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Introduction

The relatively permissive regulatory environment provided by the UK government has allowed the country to become a global leader in the stem cell field. Supporting research from all sources, including adult, fetal and embryonic stem cells, UK scientists have had the freedom to progress this medical frontier in basic stem cell research, opening up enormous potential for the development of new treatments for disease and injuries. Conversely, the US government does not echo this liberal regulatory approach, instead taking a strong stand on refusing to fund its progress. Most US states currently only support the use of adult stem cell research or no research at all, due to strong ethical and moral issues against the use of human embryonic stem cells (hESCs) unless donated by fertility clinics. Presentations at this meeting suggested that public opinion in the US does not generally match that of its government, and thus scientists and researchers are hoping that a change of Government office will bring with it a change in US policies, eventually allowing breakthroughs to be made within this medical field. With US \$3 billion stem cell funding presented to the state of California via a 2004 bond measure designed to get around the Bush administration's restrictions on the funding of such research, it was questioned whether this state may eventually 'catch-up' with the UK; the general opinion was that this was not the case. Regulations also vary among the European countries, with some taking a more restrictive view than others. In Germany for example, strong restrictions are placed on the use of ESCs in research. As they are only able to use animal models, many scientists feel they are simply "setting the platform" for other countries. To date, the mouse has been the primary model of choice for this research; however, many scientists are now attempting to use non-human primate models, such as the monkey, in order to provide results that more closely translate into human data.

Terrapinn's second annual European Stem Cells and Regenerative Medicine conference successfully provided a forum for leading members of both the scientific and commercial stem cell community. Attracting approximately 100 delegates, the event comprised a series of presentations and panel discussions, as well as an opportunity to network via a novel 'speed-networking' session. This report focuses on the therapeutic areas that are currently benefiting from stem cell research. Many companies are placing a large emphasis on the development of stem cell-based therapies for large-scale indications as a result of the huge market potential throughout Europe and the US. With a brief introduction to the strength and challenges that are facing the field, this document will then describe the progress that is being made in these areas, and the studies that designed to help the transition from bench to bedside.

UK stem cell research - a swot analysis

Mark Bale (Department of Health, UK) discussed the present opportunities and challenges facing UK stem cell research. This field continues to demonstrate significant progress, driven mainly by a robust research climate and the stable regulatory environment. The main source of funding for this type of work has been provided by research councils and charities, such as the MRC and the Wellcome Trust. More recently however, the UK Stem Cell Initiative (UKSCI), established in 2005 by Chancellor Gordon Brown, recommended that the government should provide a funding cost strategy for UK stem cell research between 2006 and 2015, in order to match that already provided by the UK Stem Cell Foundation (UKSCF). The government agreed to support this action, and the program is now in its second year, providing a maximum of STG 10 million a year to stem cell-based projects. In addition to a growing fund base, it is hoped that as a global leader in the field, the UK will successfully attract foreign researchers with new skills and ideas that can drive an international agenda. The UKSCI also identified the need for a public-private partnership between pharma, healthcare and biotech companies and the UK government in order to develop stem cells as a resource for discovery in medicine. The establishment of the world's first cell bank in 2004 has allowed the UK to stand out from the crowd of stem cell researchers. This cell bank provides a repository for human stem cell lines of all types, developed under appropriate and accredited quality systems, both for basic research and the development of clinical applications.

Despite these and many more initiatives for stem cell research in the UK, delegates at this conference were very aware of the obstacles that still lie in the path of its success. Dr Bale stressed the lack of IP and licensing clarity, as well as a distinct shortage of venture capitalist interest, the source from which the US currently obtains most of its funding, and big pharma support. Despite increased funding available for basic stem cell research in the UK, there remains a lack of translational funding, a critical factor if stem cell therapies are to be taken into the clinic.

In a panel discussion based around the stem cell infrastructure, Mark Walport, Director of the Wellcome Trust (UK), stressed that we must not "over-hype" the area and rush potential products to the clinic. This speaker feels that although it is certainly an important field, growing from strength to strength, research is not yet at a stage to warrant the level of funding required to take products to the clinic, and beyond, to market. Instead, it was emphasized that by taking it slowly and ensuring the best studies are performed at the right time, a more accurate and wide range of data will be obtained, and the UK will be more likely to maintain its competitive advantage, with patients eventually receiving the best forms of therapy that scientists can develop.

Geron's hESC-derived cells

Thomas B Okarma (Geron, USA) described the ongoing progress of moving Geron's hESC-derived cells towards the clinic. The company's leading product, GRNOPC1, contains oligodendroglial progenitor cells (OPCs), which adapt to the local microenvironment they are placed in and begin to fix the specified lesion site. This compound is currently under investigation for the potential treatment of acute spinal cord injury (SCI), and Dr Okarma confirmed that, with IND-enabling studies quite far along, animals being followed for more than one year after injection and no evidence of teratoma noted, Geron is currently on target to file an IND at the end of 2007. With a view to taking this product into clinical trials, Dr Okarma went on to describe the likely clinical protocol that will be followed. An unblinded, randomized, combined phase I/II trial is to involve subacute, neurologically complete T3-T10 SCI patients. GRNOPC1 is to be administered via injection, 7 to 14 days post-injury, escalating doses up to 2×10^7 cells. Evaluation will take place at 1 week, and 1, 3 and 6 months. It was stressed that as this lesion type is so rare, the study would have to take place at six to eight different sites, as each may only be able to provide one to two suitable patients. Thus, this would allow for a conservative study approach.

Another Geron product in the pipeline is GRNCM1, which comprises cardiomyocytes derived from hESCs, and is currently under investigation for the potential treatment of heart failure. These stem cells have been shown to respond normally to cardiac drugs, to demonstrate normal ventricular electrophysiology with various patch-clamp techniques, and to improve systolic function through MRI. Efficacy was observed in an infarcted rat model, and it has been shown that the cells can be successfully cryopreserved.

Dr Okarma also provided a brief description of GRNIC1, an islet clusters product, for which human proof-of-concept has been established for the potential treatment of diabetes. This agent has been shown to produce insulin and glucagon. Although it has not yet normalized glucose

levels, early results from recent studies involving transplantation of the islets into animal models of diabetes indicate prolonged survival of engrafted cells and the detection of human insulin in their blood.

ReNeuron's novel stem cell therapy for stroke

Since US-based ReNeuron uses a highly efficient expansion stem cell technology, it focuses specifically on the development of products for large-scale indications. The company's John Sinden described the current pipeline, which consists of five novel stem cell therapies under investigation for the treatment of stroke, Huntington's disease, diabetes, retinal degenerative diseases and Parkinson's disease (PD).

Studies have shown that approximately 130,000 people in the UK, and 750,000 in the US, suffer a stroke annually. Furthermore, there are currently no existing treatments for these patients beyond the acute phase. ReNeuron's ReN001, a neural stem cell therapy, is currently under investigation for the potential treatment of the chronic symptoms of stroke. Dr Sinden described preclinical data taken from a replication and dose-response study that used banked clinical lot equivalent cells, and demonstrated that transplants of ReN001 cells restore sensory and motor function in rat stroke disability. It was confirmed that an IND for this compound has been filed, and that the agent is awaiting clinical trials. With cell banking a key property of this stem cell therapy, testing has shown that the generated cell banks do meet manufacturing standards for both clinical and commercial use. Different differential assays at different banking levels were tested for stability of differentiation, and a consistent gene expression was shown across the different banking levels. Preclinical safety studies with ReN001 demonstrated long-term safety and toxicology in primates, rodents and rats with strokes, and nonobese diabetic/severely compromised immunodeficient (NOD-SCID) mice. It also investigated biodistribution and the effects of tamoxifen on cell growth in vivo. When tamoxifen is introduced into the system, it was found that the cells cannot be reactivated. Dr Sinden described the layout of the proposed phase I study, which is hoped to start later this year. It is to be a minimally invasive procedure, involving approximately 30 patients placed under local anaesthetic. ReN001 will be injected close to the area of damage over a number of minutes, and the cells should then migrate to the lesion site, survive and demonstrate site-specific differentiation, with eventual re-establishment of function. It is hoped that following the procedure, patients will be able to go home the next day. The use of fetal material means undifferentiated cells could be used providing easy preparation of the product for commercial distribution; it was stressed that this will be more difficult for other indications.

Dr Sinden felt that the standard approach to clinical development may not be appropriate for ReN001. Instead he described how phase I studies may be better broken down into a series of small studies in order to examine various aspects of the treatment, including dose, location of implant, optimization of the cell delivery process and optimization of safety monitoring techniques. For phase II studies, Dr Sinden suggested an evaluation of effectiveness of treatment in groups of patients with different severity of disease and underlying disease complications. He also emphasized the need for long-term follow up in patients, with additional rigorous neurological and safety-related tests. The first-in-man safety study will involve patients with chronic ischemic stroke, for proof-of-stable neurological deficit and a conservative protocol, described as a "creep and go" approach. Safety parameters and stopping rules will be closely monitored by the independent Data Safety and Monitoring Board (DSMB), and there will be a detailed long-term follow-up over many years.

ReN002, ReN003, ReN004 and ReN005 are also undergoing preclinical investigation, for the potential treatment of type 1 diabetes, retinal diseases and PD, respectively.

Entering the bio-aesthetic arena with Intercytex

Paul Kemp (Intercytex, USA) introduced the concept of using stem cell research for bio-aesthetics - an ever-growing market. Focusing exclusively on skin diseases, Intercytex currently has several products in its pipeline. ICX-PRO has entered phase III clinical trials for the potential treatment of chronic wounds, such as venous leg ulcers and diabetic foot ulcers. This compound is easy to manufacture, taking just one day to prepare, and to deliver. It consists of human fibroblasts formulated in a human fibrin matrix, and can be applied directly to the wound site. Dr Kemp described clinical data from an open-label, phase II trial involving 90 patients. This study, which is now complete, demonstrated good safety and efficacy data at 24 weeks, with 80% of patients with hard-to-heal ulcers showing clinical benefit, and 41% of patients with wounds less than 20 cm² showing complete wound closure. A double-blind, controlled phase III trial is currently ongoing. This study is taking place at 32 sites across the US, Canada and the UK. It involves three arms: control, vehicle (Fibrin) and ICX-PRO. An interim review by the DSMB recommended that the trial continue but with an increase in study size, and Intercytex has complied. Enrolment for this study is expected to be completed by the fourth quarter of 2007, with data to be released mid-2008. The company also anticipated filing a BLA in the second half of 2008.

Dr Kemp went on to describe Vavelta (ICX-RHY), an allogeneic human fibroblast therapy that repopulates the skin with young, active cells. This aesthetic-based therapy works by stimulating

soft tissue augmentation, generating collagen and hyaluronic acid to smooth out wrinkles and scars. Administration involves a superficial injection into the upper dermis, and studies have shown it to have a 7-day shelf life at the clinic. A phase I trial involving 10 patients was completed in July 2006, and no safety issues were identified. Two phase II trials that were due to start in the first half of 2007 in the UK were also described. Treatments for the first study, involving nasolabial folds, have begun in London, while those for the second study, involving acne scars, are due to commence in Birmingham in the second quarter of 2007. At this time, data from these studies were expected to be released during the fourth quarter of 2007. With a potential UK market opportunity worth US \$35 million, launch plans have already been put in place, with the first commercial sale in the UK planned for the fourth quarter of 2007. Dr Kemp emphasized the need for this data to be completed prior to the product being taken to the US.

Dermal papilla (DP) cells, located at the base of the hair follicle, have been shown to have hair-inductive properties, and when cultured DP cells are re-implanted into a patient, they have been found to promote new hair growth. ICX-TRC, also referred to as the "hairy generation cell" by Dr Kemp, can work via two methods - by increasing the thickness of hair follicles that are already present, and by producing brand new follicles. To date, this has been demonstrated in animal models. Dr Kemp described how a completed phase I study involving seven patients demonstrated no safety issues, with five of the seven subjects showing increased hair numbers following treatment. Delivery of these cells is crucial, with a rapid injection making the cells go to the bottom of the dermis layer, which is useless as the cells need to locate to the keratinocytes on the superficial surface in order to allow for follicle growth. The optimal delivery method is via a modified version of the Hamilton syringe, which is now an approved medical device. Phase II efficacy trials are currently ongoing with this compound, involving approximately 10 patients per cohort. This program was designed to optimize formulation/delivery of ICX-TRC. The first cohort has completed enrolment, with six patients being treated. Preliminary data are anticipated to be released in the second half of 2007.

ICX-SKN comprises allogeneic human dermal fibroblasts formulated in a collagen-matrix overlaid with keratinocytes, as a skin graft product to repair 'holes' formed during trauma or surgery. Dr Kemp described the cells as a modification of ICX-PRO. A phase I trial is currently ongoing to investigate the replacement of excision biopsy with the ICX-SKN cells. Safety and persistence were to be followed-up at one month following application. Dr Kemp stated that preliminary results are very encouraging, and results will be available in the second quarter of 2007.

Novocell - developing a novel stem cell therapy for diabetes

Diabetes is the fifth leading cause of death in the developing world, with approximately 7% of the US population affected by the condition. Alan Smith (Novocell, USA) discussed the current need for tighter glucose control, a reduction in future medical complications, and, more specifically, a form of long-term islet cell protection and replacement. Although the establishment of the Edmonton protocol has allowed the successful transplantation of 550 patients since 2000, it still has many limitations, and so a new alternative solution is sought. Dr Lewis described the ongoing studies with implants comprising human pancreatic islets encapsulated with polyethylene glycol (PEG) for the potential treatment of type 1 diabetes. This approach consists of a subcutaneous delivery of human islets without chronic immunosuppression. The FDA approved phase I/II trials using human primary islet cells in 2005, and phase I/II trial implants were completed on August 11 2006. This study has demonstrated preliminary safety and efficacy, as well as supporting the feasibility of subcutaneous administration. It has also been shown that transient low dose immunosuppression is sufficient, and that there is no autoantibody induction present. Dr Smith also mentioned that as a result of these studies, Novocell has successfully established a positive relationship with the FDA. The concept of using stem cell islets instead of primary islets brings with it a series of advantages. Problems associated with primary islets include their limited availability and the need for multiple implants when used in patients. Embryonic stem cells for the pancreatic islets are located in the ectoderm germ layer. Dr Smith described how Novocell's encapsulated stem cell-derived pancreatic endocrine cells require only a single implant, and have been found to produce glucagon, c-peptide, ghrelin and somatostatin. They have also produced insulin levels similar to that of human islet cells, and have formed islet-like structures in vivo. There is no chronic immunosuppression associated with the use of these cells, and patients are treated on an outpatient basis. Furthermore, the cells have demonstrated durability of a minimum of two years. However, it was stressed that islet cell transplantation is still in its infancy, with only 600 treatments to date, compared to over 400,000 for solid organ transplants. With continued progression, Dr Smith feels that this therapy approach could prove invaluable for the treatment of all insulin-requiring diabetics, including severe type II patients, in the future.

Aastrom - stem cells for regenerative medicine

Aastrom's focus is on the development of treatments for bone, vascular, cardiac and neural diseases. In particular, the company is developing an injectable, intramuscular, bone marrow-derived adult stem cell therapy (tissue repair cells (TRCs)), using its Replicell system to amplify cell number, as a potential treatment for vascular tissue repair in diabetics, joint repair, bone grafting and osteoporosis. Aastrom's Elmar Burchardt (USA) described a completed 36-patient, US phase I/II long-bone fracture trial, discussing interim results showing that the therapy regenerated bone with no adverse events observed. The US study was assessing the TRCs for

treating severe fractures that had failed prior treatment interventions. Dr Burchardt confirmed that final data from this study are to be released in the second half of 2007.

In January 2007, Aastrom's osteonecrosis program was initiated, enrolling and treating patients in a pivotal clinical trial in Spain. It was explained that data from this study should result in market authorization for Spain and Europe. He also said that a US pivotal trial was due to start in the first half of 2007 for this indication. Dr Burchardt also described Aastrom's plans to initiate a phase I/II pilot trial with these cells in patients with chronic heart disease in 2007. This program, for which the FDA has granted Orphan Drug designation for dilated cardiomyopathy, is currently in preclinical studies.

An additional program area with this cellular therapy product is in neural regeneration. Approximately 250,000 patients are currently living with SCI, and the standard of care is extremely limited. Preclinical research for this program is now complete, and it is hoped that phase I/II trials for SCI will be initiated by the end of 2007.

Cytori - adipose-derived stem cell therapy

Eric Daniels (Cytori Therapeutics, USA) described the advantages of his company's adipose-derived stem cell therapy, which is currently under development for the treatment of various indications. This 'real-time' therapy approach is an automated procedure which produces multiple cell types via a variety of different mechanisms. The RESTORE study forms part of an ongoing program investigating the therapy in reconstructive surgery, and this safety and efficacy trial involved 19 patients treated post-partial mastectomy, with follow-up at 6 and 12 months. Data are due to be released by the end of 2007, and product launch for this indication is expected in Europe in early 2008.

The PRECISE study for the chronic ischemia trial was also discussed. This study was designed to assess clinical functional and imaging endpoints, with overall outcomes evaluated after a 6-month follow-up. It was confirmed that results would be reported in the second half of 2008, with completion of the study anticipated for January 2011. Dr Smith then described the APOLLO study for acute myocardial infarction (AMI), which is due to commence enrolment in Europe in the second quarter of 2007, with a total of 48 patients to be recruited. The endpoints for this trial will be EF, perfusion and wall-motion.

Preclinical research has also been completed for gastrointestinal and vascular disorders and this therapy is awaiting clinical trials. An orthopedic program is currently undergoing preclinical investigation.

Summary

This meeting provided an opportunity for experts and leaders in the field of stem cell research to gather, network and discuss the scope of potential therapeutic approaches and the progress that has been made to date. While it is clear that product developments are moving forward, with preclinical studies demonstrating good safety and efficacy data in a variety of tested models, researchers must continue to approach this area with a careful hand, performing all necessary tests to obtain a complete data field, and not rushing the product to the clinic for the sake of market opportunities. Increased funding and permissive regulations surrounding embryonic stem cell research has placed the UK as a leading authority in this field, but indications suggest that this may change over time, with major US-based companies taking significant strides towards catching them up.