SPANISH NATIONAL CANCER RESEARCH CENTRE

CNIO - "LA CAIXA" FOUNDATION FRONTIERS MEETINGS 2017

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

IN MEMORY OF SUSAN LINDQUIST

Organisers

Nabil Djouder
Spanish National Cancer Research Centre
(CNIO), Madrid, Spain

Wilhelm Krek
Institute for Molecular Health Sciences
Zurich, Switzerland

Paul Workman
The Institute of Cancer Research
London, UK

Xiaohong Helena Yang
Cancer Cell
Cambridge, US

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA, INDUSTRIA Y COMPETITIVIDAD
Instituto de Salud Carlos III
EXCELENCIA SEVERO OCHOA
cnio Centro Nacional de Investigaciones Oncológicas
"la Caixa" Foundation

SPANISH NATIONAL CANCER RESEARCH CENTRE

CNIO - "LA CAIXA" FOUNDATION
FRONTIERS MEETINGS 2017

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

cnio Centro Nacional de Investigaciones Oncológicas

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

Summary

SPANISH NATIONAL CANCER RESEARCH CENTRE
CNIO - "LA CAIXA" FOUNDATION
FRONTIERS MEETINGS 2017

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

PROGRAMME

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

Venue:
Spanish National Cancer Research Centre – CNIO Auditorium, Madrid, Spain

Chairpersons and organizing committee:
Nabil Djouder, Spanish National Cancer Research Centre, Madrid, Spain
Wilhelm Krek, Institute for Molecular Health Sciences, ETH, Zurich, Switzerland
Paul Workman, The Institute of Cancer Research, London, UK
Xiaohong Helena Yang, Cancer Cell, Cambridge, USA

Rationale:

Molecular chaperones play key roles in the folding, stability and activity of proteins in normal cell homeostasis and disease pathology, including cancer. However, despite recent progress we have much to learn in comprehending the precise details of the molecular function of chaperones and how they support cancer initiation and progression. This conference will focus on recent developments in our understanding of the structure and function of molecular chaperones such as HSP90, including use of model organisms. We will also address how chaperones act in networks with other proteins to create cancer phenotypes, how chaperones facilitate and support cancer evolution, and how better to target chaperones for cancer treatment.

Speakers

Udai Banerji
The Institute of Cancer Research, London, UK

Johannes Buchner
Technical University Munich, Germany

Bernd Bukau
Center for Molecular Biology of Heidelberg University, German Cancer Research Center (DKFZ), Germany

Gabriela Chiosis
Memorial Sloan Kettering Cancer Center, New York, US

Ana Maria Cuervo
Albert Einstein College of Medicine, New York, US

Erica A. Golemis
Fox Chase Cancer Center, Philadelphia, US

Mathias Heikenwälder
DKFZ - German Cancer Research Center, Heidelberg, Germany

Charalampos Kalodimos
College of Biological Sciences, University of Minnesota, St. Paul, US

Michael Karin
University of California, San Diego, US

Randal J. Kaufman
Stanford Burnham Prebys Medical Discovery Institute, San Diego, US

Oscar Llorca
Centre for Biological Research (CIB-CSIC), Madrid, Spain

Matthias P. Mayer
Center for Molecular Biology of Heidelberg University, Heidelberg, Germany

Shelli R. McAlpine
University of New Southwales, Sydney, Australia

Marc Mendillo
Northwestern University Feinberg School of Medicine, Chicago, US

Guillermo Montoya
Novo Nordisk Foundation Center for Protein Research, Denmark

Richard Morimoto
Northwestern University, Evanston, US

Kazuhiro Nagata
Kyoto Sangyo University, Japan

Shuichi Ohkubo
Taiho Pharmaceutical Co., Ltd., Tokio, Japan

Laurence Pearl
University of Sussex, Brighton, UK

David Pincus
Whitehead Institute for Biomedical Research, Cambridge, US

Lea Sistonen
Abo Akademi University, Finland

Patricija van Oosten-Hawle
University of Leeds, UK

Cara Vaughan
School of Crystallography, Birkbeck College, London, UK

Paul Workman
The Institute of Cancer Research, London, UK

Tuesday May 2nd, 2017

13:00 Registration - welcome coffee for all participants (Main Hall)

14:45 - 15:00 Welcome address

15:00 - 16:00 **Keynote Lecture**
Chair: Nabil Djouder and Paul Workman

Regulation of proteostasis networks in development, aging and cancer
Richard Morimoto
Northwestern University, Evanston, US

16:00 - 16:30 *Coffee break (social room)*

16:30 - 18:30 **Protein Quality Control**
Chair: Shelli R. McAlpine
This session will present recent work and discuss how proteins are appropriately folded to ensure their proper functions

16:30 - 17:00 Protein quality control in the ER: ERAD and autophagy
Kazuhiro Nagata
Kyoto Sangyo University, Japan

17:00 - 17:30 Dynamics of Hsp70 and Hsp90 mediated regulation of the conformation of p53 and p53 Cancer Variants
Matthias Mayer
ZMBH, Heidelberg, Germany

17:30 - 17:45 Transcriptional rewiring by stress responses in the tumor microenvironment
SHORT TALK
Ruth Scherz-Shouval
Weizmann Institute of Science, Rehovot, Israel

Tuesday May 2nd, 2017

17:45 - 18:00 Analysis of the interplay and regulation of HDAC6 and HSP90


Oliver Krämer
University Medical Center of Johannes Gutenberg, University Mainz, Mainz, Germany

18:00 - 18:30 The epichaperome in cancer – role and significance
Gabriela Chiosis
Memorial Sloan-Kettering Cancer Center, New York, US

19:00 - 21:00 *Welcome dinner for the speakers*

Wednesday May 3rd, 2017

08:30 - 12:30 **Folding, misfolding and aggregation**
Chair: Oscar Llorca
This session will cover the most recent mechanistic advances of how chaperones and other stress-inducible proteins recognize and deal with misfolded and damaged proteins inducing their aggregation and degradation

08:30 - 09:00 Regulation of chaperone machineries
Johannes Buchner
TUM Technische Universität München, Germany

09:00 - 09:15 The role of CCT-PhLP1 system in the folding of mLST8, a key component of mTOR complex


Jorge Cuéllar Pérez
National Centre for Biotechnology, Madrid, Spain

Wednesday May 3rd, 2017

09:15 - 09:30 Dependency on the URI1 onco-chaperone defines a subset of cancer cells with vulnerabilities to transcription and RNA processing inhibitors
SHORT TALK
Lukas Frischknecht
Institute of Molecular Health Sciences, ETH Zurich, Zurich, Switzerland

09:30 - 10:00 A versatile chaperone network promotes the aggregation and disaggregation of proteins
Bernd Bukau
ZMBH, University of Heidelberg, and DKFZ - German Cancer Research Center, Germany

10:00 - 10:30 Structural and functional basis of protein Phosphatase5 specificity
Cara Vaughan
Birkbeck University of London, UK

10:30 - 11:30 *Coffee break and group picture (social room)*

11:30 - 12:00 Structural basis for the interaction of molecular chaperones with non-native proteins
Charalampos Kalodimos
College of Biological Sciences, University of Minnesota, St. Paul, US

12:00 - 12:30 Structure and functional analysis of human CCT
Guillermo Montoya
Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

12:30 - 14:00 *Lunch (cafeteria)*

Wednesday May 3rd, 2017

14:00 - 17:15 **Stress Mechanisms in Cancer**
Chair: Guillermo Montoya
This session will discuss the unfolded protein response programmes and other stress mechanisms

14:00 - 14:30 Essential function and dynamic regulation of heat shock factor:
A paradigm from yeast for its role in cancer
David Pincus
Whitehead Institute for Biomedical Research, Cambridge, US

14:30 - 15:00 Synergistic and opposite effects of heat shock transcription factors in cell stress and cancer
Lea Sistonen
Åbo Akademi University, Turku, Finland

15:00 - 15:15 Hsp90 releases the break on the Hsp70 folding path


Tania Morán Luengo
Bijvoet Center for Biomolecular Research, Utrecht University, The Netherlands

15:15 - 15:30 Prefoldin contributes to transcription elongation in both yeast and human cells


Sebastián Chávez
Institute of Biomedicine of Seville (IBiS), Virgen de Sevilla Hospital, CSIC-University of Seville, Spain

15:30 - 16:15 *Coffee break (social room)*

16:15 - 16:45 Cryo-EM structure of the HSP90 co-chaperone required for assembly of the ATM/ATR/mTOR family of kinases
Oscar Llorca
CIB,
Madrid, Spain

Wednesday May 3rd, 2017

16:45 - 17:15 Delineating and exploiting stress response network addictions in malignancies
Marc Mendillo
Northwestern University, Chicago, US

17:30 - 19:30 Poster session – Snack for all participants (social room)

21:00 *Dinner for the speakers*

Thursday May 4th, 2017

08:30 - 12:15 **Chaperones in Cancer**
Chair: Nabil Djouder
This session will present recent advances and breakthroughs of in vivo models generated to understand chaperones' biological relevance in cancer and how alterations in protein quality control contribute to cancer.

08:30 - 09:00 Chaperoning Selective Autophagy in Cancer Biology
Ana María Cuervo
Albert Einstein College of Medicine, New York, US

09:00 - 09:30 On the role of Hsp60 and mitochondrial UPR to drive intrahepatic cholangiocellular carcinoma
Mathias Heikenwälder
German Cancer Research Center, Heidelberg, Germany

09:30 - 10:00 The transcription factor PQM-1 is a novel regulator of proteostasis and mediator of transcellular chaperone signalling in C. elegans
Patricija Van Oosten-Hawle
University of Leeds, UK

Thursday May 4th, 2017

10:00 - 10:15 The co-chaperone URI maintains crypt identity and protects against colorectal cancer


Almudena Chaves
Spanish National Cancer Research Centre, Madrid, Spain

10:15 - 10:30 Loss of the proteostasis factor AIRAPL causes myeloid transformation by deregulating IGF-1 signaling


Olaya Santiago Fernández
The University Institute of Oncology of Asturias (IUOPA), University of Oviedo, Spain

10:30 - 11:15 *Coffee break (social room) (certificates and invoices will be available at the reception desk)*

11:15 - 11:45 Metabolism, inflammation and immunity in liver cancer
Michael Karin
University of California, La Jolla, US

11:45 - 12:15 ER protein misfolding causes mitochondrial dysfunction leading to oncogenesis
Randal J. Kaufman
Sanford Burnham Prebys Medical Discovery Institute, La Jolla, US

12:15 - 13:30 *Lunch (cafeteria)*

Thursday May 4th, 2017

13:30 - 17:00 **Targeting chaperones: chaperonotherapy**
Chair: Lea Sistonen
This session will discuss the chemistry, drug design and allosteric regulation with recent advances in generating new therapeutic approaches to target chaperones for cancer treatment

13:30 - 14:00 Designing molecules that target heat shock proteins: an approach for inhibiting Hsp90, Hsp70 and Hsp27
Shelli R. McAlpine
University of New South Wales, Sydney, Australia

14:00 - 14:30 What have we learned from the clinical development of HSP90 inhibitors?
Udai Banerji
The Institute of Cancer Research, London, UK

14:30 - 14:45 Computational studies of the Hsp90 system to design new anticancer drugs
SHORT TALK
Giorgio Colombo
Institute for Molecular recognition chemistry, Milan, Italy

14:45 - 15:00 Integrating multiscale network modeling and computational systems biology with biophysical characterization of the Hsp90 interactions with cochaperones and protein clients: atomistic reconstruction of allosteric regulatory mechanisms and client recruitment by the chaperone machine
SHORT TALK
Gennady Verkhivker
School of Pharmacy, Chapman University, Orange, US

Thursday May 4th, 2017

15:00 - 15:30 *Coffee break (social room)*

15:30 - 16:00 HSP90 inhibition in cancer versus ciliopathies
Erica Golemis
Fox Chase Cancer Center – Philadelphia, US

16:00 - 16:30 The discovery and development of oral HSP90α/β inhibitor, TAS-116
Shuichi Ohkubo
Taiho Pharmaceutical Co., Ltd, Tokyo, Japan

16:30 - 17:00 Pathways of HSP90 client protein degradation
Laurence Pearl
University of Sussex, Brighton, UK

17:00 - 17:15 Prizes for best poster and best short talk

17:15 - 18:00 ***Closing Lecture***
Drugging the cancer genome and the cancer state with inhibitors of HSP90, HSP70 and the HSF1 pathway
Paul Workman
The Institute of Cancer Research, London, UK

Wrap up and concluding remarks

18:00 - 18:15 **Paul Workman**

Farewell Snack for all participants

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

KEYNOTE LECTURE

Chair: Nabil Djouder and Paul Workman

Regulation of proteostasis networks in development, aging and cancer

Richard I. Morimoto
Northwestern University, Evanston, US

Tuesday May 2nd, 2017

KEYNOTE LECTURE

Chair: ***Nabil Djouder*** *and* ***Paul Workman***

Regulation of proteostasis networks in development, aging and cancer

Richard I. Morimoto
Northwestern University, Evanston, US

Tuesday May 2nd, 2017

Regulation of proteostasis networks in development, aging and cancer

Richard I. Morimoto
Bill and Gayle Cook, Rice Institute for Biomedical Research, Department of Molecular Biosciences, Northwestern University Evanston, US

Proteostasis is the biological context that complements the physical chemistry of proteins, and the cellular environment in which they evolved to achieve function. A common feature of environmental stress, disease and aging is the accumulation of damaged proteins that can interfere with function, and lead to protein aggregates that sequester other metastable proteins, chaperones, and the proteasome. This places a tremendous demand on the robustness of the proteostasis network in metazoans during development and in the transition to post-reproductive adulthood. To address this, we have focused on HSF-1, the stress responsive factor of the heat shock response (HSR), which is essential in early development, for longevity in *C. elegans*, and to protect cells and tissues against proteotoxicity at all life stages. During larval development, HSF-1 partners with the E2F complex to regulate an HSF-1 developmental transcriptome comprised of a genes encoding a specific subset of chaperones and for anabolic metabolism that is distinct from the HSR. Then, upon entry in adulthood, the HSR is abruptly repressed at reproductive maturity by signals from the germ line stem cells involving epigenetic repression by H3K27me3 binding at stress gene loci that alters the chromatin state to prevent HSF-1 binding leading to the decline of proteostasis. These observations suggest a direct mechanistic consequence of the age-associate collapse of proteostasis that precedes the onset of diseases of protein conformation as occurs in neurodegeneration. Likewise, we suggest that the relationship between E2F and HSF-1 in development is likely relevant to the situation in cancer as half of the genes regulated by HSF-1 in transformed cells also bind to E2F. Organismal proteostasis therefore represents balance and coordination among cell stress responses to ensure cellular and tissue health and longevity or risk for disease.

Richard I. Morimoto, Department of Molecular Biosciences, Rice Institute for Biomedical Research, Northwestern University, Evanston, IL 60208, USA

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

Session #1

Protein quality control

Chair: ***Shelli R. McAlpine***

Tuesday May 2nd, 2017

Protein quality control in the ER:ERAD and autophagy

Kazuhiro Nagata
Institute for Protein Dynamics, Kyoto Sangyo University, Kamigamo Motoyama, Kita-ku, Kyoto, Japan

Terminally misfolded secretory and membrane proteins are retro-translocated from the endoplasmic reticulum (ER) into the cytosol where they are degraded via ubiquitin-proteasome pathway, a process termed as ER-associated degradation (ERAD). We first identified a novel protein EDEM (ER-degradation enhancing a-mannosidase-like protein) and reported that EDEM recruits glycoproteins misfolded in the ER from synthetic pathways to degradation pathways in a mannose trimming-dependent manner. We also found a novel protein ERdj5, an ER-resident disulfide reductase, as an EDEM-binding protein and identified its function playing a central role in ERAD by cleaving the disulfide bonds of the misfolded proteins that are recognized by EDEM. Recently, we found that ERdj5 reduces the luminal disulfide bond of SERCA2b, a Ca^{2+}-ATPase on the ER membrane, thereby activating its pump function. Notably, we found that ERdj5 activates SERCA2b at lower ER luminal [Ca^{2+}] ([Ca^{2+}]$_{ER}$), while higher [Ca^{2+}]$_{ER}$ induces ERdj5 to form oligomers that are no longer able to interact with the pump, suggesting [Ca^{2+}]$_{ER}$-dependent regulation. These results identify ERdj5 as a master regulator of ER calcium homeostasis, and thus shed light on the importance of crosstalk among redox, Ca^{2+} and protein homeostasis in the ER.

We also found another novel J-protein in the ER, ERdj8, which negatively regulates macro-autophagy. Autophagy degrades abnormal organelle and proteins, and hence retains the intracellular homeostasis. ERdj8 localizes at the ER-mitochondria contact site, at which autophagosomal isolation membranes originate. We identified that ERdj8 regulates the size of autophagosomes by retarding the dissociation of isolation membranes from the ER. The mechanism determining the size of autophagosomes has never been reported, and our finding would provide a novel insight on the regulation of cellular homeostasis by autophagy.

Dynamics of Hsp70 and Hsp90 mediated regulation of the conformation of p53 and p53 cancer variants

Matthias P. Mayer
Zentrum für Molekulare Biologie der Universität Heidelberg (ZMBH),
DKFZ-ZMBH-Alliance, Heidelberg, Germany

The tumor suppressor p53 is an important cellular sensor and regulator of DNA damage, senescence and apoptosis, protecting cells from malignant transformations. However its activity has to be timed and balanced closely, as too much of it is lethal. While the proteolytic degradation of p53 depends on Mdm-2, p53´s folding equilibrium is regulated by the Hsp70 and Hsp90 chaperone network. It maintains the function of p53 at stress conditions, but also is responsible for a multifaceted regulation of its activity and half-life at physiological temperature. Chaperones interact transiently with the DNA binding domain (DBD) of wt p53, but associate with many cancer mutants in an abnormally stable manner and aggravate their dominant-negative and gain-of-function effects. Little is known about how Hsp70 and Hsp90 contribute to the conformational regulation of p53.

Using hydrogen exchange mass spectrometry and biochemical methods, we analyzed the conformational states of p53-DBD-wt at physiological temperature and conformational perturbations in several frequent cancer mutants. We show that the Hsp70/Hsp40 system shifts the conformational equilibrium of p53 towards a flexible inactive state. In contrast, Hsp90 protects the DBD of p53 from unfolding. We propose that the Hsp70 and the Hsp90 chaperone systems assume complementary functions to optimally balance conformational plasticity with conformational stability.

Marta Boysen1 & Matthias P. Mayer

SHORT TALK

Transcriptional rewiring by stress responses in the tumor microenvironment

Gil Friedman, Yehuda Salzberg, David Dierks, Patricia Do-Dinh, Nil Grunberg, Natalia Vinnikov, and **Ruth Scherz-Shouval**

Department of Biomolecular Sciences, Weizmann Institute of Science, Rehovot, Israel

For tumors to expand, metastasize, and evade immune surveillance, cancer cells must recruit and reprogram normal cells in their environment to support them. These cells include macrophages, fibroblasts, and endothelial cells collectively termed the tumor microenvironment (TME), or tumor stroma. Despite accumulating evidence for contribution of the stroma to cancer phenotypes, little is known about the factors that drive the transcriptional rewiring of normal cells within tumors. Our lab aims to elucidate the mechanisms by which tumors reprogram their local environments, and to understand how cancer cells and stroma co-evolve

Our hypothesis is that cancer cells hijack normal cytoprotective stress responses, and subvert them to enable stromal reprogramming. Recently we have shown that Heat-shock Factor 1 (HSF1), master regulator of the heat-shock response, plays a crucial role in this process. Across a broad range of human cancers, HSF1 is activated not only in the malignant cells themselves, but also in cancer-associated fibroblasts (CAFs). In early stage breast and lung cancer, high stromal HSF1 activation is strongly associated with poor patient outcome. HSF1 drives a transcriptional program in CAFs that complements, yet is completely different from, the program it drives in adjacent cancer cells. This CAF program is uniquely structured to support the malignant potential of cancer cells in a non-cell-autonomous way. Here we further explore the HSF1-dependent co-evolution of cancer and stroma.

We show that HSF1 is activated in different cell types of the TME, driving unique transcriptional programs in each cell type that together promote tumor phenotypes. We dissect the mechanism of stromal HSF1 activation, identify key components of the HSF1-dependent stromal transcriptional programs and highlight the prognostic implications of cell-autonomous and non-cell-autonomous activation of HSF1 in cancer.

Analysis of the interplay and regulation of HDAC6 and HSP90

SHORT TALK

Beyer M. and **Oliver H. Krämer**

Department of Toxicology, University Medical Centre of Johannes Gutenberg University Mainz, Mainz, Germany

Histone deacetylases (HDACs) are important epigenetic regulators that remove acetyl groups from lysine residues. 18 HDACs are present in mammals. Current research strives to determine individual functions of HDACs and to design selective and potent HDAC inhibitors (HDACi). HDAC6 contains two active catalytic domains and an ubiquitin binding site, which helps to maintain protein homeostasis. HDAC6 locates to the cytoplasm and its typical substrates are non-histone proteins. The chaperone heat shock protein 90 (HSP90) assists in the folding of normal and leukemogenic proteins. Acute myeloid leukemia (AML) is characterized by myeloid precursors lacking differentiation capacity. 30% of AML patients carry internal tandem duplications (ITD) in the FMS-like tyrosine kinase 3 (FLT3). Such patients are often resistant against chemotherapy, have higher risks of relapse, and poor survival rates. It has been reported that HSP90, HDAC6, and FLT3 interact physically and functionally. Hence, drugging the HDAC6-HSP90-FLT3 interplay could be a novel therapeutic option. Treatment of human FLT3-ITD-positive AML cells with the novel and highly selective HDAC6 inhibitor Marbostat-100 neither alters cell cycle distribution nor does it increase apoptosis. Marbostat-100 induces hyperacetylation of the HDAC6 target Tubulin, but Marbostat-100 does not modulate the acetylation of HSP90 or the phosphorylation and stability of FLT3. In contrast, the HSP90 inhibitor Onalespib (AT13387) propels a loss of HDAC6 and phosphorylated and total FLT3, and leads to apoptosis. A combinatory treatment of AML cells with Marbostat-100 and AT13387 combines favorably against AML cells. Analyzing oncogenic mutants of the tumor suppressor p53, we also see no regulation of mutant p53 by HDAC6 in pancreatic cancer cells.

Thus, contrary to what was previously thought, HSP90 and HDAC6 act in different, and not epistatic pathways on oncogenic drivers. Marbostat-100 is a novel and precise tool to analyze HDAC6.

The epichaperome in cancer – role and significance

Gabriela Chiosis
Memorial Sloan Kettering Cancer Center, New York, US

Our conventional view on cancer is of a cellular state with an accumulation of misfolded proteins created by an increased mutational load and a hostile microenvironment. To buffer proteome alterations and maintain functionality cells increase the production of heat shock proteins. This talk seeks to provide a complementary view. We find that cancer cells regulate proteome stress not by chaperone overexpression but rather by a re-wiring of the chaperone units. We identified large proteome imbalances, such as produced by MYC activation, that re-wire chaperone units into large chaperone networks. These networks, created by a change in the cellular milieu rather than defects in chaperone structure or expression, we term the epichaperome. Why is this significant? These networks protect certain cancers against cell death during their transformation into malignancies. While chaperone units are abundant and expressed virtually in every cell in the human body, epichaperome networks are unique to cancer cells. Our mechanistic findings therefore provide a new target of intervention in cancer that is based not on genetics or individual chaperones, but rather on the properties of chaperone protein networks.

NOTES

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

Session #2

Folding, misfolding and aggregation

Chair: ***Oscar Llorca***

Wednesday May 3rd, 2017

Regulation of chaperone machineries

Johannes Buchner
Technische Universität München, Garching, Germany

Cells have developed a quality control system that ensures that the cellular proteome folds correctly, keeps its native conformation and that unproductive side reactions are prevented. This is especially important under stress conditions such as high temperature when massive protein unfolding occurs or in the context of diseases when the cellular protein homeostasis is out of control.

The key elements of the cellular stress defense system are molecular chaperones. These cellular machines of protein folding share the remarkable ability of specifically recognizing non-native proteins and assisting their folding to the native state. There are several classes of molecular chaperones that evolved independently and are both structurally and mechanistically not related, such as the small heat shock proteins, Hsp70 and Hsp90. Of special interest is how these potent machineries are regulated. A key aspect that sets different chaperone families apart is whether they utilize ATP hydrolysis for assisting protein folding. Progress in recent years provided insight into the mechanistic principles of chaperones. With a view to define the key traits of chaperone machines, we set out to reconstitute their mode of action using purified components. Our analysis reveals intriguing differences in the mode of action including sophisticated regulatory and control elements.

SHORT TALK

The role of CCT-PhLP1 system in the folding of mLST8, a key component of mTOR complex

Jorge Cuéllar[1], Madhura Dhavale[2], Takuma Aoba[2], Rebecca L. Plimpton[2], W. Grant Ludlam[2], Aman Makaju[3], Sarah Franklin[3], Barry M. Willardson[2] and José M. Valpuesta[1]

[1] Centro Nacional de Biotecnología, Campus de la Universidad Autónoma de Madrid, Madrid, Spain
[2] Department of Chemistry and Biochemistry, Brigham Young University, Provo UT, US
[3] Department of Internal Medicine, Nora Eccles Harrison Cardiovascular Research and Training Institute, University of Utah, Salt Lake City, UT, US

The mechanistic target of rapamycin (mTOR) protein forms two multi-protein signaling complexes, identified as mTORC1 and mTORC2, that are master regulators of cell growth, metabolism, survival and autophagy in response to growth factors, nutrients, oxygen and stress. As a result, they are involved in many pathological processes including cancer and represent high-value therapeutic targets. mLST8 is a 37 kDa beta-propeller protein which, together with mTOR, is a core component of both mTOR complexes.

We have previously characterized by coupling Cryo-EM and XL-MS, the folding pathway of another beta-propeller protein, G protein beta subunit, a process assisted by CCT and its cochaperone PhLP1. A logical extension of our work on G-beta was to ask if beta-propeller proteins involved in other important signaling complexes such as mLST8 share the same folding mechanism. We tested the binding of mLST8 to CCT and PhLP1 by immuno-precipitation (IP) and found strong evidence of the formation of a ternary complex. Knockdown experiments on particular CCT subunits showed that there was no direct interaction between mLST8 and PhLP1 and further confirmed that the ternary complex is assembled through CCT.

Recently we have started the structural characterization of the purified CCT-PhLP1-mLST8 complex by combining CryoEM and XL-MS. A preliminary 3D reconstruction indicates that mLST8 binds deep within the CCT folding cavity in close association with the CCT alpha and CCT gamma subunits, as pointed by XL-MS. The comparison of these results with those obtained for G-beta show some similarities, since both proteins contact the same CCT subunits, but also some differences as the two proteins interact with different regions of the CCT subunits. A deeper characterization will allow to establish whether mLST8 interacts with CCT in a near-native state as G-beta does and will help understand whether the role of PhLP1 in releasing the substrate is also shared between the two pathways.

SHORT TALK

Dependency on the URI1 onco-chaperone defines a subset of cancer cells with vulnerabilities to transcription and RNA processing inhibitors

Lukas Frischknecht[1*], Yann Christinat[1*], Patricia Marti[1], Christian Britschgi[1] and Wilhelm Krek[1]

[1] Institute of Molecular Health Sciences, ETH Zurich, Zurich Switzerland
[*] those authors contributed equally to this work

URI1 is a member of the prefoldin chaperone family that forms multiprotein complexes with established oncogenic properties in various cancer types (1, 2, 3). URI1 is also found amplified in various cancers where it provides a survival function (4). To delineate further potential mechanisms of oncoprotein function associated with URI1 in human cancer and to uncover potential therapeutic opportunities within the prefoldin chaperone space, we embarked on an analysis of URI1 dependency across cancer cells in the Achilles database (http://www.broadinstitute.org/achilles), which contains information from loss-of-function screens in 216 cancer cell lines. This effort revealed an URI1 onco-chaperone gene network comprised of four subgroups involved in transcription, RNA processing, nuclear transport and protein degradation that demonstrated very similar survival properties as URI1. Further in silico analysis revealed that the dependency of cancer cells for their survival on genes in this new network correlated with copy number alterations of 18 of these genes as well as on the transcriptional burden of cancer cells as assessed by the copy number of a list of established driver oncogenes. Chemical inhibition of components of the individual subnetworks validated differential sensitivity of cancer cells as a function of hemizygous loss of network genes and oncogene copy number. The copy number changes of the 18 genes correlating with network sensitivity are driven by amplification or deletion of neighboring oncogenes and tumor suppressor genes respectively. The strongest correlation was observed with the copy number of POLR2E, a shared subunit of all three nuclear RNA polymerases and established chaperone target of URI1. POLR2E hemizygous deletions are frequently observed in melanoma and lung cancer as a flanking gene of the tumor suppressor STK11. Furthermore, POLR2E displayed properties of a CYCLOPS (copy number alterations yielding cancer liabilities owing to partial loss) gene in melanoma cell lines in that its down-regulation in copy neutral cell lines increased the sensitivity to RNA polymerase inhibition. In summary, our results show that collateral hemizygous deletions of 'housekeeping-genes' that comprise the URI1 onco-chaperone network might be interesting novel therapeutic targets especially in cancers characterized by increased demand on the functions of the identified gene networks.

A versatile chaperone network promotes the aggregation and disaggregation of proteins

Bernd Bukau
Center for Molecular Biology of Heidelberg University (ZMBH),
German Cancer Research Center (DKFZ), DKFZ-ZMBH Alliance,
Heidelberg, Germany

Misfolded proteins are sticky and tend to form intracellular aggregates underpinning age-related deterioration and disease. Normally, multi-tiered cellular quality control systems monitor and repair protein damage, limiting aggregation. Severe stress however overloads these systems allowing aggregates to accumulate. This activates a cellular machinery which mediates the organized aggregation of misfolded proteins as well as the subsequent solubilisation and refolding and of aggregated proteins. This machinery plays a pivotal role in cell survival under protein folding stress and in counteracting disease and age-associated cell toxicities.

Small heat shock proteins (sHsp) constitute an evolutionary conserved yet diverse family of chaperones acting as first line of defense against proteotoxic stress. The yeast sHsps Hsp42 and Hsp26 promote the storage of misfolded proteins in native-like conformation which facilitates disaggregation by ATP dependent chaperone systems. In plants, fungi and bacteria the central disaggregation machinery is a powerful bi-chaperone system comprised by the AAA+ disaggregase Hsp100 (Hsp104, ClpB) and the cooperating Hsp70 chaperone with its co-chaperones, J-domain proteins (JDPs) and nucleotide exchange factors (NEFs). Metazoan cells lack Hsp100 disaggregases, but have evolved a potent Hsp70-based disaggregation machinery which relies on synergistic action of Hsp70 and its co-chaperones. This activity has broad specificity and can even disassemble amyloid fibrils of α-synuclein. A different disaggregation strategy has therefore evolved in evolution of metazoa.

Nadinath Nillegoda, Anne Wentink, Axel Mogk, Bernd Bukau

Structural and functional basis of protein Phosphatase5 specificity

Cara Vaughan
Institute of Structural and Molecular Biology (ISMB), School of Crystallography, Birkbeck College, London, UK

The molecular chaperone Hsp90, together with its cochaperone Cdc37, is responsible for the activation of approximately 60% of the kinome, many of which are involved in pathways that are dysregulated in cancer. Our previous research showed that the process of kinase activation requires the regulated dephosphorylation of Cdc37 by the Hsp90 dependent phosphatase PP5 and that this reaction occurs when all three proteins are simultaneously bound to each other. In order to understand the molecular determinants of the dephosphorylation, and its mechanistic requirements for client kinase activation, we solved the crystal structure of a peptide of Cdc37 trapped in the catalytic groove of the PP5 catalytic domain. The structure reveals that Cdc37 binds in a manner that utilizes primarily backbone interactions, but that some specificity is provided by the PP5 catalytic domain at the -2 position. Mutations that prevent the activity of PP5 towards Cdc37 in vitro, trap a range of substrates on Hsp90 chaperone complexes in vivo, indicating that Cdc37 dephosphorylation is a requirement for client-kinase release during Hsp90's ATP-driven cycle. Mutations on Cdc37 that prevent PP5 dephosphorylation in vitro reduce client kinase association with Hsp90 in vivo, indicating the importance of residues in the proximity of the phosphorylation site for client kinase recruitment to Hsp90. Finally our data show that mutations that compromise the activity of PP5 enhance the affinity between Hsp90 and its ATP-competitive inhibitor, ganetespib.

Structural basis for the interaction of molecular chaperones with non-native proteins

Charalampos Kalodimos
College of Biological Sciences, University of Minnesota, St. Paul, US

Scarcity of high-resolution structural data has impeded an understanding of the recognition and anti-aggregation mechanisms of molecular chaperones. We recently reported the first ever structures of molecular chaperones in complex with unfolded proteins. We used advanced NMR spectroscopy techniques and isotope labeling approaches to determine the solution structure of the 50 kDa Alkaline Phosphatase (PhoA) captured in the unfolded state by three molecules of the Trigger Factor (TF) chaperone (~50 kDa), forming a ~200 kDa complex in solution [1]. We determined the high-resolution structure of each one of the TF molecules in complex with the corresponding unfolded PhoA region and reported how a chaperone dynamically engages its substrate. Very recently, we reported the structure of SecB, a chaperone that exhibits strong antifolding activity, in complex with PhoA and maltose binding protein (MBP) captured in their unfolded states [2]. The structural data revealed a unique complex architecture that explains the activity on the chaperone. Taken together, the data show how the different architectures of chaperones result in distinct binding modes with client proteins that ultimately define the activity of the chaperone.

References

[1] T. Saio, X. Guan, P. Rossi, A. Economou, and C.G. Kalodimos *Science*, **344**, 1250494-13 (2014)
[2] C. Huang, T. Saio, P. Rossi and C.G. Kalodimos *Nature*, **537**, 202-206 (2016)

Structural and functional analysis of human CCT

Guillermo Montoya
Protein Structure & Function Programme, Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences and Integrative Structural Biology Cluster (ISBUC) at the University of Copenhagen, Copenhagen, Denmark

CCT (chaperonin containing TCP-1, also known as TRiC) is a molecular machine that forms a high molecular weight complex (1000 KDa). CCT is emerging as a key molecule during mitosis due to its essential role in the folding of many important proteins involved in cell division (Cdh1, Plk1, p27, Cdc20, PP2a regulatory subunits, tubulin or actin). The assembly is formed by eight different subunits called CCT α, β, γ, δ, ε, ζ, η and θ in mammals corresponding to CCT1–8 in yeast. The chaperonin monomers share a common domain structure (Muñoz et al 2011) including an equatorial domain, which contains all the inter-ring contacts, most of the intra-ring contacts and the ATP binding site, whose binding and hydrolysis triggers the conformational changes that take place during the functional cycle; an apical domain, which contains the substrate-binding region, and the intermediate domain which links the other two domains. The recombinant human complex could be obtained regularly using a co-expression strategy improving the sample yield of pure complex. This improvement of the expression has aided us to further refine the hCCT isolation protocol obtaining a very pure and homogeneous sample. The recombinant complex allowed us to solve the structure of the human CCT assembly using high resolution cryo Electron Microscopy at different stages of the chaperonin cycle.

NOTES

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

Session #3

Stress mechanisms in cancer

Chair: ***Guillermo Montoya***

Wednesday May 3rd, 2017

Essential function and dynamic regulation of heat shock factor: a paradigm from yeast for its role in cancer

David Pincus
Whitehead Institute for Biomedical Research, Cambridge, US

Heat shock factor (Hsf1), the transcription factor responsible for controlling the expression of cytosolic chaperones in eukaryotes, is essential for malignancy in many human cancers. However, its essential function and the mechanisms that regulate its transcriptional activity remain unclear. As in many cancer cells, Hsf1 is essential in yeast. To define the roles that Hsf1 plays to maintain yeast viability, we employed a chemical genetics approach to rapidly deplete Hsf1 from the nucleus and thus inactivate its transcriptional activity. We found that Hsf1 inactivation resulted in proteostasis collapse and eventual cell death. Using NET-seq, RNA-seq and ChIP-seq, we defined a set of 18 genes that depend on Hsf1 for their basal transcription. All but one of these genes encodes a chaperone or other proteostasis factor. By expressing the Hsf1 target genes from Hsf1-independent promoters, we were able to show that expression of only two genes – encoding the Hsp70 and Hsp90 chaperones – was sufficient to support cell growth in the absence of Hsf1 activity. Thus, the essential function of Hsf1 is to drive basal expression of chaperones to achieve proteostasis. To define the regulatory mechanisms that control Hsf1 during heat shcok, we combined biochemistry, genetics, synthetic biology and mathematical modeling to reveal a dynamic interaction between Hsf1 and the chaperone Hsp70. In addition, we identified numerous heat shock-induced sites of phosphorylation on Hsf1. Strikingly, however, Hsf1 retained heat shock-inducible activity when we completely removed its ability to be phosphorylated, but phosphorylation does allow Hsf1 to sustain activity during chronic heat shock. Our work reveals two uncoupled forms of regulation – an ON/OFF chaperone switch and a tunable phosphorylation gain – that allow Hsf1 to flexibly integrate signals from the proteostasis network and cell signaling pathways. Taken together, these studies present a paradigm for Hsf1 function and regulation that should serve as the null hypothesis for its role in cancer and regulation in mammalian cells.

Synergistic and opposite effects of heat shock transcription factors in cell stress and cancer

Lea Sistonen
Faculty of Science and Engineering, Åbo Akademi University Turku Centre for Biotechnology, Åbo Akademi University and University of Turku, Turku, Finland

Plasticity of transcriptional programs is fundamental for the identities of cells and their responses to various stimuli. Heat shock response is a well-conserved protective mechanism characterized by the activation of heat shock factors (HSFs) and subsequent transcription of heat shock proteins (Hsps). Hsps maintain protein homeostasis and enhance cell survival upon stress. In many cancers, the expression of Hsps is abnormally high, and HSF1 is also overexpressed and known to rewire the transcriptome. Although the importance of HSF1 in various cancer types is well documented, the role of HSF2 is poorly understood. Intriguingly, low HSF2 levels in patient-derived prostate cancer biopsies correlate with the high Gleason score and positive metastasis status. Furthermore, both in 3D organotypic cell cultures and in the *in vivo* xenograft chorioallantoic membrane model (CAM), HSF2 depletion from PC-3 cells inhibited spheroid differentiation and promoted the invasive behavior of the cancer cells, suggesting an important role for HSF2 in cancer progression. To investigate the mechanisms by which human cells promptly reprogram transcription upon acute heat stress, we profiled the genome-wide nascent transcripts in K562 cells. The results from Precision Run-On sequencing (PRO-seq) revealed an induction of hundreds of genes and a repression of thousands of genes in heat-shocked cells. In addition to protein-coding genes, many distal regulatory elements that possessed an open conformation prior to stress, were actively transcribed and we named them as distal Transcribed Regulatory Elements (dTREs). PRO-seq showed that the release of promoter-proximal RNA Polymerase to productive elongation is the decisive step for either stress-induced transcriptional upregulation or downregulation. To understand how RNA synthesis is regulated in dynamic chromatin environment, we analyzed the chromatin architecture and how HSF1 interacts with the local chromatin as well as how the transcriptional stress response of genes and dTREs is coordinated across the human genome. Our results highlight the delicate spatial organization of chromatin that pre-wires gene expression and defines the directionality at the promoters upon stress.

Hsp90 releases the break on the Hsp70 folding path

Tania Morán Luengo[1], R. Kityk[2], M. P. Mayer[2], S. D. G. Rüdiger[1]

[1] Cellular Protein Chemistry, Bijvoet Center for Biomolecular Research, Utrecht University, The Netherlands
[2] Zentrum für Molekulare Biologie der Universität Heidelberg (ZMBH), Heidelberg, Germany

Protein folding in the cell relies on the orchestrated action of conserved families of molecular chaperones, the Hsp70 and Hsp90 systems. Hsp70 exhibits refolding activity but Hsp90 does not. The overall process has always remained unclear, since Hsp90 function has not been established.

Making use of *in vitro* folding assays, we observed that under relevant physiological conditions, protein folding capacity of Hsp70 is highly dependent on Hsp90. We show that the process through which Hsp90 takes over the Hsp70-bound substrate occurs in an ATP dependent manner early on the folding path, followed by a slow reaction that leads to functional protein. Together, our data show that Hsp90 facilitates protein folding by breaking the Hsp70 folding cycle.

Prefoldin contributes to transcription elongation in both yeast and human cells

Laura Payán-Bravo[1], Xenia Peñate[1], Gonzalo Millán-Zambrano[1], Silvia Jimeno-Gonzalez[2], Jason Gerkhe[3], Michael Carey[3], José Carlos Reyes[2] and **Sebastián Chávez[1]**

[1] Instituto de Biomedicina de Sevilla (IBiS), Hospital Virgen del Rocío-CSIC-Universidad de Sevilla, Seville, Spain
[2] Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER), CSIC, Seville, Spain
[3] Department of Biological Chemistry, UCLA School of Medicine, Los Angeles, California, US

Prefoldin is a cochaperone, present in all eukaryotes, that cooperates with the chaperonin CCT. It is known mainly for its functional relevance in the cytoplasmic folding of actin and tubulin monomers during cytoskeleton assembly. However, the subunits of this heterohexameric complex have also been found in the nucleus, and are functionally connected with nuclear processes in yeast, plants and metazoa.

We have described that yeast prefoldin is recruited to coding regions in a transcription-dependent manner, and that prefoldin mutants, lacking individual subunits of the complex, show transcription elongation defects, an abnormal distribution pattern of total and elongation-related forms of RNA pol II along genes, and a broad set of genetic interactions with mutant lacking chromatin factors. In agreement to this, prefoldin mutants show substantially higher levels of histones bound to transcribed genes. Moreover, prefoldin-depleted extracts showed decreased in vitro transcription activity on a chromatinized template.

We have also found that depletion of the human PFDN5 subunit causes a marked decrease in the proportion of Ser2-phosphorylated RNA polymerase II that is bound to transcribed genes. This type of phosphorylation is a well-known marker of the elongating form of this enzyme and is functionally associated to co-transcriptional mRNA processing. Accordingly, human PFDN5 depletion produced defects in co-transcriptional splicing in CTNNBL1, a long human gene commonly used to analyze transcription elongation.

All this evidence points to a general contribution of eukaryotic prefoldin to gene expression by influencing RNA polymerase II-dependent transcription elongation.

Cryo-EM structure of the HSP90 co-chaperone required for assembly of the ATM/ATR/mTOR family of kinases

Oscar Llorca
Spanish National Research Council (CSIC), Centre For Biological Research (CIB), Madrid, Spain

Phosphatidylinositol-3-kinase-like kinases (PIKKs) are a family of large protein kinases comprising several members (ATM, ATR, DNA-PKcs, TRAPP, SMG1 and mTOR), with essential roles in DNA repair and DNA damage signaling, among other functions. Correct folding and assembly of PIKK complexes requires the HSP90 chaperone as well as a complicated HSP90 co-chaperone, being a multi-protein complex itself, and possessing several components with inherent ATPase activity.

Our structural and functional understanding of HSP90-mediated maturation of PIKKs is poor. We have reconstituted complexes containing several of the components of this co-chaperone, and their structure is being analyzed by single-particle cryo-electron microscopy (cryo-EM). Cryo-EM images reveal that these are flexible complexes, and we are using several image processing strategies to solve their structure. Our on-going work is providing new information about the structure and function of the HSP90 co-chaperone required for maturation of PIKKs. This work is part of a collaboration with the group of Laurence H. Pearl (University of Sussex, Brighton, UK).

Delineating and exploiting stress response network addictions in malignancies

Marc Mendillo
Northwestern University, Chicago, US

Heat Shock Factor 1 (HSF1), the master transcriptional regulator of the heat-shock response, is a powerful enabler of carcinogenesis. HSF1-deficient mice have a profound resistance to tumor formation and a variety of malignant human cell lines also depend on HSF1 for growth and survival. We previously found that HSF1 is activated in tumors of diverse origin, in a manner that is distinct from its activation during heat-shock. In these tumors, HSF1 activation is strongly associated with metastasis and death. To better understand HSF1 function in cancer, we employed an integrated approach to identify HSF1 regulatory proteins responsible for sculpting the HSF1 cancer program. This included a systematic assessment of most transcription factors, chromatin modifying factors, and kinases, as well as other regulatory factors, for interaction with HSF1 in cancer cells. In this survey, HSF2, an HSF1 paralog, was the top scoring HSF1-interacting transcription factor and scored fifth among all of the nearly 2500 clones we tested. Using diverse methods, we characterized HSF2 function in cancer and assessed how HSF2 activation affects the HSF1 cancer program. Our findings suggest a complex interplay between HSF1 and HSF2 that ultimately impacts malignant progression. Lastly, I will discuss our strategies to reveal vulnerabilities dependent on the oncogenic activation of HSF1 and HSF2 that we can exploit as a therapeutic strategy to target cancers of diverse origin.

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

Session #4

Chaperones in cancer

Chair: ***Nabil Djouder***

Thursday May 4th, 2017

Chaperoning selective autophagy in cancer biology

Ana María Cuervo
Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, New York, USA

Autophagy mediates the digestion of cytosolic material in lysosomes and is often the first-front of defense against cellular stress. Selective forms of autophagy often use chaperones for cargo targeting into the lysosomal compartment for degradation. Our group is interested in two selective forms of autophagy depending on hsc70, namely chaperone-mediated autophagy and endosomal microautophagy. We have identified that decline in CMA activity is a risk factor for malignant transformation, but that once cells become cancerous they depend on CMA for the maintenance of their cellular energetics and as a mechanism of defense against genotoxic damage. In this talk, I will discuss some of our findings on the specific functions of hsc70 in the cross-talk among different autophagic pathways and on the consequences of alterations in this cross-talk in cancer cell biology.

Kupffer-cell derived TNF triggers cholangiocellular tumorigenesis through JNK due to chronic mitochondrial dysfunction and ROS

Mathias Heikenwälder
DKFZ, German Cancer Research Center, Heidelberg; Helmholtz Zentrum for Health and Disease, Munich, Germany

Intrahepatic cholangiocarcinoma (ICC) is a malignant liver cancer typically diagnosed at therapy-resistant advanced stages, with poor prognosis and increasing incidence worldwide. Cellular origins and molecular mechanisms underlying ICC progression are poorly understood. ICC is observed both in diseases affecting biliary epithelial cells (BECs) such as primary sclerosing cholangitis and in diseases that cause chronic hepatocyte injury and usually predispose to HCC development such as chronic hepatitis C or B virus infection, chronic alcohol abuse, and non-alcoholic steatohepatitis (NASH). Since a common feature of these etiologies is chronic liver damage, concomitant mitochondrial dysfunction and high levels of ROS, understanding how the latter shape the liver microenvironment and liver cancer progression may provide novel intervention strategies. Analyzing human and murine ICC as well as hepatocellular carcinoma (HCC), we found that mitochondrial dysfunction and oxidative stress trigger a niche favoring cholangiocellular overgrowth and tumorigenesis.

To address the role of mitochondrial dysfunction and ROS in ICC development, we established a novel mouse model of chronic mitochondrial dysfunction in the liver by genetically deleting the main mitochondrial chaperone HSP60 from liver parenchymal cells. Liver damage, ROS and paracrine TNF from Kupffer-cells caused JNK-mediated cholangiocellular proliferation and oncogenic transformation. Anti-oxidant treatment, Kupffer-cell depletion, genetic TNFR1-deletion or pharmacological pJNK-inhibition reduced cholangiocellular pre-neoplastic lesions. Liver-specific JNK1/2 deletion led to enhanced survival and tumor reduction in AKT/NOTCH or p53/Kras induced ICC-models. In human ICC high TNF-expression nearby ICC lesions, cholangiocellular JNK-phosphorylation and ROS accumulation in surrounding hepatocytes is present. Thus, Kupffer-cell-derived TNF favors cholangiocellular proliferation/differentiation and carcinogenesis. Targeting the ROS/TNF/JNK-axis may provide novel opportunities for ICC therapy.

Detian Yuan[1,2] and Mathias Heikenwalder[1,2]

[1] Division Chronic Inflammation and Cancer, German Cancer Research Center (DKFZ), Neuenheimer Feld, Heidelberg, Germany.
[2] Helmholtz Zentrum for Health and Disease, Munich, Germany.

SHORT TALK

The transcription factor PQM-1 is a novel regulator of proteostasis and mediator of transcellular chaperone signalling in *C. elegans*

Patricija van Oosten-Hawle
Faculty Biological Sciences and Astbury Centre, University of Leeds, Leeds, UK

The significance of cell protective stress response mechanisms is now widely appreciated to not just act at the level of single cells, but at the "multicellular" level. Evolutionary conserved stress responses initiate "transcellular chaperone signalling" (TCS) that allows protective chaperone expression to be signalled from one tissue to another. How TCS functions at the molecular level however remains an open question to date. Using a systems-wide approach and further genetic analysis, we have identified the GATA transcription factor PQM-1 as a mediator of TCS in C. elegans. We demonstrate that PQM-1 is required for proteostasis maintenance and show how depletion of *pqm-1* suppresses induction of TCS-mediated *hsp90* expression in several target tissues. Transcriptional activity of PQM-1 in the *C. elegans* intestine is increased during TCS-activating conditions, suggesting the requirement of the intestine as a key organ to transduce TCS across different tissues.

Dan O'Brien, Rebecca Aston, Vijay Shanmugiah, David Westhead and Patricija van Oosten-Hawle. Faculty of Biological Sciences and Astbury Centre, University of Leeds, UK.

SHORT TALK

The co-chaperone URI maintains crypt identity and protects against colorectal cancer

Almudena Chaves[1], Mahmut Yilmaz[1], Cristian Perna[2] and Nabil Djouder[1*]

[1] Cancer Cell Biology Programme, Growth Factors, Nutrients and Cancer Group, Centro Nacional Investigaciones Oncológicas, CNIO, Madrid, Spain
[2] Department of Pathology, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain
[*] Department of Pathology, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer death worldwide but, predictive biomarkers and molecular mechanisms remain elusive. In absence of genetic risk factors, environmental stressors including poor diets and fecal bacteria infection can lead to intestinal pathologies progressing to CRC. Here, we show that unconventional prefoldin RPB5 interactor (URI), a co-chaperone protein is down-regulated in murine intestinal epithelium by absence of nutrients or H. pylori infection and URI expression protects the intestinal layer from environmental stress. Genetic URI ablation in murine intestine disrupts intestinal homesotasis, increasing DNA damage and p53-dependent apoptosis. Mechanistically, URI loss activates β catenin/c-MYC axis specifically in the crypt, inducing proliferation/ stemness and reducing differentiation. c-Myc ablation reinstates intestinal homeostasis and abolishes tumor formation. Thus, URI is essential to maintain crypt identity, conferring to the intestine a protective capacity against environmental stress-induced intestinal pathologies and CRC. Targeting c-MYC/p53 pathway may be valuable strategic therapies in high-risk patients.

SHORT TALK

Loss of the proteostasis factor AIRAPL causes myeloid transformation by deregulating IGF-1 signaling

Olaya Santiago-Fernández, Fernando G. Osorio & Carlos López-Otín

Departamento de Bioquímica y Biología Molecular, Facultad de Medicina,
Instituto Universitario de Oncología (IUOPA), Universidad de Oviedo, Oviedo, Spain
Centro de Investigación Biomédica en Red de Cáncer, Madrid, Spain

Maintenance of protein homeostasis is a key requirement for all organisms in order to tolerate environmental stress, and its disruption may trigger different pathologies such as cancer and neurodegenerative diseases. AIRAPL (arsenite-inducible RNA-associated protein-like protein) plays a key role in preserving cellular proteostasis and its deficiency in C. elegans leads to protein aggregation and lifespan reduction. We have recently developed and characterized AIRAPL-deficient mice, and remarkably found that they show a fully-penetrant myeloproliferative neoplastic process early in life. This process resembles the human myeloproliferative neoplasms (MPNs) showing common signs and characteristics, and patients suffering from this syndrome also present a reduction in AIRAPL levels in peripheral blood and bone marrow. In this case, neither genetic alterations nor epigenetic changes were seen in the gene codifying for AIRAPL, but a notable upregulation in miR-125a-3p, which in turn regulates the levels of AIRAPL, was detected in these patients. Regarding the molecular mechanism, proteomic analyses demonstrated that AIRAPL controls the IGF-1 pathway by promoting the ubiquitination and degradation of IGF1 receptor (IGF1R) at the endoplasmic reticulum. Furthermore, both genetic and pharmacological inhibition of IGF1R in AIRAPL-deficient mice prevented myeloid transformation. Overall, these findings demonstrate the antineoplastic role of AIRAPL through IGF1R regulation, supporting the existence of a common bond between alterations in proteostasis control and oncogenic transformation of myeloid cells, paving the way for new therapeutic approaches to fight these neoplasms.

Metabolism, inflammation and immunity in liver cancer

Michael Karin
Laboratory of Gene Regulation and Signal Transduction,
Departments of Pharmacology and Pathology and Medicine, San Diego, USA

Although discussion of the obesity epidemic spreading around the developed world had become a cocktail party cliché, the impact of obesity on public health and the economy of healthcare is profound and long-lasting. In the past decade, cancer had joined the long list of chronic debilitating diseases whose risk is greatly increased by obesity and hypernutrition. The impact of obesity on cancer risk is most striking in the liver and pancreas, two organs that are directly engaged in lipid metabolism. To better understand how obesity leads to non-alcoholic steatohepatitis (NASH), a chronic fat-induced liver inflammation that progresses to liver fibrosis and then to cancer, we had developed a new mouse model that develops NASH-like disease in response to ingestion of high fat diet. Using this model, we found that endoplasmic reticulum (ER) stress and TNF-driven inflammation play key roles in the development of NASH and its progression to hepatocellular carcinoma (HCC). We also found that interference with TNF signaling or administration of compounds that relieve ER stress can be used to prevent NASH development and may be effective in reducing HCC risk. Another important pathway that contributes to NASH-driven HCC development depends on accumulation of the autophagy receptor p62/SQSTM1, the main component of Mallory Denk Bodies (MDB). p62 accumulates in response to oxidative stress and hypernutrition and leads to activation of NRF2, which protects HCC progenitor cells from oncogene-induced death, thereby allowing these cells to accumulate numerous driver mutations. In addition, we have identified NASH-stimulated immunosuppressive mechanisms that interfere with the acquisition of an anti-HCC immune response. Interference with these immunosuppressive mechanisms represents an effective strategy for the treatment of NASH-induced HCC, a heretofore incurable malignancy.

ER protein misfolding causes mitochondrial dysfunction leading to oncogenesis

Randal J. Kaufman
SBP Discovery Institute,
La Jolla, US

The endoplasmic reticulum (ER) uses ATP for protein folding and secretion, and perturbation of cellular bioenergetics can cause protein misfolding in the ER, i.e., ER stress. The unfolded protein response (UPR) is an adaptive response designed to resolve protein misfolding in the ER that is signaled through three transmembrane sensors, primarily IRE1α, ATF6α, and PERK. If protein misfolding is not resolved, cells initiate apoptosis. To prevent apoptosis, cells require PERK mediated phosphorylation of eukaryotic initiation factor 2 (eIF2) on the alpha subunit to attenuate protein synthesis. Paradoxically, a number of mRNAs, including *Atf4* mRNA, require eIF2α phosphorylation for efficient translation. In response to ER stress, a second signal is required which we propose is mitochondrial production of reactive oxygen species. Recently, we demonstrated that protein misfolding in the ER causes oxidative stress that in combination with a high fat diet leads to non-alcoholic hepatosteatosis (NASH) and hepatocellular carcinoma.

NOTES

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

Session #5

Targeting chaperones: chaperonotherapy

Chair: ***Lea Sistonen***

Thursday May 4th, 2017

Designing molecules that target heat shock proteins: an approach for inhibiting Hsp90, Hsp70 and Hsp27

Shelli R. McAlpine
University of New South Wales (UNSW), School of Chemistry,
Sydney, Australia

Heat shock proteins (Hsps) are critical for maintaining proteins within the cell. When these chaperone functions function inadequately or in excess they produce diseases. This presentation will describe our general approach to designing new molecules that target Hsps 90, 70 and 27, all of which are heavily involved in folding and maintaining proteins. Starting from peptide sequences that mimic portions of co-chaperone binding domains that interact with the Hsps, we describe the design, synthesis and the latest development on our three new series of compounds that target Hsp90, 70, and 27 respectively. Highlighted will be our efforts to produce compounds that bind to the protein targets, block interactions between co-chaperones, inhibit the protein function, and produce cell permeable molecules.

What have we learned from the clinical development of HSP90 inhibitors?

Udai Banerji
Clinical Pharmacology and Trials Team, The Institute of Cancer Research, London, UK

Multiple different chemical classes of HSP90 inhibitors have been developed with robust efficacy in preclinical models. However, despite this, significant HSP90 inhibitors have not yet been licensed for anticancer therapy.

It is time to reflect on why this has not happened. Is there a valid therapeutic index in patients? Was the expectation that single agent activity would be seen overtly optimistic? Were the correct combination therapies chosen? Were the correct predictive and pharmacodynamics biomarkers chosen? Was the introduction into treatment made at a time when a multi-resistant phenotype had developed too late?

Learning from our experience we should chart the best way forward for this class of agents in order to progress through to licensed anticancer drugs. Lessons may be learned from the development of HSP90 inhibitors that we can take forward with future drugs targeting the chaperone superfamily and other cancer drug targets that influence post-translational modification of proteins.

SHORT TALK

Computational studies of the Hsp90 system to design new anticancer drugs

Elisabetta Moroni[1], Carlos Sànchez-Martìn[2], Andrea Rasola[2], Ilda D'Annessa[3], Antonella Paladino[3], **Giorgio Colombo[3]**

[1] IRCCS Multimedica, Milano, Italy
[2] Dipartimento di Scienze Biomediche - DSB, Università di Padova, Padova, Italy
[3] Istituto di Chimica del Riconoscimento Molecolare, CNR, Milan, Italy

Controlling Hsp90 chaperone pathways through chemically designed modulators may provide novel opportunities to develop therapeutics and chemical tools. Herein, we tackle this problem through computational studies of Hsp90 and several representatives of client kinases.

First, we examine the origins of the stimulation of ATPase and closure kinetics in Hsp90 by designed allosteric modulators. To this end, we apply atomistic molecular dynamics (MD) simulations and analysis of the effects of the ligand-protein cross-talk on the internal dynamics of the chaperone. A critical aspect of this study is the development of a quantitative model that correlates Hsp90 activation to the presence of a certain compound. In particular, the model makes use of information on the dynamic adaptation of protein structure to the presence of the ligand, which allows to capture the most relevant conformational states in the activation process. We test this model by rationally designing and experimentally validating new allosteric modulators with improved stimulation profiles and encouraging anticancer activities. This computational protocol is then applied to Trap1, revealing new allosteric ligands with high isoform selectivity.

Next, we focus on Hsp90 clients: starting from the analysis of the TK family of proteins, we develop a model that quantitatively correlates the energetic stabilization profile of each kinase to its "Hsp90-clientness". We then extend this model to other kinase families, identifying the determinants of folding/unfolding that correlate with the tendency to form complexes with Hsp90. We use this information to design kinase-mimics that target Hsp90 and may act as Hsp90-targeted Protein-Protein inhibitors.

SHORT TALK

Integrating multiscale network modeling and computational systems biology with biophysical characterization of the Hsp90 interactions with cochaperones and protein clients: atomistic reconstruction of allosteric regulatory mechanisms and client recruitment by the chaperone machine

Gennady Verkhivker[1,2] and Kristin Blacklock[3]

[1] Department of Biomedical and Pharmaceutical Sciences, School of Pharmacy, Chapman University, One University Drive, Orange CA, US
[2] Department of Pharmacology and Skaggs School of Pharmacy, University of California San Diego, Gilman Drive, San Diego, CA, US
[3] Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ, US

The synergistic roles of Hsp90-Cdc37 chaperone machinery and protein kinases in biology and disease have stimulated extensive structural and functional studies of regulatory mechanisms underlying the Hsp90-kinase interactions. By integrating multiscale modeling of the Hsp90 chaperone and Other Information: tyrosine kinases clients with systems biology analysis and biophysical characterization of the chaperone-kinase interactions, we characterize dynamics and energetics of allosteric regulation between the Hsp90-Cdc37 chaperone and protein tyrosine kinase clients at the atomic level. Our findings have revealed a hierarchy and a multi-stage framework of the allosteric mechanism, in which Cdc37 N-terminal domain can orchestrate a cascade of allosteric interactions with the Hsp90 chaperone and Cdk4 client by probing conformational heterogeneity and energetic polarization in the kinase lobes. The results have suggested that the chaperone-induced remodeling of conformational landscapes in client kinases may operate through a reciprocal entropy transfer in which protection of the partially unfolded kinase states by Hsp90 may spatially confine client ensemble and accelerate refolding The organization and thermodynamics of the residue interaction networks in the chaperone-kinase complexes have supported the indispensable mediating role of Cdc37 in allosteric regulation. Modeling of allosteric pathways in the chaperone-kinase complexes has also delineated structural and energetic signatures of allosteric hotspots, particularly linking sites of post-translational modifications in Hsp90 with their role in allosteric interactions and client regulation. Using multiscale modeling, energetic scanning and NMR studies, we have also examined conformational landscapes of a wide range of kinase clients and nonclients, discovering how client status is strongly linked with the dynamic and energetic polarization of the kinase lobes in in the inactive states.

Blacklock K, Verkhivker GM. Computational modeling of allosteric regulation in the Hsp90 chaperones: a statistical ensemble analysis of protein structure networks and allosteric communications. *PLoS Comput Biol*. 2014;10: e1003679.

Stetz G, Verkhivker GM. Computational analysis of residue interaction networks and coevolutionary relationships in the Hsp70 chaperones: A community-hopping model of allosteric regulation and communication. *PLoS Comput Biol*. 2017;13 :e1005299.

HSP90 inhibition in cancer versus ciliopathies

Erica Golemis
Molecular Therapeutics, Fox Chase Cancer Center,
Philadelphia, US

Heat shock protein 90 (HSP90) binding supports the expression and/or the activity of numerous client proteins that contribute to cancer growth. As a result, tumors typically express high levels of active HSP90. Autosomal dominant polycystic kidney disease (ADPKD) occurs in ~1 in 500 people, and arises from inherited mutations in the genes PKD1 or PKD2, which encode polycystins that heterodimerize on the cellular monocilium, making ADPKD the most common ciliopathy. Although the clinical presentation of ADPKD is marked by formation of renal cysts rather than invasive tumors, many signaling proteins activated and known to have driver function in cancer are also activated and contribute to pathogenesis of ADPKD. Since many of these proteins are HSP90 clients, we have evaluated HSP90 expression and the activity of HSP90 inhibitors in mouse models for ADPKD. We find that HSP90 is highly expressed in early renal cysts, and HSP90 inhibition is extremely effective at controlling cystogenesis in multiple models for ADPKD. Intriguingly, HSP90 inhibition not only reverses many signaling defects associated with this disease, but also directly impacts ciliation. HSP90 inhibitors rapidly induce ciliary disassembly *in vitro*, and result in sustained loss of cilia *in vivo*, based on activation of key disassembly factors. As cilia have recently emerged as hubs for multiple signals involved in tumor-stromal communications that promote tumorigenesis, these activities are potentially relevant to the use of HSP90 inhibitors in regulation of tumor microenvironmental cues.

The discovery and development of oral HSP90α/β inhibitor, TAS-116

Shuichi Ohkubo
Taiho Pharmaceutical Co., Ltd.,
Tokyo, Japan

Heat shock protein (HSP)90 is a molecular chaperone that regulates the activity and stability of a diverse range of "client" proteins, which includes many of the cancer-associated factors that cancer cells become "addicted" to for their survival and proliferation. Since HSP90 inhibition results in the simultaneous disruption of multiple oncogenic signaling pathways, the targeting of HSP90 is considered a powerful approach for the treatment of targeted therapy–resistant tumors that have arisen from mutations within the target itself or from activation of alternative signaling. Several HSP90 inhibitors have been developed and some have shown clinical activities in certain types of tumors; however, none are currently approved for any cancer indication. Here, we will review the development of HSP90 inhibitors and discuss the issues that have hampered their clinical development. Then we will present the discovery and development of TAS-116, which is a non-ansamycin, non-purine and non-resorcinol, orally active, highly selective inhibitor of HSP90α and β. Oral administration of TAS-116 resulted in potent antitumor activity accompanied by depletion of HSP90 clients in various human tumor xenograft mouse models. Importantly, in a rat model, TAS-116 showed a favorable therapeutic index due to limited exposure of TAS-116 to nontarget tissues such as eyes and greater exposure to target tumor tissues. A first-in-human Phase I trial of TAS-116 is ongoing in patients with solid tumors in Japan and UK. Also, phase II study in patients with advanced gastrointestinal stromal tumors (GIST) is currently ongoing based on preclinical evidence and anti-tumor activity of TAS-116 in GIST patients including a confirmed partial response observed in the Phase I trial. We will discuss the therapeutic potential of TAS-116 based on those preclinical and clinical findings.

Pathways of HSP90 client protein degradation

Laurence Pearl
Genome Damage and Stability Centre, School of Life Sciences, University of Sussex, Brighton, UK

Pharmacological inhibition of the conformationally-coupled ATPase cycle of the HSP90 chaperone, promotes ubiquitylation and proteasomal degradation of client proteins. These include many oncogenic protein kinases, providing the rationale for HSP90 ATPase inhibitors as cancer therapeutics. Client protein kinase ubiquitylation and degradation is also promoted by ATP-competitive protein kinases inhibitors, which prevent binding of the kinase co-chaperone Cdc37 and deprive the client proteins of access to the HSP90 chaperone system. Despite the importance of these processes the mechanism by which HSP90 ATPase inhibition triggers ubiquitylation is not well understood. In particular, the nature of the E3 ubiquitin ligase(s) complexes involved and the degron(s) that they recognize are largely unknown.

To gain insight into how client protein kinases are specifically targeted for ubiquitylation and degradation following HSP90 inhibition, we have developed a cell based assay system amenable to high-throughput siRNA screening. Using this have identified components of independent pathways involved in degradation of HSP90 client kinases such as CRAF. One pathway involves CUL5 and its associated scaffold proteins Elongin B and Elongin C, while the other requires the poorly described HECT-family E3 ligase HECTD3. Our data identify HECTD3 as an important and novel player in the HSP90 inhibitor-dependent degradation of protein kinase clients.

Drugging the cancer genome and the cancer state with inhibitors of HSP90, HSP70 and the HSF1 pathway

Paul Workman
Cancer Research Cancer Therapeutics Unit, The Institute of Cancer Research, London, UK

My laboratory has an ongoing interest in molecular chaperones, the HSF1 pathway and proteostasis mechanisms as processes that support oncogenesis and the malignant state. In addition, within the ICR's CRUK Cancer Therapeutics Unit, we have been instrumental in discovering a number of chemical probes and drugs aimed to exploit the dependence of cancer cells on these mechanisms – as part of an overall approach to exploit so-called 'non-oncogene addiction' and tackling the therapeutic challenge of drug resistance. I will 1) provide an update on the discovery and clinical development of our HSP90 inhibitor luminespib (AUY922; collaboration with Vernalis); 2) illustrate our recent studies on target validation and discovery of inhibitors for the HSP70 family; and 3) describe our recent discovery of a potent and selective inhibitor pf the HSF1 pathway, with activity in animal models of ovarian cancer. I will conclude by reviewing future prospects and challenges in the field.

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

ORGANISERS AND SPEAKERS' BIOGRAPHIES

Nabil Djouder
Growth Factors, Nutrients and Cancer Group, Cancer Cell Biology Programme,
Spanish National Cancer Research Centre,
Madrid, Spain

Dr. Nabil Djouder, born in France, obtained his PhD in Molecular Pharmacology from the University of Strasbourg (France) and the University of Freiburg (Germany), where he worked in the laboratory of K. Aktories. He studied the molecular mechanisms underlying the activation of mast cells by cross-linking high affinity antigen receptors (Fcε-RI) and the involvement of small GTPases from the Rho family in this activation.

In 2001 he moved to Basel (Switzerland) as a postdoctoral research fellow and joined the laboratory of W. Krek at the Novartis Friedrich Miescher Institute. He has since worked in the field of growth control, cancer, and associated metabolic disorders. Most of his research focuses on the mTOR/S6K pathway and the integration of growth factors, nutrients, and energy homeostasis.

In 2003 he moved with W. Krek to the Institute of Cell Biology at the Eidgenössische Technische Hochschule (ETH) in Zurich. He became a member of the Competence Centre for Systems Physiology and Metabolic Diseases (CCSPMD). In September 2009 Nabil Djouder joined the CNIO as a Junior Group Leader, establishing his group in the field of Growth factors, Metabolism and Cancer.

Wilhelm Krek
ETH Zurich, Inst. f. Molecular Health Sciences,
Zurich, Switzerland

Dr. Wilhelm Krek has been Full Professor of Cell Biology at ETH Zurich since 2003. He studied Chemistry at the Technical University Graz/Austria and performed his PhD work at the Swiss Cancer Institute in Lausanne/Switzerland. After his postdoctoral training at the Dana Farber Cancer Institute/Harvard Medical School in Boston/USA, he joined in 1995 the Friedrich Miescher Institute in Basel/Switzerland as an independent investigator. He received several honors including the Robert Wenner, the Friedrich Miescher and Steiner Cancer Research Awards and is elected member of EMBO. Wilhelm Krek has been co-founder and founding chair of the Institute of Molecular Health Sciences at ETH Zurich and of the NEXUS Personalized Health Technologies Platform. He also co-founded the ETH spin-off ProteoMediX. His research interest focuses on the biology of hypoxia signaling in the progression of malignant and metabolic disorders and on converting aspects of their discoveries into precision medicines.

Paul Workman

FRS FMedSci, Cancer Research Cancer Therapeutics Unit, The Institute of Cancer Research, London, UK

Currently, Professor Paul Workman FRS FMedSci is CEO and President of The Institute of Cancer Research (ICR), London. From 1997 - 2016 he was Director of the CRUK Cancer Therapeutics Unit at ICR – the world's largest non-profit cancer drug discovery group. Paul has been responsible for more than 20 molecularly targeted cancer drugs entering clinical trial, including protein kinase, PI3 kinase and HSP90 inhibitors.

Before joining ICR, Paul spent 4 years leading cancer research at AstraZeneca and prior to that worked at Glasgow, Stanford and Cambridge Universities. He was a scientific founder of Piramed Pharma (acquired by Roche) and Chroma Therapeutics.

In addition to running his own lab, as CEO and President of ICR, Paul now guides strategic developments in the field of basic, translational and clinical cancer research. He talks, writes and blogs about cancer research and treatment and also about the drug discovery ecosystem. He published more than 535 scientific articles.

Paul has won numerous awards and fellowships including being elected as a Fellow of the Royal Society in 2016 and was also named in the Evening Standard's Progress 1000 list of the most influential people in London.

Xiaohong Helena Yang
Cancer Cell,
Cambridge, US

Dr. Xiaohong Helena Yang received her PhD degree from the Molecular Genetics program jointly established by Stony Brook University and Cold Spring Harbor Laboratory. Before joining *Cancer Cell* as Scientific Editor in 2008, She held staff positions in the US including Ionis Pharmaceuticals Inc., Massachusetts General Hospital and Harvard Medical School. At *Cancer Cell* she manages manuscript submissions, the peer-review process and front matter contents in all topic areas covered by the journal. She was appointed Deputy Editor in 2015. In additional to her editor role, Dr. Yang has been Cell Press's Editorial Development Advisor since 2012 focusing on the organization's development in Greater China. In conjunction with this role, she has also acted as publisher of *Molecular Plant*, Cell Press's first partnership journal from China and Asia, since 2015.

Udai Banerji

MD PhD FRCP Team Leader, Clinical Pharmacology and Trials Team,
The Institute of Cancer Research, London, UK

Dr Udai Banerji is currently an honorary consultant in Medical Oncology at the Royal Marsden, London, UK. He is Deputy Head of the Drug Development Unit, which has a portfolio of over 30 phase I trials, and he is involved in running a number of these trials. His interests include the discovery and applications of HSP90, PI3K, AKT and mTOR inhibitors. He has been a principal investigator of over 25 phase I studies and has been a sub-investigator on over 100 phase I studies.

In addition to Phase 1 trials, Dr Banerji's independent laboratory interests include the use of pharmacodynamic biomarkers. He heads the Clinical PD Biomarker Group at The Institute of Cancer Research, which focuses on the quantification of biomarkers in normal tissue (platelet-rich plasma, peripheral blood mononuclear cells and hair follicles) and tumour tissue to be used as pharmacodynamic biomarkers in Phase I studies. He also runs a laboratory team with interests in understanding dynamic signaling networks to devise interesting drug combinations.

Johannes Buchner
Department Chemie, Technische Universität München,
Munich, Germany

Dr. Johannes Buchner received his PhD from the University of Regensburg, Germany, After a postdoctoral stay at the National Cancer Institute of the NIH in Bethesda, USA, he was a group leader at the University of Regensburg. Since 1998 he is a professor at the Technische Universität München, Munich, Germany. His research interests include mechanistic studies on molecular chaperones, principles of antibody folding and association, as well as their evolution. Johannes Buchner received several prizes for his work, including the Hans Neurath Award, the Kossel-Award and the Schleiden Medal.

Bernd Bukau
University of Heidelberg, Center for Molecular Biology Heidelberg (ZMBH), Heidelberg, Germany

Dr. Bernd Bukau studied biology at the Universities of Besançon and Konstanz and received his PhD in bacterial genetics with Prof. Winfried Boos at the University of Konstanz. After three years as a postdoctoral fellow with Prof. Graham Walker, Massachusetts Institute of Technology (USA), he joined the group of Prof. Hermann Bujard where he built up an independent research group at the Center for Molecular Biology of the University of Heidelberg (ZMBH). In 1997 he took over the chair in biochemistry at the Medical Faculty in Freiburg, and in 2002 he accepted a professorship at the ZMBH in molecular biology. He was Deputy Director of the ZMBH from 2002-2004, and is the Executive Director of the institute since 2004. Also, he is Co-Founder and Co-Director of the Alliance between the ZMBH and the German Cancer Research Center (DKFZ) since 2008 and speaker of the Collaborative Research Center „Cellular Surveillance and Damage Respose" (SFB 1036) since 2012. Prof. Bukau has received several research awards including the Gottfried Wilhelm Leibniz-Price of the German Science Foundation and is member of EMBO. His research focus is the regulation of the heat shock response and the mechanisms of molecular chaperones.

Gabriela Chiosis

Memorial Sloan Kettering Cancer Center
Member and Tri-Institutional Professor, Program in Chemical Biology
Attending Chemist, Breast Cancer Service, Department of Medicine, Memorial Hospital, Memorial Sloan Kettering Cancer Center,
Professor, Weill Graduate School of Medical Sciences, New York
Faculty, Cancer Biology Program of the Gerstner Sloan Kettering Graduate School

Dr. Gabriela Chiosis received her graduate training at Columbia University in New York and joined Memorial Sloan Kettering Cancer Center in 1998, first as a fellow and, since 2005, as faculty. She has authored over 130 scientific articles which were published by virtually all well respected scientific and medical journals, holds over 190 patents and patent applications which are related to the discovery of novel compounds as therapeutic agents or diagnostics in human medicine, is serving as a reviewer for over 50 well-known scientific and medical magazines and on several scientific panels. She is also a co-founder of and Chief Scientific Officer at Samus Therapeutics Inc, and also serves on its Board of Managers. Novel compounds and diagnostics discovered by her lab are the platform for the development of inhibitors currently in clinical evaluation in patients with advanced cancers.

Ana Maria Cuervo

Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, New York, US

Dr. Ana Maria Cuervo is the R.R. Belfer Chair for Neurodegenerative Diseases, Professor in the Departments of Developmental and Molecular Biology and of Medicine of the Albert Einstein College of Medicine and co-director of the Einstein Institute for Aging Studies. She obtained her M.D. and a Ph.D. in Biochemistry and Molecular biology from the University of Valencia (Spain) and received postdoctoral training at Tufts University, Boston. In 2002, she started her laboratory at the Albert Einstein College of Medicine, where she continues her studies in the role of protein-degradation in neurodegenerative diseases and aging.

Dr. Cuervo has been the recipient of prestigious awards such as the P. Benson and the Keith Porter in Cell Biology, the Nathan Shock Memorial Lecture, the Vincent Cristofalo and the Bennett J. Cohen in basic aging biology and the Marshall Horwitz for excellence in research. She delivered prominent lectures such as the Robert R. Konh, the NIH Director's, the Roy Walford, the Feodor Lynen, the Margaret Pittman, the IUBMB Award, the David H. Murdoxk, the Gerry Aurbach and the Harvey Society Lectures. She is currently co-Editor-in-Chief of Aging Cell and associate editor of Autophagy and member of the NIA Scientific Council and of the NIH Council of Councils.

Erica Golemis

Ph.D., Professor Deputy Chief Science Officer Co-Chair, Molecular Therapeutics,
Fox Chase Cancer Center, Philadelphia, US

Dr. Erica Golemis received her PhD in Biology from Massachusetts Institute of Technology. Her graduate studies used bioinformatics approaches to identify the common enhancer core for a large set of leukemia inducing viruses, and provided groundwork for the discovery of the key RUNX/AML leukemic regulators. She then conducted postdoctoral studies in Cancer Biology at the Massachusetts General Hospital, Harvard Medical School, where she was lead developer of the Interaction Trap, a yeast two-hybrid system that became a major platform for the identification of protein-protein interactions in the 1990s. Dr. Golemis established an independent laboratory at Fox Chase Cancer Center in 1993. Her current position at Fox Chase is Professor, Co-Leader of the Molecular Therapeutics Program, and Deputy Chief Scientific Officer. Her group has integrated historical interests in protein interaction networks into investigation of the root causes of aggressive cancer, with much of this work focusing on the Aurora-A and NEDD9 oncogenes. Over the past decade, a significant body of work has focused on leveraging signaling similarities between cancer and autosomal dominant polycystic kidney disease (ADPKD). This work has supported repurposing of drugs between diseases, and insights into HSP90 action, and the value of HSP90 inhibitors, in ADPKD.

Mathias Heikenwälder
W3 Professor and Division head "Chronic Inflammation and Cancer"
DKFZ, German Cancer Research Center,
Heidelberg, Germany

I am a trained molecular biologist and microbiologist, with expertise in immunology and a strong link to translational cancer research evoked by 10 years of work and expertise in a Pathology Institution (Clinical Pathology, University Hospital Zurich). Since October 2015 I am Department head at the German Cancer Research Center (DKFZ) in Heidelberg focusing on the link between chronic inflammation and cancer, with the main focus on gastrointestinal and hepatobiliary malignancies.

Our laboratory aims at understanding the role of chronic inflammation induced tissue damage and cancer formation using human patient cohorts, human tissues and relevant mouse models - with the final aim to generate valid models potentially used for pre-clinical research. Thus, we focus on comparative studies of tissue specimen of human patients and animal models, recapitulating human disease on a histo-pathological and pathophysiological level. We engage in molecular biology based techniques, establish novel mouse models (e.g. conventional transgenes; CRISPR-Cas) complemented with sophisticated ways to receive as much information from tissue samples through histology (e.g. light microscopy/ immune fluorescence/ FISH/ in situ hybridization; white laser microscopy), other in vivo imaging techniques (e.g. MRI) as well as through FACS analyses of tissue homogenates. At the same time we are also interested in the systemic functional effects of pathologies and the interplay between several affected non-lymphoid tissues and the immune system.

Testing several established and novel therapeutic compounds in a single but also combinatorial fashion is a strong focus of current work employing established and stratified pre-clinical mouse models. Moreover, we take part and currently also organize pre-clinical Phase I trials.

Charalampos Kalodimos
College of Biological Sciences, University of Minnesota,
St. Paul, US

Dr. Charalampos Babis Kalodimos is a Distinguished Professor at the Medical School of the University of Minnesota since 2015. He obtained his bachelor degree from University of Ioannina in Greece and his PhD from the Institute Curie in Paris. From 1999-2003 he worked as a postdoctoral fellow in the group of Robert Kaptein in Utrecht, The Netherlands, where he was introduced in the world of biomolecular NMR. His group works on two main directions: first, the determination of the structural and dynamic basis for the function and assembly of large protein machineries; and second, the determination of the role of internal protein dynamics in regulating protein activity and allosteric interactions. He has received numerous awards including the Young Investigator Awards from the Protein Society, the Biophysical Society, and the New York Academy of Sciences, the Stig Sunner Award and the Raymond and Beverly Sackler International Prize in the Physical Sciences.

Michael Karin

Laboratory of Gene Regulation and Signal Transduction,
Departments of Pharmacology and Pathology and Medicine, San Diego, USA

Dr. Karin was born in Tel Aviv, Israel and received the Bachelor of Science degree in 1975 from Tel Aviv University, with a major in Biology. In 1975 he arrived in the US and in 1979 received a Ph.D. degree in Molecular Biology from the University of California, Los Angeles. Dr. Karin followed his graduate studies with postdoctoral fellowships at the Fox Chase Institute for Cancer Research, working in the laboratory of Dr. Beatrice Mintz, and the laboratory of Dr. John Baxter at the University of California, San Francisco. Dr. Karin joined the faculty at the University of California, San Diego in 1986, where currently he is a Distinguished Professor of Pharmacology.

Dr. Karin has received numerous awards including the Oppenheimer Award for Excellence in Research from the Endocrine Society in 1990, an American Cancer Society Research Professorship in 1999, the C.E.R.I.E.S. Research Award for Physiology or Biology of the Skin in 2000, the Harvey Prize in Human Health in 2011, the Brupbacher Prize in Cancer Research in 2013 and the William B. Coley Award for Distinguished Research in Basic and Tumor Immunology in 2013. Dr. Karin was elected to the National Academy of Sciences in 2005, as a Foreign Associate of EMBO in 2007, and to the Institute of Medicine in 2011. Dr. Karin also serves on several advisory boards and was cofounder of Signal Pharmaceuticals (currently Celgene).

Dr. Karin has spent his entire academic career investigating stress and inflammation signaling covering the entire gamut of research approaches from basic biochemistry through molecular cell biology to animal pathophysiology. After discovering how environmental stress caused by either infection, inflammation or exposure to toxic substances leads to activation of AP-1, NF-κB and other transcription factors, his lab began to examine the role of the key signaling pathways controlling these transcription factors in the pathogenesis of cancer, degenerative and metabolic diseases. The Karin group has identified some of the fundamental mechanisms through which inflammation and obesity promote tumor development and progression and contribute to type II diabetes. They had established the mechanisms through which members of the IL-6 cytokine family contribute to the development of colorectal and liver cancer through activation of STAT3 and other transcription factors. They had also established the complex and cell type specific mechanisms through which NF-κB activation via IκB kinases (IKK) controls development and progression of colon, liver and prostate cancers. They were amongst the first to demonstrate that not only innate immune cells, such as macrophages, but also adaptive immune cells, including T regulatory cells and B lymphocytes, also contribute to tumorigenesis and its progression. Through this work, Dr. Karin has contributed to the founding of the Inflammation and Cancer field.

Randal J. Kaufman
SBP Discovery Institute,
La Jolla, US

Dr. Kaufman, a leader in basic biomedical research, has made fundamental contributions to translational medicine in his industrial and academic careers. He received a Ph.D. in Pharmacology at Stanford University and performed post-doctoral work with Dr. Phillip Sharp at the MIT Center for Cancer Research. After post-doctoral work, he was a founding scientist the biotech Genetics Institute Inc., where he developed gene cloning and expression strategies in mammalian cells. His team isolated clotting factor genes and engineered cells to produce the recombinant proteins for therapeutic use, that revolutionized protein replacement for hemophilia A. In 1994, he moved to take positions of Investigator at the HHMI and Warner-Lambert/Park-Davis Professor in Medicine and the Department of Biological Chemistry at the University of Michigan Medical Center. In Michigan, his pioneering studies to identify rate-limiting steps in protein secretion elucidated the roles of protein chaperones and enzymes that limit protein folding, processing and trafficking within the early secretory pathway. His ground breaking studies in this area were paradigm-shifting toward future genetic engineering of mammalian cells to efficiently secrete therapeutic proteins and contributed to the discovery of the unfolded protein response (UPR), which has exploded into an entirely new field of investigation. After elucidating the molecular sensors and mechanisms that signal the UPR through PERK, IRE1 and ATF6, Kaufman extended his studies using murine genetic models to show that UPR signaling is essential for normal physiology and also contributes to the progression of diverse pathologies including metabolic syndrome, diabetes, inflammation and cancer. His recent studies identified a molecular mechanism by which protein synthesis causes oxidative stress and dictates whether a cell survives or dies upon accumulation of misfolded proteins in the ER.

Oscar Llorca

Spanish National Research Council (CSIC), Centre For Biological Research (CIB), Madrid, Spain

Dr. Llorca graduated in the University of Navarre in 1992, and then moved to Madrid for his PhD studies. In 1996, Oscar Llorca obtained his Ph.D. in Molecular Biology at the National Centre for Biotechnology (CNB) under the supervision of JL Carrascosa and JM Valpuesta. At the CNB, Llorca performed influential work on the structural characterization of prokaryotic and eukaryotic chaperonins using electron microscopy. He joined the Chester Beatty Laboratories (Institute of Cancer Research, London) in 2000 as a postdoctoral scientist in the section of Cell and Molecular Biology supported by a prestigious Marie Curie Fellowship. He characterized DNA repair complexes under the supervision of Keith R. Willison and in collaboration with the Imperial College. In June 2002, Oscar Llorca became a Group Leader at the Centre for Biological Research (CIB) in Madrid, belonging to the Spanish National Research Council (CSIC). At the CIB, Llorca leads an independent group applying single-particle cryo-electron microscopy to macromolecular complexes involved in DNA repair and RNA degradation. A significant part of his efforts have focused in the structural understanding of the PIKK family of kinases. Llorca has also worked in Structural immunology of complement regulation in innate immunity.

Matthias P. Mayer

Zentrum für Molekulare Biologie der Universität Heidelberg (ZMBH), DKFZ-ZMBH-Alliance, Heidelberg, Germany

10/82 – 07/87	Study of Biology at the University of Freiburg, Diploma in cell biology
08/87 – 02/90	Doctoral work in cell biology at the University of Freiburg, Dr. rer. nat. 6.2.90 (supervisor: Prof. H. Kleinig) Thesis title: The desaturation reactions in carotenoid biosynthesis of *Narcissus pseudonarcissus* L.– Investigations to enzymology and mechanism.
02/90 – 03/92	Postdoctoral Research Associate, Department of Chemistry, University of Utah, Salt Lake City, Utah, USA (PI: Prof. C. D. Poulter); Research project: Characterization of protein farnesylation in *Saccharomyces cerevisiae*.
04/92 – 07/97	Maître Assistant, Centre Médical Universitaire, Genève, Switzerland (PI: Prof. C. Georgopoulos); Research project: Analysis of protein-protein interactions
08/97 – 05/02	Senior Research Associate, Institute for Biochemistry and Molecular Biology, Faculty for Medicine, University of Freiburg; Habilitation in Biochemistry and Molecular Biology 31.1.2002 (mentor: Prof. B. Bukau); Title: Cellular functions and mechanism of the Hsp70 chaperone system.
06/02 – 09/05	Project group leader, Zentrum für Molekulare Biologie der Universität Heidelberg (ZMBH); Research focus: Molecular mechanism of Hsp70 chaperones
since 10/2005	Research group leader, Zentrum für Molekulare Biologie der Universität Heidelberg (ZMBH); Research focus: Regulation of protein conformation – Molecular chaperones of the Hsp70 and Hsp90 families.
11/2011	apl. Prof. at the University of Heidelberg

Shelli R McAlpine
University of New South Wales,
Sydney, Australia

Dr. Shelli McAlpine was born in California, and grew up in Australia. She returned to the US for her B.S. degree, where she graduated from the University of Illinois (1991). She was a Research Associate at Merck and Co (1991-1992), and did her Ph.D. at University of California, Los Angeles (1993-1997). She was a postdoctoral fellow at Harvard University (1997-2000) under Professor Stuart Schreiber. She became an Assistant Professor San Diego State University in 2000, was promoted to Associate Professor in 2006 and then to Professor in 2010. She is currently an Associate Professor at the University of New South Wales (2011-current). Shelli specializes in medicinal chemistry, performing research that is on the frontiers of chemical biology. Her focus is on synthesizing new small molecules that target heat shock proteins 90, or 70, or 27. These three chaperones are all involved in the protein folding process and they regulate cell growth pathways. Inhibiting the function of these three heat shock proteins has implications not only for cancer, but for diseases where protein folding is problematic such as Alzheimer's.

Marc Mendillo
Northwestern University,
Chicago, US

Dr. Marc Mendillo, Ph.D., is an Assistant Professor in the Department of Biochemistry and Molecular Genetics at Northwestern University Feinberg School of Medicine and a full member of the Robert H. Lurie Comprehensive Cancer Center. He received his PhD from the University of California, San Diego where he investigated the mechanism of DNA mismatch repair with Dr. Richard Kolodner. He then pursued postdoctoral training at the Whitehead Institute at MIT with Susan Lindquist, a pioneer in the field of protein folding. In 2015, Dr. Mendillo established his independent group at Northwestern University, where he bridges biochemistry, genetic and chemical biology approaches with systematic high-throughput and genomic methods to define how cellular stress response pathways are co-opted and regulated in cancers with an eye on revealing vulnerabilities that can be exploited for diagnostic and therapeutic purposes, and ultimately adding to the next generation of the anticancer armamentarium. Dr. Mendillo has received a number of distinctions including being named a Kimmel Scholar, Lynn Sage Scholar and Zell Scholar. He has also received a Pathway to Independence Award from the NIH and a fellowship from the American Cancer Society.

Guillermo Montoya

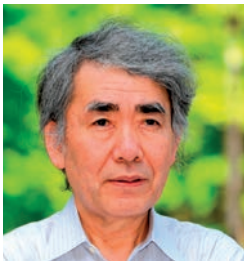
Research Director, Protein Structure and Function Programme
Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Dr. Guillermo Montoya began his scientific career studying the energy transfer process of Photosystem II using picoseconds laser time-resolved spectroscopy. He moved to the Max PIanck für Biophysik in Frankfurt am Main, where he worked in protein crystallography with Prof. Hartmut Michel. After two years, he moved to I. Sinning's group at EMBL-Heidelberg. He pioneered the study of the structure of the signal recognition particle, an essential ribonucleoprotein complex involved in protein targeting and its membrane receptor Ftsy. In 2002, he joined CNIO as group leader. Since then his work has been focused in the study of protein-protein and protein-DNA complexes involved in cell cycle and genome maintenance. In 2007, Montoya was promoted to senior group leader at CNIO. During that time, his group has solved structures of homing endonucleases setting the basis to redesign their DNA binding specificity. In 2011, his group solved the first crystal structure of a chaperonin (TriC/CCT) in complex with tubulin, thus shedding light on the molecular mechanism used by this machine to fold a protein. In 2014 Montoya became Professor at the University of Copenhagen (UCPH) and Research Director of the Protein Structure & Function Programme at the Novo Nordisk Foundation Centre for Protein Research (http://www.cpr.ku.dk/). Montoya is also the Chairman of ISBUC, the Integrative Structural Biology Cluster at UCPH (http://isbuc.ku.dk/).

Richard I. Morimoto

Bill and Gayle Cook Professor of Biology, Director, Rice Institute for Biomedical Research,
Department of Molecular Biosciences, Northwestern University,
Evanston, US

Dr. Rick Morimoto is the Bill and Gayle Cook Professor of Biology and Director of the Rice Institute for Biomedical Research in the Department of Molecular Biosciences at Northwestern University. He holds a B.S. from the University of Illinois, a Ph.D. in Molecular Biology from The University of Chicago, and was a postdoctoral fellow at Harvard University. His research has been on the heat shock response, and the function of molecular chaperones and the proteostasis network in biology to maintain cellular health and to respond to challenges from environmental and physiological stress, aging and diseases of protein conformation including neurodegeneration, metabolic diseases, and cancer. Morimoto has published over 270 papers and edited five books. Some of the academic honors and awards include MERIT awards from the National Institutes of Health, elected membership in the American Academy of Arts and Sciences, the American Association for the Advance of Science, Commandeur Ordre des Palmes Académiques (France), and the Feodor Lynen Medal of the German Society of Biochemistry and Molecular Biology. He is a co-founder of Proteostasis Therapeutics, Inc. a Biotech in Cambridge, MA to discover small molecule therapeutics for diseases of protein conformation.



Kazuhiro Nagata

Institute for Protein Dynamics, Kyoto Sangyo University, Kamigamo Motoyama, Kita-ku, Kyoto, Japan

1971	Bachelor, Department of Physics, Kyoto Univ.,
1979	PhD, Kyoto Univ. (Biophysics) and Lecturer, Chest Disease Research Institute (CDRI), Kyoto Univ.,
1984-1986	Visiting Associate, NCI (NIH),
1986-1998	Professor, CDRI, Kyoto Univ.,
1998-2010	Professor, Institute for Frontier Medical Sciences, Kyoto Univ.,
2010-2017	Dean and professor, Faculty of Life Sciences, Kyoto Sangyo Univ.,
2017	Director and professor, Institute for Protein Dynamics, Kyoto Sangyo Univ.,
1999-2004	Editor-in-chief, Cell Structure and Function
2002-2005	President, Japanese Society for Cell Biology
2003-2010	Vice President, Asian-Pacific Organization for Cell Biology
2004-2005	President, Cell Stress Society International
2009	Awarded the Medal with Purple Ribbon

Shuichi Ohkubo
Taiho Pharmaceutical Co., Ltd., Global Chief Medical Officer,
Tokyo, Japan

Dr. Shuichi Ohkubo is the Product Chair of TAS-116 at Taiho Pharmaceutical Co., Ltd. He has over 20 years of academic and industry experience in oncology research, drug discovery and development. He received his doctoral degree in Molecular Biology from Kanazawa University, Japan in 1995, and then joined Taiho Pharmaceutical Co., Ltd. as a Senior Scientist. While his involvement in several drug discovery programs in Taiho, he joined the group of Prof. Carol Prives at Columbia University and Prof. Matthew Shair at Harvard University as a Postdoctoral Fellow. Recently, his group is focusing on researching novel therapeutic strategies for modulation of protein homeostasis. Among the drug candidates discovered by his group, new HSP90 inhibitor and NEDD8-activating enzyme (NAE) inhibitor are being evaluated in several clinical trials, and he has full responsibility to lead the development of these inhibitors and research for novel candidates in this field.

Laurence Pearl

Genome Damage and Stability Centre, School of Life Sciences, University of Sussex, Brighton, UK

Dr.Laurence Pearl is Professor of Structural Biology in the Genome Damage and Stability Centre and heads the School of Life Sciences at the University of Sussex, where he moved in July 2009. For the previous 10 years he was Chairman of the Section of Structural Biology at the Institute of Cancer Research in London. His laboratory studies the structural biology of the DNA Damage Response and the HSP90 molecular chaperone system, and seeks to translate these basic studies for the development of new drugs for the treatment of cancer and other diseases. He is a Wellcome Trust Senior Investigator, a Fellow of the Royal Society (FRS), a Fellow of the Academy of Medical Sciences (FMedSci) and an elected member of the European Molecular Biology Organisation (EMBO) and the *Academia Europeae*. In 2013 he shared the CR-UK Translational Cancer Research Prize (with Paul Workman, ICR) for uncovering HSP90 as a novel target in cancer therapy and for the development of the leading HSP90 inhibitor, AUY922.

David Pincus
Whitehead Institute for Biomedical Research,
Cambridge, US

I got my start in science as a technician at the Molecular Sciences Institute after graduating from UC Berkeley in 2004 where I worked under Roger Brent to identify and define roles for pheromone-induced sites of phosphorylation in the yeast mating pathway. Inspired by the power of combining experimental and computational approaches, I began graduate school at UCSF by working with Wendell Lim to explore the evolution of phospho-tyrosine signaling before joining the labs of Peter Walter and Hana El-Samad for my thesis research to investigate how the Unfolded Protein Response (UPR) maintains homeostasis in the endoplasmic reticulum. In my current position as a Whitehead Fellow, I have spent the last four years running a laboratory that includes a postdoc, a technician and myself. The initial focus of our work has been applying the investigative framework I developed to study the UPR to define the essential function and dynamic regulation of the yeast heat shock transcription factor (Hsf1).

Lea Sistonen

Faculty of Science and Engineering, Åbo Akademi University
Turku Centre for Biotechnology, Åbo Akademi University and University of Turku,
Turku, Finland

Academic Education
- Master of Science (M.Sc.), Cell Biology, 1984, Åbo Akademi University, Turku, Finland
- Philosophy Doctor (Ph.D.), Genetics, 1990, University of Helsinki, Helsinki, Finland
- Docent in Cell and Molecular Biology, 1994, Åbo Akademi University, Turku, Finland

Research Experience and Academic Positions
- Graduate student: Univ. of Helsinki, Finland; supervisor: Kari Alitalo, 1986-1990, funding from the Academy of Finland
- Post-doctoral fellow: Northwestern Univ., Evanston, IL, USA; supervisor: Richard I. Morimoto, 8/1990-10/1993, funding from the Academy of Finland and post-doctoral fellowship NIH Fogarty International, USA
- Senior Scientist: Turku Centre for Biotechnology, 1994-2000, funding from the Academy of Finland, 8/1998-7/2000
- Professor: Cell and Molecular Biology, ÅAU, 8/2000-7/2004, 8/2009-present; Academy Professor, 8/2004-7/2009
- Visiting Professor: Richard I. Morimoto's Laboratory, Northwestern University, Evanston, IL, USA, 8/2003-7/2004, funding from the Academy of Finland; 1-6/2013, funding from the Sigrid Jusélius Foundation

Ongoing Research Projects and Major Research Grants
- Principal Investigator (PI) of "Integration of proteostasis networks by genome-wide transcriptional re-programming in cell stress", Academy of Finland 2016-2020 (548.9 k€)
- PI of "Stress-inducible transcriptional regulation and the cell cycle", Academy of Finland 2012-2016 (678.3 k€), Sigrid Jusélius Foundation, 2012-2019 (385 k€), Magnus Ehrnrooth Foundation, 2016 (10 k€)
- Co-IP of "Proteostasis as a regulator of cell proliferation and survival", together with John E. Eriksson: Magnus Ehrnrooth Foundation, 2013-2015 (170 k€); The Finnish Cancer Organizations, 2015-2017 (100 k€)

Personal Awards and Prizes Awarded to the Research Team
- Member of the Finnish Society of Sciences and Letters
- *Societas Scientiarum Fennica*, elected 2003
- Member of the Finnish Academy of Science and Letters
- *Academia Scientiarum Fennica*, elected 2004
- Member of the Swedish Academy of Engineering Sciences in Finland, elected 2011
- Fellow of the Cell Stress Society International (CSSI), elected 2015
- Personal awards from Aurator, Finland, 2002 (7.9 k€), Oskar Öflund Foundation, Finland, 2005 (10 k€)
- Medix Prize for biomedical research in Finland, 2006 (10 k€)
- Elias Tillandz Prize for the best publication within BioCity Turku, 2006 (6 k€), 2011 (4 k€), 2014 (6 k€), 2015 (6 k€)
- Chancellor's Prize for the best publication at Åbo Akademi University, 2014 (2 k€, shared with Julius Anckar)

Patricija van Oosten-Hawle
Faculty Biological Sciences, University of Leeds,
Leeds, UK

Dr. Patricija van Oosten-Hawle is a group leader and Lecturer in Molecular and Cell Biology at the University of Leeds, UK. After receiving her PhD at the Vrije Universiteit in Amsterdam, the Netherlands in 2008, she joined the laboratory of Prof. Richard I. Morimoto at Northwestern University, USA to complete her postdoctoral training. Her current research focuses on molecular mechanisms of transcellular chaperone signalling and how organismal proteostasis is maintained during development and aging, using the nematode worm *C. elegans* as a model organism.

Cara Vaughan
Institute of Structural and Molecular Biology (ISMB), School of Crystallography, Birkbeck College, London, UK

After a Chemistry degree at the University of Glasgow I completed my PhD in protein crystallography in the lab Prof Sir Alan Fersht at the University of Cambridge where I determined the structures of model proteins used in protein folding experiments. This triggered my interest in protein folding in the cellular and disease context. After a short postdoc in Italy at the Istituto di Ricerche di Biologia Molecolare (IRMB), I moved to London to work with Prof Laurence Pearl at the Institute of Cancer Research. There I joined a research team investigating the structure and function the molecular chaperone Hsp90. In 2007 I got an independent position, as a Lecturer in the Institute of Structural and Molecular Biology (a joint research institute between UCL and Birkbeck College) and have remained there ever since. My research continues to focus on Hsp90 and in particular we are interested in understanding how post-translational modification of cochaperones regulate Hsp90 function. We use a combination of structural, biochemical and biophysical approaches in our work.

Paul Workman

FRS FMedSci, Cancer Research Cancer Therapeutics Unit, The Institute of Cancer Research, London, UK

Currently, Professor Paul Workman FRS FMedSci is CEO and President of The Institute of Cancer Research (ICR), London. From 1997 - 2016 he was Director of the CRUK Cancer Therapeutics Unit at ICR – the world's largest non-profit cancer drug discovery group. Paul has been responsible for more than 20 molecularly targeted cancer drugs entering clinical trial, including protein kinase, PI3 kinase and HSP90 inhibitors.

Before joining ICR, Paul spent 4 years leading cancer research at AstraZeneca and prior to that worked at Glasgow, Stanford and Cambridge Universities. He was a scientific founder of Piramed Pharma (acquired by Roche) and Chroma Therapeutics.

In addition to running his own lab, as CEO and President of ICR, Paul now guides strategic developments in the field of basic, translational and clinical cancer research. He talks, writes and blogs about cancer research and treatment and also about the drug discovery ecosystem. He published more than 535 scientific articles.

Paul has won numerous awards and fellowships including being elected as a Fellow of the Royal Society in 2016 and was also named in the Evening Standard's Progress 1000 list of the most influential people in London.

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

POSTER SESSIONS

Role of DNA mutations in breast cancer

Adouda Adjiri

Faculty of Sciences Department of Physics,
Setif-1 University, El Bez Campus, Algeria

Cancer in general and breast cancer in particular, remains an incurable disease in spite of great achievements reached in cancer research through sequencing. The present work discusses the role of DNA mutations in cancer initiation and development and how identification of DNA mutations in cancerous cells has influenced our approach for anti-cancer drug design. Results in HER2-type of breast cancer from different research groups suggest that DNA mutations targeted in breast cancer may not have a causal role.

To design more effective cancer drugs with durable and positive outcome; future cancer research needs to move beyond the sequencing era and explore changes which are taking place in cancer cells at levels other than the DNA. Mutations in the DNA do occur and for a multitude of reasons but without necessarily causing cancer. More focus should be given to the event responsible of the switch of a cell from normalcy to malignancy. While targeted therapy continues to improve the outcome of many breast cancer patients, it is however unlikely to lead to the eradication of breast cancer.

A Role for GRP78 in the actions of IGFBP-2 and -3 in breast cancer cells

Ahmad Alghamdi, Hanna Zielinska, Claire Perks & Jeff Holly

IGFs & Metabolic Endocrinology Group, School of Clinical Science,
Faculty of Health Sciences, University of Bristol, UK

Glucose-regulated protein 78 (GRP78), a member of the heat shock protein family that functions as a master regulator of the endoplasmic reticulum (ER) stress pathway (the unfolded protein response (UPR)),has been heavily implicated in many cellular processes, including cancer cell proliferation, survival and metastasis. We have previously shown that both IGFBP-2 and IGFBP-3 are implicated in affecting cancer cell survival and growth in a context-dependent manner. We aimed to assess if GRP78 interacted with IGFBP-2 and IGFBP-3 and if this was important for their actions. Using immunoprecipitation we confirmed that IGFBP-2 and IGFBP-3 each bound to GRP78 in whole cell lysates Silencing IGFBP-2 in ERα-positive cells using siRNA led to a reduction in GRP-78 that was associated with a decrease in cell invasion and conversely silencing GRP-78 led to a reduction in IGFBP-2. Adding exogenous IGFBP-2 to ERα-negative cells caused an increase in the levels of GRP78 that was associated with an increase in cell growth. Silencing GRP78 in ERα-negative cells on plastic switched the actions of IGFBP-3 from being pro-apoptotic to acting as a survival factor and on fibronectin silencing GRP78 enhanced the ability of IGFBP-3 to act as a survival factor. These data suggest that the effects of both IGFBP-2 and IGFBP-3 are influenced by the presence of GRP78.

Expression of HSF1 and Hsp90 in human brain tumors: an immunohistochemical analysis

Martha Assimakopoulou[1], Athanasia Moutafidi[1], Vassiliki Zolota[2]

[1] Department of Anatomy-Histology and Embryology, School of Medicine, University of Patras, Rion, Greece
[2] Department of Pathology, School of Medicine, University of Patras, Rion, Greece

Heat shock protein (Hsp90) is a central participant in a multistep chaperoning process that folds and stabilizes a wide range of cellular clients including key oncogenic proteins. The main transcription factor regulating Hsp90 expression is HSF1 (Heat Shock transcription Factor 1). HSF1 is activated in response to environmental stimuli (e.g. elevated temperature, bacterial or viral infection, and oxidative stress) as well as altered kinase signaling (e.g. RAS/MAPK, PI3K/Akt) characteristic for cancer cells. Thus, HSF1 regulates both Hsps genes but also, numerous non-Hsps, cancerspecific genes and modulates different signaling pathways. On the other hand, expression of Hsp90 is not exclusively dependent on HSF1 and is up-regulated by a variety of other transcriptional regulators in a number of cellular processes such as inflammation, immune response, cell growth and development. High expression of Hsp90 has been reported in human brain tumors. The aim of this study was to estimate immunohistochemically, using specific antibodies, the expression levels of HSF1, in relation to Hsp90, in 89 human brain tumors (gliomas, meningiomas and, medulloblastomas). Expression of proteins was examined in adjacent (semi-serial) sections and the labeling index (LI), defined as the percentage of positive (labeled) cells out of the total number of tumor cells counted in ten non-overlapping fields, was determined. Nuclear for HSF1 and cytoplasmic for Hsp90 localization was detected in a high percentage of tumor cells in the majority of tumors. However, different patterns of HSF1/Hsp90 co-expression were observed: a significant percentage of tumors exhibited HSF1 immunoreactivity, being Hsp90 immunonegative, a few tumors showed intense immunoreactivity for Hsp90 but not for HSF1 and, finally, there were tumors immunopositive or immunonegative for both proteins. In glioblastomas multiforme (grade IV), the expression of HSF1 was significantly higher compared to Hsp90 expression ($p<0.01$). Furthermore, glioblastomas multiforme (grade IV) showed significant higher expression for HSF1 compared to diffuse fibrillary astrocytomas (grade II) ($p<0.01$). These results indicate the involvement of HSF1 in brain tumors pathogenesis and imply the existence of HSF1-independent mechanisms for regulation of Hsp90 expression in these tumors.

The co-chaperone URI controls PDX-1 expression and protects against type 2 diabetes

Hugo Bernard[1], A. Teijeiro[1], A. Chaves[1], A. Novials[2]; C. Perna[3] and N. Djouder[1]

[1] Growth Factors, Nutrients and Cancer Group, CNIO, Madrid, Spain
[2] August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain
[3] Department of Pathology, Universidad de Alcalá de Henares, Alcalá de Henares, Madrid, Spain

Mutations in the homeodomain-containing transcription factor pancreatic duodenal homeobox 1 (PDX-1) can cause a monogenic form of diabetes (maturity onset diabetes of the young 4 or MODY4) in humans, and silencing PDX-1 in mouse pancreatic β cells causes diabetes.

As Western society has shifted to a higher caloric diet with nutrient overload and more sedentary lifestyle, and the incidence of type 2 diabetes (T2D) has increased to epidemic proportions, we aim to better understand how PDX-1 alterations occur in response to nutrient excesses.

In recent years, epigenetics has become an emerging issue in a broad range of diseases such as T2D, obesity, inflammation, and neurocognitive disorder. Pdx-1 epigenetic modifications and its silencing may play a role in T2D.

Epidemiological and animal studies have demonstrated a close link between nutrition and chronic metabolic disease mainly due to covalent modifications of DNA and core histones. Nutrients play a key role in provision of methyl donors for DNA and protein methylation inducing DNA hypermethylation and histone modifications, thereby modifying the expression of critical genes associated with physiologic and pathologic processes.

Using murine models of T2D combined with biochemical and cell biological techniques, as well as genomic approaches and human data, we demonstrate that the unconventionel prefoldin RPB5 interactor URI links nutrient surpluses to PDX-1 epigenetic modification, potentially regulating PDX-1 expression and protecting against development of T2D. We propose that mechanisms regulating PDX-1 expression may represent potential targets against T2D.

Structural studies of the CCT-gelsolin complex

María Teresa Bueno[1], Jorge Cuéllar[1], Andreas Svanström[2], Julie Grantham[2] and José M. Valpuesta[1]

[1] Centro Nacional de Biotecnología, Consejo Superior de Investigaciones Científicas, Madrid, Spain
[2] Department of Chemistry and Molecular Biology, University of Gothenburg, Gothenburg, Sweden

The eukaryotic cytosolic chaperonin CCT (Chaperoning Containing T-CP1) is a molecular machine involved in assisting the folding of proteins that regulate in important cellular processes. This chaperonin consists of a large cylindrical oligomer formed by two rings each one built by eight different subunits (~60kDa). It was originally thought that the function of CCT was the folding of the cytoskeletal proteins actin and tubulin but subsequent studies have shown that CCT interacts with a wide range of proteins. Some of these proteins bind to CCT but do not requiere interactions with CCT in order to get its proper folding and to be functional. Gelsolin is an actin filament severing protein that increases actin dynamics by generating filament ends for further actin polymerization, and previous studies have shown its interaction with CCT. This binding is slow and gelsolin is accumulated over time on CCT suggesting that this protein is not a real folding substrate of the chaperonin. In fact, although bacteria lack CCT, gelsolin can successfully be produced as a native soluble protein in bacteria. Therefore, CCT could have a regulatory effect on gelsolin, acting indirectly in the actin filament dynamics.

The main aim of this project is the structural characterization of the CCT-Gelsolin complex using electron-microscopy in order to elucidate the binding mechanism that mediates such interaction and whether CCT has an actual role on actin dynamics regulation. To face this goal, our first step has been to carry out binding assays between CCT and Gelsolin adding DTSSP (3,3´-dithiobis[sulfosuccinimidylpropionate]) to crosslink the complex, which was later purified by gel filtration and this sample is being used for further structural characterization which is currently in progress.

Understanding the role of URI during ontogenesis

Sergio De la Rosa and Nabil Djouder

Cancer Cell Biology Programme, Growth Factors, Nutrients and Cancer Group,
Centro Nacional Investigaciones Oncológicas, CNIO, Madrid, Spain

Cancer is widely related with developmental embryonic process by mimicking mechanisms of cell motility and invasiveness, self-renewing and pluripotency and microenvironmental related-effects on parenchyma such as inflammation. Understanding these processes during embryology may help us to better understand basic mechanisms of cancer development.

Unconventional Prefoldin RBP5 interator (URI) is a member of the R2TP/URI-prefoldin like complex. It is a heterohexameric chaperone complex composed of 6 prefoldin subunits that may harbour some chaperones activities. Previously, URI has been reported to be a downstream target of the mTOR/S6K1 pathway and has oncogenic activities in ovarian and liver cancers. URI also suppresses DNA damage in *C. elegans*. Accordingly, URI deficiency associates with p53 responses in a subset of colorectal cells. URI may thus control and protect genome integrity in response to environmental stress-mediated genotoxicity. Recent data from our lab suggest that ubiquitous deletion of URI leads to embryonic lethality. Understanding when and how URI deletion causes defects in embryonic development may help us to decipher the role of URI during carcinogenesis.

Photoactivatable HSP47: an optogenetic tool to regulate collagen assembly & tumor microenvironment

Essak S. Khan[1,2], J. I. Paez[1], S. Sankaran[1], I.M. Weiss[3], A. del Campo[1,2]

[1] INM – Leibniz-Institut für Neue Materialien, Saarbrücken, Germany
[2] Universität des Saarlandes, Saarbrücken, Germany
[3] Universität Stuttgart, Stuttgart, Germany

Molecular chaperones are folding modulators that play a central role in the conformational quality control of the proteome by interacting with, stabilizing and remodeling a wide range of specific proteins or non-native polypeptides. In pathological conditions like cancer a class of molecular chaperones called Heat shock proteins (HSPs) causes chaperonopathies. Hsp47, a 47 KDa endoplasmic reticulum-resident heat shock protein involved in collagen maturation and assembly, has recently been discovered to regulate the tumor microenvironment by promoting expression of factors responsible for tumor cell proliferation, invasion and angiogenesis. In this contribution, we present a semisynthetic-recombinant strategy for developing photoactivatable HSP47 using Intein Protein Ligation Approach, and demonstrate the possibility of photoregulation of Collagen assembly & tumor microenvironment related implications in a controlled manner.

Unveiling the organization and mechanistic features of the protein translocation complex involved in chaperone-mediated autophagy

María Rosario Fernández-Fernández*[1], Lissette Ochoa-Ibarrola[1], Ana María Cuervo[2] and José María Valpuesta*[1]

[1] Centro Nacional de Biotecnología-Consejo Superior de Investigaciones Científicas, Cantoblanco, Madrid, Spain
[2] Albert Einstein College of Medicine, Bronx, New York, US
* Corresponding authors: mrfernandez@cnb.csic.es, jmv@cnb.csic.es

CMA is a type of selective autophagy in which cytosolic proteins bearing a specific motif in their sequence (KFERQ) are identified one-by-one by Hsc70 and delivered to the surface of the lysosome. The Hsc70/substrate complex, presumably with the aid of other chaperones and co-chaperones, interacts with a lysosomal membrane receptor (LAMP2A). Upon substrate binding LAMP2A assembles into an oligomeric structure to form the translocation complex (CMA-TC). The driving force for substrate translocation is a lysosomal form of Hsc70 (Lys-Hsc70), which pulls the protein into the lysosome for degradation. Many aspects of CMA remained to be established including the structural organization of the CMA-TC, aspects of substrate recruitment, binding to the receptor and/or translocation. As a top-down strategy to understand the structure of the translocation complex we have reconstituted empty lysosomes from purified lysosomal membranes. They preserve membrane components but do not keep the luminal content. The prediction is that upon substrate binding the CMA-TC is built but the protein will not be translocated. We have cryopreserved lysosomes and subjected them to cryoEM. The comparison in the absence and presence of substrate has allowed us to identify potential CMA-TC. We will attempt 3D reconstructions of CMA-TC by using cryo-electron tomography. The contribution to the formation of the complex of cytosolic Hsc70 or additional chaperones/co-chaperones has also been assayed. For the characterization of substrate binding to the CMA-TC we have used fluorescence anisotropy. The binding experiments have been performed with a fluorescein-labeled peptide that mimics the LAMP2A cytosolic region in combination with different versions of the Hsc70/substrate complex and a fluorescein-labeled peptide containing the KFERQ sequence in combination with different versions of Hsc70. The effect of other chaperones and co/chaperones on binding has also been explored.

Elucidating the role of MCRS1 in liver cirrhosis

Amanda Garrido[1], Cristian Perna[2] and Nabil Djouder[1*]

[1] Cancer Cell Biology Programme, Growth Factors, Nutrients and Cancer Group, Centro Nacional Investigaciones Oncológicas, CNIO, Madrid, Spain
[2] Department of Pathology, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain
* Correspondence: ndjouder@cnio.es

Cirrhosis is characterized by the loss of liver function due to chronic injury, and accounts as a significant risk factor for the development of hepatocellular carcinoma. Apart from alcohol consumption, the etiology of this disease remains unclear, and liver transplantation is the only curative option available for patients. This highlights the need of a better understanding on the leading causes of cirrhosis and the factors involved in its progression.

The enterohepatic circulation, which connects gut and liver, plays an important role in inter-organ homeostasis. Therefore, deregulation of this connective pathway may lead to liver diseases. In our lab, we are focusing on studying the role and functions of microspherule protein 1 (MCRS1), which may participate in maintaining cellular homeostasis. We generated a mouse model for inducible and hepatocyte-specific MCRS1 loss-of-function. Deletion of MCRS1 specifically in hepatocytes causes cirrhosis, liver failure and death of mouse with a median survival of 9 weeks. Further analysis demonstrate an intestinal barrier defect suggesting a cross-talk between gut impairment and development of liver disease.

Using MCRS1 mouse model, we thus aim to better elucidate the molecular mechanisms implicated in the crosstalk between liver and gut, and how dysbiosis may participate in liver dysfunctions. Our findings may shed light on the physiopathology of cirrhosis and help to identify new targets for its prevention and treatment.

Biochemical characterization of a chaperone complex involved in macroautophagy

Marcos Gragera Cabezudo, Fernandez-Fernandez MR*, Valpuesta JM*

[1] Centro Nacional de Biotecnología. Consejo Superior de Investigaciones Científicas, Madrid, Spain
* Corresponding authors: mrfernandez@cnb.csic.es and jmv@cnb.csic.es

To promote cell viability, eukaryotic cells have developed regulated pathways to maintain a fine balance between protein synthesis, folding, trafficking and degradation (proteostasis). Disruption of this homeostasis network may lead to the onset of pathologies such as cancer or neurodegenerative disorders. Therefore, cells count on several strategies to remove and prevent accumulation and aggregation of potentially toxic proteins, such as the ubiquitin-proteasome system (UPS) and autophagy. Three types of autophagy have been described so far: chaperone-mediated autophagy (CMA), micro- and macroautophagy, where the chaperone Hsp/Hsc70 has a central role in all of them. In macroautophagy, Hsp/Hsc70, in collaboration with other partners (CHIP, BAG3, HspB8, p62), forms a complex that recognizes, ubiquitinates and delivers aggregate-prone proteins towards special locations in cells (aggresomes). Here, such proteins are engulfed in double membrane vesicles called autophagosomes that subsequently fuse with lysosomes for their degradation. Since this system is quite relevant for the removal of protein aggregates, macroautophagy is attracting the attention as a potential therapeutic target in diseases characterized by the accumulation of misfolded and aggregated proteins (Parkinson, Alzheimer and Huntington diseases, ALS). This work focuses on the biochemical and structural characterization of the Hsp70-containing macroautophagy complex. First, we have cloned, expressed and purified some of the proteins involved in the formation of the complex: Hsp70, CHIP, BAG3 and HspB8. Then, we are reconstituting in vitro all the potentially relevant subcomplexes and studying them by electron microscopy. This, in combination with other biochemical and computational approaches, will provide relevant insights to understand how the macroautophagy machinery works.

URI-induced NAD$^+$ depletion in DNA damage and cancer development

Tatiana P. Grazioso[1], Krishna S. Tummala[1] and Nabil Djouder[1*]

[1] Cancer Cell Biology Programme, Growth Factors, Nutrients and Cancer Group, Centro Nacional Investigaciones Oncológicas, CNIO, Madrid, Spain
[*] Correspondence: Nabil Djouder (ndjouder@cnio.es)

Oncogene-induced DNA damage has the potential to initiate tumorigenesis. The unconventional prefoldin RPB5 interactor (URI), a co-chaperone protein, forms a complex with the heat shock protein 90 (HSP90) to sequester the aryl hydrocarbon and/or estrogen receptors in the cytoplasm preventing their transcriptional activity, thereby inhibiting the transcription of metabolic enzymes implicated in the catabolism of tryptophan to *de novo* NAD$^+$ synthesis. Specific URI overexpression in murine hepatocytes causes reduction in NAD$^+$ levels leading to DNA damage and the formation of spontaneous, heterogeneous and aggressive hepatic tumors. Interestingly, restoring NAD$^+$ pools with nicotinamide riboside (NR), a vitamin B3 derivate, prevents DNA damage and tumor formation. NR seems to be an efficient therapy for the treatment of cancers in which predictive and prognostic factors can be identified as oncogene-induced NAD$^+$ depletion leading to genotoxic stress. Here we propose to develop a screening strategy to find new NAD$^+$ boosters which can be more stable than NR and efficiently abolish DNA damage. The new NAD$^+$ boosters will be tested in cancer genetic and patient-derived xenograft models for disease prevention and treatment.

Heat shock protein 90 as molecular target in non-small cell lung cancer cell lines

Ángela Marrugal[1,2], I Ferrer[1,2], MD Pastor[3], A Quintanal-Villalonga[1,2], L Ojeda-Marquez[1,2], S Molina-Pinelo[3*], L Paz-Ares[1,2,4*]

[1] Instituto de Investigación Hospital Doce de Octubre (i+12), Madrid, Spain
[2] Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain
[3] Instituto de Biomedicina de Sevilla (IBIS) (HUVR, CSIC, Universidad de Sevilla), Sevilla, Spain
[4] Medical Oncology Department, Hospital Universitario Doce de Octubre, Madrid, Spain
[*] S Molina-Pinelo and L Paz-Ares contributed equally to this work

Background and context:
Heat Shock Protein 90 (HSP90), is an interesting target for cancer therapy because it is involved in the stabilization of different oncogenic proteins. Thus, increased level of HSP90 has been related to poor prognosis in some types of tumors. Concretely, in non-small cell lung cancer (NSCLC), two of its most important drivers: EGFR and EML4-ALK are client proteins of HSP90 and greatly depend on it. Therefore, this chaperone is extremely important in NSCLC and its inhibition could lead to better clinical outcome for this disease. However, stronger evidence supporting the efficacy of HSP90 inhibition in several molecular subgroups of NSCLC will be essential for a successful clinical development.
Methods:
Different NSCLC cell lines, selected according to its relationship with HSP90, were used. The panel was constituted by H3122 (EML4-ALK rearrangement) and HCC827 (EGFR mutated) whose oncoproteins drivers are HSP90 client proteins, A549 (KRAS mutated) with a driver that indirectly depends on HSP90, along with H1781 (EGFR, KRAS, ALK wild type) as control cell line. To study the response of the cell lines to HSP90 inhibition, its activity was pharmacologically interrupted by geldanamycin (17-AAG and IPI-504) and resorcinol (STA-9090 and AUY-922) derivates. Then, HSP90-dependent client proteins and other related chaperones were evaluated by western blot. Finally, we identified the proteomic profile linked to HSP90 inhibition by two-dimensional polyacrylamide gel electrophoresis (2D-PAGE).
Results:
HSP90 inhibition resulted in decreased expression of analyzed proteins, in the NSCLC cell lines. H3122 and HCC827 were the most sensitive cell lines to the inhibitors, showing the strong dependence on HSP90 in the EML4-ALK and EGFR oncoproteins drivers. In the cell line harboring the EML4-ALK translocation, we detected 5 down-regulated protein spots and 16 up-regulated in the untreated versus inhibited cell line. The untreated EGFR positive cell line presented 80 down-regulated spots whereas 104 were up-regulated compared to inhibited cell line. The results showed a differential proteomic signature in the cell lines under the influence of the HSP90 inhibitors. Besides, HSP70 overexpression after treatment compared to unprocessed cell lines was detected in all of cell lines studied. It supported the responsiveness to HSP90 inhibition.
Conclusions:
Oncogenic client proteins degradation, along with HSP70 induction showed proof of treatment response. We identified a proteomic profile associated with HSP90 inhibition where have been detected the deregulation of several pathways involved in NSCLC tumorigenesis.

Nucleolar and ribosomal DNA condensation upon heat-shock treatment and fragmentation under rapamycin and Cdc14 downregulation in yeast

Emiliano Matos-Perdomo[1,2], Félix Machín[1]

[1] Unidad de Investigación-Hospital Universitario Ntra. Sra. de Candelaria, Santa Cruz de Tenerife, Spain
[2] Universidad de La Laguna, Tenerife, Spain

Chromosome structure in the yeast Saccharomyces cerevisiae is only visible at the microscopic level in the chromosome XII. The ribosomal DNA (rDNA) located in the long arm of this chromosome has been used to observed different phenomena of compaction, segregation and chromosomal structure at different phases of the cell cycle. The metaphase structure ("loop") depends, among others, on the condensin complex; and its segregation during anaphase depends also in that complex and on the cell cycle phosphatase Cdc14 (1). This loop structure together with nucleolar markers, can be used to study the effect of different stresses such as Heat-Shock or rapamycin treatment on the rDNA and nucleolus. The nucleolus has been proposed as a sensor and surveillance mechanism through nucleolar stress checkpoint. This study aims to elucidate chromosome and nucleolar remodelling under heat-stress and the influence of Cdc14 in this process. For this, we used different tagged proteins that bind to the rDNA locus for their monitoring and visualization with fluorescent microscopy under heat-stress conditions, besides, we applied several molecular and immunological techniques. We employed an auxin based degron system to degrade proteins by the proteasome. We found that the rDNA chromosome structure is condensed under heat-stress conditions, being this an appropriate model for its study, also we verified that the auxin mediated degradation system is a useful tool for this purpose. Besides, we found that Cdc14 downregulation under rapamycin treatment causes nucleolar fragmentation. Cdc14 has been shown to dephosphorylate Hsp90 at T101 while Hsp90 phosphorylation sensitizes renal carcinoma cells to Hsp90 inhibitors (2). Nucleolar reorganization, inhibition of rDNA transcription and ribosomal biogenesis are novel potential targets in cancer therapy.

(1) Machín, F; Torres-Rosell, J; Jarmuz, A; Aragón, L. 2005. J Cell Biol.
(2) Woodford MR; et al. 2016. Cell Rep.

Proteomic analysis of HSF1 interacting proteins

Petr Muller, Jakub Faktor, Veronika Martinkova, Michal Pastorek, Filip Trcka, Michal Durech, Borivoj Vojtesek

Masaryk Memorial Cancer Institute, Regional Centre for Applied Molecular Oncology, RECAMO, Czech Republic

The master regulators of heat shock response in eukaryotic cells is Heat Shock Factor 1 (HSF1) that function as a central sensor of proteotoxic stress. Increased temperature causes unfolding of the C-terminal domain of HSF1, uncovering hydrophobic leucine zippers and resulting in formation of HSF1 trimers that bind DNA. In a regulatory feedback loop, Hsp90/Hsp70 induced by active HSF1 trimers bind and stabilize the inactive monomeric form of HSF1. While the negative regulation of HSF1 through chaperones HSP70/HSP90 is well described, the factors activating HSF1 are largely unknown.

Our study was therefore aimed to identify proteins that interact with activated HSF1 in response to various stress conditions. We used lentiviral vectors to establish stable human cell lines expressing either fluorescent mmCherry-HSF1 or SBP tagged HSF1 for pull-down studies. The cells containing fluorescent HSF1 were exposed to different stresses and assessed for re-localization HSF1, its association with chromatin and formation of nuclear stress bodies. The most potent treatments were used in subsequent proteomic study focused on quantitative detection of HSF1 interacting proteins. We used acquisition of all theoretical mass spectra (SWATH) to quantitatively measure the proteins that interact with SBP tagged HSF1 in control and treated cells. The proteins that bind HSF1 in response to various stress conditions include chromatin remodeling AAA+ proteins, ribosomal proteins and stress-activated phosphatases, whereas several Ras related proteins Rab were found to dissociate activated HSF1. The results revealed several protein families that significantly associate or dissociate HSF1 in response to stress conditions. Identification of interaction partners revealed new pathways activating HSF1 and suggests new mechanisms that are necessary for HSF1 mediated gene transcription.

Authors PM, FT were supported by grant GACR 16-20860S, BV and JF was supported by grant GACR 16-7321S

Structural studies of the chaperone-mediated autophagy's translocating complex

Lissette Ochoa-Ibarrola, Cuervo AM, Fernandez-Fernandez MR*, Valpuesta JM*

Centro Nacional de Biotecnología (Consejo Superior de Investigaciones Científicas), Madrid, Spain

Chaperone-mediated autophagy (CMA) is a selective mechanism for the degradation of cytosolic proteins in lysosomes. CMA contributes to the removal of altered proteins as part of the cellular quality-control system. Cytosolic proteins are identified one-by-one by heat shock cognate protein 70 (Hsc70) and delivered to the surface of the lysosome. The Hsc70/substrate complex, presumably with the aid of other chaperones and co-chaperones, interacts with LAMP2A a lysosomal membrane receptor. LAMP2A is a 96 kDa heavily glycosylated membrane protein of unknown structure. Upon substrate binding, LAMP2A assembles into an oligomeric structure to form the translocation complex (CMA-TC). Many aspects of CMA remain to be established, including the structural organization of the CMA-TC, aspects of substrate recruitment, binding to the receptor and/or translocation. We are working in the structural characterization of the CMA-TC using cryo-electron microscopy and cryo-electron tomography. For this purpose we have two main objectives: a) the purification and structural characterization of both the glycosylated and non-glycosylated LAMP2A overexpressed in eukaryotic and bacterial systems, respectively. b) the structural characterization of the CMA-TC in its native environment using vesicles reconstituted from lysosomal membrane extracts in the absence and presence of specific substrates.

Discovery of an orally bioavailable chemical probe (CCT251236) from a heat shock factor 1 (HSF1) phenotypic screen

Marissa V. Powers[1], Emmanuel De Billy[1], Swee Y Sharp[1], Matthew D Cheeseman[1], Nicola E A Chessum[1], Carl S Rye[1], A. Elisa Pasqua[1], Michael J Tucker[1], Birgit Wilding[1], Lindsay E Evans[1], Susan Lepri[1], Meirion Richards[1], Salyha Ali[1,2], Martin Rowlans[1,2], Lisa O'Fee[1], Asadh Miah[1], Angela Hayes[1], Alan T Henley[1], Robert te Poele[1], Loredana Pellegrino[1], Florence Raynaud[1], Rosemary Burke[1], Rob L M van Montfort[1,2], Suzanne A Eccles[1], Paul A Clarke[1], Keith Jones[1] and Paul Workman[1]

[1] Cancer Research UK Cancer Therapeutics Unit at The Institute of Cancer Research, London, UK
[2] Division of Structural Biology at The Institute of Cancer Research, London, UK

HSF1 is a transcription factor which orchestrates the rapid response of healthy cells to acute proteotoxic stress. Malignant transformation induces dramatic changes in a variety of biological processes. Altered ratios of protein production, folding and degradation coupled with greater levels of mutated proteins in cancer cells disrupts normal proteostasis inducing a state of chronic proteotoxic stress. Elevated levels of activated HSF1 has been detected in cancer cells with strong correlation between HSF1 activity and poor clinical outcome. Hence, targeting HSF1 transcription is a viable strategy to inhibit non-oncogene addiction and exploit proteotoxic stress in cancer. However, HSF1 is a ligand-less transcription factor making direct inhibition with small molecules improbable. Therefore, we developed a cell-based phenotypic screen to identify inhibitors to target the HSF1 regulatory pathway. We conducted a high throughput Arrayscan assay of 200,000 compounds to measure inhibition of HSF1-mediated HSP72 induction stimulated by an HSP90 inhibitor. We identified a singleton hit with a bisamide core, CCT245232, that showed potent antiproliferative activity in a range of human cancer cell lines but had poor physiochemical properties and an unacceptable pharmacokinetic profile. Improvement of the physiochemical properties of CCT245232 generated the orally bioavailable tool compound CCT251236 which has potent antiproliferative activity in human ovarian cancer cell lines in vitro and in human ovarian xenograft models. Using a probe based on CCT251236 a chemo-proteomic approach identified pirin as a high affinity molecular target. Binding of CCT251236 to pirin was confirmed in biophysical assays. CCT251236 reproduces the reported anti-migratory phenotype for pirin modulation but inhibition of pirin alone does not explain the cellular phenotype observed with CCT251236. We are currently optimising the properties of our chemical tool to identify a clinical candidate.

Targeting the proneoplastic role of the mitochondrial chaperone TRAP1

Carlos Sanchez-Martin[1], Ionica Masgras[1], Francesco Ciscato1, Giorgio Colombo2, Elisabetta Moroni[3], Anna Maria Brunati[4], Stefano Indraccolo[5], Federica Chiara[6], Elena Papaleo[7], Giuseppe Cannino[1], Marco Pizzi[8], Paolo Bernardi[1], Andrea Rasola[1]

[1] CNR Institute of Neuroscience and Department of Biomedical Sciences, University of Padova, Italy
[2] CNR Institute of Molecular Recognition Chemistry, Milano, Italy
[3] IRCCS Multimedica, Milano, Italy
[4] Department of Molecular Medicine, University of Padova, Italy
[5] Istituto Oncologico Veneto, IRCCS, Padova, Italy
[6] Department of Cardiac, Thoracic, and Vascular Sciences, University of Padova, Italy
[7] Computational Biology Laboratory, Unit of Statistics, Bioinformatics and Registry, Danish Cancer Society Research Center, Copenhagen, Denmark
[6] Department of Medicine, University of Padova, Italy

We have previously shown that the mitochondrial chaperone TRAP1, a conserved member of the Hsp90 family, is involved in the metabolic rewiring of tumor cells by down-regulating the oxidative phosphorylation through inhibition of succinate dehydrogenase (SDH), the complex II of the respiratory chain. In this way, TRAP1 prompts tumor growth through a succinate-dependent stabilization of the transcription factor HIF1 alpha. Moreover, SDH inhibition has an antioxidant effect that shields neoplastic cells from lethal oxidative insults. We have now found that TRAP1 is involved in a mitochondrial signaling cascade following deregulated activation of the Ras/ERK kinase pathway. In mitochondria, active ERK1/2 phosphorylates TRAP1 and this enhances TRAP1-dependent inhibition of SDH activity and contributes to neoplastic growth. Our results indicate that TRAP1 is a major player in the metabolic regulation of tumor cells, suggesting that it could be a good target to exploit novel anti-neoplastic strategies. In this context, we have exploited molecular dynamics approaches to identify TRAP1 regions that can be potentially targeted by selective TRAP1 inhibitors acting in an allosteric way. Based on this information we have fished out and tested a set of compounds, finding that these molecules were able to inhibit TRAP1 ATPase activity in a highly selective way. Complex II activity and cell death assays in the presence of the most selective and efficient TRAP1 inhibitors are currently underway. Our studies provide evidence that novel computational approaches can be utilized to design highly selective TRAP1 inhibitors. These molecules are useful tools for the comprehension of the role played by TRAP1 in the regulation of signaling and metabolic pathways in tumor cell mitochondria, and can be further developed in order to delineate innovative antineoplastic strategies.

Role of small heat shock proteins in synaptogenesis

Elena Santana, Alberto Ferrús and Sergio Casas-Tintó

Instituto Cajal, CSIC, Madrid, Spain

Environmental changes like heat, cold or luminic stress cause accumulation of ROS and an increase of unfolded proteins which trigger cell stress and death. In the context of synaptogenesis, stress can lead to changes in synaptic plasticity. Molecular chaperones are proteins involved in the refolding of misfolded proteins under stress situations. Besides this function, we have demonstrated in our study that small chaperones can change synapse number in neurons from *Drosophila melanogaster*. Furthermore, modulation of chaperone expression levels induces changes in locomotion and circadian rhythm. In this project we explore the role of the Small Heat Shock Proteins (sHsp) Hsp23 and Hsp26 in synaptic function, the molecular mechanism that lead to synaptic changes and the proteins involved in the process. Moreover, we examine changes in synapse number under stress situations and the contribution of sHsp to synapse number restoration. Furthermore we explore the molecular mechanism of activation of Hsp23 and Hsp26 by an unknown gene called CG1561. The final goal is to decrypter the molecular mechanisms which regulate behavior and locomotion upon stress through chaperone activity and propose sHsp as targets to modulate the impact of environmental stress in neurons.

19

The co-chaperone URI controls inflammation-associated IL-17A to induce non-alcoholic steatohepatitis and its progression to hepatocellular carcinoma

Ana Teijeiro[1], Ana L. Gomes[1], Stefan Burén[1], Krishna S. Tummala[1], Mahmut Yilmaz[1], Ari Waisman[2], Jean-Philippe Theurillat[3], Cristian Perna[4], and Nabil Djouder[1]

[1] Cancer Cell Biology Programme, Growth Factors, Nutrients and Cancer Group, Centro Nacional de Investigaciones Oncolo´ gicas, CNIO, Madrid
[2] Institute for Molecular Medicine, University Medical Center, Johannes Gutenberg University of Mainz, Mainz, Germany
[3] Functional Cancer Genomics Group, Institute of Oncology Research (IOR), Bellinzona, Switzerland
[4] Department of Pathology, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain

Obesity increases hepatocellular carcinoma (HCC) risks via unknown mediators. We report that hepatic unconventional prefoldin RPB5 interactor (URI), with co-chaperone activities, couples nutrient surpluses to inflammation and non-alcoholic steatohepatitis (NASH), a common cause of HCC. URI-induced DNA damage in hepatocytes triggers inflammation via T helper 17 (Th17) lymphocytes and interleukin 17A (IL-17A). This induces white adipose tissue neutrophil infiltration mediating insulin resistance (IR) and fatty acid release, stored in liver as triglycerides, causing NASH. NASH and subsequently HCC are prevented by pharmacological suppression of Th17 cell differentiation, IL-17A blocking antibodies, and genetic ablation of the IL-17A receptor in myeloid cells. In addition, reducing URI levels prevented NASH development, suggesting that URI is responsible for the pathogenesis and pathophysiology of NASH-induced HCC. Human hepatitis, fatty liver, and viral hepatitis-associated HCC exhibit increased URI and IL-17A, correlating positively with steatosis. URI is therefore essential for NASH and its progression to HCC, and IL-17 blockers may prevent IR, NASH, and HCC in high-risk patients.

Madrid 2nd- 4th May 2017

MOLECULAR CHAPERONES IN CANCER

Previous CNIO Frontiers Meetings and CNIO Cancer Conferences

2017

PRIMARY AND SECONDARY BRAIN TUMORS

19/02/2017 - 22/02/2017

Organisers: Massimo Squatrito, Manuel Valiente, Richard Gilbertson, Michael Weller

2016

CANCEROMATICS III – TUMOR HETEROGENEITY

13/11/2016 – 16/11/2016

Organisers: Fátima Al-Shahrour, Núria Malats, Alfonso Valencia, Chris Sander

2015

METASTASIS INITIATION: MECHANISTIC INSIGHTS AND THERAPEUTIC OPPORTUNITIES

28/09/2015 - 30/09/2015

Organisers: David Lyden, Yibin Kang, Gemma Alderton, Victoria Aranda, Li-kuo Su, Héctor Peinado

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT

22/03/2015 - 25/03/2015

Organisers: Manuel Hidalgo, Alberto Bardelli, Lillian Siu, Josep Tabernero

2013

CHROMOSOME INSTABILITY AND ANEUPLOIDY IN CANCER

27/05/2013 - 29/05/2013

Organisers: Robert Benezra, Ana Losada, Marcos Malumbres, René Medema

2012

ALLOSTERIC REGULATION OF CELL SIGNALLING

17/09/2012 - 19/09/2012

Organisers: Francesco Gervasio, Ermanno Gherardi, Daniel Lietha, Giulio Superti-Furga

2011

RECAPTURING PLURIPOTENCY: LINKS BETWEEN CELLULAR REPROGRAMMING AND CANCER

07/11/2011 - 09/11/2011

Organisers: Maria A. Blasco, Konrad Hochedlinger, Manuel Serrano, Inder Verma

CANCEROMATICS II : MULTILEVEL INTERPRETATION OF CANCER GENOME

28/03/2011 - 30/03/2011

Organisers: Søren Brunak, Stephen Chanock, Núria Malats, Chris Sander, Alfonso Valencia

BREAST CANCER

07/02/2011 - 09/02/2011

Organisers: Joaquín Arribas, José Baselga, Miguel Ángel Piris, Lajos Pusztai and Jorge Reis-Filho

2010

CANCER PHARMACOGENETICS: PERSONALIZING MEDICINE

22/11/2010 - 24/11/2010

Organisers: Javier Benítez, William E. Evans, Miguel Martín and Magnus Ingelman-Sundberg

MOLECULAR CANCER THERAPEUTICS

08/03/2010 - 10/03/2010

Organisers: Gail Eckhardt, Roy S. Herbst and Manuel Hidalgo

2009

THE ENERGY OF CANCER

02/11/2009 - 04/11/2009

Organisers: Toren Finkel, David M. Sabatini, Manuel Serrano and David A. Sinclair

CANCER-OM-ATICS : MULTILEVEL INTERPRETATION OF CANCER GENOME DATA

06/07/2009 - 08/07/2009

Organisers: Søren Brunak, Núria Malats, Chris Sander and Alfonso Valencia

STEM CELLS AND CANCER

23/02/2009 - 25/02/2009

Organisers: Elaine Fuchs, Maria A. Blasco, Eduard Batlle and Mirna Pérez-Moreno

2008

SIGNALLING UPSTREAM OF mTOR

03/11/2008 - 05/11/2008

Organisers: Dario R. Alessi, Tomi P. Mäkelä and Montserrat Sánchez-Céspedes

STRUCTURE AND MECHANISMS OF ESSENTIAL COMPLEXES FOR CELL SURVIVAL

23/06/2008 - 25/06/2008

Organisers: Niko Grigorieff, Eva Nogales and Jose María Valpuesta

DEVELOPMENT AND CANCER

04/02/2008 - 06/02/2008

Organisers: Konrad Basler, Ginés Morata, Eduardo Moreno and Miguel Torres

2007

LINKS BETWEEN CANCER, REPLICATION STRESS AND GENOMIC INTEGRITY

05/11/2007 - 07/11/2007

Organisers: Oskar Fernández-Capetillo, Jiri Lukas, Juan Méndez and André Nussenzweig

MYC AND THE TRANSCRIPTIONAL CONTROL OF PROLIFERATION AND ONCOGENESIS

11/06/2007 - 13/06/2007

Organisers: Robert N. Eisenman, Martin Eilers and Javier León

MOLECULAR MECHANISMS IN LYMPHOID NEOPLASM

19/02/2007 - 21/02/2007

Organisers: Elias Campo, Riccardo Dalla-Favera, Elaine S. Jaffe and Miguel Angel Piris

2006

TELOMERES AND TELOMERASE-CNIO / JOSEF STEINER CANCER CONFERENCE

13/11/2006 - 15/11/2006

Organisers: Maria A. Blasco and Jerry Shay

MEDICINAL CHEMISTRY IN ONCOLOGY

02/10/2006 - 04/10/2006

Organisers: Fernando Albericio, James R. Bischoff, Carlos García-Echeverria and Andrew Mortlock

INFLAMMATION AND CANCER

22/05/2006 - 24/05/2006

Organisers: Curtis Harris, Raymand Dubois, Jorge Moscat and Manuel Serrano

PTEN AND THE AKT ROUTE

08/05/2006 - 10/05/2006

Organisers: Ana Carrera, Pier Paolo Pandolfi and Peter Vogt

2005

CANCER AND AGING

07/11/2005 - 09/11/2005

Organisers: Maria A. Blasco, Kathy Collins, Jan Hoeijmakers and Manuel Serrano

MAP KINASES AND CANCER

30/05/2005 - 01/06/2005

Organisers: Philip Cohen, Roger Davis, Worcester, Chris Marshall and Ángel Nebreda

ANIMAL TUMOUR MODELS AND FUNCTIONAL GENOMICS

07/03/2005 - 09/03/2005

Organisers: Allan Balmain, Mariano Barbacid, Anton Berns and Tyler Jacks

2004

CADHERINS, CATENINS AND CANCER

29/11/2004 - 01/12/2004

Organisers: Amparo Cano, Hans Clevers, José Palacios and Franz Van Roy

STRUCTURAL BIOLOGY OF CANCER TARGETS

27/09/2004 - 29/09/2004

Organisers: Ernest Laue, Guillermo Montoya and Alfred Wittinghofer

2003

APOPTOSIS AND CANCER

01/12/2003 - 03/12/2003

Organisers: Gabriel Nuñez, Marisol Soengas and Scott Lowe

SMALL GTPases IN HUMAN CARCINOGENESIS

16/06/2003 - 18/06/2003

Organisers: Juan Carlos Lacal, Channing Der and Shuh Narumiya

TARGETED SEARCH FOR ANTICANCER DRUGS

17/03/2003 - 19/03/2003

Organisers: Amancio Carnero and David H. Beach

2002

MECHANISMS OF INVASION AND METASTASIS

18/11/2002 - 20/11/2002

Organisers: Joan Massagué and Richard Hynes

THE CELL CYCLE AND CANCER

30/09/2002 - 02/10/2002

Organisers: Marcos Malumbres, Charles Sherr and Jiri Bartek

CANCER EPIGENETICS : DNA METHYLATION AND CHROMATIN

29/05/2002 - 31/05/2002

Organisers: Manel Esteller and Stephen B. Baylin

SPANISH NATIONAL CANCER RESEARCH CENTRE
CNIO - "LA CAIXA" FOUNDATION FRONTIERS MEETINGS 2017

Madrid 2—4 May 2017
Abstract Submission deadline 30 March, 2017
Application deadline 3 April, 2017*

MOLECULAR CHAPERONES IN CANCER

IN MEMORY OF SUSAN LINDQUIST

Organisers

Nabil Djouder
Spanish National Cancer Research Centre (CNIO), Madrid, Spain

Wilhelm Krek
Institute for Molecular Health Sciences, Zurich, Switzerland

Paul Workman
The Institute of Cancer Research, London, UK

Xiaohong Helena Yang
Cancer Cell, Cambridge, US

Confirmed Speakers

Udai Banerji
The Institute of Cancer Research, London, UK

Johannes Buchner
Technical University Munich, Germany

Bernd Bukau
Center for Molecular Biology of Heidelberg University, German Cancer Research Center (DKFZ), Germany

Gabriela Chiosis
Memorial Sloan Kettering Cancer Center, New York, USA

Ana Maria Cuervo
Albert Einstein College of Medicine, New York, USA

Erica A. Golemis
Fox Chase Cancer Center, Philadelphia, US

Mathias Heikenwälder
DKFZ - German Cancer Research Center, Heidelberg, Germany

Charalampos Kalodimos
College of Biological Sciences, University of Minnesota, St. Paul, US

Michael Karin
University of California, San Diego, USA

Randal J. Kaufman
Stanford Burnham Prebys Medical Discovery Institute, San Diego, USA

Oscar Llorca
Centre for Biological Research (CIB-CSIC), Madrid, Spain

Matthias P. Mayer
Center for Molecular Biology of Heidelberg University, Heidelberg, Germany

Shelli McAlpine
University of New Southwales, Sydney, Australia

Marc Mendillo
Northwestern University Feinberg School of Medicine, Chicago, US

Guillermo Montoya
Novo Nordisk Foundation Center for Protein Research, Denmark

Richard Morimoto
Northwestern University, Evanston, US

Kazuhiro Nagata
Kyoto Sangyo University, Japan

Shuichi Ohkubo
Taiho Pharmaceutical Co. Ltd., Tokyo, Japan

Laurence Pearl
University of Sussex, Brighton, UK

David Pincus
Whitehead Institute for Biomedical Research, Cambridge, US

Lea Sistonen
Abo Akademi University, Finland

Patricija van Oosten-Hawle
University of Leeds, UK

Cara Vaughan
School of Crystallography, Birkbeck College, London, UK

Paul Workman
The Institute of Cancer Research, London, UK

*Limited capacity of 130 people. CNIO reserves the right to close registration and abstract submission when we reach full capacity.

For further information and to apply please go to www.cnio.es/events
Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández Almagro 3, 28029 Madrid

EXCELENCIA SEVERO OCHOA 2012 - 2016

cnio Centro Nacional de Investigaciones Oncológicas

"la Caixa" Foundation

The Company of Biologists

MERCK


SPANISH NATIONAL CANCER RESEARCH CENTRE
CNIO - "LA CAIXA" FOUNDATION
FRONTIERS MEETINGS 2017
Madrid 19 — 22 February 2017
Application deadline January 19th
Abstract submission deadline December 19th
PRIMARY AND SECONDARY BRAIN TUMORS
Organisers
Massimo Squatrito
Spanish National Cancer Research Centre (CNIO), Madrid, Spain
Manuel Valiente
Spanish National Cancer Research Centre (CNIO), Madrid, Spain
Richard Gilbertson
CRUK Cambridge Institute, UK
Michael Weller
University Hospital Zurich, Switzerland
Confirmed Speakers
Suzanne Baker
Brain Tumor Research Division, St. Jude Children's Research, Hospital, Memphis, US
Gabriele Bergers
Vesalius Research Center, Leuven, Belgium
Priscilla Brastianos
Massachusetts General Hospital, Harvard Medical School, Boston, US
Amy B. Heimberger
The University of Texas MD Anderson Cancer Center, Houston, US
Eric Holland
Nancy and Buster Alvord Brain Tumor Center, Fred Hutchinson Cancer Research Center, UW Medicine, US
Luis F. Parada
Brain Tumor Center, Albert C. Foster, MSKCC, New York, US
Stefan Pfister
DKFZ, Heidelberg, Germany
Matthias Preusser
Comprehensive Cancer Center Vienna, Medical University of Vienna, Austria
Nicola Sibson
CRUK/MRC Oxford Institute for Radiation Oncology, UK
Joan Seoane
Vall d'Hebron Institute of Oncology, Barcelona, Spain
Riccardo Soffietti
University and City of Health and Science University Hospital of Turin, Italy
Michael Taylor
The Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, Ontario, Canada
Roeland Verhaak
The University of Texas MD Anderson Cancer Center, The Jackson Laboratory for Genomic Medicine, US
William A. Weiss
UCSF, Helen Diller Family Comprehensive Cancer Center, San Francisco, US
Wolfgang Wick
DKFZ, Heidelberg, Germany
Frank Winkler
DKFZ, Heidelberg, Germany
For further information and to apply please go to www.cnio.es/events
Centro Nacional de Investigaciones Oncológicas (CNIO)
Melchor Fernández Almagro 3, 28029 Madrid
EXCELENCIA SEVERO OCHOA 2013 - 2016
GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA, INDUSTRIA Y COMPETITIVIDAD
cnio
Centro Nacional de Investigaciones Oncológicas
"la Caixa" Foundation
Fisher Scientific
MERCK
nature medicine
novocure

16/17 CNIO Distinguished Seminars

Sep—Dec 2016

Friday 16 Sep
Francisco J. Martínez Mojica
University of Alicante, Spain

Friday 14 Oct
Francisco J. Ayala
University of California, Irvine, US

Friday 21 Oct
Mike Hall
BiozentrumUniversity of Basel, Switzerland

Friday 28 Oct
Charles Brenner
University of Iowa Carver College of Medicine Iowa, US

Friday 11 Nov
Stig E. Bojesen
Herlev Hospital, University of Copenhagen, Denmark

Friday 2 Dec
Celeste Simon
The Abramson Family Cancer Research Institute, University of Pennsylvania Perelman School of Medicine, Philadelphia, US

Friday 16 Dec
Hans-Guido Wendel
Memorial Sloan Kettering Cancer Center, New York, US

Jan—Jun 2017

Friday 13 Jan
Elaine Fuchs
Howard Hughes Medical Institute, The Rockefeller University, NY, US

Friday 20 Jan
Raul Mostoslavsky
Massachusetts General Hospital, Harvard Medical School, Boston, US

Friday 27 Jan
Benjamin L. Ebert
Brigham and Women's Hospital, Harvard Medical School, Boston, US

Friday 17 Feb
Nuria Oliver
DataPop Alliance, New York, US

Friday 10 Mar
Tom Kirkwood
Institute for Cell and Molecular Biosciences, Newcastle University, UK

Friday 17 Mar
Reinhard Faessler
Max Planck Institute of Biochemistry, Munich, Germany

Friday 24 Mar
Ioannis Aifantis
NYU School of Medicine, US

Friday 31 Mar
José Luis Sanz
Autonomous University of Madrid, Spain

Friday 7 Apr
Jacob Hanna
Weizmann Institute of Science, Behovot, Israel

Friday 21 Apr
Geneviève Almouzni
Institut Curie Research Centre, Paris, France

Friday 28 Apr
Kari Alitalo
Institute of Biomedicine, Biomedicum Helsinki, University of Helsinki, Finland

Friday 5 May
Vera Gorbunova
University of Rochester, NY, US

Friday 12 May
Anne Brunet
Stanford University School of Medicine Stanford, US

Friday 19 May
Oscar Marín
MRC Centre for Developmental Neurobiology, King's College London, UK

Friday 16 Jun
Guillermo Oliver
Feinberg Cardiovascular Research Institute, Northwestern University, Chicago, US

Out-of-the Box Seminars supported by

Organisers

www.cnio.es/eventos/seminars
Melchor Fernández Almagro 3
28029 Madrid, Spain

NOTES

NOTES

NOTES

NOTES

NOTES

Centro Nacional de Investigaciones Oncológicas (CNIO)
Spanish National Cancer Research Centre
Melchor Fernández Almagro, 3
28029 Madrid, Spain
www.cnio.es

Coordination and edition:
Mercedes Moro, CNIO, Madrid, Spain
Production of art and design by Soda Graphics
Photographic archive CNIO

Printed in Spain

As a non-profit organisation, we would like to thank all those who sponsored this conference. Such contribution helps us to ensure that our conferences will continue to establish the CNIO as a point of reference for the international cancer research community.