

## Curriculum Vitae – Emilio Casanova

**Name** Emilio Casanova, Univ. Prof. Dr.  
**Affiliations** Ludwig Boltzmann Institute for Cancer Research (LBI-CR)  
Medical University of Vienna  
Center for Physiology and Pharmacology  
Währingerstr. 13a, A-1090 Vienna, Austria  
Phone: (+43-1)-4016071210 Fax: (+43-1)-40160931300  
**Email** emilio.casanova@lbicr.lbg.ac.at  
**Date of Birth** August 25, 1969  
**Citizenship** Spain

## University Studies

1997 PhD thesis “Molecular analysis of the protein kinases JNK/SAPK in mouse” supervised by Dr. Pedro Calvo Fernandez and Dr. Miguel A. Chinchetru Manero, University of Leon, Spain.  
1993-1997 PhD student in the Department of Biochemistry and Molecular Biology, University of Leon, Leon, Spain.  
1992-1993 Diploma thesis: “Effects of the chronic ethanol treatment on barbiturate modulation of muscimol binding to GABA<sub>A</sub> receptors in rat brain cortex”.  
1987-1992 Study of Biology, University of Leon, Leon, Spain

## Research and Professional Experience

2014-present Professor at the Medical University of Vienna (endowed chair), Vienna, Austria.  
2006-2014 Group leader at the Ludwig Boltzmann Institute for Cancer Research, Vienna, Austria  
2002-2006 Postdoc with Dr. Bernhard Bettler at the Biozentrum, Basel, Switzerland  
1997-2002 Postdoc with Dr. Günther Schütz at the German Cancer Research Center (DKFZ), Heidelberg, Germany.

## Achievements

Funded Grants	n=06	
Original publications	n=50	IF 368.3
First or last author in original articles	n=21	IF 118.1
Reviews	n=6	IF 18.9
Total Impact Factor		IF 387.2
H-Factor	24	(according to google scholar)
Citations	3520	(according to google scholar)
Edited books:	n=1	
Book chapters	n=2	

## **Honors and Awards**

Extraordinary award on Diploma thesis from University of Leon (1993)

Extraordinary award on PhD thesis from University of Leon (1997)

Guest-Professor at the University of Ulm (October 2016)

## **Evaluations**

My research performance within the LBI-CR was positively evaluated in 2008 by Dr. Gerard Evan, Dr. Thomas Graf and Dr. Tak Mak. Furthermore, in 2011 the LBI-CR successfully passed an external evaluation by Dr. Thomas Look, Dr. Gerard Evan and Dr. Thomas Graf and it was prolonged by additional seven years. The final evaluation of the institute took place in 2015 by Dr. Gerard Evan, Dr. Aly Karsan and Dr. Achim Leutz, when my research performance was evaluated as “**2, Outstanding (extremely strong with negligible weaknesses)**” according to 1 – 9 rating scale.

## **Expert opinion for:**

PlosOne, Biotechniques, Frontiers in Biosciences, Hepatology, Journal of Hepatology, Molecular Therapy-Nucleic Acids, BMC cancer, Gut, Molecular cancer, Stem cell reports, International journal of cancer, Oncotarget, Biotechnology and Genetic Engineering Reviews, Process Biochemistry, National Research Development and Innovation Office (NKFIH). Lower Austria Research and Education m.b.H.(NFB), ACS Synthetic Biology, Cancer Research, Hormone and Metabolic Research.

## **Editor of:**

Book: “Mouse Models of Cancer”, Methods in Molecular Biology, Humana Press. January 2015 (Editors: Robert Eferl and Emilio Casanova)

## **Membership in scientific associations:**

Member of the “European Association for the Study of the Liver”, (EASL).

## **Grants:**

Co-founder of the Ludwig Boltzmann Institute for Cancer Research (LBI-CR)

The LBI-CR with funding of up to 1.2 million Euros was founded by the Ludwig Boltzmann Society and five partners in 2005 after a competitive review process. After 14 years and its scheduled end in 2018 it will have spent more than 20 million Euros with an overall contribution of further external grants of more than 20%. The institute is formed by five groups and is dedicated to the generation and analysis of transgenic mice that model human diseases with a special focus on basic cancer research. After an interim evaluation the initial seven year contract was extended to an additional seven year term, which will end in 2018.

## CV Emilio Casanova

Funding Agency/Title	Holder/s	Euros (total)	Date
FFG: GENAU "Austromouse": "Conditional mutagenesis of the <i>Stat5/3</i> locus"	EC/RE	184K	9/2009 - 12/2012
FFG-Bridge: "BAC-based Expression System Technology"	EC	531K	3/2011 - 3/2014
CCC Research Funding: "Regulation of cholestasis-induced HCC formation by Stat3"	RE/EC/MT	96K	9/2011 - 9/2014
FWF: "Growth hormone resistance and liver fibrosis"	EC/MT	287K	4/2013 - 8/2017
Horizon 2020 : EAVI2020	EC/Consortia	201K	1/2015 - 1/2020
FFG: "CarboLIB"	EC	665K	1/2016 – 1/2019

RE: Robert Eferl; MT: Michael Trauner. EC: Emilio Casanova  
 FFG: "Die Österreichische Forschungsförderungsgesellschaft"  
 FWF: "Fonds zur Förderung der wissenschaftlichen Forschung"  
 CCC: Comprehensive cancer center Vienna.  
 EAVI2020: European AIDS Vaccine Initiative 2020

### Industrial funding:

Company Name/project	Project Leader	Euros (total)	Date
POLYMUN Scientific Immunbiologische Forschung GmbH: "Development of BAC-based expression vectors applied to protein production in mammalian cells"	EC	55K	1/2015 - 12/2015
The Antibody Lab GmbH: "Production of Secretory IgA "	EC	439K	1/2015 - 12/2018
University of natural resources "Humira antibody production"	EC	15K	1/2016 - 3/2016

### Patents:

#### Title: "Method for the generation of a non-human animal with an oncogene"

Application number: 07450118.0-2405

Date: 2.07.07

Applicant/Proprietor: Ludwig Boltzmann Gesellschaft GmbH

Inventors : Robert Eferl, Emilio Casanova, Dagmar Stoiber, Richard Moriggl, Johannes Schmid, Lukas Kenner, Rainer Zenz, Monica Musteanu and Leander Blaas

#### Title: "Artificial Chromosome Vector"

Application number A 1859/2008

Date 28.11.2008

Applicant/Proprietor: Emilio Casanova, Anton Bauer

Inventors: Leander Blass, Anton Bauer, Emilio Casanova

## Peer-Reviewed Publications Original Articles

- 1 Post M, Cuapio A, Osl M, Lehmann D, Resch U, Davies D, Bilban M, Schlechta B, Eppel W, Nathwani A, Stoiber D, Spanholtz J, **Casanova E**, Hofer E. The transcription factor ZNF683/HOBIT regulates human NK-cell development. *Front Immunol*. [Impact Factor: 6.4] 2017 May 15;8:535
- 2 Svinka J, Pflügler S, Mair M, Marschall HU, Hengstler JG, Stiedl P, Poli V, **Casanova E**, Timelthaler G, Sibilia M, Eferl R. Epidermal growth factor signaling protects from cholestatic liver injury and fibrosis. *J Mol Med*. [Impact Factor: 4.7] 2017 Jan;95(1):109-117
- 3 Cuapio A, Post M, Cerny-Reiterer S, Gleixner KV, Stefanzi G, Basilio J, Herndlhofer S, Sperr WR, Brons NHC, **Casanova E**, Zimmer J, Valent P, Hofer E. Maintenance therapy with histamine plus IL-2 induces a striking expansion of two CD56bright NK cell subpopulations in patients with acute myeloid leukemia and supports their activation. *Oncotarget* [Impact Factor: 5.2] 2016 Jul 19;7(29):46466-46481
- 4 Zboray K, Sommeregger W, Bogner E, Gili A, Sterovsky T, Fauland K, Grabner B, Stiedl P, Moll H, Bauer A, Kunert R, **Casanova E**. Heterologous protein production using euchromatin-containing expression vectors in mammalian cells *Nucleic Acids Res*. [Impact Factor: 10.2] 2015 Sep 18;43(16):e102
- 5 Grabner B, Schramek D, Mueller KM, Moll H, Svinka J, Hoffmann T, Bauer E, Blaas L, Hruschka N, Zboray K, Stiedl P, Nivarthi H, Bogner E, Gruber W, Mohr T, Harun Zwick R, Kenner L, Poli V, Aberger F, Stoiber D, Egger G, Esterbauer H, Zuber J, Moriggl R, Eferl R, Györfy B, Penninger J, Popper H, **Casanova E**. Disruption of STAT3 signaling promotes KRAS induced lung tumorigenesis. *Nature Communications*. [Impact Factor: 12.1] 2015 Mar 3;6:6285.
- 6 Pathria P, Gotthardt D, Prchal-Murphy M, Putz EM, Holcman M, Schleder M, Grabner B, Crncec I, Svinka J, Musteanu M, Hoffmann T, Filipits M, Berger W, Poli V, Kenner L, Bilban M, **Casanova E**, Müller M, Strobl B, Bayer E, Mohr T, Sexl V, Eferl R. Myeloid STAT3 promotes formation of colitis-associated colorectal cancer in mice. *Oncotmunology*. [Impact Factor: 7.7] 2015 Jan 22;4(4):e998529
- 7 Stiedl P, McMahon R, Blaas L, Stanek V, Svinka J, Grabner B, Zollner G, Kessler SM, Claudel T, Müller M, Mikulits W, Bilban M, Esterbauer H, Eferl R, Haybaeck J, Trauner M, **Casanova E**. Growth hormone resistance exacerbates cholestasis-induced murine liver fibrosis. *Hepatology*. [Impact Factor: 13.3] 2015 Feb;61(2):613-26 .
- 8 Jais A, Einwallner E, Sharif O, Gossens K, Lu TT, Soyal SM, Medgyesi D, Neureiter D, Paier-Pourani J, Dalgaard K, Duvigneau JC, Lindroos-Christensen J, Zapf TC, Amann S, Saluzzo S, Jantscher F, Stiedl P, Todoric J, Martins R, Oberkofler H, Müller S, Hauser-Kronberger C, Kenner L, **Casanova E**, Sutterlüty-Fall H, Bilban M, Miller K, Kozlov AV, Krempler F, Knapp S, Lumeng CN, Patsch W, Wagner O, Pospisilik JA, Esterbauer H. Heme oxygenase-1 drives metaflammation and insulin resistance in mouse and man. *Cell* [Impact Factor: 30.4]. 2014 Jul 3;158(1):25-40.
- 9 Kovacic B, Hoelbl-Kovacic A, Fischhuber KM, Leitner NR, Gotthardt D, **Casanova E**, Sexl V, Müller M. Lactotransferrin-Cre reporter mice trace neutrophils, monocytes/macrophages and distinct subtypes of dendritic cells. *Haematologica*. [Impact Factor: 7.7] 2014 Feb 21
- 10 Kantner HP, Warsch W, Delogu A, Bauer E, Esterbauer H, **Casanova E**, Sexl V, Stoiber D. ETV6/RUNX1 induces reactive oxygen species and drives the accumulation of DNA damage in B cells. *Neoplasia* [Impact Factor: 5] 2013 Nov;15(11):1292-300
- 11 Mader A, Prewein B, Zboray K, **Casanova E**, Kunert R. Exploration of BAC versus plasmid expression vectors in recombinant CHO cells. *Appl Microbiol Biotechnol*. [Impact Factor: 3.4] 2012 Oct 19
- 12 Musteanu M, Blaas L, Zenz R, Svinka J, Hoffmann T, Grabner B, Schramek D, Kantner HP, Müller M, Kolbe T, Rülcke T, Moriggl R, Kenner L, Stoiber D, Penninger JM, Popper H, **Casanova E\***, Eferl R\*. A mouse model to identify cooperating signaling pathways in cancer. *Nat Methods*. [Impact Factor: 25.1] 2012 Sep;9(9):897-900. \*Equally contributed

- 13 Mueller KM, Kornfeld JW, Friedbichler K, Blaas L, Egger G, Esterbauer H, Hasselblatt P, Schlederer M, Haindl S, Wagner KU, Engblom D, Haemmerle G, Kratky D, Sexl V, Kenner L, Kozlov AV, Terracciano L, Zechner R, Schuetz G, **Casanova E**, Pospisilik JA, Heim MH, Moriggl R. Impairment of hepatic growth hormone and glucocorticoid receptor signaling causes steatosis and hepatocellular carcinoma in mice. *Hepatology*. [Impact Factor: 13.3] 2011 Oct;54(4):1398-409.
- 14 Eckelhart E, Warsch W, Zebedin E, Simma O, Stoiber D, Kolbe T, Rüllicke T, Mueller M, **Casanova E\***, Sexl V\*. A novel Ncr1-Cre mouse reveals the essential role of STAT5 for NK cell survival and development. *Blood*. [Impact Factor: 13.2] 2011 3;117(5):1565-73. \*Equally contributed
- 15 Grabner B, Blaas L, Musteanu M, Hoffmann T, Birbach A, Eferl R and **Casanova E**. A mouse tool for conditional mutagenesis in ovarian granulosa cells. *Genesis* [Impact Factor: 2.1] 2010 1;48(10):612-7.
- 16 Guetg N, Aziz S, Holbro N, Turecek R, Riad S, Gassmann M, Moes S, Jenoe P, Oertner T, **Casanova E** and Bettler B. NMDA Receptor-Dependent GABAB Receptor Internalization via CaMKII Phosphorylation of Serine 867 in GABAB1. *Proc Natl Acad Sci U S A*. [Impact Factor: 9.7] 2010 3;107(31)
- 17 Mair M; Zollner G; Schneller D; Musteanu M; Fickert P; Gumhold J; Schuster C; Fuchsbichler A; Bilban M; Tauber S; Esterbauer H; Kenner L; Poli V; Blaas L; Kornfeld JW; **Casanova E**; Mikulits W; Trauner M; Eferl R. Stat3 protects from liver injury and fibrosis in a mouse model of sclerosing cholangitis. *Gastroenterology*. [Impact Factor: 18.4] 2010 138(7):2499-508
- 18 Musteanu M, Blaas L, Mair M, Schlederer M, Bilban M, Tauber S, Esterbauer H, Mueller M, **Casanova E**, Kenner L, Poli V and Eferl R. Stat3 is a negative regulator of intestinal tumor progression in ApcMin mice. *Gastroenterology*. [Impact Factor: 18.4] 2010 138(3):1003-11
- 19 Blaas L, Kornfeld JW, Schramek D, Musteanu M, Zollner G, Gumhold J, Schneller D, Esterbauer H, Mair M, Kenner L, Mikulits W, Eferl R, Moriggl R, Penninger J, Trauner M and **Casanova E**. Disruption of the GH-STAT5-IGF-1 axis severely aggravates liver fibrosis in a mouse model of cholestasis. *Hepatology*. [Impact Factor: 13.3] 2010 51(4):1319-260
- 20 Birbach A, **Casanova E** and Schmid JA. A Probasin-MerCreMer BAC allows inducible recombination in the mouse prostate. *Genesis*. [Impact Factor: 2.1] 2009 47(11):757-64
- 21 **Casanova E\***, Guetg N\*, Vigot R, Seddik R, Julio-Pieper M, Hyland NP, Cryan JF, Gassmann M and Bettler B. A Mouse Model for Visualization of GABA(B) Receptors. *Genesis*. [Impact Factor: 2.1] 2009 47(9):595-602. \* Equally contributed
- 22 Blaas L, Musteanu M, Eferl R, Bauer A and **Casanova E**. Bacterial artificial chromosomes improve recombinant protein production in mammalian cells. *BMC Biotechnol*. [Impact Factor: 2.4] 2009 14;9(1):3
- 23 Wellendorph P, Johansen L, Jensen A, **Casanova E**, Gassmann M, Deprez P, Clement-Lacroix P, Bettler B and Bräuner-Osborne H. No evidence for a bone phenotype in GPRC6A knockout mice under normal physiological conditions. *J Mol Endocrinol*. [Impact Factor: 3.6] 2009 42(3):215-23
- 24 Maison SF, **Casanova E**, Holstein GR, Bettler B and Liberman MC. Lack of GABA<sub>B</sub> receptors in cochlear neurons suggests modulation of outer hair cell function by type-II afferent fibers. *J Assoc Res Otolaryngol*. [Impact Factor: 2.5] 2009 10(1):50-63
- 25 Bentzinger CF, Romanino K, Cloëtta D, Lin S, Mascarenhas JB, Oliveri F, Xia J, **Casanova E**, Costa CF, Brink M, Zorzato F, Hall MN and Rüegg MA. Skeletal Muscle-Specific Ablation of raptor, but Not of rictor, Causes Metabolic Changes and Results in Muscle Dystrophy. *Cell Metab*. [Impact Factor: 18.2] 2008 8(5):411-24
- 26 Blaas L., Musteanu M., Zenz R., Eferl R. and **Casanova E**. PhiC31 Mediated Cassette Exchange into a BAC. *Biotechniques*. [Impact Factor: 2] 2007 43(5):659-60, 662, 664
- 27 Lemberger T, Parlato R, Dassel D, Westphal M, **Casanova E**, Turiault M, Tronche F, Schiffmann SN, Schutz G. Expression of Cre recombinase in dopaminergic neurons. *BMC Neurosci*. [Impact Factor: 2.3] 2007 3;8(1):4
- 28 Yuan X, Zhou Y, **Casanova E**, Chai M, Kiss E, Grone HJ, Schutz G, Grumt I. Genetic Inactivation of the Transcription Factor TIF-1A Leads to Nucleolar Disruption, Cell Cycle Arrest, and p53-Mediated Apoptosis. *Mol Cell*. [Impact Factor: 14.7] 2005 1;19(1):77-87

- 29 Alberti, S., Krause, SM., Kretz, O., Philippar, U., Lemberger, T., **Casanova, E.**, Wiebel, FF., Schwarz, H., Frotscher, M., Schütz, G., and Nordheim, A. Neuronal migration in the murine rostral-migratory stream requires serum response factor. *Proc Natl Acad Sci U S A*. [Impact Factor: 9.7] 2005 26;102(17):6148-53
- 30 Callejo AI, **Casanova E**, Calvo P, Galetto R, Rodriguez-Rey JC, Chinchetru MA. Characterization of the promoter of the mouse c-Jun NH(2)-terminal/stress-activated protein kinase alpha gene. *Biochim Biophys Acta*. [Impact Factor: 5] 2004 24;1681(1):47-52
- 31 Zhang Z, Hofmann C, **Casanova E**, Schütz G and Lutz B. Generation of a conditional allele of the *CBP* gene in mouse. *Genesis* [Impact Factor: 2.1] 2004 40(2):82-9
- 32 Haller\* C, **Casanova E\***, Müller M\*, Vacher C, Vigot R, Barbieri S, Gassmann M, and Bettler B. A Floxed Allele for Conditional Inactivation of the *GABA<sub>B(1)</sub>* Gene. *Genesis* [Impact Factor: 2.1] 2004 40(3):125-30. \*Equally contributed
- 33 Marsicano G, Goodenough S, Monory K, Hermann H, Eder M, Cannich A, Azad SC, Cascio MG, Gutierrez SO, van der Stelt M, Lopez-Rodriguez ML, **Casanova E**, Schutz G, Zieglgansberger W, Di Marzo V, Behl C, Lutz B. CB1 cannabinoid receptors and on-demand defense against excitotoxicity. *Science* [Impact Factor: 37.2] 2003 3;302(5642):84-8
- 34 **Casanova E**, Fehsenfeld S, Lemberger T and Schütz G. Alpha complementation in the Cre recombinase enzyme. *Genesis* [Impact Factor: 2.1] 2003 37(1):25-9
- 35 **Casanova E\***, Fehsenfeld S, Lemberger T, Shimshak DR, Sprengel R and Mantamadiotis T. A Er-based Double iCre Fusion Protein Allows Partial Recombination in Forebrain. *Genesis* [Impact Factor: 2.1] 2002 34(3):208-14 \*Corresponding author
- 36 **Casanova E**, Fehsenfeld S, Greiner E, Stewart AF and Schütz G. Conditional Mutagenesis of *CamKIV*. *Genesis* [Impact Factor: 2.1] 2002 32(2):161-4
- 37 **Casanova E**, Fehsenfeld S, Greiner E, Stewart AF and Schütz G. Construction of a Conditional Allele of *RSK-B/MSK2* in the mouse. *Genesis* [Impact Factor: 2.1] 2002 32(2):158-60
- 38 Shimshak DR, Kim J, Hübner MR, Spengel DJ, Buchholz F, **Casanova E.**, Stewart AF, Seeburg PH and Sprengel R. Codon-improved Cre recombinase (iCre) expression in the mouse. *Genesis* [Impact Factor: 2.1] 2002 32(1):19-26
- 39 **Casanova E**, Lemberger T, Fehsenfeld S, Greiner E and Schütz G. Rapid localization of a gene within BACs and PACs. *Biotechniques* [Impact Factor: 2.2] 2002 32(2):240-2
- 40 **Casanova E**, Fehsenfeld S, Mantamadiotis T, Lemberger T, Greiner E, Stewart AF and Schütz G. A *CamKIIa* iCre BAC allows brain-specific gene inactivation. *Genesis* [Impact Factor: 2.1] 2001 31(1):37-42
- 41 **Casanova E**, Callejo AI, Calvo P and Chinchetru MA. Analysis of splicing of four mouse *JNK/SAPK* alpha variants. *Neuroreport* [Impact Factor: 1.4] 2000 7;11(2):305-9
- 42 Kellendonk C, Tronche F, **Casanova E**, Anlag K, Opherk C and Schütz G. Inducible Site-specific Recombination in the Brain. *J. Mol. Biol.* [Impact Factor: 4.6] 1999 8;285(1):175-82
- 43 Alonso-Llamazares A, Lopez-Alonso J, del Barrio M, **Casanova E**, Calvo P and Chinchetru MA. Cloning of chicken and mouse  $\alpha 1b$  adrenergic receptor. *Biochim. Biophys. Acta* [Impact Factor: 5] 1998 13;1396(3):263-6
- 44 Alonso-Llamazares A, **Casanova E**, Zamanillo D, Ovalle S, Calvo P and Chinchetru MA. Phosphorylation of the third intracellular loop of the mouse  $\alpha 1b$ - Adrenergic receptor by cAMP-dependent protein kinase. *Brain Res. Bull.* [Impact Factor: 3] 1997 42(6):427-30
- 45 **Casanova E**, Garate C, Ovalle S, Calvo P and Chinchetru MA. Identification of four splice variants of the mouse stress activated protein kinase *JNK/SAP* a isoform. *NeuroReport* [Impact Factor: 1.4] 1996 17;7(7):1320-4
- 46 **Casanova E**, Alonso-Llamazares A, Zamanillo D, Garate C, Calvo P and Chinchetru MA. Identification of a long huntingtin mRNA transcript in mouse brain. *Brain Res.* [Impact Factor: 2.8] 1996 16;743(1-2):320-3
- 47 Ovalle S, **Casanova E**, Garate C, Alonso-Llamazares A, Chinchetru MA and Calvo P. Immunodetection of serotonin transporter from mouse brain. *NeuroReport* [Impact Factor: 1.4] 1995 27;6(17):2353-6

- 48 Alonso-Llamazares A, Zamanillo D, **Casanova E**, Ovalle S, Calvo P and Chinchetru MA. Molecular cloning of  $\alpha 1$ -adrenergic receptor and tissue distribution of  $\alpha 1$ -adrenergic receptors subtypes in mouse. *J. Neurochem.* [Impact Factor: 4.1] 1995 65(6):2387-92
- 49 Zamanillo D, **Casanova E**, Alonso-Llamazares A, Ovalle S, Chinchetru MA and Calvo P. Identification of a cyclic adenosine 3', 5'-monophosphate-dependent protein kinase phosphorylation site in the carboxy terminal tail of D1 dopamine receptor. *Neurosci. Lett.* [Impact Factor: 2.2] 1995 31;188(3):183-6
- 50 Negro M, **Casanova E**, Chinchetru MA, Fernandez-Lopez A and Calvo P. Differential effect of chronic ethanol treatment on barbiturate and steroid modulation of muscimol binding to rat brain cortex. *Neurosci. Lett.* [Impact Factor: 2.2] 1993 6;158(1):83-6

## Review Articles

- 1 Grabner B, Moll HP, **Casanova E**. Unexpected tumor suppressive role for STAT3 in KRAS-induced lung tumorigenesis. *Molecular & Cellular Oncology.* 2016 May; 3(3): e1036199
- 2 Kunert R and **Casanova E**. Recent advances in recombinant protein production: BAC-based expression vectors, the bigger the better. *BioEngineered.* [Impact Factor: 1.7] 2013 Jul-Aug;4(4):258-61. Commentary
- 3 Rampetsreiter P, **Casanova E** and Eferl E. Genetically modified mouse models of cancer invasion and metastasis. *Drug Discovery Today,* [Impact Factor: 6.4] 2011 8, No. 2–3. Review
- 4 Mair M, Blaas L, Osterreicher CH, **Casanova E**, and Eferl R. JAK-STAT signaling in hepatic fibrosis. *Front Biosci.* [Impact Factor: 2.5]. 2011 Jun 1;17:2794-811. Review
- 5 Tronche F, **Casanova E**, Turiault M, Sahly I, Kellendonk C. When reverse genetics meets physiology: the use of site-specific recombinases in mice. *FEBS Lett.* [Impact Factor: 3.6] 2002 529: 116-121. Review
- 6 Chinchetru MA, **Casanova E** and Calvo P. Stress-activated protein kinases (JNK/SAPKs) of mammalian brain. *Trends in Comparative Biochem.and Physiol.* 1998 4: 255-259. Review

## Book Chapters

- 1 Stiedl P, Grabner B, Zboray K, Bogner E and **Casanova E**. Modeling cancer using genetically engineered mice. *Methods in Molecular Biology.* 2015;1267:3-18.
- 2 Blaas L, Musteanu M, Grabner B, Eferl R, Bauer A and **Casanova E**. The Use of Bacterial Artificial Chromosomes for Recombinant Protein Production in Mammalian Cell Lines. *Methods in Molecular Biology.* 2012 824:581-93.

## **Invited lectures**

- 1 Title: "KRAS-Mutated Lung Cancer Depends on ErbB Signaling"  
April 201 Institute of Genetics, Medical University of Vienna, Vienna, Austria
- 2 Title: "BAC-based expression vectors for recombinant protein production: The bigger, the better"  
April 2017 Institute of Genetics, University of Stuttgart, Stuttgart, Germany
- 3 Title: "Recombinant HIV envelope proteins"  
November 2016 annual meeting of the EAVI2020 consortia, Barcelona, Spain
- 4 Title: "Unexpected oncosuppressive role for STAT3 in KRAS-induced lung tumorigenesis"  
October 2016 Visiting professor, University of Ulm, Germany
- 5 Title: "Modelling cancer using transgenic mice and beyond"  
October 2016 Visiting professor, University of Ulm, Germany
- 6 Title: "Genetically engineered mouse models"  
May 2016 Department of Pediatrics, Semmelweis University, Budapest Hungary
- 7 Title "BAC-based vectors for recombinant protein production: The bigger, the better"  
June 2016, Center of pharmacology and physiology retreat. Hollabrunn Austria
- 8 Title: "Disruption of STAT3 signaling promotes KRAS induced lung tumorigenesis"  
April 2016 Institute of Research in Biomedicine, Barcelona, Spain
- 9 Title: "Growth hormone and liver fibrosis: old dog new tricks?"  
February 2016. Department of pathology, Medical University of Graz, Graz, Austria
- 10 Title: "Disruption of STAT3 signaling promotes KRAS induced lung tumorigenesis"  
October 2015 Institut de Recherche en Cancérologie de Montpellier, France
- 11 Title: "Disruption of STAT3 signaling promotes KRAS induced lung tumorigenesis"  
March 2015 NATURIMMUN consortia, Bergisch-Gladbach (Cologne), Germany
- 12 Title: "Disruption of STAT3 signaling promotes KRAS induced lung tumorigenesis"  
October 2014 Karolinska Institute, Stockholm, Sweden
- 13 Title: "Disruption of STAT3 signaling promotes KRAS induced lung tumorigenesis"  
October 2014 Instituto de Biología y Genética Molecular in Valladolid, Spain
- 14 Title: "Disruption of STAT3 signaling promotes KRAS induced lung tumorigenesis"  
September 2014, Austrian Association of Molecular Life Sciences and Biotechnology, Vienna, Austria
- 15 Title: "Growth hormone and liver fibrosis: old dog, new trick"  
May 2014, MUW Research Retreat at Schloss Haindorf; Langenlois, Austria
- 16 Title: "Disruption of STAT3 signaling promotes KRAS induced lung tumorigenesis"  
November 2013, University of Ulm, Ulm, Germany.
- 17 Title: "Disruption of STAT3 signaling promotes KRAS induced lung tumorigenesis"  
October 2013, Institute of scientific research "Alberto Sols" CSIC, Madrid, Spain
- 18 Title: "Disruption of STAT3 signaling promotes KRAS induced lung tumorigenesis"  
April 2013, LBICR research retreat, Obergurgl, Austria  
Title: "The Use of Bacterial Artificial
- 19 Chromosomes for Recombinant Protein Production in Mammalian Cell Lines"  
April 2013, Pharmacology research retreat, Haindorf, Austria



- 20 Title: "The Use of Bacterial Artificial Chromosomes for Recombinant Protein Production in Mammalian Cell Lines"  
November, 2012. PEGS-Europe summit, Vienna, Austria.
- 21 Title: "A mouse model to identify cooperating signaling pathways in cancer"  
September 2012. Institute for Genetics, Cologne, Germany
- 22 Title: "Bacterial artificial chromosomes improve recombinant protein production in mammalian cell lines"  
February, 2011. RPP 6 Conference Meeting, Vienna, Austria.
- 23 Title: "Life imaging of GABA(B) Receptors in vivo"  
October, 2010. University of Patras, Patras, Greece.
- 24 Title: "Mouse models for cancer and liver fibrosis"  
September, 2010. "Research Retreat in Sopron", Hungary.
- 25 Title: "Role of Stat5 in liver fibrosis"  
May, 2010. Leibniz Institute for Age Research – Fritz-Lipmann-Institute. Jena, Germany.
- 26 Title: "Life imaging of GABA(B) Receptors in vivo"  
April, 2009. Faculty of Pharmaceutical Sciences, Copenhagen, Denmark.
- 27 Title: "Role of Stat5 in liver fibrosis"  
April, 2009. "Research Retreat Vienna", Austria.
- 28 Title: "Role of Stat5 in liver fibrosis"  
January, 2009. Collège de France, Paris, France.
- 29 Title: "Role of Stat5 in liver fibrosis"  
September, 2008. "Research Retreat in Sopron", Hungary.
- 30 Title: "Life imaging of GABA(B) Receptors in vivo"  
May, 2008. Neuroscience institute, Alicante, Spain.
- 31 Title: "Life imaging of GABA(B) Receptors in vivo"  
October, 2007. Instituto de Biología y Genética Molecular, Valladolid, Spain.
- 32 Title: "Analysis of GABA(B) Receptors"  
February, 2007. Leibniz Institute for Age Research – Fritz-Lipmann-Institute. Jena, Germany.
- 33 Title "Life imaging of GABA(B) receptors"  
September, 2005. 11th Scientific Symposium of Austrian Pharmacology Society (APHAR) Vienna.
- 34 Title: "Conditional Gene Targeting"  
March, 2005. Leibniz Institute for Age Research – Fritz-Lipmann-Institute. Jena, Germany.
- 35 Title: "Conditional mutagenesis in the brain"  
October, 2004. Controlling gene expression inducible in mice: conditional mutagenesis, inducible expression and RNAi. Marseille, France.

## **Teaching:**

May-July, 1995: Intensive course of Molecular Biology, University of the Leon, Leon, Spain

1994-1997: Practical courses of chemistry and biochemistry, University of Leon, Leon, Spain.

2002-2006: Practical courses of neurophysiology, University of Basel, Basel, Switzerland.

2006- present: Organizer and responsible person of the following seminars in the Ludwig Boltzmann Institute for Cancer Research, Vienna, Austria:

“Signal transduction and tumorigenesis” (094 PhD-Doctoral Program)

“JC Transgenic mouse models” (094 PhD-Doctoral Program)

“TS Transgenic mouse models” (094 PhD-Doctoral Program)

Since 2015: Human medicine at the Medical University of Vienna. Physiology of biological systems (second semester). Following seminars:

- 1) Heart and circulation
- 2) Vegetative system
- 3) Blood and red cells
- 4) Immune system
- 5) Metabolism

MUW PhD program: “Cell signal-transduction and disease”. “Lecture: Modelling cancer using transgenic mice and beyond”

## **Supervision:**

### **Postdocs**

2014-present: Dr. Herwig Moll

2015-present: Dr. Venugopal

2016-present: Dr. Emanuel Kreidl

### **Diploma students**

2009-2010: Victoria Stanek

2013-2014: Natacha Hruschka

2016-2017: Klemens Pranz

### **PhD students**

2006-2010: Dr. Leander Blaas

2009-2015: Dr. Beatrice Grabner

2010-2015: Dr. Patricia Stiedl

2011-2017: Katalin Zboray

2014-present: Mirte Post

2015-present: Julian Mohrherr

### **Technicians**

1999-2002: Sandra Fehsenfeld

2006-2009: Deeba Khan

2011-2015: Edith Bogner

2015-2016: Marion Abele

2016-present: Theresa Friedrich

2016-present: Laura Wandruszka

2017-present: Azra Trbic

## Research topics

My main research goal is to unravel the contribution of key cellular signaling pathways to tumorigenesis. To this aim, we make use of genetically modified mouse models (conditional knock-outs, knock-ins, BAC-based transgenic, etc.) mimicking human tumorigenesis. In addition, we complement our studies in the mouse autochthonous tumors by performing gene gain and loss-of-function experiments (e.g. lentiviral overexpression and/or CRISPR/Cas9-induced knock-outs) in human cancer cell lines and xenograft mouse models and by analyzing human tumor biopsies.

Currently, my research group focuses on four main topics:

- 1) The role of the GH (Growth hormone)-STAT5 (Signal transducer and activator of transcription 5)-IGF1 (Insulin-like growth factor 1) axis in liver cirrhosis and hepatocellular carcinoma (HCC).
- 2) Genetically dissection of the role of the AKT isoforms (AKT1, 2 and 3) in mammary gland tumors.
- 3) Contribution of STAT3 (Signal transducer and activator of transcription 3) and EGFR (Epidermal growth factor receptor) to K-RAS dependent lung tumors.
- 4) Exploring the possibilities of using BAC-based expression vectors applied to mammalian recombinant protein production, which could provide anti-cancer treatments, a collaborative project with POLYMUN Scientific Immunobiologische Forschung and the Antibody Lab, two Austrian companies working in the field of recombinant protein production.

### **Topic 1: GH-STAT5-IGF1 axis in liver cirrhosis and HCC.**

Liver fibrosis constitutes a considerable health problem in the human population. Growth hormone resistance (GH) syndrome has been largely associated with liver cirrhosis in humans and it has been considered as a mere consequence of liver dysfunction attributed to fibrosis. We have shown that mice devoid of STAT5 in hepatocytes (a model for GH resistance) develop a severe liver cirrhosis phenotype when they are challenged with genetic and pharmacological models of cholestasis thus suggesting that GH resistance actively contributes to the onset and development of fibrosis (Blaas *et al.*, Hepatology 2010; Mair *et al.*, Gastroenterology 2010; Mair *et al.*, Front Biosci. 2011). Currently, we are extending these studies by analyzing the role of Growth hormone receptor (GHR) in liver fibrosis and HCC. We make use of GHR knock-outs (GHR<sup>-/-</sup>) animals as model of systemic GH resistance. Challenging GHR<sup>-/-</sup> animals by crossing them with the MDR2<sup>-/-</sup> strain (Multidrug resistance protein 2 knock-out, a mouse model for primary sclerosing cholangitis and HCC) results in massive liver fibrosis phenotype. Analysis of this model reveals that hepatocytes lacking GHR signaling are more sensitive to bile-acid induced damage, thus suggesting that impairment of GH signaling plays an active role in the development of liver cirrhosis. Interestingly, despite of the liver fibrosis observed in the GHR<sup>-/-</sup>:MDR2<sup>-/-</sup> double knock-outs, these mice virtually do not develop HCC. Thus, disruption of GH signaling contributes to the development of liver fibrosis but blocks liver tumorigenesis (Stiedl *et al.*, Hepatology 2015). We are currently investigating the molecular pathways responsible for the suppression of liver tumorigenesis upon abrogation of GH signaling. These findings should contribute to the understanding of the development of liver cirrhosis, a life threatening irreversible liver disease, and its progression to HCC.

**Topic 2: The “AKT Multi-Hit”: A mouse model to study oncogene cooperativity in breast tumors.**

Acquired mutations in cancer cells may (or may not) cooperate in the development of tumors. Combinations of mutations that interact in tumorigenesis should be selected in a Darwinian fashion. To study how oncogenes cooperate in the development of tumors, we have generated, in a coordinated effort within the LBI-CR institute, the so called “Multi-Hit” model. This model allows the expression of three oncogenes in an inducible and random manner. Combinations of these oncogenes that cooperate in tumorigenesis are positively selected and result in faster or more aggressive tumors. Identification of the combination of oncogenes present in the resulting tumors allows to elucidate oncogene cooperativity (Musteanu *et al.*, Nature Methods 2012). To illustrate this idea, we have generated a transgenic mouse that allows the inducible and random expression of the three AKT family members (AKT-1, 2 and 3) based on the Cre/loxP system. Induction of the AKT isoforms results in breast tumors (among other types of tumors). Analysis of ten mammary gland tumors reveals that all of them express the AKT-3 isoform, none expresses AKT-2 and some of them express AKT-1. This would suggest that in this system, breast tumors are dependent on AKT-3 (and AKT-3 is positively selected in tumor formation) while AKT-2 would behave as a tumor suppressor and is contra-selected in tumor formation. This example shows that the Multi-Hit technology is operational and can be used to study oncogene cooperativity. These mouse models go far beyond the tumor models in mice which are based on single mutations and reflect rather the complex nature of human tumors and serve in addition as useful tools to test anti-tumor therapies. In the future, we will implement the technology and extend its applications.

**Topic 3: Role of STAT3 and EGFR in K-RAS induced lung tumors.**

Lung cancer is leading the worldwide cancer related deaths. It can be divided into two main types: Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), the later accounting for 80% of the cases. Common genetic alterations associated with lung cancer are the loss of tumor suppressors, like p53, LKB1 etc. and activating mutations, overexpression, amplification of oncogenes, such EGFR and K-RAS. In lung tumors, EGFR signals through K-RAS, PI3K and STAT3. STAT3 regulates important pathways in tumorigenesis, through upregulation of genes encoding apoptosis inhibitors (BCL-XL, BCL-2, MCL-1 and survivin). In patient samples and NSCLC cell lines nuclear pSTAT3 is upregulated and correlates with subsequent suppression of apoptosis in NSCLC tumors; however, the role of STAT3 in lung cancer *in vivo* has not yet been investigated. We have established a genetic mouse model that allows to induce K-RAS-dependent lung tumors and simultaneously genetically ablates STAT3. Analysis of this model showed that mice with deleted STAT3 and activated K-RAS have a shorter life span when compared to control animals (K-RAS activated, STAT3 proficient). Furthermore, animals with deleted STAT3 and activated K-RAS have a significant increase in tumor burden and develop more adenomas and adenocarcinomas than the control animals (K-RAS activated, STAT3 proficient). This data suggest that disruption of STAT3 signalling promotes tumorigenesis in K-RAS induced tumors. Mechanistically, we have shown that tumors lacking STAT3 expressed increased levels of IL8, infiltration of granulocytes and macrophages, increased tumor vascularization and therefore augmented tumor growth and progression (Grabner *et al.*, Nature Communication 2015 and Grabner *et al.*, Mol Cell Oncology 2015). Interestingly, patients suffering from rheumatoid arthritis treated with tofacitinib (a Janus Kinase [JAK] inhibitor which mainly inhibits JAK1 and 3, with a reduced inhibition of JAK2) have a statistical significant risk of developing lung cancer. JAKs are upstream activators of STAT3. Therefore, we are now using genetic and pharmacological mouse models to investigate the impact of suppressing JAK signalling in lung tumorigenesis.

Amplification/overexpression of the EGFR and mutations in the K-RAS gene play a critical role in lung cancer, but genetic alterations in EGFR and K-RAS seem to be mutually exclusive in lung tumors. Furthermore, patients harbouring K-Ras activating mutations seems do not respond to EGFR tyrosine kinase inhibitors, although this issue is still under debate. To analyze the role of the EGFR in K-RAS-dependent lung tumors at the genetic level, we deleted EGFR in a K-RAS-induced model of lung tumors. Interestingly, mice with deleted EGFR have a longer life span than control animals. This observation suggests that EGFR plays a role in K-RAS-dependent lung tumors, which is in contrast to the common believe, and it may have an impact on the use of EGFR blockers in patients with lung tumors containing K-RAS mutations.

**Topic 4: Bacterial Artificial Chromosomes as expression vectors in recombinant protein production in mammalian cells.**

Bacterial Artificial Chromosomes (BACs) are large vectors that can contain up to 400 Kb. They may accommodate an entire locus with all the regulatory elements that control the transcription of a gene. Thus, BACs harboring the appropriate locus contain their own chromatin environment and they are not affected by the surrounding chromatin to their genomic integration site. Due to these characteristics, BACs are largely used in the mouse transgenic field. Interestingly, these attributes make the BACs very attractive expression vectors for recombinant protein production in mammalian cells at the industrial scale. In collaboration with two industrial partners, POLYMUN Scientific Immunbiologische Forschung GmbH and The Antibody Lab GmbH, we are developing BAC-based expression vectors suitable for recombinant protein production (Blaas *et al.*, BMC 2007; Blaas *et al.*, Methods Mol. Biol. 2012; Mader *et al.*, Appl Microbiol Biotechnol 2012, Kunert and Casanova, Bioengineered. 2013, Zaboray, Nucleic Acids Res 2015). The aims of this project are:

- 1) Generate a flexible tool box of BAC-based expression vectors in mammalian cells
- 2) Test the feasibility of the system for producing diverse therapeutic proteins (e.g. antibodies)

## **References**

**Prof. Michael Freissmuth**

Institute of Pharmacology, Medical University of Vienna  
Vienna, Währinger Str. 13a  
Austria  
Email: michael.freissmuth@meduniwien.ac.at

**Prof. Thomas Look**

Department of Pediatric Oncology, DFCI, Harvard Medical School.  
Boston, MA 02115  
USA  
Email: thomas\_look@dfci.harvard.edu

**Prof. Gustavo Leone**

Comprehensive Cancer Center  
808 Biomedical Research Tower  
460 W 12th Ave  
Columbus, Ohio 43210  
USA  
Email: gustavo.leone@osumc.edu

**Prof. Kay-Uwe Wagner**

University of Nebraska Medical Center  
985950 Nebraska Medical Center, DRCII  
Omaha, NE 68198-5950  
USA  
Email: kuwagner@unmc.edu

**Prof. Nancy E. Hynes**

Friedrich Miescher Institute  
for Biomedical Research  
Maulbeerstrasse 66  
P.O. Box 2543  
4002 Basel  
Switzerland  
Email: nancy.hynes@fmi.ch

**Vienna, June, 2017**

**Prof. Emilio Casanova**