PLASMAS FROIDS POUR LE BIOMEDICAL

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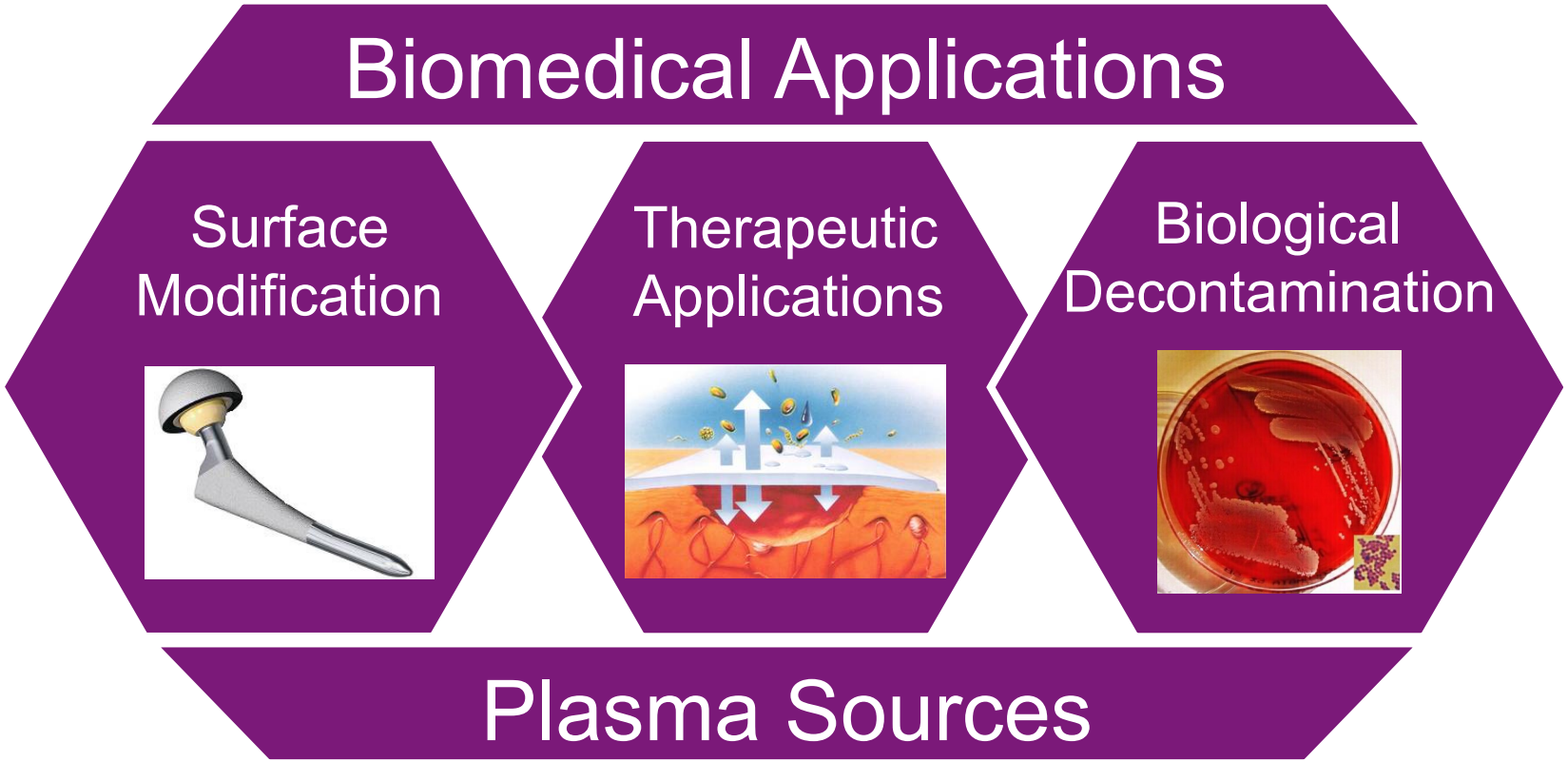
14èmes Journées d'Échanges du Réseau des Plasmas Froids – La Rochelle – 17 octobre 2018

PLASMA MEDECINE



Atmospheric Pressure Plasma Sources

Favoured *Required* *Favoured/Required*

Plasma Physicists, Engineers, Biologists, Biochemists, and Medical doctors

H.-R. Metelmann et al. (eds.), *Comprehensive Clinical Plasma Medicine*, Springer Nature 2018

Medical applications of low temperature non-thermal plasmas

A new (old) field…

478 ELECTRICAL EXPERIMENTER September, 1919

VIOLET RAYS

STARTLING NEW ELECTRICAL TREATMENT

FOR HEALTH, ENERGY, BEAUTY

You can now try the wonderful new Violetta—Violet Ray Machine—10 days free in your own home. Give yourself daily treatments—at less than 1 cent per treatment. Rid yourself of headaches, catarrh, constipation, lumbago, insomnia, nervousness. Relieve your pain from neuritis, rheumatism, indigestion, neuralgia. Give yourself beauty treatments—remove eczema, pimples, blackheads, obesity. Make your body a human dynamo of energy and make your skin fine in texture and free from blemishes or sallowness. Double your strength, sharpen your appetite, soothe your nerves, beautify your complexion. Try Violetta 10 days free.

VIOLETTA—NOT A VIBRATOR

The Violetta does not shock or pain. It does not bind the muscles. It is not a vibrator. The Violetta soothes or stimulates, sending the magic healing power of electricity through every cell, tissue, and organ of the body. Electricity in its highest remedial form. Wonderful and painless even to infants. No other form of electricity for home use is so amazing in its results.

10 DAYS' FREE TRIAL IN YOUR OWN HOME

You can try the Violetta in your own home on our 10 days' trial plan. Not one cent do you have to pay if you are not pleased. Why suffer from physical ailments or from the handicap of a sallow, pimply, imperfect skin when you can try this wonderful treatment in your home without risk. The Violetta is used by thousands of physicians and drugless healers as well as by such prominent beauty specialists as E. Burnham, Chicago, Yvette Parlors in eighteen cities, and hundreds of others. Every penny you pay returned instantly if you are not pleased with the Violetta after 10 days' trial. Write for book describing Violetta Outfits and amazing results of Violet Ray treatments.

Try the Violetta in Your Own Home For

Asthma, Barbers' Itch, Boils, Blackheads, Bunions, Gallstones, Catarrh, Chilblains, Colds, Corns, Constipation, Dandruff, Deafness, Earache, Eczema, Eye Disease, Falling Hair, Hay Fever, Headache, Goitre, Insomnia, Lumbago, Nervousness, Neuralgia, Neuritis, Obesity, Pains, Paralysis, Piles, Pimples, Rheumatism, Skin Diseases, Sore Throat, Sprains, Tonsilitis, Whooping Cough

What Physicians and Users Say

Trixie Friganza, well known actress says "Cheerfully will I add my praise for Violetta. It's the best 'pain chaser' and 'soother' I've had the good fortune to find. It's WONDERFUL. It cured my brother of neuritis. As for myself I use it for facial treatments and general massage. I cannot say too much for it."

Dr. Bert H. Rice, of Vinton, Iowa, says: "I have good results with the Violetta High Frequency Instrument in all cases of neuralgia. Almost instant relief in Facial Neuralgia."

K. L. Allen, D.C., 205 Boone National Building, Boone, Iowa, says: "I have had very good results with the application of High Frequency Current in cases of Paralysis, Rheumatism and Neuritis, and think it a great help in drugless healing."

Dr. Daniels, Lisbon, North Dakota, says: "Have used the VIOLETTA in such cases as Goitre, Bronchitis, Pleurisy, Neuritis, Neuralgia and Lumbago, and find it very beneficial. In fact, I would not be without it in my office."

WRITE FOR BOOK FREE

Just send your name on a post card or use the coupon below for convenience. We want you to know what physicians drugless healers, sanitariums, beauty specialists and individual owners say about Violet Ray treatments with the Violetta. We want you to know how it removes pain as if by magic—how it clarifies the skin almost over night—why it is painless, harmless, even to infants.

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326 West Madison Street, Chicago, Ill.

Please send me your free book and 10 days' trial offer on the Violetta Violet Ray Machine. This incurs no obligation on your part.

Name.....
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MAIL COUPON OR POSTAL

We will tell you about our 10 days' trial plan and prove to you that no other machine ever made is in the Violetta class. The only self-contained Violet Ray Machine on the market. Sold direct to you or through your electrical dealer. Write today for free book and trial offer.

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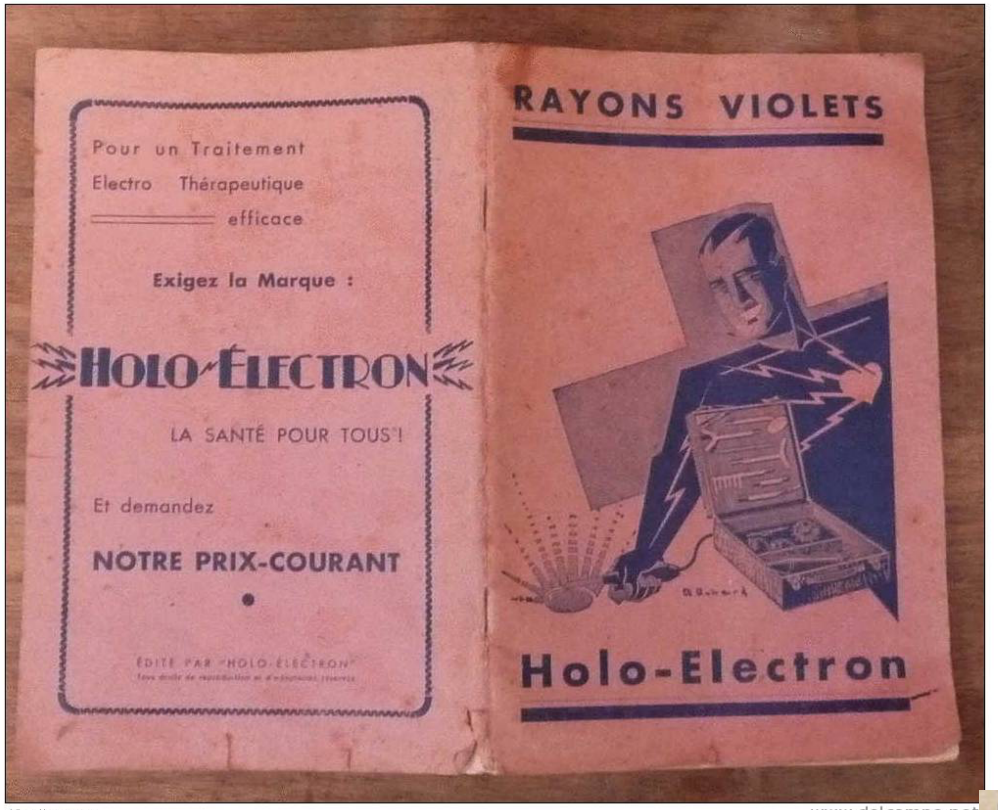
You benefit by mentioning the "Electrical Experimenter" when writing to advertisers.

Violet rays: since the beginning of the 20th century

In use for decades,
but its efficacy has not been evaluated!

Et maintenant en français…



Already in use but not cold plasmas

Electro-surgery
Electro-cauterization

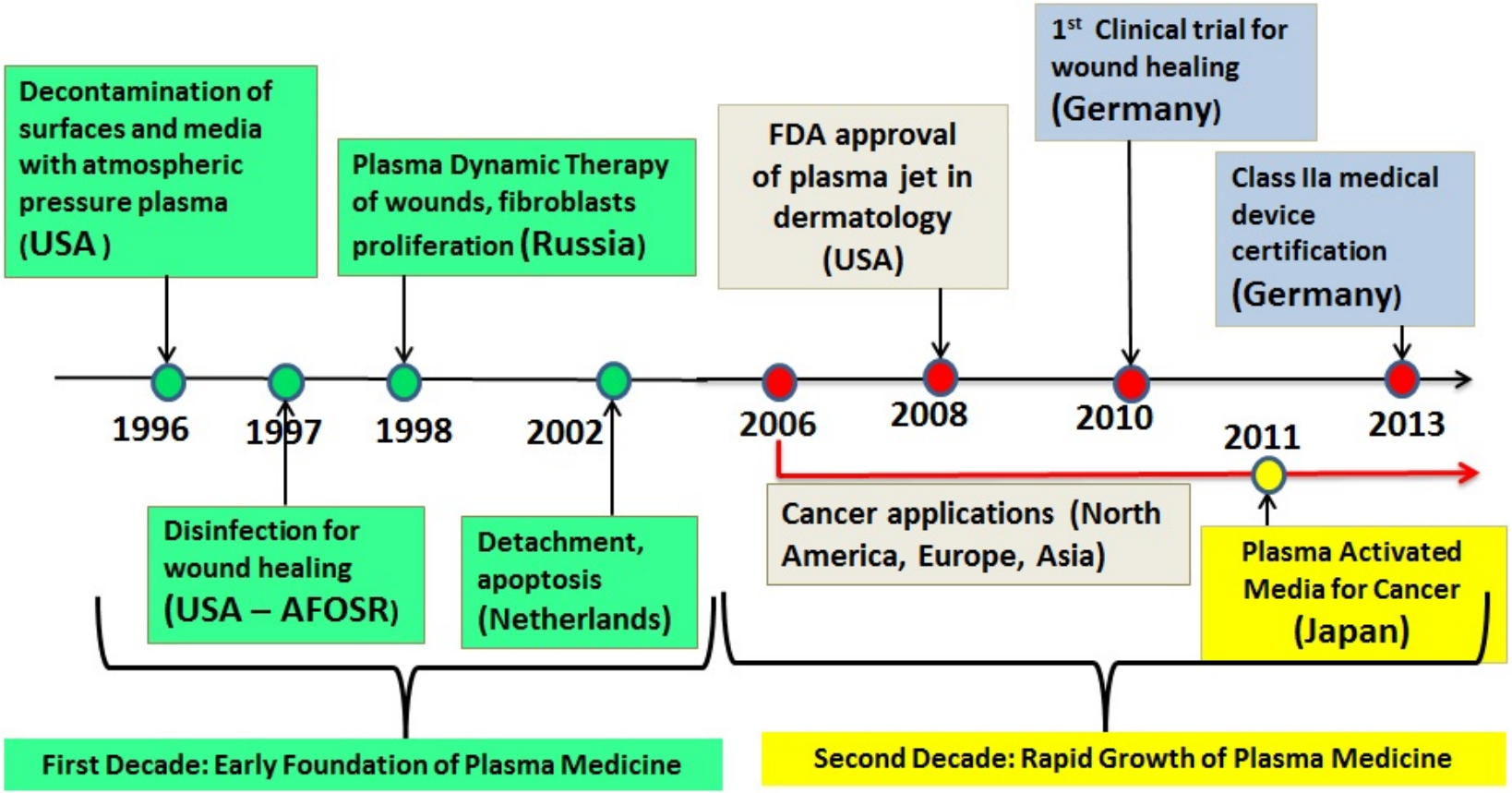
Superficial resection of diseased tissue

Professor Horace Roman,
MD, PhD,
CHU University Hospital,
France.

PLASMA SURGICAL
The energy to advance care

Rouen

PLASMA MEDECINE



Plasma **2018**, *1*, 5; doi:10.3390/plasma1010005

PLASMAS FOR THERAPEUTIC APPLICATIONS

Medical applications of low temperature non-thermal plasmas

Air environment at atmospheric pressure
$T_{gas} < 40°C$, cooler even better
Liquid interface

Therapeutic applications require:

1/ non-equilibrium plasmas:

$Te = 1\text{-}10\ eV \neq Tg = 300\ K\ (0.025\ eV)$

2/ atmospheric pressure

1+2 = real challenge ➡ what kind of electrical discharges ?

ELECTRIC BREAKDOWN

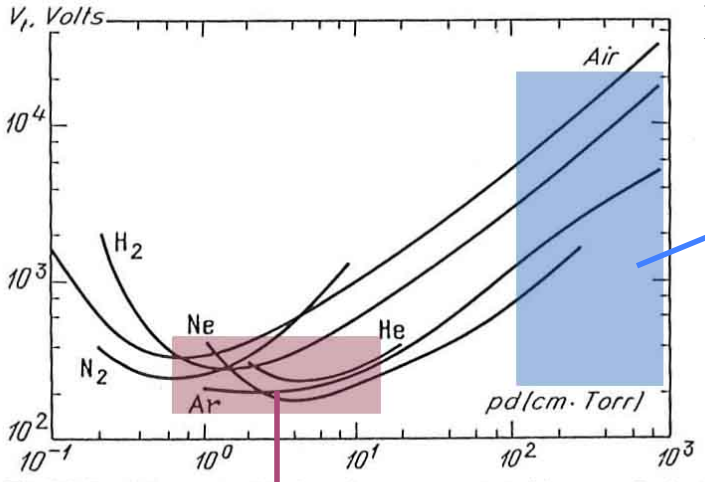


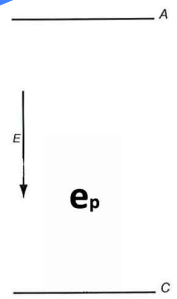
Fig. 7.2. Breakdown potentials in various gases over a wide range of *pd* values (Paschen curves) on the basis of data given in [7.1, 2]

Yu. Raizer, Gas Discharge Physics

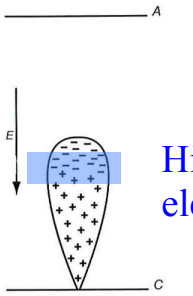
Atmospheric pressure

Pd=100 → d=1.3 mm !

streamers

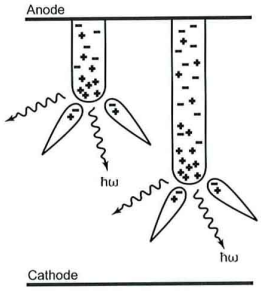


1: primary electron

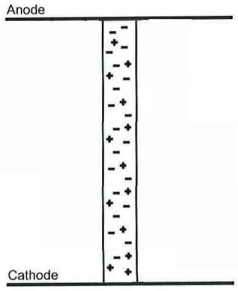


High space-charge electric field

2: avalanche in a few ns



3: streamer
velocity: 10^8 cm/s



4: conductive chanel
diameter: 100s μm

Glow discharges

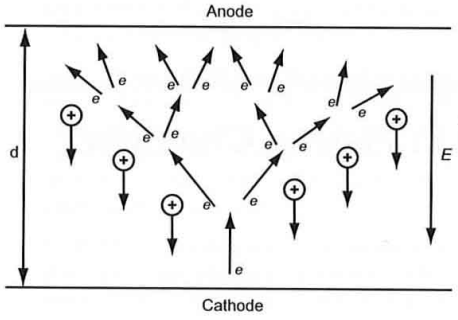


Figure 4–1. Townsend breakdown in a gap

A. Fridman, Plasma Chemistry

5: glow to arc transition ⟶ thermal plasma

How to avoid the glow to arc transition ?

NON-EQUILIBRIUM PLASMAS AT ATMOSPHERIC PRESSURE

Key point: how to avoid the glow to arc transition ?

1/ external preionization:

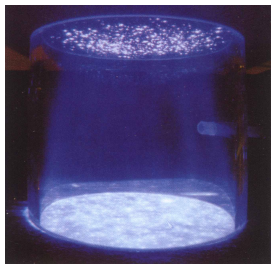
Overlapping the streamer heads

Very efficient but complex and expensive
High value products: high power lasers

Gap 25 cm, Ne/SF_6/F_2

2/ current limitation:

résistive

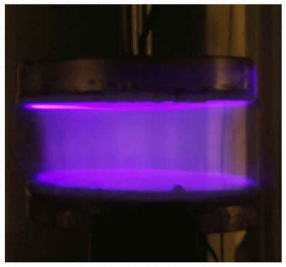


Laroussi et al:
IEEE Trans. Plasma Sci. (2002)

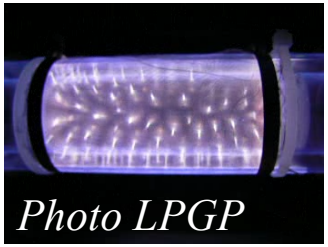
Gap 4.5 cm, He/air

Capacitive (DBD)

homogeneous



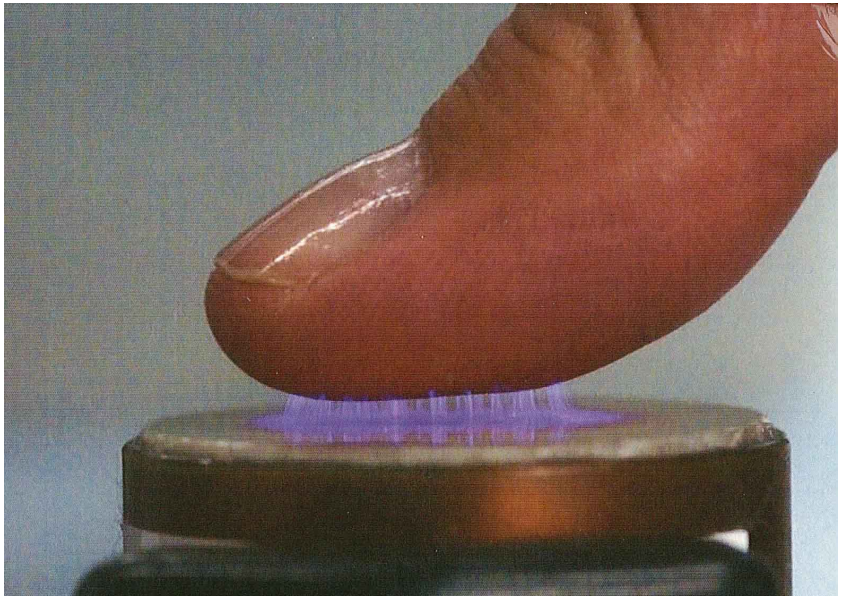
filamentary



Classical discharges = discharges between 2 electrodes inside a closed chamber

OPEN DISCHARGES

FE-DBD



A. Fridman Drexel University

treatment over a large surface area

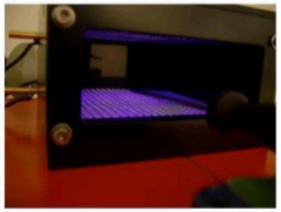
but

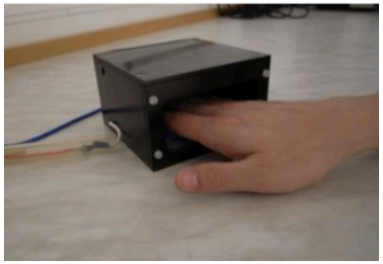
short gap (few mm): external treatment

Direct DBD

Tissue exposed to plasma
Charged, excited species, radicals
UV, electric field
Tolerable current through tissue

Surface DBD

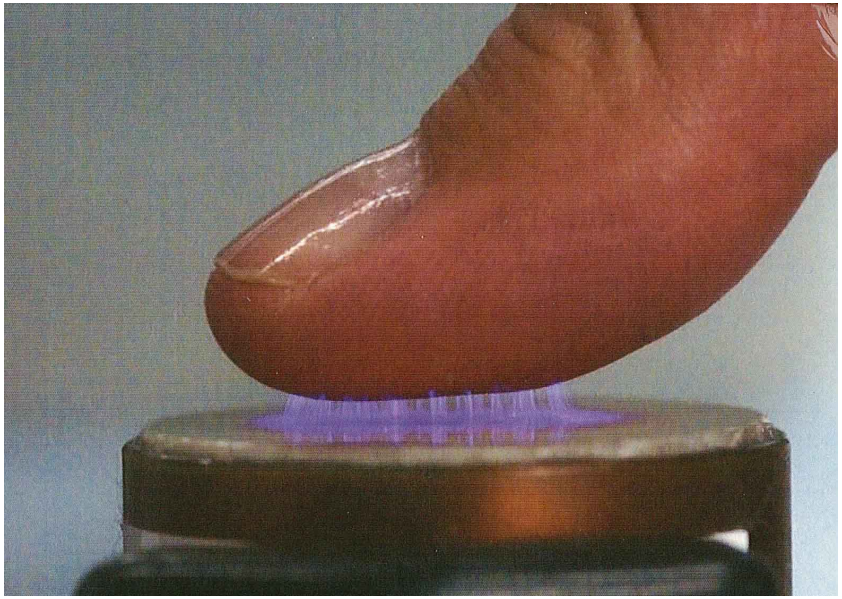




Plasma afterglow
No current, very small amount of ions
Mainly long-lived reactive species
UV rays

OPEN DISCHARGES

FE-DBD



A. Fridman Drexel University

treatment over a large surface area

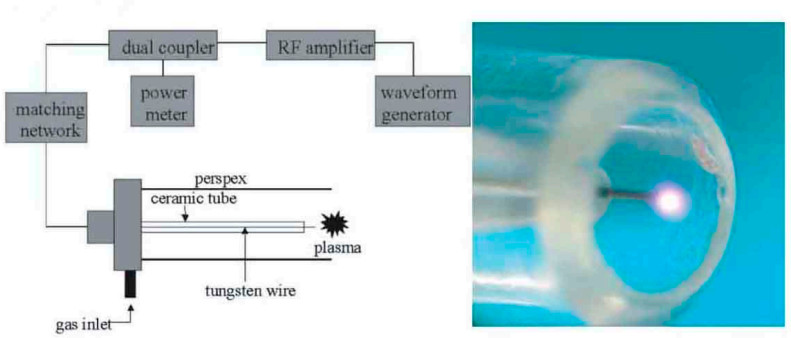
but

short gap (few mm): external treatment

Plasma needle

"a non-destructive atmospheric plasma source for fine surface treatment of (bio)materials."

E Stoffels et al
Plasma Sources Sci. Technol. 11 (2002) 383–388



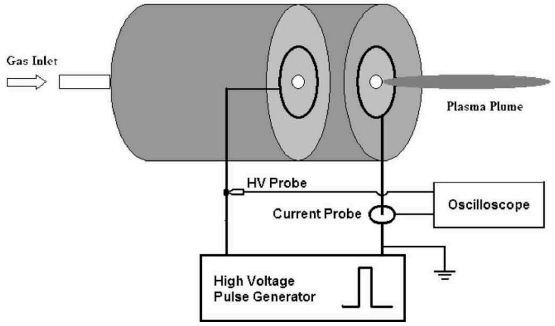
RF discharge (usually high Tg)

Needle tip is at room temperature: biomedical applications allowed

PLASMA JETS

Room-temperature atmospheric pressure plasma plume for biomedical applications

M. Laroussi[a)] and X. Lu APPLIED PHYSICS LETTERS **87**, 113902 (2005)



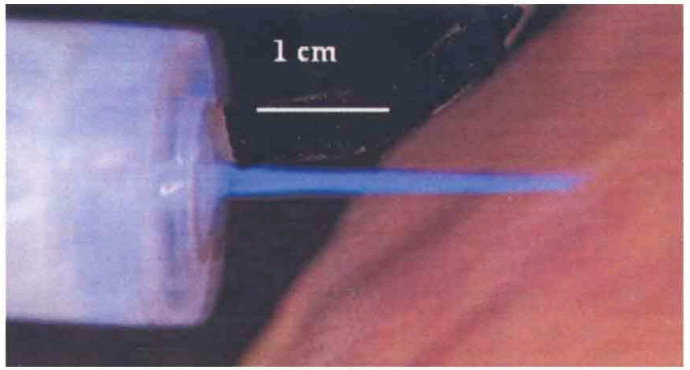


FIG. 2. (Color online) Photograph of the plasma plume in contact with human skin.

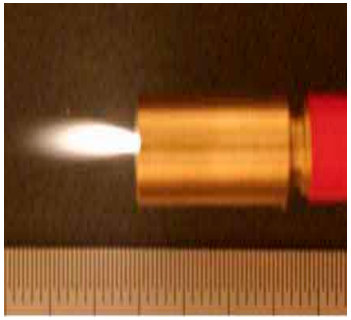
Dynamics of an atmospheric pressure plasma plume generated by submicrosecond voltage pulses

XinPei Lu and Mounir Laroussi[a)] JOURNAL OF APPLIED PHYSICS **100**, 063302 (2006)

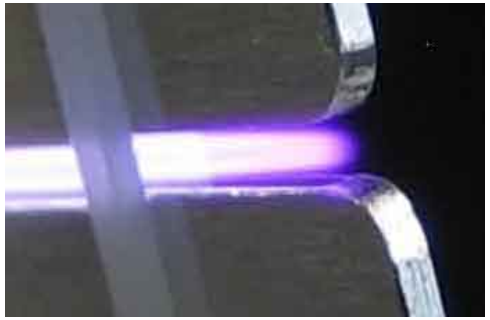
plasma pencil," is driven by few hundred nanosecond wide pulses at repetition rates of a few kilohertz. Correlation between current-voltage characteristics and fast photography shows that the plasma plume is in fact a small bulletlike volume of plasma traveling at unusually high velocities.

PLASMA JETS

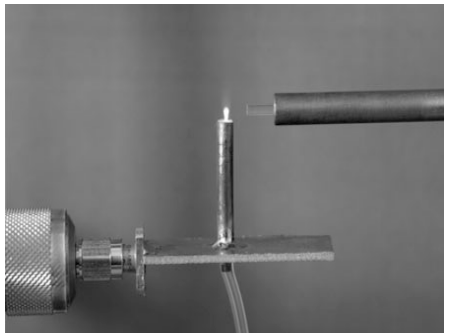
DC microplasma



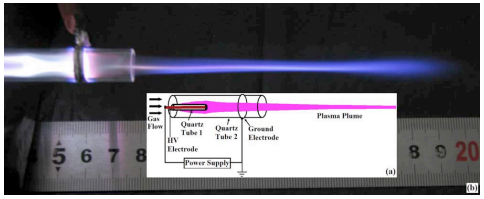
RF plasma jet

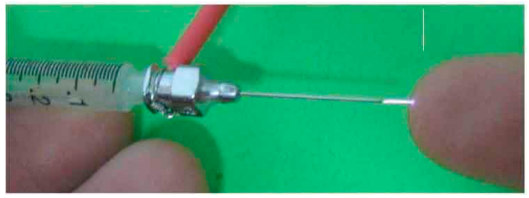


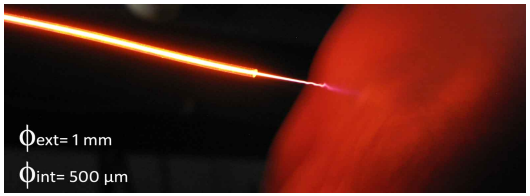
microwave

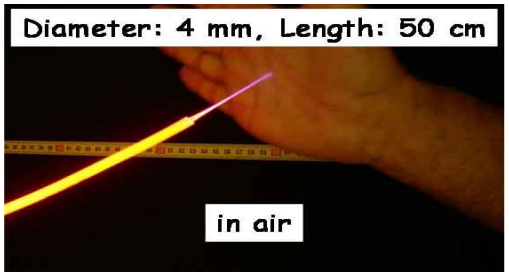


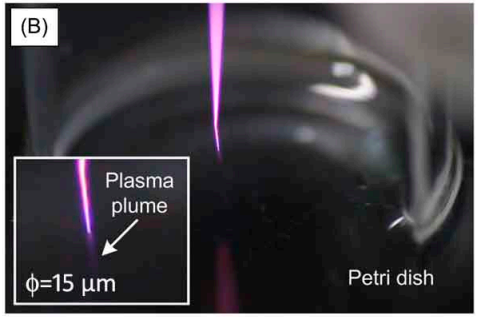
HV-LF excitation

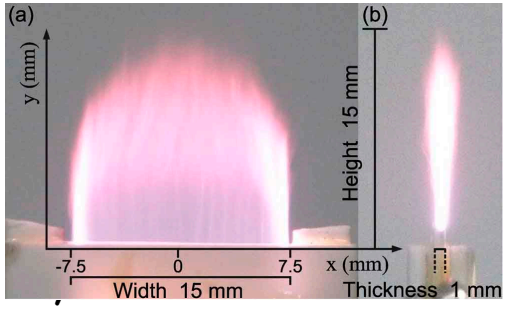












PLASMA JETS

All kinds of electrical excitations: DC, AC, RF, MW, continuous or pulsed

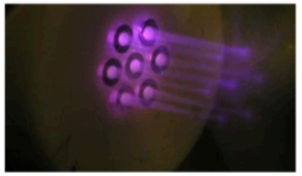
Rare gases (with or without admixtures: O_2, N_2, H_2O_2,…) but also pure N_2 or Air

Unlimited terminology: APPJ, Plasma Plume, Plasma Pencil, Plasma Gun, Plasma Torch,…

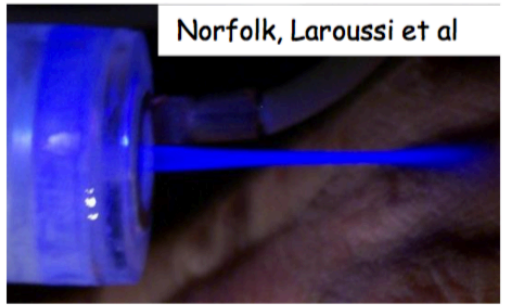
Discharge operated in a non-sealed electrode arrangement
plasma « expansion » outside the discharge region
either through high gas flow or determined by the electric field

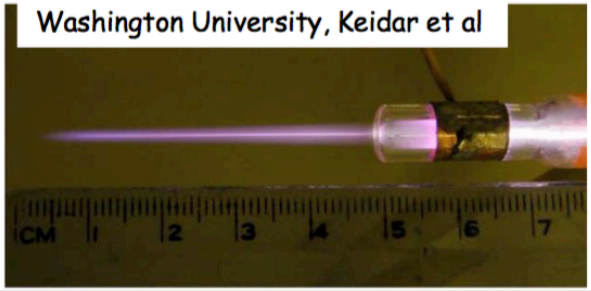
Plasma or afterglow (effluent) delivery on targets

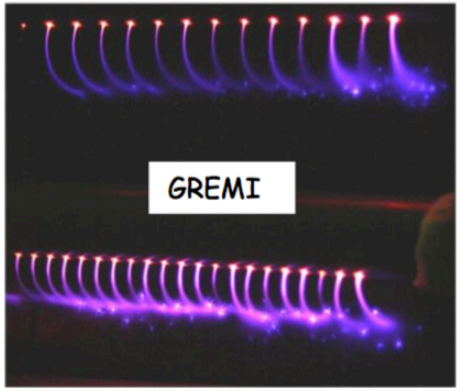
PSST 19 (2010) 025003
Z. Cao et al



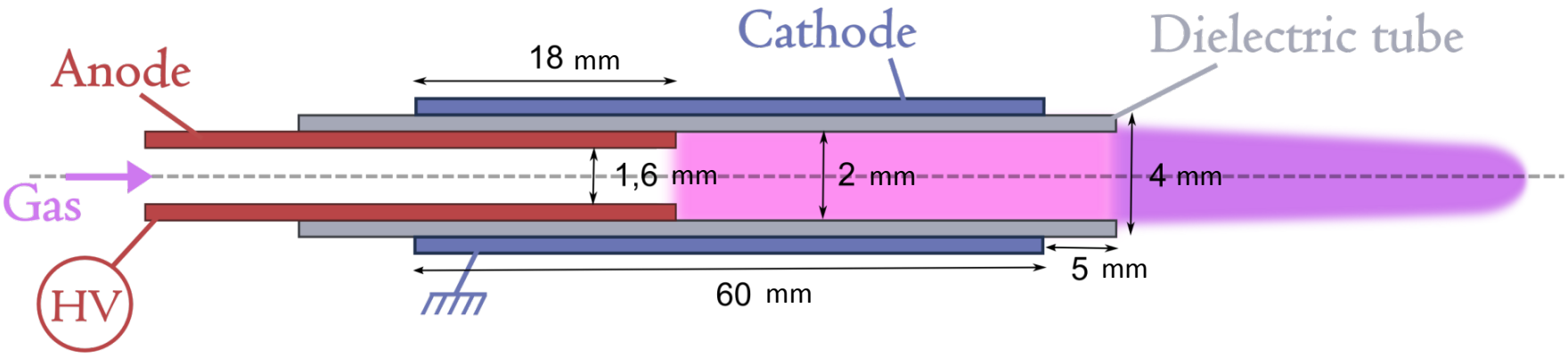
Osaka University

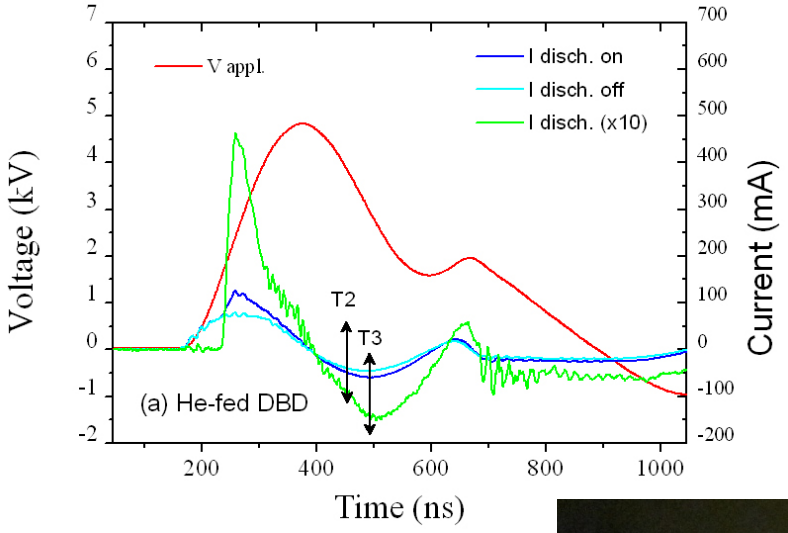






MICROPLASMA JET





Coaxial DBD

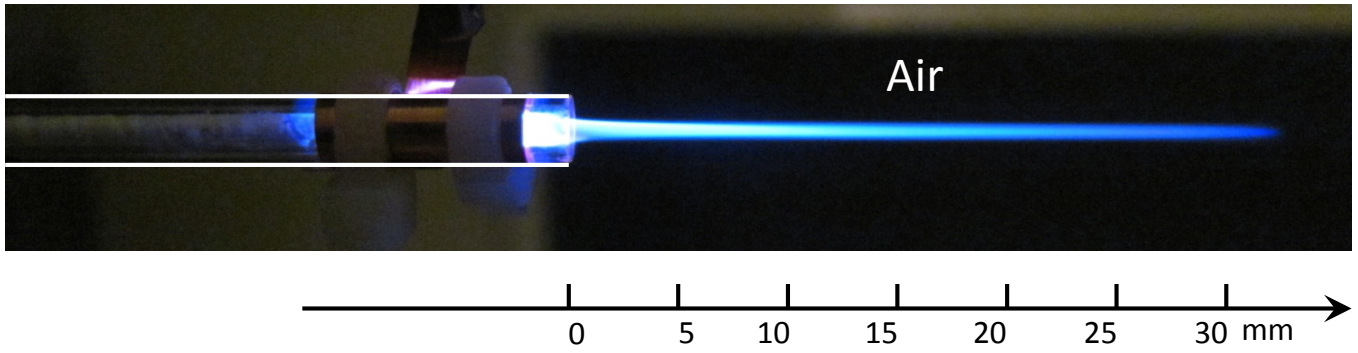
Applied voltage (pulsed) : **3–40 kV (100ns–10µs)**
(typically 5 kV, 500 ns)

Frequency : **1–50 kHz** (typically 20 kHz)

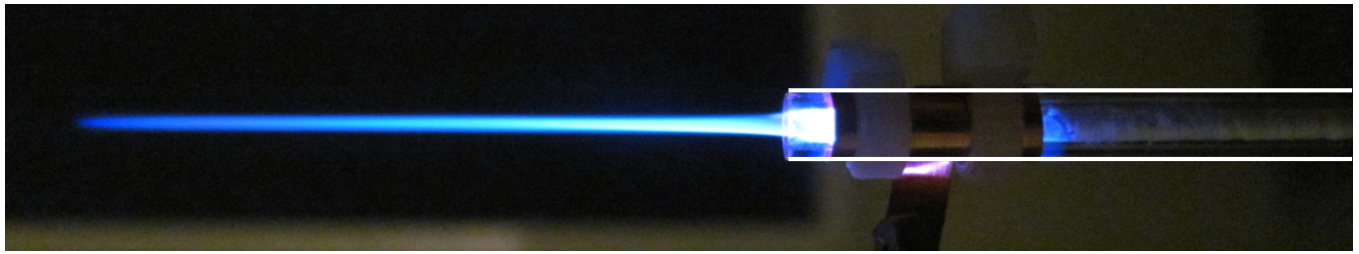
Gas : **He, Ar, with or without O_2/N_2/H_2O**

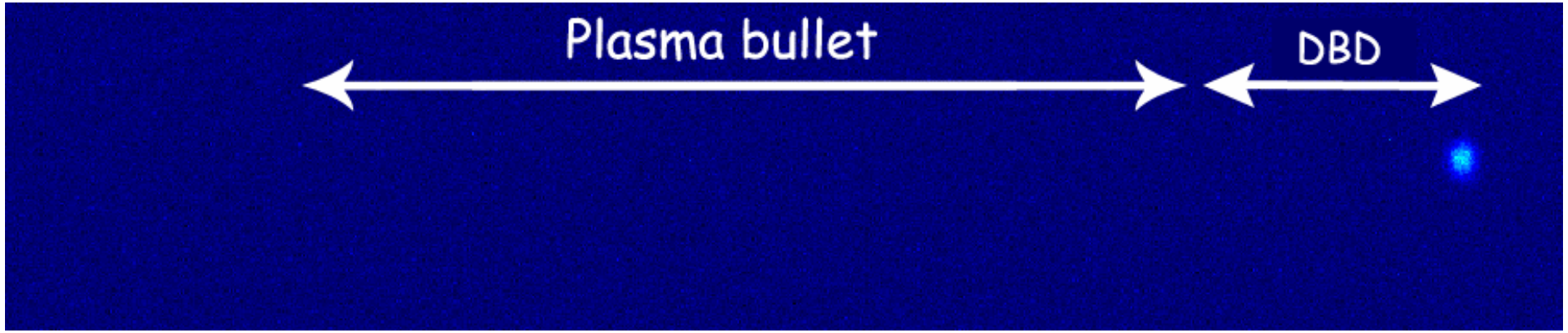
Gas flow : **50 to 5000 sccm**

Helium →



MICROPLASMA JET





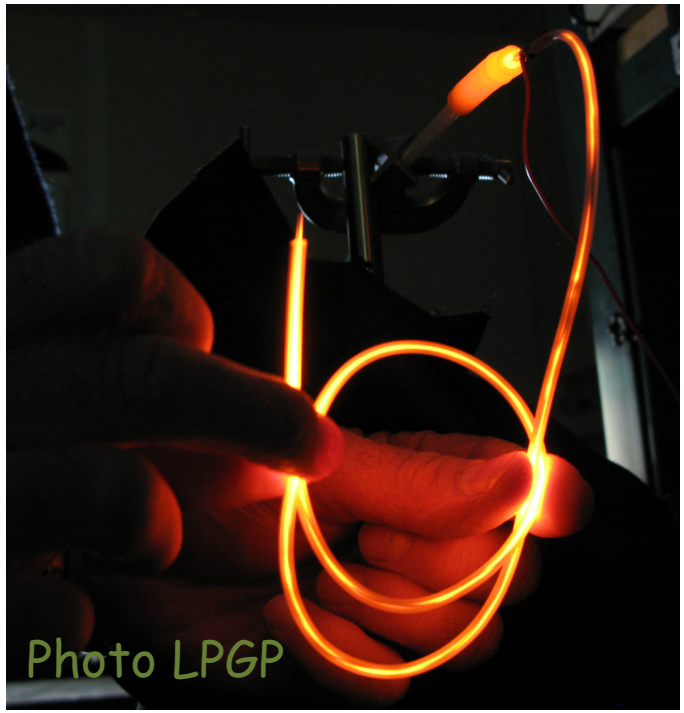
The plasma jet is not continuous; it is rather a streamer guided by the gas channel

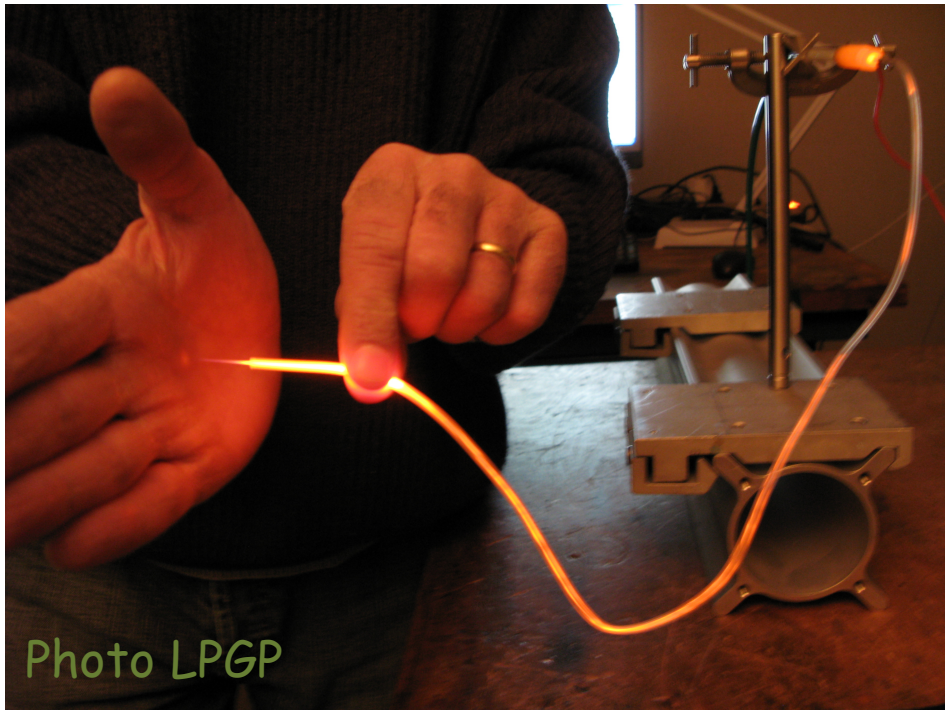
The velocity of the “guided streamer” is of several hundreds km/s

Stable at atmospheric pressure
Low gas temperature ≈ 300-350 K

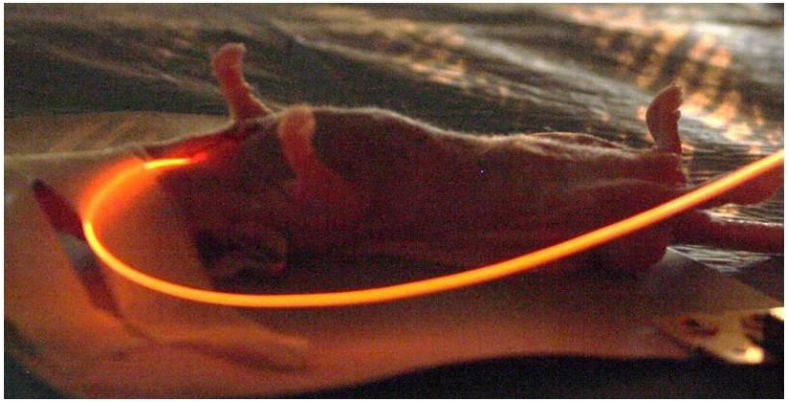
ENDOSCOPIC TREATMENTS

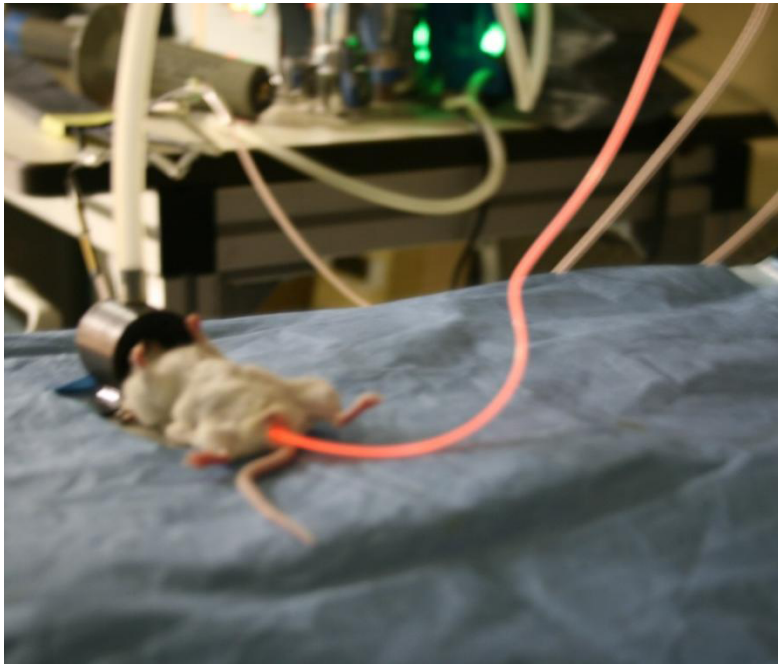
Possible use for endoscopic treatments

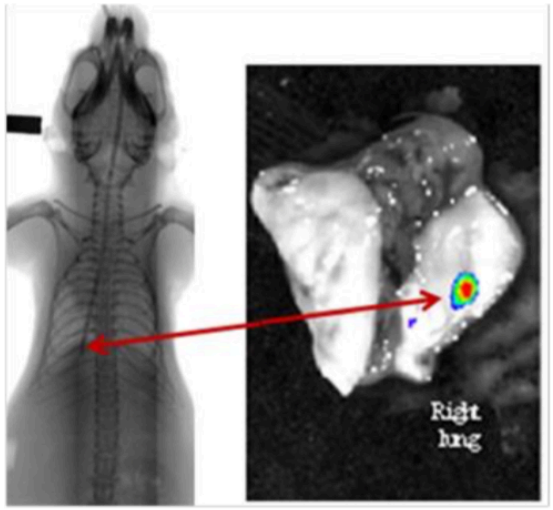


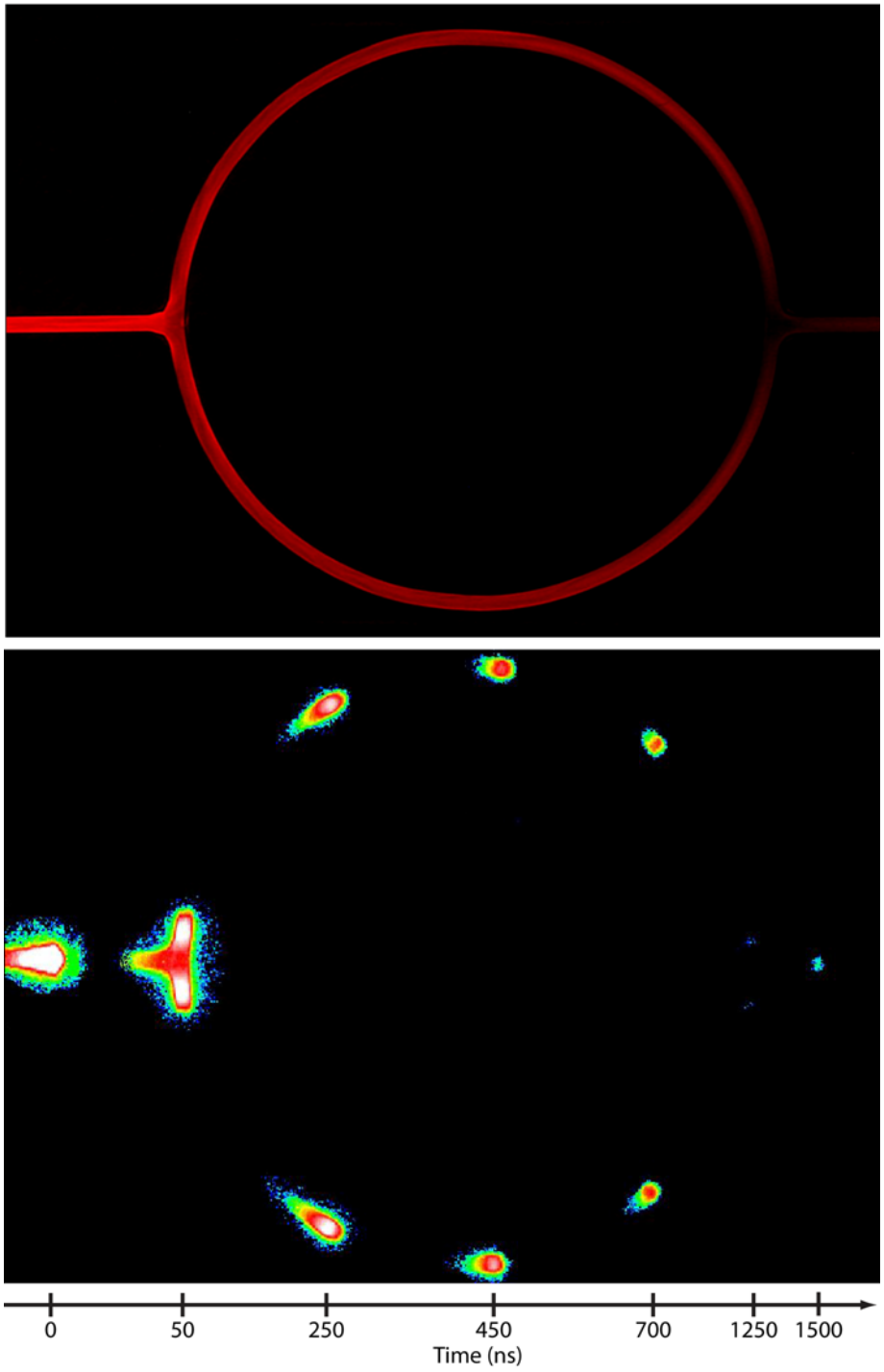


Plasma Gun





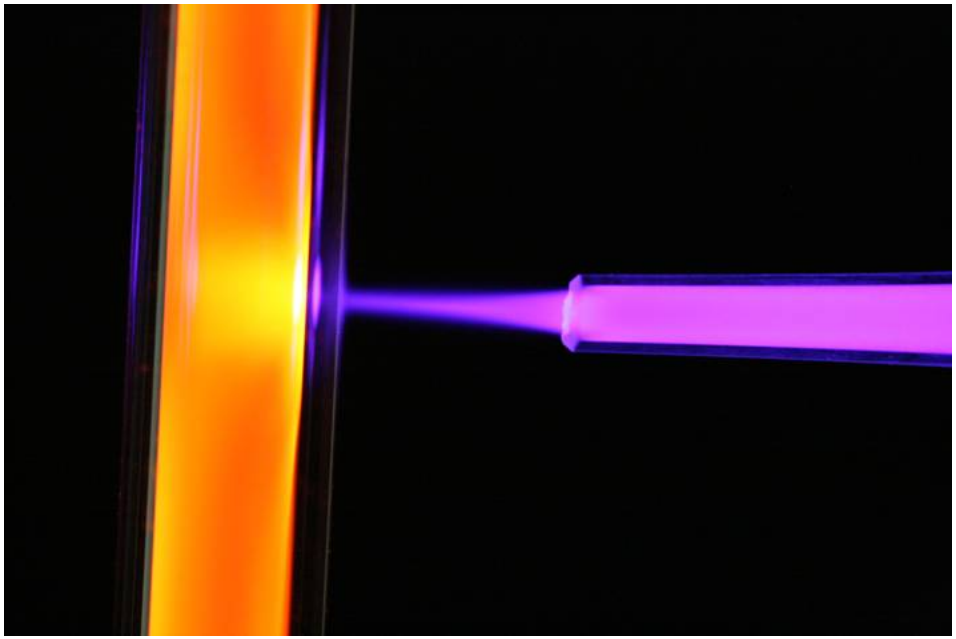




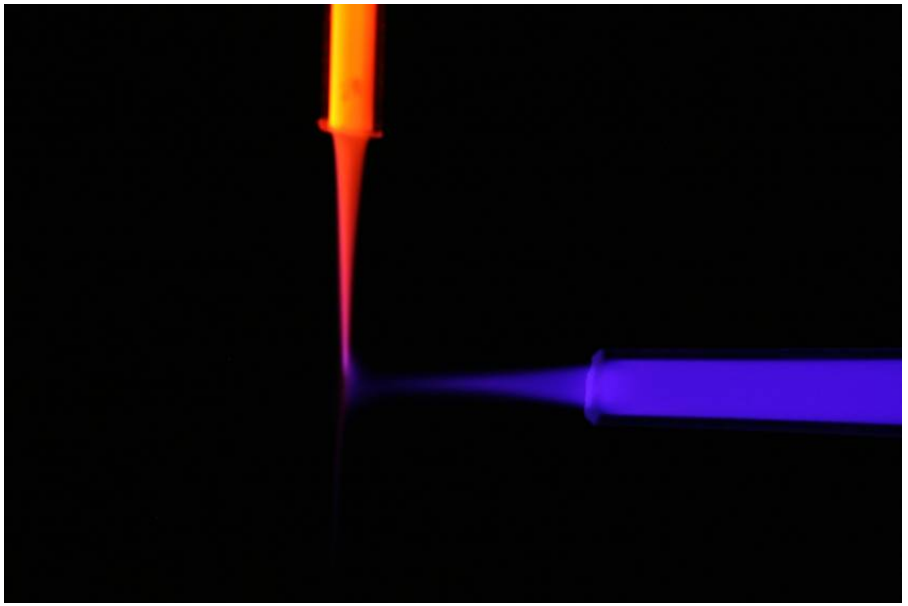
GREMI

Splitting

Splitting



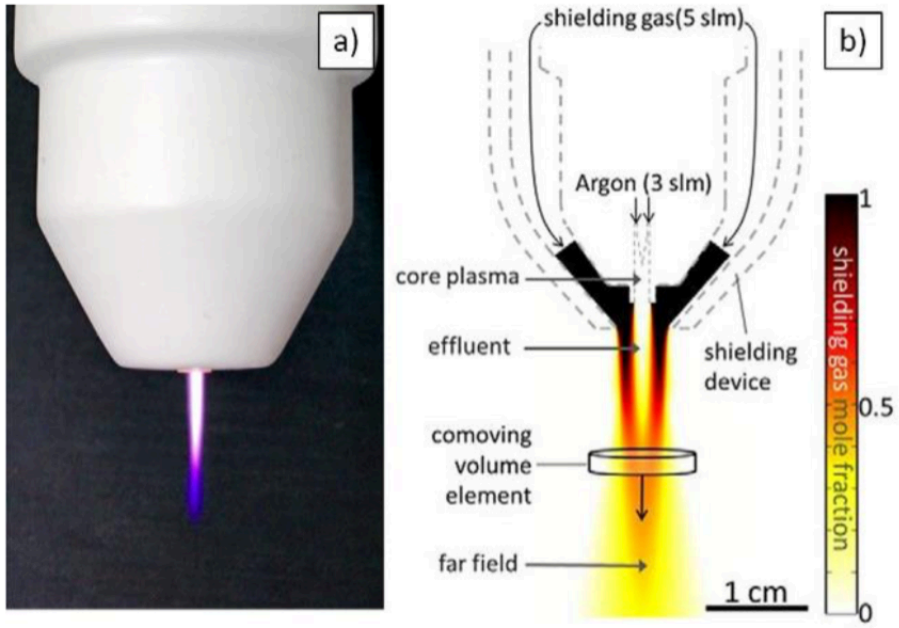
Transfer



Mixing

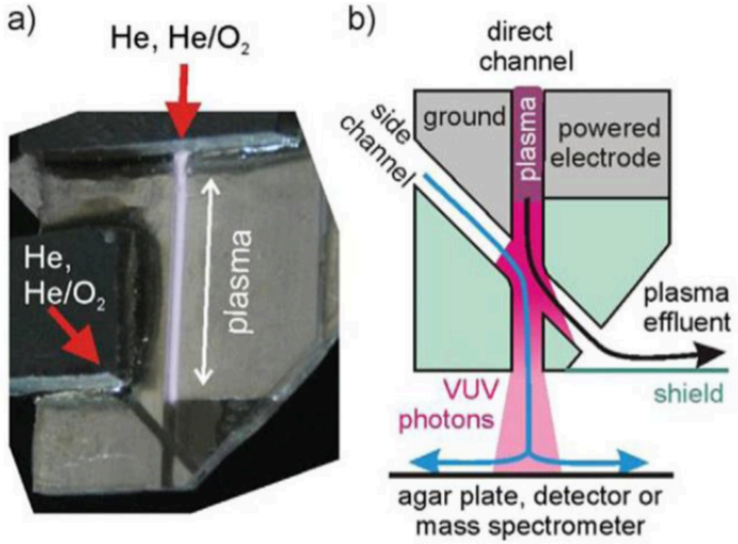
RS PRODUCTION AND CONTROL

Plasma torch afterglow/effluent: KinPen



Visualization of kinpen plasma jet source with shielding gas. (a) photograph and (b) schematic and visualization of the shielding gas curtain by CFD simulation.

µAPPJ: afterglow: UV phtons/reactive species

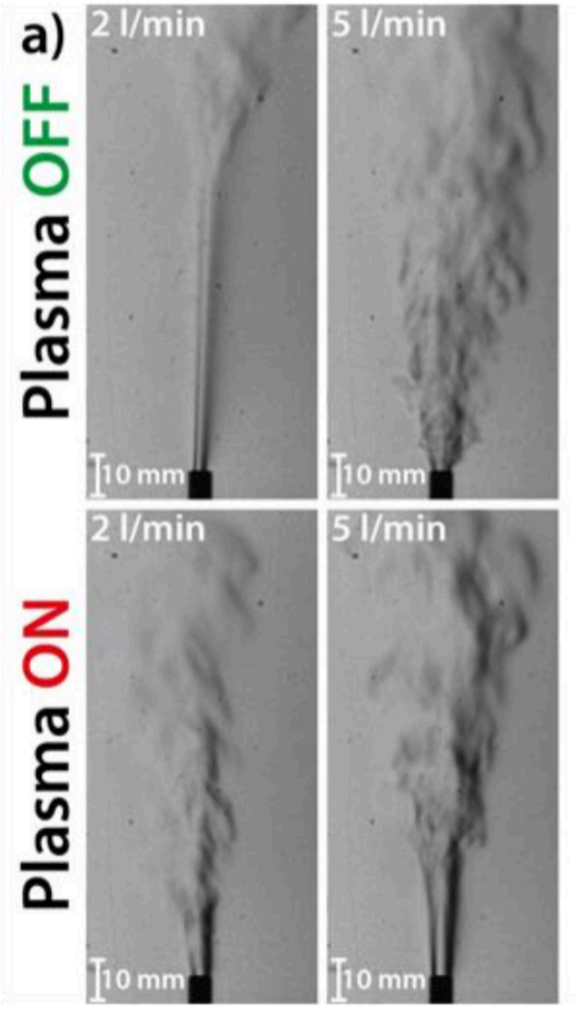


Photograph (a) and sketch (b) of the modified *µAPPJ* (so-called X-jet) setup.

J Winter *et al* Plasma Sources Sci. Technol. **24 (2015) 064001**

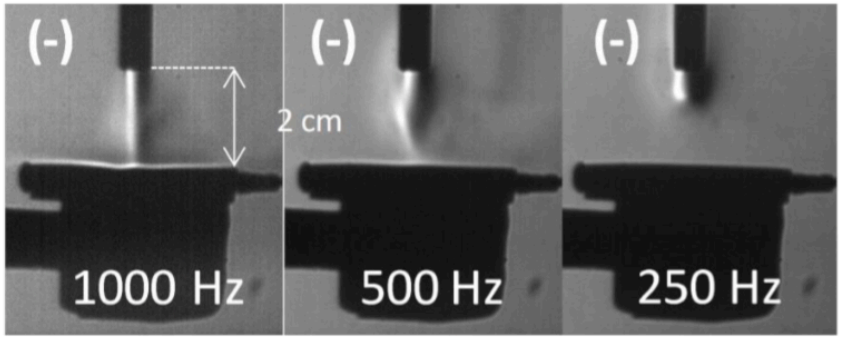
FLUID DYNAMICS

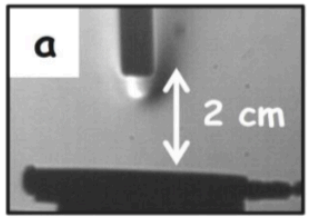
Free jet in ambient air



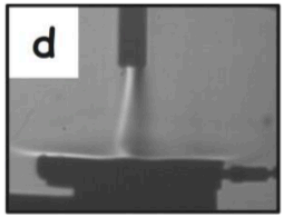
Upstream and downstream shift of the laminar to turbulent transition

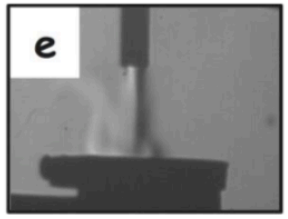
Pulse repetition rate influence





Plasma OFF

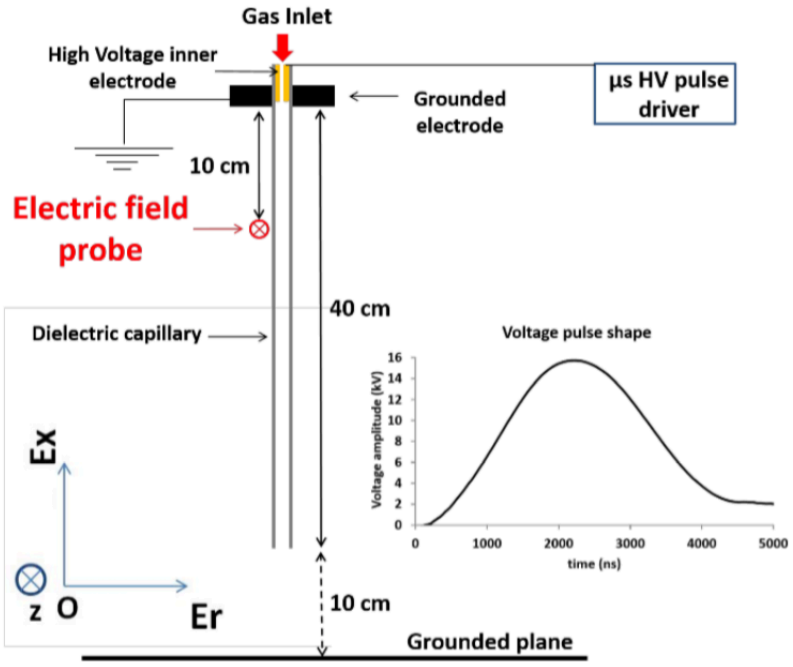




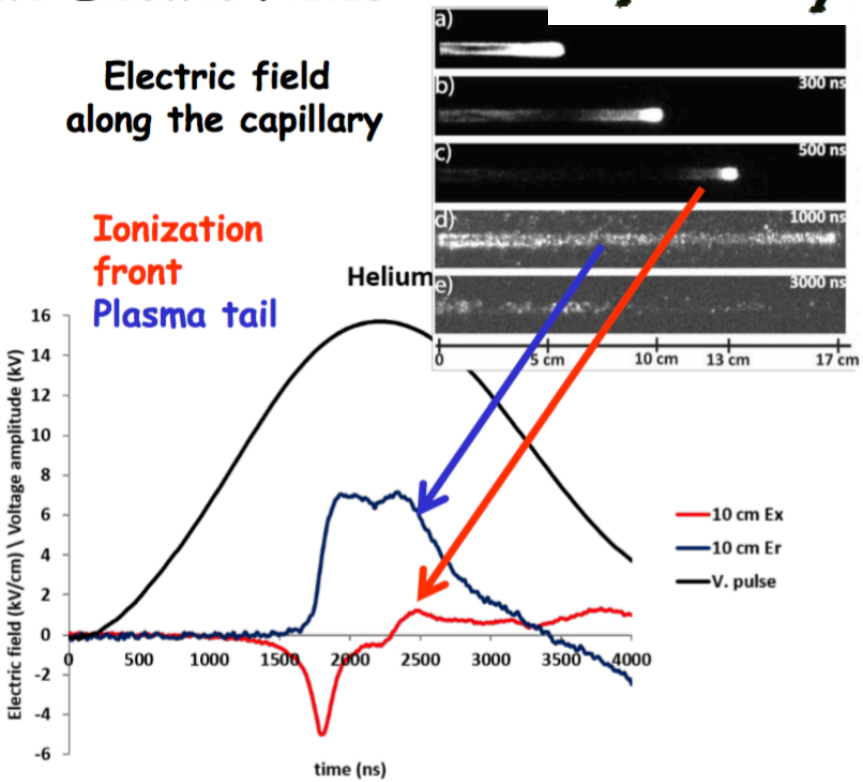
Grounded target

Floating potential target

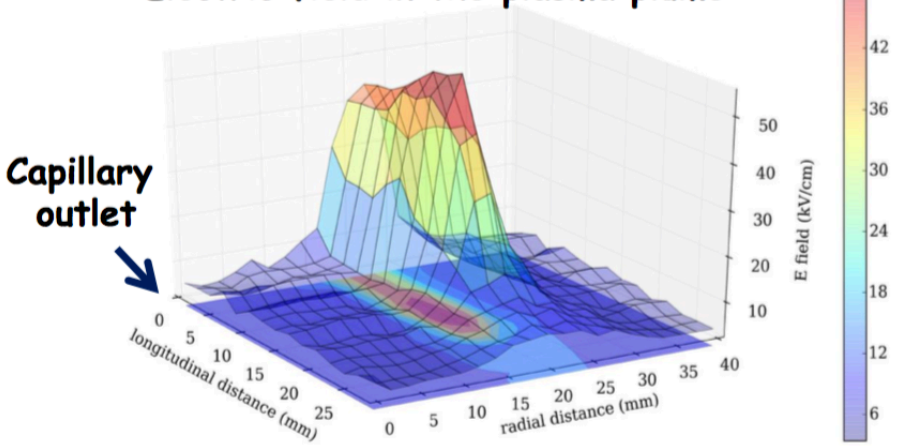
Plasma jets generate Electric Fields



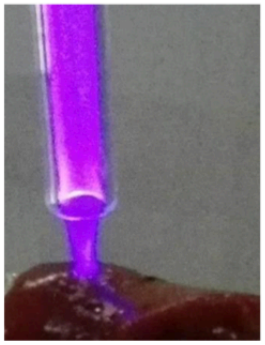
Electric field along the capillary

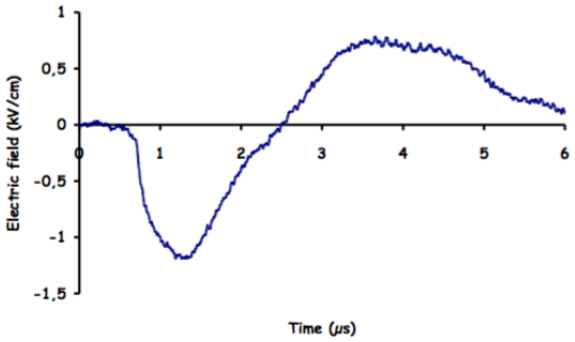


Electric field in the plasma plume



Electric field under 3 mm liver layer



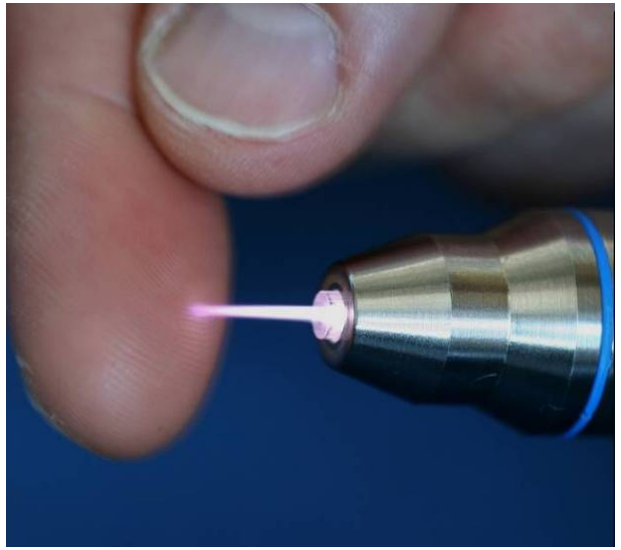


kINPen™: basic module

kINPen 09 (@ INP Greifswald)

Dimension:
L=190mm,Ø 20mm
Weight:
170g
HF-Voltage:
1,1MHz;2…6kV
Gas temperature:
30°C - 150°C
Gas flow:
1-5 slm

- Athmosperic pressure plasma
- Cold plasma jet
- Variable in length (some mm)
- Easy to use and handle
- Generation of UV/VUV radiation and chemically active species (radicals)
- CE - certified



INP Greifswald

> Klinikum Schwabing

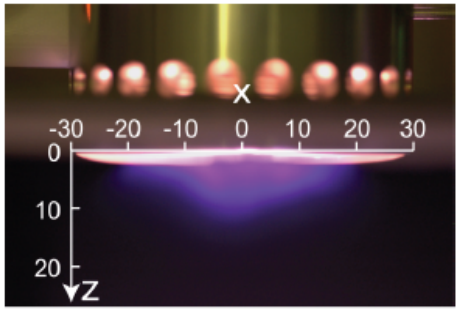
Phase II study : MicroPlaSter

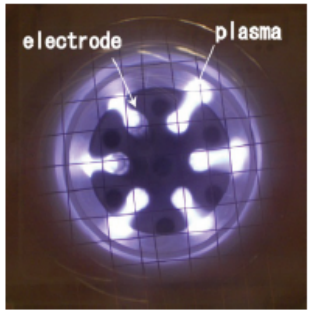
Georg Isbary

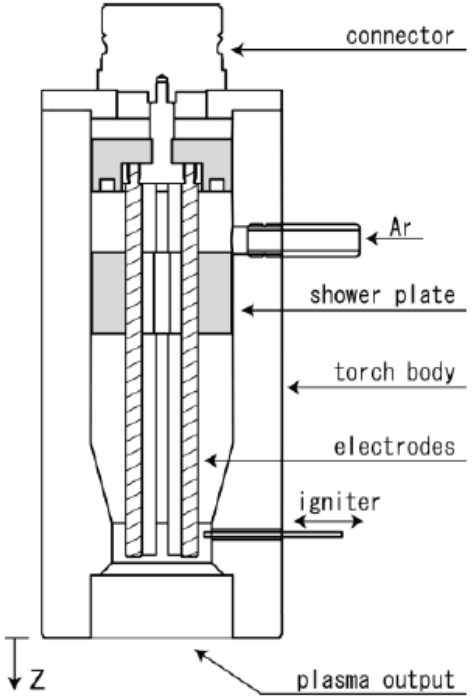
städtisches
>Klinikum
München

distance to wound controlled by ultrasounds

The new device - MicroPlaSter ß







- Used gas: argon
- Voltage = 50 - 100 V
- Frequency = 2,3 GHz
- Power = 100 W

Microwave Plasma

städtisches >Klinikum München

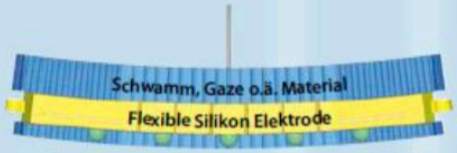
DBD based medical device

CINOGY

Kernstück ist eine kompakte Plasmaquelle, die lokal gezielte Gasentladungen auf dem erkrankten Hautbereich erzeugt. PlasmaDerm® erzeugt einen desinfizierenden Effekt, welcher in diversen Versuchen nachgewiesen wurde. Es gibt kein vergleichbares Verfahren, welches die beschriebenen Effekte des Plasma, elektromagnetische Felder, Gaspezies und UV Licht, so wirkungsvoll in einem Behandlungsschritt ermöglicht, wie PlasmaDerm®.

In vielen Versuchsreihen wurde nachgewiesen, dass keinerlei Gefährdungspotential für den Patienten zu erwarten ist.

Verschiedene Applikationsformen (siehe Abbildung) sind im Verbund, mit Schwamm, Gaze oder anderen Materialien, sowie als Einzellösung (flexible Silikonelektrode o.ä.) möglich.



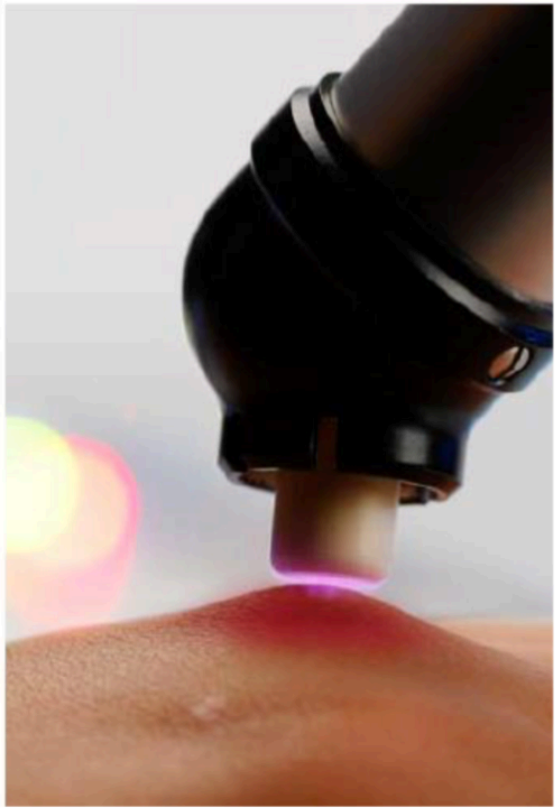
CINOGY GmbH

Max-Näder-Str. 15
37115 Duderstadt/Germany
Tel: +49 5527 848 3771
Fax: +49 5527 848 83771

plasma@cinogy.de
www.cinogy.de

PlasmaDerm®

Verfahren im Bereich Plasmatechnik



CELLULAR EFFECTS

Cellular effects *in vitro* induced by cold atmospheric plasmas

Lethal effects*:*

– Inactivation/killing of microorganisms (prokaryotic cells) including antibiotic-resistant pathogens

– Inactivation or killing of mammalian cells (eukaryotic cells) including cancer cells mainly via induction of apoptosis depending on intensity (time) of plasma impact

Non-lethal effects:

– Influence on/stimulation of metabolism of microorganisms (prokaryotic cells)

– Specific/selective effects on mammalian cells (eukaryotic cells):

Influence on cell migration

Influence on expression of surface proteins responsible for cell-cell and cell-matrix interactions

Influence on/stimulation of cell proliferation

Influence on/stimulation of angiogenesis

Reversible impact on DNA integrity, influence on cell cycle

Reversible permeabilization of cell membranes (“plasma poration”)

Non-thermal blood coagulation

MECHANISMS

Mechanisms of the biological effects of cold atmospheric plasmas *in vitro*:

– Significant biological plasma effects are caused by plasma-induced changes to the liquid environment of cells

– Reactive oxygen and nitrogen species (ROS, RNS/RONS) generated in or transferred into liquid phases play a dominant role in biological plasma effects.

Reactive oxygen species (ROS)	Reactive nitrogen species (RNS/RONS)
Superoxide: $O_2^{-}\bullet$	Nitric oxide: •NO
Hydrogen peroxide: H_2O_2	Nitrogen dioxide: $\bullet NO_2$
Hydroxyl radical: •OH	Peroxynitrite: $ONOO^-$
Singlet oxygen: $^1O_2$	
Ozone: O_3	
Organic radicals: RO•, $RO_2\bullet$	

THERAPEUTIC APPLICATIONS

- Sterilization and decontamination
- Skin and tissue sterilization
- Hygiene

- Dermatology
- Dental care
- Blood coagulation and primary hemostasis
- Inflammation

- **Wound and ulcer care** (clinical studies)
- **Antitumoral effect and tumor treatment** (case studies)

Treatments *in vitro* and *in vivo* (animal models and clinical tests)

CHRONIC WOUNDS HEALING

– Open, highly infected skin lesion

– Persistent for more than 3 months without healing progress

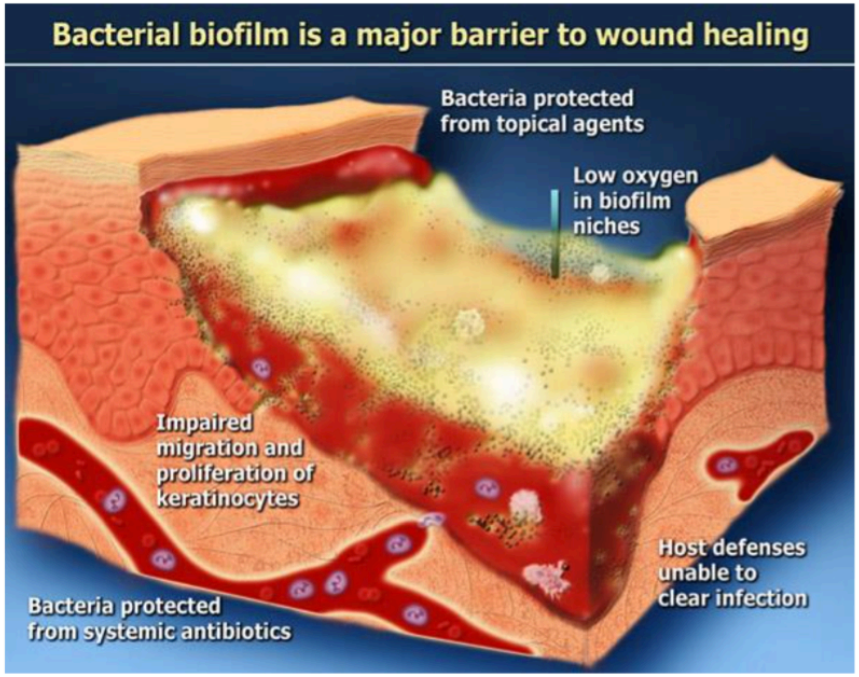
– Not cured after 12 months of therapy

– Main causes are circulatory disorders of veins or arteries

– Diabetes, spinal cord injury, other disorders that cause immobility

– Risk factors: age, pregnancy, obesity, smoking, former severe leg injury, venous thrombosis, standing and sitting for long periods

– Standard wound care: debridement, saline solution, modern wound dressing, compression stocking



http://www.coe.montana.edu/biofilmbook/module_07/Mod07_S03_Blue.htm

http://medpic.org/p/chronic_non-healing_wounds_pictures

MicroPlaSter

städtisches
Klinikum
München

städtisches
>Klinikum
München

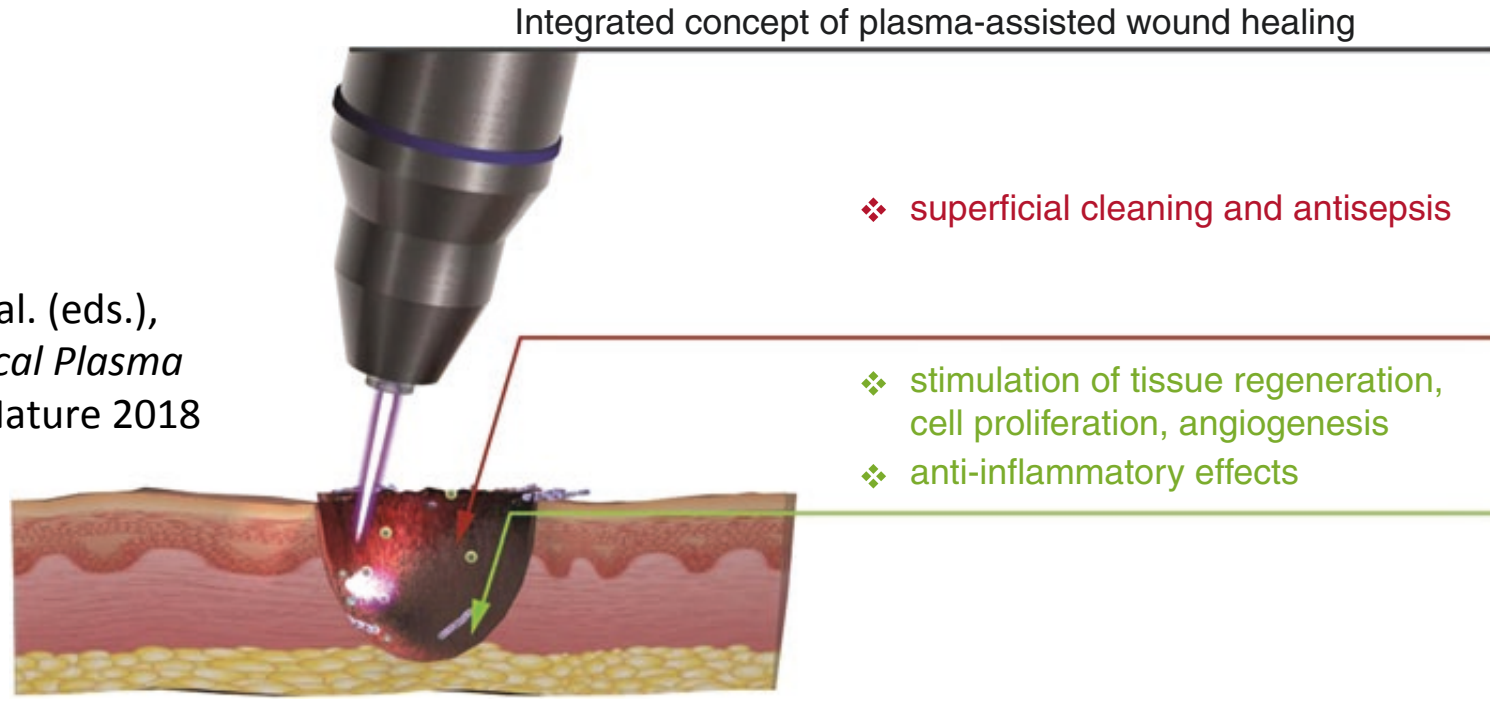
Pat.72: Therapy area

CHRONIC WOUNDS HEALING

– UV radiation and reactive gas species (i.e. O_3)
  Disinfection

– Nitric oxide (NO) or other nitrogen species (NO_X)
  Stimulation of tissue regeneration
  Wound acidification

– Electric current
  Stimulation of micro-circulation and angiogenesis



H.-R. Metelmann et al. (eds.), *Comprehensive Clinical Plasma Medicine*, Springer Nature 2018

CANCER TREATMENT

Cold atmospheric plasmas are able to induce apoptosis in cancer cells

in vitro

Drexel Plasma lab (Fridman et al) **(1st 2007)**

in vivo

PLASMED – GREMI, CIPA-TAAM, CBM, Germitech, INEL, CERB **(1st 2009)**

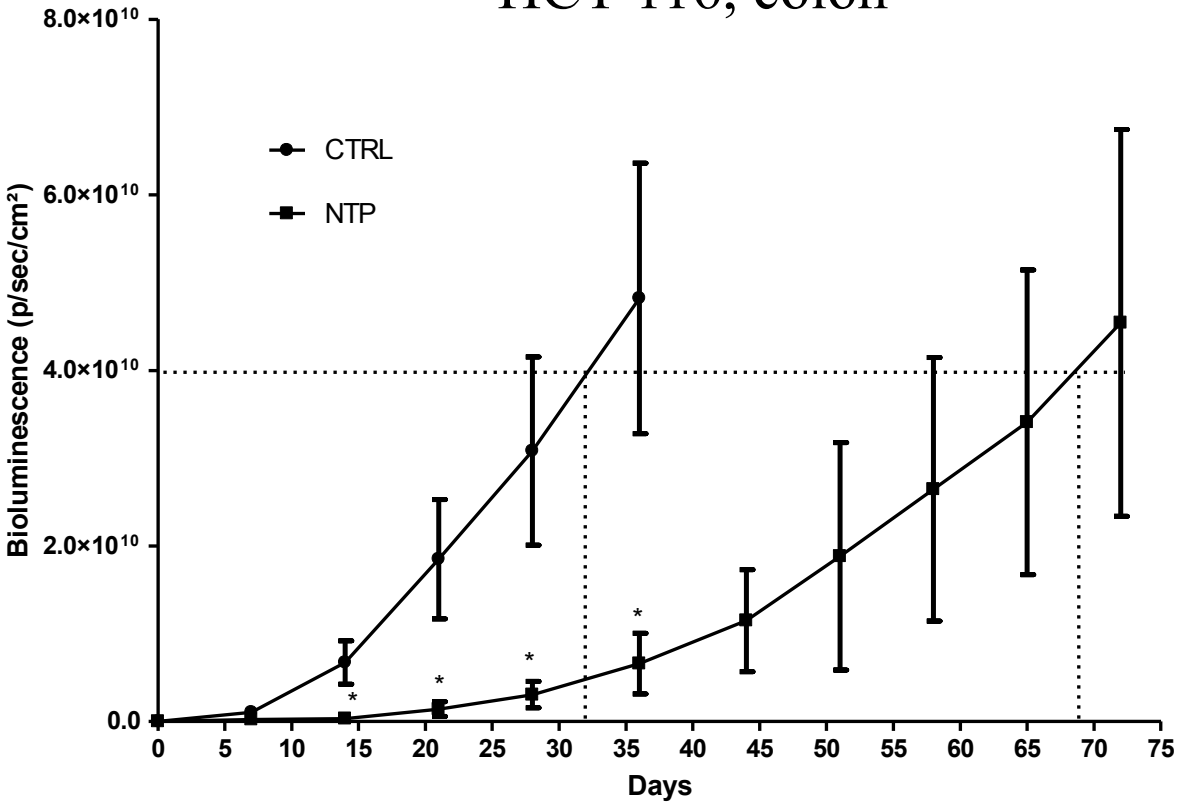
Antitumor activity of plasma has been demonstrated ***in vitro*** on:

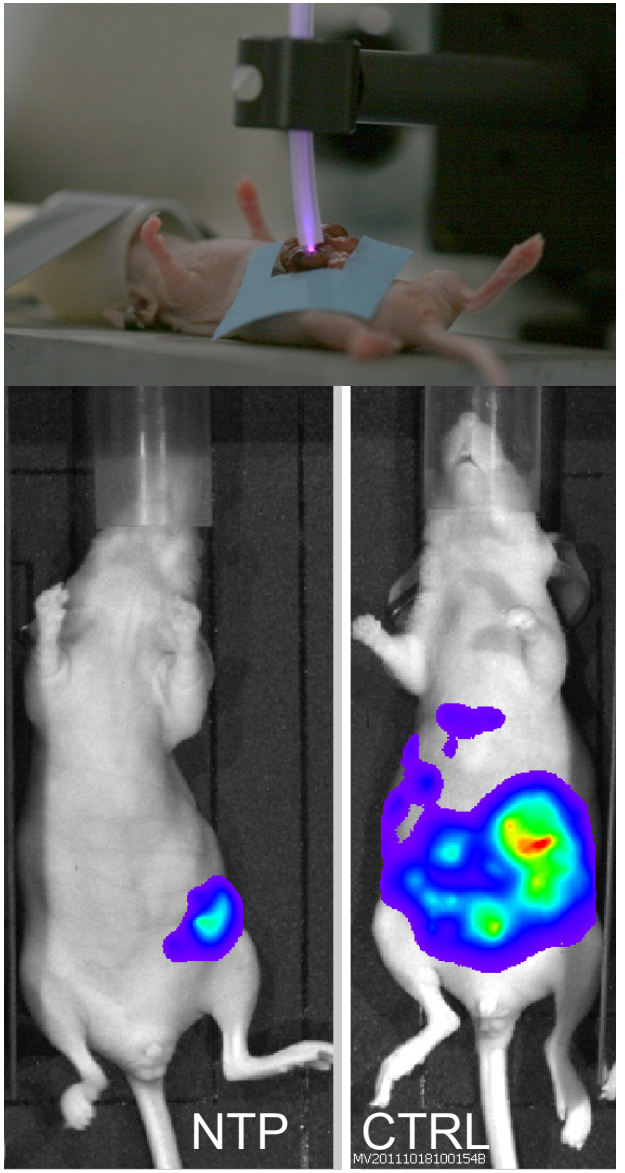
Melanoma (G361, B16, A2058)
Glioblastoma (U87MG)
Hepatocellular carcinoma (BEL-7402, HepG2)
Colorectal carcinoma (SW480, HCT-116, COLO320DM)
Lung carcinoma (A549, H460)
Breast carcinoma (MCF-7)
Cervix carcinoma (HeLa)
Oral carcinoma (HSC-2, SCC-15)
Pancreatic carcinoma (MiaPaca, COLO357)
…

non systemic treatment with little or no side effects

CANCER TREATMENT

in vivo antitumoral activity
HCT-116, colon



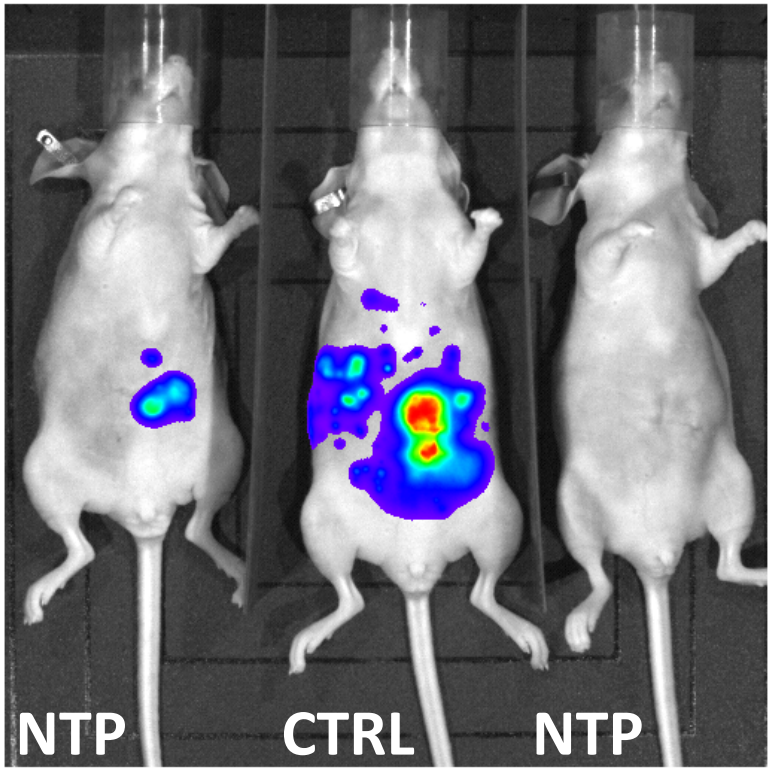


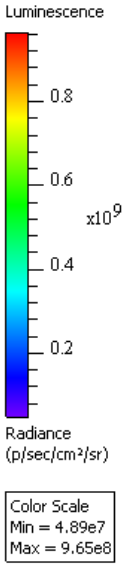
→ increase of mice lifespan of 115%

CANCER TREATMENT

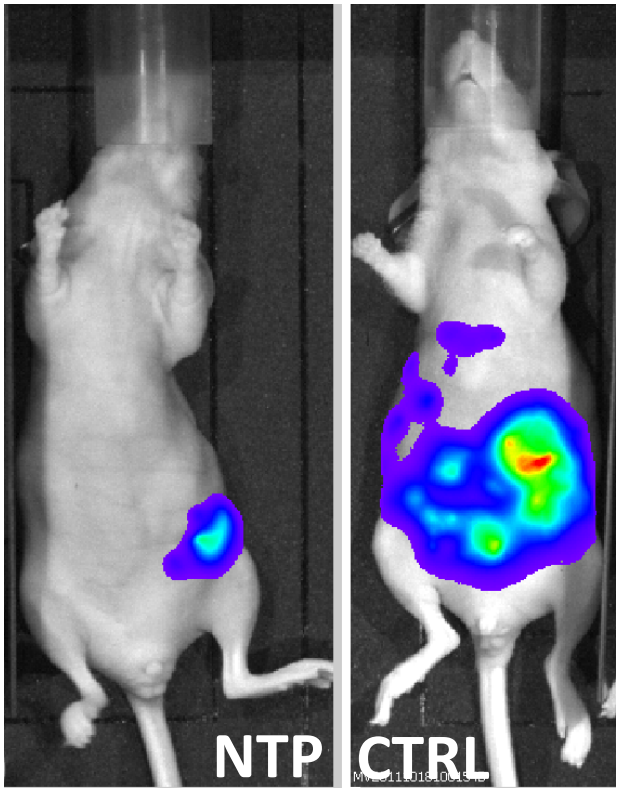
HCT 116 Colon

NTP
FE DBD treatment





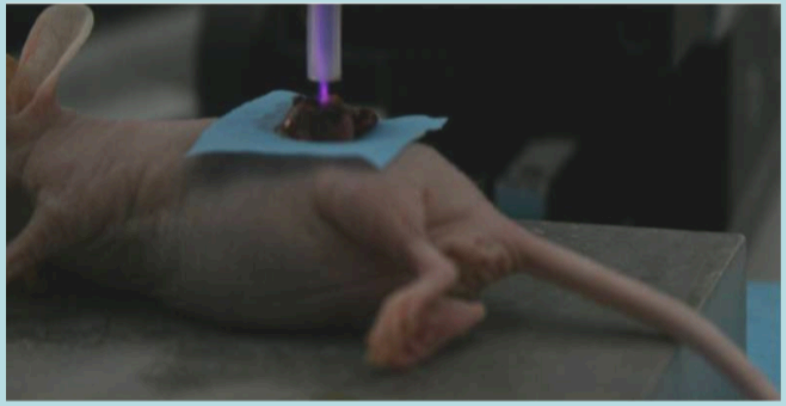
NTP
Plasma Gun treatment



→ anti-metastatic effect

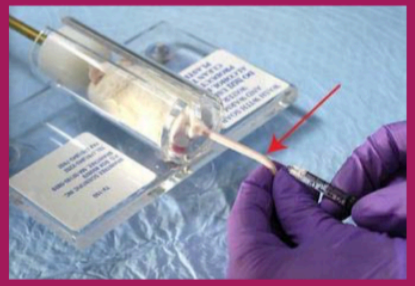
Antitumor action of Plasma Gun and Chemo on Pancreas

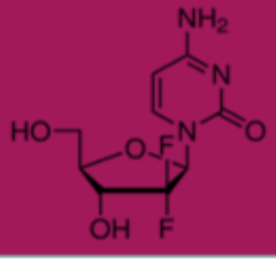
L. Brullé *et al* PLOS ONE, 7, DOI: 10.1371/journal .pone .0052653 (2012)



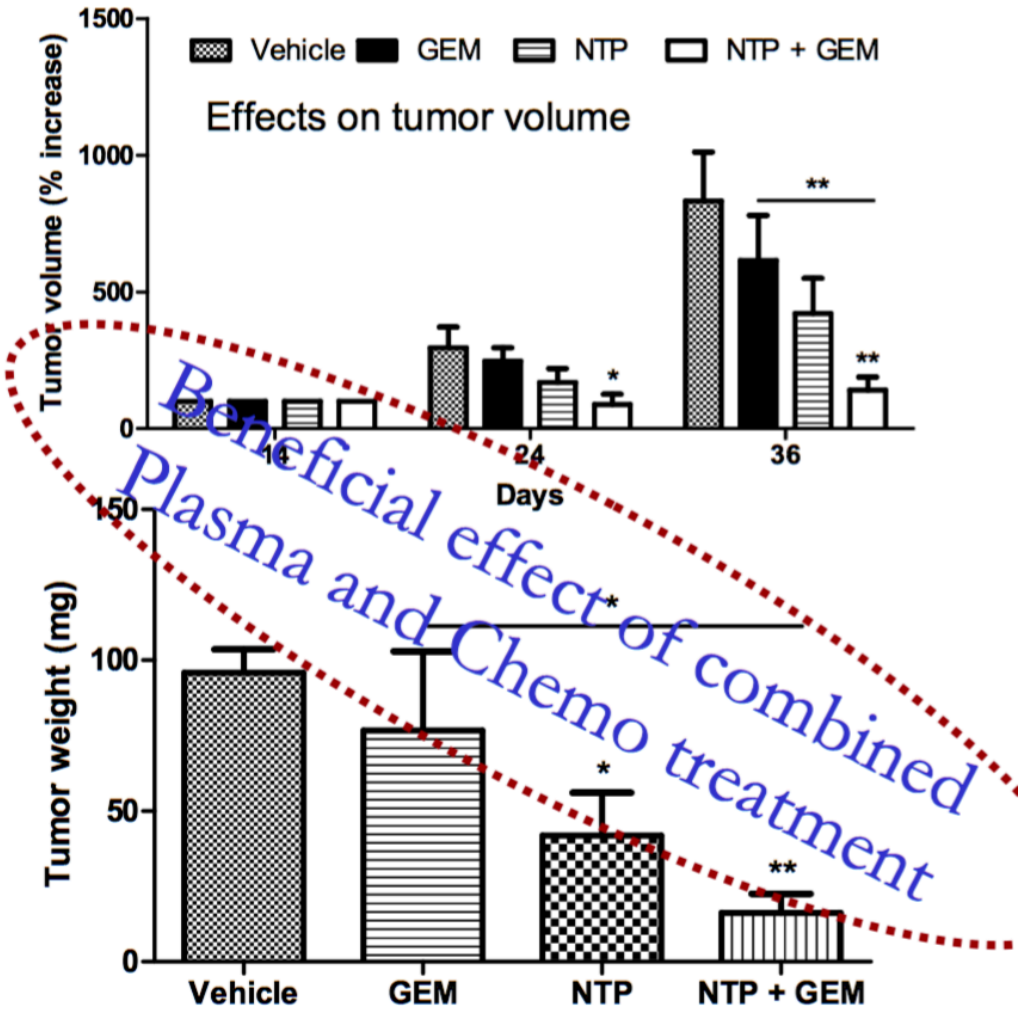
Plasma gun delivery on externalized pancreas
(10 mn, 2 kHz, 3 fractions)

Gemcitabine
200 mg/kg each 5 days





4 mouse groups:
Ctrl, Chemo, Plasma and (Chemo+Plasma)

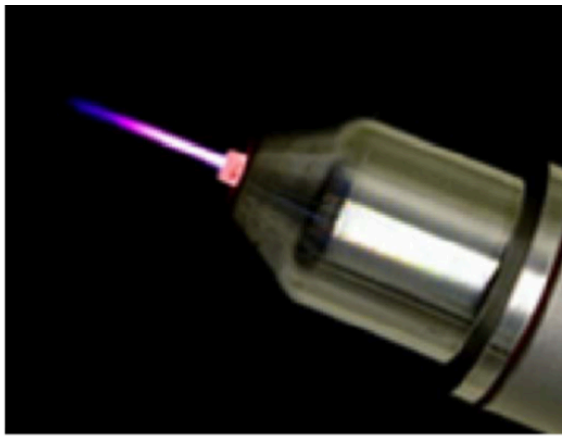


Effect on tumor weight the day of euthanasia (D36)

CASE AND CLINICAL STUDIES

Case study kINPen MED

Argon



MHz pulsed at 2.5 kHz

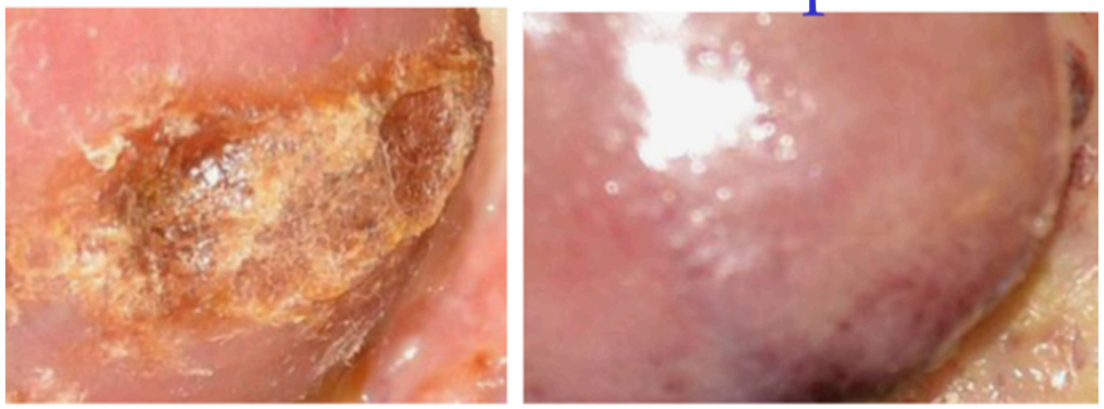


Fig. 3. (a) Infected cancer ulcer of the tongue in an area with pathohistologically confirmed cancer cells and (b)wound healing under CAP treatment.

Clinical Plasma Medicine
http://dx.doi.org/10.1016/j.cpme.2015.02.001

MECHANISMS

– RONS generally acknowledge to be important in plasma therapeutics

– E-fields and photons are important in some cases (e.g. gene transfection/transdermal delivery; photon-induced chemistry)

Existing therapies using RONS:

– antibiotics
– antifungals
– antiparasiticals
– cancer therapy ➡ wide recognition of positive role of RONS in cancer therapy
  - PDT ($O_2(a)$)
  - radiation
  - chemo

Plasma-generated RONS effects are confined to near-surface regions and are applied on timescales short compared to biological responses

BUT

Observed plasma therapeutic effects suggest longer time and length scales are involved in plasma therapeutics

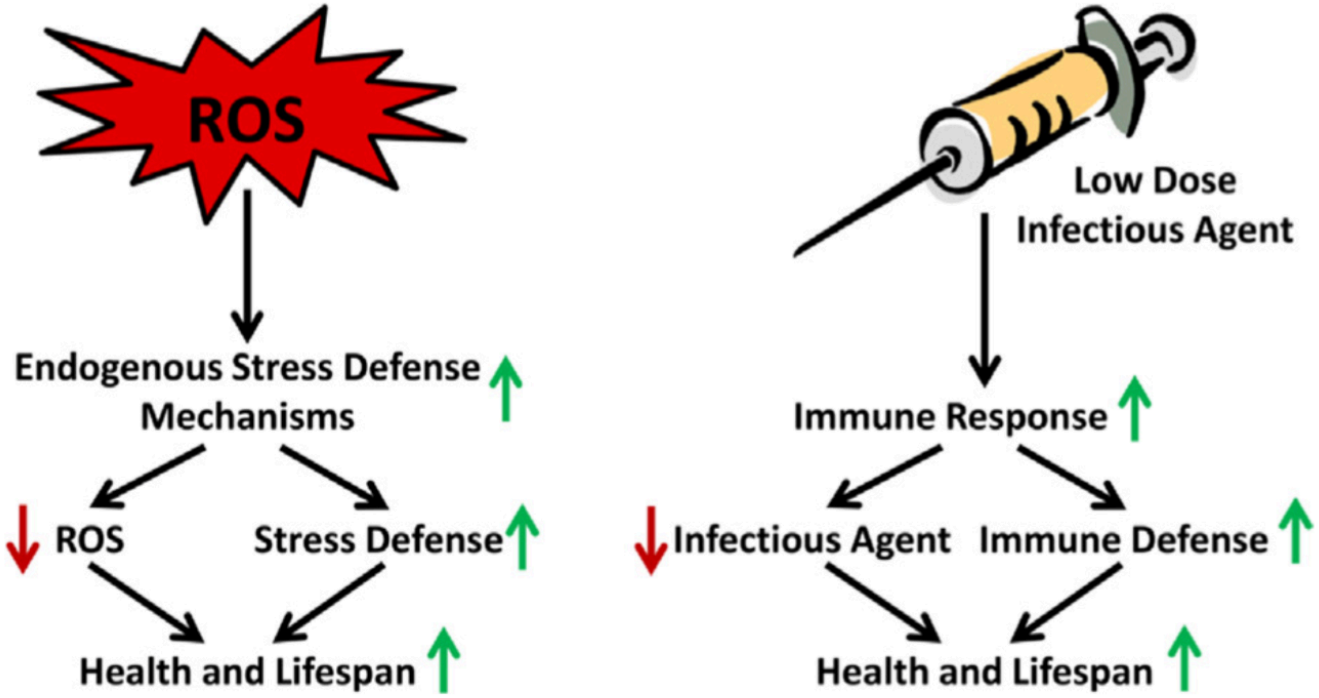
MECHANISMS

Hypothesis: plasma triggers a therapeutic response via RONS

1. Burst (10-100s) of RONS from plasma react with liquid and then layer of surface cells
2. Generation of longer-lived species: H_2O_2, oxidized/nitrated proteins, peptides, amino acids, lipids, etc
3. These species diffuse to and enter cells or act as ligands to membrane surface receptors
4. This initiates cell responses: DNA damage, cell cycle arrest, and other redox mediated stresses associated with mitochondria
5. Cells try to adpat, e.g. by generating anti-oxidant enzymes
6. Cells too weak or unable to adapt may die, strengthening the organism
7. Stressed cells will communicate to adjacent and distant cells, e.g. via release of cytokines
8. Immune system stimulations and/or blood flow or oxygenation may results
9. Net result is similar to what is intended by immune system response: trigger and activate tissue repair, protect against infections, destroy tumours

How increased oxidative stress promotes longevity and metabolic health: The concept of mitochondrial hormesis (mitohormesis)

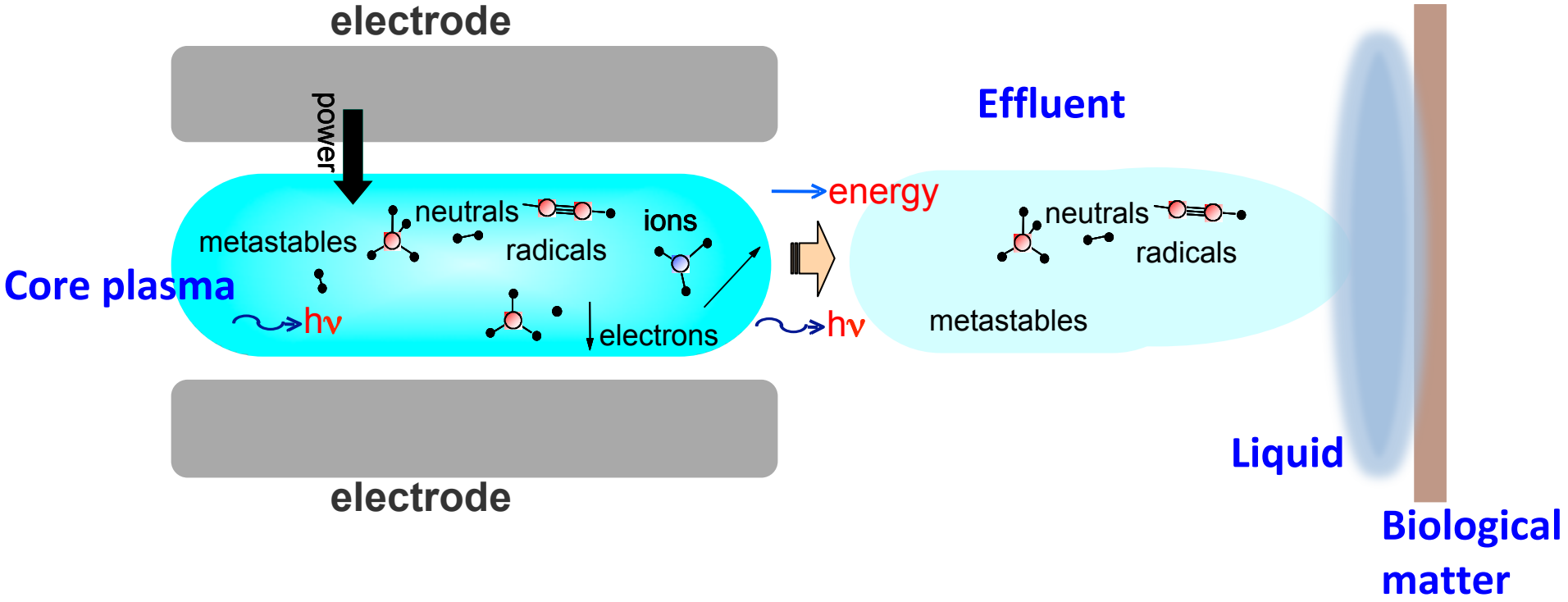
Michael Ristow [a,b,*], Kim Zarse [a]



ROS suggested to act like vaccines: organism adapts to stress and becomes stronger

Plasma-generated RONS both **simulate** and **stimulate** natural healing responses

Energy transport through multiple interfaces



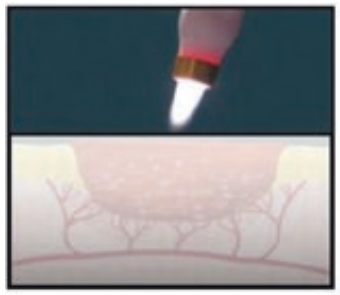
Core plasma power input ➔ active plasma chemistry
Core plasma & effluent interface ➔ steep gradients
Effluent region ➔ passive plasma chemistry
Effluent & liquid interface ➔ multi-phase interaction
Liquid solution ➔ liquid chemistry
Liquid & bio interface ➔ **bio-chemistry**

Challenges & Opportunities

- **Multiphase interfaces:**
  - Plasma – gas – liquid – surface (solid)
- **Multispecies:**
  - Electrons, pos. ions, neg. ions, neutrals, radicals, excited species, photons
- **Multiscale problem – time:**
  - Electron dynamics: ps – ns
  - Ion dynamics: 100 ns – μs
  - Plasma chemistry: 100 μs – ms
  - Surface chemistry: s – min
- **Multiscale problem – space:**
  - Surface structures: nm – μm
  - Charged particle gradients: μm – m
  - Neutral particle gradients: 10 μm – m

CONCLUSIONS

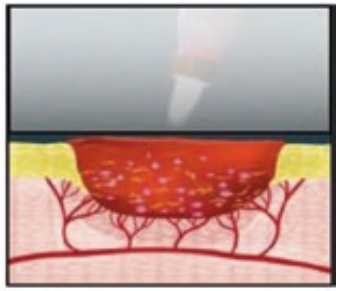
Plasma sources



- development
- adaptation
- diagnostics
- optimization, control, monitoring
- experimental applications

in vitro

Biological effects



- physiological liquids
- cells:
  - microorganims
  - mammalian cells
- cell and tissue cultures:
  - not contaminated/infected
  - contaminated/infected
- isolated tissues/organs
- organisms:
  - animal experiments
  - clinical tests/trials

in vivo

Therapeutic Applications

H.-R. Metelmann et al. (eds.), *Comprehensive Clinical Plasma Medicine*, Springer Nature 2018

– control of the reactive species delivery
– understanding of the process chain leading to the therapeutical effects
– optimisation of the applications (dose?)