Interview

Discussions on the development of human embryonic stem cell-based therapies

Dr Jane Lebkowski joined Geron Corporation in 1998 and is currently Senior Vice President and Chief Scientific Officer of the Regenerative Medicine Division. Dr Lebkowski heads Geron's human embryonic stem cell program, and is responsible for all research, preclinical development, product development, manufacturing and clinical development activities. Prior to Geron, Dr Lebkowski was Vice President of Research and Development at Applied Immune Sciences. Following the acquisition of Applied Immune Sciences by Rhone Poulenc Rorer (RPR, currently Sanofi-Aventis), Dr Lebkowski remained at RPR as Vice President of Discovery Research. During Dr Lebkowski's tenure at RPR, she coordinated preclinical investigations of gene-therapy approaches for treatment of cancer, cardiovascular disease and nervous system disorders, and directed vector formulations and delivery development. Dr Lebkowski received her PhD in Biochemistry from Princeton University in 1982, and completed a postdoctoral fellowship at the Department of Genetics, Stanford University (CA, USA) in 1986. Dr Lebkowski has published over 70 peer-reviewed papers and has 12 issued US patents. Dr Lebkowski serves as the co-chair of the Industrial Committee of the International Society for Stem Cell Research and serves on the editorial boards of several scientific publications.

Jane S Lebkowski

*Senior Vice President & Chief Scientific Officer, Regenerative Medicine
Geron Corporation, 230 Constitution Drive,
Menlo Park, CA 94025, USA
Tel.: +1 650 473 7700;
Fax: +1 650 473 7750
JLebkowski@Geron.com*

■ **How did you become involved with stem cell research & regenerative medicine?**

I first became involved in stem cells and regenerative medicine 25 years ago. Initially, I worked at a biotech company, called Applied Immune Sciences, and focused on hematopoietic stem cells and bone marrow transplantation. I was involved with that and various cell therapies for approximately 10 years before joining Geron. I joined Geron in 1998, thinking I was going to be working on a telomerase-related project, but a month later Jamie Thomson announced his derivation of human embryonic stem cells (hESCs). He called Geron because we had been funding his work and, lo and behold, I was working on ESCs!

■ **What key areas does Geron's regenerative medicine program focus on?**

Our regenerative medicine program is entirely focused on ESCs. There are four main cell types on which we are focusing our work. The first are oligodendrocyte progenitors for spinal cord injury and other CNS diseases. Second, we are looking at cardiomyocytes for heart

failure and acute myocardial infarction. In addition, we are working on islet cells for diabetes and dendritic cells for immunotherapy applications in infectious diseases and cancer. An additional application for immature dendritic cells is to induce tolerance to ESC-based grafts.

■ **Geron's goal is to use hESCs for therapeutic purposes. How have you gone about negotiating the regulatory process?**

It was a continuous process. We had our first interaction with the FDA as long ago as 2000. From there it has been a series of discussions. From that first meeting in 2000, we met periodically to talk about the studies Geron was planning and what the FDA was looking for us to do. We discussed the reports that were generated for the investigational new drug (IND) application that we submitted.

It started with proof-of-concept work, to show that these cells could have some benefit for patients. And then came the very long and very extensive safety studies. Those were the most challenging studies because they involved the use of a lot of animals over a long period of time. It was a challenge. We had a very dedicated

“The planned trial will enroll the most severely injured patients who will be treated with a small dose of cells. Our primary goal is safety.”

team and a very good contract research organization who conducted a lot of the studies, especially the safety evaluations.

■ **Will Geron’s work with the FDA pave the way for more hESC-based therapies?**

In terms of the implications for other companies looking to conduct clinical trials with hESC-based therapies, I think the main thing they will gain from our experience is that pathway is more defined. However, that pathway will likely vary depending on the clinical application you are looking to treat. If you are looking to treat patients with less severe disease, the bar will be set higher.

■ **Are you hopeful of seeing a clinical benefit, in addition to the primary safety end point in your planned clinical trial?**

We would love to see clinical benefit, and will be looking for any signs of efficacy, but it is not something that should be expected in this first trial. The planned trial will enroll the most severely injured patients who will be treated with a small dose of cells. Our primary goal is safety.

■ **What specific safety hurdles associated with ESC-derived therapy must be overcome to be confident that a therapy will be safe?**

There will need to be long-term follow-up of patients. In our first clinical trial we will be following patients for a year. They will then be followed in a second for a total of 15 years. The greatest hurdle will be proving that there is no risk of forming extraneous tissues in the graft site. That is the thing people worry about right now. To address that risk you have to look at the cellular composition of your product. Teratomas are benign tumors, not malignant, and depending on the location can be easily resected. That being said, you do not want to be causing extraneous tissue to form in people.

In our preclinical trials, we looked for all kinds of safety issues, not just tumors. One theoretical safety issue we examined in our toxicology studies was allodynia, the sensation of pain to a stimulus that is not normally painful. We performed tests on

our rodent models and found no evidence of allodynia. We also performed assessments of systemic or clinical toxicity. We took a very broad brush to look for any safety issues.

■ **In the past, the regenerative medicine industry has struggled to translate stem cell research into stem cell therapies. What do you think have been the main hurdles to clinical translation & how might these be overcome?**

There have been two major hurdles in the field of cell therapy in general. The first is to show that the cells are efficacious and the second is cost.

The challenge is to show, in definitive clinical trials, that a cell therapy has efficacy. There is one company called Dendreon that has some encouraging data regarding a cell-based therapy for prostate cancer based on dendritic cells. There is also Genzyme, which is commercializing cartilage replacements for orthopedic applications. However, there are few companies yet who have shown definitive efficacy with any type of cell therapy, let alone a stem cell therapy.

The other major hurdle has been a lack of funding in the area. For years, the combination of politics, perceived ethical questions and novelty in the science prevented capital flowing into the field.

However, I think the tide is starting to turn. As companies start to have success (e.g., if Dendreon get their biologics license application approved by the FDA) that will help the field considerably. If our planned trial goes well, that could help the field. As the field makes progress, you will see more availability of funding.

■ **What advice would you give to a startup company entering the regen industry?**

My advice would be to talk to your regulatory bodies as frequently as you possibly can to really lay out the path for a particular project. I would try to focus on one or two projects and hit your milestones, because achieving those milestones is what is going to bring in the funding that is going to be required to keep your company operational and successful. Start with projects that are relatively simple rather than complex multicomponent projects,

“...there are few companies yet who have shown definitive efficacy with any type of cell therapy, let alone a stem cell therapy.”

and focus on your pathway: do not be distracted by too many projects.

The economic downturn has hit biotech very hard and it's a challenge to raise money in this environment. So it is all the more important that when you are looking at starting a new company, you understand how your going to achieve your important milestones in order to maintain continued funding.

■ Do you think there has been a change in the regulatory & political environment for stem cell research in the USA since the inauguration of Barack Obama?

Yes, I feel there is a new optimism about stem cell research, and as money becomes available for research, the academic community can explore a large number of interesting questions, which could lead to many different applications for derived cells, as tools and therapies.

Financial & competing interests disclosure

JS Lebkowski is an officer and employee of Geron Corporation. She has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

“...I feel there is a new optimism about stem cell research, and as money becomes available for research, the academic community can explore a large number of interesting questions, which could lead to many different applications for derived cells...”