BANBURY CENTER REPORTS

# Better cancer therapy from redox biology

Banbury Center, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
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**Organizers:**
David Tuveson, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
Christine Chio, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA

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## BACKGROUND

*An unanswered question in human health is whether anti-oxidation prevents or promotes cancer. Anti-oxidation has historically been viewed as chemo-preventive but emerging evidence suggests that antioxidants may be supportive of neoplasia. To leverage cellular redox changes towards the development of a safe and effective therapeutic strategy necessitates experimental delineation of specific redox signaling pathways that are uniquely required by cancer cells to grow and to survive.*

*This Banbury meeting on redox biology centered on the complexity of redox regulation in the context of cancer biochemistry and therapy. Specifically, the meeting aimed to explore ROS genesis and metabolism in cancer cells, as well as the "productive" and "destructive" signal transduction by free radicals through the oxidation of intermediates such as protein encoded cysteine and methionine residues.*

## DETAIL

Redox chemical reactions represent a principle constituent of all life. Despite this, our current understanding of redox biochemistry inside living cells remains surprisingly elusive in both physiological and pathological settings. In the context of tumorigenesis, there is much excitement over the possibility of harnessing differences in cellular redox states to develop novel therapeutic strategies. To date, most effort has been invested in defining the role of reactive oxygen species (ROS) as a tumor promoting or a tumor-suppressing agent, with abundant evidence supporting either argument. ROS on the one hand, can suppress cell growth through genotoxic stress and mRNA translational arrest; and on the other hand, can promote cell growth through activation of mitogenic signaling cascades. The role of ROS in cellular outcome is clearly more diverse than anticipated. Cellular responses to ROS reflect a complex integration of ROS type, location and levels. This presents a conundrum on how we should approach ROS therapy in cancer.

Participants in the April 2017 Banbury Center meeting on *Better Cancer Therapy from Redox Biology* explored the complexity of redox regulation in the context of cancer biochemistry and therapy. The goal is to synthesize this information to inform the design of therapeutic strategies to selectively target neoplastic cells. Specifically, the group explored the selective role of different ROS-generating mitochondrial components in physiology and development, as well as the application of genomic screens to identify pharmacologically actionable liabilities that are created in cancer cells. The intricacy of redox biology is highlighted by the cell compartment-specific functions of different free radical species, their interaction with metals and also target selectivity. Indeed, ROS involvement in cancer is not confined to indiscriminate macromolecular damage. The regulation of ROS is both topological and temporal. Given this, the potential number of ROS-specific effectors is predicted to be massive and underexplored.

Cancer is a complex entity that co-evolves with a microenvironment comprised of an extracellular matrix, fibroblasts and immune cells, all of which dynamically communicate in paracrine and juxtacrine manners. As such, the role of redox homeostasis extends beyond tumor cell intrinsic properties and is involved in mediating organ-specific tumor development, metastatic properties, as well as immune cell activation and function.

Emerging technologies that identify ROS, including protein- and chemical-based probes to track and quantify free radical species in both space and time, were discussed during this meeting. The application of these new technologies will be invaluable to deciphering the selective role of different reactive oxygen species in specific cell types and cell compartments within the tumor mass and will inform the design of more effective therapeutic strategies against cancer.

*Christine Chio & David Tuveson*
*April 2017*

## MEETING SESSIONS

**Session I: Free radicals and antioxidants in physiological functions**
Chair: Arne Holmgren, Karolinska Institute, Stockholm, Sweden

James Watson, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
*To Overcome Chemo-Resistant Cancers, Use Natural Product Quinones*

Christine Winterbourn, University of Otago, Christchurch, New Zealand
*Cellular mechanisms for regulating hydrogen peroxide metabolism and oxidative stress*

Ursula Jakob, University of Michigan, Ann Arbor, Michigan, USA
*Role of polyphosphate in oxidative stress defense*

Nicholas Tonks, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
*Redox regulation of Protein Tyrosine Phosphatases for therapeutic development*

Navdeep Chandel, Northwestern University, Chicago, Illinois, USA
*Functional genomic screens to uncover redox biology*

Paul Schumacker, Northwestern University, Chicago, Illinois, USA
*Mitochondrial regulation of cell proliferation*

**Session II: Free radicals and antioxidants in cancer**
Chairs: Arne Ostman, Karolinska Institute, Stockholm, Sweden, and Karen Liby, Michigan State University, East Lansing, Michigan, USA

Karen Vousden, Francis Crick Institute, London, United Kingdom
*Modulating TIGAR to probe ROS functions in tumour development and metastasis*

Tak Mak, University of Toronto, Ontario, Canada
*Modulation of oxidative stress as an anticancer strategy*

Edward Schmidt, Montana State University, Bozeman, Montana, USA
*Endogenous oxidants and cellular antioxidant systems in liver cancer*

Martin Bergo, Karolinska Institutet, Huddinge, Sweden
*Antioxidants cause long-term programming of lung cancer cells into a metastatic phenotype*

Nissim Hay, University of Illinois, Chicago, Illinois, USA
*Akt, hexokinase 2, ROS, and cancer therapy*

**Session III: NRF2 in redox homeostasis and metabolism**
Chair: Michael Espey, National Cancer Institute, Rockville, Maryland, USA

John Hayes, University of Dundee, Dundee, United Kingdom
*The mechanisms of repression of transcription factor Nrf2 and its crosstalk with lipid metabolism*

Christine Chio, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
*Nrf2 promotes mRNA translation in pancreatic cancer*

Masayuki Yamamoto, Tohoku University, Sendai, Japan
*Molecular basis of Keap1-Nrf2 system and Cancer*

Thales Papagiannokopolus, New York University Medical School, New York, USA

*Pro-tumorigenic NRF2 antioxidant program causes defects in central carbon metabolism*

Gina DeNicola, Moffitt Cancer Center, Tampa, Florida, USA
*Compartmentalization of ROS production and metabolism*

Donna Zhang, University of Arizona, Tucson, Arizona, USA
*NRF2: an integrator of cellular iron and redox signaling*

**Session IV: Redox imaging**
Chair: Tobias Dick, German Cancer Research Center, Heidelberg, Germany

Vsevolod Belousov, Russian Academy of Sciences, Moscow, Russia
*Metabolic engineering tools and fluorescent probes for redox biology*

Kevin Brindle, University of Cambridge, Cambridge, United Kingdom
*Imaging oxidative stress in vivo*

Christopher Chang, University of California, Berkeley, California, USA
*Chemical Imaging and Proteomics Probes for Studying Redox Biology*

Tobias Dick, German Cancer Research Center, Heidelberg, Germany
*Understanding the 'anti-oxidant' N-acetyl cysteine*

Yi Yang, East China University of Science and Technology, Shanghai, China
*Genetically encoded sensors for redox biology and their applications in drug screening*

Michael Murphy, MRC Mitochondrial Biology Unit, Cambridge, United Kingdom
*Therapeutic alteration to the mitochondrial redox environment*

**Session V: Therapeutics**
Chair: Thomas Miller, IC-MedTech, Las Vegas, Nevada, USA

David Boothman, University of Texas Southwestern Medical Center, Dallas, Texas, USA
*Leveraging NQO1 bioactivatable drugs for tumor-selective ROS production and anti-tumor activity*

Garry Buettner, University of Iowa, Iowa City, Iowa, USA
*Using science to guide clinics trials for cancer treatment where redox biology is at the center*

Douglas Spitz, University of Iowa, Iowa City, Iowa, USA
*$O_2^{\bullet-}$ and $H_2O_2$-Mediated Disruption of Fe Metabolism Causes the Differential Susceptibility of NSCLC and GBM Cancer Cells to Pharmacological Ascorbate*

Sean Morrison, University of Texas Southwestern Medical Center, Dallas, Texas, USA
*Distant metastasis requires cancer cells to adapt to cope with oxidative stress*

Elizabeth Parkinson, University of Illinois, Urbana, Illinois, USA
*Deoxynyboquinones as NQO1-targeted anticancer compounds*

**Session VI: Wrap-Up and Next Steps (David Tuveson and James Watson)**

## MEETING PARTICIPANTS

Vsevolod Belousov, Russian Academy of Sciences, Russia
Martin Bergo, Karolinska Institutet, Sweden
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Christopher Chang, University of California Berkeley, USA
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