

# BIOCENTURY

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## EMERGING COMPANY PROFILE

# Hangzhou Highlightll: Twice the target, hold the tox

BY JEFF CRANMER, EXECUTIVE EDITOR

Sutent inventor and serial entrepreneur Chris Liang believes Hangzhou Highlightll's TYK2/JAK1 inhibitor could deliver dual selectivity without the toxicity of a more advanced Pfizer compound against the same targets to treat a broad range of autoimmune diseases. Both compounds would need to find a foothold in a crowded marketplace.

Hangzhou Highlightll Pharmaceutical Co. Ltd. announced Thursday that it raised more than RMB210 million (\$30 million) across its series B and B+ rounds, with Hankang Capital leading the series B+.

Liang, the principal inventor of blockbuster cancer drug Sutent sunitinib, co-founded the company in 2017 while he was CSO at another company he co-founded, Florida-based oncology company Xcovery Holding Co. LLC.

At Xcovery, Liang discovered and led the development of two drugs: ensartinib, an ALK inhibitor approved by China's NMPA in November for non-small cell lung cancer (NSCLC), and vorolanib, a multikinase inhibitor in Phase III testing with everolimus for renal cell carcinoma (RCC) with a regulatory submission planned in China by year-end. Both therapies are also in late-stage testing in the U.S.

With Xcovery becoming a commercial company, Liang decided to devote his full attention to what he likes best: discovering and developing therapies. An Xcovery shareholder, Liang remains an adviser to the company, which is majority owned by Beta Pharmaceuticals Co. Ltd. (SZSE:300558).

Liang's decision to take the reins of Hangzhou prompted Hankang to lead the B+ round: It was a "game changer" for us, Hankang's Vince Deng told BioCentury, which prioritizes the C-suite when investing. He cited Liang's track record as both a scientist and an entrepreneur.

Liang formed Hangzhou Highlightll with Xiangdong Liu, a veteran of Incyte Corp. (NASDAQ:INCY), with the goal of identifying a selective JAK inhibitor.

### COMPANY PROFILE

Hangzhou Highlightll Pharmaceutical Co. Ltd.

Hangzhou, China

**Technology:** TYK2/JAK1 inhibitor for autoimmune and inflammatory diseases

**Origin of technology:** In-house

**Disease focus:** Autoimmune, inflammatory, neurology

**Clinical status:** Phase I

**Founded:** 2017 by Chris Liang and Xiangdong Liu

**Academic collaborators:** N/A

**Corporate partners:** N/A

**Number of employees:** 18

**Funds raised:** RMB250 million (\$38 million)

**Investors:** Hankang Capital, Kaitai Capital, eFung Capital, Lakeside Capital

**CEO:** Chris Liang

**Patents:** 1 issued covering selective TYK2/JAK1 inhibitors

The problem with first-generation JAK inhibitors such as Xeljanz tofacitinib is that they non-selectively bind multiple members of the JAK family. While blocking the JAK family has anti-inflammatory activity, inhibition of JAK2 and JAK3 has been linked to adverse events including cardiovascular toxicity and a cancer risk.

Selectively blocking JAK1 leads to a better safety profile, and blocking another JAK family member — TYK2 — may improve therapeutic index and increase anti-inflammatory effects, according to Liang.

He pored over the literature before coming across a scaffold used by Genentech Inc. in the early 2010s. After improving upon what he saw as the scaffold's drawbacks, Liang said he fine-tuned the compound into what eventually became Hangzhou Highlightll's lead compound, TLL018, an inhibitor of JAK1/TYK2.

“It’s amazingly selective,” Liang said. “Besides JAK1 and TYK2, it doesn’t hit anything else.” He added that the safety profile is also “very clean.”

On Feb. 4, FDA issued a warning that preliminary results from a clinical safety trial of Xeljanz, which is marketed by Pfizer Inc. (NYSE:PFE) and targets JAK1 and JAK3, “show an increased risk of serious heart-related problems and cancer.”

Phase I data showed TLL018 was well tolerated with no off-target effects.

TYK2 has increasingly become a target of interest for biopharmas, Liang said. According to BCIQ’s BioCentury database, more than a dozen TYK2 inhibitors are in the clinic for nearly 20 different indications spanning autoimmune and inflammatory diseases in addition to various cancers.

The challenge with targeting TYK2 has been designing selective inhibitors that don’t cross-react with the other three members of the JAK family.

Rheumatoid arthritis drug Smyraf peficitinib from Astellas Pharma Inc. (Tokyo:4503) is approved in Japan, making it the only approved therapy that hits TYK2, although it also hits multiple JAKs.

Beyond TLL018, the only other JAK1/TYK2 inhibitor in the clinic is Pfizer’s brepocitinib, which is in Phase II testing for alopecia areata, atopic dermatitis, lupus, psoriasis and psoriatic arthritis. In addition to the five monotherapy trials, the compound is in four Phase II combination studies.

But Liang said TLL018 has higher selectivity over JAK2 and JAK3 than other JAK inhibitors, including Pfizer’s therapy, thereby avoiding toxicity issues.

Hangzhou Highlightll is readying to start Phase II testing of TLL018 in ulcerative colitis in the U.S. and Europe. Chinese physicians lack the experience in the indication, said Liang, explaining the decision not to run early trials in the country.

Liang believes that because TLL018 inhibits TYK2 and JAK1 that it could be more efficacious than ulcerative colitis therapies Xeljanz and Stelara ustekinumab from Johnson & Johnson (NYSE:JNJ), an IL-23/IL-12 inhibitor. IL-12 and IL-23 act upstream from the JAKs, activating the kinases upon engagement.

TLL018 and brepocitinib would also likely need to compete with Humira adalimumab successor Skyrizi risankizumab, an inhibitor of the p19 subunit of IL-23 from AbbVie Inc. (NYSE:ABBV) that is in Phase III testing for the indication, as well as anti-TNFs.

Psoriasis is also of interest to Hangzhou Highlightll, Liang said, pointing to Pfizer data showing 100 mg brepocitinib reduced PASI score by more than 96% in 4 weeks. Data were published in 2018 in *The Journal of Clinical Pharmacology*.

RA is the third indication Liang said was of near term interest. The company plans to run trials in RA and psoriasis in China, with any Phase III trials across the TLL018’s first three indications being global studies.

Liang said the company plans to seek a partner for its lead compound outside of China, noting the size of Phase III trials required to support approval in the indications it’s pursuing.

Hangzhou Highlightll has three in-house compounds in preclinical testing for CNS, dermatological and immuno-oncology indications. Details are not disclosed.

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## TARGETS

ALK – Anaplastic lymphoma kinase

IL-12 – Interleukin-12

IL-23 – Interleukin-23

JAK-1 – Janus kinase-1

JAK-2 – Janus kinase-2

JAK-3 – Janus kinase-3

TNF – Tumor necrosis factor

TYK2 – Tyrosine kinase 2

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