BIOGRAPHICAL SKETCH

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NAME: Porteus, Matthew Hebden

eRA COMMONS USER NAME (credential, e.g., agency login): MPORT3

POSITION TITLE: Associate Professor

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
Harvard University, Cambridge, MA	A.B.	1982-1986	History and Science
Stanford University, Stanford, CA	Ph.D.	1987-1994	Neuroscience
Stanford University, Stanford, CA	M.D.	1987-1994	Medicine
Boston Children's Hospital		1994-1996	Pediatric Residency
Boston Children's Hospital/Dana Farber Cancer Institute		1996-1999	Hematology/Oncology Fellowship
MIT/Caltech		1997-2003	Post-Doctoral Work (Dr. David Baltimore)

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 post-doctoral 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), 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 Our lab has used these tools to engineer human ESC lines and iPS lines in both published and unpublished work.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 TALENs and 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. As our expertise in genome editing has increased, we are also using genome editing as a tool to create chromosomal translocations that define specific pediatric cancers as a way to better understanding the ontogeny of such cancers. Finally, 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, a pre-major advisor for first-generation Stanford undergraduates, 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 serve on the Selection Committee for physician-scientist track in the Pediatric Residency program.

1. **Porteus, M.H.*** and Baltimore, D. (2003). Chimeric Nucleases Stimulate Gene Targeting in Human Cells. Science. 300: 763.
2. 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. PMID 23358186.
3. Hendel, A, Kildebeck, EJ, Fine, E, Clark, J, Bao, G, and **Porteus, MH*.** (2014) Detecting genome editing outcomes at endogenous loci using SMRT sequencing. Cell Reports 10: 293-305. PMID 24685129.
4. 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. PMID 26121415.
5. Dever, DP, Bak, RO, Reinisch, A, Camarena, J, Washington, G, Nicolas, CE, Pavel-Dinu, M, Saxena, N, Wilkens, AB, Mantri, S, Uchida, N, Narla, A, Majeti, R, Weinberg, KI, and **Porteus, MH*.** (2016) CRISPR/Cas9 Beta-globin gene targeting in human hematopoietic stem cells. Nature 539: 384-389. PMID 27820943.

B. Positions and Honors

Positions and Employment

1982	Summer Research Assistant (Dr. Michael Marmor), Stanford University
1986	Summer Research Assistant (Dr. Larry Steinman), Stanford University
1994-1995	Intern in Pediatrics, Children's Hospital, Boston
1995-1996	Resident in Pediatrics, Children's Hospital, Boston
1996-1999	Fellow in Pediatric Hematology/Oncology, Children's Hospital/Dana Farber Cancer Institute, Boston
1997-1999	Post-Doctoral Research Fellow (Dr. David Baltimore), Massachusetts Institute of Technology
1999-2003	Post-Doctoral Research Scholar (Dr. David Baltimore), California Institute of Technology
2003-2010	Assistant Professor of Pediatrics and Biochemistry at UT Southwestern Medical School
2010-present	Associate Professor of Pediatrics at Stanford University
2010-present	Affiliated Member of the Stanford Stem Cell Institute
2010-present	Member Stanford Cancer Biology Program
2014-present	Member Chemistry, Engineering, & Medicine for Human Health Program, Stanford University
2013-present	Associate Program Director, Stanford Medical Scientist Training Program
2015-present	Associate Program Director, Pediatric Hematology/Oncology Fellowship Program
2016-present	NHLBI Advisory Committee on Sickle Cell Disease
2016-present	Board of Directors, American Society of Gene and Cell Therapy (ASGCT)
2017-present	Chan-Zuckerberg Biohub Investigator

Honors

1986	Magna Cum Laude, Harvard University
1987-1994	Medical Scientist Training Program, Merck Scholar
1999	Board Certified in Pediatrics
2000	Board Certified Pediatric Hematology/Oncology
1999-2002	Physician Post-Doctoral Scholar, Howard Hughes Medical Institute
2002-2007	Career Development Award Recipient Burroughs-Wellcome Fund
2013, 2014	Finalist (Interview Stage) for NIH Pioneer Award

C. Contribution to Science

1. 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.

1. **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.
2. **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. First to demonstrate that engineered nucleases could be used to stimulate specific gene modification in human somatic and pluripotent cells (genome editing in human cells).

1. 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.
2. **Porteus, M.H.*** (2006). Mammalian Gene Targeting with Designed Zinc Finger Nucleases. Molecular Therapy, 13: 438-446
3. Zou, J., Maeder, M.L., Mali, P., Pruett-Miller, S.M., Thibodeau-Beganny, S., Chou, B-K., Chen, G., Ye, Z., Park, I-H., Daley, G.Q., **Porteus, M.H.***, Joung, J.K.*, and Cheng, L.* (2009) Gene Targeting of a disease-related gene in human induced pluripotent stem and embryonic stem cells. Cell Stem Cells 5: 97-110.
4. Breese, EH, Buechele, C, Dawson, C, Cleary, ML*, and **Porteus, MH*.** Use of genome engineering to create patient specific MLL translocations in primary human hematopoietic stem and progenitor cells. PLoS One. 2015 10(9):e0136644. PMID 26351841.

3. Expertise in the utilization of AAV as a donor delivery vector for nuclease mediated genome editing by homologous recombination.

1. **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.
2. Hirsch, M, Green, L, **Porteus, MH**, and Samulski, J. (2010) Self-complementary AAV Mediates Gene Targeting and Enhances Endonuclease Delivery for Double-Strand Break Repair. Gene Therapy 17: 1175-1180.
3. Ellis, BL, Hirsch, ML, Samulski, JR, and **Porteus, MH*.** (2011) Gene Targeting Mediated by AAV6 and Zinc-Finger Nucleases in Human and Mouse Cells. Hum. Gene Ther. 22: 93-100. PMID 20626321.
4. Bak, RO* and **Porteus MH*.** (2017) CRISPR-Mediated Integration of Large Gene Cassettes using AAV Donor Vectors. Cell Reports 20(3): 750-756. PMID 28723575.

4. First to combine the use of homologous recombination mediated genome editing with anti-HIV restriction factors to create R5-tropic and X4-tropic HIV resistant cells.

1. 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. PMID 23358186.

5. Broad expertise in the use of engineered nucleases for genome editing.

1. Voit, RA, Hendel, A, Pruett-Miller, SM, and **Porteus, MH*.** (2014) Nuclease-mediated gene editing by homologous recombination of the human globin locus. Nucl. Acids Res. 42: 1365-1378. PMID 24157834.
2. 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. PMID 26121415.
3. Dever, DP, Bak, RO, Reinisch, A, Camarena, J, Washington, G, Nicolas, CE, Pavel-Dinu, M, Saxena, N, Wilkens, AB, Mantri, S, Uchida, N, Narla, A, Majeti, R, Weinberg, KI, and **Porteus, MH*.** (2016) CRISPR/Cas9 Beta-globin gene targeting in human hematopoietic stem cells. Nature 539: 384-389. PMID 27820943.
4. Bak, RO, Dever, DP, Reinisch, A, Cruz, D, Majeti, R*, and **Porteus, MH***. (2017) Multiplexed genetic engineering of human hematopoietic stem and progenitor cells using CRISPR/Cas9 and AAV6. Elife, *manuscript in press.*

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

D. Research Support

Ongoing Research Support

R01 AI120766 (Porteus)	09/01/15-02/29/20	1.81 calendar
NIH		$125,442

Genome Editing by Homologous Recombination to Create HIV Resistant Immune System

This proposal is focused on the development of homologous recombination mediated genome editing to create an engineered population of highly HIV resistant cells for the stable long-term cure of patients with HIV.

R01 AI097320 (Porteus) 12/01/12-11/30/17 1.81 calendar
NIH $227,113
Pre-Clinical Development of Nuclease Mediated Gene Therapy for SCID
The goal of this proposal is to develop gene targeting by homologous recombination as a gene therapy approach for the treatment of severe combined immunodeficiency diseases. This is a discovery phase project that now focuses on Wiskot-Aldrich Syndrome and Chronic Granulomatous Disease.

R01 HL123968 (Wu) 08/08/14-5/31/18 .24 calendar
NIH $3,630
Modeling Susceptibility to Chemotherapy-Induced Cardiotoxicity Using Human iPSCs
The goal of this study is to investigate the application of patient-specific induced pluripotent stem cell derived cardiomyocytes (iPSC-CMs) to discover genetic markers of doxorubicin-induced cardiotoxicity (DIC) and to establish the molecular mechanisms by which they alter the risk of this complication.

R01 HL126527 (Wu) 03/10/2015-01/31/2019 .36 calendar
NIH $5,700
Genome Editing of Human iPSCs to Study Inherited Hypertrophic Cardiomyopathy
The goal of this grant is to demonstrate the feasibility of elucidating myofilament diseases with patient specific HCM iPSC-CMs and genome-edited iPSC-CMs. We will determine the extent of disease by performing molecular and functional analyses of iPSC-CMs and then recapitulate sarcomeric HCM disease phenotype with genome editing technology.

PC1-08111 (Porteus, Roncarolo Co-PI) 10/01/2015-03/31/2018 3.60 calendar
California Institute for Regenerative Medicine $175,834
Pre-clinical development of gene correction therapy of hematopoietic stem cells for SCID-X1
The goal of this program is to develop a specific gene correction procedure that could be applied to almost every patient with SCID-X1 rather than to it naturally occur in an extremely rare lucky few. The goal of this project is to bring it to the pre-IND stage of development.

R01 HL133272 (Wu) 07/212016-04/30/2021 .36 calendar
NIH/NHLBI $5,700
Molecular Imaging of Cardiac Pluripotent Stem Cells
This study will use novel molecular imaging strategies to track the longitudinal fate of transplanted iPSC-CMs in rodent and large animal models.

Chan-Zuckerberg Investigator (Porteus) 05/01/2017-04/30/2022
Chan-Zuckerberg Biohub $300,000/year
Genome Editing to Develop Cell Based Curative Therapies
This grant is focused on combining genome editing with the principles of synthetic biology to engineer novel cell and stem cell based therapeutics.

No grant number (Porteus) 07/1/2013-06/30/2018
Amon Carter Foundation $80,000/year
Research in Gene Therapy for Pediatric Genetic Diseases
The goal of this project is to use genome editing to modify stem cells by homologous recombination to secrete therapeutic proteins

OVERLAP
None