# 2005 Spring Symposium Review

By Inge Ivens

The GETA Spring meeting was jointly sponsored by NorCal SOT. The meeting topic was "Stem Cell Applications in Pharmacology and Toxicology." The stem cell topic proved to be a very timely subject, especially for California scientists. The day-long meeting on May 24th at SRI International was very successful. We had selected great speakers with excellent presentations. The number of participants exceeded our expectations: after the morning registration, more than 100 participants had signed up and we had registered 13 posters.

Stem cell research has made large strides in recent years and bears great promises for human therapies, research and development of drugs. We had four very knowledgeable speakers who gave excellent presentations. In the morning Julie Baker, Assistant Professor from Stanford, introduced us to embryonic and adult stem cell functions and their differences and their potential applications. She was followed by David Schaffer, Assistant Professor from UC Berkeley speaking about Proposition 71 and the presence and discovery of stem cells in the nervous system (interestingly first found in birds). In the afternoon Emer Clarke and Ralph Snodgrass introduced us to currently available assays and stem cell application in drug discovery and development. We were able to give 5 poster awards, 2 for student posters. During the presentations and at lunch and the afternoon breaks we enjoyed lively discussions with the speakers and participants. SRI contributed with its great facilities to the success of this meeting. Thanks to all who helped to make this meeting a great success.

The following presents summaries of three of the presentations:

**Molecular Engineering of Stem Cell and Gene Therapies in the Nervous System** by David Schaffer, Ph.D.

Stem cell research has made large strides in recent years, and the advent of Proposition 71 in California promises to enhance stem cell efforts in the state. In particular, new molecular therapies based on stem cells and gene delivery have significant potential for tissue engineering and repair for numerous diseases. Before these approaches can succeed, however, a number of fundamental engineering challenges must be overcome. Neural stem cells are present throughout the adult nervous system, but we must learn at a quantitative, molecular level the signaling mechanisms that control these cells before we can harness them for neuroregeneration. We have identified novel signaling factors that regulate neural stem cells and are investigating the mechanisms by which the cells process these signals into functional decisions. Gene therapy is also highly promising for tissue repair, particularly in its potential synergy with stem cell approaches, but gene delivery vectors still require engineering for enhanced efficiency and safety. We are therefore pursuing novel directed evolution approaches to overcome numerous challenges in the performance of viral vectors.

**Toxicity Testing Using Stem Cell Assays** by Emer Clarke

The understanding of the various cell populations that contribute to hematopoiesis and clinical engraftment has been facilitated during the last 40 years through the rigorous study of cell phenotype and the development of functional assays. Hematopoietic stem cells and progenitor

assays can be used as a research tool to investigate growth and differentiation of cells in response to positive and negative regulators of hematopoiesis. In addition, these assays provide us with tools to assess the potential toxicity of compounds on specific primitive hematopoietic (myeloid, erythroid, megakaryocytic) cell populations. Within the bone marrow there are non-hematopoietic cell populations that are less well characterized. Mesenchymal cells are very rare, existing at an estimated frequency of 1 in 100,000 human bone marrow cells. These primitive cells go through a series of proliferation and differentiation steps to produce various mature tissue cell populations in a process termed mesengenesis. The phenotype of the mesenchymal precursor in the bone marrow has remained elusive but may be quantified in vitro using the colony forming unit-fibroblast (CFU-F) assay. This affords us the possibility of assessing the influence of compounds on microenvironmental cells or tissue development. The addition of compounds including 5-fluorouracil, taxol and hydroxyurea have demonstrated that hematopoietic and microenvironmental cell populations differ in their tolerance to the drugs–a feature which may be of interest if new compounds are being directed towards the treatment of specific cellular or tissue based malignancies. Until recently, it was believed that in the adult, the central nervous system had limited capacity for new cell genesis. However, researchers have now identified primitive cells in the brains of mouse, rats and man that have extensive proliferative potential *in vitro*. When cultured under appropriate conditions, the developing neurospheres can differentiate into neural cells, oligodendrocytes and astrocytes. This recently described *in vitro* assay may allow the screening of multiple compounds to generate a few targeted lead compounds, which then can be directed to the most appropriate animal model for further examination. The continuous examination of primitive cell populations and an understanding of the molecules that regulate their growth, should facilitate a more directed approach to the development of highly targeted drugs and address toxicity issues early in drug development.

**Embryonic Stem Cells: Biological Tools for Drug Discovery and Development** by H. Ralph Snodgrass

Diseases like cancer, Alzheimer's, diabetes, stroke, heart disease, and various traumatic brain and spinal cord injuries are still not well treated. The enormous biological power of embryonic stem cells gives scientists the ability to experimentally study–under carefully controlled conditions–the growth and development of the many different cell types that are important to diseases like cancer, Alzheimer's, diabetes, stroke, heart disease, and various neurological diseases. Embryonic stem cells provide a clinically relevant biological system that offers an unprecedented powerful discovery tool for understanding these disease processes, evaluating drug effects, and ultimately developing novel therapies for devastating diseases. In addition, embryonic stem cell differentiation systems offer the ability to produce virtually unlimited amounts of mature cells for predictive toxicology screening assays, which is a major cause of drug failures. There has been significant discussion about the utility of embryonic stem cells for cell-based therapies. This talk addressed the utility of embryonic stem cells as research tools for conventional drug discovery, drug screening, and predictive toxicology assays.