<u>Joint Research Project "ActiHeal"</u>: Development of technologies for the activation and clinical application of tissues and cells for the treatment of chronic wounds

<u>Project Partner</u>: Competence Center for Diabetis Karlsburg and Leibniz Institute for Plasma Science and Technology; Rostock University Medical Center - Department of Cell Biology; University of Rostock - Chair of Microfluidics

<u>Funding</u>: Ministry of Economics, Employment and Health Mecklenburg-Vorpommern together with the European Union (EFRE-Project)

The diabetic foot is one of the most common and most severe complications of diabetes mellitus and it is the most common cause for the need of hospitalization of diabetic patients [1]. The underlying cause of the diabetic foot are chronic wounds that are frequently accompanied by chronic infections. The diabetic foot leads to roughly 40.000 amputations a year in Germany alone. The consequential impairments to the quality of life of the patients and the costs to the health care system are immense. The goal of this joint project of medical industry as well as medical, biological and engineering reserach is the development of innovative technologies for the activation and clinical application of tissues and cells for the treatment of chronic wounds. This way the project partners aim to elevate the quality of life of diabetic patients and to help prevent and alleviate some of the typical complications that come with the diabetic condition.

The technologies that are to be developed in the course of this project may represent tools for therapies to be applied to several aspects of the diabetic foot. The regeneratively active cells of the stromal vascular fraction (SVF) of the adipose tissue possess a vascular as well neurogenic progenitor status [2,3]. Furthermore, the SVF contains cells types that possess the ability to release proangiogenic factors [4]. If a diabetic wound has occurred, secondary infections and inflammation are upon the most common complications, that keep the wound from closing and [5]. The SVF intended as one treatment element possesses cellular components exuding immunomodulatory factors that execute antiinflamatory as well as immunostimulatory functions antagonizing infection and inflammation [6,7]. Other components intended to be treatment elements are photo- and cold atmosheric plasma-biomodulation of the SVF cells. The modulation of the redox balance and inflamatory processes by cold atmosheric plasma in cells that are involved in the wound healing process has been shown. Also, for photobiomodulation a positive effect on the inflammatory and regenerative potential on cells involved in wound healing has been shown [8]. Different preparations of adipose tissue are being clinically applied for the treatment of chronic wounds already. These include adipose tissue dissociated by the liposuction only, micro tissue clusters dissociated from the tissue by mechanical shear force and SVF cells separated from the tissue by enzymatic digestion [9,10].

The described preparation and modulation options for the regeneratively active components of the adipose tissue ought to be realised in a closed system und conditions as physiological as possible. Such a modular yet closed system that allows the physician the preparation as well as the controlled application in during one surgery will be setting new standards.

- Diabetes-Deutschland, Wie oft tritt das diabetische Fußsyndrom (DFS) auf? Häufigkeiten,
 (2001) 1. https://www.diabetes-deutschland.de/archiv/1520.htm (accessed 14 April 2019).
- [2] V. Planat-Benard, J.S. Silvestre, B. Cousin, M. Andre, M. Nibbelink, R. Tamarat, M. Clergue, C. Manneville, C. Saillan-Barreau, M. Duriez, A. Tedgui, B. Levy, L. Penicaud, L. Casteilla, Plasticity of human adipose lineage cells toward endothelial cells: physiological and therapeutic perspectives, Circulation. 109 (2004) 656–663. doi:10.1161/01.CIR.0000114522.38265.61.

- B.A. Bunnell, B.T. Estes, F. Guilak, J.M. Gimble, Differentiation of adipose stem cells, Methods Mol. Biol. 456 (2008) 155–171. doi:10.1007/978-1-59745-245-8_12.
- W.K. Ong, S. Sugii, Adipose-derived stem cells: Fatty potentials for therapy, Int. J. Biochem.
 Cell Biol. 45 (2013) 1083–1086. doi:10.1016/j.biocel.2013.02.013.
- [5] N.D. Barwell, M.C. Devers, B. Kennon, H.E. Hopkinson, C. Mcdougall, M.J. Young, H.M.A. Robertson, D. Stang, S.J. Dancer, A. Seaton, G.P. Leese, Diabetic foot infection : Antibiotic therapy and good practice recommendations, Int. J. Clin. Pract. 71 (2017) 1–10. doi:10.1111/jicp.13006.
- [6] N.H. Riordan, T.E. Ichim, W.P. Min, H. Wang, F. Solano, F. Lara, M. Alfaro, J.P. Rodriguez, R.J. Harman, A.N. Patel, M.P. Murphy, R.R. Lee, B. Minev, Non-expanded adipose stromal vascular fraction cell therapy for multiple sclerosis, J. Transl. Med. 7 (2009) 1–9. doi:10.1186/1479-5876-7-29.
- [7] A.A. Leto Barone, S. Khalifian, W.P.A. Lee, G. Brandacher, Immunomodulatory effects of adipose-derived stem cells: Fact or fiction?, Biomed Res. Int. 2013 (2013). doi:10.1155/2013/383685.
- [8] U. Oron, Light therapy and stem cells: a therapeutic intervention of the future?, Interv. Cardiol. 3 (2011) 627–629. doi:10.2217/ica.11.74.
- [9] D.W. Borowski, T.S. Gill, A.K. Agarwal, M.A. Tabaqchali, D.K. Garg, P. Bhaskar, Adipose tissuederived regenerative cell-enhanced lipofilling for treatment of cryptoglandular fistulae-in-ano: The ALFA technique, Surg. Innov. 6 (2015) 593–600. doi:10.1177/1553350615572656.
- [10] G. Marino, M. Moraci, E. Armenia, C. Orabona, R. Sergio, G. De Sena, V. Capuozzo, M. Barbarisi, F. Rosso, G. Giordano, F. Iovino, A. Barbarisi, Therapy with autologous adipose-derived regenerative cells for the care of chronic ulcer of lower limbs in patients with peripheral arterial disease, J. Surg. Res. 185 (2013) 36–44. doi:10.1016/j.jss.2013.05.024.