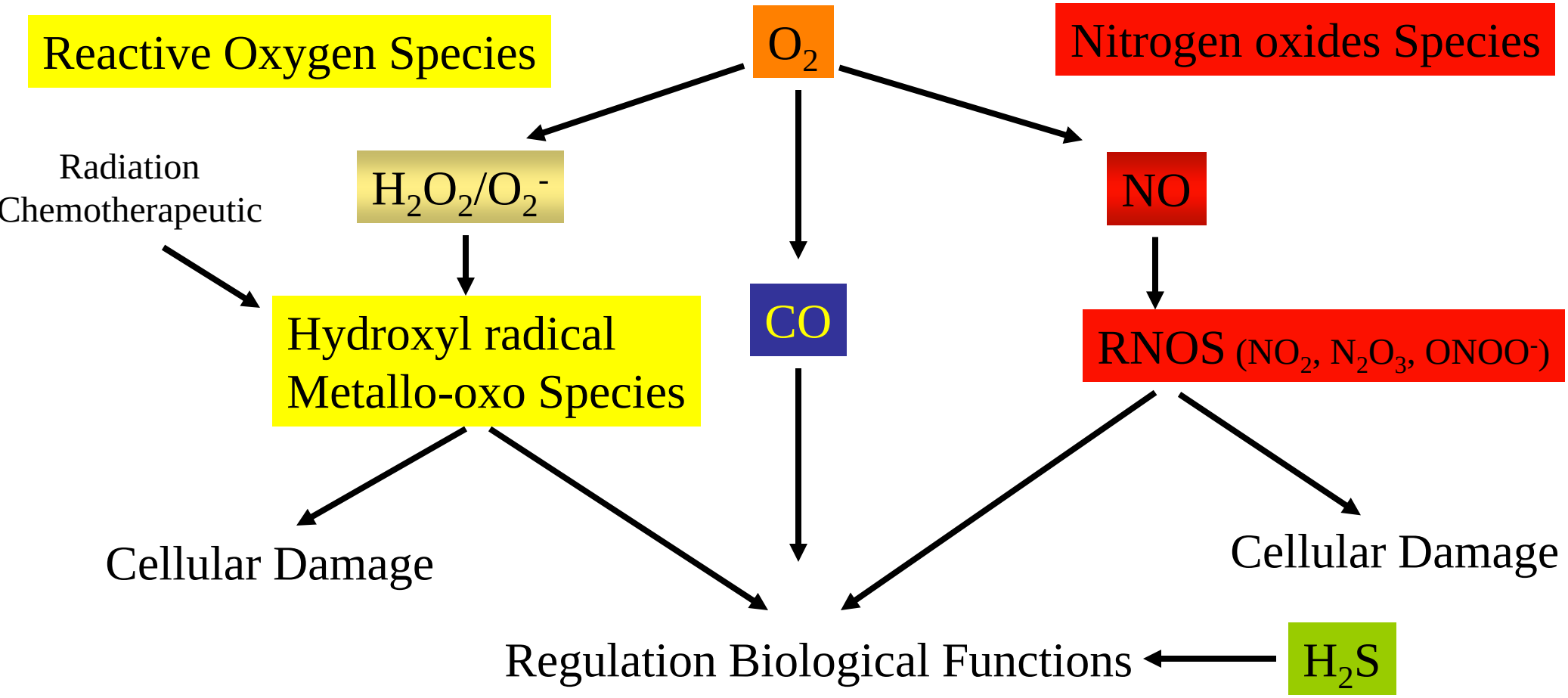
Research Program of the Cancer Redox Faculty

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



Cancer Redox Biology Faculty

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

Date	Lecture	Speaker
Sept. 26	Introduction	T. Moody
	Redox Chemistry	D.Wink
Oct. 3	Redox Biology	D. Wink
	Cell Biology	M. Espey
Oct. 10	Signal Transduction	T. Moody
	Carcinogenesis	G. Yeh
Oct. 17	Physiology	M. Gladwin
	Inflammation	P. Hussain/C. Harris
Oct. 24	Central Nervous System	R. Pluta
	Angiogenesis	D. Roberts
Oct. 31	Biomarkers	S. Wang
	Cancer Therapy	J. Mitchell
Nov. 15	Immunology	M. Espey
	Epidemiology	S. Ambs

Research Accomplishments: collaborative publications

Isenberg JS, Ridnour L, Espey MG, Wink DA, Roberts DD. Nitric Oxide in Wound Healing (2005) Microsurgery 25(5):442-51

Thomas DD, Espey MG, Ridnour L, Hofseth LJ, Mancardi D, Harris CC, and Wink DA. HIF-1α, ERK and p53 are regulated by distinct threshold nitric oxide concentrations in human breast MCF7 cells (2004) Proc. Natl. Acd. Sci. 01(24):8894-9.

Isenberg JS, Ridnour LA, Espey MG, Roberts DD, Wink DA. Thrombospondin-1 Inhibits Endothelial Cell Responses to Nitric Oxide in a cGMP-Dependent Manner (2005) Proc. Natl. Acad Sci. 102:13141-6

Ridnour L, Isenberg JS, Espey MG, Thomas DD, Roberts DD, Wink DA. Nitric Oxide Regulates Angiogenesis through a Functional Switch Involving Thrombospondin-1. (2005) Proc. Natl. Acad Sci. 102:13147-52

Isenberg JS, Ridnour LA, Thomas DD, Wink DA, Roberts DD, Espey MG (2006) Guanylyl cyclase-dependent chemotaxis of endothelial cells in response to nitric oxide gradients. Free Radic Biol Med. 40:1028-33

Ridnour LA, Thomas DD, Mancardi D, Donzelli S, Paolocci N, Pagliaro P, Miranda KM, Krishna MC, Fukuto J, Grisham MB, Mitchell JB,. Espey MG, and Wink DA. Antioxidant properties of nitric oxide in cellular physiological and pathophysiological mechanisms. The implications of biological balance between •NO and oxidative stress. (2004) Current Med. Chem. (in Press)

Thomas DD, Ridnour L, Donzelli S, Espey MG, Mancardi D, Isenberg JS, Feelisch M, Roberts DD, Wink DA. Nitric oxide and Related Nitrogen Oxides: Chemistry of Protein Adducts (Dalle-Donne I, Scaloni A, Butterfiled A Eds) in *Redox Proteomics: from Protein Modifications to Cellular Dysfunction and Diseases*, Wiley Interscience NY, NY (in Press)

Ridnour LA, Thomas DD, Donzelli S, Espey, MG Roberts DD, Wink DA, Isenberg JS (2006) The Biphasic Nature of Nitric Oxide Responses in Tumor Biology Antioxidant and Redox Signaling (in Press)

Donzelli S, Switzer CH, Thomas DD, Ridnour LA, Espey MG, Isenberg JS, Tocchetti CG, King SB, Lazzarino G, Miranda KM, Roberts DD, Feelisch M, and Wink DA, (2006)The activation of metabolites of nitric oxide synthase by metals is both redox- and oxygen-dependent: a new feature of nitrogen oxide signaling. Antioxid. Redox Sig. In press.

Isenberg JS, Wink DA, Roberts DD (2006) Thrombospondin-1 antagonizes nitric oxide-stimulated vascular smooth muscle cell responses Cardiovascul. Res. (in press)

Thomas DD, Ridnour LA, Espey MG, Donzelli S, Ambs S, Hussain SP, Harris CC, W DeGraff W, Roberts DD, Mitchell JB, and Wink DA (2006) SUPEROXIDE FLUXES LIMIT NITRIC OXIDE-INDUCED SIGNALING J Biol Chem. (in press)

Isenberg JS, Ridnour LA, Dimitry J, Frazier WA, Wink DA, Roberts DD. (2006) CD47 is necessary for inhibition of nitric oxide-stimulated vascular cell responses by thrombospondin-1. J Biol Chem. (in press)

Roberts DD Isenberg JS, Ridnour LA, Wink DA,. (2006) Nitric oxide and its Gatekeeper Thrombospondin-1 in Tumor Angiogenesis Clinical Cancer Res. (in press)

Prueitt RL, Boersma BJ, Howe TM, Goodman JE, Thomas DD, Ying L, Pfiester CM, Yfantis HG, Cottrell JR, Lee DH, Remaley AT, Hofseth LJ, Wink DA and Ambs S. Inflammation and IGF-I Activate the Akt Pathway in Breast Cancer (2006) Int. J. Cancer (in press)

Current Redox Faculty Focus (2005-2006)

Redox -Based NSAIDs

Major advantages of redox-based NSAIDs:

a) alleviate the gut toxicity 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

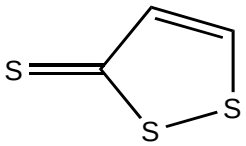
Redox-Based NSAIDs Current Being Examined by the CRBF

NSAID — Redox-active Moiety

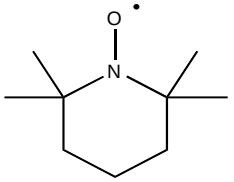
Aspirin
Indomethacin
Sulindac
Diclofenac

Nitrogen Oxide
- Organic nitrates — $RONO_2$
- HNO donors — RNO
- NONOate — RN(NO)NO)

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



SOD mimetics
- Nitroxides



Current Collaborators

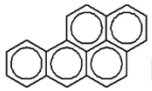
Piero Del Soldato (CTG)	**S-NSAIDs**
Bruce King	**Nitrogen Oxide**
(Wake Forest Univeristy)	**SOD mimetics**
Larry Keefer	**Nitrogen Oxide**
(LCC/CCR/NCI)	

Division of Cancer Prevention

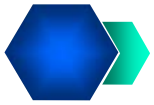
Chemoprevention Properties Redox-based NSAIDs

Grace Yeh LM/CCR

Phase I



Polyaromatic Hydrocarbons (PAH)



AhR/ARNT (HIF1B)

~T/GnGCGTG ~

Xenobiotic Response Element (XRE)

Cytochrome p450 (CYP)

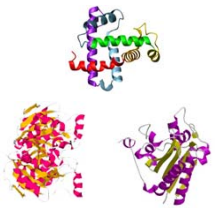
Phase II

Oxidants Electrophiles H^+

Nrf2/Keap1

~TGACAGAGC ~

Antioxidant Response Element (ARE)



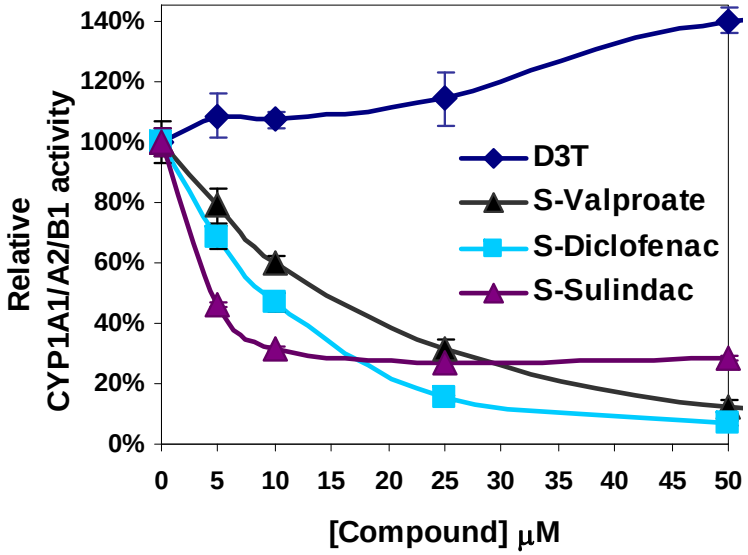
GST

UGT NQO1

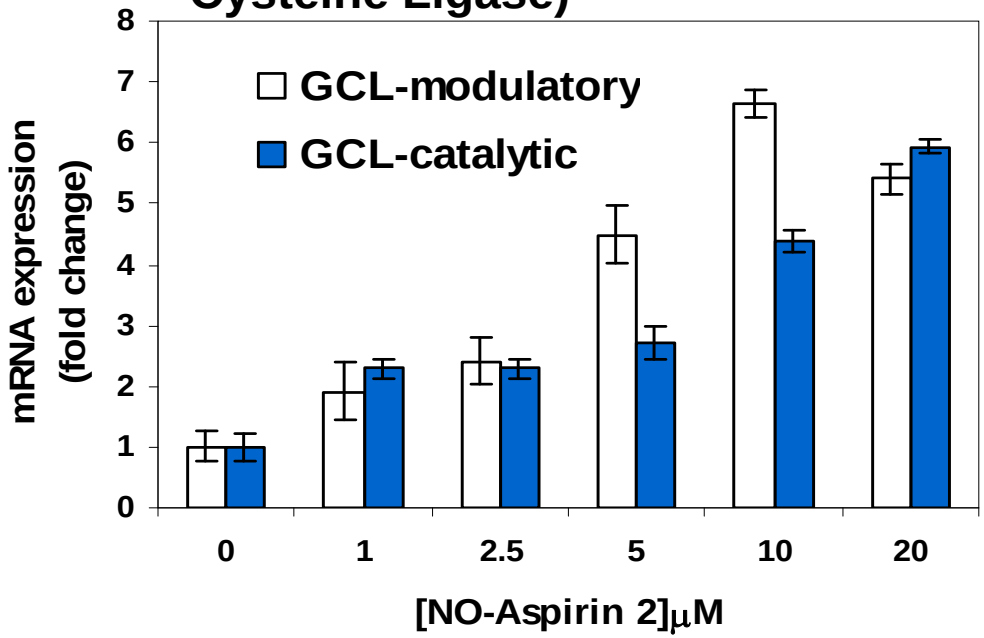
Carcinogens

Summary of Current Findings

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



NO-Aspirin induces Phase II mRNA expression (Glutamate Cysteine Ligase)



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 NSLC and HT-29 inhibit PGE2 synthesis

in vitro data

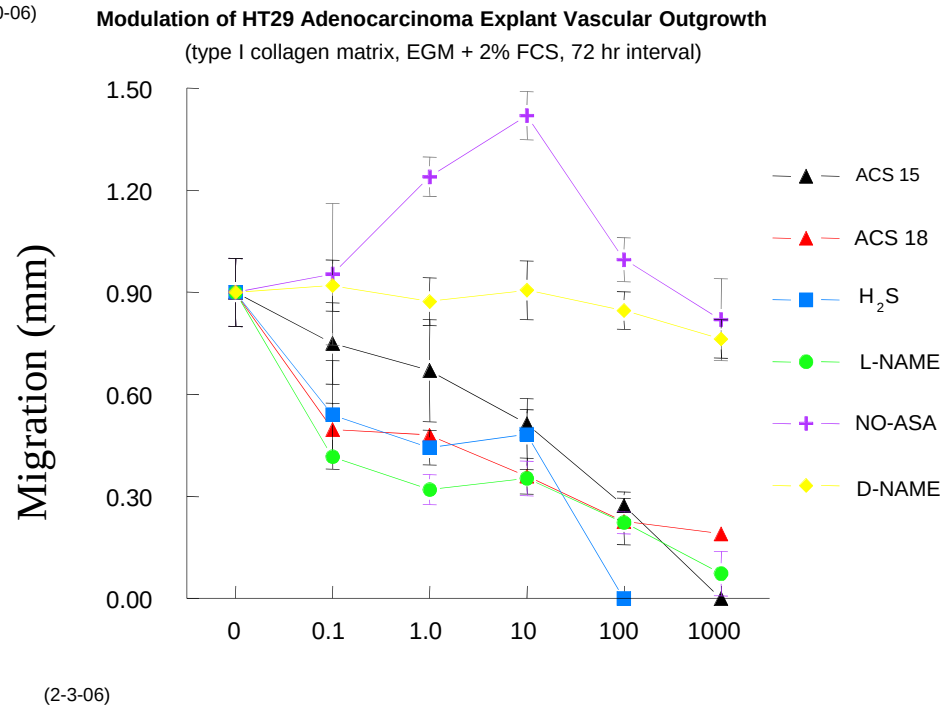
S-NSAID in PC3 xenograph show 80% reduction in tumor growth rate

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

(2-20-06)



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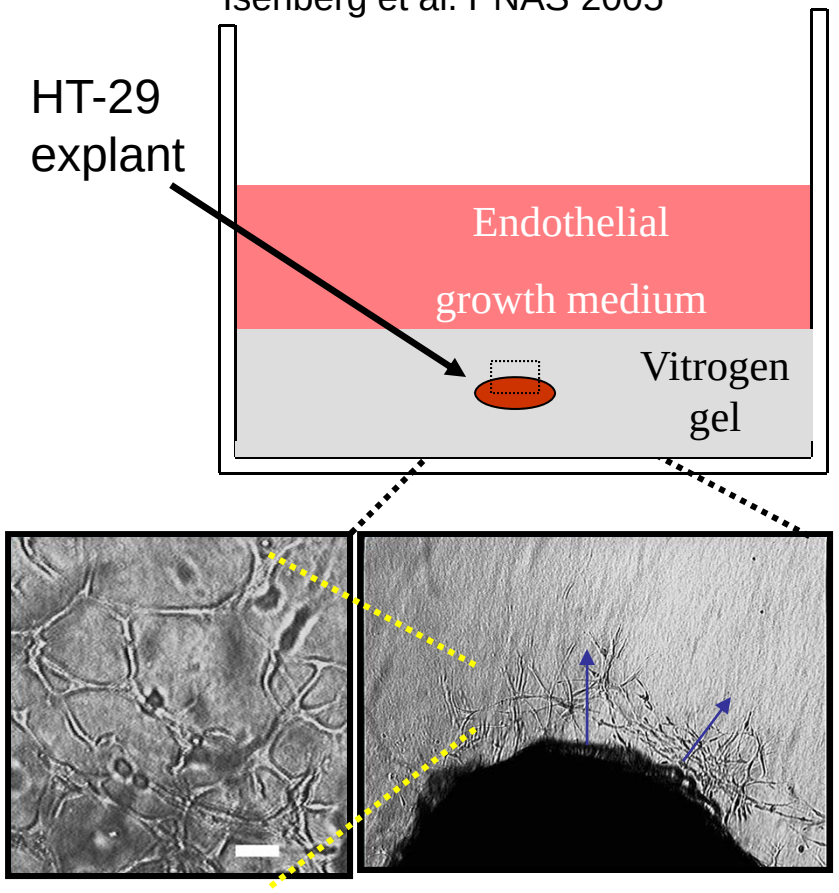
Isenberg et al. 2006 submitted

Isenberg, Matrix Biol 2005

Isenberg et al. PNAS 2005



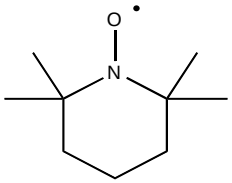
Conclusions

- S-NSAIDSs have anti-angiogenic properties
- NO based NSAIDs have pro-angiogenic properties

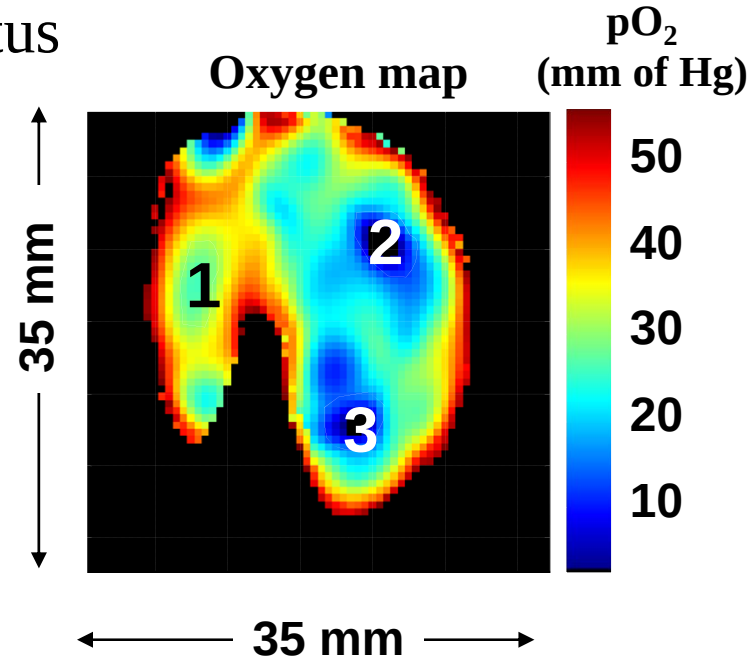
Oxygen and Redox EPR and MRI Imaging with Nitroxides

Murali Krishna and James Mitchell RBB, CCR

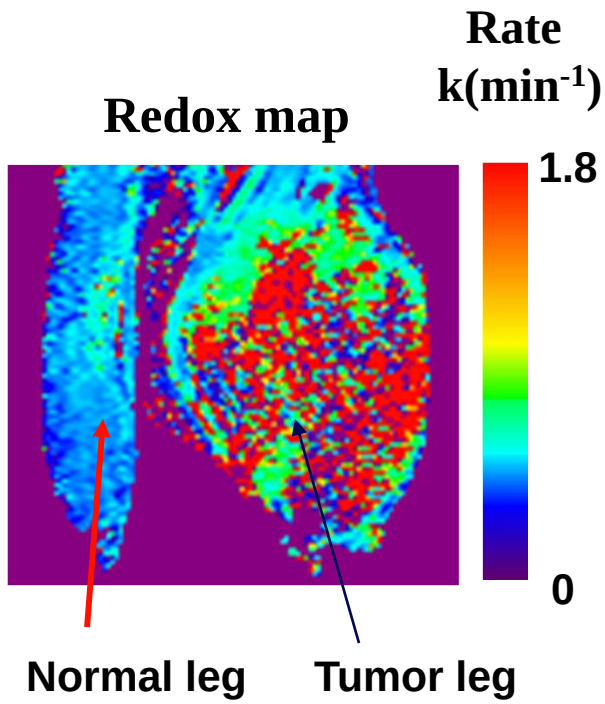
1) Determine oxygen status
2) Redox status tissue
3) Tissue perfusion
4) Drug mobility



Nitroxides



Magn. Reson. Med. 2006



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