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 of 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 of Intravital Microscopy, University Medical Center Utrecht, Netherlands**

2017 **Group leader, Nederlands Kanker Institute-Antoni van Leeuwenhoek (NKI-AvL)**
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 development, tumor formation and metastasis”
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.

Publications

Original publications:

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, ***Nature,*** 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,*** pii: S0016-5085(17)35631-35637.
3. Fumagalli A, Drost J, van Boxtel R, de Ligt J, Begthel H, Beerling E, Hong Tan E, Sansom OJ, Cuppen E, Clevers H, **van Rheenen J**, (2017) Genetic dissection of colorectal cancer progression by orthotopic transplantation of engineered cancer organoids, ***Proc Natl Acad Sci USA,*** 114(12):E2357-E2364.
4. Beerling E, Oosterom I, Voest E, Lolkema M, **van Rheenen J,** (2017) Intravital characterization of tumor cell migration in pancreatic cancer. ***Intravital,*** 18;5(3):e1261773
5. 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 Rep***, 14(10):2281-2288.
6. Vecchione L, Gambino V, Raaijmakers J, Schlicker A, Fumagalli A, Russo M, Villanueva A, Beerling E, Bartolini A, Mollevi DG, El-Murr N, Chiron M, Calvet L, Nicolazzi C, Combeau C, Henry C, Simon IM, Tian S, in ‘t Veld S, D’ario G, Mainardi S, Beijersbergen RL, 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,*** 165(2):317-330.
7. Zomer A, Steenbeek SC, Maynard C, **van Rheenen J**. (2016) Studying extracellular vesicle transfer by a Cre-loxP method, ***Nat Protoc,*** 11(1):87-101.
8. 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***, 59(11):2387-2392.
9. 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,*** 22(11):1294-1302.
10. Sasaki N, Sachs N, Wiebrands K, Ellenbroek SI, Fumagalli A, Lyubimova A, Begthel H, van den Born M, van Es JH, Karthaus WR, Li VS, López-Iglesias C, Peters PJ, **van Rheenen J**, van Oudenaarden A, Clevers H, (2017) Reg4+ deep crypt secretory cells function as epithelial niche for Lgr5+ stem cells in colon. ***Proc Natl Acad Sci USA***, 113(37):E5399-407.

11. Prunier C, Josserand V, Vollaire J, Beerling E, Petropoulos C, Destaing O, Montemagno C, Hurbin A, Prudent R, de Koning L, Kapur R, Cohen PA, Albiges-Rizo C, Coll JL, **van Rheenen J**, Billaud M, Lafanechère L, (2016) LIM Kinase inhibitor Pyr1 reduces the growth and metastatic load of breast cancers., ***Cancer Res***, 76(12):3541-3552.
12. Zomer A, Maynard C, Verweij FJ, Kamermans A, Schäfer R, Beerling E, Schiffelers RM, de Wit E, Berenguer J, Ellenbroek SIJ, Wurdinger T, Pegtel DM, **van Rheenen J,** (2015) In vivo imaging reveals extracellular vesicle-mediated phenocopying of metastatic behavior, ***Cell***, 161(5):1046-1057.
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14. Ritsma L, Ellenbroek SIJ, Zomer A, Snippert HJ, de Sauvage FJ, Simons BD, Clevers H, **van Rheenen J**, (2014) Intestinal crypt homeostasis revealed at single stem cell level by in vivo live-imaging, ***Nature***, 507(7492):362-365.
15. Manning CS, Jenkins R, Hooper S, Gerhardt H, Marais R, Adams S, Adams RH, van **Rheenen J**, Sahai E, (2013), Intravital imaging reveals conversion between distinct tumor vascular morpholgies and localized vascular response to Sunitinib, ***IntraVital***, 2(1): e24790.
16. Janssen A, Beerling E, Medema R, **van Rheenen J**, (2013), Intravital FRET imaging of tumor cell viability and mitosis during chemotherapy. ***PLoS One*****,** 895:e64029.
17. Fritz RD, Letzelter M, Reimann A, Martin K, Fusco L, Ritsma L, Ponsioen B, Fluri E, Schulte-Merker S, **van Rheenen J,** Pertz O, (2013), A versatile toolkit to produce sensitive FRET biosensors to visualize signaling in time and space. ***Sci Signal*****,** 6(285):rs12.
18. 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.
19. Ritsma L, Steller EJA, Ellenbroek SIJ, Kranenburg O, Borel Rinkes IHM, **van Rheenen J**, (2013), Surgical implantation of the abdominal imaging window for intravital microscopy. ***Nat Protoc,*** 8(3):583-594.
20. Ritsma L, Steller EJA, Beerling E, Loomans CJM, Zomer A, Gerlach C, Vrisekoop N, Seinstra D, van Gurp L, Schäfer R, Raats DA, de Graaff A, Schumacher TN, de Koning EJP, Borel Rinkes IH, Kranenburg O and **van Rheenen J**, (2012), Intravital microscopy through an abdominal imaging window reveals steps during liver metastasis, ***Sci Transl Med,*** 4(158):158ra145.
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35. Stroeken PJ, Alvarez B, **van Rheenen J**, Wijnands YM, Geerts D, Jalink K, Roos E, (2006), Integrin cytoplasmic domain-associated protein-1 (ICAP-1) interacts with the ROCK-I kinase at the plasma membrane. ***J Cell Physiol*****,** 208(3):620-628.
36. **van Rheenen J**, Achame EM, Janssen H, Calafat J, Jalink K, (2005), PIP2 in rafts: a critical re-evaluation, ***EMBO J*****,** 24(9):1664-1673.
37. Zwart W, Griekspoor A, Kuyl C, Marsman M, **van Rheenen J**, Janssen H, Calafat J, van Jam M, Janssen L, van Lith M, Jalink K, Neefjes J, (2005), Spatial separation of HLA-DM/HLA-DR interactions within MIIC and phagosomal immune escape, ***Immunity*****,** 22(2):221-233.
38. Danen EHJ, **van Rheenen J,** Franken W, Jalink K, Sonnenberg A, (2005), Integrin-specific regulation of focal contact dynamics, polarization, and migratory strategy. ***J Cell Biol*****,** 169(3):512-526.
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Reviews:

1. Suijkerbuijk SJE, **van Rheenen J**, (2017) From good to bad: intravital imaging of the hijack of physiological processes by cancer cells, ***Dev Biol***. 428(2):328-337.
2. Zomer A, van Rheenen J, (2016) Implications of extracellular vesicle transfer on cellular heterogeneity in cancer; what are the potential clinical ramifications?, ***Cancer Res,*** 76(8):2071-2075.
3. Alieva M, Ritsma L, Giedt RJ, Weissleder R, **van Rheenen J**, (2014) Imaging windows for long-term intravital imaging: general overview and technical insights, ***IntraVital*****,** 3(2):e29917.
4. Ellenbroek SIJ, **van Rheenen J**, (2014) Imaging hallmarks of cancer in living mice, ***Nat Rev Cancer***, 14(6):406-418.
5. van Golen RF, Reiniers MJ, Vrisekoop N, Zuurbier CJ, Olthof PB, **van Rheenen J**, Vangulik T, Parsons BJ, Heger M, (2014), The mechanisms and physiological relevance of glycocalyx degradation in hepatic ischemia/reperfusion injury. ***Antioxid Redox Signal***, 21(7):1098-1118.
6. Bonapace L, Wyckoff J, Oertner T, **van Rheenen J**, Junt T, Bentires-Alj M, (2012), If you don't look, you won't see: intravital multiphoton imaging of primary and metastatic breast cancer. ***J Mammary Gland Biol Neoplasia,*** 17(2):125-129.
7. Ritsma L, Ponsioen B, **van Rheenen J,** (2012), Intravital imaging of cell signaling in mice, ***IntraVital,*** 1(1): 1-9.
8. Beerling E, Ritsma L, Vrisekoop N, Derksen PW, **van Rheenen J,** (2011), Intravital microscopy: new insights into metastasis of tumors. ***J Cell Sci*****,** 124(Pt 3):299-310.
9. Zomer A, Beerling E, Vlug EJ, **van Rheenen J**, (2011), Real-time intravital imaging of cancer models. ***Clin Transl Oncol*****,** 13(12):848-854.
10. Wolf K, Alexander S, Schacht V, Coussens LM, von Andrian UH, **van Rheenen J**, Deryugina E, Friedl P, (2009), Collagen-based cell migration models in vitro and in vivo. ***Semin Cell Dev Biol*****,** 20(8):931-941.
11. Jalink K, **van Rheenen J,** (2009), FilterFRET: quantitative imaging of sensitized emission. ***Laboratory Techniques in Biochemistry & Molecular Biology: FRET and FLIM imaging techniques***, 33:289-349.
12. **van Rheenen J**, Condeelis J Glogauer M, (2009), A common cofilin activity cycle in invasive tumor cells and inflammatory cells. ***J Cell Sci,*** 122(3): 305-311.
13. 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):143-152.

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 body has developed cellular mechanisms to get rid of these dangerous APC-negative cells that can initiate tumor growth. In the context of the Dr. Josef Steiner research project, 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* and how tumor initiation is affected by different dietary regimes. To do this, we developed a technique called 'intravital imaging' were we can film the cells of intestines in living mice through tiny glass windows placed on their bellies (after recovery from surgery, mice are not bothered by this intervention anymore and behave normally). Some mice will be exposed to a typical Western diet that is overloaded with fat-derived calories. Another group of mice will have an opposite type of diet with calorie intake being strongly restricted. The mice of the control group will receive a normal healthy diet. Under these conditions, we will film the birth of APC-negative cells and investigate, how the body either eliminates these tumor-initiating cells or by which means some of these cells can escape the protection mechanisms and initiate a tumor.

To understand how the intestine can get rid of the dangerous APC-negative cells, we first need to understand the renewing process of the intestinal epithelium. 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 the 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 towards the tip of the villus where they arrive after three days and shed into the lumen (Fig. 1a). Therefore, the cells that lose APC, while being in the 'intestinal lining escalator' towards the tip of the villus, 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, the plate will finally 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, by ways of 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 while varying the diets of the animals.

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

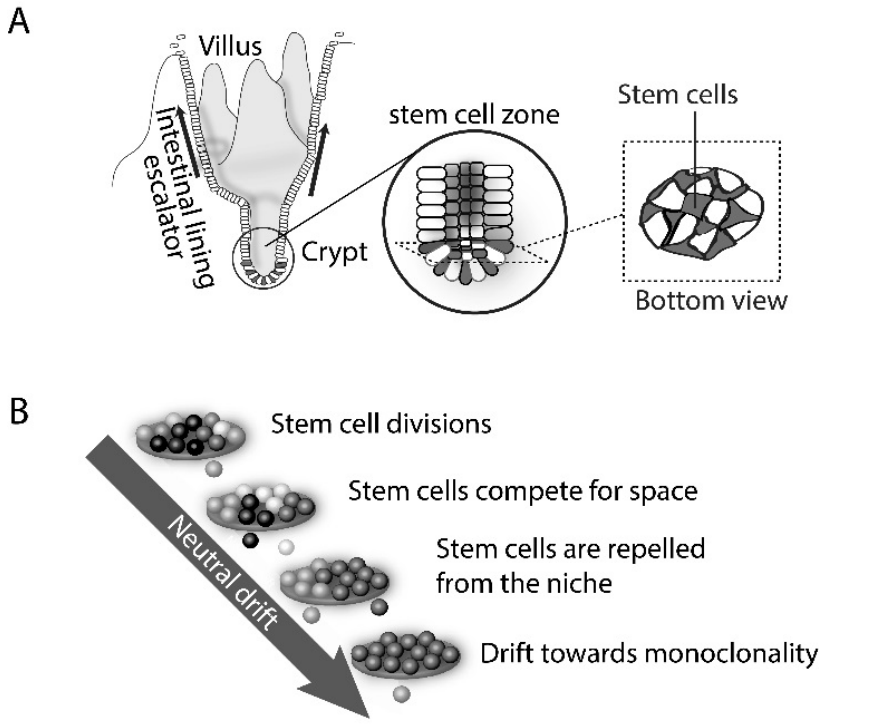

Figure 1, homeostasis of intestinal tissue A) Cartoon of intestinal homeostasis, where cells are born at the stem cells, and get transported to the villus by the intestinal lining escalator. B) Cartoon of multiplying stem cells that compete for space in the stem cell zone and become clonal.