

# Breaking through the breakthrough hype

Why a hot research finding reported in today's newspaper may not make it into the clinic for 10 years, if at all! It's not a conspiracy, it reflects how little we really know and the many hurdles that have to be overcome to take a promising laboratory result and convert it into a new treatment. Seemingly every day we hear about breakthroughs in cancer research that promise new treatments, cures, preventions, etc. How can this be reconciled with the fact that there have been only marginal gains in overall cancer survival (with some notable exceptions)? There are several factors, each of which are complicated and require explanation but the first thing to get out of the way is the idea that scientists are, in any way, suppressing their findings. Canada spends billions of dollars on the healthcare system and it is a huge industry. The pharmaceutical companies are also multi-national, globalized behemoths. So why can't such an enormous enterprise crack cancer (or other health problems)? The theory that pops up all over the place is that in fact the researchers of the world have cracked it but that the medical profession and the pharmaceutical industry are in cahoots to keep these new wonder drugs and discoveries away from the public in order to maintain profits and jobs in their sector. This is nonsense but I am often asked about it and it merits a considered answer. Firstly, conspiracy theorists overlook the obvious fact that the families of the tens of thousands of people working in the healthcare/research professions and drug industry also suffer from the same illnesses for which cures are supposedly being withheld. Secondly, there are hundreds of independent organizations, institutes, universities, charities and companies employing brilliant minds to make discoveries. The effort is extraordinarily competitive at all levels. Setting aside the enormous incentive to alleviate suffering, there are huge economic benefits associated with disease prevention and cure. In such an environment, the likelihood of suppression of important advances is, thankfully, next to zero. Coming back to the fundamental argument, if we are spending billions on research and there are breakthroughs but few cures, what is going on. To understand the relationship between scientific discovery and clinical impact, I need to explain the processes involved in modern research.

The process of public research. Despite common beliefs otherwise, the majority of basic research funding in the biological sector is performed in public funded research laboratories. These may be with universities, hospital-based research institutes or not-for-profit laboratories. In Canada, cancer research is primarily funded by the Canadian Institutes of Health Research (one of which is the Institute of Cancer Research) and the National Cancer Institute of Canada. The former is federally funded, the latter is a charitable organization that funds cancer research on behalf of the Canadian Cancer Society, the Terry Fox Foundation and the Canadian Breast Cancer Research Initiative. In addition, there are many smaller charities that support various aspects of cancer research (including the Marilyn Van Stone Foundation). The total budget for cancer research in Canada by these agencies is approximately C\$100 million per year. By comparison, the cancer research budget in the USA is between US\$5-8 billion (which, coincidentally, is close to the actual healthcare cost of the cancer "burden" in Canada).

Accessing funds. In the case of the larger funding agencies, scientists apply for funds to perform research projects by submitting a grant proposal. This is usually 10-20 pages describing the proposed research, its background, the reasons why the research is important, what it is hoped to achieve and what the state-of-the-art is. It can take up to a month to prepare an application and each one requires significant preparation by means of literature references, preliminary data and organization of resources. A number of safe-guards must be shown to be in place (such as safe radioactive material handling, ethical considerations and oversight). A line-by-line budget is included along with justifications of proposed expenses. Finally, the application is signed by various officials who are responsible for ensuring appropriate accounting, reporting and administrative support. Many copies of each completed application are delivered to the funding agency where they are sorted and then sent back to the scientists! Not to the scientist who is applying, of course, but to other scientists who are considered experts in the area and are qualified to review, critique and assess the application. This is called peer-review and the entire process is confidential – this protects both the work of the applicant and the reviewer who can judge the work fairly, without worry of recrimination. In the case of Canadian applications, reviewers all over the country and the USA are used. Once or twice a year, committees of scientists (and, in the case of the NCIC, lay members) meet in Ottawa or Toronto and collectively discuss and then rank the applications from that year. A score is attributed to each application and the comments of the reviewers (which often run to several pages) are forwarded to the applicants to help improve their ideas. Typically over half of the applications are rated highly enough for funding. However, it is rare that more than 3 out of 10 receives funding. This is because there are simply not enough dollars to fund everything that merits it. The "rejected" applications can be re-submitted in the next competition and the cycle repeats. If funded, a grant is awarded to the administering institution on behalf of the scientist – usually for a period of 3 to 5 years. The values of these grants range from about \$40,000 to \$200,000 per year. Some competitions are designed for groups of scientists who closely collaborate – such group grants can be over \$1,000,000 per year. This sounds like (and is!) a lot of money. Why is research so expensive? Much of the funding goes into paying for people. Research is performed by several types of people: graduate students who are studying for a Masters degree or PhD (which takes 2-6 years) are paid about \$20,000. Once they graduate with a doctorate degree, they can continue their studies (in a different laboratory) as postdoctoral fellows. These researchers earn between \$30-40,000 and have spent at least 8 years in training. The laboratory heads (known as principal investigators) run the laboratories, write the grants, teach and employ the students and fellows. Unlike the students and fellows, their salaries are not paid by the grants. Instead, they are paid by the universities and institutes in which they work. The principal investigators also employ highly trained technicians. Laboratory science is therefore very labour-intensive. On top of the salaries, the materials required for research cannot be

bought at Wal-Mart. Chemicals, reagents and specialized plastics must be sourced from scientific suppliers. On average, each scientific worker consumes \$25,000 of materials a year. Unusual appliances and equipment are also needed. A single bench-top centrifuge can cost the equivalent of a small car. Modern science is propelled by a combination of advancing knowledge and new technologies. This means that researchers must devote a lot of time to reading about developments to stay on top of the ever-growing knowledge base. Lately, this has been greatly helped by the internet (which was actually started by scientists who wished to collaborate and communicate). Computers are therefore a common fixture in modern labs. Other, more expensive, machinery is also commonplace. Five years ago, a piece of equipment for determining the particular sequence of 400 segments of DNA might have cost \$5000. Today, the state-of-the-art "sequencing" machines cost \$300,000 but have a throughput of over 1,000 times that of the five-year old machines. If scientists use the old equipment, they fall behind and are less efficient. In many cases, new technologies allow scientists to do things that simply were not possible a few years ago. As a consequence, there is a constant need and turnover of equipment.

Communication of research discoveries. With thousands of researchers working on cancer, how is the new information disseminated? How is duplication avoided? Who judges the significance of a result? The primary means of information dissemination is by publication of data in scholarly journals. For example, there are over 1,000 journals that cover cancer research. Some are more "prestigious" than others – in essence, there is a pecking order among the journals. The "top-tier" journals are more widely read and their contents are more commonly cited. As a consequence, researchers try to have their work published in these journals. The top journals are therefore very picky and selective – choosing only the most striking papers or those that appear to be most interesting. Every research paper submitted to a journal is peer-reviewed. Top-tier journals reject over 90% of papers submitted to them. Publication of a study in a lower ranking journal does not mean it is of poor quality or irrelevant – the results simply may not be quite as exciting. Scientific standards are very high and if a result cannot be repeated, the original finding is soon displaced (if there is evidence of misconduct or fraud, the consequences are dire for the scientist). Each paper is "peer-reviewed" by at least 2 or 3 anonymous scientists. The primary publication of papers provides a constant flow of high quality information. A scientist cannot publish a piece of work unless it is original. This prevents copying or duplication although it is quite common to find two or three researchers in different parts of the world simultaneously publishing similar findings. Using advanced computer tools and reference collections, a piece of work published tomorrow can be on the desktops of 10,000 scientists within an hour of release. To help in assimilating this vast amount of new knowledge, reviews of particular fields are frequently commissioned. Instead of having to read 200 individual papers, a researcher can first turn to a recent review in which an expert in the field has brought together those papers, melding them into a single article which points to the original articles but conveniently summarizes them. Thus, scientific research is carefully documented, processed, published, reviewed and assimilated.

The role of pharmaceutical companies. Research is conducted in public laboratories in most countries of the world. In addition, pharmaceutical companies conduct their own research. These are typically large, multi-national corporations. Due to the costs of drug development, academic scientists cannot afford to develop drugs, which may cost over \$100 million to bring to fruition. The drug companies have enormous libraries of chemical compounds along with robotic instrumentation to allow efficient screening for new therapeutic agents. They also have the infrastructure to test, refine and develop a new drug. The major pharmaceutical companies each have a handful of "blockbuster" drugs. However, these have limited patent life and since it takes years to bring a drug from the laboratory to the clinic and the patent clock starts ticking at submission not at the time the drug hits the clinic, the window of time for recouping costs and making a profit can be relatively short. Once the patent expires, any company can make the drug which brings the cost down. The patent protection therefore allows a company an opportunity to recoup its investment in developing a drug. Without this shield, no company could afford to develop new molecules.

Why does it take so long to bring a new drug into use? After a promising drug has been discovered and refined (which may take 5 or more years) it must be extensively tested on humans. Testing of a promising new drug in humans requires approval by the Federal Drug Administration (FDA). This is a US government agency that screens all drugs that may be used to treat Americans. In Canada, the sister agency is the Health Protection Branch (HPB) of Health Canada. HPB maintains close links with the FDA and other similar national agencies. It is through this cooperation that problems found in one drug in one country are rapidly communicated around the world. Due to the size of the US market, the FDA plays a large role in global drug certification. Getting a drug approved by the FDA is not an easy, cheap or quick matter. The FDA requires full (confidential) disclosure of all tests performed by the company in the development of the drug. It may ask for new tests or for work to be repeated. If approval for human testing is granted, the drug may enter clinical trials. This is where the cost of drug development really spirals. Typically, a new drug must go through a series of escalating trials. The initial Phase 1 trials are not designed to demonstrate whether the drug works. Instead they are designed to find the safe dosage of drug. Patients are treated with increasing amounts of the drug and the first appearance of side-effects is carefully monitored (at which point the amount of drug is reduced). In cancer research, most conventional chemotherapeutic drugs are poisonous. In addition to killing the cancer cells, they will kill normal cells as well. The window between the amount of drug needed to kill the tumour cells and the amount that causes bad side-effects is often small. This "therapeutic window" must be carefully defined. Although Phase 1 trials involve small numbers of patients and do not directly test for the effectiveness of the drug, the researchers do look for evidence of benefit and in some cases this is observed. But if the trial is not about curing a disease, how is it ethical to give an experimental drug to patients? All clinical trials require ethical approval. All hospitals refer proposals for clinical trials to a research ethics board that comprises researchers, clinicians and lay members, none of whom is allowed to have any financial interest in the drugs being assessed. Each approved trial involving human patients requires that patient to sign a consent form that explains the reason for the trial, the possible risks and who is conducting it. All patients have the right to refuse to participate in a trial and their care is not affected by the decision. In many cases of new cancer drugs, there are few treatment options left for the patients, apart from experimental therapies. Thus, the trial may offer hope or the patient may wish to help people who contract the disease in the future.

The next level of clinical trial, Phase II, is based on the safe dosage information from the first trial. Whereas in Phase I

cancer trials, patients with a variety of types of cancer may be eligible for the same trial, Phase II studies tend to focus on a particular type of disease. These trials are specifically designed to test for beneficial effect. As such, a variety of tests are performed to measure the tumour response, drug effects on the patient and the effect of different dosage regimens. Larger numbers of patients are needed and the cost is therefore increased. Once the trial has closed, the data is analyzed and submitted to the FDA. Due to the large numbers of trials, there are many standardized tests and statistical analyses to which the mounds of data are subjected. The FDA is an independent body which objectively oversees the tests. Thus, if the data do not provide evidence of efficacy, the trial will be noted as such and permission to extend the research into a Phase III trial will be denied. If the data look promising, the next stage is a randomized Phase III trial. Here, the new drug is administered to half of the patients (usually in combination with another, established therapy). The remainder receive a placebo - a dummy drug. Again, strict ethical considerations are enforced. But how can it be reconciled that half of the patients receive no new drug? The problem is that for approval, a new drug must be demonstrated to be effective and have some form of benefit over existing therapies. The only way to assess this effectively is via a double-blind, placebo-controlled trial in which neither the clinicians nor the patients know whether they are receiving drug or placebo. However, the results are usually assessed during the trial. If it is clear that the new drug is conferring a clear beneficial effect, the trial may be prematurely ended and all of the patients may receive the drug. Finally, a Phase IV trial may be required to assess new indications for drug therapy, combinations with existing therapy, etc. As the trials proceed from Phase I to IV, the cost increases. By the time a typical new drug reaches the point of eligibility for approval, \$200-500 million may have been spent on its development. Even upon approval, there is no guarantee that clinicians will choose to use it and provincial drug plans may not opt to cover the cost. The high cost of drug development has a number of consequences. Firstly, pharmaceutical companies know that on average for every 100 new drugs developed in the laboratory, only one will enter the clinic. Therefore, they have to hedge their bets. Promising new drugs are ditched if there is a sign of an early problem. Drugs that do make it through the process tend to be incremental in effect, owing to the reduced likelihood that they will induce deleterious effects in a small fraction of patients. Since it is only in the last stages of testing that large numbers of patients are exposed to a new drug, companies reduce risk by targeting the major cancers instead of the rarer cancers (however, there is an orphan drug program that subsidizes development of therapeutics for diseases with restricted patient numbers). Patience and patients. This article has touched upon the convoluted processes that go into scientific discovery. The funding process, publication of data, testing of new drugs and development of new therapeutics. Given these hurdles and the costs involved in bringing a new drug safely to market, it is not surprising that progress appears to be slow. There is a huge distance between a promising scientific finding and conversion of that finding into clinical use. This gulf includes the need for much more research, huge amounts of funding (much of it by drug companies) and the many hurdles of clinical trials. So why do scientists release information about "breakthroughs" to the press when they know that even if they can be converted into a useful therapy, this won't occur for many years? In part this serves to attract attention to the researcher and their institution. This may help in attracting new funds and improving the profile of the hospital or university thus accelerating the research that can be done. In part the release of information is in response to the insatiable appetite of people for new information (and the press are only too happy to seek it out). The driving forces and mechanisms underlying life represent an enormous, largely unexplored frontier. We have an immense task to understand even the most basic diseases, their causes and means to prevent their occurrence. At the same time, these diseases affect us all – we have a common, vested interest in combating these illnesses. As such, it makes for a good read and there is always another discovery just around the corner. So the next time you read about a breakthrough in the newspaper or on television think of it as a glimpse into the future, a peek of the tip of an iceberg that represents the on-going and largely invisible worldwide effort to improve quality of life and reduce human suffering. Then, spare a thought for the selfless efforts of the many charities that are supporting and encouraging this research.

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