HESI PPAR AGONIST PROJECT COMMITTEE

Samuel M. Cohen, MD, PhD
(University of Nebraska Medical Center)
Project Committee Scientific Advisor

HESI Assembly of Members Meeting
January 19, 2009
Tucson, AZ

PPAR AGONIST PROJECT COMMITTEE
Mission

The mission of the HESI PPAR Agonist Project Committee **is to develop an improved scientific understanding of the human relevance** of emerging rodent tumor data for PPAR agonists which hold promise in drug research and development.

PPAR AGONIST PROJECT COMMITTEE
2008 Participation

Industry

AstraZeneca
Eli Lilly and Company
GlaxoSmithKline
F. Hoffmann-La Roche Ltd.
Johnson & Johnson Pharmaceuticals
Kalypsys, Inc.
Merck & Company
Metabolex, Inc.
Mitsubishi Pharma Corporation
Novartis Pharmaceuticals Corporation
Perlegen Sciences, Inc.
Pfizer Inc.
Sankyo Co., Ltd.
sanofi-aventis
Servier Group
Takeda Pharmaceutical Company, Ltd.

Public Participation (Government and Academia)

Imperial College London
Indiana University School of Medicine
Instituto Nacional da Farmácia e do Medicamento (INFARMED)
University of Nebraska Medical Center
University of North Carolina, Chapel Hill
US FDA Center for Drug Evaluation and Research

PPAR AGONIST PROJECT COMMITTEE
Leadership – Steering Team

Co-Chairs
Dr. Tim Hammond (AstraZeneca R&D)
Dr. Jon Cook (Pfizer Inc.)

Hemangiosarcomas Working Group
Dr. Heike Hellmold (AstraZeneca R&D)
Dr. James Klaunig (Indiana University School of Medicine)

Liposarcomas/Fibrosarcomas Working Group
Dr. John Evans (AstraZeneca R&D)
Dr. Christopher Powell (GlaxoSmithKline)
Dr. James Swenberg (University of North Carolina, Chapel Hill)

Urinary Bladder Working Group
Dr. Samuel Cohen (University of Nebraska Medical Center)
Dr. Roger Brown (GlaxoSmithKline)

PPAR AGONIST PROJECT COMMITTEE
Statement of Issue

- PPAR isoforms (alpha, beta/delta, gamma) represent a therapeutically important class for the treatment of diabetes and dyslipidemia.

- PPAR agonists are associated with hemangiosarcoma in mice, but not rats.

- Hemangiosarcoma arises in rodents and dogs after exposure to other classes of compounds, genotoxic and nongenotoxic.

- The nongenotoxic modes of action (MOA) are not fully understood.

- The human relevance of hemangiosarcoma in rodents is not well understood.

HESI-SPONSORED PATHOLOGY WORKING GROUP TO REVIEW HEMANGIOSARCOMAS IN MICE AND HAMSTERS AND LIPOSARCOMAS / FIBROSARCOMAS IN RATS (January 2007)

- **Goal:** to establish consistent tumor diagnostic criteria and nomenclature, and assess evidence of preneoplastic changes.
- Companies contributed slides from a total of 420 cases from studies in mice and 99 cases from studies in rats.
- Slides were randomized and triple blinded.
- Independent expert pathologists examined slides (EPL, Inc.)

Results: Specific diagnostic criteria and nomenclature recommended for classification of proliferative vascular lesions in mice or hamsters, and proliferative mesenchymal changes in rats for PPAR agonists. See Hardisty et al. (2007).

Hardisty et al. 2007. *Toxicol Pathol.* 35, 928-941.

HESI-SPONSORED PATHOLOGY WORKING GROUP TO REVIEW THE URINARY BLADDER FROM CYNOMOLGUS MONKEYS (June 26-27, 2007)

- **Goal:** to establish consistent diagnostic criteria for urothelial changes in monkeys and assess potential relationship of these changes with PPAR agonist treatment.
- Six companies contributed slides from a total of 197 cases from studies in monkeys.
- Slides were randomized and triple blinded.
- Seven independent expert pathologists examined slides (EPL, Inc.)
- Additional immunohistochemistry investigation to further characterize urothelial vacuoles identified as an apparent PPAR agonist treatment-related finding.
- **Work products:** technical report; published scientific paper; illustrated lexicon (CD ROM) for funding companies

Hardisty et al. 2008. *Toxicol Pathol.* 36, 769-776.

PPAR AGONIST PROJECT COMMITTEE

Sarcomas Data-Sharing Meeting

- August 2007 sarcomas data-sharing meeting organized and conducted to protect confidentiality.

  -- Prior to the meeting, company scientists and their managements determined whether and which data could be shared on PPAR agonists that are marketed, discontinued, or currently in development.

  -- Ten companies agreed to share data.

- Meeting participants developed a revised working hypothesis for the MOA of hemangiosarcoma induced by PPARs in mice.

  -- Data gaps and research needs were articulated.

Society of Toxicology
Contemporary Concepts in Toxicology (CCT) Workshop

Hemangiosarcoma in Rodents: Mode-of-Action Evaluation and Human Relevance Workshop

December 4-5, 2008
Arlington, VA

WORKSHOP ORGANIZING COMMITTEE

Co-Chairs:
Samuel M. Cohen (University of Nebraska Medical Center)
Jon C. Cook (Pfizer Inc.)

Neil Carmichael (ECETOC)
Vicki L. Dellarco (US EPA Office of Pesticide Programs)
Nancy G. Doerrer (HESI)
Timothy G. Hammond (AstraZeneca R&D)
Jerry F. Hardisty (Experimental Pathology Laboratories, Inc.)
Heike Hellmold (AstraZeneca R&D)
Abigail C. Jacobs (US FDA CDER)
David Jacobson-Kram (US FDA CDER)
James E. Klaunig (Indiana University School of Medicine)
David E. Malarkey (NIEHS NTP)
Martin A. Philbert (University of Michigan)
Christopher J. Powell (GlaxoSmithKline)
Richard D. Storer (Merck Research Laboratories)
James A. Swenberg (University of North Carolina at Chapel Hill)

WORKSHOP SPONSORS

Society of Toxicology

HESI

Aclairo Pharmaceutical Development Group

AstraZeneca

Daiichi-Sankyo

GlaxoSmithKline

Merck

Pfizer Inc.

sanofi aventis

Society of Toxicologic Pathology

SOT Regulatory and Safety Evaluation Specialty Section

Takeda

PURPOSE AND GOALS OF THE SOT-CCT WORKSHOP

PURPOSE

The purpose of the workshop was to explore the modes of action (MOAs) and human relevance of hemangiosarcoma induced in rodents by various classes of compounds.

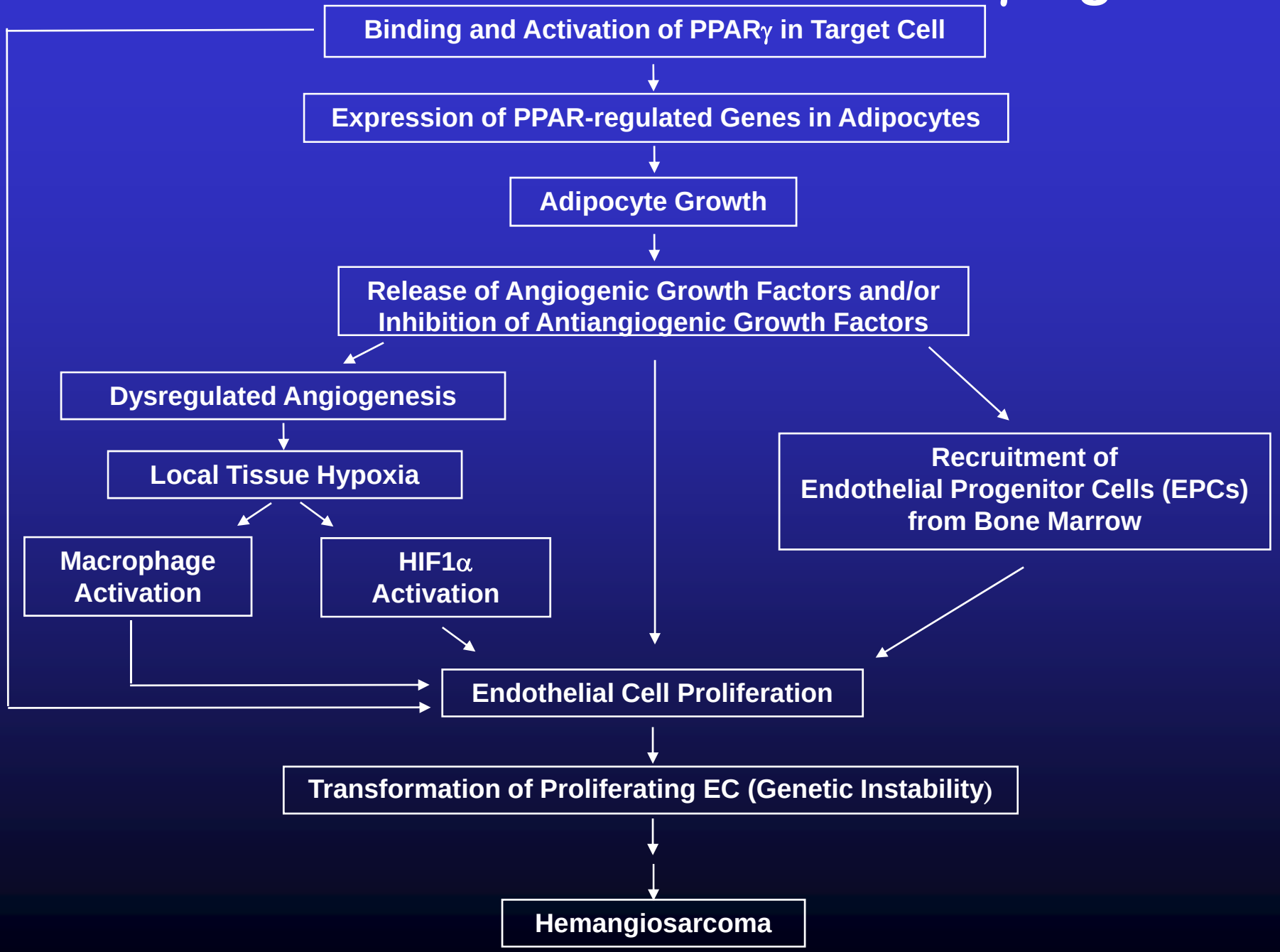
GOALS

1) Summarize current understanding of MOAs for various compound classes.

2) Share data and information with the scientific and regulatory communities to promote and guide future research on nongenotoxic MOAs for hemangiosarcoma in rodents.

3) Identify research tools and approaches to studying hemangiosarcoma and related vascular lesions.

HESI – MOA Framework for PPARγ Agonists



WORKSHOP OUTCOME

WORKSHOP NOTEBOOK IS POSTED ON THE SOT WEBSITE.

PUBLICATION: A mini-review of the workshop will be submitted for publication by the Session Co-Chairs to *Toxicological Sciences* during the first quarter of 2009.

PPAR Agonist Project Committee will sunset upon publication of the workshop proceedings.