DR. JOSEF STEINER KREBSFORSCHUNGSPREIS 2007

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Der Dr. Josef Steiner Krebsforschungspreis 2007
wird Herrn Dr. Reuven Agami verliehen.
Herr Agami ist holländisch/israelischer Doppelbürger
und arbeitet als ausserordentlicher Professor an der Abteilung für
Tumorbiologie am Niederländischen Krebsinstitut.
Die Preissumme beträgt CHF 1‘000‘000.

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Doktor Josef Steiner, Inhaber der „Dr. Steiner Apotheke und Bahnhofdrogerie“ in Biel, hat bei seinem Tode im Jahre 1983 ein grosses Vermögen hinterlassen, welches entsprechend seinem letzten Willen die finanzielle Basis der Dr. Josef Steiner Krebsstiftung bildet. Ziel der Stiftung ist die Förderung der Krebsforschung und die Auszeichnung hochverdienter Wissenschafter auf allen Gebieten der Krebsforschung. Als erster Preisträger konnte 1986 ein Schweizer, Dr. Peter Cerrutti, geehrt werden. Seither konnten zahlreiche hervorragende Wissenschafter aus Europa, USA und Australien mit dem Dr. Josef Steiner Preis ausgezeichnet werden.

Im Bestreben, die Krebsforschung im Sinne des Stifters effizient und nachhaltig zu fördern, wird seit 1998 ein hervorragendes Forschungsprojekt für die Periode von drei bis vier Jahren mit einem Betrag von 1’000’000 Schweizerfranken unterstützt. Der Forschungsgruppenleiter oder die Forschungsgruppenleiterin wird zusätzlich mit einem persönlichen Preis in der Höhe von 50'000 Schweizerfranken ausgezeichnet.

Die Auswahl des preisgekrönten Projektes erfolgte nach einem mehrstufigen strengen Auswahlverfahren. Der Dr. Josef Steiner Preis 2007 wurde in renommierten Wissenschaftszeitschriften ausgeschrieben. Die eingereichten Projektskizzen wurden vom Stiftungsrat und einer aus Fachvertretern zusammengesetzten Preiskommission gesichtet und bewertet. Als Kriterien wurden die wissenschaftliche Qualität und die Originalität der Projektskizzen, die Qualifikation der Projektverfasser, sowie die Beurteilung der Machbarkeit der vorgeschlagenen Projekte in Betracht gezogen. Jüngeren Forschern wurde der Vorzug gegeben. Fünf hervorragende Projektskizzen wurden ausgewählt und die Verfasser aufgefordert, ein überarbeitetes und detailliertes Projekt einzureichen. Für jedes Projekt wurden mindestens drei externe Gutachten eingeholt.

Zusätzlich wurden die fünf Projektverfasser zu einem Symposium eingeladen, welches am 11. Januar 2007 an der Universität Bern stattgefunden hat. Anlässlich dieses Symposiums konnten die Forscherinnen und Forscher ihre Projekte vorstellen. Aus diesem strengen Auswahlverfahren ist Herr Prof. Dr. Reuven Agami als Sieger hervorgegangen. Der Titel seines Projektes lautet: “*Identification and characterization of microRNAs with the capacity to affect tumor growth and responsiveness to therapy”.*

EGO
IOSEPHUS STEINER
SVIZZENSIS E VICO ALPTHAL ORIUNDUS IBIQUE NATUS
RERUM NATURALIUM DOCTOR
PHARMACOPOLAE MUNERE IN MUNICIPIO BIEL PRO VIRILI PARTE
AC FORTUNA FAVENTE PERFUNCTUS
TRIBUS VIRIS PERITIS IN CONSILIUM DELECTIS AUCTORIBUS

DR. REUVEN AGAMI

QUI INDAGATOR SAGACISSIMUS MEATUS INTRACELLULARES ILLUSTRAVIT,
PER QUOS CELLULAE, QUARUM DNA LAESA EST,
VELUT SIGNO DATO INCITANTUR,
UT SUUM INTERITUM IPSAE MOLIANTUR,
PRIUSQUAM IN CANCRI FORMAM MUTARI POSSINT,

QUI INGENIOSISSIME NOVAS VIAS APERUIT,
QUIBUS IN TANTO GENORUM NUMERO,
QUO ANIMALIA VERTEBRATA SUNT PRAEDITA,
GENA ADHUC INCOGNITA,
QUAE AUT IMPEDIANT NE CANCER EXSISTAT
AUT CONTRA EFFICIANT UT CANCER EXORIATUR,
RNAI ADIUVANTE INVESTIGARI POSSINT,

QUI DE NOVIS MEDENDI RATIONIBUS ATQUE VIIS,
QUIBUS RNAI ADIUVANTE TALIA GENA,
QUAE CANCRUM EFFICIANT,
SINGULA INFRINGI ATQUE EXSTINGUI POSSINT,
OPTIME MERITUS EST,

PRAEMIUM SUPREMA VOLUNTATE MEA PROPOSITUM
QUINTUM DECIMUM TRIBUI IUBEO

BERNAE DIE II MENSIS NOVEMBRIS ANNI MMVII

CONSILII PRAESES

Laudatio für Reuven Agami

Reuven Agami, ausserordentlicher Professor am Niederländischen Krebsforschungsinstitut in Amsterdam erhält den Dr. Josef Steiner Krebsforschungspreis in Anerkennung seiner Verdienste um die Aufklärung der Bedeutung der microRNA (miRNA) in der Enstehung von Krebs.

MicroRNA ist eine erst kürzlich entdeckte Genfamilie welche in allen Pflanzen und Tieren, der Mensch eingeschlossen, vorhanden ist. Im menschlichen Genom sind tausende dieser miRNAs vorhanden. Im Gegensatz zu den bekannten Genen, kodieren miRNA keine Proteine, sondern regulieren die Funktion der andern, protein-kodierenden Gene. Man geht davon aus, dass alle protein-kodierenden Gene unter der Kontrolle von einem oder mehreren miRNA stehen. Die miRNA interferiert nicht direkt mit den protein-kodierenden Genen, sondern hemmt das unmittelbare Genprodukt, die Messenger-RNA (mRNA), die ihrerseits das Protein kodiert. Die miRNA besitzt zur mRNA komplementäre Nukleodid-Sequenzen, welche es der miRNA erlaubt an diese mRNA zu binden, und somit die Proteinsynthese (Translation) zu hemmen. Die Bindung eines oder mehrer miRNA an eine mRNA führt somit in jedem Fall zu einer Reduktion eines bestimmten Proteins. Man vermutet, dass die zahlreichen miRNAs das für eine Zelle relevante Expressionsmuster der mRNA garantieren und somit für die Aufrechterhaltung der Zellidentität und Zellintegrität verantwortlich sind.

Reuven Agami hat entdeckt, dass bestimmte miRNAs fälschlicherweise mRNA unterdrücken können, welche für die Aufrechterhaltung der normalen Zellfunktion unbedingt notwendig sind. Als Folge davon kann die normale Zellidentität gestört werden; die normalen Zellen entarten zu Krebs. Im Gegensatz dazu fand Reuven Agami auch miRNA welche die Expression von bekannten Krebsgenen unterdrücken können.

Die bedeutende und weltweit stark beachteten Arbeit von Reuven Agami lassen vermuten, dass er mit Hilfe der miRNA Technik nicht nur bedeutende Fortschritte im Verständnis der molekularen Kontrolle der Krebsentstehung erzielen wird, sondern es besteht auch die begründete Hoffnung, dass miRNA in Zukunft therapeutisch für die Behandlung von Krebsleiden eingesetzt werden können.

Laudatio for Reuven Agami

Reuven Agami, Associate Professor at the Netherland Cancer Institute Amsterdam, is recipient of the Dr. Josef Steiner Award 2007. He receives this prize in recognition for his development and application of methodologies based on RNA interference (RNAi), the ability of double-stranded RNA to efficiently and potently silence any gene in plants, animals and humans, to systematically define cancer gene functions on a genome-wide scale.

Reuven Agami has spend his entire career working to unravel at the molecular level how damage of the genetic information, the DNA, makes normal cells genetically unstable and cancer prone. Already as a graduate student at the Weizmann Institute of Science, Israel and later as a postdoctoral fellow at the Netherland Cancer Institute, Amsterdam, he has discovered novel signaling pathways through which cells initiate their own demise if they experience DNA damage. He noted that key components of these pathways represent oncogenes and tumor suppressor genes, providing a mechanism by which cancer genes promote the accumulation of additional genetic alterations and tumor cell evolution.

As a principal investigator at the Newtherland Cancer Institute, Reuven Agami continued to vigorously pursue his work on the DNA damage response pathway. However, rather than teasing apart the pathway by removing genes one at a time and looking at the effect, Agami began to develop RNAi-based methodologies that allow any gene of known sequence to be stably shut down and the corresponding loss-of-function phenotype studied. This methodology allowed to systematically silence genes on a genome-wide scale using large rationally designed libraries targeting many thousands of genes and thus provided a novel functional genomics approach to the investigation of many aspects of mammalian cell behaviour, including the DNA damage response and oncogenic transformation.

RNAi represents an evolutionary conserved cellular defense for controlling the expression of foreign genes. It is triggered by double-stranded RNA molecules which silence a gene by elimination of the mRNA corresponding to that gene. RNAi has already become an important research tool in biology and biomedicine and is being developed for application in cancer therapy. In 2002, the journal *Science* named RNAi ‘the technology of the year’ and in 2006, the Nobel Prize in Physiology and Medicine was given for the discovery of RNAi.

Work in this field is by no means finished and the application of this technology is likely to provide unexpected and rich insight into the molecular circuitry underlying tumor cell evolution. Agami not only set the stage for RNAi-mass screening of mammalian genes but also applied this new technology to identify

heretofore unknown genes with tumor suppressor function. The impact of Agami's work on cancer research has been already superb and led him to become elected as an EMBO Young Investigator and recipient of the European Young Investigator Award in 2004. With the Dr. Josef Steiner Prize, the committee is honoring a highly creative scientist and hopes that this prize will prove to be a major incentive for further scientific research in the mechanism and application of RNAi in cancer biology and medicine.

Curriculum Vita Reuven Agami (*1965)

Since September 2005: Associated professor at the Division of Tumor Biology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
September 2001 - September 2005: Assistant professor at the Division of Tumor Biology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
June 1998 - September 2001: Post-doctoral fellowship at the Division of Molecular Carcinogenesis, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
1993-1999: PhD at the Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel. Official date of graduation is 8th June 1999.
1991-1993: MSc at the Department of Membranes and Biophysics, The Weizmann Institute of Science, Rehovot, Israel.
1987-1991: BSc at Tel-Aviv University, Israel.

I performed my PhD research (Thesis: Cell cycle and apoptosis control induced by the tyrosine kinase c-Abl) within the department of molecular genetics at the Weizmann Institute of Science, Israel. During this period I identified a novel DNA-damage-induced apoptosis pathway that requires the activation of c-Abl kinase and tyrosine phosphorylation of the p53 homologue-p73a. This work was published in the top journal Nature. In 8th June 1999 I recieved my PhD. As a post-doctorate fellow in the group of Prof. Rene Bernards, I initiated my own line of research to identify rapid molecular events that initiate p53-independent DNA damage responses. In July 2000, my work was published in the top journal Cell. In September 2001, I started my own group at the Netherlands Cancer Institute and in September 2005 I became a staff member (associated professor). In these years I developed an

RNAi vector system (pSUPER) to stably inhibit gene expression in mammalian cells. This work was published in 2002 in the top journal Science. Since then, the pSUPER system is used worldwide and also in the two research topics in my group. The first research line focuses on the identification of novel DNA damage checkpoint genes that govern cell cycle responses following genotoxic stress. The second research line is the identification of novel tumor suppressor genes using transformation of primary human cells. Here we established a tumor suppressor role for the transcription factor PITX1, work that was published in 2005 in Cell. Recently, we developed research tools to identify cancerous miRNAs. First part of this work was published last year (Voorhoeve et al., 2006) in Cell. The second part is under revision now (le Sage C., Nagel R. and Agami R.,).

Honors and Awards Reuven Agami
1999: EMBO long-term fellowship.
2001: Netherlands Cancer Institute (AVL) award.
2002: Elected fellow of the central for biomedical genetics (CBG).
2004: European Young Investigator Award (EURYI).
2004: VIDI grant.
2004: EMBO young investigator (YIP) award.
2006: Elected young academy member of the Royal Netherlands Academy of Sciences (DJA-KNAW).
2007: Awarded the Dr. Joseph Steiner Prize, Switzerland - 2007.
2007: Elected EMBO member

Unraveling Functions of microRNAs in Cancer

miRNAs
MicroRNAs (miRNAs) is a newly identified gene family found in all vertebrates, plants, and invertebrate species. All miRNAs encode short RNA of 22-nucleotides (nt). Recent estimations suggest the existence of thousands miRNA genes in the human genome. miRNAs are not translated to protein but rather regulate the expression of other protein-coding genes. It appears that the majority of protein-coding genes might be under the regulation of one or more miRNA. Exactly how miRNAs influence expression of genes is not yet known. It is generally believed that miRNAs regulate gene expression after message RNA (mRNA, RNA that codes for protein) was produced from the protein-coding gene. The miRNAs bind to mRNAs, through fully or partly complementary target sequences. The result of this binding can be either degradation of the RNA or inhibition of the translation process. Translation is the process that converts RNA to protein. In general, target mRNAs containing fully complementary sequences to the miRNA, will be degraded by an RNA-interference mechanism, whereas targets with partial complementarity will be subjected to translation inhibition and mRNA decay. In all cases, though, the binding of miRNAs to mRNAs results in slower production of a particular protein.

Functionally, miRNAs have been suggested to play a role in maintaining the reliability of mRNA expression patterns. The miRNA and its predicted targets are expressed in a mutually exclusive manner, ensuring that any illegitimate expression of an mRNA in a non-relevant tissue is suppressed. In other words, a messenger RNA is expressed in one cell while a targeting miRNA is expressed in a neighboring cell, taking care that no leakage expression occurs in the second cell type, thus helping preserving the different identities of both cell types. In contrast, certain miRNAs have been shown to elicit a more specific function, which is exerted by the inhibition of a limited number of targets normally expressed in the same cell. These miRNAs likely to participate in cell fate decisions during cell growth and differentiation. Importantly, whether a given miRNA acts to suppress illegitimate expression, or targets directly a subset of genes, its aberrant expression bares the capacity to cause phenotypic abnormalities in the cellular level, as well as in the level of the organism. Based on this assumption, we chose to unravel cancer-related functions of miRNAs using a functional genetic approach.

Functional genetic approaches identify cancerous miRNAs

Approach 1: To identify novel functions of miRNAs, we took a functional genetic approach. We built a vehicle to force the expression of any given miRNA we choose. Then, we created a large collection of vehicles to allow the forced expression of almost all known human miRNAs. Additionally, we made a chip to detect and quantify all these vehicles. We used these tools to identify novel cancer causing miRNAs. The idea was to use normal human cells that are sensitive to the emergence of oncogenic mutations. An oncogene is defined as a cancer promoting change in a gene. Once such a change occurs, normal human cells contain signaling pathways that take care to prevent abnormal cell growth. We asked: are there any miRNAs that will numb this defence response and allow the cells to tolerate oncogenic events? – a process that ultimately leads to cancer. Screening our library revealed a miRNA gene family named miR-372 that was capable of doing it. Further investigation uncovered the mechanism (targeting genes) and, most importantly, the oncogenic role of this family in the development germ cell tumors.

Approach 2: Here we concentrated on protein-coding genes whose role in cancer was already established. By screening our miRNA library, we experimentally identified several miRNAs that inhibit the expression of one or some of these cancer genes. The functional relationship between the cancer gene, the miRNA and cancer is subsequently unraveled using cell systems and human tumor material. For example we uncover the role of one miRNA (miR-221) in controlling p27, a tumor suppressor and cell cycle inhibitor, and unraveled their function to promote cancerous growth of brain tumors. Most remarkably, inhibition of the miRNA activity stopped proliferation of cancer cells. We are now examining possibilities to adapt this technology to cancer treatment in animal models.

Future prospective

I propose to test the idea that some miRNAs may confer resistance to cancer therapy:

miRNAs in Anti-hormonal therapy: Specific types of tumors, most commonly from breast and prostate origin, rely on hormones such as estradiol and

dihydrotestosterone to survive and grow. Anti-hormone therapy is a treatment that targets tumors by blocking their ability to respond to the hormones on which they depend. Anti-hormones include, for example, the anti-estrogens tamoxifen and fulvestrant for the treatment of breast cancer, and the anti-androgens flutamide and bicalutamide for the treatment of prostate cancer. However, often the hormone-dependent tumors eventually evolve to become hormone-independent, and thus resistant to anti-hormonal treatments. Since the response of tumor cells to anti-cancer therapy is a consequence of their genetic composition, and because miRNAs are potent regulators of gene expression, we hypothesize that miRNAs may play a role in the regulation of cellular pathways that can lead tumor cells to gain resistance to anti-hormonal therapy. Using the genetic approaches illustrated above we are aiming at the identification of miRNAs whose function can change cell reaction to anti-hormonal therapy.

miRNAs in Genotoxic drugs therapy: Chemotherapy is very often used as anti-cancer drugs to treat cancerous cells. Examples are doxorubicin, methotrexat, 5FU and paclitaxel. These drugs kill replicating cells therefore have higher efficiency in eliminating cancer cells. However, quite often resistant-tumors appear following treatment. To uncover whether miRNAs play a role in this phenomenon, we are taking two approaches. First we are comparing the expression of hundreds of miRNAs in resistant versus sensitive tumors. We are using mouse models and human tumor material for that. Second, we perform genetic screens in cellular models to find miRNAs that can confer resistant phenotype to – otherwise – sensitive cells.

miRNAs in Metastasis: Metastasis occurs when genetically unstable cancer cells adapt to a tissue microenvironment that is distant from the primary tumor. This process involves both the selection of behavior that are advantageous to cancer cells. We hypothesize that part of this adaptation can either be induced or will require changes in miRNA expression. Using expression analysis as well as functional genetic screens, as explained above, we aim here to identify miRNAs that are potent inducers of metastasis.