BIOGRAPHICAL SKETCH

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NAME: ROELAND NUSSE

eRA COMMONS USER NAME (credential, e.g., agency login): RNUSSE

POSITION TITLE: PROFESSOR OF DEVELOPMENTAL BIOLOGY

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Amsterdam	B.Sci.	06/1975	Biology
The Netherlands Cancer Institute	Ph.D.	06/1980	Molecular Biology
Univ of California, San Francisco	Postdoc	02/1982	

A. Personal Statement

For more than 35 years, since I was a graduate student, I have been interested in signaling between cells during normal development and in cancer. Initially, I worked on breast cancer in mouse models, identifying Wnt genes. Later, I made discoveries in the fields of developmental biology, cancer, Drosophila embryogenesis and growth factors. My work has also led to a better understanding of the link between normal stem cells and cancer, and has provided essential tools to control the growth of stem cells. My current research has led to identifying stem cells in various tissues and how these cells are implicated in disease.

B. Positions and Honors

Positions and Employment

1980-1982 Postdoctoral Fellow, Univ of California, San Francisco with Dr. H.E. Varmus
1982-1989 Staff Scientist, The Netherlands Cancer Institute, Amsterdam
1983-1989 Head of Department of Molecular Biology, The Netherlands Cancer Institute
1990-1994 Associate Professor, Department of Developmental Biology, Stanford University
Associate Investigator, Howard Hughes Medical Institute
1994-present Professor, Department of Developmental Biology, Stanford University
Investigator, Howard Hughes Medical Institute
2007-present Chair, Department of Developmental Biology, Stanford University
2014-present Co-leader, Cancer Stem Cell Program, Stanford Cancer Institute

Other Experience and Professional Memberships

1994-1996 Reviewer, US ARMY Breast Cancer Program
1995-1999 Member NIH BIOL-2 Study Section
1999-2005 Editorial Board, Development
2003-present Editorial Board, PLoS Biology
2004 Member Scientific Think Tank on Stem Cells and Cancer
2005 Member Site Visit Team, Lab for Cellular and Molecular Biology, NCI
2016 Editorial Board PNAS

Honors

1980-1981	Fulbright Fellowship
1988	Member of the European Molecular Biology Organization
1997	Member (Correspondent) of the Royal Dutch Academy of Sciences
1998	Honorary Member, Japanese Biochemical Society
2000	Peter Debeye Prize, University of Maastricht, The Netherlands
2001	Member of the American Academy of Arts and Sciences
2003	Named "Research Leader in Medical Physiology" in Annual Scientific American 50
2010	Member of the National Academy of Sciences USA
2012	Virginia and Daniel K. Ludwig Professor of Cancer Research
2015	Flexner Discovery Lecturer Vanderbilt University
2015	Feodor Lynen Medal, Miami Winter Symposium
2017	Breakthrough Prize in Life Sciences

C. Contribution to Science

My main research efforts have been centered around the function of Wnt signaling in cancer, development and stem cells. Among my contributions is the original discovery of the first Wnt gene (at the time called int1). Together with Varmus, I identified Wnt as an oncogene in mouse breast cancer, where it is activated by a process called insertional mutagenesis. Apart from the actual discovery of Wnt, the finding stands out as the first case of insertional mutagenesis as a method to find cancer-causing genes, and has led to numerous subsequent studies using the same approach. Wnt signaling is unique in its diverse effects, ranging from controlling gene expression to cell polarity, and is the most ancient signaling mechanism in multi-cellular animals. The Wnt pathway is widely implicated in cancer and other diseases and is now a major area of research worldwide.

Nusse, R., and Varmus, H.E. (1982). Many tumors induced by the mouse mammary tumor virus contain a provirus integrated in the same region of the host genome. Cell *31*, 99-109.
van Ooyen, A., and Nusse, R. (1984). Structure and nucleotide sequence of the putative mammary oncogene int-1; proviral insertions leave the protein-encoding domain intact. Cell *39*, 233-240.
Nusse, R., van Ooyen, A., Cox, D., Fung, Y.K., and Varmus, H. (1984). Mode of proviral activation of a putative mammary oncogene (int-1) on mouse chromosome 15. Nature *307*, 131-136.

Over the years, my lab has made several major discoveries in the area of Wnt signaling, including the identification of *wingless* in *Drosophila* as the homolog of *Wnt1*. This seminal finding opened the field to the use of fly genetics to understand Wnt signaling mechanisms. Following genetic and other approaches, we and others have shown that the genes *armadillo* (b-catenin) and *dishevelled* play key roles in Wingless signaling. A major breakthrough we made working together with Jeremy Nathans, was the identification of Frizzleds as receptors for Wingless and other Wnts.

Rijsewijk, F., Schuermann, M., Wagenaar, E., Parren, P., Weigel, D., and Nusse, R. (1987). The Drosophila homolog of the mouse mammary oncogene int-1 is identical to the segment polarity gene wingless. Cell *50*, 649-657.
Noordermeer, J., Klingensmith, J., Perrimon, N., and Nusse, R. (1994). dishevelled and armadillo act in the wingless signalling pathway in Drosophila. Nature *367*, 80-83.
Van Leeuwen, F., Samos, C.H., and Nusse, R. (1994). Biological-Activity of Soluble Wingless Protein in Cultured Drosophila Imaginal Disc Cells. Nature *368*, 342-344.
Bhanot, P., Brink, M., Samos, C.H., Hsieh, J.C., Wang, Y., Macke, J.P., Andrew, D., Nathans, J., and Nusse, R. (1996). A new member of the frizzled family from Drosophila functions as a Wingless receptor. Nature *382*, 225-230.

A major later accomplishment of my group was the first successful purification of active Wnt proteins, showing that they are lipid-modified and act as stem cell growth factors. The goal of isolating active Wnt had been pursued by numerous labs, but the my lab was the first to solve this long-standing problem. As a consequence of this break-through, Wnt proteins are now used by researchers world-wide as stem cell self-renewing factors.

Willert K, Brown JD, Danenberg E, Duncan AW, Weissman IL, Reya T, Yates JR 3rd, Nusse R. (2003). Wnt proteins are lipid-modified and can act as stem cell growth factors. Nature 423(6938):448-52. Epub 2003 Apr 27. PMID: 12717451
ten Berge, D., Kurek, D., Blauwkamp, T., Koole, W., Maas, A., Eroglu, E., Siu, R.K., and Nusse, R. (2011). Embryonic stem cells require Wnt proteins to prevent differentiation to epiblast stem cells. Nature cell biology *13*, 1070-1075.

In our most recent work, we have designed cell fate tracking experiments to study stem cells in vivo. We identified Wnt-responsive stem cells by their expression of Axin2 (a common Wnt target gene) and generated a mouse strain with the CreERT2 recombination signal inserted into the Axin2 locus, Axin2-Cre. By clonal labeling, we showed that single stem cells differentiate into different cell types of the tissues of interest. Unexpectedly, in the liver, we found that hepatocytes that reside in the pericentral domain of the liver demonstrate stem cell behavior. Although these cells are functional hepatocytes, they are diploid and thus differ from the mostly polyploid mature hepatocyte population. They are active in homeostatic cell replacement. Adjacent central vein endothelial cells provide the essential source of Wnt signals for the hepatocyte stem cells and thereby constitute the liver stem cell niche. By gaining understanding on liver stem cells and Wnt signals, we have been able to expand normal hepatocytes in cell culture, with retention of regenerative potential of the cells.

Zeng, Y.A., and Nusse, R. (2010). Wnt proteins are self-renewal factors for mammary stem cells and promote their long-term expansion in culture. Cell Stem Cell *6*, 568-577.
van Amerongen, R., Bowman, A.N., and Nusse, R. (2012). Developmental stage and time dictate the fate of Wnt/beta-catenin-responsive stem cells in the mammary gland. Cell Stem Cell *11*, 387-400.
Lim, X., Tan, S.H., Koh, W.L., Chau, R.M., Yan, K.S., Kuo, C.J., van Amerongen, R., Klein, A.M., and Nusse, R. (2013). Interfollicular epidermal stem cells self-renew via autocrine Wnt signaling. Science *342*, 1226-1230.
Wang, B., Zhao, L., Fish, M., Logan, C.Y., and Nusse, R. (2015). Self-renewing diploid Axin2(+) cells fuel homeostatic renewal of the liver. Nature *524*, 180-185.
Peng, W., Logan, C., Fish, M., Anbarchian, T., Aguisanda, F., Alvares-Verala, A., Wu, P., Jin, Y., Zhu, J., Grompe, M.*, et al.* (2018). Tissue Repair Signals and In Vitro Culture: Inflammatory Cytokine TNF. Cell *In press*.

All publications
http://web.stanford.edu/group/nusselab/cgi-bin/lab/publications

D. Research Support

Ongoing Research Support

NA 9/1/18–8/31/19
Howard Hughes Medical Institute
NA
Dr. Nusse is an employee investigator of the Howard Hughes Medical Institute. Funds are not project based and are not awarded for a specific project. All HHMI budgets are determined annually.
Dr. Nusse's appointment as an HHMI investigator goes to 8/31/18 and can be renewed afterwards.

DISC2-09565 Nusse (PI) 6/1/17–5/31/19
CIRM
"Preclinical development of human hepatocyte progenitor cells for cell therapy"
The goal of this project is to develop patient-specific hepatocyte progenitor cells that can be expanded in vitro and used for therapeutic cell transplantation for treatment of liver disease.