BIOGRAPHICAL SKETCH

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NAME: Porteus, Matthew Hebden

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POSITION TITLE: Professor of Pediatrics

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Harvard University, Cambridge, MA	A.B.	09/1982	06/1986	History and Science
Stanford University, Stanford, CA	Ph.D.	09/1989	06/1994	Neuroscience
Stanford University, Stanford, CA	M.D.	09/1987	06/1994	Medicine
Boston Children's Hospital, Boston, MA	Residency	07/1994	06/1996	Pediatric Medicine
Boston Children's Hospital/Dana Farber Cancer Institute	Fellowship	07/1996	06/1999	Hematology/Oncology
Massachusetts Institute of Technology, Cambridge, MA/California Institute of Technology, Pasadena, CA	Postdoctoral	07/1997	06/2003	Biology

A. Personal Statement

I am a physician/scientist whose goal is to develop safe and effective therapy for patients with monogenic diseases such as β-thalassemia, sickle cell disease, hemophilia, and severe combined immunodeficiency and and for infectious diseases such as HIV. Towards this end I have completed clinical training in pediatric hematology/oncology and in my clinical practice attend on the pediatric hematopoietic stem cell transplant service. My research program is focused on using homologous recombination as a precise method of genome modification for therapeutic and research purposes. As a postdoctoral fellow in Dr. David Baltimore's laboratory I demonstrated that gene targeting by homologous recombination could be stimulated 50,000-fold in human somatic cells by the induction of a DNA double-strand break in the target locus. Moreover, I showed that zinc finger nucleases could stimulate gene targeting in human somatic cells to potentially therapeutic levels. In my independent research program, we have focused on improving the safety and efficacy of genome modification by homologous recombination in mammalian cells. In order to achieve targeted genome modification we have used a variety of platforms including zinc finger nucleases, TAL effector nucleases (TALENs), CRISPR/Cas9 and AAV. Our lab has used these tools to engineer human ESC lines and iPS lines in both published and unpublished work. We have engineered CRISPR/Cas9 nucleases to over 15 different target genes and have been successful in gene targeting at all these target sites. In addition to using homologous recombination to correct disease-causing mutations, we are also using homologous recombination based genome editing as a synthetic biology tool to engineer cells to adopt new therapeutic functions, including fibroblasts and hematopoietic cells to secrete therapeutic proteins (including clotting factors and lysosomal enzymes) and to engineer immune cells to be HIV resistant. In 2013 my group was the first to demonstrate that efficient knock-in of multiple HIV-resistance genes can confer resistance to R5 and X4-tropic HIV infection in vitro usting zinc-finger nucleases. We are actively involved through multiple collaborations in using genome editing as a research tool for various important biomedical problems including the use of knock-outs and knock-ins to understand the biologic function of specific genes.

In addition, I am the Associate Director of the Stanford MSTP, the co-PI on the Pediatric Non-Malignant Hematology T32 through the Division of Pediatric Hematology/Oncology at Stanford, the Associate Director of

the Pediatric Hematology/Oncology fellowship program and the Associate Director of the Center for Definitive and Curative Medicine at Stanford. I am committed to training and mentoring, and currently have 4 postdoctoral fellows and two PhD students, and two MD students in my lab. In 2022, two post-doctoral fellows left the lab to take faculty positions at UCSF and Nationwide Children's Hospital.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2018-Present	Professor, Department of Pediatrics at Stanford University, Stanford, CA
2017-2021	Chan-Zuckerberg Biohub Investigator
2010-2018	Associate Professor, Department of Pediatrics at Stanford University, Stanford, CA
2003-2010	Assistant Professor, Department of Pediatrics and Biochemistry at UT Southwestern Medical School, Dallas, TX
1982, 1986	Summer Research Assistant, Stanford University, Stanford, CA

Other Experience and Professional Memberships

2016-Present	NHLBI Advisory Committee on Sickle Cell Disease
2016-2019	Board of Directors, American Society of Gene and Cell Therapy
2015-2020	Associate Program Director, Pediatric Hematology/Oncology Fellowship Program
2014-Present	Member Chemistry, Engineering, & Medicine for Human Health Program, Stanford University
2013-Present	Associate Program Director, Stanford Medical Scientist Training Program
2010-Present	Member of the Stanford Stem Cell Institute
2010-Present	Member Stanford Cancer Biology Program
2000	Board Certified Pediatric Hematology/Oncology
1999	Board Certified in Pediatrics

Honors

2013, 2014	Finalist (Interview Stage) for NIH Pioneer Award
2002-2007	Career Development Award Recipient Burroughs-Wellcome Fund
1999-2002	Physician Post-Doctoral Scholar, Howard Hughes Medical Institute
1987-1994	Medical Scientist Training Program, Merck Scholar
1986	Magna Cum Laude, Harvard University

C. Contributions to Science

1. I identified the first homeobox gene expressed specifically in the developing mammalian forebrain and identified a collection of genes specifically expressed in the developing mammalian forebrain compared to the adult forebrain.
   a. Porteus, M.H., Bulfone, A., Ciaranello, R.D., and Rubenstein, J.L.R. (1991). Isolation and characterization of a novel cDNA clone encoding a homeodomain that is developmentally regulated in the ventral forebrain. *Neuron* 7: 221-229.
   b. Porteus, M.H., Brice, A.E.J., Bulfone, A., Usdin, T.B., Ciaranello, R.D., and Rubenstein, J.L.R. (1992). Isolation and characterization of a library of cDNA clones that are preferentially expressed in the embryonic telencephalon. *Mol. Brain Res*. 12: 7-22.
2. I have demonstrated expertise in applying engineered nucleases to stimulate specific gene modification in human somatic and pluripotent cells (i.e., genome editing in human cells).
   a. Urnov, F.D., Miller, J.C., Lee, Y-L., Beausejour, C.M., Rock, J., Augustus, S., Jamieson, A.C., Porteus, M.H.*, Gregory, P.D., and Holmes, M.C. (2005). Highly Efficient Endogenous Human Gene Correction Using Designed Zinc Finger Nucleases. *Nature*. 435: 646-51.
   b. Hendel, A, Bak, RO, Clark, J, Steinfeld, I, Kennedy, A, Roy, S, Wilkens, A., Bacchetta, R., Dellinger, D, Bruhn, L*, and Porteus, MH*. Chemically modified guide RNAs enhance CRISPR/Cas genome editing in primary cells. *Nature Biotechnology*. 2015 33(9):985-9. PMCID: PMC4729442.

c. Vaidyanathan S, Salahudeen AA, Sellers ZM, Bravo DT, Choi SS, Batish A, Le W, Baik R, de la O S, Kaushik MP, Galper N, Lee CM, Teran CA, Yoo JH, Bao G, Chang EH, Patel ZM, Hwang PH, Wine JJ, Milla CE, Desai TJ, Nayak JV, Kuo CJ, Porteus MH***.** High-Efficiency, Selection-Free gene repair in airway stem cells from cystic fibrosis patients rescues CFTR function in differentiated epithelia. 2020. Cell Stem Cell. 26(2): 161-174. PMID 31839569.

d. Martin, RM, Ikeda, K, Uchida, N, Cromer, K, Nishimura, T, Dever, DP, Camarena, J, Bak, R, Lausten, A, Jakobsen, MR, Wiebking, V, Sebastiano, V, Nakauchi, H, and Porteus, MH***.** Highly Efficient and Marker-free Genome Editing of Human Pluripotent Stem Cells by CRISPR-Cas9 RNP and AAV6 Donor-Mediated Homologous Recombination. Cell Stem Cell 2019 24: 821-828. PMID: 31051134.

3. I have demonstrated expertise in the development of genome editing technologies.
   a. Porteus, M.H.*,* Cathomen, T., Weitzman, M.D., and Baltimore, D. (2003) Efficient Gene Targeting Mediated by AAV and DNA Double-Strand Breaks. *Mol. Cell Biol*. 23(10): 3558-3565. PMCID: PMC164769
   b. Bak, RO* and Porteus MH*. (2017) CRISPR-Mediated Integration of Large Gene Cassettes using AAV Donor Vectors. *Cell Reports* 20(3): 750-756. PMCID: PMC5568673.
   c. Dever, DP, Bak, RO, Reinisch, A, Camarena, J, Washington, G, Nicolas, CE, Pavel-Dinu, M, Saxexa N, Wilkens, AB, Mantri, S, Uchida, N, Narla, A, Majeti, R, Weinberg, KI, and Porteus, MH***.** CRISPR/Cas9 Beta-globin gene targeting in human hematopoietic stem cells. Nature 2016 Nov 17 539: 384-389. PMID 27820943.
   d. Vakulskas, CA, Dever, DP, Retting, GR, Turk, R, Jacobi, AM, Collingwood, MA, Bode, NM, McNeill, MS, Yan, S, Camarena, J, Lee, CM, Park, SH, Wiebking, V, Bak, RO, Gomez-Ospina, N, Pavel-Dinu, M, Sun, W, Bao, G, Porteus, MH**,* and Behlke, MA*. A novel high-fidelity Cas9 variant enables high frequency correction of disease-causing SNP in human hematopoietic stem and progenitor cells. Nature Medicine 2018 24(8): 1216-1224. PMID: 30082871.
4. My group has expertise in the development of genome editing of cells with a goal to treat or cure patients with a wide variety of diseases.
   a. Voit, RA, McMahon, MA, Sawyer, SL, and Porteus, MH**.* (2013) Generation of an HIV Resistant T-Cell Line by Targeted "Stacking" of Restriction Factors. *Molecular Therapy* 21: 786-795. PMCID: PMC3616536.
   b. Pavel-Dinu, M, Wiebking, V, Dejen, BT, Srifa, W, Mantri, S, Nicolas, CE, Lee, C, Bao, G, Kildebeck, EJ, Punjya, N, Sindhu, C, Inlay, MA, Saxena, N, DeRavin, SS, Malech, H, Roncarolo, MG, Weinberg, KI, and Porteus, MH***.** Genome editing of long-term human hematopoietic stem cells for SCID-X1. Nat Commun. 2019 10:1634. PMID: 30967552.
   c. Cromer MK, Camarena J, Martin RM, Lesch BJ, Vakulskas CA, Bode NM, Kurgan G, Collingwood MA, Rettig GR, Behlke MA, Lemgart VT, Zhang Y, Goyal A, Zhao F, Ponce E, Srifa W, Bak RO, Uchida N, Majeti R, Sheehan VA, Tisdale JF, Dever DP, Porteus MH***.** Gene replacement of alpha-globin with beta-globin restores hemoglobin balance in Beta-thalassemia-derived hematopoietic stem and progenitor cells. 2021. Nat Med 27: 677-687. PMID: 22737751.
   d. Lattanzi, A, Camarena, J, Lahiri, P, Segal, H, Srifa, W, Vakulskas, CA Frock, RL, Kenrick, J, Lee, C, Talbott, N, Skowronski, J, Cromer, MK, Charlesworth, CT, Bak, RO, DiGiusto, D, Tisdale, J, Wright, JF, Bhatia, N, Roncarolo, MG, Dever, DP**,* Porteus, MH**.* Development of beta-globin gene correction in human hematopoietic stem cells as a potential durable treatment for sickle cell disease. 2021. Science Transl Med. 13*568): eabf 2444. PMID: 34135108.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1h_4alb7KwU5v/bibliography/45302184/public/?sort=date&direction=ascending