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Beyond seasons and borders, Beyondspring seeks cross-cultural cancer answer

By Marie Powers, Staff Writer

Beyondspring Pharmaceuticals Inc. literally sprang to life in June 2013 with a phase II cancer compound already in hand. In the second quarter, the company's lead compound, plinabulin, is set to enter a pivotal phase III trial in patients with non-small-cell lung cancer (NSCLC), a notoriously obstinate indication.

But the challenge doesn't deter Beyondspring founder, chairman and CEO Lan Huang, who named the company not only to suggest its goal of bringing hope to patients by harvesting new therapeutic approaches but also to allude to a business model that reaches beyond borders to integrate global R&D and clinical resources.

"The foundation for Beyondspring is to solve this highly unsustainable problem with innovative drug discovery," Huang told *BioWorld Today*. "We're trying to use integrated global clinical resources – especially clinical resources from China – to bring a paradigm shift to the R&D model so that we can develop drugs in a more time-efficient and cost-efficient manner."

Beyondspring, headquartered in New York with clinical operations in China, is the fourth venture for Huang, who holds multiple patents for biotech products in oncology and dermatology indications. In 2009, she was the recipient of China's Thousand Talent Innovator Award.

With a PhD in chemistry from the University of California at Berkeley, Huang is a member of China's growing cadre of Western-educated returnees, equally comfortable on both sides of the globe. She co-founded Wuxi MTLH Biotechnology Co. Ltd., whose self-designed cancer peptide drug was partnered with Shanghai Pharmaceutical Group in 2010, and Paramax International, a Chinese contract research organization (CRO) that was sold to global CRO Research Pharmaceutical Services and, subsequently, to Warburg Pincus in 2011. Huang also worked with Forward Ventures, where she led partnering initiatives between Forward's portfolio companies and Chinese pharmaceutical companies. To manage Beyondspring, she splits her time between the U.S. and China.

Huang knows her way around cancer metabolism, as well, publishing translational research on cancer signaling pathways involving Ras and P53 in leading scientific journals. Beyondspring was formed to take "a mechanism-based approach" to drug discovery and development, up to and including pivotal trials, by reducing background noise and increasing the chances of success in the clinic.

The company's lead asset is plinabulin, a triple-targeting cancer agent with a mechanism of action that allows for growth inhibition and triggering of apoptosis in malignant cells. The synthetic analogue of a marine microbial product was developed by San Diego-based Nereus Pharmaceuticals Inc., founded in 1998 by scientists from Genentech Inc. and the Scripps Institute of Oceanography. The company worked more than a decade to advance the technology, raising more than $145 million along the way. (See *BioWorld Today*, Jan. 5, 2005, and Aug. 10, 2007.)

As part of its launch strategy, Beyondspring acquired the global rights to plinabulin, then in phase II development, from Nereus. The company then rounded out its development team by hiring oncology drug veteran Gloria Lee as chief medical officer and bringing in G. Kenneth Lee, chief scientific officer at Nereus, to fill the same role at Beyondspring.

'FIRST CHINA-U.S. DEVELOPED DRUG TO ENTER GLOBAL STAGE'

From the get-go, Beyondspring was focused on moving plinabulin quickly into a phase III program. In preclinical studies, the compound showed favorable safety and antitumor activity in vasculature-dependent tumor indications, demonstrating potential efficacy across an array of cancers, including gastrointestinal, breast, ovarian, prostate and hematological cancers.

Considering the unmet medical need in NSCLC and the fact that phase I and II trials were completed successfully – with phase II data shared at last year's American Society of Clinical Oncology meeting in Chicago – that indication was selected for a pivotal phase III study that will seek to satisfy global registration requirements. Beyondspring met with the FDA, Huang said, and received its blessing to conduct a single, global trial that will enroll approximately 400 patients – 75 percent of them in China and the remainder in the U.S. and other Western countries.

Plinabulin uses multiple mechanisms of action, exhibiting

anti-angiogenesis, obliteration of existing tumor vasculature and induction of tumor cell apoptosis through the Ras-JNK pathway. The agent destabilizes the tubulin network in endothelial cells in the tumor, resulting in the selective collapse of established vasculature and subsequent tumor necrosis, with antitumor activity achieved alone and in combination with cytotoxic agents.

Plinabulin's vascular-targeting action suggests preferential sensitivity in larger tumors, so the company also is focused on lung lesions greater than 3 cm in diameter that are EGFR and ALK wild type, which have proved more difficult to treat.

Last month, Beyondspring filed a composition-of-matter patent application with the U.S. Patent and Trademark Office to cover compositions comprising plinabulin and one or more immune checkpoint inhibitors with the goal of extending the company's intellectual property portfolio in cancer treatment to include combination therapies. Preclinical studies showed more effective immune response and synergistic antitumor effect by combining plinabulin with one or more checkpoint inhibitors, which couldn't have a more winning appeal in today's hot immune-oncology market.

The application was a savvy business move, as well. If granted, the patent will provide Beyondspring with long-term market exclusivity, extending plinabulin's composition and use patent protection in cancer from 2025 to 2036.

"In our phase II study, the combination of plinabulin and docetaxel demonstrated a superior duration of response of 12.7 months compared to 1.5 months with docetaxel alone – a response that is consistent with the mechanism of lasting response associated with immune-therapy agents," Huang pointed out. "We believe that plinabulin's ability to leverage the body's immune system will increase its potential across oncology applications to treat a broad range of cancers."

The phase III design will largely mimic the phase II trial, with the experimental arm consisting of combination plinabulin (30 mg/m2) and docetaxel (75 mg/m2) vs. a control arm of docetaxel alone (75 mg/m2). The primary endpoint is overall survival, with secondary endpoints including progression-free survival, response rate, duration of response and safety.

Beyondspring has additional assets, including a preclinical peptide PDGFR antagonist that Huang designed. The protein structure-based drug has the potential to treat several cancer indications that exhibit PDGFR overexpression, including liver cancer, NSCLC and brain tumors.

The company is in discussions to in-license additional candidates, including a clinical-stage cancer immunotherapy agent and a preclinical oncology asset.

And it has the means to do so. Earlier this year, Beyondspring closed a $20 million series A led by Chinese investors Fosun Group and Shenzhen Sangel Venture Capital Co. Ltd., a specialized life science venture fund whose founding managing director is Mulong Liu, a founding R&D member of Mindray Medical International Ltd., China's largest medical device company.

Huang called the financing "strategy money," designed to help Beyondspring to execute its development plan.

"This money will finish the phase III trial and get us to data," she said, with some in reserve to study plinabulin in follow-on indications. The company will seek additional funding once it moves the drug into other advanced studies.

Beyondspring also plans to pursue a hybrid commercial strategy by seeking partners in the U.S., where "marketing is not our strength," Huang acknowledged.

But China is a different story.

"In China, all of the team members have many years of experience at bringing oncology drugs to the market," Huang said. "With this compound, we could commercialize the drug ourselves and become the first China-U.S. developed drug to enter the global stage."