

CURRICULUM VITAE

Name Johannes (Hans) 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 at the Dana-Farber Cancer Institute, Harvard Medical School, Boston MA, USA
1989 - 1991 Assistant Professor, 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 - present Professor in Molecular Genetics at University Medical Center Utrecht
2002 - present Principal Investigator of a research group of ~40 scientists at Hubrecht Institute, Utrecht
2012 - 2015 President of the Royal Netherlands Academy of Sciences (KNAW), Amsterdam
2014 - 2020 Chief Scientific Officer of HUB Organoids Technology, Utrecht
2015 - 2019 Chief Scientific Officer/Director Research of the Princess Máxima Center, Utrecht
2015 - present Principal Investigator at the Princess Máxima Center, Utrecht
2017 - present Onco Investigator
2019 - 2022 Supervisory Board member of F. Hoffmann-La Roche Ltd, Basel, Switzerland
2022 - 2025 Head of Pharma, Research and Early Development (pRED) and Member of the Enlarged Executive Committee of F. Hoffmann-La Roche Ltd, Basel
2025 - present Distinguished group leader Hubrecht Institute and Princess Maxima Center, Utrecht
2024 - 2025 Ad interim director of Roche's Institute of Human Biology, Basel, Switzerland

Prizes, awards

2000 Catharijne-prize for medical research, Utrecht
2001 Award from the European Society for Clinical Investigation, Nice
2001 Spinoza Award of the Netherlands Research Council (NWO, Den Haag)
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 (USA)
2012 The Heineken Prize for Medicine, Amsterdam
2012 Knight in the Order of the Netherlands' Lion
2013 The Breakthrough Prize in Life Sciences, San Francisco
2014 Massachusetts General Hospital Award in Cancer Research, Massachusetts

2014	Fellow of the AACR Academy, Washington
2014	Struyvenberg European Society for Clinical Investigation (ESCI) medal, Utrecht
2014	National Icon of the Netherlands, Amsterdam
2015	ISSCR-McEwen Award for Innovation, San Francisco
2016	The Academy Professor Prize of the Royal Netherlands Academy, Amsterdam
2016	Kazemi Award for Research Excellence in Bio-Medicine, Teheran
2016	The Körber European Science Prize, Germany
2016	Swammerdam medaille, Amsterdam, Netherlands
2016	The Ilse & Helmut Wachter award, Hamburg, Germany
2017	Princess Takamatsu Award of Merit, Tokyo, Japan
2017	Großes Verdienstkreuz mit Stern, Germany
2018	Academia Europaea Erasmus Medal, Barcelona, Spain
2019	Keio Medical Science Prize, Tokyo, Japan
2019	Citation Laureate, Web of Science Group
2021	Pezcoller Foundation-AACR International Award
2022	Ammodo Science Award
2024	Charles Weissmann Award, Zurich, Switzerland
2025	The Animal Protection Research Prize, Berlin, Germany
2025	Abarca Prize, Madrid

Prize juries

2008 - 2015	Louis Jeantet Prize, Geneva
2013 - 2015	Canada Gairdner Award, Toronto
2014 - present	Breakthrough Prize in Life Sciences, San Francisco
2015	Pezcoller Foundation - AACR International Award for Cancer Research, Italy
2015	Dr. Paul Janssen Award, Bruxelles
2017 - 2023	Francqui Prize, Bruxelles
2017 - 2021	Shaw Prize, Hong Kong
2017	Kovalenko Medal, National Academy of Sciences Washington
2021	Chair Cancer Research Committee of AACR Award for Lifetime Achievement, US
2022 - present	World Laureates Association Prize, Shanghai

Honorary Professorships

2002 - present	Central South University, Chang Sha, China
2014 - 2015	TEFAF Oncology Chair, Maastricht
2015 - 2016	Visiting professor, Weizmann Institute, Rehovoth, Israel
2016 - present	Distinguished Visiting Professor, University of Hong Kong
2015	Visiting professor, University of Melbourne, Australia
2019 - present	Honorary Director, Fudan Organoid Center, Fudan University, Shanghai
2021	Honorary Doctorate Catholic University of Leuven, Belgium

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	International 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

2019	Member of the New York Academy of Sciences, New York
2019	Foreign Member of the Royal Society of London
2019	Honorary Fellowship of the Royal Society of Edinburgh, Scotland's National Academy of Science and Letters
2026	Member of the European Academy of Engineering

Boards

2005 - 2015	Member of the Scientific Advisory Board of Swiss Institute for Experimental Cancer Research, Lausanne
2006 - 2008	President of the International Society of Differentiation (ISD)
2007 - 2010	Member of the National Scientific Advisory Board NKI-AVL, Amsterdam
2012 - 2015	Member of the Board of the American Association of Cancer Research
2015 - 2022	Member of the Scientific Advisory Board of the Institute of Molecular Pathology, Vienna
2016 - 2021	Member of the Scientific Advisory Board of Kallyope, New York
2016 - present	Member of the Scientific Advisory Board of the Francis Crick Institute, London
2016 - 2021	Member of the Scientific Advisory Board of Decibel Therapeutics, Boston
2016 - 2022	Member of the Scientific Advisory Board of Surrozen, San Francisco
2017 - 2018	President of the International Society for Stem Cell Research (ISSCR)
2018 - 2021	Member of the Scientific Advisory Board of Merus, Utrecht
2018 - 2022	Scientific advisor Life Science Partners, Amsterdam
2019 - 2022	Non-executive member of the Board of Directors of Roche Holding Ltd, Basel
2020 - 2021	Member of the Scientific Advisory Board of Volestra Therapeutic Inc., New York
2020 - 2022	Chair of the Scientific Advisory Board DImed Inc., Shanghai
2020 - 2022	Chair of the Scientific Advisory Board of Xilis, at Duke University (NC)

Editorial boards

2004 - present	Member of the Editorial Board of EMBO Journal
2008 - present	Member of Editorial Board of Disease Models & Mechanisms (DMM)
2009 - present	Member of the Editorial Board of Cell
2012 - 2024	Member of the Editorial Board of Stem Cell Reports
2013 - present	Member of the Editorial Board of Cell Stem Cell
2014 - 2022	Member of the Editorial Committee of Annual Review of Cancer Biology
2015 - present	Member of the Editorial Board of EMBO Molecular Medicine
2020 - present	Member of Scientific Advisory Board of Med (Cell Press)
2025 - present	Honorary advisor of the Editorial Board of Stem Cell Reports
2026- present	Member of the Editorial Board of Vita

Grants

Our work has been funded by many different granting organizations including KWF, EU (3 ERC Advanced Grants), two CRUK Grand Challenge grants, BSIK, NWO and ZONMW (including 3 Gravitation Programmes), NIH, CRUK, Helmsley Foundation, SNSF, Leducq Foundation, Paradifference Foundation, Lung Foundation Netherlands, Mark Foundation, Stand up 2 Cancer.

Contributions to Science

Lgr5 stem cells, Wnt signaling & cancer, Organoids

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. When Wnt signaling is inactive, 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/TCF7L2, 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 stem cell activity in 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).

Lgr5 as adult stem cell marker

Amongst the intestinal Wnt target genes (13), we found the *Gpr49/Lgr5* gene to be unique in that it marks small cycling cells at crypt bottoms. Lgr5⁺ cells represent the epithelial stem cells of the small intestine and colon (23), the hair follicle (24), the stomach (28) and many other tissue stem cell types. Lgr5 cells also represent the cells-of-origin of adenomas in the gut (25) and within adenomas Lgr5 stem cells act as adenoma stem cells (36). Lgr6 marks multipotent skin stem cells (29).

Lgr5 stem cell biology

The Wnt target gene encoding the transcription factor Achaete scute-like 2 controls the intestinal stem cell state (26). Lgr5 crypt stem cells behave in unanticipated ways: Against common belief, they divide constantly and in a symmetric fashion. Stem cell numbers remain fixed because stem cells compete 'neutrally' for niche space (30). This phenomenon was confirmed by in vivo imaging (44). Daughters of the small intestinal stem cells, the Paneth cells, serve as crypt niche cells by providing Wnt, Notch and EGF signals (33). In a very recent study, we describe how intestinal epithelial cells die at the end of their one week lifespan, on the tips of villi (80).

Lgr5 is the R-spondin receptor

Lgr5 resides in Wnt receptor complexes and mediates signaling of the Wnt-agonistic R-spondins (31), explaining the unique dependence of Lgr5 stem cells on secreted 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 in a negative feedback loop (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. Modeling of infectious, hereditary disease and cancer in organoids (reviewed in 51)

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 organoids. Some examples are mini-guts (27, 32), mini-stomachs (28), colon cancer organoids (32, 47), liver organoids (39, 46, 55), prostate organoids (45), breast cancer organoids (53), ovarian cancer organoids (59), pancreas cancer organoids (48), and even snake venom gland organoids (61). 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 (32, 47, 53). The direct cloning of multiple individual cells from primary tumors allows molecular and functional analysis of tumor heterogeneity with unprecedented resolution (54).

Organoids from fetal human tissue. Some human organoid types can't be grown from postnatal tissues. We have shown that brain organoids can be established from mid-gestation human fetal brain tissue (73), and that tripotent pancreas organoids (acing, ductal, endocrine) can be grown and subcloned over several years, starting from human fetal pancreas material (78).

Organoids are readily amenable to CRISPR-mediated genome modification to model for instance malignant transformation (49) and mutagenesis upon faulty DNA repair (52), or to rapidly create knock-in alleles of genes of interest (62, 66). Human rectal organoids model the hereditary disease Cystic Fibrosis, are now routinely used to predict drug response in CF patients. In 2013, we have provided the first proof-of-concept for CRISPR-mediated repair of a hereditary mutation in patient stem cells (43, 64). Human organoids also model infectious disease, as demonstrated for instance for *Cryptosporidium* (55), a mutagenic *E. coli* strain (63) and for SARS-CoV-2 (65).

Characterization of rare epithelial cell types using (human) intestinal organoids.

Human organoids can be cultured under conditions designed to generate rare epithelial cell types.

Enteroendocrine cells (EECs): The transcriptional hierarchy of the six EEC lineages, including the incretin Glp1-producing L cells, was mapped in mouse and man (58, 66). Using an unbiased transcription factor CRISPR screen, ZNF800 was identified as master repressor of EEC differentiation (72), while single cell deep mRNA sequencing of human organoid EEC followed by targeted CRISPR mutation and pharmacologic activation of hormone secretion delineated roles of individual human EEC sensors in hormone secretion. These receptors represent potential pharmacological targets to influence appetite, bowel movement, insulin sensitivity and mucosal immunity (76).

Tuft cells: An IL4/IL13-driven organoid protocol allows the generation of large numbers of Tuft cells, which was used to demonstrate that these cells act as regenerative (reserve) stem cells in the human intestine (75).

BEST4+ cells: These cells, unique to man, were previously only known from sc-mRNA sequencing datasets. A specific organoid culturing protocol allowed the generation of these cells in large numbers. We demonstrated that BEST4 cells are induced by γ -interferon, control water and electrolyte balance across the gut epithelium and are responsible for bacterially induced diarrhea (79).

M cells: As well as facilitating luminal antigen transport to Peyer's path immune cells, we show that human M cells also directly present antigens (i.e gluten) via their class II major histocompatibility complex (MHC-II) (81).

In sum, stem cell-derived organoids (as first described by Sasai for pluripotent stem cells and by us for adult stem cells) are rapidly gaining ground as research tools in a wide range of scientific disciplines, including basic developmental and cell biology, infectiology, toxicology and research on hereditary diseases and cancer.

Selected papers (out of ~900 peer-reviewed papers with ~223,000 citations in Scopus; h-index 223)

1. van de Wetering, M., Oosterwegel, M., Dooijes, D. and Clevers, H., 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., Hofhuis, F., Robanus-Maandag, E., te Riele, H., van de Wetering, M., Oosterwegel, M., Wilson, A., MacDonald, H.R. and Clevers, H. An HMG box containing T-cell factor required for thymocyte differentiation. **Nature** 374:70-74 (1995)
3. Schilham, M., Oosterwegel, M., Moerer, P., Jing, Y., de Boer, P., van de Wetering, M., Verbeek, 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. Xtc-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. **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., Batlle, E., Coudreuse, D., Haramis, A-P., Tjon-Pon-Fong, M., Moerer, P., van den Born, M., Soete, G., Pals, S., Eilers, M., Medema, R. and Clevers, H. The beta catenin/TCF4 complex imposes a crypt progenitor phenotype on colorectal cancer cells. **Cell** 111:241-250 (2002)
14. Batlle, E., Henderson, J.T., Beghtel, H., van den Born, M., Sancho, E., Huls, G., Meeldijk, J., Robertson, J., van de Wetering, M., Pawson, T. and 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. and 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. and Clevers, H. 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., Jonkhoeer, S., Offerhaus, G.J. and 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. and 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. and 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., Jonkhoeer, S., Gregorieff, A., van de Born, M., Malats, N., Sancho, E., Boon, E., Pawson, T., Gallinger, S., Pals, S. and 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. and 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. and 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. and Clevers, H. Lgr5(+ve) stem cells drive self-renewal in the stomach and build long-lived gastric units *in vitro*. **Cell Stem Cell** 6:25-36 (2010)
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. and Clevers, H. Lgr6 marks stem cells in the hair follicle that generate all cell lineages of the skin. **Science** 327:1385-1389 (2010)
30. 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)
31. 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. and Clevers, H. Lgr5 homologues associate with Wnt receptors and mediate R-spondin signalling. **Nature** 476:293-297 (2011)
32. Sato T., Stange, D.E., Ferrante, M., Vries R.G., Van Es, J.H., van den Brink, S., van Houdt, W.J., Pronk, A, van Gorp, J., Siersema, P.D. and Clevers, H. Long-term expansion of epithelial organoids from

- human colon, adenoma, adenocarcinoma, and Barrett's epithelium. **Gastroenterology** 141: 1762-1772 (2011)
33. 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. and Clevers, H. Paneth cells constitute the niche for Lgr5 stem cells in intestinal crypts. **Nature** 469:415-418 (2011)
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 36. Schepers, A.G., Snippert, H.J., Stange, D.E., van den Born, M., van Es, J.H., van de Wetering, M. and 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. and 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. and Clevers, H. In vitro expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration. **Nature** 494:247-250 (2013)
 40. Sato, T. and 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. and 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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