Plasma Research on the ISS – Applications on Earth

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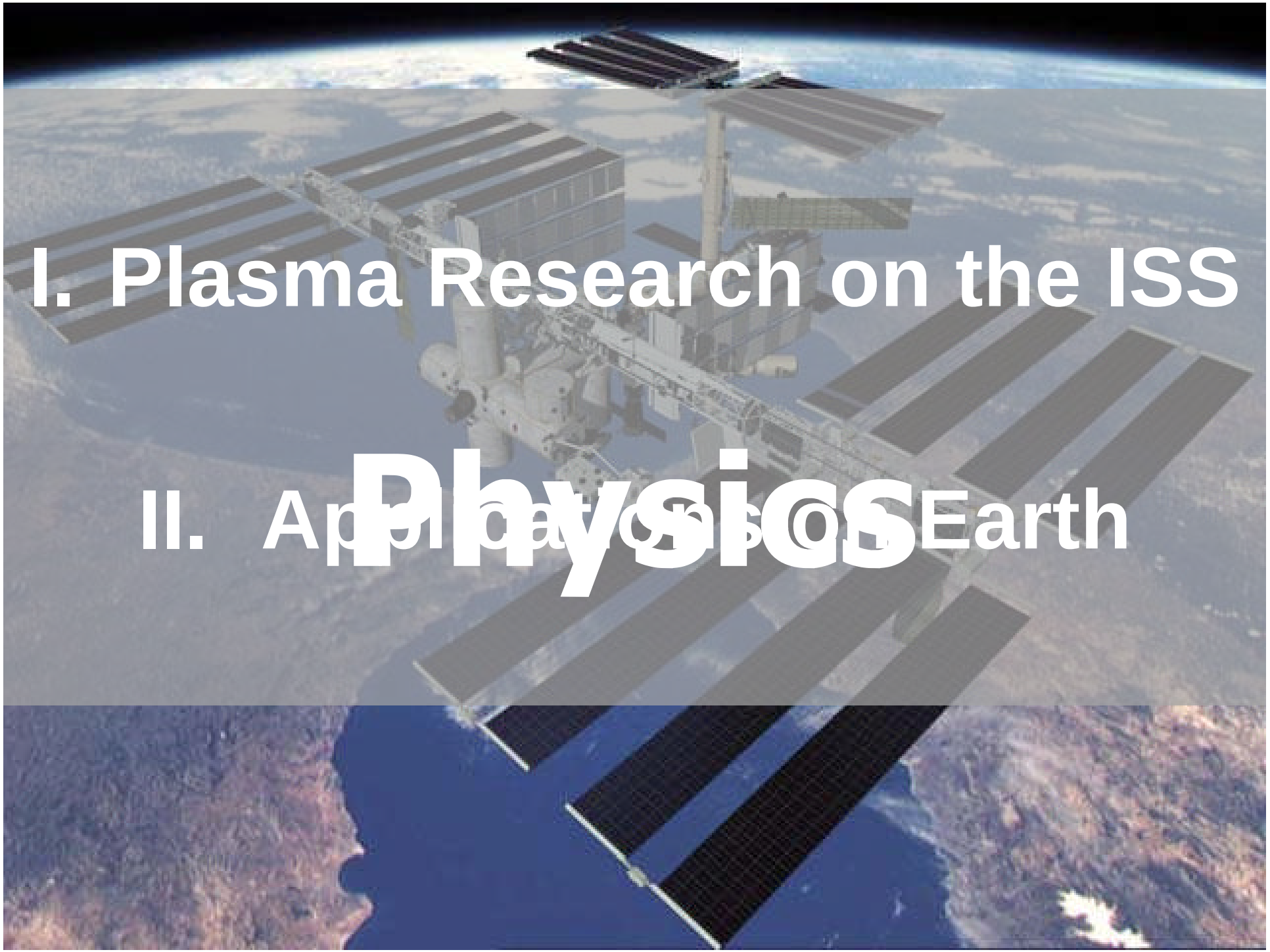
and the PK-3 Plus Team

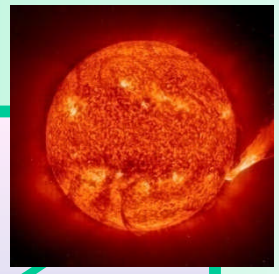
and the Plasma Medicine Network

Max-Planck Institut für extraterrestrische Physik


I. Plasma Research on the ISS
II. Applications to Earth
Physics

Plasmas – an extreme state of matter

What is Plasma?



plasma

100.000°

10.000°

1.000°

100°

10°

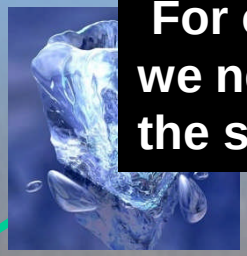
0°

Temperature

atomic

molecular

liquid



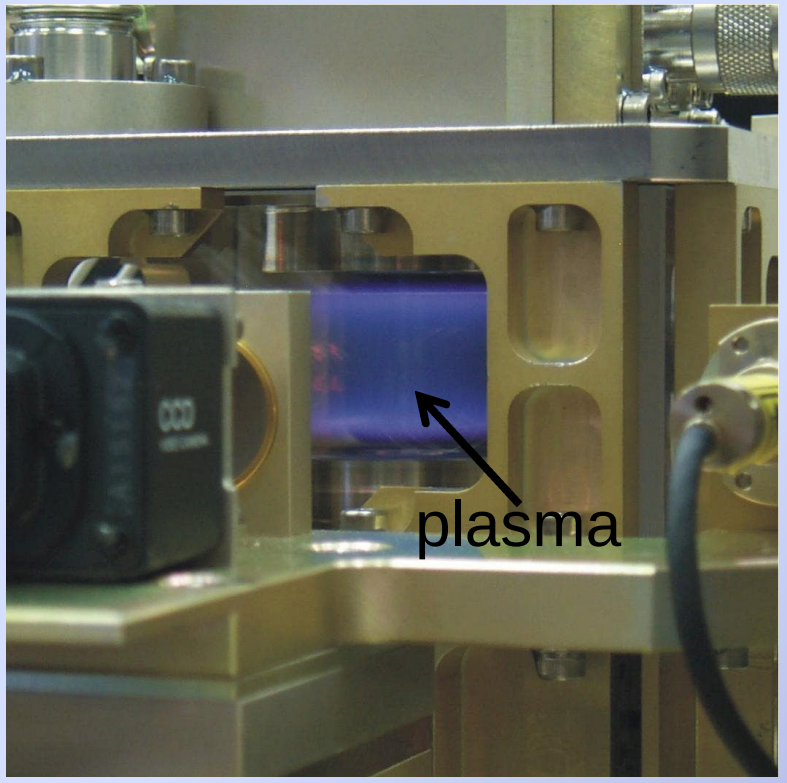
solid

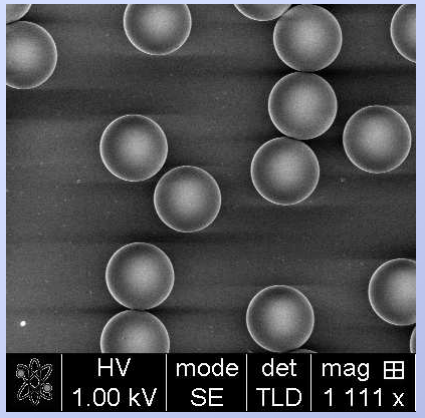
For our space experiments we need a „Cold Plasma“ in the strong coupling regime

State of matter

Strongly coupled cold plasma?

Cold low pressure plasma + Microparticles (dust)





Polymer (MF) microspheres:

- **diameter: $d \approx 9$ µm***
- **charge: $Q \approx -10^4\ e$**
- **spacing: $a \approx 0.6$ mm**

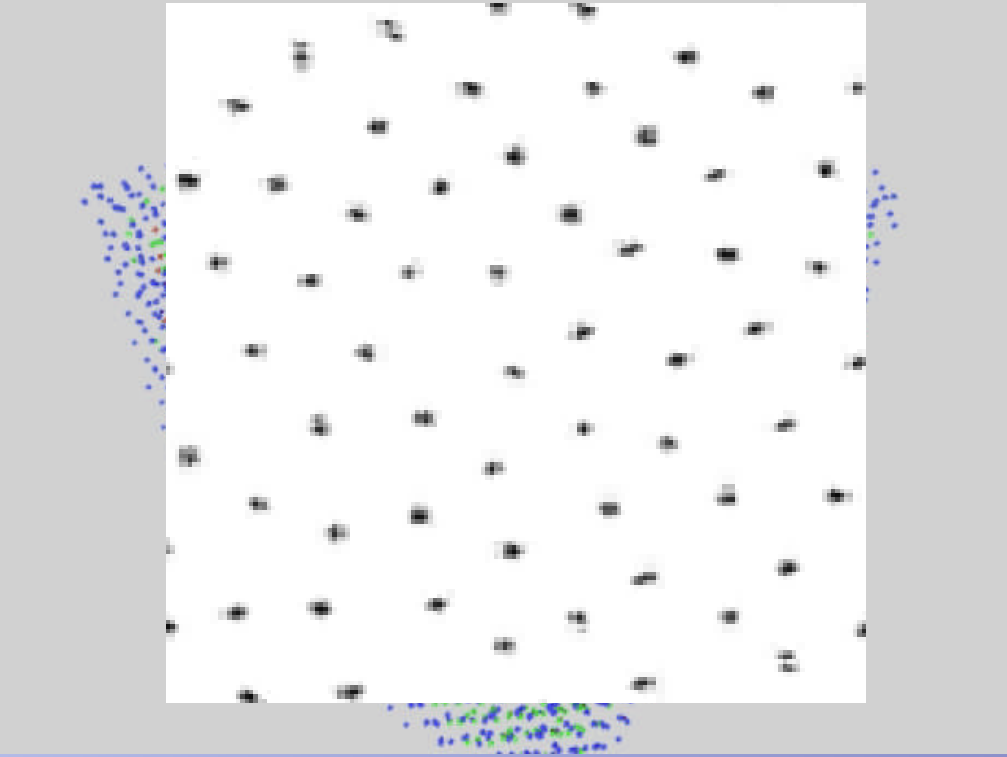
***µm=1/1000 mm**

→ Complex or Dusty Plasma

Complex Plasma - New Physics

Complex plasmas provide a new experimental approach for fundamental studies of strong coupling phenomena – "fully resolved dynamics at the individual particle level".

- Particles individually visible
- Atomistic dynamics virtually undamped
- Systems up to 10^9 particles
- Model system for liquids
- Model system for crystals
- Binary mixtures



(dynamics of microparticles in a monolayer exp.)

(local structure: ● fcc ● hcp ● liquid)

PK-3 Plus on the ISS

- complex plasma research under microgravity conditions
- finishing after 7 years and 21 missions with more than 70 individual experimental runs
- PK-3 Plus opened up a new future of interdisciplinary research

→ complex plasma as a state of soft matter

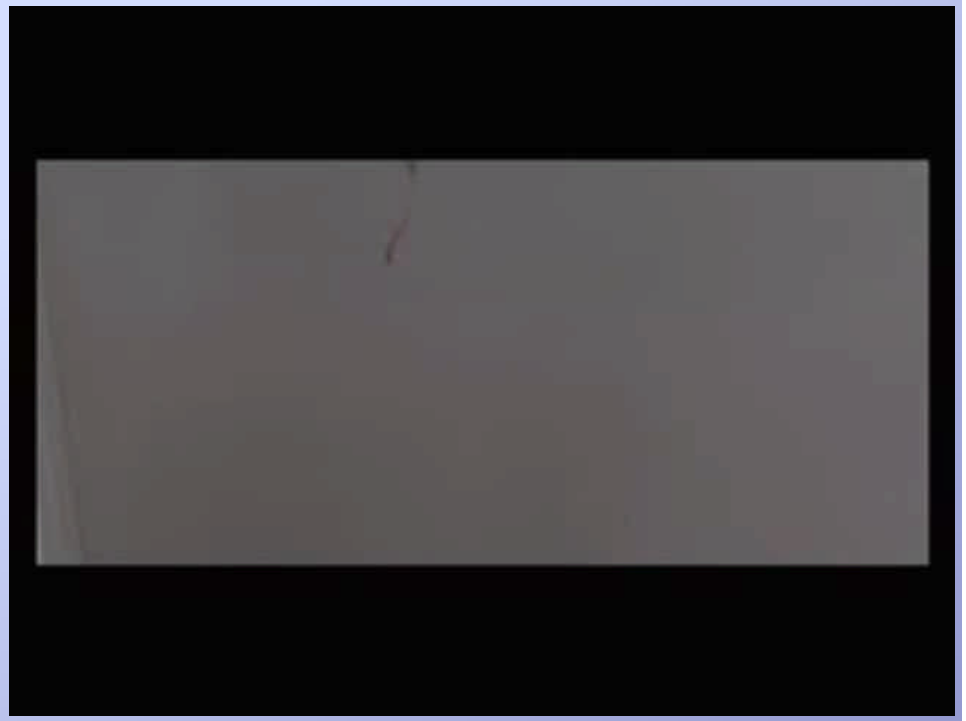
→ example: demixing of binary fluids

Acknowledgements: Thanks to DLR/BMWi, MPG and our Russian partners, to Kayser-Threde, the science team, the cosmonauts, etc.

What is fluid demixing?

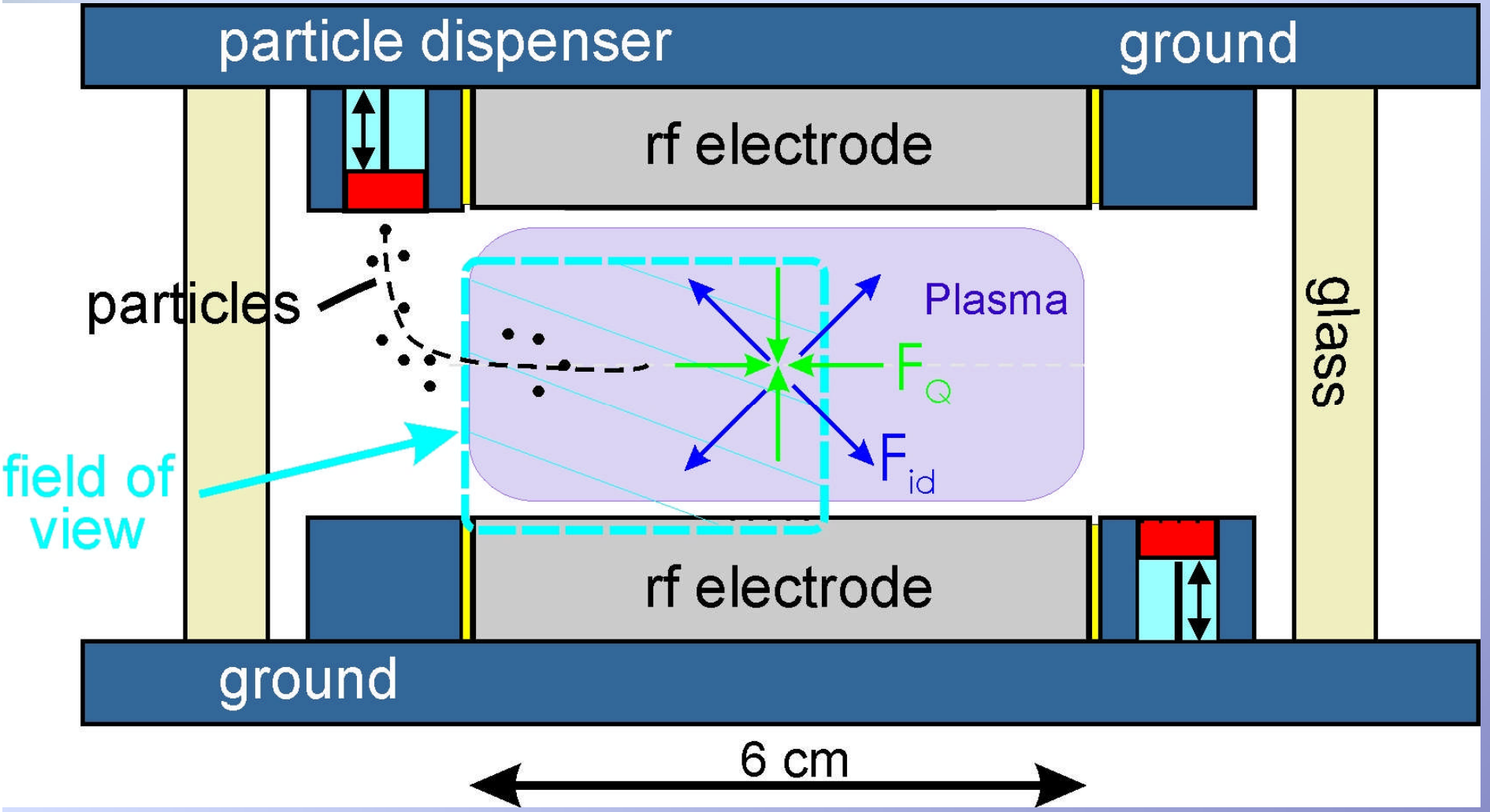
Water and oil

Water and ink

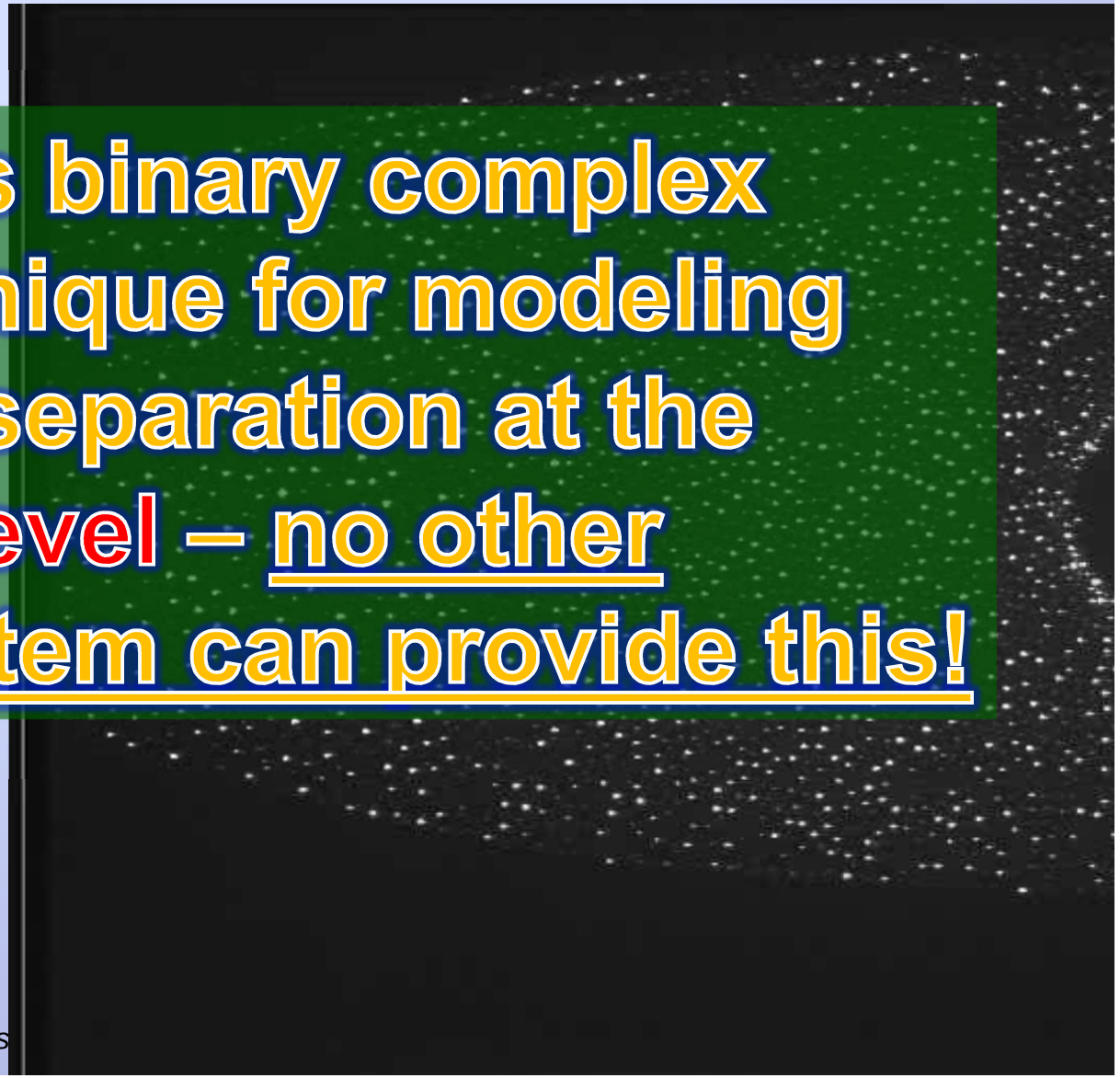


We need a natural model system to study demixing at the level of individual molecules!

Microgravity experiments on ISS



Formation of a droplet



3.4 μm particles in
a cloud of 9.2 and 6,8 μm
particles (ratio 0.
mm).

This makes binary complex plasmas unique for modeling the phase separation at the atomistic level – no other known system can provide this!

µg-research in complex plasmas

PK-3 Plus

PK-4

PKE-Nefedov

PK-2

PK-1

TEXUS

PlasmaLab

Discovery
Plasma Crystal

1994 1996 1998 2000 2010 2012

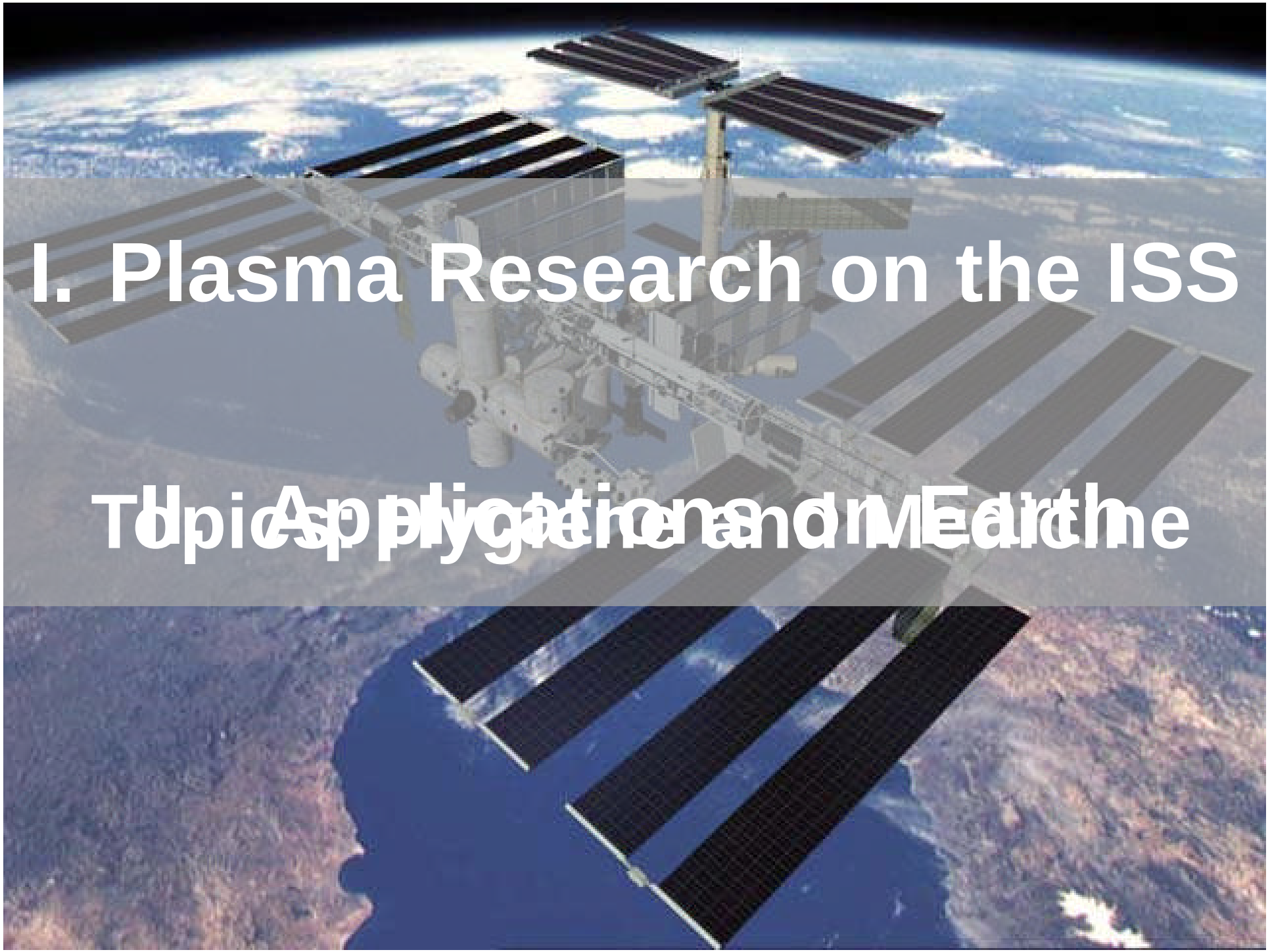
at the forefront of technology for the ISS enables …

TEXUS

PK-3 Plus

PK-1 & PK-2

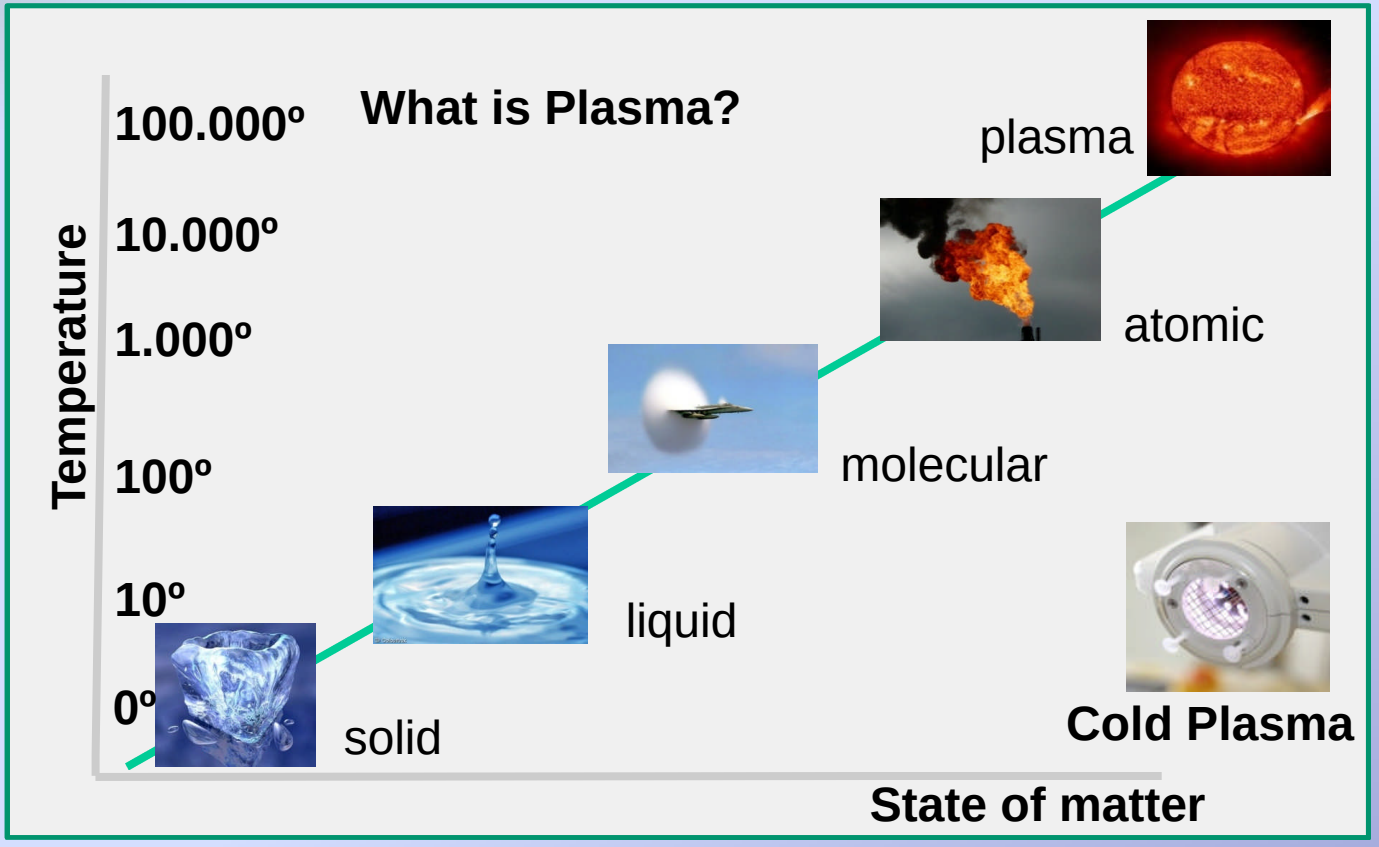
PKE-Nefedov



I. Plasma Research on the ISS

Topic: Application on Earth

Cold Atmospheric Plasmas
Technology from Space - for a safer world



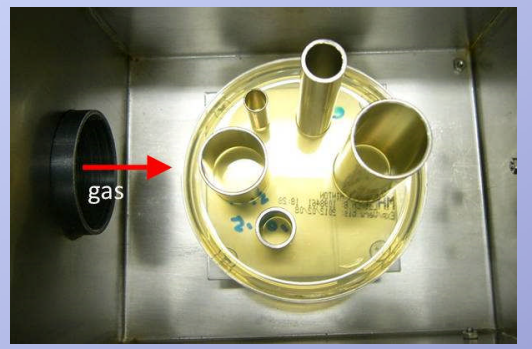
"Cold Plasma" is a partly ionised gas (or air).

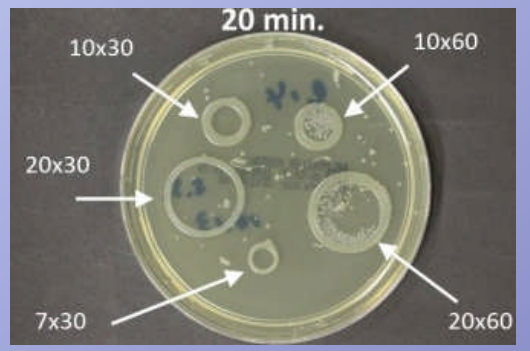
Cold Plasma contains neutral gas, charged particles, excited atoms and molecules and reactive species.

It is produced at room temperature and atmospheric pressure.

Why Cold Atmospheric Plasma?

- CAP can be applied to all temperature-sensitive surfaces including skin and mucosa.
- CAP (as a gas) is a new medium with quick access even to complicated surface structures.
- CAP chemistry can be designed for different therapeutic applications.
- CAP effectively and quickly inactivates bacteria, fungi, viruses and spores.

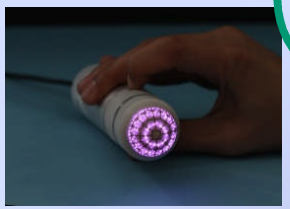




Cold Atmospheric Plasma Devices








In our group a range of different technologies for the production of CAP were developed.

1. Microwave Argon plasma device – MicroPlaSter *
2. Surface Micro Discharge (SMD) (can also be powered by rechargeable batteries) **
3. Venturi devices (to operate under high pressure and air flow)***
4. Piezo powered devices****

* Shimizu et al. Plasma Process. Polym. 2008, Patent MI-No. 3515
** Morfill et al. NJP 2009, Patent Application MI-No. 4063
*** Shimizu et al. in preparation, Patent Aplication MI-No. 3721
**** Patent Application MI-No. 4301

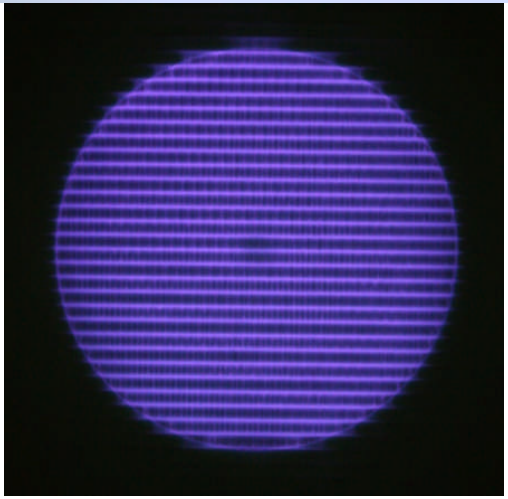
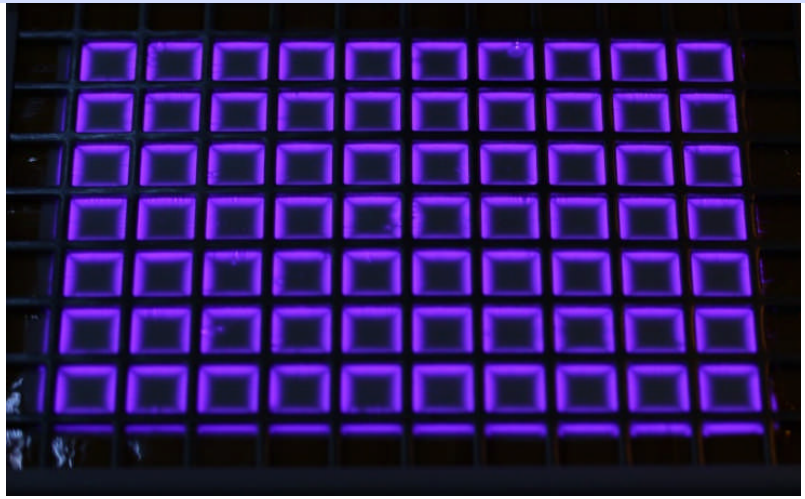
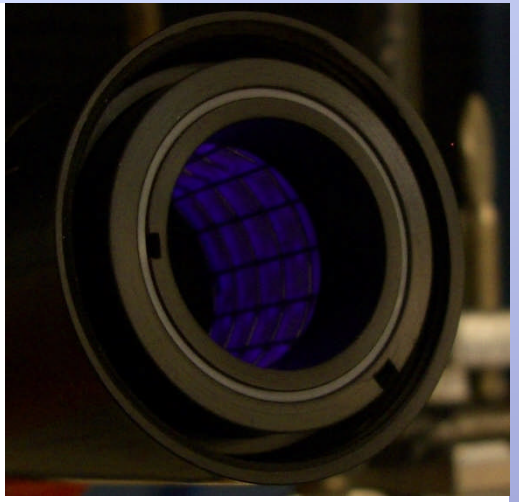
Plasma treatment of chronic wounds – clinical studies

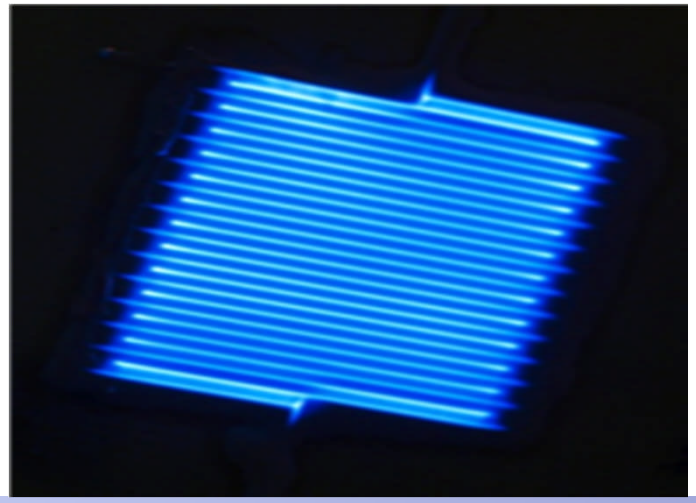
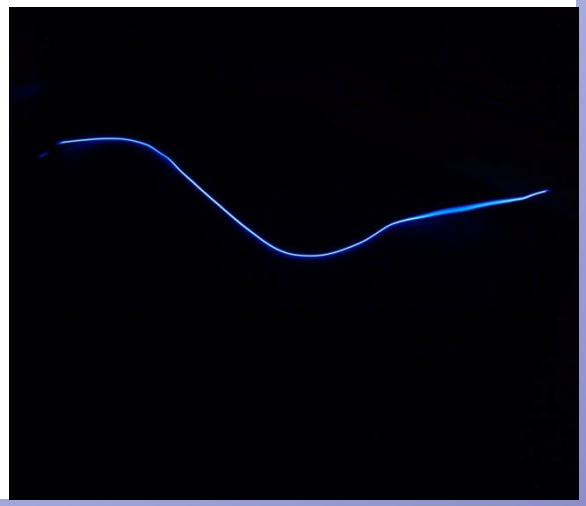
Microwave driven cold atmospheric argon plasma device used for the **clinical phase II studies** on patients.

Technical details:
- used gas: Argon 2-4 l/min
- frequency = 2.45 GHz
- power = ca. 100 W

Developed in cooperation with Adtec Ltd. (Japan),
Shimizu et al. Plasma Processes and Polymers (2008)

Surface Micro Discharge (SMD) Technology

Surface Micro Discharge (SMD) Technology

Cold Air Plasma Properties

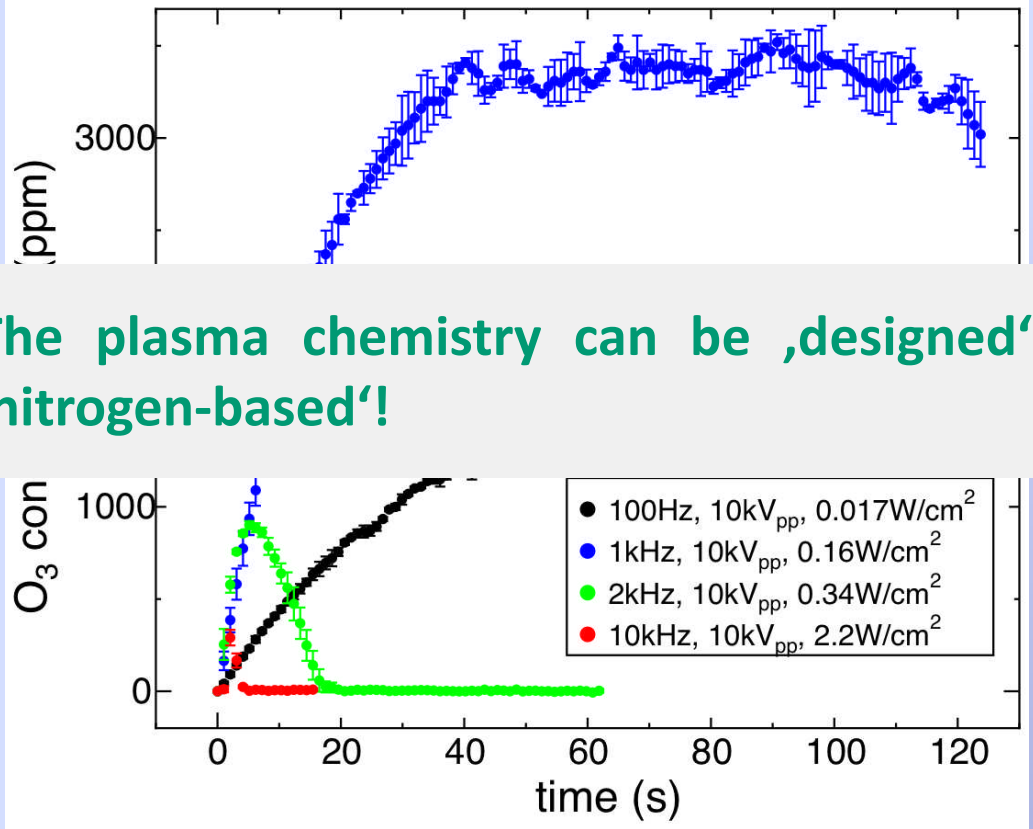
- After plasma ignition, over 600 chemical reactions take place in air – producing a reactive **plasma cocktail** composed of electrons, ions, neutrals, reactive species (mainly reactive oxygen species (ROS) and reactive nitrogen species (RNS)) and UV light.

- **Plasma cocktail:**
  - Positively charged species (N^+, N_2^+, N_3^+, N_4^+, O^+, O_2^+, NO^+, NO_2^+, H^+, H_2^+, H_3^+, OH^+, H_2O^+, H_3O^+)
  - Negatively charged species (e^-, O^-, O_2^-, O_3^-, O_4^-, NO^-, N_2O^-, NO_2^-, NO_3^-, H^-, OH^-)
  - Neutral species (excited N_2, excited O, H, N, O, excited O_2, O_3, NO, N_2O, NO_2, N_2O_3, N_2O_4, N_2O_5, H_2, OH, HO_2, H_2O_2, HNO, HNO_2, HNO_3)

- The air plasma and its chemical products revert back to the original state (air) after a short time period. There are no residues, no waste disposal – cold plasma is 100% environmentally friendly.

Plasma Design –
Air Chemistry of SMD Plasmas

Ozone concentration as a function of time



→ **The plasma chemistry can be ‚designed' to be either ‚oxygen-' or ‚nitrogen-based'!**

Quenching by nitric oxides:

$O_3 + NO \rightarrow O_2 + NO_2$

$O_3 + NO_2 \rightarrow O_2 + NO_3$

Plasma Design –
Air Chemistry of SMD Plasmas

Antimicrobial species generated from oxygen and nitrogen

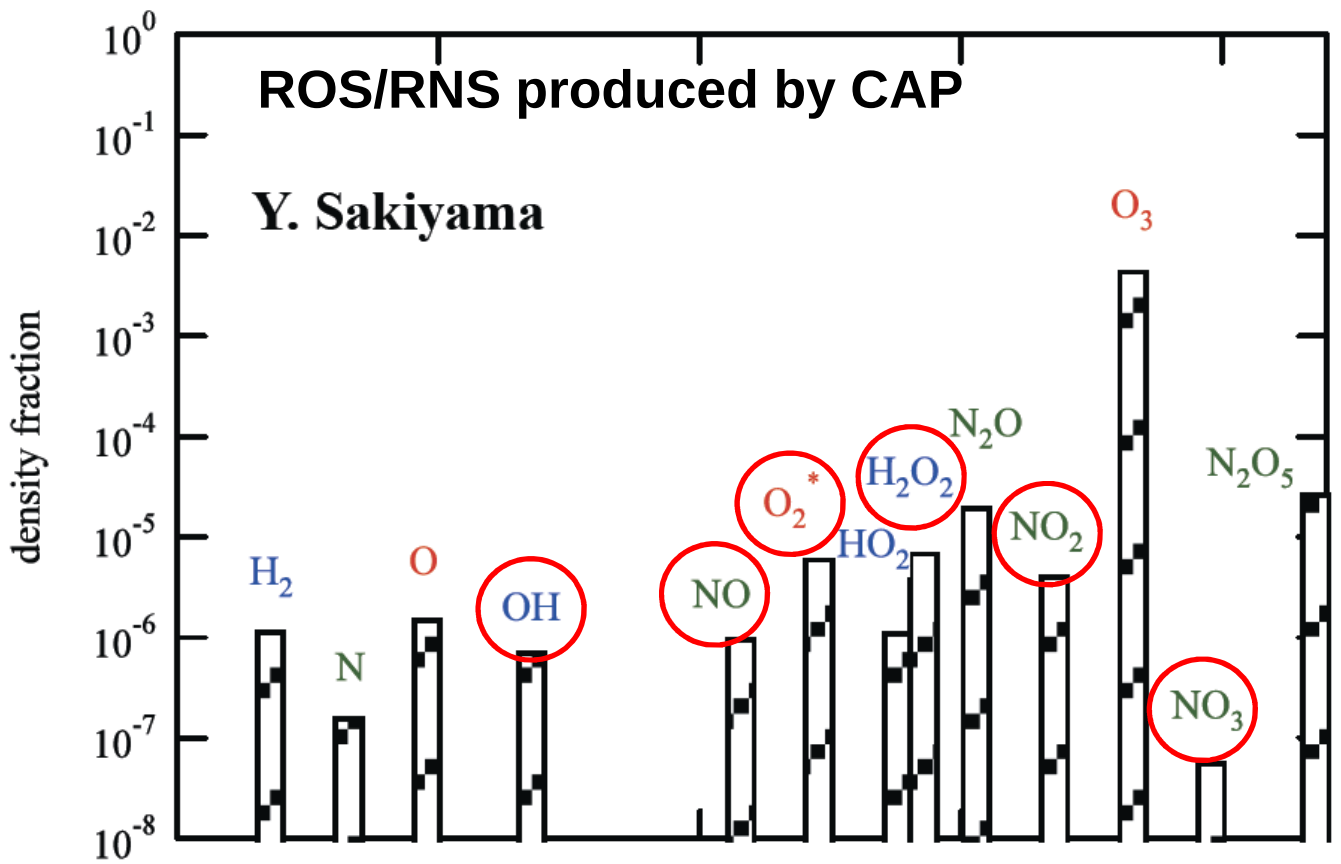
Reactive oxygen species

- $\cdot O_2^-$ (superoxide anion)
- OH· (hydroxyl radical)
- H_2O_2 (hydrogen peroxide)
- ClO^- (hypochlorite anion)

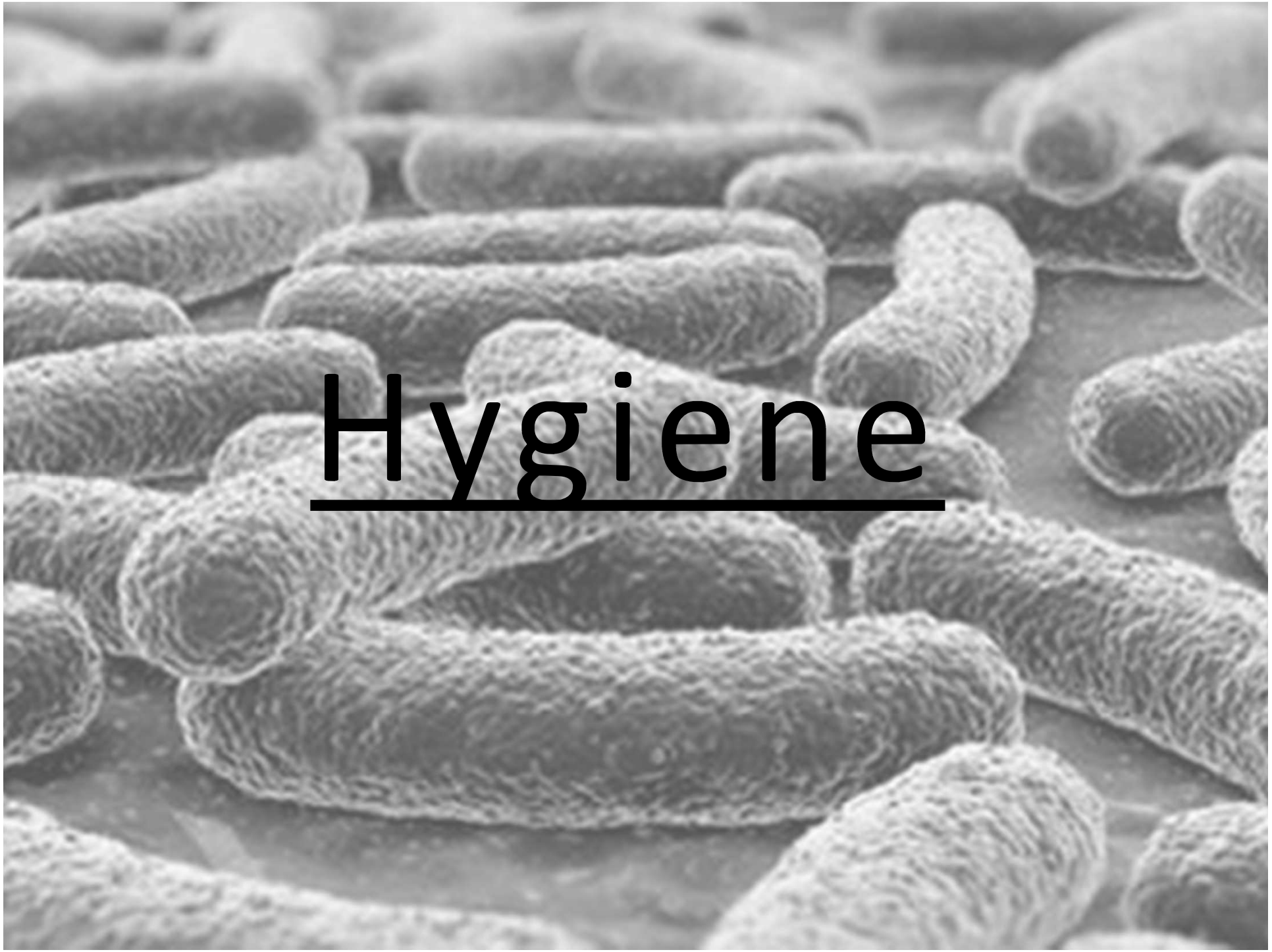
Reactive nitrogen species

- NO (nitric oxide)
- NO_2 (nitrogen dioxide)
- $ONOO^-$ (peroxynitrite)

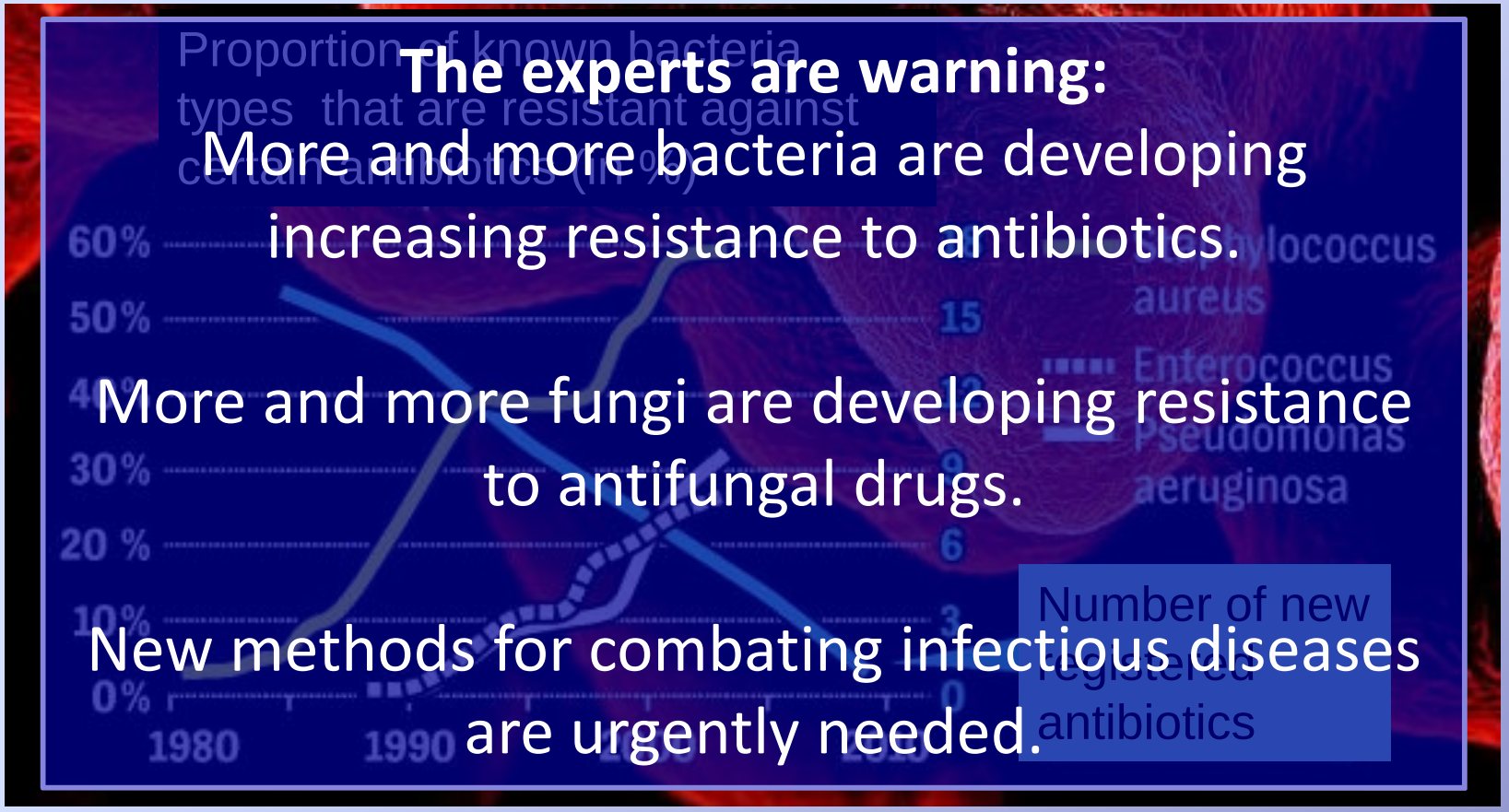
Figure 3-13
Kuby IMMUNOLOGY, Sixth Edition



Provided by Prof. David Graves


Hygiene

Infection Control – The Issues



The experts are warning:

More and more bacteria are developing increasing resistance to antibiotics.

More and more fungi are developing resistance to antifungal drugs.

New methods for combating infectious diseases are urgently needed.

Der Spiegel, 2011 - Source: CDC/USA

The Facts – Resistance/Multiresistance

Worldwide prevalence of MRSA displayed by country (The Lancet 2006)

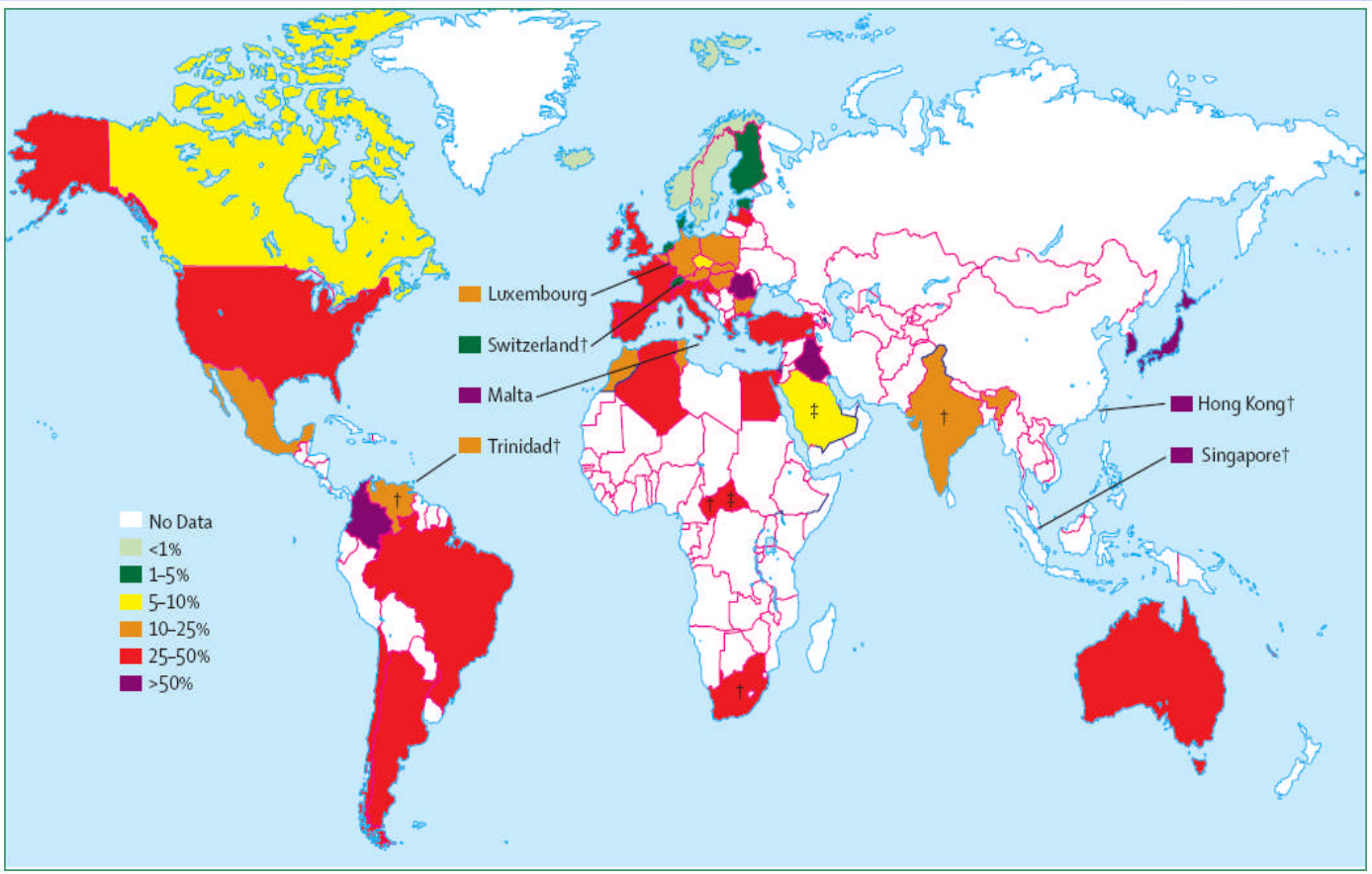
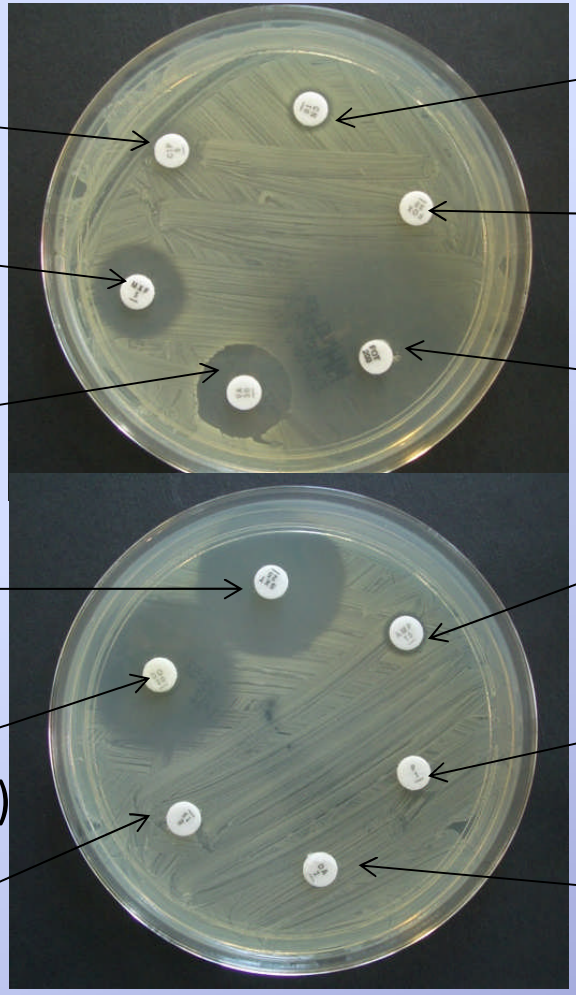


Figure 1: Worldwide prevalence of MRSA displayed by country*

Plasma Inactivation of Different Bacteria

Drug-Resistance of the MRSA strain used

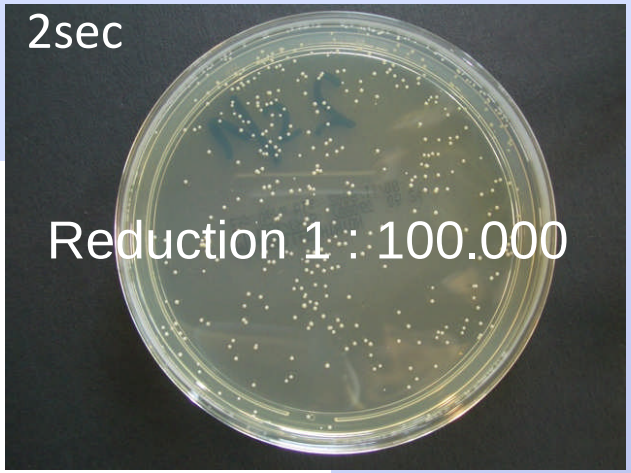


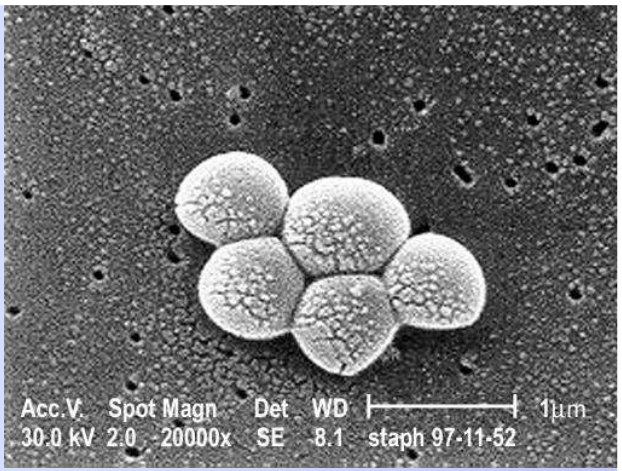
First line drugs
bold letters

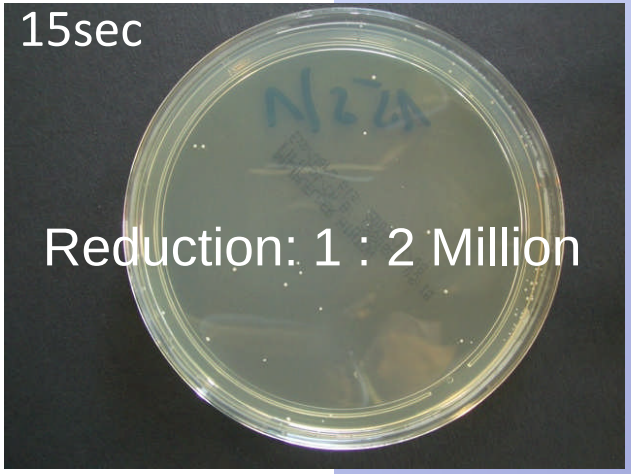
Zimmermann et al. NJP 2012

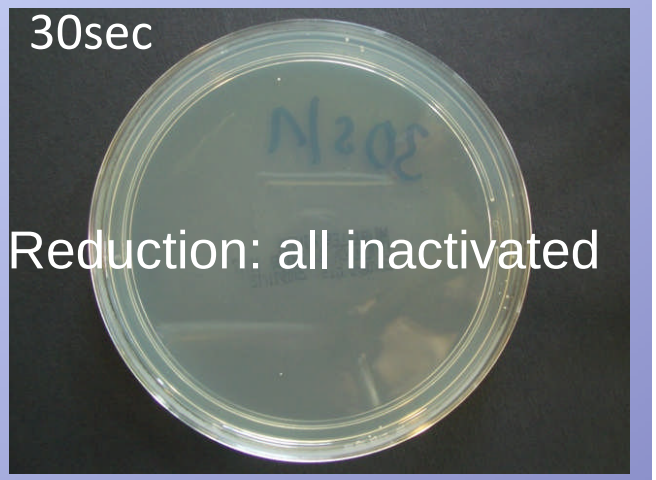
Plasma Inactivation of Different Bacteria

Drug-Resistance of the MRSA strain used









Zimmermann et al. NJP 2012

Plasma Inactivation of Different Bacteria

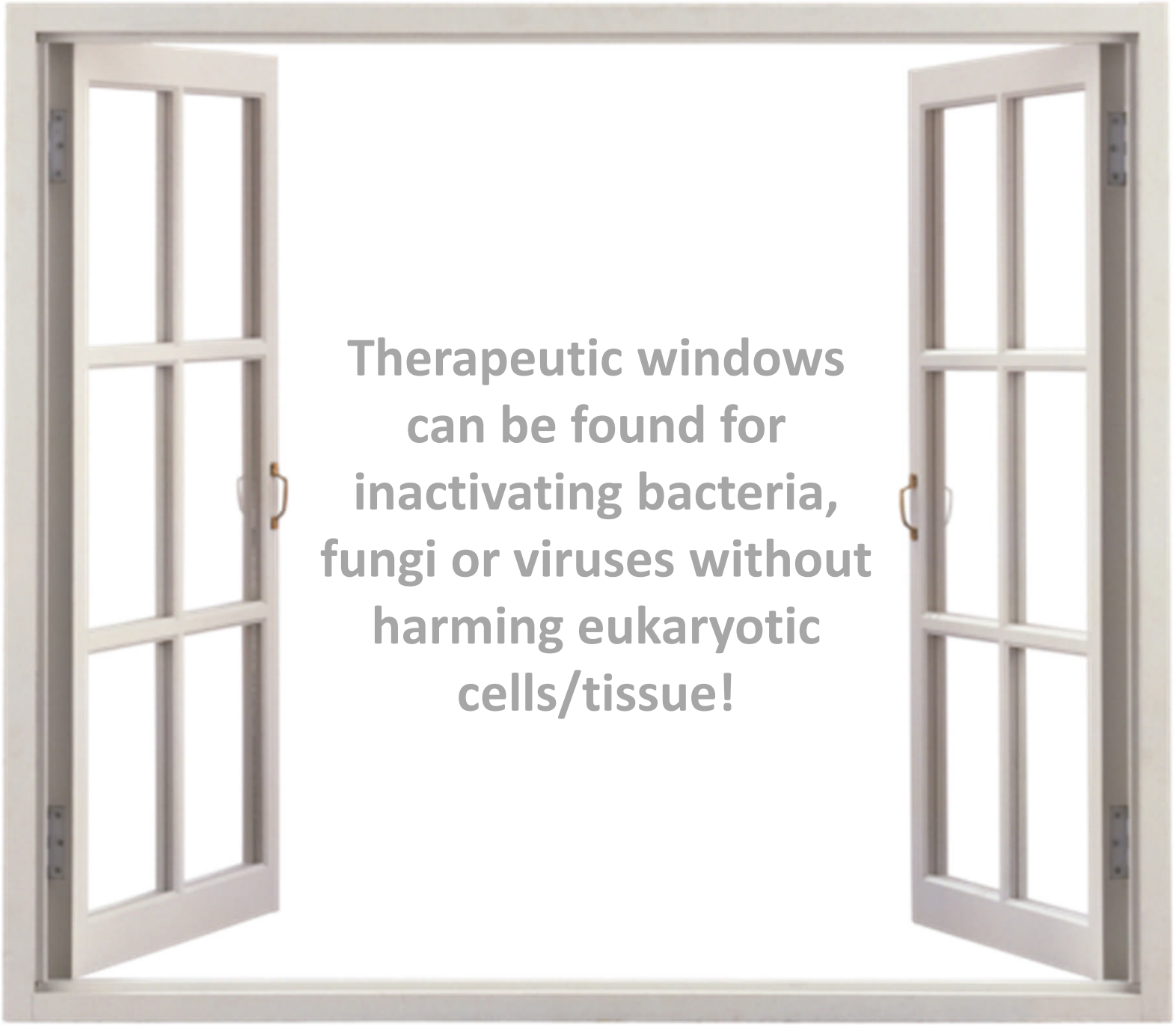
Gram-positive bacteria:

- *Staphylococcus aureus*
- *Methicillin-resistant Staphylococcus aureus*
- *Deinococcus radiodurans*
- *Staphylococcus epidermidis*
- *Enterococcus faecalis*
- *Vancomycin-resistant Enterococcus faecium*
- *Enterococcus mundtii*
- *Bacillus cereus*
- *Bacillus pumilus*
- *Clostridium difficile*
- *Group A Streptococcus pyogenes*
- *Corynebacterium jeikeium*
- *Pseudomonas aeruginosa*
- *Lactobacillus sakei*

Gram-negative bacteria:

- *Escherichia coli K12*
- *Escherichia coli*
- *Enterohaemorrhagic Escherichia coli (EHEC)*
- *Burkholderia cepacia*
- *Pseudomonas aeruginosa*

Zimmermann et al. NJP 2012
Zimmermann et al. PPP 2012
Shimizu et al. NP 2011
Klaempfl et al. AEM 2012
Morfill et al. NJP 2009
Li et al. PPP 2011
Maisch et al. PloS One 2012
Maisch et al. JIMB 2012

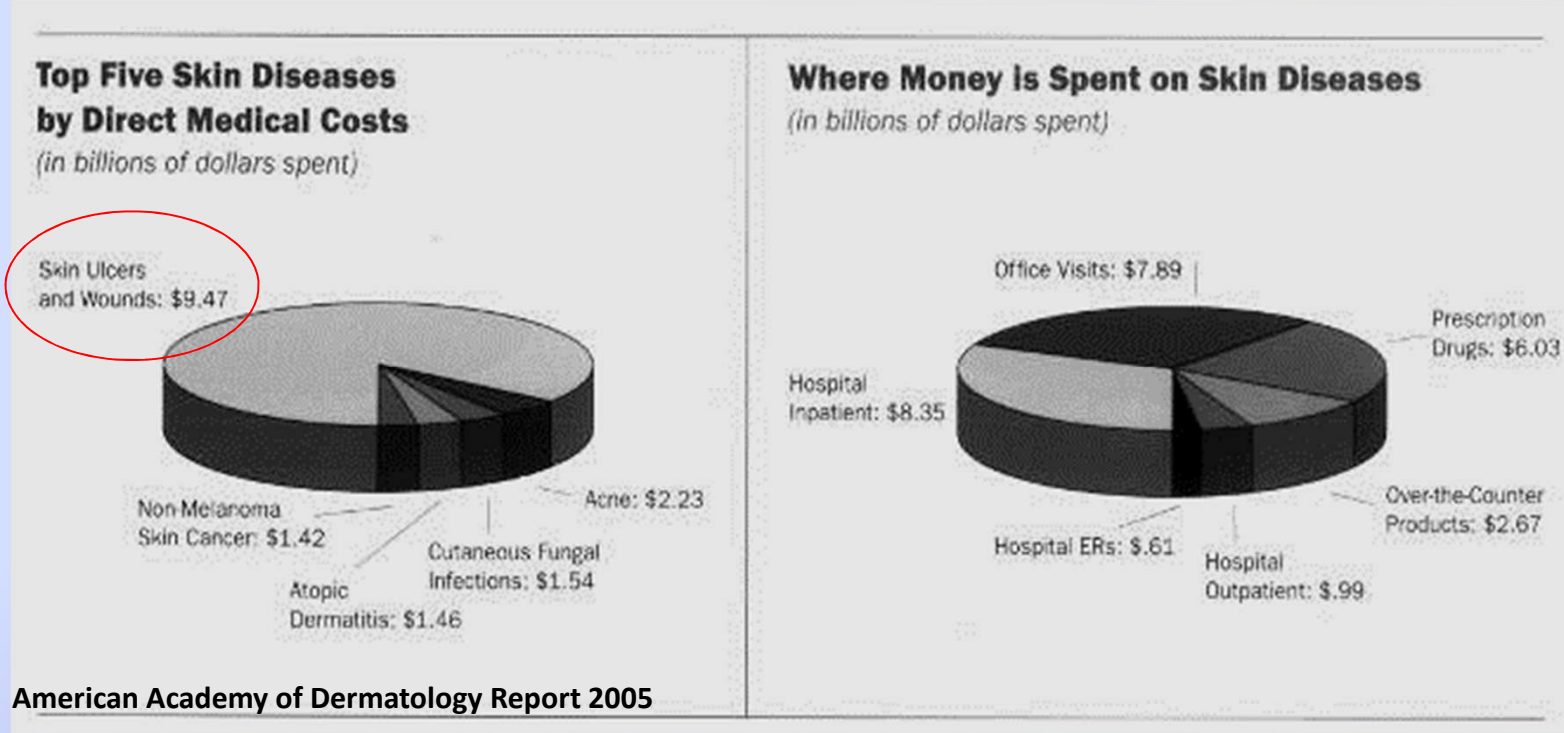

Therapeutic windows
can be found for
inactivating bacteria,
fungi or viruses without
harming eukaryotic
cells/tissue!

Medicine

Wound Disinfection
Wound Healing
Treatment of Skin Diseases

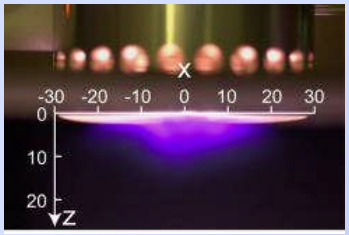
Chronic Wounds – The Issues

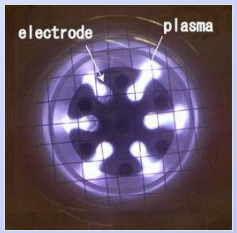
- Prevalence ~ 1-2 % in German Population (> 800.000 patients)
- Venous ulcers require an average of 24 weeks to heal, 15% never heal, recurrence is found once or multiple times in 15-71% of cases
- Patients are prone to secondary infections – better infection control is needed.



American Academy of Dermatology Report 2005

Plasma Device - MicroPlaSter ß





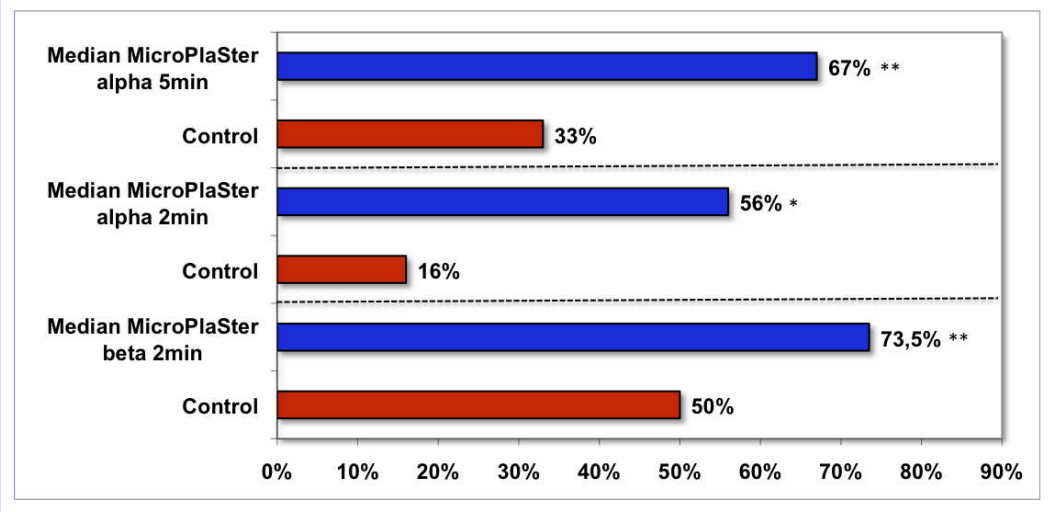
Microwave driven cold atmospheric argon plasma device (MicroPlaSter ß) (developed in cooperation with Adtec Ltd.) used for the **clinical studies** on patients.

<u>Technical details:</u>

- used gas:
  Argon 2-4 l/min
- frequency: 2.45 GHz
- power: ~100 W

Shimizu et al. Plasma Process. Polym. 2008

Clinical Study on Chronic Wounds

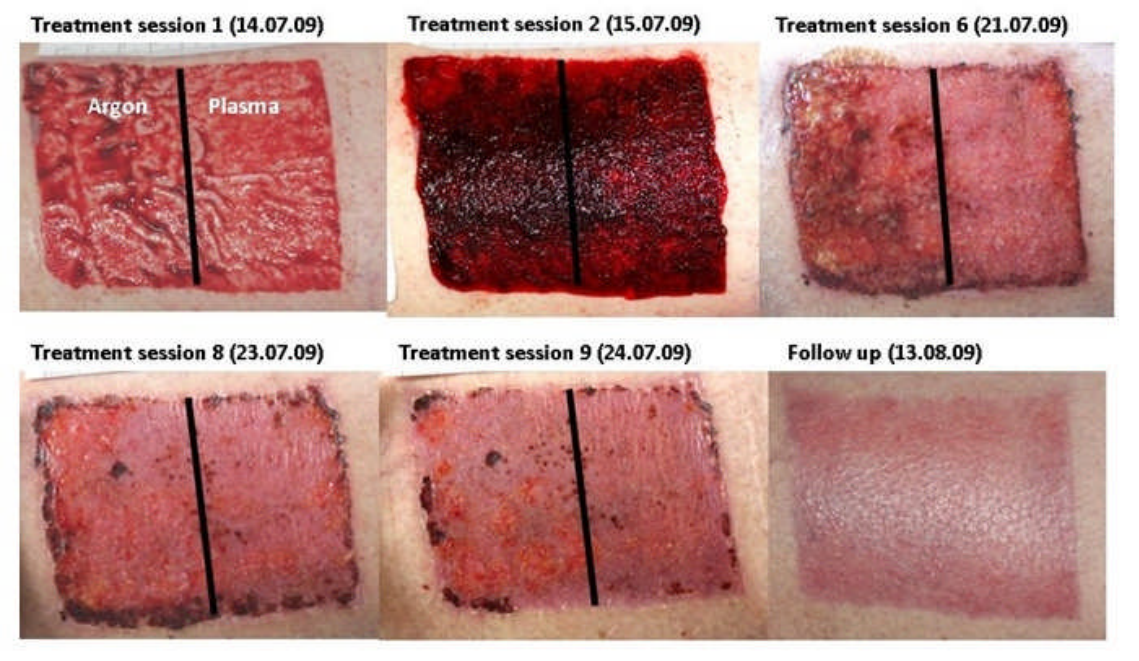


Isbary et al. BJD 2010, Isbary et al. BJD 2012

In an add-on therapy more than 3000 plasma treatments (of 2-5 min) so far showed a highly significant higher germ reduction (independent of the bacterial species and resistance level) in the plasma treated chronic wounds compared with the control wounds.

No negative side effects or allergic reactions were observed and the painless treatment was well tolerated by the patients.

Clinical Study on Skin Graft Wounds



left side: treated with argon
right side: treated with plasma

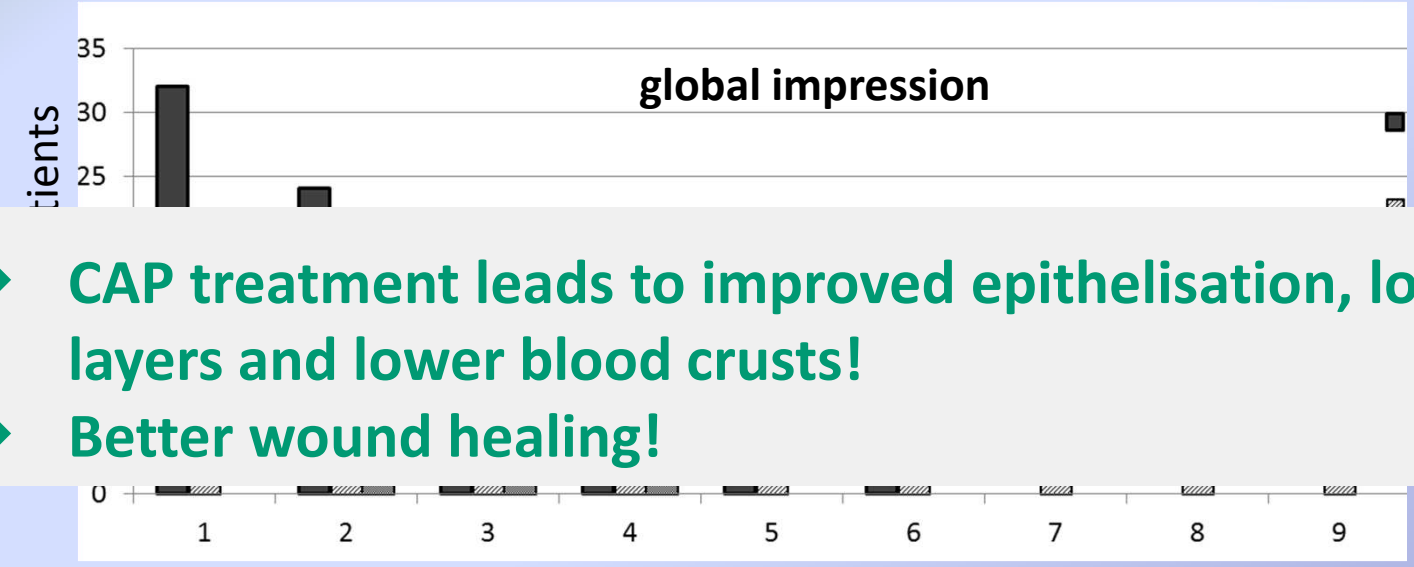
Heinlin et al. submitted to Wound Rep. Reg 2013

Plasma treatment of acute wounds due to mesh grafts:

- One half of the wound was plasma treated in addition to the topical treatment.

- Assessment of the wound development was carried out by different medical experts based on different criteria (fibrin layers, re-epithelialisation, blood crust, wound surroundings)

Clinical Study on Skin Graft Wounds



→ **CAP treatment leads to improved epithelisation, lower fibrin layers and lower blood crusts!**

→ **Better wound healing!**

Treatment session	1	2	3	4	5	6	7	8	9
advantage for plasma	2	9	17	16	8	7	5	2	2
no difference	32	24	15	13	5	4	0	0	0
advantage for argon	0	1	2	1	0	0	0	0	0
p-value	0.25	**0.011**	**<0.001**	**<0.001**	**0.004**	**0.008**	**0.031**	0.25	0.25

Heinlin et al. Wound Rep. Reg. 2013

Next Generation CAP Device

Surface Micro Discharge Technology

Device details:

- handheld and battery-operated plasma device
- diameter of the electrode: 2.8 cm
- different nozzles with different opening radius

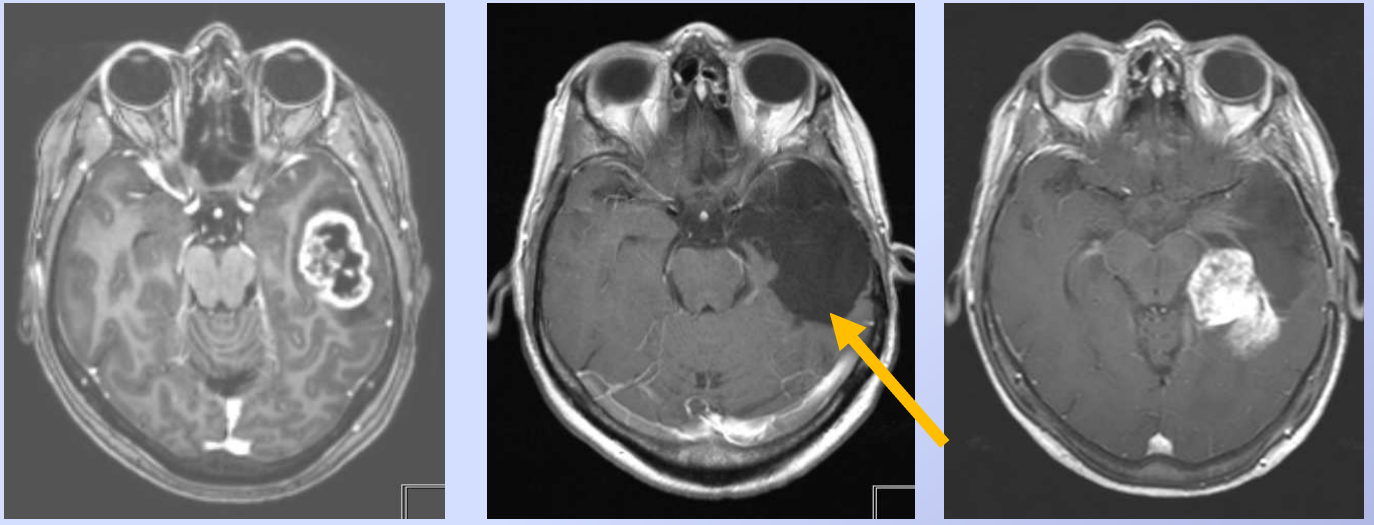
Plasma details:

- applied voltage ~ 7 kV_{pp}
- frequency ~ 6.75 kHz
- power ~ 0.5 W/cm^2
- used gas: surrounding air
- transport of plasma species: diffusion

Medicine

Cancer Treatment

Glioblastoma (Braintumor)

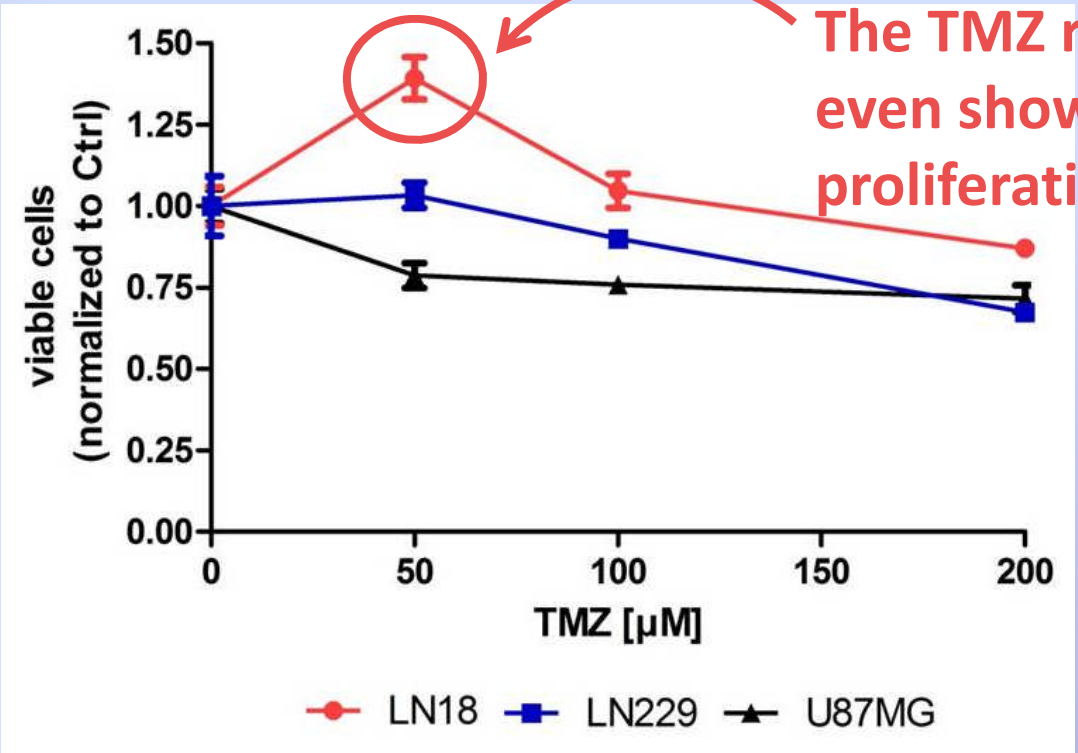


08/07 06/08 09/08

- Classified after WHO as grade IV tumor
- Highly aggressive, relapse occurs regularly
- Standard treatment regime consists of surgery, radiation and chemotherapy
- Poor prognosis, median survival 14.6 months

Glioblastoma (Braintumor)

Treatment with standard chemotherapeutic TMZ



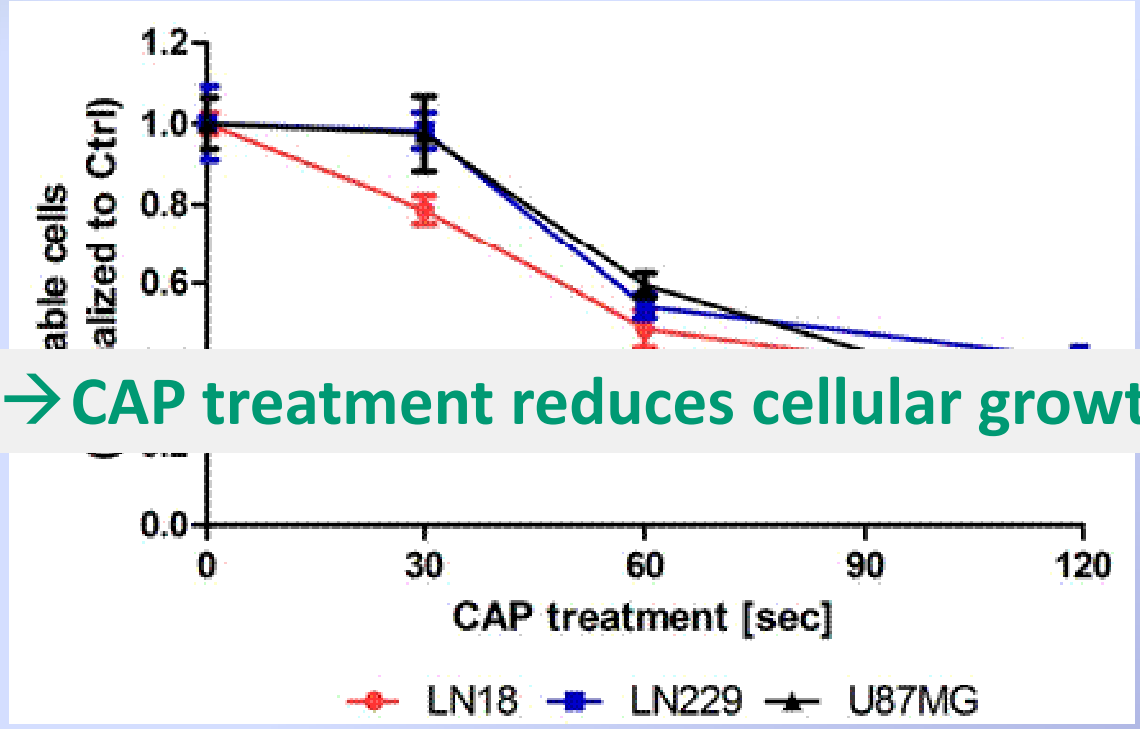
The TMZ resistant cell line LN18 even shows induction of proliferation for 50 µM of TMZ!

Almost no inhibition of proliferation with the standard chemotherapeutic Temozolomide (TMZ).

Köritzer et al. in revision PLoS One 2013

Glioblastoma (Braintumor)

Treatment with cold atmospheric plasma (CAP)

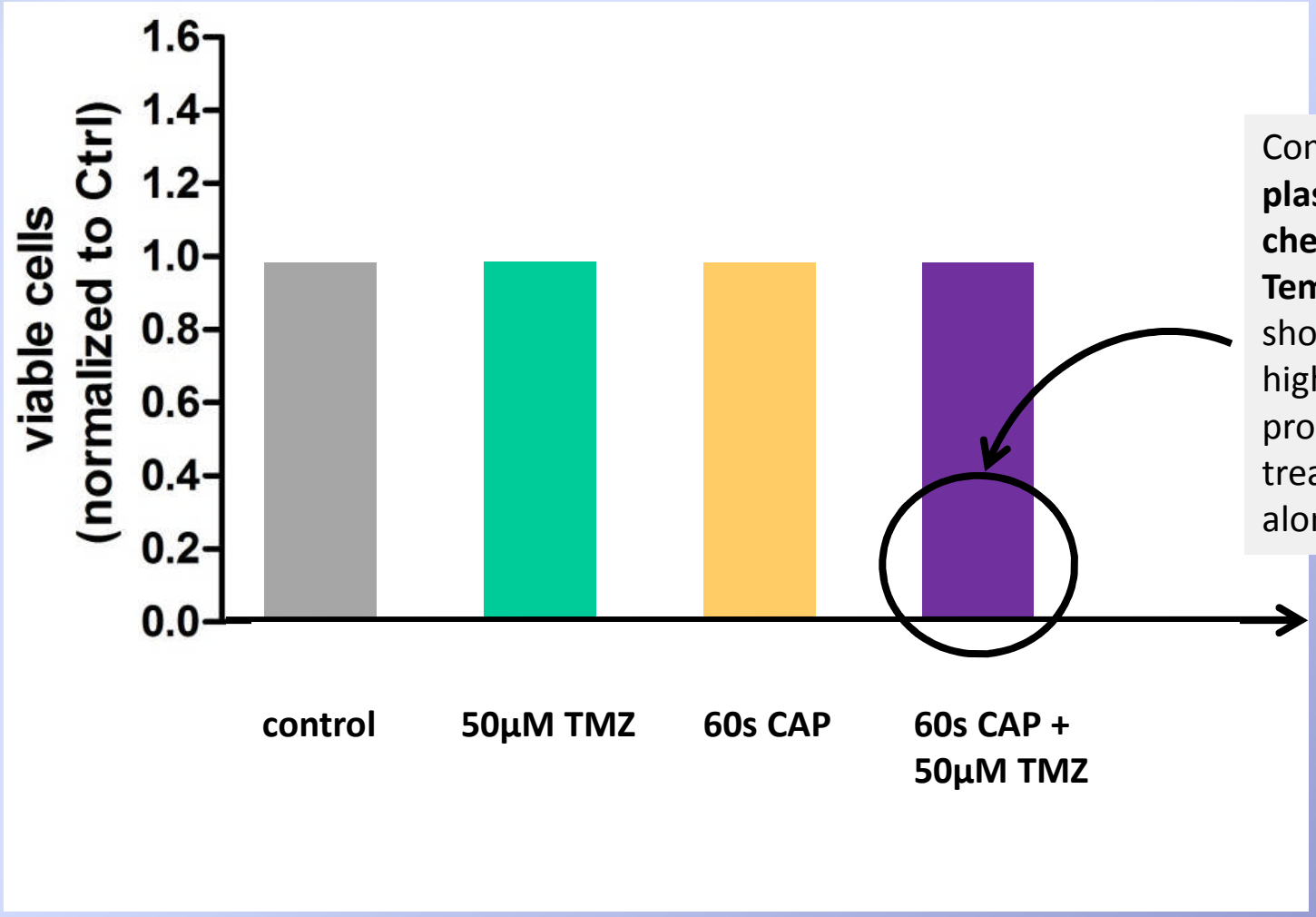


→ CAP treatment reduces cellular growth for all three cell lines!

Strong inhibition of proliferation for all 3 cell lines after the plasma treatment.

Glioblastoma (Braintumor)

Combination Treatment: Plasma + chemotherapeutic TMZ



Combination therapy - **plasma** and **chemotherapeutic Temozolomide** (TMZ) - showed **a factor five** higher inhibition of proliferation than the treatment with TMZ alone!

Plasma Medicine

- Possible application areas for CAPs in hygiene are:
  - sterilization of medical equipment
  - hand disinfection
  - water sterilization
- Possible application areas for CAPs in medicine are:
  - treatment of chronic wounds
  - treatment of different skin diseases
- One further challenging medical task is the treatment of CAP accessible tumors.
- **Nevertheless CAPs have to be 'designed' and carefully tested for each application - therefore requiring expertise from physics, engineering, (micro)biology and medicine!**

  → longterm basic research necessary!

MPE Cooperation

- PK-3 Plus Team -

Germany:
- Max Planck Institute for Extraterrestrial Physics
- University Düsseldorf
- University Gießen
- DLR-Institute for Material Physics in Space
- Kayser-Threde

Russia:
- Joint Institute for High Temperature, RAS
- RKK-Energia

USA:
- University Auburn
- University Berkeley
- University Iowa

France:
- GREMI, University Orleans

Japan:
- JAXA, Tokyo
- University Kyoto

- Plasma Medicine Network -

Germany:
- Max Planck Institute for Extraterrestrial Physics
- Max Planck Innovation GmbH
- Department of Dermatology, Hospital Schwabing, Munich
- Medizet Department Microbiology, Schwabing, Munich
- Department of Dermatology, University Hospital Regensburg
- Institute for Pathology, University Regensburg
- Department of Neuropathology, TUM, Munich
- Institute of Experimental Oncology, TUM, Munich
- Department of Toxicology, TUM, Munich
- University of Veterinary Medicine, Hannover
- Department of Infectiology and Virology, University Heidelberg
- German Aerospace Center (DLR), Cologne
- German Aerospace Center (DLR), Bonn
- Department of Otorhinolaryngology, Head & Neck Surgery, LMU, Munich

Russia:
- Joint Institute for High Temperature, RAS
- Institute for Biomedical Problems, RAS
- Institute for Epidemiology and Microbiology, RAMS
- Institute for Theoretical and Experimental Biophysics, RAS
- Shemyakin and Ovchinnikov Institute of Bioorganic, RAS
- Institute for Problems of Chemical Physics, RAS
- Institute for Physical Chemical Medicine, RAMS

USA:
- University of California, Berkeley
- Old Dominion University, Norfolk, VA

United Kingdom:
- Loughborough University, Leicestershire
- ADTEC Europe Ltd.


Thank you for
your attention!
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