Meeting report

A full menu for stem-cell research
Francesca M Spagnoli and Ali H Brivanlou

Address: Laboratory of Molecular Embryology, The Rockefeller University, 1230 York Avenue, New York, NY 10021, USA.

Correspondence: Ali H Brivanlou. E-mail: brvnlo@mail.rockefeller.edu

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The stem-cell meeting held at the Institut Pasteur in December 2004 proved that the nascent field of stem-cell biology has rapidly become one of the most exciting and active fields in current research. Leading scientists from a range of disciplines relevant to stem-cell biology covered a gamut of current topics, including the properties of human and mouse embryonic and adult stem cells, attempts to manipulate stem cells, and the first clinical attempts at cell-based therapies. Here we describe some of the high points.

Embryonic stem cells and their potentialities
Stem cells are endowed with the ability to perpetuate themselves through self-renewal and to differentiate into many specialized cell types. This remarkable dual capacity raises many questions and holds enormous potential for regenerative medicine. A crucial question is how a stem cell decides to self-renew rather than to differentiate, and which signaling pathways are at work in the two different states. Recently, thanks to the work of several groups, including those of Peter Andrews (University of Sheffield, UK), Austin Smith (University of Edinburgh, UK) and our own, the molecular signature underlying the 'stemness' state of human embryonic stem cells (hES cells) is being defined. Andrews reported karyotypic changes in three independent hES cell lines involving the gain of chromosome 17q and occasionally 12p. These changes may provide a selective advantage for the propagation of undifferentiated hES cells, and a detailed analysis of the genes present in these chromosomal regions might further elucidate the molecular mechanisms underlying self-renewal. However, such detrimental karyotypic changes need to be taken into account for future therapeutic applications of hES cells. One of us (A.H.B.) reported work in our group on the importance of the Wnt and TGFβ pathways in maintaining stemness.

The fundamental challenge of work on stem cells lies in unlocking the mechanism that directs the differentiation of pluripotent stem cells into specific cell lineages in vitro. To accomplish this, appropriate culture conditions must be established so as to generate specific cell types from ES cells and obtain homogeneous populations. Many laboratories are working in this direction, and focusing their efforts on a specific cell type: Henrik Sembe (Lund University, Sweden) reported progress on the differentiation of pancreatic cells and Ron McKay (National Institute of Neurological Disorders and Stroke, Bethesda, USA) on the differentiation of dopamine neurons. Austin Smith provided an example of a niche-independent differentiation phenomenon using a green fluorescent protein (GFP) knock-in reporter ES cell line in which GFP replaced the open reading frame (ORF) of the neural-specific gene Sox1. Both mouse and human ES cells containing the GFP reporter commit to a neural fate in culture in vitro in the absence of serum and leukemia inhibitor factor (LIF); 60% of the cells were GFP-positive at 4 days. Therefore, as already suggested by experiments in amphibian embryos, no exogenous inductive stimuli (except perhaps for autocrine fibroblast growth factor signaling) seem to be required for the commitment of ES cells to a neural fate. If the in vitro results with the GFP reporter are confirmed, we have learned a lesson from embryology.

Adult stem cells and tissue repair
A substantial part of the meeting was devoted to adult stem cells and their potential for tissue repair. Adult stem cells are generally considered tissue-specific - only able to give rise to progeny cells corresponding to their tissue of origin. In some tissues, for example the liver and the pancreas, the existence
of a resident stem-cell population remains controversial. Adult skeletal muscle can regenerate following injury and this process seems to be mediated primarily by stem cells, known as myogenic satellite cells, present in adult muscle fibers. But are satellite cells the only source of skeletal muscle regeneration? Bruno Peault (Children’s Hospital, Pittsburgh, USA and Inserm, Villejuif, France) reported the identification in his laboratory of alternative adult stem-cell populations in skeletal muscle. His group found that within the satellite-cell compartment in human muscle, 1% of the cells also coexpress endothelial markers; these cells have dramatic myogenic potential in vivo. Similar results were obtained with genuine endothelial cells sorted from human adult muscle. Is there a stem-cell reserve in blood-vessel walls? Perhaps the answer lies in mesoangioblasts, a “novel class” of mesodermal progenitor cells described by Giulio Cossu (Stem Cell Research Institute, Milan, Italy). These cells are physically associated with vessels, coexpress early endothelial and myogenic markers, and are capable of differentiating into mesodermal lineage cells in vivo, including blood, cartilage, and skeletal and cardiac muscle cells. In addition, wild-type or genetically corrected mesoangioblasts delivered into the arterial blood system can correct mouse and dog models of limb-girdle muscular dystrophy. Taken together, these observations suggest a lineage kinship between vascular progenitors and progenitors of extraxascular mesodermal tissue throughout development and post-natal life.

The existence of a resident pool of stem cells in cardiac muscle, on the other hand, remains controversial. Ketty Schwartz (Groupe Hospitalier Pitie-Salpetriere, Paris, France) described the successful use of skeletal muscle satellite cells as an alternative for cell-transplantation therapy for heart failure. After successful long-term experiments in animal models of infarcted myocardium, her group proceeded to a phase I clinical trial in a small number of patients (ten) with severe ischemic cardiomyopathy. Encouraging results were obtained after 10 months of follow-up. An international phase II trial including 300 patients is in progress and the first results of this will be available in 2006; the trial is known as MAGIC, for myoblast autologous grafting in ischemic cardiomyopathy. Although this is exciting news and represents the first courageous trials carried out in patients, the approach has a fundamental limitation: skeletal myoblasts do not convert into true cardiomyocytes and, accordingly, no electrical coupling occurs between the host and grafted cells. Further analysis is required if we are to identify any other, more appropriate, sources of stem cells.

Development of a cell-based therapy for liver failure and inherited metabolic disease has become a necessity as a result of the limitations of liver transplantation. Several groups are searching for an ideal source of hepatic cells for transplantation. To try to identify a source, Markus Grompe (University of Oregon, Eugene, USA) took a lesson from the field of embryology, namely our knowledge about the close developmental relationship between the pancreas and liver. He reported that, in the fumarylacetoacetate hydrolase (FAH) liver-disease model in the mouse, diseased livers became repopulated with hepatocytes following intrasplenic transplantation of a suspension of adult pancreatic cells. From this he concludes that the adult pancreas contains hepatocyte progenitor cells. Two possible scenarios can be predicted: a differentiation event from a common hepatopancreatic stem cell, or transdifferentiation of adult cells.

Tissue-specific adult stem cells are not pluripotent, but recent evidence has suggested that rare stem cells with high developmental plasticity can be isolated from adult bone marrow and might represent a better source for cell therapy. The conclusion of the meeting on this was unambiguous: both Irving Weissman (Stanford University, USA) and Grompe reported that cell fusion rather than tissue-specific differentiation explains how transplanted bone-marrow cells adopt the phenotype of the host tissue. Nevertheless, Grompe emphasized that cell fusion can be considered a relevant therapeutic strategy. He described an elegant serial transplantation approach using increasingly lineage-restricted donor bone-marrow cell populations. This work has shown that fusion occurs in mouse liver between host hepatocytes and transplanted macrophages. Further insight into the factors that govern in vivo cell fusion and the nature of reprogramming of the macrophage nucleus to a hepatocyte gene-expression pattern will make this approach therapeutically relevant.

**Cancer stem cells**

Self-renewal is the hallmark of both stem cells and cancer cells, and in his talk on leukemia stem cells, Weissman addressed this intriguing parallel. Many pathways classically associated with cancer also control stem-cell self-renewal. He pointed out that stem cells continue to divide over a long period of time and, as a consequence, they are more likely to accumulate mutations, which may cause neoplasia. We can thus postulate that tumors might originate from the transformation of normal stem cells. Work in Weissman’s laboratory has established the role of a leukemia stem cell in leukemia. If the results hold true for other tumors, the new challenge of cancer therapy will be to identify and characterize the cancer stem cell in order to eliminate it.

It is an exhilarating time for stem-cell research. The work presented at the meeting suggested that stem-cell research will lead to insights in a variety of fields, such as embryology, cell-based therapy and the origin of cancer. We look forward to seeing advances in the field, perhaps at the next EuroConference.