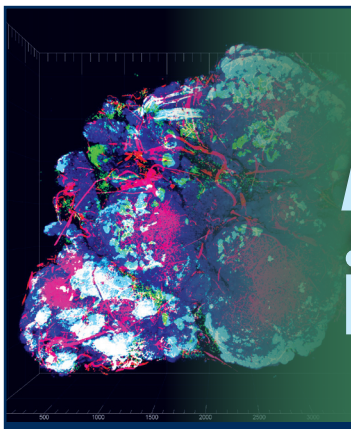

Adaptations to Hypoxia in Physiology and Disease

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_2 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
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KEYSTONE SYMPOSIA
on Molecular and Cellular Biology

Adaptations to Hypoxia in Physiology and Disease (X4)

Scientific Organizers: M. Celeste Simon, Amato J. Giaccia and Randall S. Johnson

Sponsored by Takeda Pharmaceutical Company Limited

Tumor Metabolism: Mechanisms and Targets (X3)

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

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Abstract & Scholarship Deadline: November 8, 2016 / Abstract Deadline: December 8, 2016 / Discounted Registration Deadline: January 12, 2017

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

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 Respire?

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

Elizabeth Maher, University of Texas Southwestern Medical Center, USA
Bioenergetic Substrate Reprogramming: A Common Mechanism in Cancer?

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

Jurre J. Kamphorst, CR-UK Beatson Institute and University of Glasgow, UK
Short Talk: Triglycerides buffer membrane phospholipid saturation during hypoxic stress

Cosimo Commisso, Sanford-Burnham Medical Research Institute, USA
Short Talk: Not Dying of Starvation: Nutrient Stress Controls Macropinocytosis in Tumor Cells

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

Andy 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, University of California, San Diego, 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, Sanford Burnham Prebys Medical Discovery Institute, USA
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

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

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

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 Dundee, 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

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

Tumor Progression and Suppression by Metabolic Enzymes (X3)

***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 Integrated Cancer Center, 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

Ethan Emberley, 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

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

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

Merve Erdem, Uniklinik Aachen, Germany
HIF-1alpha 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

O2 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