A drug of one's own

The Economist. London: Dec 14, 2002. Vol. 365, Iss. 8303; pg. 36

(Copyright 2002 The Economist Newspaper Ltd. All rights reserved.)

For three decades, Ronald Levy has been seeking ways to use the body's immune system to fight cancer--much as it does the common cold. His goal has been to create "personalised drugs", first in the form of antibodies and now as vaccines, capable of destroying a patient's actual malignancy

IN 1981 Ronald Levy bought himself a yellow station-wagon, with plenty of room for his three young daughters. At the time, he was about to test a new experimental drug for B-cell lymphoma, an often deadly form of cancer that is becoming increasingly common. Which, he wondered, would last longer--his patient or his car? As it turned out, the patient, Philip Karr, won, and is now 88 years old; the car has long gone to the scrapyard of man-made machinery. Mr Karr's miraculous recovery marked the first successful use of antibodies against cancer.

For more than three decades, Dr Levy, now chief of the oncology division at Stanford University School of Medicine, has researched how a person's immune system can be coaxed into fighting cancer--much as it fights the common cold. Thirty years ago, this was a novel idea. Next to surgery, aggressive treatments, such as radiation and chemotherapy, were often considered the only options for survival. Unfortunately, they routinely did patients as much harm as good--by killing off all dividing cells, cancerous or healthy. But with Dr Levy's "proof of concept", explains Dawn Willis of the American Cancer Society, "a whole new field opened up."

The promise of antibodies (or "magic bullets" as they were known at the time) boosted funding for biotech start-ups round the world, and helped Dr Levy to co-found a company, IDEC Pharmaceuticals, in 1985. But commercial success did not come easily. It took more than a decade before a modified version of the antibody was developed by IDEC and got to market, though not customised for each patient, as Dr Levy had originally hoped. In 1997, the Food and Drug Administration (FDA) in Washington, DC, approved Rituxan--the first monoclonal antibody for use against cancer.

The one quality that can be singled out for Dr Levy, says his former research fellow, Larry Kwak, is his perseverance. During his career, Dr Levy watched antibodies go in and out of fashion. He watched medicine based on good science abandoned because it cost too much. Through it all, he never stopped believing that antibodies would evolve into established drugs that could make a significant contribution to a patient's survival.

Also, he never gave up on the customised approach. Since the late 1980s, Dr Levy has been working on another promising treatment against B-cell lymphoma: a patient-specific cancer vaccine. Rather than offering protection against the disease, its aim is therapeutic, for those already afflicted. A few bold biotech start-ups are betting that they can find a cheap enough way to make the medicine. Late-stage clinical trials, usually the last step before receiving approval from the FDA, are already under way. Quite soon, it appears, Dr Levy might at last see his made-to-order approach bear fruit.

War on cancer

A Stanford graduate, Dr Levy began his training in cancer immunology in 1970, when he signed up for a two-year stint at the National Cancer Institute (NCI). At the time, the fellowship was a convenient way for young American scientists to avoid the Vietnam draft, a thought that was certainly in his mind. But it also gave Dr Levy the opportunity to study with other up-and-coming researchers, such as Dr Steven Rosenberg, who would become chief of the NCI's surgery branch and a leader in tumour immunology and immunotherapy.

Those were exciting times--Richard Nixon had just declared his "war on cancer", and funds poured into research projects. The idea was to make the connection from laboratory science to clinical medicine, says Dr Levy. There was a feeling that great discoveries were just around the corner.

Meanwhile, two different research teams in Britain did make some big breakthroughs. They would set Dr Levy on course for the next quarter-century. Each healthy B-cell expresses a unique "marker" protein on its surface, which it uses for binding antigens. When B-lymphocytes detect a foreign substance in the body, they respond by dividing and turning into little factories, churning out the same protein over and over again. This then binds to the antigen, tagging the invader for destruction.

In B-cell lymphoma, one cell also divides endlessly, but this time without a purpose. In 1975, George and Freda Stevenson, of the University of Southampton in Britain, discovered that, in each individual patient, all malignant B-cells display the same "marker" protein, which could be used as a target. At the same time, Cesar Milstein and Georges Kohler, of the Medical Research Council's Laboratory of Molecular Biology in Cambridge, worked out how to make monoclonal antibodies (they later received a Nobel prize). They fused two types of mouse cells--a tumour cell and a lymphocyte. The new hybrid cell had properties of both. It was not only immortal, but could also produce antibodies forever.

When Dr Levy realised the implications, it became clear that he not only had a way to identify and target all cancerous B-cells in one patient, but would also have the ability to create a potent customised therapy that would exploit a B-cell's unique marker protein. By 1975, Dr Levy was hired by Stanford and eager to test his ideas in his own lab.

Just one question remained: should he develop a patient-specific antibody able to latch on to the target directly, or formulate a customised vaccine that could train a patient's immune system to launch its own attack? After asking a few colleagues from around the world, including the Stevenson team, he settled on making the antibody.

Great expectations

When the Karr case became public in 1982, Dr Levy's phone began ringing non-stop. Patients lined up for the new treatment as the press came knocking at the door. Venture capitalists came, poised to exploit the next generation of blockbuster drugs. This frenzy helped Dr Levy to start IDEC Pharmaceuticals.

Yet the road to success was rocky. Although Dr Levy was able to repeat his findings, many other researchers were not. There were two difficulties: in some cases, the human immune system reacted strongly against the foreign mouse molecules and neutralised the antibodies; and many antibodies were not aimed at the right targets and simply had little effect. It would take more than a decade to sort out these problems.

Dr Levy proved that his particular antibodies worked, but the cost of making them was still prohibitive. After years in clinical trials, IDEC abandoned the lengthy process of producing custom batches for individual patients. The company almost went bankrupt in the process. "Ironically, we had a treatment that worked [but] couldn't deliver," recalls Dr Levy. The science was good, says William Rastetter, IDEC's boss for the past 16 years, but it did not prove cost-effective.

By the early 1990s, the conventional wisdom on Wall Street was that antibodies just did not work. But IDEC continued, this time round with a new target found on many cancerous B-cells. Now all patients could receive the same antibody. Manufacturing the drug turned out to be economically feasible, and it produced measurable responses in about half of all patients. In 1997, the FDA approved Rituxan, making it not only the first cancer antibody ever adopted for widespread use, but also the first lymphoma medication to hit the market in 20 years. It has since become a $1 billion drug.

Many in the field give Dr Levy credit for laying the foundation for Rituxan's success, but he also never gave up trying to make "a drug of one's own". Since 1988, he has led about a dozen small studies, testing a patient-specific cancer vaccine. So far, the results have been encouraging: at least half the 200 or so people who received the medicine showed an immune response, and many stayed in remission for longer than the two years that are typical following chemotherapy. In a few cases, tumour shrinkage was observed, lasting four to five years. Several patients have remained disease-free for years after receiving the treatment. But, even if the vaccine eventually proves successful in large randomised clinical trials, one big question will remain: can it be manufactured cheaply enough to be cost-effective?

After struggling with this for nearly two decades, Dr Levy remains as determined as ever to find a solution. For one thing, vaccines are only half as much trouble to make as antibodies. Rather than manufacturing the antibody, scientists isolate the "marker" protein and mix it with an immune booster, hoping that the formula will coax the patient's own immune system into launching an attack on

the cancerous cells. To perfect the process, Dr Levy is prepared to work with anyone who has a good idea. "He's Darwinian about it," says Dan Denney, chief executive of Genitope, a biotech company in Redwood City, California.

It would be better if making "drugs of one's own" did not cost so much. But surgery--another form of customised therapy for cancer--is far from cheap. "We do it because it works, not because it's cheap," says Dr Levy. But unlike the business of surgery, with its highly specialised practices, the pharmaceutical industry has evolved around the drug-making notion of "one size fits all". Dr Levy hopes that one day the two concepts will merge--so that people can be treated pharmacologically as the individuals they are.

That wish could come true in the case of B-cell lymphoma. A handful of his former research fellows have gone on to do their own studies in the field. The closest to success looks like being Dr Kwak, now a principal investigator at NCI's experimental transplant and immunology branch. After completing a series of small, successful studies, Dr Kwak is now conducting his own late-stage trial.

So far, no cancer vaccine--customised or otherwise--has reached the market. But for B-cell lymphoma patients, the wait may be coming to an end. If everything goes to plan, data from Genitope's trial may be released two years from now. And if the FDA deems the study a success, approval could follow a year or so later--a quarter of a century after Dr Levy bought himself a yellow station-wagon and rid Philip Karr of B-cell lymphoma. "The irony of it all", comments Brook Byers, a partner at Kleiner Perkins Caufield & Byers, a venture-capital firm in Silicon Valley that was one of the original investors in IDEC, "is that 'personalised medicine' is now the new thing."

"Dr Levy proved that his antibodies worked, but the cost of making them was prohibitive."

Indexing (document details)
Subjects:
Cancer, Antibiotics, Biotechnology, Medical research, Personal profiles
Classification Codes
9190 United States, 8641 Pharmaceuticals industry, 5400 Research & development
Locations:
United States, US
People:
Levy, Ronald
Document types:
Feature
Publication title:
The Economist. London: Dec 14, 2002. Vol. 365, Iss. 8303; pg. 36
Source type:
Periodical
ISSN:
00130613
ProQuest document ID:
267244941
Text Word Count
1772
Document URL:
http://proquest-.umi-.com/pqdweb-?did=267244941-&Fmt=3-&clientId=12498-&RQT=309-&VName=PQD