

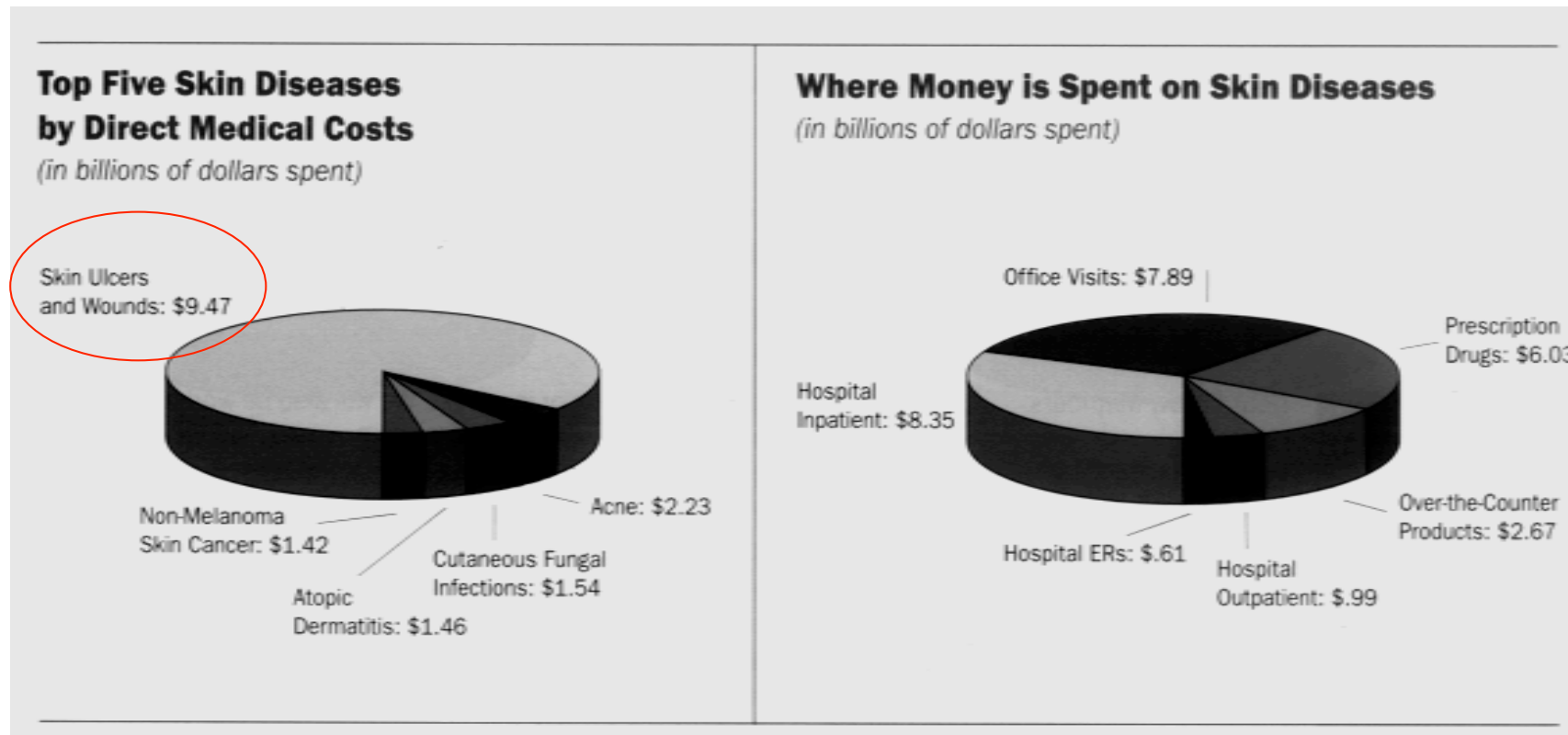


Niedertemperatur Argon Plasma – Eine neue Strategie zur Behandlung chronisch infizierter Wunden

Dr. Georg Isbary

Chronische Wunden – ein großes Problem für das Gesundheitswesen

- Prävalenz Deutschland ~ 1% (~ 800.000 Patienten)
- Inzidenz jenseits des 80. Lebensjahr ~ 4-5%*
- Geschätzte Kosten: 1-2% des jährlichen Budgets für Gesundheit**



American Academy of Dermatology Report 2005

Weiteres Problem – Resistenz von Bakterien

- "Bakterien können gegen Antibiotika resistent werden“, warnte bereits Alexander Fleming, als er 1945 den Nobelpreis für Medizin in Empfang nahm.
- European Antimicrobial Resistance Surveillance System (EARSS) 2007: Resistenzen werden von Jahr zu Jahr zu einem größeren Problem (speziell bei Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Escherichia Coli, Klebsiella pneumoniae and Pseudomonas aeruginosa)
- Weltgesundheitsorganisationen betrachten multiresistente Bakterien wie MRSA als globale Bedrohung*
- 19,5 % der Staph. aureus in Deutschland sind MRSA (EARSS 2008)
- Bedrohlich sind die steigenden Resistenzen gegenüber Reserveantibiotika wie Vancomycin innerhalb der letzten 6 Jahre resistente Bakterien (EARSS 2007)
- November 2008 Regierung startet DART-Programm (Deutschen Antibiotika-Resistenzstrategie)

*Grundmann H, Aires-de-Sousa M, Boyce J et al. Emergence and resurgence of methicillin-resistant Staphylococcus aureus as a public-health threat. *Lancet* 2006; **368**: 874-85.

Weltweite Prävalenz von MRSA (The Lancet 2006)

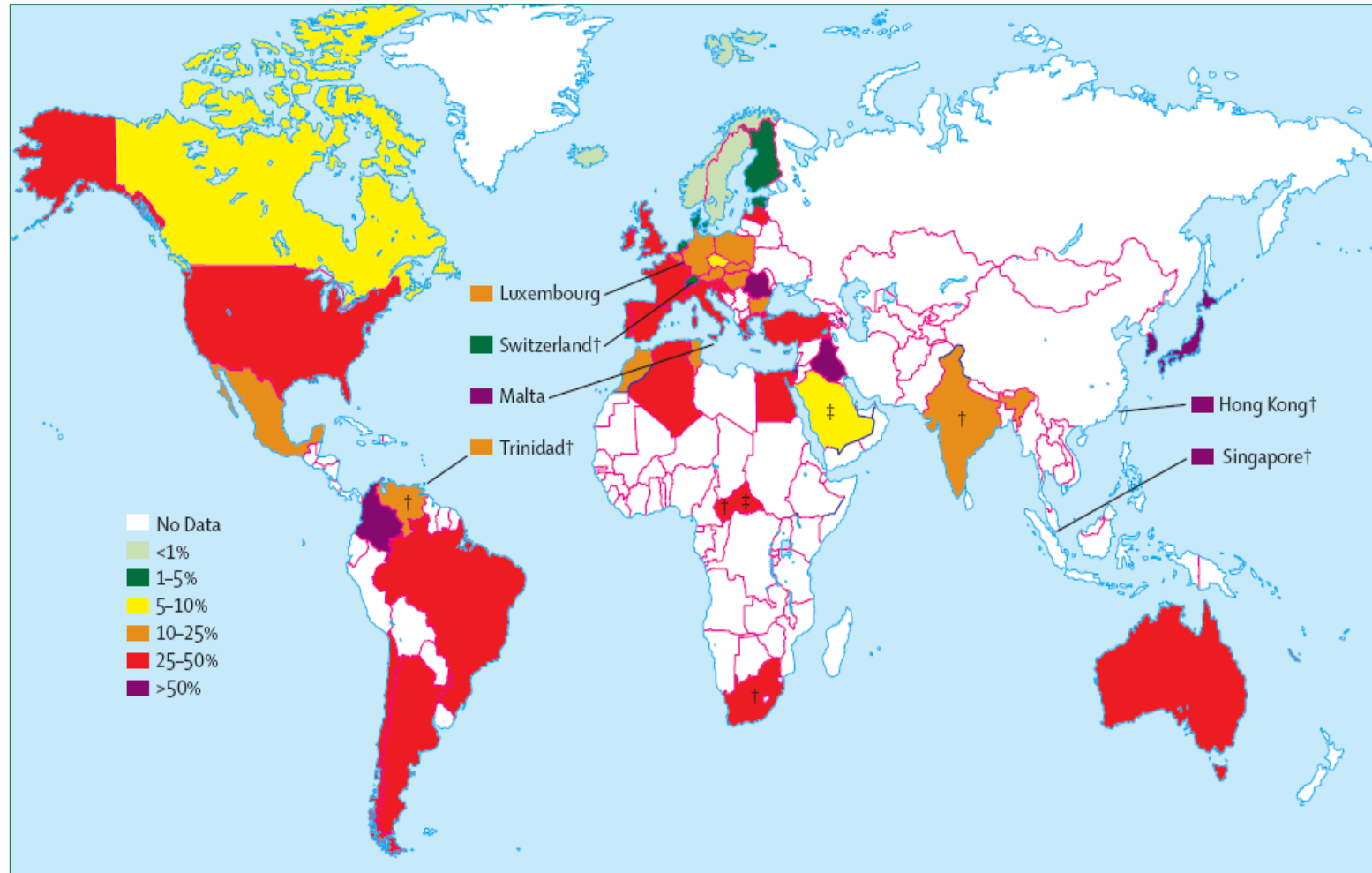


Figure 1: Worldwide prevalence of MRSA displayed by country*

*All presented MRSA proportions are from peer-reviewed studies undertaken since 1998.³²⁷⁴⁻⁸⁵ Prevalence estimates for Morocco, Algeria, Tunisia, Egypt, Jordan, Lebanon, and Turkey are from the antimicrobial resistance in the Mediterranean region website⁸⁶ at www.slh.gov.mt/armed/earss.asp. Studies providing most recent estimate of the MRSA proportion taken into account. If more than one study reported over same period, study including different types of clinical isolates was preferred over studies including only one specific type of specimen. †=Prevalence estimates are based on a study that included only one hospital. ‡=Prevalence estimates are based on studies between 1993 and 1997.

Resistenz von Bakterien

- 1999 – 2005: 62% Anstieg der Staphylococcus aureus-bedingten Klinikeinweisungen*
- In der selben Periode verdoppelte sich die Zahl der MRSA-bedingten Einweisungen (119%, jährlicher Anstieg von ~14%)*
- Infektionen mit MRSA töten in den USA etwa 19.000 Patienten pro Jahr (diese Zahl entspricht der Sterberate von AIDS, Tuberkulose und viraler Hepatitis zusammen)**
- 2006: 40.000 Todesfälle durch Infektionen in Deutschland (14% Anstieg 2002-2006)***
- Antibiotikaresistenzen erschweren nicht nur die Schwere der Erkrankung, sondern auch die Sterberate und die direkten Kosten um 30-100%***

*Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant Staphylococcus aureus, United States, 1999-2005. *Emerg Infect Dis* 2007; **13**: 1840-6

Klevens RM, Morrison MA, Nadle J et al. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. *Jama* 2007; **298: 1763-71

*** Report Deutsche Antibiotika-Resistenzstrategie

****Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. *Clin Infect Dis* 2003; **36**: 1433-7.

Nebenwirkungen durch Antibiotika

- ~10% der stationären Patienten haben eine Allergie gegenüber Penizillin (wobei nur 10% dieser Patienten haben tatsächlich allergische Reaktionen während der Behandlung)*
- Problematisch ist dabei die Kreuzreaktivität, z.B. Cephalosporine*
- Antibiotika assoziierte Durchfälle treten in 5-30% der Fälle während der Behandlung auf oder sogar bis 2 Monate nach Beendigung der Behandlung**, ***

*Greenberger PA. Drug allergy. Part B: Allergic reactions to individual drugs: low molecular weight. *Patterson's Allergic Diseases* 2002; 335-59

McFarland LV. Epidemiology, risk factors and treatments for antibiotic-associated diarrhea. *Dig Dis* 1998; **16: 292-307

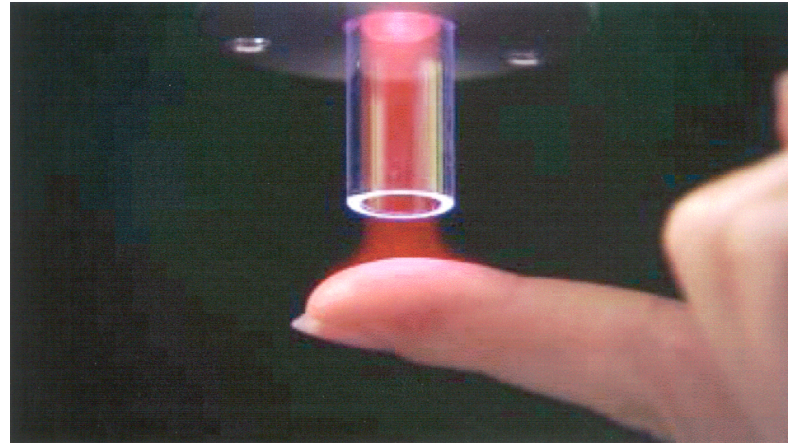
***Wistrom J, Norrby SR, Myhre EB et al. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. *J Antimicrob Chemother* 2001; **47**: 43-50

Zukunft der Antibiotika

- „Wirksame Antibiotika werden in Zukunft so wertvoll sein, wie sauberes Trinkwasser“
- Die Entwicklung von sog. „genomic derived or target based“ Antibiotika braucht sehr lange:
 - für gram + Keime ~ 2012*
 - für gram – Keime ~ 2016 - 2021*
- PROBLEM: Auch die neuen Antibiotikagenerationen werden die gleichen Probleme haben wie die bereits zur Verfügung stehenden (Resistenz, allergische Reaktionen und andere Nebenwirkungen)

*Payne DJ, Gwynn MN, Holmes DJ et al. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nat Rev Drug Discov* 2007; **6**: 29-40

Niedertemperatur Plasmen – eine neue Strategie



- **Reaktive Spezies (ROS/RNS)**
- **Ladungen**
- **Elektrische Felder**
- **UV**
- **Hitze**

Die Vorteile der Anwendung von Niedertemperatur-Argon-Plasma bei Wunden

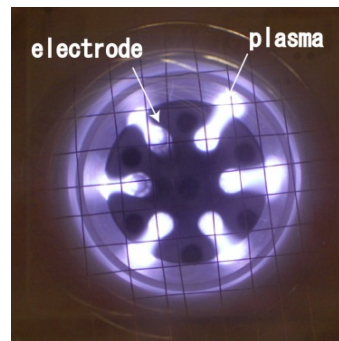
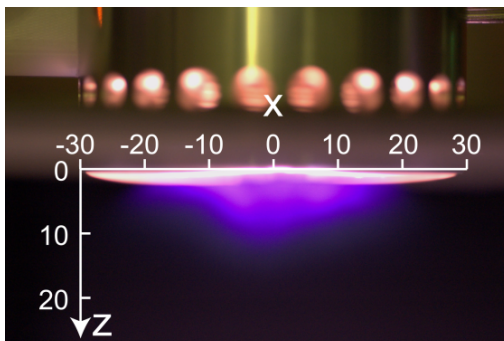
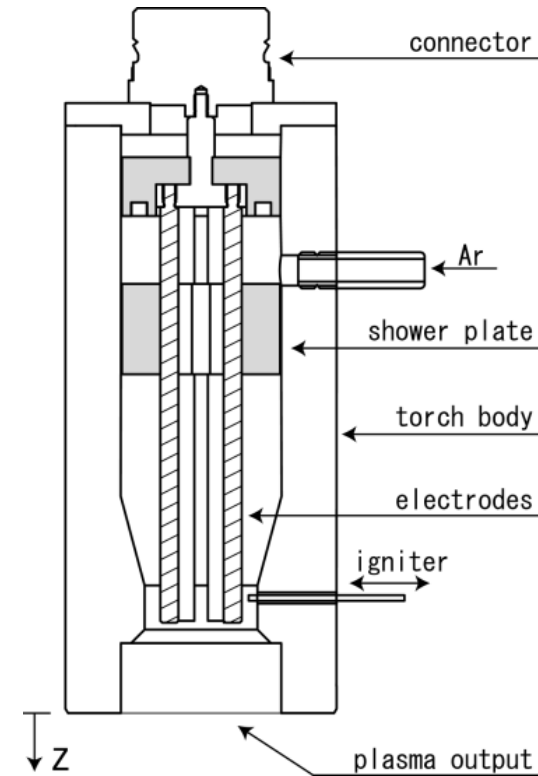
- In-vivo Anwendung die umgebendes Gewebe nicht schädigt
- Medizinischer „Cocktail“ – Mischung/Zusammensetzung kann variiert werden
- Kontaktfreie Anwendung, die rauhe Oberflächen/Areale bis in den Mikrometerbereich erreicht
- Bakterizid (Fungizid und Viruzid)
- Physikalische Methode → Resistenzen und allergische Reaktionen sind weniger wahrscheinlich
- Beschleunigte Wundheilung

Phase II Studie: MicroPlaSter α (ADTEC Plasma Technology Co. Ltd., Hiroshima/London)



Ultraschallunterstützte Distanzkontrolle

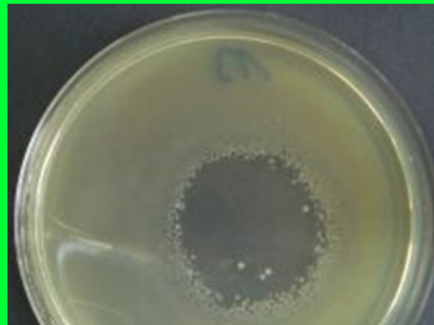
Das aktuelle Gerät - MicroPlaSter β



- verwendetes Gas: Argon
- Spannung = 50 - 100 V
- Frequenz = 2,3 GHz
- Leistung = 100 W

⇒ Plasma wird mittels Mikrowellentechnologie erzeugt
Shimizu et al. 2008

Rückblick Phase I: Wirkung von Argon-Plasma gegenüber verschiedener Bakterienstämme



Escherichia coli

present on
healthy persons



Enterococcus faecalis

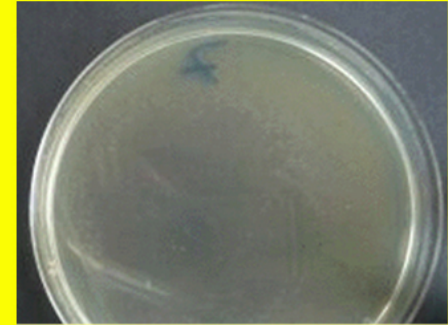


Group A streptococcus

facultative pathogenic, occasional resistance



*methicillin-resistant
Staphylococcus aureus*



*vancomycin-resistant
Enterococcus faecium*

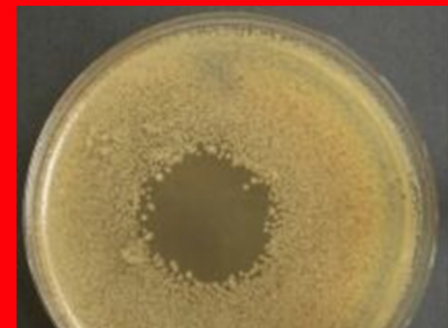
facultative pathogenic, seldom present on healthy skin



*Pseudomonas
aeruginosa*



Burkholderia cepacia

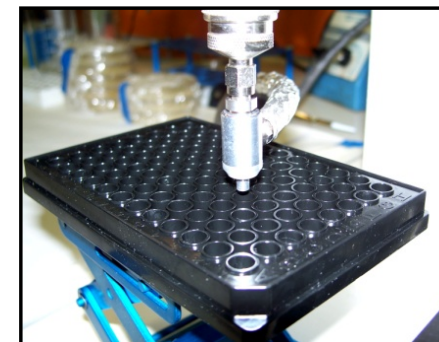
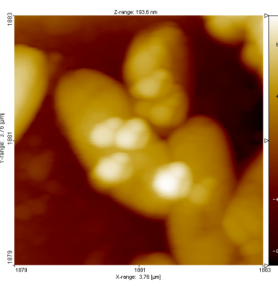
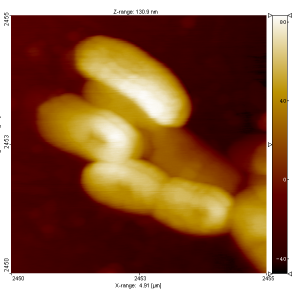
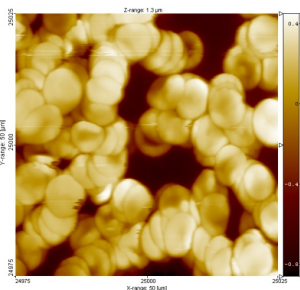
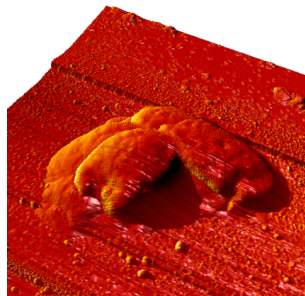
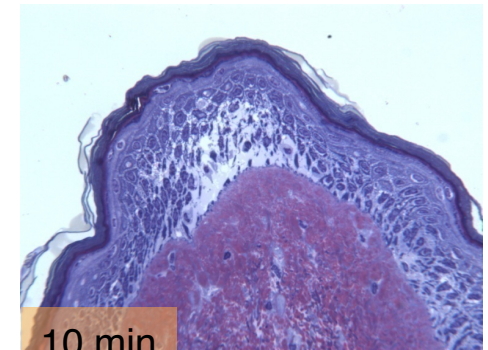
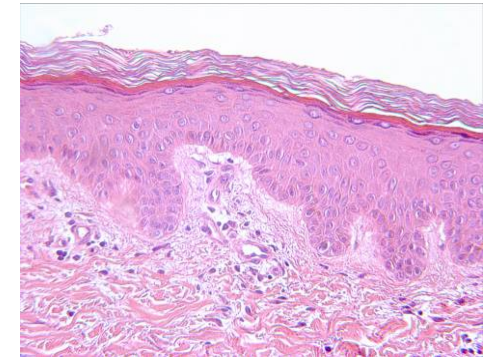
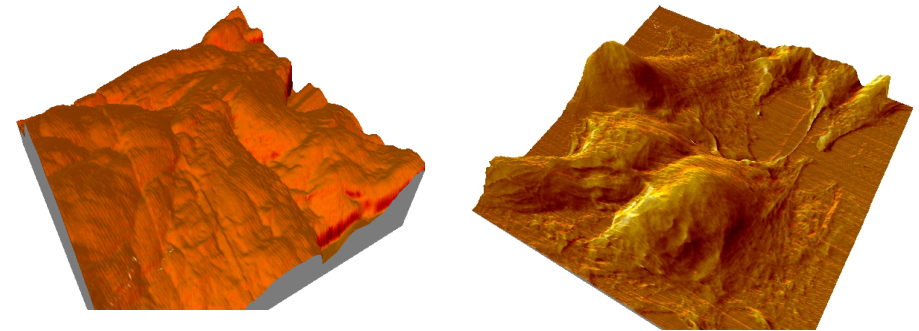


Bacillus cereus

Rückblick: Phase I

In Phase I wurden zahlreiche Tests zur Dosisfindung und zur Unbedenklichkeit der Plasmaanwendung durchgeführt: u.a. Histologien, Bluttests, mikroskopische Aufnahmen, AFM, Zellversuche...

Weitere Untersuchungen mit Fibroblasten, Keratinozyten, Zellkulturen, Toxizitäts-, Mutagenitäts- und Antikörpertests laufen...



Chronische Wunden in der Dermatologie



Venöse Ulkus



Arterielle Ulkus



Infektionen



Diabetisches Ulkus



Karzinome



Pyoderma gangraenosum

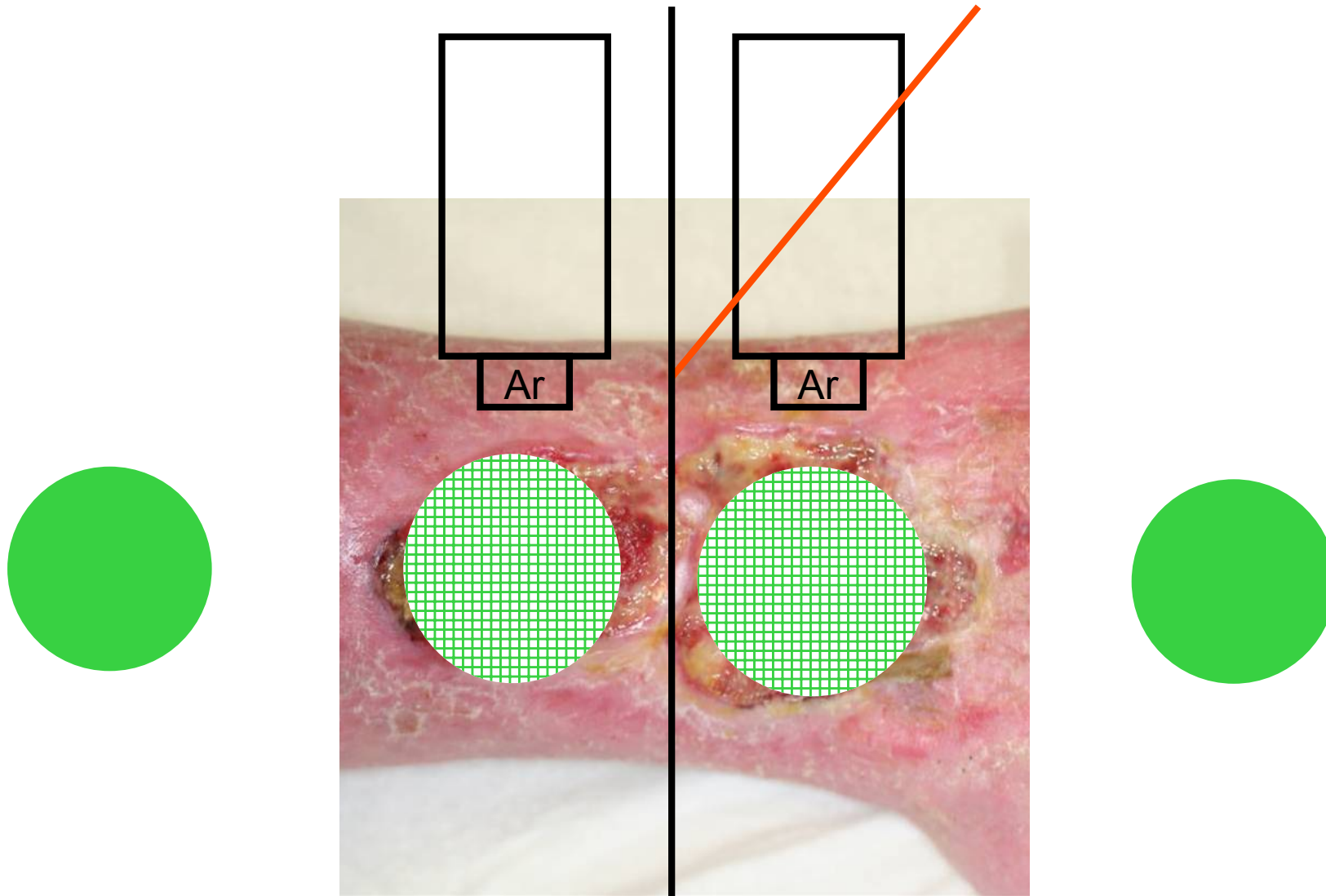
Vor der ersten Behandlung: manuelle Nekrolyse oder die Anwendung einer Wasserstrahltherapie Debritom® (medaxis, Switzerland)



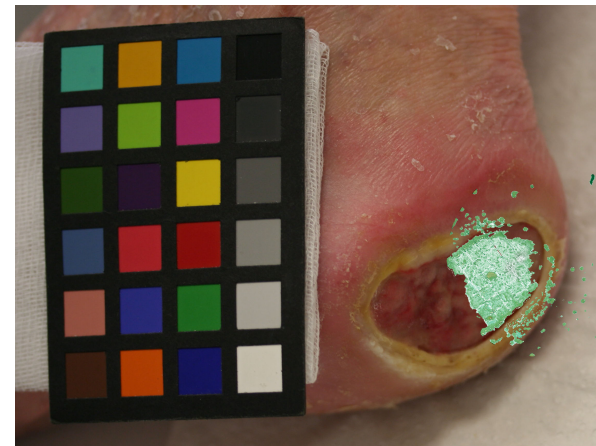
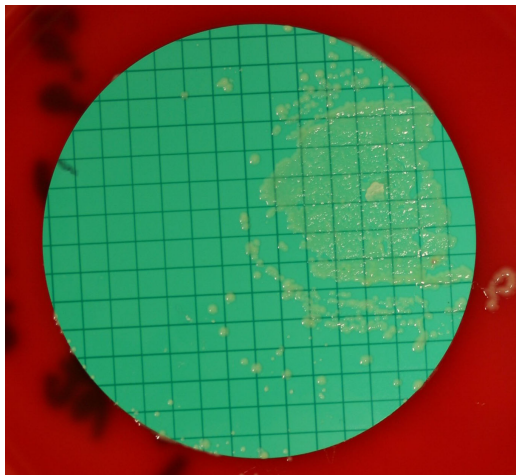
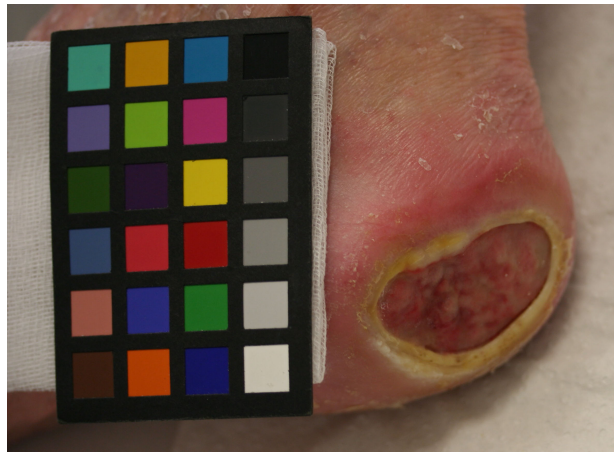
Standardabstriche scheitern bei der Keimzahlbestimmung und der Reproduzierbarkeit



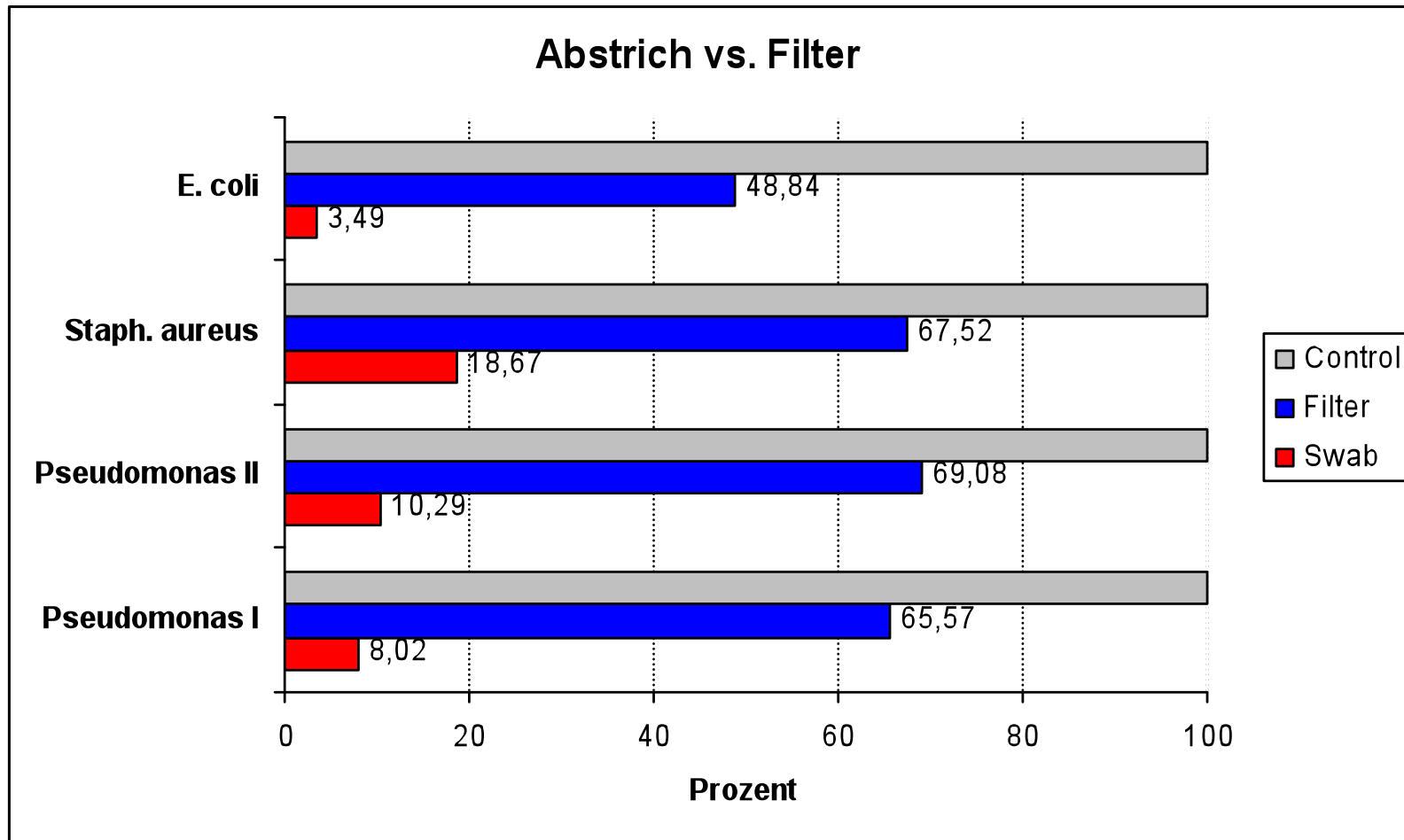
Ablauf der Behandlung



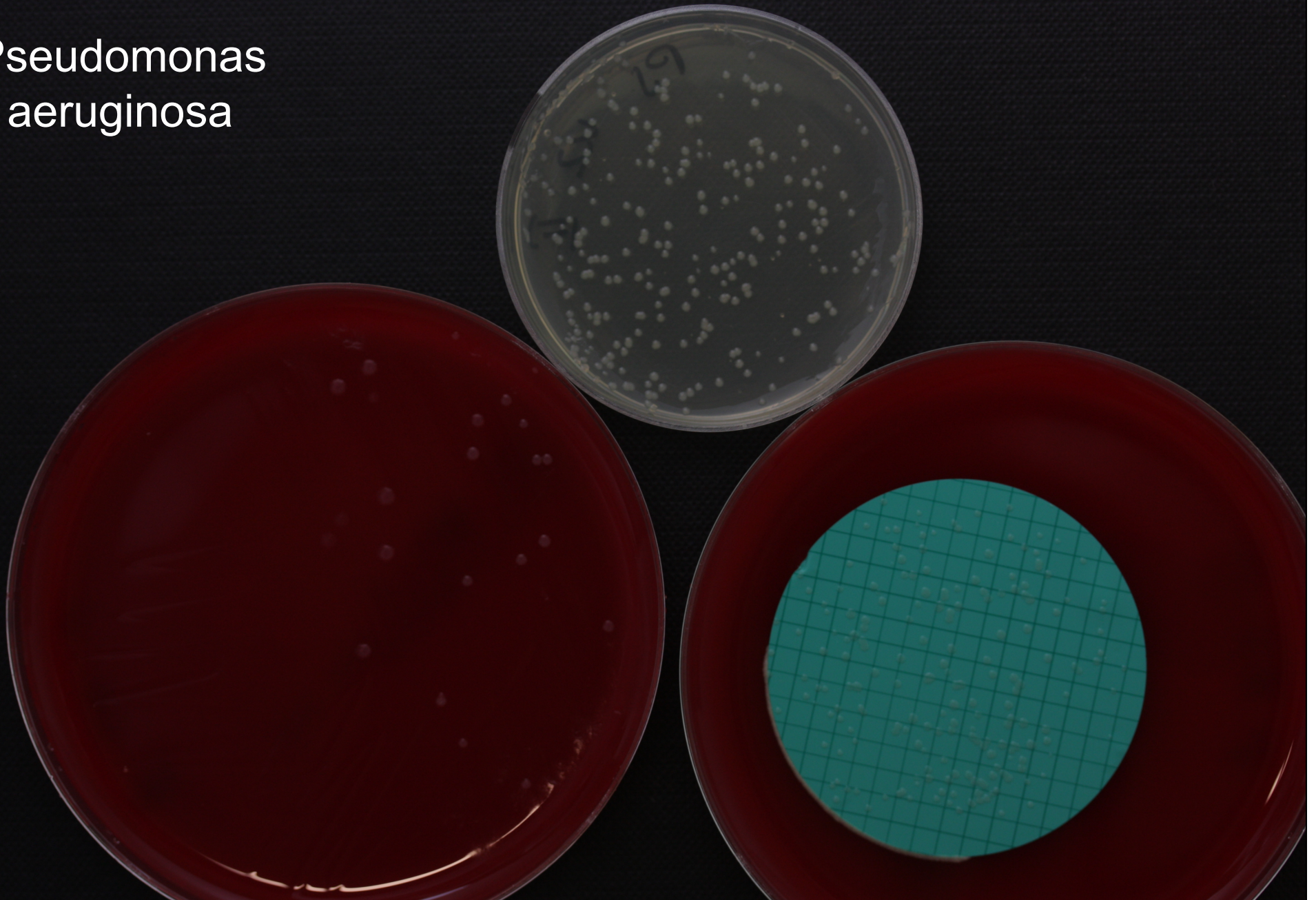
Anwendung von Nitrozellulose Filtern für die Keimzahlbestimmung



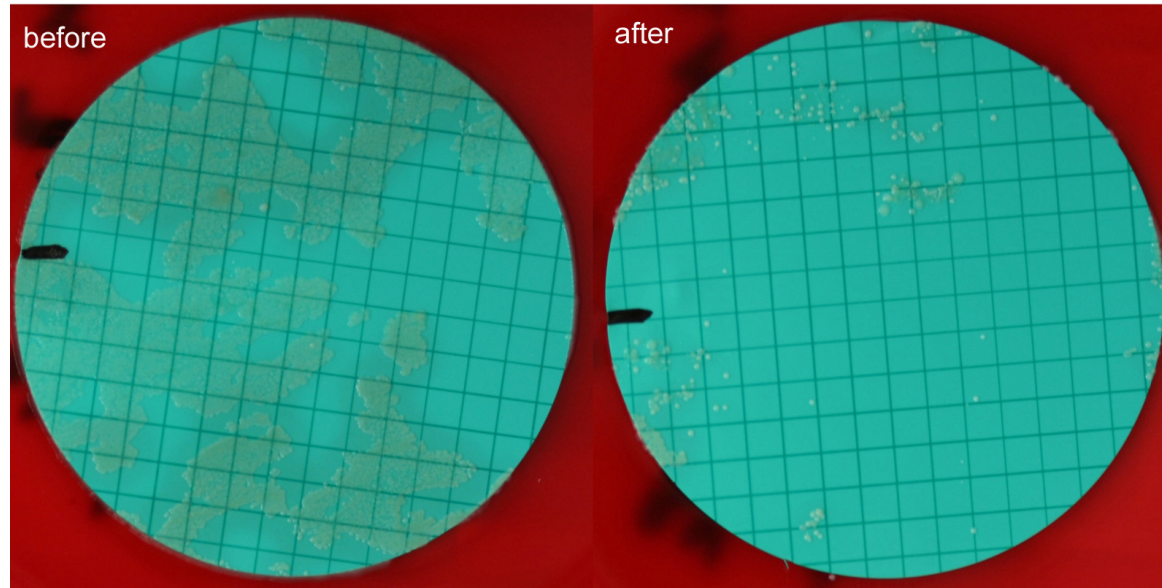
Zwischenversuch: Abstrich vs. Filter



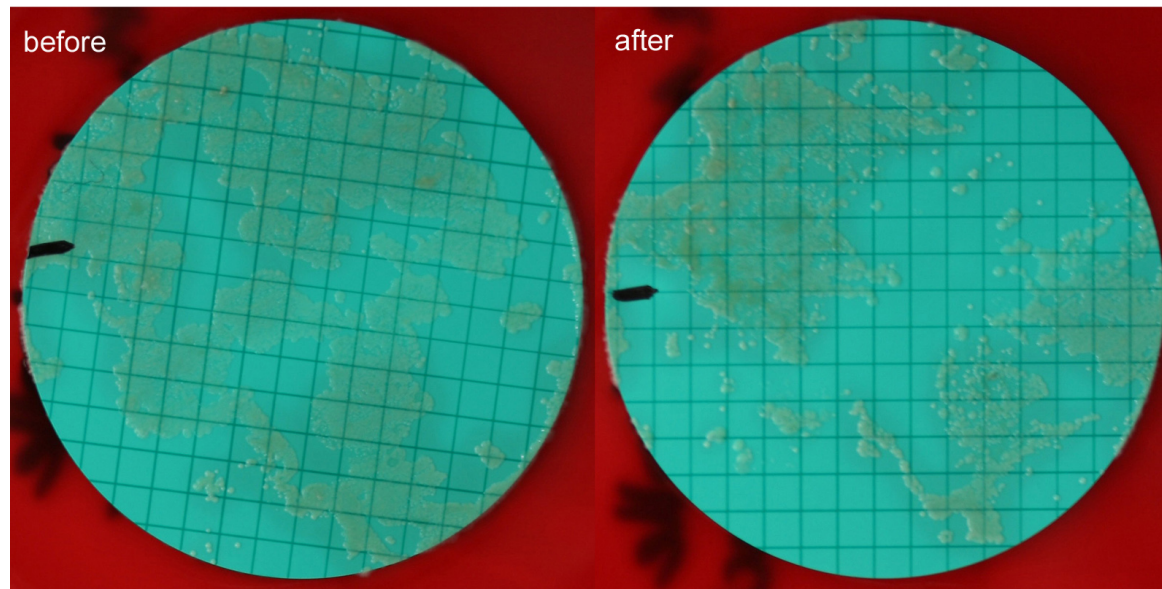
*Pseudomonas
aeruginosa*



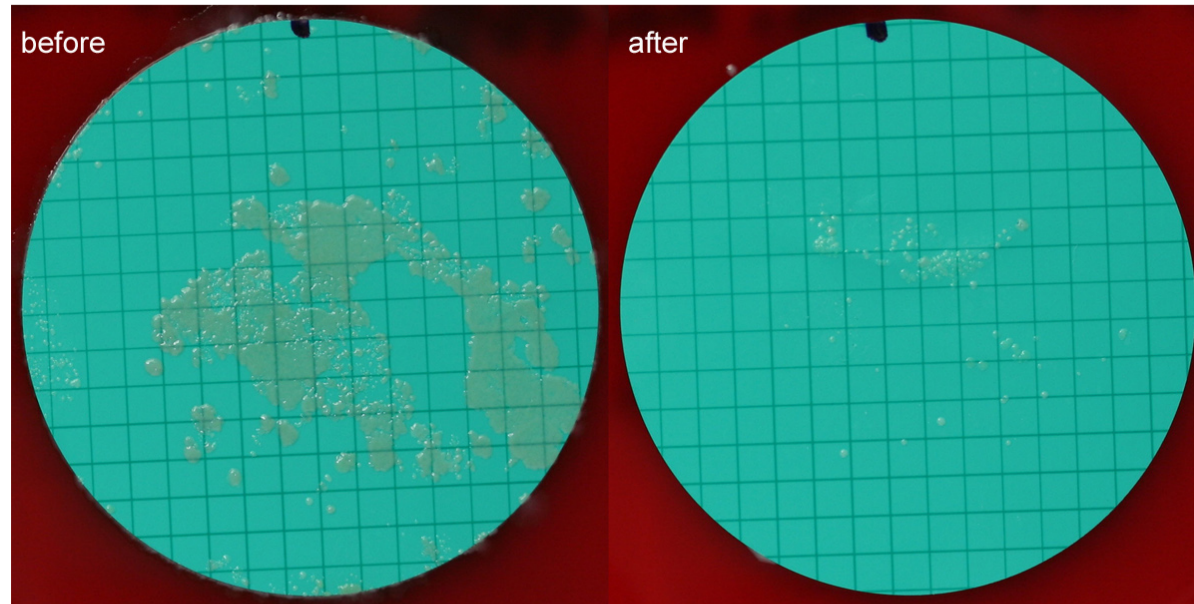
MRSA before and after plasma treatment



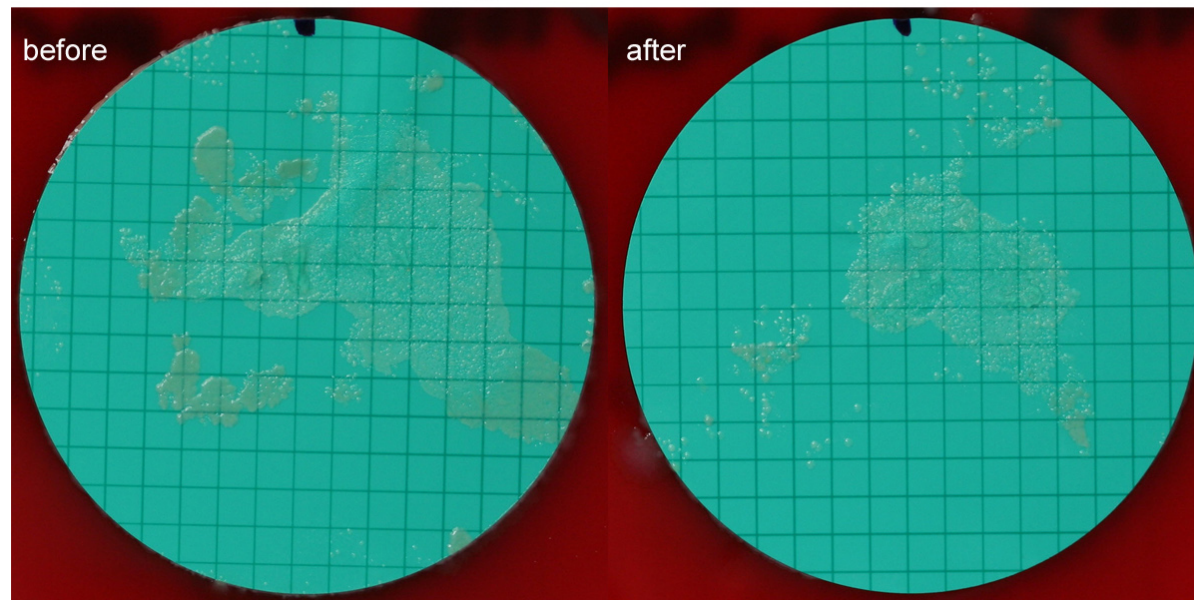
MRSA before and after control



PSAE changes before and after plasma treatment



PSAE changes before and after control



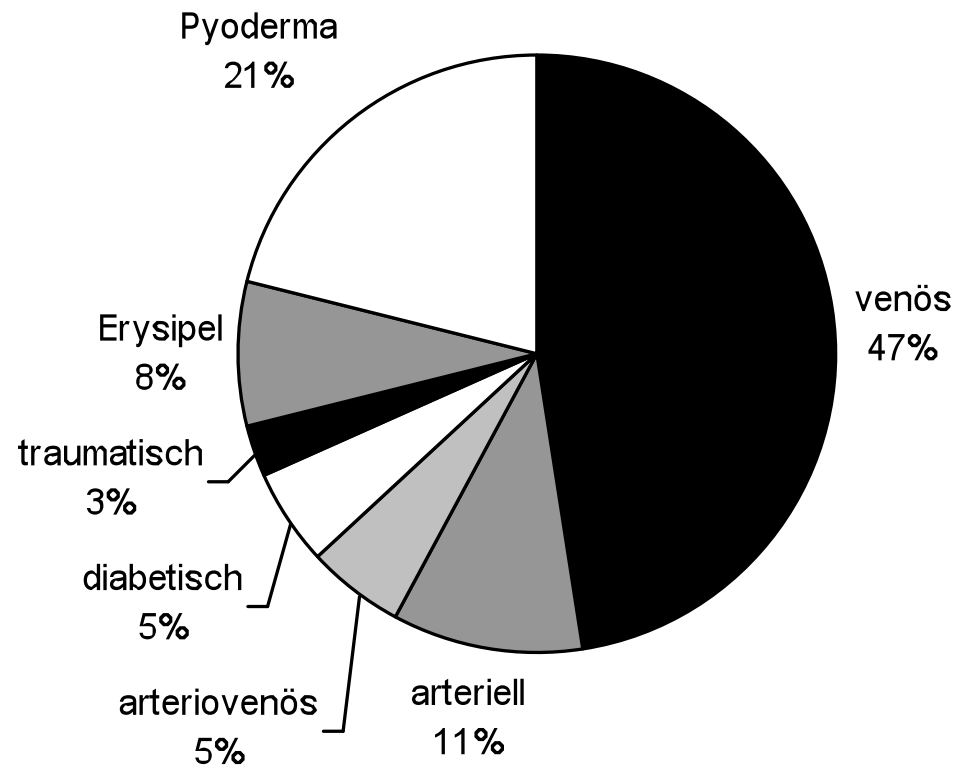
Phase II Studie – MicroPlaSter α

- Über 1500 Behandlungen (1 bis 169, Ø 9,1 pro Patient)
- 166 Patienten

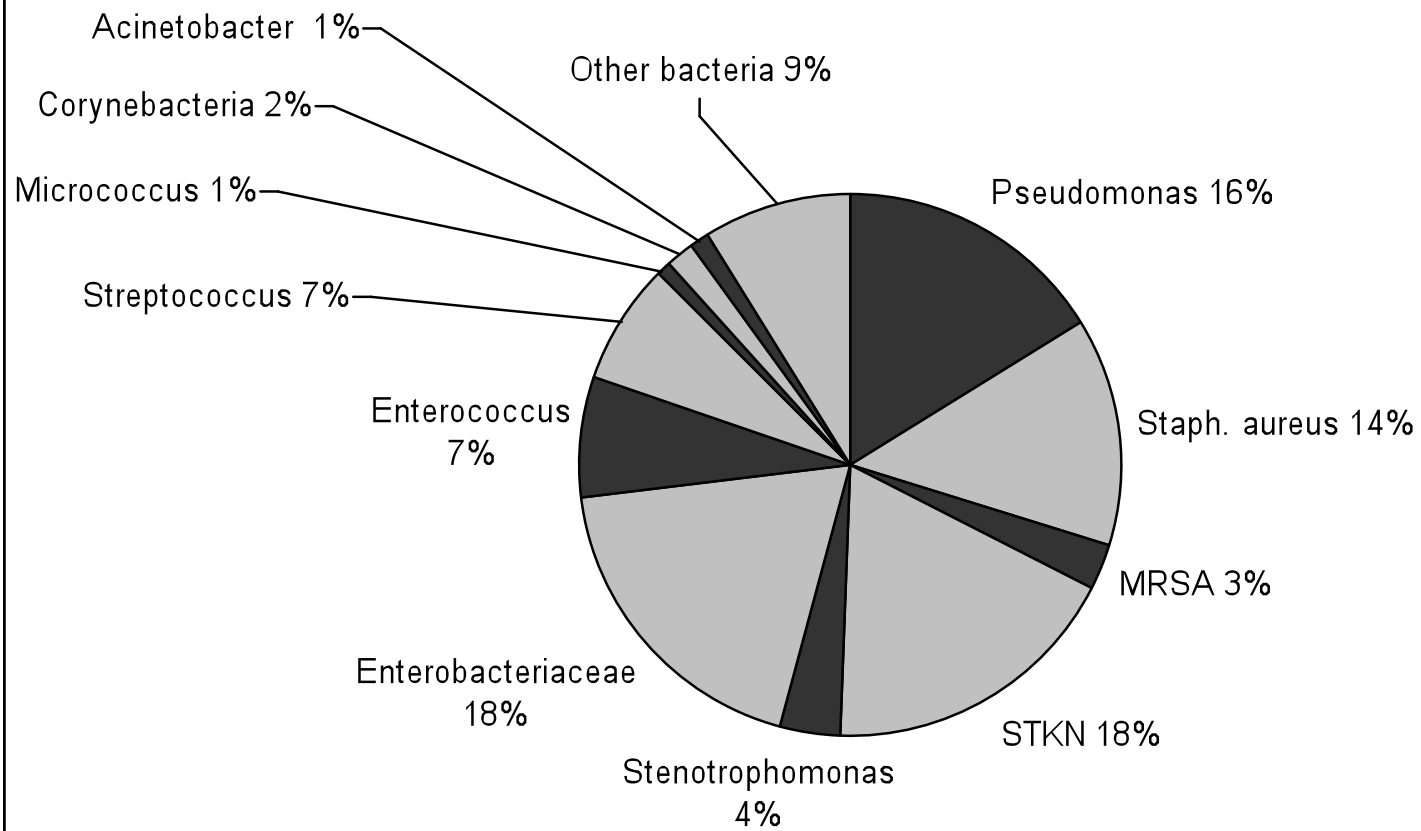
Zwischenauswertung (Effektivität vom Plasma)

- 36 Patienten
 - 291 Behandlungen
 - 5 min Behandlungszeit
 - Hauptdiagnose: venöse Ulkus
-
- Ergebnisse beziehen sich rein auf Filterauswertungen

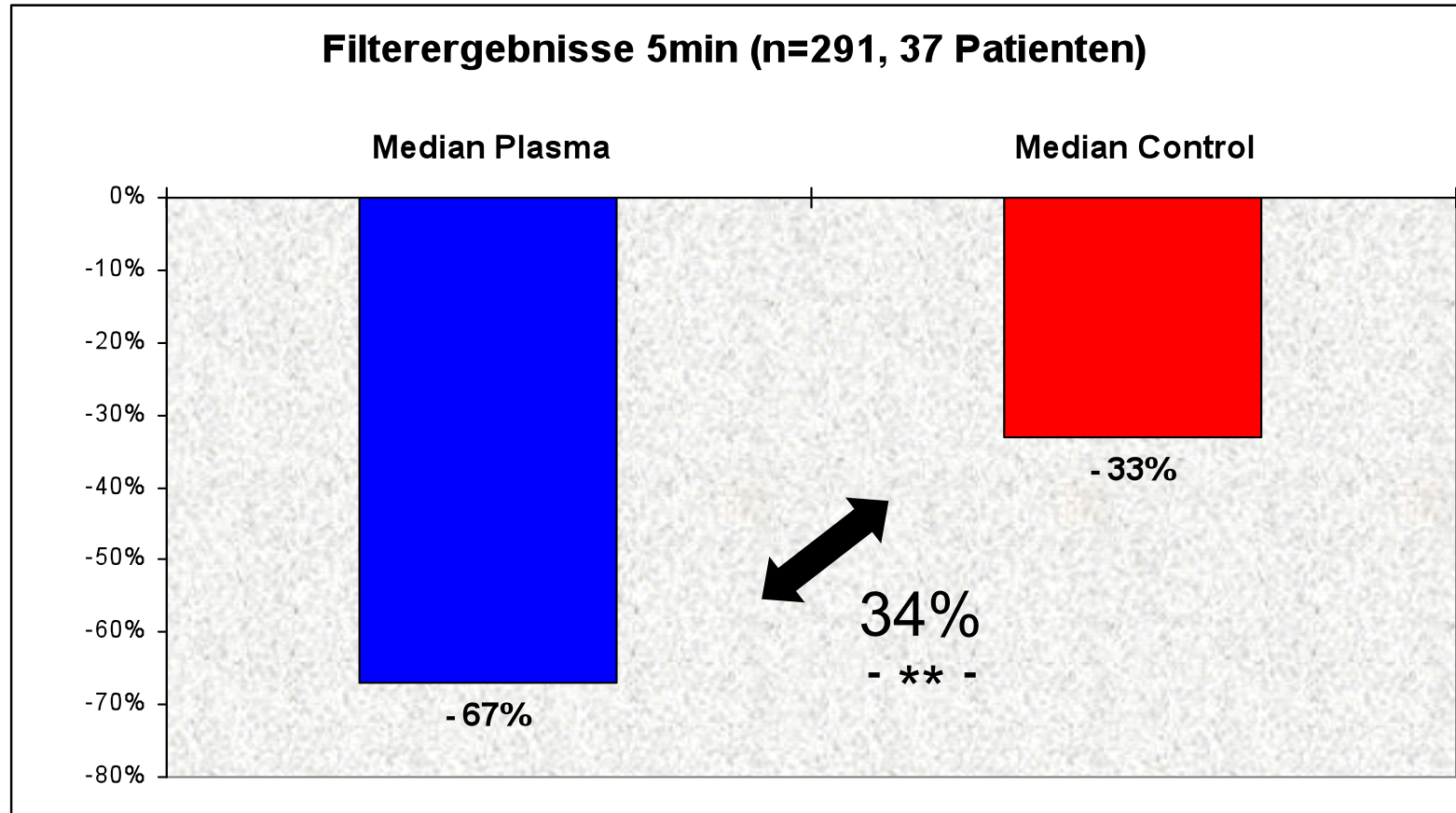
Hauptdiagnose der Ulzera



Keimart auf der Wunde

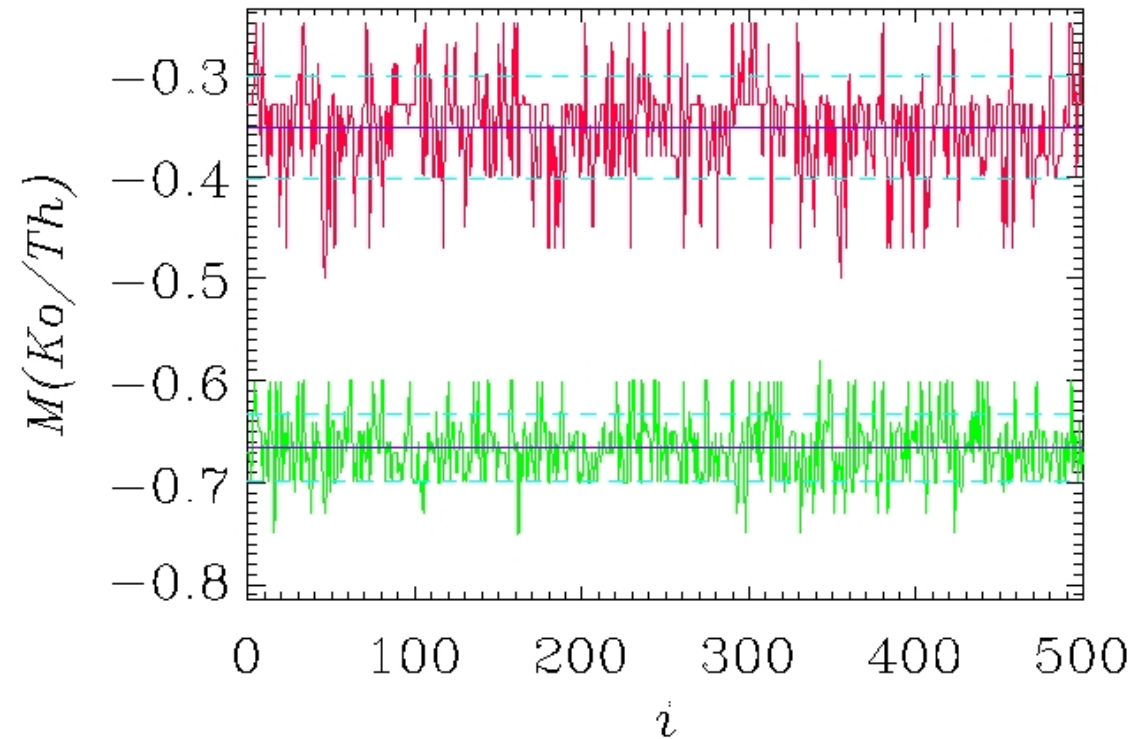


Ergebnisse: 5 min Behandlung



Hoch signifikant ($p < 10^{-6}$) höhere Keimreduktion (34%) in Plasma behandelten Wunden

Ergebnisse: 5 min Behandlung



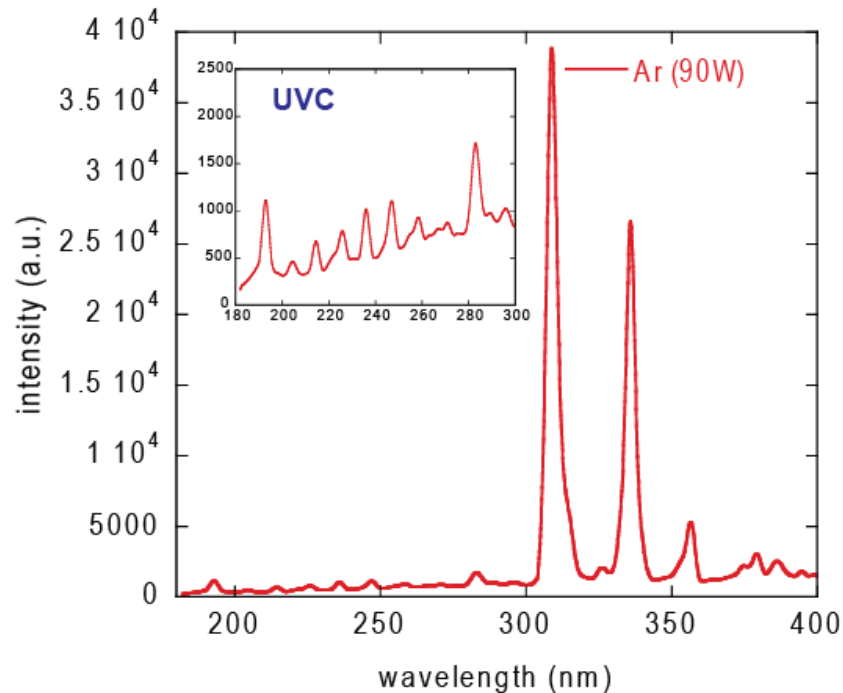
Ergebnisse des korrespondierenden
Bootstrap-Tests

Zwischenauswertung (Effektivität vom Plasma)

- 14 Patienten
- 70 Behandlungen
- 2 min Behandlungszeit

- Ergebnisse beziehen sich rein auf Filterauswertungen

UV-Spektrum des Argonplasmas



UV-Spektrum MicroPlaSter

- Effektive Lichtleistung: $\sum P_{\text{eff}}(\lambda) \times \Delta\lambda = 9.3 \mu\text{W}/\text{cm}^2 = 0.09 \text{ W}/\text{m}^2$
- Maximaldosis für gesunde Haut = $0.30 \text{ W}/\text{m}^2$
(WHO Richtlinien – ICNIRP)

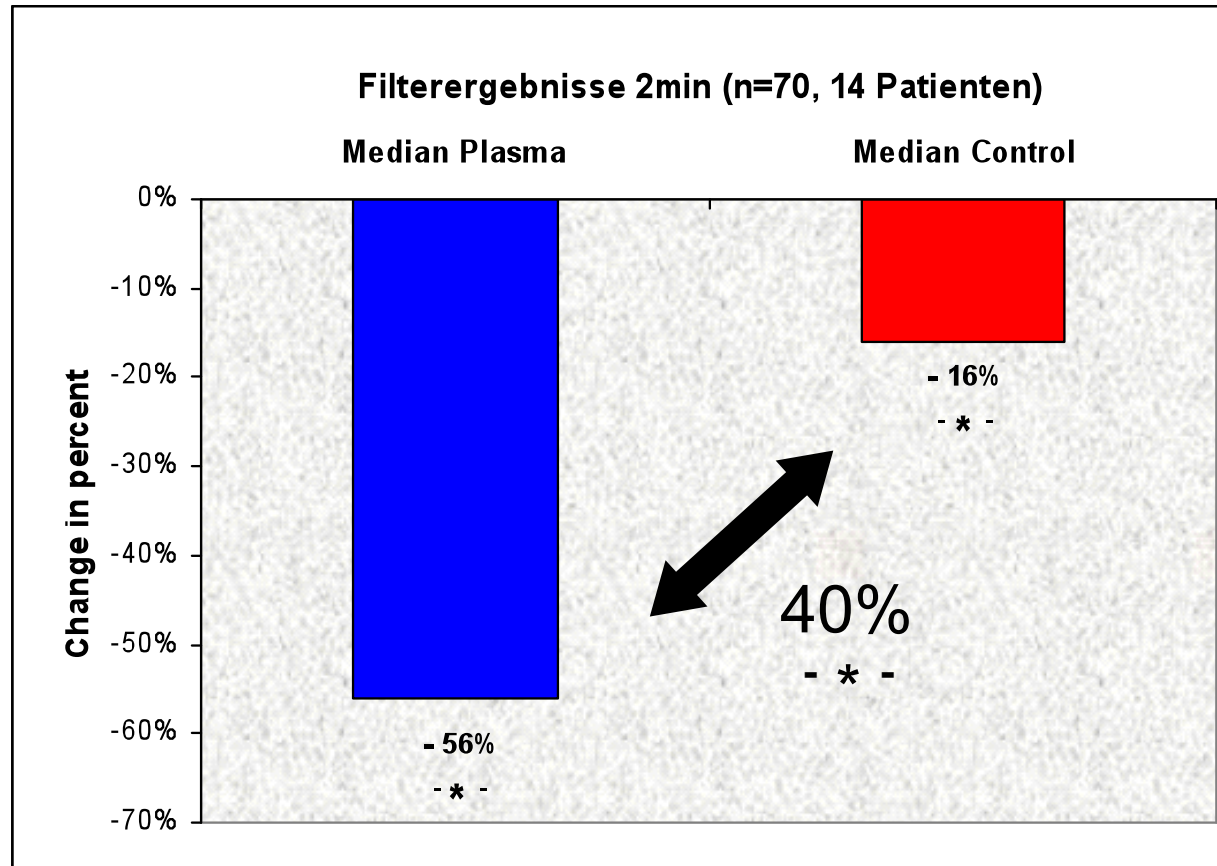
Empfehlung des SCCP (Europäische Kommission) - Report 0949/05 für offene Wunden bzw. ungeschützte Haut

- Ableich mit weiterer Wichtungsfunktion :
- $\Sigma P_{\text{eff}}(\lambda) \times \Delta\lambda = 21.1 \mu\text{W}/\text{cm}^2 = 0.21 \text{ W}/\text{m}^2 < 0.3 \text{ W}/\text{m}^2$

- Messungen in Garching haben ergeben, dass die UVC Dosis von einer Minute Plasmabehandlung der Dosis von 5 Minuten direkter Sonnenbestrahlung entsprechen.
- (Steffes B., Shimizu T. et al. 2008, 2009)

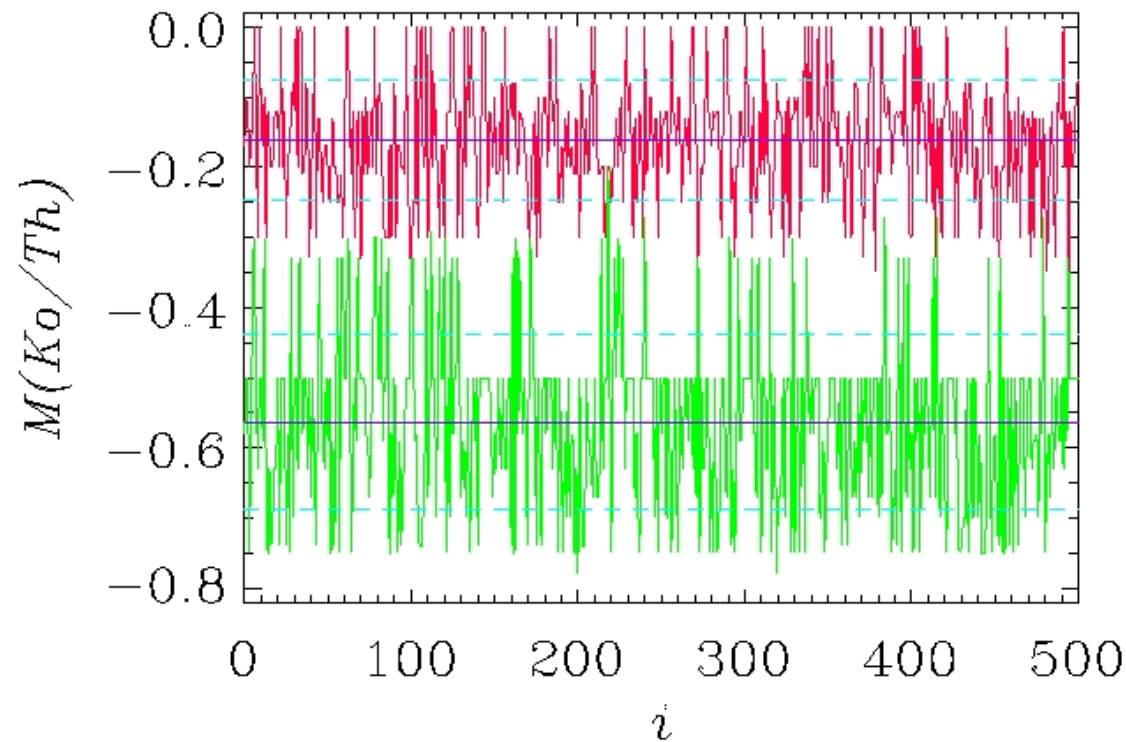
Scientific Committee on Consumer products

Ergebnisse: 2 min Behandlung



Signifikant ($p < 0.016$) höhere Keimreduktion (40%)
durch Plasma

Ergebnisse: 2 min Behandlung



Ergebnisse des korrespondierenden
Bootstrap-Tests

Beschleunigte Wundheilung durch Plasma?

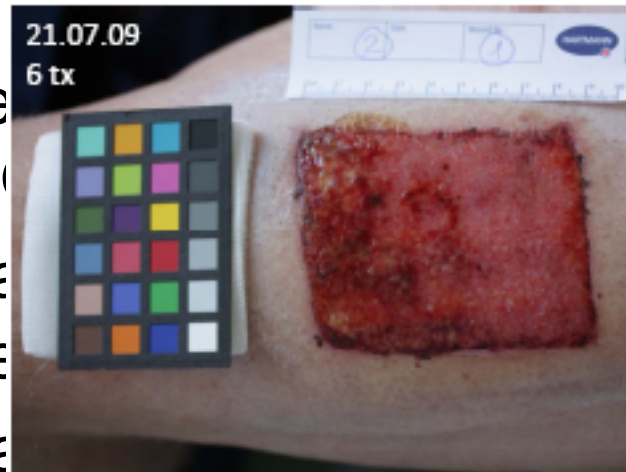
- Schwierig zu evaluieren und die Auswertung läuft, aber:
- Erste positive Eindrücke durch eine Studie an Spalthauttransplantationen in Regensburg

- Weitere Untersuchungen:

Keratinozyten: induzierte
bFGF, GM-CSF, VEGF

Fibroblasten: Plasma
IFN γ , MMP1, collagenase

Plasma

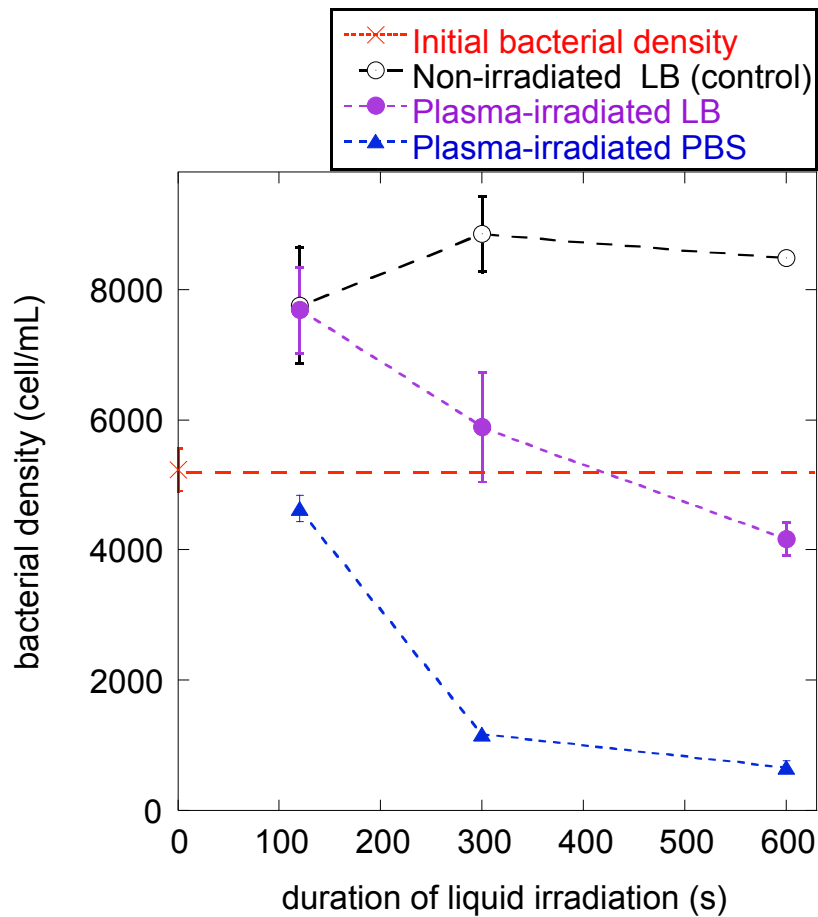


en (EGF,
TIMP1/4

, IL-10, TNF α ,

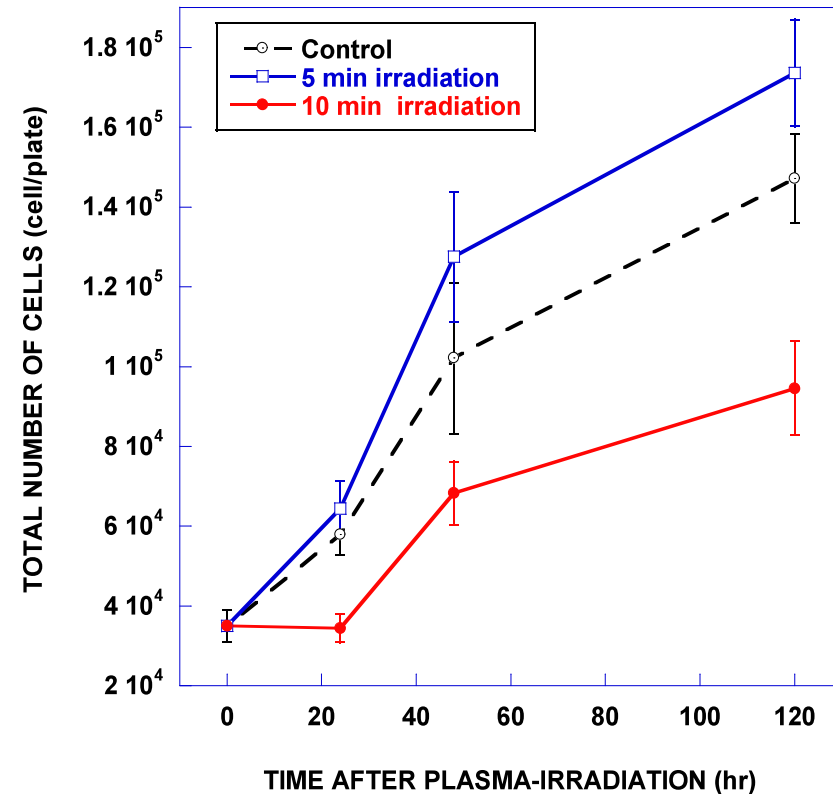
TGF β 1

Plasma Dosis Effekt auf Bakterien und Zellen



Reduktion der E. coli Dichte in PBS und LB Medium, bestrahlt mit Plasma.

Nosenko et al. 2009



1. Induktion der Zell Proliferation in Medium, welches 5 min mit Plasma behandelt wurde.
2. Inhibition der Zell Proliferation in Medium, welches 10 min mit Plasma behandelt wurde.

Pat.72: Wunde im Verlauf der Plasmabehandlung



Zusammenfassung

- Hoch signifikant (34%, $p < 10^{-6}$) höhere Keimreduktion bei Wunden mit 5min Plasmabehandlung gegenüber der Kontrolle
- Signifikant (40%, $p = 0.016$) höhere Keimreduktion auch bei 2min Plasma Behandlung
- Keine Nebenwirkungen bisher, bei sehr guter Verträglichkeit
- Nitrozellulose Filter sind Standard-Abstrichen in Hinblick auf die Reproduzierbarkeit und Keimdetektierung überlegen



Wir denken, das Plasma zu Zeiten multiresistenter Keime ein aussichtsreicher neuer Therapieansatz zur Keimreduktion von chronisch infizierten Wunden darstellt!

Weitere Anwendungsmöglichkeiten der Niedertemperatur Plasmen

The collage features three main elements:

- Top Left:** A ZDF news broadcast showing a medical device in a laboratory setting.
- Top Middle:** A screenshot of the BBC News website, highlighting the 'Technology' section in the sidebar.
- Center:** A screenshot of a New York Times Business article titled "Hospital-Clean Hands, Without All the Scrubbing" by Anne Eisenberg, published on February 13, 2010. The article describes a prototype hand sanitizer that uses plasma to kill germs like MRSA in just four seconds. It includes an image of the device and a quote from Gregor Morfill, the inventor.
- Bottom Right:** A partial view of a Klinikum München logo and a medical device.



- News Front Page
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- Europe
- Middle East
- South Asia
- UK
- Business
- Health
- Science & Environment
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- Programmes
- Have Your Say
- In Pictures
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- On This Day
- Editors' Blog
- BBC World Service

The New York Times Business

WORLD U.S. N.Y. / REGION BUSINESS TECHNOLOGY SCIENCE HEALTH SPORTS OPINION

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Financial Tools: Select a Financial Tool [v]

More in Business »: Global Business Markets Economy

The New York Times ON THE WEB

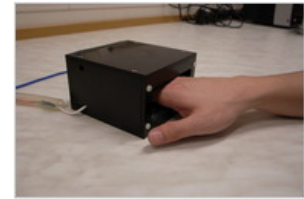
NOVELTIES

Hospital-Clean Hands, Without All the Scrubbing

By ANNE EISENBERG
Published: February 13, 2010

HOSPITAL workers often have to wash their hands dozens of times a day — and may need a minute or more to do the process right, by scrubbing with soap and water. But new devices could reduce the task to just four seconds, cleaning even hard-to-reach areas under fingernails.

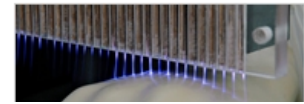
[Enlarge This Image](#)



Phil Wilson

A prototype hand sanitizer, left, designed by Gregor Morfill.

[Enlarge This Image](#)



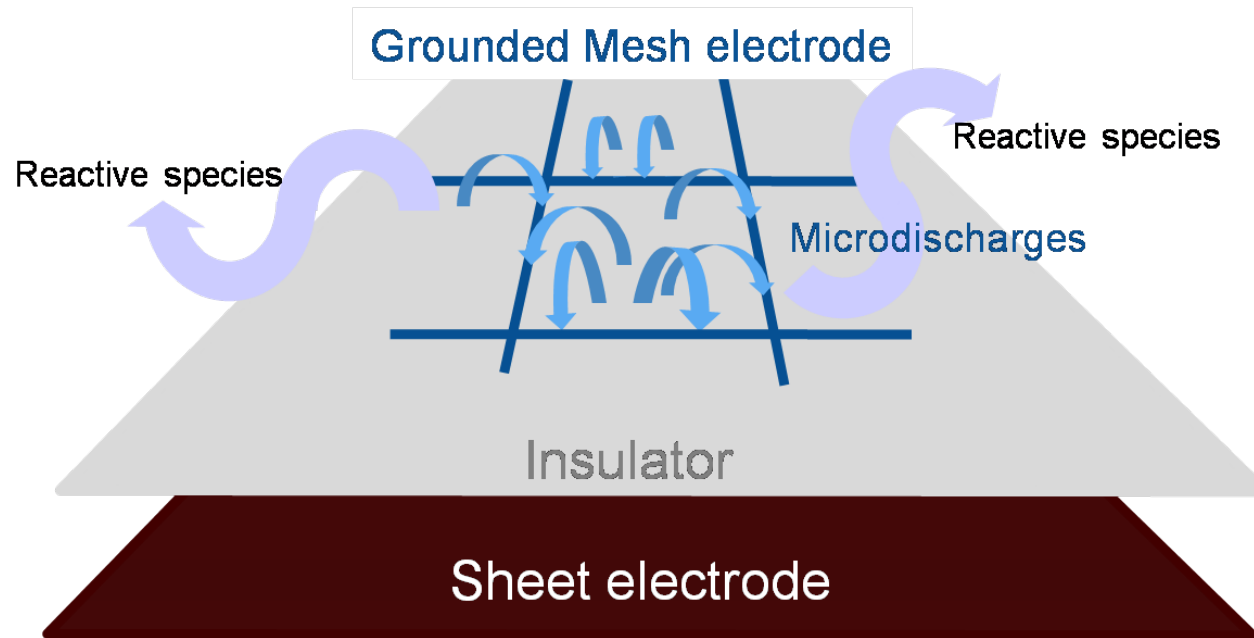
Instead of scrubbing, the workers would put their hands into a small box that bathes them with plasma — the same sort of luminous gas found in neon signs, fluorescent tubes and TV displays. This plasma, though, is at room temperature and pressure, and is engineered to zap germs, including the drug-resistant supergerm [MRSA](#).

The technology is being developed in several laboratories. Gregor Morfill, who created several prototypes using the technology at the Max Planck Institute for Extraterrestrial Physics in Garching, Germany, says the plasma quickly

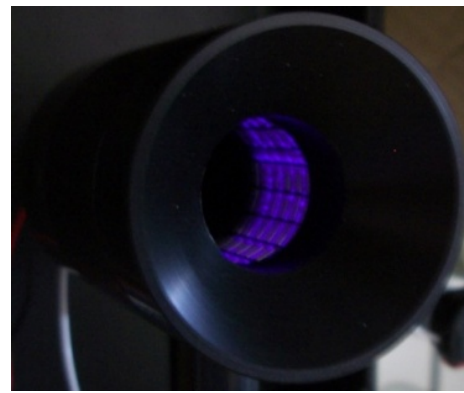
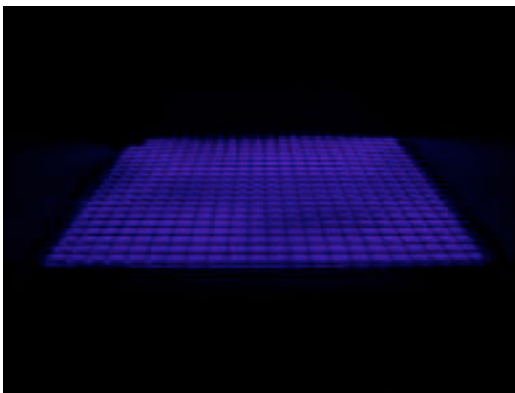
- SIGN IN TO RECOMMEND
- TWITTER
- SIGN IN TO E-MAIL
- PRINT
- REPRINTS
- SHARE

CRAZY HEART
NOW PLAYING
3 ACADEMY AWARD NOMINATIONS

Barrier Corona Discharge



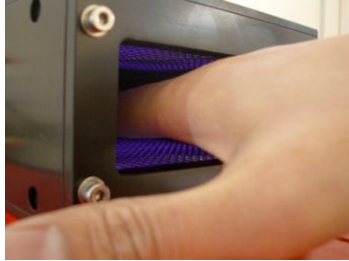
- Verwendetes Gas: Luft
- Spannung = 18 kV
- Frequenz = 12.5 kHz
- Leistung = 0.5 W/cm²



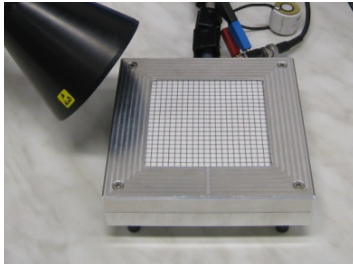
⇒ Viele Mikroentladungen erzeugen hier das Plasma.

Morfill et al. 2009

Anwendungen im Gesundheitsbereich



Handdesinfektion (HandPlaSter)



Behandlung von Fußpilz (FootPlaSter)

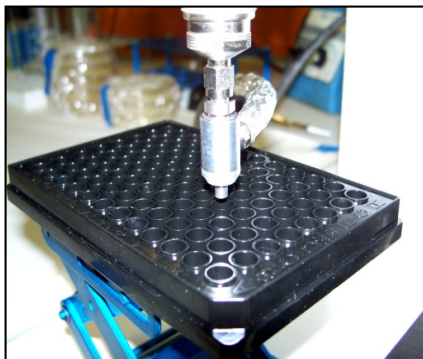


Mundhygiene (OralPlaSter)



Persönliche Hygiene
(DeoPlaSter)

Anwendungen im Medizinbereich



- Wundbehandlung
- Behandlung von Hautkrankheiten (Prurigo)
- Parodontoseprophylaxe
- Verbesserung der Narbenbildung
- Behandlung von Schnittwunden

Weitere Studie: Juckreizerkrankungen

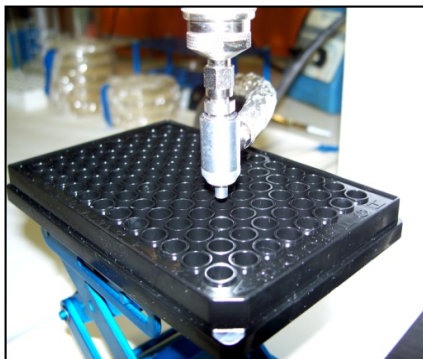


Prurigo nodularis Hyde



Pruritus simplex subacuta

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www.mpe.mpg.de/theory/plasma-med/index.html

 **PLASMA HEALTH CARE**
A project initiated by the Max Planck Institute for Extraterrestrial Physics

Home

Home



Plasma Health Care:
An integrated programme of research and development

- From the laboratory to the hospital
- From the laboratory to industry
- From the laboratory to people

For the benefit of all.

>> Download the brochure!

Get more information:

- Basic Research
- Applied Research
- Technology Transfer
- The Research Team
- Publications
- Talks & Presentations
- Workshops

... or use the menu on the left side.

Plasma Health Care in the Media:

German Television:

- 17-12-2009, 3sat "nano": [View](#)
- 17-12-2009, ZDF "heute journal": [View](#) (proceed to 16:42 min:sec) or watch clip [here](#).
- 27-12-2009, BR "Rundschau": [View](#)
- 07-01-2010, ZDF "Drehzscheibe Deutschland": [View](#) (proceed to 23:06)

News & web pages: (MORE...)

- BR online: [Read this](#) and also [this](#) (12-2009).
- Münchner Merkur (20-12-2009)
- FAZ article (10-01-2010)
- Pforzheimer Zeitung (16-01-2010)
- Physik Journal and 3sat nano (01-2010)
- TAZ (13-02-2010)
- The New York Times (14-02-2010)

Das Plasma Netzwerk

R&D Network:

- **Plasma physics** (MPE, Eindhoven, Loughborough)
- **Plasma Diagnostics** (MPE, Eindhoven)
- **Plasma Chemistry** (MPE, Berkeley)
- **Plasma Engineering** (MPE, ADTEC)
- **Plasma Biology** (MPE, TUM, Regensburg)
- **Plasma Microbiology** (Schwabing, Regensburg)
- **Plasma Medicine** (Schwabing, Regensburg)
- Also there is a cooperation in all fields with six Research Institutes from the Russian Academy of Science and the Russian Academy of Medical Science
- **Technology Transfer** (Max-Planck Innovation GmbH)

Der Dank gilt Allen, die sich an diesem Projekt beteiligt haben



Gregor Morfill
Tetsuji Shimizu
Bernd Steffes
Wolfram Bunk
Roberto Monetti
Julia Zimmermann
Tetyana Nosenko
René Pompl



Michael Landthaler
Sigrid Karrer
Julia Heinlin
Tim Maisch



Shuitsu Fujii
Mary McGovern

> Klinikum Schwabing

Wilhelm Stolz
Hans-Ulrich Schmidt
Birgit Peters
Katrin Ramrath
Matthias Georgi
Julia Schäfer
Carolin Eckhardt

Vielen Dank für Ihre Aufmerksamkeit!

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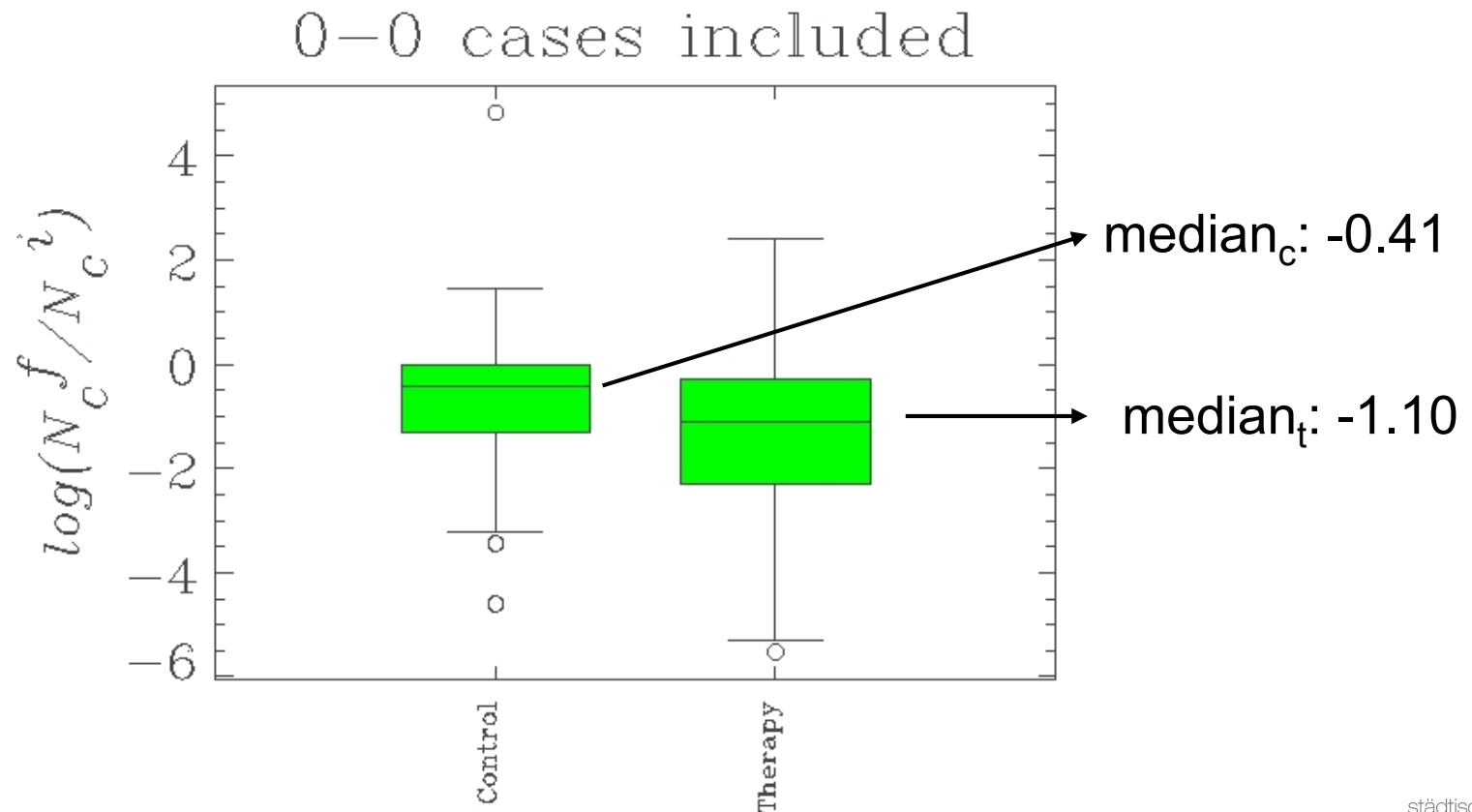
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Vielen Dank

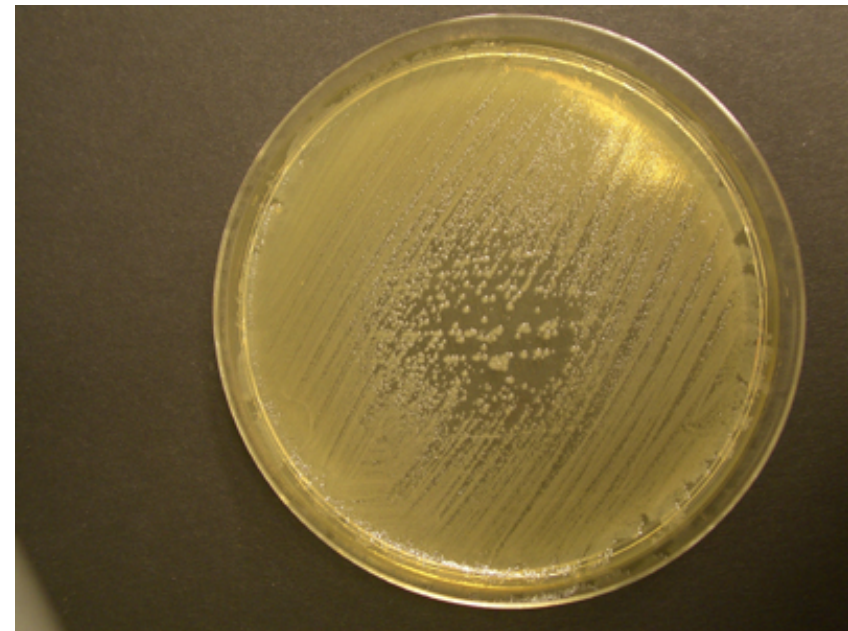
Ergebnisse: 5 min Behandlung



In vitro proof of principle: phase I study to evaluate the bactericidal effect of plasma

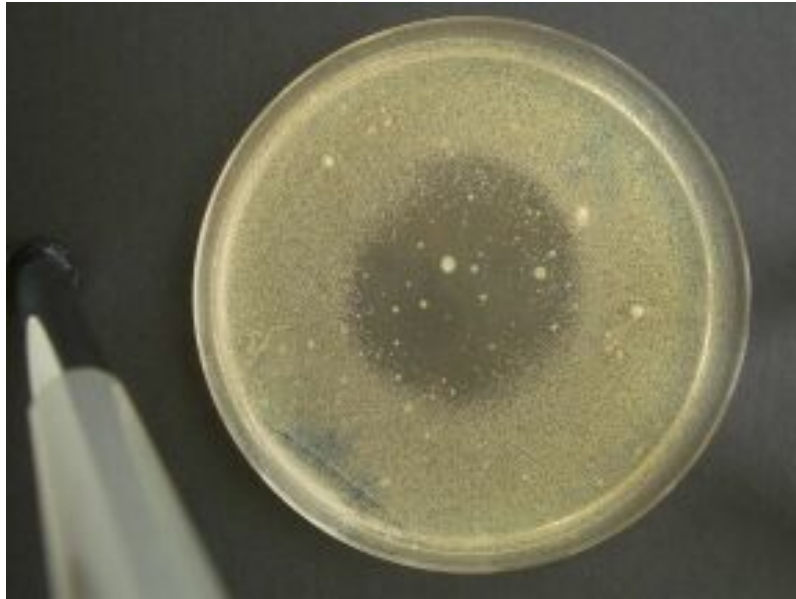


Treatment with disinfectant (Dermacid®)

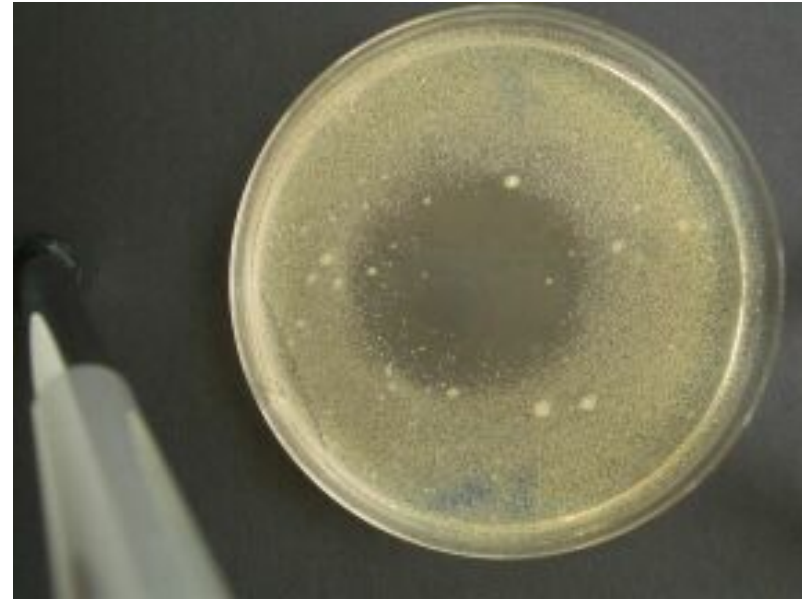


Treatment with argon plasma

Effectiveness against yeasts



60 s

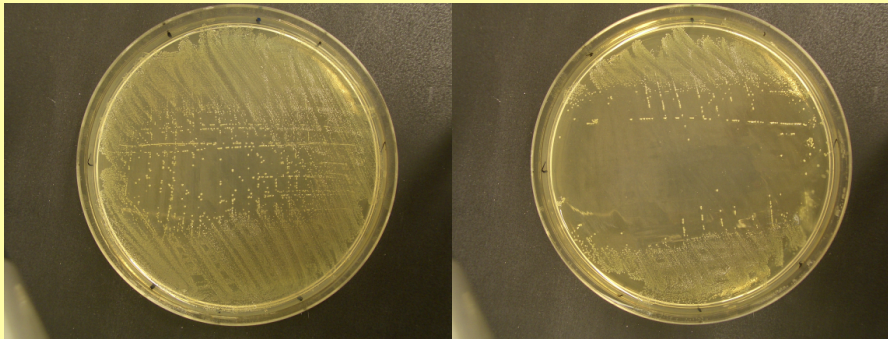


120 s

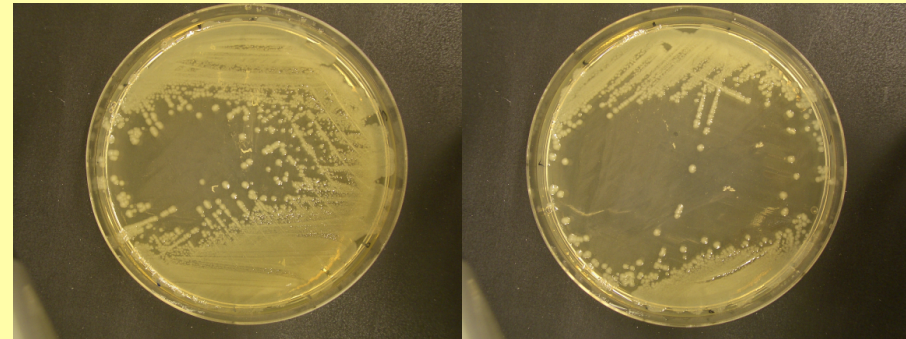
Candida albicans

Plasma-effect is lasting

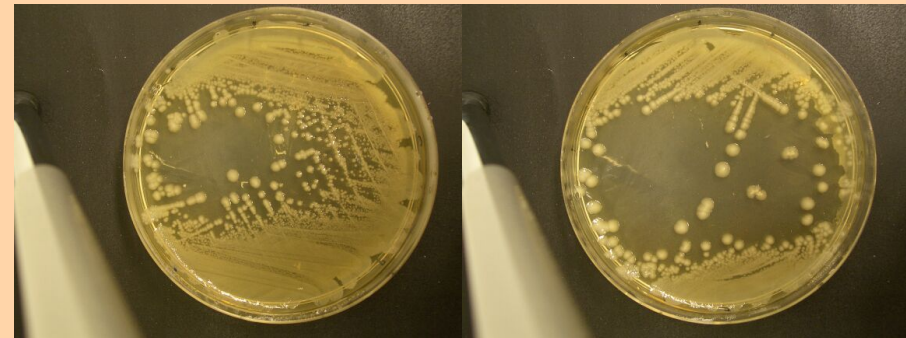
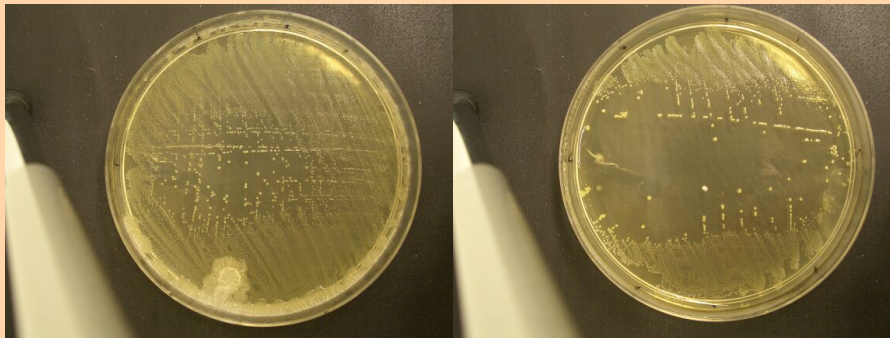
Enterococcus mundtii (gram-positive)



Escherichia coli (gram-negative)



After 24 hours



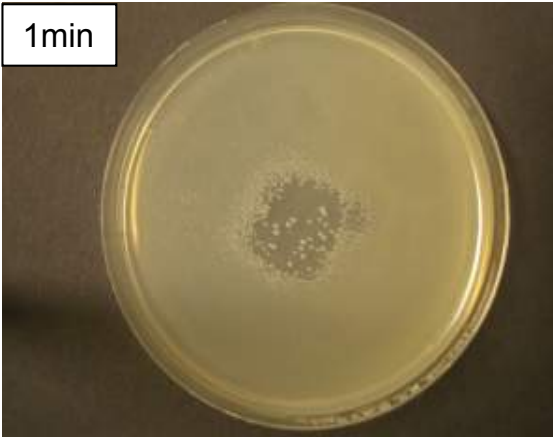
After 48 hours



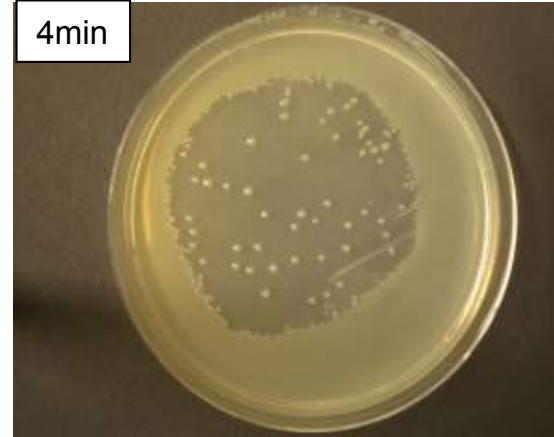
UV effect on bacteria (E. coli)

without quartz glass

1min

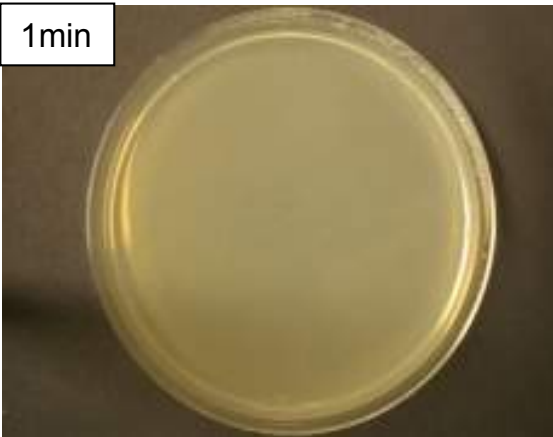


4min

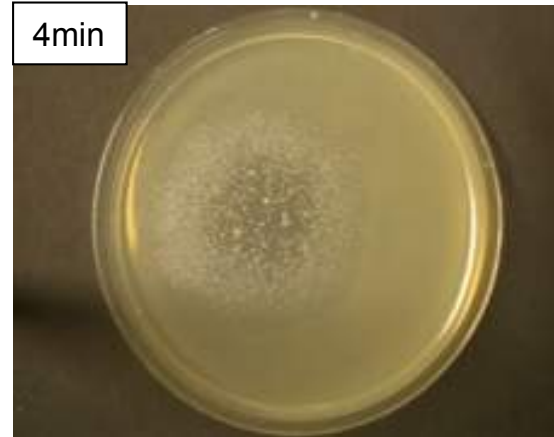


with quartz glass

1min



4min



Optical emission spectra of UV radiation produced by the MicroPlaSter and the sun

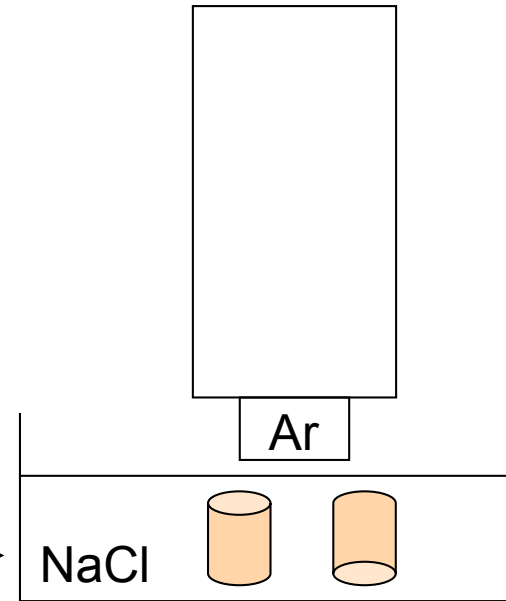
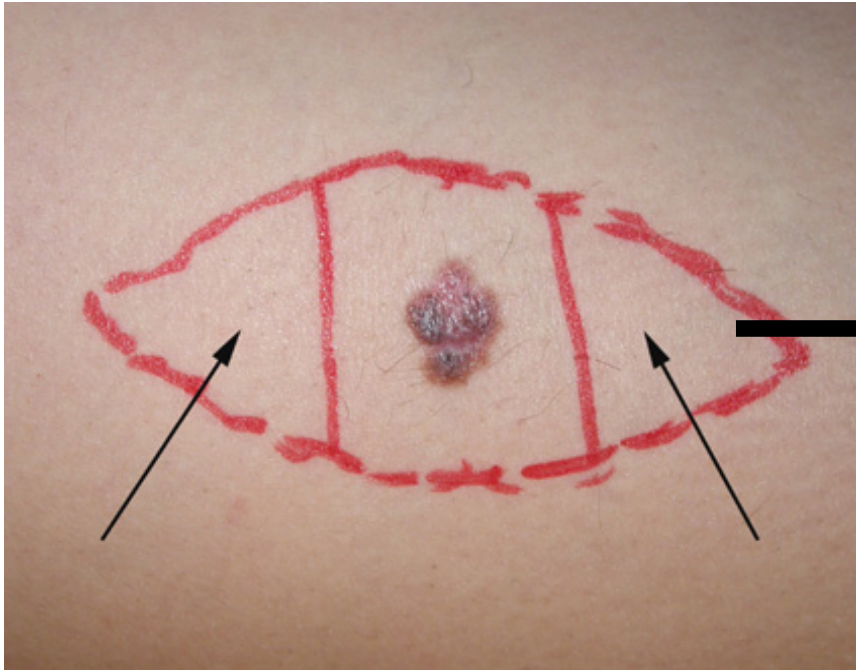
UV Power ($\mu\text{W}/\text{cm}^2$)

	UVC	UVB	UVA
Sun	1-2,5	30-50	~600
MicroPlaSter	10-16	40-60	<100

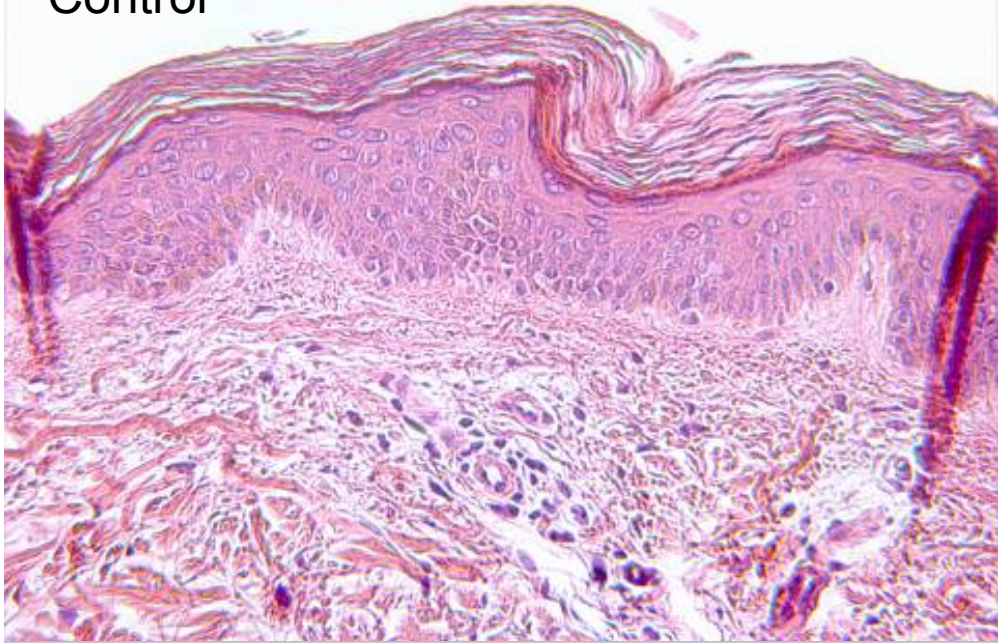
microwave power 60W, main (Ar) gas flow rate 1300sccm, z 20mm

1min of MicroPlaSter treatment gives the same UVC dose as 5min sunlight. For UVB 1min of treatment is equivalent to 1min solar exposure. For UVA 1min of treatment corresponds to 10s of sun exposure.
(Steffes B., Shimizu T. et al. 2008, 2009)

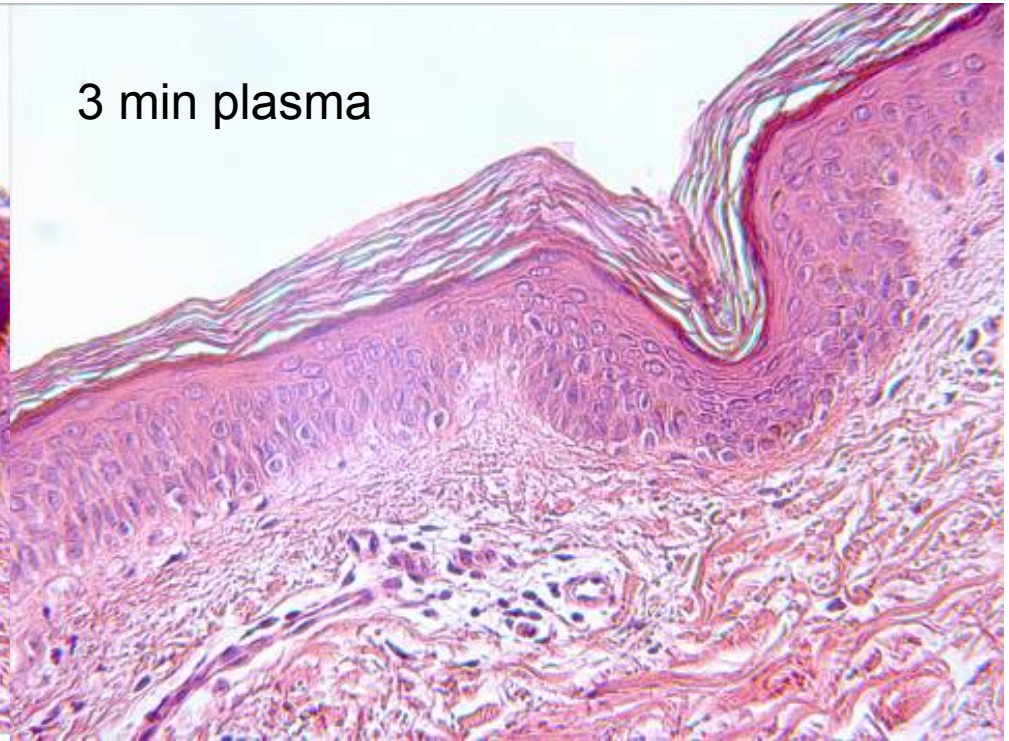
Other safety aspects tested in phase I



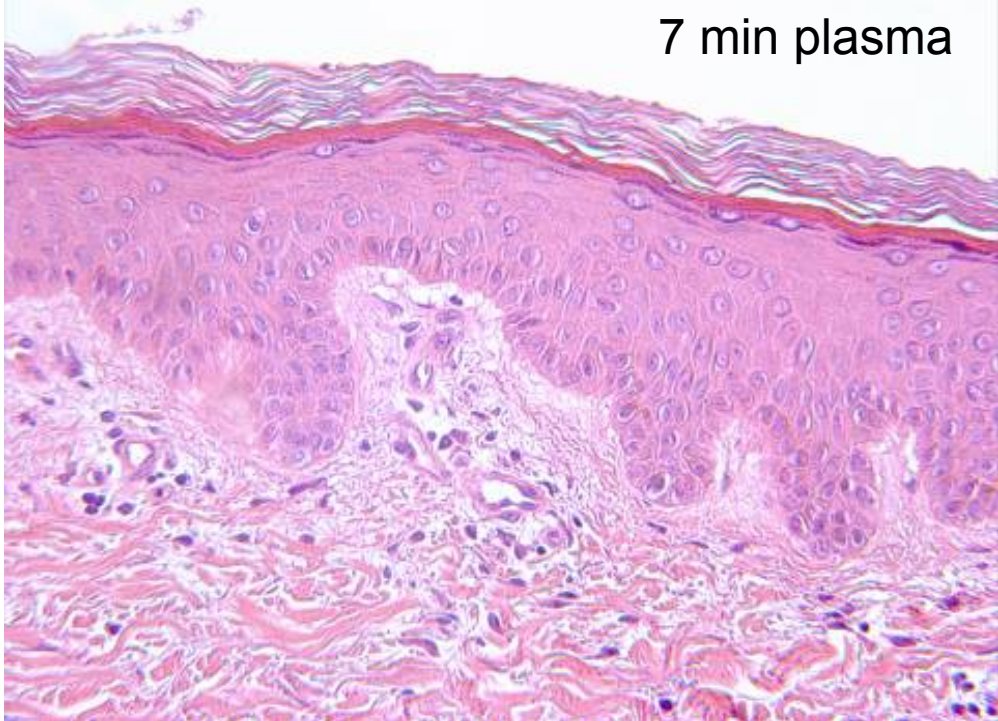
Control



3 min plasma



7 min plasma



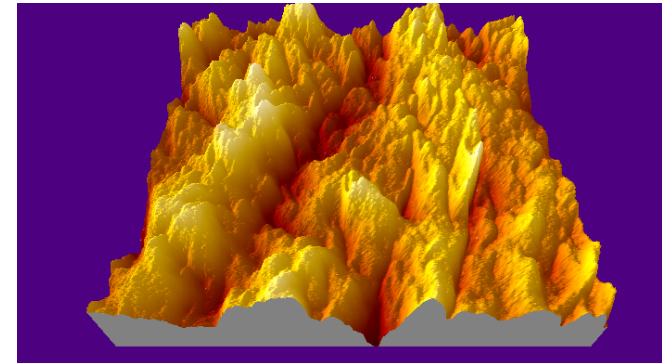
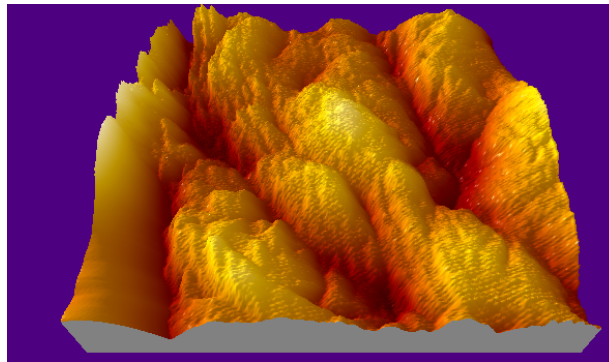
No changes in histologies of healthy skin treated with low-temperature argon plasma

Atomic force microscopy (AFM*) of human skin and HeLa cells after plasma treatment

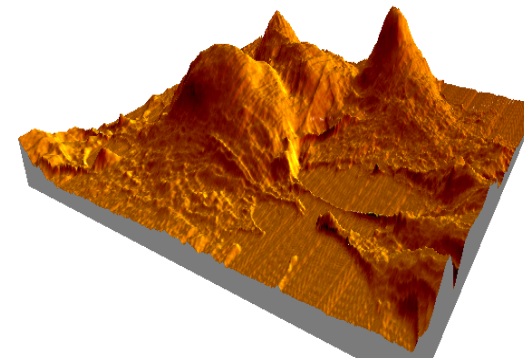
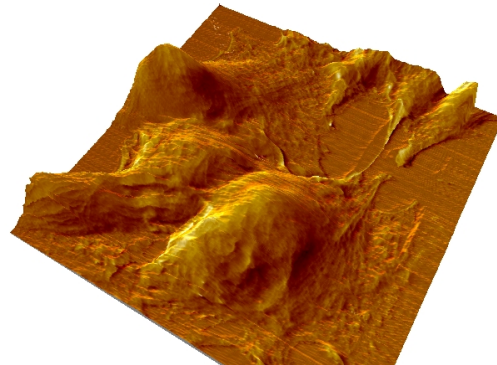
4 min argon plasma:

Untreated controls:

Human skin:

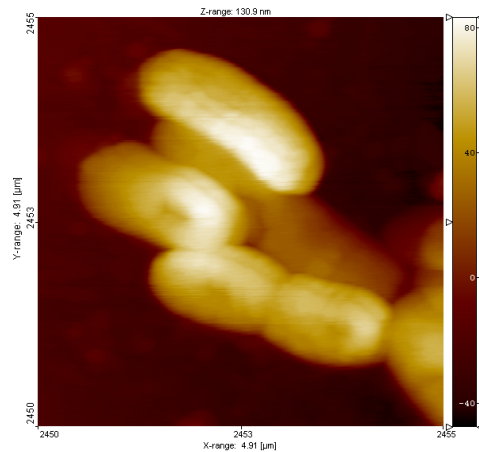


HeLa cells:

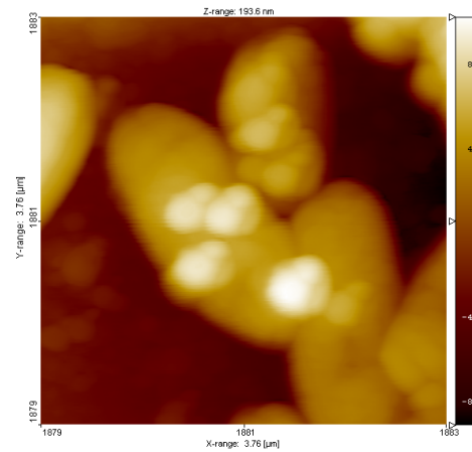


* This was done at the Department Geo- und Umweltwissenschaften, Ludwig-Maximilians-University of Munich (Prof. Dr. Heckl)

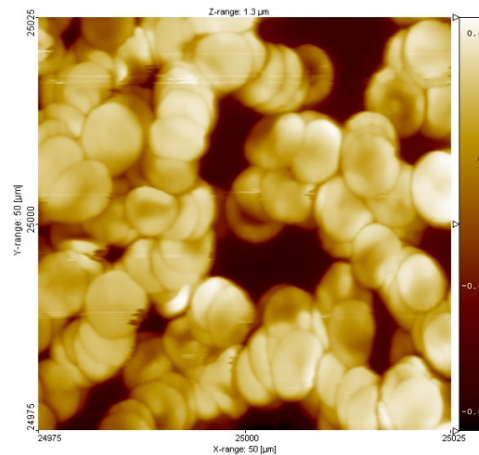
Microscopic images of E. coli bacteria and blood cells after plasma treatment



Control



Damaged E. coli bacteria after 4min of plasma treatment



Intact blood cells after 10min of plasma treatment

Evaluating Strategies to Improve Patient Outcomes: Community-Acquired and Nosocomial MRSA

Faculty: Kamal M.F. Itani, MD, FACS; Lena M. Napolitano, MD, FACS, FCCP, FCCM; Dennis L. Stevens, MD, PhD; CME Reviewer: Andrew W. Urban, MD

