# Towards Clinical Trials: Medical Phase I Requirements and Execution

Julia L. Zimmermann[1], Yang-Fang Li[1], Tetsuji Shimizu[1], Veronika Boxhammer[1], Julia Köritzer[1], Tim Maisch[2], Christian Welz[3], Jin Jeon[1], Tobias G. Klämpfl[1], Ulrich Harreus[3], Anja Bosserhoff[4], Wilhelm Stolz[5], Hubertus Thomas[1], Gregor E. Morfill[1] and Georg Isbary[5]

[1] *Max-Planck Institute for Extraterrestrial Physics, Garching, 85748, Germany*
[2] *University Hospital, Regensburg, 93042, Germany*
[3] *Ludwig-Maximilians-University, Munich, 81377, Germany*
[4] *University Regensburg, Regensburg, 93053, Germany*
[5] *Hospital Munich Schwabing, Munich, 80804, Germany*
E-mail: zimmermann@mpe.mpg.de

In the past seven years cold atmospheric pressure plasmas (CAPs) have demonstrated their ability to reduce secondary infections in chronic wounds [1] and alleviate skin diseases (Hailey-Hailey) [2] of patients in clinical phase II studies. Based on these encouraging results a handheld and battery-driven CAP device - using the Surface Micro Discharge (SMD) Technology and the surrounding air for plasma production - was developed, characterized and tested in a medical phase I study:

**Efficacy tests *in vitro* and *ex vivo***

To demonstrate the efficacy of the SMD device *in vitro*, different bacteria on agar were treated with CAP: a reduction of 5 log is achievable for all bacteria in 10s. Furthermore the influence of different humidity and angles on the bactericidal efficacy of the SMD device was evaluated. Experiments with bacteria on *ex vivo* porcine skin to simulate *in vivo* conditions revealed a 3 log reduction in 60s of treatment. Furthermore tests with *Candida albicans* on agar (5 log in 30s), adenoviruses in solution (6 log in 240s) [3] and endospores on metal plates (6 log in 3-5 min) were carried out with devices using the same SMD technology.

All required **electrical safety tests** (EN 60601-1) were carried out with a so-called notified body. Furthermore the measurement of **UV** and **toxic gas emission** showed, that - within CAP treatment times of up to 60s - the emission is far below the limits given by ICNIRP and NIOSH/OSHA for inhalation.

**Biological safety tests *in vitro* and *ex vivo***

To demonstrate the safe usage of the SMD device, several biological experiments - including *in vitro* cell culture, tissue and *ex vivo* blood and skin tests were carried out:

Cell culture experiments on fibroblasts revealed a "safe therapeutic window" for CAP treatment times of up to 30s. Furthermore times of up to 240s did not induce mutagenicity beyond naturally occurring spontaneous mutations. Histology analysis and gamma H2AX detection of DNA double strand breaks did not show any differences between CAP treated (up to 20 min) and untreated excised human skin. Experiments using mini organ cultures of mucosa did not possess an increase in apoptosis/necrosis for treatment times of up to 60s. Furthermore no increase in DNA double strand breaks were detectable for times of up to 120s. These results were summarized in a medical proposal to get approval for a clinical phase II study on infected wounds. Further medical trials on fungi-related (tinea) and virus-related (herpes, warts) diseases are planned.

**References**

[1] Isbary G., Morfill G., Schmidt HU et al., Br J Dermatol (2010), **1,** 78-82
[2] Isbary G., Morfill G., Zimmermann J et al., Arch Dermatol (2011), **4,** 388-90
[3] Zimmermann JL, Dumler K, Shimizu T et al., J.Phys. D: Appl. Phys. (2011), **44,** 505201