Jin LI – Chairman & CEO, HitGen, China

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Dr Jin Li explains Chinese firm HitGen's unique drug discovery technology platform, how its ability to screen billions of molecules has the potential to significantly increase success rates in early drug discovery, and the next steps for the company's expansion.

Dr Li, could you start by introducing your motivation for establishing HitGen back in 2012?

HitGen was established in 2012 in the city of Chengdu in Sichuan province, China. Since our inception, we have focused on the development and application of an important drug discovery technology platform: DNA-encoded chemical library (DEL) design, synthesis and selection (a technology for using DNA barcodes to organize large libraries of chemical compounds). This technology's main purpose is to significantly increase the molecular diversity for the screening of new chemical leads or hits to interact with new drug targets.

Traditionally, once the biological target for a certain disease has been determined, pharma companies try to find a chemical or biological molecule that can modulate the biological function of that target in order to achieve some kind of therapeutic effect. Now, traditional small-molecule screening libraries involve a few million molecules, which has already been a tremendous resource for the industry over the past 30 to 40 years. Conventionally, high-throughput screening (HTS) has been the main drug discovery technology platform used to identify potential leads but it can only

screen a few million molecules at a time. It was – and still is – difficult to find small molecules to modulate the functions of many important biological targets, such as protein-protein interactions (PPIs).

DELs can screen up to hundreds of millions or even billions of molecules. This dramatic increase in molecular diversity has the potential to increase the success of early drug discovery tremendously.

This technology had been invented by Nobel laureate Sydney Brenner and Richard Lerner of the Scripps Research Institute in the 1990s but its industrialization and broader application took many more years, with the technology really only adopted in the 2000s, when a few pharma companies in the US and Europe started to use it. At that time, I had been working with AstraZeneca in the UK in the lead generation space for many years, so when I noticed this promising technology, I decided to seize the opportunity to build a company specializing in the development and applications of this technology in China.

Back then, very few companies were using this as a core platform for lead generation, and they were all in the US and Europe. In the 2010s, China was starting to develop an innovative biopharma industry. I knew that in order for Chinese companies to develop novel drugs and New Chemical Entities (NCEs), this technology platform would be a critically important resource and I had the personal experience and capabilities in the early drug discovery space to bring it to China. That was what incentivized me to establish HitGen in 2012.

Of course, it was not easy to introduce such a novel technology in China. I had to secure initial funding from private investors, VCs and government grants. DEL technology was essentially unknown within the Chinese market and many people were sceptical about the claim that DELs could screen up to a billion molecules because the standard compound screening collections were only in the range of a few million. I had to educate the market and investors to foster an understanding of the technology as well as the trends and developments in the US and European markets.

How has HitGen continued to innovate and develop your DEL platform technology?

We have been constantly evolving since 2012. At that point, we set the goal of building a DEL of one billion molecules within three years. By now, we have a platform of over 500 billion small molecules, and in terms of published numbers, we probably have the largest DEL collections in the world. By the end of this year, we hope to have built a DEL of over one trillion small molecules!

In addition to DELs' core competitive advantage of increased molecular diversity, as I highlighted previously, we have also improved on other aspects such as molecular type, molecular properties and other pharmaceutical considerations. This is part of our library design, synthesis and selection process.

The DELs themselves are one aspect but we have also built all the necessary corresponding research capabilities for screening, data analysis, hits confirmation and downstream evaluation so that we can offer our platforms to our collaboration partners and the general industry to support their drug discovery efforts.

Over the past few years, we have formed partnerships with most of the Top 20 global Big Pharma companies as well as over 100 biotechs and research foundations to help advance their drug discovery projects on an exclusive basis. This has been a significant revenue stream for us both in the present as well as in the future as our partners' programs progress into clinical trials and meet various milestones. This works very well for us because DELs are a tremendously efficient resource that can last for a long time.

You are also working on your own portfolio of assets. Could you share more about how your pipeline is progressing?

We currently have two Phase I assets in China. The first, HG146, is a Class I/IIb-selective HDAC inhibitor for multiple myeloma and selected solid tumor indications. The second, HG030 is a second-generation TRK inhibitor, which is the first second-generation TRK inhibitor to receive IND approval and is entering the clinic in China, also for solid tumor indications.

We have a third asset, HG381, for which we hope to submit for IND approval by end-2020. This is an IV injectable STING agonist that leverages innate immunity to fight cancer. Hopefully we can be the first to bring such an asset to the Chinese market as well.

We also have a number of exciting pre-clinical programs. Most of our programs target novel mechanisms in cancer, such as epigenetics, immuno-oncology, cell cycle control, etc. In addition to oncology, we also work in inflammation/immunology, with for instance, one of our programs in auto-immune diseases targeting IL-17(A). Most of the assets in the clinic or on the market for this target are antibodies but we are using an orally bioavailable small molecule, which has already shown encouraging signs of possessing similar activity to antibodies in our *in vivo* model. We are still doing further optimization to improve the properties of this molecule but we hope that it will

become a clinical candidate in the not too distant future, either in our own portfolio or as a potential asset to be out-licensed.

With such different business activities, how is HitGen organized in terms of resources and business operations?

We now have over 400 employees but the company has always retained a strong research focus so we are organized a little differently from traditional R&D biotechs or other pharma companies. We want each business unit to focus on a particular research area in the drug discovery process while being linked to the relevant commercial and market needs. We currently have three research/business units.

The first is our Discovery Chemistry Unit, which focuses on the design and synthesis of DELs, for both internal and external use. For instance, we work on library design and synthesis based on our partners' commercial needs. This Unit is also responsible for the construction of our internal DELs for downstream application screening. This is our largest unit because the work is both instrument- and manpower-intensive as we need to produce hundreds of billions of molecules.

The second is our Lead Generation Unit. Once we have a biological target, we screen our existing DELs or our customers' own libraries against that target to generate validated leads, either for our partners or to advance our own programs. This is our second-largest unit.

The third is our Discovery Project Unit, which takes the validated leads and advance them through the pre-clinical stage to produce IND packages for submission and/or out-licensing.

The first two Units are already profitable and I hope the third will become profitable soon.

With your focus on such a niche technology platform like DEL, what are the challenges you face with recruitment, especially given China's competitive talent environment?

We do work in a very niche technological area but like any new technology in the industry, it is based on foundational science: medicinal chemistry, automation, molecular biology, biochemistry and biophysics, computational biology, computational chemistry, bioinformatics and so on. From there, it is about bringing these different areas together and setting the team a clear goal to achieve. DELs are a multidisciplinary technology operating platform so we have to integrate many different disciplines and specialties together.

What is beneficial is that HitGen has a lot of expertise. Our CSO, Dr Barry Morgan, is one of the pioneers in the DEL space; he was previously SVP for Chemistry and Discovery Sciences with Praecis Pharmaceuticals and became VP of Molecular Discovery at GSK in Boston when GSK acquired Praecis in 2007. Many of our other colleagues similarly joined me in 2012 so within the company, we have probably the most experienced DEL team in China. We have been innovating far beyond the original technology platform so we have that early-start advantage as well as the leadership position. In addition, we also have probably some of the largest DELs available globally and we have gained a lot of experience in the screening many different targets and molecules. That helps us immensely in training the next generation of talents, which is important so that we can continue to push the boundaries of this innovative technology platform.

With so many biopharmaceutical advances including the increasing prevalence of biologics, cell and gene therapies and so on, what role do you think small molecules will continue to play in terms of driving innovation within the industry?

I think there are two sides to this. On one hand, it is true that small molecules are a more mature field. The characteristics of small molecule therapeutics are well-known and well-established. It can target any part of the body, it is either orally available or injectable, and the industry knows how to manage small molecules fairly well. Not much will probably change here.

However, on another hand, there are many exciting developments within this space. There is a lot of potential to use small molecules to target the new biological mechanisms uncovered over the past couple of decades – in fact, the speed of discovery is actually accelerating. Even with traditional targets like proteins, we are still only targeting a small percentage of them. We used to focus predominantly on small molecules as inhibitors or activators of proteins important for disease onset and progression. Today, we are exploring many different therapeutic mechanisms for small molecules. For instance, we have small molecules that could cause protein degradation, multifunctional small molecules that recruit protein partners to affect other disease-causing proteins, as well as small molecules targeting RNA or RNA-modifying enzymes, and many others. Small molecules could do a great job targeting RNA. Another important advantage is that small molecules can enter cells or penetrate the blood-brain barrier. So far, we can see that neurological diseases have been a difficult area for biologics to tackle.

That being said, all modalities are important but we are a strong advocate for the innovative potential of small molecule therapeutics, which we believe will continue to have a major role in the

industry’s development.

Moving forward, could you articulate your strategy for HitGen’s continued growth?

It has given our investors even more confidence in us, and increased HitGen’s visibility as well as funding for the next stage of our development. We have a clear vision for the next three to five years.

The top priority is to continue to innovate. We want to strengthen our leadership position in the DEL area. We also believe that this technology has a lot more to offer for drug discovery. The chemical space is so vast, there is almost endless potential to explore, and we are not even close to finishing the job. At the same time, we know that biology is now driving many drug discovery opportunities so we want to see how we can use our technology to explore targets and mechanisms of action in this space. For instance, AstraZeneca’s Tagrisso®, has been a huge success in non-small-cell lung cancer (NSCLC), showing that it is possible to develop covalent small-molecule kinase inhibitors. We have created a library of a vast number of small molecules with covalently attached moieties using DEL technology to explore the potential here.

We are also continuing to push the boundaries of science by producing fragment-based DELs. Traditional fragment-based lead discovery (FBLD) coupled with structural biology has proven to be really effective but not very efficient, using huge amounts of resources to explore only a few thousand fragments. With our DELs, we could screen hundreds of thousands of fragments in a very short period of time. Generally speaking, we believe that there are still many more areas we can explore and innovate in order to generate greater impact and value.

The second priority is to continue to build our downstream capabilities for exploiting the output from DEL screening and turn leads into clinical candidates.

Thirdly, we want to advance our own pipeline in a steady fashion so that we can gradually explore different commercial outcomes. For instance, we might out-license some assets, some for global markets and some for ex-China markets. Now that China has implemented a Marketing Authorization Holdership (MAH) system, we might also consider launching products on the China market ourselves, since we would be able to partner with other companies for the manufacturing and distribution.

Finally, we want to strengthen our innovation foundation. Our operations are fairly concentrated in Chengdu at the moment, though we have a few colleagues in Boston and Europe. We aim to build a

presence, probably in the form of small research centers, in the UK and the US, which would enable us to join the research and innovation community in the US and Europe while bringing us close to our partners in those regions.

Finally, China's biopharma industry has advanced so rapidly in the past two decades. What are you looking forward to the most for the next few years?

Ultimately, I hope we can maintain the momentum within the industry. The pharma industry requires long-term, sustained investment. We cannot stop the efforts after a few years or even a few decades. It is critical that the financial markets continue to see this industry as an important and profitable segment to invest in. I also believe that continued effort, investment and innovation in the biopharmaceutical industry will bring more innovative and life-changing therapeutics to the patients who need them.

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