Research Program of the Cancer Redox Faculty

Steering Committee: Curt Harris, Stefan Ambs, Perwez Hussain LHC/CCR/NCI
David Roberts LP/CCR/NCI
Grace Yeh LM/CCR/NCI
Terry Moody CCR/NCI
Sophia Wang, DCEG/NCI
Richard Pluta Surgery NINDS,
Mark Gladwin CC/NHLBI
James Mitchell, Murali Krishna, David Wink RBB/CCR/NCI
Redox Biology in Cancer Research

Oxidative Stress
Radicals
Antioxidants
Nitrosative Stress

Carcinogenesis
Inflammation
Cancer treatment
Cancer Prevention

O2

CO

H2O2/O2-

H2S

RNOS (NO2, N2O3, ONOO-)

NO

Hydroxyl radical
Metallo-oxo Species

Cellular Damage

Regulation Biological Functions

Cellular Damage
Goal: to bring together researchers within CCR/ NIH and the extramural community to provide a vehicle to discuss and facilitate collaboration in redox biology.

Priorities set by the Steering Committee

1) Established a course in “Redox Biology in Cancer”
   a) Complimentary Seminars (Fall)

2) Workshops to expand on promising areas identified by the steering committee
   a) Imaging and Biomarkers for Oxidative Stress
      Feature Speaker “Britton Chance”
   b) Redox-Based NSAIDs “A novel solution to an old Problem”
      Feature Speaker “Louis Ignarro”

3) Focus collaborative research on identified areas of need
## Redox Biology Course

**Coordinator:** Terry Moody CCR/NCI

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Research Accomplishments: collaborative publications


Current Redox Faculty Focus (2005-2006)

Redox-Based NSAIDs

Major advantages of redox-based NSAIDs:
   a) alleviate the gut toxicity of conventional NSAIDs
   b) some moieties have anti-thrombotic properties

We have examined these novel compounds for potential use in

1) Chemoprevention
2) Treatment
3) Imaging
Redox-Based NSAID Current Being Examined by the CRBF

**Current Collaborators**

- Piero Del Soldato (CTG) S-NSAIDs
- Bruce King Nitrogen Oxide (Wake Forest University)
- Larry Keefer (LCC/CCR/NCI) SOD mimetics

- Thiol-based NSAIDs (S-NSAID)
  - ADT
  - Oltipraz

- SOD mimetics
  - Nitrosoxides

**Redox-active Moiety**

- Nitrogen Oxide
- Organic nitrates
- HNO donors
- NONOate

- Thiol-based NSAIDs (S-NSAID)
  - ADT
  - Oltipraz

- SOD mimetics
  - Nitrosoxides

**NSAID**

- Aspirin
- Indomethacin
- Sulindac
- Diclofenac

**Redox active Moiety**

- Nitrogen Oxide
  - Organic nitrates
  - HNO donors
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Chemoprevention Properties Redox-based NSAIDs

Grace Yeh LM/CCR

**Phase I**

- Polyaromatic Hydrocarbons (PAH)
- AhR/ARNT (HIF1B)
- ~T/GnGCGTG ~
- Xenobiotic Response Element (XRE)
- Cytochrome p450 (CYP)

**Phase II**

- Oxidants Electrophiles
- Nrf2/Keap1
- ~TGACAGAGC ~
- Antioxidant Response Element (ARE)
- GST
- UGT
- NQO1

Carcinogens
Summary of Current Findings

S-Valproate and S-NSAIDs inhibit Phase I enzyme activity

Future Direction
- Investigate S-NSAIDs in PAH-induced mammary and lung tumor models
- Identify other moieties from Division of Cancer Prevention which have chemopreventive properties
Cancer Treatment

Goal: To identify agents that can help increase efficacy of conventional therapies: Radiation and Chemotherapy

Preliminary

*In vitro* models

Tumor have similar efficacy in as parent NSAIDs in NSCLC and HT-29 inhibit PGE2 synthesis

*In vitro* data

S-NSAID in PC3 xenograft show 80% reduction in tumor growth rate

Angiogenic Properties

Dave Roberts, Biochemistry Section/LP: In vitro and ex vivo studies
Anti-angiogenic activities of redox NSAIDs in HT-29 colon carcinoma explants

Conclusions

• S-NSAIDSs have anti-angiogenic properties
• NO based NSAIDs have pro-angiogenic properties
Oxygen and Redox EPR and MRI Imaging with Nitroxides

Murali Krishna and James Mitchell RBB, CCR

1) Determine oxygen status
2) Redox status tissue
3) Tissue perfusion
4) Drug mobility

Nitroxides

Oxygen map

Redox map


Cancer Res. 2006

Future: NSAID based nitroxides for potential MRI imaging

Marnett “Chemical Biology Workshop”

Bruce King Wake Forest University
Aspirin-nitroxide
Indomethacin-nitroxide
Model For Testing Redox Based Compounds Placement of Proposed Personal and Support

CCR/NIH
Industry
Academia
DCP

Redox Reagents
Chemical
Biochemical

Cellular Models

Animal Model

Clinical Trials
Epidemiological Studies

Therapeutic Agent Screening

Redox Mechanisms
“Systems Biology Approach”

Biomarkers
Redox Imaging