PPAR AGONIST PROJECT COMMITTEE

Mission
The mission of the HESI PPAR Agonist Project Committee was to develop an improved scientific understanding of the human relevance of emerging rodent tumor data for PPAR peroxisomal proliferator-activated receptor) agonists that hold promise in drug research and development. Participating scientists from international regulatory agencies, academia, and the pharmaceutical industry will develop consensus on the implications and longterm effects of PPAR agonist exposure by examining and integrating available preclinical data and evaluating the need for additional laboratory research.

2008 Participants
AstraZeneca AB
Eli Lilly and Company
GlaxoSmithKline
Hoffmann-La Roche Inc.
Imperial College London (UK)
Indiana University School of Medicine
Institute de Rechereches Internationales SERVIER
Instituto Nacional da Farmácia e do Medicamento (INFARMED, Portugal)
Johnson & Johnson Pharmaceuticals
Merck & Co., Inc.
Metabolex, Inc.
Mitsubishi Tanabe Pharma Corporation
Novartis Pharmaceuticals Corporation
Pfizer, Inc.
Sankyo Co., Ltd.
sanofi-aventis
Takeda Pharmaceutical Company Limited
University of Nebraska Medical Center
University of North Carolina, Chapel Hill
US Environmental Protection Agency
  Office of Pesticide Programs
US Food and Drug Administration
  Center for Drug Evaluation and Research

Committee Publications
Hardisty, J.F., et al., Histopathology of hemangiosarcomas in mice and hamsters and liposarcomas/fibrosarcomas in rats associated with PPAR agonists. Toxicol Pathol, 2007. 35(7): p. 928-41.

Hardisty, JF, Anderson, DC, Brodie, S, Cline, JM, Hahn, FF, Kolenda-Roberts, H, Lele, SM, Lowenstine, LJ. 2008. Histopathology of the urinary bladders of cynomolgus monkeys treated with PPAR agonists. Toxicol Pathol., 36, 769-776.

Cohen, SM, Storer, RD, Criswell, KA, Doerrer, NG, Dellarco, VL, Pegg, DG, Wojcinski, ZW, Malarkey, DE, Jacobs, AC, Klaunig, JE, Swenberg, JA, Cook, JA. 2009. Hemangiosarcoma in rodents: mode-of-action evaluation and human relevance. Toxicol Sci. doi:10.1093/toxsci/kfp131.

Fact Sheet

ILSI Health and Environmental Sciences Institute

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. Participating scientists from international regulatory agencies, academia, and the pharmaceutical industry will develop consensus on the implications and long-term effects of PPAR agonist exposure by examining and integrating available pre-clinical data and evaluating the need for additional laboratory research.

BACKGROUND

Peroxisomal proliferator-activated receptors (PPARs) are involved in the pathogenesis of insulin resistance, diabetes, and related complications. Consequently, the identification of PPAR subtypes and the potential for their activation provides promising therapeutic targets for the management of type 2 diabetes mellitus. Available data from rodent carcinogenicity studies, however, demonstrate that PPAR agonists can be tumorigenic in one or more species of rodents at multiple sites. The most commonly observed tumor types are hemangiosarcomas, fibro- and liposarcomas, and, in some cases, urinary bladder tumors. Mechanistic data are not yet available to explain the mode(s) of action for most of these tumor types. Outstanding questions exist regarding potency, species differences, safety margins, and other issues.

ACTIVITIES AND ACCOMPLISHMENTS

The HESI PPAR Agonist Project Committee was established in 2005 by a group of pharmaceutical companies to advance research on and understanding of the modes of action and human relevance of this emerging rodent tumor data for PPAR agonists.

During 2005, Co-Chairs were identified, and a Steering Team and Working Groups were formed. Academic and government scientists were invited to join the committee. The Project Committee developed a mission and work plan. Each Working Group developed proposed mode-of-action frameworks for human relevance on the tumor types of interest.

In 2006, the PPAR Agonist Project Committee developed hypotheses for and planned two Pathology Working Groups (PWGs). The purpose of the PWGs was to develop consensus on tumor diagnosis and consistency of diagnosis across multiple studies. These PWGs were conducted in 2007:

- In January 2007, Experimental Pathology Laboratories, Inc., Research Triangle Park, NC, conducted a PWG to Review Hemangiosarcomas in Mice and Hamsters and Liposarcomas/Fibrosarcomas in Rats on behalf of the HESI PPAR Agonist Project Committee. The PWG focused on establishing consistent tumor diagnostic criteria and assessing evidence of preneoplastic changes. A paper summarizing the results of the PWG has been published in *Toxicologic Pathology*. Posters describing the results of the PWG were presented at the June 2007 26th Annual Symposium of the Society of Toxicologic Pathology in Puerto Rico.

- In June 2007, EPL, Inc., conducted a PWG to Review the Urinary Bladder from Cynomolgus Monkeys on behalf of HESI. The purpose of this PWG was to determine the presence of true hyperplasia in monkey urothelium versus hyperplasia in the range of normal. A manuscript developed by the PWG has been submitted for publication in *Toxicologic Pathology*.

The PPAR Agonist Project Committee expects that the PWGs will provide a substantial basis upon which industry, government, and academia may design future experiments to address the mode of action associated with PPAR agonists and establish, with greater certainty,

the human relevance of rodent tumors.
In August 2007, the HESI PPAR Agonist Project Committee sponsored a meeting of companies that agreed to share data on PPAR agonists. The meeting was organized and conducted to protect confidentiality to the extent required by each participating company while, at the same time, enabling the Project Committee to move forward with developing hypotheses about the mode/mechanism of action (MOA) for hemangiosarcomas, liposarcomas, and fibrosarcomas induced in animals by PPAR or dual PPAR agonists. 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. In light of the data presented and discussed during the meeting, participants developed a revised working hypothesis for the MOA of hemangiosarcomas. Data gaps and research needs were articulated. The MOA continues to be a work in progress.

Based on the collective data-sharing exercise, the PPAR Agonist Project Committee developed a mode-of-action (MOA) framework for hemangiosarcoma induction. Several important knowledge gaps and uncertainties were identified. Because over 20 agents (i.e., pharmaceuticals, pesticides, and industrial chemicals) have been observed to induce vascular neoplasms in experimental studies in rodents, a workshop was convened in December 2008 in partnership with the Society of Toxicology (SOT). The goals of the SOT Contemporary Concepts in Toxicology (CCT) workshop were to 1) summarize current understanding of modes of action (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, and 3) identify research tools and approaches to studying hemangiosarcoma and related vascular lesions.

Approximately 100 scientists attended the December 2008 workshop. Sixteen speakers representing industry, government, and academia presented research and scientific overviews of emerging data. Posters were presented. A report summarizing the workshop presentations and discussions will be submitted for publication in *Toxicological Sciences*.

FUTURE ACTIVITIES

The PPAR Agonist Project Committee will officially "sunset" after publication of the workshop proceedings in the open literature in 2009.

If companies express further interest in exploring the mode/mechanism of action of sarcoma development for other classes of compounds or specific mechanistic questions related to PPAR agonists, they will be encouraged to submit proposals through the HESI emerging issues process as a new initiative.

OUTREACH

To share information about its scientific activities, the PPAR Agonist Project Committee has engaged in multiple outreach activities:

2006:
- Japanese Society of Toxicology Annual Meeting, Nagoya, Japan (presentation)

2007:
- 26th Annual Symposium of the Society of Toxicologic Pathology, Puerto Rico (two posters on mesenchymal lesions in the rat and vascular lesions in the mouse, respectively)

2008:
- 47th Annual Meeting of the Society of Toxicology, Seattle, WA (two posters on mesenchymal lesions in the rat and vascular lesions in the mouse, respectively)

2009:
- Japanese Society of Toxicologic Pathology Annual Meeting, Hamamatsu, Japan (presentation)

LEADERSHIP AND INFORMATION

Co-Chair..... Dr. Tim Hammond
(AstraZeneca R&D)
Co-Chair.....Dr. Jon Cook
(Pfizer Inc.)
Scientific Advisor..... Dr. Samuel Cohen
(University of Nebraska Medical Center)

Scientific Advisor ..... Dr. James Klaunig
(Indiana University School of Medicine
HESI Staff.....Nancy G. Doerrer, MS
Ms. Cyndi Nobles

For more information, contact:
Nancy G. Doerrer, MS
at 202-659-3306 or ndoerrer@hesiglobal.org.

PROJECT COMMITTEE MEMBERSHIP

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

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 Food and Drug Administration
(Center for Drug Evaluation and Research)

PUBLICATIONS

Hardisty, JF, Elwell, MR, Ernst, H, Greaves, P, Kolenda-Roberts, H, Malarkey, DE, Mann, PC, Tellier, PA. 2007. Histopathology of hemangiosarcomas in mice and hamsters and liposarcomas/fibrosarcomas in rats associated with PPAR agonists. *Toxicol Pathol*., 35, 928-941.

Hardisty, JF, Anderson, DC, Brodie, S, Cline, JM, Hahn, FF, Kolenda-Roberts, H, Lele, SM, Lowenstine, LJ. 2008. Histopathology of the urinary bladders of cynomolgus monkeys treated with PPAR agonists. *Toxicol Pathol*., 36, 769-776.

Committee Presentations and Data Resources

December 4-5, 2008: International workshop on “Hemangiosarcoma in Rodents: Mode-of-Action Evaluation and Human Relevance,” Arlington, Virginia. Society of Toxicology (SOT) Contemporary Concepts in Toxicology (CCT) series. Sponsored by the HESI PPAR Agonist Project Committee, Aclairo Pharmaceutical Development Group, AstraZeneca, Daiichi-Sankyo, GlaxoSmithKline, Merck Research Laboratories, Pfizer, sanofi-aventis, the Society of Toxicologic Pathology, SOT, the SOT Regulatory and Safety Specialty Section, and Takeda.

January 19, 2009: HESI PPAR Agonist Committee Presentation.

"PPAR Agonist Tumorigenicity." Presented at the 2009 HESI Annual Meeting. Tucson, Arizona. Presentation by Dr. Samuel Cohen, University of Nebraska Medical Center.

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.

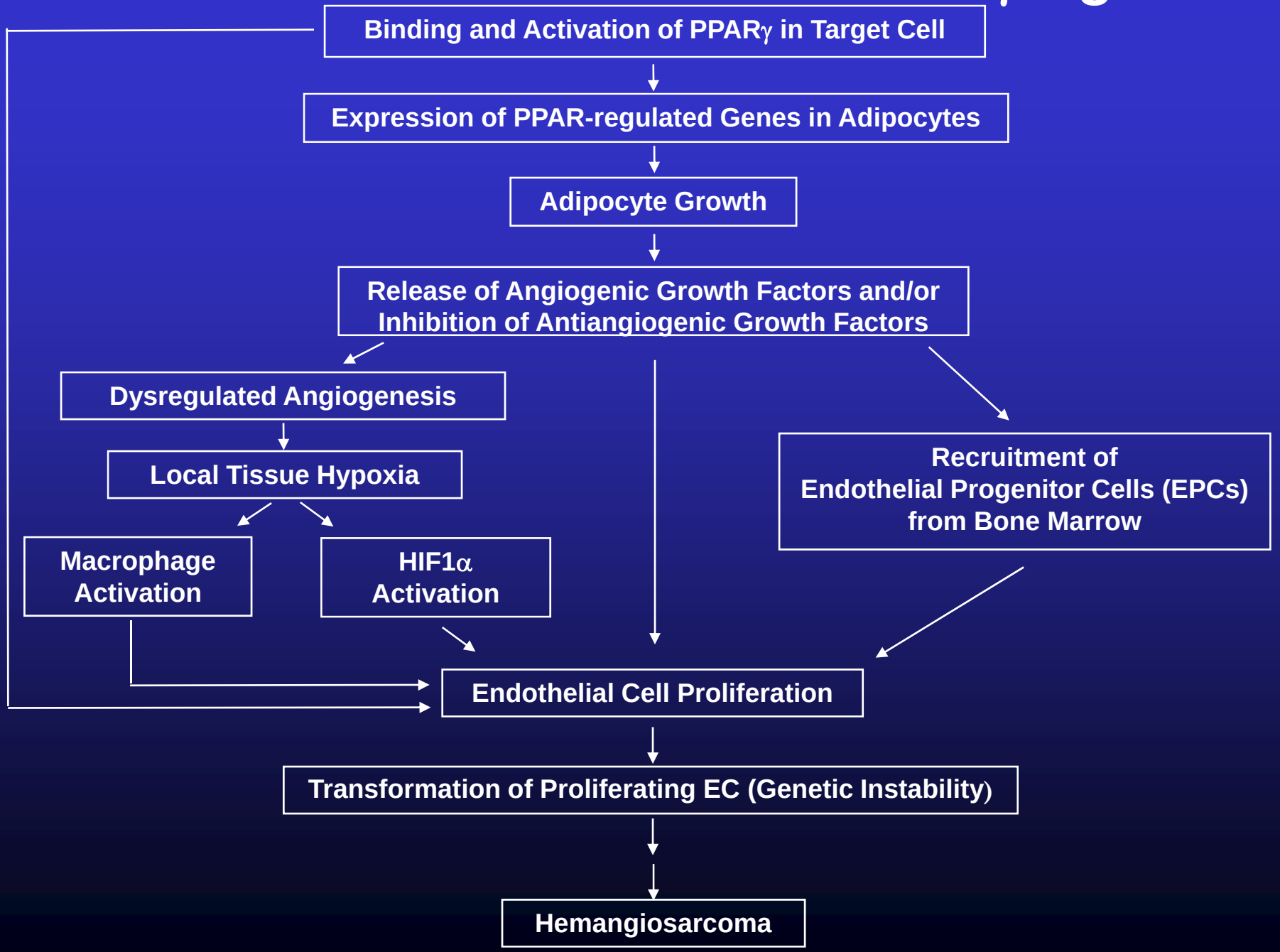
GOALS

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.