



# Adaptations to Hypoxia in Physiology and Disease

March 5–9, 2017 | Whistler Conference Centre | Whistler, British Columbia | Canada

## Scientific Organizers:

**M. Celeste Simon**, HHMI/University of Pennsylvania, USA

**Amato J. Giaccia**, Stanford University, USA

**Randall S. Johnson**, University of Cambridge, UK

## Joint with the meeting on **Tumor Metabolism: Mechanisms and Targets**

Cellular responses to changes in oxygen availability have important implications for both physiology and pathophysiology, in particular in the setting of solid tumor progression. A number of hypoxia-inducible pathways have been characterized, such as the large transcriptome regulated by hypoxia-inducible factors (HIFs). However, many other oxygen-sensing pathways exist within the cell. The aim of this meeting is to disseminate up-to-date information on basic mechanisms of cellular and tissue hypoxia responses, and discuss the impact of these responses on physiology and cancer, with an emphasis on HIF-independent, but nevertheless fundamental, oxygen-sensing pathways. Outcomes of this meeting will include the dissemination of new scientific knowledge, the discussion of new methodologies, the education of graduate students and postdoctoral fellows in this discipline, and promotion of new collaborations between clinicians, basic researchers and industrial partners. This will be the eighth Keystone Symposia meeting on Hypoxia, which brings together academic, clinical and industrial researchers to enhance synergy between these groups and develop translational strategies for targeting hypoxic stress responses for therapeutic benefit.

## Session Topics:

- Hypoxia and Tumor Metabolism (Joint)
- Hypoxic Influences on Intracellular Homeostasis
- Physiological Responses to Hypoxia
- Workshop 1: Late-Breaking News
- Metabolic Adaptations of Cells within the Tumor Microenvironment (Joint)
- Biochemical and Epigenetic Responses to Hypoxia
- Hypoxia and the Tumor Stroma
- Hypoxia and Tumor Progression
- Workshop 2: Late-Breaking News
- O<sub>2</sub> Availability and Stress Responses

**Abstract Deadline: December 8, 2016**

**Discounted Registration Deadline: January 12, 2017**



Note: Abstracts submitted by the abstract deadline will be considered for short talks on the program.  
Upper image of courtesy of National Cancer Institute/Univ. of Maryland  
Greenebaum Cancer Center

Meeting Hashtag: #KShypoxia  
[www.keystonesymposia.org/17X4](http://www.keystonesymposia.org/17X4)

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# KEYSTONE SYMPOSIA

on Molecular and Cellular Biology

## Adaptations to Hypoxia in Physiology and Disease (X4)

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## Tumor Metabolism: Mechanisms and Targets (X3)

Scientific Organizers: Brendan D. Manning, Kathryn E. Wellen and Reuben J. Shaw

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### SUNDAY, MARCH 5

#### Arrival and Registration

### MONDAY, MARCH 6

#### Welcome and Keynote Address (Joint)

\***M. Celeste Simon**, University of Pennsylvania, USA

**Chi Van Dang**, University of Pennsylvania, USA

*MYC as the Master Regulator of Proliferative Metabolism*

#### Hypoxia and Tumor Metabolism (Joint)

\***Amato J. Giaccia**, Stanford University, USA

**William G. Kaelin, Jr.**, Dana-Farber Cancer Institute, USA

*2-Oxoglutarate-Dependent Dioxygenases and Cancer*

**Nicholas Denko**, Ohio State University, USA

*Hypoxic Regulation of Mitochondrial Function*

**Andrew M. Intlekofer**, Memorial Sloan Kettering Cancer Center, USA

*Short Talk: Acidification Enhances Production of L-2-Hydroxyglutarate through Alternative Substrate use by Dehydrogenase Enzymes*

**James A. Nathan**, Cambridge Institute for Medical Research, UK

*Short Talk: Oxygen Sensing and Metabolism: The Role of the 2-Oxoglutarate Dehydrogenase Complex and Mitochondrial Protein Lipoylation*

**Karen H. Vousden**, Crick Institute, UK

*A Role for p53 in the Adaptation to Metabolic Stress*

#### Workshop 1 (X3)

\***Costas A. Lyssiotis**, University of Michigan, USA

**Sumin Kang**, Emory University, USA

*Phosphorylation-Mediated Activation of Lactate Dehydrogenase A Promotes Cancer Cell Invasion and Tumor Metastasis*

**Issam Ben-Sahra**, Northwestern University, USA

*Nucleotide Sensing by the mTORC1 Signaling Network*

**Atsuo T. Sasaki**, University of Cincinnati, USA

*SSK2 Couples Nucleolar Transcription and Anabolic GTP Metabolism for Gliomagenesis*

**Isaac Spencer Harris**, Harvard Medical School, USA

*Understanding the Vulnerabilities in Cancer Cells Upon Inhibition of Glutathione Synthesis*

**Won Dong Lee**, Technion - Israel Institute of Technology, Israel  
*Inferring Compartmentalized Mitochondrial, Nuclear, and Cytosolic Metabolic Fluxes via Isotope Tracing with Cell Fractionation*

**Lauren E. Drake**, University of Chicago, USA

*BNip3 Loss Promotes Hepatocellular Carcinoma Growth through Increased Lipogenesis*

**Salvador Aznar Benitah**, ICREA and Institute for Research in Biomedicine, Spain

*Identifying and Targeting Metastatic-Initiating Cells through the Fatty Acid Receptor CD36*

**Jing Chen**, Winship Cancer Institute, Emory University, USA  
*Prevention of Dietary-Fat-Fueled Ketogenesis Attenuates BRAF V600E Tumor Growth*

#### Hypoxic Influences on Intracellular and Tissue Homeostasis (X4)

\***Richard K. Bruick**, University of Texas Southwestern Medical Center, USA

**Young Il Yeom**, Korea Research Institute of Bioscience and Biotechnology, South Korea

*Lactate-Induced Responses to Hypoxia*

**Geert Carmeliet**, KU Leuven, Belgium  
*Glutamine, Glycogen and Bioenergetics*

**Othon Iliopoulos**, Massachusetts General Hospital Cancer Center, USA

*Glutaminase and PARP Inhibitors Synergistically Suppress ROS and Pyrimidine Dependent Growth of VHL-Deficient Renal Cell Cancer: A Novel Strategy for Treatment of Hypoxia-Driven and HIF-Expressing Tumors*

**Thomas Markus Leissing**, University of Oxford, UK

*Short Talk: Structural Basis for the Inhibition of Prolyl-Hydroxylase Domain Containing Proteins (PHDs) by Clinical Candidates for Anaemia Treatment*

#### Oncogenic Control of Metabolism (X3)

\***Heather Christofk**, University of California, Los Angeles, USA

**Lewis C. Cantley**, Weill Cornell Medicine, USA

*PI3K Signaling and Glucose Metabolism in Tumors*

**Almut Schulze**, University of Würzburg/Theodor-Boveri Institute, Germany

*Targeting Glucose and Lipid Metabolism in Cancer*

**Brendan D. Manning**, Harvard School of Public Health, USA

*A Coordinated Anabolic Program Downstream of mTOR*

**Alejo Efeyan**, Spanish National Cancer Research Institute, Spain

*Short Talk: Oncogenic Mutations in the Nutrient Sensing Pathway Upstream of mTORC1 Alter B Lymphocyte Functions in Novel Genetically-engineered Mice*

#### Poster Session 1

### TUESDAY, MARCH 7

#### Physiological Responses to Hypoxia (X4)

\***Maria F. Czyzyk-Krzeska**, University of Cincinnati, USA

**Peter F. Carmeliet**, University of Leuven, VIB, Belgium  
*Metabolic Adaptations of Tumor Blood Vessels*

**Frank S. Lee**, University of Pennsylvania School of Medicine, USA  
*Short Talk: Studies on the Zinc Finger of Prolyl Hydroxylase Domain Protein 2 (PHD2), a Hypoxia Inducible Factor-alpha Hydroxylase*

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**Francisco J. Quintana**, Harvard Medical School, USA  
*Regulation of CNS Inflammation by Hypoxia-Responsive Signaling*

**Mark R. Boothby**, Vanderbilt University Medical Center, USA  
*Short Talk: Germinal Center Hypoxia and Regulation of mTORC1 Activity in B Cells Shape Antibody Response Qualities*

**Janine T. Erler**, University of Copenhagen, Denmark  
*Hypoxia-Driven ECM Remodelling during Cancer Progression*

**Navdeep S. Chandel**, Northwestern University, USA  
*Why Mammalian Cells Breathe?*

### Metabolic Strategies in Cancer (X3)

\***Jared Rutter**, University of Utah, USA

**Matthew G. Vander Heiden**, Massachusetts Institute of Technology, USA

*Metabolic Adaptations to Allow Tumor Cell Proliferation*

**Jurre J. Kamphorst**, CR-UK Beatson Institute and University of Glasgow, UK

*Triglycerides Buffer Membrane Phospholipid Saturation during Hypoxic Stress*

**Ralph J. DeBerardinis**, University of Texas Southwestern Medical Center, USA  
*Heterogeneous Metabolic Phenotypes and Liabilities in Human Cancer*

**Sarah-Maria Fendt**, VIB Leuven, Belgium  
*Cancer Metabolism during Metastasis Formation*

**Cosimo Commisso**, Sanford-Burnham Medical Research Institute, USA

*Short Talk: Not Dying of Starvation: Nutrient Stress Controls Macropinocytosis in Tumor Cells*

**Elizabeth Petri Henske**, Brigham and Women's Hospital, USA  
*Short Talk: Therapeutic Targeting of mTORC1-Dependent Metabolic Vulnerabilities in TSC and LAM*

### Workshop 1: Fundamental Processes of Oxygen Sensing (X4)

**James A. Smythies**, University of Oxford, UK  
*Utilisation of Next Generation Sequencing Technologies to Identify Novel Contributors to Hypoxia Inducible Factor Binding Site Selectivity*

\***Luis del Peso**, Universidad Autonoma, Spain  
*Transcriptional Repression in Hypoxia is Mediated by the Sin3A Histone Deacetylase Complex*

**Johannes Schödel**, Universitätsklinikum Erlangen, Germany  
*Complex Regulation of Glucose Transporter 3 Expression by HIF*

**Andrew Fraser**, University of Toronto, Canada  
*How Worms Hold Their Breath: The Unusual Metabolic Response of Nematodes to Hypoxia and the Importance for 2 Billion Humans*

**Roman Vozdek**, University of California, San Francisco, USA  
*Novel Uncharacterized Protein Tyrosine Kinase Senses Hypoxia to Mediate HIF-1 Independent Transcriptional Response in C. elegans*

**Austin Gabel**, University of Maryland, Baltimore County, USA  
*Understanding Induction of Suspended Animation In Zebrafish*

**Farhad B. Imam**, Bill & Melinda Gates Foundation, USA  
*Cellular and Metabolic Studies of Hypoxia-Sensitive Mutants in irs2 and ctrc3, Key Regulators of Glucose and Fatty Acid Metabolism*

### Metabolic Adaptations of Cells within the Tumor Microenvironment (Joint)

\***Erika L. Pearce**, Max Planck Institute of Immunobiology and Epigenetics, Germany

**Raghu Kalluri**, University of Texas MD Anderson Cancer Center, USA  
*The Functional Contribution of Exosomes in Cancer Metabolism and Metastasis*

**Randall S. Johnson**, University of Cambridge, UK  
*The Metabolic Role of Hypoxic Response in T Cell Activation*

**Shannon J. Turley**, Genentech, Inc., USA  
*Leukocyte Function and Positioning in Diverse Stromal Niches*

**Hong Xie**, University of Pennsylvania, USA  
*Short Talk: Balancing Anabolic Metabolism with Homeostatic Stress Responses in Myc-Transformed Cancer Cells*

### Poster Session 2

#### WEDNESDAY, MARCH 8

#### Biochemical and Epigenetic Responses to Hypoxia (X4)

\***Frank S. Lee**, University of Pennsylvania School of Medicine, USA

**Peter J. Ratcliffe**, University of Oxford, UK  
*Genome Wide Studies of the Hypoxia Transcriptome*

**Daniel Cooper**, Duke University School of Medicine, USA  
*Short Talk: Hypoxia and Radiation Regulate HIF1alpha Gene Targets in a Context-Dependent manner*

**Fraydoon Rastinejad**, University of Oxford, UK  
*Structures and Drug-Binding Potentials of HIF-alpha-ARNT Heterodimers*

**Isha Jain**, Massachusetts General Hospital, USA  
*Short Talk: Hypoxia as a Therapy for Mitochondrial Disease*

**Eli M. Wallace**, Peloton Therapeutics, USA  
*Small Molecule HIF-2a Antagonists and Their Therapeutic Applications*

**Maria F. Czyzyk-Krzeska**, University of Cincinnati, USA  
*Oncogenic and Tumor Suppressive Autophagic Programs in Renal Cell Carcinoma*



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### Metabolism, Signaling and Epigenetics (X3)

\***Matthew G. Vander Heiden**, Massachusetts Institute of Technology, USA

**Aimee L. Edinger**, University of California, Irvine, USA  
*Macropinocytosis Drives Cancer Cell Growth in Both Nutrient-Limiting and-Replete Conditions*

**Jason Locasale**, Duke University School of Medicine, USA  
*Diet, Cancer, and Epigenetics*

**Joshua D. Rabinowitz**, Princeton University, USA  
*Multiple Functions of Mitochondrial Folate Metabolism*

**Kathryn E. Wellen**, University of Pennsylvania, USA  
*Acetyl-CoA at the Crossroads of Metabolism and Epigenetics*

**Christian C. Dibble**, Beth Israel Deaconess Medical Center, USA  
*Short Talk: PI3K Signaling Controls de novo Biosynthesis of Coenzyme A from Vitamin B5*

**Jordan Meier**, NCI, National Institutes of Health, USA  
*Short Talk: Defining Metabolic Mechanisms of Epigenetic Signaling using Chemoproteomics*

### Workshop 2 (X3)

\***Aimee L. Edinger**, University of California, Irvine, USA

**Liron Bar-Peled**, The Scripps Research Institute, USA  
*A Druggable Transcriptional Vulnerability in NRF2-Dependent Lung Cancers*

**Volkan I. Sayin**, New York University School of Medicine, USA  
*Somatic Editing of Keap1/Nrf2 Antioxidant Response is Pro-Tumorigenic and Promotes a Targetable Genotype-Dependent Metabolic Switch in KRAS-Driven Lung Cancer*

**Valeria Santoro**, Bayer Pharma AG, Germany  
*Mitochondrial Folate Transporter (SLC25A32) Protects Against ROS-Mediated Cancer Cell Death*

**Zhimin Lu**, University of Texas MD Anderson Cancer Center, USA  
*Phosphoglycerate Kinase 1 Phosphorylates Beclin1 to Induce Autophagy*

**Boyi Gan**, MD Anderson Cancer Center, USA  
*LncRNA NBR2 Regulates AMPK-Mediated Energy Stress Response and Modulates Cancer Cell Sensitivity to Biguanides*

**Bin Zheng**, Massachusetts General Hospital, Harvard Medical School, USA  
*Targeting Metabolic Vulnerabilities of MDSCs to Enhance the Anti-Tumor Activity of PD-1 Blockade*

**Giulia Agnello**, Aeglea BioTherapeutics, USA  
*Therapeutic Depletion of Arginine via Arginase I (AEB1102, Pegzilarginase) Administration Inhibits Tumor Growth and Further Sensitizes the Tumor to Immunotherapy with Anti-PD1 and Anti-PD-L1*

**Prasenjit Dey**, MD Anderson Cancer Center, USA  
*Collateral Lethality as a Therapeutic Target in Cancer*

### Hypoxia and the Tumor Stroma (X4)

\***Ester M. Hammond**, University of Oxford, UK

**M. Celeste Simon**, University of Pennsylvania, USA  
*HIFs and Metabolic Adaptations in Renal Cancer*

**Mia J. Phillipson**, Uppsala University, Sweden  
*Contribution of Immune Cells in Restoration of Hypoxic Tissues*

**Sonia Rocha**, University of Liverpool, UK  
*PBRM1, a Highly Mutated Member of the SWI/SNF Complex in Renal Cancer, has an Unconventional Role in the Control of the Hypoxia Response*

**Jong Park**, University of Maryland, Baltimore County, USA  
*Short Talk: Role of Lactate-NDRG Signaling in Low Oxygen Tolerance*

### Interplay with Other Cell Types and Tissues (X3)

\***Ralph J. DeBerardinis**, University of Texas Southwestern Medical Center, USA

**Erika L. Pearce**, Max Planck Institute of Immunobiology and Epigenetics, Germany  
*Biosynthetic Needs of Immune Cells and Effects on Immunotherapy*

**Nada Y. Kalaany**, Boston Children's Hospital at Harvard Medical School, USA

*Metabolic Dependencies in Obesity-Associated Pancreatic Cancer*

**Scott Bultman**, University of North Carolina at Chapel Hill, USA  
*Regulation of Tumor Metabolism by the Microbiome*

**Costas A. Lyssiotis**, University of Michigan, USA  
*Short Talk: Stromal Support of Pancreatic Tumor Metabolism*

### Poster Session 3

#### THURSDAY, MARCH 9

### Hypoxia, Inflammation and Tumor Progression (X4)

\***Emin Maltepe**, University of California, San Francisco, USA

**Amato J. Giaccia**, Stanford University, USA  
*Clear Cell Renal Cancers: Lipid Droplets*

**Cormac Taylor**, University College Dublin, Ireland  
*The Role of Hypoxia in Immunity and Inflammation*

**G-One Ahn**, Pohang University of Science and Technology, South Korea  
*Short Talk: Tumor-Associated Macrophages Can Exacerbate Tumor Hypoxia and Glycolysis*

**Gregg L. Semenza**, Johns Hopkins University School of Medicine, USA  
*PHGDH Expression Is Required for Mitochondrial Redox Homeostasis, Breast Cancer Stem Cell Maintenance and Lung Metastasis*

**Christian Metallo**, University of California, San Diego, USA  
*Reprogramming of Amino Acid Metabolism by Hypoxia*

**Erinn B. Rankin**, Stanford University, USA  
*Short Talk: Hypoxic Signaling in the Tumor-Mesothelial Niche*

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**Tumor Progression and Suppression by Metabolic Enzymes (X3)**

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\***Sarah-Maria Fendt**, VIB Leuven, Belgium

**David M. Sabatini**, Whitehead Institute for Biomedical Research, USA  
*CRISPR Screening for Metabolic Dependencies in Cancer Cells*

**Jared Rutter**, University of Utah, USA  
*Pyruvate Metabolism and Cell Fate Decisions*

**Heather Christofk**, University of California, Los Angeles, USA  
*Metabolic Transitions in Cancer: Lessons from Viral Infection*

**Eyal Gottlieb**, Technion - Israel Institute of Technology, Israel  
*Metabolic Dependencies of Leukemic Stem Cells*

**Oliver Maddocks**, University of Glasgow, UK  
*Short Talk: MTAP Deletion and Polyamine Pathway Activity Combine to Confer Cysteine Essentiality in Cancer Cells*

**Susan Demo**, Calithera Biosciences, USA  
*Short Talk: CB-839, a Selective Glutaminase Inhibitor, has Anti-Tumor Activity in Renal Cell Carcinoma and Synergizes with Everolimus and Cabozantinib*

### Workshop 2: Hypoxia and Disease Processes (X4)

\***Peppi Koivunen**, University of Oulu, Finland  
*Notch Downregulation and Extramedullary Erythrocytosis in HIF Prolyl 4-Hydroxylase-2-Deficient Mice*

\***Qing Zhang**, University of North Carolina at Chapel Hill, USA  
*ZHX2 Promotes ccRCC as a Potential pVHL Target by Activating NF- $\kappa$ B*

**Jason Boehme**, University of California, San Francisco, USA  
*Preservation of Myocardial Contractility during Acute Hypoxia with OMX—A Novel Oxygen Delivery Biotherapeutic*

**Sara M. Timpano**, University of Guelph, Canada  
*Human Cells Cultured Under Physiological Oxygen Utilize a Different Mode of Translation Initiation, Have Higher Proliferation Rates, Less Oxidized DNA and More Tubular Mitochondria*

**Norihiko Takeda**, University of Tokyo, Japan  
*HIF-1-PDK1 Axis Induced Active Glycolysis Plays an Essential Role in Macrophage Migratory Capacity*

**Merve Erdem**, Uniklinik Aachen, Germany  
*HIF-1 $\alpha$  in Myeloid Cells Affects Peripheral Lipid Metabolism in Cancer Cachexia*

**Jamie D. Weyandt**, Vanderbilt University Medical Center, USA  
*Loss of Fumarate Hydratase Upregulates Glycolytic Metabolism in a Mouse Renal Carcinoma Cell Line*

### O<sub>2</sub> Availability and Stress Responses (X4)

\***Randall S. Johnson**, University of Cambridge, UK

**Constantinos Koumenis**, University of Pennsylvania, USA  
*Genome-Wide Analysis of Hypoxic Responses in Cells and Tumors Reveals Novel Splicing Pathways Impacting Macromolecular Synthesis*

**Bradly G. Wouters**, University Health Network, Canada  
*ULK1 Regulates Oxygen Metabolism, Hypoxia Tolerance and Is a Therapeutic Target in Pancreatic Cancer*

**Ester M. Hammond**, University of Oxford, UK  
*Ribonucleotide Reductase Favors the RRM2B Subunit to Maintain DNA Replication in Hypoxia*

### Metabolic Vulnerabilities in Cancer (X3)

\***Almut Schulze**, University of Würzburg/Theodor-Boveri Institute, Germany

**Eileen P. White**, Rutgers University, USA  
*Inhibiting Autophagy as a Cancer Therapy*

**Katya Marjon**, Agios Pharmaceuticals, USA  
*Metabolic Collateral Vulnerabilities of MTAP-Deleted Cancers as Therapeutic Opportunities*

**Reuben J. Shaw**, The Salk Institute for Biological Studies, USA  
*The AMPK Pathway: Cancer Fighter, Cancer Promoter*

**Meeting Wrap-Up: Outcomes and Future Directions (Organizers) (X4)**

**Meeting Wrap-Up: Outcomes and Future Directions (Organizers) (X3)**

**FRIDAY, MARCH 10**

**Departure**