Impromptu Seminar

Venue: **AKH, Anna Spiegel Building, Seminar Room 25.03.006, Währinger Gürtel 18 – 20, 1090 Wien**

(Harald Sitte, Tel.: (01) 40160 31323, *harald.sitte@meduniwien.ac.at*)

Peter Chiba, Tel.: (01) 40160 38005, peter.chiba@meduniwien.ac.at)

Tuesday 25.03.2014 14:00 s.t. **Andras Varadi** (host: P. Chiba)

Laboratory of Active Transport Proteins
Institute of Enzymology, RCNS
Hungarian Academy of Sciences
Budapest

"Chemical Chaperon Therapy Reduces Calcification in Mice Expressing Misfolded Human ABCC6 Mutants"

Andras Varadi (mailto:varadi.andras@ttk.mta.hu)

Abstract:
Pathological soft tissue calcification in pseudoxanthoma elasticum or in generalized arterial calcification of infancy is caused by ABCC6 mutations. We have transiently expressed seven human ABCC6 mutants (with preserved transport activity) in vivo in mouse liver by utilizing hydrodynamic tail vein injection and found that their plasma membrane targeting was impaired, however the wild-type (wt) human ABCC6 showed plasma membrane localization. We demonstrated that while the disease-associated missense ABCC6 mutants expressed in the liver of Abcc6-/- mice do not reduce calcification, administration of 4-phenyl butyrate (4-PBA) attenuates in vivo calcification by directing the mutants to the plasma membrane. We propose that the off-label use of 4-PBA may offer an allele-specific intervention for ABCC6-associated disorders. 4-PBA is approved by U.S. Food and Drug Administration for clinical use in urea cycle disorders and thalassemia 4-PBA, and independent of its primary clinical use, it is a histone deacetylase inhibitor, most probably influencing transcription of ER chaperones as well as components of the ER-associated degradation system.

Biographical notes:
András Váradi is head of a leading laboratory in ABC protein research at the Institute of Enzymology of the Hungarian Academy of Sciences in Budapest with a focus on the molecular mechanism of human multidrug ABC-transporters (MDR1 multidrug resistance protein/P-glycoprotein), membrane topology of ABCC1/MRP1 and characterization of its regulatory domain. In 2001 Dr. Váradi initiated a project to study the function of the ABCC6 protein; mutations in the *ABCC6* gene are associated with two genetic diseases associated with arterial calcification symptoms (pseudoxanthoma elasticum and general arterial calcification of infancy). The project allowed expression of the protein, demonstration of its ATP-dependent transport activity as well as mapping of disease causing missense mutations, which most often result in incorrect cellular localization of the protein. Preclinical models to correct the cellular localization of mutants suggest the possibility for allele-specific intervention in the two disorders. Ongoing research involves mapping of regulatory regions in the human *ABCC6* gene responsible for its organ-specific expression, and identification of elements of the corresponding signal transduction pathways.

Dr. Váradi is organizer of two most important biannually alternating scientific conferences of the field: the *ABCC6-Budapest Meetings* and the *International PXE Research Meetings* (Bethesda, Md, USA). He is member of the Foreign Advisory Board of The Biochemical Journal (London), and member of the Scientific Advisory Board of the Department of Health of Hungary. Dr. Váradi has been elected member of Academia Europeae in 2013. He is also involved in teaching a molecular biology graduate course at Semmelweis Medical University of Budapest. Beside his scientific activity he writes short fiction stories and publishes reviews on art photography.