

## **Stem Cells for Safer Medicines: First 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 cells 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 a reduction in animal use by improved selection of compounds, thereby reducing the number of animals used in research on compounds that fail in later clinical studies.

The SC4SM initiative is a five year programme, with a pilot (first) phase stretching through to the end of 2008. The Scientific Advisory Board, comprising stem cell and safety sciences experts from industry and academe, has identified an opportunity for the UK in focusing in the first phase of the SC4SM programme on the derivation, characterisation and validation of hepatocytes.

The pilot year will conduct of a series of projects, open to both commercial and academic collaborators, to understand the size of the biology gap to inform approaches in the subsequent 4-year programme. Specifically, the pilot projects will:

- focus the research effort to consistently obtain presumptive hepatocytes from human embryonic stem cell (hESC) lines with standardised protocols that can be applied reproducibly across a number of lines (majority of funding); and
- establish functional readouts from lines to validate and utilise differentiated cells in high throughput toxicology screens (one project).

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 fully differentiated cells with specific and standardised phenotypes, in sufficient quantity, 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 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 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.

The single most important component of a high throughput toxicity screen is the cell type used. For hepatotoxicity testing, the primary human hepatocyte is the natural choice since the more readily available hepatoma cell lines lack the differentiated phenotype that may be important for determining toxicity. Similarly, animal primary cells may not match the appropriate phenotypic characteristics. However, the availability of high quality primary human hepatocytes is limited and therefore not practicable for regular hepatotoxicity testing without donor-to-donor variability. Currently it is not possible to efficiently expand human primary hepatocytes and when available, these cells rapidly lose their key characteristics such as drug metabolising enzymes.

Differentiation and expansion of stem cells into cells approximating primary hepatocytes (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 claims on the differentiation of “hepatocyte-like” cells from embryonic stem cells. However a number of questions remain including:

- Can the hepatocyte-like cells be consistently differentiated in numbers sufficient for screening?
- How relevant are the hepatocyte-like cells for predictive toxicology screening?
- What functional read-outs are required to ensure confidence that routinely differentiated cells have hepatocyte relevant behaviour?
- Can the protocols developed be applied to a number of stem cells lines to consistently differentiate hepatocytes with a range of genotypes?
- Are the protocols potentially scalable?

Inherent in the current state of art in the derivation of hepatocyte-like cells, are a number of unresolved issues, such as: Is primitive or definitive endoderm the preferred source of hepatocyte-like cells? Are there significant differences between hESC lines in their ability to generate hepatocyte-like cells? Can hepatocyte developmental biology be applied to direct expandable hepatocyte progenitor/stem cells from hESCs?

Further phases of the SC4SM initiative will look at additional challenges in the derivation and validation of other cells, such as cardiomyocytes. However progression beyond the first phase depends upon two factors: achieving the scientific objectives regarding the derivation of functional hepatocyte lines with protocols and standards for consistent

differentiation; and 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 in the first half of 2008 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.

## **SCOPE FOR APPLICATIONS**

Industry-oriented basic research proposals are invited from applicants with expertise in the culture and handling of progenitor cell biology, hepatocytes and derivation of intermediate and/or hepatocyte-like cells. Projects can be carried out in partnership with third parties, such as small emerging biotechnology companies. All collaborators and

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

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

academic groups funded will be required to comply with SC4SM's Ethics and IPR policies<sup>3</sup>.

1. Derivation of hepatocytes – up to four projects will be funded:
  - to develop protocols and standards to consistently obtain presumptive hepatocytes from hESC lines with standardised protocols that can be applied reproducibly across a number of lines; and
  - to apply existing protocols to multiple cell lines to measure and determine reproducibility.
2. Functional read-outs for validation - one project will be funded:
  - to establish functional readouts from lines to validate and utilise differentiated cells in screens, and developing new read-outs to support high throughput toxicology screens.

For both projects, proposals should clearly detail the route to validation, criteria for success, and eventual thoughts around an implementation plan. Applicants funded will be asked to coordinate with each other and collaborate 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 £800,000 will be available in the pilot phase, with the expectation that up to four 1-year projects will be funded for the derivation of hepatocytes (£595,000); and one project for developing functional readouts for validation (£205,000). A consortium approach in bidding for funding would be encouraged.

Where funding is sought for multiples approaches in deriving hepatocytes, applicants must clarify the different approaches being pursued.

## **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.

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

- 3 October 2007: Call for proposals launched and expressions of interest sought. Closing date for expressions of interest is 24 October 2007 at 17:00
- 24 October 2007: Closing date for expressions of interest
- 26 October 2007: Briefing Workshop, London, and publication of full call information. All those expressing interest are encouraged to attend the workshop, or send a representative (registration by 19 October)
- 3 December 2007: Full proposals submitted by 17:00
- Mid-January 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 Workshop for applicants will be held on 26 October 2007 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 3 December 2007. The application form and supporting information will be made available on the 26 October 2007 at the Briefing Workshop 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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