

CURRICULUM VITAE

Name Johannes Carolus Clevers (1957)
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Education

1975-1982 M.Sc. ("Doctoraal") in Biology. University of Utrecht
1978-1984 M.D. ("Artsexamen") University of Utrecht
1984-1985 Ph.D. ("Promotie") University of Utrecht

Scientific Training/positions

1985 – 1989 Postdoctoral Fellow. Cox Terhorst Lab. Dana-Farber Cancer Institute, Harvard Medical School, Boston MA, USA
1989 – 1991 Universitair Docent, Department of Clinical Immunology, University of Utrecht
1991 – 2002 Professor and Chairman, Dept. of Immunology, Faculty of Medicine, University of Utrecht
2002 – 2012 Director of the Hubrecht Institute, Royal Netherlands Academy of Arts and Sciences
2002 – Professor in Molecular Genetics, University Medical Center Utrecht
2012-2015 President of the Royal Netherlands Academy of Sciences
2015 – Director Research of the Princess Máxima Center for pediatric oncology

Prizes, awards

2000 Catharijne-prize for medical research
2001 Award from the European Society for Clinical Investigation
2001 Spinoza Award of the Netherlands Reserach Council (NWO)
2004 Louis-Jeantet Prize for Medicine, Geneva, Switzerland
2005 the Science and Society Prize, Amsterdam
2005 the French honor of "Chevalier de la Legion d'Honneur"
2005 Katharine Berkan Judd Award, New York
2006 Rabbi Shai Shacknai Memorial Prize for Immunology and Cancer Research, Jerusalem
2008 Josephine Nefkens Prize for Cancer Research (Erasmus MC, Rotterdam)
2008 Meyenburg Cancer Research Award, Germany
2009 The Queen Wilhelmina Dutch Cancer Society Award, Amsterdam
2010 The United European Gastroenterology Federation (UEGF) Research Prize
2011 The Ernst Jung Medical Award, Germany
2011 Kolff prize, Amsterdam
2012 Association pour la Recherche sur le Cancer (ARC) Léopold Griffuel Prize, Paris
2012 William Beaumont prize of the American Gastroenterology Association
2012 The Heineken Prize for Medicine
2012 Knight in the Order of the Netherlands' Lion
2013 The Breakthrough Prize in Life Sciences
2014 Massachusetts General Hospital Award in Cancer Research
2014 TEFAF Oncology Chair 2014, Maastricht
2014 Fellow of the AACR Academy
2014 Struyvenberg European Society for Clinical Investigation (ESCI) medal
2014 National Icon of the Netherlands
2015 ISSCR-McEwen Award for Innovation
2016 the Academy Professor Prize of the Royal Netherlands Academy
2016 Kazemi Award for Research Excellence in Bio-Medicine
2016 The Körber European Science Prize, Germany
2016 Swammerdam medaille (Amsterdam)
2016 The Ilse & Helmut Wachter award, Hamburg, Germany
2017 Princess Takamatsu Award of Merit, Tokyo

Prize juries

2008 - 2015 Louis Jeantet Prize (Geneva)
2013 - 2015 Canada Gairdner Award (Toronto)
2014 - Breakthrough Prize in Life Sciences (San Francisco)
2015 2015 Pezcoller Foundation-AACR International Award for Cancer Research
2015 - Dr. Paul Janssen Award
2017 Francqui Prize 2017 (Bruxelles)
2017- Shaw Prize (Hong Kong)
2017 Kovalenko Medal (National Academy of Sciences)

Honorary Professorships

2002 - Central South University, Chang Sha, China
2014-2015 TEFAF Oncology Chair
2016 - Distinguished Visiting Professor, University of Hong Kong
2015-2016 Visiting professor, Weizmann Institute, Rehovoth, Israel
2015 Visiting professor, University of Melbourne, Australia

Elected Memberships

1999 Member European Molecular Biology Organisation (EMBO)
2000 Member of the Royal Netherlands Academy of Sciences (KNAW)
2009 Member of the Academia Europaea
2012 Member of the American Academy of Arts and Sciences
2012 Member of the 'Koninklijke Hollandsche Maatschappij der Wetenschappen' (Royal Netherlands Society of Sciences and Humanities)
2014 Member of the National Academy of Sciences of the USA
2016 Member of the Academie des Sciences de l'Institut de France
2017 Member of the Orden Pour le Mérite für Wissenschaften und Künste, Germany

Advisory Boards etc

2005 - 2015 Member of the Scientific Advisory Board of Swiss Institute for Experimental Cancer Research (ISREC, Lausanne)
2006 - 2008 President of the International Society of Differentiation (ISD)
2007 - Member of the National Scientific Advisory Board NKI-AVL
2012 - 2015 Member of the board of the American Association of Cancer Research
2015 - Member of the the Scientific Advisory Board of the Institute of Molecular Pathology (IMP), Vienna
2016 - Member of the Scientific Advisory Board of the Francis Crick Institute (London)
2016 - Member of the Scientific Advisory Board of Decibel Therapeutics, Boston.
2016 - Member of the Scientific Advisory Board of Surrozen, San Francisco
2016 - Member of the Scientific Advisory Board of Kallyope, New York
2017 - 2018 President of the International Society for Stem Cell Research (ISSCR)

Research summary

Lgr5 stem cells, Wnt signaling & cancer

Tcf as Wnt effector

In 1991, we reported the cloning of a T cell specific transcription factor that we termed TCF1 (1). Related genes exist in genomes throughout the animal kingdom. We have shown in frogs (4), flies (7) and worms (11) that the TCF proteins constitute the effectors of the canonical Wnt pathway. Upon Wnt signaling, β -catenin binds and activates nuclear TCFs by providing a trans-activation domain. For these studies, we designed the widely used pTOPFLASH Wnt reporters. In the absence of Wnt signaling, we found that Tcf factors associate with proteins of the Groucho family of transcriptional repressors to repress target gene transcription (9).

Wnt signaling in cancer

The tumor suppressor protein APC forms the core of a cytoplasmic complex which binds β -catenin and targets it for degradation in the proteasome. In APC-deficient colon carcinoma cells, we demonstrated that β -catenin accumulates and is constitutively complexed with the TCF family member TCF4, providing a molecular explanation for the initiation of colon cancer (5).

Wnt signaling in adult stem cells

In mammals, physiological Wnt signaling is intimately involved with the biology of adult stem cells and self-renewing tissues (18,19). We were the first to link Wnt signaling with adult stem cell biology, when we showed that TCF4 gene disruption leads to the abolition of crypts of the small intestine (8), and that TCF1 gene knockout severely disables the stem cell compartment of the thymus (2). The Tcf4-driven target gene program in colorectal cancer cells is the malignant counterpart of a physiological gene program in self-renewing crypts (13, 14, 21).

Lgr5 as adult stem cell marker

Amongst the Wnt target genes, we found the Lgr5 gene to be unique in that it marks small cycling cells at crypt bottoms. These cells represent the epithelial stem cells of the small intestine and colon (23), the hair follicle (24), the stomach (28) and -probably- all other epithelial stem cell types of the mammalian body. They also represent the cells-of-origin of adenomas in the gut (25) and within adenomas Lgr5 stem cells act as adenoma stem cells (36). The related Lgr6 marks multipotent skin stem cells (29).

Lgr5 stem cell biology

Lgr5 crypt stem cells behave in unanticipated ways: Against common belief, they divide constantly. Stem cell numbers remain fixed because stem cells compete 'neutrally' for niche space. Thus, they do not divide asymmetrically (32), a phenomenon that was confirmed by in vivo imaging (43). Daughters of the small intestinal stem cells, the Paneth cells, serve as crypt niche cells by providing Wnt, Notch and EGF signals (30).

The Wnt target gene encoding the transcription factor Achaete scute-like 2 controls the fate of the intestinal stem cell (26).

Lgr5 is the R-spondin receptor

Lgr5 resides in Wnt receptor complexes and mediates signaling of the R-spondin Wnt agonists (33), explaining the unique dependence of Lgr5 stem cells of various epithelia on R-spondins in vivo and in

vitro. Two other Wnt target genes, RNF43 and ZNRF3, encode stem cell-specific E3 ligases that downregulate Wnt receptors. They serve in a negative feedback loop to control the size of the stem cell zone (35). Independent work by the Feng Cong lab has first shown that R-spondin, when bound to Lgr5, captures and inactivates RNF43/ZNRF3.

Long-term clonal culturing of organoids from Lgr5 stem cells

Wnt signaling intimately interacts with the BMP and Notch cascades to drive proliferation and inhibit differentiation in intestinal crypts and adenomas (17, 20). Based on these combined insights, we have established Lgr5/R-spondin-based culture systems that allow the outgrowth of single mouse or human Lgr5 stem cells into ever-expanding mini-guts (27, 31), mini-stomachs (28), colon cancer organoids (31, 48) liver organoids (39, 46), prostate organoids (45), breast cancer organoids (53) and organoids representing multiple other adult tissues. These epithelial organoid cultures are genetically and phenotypically extremely stable, allowing transplantation of the cultured offspring of a single stem cell, as well as disease modeling by growing organoids directly from diseased patient tissues (46). The direct cloning of multiple individual cells from primary tumors allows molecular and functional analysis of tumor heterogeneity with an unprecedented resolution (54). Human organoids are readily amenable to CRISPR-mediated genome modification to model for instance malignant transformation (49) and mutagenesis upon faulty DNA repair (52).

As proof-of-concept, the CFTR locus was repaired in single gut stem cells from two Cystic Fibrosis patients, using CRISPR/Cas9 technology in conjunction with homologous recombination. Repaired stem cells were clonally expanded into mini-guts and shown -in a swelling assay- to contain a functional CFTR channel (43). The organoid-based swelling assay has meanwhile become clinical practice in the Netherlands to identify patient with rare mutations that respond to the Vertex drugs. To this end, we founded the non-for-profit HUB foundation which currently builds a biobank of all 1500 Dutch CF patients funded by our national insurance companies. The HUB also maintains large biobanks of colon-, breast-, lung- and pancreas cancer organoids, accessible by academia and industry.

Key Publications out of ~ 550 peer-reviewed papers, yielding ~ 80,000 citations; h-index of ~144.

- 1) van de Wetering, M., Oosterwegel, M., Dooijes, D., and Clevers, H.C. Identification and cloning of TCF-1, a T cell-specific transcription factor containing a sequence-specific HMG box. **EMBO J.** 10:123-132 (1991)
- 2) Verbeek, J.S., Ison, D., Hoffhuis, F., Robanus-Maandag, E., te Riele, H., van de Wetering, M., Oosterwegel, M., Wilson, A., MacDonald, H.R. and Clevers, H.C. An HMG box containing T-cell factor required for thymocyte differentiation. **Nature** 374: 70-74 (1995)
- 3) Schilham, M., Oosterwegel, M., Moerer, P., Jing Ya, de Boer, P., van de Wetering, M., Verbeek, S., S., Lamers, W., Kruisbeek, A., Cumano, A., and Clevers, H. Sox-4 gene is required for cardiac outflow tract formation and pro-B lymphocyte expansion. **Nature** 380: 711-714 (1996)
- 4) Molenaar, M., Van de Wetering, M., Oosterwegel, M., Peterson-Maduro, J., Godsave, S., Korinek, V., Roose, J., Destree, O. And Clevers, H. Xtcf-3 Transcription factor mediates beta-catenin-induced axis formation in xenopus embryos. **Cell** 86: 391-399 (1996)
- 5) Korinek, V, Barker, N., Morin, P.J., van Wichen, D., de Weger, R., Kinzler, K.W., Vogelstein, B., and Clevers, H. Constitutive Transcriptional Activation by a beta-catenin-Tcf complex in APC-/- Colon Carcinoma. **Science** 275: 1784-1787 (1997)

- 6) Morin, P.J., Sparks, A., Korinek, V., Barker, N., Clevers, H., Vogelstein, B., and Kinzler, K. Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. **Science** 275: 1787-1790 (1997)
- 7) van de Wetering, M., Cavallo, R., Dooijes, D., van Beest, M., van Es, J., Loureiro, J., Ypma, A., Hursh, D., Jones, T., Bejsovec, A., Peifer, M., Mortin, M., and Clevers, H. Armadillo co-activates transcription driven by the product of the Drosophila segment polarity gene dTCF. **Cell** 88, 789-799 (1997)
- 8) Korinek, V., Barker, N., Moerer, P., van Donselaar, E., Huls, G., Peters, P.J. and Clevers, H. Depletion of epithelial stem cell compartments in the small intestine of mice lacking Tcf 4. **Nat Genet** 19: 379 383 (1998)
- 9) Roose, J., Molenaar, M., Peterson, J., Hurenkamp, J., Brantjes, H., Moerer, P., van de Wetering, M., Destree, O., and Clevers, H. The Xenopus Wnt effector XTcf-3 interacts with Groucho-related transcriptional repressors. **Nature** 395: 608-612 (1998)
- 10) Roose, J., Huls, G., van Beest, M., Moerer, P., van der Horn, K., Goldschmeding, R., Logtenberg, T., and Clevers, H. Synergie between tumor suppressor APC and the beta-catenin/Tcf4 target gene Tcf1. **Science** 285: 1923-1926 (1999)
- 11) Korswagen, R., Herman, M. and Clevers, H. Separate beta-catenins mediate Wnt signaling and cadherin adhesion in *C. elegans*. **Nature** 406: 527-532 (2000)
- 12) Bienz, M., and Clevers, H. Linking colorectal cancer to Wnt signaling. *Review* **Cell** 103: 311-320 (2000)
- 13) van de Wetering, M., Sancho, E., Verweij, C., de Lau, W., Oving, I., Hurlstone, A., van der Horn, K., Battle, E., Coudreuse, D., Haramis, A-P., Tjon-Pon-Fong, M., Moerer, P., van den Born, M., Soete, G., Pals, S., Eilers, M., Medema, R., Clevers, H. The beta catenin/TCF4 complex imposes a crypt progenitor phenotype on colorectal cancer cells. **Cell** 111: 241-250 (2002)
- 14) Battle, E., Henderson, J.T., Begthel, H., van den Born, M., Sancho, E., Huls, G., Meeldijk, J., Robertson, J., van de Wetering, M., Pawson, T., Clevers, H. Beta- catenin and TCF mediate cell positioning in the intestinal epithelium by controlling the expression of EphB/ephrinB. **Cell** 111: 251-263 (2002)
- 15) Hurlstone, A.F., Haramis, A.P., Wienholds, E., Begthel, H., Korving, J., van Eeden, F., Cuppen, E., Zivkovic, D., Plasterk, R.H., Clevers, H. The Wnt/beta-catenin pathway regulates cardiac valve formation. **Nature** 425: 633-637 (2003)
- 16) Baas, A.F., Kuipers, J., van der Wel, N.N., Battle, E., Koerten, H.K., Peters, P.J., Clevers, H.C. Complete polarization of single intestinal epithelial cells upon activation of LKB1 by STRAD. **Cell** 116: 457-466 (2004)
- 17) Haramis, A.P., Begthel, H., van den Born, M., van Es, J., Jonkheer, S., Offerhaus, G.J., Clevers, H. De novo crypt formation and Juvenile Polyposis upon BMP inhibition. **Science** 303: 1684-1686 (2004)
- 18) Radtke, F and Clevers, H., Self-renewal and cancer of the gut: Two sides of a coin. *Review* **Science** 307: 1904-1909 (2005)
- 19) Reya, T., Clevers, H., Wnt signalling in stem cells and cancer. *Review*. **Nature** 434: 843-850 (2005)
- 20) Van Es, J.H., Van Gijn, M.E., Riccio, O., van den Born, M., Vooijs, M., Begthel, H., Cozijnsen, M., Robine, S., Winton, D.J., Radtke, F., Clevers H. Notch pathway/ γ -secretase inhibition turns proliferative cells in intestinal crypts and neoplasia into Goblet cells. **Nature** 435: 959-963 (2005)
- 21) Battle, E., Bacani, J., Begthel, H., Jonkheer, S., Gregorieff, A., van de Born, M., Malats, N., Sancho, E., Boon, E., Pawson, T., Gallinger, S., Pals, S., Clevers, H. EphB activity suppresses

- colorectal cancer progression.
Nature 435: 1126-1130 (2005)
- 22) Clevers, H. Wnt/ β -catenin signaling in development and disease, Review
Cell 127: 469-480 (2006)
- 23) Barker, N., Van Es, J.H., Kuipers, J., Kujala, P., Van den Born, M., Cozijnsen, M., Haegebarth, A., Korving, J., Begthel, H., Peters, P.J., Clevers, H. Identification of stem cells in small intestine and colon by the marker gene LGR5.
Nature 449: 1003-1007 (2007)
- 24) Jaks, V., Barker, N., Kasper, M., van Es, J.H., Snippert, H.J., Clevers, H., Toftgård, R. Lgr5 marks cycling, yet long-lived, hair follicle stem cells.
Nat Genet. 40: 1291-1299 (2008)
- 25) Barker, N., Ridgway, R.A., van Es, J.H., van de Wetering, M., Begthel, H., van den Born, M., Danenberg, E., Clarke, A.R., Sansom, O.J., Clevers, H. Crypt Stem Cells as the Cells-of-Origin of Intestinal Cancer.
Nature 457: 608-611 (2009)
- 26) van der Flier, L.G., van Gijn, M.E., Hatzis, P., Kujala, P., Haegebarth, A., Stange, D.E., Begthel, H., van den Born, M., Guryev, V., Oving, I., van Es, J.H., Barker, N., Peters, P.J., van de Wetering, M. and Clevers, H. Transcription Factor Achaete Scute-Like 2 Controls Intestinal Stem Cell Fate.
Cell 136: 903-912 (2009)
- 27) Sato, T., Vries, R., Snippert, H., van de Wetering, M., Barker, N., Stange, D., van Es, J., Abo, A., Kujala, P., Peters, P., and Clevers, H. Single Lgr5 gut stem cells build crypt-villus structures in vitro without a stromal niche.
Nature 459 :262-265 (2009)
- 28) Barker, N., Huch, M., Kujala, P., van de Wetering, M., Snippert, H.J., van Es, J.H., Sato, T., Stange, D.E., Begthel, H., van den Born, M., Danenberg, E., van den Brink, S., Korving, J., Abo, A., Peters, P.J., Wright, N., Poulsom, R., Clevers, H. Lgr5(+ve) stem cells drive self-renewal in the stomach and build long-lived gastric units *in vitro*.
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- 29) Snippert, H.J., Haegebarth, A., Kasper, M., Jaks, V., van Es, J.H., Barker, N., van de Wetering, M., van den Born, M., Begthel, H., Vries, R.G., Stange, D.E., Toftgård, R., Clevers H. Lgr6 marks stem cells in the hair follicle that generate all cell lineages of the skin.
Science 327: 1385-1389 (2010)
- 30) Sato, T., van Es, J.H., Snippert, H.J., Stange, D.E., Vries, R.G., van den Born, M., Barker, N., Shroyer, N.F., van de Wetering, M., Clevers, H. Paneth cells constitute the niche for Lgr5 stem cells in intestinal crypts.
Nature 469: 415-418 (2011)
- 31) Sato T, Stange DE, Ferrante M, Vries RG, Van Es JH, Van den Brink S, Van Houdt WJ, Pronk A, Van Gorp J, Siersema PD, Clevers H. Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium.
Gastroenterology 141: 1762-1772 (2011).
- 32) Snippert, J., van der Flier, L.G., Sato, T., van Es, J.H., van den Born, M., Kroon-Veenboer, C., Barker, N., Klein, A.M., van Rheenen, J. Benjamin D. Simons, B.D. and Clevers, H. Intestinal Crypt Homeostasis results from Neutral Competition between Symmetrically Dividing Lgr5 Stem Cells.
Cell 143:134-44 (2010)
- 33) de Lau, W., Barker, N., Low, T.Y., Koo, B.K., Li, V.S., Teunissen, H., Kujala, P., Haegebarth, A., Peters, P.J., van de Wetering, M., Stange, D.E., van Es, J., Guardavaccaro, D., Schasfoort, R.B., Mohri, Y., Nishimori, K., Mohammed, S., Heck, A.J., Clevers, H. Lgr5 homologues associate with Wnt receptors and mediate R-spondin signalling.
Nature 476: 293-297 (2011)
- 34) Li, V.S., Ng, S.S., Boersema, P.J., Low, T.Y., Karthaus, W.R., Gerlach, J.P., Mohammed, S., Heck, A.J., Maurice, M.M., Mahmoudi, T. and Clevers H. Wnt signaling inhibits proteasomal β -

- catenin degradation within a compositionally intact Axin1 complex.
Cell 149: 1245-1256 (2012)
- 35) Koo, B-K., Spit, M. Jordens, I., Low, T.Y., Stange, D.E., van de Wetering, M., van Es, J.H., Mohammed, S., Heck, A.J.R., Maurice, M.M. and Hans Clevers. Tumour suppressor RNF43 is a stem cell E3 ligase that induces endocytosis of Wnt receptors.
Nature 488: 665-669 (2012)
- 36) Schepers, A.G., Snippert, H.J., Stange, D.E., van den Born, M., van Es, J.H., van de Wetering, M., Clevers, H. Lineage Tracing Reveals Lgr5+ Stem Cell Activity in Mouse Intestinal Adenomas.
Science 337: 730-735 (2012)
- 37) van Es, J.H., Sato, T., van de Wetering, M., Lyubimova, A., Yee Nee, A.N., Gregorieff, A., Sasaki, N., Zeinstra, L., van den Born, M., Korving, J., Martens, A.C., Barker, N., van Oudenaarden, A., Clevers, H. Dll1(+) secretory progenitor cells revert to stem cells upon crypt damage.
Nat Cell Biol. 14: 1099-1104 (2012)
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- 39) Huch, M., Dorrell, C., Boj, S.F., van Es, J.H., van de Wetering, M., Li, V.S.W., Hamer, K., Sasaki, N., Finegold, M.J., Haft, A., Grompe, M., Clevers, H. In vitro expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration.
Nature 494: 247-250 (2013)
- 40) Sato, T., Clevers, H.. Growing self-organizing mini-guts from a single intestinal stem cell: mechanism and applications. Review
Science 340: 1190-1194 (2013)
- 41) Clevers, H. The intestinal crypt, a prototype stem cell compartment.
Cell. 154: 274-284 (2013)
- 42) Stange, D.E., Koo, B.K., Huch, M., Sibbel, G., Basak, O., Lyubimova, A., Kujalla, P., Bartfeld, S., Koster, J., Geahlen, J.H., Peters, P.J., van Es, J., van de Wetering, M., Mills, J.C., Clevers, H. Differentiated Troy+ chief cells act as 'reserve' stem cells to generate all lineages of the stomach epithelium.
Cell 155: 357-368 (2013)
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- 46) Huch, M., Gehart, H., van Boxtel, R., Hamer, K., Blokzijl, F., Verstegen, M., Ellis, E., van Wenum, M., Fuchs, S., de Ligt, J., van de Wetering, M., Sasaki, N., Boers, S., Kemperman, H., de Jonge, J. IJzermans, J., Nieuwenhuis, E., Hoekstra, R., Strom, S., Vries, R., van der Laan, L., Cuppen, E., Clevers, H. Long-term culture of genome-stable bipotent stem cells from adult human liver.
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