MEDICINE

Stricter standards sought to curb stem-cell confusion

Initiative aims to clarify description of mesenchymal cells.

BY HELEN SHEN

Pamela Robey is used to being sent samples by scientists who are anxious to know whether the mesenchymal stem cells (MSCs) they have extracted from fat can be coaxed to turn into either bone or cartilage.

Robey, who directs the Stem Cell Unit at the US National Institutes of Health (NIH), is also used to delivering bad news to many of those who seek her help. "They usually are not happy," she says, when her attempts to differentiate the cells produce little more than fatty globules.

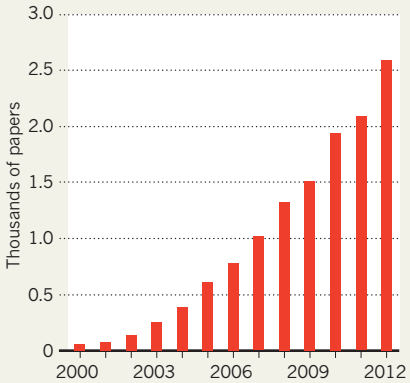
To Robey, that disappointment reflects a pervasive misunderstanding about what MSCs are and what they can do — one that is fuelled by a lack of information. MSCs have been proposed as treatments for a wide range of ailments including heart and brain injury, joint damage, Crohn's disease and multiple sclerosis. But some scientists say that these clinical aspirations have far outrun the basic science. "It always seems a little bit like hocus pocus when you're treating everything from skeletal to immunological disorders," says George Daley, director of the Stem Cell Transplantation Program at Boston Children's Hospital in Massachusetts.

An international group of scientists, industry experts and governmental organizations is trying to introduce scientific clarity to the burgeoning field of MSCs. The group, which met for the first time in late March at NIH headquarters in Bethesda, Maryland, hopes to introduce more rigorous research practices, and eventually to create scientific standards that could guide the commercial development of MSC-based therapeutics. The efforts, applauded by some, are now attracting criticism both from those who advocate MSCs as therapeutics and from those who think that the potential of the cells is oversold.

Even the definition of what constitutes an MSC is a matter of debate. First described in the 1960s as bone-marrow cells that can regenerate bone, the name MSC has expanded to include cells from fat, and from dental and other tissues — although early claims that MSCs could give rise to a panoply of different cell types have fizzled out in animal tests. As a first step towards standardization, the group is developing guidelines for research journals to help them cope with the sharp rise in the number of MSC studies being published (see 'Growth medium'). Ideas being floated include requiring authors to define clearly the animal and tissue sources of their cells, and the experimental conditions used to culture them — details that are often omitted from published papers.

GROWTH MEDIUM

The number of papers that mention mesenchymal stem cells has risen dramatically in the past decade.



SOURCE: PUBMED

"People have to be much more rigorous in defining MSCs, their sources, which tissues you can obtain them from, and what you can use them for," says Paolo Bianco, a stem-cell researcher at the Sapienza University of Rome, who is not involved in the initiative.

Robey, who is on the steering committee of the new working group, is more blunt. "Most of the MSC biology is not rigorous," she says. "Other stem-cell biologists tend to look down their noses at the field."

CLEAR DEFINITION

The group is also discussing whether authors should quantify what percentage of MSCs in a given preparation truly are stem cells. Tests, including detecting the presence of certain cell-surface molecules, that were once used as baseline criteria for defining MSCs are now known to identify a wide variety of cells, only a tiny fraction of which may be able to self-renew and differentiate into multiple cell types.

The team has not yet approached journals to gauge interest in adopting the guideline plan, and "whether or not they'll accept it, I don't know", says steering-group chairman Armand Keating, who directs the Cell Therapy Program at Princess Margaret Hospital in Toronto, Canada.

In the coming year, the working group faces the more daunting task of establishing one or more reference lines of MSCs, against which researchers and companies can readily assess the identity, purity and potency of their cells.

But some researchers say that attempts to standardize cells will do little to benefit science, because a solid theoretical basis for using MSCs as broad therapeutics is lacking. "If I want to treat a disease of the brain with cells that for all intents and purposes are bone cells, the first thing I should come up with is a clear rationale," says Bianco.

The group's efforts also worry Arnold Caplan, a stem-cell researcher at Case Western Reserve University in Cleveland, Ohio, who introduced the modern concept of MSCs in 1991 (A. I. Caplan *J. Orthop. Res.* **9,** 641–650; 1991). He believes that the cells could potentially treat a broad range of conditions by secreting biochemicals that reduce inflammation and promote healing, and says that overly proscriptive journal guidelines could prevent the publication of promising results.

It is also hard to know how adoption of more rigorous experimental standards would affect the already strong consumer demand for treatments derived from MSCs. Lee Buckler, founder of the consulting firm Cell Therapy Group, based in Vancouver, Canada, says that introducing standard cell lines and tests into MSC research could make it easier to compare different therapeutic products. "Some companies are going to feel delighted," he says, but adds that more-established businesses may find their products suddenly threatened by competing claims that are founded on clearer points of reference.

If the standards, once arrived at, facilitate the systematic design and evaluation of preclinical trials of MSCs and their products, they could help biotechnology companies to attract large pharmaceutical firms to bring their MSC products to market, says Robert Deans, executive vice-president of Athersys in Cleveland, Ohio, which is developing MSC-derived treatments. Deans, who is participating in the standards working group, says that, until now, "pharma hasn't invested a lot. There's not enough consensus on these cells." ■