Greetings
It is a pleasure to be able to write this message to thank everyone for your continuing support and interest in our vigorous Specialty Section. The SOT meeting in New Orleans is now a memory but the RSESS continues to grow and thrive with support from our members and the hard work of the previous and new officers of the section. I take this opportunity to welcome Jim Green as President Elect, Jim MacGregor as Vice President, Vijayapal Reddy as Secretary/Treasurer and Councilors Andrea Weir and Suzanne Fitzpatrick. The continuing help and support from our Past President, Ron Gerson, is always appreciated as we new officers strive to remember all of the things required in the SS. We are all looking forward to continuing our successful programs in 2005 to plan our activities for the 2006 SOT meeting in San Diego.

The SOT has accelerated its goal to involve the officers of the specialty sections in SOT activities and a teleconference on June 16th was conducted to update the specialty section Presidents and Vice Presidents with society news, procedures and goals. A second teleconference was conducted in July with the Secretary/Treasurers of each specialty section to maintain communications on society activities. The goals of the SOT to work with the SS officers will continue with a face-to-face meeting of SS Presidents and Vice Presidents in Chicago on August 8-9, 2005.

Membership
Our section is one of the largest Specialty Sections in the SOT and continues to grow slowly but steadily. Our dues paid membership for the last 3 years:

2003 - 350 members
2004 - 359 members
2005 - 364 members

The RSESS is actively seeking to add students to our membership. We have contacted the SOT student organization as well as winners of our travel awards in 2005 to encourage their participation. Student members can join one specialty section with-
website and we will be sending notices and reminders to all of our members and universities in the SOT directory later in the year.

March 2005 Annual Business Meeting and “Great Debate”

- The annual business meeting with the membership allowed presentation of a status report on activities of the RSESS and section finances. The intention of the RSESS to seek student members and to support future workshops and symposia with RSESS financial assistance was stressed as a continuing goal of the SS.

- The officers of the RSESS worked in 2004 and 2005 to “modernize” the outdated by-laws of the SS in order to more accurately reflect current practices, procedures and responsibilities of the officers. The revised RSESS By-Laws were circulated to membership and an approval sheet was circulated to voting members at the 2005 business meeting. In the absence of a quorum, the revised RSESS by-laws were circulated by email to the voting membership by SOT Headquarters. Revised by-laws were approved by a quorum of the voting (i.e., paid) membership according to information from the SOT received on April 4, 2005.

- Attendance at our annual business meeting and debate on topics of current interest continues to be strong. In 2005, the RSESS sponsored a lively debate and invited participation by the Carcinogenesis SS. The topic was based on a premise in a recent article (Toxicol. Sci. 2004;80:225-9) by Dr. Samuel Cohen proposing that the rodent 2-year carcinogenicity assay is no longer necessary. The topic of the debate (typically chosen to highlight opposing viewpoints to be represented was entitled “The Rodent Carcinogenicity Assay: Relevant or Relic”? Speakers at the debate were:
  - Dr. Samuel Cohen, University of Nebraska Medical Center, Omaha, NE
  - Dr. Abigail Jacobs, USFDA, Rockville, MD
  - Dr. Chris Portier, NIEHS, Research Triangle Park, NC

An “unofficial” count of members that were attendees at the debate was approximately 150, indicating the level of interest in this topic for an early evening activity in New Orleans.

Planned Activities

August 2005 Annual Officers Teleconference

- Teleconference of RSESS officers scheduled for August 16, 2005 to discuss section financial status, scientific issues and arrangements and scheduling of annual officers face-to-face meeting at SOT headquarters

November 2005 Annual Officers Meeting

The face-to-face meeting in the Fall is typically the time that the RSESS officers begin to discuss topics and potential speakers for the mini-debate topic for the next annual SOT meeting. In addition, suggestions are considered for modifications to the SS website and for
President’s Message—Cont.

other initiative suggested by the SOT. During this meeting, nominees will be selected for election as RSESS officers and arrangements for 2006 SOT meeting will be discussed. The RSESS welcomes our members to inform one of our officers about desires to serve as an officer of the RSESS.

2007 Planning

It seems every President of the RSESS is surprised at this time of year to be informed that it is time to start planning for the SOT meeting 2 years from now and this year is no exception. The SOT Program and Continuing Education Committees have asked for the RSESS to submit ideas for symposia, workshops, roundtables and continuing education courses for SOT meeting in Charlotte, NC in 2007! Proposals are due to the SOT in the middle of April 2006 (exact date will be set later) and topics for the 2007 meeting will reviewed and finalized early in May for consideration by the Program Committee.

Ron Slesinski
President, RSESS

Awards - Student Travel Awards

In 2005, RSESS presented five travel awards of $500 each. Three awards were sponsored by RSESS, one $500 award was sponsored by Burdock Group and one award of $1,000 was sponsored by the MERCK Company to the following students:

Reiko Anahara, Bioenvironmental Medical Graduate school, Chiba University, Chiba, Japan
LaNissa Brown, Meharry Medical College, Nashville, TN (Burdock Group Award)
Flavia Pereira, Dept. of Biomed. and pharmaceutical Sciences, University of Mt, Missoula, MT
Nan Mei, Division of Biochemical Toxicology, NCTR, FDA, Jefferson, AR (MERCK Company Award)

Jianyong Wang, The University of Arkansas for Medical Sciences, Jefferson, AR

Each student award winner also received $100 gift certificate from Taylor Francis Publishing

Mini-debate at annual Business Meeting entitled "The Rodent Carcinogenicity Assay: Relevant or Relic"?

Speakers from left to right Samuel Cohen, Chris Portier and Abigail Jacobs

New Risk Assessment Requirements in the European Union

Codex Alimentarius has directed all of the Codex Committees to initiate a more formal approach to incorporating risk assessment methodology for all Codex scientific reviews, not just those involving safety issues. For more information on the specific guidance issued, see http://www.codexalimentarius.net/web/reports.jsp?lang=en where the reports of various committees are available.

Last year, an expert review was initiated under the International Programme on Chemical Safety, WHO/ILO/UNEP. An Expert Committee of 18 members met in a closed workshop in Geneva in May 2005 to consider the issues and draft a report. The report is in final stages of preparation in conjunction with Codex Alimentarius. A context paper prepared in advance for the Expert group identifying issues related to risk assessment methods applied to nutrients and related substances is available at: http://www.who.int/ipcs/highlights/nutrientproject_may18/en/

The membership of the expert committee has not been disclosed, but, according to the website, will be made available when the final report is put on the web for comment for a period of 30 days. This is expected in a few months.

Alison Yates
ENVIRON International Corporation
Genetic Toxicology and Carcinogenicity Assessments of Biological Drugs

A workshop entitled, “Preclinical Development of Biologicals and Biotech Derived Pharmaceuticals: Principles and Practices” took place in February of 2005. The meeting was co-chaired by FDA pharm/tox leadership and the Preclinical Safety Expert group of the Biotechnology Industry Organization (BioSafe). Approximately 60 FDA pharm/tox reviewers attended didactic seminars on toxicity testing of biological drugs, including those on “Genotoxicity and Carcinogenicity Assessments of Biological Drugs”.

An overview of ICH guidance preceded case study presentations. Emphasis was placed on ICHS6 because genetic toxicity testing of biological drugs is specifically addressed in ICHS6 but not in genetic toxicology guidance ICHS2a or 2b. A number of important points were discussed: 1) Genetic toxicity tests should not be routinely completed for biological drugs; 2) An “organic linker” is a chemical modification and not a series of amino acids; 3) Standard genetic toxicology tests are designed to detect direct DNA damage, which is not anticipated with most biological drugs; and 4) Standard genetic toxicology tests are not designed to evaluate spontaneous mutations that may arise from mitogenic biological drugs. These points were supported by a pivotal publication that reviewed 177 genetic toxicity tests completed for 78 biologic drugs and concluded that such tests are generally inappropriate and unnecessary (Mutat Res 436: 137-56). A decision-making flow chart for genetic toxicity testing of biological drugs was presented.

Despite ICHS6 guidance, it was noted that genetic toxicity tests have been completed for most approved biological drugs. For many of these drugs, testing was completed prior to Step 4 implementation of ICHS6 in 1997. A case study of genetic toxicity studies completed for the

DNase Pulmozyme® was presented. Genetic toxicity tests with Pulmozyme® demonstrated that the high molecular weight of biological drugs prohibits their entry into cells under normal conditions. A positive genetic toxicity result only occurred following electroporation of bovine DNase into cells. Importantly, the positive from this artificial genetic toxicity test does not appear on the label. Although in vivo genetic toxicity tests for an enzyme such as DNase may be appropriate because of its pharmacology, it’s also apparent that genetic toxicity tests are still conducted for biological drugs even though they are neither scientifically sound nor required based on ICH guidance. Participant consensus that genetic toxicity tests were not needed for a case study of a human hormone peptide Fc fusion protein was encouraging. Vigilance by both industry and regulators is needed to ensure a case-by-case evaluation is used for biologics and genetic toxicity studies are only done when scientifically justified.

Similar to genetic toxicity, ICH guidance was discussed during the carcinogenicity session. Both ICHS6 and the carcinogenicity guidance ICHS1A indicate that carcinogenicity studies are generally inappropriate for biological drugs, but such studies should be considered if the product is biologically active and non-immunogenic in rodents, and other studies have not provided sufficient information to allow an assessment of carcinogenic potential. A decision-making flow chart for 2-year rodent carcinogenicity testing of biological drugs was presented.

Case studies on the carcinogenicity testing of biological drugs were discussed. The “Carcinogenicity Studies Waiver Discussion” that’s in the approval information...
Genetic Toxicology and Carcinogenicity Assessments of Biological Drugs—Cont.

for Fuzeon® was presented. The most compelling reasons for not conducting studies given by the CDER Executive Carcinogenicity Assessment Committee were: Fuzeon® is composed of naturally occurring amino acids that are metabolized and incorporated into body tissues and as such, there are no classical structural alerts suggesting a carcinogenic risk; and that polypeptides that are known to be carcinogenic are hormones or demonstrate hormonal activity. A waiver was granted (http://www.fda.gov/cder/foi/nda/2003/21481_Fuzeon_Pharmr_P1.pdf).

Case studies for recombinant growth hormone and parathyroid hormone demonstrated the differences between these two biological drugs that necessitated carcinogenicity studies only for the later. Carcinogenicity studies are not needed for endogenous substances given primarily as replacement therapy, such as human growth hormone. In contrast, carcinogenicity studies should be considered for biological drugs that are biologically active and nonimmunogenic in rodents, are given at supraphysiological levels, and are not identical to the endogenous protein. Analogues of parathyroid hormone (PTH) fit these criteria and also stimulate bone growth; therefore, carcinogenicity studies are appropriate for PTH analogues. Bone tumors have been observed in carcinogenicity studies in rats given chronic exaggerated pharmacological doses PTH analogues. Although not a certainty with all hormone analogues, this illustrates the threshold effect for tumors in rodents that can occur in target tissues following chronic exaggerated pharmacological doses. Although 2-year carcinogenicity assays are appropriate for many hormone analogues, most other biological drugs are not pharmacologically active or are highly immunogenic in rodents.

A case study of a potential alternative to a 2-year rodent carcinogenicity was presented. Transgenic mice can be used if they are thoroughly characterized, which includes: a good understanding of the biology of the target of the biological drug, similar tissue distribution of the target across species, the physiological response of the hitting the target is conserved across species, and the pharmacokinetics of the biological drug in mice is similar to humans. Transgenic mice were used to evaluate the effect of keliximab on immune surveillance in a melanoma metastasis model (Human & Experimental Toxicology 19:230-243). Keliximab had no effects in this model.

In summary, genetic toxicology testing and carcinogenicity studies should not be routine for biological drugs. A rational scientific approach should be used to determine the necessity of these studies as well as the appropriate model and study design. It is the responsibility of both industry and regulators to be diligent in using ICHS6 for guidance in developing biological drugs. BioSafe is committed to identifying key scientific and regulatory issues related to the nonclinical safety evaluation of biological drugs, and is currently working on a manuscript to help design chronic toxicity assessments.

Shawn Heidel
Eli Lilly and Company