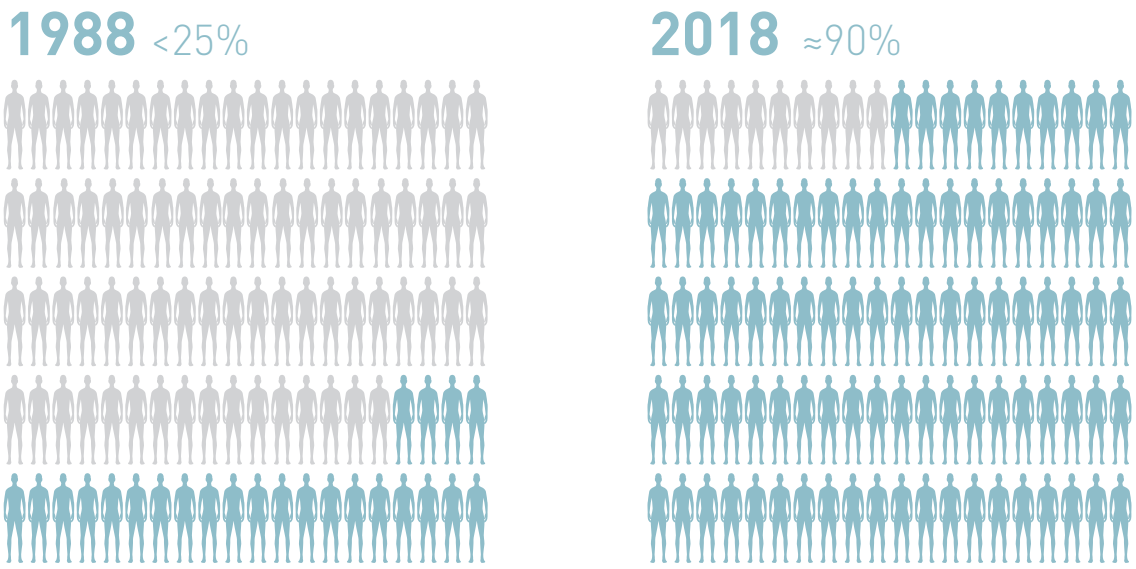
Unique treatment cures once deadly cancer

The recipients of the Sjöberg Prize 2018, Zhu Chen, Anne Dejean and Hugues de Thé, have clarified molecular mechanisms and developed a revolutionary treatment for acute promyelocytic leukaemia. Three decades ago, three of every four patients died within two years, but now almost everyone who receives the new treatment is cured.

The element arsenic is often associated with its toxic properties, but has a history of use in traditional medicine. This year's Sjöberg Laureates have demonstrated that arsenic is a necessary component in a new and effective treatment for a specific form of leukaemia, acute promyelocytic leukaemia. In recent years, this tailored treatment has proven to have dramatic results: for what was once one of the deadliest forms of cancer, it is now possible to cure nine out of ten patients who receive new treatment.



From probable death to probable cure. Using the treatments available in the 1980s, more than 75 per cent of patients with acute promyelocytic leukaemia died within two years. With the current treatment, nine out of ten patients are cured.

This year's Laureates facilitated this revolutionary development by thoroughly mapping the molecular mechanisms responsible for the disease, as well as by testing an active treatment that combines two substances: a form of vitamin A called all-trans retinoic acid (ATRA) and an arsenic compound, arsenic trioxide. This treatment is unique because it is the first standard treatment for acute leukaemia that does not include chemotherapy.

Although the inspiration for the use of arsenic originally came from traditional medicine, this combination therapy is scientifically tested and proven. The treatment's development is also an excellent example of research that was based upon academic interest in dialogue with clinical needs.

An unusually problematic cancer to treat

All types of cancer stem from individual cells in the body that, for some reason, start to behave incorrectly. New cells are continually created, but when they are damaged they should undergo programmed cell death, called apoptosis. This control system does not work in cancer; the damaged cells continue to divide. Solid tumours are formed in cases of breast or prostate cancer, but when white blood cells run amok the faulty cells accumulate in the blood and bone marrow. A collective name for this type of cancer is leukaemia.

All blood cells are formed from stem cells in the bone marrow, where promyelocytes are an important type of blood cell. This is an immature cell that normally develops into various kinds of white blood cells. Acute promyelocyte leukaemia, or APL, is a very rare form of leukaemia, annually affecting around 1.5 people per million. Unlike many other forms of cancer that primarily affect older people, APL can occur at any age. People who are afflicted often suffer from fatigue and bleeding that is difficult to stop, such as nose bleeds, gynaecological bleeding or brain haemorrhages. This is because components in the coagulation system are broken down and the blood cannot coagulate.

The disease was first described in 1957 by a Norwegian doctor, Leif Hillestad, who reported on three patients who, in just a few weeks, died from a variety of acute leukaemia. Their blood had an unusually high proportion of promyelocytes. This was because the cells appeared to have paused their development and not developed into mature blood cells, as would normally happen. Hillestad's conclusion was that the disease "appears to be the most malignant form of acute leukaemia" and that a logical name for it would be acute promyelocyte leukaemia. Treating APL was a nightmare for doctors, because the patients suffered from unpredictable and life-threatening bleeding. Chemotherapy began to be used in the early 1970s, but the disease's mortality rate remained high. By the end of the 1980s the prognosis remained extremely poor – two years after falling ill, barely 25 per cent of patients were still alive.

The first step: treatment with vitamin A

At that time, intensive research was being conducted to improve the understanding of leukaemia and how it could be treated. One method was the cultivation of human blood cancer cells, which could be used to test how different substances affected them and to examine whether they could be made to liken normal cells. In these tests, researchers concluded that retinoic acid, ATRA, worked well. The first study in which ATRA was tested on APL patients took place at the Ruijin Hospital in Shanghai in 1987. The results were good and showed that treatment with ATRA had fewer side effects than treatment with chemotherapy.

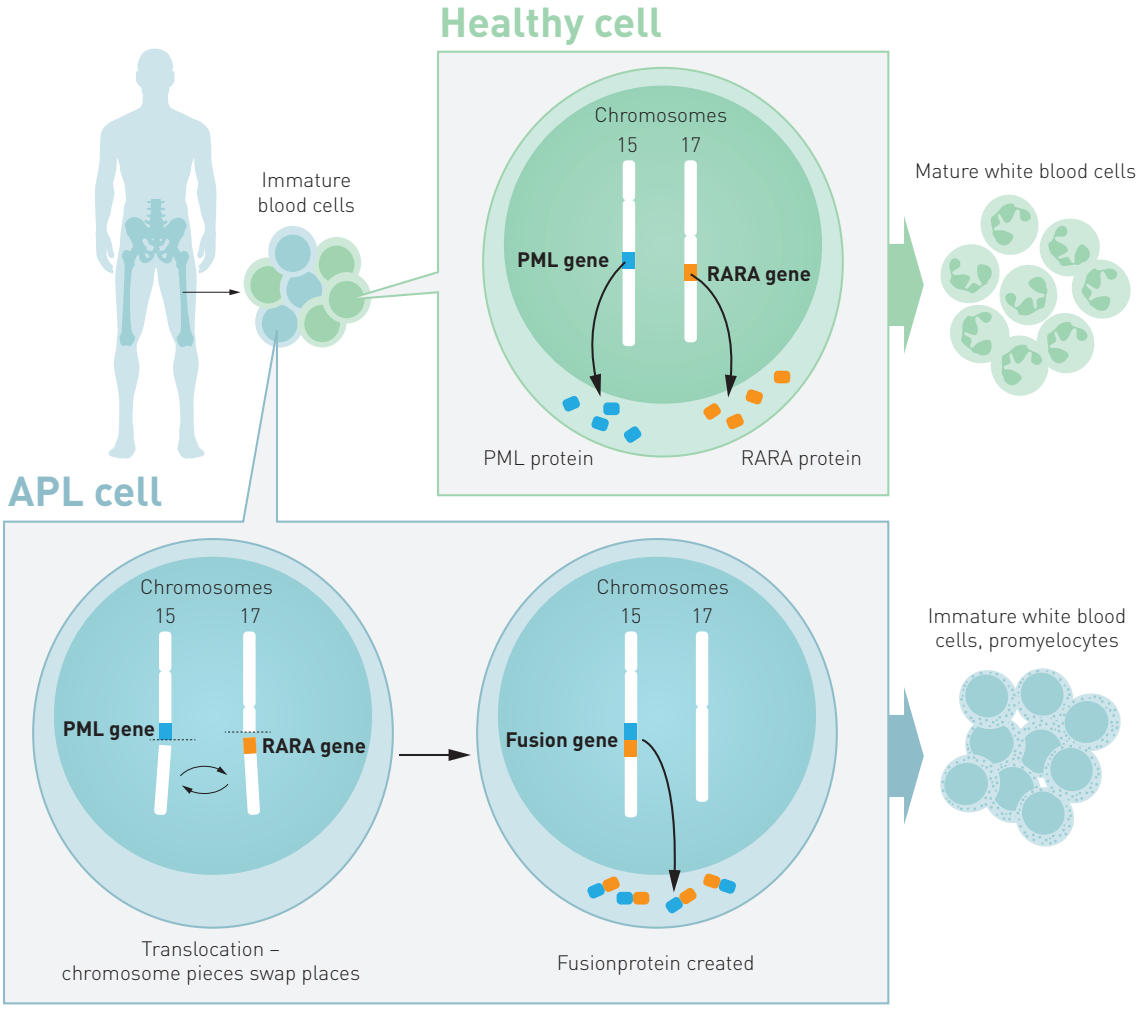
At the end of the 1980s, all three of this year's Sjöberg Laureates were in Paris. Zhu Chen was working at Hôspital Saint-Louis, Université Paris VII, while Hugues de Thé and Anne Dejean were working together in her laboratory at the Institut Pasteur.

Cloning the disease gene

By 1977, twenty years after APL was first described, a specific genetic mutation could be linked to the disease. This mutation occurs as the cell is developing in the bone marrow and is a translocation, in which pieces of the long arms of two chromosomes (15 and 17) swap places. Even by the end of the 1980s, what this part of gene looked like in APL remained a mystery, one which would be solved by two of this year's Laureates.

Anne Dejean and Hugues de Thé were studying retinoic acid-activated signalling in liver cancer. Because ATRA, which is also a type of retinoic acid, worked so well on APL they became

interested in further investigating the area of the gene in which the translocation had taken place. Both researchers were well-suited for this work because they were experts on retinoic acid receptors. Also, it was known that the gene for the retinoic acid receptor to which ATRA normally bonds is on chromosome 17, close to the area where the translocation occurs.



Translocation creates a fusion protein. The chromosomes in our cell nuclei can break, and the pieces can change places with each other, which is called translocation. This is how pieces of chromosomes 15 and 17 in an immature blood cell can swap places, and the new genes that are formed can create a fusion protein, which prevents the immature blood cells from developing into mature blood cells.

They studied cells from patients to find out what the gene looked like in APL and, in an important article in 1990, they were able to demonstrate that APL patients have retinoic acid receptors that have been put together abnormally. Translocation means that something called a fusion gene is created, one that is made using genetic material from two original genes. The next step in understanding how APL occurs was to map the entire fusion gene. This work took time but, in 1991, Anne Dejean and Hugues de Thé reported that they had succeeded in cloning the entire fusion gene.

Faulty protein causes the disease

The fusion gene is an oncogene, which means that it can cause cancer. The oncogene forms a template for a fusion protein called PML-RARA. Subsequent studies demonstrated that the production of this protein in promyelocytes disrupts their cellular signalling, thus preventing them from maturing.

What differentiated APL from other forms of leukaemia and how this elusive gene was structured was now clear. However, the problem had not been solved for the patients, because those who were only treated with ATRA often suffered relapses within just a few months. Chemotherapy was still required for the treatment to have a lasting impact, resulting in many side effects and reducing the patients' quality of life during treatment. Furthermore, relapses were not uncommon, even when ATRA and chemotherapy were combined.

Arsenic as a pharmaceutical

As stated in the introduction, the other component in this new and effective combination therapy is a chemical compound that contains arsenic. Arsenic is best known as a poison, but has been used as a pharmaceutical for more than 2,000 years, both in traditional Chinese medicine and by the "father of medicine", Hippocrates. For treating cancer, arsenic continued to appear as an ingredient in pharmaceuticals in the 18th and 19th centuries – and even more recently. For example, a solution containing arsenic was used in the US in the 1930s to treat chronic myeloid leukaemia, but was phased out in the 1950s when chemotherapy was introduced.

In China, various arsenic solutions that had originally been used in traditional medicine were tested. Ting-Dong Zhang from Harbin Medical University reported that a solution of arsenic trioxide and mercurous chloride had some effect on patients with myeloid leukaemia. In the early 1990s, a solution with solely arsenic trioxide was described as having a positive effect on APL.

The second stage: studies of arsenic's effect on APL

Zhu Chen had returned to Shanghai in 1989 and founded his own laboratory, where he worked with his wife, Sai-Juan Chen, who heard about the early attempts to treat leukaemia with arsenic trioxide at a meeting in 1994. During the Cultural Revolution, Zhu Chen had worked as a barefoot doctor in the Chinese countryside, giving him experience of using the available methods and materials. He later described how this was why he felt it could be worth following the route of folk medicine. Zhu Chen's group conducted trials on cells to study the effects of arsenic trioxide. They saw two clear effects: one was that exposure to arsenic trioxide could make the APL cells, which had paused and not developed into mature white blood cells, continue maturing. An even clearer effect of arsenic trioxide was that these faulty cells could be made to undergo programmed cell death, apoptosis.

These results meant that the researchers chose to continue and test how arsenic trioxide worked as a treatment. In 1995 they conducted a small study using ten patients with relapsed APL following treatment with ATRA and chemotherapy. Nine of them were cured after receiving arsenic trioxide. Over the following years, newly diagnosed APL patients were also treated. In a landmark study from 1997, Zhu Chen was able to prove that arsenic trioxide was an effective treatment for APL. Fifteen patients who had been treated with ATRA, but who had suffered relapses, received daily injections of arsenic trioxide for about a month, and 14 people were cured. These results were confirmed by a another study the following year.

The third stage: combining ATRA and arsenic

However, arsenic trioxide alone did not seem to be the entire answer. Zhu Chen remembered that he had treated five APL patients who received a combination of arsenic trioxide and ATRA, and that all five were cured. At the same time, Hugues de Thé's group reported that leukaemia cells in mice with APL died if they were exposed to this combination. Perhaps both substances together created a synergy effect?

In 2000, Zhu Chen collaborated with Hugues de Thé on a clinical study in which ATRA and arsenic trioxide were combined. All 20 patients who received this combination were disease-free after 18 months. The results were published in 2004 and, subsequently, newly diagnosed APL patients in China received this combination therapy. Notable results could be seen in 2009: the five-year survival without relapse was 95 per cent and total survival, in which relapsed patients were retreated, was 97 per cent.

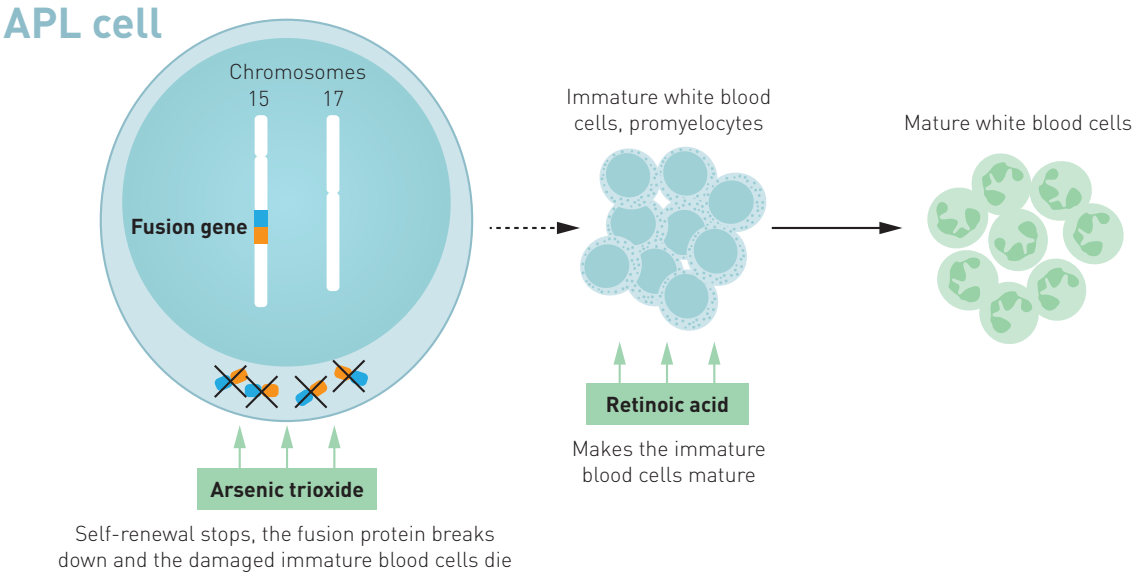
Randomised studies confirm the effect

However, for a more widespread introduction of the new combination therapy it had to be compared to the treatment then in use: ATRA with chemotherapy. In an initial study, published in 2013, ATRA was given as tablets and arsenic trioxide as a drip five days a week. This combination was as effective as the traditional treatment, but had fewer side effects in the form of damaged bone marrow, infections and in-patient care. In the long-term, a follow-up showed that total survival improved, which was published in 2016. The results of the second randomised study came in 2015. In this, the patients received arsenic trioxide twice a week instead of five times. The benefits of this were that it was easier for patients, and there was an observed reduction in the risk of liver damage. The results of these studies confirmed that this combination therapy was superior to treatment with ATRA and chemotherapy.

ATRA and arsenic break down the fusion protein

Why does the combination of these two substances provide such good results? ATRA binds to the RARA part of the fusion protein, and Zhu Chen, again working with Hugues de Thé, showed that arsenic trioxide binds directly to the PML part. Together, ATRA and arsenic trioxide cause highly effective degradation of the fusion protein.

Treatment with ATRA initiates the rapid development of promyelocytes into mature white blood cells. Arsenic trioxide primarily initiates programmed cell death, apoptosis, in the cells containing the harmful fusion protein. Altogether, this means that the cancer cells disappear because they lose the ability to renew themselves.



The combination cures the disease. While arsenic trioxide makes the damaged cells undergo programmed cell death, the retinoic acid makes the immature cells develop into mature blood cells.

Combining two substances in this way also prevents the cancer cells developing resistance to the treatment, so the patients have a minimal risk of relapse. In many countries, this combination is now the first choice of treatment for APL.

Important lessons for other forms of cancer

It is greatly thanks to this year's Laureates that a disease which was almost always fatal thirty years ago, is now the form of leukaemia with the very best prognosis. This tailored combination therapy is also unique, as it was the first chemotherapy-free standard treatment for acute leukaemia. The results are excellent, but there are still questions that need to be answered. One is whether the treatment could lead to side effects in the long-term, after 20–30 years.

Arsenic trioxide is currently administered via a drip, which is both expensive and time-consuming. Within a few years it will probably be possible to provide treatment with arsenic in tablet form. Targeting treatment on a faulty protein also provides hope of being able to similarly deal with other types of cancer. For cancers that are caused by a specific fusion protein, this protein could be broken down using targeted treatment.

Anne Dejean now primarily dedicates her research to the continuing study of liver cancer, and to investigating the significance of protein modification in how cancer develops. Hugues de Thé is interested in the potential for producing treatment methods for cancer that combine stimulating the cancer cells' maturation and blocking their ability to renew themselves, while Zhu Chen is investigating genetic and molecular changes in other forms of leukaemia.

The three Laureates remain very active in the field of cancer research. The hope is that the Sjöberg Prize, which mainly comprises research funding, will pave the way for further progress and lead to cures for more forms of cancer.

LINKS AND FURTHER READING

Further information on this year's prize is available at the website of the Royal Swedish Academy of Sciences, *www.kva.se/sjobergprize*

Video

Complexity Through Protein Modification. Dialogues, Fondation Hugot du Collège de France, 2017. Conversations with Hugues de Thé and Tony Hunter (Sjöberg Laureate 2017) and others.
https://www.youtube.com/watch?v=Jzrp_6ogUZU

Leucémie promélocytaire, un modèle scientifique. Collège de France, 2017.
Short introduction to promyelocytic leukaemia in French by Hugues de Thé
https://www.youtube.com/watch?v=bUjigudks0g

Synergistic targeting therapies against oncoproteins for acute myeloid leukemia. Cold Spring Harbor Asia, 2012.
Lecture by Zhu Chen
https://www.youtube.com/watch?v=KXEUw8oNBDE

Scientific overview articles

Lessons taught by acute promyelocytic leukemia cure. Hugues de Thé. Lancet, 2015 Jul 18;386(9990):247-8.
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)61278-8/fulltext

From an old remedy to a magic bullet: molecular mechanisms underlying the therapeutic effects of arsenic in fighting leukemia. Sai-Juan Chen et al. Blood 2011 117:6425-6437.
http://www.bloodjournal.org/content/117/24/6425.long?sso-checked=true

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