INNOVATION

ON TARGET: CHI-MED ZEROES IN ON FATAL AND CHRONIC DISEASES

Modern research-intensive pharmaceutical firms are a powerful corporate force in the world for good reason. If medicine still depended on shamans and witch doctors, the world would be a miserable place. The phrase, "It's serious, but there's a new drug ..." means hope for the afflicted. These companies, however, are usually the final stage in a chain of companies that seek new ways to heal.

At the beginning of the chain, there is Hutchison China MediTech Limited, aka Chi-Med.

Fifteen years ago, visionaries within the Hutchison Group asked if there was a better way to produce more effective drugs faster, helping more people. They set out a strategy and put their ideas into action. Christian Hogg, the CEO of Chi-Med, was recruited to lead the new company in 2000. Speaking to *Sphere*, he explains, "14 years ago, Mr Simon To, Managing Director of Hutchison China, and I started working towards developing a pharma business with the support of the Group." They found a way to meet major unmet medical needs in China and globally, and to pursue exciting, albeit challenging, business opportunities for the Group.

THE PROBLEM WITH DRUGS

Among the few drugs that make it to market, their high cost reflects the expenses associated with testing both those that succeed and those that fail to pass muster. Chi-Med hit on a novel R&D strategy that breaks down into a three-part approach. Research lines are in botanicals; small molecules with validated, or known, targets; and small molecules with novel, or previously unproven, targets.

BOTANICALS: HERBOLOGY

Qinghaosu is a well-known botanical wonder drug that exploded onto the world's consciousness in the 1990s. Effective against malaria, it has been known since the fourth century's Ge Hong described it in *The Handbook of Prescriptions for Emergencies*. Novartis developed it and, under the name artemisinin, its use became globally widespread.

Chi-Med tapped the same well of knowledge: the Chinese pharmacopoeia. The scientists at Chi-Med extract key compounds from a complex mix of biological elements to determine exactly what compounds do and how effective they are. Well-known examples of popular drugs include artemisinin and the cancer drug tamoxifen, derived from the Pacific yew tree.

> **"It started with a belief by Hutchison senior management in traditional Chinese medicine and its global applications."**
>
> Christian Hogg, CEO of Chi-Med

KNOWN TARGETS: CLEAN POWERFUL HITS

The second approach, using small molecules against known targets, makes use of current scientific knowledge to refine first-generation drug therapies that often have multiple side effects and associated toxicities. At one time, testing

was hit or miss – educated guesswork at best. But now, our understanding of biochemistry has given us tools to dramatically focus our efforts.

Chi-Med looks at existing therapies that might affect many pathways relevant to the cancer under attack and focuses on them. Mark Lee, Vice President, Corporate Finance and Development of Chi-Med, explains how improving this process benefits patients, saying, "You can ramp up the dose and hit the target hard." This allows doctors to increase dosage, killing tumours faster, and more importantly, completely.

In cancer treatment, the newest drugs developed by large pharmaceutical firms are often too expensive for many patients around the world. Some of those patients are in China, which now has the highest number of new cancer patients in the world. As a China-focused company, Chi-Med is well placed to deliver more affordable, targeted therapies suitable for the huge and growing Chinese market.

Focused: "You can ramp up the dose and hit the target hard."

Mark Lee, Vice President, Corporate Finance and Development, Chi-Med

One such drug is Fruquintinib. This anti-cancer molecule has been developed using Chi-Med's model of refining existing, less specific medicines to find a more effective treatment with fewer side effects. More are to come.

NOVEL TARGETS: DISEASE UNDER FIRE

The third approach, targeting small molecules against novel targets, means taking on a disease in a completely new way with a new molecular formulation.

In recent years, rules in the US concerning drug testing for patients with terminal illnesses have been changed. Now, where a prognosis is fatal, promising new drugs are allowed to be tested on those for whom other drugs have failed already. From these treatments, researchers know immediately whether a drug has any impact and side effects. This reduces uncertainty, time and cost and enables drugs to come to market faster. This means more people have their lives, and time with loved ones, extended. In some cases, formerly fatal diseases can be beaten back and lives saved.

The new designation of 'Breakthrough Therapy' means that promising drugs can be approved and delivered to suffering patients faster – in 60 days or less if approved. As the US is still the biggest market in the world by expenditure, this can cut half a decade or more off testing and allows researchers to understand how their drugs work much faster so that they can improve them and help even more people.

Chi-Med houses diverse operations under one roof in the Shanghai research centre which allows for a high degree of collaboration among colleagues.

Chi-Med has a number of promising drugs that could be helping cancer sufferers soon (see Volitinib below). It also has an inflammation candidate beginning pre-clinical trials with partner Janssen (a Johnson & Johnson subsidiary).

WORLD CLASS BRAINS

Chi-Med hasn't made this happen alone and it hasn't followed a traditional path. Its internal and external partners are a big part of the story and Mr Hogg credits many people and companies for helping Chi-Med along the way.

Scientists, for example. The company may not operate in a traditional Western research locus like New Jersey, Boston or Basel – but has all their best scientists. They are the alumni of the world's best universities and most advanced pharmaceutical research centres. They have worked with the world's most sophisticated research-intensive firms like Pfizer, Novartis, Celgene, Roche and Phenomix.

It's not just the executive leadership. The company is unusual in that, for an early-stage firm, it has a sizeable staff contingent. Companies doing research in early stage molecule investigation in the US or Europe may seize on one molecule and set up a company that never has more than 10 people. Mr Hogg explains that Chi-Med has "almost 250 full-time scientists and staff in our R&D business … all in Shanghai." Traditional firms will outsource almost all their processes, testing and production of materials. Chi-Med does it all on-site. "Everything is done internally … we want to keep the expertise and we want to build up our own team over time." Having this intellectual firepower under one roof doesn't just make for cost-effectiveness, but also leads to faster sharing of results and ideas. It has a huge impact on operational effectiveness.

Botanicals R&D is looking at plants with promise to be developed into drugs.

SOLID SUPPORT

Mr Hogg is clear about the support the company has received over the past 14 years. "Over a long period of time, the company, Hutchison, has been massively supportive with a long-term view. This is not a short-term project, this is a long-term project that requires an enormous amount of patience and commitment by everybody."

The Hutchison Whampoa Group is known and respected for its companies in a wide range of industries. However, in 2000, pharmaceutical research was not one of those industries. The Group then started making acquisitions of firms in China. While these companies were being reformed to make them profitable, Chi-Med launched its research programme, a serious, investment-intensive undertaking. The investment required for even one drug to be developed is in the scores of millions, not including late-stage development and global distribution.

While the company did have a listing on the London Stock Exchange's AIM market, it had a real moment of validation when Mitsui Global Investment's healthcare specialist division chose to support the

With top-notch technical equipment at hand, Chi-Med is able to develop precise formulation processes for the manufacturing of new drugs and ensure stability and consistency in every dose.

company through an investment. One of the best in the business had taken a long hard look at Chi-Med – and liked what they saw. "We were able to convince Mitsui – they are very experienced biotech investors and great people to work with, and they knew [that Chi-Med was on the right track]. They put money in here into the drug R&D and it was about USD20 million then. That got us through to 2011," says Mr Hogg.

A crucial step in taking drugs into the final stages of development and hopefully preparation for global development is partnering with a major pharmaceutical company. Commitment to support expensive global trials – and later marketing and sales muscle – tells the market that the industry leaders with decades of global experience have done their due diligence and believe in the product's potential.

Having a pipeline of promising new drugs demands access to a steady supply of funds and expertise to make sure that drugs get through final testing and into the hands of doctors and patients to save lives.

BIG PLANS, BIG PARTNERS

Chi-Med has the solid support of global leaders, such as Swiss giant Nestlé Health Science who are supporting the development of its gastrointestinal drug. They have joined forces in the joint venture Nutrition Science Partners. Nestlé, as a global leader in food production as well as drugs, is the best of partners for producing the botanicals necessary to support drug production, and will also bring the resources of Prometheus Labs to support research, as well as its global sales and distribution network. Nestlé has the rights to work with Chi-Med and their vast library of 1,500 purified natural products and 50,000 extracts from traditional plants.

A partner on the 'known target' approach is America's Eli Lilly & Company. The global giant is keen on Fruquintinib, a drug that promises to help a range of cancer patients with solid tumours. Lung, colorectal, gastrointestinal and renal cancer all show promise as being likely targets for the drug, making it a potential blockbuster.

AstraZeneca is another partner interested in Chi-Med's Volitinib – an anti-cancer molecule that could be paired with AstraZeneca's powerful AZD9291 for a tumour-busting cocktail effective against resistant lung cancer tumours.

PROMISE FOR THE FUTURE

With cancer drugs in particular, the upside can be tremendous. A drug approved to treat one condition, which may be rare by itself, often holds promise for treating other cancers. The health benefits and financial upside can be immense, with both millions of people experiencing life improvement and the company reaping significant profits that can fund research into more drugs.

This investment will see its first novel drugs ideally come to market some time in 2016 if all goes well – 16 years after the venture began. It has taken a long-term commitment by HWL and the people at Chi-Med, who have been there from the start, to see the results begin to come in. New promising molecules and botanicals will need to be found and put into the pipeline to bring more cures and treatments to an eager world.

Chi-Med and Hutchison's commitment, hard work, and innovative thinking have brought them to this point and will carry them beyond. This is how Hutchison heals. □