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 - 2020	Professor in Molecular Genetics at University Medical Center Utrecht
2002 - 2022	Principal Investigator of a research group of ~40 scientists at Hubrecht Institute, Utrecht As of March 2022, Guest Scientist/Advisor of this research group
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 - 2022	Principal Investigator at the Princess Máxima Center, Utrecht As of March 2022, Guest Scientist/Advisor of this research group
2017 -	Oncode Investigator
2020 -	Professor of Molecular Genetics at University Utrecht
2022 -	Head of Pharma, Research and Early Development (pRED) and Member of the Enlarged Executive Committee of F. Hoffmann-La Roche Ltd, 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 Reserach 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 Nederlands' 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

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 - present	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

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

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 - present	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 - present	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)

Grants

Our work has been positively judged by many different financing 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.

Contributions to Science

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, ß-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 ß-catenin and targets it for degradation in the proteasome. In APC-deficient colon carcinoma cells, we demonstrated that ß-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 selfrenewing 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. These 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. The 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 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 cells 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). The transcriptional hierarchy of the various enteroendocrine lineages was mapped in mouse and man (58, 66).

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).

Human organoids allow functional analyses of rare cell types, such as enteroendocrine cells (66). They 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).

In sum, 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 ~740 peer-reviewed papers with ~140,000 citations in Scopus; h-index 186)

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., Destrée, 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. **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., Batlle, 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., Jonkheer, 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. Batlle, 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. 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)
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 Clevers, H. 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. 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)
38. Boj, S,F., van Es, J.H., Huch. M., Li, V.S., Jose, A., Hatzis, P., Mokry, M., Haegebarth, A., van den Born, M., Chambon, P., Voshol, P., Dor, Y., Cuppenm E., Fillat, C. and Clevers, H. Diabetes risk gene

and Wnt effector Tcf7l2/TCF4 controls hepatic response to perinatal and adult metabolic demand. **Cell** 151:1595-1607 (2012)
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)
43. Schwank, G., Koo, B.K., Sasselli, V., Dekkers, J.F., Heo, I., Demircan, T., Sasaki, N., Boymans, S., Cuppen, E., van der Ent, C.K., Nieuwenhuis, E.E., Beekman, J.M. and Clevers, H. Functional Repair of CFTR by CRISPR/Cas9 in Intestinal Stem Cell Organoids of Cystic Fibrosis Patients. **Cell Stem Cell** 13:653-658 (2013)
44. Ritsma, L., Ellenbroek, S.I., Zomer, A., Snippert, H.J., de Sauvage, F.J., Simons, B.D., Clevers, H. and van Rheenen, J. Intestinal crypt homeostasis revealed at single-stem-cell level by in vivo live imaging. **Nature** 507:362-365 (2014)
45. Karthaus, W.R., Iaquinta, P.J., Drost, J., Gracanin, A., van Boxtel, R., Wongvipat, J., Dowling, C.M., Gao, D., Begthel, H., Sachs, N., Vries, R.G., Cuppen, E., Chen, Y., Sawyers, C.L. and Clevers, H. Identification of Multipotent Luminal Progenitor Cells in Human Prostate Organoid Cultures. **Cell** 159:163-175 (2014)
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., Niewenhuis, E., Hoekstra, R., Strom, S., Vries, R., van der Laan, L., Cuppen, E. and Clevers, H. Long-term culture of genome-stable bipotent stem cells from adult human liver. **Cell** 160:299-312 (2015)
47. van de Wetering, M., Francies, H.E., Francis, J.M., Bounova, G., Lorio, F., Pronk, A., van Houdt, W., van Gorp, J., Taylor-Weiner, A., Kester, L., McLaren-Douglas, A., Blokker, J., Jaksani, S., Bartfeld, S., Volckman, R., van Sluis, P., Li, V.S.W., Seepo, S., Sekhar Pedamallu, C., Cibulskis, C., Carter, S.L., McKenna, A., Lawrence, M.S., Lichtenstein, L., Stewart, C., Koster, J., Versteeg, R., van Oudenaarden, A., Saez-Rodriguez, J., Vries, R.G.J., Getz, G., Wessels, L., Stratton, M.R., McDermott, U., Meyerson, M., Garnett, M.J and Clevers, H. Prospective derivation of a 'Living Organoid Biobank' of colorectal cancer patients. **Cell** 161:933-945 (2015)
48. Boj, S.F., Hwang, C.I., Baker, L.A., Chio, I.I., Engle, D.D., Corbo, V., Jager, M., Ponz-Sarvise, M., Tiriac, H., Spector, M.S., Gracanin, A., Oni, T., Yu, K.H., van Boxtel, R., Huch, M., Rivera, K.D., Wilson, J.P., Feigin, M.E., Öhlund, D., Handly-Santana, A., Ardito-Abraham, C.M., Ludwig, M., Elyada, E., Alagesan, B., Biffi, G., Yordanov, G.N., Delcuze, B., Creighton, B., Wright, K., Park, Y., Morsink, F.H., Molenaar, I.Q., Borel Rinkes, I.H., Cuppen, E., Hao, Y., Jin, Y., Nijman, I.J., Iacobuzio-Donahue, C., Leach, S.D., Pappin, D.J., Hammell, M., Klimstra, D.S., Basturk, O., Hruban RH, Offerhaus GJ, Vries RG, Clevers H, Tuveson DA. Organoid models of human and mouse ductal pancreatic cancer. **Cell** 160: 324-338 (2015)
49. Drost, J., van Jaarsveld, R.H., Ponsioen, B., Zimberlin, C., van Boxtel, R., Buijs, A., Sachs, N., Overmeer, R.M., Offerhaus, G.J., Begthel, H. Korving, J., van de Wetering, M., Schwank, G. Logtenberg, M., Cuppen, E., Snippert, H.J., Medema, J.P., Kops, G.J.P.L. and Clevers, H. Sequential cancer mutations in cultured human intestinal stem cells. **Nature** 521:43-47 (2015)
50. Farin, H.F., Jordens, I., Mosa, M.H., Basak, O., Korving, J., Tauriello, D.V.F., de Punder, K., Angers, S., Peters, P.J. Maurice, M.M. and Clevers, H. Visualization of the short-range Wnt gradient in the intestinal stem cell niche. **Nature** 530:340-343 (2016)
51. Clevers, H. Modeling development and disease with organoids. **Cell** 165:1586-1597 (2016)

52. Drost, J., van Boxtel, R., Blokzijl, F., Mizutani, T., Sasaki, N., Sasselli, V., de Ligt, J., Behjati, S., Grolleman, J.E., van Wezel, T., Nik-Zainal, S., Kuiper, R.P., Cuppen, E. and Clevers, H. Use of CRISPR-modified human stem cell organoids to study the origin of mutational signatures in cancer. **Science** 358:234-238 (2017)
53. Sachs, N., de Ligt, J., Kopper, O., Gogola E., Bounova G., Weeber, F., Balgobind, A.V., Wind, K., Gracanin, A., Begthel, H., Korving, J., van Boxtel, R., Duarte, A.A., Lelieveld, D., van Hoeck, A., Ernst, R.F., Blokzijl, F., Nijman, I.J., Hoogstraat, M., van de Ven, M., Egan, D.A., Zinzalla, V., Moll, J., Boj, S.F., Voest, E.E., Wessels, L., van Diest, P.J., Rottenberg, S., Vries, R.G.J., Cuppen, E. and Clevers, H. A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity. **Cell** 172:373-386 (2018)
54. Roerink, S., Sasaki, N., Lee-Six, H., Young, M., Alexandrov, L., Behjati, S., Mitchell, T., Grossmann, S., Lightfoot, H., Egan, D., Pronk, A., Smakman, N., van Gorp, J., Anderson, E., Gamble, S., Alder, C., van de Wetering, M., Campbell, P., Stratton, M. and Clevers, H. Intra-tumour diversification in colorectal cancer at the single-cell level. **Nature** 556:457-462 (2018)
55. Heo, I., Dutta, D., Schaefer, D.A., Lakobachvili, N., Artegiani, B., Sachs, N., Boonekamp, K.E., Bowden, G., Hendrickx, A.P.A., Willems, R.J.L., Peters, P.J., Riggs, M.W., O'Connor, R. and Clevers, H. Modelling Cryptosporidium infection in human small intestinal and lung organoids. **Nat Microbiol.** 3:814-823 (2018)
56. Hu, H., Gehart, H., Artegiani, B., Löpez-Iglesias, C., Dekkers, F., Basak, O., van Es, J., Chuva de Sousa Lopes, S.M., Begthel, H., Korving, J., van den Born, M., Zou, C., Quirk, C., Chiriboga, L., Rice, C.M., Ma, S., Rios, A., Peters, P.J., de Jong, Y.P. and Clevers, H. Long-Term Expansion of Functional Mouse and Human Hepatocytes as 3D Organoids. **Cell** 175:1591-1606 (2018)
57. Tuveson, D. and Clevers, H. Cancer modeling meets human organoid technology. **Science** 364:952-955 (2019)
58. Gehart, H., van Es, J.H., Hamer, K., Beumer, J., Kretzschmar, K., Dekkers, J.F., Rios, A. and Clevers, H. Identification of Enteroendocrine Regulators by Real-Time Single-Cell Differentiation Mapping. **Cell** 176:1158-1173 (2019)
59. Kopper , O., de Witte, C.J., Lõhmussaar, K., Valle-Inclan, J.E., Hami, N., Kester, L., Balgobind, A.V., Korving, J., Proost, N., Begthel, H., van Wijk, L.M., Revilla, S.A., Theeuwsen, R., van de Ven, M., van Roosmalen, M.J., Ponsioen, B., Ho, V.W.H., Neel, B.G., Bosse, T., Gaarenstroom, K.N., Vrieling, H., Vreeswijk, M.P.G., van Diest, P.J., Witteveen, P.O., Jonges, T., Bos, J.L., van Oudenaarden, A., Zweemer, R.P., Snippert, H.J.G., Kloosterman, W.P. and Clevers, H. An organoid platform for ovarian cancer captures intra- and interpatient heterogeneity. **Nat Med.** 25:838-849 (2019)
60. Tuveson, D. and Clevers, H. Cancer modeling meets human organoid technology. **Science** 364:952-955 (2019)
61. Post, Y., Puschhof, J., Beumer, J., Kerkkamp, H.M., de Bakker, M.A.G., Slagboom, J., de Barbanson, B., Wevers, N.R., Spijkers, X.M., Olivier, T., Kazandjian, T.D., Ainsworth, S., Iglesias, C.L., van de Wetering, W.J., Heinz, M.C., van Ineveld, R.L., van Kleef, R.G.D.M., Begthel, H., Korving, J., Bar-Ephraim, Y.E., Getreuer, W., Rios, A.C., Westerink, R.H.S., Snippert, H.J.G., van Oudenaarden, A., Peters, P.J., Vonk, F.J., Kool, J., Richardson, M.K., Casewell, N.R. and Clevers, H. Snake Venom Gland Organoids. **Cell** 180:233-247 (2020)
62. Artegiani, B., Hendriks, D., Beumer, J., Kok, R., Zheng, X., Joore, I., Chuva de Sousa Lopes, S., van Zon, J., Tans, S. and Clevers, H. Fast and efficient generation of knock-in human organoids using homology-independent CRISPR-Cas9 precision genome editing. **Nat Cell Biol**. 22:321-331 (2020)
63. Pleguezuelos-Manzano, C., Puschhof, J., Huber, A.R., van Hoeck, A., Wood, H.M., Nomburg, J., Gurjao, C., Manders, F., Dalmasso, G., Stege, P.B., Paganelli, F.L., Geurts, M.H., Beumer, J., Mizutani, T., van der Linden, R., van Elst, S.; Genomics England Research Consortium, Top J., Willems, R.J.L., Giannakis, M., Bonnet, R., Quirke, P., Meyerson, M., Cuppen, E., van Boxtel, R. and Clevers, H. Mutational signature in colorectal cancer caused by genotoxic pks+ E. coli. **Nature** 580:269-273 (2020)
64. Geurts, M.H., de Poel, E., Amatngalim, G.D., Oka, R., Meijers, F.M., Kruisselbrink, E., van Mourik, P., Berkers, G., de Winter-de Groot, K.M., Michel, S., Muilwijk, D., Aalbers, B.L., Mullenders, J., Boj, S.F., Suen, S.W.F., Brunsveld, J.E., Janssens, H.M., Mall, M.A., Graeber, S.Y., van Boxtel, R., van der Ent,

C.K., Beekman, J.M. and Clevers, H. CRISPR-Based Adenine Editors Correct Nonsense Mutations in a Cystic Fibrosis Organoid Biobank. **Cell Stem Cell** 26:503-510 (2020)
65. Lamers, M.M., Beumer, J., van der Vaart, J., Knoops, K., Puschhof, J., Breugem, T.I., Ravelli, R.B.G., van Schayck, J.P., Mykytyn, A.Z., Duimel, H.Q., van Donselaar, E., Riesebosch, S., Kuijpers, H.J.H., Schipper, D., van de Wetering, W.J., de Graaf, M., Koopmans, M., Cuppen, E., Peters, P.J., Haagmans, B.L. and Clevers, H. SARS-CoV-2 productively Infects Human Gut Enterocytes. **Science** 369:50-54 (2020)
66. Beumer, J., Puschhof, J., Bauzá-Martinez, J., Martínez-Silgado, A., Elmentaite, R., James, K.R., Ross, A., Hendriks, D., Artegiani, B., Busslinger, G., Ponsioen, B., Andersson-Rolf, A., Saftien, A., Boot, C., Kretzschmar, K., Geurts, M.H., Bar-Ephraim, Y.E., Pleguezuelos Manzano, C., Post, Y., Begthel, H., van der Linden, F., Lopez-Iglesias, C., van de Wetering, W.J., van der Linden, R., Peters, P.J., Heck, A.J.R., Goedhart, J., Snippert, H., Zilbauer, M., Teichmann, S.A., Wu, W. and Clevers, H. High Resolution mRNA and Secretome Atlas of Human Enteroendocrine Cells. **Cell** 181:1291-1306 (2020)
67. Lohmussaar K., Oka R., Espejo Valle-Inclan J., Veersema S., [...] van Boxtel R., Clevers H. Patient-derived organoids model cervical tissue dynamics and viral oncogenesis in cervical cancer. **Cell Stem Cell** 28:1-17 (2021)
68. Bannier-Hélaouët M., Post Y., Korving J. [...] Imhoff S., Clevers H. Exploring the human lacrimal gland using organoids and single-cell sequencing. **Cell Stem Cell** 28:1-12 (2021)