Open access jumps the pond

The open access movement has fueled debates in the US between advocates of free access to biomedical literature and publishers that depend on subscription revenue for their livelihood. The controversy now travels to the United Kingdom, where funding organizations are working to establish a public-access archive for research articles.

London's Wellcome Trust, the UK Medical Research Council, and other UK-based granting agencies are financing the effort to establish a counterpart to the US's PubMed Central, an online repository of journal content managed by the National Center for Biotechnology Information at the NIH. It was launched 5 years ago and now contains reports from about 180 journals that participate voluntarily. The goal of the storehouse is to preserve and provide free, unrestricted access to biomedical literature. The UK version should be similar to PubMed Central, using the same software and archiving comparable content.

"The archive aims to provide free, fully searchable access to research papers and data. For the value from research to be maximized, we need to ensure that the knowledge is freely and widely available to those who need to see it. The value of having a central archive is clear," a spokesperson from Wellcome Trust told the *JCI*.

Since May 2, 2005, the NIH has requested that investigators supported by NIH grants submit electronic copies of accepted research articles to PubMed Central

within 1 year of publication. PubMed Central then offers free access to such articles. The NIH developed the public-access policy as a result of pressure by Congress and patient organizations advocating free access to biomedical and life science literature supported by taxpayer funds.

Following on the heels of this NIH request, Britain's Wellcome Trust announced on May 19 that after October 1, 2005, all of its grant recipients will be required — not requested, as with the NIH — to deposit any accepted articles arising from their funded research in an open access directory within 6 months of publication.

The group of funding agencies is currently seeking an organization to run the database. According to the Wellcome Trust spokesperson, "The sooner the project can practicably begin, the better. A UK PubMed Central will improve the efficiency and power of research and the sooner that's available, the better it is for researchers."

But some UK scientists are not so easily convinced. "I detect in the UK that scientists still have very mixed feelings about open access," said David Paterson, physiology professor at Oxford University. He pointed out that several charity-based societies, like the Physiological Society, depend upon subscription revenue from their journals to operate and the policy could have a negative effect on them. Just as it has in the US, the UK initiative may vex some journal editors and publishers, who feel that the integrity of their businesses is being questioned.

The Wellcome Trust and other major science funders in the UK are working together to establish their own open access online archive. Photo courtesy of the Wellcome Trust.

Some point to the potential problem of having more than one version of an article in circulation, specifically, the accepted manuscript before copy editing found in the free access repository and the edited article as it appears in its published form. "Where is the definitive article? What gets referenced?" Paterson asked.

Despite the potential pitfalls — the same ones faced in the US by NIH researchers — many UK scientists are in favor of the proposal. Stephen Dunnett, a professor at Cardiff University in Wales and an advocate of open access, said, "The present situation where publicly funded research is kept to restricted access...seem[s] fundamentally wrong."

Stacie Bloom

Stem cell division

When Woo Suk Hwang and his group at Seoul National University announced their creation of human stem cell lines that matched the donors' own DNA, the media craze began. Surely this achievement marked the beginning of eagerly awaited tailor-made therapies for patients with spinal cord injuries, diabetes, Alzheimer disease, and a host of other congenital and acquired disorders. Or did it?

Before patient-specific stem cells, or any other stem cells, can be used for human therapeutics, there are hurdles to overcome. These barriers in the translation of bench experiments to bedside remedies do not just include the obvious ethical, political, and funding problems that are so widely

deliberated. The more relevant hurdles that stymie clinical stem cell therapies are the scientific ones — those that are often overlooked in the lay press, which contributes to public unawareness of just how far we still are from using stem cells in a clinically meaningful manner.

Norio Nakatsuji is the director of the Institute for Frontier Medical Sciences at Kyoto University and is the only investigator in Japan whose laboratory creates human embryonic stem cell lines. Nakatsuji notes that before clinical trials can go forward, the production of these stem cell lines must be improved so that they are clinical-grade. The cells should be produced in a highly sterile facility, he says, using

human feeder cells or a no-feeder cell protocol and culture media without animal serum or proteins. Although not currently available, Nakatsuji speculates that such clinical-grade human embryonic stem cells will be obtainable within a few years. But the future existence of these cells is still not the panacea some may think it is.

"Just injecting stem cells is not going to work," said Shahin Rafii, a physician and stem cell scientist at Cornell University Medical College. "First, you have to be able to differentiate the cells into functional, transplantable tissues. We don't really know how to do this yet."

Directing the differentiation of the cells is just one obstacle. Scientists also do not know whether differentiated patient-specific stem cell lines would be immunologically tolerated by the donor/host or whether they would be safe or effective. Yet another problem is that stem cell lines created from patients with diseases will carry features of the disease and would likely not be useful for treating those patients.

Beyond difficulties with the cells themselves, the adult tissue environment where the cells need to thrive also hinders the progression to clinical transplantation. "For cell therapy to work you need to be able to get the cells to engraft and expand after transplantation," Marcus Grompe, a hepatic stem cell researcher at Oregon Health & Science University, told the *JCI*. "That part is very difficult and has not been solved at all for some key tissues . . . we are still several years away from clinical trials."

In order to be useful for treating neurodegenerative diseases, for example, the stem cells need to survive in the damaged and diseased brain, make proper synaptic connections, and form appropriate pathways for proper neural function. "We have no idea — at least not yet — of how to accomplish this feat," said Steve Goldman, chief of the Division of Cell and Gene Therapy at University of Rochester Medical Center.

"Making matters worse," Goldman explained, "once a desired cell type is generated from an embryonic stem cell, its isolation to appropriate levels of purity is by no means

Culture trays containing human embryonic stem cells. Photo courtesy of James Thomson and Jeff Miller (University of Wisconsin-Madison, Madison, Wisconsin, USA).

straightforward." Isolating pure stem cells is not foolproof, and remnant cells typically persist. These cells can generate a whole host of tumors even if they are completely diploid and genomically stable.

Another issue, according to Rafii, is proper vascularization of these transplanted cells to ensure that their blood supply is adequate. Rafii said that it may be necessary to nanofabricate small blood vessels and put these into the cells before transplantation.

Although no miracle cures have been found yet, these obstacles are not cause for pessimism. According to Charles Jennings, executive director of the Harvard Stem Cell Institute, "It is a fast-moving field. Human embryonic stem cells were just isolated in 1998. It's still early."

Stacie Bloom

Prominent investigator wins diabetes research award

Philipp Scherer was presented with the American Diabetes Association's 2005 Outstanding Scientific Achievement Award on June 13, 2005. Scherer is an associate professor in the Department of Cell Biology & Medicine at Albert Einstein College of Medicine. He spoke with the *JCI* about this award, his research, and his career.

JCI: Which of your accomplishments do you feel led to this award?

Scherer: We are probably best known for our work on the adipocyte-specific secretory protein adiponectin/Acrp30.

This protein has proven to be an excellent biomarker for systemic insulin sensitivity, and also a predictive marker for cardiovascular risk in a large variety of patient populations. Beyond its use as a marker in the clinical setting, this protein is directly implicated as a potent insulin sensitizer and antiatherosclerotic mediator.

I like to think that my group has had an impact in other areas of adipocyte biology as well. We have further established the role of adipose tissue as an endocrine organ through the description of physiological effects of an array of adipocyte-

derived secretory products (adipokines) that include resistin, acute phase reactants, and proinflammatory cytokines as well as the involvement of the p38 MAPK pathway during adipogenesis.

JCI: What do you think is the most important discovery you have made?

Scherer: The initial cloning and analysis of adiponectin. We isolated Acrp30 in 1993 while I was a postdoc in Harvey Lodish's laboratory at the Whitehead Institute, and we published these findings in 1995. Additional groups described this protein subsequently in 1996, and it was known by