## XLI JCET LECTURE, 19.09.2014, 9.00

## Development of Aptamers into Cellspecific Ligands for Imaging and Therapy

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DNA and RNA aptamers interact with their target proteins with high selectivity, specificity and affinity. The SELEX method consists of iterative cycles of in vitro screening of a combinatorial oligonucleotide library containing to 10<sup>16</sup> different molecules and possible secondary and tertiary structures for target binding followed by PCR amplification of selected sequences. Aptamer ligands can be developed against almost any target protein. Due to the wide spectrum of applications, these novel molecules are used in numerous pharmacological, clinical and industrial processes. In the beginning, RNA and DNA aptamers were identified which bind to proteins that naturally interact with nucleic acids or small molecules such as ATP. In the following years, the use of the SELEX technique was extended in order to isolate oligonucleotide ligands for a wide range of proteins of importance for therapy and diagnostics, such as growth factors, cell surface antigens, entire cells and even whole organisms. Recently, the use of in vitro selection methods have been extended to living organisms such as bacteria, trypanosomes and *Plasmodium falciparum*-infected erythrocytes. Moreover, since it became apparent that aptamers are capable to distinguish between little differences in cell surface-marker-proteins expressed by i.e. cancer cells, parasite-infected cells or stem cells in comparison to normal somatic cell, they have been developed into promising agents for diagnostic and therapeutic applications. In this talk, I will focus on new accomplishments of the aptamer technology, and demonstrate some examples from my own research in developing aptamers against stem and tumor cells and parasite antigens.

## Curriculum Vitae

Prof. Henning Ulrich studied Biology at the Universities of Hamburg and Kiel (Germany) and performed his master thesis in Biochemical Parasitology, followed by a PhD. in Biochemistry and Neuroscience at the University of Hamburg, Germany. He completed his training by postdoctoral research at the Center of Molecular Neurobiology at the University of Hamburg and Cornell University, NY, the latter one financed by a fellowship of the American Heart Association. He came to the Institute of Chemistry at the Sao Paulo University as a visiting scientist, where he was then appointed as faculty member. Here he habilitated in Biochemistry, is currently Associate Professor and head of the laboratory of neuroscience, working on stem cells and mechanisms of neurogenic differentiation.

Another principle line of the laboratory is development of combinatorial library approaches for obtaining bioactive ligands and inhibitors, denominated aptamers, of disease-relevant proteins. We use the SELEX (Systematic Evolution of Ligands by Exponential Enrichment) technology for targeting proteases, signal transduction and cell surface epitopes of stem and cancer cell and parasites. Dr. Ulrich has published more than 100 papers in peer-reviewed journals (H-factor of 23, ca. 1500 citations), 3 books and 14 book chapters and participated in three patents. Two patent applications focus on the diagnostic and therapeutic use of aptamers.ations/year).

## PUBLICATIONS

Peer-reviewed publications (total of 101).

- 1. <u>Ulrich H</u>, Nascimento IC, Bocsi J, Tárnok A (2014) Immunomodulation in stem cell differentiation into neurons and brain repair. Stem Cell Reviews, in press.
- 2. Oelkrug C, Sack U, Boldt A, Nascimento IC, <u>Ulrich H</u>, Fricke S (2014 Antibody- and aptamerstrategies for GvHD prevention. Journal of Cellular and Molecular Medicine (Online), in press.
- 3. Lee G, Maclean DM, <u>Ulrich H</u>, Zhao X, Aronowski J, Jayaraman V (2014) RNA Based Antagonist of NMDA Receptors. ACS Chem Neurosci. 5: 559-567.
- 4. Glaser T, de Oliveira SL, Cheffer A, Beco R, Martins P, Fornazari M, Lameu C, Junior HM, Coutinho-Silva R, <u>Ulrich H</u> (2014) Modulation of Mouse Embryonic Stem Cell Proliferation and Neural Differentiation by the P2X7 Receptor. PLoS One. 2014 May 5;9(5):e96281.
- Mencin N, Šmuc T, Vraničar M, Mavri J, Hren M, Galeša K, Krkoč P, <u>Ulrich H</u>, Šolar B (2014) Optimization of SELEX: Comparison of Different Methods for Monitoring the Progress of in vitro Selection of Aptamers. Journal of Pharmaceutical and Biomedical Analysis, 91C, 151-159.
- 6. <u>Ulrich H</u>, Bocsi J, Glaser T, Tárnok (2014) Cytometry in the brain: From Studying Differentiation towards Diagnostic Applications in Brain Disease and Regeneration therapy. Cell Proliferation, 47, 12-9.
- 7. Sousa BR, Parreira RC, Fonseca EA, Amaya MJ, Tonelli FMP, Lacerda S M. S. N., Lalwani P, Santos AK, Gomes KN, <u>Ulrich H</u>, Kihara AH, Resende RR (2014) Human adult stem cells from diverse origins: an overview from multiparametric immunophenotyping to clinical applications. Cytometry A 85A, 43-77.
- 8. Oliveira SL, Pillat MM, Cheffer A, Lameu C, Schwindt TT, <u>Ulrich H</u> (2013). Functions of neurotrophins and growth factors in neurogenesis and brain repair. Cytometry A 83, 76-89.
- 9. <u>Ulrich H</u>, Wrenger C. (2013). Identification of aptamers as specific binders and modulators of cell-surface receptor activity. Methods Mol Biol. 2013;986:17-39.

- Zimbres FM, Tárnok A, <u>Ulrich H</u>, Wrenger C. (2013) Aptamers: novel molecules as diagnostic markers in bacterial and viral infections? Biomed Res Int. 2013:731516. (H. Ulrich and C. Wrenger corresponding authors)
- Morais KL, Ianzer D, Miranda JR, Melo RL, Guerreiro JR, Santos RA, <u>Ulrich H</u>, Lameu C (2013). Proline rich-oligopeptides: diverse mechanisms for antihypertensive action. Peptides. 48:124-33.
- 12. Cheffer A, Tárnok A, <u>Ulrich H</u> (2013) Cell cycle regulation during neurogenesis in the embryonic and adult brain. Stem Cell Reviews 9:794-805.
- Nery AA, Magdesian MH, Trujillo CA, Sathler LB, Juliano MA, Juliano L, <u>Ulrich H</u>, Ferreira ST (2013) Rescue of amyloid-Beta-induced inhibition of nicotinic acetylcholine receptors by a peptide homologous to the nicotine binding domain of the alpha 7 subtype. PLoS One. 2013 Jul 22;8(7):e67194. (H. Ulrich and S.T. Ferreira corresponding authors)
- 14. Torres-Rivera W, Pérez D, Park KY, Carrasco M, Platt MO, Eterović VA, Ferchmin PA, <u>Ulrich</u> <u>H</u>, Martins AH (2013) Kinin-B2 receptor exerted neuroprotection after diisopropylfluorophosphate-induced neuronal damage. Neuroscience 247:273-9.
- 15. Braga MC, Nery AA, <u>Ulrich H</u>, Konno K, Sciani JM, Pimenta DC (2013) α -RgIB: A Novel Antagonist Peptide of Neuronal Acetylcholine Receptor Isolated from Conus regius Venom. International Journal of Peptides 2013:543028.
- 16. de Pascual R, Miranda-Ferreira R, Galvão KM, Lameu C, <u>Ulrich H</u>, Smaili SS, Jurkiewicz A, García AG, Gandía L (2013) Lower density of L-type and higher density of P/Q-type of calcium channels in chromaffin cells of hypertensive, compared with normotensive rats. Europian Journal of Pharmacology 706, 25-35.
- 17. <u>Ulrich H</u>, Wrenger C (2013) Identification of aptamers as specific binders and modulators of cell-surface receptor activity. Methods in Molecular Biology 986:17-39.
- 18. Glaser T, Resende RR, <u>Ulrich H</u> (2013) Implications of purinergic receptor-mediated intracellular calcium transients in neural differentiation. Cell Commun Signal. 2013 11:12.
- Gonçalves JC, Silveira AL, de Souza HD, Nery AA, Prado VF, Prado MA, <u>Ulrich H</u>, Araújo DA (2013) The monoterpene (-)-carvone: a novel agonist of TRPV1 channels. Cytometry A 83, 212-9. (Prado MA, <u>Ulrich H</u>, Araújo DA autores correspondentes)
- 20. Donnenberg VS, <u>Ulrich H</u> (2013) Mesenchymal stem cells, therapy, and cytometry. Cytometry A. 83:8-10.
- 21. Oliveira SL, Pillat MM, Cheffer A, Lameu C, Schwindt TT, <u>Ulrich H</u> (2013) Functions of neurotrophins and growth factors in neurogenesis and brain repair. Cytometry A. 83, 76-89.
- 22. Nery AA, Nascimento IC, Glaser T, Bassaneze V, Krieger JE, <u>Ulrich H</u> (2013). Human mesenchymal stem cells: from immunophenotyping by flow cytometry to clinical applications. Cytometry A. 83:48-61.
- 23. Nunes-Alves, A.; Nery, A.A.; <u>Ulrich, H</u> (2013) Tobacco nitrosamine N-nitrosonornicotine as inhibitor of neuronal nicotinic acetylcholine receptors. Journal of Molecular Neuroscience 49, .52-61, 2013.