Dankesrede

von Prof. Craig C. Mello

anlässlich der Verleihung des Paul Ehrlich- und Ludwig Darmstaedter-Preises 2006

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Es gilt das gesprochene Wort!

Meine Damen und Herren, ladies and gentlemen, my dear family and friends

It is such a great honor to be here today with Dr. Andrew Fire to have our research on RNAi recognized with the Paul Ehrlich and Ludwig Darmstaedter prize. Science is an exciting, even beautiful, human enterprise involving not only those who do the science but also those who support it, constructively criticize it, and help it to move forward. On a personal level I am sustained in my work by the love and support of my family, especially my wife Edit. And of course by my daughter Victoria who I will tell you more about in a moment, and my mother-in-law Aniko, who are all here with me today.

I'd like to thank the Ehrlich foundation for playing the extremely important role of promoting the public understanding and appreciation of basic science. Through your efforts you remind us of the amazing progress we have made in medical science during the past century, and you promote awareness of exciting new discoveries that hold promise for unparalleled medical advances in the future.

In preparing my remarks for today, I spent some time looking back on the history of Paul Ehrlich and his contemporaries. This process of looking back over the years at where we've come from is humbling, awe inspiring, and provides some important cautionary lessons.

First the humbling and awesome part: it is simply amazing what Paul Ehrlich accomplished more than 100 years ago. Starting from the simple premise that pathogens might have unique surface receptors (or sidechains as he called them) he envisioned drugs (Zauberkugel/magic bullets) that would attack the parasite invader leaving the host cells unaffected. Amazingly, he and his research group were able to systematically test hundreds of chemical compounds for these special 'magic' properties, and succeeded in finding compounds effective against pathogens, most notably the syphilis spyrochete.

One of the most important aspects of this story is the inspiration it gave to succeeding generations of medical researchers. Ehrlich demonstrated with his 'can-do' attitude that a systematic screening approach can find useful new drugs. In short he developed the engine that still drives the pharmaceutical industry to this day. Perhaps one of the biggest challenges he faced was a psychological one, never mind the daunting logistics of collecting thousands of compounds, developing assays and testing them. He did this work based on his conviction that beneficial compounds exist and need only to be found through screening. Ehrlich's example made believers out of his colleagues, (out of all of us), and inspired generations of researchers to vigorously and systematically pursue their ideas.

I can't help but think that two young contemporaries of Paul Ehrlich, Frederick Banting and Charles Best were inspired by his example. These young Canadian researchers, in work begun in 1921 just 6 years after the death of Paul Ehrlich, discovered the hormone insulin. They succeeded where numerous others before them had failed. I'll say a few more words about the story of Banting and Best, because their story exemplifies a new kind of magic bullet, and their work has touched my own career and family.

My five year old Victoria who is here today has juvenile diabetes and receives insulin every day of her life. Thanks to the work of Banting and Best and subsequent generations of biological scientists she is thriving. Insulin is not a cure for Diabetes; rather it is a magic bullet that replaces something that the body can no longer produce itself. Victoria wears a pump that delivers recombinant human insulin subcutaneously.

Before it saved Victoria's life, the story of insulin had already touched my own life by inspiring me to pursue a career in molecular biology. I first learned about insulin when a neighborhood child developed diabetes. I remember discussing at our dinner table with my parents that this child was being treated using insulin purified from the pancreas of animals. A few years later, when I was in high school, I read in the newspaper that the human insulin gene had been cloned and inserted into a bacterial cell. I was amazed that the bacterium could read the human genetic code, put the amino acid subunits together, and produce a functional human protein. This biological fact, and the doors that this new technology opened, captured my imagination and propelled me toward my present career.

Prior to the work of Banting and Best, several clues pointed toward the pancreas as the important tissue affected in Diabetes. Notably, this field began 1869 with the dissertation work of a young German scientist Paul Langerhans who recognized a specialized region in the pancreas now known as islets of Langerhans. This region was recognized as one that is damaged in diabetic pateints. Unfortunately the pancreas, in addition to its production of hormones including insulin which are secreted into the blood stream, also produces digestive enzymes. Attempts to extract curative agents from pancreatic tissue were doomed to failure by the presence of the digestive enzymes that rapidly destroyed the insulin during the extraction procedure.

Frederick Banting was a skilled young surgeon and he followed up on observations that ligating the excratory ducts of the pancreas in animals could lead to atrophy of the corresponding regions of the pancreas involved in producing the digestive enzymes. After surgically sealing off these ducts and waiting a suitable period, and then harvesting the remaining healthy tissue from the pancreas, he and Charles Best were able to obtain an extract in which the insulin hormone was stable and thus could be purified in subsequent enrichment steps. For more than 50 years after Banting and Best's discovery, diabetic patients relied on insulin extracted from animal tissues. While this was a life-saving therapy it resulted in complications and immunologic responses.

Not until over twenty years after its discovery and development as a therapy for diabetes did we finally learn the molecular nature of the insulin protein. Insulin was the first protein whose amino acid sequence was determined, thanks to the brilliant work of Frederick Sanger, work for which Sanger won the nobel prize in 1958. Incidentally, Sanger also shared a Nobel prize in 1980 for his work in devising another ingenious method for sequencing the DNA which encodes the recipe for insulin and all the other proteins that make up our bodies.

In 1922, just one year after Banting and Best began their research, purified insulin was tested on the first human patient. Children who were on their deathbeds were given insulin and with daily injections were cured almost miraculously. Banting, Best and their co-workers were a world-wide sensation overnight. They were overwhelmed by the outpouring of gratitude from thousands of diabetic children whose lives had been saved by their discovery. The son of Dr. Best related that "a difference of the attitudes of patients treated with insulin compared to those treated with penicillin (or other drugs) is -- that diabetics are reminded every day of their gift of life."

The story of insulin is an amazing story about the triumph of medical science. And yet it is an unfinished story. Insulin is not a cure for Diabetes. Last year the Ehrlich foundation recognized basic stem-cell research (cloning techniques) that may one day be part of a real cure for Diabetes and numerous other conditions.

The story of insulin is also amazing because it begins in Paul Ehrlich's era and highlights every major advance in medical science since his time. Insulin was the first hormone isolated and used as a therapeutic. It was the first protein whose amino acid sequence was determined. The insulin gene was the first human gene to have its nucleotide sequence determined, and insulin was the first human protein to be produced in a bacterium for therapeutic purposes.

Today, just one hundred years after the landmark work of Paul Ehrlich, we have in hand the complete genome sequence (the genetic blueprint) of the human, and of numerous other animals. We have powerful gene profiling techniques that allow us to determine which genes are expressed in tumors or in other abnormal cells or tissues. With RNAi we have a tool that allows us to shut down individual genes, with great specificity. This tool is being used extensively in the laboratory to study gene function.

Because of all of this work, we now stand on the threshold of an era of unprecedented medical advances. Recombinant-DNA technology, applied to the delivery of RNA interference, has tremendous potential in both agriculture and human therapeutics. The public needs to be educated about the many potential benefits (and the risks) associated with these technologies. Keeping in mind that we will very likely need these tools to cope with the pressures of environmental degradation, climate change and the many other burdens our growing population has placed on the planet. We will need to make some hard choices in our lifetimes and 'frankenfood' will not seem so bad (when you are hungry) or as I would argue when you better understand it. This same technology has been safely helping children like Victoria for almost 30 years.

Ehrlich developed magic bullets that kill a pathogen leaving the host cells intact. Banting and Best developed a magic bullet (insulin) that replaces a missing function in the body. RNAi provides yet another kind of magic bullet—one that can distinguish bad genes from good genes, knocking down the activity of disease-related genes without disturbing the function of healthy genes in our cells.

We now have the potential to make rapid progress in understanding and developing new innovative therapies, and we will. However, we need the support of our governments and of our fellow citizens to truly realize the potential of this new medical technology. The discovery of insulin provides a telling example, Banting had to plead with Macloud, the powerful department head at Toronto University, for space and funds to do his experiments on insulin. Macloud, to his credit gave him the space and later recognized the importance of the discovery and diverted his whole research team to the purification of insulin, work for which Macloud shared in the Nobel prize for insulin. If not for the opportunity at what amounted to a temporary research position, Banting and Best most likely would not have initiated their study of diabetes. With the coming economic crisis and World War II, it is easy to imagine that this chance at a cure could have been lost for another 20 years, at a terrible cost in human life and suffering.

This is the cautionary part of this story. By not funding basic biological science to much greater levels, ten fold the current spending levels would be a reasonable goal, we are needlessly prolonging human suffering and death. In the United States after doubling the NIH budget in the 1990s the budgets for basic medical research are flat and sinking. I hope that we can work together to educate the public about the bright prospects for medical science and the false economy (and immorality) of not fully funding this field of science.

Finally, in closing, I want to take this opportunity to thank Andrew Fire. Andy has been a tremendous colleague and inspiration to me. We have known each other for 20 years now. We worked closely on the development of DNA transformation technology for C. elegans, work that prepared us for the collaboration that led to the discovery of RNAi. I also owe many thanks to the postdocs and graduate students (from all around the world) who have played and continue to play a central role in the work of my laboratory. Finally, Andy and I would not be here today if not for numerous others, working in plant, animal and fungal systems who have helped to demonstrate the wide conservation (and utility) of the RNAi mechanism.

Thanks again!