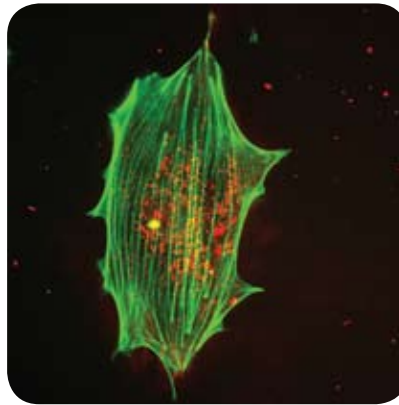
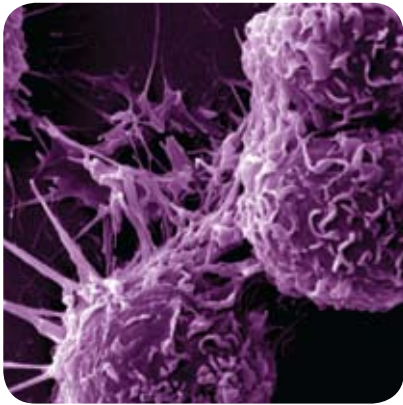


# Stem Cells as Therapy: Where have we been? Where are we now? Where are we going? (and how fast?)



Report of a Conference organised by  
The Royal Society of Edinburgh  
and  
The Caledonian Research Foundation

Thursday 30 April 2009

The Royal Society of Edinburgh  
22–26 George Street, Edinburgh

***The Royal Society of Edinburgh***  
***and***  
***The Caledonian Research Foundation***

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Report by Jennifer Trueland

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# ***Stem Cells as Therapy: Where have we been? Where are we now? Where are we going? (and how fast?)***

## **Introduction/Summary**

Stem cells may well hold the key to finding treatments for previously incurable conditions. But they tend to divide populations. While many are excited about their possible therapeutic applications, others see them as an ethical affront and are uneasy about their use. Stem cell research has, however, been one of the fastest growing areas of biomedical science in the last decade. The recent election of US President Barack Obama – who is in favour of stem cell research – is likely to accelerate that further.

Leaving aside the ethical debate, just how close are we to turning dreams of a range of stem cell therapies into clinical reality? This conference, organised by the Royal Society of Edinburgh and the Caledonian Research Foundation, brought together some of the world's leading figures in stem cell research to discuss the scientific barriers which must be overcome.

Taken in three sections, the conference heard about achievements to date, reviewed the current state of research and took a look into the future – including developments in the regulatory framework which governs the field. Significant questions and hurdles remain, but there was a sense of optimism that, given the right policy and research environment and backing, stem cells may one day become routine therapy.

## **Session One – *Where have we been?***

**Chairs: Professor Sir John Savill FRSE**, Chief Scientist, Scottish Government

**Professor John Coggins OBE FRSE**, Chair, CRF and Vice-Principal, University of Glasgow

### **Sir John Gurdon FRS**

Wellcome Trust/Cancer Research UK Gurdon Institute, University of Cambridge

#### ***Nuclear reprogramming in eggs and oocytes***

Described as a 'father figure' in the field of stem cells because of his pioneering work with frog cloning in the 1960s, Sir John introduced the day with an overview of nuclear reprogramming. In nature, cells do not change from one pathway to another – once they have started developing, they will continue to become the specific adult cells they started out to be. But experimental nuclear reprogramming can be used to encourage other, unrelated, cells to grow. This works most efficiently where the nucleus of a somatic cell is transplanted to an egg which has had its own nucleus removed.

The advantage of this process is that it is natural and highly efficient and does not require new genes. The disadvantages are that human eggs are hard to obtain, so, realistically, it would not be possible to obtain enough.

The long term aim is therefore to identify the mechanisms and substances with reprogramming ability, then use them to improve the success rates of creating replacement cells from easily obtainable tissues such as skin or blood.

He asked three questions: how efficient is

reprogramming by eggs and oocytes?; what causes the failures of nuclear transfer?; and, what mechanisms are used by eggs and oocytes for reprogramming?

Using nuclear transfer to eggs to switch between cell types is around 30 per cent efficient. Unsuccessful reprogramming may be due to epigenetic memory, whereby the cell 'remembers' what it was supposed to be in the first place.

This may be explained by the presence of histone H3.3, which appears to be required for epigenetic memory. If this is removed, it is possible to make the cells 'forget' what was once their destiny and happily become different types of cells.

Sir John then discussed some of the specific mechanisms which may lead to efficient transfer. Chromatin decondensation seems to be necessary to 'switch on' pluripotency in cells, so could be the first crucial step. The DNA has to be demethylated (which essentially means having its memory taken away) for epigenetic reprogramming. Sir John said that although you might think that transcription factors would be required, they are not. Also, it is important to switch processes 'on', but not 'off'.

The egg is a remarkable thing and a better understanding of how it works will help us make more efficient the switches for reprogramming and cell replacement.

## **Professor Roger Pedersen**

MRC Cambridge Centre for Stem Cell Biology & Medicine, Cambridge

### ***Mechanisms of pluripotency and differentiation in human pluripotent stem cells***

Pluripotent stem cells are capable of generating all body tissue and are potentially a source of important new therapies. Understanding how human embryonic stem cells (hESC) maintain their pluripotent state may be the key to translating stem cell research to therapeutic applications.

Comparisons between mouse and human stem cells are helping us to understand more about how they work. There are significant differences between mouse ESCs and hESCs. Unlike in mice, pluripotency in hESCs is maintained by the growth factors Activin and Nodal. Differences between the mouse and human cells have a developmental, rather than a species, origin, and human stem cells (including induced pluripotent stem cells) represent the state of pluripotency in the pre-gastrula stages of mammalian embryos. Activin/Nodal inhibition in hESCs induces neuroectoderm differentiation. The question is how does Activin/Nodal signalling regulate the cell fate decision between pluripotency and neuroectoderm differentiation?

Professor Pedersen discussed research which is taking forward our understanding of the biological mechanisms of stem cells. This has included analysis of the roles of the Smad proteins and their binding partners, as well as isolating and studying relevant growth factors.

Other research has looked at the role of Activin/Nodal in Nanog expression (a critical factor in cell pluripotency) and has found that it depends on the growth factors, while Nanog transcription is regulated by Smad2 and Smad3 binding sites. This is important because Nanog over-expression maintains pluripotency in hESCs.

Therefore, Activin/Nodal signalling maintains pluripotency through its regulation of Nanog expression and Nanog activity will inhibit neuroectoderm differentiation.

He also discussed the role of SIP1, which promotes and accelerates neuroectoderm differentiation in hESCs. But Activin/Nodal signalling represses SIP1 expression through Nanog and OCT4 and also directly by Smad2 and 3, while SIP1 is activated by SOX2.

All these factors affect cell fate decisions and help determine pluripotency, and improving our understanding of them in the lab will accelerate the development of new stem cell therapies.

## **Professor Robin Lovell-Badge FRS**

Head of Division, Division of Stem Cell Biology and Developmental Genetics, MRC National Institute for Medical Research

### ***Many ways to pluripotency – embryonic, adult and inducible pluripotent stem cells***

Embryonic stem cells are pluripotent, that is, they have the ability to become any of the differentiated cell types in the adult body. But there are ways of obtaining relatively stable stem cell lines from a number of sources, including blastocysts, teratocarcinoma tumours and early (post-implantation) embryonic or foetal tissue.

Adult stem cells have been used for therapy for many years – for example in bone marrow transplants and skin grafts – but they tend only to give rise to the same cell type.

Adult and embryonic stem cells can also be encouraged to pluripotency by using genes such as SOX2, so that they become induced pluripotent stem cells. These stem cell genes are required for the establishment and maintenance of tissues, to permit or encourage self-renewal and confer the ability to differentiate into one or more cell types.

Looking for these genes and seeing how they act in different types of stem cell is providing valuable information about how cells work. For example, SOX2, OCT4 and Nanog are thought to regulate many genes that define the embryonic stem cell state, and SOX2, OCT4, KLF4 and cMYC can reprogramme fibroblasts to ES-like iPS cells.

Professor Lovell-Badge talked about the role of SOX9 in the generation of neural stem cells – the number of neurones and oligodendrocytes, for example, is reduced if SOX9 is removed.

SOX2 marks several stem cell types in adults and is also expressed in several differentiated cell types, but its regulatory region is very complex.

There are a number of ways to induce or improve pluripotency, but questions remain, not least around safety. Professor Lovell-Badge concluded by saying that robust assays for pluripotency, or proxies for this, are needed, especially for human ES and iPS cells. These should include organised and consistent *in-vitro* differentiation assays; teratoma assays; chimera studies (except in humans); and profiling to look for activity of both the pluripotency gene network and chromatin status.

## Session Two – *Where are we now?*

**Chairs: Professor Charles ffrench Constant**, Professor of Medical Neurology, Centre for Clinical Brain Sciences, University of Edinburgh  
**Professor David Barlow FRSE**, Executive Dean of Medicine and Professor of Reproductive Medicine, University of Glasgow

### **Professor Ian Duncan CorrFRSE**

Professor of Neurology, University of Wisconsin, USA

#### ***Repair of myelin disorders using stem cells; exogenous vs endogenous strategies***

Myelin, the protective layer which surrounds nerve cells, is an important target for treating neurological disorders. Of these, the most common disease is multiple sclerosis (MS), where the myelin degenerates (demyelination). There are also a number of serious inherited disorders where myelin does not form. There are no current treatments which promote the repair or formation of myelin, but Professor Duncan described various strategies by which stem cells might be used to build or replace this insulating or protective sheath, providing potential cures.

In his talk, Professor Duncan concentrated on MS, a chronic, demyelinating condition, which is particularly common in Scotland, is pathologically complex and for which there are treatments but no cure.

One of the hallmarks of the disease is demyelination of the brain and spinal cord (CNS), to which, in the early stages of the disease, the CNS appears to respond with a partial remyelination. As the disease progresses, however, the CNS seems to lose its ability to respond.

Myelin arises from a well-studied cell, the oligodendrocyte. Understanding the lineage of these cells, from the earliest stages of embryonic differentiation to the production of oligodendrocyte progenitors, may provide clues about the best way to provide therapies.

Professor Duncan described two approaches: exogenous treatment, where cells are effectively transplanted to replace myelin; or endogenous, where existing cells are 'recruited' and persuaded to repair the myelin loss. The latter method may well avoid the risks of immune reactions, but may have other risks, and, in any case, the recruitment process is not sufficiently understood as yet. The former has shown more promising results so far in animal models.

Research to date may not have been conclusive, but has suggested that both methods are promising. It might be, said Professor Duncan, that the two techniques could be used together to provide a better outcome. There will be challenges, however, in translating the animal model findings into humans, not least because the human brain is much larger.

### **Professor Paul Sharpe**

Department of Craniofacial Development, Dental Institute, King's College, London

#### ***Tooth morphogenesis: from embryonic development to postnatal tooth regeneration***

For thousands of years, man has replaced lost teeth. Today we tend to use dental implants, involving a metal substitute for the root – not so very different from an iron peg found in the mouth of a Roman from 2,000 years ago. It's all been about inert substances, not biology, said Professor Sharpe.

All this could be about to change. He described the development of a biological process to use stem cells to create replacement teeth. This could have huge quality-of-life benefits; could revolutionise treatments for people with diseases such as osteoporosis (who may lose teeth and the bone in the jaw) and could also provide important clues for how best to use stem cells to replace other organs.

Professor Sharpe said it was important to understand the development of the tooth. He took it right back to the epithelium and mesenchymal cells which form an embryonic tooth primordium. The idea was to identify the cells, start the process, and then you should get a tooth, he said, adding that while the idea is simple, doing it is more difficult.

Using mouse models, they have found cells (both embryonic and adult) which will form tooth primordia and then develop into complete teeth when transplanted into the mouth.

There is a need, however, to identify human cells – and also find a source of these. Professor Sharpe described how dental stem cells are a 'fantastic' mesenchymal cell source – one of the reasons why commercial companies are now 'banking' 'baby' teeth which children lose naturally. But there remain challenges, including a relative lack of knowledge about these cells, where they are found and how they function. In order to improve this understanding, Professor Sharpe is using mouse models to determine the genetic processes involved in the repair of damaged teeth – the idea being to learn more about the mesenchymal cells believed to be in adult molars.

## **Professor Olle Lindvall**

Section of Restorative Neurology, Wallenberg Neuroscience Centre, Lund University Hospital, Sweden

### ***Stem cell therapy for neurological disorders***

While there is some evidence that stem cell therapies for some disorders of the brain would work in principle, Professor Lindvall urged a cautious approach, pointing out that there was still a lot to learn. Stem cells have possibilities, he said, but it would take time to develop 'roadmaps' to the clinic. In particular, he warned against 'scientifically ill-founded' trials in patients and said more research was needed to get a better understanding both of the diseases themselves and how potential treatments worked.

Professor Lindvall made special reference to Parkinson's disease (PD), where there is proof-of-principle that neuronal replacement can work. But he said there were many issues to be considered. Any stem cell therapy would have to be clinically competitive, in that it would have to be better than existing treatments for PD. Specific cell types, for example, dopamine neurones, would have to be generated; good animal models would be needed and the biological mechanisms underlying the observed functional effects would have to be understood.

Trials using human foetal dopamine neurones are promising, but have limitations, he said. For example, there is a limited availability of human foetal tissue. There is also the question of whether the grafted tissue is likely to become affected by the disease. Research so far suggests that patients will be fine ten years after treatment, but that disease will progress in some in 16 years.

To make a successful treatment, a good supply of standardised dopamine neurones would be needed. There have been recent interesting developments in animal models, but there are risks. For example, stem cell therapies (as tried on rats) could be tumour-forming. There is also a question about what type of stem cell would be best and research should be carried out on each in parallel. There is also the possibility that the brain could be stimulated to produce new, healthy cells of its own.

Challenges include making treatments more effective – improving survival of neurones is a major goal, he said. Minimising unwanted side-effects is also vital.

In summary, Professor Lindvall said that stem cell therapies for neurological disorders were possible, but were a long-term prospect. More information is

needed on the mechanisms of the disease and on the biology underlying the functional effects. Research on exogenous and endogenous stem cells should continue to work in parallel, and potential problems should not be underestimated.

## **Professor Keith Muir**

Division of Clinical Neuroscience, University of Glasgow

### ***Taking stem cells into clinical trials***

Professor Muir described the development of what will be the first clinical trial on stroke patients using foetal-derived stem cells. He started by saying that, as a clinician, stem cell treatments had seemed a 'distant possibility'. Now they are closer to hand, but hold a number of challenges, not all of them clinical.

Stroke is a good starting point, he said, because it is a single, focal brain injury, is common and causes disability with limited recovery – there is a huge clinical need for effective treatments.

The trial will involve injecting foetal-derived neural cells directly into the brains of stroke patients, in the hope that they will differentiate into brain tissue, neurones and other tissue and lead to repair, either directly or by stimulating the existing cells and connections to repair themselves.

There have been enormous challenges in designing the trial, which received approval from the Medicines and Healthcare Products Regulatory Agency (MHRA) in January 2009. These include choosing patients – and there is a big variety in stroke patients and most are older people with other diseases. There are also problems with recruitment of patients, as many are automatically excluded, for reasons ranging from a lack of ability to consent, to clinical suitability. There are also challenges around finding methods of showing if the treatment is working – it is not possible to 'mark' the cells to see what they are doing – and in ensuring safety. There are questions around control groups, whether patients should be immunosuppressed and about length and type of follow-up. The proposed solutions for the first trial would probably change in future trials, he said. Professor Muir also described regulatory hurdles, with two distinct bodies overseeing scientific review at present (MHRA and also the Gene Therapy Advisory Committee). Another pressure is media interest – and dealing with public expectation. Desperate patients and their families have contacted him saying they would sell everything and move to Glasgow just to be part of the trial.

## **Professor Alan Colman**

Singapore Stem Cell Consortium, (A\*STAR),  
Institute of Medical Biology, Singapore

### ***Translational applications of pluripotent stem cells – hESC and iPSC***

Cell therapy has reached some interesting milestones and there are promising therapies in development, but there is still some way to go and the challenges should not be underestimated.

Professor Colman outlined the potential uses and pros and cons – as we know them so far – of human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSC). He also gave some examples of how they are being used in research.

Proposed uses for hESC include drug screening and allogenic cell therapy and also, possibly, for autologous cell therapies. He described some current research, including the work of Coffey and others in London to ‘cure’ age-related macular degeneration (AMD) – a common cause of sight-loss – by using stem cells to make replacement macular cells.

Cells could also be made and used in drug screening, which should improve safety and avoid situations where drugs have to be withdrawn because they are causing harm in some patients.

Prospects are less good for autologous therapies, however, partly because it is difficult to make the right cell type in sufficient numbers.

Adult stem cells or iPSC have the potential to be created in far greater numbers – which might make them more suitable for autologous treatments. Here the limitations include finding ways of getting the cells to the affected site without causing problems. These cells make it possible to create an almost unlimited amount of material for drug screening and for research to study the biology of diseases. But a major challenge will be growing and ageing them quickly enough so that they are of use in examining late-onset diseases, such as motor neurone disease.

## **Panel Discussion**

Asked if the mechanisms in Europe for getting new therapies to the market are counter-productive, and if it could be done more quickly and safely, Professor Muir said he felt that regulatory processes are still developing and need a rigorous review. Rigorous regulation is important, but the current process could be improved.

Professor Lindvall said he felt that stem cell therapies are moving too quickly into the clinic and that they should be developed in a responsible way.

From the floor, Professor David Baird said that moving forward in a rational way has the potential to stifle innovation. IVF has been developed in a ‘chaotic’ fashion, he said, and the more it has become regulated, the more innovation has decreased. He said more account should be taken of consumer groups and of patients willing to take risks. Professor Lindvall said he had been a clinician for 30 years and his first ambition was to do something good for his patients. But he warned against rushing into treatments, for example, for Parkinson’s disease, for which there are existing therapies. If a stem cell treatment causes a tumour, for example, it could kill stem cell research for 25 years.

Professor Muir added that one problem is that while patients are willing to take part in trials, nobody wants the placebo – patients are willing to take risks.

## Session Three – *Where are we going? (and how fast?)*

**Chair: Professor Neva Haites OBE**, Vice-Principal, University of Aberdeen

### **Professor Sian Harding**

Professor of Cardiac Pharmacology and member of the Nuffield Council on Bioethics, National Heart & Lung Institute, Imperial College, London

#### ***Translating research into reality***

Reality, said Professor Harding, has been 'messier than planned', when it comes to translating stem cell research into clinical treatments. Although clinical trials using cells derived from autologous bone marrow and skeletal muscle cells have been taking place for over ten years, and some results have been promising, there are still a number of challenges to overcome before the treatments become a clinical reality.

The heart can be subject to many different kinds of damage, and the high incidence of heart disease makes it an important therapeutic target. Damage can be caused by a single event, such as a heart attack, or by a reaction to prolonged toxic stimulus, and a process leading to heart failure is likely to set in. Heart failure has a poor prognosis and sufferers have a reduced quality of life, and transplant is still the only option for a cure.

What we are looking for is repair of the contracting muscle of the heart, and stem cell technology is a possible way forward. But what kind of stem cells? There have been trials using skeletal myoblasts, which showed some early benefit, but also suggested that there was a risk of the unwanted side-effect of arrhythmia. One trial, the Myoblast Autologous Grafting in Ischaemic Cardiomyopathy (MAGIC), was stopped early because there was no evidence of benefit, although the treatment appeared safe and may have had positive secondary effects. Bone-marrow derived cells have produced modest improvement with no safety issues, but act indirectly rather than by creating new muscle.

Many questions remain around the efficacy of bone marrow stem cell treatment for heart disease. For example, are the trials using enough cells? Could paracrine factors do the same? Are the cells from patients impaired, and is this impairment actually a factor in the progression of the disease?

Embryonic stem cells have been shown in the lab to produce contracting myocardial muscle cells, but are more difficult to translate to clinical situations. There are hurdles to overcome in terms of immune reaction, tumour formation and potential arrhythmias, as well as ethical issues. It may be that patient-specific embryonic-like cells from skin or other areas might be

an answer to some of these problems. Alternatively, using or stimulating the intrinsic cardiac progenitor cells might produce a greater benefit.

For the cardiac area, we are at a stage where the first reliable clinical trials are informing and directing progress, but a consensus has not yet been reached on cell type, or even whether extrinsic application of stem cells can be replaced by stimulation of the natural repair process of the patient.

### **Dr John Connolly**

Health of Cell & Gene Therapies, Department of Health, London

#### ***Regulation of stem cell therapies in the UK***

Dr Connolly outlined the current regulatory and legislative framework which governs stem cell and gene therapy research in the UK. He described recent developments – such as publication of a UK regulatory route-map, which provides a one-page picture of the regulatory process – and he stressed that regulators are willing to listen and trying to learn.

The current system is complex – as evidenced by the route-map – but so is the science. The different regulatory bodies, including the Human Fertilisation and Embryo Authority (HFEA), the Gene Therapy Advisory Committee (GTAC) and the Medicines and Healthcare products Authority (MHRA), have shown a willingness to work together in order to improve the overall regulatory environment in the UK.

Regulation can be a good thing, said Dr Connolly, as it can improve the quality of research. There is a general acceptance that the process is evolving and can be improved but there are barriers to making that happen quickly – not least that there is still considerable scientific uncertainty surrounding the clinical application of stem cells and that most policies require Pan-European agreement before they can be taken forward.

He said that regulators are not risk averse and are willing to discuss research proposals to help find the best way forward. There are other helpful documents, including a handbook published recently by the International Society for Stem Cell Research. This publication is also helpful in combating 'stem cell tourism' – where patients are enticed into taking part in 'trials' which are ethically dubious, not based on evidence, and usually cost the participants a great deal of money. In some cases, even if the 'trials' are advertised as 'free', they can involve the individual

paying vast amounts for travel and accommodation costs. Although regulators and others are working to tackle the purveyors of such treatment, patients can be desperate and may accept some extreme risks, financial and otherwise. It only needs one apparent success to make a media story, he said, and vulnerable patient groups are being targeted.

### **Sir Ian Wilmut OBE FRS FRSE**

Scottish Centre for Regenerative Medicine,  
University of Edinburgh

#### ***A surfeit of opportunities: which cell is best?***

Stem cells provide new opportunities but it's a distraction to ask which cell is best; we need them all, Sir Ian suggested. As well as opportunities for new therapies, stem cells have the potential to give us a better understanding of disease and may accelerate drug discovery.

Many inherited diseases have no treatment. Stem cells may offer an answer, not only in leading to potential therapies but in helping us to study the cause of the disease and to find new drugs.

For example, family history is known to be a factor in ten per cent of cases of motor neurone disease. Mutations in the SOD1 gene cause 20 per cent of the cases of inherited MND, but it may be that deposits of an abnormal protein, TDP43 actually cause many cases of the disease. Drug development is lengthy and expensive, but it could be possible to accelerate discovery using stem cells from human patients with the disease in appropriate mouse models. This could be optimistic, however, as symptoms typically show at the age of 50 – so it would take a long time to see the effects.

Use of stem cells in drug testing may also help prevent development of dangerous drugs with unexpected side-effects. Late withdrawal of a product is very expensive – it is estimated to cost the pharmaceutical industry \$8 billion a year. If this could be reduced by creating high throughput screening using induced pluripotent stem cells, then it could produce safer drugs, more quickly and more economically. He also spoke about the possible use of stem cells to help the liver to repair itself, leading to the aspiration of a stem cell therapy for cirrhosis.

Looking to the future, stem cell technology provides real opportunities, but there are still many unanswered questions and points for debate. A way forward would be to bring together all those who are involved in stem cell research to create collaborations which pool expertise and lead to the best chance of advances in the understanding of and treatment for disease.

## **Panel Discussion and Close**

Dr Connolly was asked how the complex regulation road map compared with that of other countries. He responded that the UK was the only country which had mapped it out. He acknowledged that it is complex, but said that he is open to suggestions about how it could be improved – and stressed that regulators are approaching the issue with a degree of humility.

Asked if the wealth of regulation put people off researching in the UK, in favour of going somewhere less regulated, Dr Connolly said it is a mixed picture. While some may be put off, others find that the quality of regulation in the UK is helpful, because, for example, investors see regulatory approval as a positive thing.

Asked whether there should be more focus on potency and purity of stem cells, Professor Harding said that in cardiac terms, purity is not possible, because a number of different cells would be needed.

Professor Haites wound up the event by thanking the organisers and the speakers and all those who had contributed.

# Stem Cells Conference Poster Competition

Applications had been invited from early-career (PhD/Post-doc) researchers to present posters on any aspect of the clinical or biomedical sciences relating to the development of stem cell-based therapy for the alleviation of disease. All those presenting posters received bursaries which contributed to the cost of their attendance at the Conference and modest prizes were awarded to the winner and runner up.

## Poster Competition Entries

**German Miguel Arocena**, University of Aberdeen  
**Gregory Badouin**, University of Aberdeen  
**Julie Crawford**, University of Edinburgh  
**Dr Nicole Kane**, University of Glasgow  
**Dr Tobias Kurth**, University of Aberdeen

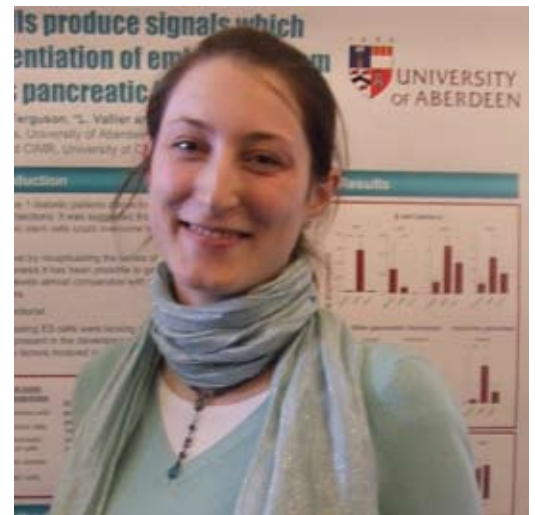
**Xiotoeng Meng**, University of Aberdeen  
**Gioia Petrigli Poliodori**, University of Aberdeen  
**Athirah Sanusi**, University of Aberdeen  
**Sanbing Shen**, University of Aberdeen  
**Daniela Uroic**, University of Aberdeen

## Poster Competition Winners

Winner: **Daniela Uroic**

University of Aberdeen for her poster entitled:

*MIN6 beta cells produce signals which induce differentiation of embryonic stem cells towards pancreatic beta cells*



Runner up: **Nicole Kane**

University of Glasgow for her poster entitled:

*Efficient, scalable and robust two-dimensional feeder-free and serum-free generation of functional vascular endothelial cells from human embryonic stem cells*



# Appendix One

## Programme

Thursday 30 April 2009

### Session One – *Where have we been?*

Chairs: **Professor Sir John Savill FRSE**, Chief Scientist, Scottish Government Health Department  
**Professor John Coggins OBE FRSE**, Chair, Caledonian Research Foundation  
and Vice-Principal, University of Glasgow

10.30: Welcome by **Professor John Coggins OBE FRSE**

10.35: *Nuclear reprogramming in eggs and oocytes*

**Sir John Gurdon FRS**

Wellcome Trust/Cancer Research UK Gurdon Institute, University of Cambridge, UK

11.15: *Mechanisms of pluripotency and differentiation in human pluripotent stem cells*

**Professor Roger Pedersen**

MRC Cambridge Centre for Stem Cell Biology & Medicine, Cambridge, UK

11.35: *Many ways to pluripotency – embryonic, adult and inducible pluripotent stem cells*

**Professor Robin Lovell-Badge FRS**

Head of Division, Division of Stem Cell Biology and Developmental Genetics, MRC National Institute for Medical Research

12.15: Lunch/Poster session

### Session Two – *Where are we now?*

Chairs: **Professor Charles ffrench Constant**, Professor of Medical Neurology, Centre for Clinical Brain Science, University of Edinburgh

**Professor David Barlow FRSE**, Executive Dean and Professor of Reproductive Medicine, University of Glasgow

13.10: *Repair of myelin disorders using stem cells: exogenous vs. endogenous strategies*

**Professor Ian Duncan Corr FRSE**

Professor of Neurology, University of Wisconsin, USA

13.30: *Tooth morphogenesis: from embryonic development to postnatal tooth regeneration*

**Professor Paul Sharpe**

Department of Craniofacial Development, Dental Institute, King's College London, UK

13.50: *Stem cell therapy for neurological disorders*

**Professor Olle Lindvall**

Section of Restorative Neurology, Wallenberg Neuroscience Centre, Lund University Hospital, Sweden

14.10: *Taking stem cells into clinical trials*

**Dr Keith Muir**

Senior Lecturer in Neurology INS, University of Glasgow

14.50: *Translational applications of pluripotent stem cells – hESC and iPSC*

**Professor Alan Colman**

Singapore Stem Cell Consortium, Institute of Medical Biology, Singapore

15.10: Panel Discussion (All Session One and Two speakers)

15.30: Coffee/Poster session

**Session Three – *Where are we going? (and how fast?)***

Chair: **Professor Neva Haites OBE**, Vice-Principal, University of Aberdeen

15.50: *Translating research into reality*

**Professor Sian Harding**

Professor of Cardiac Pharmacology & Member, Nuffield Council on Bioethics,  
National Heart & Lung Institute, Imperial College, London, UK

16.10: *Regulation of stem cell therapies in the UK*

**Dr John Connolly**

Head of Cell & Gene Therapies, Department of Health, London, UK

16.30: *A surfeit of opportunities: which cell is best?*

**Sir Ian Wilmut OBE FRS FRSE**

Scottish Centre for Regenerative Medicine, University of Edinburgh, UK

17.00: Panel Discussion and Close (All Session Three speakers)

17.20: Conference Drinks Reception

# Appendix Two

## Speakers' Biographies

### **Sir John Gurdon FRS**

Wellcome Trust/Cancer Research UK Gurdon Institute, University of Cambridge, UK

Educated at Eton College, where he did Classics, having been advised that he was unsuited for science, and Christ Church, Oxford (Zoology). PhD with Michael Fischberg, on nuclear transplantation in *Xenopus*. Obtained the first clone of genetically identical adult animals. Demonstrated genetic totipotency of somatic cell nuclei by obtaining sexually mature frogs from the nuclei of intestinal epithelium. Did postdoctoral work at Cal-Tech, on bacteriophage genetics. Moved to MRC Molecular Biology Laboratory in Cambridge (Chairman Max Perutz), subsequently becoming Head of Cell Biology Division. In 1983, accepted John Humphrey Plummer Professorship of Cell Biology in University of Cambridge, in Zoology Department. Initiated, with Professor R Laskey, Cancer Research Campaign Unit of Molecular Embryology in Zoology Department Cambridge. In 1990 moved to new Wellcome CRC Institute of Cancer and Developmental Biology in Cambridge, and served as Chairman 1990–2001. From 2001, the Institute was renamed The Gurdon Institute. Master of Magdalene College, Cambridge 1995–2002, and Governor (= Trustee) of the Wellcome Trust 1995–2000.

Main directions of research have been:

- (i) nuclear transplantation and the reprogramming of somatic nuclei;
- (ii) the use of *Xenopus* eggs and oocytes for mRNA microinjection, and hence gene overexpression;
- (iii) analysis of signalling in normal development, and the use of signalling factors for the redirection of cell differentiation.

Has received various recognitions for his work (see Who's Who).

Interests: skiing, tennis, horticulture, Lepidoptera

### **Professor Roger Pedersen**

MRC, Cambridge Centre for Stem Cell Biology and Medicine, Cambridge

Roger Pedersen received degrees in biology from Stanford (AB 1965) and Yale (PhD, 1970) and did postdoctoral work at Johns Hopkins. In 1971, he joined the University of California, San Francisco, where he studied developmental potency and fate in mammalian embryos. In 2001 he moved to the University of Cambridge, where he continues his research on human embryonic stem cells as Professor of Regenerative Medicine. In addition, in September 2008, Professor Pedersen became the first Director of The Laboratory for Regenerative Medicine, the translational phase of the Cambridge Stem Cell Initiative.

### **Professor Robin Lovell-Badge FRS**

Division of Stem Cell Biology and Developmental Genetics, MRC National Institute for Medical Research

Professor Lovell-Badge is an Honorary Professor in the Department of Anatomy and Developmental Biology, University College, London, and a Visiting Professor in the Department of Biochemistry, University of Hong Kong. He is also President of the Institute of Animal Technology. He serves on several committees and advisory boards, including the Scientific and Clinical Advances Advisory Committee for the HFEA. He was elected a Member of the European Molecular Biology Organization in 1993, a Fellow of the Academy of Medical Sciences in 1999, and a Fellow of the Royal Society in 2001. He is the recipient of the 1995 Louis Jeantet Prize for Medicine, the Amory Prize for 1996 (Awarded by the American Academy of Arts and Sciences), and the Feldberg Foundation Prize for 2008.

Robin Lovell-Badge obtained his PhD in Embryology at University College London in 1978 under Martin Evans. After postdoctoral research in Cambridge and Paris, he established his independent laboratory in 1982 at the MRC Mammalian Development Unit, University College, London, directed by Anne McLaren. In 1988 he moved to the National Institute for Medical Research in Mill Hill, London, becoming Head of what is now called the Division of Stem Cell Biology and Developmental Genetics in 1993. He has had long-standing interests in the biology and uses of embryonic stem cells, in how genes work in the context of development, and how decisions of cell fate are reached during embryogenesis. Major themes of his current work include sex determination, development of the nervous system, and the biology of stem cells within the early embryo, the CNS and the pituitary.

### **Professor Ian D Duncan CorrFRSE**

Professor of Neurology, University of Wisconsin, USA

Qualified from the University of Glasgow Veterinary School (BVMS) 1971, PhD Glasgow University, Experimental Neuropathology; Post-Doctoral Fellow, McGill University, Montreal 1977-81; Scholar of the Medical Research Council of Canada 1981-82; Associate Professor then Professor, University of Wisconsin Madison 1982-present. Fellow of the Royal College of Pathologists, 1996, Corresponding Fellow of the Royal Society of Edinburgh, 2006.

### **Professor Paul T Sharpe**

Department of Craniofacial Development, Dental Institute, Kings College London, Floor 27 Guy's Hospital, London

Professor Paul Sharpe is the Dickinson Professor of Craniofacial Biology at Kings College London and founder/scientific Director of Odontis Limited, a university spin-out company that specialises in tissue engineering of teeth. He graduated with a degree in biology from York University (1977) and a PhD in Biochemistry from Sheffield University (1981). Following postdocs in Sheffield, Wisconsin and Cambridge he became lecturer in molecular embryology at the University of Manchester in 1987 where he established a research group working on the molecular control of tooth development. Following promotion to Reader in 1991 he was recruited to his present Chair at the Dental Institute of Guy's Hospital (later to merge with Kings College), where he established a new basic research department, the Department of Craniofacial Development. The department, of which he remains head, now consists of 15 academic research groups with over 80 research staff. In 2002 he became Director of Research for the Dental Institute and head of the Division of Craniofacial Development, Orthodontics and Microbiology.

His basic research work continues to explore the genetic interactions that control tooth development. In 2004 he was awarded the Craniofacial Biology Research Award by the International Association for Dental Research in recognition of his contribution to the understanding of how teeth develop, and in 2006 his paper *Stem cell-based tissue engineering of teeth* received the William J Gies award for best publication in Biomaterials and Bioengineering from the same organisation.

### **Professor Olle Lindvall**

Section of Restorative Neurology, Wallenberg Neuroscience Centre, Lund University Hospital, Sweden

Dr Olle Lindvall is Professor of Clinical Neurology and Chairman of the Division of Neurology at the University Hospital, Lund, Sweden. He has served as Vice-Dean of the Medical Faculty at the University of Lund 1997–1999, member of the Board of the Swedish Research Council (medical division) 2001–2006, and clinical coordinator in the EU-sponsored integrated project EuroStemCell 2003–2007. He has received numerous Prizes and Awards. Dr Lindvall has been a member of the Board of the International Society for Stem Cell Research (ISSCR) since 2004, and since 2005 a member of the Board of Reviewing Editors for *SCIENCE* and member of the Scientific Advisory Board of the Michael J Fox Foundation for Parkinson's Research. He was co-chair of the ISSCR Task Force on the Clinical Translation of Stem Cells 2007–2008. In 2008 Lindvall was elected a member of the Royal Swedish Academy of Sciences.

Since 1983 Dr Lindvall has headed the clinical neurotransplantation program at the University of Lund. This program has pioneered cell replacement strategies and been the first to show proof-of-principle, ie, that transplanted neurons can survive, grow, restore transmitter release, become functionally integrated, and give rise to clinically measurable improvements in the diseased, 50–60 year-old human brain. Current research interests in Lindvall's laboratory are the development of stem cell-based approaches for cell replacement in Parkinson's disease and stroke, and of gene therapeutic strategies for neuroprotection and neuroregeneration in Parkinson's disease. Much focus is on the role and possible therapeutic relevance of neurogenesis from the adult brain's own neural stem cells in stroke and epilepsy.

### **Dr Keith Muir**

Senior Lecturer in Neurology INS, University of Glasgow

Keith Muir has been involved in acute stroke research since 1992, and after clinical training in Neurology, was appointed Senior Lecturer in Neurology at the University of Glasgow in 2001. He leads clinical stroke research at the Institute of Neurological Sciences, Glasgow, with particular interests in thrombolytic drug therapy in acute stroke, and the application of brain imaging to clinical trial design and management. In January 2009, he was appointed to the SINAPSE Chair of Clinical Imaging. Involvement in stem cell research is through developing a "first in man" clinical trial in collaboration with a commercial group developing a foetal stem cell line for stroke, and academic studies on imaging methods for cell tracking *in vivo*.

### **Professor Alan Colman**

Wolfson Centre for Age-Related Research, King's College London and A\*STAR Institute of Medical Biology, Singapore

Alan Colman is currently Professor of Regenerative Medicine at King's College, University of London, UK. He is also Executive Director of the Singapore Stem Cell Consortium and Principal Investigator at the A\*STAR Institute of Medical Biology, in Singapore. His main interests concern basic research into stem cells and the translation of that research into the clinic. Alan Colman obtained a BA degree in Biochemistry in Oxford (1971) and a PhD under John Gurdon, a pioneer of the field of nuclear transfer, at the Laboratory of Molecular Biology in Cambridge, UK (1974). After a series of academic appointments in Oxford and Warwick Universities, he became Professor of Biochemistry in the University of Birmingham, UK. The focus of his academic career was the area of eucaryotic protein secretion, with a particular emphasis on the use of frog oocytes and eggs as *in vivo* test tubes. From 1987 until March 2002, he was research director of the company PPL Therapeutics in Edinburgh, UK. This company specialised in the production of transgenic livestock that produced human therapeutic proteins in their milk. PPL attracted considerable media attention because of their participation, together with the Roslin Institute, in the technique of somatic nuclear transfer. This work led to Dolly, the world's first sheep cloned from an adult somatic cell (1996), Polly and Molly, the first cloned transgenic livestock (1997), Diana and Cupid, the first livestock with targeted genetic changes (2000), Millie *et al.*, the first cloned pigs (2000) and, finally, Austin and crew, the first homozygous, alpha gal transferase knock out pigs (2003). From 2002–2007, he was CSO and then CEO for the Singaporean human embryonic stem cell company, ES Cell International.

Alan lists amongst his hobbies, mountain biking, scuba diving, white water rafting, skiing, and trying to approach old age gracefully.

### **Professor Sian Harding**

Professor of Cardiac Pharmacology & Member, Nuffield Council on Bioethics, National Heart & Lung Institute, Imperial College, London, UK

Professor Sian Harding obtained her Ph.D. in Pharmacology from King's College, London in 1981. She became Professor of Cardiac Pharmacology at the National Heart and Lung Institute, a Division of the Imperial College Faculty of Medicine, in 2002. Her work has been funded by the British Heart Foundation, the Wellcome Trust, the Medical Research Council, the Biochemical and Biophysical Research Council, the NC3Rs, Pfizer, GSK and SmithKline Beecham. Professor Harding is President of the European Section of the International Society for Heart Research and a member of the Nuffield Council on Bioethics. She is PI on the first UK Gene therapy Trial aimed at improving cardiac contractility, and is part of the Scientific Advisory Board of *Stem Cells for Safer Medicines*. She has been elected Fellow of both the American Heart Association and the European Society of Cardiology.

**Dr John Connolly**

Head of Cell & Gene Therapies, Department of Health, London, UK

John graduated from the Genetics Department at Trinity College Dublin in 1991. He carried out his postgraduate studies at the Departments of Genetics at Cambridge and Leicester Universities and Cold Spring Harbor Laboratory (CSHL) in New York, obtaining his PhD in Neurogenetics in 1997. Subsequent to further postdoctoral research in CSHL and Fondation Jean Dausset in Paris on transgenic models of neurodegenerative diseases, John worked in the pharmaceutical industry on the development of new anti-psychotic treatments. Since 2004, he has worked on stem cell and cloning policy for the UK Government at the Department of Health in London. He is currently Head of Cell and Gene Therapies, with a team responsible for ethical oversight of gene therapy and stem cell clinical trials, providing the Secretariat to the UK's Gene Therapy Advisory Committee, developing policy to support stem cell research and therapy, and horizon-scanning for new and emerging technologies that have potential to impact on future healthcare.

**Sir Ian Wilmut OBE FRS FRSE**

Scottish Centre for Regenerative Medicine, University of Edinburgh, UK

Ian Wilmut is the Director of the MRC Centre for Regenerative Medicine at the University of Edinburgh. The Mission of the Centre is to develop new treatments for human disease through innovative research with stem cells. The new Centre covers the full spectrum of research – from basic mechanisms of stem cell regulation, via rigorous translational studies, to clinical trials with stem cells and their derivatives. Purpose designed facilities that will be completed in Spring 2011 are being built alongside the new Royal Infirmary of Edinburgh. The research of Ian's own group is directed toward understanding the mechanisms that bring about reprogramming of nuclei and with exploiting new opportunities for reprogramming cells to study degenerative diseases, such as Motor Neurone Disease.

## The Caledonian Research Foundation (CRF)



The Caledonian Research Foundation is a Scottish Charity which has supported and encouraged independent research in Scotland, particularly in the biomedical sciences, since 1990. It was originally established in 1977 as the Inveresk Research Foundation (IRF), an independent scientific research organisation which received income from the contract research company, Inveresk Research International (IRI). Following a management buyout of IRI in 1990, the assets that had supported IRF were used to establish the Caledonian Research Foundation.

In Spring 2009 the CRF agreed to join with the RSE Scotland Foundation to deliver a joint programme of activities in support of research in Scotland. The CRF transferred its activity portfolio and assets, around £6.3m, to the RSE Scotland Foundation, which is now responsible for delivering these within its wider programme of activities. The CRF will cease to exist as an independent organisation from the summer of 2009, but its charitable objectives will continue to be met through the RSE Scotland Foundation.

The Royal Society of Edinburgh already delivered some activities on behalf of the CRF, which made the transfer of the CRF's assets and operations to the RSE Scotland Foundation, and its responsibility for the wider portfolio, both sensible and seamless. To ensure the smooth transition, three CRF Governors have also become RSE Scotland Foundation Trustees until 2012.

The types of CRF activities which now rest within the RSE Scotland's Foundation remit are:

- Research Fellowships for early career academic staff carrying out advanced work in the biomedical sciences in Scottish higher education and research institutions.
- European Visiting Fellowships to enable scholars of the Arts and Letters from elsewhere in Europe to spend short period working in Scotland and *vice-versa*.
- Postgraduate Scholarships for students undertaking research leading to a PhD degree in Scotland, managed by the Carnegie Trust for the Universities of Scotland
- An annual Prize Lectureship to bring an academic of international repute to visit Scotland research centres and give lectures.
- An annual International Conference on aspects of the biomedical sciences.

## The Royal Society of Edinburgh (RSE)

The Royal Society of Edinburgh is Scotland's National Academy. It is an independent body with charitable status. The Society organises conferences and lectures for the specialist and for the general public. It provides a forum for informed debate on issues of national and international importance. Its multidisciplinary Fellowship of 1500 men and women of international standing provides independent, expert advice to key decision-making bodies, including Government and Parliaments.



The Society's Research Awards programme annually awards over £2m to exceptionally talented young researchers to advance fundamental knowledge, and to develop potential entrepreneurs to commercialise their research and boost wealth-generation.

Among its many public benefit activities, the RSE is active in classrooms from the Borders to the Northern Isles, with a successful programme of lectures and hands-on workshops for primary and secondary school pupils.

The Royal Society of Edinburgh working as part of the UK and within a global context, is committed to the future of Scotland's social, economic and cultural well-being.

## The RSE Scotland Foundation

The RSE Scotland Foundation was established in 1996 and is a charitable body connected to the Royal Society of Edinburgh. The charitable purpose of the Foundation is to advance the education of the public in Scotland in science, engineering or technology.



