DR. JOSEF STEINER KREBSFORSCHUNGSPREIS 2017

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Der Dr. Josef Steiner Krebsforschungspreis 2017
geht an Herrn Prof. Dr. Jacco van Rheenen.

Herr van Rheenen ist Professor für intravitale Mikroskopie am
Universitätsspital Utrecht, Niederlande.
Die Preissumme beträgt gesamthaft CHF 1‘000‘000.

Dr. Josef Steiner Krebsforschungspreis 2017

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 bildete. 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, Australien und der Schweiz 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 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 2017 wurde in renommierten Wissenschafts-zeitschriften 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. Vier hervorragende Projektskizzen wurden ausgewählt und die Verfasser aufgefordert, ein überarbeitetes und detailliertes Projekt einzureichen. Für die Projekte wurden 2 vergleichende Beurteilungen von externen Gutachtern eingeholt.

Zusätzlich wurden die vier Projektverfasser zu einem Symposium eingeladen, welches im Januar 2017 an der Universität Bern stattgefunden hat. Anlässlich dieses Symposiums konnten die Forscherinnen und Forscher ihre Projekte vorstellen. Aus diesem strengen Auswahlverfahren ist Hr. Prof. Dr. Jacco van Rheenen als Sieger hervorgegangen.

Laudatio für Herrn Prof. Dr. Jacco van Rheenen

Die Dr. Josef Steiner Stiftung verleiht den Josef Steiner Krebsforschungspreis an Herrn Prof. Dr. Jacco van Rheenen in Anerkennung seiner bahnbrechenden Forschungsergebnisse über die Mechanismen der Metastasierung von Tumorzellen in lebenden Tieren. Mit einer beeindruckenden Kombination von genetischen Modellen und intravitaler Bildgebung konnte er das dynamische Verhalten und das Schicksal einzelner Tumorzellen in Primärtumoren und an entfernten Organen visualisieren. Diese Ergebnisse haben die Tragweite der Zell-Zell-Kommunikation über grössere Distanzen und der Tumorzellplastizität für die Metastasierung offenbart und neue Zielproteine für Anti-Krebs-Strategien aufgedeckt.

Curriculum Vitae Jacco van Rheenen

Group Leader Cancer Biophysics,
Hubrecht Institute/ Netherlands Cancer Institute
Professor Intravital Microscopy
University Medical Center Utrecht
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Actual Positions

2008 **Group leader, Hubrecht Institute, Royal Netherlands Academy of Arts and Sciences**
Institute for Developmental Biology & Stem Cell Research, Utrecht, Netherlands

2014 **Full Professor in Intravital Microscopy, University Medical Center Utrecht, Netherlands**

2017 **Group leader, Nederlands Kanker Institute-Antoni van Leeuwenhoek (NKI-AvL)**
The largest Oncology Institute in the Netherlands, Amsterdam, Netherlands

Education

2005 **PhD degree in Biophysics, Netherlands Cancer Institute / Leiden University (supervisors: Dr. Kees Jalink and Prof. Dr. Jacques Neefjes), Netherlands**

2000 **MSc degree in Biology, University of Amsterdam, Netherlands**

Postdoctoral Training

2006-2008 Albert Einstein College of Medicine, Yeshiva University, Bronx, USA.
Department of Anatomy & Structural Biology
Lab. Prof. Dr. John Condeelis
Position: Fundamental and (pre) clinical cancer research fellow from the Dutch Cancer Society (KWF).

2005-2006 **Netherlands Kanker Institute-Antoni van Leeuwenhoek (NKI-AvL)**
Division of Cell Biology
Lab: Dr. Arnoud Sonnenberg
Position: Postdoctoral Research Fellow

Fellowships, Grants and Awards

2017 Dr. Josef Steiner Cancer Research Foundation Award
2017 Blue Flame Award, Addgene
2017 Dutch Cancer Society grant, “The intermediate filament network in glioma invasion into consideration”
2016 Dutch Cancer Society grant, “Understanding the role of SOX4 in educating the mammary tumor niche: the potential for personalized therapeutic targeting”,
2015 European Research Council (ERC) consolidator grant
2014 Best seminar at the research colloquium Cardiology, University Medical Center Utrecht
2014 Marie Curie, Innovative Training Networks “Integrated Component Cycling in Epithelial Cell Motility” (InCeM)
2014 NWO Earth and Life Sciences Open Program: “Identifying the physiological relevance of RNA transfer by microvesicles”.
2013 NWO Gravitation, participant of the Cancer Genomics Centre Netherlands
2013 Stem Cells Young Investigator Award
2012 Research grant from the Association for International Cancer Research
2010 A NWO equipment grant “A spinning disk confocal microscope to image epithelial and endothelial”

2009	Dutch Cancer Society grant: "MenaINV-induced EGFR clustering causes mammary carcinoma cells to become invasive."
2008	NWO VIDI personal grant "Influence of extracellular matrix remodeling by stromal cells on invasion and intravasation of mammary tumor cells."
2008	A NWO equipment grant "A two-photon microscope containing two infrared lasers to excite cyan, green, yellow and red fluorophores in living animals."
2006	Fellowship for fundamental and (pre-)clinical cancer research from the Dutch Cancer Society (KWF). Intravital imaging of metastasis and the immune responses at single cell resolution.

Publiations

1. Scheele CL , Hannezo E, Zomer A, Langedijk NSM, Simons BD, **van Rheenen J**, (2017) Identification of mammary stem cells and their dynamics during branching morphogenesis, resubmission ***Nature,*** Feb 16;542(7641):313-317.
2. Bruens L, Ellenbroek SIJ, **van Rheenen J**, Snippert HJ. (2017) In vivo Imaging Reveals Existence of Crypt Fission and Fusion in Adult Mouse Intestine, ***Gastroenterology.*** May 25. pii: S0016-5085(17)35631-7.
3. Suijkerbuijk SJE, **van Rheenen J.**, (2017) From good to bad: Intravital imaging of the hijack of physiological processes by cancer cells, ***Dev Biol***. 2017 May 1. pii: S0012-1606(17)30054-4.
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5. Beerling E, Oosterom I, Voest E, Lolkema M, ***van Rheenen J.*** (2017) Intravital characterization of tumor cell migration in pancreatic cancer. ***Intravital.*** 2016 Nov 18;5(3):e1261773
6. Beerling E., Seinstra D., de Wit E., Kester L., van der Velden D., Maynard C., Schäfer R., van Diest P., Voest E., van Oudenaarden A., Vrisekoop N., **van Rheenen J.** (2016) Plasticity between epithelial and mesenchymal states unlinks EMT from metastasis-enhancing stem cell capacity, ***Cell Reports***, Mar 15;14(10):2281-8.
7. Vecchione L, Gambino V., Raaijmakers J, Schlicker A., Fumagalli A., Russo M., Villanueva A., Beerling E., Bartolini A., Mollevi D.G., El-Murr N, Chiron M, Calvet L., Nicolazzi C., Combeau C., Henry C., Simon I.M., Tian S., in 't VeldS., D'ario G., Mainardi S., Beijersbergen R.L., Lieftink C., Linn S., Rumpf-Kienzl C., Delorenzi M., Wessels L., Salazar R., Di Nicolantonio F., Bardelli A., **van Rheenen J.,** Medema R., Tejpar S. and Bernards R. (2016) A vulnerability of a subset of colon cancers with potential clinical utility, ***Cell,*** Apr 7;165(2):317-30.
8. Zomer A., Steenbeek S.C., Maynard C., **van Rheenen J**. (2016) Studying extracellular vesicle transfer by a Cre-loxP method, ***Nat Protoc.*** Jan;11(1):87-101.
9. Zomer A., van Rheenen J. (2016) Implications of extracellular vesicle transfer on cellular heterogeneity in cancer; what are the potential clinical ramifications?, ***Cancer Research***
10. van Gurp L., Loomans CJM, van Krieken PP, Dharmadhikari G, Jansen E, Ringnalda F, Beerling E, **van Rheenen J,** de Koning EJP, (2016) Sequential intravital imaging reveals in vivo dynamics of transplanted pancreatic tissue under the kidney capsule, ***Diabetologia***, Nov;59(11):2387-92.
11. Frentzas S, Simoneau E, Bridgeman VL, Vermeulen PB, Foo S, Kostaras E, Nathan MR, Wotherspoon A, Gao ZH, Shi Y, Van den Eynden G, Daley F, Peckitt C, Tan X, Salman A,

Lazaris A, Gazinska P, Berg TJ, Eltahir Z, Ritsma L, **van Rheenen J**, Khashper A, Brown G, Nyström H, Sund M, Van Laere S, Loyer E, Dirix L, Cunningham D, Metrakos P, Reynolds AR. (2016) Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases. ***Nat Med.*** 2016 Nov;22(11):1294-1302

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18. Ellenbroek S.I.J., **van Rheenen J**, (2014) Imaging hallmarks of cancer in living mice, ***Nat Rev Cancer***, 14(6):406-418
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23. Ritsma L, Vrisekoop N, **van Rheenen J**. (2013), In vivo imaging and histochemistry are combined in the cryosection labelling and intravital microscopy technique. ***Nat Commun***., 4:2366
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47. Kedrin D, **van Rheenen J**, Hernandez L, Condeelis J, Segall JE. (2007), Cell motility and cytoskeletal regulation in invasion and metastasis. ***J Mammary Gland Biol Neoplasia***., 12(2-3): 143-52.
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50. **van Rheenen J**., Achame E.M., Janssen H., Calafat J., Jalink K. PIP2 in rafts: a critical re-evaluation, ***EMBO J***., (2005), 24: 1664-1673.
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Prof. Dr. van Rheenen beschreibt seine preisgekröntes Projekt wie folgt:

Filming the birth of intestinal tumors: How does diet influence the cellular protection mechanisms that eliminate tumor-initiating cells?

With increasing age and a changing life-style, such as high calorie diets, colorectal cancer has become one of the most common types of cancers. In healthy intestinal tissues, every 3 days the lining gets renewed by replacing old cells by new cells. Tumors are initiated when DNA of these cells gets damaged, leading to instructions to multiply in an uncontrolled fashion. In more than 80% of all human colorectal tumors, uncontrolled cell growth is driven by DNA damage that mediates loss of the tumor suppressor gene adenomatous polyposis coli (APC). Although it is well accepted that loss of APC is a tumor-initiating step, not every cell that loses APC (**APC-negative cells**) will function as a tumor-initiating cell. Fortunately our bodies have developed cellular mechanisms to get rid of these dangerous APC-negative cells that can initiate tumor growth. Here in this grant we will study how Western-style diet influences these cellular protection mechanisms.

Our project will be the first to literally *see a tumor being born*, under different dietary regimes. To do this, we developed a technique called 'intravital imaging': we can film the cells of intestines in living mice through tiny glass windows placed on their bellies (the mice still function normal after recovery). Some mice will have a diet like most Western diets these days: overloaded with calories coming from fat. Another group of mice will have the opposite type of diet: their calorie intake will be strongly restricted. There is also a third group, the control group, with mice that receive a normal healthy diet. Under these conditions, we will film the birth of APC-negative cells, and look at how the body either eliminates these tumor-initiating cells or how some of these cells can escape the protection mechanisms to initiate a tumor.

To understand how bodies can get rid of the dangerous APC-negative cells, we first need to understand how the lining of intestinal epithelium gets renewed. The intestinal epithelium is a highly repetitive sheet of crypt-villus units (Fig. 1a), where at the bottom of the crypts the cells reside that give rise to all other cells in the crypt and villus, the so called **stem cells**. Each crypt contains 14-16 of these highly proliferative stem cells (Fig. 1a). Upon every division, stem cells need to compete for space, whereby one stem cell is repelled out of the stem cell zone. Cells that are repelled from this zone, multiply and start to move up like an escalator towards the tip of the villus where they, after three days, arrive and shed into the lumen (Fig. 1a). Therefore, the cells that lose APC, while being in the 'intestinal lining escalator', get shed into the lumen before they can initiate a tumor. By contrast, the stem cells remain localized at the bottom of the crypt. Therefore, loss of APC in these cells is dangerous, since it can potentially lead to cancer.

Does loss of APC in stem cells always lead to tumors? No! Think of a plate (stem cell zone) that is completely filled with marbles (stem cells) of different colors (Fig. 1b). If one of the colored marbles (stem cells) multiplies thereby giving rise to two new marbles with the same color, another marble with a different color will be repelled from the plate due to limited space on the plate (Fig. 1b). If this happens over and over, at some point the plate will be filled with marbles of the same color (Fig. 1b). The same happens with the stem cells in the stem cell zone (e.g. "healthy" and APC-negative stem cells). The offspring of "healthy" stem cells can repel APC-negative stem cells from the stem cell zone, where through the 'intestinal lining escalator' these APC negative cells get shed and lost into the lumen. Since the stem cell zone has many more "healthy" stem cells than APC-negative cells, most of the APC-negative cells

will be eliminated by this competition. However, some APC-negative stem cells do not get repelled by the “healthy” stem cells and initiate tumors. By filming and characterizing all APC-negative cells that escape from the cellular protection mechanisms, we can explore whether and how APC-negative cells escape from the cellular protection mechanisms.

Since calorie intake has been linked to tumor incidence and has been shown to severely influence the cellular composition of intestinal tissues (e.g. more stem cells upon a calorie-restricted diet), we hypothesize that: an altered cellular composition of intestinal tissue (e.g. due to calorie-restricted diet) changes the cellular protection mechanisms and therefore the ability of APC-negative cells to initiate intestinal tumors. We will shed light on this by filming the competition between “healthy” and APC-negative cells at the various diets.

Aside from characterizing the cellular protection mechanisms that are present in intestinal tissue to eliminate tumor-initiating cells for the first time, we also hope to be able to find a way to influence these protection mechanisms other than via diets. The experiments will try to identify drug targets and potentially drug treatments that mimic dietary changes, preventing the initiation of intestinal cancer.

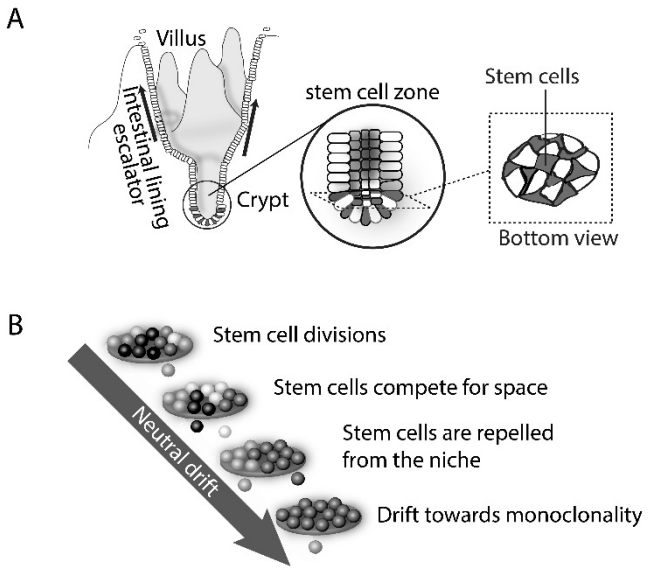

Figure 1, homeostasis of intestinal tissue A) Cartoon of intestinal homeostasis, where cells are born at the stem cells, and get transported to the villus by the intestinal lining escalator. B) Cartoon of multiplying stem cells that compete for space in the stem cell zone and become clonal.