Anticancer Bioscience
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Treating cancer with novel synthetic lethal therapies

Driven by its small molecule libraries, biotech company Anticancer Bioscience has identified a line of oncology programs that could work as single agents or combination therapies.

Anticancer Bioscience (ACB) is using deep knowledge of cell and cancer biology to develop next-generation targeted oncology therapies. Equipped with completely novel, proprietary synthetic and natural product small molecule libraries, the biotech company has discovered compounds with innovative mechanisms of action that exploit the genetic and epigenetic vulnerabilities of cancers, for example, with MYC overexpression. The programs have now advanced to the point that ACB is preparing to take its lead candidates into the clinic.

ACB is a truly global biotech. After 20 years of innovative research under the mentorship of Nobel laureate, J. Michael Bishop at the University of California, San Francisco, the company's scientific founder, Dun Yang, returned to China, to establish the J. Michael Bishop Institute of Cancer Research, with ACB as its commercialisation partner. Working out of its R&D and operational headquarters in BioTown, Chengdu, China, ACB is coordinating teams at sites in India, Australia, the UK, and the US, enabling it to access global experts in fields such as medicinal chemistry, machine learning and bioinformatics.

ACB's expertise in synthetic lethal approaches to precision oncology, MYC biology and cancer cell biology has enabled it to build a broad pipeline. Rather than focus on a single asset or one biological mechanism, the biotech has established five innovative R&D programs. Each of the programs is designed to deliver treatments that work in patients with the most aggressive and treatment-resistant forms of cancers.

The goal is to deliver first-in-class oncology drugs against unexplored targets and, in doing so, have a major impact on the lives of patients. In working toward that goal, ACB has established a set of programs that could yield candidates that work as single agents and in combinations to boost efficacy and overcome drug resistance by acting through distinct modes of action.

ACB's pipeline is led by an oncogene-enabled synthetic lethality program, MYC-SL, that is focused on targeting cells with overexpression of MYC, and a drug combination to restore contact inhibition of proliferation. The other three programs focus on centrosome declustering therapy, tumor suppressor synthetic lethality and polyploid cell synthetic lethality (Fig. 1).

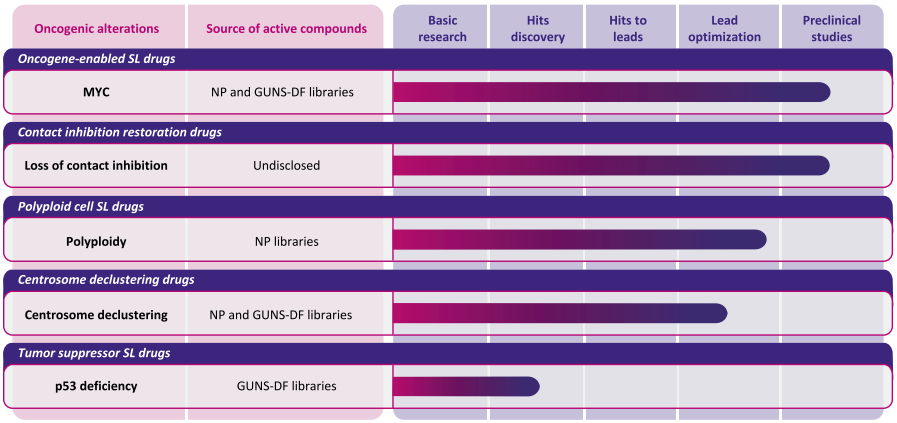

Fig. 1 | Anticancer Bioscience's pipeline. The exciting pipeline is built upon a deep knowledge of cancer biology and synthetic lethality expertise. The lead program is focusing on targeting cells with overexpression of MYC. NP, natural product; SL, synthetic lethality.

Innovating to access chemical diversity

ACB has built novel compound libraries to fuel its development pipeline. Its small molecule libraries are designed for high-throughput screening for drug leads. These libraries, designated as General Unity Novel Scaffold-Drug Fragment libraries (GUNS-DF), have novel fragment-like scaffolds for building highly diverse arrays of new chemical entities (Fig. 2). The libraries were designed using a cheminformatic approach to identify several high frequency elements (HFEs) around which new scaffolds that act as isosteres for HFEs could be designed and validated. Ultimately, expansion of lead small molecules is guided using protein conformation-based drug design principles.

The approach has yielded a library of new chemical entities that satisfy the properties of oral drugs, reducing the risk of early-phase attrition. Screening the library for compounds designed to inhibit kinases, motor proteins and other ATP-binding proteins generates structure-activity relationship data that shorten the time required for lead optimization.

ACB has built the synthetic libraries while working on an ambitious natural product library screening platform. The natural products library gives ACB access to a more diverse set of compounds than can be found in synthetic libraries. That diversity is enabling ACB to pursue hard-to-drug targets.

Many companies would like access to such diversity, but ACB is a rare example of an organisation that has put in the effort needed to build a natural products library. The project has entailed collecting a random sampling of plants from southwest China—a region home to 60% of the country's floral diversity—building gardens and establishing a growing network of partners that cultivate medicinal herbs on a large scale. ACB is also working with national reserves to study and preserve endangered plants.

These activities have given ACB a repository of 17,500 primary phytochemical extracts, more than 1,200 partially purified extract fractions and around 2,500 pure natural compounds from 2,600-plus plants, representing more than 1,500 plant species used in Traditional Chinese Medicine.

While ACB is still adding to the libraries, the resources have now grown to the point that researchers can access the chemical diversity they need to address whatever hypothesis they want to test. Freed from the constraints of chemical diversity, ACB now must decide only whether to keep generating new programs or focus on existing drug candidates.

> **"ACB has the expertise, ambition and resources to take the MYC-SL and contact inhibition restoration programs into human testing. Realisation of the full potential may require establishment of collaboration**

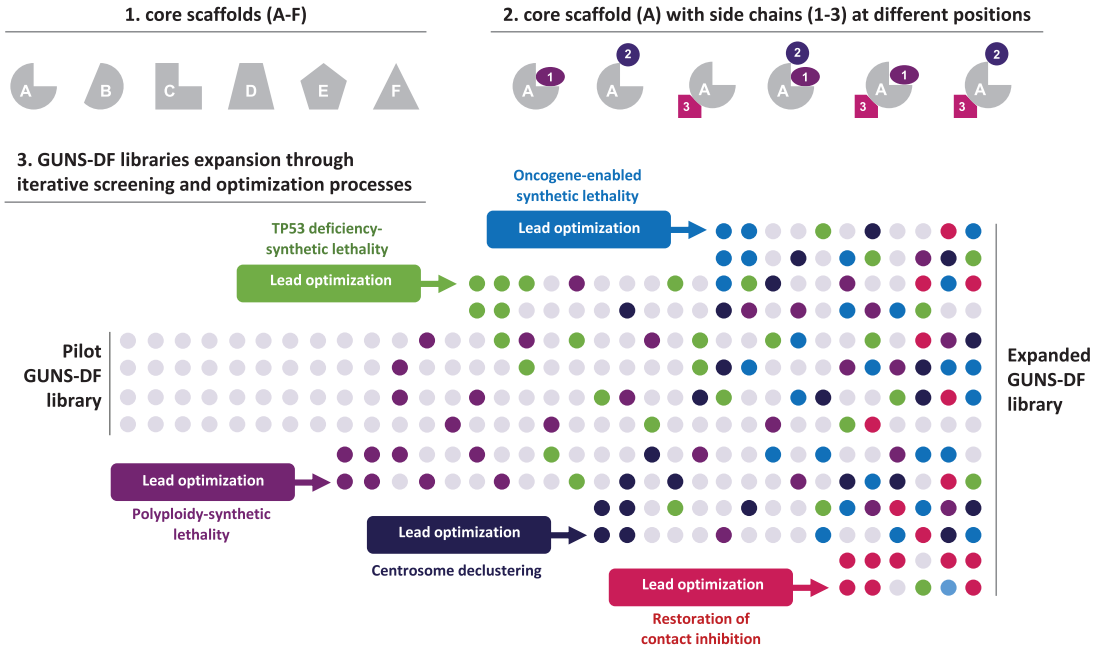

Fig. 2 | The proprietary synthetic small molecule library–GUNS-DF. The diversity of the library is increased through synthesis of additional compounds during the lead optimisation process.

Moving into clinical development

ACB's early-stage work has put the company in a position to move two candidate therapies into human testing in the near term. MYC-SL is the most advanced of the programs and its lead compound is a first-in-class anticancer therapeutic, inhibiting a novel MYC synthetic lethal target. To support the oncogene-enabled synthetic lethality program, ACB created a high-throughput compound screening system capable of simultaneously uncovering both drug targets and predictive biomarkers.

Equipped with its novel screening system, ACB has used bioactivity guided optimization to generate more than two dozen highly potent molecules, from across three distinct chemical classes. All inhibit a novel synthetic lethal target that has not been explored clinically or with drug candidates currently in clinical development. No published literature describes the role of the target as a MYC synthetic lethal partner, positioning ACB to develop its first-in-class anticancer therapeutic.

All three classes of novel MYC-SL small molecule discovered at ACB have good pharmacokinetics, excellent drug-like properties, and robust activity in preclinical models, including tumor regression with lead candidates. In vitro assays demonstrate that ACB's compounds elicit potent cytotoxicity at low nM concentrations in a large panel of cell lines.

Encouraged by the early data, ACB is now working on final candidate selection with the aim of taking at least one asset from the three MYC-SL compound classes into clinical trials by the end of 2022.

The MYC-SL program is advancing toward human testing in parallel to a second project focused on the restoration of contact inhibition. In this program, ACB came up with a radically different answer to the question of how to control cancer. Rather than try to kill dividing tumor cells, as most cancer drugs do, the contact inhibition program was designed to find compounds that halt them in their tracks another way.

Cell-cell and cell-matrix contacts stop healthy cells from overgrowing. However, that effect, known as contact inhibition of proliferation, is lost in tumors, enabling cells to keep proliferating. Recognizing the potential to stop tumor growth without triggering the drug-resistance mechanisms that affect other medicines, ACB established a high content screening assay to identify agents that restore contact inhibition of proliferation. The assay identified two drugs.

The drugs synergistically suppressed the formation of tumor cell spheroids in soft agar assays, but the greater test came when ACB moved into preclinical murine models, where cells grow as a mass, rather than in a single layer. The program successfully made the transition in vivo, generating evidence of efficacy in animal models that emboldened ACB to aim to take the program into the clinic by 2022.

Partnering to unlock opportunities

ACB has the expertise, ambition and resources to take the MYC-SL and contact inhibition restoration programs into human testing. However, realisation of the full potential of the diverse platforms and drug candidates developed by ACB may require establishment of collaboration. Recognizing this, ACB is looking to enter into partnerships with pharma and biotech companies.

The company is interested in a broad range of agreements, including co-development arrangements, regional partnerships and alliances with large pharma and biotech companies that are developing oncology and immuno-oncology therapies that may work synergistically with ACB drug candidates. Pharma and biotech companies interested in partnering with ACB can choose from a number of programs, all of which are based on its deep knowledge of cell and cancer biology, and the innovative platform technologies that gave rise to the MYC-SL and contact inhibition restoration candidates.

Each of the programs has the potential to generate first-in-class candidates that improve outcomes for a large number of oncology patients. The centrosome program, for example, targets a relatively unexplored hallmark of cancer cells in the belief using small molecules to decluster amplified centrosomes will disrupt mitotic spindle function and, by extension, tumor growth.

Another ACB program is exploring synthetic lethal therapy for tumors lacking the function of tumor suppressor proteins such as TP53 and RB. The program focus is on small molecule inhibitors and the novel vulnerabilities enabling tumor suppressor synthetic lethality that ACB has uncovered in its high-throughput screens.

ACB has now advanced its discovery programs to the point that it is starting to share details of its progress and is meeting with potential partners and investors to secure support for the next stage of development. As ACB executes on its ambitious strategy, it will work on programs both independently and collaboratively to meet its goal of improving outcomes in patients with poorly differentiated and aggressive cancer, thereby realising the therapeutic potential of Yang's vision and Bishop's heritage.

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