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Driving Down the Cost of Stem Cell Manufacturing

If stem cells are to be used routinely in drug discovery and therapeutic applications it is essential that cell production becomes easier and more affordable.

Sue Pearson, Ph.D.

In the week that cell therapy firm, Dendreon filed for bankruptcy, speakers at the London Regenerative Medicine Network (LRMN) meeting at University College London (UCL) continued to make compelling cases for the routine use of stem cells in drug discovery and regenerative medicine. “Traditional medicines in use today cannot address many conditions effectively,” explained Gil Van Bokkelen, Ph.D., chairman and CEO of cell therapy firm Athersys. “In the U.S. alone we’re spending $250 billion dollars annually to treat diabetes, cardiovascular, neurological, pulmonary, and kidney disease yet the treatment is not always effective and quality of life is often poor. For example, if you have a heart attack, the chance of having chronic heart failure within five years is high.”

According to Dr. Van Bokkelen in the next 20 years there will be 80% more people over 65 years old in the U.S. (more than 72 million people by 2030, up from 40 million in 2010). In Japan, this will be most visible as more than 30% of their population will be over age 65 by 2030. Healthcare costs increase dramatically with age and can be up to 5 to 10 times more annually among the elderly because this is when conditions such as stroke, cancer, and heart disease become more prevalent.

“The aging population coupled with the shortage of trained doctors means we are facing the Mount Everest of healthcare in terms of spending and lack of treatments. The public are under the misconception that it is expensive new drugs that are the cause of increased healthcare spending but in fact only 10 % of the U.S. healthcare budget goes toward prescription medicines, while a far greater amount is devoted to supportive or palliative care (hospital care, nursing homes and physician services) to care for those that can no longer care for themselves,” Dr. Van Bokkelen said.

The use of stem cells as a regenerative tool could be more effective than current treatment regimes as Dr. Van

Bokkelen stated: “Cells are able to do things in a dynamically regulated way, and their multi-modal nature is the power behind their effectiveness.”

Repairing the Damage

As an example of how stem cells can be used in regenerative medicine to treat post-stroke damage, Dr. Van Bokkelen presented information on MultiStem®, a cell therapy that is manufactured from human stem cells obtained from adult bone marrow or other non-embryonic tissue sources. He showed that in preclinical rat models, MultiStem dramatically down regulates inflammatory proteins thought to cause damage post-stroke and up regulates neurotrophic factors, which promote repair. “Even when we inject MultiStem one day after the ‘stroke’ there is a profound difference in the up- and down regulation of these proteins. This is encouraging as only around eight percent of stroke patients get tissue plasminogen activator within the four- hour effective treatment window, and this means many people that have a stroke suffer irreparable damage,” Dr. Van Bokkelen noted.

Currently, Athersys is running a clinical trial with 140 patients at stroke centers in the U.K. and U.S. MultiStem is being administered intravenously one- to two days after a stroke has occurred, where published preclinical results have shown substantial benefit even when the cell therapy is administered up to a week after the stroke. The firm aims to announce results from this Phase II trial in early 2015, around the end of the first quarter.

Zami Aberman, chairman and CEO of Pluristem Therapeutics, a developer of placenta-based stem cell products also presented positive data on how its PLX (PLacental eXpanded) cells are being used in orthopaedics to help improve muscle repair post hip replacement surgery. “We treated 20 patients with 150 x 10^6 and 300 x 10^6 PLX cells and they demonstrated up to 500 percent improvement in their MVIC (maximal volitional isometric contraction), a standard measure for hip movements up to 26 weeks post operatively,” Aberman explained.

Aberman also discussed how PLX cells are being used to treat hind limb ischemia. He presented pre-clinical data to show that mice injected with PLX had an improved blood flow to their affected leg. He presented clinical data from a two dose-escalating, Phase I/II study in which 27 patients suffering from critical limb ischemia injected with 150-600 x 10^6 PLX cells showed a risk reduction of limb amputation of 59%, 12 months post-treatment, compared to patients that did not receive the cells. “When we first made stem cells from placenta ten years ago, everyone said this was not a good source of cells for regenerative medicine. Now the miracle of birth is helping to produce some really promising therapeutics,” Aberman said.

Making Effective Targeted Treatments

Aidan Courtney, CEO of Roslin Cells, was bullish about how the use of stem cells can change from a minority sport to a major force in healthcare in the future. He stated: “In the next 20 years the cost of stem cells will come down and down via small tweaks in technology, which have come from large leaps in imagination.” Courtney discussed how stem cells could be used in drug discovery and detailed the setting up of the

European Bank for iPScs (EBiSc), a European public-private partnership project coordinated by Pfizer, managed by Roslin Cells, and supported by the Innovative Medicines Initiative (IMI) and members of the European Federation of Pharmaceutical Industries and Associations (EFPIA). Courtney states: “EBiPSc will provide access to a wide range of consistent research-grade reference stem cells for both academic and clinical research into all kinds of diseases and is a fantastic project.”

Courtney also described how using iPScs could help with improving treatment regimens. He noted; “Stratifying patients by taking cells from those with a specific disease, producing iPScs from those cells and then deciding which therapy would be most effective based on that data will improve healthcare outcomes. iPScs are game changing and they are the transistors of our era. Just as transistors made radios and computers possible IPScs will also enable amazing advances in healthcare.”

Regulatory Landscape

Seeing stem cells being used routinely as therapeutic still face a hostile regulatory landscape in many countries but this is changing in others. “In Japan, the PMDA (Pharmaceuticals and Medical Devices Agency) has a bold new vision and is helping by putting in place a framework to make running cell therapy trials more accessible. The U.K. too is moving towards trying to make running cell therapy trials more straightforward,” Van Bokkelen explained.

According to Ian Rees, unit manager and innovation at the MHRA (Medicines and Healthcare and Products Regulatory Agency), this sector needs a single point of access for advice. This is why the MHRA in 2014 introduced a new one-stop-shop website with a single point of access to regulatory advice from the four regulatory bodies the U.K.; the MHRA, the Human Fertilisation and Embryology Authority (HFEA), Human Tissue Authority (HTA), and the Health Research Authority (HRA) that work in the sector. “Getting a single response to questions and providing an opportunity for one to one meetings will ensure that cell therapy developers and regulatory bodies become fellow travellers on the journey from bench to bedside,” Rees concluded.

The Future

For stem cells to be used routinely in drug discovery and therapeutic applications in the future, the LRMN speakers stated that cell production also has to become easier and more affordable. To achieve this Courtney believes a number of changes have to occur in the next 20 years. He outlined that the harvesting of stem cells from blood or urine needs to become routine so that obtaining starting material for stem cell production will be less invasive. He also explained that by 2034, stem cells should be produced in automated systems with rapid in-line analytics with little human input for the culture, testing and production of stem cells. He cited the laboratory currently being set up by equipment manufacturer, Tokyo Electron at Stevenage Biocatalyst as a model of what automated stem cell production is moving towards looking like.

Aberman agreed that having the right technology is crucial. “Our progress with cell therapy in the beginning was so slow because we did not have the tools to scale up. When you grow stem cells in 2D instead of 3D they change their expression properties and we have had to develop a 3D bioreactor process to produce stem cells

which are effective." Aberman continued: "We now culture our stem cells in bioreactors using a 3D polystyrene and polypropylene scaffold to which stem cells can adhere to and have found this is around 70 times more efficient than 2D culturing. We can produce 30 doses of 300 x 10^6 cells per run from a five liter bioreactor and 150 doses of 300 x 10^6 cells from a 25 liter bioreactor so we can scale up our process."

Courtney also predicted that the cost of reagents and media for the culturing and production of stem cells has to become lower and these cell culture products should be designed to deliver consistent results in automated systems.

"In the past decade there is an increasing sense of confidence in the cell therapy industry as it may actually offer solutions for many unmet clinical needs. However, we need more funding to be able to do proper pre-clinical and clinical studies, as well as develop and refine large-scale production technologies. Cell therapy is regarded now as safe so we need this funding to make their manufacturing affordable and provide compelling evidence for their effectiveness," Van Bokkelen summarized.