

BIOGRAPHICAL SKETCH

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NAME Andras Varadi	POSITION TITLE Head of Research Group; The Laboratory of Active Transport Proteins
eRA COMMONS USER NAME	

EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Eotvos University of Budapest	MS	1967-72	Chemistry
Eotvos University of Budapest	PhD	1972-75	Chemistry
Inst. Enzymology, Hung.Acad.Sci.	postdoc	1975-83	Biochemistry
Cornell University/Ithaca N.Y.	postdoc	1983-85	Biochemistry

A. Personal Statement

Dr. Varadi established himself as the head of the one of the leading laboratories in ABC protein research, especially in basic biochemistry of these type of transporters. His research group has been organized in the Institute of Enzymology in 1989 focusing on the molecular mechanism of active transport protein. They started to investigate the molecular mechanism of human multidrug ABC-transporter (eg. MDR1 multidrug resistance protein or P-glycoprotein) and to study the membrane topology and functional domains of the second multidrug transporter, MRP1/ABCC1. They elaborated the membrane topology of ABCC1/MRP1, and identified its intracellular regulatory domain. In 2001 he initiated a project to study the function of ABCC6 protein; mutations in ABCC6 gene are associated with pseudoxanthoma elasticum. They expressed the protein, the very first time, and demonstrated its ATP-dependent transport activity and showed that loss of activity is the cause of PXE in the case of certain mutants. They published the first study on the transcriptional regulation of the human *ABCC6* gene, and determined the corresponding signal transduction pathway. A.V. was invited plenary speaker on the FEBS Special Meetings on ABC Proteins, Innsbruck (Austria) in 2006 and in 2008 and on the Gordon Research Conference "Elastin and Elastic Fibers" in 2005. He organized special symposia on the molecular background of PXE in Budapest in 2007, 2009 and in 2011.

B. Positions and Honors

Positions and Employment

1985 - 88 Research fellow (assistant professor level) in the Institute of Enzymology, Hungarian Academy of Sciences;
1988 - 91 Visiting scientist, Department of Internal Medicine, Yale University, School of Medicine (three visits);
1989 – 2000 Group leader (associate professor level) in the Institute of Enzymology, Hungarian Academy of Sciences;
2000 – present Head of Laboratory (full professor level) in the Institute of Enzymology, Hungarian Academy of Sciences;
2008 Fulbright visiting research professor at the Department of Dermatology, Thomas Jefferson University.

Other Experience and Professional Memberships

Member of the Molecular Biology-Biochemistry Committee of the Hungarian Academy of Sciences;
Member of the Scientific Advisory Committee of the Ministry of Health;
Member of the Advisory Board of The Biochemical Journal (London).
Head of Grant Committee, Functional Genomics Programme, European Science Foundation, 2003-2007
Member of the External Advisory Board of the Methusalem Project of the Ghent University). 2009-2016
Member of the PXE Science Discussion Panel organized at NIH, Bethesda, USA by the PXE International

Research Awards:

2002: PXE International Research Award,
2004: Award of the Hungarian Academy of Sciences

C. Selected Peer-reviewed Publications (Selected from 88 peer-reviewed publications)

Most relevant to the current application

Olivier Le Saux, Krisztina Fülöp, Yukiko Yamaguchi, Attila Iliás, Zalán Szabó, Christopher N. Brampton, Viola Pomozi, Krisztina Huszár, Tamás Arányi and András Váradi² (2011): Expression and *in vivo* Rescue of Human ABCC6 Disease-causing Mutants in Mouse Liver
PLoS One (accepted manuscript)

Szabó Z, Váradi A, Li Q, Uitto J. (2011) ABCC6 does not transport adenosine - Relevance to pathomechanism of pseudoxanthoma elasticum.
Mol Genet Metab. [Epub ahead of print]

Brampton C, Yamaguchi Y, Vanakker O, Van Laer L, Chen LH, Thakore M, De Paepe A, Pomozi V, Szabó PT, Martin L, Váradi A, Le Saux O. (2011) Vitamin K does not prevent soft tissue mineralization in a mouse model of pseudoxanthoma elasticum.
Cell Cycle. **10** 1810-20.

Arányi T, Fülöp K, Symmons O, Pomozi V, Váradi A. (2011) Predictable difficulty or difficulty to predict.
Protein Sci. **20** 1-3;

Váradi A, Szabó Z, Pomozi V, de Boussac H, Fülöp K, Arányi T. (2011) ABCC6 as a target in pseudoxanthoma elasticum.
Curr Drug Targets. **12** 671-82.

Li Q, Sadowski S, Frank M, Chai C, Váradi A, Ho SY, Lou H, Dean M, Thisse C, Thisse B, Uitto J. (2010) The abcc6a gene expression is required for normal zebrafish development.
J Invest Dermatol. **130** 2561-8.

de Boussac H, Ratajewski M, Köblös G, Sachrajda I, Tordai A, Pulaski L, Buday L, Váradi A and Arányi T (2010) The ERK1/2 – hepatocyte nuclear factor 4 α axis is a major regulator of human ABCC6 gene expression in the liver
J Biol Chem. **285**, 22800-8.

Köblös G, Andrikovics H, Prohászka Z, Tordai A, Váradi A and Arányi T (2010) The R1141X Loss-of-Function Mutation of the ABCC6 Gene Is a Strong Genetic Risk Factor for Coronary Artery Disease.
Genet Test Mol Biomarkers **14** 75-8

Li Q, Sadowski S, Frank M, Chai C, Váradi A, Ho SY, Lou H, Dean M, Thisse C, Thisse B, Uitto J. (2010) The abcc6a gene expression is required for normal zebrafish development.
J Invest Dermatol. **130**, 2561-8.

Fulop K, Barna L, Symmons O, Zavodszky P and Váradi A (2009) Clustering of disease-causing mutations on the domain-domain interfaces of ABCC6
Biochem Biophys Res Commun **379** 706-709

Li Q, Jiang Q, Pfendner E, Váradi A and Uitto J (2009), Pseudoxanthoma elasticum: clinical phenotypes, molecular genetics and putative pathomechanisms.
Exp.Dermatol. **18** 1-11

Symmons O, Váradi A and Arányi T (2008) How segmental duplications shape our genome: recent evolution of ABCC6 and PKD1 Mendelian disease genes.
Mol Biol Evol **25** 2601-2613

Arányi T, Ratajewski M, Bardóczy V, Pulaski L, Bors A, Tordai A and Váradi A (2005), Identification of a DNA methylation-dependent activator sequence in the pseudoxanthoma elasticum gene, ABCC6.
J Biol Chem **280**, 18643-50

Sinkó E, Iliás A, Ujhelly O, Homolya L, Scheffer GL, Bergen AA, Sarkadi B and Váradi A (2003), Subcellular localization and N-glycosylation of human ABCC6, expressed in MDCKII cells.

Iliás A, Urbán Z, Seidl TL, Le Saux O, Sinkó E, Boyd CD, Sarkadi B and Váradi A (2002),
Loss of ATP-dependent transport activity in pseudoxanthoma elasticum-associated mutants of human ABCC6 (MRP6).
J Biol Chem **277**, 16860-7

Additional recent publications of importance to the field (in chronological order)

Szakács G, Váradi A, Ozvegy-Laczka C and Sarkadi B (2008)
The role of ABC transporters in drug absorption, distribution, metabolism, excretion and toxicity (ADME-Tox).
Drug Discov Today **13**, 379-393

Sarkadi B, Homolya L, Szakács G and Váradi A (2006)
Human multidrug resistance ABCB and ABCG transporters: participation in a chemoinnity defense system.
Physiol Rev **86**, 1179-236

Tusnády GE, Sarkadi B, Simon I and Váradi A (2006)
Membrane topology of human ABC proteins.
FEBS Lett **580**, 1017-22

Szentpétery Z, Kern A, Liliom K, Sarkadi B, Váradi A and Bakos E (2004)
The role of the conserved glycines of ATP-binding cassette signature motifs of MRP1/ABCC1 in the communication between the substrate-binding site and the catalytic centers.
J Biol Chem **279**, 41670-8

Kern A, Szentpétery Z, Liliom K, Bakos E, Sarkadi B and Váradi A (2004)
Nucleotides and transported substrates modulate different steps of the ATPase catalytic cycle of MRP1/ABCC1 multidrug transporter.
Biochem J **380**, 549-60

Szakács G, Özvegy C, Bakos É, Sarkadi B and Váradi A (2001)
Role of glycine-534 and glycine-1179 of human multidrug resistance protein (MDR1) in drug-mediated control of ATP hydrolysis.
Biochem J **356**, 71-5

Klein I, Sarkadi B and Váradi A (1999)
An inventory of the human ABC proteins.
Biochim Biophys Acta **1461**, 237-62

D. Research Support

Ongoing Research Support

Project Number **NKTH-OTKA CK-80135**
Principal Investigator Andras Varadi
Source Hungarian Scientific Research Fund (OTKA)
Title of Project or Subproject A novel important protein factor in arterial calcification, the ABCC6 transporter: search for crucial metabolites and development of assays
Dates of Approved/Proposed Project 2010-2011

Project Number **OTKA NK-81204**
Principal Investigator Andras Varadi
Source Hungarian Scientific Research Fund (OTKA)
Title of Project Complex study of the ABCC6 gene and the encoded protein: from transcriptional regulation of the gene associated to genetic diseases to structure-based mechanism of the transporter.
Dates of Approved/Proposed Project 2010-2014

Project Number **R01AR055225-01A2**
Principal Investigator PI: Jouni Uitto; CoPI/subcontractor: Andras Varadi;
Source National Institute of Health

Title of Project Model Systems for PXE
Dates of Approved/Proposed Project 2008-2012

Completed Research Support

Project Number **OTKA NK-48729**
Principal Investigator Andras Varadi
Source Hungarian Scientific Research Fund (OTKA)
Title of Project ABC transporters of lipid metabolism
Dates of Approved/Proposed Project 2005-2008

Project Number **OTKA NI-68950**
Principal Investigator Andras Varadi
Source Hungarian Scientific Research Fund (OTKA)
Title of Project or Subproject ABC transporters: from regulation of gene expression to transport function
Dates of Approved/Proposed Project 2007-2009
Major Goals of Project: Structure-function and regulation of expression of ABCG5/G8 and ABCC6

Project Number **5137 FP6-2002-Mobility-1 MC RTN**
Principal Investigator in the participating laboratory
Source European Science Council
Title of Project or Subproject Lipid Flippases - Protein-mediated lipid translocation network
Dates of Approved/Proposed Project 2005-2008