

## **Stem Cells for Safer Medicines: Second call for proposals**

### **SUMMARY**

The Stem Cells for Safer Medicines (SC4SM) initiative is a public-private collaboration, established through the vehicle of a not-for-profit company, whose mission is:

*To enable the creation of a bank of stem cell lines with open protocols and standardised systems in stem cell technology that will enable consistent differentiation of stem cells into stable homogenous populations of particular cell types, with physiologically relevant phenotypes suitable for toxicology testing in high throughput platforms.*

Pharmaceutical and biopharmaceutical companies are facing increased pressures to speed drug discovery and reduce R&D costs, and unexpected adverse reactions and toxicities to new medicines during clinical trials remains a key challenge. Being able to reduce the incidence of this candidate attrition would enhance both productivity of drug development and volunteer and patient safety. This should also lead, in the long-term, to refinement and reduction in animal use by improved selection of compounds.

The SC4SM initiative is a five year programme, with a pilot (first) phase stretching through to late 2009. The pilot year will conduct a series of projects, open to both commercial and academic collaborators, to improve understanding of the fundamental biology and inform approaches in the subsequent 4-year programme.

The first call for proposals in October 2007 focused on research to obtain presumptive hepatocytes from human embryonic stem cell lines, and the establishment of functional readouts to validate differentiated cells in high throughput toxicology screens.

The Scientific Advisory Board has now identified a further opportunity for the UK in the first phase of the SC4SM programme in focusing on the characterisation and validation of cardiomyocytes derived from human embryonic stem cell lines.

Proposals are invited for industry-oriented basic research projects with specific goals. Non-member companies of the consortium are invited to contribute to specific projects in collaboration with individual academic groups – conditions for participation are highlighted under the Funding Allocation and Proposal Details sections.

### **BACKGROUND**

Early identification of potential toxicities in drug development will be essential in reducing attrition during late stage development of new medicines due to unexpected safety issues. The provision of validated (predictive) high-throughput cell-based *in vitro* toxicity screens may be highly beneficial in this respect. However, the effectiveness of these is currently severely limited by the lack of availability of relevant cell types (i.e. human, target organ phenotype) that are adequately validated and technology to integrate these into high throughput systems with relevant functional read-outs.

Stem cells provide a route to deriving sufficient quantities of fully differentiated cells with specific and standardised phenotypes that can be used in high-throughput *in vitro* toxicity screens. This is seen to be a challenging aim in itself, and is very likely to have significant benefit in elucidating fundamental mechanisms of cell differentiation, and for

wider applications than the development of predictive toxicology assays and instrumentation alone.

The purpose of the pilot phase will be to demonstrate proof of concept for the consistent derivation of hepatocytes and cardiomyocytes as a model for the longer term programme, the strategy of which will be mapped out in parallel to the first pilot phase funding. This will form the basis on which a decision will be made on financial commitment and strategy to complete the five year programme.

Drug-induced cardiac adverse events can be divided into two groups, acute and chronic effects. Immediate electrophysiological effects of drugs are typically mediated by their direct or indirect interaction with cardiac ion channels, cell surface receptors and kinases in ventricular myocardium and/or the heart conduction system, which may lead to cardiac arrhythmia. Long-term damage can be mediated by direct myocardial injury mainly resulting from impaired cellular homeostasis and oxidative stress. Development of *in vitro* assays based on the human stem cell-derived cardiomyocytes would provide an opportunity to assess the specific cardiotoxicity end-points early in the drug development process.

The single most important component of a high throughput toxicity screen is the cell type used. For drug-induced cardiac toxicity testing, primary myocytes are the natural choice – e.g. from human, dog, rabbit. However, the availability of high quality primary human cardiomyocytes is very limited, and subject to donor-to-donor variability. Adult primary cardiomyocytes of any species survive for only a few days in culture and have no capacity for expansion. There are few immortalised lines with a cardiac phenotype, and these are of rodent atrial origin. There is therefore a pressing need for a new *in vitro* model of human cardiomyocyte function.

Differentiation and expansion of stem cells into cells approximating primary cardiomyocytes (or indeed any other required primary cell) therefore offers important potential to provide continuous and readily available supplies of cells with limited variability, which may also retain their differentiated phenotype for longer periods. Current developments in progenitor cell biology (e.g. embryonic and adult stem cells) suggest that such a goal is achievable and should improve the quality of predictive toxicity testing.

Recently there have been a number of reports on the differentiation of “cardiomyocyte-like” cells from embryonic stem cells. However a number of questions remain including:

- Can the cardiomyocyte-like cells be consistently differentiated and purified in numbers sufficient for screening?)
- How relevant are the cardiomyocyte-like cells for predictive toxicology screening?
- What functional read-outs are required to ensure confidence that routinely differentiated cells have cardiomyocyte relevant behaviour?
- Can the protocols developed be applied to a number of stem cells lines to consistently differentiate cardiomyocytes with a range of genotypes?
- Are the protocols potentially scalable? What is the smallest cellular unit that could be used for testing (small number of beating cells, spheroid, beating vesicular structure of a particular size etc)?

Subsequent phases of the SC4SM initiative will expect to progress to full analytical evaluation of promising hepatocytes and cardiomyocytes and development of enabling stem cell technologies, look at additional challenges in the derivation and validation of other cells, complex systems, and scale up. However progression beyond the first phase depends upon two factors: achieving the scientific objectives regarding the derivation of cell lines that can deliver cultures with hepatocyte and cardiomyocyte functional profiles, with protocols and standards for consistent differentiation; and matching the objectives of the full scientific programme that will be mapped out in parallel by the Scientific Advisory Board.

## **ETHICS FRAMEWORK**

The application of stem cell technology can engender differing feelings among the public around the world. Pharmaceutical companies have to operate in this global context and take note of the views of their various stakeholders. After close consideration the consortium has agreed an Ethics Policy for the first phase of funding.

For the purposes of this call, research sponsored by or co-ordinated through the Stem Cells for Safer Medicines consortium will only utilise stem cell lines from the UK Stem Cell Bank, and that are fully compliant with the criteria below, reflecting the conditions for inclusion in the NIH Registry<sup>1</sup> in the USA and the UK Stem Cell Bank<sup>2</sup>. Their use will require approval by the Steering Committee of the UK Stem Cell Bank – to speed this process, applicants are advised to submit their application at the point of grant application.

- The stem cells must have been derived from adult, cord-blood sources or unused fertilised eggs created for reproductive purposes (embryonic stem cells).
- Fully informed consent must have been obtained prior to the donation of a fertilised egg or other source of stem cell lines for scientific research.
- There must be no financial or other inducements for donation of a fertilised egg, cord-blood or source of adult stem cells.
- Donation, management and distribution must comply with guidance and ethical codes in the countries from which the stem cell lines were sourced.
- Only stem cells lines already banked or registered to be banked should be used.
- Prior to any research utilising cell lines derived from human embryonic stem cells, there must be a clearly defined purpose to increase knowledge about serious disease and/or to apply such knowledge in developing treatments for serious disease.
- Stem Cells for Safer Medicines and research funded by the consortium will not use human-animal hybrid cloned stem cell lines (cytoplasmic hybrids).

An independent Ethical Review Board (ERB) will be established to provide advice on the ethical, social and legal framework for research funded by the SC4SM initiative. In particular the ERB will advise the consortium on the impact of scientific developments in light of the public and legal environment.

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<sup>1</sup> <http://stemcells.nih.gov/research/registry/>

<sup>2</sup> <http://www.ukstemcellbank.org.uk/>

## SCOPE FOR APPLICATIONS

Industry-oriented basic research proposals are invited from applicants with expertise in stem or progenitor cell biology, cardiomyocytes and derivation of cardiomyocyte-like cells. Projects can be carried out in partnership with third parties, such as small emerging biotechnology companies. All collaborators and academic groups funded will be required to comply with SC4SM's Ethics and IPR policies<sup>3</sup>.

A key aim of this call is to characterise human stem or progenitor cell-derived cardiomyocyte cells, increase proportion and purity of hESC derived cardiomyocytes (hESC-CM) and increase the reproducibility of cardiac cell differentiation. Since the appearance of the cardiomyocyte phenotype has been regularly reported for human ESC lines, applicants will likely have achieved this before submission, however submissions proposing novel approaches and technologies to generate cardiomyocytes more effectively and efficiently will also be considered. HESC applications incorporating iPS as one of the derivation routes will also be considered, but applicants must demonstrate that they are already achieving consistent production of cardiomyocytes to a similar level as hESC-CM.

1. Derivation and physiological characterization of promising human stem cell-derived cardiomyocyte cells for indication of utility in toxicology:

- to obtain hESC-derivatives differentiated into stable homogenous population of physiologically relevant phenotype with standardized protocols that can be applied reproducibly across a number of lines. Ventricular-like cardiomyocytes are the main interest for cardiotoxicity studies, though future phases may include nodal pacemaker-like cell cultures which can be used to predict drug-induced sinus arrhythmias and atrio-ventricular blocks.
- to apply existing protocols to multiple cell lines to measure and determine reproducibility;
- to assess functionality of the cell phenotype, including contractility, ion channel gene/protein expression profiling and ion current measurements (e.g. main inward ( $\text{Na}^+$ ,  $\text{Ca}^{2+}$ ) and outward ( $\text{K}^+$ ) currents, Na/Ca exchanger, Na/K-ATPase etc).

2. Functional read-outs for validation:

- to establish functional readouts from hESC-CM to validate and utilise differentiated cells in screens, and develop new assays to support high throughput toxicology screens. The goal is for predictivity to be equal or superior to existing assays for clinical effects;
- to validate differentiated cells against key reference compounds with known adverse effects on cardiac function and structure. This should show the capacity of the cells for arrhythmogenesis and susceptibility to cellular injury. Comprehensive validation of promising cells against a reference set may be continued in the next phase of the SC4SM programme. Electrical parameters of the cells can be measured using conventional or automated patch clamp and microelectrode array (MEA) technology. Translational safety biomarkers for toxic myocardial injury may include cardiac troponin, CK-MB and LDH-1/2.

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<sup>3</sup> Available on [www.sc4sm.org](http://www.sc4sm.org)

For both objectives, proposals should clearly detail the route to validation, criteria for success, and eventual thoughts around an implementation plan. Submissions are welcome from stem cell groups, analytical groups or both in collaboration. Pharmaceutical members may also contribute analytical expertise to the funded project(s).

Applicants funded will be asked to coordinate with each other (if more than one project is funded) and collaborate with other SC4SM grantholders where appropriate, to enhance the likelihood of success and progress the overall programme. Investigators will also be required to share new data and ideas (for example, on a secure password-protected site) throughout the duration of the projects. If successful, the expectation is that the investigators may be involved in the development of phase 2 of the SC4SM initiative. A symposium will be held in the third quarter of 2008 both to discuss progress and discuss the longer-term scientific strategy being prepared by the Scientific Advisory Board, at which applicants funded in the first phase will be required to participate.

### **ELIGIBILITY**

Research groups from academia and SMEs in the UK may apply. Pharmaceutical companies who are not Members of SC4SM may participate in parallel projects as contributing partners on a matched-funding basis. SMEs outside the UK may also participate in consortia but will not be eligible to apply for funding.

### **FUNDING ALLOCATIONS**

An indicative budget of £160,000 will be available for this call, with the expectation that up to two 1-year projects will be funded for the characterisation of cardiomyocytes and development of functional readouts for validation. A consortium approach in bidding for funding would be encouraged.

### **APPLICATION PROCEDURE**

There will be a 2-step application procedure. Prospective applicants should submit an Expression of Interest Form in the first instance – the form may be downloaded from the SC4SM website, or obtained on request from [info@sc4sm.org](mailto:info@sc4sm.org) or on 020 7747 8877.

### **TIMELINES**

- 17 September 2008: Call for proposals launched and expressions of interest sought.
- 10 October 2008: Closing date for expressions of interest and registration for briefing meeting, by 17:00
- 22 Oct 2008: Briefing Meeting, London, and publication of full call information – all those expressing interest are encouraged to attend, or send a representative (registration by 10 October)
- 1 December 2008: Full proposals to be submitted by 17:00
- February 2008: Notification of applicants

Receipt of Expressions of Interest (EOIs) will initiate liaison with the SC4SM office, who will aim to provide an appropriate steer on the call to applicants; EOIs will inform on key

topics for the Briefing Workshop. EOIs will be circulated to the Scientific Advisory Board, except where there may be potential conflicts of interest.

The Briefing Meeting for applicants will be held on xxx 2008 in central London, in order to provide further information on the call and to address any questions. Applicants may register for the workshop via the EOI, or by email ([info@sc4sm.org](mailto:info@sc4sm.org)).

Full applications must be received by 17:00 on 1<sup>st</sup> December 2008. The application form and supporting information will be made available on 22 October 2008 at the Briefing Meeting and at [www.sc4sm.org](http://www.sc4sm.org).

### **ASSESSMENT**

Full proposals will be assessed through independent peer review and with oversight by the Scientific Advisory Board. Proposals will be assessed on:

- alignment with the scientific objectives of the initiative;
- quality of the scientific proposal;
- potential for scale-up; and
- likelihood of success, including an assessment of the ability to deliver.

### **CONTACT DETAILS**

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