Tox21 seminar highlights stem cell technology

By Ernie Hood

Scientists were given a glimpse into the near future at a Nov. 19 Tox21-sponsored seminar at NIEHS titled "Innovating Preclinical Drug Discovery."

The talk was presented by renowned stem cell researcher Stephen Minger, Ph.D., *(http://ccrm.ca/StephenMinger)* who is global head of research and development for cell technologies at GE Healthcare Life Sciences in the U.K. Minger's seminar was the latest in a series of talks, including ones by scientists involved in drug development, sponsored by NTP in its exploration of new methodologies with potential for advancing predictive toxicology for the Tox21 interagency consortium.

Minger described, in detail, his group's utilization of a human embryonic stem cell (hESC) line known as H7 that was derived from a single embryo, has been immortalized, and is genetically stable. "For us, this represents a treasure trove, because I can make cells from the same cell line every week for years, and provide them to customers and partners, and they will come from the same genome," he said.

Focus on drug toxicity

According to Minger, the driving force for the characterization of the H7 hESC line was to help address a major problem facing big pharmaceutical companies. "Every year, pharma will spend billions of dollars taking compounds through preclinical development using animal cells, tumor lines, and animal models [into] Phase I, Phase II, and Phase III trials. Drugs get licensed by the FDA, and then they have to be withdrawn or have their use significantly curtailed because of unforeseen cardiotoxicity."

The H7 hESC line, along with the high content analysis (HCA) cell imaging tools his company has developed, offers a potential solution to help the drug companies screen candidate compounds for even subtle signs of cardiotoxicity very early in the drug development process. This could potentially save hundreds of millions, or even billions, of dollars, not to mention tens of thousands of lives, by allowing early cessation of development of problematic drugs.

"We've developed a protocol where we take about 5 billion undifferentiated human ES cells - these are cells that can turn into any cell type in the body - and we direct their differentiation using a series of cytokines and small molecules to first commit to being mesoderm, one of the three primary germ layers that gives rise to the heart," Minger said. The cells are eventually matured into highly functional adult cardiomyocytes, or cardiac muscle cells. A lot composed of 50 percent cardiomyocytes, along with smaller percentages of fibroblasts and nodal cells, is then produced. The cardiomyocytes beat in synchrony at 45-75 beats per minute.

"So, they look like human cardiomyocytes, and functionally they act like human cardiomyocytes. The big question is, are they predictive? That is, can I test compounds on them that looked clean all the way through development, but then failed post-licensing by the FDA?" Minger asked.

Tox21 interest

NTP Biomolecular Screening Branch Chief Raymond Tice, Ph.D., said that Tox21 is already conducting high throughput screening studies, using differentiated human stem cells, and that the future applications described by Minger make a great deal of sense. "We're being amazed every day by the new technologies and techniques that are being developed," Tice said. "This presentation by Dr. Minger is another indicator of what the future will look like, in terms of our ability to perform toxicity testing that is more pertinent to human health."

Minger presented data illustrating several of the tests his group and an independent contract research organization had run, comparing results from traditional assays and newly developed stem cell-based assays in detecting cardiac side effects caused by a variety of drugs, most of which had been removed from the market due to cardiac issues. The blinded tests showed that the cardiomyocytes would have detected the cardiac issues early in the compounds' development. (Photo courtesy of Steve McCaw)

Working with a contract research organization that specializes in testing drugs for cardiac toxicity, studies showed that the cardiomyocytes are predictive. "I could have told the pharma companies on day one that, with a given compound, you've got a potential problem here," he added.

Other applications

Minger's group is also working to develop methods to multiply human hematopoietic stem cells (HSCs), which are vital for bone marrow transplants and have proven resistant to *in vitro* expansion. Seeking a therapeutic agent to address that resistance, the group screened 122,000 compounds, in less than a year, using HCA imaging, and are now testing five compounds that show promise.

Minger noted that, essentially, his group is developing platform technology to allow for the expansion of any cells, whether for assay development or therapeutic applications. The group is currently working with several major research institutions and companies to advance the technology in several different cell types.

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)

Prior to joining GE Healthcare Life Sciences in 2009, Minger was director of the Stem Cell Biology Laboratory at King's College in London. There, his team generated the first human embryonic stem cell line in the U.K. and went on to produce other stem cell lines, including those containing mutations for cystic fibrosis and Huntington's disease. (Photo courtesy of Steve McCaw)

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