Real progress in the fight against cancer

Medical scientists excited about dramatic potential of university-developed drugs

A CURE FOR cancer is often posited as the ultimate medical scientific breakthrough. While not claiming any miracles just yet, we can say for sure that our colleagues’ hi-tech work at the DNA level has produced a dramatic new treatment that has cancer doctors around the world excited. This section relates how scientists at Lo Ka Chung Centre for Natural Anti-Cancer Drug Development of The Hong Kong Polytechnic University produced a revolutionary drug which fights tough forms of cancer seen as death sentences for millions of people every year. It started as a fight against a single form of cancer, but has grown into a drug that attacks many different forms of the disease. These breakthroughs are not only a coup for the University, but a first for Hong Kong.

Fighting a terrifying enemy
Breakthroughs in the fight against the world’s most dreaded killer do not take place in police investigation rooms. They take place in university laboratories. And the investigators are not detectives, but scientists.

The fight against cancer is not a single war, but a series of thousands of battles waged simultaneously in laboratories around the world. It’s a frustrating fight, since the enemy is infinitely adaptable while genuine breakthroughs are few. That is why the achievements of the Department of Applied Biology and Chemical Technology at The Hong Kong Polytechnic University have been so widely celebrated.

The project has been driven by Prof. Thomas Yun-chung Leung and Dr Thomas Wai-hung Lo. Dr Paul Ning-man Cheng has also been involved. They first made headlines by making significant steps in the fight against liver cancer, one of the top five cancers in the world, and the second most common form of cancer in Hong Kong and the Chinese mainland. (A million cases of liver cancer are diagnosed every year around the world, of which a quarter are in China. In Hong Kong SAR, 1,500 new victims are identified every year.)

Scientists have long known that liver cancer tumour cells need an amino acid called arginine to grow. If one could deplete the arginine, the growth of tumours would stop. “If we can use arginase (an arginine-depleting enzyme) to remove arginine from the blood, we then stop its supply to the liver cancer cells,” said Prof. Leung. “This is able to effectively starving the cancer cells to death.”

However, naturally occurring arginase has a very short half-life, which means it loses its efficacy at high speed. It disappears too fast to be used for therapeutic purposes.
The three PolyU scientists decided to look for a way to prolong the useful life of arginase. They used state-of-the-art DNA technology and enzyme formulation to change the basic arginase “recipe”. Their breakthrough was in producing a substance which they defined as a “recombinant human arginase”. In practical terms, this turned out to be arginase with a significantly prolonged half-life in which retained its efficacy for long enough to be of significant therapeutic use.

Early trials quickly got cancer specialists excited. Pre-clinical studies conducted on the use of this drug in monkeys, the primates closest to human beings, showed that the drug was effective in depleting the arginine level without any observable side effects. Since liver cancer patients survive on average less than six months after diagnosis, the breakthrough was significant.

But the PolyU team realized that they could expand their fight to other forms of cancer. That’s when they realized the excitement was only just beginning.

that the therapy is targeted only at the unwanted cells, and is thus very safe to use — a key consideration in cancer treatments, which can cause negative effects to health. Most cancer types, including liver cancer, malignant melanoma, pancreatic carcinoma, prostate cancer, kidney cancer, lung cancer, stomach cancer, esophageal cancer, colorectal cancer, leukemia, and breast cancer, lack genes which are important for arginine synthesis. Therefore they cannot synthesize arginine internally, and depend on arginine supply from the blood.

So the systemic arginine depletion caused by the new drug, BCA-PEG20, can lead to the death of these cancers cells. Finally, these two scientists had a way to introduce something into the body which killed cancer cells but left other cells entirely undamaged. The next job was to test it out.

Tests proved it worked
With support from the Lo Ka Chung Charitable Foundation and the Simatelex Charitable Foundation, the scientists tested the drug on mouse models of human liver cancer, lung cancer, stomach cancer, esophageal cancer, colorectal cancer and breast cancer. The results caused great celebration. The drug inhibited the growth of all these human tumours, including ones that had developed resistance to ADI-PEG (another arginine-depleting enzyme). In the US and other countries, ADI-PEG is currently in phase III clinical trials on liver cancer, and is expected to be in market in 2013 or 2014.

A second generation breakthrough
More recently, Prof. Leung and Dr Lo launched their second generation anti-cancer drug, called BCA-PEG20. This turned out to be even more dramatic. Using state-of-the-art DNA technology and protein engineering, they designed and synthesized an effective, safe, highly stable biotech drug with potent anti-cancer activities.

The main constituent is the thermo stable bacterial arginase, an efficient enzyme that degrades arginine, an amino acid that is essential for cancer cells but not normal cells. Patents have been filed in the US and other countries.

The new drug works by starving cancer cells through the depletion of arginine, which is a key nutrient for all cancer types. Tumour cells grow much faster than normal cells and they need to get more arginine from the blood for protein synthesis. Healthy human cells are able to synthesize arginine by themselves, therefore arginine depletion in the blood causes no harm to normal human cells. This means
Traditional chemotherapies kill both cancer cells and normal cells, causing serious side effects, such as alopecia, abdominal pain, diarrhoea, mouth sores, depression, weakness, allergic reactions and so on. But the new drug is a targeted biological drug, so is much safer.

The new drug has enormous potential. The market is extremely big. In the near future, when BCA-PEG20 hits the market with approval to treat, for example, metastatic colorectal cancer, the scientists have calculated that it could expand its franchise and rise, for that indication alone, to be a US$3 billion drug. If it is used in addition for other cancers, the potential for success is enormous.

The road to success

The path to creating the drugs was a long one. The development project started in 2001 with initial support from the Innovation and Technology Fund. Over the years, the project received more than HK$8 million in funding from the government and from industry.

With the support of the University of Hong Kong’s Li Ka Shing Faculty of Medicine (HKU), the team’s first drug, aimed at liver cancer, was put forward for formal clinical trials at the Queen Mary Hospital in 2005. The HKU centre also participated in repeated animal studies to confirm the efficacy of the drug on mice. In early presentations explaining how the initial drug worked, a memorable image was one of two mice, one with its distended cancerous liver clearly visible through its skin, and the other, treated with the drug, with no visible sign of cancer. In press conferences, videos were shown of a human sufferer showing marked improvement after treatment. More importantly, fifteen patients were enrolled in a phase 1 clinical study. It was found that the team’s first drug has a manageable safety profile and is potentially a superior arginine depleting agent than ADI-PEG in the treatment of liver cancer due to its low toxicity profile and sustainable arginine depletion.

It was also a significant discovery for the team’s home town. These are the first significant drugs developed in Hong Kong that have reached the stage of clinical trials, marking cornerstones in the development of bio-technology in Hong Kong.

Now that a second-generation drug has been produced, targeting a much wider range of cancers, the real excitement is only just beginning.