NOVOGEN

THE FUTURE OF
CANCER THERAPY

A HISTORY OF CHEMOTHERAPY

Up until just after the Second World War, there was no concept that drugs could be used to stop cancers growing. Surgery was essentially the only option, and then only reserved for the most easily removed tumours. Having an established, aggressive cancer at that time was in effect a death sentence. The first attempt at chemotherapy for cancer using scientific rationale was in 1946, and in one of the great ironies of medicine, owes its origins to war and to the notion of inflicting harm and misery on people. In the six decades since, the science of cancer chemotherapy has lurched ahead in fits and starts, with occasional periods of excitement and great promise breaking decade-long periods of little or no progress. The history of chemotherapy is marked by a number of key developments.

1. First patient, first anticancer drug

Remarkably, the beginnings of chemotherapy are to be found in chemical warfare and a tragic, but ultimately fortuitous, war-time bungle. The story starts in the First World War with the development by Germany of nitrogen mustard gas that was used to such deadly effect in the trenches of Belgium and France. The gas was highly toxic, burning the skin, eyes and lungs of soldiers who inhaled it. Chemical warfare subsequently was banned by international treaty, so ensuring that the Second World War was essentially free of the use of toxic gases in the field. However, despite the treaty, both sides in the war were carrying out research into chemical warfare on a clandestine basis, with the US stockpiling nitrogen mustard gas in case Germany decided to use it as it had some 25 years earlier in France.

In 1943, after the Allies had landed in Italy and were pushing up towards Germany, the US sent a supply of nitrogen mustard gas by ship to the Italian front, storing it in the Italian port of Bari. On the night of December 2, German bombers attacked the port, inflicting considerable damage including the warehouses holding the nitrogen mustard gas, releasing the gas across the city and exposing military personnel and civilians alike to the gas. Compounding the tragedy, neither military nor civilian physicians were informed about the presence of mustard gas in the city, leading to failure to properly treat hundreds of people affected by the gas. The extent of the damage associated with the release of the mustard gas is shrouded in controversy to this day, in part because of confusion over the proportion of casualties attributed directly to the bombing, and in part because of the highly classified nature of the event, with Churchill ordering that all records of the event be destroyed. Whatever the truth, it is uncontested that a considerable number of military personnel and civilians died as a result of exposure to mustard gas. The ongoing argument is over the extent of the casualties.

Aware of the implications of what had happened, the US military sent pathologists to Bari to conduct autopsies on the casualties. The extent of what they found has never been disclosed, but one thing that they did find and did disclose is an unexpected finding of profoundly low levels of white blood cells in gas-affected bodies, with shrinkage of lymph nodes being particularly noted. Curiously, this effect had never been noted in the First World War despite the casualty rate from mustard gas poisoning running into the tens of thousands.

This discovery so piqued the interest of the US Department of Defence that it recruited two pharmacologists, Drs. Goodman and Gilman, to look at the potential therapeutic applications of such an effect. Lymphoma, or cancer of lymph nodes, was an obvious target. The thinking was obvious – here is a cancer characterised by malignant swelling of lymph nodes, while on the other hand, nitrogen mustard gas was capable of shrinking lymph nodes in healthy people. The first step of the army pharmacologists was to come up with an injectable form of the gas that would allow a more defined dose to be delivered.

To do this, they played around with the chemical structure of the nitrogen mustard molecule in order to convert it from a gaseous form to a liquid form. This sort of effort is the basis of organic chemistry – changing the structure of chemicals in the same way that oil molecules can be turned into molecules of petrol, or diesel, or kerosene, or plastics.

One of the new structures that they settled on for further testing was the drug mustine. After confirming that mustine reduced lymphomas in mice, they then collaborated in 1945 with a thoracic surgeon, Dr. Linskog, to use mustine in a patient with non-Hodgkin's lymphoma. The effect was dramatic, with the lymph nodes showing significant shrinkage. Unfortunately the response only lasted a few weeks, but the significance of this event was the promise of the principle that cancer could be treated by chemotherapy.

At the time, there was no real understanding of how the drug was working. Here was a drug whose heritage was a capacity to inflict severe burns on the skin, eyes and lining of the lungs, and yet there was nothing particularly obvious at the time to link a burning effect to how it might be functioning as an anticancer agent. It would be another decade before it was discovered that mustine was working by attaching itself to the DNA of the cancer cell in a way that prevented the DNA from functioning normally. Just as the cancer had been caused in the first place by DNA damage, mustine was doing the same thing, only many times greater. The initial damage that led to cancer in the first place, by definition must have been relatively mild in order for the cell to survive and to evolve into a cancer cell. The amount of damage being inflicted on the DNA by mustine was so great that the cell had no option but to die. When used as a chemical warfare agent, the nitrogen mustard gas was inflicting lethal damage on the DNA of the cells lining the respiratory tract. In Dr Linskog's patient, it was doing the same thing, but concentrating its action on the lymphoma tumour.

Ironically, although these early scientists were completely in the dark as to exactly how mustine was working, their discovery set the pattern for the way in which the vast majority of anticancer drugs would be developed over the next 60 years. The overarching principle that has guided the development of anticancer drugs has been that irreversible damage to a cancer cell's DNA will put that cell's ability to survive in jeopardy.

Some drugs inflict so much damage on the DNA that the cancer cell simply cannot survive. These are known as cytotoxic drugs. These drugs usually result in almost immediate shrinkage or even complete disappearance of the cancer. Other drugs are less damaging, to the point where the cell is too damaged to divide but not so damaged that it will die. These drugs are known as cytostatic chemotherapies. The effect of these drugs is to stop the growth and spread of the cancer, without necessarily shrinking the cancer.

The principal downside of this approach is that such drugs are by their very nature non-selective. A drug that disrupts DNA function doesn't distinguish between the DNA of a cancer cell and that of a normal, healthy cell. An anticancer drug once inside the body is perfectly able to penetrate any tissue in that body and to attach itself to any and all DNA, irrespective of whether it is healthy or cancerous DNA. The saving grace, the reason why most cytotoxic anticancer drugs can shrink cancers without shrinking our liver or heart to the same extent, is that the effect of the drug is dependent on the extent of DNA activity in the tissue. It is only when a cell is actively dividing that its DNA is at risk of damage from the drug. Cells that are sitting quietly, functioning normally but not dividing, are not at any particular risk of damage from the cytotoxic drug. That is the case for most of the major organs in our body. The rate of cell turnover in most parts of the body (such as the liver or heart) is so relatively low, that they are spared the worst effects of cytotoxic drugs.

The danger in this strategy lies with those parts of the body that have a high rate of cell turnover. Notably, the lining of the gut which is replaced every few days; red and white blood cells have a limited lifespan and need to be regenerated within the bone marrow of the long bones on a regular basis; and hair is being constantly produced within the hair follicles of the skin. This means that tissues such as these are going to be highly susceptible to the effects of DNA. The side-effects of gastro-intestinal toxicity are severe nausea, vomiting and diarrhoea. The side-effects of bone marrow toxicity are low levels of red blood cells, resulting in anaemia, and low levels of white blood cells, predisposing the patient to serious infections. The side-effect of hair follicle toxicity is baldness. These unwanted consequences on healthy tissue have exactly the same underlying mechanism of action as the burning symptoms seen in the eyes and lungs of World War 1 soldiers, and those seen in the citizenry of Bari.

The use of cytotoxic anticancer drugs is based on the simple principle that the most rapidly dividing cells in a cancer patient's body are the cancer cells, making them proportionally more likely to take up the drug than any other tissue. But tissues such as bone marrow and the gut inevitably will be hit by some collateral damage, making chemotherapy a delicate balance between poisoning as many cancer cells as possible while sparing as many healthy cells as possible – a delicate clinical dance between curing and harming. The side-effects of such chemotherapy also mean that there is a limitation to the number of times that the therapy can be given or the length of time that it can be given. It is highly likely that chemotherapy with such anticancer drugs could effectively destroy most cancer cells in the body if they could be given in sufficiently high doses for enough time, but that would come at the cost of almost total destruction of the body.

This delicate see-sawing between killing cancer cells and killing healthy cells also means that this approach is less likely to work with those cancers that are relatively slow-growing. Prostate cancer is an example of a slow-growing cancer. Chemotherapy with the kind of anticancer drugs that we are considering here is uncommonly used in early stage prostate cancer because the length of time that the treatment would need to be given as a function of the slow rate of turnover of the cancer would result in unacceptably high levels of side-effects.

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Anyway, back to our history.

The mechanism by which mustine damages DNA is referred to as alkylation, a chemical term referring to the way in which the drug attached itself to the DNA, changing the DNA's structure to the point where it could no longer function normally. In the 1950s, this discovery went on to spawn a family of anticancer drugs known as nitrogen mustard alkylating agents. Of these, the drugs chlorambucil (1957), melphalan (1957), cyclophosphamide, (1959) and streptozotocin (1982) are probably the best-known members of this family, and remain in wide use today for the treatment of cancers such as breast cancer, ovarian cancer, bladder cancer and chronic lymphocytic leukaemia. And despite its 60-year old age, mustine continues to be used occasionally today, mainly in a combined form with estrogen called estramustine, to treat prostate cancer.

2. Second anticancer drug

Mustine represented a promising start. Its effect on lymphoma was less than striking, but it did serve to prove that a cancer could respond to a toxic drug without jeopardising the life of the patient. What was required now was the development of drugs with more powerful actions. That step came just a few years later as a result of work coincidentally underway in Boston at Harvard Medical School. This work concerned the role of folic acid in cancer. As with mustine, the Boston work was not based on any particular understanding of cancer or the fact that damaging a cancer's cell DNA was a good strategy to pursue for drug development. Instead, the work was based on an astute sense of logic along with a single-minded determination by a paediatric pathologist, Dr. Sidney Farber (1903-1973).

The background to this work was a discovery a few years earlier in 1937 that a form of anaemia known as 'tropical anaemia' in children in Bombay (Mumbai), India, was correctable by supplementation with brewer's yeast. The unknown factor in the yeast initially was called Wills factor, after Lucy Wills its discoverer, but subsequently identified as folic acid (or vitamin B9). These days we recognise that folic acid is an important nutrient because it is an essential building block of DNA and therefore is in high demand for rapidly growing cells, which is why nutritionists recommend folic acid supplementation for pregnant women and infants. But back in the 1940s, the connection between folic acid and DNA and cell growth had yet to be made. The extent of understanding about the role of folic acid in the body was based on the Wills work showing that folic acid corrected anaemia in children by stimulating the growth of bone marrow, the source of both red and white blood cells.

Sydney Farber was attracted to this story because of his interest in the treatment of leukaemia. Farber worked at the Children's Hospital in Boston which handled many cases of childhood leukaemia. At that time, this was a largely untreatable, painful disease that often led to death within weeks of diagnosis. Farber's logic was simple – if folic acid stimulated healthy bone marrow to make red and white blood cells, then perhaps it also played a critical role in the excessive activity of bone marrow in producing white blood

cells in leukaemia patients. He reasoned that by blocking the uptake of the cancer cells in bone marrow of folic acid, the production of leukaemic cancer cells might be slowed.

Chemists at Lederle (now part of Wyeth) had successfully synthesized folic acid in 1945. In collaboration with Lederle, Farber had drugs designed that looked like folic acid, but which could not work like folic acid. The notion was that they would look sufficiently like folic acid to fool cells into taking them up, but once inside the cell would fail to provide whatever benefit the folic acid was thought to be providing. One of these drugs, aminopterin, proved very effective at doing this. When aminopterin was injected into the body, its levels in the body vastly exceeded the level of folic acid, leading to cancer cells taking it up to a much greater extent that folic acid. The rapidly dividing cancer cell with its high demand for folic acid needed to service its DNA expansion, suddenly found itself with non-functioning DNA because it contained aminopterin and not folic acid.

In 1947, Farber treated a group of 16 children who were seriously ill with acute lymphoblastic leukemia with aminopterin and achieved remission in 10 patients, meaning that the clinical symptoms of the leukaemia disappeared. As with mustine in lymphoma patients, the remissions with aminopterin proved to be fairly short- lived, but again this was a key step in reinforcing the principle that aggressively- growing cancer cells could be successfully challenged by drugs.

Farber published his findings in 1948 to curiously mixed reactions. The cancer research community, including his Harvard University colleagues, was largely dismissive. Part of this reaction appeared to be professional jealousy and had to do with a discovery of such magnitude being made by an unknown scientist working in a forgotten basement laboratory with little in the way of research funding. But there also was the accusation that leukemia was incurable and that affected children should be allowed to die in peace and dignity without needlessly suffering side-effects of chemotherapy. In the context of the day, where the idea that childhood leukaemias were curable by chemotherapy was unthinkable, such a view is perhaps understandable. And it has to be said that this is a debate that is as pertinent today as it was then, particularly in relation to the use of chemotherapy to extend life marginally in terminal cancer patients at the expense of quality of life. However, that point remains that Farber□s work opened the door to research that ultimately shifted childhood leukaemias from a fatal disease to a largely curable disease. Interestingly, it was the non-research community, the doctors at the coal-face who were dealing with dying children, who gave Farber his greatest support and encouragement. Their eagerness to embrace anything that gave them an ability to alleviate suffering in children with leukaemia ensured that chemotherapy, at least for leukaemias, had a firm foundation.

Aminopterin was replaced 5 years later by a more powerful version known as methotrexate (1953), and that drug remains a standard anticancer drug in use today. In 1958, methotrexate was shown to be an effective cure of choriocarcinoma, a rare cancer of the placenta in pregnant women. Despite its rarity, the significance of this discovery was that it was the first report of a solid cancer being cured by chemotherapy and was a critical step in establishing the concept of using chemotherapy to treat solid cancers as well as leukaemia where the cancer cells are single and unattached and not formed into a mass structure.

3. Co-coordinating the research effort

As pivotal as the pioneering efforts of individuals such as Sidney Farber were to the establishment of the principle of chemotherapy, there is no doubt that it was the subsequent major injection of funds by governments and drug companies that ensured that chemotherapy expanded to meet its potential, and the one institution that stands out in this regard is the US National Cancer Institute. The extent of that impact is evidenced by the fact that by the mid-1990s, the NCI had played a role in the development of two-thirds of all anticancer drugs in use at that time.

The NCI was created in 1937 by President Theodore Roosevelt as an independent research institute, and then brought under the umbrella of the National Institutes of Health based in Maryland in1944. One of the key contributions of the NCI has been to establish methodologies for screening potential anticancer compounds at a time when drug companies were beginning to show some interest in the development of anticancer drugs, but had little or no in-house facilities to evaluate their usefulness. The NCI eventually became a one-stop shop for cancer research, where it conducted its own basic research, provided a screening resource for other researchers, provided funding for other researchers, and coordinated the clinical testing of new anticancer drugs. It is a model that other countries had emulated to a greater or lesser degree, but the amount of funding that the NCI receives has ensured that it remains the pre- eminent cancer research institute that it always has been.

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4. Drugs from Nature

At the outset, scientists at the NCI and elsewhere adopted two main approaches to the discovery of anticancer drugs. The first was the approach taken by the Boston team in the development of aminopterin. This is known as rational drug design – meaning that you start with a known function (in this case the essential need for folic acid by the cancer cell), and you design a drug that deliberately interferes with that need. The other approach is more random…..to look for existing compounds within Nature. This approach doesn't require any understanding of how a potential drug might work, just the fact that it kills cancer cells. It is a needle-in-a-haystack approach that involves searching through the millions of species of plants, marine life, insects, coral etc. for naturally-occurring chemicals with anticancer activity.

Why would something like a plant or a coral or a microbe need to contain a compound capable of fighting cancer? Well, it doesn't….that is, these organisms don't succumb to any condition evenly remotely related to cancer, but most living things do need to make compounds that help them fight off predators such as a disease-causing organism, and one way to do that is to make the protective compound able to poison any threatening predator. Poisoning generally means that you disturb the invading-organisms biochemical processes to the point where it is dissuaded from attacking or perhaps is even lethal enough to kill it. And anything that is capable of causing that amount of harm to any living cell certainly has the potential to make a cancer cell sick.

This looking-for-a-needle-in-a-haystack approach is a painstakingly tedious experience that is rarely rewarding. In fact it is more like looking for a needle in 10,000 haystacks. It usually means teams of people going out and collecting samples from jungles or forests or coral reefs, and then screening chemical extracts from hundreds of thousands of samples for some evidence of an ability to stop cancer cells from

growing in the laboratory. And this is exactly the effort that the NCI embarked on in the 1950s. In 1956, Dr Gordon Zubrod was appointed head of the Division of Cancer Treatment in the NCI. Dr Zubrod formerly had been in charge of development of anti-malarial agents for the US Army and had a keen interest in natural product research, holding the not unreasonable view that Nature probably holds the keys to most of our ailments, particularly the degenerative diseases such as cancer, and that it is just a matter of investing enough time and effort to find those keys.

In 1958, Dr Zubrod set about establishing an ambitious program to test over 30,000 species of North American plants for anticancer activity. The botanists charged with this collection job gathered up sack-fulls of twigs, needles, leaves and bark from thousands of different trees and bushes and sent them back to the NCI. Back in the NCI laboratories, crude extracts were made from these samples by dissolving the plant material in different solvents such as water or alcohol. These crude extracts, each containing thousands of individual chemicals, were tested for their ability to kill cancer cells growing in a test-tube. Where an extract proved to have anticancer activity, the enormous task of separating out the thousands of chemicals within each active extract then had to be undertaken in order to identify the active ingredient or ingredients.

The number of man-hours involved in identifying and then purifying a single active extract runs into the hundreds of thousands. One of the trees sampled was the Pacific yew tree, a slow-growing, old-growth forest tree on the Pacific Northwest coast of the US, with a sack of twigs and bark and leaves arriving back at the NCI in 1963. The extract from the bark (but not the twigs or needles) caused considerable excitement when it was found to have significant anticancer activity in the test-tube, triggering a lengthy 4-year process to identify the active ingredient amongst the thousands of other chemicals within the bark. That active ingredient eventually was identified as taxol, destined to become one of the most commonly used anticancer drugs in the modern era. The discovery and identification of taxol took another 8 years of painstaking research, with its chemical structure finally being published in 1971. However, that was not the end of the challenge. The chemical structure proved so difficult to synthesise that early animal studies and subsequent clinical trials of the drug had to be conducted using naturally- extracted material, a cumbersome exercise that required chemists to isolate the drug from tonnes of bark being collected from forests in the US Northwest. Given that all the bark from a fully-grown Pacific yew tree only yielded 500 mg of drug (enough for about 5 doses), few Pacific yew trees were left across North America with their bark intact. Progress was only going to be made if the drug could be synthesised, but it was to be another 10 years before that problem was cracked.

By the time the whole natural product program was abandoned by the NCI in 1981, over 114,000 plant extracts and 16,000 animal extracts had been screened for anti- cancer activity. Over that 20-year period involving tens of millions of man-hours of botanists who collected samples, chemists who conducted the extraction of samples, and biologists who tested the extracts in the laboratory, taxol was the only drug of any significance that they had to show for all that effort. Taxol (1992) went on to be commercialised by the drug company, Bristol-Myers Squibb, and to become a mainstay of chemotherapy for a range of cancers including ovarian and lung cancer. Since then, chemists have found that relatively minor alterations to its structure produces new drugs with increased and different activities. As a family of compounds, taxol and its new spinoffs are known as taxanes. They work in a similar way to taxol, but do it in a better or stronger or different way. The best known of these is docetaxol, a drug used to treat a range of cancers including prostate, breast and lung cancer.

While taxol might have been the NCI□s only real success in its natural products program, the institute still played a key role through its collaborative efforts in the development of a number of other important anticancer of natural origin. Drug companies and private research institutes were active in this area as well, sending their promising samples off to the NCI to take advantage of their screening resources.

Extracts from a deciduous tree (Camptotheca acuminata) found in Southern China were sent to the NCI and found to have promising anticancer activity in the test-tube. The active ingredient subsequently was identified in 1966 as camptothecin. In clinical studies, however, camptothecin proved to be a disappointingly weak anticancer agent, but subsequent changes to its chemical structure resulted in the development of the more powerful drugs, topotecan and irinotecan. Topotecan is used for small cell lung cancer and ovarian cancer, and irinotecan (1994) for colorectal cancer.

Anther plant, the Madagascar periwinkle, similarly has provided an important family of anticancer drugs known as vinca alkaloids. The discovery of these drugs has its roots in herbal medicine, where extracts of the Madagascar periwinkle had been used for centuries in Madagascar for the treatment of diabetes and hypertension, and as a disinfectant. The sap of this plant was poisonous, and subsequent chemical analysis of the sap found that it contained a wide range of toxic chemicals known as alkaloids. Two of these alkaloids subsequently were identified as vincristine and vinblastine. The NCI played a key role in identifying the anticancer properties of vincristine, with the drug being approved in 1963 as a treatment for leukaemia. Two Canadian researchers subsequently identified the anticancer properties of vinblastine when it was given as a tea to animals and found to cause a profound fall in their white blood cell levels. These two drugs were used initially to treat leukaemia and lymphoma as alternatives to mustine and aminopterin, although they are used far more widely now for solid cancers such as breast and lung cancers.

The other significant anticancer agent to be discovered in this way is doxorubicin. This compound owes its existence to work in the 1950s by an Italian research company that had initiated a program to search for newly identified soil microbes that hopefully would have antibiotic or anticancer activity. A particular soil sample collected from the area surrounding the Castel del Monte, a 13th century Italian castle, provided a new strain of bacteria that produced a bright red pigment. Coincidentally, independent French and Italian scientists subsequently discovered that this compound showed good anticancer activity against a range of mouse tumors.

In recognition of this joint discovery, the two teams named the compound daunorubicin, after Daunii, a pre-Roman tribe that occupied the area of Italy where the compound was isolated, and the French word for ruby, rubis, describing the drug’s color. Clinical trials of daunorubicin began in the 1960s, leading to the drug being used to treat acute leukemia and lymphoma.

The Italian scientists then discovered that minor changes to the structure of daunorubicin increased both the strength of the anticancer activity and the range of cancers that it affected, including a range of solid cancers. They named this new compound adriamycin after the Adriatic sea, the name then being changed

to doxorubicin when the drug came to market in 1974. Doxorubicin now is one of the most widely used drugs in the treatment of cancer.

5. Combination chemotherapy

Prior to the mid-1960s, the standard method of chemotherapy for any cancer involved the single use of available drugs. Treatment would start with one drug and then move onto a second drug when the first one either failed to work after several weeks of trying or when an initial response was followed by a return of the cancer. The development of drug resistance remains one of medicine's great challenges whether it is in the field of infection (eg. Golden Staph), or parasites (eg. malaria) or cancer. Faced with annihilation by drugs, organisms have a remarkable capacity to fight back by developing resistance to those drugs. Cancer cells share this biological capacity along with bacteria and parasites.

Considerable experience already had been gained with this phenomenon in tuberculosis, where the general experience was that the successive use of different antibiotics usually led to the infection becoming resistant to all antibiotics. But when antibiotics with different mechanisms of action were given as a combination, the risk of resistance developing was much less likely to happen. In the mid-1960s it was decided to test this notion with cancer. One group reported on the treatment of children with acute lymphoblastic leukaemia (ALL) with a combination of four drugs – methotrexate, vincristine, 6-mercaptopurine and prednisone – with most patients showing long-term remission. Subsequent refinements of this multiple therapy approach have led to ALL becoming a largely curable disease.

A couple of years later, a second group from the NCI extended this observation to solid cancers, showing that a combination of mustine, vincristine, procarbazine and prednisone could lead to long-term remission in Hodgkin's and non-Hodgkin's lymphomas. Combination therapy comprising two or more anticancer drugs has become the standard form of chemotherapy in use today.

6. The platinums

The platinum-based drugs are worthy of highlight since, along with the taxanes and doxorubicin, they are the most widely used anticancer drugs today. Their history also underlines the extent to which a mixture of serendipity and scientific curiosity can play in the discovery of major drugs, in the same way that penicillin was discovered. They also play a role in the phenoxodiol story and are worth looking at from that point alone.

The platinum-based drugs are so-called because they are chemicals based around a central atom of platinum. They include cisplatin and its more recent derivatives, carboplatin and oxaliplatin. The origins of this drug date back to 1845, when a chemist by the name of Peyrone first showed that compounds could be made based around a platinum atom. There was little interest in this family of compounds until the 1960s when a researcher at Michigan State University made a fortuitous discovery. Barnett Rosenberg was interested in the effects of electricity on the growth of bacteria when he unexpectedly found that bacteria stopped dividing when placed in an electric field. This was an exciting observation, suggesting a potentially

new form of sterilization. Believing that the effect was related to the action of the electric field per se, Rosenberg spent months trying to unravel the mechanism. To his disappointment, he ultimately found that the inhibitory effect was nothing more than an artifact, with the platinum electrode being used to generate the electric field undergoing electrolysis, producing platinum-based compounds that were inhibiting the ability of the bacteria to divide. This might have been a disappointing result for the future of sterilization, but it was a mightily important step in the future of chemotherapy.

Fortunately for chemotherapy, Rosenberg had the foresight to see the potential of this accidental discovery, deciding to work with NCI to investigate the use of platinum- based compounds as potential anticancer agents. That led them back to the original work by Peyrone over a century earlier in terms of the chemistry required to create platinum-based compounds.

One of these compounds, cisplatin (1978), proved to be a highly effective anticancer agent, subsequently becoming one of the most widely- used chemotherapies and revolutionizing the treatment of a wide range of common cancers. In particular, it provided an effective cure for testicular cancer. It took another two decades to understand how cisplatin was working, which was by binding to the DNA and physically preventing the DNA from dividing.

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7. Rational drug design

The era of finding new anticancer drugs by accident (such as the platinums) or by trawling through Nature (such as the taxanes) is largely over. The wheel has come full circle and we have now returned back to the roots of chemotherapy as in the case of the folic acid antagonists. This is the era of rational drug design. This is the Trojan horse approach. Step 1 being identification of a particular chemical reaction within the cell that is essential to DNA function. Step 2 being to identify a chemical that is essential to that reaction and which the cell needs to source externally. Step 3 being to design a facsimile of that chemical, that looks sufficiently similar to the original to fool the cell into taking it up, but is sufficiently different that it fails to work.

In this process, the drug starts its life on a chemist's drawing board. The odds of such a drug working are a whole lot better than the hit and miss approach of collecting samples from jungle plants, but it has one very large drawback – you need to have a target to start with. That's the main benefit of the trawling-through-Nature approach – you don't need to know how the drug works to find the drug in the first place– that can always be worked out later. But with rational drug design, knowing how the drug works and what part of the cancer cell it needs to attach to is essential pre-knowledge.

Our knowledge of the cancer process has grown sufficiently over the past two decades that, combined with the computer power and computer-assisted design, new generations of anti-cancer drugs have become possible with chemical structures not previously seen in Nature. The basic premise of rational drug design is, if you know what the target in the cancer cell looks like, then it should be possible to construct a drug that will target it and block it. This is the lock-and-key approach that is the basis of most drug discovery today. In the trawling-through-Nature approach to drug discovery, the scientist essentially is relying on the chance discovery of keys – in the same way that a beachcomber might use a metal-detector to scan an

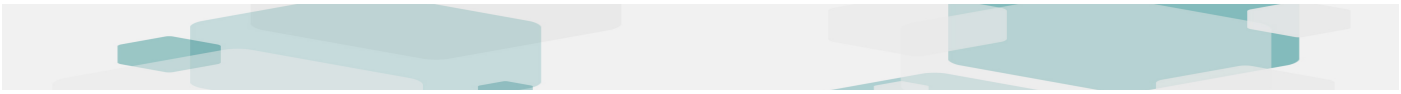
entire beach looking for a lost key. In the rational drug design approach, the scientist already has the lock, and simply has to craft a key to fit into it.

Aminopterin and its derivative, methotrexate, were the first examples of rational drug design. Folic acid had been identified as an essential nutrient for rapidly dividing cells, so it was just a matter of designing a drug that was close enough in appearance to folic acid to fool the cancer cell, but was sufficiently different that it completely failed to function once it was incorporated into the cell.

The first modern example of rational drug design is the breast cancer drug, tamoxifen. Although, ironically, it was contraception and not cancer that was the driving force behind its discovery. The whole concept of how sex hormones worked was exciting a lot of commercial interest in the 1950s because of the world's growing interest in chemical contraception. That interest eventually led to the arrival of the oral contraceptive pill on the world scene in the early 1960s, but at the same time a number of drug companies were also looking for anti-estrogen compounds in the hope of finding a successful morning-after contraceptive. The concept was to find a compound that looked sufficiently similar to estrogen that it would fool the estrogen receptor on a cell into letting it bind to it, thereby blocking the real estrogen from getting there, but would not trigger the receptor in the way that the real estrogen would.

In 1962, a team of endocrinologists under the direction of Arthur Walpole at ICI (now Astra-Zeneca), successfully developed tamoxifen as an anti-estrogen. Developed as a contraceptive, the drug never was commercially successful, although ironically it did come to market in a minor way as a fertility treatment. The true application of tamoxifen started in the late 1960s when the link between estrogen and breast cancer started to become obvious, leading to the notion that an antiestrogen might just provide some anticancer activity. In the face of considerable reluctance by ICI, Walpole personally championed the potential therapeutic value of tamoxifen, with a clinical study in London in 1971, subsequently showing convincing benefit of the drug in women with advanced breast cancer. Tamoxifen then was approved in 1973 for such use. Remarkably, the drug failed to ignite much interest among oncologists, mainly because the survival benefit was not large. It then took some years before it was realised that this benefit was being diluted because not all cases of breast cancer express the estrogen receptor, meaning that their growth is fuelled by estrogen. Approximately 70% of cases of breast cancer are now known to be estrogen receptor-positive, and when tamoxifen is isolated to these cases, the clinical benefit becomes apparent. This has led to tamoxifen being used predominantly today in early breast cancer following a 1998 study showing that tamoxifen provided a clear survival benefit in women with early-stage, estrogen receptor-positive breast cancer.

The third example of rational drug design is based on antibody technology. The concept here is to develop an antibody to knock out a particular target on the cancer cell, in the same way that our immune system makes antibodies to nullify the effect of bacteria and viruses. The antibody finds it specific target, attaches to it, and completely blocks the target's ability to function. Two such antibodies are herceptin and avastin (both developed by the US company, Genentech) directed against the estrogen receptor in the case of herceptin (approved 1998) and a blood vessel growth factor in the case of avastin (approved 2004).



The difference between drugs like tamoxifen and methotrexate on the one hand, and antibodies on the other hand, is fairly minor. Tamoxifen and methotrexate look like the molecules that they are meant to replace, and they are constructed in a laboratory in a step-wise fashion by synthetic chemistry. Antibodies, on the other hand, are made by immune cells that have been vaccinated against the specific target; the resulting drug is a protein, and looks nothing like the molecule that it is intended to block. Tamoxifen and methotrexate are produced in factories using lots of strange chemicals and heat. Monoclonal antibodies like herceptin and avastin are produced from human immune cells growing in vast tanks under sterile conditions.

Tamoxifen behaves like a pseudo-estrogen in inserting itself into a tiny part of the estrogen receptor, and it interacts with all types of estrogen receptors. Herceptin in contrast targets a type of estrogen receptor known as the HER2/neu receptor and it works by physically smothering the entire receptor, thereby depriving estrogen of any chance to reach the receptor. The HER2/neu estrogen receptor is only relevant to about 20% of cases of breast cancer. This type of estrogen receptor is present in all normal breast cells and all breast cancer cells, but only at very low levels. In about 20% of cases of breast cancer, the receptor is present in sufficiently large amounts that it is significant to the cancer cells survival, and it is here that herceptin provides a clinical benefit. Although considerable debate continues as to the cost-benefit nature of herceptin. The failure of about 70% of breast cancer cases to show any significant response, the high rate of resistance that develops to the drug, and the relatively high rate of adverse side-effects, all need to be measured against the relatively modest clinical benefit that it provides.

Avastin is an antibody directed against a protein that is responsible for promoting the growth of blood vessels. It is approved for the treatment of colorectal cancer and lung cancer. The rationale behind its development is the need of cancer tissue to have its own blood supply, capable of supplying nutrients to a rapidly growing tissue. To do this, the cancer cells produce a protein known as vascular endothelial growth factor whose role is to stimulate the production of blood vessels in a process known as angiogenesis. Avastin blocks this growth factor, restricting the flow of blood to the cancer tissue and slowing its growth. As with herceptin, the clinical benefit from avastin is modest, providing increased survival of several months in patients with late stage cancers.

The fourth, and final, example of rational drug design is the drug, gleevec, representing the epitome of this approach by bringing together all the tools of modern medicine to design a drug that is highly targeted and that finally (as with tamoxifen, herceptin and avastin) does not rely on the blunt instrument of damaging DNA in order to block a cancer cell. Gleevec represents the sort of drug that all oncologists dream about and all cancer patients wish was available for them…. a drug that will provide a rapid cure or long-term remission without any significant side effects.

Gleevec (or Glivec) represents the true hope of rational drug design …a drug that is design to hit a specific target that is unique to cancer cells and that is essential to the survival of the cancer cells, but which will spare all non-cancer cells. The cancer in question is chronic myeloid leukaemia.

This cancer is characterised by having genetic material swapped between chromosomes, resulting in the formation of a new gene. This new gene produces a protein that causes the cancer cell to divide uncontrollably. Brian Druker, an oncologist at Oregon health Science University was pursuing a research program endeavouring to find a drug that would block that protein, an action that he was convinced would

stop the cancer in its tracks. By chance he discovered that the large Swiss-based drug company, Novartis, had a number of test drugs that fitted this need, and one of them, gleevec, was selected for further studies. A Phase 1 study was started in 1998, resulting in all 31 patients in the study showing complete remissions. That outcome then was confirmed in larger trials, leading to the drug being approved in 2000 for the treatment of chronic myeloid leukaemia.