2017 PISA

Pathobiology for Investigators, Students and Academicians

# Meeting Program

## Genome and Environment: Implications in Development, Regeneration, Injury, Immunity, and Malignancy

American Society for Investigative Pathology

ASIP.org

**Pittsburgh, PA**

September 25-27, 2017

# Guest Societies & Sponsors

Society for Experimental Biology and Medicine

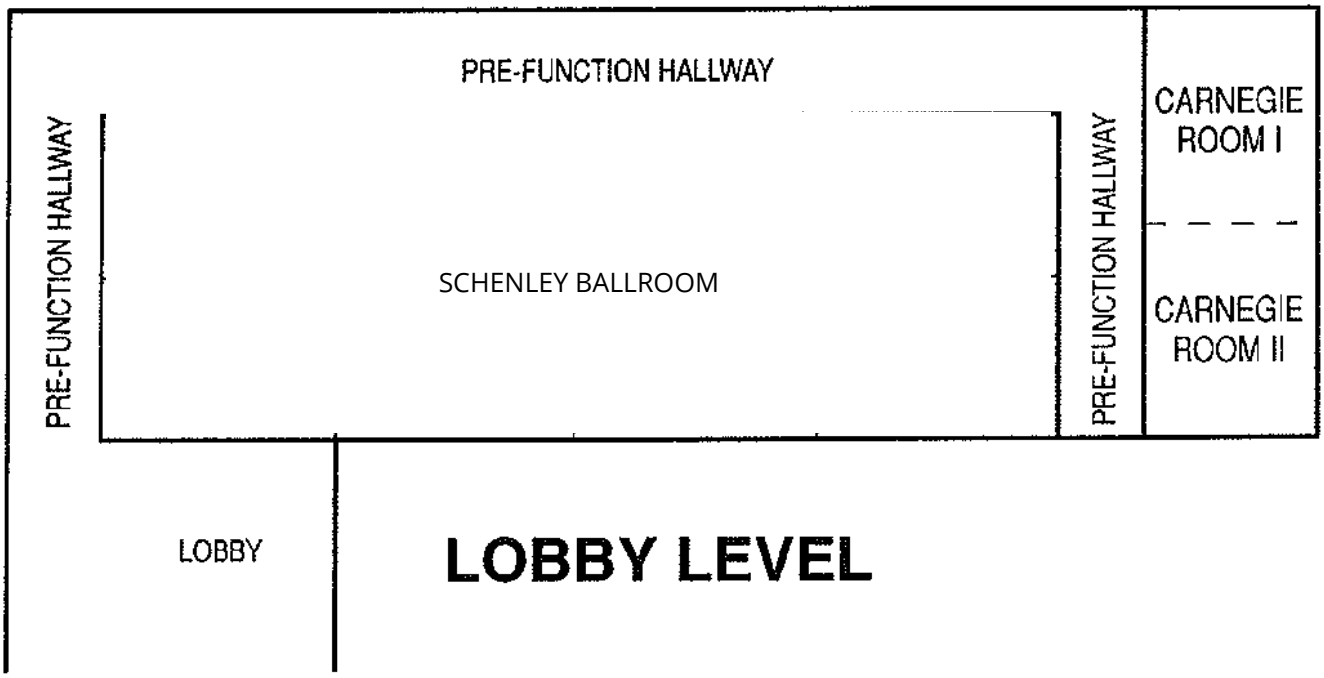
Histochemical Society

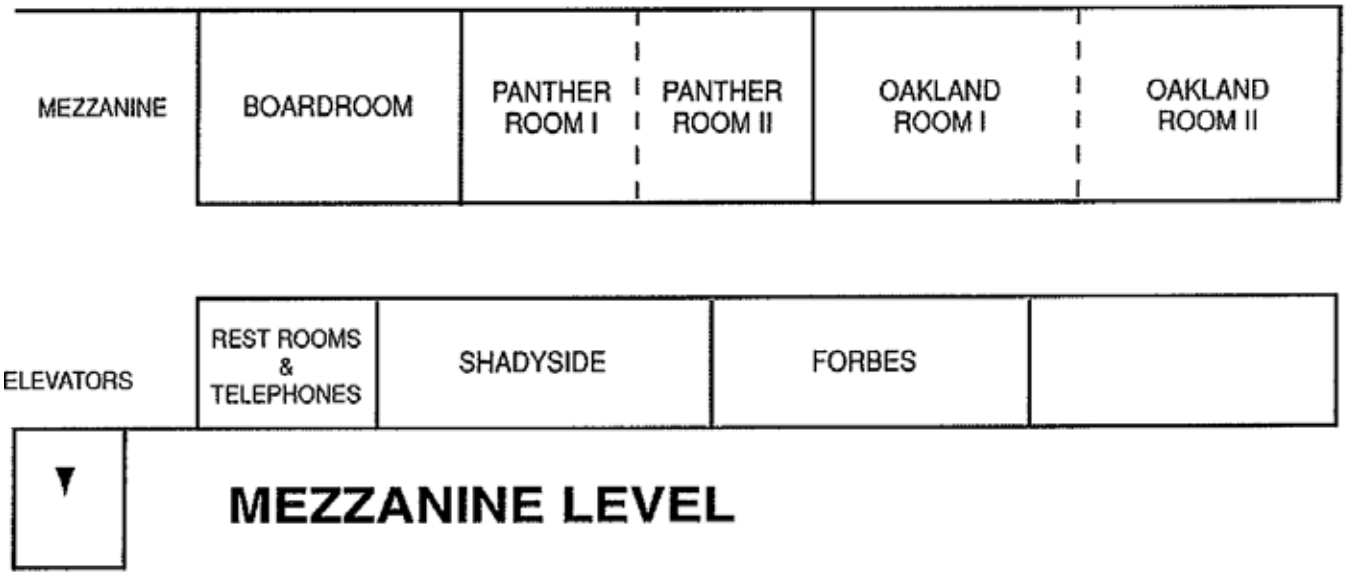
University of Pittsburgh

# Contents

WYNDHAM

*Pittsburgh University Center*



# Guide to PISA 2017

## *Welcome*

ASIP is proud to host this interactive, abstract-driven, focused scientific conference entitled "*Genome and Environment: Implications in Development, Regeneration, Injury, Immunity, and Malignancy*" at the Wyndham Pittsburgh University Center, Pittsburgh, PA. Timely and innovative technologies have vastly impacted our understanding of disease pathogenesis in the last decade, which have come from our improved understanding of the fundamental principles of pathology at cellular and molecular levels. Indeed the fields of immunity/inflammation, vascular and mucosal pathobiology, cell-cell communications, and microbiome/infectious diseases have undergone an unprecedented growth as we reinforce or challenge existing paradigms and discover new ones.

PISA 2017 is aimed at delivering attendees the most exciting and up-to-date concepts in pathogenesis and translational medicine. World acclaimed scientists will deliver lectures, while experienced members of the PISA Steering Committee will moderate discussion during these sessions to generate a cordial, collegial and contemporary environment for learning and networking. The major lectures will be interspersed with abstract-driven talks. Additionally, poster discussion sessions will be held on the mezzanine level and will build an intimate setting for intellectual exchange and constructive criticism, especially for trainees and junior faculty.

We hope you will take the opportunity to meet and discuss your science with your fellow attendees and invited speakers, not only during the poster-viewing sessions on Monday and Tuesday afternoons, but also in the networking lunch sessions on Monday and Tuesday, and the Gateway Clipper / Dinner / Awards Presentation on Monday evening.

### Abstracts

90% of the submitted abstracts (with an author index) are published in the October 2017 issue of T*he American Journal of Pathology (AJP*). Complimentary copies of the Journal will be distributed with your Meeting Book at registration on Monday morning. The seven abstracts whose authors opted out of publishing in AJP and four late-breaking abstracts are included as Supplemental Meeting Abstracts in the Meeting Book.

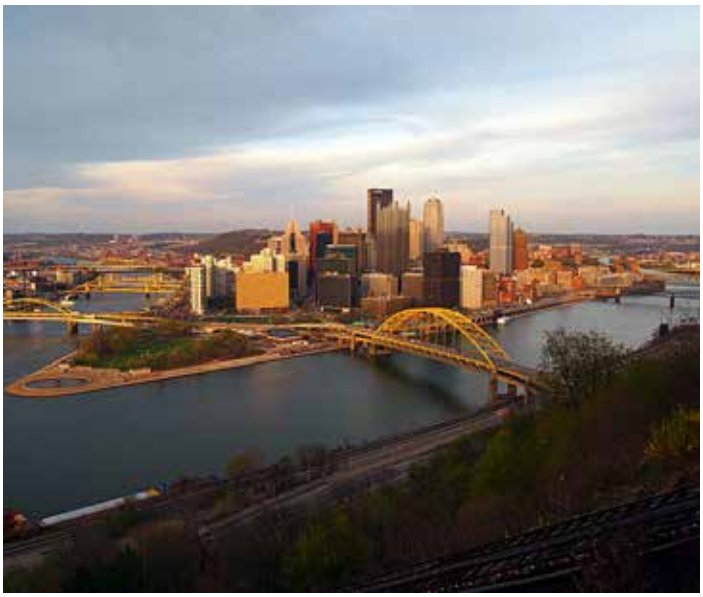
### Posters

For your convenience, the Meeting Book includes a comprehensive list of posters. The Monday afternoon poster session is immediately followed by the Gateway Clipper Cruise and Dinner. There is a wine and cheese reception during the Tuesday afternoon poster session. Posters are located on the mezzanine level based on topic category.

**Cancer** ..... Mezzanine Lobby
**Immunology and Inflammation** ..... Panther Room
**Infectious Diseases** ..... Forbes Room
**Kidney Pathobiology** ..... Shadyside Room
**Liver Pathobiology** ..... Oakland Room
**Neuropathology** ..... Forbes Room
**Pulmonary Pathobiology** ..... Shadyside Room
**Regenerative Medicine and Stem Cells** ..... Shadyside Room

### Gateway Clipper Dinner Cruise and Awards Presentation

Immediately following the Monday afternoon poster session, charter buses will pick you up at the Wyndham Pittsburgh University Center outside the hotel. Buses will leave at 5:15 PM. There will be a very brief ASIP business meeting and awards presentations during the dinner. After the cruise, charter buses will transport you back to the hotel at around 9:00 PM.



## Awards

**Junior Faculty and Trainee awardees must be present at the Gateway Clipper Cruise to accept their award or it will be forfeited.**

The following awards will be presented:

### Robbins Distinguished Educator Award

- Emanuel Rubin

### George K. Michalopoulos Junior Faculty Travel Awards

- Sonali Jindal
- S. Wesley Long

### Trainee Travel Awards:
### A. D. Sobel – ASIP Education Fund Scholar

- Zachary S. Wilson

### ASIP Trainee Travel Awards

- Sven Flemming
- Ronik Khachatoorian
- Brandon Lantino
- David J. Li
- Anny-Claude Luissint

### ICPI Trainee Travel Award

- Hanumantha Rao Madala

### Lawrence and Marion Muller Memorial Trainee Travel Award for Excellence in Neurodegeneration Research

- Shyanne Page

### Promoting Diversity in Science Trainee Travel Award

- Evan R. Delgado

### Rojkind-Monga Trainee Travel Award for Excellence in Liver Pathobiology Research

- Amanda M. Clark
- Eric K. Kwong

### Poster Awards

## Monday Networking Lunch

Lunch will be held in the Bridges Lounge on the main level of the hotel. If you requested and were assigned a one-on-one PathStar lunch "date", the PathStar tables are in the front.

## Tuesday Networking Lunch

Tuesday lunch will also be held in the Bridges Lounge. You have the option of attending and participating in the Lunch & Learn Workshop during this time.

## Lunch & Learn Workshop

***Science, Statistics, and Getting it Right: An Interactive Discussion of Common Problems***, presented by Dan A. Milner, Jr. (ASCP), will take place during the Tuesday lunch period in the Schenley Ballroom. The Lunch & Learn Workshop is co-sponsored by the ASIP Committee for Career Development & Diversity and the ASIP Education Committee. You must pre-register (complimentary registration) so that we can arrange to have sufficient lunches available. If you did not pre-register before the meeting, you may do so at the registration desk on Monday morning. If you are attending the Lunch and Learn Workshop, the buffet line will be outside the ballroom immediately after Session 5.

# Lunch & Learn: Science, Statistics and Getting it Right

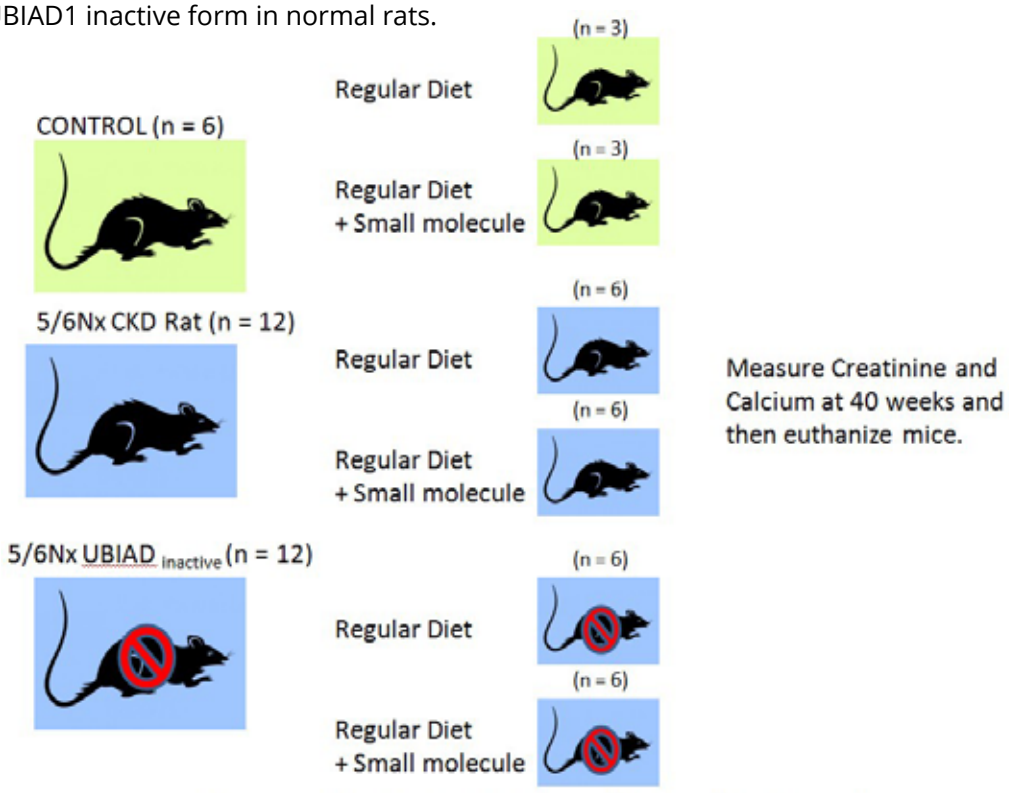
*A Workshop Sponsored by ASIP Committee for Career Development & Diversity and ASIP Education Committee*

**Dan A. Milner, Jr.**
American Society for Clinical Pathology, Chicago, IL

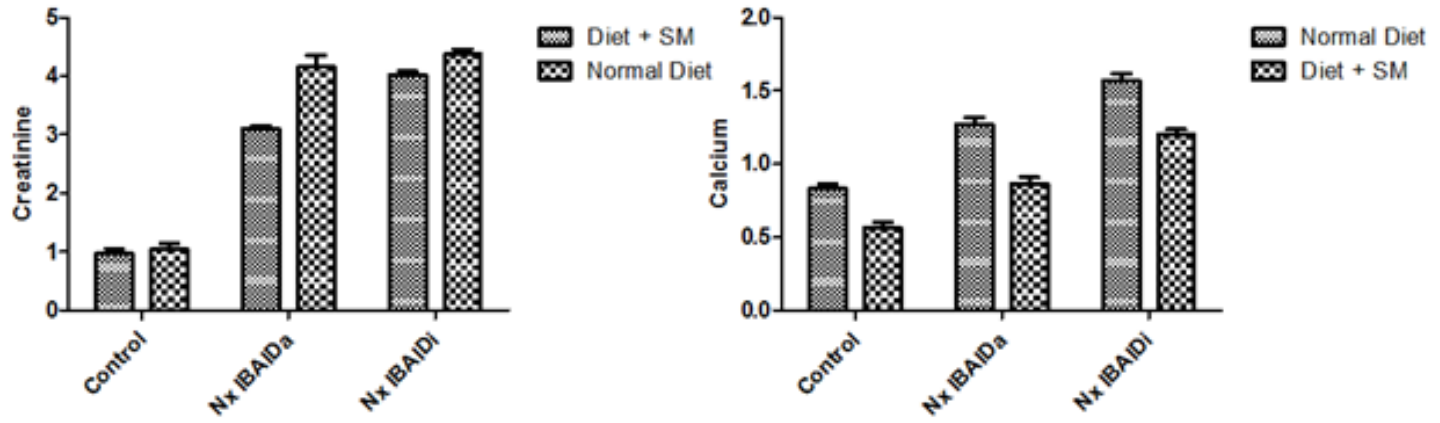
September 26, 2017 • 12:30 PM – 1:25 PM
*Vignettes Edited by Mark E. Sobel, MD, PhD, ASIP, Rockville, MD*

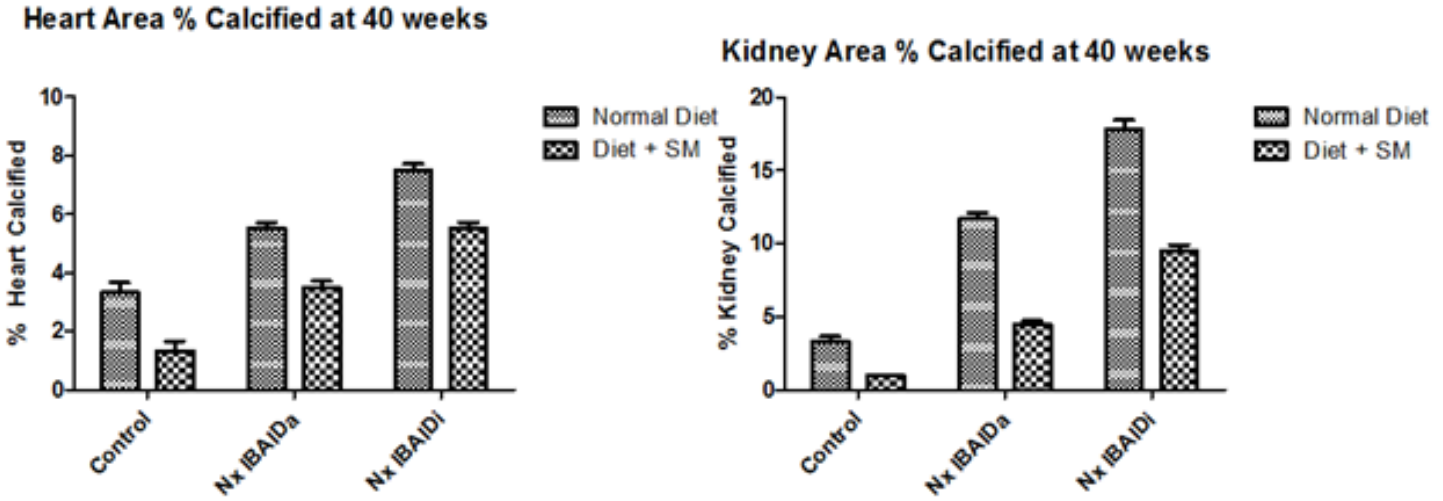
**Vignette 1**

A small molecule screening program using human endothelial cell lines that develop calcification in the presence of calcification-inducing media identifies a molecule that drastically reduces the process.
Interestingly, this molecule has extremely high oral bioavailability and is eliminated by direct excretion in the urine. The working biological hypothesis is that the molecule enhances the activity of UBIAD1 (an intracellular cholesterol regulator). Your laboratory has a working model of the 5/6Nx rat chronic kidney disease system and a collaborator happens to have a CRISPR/CAS9 tool to replace the UBIAD1 gene with an inactive form of the protein. In your system, the 5/6Nx rats develop chronic kidney disease including vascular calcifications and you monitor the disease using a peripheral blood measure of creatinine prior to euthanasia. In your collaborator's system, serum calcium is elevated in the UBIAD1 inactive form in normal rats.




You design an experiment to test the small molecule in your system as follows: At the end of 40 weeks, you measure the creatinine and calcium (see graph on the next page) of all of the rats and then sacrifice them. Using histology (H&E and Von Kassa stain) along with ImageJ (a free software program that allows you to do image based analyses, such as count cells or parse out a specific feature (nuclei, cytoplasm, etc) – download from http://imagej.nih.gov/ij/). You quantify the amount of calcification in the kidneys and the heart (see graph on the next page).




## Questions:

1. Are the differences in measurements of creatinine, calcium, and tissue calcification different between the groups? Which ones?

2. When approaching data such as this, a few questions need to be answered prior to beginning any analysis (and should best be thought of before designing the experiment!). These include the following:

    i. What kind of variables do I have?

    ii. What kind of statistical test(s) can I perform?

    iii. What kind of result am I looking for?

## Vignette 2

A group of 1175 healthy subjects (43% Caucasian, 33% African or African American, 24% Hispanic/Latino) were recruited from college campuses in the Boston area (from among 26 different colleges) and were asked to provide a buccal swab for DNA sequencing along with a detailed questionnaire regarding their family history and medical health as well as a tube of blood for laboratory testing. They also agreed to complete a follow up survey every 5 years for the next 25 years in order to look at new diagnoses and diseases. For each patient, an aliquot of blood as well as the buccal swab were both used to sequence each patient to 40X coverage as well as perform comparative genomic hybridization to a sequenced and assembled reference genome. All genomes were cataloged for mutations included insertions/deletions, single nucleotide polymorphisms, and gene duplication. The survey included questions about all of the following: diabetes, hypertension, malignancy (specifically of breast, lung, colon, prostate, kidney and/or brain), infections (including frequency and specifically for mononucleosis, ear infections, head colds, urinary tract infections, toenail infections, persistent/excessive acne), diet, and exercise habits. All of the subjects were counseled to use a free pedometer (provided by the study team) which was connected to the internet and report their daily activity, which was monitored by the study.

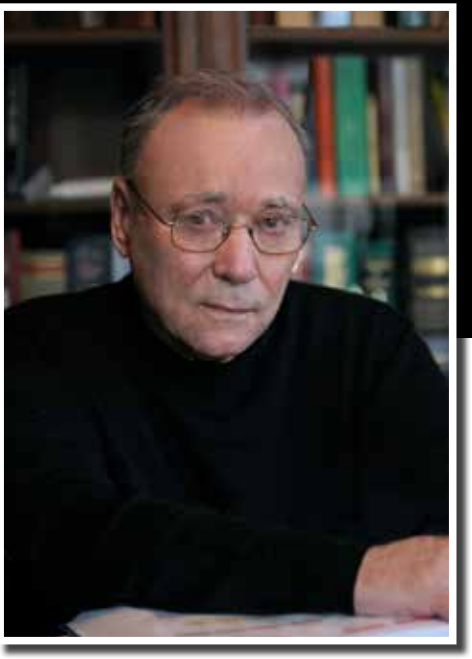
After 10 years (3 total surveys), a manuscript was published by a non-competing group in a mouse model showing that a specific mutation of pyruvate dehydrogenase kinase 4 (PDK4) caused a massive decrease in mouse activity as well as obesity in mice. You propose to look at the pedometer data of the study's subjects' activity to see if there is an association with fewer steps and mutations in PDK4. Your PI, however, thinks that such an association may be polygenetic (or even spurious in the mouse) and the entire genome should be examined in the context of all of the data.

### Questions:

1. How would you go about investigating any potential associations in your data set?
2. What statistical considerations are important in thinking about this question?
3. How should the pedometer data be parsed for the analysis?

American Society for Investigative Pathology

# 2018 Robbins Distinguished Educator Award



## Emanuel Rubin, MD

**Thomas Jefferson University Medical Center**

# Social Media Guide

*Whether you're new or experienced with Social Media, this guide has all you need to know!*
*Get ready to:*

- Follow other scientists
- Start tweeting about **#PISA2017**
- Share and retweet

## Get ready to be Social! The Official hashtag is:

# #PISA2017

## Which Social Media Should I Use and Why?

### Facebook

- Join the **Attending #PISA2017** group to continue the conversation before, during and after PISA
- Join a Scientific Interest Group:
  - Breast Cancer
  - Club Hepatomania Liver
  - Neuropathology
  - Vascular & Mucosal Pathobiology

### Instagram

Share photos of:

- Your Lab
- You and Colleagues at the conference
- Networking meals

### LinkedIn

- Connect with other attendees and mentors
- Share your **#PISA2017** experiences

### Twitter

- Build your brand recognition of your name, interest and expertise
- Connect with other colleagues and pathologists
- Share what you've learned during sessions

### YouTube

- Videos of you and your research
- How to Jumpstart your Pathology Career via Social Media

## Have a question while you're in a plenary session, but too shy to ask?

- If you have a question in a session, tweet your question with the hashtag #PISA2017.
- Please note that if time is limited, preference will be given to questions posed by raising your hand.

## Get Ready for our NEW Photo Booth

- Walk the ASIP Red Carpet and take your photos in the **photo booth** in the Pre-Function Hallway where you can share instantly!
- Don't forget you can also post live!
- **Please don't post any research or photos without permission.**

## Come visit the #PISA 2017 Photo Booth!

- Take your photo at the new #PISA2017 Photo Booth and instantly share with social media!


**Facebook**
**Instagram @ASIPath**
**LinkedIn**
**Snapchat**
**Twitter @ASIPath**
**YouTube**

# Step-by-Step Guide To Scientific and Networking Sessions

## Monday September 25

**7:00 AM – 7:40 AM**
Register / Pick Up your Badge, Display Your Poster
Pre-registrants can pick up their badges at Registration (Hotel Lobby) starting at 7:00 AM. You can also register on-site during this time. Put up your poster(s) during this time. Posters are assigned specific rooms on the mezzanine level based on topic category. (see page 3) All posters should be displayed by 7:45 AM. Breakfast is on your own so reserve some time to get a beverage and a bite to eat.

**Monday Morning**
**7:45 AM – 12:30 PM**
Plenary Sessions
The scientific sessions will be held in the Schenley Ballroom with a Welcome starting at 7:45 AM. The theme on Monday is Tissue Microenvironment and Organ Pathobiology. The first plenary session is Barbarians at the Gate: Building a Different Kind of Wall (Microbiome, Junctions, Injury, and Infections) and is chaired by Rick Mitchell and Kari Nejak-Bowen. Asma Nusrat, Alison Morris, Barbara Methé, and Timothy Hand are invited speakers. The selected short abstract-driven talk is #ID6 and will be presented by Ronik Khachatoorian.

The second plenary session of the morning is Inflammation, Resolution, and Wound Healing: Knitting the Raveled Sleeve of Care and is chaired by Rick Mitchell and Cecelia Yates. Edward Botchwey, Robert Schwabe, Carol Bostwick, and Cecelia Yates are invited speakers. The selected short abstract-driven talk is #IMIN18 and will be presented by Zachary Wilson.

**12:30 PM – 1:25 PM**
Networking Lunch
Lunch will be served in the Bridges Lounge (right of the hotel lobby). If you have requested a "lunch date" with a PathStar, the reserved tables are set up in the front of the room.

**Monday Afternoon**
**1:30 PM – 3:20 PM**
Plenary Session
Immediately after lunch, the third plenary session of the day, on Cancer-associated Stroma and Tumor Immunology: Dismantling the Environmental Protection, will be chaired by Paul Monga and Cecelia Yates. Dario Vignali, Hal Dvorak, and Hassane Zarour are invited speakers. The selected short abstract-driven talk is #L16 and will be presented by Yuhua Xue.

**3:30 PM – 5:00 PM**
Poster Viewing
View the posters and familiarize yourself with those posters you want to come back to on Tuesday. Posters are organized in different rooms on the second floor based on topic category. This is a great opportunity to exchange ideas, and develop collaborations!

**Monday Evening**
**5:15 PM – 9:00 PM**
Dinner Cruise and Awards Presentations
*But wait, there's more!*
Be outside the hotel (Lytton Avenue) by 5:15 PM for the Gateway Clipper Dinner and River Cruise. During the dinner, awards will be presented to:

- The Robbins Distinguished Educator Award
- Junior Faculty Travel Awardees
- Trainee Travel Awardees
- Poster Awardees

## Tuesday September 26

**Tuesday Morning**
**7:55 AM – 12:30 PM**
Plenary Sessions
Plenary session 4 closes out the theme of Tissue Microenvironment and Organ Pathobiology with a session on Premetastatic Niche and Regulation of Tumor Metastasis: Instituting a Travel Ban, chaired by Piyali Dasgupta and Paul Monga. Rama Khokha Theresa Whiteside, and Alan Wells are invited speakers. The selected short abstract-driven talks are #C15 and #C6 and will be presented by Nick Nolan and Diane Bielenberg, respectively.

Plenary session 5 introduces the second major theme of the conference: Combating Diseases through Improved Diagnostics and Therapeutics with a symposium on Cancer Epigenetics: Chromatin Landscape to Therapeutics, chaired by Phil Iannaccone and Bill Coleman. Qin Yan, James Herman, Sara Sukumar, and Hun-Way Hwang are invited speakers. The selected short abstract-driven talk is #C9, presented by Veronika Butin-Israeli.

**12:30 PM – 1:25 PM**
Lunch and Optional Lunch & Learn Workshop
Join us for lunch in Bridges Lounge. Or, if you have registered for the Lunch & Learn Workshop on Science, Statistics, and Getting it Right: An Interactive Discussion of Common Problems, pick up your lunch outside the plenary room and take a seat back in the Schenley Ballroom. Dr. Dan Milner will present two vignettes of statistical conundrums. We encourage you to read them in advance and think about answers to the questions. Dan will guide the audience to the answers to the questions and a comprehensive Lunch & Learn handout with explanations will be distributed to participants. This workshop is co-sponsored by the ASIP Committee for Career Development & Diversity and the ASIP Education Committee.

**Tuesday Afternoon**
**1:30 PM – 3:35 PM**
Plenary Session
The sixth plenary session on The Role of Biopsy in Precision Medicine: Making Diagnostics Great Again! will be chaired by Greg Tsongalis and Bill Coleman. Invited speakers are Helen Fernandes, Richard Schilsky, Greg Tsongalis, and Aatur Singhi. Sonali Jindal, one of the recipients of the George K. Michalopoulos Junior Faculty Travel Award, will present a short abstract-driven talk (#C10).

**Tuesday Afternoon**
**3:45 PM – 5:30 PM**
Poster Viewing / Wine & Cheese Reception
Posters are organized in different rooms on the second floor based on topic category. This is a great opportunity to exchange ideas, and develop collaborations!

***Dinner is on your own.***

## Wednesday September 27

**Wednesday Morning**
**7:55 AM – 12:30 PM**
Plenary Session
We continue with the theme of Combating Diseases through Improved Diagnostics and Therapeutics with the seventh plenary session on Diagnostic Imaging Modalities: Incredible and Hugely Amazing, chaired by Stan Cohen and Cecelia Yates. Tom Fuchs, Junjie Yao, Yukako Yagi and Prithu Sundd are invited speakers.

The final plenary session of the conference is on Signaling and Therapeutics: Targeting the Bad Hombres, chaired by Bill Coleman and Paul Monga. Brian Lehmann, Marc Abrams, Malabika Sen, and Kari Nejak-Bowen are invited speakers. Hanumantha Rao Madala will present a short abstract-driven talk (#C26).

***Boxed lunches are available to participants to facilitate your departure.***

# PISA 2017 Program

## Monday September 25

7:00 AM - 7:40 AM
***Registration (Hotel Lobby)***

7:45 AM - 7:55 AM
***Welcome***
**Satdarshan Paul S. Monga**, University of Pittsburgh and **Mark E. Sobel**, ASIP

## Session 1

### Barbarians at the Gate: Building a Different Kind of Wall (Microbiome, Junctions, Injury and Infections)

Chairs: **Richard Mitchell,** Brigham & Women's Hospital and **Kari Nejak-Bowen**, University of Pittsburgh

7:55 AM - 8:00 AM
***Introduction***
Kari Nejak-Bowen
University of Pittsburgh

8:00 AM - 8:30 AM
*Plasticity of the Mucosal Barrier: Insights into Regulation of Epithelial Repair*
Asma Nusrat
University of Michigan

8:30 AM - 9:00 AM
*Oral Microbiome and Pulmonary Hypertension*
Alison Morris
University of Pittsburgh

9:00 AM - 9:30 AM
*Pulmonary Microbiome and Lung Diseases*
Barbara Methé
University of Pittsburgh

9:30 AM - 9:45 AM
*Maternal Antibodies, the Neonatal Microbiota, and Necrotizing Enterocolitis*
Timothy Hand
University of Pittsburgh

9:45 AM - 10:00 AM
**Abstract-Driven Talk (ID6)**
*A Potential Broad Spectrum Host-Targeting Antiviral Peptide Blocks Zkia Virus Infection*
Ronik Khachatoorian
University of California, Los Angeles

10:00 AM - 10:25 AM
***Coffee Break***

## Session 2

### Inflammation, Resolution, and Wound Healing: Knitting the Raveled Sleeve of Care

Chairs: **Richard Mitchell**, Brigham & Women's Hospital and **Cecelia Yates**
University of Pittsburgh

10:25 AM - 10:30 AM
***Introduction***
Richard Mitchell
Brigham & Women's Hospital

10:30 AM - 11:00 AM
*Biomaterials and their Grudging Acceptance by the Host*
Edward Botchwey
Georgia Institute of Technology

11:00 AM - 11:30 AM
*How Injury Promotes Fibrosis and Cancer Development in the Liver*
Robert Schwabe
Columbia University

11:30 AM - 12:00 PM
*Autoimmune Lung Fibrosis and Skin*
Carol Bostwick
Medical University of South Carolina

12:00 PM - 12:15 PM
*More than Skin Deep: Understanding the Variables in Cutaneous Wound Healing*
Cecelia Yates
University of Pittsburgh

12:15 PM - 2:30 PM
Abstract-Driven Talk: (IMIN18)
*The Role of Vinculin In Neutrophil ß2 Integrin Adhesion and Motility*
Zachary S. Wilson
Brown University

12:30 PM - 1:25 PM
***Lunch*** (Bridges Lounge)

## Session 3

### Cancer-associated Stroma and Tumor Immunology: Dismantling the Environmental Protection

Chairs: **Satdarshan Paul S. Monga**, University of Pittsburgh and **Cecelia Yates,** University of Pittsburgh

1:30 PM - 1:35 PM
***Introduction***
Cecelia Yates
University of Pittsburgh

1:35 PM - 2:05 PM
*Regulatory T Cells*
Dario Vignali
University of Pittsburgh

2:05 PM - 2:35 PM
*Tumor Microenvironment*
Harold Dvorak
Beth Israel Deaconess Medical Center, Harvard Medical School

2:35 PM - 3:05 PM
*Next Target for Immune Checkpoint Blockade in Cancer*
Hassane Zarour
University of Pittsburgh

3:05 PM - 3:20 PM
**Abstract-Driven Talk: (L16)**
*Glypican-3 and CD81 Promote Development of Hepatocellular Carcinomas and Hepatoblastoma in Normal Hepatocytes and Liver Stem Cells through Negative Selection*
Yuhua Xue
University of Pittsburgh

## Posters

3:30 PM - 5:00 PM .....
View the Posters (Mezzanine Level)
**Cancer** ..... Mezzanine Lobby
**Immunology and Inflammation**..... Panther Room
**Infectious Diseases**..... Forbes Room
**Kidney Pathobiology** ..... Shadyside Room
**Liver Pathobiology**..... Oakland Room
**Neuropathology**..... Forbes Room
**Pulmonary Pathobiology**..... Shadyside Room
**Regenerative Medicine and Stem Cells**..... Shadyside Room

## ASIP Awards Presentation and Business Meeting

5:15 PM - 9:00 PM
**Gateway Clipper Dinner and Cruise**

# Tuesday, September 26

## Session 4

### Premetastatic Niche and Regulation of Tumor Metastasis: Instituting a Travel Ban

Chairs: **Piyali Dasgupta**, Marshall University and **Satdarshan Paul S. Monga**, University of Pittsburgh

7:55 AM - 8:00 AM
***Introduction***
Piyali Dasgupta
Marshall University

8:00 AM - 8:30 AM
*Exosomes and Microenvironment*
Rama Khokha
University of Toronto

8:30 AM - 9:00 AM
*Exosomes in Tumor Progression and Treatment*
Theresa Whiteside
University of Pittsburgh

9:00 AM - 9:30 AM
*Tumorigenesis, Metastasis, Wound Healing, Vascular Modeling - Liver (Organs) on Chip*
Alan Wells
University of Pittsburgh

9:30 AM - 9:45 AM
**Abstract-Driven Talk: (C15)**
*Anti-Metastatic Activity of Capsaicin in Human Lung Adenocarcinoma*
Nicholas A. Nolan
Joan C. Edwards School of Medicine

9:45 AM - 10:00 AM
**Abstract-Driven Talk: (C6)**
*Targeting Neuropilin-2 Prevents Pancreatic Ductal Adenocarcinoma Progression*
Diane R. Bielenberg
Harvard Medical School, Boston Children's Hospital

10:00 AM - 10:25 AM
***Coffee Break***

## Session 5

### Cancer Epigenetics: Chromatin Landscape to Therapeutics

Chairs: **Philip Iannaccone**, Northwestern University and **William B. Coleman**, University of North Carolina at Chapel Hill

10:25 AM - 10:30 AM
***Introduction***
Philip Iannaccone
Northwestern University

10:30 AM - 11:00 AM
*Histone Modifications in Cancer and Therapeutic Targeting of Histone Modifying Enzymes*
Qin Yan
Yale University

11:00 AM - 11:30 AM
*The Cancer Methylome - Driver of Cancer Development and Target for Cancer Therapy*
James Herman
University of Pittsburgh

11:30 AM - 12:00 PM
*Targeting the Epigenome in Cancer Therapeutics*
Sara Sukumar
Johns Hopkins University

12:00 PM - 12:15 PM
*Decode mRNA Alternative Polyadenylation and Discover New Biology with cTag-PAPERCLIP*
Hun-Way Hwang
University of Pittsburgh

12:15 PM - 12:30 PM
**Abstract-Driven Talk: (C9)**
*Role of Polymorphonuclear Leukocytes in Inhibition of DNA Repair and Induction of Genomic Instability*
Veronika Butin-Israeli
Northwestern University

12:30 PM - 1:25 PM
***Lunch (Bridges Lounge)***

12:30 PM - 1:25 PM
***Lunch & Learn Workshop* (Schenley Ballroom)**
***pre-registration required***
*Science, Statistics, and Getting it Right: An Interactive Discussion of Common Problems*
*Sponsored by the ASIP Committee for Career Development and Diversity and the ASIP Education Committee*
Dan A. Milner, Jr.
American Society for Clinical Pathology

## Session 6

### The Role of Biopsy in Precision Medicine: Making Diagnostics Great Again!

Chairs: **Gregory Tsongalis,** Dartmouth-Hitchcock Medical Center and **William B. Coleman**, University of North Carolina at Chapel Hill

1:30 PM - 1:35 PM
***Introduction***
Gregory Tsongalis
Dartmouth-Hitchcock Medical Center

1:35 PM - 2:05 PM
*Adequacy of Cytology Specimens: FNA's and Smears for Interrogation of Genomic Variants*
Helen Fernandes
Columbia University Medical Center

2:05 - 2:35 PM
*The ASO TAPUR Trial: A Molecular Driven Approach to Targeted Therapy*
Richard L. Schilsky
University of Chicago

2:35 - 3:00 PM
*Cancer Genomics in the Era of Next-Generation Sequencing*
Gregory Tsongalis
Dartmouth-Hitchcock Medical Center

3:00 PM - 3:15 PM
*Pancreatic Cancer*
Aatur Singhi
University of Pittsburgh

3:15 PM - 3:30 PM
**Abstract-Driven Talk: (C10)**
*Multiplexed Analysis of Myoepithelial and Immune Cell Biomarkers to Predict Progression of Ductal Carcinoma In Situ*
Sonali Jindal
Oregon Health & Science University

## Posters and Wine & Cheese Reception

3:45 PM - 5:30 PM
View the Posters (Mezzanine Level)
**Cancer** ..... Mezzanine Lobby
**Immunology and Inflammation** ..... Panther Room
**Infectious Diseases** ..... Forbes Room
**Kidney Pathobiology** ..... Shadyside Room
**Liver Pathobiology** ..... Oakland Room
**Neuropathology** ..... Forbes Room
**Pulmonary Pathobiology** ..... Shadyside Room
**Regenerative Medicine and Stem Cells** ..... Shadyside Room

# Wednesday September 27

## Session 7

### Diagnostic Imaging Modalities: Incredible and Hugely Amazing

Chairs: **Stanley Cohen**, Rutgers-NJMS and **Cecelia Yates**, University of Pittsburgh

7:55 AM - 8:10 AM
***Introduction***
Stanley Cohen
Rutgers - NJMS

8:10 AM - 8:40 AM
*The Silicon Assistant: Artificial Intelligence and Image Interpretation*
Thomas Fuchs
Memorial Sloan Kettering Cancer Center

8:40 AM - 9:10 AM
*Breaking the Limits in Photoacoustic Imaging*
Junjie Yao
Duke University

9:10 AM - 9:40 AM
*Translational Research in the Digital Dome*
Yukako Yagi
Memorial Sloan Kettering Cancer Center

9:40 AM - 9:55 AM
*In Vivo and Ex Vivo Imaging Reveals a Role for Platelet Inflammasome in Sickle Cell Disease*
Prithu Sundd
University of Pittsburgh

9:55 AM - 10:25 AM
***Coffee Break***

## Session 8

### Signaling and Therapeutics: Targeting the Bad Hombres

Chairs: **William B. Coleman**, University of North Carolina at Chapel Hill and **Satdarshan Paul S. Monga,** University of Pittsburgh

10:25 AM - 10:30 AM
***Introduction***
William B. Coleman
University of North Carolina at Chapel Hill

10:30 AM - 11:00 AM
*New Approaches to Therapy in Triple-Negative Breast Cancer*
Brian Lehmann
Vanderbilt University

11:00 AM - 11:30 AM
*Targeting β-catenin for Cancer*
Marc Abrams
Dicerna Pharmaceuticals

11:30 AM - 12:00 PM
*Lung Cancer Epigenetics and Therapeutics*
Malabika Sen
University of Pittsburgh

12:00 PM - 12:15 PM
*β-catenin Modulation in Cholestatic Liver Disease*
Kari Nejak-Bowen
University of Pittsburgh

12:15 PM - 12:30 PM
**Abstract-Driven Talk: (C26)**
*Synthesis of a Novel Non-Diuretic, Brain-Penetrating, Ethacrynic Acid Analog and Demonstration of its Potent Efficacy in Orthotopic Glioblastoma Models*
Hanumantha Rao Madala
Texas Tech University Health Sciences Center

12:30 PM
***Farewell (Boxed Lunches Available for Pickup)***

**Please complete a meeting evaluation survey.**
https://www.surveymonkey.com/r/9S3PGPL

# Meeting Abstracts Supplement

Abstracts for PISA 2017 were reviewed by the American Society for Investigative Pathology PISA 2017 Steering Committee.

The *American Journal of Pathology* was not involved in the peer review process.

## Table of Contents

Supplemental Abstracts



The following submitted and accepted abstracts opted out of publication in *The American Journal of Pathology*: ID2, ID4, ID7, L5, L12, L29, R2.

The following abstracts were submitted as late-breaking and were therefore not included in *The American Journal of Pathology*: C27, C28, P1, P2.

## CANCER

**C27 Synchronous Inverted Papilloma and Recurrent Respiratory Papillomatosis**

*J.D. Oliver, N.S. Patel, D.C. Ekbom, J.K. Stokken*
*Mayo Clinic, Rochester, Minnesota, USA*

**Introduction:** Recurrent respiratory papillomatosis is a chronic disease of viral origin affecting the larynx, trachea, and lower airways. Inverted papilloma, most commonly originating from the lateral nasal wall, is typically a single, expansile, locally aggressive tumor that remodels bone around the site of origin. Although single, exophytic papillomata in the nasal vestibule are fairly common, diffuse intranasal papillomatosis has only been reported in cases without coexistent recurrent respiratory papillomatosis. **Case Summary:** We report a case of histopathologically proven inverted papilloma occurring in a patient with recurrent respiratory papillomatosis affecting the nasal cavity, larynx, and trachea. This constitutes the first report of nasal involvement in recurrent respiratory papillomatosis. Viral *in situ* hybridization studies demonstrated evidence of human papilloma virus (HPV) in both the septum and middle turbinate subsites. Repeat nasal excision with margin analysis is planned. **Discussion:** This report emphasizes the importance of considering a broad differential diagnosis in patients with papillomata, and obtaining comprehensive histopathologic evaluation of lesions in multiple subsites in order to rule out inverted papilloma or overt malignant transformation, particularly if high-risk HPV subtypes are identified. The proposed pathogenesis of HPV in inverted papilloma lesions remains controversial in the literature, and is less-known currently than the mechanism of HPV driving the transformation of inverted papilloma to squamous cell carcinoma. Our case provides support to the theory of HPV involvement in the pathogenesis of both inverted papilloma and recurrent respiratory papillomatosis lesions.

**C28 Early Actions of Anti-VEGF/VEGFR Drugs on Angiogenic Blood Vessels**

*H.F. Dvorak[1], B. Sitohy[2], S. Chang[3], T.E. Sciuto1, E. Masse[1], M. Shen, P.M. Kang[1], S. Jaminet[1], L.E. Benjamin[4], R.S. Bhatt[1], A.M. Dvorak[1], J.A. Nagy[1]*
*[1]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA; [2]Umeå University, Umea, Sweden; [3]Weill Cornell Medical College, New York, New York USA; [4]KathadinRx, Inc, Bangor, Maine, USA*

Tumors induce their heterogeneous vasculature by secreting vascular endothelial growth factor (VEGF)-A. Anti-VEGF/VEGF receptor (VEGFR) drugs are helpful in treating cancer but their mechanisms of action are poorly understood. An adenovirus expressing VEGF-A (Ad-VEGF-A164) replicates the tumor vasculature in mice absent tumor cells. Mother vessels (MV) are the first angiogenic vessel type to form in tumors and following Ad-VEGF-A164. Multi-day treatments with a VEGF trap reverted MV back to normal microvessels. We now show that, within hours, a single dose of several anti-VEGF drugs collapsed MV to form glomeruloid microvascular proliferations (GMP), accompanied by only modest endothelial cell death. GMP, common in many human cancers but of uncertain origin, served as an intermediary step in MV reversion to normal microvessels. The vasodisruptive drug combretastatin CA4 also targeted MV selectively, but acted differently, extensively killing MV endothelium. Anti-vascular changes were quantified with a novel Evans blue dye assay that measured vascular volumes. As in tumors, Ad-VEGF-A164 strikingly increased eNOS expression. The eNOS inhibitor L-NAME mimicked anti-VEGF/VEGFR drugs, rapidly collapsing MV to GMP. Inhibition of eNOS reduces synthesis of its vasodilatory product, nitric oxide, leading to arterial contraction. Patients and mice receiving anti-VEGF/VEGFR drugs develop hypertension, reflecting systemic arterial contraction. Taken together, anti-VEGF/VEGFR drugs act in part by inhibiting eNOS, causing vasocontraction, MV collapse to GMP, and subsequent reversion of GMP to normal microvessels, all without extensive vascular killing.

## INFECTIOUS DISEASES

**ID2 Whole-Genome Sequencing of Human Clinical *Klebsiella pneumoniae* Isolates Discovers Misidentification and Misunderstandings of *K. pneumoniae, K. variicola,* and *K. quasipneumoniae***

*R.J. Olsen[1], S.E. Linson[1], M. Ojeda-Saveedra[1], C. Cantu[1], J.J. Davis[2], T. Brettin[2], J.M. Musser[1], S.W. Long[1]*
*[1]Houston Methodist Research Institute, Houston, Texas, USA; [2]Argonne National Laboratory, Argonne, Illinois, USA*

*Klebsiella pneumoniae* is a major cause of human morbidity and mortality worldwide. The emergence of highly drug resistant strains is particularly concerning for public health. *K. pneumoniae* isolates are generally classified in three distinct phylogenetic groups: *K. pneumoniae*, *K. variicola,* and *K. quasipneumoniae*. *K. variicola* and *K. quasipneumoniae* have often been described as opportunistic pathogens that are less virulent to humans than *K. pneumoniae*. We recently sequenced the genomes of 1,777 extended-spectrum beta-lactamase (ESBL)-producing *K. pneumoniae* isolates recovered from patients with infections in our health care system and discovered that 28 strains were phylogenetically related to *K. variicola* and *K. quasipneumoniae*, and one strain is from a novel *Klebsiella* species. Whole genome sequencing of 96 non-ESBL producing *K. pneumoniae* isolates found 12 additional *K. quasipneumoniae* strains. MALDI-TOF analysis identified all patient isolates as *K. pneumoniae*, suggesting a potential pitfall in conventional clinical microbiology laboratory identification methods. Whole-genome sequence analysis revealed extensive sharing of core gene content and plasmid replicons among the *Klebsiella* species. Unexpectedly, for the first time, one *K. variicola* strain was found to carry a plasmid with the New Delhi Metallo-beta-lactamase-1 (NDM-1) gene. We also discovered evidence of homologous recombination in one *K. variicola* strain. Review of clinical data revealed that infections caused by *K. variicola* and *K. quasipneumoniae*, although less frequent, were as severe as infections caused *K. pneumoniae*. Taken together, these data challenge our current understanding of the inter-relationships between the phylogenetic groups of *K. pneumoniae*.

**ID4 Andrographolide, a Diterpenoid Lactone, Induces Oxidative Stress Leading to Death in *Trypanosoma brucei***

*M. Banerjee[1], S. Chattopadhyay[2], S.K. Mukherjee[1]*
*[1]University of Kalyani, Kalyani, India; [2]TCG Life Sciences Ltd, Kolkata, India*

African sleeping sickness is a parasitic disease in humans and livestock caused by *Trypanosoma brucei* throughout sub-Saharan Africa. Absence of appropriate vaccines and prevalence of drug resistance proclaim that a new way of therapeutic interventions is essential against African trypanosomiasis. In the present study, we have looked into the effect of andrographolide, a diterpenoid lactone from *Andrographis paiculata*, on *T. brucei* PRA 380. Although andrographolide has been recognized as a promising anti-cancer drug, its usefulness against *Trypanosoma* spp remained unexplored. It showed promising anti-trypanosomal activity with an $IC_{50}$ value of 8.3 μM assessed through SYBR Green cell viability assay and also showed no cytotoxicity towards normal murine macrophages. Cell cycle analysis revealed that andrographolide could induce sub-$G_0/G_1$ phase arrest. Flow cytometric analysis also revealed that incubation with andrographolide caused exposure of phosphatidyl serine to the outer leaflet of plasma membrane in *T. brucei* PCF. This event was preceded by andrographolide-induced depolarization of mitochondrial membrane potential ($\Delta\psi m$) and elevation of cytosolic calcium. Andrographolide also caused elevation of intracellular reactive oxygen species (ROS) as well as lipid peroxidation level, and depletion in reduced thiol levels. Taken together, these data indicate that andrographolide has promising antitrypanosomal activity mediated by promoting oxidative stress and depolarizing the mitochondrial membrane potential and thereby triggering an apoptosis-like programmed cell death. Therefore, this study merits further investigation for the therapeutic possibility of using andrographolide for the treatment of African trypanosomiasis.

**ID7 Population Genomic Analysis of 1,872 Extended-Spectrum β-Lactamase–Producing *Klebsiella Pneumoniae* Isolates, Houston, TX: Unexpected and Continued Abundance of Clonal Group 307**

*S.W. Long[1], R.J. Olsen[1], T.N. Eagar[1], S.B. Beres[1], P. Zhao[1], J.J. Davis[2], T. Brettin[2], F. Xia[2], J.M. Musser[1]*
*[1]Houston Methodist Hospital, Houston, Texas, USA; [2]Argonne National Laboratory, Argonne, Illinois, USA*

*Klebsiella pneumoniae* is a major human pathogen responsible for high morbidity and mortality rates. The emergence and spread of strains resistant to multiple antimicrobial agents and documented large nosocomial outbreaks are especially concerning. To develop new therapeutic strategies for *K. pneumoniae*, it is imperative to understand the population genomic structure of strains causing human infections. To address this knowledge gap, we sequenced the genomes of 1,777 extended-spectrum β-lactamase–producing *K. pneumoniae* strains cultured from patients in the 2,000-bed Houston Methodist Hospital system between September 2011 and May 2015, representing a comprehensive, population-based strain sample. Strains of largely uncharacterized clonal group 307 (CG307) caused more infections than those of well-studied epidemic CG258. To confirm the persistence of the predominant clonal group, CG307, we sequenced an additional 95 ESBL *K. pneumoniae* strains from 2017. We confirmed that the CG307 and CG258 are still the predominant clonal groups; however, new clonal groups may be emerging. Strains varied markedly in gene content and had an extensive array of small and very large plasmids, often containing antimicrobial resistance genes. Some patients with multiple strains cultured over time were infected with genetically distinct clones. We identified 15 strains expressing the New Delhi metallo-β-lactamase 1 (NDM-1) enzyme that confers broad resistance to nearly all beta-lactam antibiotics. Transcriptome sequencing analysis of 10 phylogenetically diverse strains showed that the global transcriptome of each strain was unique and highly variable. Experimental mouse infection provided new information about immunological parameters of host-pathogen interaction. We exploited the large data set to develop whole-genome sequence-based classifiers that accurately predict clinical antimicrobial resistance for 12 of the 16 antibiotics tested. We conclude that analysis of large, comprehensive, population-based strain samples can assist understanding of the molecular diversity of these organisms and contribute to enhanced translational research.

## LIVER PATHOBIOLOGY

**L5 Mechanisms of Interactions Between mTOR and Wnt-β catenin in Liver Pathogenesis**

*A.O. Michael, J. Russell, T. Pradhan-Sundd, S.P. Monga*
*University of Pittsburgh, Pittsburgh, Pennsylvania, USA*

The liver performs critical functions indispensable to survival. These functions are performed by hepatocytes and are governed by signaling pathways. The most critical pathways are those involved in cell growth, proliferation, and metabolism. These outputs in a normal liver ensure cellular energy balance, but become aberrant in a diseased liver, such as hepatocellular carcinoma (HCC), which is the fifth leading cause of cancer-related deaths worldwide. In many cases, HCC occurs within an established background of chronic liver disease and cirrhosis; an aftermath of prolonged cycles of inflammation, necrosis, and hepatocyte regeneration in the liver. This step-wise injury progression from chronic hepatitis to cirrhosis often leads to chromosomal damage, mutations and eventually, hepatic carcinogenesis. Two pathways of interest in liver pathophysiology are the mechanistic target of rapamycin (mTOR) and the Wnt/β-catenin signaling. We investigated the interactions between mTOR and β-catenin signaling in normal liver physiology as well as in a clinically relevant HCC model. Preliminary studies have established a mouse model that mirrors human HCC through co-expression of point-mutant β-catenin and hMet. Based on these observations, our central hypothesis is that mTOR is regulated by β-catenin signaling in hepatic physiology in pericentral hepatocytes and in hepatic pathology to contribute to HCC development. We used LRP5/6, albumin-CRE knock out mice and human HCC Hep3B cells. Knocking out β-catenin inhibited phosphorylation of mTOR. In addition, downstream targets of mTOR, such as ribosomal protein S6 and 4E-BP1 were also affected. These studies provide evidence on the interactions between mTOR signaling and Wnt/β-catenin signaling pathways, with the potential to identify anti-mTOR/Wnt novel candidate chemopreventive targets, and provide information on the efficacy of these targets for clinical development.

**L12 Lack of β-catenin in Hepatocytes Impairs Proliferation and Promotes Liver Progenitor Cell–Mediated Repair in Response to Hepatic Injury**

*J. Russell[1], H. Okabe[2], M. Poddar[1], S. Singh[1], M. Abrams[3], K. Nejak-Bowen[1], S.P. Monga[1]*
*[1]University of Pittsburgh, Pittsburgh, Pennsylvania, USA; [2]Kumamoto University, Kumamoto, Japan; [3]Dicerna Pharmaceuticals, Boston, Massachusetts, USA*

Liver regeneration is normally mediated by hepatocyte proliferation. If hepatocyte proliferation is impaired, biliary epithelial cell (BEC)-derived liver progenitor cells (LPCs) are activated and mediate regeneration by differentiating into hepatocytes. The choline-deficient ethionine-supplemented (CDE) diet model of liver injury is known to induce proliferation of LPCs, but does not block hepatocyte proliferation. β-catenin signaling plays an important role in liver regeneration by promoting hepatocyte proliferation. Therefore, we hypothesized that β-catenin loss in hepatocytes would impair hepatocyte proliferation and lead to BEC-derived LPC-mediated hepatic repair in the CDE diet model. We performed genetic fate tracing in mice by utilizing adeno-associated virus serotype 8 carrying thyroid binding globulin–driven Cre (AAV8-TBG-Cre) to simultaneously delete β-catenin and permanently label hepatocytes with EYFP (KO2 mice). Importantly, in this model BECs contain β-catenin and do not express EYFP. After two weeks of CDE diet, KO2 mice displayed increased liver injury and a lack of hepatocyte proliferation compared to β-catenin WT littermates. Finally, in KO2 mice allowed two weeks recovery on normal diet after CDE diet, we detected clusters of hepatocytes which expressed β-catenin and did not express EYFP, indicating that they originated from the BEC compartment. We did not observe expansion of EYFP-negative hepatocytes in control mice where hepatocytes retained β-catenin expression. Furthermore, we performed positive lineage tracing using a BEC/LPC marker-driven Cre recombinase to label BECs/LPCs with EYFP. In these mice we utilized GalXC-*CTNNB1*, a drug containing anti-β-catenin small interfering RNA (siRNA) conjugated to a hepatocyte-targeting ligand, to knockdown expression of β-catenin specifically in hepatocytes (KO3 mice). KO3 mice on CDE diet followed by recovery showed clusters of EYFP-positive hepatocytes, indicating BEC/LPC differentiation to hepatocytes. Thus, our results support the hypothesis that LPCs mediate liver regeneration when hepatocyte proliferation is impaired.

**L29 Prohibitin1 Acts as a Negative Regulator of Wnt-β Catenin Signaling in Murine Liver and Human Hepatocellular Carcinoma Cells**

*N. Mavila, Y. Tang, J. Berlind, K. Ramani, S. Lu*
*Cedars Sinai Medical Center, Los Angeles, California, USA*

**Background:** Prohibitin1 (PHB1) is a mitochondrial chaperone protein with multiple functions. Liver specific PHB1 knock out (Phb1KO) mice develop severe liver injury and hepatocellular carcinoma (HCC). PHB1 has been shown to regulate cell proliferation partly via down-regulation of cMyc and cCyclinD1 transcription. The objective of this work is to determine the molecular mechanism by which PHB1 down-regulates cell cycle regulatory genes and cell proliferation. Our hypothesis is that PHB1 suppresses Wnt-β catenin signaling and acts as a negative regulator of cell proliferation in liver and HCC. **Methods:** PHB1 and Wnt mRNA levels were quantified by real-time PCR. PHB1, GSK3β, AKT protein levels were quantified by Western blotting. Wnt localization was determined by immunofluorescence staining of Phb1KO liver tissue sections. PHB1 depletion *in vitro* in HepG2 cells was performed by RNA interference. *In vitro* T-cell factor (TCF) promoter activity was measured by TOP FLASH reporter assay. **Results:** Phb1KO livers expressed increased levels of WNT7a, WNT10a, and WNT16 mRNAs compared to Flox littermates. Immunofluorescence staining revealed increased expression of WNT7a and WNT10a in

hepatocytes and non-parenchymal cells in Phb1 KO livers compared to Flox controls. Western blot analysis of whole liver extracts from Phb1KO livers showed downstream activation of Wnt signaling as determined by increased phosphorylation of phosphoSer9-glycogen synthase kinase3β and phosphoSer473-AKT. *PHB1* gene silencing in HepG2 cells resulted in ~2-fold activation of TCF promoter activity whereas its overexpression suppressed the same *in vitro*. *In vitro* pharmacological inhibitor studies have demonstrated that in HepG2 cells PHB1 regulates Wnt signaling in part via P13K and PP2A pathways. **Conclusion:** PHB1 acts as a negative regulator of cell proliferation via transcriptional repression of WNT ligands and its downstream activation in murine liver and human HCC cells.

## PULMONARY PATHOLOGY

**P1 FBXO17 Regulates Lung Epithelial Cell Proliferation by Targeting Glycogen Synthase Kinase-3β for Proteasomal Degradation**

*T.L. Suber, I. Nikolli, R. Mallampalli, J. Zhao, Y. Zhao*
*University of Pittsburgh, Pittsburgh, Pennsylvania, USA*

Glycogen synthase kinase-3β (GSK3β) is a highly conserved serine-threonine kinase that is a critical regulator of cell differentiation, metabolism, development, and inflammation. GSK3β-mediated phosphorylation is a key step in targeting substrates of Skp1/Cul1/F-box protein (SCF) E3 ubiquitin ligases to the proteasome for degradation. We recently identified FBXO17 as a novel F-box protein that targets GSK3β for polyubiquitination and proteasomal degradation in lung epithelial cells. In the current study, we explored the mechanism of FBXO17 binding to GSK3β and the effects on epithelial cell survival and proliferation. Through the generation of multiple deletion mutant constructs and co-immunoprecipitation assays, we identified a 50-amino acid region in FBXO17 that was required for association with GSK3β. We then asked whether FBXO17 differentiated between active and inactive forms of GSK3β using S9A mutant (constitutively active) and K85A mutant (dominant-negative) plasmids. Cells were treated with cyclohexamide and lysates were collected at 0, 2, 4, and 8 h. While there were no significant differences between wild-type and constitutively active S9A GSK3β stability, the K85A mutant was less stable, highly polyubiquitinated, and appeared to be more sensitive to FBXO17-mediated degradation. Finally, we explored whether FBXO17 has a role in cell proliferation through regulation of GSK3β stability. Using A549 cells, we transfected plasmids expressing histidine (V5)-tagged FBXO17. We observed increased cell proliferation using a bromodeoxyuridine (BrdU) colorimetric plate assay. However, expression of mutant FBXO17 without the F-box motif does not increase proliferation, suggesting that FBXO17 targeting of GSK3β, and likely other proteins, is required for these downstream effects. Our preliminary data raise additional questions about the role of FBXO17 in epithelial cell proliferation and repair.

**P2 Novel Role of Axl Kinase in Endothelial Cell Proliferation and Pulmonary Arterial Hypertension**

*A. Gorelova, S. Sahoo, P. Pagano*
*University of Pittsburgh, Pittsburgh, Pennsylvania, USA*

Pulmonary arterial hypertension (PAH) is a disease of unclear etiology culminating in right ventricle (RV) failure and death. Recent advances in the study of PAH suggest that lung endothelial cell proliferation instigates vascular remodeling and increases in RV pressures. We postulated that Axl receptor tyrosine kinase mediates endothelial proliferation and hemodynamic changes in PAH. Immunofluorescence of human lung microvessels (PAH vs. non-PAH subjects) displayed the presence of Axl on the endothelium but not medial smooth muscle. Digitized microscopy revealed that Axl tended to increase on PAH vessel endothelium (1.65 ± 0.15-fold vs. non-PAH; n=3-4; p=0.057). To address Axl's role *in vivo*, an Axl inhibitor R428 was employed in a preclinical PAH model. C57Bl/6 mice were subjected to hypoxia at pO2=10% and VEGF receptor antagonist SU5416 (Su/Ch) or normoxia (Norm) for 3 wks. Indeed, Su/Ch caused a significant rise in lung Axl protein and mRNA (7.1 ± 0.4- & 2.4 ± 0.5-fold, Su/Ch vs. Norm, protein & mRNA, respectively; n=3-6; p<0.01). As predicted, RV pressure (RVP) rose from 27 ± 0.7 to 43 ± 1.8 mmHg (Norm vs. Su/Ch; n=6; p<0.01). A decrease in RVP was not observed with twice-daily gavage of 75 mg/kg R428 (42.7 ± 0.8 mmHg, Su/Ch + R428; n=6). A similar pattern emerged with mean PA pressure (18.3 ± 0.3 and 28.6 ± 1.2 mmHg, Norm vs. Su/Ch, p<0.01; 28.7 ± 0.9 mmHg, Su/Ch + R428), RV resistance (1403 ± 256 vs. 2703 ± 464 Wood units, Norm vs. Su/Ch, n/s; vs. 3610 ± 625 Wood units, Su/Ch + R428) and Fulton index (0.26 ± 0.01 and 0.34 ± 0.02, Norm vs. Su/Ch, p<0.05; 0.38 ± 0.04, Su/Ch + R428). Our preliminary results support upregulated Axl in human PAH lung endothelium (and in total lungs of PAH mice) and thus suggest that Axl may play a role in vascular endothelial proliferation/remodeling in human PAH. It remains to be determined whether drug bioavailability or severity of disease precluded an ameliorative effect of Axl inhibitor in our preclinical studies.

## REGENERATIVE MEDICINE AND STEM CELLS

**R2 Hedgehog and Wnt Signaling Enhances Interleukin 1 Receptor Signaling in Spheroidal Aggregates of Mesenchymal Stem Cells**

*K. Tamama, S.R. Steimer*
*University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA*

Preparation of mesenchymal stem cells (MSCs) as 3D spheroidal aggregates is a novel preparatory and delivery method. Spheroid formation causes dramatic changes in their gene expression profile (10.2% of the genes up-regulated and 6.3% of the genes down-regulated) with cellular rejuvenation (cytoplasmic remodeling with reduced cell size, enhanced stem cell-like characteristics, and delayed replicative senescence). Previous studies including ours showed that interleukin 1 receptor (IL1R) inflammatory signaling is pivotal for the dramatic change of the gene expression profile upon spheroid formation of MSCs, despite the concurrent induction of BMPR signaling that strongly suppresses IL1R signaling. That indicates the presence of unidentified signaling that potentiates the IL1R signaling in MSC spheroids.Microarray data showed that Sonic hedgehog (*SHH)* and *WNT5A* are also up-regulated in MSC spheroids. As *SHH* and *WNT5A* were reported to potentiate NF-κB signaling, the main signaling downstream of IL1R, we hypothesized that induction of SHH and WNT5A signaling enhances IL1R signaling upon spheroid formation in MSCs and tested this hypothesis by using cultured human bone marrow MSCs. Both *SHH* and *WNT5A* gene expression was up-regulated in MSCs upon spheroid formation. Exogenously added WNT5A or SHH proteins induced the gene expression of inflammatory cytokines (IL1B and IL8), whereas a hedgehog pathway inhibitor (SANT-1) strongly reduced it. Exogenously added SHH protein induced *WNT5A* expression, whereas exogenously added WNT5A protein induced *SHH* expression. Endogenous *DKK1* expression was strongly down-regulated in MSC spheroids; however, exogenously added DKK1 protein caused minimal change in the gene expression of inflammatory cytokines. In conclusion, both SHH and noncanonical Wnt signaling are induced upon spheroid formation, potentiating IL1R signaling in MSCs. This could explain why IL1R signaling is strongly induced in MSC spheroids, in spite of the concurrent activation of inhibitory BMPR signaling.

## Supplemental Abstracts Author Index

The American Journal of
# PATHOLOGY
Cellular and Molecular Biology of Disease


## Introducing our New
# Editor-in-Chief

*Martha B. Furie, PhD*

The American Society for Investigative Pathology (ASIP) is pleased to announce the appointment of Martha B. Furie, PhD, as the next Editor-in-Chief for ***The American Journal of Pathology (AJP)***. Dr. Furie is a professor of Pathology, and Molecular Genetics and Microbiology, as well as the director of the graduate program in genetics at Stony Brook University, in Stony Brook NY. Throughout her career, Dr. Furie has focused her research on immune interaction with bacterial pathogens including those that cause Lyme disease and tularemia. Dr. Furie joined the American Society for Investigative Pathology in 1992, and shortly after became an editorial board member for *AJP*. In 2008, she took on the added responsibility of becoming an Associate Editor for the Journal, and in 2013 accepted the position of Senior Associate Editor under outgoing Editor-in-Chief, Dr. Kevin Roth. During this time Dr. Furie also served in many other capacities for ASIP: Program Chair for the annual meeting (2004-2006), Chair of the Education Committee (2006-2009), member of the ASIP Council (2006-2013), and ASIP President (2011-2012). Dr. Furie will be the 14th Editor-in-Chief of *AJP* and the first woman to serve in the position since the Journal's original inception in 1896 (then titled *The Journal of the Boston Society of Medical Sciences*).

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# Posters

**CANCER**

**C1** **Disruption of Choline Acetyltransferase Activity Suppresses Lung Adenocarcinoma Growth in Smokers,** *A.T. Akers*

**C2** **Anti-Angiogenic Activity of Memantine, a Dual α7-nAChR/NMDAR Antagonist, in Human Small Cell Lung Cancer,** *Z. Robateau*

**C3** **Capsaicin Sensitizes Human Small Cell Lung Cancer Cells to the Proapoptotic Activity of Camptothecin,** *J.R. Friedman*

**C4** **StarD10 as a Novel Colon Cancer Diagnostic Marker,** *A. Floris*

**C5** **Membrane Protein From Infective *Leishmania donovani* Induces Apoptosis in HepG2 cells: Involvement of Reactive Oxygen Species–Dependent P53-Mediated Mitochondrial Death Cascade,** *S. Mandal*

**C6** **Targeting Neuropilin-2 Prevents Pancreatic Ductal Adenocarcinoma Progression,** *D.R. Bielenberg*

**C7** **Differential Roles of β-Catenin and Yap during Development of Hepatoblastomas in Mice,** *J. Tao*

**C8** **Endoscopic Ultrasound Guided Fine Needle Aspiration/Brush in Cytopathology Diagnosis: A 15-Month Study,** *T. Santosh*

**C9** **Role of Polymorphonuclear Leukocytes in Inhibition of DNA Repair and Induction of Genomic Instability,** *V. Butin-Israeli*

**C10** **Multiplexed Analysis of Myoepithelial and Immune Cell Biomarkers to Predict Progression of Ductal Carcinoma *In Situ,*** *S. Jindal*

**C11** **MALT1 is a Key Mediator of Epithelial-Mesenchymal Transition in AGTR1-Positive Breast Cancer,** *J. Lee*

**C12** **IDH1 Mutation-Inspired α-Ketoglutaric Acid Mimics for Epigenetic Therapy of Higher Grade Gliomas,** *H. Madala*

**C13** **Biocompatible and Biodegradable Nanodrug Specific for Anaplastic Large Cell Lymphoma,** *Z. Zeng*

**C14** **Inflammation Enhances the Immunosuppressive Properties of Colorectal Cancer Cell–Derived Exosomes,** *R. Domenis*

**C15** **Anti-Metastatic Activity of Capsaicin in Human Lung Adenocarcinoma,** *N.A. Nolan*

**C16** **Anti-Invasive Activity of Capsaicin and its Analogs in Human Small Cell Lung Cancer,** *K.W. Colclough*

**C17** **GRK2, a Novel Tumor Suppressor, Modulates MALT1 Oncoprotein,** *J. Cheng*

**C18** **Cofilin is a cAMP Effector in Mediating Actin Cytoskeleton Reorganization and Steroidogenesis in Mouse and Human Adrenocortical Tumor Cells,** *G. Mantovani*

**C19** **Induction of ROS and Mitochondrial Dysfunction by a Novel Chromone Linked Nitrone Derivative Promotes Caspase-Dependent Apoptosis in Human Hepatocellular Carcinoma and Cervical Carcinoma Cell lines,** *S. Mandal*

**C20** **Aptamer-Engineered Cell-Derived Particles for Targeted Cancer Therapy,** *N. Zhao*

**C21** **A Multi-Organ Microphysiological System that Models Dormant-Emergent Metastatic Breast Cancer Progression,** *A.M. Clark*

**C22** **The Effect of c-Met Inhibitor EMD-1214063 on Hepatocellular Carcinoma in hMet-β-catenin Mouse Model,** *N. Zhan*

**C23** **Mitochondrial Dysfunction Causes Retinoic Acid Signaling Pathway Disturbance in Oral Precancer progression,** *R. Pandey*

**C24** **Development of Stable and Brain-Penetrating Disulfiram Nanoparticles: Characterization and Efficacy in Glioma Cell Culture and Xenograft Models,** *H. Madala*

**C25** **Modeling Metastasis from Invasion to Colonization on a Human Physiomimetic Chip,** *A.M. Bradshaw*

**C26** **Synthesis of a Novel Non-Diuretic, Brain-Penetrating, Ethacrynic Acid Analog and Demonstration of its Potent Efficacy in Orthotopic Glioblastoma Models,** *H. Madala*

**C27** **Synchronous Inverted Papilloma and Recurrent Respiratory Papillomatosis,** *J.D. Oliver*

**C28** **Early Actions of Anti-VEGF/VEGFR Drugs on Angiogenic Blood Vessels,** *H.F. Dvorak*

## INFECTIOUS DISEASES

**ID1** **Opacification Domain of Serum Opacity Factor Inhibits Beta-Hemolysis and Contributes to Virulence of *Streptococcus pyogenes,*** *L. Zhu*

**ID2** **Whole-Genome Sequencing of Human Clinical *Klebsiella pneumoniae* Isolates Discovers Misidentification and Misunderstandings of *K. pneumoniae, K. variicola,* and *K. quasipneumoniae,*** *R.J. Olsen*

**ID3** ***Andrographis paniculata* Inhibits Quorum Sensing, Virulence, and Biofilm Formation of *Pseudomonas aeruginosa* and Alleviates the Inflammatory Injury into Infected Macrophages,** *M. Banerjee*

**ID4** **Andrographolide, a Diterpenoid Lactone, Induces Oxidative Stress Leading to Death in *Trypanosoma brucei*,** *M. Banerjee*

**ID5** **Secondary Sclerosing Cholangitis in Localized Hepatobiliary Tuberculosis Simulating Cholangiocarcinoma: A Rare Case Report,** *A. Jain*

**ID6** **A Potential Broad-Spectrum Host-Targeting Antiviral Peptide Blocks Zika Virus Infection,** *R. Khachatoorian*

**ID7** **Population Genomic Analysis of 1,872 Extended-Spectrum β-Lactamase–Producing *Klebsiella Pneumoniae* Isolates, Houston, TX: Unexpected and Continued Abundance of Clonal Group 307,** *S.W. Long*

## IMMUNOLOGY AND INFLAMMATION

**IMIN1** **Advanced Glycated Products, Fibroblast Growth Factor-23, and Cardiovascular Remodeling in Chronic Kidney Disease on Dialysis (CKD-G5D): The Protective Role of sRAGE,** *M.M. Corsi Romanelli*

**IMIN2** **Inflammation and Edema: Neuropilins Guide the Way,** *D.J. Li*

**IMIN3** **WITHDRAWN**

**IMIN4** **Study of Colonoscopic Biopsies in Cases of Chronic Non-Bloody Diarrhea with Emphasis on Microscopic Colitis,** *A. Jain*

**IMIN5** **Patient-Specific 'Immune Repair' Improves Glycemic Control in Diabetes Mellitus: Evidence for a Comprehensive Immunopathogenesis Hypothesis,** *R. Jaffe*

**IMIN6** **Intravital Analysis of Acute Pulmonary Thromboembolism in Live Mice,** *T. Brzoska*

**IMIN7** **Neutrophils Occlude Precapillary Arterioles to Promote Neutrophil Extracellular Trap–Dependent Lung Injury in Sickle Cell Disease,** *R. Vats*

**IMIN8** **WITHDRAWN**

**IMIN9** **Increased Intestinal Permeability Secondary to Junctional Adhesion Molecule: A Deficiency Results in Impaired Macrophage-Dependent Neutrophil Recruitment in the Peritoneum,** *A. Luissint*

**IMIN10** **Macrophage Polarization Dictates the Outcome of Infection with Intracellular *Ehrlichia* in Non-Lipopolysaccharide Sepsis Model,** *T. Tominello*

**IMIN11** **USP48 Suppress E-cadherin Expression and Epithelial Barrier Function through Modulation of TRAF2 and JNK Signaling,** *S. Li*

**IMIN12** **Neuroinflammatory Gene Expression Changes after Chronic Constriction Injury of the Sciatic Nerve in Rat Following Administration of Macrophage Targeted Nanoparticles,** *A. Stevens*

**IMIN13** **Macrophage Targeted Nanotherapeutics with 30-Day–Long Anti-Inflammatory and Analgesic Action,** *L. Liu*

**IMIN14** **Search for Gut Microbiota–Mediated Composition and Influence on Type 2 Diabetes Mellitus,** *H.R. Moore*

**IMIN15** **Inflammatory Response of Macrophages Following Administration of Anti-Inflammatory Drug–Loaded Nanoemulsion in a Rat Chronic Constriction Injury Model,** *M. Saleem*

**IMIN16** **A Novel *In Vivo* Approach to Investigate Contributions of Epithelial Expressed Tight Junction–Associated Proteins in Regulating Neutrophil Migration Across Colonic Epithelium,** *S. Flemming*

**IMIN17** **A Novel Classification System and Global Gene Signature Model to Predict Progression and Severity in Systemic Scleroderma,** *Z.I. Johnson*

**IMIN18** **The Role Of Vinculin in Neutrophil β2 Integrin Adhesion and Motility,** *Z.S. Wilson*

## KIDNEY PATHOBIOLOGY

**K1** **Demonstration of Random Bias in Measuring Albumin in Hemodialysis Patients,** *K. Born*

## LIVER PATHOBIOLOGY

**L1** **Biosafety Assessment of Petroleum Ether Oil of *Ricinus communis* C in Wistar Rats,** *A.C. Adeyemo*

**L2** **Bromodomain and Extra-terminal (BET) Proteins Regulate Hepatocyte Proliferation in Hepatocyte-Driven Liver Regeneration,** *J.O. Russell*

**L3** **Dysregulated Bile Transporters and Liver Tight Junctions Enable Chronic Liver Injury,** *T. Pradhan-Sundd*

**L4** **Reintroduction of Mast Cells Induces Biliary Damage/Senescence, Steatosis, Inflammation, and Hepatic Fibrosis in Mast Cell–Deficient Mice Fed High-Fat Diet,** *L. Kennedy*

**L5** **Mechanisms of Interactions Between mTOR and Wnt-β catenin in Liver Pathogenesis,** *A.O. Michael*

**L6** **Platelet-Derived Growth Factor Receptor α Contributes to Hepatic Fibrosis by Promoting Hepatic Stellate Cell Proliferation and Migration during Chronic Liver Injury,** *A. Kikuchi*

**L7** **Metastatic Pattern of Hepatocellular Carcinoma: Privileged Portal Metastasis in Light of Co-Evolution of an Insulin-Carrying Portal System and the Liver in Chordate Phylogeny,** *V.M. Subbotin*

**L8** **Expression of Stem Cell Markers CD133 and CD49f in Alcoholic and Non-Alcoholic Steatohepatitis,** *S. Gudiwada*

**L9** **Hepatocyte Proliferation Induced by CAR agonist, TCPOBOP (1,4-Bis [2-(3,5-Dichloropyridyloxy)] benzene), is Suppressed after Combined Inhibition of MET and EGFR Signaling in Mice,** *B. Bhushan*

**L10** **The Role of Sphingosine Kinase 2 in Alcohol-Induced Hepatic Inflammation and Injury,** *E.K. Kwong*

**L11** **A Role for Polyploid Hepatocytes in Liver Repopulation and Adaptation to Chronic Injury,** *P.D. Wilkinson*

**L12** **Lack of β-catenin in Hepatocytes Impairs Proliferation and Promotes Liver Progenitor Cell–Mediated Repair in Response to Hepatic Injury,** *J. Russell*

**L13** **Treatment of a Mouse Model of Cholestasis with a Thyromimetic Improves Biliary Injury but Exacerbates Hepatocyte Injury,** *K.P. Kosar*

**L14** **Loss of β-Catenin Protects Mice from 3,5-diethoxycarbonyl-1,4-dihydrocollidine–Induced Porphyria,** *H. Saggi*

**L15** **Iron Overload in Liver Biopsy: A Morphological Approach,** *A. Jain*

**L16** **Glypican-3 and CD81 Promote Development of Hepatocellular Carcinomas and Hepatoblastoma in Normal Hepatocytes and Liver Stem Cells through Negative Selection,** *Y. Xue*

**L17** **Macrophage-specific Wnts Have Dual Role as Tumor Promoter or Tumor Suppressor in Hepatocellular Carcinoma After DEN/CCL4 Model of Tumorigenesis,** *M.E. Preziosi*

**L18** **WITHDRAWN**

**L19** **Wntless Loss from Hepatic Stellate Cells is Dispensable for Liver Fibrosis,** *R. Zhang*

**L20** **A Role for SLC25A34, a Putative Oxaloacetate Carrier, in Non-Alcoholic Fatty Liver Disease,** *N. Roy*

**L21** **Hepatocyte High-Mobility Group Box 1 Protects against Hepatic Steatosis,** *M. Lin*

**L22** **GC-1, a Thyroid Hormone Receptor-beta Agonist, Inhibits Met-β-Catenin–Driven Hepatocellular Cancer through Met Suppression,** *Q. Min*

**L23** **Co-Expression of Mutant β-Catenin and Yap in Mice Leads to Diverse Molecular Pathology in Hepatoblastoma,** *Q. Min*

**L24** **Regulation of Oncogenic Signaling Pathways in Hepatocellular Carcinoma by the Pleiotropic Scaffold Protein IQGAP1,** *E.R. Delgado*

**L25** **Time-Dependent Alteration of Global Gene Expression Profile in Liver after Deletion of c-MET in Adult Mice: Reprogramming to Maintain Hepatostat?** *B. Bhushan*

**L26** **Leukocyte Specific Protein-1 Controls ERK1/2 Activation, Hepatocellular Proliferation, and Sorafenib Sensitivity,** *K. Koral*

**L27** **The Apelin/Apelin Receptor Axis Promotes Biliary Proliferation and Liver Fibrosis during Biliary Cholestasis,** *A. O'brien*

**L28** **A Novel MAVS Signaling Complex Mediates Obesity-Induced Hepatic Insulin Resistance,** *D. Hu*

**L29** **Prohibitin1 Acts as a Negative Regulator of Wnt-β Catenin Signaling in Murine Liver and Human Hepatocellular Carcinoma Cells,** *N. Mavila*

## NEUROPATHOLOGY

**N1** **Up-Regulation of Cyclin A2 Causes Resolution of DNA Double Strand Breaks, Aiding in Neurodegenerative Disease,** *S. Mahajan*

**N2** **A Sex-Specific Model of the Blood–Brain Barrier: Use of Patient-Derived Stem Cells to Determine Male and Female Response to Ischemic Stroke,** *S. Page*

## PULMONARY PATHOBIOLOGY

**P1** **FBXO17 Regulates Lung Epithelial Cell Proliferation by Targeting Glycogen Synthase Kinase-3β for Proteasomal Degradation***, T.L. Suber*

**P2** **Novel Role of Axl kinase in Endothelial Cell Proliferation and Pulmonary Arterial Hypertension***, A. Gorelova*

## REGENERATIVE MEDICINE AND STEM CELLS

**R1** **Dual Method Verification of Adipogenesis in Cultures Containing an Adipose-Derived Delivery System for Adipose Restoration,** *C. Mahoney*

**R2** **Hedgehog and Wnt Signaling Enhances Interleukin 1 Receptor Signaling in Spheroidal Aggregates of Mesenchymal Stem Cells,** *K. Tamama*

**R3** **WITHDRAWN**

**R4** **Cooperation by Multipotent Stromal Cells and Fibroblasts Educates Wound Microenvironment to Improve Scarring,** *B. Lantonio*

**R5** **M2 Macrophage Phenotype Modifies the Wound Microenvironment to Improve Aged-Deficient Tissue Repair,** *C. Yates*

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