SPOTLIGHT ON STEM-CELL RESEARCH

Developing technical skills for stem-cell research

Interested in working with stem cells? Find out what it takes to succeed in this dynamic field.

"More and more people in my lab know at least how to write a few lines of program."

Didier Trono, École Polytechnique Fédérale de Lausanne

HOW IS a stem cell like an orchid? Both are difficult to grow, says leading stem-cell researcher Stephen Minger. To succeed in culturing stem cells, you need to have "a green thumb", he says, and "a mindset of getting inside cells and figuring out what they need. It's something that takes dedication and passion."

Minger's take on stem-cell research has brought him to the role of global head of research and development of cell technologies at GE Healthcare Life Sciences, but there are many ways to make a mark. Knowing how to culture stem cells and derive specialized cell types is one of the most important skills in the field, and there are many valuable supporting roles. Stem-cell investigators arm themselves with a diverse range of techniques to stay at the cutting edge of science. So where should you focus your efforts?

KING'S COLLEGE LONDON

Researchers working on stem cells for clinical use, such as this scientist at King's College London School of Medicine, must abide by strict protocols.

Nurturing growth

The optimal growth media for culturing stem cells is constantly being refined. "In recent years, scientists have been trying to mimic the natural environments of stem cells," says Joel Glover, director of the Norwegian Center for Stem Cell Research (NCS). One example of this approach is using exotic gas mixtures to reproduce the hypoxic conditions in which many stem cells develop; another method involves refining which growth factors to use and when to apply them.

Another area attracting a lot of attention is 3-D scaffolding. An encouraging application of this technology was shown in 2011 when researchers at the Karolinska Institute in Sweden gave a patient a new trachea made from a 3-D scaffold seeded with his own stem cells. NCS's Glover suggests that organ printing — using inkjet printers to deposit cells into specific 3-D patterns — might prove useful for stem-cell researchers in the future. Lorenz Studer, director of the Center for Stem Cell Biology at Memorial Sloan–Kettering Cancer Center (MSKCC) in New York is optimistic about the technology's potential. He predicts that as more scientists study how stem cells behave in a 3-D context, knowledge of 3-D imaging techniques such as two-photon excitation microscopy will become increasingly valuable.

The role of genetics

A major proportion of stem-cell research involves the genetic modification of cells. A commonly used technique to deliver genes into stem cells uses viral vectors such as lentiviruses. "They're really workhorses of stem-cell research," says Didier Trono, professor and dean at the School of Life Sciences at École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland. Working with viral vectors in the lab may require an enhanced biosafety level — recombinant lentiviruses can be hazardous — so experience with the relevant protocols is advantageous.

Epigenetics — the study of heritable changes in gene function not involving changes in DNA — is of growing importance in stem-cell research. Researchers are trying to determine how epigenetic changes influence cell differentiation, tissue homeostasis and the cell's response to external signals. Familiarity with new

US stem-cell research funding

Top 10 stem-cell research projects funded by US National Institutes of Health (NIH) in 2011

Project name	Recipient organisation	Amount (US$)
Cell therapy for diabetic peripheral neurovascular complications	Emory University	$6.1m
Global annotation of regulatory elements in the human genome	Hudson-Alpha Institute for Biotechnology	$4.1m
KOMP phase II mouse production and cryopreservation	University of California Davis	$4.0m
Research on inhalation toxicology of environmental chemicals	Alion Science and Technology Corporation	$3.9m
Causal transcriptional consequences of human genetic variation	Harvard University (Medical School)	$3.8m
Adult stem cells for therapy of visual disorders	Scripps Research Institute	$3.8m
Center for Cell Circuits	Broad Institute	$3.7m
Growth control in multiple myeloma	University of Arkansas for Medical Sciences	$3.7m
Blood & Marrow Transplant Clinical Trials Network Data Coordinating Center	Medical College of Wisconsin	$3.5m
Transcriptional functions of nuclear receptors in cancer cells	NIH	$3.4m
Mechanisms and biological consequences of the nuclear receptor CAR activation	NIH	$3.3m

Source: NIH

STEMCELL TECHNOLOGIES INC

Biotechnology company Stemcell Technologies' research facility in Vancouver, Canada.

technology will be needed to find the answers. "The arrival of high-throughput techniques for analyzing epigenetics has helped usher in a revolution in the field," says Trono. Epigenetics technologies include ChIP-on-chip, which combines chromatin immunoprecipitation (ChIP) with microarray technology, and ChIP-seq, which combines ChIP with sequencing of the resulting DNA fragments.

Sorting and studying

Once stem cells are prepared and cultured, sorting them into purified populations via techniques such as flow cytometry — identifying cells using fluorescent-tagged antibodies — is a crucial skill. But sorting alone doesn't guarantee finding what you're looking for; appearances can be deceiving in stem-cell research. It's necessary to study a cell's function as well as its form. "You have to look at more than just the morphology and markers of a cell," says Glover of NCS. "For instance, you can take adult stem cells and [make] them look like neurons, but they just don't do anything neurons do. You need additional careful functional analysis of derived cells, such as of their electrophysiology or their pattern of hormone release." Image cytometry also helps researchers analyze how proteins of interest are expressed in cells, as does confocal microscopy.

A process called mass cytometry — a variation on flow cytometry — offers researchers a novel way to analyze the characteristics of a population of stem cells. The technique, first described by researchers at Stanford University School of Medicine and their colleagues in May 2011, uses antibodies tagged with various isotopes of rare-earth metals instead of fluorescent molecules. The cells are vaporized and their constituent parts analyzed by a mass spectrometer. This approach allows scientists to simultaneously measure dozens of features located on the surface and inside cells, whereas conventional fluorescence-based flow cytometry can only measure a few features at a time. It's a relatively new but significant addition to a stem-cell researcher's toolbox, says Keith March, director of the Indiana Center for Vascular Biology and Medicine (ICVBM).

Knowledge of animal physiology can be beneficial in understanding the behaviour of stem cells and derived cells in living organisms. "If you engraft the cells, techniques such as contrast-enhanced ultrasound or positron emission tomography (PET) imaging can help you monitor how they integrate," adds March. Experience of surgery, animal behaviour and systems biology can all help assess the broader implications of stem-cell research.

Into the clinic

A major goal for stem-cell researchers is to turn basic science into clinical therapies. Efforts in this direction are ramping up across the globe. The Lund Stem Cell Center in Sweden recently established a lab dedicated to stem cells and restorative neurology to study the adult brain's neural stem cells, while scientists at the Université Libre de Bruxelles in Belgium demonstrated that the mammary gland contains different types of long-lived stem cells, a finding that could help unravel the cause of breast cancers. On the other side of the Atlantic, researchers at the Stanford Institute for Stem Cell Biology and Regenerative Medicine in California have found that human induced pluripotent stem cells (iPSCs) can be used to model cardiovascular disease and a team at the Yale Stem Cell Center in Connecticut are using iPSCs to model the effect of hepatitis B and C infection on human hepatocytes in a mouse host.

Scientists at the New York Stem Cell Foundation have generated pluripotent stem cells by adding adult nuclei to unfertilized oocytes, a strategy that could help develop patient-specific stem cells for transplants that would not be rejected by the patient's immune system.

Scientists working with clinical-grade stem cells must adhere to good manufacturing practices (GMPs) and employ good clinical practices (GCPs) — regulations regarding what is allowed to go into the human body. "Everything has to be traceable — you must be sure that no reagent has expired or been kept at the wrong temperature, that everything was sterile, and that you have written evidence this is correct," says Dusko Ilic, senior lecturer in » stem-cell science at King's College London School of Medicine in the United Kingdom. "All work has to be done by two people; you both have to witness and sign forms. And there are government inspections checking that we are complying with conditions."

To follow GMPs you need an "extremely meticulous personality", says Studer of MSKCC, and you must be able to repeat a procedure multiple times in a highly controlled manner. "You need to be the type that thinks very carefully from one step to the next, who makes flow diagrams," he says. "Proper planning and organizational skills are crucial."

Strict controls are also necessary to scale up the production of stem cells to a commercially viable level. "We lock on to a standard operating procedure to churn out very reproducible results and the required amount of cells every week," says Minger of GE Healthcare. "It's extremely challenging — we're working on inherently unstable biological entities."

Technically minded

As in many fields of biology, advances in high-throughput techniques that generate massive data sets mean experience in bioinformatics and computational biology has become invaluable in stem-cell research. "These are skills that definitely give you an edge," says EPFL's Trono. "More and more people in my lab know at least how to write a few lines of program." Minger adds that understanding statistical analysis is also important. "You want to know if your results are just random noise or something you can consistently come up with," he says.

An alternative avenue into stem-cell-related research is developing the reagents, instruments and techniques that researchers use at a biotechnology company such as Stemcell Technologies. "You have to be resourceful, creative and good at troubleshooting to develop a technique, and have good knowledge of the biology of cells and cell types," says Terry Thomas, senior vice-president of research and development at Stemcell Technologies' headquarters in Vancouver, Canada.

Division of labour

In many labs, tasks are typically divided between scientists with PhDs who conduct research and secure grants, and technicians without doctorates who follow set protocols. In stem-cell research, the lines can become blurred. "Postdocs usually carry out the differentiation of cells, but that's not necessarily the rule — technicians at our lab also do basic differentiation of neurons from stem cells," says Studer of MSKCC.

Increasingly, aspects of stem-cell research are outsourced to specialized companies. This ranges from DNA sequencing, cell characterization and bioinformatics analysis to "entire preclinical studies", says ICVBM's March. Collaborations with other research groups can also help provide GMP and GCP services.

The fast pace of discovery in stem-cell research gives a wide range of researchers the potential to enter the field. M. William Lensch, faculty director of education at the Harvard Stem Cell Institute, says he and his colleagues are often inspired by a technique or technology from an unrelated scientific discipline: "If we can retool existing methodologies or develop new techniques, that will help put us ahead."

With the myriad strands of discovery in the stem-cell field, opportunities abound for meticulous, inquisitive researchers who want to be at the forefront of a vital and cutting-edge science. ■

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The **Institute of Molecular Biology (IMB)** Mainz, Germany, is a new research center of excellence situated on the campus of the University of Mainz and integrated into its scientific community. IMB is generously funded by the Boehringer Ingelheim Foundation with 100M Euro. Projects at the institute are interdisciplinary and focus on epigenetics, DNA repair, development and the interfaces between these fields. Scientists at IMB are supported by strong Core Facilities. We seek collaborative candidates with an innovative research profile in advanced mass spectroscopy and a strong publication record. Positions are initially for 5 years and can be renewed. Recruitment packages include an attractive salary, generous start-up funds and a 5-year budget for personnel and consumables. There are no teaching obligations, but teaching opportunities are available at the University, e.g. for individuals wishing to obtain a German Habilitation.

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LUND UNIVERSITY

LUND STEM CELL CENTER

Stem Therapy

With eight faculties and several research centers and specialized schools, Lund University is the largest institution of research and higher education in Sweden.

StemTherapy is a strategic research environment at the Faculty of Medicine funded by the Swedish Research Council. The overall objective of StemTherapy is to advance the development of stem cell-based cell replacement therapies for diabetes, stroke and hematological diseases and to build a strong base of knowledge about stem cells and disease mechanisms to pave the way for future efforts to devise new therapies. StemTherapy addresses this by assembling very strong competence in basic stem cell biology and clinical cell therapy. We have established extensive collaborative ties with national and international institutions to increase diversity, quality and innovation.

Group leader positions

StemTherapy is now seeking outstanding scientists for two open positions as Junior Group Leader. We are interested in candidates with important research contributions, the ability to develop a strong research program, and the commitment to interact with other scientists and staff within StemTherapy and at the Faculty of Medicine. Investigators with interests in ES/iPS cell biology as well as clinical investigators are encouraged to apply. However, candidates from all areas of stem cell biology will be considered.

We offer a competitive start-up package in a dynamic and international environment. The initial appointment will be for 5 years, followed by the possibility for successful candidates to compete for permanent senior positions in the specified research area. The positions are open for appointment from October 1st, 2012 or after agreement. The Junior Group Leaders are expected to develop a strong research program and contribute to common activities within StemTherapy such as seminars and PhD courses.

Application:
The application must be in English and should include:

1. **Curriculum vitae incl. career record and educational merits**
2. **A short description of previous research experience and a summary of current and proposed research program (max. 5 pages)**
3. **A complete list of publications with 5 selected papers marked that the applicant wishes to highlight in the assessment**
4. **Relevant degree and educational certificates**

Furthermore, 3 letters of recommendation should be arranged and be sent directly to Christina Parknäs (Christina.Parknas@med.lu.se) by the recommending person.

The application and 4 copies thereof (including the documents listed above) should be sent by mail to Christina Parknäs, Lund Stem Cell Center, BMC B10, 221 84 Lund, Sweden. Deadline for applications is August 1, 2012.

StemTherapy is part of the Lund Stem Cell Center (SCC) which was established in 2003 as one six Swedish strategic centers of excellence in life sciences. The Center, which has become one of the largest in the field in Europe, consists of 20 research groups, a renowned research school with both PhD and postdoc programs as well as several state-of-the-art core facilities; all supported by a well-functioning infrastructure and administration.

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