Biomedical Applications of Ambient Gas Plasma: The Confluence of Redox Biology and Plasma Science

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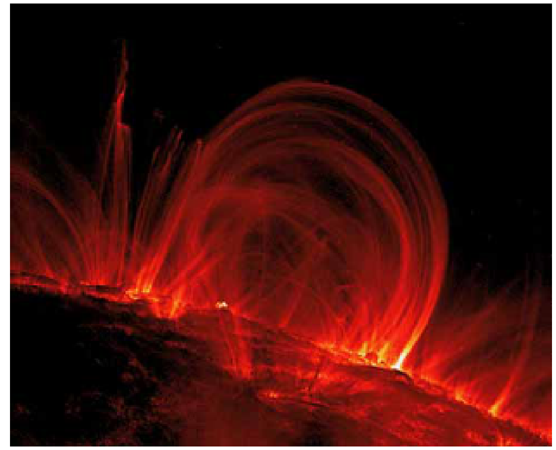
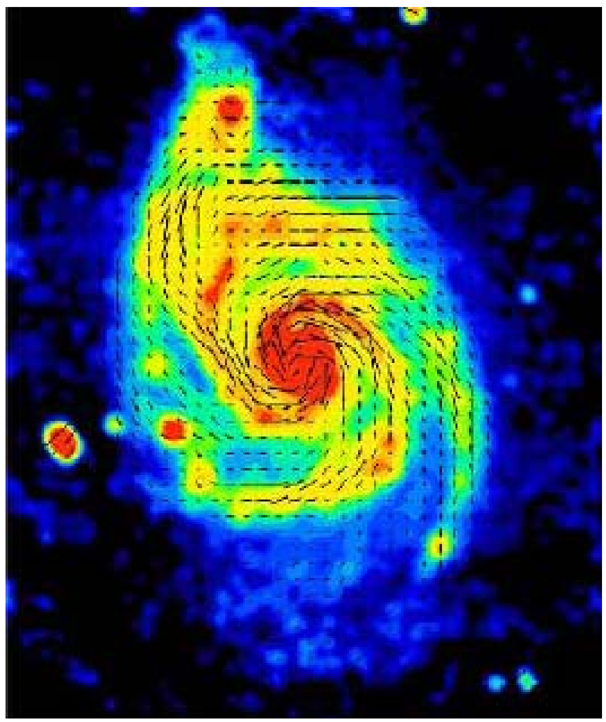
Natural *Ionized Gas* Plasmas

Aurora



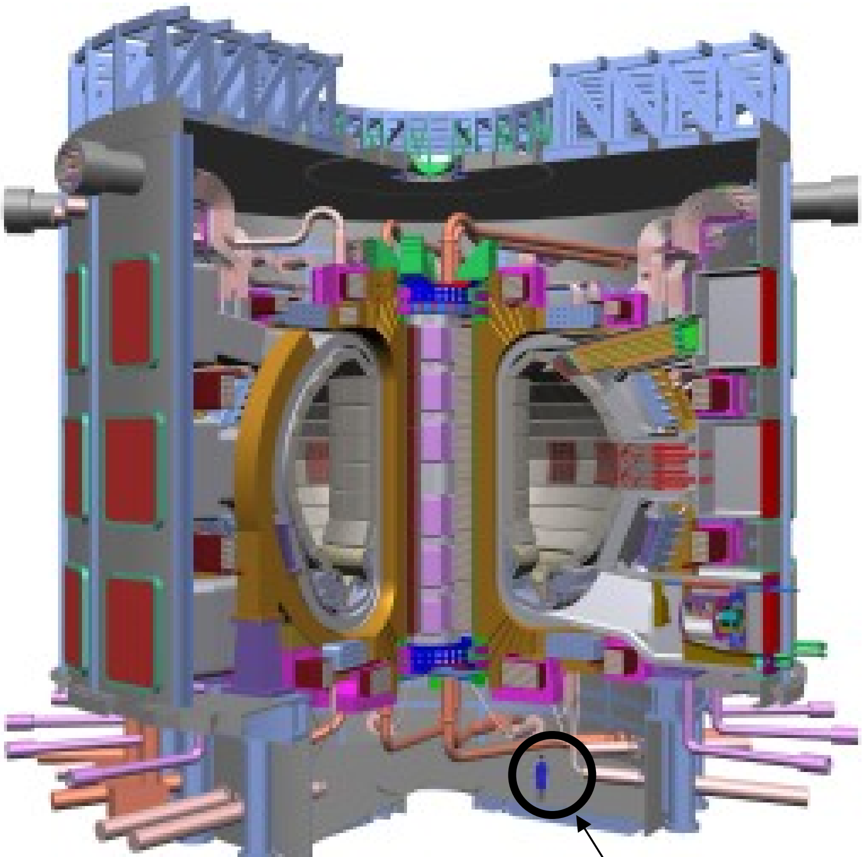
Lightning

Solar Corona

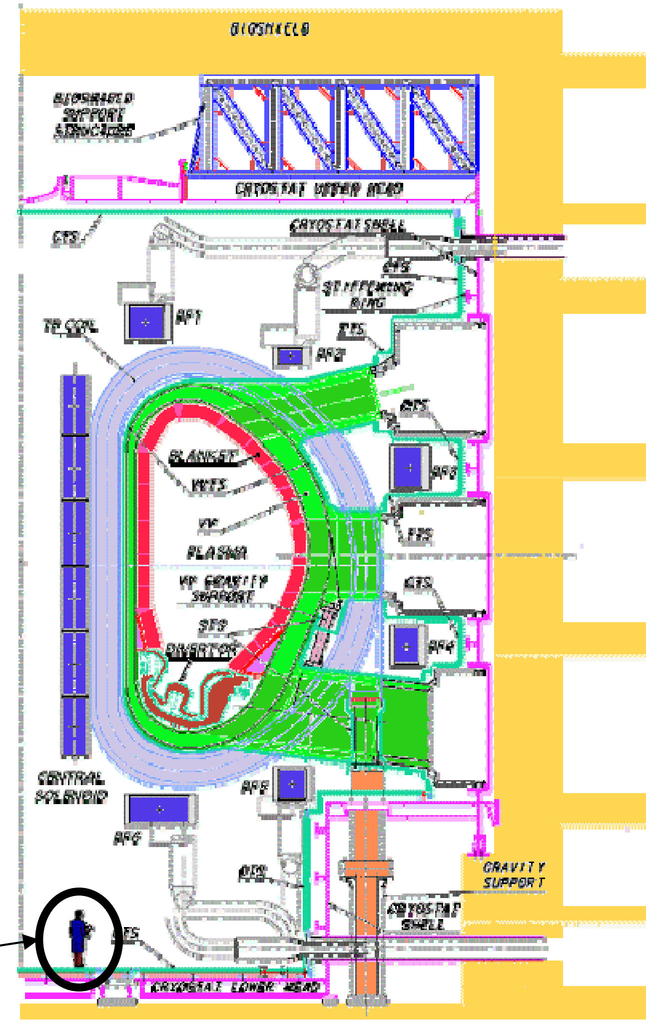


‘Whirlpool galaxy’ M51; plasma emission and magnetic field lines

Tokamaks – Plasma Fusion

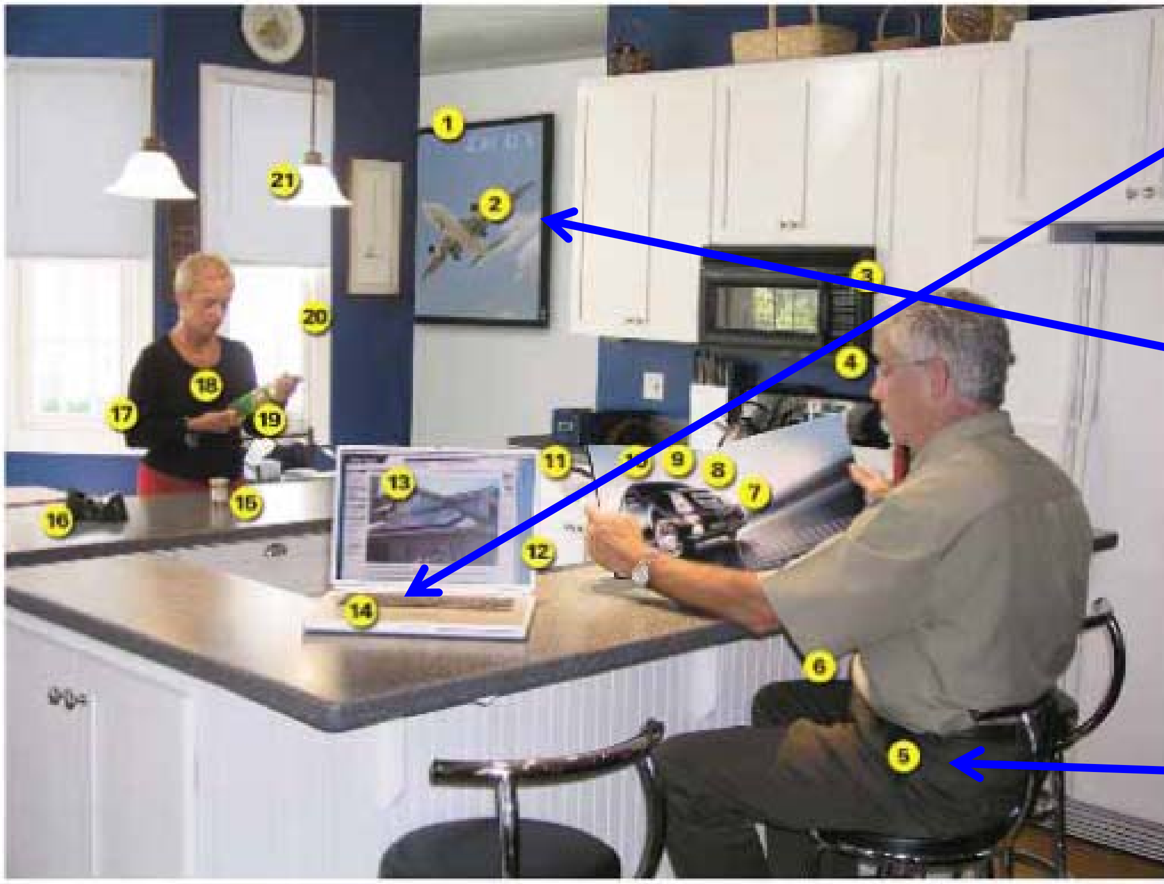


Notice scale!



ITER: International Thermonuclear Experimental Reactor: plasma fusion for electric power generation

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



Plasma-processed microelectronics

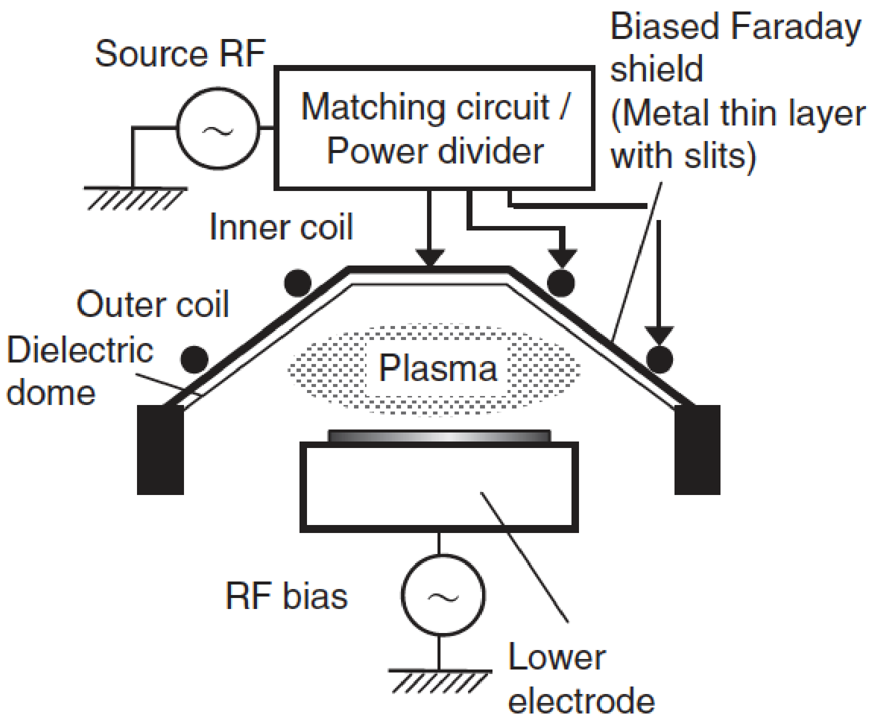
Plasma TV

Plasma ion-implanted artificial hip

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

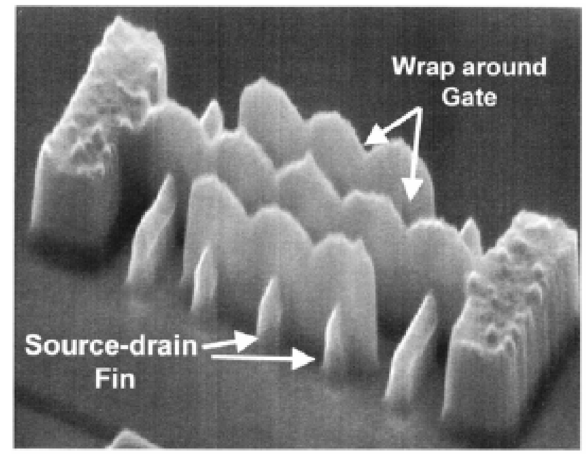
* Plasma 2010 NRC, 2007

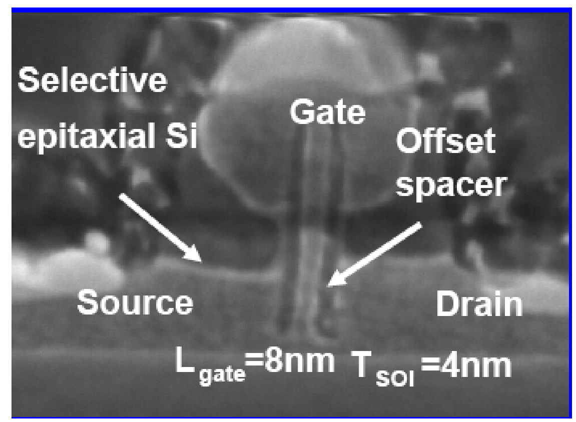
Plasma Etching: IC Manufacture



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

Advanced devices





Courtesy Y. Zhang, IBM Research

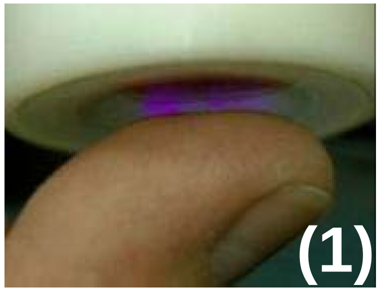
Plasmas used to process semiconductors to make integrated circuits (ICs) – ***Nano***electronics has replaced ***micro***electronics: sub-10 nm critical dimensions

Plasma biomedicine/sources/chemistry

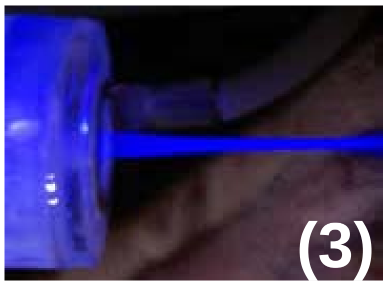
Abbreviated History of Gas Plasmas In Biomedicine

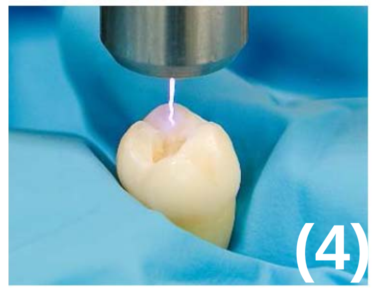
- 2011 M. Vandamme/M. Keidar: *in vivo* cancer tumor treatment (jet/DBD)
- 2010 G. Isbary: clinical trial for wound healing (MW Ar plasma)
- 2007 G. Fridman: *in vitro* cancer cell treatment (Air DBD)
- 2003 E. Stoffels: non-destructive cell handling (He plasma needle)
- 2000 Plasma Surgical Company: 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

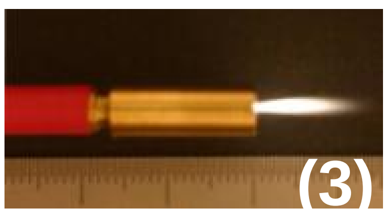
Atmospheric Pressure Plasma Sources for Biomedical Applications

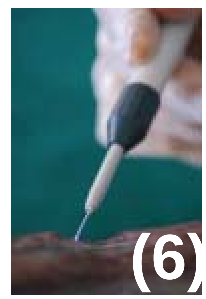


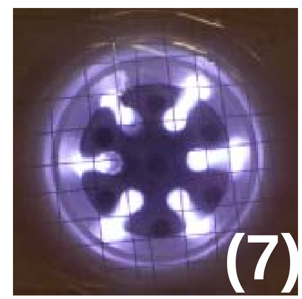
(1) Drexel University (USA)
(2) Cinogy GmbH (GER)
(3) Old Dominion University (USA)
(4) IOM Leipzig (GER)
(5) Eindhoven Univ. of Techn. (NED)
(6) New York University (USA)
(7) MPE Garching (GER)
(8) University of Orléans (FRA)
(9) McGill University, Montreal (CAN)
(10) Loughborough University (UK)
(11)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

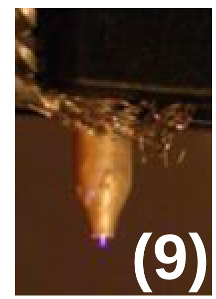


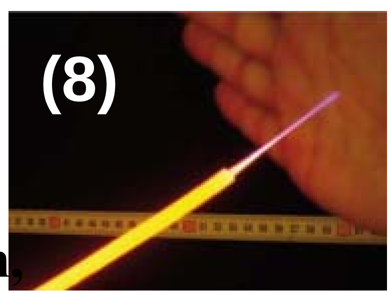


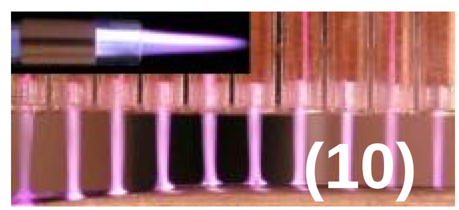


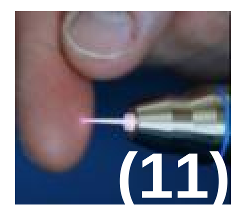










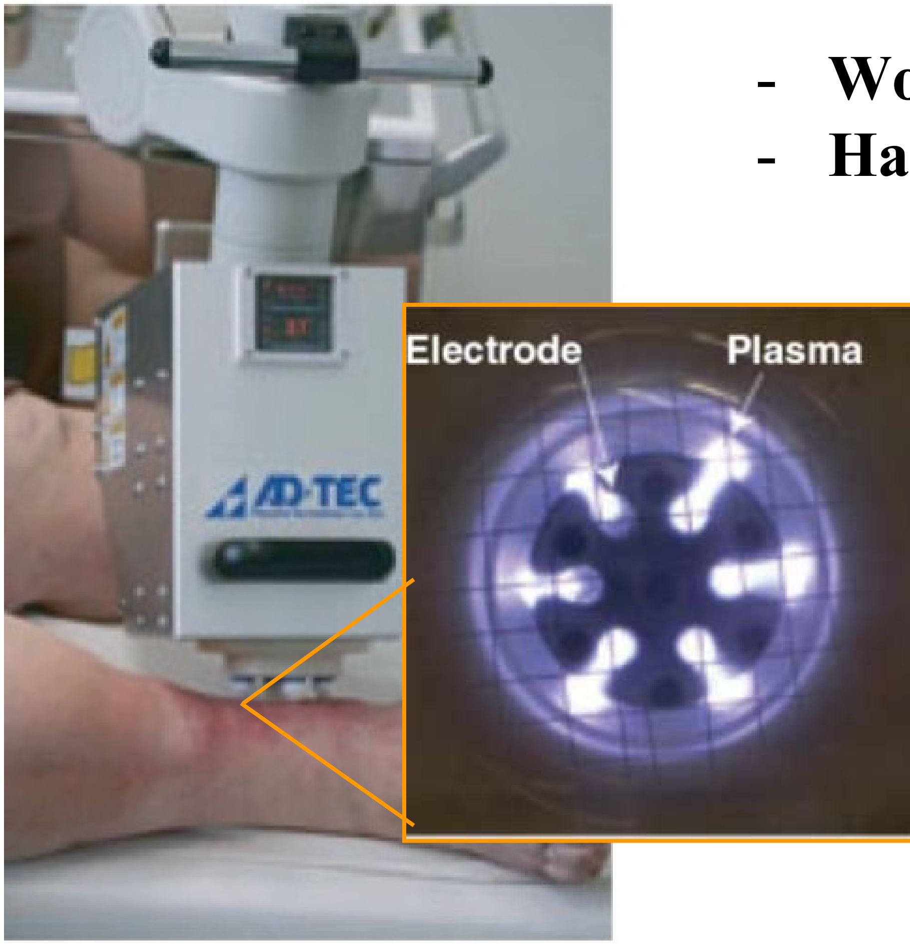


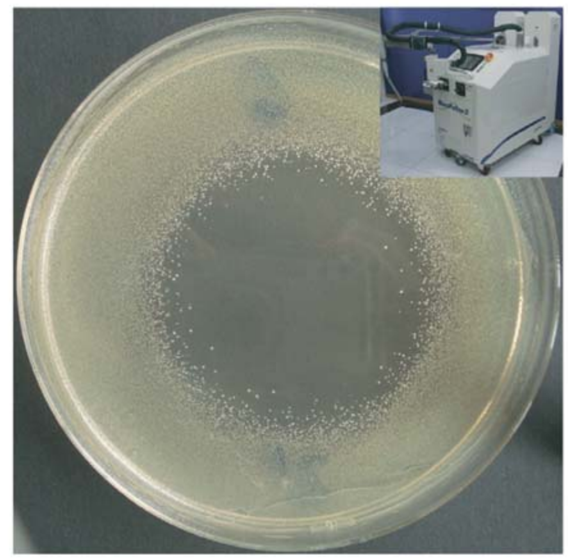
Courtesy:
K.D. Weltmann, Greifswald

Plasma Sources in Biomedicine: Microwave Ar plasma torch

J. Heinlin, *JDDG* 8 (2010) 968; G. Isbary, Br. J. Dermatol. 163 (2010) 78, Arch. Derm., 147 (2011), 388.

- **Wound sterilization**
- **Hailey-Hailey disease treatment**





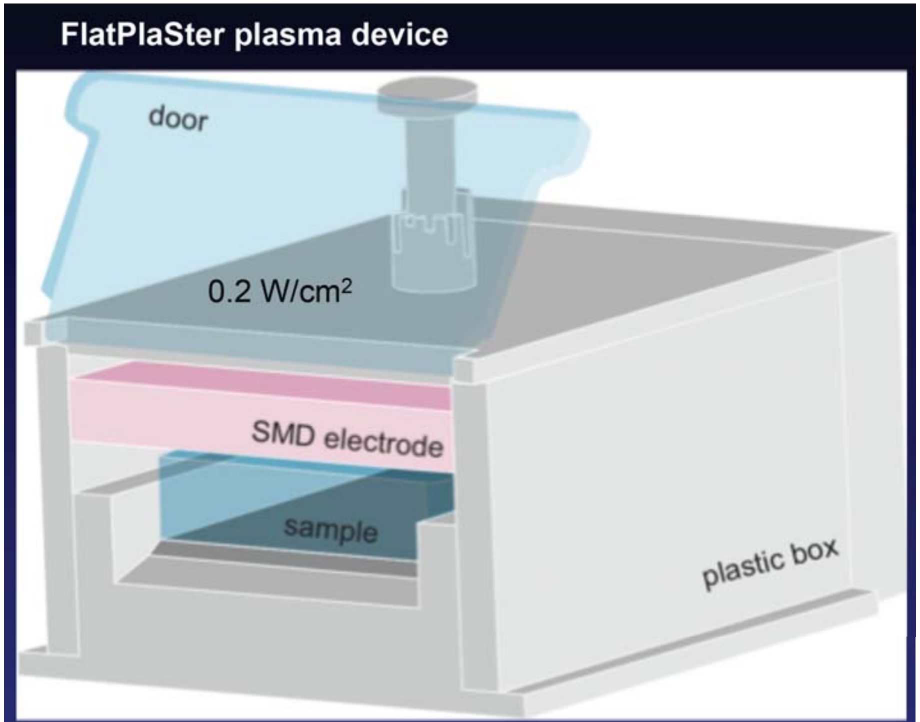
Prof.-Dr. G. Morfill
MPE, Garching, Germany

Decolonisation of MRSA, *S. aureus* and *E. coli* by Cold-Atmospheric Plasma Using a Porcine Skin Model *In Vitro*

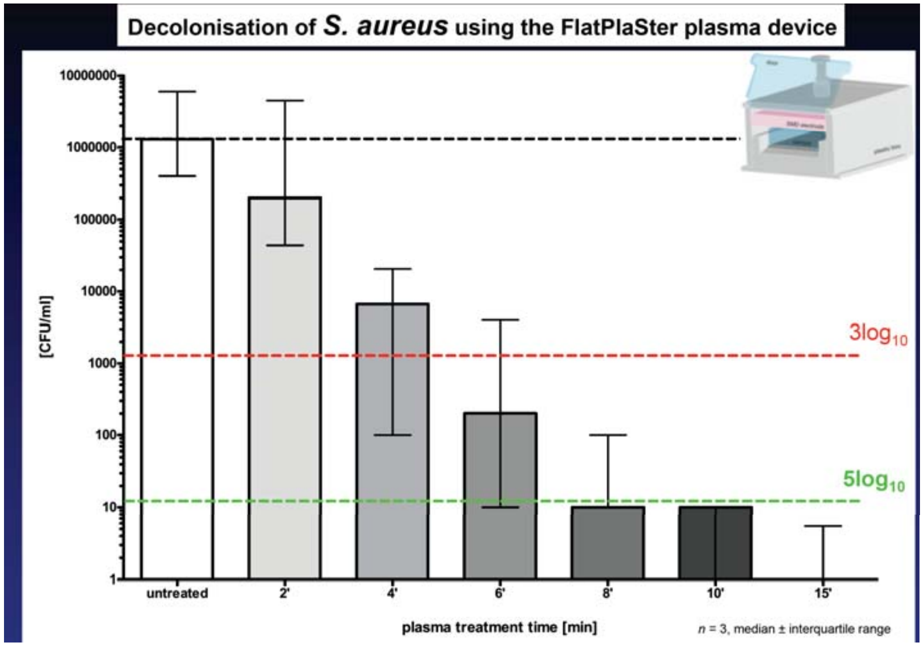
Tim Maisch[1]*, Tetsuji Shimizu[2], Yang-Fang Li[2], Julia Heinlin[1], Sigrid Karrer[1], Gregor Morfill[2], Julia L. Zimmermann[2]

1 Department of Dermatology, Regensburg University Hospital, Regensburg, Bavaria, Germany, **2** Max Planck Institute for Extraterrestrial Physics, Garching, Bavaria, Germany

PLoS ONE 7(4): e34610. doi:10.1371/journal.pone.0034610 (2012)



High sinusoidal voltage of 9 kVpp with 1 kHz in frequency was applied between the brass electrode and the mesh electrode producing the plasma on the mesh side



Plasma-induced wound healing: various anecdotal reports

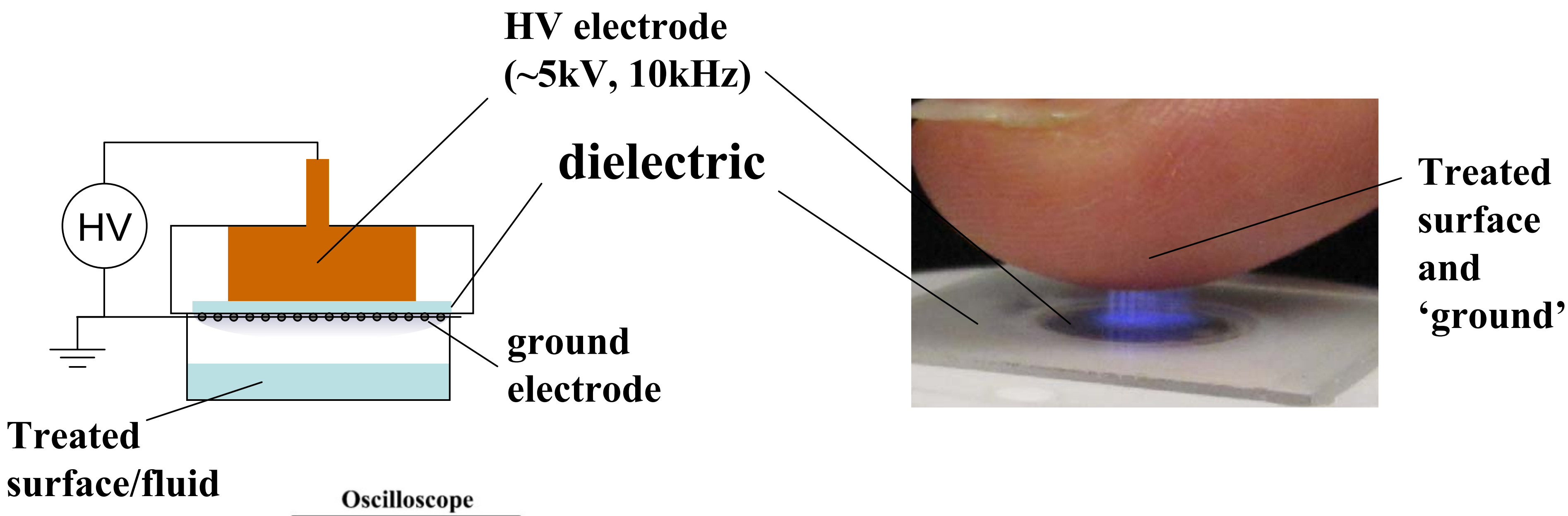
Treatment of Topical Wounds: Tissue Regeneration: Suppurated Burn Wound (2009 conference)*

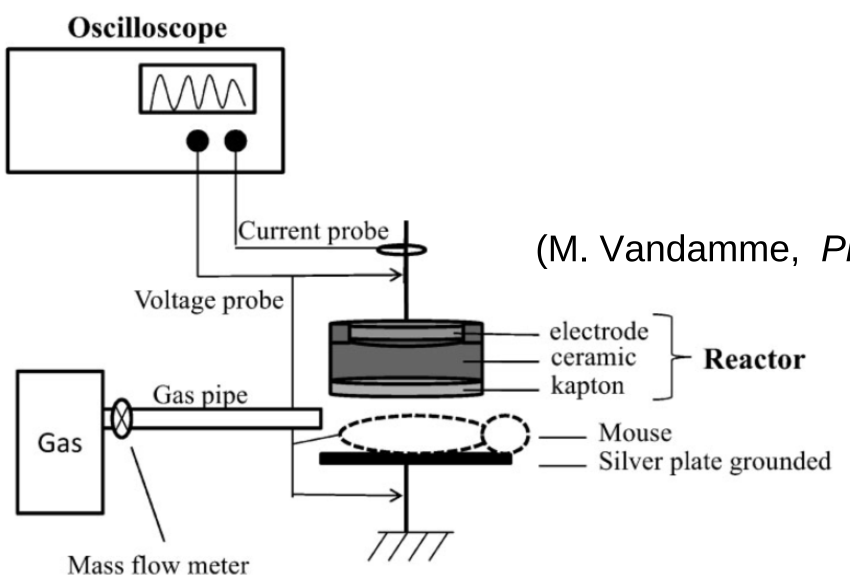
Before treatment

After 7 days/ 5 sessions plasma treatment

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

Plasma Sources in Biomedicine: Indirect and Direct DBD

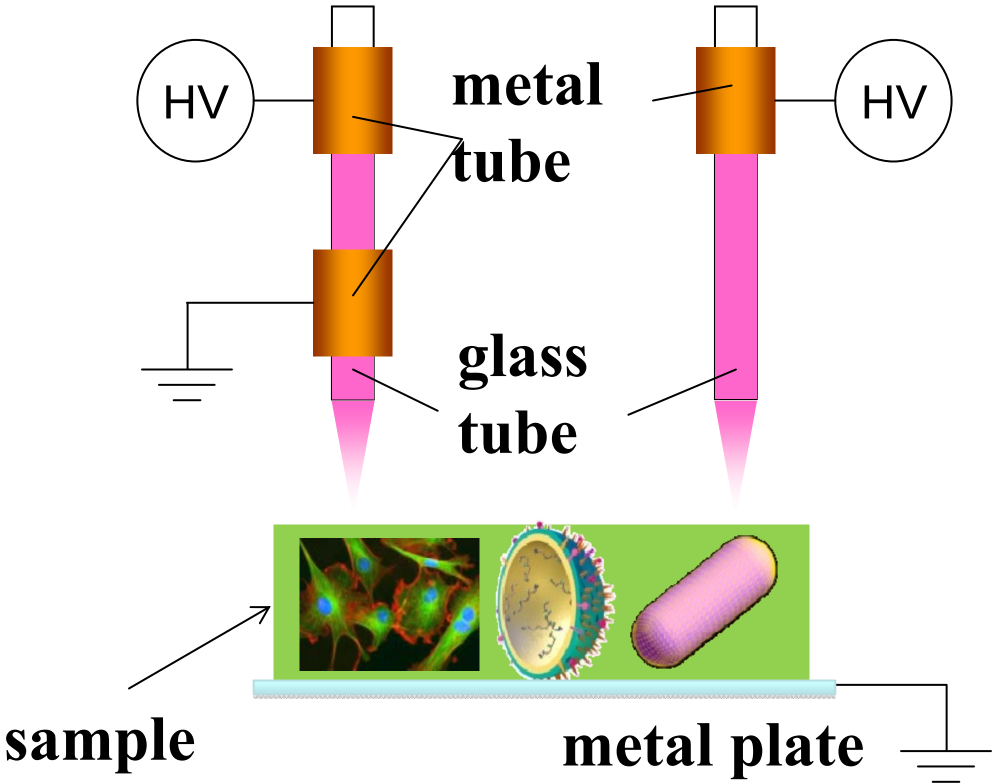


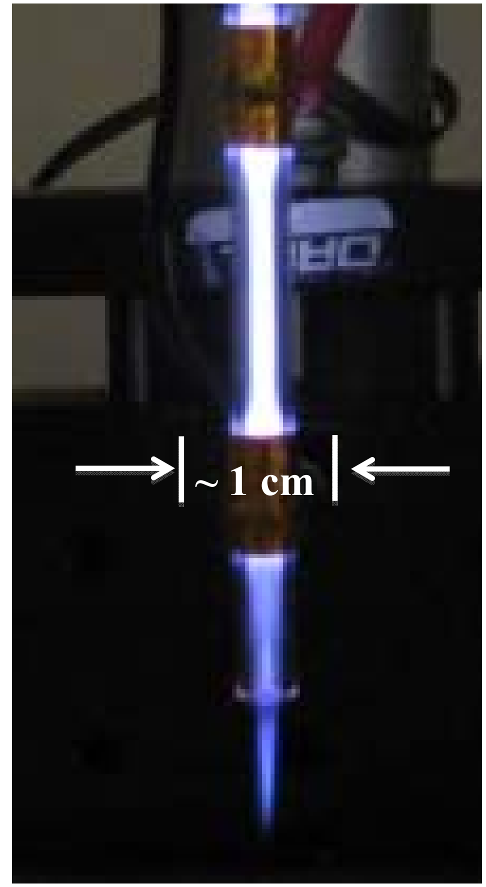


(M. Vandamme, *Plasma Process. Polym.* 7 (2010) 264)

Prof. J.-M. Pouvesle,
Univ. d'Orléans, France

Rare Gas Jet Discharge (He or Ar)

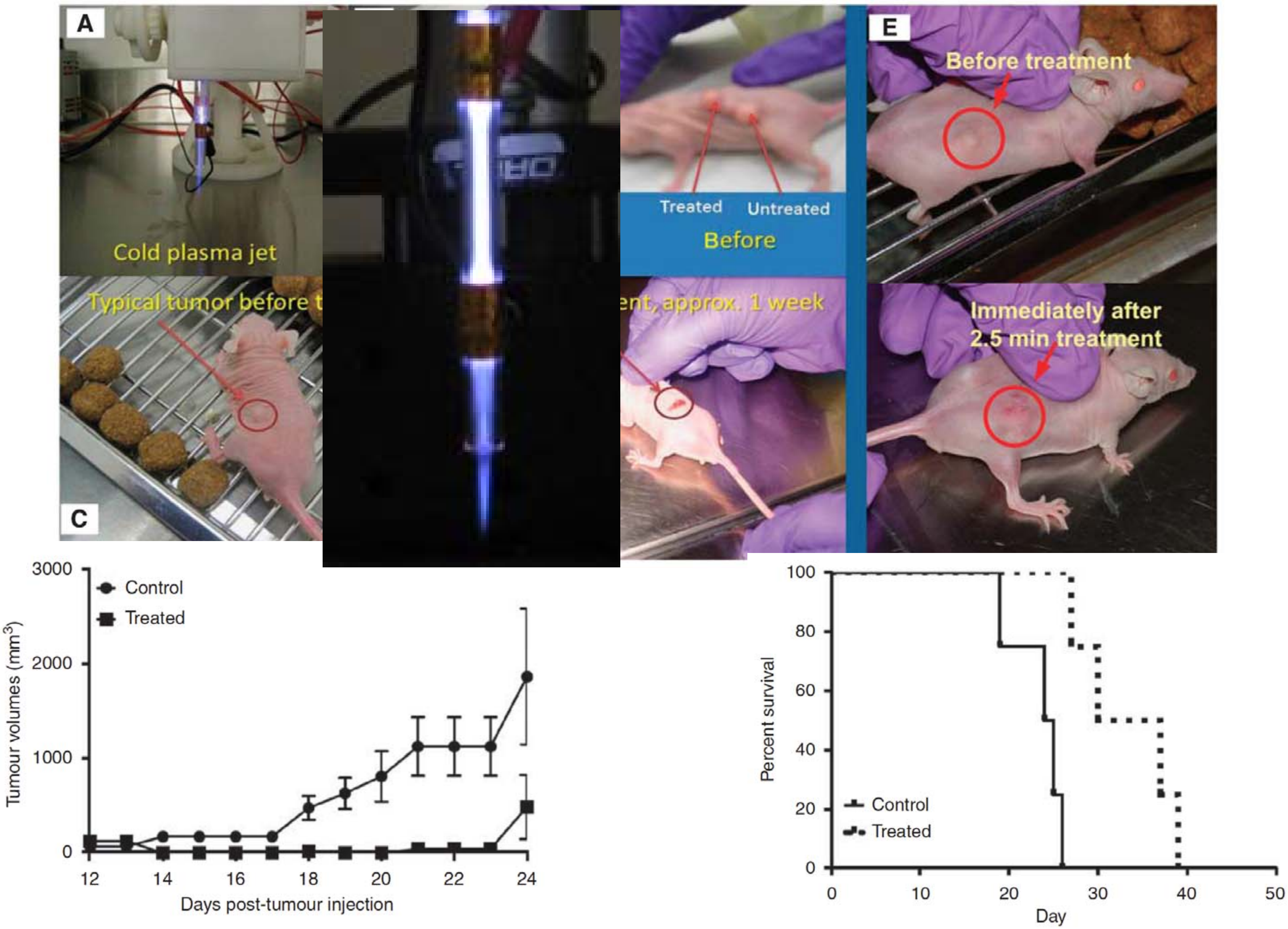




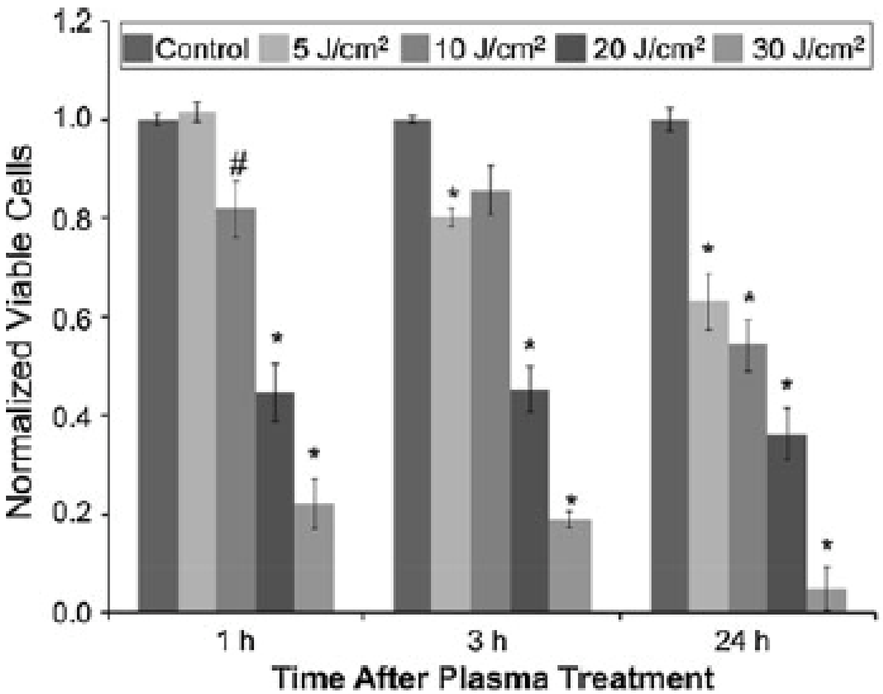
Note: *scalable via parallel jet arrays*

M. Kong, Loughborough Univ., UK

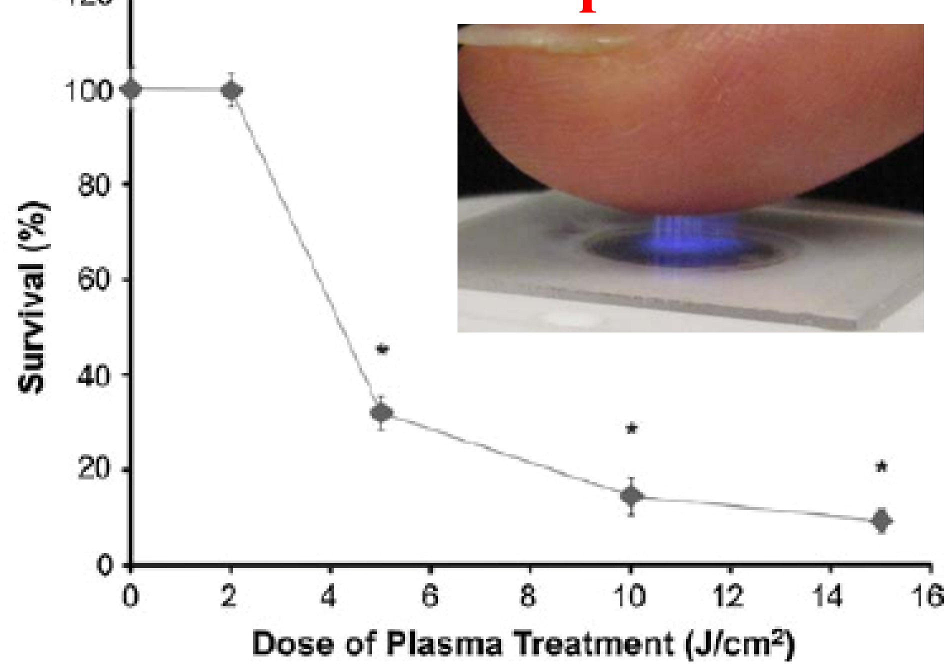
British Journal of Cancer (2011) **105**(9), 1295 – 1301 Keidar et al., Dec. 2011; melanoma murine model



…and *in vitro* (melanoma cells)



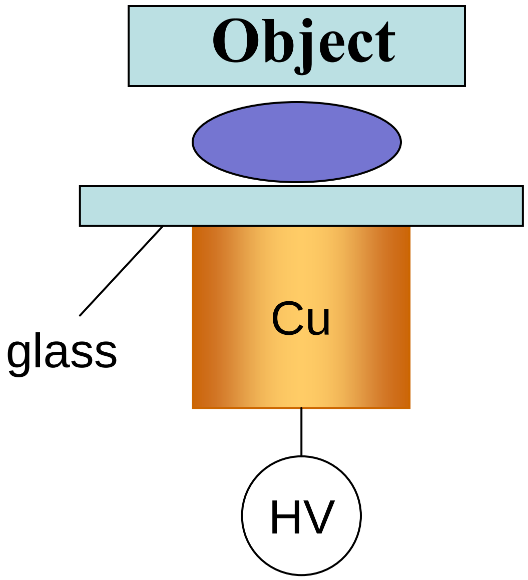
FE-DBD plasma in air



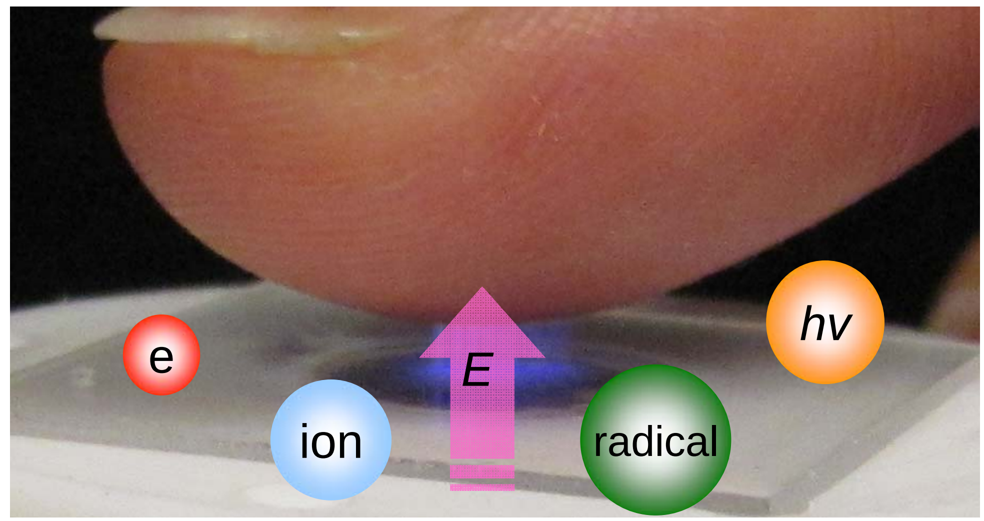
Non-thermal Plasma Induces Apoptosis in Melanoma Cells via Production of Intracellular Reactive Oxygen Species

Sensenig et al., Oct. 29, 2010
Annals Biomed. Eng.

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



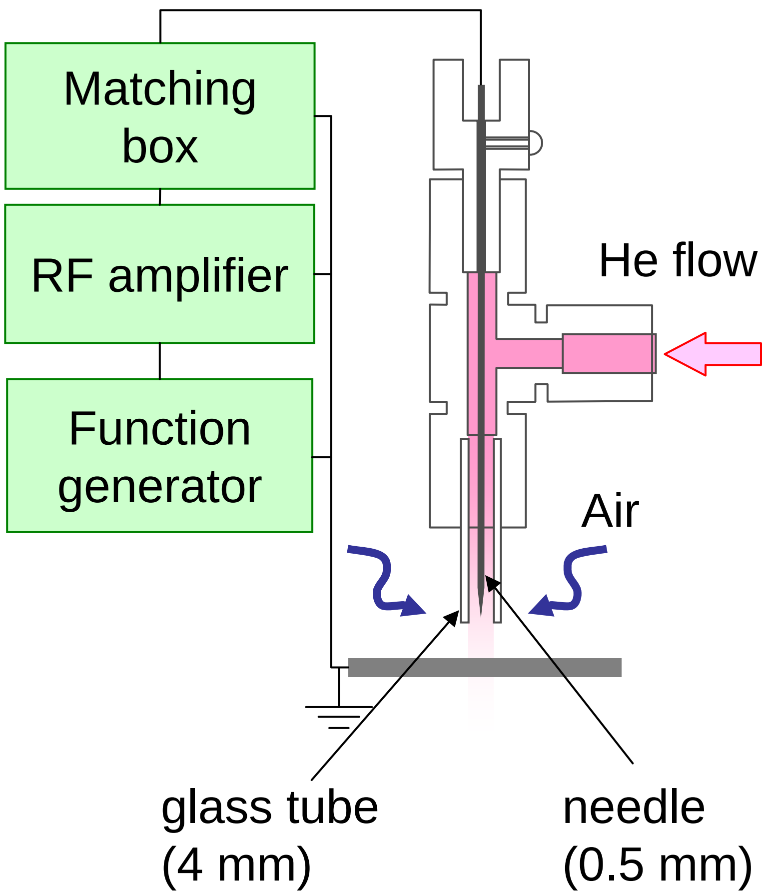
Plasmas in ambient air at room temperature

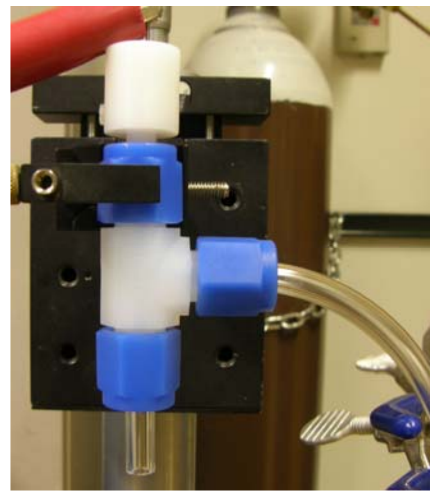


• voltage:	10-20 kVpkpk
• frequency:	1-10 kHz
• power:	~ 1W
• distance to finger:	1-3 mm
• gas:	static air in California

Plasma Needle: Can We Understand It?

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



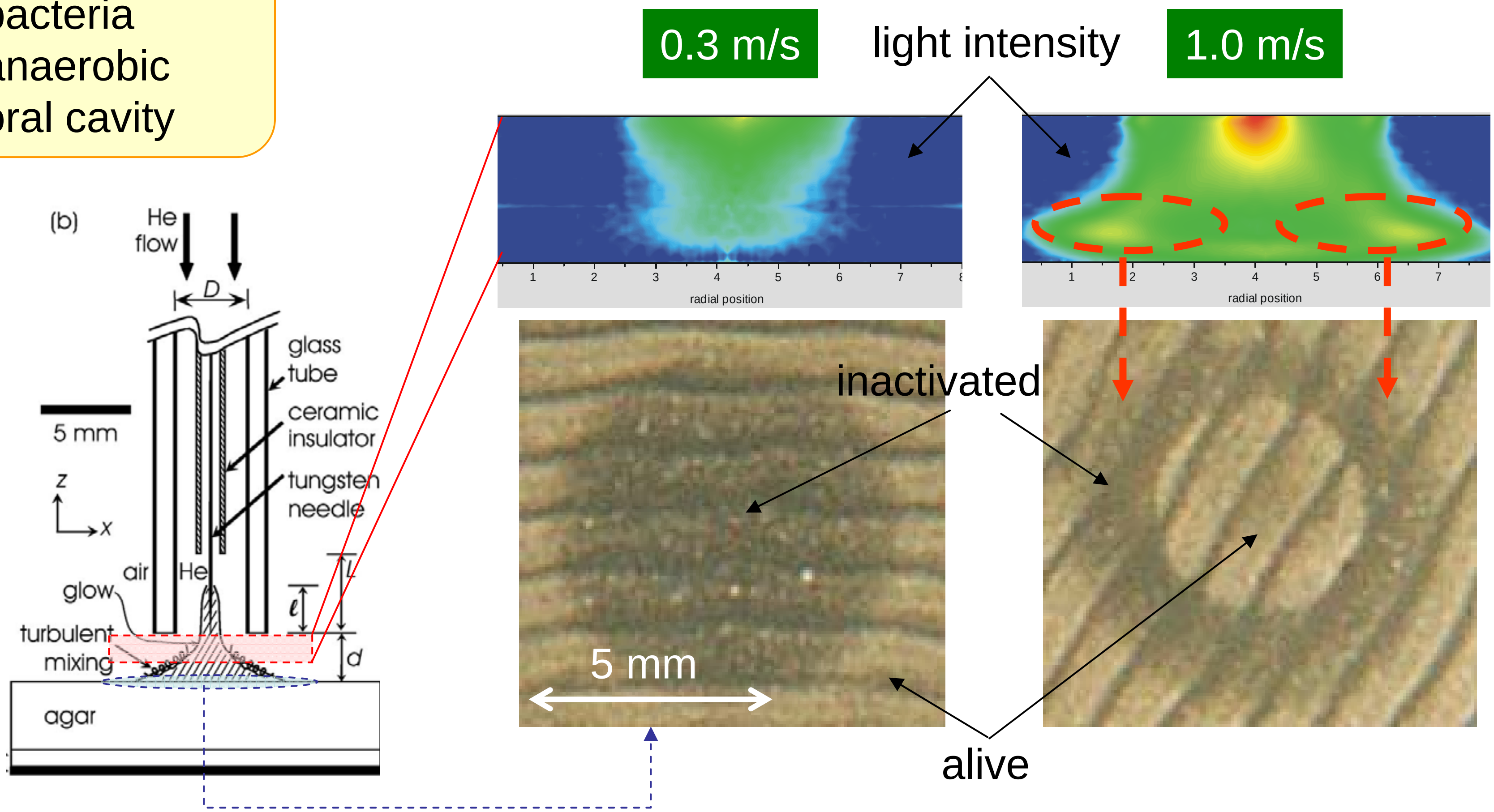


- Frequency: RF (13.56MHz)
- Voltage: 200-400 V_{pkpk}
- He flow rate: ~1 slpm (Re_d < 100)
- Power consumption: ~1 W
- Distance to sample: 1-5 mm

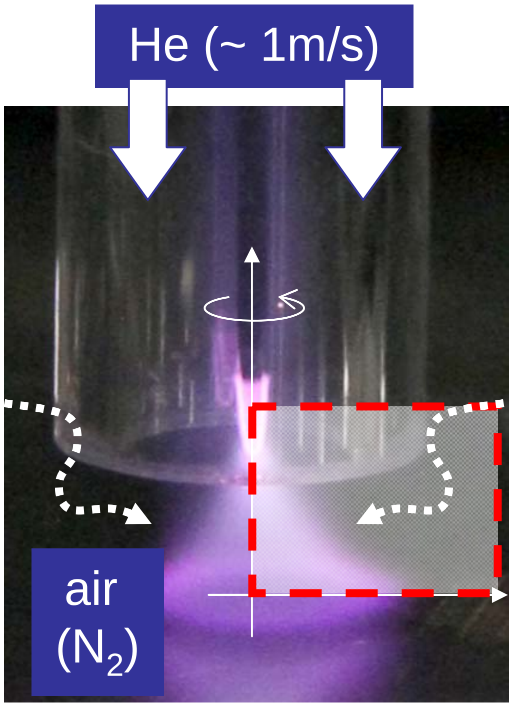
Plasma needle: Bactericidal effects

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)

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

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

$$\nabla\cdot\left(-\lambda\nabla T+\mathbf{u}c_{\mathrm{p}}T\right)=\Phi+\sum q_i\boldsymbol{\Gamma}_i\mathbf{E}+Q_{el}$$ (energy conservation)

ion momentum
collisional heating

temperature
velocity
species density

Plasma dynamics

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

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

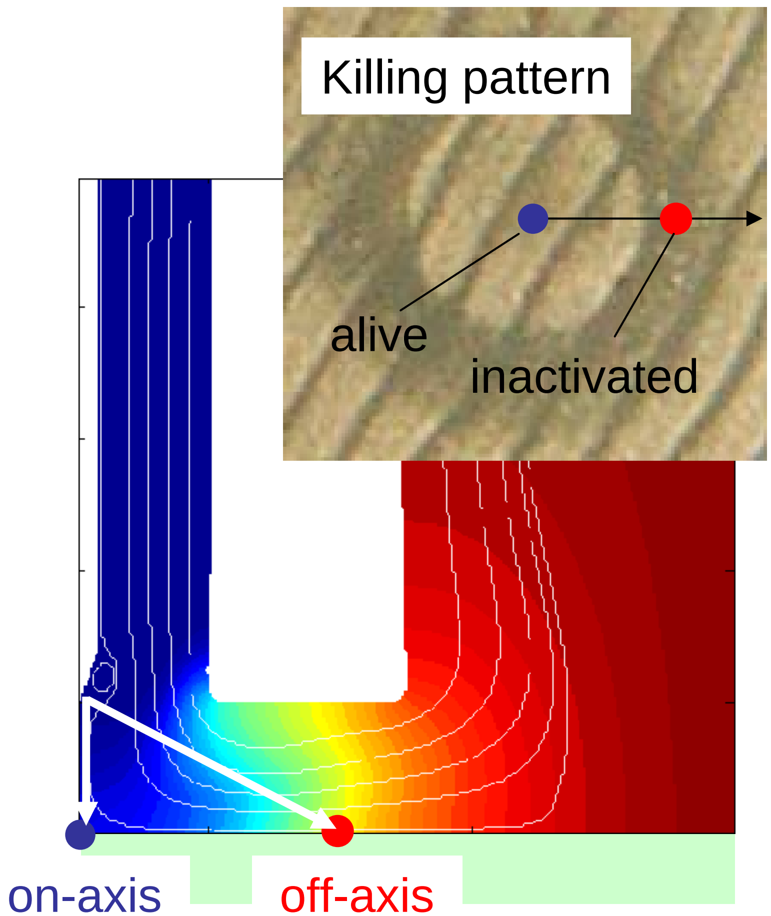
$$\frac{\partial(n_e\varepsilon)}{\partial t}+\nabla\cdot\left(\frac{5}{3}\varepsilon\boldsymbol{\Gamma}_e-\frac{5}{3}n_eD_e\nabla\varepsilon\right)=-\boldsymbol{\Gamma}_e\cdot\mathbf{E}-Q$$ (electron energy)

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

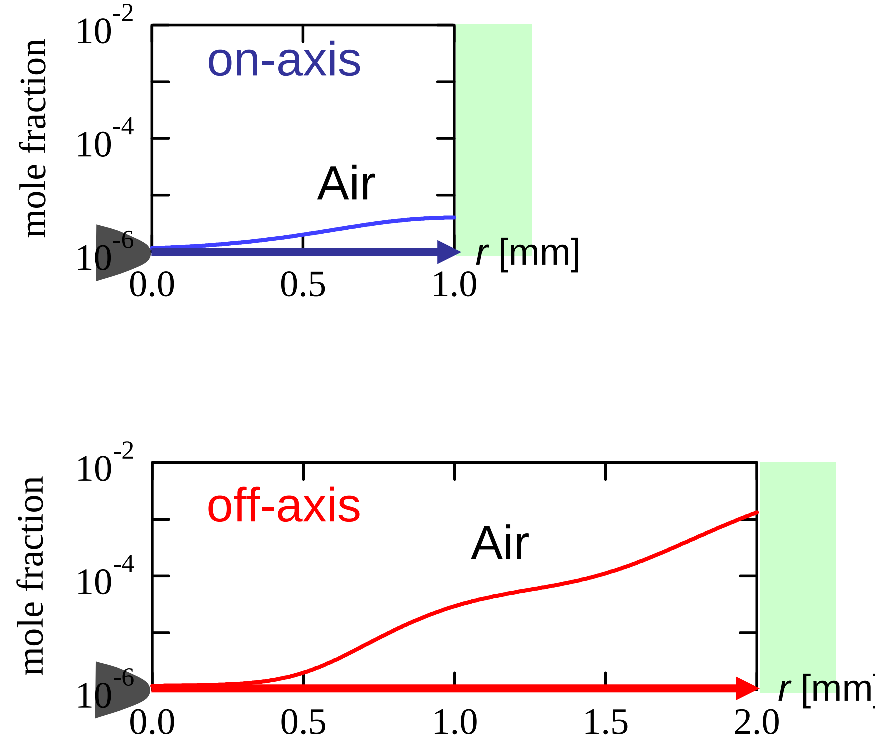
Y. Sakyiama et al, J. Appl. Phys. 101 (2007) 073306 and J. Phys. D 41 (2008) 95204

Chemistry Model: On-Axis and Off-Axis

Mole fraction of air (log scale)



1D plasma model



Chemistry Model

46 species

negative particles: e, O^-, O_2^-, O_3^-, O_4^-, H^-, OH^-

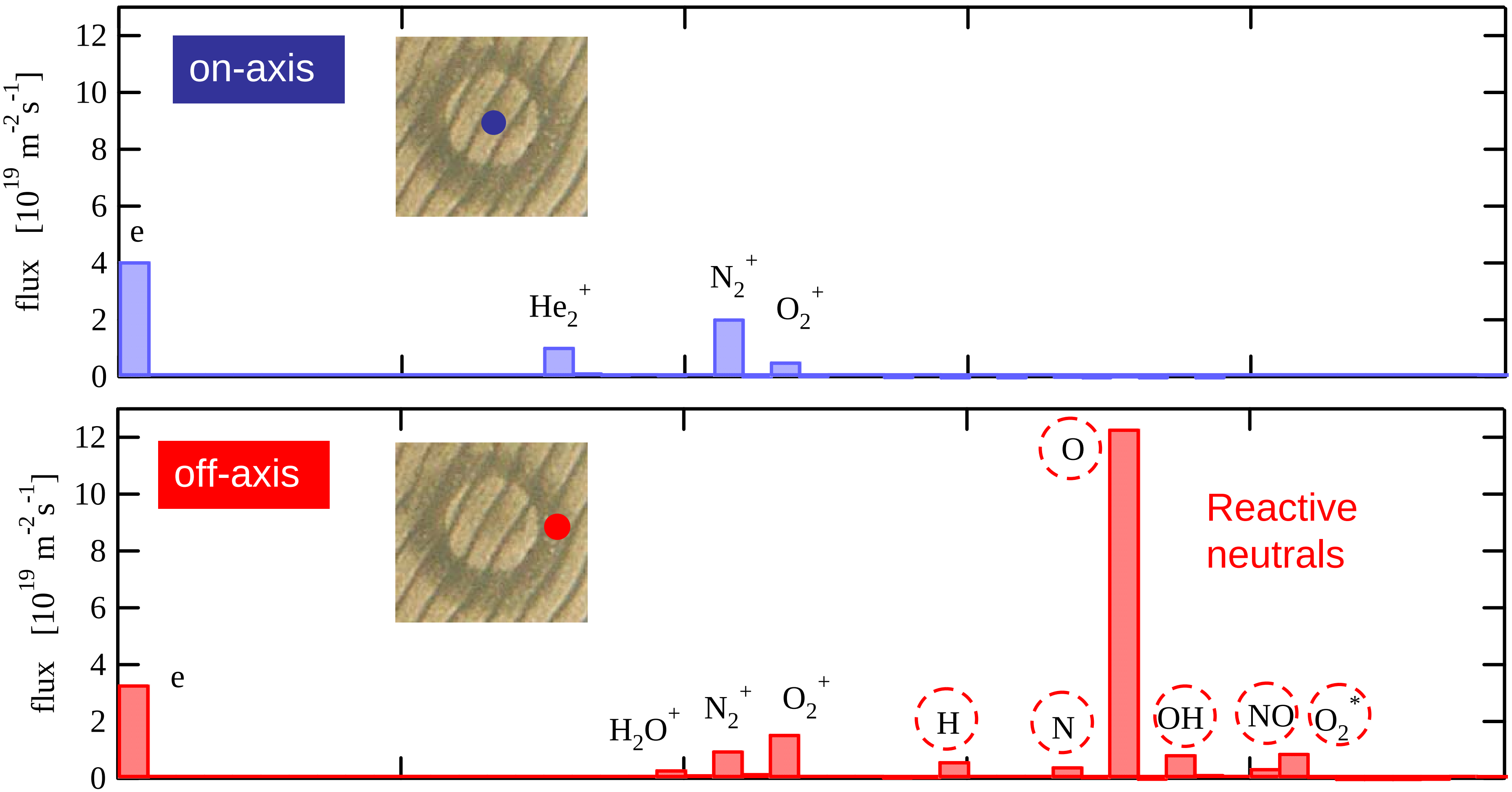
positive particles: He^+, He_2^+, N^+, N_2^+, N_3^+, N_4^+, O^+, O_2^+, O_4^+, NO^+, N_2O^+, NO_2^+, H^+, OH^+, H_2O^+, H_3O^+

neutrals: He, He^*, He_2^*, N, N^*, N_2, N_2^*, N_2^{**}, O,O^*, O_2, O_2^*, O_3, NO, N_2O, NO_2, NO_3, H, H_2, OH, H_2O, HO_2, H_2O_2

214 elementary reactions

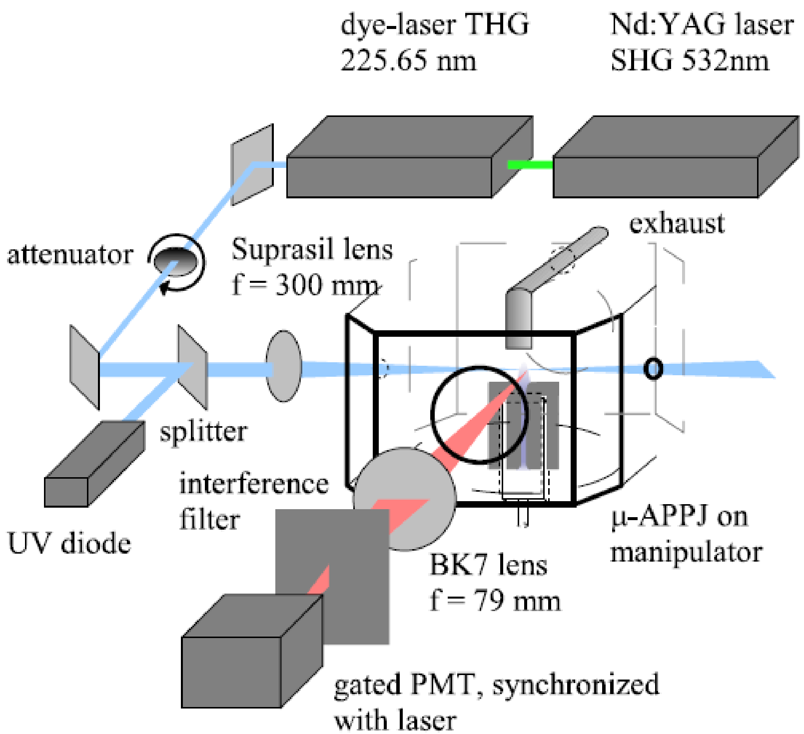
- 21 electron impact excitation/ionization/dissociation reactions
- 20 Penning and associative ionization reactions
- 26 electron recombination/attachment reactions
- 65 charge transfer reactions
- 51 ion recombination reactions
- 31 neutral-neutral reactions

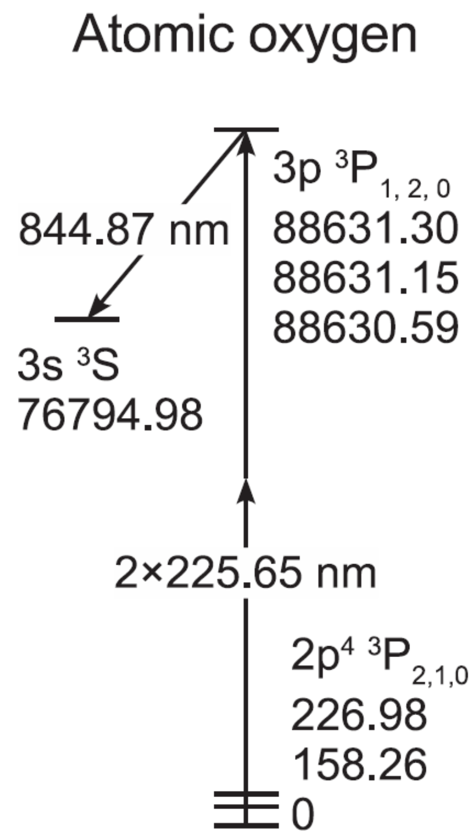
Species Fluxes to Surface



Model Validation: O Atom Measurement *

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

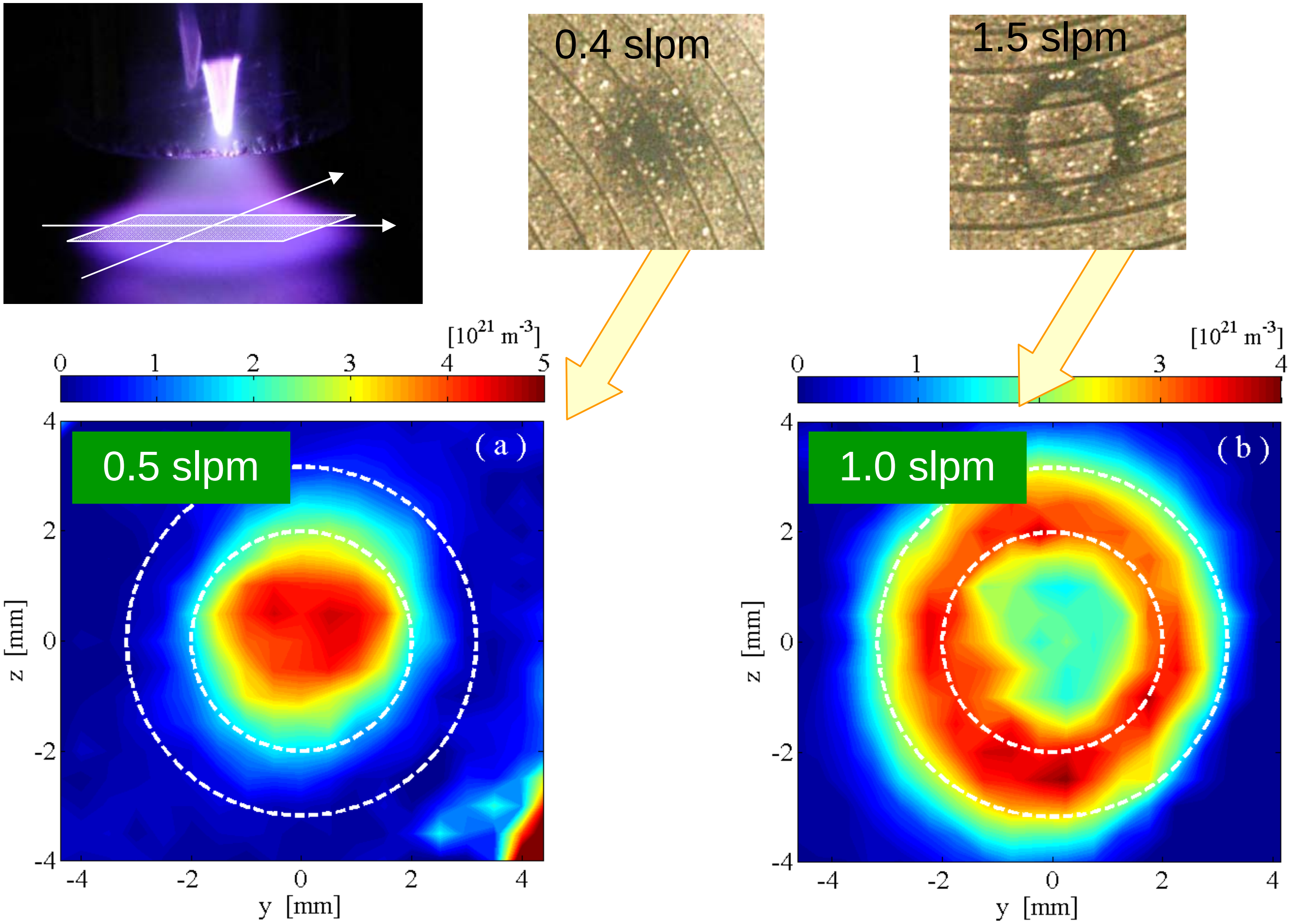




* Thanks to:
Volker Schulz-von der Gathen,

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

Measured O Atom Density: Qualitative Agreement with Model

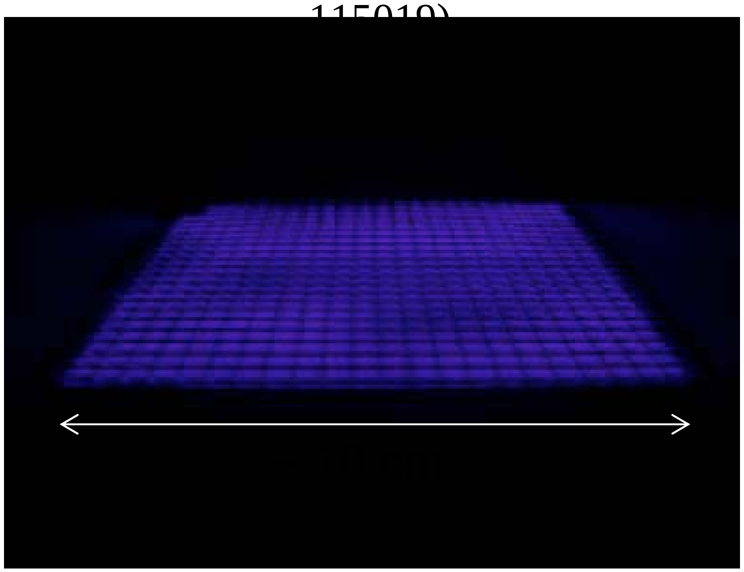


Y. Sakiyama, et al., *Appl. Phys. Lett*. 97 (2010) 151501.

Atmospheric Pressure Air: SMD Device Configuration

SMD = surface micro-discharge

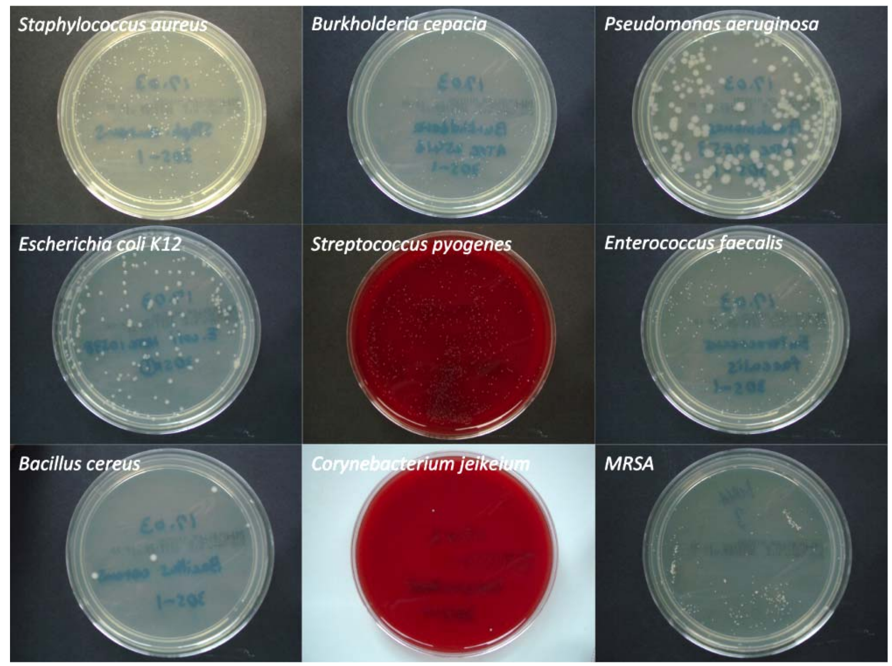
(G. Morfill et al., New J. Phys. **11** (2009) 115019)



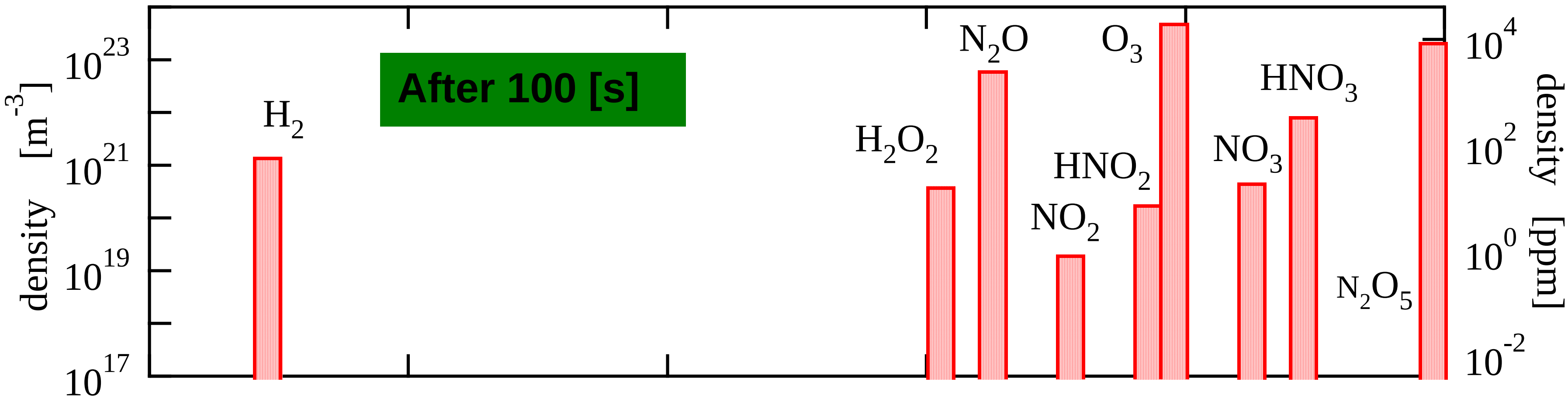
Frequency	1-10 kHz
Voltage	1-10 kV_{pp}
Power	0.01-1 W/cm^2
Distance to sample	1-10 mm
Exposure time	1-1000 s

Anti-microbial effect

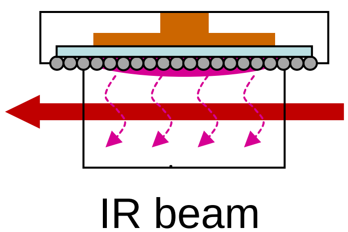
- ~10^7 cfu/ml
- 4-5 log-reduction in 30 s



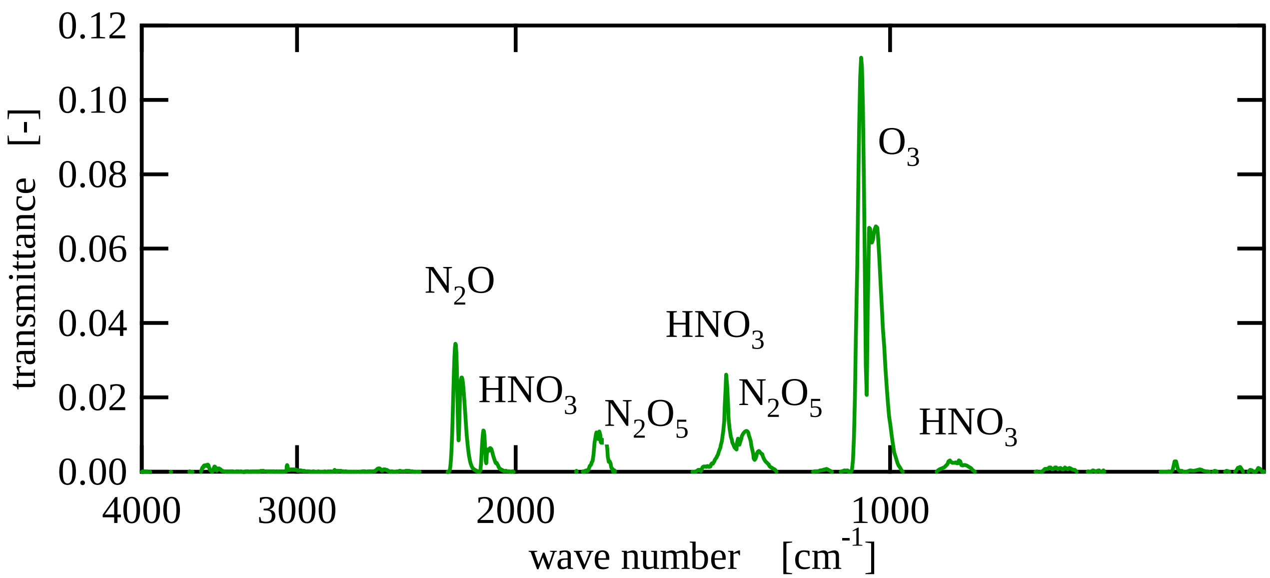
Model Predictions and Measurements



FTIR measurement (qualitative comparison)



200 scans for
60-120 [s]



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

Early Studies of RONS in Biomedicine

THE THEORY OF REVERSIBLE TWO-STEP OXIDATION INVOLVING FREE RADICALS

L. MICHAELIS AND M. P. SCHUBERT

Laboratories of The Rockefeller Institute for Medical Research, New York, New York

Received March 17, 1938

Chem. Reviews, 1938

FREE RADICALS IN BIOLOGICAL MATERIALS

By PROF. BARRY COMMONER, JONATHAN TOWNSEND and GEORGE E. PAKE

Nature, 1954

Oxygen Poisoning and X-irradiation: A Mechanism in Common[1]

Rebeca Gerschman, Daniel L. Gilbert, Sylvanus W. Nye, Peter Dwyer, and Wallace O. Fenn[2]

Science, 1954

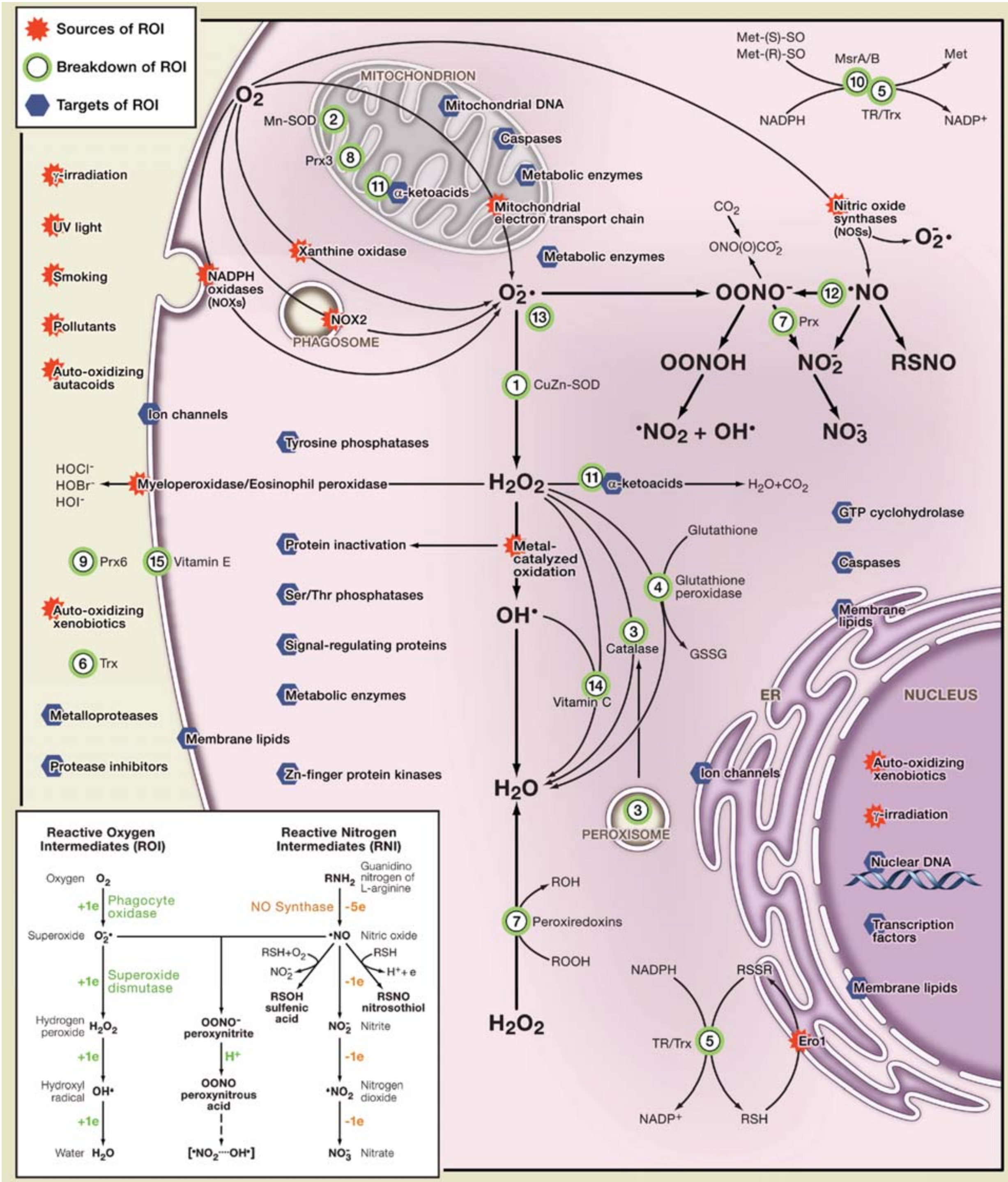
AGING: A THEORY BASED ON FREE RADICAL AND RADIATION CHEMISTRY

DENHAM HARMAN, M.D., Ph.D.

(From the Donner Laboratory of Biophysics and Medical Physics, University of California, Berkeley)

Science, 1956

RONS in normal physiology and disease



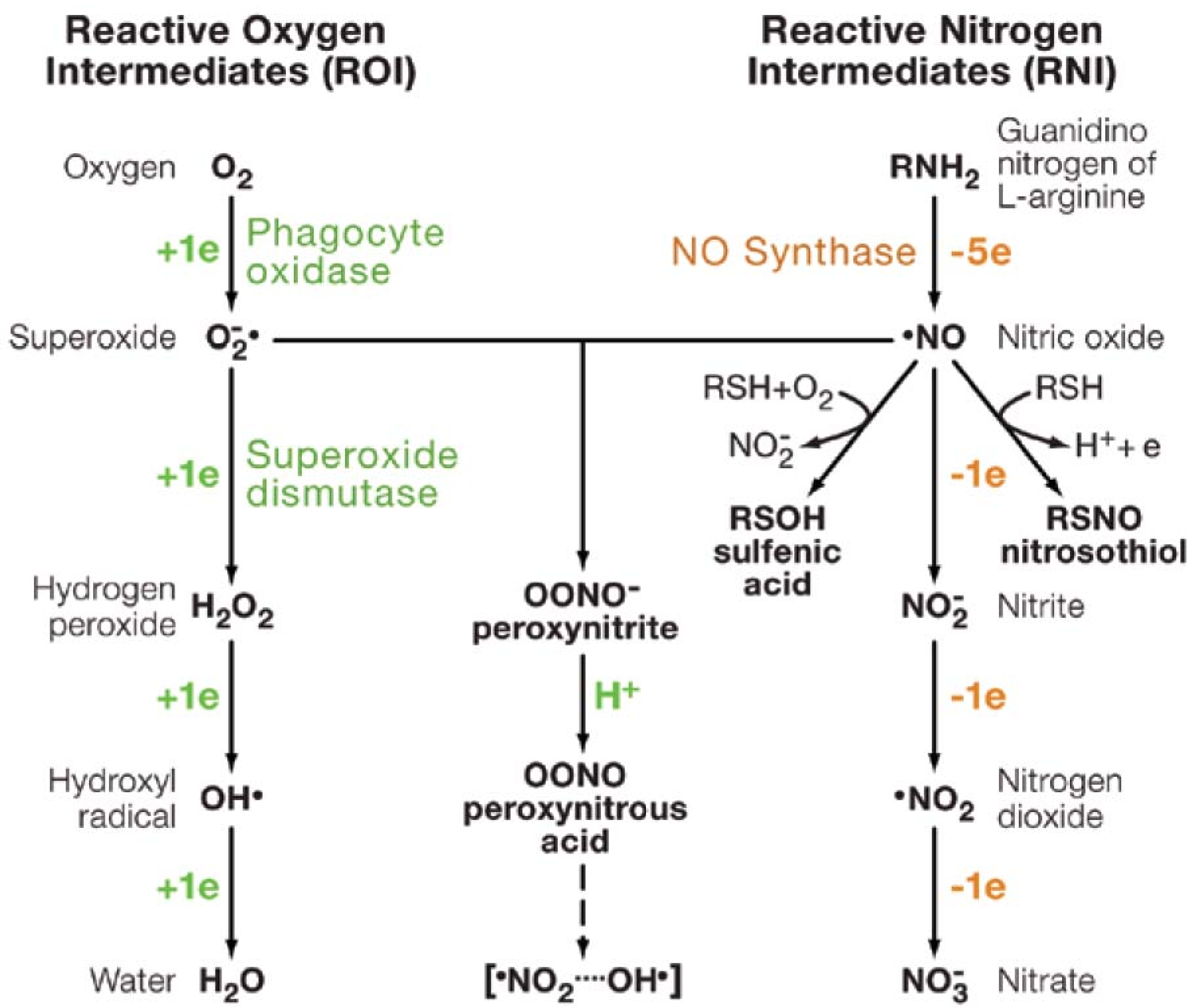
SnapShot: Reactive Oxygen Intermediates (ROI)

Carl Nathan and Aihao Ding
Weill Cornell Medical College, New York, NY 10065, USA

Cell *140*, March 19, 2010

Overview of some cellular reactions/roles of RONS

Subset of RONS



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

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

Barry Halliwell

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*

RONS

Oxidative Burst

Immune Responses

Signaling
- -MAP kinase
- -Redox-sensitive transcription factors

Vascular Tone
- -Vasodilation
- -Blood pressure
- -Inhibit platelet aggregation

Cellular Response
- -Apoptosis
- -Metabolic turnover
- -Proliferation/differentiation

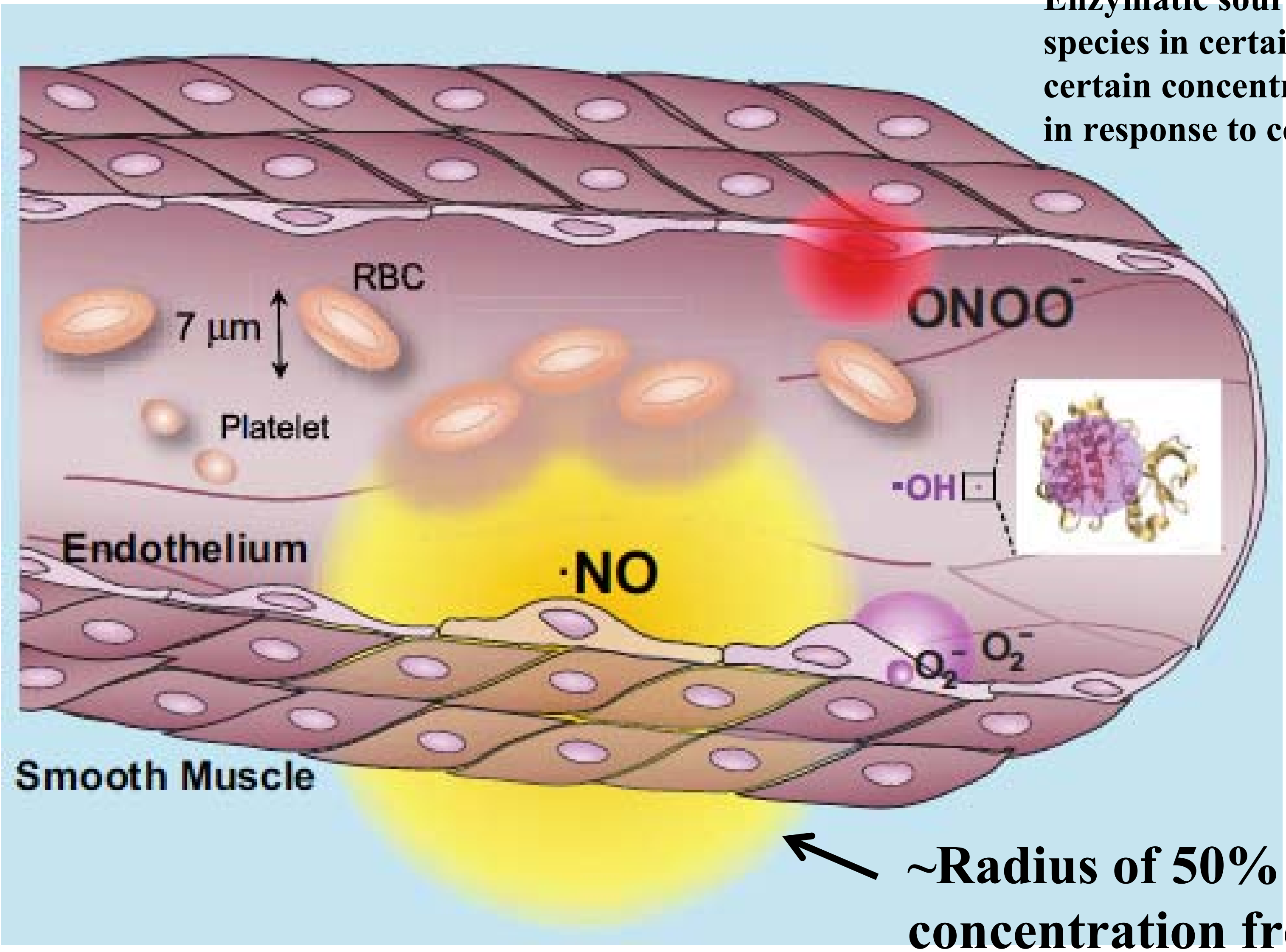
Neurotransmission
- -Pre/post synaptic transmitter
- -Long term potention/depression

Biomolecule Modification
- -Lipid/Protein function
- -Enzyme inhibition
- -Membrane stability

*Chiurchiu and Maccarrone, 2011
Antioxidants and Redox Signaling

In Vivo RONS Lifetimes/Diffusion Distances: Short!

Enzymatic sources create
species in certain places at
certain concentrations
in response to certain events

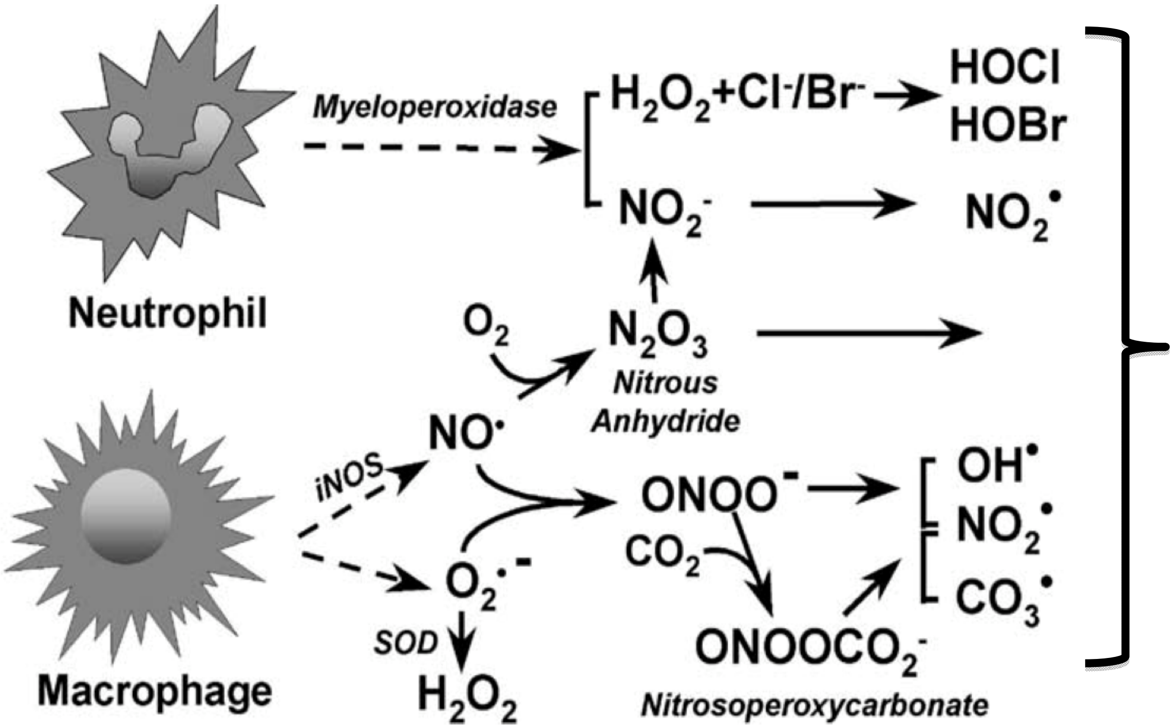


~Radius of 50% peak concentration from source

Pacher et al., Physiol. Rev., 87, 315, 2007

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

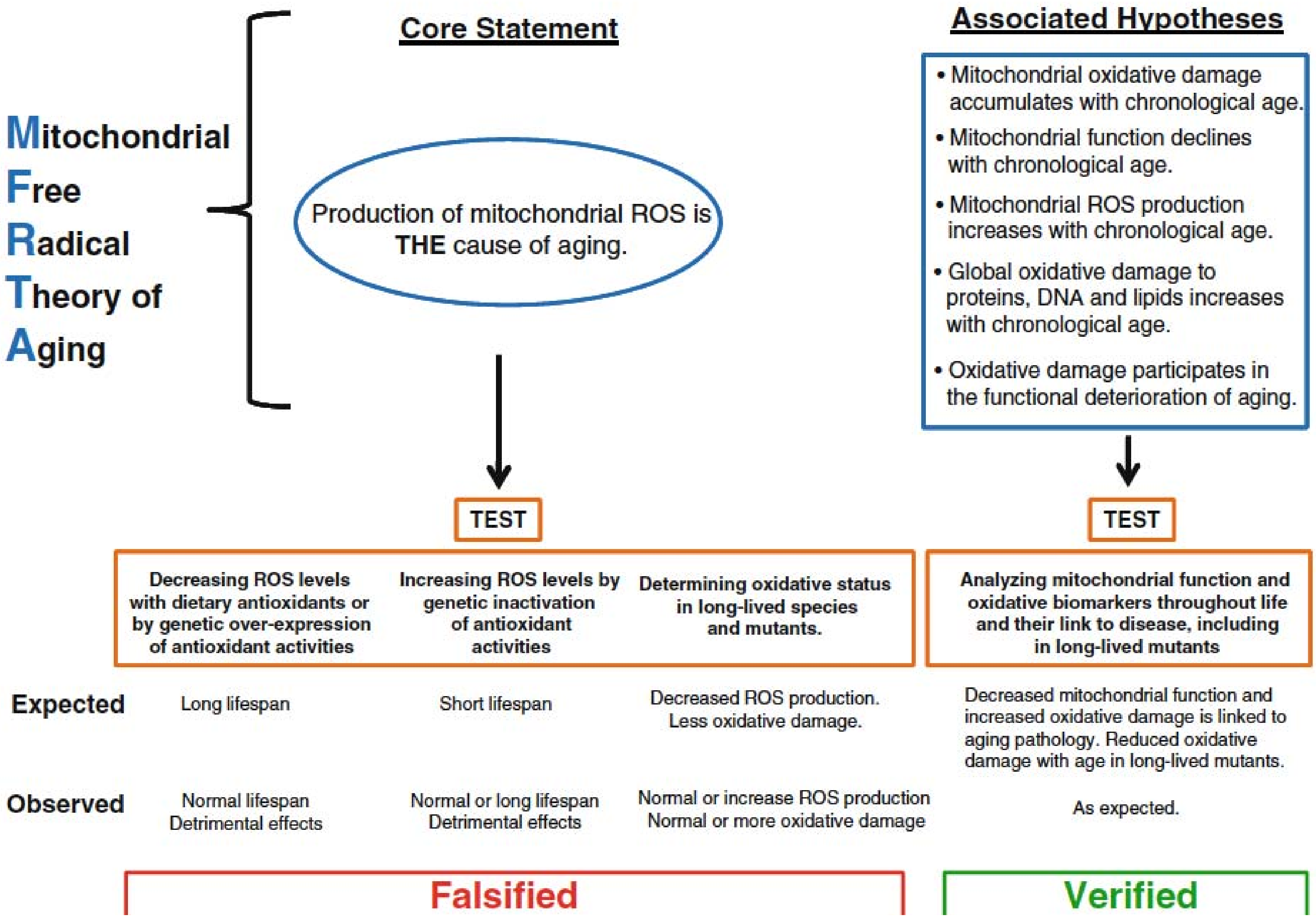
9. *Eyes*
   a. Macular degeneration
   b. Cataracts

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

Cell. Mol. Life Sci. (2010) 67:1–8

When a Theory of Aging Ages Badly

J. Lapointe and S. Hekimi



Antioxidants: Molecules, medicines, and myths

John M.C. Gutteridge [a], Barry Halliwell [b,*]

Biochemical and Biophysical Research Communications 393 (2010) 561–564

"Because free radicals played such a major role in the evolution of plants and animals they are an essential part of the basic biology we study today…"

"The ability to sterilize a site of infection by rapid production of ROS can keep us alive. …it certainly did before antibiotics and antivirals entered clinical medicine."

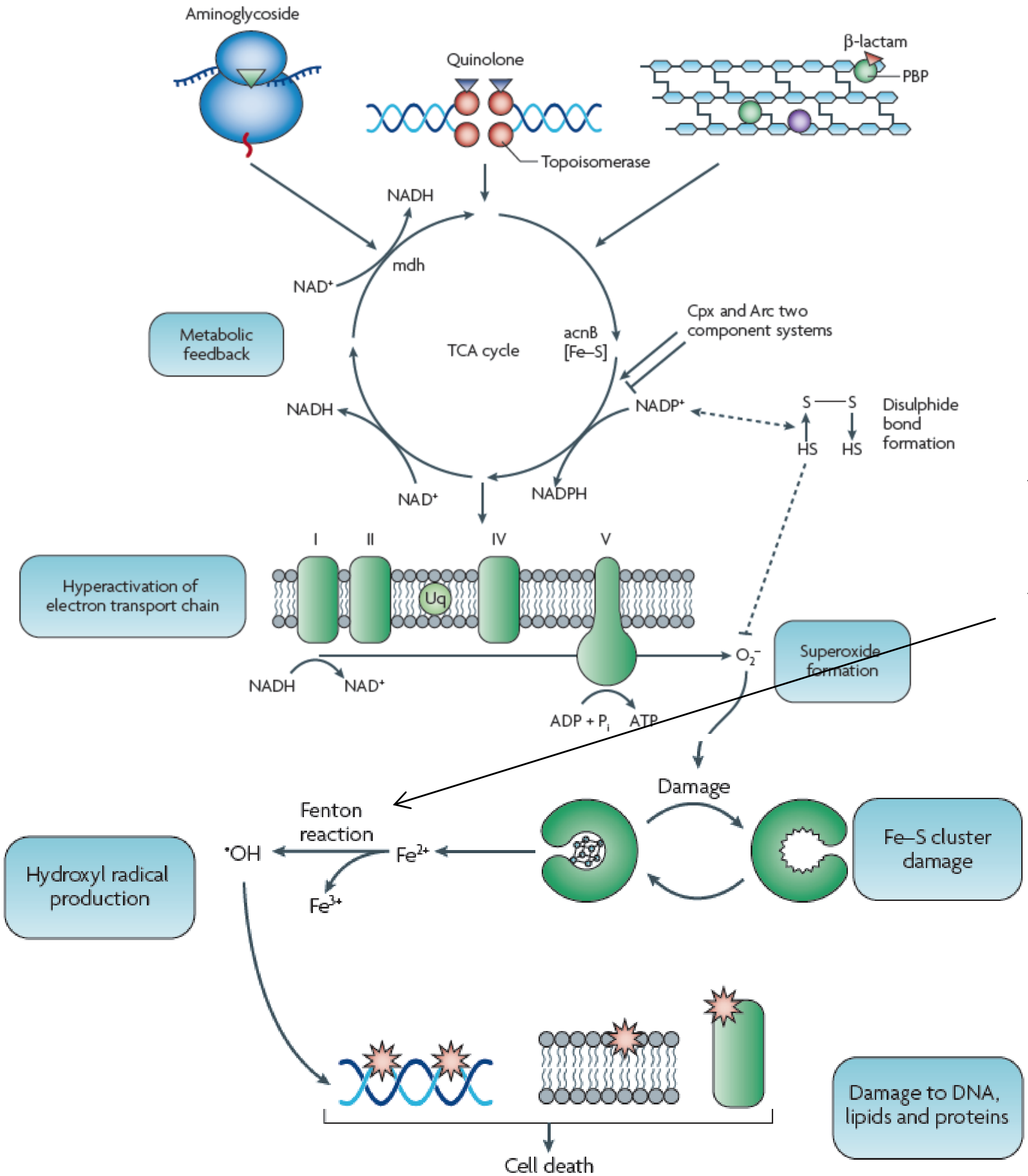
"During the 1980's, antibiotics were shown to be redox active and generate ROS. This led Gutteridge, Kovacic et al., in 1998 to propose that antibiotics mimic phagocytic cells by having a common mechanism of microbial killing using ROS. This concept has since been re-presented in detail [by Collins et al., 2007]."

RONS in current therapeutics

RONS as Therapy: Antibiotics

A Common Mechanism of Cellular Death from Bactericidal Antibiotics

Collins et al.
Cell, 2007



A complex series of reactions creates OH via Fenton: all antibiotics allegedly function this way.

Phagomimetic Action of Antimicrobial Agents

Free Rad. Res., 1998

JOHN M. C. GUTTERIDGE[a,*], GREGORY J. QUINLAN[a] and PETER KOVACIC[b]

"A wide variety of extracted and synthesized drug molecules have electron transfer capabilities which allow them to generate ROS."

"In particular, many antibiotics that kill or inhibit bacteria, yeasts and cancer cells readily transfer electrons to oxygen making O_2^- and H_2O_2…"

"This type of chemistry is very similar to that which evolved within phagocytic cells as part of their microbial killing amoury."

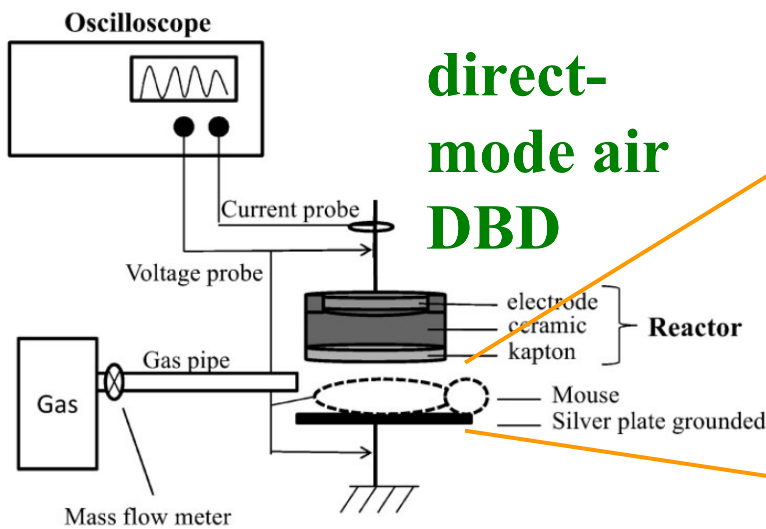
RONS as Therapy: Not So New!

Recall: DBD Air Plasma Cancer Cell Treatment

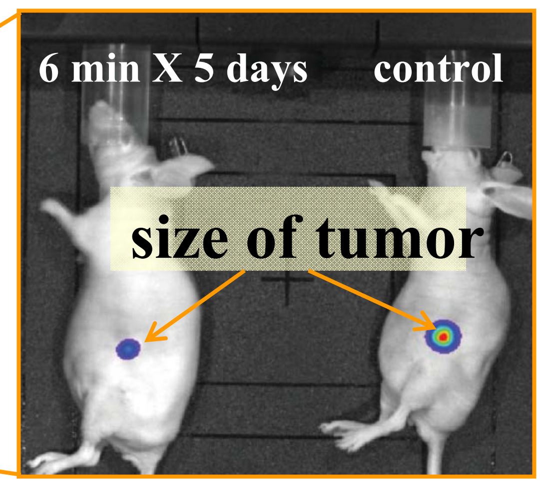
Leader: J.-M. Pouvesle, GREMI, Orléans, France

direct-mode air DBD (*in vivo*)

(M. Vandamme, *Plasma Process. Polym.* 7 (2010) 264)



direct-mode air DBD



First *in-vivo* demonstration of anti-cancer actions of plasmas…

Bio-Radicals Formed by Ionizing Radiation

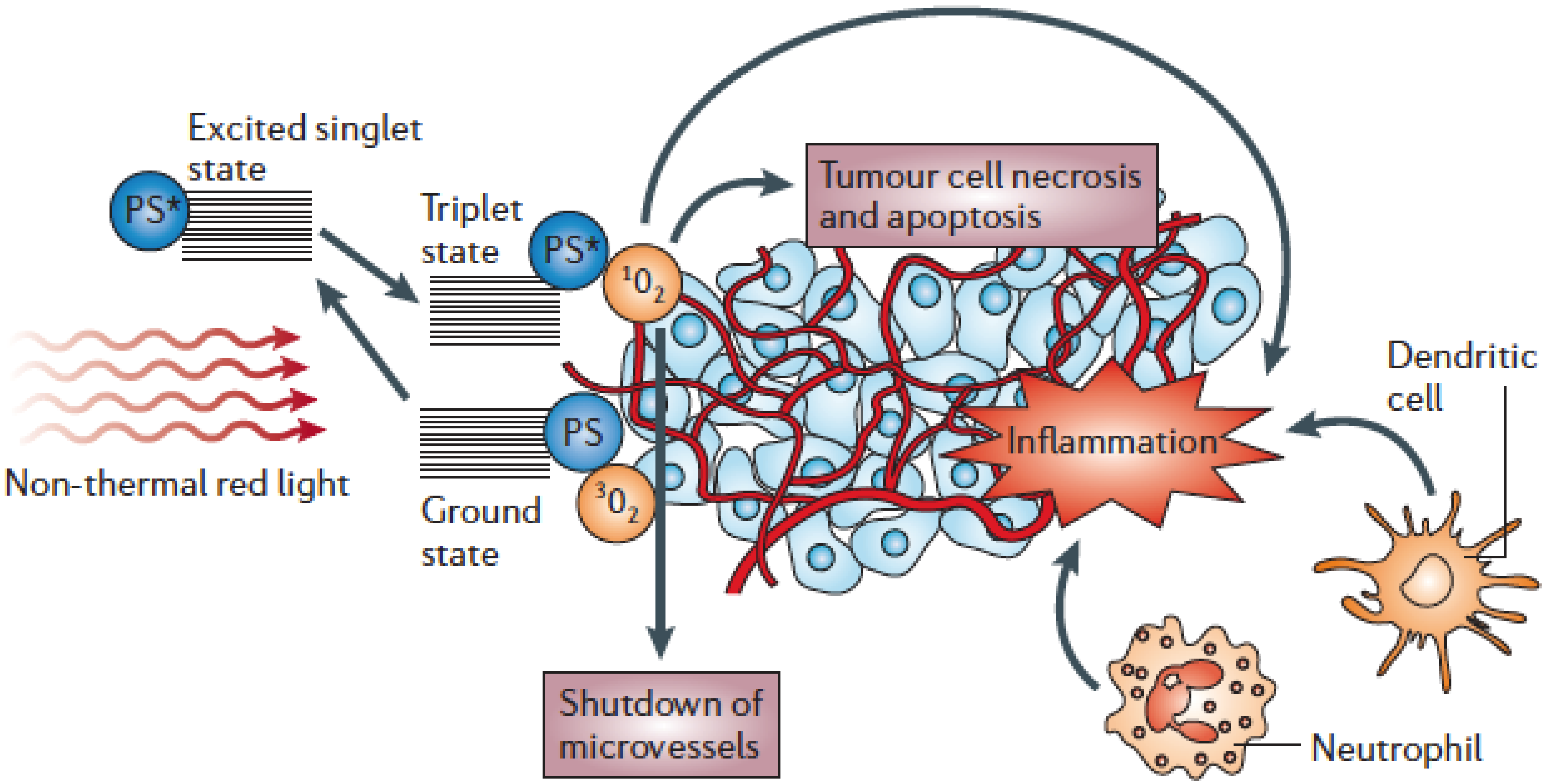
Int. J. Radiat. Biol., Vol. 85, No. 1, January 2009, pp. 9–25

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 $^1O_2$



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

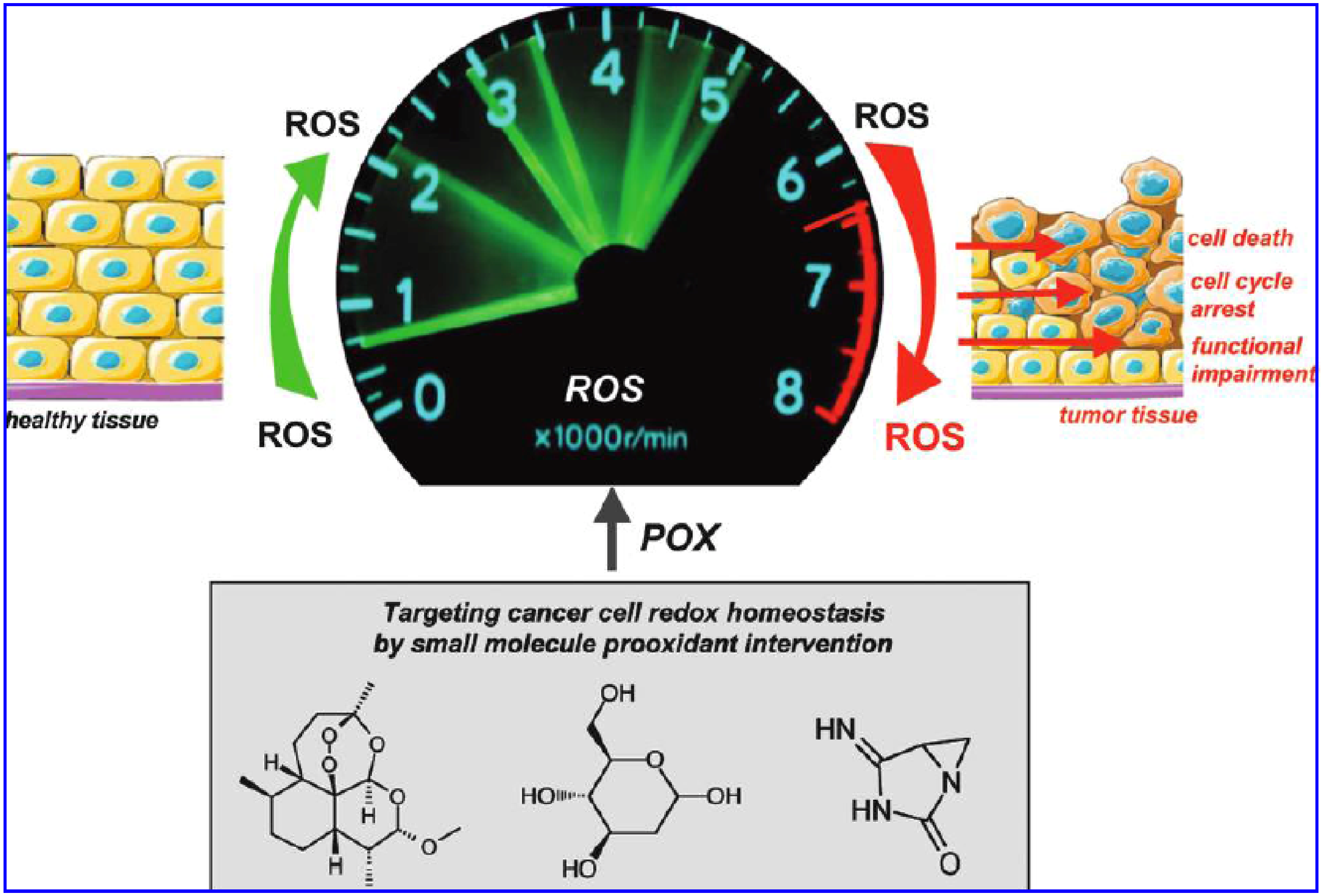
Redox-Directed Cancer Therapeutics: Molecular Mechanisms and Opportunities

ANTIOXIDANTS & REDOX SIGNALING
Volume 11, Number 12, 2009

DOI: 10.1089/ars.2009.2541

Comprehensive Invited Review

Georg T. Wondrak

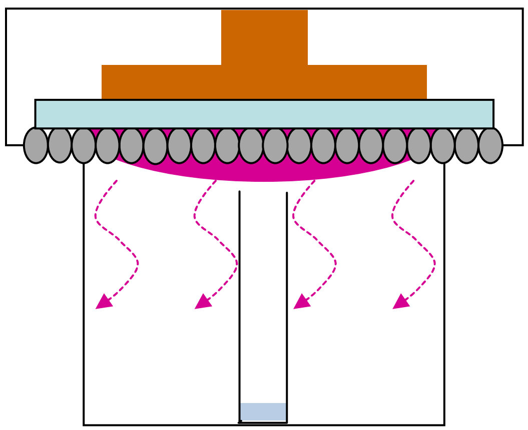


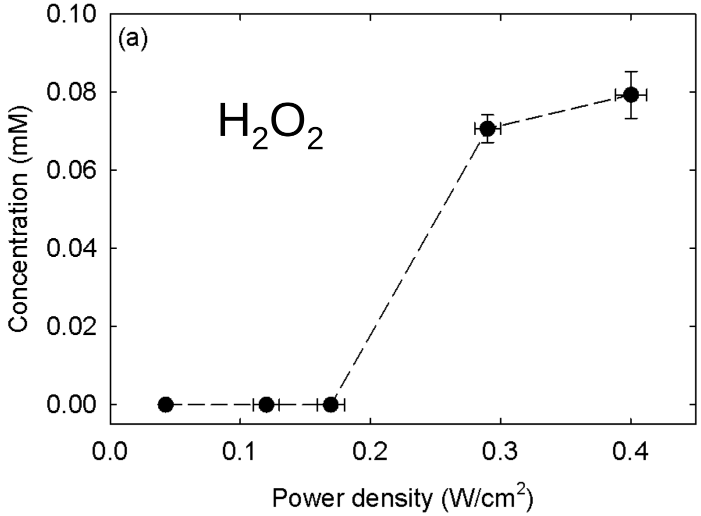
Implications/questions for plasma medicine

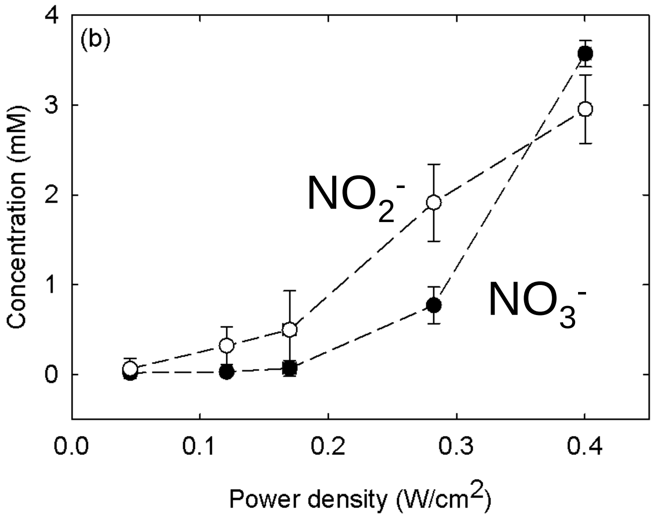
Reflections on Plasma-Generated Reactive Species Dynamics

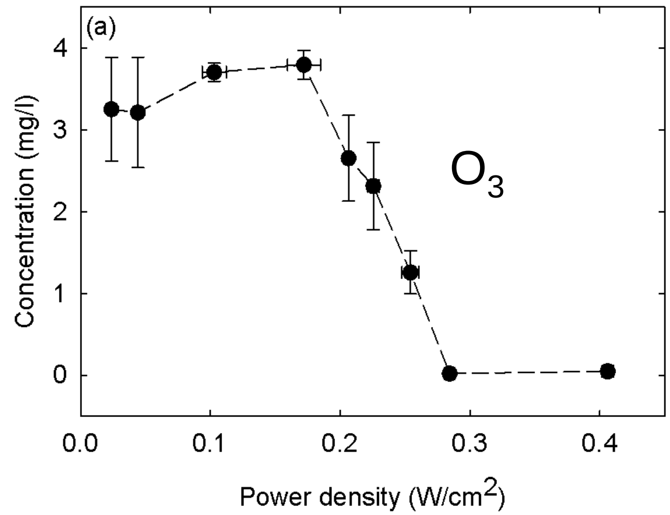
- Many gas phase RONS will react quickly in biological fluid phase
- How can they have persistent bio-medical effects?
- *Possibly by forming nitrated/oxidized lipids, proteins, etc.*
- Example of nitrated fatty acids (NO_2-FAs)

Example: Air SMD-Water Chemistry*



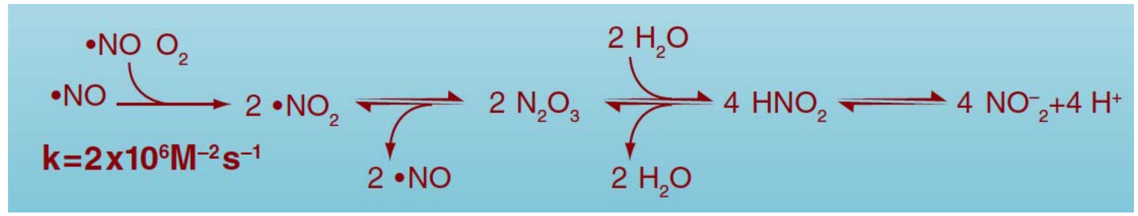


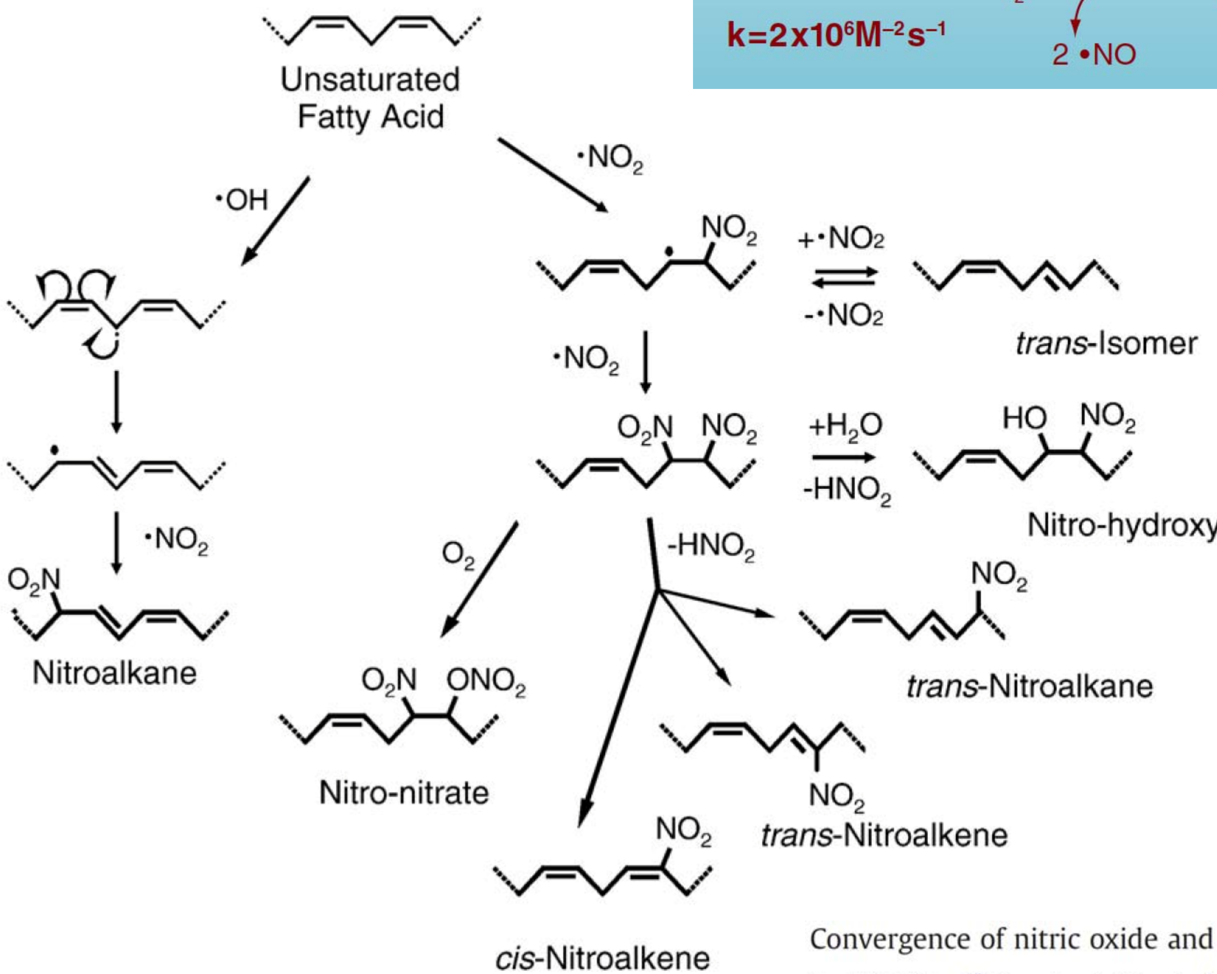




*Pavlovich et al., accepted PPP, 2012

Nitrated Fatty Acids NO_2-FAs: Radical Reaction Pathways





Known **products of air plasma in water: N_yO_x are *known* to react with PUFAs to form NO_2-FAs**

Convergence of nitric oxide and lipid signaling: Anti-inflammatory nitro-fatty acids

Paul R.S. Baker [a,*], Francisco J. Schopfer [a], Valerie B. O'Donnell [b], Bruce A. Freeman [a,*]

Free Radical Biology & Medicine 46 (2009) 989–1003

Nitroalkene *Biological/Therapeutic Activities*

	Chemical name	Biological action/activity	Reference
LNO_2	Nitrated linoleic acid	• Relaxes preconstricted rat aortic rings	(88,104)
		• Inhibits $O_2{}^{\cdot-}$ release in PMN, platelet aggregation and macrophage degranulation	(110,111)
		• Upregulates HO-1 expression	(117)
		• Inhibits LPS-induced cytokine release	(119)
		• Inhibits NF-κB mediated gene expression	(118)
		• Binds and activates PPARγ	(162,163)
		• Cardioprotective against ischemia-reperfusion injury	(100)
OA-NO_2	Nitrated oleic acid	• Directs protein/membrane association	(109)
		• Inhibits stimulus-induced cytokine release	(119)
		• Inhibits NF-κB mediated gene expression	(118)
		• Activates PPARγ	(99)
		• Increases glucose uptake and insulin sensitivity	(99)
AA-NO_2	Nitrated arachidonic acid	• Decreases NOS2 expression	(91)
		• Relaxes preconstricted rat aortic vessels	(91)
$CLNO_2$	Nitrated cholesteryl linoleate	• Decreases NOS2 expression	(90)
		• Upregulates HO-1 expression	(90)
		• Inhibits stimulus-induced cytokine release	(90)
		• Inhibits NF-κB mediated gene expression	(90)

Convergence of nitric oxide and lipid signaling: Anti-inflammatory nitro-fatty acids

Paul R.S. Baker [a,*], Francisco J. Schopfer [a], Valerie B. O'Donnell [b], Bruce A. Freeman [a,*]

Free Radical Biology & Medicine 46 (2009) 989–1003

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.

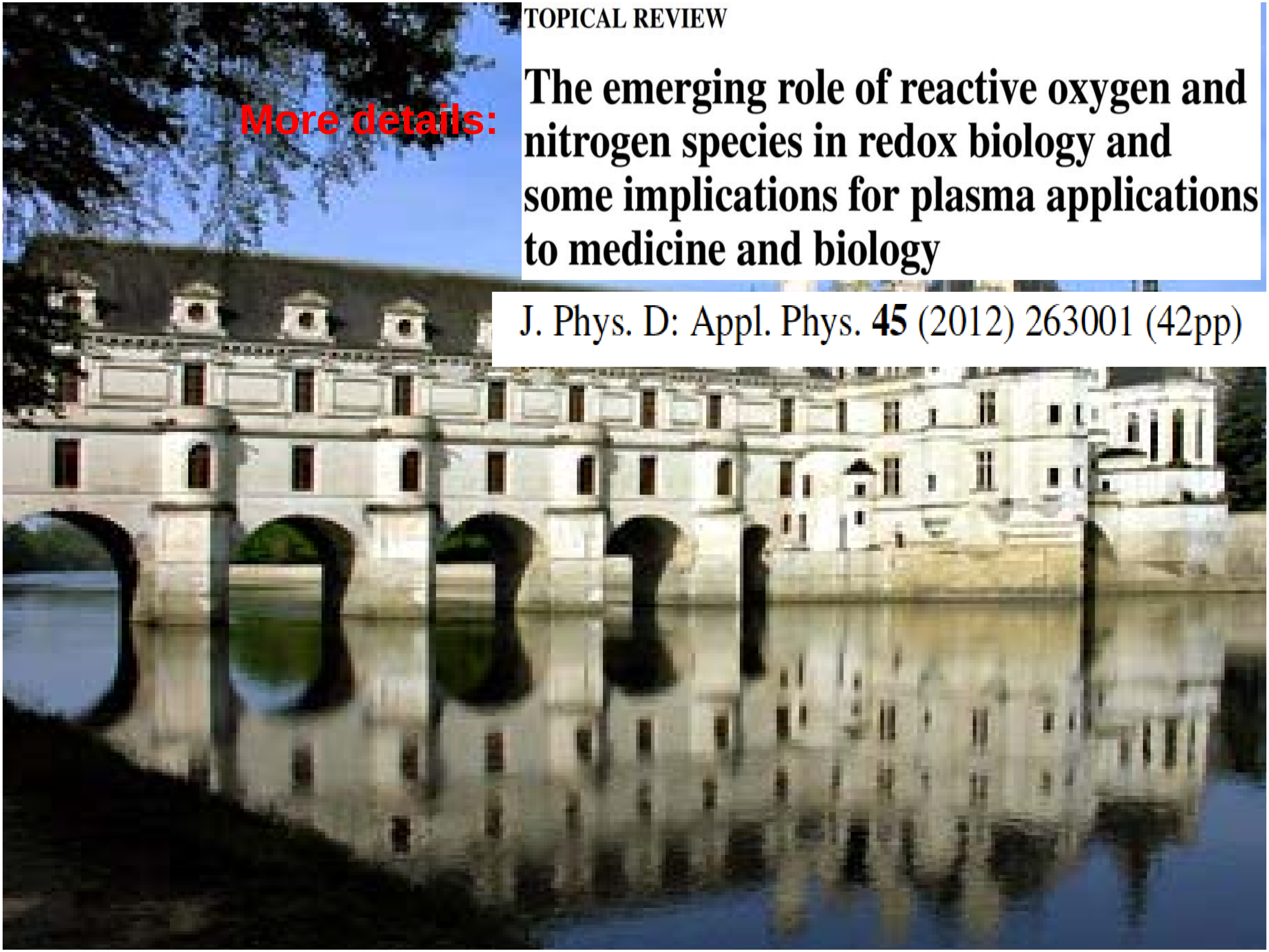
In other words, it is NOT SURPRISING that plasma medicine works - it is based on RONS chemistry that works in other therapies

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)