to lack of a suitable bone marrow donor. If I had to choose for my children, I would prefer a small risk of leukemia, which is usually treatable, over certain death from infection, or the torture of bone marrow transplantation. Nevertheless, this wasn't the way the situation was seen by regulators and journalists. 27 gene therapy trials were halted on 15 Jan 2003 and the *New York Times* and *Washington Post* again had headlines.[85]

The moratorium was lifted later on and during subsequent years data from several US and European trials accumulated, and it was found that leukemia only occurs in about one out of ten patients and it requires very specific conditions. The treatment protocol was different in all trials and in most of them no leukemia was seen.[86] Thus, by simple clinical optimization of the treatment protocol, leukemia risk might be completely avoidable. Perhaps a better way would be to switch to lentivirus, which is a different type of retrovirus, a human virus, and has a different integration pattern. It didn't take long for the investigators to figure this out and in 2014 stellar results were published; SCID could still be cured and leukemia was not seen.[87]

Lentivirus has had its own regulatory hurdles since it is based on human immunodeficiency virus (HIV) which understandably tends to make regulators and patients nervous. However, the virus has been modified in such a way that it cannot cause HIV and there is no known conceivable biological mechanism for it to revert to HIV.[88] The perceived risks associated with lentivirus have delayed its clinical use and only a few trials had been completed at the time of writing of this book. Another possibility is to include a "suicide"

transgene in the mouse retrovirus, allowing killing of the infected cells, in case of too much proliferation, ie. leukemia.[89]

## Lessons from Siberia

There is a Finnish saying that "Siberia will teach you". It means that once you are in the perma-frost tundra with 9 month winters, starving in a gulag, thousands of kilometers from home with only mosquitoes and horse flies to reduce the disease-ridden tedium of the daily battle for survival – and these only in the few weeks of summer – you will learn to be humble. In other words, the saying means that you learn the hard way. Just for clarification, Siberia is not in Finland but sufficiently near to give realistic menace to the saying and in fact while Finland was part of Russia between 1809 and 1917, forced labor in Siberia was a common form of punishment.

Undaunted by the depressing outlook in the gene therapy field, I proceeded with trying to set up my new laboratory. I met with the professor who had recruited me to Helsinki but it turned out I had misunderstood the situation, or perhaps it had changed. Evidently, there was no space for the group I wanted to build and no help with funding emerged. I had obtained some initial funding from some local foundations and therefore proceeded to hire a couple of graduate students. As their starting date approached, the problem of lack of space became more acute. There was a depressing newspaper article revealing that many of the senior oncologists involved in research had left the department recently and thus perhaps the environment was not conducive for research (the Department has since been reorganized giving hope that things can change also for the better). At the time I was quite disappointed by the lack of support, but with time I've realized that my experience was not unique, but in fact rather common in Finland and elsewhere. I had acclimatized too well to the world-class environments that had surrounded





me during my PhD and thereafter in Birmingham, and was having a hard time getting used to the academic realities in small Finland. Also, PhD students and post-docs are the main labor force in the scientific community and thus useful as such to group leaders and senior scientists. However, when attempting to become an independent scientist and collect funds for setting up group, one now becomes a competitor and the competition for resources is merciless.

I guess one could argue that I should have re-evaluated my geographical situation at that time. Nevertheless, I had agreed to start as a resident at the Oncology clinic on the 2nd of January 2003. Even more binding was the large mortgage me and my girl-friend had signed… And we both agreed that obtaining a specialization was important for our future plans, whatever they were going to be. I remember one older colleague jokingly explaining to me that being a specialist in any medical field is equivalent to *James Bond's* "Licence to Kill". What he meant was that putting in 5–6 years of residencies, hundreds of nights on call and the huge amounts of patients one meets during this time, one obtains a lot of experience and knowledge, which result in skills, self-confidence and respect. In medicine, experience and knowledge are critical, and one cannot do anything new without these skill sets, and thus I was determined to complete my residencies despite the headwind.

## Surviving anti-recruitment

Thus, I contacted other department heads on campus to see if they would allow me to launch my research group with the funding I had already obtained. My naïve thinking was that I was bringing a new technology to the University, as there were no groups working on gene therapy in Helsinki, and that this technology could be applied in many different ways. Also, I had a great CV and track record which suggested that I would receive further funding in addition to the grants already obtained. However, I hadn't realized that the system

didn't support recruitment of new people. Instead, newcomers or returnees were typically seen as competitors for resources.

Further, I started to realize that the counterside of academic freedom is that there is not necessarily a common goal at the University. At the time, there were few strategic funds set aside for important or new areas of work although there are now signs this might be changing. It is great from the academic freedom perspective if researchers are free to work in whichever field fancies their taste, but this may not be optimal from the point of view of the organization or society. Since the situation was that the University didn't give any financial support to most groups, except for paying the rent and providing internet connections in return for overheads, there was in fact little connection between the research and the University. During writing of this book, I have paid more attention to these things and I would like to think that despite a climate of declining funding, I would argue leadership has recently been improving at all levels of the University and that more money is targeted towards high quality important work.

Initially I thought this was a local or perhaps national Finnish phenomenon but I later I have learned that this is actually the typical European situation, with some notable exceptions. Most European Universities are funded directly by governments and thus there is no incentive to be better than the others. If high quality research does not increase the funding of Universities, why should they recruit scientists? At the University of Helsinki, just as at many other European Universities, the past decade has been a continuous financial crisis. The University has come up with a reasonably smart way to minimize their losses. New people are not chosen to fill vacant positions but instead the money is put into a pool controlled by the central administration which appoints professors, lecturers and post-docs, typically for 3 and 5 year positions. This is a good start but without a "package" to support research costs, it is not easy to attract the best people globally.

Scientists always complain about the funding situation but we





seldom remember that in reality scientific research is a luxury product. Sure, it is a useful investment in the future, good for competitiveness of the economy and great way to employ people since it is labor-intensive and not easily fully automated, but no one will die immediately if research funding is cut. Thus, budget cuts in science are more easily done than say cuts in health care, defense, the police force or fire-men. Also, since there is much mobility and flexibility in the careers of scientists, budget cuts don't lead to public demonstrations, researchers just vote with their feet or go find "a real job" like some of my group members like to say.

Despite practical monetary limitations, the University manages to rank reasonably in international comparisons. In *the Times* Higher Education evaluation, the University is the best in Finland, the 36th best in Europe and at number 103 globally.[90] It can be argued if this is a good achievement or not. On one hand, this is not bad for a country with 0.07% of the world's population. Comparing to school rankings such as Programme for International Student Assessment (PISA), where Finland has been ranked number 1 globally several times, one view is that a lot of potential is lost after High School.[91]

The University should be applauded for recently initiating a tenure-track program, which has been standard in Anglo-American Universities for decades. Tenure-track means that one can keep their job beyond the initial 3–5 years if they are reasonably productive. After the second 5 year stretch they can then have a regular position, just like at any ordinary work place. Sounds appealing? The only problem is that tenure track positions are available for less than 1% of the 4000 scientists working at the University. It appears the tenure-track system is expanding which would be great news for Finnish science.

However, currently almost all research and teaching personnel younger than 50 years old have temporary positions. It is asking a lot from young people to start raising a family in this type of insecurity, especially since unemployment in general is again on the increase. Also, one can wonder how this situation relates to the wish of the

University to become more international. I had a post-doc from Bangladesh who told me that his mother wouldn't allow him to marry before he has a non-temporary position. I told him it was sound advice. Not surprisingly, he moved to North America after one year. I don't think the University is to blame for this situation; they have an impossible task of trying to achieve goals set by legislation, with declining funds, compounded by a stable increase in salaries and their side costs in Finland. Also, because the University has been so effective in training PhDs, they now have a problem with what to do with them. Industry swallows some of them, and government some, but many go and do post-docs and then return with ambitions for their own group. Historically, employment at universities has been a complex mixture of temporary positions, grants, extensive mobility and absolute disregard for workers' rights. However, this does not seem feasible any longer as employees nowadays demand stable employment.

Eventually, after talking to two dozen professors, I received a positive reply from *Pekka Häyry* and *Risto Renkonen*, who were heading the Rational Drug Design research program. Their space wasn't that large but their people had flexibility and thus we fit in. They helped us apply for biosafety level 2 permits required for gene therapy work and thus we were on a roll. Unfortunately, a few years later *Pekka Häyry*, the grand old man of transplantation in Finland, retired. However, Risto has continued to be a strong supporter over the years. He is also emerging on the Faculty and University levels as one of the few professors with genuine leadership qualities. I think *Pekka Häyry* will write his own book one day but what I have gathered is that he had similar experiences to mine at the University. It seems to be incredibly difficult to do anything new. While patients want and need new interventions, jealous colleagues and bureaucratic administrators don't see it in the same way.

Another strong supporter was *Leena Peltonen-Palotie*, who was the Scientific Dean of the Faculty for a long time. A global leader in





her own field of molecular genetics, she was also a compassionate mentor and had a genuine wish to improve science and translational research in Helsinki, including interaction of the University Hospital and the University. I proposed to set up a "phase 1 center" at the Hospital, which would have specialized in doing early stage clinical trials. Some supporters emerged, but also fierce opposition from territory-conscious hospital department heads. Descriptive of the situation, Professor *Peltonen-Palotie* told me that when she discussed the initiative with my direct superior at the Hospital, the response was: "I also want my own center for doing trials".

## The cancer gene therapy group is born

The name of the Cancer Gene Therapy Group (CGTG) was modeled after CBGB, the Country, Bluegrass and Blues Inn, a famous New York punk venue. The logo results from a competition we had in the group in 2003 and the winning suggestion was designed by a master's thesis student in the group at the time. The green stems from the official color of the medical faculty of the University and obviously adenovirus had to be featured in some way.

In hindsight, I guess those initial years as a truly independent group leader were characterized by struggling for physical space and funding to kick-start the group, and just trying to get some projects finished, without yet having the braveness to think about truly original ideas or the luxury to execute anything ambitious, as we were living hand-to-mouth. Some of our projects were just follow-up of work performed in the US. I had a lot of ideas but many of them were just lateral work instead of trying to go forward into something new. I did have a lot of energy, but residencies were taking their toll and much of my remaining time was taken up by grant applications and setting up of EU collaborations. Although I was working days at the Oncology clinic, we didn't have kids and thus nights and weekends were free for science. Eventually my

grant writing efforts paid off and we got funded for two largish – by European if not US standards – EU grants which helped the group along for several years and allowed some freedom with regard to new research directions.

2007 was an incredibly successful year. Before even completing my residencies, I received the K. Albin Johansson Research Professorship, the first ever professorship in Finland named after a person. The K. Albin Johansson foundation gave the funds to the Foundation for the Finnish Cancer Institute which then selected the recipient. In the call, I was ranked number two among about 80 applicants but they gave it to me because they wanted to get "a splash", which is certainly what happened, and perhaps they got a bit too wet for their comfort. Concurrently, I received the European Research Council Starting Grant, a new grant mechanism given for the first time that year. The amount of money was substantial from a European perspective, 1.6 million euros, divided over 5 years. The competition was extremely fierce and the funding rate was only 3.3%. That same fall we also received the Cancer Organizations large grant, which is the most prestigious cancer research grant in Finland, and an Academy of Finland project grant. However, with all this luck in hunting, the sharks smelled blood and vultures also started circling.

CGTG was extremely successful as long as we stayed in the laboratory and didn't attempt to cross the "Valley of Death" to treat patients. We started to receive all kinds of funding, a lot of papers were being written, PhDs were being completed and students went on to have successful careers afterwards. Our group was among the largest on campus which might have raised some eyebrows among the most famous scientists twice my age. We were the largest group in Europe working on oncolytic viruses and accordingly started having a major impact in scientific journals and meetings.

The media took note and quite a lot of newspaper articles appeared on this interesting "new" therapy turning viruses into something useful. A bunch of TV programs were made and we were becoming





almost local celebrities. One journalist called me the "celebrity scientist", a title I certainly didn't want, although I had little idea how much damage this status would later cause. I was even selected "the Outstanding Young Person of the World" by Junior Chamber International. I travelled to South Korea to collect the award, given to 10 people globally that year. Other awardees included an Indian micro-banker, human rights activists and *Jyrki69*, a rocker doing *pro bono* work for United Nations Educational and Cultural Organization UNESCO.

Although I never liked the publicity, at the time I figured that it was worth the trouble if it could help with our funding, and perhaps help with moving things into the clinical phase. Before I was tainted by perceptions of commercial conflicts and before doing the unthinkable – actually treating a patient with the "new therapy" – my way of bluntly saying things like they are was a valuable asset which the media liked.

In hindsight, I think we also attracted a lot of jealousy. Not being an envious person myself, I think I failed to realize how much our success and visibility would hurt us down the line. Some of the newspaper articles were indeed written in such a way that even some group members complained, even if I tried to explain that it is the journalists' job to make their story provocative and interesting to make it sell.

I didn't yet realize one unpleasant aspect of the media. First they make a "hero" story and then some time later they utilize the publicity they themselves created to make a "fallen hero" story, featuring some other angle or even just reporting rumors and insinuations. Thus a lot can be written without any deeds needed on part of the subject.

However, it would be unfair to group all journalists into one group. If any one term can be used to describe them, I would propose that they are individuals who like to think with their own brain. As far as I understand journalists' modus operandi, a good newspaper piece always has a clear message, and it obviously depends on the journalist what message they decide to deliver. Most stories involving

humans have two sides so there is some freedom with regard to the point-of-view. I'm sure that in general they would prefer their message to be important and true, preferably something with societal impact. I assume that to journalists the example set by *Bernstein* and *Woodward* of Watergate fame is similar to the work done by *Coley*, *Pasteur* and *Semmelweis* in medicine. However, not all stories turn out to have the weight of Watergate, but the bills need to be paid, the deadline is approaching, the Editor demanded something big, and thus sometimes the stories reflect these realities. Also, even if you are not the first one to the scoop, there is always the other side of the story to be reported or hinted at, and thus the news starts to feed itself.

## Is there a Valley of Death?

Before we go into the gory details of clinical trial regulation, lets first ask if there is a Valley of Death; the place where most translational projects die? The short answer is that the attrition rate is difficult to quantitate scientifically, since there are no statistics indicating projects which were never started, nor are there figures for incomplete projects, changes of plans or exhaustion due to bureaucracy. However, as an experiment, I collected some figures from PubMed,[92] the main medical publication database, and clinicaltrials.gov,[93] the most important clinical trials database, both sponsored by the US government (Figure 9).

There are many biases in this type of quick-and-dirty comparison. For example, many preclinical projects only aim at increasing scientific knowledge and do not even attempt to result in human application. Traditional basic research would be a good example of this, and basic researchers often work with exotic non-human organisms such as the fruit fly, frog, round worm or zebra fish, and these publications rarely lead to direct human application.

Moreover, it is not easy to compare the different trial phases to





each other. On the traditional drug development path, one would expect attrition of many molecules after phase 1, due to toxicity, or after phase 2, due to lack of efficacy, but this is not evident in the numbers below. One reason is that often several, even dozens of phase 2 trials are performed with one drug, to examine different schedules or combinations with other drugs. Also, most phase 1 trials are in fact "positive", in the sense that less than a third of molecules are dropped because of toxicity. Thus most could be developed further into phase 2 trials, if funding would permit and if the initial biological or efficacy data obtained in the phase 1 would be promising enough, even if these are not the main endpoints. Even approved drugs may be subjected to further phase 2 trials if they are used in a new disease indication.

Although positive phase 3 trials – one or more – are typically needed for product approval, many approved drugs are studied in further phase 3 trials, to optimize their use or study combination regimens. The large difference in numbers between phase 3 trials and approved drugs probably doesn't reflect the success rate of phase 3 trials aiming at product approval, which has been reported to typically fall between 25–50%,[94] but instead the fact that most phase 3 trials aim at optimizing treatments with approved products.

In conclusion, with these aforementioned caveats in mind, because the biggest difference in the number of publications (nearly 1000-fold) is between preclinical projects and Phase 1 trials, the data are compatible with a strong emphasis on preclinical work, and a major obstacle in translating findings into clinical trials. Thus, this experiment is in support of the existence of a Valley of Death.

## On the EU clinical trials directive *or* Why can't we cure cancer

All of the work performed in CGTG was preclinical up to 2007. Nev-

ertheless, I hadn't given up on my reasons for returning to Finland.

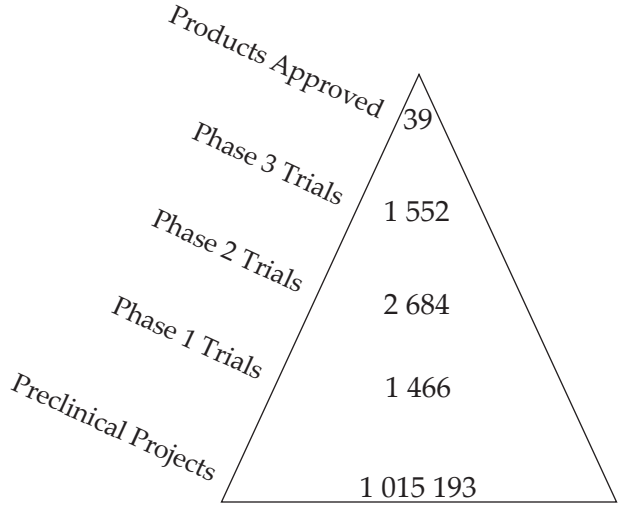



**Figure 9. Is there a Valley of Death?**

In 2012, 39 medical products were approved by the FDA,[95] a record high since 1996. Thousands of clinical trials were done, and there was little evidence for attrition between the different trial phases. However, in 2012, there were almost 1000-fold more preclinical projects published than Phase 1 trials initiated, which is compatible with a difficulty in translating preclinical findings into human trials. Sources: FDA, www.clinicaltrials.gov, www.ncbi.nlm.nih.gov/pubmed/. The trial numbers are from www.clinicaltrials.gov, with restriction to interventional trials open in 2012. Trials searches were also performed with PubMed, resulting in identical ratios between the phases of trials, but circa 30% lower numbers (1069, 1876 and 1013 Phase 1, 2 and 3 trials, respectively), which is compatible with the well-known phenomenon of a significant proportion of trials never being published. Databases were accessed on 26 Aug 2013.





In the early 2000s, the thinking in the US was that the FDA was overly strict on gene therapy, and since some pioneering cancer gene therapy work had been performed by *Seppo Ylä-Herttuala* in Kuopio,[96] my thinking was that it seems to be easier in Finland. And it probably was, until 2004, when the EU Clinical Trials Directive descended on Europe.[97] In contrast to natural disasters such as earthquakes and tsunamis, whose death toll can be estimated by the number of corpses or by assessing how much the population in the affected areas decreased, it is more difficult to quantitate how many deaths were caused by the directive, since the victims result from the slowing down of improvements in medical technologies. There are many authoritative texts on the deficiencies of this disastrous directive[98] but I will give my five cents here. My view is that of a practicing oncologist, who also has studied experimental therapies, understands the science and believes that new approaches are needed to supplement our armamentarium against cancer.

To summarize, the clinical trials directive has reduced clinical trials in Europe, and made them much more expensive. The impact on innovation is dramatic, although again difficult to quantitate; how do you measure something that was not even started because of crippling regulations? Of note, the directive was developed with only drug approval in mind and it is completely unsuitable for regulating research, to which it is nevertheless applied.

Most humans die of diseases potentially treatable with developmental technologies. If, however, those technologies never reach the patient or are slower to do so, patients may be dying unnecessarily or not living as long as they could have. If this is true, the parties making clinical research more difficult are responsible for deaths of thousands or millions of people. Similarly to many forms of democratic government, in many countries there is a three-directional balance in regulation of medical issues (Figure 10). Bringing new products to the market is usually accomplished by the pharmaceutical industry. Governmental regulation was set up for the purpose

of keeping these companies in check. However, since there are no consequences if the regulatory bodies do not approve products, but they can get punished if an approved drug or a drug in trials results in serious adverse events, they tend to be very conservative and will always err on the side of caution. Obviously, the best way to ensure patients don't get side effects from drugs is to not treat them with any. If this philosophy would be implemented fully, it would also result in significant savings in the amount of money spent on medications. Using cancer as an example, by far the most cost-effective approach is just to give patients pain medication and nothing else. This way the patients die much faster than after active oncological therapy and therefore significant amounts of money are saved on drugs, hospital stay, sick leave compensation and pensions. This is the provocative view of course. Another view on effective cancer treatments is that productive lives and careers can be saved. Cancer is quite common in employed people and in fact it is among the biggest killers in 40–65 year olds.[99] Thus, if the tumor can be stopped, individuals can keep working and paying taxes.

Obviously, just trying to save money on cancer treatment (instead of trying to stop the tumor) is not be in the interest of patients and therefore traditionally pressure from them, or from society in general, has helped keep regulation in check, so that new drugs and new clinical approaches can still be brought to humans, completing the third prong of the balancing instrument (Figure 10). Yet, after the clinical trials directive, regulation in Europe became much more complicated and expensive than before. Drug companies understood this quickly and started doing their trials in non-EU countries. Academic trials with new drugs ceased almost completely. Although few people have, one could question the logic of having the drug control authority overseeing research. No doubt they are the experts in licensing and approval of new drugs, but what is their mandate for regulating research? Medical research aims at understanding diseases and seeks ways to cure or treat them. Ultimately, drug development often results, but only very few trials, the tip of the





iceberg (a subgroup of Phase 3 trials), attempt to gain market approval for a drug. Nevertheless, it is the same people assessing all kinds of trials, and they use the same criteria.

In many countries including Finland, doing trials has become prohibitively expensive, which again makes the regulator's job easier; fewer trials means less chance of them being blamed for allowing a trial which resulted in an adverse event. In some countries like the US and UK patient organizations attempt to keep the system in balance by applying pressure on governments and regulation to ensure that new technologies can be tested in trials. However, in other countries the contribution of patient organizations is minimal. While there are such organizations in most developed countries, their activities tend to be rather low profile and there is no culture of demanding more. In this the US patient organizations could certainly teach some lessons to the rest of the world.

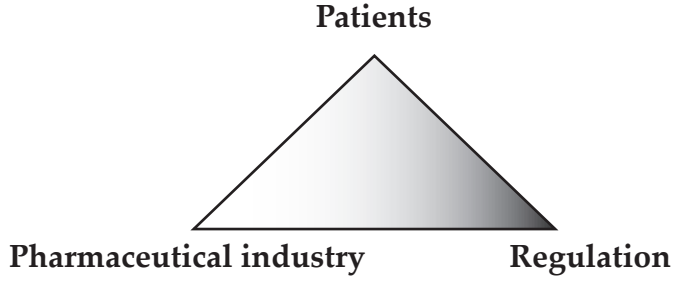



**Figure 10. A simplistic illustration of the relationships between drug developers, regulators and patients.**

If functional, each party keeps the others in check.

In a paper published in *British Medical Journal* by myself and the Head of the Pirkanmaa district of Oncology *Pirkko Kellokumpu-Lehtinen*,[100] we described some of the damage wrought by the directive. The official political aims of the directive were to a) improve the protection of patients, b) improve the reliability of research reporting

and c) to harmonize and increase the competitiveness of European clinical research. The mechanism for reaching these goals was by raising the bar for all clinical trials to the level of the most stringent trials performed in the most healthy patients. In other words risk-benefit analysis was not allowed to impact trial design or execution. In the context of cancer trials, where healthy volunteers are not utilized, it meant that full "industrial phase 3 type" rigor was now implemented even in early phase academic trials with the most severely ill patients in dire need of new options.

Now, raising the bar for all clinical trials may not seem a bad idea to your average EU politician but in practical terms it has disastrous effects for the research community, ultimately affecting all humans as development and optimization of therapies is slowed down. In evolving technologies including oncolytic viruses, it should be realized that there is much to learn and therefore most early projects will not lead to product approval. Phase 1 trials never lead to product approval. Instead, the usual developmental process entails consecutive laboratory-bedside-laboratory cycles. This is an example of how clinical research can be distinct from the drug approval process and exemplifies how crazy it is to require the same rules for both types of trials. If full industrial drug-level production is required from each phase 1 trial, the cycling of bench to bedside and back becomes incredibly expensive and – in fact – impossible with current regulations in place.

I remember one prominent Finnish regulator explaining how they are helping the Sponsor – a Sponsor is always required according to EU thinking, scientists and clinicians alone are not allowed to do a trial - and the Investigators by making sure the phase 1 trial already incorporates all aspects necessary for completing a phase 3 trial. Obviously she had not considered that this approach makes doing phase 1 trials incredibly expensive, and is quite wasteful since a lot of money is spent on setting up processes which will never be taken to phase 3. The practical translational scientist's thinking is that phase 1 should be kept as lean as possible without risking patient





safety, in order to facilitate cycling from the bench to bedside and back. Our US colleagues are often critical of the FDA, but it must be said that the FDA realizes this aspect much better than their Finnish counterparts.

I'm sure there was good intent behind the EU clinical trials directive but it failed miserably. In typical EU style, the directive in itself wasn't binding in any practical terms and thus it was adopted in different ways by different countries. Some countries like Italy and France were smart about it and allowed a lot of flexibility while other countries including Finland implemented the directive to the letter or even exceeding the requirements. Thus, harmonization failed.

Another goal was to improve the competiveness of European biotechnology and pharmaceutical companies. As evidenced by plummeting numbers of clinical trials since the directive, especially earlier phase trials, also this was unsuccessful. For a presentation I gave in March 2013 I collected the public numbers from FIMEA's ("Finnish FDA") web pages.[101] The number of clinical trials in Finland overall had decreased from 293 to 141 between 2004 and 2011, constituting a 52% decrease. The number of academic trials had decreased from 90 to 30 (-67%). There were no statistics on academic clinical trials performed with drug development, but I bet the number was 0.

I never understood how increasing the price of trials and the associated regulatory burdens would increase the competiveness of EU companies but this goal is nonetheless stated in the directive. Perhaps it is a descriptive feature of the EU philosophy and part of the reason why the directive was so bungled up, that clinical trial regulations were not determined by the Health and Consumers or Research and Innovation directorates but instead the Enterprise and Industry directorate. Don't get me wrong, I voted for joining the EU, and still support being part of it, and they've been the biggest funders of our research, but it must be admitted that EU decision-making is a non-transparent mess no-one can make sense out of.

A key objective of the Directive was increasing patient safety. I guess this was achieved in the sense that if there are no trials, patients are not exposed to trial medication related adverse events. However, patients are still exposed to the usual side effects of existing therapies – including the close molecular relatives of chemical weapons of mass destruction – and the adverse effects of routine treatment can be significant. For example, one of the most toxic approaches in medicine is bone marrow transplantation, with mortality rates approaching 50% in some indications.[102] In some cases this therapy could be replaced by new approaches such as gene therapy, as discussed above using SCID as an example.

## What is "evidence based" in oncology?

Most chemotherapy regimens have a mortality rate of a few percent but it can go up to about 6% or even more than 20% when the intensity of the therapy is increased.[103] High dose chemotherapy of solid tumors, especially breast cancer, was in vogue for a while but the field was tainted by falsified data from *Dr Werner R. Bezwoda*, one of the leading investigators, and when his results were disregarded it was realized that the patients were being hurt, not helped with dose intensification.[104] It was believed that just by increasing the dose eventually patients might be cured. Nevertheless, this was based on incomplete understanding of cancer as a disease. Namely, there will always be subsets of cancer cells such as cancer stem cells, that cannot be killed with any given chemotherapeutic. When placed under selective pressure, these subsets will outgrow and cause resistance.

For the record, and in contrast to what one might read on the internet (search with "chemotherapy doesn't work" for example), chemotherapy is used because it works. It can make tumors smaller in many cases, many patients live longer, and some are even





### Cancer stem cells

With regard to cancer therapy, a particularly troublesome subset of cells is tumor initiating cells, also called cancer stem cells. These cells have the ability to pump out toxic substances including most cancer drugs.[105] They are also resistant to radiation due to hyperactive DNA repair mechanisms.

A possibly attractive feature of oncolytic viruses, in particular capsid modified adenoviruses, is their ability to kill such cells.[106] It is not precisely understood how important this aspect of oncolytic viruses is in the context of their overall efficacy but it is intriguing.

cured, although usually not when the diagnosis is a metastatic (=spreadsolid tumor (ie other than leukemia or lymphoma).[107] However, there are even some solid tumors that can be cured, such as many testicular cancers or some childhood tumors.[108] Moreover, chemotherapy has cured millions of patients when used as adjuvant therapy in a minimal residual disease setting.[109] Given that chemotherapy cannot eradicate cancer stem cells which underlie tumor metastases,[110] good efficacy in the adjuvant setting may relate to immunogenic cell death resulting in an effective immune response against cancer when there are no large tumor masses causing immunosuppression. Although some immunologists would agree with this hypothesis, the larger oncology community probably doesn't understand tumor biology well enough yet.

Nevertheless, the problem with chemotherapy is its frequent toxicity. Even with the more gentle chemotherapy regimens more than half of patients may experience severe and even life-threatening adverse events, although oncologists are quite good in managing these effects, resulting in low mortality. One often overlooked feature of "routine" therapy is the fact that drugs are rarely used in the same way as they were in the pivotal trials that demonstrated their safety and efficacy. To ensure rigorous and homogeneous trial patient populations, the inclusion and exclusion criteria for practice-modifying trials are typically quite restrictive. For example, many trials have an upper age limit of 65 or 70 years while real life patients can be older

than that. Also, typical entry criteria require very good performance score and lack of co-morbidities which may not always be the case in routine clinical practice.

Thus, a common caveat is that the trial population no longer resembles a real-life patient population. Also, in the case of cancer drugs, in most cases activity was demonstrated as first line treatment, meaning that they were used as the first treatment when eg. metastatic disease was diagnosed. However, based on such studies, these drugs are now considered "evidence based" and are subsequently used also in second, third, fourth and fifth line.

Finally, the typical set-up in practice-defining cancer trials is comparison of regimen A to regimen B and a typical result might be that 60% of patients benefited from A while 45% benefited from B. Thus A is considered a new standard of care if there were enough patients to give a statistically significant difference between the groups, typically defined as less than 5% chance of the finding being due to chance alone ($P<0.05$). However, this conclusion overlooks the fact that 40% of patients treated with A in this example did not benefit. In fact, some patients treated with A without benefit might have benefited from B. Many of these issues are difficult to prove because trials are incredibly expensive, and thus we must live with what evidence we have, but my point is that cancer therapy is nearly always experimental on the patient level. We almost never know if the treatment we select will actually help the patient or if there might have been another one that would have been better with regard to safety and efficacy. These questions could nevertheless be clarified with further research.

The EU clinical trials directive was especially damaging for academic research which doesn't usually have the same deep pockets as industry research. Pharmaceutical companies can be effective in bringing new drugs to market rapidly, to maximize the years the patent lasts, but they were previously rarely interested in defining the subpopulation of patients that benefit from the





drug, since this would restrict its use. This has changed somewhat over recent years when several drugs including *trastuzumab* and *gefitinib* first "failed" when they were used in unrestricted organ defined patient populations (breast and lung cancer, respectively).

However, near-failure forced the companies to look more carefully at the patient subsets that would be likely to benefit. Specifically, conventional Big Pharma wisdom initially resulted in both drugs being used in unselected patient groups without regard for the predicted mechanism of action. However, trastuzumab targets the Her2 receptor while gefitinib blocks active EGFR. When analysis was restricted to patients with high Her2 or mutated EGFR, respectively, the data was suddenly much more impressive.[111] Subsequently, the drugs became commercial successes, and this would not have happened if the benefiting subpopulations would not have been identified. Importantly, academic research independent from companies had a key role in these advances which have subsequently improved the therapy of millions of patients. Big Pharma took note of academic work and now it is perfectly acceptable to develop drugs for subpopulations, and in fact sometimes these subpopulations are very small.[112]

"Targeted therapy", referring to monoclonal antibodies and small molecular inhibitors of tyrosine kinases, has not quite provided the breakthrough it was hyped up to deliver, mostly because tumors are able to develop resistance rapidly. The more specific the target, the faster a tumor will usually outgrow with a "target-negative" or "target-mutated" or "target-circumvented" subclone, under the selective pressure of the treatment, fueled by the hundreds of mutations each tumor contains.[113] Advanced cancers are defective in all 12 central growth control pathways and even if one of them is blocked, growth signals will soon find another way.[114] It is like trying to build a dam on the Amazon delta; water will just flow down another channel.

Despite this frustrating situation, targeted therapies have gradually entered the routine treatment of many tumor types. *Rituximab* is

used universally in CD20+ lymphomas, *trastuzumab* in Her2+ breast, ovarian, gastric and esophageal cancer, while *bevacizumab* is standard in treatment of intestinal cancer. Moreover, there are some smaller indications where genuine breakthroughs have emerged. These include Philadelphia-chromosome positive chronic myeloid leukemia, gastrointestinal stromal tumor, ALK positive lung cancer, BRAF mutant melanoma and the number keeps increasing every year.[115] After being viewed suspiciously by companies for a long time, biomarkers able to define the benefiting patient population more carefully have entered clinical use and are considered absolutely critical by many who understand the heterogeneous nature of cancer. Some drugs are approved for use only following a biomarker test. For example, panitumumab, a monoclonal antibody against the epidermal growth factor receptor, can only be used in tumors with a non-mutated KRAS.[116] Academic clinical research contributed in a major way to all of these developments.

## Effects of increases in regulation on academic clinical research

Each drug company normally has their own products whose development has cost of lot of money and thus they are unlikely to risk a trial comparing "new drug A" to "new drug B". However, this sort of trial set-up would be most useful for society to interrogate cost versus benefit and traditionally academic research has filled the gap. Unfortunately, these type of trials are much less feasible in the EU after the clinical trials directive (Figure 11).

The biggest impact of the directive was on academic research with new drugs. The directive unequivocally states that full GMP (good manufacturing practices) is required from all clinical trials. GMP is a pharmaceutical standard which is typically applied to drugs for sale at pharmacies. There is obviously a need for such a standard to ensure safe treatment in routine clinical practice.





However, it is quite expensive to produce some types of drugs according to full industrial GMP. This applies especially to complex biologicals such as oncolytic viruses. For this reason, the prior system was that "GMP-lite" or "phase 1 GMP" is required for phase 1 and maybe small phase 2 trials, while full industrial GMP was not required until the phase 3 trial which aimed at product registration. This thinking is still successfully implemented everywhere else but Europe, where the clinical trials directive determined that even phase 1 trials with a complex biological would have to produced according to full industrial GMP. Again, some EU countries were a little smarter about this while some countries such as Finland followed the directive to the letter or even exceeding the tightened requirements.

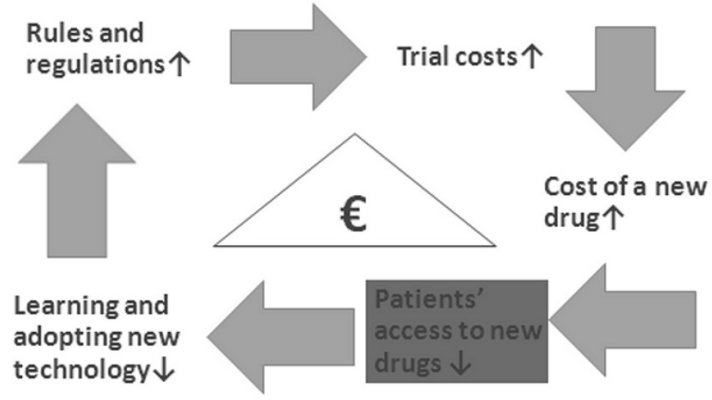



**Figure 11. The vicious circle that makes clinical trials more expensive. In the middle is the pyramid of clinical trials.**

For each drug which makes a profit (the top of the pyramid), dozens of phase 2 trials (middle) and hundreds of phase 1 trials (bottom) are needed. The sponsor paying for the all of these trials then needs to price their drug in such a way that they can afford the entire pyramid.

These points are difficult to argue because the regulators' first comment will be that patient safety must be foremost. Of course it must. But there is absolutely no data that the GMP-ness applied say in 2000 in oncolytic virus production would have resulted in any adverse events to patients. In many trials, there are adverse events but they are usually caused either by the underlying disease or the active substance present in the drug formulation, but not because of how it was produced. The regulatory pharmacist's view of the human body seems to be that it is absolutely pure and clean and thus all drugs also need to be. Unfortunately this is an optimistic view. Humans are infested with all kinds of maladies, microbes and impurities. Especially so when a tumor is present. Tumors are known to allow growth of all kinds of bacteria,[117] probably because of the immunosuppressive tumor microenvironment which is a safe harbor for microbes. To say nothing of the colon for example which contains more bacteria that the human body has cells. And when something is injected into the body, all GMP-ness is lost when the needle is stuck through the skin and through tissues into the target, since the skin and many other tissues are impure.

All ethical medical researchers agree that patient safety is the most important thing. Even *Hippocrates,* or whoever wrote in his name at his School of Kos,[118] said that "the most important thing is not to harm the patient". While this continues to be a strong guiding principle in medicine, it is also know that all medical interventions have some risk of harm and the physician's job is to judge the risk-benefit ratio for each patient in each case. This is the day-to-day routine work of all practicing physicians. For example, if the patient's medical problem is a minor one, and does not pose the risk of serious consequences, or will most likely heal spontaneously, the doctor will try to avoid interventions that could cause adverse events.

Lets say a patient had mild blood pressure, a head-ache, or thinning hair. Few physicians would prescribe a poorly understood, potentially





risky, advanced therapy medical product for these conditions. However, if the patient has an advanced tumor that has been treated with all available routine treatments but is still progressing, the situation is different. Such tumors pose a 100% risk of death if they cannot be stopped and therefore emergency measures are indicated.

Lets say someone is hit by a car and lies bleeding in the street. Do you press your hand on the artery even though your hand may not be full industrial GMP or do you allow the patient to bleed to death and tell them to come back in 10 years when you have have developed a GMP version of the procedure, acquired a patent for it, founded a company, obtained funding, proceeded through phase 1 –3 trials and were lucky enough to be approved by the regulators?

If there are no off-the-shelf solutions available then the physician's duty is to come up with experimental approaches. This is one of the defining philosophical features of medicine and has been written up in eg. article 35 (Box 2) of the World Medical Association Declaration of Helsinki (initially §32, then §35, now §37).[119] This declaration

> §35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with i*nformed consent* from the patient or a legally authorized representative, *may use an unproven intervention* if in the physician's judgement it offers *hope of saving life, re-establishing health or alleviating suffering*. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. *In all cases, new information should be recorded and, where appropriate, made publicly available.*

**Box 2. Article 35 of the World Medical Association Declaration of Helsinki.**

This is is the foremost ethical guideline for medical professionals globally and it's most important goal is to define the rights of patients with regard to medical research. Of note, the Declaration is updated at intervals and thus the number of this article keeps changing but the content has remained essentially unchanged in the different versions.

is the foremost ethical guideline for medical professionals globally and it's most important goal is to define the rights of patients with regard to medical research.

Thus, optimally, experimental measures should be tested in clinical trials but if this is not possible the physician should still try to help the patient. Most physicians and patients would say that a higher risk is acceptable in a situation where the disease is more threatening. Therefore, most phase 1 clinical trials with oncolytic viruses have featured a lighter version of GMP since they have targeted patients with 100% risk of death from their disease. Not, however, in Finland after the clinical trials directive.

In fairness, all the blame for the increasingly difficult process of getting new drugs into humans should not be attributed solely to the EU clinical trials directive. In truth, the process has been going on for a longer time, especially in Europe, where patient organizations demanding improved therapies have a smaller voice, and the mostly government paid health-care providers looking to save money have more say; new drugs tend to cost more than older ones whose patents have expired. As mentioned before, no treatment is the cheapest option for those who pay the bill.

A big part of this process is Big Pharma wanting to focus the capability of drug development into their own hands, and one way to achieve this is to make trials impossible for all other players. *Louis Pasteur,* one of the all-time greats in medicine said that "there is no such thing as applied science, only the application of science".[120] This statement, still heard in basic research meetings, has in my opinion not stood the test of time. The application of research into patient care has become increasingly difficult, even prohibitively so, while claiming one's basic research as applied "translational" research, to imply societal benefits, has become more common. Revealingly, I would postulate that most people at gene therapy meetings agree that the best-before date of *Pasteur's* comment has expired, while at a basic research meetings illusions seem to remain.

At writing of this chapter in Summer 2014, the Clinical Trials directive is being revised (EU/536/2014).[121] It will be interesting to see if some of the above-mentioned problems will be resolved, or if the new Directive will just mean even more regulations and even further increases in costs of trials, as often happens in EU legislation.





## Getting a trial started through RAID

Well, I didn't know most of these things when I started to try setting up our trials after returning to Finland. In the US, there is a wonderful government mechanism for applying for GMP (GMP-lite, to be exact) production of experimental therapies for academic trials. The Rapid Advancement of Innovative Disease interventions (RAID) program pays not only for production but also for biodistribution and toxicity studies.[122] The program is not absolutely restricted to US sites so in 2003 I went ahead and applied for RAID funding for the virus I thought was our most exciting one at the time.[123] The application was successful and therefore we started working with the National Cancer Institute to get the virus ready for the trial. I travelled to Frederick, MD to facilitate the process and we did a bunch of potency assays in the lab to help with production. I recruited investigators and co-investigators from the Women's Hospital in Helsinki since the trial was planned to be in ovarian cancer. I wrote the trial protocol and started to apply for funding.

Although I love the RAID as a mechanism, and I wish we had something similar in Finland or EU, it is maybe not the fastest way to get virus produced. Production was completed in 2006 and the animal testing was finished in 2007. However, I had not been able to acquire funding for the clinical part of the trial. My estimate of the trial budget was about €700 000 but I had managed to raise only €73 950. Again, unlike the US, there is no government or EU mechanism for academic clinical trials. In fact, the feedback I received for one EU application was that it would be a waste of precious EU money to support clinical trials since that is the

realm of drug companies.

Thus, no trial would happen in Finland with that virus. In fact, I didn't fight very hard for that trial since my initial RAID application had suggested that the trial be performed at two sites, the other one in Birmingham, AL. *Ronnie Alvarez* had arranged funding and was able to complete the trial and this was the thing that mattered. I didn't even feel that disappointed that my name was not eventually on the manuscript.[124] To me the main thing was that the trial had happened. Another reason for me not being so insistent with that virus was that by 2007 I had serious doubts if FIMEA (the Finnish FDA) would consider the US GMP-lite good enough quality for doing a trial in Finland, since they had taken a tough position on another trial I had tried to set up as will be explained.

## Industrial collaboration

In March 2005 I attended the Oncolytic Viruses meeting in Banff Canada. On the last night there was a party and I befriended *David Kirn*, whose company Jennerex was making strides forward with their vaccinia virus based oncolytic. They were looking for trial sites and I was looking for a trial. In fact it is interesting how things work out, it was the morning after the conference party and I was recuperating in the Jacuzzi at the hotel spa where David also appeared. We started talking and soon we were having phone conferences to arrange initiation of the trial. Jennerex should be given credit for their persistence with FIMEA but in the end it was to no avail.

***Here is an abbreviated description of our efforts to get this trial started:***

*7/05 approved by US FDA as an investigational new drug, meaning that its use would be OK for a Phase I trial in cancer patients*





*7/05 positive statement by Helsinki University Central Hospital (HUCH) ethics committee (Helsinki, Finland)*
*9/05 approval by Finnish Gene Technology board*
*8/05 Finnish FDA (Lääkelaitos/FIMEA) application. Their response was to require larger biodistribution and toxicity studies (estimated cost ca. €200 000), full sequencing (estimated cost €400 000).*
*Jennerex performed more biodistribution and toxicity studies as requested by FIMEA, which caused a 9 month delay*
*Our FIMEA application was resubmitted 5/06.*
*They required further data leading to a 3rd resubmission with more data on 10/06*
*After much deliberation, FIMEA finally agreed to a face-to-face meeting in 12/06. Their normal procedure is just looking at documents and replying in writing. The result of the personal meeting was that we were able to learn that they felt that a new virus batch would be needed because the master cell bank GMP certificate was not available from the original company that had produced it. The problem was that that company had gone bankrupt and therefore the certificate was held only by the US FDA.*
*I tried to resolve the issue by suggesting a phone conference between FIMEA and FDA where the latter could confirm that they indeed have the GMP certificate, but FIMEA's position was that they required the actual original physical certificate in their possession. The FDA's position was that according to US law they cannot give out the original GMP certificate.*
*Thus, to do a trial in Finland, a new preparation of virus would be needed. My information was that Jennerex started preparing production during the spring of 2007.*
*However, in 8/07 I received a rejection letter from FIMEA, indicating that their questions were not answered in time. This was obviously quite surprising since they had asked for a new production run and they must be aware that it takes a year or more to produce and characterize an oncolytic virus lot. And we had not been given a deadline by which the questions should have been answered. The Department Head in*

*charge was retiring and perhaps he wanted to "clean his table" before leaving. Nevertheless, for me personally this was a disappointment since after having worked at this very hard for 2.5 years, arranging all the facilities at both the Women's Hospital, the Cancer Clinic, obtaining an Ethics Committee statement and Gene Technology board approval, the trial was swept away with the rest of the trash on his table, without prior notice to us.*

*At this point, Jennerex evidently got the message and the trial was eventually performed in the US, Canada and South Korea without further attempts in Finland.*[125]

By the way, 90% of patients in this trial displayed disease control and 30% had a partial response, while safety was excellent throughout. These could have been Finnish patients benefiting…

I had also been working on another approach to try to get a trial going. We submitted a patent on a new type of oncolytic adenovirus, featuring a polylysine modification of the capsid, for enhanced delivery to tumor cells.[126] I then talked to all the main oncolytic virus companies and the Finnish offices of Big Pharma companies. Following a lot of hard work and talking, with support from the Finnish representatives of Big Pharma, I was eventually able to get some face time even with global level Research and Development officers, but in the end there was not enough belief in the technology to take it into a clinical trial and we had to let the patent application dissolve.

In my enthusiasm to get something going on clinically, I even tried to work with a US company using a rather conventional gene replacement strategy for treatment of tumors of Li-Fraumeni syndrome patients. This syndrome is caused by hereditary mutations in p53, a tumor suppressor gene.[127] The company's idea was to use a conventional adenovirus vector for delivery of p53 into the tumors that regularly develop in these patients.[128] I'm not sure I believed this would work that well given the limited nature of gene delivery achieved with conventional (non-oncolytic) vectors but I





still organized the facilities for treatment, and talked to the clinical geneticists who see these patients. After a while, e-mails sent to the company were not answered any more and shortly afterwards I learned they were out of business.[129]

## Treatment instead of a clinical trial

During these interactions with FIMEA, the "Finnish FDA", I had learned something interesting. It was in Summer 2005 that *Ali Bardy*, a Department Head at FIMEA told me: "If you only want to treat patients, and not develop a product, why don't you give the virus as treatments instead of a trial".[130] Perplexed, I asked him if this was legal and his reply was: "If a doctor had medical experience or biological evidence that a treatment might help their patient, they can even feed them iron nails if necessary".[131] He was referring to the World Medical Association Declaration of Helsinki and the general ethical principles of physicians, which require trying to help the patient as best they can. Not that I intended to feed my patients iron nails, this suggestion nevertheless sounded interesting and worth looking into.

While the planned trial with Jennerex was being slowly but surely coming apart, and there were no grants to take the RAID produced Ad5/3-D24 into a trial in Finland, and our Ad5-D24-pK7 patent didn't raise sufficient interest from companies, I gradually became more and more intrigued by the idea of treatment instead of a trial. Not that treatments would replace the need for trials, as only the latter can provide rigorous scientific information, but perhaps we might be able to help some patients with our viruses which were now just gathering ice in the freezer. Especially since the Department Head who had given me this advice was the same person who was responsible for the vaccinia trial at FIMEA, I assumed he would be the foremost expert on the issue. When interviewed by the police in 2013 ("When it rains…" chapter below), he didn't

remember giving such advice, but fragments of our discussions can be found in e-mails[132] which form part of the 499 pages of prejudicial inquiry instigated by his successor, more of which later. However, at the time I took his advice at face value and started to look into the legal aspects of experimental therapies with drugs lacking marketing approval. Here is an abbreviated list of all the governmental and non-governmental bodies I discussed the approach with. A complete listing can be found in the police files from the 2012–2013 investigation.[133]

***These publicly available materials might one day constitute an interesting set of materials from someone interested in the relevant legal and societal aspects:***

*2006 Finnish Medical Association*
*2006 HUCH Institute (responsible for arranging trials at the University Hospital in Helsinki)*
*2006 The National Advisory Board on Social Welfare and Health Care Ethics ETENE (the leading ethical body in Finland)*
*2006 HUCH local Ethics committee*
*2006 Gene technology board of Finland*
*2007 Ministry of Social Affairs and Health*
*2007 FinOHTA (Finnish Office for Health Technology Assessment, the Finnish version of National Institute for Health and Care Excellence NICE in the UK)*
*2007 Ethical Board of the Finnish Medical Association*
*2007 Lecture at FIMEA to a packed hall*
*2009 Social Affairs and Health Committee of the Finnish Parliament*
*2009 Written statement to FIMEA regarding implementation of the EU Advanced Therapy Directive*
*2010 and 2011 Discussions at FIMEA*

To summarize, the legal texts and FIMEA contacts most relevant for this approach are listed below. A more detailed listing presented





in a legal context can be found in publically available police and court files.[134] Some texts referenced below were written only after we had started our treatments, but I am listing them here for completeness. This is not an exhaustive list by any means, since I was – and still am – a big believer in transparency, so I was in contact with various regulators at regular intervals, with the purpose of keeping them aware of what we are doing and hoping to receive useful advice. However, many of those contacts were informal and lacked written minutes since I didn't think I would end needing them in court!

*Patient by patient gene therapy treatment used as a specific case example in a PhD thesis (Salla Lötjönen. Lääketieteellinen tutkimus ihmisillä, thesis from the University of Helsinki Faculty of Law 2004).*
*[Legal issues in biological medicine], Lasse Lehtonen. Bio-oikeus lääketieteessä, Edita, Helsinki 2006.*
*Law on medical professionals. Finland 559/1994, 15§.*
*World Medical Association Declaration of Helsinki article 37 (initially §32, then §35, then §37).*
*Advanced therapy directive EU/1394/2007 ("Hospital exemption: treatments under the sole responsibility of the treating physician").*
*National Medicolegal Department evaluation (18 Apr 2008).*
*Minister of Basic Services Paula Risikko (March 09 2008).*
*Finnish Parliament committee on Social Affairs and Health (1 Apr 2009, HE 21/2009 vp).*
*Discussion with FIMEA on Dec 9th 2009 regarding Oncos' application for non-industrial production under the Advanced Therapy Directive (Dnro 608/03.01.01/2009).*
*Regional Government of Southern Finland (22 Dec 2009).*
*1 Jan 2010. Finnish FDA (FIMEA) regulations based on the Advanced Therapy Directive.*
*FIMEA Scientific advice on Jan 22nd 2010.*
*FIMEA Scientific advice on Mar 3rd 2011.*

To summarize these discussions and the legal texts, there was no

disagreement regarding the rights of a patient and doctor to decide on therapy, in a situation where routine therapeutic options have been exhausted. In other words, all authorities and texts agreed that giving oncolytic viruses as an experimental therapy was allowed. It turned out that the strongest medicolegal/ethical reference was the World Medical Association Declaration of Helsinki, whose article 35 (§32 in older versions of the Declaration and §37 since 2014) states the case quite clearly (Box 2 above).

I also felt the upcoming EU Advanced Therapy directive[135] gave strong legal premises for personalized oncolytic virus therapy.

Although the final version was slow in coming, and implementation into national regulations took an even longer time, a draft was available already in 2005.[136] The Advanced Therapies Directive defines the "Hospital Exemption", allowing, or even encouraging, individualized patient-by-patient treatment with gene therapy and stem cells. The directive clarifies that it applies also to oncolytic viruses and that they will be considered drugs. This clarification is welcome since it had been argued that oncolytic viruses are in many ways closer to treatments such as in vitro fertilization or stem cell transplantation than conventional pharmaceuticals. Even if the bar is now raised higher for treatment with oncolytics, at least it is clear how they are seen by regulators.

The "Hospital Exemption" is important because it determines that patients can be treated with Advanced Therapeutics outside of clinical trials under the sole responsibility of the physician. National bodies such as FIMEA in Finland are required to oversee these treatments by regulating production and by requiring adverse event reporting. Importantly, a clear distinction in made between experimental therapies and clinical trials. While physicians who both see patients and have been involved in trials are well aware of the differences between these two, it was shocking to learn that this was not true for a powerful Department Head at FIMEA, as the narrative will explain later. Table 1 outlines the main differences between treatments and trials.





I figured experimental therapy under EC/1394/2007 was worth a shot and therefore in 2006 I started organizing virus production. At that point I had no idea where I would give the treatments since it had become clear that the Head of the University Hospital Cancer Clinic was not that interested. The facilities at the Cancer Clinic which had been approved by the Gene Technology Board and Ethics committee for oncolytic virus treatment were suddenly converted into an electrocardiography laboratory. The message of this abrupt reorganization was rather clear but just to get closure I asked the Department Head what his response would be if I would eventually ask for his signature to give oncolytic viruses at the Clinic. His reply was that perhaps these treatments were best given elsewhere. Even if he had initially recruited me from the US, his support had disappeared when he learned that I had plans for a research group of my own. It seemed to me that with every newspaper article on our work he became less and less supportive.

One issue causing much tension in academic centers globally, although not necessarily the case here, is that the selection process of academic leaders tends to focus on scientific merits. Thus it is not rare to encounter smart and hard-working people in critical leadership positions but lacking leadership qualities. Also, as usual with ambitious individuals who have attained their positions with their own merits, it varies how well they are able to adjust to realize that their own success is now measured by the success of the organization they were selected to lead. "Promotion until incompetence" is common in all fields of professional life, meaning that successful people are promoted until they end up in a position where they are no longer successful, resulting in lack of further promotions. Since it is usually not advisable, or even possible, to let famous scientists go, one way to resolve leadership issues is by changing the organization to "work around" the problem. However, this rarely happens with a schedule that would be useful for young scientists in a conundrum, typically the only option is to "vote with your feet".

**Table 1. Differences between clinical trials and experimental treatment.**

| Trial | Treatment |
|---|---|
| Predetermined protocol | Patients treament case by case |
| Strict inclusion criteria | No absolute inclusion or exclusion criteria |
| Sometimes placebo included | No placebo |
| May involve interventions without benefit to the patient, for example biopsies | Only procedures directly relevant for the patient are performed |
| May have a sponsor with commercial interest | Cost paid by patient, community, insurance |
| Clinical trials are tightly regulated and very expensive | Few regulations apply (559/1994, 15§ in Finland), except for "advanced therapies"(EU 1394/2007) |
| May benefit society and facilitate products eventually available to millions | Goal is to help patient |
| May or may not benefit the patient | Limited benefit to society |

I was sort of relieved that I was now forced to look elsewhere. Like in a bad marriage, separation can be the right thing for all parties. I had clunged on by the skin of my teeth for 5 years, mostly because I still had the idea of being an academic clinician-scientist in my head. Also I realize now in retrospect that I was far too optimistic in hoping that eventually "the greater good", important science and patient's access to an exciting new technology, would prevail over envy and internal politics.

Basically, my default setting had been to attempt to follow the footsteps of world-class scientists such as *Paul Ehrlich, William Coley, Robert Koch, Louis Pasteur* et al. More concurrent examples of practice-changing potential in our field include *Harald zur Hausen, Steve Rosenberg, Malcolm Brenner, Carl June* and *Eva Galanis*, all of





whom work from the stronghold of the University laboratory. My philosophy at the time was well summarized in a slide I presented in a lecture to medical students in 2004 (Table 2). However, I was now being pushed away from the academic environment, and I curiously embraced my new future, whatever it was going to be, yet with some trepidation.

Temporarily lacking a host institution where to give the treatments, if they could be ever started, I was nevertheless optimistic that if there was oncolytic virus therapy available, patients would come. This thinking was based on the numerous e-mails and phone calls I had received from patients and their relatives. We had a high publicity profile at the time, because of our laboratory work, my awards, and the newspaper articles that followed, and I was frequently contacted by individuals wanting to receive therapy. For several years, I had been explaining to them that – despite intensive efforts – unfortunately we didn't have anything to offer.

Looking into production requirements, I found out that there were none, when it came to oncolytic viruses given as therapy. At the time,[137] there wasn't even legal agreement if viruses were a drug or more a treatment like surgery, transplantation or in vitro fertilization for example; all of these are effective treatments which cannot be easily pressed into the mold of a conventional drug. All the same, I figured clean, high quality production seemed like a good idea and we looked at several options within Finland. Eventually, our strongest supporter *Pekka Häyry*, who performed some of the first kidney transplants in Finland while still a second year surgical fellow, came through for us and arranged a suite at one of the University buildings, and funding to renovate it into a facility compatible with sterile production of oncolytic viruses. After renovations, I was quite proud of it and the production team looked quite impressive in their head-to-toe outfits.

**Table 2. A slide I presented as part of my lecture to medical students in 2004.**

| Suggestions to clinical scientists |
| --- |
| Always do good work, never cut corners. |
| Disregard advice and avoid mentors who value quantity over quality. |
| Never do science for merit purposes only. |
| Don't worry about impact factors, good science will eventually be recognized. |
| Be polite, go to parties, network and talk to people. The world of science is small (especially in Finland). |
| *You'll meet the same people going down as you did going up* (unknown rocker). |
| *Boldly go where no man has gone before* (Star Trek). |

Various tests on the viruses, equipment, disposables, storage medium and stability of the product followed and the first production run was executed in Summer 2007. As the first virus we chose a highly tumor selective virus we had published earlier.[138] We figured safety was most important since no-one had used a tropism-modified virus in humans before. Tropism-modification means that the virus had been engineered in such a way that it did not use its normal receptor any more but instead entered tumor cells more effectively than the normal serotype 5 adenovirus.

There are many ways to achieve this but our favorite was to borrow a part of the virus, the fiber knob, from a different type of adenovirus, that of serotype 3. The scientific rationale for this was quite strong as there were dozens of reports that the receptor for the normally used adenovirus type 5, the coxsackie-adenovirus receptor, was frequently





low in advanced tumors.[139] Even the reason was known; this receptor is an adhesion molecule, meaning a molecule which mediates contact and communication with neighbours, and since many adhesion properties are abnormal in tumors cells, it was logical that the receptor was poorly expressed in advanced tumors. When tumors gain in aggressiveness and work their way toward a metastatic behavior, they need to lose their concern for nearby cells in order to escape their normal location in the body.

## The first patient

During 2007, I had been trying to work out where treatments would be given. Since the University Hospital Cancer Clinic was not an option, and the next Academic Medical Center would have been 150 km away, and my family situation did not allow me to move elsewhere, I talked to the private hospitals in Helsinki. I received quite variable responses. In one hospital, my phone calls were never returned. In another, I got the Chief Physician on the phone but his lack of understanding of the subject quickly annoyed him and he was in a hurry to go and operate. However, at the Eira hospital, the oldest and most prestigious private hospital in the country, there was significant interest. We met and started planning the treatments. I visited the place and we started to put the relevant things into place. A room was identified where we could prepare the virus for injection. Gene Technology Board approval was obtained for the facilities and I talked with the radiologists and radiology nurses. However, in August 2007 I received an interesting e-mail, asking me if it would be OK to forward my plans to a new party whose goals would be synergistic with our goals.

*Timo Joensuu,* a former colleague of mine from the University Cancer Clinic, had decided to take the big leap and set up the first private oncology hospital in Finland. His co-founders included an experienced serial entrepreneur and a financial expert. They had

ambitious plans for building their own hospital from the ground up, to make sure everything would be optimal in every way, with the goal of becoming the most prestigious and advanced cancer clinic in Northern Europe. Since oncology is increasingly a multi-disciplinary approach, an important goal was to have radiation therapy, medical oncology and advanced imaging under the same roof. Through partnering with the Eira hospital they also set up a hospital ward for overnight stays, and a laboratory for blood tests. Computer tomography (CT) equipment is routine nowadays but this hospital would also have a positron emission tomography computer tomography (PET-CT), high-power magnetic resonance imaging equipment (MRI) and single positron emission computer tomography (SPECT) equipment. Their linear accelerators would be top-notch and there was an agreement with the supplier to have easy access to the newest software which is key to optimal radiation delivery. These equipment placed *Timo Joensuu's* dream hospital ahead of most University hospitals in Finland with regard to technology.

Docrates Clinic (later Comprehensive Cancer Center Docrates and Docrates Hospital) started its operations in Fall 2007 in the facilities of Eira hospital and Docrates' own building was opened on April 29th 2009. While things had worked out well also at Eira, it was truly magnificent working in an environment where everything had been planned with cancer patients and modern oncology in mind. I especially liked the fact that if a patient needed imaging, lab tests or procedures, they were available immediately, typically within one day. In general, the public health care system in Finland works reasonably well, but it is not designed from a patient's perspective. Instead, the goal is to minimize costs while maximizing capacity and retaining an acceptable level of care. This is achieved through limiting resources and queuing patients for almost everything, including imaging, doctor's appointments, initiation of treatment. They even had to write a law where the length of the queue for a hospital referral was limited to 3 months,[140] but who wants to wait for 3 months if they are ill?





Not surprisingly, the private sector is doing well in Finland. And this helps the public sector save further money as the people who can afford it seek treatment in the private sector. The more the public sector saves, the more people will use the private sector resulting in further savings to the public sector. No wonder the system can proudly announce it is the most cost effective in the world.[141] There was a time when there was public reimbursement of health care costs accumulated in the private sector but reimbursement rates have been frozen for decades, and they are now only 10–25% of actual costs. Consequently, people have started to acquire private health care insurance in addition to the mandatory public insurance they pay as part of their taxes. 20% of Finns already have such insurance and the figure is increasing rapidly.[142]

Finland uses a low percentage, about 9.1% in 2012, of its gross national product on health care.[143] This is lower than most Western countries, and about half of what is used in the US.[144] Mostly the low costs are achieved through low salaries of health care professionals, but also by employing nurses and physicians as gatekeepers to resources. It is one of the most common questions Finnish cancer patients have when they see an oncologist in the private sector: "Am I not receiving all the treatments that might help me because they are trying to save money?" Fortunately this is usually not the case but this worry reveals the way the system works; patients are well aware that money is tight and getting tighter every year.

Personally I disliked the gatekeeper role. I had always thought that in a relatively well off country like Finland there must be enough money for high quality treatment of patients with severe disease. And nothing is more severe than cancer. This seems not to be the case however. Resources in health care are divided on a historical basis and cancer has become a dominant cause of morbidity and mortality relatively recently. When the University hospital system was set up in the late 50s, internal medicine, cardiology, infectious diseases, pediatrics, gynecology and other diseases common at the time were more important than cancer, from a public

health perspective. Also, there were very few treatments available for cancer and thus there was little to spend money on. Pain killers are not very expensive and without any effective anti-tumor therapies you don't need to use them long.

The history of oncology in Finland mirrors the rest of the West in the first part of the 20th century. For most tumors, when the patient was beyond surgery there was only radiation therapy, which was poorly understood and used in a haphazard manner. The planning of treatment fields was restricted by the fact that the required technology had not been developed yet. Descriptive of the situation is that the Finnish Cancer Organization, a private organization, arranged for an excursion to Africa in 1936 to buy some radium, so that radiation therapy could be given.[145]

However, in the new millennium, cancer has become a predominant public health issue and in many countries it is already the most or second most common cause of death, having caught up with ischemic heart disease.[146] Unfortunately, division of resources in the Finnish public sector lags much behind these epidemiological developments and in many ways still reflects the public health situation of decades ago. Currently, about 20% of deaths are due to cancer while only 5% of health care is spent on cancer.[147] The incidence of cancer continues to increase and soon 30% of deaths will be due to cancer but it is unlikely we will see a similar proportion of resources allocated.[148] I am writing about the Finnish situation because that is the one I am familiar with but my guess is that many Western countries have similar concerns, at least the ones where public health insurance dominates.[149]

When I worked in the University Hospital (2003–2007), it was quite common to read in the medical record that the patient had had to first wait to see a primary care physician, then queue for a radiological examination, wait two weeks for the radiological statement, again see the primary care physician, wait 2 weeks for a biopsy to be taken and then another 2 for the pathologist to issue their statement. With the pathological diagnosis, the patient could then





be referred to a hospital, where the referral would be directed to either a surgeon or oncologist, depending on the diagnosis, who might be able to see the patient within 4 weeks. If surgery was indicated it could perhaps be done in 4 weeks unless the summer holidays have messed up "the lists". If adjuvant therapy was indicated, the patient might be able to see an oncologist within 6 weeks of the operation with chemotherapy starting 4 weeks afterwards. In this provocative "worst case scenario" example, it would have taken nearly half a year from cancer related symptoms to the day when adjuvant chemotherapy was started, and several long months from symptoms to surgery. In gross cases the diagnosis might be delivered in early June while the first available "slot" for operation was after the holidays in late August. Fancy spending 3 months with your tumor?

Hopefully these sort of extreme cases are rare but every Finnish oncologist knows that many patients do complain about long delays. If it weren't for many empathic doctors and nurses cutting the red tape and slipping their patients through the queues with unofficial means, the situation would be much worse for many patients. Another aspect of the complicated system with multiple gatekeepers and complex logistics is that frequently referrals get lost somewhere. Many patients are quite trusting and long-suffering, and wait for a long time before they call the hospital up to inquire about the appointment they have been anxiously waiting for.

My point is that the system, although it appears to eventually deliver modern and highest quality cancer care according to statistics, does not operate from the patient's perspective but from the system's, resulting in the patient queuing at every step. Everyone who has been seriously ill knows how frustrating it is to wait for results or appointments, when in fact there is no medical reason for the delay. In a perfect scenario, the patient would see an oncologist in the morning, have imaging done immediately afterwards, followed by a biopsy the same afternoon. Staining of the tissues and a pathologist's analysis take a few hours so the patient could have the news on the afternoon of the next day, meeting again with his oncologist.

Together they would decide on the treatment which can start the next day, ie 48 hours after the patient booked his first appointment because of a symptom they just experienced. This is not science fiction but it actually happens at Docrates and many other top cancer hospitals globally. Sometime my patients have been actually quite shocked when they realize that things are moving really fast since their mindset is prepared for prolonged queuing. It is not that the public sector are lazy or evil, it is just that cancer is becoming more and more common, and the more and better you treat patients, the longer they will survive, needing more therapy, and at the same time resources are not increasing. Without a doubt there is much that could be achieved by organizing the logistics of cancer diagnosis and treatment better, at least in Finland. With the number of patients increasing rapidly, this is a formidable challenge.

It is an interesting question if waiting several months from symptoms to treatment affects the prognosis. There are few reliable studies on this as the final answer would require randomization to "no waiting" and "waiting for several months", and then a decade of follow-up. I'm sure no ethics committee would allow patients to be randomized into a "waiting" arm. Interestingly, there is no outrage that delays at several steps are the norm for most patients, despite some information suggesting that it is not safe to just wait around while the tumor continues to become more malignant and more likely to be able to shed metastases.[150]

Seemingly in contrast to reports suggesting that delays are dangerous, there also studies suggesting the lack of impact of treatment delay on prognosis, but these are typically underpowered to detect effects.[151] For a difference to have statistical significance, which is nearly synonymous with medical professionals believing the result, there needs to be enough cases, otherwise the variation between patients will mask a true difference. Also, a non-randomized setting might skew the results; the worst-looking cases might be fast-forwarded through the system – doctors and nurses fortunately know how to make this happen – while the seemingly





innocuous are forced to take the normal long route and in some cases non-aggressive tumors can even just be followed up if the patient is frail.[152]

In summary, since no randomized information is available, the data is by definition unreliable, but regardless of what data we do have, we cannot exclude the possibility that the patient is harmed by waiting. From a biological perspective, it can only be harmful to allow the tumor to grow while waiting around for treatment. With a tumor growing, every day will worsen the odds. Thinking about the situation from the opposite perspective, I'm sure no one can come up with a positive side for waiting for treatment when the diagnosis is cancer.

The possible exception to this rule could be "watchful waiting", a somewhat controversial philosophy sometimes employed for elderly patients diagnosed with seemingly low-risk tumors, especially prostate cancer.[153] Prostate cancer may be different from many other tumor types in that a significant proportion of cases grow so slowly that they have no clinical relevance if the patient is already quite old. More frankly, the utility of not treating in this scenario relies on the patient dying of something else before the tumor becomes an issue, and if this happens, the patient was spared the side effects of active treatment, and the payer saved on costs. If treatment nevertheless is eventually given, waiting may have harmed the patient since the tumor had become more dangerous than it was at diagnosis.

A typical solid tumor (=tumors other than leukemia and lymphoma) may grow for 10 years or longer before detected. Against this backdrop, it could be argued that a few months do not make a difference but it is difficult to be sure. Those few months might make the difference between operability of the tumor, or whether mortal metastases had been shed from the tumor before treatment. Even if the tumor is incurable, allowing unhindered growth is not good from a prognostic point of view because larger tumors have more diverse malignant clones, higher invasiveness, are more immunosuppressive and angiogenic. From the point of tumor control,

there are no exceptions to the rule that delaying treatment is never a good idea, if treatment is planned. Many elderly and ill patients cannot be treated actively for their cancer because the treatment would cause more harm than the tumor, but this is a different situation because the decision to not treat (except with palliative measures such as pain killers and radiation) is made up front.

Immediately after meeting *Timo Joensuu*, it became clear that this would be a win-win situation. I knew him from our time together at the Department of Oncology and he had always been a champion of patient-centered approaches including new treatments. His idea regarding the new hospital was that he wanted it to revolve around the patients' needs, not the system's. Our first virus production run was complete and testing of the virus batch had been done. Over the years I had received a lot of e-mails and phone calls from patients requesting treatment with oncolytic virus. Now that we were ready to start I replied to some of the most recent of them explaining that we have the treatment now set up as an experimental therapy if they would like to try it.

Already the first patient evaluated for treatment was an indicator of some of the issues we would be facing over the coming years. He was a three-year old boy with sarcoma whose parents were forcefully determined to have him treated. In a parent's role I would have behaved the same, but as an oncologist I worried that he was already too far advanced with his disease. The situation was resolved when he was not able to show up for an appointment since he had to be admitted into his own Hospital due to worsening of his condition. He died 3 weeks later so it would have probably been much too late to change the course of the disease.

The second patient evaluated, who became the first patient treated, had advanced lung cancer but he and his wife had a rational view on the situation and calmly accepted the risks, even when I told them that no humans have been treated with a serotype chimeric virus before, and that in fact he would be the first patient treated by us in general. The big day was 12th of November 2007. Half of the





virus was given intravenously with the goal of reaching the biggest tumor mass in the lung while half was injected locally into his scalp metastases. There were few symptoms and thus the treatment was well tolerated.[154]

However, I don't think I've ever slept as poorly as during the initial weeks after the first treatment. I worried constantly and waited for the phone to ring with some terrible news. No such news was delivered, and in fact the treatment went remarkably well. The injected scalp tumors disappeared completely so there seemed to be efficacy but it is difficult to say if he benefited much overall since a few months later his condition worsened and he died of tumor progression. In the autopsy, the lung tumor was larger than in the pre-treatment imaging. At that time, and in fact for several years afterwards, we were unaware that tumor size is quite a poor indicator of treatment benefits or lack thereof. Eventually, we were able to access his autopsy specimens and virus was found also in non-injected tumors, suggesting that we might have been able to impact the overall situation.[155]

The second patient was treated 4 weeks after the first and from there on the patients started coming in regularly. There was no advertising, beyond the few e-mails I replied to before the first treatment but the news was spreading between patients on the internet. The typical patient wanting to be treated had been through all available routine therapies, and often a few experimental therapies, and had a progressing tumor but was still in reasonable health. Often they just wanted to have one more chance, regardless of the risks. They often felt that even if they did not benefit themselves, perhaps their treatment might somehow help science forward, even after understanding that they were not enrolling in a trial. These motivations are typical reasons for patients to want to enter clinical trials[156] and the same seemed to be true for our experimental therapy. Patients did not seem to mind that this was not a trial; in fact they found the concept of individually planned therapy attractive. I guess even many scientists and regulators might feel the same

way if they were patients. If there is a possibility of receiving an experimental therapy, would you rather receive it from a top expert as a treatment individually designed for you, with treatment benefit as the only goal, or receiving it as part of a trial, where there might be the risk of receiving a sub-therapeutic dose, or even placebo, depending on trial design?

No doubt science is better served by controlled trials, where the patient population is often more homogeneous and more data can be obtained from each patient, but this would be a science centered, not patient centered point-of-view. As discussed earlier, clinical trials regulations in Finland and most EU countries are such that only companies can do trials, especially when it comes to new drugs. Thus, in fact the "scientific" perspective becomes a company perspective. From a company point-of-view, drug development goes faster if new drugs are given in trials instead of as individualized treatments. In particular, a biotech company's goal is to proceed to pivotal trials, possibly leading to product approval, as soon as possible. Even if patient data might be available from individualized therapies, its impact with regard to corporate development would depend on the weight regulators would place on such data.

In our case, since we lacked the funds to do a trial, it was not a question of deciding to either give the treatment in trials or as an individualized therapy. Instead, the choice was between treating in the personalized therapy scheme or not treating humans at all. Initially, I was quite relaxed regarding which patients to treat, since it was not known at all who would benefit. In hindsight, I was perhaps somewhat optimistic and treated some patients who were quite ill already and had huge tumors. Since the viruses we had made had not been used in humans before, and they were very potent in animal models, the optimism was not unfounded. In fact, we were worried that we would have tumor lysis syndrome and clogging of kidneys due to tumor leftovers. We were also quite concerned about acute safety, since these were potently replicating agents, much more oncolytic than anything used in humans before. I even





arranged for my friend – who is an anesthesiologist and therefore an expert in emergency situations – to be on call in case there was a serious problem, even the need for resuscitation. He was never needed as the safety of the treatments proved to be excellent. Also, there were signs of activity even in the very first patients so it was an exciting time.[157]

Nevertheless, I continued to worry since my whole professional career was riding on the personalized therapy approach. If there would be some disaster, it would surely have ended my research and oncology careers. Before we had started, I had discussed this with my wife, who agreed to move with me to some other country if worst came to worst. Also my scientific colleagues worried because a repeat of the *Gelsinger* incident might have been terrible for the whole oncolytic virus field. After a few months of treatments, I summarized the initial patients into an abstract which I submitted to an American Association for Cancer Research meeting with much anticipation.[158] I thought the individualized therapy scheme would be considered revolutionary and receive much attention but this was not the case. The abstract was only accepted as a poster and not an oral presentation, and a scant few people came to the poster. The larger cancer research community was not interested, at least not yet.

## Virotherapy starts to look like immunotherapy

After the first 6 months we realized that the very advanced cases we had been treating were unlikely to present any miracle cures and instead they were quite labor-intensive patients in the sense that they had a lot of symptoms due to disease and it was difficult to say if the virus was adding to them, or if the virus was helping the patient much. We analyzed their blood to see how much virus replication was going on in the tumor, the idea being that maybe the need for another treatment could be individually gauged in this

way. Virus typically circulated for several weeks or even months confirming the potent nature of the viruses. A typical result was that virus circulation lasted for about 2 months so this led us to give additional treatments every couple of months. Neutralizing antibodies were also measured, with the idea that this might indicate if a patient should be treated or retreated, but antibodies didn't seem to impact virus replication or safety. In particular, baseline antibody levels – conventionally thought to impact the ability of viruses to deliver genes - didn't seem to impact safety or efficacy.

Quite early on we discovered that there is a lot going on immunologically. Cytokines, which were measured as a safety measure, were induced, although not to any dangerous levels, antibodies increased, and a lot of swelling and redness developed around both injected and non-injected tumors, indicating the systemic nature of the response. It all seems quite naive now in hindsight but in fact almost the entire field seemed to have missed the fact that oncolysis is incredibly immunogenic. The reason why we had been blind to this is that most scientists like to do their research in the laboratory on cell culture plates. The data is a lot cleaner that way and every detail can be rigorously controlled for.

Animal work is much more messy, expensive, and then there is the risk of becoming the target of animal activists. Also, the added complexity of animal models means that the same level of rigor cannot be obtained as in vitro. For these reasons, many or even most scientists prefer the in vitro experiment. Like one experienced colleague joked, for a basic scientist "translational" means making the jump from a cell line to an animal experiment. For non-basic researchers, "translational" usually means getting a technology from the bench to bedside, ie. from the laboratory into patients.

For those brave enough to do animal experiments, there are some difficult choices regarding the model. Small animals and especially rodents are much less expensive and easier to work with than larger animals which on the other hand might resemble humans more than rodents do. Primates are closest to humans but their use is difficult





due to animal regulations and the cost of their procurement and housing. Thus, almost always the animal of choice is the house mouse, *mus musculus*, which has contributed more to science than any other animal, possibly human trial patients included. Mice are easy to work with and their biology is extremely well understood, even better than human biology. Importantly for science, there are reagents and resources which can be utilized for studying almost anything happening in their body. There are various inbred strains making the mice virtually identical genetically, which is useful for reducing variation in vivo. There are also knock-out and knock-in mice, genetically engineered to lack or possess a certain feature, facilitating testing of hypotheses. Thus, mice are a beautiful tool for research but they are not perfect, and quite imperfect in fact, for therapeutics which are rather human-specific, such as oncolytic adenoviruses.

One issue is that human adenoviruses tend to be replication incompetent in all other animals. The point in the oncolytic platform is the replication of the agent and if the model is not permissive to this then an important aspect relevant to safety and efficacy is not taken into account. Another problem is that mice are quite hardy and can take a lot of damage which humans would never sustain. Therefore, toxicity studies are poorly predictive. Most importantly, there are major differences between mouse and human tumors. Humans tend to get cancer at an advanced age, while mice rarely live two years. Typical human solid tumors take a decade or more to develop and thus it is clear that the same complexity cannot be achieved in the mouse even by genetic manipulation of its tumor suppressor and oncogenes. Human tumors cannot be grown in normal mice since their immune system would reject it.

The solution is to use immune deficient mice, of which there are several strains. The most common one lacks T cells but other strains lack also B cells and/or NK cells. With these deficiencies, human tumors can grow in mice, especially when injected in the rich subcutaneous region of the flank. Thus, the typical cancer

research animal experiment features T-cell deficient "nude" (these mice also lack hair in addition to T-cells) mice with human tumors growing in the subcutaneous tissue of one or both flanks. Mouse tumors are typically grown from a cell line cultured in the lab, again a big difference from human tumors which arose spontaneously but have since evolved considerably under different selective pressures present *in situ* in the human tumor microenvironment, resulting in a process closely analogous to evolution but fast-forwarded. In mouse models with human xenografts, the microenvironment is still from mouse, which can result in many differences when compared to human-human systems.

In retrospect, it is therefore understandable that scientists in the oncolytic virus field were not thinking about immunology. On the other hand it emphasizes how laboratory work can go in a completely wrong direction in the absence of human information. This conclusion depends of course if the goal is a) to optimize one's CV and list of publications, or b) to develop treatments for: b1) humans or b2) mice. While most research funding is granted by humans, for work that would eventually benefit humans, this is not necessarily evident from the huge amount of mouse data published by the best scientists. In fact, a cynic might claim that category b1 is by far the smallest category in modern biomedical science. Translation into trials is a much used slogan and many if not most basic cancer research papers end with the long term goal of their findings eventually improving available treatment options for humans. But in fact there is little actual translational work ongoing as compared to pure preclinical work, as discussed in the "Is There a Valley of Death" chapter above.

Instead, it seems that to have a successful career in cancer research one should either: 1) do basic research and claim that it has translational implications; 2) focus on pharmaceutical company dominated clinical research; or 3) do some correlative analysis on clinical samples and claim that this is translational research. The way I understand the term translational research, it means taking





approaches from the laboratory to patients. However, because this is so difficult and slow, it is not necessarily compatible with a productive scientific career, and even if projects are successful, the impact factor of the publications will not be as good as in categories 1) and 2) (Table 3).

**Table 3. The Do's and Do not's of translational medicine.**

| | |
|---|---|
| Do question the teachings of medicine; they are often wrong. | Don't expect to meet with approval when you rock the boat. |
| Do push forward novel ideas. | Don't be frustrated when the establishment doesn't agree. |
| Do start a company if you wish to make clinical trials happen; it is often the only way. | Don't accept that having a company causes unsurmountable conflict-of-intrest. |
| Do manage conflict-of-interest. | Don't fold when your passion is incorrectly interpreted as greed. |
| Do take a personal interest in pushing forward into trials; it may not happen without you, | Don't lose faith in humankind when bad press happens. |
| Do talk to journalists. | Don't become a cynic when your motives are missunderstood or misrepresented. |
| Do everything you can to help the patient. | |

## From oncolytic therapy to personalized oncolytic vaccines

Since oncolysis seemed to induce a lot of immune response in the tumors of our patients, we hypothesized that this could also lead to anti-tumor immune response. To make the most out of this effect, we constructed the next generation of viruses, this time coding for an immunostimulatory molecule. We wanted to be practical to ensure smooth transition of preclinical work into treatments and obviously safety is always the key thing in medicine. Thus, we didn't go for

the coolest and newest cytokine just recently discovered, since the safety of new molecules remains unknown until tested in clinical trials. In contrast, granulocyte-macrophage colony stimulating factor (GMCSF) is an older molecule used widely in the 1980s because one of its properties is induction of white blood cells in blood, and it was used to counteract the killing of these cells by chemotherapy. Although GMCSF was eventually replaced by its better tolerated cousin GCSF for induction of white blood cells, its safety in cancer patients had been well demonstrated.

There were also plenty of earlier studies into the immunological component of GMCSF, which is the main difference to GCSF. GMCSF has some immediate effects on the immune system, including recruitment of Natural Killer (NK) cells, which are just as potent as the name suggests.[159] Immediate responses of the immune system are considered part of the "innate" immune system, which is there all the time, waiting for things to happen. In contrast, the "adaptive" immune system needs to first be warned that something is wrong ("the danger signal"), then it needs a target ("epitopes") and then it needs some time to mount the response, from a few days to a few weeks, depending on the insult and if the adaptive system has previously received the same insult, for example a pathogen, such as a virus or bacteria. If the insult has been previously encountered, there is immunological memory, and specialized cells responsible for this phenomenon, which allows more rapid response the next time round.

Adaptive immunity falls into two categories, humoral and cellular. The former is mostly mediated by antibodies, which can be very effective in blocking the entry of pathogens into normal tissues of the body, in a process called opsonization, which basically means covering of all sides of the pathogen by antibodies, so that it is physically unable to interact with cells it would like to enter. Opsonized pathogens are then removed from the body by special waste disposal cells. Antibodies can also "point out" abnormal features. For example, in cancer therapy, antibodies can be specific





for a tumor epitope and the Fc part of the antibody ("the tail") then tells immunological cells and complement, which is another interesting part of the humoral immune system, to kill the target.

The cellular adaptive response is even more complicated and much has been learned in recent decades. However, in one word, immunology is complex, and there remains much to understand. Immunology meetings can be depressing because even the experts don't seem to be able to agree on even basic issues. The main reason is the difficulty in studying body-wide phenomena in a comprehensive manner. As mentioned before, scientists like to focus on things that can be rigorously simplified to an experiment on a Petri dish. The immune system, however, only works in intact organisms and all components interact with each other. Also, if we are studying tumor immunology for example, things happening in the mouse blood or spleen, the most usual organs analyzed because they are the easiest to obtain, may not reflect things occurring at the tumor.

The blood is the highway immunological cells use to get to the target, which in the case of tumor immunology is the tumor. Lets say it were an important football game. Right before and after the game the highways might be crammed but during the game the roads might be empty. Thus, trying to understand things going on at the tumor ("the stadium") by counting different colored cars on the highway could be misleading. An obvious answer would be to focus on the tumor, but then there is the problem that you can't look at the same mouse tumor over time, if you have removed it for analysis earlier. In humans, biopsies are often done instead of removing the entire tumor, especially when surgery is not indicted, but repeat biopsies can be quite difficult to obtain ethics committee approval or patient consent for. Even if repeat biopsy can be done, biopsy needles don't always hit the tumor, or they may hit stromal or necrotic areas which are located within the tumor but lack malignant cells. Even if all of the above can be overcome, biopsies will hit different regions of the tumor since the area removed before is no longer there, and in different areas different things might be going on.

Another annoying feature of the cellular immune system is its plasticity. Cell types can morph into each other and sometimes a subtle change can make a big difference with regard to function. Prompted by a nearby cell, a molecule can be down-regulated resulting in conversion of an anti-tumor cell into a suppressive cell bad for immunotherapy. Keeping in mind the tendency of scientists to want to simplify things to the level of single molecules, in order to make sense out of complex phenomena, the constant changing of the target can easily lead to confusing results. Imagine being tasked with trying to count the sports utility vehicles, trucks, compacts and motorcycles at the stadium during the aforementioned football game, but before you get to half-time, some of the trucks have changed into SUVs, the red compacts changed into blue ones, the motorcycles have disappeared and instead a bus has been parked at the stadium entrance. To make things worse, every month there are new classes of vehicles. What used to be called "cars", are now being reclassified as "Fords" and "VWs" and into further subclasses (VW Jetta, VW New Beetle) and the same car model can have different names in different countries (VW Jetta is identical to VW Bora).

A further level of complexity and confusion is introduced by animal models. The immune systems of mice and humans are quite different. For other animals the problem is that there are barely any tools such as antibodies to study their immune system. The lack of predictivity of animal models with regard to humans is especially prominent in cancer immunology. In humans, tumors typically develop over a decade or more, and harbor incredible complexity which underlies an impressive capacity for acquiring resistance to any therapy, constituting the reason why advanced and metastatic tumors can be cured only rarely. Mice only live for a few weeks after implantation of tumor xenografts, so it is fairly obvious that the human level of complexity cannot develop in either the tumor or in the immune system. Moreover, much of the ability of tumors to mutate and adapt stems from the microenvironment or stroma, which are from the mouse in human xenograft experiments and thus not representative





of the human situation.

Thus is comes as no surprise that it is not fully understood how cellular adaptive immunity works in the context of cancer therapy. However, most scientists agree on some of the basic components, which include antigen presenting cells such as dendritic cells, the master controllers of adaptive immunity. Like Jabba the Hutt in the *Star Wars* movies, these cells mostly sit in place and sample the surrounding milieu for tasty tidbits called epitopes. If the samples seem OK, tolerance reigns and no immune response is mounted.

If, however, an epitope seems abnormal, such as deriving from a pathogen, young Jabba can become stimulated and mature into an activated dendritic cell, capable of mounting an immune response. Typically, this involves getting up, getting angry and travelling to regional headquarters which is the local lymph node. From there, Jabba can mobilize his troops in a coordinated manner. Classically, Jabba first instructs his captains, called Helper T cells, who then go and instruct the troops, the Cytotoxic T cells, which do most of the actual killing. However, Jabba can also talk directly to the troops by using "cross-presentation". These cell types can be identified based on surface receptors such as CD4 and CD8.

It is important that Jabba is mostly tolerant because otherwise there would be a risk of immune response against normal tissues, following any damage to them. A classic example is rheumatic fever, where a bacterium (*Streptococcus pyogenes)* damages some normal tissues, but the resulting immune response is so strong that it is directed not only against the bacterium but also against the normal tissues where the bacterium was. Although this particular disease is rare nowadays, autoimmune diseases in general are quite common and it can be generalized that they result from too strong immune responses.

One view of tumors is that they result from failure of the immune system to eradicate abnormal cell clones. If autoimmunity is too much immune response, tumors represent too little immunity. Critical to the immune response being mounted, Jabba needs to get angry. In some cases, this happens very fast, when he tastes

something obviously dangerous, such as a "pathogen associated molecular pattern" (PAMP), present in most viruses for example. With regard to tumor immunology, however, this is usually not the case, since cancer cells arise from our own bodies and in fact in many ways still resemble our normal cells. During development of the tumor into a clinical entity, it acquires dozens of features not present in normal cells. Therefore, all tumors have abnormal epitopes which in theory could be recognized by Jabba and colleagues. Most of these are, however, weaker epitopes than pathogen derived targets. Thus, the "danger signal" is important. Jabba has to decide between tolerance and immune response, and if the epitope is only mildly annoying, and there is no danger signal, he will probably remain in the lazy comfort of inactivity.

In contrast, if a danger signal is provided, even a weak tumor epitope can result in Jabba mobilizing. It turns out that oncolysis is one of the strongest danger signals around, because it produces a tremendous amount of destruction and discord at the tumor.[160] Importantly, new viruses produced from dying tumor cells also provoke Jabba because they contain pathogen associated patterns, the PAMPs mentioned a few times earlier.[161] Thus, the oncolytic virus promotes anti-tumor immunity not only by releasing tumor epitopes for Jabba to sample, but also by providing the danger signal necessary for an immune response. Oncolysis therefore can be considered an approach for creating a personalized cancer vaccine for each patient. A big advantage over traditional cancer vaccines, where epitopes need to be decided in advance, is the ability of the virus to release whichever epitopes are present in each tumor. If and when there is intratumoral heterogeneity, oncolysis should be nevertheless able to release whichever epitopes are relevant for each tumor subclone. Importantly, GMCSF is a potent molecule for luring Jabba to the tumor, and increasing the general sense of urgency for mounting an immune response.[162]

Having survived and grown often for a decade or more, tumors are not easy adversaries for Jabba's troops. They are capable of several means of camouflage, subversion, propaganda, misinformation,





bribery, counterattack, metamorphosis and self-sacrificing heroics. If all else fails, they are content to wall up their town and remain hidden, biding their time, making plans, and then reappearing stronger than before. Many of these tactics can be grouped under the general term of immunosuppression. Tumors can produce immunosuppressive molecules which can make tumor epitopes invisible to immune cells and can even turn good anti-tumor cells into bad immunosuppressive ones. They can also recruit, train and multiply the body's own immunosuppressive cells, which are normally needed by the body to protect against autoimmunity. The most important of these cells are regulatory T-cells,[163] which can work against all three classes of anti-tumor cell mentioned above: Natural Killer cells, CD4+ helper cells, and CD8+ cytotoxic T cells. Another important suppressive cell type is myeloid derived suppressors.[164]

Thus, there is constant interplay between the immune system, which is trying to eradicate abnormal cells, and the tumor, which recruits the body's own anti-autoimmune mechanisms, brainwashes them, and sends them to fight against the anti-tumor immune response. When clinical tumors appear, they are by definition beyond the control of the immune system. If they were not, we would never see them. But lets for a moment consider what happens before a malignant clone can be detected by the immune system. Even at early phases of carcinogenesis, mutations occur, resulting in potentially immunogenic epitopes. Thus, almost from the start the tumor is under selective pressure from the immune system, and for growing, it must adapt, and this process is called immunoevasion.

The hypothesis is that tumors, and in particular their immunosuppressive and immunoevasive character evolves through three stages of immunoediting, constituting the three "E:s" of immunoediting: elimination, equilibrium, and escape.[165] In the first stage, most abnormal cellular clones are detected by the immune system and killed. We never even knew that we had cancer. It is difficult and in fact impossible to know how frequently this occurs, but based on the high incidence of cancer in severely immunocompromized individuals, such

as AIDS patients or transplant recipients, this is likely to be a common phenomenon. Thus, most immunogenic clones are edited out.

Every now and then a clone manages to survive the initial assault of the immune system. This clone can then develop further mutations, giving it all kinds of advantages, including the Hallmarks of Cancer.[166]

Each of these hallmarks of cancer is dependent on abnormally structured or expressed proteins, which should increase the burden of epitopes potentially interesting to the immune system. As mutations increase, the epitope burden increases, resulting in even more immune response. Some clones are immunoedited out, but some may be devious enough to induce even more immunosuppression, eventually resulting in a state of equilibrium. It is likely that in many cases this state can last for decades, and often the individual will die of something not related to the tumor. This would explain the high incidence of indolent cancer found in autopsy series of patients who died of something completely different.[173]

Especially in the field of prostate cancer it is hotly debated if seemingly innocuous tumors should still be treated. One can argue that such "turtles" are in an immunological equilibrium state and many of them will never progress to the "rabbits" that can kill the patient. The point of view of many oncologists is that, since they mostly see the "rabbits" that emerged, it is not safe to watch and watch over the "turtle". Urologists may have a different view since they see the adverse events surgery can cause, but on the other hand they don't see the patients who die of hormone refractory prostate cancer.

It cannot be denied that the weakness in trying to differentiate turtles from rabbits is that there is no way to be certain that a region of the turtle might not be a potential rabbit. "Watchful waiting" usually employs monitoring of prostate specific antigen (PSA), a molecule produced by normal and malignant prostate cells, and intermittent prostate biopsies. However, tumor progression does not always result in PSA increase and in fact the most





aggressive tumors typically don't produce a lot of PSA. In oncology, the pathologist always has the last word, but they can only assess the part of the tumor which was biopsied. Biopsy needles only hit a small proportion of the tumor so there is no guarantee that there might not be aggressive tumor right next to the biopsied needle tracts.

Coming back to the third "E", most cases of cancer, diagnosed as growing and symptomatic cell masses, probably represent escape clones from a cell population which was previously under equilibrium. Keeping in mind the tremendous number of new mutations arising in tumor cells, and the continuous selection pressure mediated by the immune response, it is not surprising that escape variants develop. In fact, since tumors mostly arise late in life, the ability of the immune system to control tumors for decades is amazingly good.

The immunogenic potential of oncology treatments other than oncolytic virus is a book topic in its own right. Mainstream oncology may not yet agree, but personally I am convinced that a part of the efficacy of chemotherapy and radiotherapy are mediated by immune response resulting from

### The Hallmarks of Cancer

While earlier descriptions on the nature of cancer focused on its potential for invasion, metastasis and dysregulated growth, *Douglas Hanahan* and *Robert Weinberg* received wide attention for summarizing the molecular cancer biologist's view at the turn of the millenium.

In their 2000 Cell paper,[167] they identified the defining features of cancer as 1) self-sufficiency in growth signals, 2) insensitivity to anti-growth signals, 3) ability to evade apoptosis, the physiological form of cell death, 4) limitless reproductive potential, 5) dysregulated angiogenesis, 6) capacity for tissue invasion and metastasis. In 2010, they updated the list by adding: 7) deregulated metabolism, 8) ability to evade the immune system, 9) instability of DNA, 10) chronic inflammation. One key realization is that basically all tumors have these key features.

With the 2010 addendum the immune system had entered the molecular biologists' world with no less than 50% of the new entries in the Hallmarks of Cancer listing.[168] An immunologist's list of Hallmarks might start with the ability to evade the immune system since this characteristic is absolutely required for the clone to start acquiring the remaining features.

immunogenic cell death,[174] and for monoclonal antibodies there is already convincing data.[175]

### Growth control pathways and how they relate to oncolytic viruses

A healthy cell is like a medieval city with 12 protective walls around it, known as growth control pathways. For the tumor to be able to take over the city, it much reach the king's castle in the center, and to do that it much breach each of the 12 protective mechanisms the cell has.[169] However, each wall can be breached at one or more sites (usually several), and for different cities (different tumors) the walls have been overcome in different ways. Thus, when observing conquered cities (clinical cancers), a universal feature is that each of the 12 walls is breached, but the damage to the walls is usually different in each tumor.[170]

A conclusion from these observations is that when planning retaking of the city (treatment of the tumor), it is futile to try to repair each defect, there are just too many of them, and since they will be different in each city, it is difficult to prove the efficacy of such an approach. Instead, it seems wiser to take advantage of the fact that each of the city's defenses is damaged. Since in tumor therapy we don't need to save the city, we just need to destroy it, why not send in shock troops that can take advantage of the breaches in the walls and then blow up the city once they have reached the king's castle. Anyone guess what these shock troops are ?

The same 12 protective circuits that guard against cancer guard also against viruses. Logically, it makes no difference to the medieval city what the invading army is, it must protect itself against all enemies. However, if the walls were breached by an invader earlier, it is easy for the next army to march in through the destroyed defenses. Like a band of brigands, cancer is not going to bother with wall repairs, it is too busy with gluttony, inebriation, rape, pillage and plunder. Thus, the damage the cell sustained during carcinogenesis makes it vulnerable to viruses. Moreover, the fact that protective circuits are damaged can be used to engineer selectivity into viruses. For example, one key protective circuit is the p16/Rb pathway. This pathway is always damaged in tumors, resulting in excess E2F in cells, whose presence can be used to drive virus replication.[171] There are dozens of other examples of how features of cancer cells can be used for making oncolytic viruses.[172]





To summarize a fledgling field, it has been proposed that different modes of cancer cell death result in different immunological consequences. Apoptosis, classical silent cellular suicide, does not raise the eyebrows of the immune system. Necrosis, a more violent form of death, resulting for example from death of apoptosis resistant tumor cells, may be more proficient in this regard.[176] Apoptosis resistance is a typical feature of mortal tumors. My hypothesis is that oncolytic cell death, which may be mechanistically related to autophagy,[177] a third mode of cell death, constitutes a particularly immunogenic variant of death, especially when potentiated by the presence of pathogen associated molecular patterns deriving from the virus.[178]

With this short introduction into tumor immunology, it comes as no surprise that it is not fully understood how GMCSF works. There are plenty of publications but they do not agree and as usual most of the data is from mice. Moreover, the actions of mouse GMCSF in mice is different from that of human GMCSF in humans. Nevertheless, most of the available literature suggests that GMCSF has several powerful immunological effects. One of them is direct recruitment of Natural Killer cells, which are potent in killing of tumor cells which have lost some of the key features of human normal cells, such as expression of human leukocyte antigen.[179] In a typical embodiment of how scientists dazzle lay men in order to demonstrate their learnedness, this molecule has a completely different name in other animals, as it is called major histocompatibility complex.

A more important effect of GMCSF may be its ability to recruit Jabba and colleagues – referring to my previous *Star Wars* example - to the tumor site, and help in maturing Jabba into action.[180] All immunological molecules have their dark sides but the good thing about GMCSF, in comparison to the newest and coolest cytokine, is that some of those aspects are known, in both mice and humans. The main caveat is the effect of GMCSF on myeloid derived suppressor cells, an important immunosuppressive cell type with actions similar

to, but distinct from, regulatory T-cells.[181] These effects are particularly prominent when GMCSF is given at a high systemic dose, such as resulting from intravenous or subcutaneous administration. The beauty of the virus mediated approach is that GMCSF is produced locally, where its useful aspects count the most, while systemic levels remain low, reducing the likelihood of untoward effects.[182]

With these considerations in mind, we made the next generation of viruses, coding for GMCSF. To ensure local production of GMCSF, the transgene (=the foreign gene, the payload) coding for it was switched in to replace a couple of adenovirus genes, resulting in GMCSF production only when the virus replicates.[183] Since replication of oncolytic viruses occurs selectively in tumor cells, also GMCSF production linked to replication is expected to occur there, and this was confirmed in animal work.[184] Construction of new viruses may seem like science fiction but with our current understanding of molecular biology and virology, it is actually not that difficult.

However, it is critical to keep biosafety issues in mind when designing viruses so that whatever happens to the new virus in the human body or elsewhere, a superbug does not result. This is one of the reasons I've always liked adenovirus over the dozens of other oncolytic virus platforms being studied. All of us have been infected with many types of adenoviruses several times, usually with mild symptoms. Thus, even if the tumor selective virus would revert back to a non-selective form, it would not be dangerous. GMCSF arming seems particularly safe in this regard as it makes the virus more immunogenic, and thus more visible to the immune system.

Selection of the transgene is also critical. Although some brave scientists (some might call them foolhardy) are doing it, it might not be a generally accepted good idea to insert an immunosuppressive transgene, since this could help the virus avoid the immune system thus creating the possibility of an uncontrollably replicating agent. Immunostimulatory pay-loads such as GMCSF, however, are likely to make the virus more visible to the immune system, creating





a second level of safety, in addition to the main selectivity switch engineered into the virus which allows it to replicate preferentially in tumor cells, as discussed in the "Rationally designed oncolytic viruses" chapter above.

Even though a long time has passed since we designed the GMCSF armed generation of viruses, and many more advanced constructs have been built, they still represent a beautifully economic and potent virus design. Compact, sleek, dynamic and deadly for tumor cells, while being wonderfully safe for patients. My favorite aspect of these type of viruses is that they kill tumor cells in at least three ways, in fact generating a personalized cancer vaccine for each patient. Oncolysis kills cancer cells releasing epitopes for Jabba and company to sample. Whichever epitopes are relevant for each tumor are released, and even if the dominant epitope changes over time in "epitope escape", a common form of resistance to cancer vaccines, oncolysis would be expected to keep up with the changing tumor. Oncolysis, the associated cytokine storm and the presence of a lot of virus acts as a potent danger signal to make sure Jabba gets aggravated. GMCSF is a potent molecule for recruiting and maturing Jabba and company. Thirdly, as mentioned above, GMCSF recruits Natural Killer cells, the ultimate cancer cell killing machines.

## GMCSF armed viruses

Exciting things started happening as soon we got the GMCSF armed viruses into patients. Some tumors disappeared completely and in other patients tumors stabilized for an extended time.[185] To optimize treatment for each patient, we thought it was important to understand what was happening on a molecular level, since this might allow us to identify who to treat, how long to treat them and when to treat them again, or how to modify the treatment scheme. We wanted to be able to evaluate each patient for likelihood of the therapy working so that no one would be treated without a chance

of benefiting. Thus, we had to develop our immunology skills and eventually we graduated from just counting "the captains" and "the troops" to assessing tumor specific and virus specific cells. In fact, we were the first to observe and report that oncolysis per se, and in particular when potentiated with GMCSF, led to tumor specific immunity in patients.[186] The most satisfying part of these developments has been following up the patients and being able to see that many of them lived for an unexpectedly long time after therapy[187] and many may still be alive.

Although adenovirus is in many ways an appealing virus for cancer gene therapy, it may have one problem. Viruses typically enter cells through receptors, and in case of adenovirus type 5 which is by far the most commonly used virus in gene therapy, the primary receptor is called the coxsackie-adenovirus receptor.[188] This molecule, however, is not in cells so that viruses could enter but instead has a function in adhesion, meaning cell-to-cell contact and relating to the way cells form organs. One central feature of cancer is its ability to invade through structures and a defining feature of tumors is their ability to grow in an uncontrolled manner. One way that growth is regulated in normal tissues is through cell-to-cell contacts and thus tumors are universally defective in adhesion functions. Consequently also the adenovirus receptor is frequently abnormally expressed in tumors, meaning that it may be present in advanced cancers at lower levels than in normal tissues, or its location may be abnormal, compromising virus entry. The more advanced the tumor, the higher degree of abnormality in adhesion, resulting in more problems for the adenovirus type 5 in entering cells. As experimental therapies are typically initially used in patients whose disease cannot be cured with other approaches, they usually have quite advanced disease. Consequently, an unmodified adenovirus type 5 capsid (=outer shell, which determines where the virus goes) is actually maybe not the optimal virus to use for treatment of cancer.[189]

This potential problem has been known by adenovirologists since about 1996 and as soon as it was discovered it became possible to





do something about it. Viruses can be modified in many ways and it is easy to change the surface of the virus in such a way that it enters cells differently. This is called tropism modification or transductional targeting.[190] The goal is to enhance entry into tumor cells while reducing entry into normal cells. All kinds of modifications have been engineered in laboratory projects but by the end of 2012 only two clinical trials have used adenoviruses that are not dependent on the usual adenovirus receptor. One of those trial was sponsored by Oncos Therapeutics, the company I co-founded, and the other one I helped set up at the University of Alabama at Birmingham. Of note, all oncolytic adenoviruses used in phase 2 or phase 3 trials have been based on type 5. Thus, tropism modified viruses could result in exciting data once they get that far.

Effective entry into cancer cells is very important for the efficacy of oncolytic viruses[191] and thus we next moved to make GMCSF viruses not dependent on the coxsackie-adenovirus receptor.[192] The very first virus we used in patients in the Advanced Therapy Access Program, the personalized patient treatment program, already featured a capsid modification but that virus was not armed with a transgene.[193] The thinking was that initially we needed to be sure of safety and thus that virus had two different modifications that restricted its replication to tumor cells. Also, on a general level, in my mind it was unclear at the time if arming of viruses was needed or perhaps oncolysis *per se* might be sufficient for helping the patient. However, with the safety of the capsid modification established with the first virus, and the safety of GMCSF production confirmed with the second virus, the third virus featured the combination of these two aspects.[194]

The third virus, CGTG-102, was safe, and seemed quite promising for treatment of many types of tumors.[195] Following founding of Oncos Therapeutics, of which more later, CGTG-102 became the lead clinical agent of the company and entered clinical trials in 2012. This virus employs a neat trick to avoid the potential problem with the usual adenovirus receptor. There are more than 60 different types

of human adenoviruses and although almost all of them use the coxsackie-adenovirus receptor, there are a few that don't. Type 3 adenovirus is one such virus and its receptor – proposed to be another adhesion molecule called desmoglein 2,[196] although the jury is still out – is not down-regulated in advanced tumors.[197] If anything, the Ad3 receptor seems to be present to higher degree in advanced tumors than in normal tissues.[198] We just switched the receptor binding part of the type 3 virus (called the fiber knob) into a GMCSF coding type 5 virus.[199] The logic was that we wanted to retain the good safety and other appealing features of the type 5 virus while avoiding the receptor down-regulation problem.

Although now we know that the 5/3 chimerism approach is safe in patients and also the efficacy data seems promising, prior to clinical use there was no guarantee of this. Since we didn't want to have all the eggs in that basket, also another virus modification was employed. In this second approach, we added a few amino acids into the fiber knob of adenovirus type 5 to allow it to enter through integrins, an other class of adhesion molecules, having something in common with desmoglein 2 in that they are not down-regulated during tumor progression. Again, to optimize the likelihood of patient safety and benefits, the same logic was employed. First an unarmed virus was used and then we moved to use a GMCSF armed variant.[200] Integrin targeting remains a promising approach but only one clinical trial has been performed thus far, by the aforementioned *Ronnie Alvarez* and colleagues, and I also contributed while I was the Director of Clinical Trials at the Gene Therapy Center in Birmingham, Alabama.

**Transductional targeting for increasing gene delivery to tumor cells.**

In most clinical trials performed thus far, adenovirus serotype 5 has been used. The adenovirus receptor CAR (coxsackie-adenovirus receptor) is a present at high levels on normal cells.

This results in high level delivery to normal tissues which is not the aim in cancer therapy. CAR is involved in cellular contact, and this feature is abnormal in most tumor tissues which have the ability of invade and metastasize.

Thus it was not a complete surprise when it was discovered that CAR expression is low on many or most tumors, and in fact this correlates with aggressiveness of the tumor.

The more aggressive it is, the less CAR. However, tumors have other receptors which can be used for entry. If they are taken advantage of, high transduction can be achieved.





To take the tumor targeting approach one step further, and to avoid the problem of the coxsackie-adenovirus receptor completely, we made a class of viruses based entirely on Ad3. Although making these viruses was much more difficult than manipulating the usual Ad5, eventually it was successful and more than 20 patients were treated following preclinical work in the laboratory.[201]

Because of the special perception many lay people, and journalists especially, have on gene therapy, increasing the safety of oncolytic adenoviruses has had a central role in the past decade. One could argue that there is no good reason for this since safety has been excellent in trials performed thus far, even with viruses with low selectivity such as ONYX-015 and its relatives.[202] Nonetheless, also we made a generation of viruses more selective than the first generation of GMCSF coding viruses, by adding a second mechanism to restricting virus replication to tumor cells. This virus, CGTG-602, seemed very promising in patients,[203] but it is not really possible to compare different viruses used in the Advanced Therapy Access program with each other, since the are many differences between the types of patients that were treated and how the treatments were given. Given the extremely rapid learning process inherent to the program, many things changed in the treatments over the years.[204]

## Viruses with other transgenes

GMCSF continues to be a highly appealing arming device for oncolytic viruses, and it is no coincidence that also other types of viruses

besides adenovirus have been armed with GMCSF and taken to trials by several companies.[205] Randomized trials are in progress with GMCSF armed oncolytic herpes and vaccinia viruses and one of these could result in the first oncolytic virus product approved in the West, with reference to the fact that two adenovirus based products have already been approved in China. However, there are many other interesting arming devices. We had an EU supported research project where we studied a molecule called CD40 ligand, which has many appealing immunological activities. Inspired by these data we subsequently made a capsid modified oncolytic adenovirus coding for this molecule and took it into the Advanced Therapy Access Program.[206]

This virus was a good example of the power of the personalized therapy program in full swing. It took only 10 months from the day we started constructing the virus to the first patient treated. This demonstrates that the great majority of time used in setting up clinical trials, typically taking 5 years or more for the same process, is not because of technical or scientific issues, but because of regulatory delays and bureaucracy. Keeping in mind that there are millions of patients in need of new cancer therapies, it is difficult to defend the ever increasing regulatory burden placed on drug developers. Nevertheless, rules and regulations keep increasing every year, resulting in longer development times but also in increasing costs, which will be eventually built into the cost of approved drugs.

Oncolysis is strongly synergistic with radiation. One appealing approach that might be usable for treatment of any tumor is virus-mediated concentration of an orally administrable radioactive molecule into tumors. Sounds crazy? Maybe, but this is a clinically tested approach building on a century of experience with treatment of thyroid cancer with radioiodide. Thyroid cells, including most thyroid cancers, express a sodium-iodide symporter, needed to make thyroid hormones. Since this symporter is not really expressed much by most other tissues in the human body, it is a highly specific and effective diagnostic and therapeutic tool for thyroid cancer. In





our current oncology community which obsesses over novel targeted therapies, it seems to be frequently forgotten that radioiodide therapy has been around since the 1930s and continues to be the most selective and effective therapy for metastatic thyroid cancer, by a far margin.

To clarify, radiolabelled iodide is a uniquely specific therapy for thyroid cancer because the thyroid is the only organ which needs iodide. The thyroid takes up iodide from blood by using an iodide transporter, which is a protein. And almost any protein can be coded from a transgene allowing gene therapy to be used for targeting radioiodide to the tissue of choice.

Thus, we made oncolytic adenoviruses coding for the iodide transporter and showed that we can concentrate radioiodide to tumor cells in vitro and in animal experiments. Then we made clinical quality virus and offered one patient treatment. Because her situation was difficult, we thought that we could enhance efficacy of the oncolytic therapy by combining it with the radioiodide. The approach is attractive for personalized therapy because we could determine expression of the radioiodide transporter protein by imaging, to see if iodide accumulated in tumors to sufficient degree to allow administration of therapeutic doses of radioiodide.

However, in this case it did not. Treatment of this single patient demonstrated that our virus design was not optimal.[207] Since we were good at making viruses with high oncolytic potency, this also meant that virus replication occurred rapidly and infected tumor cells died fast. Our arming device was such that transgene expression activated about 8h after infection, and if oncolysis follows soon after, this does not leave much time for the iodide transporter protein to be expressed on the membrane of tumor cells, and even if some iodide would be accumulated, lysis of the cell would soon result in its loss. Although a disappointing result, this allowed us to close the issue and move on to other strategies. The patient did not receive a therapeutic (=large) dose of iodide, only an imaging dose, but she may have benefited from the oncolytic effect of the

virus. In a typical embodiment of the patient-centered approach descriptive of the Advanced Therapy Access Program, we switched to the usual GMCSF coding viruses for her following treatments, something which would never be possible in a clinical trial.

The next idea I had was utilizing the oncolytic adenovirus platform for production of a therapeutic monoclonal antibody. Monoclonal antibodies made their breakthrough into routine clinical use with *rituximab* and *trastuzumab* in the late 1990s, following two decades of promise and perceived failures. In fact, antibodies are the original "magic bullet" envisioned by *Paul Ehrlich* in the late 1800s. Although antibodies are more selective than most drugs, they do have off-target effects which can cause adverse reactions to the patient. For example, the target of trastuzumab is Her2, which is expressed by a quarter of breast cancers, but also the normal heart. Rituximab targets CD20 which is expressed by lymphoma cells but also normal blood cells. These off-target effects can limit the dose of antibody that can be given, resulting in less than optimal concentrations at the tumor. Also, such antibodies need to be administered frequently and are quite expensive. Thus, it would be appealing if we could make the antibody locally at the tumor. Moreover, one issue with humanized (ie still partially mouse) antibodies such as *trastuzumab* is hypersensitivity reactions which can be life-threatening. Producing the antibody from a human cell at the tumor would result in a 100% human protein which would completely avoid the risk of allergic reaction.

There are limitations how much material can be cloned into the genome of an oncolytic adenovirus; once the genome exceeds 105% of the normal size, the ability of the virus to package into functional virions (new viruses) decreases rapidly. If I were prone to religious notions, I would postulate that it seems almost divine guidance that with our arming strategy, the DNA for an entire monoclonal antibody can just barely be fit into the genome, resulting in a size of exactly 105%. We made several such viruses but perhaps the most appealing one codes for an antibody against CTLA4 (cytotoxic





T-lymphocyte-associated protein 4).[208]

Cancer immunotherapy has been around for more than a century, starting with *Coley's* toxins in the 1880s, but breakthroughs have been slow in emerging. Bacillus Calmette-Guerin (BCG) was developed a century ago as a tuberculosis vaccine but has been used since the 1990 for treatment of bladder cancer and is in fact the most effective therapy for superficial bladder tumors.[209] Vitespen (Oncophage)[210] is a vaccine made from the patient's own cells and it is approved in Russia but not elsewhere. Sipuleucel-T is a cellular immunotherapy product, incidentally featuring GMCSF,[211] and has been approved for treatment of metastatic prostate cancer although the company sadly went bankrupt in 2014.[212]

Of note, the first cancer immunotherapeutic approved globally was ipilimumab in 2011, which binds to CTLA4, a key molecule in tumor induced immunosuppression.[213] This antibody does not in fact induce any new immunity, but relies on decreasing tumor induced immunosuppression, and any benefits patients derive result from pre-existing immunity being present. In other words, this antibody merely releases the immunosuppressive hand-brake. While this seems quite effective in a subpopulation of melanoma patients, and might also work in some other tumor types, there are issues with safety. Many patients get autoimmune reactions and some die of them. This is not completely surprising keeping in mind that the purpose of immunosuppression in the normal body is to guard against autoimmunity and thus lifting suppression on a body wide level would be expected to result in exactly what it seen with *ipilimumab*. However, if the antibody could be produced locally, higher effects could be perhaps seen at the tumor with possibly reduced systemic exposure, which is the cause of adverse events. The oncolytic platform would provide the additional benefit of "pressing down on the gas", since oncolysis can induce de novo anti-tumor immunity. Thus, we made a virus coding for an anti-CTLA4 molecule,[214] but this never made it to patients in the Advanced Therapy Access Program, since the program had already started begun

to self-destruct, or perhaps a more accurate description would be that the foundations the program had been laid upon had begun to crumble… Not scientifically, medically or ethically, but because of commercial reasons.

## Patient stories

The Advanced Therapy Access Program, in which oncolytic adenovirus therapy was optimized for each individual, was all about patients. Only patients whose tumor could not be cured with available therapies were accepted for treatment, and the great majority were in a life threatening situation since their tumor was growing after all other available therapies, both routine and often also experimental, had been tried. In clinical trials, the official endpoint is usually not about the patient, but about the safety or efficacy of the intervention. In contrast, in a treatment, the only acceptable endpoint is trying to help the patient (see Tabel 1 ”treatments versus trials” a few chapters back). For many physicians, the main motivation for their career choice is trying to help patients. The ability to do good is a powerful force which sustains physicians despite all the problems and difficulties faced in their work daily. A nihilist might propose that helping patients feels so good because it is the ultimate demonstration of your ability from an evolutionary point of view: not only are you able to take care of yourself, and your family, but you have resources left over to care for strangers. Thus, a provocative ultra-biological reductionist view on a complex ultra-humane behavioral trait would be that being able to help is the final demonstration of the superiority of your genes over those of competitors. This would nonetheless explain why doctors and nurses seem to be classic sex symbols and preferred spouses ; )

On the question of nurses' role in cancer therapy my opinion is that they are the most selflessly giving party in the fight against cancer. They form the front line in facing the patients who recently





received their diagnosis, they are the ones who perform the bulk of communication with patients, before and after the oncologists' appointments, explaining and interpolating the message, they are the ones who actually give the treatments as prescribed by the oncologist. In particular, they administer the care which is often just as important as the drug, and sometimes more so. In many cases, the nurses give the oncologist vital knowledge: how the patient is really doing, is there pain, what are the goals of therapy, how is the family reacting? Patients often perform when they are seeing the doctor, while being much more honest with the nurse, who has more time and is less of an authority figure. When discussing medical progress, physicians get all the glory while nurses are often forgotten, just as I did, before I added them on 'dedicated' page. The only nurse I can think of with a prominent role in medical history is *Florence Nightingale*, of Crimean War fame. I'm not saying there aren't other nurses who contributed to medical progress in a major way, I'm just trying to point out that nurses are much undervalued when considering medicine as a field.

Everyone involved in the care of patients with cancer have it tough, since the disease is often incurable, the side effects of treatment can be significant, the benefits frequently small and in many countries time and other resources seem to be limiting. Not only is the disease a worthy enemy but the troops attempting to defeat it seem to be in disarray. Most physicians have experience with complaints from patients, unhappy relatives, shortage of time, lack of resources, nasty Head Nurses, unfair Chief Physicians, bureaucratic administrators, overtime, on-call, tiredness, burn-out, depression, working while ill because patients have been booked, picking up your kids late from kindergarten, not enough time with your family, just to mention a few things.

As oncologists know perhaps better than the average physician, possibly the hardest things are the human situations. Although death from cancer is usually not painful, when palliative care is administered appropriately, it is the giving up on life that is hard. Some elderly people face their fate with calm resignation, sometimes

even saying “I’ve lived long enough and it was a full life”, but this you don’t hear from those thirty-fourtyish mothers and fathers of young children. They should be in the prime of their life, professionally and personally, with careers, with kids in kindergartens and schools, lots of future plans, mortgages, commitments and responsibilities.

Even before these patients realize their health is crumbling away, and that their or their family’s life will never be the same, the oncologist sees death written across the medical chart in a bold invisible font. He then has to decide how to start communicating this situation to the patient and relatives. There are several strategies, none of which were taught in medical school as far as I remember, but need to be self-learned. My favorite coping skills are empathy and professionalism. These two indegredients, when mixed as appropriate for each scenario, can resolve many difficult situations. Empathy is big word but it just boils down to putting yourself in the other’s position, and to be able to do that one must cut back on talking and listen. By professionalism I mean staying in the role of the physician, applying medical skills and scientific knowledge as tools for helping the patient as much as possible. I would argue that the most important medical skill for oncologists is risk/benefit assessment; there are many medical technologies and drugs out there, and it is key to help the patient decide which approaches to try in each situation, taking into account the patient’s tumor and other diseases, prior treatments, socio-economical aspects and most importantly, the patient’s own goals and wishes which are often unspoken. Many things in the modern world can be done better by computers than humans but this assessment will probably be one of the last to be automatized because the variables cannot be easily reduced to numbers.

Regardless of how the oncologist decides to approach the situation, the patient and relatives invariably go through three phases: rejection, projection and rationalization. Initially, the idea of having a mortal tumor is not believed: “there must be a mistake!” Alternatively, “it is just





an infection, not cancer”. Then, someone is to blame: “that doctor I went to a year ago should have realized I have cancer”. Or: “the surgeon did not operate well enough”. Finally, a form of forced logic emerges: “it must have been that burned sausage I ate 10 years ago”, or, “could this have started when I was 12 and fell of my bike and hurt my chest”?

In many ways, the fate of young adults with incurable cancer is even crueler and more unfair than the middle aged patient’s, and I won’t even mention pediatric oncology. Regardless of their age and situation in life, every cancer patient undergoes crisis, even if the tumor is curable. To do their job well, the oncologist must get himself involved. In order to be empathic, one needs to lower their guard and allow the other person in. Thus, even though oncologists eventually learn to put up mental barriers in order to not get too much personally influenced, and experience hardens the soul to some degree, I don’t think it is possible to stay completely unaffected and be a good oncologist. Therefore, every patient uses up part of the mental resources of the oncologist. Some patients get through the barriers more than others and even if you try to sustain your innermost firewalls, this is hard to do every day the year around and thus something tends to slip through every now and then. It is the hardest profession I can imagine and my respect goes to those who are able to do it daily for decades.

The Advanced Therapy Access Program consists of 290 patient stories, some of which are imprinted into my memory for life. A couple of the patients have appeared on TV to tell their story, with no influence from me. I’ve already mentioned the heroic first patient who was brave enough to be the initial one to be treated with a new virus, in a new type of treatment program.

One of our earliest patients was a 6 year old neuroblastoma patient who had been heavily pretreated, but had tumor progressing in his bone marrow and near the left kidney. His mother was very resourceful and eventually convinced me to treat her son. The treatment was coordinated with his local pediatric oncologist in Northern Finland

and it was a success. His bone marrow was free of disease after the first treatment, the primary near the left kidney became a lot smaller, and the boy was able to return to school, which he had had to leave because of bone pains. His mother organized a petition to keep the Advanced Therapy Access Program going, when it was first threatened with increased production requirements in 2008. 8851 names were collected into the address which was handed over to the Ministry of Social Affairs and Health 8th of Sep 2008. Possibly this address, basically the work of this one active mother, postponed the increase in production requirements for several years. Eventually the boy relapsed and received second and third treatments, all of which seemed to have some effect but finally there was a problem with one of his blood values, possibly due to exhaustion of his bone marrow after all the heavy chemotherapy treatments he had received. In the end, after all the bravery displayed by the patient and his mother, we were unable to continue treatments and he died. However, the oncolytic virus treatments had kept him alive for a year and a half and I'm sure this was valuable time for him and his family.

The incredible determination of the boy's mother made a lasting impression. Not only did she get her son treated with an experimental therapy, when all else had failed, but she also organized the petition to be taken to politicians. She always seemed so strong when her son was there. However, when we anesthetized him for a challenging injection, something we only needed to do in young children, she immediately broke down in tears once her son was asleep. Her story is a beautiful example of how parents fight for their children and not only that but also keep up their role as the strong parent, willing and able to shoulder the pain and uncertainty on behalf of their child.

Another case I remember well was a middle aged woman, who had been battling her breast cancer for some time. She was very adept with getting access to experimental therapies and had managed to keep her tumor load quite low despite eventually





progressing on each therapy administered to her. We treated her with a GMCSF coding virus and for a long time thought we had cured her but eventually the tumor relapsed after 9 months and we had to treat her again. She had some chemotherapy at some point, which did not work, and a tumor grew near her liver elevating some lab values, which prevented further oncolytic virus therapy and she died. She and her husband were active in trying to influence the government to allow the treatments to continue. The husband was well connected and promised to arrange me a governmental medal of recognition if I could cure his wife. Unfortunately I never earned it. She knitted some socks for my son, and I am still reminded of her because now it is my third child whose foot fits those socks and she wears them at our cabin.

Another breast cancer patient we treated a dozen times, and each time her tumor markers would go down, but not to zero. She had a very personal style in writing her letters to keep us updated on her situation and it was like following a reality TV show – except this was real and not just "reality" – as we waited for the next tumor marker measurements to arrive over the e-mail. Eventually, she had a new tumor behind her eye, which we could not treat. She received radiation therapy which did not help and she died.

One young man had a sarcoma in his right shoulder, and metastases in his lungs. The virus treatment didn't shrink the primary tumor much, but disease stabilization was achieved, and he went on to be operated several times, and received further virus treatments as well. He continued vigorous exercising all through the treatments, except when recuperating from surgery. He went on to apply for medical school, got accepted, and is still alive at writing of this chapter. He penciled a beautiful drawing for us which still hangs in the nurse's office at Docrates.

A young woman, a property salesman, had an ocular melanoma metastatic to her liver. We treated it a few times and the tumor shrank somewhat, not dramatically, but she is still alive and well 4 years later, and hasn't seen an oncologist for a year and a half.

Another young woman I remember well for different reasons. In her case the treatment did not work, or did not have time to work, since the disease progressed rapidly. In a classic example of projection, her parents filed a complaint claiming that we had given them false hope. They insisted that we had promised that their daughter would be cured. Obviously the complaint was not going to go anywhere since both parents and the patient herself had signed a detailed informed consent form, explaining that there is no guarantee of anything, but it was still a nasty episode and almost the only negative incident in the entire patient series. In fact, comparing to my struggles with my academic colleagues, the patient treatments were a breeze! All patients were fully aware of the experimental nature of the treatment and since they had approached us on their own initiative, they were glad to treated.

Another case straight out of the psychology text book was a physician whose wife could not be treated because of extensive liver metastases, and he was extremely unhappy about this. In a typical embodiment of projection, he wrote an angry e-mail promising to cause problems to Docrates Hospital, because he had been billed for a telephone consultation, which he was no doubt expecting to get for free. One didn't need to be a psychologist to see that his grief was not caused by the 60 euro bill but his sorrow over his wife.

Not all patients seemed to benefit from therapy. One lady was very insistent on continuing despite no objective evidence of benefit and became one of the first patients where we combined chemotherapy and virus injections. Another woman in whom the treatment didn't seem to work still wanted to have a picture taken of me, her and the nurse, and sent it to us, and that picture looks at me every time I open the top drawer at my desk at Docrates.

One of the most easy to remember stories is a sarcoma patient who had a huge metastasis in her right lung. The tumor was the size of a soccer ball and there was basically no right lung remaining. She had a lot of difficulty breathing, could only walk a few hundred meters, and had to rest for several hours during the day. End-of-life





care had been initiated and she had even prepared a list of guests for her funeral already. Nevertheless, after three months of treatment, the tumor was in complete metabolic response, she was up and about, walking in the woods, and didn't need to rest in bed any more. At 9 months, she was completely free of symptoms, and was able to use her funeral list to invite her friends to her 50th birthday. Unfortunately, at 12 months the tumor started progressing. Despite having been deemed as refractory to chemotherapy a year earlier, we now convinced the local oncologist to try, and four months later it seemed like the disease had stabilized again. It may be an important aspect of oncolytic virus therapy, and any immunotherapy in fact,[215] that it can sensitize tumors to chemotherapy, and the opposite is also true. Chemotherapy can boost the immune response induced previously by the virus, by releasing tumor epitopes and by debulking suppressive cell subsets.[216]

Looking back on the 290 patients, it is amazing how well nearly all interactions with them went. Considering that all patients were incurable with routine therapies, and were typically progressing after everything else had been tried, in theory this is not the easiest patient population psychologically, on either side. Now that some time has elapsed since closing of the program, the full magnitude of the heroism of the patients is starting to dawn on me.

For a professional trained in viruses, cancer biology and oncology, oncolytic viruses do not seem frightening, but to the lay man I'm sure it is very different. Yet, each of these 290 patients overcame their prejudices and braved the treatment. Many of them travelled a long distance to receive therapy. In addition to Finland, we had patients from Brazil, Singapore, Russia, Sweden, the Netherlands, Qatar, Belgium, Estonia, Poland, Germany and probably other places. The experimental nature of the treatment was carefully explained to each patient orally and in writing, and they were glad to be able to receive it. I'm sure there are thousands of patients who looked at the issue over the internet, decided against the treatment and never appeared for a consultation. A third of the patients I met with

did not get treated, typically because they wanted to try some other therapy first and when they returned, their situation had worsened too much to allow treatment.

## Academic life

When I first started looking into the field of gene therapy in 1998, I assumed that new therapeutics could and should be tested first in the lab and then in clinical trials designed by academic scientists. Moreover, it seemed clear that marketing, distribution and sales are activities performed by drug companies, and thus the hand-over from academia to pharmaceutical companies should happen somewhere around the phase 1–2 or phase 2–3 junctions. However, I thought that phase 1 trials, whose purpose is not necessarily to get move a molecule down the development path towards an approved drug, but instead to learn from the trial and then return to the lab and make a better drug, could be performed by academic investigators.

Nevertheless, times were changing, and especially in the EU all clinical trials were increasingly being viewed as corporate activities, especially after the Clinical Trials Directive of 2004. Oddly, with the new rules, clinical trials were no longer seen as either research or drug development but instead all trials were regulated as if they were the latter. While the clinical trial climate was changing into a fully corporate activity, a Department Head from FIMEA suggested another approach (see the "Treatment Instead of a clinical trial" chapter above) and thus we started looking at the possibility of treating patients in an individualized manner in what we called the Advanced Therapy Access program (ATAP), and this was started in 2007. For the record, ATAP was not planned as a replacement for trials, or to circumvent trial regulations, but it was simply a way of placing oncolytic viruses within reach of patients in need of new therapies.





Although the legality of ATAP had been clearly established through my extensive interactions with all possible regulatory bodies, patient-by-patient individualized treatments were never going to provide the type of information needed for drug development. With mounting efficacy data from the treatments, it became clearer and clearer that the therapy might be working and thus it became more and more important to convert it into a trial. There were 14 million cases of cancer in 2012[217] and it was obviously not possible to treat even one in 100 000 of these in our individualized treatment program. The only way to make sure all patients who might benefit from the therapy would have access to it, is to make it available in pharmacies, and the only way to get it there is to demonstrate the efficacy in randomized trials and get the drug approved by the appropriate regulatory bodies. If there would have been no indication of the therapy working, then there would have been no need for trials.

Even if commercialization is always mentioned in the plans of Universities globally, in practice there is not much activity in this area at most Universities, but then there are a few dozen where it happens a lot. The University of Helsinki is part of the former group and I found the prevailing climate frosty to put it mildly. Most opinion leaders in the Medicial Faculty were quite conservative, viewing corporate activities as something which is an obstacle to "pure science", at best, and corruptive and unethical, at worst. Since there is almost no history of biotech success in Finland, this area is not well understood, and thus viewed suspiciously. Fortunately there were also a few people who understood the utility of spin-out companies and supported us in the process, and I remain optimistic that things will get easier with the University becoming more integrated with society and its needs.

At the time there was one biotech company operating within the Faculty premises which had some interest in what we were doing. I had tried to get them interested in commercialization of our viruses but without success. Their Board and CEO met with me and while the

business expert, immunology and virology experts were positive, the clinical infection specialist – a well respected opinion leader at the University Hospital – killed the collaboration in swift order. He said there was no conclusive data to demonstrate that our oncolytic viruses work and thus there was no purpose in collaborating. Clearly he was used to having Big Pharma show him the data from clinical trials and in the absence of such data he didn't see a way forward. This is a fairly typical embodiment of the provincial view on drug development: it is something that happens elsewhere; lets see their data and then decide if we should also start using the drug when it becomes available through Big Pharma. In this type of environment, there was little understanding of the role of start-ups or biotechnology companies. However, in Finland which no longer lives on the forest or metal industries, and Nokia Mobile Phones has been sold to Microsoft, there is increasing realization that start-up and small/medium enterprizes are needed to pull the economy out of the slump caused by globalization and to employ tax-payers.

One of our most significant papers was published in May 2010 in Cancer Research.[218] We had made GMCSF coding oncolytic adenoviruses and treated some patients. The results were very impressive; two patients had complete disappearance of tumors in computer tomography imaging scans. The manuscript also provided the first human data that oncolytic therapy can induce an immune response against tumors. This paper received a lot of publicity in Finland and internationally. However, evidently our high profile, and the exciting data, irritated some colleagues. Moreover, the fact that these patients had been treated in the private sector, not the University hospital, seemed to aggravate some public sector opinion leaders, perhaps because suddenly the protected mandate of the Academic Hospital was being challenged by high quality clinical work done elsewhere.

I guess it is an oft-repeated urban legend that the academic environment is a haven for back-stabbing and pulling the rug underneath people's feet but I was still shocked by the magnitude





of how true this was. I was [naively] expecting people to see the promise in the technology and see it as a positive thing that we had been able to treat some patients. I hope and trust there were many colleagues who silently felt this way, but I rarely received feedback from them. There were a couple of staunch supporters, fortunately including the Dean, but it is limited what individual supporters can do. In science and medicine, your reputation is what makes or breaks your career. If there is a famous member of the local scientific community, it is very easy for them to destroy a young scientists' reputation. All it takes is a few meaningful looks, some raising of the eyebrows and a few hints about "possible ethical issues". Many academics love to gossip about "ethical problems" involving the work of their colleagues, especially when they are competing for the same grants. It is a devious strategy since there is really no need for any evidence as ethics is a fully philosophical concept, it is all in the eye of the beholder. Shooting down colleagues is work done over coffee or drinks at various networking events, and as usual, those who are not present are the easiest targets.

Several cold showers resulted. I will not disgrace my book by describing the stories here because they are just too pitiful and the characters too petty. Nevertheless, my reputation was suffering and reputation is the most important factor determining science funding. Why did I continue with patient treatments? Certainly, it would have been better for my academic career if I would have cut my losses, licked my wounds, and limped back to the stronghold of the university laboratory. I should have probably done this in 2008. However, I did not do this because patients were benefiting from therapy! Tumors frequently stopped growing and sometimes they even disappeared completely. Patients were feeling better than before therapy and in many cases their survival seemed to be exceeding all expectations.[219] Thus, one could even argue that it would have been unethical to stop the treatments.

Moreover, we were just getting started with implementing clinically all the scientific ideas that had been brewing in the lab for the past

decade, and on which we and others had published on extensively. There were new viruses in the freezer, there were approaches to improve the immunological effects of the therapy, there were ways to improve virus replication, there were combination regimens, just to name a few things. An important practical aspect was that we were also learning how to give the therapy. For example, how often to inject, how to do the injections, what to measure in patients to ensure continued safety, and how to evaluate outcome in order to decide which patients to keep treating and which not. Critically, we were learning how to optimize treatment for each patient. Thus, if the treatments already seemed to be working, perhaps in 6 months they would be working even better. Maybe we would even start seeing cures of patients. For a patient oriented oncologist, it did not seem possible to stop giving the treatments with these possibilities looming on the horizon.

## Publish or perish

A depressing realization is that many scientists supposedly working for improving human therapeutics don't seem to give a second thought to actual human application. Instead, the main goal often seems to become a famous, respected, even feared, much-publishing Great Scientist. It becomes a closed tournament of sorts, each knight battling for the highest honors, with whichever means, with little regard for the actual goal of their work. A bit like politics, I suppose. I guess initially most politicians want to benefit their voters and humankind in general, but often get bogged down in the day-to-day, election-to-election battle against their colleagues. Combat becomes the end instead of the means and after a while the initial goal is forgotten and only success matters.

There is a lot of truth in the saying that academics are so eager to fight with each other because the stakes are so low. This phrase has been attributed to US President *Woodrow Wilson* who evidently





frequently complained about the personal nature of academic politics, asserting that the intensity of academic squabbles was a function of the triviality of the issue at hand. He had served as President of Princeton University for 8 years so no doubt he was an expert on the matter.

When you have your permanent position at a University, you have your narrowly focused research projects, there is little need to be friendly, constructive or thinking out-of-the-box. Free thought and expression are in key roles at Universities and obviously these are wonderful things, but when coupled to the lack of common goals, the environment may become unconducive to concrete and significant gains. In the world outside of academics, most people would agree that to achieve important goals, people and teams need to pull together in the same direction. Either you win or lose together.

In the worst case, the opposite may become true in academics. If your colleague wins, you lose; the grant, for example. Thus, success becomes defined by small steps, usually coming in the form of publications, which may be submitted as "minimal publishable units" if there is a need to provide an impression of productiveness. While there is no doubt that publishing of results is in the interest of humankind, one could argue that the process of science has become partially sidetracked due to excessive importance placed on the number of publications as a measure of productivity. The reason why the number of publications is more important than their quality is that there is no good way of measuring the latter. There are many bibliometrics such as impact factors, number of citations, Hirsch-index (= the number of papers cited more times than the numerical value of the index), etc but none of them provide an objective measure of quality.

In order to become successful as a scientist, one needs to publish. One needs to publish, publish and continue publishing a lot. Publish or perish remains as true as ever. The easiest way to publish frequently it is to define your objectives narrowly and to use rigorous experimental conditions, best found in vitro or in animal experiments. This

approach works well in basic research, which has been very important in all fields of medicine, but it is less than optimal in translational or clinical research, and it is antagonistic to cross-field approaches, innovation and thinking out of the box. Getting publications becomes the goal, often the only goal, instead of being a mere means of communicating results to the community. Since the continuation of your career, promotions and positions are basically decided on publications, it is no wonder that the system encourages quantity over quality.

There are many merits to the idea of peer-review, that is, the notion that your colleagues evaluate the quality and validity of your work. However, it has its problems, and since there are no alternatives available in science evaluation, one could also argue that peer-review is also the worst system. The peers reviewing are typically your competitors which means they have motivation to delay, steal and discredit. Peer review is performed anonymously, which allows opportunity to take pot-shots at your competitors without fear of repercussion. A common tactic is to repeatedly ask for major revisions, thus delaying your competitor, while mobilizing all possible resources to repeat the work and maybe slip it into a friendly journal before the original paper gets published.

Even if the reviewers happen to not be direct competitors, which is unlikely in small fields such as oncolytic viruses, it is more than likely that they are respected experts in the field. Often such individuals are senior, conservative, and quite established in their own narrow sector of work. Thus, any thinking-out-of-the-box is likely to be disbelieved and shot down. Another issue is the general narrowness of the fields of expertise that scientists of today have. For truly effective translational research in the field of gene therapy, projects often involve molecular biology, virology, cancer biology, cell biology, immunology, animal physiology, genetics and statistics. When trying to publish papers going several steps further from preclinical work, to include safety, efficacy and immunological data from patients, even more problems are encountered, since each peer reviewer is





looking at the manuscript from his perspective. If you are an expert in T-cell immunology, for example, you may be easily unimpressed with that part of the paper, and thus focus on criticizing this area. You don't understand the other areas so you don't worry about them, or the higher level view on the project. Each reviewer does the same and thus a lot of critique is received but no one evaluates if the project overall was worthy.

The way to be successful in peer reviewed science is to study a really narrow area, where you are the best expert. This way reviewers can only be impressed or wrong. Many scientists argue that peer-review as a system does not fit into the globalized multicultural society of today, where information can be disseminated in an unlimited manner with the press of the button, and where access to data is not limiting, but the individuals' capacity to process it, and where there is much more information than anyone could ever hope to digest. Also, fierce global competition is the order of the day and encouraged on local, national and international levels. Getting better papers than your competitors converts into salaries for yourself and your group members, which convert into mortgages being paid and dinner on the table.

The historical roots of peer review and modern science in general are in post-medieval Europe, where upper classes of society with inherited money had no need to work for survival. Many occupied themselves with social activities, politics and warfare, but some took up science as a way to pass the time. Typically, each scientist funded themselves and laboratories consisted of one or two people and no-one's sustenance depended on publications. In this gentlemanly society, I'm sure the peer review system worked in a much fairer way. Nevertheless, as pointed out by a colleague, I can rant all I want, but what are the alternatives to peer review to assess quality in science?

If it is so terrible in Academia, why am I still there? Because that is where most of the cool science happens. Moreover, with every year that I get older, I increase in my appreciation of the smart young

students ready to take on the world. It is a lot of fun seeing them develop from ignorant and ambitious to capable and determined. Also, one gets used to freedom of expression. Would I be able to write the things in this book if I worked in a big company?

## Oncos Therapeutics is founded

A man's greatness can be measured by his enemies, according to the famous quote attributed to *Donn Piatt*. If this is true then we were probably doing something right. Although our opponents were few in number, they were powerful, well connected and established seniors in the Finnish academic medical community. Thus, it was becoming clear that the treatment program could not continue as a University activity. I had been receiving advice that I should found a company but being a scientist and physician at heart, it took me a while to get used to this idea.

Also, I realized that one person cannot do everything himself, and by this time I already had 2 kids and wanted to spend time with them as well. Therefore, I was on the lookout for a partner to help me set up a company and eventually a promising candidate was identified through a mutual friend. We met on 22 Oct 2008 and things started moving quickly thereafter. Oncos Therapeutics Limited was founded, our GMCSF coding viruses were patented and we started working on setting up our first trial.

Even with the patent submitted, and the presence of animal and human data suggesting that the viruses were safe and effective, it was not easy to get funding for the company. The global economy was in recession and oncolytic viruses were an unproven field. Immunotherapy in general had a commercial reputation of failure and adenoviruses were almost a swear word in the post-*Gelsinger* climate.

*Will Smith's* 2007 film *I Am Legend,* where oncolytic viruses turn humans into zombies, did little to alleviate fears, despite





being an entertaining movie. Following more than a year of discussions, a European venture capital company became interested and the contract was signed 11 Dec 2009. After several months of Due Diligence, another interesting first experience for me, the investment was received. The Finnish government has a loan program to help start-up companies and matching funds were obtained, eventually totaling more than 10 million euros, if one does the math on publicly available information. At the time, it seemed like a lot of money, but I had no idea how fast it would burn when ignited by a hardworking CEO…

One of the first things Oncos did was take over the Advance Therapy Access Program. There was a mutual need for this as it had become clear that the University didn't want it and on the other hand one of the two purposes Oncos was founded for was to run the Program; the second being to convert oncolytic adenoviruses into drugs.

It is actually incorrect to say that the University didn't want ATAP since the University is not a single entity, and has no common goals, but consists of a large number of individuals all having their own view on how things should be done. I guess this is the purpose of University, to engender free thought and freedom of the individual, and while these are extremely important issues for society, they are not conducive for moving something concrete and difficult forward. Thus, the correct wording should be that there was sufficient opposition at the University to guarantee lack of progress there, even though some individuals were also quite supportive. And I remain optimistic that there is also a silent majority which approved even if I never heard them. Perhaps they will give me feedback upon reading of this book.

## How to produce virus for human use

When virus production became a corporate activity, suddenly

it became more difficult and expensive. Two factors contributed to this. First, now people responsible for production were not people who understood oncolytic viruses and therefore they applied standard pharmaceutical and engineering approaches, few of which are automatically applicable to viruses.

Second, now that the activity was that of a company, there was a lot more done "just in case", to prepare for audits, and to raise production closer to the industrial good manufacturing practices (GMP) standard, needed for drugs on sale at pharmacies. While these changes can be seen as positive from the company's point of view, they did dramatically reduce the speed and increase the cost of production. Only two lots of virus were produced by Oncos during the first year when it was fully a company activity, while more that 20 had been produced the previous year by CGTG, at the University. Importantly, there has been no change in adverse events regardless of how the virus has been produced.

There is no doubt that good quality production is important for any drug. It would be wrong to expose patients to adverse events due to production issues. There are a couple of scares reported in the history of pharmacology, such as the contamination of both *Salk* and *Sabin* polio vaccines by SV40 virus. There is no disagreement that contamination was present, but there has been much discussion if this caused any consequences. SV40 – like many microbes – can probably be found in some tumors, and it can participate in carcinogenesis in the laboratory, but there is little evidence of a causative role in humans. The most prestigious opinion in this regard is from 2004 when the National Cancer Institute stated that SV40 does not cause cancer in humans, based on several large studies.[220]

Another type of contamination was also present in *Salk's* polio vaccine. It contained small amount of wild type (=not inactivated) polio, which caused polio in many children but also helped make it the most effective vaccine available, because shedding of wild type polio from some vaccinated individuals resulted in "herd immunity", meaning that not everyone needed to be vaccinated, but 100%





population coverage was still obtained.

While the early polio vaccines were not perfect by any means, their risk should be put in perspective. Polio was a terrible disease affecting a big part of the population, especially children, resulting in crippling, paralysis, death, or a tortured life inside "iron lungs", which were artificial ventilators. An excellent book on the polio vaccine story is *Paul Offit's The Cutter Incident* from 2005.[221] Polio continues to be one of the few dramatic success stories of modern medicine. This terrible affliction has been almost completely eradicated, and the wild type component of Salk's vaccine contributed to this in a major way, albeit with a price, since some people did get polio because of the vaccine. This is a general aspect of vaccines, they deliver their benefits on the level of society, while individuals may or may not benefit.

Thus, contamination of medicines or vaccines can result in side effects, but in fact these instances are extremely rare compared to adverse events caused by the activities of the drug substance. In other words, "on-target" or "off-target" molecule-specific activities are almost always far more dangerous than the effects of excipients resulting from how the drug was produced.

For example, one of the most prominent recent drug development disasters is *the Tegenero incident* from 2006.[222] In a horribly planned phase 1 clinical trial, six healthy volunteers were given the drug within a few hours. This was a first-in-man trial with a drug that couldn't be properly tested in animals because of species incompatibility issues. Despite the proposed mechanism of action of the drug, a super-immune-activator, all six men were dosed simultaneously and thus when the immunological adverse events started emerging, all six were affected. None of them died and it seems most eventually recovered without major damage but keeping in mind these were healthy volunteers, it was clearly terrible planning to expose 6 people simultaneously. Nevertheless, the key message in the context of manufacture is that the adverse events were not caused by the production method, but the actual mechanism of

action of the drug.

One variation of an adverse event is the *Pandemrix* debacle from 2009.[223] Initially denied by public health authorities, it was later accepted that this influenza vaccine did increase the risk of narcolepsy. At writing of this book, it is not completely clear what the mechanism was, but probably both the inactivated components of the virus and the adjuvant present in the vaccine played a role (adjuvants are used to make vaccine more immunogenic).[224] Again, an example of the active substances causing the adverse event, not the production method.

One can argue that even a single adverse event due to production is unacceptable, especially for a drug in routine use and for sale in pharmacies. However, if full industrial GMP is applied to every drug just entering clinical trials, the cost of trials will become prohibitive and in fact prevent testing of many drugs. Unfortunately, this is the current situation at least in the EU. All groups working with oncolytic viruses have promising agents which they have tested in vitro and in animal models, but most of them will never be able to do even a single clinical trial. The most important reason for this is that virus production according to GMP and testing according to the European or US pharmacopeia is much too expensive for academic groups and it is cripplingly expensive also for start-up companies.

In medicine, the main job of the physician is to weigh the risks and benefits of interventions. According to this logic, completely different production standards should apply to vaccination of healthy individuals versus treatment of patients with a life-threatening disease.

It is difficult to argue with pharmacology oriented regulators on this since the rules they follow are not concerned with whether a patient gets treated or not, or if cancer can be cured. Regulators try to do the best job they can in following the instructions they have (eg. the European or US Pharmacopeia) and this results in meticulous adherence to the current GMP standard. Although GMP may sound like a standard, it is not a static one. Every year some details are added, typically since new data or hypothesis emerged suggesting





some new potential safety risk. Of note, usually increases in GMP requirements are not based on evidence that they would be necessary.

There is a double standard in place. For efficacy, extremely rigorous evidence is required, often from several trials, but for safety regulations there is no requirement for evidence, and therefore the latter increase, making demonstration of the former more difficult. There is no counterbalance to increases in regulation except in those countries where patient advocacy groups are sufficiently vociferous.

Outside of the US, there are no patient or physician societies vocally demanding improved access to new drugs, which could be achieved by relaxing the rules on early phase trials. In contrast, there is a whole industry living off clinical trial regulations. They provide the testing required for GMP drug production, typically at a high cost, and they have their lobbyists in Brussels and Washington DC. Lets say a simple test performed on a virus production lot in the lab costs 100 euros. To do the same test and get a “Good Laboratory Practices” (a testing standard applied to GMP) stamp on it, can cost 10 000 euros. To add insult to injury, these testing companies normally don’t know how to do these tests, if they are a bit exotic. Thus, you not only pay them to do the testing, but you also spend your resources to teach them how to do it and pay for them practicing.

## Clean virus for dirty tumors

Oncologists know that tumors are dirty. They are frequently infested by bacteria and yeast, and sometimes they smell really bad and secrete a revolting form of ooze.[225] Nonetheless, if you want to inject something into this mess, the injected substance needs to be produced in an ultra-sterile manner and proven to lack any microbes, including exotic sub-Saharan retroviruses never encountered elsewhere. Even if you are injecting something intravenously, there are going to be many contaminants picked up from the skin when sticking the needle through. Human bodies are not sterile in

any way. For example, there are far more bacteria in the intestinal tracts than there are cells in the body.

When Oncos took over production, a person was named responsible for quality, and obviously that person wanted to do a good job, and in fact did so. Consequently, production took a further step towards industrial GMP quality, which increased the cost. Another issue was that we couldn't agree which specifications to use for approval of a virus production lot. The next virus planned for ATAP was the one coding for a monoclonal antibody against CTLA4,[226] discussed in the "Viruses with other transgenes" chapter above. Since the payload in this virus is the maximum size, the virus doesn't package as well as viruses with smaller payloads. Thus the functional to physical particle titer suffers somewhat but this is not critical for biological activity since the virus self-renews by replicating. Regulatory recommendations have been written with a non-replicating gene delivery vehicle in mind and for such vectors this ratio is important as the input amount of virus is all that you get. With a self-amplifying system the input functional titer is not so important but rather just a characteristic of each virus; the virus amplifies in the tumor and thus input virus is only the very first step in the process. My inability to convey this convincingly within Oncos led to a lot of delay and major efforts spent on process development and ultimately this virus never made it into patients.

Meanwhile, the oncology community in Finland was puzzling over our individualized therapy approach. Our first paper on GMCSF armed viruses received quite a lot of media attention which did not go unnoticed by my public sector colleagues. The Finnish Oncology Society – whose key opinion leaders included the professor who had "recruited" me to Helsinki – published criticism on their web pages, implying that they were not convinced with the results reported in the article. The text deviously hinted that there was something inappropriate in the manuscript without being specific on what they meant. I was a member of the society but of course they never asked me anything about the paper, instead preferring to post their





message on the internet. Their purpose was never to look into the data but just to blackball the approach, possibly because it was given at a private hospital while the opinion leaders at the society all worked in the public sector.

These sort of incidents caused a lot of personal suffering but it also served to separate supporters from the rest. For example, one of the coauthors of this high-profile paper apparently believed some of the gossip and lies circulating in the oncology community and wanted to separate himself from the data. He had been eager to be an author on the paper, but now he was just as eager to disbelieve the data.

If there is any good that can come out of these sort of experiences, it is that you realize who your true supporters are. *Timo Joensuu*, Chief Physician at Docrates, has never wavered in his support, even in the more testing times. Being the multitalent that he is, he has been a seminal part of many aspects of the Advanced Therapy Access Program. He helped with selection of the right patients, he saw several of my patients at follow-up visits if I was out of the country, he has provided useful commentary to our manuscripts and he even played a big part in organizing the funding needed for building of Oncos' laboratory.

Whenever I felt insecure about the treatment scheme, he was able to remind me why we are doing it. This sort of commitment creates a tremendous amount of loyalty, a virtue which is generally in short supply in the academic medical community.

Another staunch supporter has been *Risto Renkonen*, Head of the Transplantation Laboratory at the University of Helsinki. It has been fortunate indeed for our endeavors that he has been Dean of the Medical Faculty since 2009, and if this had not been so, things might have developed quite differently.

## The end of the Advanced Therapy Access Program

The writing was on the wall during the fall of 2011. Oncos'

management was saying that ATAP is too expensive, that we were not learning enough to justify the cost. The Finnish Medicines Agency FIMEA, charged with regulating the program, had been gradually tightening the screws which again added to the costs of running the program. As an oncologist I wanted to keep trying to help patients, and I also thought that by doing we could learn, just like a surgeon improves his skills by operating. However, in a company the CEO ultimately decides things and thus I knew I was fighting a losing battle.

However, ATAP was still limping along on its last legs when the bomb dropped at my University group. I was taking my son and his friends to soccer practice on Nov 15th 2011, when I got an e-mail from the company. The next day, further e-mails followed. I was told an investigation is being launched against me since I am suspected of hiding scientific disagreements from the company. It turned out that the CEO had been meeting with many of my group members without my knowledge and – not being a scientist – had evidently been surprised that there were many different opinions in the group.

One example was related to a clinical trial we wanted to do in dogs. Virus had been produced in the same way as for human trials with that type of virus but we had one scientist in the group who felt that this production level was not enough. Dr X was one of the most senior scientists in the group, but her previous work had been in another field and thus she had only superficial knowledge about gene therapy or oncolytic viruses, and no experience in translation of laboratory findings into animals or humans. She had indicated to the group member responsible for the trial that she would be in contact with authorities about her views, and to protect the student I moved her to work with another senior scientist. Other students of Dr X had also been unhappy and their relationship was increasingly unproductive so they were also moved while retaining the official roles of the people involved.

A problem for some non-medical scientists such as Dr X, working in the medical field, is that they don't always understand the





complexity of clinical data, which stems from the fact that every patient and every tumor is different while in the laboratory identical cells or inbred mice are used. Since the beginning of our patient treatments, there were a few members of the group who were critical of human data, pointing out the "lack of controls", preferring the rigorous conditions of the laboratory experiment. I always wondered if these people just didn't understand why they are being funded (to develop medicines for humans) or if they just felt that someone else should be doing that while they can focus on their cell line work with the satisfaction of full control of the conditions.

Given that more than 60 scientists had worked at CGTG by that time, the few scientists unhappy with our human translation were a very small minority. All of them were non-medically-trained, and I guess it would have been possible to change my recruitment policy, but I nevertheless kept accepting also basic science trained people, since I believed and still believe, rightly or wrongly, that a rich combination of different backgrounds would eventually benefit the group and science performed therein.

While the great majority of basic scientists joining the group leaped at the possibility of seeing their work make a difference in humans, this was not always the case. I didn't worry since I have never shied away from speaking my mind, even in disagreement, and thus I expect this also from others. To me, disagreeing, even emphatically if need be, is normal, useful, and enriches the scientific process. If you don't allow disagreement, you won't get new ideas, you won't see the caveats in established concepts, and you won't get the best out of the young smart brains.

Not all arguments can be resolved with a compromise and sometimes a conclusion can be that one must agree to disagree. Yet, the lack of harmony which creeped into the group in the fall of 2011 is my responsibility, since I don't think I appreciated how foreign human oncology, with its inherent complexities, were to scientists trained only in the laboratory. Also, I was probably splitting my time into too many different directions, including being home with the

kids every now and then, and thus wasn't giving enough face-time to group members.

While many of the best people enjoyed their freedom and this allowed them to excel, perhaps some of the others would have benefited from more interaction with me. The challenge of any leader with personnel is to try to understand each employee's "operating system". Each one is going to be very different and there is no manual so basically you have to play with the system to figure it out. Given time, one can usually work out each person's operating system but interaction is required and some systems are more complex than others, and some may be so byzantine that they cannot be worked out even with time. And some operating systems may have serious flaws which only become apparent in a special set of circumstances.

What had happened was that Dr X had taken her opinions about the dog trial, and a collection of other gripes she had developed over the years, real or invented, to the Faculty, no doubt knowing that according to University policy such claims are immediately transferred to the Chancellor, who is responsible for "ethical issues" at the University. Policy is quite straight forward in this regard since "ethical problems" and the subsequent media exposure are what Universities fear the most. Whenever a claim of ethical issues is made, an official pre-inquiry is launched. Unfortunately, University policy does not include asking the complainant or the accused to sit down and discuss the issue, nor does it require any University officials to mediate, regardless of the motive for the complaint. The whole debacle could have perhaps been avoided if even one

University representative had chosen to ask for the parties to sit down and discuss the issues. In fact, no one told me that a complaint had been filed, until I heard it through Oncos.

The process took its own course, dragging along over several months of purgatory. Academic people love to gossip and nothing is more juicy than an investigation about "ethical issues". Human nature is such that people tend to assume that there must be some truth to any accusation, no smoke without a fire, right, and the rumors





take on a life of their own. Morale in the group plummeted and over the next year several people left.

Personally this was easily the most difficult time of my career thus far. I had fought and bled for the group, arranging funding, making an environment suitable for productive research, spending long nights and weekends over projects and grant applications, lobbying left and right, facing the critique of my colleagues and so on. Dr X was not the most productive of scientists but I had been patient and even arranged technical support, and switching to another technician after she fell out with the first one. I arranged for her to work on a project where she didn't have to be involved with patient issues and where her low productivity would not be a show-stopper. I guess I should have remembered *Napoleon's* cardinal rule to never reinforce failure.

The Chancellor's pre-inquiry committee did their work meticulously and after several months came up with their report. Importantly, none of Dr X's complaints were substantiated in the report. They made it a point to underline that there was nothing wrong with the science. However, as punctilious people do, the investigators had come up with some questions of their own. Both experts had been trained in medicine and had a lot of experience in basic research, but neither was a clinician and had probably not seen a patient in the past 40 years. Neither had any experience in oncology, gene therapy or clinical translation. Thus, it was logical that their questions were about the clinical side of things and they had problems in understanding the differences between a treatment and a trial.

As a lawyer friend of mine remarked, if the written output of any professional would be subjected to this sort of scrutiny, made sharper by the power of hindsight, all of us would be found imperfect regularly. The pre-examiners' report came up with several small things they were unhappy with and my options were to demand a full investigation or accept their report. A full investigation would have meant that the torture would have continued for another 6–12 months and who knows who would have been the experts

this time around. Maybe someone working with cell lines who would have felt that treating of humans with experimental medicines is unethical on a general level.

I once met a respected basic scientist who publicly claimed without blinking that in his opinion the biggest problem in science is exposing humans to new drugs before they are fully characterized in the laboratory. I cannot believe that he actually felt that clinical trials are unethical in general, nor can I accept as true that he would be unaware of the inadequacies of laboratory models with regard to humans. Instead, I believe he had unconsciously learned to keep saying this to increase funding for his field, and his own work, which involved basic research with cell lines. There is also the possibility that once you say something enough times, you start believing it, even if at the outset you didn't think so, and if you stopped for a moment you would realize that you are deceiving yourself. My point is that if we would have had such a person evaluate us, I'm sure he would have had a field day crucifying us. I had already learned that there were plenty of people out there wanting to shoot us down so I was worried who they would select for the full examination, if I had asked for it. Further, as in peer-review, it is usually not the objective, uninvolved colleagues who are willing to spend their free time on such evaluations. It is typically someone who has some personal motivation to become involved.

The morale in the group was incredibly low. A continuation to my five year research professorship, nearing its end, had not been signed due to rumors circulating about an investigation, and the treatment program had now been closed by Oncos. Our first clinical trial had started but negative exposure might have put that at risk, and certainly it would have compromised the ongoing fund raising efforts necessary to keep Oncos' trials moving forward. Thus, I figured I would bite the bullet and move on with life. Even though I disagreed with many aspects of the pre-examiners' report, I would take the hit and begin rebuilding whatever could be rescued from the ashes of what had been my career and my research group.





Moving on was not so simple, however. The ultimate executive body at the University is the Rector and he took a lenient position on the Chancellor's report. This was something of a pleasant surprise since heretofore most University officials had seemed mostly concerned with minimizing negative exposure. Not surprisingly, the Rector's decision made Dr X unhappy and she proceeded to file a complaint to the "Supreme court" of national research ethics, which decided that they would not take the case since the pre-examination had been unusually profound. One could speculate that maybe the Chancellor had had a point after all in being strict at the pre-examination phase. It could be seen as good tactics to find something to complain about, even if the science was impeccable, so that the University wouldn't seem too lenient.

However, if this sort of compromise is a usual outcome, one could argue that filing any complaint becomes a self-fulfilling prophecy. If it is not the goal to decide if the complaint had merit or not, on a yes/no scale, but instead the pre-examiners can present their opinions on any subject, and the University decides on a slap-on-the-wrist just to placate the complainant, to make sure they can't be criticized for not taking "an ethical complaint" seriously, and to reduce further exposure to the University, then the substance of the complaint does not play any role in the process. Thus anyone can be attacked successfully, for example to get revenge, without there needing to be any substance to the accusations.

In 2013 there was a poorly written article on research ethics in a subscription-free journal delivered to all Finnish medical professionals. Among other cases, Dr X's complaints were featured. The article sloppily confused terminology of critical importance with regard to research ethics and would clearly have been grounds for legal action if I had not feared the resultant publicity. Of note, the article reports Dr X's complaints but not my replies. The journalist used my name in her text but did not ask me for any comments and thus the paper was published with several mistakes. I asked the journalist to correct the mistakes but she only changed one

single word in the internet version of the text, which did nothing to correct the message.

It is interesting that journalists can write anything, without any requirement for truthfulness or correctness, even if they are reporting on issues regarding truthfulness and correctness. Talk about a double standard! And in the internet era, their text can be found for eternity just by googling, as I initially thought, but fortunately learned otherwise. Even if the example above suggests a variable journalistic standard, the journal has invested in Google-optimization of their articles. The article was written in a provocative fashion and "ethical issues" are interesting to the medical community and beyond. Thus, after a while a Google search with my name resulted in this text popping up on the first page. However, after searching the internet for means to deal with untoward Google results, I repeatedly came across the very simple advice of just contacting the Editor. The journal had recently changed Editors and thus I did as suggested and after a pleasant 30 min telephone discussion, the new Editor promised to remove the poorly written piece. I contacted Google, asking them to update the page and a day later the problem was in the past.

Nevertheless, a lesson I could have done without is that once something is written about you on the internet, and scores highly on Google, you are tainted, possibly for a long time. And not just nationally, but globally. This was demonstrated when a German colleague told me that when he searched with my name and just clicked "translate" on the Google page, the article was on his screen in German.

The pre-examination had taken 8 months and in the meanwhile many things had changed with the patient treatments. To minimize risks to the company, it had decided to stop enrollment of new patients in the immediate aftermath of Dr X's complaint. Since it would have been unethical to stop abruptly, treatment of patients already in the program was continued until April 2012, when the Finnish Medicines Agency FIMEA decided that we could no longer





use the earlier virus lots in our freezers, but should instead produce new ones according to their most recent production requirements.

FIMEA knew Oncos had finished building their production suite, and probably figured that they could require remaking of all of the viruses. However, what they did not know is that Oncos was using the production suite for process development, in preparation for large scale industrial production. Thus, Oncos could not set aside the suite for the 6–12 months of production the half a dozen of viruses in current use would have required.

Also, with the increases in production requirements, the cost was now prohibitive and according to my own personal estimate (with this wording, no one can sue me), more than a million euros would have been required to produce, again, and test the viruses. This would have converted into an investment of tens of thousands of euros per patient needed from Oncos.

Even with my physician's math skills I realized that this was just not going to work and thus the program was laid to rest. Although enrollment of new patients stopped soon after the endeavors of Dr X, I think the Advanced Therapy Access Program (ATAP) would have stopped soon anyway. Oncos management wanted to focus on process development for just one virus, and make Oncos a one-product company, typical of biotech start-ups. This incident gave management leverage on the level of the Board of Directors, where there was initially much more enthusiasm for patient treatments, learning from them, and taking several viruses into trials.

The official main reason for stopping ATAP was that Oncos decided to focus on its clinical trials. Although this is true, the details written here shed light on the other aspects involved. Being a small company, it would have been difficult to manage both ATAP and the ambitious process development projects envisioned. Process development means converting a small scale laboratory production method into an industrial scale process compatible with selling of licensed pharmaceuticals. A large proportion of Oncos management and personnel were engineers so it is logical that there was a

preference for engineering projects instead of medical issues and this was reflected in how the company's resources were spent. This did not coincide with my vision, however, since I thought there was much to learn and the only way we could learn was by treating patients.

Also, I liked being able to help patients and I thought the experience resulting from ATAP would also be beneficial to both Oncos and humankind. We had 6 patents, with about 20 different viruses, 10 of them already used in ATAP, and my vision for Oncos was a "phase 1" company, which would take several viruses into iterative clinical trials, and then let some other companies make them into products. I felt we had a handful of extremely promising viruses which all would have their specific uses; different tumor types, application routes and combinations with standard therapy. However, I was overruled, and since I was not going spend my time fighting a battle over this, I progressively started taking a smaller role in the company.

## When it starts raining, it pours

If I thought my troubles were over with the complaints of Dr X winding down in the summer of 2012, I was wrong. There was more to come. A new Department Head, *Dr Esko Nuotto*, had been appointed at FIMEA, and he did not like the Advanced Therapy Access Program. As witnessed by my lawyer *Klaus Nyblin* and the Chief Physician of Docrates in the Spring of 2012, the FIMEA Department Head loudly informed them that he was "extremely annoyed" by ATAP.[227] There was a new sheriff in town and he was going to make sure everyone knew he was not one to be taken lightly.

In January 2012, *Dr Nuotto* wrote me a letter asking me to explain "why we are doing clinical trials without a trial permit".[228] I wrote a detailed reply explaining the dozens of interactions we had had with authorities, including FIMEA, underlining the Ethics committee's statement that the treatments were not a trial, briefly explaining the differences between a trial and an experimental treatment,





a distinction I assumed he was quite familiar with. In retrospect, I guess I should have taken this even more seriously and immediately proceeded to recap all my interactions with all the different governmental and non-governmental bodies, including his predecessor at FIMEA, who was the one who suggested ATAP in the first place (see "Treatment instead of a clinical trial" chapter). Also, I could have reminded him that he was there in the audience November 2007, when I gave a talk at FIMEA and told the packed hall that we were starting patient treatments with oncolytic viruses, and he was so interested that he came to talk to me after the lecture. He had also participated in many of the meetings we had had at FIMEA over the past several years. Nevertheless, I didn't realize this was a man with a mission, and my reply to him was "only" 3 pages long. Little did I know that the storm he was raising would result in thousands of pages of text and €229 958 in legal costs.

I had presumed all along that the worst case scenario was that FIMEA would ask us to stop ATAP, but this never happened. A few months later, however, an e-mail arrived from *Dr Nuotto*,[229] informing me that he has asked the police to investigate if we have broken the law on clinical trials. This e-mail was a few weeks after FIMEA's decision[230] to not allow use of older production lots. Thus, although there was an EU Regulation encouraging patient-by-patient treatment with advanced therapeutics including oncolytic viruses,[231] and FIMEA had specific rules in place,[232] and we had several dozens of interactions with them, including a production permit, audits, annual reporting, and an invited publication in FIMEA's own journal, meticulously reviewed by FIMEA, and we had never been told that there was anything wrong with the treatments, *Dr. Nuotto* had now asked the police to investigate us. The police cannot be expected to have expertise on the differences between trials and treatments, and therefore it is unsurprising that when requested by a fellow government official they had no choice but to interview all the people suggested by *Dr Nuotto* and then pass the ball to the prosecutor.

Either he wanted to make a name for himself at FIMEA and was

acting mostly on his own initiative, or FIMEA had a broader plan of shutting down the program. We never found out as FIMEA refused to meet us even after the court case. Another possible explanation for the actions of *Dr Nuotto*, and these are not mutually exclusive scenarios, relates to widely publicized regulatory farce that had occurred in Finland a few months earlier. It had been discovered by journalists that there had been 2 "physicians" working in Finland without medical degrees and the media cooked up quite a scandal out of it.[233] Human interest stories were easy to come up with and headlines such as "have I been treated by a false doctor", "my condition became worse because I was treated by an impostor" led to regulators being blamed for not regulating staunchly enough. A number of regulators were interviewed by the police and three were eventually found guilty and fined in April 2013.[234] The fines were only a few thousand euros but there must have been a lot of unhappiness within the regulatory circles since this was the first time they were held accountable for something like this. I would not be surprised if many regulators have started prioritizing covering their behinds, in order to not be blamed for not being strict enough.

Legal cases or threats thereof are becoming more common in the regulation of research and medicine in many countries including Finland. For example, the National Institute for Health and Welfare (THL) was investigated by the Chancellor of Justice for conflict of interest because it had received research funding from Glaxo-Smith-Kline and had also bought the ill-fated *Pandemrix* vaccine from them.[235] Three National Supervisory Authority for Welfare and Health (Valvira) regulators were convicted in the "false doctor" case as mentioned above.[236] Several scientists have been accused and in some cases convicted of misdoings relating to record keeping of research funding.[237]

A new angle on the role of media in research regulation was a recent case where a philosophist-turned-entrepreneurer was targeted in a media frenzy for accepting a public grant.[238] The accusations were that the grant had not been open to free public competition. Interestingly, it was not the people who had decided on the grant





who were being attacked, but the recipient. The likely reason is that a decade earlier the recipient, *Pekka Himanen*, was the youngest Finn to receive a PhD and was considered a super-talent, a whiz-kid, a brilliant mind. Now media had the chance to pull him down from the pedestal, to tear him apart, to sell some newspapers.

Compounding many of these cases is the commercial angle. Although the public position of the Finnish government is that they support entrepreneurism, the previous half century of social democratic heritage doesn't rub off quickly. Whenever there is a commercial interest, a condemning story-line is easy to come up with. Commercial interests are typically viewed as a corruptive force. Journalists like to write about scientists who have allegedly not kept good enough track of their research accounts, the false doctor had made a lot of money, the whiz-kid philosophist had received an expensive contract from the government, drug companies had compensated the public health institute for vaccine studies and so on.

The public health care system in Finland, once among the best globally, has been gradually deteriorating for a few decades, and there is continuous discussion on the role of the private sector. Some people feel that no tax money should be used for buying services from the private sector while others feel that the private sector can provide services more cost-effectively than the slow-moving and bureaucratic public system.

In my case, the facts that I had founded a biotech company and that ATAP treatments were given at a private clinic have certainly fuelled accusations and jealousies.

## At the bottom of the hole

Having always been a career-oriented person and a hard worker, much of my self-valuation consisted of success at work. In the Spring of 2012, nothing was going right professionally and accordingly my self-appreciation hit rock bottom. It seemed like everything I had

worked for over the past 20 years had collapsed: the research group, the company, patient treatments. The thing that angered me the most was that people might be able to use these incidents as reasons to not believe the 200 scientific papers we had published, in particular the data that had accumulated from the Advanced Therapy Access Program.

At the time, I wasn't getting much enjoyment out of research or life in general, but one of the bright moments was when I received an e-mail from *Bert Vogelstein* in September 2012. He is the most cited scientist globally and the leader of the field of cancer genetics. I met him once when I visited John Hopkins in Baltimore and it was interesting to hear that he had also had some ideas regarding replication competent organisms, which were bacteria in his case, and had in fact performed one trial with the approach. I've included his e-mail here, with his permission, since it made me feel so good after all the thumps I had taken:

> *Just wanted to encourage you to continue the innovative approaches you are trying. N=1 is the way to go to test such therapies, despite what others say.In my view, conventional Phase I trials raise far more concerning ethical issues than those associated with ATAP's approach.*
>
> *Best, Bert*
> *Bert Vogelstein, Director, Ludwig Center at Johns Hopkins*
> *Investigator, Howard Hughes Medical Institute*

## Is over-regulation restricting patient's access to new treatments?

Yes. While patient safety is always foremost in medicine, protection of individuals can be taken too far. As discussed in detail in this book, around 2004 the critical point was reached in Europe, after the Clinical Trials Directive made clinical trials much more expensive, resulting in many trials moving to non-EU countries. Academic trials suffered the most, and academic trials with new agents stopped completely.





Clinical trials featuring pharmaceuticals were no longer seen as research but drug development even if marketing approval was not the aim of the trial. The US FDA has consistently out-smarted EU regulators and more than ever the US is the most rational place to do trials. Many Asian countries are also appealing, but EMA and FDA are jealous in the sense that they are unlikely to approve a drug which was not tested on their continent, and the EU and the US continue to be the largest markets for pharmaceuticals.

Overregulation resulted in the end of the Advanced Therapy Access Program by making virus production too expensive and FIMEA's *Dr Nuotto* took regulation to a further level by involving the police. Another interesting regulatory case is the dog trial mentioned earlier. We had promising preclinical data from the laboratory that we might be able to treat dogs with an oncolytic vaccinia virus armed with CD40L.[239]We had originally developed this virus for humans but it turned out that dog tumor cells were also permissive for vaccinia and the transgene. Cancer is just as common in dogs as in humans so we could have helped some pets and their owners but there was also terrific opportunity to learn something important with regard to treatment of humans.

Dogs constitute a useful large animal model much closer to human cancer than mouse models for example. The trial was approved by FIMEA and Animal Ethics Committees, but the Gene Technology Board required an 8 day quarantine before dogs could be released from the Animal Hospital. This proved too much for Finnish dog owners as not a single patient could be recruited during the 1.5 years the trial was open, despite several articles introducing the trial to dog owners and veterinarians. There is no rationale for 8 days of quarantine since wild type vaccinia (not selective for tumor cells) has been used in vaccination of 100 millions of humans against small-pox. And in fact viruses related to vaccinia are widely used as rabies vaccines in canines. Thus, a further example of how over-regulation thwarted a promising approach.

Finally, *Dr Nuotto* and *Ms Konttinen* at FIMEA and TUKIJA (the

National Committee on Medical Research Ethics), respectively, made sure physicians will think twice, thrice, even four times before attempting to help patients with gene therapy or stem cells under the Advanced Therapy Directive, as will be discussed in more detail in the "Trial versus treatment in court" chapter.

## Is there a way forward for personalized therapy with advanced therapeutics?

In the current regulatory climate in Finland, I don't think there is a way forward for personalized therapy with oncolytic viruses under the EU Advanced Therapy directive (EC/1394/2007, see "Treatment instead of a trial" chapter). Local interpretation of the directive is very much up to national bodies and I wouldn't be able to comment on other countries, but with regard to FIMEAs position it is impossible to marry their most recent version of the production requirements with the condition of treating on a "non-industrial scale" defined by one FIMEA regulator as 15–20 patients at most, because the per patient cost is too high. However, FIMEA has ensured safety since patients are effectively protected from possible adverse events since they won't be treated. Patients will die of their cancer and even if some of these deaths could have been prevented or post-poned it is not the regulators' concern. If you have incurable cancer today, you cannot wait for the drug to become eventually approved a decade later. I still get e-mails and letters weekly from patients asking to be treated with oncolytic viruses, but I have stopped answering since there is nothing I can say to help them.

Further, the incredibly unpredictable behavior of FIMEA, including the surprise in the form of a police investigation following 5 years of peaceful and transparent interaction, will discourage and frighten physicians in the entire EU. In the totalitarian societies of the previous millenium it was quite common for citizens to just disappear but in modern democratic societies people have come





to expect that if they openly communicate with the government, including regulators, they should be safe from persecution by the police. Not so, however, in this case, where the treatment program was first suggested by a Department Head of FIMEA, FIMEA had approved and audited virus production for ATAP, dozens of interactions with FIMEA and other government bodies took place, and several meetings with FIMEA were well documented with official minutes. These meeting minutes describe how we disclosed all available data from the treatment program including the scientific articles describing the results.

We even wrote an article about ATAP for their magazine "Sic!", following invitation by FIMEA.[240] The article described in detail the difference between treatments and trials, and what ATAP was about, and it was even edited by a FIMEA Chief Physician. Despite all these interactions, FIMEA's *Dr Esko Nuotto* asked the police to launch an investigation and even volunteered to act as "witness". He showed remarkable activity in propagating the case, printing out newspaper articles and interviews of me, underlining passages, and sending them to the police, claiming that the journalists' texts, often provocative as they are, prove his point. He proposed an unusual interpretation of Finnish law, claiming that the case would not expire as long as there is less than 2 years from any of our publications on ATAP instead of the typical legal interpretation.

Personally, I don't think this sort of arbitrary behavior by government officials should happen in open, developed, democratic societies. All it required was one man with a strong opinion, who decided to organize the e-mail to the police (the letter was signed by *Dr Nuotto* from FIMEA and Ms Konttinen from TUKIJA). Even if he might have reconsidered the issue later, he obviously could not retract his investigation request without losing face and thus had to stand behind his message. The police took 18 months to decide what they want to do, and in the end their conclusion was almost one to one the statement of this one man.

The prosecutor *Mari Mattila* took 6 months to decide that *Dr*

*Nuotto's* statement, even if it was different from the several dozen previous opinions of FIMEA, was the new truth. According to many lawyers involved, the case is absurd because of our dozens of prior contacts with FIMEA. We assembled these interactions into 499 pages of pre-examination material but to no avail. Maybe the prosecutor didn't have time to look at the material or perhaps she just couldn't understand the difference between a treatment and a trial. She chose to believe her governmental colleague's opinion instead of looking at the data. Thus all the government officials involved were taking a common stand, not because of the evidence, but because they are government officials.

## Trial versus treatment in court

The police were unable to tell the difference between treatment and trial, and with a governmental colleague telling them that ATAP was the latter, they passed the ball on to the prosecutor. The prosecutor had no more medical expertise than the police and thus passed the ball on to the court. Then, in September 2014, after more than 2.5 years since the e-mail from *Dr Nuotto* to the police, the court hearing began.[241]

Demonstrating that all of my idealism had not been lost in the previous 2.5 years, I managed to be shocked by the testimony of *Dr Nuotto*. He had done his utmost to prepare, including googling for "new evidence". Nevertheless, he was not able to demonstrate which part of our publications showed that the treatments were a trial, other than forcefully repeating his opinion, and the notion that "in unclear cases FIMEA (ie. *Esko Nuotto*) decides what is a trial and what is treatment." He criticized us for "not openly disclosing to FIMEA our intents", but on the other hand he remembered that I had given a lecture at FIMEA in November 2007 on this particular topic, and that basically the entire FIMEA had been present, based on the head count. He also remembered discussing with me immediately after





the lecture, and telling me that "doctors cannot be accused for giving treatments" and that "treatments need no approval from FIMEA". He also admitted not having read FIMEA's own journal Sic!, where we had published a detailed article on ATAP in 2011.[242] He did not feel that my written statement to FIMEA in 2009, regarding the production requirements for oncolytic viruses, where two of our manuscripts had been included, was enough of a disclosure of what we were doing. Neither did he feel that the annual ATAP safety reports submitted to FIMEA, nor the sit-down meeting we had had in 2011 with FIMEA, where he had himself been present, and where I had shown dozens of slides on ATAP data, were of sufficiently detailed nature to disclose the details of the treatments and our plan to publish the data, even if those publications were attached to the written materials.[243]

It was discovered that *Dr Nuotto* was enrolled in another legal argument relating to clinical trial regulations. In an issue relating to trial patients right to withdraw consent, he had taken a view disctinct different from the Parliamentary Ombudsman (the governmental body responsible for oversight over public officials)[244] and the Data Protection Ombudsman.[245] As a consequence, the Helsinki and Uusimaa Hospital District had written a complaint about him, saying that *Dr Nuotto's* creative interpretation of the law is causing them to lose trials and thus costing them money.[246]

*Dr Nuotto's* testimony and his tendency for creative interpretation of the law and trial regulations result in harmful consequences to medical professionals in Finland and beyond. For example, in Spring 2012, when he was "annoyed with ATAP",[247] he did not decide to advise us to stop treating patients, nor did he order an injuction on ATAP, but instead he decided to ask the police to investigate. His testimony, as all other court materials, are publicly available.[248] However, what became clear in court was that he did not understand FIMEAs own Procedures.[249] Prior to contacting the police, he should have first talked to FIMEAs lawyers. The outcome of the court case[250] suggests that if he would have followed FIMEA's

Procedures, the case could have been avoided, because the facts were unequivocal regarding the legality of ATAP.

Even though his testimony left much to be desired with regard to understanding of science and medicine, or FIMEAs own rules and procedures, I was impressed by his political skills, no doubt deriving from his 2 decades working inside government. For example, we had attempted to bring other people from FIMEA to testify, to ensure that it would be clear that many people at FIMEA understood the nature of ATAP. However, we soon noticed that FIMEA had closed ranks against the outside world, and there was little interest in providing an opinion contrasting with *Dr Nuotto's*.[251] One could argue that FIMEA's job should relate more to the interests of patients or society and less to protecting colleagues but I'm sure this is naïve thinking. The law of omerta prevailed.

*Dr Nuotto* had the prosecutor bring in *Dr Ali Bardy*, his predecessor, from whom I had initially received the suggestion for treatments with oncolytic viruses ("Treatment instead a clinical trial" chapter). He had forgotten all discussions with me, including his suggestion for "feeding iron nails to patients", but we refreshed his memory with some e-mails that remained from our interactions.[252]

Another deft move was to have the initial letter to the police signed also by a representative of another government body, National Committee on Medical Research Ethics, TUKIJA. The prosecutor brought in the general secretary of TUKIJA, *Outi Konttinen*. This is when the hearing started to turn into a farce. Ms Konttinen first explained that – as requested by *Dr Nuotto* – TUKIJA had read through one of our ATAP articles, and found it clearly a description of a clinical trial. However, when she was questioned what is the difference between a trial and treatment, she did not know. She had never heard of retrospective case series studies and was unfamiliar with the entire concept of epidemiology. She pointed out some parts of the article which in her opinion were evidence that it was a trial. In one figure she pointed out that there was a control group, but when we made her read the figure legend, she





realized it was an experiment done with Syrian hamsters in the laboratory.[253]

In the opinion of *Ms Konttinen*, if physicians summarize data in figures or tables, it is clear evidence of the subject matter being from a clinical trial. When we had her look at three other articles from Finland, which described treatment series or case reports, she classified all of them as clinical trials. It is amazing that a person with so little expertise in medicine or research can be the general secretary of the highest national body on research ethics. Even in the name of TUKIJA there is the word "Medical", so one would assume a basic level of medical knowledge. As *Ms Konttinen* was quick to point out, she does not have a medical degree (she is a social scientist), but this makes it even worse. An untrained person with no knowledge about medicine, clinical research or science is acting on behalf of the government to convince the police and prosecutor that something she does not have even a basic understanding about is nevertheless against the law.

*Ms Konttinen* did, however, attempt to compensate for her ignorance by being proactive. The session was running late, my wife was on call, and when I stepped out of the room to make some calls to organize a babysitter for the kids, *Konttinen* immediately pulled out a sheaf of printouts, evidently from one of my student's theses (where I was not even an author). She wanted to have this included as new evidence that I had been doing a clinical trial without a permit. I think all present were astounded by this show of initiative on part of a witness. Personally I marveled that for both of the prosecutor's key witnesses (*Nuotto* and *Konttinen*), the main source of information was the internet. The paperwork officially submitted to them at FIMEA and TUKIJA they had not read, did not understand or had forgotten about.

What would have been an alternative course of action for *Ms Konttinen*? According to Finnish law, governmental bodies are required to hear both parties before writing statements. However, TUKIJA or *Ms Konttinen* never contacted me, she just signed the letter which

asked the police to investigate. In contrast, *Dr Nuotto* did contact me, but only after he had already obtained TUKIJAs support for his case. In fact, it turns out *Dr Nuotto* and *Ms Konttinen* had had a series of meetings in the last parts of 2011, while *Nuotto's* e-mail to me was in January 2012.

Not being a lawyer, I never understood how *Dr Nuotto* and *Ms Konttinen* were able to launch the investigation, as representatives of TUKIJA and FIMEA, and then act as witnesses. To me it was clear that they had staked their credibility on the investigation, and if the result would be no conviction, then they would have made a major mistake, taking into account the consequences to the parties involved. The consequences include 2.5 years of purgatory for the accused, €229 958 in legal costs, and the fact that the concept of treatment under the EU Hospital exemption suffered a lethal blow and thus many patients who might have benefited from oncolytic virus were not treated.

To counter the prosecutor's witnesses, we had a number of people on the stand. The Dean of the Medical Faculty, a Professor of Legal Medicine, a CGTG member, a government representative with whom I had discussed ATAP in 2006, and a radiologist who had given some of the injections to the patients. In addition, I was heard for almost a full day, and poor *Dr Timo Joensuu,* who was being accused for being "accessory" and "providing me the premises for the crime" was heard for half a day. Then we went through a few dozen documents. Taken together with closing statements, we spent 5 days in court. Then, there was an agonizing 4 week wait for the decision.

It was a bit anticlimactic to finally receive the judge's decision. The case was won, with a huge margin. The judge *Riitta Savolainen* had prepared well for the case, she understood the difference between a treatment and a trial, she agreed that the last article of the Declaration of Helsinki requires physicians to publish results of also treatments, not just trials. She did not give much weight to *Nuotto's* and *Konttinen's* opinions, since they had been unable to identify anything in our ATAP articles that would have indicated





that they were in fact a trial, not a series of patients treated with experimental therapy.

The underwhelming aspect was that all of this information had been available already in 2012, and if *Nuotto* and *Konttinen* had had expertise in the issues, or if they would have been willing to listen to advice from people who did, they probably would not have initiated the police investigation. Certainly by the time the pre-examination ended in September 2013 all of the relevant facts had been assembled and thus the prosecutor could have stopped the process then.

A cynic could speculate that one explanation for *Nuotto* and *Konttinen's* behavior could be that they did know they would lose but they were annoyed by ATAP[254] and thus wanted make sure no one does it in the future. Even if the case was overwhelmingly won, the judge ordered the government to cover only €73 801 of the legal costs, leaving us with more than €156 000 of legal bills. Plus the process had taken more than 2.5 years during which I had been unable to find employment as a scientist. After the decision there were 7 more days of limbo before we heard that the prosecutor is not going to appeal.

## Epilogue

In theory, there is something good that could come out of the legal case. Finland is now the only country in the world where the legality of giving experimental therapies and publishing the results has been tested in court and the result was clear. Therefore, if someone is crazy enough to try it again, there would be a legal precedent.

However, in the meanwhile, I have had a hard time finding employment as a researcher, and grant funding to my research group has decreased. These things might be coincidence, due to the unpredictable nature of science funding, but given our tremendous productivity scientifically, a connection to events described here is not improbable as gossip and rumors spread rapidly. It is clear that the pending court case prevented me from becoming employed as a scientist.

At one Finnish foundation whom I had told about the court case, when confronted by the rumors they had heard, I was several times ranked as number 1 by internal and external experts, but each time the foundation selected someone else for the professorship. I obtained a prestigious professorship in Germany, but when I told them about the police investigation which they had already heard about, I was informed that I cannot become a civil servant if I am being suspected of a crime related to my work. By the time the trial was over, the position had expired. Soon after – and only after – the trial was over, I was appointed professor at the University of Helsinki.

After the trial *Dr Nuotto* was quoted by press[255] as saying that the case forms no legal precedent[256] to experimental therapies in Finland, in one of his novel legal interpretations. He also said that the prosecutor was wrong in not taking the case all the way to Supreme Court.[257] Finally, he proved that he still had not learned the difference between trials and treatments, for example in the context of their regulation.[258] In fact, despite hundreds of pages of legal text





accumulated during the police investigation he had initiated, he claimed that there is no such thing as experimental therapy.[259]

To understand if *Dr Nuotto's* position was his own or FIMEA's, we formally requested an audience with the Head of FIMEA, but were unsuccessful.[260] Thus, we don't know if they mean to launch a police investigation every time a physician publishes data from experimental therapeutics. What is clear is that they do not give advice to physicians regarding their position on such issues. Eventually, one of the FIMEA lawyers called my lawyer, *Klaus Nyblin*, and indicated that according to FIMEA leadership, *Nuotto's* position was his own, and that his statements as quoted in the aforementioned article were not necessarily the position of FIMEA.[261] The FIMEA lawyer said that they have too much other work to be able to meet over something like this. Thus, they have time to launch legal cases which take thousands of hours of work, and affect people's careers for years or permanently, not to mention the impact on patients, but they don't have 30 minutes to discuss if experimental therapies for cancer and other diseases can ever be used in Finland in the future. I doubt Finnish citizens will agree with FIMEAs priorization.

Of note, even if this book has focused on cancer, many other diseases are regularly treated with experimental therapies as well. In 2014, there was a major Ebola epidemic in West Africa. In an interesting contrast, in the same issue of the same journal where *Dr Nuotto* ranted against the court's decision which went against his opinion, there was also a long piece on experimental therapies being used in treatment of Ebola, and how the World Health Organization WHO recommends their use because there are no effective routine therapies available.[262] In fact, Ebola is quite similar to metastatic chemotherapy refractory solid tumors, with the possible difference that the mortality in the latter case is 100% while in Ebola it is fortunately much less even if untreated. These are just a few examples. There are plenty of diseases out there which could be treated with scientifically sound approaches, if not stifled by overregulation.

In contrast to my own fortunes, gene therapy and oncolytic viruses are making tremendous steps forward. In November 2012 *alipogene tiparvovec* (*Glybera*) became the first approved gene therapeutic outside of China. The agent is an adeno-associated virus coding for lipoprotein lipase, a protein which is missing in lipoprotein lipase deficiency, a rare but deadly disease lacking any other current treatment options.[263]

Although eventually resulting in a landmark in the history of medicine, the EMA approval of *Glybera* is more farce than a success story in my opinon. Before approval, it had been three times rejected and the original sponsor of the drug had gone bankrupt.[264] Thus, although the approval of the first gene therapeutic in the EU is positive on a general level, the way it happened is probably quite discouraging to putative investors in gene therapy. The story has been detailed in manuscripts freely available on the web.[265] *Bryant et al.* is particularly informative, and perhaps because it is written by non-Europeans, gives interesting insight into the drug approval process of the EU.[266]

However, one angle of the *Glybera* story I have not yet seen discussed publicly is the biotech perspective. Four rounds of vacillation by the EMA resulted in the bankruptcy of Amsterdam Molecular Therapeutics, before EMA finally gave approval to *Glybera*, which was rescued by a new company Uniqure.[267] Isn't there something terribly wasteful about this process? Shouldn't patients, physicians and investors be saying that the process should be less tortuous? In the end all of us are influenced since the cost of drug development is reflected in the cost of new drugs. Also, it can be discussed if the approval of *Glybera* can be called a success since regulators require the enactment of a pharmacovigilance program, a risk management plan, biannual periodic safety update reports, and the formation of a registry of every patient dosed. All such additional aspects, never required for conventional drugs, will increase the cost of the drug, decreasing its use, reducing the interest of companies in taking new technologies further. One





alternative for avoiding unfair discrimination against gene therapy would be regulatory support mechanisms so that the additional efforts required by regulators would not fall on the Sponsor.

With regard to Oncos, their first trial with a GMCSF encoding oncolytic adenovirus has been completed.[268] The data is as expected from ATAP and Oncos is eagerly awaiting further funding in order to take the approach forward.

In the broader oncolytic virus field, a randomized phase 3 trial was finally completed also outside of China. In March 2013 Amgen reported that their global trial with *talimogene laherparepvec* (T-Vec) had met its primary endpoint, durable response rate.[269] Progression free survival data was also positive as reported at ASCO 2013 and 2014.[270] On April 28th 2015 FDA voted 22–1 in favor of approving T-Vec.

These developments could lead to product approval by FDA and EMA later on although decisions are pending at writing of this text. T-Vec, an oncolytic herpes virus, has the same arming device (GMCSF) as many of the viruses we used in ATAP, including CGTG-102 tested in Oncos' trial, and thus its success supports the results seen in ATAP.

Thus, the future of gene therapy, including oncolytic viruses, is looking very bright indeed. Following two decades of promise the field is starting to justify the expectations placed in it. Importantly, many of the basic concepts theorized in the laboratory have proven valid also in patients. However, there is much to do to be able to help each patient with currently incurable cancer. My personal belief is that each patient should be treated individually as no shoe fits every foot. It is widely recognized that the tumor of each patient is distinct from every other tumor and each patient is also different from all other patients, and in my mind it logically follows that also treatment should be. ATAP was an attempt to do this in the context of oncolytic adenoviruses, and although the program survived only four years, and many unfortunate things occurred afterwards as described here, perhaps something similar will be possible in some other place, at some other time.

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# Appendix

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Oncolytic viruses for treatment of cancer

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When I heard about the concept, I immediately loved it. Everything I had learned about medicine, cancer biology, genetics and oncology indicated to me that this was a potent approach currently completely untapped. I figured that since we have been unable to cure most metastatic solid tumors heretofore, something completely different needs to be employed. Realistically, "magic bullets" are probably not easy to find and therefore something that can be combined with other therapies, for enhanced synergy without overlapping adverse events, would be appealing.

Oncolytic viruses kill cancer cells by replicating in them. Normal cells are spared since the virus is modified so that the virus doesn't amplify in them. Oncolysis is highly immunogenic and in fact results in a personalized cancer vaccine for each patient. I love the pragmatism of the approach: whichever epitopes (features of the tumor cell) are most relevant immunologically for each tumor, will be released by oncolysis. For immunity – as opposed to tolerance – a "danger signal"

is important, and adenoviral oncolysis excels in this regard.

How did I get involved in cancer research? I still remember the moment in the second year of medical school when I realized that the biggest unmet clinical need in medicine is metastatic cancer. I'm an incurable passionate optimist and a sucker for good-versus-evil stories. Cancer is the most devious imaginable enemy and oncolytic viruses the unlikely young hero from out of town. The hero struggles initially but eventually comes of age and wins the day. Along the way there are epic battles, love-and-loss, betrayal, even despair. I guess I had been searching for a mission and now I had discovered it. Initially, I thought understanding cancer genetics would be key for curing the disease and therefore that was what I did for my PhD. However, I realized that genetics was only a first step, and that it needed to be applied in a more pragmatic approach to help patients.

My plan became to use oncolytic viruses to cure cancer. Maybe not every patient but at least some. Later on I came up with a more concrete goal: since we can't eradicate cancer as a disease, as it is a side effect of evolution (mutations in genes allow evolution, and they can also give rise to cancer), and since all of us must die one day, lets at least try to make sure no one under 65 dies of cancer. I realized this was unrealistic but perhaps having an ambitious goal would allow some concrete, if more modest, actual steps forward.

After completing medical school and a concurrent PhD, and recuperating from the associated burnout, I was ready for the next step. I considered my post-doc group carefully and decided on *David Curiel's* group in Birmingham, Alabama. I liked his focus on adeno-virus, which I thought was the most promising cancer gene therapy agent, and the fact that there were about 80 people there, giving critical mass and indicating sufficient funding. Also, Birmingham is a great city for a lover of music, food and the outdoors.

Since my goal was taking the approach to humans, the fact that there were trials ongoing there was intriguing. However, I would learn that trials are in fact incredibly difficult to make happen. To





a lay-man it seems obvious that if there is an unmet clinical need, and a promising technology, it should be taken from the laboratory to patients. There is little point in preclinical research unless it leads to clinical application. Regulatory bodies are sometimes blamed for thwarting progress but this seems a bit unfair since they are just doing what we as society have mandate them with. Nevertheless, at the same time we are unhappy with both the slowness of clinical translation and the cost of new drugs. As if it weren't logical that the more expensive and slow each trial is, the costs will have to be compensated in the prices of the few drugs that make it through all trial phases into products. Pharmaceutical companies are viewed as greedy but at the same time regulation has made sure that only companies can do trials. This is painfully obvious in the EU where the clinical trials directive was written by the "Enterprise and Industry" directorate of the Commission, instead of for example "Health and Consumers" or "Research and Innovation".

In Birmingham we made swift progress in building and analyzing a new generation of oncolytic adenoviruses in the laboratory. There is a wonderful National Cancer Institute (NCI) mechanism which funds for the Good Manufacturing Practices (GMP) quality production, toxicity and biodistribution testing of novel therapeutics. We were fortunate to obtain several of these awards while in Birmingham and eventually three clinical trials resulted.

After 3 years in the US, I was becoming almost more American than Finnish so I had to make a choice. At the time Finland was a great country to do trials, but I also wanted to give clinical work a try since I had realized that to make a real clinical impact, I had to have a specialty. In Finland I could get both medical and radiation oncology in a combined specialty in five years. Thus, I moved back and embarked on specialization, while at the same time setting up my laboratory at the University.

We were doing preclinical work but all the time the goal was getting into humans. Unfortunately, clinical translation became significantly more difficult with the EU clinical trials directive

(2001/20/EC) in 2004. The directive attempted to harmonize trial regulations by raising the bar throughout, so that all trials now had the same requirements as multicenter transnational phase 3 trials. While this might sound like a good idea, it made academic, investigator initiated early-stage trials practically impossible, especially when they involved new treatment agents. With regard to oncolytic viruses, production became a nearly unsurmountable obstacle since industrial manufacturing was required even for phase 1 trials. Since preclinical models are poorly predictive ("useless", a sceptic would say) of patient data for many human-specific agents including oncolytic adenoviruses, fast development would require a flexible bench-to-bedside-and-back process, which is not possible if every trial needs to employ and industrial production process.

The tightened regulatory environment became excruciatingly clear when I tried to get an oncolytic vaccinia virus trial approved in Finland in 2005. The product had already been approved by the US FDA for phase 1 trials but the Finnish FDA (FIMEA) did not think production quality was sufficient and after 2 years of discussions they gave a final rejection.

The NCI mechanism that we had employed in the US is not restricted to American investigators and I was able to get a virus produced for a trial in Finland. However, it became clear that the production level applied in the US for phase 1 academic trials (some people call it "GMP light") would not be sufficient in Finland. The FDA (but not FIMEA) differentiates between trials likely to be part of the bench-to-bedside-and-back process and industry trials which usually aim at proceeding to phase 3 trials. With regard to the former, developing an industrial production process would be prohibitively expensive, while for the latter having this in place early on can help the company proceed faster.

It is unfortunate how rarely patients are considered in discussions about clinical trial rules. Regulators view trials as something which is in the interest of companies while researchers are interested in meticulously forwarding the science. However, patients with





incurable disease would need something today, not after ten years. The fewer trials are out there, the fewer patients have access to experimental therapeutics.

Although our NCI award covered the most expensive aspects of a phase 1 trial, it did not cover the actual treatments, since in the US clinicians are often able to get NIH grants for trials. However, in Finland no such mechanisms exist and I was only able to collect about 10% of the required amount through Finnish grants. In one EU application a reviewer pointed out that it would be a waste of money to fund a trial since they are within the realm of companies.

Through my frequent interactions with regulators I learned of the Advanced therapies directive (EC/1394/2007), which defines the "hospital exemption", allowing, or even encouraging, individualized patient-by-patient treatment with gene therapy and stem cells. In essence the exemption determines that patients can be treated outside of clinical trials under the sole responsibility of the physician. Nevertheless, national bodies are required to oversee these treatments by regulating production and by requiring adverse event reporting. I started discussing with authorities, lawyers and ethics bodies the possibility of treating patients in what we called the Advanced Therapy Access Program (ATAP). In fact the approach was initially suggested by a department chief at FIMEA, who pointed out that the World Medical Association Declaration of Helsinki (the globally accepted ethical framework for clinical research) article 35 basically requires physicians to look beyond routine therapies when the patient's disease cannot be cured with available modalities.

We set up a production suite at the University and the first patient was treated in November 2007. Having established safety with the first virus, we next moved to enhance efficacy. It had become evident that pure oncolysis was unlikely to eradicate advanced tumor because of intratumoral complexities such as high pressure, necrotic areas and non-tumoral (stromal) areas within tumors, all of which would compromise intratumoral viral dissemination. One way to overcome this is arming of the virus with an

immunostimulatory molecule; an immune response against the tumor would help in eradicating non-infected malignant cells both locally and also at metastatic sites. I knew enough of immunology to figure that adenovirus was a perfect immunological agent due to its innate immunogenicity and co-stimulatory activity.

The first virus in this family coded for granulocyte-macrophage colony stimulating factor (GMCSF) which had been effective in cancer vaccine studies. The virus proved to be safe and there were several striking examples of efficacy, including complete disappearance of all disease in some patients. Another transgene we employed was CD40L, a molecule which has several properties appealing for cancer immunotherapy. This virus also provided a striking example of the power of ATAP in full swing. It took a mere 10 months from the day when we started making the virus to the first patient treated.

One of the most useful aspects of ATAP was the rapid learning curve. If we learned something important in a patient or at a scientific meeting, we could apply this knowledge with the very next patient. ATAP had begun as an academic endeavor but the University wasn't actually too happy about it. Many colleagues felt that production, patient treatments and clinical research should not be done at the University. Also, with the safety and efficacy data mounting in ATAP, it was becoming clear that we needed to move to clinical trials. ATAP is in no way a replacement for trials and only through the latter can we gain formal evidence of safety and efficacy, and only through developing a product can we give a larger number of patients access to the technology.

Based on my earlier experiences, I knew for a fact that a trial could not be done in Finland with public money and thus the only solution was companies. For corporations to have an interest, the intellectual property needs to be protected, so that they can get their money back in case their investment proves successful. With this in mind we submitted our first patent in 2005 and tried to get companies interested but without success. I was told by many people that I should found my own company. I had nothing against that except





that one person's resources are limited, regardless of how hard he works. Eventually, *Pekka Simula* was suggested by a mutual friend, resulting in plans for Oncos Therapeutics Ltd being drawn up rapidly. Oncos raised 4 million euros from HealthCap in 2010 and the Finnish government matched it through TEKES, which by the way is an awesome organization and certainly the best reason to try set up a biotech company in Finland. Without TEKES, I would advise setting up a company in some country with a venture capital community and a network of biotechnology professionals. However, the wonderful mechanisms and staff of TEKES make up for these deficiencies. Rewinding to 2010, 8 million euros seemed like a lot of money but in fact it is barely sufficient to treat about 20 patients in phase 1 trials.

ATAP was transferred from the University to Oncos but its end was already nearing. The Directive that had inspired ATAP was finally integrated into Finnish law and FIMEA regulations. Production requirements were discussed in the Social Affairs and Health Committee in Finnish parliament, as the directive in fact makes a clear distinction between industrial and non-industrial production. Patients had heard about the possible impact of full GMP on ATAP and they had collected 8000 names in a petition to keep the treatments going. Since there had been several programs on TV featuring patients who had benefited from ATAP. The committee asked to see me and I gave them a short presentation flowed by lively discussion.

Oncos and FIMEA communicated closely for a production license but eventually no virus was produced according to the new standard as the amount of money spent subventing treatments would simply not justify the information gained. Oncos is a small company and all of its resources were needed for getting clinical trials started. For a while we were able to use our earlier production lots but this temporary permission ended in Spring 2012. Keeping in mind that we had been using 10 different viruses, and the whole idea in ATAP was personalized therapy, production of a single lot of virus would not

have allowed ATAP to continue. Also, it can be discussed how many patients can be treated with one virus under the hospital exemption for it to still remain patient-by-patient. Thus, oncolytic viruses and other forms of viral gene therapy may not be compatible with the exemption unless production requirements can be relaxed.

Thus, in Spring 2012 ATAP was closed but three clinical trials had been initiated by Oncos. My own future prospects probably involve a need to make some choices. Running the research group, helping Oncos set up trials, seeing patients and trying to be a father to three children is clearly too many things. If I knew which one of my three jobs is the best way to help the young hero to beat the enemy, I would surely choose that path.