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CAMBRIDGE HEALTHTECH MEDIA GROUP
PharmaWeek
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Week of 11.13.08

HUYA: A Conduit Between Chinese Pharma and US Clinical Trials

By Alissa Poh

November 13, 2008 | China plus the drug industry plus newspaper headlines has seldom equaled positive reading. Yet where pharma is concerned, two things can't be denied. First, China has certainly become a key player in global biotech, especially over the last five years, with its economy loosening up and the government allowing capitalist-type ventures in parts of the country. As well, those in pharma constantly lament the lack of new, high-quality compounds for drug development – a process that isn't getting any less expensive, while the pool of sources is drying up.

Perhaps it needs to be better recognized that drug manufacturing, and the brainpower behind drug discovery, are really quite distinct. If married in the right way(s) between China and a pharma powerhouse like the US, the combination could turn out pretty appealing. Such was the observation of Mireille Gingras, president and CEO of San Diego-based HUYA Bioscience International, who noted that significant numbers of Chinese individuals, after being educated and trained in top US institutions, were returning home to start their own biotech businesses. And naturally, they were bringing with them Western-style small-molecule discovery and development approaches. Gingras realized that this could be one answer, at least, to the problem of shrinking US and European source pools; it would also provide unique partnership opportunities with Chinese companies and research institutes.

So Gingras pioneered an "Integrated Co-development Model" at HUYA, where the company first identifies and licenses early stage lead compounds in China with promising efficacy and toxicity data in laboratory and animal models. HUYA then extends research on these drug candidates through partnerships with Chinese institutions.

"These compounds have been taken through full Western-style INDs in China," says Michael Newman, executive vice president of HUYA's oncology unit. "We do have to repeat most of the GLP toxicology studies, since theirs aren't yet fully up to US standards. But their preclinical data is invaluable – we already know a compound's PK, what doses to use; we also know there aren't any red flags in the safety package, and it has reasonable pharmaceutical properties." In other words, HUYA can hit the ground running when it comes to studying these novel drug candidates on home turf; it's also a winning situation for Chinese biotechs, as this model streamlines the development of their products in the US, for the Western biopharma market.

Developing cancer drugs – the epigenetic approach

Newman and others at HUYA are currently most excited about the results of a China-based Phase I trial with Chidamide (HBI-8000 in the US), a novel histone deacetylase (HDAC) inhibitor of the benzamide class, first discovered by scientists at Chipscreen Biosciences in Shenzhen.

The basic idea behind HDAC inhibitors has to do with gene transcription, which is regulated in part by chromatin compaction, or how tightly DNA is wound around accessory proteins called histones. When these histones are acetylated, chromatin is more open and transcription occurs at a higher rate – for as yet unknown reasons, this tends to enhance the expression of tumor suppressor genes. When it comes to

cancer, then, elevated HDAC levels are not uncommon, resulting in tighter winding of DNA around histones and decreased expression of tumor suppressor and apoptosis-inducing genes.

“We still don’t understand why it’s mainly cell proliferation-related genes that appear to be regulated by histone acetylation, but so far that seems to be the case,” Newman says. “When people started finding compounds that seemed to have the ability to cause cancer cells to revert back to a non-cancerous state, it turns out that some of these, ultimately, were HDAC inhibitors.”

Over the last 10 to 15 years, four different classes of HDAC inhibitors have been discovered and taken into the clinic: hydroxamic acids, cyclic peptides, short-chain fatty acids, and benzamides. “They had a very exciting profile, preclinically,” Newman emphasizes, “since they tended to be broad-spectrum antitumor compounds in vitro and in vivo, as well as relatively non-toxic against normal cells, with a larger therapeutic index than just about any other class of cancer drugs.”

The initial buzz started dying down when early generations of HDAC inhibitors got to the clinic and it was observed that they had activity right out of the gate against T-cell lymphomas (in particular, cutaneous T-cell lymphoma, or CTCL), but not much else. Then there were side effects other than GI issues, namely fatigue, QTc prolongation, and bone marrow suppression. Researchers in the field came away with two conclusions – that many of these compounds weren’t optimal from a pharmaceutical point of view; most would also need to be combined with the likes of cytotoxic and signal-transduction agents to be truly effective, in which case bone marrow suppression would be a particularly problematic side effect.

To date, there is only one FDA-approved cancer drug in this category – Merck’s Zolinza (vorinostat, of the hydroxamic acid class), specifically for CTCL. Approximately 10 to 12 more HDAC inhibitors are in various stages of clinical development, and a large number of follow-up trials are being conducted with Zolinza for other indications. Recent results from inhibitors in the benzamide class, however, have been regenerating excitement in the field for the first time in years – namely compounds SNDX-275 (Syndax), and MGCD-0103 (Celgene). The latter has demonstrated activity against acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), and both Hodgkin’s and non-Hodgkin’s lymphomas. In general, too, benzamide HDAC inhibitors have been noted to possess better PK profiles and fewer dose-limiting toxicities.

“MGCD-0103 looked like the compound to beat,” Newman remarks. Enter Chipscreen Biosciences, whose US-trained scientists, aware that benzamide HDAC inhibitors looked most promising, carried out computer-aided rationale design and QSAR studies on both SNDX-275 and MGCD-0103, using the published crystal structure of a bacterial HDAC. Studying these virtual enzyme-inhibitor interactions allowed them to make several predictive structural changes which, upon synthesis, eventually resulted in Chidamide. HUYA then approached Chipscreen for licensing rights to the compound, helping the Chinese group to write their Phase I protocol. At the same time, they initiated preclinical development studies in the US.

“This was really the first test case for our whole business model,” Newman remarks. “We told the FDA that we wanted to use Chipscreen’s data to not only inform our preclinical development, but also to determine the highest possible starting dose [for the clinic] here in the US. And we were actually quite worried – this was over a year ago, when there was a lot of bad news about Chinese pharma. It wasn’t a good time to be asking the FDA to trust Chinese data, to say the least.”

Not surprisingly, Newman and the HUYA team were “blown away” when the FDA responded both quickly and positively to their preclinical/Phase I plans. Newman calls it a “very significant validation of our business model.” Chidamide has since been taken through full preclinical development studies in the US, after being remanufactured through local contract research organizations, since HUYA had no desire to take any risks along those lines – “we wanted full control and western GMP involved,” Newman says.

Phase I Chidamide data generated by Chipscreen in China are “as good or better than it gets with a typical oncology trial at this phase,” Newman says. This low nanomolar, orally bioavailable HDAC inhibitor has a significantly longer half-life than that of its hydroxamic acid brethren (namely Zolinza): 18 hours as opposed to

two. Given the research showing that it's necessary to incubate tumor cells with an HDAC inhibitor for at least 16 hours before the cells start dying off, this is pretty good news, Newman says. As well, the only dose-limiting toxicities observed have been GI-related, increasing Chidamide's combination potential with other anti-tumor agents, including the standard duo (paclitaxel and carboplatin) for non-small cell lung cancer, and possibly Rituxan for non-Hodgkin's lymphoma. These two areas will be HUYA's main focus with Chidamide/HBI-8000 in the near future, since the landscape for CTCL is somewhat crowded, according to Newman. And of course, this being only the first trial, the compound will need to be put into a lot more patients to verify its profile, he adds. Both Phase II/III (China) and Phase I (US; solid tumor/lymphoma) trials are on track for the first quarter of 2009.

Extending both portfolio and partnerships

With joint headquarters in San Diego and Shanghai, offices in Beijing and Hangzhou, not to mention flourishing relationships with large science parks such as Zhangjiang Biotech, HUYA certainly appears to be in a great position to leverage China's major hubs of biotech activity.

"We currently have first-look agreements with a dozen biotechs and institutes, where we're the first to see the compounds coming through their pipelines, and can negotiate exclusive rights to these," Newman says. HUYA's portfolio now comprises a total of 528 compounds in various stages of preclinical and clinical development, for a variety of indications. Oncology tops the list, with cardiology not far behind – HBI-3000, a novel anti-arrhythmic compound licensed from the Shanghai Institute of Materia Medica, is now entering Phase II trials in China and, after a similarly successful pre-IND meeting with the US FDA, is also on track for the initiation of clinical trials in early 2009.

HUYA also lauds the US FDA's move to set up an office in Beijing by year's end, to help alleviate concerns about Chinese drugs. "It's a recognition that major things are happening in China with respect to the pharmaceutical industry," Newman says. And since HUYA is currently the leader in US/China pharmaceutical co-development, "we feel we're positioned to play a role in helping to enhance and generate Western standards [in China]."