Book of Abstracts

Workshop

"Translational Cancer Research"

November 10 – 11, 2011

Faculty of Medicine, University of Rijeka

Croatia

TransMedRI

CAPACITIES

Workshop

"Translational Cancer Research"

November 10 – 11, 2011

Faculty of Medicine, University of Rijeka

Braće Branchetta 20, Rijeka, Croatia

Organiser

Professor Siniša Volarević

Faculty of Medicine, University of Rijeka

Department of Molecular Medicine and Biotechnology

Croatia

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I Programme 6

II Abstracts

Mutation of epigenetic regulators in myeloid malignancies 9
Joop Jansen, the Netherlands

Stem cell transplantation for ALL – current status and future trends 10
Boris Labar, Croatia

When epigenetics becomes dangerous: MLL fusion proteins and their role in leukaemia 11
Robert Slany, Germany

The CD40 receptor: from signalling pathways to cancer therapies 12
Aristides Eliopoulos, Crete, Greece

Translation cancer research challenges: EORTC BCG experience 13
Tanja Čufer, Slovenia

mTOR pathway inhibition inducing tumour regression in a mouse model of hepatocellular carcinoma 14
Sara Kozma, Spain

The role of p53 in the life of stem cells 15
Varda Rotter, Israel

Immune cell contribution to mammary tumour metastasis 16
Seth B. Coffelt, the Netherlands

Identifying means to treat Myc-induced cancers 17
Jonas Nilsson, Sweden

DNA damage response and cancer development 18
Athanassios Kotsinas, Greece

III Speakers' scientific interests and selected publications (in alphabetical order)

Seth B. Coffelt
The Netherlands Cancer Institute, Amsterdam, the Netherlands **20**

Tanja Čufer
University Clinic Golnik and Faculty of Medicine Ljubljana, Ljubljana, Slovenia **21**

Aristides Eliopoulos
University of Crete Medical School and Institute for Molecular Biology and Biotechnology, Heraklion, Crete, Greece **23**

Joop Jansen
Radboud University Nijmegen, Medical Centre St. Radboud and Nijmegen Centre for Molecular Life Sciences, Nijmegen, the Netherlands **24**

Athanassios Kotsinas
National Kapodistrian University of Athens, Medical School, Athens, Greece **25**

Sara Kozma
Bellvitge Biomedical Research Institute - IDIBELL, Barcelona, Spain **26**

Boris Labar
University of Zagreb, Faculty of Medicine, Zagreb, Croatia **27**

Jonas Nilsson
University of Gothenburg, Sahlgrenska Cancer Center, Gothenburg, Sweden **29**

Varda Rotter
The Weizmann Institute of Science, Rehovot, Israel **30**

Robert Slany
Friedrich Alexander University Erlangen, Erlangen, Germany **32**

I Programme

Thursday, November 10, 2011

09:00 – 09:10 Opening remarks

Session I : Haematooncology

09:10 – 10:00 Joop Jansen, the Netherlands
Mutation of epigenetic regulators in myeloid malignancies

10:00 – 10:50 Boris Labar, Croatia
Stem cell transplantation for ALL – current status and future trends

10:50 – 11:40 Robert Slany, Germany
When epigenetics becomes dangerous: MLL fusion proteins and their role in leukaemia

11:40 – 11:55 General discussion

12:00 – 14:00 Lunch (catering)

Session II : Translational Cancer Research

14:00 – 14:50 Aristides Eliopoulos, Crete, Greece
The CD40 receptor: from signalling pathways to cancer therapies

14:50 – 15:40 Tanja Čufer, Slovenia
Translation cancer research challenges: EORTC BCG experience

15:40 – 16:10 Coffee break

16:10 – 17:00 Sara Kozma, USA
mTOR pathway inhibition inducing tumour regression in a mouse model of hepatocellular carcinoma

17:00 - 17:15 General discussion

18:00 Dinner

Friday, November 11, 2011

Session III: Molecular Aspects of Tumourigenesis

09:00 – 09:50	Varda Rotter, Israel *The role of p53 in the life of stem cells*
09:50 – 10:40	Seth B. Coffelt, the Netherlands *Immune cell contribution to mammary tumour metastasis*
10:40 – 11:00	Coffee break
11:00 – 11:50	Jonas Nilsson, Sweden *Identifying means to treat Myc-induced cancers*
11:50 – 12:40	Athanassios Kotsinas, Greece *DNA damage response and cancer development*
12:40 – 12:55	General discussion
14:30	Lunch

Moderator: Professor Siniša Volarević

II Abstracts

MUTATION OF EPIGENETIC REGULATORS IN MYELOID MALIGNANCIES

Joop Jansen

Radboud University Nijmegen, Medical Centre St. Radboud and Nijmegen Centre for Molecular Life Sciences, Laboratory of Haematology, Nijmegen, the Netherlands

Until recently, the genetic aberrations that are causally linked to the pathogenesis of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) were largely unknown. Using novel technologies like high-resolution SNP-array analysis and next generation sequencing, various genes have now been identified that show recurrent mutations in these diverse groups of malignancies. Strikingly, several of the newly identified genes function to regulate gene expression by epigenetically changing chromatin. Aberrant epigenetic modifications have been described in many types of cancer, including myeloid malignancies. It has been proposed that repression of genes that are crucial for the cessation of the cell cycle and induction of differentiation might contribute to the malignant transformation of normal hematopoietic cells. The TET2 gene is currently the most frequently mutated gene in MDS known so far (20-25% of the cases), and is also frequently mutated in various types of MPN (including CMML, where it is mutated in 30-40% of the cases). It was shown to convert methylated cytosines (correlating with repression of gene expression) into 5-hydroxy-methyl cytosine, which might allow re-expression of genes that were shut-off by cytosine methylation of gene regulatory DNA sequences. In addition, mutations of the DNA-methyltransferase 3A gene (DNMT3A) were found, also interfering with DNA-methylation. Apart from this, mutations in genes that regulate epigenetic modifications of histones have been found in both MDS and MPN, such as EZH2. The response of patients with mutations in these epigenetic regulators to therapies that aim at epigenetic processes will be discussed.

Abstract

STEM CELL TRANSPLANTATION FOR ALL – CURRENT STATUS AND FUTURE TRENDS

Boris Labar

University of Zagreb, Faculty of Medicine, Division of Haematology, Zagreb, Croatia

Acute lymphoblastic leukaemia (ALL) is a malignant disease that originates from B or T lymphocyte precursor. The treatment of adult patients with ALL consists of a remission induction and consolidation, a haematopoietic stem cell transplantation and maintenance phase. Due to a high incidence of recurrence the prognosis of adult patients with ALL remains unsatisfactory. Overall survival rates range between 35 and 45% as reported by the major European cooperative leukaemia groups. Allogeneic stem cell transplantation seems to be the most effective postremission therapy. In EORTC ALL-4 trial the efficacy of allogeneic transplantation was compared with the other treatment approaches. All standard and high risk ALL patients under the age of 51 years in complete remission, who had a family donor (n=80) underwent allogeneic stem cell transplantation, whereas the remaining patients (n=96) were randomized either to receive autologous transplantation followed by low dose maintenance therapy or intensive consolidation/intensification courses. According to intention to treat analysis disease-free survival and overall survival were not different for the patients with or without a donor (40% versus 37%, and 46% versus 43%, respectively). The relapse incidence was significantly lower in the donor group (37% versus 60%), whereas the treatment related toxicity was higher (22% versus 2%, respectively).

WHEN EPIGENETICS BECOMES DANGEROUS: MLL FUSION PROTEINS AND THEIR ROLE IN LEUKAEMIA

Robert Slany

Friedrich Alexander University Erlangen, Department of Genetics, Erlangen, Germany

MLL fusion proteins are derived from chromosomal translocations that fuse the N-terminal portion of the histone methyltransferase MLL to a variety of different fusion partners. The resulting chimeric molecules induce high-risk acute leukaemias predominantly in infants. Our recent studies demonstrated that this class of oncoproteins works by a novel mechanism. Most MLL fusions aberrantly recruit a protein complex (elongation assisting protein =EAP, also named SEC for super elongation complex) that stimulates efficient transcriptional elongation by providing CDK9 activity accompanied by histone H3K79 methylation catalyzed by the methyltransferase DOT1L. As a consequence genes that rely on elongation control as means of regulation and here in particular the clustered HOX homeobox genes and their protein cofactors are ectopically overexpressed. The continuous presence of HOX-activity leads to a block in differentiation and the outgrowth of an aggressively proliferating precursor population. Upon acquisition of secondary mutations these pre-leukemic cells may give rise to acute leukaemia. In a second line of research we were able to show that the oncogene c-MYB is a decisive factor in the HOX-mediated program of transformation. By identification of "druggable" targets within the oncogenic "relay" from MLL-fusions to HOX proteins and their downstream targets we are hoping to develop new strategies to treat aggressive leukaemia.

Abstract

THE CD40 RECEPTOR: FROM SIGNALLING PATHWAYS TO CANCER THERAPIES

Aristides Eliopoulos

University of Crete Medical School and Institute for Molecular Biology and Biotechnology, Heraklion, Crete, Greece

Biological agents are increasingly recognized as potential therapies for refractory cancer. CD40 receptor agonists are promising biotherapeutic agents that elicit multiple anti-tumour properties, including cancer cell death, *in vitro* synergy with chemotherapeutic agents, normalization of the tumour microenvironment and induction of anti-tumour immunity. Apoptosis induction by CD40 agonists is dramatically augmented upon disruption of PI3-kinase and ERK survival signals and is initiated within a cytosolic death-inducing signalling complex following mobilization of receptor-bound TRAF2 to the cytoplasm. The death kinase RIP1 is an integral component of this complex and is required for CD40 ligand-induced caspase activation and tumour cell killing. Consequently, degradation of the RIP1 K63 ubiquitin ligases cIAP1/2 by a Smac mimetic compound amplifies CD40-mediated cell death. Whereas bladder carcinoma cells implanted into immunocompetent mice responded poorly to CD40 ligand or Smac mimetic compound alone, administration of both agents dramatically attenuated tumour growth and increased survival of the mice. These findings provide a telling example of how the expansion of our understanding of the mechanisms that govern cell death offers exciting prospects for the development of novel therapeutic strategies.

TRANSLATION CANCER RESEARCH CHALLENGES: EORTC BCG EXPERIENCE

Tanja Čufer

University Clinic Golnik, Medical Faculty Ljubljana, Ljubljana, Slovenia

The EORTC Breast Cancer Group (BCG) is a multidisciplinary group involving surgeons, medical and radiation oncologists, pathologists, basic scientists, and clinical research fellows. The main goals of the BCG are to carry high quality international clinical trials covering all areas of breast cancer care. Over the past several years the EORTC has become increasingly active in the field of translational research. In particular, translational research evaluating correlations between clinical outcomes and biologic tumour characteristics has become a high priority in the strategy of the BCG. Examples of trials with a strong translational research component are the EORTC 10994 (p53 l) and EORTC 10041 (MINDACT) trials. The results of the EORTC 10994 trial evaluating the predictive value of p53 have recently been published in the Lancet Oncology. Importantly, enrolment in this trial demanded the availability of a snap frozen core biopsy from each patient, making this enterprise one of first and the largest breast cancer trials with collected fresh frozen samples from all patients. Based on this positive experience, in the frame of the MINDACT trial, that evaluated the clinical utility of the 70-gene genomic for selecting early breast cancer patients that might be spared of toxic adjuvant chemotherapy, tumour and blood/serum samples from all enrolled patients for current and future translational research have been collected. However, there might be some barriers in accomplishment of TR for each particular trial, such as unsettled regulatory issues regarding the material handling, intellectual properties, and most importantly a serious lack of independent funding for translational research. Based on the current EORTC-BCG experience, high quality clinical trials with a strong translational research component and/or answering a molecular biology-based primary question are feasible in a multicenter and multinational setting in Europe.

Abstract

mTOR PATHWAY INHIBITION INDUCING TUMOUR REGRESSION IN A MOUSE MODEL OF HEPATOCELLULAR CARCINOMA

Sara Kozma

Bellvitge Biomedical Research Institute - IDIBELL, Barcelona, Spain

Hepatocellular carcinoma (HCC) affects more than half a million people worldwide and is the third most common cause of cancer deaths. Given the need for novel therapies and that mTOR signalling is upregulated in a majority of HCCs, we compared the effects of the FDA-approved mTOR-allosteric inhibitor, RAD001, with a new generation PI3K/mTOR ATP-site competitive inhibitor, BEZ235. Unexpectedly, we found the two drugs acted synergistically in inhibiting proliferation of cultured HCC cells. In a mouse model approximating human HCC with poor prognosis, the two drugs in combination, but not as single agents, induced a dramatic regression in tumour development. We are reporting the analyses of mTOR downstream signalling, microarray and electron microscopy studies of HCC treated with the drug combination. As synergy is achieved at low doses of both drugs, the combination decreases potential toxicity, while enhancing target specificity. These observations have led to an investigator initiated Phase 1B-2 dose escalation trial with RAD001 combined with BEZ235 in patients with advanced solid tumours, including HCC.

THE ROLE OF p53 IN THE LIFE OF STEM CELLS

Varda Rotter

The Weizmann Institute of Science, Department of Molecular and Cell Biology, Rehovot, Israel

p53 deficiency was recently demonstrated to enhance the efficiency of somatic cells reprogramming. As p53 is usually mutated in human tumours and many mutated forms were shown to gain novel activities, we aimed to study the function of mutant-p53 in reprogramming. Our data indicate a novel gain-of-function property for mutant-p53, which dramatically enhanced the efficiency of this process compared to cells lacking p53. Importantly, this novel activity of mutant-p53 was accompanied with alterations in the characteristics of the reprogrammed cells; while p53-knockout cells, reprogrammed with only *Oct4* and *Sox2*, maintained their pluripotent capacity *in vivo,* reprogrammed cells expressing mutant-p53 lost this capability, and gave rise to malignant tumours. This novel gain-of-function of mutant-p53 is not attributed to its effect on proliferation, as both p53-knockout and mutant-p53 cells displayed similar proliferation rates. In addition, we demonstrate an oncogenic activity of *Klf4*, as its overexpression in either p53-knockout or mutant-p53 cells induced aggressive tumours. Overall, our data highlight the notion that reprogrammed cells with the capacity to differentiate into the three germ layers *in vitro* can form malignant tumours, suggesting that in genetic instable cells, reprogramming may result in the formation of cells with cancer forming potential.

Abstract

IMMUNE CELL CONTRIBUTION TO MAMMARY TUMOUR METASTASIS

Seth B. Coffelt

The Netherlands Cancer Institute, De Visser laboratory, Department of Molecular Biology, Amsterdam, the Netherlands

For more than a hundred years, it has been known that tumours consist of both malignant cells and a number of stromal cell types, including immune cells. While tumour cells have received most of the attention, recent studies indicate that stromal immune cells are a dynamic, flexible component of solid tumour masses. Researchers have uncovered a paradoxical role of the immune system in cancer development and progression. Both tumour-protective and tumour-promoting properties have been attributed to immune cells, increasing the complexity of the disease. The overall goal of our lab is to address the function of the innate and adaptive immune system during sporadic mammary cancer progression and metastasis formation. For these purposes, we utilize two transgenic mouse models that develop spontaneous mammary tumours. We have determined that the absence of the adaptive immune system does not affect pulmonary metastasis formation in one model, but does result in almost complete abrogation of metastasis in another model. Our findings suggest that distinct subtypes of metastatic breast cancer are differently modulated by the adaptive immune system. Ultimately, the outcome of these studies may shift therapeutic focus from a cancer cell intrinsic point of view towards a more combined cancer cell intrinsic and extrinsic point of view.

Research support: Marie Curie Intra-European Fellowship (IEF 275610), Dutch Cancer Society (KWF 2006-3715 and 2011-5004), the Netherlands Organization for Scientific Research (NWO-VIDI 917.96.307), and the Association for International Cancer Research (AICR 11-0677).

IDENTIFYING MEANS TO TREAT MYC-INDUCED CANCERS

Jonas Nilsson

University of Gothenburg, Sahlgrenska Cancer Center , Gothenburg, Sweden

We try to identify new means to treat cancer based on knowledge about the *MYC* oncogenes. These genes encode transcription factors that regulate a vast amount of genes important for cell proliferation, metabolism and protein synthesis. One of the three members of the *MYC* family is deregulated in most human cancer suggesting that novel therapies could be found downstream or parallel to their activation.

We have asked the question if novel therapeutic targets can be identified among those genes regulated by Myc. By pharmacological or genetic inactivation of select Myc-regulated genes in transgenic mice overexpressing c-Myc in B lymphocytes we have assessed if tumour development is affected by gene loss. Indeed, some genes like Odc and Srm are important for lymphomagenesis, whereas others are not.

We have also studied the consequence of Myc overexpression on the response of cells to DNA damage exerted by drugs and irradiation. We found that Myc sensitizes cells to DNA damage by suppressing anti-apoptotic proteins and by promoting checkpoint override resulting in apoptosis. In these studies we made the unexpected and interesting finding that Myc stimulates the checkpoint kinases Chk1 and Chk2. We have and are continuing to exploit this finding therapeutically by utilizing novel inhibitors.

Abstract

DNA DAMAGE RESPONSE AND CANCER DEVELOPMENT

Athanassios Kotsinas

National Kapodistrian University of Athens, Medical School,
Laboratory of Histology-Embryology
Athens, Greece

Cells are under continuous genotoxic stress. Certain forms of genetic aberrations, like the DNA double strand breaks (DSBs), are lethal. Therefore, cells have devised mechanisms to resolve such insults in their genome. A prominent cell reaction is the activation of the DNA damage response (DDR) pathway. In early stages of cancer development, when the lesions are premalignant, various genotoxic insults can lead to oncogenic activation. In turn activated oncogenes impose a replication stress on the cells. This stress is known to induce DSBs resulting in activation of the DDR pathway. This pathway, depending upon the severity of the damage, will activate through its final effector the p53, the antitumour barriers of cell cycle arrest, senescence or apoptosis. Nevertheless, a continuous replication stress exerts a selection pressure for p53 loss, through various means, leading finally to the escape of cells from the anti-tumour barriers. As a result two interlinked effects can take place. Genomic instability and emergence of new cell clones with distinct and more aggressive behavior. These acquired characteristics will further fuel the progression of neoplasias to more advanced and malignant stages.

III Speaker info

Seth B. Coffelt, Ph.D.

The Netherlands Cancer Institute, De Visser laboratory,
Department of Molecular Biology
Amsterdam, the Netherlands

s.coffelt@nki.nl

SCIENTIFIC INTERESTS

Breast cancer metastasis is a foreboding and prevalent disease for women around the world. Over 90% of breast cancer deaths are caused by metastatic disease emphasizing the urgency for more research in this area. While experimental evidence indicates that tumour cells must acquire specific genetic mutations to disseminate and colonize distant organs, these genetic alterations are not sufficient for successful metastasis formation. Our primary interests are focused on determining how the immune system contributes to these processes.

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Speaker info

Professor Tanja Čufer, M.D., Ph.D.

University Clinic Golnik and Medical Faculty Ljubljana
Ljubljana, Slovenia

tanja.cufer@klinika-golnik.si

SCIENTIFIC INTERESTS

Dr. Čufer's major scientific interest are breast cancer, lung cancer, and molecular biology of cancer. She plays an active role in new drug development and she has been principal investigator in more than 20 multi-national clinical trials. She is very active in academic research in oncology. Her fruitful professional work resulted in more than 200 articles, books and book chapters in the field of oncology. She is also a member of several editorial boards and a reviewer for numerous international medical journals, such as The Breast, Clin Lung Cancer, Cancer Treat Rev, Ann Oncol etc. From 1987 she is an active member of the EORTC Breast Cancer Group; from 2009 she is chairing the group. In the period 2006-2009 she served as a member of the EORTC Board. Currently she is chairing the of ASCO International Affairs committee, IAC CPGC and IAC ICTW working group.

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Speaker info

Professor Aristides Eliopoulos, Ph.D.

University of Crete Medical School and
Institute of Molecular Biology and Biotechnology
Crete, Greece

eliopag@imbb.forth.gr

SCIENTIFIC INTERESTS

Our research focuses on signal transduction pathways underlying cancer cell growth and death with emphasis on the regulation of TNF Receptor-associated factor (TRAF)-mediated signalling. TRAFs are adaptor molecules which link various TNF family receptors (e.g. CD40) and viral proteins (e.g. EBV-encoded LMP1) to the activation of oncogenic and pro-inflammatory signalling pathways, such as NF-κB and MAPKs. The efforts of my lab are currently directed at the physical and functional mapping of the CD40 / TRAF signalling networks and the impact of post-translational modifications such as SUMOylation and ubiquitination on CD40 signalling.

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Dr. Joop Jansen

Radboud University Nijmegen, Medical Centre St. Radboud and
Nijmegen Centre for Molecular Life Sciences
Nijmegen, the Netherlands

J.Jansen@labgk.umcn.nl

SCIENTIFIC INTERESTS

Research addresses the molecular basis of myeloid leukaemia, myelodysplastic syndromes and other myeloproliferative neoplasms. Projects focus on the role of transcription factors and epigenetic regulators. Recently, various novel genetic aberrancies (including *TET2* and *EZH2)* were identified in myelodysoplastic syndromes using SNP array technology.

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Speaker info

Dr. Athanassios Kotsinas

National Kapodistrian University of Athens, Medical School,
Laboratory of Histology – Embryology
Athens, Greece

akotsin@med.uoa.gr

SCIENTIFIC INTERESTS

1. Cell cycle regulation: The pRb-E2F axis and upstream factors, like RAS and CDKIs, converging to this axis or downstream factors affected by this axis, such as Cdc6 and Cdt1. The p53 network and its impact on the cell cycle;

2. DNA damage responses: The DNA damage response (DDR) pathway, with emphasis on factors that lead to replication stress, and aberrations in the components of this pathway along with their impact on the cell cycle;

3. Genomic instability in cancer: Genetic aberrations at the whole genome level and in the genes mentioned above.

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Professor Sara Kozma, Ph.D.

Bellvitge Biomedical Research Institute - IDIBELL, Barcelona, Spain

kozmasc@ucmail.uc.edu

SCIENTIFIC INTERESTS

The focus of our research is the regulation of cellular growth via the mammalian Target of Rapamycin, mTOR, signalling pathway driven by nutrients, energy and growth factors. The up-regulation of the mTOR pathway has been reported in numerous human cancers. Our laboratory is developing mouse models with genetically defined alterations in components of the mTOR pathway, to study the implication of mTOR in human malignancies. These mouse models are also used in preclinical trials to address questions such as molecular efficacy, cell cycle progression, cell death and pathologic phenotypes in response to drugs tested *in vitro* or in cell culture.

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Speaker info

Professor Boris Labar, M.D., Ph.D.

University of Zagreb, Faculty of Medicine, Division of Haematology,
Zagreb, Croatia

boris.labar@inet.hr

SCIENTIFIC INTERESTS

1. Treatment of acute leukaemia and Ph positive chronic myeloid leukaemia. Therapy for Ph negative myeloprolifertive neoplasm;

2. Allogeneic stem cell transplantation for acute leukaemia, myelodysplastic syndrome and severe aplastic anaemia;

3. Treatment of paroxysmal nocturnal haemoglobinuria.

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Speaker info

Jonas Nilsson, Ph.D.

University of Gothenburg, Sahlgrenska Cancer Center,
Gothenburg, Sweden

jonas.a.nilsson@surgery.gu.se

SCIENTIFIC INTERESTS

We use a range of molecular and cellular biology techniques in mouse and human cells and mouse models and genetic strategies to define mechanisms and treatment of human diseases using knockout and transgenic mice. Moreover we are using xenografts to translate our findings into clinically relevant disease model.

SELECTED PUBLICATIONS

1. Höglund A, Nilsson L, Muralidharan SV, Hasvold LA, Merta P, Rudelius M, Nikolova V, Keller U, **Nilsson JA**. Therapeutic implications for the induced levels of Chk1 in Myc-expressing cancer cells. *Clin. Cancer Res*., 2011 [Epub ahead of print]

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Professor Varda Rotter, Ph.D.

The Weizmann Institute of Science, Department of Molecular Cell Biology, Rehovot, Israel

varda.rotter@weizmann.ac.il

SCIENTIFIC INTERESTS

My scientific career is closely connected with the p53 field and as an active pioneering member in this community. I have independently discovered a 50KDa protein that was expressed at high levels in cells transformed by the *abl* oncogene and identified one of the first p53-specific monoclonal antibodies. She was the first to show that high p53 levels are frequently detected in human and mouse tumours, and she suggested that p53 could be regarded as a tumour specific marker. The most seminal aspect of my contribution to the p53 field is the establishment of the paradigm that mutant p53 has a gain of function in carcinogenesis. In recent years, my laboratory leads successfully the quest to identify genes whose modulation underlies mutant p53 gain-of-function. Over the past years, we focused on establishing *in vitro* models for studying the role of p53 in cancer progression. These efforts yielded a number of different novel types of malignant transformation models of great potential. Furthermore, through extensive gene expression analysis and adoption of system biology approaches, important for the understanding of the molecular mechanisms that underlie distinct steps in the conversion of normal cells into fully malignant cells. Recently, our laboratory re-examined the role of p53 in cell differentiation and development with a special focus on stem cells. We found that p53 is central in regulating cell reprogramming and that p53 plays a pivotal role in preventing malignant transformation of induced pluripotent stem cells. Mutant p53 exerts a gain of function activity in inducing cancer stem cell.

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Professor Robert Slany, Ph.D.

Friedrich Alexander University Erlangen, Department of Genetics,
Erlangen, Germany

rslany@biologie.uni-erlangen.de

SCIENTIFIC INTERESTS

Our general scientific interest is to understand the genetic and epigenetic control of normal and malignant hematopoiesis. We are using MLL fusion proteins and their downstream targets, the HOX proteins, to elucidate basic principles of genetic control that governs self-renewal and differentiation decisions. Ultimately we'd like to understand the molecular machinery behind these processes and to find points of intervention that can be addressed in a therapeutic setting.

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