SYMPOSIUM

StemCONN: Realizing the Promise

StemConn 2013

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On April 3, 2013, the fourth biennial StemCONN conference took place at the Omni Hotel at Yale in New Haven, Connecticut. This conference featured talks by scientists from across the country who are currently at the forefront of stem cell research, as well as talks by Edison Liu, President and CEO of the Jackson Laboratory, and Jonathan Rotherberg, PhD, a Yale alumnus and Ion Torrent Systems Founder and CEO. The conference highlighted the importance of stem cell research to both science and medicine and emphasized the necessity of continued government funding for this research, both in Connecticut and nationwide.

INTRODUCTION

It has never been more evident that Connecticut has become an international leader in stem cell research. StemCONN, a biennial conference which began in 2007, is a celebration of state-sponsored stem cell research and the promising technologies and research facilities being constructed nationwide that focus on developing stem cell treatments for a variety of diseases. The conference in April 2013 opened with statements by Diane Krause, MD, PhD, of Yale, the chair of the StemCONN Organizing Committee, applauding the work of researchers at Yale and across the country. Governor Dannel Malloy followed with inspiring words about how StemCONN has progressively grown in size since its inaugural conference year. Connecticut’s U.S. Senator Richard Blumenthal spoke in true politician’s form, highlighting the “cata-

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†Abbreviations: HIPSC, human induced pluripotent stem cell; SAD, sporadic Alzheimer’s disease; FAD, familiar Alzheimer’s disease; ESC, embryonic stem cell; AML, acute myeloid leukemia; CML, chronic myeloid leukemia.

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strophic loss of opportunities” that would occur should funding for stem cell research cease and urging the audience to use incentives to persuade our government that the research in this field is necessary. As would any good politician, he promised to continue to seek federal support for science, specifically stem cell therapies. The invited speakers that followed further highlighted the importance of stem cell work to medicine and science alike and the incredible advancements that can be achieved through working with and manipulating these cells.

TOPICS

Morning Session: Neuronal Stem Cells

One fact emphasized consistently throughout the symposium was that treating disease in our country costs 100 times as much as funding research for disease therapy. Dr. Larry Goldstein of the University of California San Diego made this point in one of his opening slides. Dr. Goldstein presented his research on the progressive, incurable, and incredibly common Alzheimer’s disease. He made several interesting points critiquing the “Amyloid Cascade Hypothesis” that is commonly believed to be the model of Alzheimer’s progression. One problem with this model is that drugs created to target important components of the cascade fail to work in humans and do not have the desired effects. Additionally, he brought up the noteworthy point that working mouse models of Alzheimer’s disease do not exactly phenocopy the disease as presented in humans. These differences, though they may appear to be insignificant, may in actuality have huge effects on how drugs will work in one model versus another. As he stated, we can use mice to “generate ideas, but we can’t fix the problem.”

Dr. Goldstein’s approach in coming up with alternative therapies is to use human-induced pluripotent stem cells (HIPSCs†) and differentiate them into neurons. His lab has taken these HIPSCs from humans with sporadic Alzheimer’s disease (SAD) and familial Alzheimer’s Disease (FAD) and shown that these cells can mimic some of the cellular phenotypes seen in Alzheimer’s in vitro. He did admit, however, that the process of generating these cells is laborious, and there is genetic variability in the samples they have tested. He highlighted the work that was recently published in Nature in 2012, in which his lab demonstrated that these effects can be quantified in culture and used to study early progression of the disease and possible drug responses. He further pointed out that genetic variability is important to research, as certain people may respond differently to risk factors, possibly having “protective haplotypes” that would cause them to react differently to clinical trials.

Stem cell differentiation into neurons was also the topic of the second talk of the symposium given by Dr. Laura Grabel of Wesleyan University. Whereas Dr. Goldstein focused on his lab’s work on Alzheimer’s disease, Dr. Grabel’s work highlighted the potential of these stem cells in the treatment of another common brain disorder: epilepsy. Epilepsy is a disease caused by the loss of interneurons, and many patients are refractory to current treatments. Recently, Dr. Grabel’s lab has had success differentiating mouse embryonic stem cells (ESCs) into interneurons, which have then been successfully transplanted into epileptic mouse models. These transplanted ESCs express neuronal markers in vivo and amazingly take up the host’s brain circuitry and show normal firing patterns (published in J. Neuroscience, 2012). Currently, she is expanding this research into human ESCs and aiming to start with interneuron-specific progenitors to make the protocol more efficient.

Afternoon Session: Hematopoietic Stem Cells

The afternoon session switched to another class of stem cells: hematopoietic stem cells. Dr. Jun Lu, a core member of Yale’s own Stem Cell Center, gave an engaging talk on the roles of microRNAs (miRNAs) in regulating the proliferation and differentiation of hematopoietic cells, which are often lost as a side effect of some cancer chemotherapies. Since original attempts to perform miRNA profiling in chemotherapy yielded too many candidates, the Lu lab created an in vivo functional screen.
in which a barcoded miRNA library was created, transplanted into the bone marrow of irradiated mice, and analyzed before and after chemotherapy. So far, Dr. Lu’s laboratory has validated several miRNA candidates (miR-150, miR-153-2) that, when overexpressed after treatment, make it more difficult for the mice to endure recovery. Knocking out miR-150, for example, led to better recovery in the mouse models. This would have clinical applications bettering chemotherapy in humans, as investigating miRNAs and the genes they target could lead to new routes for treatment and recovery from cancers and currently used cancer chemotherapies.

Additionally, Dr. Lu touched on miRNAs and their roles in hematopoietic disorders such as Acute Myeloid Leukemia (AML), myeloproliferative disease, and Chronic Myeloid Leukemia (CML). There are a few known genes that are mutated in some, but not all, cases of these diseases, leading to overproliferation and differentiation of hematopoietic stem cells. Dr. Lu made the important point that these genes also may be regulated epigenetically, or by miRNAs. One problem facing scientists today is that miRNA target screens in such research usually yield a high number of false positives, making the screens difficult to work with and even harder to apply to clinical practice. Dr. Lu’s lab has developed a high-throughput 3’UTR reporter assay, which seems to be a more reliable screening method for miRNAs that may be acting on some of these genes involved in overproliferation and differentiation of hematopoietic stem cells in vivo.

The final invited speaker to the symposium was Harvard’s Dr. David Scadden, who also talked extensively about how hematopoietic stem cells are regulated. Instead of looking inside the cell at the DNA/RNA level, Dr. Scadden’s research focuses on the exterior environment of the stem cells in the bone marrow — the stem cell niche, which is composed of osteoblasts and mesenchymal cells. By knocking down miRNA processing pathway components in developing osteoprogenitor cells of mouse models, Dr. Scadden saw severe myelodysplasia and some development of AML. These results indicate that the stem cell niche is important for cancer development and persistence. The current “multi-hit model” of cancer generally includes the stem cell acquiring a series of mutations in crucial genes relating to survival and proliferation. These “hits” within the cell encourage it to become cancerous. Dr. Scadden’s work clearly shows that some of these “hits” could come from surrounding niche cells. It is possible that the original “hit” within the stem cell could be supplemented by a “hit” in a neighboring osteoprogenitor niche cell, still leading to cancer and hyperproliferation of the stem cell itself. Dr. Scadden’s current work is also looking at how treating the interactions between the niche cells and the stem cells of the bone marrow could treat these malignancies.

While the morning session focused on using neural stem cells directly as genetic and functional tools to investigate potential therapies, the afternoon talks looked at creating treatment targets that are smaller (miRNAs of the stem cells) and larger (the stem cell niche) than the cells themselves. The talks covered a range of diseases, although it would have been nice to hear from someone working outside of the systems of the brain and blood. Overall, the symposium was a huge success and highlighted just a small amount of the fascinating work and progress that scientists have made working with these cells, both here at Yale and across the country.

CONCLUSION/OUTLOOK
The theme of StemCONN 2013 was “realizing the promise” of stem cell research. As Senator Blumenthal said his introduction, “We will all benefit from it.” Through the presentations summarized above and the other talks given at the conference, it is evident that stem cell research is growing exponentially and has an incredibly increasing amount of therapeutic potential. As scientists and doctors, we must continue to work to keep Connecticut at the forefront of stem cell research, not just for furthering our own scientific careers, but also for all of the promise that it holds for individuals worldwide.