Therapeutic Targets in Cell Death

CONFERENCE BOOK

6 & 7 June 2012
St. Petersburg State Institute of Technology, Russia
Therapeutic Targets in Cell Death

Wednesday & Thursday, 6 & 7 June 2012
St. Petersburg, Russia

CHAIRS:
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Medical Research Council (UK)
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&
Cell Death & Disease (CDDIS)
http://www.nature.com/cddis/
Welcome Address

Dear Colleagues,

We are delighted to welcome you to the first conference of its kind on ‘Therapeutic Targets on Cell Death’ in St. Petersburg.

This workshop has been sponsored by the St Petersburg Institute of Technology as part of the Special Grant of the Government of the Russian Federation for State Support of Scientific Research under the Guidance of Leading Scientists in the Russian Institutions of Higher Education. The Medical Research Council (MRC) will contribute to the organization and the journal “Cell Death and Differentiation” will publish a scientific report.

The main focus is on innovative therapeutic aspects in the field of cell death, both defining novel targets and allowing their exploitation for potential clinical use. The workshop provides a chance for researchers to share their research interests, discuss pivotal questions in the field and explore collaboration opportunities.

Recent progress in cell death, stem cell and cancer research has provided a new paradigm of direction, from analytical approaches to integration from gene to live cells, using animals and patients with constructive approaches.

The workshop will cover a variety of essential and important topics on cell death, with a special focus on the potential therapeutic potential, under the main theme: "Paradigm Shift to Integrated and Translational innovative Therapeutic Targets — Gene, Function and Diseases." We will share frontier findings, our views as well as discuss pivotal questions both in the field and approaches to therapeutic targeting. The workshop will also provide a platform for development of collaboration opportunities.

We very much hope you have a productive and enjoyable time and hope to hear from you.

Yours sincerely,

The Organisational Committee
Programme Schedule

Day 1 (Wednesday 6th June, 2012)

10.00-11.30  Registration
11.30-11.40  Welcome address from the Chairs

Opening Keynote Lecture
Chair: G. Melino
11.40-12.20 Guido Kroemer, France
“Autophagy: suicidal self-cannibalism or homeostatic recycling?”

12.20-13.30 Lunch

Afternoon Session: From Immunogenicity to autophagy and neuronal cell death
Chair: N Barlev and AV Garabadjiu

13.30-14.00 Peter Vandenabeele, Belgium
“Necroptosis, a cell death mode with important therapeutic implications”

14.00-14.30 Mauro Piacentini, Italy
“Ambra1 a key regulatory element of early and late stages of autophagy in mammals”

14.30-15.00 Marie-Lise Gougeon, France
“Viral Escape from Immunity and Therapeutic Strategies to Target HIV Reservoirs”

15.00-15.30 Coffee Break

15.30-16.00 Hans-Uwe Simon, Switzerland
“A dual role for ATG5 upon anticancer drug treatment”

16.00-16.30 Boris Zhivotovsky, Sweden/Russia
“Lung cancer: mechanisms of resistance and sensitivity to treatment”

16.30-17.00 Daniele Bano, Germany
“Regulation of basal autophagy in calpain-deficient neurons”

17.00-17.20 Visit to the Mendeleyev Museum
17.20-17.40 Inauguration of the Mol-Pharm Laboratory

19.00+ Welcome Banquet followed by
Boat trip via canals of St. Petersburg
Day 2 (Thursday 7th June, 2012)

Morning Session: Translation & Micro-RNA in Cell Death
Chair: B Zhivotovsky and P Vandenabeele

09.00-09.30  **Gerry Melino, Italy/UK**
“Involvement of p73, a p53-family member, in metabolism and
senescence”

09.30-10.00  **Alexander Ishov, USA**
“Control of epigenetic stability and transcription of
heterochromatin in normal and stress conditions”

10.00-10.30  **Eleonora Candi, Italy**
“A microRNA triggers terminal differentiation by controlling actin
cable dynamics, intercellular adhesion and cell migration”

10.30-10.50  **Coffee break**

10.50-11.10  **Anna Tsimokha, Russia**
“Possible involvement of proteasome-associated micro-RNAs in
regulation of apoptosis”

11.10-11.30  **Nickolai Barlev, UK/Russia**
“Role of p53-dependent microRNAs in tumorigenesis”

11.30-12.00  **Martin Bushell, UK**
“MicroRNA involvement in DNA damage and cancer”

Closing Keynote Lecture
Chair G. Melino

12.00-12.40  **Anne Willis, UK**
“Translational de-regulation in diffuse large B-cell lymphoma leads
to altered regulation of key cell survival pathways”

12.40-12.45  **Closing Remarks by the Chair**

12.45-13.30  **Lunch**

13.40-15.20  **Bus Tour around the historical centre of St. Petersburg**

15.20-18.00  **Visit to Hermitage Museum**

19.30-21.30  **Farewell Dinner**
NICK A. BARLEV

Dr. Nickolai Barlev gained his PhD in Molecular and Cellular Biology in 1994 at the Institute of Cytology, St. Petersburg, Russia, and the Institute of Molecular Biology, University of Aarhus, Denmark. He then went on to do a Post-doctoral fellow at The Wistar Institute, Philadelphia, USA, until 1998. After that he became a Staff Scientist at The Wistar Institute and then in 2002 he became an Assistant Professor at Molecular Oncology Research Institute (MORI), NEMC-Tufts School of Medicine in Boston, USA, for five years. In 2007, Dr. Barlev left the United States and was appointed to Reader within the Department of Biochemistry at the University of Leicester, UK. In 2008, he was also appointed as the Head of the laboratory of Regulation of gene expression in the Institute of Cytology, St-Petersburg, Russia. His general research area includes post-translational regulation of p53, DNA damage response, and the role of 26S proteasome in regulation of gene expression.

ALEXANDER V. GARABADZHIU

Professor Alexander Garabadzhiu is the prorector on scientific work at the St. Petersburg State Institute of Technology (Technical University). Garabadzhiu is the known expert in the field of biochemistry for developing medical diagnostic systems. His research area includes toxicity and pathogenic microorganisms. He has developed technological techniques, such as a new class of DNA fluorescent probes, and has worked on retinoids analogous to vitamin A, in which he developed “Adapalen.” He is a member of several editorial boards including “General Chemistry” and “Scientific Instrument Making” and editor-in-chief of “Ecological Chemistry.” He has authored more than 200 scientific publications, 5 textbooks, and has over 20 patents to his name.

GERRY MELINO

Gerry Melino is Head of the Apoptosis & Cancer Laboratory, Medical Research Council Toxicology Unit, UK, and Director of Department & Professor of Molecular Biology, Faculty of Medicine, University of Rome – Tor Vergata. His training originated in Rome, Italy, where he obtained his M.D. (1978, University of Rome) followed by clinical specialisations in Paediatrics (1981) and Clinical Oncology (1985); the Ph.D. (1984) was at the University of London, UK, where he become Consultant. He is Editor-in-Chief, of the journal Cell Death & Differentiation (www.nature.com/cdd), Cell Death & Disease (www.nature.com/cddis) and also sites on several other Editorial Boards and acts as Scientific Advisor for several Governmental Institutions. His scientific interest, with over 390 papers, focuses upon programmed cell death in neural and epidermal models, and in particular on the p53 family – p63 and p73.
Speakers

DANIELE BANO

Dr Daniele Bano received his PhD at the University of Padova (Italy). He moved as postdoctoral fellow to the MRC Toxicology Unit, University of Leicester (UK), led by Prof. Pierluigi Nicotera. Then, he joined the laboratory of Prof. Michael Hengartner at the University of Zurich (Switzerland). In 2008, he was recruited as Program Leader Track at the MRC Toxicology Unit, University of Leicester (UK). Since 2009, Daniele Bano is Research Group Leader at the German Center for Neurodegenerative Diseases (DZNE), Bonn (Germany). The focus of his research is the identification of genes that can modulate ageing, and their influence in the development of neurodegenerative disorders.

MARTIN BUSHELL

Martin Bushell is currently an MRC Senior Fellow and a Programme Leader at the MRC Toxicology Unit in Leicester. Before this, he was a BBSRC David Phillips Fellow at Nottingham University, UK and a Wellcome Trust Travelling Fellow at Stanford University, USA. MicroRNAs control the expression of 60% of protein encoding mRNAs. They are small non-coding RNA molecules that base pair in an imperfect manner to 3’UTR of target mRNAs. Martin Bushell’s laboratory investigates how microRNAs work at the molecular level and to determine the role of microRNAs in the control of gene expression following cellular stress.

ELEONORA CANDI

Eleonora Candi, received her PhD degree at the Department of Experimental Medicine and Biochemical Sciences of University of Rome ‘Tor Vergata,’ in 1995. She did her pre- and post-doctoral training, from 1993-1998, at the Skin Biology Branch, NIAMS, National Institute of Health, Bethesda, MD, USA, working under the supervision of Dr PM Steinert on transglutaminases and their substrates. From 1999 to 2001 she received a Telethon Research Fellowship to study the role of transglutaminases in the genetic disease lamellar ichthyosis. Her current scientific interest is studying the role of p63, homologue of p53, and microRNAs in epithelia development and tumour formation. She is now an assistant professor in Molecular Biology at the Faculty of Medicine at the University of Rome ‘Tor Vergata.’
MARIE-LISE GOUGEON

Dr. Marie-Lise Gougeon gained her Doctor of Science (Sc.D.) degree in Immunology in 1986 at Paris VII University, France. She became an Assistant Professor at Institut Pasteur in Paris, and in 1989 joined the research unit of the Nobel Prize Luc Montagnier where she headed a team involved in deciphering the strategies developed by HIV to escape the immune system. Meanwhile, she was appointed as the Director of the Immunology Master Course at Paris University/Institut Pasteur. In 2002, she established the Research Department “Antiviral Immunity, Biotherapy and Vaccine” that she is still heading at Institut Pasteur. She is currently appointed as Research Director at Institut Pasteur. Her research area includes the study of innate immunity to persistent viruses, and its role in protection and pathogenesis.

ALEXANDER ISHOV

Alexander Ishov obtained his PhD in Cellular and Molecular Biology, at the Russian Academy of Sciences, St. Petersburg, in 1994. He moved to The Wistar Institute, USA, as a postdoc and was subsequently appointed a position in 1997. He became Director of the Microscopy and Histotechnology Core Facility from 1999-2001. In 2003, he moved to University of Florida where he is currently located, initially as an Assistant Professor but since 2010 as an Associate Professor. His research interest includes Chemoresistance in breast cancer (exploring taxane therapy of Daxx); Nuclear Structure and Function (focusing on ND10 or PML body); Epigenetic Regulation of Gene Expression (Daxx function at heterochromatin); and Tumor Suppression (exploring Daxx as a transcription repressor).

GUIDO KROEMER

Dr. Guido Kroemer is best known for the discovery that the permeabilization of mitochondrial membranes constitutes a decisive step in programmed cell death. He has explored the fine mechanisms of mitochondrial cell death control, the molecular pathways that explain the inhibition of cell death in cancer cells, upstream of or at the level of mitochondria, and the mechanisms that make cancer cell death immunogenic, having far-reaching implications for the detection and therapeutic manipulation of cellular demise. His contributions have been recognized with numerous awards, including the prestigious Descartes Prize of the European Union and many others. He is currently affiliated to the LabEx Immuno-Oncology (that he directs), the Paris Alliance of Cancer Research Institutes (that he presides), INSERM (for which he directs the research Unit “Apoptosis, Cancer & Immunity”), Institut Gustave Roussy (where he directs the platform of metabolomics), University of Paris Descartes (where he is full professor), Centre de Recherche des Cordeliers (where he is group leader) and Hôpital Européen Georges-Pompidou (where he is hospital practitioner). He serves on more than 36 Editorial Boards including EMBO Journal, EMBO Reports, Cancer Research, Oncogene and Cell Death & Differentiation and he is Editor-in-Chief of Cell Death & Disease. With over 650 scientific publications, he is currently the most
MAURO PIACENTINI

Dr. Piacentini is Full Professor at University of Rome 'Tor Vergata,' Italy. He is also President of the Biotechnology Program at the university, is on the Board of Directors for the European Cell Death Organization and is Basic Research Director at the National Institute for Infectious Diseases in Rome. Since 1993, he has been the Founder and an Editor of the journal, ‘Cell Death & Differentiation.’ He is also a journal reviewer for Brain Research, Cancer Research, Cancer Cell, and Nature. Furthermore, Dr. Piacentini has organized several international meetings including the 14th Euroconference on "Apoptosis or Programmed Cell Death." He has co-edited a book entitled "Methods in Enzymology: Programmed Cell Death." His research interest is to understand the molecular mechanisms regulating apoptosis and autophagy under both physiological and pathological conditions. In particular, he is interested in the pathogenesis of Huntington’s disease with particular regard to the role of TG2 and mitochondria. He is also studying infectious diseases such as HIV and HCV. With autophagy, he is characterizing the role of Ambra1, a key component of the Beclin1 complex.

HANS-UWE SIMON

Hans-Uwe Simon, MD, PhD, is Professor of Pharmacology and has been Director of the Department of Pharmacology, University of Bern, Switzerland, since 2000. After obtaining a doctoral thesis, he specialized in Clinical Immunology, at the University of Jena, Germany. His Postdoc (1990-92) was completed at Mount Sinai and General Hospitals, University of Toronto, Canada. Professor Simon became a Principal Investigator and Deputy Director (1992-2000) at the Swiss Institute of Allergy and Asthma Research, University of Zurich, Switzerland, with "Habilitation" in Experimental Immunology (1996). He also obtained a Doctoral thesis (PhD 1996-2001) at the Department of Pharmacology, Hebrew University of Jerusalem, Israel. Research interests include: i) Immunopharmacology; and ii) Role of apoptosis and autophagy in inflammatory diseases and cancer. Among other academic and administrative services, he served as President of the Swiss Society of Pharmacology and Toxicology (SSPT; 2004-2007), President of the Swiss Society of Experimental Pharmacology (SSEP; 2005-2008), President of the European Cell Death Society (ECDO; 2007-2009), and President of the Union of the Swiss Societies for Experimental Biology (USSBE; 2007-2010). Currently, he is President-elect of the International Eosinophil Society (IES; 2011-2013). Professor Simon is the Editor-in-Chief of Allergy, the European Journal of Allergy and Clinical Immunology, and member of the German National Academy of Sciences Leopoldina (since 2009).
ANNA TSIMOKHA

Dr Anna Tsimokha gained her PhD in Molecular Biology in 2007 at the Institute of Cytology, St. Petersburg, Russia. She carried out her post-doctoral training at the same institute. In 2008 she became a senior research scientist in the Laboratory of gene expression regulation. Her general research interests include regulation of 26S proteasome activity, micro-RNAs and apoptosis. The work on the role of proteasomes in control of expression of apoptotic genes received a personal Fellowship Award from the President of Russian Federation.

PETER VANDENABEELE

Vandenabeele’s research group is based at the VIB Department for Molecular Biomedical Research at Ghent University, Belgium. His research activities are focused on molecular mechanisms of caspases and RIPK kinases in cell death and inflammation, which is studied at the level of biochemistry, cell biology and diseases models (intestinal biology, skin biology – headed by Prof. Wim Dedercq – and ER stress biology – headed by Prof. Mathieu Bertrand). His research increasingly use omics approaches, high content screening and development of conditional transgenic models provided by excellent core facilities present at the department (www.dmbr.ugent.be) and VIB (Flanders Institute for Biotechnology) (www.vib.be). His work has been published in more than 270 articles, which have been cited over 16,500 times. He is head of the Bachelor and Master program in Biochemistry and Biotechnology in the Faculty of Sciences at the Ghent University (with the help of Dr. Veronique Vandevoorde). Vandenabeele has been chairman of the Euroconference on Apoptosis organized in Ghent in 2003 and 2010 and his lab is housing the secretary of the European Cell Death Organization (www.ecdo.eu). He received the prestigious Methusalemen grant from the Flemish Government for continuation of fundamental research and setting up screening facilities – headed by Dr. Tom Vanden Berghe.
ANNE E. WILLIS

Professor Anne Willis obtained a BSc in Biochemistry from the University of Kent (1984). She holds a PhD in Biochemistry (1987) from University of London (Imperial College). Her PhD was carried out in the CRUK laboratories at Clare Hall. She then worked at the University of Cambridge, Department of Biochemistry (1988-1992) and held a Junior Research Fellowship (1988-1992) and a College Lectureship (1991-1992) at Churchill College, Cambridge. She moved to the University of Leicester in 1992 to take up a Lectureship (1992-2000), Readership (2002-2004) and Chair (2004) in the department of Biochemistry. She was also awarded a BBSRC Advanced Fellowship during this period (2000-2005). She moved to the University of Nottingham as Professor of Cancer Cell Biology in 2004 and was appointed BBSRC Professorial Fellow (2008-2013). In 2010, she moved her laboratory to MRC Toxicology Unit in Leicester along with accepting her current position of Director for the Unit. Her laboratory is interested in post-transcriptional control of gene expression, particularly translational control, and how this process adapts to allow cell recovery following exposure to agents that induce stress.

BORIS ZHIVOTOVSKY

Boris Zhivotovsky received his PhD in Biochemistry and Radiobiology in 1975 and his Dr. Sci. in 1989 in St. Petersburg, Russia. In 1991 he joined the group headed by Sten Orrenius at Karolinska Institutet, Stockholm, Sweden, where he was later appointed Professor and Head of the Division of Toxicology. Since 2011 he is also appointed Professor and Head of the Laboratory of investigation of apoptosis mechanisms, Faculty of Fundamental Medicine, Moscow State University. His initial work on mechanisms of radiation-induced lymphoid cell death led to a continued interest in understanding how radiation kills cells. At present, his general research interests are focused on cell-death mechanisms that are involved in the elimination of cancer cells — in particular, on deficiencies in the cell death machinery of tumour cells that are resistant to chemotherapy. He is a member of the Editorial Board of several journals, including Cell Death & Differentiation. Among other academic and administrative services, he served as a General Secretary (1999-2009) and President (2010 - ) of the European Cell Death Organization (ECDO), Member of the Board of Directors of the International Cell Death Society (2001 - ). He was a coordinator of a number of projects supported by the European Council and received several Awards, including the Descartes Prize and the The USSR State Prize in Science and Technology.
Abstracts

Regulation of basal autophagy in calpain-deficient neurons
Daniele Bano
German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

In response to nutrient deprivation and environmental changes, eukaryotic cells quickly disassemble and recycle their intracellular components in order to supply metabolites and meet the bioenergetic demand. As a part of the stress-induced survival response, the catabolic process autophagy plays a prominent homeostatic function. Firstly characterized in yeast, autophagy is evolutionary conserved across species and is required in the turnover of intracellular organelles and, along with the ubiquitin-proteasome pathway, in the protein quality control. During autophagy, intracellular organelles and macromolecules are enclosed within a double-membrane structure and targeted to the lysosome for degradation. The resulting breakdown products are subsequently recycled to the cytosol. Because of its critical housekeeping function, autophagy is tightly controlled at different stages. As recently shown, calcium-activated proteases calpains can influence autophagosomes formation and the delivery of the cargo to the lysosomes. The molecular mechanisms by which calpains regulate autophagy are still under debate. The calpain family consists of non-lysosomal cysteine proteases, which are composed of a large catalytic and a small regulatory subunits. The Ca^{2+} binding at the C-terminal domains is required for calpain activation. In mice, the genetic deletion of the small regulatory subunit Capn4 leads to the loss-of-function of intracellular calpain activity. In our work, we have demonstrated that neuronal-specific Capn4 knockout mice show an altered autophagic flux of engulfed materials to the lysosomes. Importantly, the lack of calpain activity in the central nervous system modulates the PI3K/Akt pathway and the downstream targets. Notably, the survival of calpains-deficient primary dissociated neurons is compromised compare to wild type cells. We anticipate that autophagy regulation by calpains might be of important interest for potential clinical intervention in brain disorders, especially in those pathologies resulting from aggregate-prone proteins.

Role of p53-dependent microRNAs in tumorigenesis
Nickolai Barlev
University of Leicester, Leicester LE1 9HN, UK; Institute of Cytology, 194064 St-Petersburg, Russia; State Technological University, 190013 St-Petersburg, Russia

Therapeutic strategies based on modulation of microRNA (miRNA) activity hold great promise due to the ability of these small RNAs to potently influence the fate of cancer cells, i.e. cycle progression and/or apoptosis. The tumour suppressor p53 is known to function as a transcription factor. Through the micro-array screening we found that two abundantly expressed miRNAs, miR-15/16 and miR-26a, are controlled by p53. While miR-16 is likely regulated by p53 on a post-transcriptional level, miR-26a is the direct target of p53. Ectopic expression of miR-26a induces apoptosis of tumour cells in a p53-dependent manner. Moreover, we have identified the WEE1 gene, whose product is critical for cell cycle progression through G2/M phase, as one of the targets of miR-26a. Importantly, the WEE1 protein is a well-known therapeutic target by itself, thus exemplifying the importance of our findings for cancer therapy. Future studies should provide clues to the importance of miR-26a as a prognostic marker for various types of cancer.
This work was supported by funding from RFBS (10-04-01234), grants from Federal Programme for Scientific training in Innovative Russia (16.740.11.0366), Federal Programme for the Development of Priority Directions in Scientific Russia (16.512.11.2242), Russian Government Programme for the Recruitment of leading scientists into the establishments of higher education (11.G34.31.0069) and a grant from MCB from the Russian Academy of sciences.

MicroRNA involvement in DNA damage and cancer

Martin Bushell

Medical Research Council (MRC) – Toxicology Unit,
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Over the past 10 years compelling evidence has emerged that microRNAs act as critical downstream effectors of classical oncogene/tumour suppressor networks. The archetypal examples of oncogene and tumour suppressor microRNAs are the miR-17-92 (oncomiR 1) polycistron microRNA cluster and the miR-34 family, respectively. Whilst the involvement of these two opposing families of microRNAs in oncogenesis has been known for some time, the mRNA targets through which they exert their phenotypes are only just beginning to be uncovered. Moreover, several recent reports have demonstrated that the relevant physiological targets of certain individual microRNA are actually fairly limited, with the repression of just a few targets being sufficient to explain the observed phenotype. We will present our recent work examining the role of microRNAs in the response to cytotoxic insult and how they exert their effects. In particularly, focusing of how these mechanisms are deregulated in human cancers and possible way that microRNAs could be used to treat certain cancers.

A microRNA triggers terminal differentiation by controlling actin cable dynamics, intercellular adhesion and cell migration

I Amelio, AM Lena, G Viticchiè, A Terrinoni, RA Knight, G Melino and E Candi

Department of Experimental Medicine and Biochemical Sciences, University of “Tor Vergata”, via Montpellier 1, 00133, Rome, Italy

During keratinocyte terminal differentiation, cells undergo extensive remodelling of their actin cytoskeleton, which is important to control cell mobility and to coordinate and stabilize adhesive structures necessary for functional epithelia. Limited knowledge exists on how the actin cytoskeleton is remodelled in epithelial stratification and whether cell shape is a key determinant to trigger terminal differentiation. Here, we implicate miR-24 in actin-adhesion dynamics, using keratinocytes and mouse epidermis as models, and demonstrate that miR-24 directly controls actin cable formation and cell mobility. MiR-24 overexpression in proliferating cells is sufficient to trigger keratinocyte differentiation both in vitro and in vivo and directly represses cytoskeletal modulators (PAK4, Tks5, ArhGAP19); silencing of these targets recapitulates the effects of microRNA-24 overexpression. Our results uncover a new regulatory pathway involving a terminal differentiation-promoting micro-RNA that regulates actin-adhesion dynamics.
Persistent viruses are able to subvert innate host antiviral strategies. For example, HIV-1 has evolved ways to exploit dendritic cells (DCs), thereby facilitating viral dissemination and persistence in target cells. DCs are the first targets for HIV-1 upon primary mucosal infection, but they contain some proteins, such as SAMHD1 or TREX1, which protect them from a productive viral infection. However, we recently reported that the ability of DCs to replicate HIV and to establish HIV reservoirs was dependent on their interaction with autologous natural killer (NK) cells. During this crosstalk, which is bidirectional and leads to both NK cell activation and DC maturation, we found that HIV replication can be triggered in DCs, thus contributing to viral dissemination. The pivotal role of HMGB1, an alarmin produced by innate immune cells including NK cells, was demonstrated. Moreover, HMGB1 was found involved in the resistance of infected DCs to TRAIL-dependent NK-mediated killing. Resistance to TRAIL killing was associated with the dramatic upregulation of two key inhibitors of apoptosis, cIAP-2 and c-FLIP. Importantly, HMGB1 was responsible for the upregulation of these two apoptosis inhibitors in infected DCs, and blocking HMGB1 activity restored the susceptibility of HIV-infected DC to NK cell killing. It also abrogated HIV replication in DCs. Overall, these observations provide new insights into how HIV hijacks DCs to promote viral replication and dissemination and uses the NK-DC interaction to maintain viability of long-term viral reservoirs. The possible implication of these observations in the identification of novel therapeutic targets to eliminate viral reservoirs will be discussed.

Control of epigenetic stability and transcription of heterochromatin in normal and stress conditions
Viacheslav M. Morozov1, Ekaterina V. Gavrilova1,2,3, Vasily V. Ogrzyko4 and Alexander M. Ishov1
1University of Florida, Cancer & Genetics Research Complex and Department of Anatomy and Cell Biology, 2036 Mowry Road, Room 358, Gainesville, FL 32610, USA;
2 Faculty of Biology and Soil Sciences, St. Petersburg State University, Universitetskaya nab. 7/9, St. Petersburg 199034, Russia;
3Institute of Cytology, Russian Academy of Sciences, 4 Tikhoretsky Ave, St. Petersburg, 194064, Russia;
4Institut Gustave Roussy, 39 Rue Camilles Desmoulin, 94805, Villejuif, France

Nuclear structures ND10/PML NBs are linked to multiple processes, including the maintenance of intranuclear homeostasis by sequestering proteins into “nuclear depot”. This function presumes release of proteins from PML NBs and their redistribution to the alternative, supposedly “active” locations, in response to the external stress application. To further investigate this nuclear depot function, we focused on the intranuclear distribution of protein Daxx that in normal conditions is mainly accumulated at PML NBs, and has a minor association with centromeres and pericentromeres (CEN/periCEN). Here we report that application of physiological Heat Shock (HS) changes this balance forcing very robust and reversible accumulation of Daxx on CEN/periCEN heterochromatin. Heterochromatin architecture is essential for the proper orchestration of nuclear processes, while transcription from this part of genome is required for its maintenance. To understand functional consequences of Daxx deposition at CEN/periCEN, we tested for Daxx-dependency of
heterochromatin transcription. Depletion of Daxx reduces accumulation of CEN RNA in normal conditions and periCEN RNA after HS application. Searching for the mechanism of Daxx-dependent regulation of heterochromatin transcription, we found that depletion of Daxx decreases incorporation of transcription-associated histone H3 variant, H3.3, into both CEN and periCEN. Surprisingly, HS-induced deposition of Daxx does not further elevate incorporation of H3.3 into CEN/periCEN that remained steady during stress and recovery. Instead, depletion of Daxx leads to HS-induced changes in the balance of epigenetic modifications at heterochromatin, most dramatically elevating levels of active H3K4Me2 modification at periCEN. We propose dualistic function of Daxx-containing complexes at CEN/periCEN: 1) regulation of H3.3 loading in normal conditions, and 2) protection of epigenetic status upon stress-induced accumulation, thus collectively guarding epigenetic identity of CEN/periCEN heterochromatin.

**Autophagy: suicidal self-cannibalism or homeostatic recycling?**

*Guido Kroemer*

**INSERM, U848, Villejuif, France; Metabolomics Platform, Institut Gustave Roussy, Villejuif, France; Centre de Recherche des Cordeliers, Paris, France; Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France; Université Paris Descartes, Paris 5, Paris, France**

Autophagy has been considered for some time as a mechanism of cellular self-destruction leading to cell death. We have tackled the question whether autophagy is cytoprotective or cytotoxic in two ways. First we have screened more than 1000 established or experimental anticancer agents for their capacity to induce autophagic LC3 puncta in human cancer cells, finding that some 100 were able to do so, but that none among these “autophagy inducers” killed tumor cells in an autophagy-dependent fashion. Rather autophagy inhibition sensitized the tumor cells to cell death induction. Second, we determined the impact of whole-body autophagy induction in experimental animals. We found that autophagy-inducing pharmacological agents such as resveratrol and spermidine enhanced life span in an autophagy-dependent fashion. Similarly genetic manipulations that increase longevity (such as inactivation of the C. elegans p53 ortholog Cep1 or overexpression of the SIRT1 ortholog sirt2) induce autophagy, and inhibition of autophagy abolishes their lifespan-extending effect. We found that induction of autophagy by resveratrol requires the NAD+-dependent deacetylase sirtuin 1 (SIRT1). The acetylase inhibitor spermidine stimulates autophagy independent of SIRT1 in human and yeast cells as well as in nematodes. Although resveratrol and spermidine ignite autophagy through distinct mechanisms, these compounds stimulate convergent pathways that culminate in concordant modifications of the acetylproteome. Both agents favor convergent deacetylation and acetylation reactions in the cytosol and in the nucleus, respectively. At doses at which neither resveratrol nor spermidine did stimulate autophagy alone, these agents synergistically induced autophagy, both in vitro and in vivo. Altogether, these data underscore the importance of an autophagy-regulatory network of antagonistic deacetylases and acetylases that can be pharmacologically manipulated. Moreover, our data indicate that autophagy is mostly (always?) a cytoprotective event.

**References:**


Green DR, Galluzzi L, Kroemer G. Mitochondria and the autophagy-inflammation-apoptosis axis in cell death and organismal aging. *Science* in press


Rubinsztein D, Galluzzi L, Kroemer G. Autophagy and aging. *Cell* in press


**Involvement of p73, a p53-family member, in metabolism and senescence**

**Gerry Melino**

*University Tor Vergata, Rome, Italy; Medical Research Council, Toxicology Unit, Leicester, UK*

p63 and p73 have been identified as the ancestral members of the p53 family. Despite the high sequence and structural similarity, the mouse knockouts revealed a crucial role in neural development for p73 and in epidermal formation for p63. We identified several transcriptional targets, the mechanisms of regulation of cell death, and the p63 isoform involved in epithelial development. Both genes are involved in female infertility and maternal reproduction as well as in cancer formation, although with distinct mechanisms. TAp73 knockout mice (TW Mak G&D 2008) show high tumor incidence with hippocampal dysegensis. Conversely, ΔNp73 knockout mice (TW Mak G&D 2010) show a very low incidence of cancer, with sign of moderate neurodegeneration with a significant loss of cellularity in the cortex. This indicates a tumor suppressor role for TAp73 and an oncogenic role for ΔNp73. p73 transcriptional activity requires a Tyr-99 phosphorylation by c-Abl. p73 steady state protein levels are kept low under normal physiological conditions through degradation by the 26S proteasome, mediated by the HECT-containing E3 ubiquitin ligase ITCH. We developed an ELISA high throughput screening for ITCH auto-ubiquitylation, resulting in several positive compounds that are able to modulate chemosensitivity at 10 mM concentration. These compounds could be effective in cancer treatment. In addition to this major degradation pathway, we have also described two novel mechanisms of degradation. Firstly, we identified that the orphan F-box protein FBXO45, can target both TAp73 and ΔNp73 isoforms to degradation by polyubiquitylation. FBXO45 is the human ortholog of the C.elegans F-box protein FSN-1, therefore this novel finding elucidates a conserved pathway evolved from nematode to human, by which the p53 family members are regulated by an SCF-dependent mechanism. Secondly, we identified and characterized a novel transcriptional target of TAp73, the ring finger domain ubiquitin ligase PIR (p73-induced Ring Finger). PIR seems to be the first ubiquitin ligase able to differentiate between the TAp73 and ΔNp73 isoforms. Indeed, in response to DNA damage...
TAp73 is activated to induce cell cycle arrest or apoptosis, while ΔNp73 is rapidly degraded, highlighting the significance of the relative ratio of each isoform. In conclusion, we describe novel ITCH inhibitors and two novel mechanisms of p73 degradation, by FBXO45 and by PIR. Here, we describe the involvement of p73 in senescence and metabolism. TAp73-null mice show a significant premature spontaneous aging phenotype at 12 months of age: alopecia, epidermal thinning, reduced subcutaneous fat, increased visceral fat TAp73, osteoporosis with scoliosis. This indicates a significant phenotype related to obesity and aging. Both in vivo and in vitro TAp73-null mice show unbalanced redox defenses. TAp73 is able to drive the expression of glutaminase type 2 (GLS2), acting on specific binding sites present on its promoter. In agreement with these in vitro data, TAp73-null cells show clear metabolic defects in the glutamine pathway affecting GSH and redox balance. In keeping, we show a role for TAp73 in the regulation of metabolic pathways.

**Ambra1 a key regulatory element of early and late stages of autophagy in mammals**

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Autophagy is a self-degradative process involved in the turnover of cellular components in response to nutrient starvation or to organelle damage. During this process, portions of cytoplasm are sequestered by double-membrane vesicles, the autophagosomes, and degraded after fusion with lysosomes. Different protein complexes participate to autophagosome formation including various components of the class III phosphatidylinositol-3-OH kinase complex (Ambra1, Beclin 1, Vps34, Vps15, UVRAG) and most of the Atg genes. We have identified Ambra1 as an important regulator of autophagy by interacting and regulating the Beclin1-Vps34 complex activity playing a key role in the regulation of the early steps of autophagy. However, we have recently shown that Ambra1 interacts with the lysosomal protein Spinster. Spinster is trans-membrane protein known to regulate the endosomal pathway in Drosophila neurons. Recent studies have shown that Spinster is able to bind the antiapoptotic protein Bcl2 and is involved in the execution of a caspase-independent cell death associated to autophagic vacuole formation. We have also demonstrated that Spinster is involved in the regulation of autophagosome maturation. Spinster localizes with LC3, a marker of the autophagosomal compartment. Notably, Spinster overexpression induces autophagy, while its down-regulation leads to an alteration of autophagolysosomal acidification causing a block of autophagic degradation. Finally, we showed that Ambra1 regulates Spinster activity by regulating its levels of ubiquitination. In keeping with these findings, many evidences of a crosstalk between the ubiquitin-proteasome system (UPS) and autophagy have been reported, but the molecular mechanism behind this crosstalk has not been fully elucidated yet. We found that Ambra1 interacts with several proteins involved in the UPS, in particular, with different subunits of Cullin-RING E3 ubiquitin-ligase complexes. Ambra1 interacts with different heat shock proteins involved in chaperone-mediated autophagy (CMA), a particular type of autophagy which delivers proteins to lysosome binding them to a specific chaperone complex. In line with this observation, we found that Ambra1 is associated to CMA active lysosomes. Overall, our results demonstrated that Ambra1 plays a role in several cellular degradative pathways and it could represent a novel regulative factor involved in mediating the crosstalk between autophagy, UPS and CMA. Taken together, our data show that Ambra1 is an essential positive regulator of the autophagic process.
A dual role for ATG5 upon anticancer drug treatment

Hans-Uwe Simon

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Anticancer drug therapy has previously been shown to activate both molecular cell death and autophagy pathways. In this report, we demonstrate that DNA-damaging drugs induce the expression of a key player regulating autophagy, the autophagy-related protein 5 (ATG5). Besides autophagy, these drugs also caused abnormalities in the cell nucleus culminating in mitotic catastrophe. For this effect, ATG5 contains a functional nuclear localization signal allowing its translocation to the nucleus, an observation, which could be confirmed in vivo with cancer tissues obtained from patients following radio- and/or chemotherapy. Furthermore, we show that ATG5 antagonizes survivin function(s) in the nucleus, leading to mitotic catastrophe. These results show that ATG5 acts in two distinct pathways in cytosol and nucleus, an insight which, appropriately realized, promises better and safer elimination of cancer cells.

Possible involvement of proteasome-associated micro-RNAs in regulation of apoptosis

Anna Tsimokha

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It is well known that multiple internal and external transduction cues lead to the induction of apoptosis, or programmed cell death. The resulting degradation of cellular components is primarily carried out by specialized proteases known as caspases, but the proteasome also plays important and diverse roles in the apoptotic process. During apoptosis, proteasomes localized to the nucleus translocate to outer membrane blebs characteristic of apoptosis. Importantly, the inhibition of proteolytic activities of proteasomes causes massive apoptosis only in rapidly dividing tumour cells thus making the former attractive therapeutic candidates. Using pro-erythroleukemic cell line K562 and mesenchymal non-transformed human cell line DME/F12 we have shown that proteasomes can be excreted from apoptotic cells into the medium under certain conditions and then re-enter different cells. Importantly, the uptake of proteasomes by cells treated with genotoxic reagents resulted in their enhanced apoptosis. To investigate possible mechanisms of this “bystander” apoptotic effect, we made use of the fact that proteasomes are associated with multiple short RNA species (20-300 nt). Hybridisation of the purified proteasome-bound fraction of RNA with micro-RNA arrays revealed a number of putative microRNAs present. These miRs, according to the prediction of their targets, mostly belong to the class of tumour-suppressing and pro-apoptotic miRs. Based on these findings, we measured the effect of exogenous imported proteasomes on the level of expression of apoptotic and anti-apoptotic genes in K562 cells. We observed a clear reduction of expression for anti-apoptotic bcl-2 and survivin genes. At the same time, the level of expression of the pro-apoptotic gene, bcl-xl, significantly increased. These results suggest that the role of proteasomes in regulation of apoptosis is rather complex and not only relies on the proteolytic activity but might also involve delivery of specific pro-apoptotic micro-RNAs to the target cells. Future studies should shed the light on the molecular mechanisms of proteasome shuttling and the role of proteasome-associated micro-RNAs in apoptosis.
Necroptosis, a cell death mode with important therapeutic implications

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Today, increasing evidence demonstrates that regulated necrosis is not anymore an isolated observation of a particular cell line or in certain conditions, but is also present \textit{in vivo} during development, homeostasis, immune response and pathology (1). The knowledge on the signal transduction and regulation of necrosis is one of the hot issues in cell death research. Due to the absence of clear and distinctive markers it remains difficult to study necrotic cell death \textit{in vivo} and to understand its contribution to development, homeostasis and pathogenesis. The most distinctive biochemical marker is the dependency on RIPK3 kinase activity, which allows appreciating a contribution of necrotic cell death by the use of RIPK3 knockout mice Absence of any spontaneous phenotype suggests that RIPK3 apparently is not involved in embryonic development and homeostasis (2). However, genetic deletion of RIPK3 rescues caspase-8-deficient mice from embryonic lethality (3,4), demonstrating that RIPK3-dependent necroptosis is suppressed by apoptotic regulatory mechanisms, a remarkable example how cellular processes tightly control each other and that there may be a good physiological reason why the apoptotic pathway blocks the necrotic pathway. We studied whether the regulatory mechanisms of TNF-induced necroptosis identified \textit{in vitro} were also applicable for \textit{in vivo}. Therefore we injected high dose of TNF causing systemic inflammatory response syndrome (SIRS), resulting in septic shock. We demonstrated that deletion of apoptotic executioner or inflammatory caspases had no impact on lethal SIRS despite lowered levels of apoptosis or circulating IL-1\textbeta. In contrast, deletion of the RIPK3 gene conferred complete survival and protection against necrotic cell death, reflected by reduced levels in the serum of mitochondrial DNA, lysosomal enzymes and other markers of organ damage. Interesting, also circulating inflammatory cytokines such as IL-6 and IL-1 were dramatically lowered in RIPK3 knockout mice, demonstrating that induction of necroptosis is preceding excessive inflammatory cytokine production. Pretreatment with the RIPK1 kinase inhibitor, necrostatin-1, had a similar protective effect on mortality and resulted in reduced levels of markers of organ damage and circulating inflammatory cytokines. These results demonstrate that RIPK1/RIPK3-mediated necroptosis plays an indispensable role in TNF-induced SIRS as the determinant between life and death. The crucial role of necroptosis in SIRS in infectious sepsis was further underscored by the protective effect of RIPK3 deficiency in caecal ligation puncture (CLP) model. Altogether, our findings demonstrate that regulated necrosis or necroptosis \textit{in vivo} is a crucial process and that components of the necrototic cell death pathway are potential therapeutic targets for treatment of SIRS and sepsis (5).

References

Translational de-regulation in diffuse large B-cell lymphoma leads to altered regulation of key cell survival pathways

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Deregulation of gene expression at the level of translation makes a major contribution to both cancer development and progression, although few studies have been performed on tumour cells to identify the full spectrum of mRNAs that are aberrantly regulated via this route. In diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), we show that there is increased expression of eukaryotic initiation 4B (eIF4B), a protein that can stimulate the translation of mRNAs that contain high structured 5' UTRs by increasing the activity of the DEAD-box helicase eIF4A. To identify the mRNAs whose translation was increased in DLBCL/FL as a result of elevated eIF4B levels, translational profiling was performed. Interestingly, defined subsets of mRNAs were identified, particularly those whose protein products function in apoptosis including TRADD, FAS, DAXX, BCL-2, BCL-XL, and DNA damage for example, BRCA2 and ERCC5. In support of a role for eIF4B in translational dysregulation, there was a strong correlation between eIF4B expression and DAXX, ERCC5, BRCA2 and BCL-2 in patient samples. Increased expression of these proteins correlates with poor prognosis. However, we show that by using combinations of chemotoxic agents that target the pathways in which these proteins function, it is possible overcome the cell survival advantage that is given by their aberrant expression. Mechanistically, we show that translational deregulation of these mRNAs is mediated through their 5’ untranslated regions and decreasing eIF4B levels, resulting in reduced expression of both reporter mRNAs and the corresponding endogenous proteins. Taken together, our data suggest that eIF4B would provide a new therapeutic target for DLBCL/FL.

Lung cancer: mechanisms of resistance and sensitivity to treatment

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Lung cancer (LC) is a major cause of cancer deaths in the Western world. Based on the histopathological features, LC is divided into small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC), which account for 25 and 75% of bronchogenic carcinomas, respectively. SCLC is characterized by relatively high sensitivity to treatment with anticancer drugs and radiation. However, despite the initial responsiveness, relapses occur in most cases and are accompanied by fast development of severe resistance to treatment. SCLC represents a highly malignant and particularly aggressive form of cancer with early and widespread metastases and poor prognosis. Because of early dissemination this type of tumor can not be surgically removed. If the disease is local, concomitant chemo- and radiotherapy can be curative. Unfortunately, only 10% of SCLC patients present with localized disease. Therefore, the search for new approaches to cure SCLCs is essential. Approximately 80% of all SCLC cell lines and tumors do not express caspase-8 because of hypermethylation or mutations in the CASP8 gene. Nevertheless, irrespectively of expression of this protein, almost all SCLCs are resistant to TRAIL monotherapy. However, we have discovered several ways to sensitize SCLC cells, expressing or lacking caspase-8, to TRAIL. The mechanisms of these sensitization effects will be discussed. In contrast to SCLC, NSCLC at stage I and II can be removed by surgery.
However, because of late diagnosis the majority of cases are only recognized at stage III and characterized by high resistance to both drug- and radiotherapy, and complete remission upon therapy is rare. Therefore, resistance to treatment by patients with NSCLC presents a major problem. Mechanisms responsible for intrinsic or acquired resistance to treatment involve defects/dysregulation of the apoptotic programme. Work in our group was revealed that the resistance of NSCLC to cytotoxic drugs and g-radiation is associated with dysfunction of the mitochondria. Moreover, we recently found that PKC inhibitors can re activate the full apoptotic “response” in NSCLC via ROS generation and increased intracellular Ca\(^{2+}\) concentration. The mechanisms responsible for this reactivation will also be discussed.
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About the Organisers

Laboratory of Molecular Pharmacology (St. Petersburg)
http://www.mol-pharm.com/

The Laboratory of Molecular Pharmacology obtains its funding from the Government of the Russian Federation to carry out scientific research in the physiological functions of the protein family p53 (p63, p73) and the study of mechanisms of regulation of their stability at the expense of small inhibitors of specific E3 ubiquitin ligase ITCH. The laboratory is based at the St. Petersburg Institute of Technology.

Institute of Technology (St. Petersburg)
http://www.spbtechnologicaluniversity.com/

Saint-Petersburg State Institute of Technology (Technical University) is a world-renowned centre of many branches of science including biology, chemistry, engineering, medicine and information technology. It is a leading Russian Institution of Higher Education and was founded in 1828. Today, the institute is host to 5,000 students, almost 700 professors, associate professors and doctors across 8 faculties and 60 departments, a library of 1 million books, a museum of history as well as student accommodation.

Medical Research Council (MRC)
http://www.mrc.ac.uk/

The Medical Research Council (MRC) is a government-funded, national research institution in the UK. Officially established by 1919, today the MRC has 55 research institutes, units and centres across the country – many of which are situated within hospitals or universities. Consequently, the MRC supports a variety of research across the biomedical spectrum, from fundamental lab-based science through to clinical trials, and in all major diseases.

Cell Death & Disease (CDDIS)
http://www.nature.com/cddis/

Cell Death & Disease (CDDIS) is a sister journal to the well-established and highly respected Cell Death & Differentiation (CDD) (2010 impact factor 9.050). Part of Nature Publishing Group, CDDIS is an online, open-access publication focused on the biology of cell death in the pathogenesis of human diseases or relevant animal models. Particular emphasis is given to clinical, translational and applied research through its six sections: Cancer; Cancer Metabolism; Experimental Medicine; Immunity; Internal Medicine; and Neuroscience.
Programme at a glance

Day 1 (Wednesday 6th June, 2012)

10.00-11.30 Registration
11.30-11.40 Welcome address from the Chairs
Opening Keynote Lecture
  Chair: G. Melino
11.40-12.20 Guido Kroemer, France
12.20-13.30 Lunch
Afternoon Session: From Immunogenicity to autophagy and neuronal cell death
  Chair: N Barlev and AV Garabadgiu
13.30-14.00 Peter Vandenabeele, Belgium
14.00-14.30 Mauro Piacentini, Italy
14.30-15.00 Marie-Lise Gougeon, France
15.00-15.30 Coffee Break
15.30-16.00 Hans-Uwe Simon, Switzerland
16.00-16.30 Boris Zhivotovsky, Sweden
16.30-17.00 Daniele Bano, Germany
17.00-17.20 Visit to the Mendeleyev Museum
17.20-17.40 Inauguration of the Mol-Pharm Laboratory
19.00+ Welcome Banquet shortly followed by
  Boat trip via canals of St. Petersburg

Day 2 (Thursday 7th June, 2012)

Morning Session: Translation & Micro-RNA in Cell Death
  Chair: B Zhivotovsky and P Vandenabeele
09.00-09.30 Gerry Melino, Italy, UK
09.30-10.00 Alexander Ishov, USA
10.00-10.30 Eleonora Candi, Italy
10.30-10.50 Coffee break
10.50-11.10 Anna Tsimokha, Russia
11.10-11.30 Nickolai Barlev, UK/Russia
11.30-12.00 Martin Bushell, UK
Closing Keynote Lecture
  Chair G. Melino
12.00-12.40 Anne Willis, UK
12.40-12.45 Closing Remarks by the Chair
12.45-13.30 Lunch
13.40-15.20 Bus Tour around the historical centre of St. Petersburg
15.20-18.00 Visit to Hermitage Museum
19.30-21.30 Farewell Dinner