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**RESEARCH INTERESTS**

**Understanding the Roles of RDH11 and RDH12 in Photoreceptor Cells.**

The Retinol Dehydrogenases RDH11 and RDH12 are closely related microsomal oxidoreductases located in photoreceptor inner segments. Mutations in the human *RDH12* gene induce the most severe and early onset type of inherited retinal degeneration, called Leber Congenital Amaurosis. Our lab is investigating the function of this enzyme and the molecular mechanisms leading to vision loss and photoreceptor cell death in RDH12-induced Leber Congenital Amaurosis. We are specifically interested by the detoxification role of RDH12, and other retinol dehydrogenases such as RDH11, located in photoreceptor inner segments. We have recently discovered that these enzymes can detoxify damaging aldehydes produced in photoreceptor cells during exposure to bright light. Such endogenous protection might be necessary to maintain the functional integrity of photoreceptor cells over years of normal exposure to bright cyclic daylight.

**Utilization of Imidazole-Containing Peptidomimetics to Preserve the Functional Integrity of Photoreceptor Cells.**

N-acetylcarnosine, carcinine and L-carnosine ( $\beta$ -alanyl-L-histidine), are naturally occurring compounds that belong to the family of imidazole-containing peptides or peptidomimetics, widely distributed in mammals in different physiological amounts depending on the species and the tissues considered. Their "true" physiological role remains an enigma but the following biological properties have been described for these compounds and a number of synthetic imidazole-containing derivatives: a reactive oxygen species- and a metal ions-chelating activity (antioxidant property), a lipid peroxidase-like and an aldehyde scavenging activity (detoxification of lipid peroxidation products property), an anti-glycation activity, and more recently inhibition of erroneous protein synthesis, activation of protective genes, and chaperone activities have been suggested as significant for biological roles of imidazole-containing compounds. This unique set of complementary biological activities converges in preventing and reversing oxidative modification of cellular macromolecules. This represents an unusually high potential for clinical and therapeutic pharmacological applications. The goal of our project is to experimentally evaluate the merit of these compounds in various animal models of genetic and acquired sight threatening diseases which have an oxidative stress component in their pathogenesis.

**EDUCATION/TRAINING:**

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Paris VII, France	BS	1993	Cell Biology
University of Paris XI, France	MS	1994	Endocrinology
University of Paris XI, France	PhD	1998	Endocrinology
University of Texas, Dallas, TX	Postdoc	2004	Molecular Genetics

## **RESEARCH AND/OR PROFESSIONAL EXPERIENCE:**

1991 – 1992 **Research Assistant**, Laboratoire de Pharmacologie et des Transports Ioniques, University of Paris VII, France.

1994 – 1998 **Graduate Student**, Laboratoire d'Endocrinologie Metabolisme et Developpment, CNRS UPR 1524, Meudon, France. Mentors: Dr. J. Girard and Dr. A-F. Burnol.

1998– 2004 **Postdoctoral Researcher**, Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX, USA. Mentors: Dr. J. L. Goldstein and Dr. M. S. Brown.

2004 – present **Assistant Professor of Research**, Department of Ophthalmology, University of Oklahoma Health Sciences Center, Oklahoma City, OK USA

## **AWARDS:**

Award from the **Bettencourt-Shueller Foundation** based on doctoral work and postdoctoral project, 1998.

Award from the **Philippe Foundation** based on postdoctoral project and preliminary results, 2000.

**Young Investigators Travel Award** for attending the XIth International Symposium on Retinal Degeneration (RD2004) in Perth, Western Australia, August 23-28, 2004

**ISER Travel Fellowship Award** for attending the XVI International Congress of Eye Research in Sydney, Australia, August 29-September 3, 2004.

**ARVO Foundation/Pauline and Oswald Lapp Travel Grant** to attend the Association for Research in Vision and Ophthalmology annual meeting in Fort Lauderdale, Florida, April 30 - May 4, 2006.

## **ACTIVE GRANTS:**

P20 RR017703-04 (R.E. Anderson) **07/01/07- 06/30/09**

NIH/NCRR/COBRE

Mentoring Vision Research in Oklahoma

Sub-project: **Photoreceptor Retinol Dehydrogenases and Vision** (Anne Kasus-Jacobi, PI of sub-project)

The major goals of this sub-project are (1) To determine if RDH11/RDH12 can prevent light-induced apoptosis by reducing aldehydes to alcohols in a cultured photoreceptor cell line that is sensitive to light damage. (2) To determine if RDH11 is protective against light-induced apoptosis in vivo using *Rdh11* knockout and transgenic mice. (3) To determine if RDH11 and RDH12 have overlapping functions by using transgenic *Rdh11* expression to rescue the phenotype of the *Rdh12* knockout mouse.

1R21EY018907-01A1 (Anne Kasus-Jacobi) **10/01/08- 09/30/10**

NIH/NEI

**Detoxification Role of Retinol Dehydrogenases RDH11 and RDH12**

The major goals of this project are (1) To characterize the catalytic activities of RDH11 and RDH12 towards 4-HNE in vitro and in mouse retina. (2) To determine whether RDH11 and RDH12 are protective against the formation of 4-HNE-protein adducts and the apoptosis of photoreceptors ex vivo and in vivo.

## PATENT:

### **Grb14, Grb14 Fusion Proteins, and Screening Methods.**

The invention concerns the use of Grb14 and homologous adapting proteins, as tool for screening molecules designed for the treatment of diseases involving insulin. The invention also concerns a method for detecting molecules capable of modulating the tyrosine kinase activity of the insulin receptor.

US patent No. US6,867,001 B1, date: 03/15/05

Inventors: Kasus-Jacobi A., Perdereau D., Girard J., Burnol A-F

## PEER-REVIEWED PUBLICATIONS:

**Kasus-Jacobi A.**, Perdereau D., Tartare-Deckert S., Van Obberghen E., Girard J., Burnol A-F. Evidence for a direct interaction between insulin receptor substrate-1 and Shc.

J Biol Chem. 1997 Jul 4;272(27):17166-70.

**Kasus-Jacobi A.**, Perdereau D., Auzan C., Clauser E., Van Obberghen E., Mauvais-Jarvis F., Girard J., Burnol A-F. Identification of the rat adapter Grb14 as an inhibitor of insulin actions. J Biol Chem. 1998 Oct 2;273(40):26026-35.

**Kasus-Jacobi A.**, Bereziate V., Perdereau D., Girard J., Burnol A-F. Evidence for an interaction between the insulin receptor and Grb7. A role for two of its binding domains, PIR and SH2. Oncogene. 2000 Apr 13;19(16):2052-9.

Bereziate V., **Kasus-Jacobi A.**, Perdereau D., Girard J., Burnol A-F. Inhibition of Insulin Receptor Tyrosine Kinase Activity by the Molecular Adapter Grb14. J Biol Chem. 2002 Feb 15;277(7):4845-52.

**Kasus-Jacobi A.**, Ou J., Bashmakov Y., Shelton J.M., Richardson J.A., Brown M.S., Goldstein J.L. Characterization of Mouse Short-chain Aldehyde Reductase (SCALD), an Enzyme Regulated by Sterol Regulatory Element-binding Proteins. J Biol Chem. 2003 Aug 22;278(34):32380-9.

Bertrand Cariou, Véronique Béréziat, Karine Moncoq, **Anne Kasus-Jacobi**, Dominique Perdereau, Véronique Le Marcis and Anne-Françoise Burnol. Regulation and functional roles of Grb14. Frontiers in Bioscience 2004 May 1 (9): 1626-36.

**Kasus-Jacobi A.**, Ou J., Birch D. G., Locke K. G., Shelton J. M., Richardson J. A., Murphy A. J., Valenzuela D. M., Yancopoulos G. D., and Edwards A. O. Functional Characterization of mRDH11 as a Retinol Dehydrogenase Involved in Dark Adaptation in vivo. J Biol Chem. 2005 May 27;280(21):20413-20.

Yogita Kanan, Lea D. Wicker, Muayyad R. Al-Ubaidi, Nawajes A. Mandal, and **Anne Kasus-Jacobi**. Retinol Dehydrogenases RDH11 and RDH12 in the Mouse Retina: Expression Levels During Development and Regulation by Oxidative Stress. IOVS March 2008;49(3):1071-77.

Yogita Kanan, **Anne Kasus-Jacobi**, Gennadiy Moiseyev, Kjell Sawyer, Jian-Xing Ma, and Muayyad R. Al-Ubaidi. Retinoid Recycling in Murine Cone Photoreceptors: an In Vitro Study. Exp. Eye Res. Feb 2008;86(2):344-54.

Md Nawajes A. Mandal, Jagan M.R. Patlolla, Lixin Zheng, Martin-Paul Agbaga, Julie-Thu A. Tran, Lea Wicker, **Anne Kasus-Jacobi**, Michael H. Elliott, Chinthalapally V. Rao, Robert E. Anderson. Curcumin Protects Retinal Cells from Light- and Oxidant Stress-induced Cell Death. Free Radical Biology and Medicine. 2008 Dec 24. [Epub ahead of print]

Mark A. Babizhayev, Andrea Guiotto, and **Anne Kasus-Jacobi**. N-Acetylcarnosine and histidyl-hydrazide are potent agents for multitargeted ophthalmic therapy of senile cataracts and diabetic ocular complications. *Journal of Drug Targeting*, 2009 Jan;17(1):36-63.

Babizhayev MA, **Kasus-Jacobi A**. State of the art clinical efficacy and safety evaluation of N-acetylcarnosine dipeptide ophthalmic prodrug. Principles for the delivery, self-bioactivation, molecular targets and interaction with a highly evolved histidyl-hydrazide structure in the treatment and therapeutic management of a group of sight-threatening eye diseases. *Curr Clin Pharmacol*. 2009 Jan;4(1):4-37.

### **BOOK CHAPTERS:**

**Anne Kasus-Jacobi**, David G. Birch, and Robert E. Anderson. Photoreceptor Retinol Dehydrogenases. An attempt to characterize the function of Rdh11. *Retinal Degenerative Diseases* edited by Joe G. Hollyfield, Robert E. Anderson, and Matthew M. LaVail. Springer, New York, NY, 2006.

Yogita Kanan, **Anne Kasus Jacobi**, Kjell Sawyer, David S. Mannel, Joyce Tombran Tink and Muayyad R. Al-Ubaidi. An in-vivo assay to identify compounds protective against light induced apoptosis. To be published in *Retinal Degenerative Diseases* edited by Joe G. Hollyfield, Robert E. Anderson, and Matthew M. LaVail. Springer, New York, NY, 2008.

### **MEETING PRESENTATIONS:**

#### POSTER PRESENTATIONS:

- **Anne Kasus-Jacobi**, David Birch, Albert O. Edwards, Jiafu Ou, David M. Valenzuela, John M. Shelton, Joseph L. Goldstein and Michael S. Brown. Functional Characterization of SCALD as a Retinol Dehydrogenase Involved in Dark Adaptation. XVI<sup>th</sup> International Congress of Eye Research, Sydney, Australia, September 2004.
- **Anne Kasus-Jacobi**, Jiafu Ou, David G. Birch, Michael B. Centola, Yun Z. Le, and Robert E. Anderson. Functional analysis of SREBPs in photoreceptor. Oklahoma NSF EPSCoR Annual Conference. Stillwater, Oklahoma, May 2005.
- Lea D. Wicker and **Anne Kasus-Jacobi**. RDH11 and RDH12: Localization and relative expression levels in the mouse retina. ARVO Meeting in Fort-Lauderdale, Florida, April 30-May 4, 2006.
- **Anne Kasus-Jacobi**, Yogita Kanan, Lea D. Wicker, and Muayyad R. Al-Ubaidi. Retinol dehydrogenases RDH11 and RDH12 protect 661W cells against the toxicity of aldehydes and light. ARVO Meeting in Fort-Lauderdale, Florida, May 5-May 10, 2007.
- Lea D. Wicker, Yogita Kanan, and **Anne Kasus-Jacobi**. Retinol dehydrogenases RDH11 and RDH12 in mouse retina: expression during development and regulation during light-induced oxidative stress. ARVO Meeting in Fort-Lauderdale, Florida, May 5-May 10, 2007.
- Yogita Kanan, **Anne Kasus-Jacobi**, Gennadiy Moiseyev and Muayyad R. Al-Ubaidi. Retinoid cycle analysis of a cone-specific cell line 661W. ARVO Meeting in Fort-Lauderdale, Florida, May 5-May 10, 2007.
- **Anne Kasus-Jacobi** and Lea D. Wicker. Role of retinol dehydrogenases RDH11 and RDH12 in the clearance of toxic 4-hydroxynonenal. ARVO Meeting in Fort-Lauderdale, Florida, April 27-May 1, 2008.

- Lea D. Wicker and **Anne Kasus-Jacobi**. Regulation of retinol dehydrogenase RDH12 by light and 4-hydroxynonenal-induced stress. ARVO Meeting in Fort-Lauderdale, Florida, April 27-May 1, 2008.
- Lea D. Marchette, Mark A. Babizhayev, and **Anne Kasus-Jacobi**. The pseudodipeptide carcinine protects photoreceptors from toxic products of oxidative stress. To be presented at the upcoming ARVO Meeting in Fort-Lauderdale, Florida, May 3-May 7, 2009.

PLATFORM PRESENTATIONS:

- **Anne Kasus-Jacobi**, Jiafu Ou, David Birch, Albert O. Edwards, David M. Valenzuela, Joseph L. Goldstein and Michael S. Brown. Functional Characterization of SCALD as a Retinol Dehydrogenase Involved in Dark Adaptation. XI International Symposium on Retinal Degenerations, Perth, Australia, August 2004.
- **Anne Kasus-Jacobi**, David Birch, Albert O. Edwards and Robert E. Anderson. Photoreceptor Retinol Dehydrogenases and Vision. The Foundation Fighting Blindness Annual Meeting, Dallas, Texas, April 2005.
- **Anne Kasus-Jacobi** and Lea D. Wicker. Statin treatment induces expression of target genes of sterol regulatory element-binding protein-2 (SREBP-2) in mouse retina. ARVO Meeting in Fort-Lauderdale, Florida, April 30-May 4, 2006.
- **Anne Kasus-Jacobi**, Debra A. Thompson, Mark A. Babizhayev, and Lea D. Wicker. New insight into the function of the Leber congenital amaurosis-causing gene *RDH12*. To be presented at the upcoming ARVO Meeting in Fort-Lauderdale, Florida, May 3-May 7, 2009.