Found in translation: Institute Pasteur Korea

By Lev Osherovich, Senior Writer

Institute Pasteur Korea, a branch of France's **Pasteur Institute** primarily financed by the government of South Korea, is starting to see translatable results from its partnering and drug screening efforts. Institute Pasteur Korea recently announced its third deal of the year, licensing a tuberculosis candidate to **Qurient Co. Ltd.**, an institute spinout.¹

Qurient plans to start a Phase I trial of the TB compound, Q203, early next year.

The compound is the result of the institute's microscopy-based phenotypic screening approach. In a paper published in *Nature Medicine*, a team led by IPK principal investigator Kevin Pethe outlined the discovery of Q203.

His team first developed an assay for monitoring drug response in *Mycobacterium tuberculosis*-infected macrophages, the principal host cells for the TB-causing bacteria.

Pethe then designed a screen for compounds that penetrate infected macrophages and kill *M. tuberculosis* without inhibiting the growth of the host cell. "If you can prevent infection in macrophages, you have a better chance of preventing infection *in vivo*," said Pethe.

The next challenge was to build an automated screening platform to detect the growth of bacteria in individual macrophages screened against about 120,000 drug-like compounds from a collection of commercial libraries.

"We used confocal microscopy to look for compounds that inhibit bacterial growth but do not kill the macrophage," said Pethe. "It is difficult to automate the screening process in macrophages. Many labs can do screening in multi-titer plates, but having the software to analyze the results of large-format screening using imagery required developing an automated system."

After initial screening in mouse macrophages, hits were tested for *in vitro* activity against cultured *M. tuberculosis* to confirm that the compounds had a direct antimicrobial effect.

Q203, an optimized version of the screen's best hit, was active against multidrug-resistant TB strains. It also inhibited bacterial growth *in vitro* and in cultured mouse macrophages more potently than Sirturo bedaquiline, a **Johnson & Johnson** compound that late last year received accelerated approval to treat multidrug-resistant TB.

Q203 was well tolerated and more potent than bedaquiline in a mouse model of TB.

Pethe's team found that Q203 inhibits *M. tuberculosis* cytochrome bc_1 , a bacterial enzyme complex needed for respiration. In an *in vitro* assay of bacterial respiration, Q203 inhibited ATP production in a range of *M. tuberculosis* strains but not in a strain that harbored a mutation in cytochrome bc_1 .

Bedaquiline also inhibits bacterial respiration but targets a different complex—bacterial ATP synthase.

Qurient CEO Kiyeon Nam, who coauthored the *Nature Medicine* report, said that the company's "first objective is to show that Q203 has equivalent activity in humans."

Christopher Cooper, senior director of chemistry at the **Global Alliance for TB Drug Development** (TB Alliance), said that because

Q203 hits TB differently than existing drugs, it has the potential to be combined with existing therapies such as bedaquiline or isoniazid, the standard of care for non-drug-resistant TB.

"Q203 may act via disruption of ATP synthesis and energy metabolism and could potentially contribute to treatment-shortening regimens," said Cooper. "Importantly, because Q203 targets a different component of *M. tuberculosis*' energy metabolism cascade—cytochrome bc_1 —relative to bedaquiline, which selectively acts on ATP synthase, it is conceivable that both agents may act synergistically."

The TB Alliance has an exclusive, royalty-free, worldwide license from J&J

to develop bedaquiline to treat drug-susceptible TB.

It remains to be seen whether Q203 will be more potent than bedaquiline in the clinic, but Nam thinks that the principal advantage of Q203 may be better tolerability. "Bedaquiline is not yet standard of care, but it has some liability in terms of safety. Those are on the label as a black box warning," said Nam.

Bedaquiline's black box warns of risk of increased QT interval and death. Indeed, in one trial of bedaquiline there was a small but statistically significant rise in deaths among treated patients compared with controls. It is not known whether those deaths were caused by cardiovascular events.

Nam cited Q203's favorable preclinical tolerability profile and lower dosing requirements as reasons for optimism about its safety compared with bedaquiline.

"At this moment we don't see serious issues arising in the preclinical

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**—Christopher Cooper,
Global Alliance for TB Drug Development**

studies of Q203, so we don't expect to have any major safety issues," he said.

Nam did not disclose whether Q203, which is Qurient's only advanced asset, falls under either of the two infectious disease discovery deals IPK signed this year with **Sanofi** and **Roche**.

In April, IPK expanded a 2010 HBV screening collaboration with Sanofi to include other unspecified infectious disease indications. Also in April, IPK and Qurient signed a master agreement with Roche to collaborate on drug screening for undisclosed infectious diseases.

Qurient began operations in 2009 as the commercialization arm of IPK after raising about \$9 million from the Pasteur Institute, the provincial government of Gyeonggi-do, and venture investors **Atinum Investment Co. Ltd.**, **Hanwha Investment Corp.** and **Novartis Venture Funds**.

Qurient also has compounds for atopic dermatitis, asthma and cancer in discovery and optimization

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