Interview: Benny Hu – Chairman; Tai-Sen Soong PhD – President & CEO, Senhwa Biosciences, Taiwan

"The development of novel stabilizers of G4 is an exciting anticancer approach with a potentially broad clinical applicability."

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Founded in 2012, Senhwa Biosciences is mainly engaged in the development and clinical study of small molecule drugs to treat various types of cancer, and its drug development pipelines include CX-5461, a first-in-class drug using G-quadruplex (G4) stabilizer

as a mechanism as well as the casein kinase 2 (CK2) inhibitor CX-4945. Senhwa's chairman Benny Hu and the company's president and CEO Tai-Sen Soong provide insights into the main specificities of these products and the advancement of their clinical development.

In February 2017, an article was accepted for publication in *Nature Communications* about the innovative mechanism of action by which CX-5461 operates. What sets CX-5461's mechanism apart from those of existing products?

Hu: Finding the right pathways to accelerate apoptosis of damaged tumor cells or inhibit DNA repair can slow or arrest the growth of tumor cells. While DNA repair pathways can enable tumor cells to accumulate genomic alterations that contribute to cancer, they can also be used to destroy cancer cells by repressing the repair mechanisms in damaged cancer cells. Both CX-5461 and CX-4945 are small molecule drugs and categorized as targeting DNA repair pathways for cancer treatment respectively using the G-quadruplex (G4) stabilizer and the CK2 inhibitor.
Senhwa's CX-5461, a novel molecular targeted agent, recognizes differences between cancer cells and normal cells and induces tumor cell death without impacting normal cells, as it can activate pathways of both the Pol I inhibitor and G-quadruplexes to target cancer development.
Soong: CX-5461 stabilizes G-quadruplexes to control tumor growth. G-quadruplexes (G4s) are

four-stranded nucleic acid secondary structures that are over-represented in gene promoter regions and are viewed as emerging therapeutic targets in oncology. G4 sequences are highly prevalent in the human genome and are involved in DNA replication, gene expression and regulation, telomere/chromosome maintenance and genomic instability. When the G4 structure is stabilized by drug-like molecules, it may cause replication fork stalling, DNA breaks, and transcription–replication collisions, resulting in tumor cell death. Therefore, the development of novel stabilizers of G4 is an exciting anticancer approach with a potentially broad clinical applicability.

Our recent studies, including the article published in Nature Communications that you just mentioned, show that CX-5461 is a G-quadruplex stabilizer, with specific toxicity against BRCA deficiencies in cancer cells and polyclonal patient-derived xenograft models, including tumors resistant to PARP inhibition. We then expect that administration of CX-5461 could then stabilize the structure of G-quadruplex DNA and disable the repair mechanism of tumor cells in patients with oncogenic mutation, while a combination of G-quadruplex stability and mutated oncogenes could promote apoptosis in tumor cells.

What are the main indications in which you are currently developing CX-5461?

Soong: A phase 1, open-label, dose escalation, safety, pharmacokinetic, and pharmacodynamics study of intravenously administered CX-5461 in patients with advanced hematologic malignancies is currently underway at the Peter MacCallum Cancer Centre (PMCC) in Australia. We expect to complete this trial by the end of 2017 and we plan to expand the designation of CX-5461 based on the outcome of the trials, which are sponsored by the University of Melbourne, with Senhwa listed as a drug co-developer.

In addition, we are developing CX-5461 as a new treatment for breast cancer, ovarian cancer and prostate cancer mainly for patients with DNA repair-deficiency disorder.

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In this regard, Senhwa signed an agreement with Canadian Cancer Trials Group (CCTG) to co-conduct an open-label, multicenter, phase I/II study of CX-5461 in patients with solid tumors (phase I) and in patients with breast cancer (phase II), the trial is on-going.

Finally, we plan to file an Investigational New Drug (IND) application for CX-5461 for other solid tumors in 2017.

You just mentioned that the clinical studies of CX-5461 for breast cancer and hematologic malignancies respectively won sponsorships from Canada’s Stand Up To Cancer (SU2C) and Australia’s Peter MacCallum Cancer Centre (PMCC).

Hu: These recognitions have not only substantially lowered the company’s R&D costs, but also stand as very promising validation for the upcoming development of CX-5461.

SU2C Canada's Scientific Advisory Committee, headed by Nobel laureate Phillip A. Sharp, has established a strict screening process for selecting spondees, with a focus on novelty, inventiveness, and potential for breakthrough of the drug being developed. CCTG, our partner for the phase I/II of CX-5461 conducted in Canada, is linked to Dr. Tak W. Mak and Dr. Samuel Aparicio, who led a group that won at Stand Up To Cancer Canada (SU2C-Canada) in September 2015. This Breast Cancer Dream Team will receive CAD 9 million [around USD 6.7 million] in funding over the next four years, and CX-5461 was designated as the dream team drug

Since its establishment in 2008, SU2C has founded 20 Dream Teams and sponsored the successful launch of two cancer drugs. For example, Pfizer's Ibrance (palbociclib), a breakthrough breast cancer drug also sponsored by SU2C, was approved by the US FDA in February 2015, marking the first marketing approval ever received by an inhibitor of cyclin-dependent kinase (CDK). Pfizer is guiding Ibrance annual sales to peak between USD 3 and 5 billion.

Celgene's Abraxane (paclitaxel) for pancreatic cancer, another SU2C -sponsored drug, is used in combination with gemcitabine, with annual sales forecasted to peak between USD 1 and 2 billion. Judging by SU2C's proven record of sponsorship success, we then see promising growth prospects for Senhwa's CX-5461.

Senhwa's second product, CX-4945, is a casein kinase 2 (CK2) inhibitor, the inherent complexity of which heightens the difficulty of development. What is your R&D strategy for this promising novel therapy?

Soong: CK2 (Casein kinase 2) is a protein kinase that has elevated activity in many cancers and has a direct role in DNA damage repair. The DNA repair pathways enable tumor cells to survive damage induced by treatment with chemotherapeutic agents. Inhibitors of DNA repair pathways have been shown to increase the efficacy of DNA-damaging chemotherapeutic drugs when these are used in combination.

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Normal cells with DNA that do not replicate rapidly, as in fast growing cancer cells, and cells that have all of their DNA repair mechanisms intact are able to survive the temporary shutdown of one or more of these pathways. Inhibiting CK2 has been shown to inhibit DNA repair, and this augments the lethality of the DNA damage in cancer cells that is caused by chemotherapy treatment.

CX-4945 is a selective, small molecule inhibitor of CK2. It has demonstrated favorable safety, pharmacokinetic (PK) characteristics and pharmacodynamics (PD) responses in Phase I studies, while clinical observations show that CX-4945 hits the CK2 target and modulates the expected pathways without displaying toxicity.

A combination of CX-4945 with the DNA damaging agents such as gemcitabine (Gemzar) plus cisplatin (Platinol), has been shown to act synergistically to improve the efficacy of these

anticancer treatments. This combination is currently being developed for the treatment of advanced cholangiocarcinoma, an indication for which the US FDA granted Orphan Drug Designation to CX-4945 in December 2016.

Hu: We started CX-4945 clinical trials for cholangiocarcinoma treatment in the US before expanding its study to Asia last year, particularly in South Korea and Taiwan, where incidence rates are higher. In the meantime, phase I/II clinical trials have been underway globally, with CX-4945 used in combination with first-line chemotherapies — gemcitabine and cisplatin — in an attempt to block DNA repair of tumor cells and enhance the sensitivity of cancer cells to these anticancer therapies.

Why did you decided to focus on cholangiocarcinoma?

Hu: Cholangiocarcinoma, (or bile duct cancer) is a form of cancer that is composed of mutated epithelial cells and stands as the most common type of liver cancer after hepatocellular carcinoma. Its average prevalence rate in Western countries revolves around two cases per 100,000 people, while in Asia this rate goes up to three cases per 100,000 people. Given its heightened prevalence in Asia, we estimate annual cholangiocarcinoma drug sales to reach around USD 300 million.

Early detection and diagnosis of cholangiocarcinoma is difficult and patients are typically diagnosed at advanced stages of the disease development, with only 30 percent of them being still operable, leading to very high mortality rates. In general, chances of surviving cholangiocarcinoma are particularly limited —the five-year survival rate is just 20 percent – and the best therapeutic solution offered to patients is the surgical excision of biliary tract tumors. So far, gemcitabine and cisplatin remain the key combination chemotherapy for patients with inoperable intrahepatic cholangiocarcinoma, highlighting the urgent needs to bring new, ground breaking therapies into this field.

Soong: Finally, we intend to start the clinical development of CX-4945 in other indications and plan to file an IND application with the US FDA for medulloblastoma and Basal Cell Carcinoma within the upcoming year.

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