SPOTLIGHT ON STEM CELL RESEARCH

2013: The year of the stem cell

Developments in stem cell research during 2013 created promise for a growing research field, with plenty of opportunities for young researchers both in academia and industry.

> "You need ten to a hundred trillion cells a week just to treat all the heart failures in London,"
>
> Stephen Minger, GE Healthcare Life Sciences

IN EARLY 2013, doctors at the Children's Hospital of Illinois injected a needle into the bones of a two-year-old who had spent her life in the intensive care unit after being born without a trachea. They drew out the child's bone marrow and isolated stem cells, which have the potential to develop into multiple cell types. In the lab, scientists molded her stem cells around a painstakingly constructed 3D windpipe-shaped matrix. In a seven-hour operation, doctors implanted the new organ into the girl's neck. As the stem cells multiplied and matured, her windpipe melded with the tissue around it.

Even a decade ago, such a procedure was in the realm of science fiction. As recently as the 1980s, stem cells were largely isolated from mice and hamster embryos. Animal embryonic stem cells are pluripotent—able to differentiate into mature cells of many types. In 1998, scientists first isolated human embryonic stem cells from fetal tissue. With this breakthrough, the cells had the potential to shed light on basic developmental processes, and help treat human diseases.

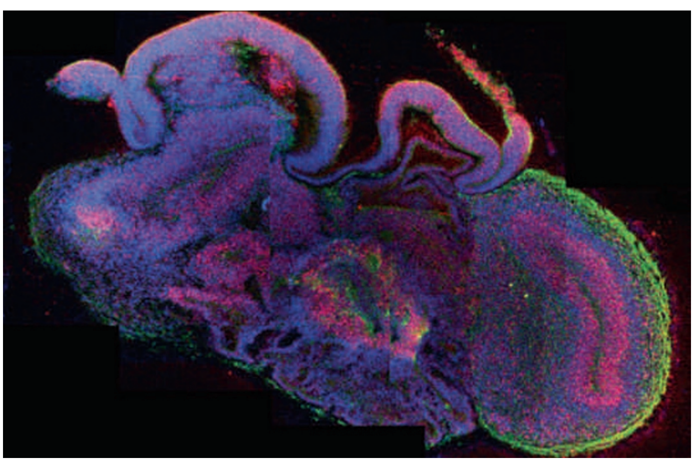
Since 2000, scientists have discovered that pluripotent cells could be isolated from cord blood and embryonic fluid, and researchers took adult cells and reprogrammed them to their stem cell state. These so-called induced pluripotent stem cells (IPSCs) changed the playing field.

The Atlantic newspaper hailed 2013 as the year of the stem cell. The past decade of research into the basic biology of stem cells, the ability to generate stem cells at will, and experiments on animal models finally began having clinical implications.

"I think everyone would agree that reprogramming of stem cells has been the major breakthrough in the stem cell field, making it possible to generate cells and drive everything forward," says Jürgen Knoblich of the Institute of Molecular Biotechnology at the Austrian Academy of Sciences.

"One of the big areas of growth has been taking discoveries made in model organisms to the clinic," says Heather Rooke, the scientific director for the International Society for Stem Cell Research. "This is an interesting time to get into the field; I think it will continue to grow and change."

As the field widens, so do job opportunities. In the US, the National Institutes of Health spent more than a billion dollars on stem cell research in 2013. And the European Parliament's Horizon 2020 research program includes significant funding for stem cell studies.



Brain organoids grown in Jürgen Knoblich's lab.

MADELINE LANCASTER AND JUERGEN KNOBLICH

Taking stem cells to the clinic

Even before scientists understood stem cell biology, clinicians were transplanting stem cells containing bone marrow from healthy donors to patients with blood cancers as a way of replenishing their blood supply.

"When it comes to blood stem cells, the basic paradigms to get these to patients are already in place, so any new findings can be translated relatively quickly," says Jonas Larsson, a biologist at the Lund Stem Cell Center in Sweden.

But even for hematopoietic stem cells, questions remain about how to keep the cells alive outside the body. Scientists can move them between people, but would like to be able to take a patient's cells, fix any genetic mutations, allow the cells to multiply, and inject them back in. That's not yet possible, but Larsson's team is testing the effects of different compounds on the properties of the stem cells, hoping to make this a reality. "If we could control these cells and expand them in a culture dish, we would suddenly have the tools to help many patients," Larsson says.

In 2013, researchers made advancements at coaxing stem cells into brain cells, liver and pancreas cells, and muscle and heart cells. The new challenge is moving from individual cells to organized organs. "We really want to be able to generate multicellular tissues," says Giuseppe Maria de Peppo, of the New York Stem Cell Foundation, who is focused on fine-tuning the procedures to create complex bones (see box).

The challenge of turning cells into organs—and determining their clinical utility—will require scientists of all backgrounds. "For tissue engineering, it's not enough to know the biology of stem cell development, you need to be able to use analytical tools, have expertise in materials science, bioreactor systems, and more," de Peppo says. But it will also take researchers with clinical experience to run the necessary trials.

Growing organs in the lab

In some labs, 2013 was the first year that stem cells were successfully coaxed into organs. In Knoblich's lab, for example, researchers created brain "organoids", 3D clumps of brain tissue that show the layering and arrangement of human brains. The organoids aren't as complex as adult brains, but resemble the organ in early fetal development.

"One of the great things stem cells will allow us to do in the near future is focus on human development," Knoblich says. His group's brain organoids illuminate aspects of normal brain development and allowed them to study what can go wrong in the brain during certain developmental disorders by introducing a mutation into the IPSCs from which the organoids spawn.

Studying stem cells, Knoblich says, is a fertile ground for scientists motivated by the potential to cure disease, and those interested in answering basic biological questions. Growing organs from stem cells in the lab helps move both these skill sets forward. "I think now is a good time to move into this field," Knoblich says. "I believe that the ability to study human biology in a human setting will cause a major change in how we do biology. We no longer have to only rely on model organisms."

At the Gurdon Institute of the University of Cambridge, Meritxell Huch is also making organoids—3D liver tissue which, when implanted into mice with liver disease, eliminates their symptoms. For young scientists interested in stem cells, Huch recommends finding a good mentor. "There is no skill that you cannot learn if you have a good mentor," she says. "

Pharma's big investment

Work on taking stem cell research to patients is not just academic. Pharmaceutical companies are well aware of the rapid advances in the field and are developing ways to commercialise the findings.

"The field has changed dramatically in the last five years simply because the safety and efficacy trials are showing both safety and efficacy," says Stephen Minger, chief scientist of cellular sciences at GE Healthcare Life Sciences. "It's moving from the lab to the clinic and into industry very quickly."

Various clinical trials are underway to test the capacity of stem cells to restore vision in patients with macular degeneration; the possibility of treating Parkinson's disease with brain stem cells; how to turn stem cells into heart cells to repair hearts; and the best way to produce immune cells for cancer treatments. GE Healthcare, Minger says, is focusing on how to increase stem cell production for these and other clinical purposes.

"You need ten to a hundred trillion cells a week just to treat all the heart failures in London," Minger says. "If you think about all diseases, the scale at which you're going to have to be producing cells is going to be enormous." So GE is developing an infrastructure that lets researchers take a stem cell from any source, put it in a bioreactor, and grow the required number of cells.

Minger worked in academia before joining the GE team, and encourages young scientists to try a variety of environments at the beginning of their career. "You have to be good at more than one thing," Minger points out. That might mean getting experience in different types of labs. "To be a good stem cell scientist you have to be a good molecular biology, you have to have bioinformatics skills, and you have to be able to understand some functional aspects of the cells you study. The days of just having a cell biology project are over."

For scientists interested in stem cell research, there is no shortage of research topics, potential collaborators in both academia and industry, and paths to take to a successful career. "There are still a lot of things to discover," says Huch. "The field is very exciting." ■

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NEW YORK STEM CELL FOUNDATION

Merging tissue engineering with stem cells

If stem cells could be coaxed into any cell type, could entire organs be grown from a stem cell population in the lab?

When it came to choosing where to focus his PhD, Giuseppe Maria de Peppo went with a tissue engineering program rather than joining a traditional biology department, thinking that it meshed best with his technology-focused background. But he took it upon himself to learn everything he could about stem cell biology.

"If you just want to engineer bone, taking cells from the bone marrow is sufficient," he says. "But if you want to generate blood vessels, cartilage and bone all in one, bone marrow cells won't work."

Just as de Peppo was beginning his PhD work, scientists had developed IPSCs. De Peppo saw them as the perfect starting place for engineering more complex bone tissues, with integrated blood vessels and cartilage. The ability to generate bone tissue, he says, has the potential for not only treating trauma injuries, but bone cancers and osteoporosis.

"This is a fast-moving field, a beautiful field, and its potential impact is massive. It really makes me feel satisfied when I come to work every single morning."

Now a postdoctoral fellow at the New York Stem Cell Foundation, de Peppo is getting closer to developing the complex tissue he's been aiming for. In 2013, he succeeded in developing mature bone tissue from individual patient's IPSCs. When implanted under the skin of mice, the tissue developed into not only bone, but integrated blood vessels as well. The results were published in *Proceedings of the National Academy of Sciences*.

Despite his research success, de Peppo hasn't stopped learning about new fields that could come in handy. "The next generation of scientists should keep their eyes wide open to follow trends and new technologies. You never know where new applications will emerge from," he says. "I had this biotechnology background, and then I started acquiring some engineering skills, but one must always learn more and more."

UNIVERSITY OF SOUTHERN DENMARK

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Professorship

in Molecular Mechanisms of Diabetes Pathogenesis

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Requirements and Expectations

Research. *The successful candidate is expected to have a strong research profile in the field of molecular mechanisms of diabetes pathogenesis, with emphasis on stem cell biology and associated technologies.*

Teaching. *The successful candidate should have a strong record of teaching. He/she will contribute to undergraduate and graduate teaching in our Biochemistry and Molecular Biology and Biomedicine study programmes. This will also include supervision of dissertation students for bachelor and master projects. In addition, the professor is expected to supervise graduate students and postdocs and participate in the training activities of the Danish Diabetes Academy.*

Start-up funding will include funding for one postdoctoral position (three years) and one PhD fellowship (three years) from DDA as well as DKK 5 million from the SDU Faculty of Science.

DEADLINE FOR APPLICATIONS: **September 15, 2014**

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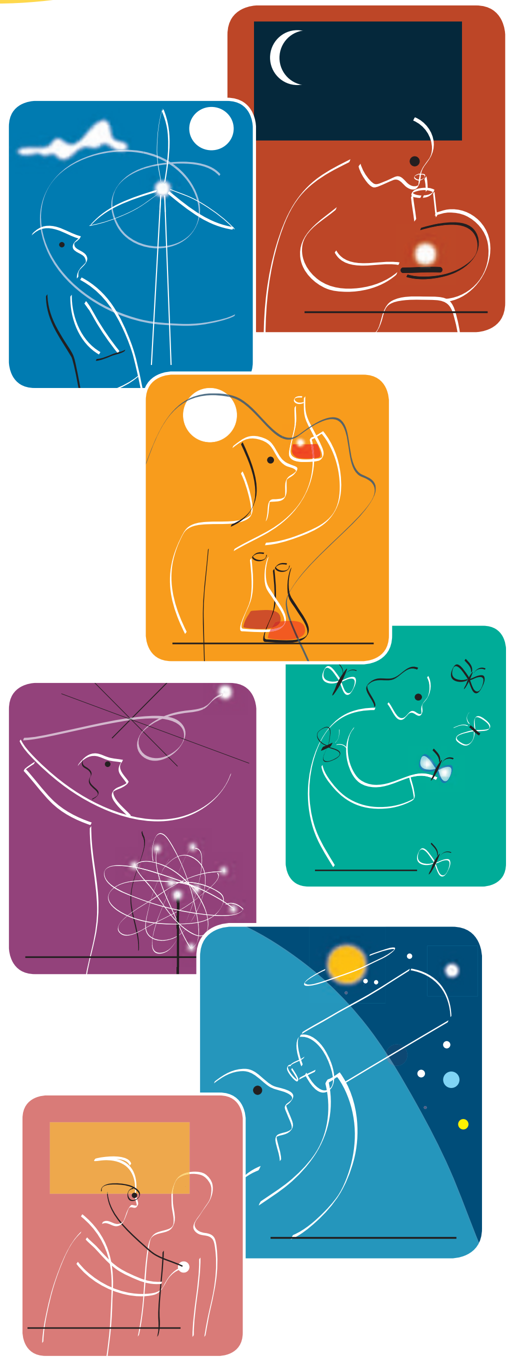

Fifty percent of all science created in Brazil is produced in the State of São Paulo. The state hosts three of the most important Latin American universities: Universidade de São Paulo (USP), Universidade Estadual de Campinas (UNICAMP) and Universidade Estadual Paulista (UNESP). Other universities and 19 research institutes are also located in São Paulo, among them the Technological Institute of Aeronautics (ITA), the National Institute for Space Research (INPE) and the National Synchrotron Light Laboratory (LNLS), besides most of Brazilian Industrial P&D.

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