COMMEMORATIVE LECTURE

# Imatinib (Gleevec®) as a Paradigm of Targeted Cancer Therapies

**Brian Druker**

*Department of Medicine, Oregon Health & Science University, Oregon, USA*

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It is a great privilege for me to be honored with an award from Keio University. I would especially like to thank the members of the award committee and my nominators for this prestigious award. Cancer is currently the number one cause of death in Japan with more than twice as many people dying from cancer than from any other cause. But as you will hear from my comments today, I am incredibly optimistic about our ability to impact cancer. To fully understand my optimism about the future of cancer research, I need to take you back 100 years, so that you can see the parallels to today.

In 1900, Japanese society was benefiting from and leading the industrial revolution. With jobs being in the cities, instead of in agriculture, people moved in large numbers to the cities. In 1900, Tokyo was the fifth largest city in the world with a population of nearly 2 million people. But, Tokyo had many problems. There was massive overcrowding. There was no running water, no sewage system, and infectious diseases were rampant. In Japan the life expectancy in 1900 was 43 years. If you had a child, they had a 1 in 10 chance of dying before age 4. Pneumonia, tuberculosis, and diarrheal diseases like cholera were the top 3 causes of death, accounting for 30% of all deaths. As late as 1914, there were outbreaks of typhoid fever.

If you went to the doctor, this is what your encounter might be like.

Video 1.
**Voice:** "Next."
**Dr. Ehrlich:** "What you have is a contagious disease, an infection just like any others. I have seen cases where it was transmitted by an inanimate object…. You musn't be disheartened. There are many as badly off as you. Many."
**Patient:** "Will I get well?"
**Dr. Ehrlich:** "You must come here twice weekly for sweat baths, observation, and medical supplies. The treatment consists largely in rubbing yourself with this ointment."
**Patient:** "Tell me doctor, will I get well?"
**Dr. Ehrlich:** "Rub a different part of the skin every night of the week so that no part of the skin is rubbed more than once weekly."
**Patient:** "There is a girl in Munich with whom I am in love…who loves me. We had planned to be married as soon as I graduate. Tell me doctor. Tell me the truth. Can we ever get married…now?"
**Dr. Ehrlich:** "I'm afraid marriage is out of the question now, sir…. You may dress now."
**Patient:** "Does anybody ever get cured?"
**Dr. Ehrlich:** "Of course. There have been many cures… many."

Of course, "Many cures," I'm afraid, was false hope.

Despite the bleak picture, scientists and politicians of the day were incredibly optimistic and were predicting that infections would soon be treatable or eradicated. What led to this optimism was the establishment of the germ theory of disease that held that infectious agents, not mythical forces, caused diseases. The pioneers of the late 1800s and early 1900s had identified the bacteria that caused tuberculosis, and many other bacteriae that caused infections were being identified. Another pioneer, Louis Pastuer, had introduced a vaccine for rabies. There was real cause for optimism as is captured in this next video.

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Dr. Druker is the recipient of the 2007 Keio Medical Science Prize.

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Reprint requests to: Dr. Brian Druker, Department of Medicine, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, L592, Portland, Oregon 97239, USA

Video 2.
**Paper on Desk:** "Cause of Syphilis Discovered."
**Dr. Ehrlich:** "[Names], everybody, come here!"
**Student #1:** "Professor, you called?"
**Dr. Ehrlich:** "Gentleman, it would seem that the germ of syphilis has been discovered."
**Student #1:** "Really?"
**Student #2:** "By whom?"
**Dr. Ehrlich:** "By one Fritz Schaudinn. The German Medical Weekly sent me these proofs for approval. Listen, 'The spirochete pallidum is a protozoan. It is a fine, steeply convoluted filament with 6-14 turns.' It is *decidedly* motile, with forward, turning, and bending movements. Tell me, does that description put your mind to anything else? It is decidedly motile, with forward, turning, and bending movements."
**Student #3:** "Why that's just like the Tyrpanosoma."
**Dr. Ehrlich:** "Right."
**Student #2:** "If the germ has been discovered, there's cause to hope for a cure."
**Dr. Ehrlich:** "Yes, there is hope."

That's precisely the point. If you understand the cause, there is hope for a cure.

The scientific breakthroughs of the 1900s translated into enormous gains against infections. In the early 1900s, public health measures such as chlorination of water, pasteurization of milk, improved sanitation and refrigeration made our food and water supplies safe.

Antibiotics, not even conceived of in 1900, were introduced in the late 1930s. Penicillin was first used in 1942. In one of the first descriptions of the use of penicillin, a 33 year old woman was hospitalized with a life-threatening pneumonia. She was delirious and her temperature reached 107 ˚F. Treatment of the day consisted of surgery, sulfa drugs, blood transfusions, and they had no effect. As a last resort, her doctors injected her with a tiny amount of an obscure, experimental drug called penicillin. Overnight, her temperature dropped to normal and the next day, she was no longer delirious. She survived to marry, raise a family, and one day, met Sir Alexander Fleming, the discoverer of penicillin. These were magic bullets for treating infections, the likes of which had never been seen before. Physicians were amazed by these drugs as disease after disease fell to these agents.

The other major advance in the 1900s was the introduction of vaccines. I suspect that many of you can remember the polio epidemic of the 1950s. Hospital ward after hospital ward filled with iron lungs. In 1952 alone, there were 10,000 cases of polio reported in Japan. In 1955, the Salk polio vaccine was introduced and by 1965, there were only 50 cases of polio in Japan. Diseases like smallpox have been eradicated with vaccination. Mumps, measles, rubella, the diseases that we all grew up with, are now memories.

In the year 2007, we face new challenges. Cancer is now the leading cause of death in this country. Hopeless encounters between doctors and cancer patients, like the one from the movie clip, are common.

But scientists of today are as optimistic as our counterparts were 100 years ago. That is because in the last decades of the 20$^{th}$ century, cancer researchers established the gene theory of cancer. That is, genes in our cells that lead to cancer have been identified. And like a century ago, where the hope was that this understanding would lead to effective treatments, this is our hope for cancer.

But we have more than hope. We have proof with Gleevec® that tells us that by understanding cancer, we can develop effective treatments. Over the past three decades, cancer researchers have identified the precise abnormality that causes the white blood cells to grow uncontrollably in a particular form of leukemia called chronic myelogenous leukemia. This leukemia accounts for 20% of all leukemias and is characterized by a white blood cell count that is up to 50 times higher than normal. In collaboration with Novartis Pharmaceuticals, my laboratory developed Gleevec®, a drug that completely shuts down the specific abnormality that drives the uncontrolled growth of white blood cells in this disease. In clinical trials, virtually all of our patients have had their blood counts return to normal, and in up to three quarters of our patients, we can no longer detect leukemia cells in their bone marrow. Remarkably, this once-a-day pill has been well tolerated, with minimal side effects. In short, it is a simple, effective treatment that disables the cancer without disabling the patient. Gleevec® is now in use worldwide and today, well over 100,000 patients have been treated. Now, the five year survival is 95% for this previously fatal leukemia. People diagnosed with this leukemia were once told they had 3-5 years to live; now they are projected to live 30 years.

Let me give you an example of a patient who has been helped dramatically by Gleevec®. LaDonna, a retired dietician first came to see me in December of 1999. Her spleen, which should normally be the size of my fist, was as big as a watermelon and pressing on her stomach so that she was barely able to eat, and she was losing weight at the rate of 3-4 pounds per week. LaDonna knew she was dying and that her time was short, maybe only weeks. She had picked out a burial plot and was deciding on the music she wanted played at her funeral. Within a week of starting Gleevec®, her spleen began to shrink and within a month she was restored to normal health. Today, I can no longer detect traces of her leukemia. LaDonna is now spending her time playing with her grandchildren, pictured here, including one she wasn't supposed to meet, a grandson named Will, who was named for her will to live.

Gleevec® has shown cancer doctors that we can develop medicines that are like magic bullets that work quickly and effectively on patients for whom there previously was no hope. Targeted therapies like Gleevec® are now

part of the mainstream. There are now over 100 targeted cancer therapies in clinical trials and over 200 in development. Every drug company's cancer pipeline has moved from chemotherapy drugs to targeted agents.

But just like penicillin does not cure all infections, Gleevec® will not work against all cancers. Think of this as a thermostat that perfectly regulates the temperature between 68 and 72 degrees. If the temperature falls below 68 the thermostat turns on and when the temperature reaches 72, it shuts off. Perfect temperature control. Just like this thermostat, our bodies regulate the numbers of cells that are produced every day, making just enough to replace daily losses. Now imagine the thermostat is broken and is stuck on. The temperature climbs, 72, 80, 90 and higher. Or in the case of cancer, the cells keep growing and growing, forming a tumor. The problem is figuring out what part has broken. Sure, we could replace the thermostat which would be expensive and may not work quite as well. Or in the case of chemotherapy, we could hit the thermostat with a hammer and hope that fixes the problem, but certainly leaves it battered or broken. Now imagine if we could take the thermostat apart, piece by piece, figure out how each part works and just replace the broken part. That's exactly what we did with Gleevec®. But our thermostat has hundreds of parts that can break, and to develop more treatments like Gleevec®, we need to figure out what part has broken in each and every cancer. With this understanding there will be even more hope for cures.

But just like antibiotics are not the only treatment for infections, we need to take a broad-based approach to treat cancer. We certainly need more drugs like Gleevec®, but we also need a better understanding of the power of the immune system so that we can harness it to attack cancer. In addition, we need a better understanding of what places us at risk of developing cancer so that we can develop strategies to prevent cancer or diagnose cancer at its earliest, most treatable stages. This is exactly what Japan has done with their efforts to identify stomach cancer at its earliest stages. These efforts have resulted in an enormous decrease in the death rate from stomach cancer in this country and I congratulate you.

I firmly believe that we have the technology in hand to solve the cancer problem and I hope that I have given you a sense of why I am so optimistic about the future. My hope for the future is that someday soon, we will think of cancer in much the same way we think of infections. Then, pictures like these, filled with survivors, will become the norm.

Thank you very much.