Akseli Hemminki

Selected pages

# CROSSING THE VALLEY OF DEATH

## With Advanced Cancer Therapy

” On a journey to make the world a better place, Dr Hemminki discovers he has to fight more than just disease. He also comes to understand it is not just the patients that have to make sacrifices in the fight to advance medical knowledge.”

# CROSSING THE VALLEY OF DEATH

## WITH ADVANCED CANCER THERAPY

**Akseli Hemminki**


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## Contents

# 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.

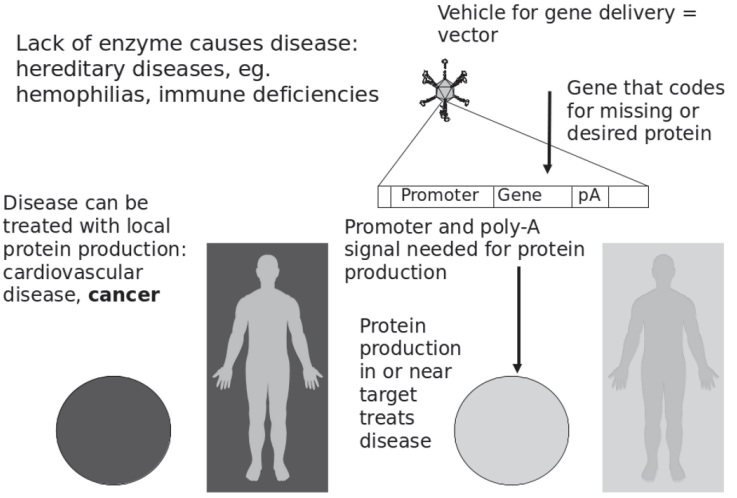
## Genes -> proteins -> function

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,

**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

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.

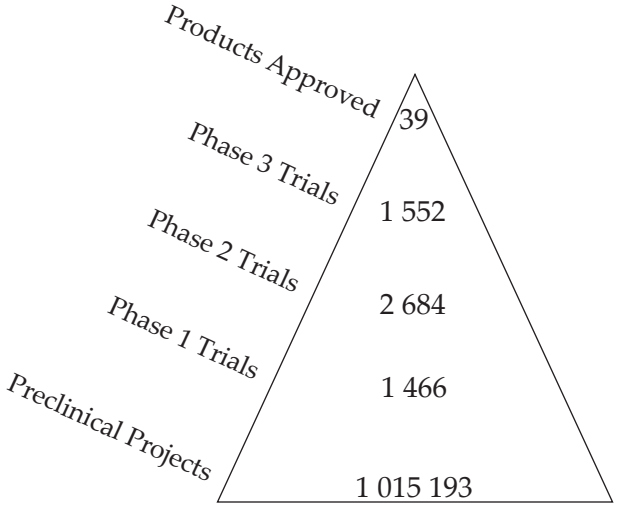



**Figure 9. Is there a Valley of Death?**

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.

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

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

## 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.

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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"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 overregulation by various government health authorities."

*Carl June,* MD

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

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