Dun Yang – President & CEO, Anticancer Bioscience

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Anticancer Bioscience is an exciting international precision oncology company, applying synthetic lethal approaches to develop targeted cancer therapies. President & CEO Dun Yang explains the company's origins, how ACB's approach differs from that of its competitors, and how he plans to make the firm into "China's Genentech."

Can you begin by introducing your background and the founding story behind Anticancer Bioscience (ACB)?

My academic career started with the completion of my PhD studies in biochemistry at Columbia University, New York, in 2000. I then moved to California, where I began my postdoctoral training at the University of California, San Francisco (UCSF), under the tutelage of Nobel Laureate, Dr J Michael Bishop (Mike Bishop). Later, I became an investigator at the George Williams Hooper Research Foundation, which is affiliated with the University of California and was directed by Mike Bishop at that time.

After working closely with Mike for more than 16 years, I moved back to my hometown of Chengdu in Sichuan Province, southwestern China, and oversaw the inauguration of the J Michael Bishop Institute of Cancer Research with Mike in late 2016. The institute aims to discover new knowledge and conduct high-risk, high impact basic research projects. I also founded Anticancer Bioscience

(ACB) to commercialize the institute’s basic research discoveries.

We established the Institute and ACB in Chengdu in order to access the huge amount of biodiversity in this region of China. The plant diversity of Sichuan province accounts for over 60 percent of plant diversity in the country. As our focus is synthetic lethal cancer therapies, we needed to look for compounds that were non-toxic to normal tissues but would manifest potent cytotoxicity in certain contexts, such as with specific oncogenic alterations. Most medicinally used natural products are known to have low toxicity and therefore, fit this need. More importantly, the natural compounds found in plants can harbour structural diversity that is unmatched by synthetic compound libraries. This biodiversity is the product of the long-term evolution of biosynthetic pathways and many compounds found in nature have drug-like properties.

How does ACB’s approach to oncology differ from that of its competitors?

ACB has explored various biological processes central to cancer cell growth and established five innovative R&D programs. Each program is designed to deliver first-in-class treatments that can be used to treat 30 percent or more of all cancer patients, including the most aggressive and resistant forms of cancers. We have identified novel compounds that can target both genetic and epigenetic vulnerabilities of cancer cells. The drugs from each of our five programs act through distinct mechanisms and have the potential to be used in combination with each other or with clinically approved therapies to treat cancer, thereby synergistically enhancing the value of our assets.

ACB’s pipeline includes an oncogene-enabled synthetic lethality program, MYC-SL, which is focused on targeting cells with overexpression of MYC, an event that occurs in over half of human tumours and is correlated with poorly differentiated and very aggressive cancer. The target in this program has not been explored with any other synthetic lethal cancer therapies to date.

The other programs include a search for drugs that restore contact inhibition of proliferation in cancer cells, decluster supernumerary centrosomes in mitotic cells, are synthetic lethal with loss of tumour suppressors, and are synthetic lethal specifically for polyploid cancer cells. Few companies are exploring these biological mechanisms and hallmarks of cancer to develop oncology drugs. We are believers in these innovative therapies because of our longstanding basic research in these fields.

What stage are you currently at with these assets and what milestones have been reached so far?

Each of our five research programs is progressing and has either potent hit compounds or optimized lead compounds, validating the feasibility and productivity of our screening platforms. The most advanced programs are the oncogene enabled SL drug program and contact inhibition restoration program.

For the MYC-SL program, we have developed five classes of compounds and accomplished lead optimization for two of the five classes. We expect to progress at least one compound into IND filing within the next year and a half and are currently engaging in IND-enabling studies.

For the contact inhibition restoration program, we have established an image-based high-throughput screening platform and completed pilot screening with a library of compounds. We discovered two drugs that can similarly restore cancer cell contact inhibition of proliferation and are without a detectable effect when the same cells are grown in sub-confluence. Additional compounds have been identified that enhance the contact inhibition of proliferation elicited by the two drugs. Since some of these drugs have already been used clinically for the treatment of diseases other than solid tumours, we are planning to repurpose these drugs for the treatment of cancer.

In addition, we have identified hit compounds that elicit synthetic lethal interaction with loss of the tumour suppressor protein p53. We also identified several natural compounds that can decluster supernumerary centrosomes in mitotic cells or preferentially kill polyploid cancer cells as opposed to their pseudodiploid counterparts. Our effort to optimize these compounds is ongoing.

Which cancers are these programs indicated for?

Because MYC is over-expressed in the majority of human cancers, our MYC-SL drugs could be used to treat a large variety of cancers. In our preclinical mouse models, our MYC-SL lead compounds have shown efficacy against triple-negative breast cancer, lung cancer, colon cancer, liver cancer, and stomach cancers. However, we have yet to decide whether we should conduct a multi-indication basket trial or simply pick a promising tumour type, using MYC as a biomarker for patient stratification.

How do you hope to leverage ACB's chemical compound and natural product libraries?

To support the development of its novel drug pipelines, ACB has constructed two types of compound library, a proprietary natural product library and a set of novel-scaffold small molecule libraries. Both serve different purposes. We exploit natural products in order to access phytochemical compounds that are more structurally diverse than synthetic compounds and therefore, have a high potential of modulating hard-to-drug targets. In contrast, our synthetic libraries, designated as General Unity Novel Scaffold-Drug Fragment (GUNS-DF) libraries, emphasize new chemical entities that satisfy the properties of oral drugs to reduce the risk of early-phase attrition. The GUNS-DF library is built on-demand as we integrate the expansion of compound diversity with the lead optimization process. GUNS-DF libraries are constantly expanding and evolving as we move through iterative screening and optimization processes against different targets associated with multiple screening projects. This is a very productive and powerful approach to drug discovery because we typically identify multiple lead compounds with low nM activity in cells after synthesizing and screening less than 500 compounds.

Will these libraries be used both in proprietary projects and in collaboration with external partners?

The utility of both libraries is not limited to the discovery of oncology drugs. In theory, the libraries should be applicable for discovering modulators for any druggable process where a screening readout can be developed. The value of these libraries will amplify with an increase in compound diversity. The application of GUNS-DF libraries to other drug development efforts should further enhance compound diversity in this platform as well. The repeated screening and directed expansion of molecules around the core scaffolds of the GUNS-DF libraries should significantly reduce the effort needed to create NCEs with drug-like properties for future projects. To maximize the value of our platform library, we could form strategic partnerships with external partners to explore the versatility of our proprietary compound libraries. In addition, since the GUNS-DF approach does not require a high-throughput screening capacity, it may be conveniently adapted by individual laboratories and small start-up companies to combine with their expertise in disease biology to expand drug discovery.

ACB has raised around USD 21 million in funding so far. How far along the road does this get you and what comes next?

This money is adequate for us to progress two products into clinical trials. The plan is to advance one combination treatment that acts through contact inhibition restoration and a second that brings forward a MYC-SL drug.

We are initiating another run of fundraising to expand our drug pipelines by advancing our other three R&D programs and increasing the compound diversity of our platform libraries. We hope to be able to announce an update on this in Summer 2021. The next milestone will be filing the IND applications, which will serve as an inflection point for further fundraising endeavours.

Aside from the biodiversity of Chengdu, what are its characteristics as a biotech hub? And, having come from the Bay Area, what are the challenges of building a company in southwestern China?

It is true that if ACB was based in South San Francisco, it would be easier to find local experts to collaborate with. Because our focus and approach differ from most other Chinese biotech companies, it can be difficult to find local partners to connect and brainstorm with. However, Chengdu is one of China's national central cities and does have many advantages, such as being a powerhouse for regional talent and being the largest biotech hub in southwestern China. We have successfully found qualified and dedicated research and facility-supporting staff in Chengdu. Moreover, most of our collaborations are with partners in the US and Europe, which we have been able to form from our base in Chengdu.

Even though ACB's R&D centre is in Chengdu, we have employees in the UK and in the US, as well as the medicinal chemistry lab in India. That is also a key differentiator from other Chinese companies. ACB is happy to hire talent wherever it might be, giving the firm a very international footprint.

What has been your experience of transitioning from a stellar career in research into being the CEO of your own company?

It has always been my dream to see my basic research breakthroughs transformed for practical use and to accomplish this by myself. Although inventors are likely more enthusiastic and determined than anyone else to translate their inventions for practical use, drug research and development are typically conducted by people distinct from those who perform basic research. Therefore, I feel fortunate to be able to do both. Despite my transition from a researcher into an

entrepreneur, my outlook and focus on using novel cellular dependencies, which are uncovered in our research focusing on cancer cell biology, to develop first-in-class oncology drugs has not changed. While developing drugs, we are also building chemical compound tools that enable us to interrogate biological processes to better understand the mechanisms underlying cellular dependencies, predicate treatment response, and identify new drug targets. Therefore, this career transition not only expands on my previous research expertise but also enables translation for clinical application.

You have stated that your ambition for ACB is to become "China's Genentech." Could you unpack this statement and what it means in practical terms?

I want ACB to be synonymous with the word "innovation" in China, as Genentech is in the US. I want ACB to bring new knowledge as well as innovative medicines to the world.

Of course, Genentech was eventually acquired by Roche. Is the plan for ACB to take a similar path or to reach a scale whereby it brings its own assets to market?

Genentech's trajectory was thanks to its positioning at the cutting edge of science and innovation coupled with the ambition to go all the way. ACB is not looking to sell soon. But instead, it aims to build a great company and versatile drug pipelines, take products through to the clinic, form partnerships along the way, and, in a 10 to 20 years' timeframe, to have created value and made a dramatic difference for patients. We do not have a short-term objective to be sold but rather a vision and a trajectory to collaborate. Particularly in oncology, where precision medicine is gaining pace and combination therapies are a huge part of the treatment landscape, collaboration is essential for a specialist oncology company to succeed.

ACB is interested in a broad range of partnerships, including co-development deals, regional partnerships and alliances with large pharma and biotech companies that are developing oncology and immuno-oncology therapies. We are currently in discussions with some large pharmaceutical and biotech companies in the US and UK. Some companies are extremely interested in our pipelines and platforms; others are looking for the possibility of whether our products have therapeutic synergy with their own proprietary products.

What is your long-term ambition for ACB?

We want to be the prime example of an innovative, science-driven biotech from China, showcasing the best of world capability in terms of innovation, rather than another Chinese me-too company. We want to advance our innovative science to develop first-in-class drugs that really make a difference to patients everywhere.

There are a lot of biotechs in China, some of which are much further along the journey in terms of bringing products to market. How do you plan on overtaking them and establishing ACB as the most compelling Chinese biotech story?

We have to let nature run its course regarding when we bring products into clinical trials and on the market. We do not have any pressure to rush our products into clinical trials, which is an important milestone for biotech companies to raise more money. Instead, we are extremely cautious about the first-in-class drugs that we are developing. We want to know more about their MOA and potential side effects to avoid their clinical failure.

To compete with other biotech companies globally, ACB has unique R&D programs that are based on our deep knowledge of new mechanisms of cancer cell biology and that explore targets other than those studied by others. We have also designed ACB to gain accelerated momentum with time. The products from each of our five programs have the potential to be rationally combined with each other as well as currently used chemotherapeutic drugs. Furthermore, compound diversity and the value of ACB’s platform libraries will be further elevated with the progression and initial success of our R&D programs. The repeated use of the core scaffolds of the GUNS-DF libraries during different screening efforts should substantially reduce the timeframe and effort needed to create additional drugs. Due to this special design, ACB is operating in its own time zone, at its own pace and is well-positioned to grow exponentially in the future.

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