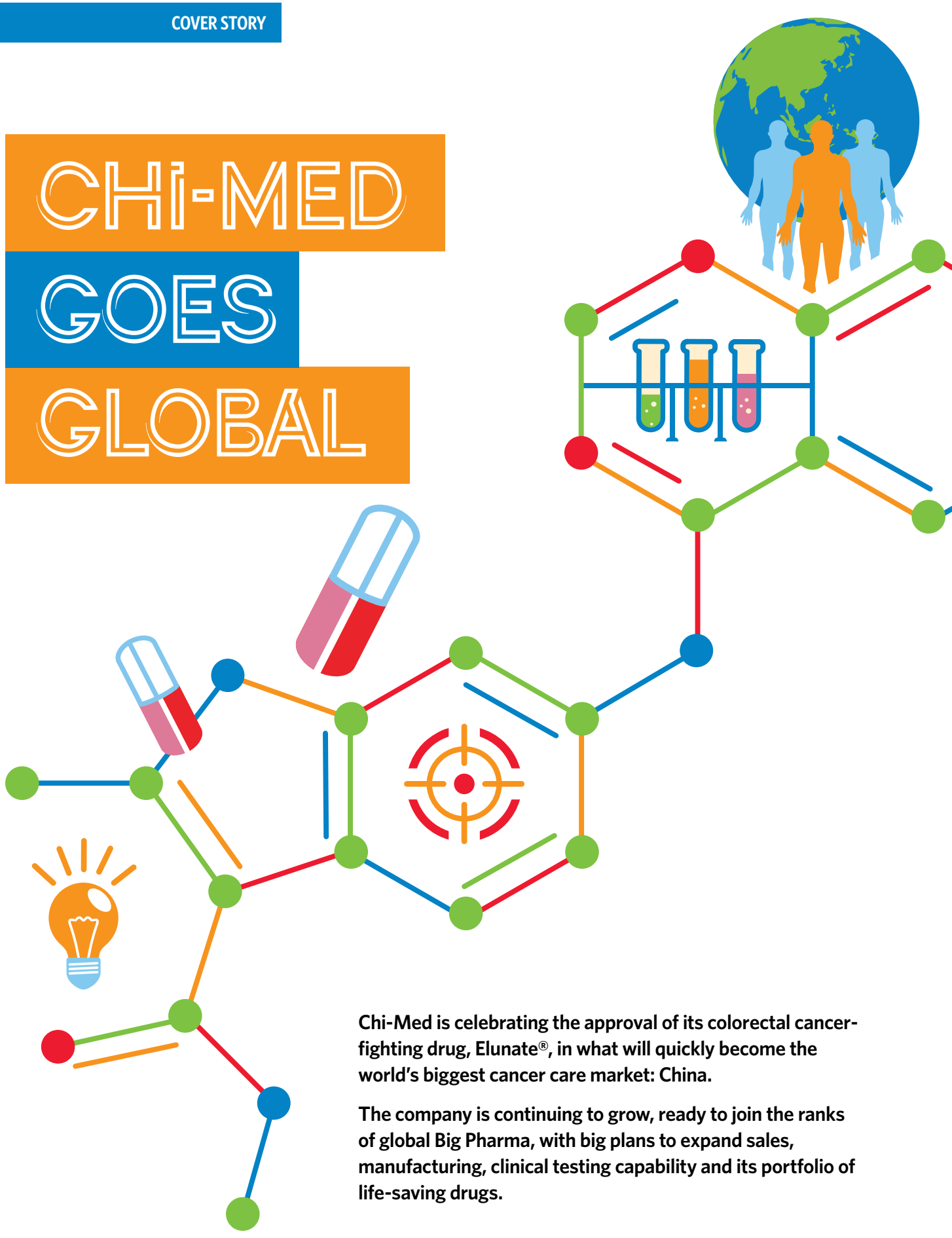
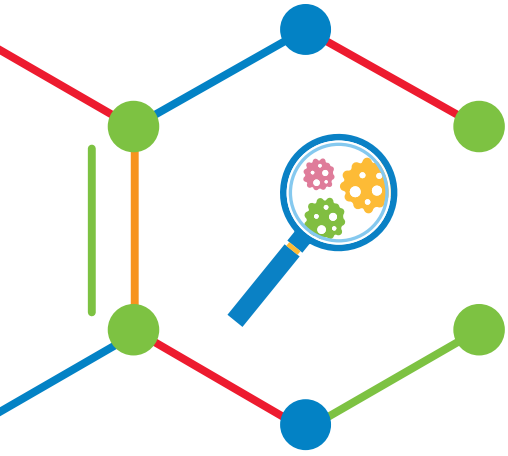
CHI-MED GOES GLOBAL



Chi-Med is celebrating the approval of its colorectal cancer-fighting drug, Elunate®, in what will quickly become the world's biggest cancer care market: China.

The company is continuing to grow, ready to join the ranks of global Big Pharma, with big plans to expand sales, manufacturing, clinical testing capability and its portfolio of life-saving drugs.



Chi-Med, more formally known as Hutchison China MediTech Limited, has been on a long journey with no guarantee of success. In the late 1990s, a whiteboard and a new CEO were the beginning. From that audacious start, a beautiful win has arrived: a new drug that brings hope to patients fighting one of the most pervasive variants of cancer, with over 1.8 million new cases diagnosed globally every year.

A FIRST IN FIGHTING CANCER

In mid-2018, Chi-Med joined an elite group of pharmaceutical companies which had succeeded to "home-grow, discover and develop a drug ... to be unconditionally approved ...", according to Simon To, Chairman of Chi-Med. Fruquintinib, now selling under the brand name Elunate®, is being prescribed to late colorectal cancer patients in China for whom other front-line treatments against colorectal cancer have failed.

This is a big deal. Modern pharma research almost exclusively sees drugs brought to market by European and American pharmaceutical giants. They scour the world, hoovering up the rights to single-molecule drugs that they shepherd through the expensive and uncertain world of regulatory approval. Support for such drugs is based on their potential for financial success in the best paying economies – the US, Japan, Europe and other rich countries. Mass trials are conducted in those markets and best serve those populations.

In the world of Big Pharma, Chi-Med is the upstart, challenging the status quo as a result of a sustained effort that started almost two decades ago.

VISION

"It's been 18 years of effort," says Christian Hogg, CEO of Chi-Med.

It began as a vision in the late 1990s and took form in 2000 with the acquisition of formerly state-owned assets with the aim of turning them around to create a modern consumer healthcare business based on existing Traditional Chinese Medicine (TCM) products.

This is very, very different from the Big Pharma names that you know. Most of the Eli Lillys and Pfizers of the world carry the name of a 19th-century chemist who founded their business in a completely unregulated world of consumer pharmaceuticals (e.g. Eli Lilly in 1876 and Charles Pfizer in 1849).

Mr Hogg was there at the beginning, in 2000. The business acquired to launch Chi-Med was achieving only around US$20 million in annual sales and was losing money. The first order of business was to improve the product line and marketing and, especially, overhaul the sales force. This was done in short order and the business began to grow – and became profitable. Today it generates over US$700 million of top-line sales.

More importantly, it has provided the funds and stability needed for Chi-Med to branch out into a relatively risky new direction: developing single-molecule drugs to be potent weapons in the war against cancer. Over the years, the profits from the consumer business gave Chi-Med

Chi-Med is the upstart, challenging the status quo.

Global Reach

Chi-Med is currently building the ability to conduct clinical trials for its portfolio in Canada, Australia, the US and Europe. As Mr To says, "Chi-Med is consistently making significant progress towards its goal of being an innovative global biopharmaceutical company, and our achievements last year amply demonstrate this."

The international biopharmaceutical company was founded in 1999 from an initial investment from CK Hutchison. Since then, Chi-Med has expanded and elevated its sales force and manufacturing capabilities for its wide range of pharmaceutical grade and consumer healthcare products.

The firm's first public listing was on the London Stock Exchange's AIM in 2006. A successful NASDAQ listing in 2016 was a further validation from the global capital markets.

Chi-Med's strong R&D and manufacturing base in Central China is going to be buttressed with new clinical trial capabilities in the Greater Bay Area, encompassing the area around Hong Kong, Macau and neighbouring Guangdong Province.

"It's been 18 years of effort."

Christian Hogg
CEO of Chi-Med

staying power during downturns in the capital markets that may otherwise have hindered fundraising.

In the early years, Mr Hogg remembers that "nobody really cared about China pharmaceuticals". But the corporate leadership at CK Hutchison did. They saw the potential and recruited Mr Hogg from Procter & Gamble, a global powerhouse, to head up their new business.

Once the consumer business was on a stable footing, Chi-Med was ready for the next phase. But it would need new talent, very different from consumer TCM. It would need a world-class researcher to build and command a world-class research facility.

WORLD CLASS FROM THE START

Many young people have graduated from the Chemistry Department of the renowned Fudan University near Shanghai. But only one, Su Weiguo, was the first Chinese national to receive a scholarship to Harvard University to study for his PhD.

He spent seven years studying with Nobel laureate in Chemistry, Professor E J Corey, one of the greatest chemists in human history.

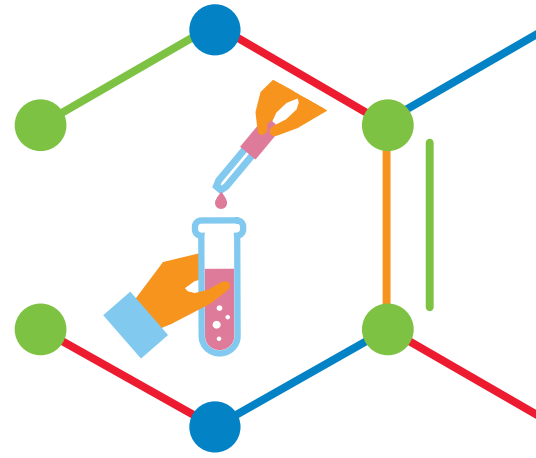
Dr Su worked with world-leading pharmaceutical firm Pfizer after he left academia. He became a mainstay of the Pfizer research team and their drug discovery process for 15 years, rising to lead the global Medicinal Chemistry Department. He joined Chi-Med and convinced the senior leadership that small-molecule oncology drug design was the way of the future. And he was right.

A STAR IS BORN

Fruquintinib was discovered two years into Chi-Med's journey searching for promising molecules to advance through the process to become an approved treatment and bona fide cancer-fighting drug.

At the same time, the CK Hutchison team – and the markets, through a listing on the AIM market of the London Stock Exchange in 2006 – were demonstrating their confidence in Chi-Med through further investment.

Meanwhile, the Chinese regulatory authorities wanted patients to have access to promising cures, and moved to improve the regulatory process for drugs of any origin. Mr Hogg explains that they reduced the time needed between moving from one trial phase to the next (assuming the latest round was successful). For promising molecules that addressed critical concerns with solid results in well-documented



research, approval procedures could be fast-tracked for priority review to potentially put life-saving drugs in the hands of patients as quickly as possible.

ATTRACTING THE HEAVYWEIGHTS

The pharma heavyweights weren't sitting on their hands, however. They noticed the success of the pharma upstart and wanted to collaborate. Over a five-year period, Chi-Med signed agreements with companies including Merck, Johnson & Johnson and AstraZeneca.

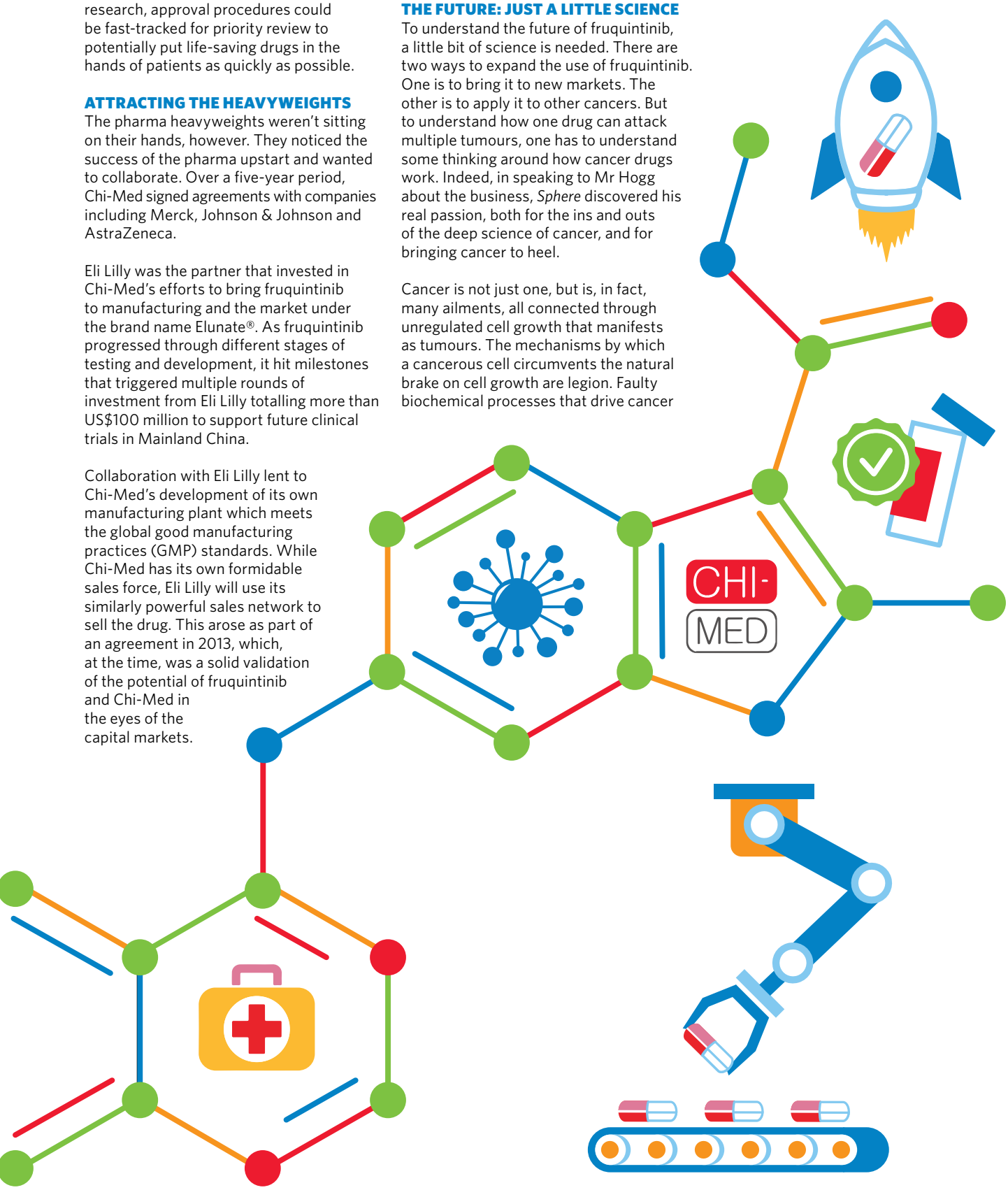
Eli Lilly was the partner that invested in Chi-Med's efforts to bring fruquintinib to manufacturing and the market under the brand name Elunate®. As fruquintinib progressed through different stages of testing and development, it hit milestones that triggered multiple rounds of investment from Eli Lilly totalling more than US$100 million to support future clinical trials in Mainland China.

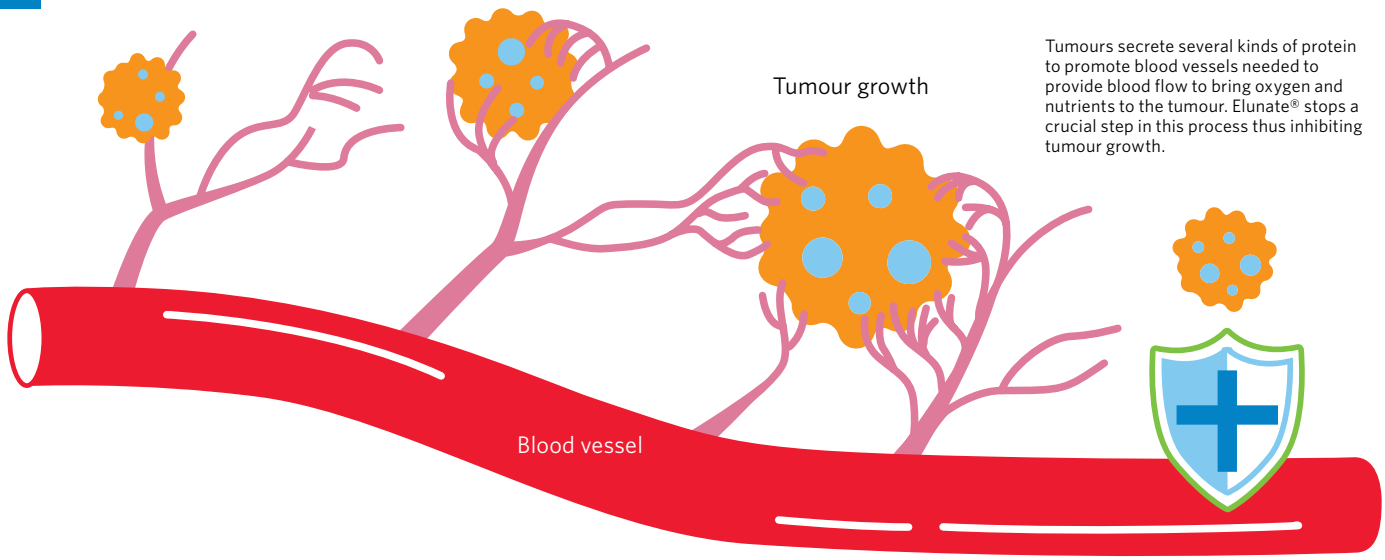
Collaboration with Eli Lilly lent to Chi-Med's development of its own manufacturing plant which meets the global good manufacturing practices (GMP) standards. While Chi-Med has its own formidable sales force, Eli Lilly will use its similarly powerful sales network to sell the drug. This arose as part of an agreement in 2013, which, at the time, was a solid validation of the potential of fruquintinib and Chi-Med in the eyes of the capital markets.

THE FUTURE: JUST A LITTLE SCIENCE

To understand the future of fruquintinib, a little bit of science is needed. There are two ways to expand the use of fruquintinib. One is to bring it to new markets. The other is to apply it to other cancers. But to understand how one drug can attack multiple tumours, one has to understand some thinking around how cancer drugs work. Indeed, in speaking to Mr Hogg about the business, *Sphere* discovered his real passion, both for the ins and outs of the deep science of cancer, and for bringing cancer to heel.

Cancer is not just one, but is, in fact, many ailments, all connected through unregulated cell growth that manifests as tumours. The mechanisms by which a cancerous cell circumvents the natural brake on cell growth are legion. Faulty biochemical processes that drive cancer





Tumours secrete several kinds of protein to promote blood vessels needed to provide blood flow to bring oxygen and nutrients to the tumour. Elunate® stops a crucial step in this process thus inhibiting tumour growth.

Over a five-year period, Chi-Med signed agreements with companies including Merck, Johnson & Johnson and AstraZeneca.

in one type of cell tissue may also be found in another cell type in another part of the body. So a drug that works for one cancer may also help stall another.

But usually, multiple processes are in play to help a tumour grow. The best approach to knock a tumour off its growth track is often to attack it on a number of fronts. For example, using drugs that block signals telling cells to split and other medicines that inhibit the growth of blood vessels that feed tumours with needed oxygen and nutrients.

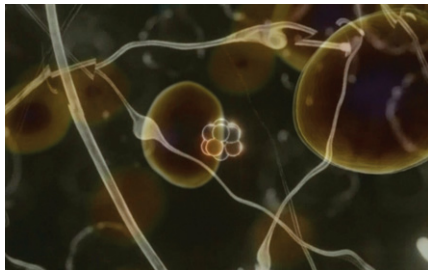
However, all these drugs often impact more than one biochemical pathway. They appear as what laymen call 'side effects' of treatment and the 'toxicity' of the drug. Think about people's gums bleeding and hair falling out during treatment. Cancer drugs attack fast-growing cells, often including gums and hair follicles.

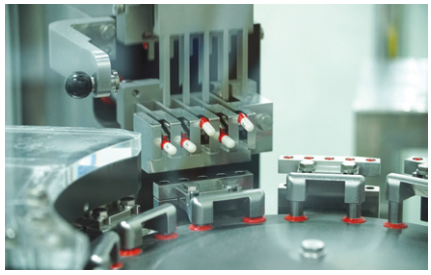
Finding and developing drugs that precisely target the biochemical pathways you want to hit is crucial. The term for this is 'selectivity' and it means drugs that cause fewer side effects and have greater efficacy in stopping the tumour from expanding. 'Clean' drugs are those with high selectivity, which don't create a host of side effects on the way to a cure. It is a single-minded obsession within Chi-Med, to choose and develop the cleanest, most selective drugs possible.

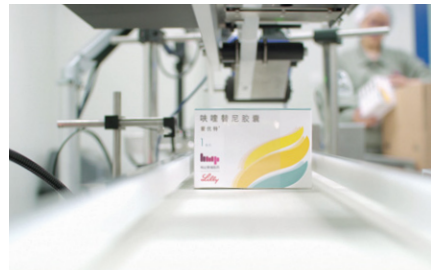
Developers of single drugs as well as those developing drug combinations both strive for selectivity. Fruquintinib is a superior performer in this area ("super clean", says Mr Hogg) and this may indicate that it can be used in treating other cancers in conjunction with drugs that might inhibit blood vessel growth or help the body's own immune system to recognise the aberration and attack it.

Research in this area has already begun and shows some promise. Again, it is not without setbacks, and the peculiarities of clinical trial targets and the pipelines of other firms complicate the competitive landscape. "The need for speed" is a key factor in drug development in order to get the medicines to market, as it is "very easy to be obsoleted," explains Mr Hogg.

For now, however, Elunate® is on the market, being prescribed and saving lives







> "Chemistry is our edge!"
>
> Christian Hogg
> CEO of Chi-Med

threatened by colorectal cancer. Other treatments may very well follow.

Another way to expand the client base is to bring Elunate® to the rest of the world. While China is the world's biggest market by virtue of its population and advanced economy, there are still millions of patients who could benefit from Elunate® over the next few decades.

COMING TO AMERICA

Chi-Med has begun another journey in seeking to move through the three phases of clinical trial needed to get Elunate® to American, European and other nations' patients.

For example, in America, Hutchison MediPharma US has been established in East Hanover, New Jersey, a global centre for pharmaceutical development. A next-door neighbour is Big Pharma firm Novartis and the area is rich in a top-notch pharmaceutical research culture. The leadership team is being built, and anchored by a world-class Chief Medical Officer hired from Eli Lilly. A team of highly qualified regulatory experts is coming on board. The office will have up to 30 staff by the end of 2019 and will also guide European clinical trials.

Mr Hogg aims to have this team on the ground to take over clinical trials for fruquintinib, sulfatinib and two upcoming blood cancer-fighting molecules which are in development.

STARTING OVER ISN'T CHEAP

The investment is considerable. The average cost of including one patient in a Phase 3 trial in the US is over US$100,000. Phase 3 trials are the big ones, in terms of people that need to be included in the trial to be acceptable to regulators. Phase 3 trials often have up to 1,000 patients. Do the maths and one begins to understand why drug costs are so high. Also consider that successful drugs have to cover the cost of development of drugs that do not make it through this process, even after all the money has been spent.

Further complicating the picture is the fact that clinical data from the China trials cannot be used in the US trials. The 'standard of care' varies in different countries, meaning that the way in which doctors treat a specific cancer varies. For example, they may use a different drug as their first line of attack, or a combination of drugs, from other countries. So fruquintinib has to be evaluated based on where it fits in the common US protocol by itself, or, more likely, as part of a blended treatment of a multi-front attack on a tumour.

The bottom line is that drug companies have to start at ground zero as they go from major market to major market. But Chi-Med is up to the task and is gearing up to build the infrastructure to bring not one, but many drugs into the pipeline to many markets around the world.

BRIGHT FUTURE – FOR CHI-MED AND GLOBAL CANCER PATIENTS

Chi-Med has established itself as the upcoming pharmaceutical firm with the first-ever single-molecule treatment discovered in China to receive an "unconditional approval" for treatment by the China Food and Drug Administration (CFDA). More will follow from Chi-Med and other firms. But Chi-Med is again leading the way by taking its drug beyond China to grow its own clinical trial infrastructure abroad.

Most biotech companies developing single-molecule treatments are small (fewer than 10 scientists) and sell-out to the big players once the molecule has been proven enough for them to take over. Chi-Med is different. The company prides itself on having over 150 biochemists doing leading-edge research under the stewardship of Dr Su, himself a world-class scientist. As Mr Hogg says, "Chemistry is our edge!"

Chi-Med is developing multiple drugs at the same time. The company has a national sales force in the world's second-biggest economy and the biggest pool of patients. It has partnerships with major players, but is not being absorbed by them.

Instead, it is continuing to expand its scientific, medical, sales and regulatory capabilities in order to join the ranks of world-class pharmaceutical firms. It is committed to growing and finding cures to humanity's worst scourges and beating back the dark of illness to bring light and hope to the people of the world. □