Non-Thermal Plasmas for Biomedicine: A New Frontier in Plasma Processing

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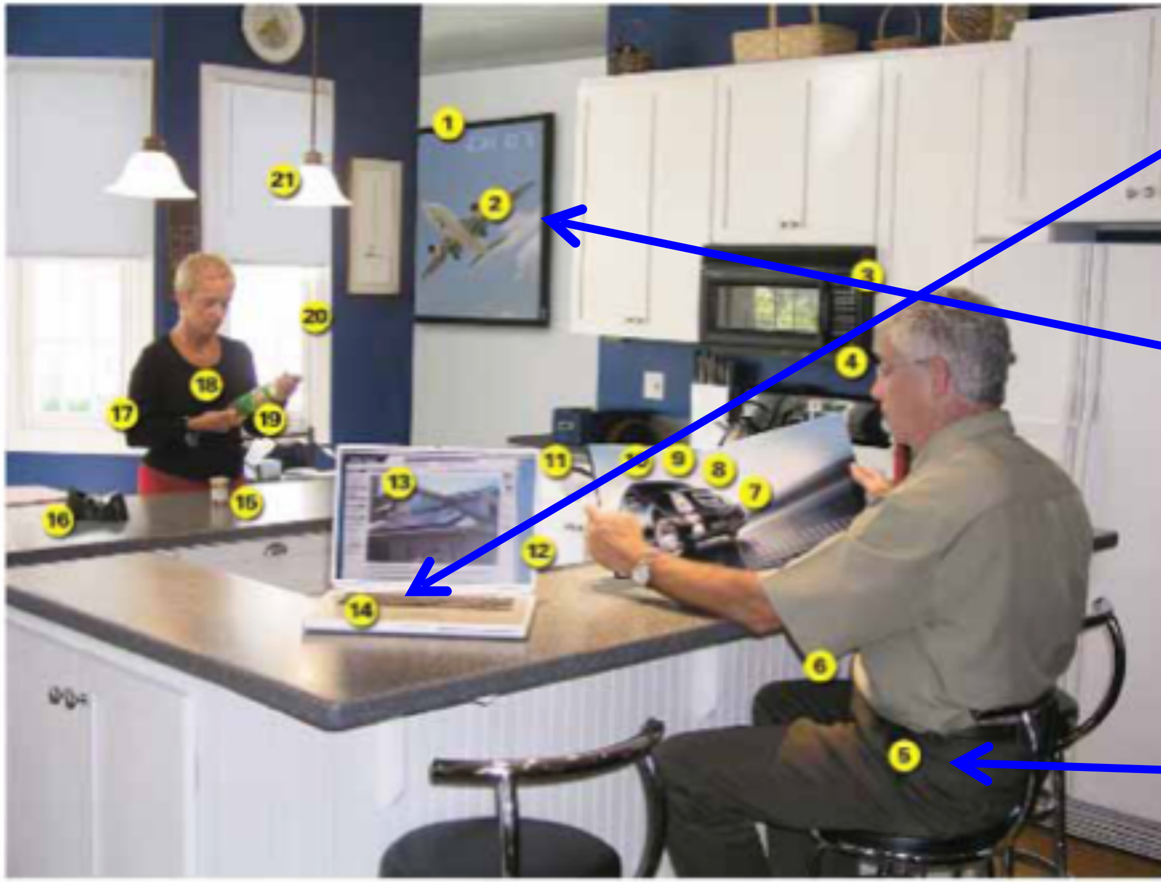
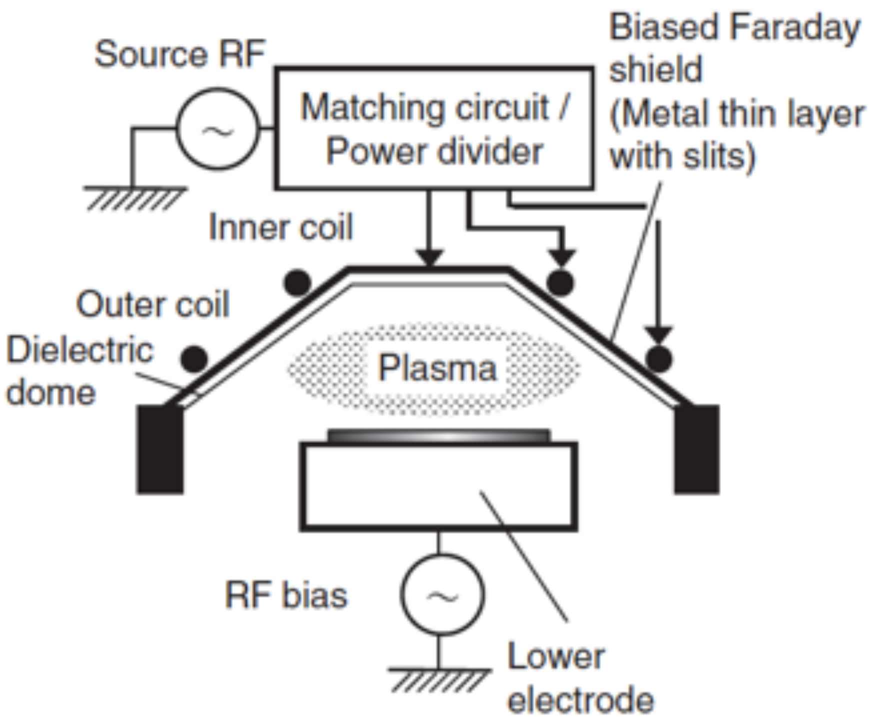
‘Low Temperature” Plasmas *“In the Kitchen”* *



01—Plasma TV
02—Plasma-coated jet turbine blades
03—Plasma-manufactured LEDs in panel
04—Diamondlike plasma CVD eyeglass coating
05—Plasma ion-implanted artificial hip
06—Plasma laser-cut cloth
07—Plasma HID headlamps
08—Plasma-produced H_2 in fuel cell
09—Plasma-aided combustion
10—Plasma muffler
11—Plasma ozone water purification
12—Plasma-deposited LCD screen
13—Plasma-deposited silicon for solar cells
14—Plasma-processed microelectronics
15—Plasma-sterilization in pharmaceutical production
16—Plasma-treated polymers
17—Plasma-treated textiles
18—Plasma-treated heart stent
19—Plasma-deposited diffusion barriers for containers
20—Plasma-sputtered window glazing
21—Compact fluorescent plasma lamp

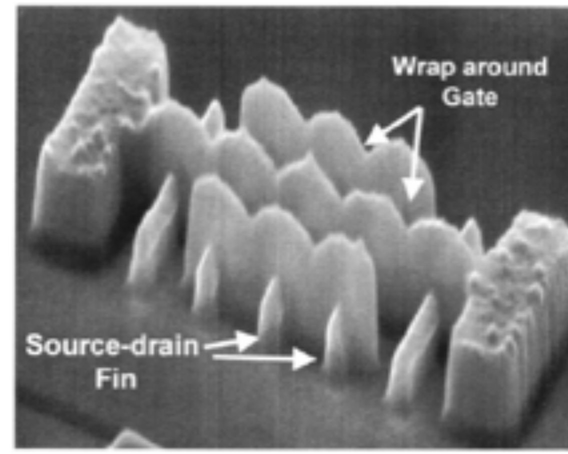
* Plasma 2010
NRC, 2007

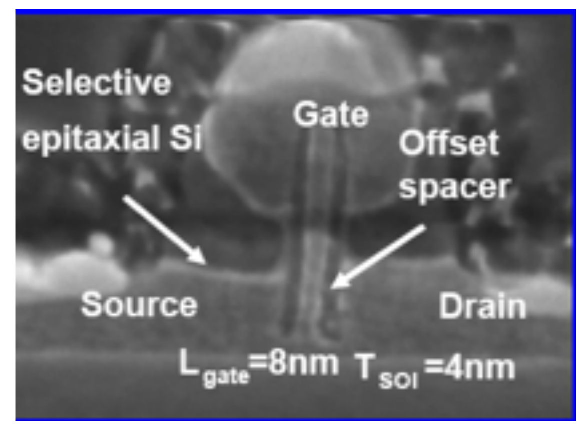
Plasma Etching: IC Manufacture



Jpn. J. Appl. Phys. Vol. 42 (2003) pp. 7547–7551
Part 1, No. 12, December 2003

Advanced devices





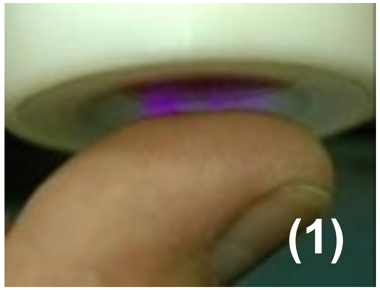
Courtesy Y. Zhang, IBM Research

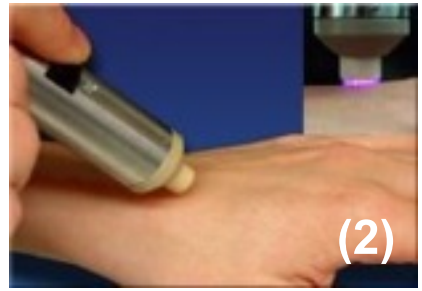
Plasmas used to process semiconductors to make integrated circuits (ICs) –
Nanoelectronics has replaced ***micro***electronics: sub-10 nm critical dimensions

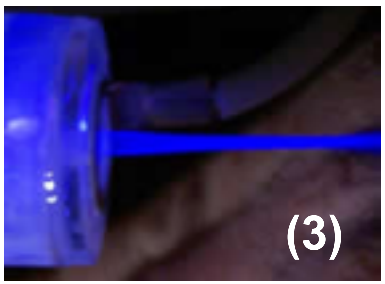
Abbreviated History of Gas Plasmas In Biomedicine

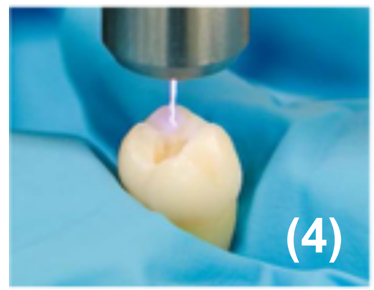
- 2011+ M. Vandamme/M. Keidar: *in vivo* cancer tumor treatment (jet/DBD)
- 2010 G. Isbary: clinical trial for wound healing (MW Ar plasma)
- 2007 G. Fridman: *in vitro* cancer cell treatment (Air DBD)
- 2003 E. Stoffels: non-destructive cell handling (He plasma needle)
- 2000 Plasma Surgical Company: Ar jet
- 1999 M. Laroussi: E. coli sterilization (He DBD)
- 1995. APC (ERBE GmbH): Ar plasma for endoscopic surgery
- 1993 Coblation (Arthrocare Co): discharge in saline solution
- 1940 Hyfrecator (Birtcher Co): low power and no ground pad
- 1926 Bovie knife: the first clinical use of a electrosurgical device
- 1893 A. d'Arsonval: compatibility of HF with nerve and muscle

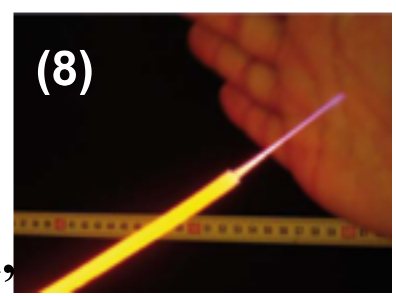
Atmospheric Pressure Plasma Sources for Biomedical Applications

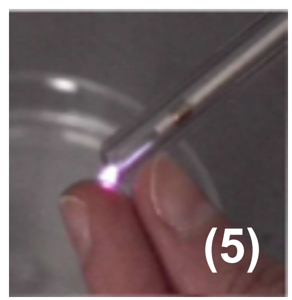


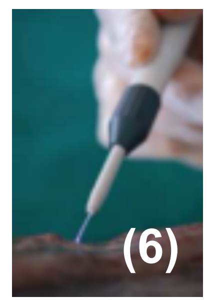


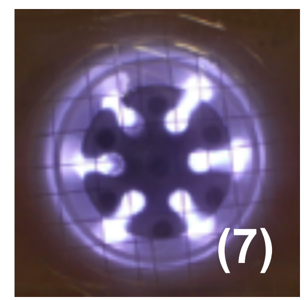


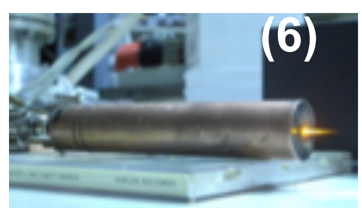










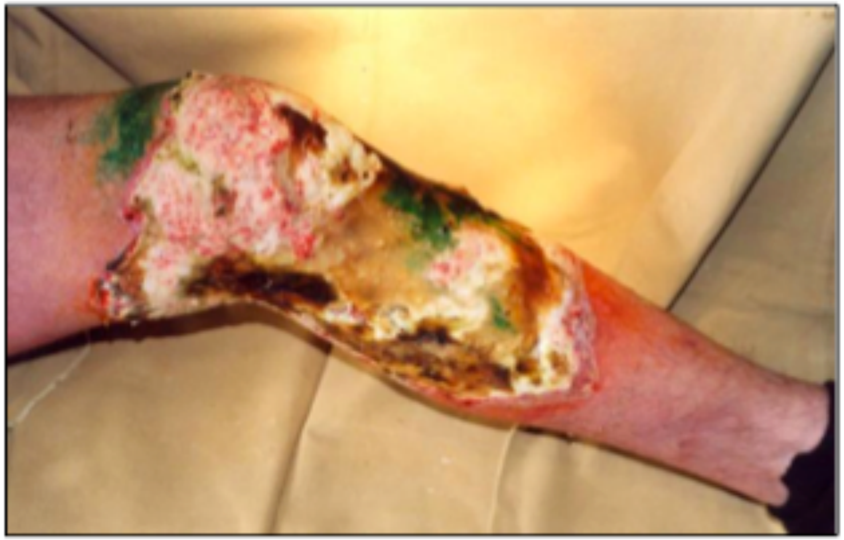


(1) Drexel University (USA)
(2) Cinogy GmbH (GER)
(3) Old Dominion University (USA)
(4) IOM Leipzig (GER)
(5) Eindhoven Univ. of Techn. (NED)
(6) New York University (USA)
(7) MPE Garching (GER)
(8) University of Orléans (FRA)
(9) McGill University, Montreal (CAN)
(10) Loughborough University (UK)
(11) INP Greifswald (GER)

Courtesy: K.D. Weltmann, Greifswald

Plasma-induced wound healing: various anecdotal reports

Treatment of Topical Wounds: Tissue Regeneration: Suppurated Burn Wound (2009 conference)*

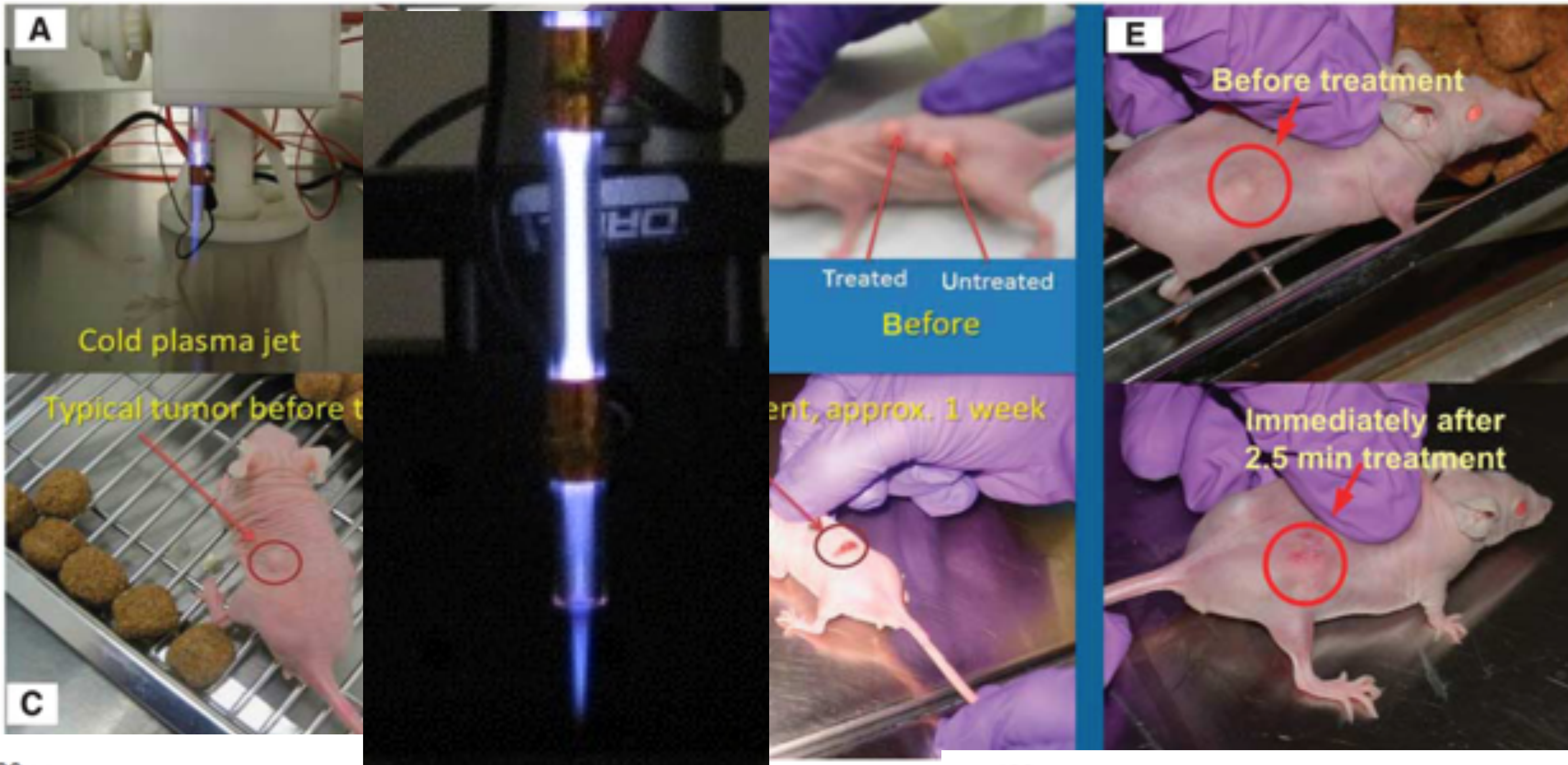


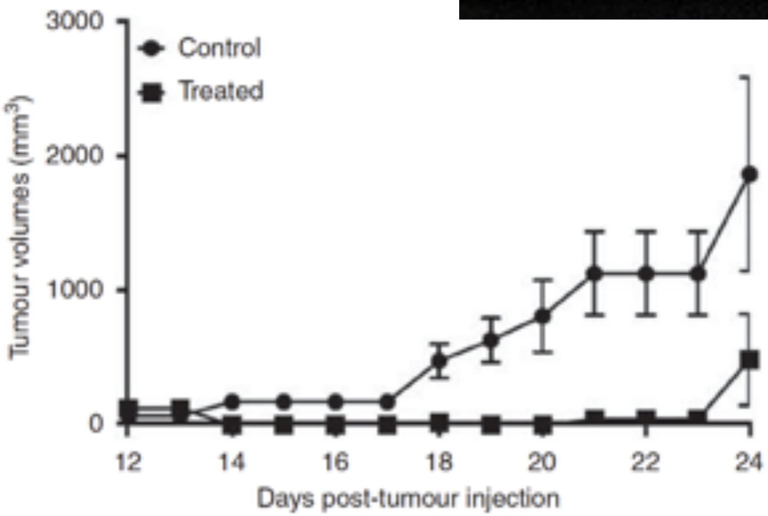
Before treatment

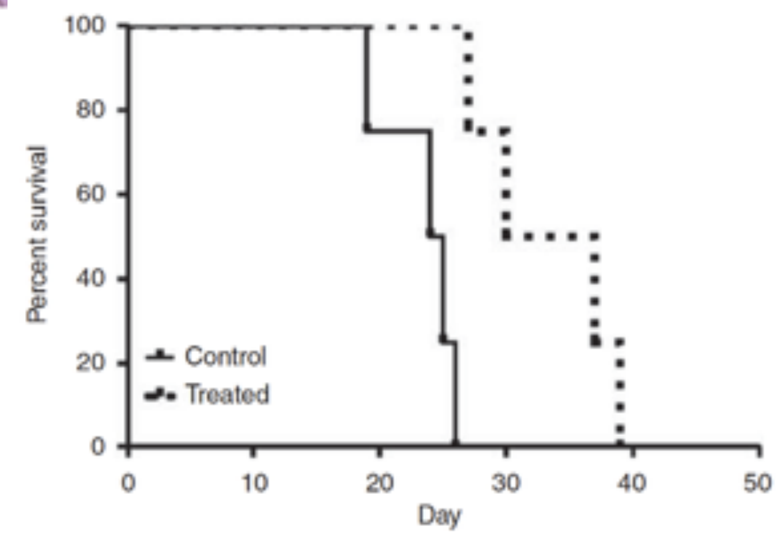
After 7 days/ 5 sessions plasma treatment

**Richard M. Satava, MD FACS*
Professor of Surgery
University of Washington

British Journal of Cancer (2011) **105**(9), 1295–1301 Keidar et al., Dec. 2011; melanoma murine model

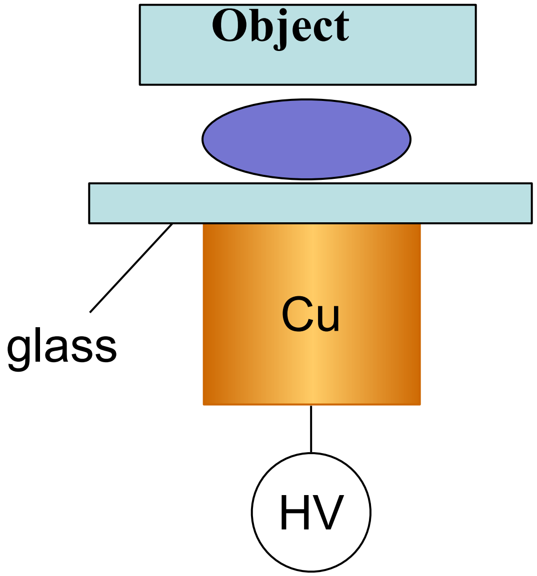




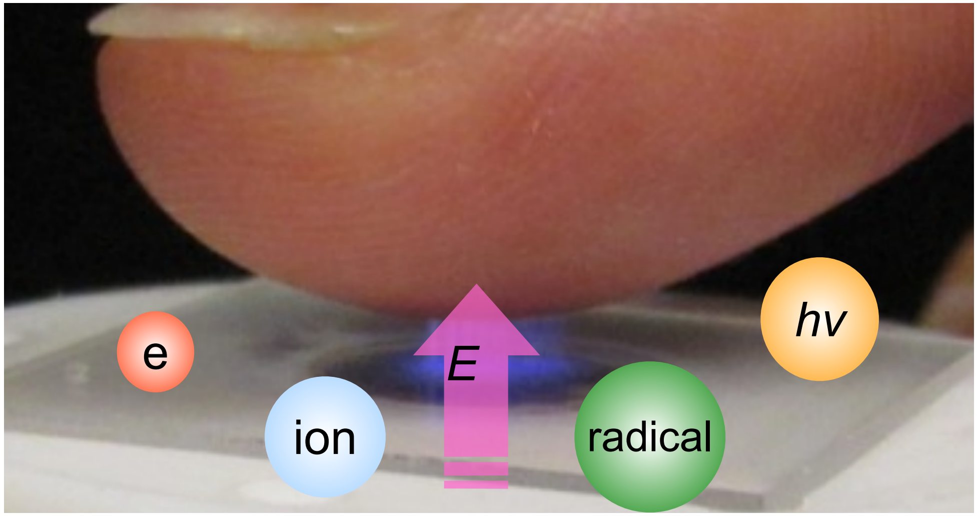



B. NTAP Therapy

What are the Key Biochemical *Agents??*
What are the Biochemical *Mechanisms??*



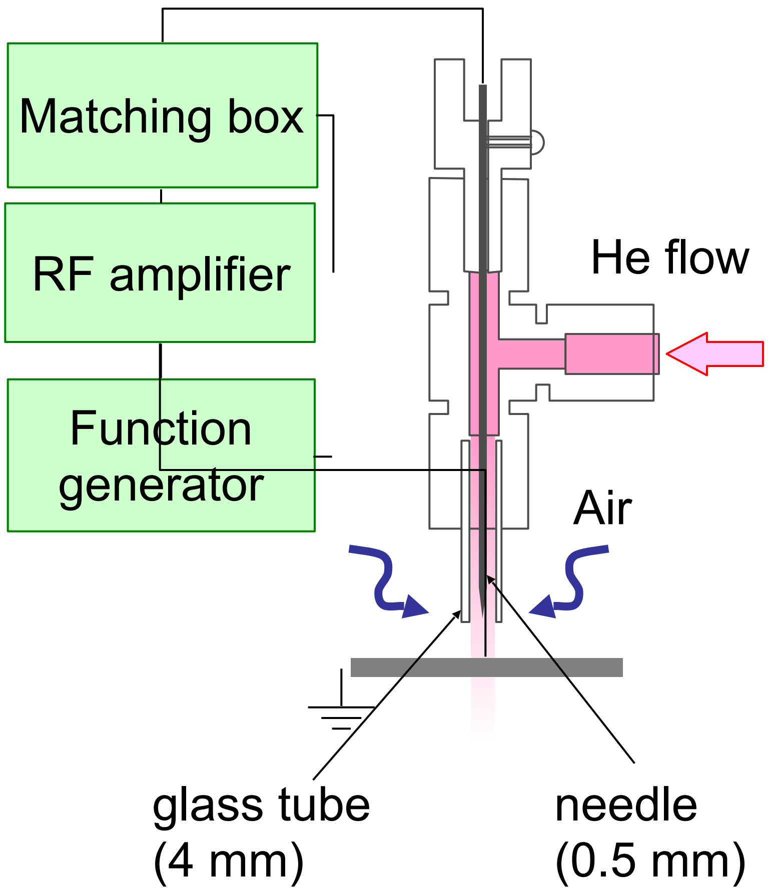
Plasmas in ambient air at room temperature

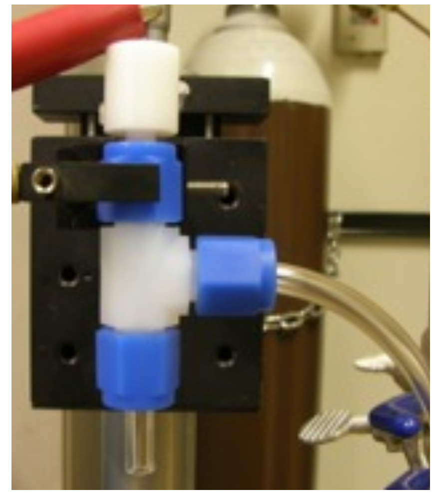


• voltage:	10-20 kVpkpk
• frequency:	1-10 kHz
• power:	~ 1W
• distance to finger:	1-3 mm
• gas:	static air in California

Plasma Needle: Can We Understand It?

E. Stoffels, et al., *Plasma Sources Sci. Tehcnol*. 11 (2002) 383.



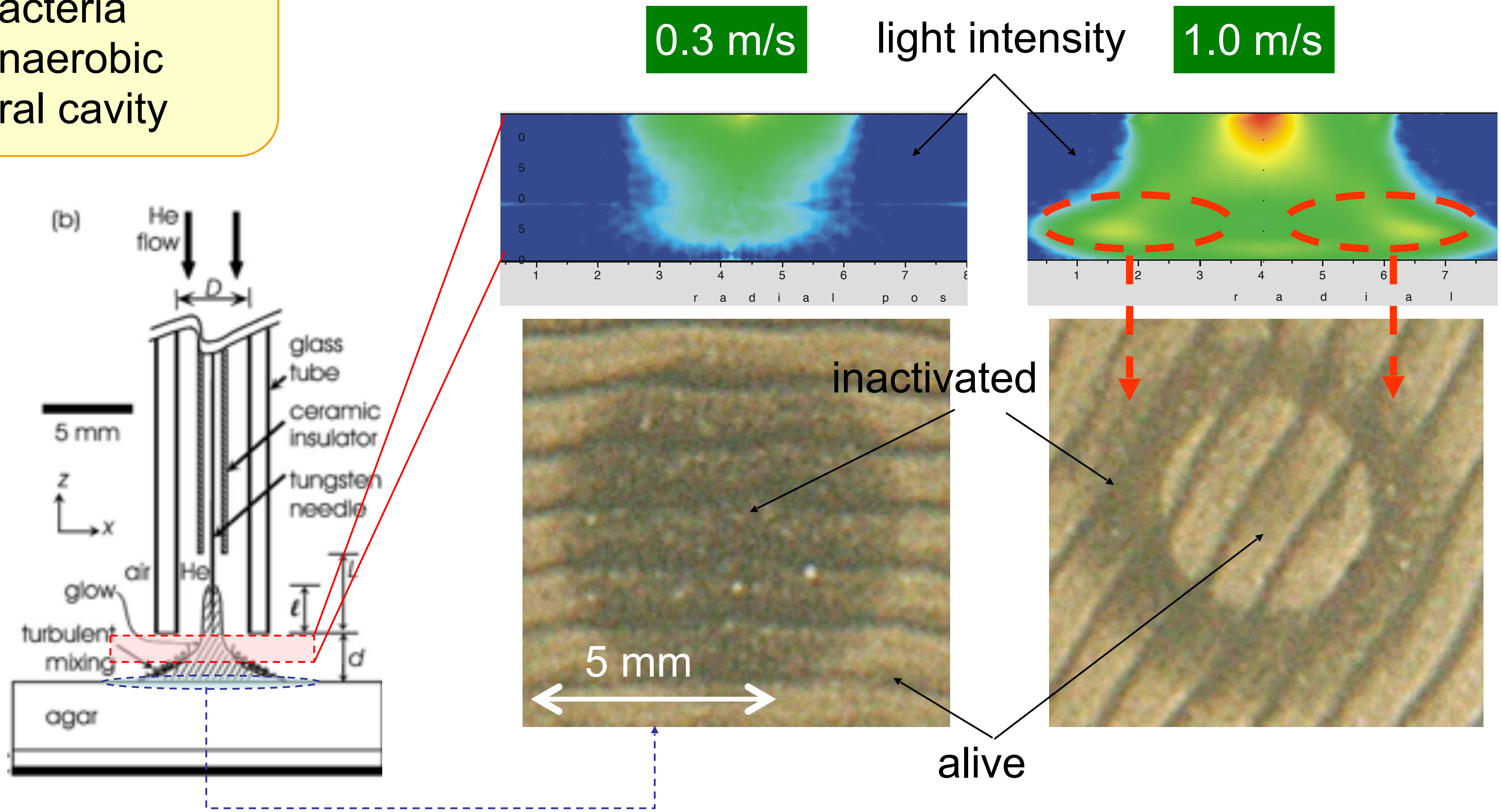


- Frequency: RF (13.56MHz)
- Voltage: 200-400 V_{pkpk}
- He flow rate: ~1 slpm (Re_d < 100)
- Power consumption: ~1 W
- Distance to sample: 1-5 mm

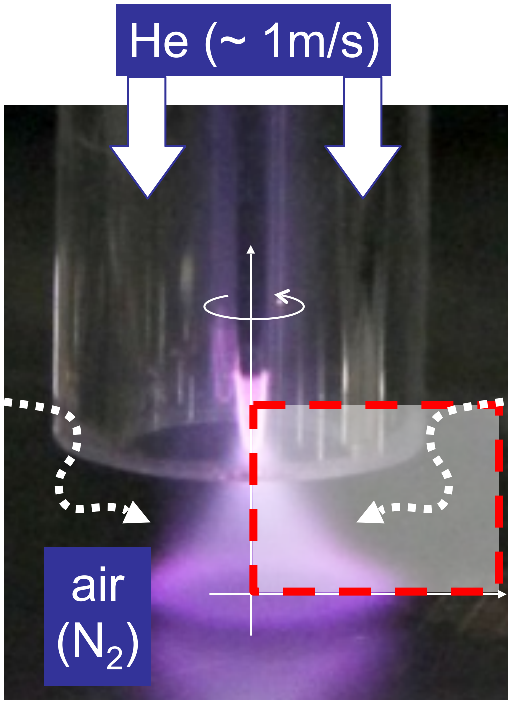
Plasma needle: Bactericidal effects

J.Goree, et al, *J.Phys.D.* 39 3479 (2006) and *IEEE Trans.Plasma Sci.* 34, 1317 (2006)

S. mutans
- bacteria
- anaerobic
- oral cavity



Fluid Model: Governing Equations



electron,
He*, He$_2$*,
He$^+$, He$_2$$^+$,N$_2$+

Neutral Gas flow (He, N$_2$)

$$\nabla\cdot(\rho\mathbf{u}) = 0, \nabla\cdot(\rho\omega_{air}\mathbf{u} - \rho D\nabla\omega_{air}) = 0$$ (mass conservation)

$$\nabla\cdot(\rho\mathbf{u}u_i) = -\nabla p - \nabla\cdot\bar{\bar{\ }} + \sum q_i n_i$$ (momentum conservation)

$$\nabla\cdot(-\lambda\nabla T + \mathbf{u}c_p T) = \Phi + \sum q_i \;{}_i + Q_{el}$$ (energy conservation)

ion momentum
collisional heating

temperature
velocity
species density

Plasma dynamics

$$\frac{\partial n_i}{\partial t} + \nabla\cdot\mathbf{\Gamma}_i = S_i$$ (mass conservation)

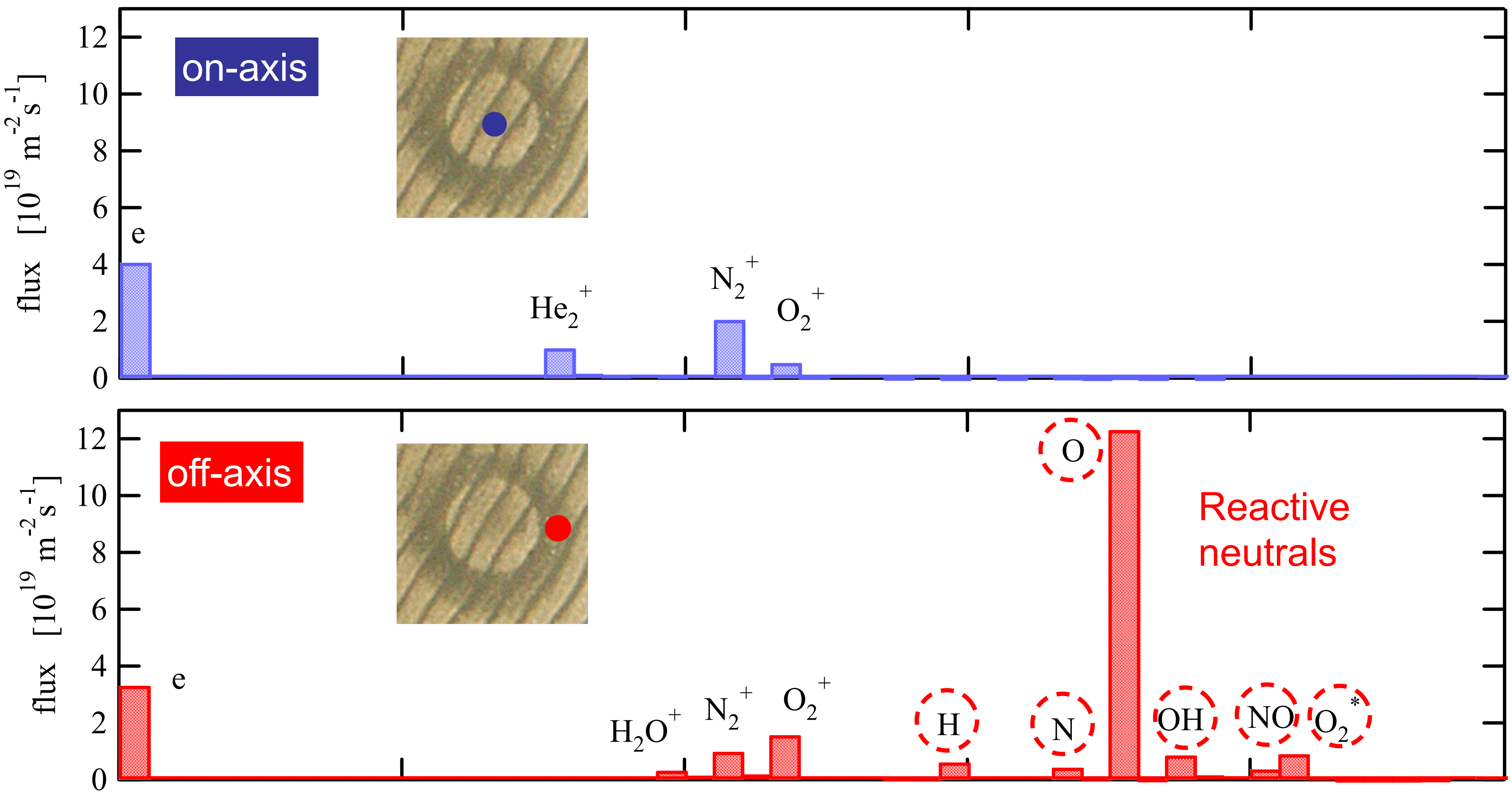
$$\mathbf{\Gamma}_i = \mathrm{sgn}(q_i)\, n_i \mu_i \mathbf{E} - D_i\nabla n_i + n_i\mathbf{u}$$ (drift-diffusion)

$$\frac{\partial(n_e\varepsilon)}{\partial t} + \nabla\cdot\left(\frac{5}{3}\varepsilon\,\mathbf{\Gamma}_e - \frac{5}{3}n_e D_e\nabla\varepsilon\right) = -\mathbf{\Gamma}_e\cdot\mathbf{E} - Q$$ (electron energy)

$$\varepsilon_0\nabla\cdot\mathbf{E} = \sum q_i n_i$$ (Poisson's equation)

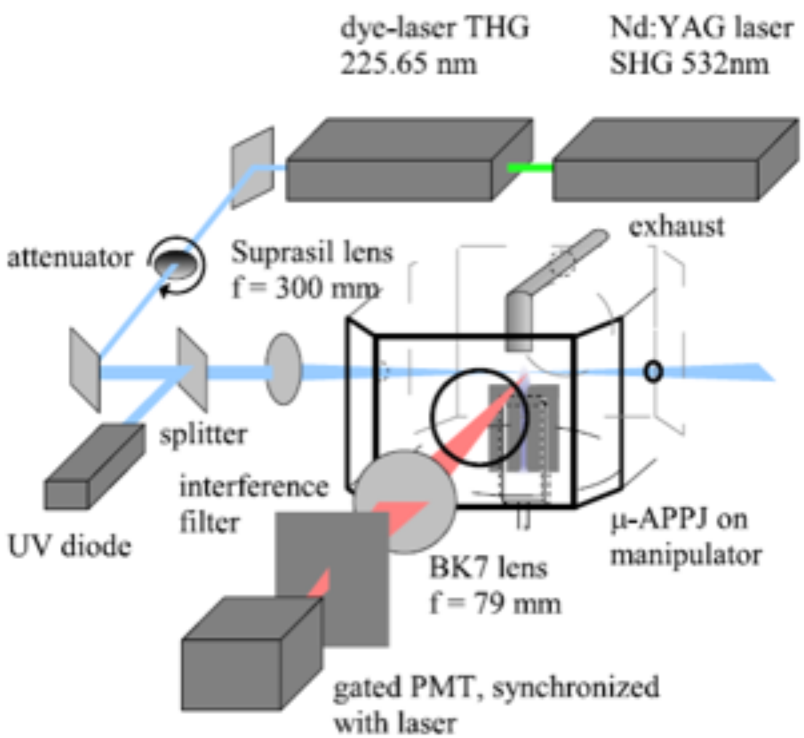
Y. Sakyiama et al, J. Appl. Phys. 101 (2007) 073306 and J. Phys. D 41 (2008) 95204

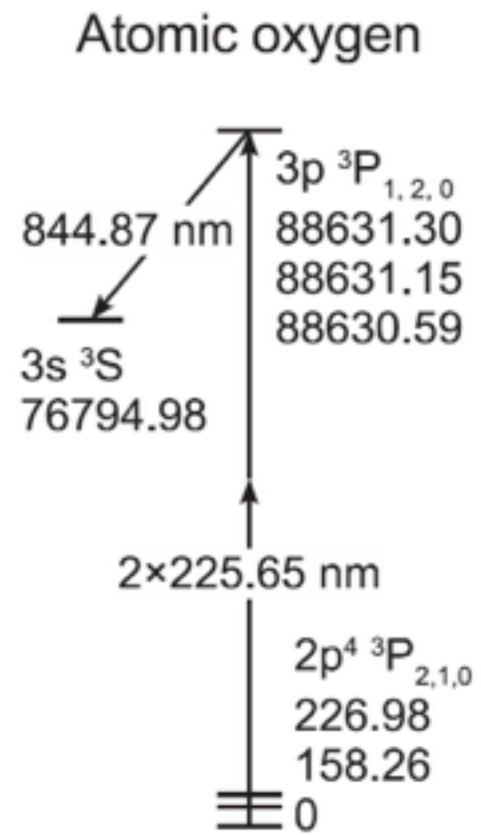
Species Fluxes to Surface



Model Validation: O Atom Measurement *

- TALIF: two photon absorbed laser induced fluorescence
- collaboration with Ruhr-Universitat Bochum (Germany)

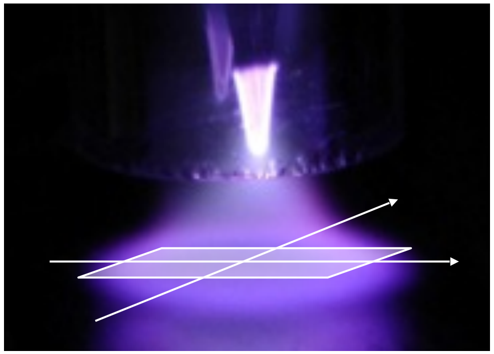


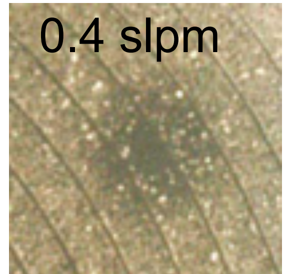


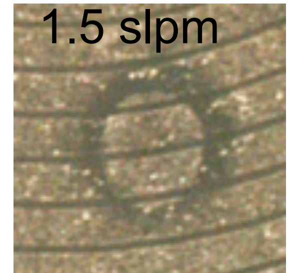
* Thanks to:
Volker Schulz-von der Gathen,

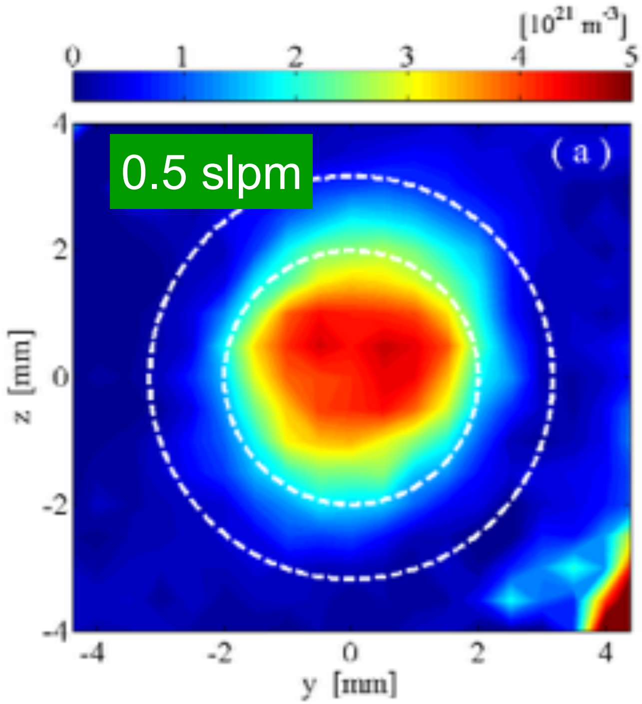
N. Knake, et al, *J. Phys. D: Appl. Phys*. 41 (2008) 194006

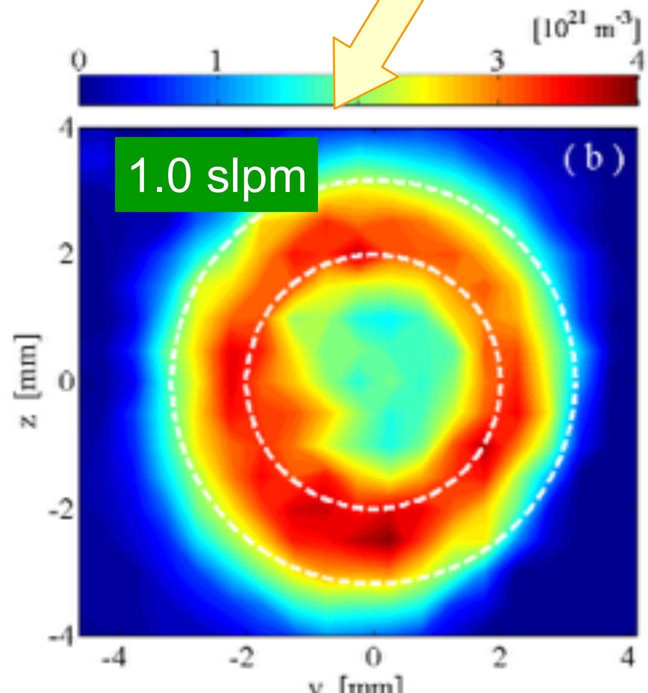
Measured O Atom Density: Qualitative Agreement with Model











Y. Sakiyama, et al., *Appl. Phys. Lett*. 97 (2010) 151501.

Reactive Oxygen and Reactive Nitrogen Species (RONS)

Reactive oxygen and nitrogen species often cited as key species in plasma biomedical applications.

But what is known about these species in biology and medicine?

One major focus of the talk is on these species and their role in biology and medicine

Related to the HUGE biomedical literature…, e.g.

Reactive Species and Antioxidants. Redox Biology Is a Fundamental Theme of Aerobic Life

Barry Halliwell[1]

Plant Physiology, June 2006, Vol. 141, pp. 312–322

The field of antioxidants and free radicals is often perceived as focusing around the use of antioxidant supplements to prevent human disease. In fact, antioxidants/free radicals permeate the whole of life, creating the field of *redox biology*. Free radicals are not all bad, nor antioxidants all good. Life is a balance between the two: antioxidants serve to keep down the levels of free radicals, permitting them to perform useful biological functions without too much damage.

See also:

Halliwell B, Gutteridge JMC (2006) Free Radicals in Biology and Medicine, Ed 4. Clarendon Press, Oxford

Reactive Oxygen Species: ROS

Radicals	Nonradicals
ROS	*ROS*
Superoxide, $O_2^{\bullet -}$	H_2O_2
Hydroxyl, $OH^{\bullet}$	Hypobromous acid, HOBr[a]
Hydroperoxyl, $HO_2^{\bullet}$ (protonated superoxide)	Hypochlorous acid, HOCl[b]
Carbonate, $CO_3^{\bullet -}$	Ozone, O_3[c]
Peroxyl, $RO_2^{\bullet}$	Singlet oxygen ($O_2{}^1\Delta g$)
Alkoxyl, $RO^{\bullet}$	Organic peroxides, ROOH
Carbon dioxide radical, $CO_2^{\bullet -}$	Peroxynitrite, $ONOO^{-}$[d]
Singlet $O_2{}^1\Sigma g^{+}$	Peroxynitrate, O_2NOO^{-}[d]
	Peroxynitrous acid, ONOOH[d]
	Peroxomonocarbonate, $HOOCO_2^{-}$

Halliwell, Plant Phys. 2006

Reactive Chlorine/Bromine Species

Radicals	**Nonradicals**
Reactive chlorine	***Reactive chlorine***
Atomic chlorine, $Cl^{\bullet}$	Hypochlorous acid, HOCl[b]
	Nitryl chloride, NO_2Cl[e]
	Chloramines
	Chlorine gas (Cl_2)
	Bromine chloride (BrCl)[a]
	Chlorine dioxide (ClO_2)
Reactive bromine	***Reactive bromine***
Atomic bromine, $Br^{\bullet}$	Hypobromous acid (HOBr)
	Bromine gas (Br_2)
	Bromine chloride (BrCl)[a]

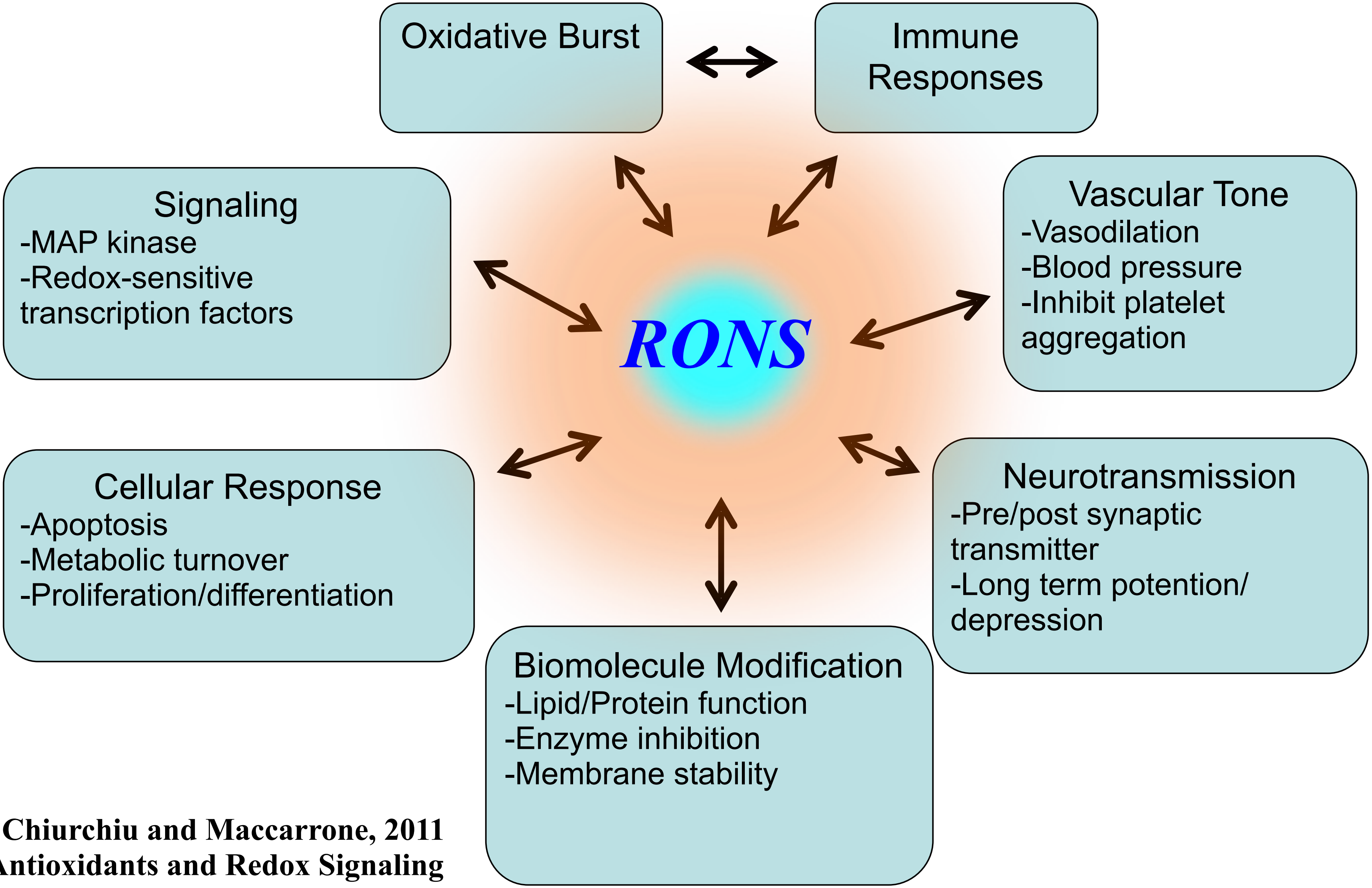
Halliwell, Plant Phys. 2006

Reactive Nitrogen Species: RNS

Radicals	**Nonradicals**
Reactive nitrogen	***Reactive nitrogen***
Nitric oxide, $NO^{\bullet}$	Nitrous acid, HNO_2
Nitrogen dioxide, $NO_2^{\bullet}$[c]	Nitrosyl cation, NO^+
Nitrate radical, $NO_3^{\bullet}$[c,f]	Nitroxyl anion, NO^-
	Dinitrogen tetroxide, N_2O_4
	Dinitrogen trioxide, N_2O_3
	Peroxynitrite, $ONOO^-$[d]
	Peroxynitrate, O_2NOO^-[d]
	Peroxynitrous acid, $ONOOH$[d]
	Nitronium cation, NO_2^+
	Alkyl peroxynitrites, ROONO
	Alkyl peroxynitrates, RO_2ONO
	Nitryl chloride, NO_2Cl
	Peroxyacetyl nitrate, $CH_3C(O)OONO_2$[c]

Halliwell, Plant Phys. 2006

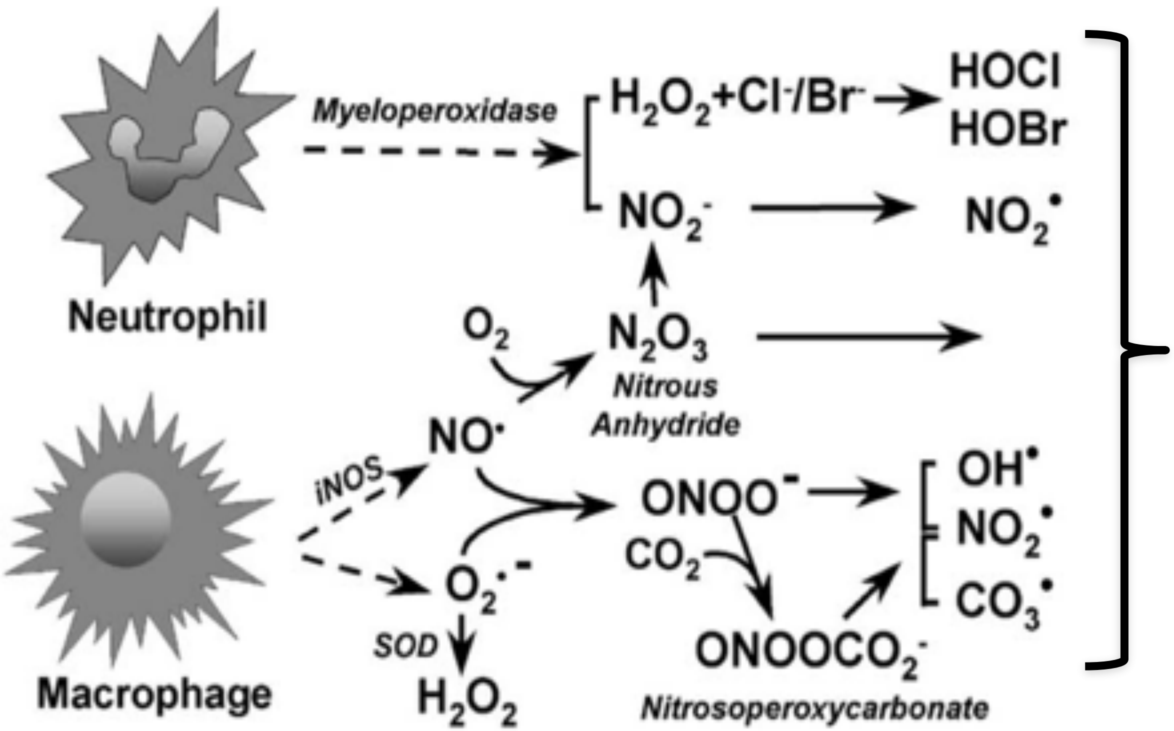
Some Physiologic/Homeostatic Actions of RONS*



***Chiurchiu and Maccarrone, 2011**
Antioxidants and Redox Signaling

Reactive Species Play Major Role in Aerobic Biology:
Example of Innate Immune System and Inflammation

Dedon and Tannenbaum, ***Archives of Biochemistry and Biophysics*, 423, 2004**



Subsequent Reactions

Many similar chemical species are created in air plasmas

Some Disease States Associated with RONS

1. *Cancer*

2. *Cardiovascular disease*
   a. Congestive heart failure
   b. Atherosclerosis
   c. Heart attack
   d. Stroke

3. *Neurodegenerative diseases*
   a. Alzheimer's
   b. Huntington's
   c. Parkinson's
   d. Multiple sclerosis

4. *Inflammatory bowel disease*

5. *Diabetes*

6. *Rheumatoid arthritis*

7. *Lung*
   a. Bronchial asthma
   b. Chronic obstructive pulmonary disease
   c. Acute respiratory distress syndrome
   d. Cystic fibrosis

8. *Skin*
   a.Chronic skin inflammation
   b.Psoriasis
   c.Atopic dermatitis
   d.Acne

9. *Eyes*
   a.Macular degeneration
   b.Cataracts

10. *Reproductive disorders*
    a.Male/female infertility
    b.preeclampsia
    c.hydatidiform mole
    d.fetal embryopathies

Bio-Radicals Formed by Ionizing Radiation

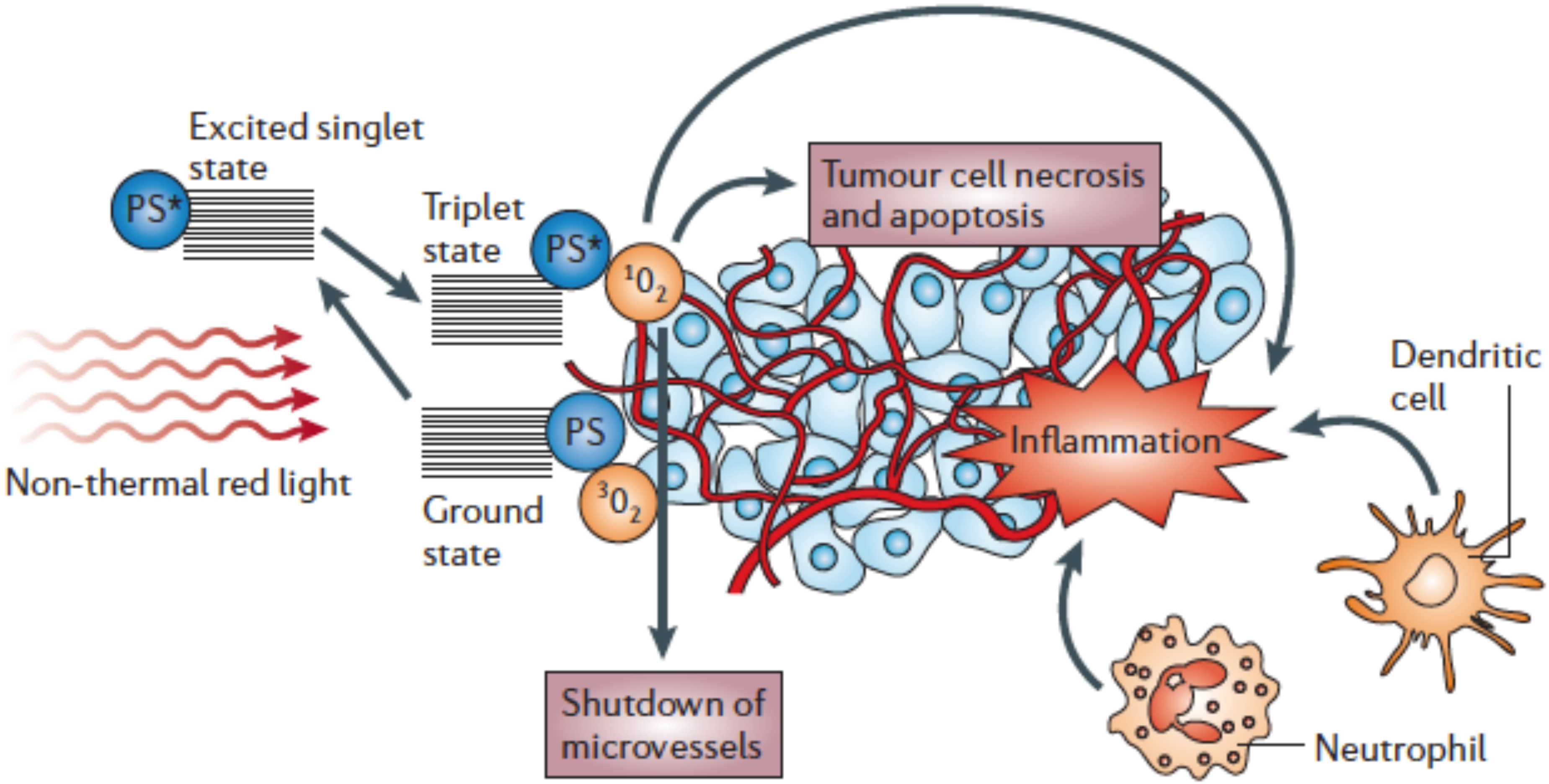
Int. J. Radiat. Biol., Vol. 85, No. 1, January 2009, pp. 9–25

O'Neil and Wardman

Name	Formula
singlet oxygen (excited state)	$^1O_2$
superoxide/hydroperoxide radical	$O_2^{\bullet -}/HO_2^{\bullet}$
hydroxyl radical	$^{\bullet}OH$
hydrogen peroxide	H_2O_2
hypochlorous acid	HOCl
hypobromous acid	HOBr
hypothiocyanous acid	HOSCN
nitric oxide radical	$NO^{\bullet}$
nitrogen dioxide radical	$NO_2^{\bullet}$
dinitrogen trioxide	N_2O_3
nitroxyl	HNO
peroxynitrite/peroxynitrous acid	$ONOO^-/ONOOH$
nitrosoperoxycarbonate	$ONOOCO_2^-$
carbonate radical	$CO_3^{\bullet -}$
carbon-centred radicals	$RC^{\bullet}(X)R'$
peroxyl radicals on carbon	$RC(OO^{\bullet})(X)R'$
thiyl radicals	$RS^{\bullet}$
disulfide radical-anions	$(RS \therefore SR')^-$
thiylperoxyl radicals	$RSOO^{\bullet}$
sulfonyl radicals	$RS(O)(O)^{\bullet}$
sulfonylperoxyl radicals	$RS(O)(O)OO^{\bullet}$
nitrogen-centred indolyl radicals	$-N^{\bullet}-$
phenoxyl radicals, e.g., tyrosine	$TyrO^{\bullet}$

Formation of radicals thought to be central to cancer radiation therapy

Photodynamic Therapy Creates $^{1}O_2$



Castano et al., Nature Revs., 2006

Cancer Chemotherapy and ROS Generation or Antioxidant Depletion/Inhibition

Agents that cause cellular ROS stress

Mechanism	Agent
ROS generation	Arsenic trioxide
	Anthracyclines
	Bleomycin
	Bortezomib
	Cisplatin
	N-(4-hydroxyphenyl) retinamide
	Emodin
GSH depletion	Buthionine sulfoximime (γ-GCS inhibitor)
	Diethylmaleate
	Ascorbic acid
Inhibition of antioxidant enzyme	Mercaptosuccinic acid (GPx)
	Aminotriazol (catalase)
	Ethacrynic acid, TLK199 (GST)
	2-Methoxyoestradiol (SOD)

Pelicano et al., 2004

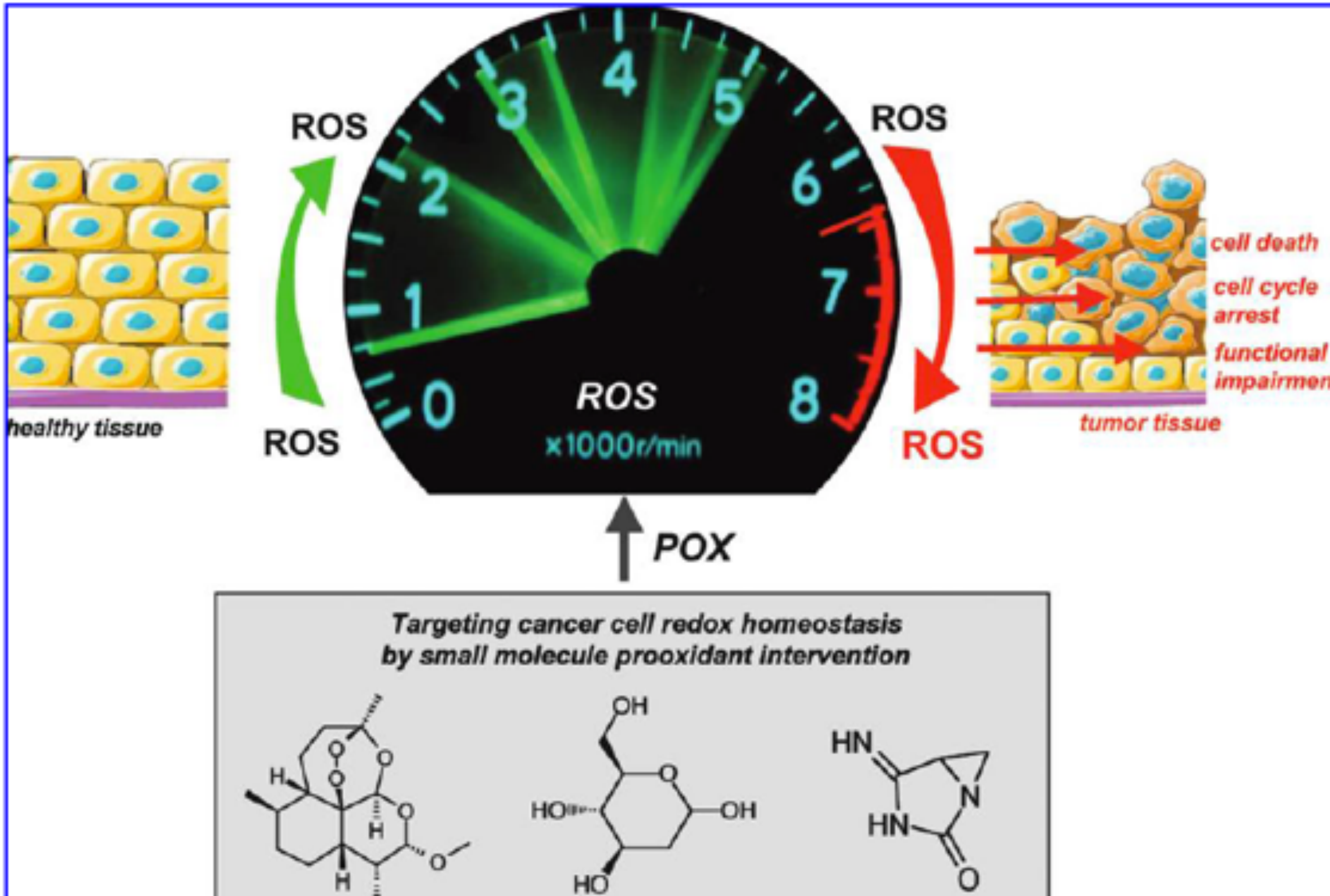
Redox-Directed Cancer Therapeutics: Molecular Mechanisms and Opportunities

ANTIOXIDANTS & REDOX SIGNALING
Volume 11, Number 12, 2009

DOI: 10.1089/ars.2009.2541

COMPREHENSIVE INVITED REVIEW

Georg T. Wondrak



Implications/questions for plasma medicine

Summary of RONS Importance in *Biological Function*

- **RONS are known to play key roles in normal physiological functions such as cell signaling, vascular tone, neural transmission, apoptosis, etc.**

- **Well established that excessive RONS can be carcinogenic and are associated with many degenerative and other important diseases and aging**

- **RONS are also known to play key roles in immune system – mostly innate (inflammatory) system, but also adaptive system**

Summary of RONS Importance in *Established Therapies*

- **The mechanisms of all antibiotics (e.g. Collins et al., 2007) and at least some antifungal and antiparasitic drugs (e.g. Artemisenin) appear to involve ROS generation.**

- **Many cancer therapies are based on the direct or indirect creation of RONS. *Radiation therapy*, *photodynamic therapy (PDT)* and certain *chemotherapies* all exploit this effect.**

In other words, it is NOT SURPRISING that plasma medicine works - it is based on RONS chemistry that works in other therapies

Confluence of Redox Biology and Plasma Science: *Status*

- **Low temperature plasmas create RONS and other reactive species in relatively high densities at ambient gas temperature**

- **Preliminary positive results for *infection control* (disinfection/sterilization and antisepsis); *wound healing*; *cancer therapy*; various *dermatology applications*; *dental wound/cavity/biofilm treatment*; others**

- **But how do plasma-generated RONS work in detail? (e.g. through reactions with lipids/proteins?); Does plasma-generation of RONS provide unique advantages?**

More details:

TOPICAL REVIEW

The emerging role of reactive oxygen and nitrogen species in redox biology and some implications for plasma applications to medicine and biology

J. Phys. D: Appl. Phys. **45** (2012) 263001 (42pp)

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Low temperature plasma biomedicine: A tutorial review[a)]

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Reactive Species from Cold Atmospheric Plasma: Implications for Cancer Therapy

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Oxy-Nitroso Shielding Burst Model of Cold Atmospheric Plasma Therapeutics

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