BIOGRAPHICAL SKETCH

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NAME: Engleman, Edgar G.

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POSITION TITLE: 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	BA	06/1967	Psychology
Columbia University College of Physicians and Surgeons	MD	06/1971	Medicine

A. Personal Statement

For the past 40 years my research has been directed at discovering ways to manipulate the immune system for the treatment and, hopefully, cure of life-threatening diseases. At the start of my career I generated monoclonal antibodies to human T lymphocytes, including anti-CD4 and anti-CD8, enabling me and others to isolate these cells and analyze their functions for the first time. I also used these antibodies to design and implement the first AIDS screening test for blood donors and study the role of CD4 in HIV infection. A decade later, having developed methods for purifying, loading and activating human dendritic cells (DCs), my group was the first to evaluate the ability of these cells to induce immunity *in vivo*, initially in patients with cancer. This work led to the development of the first FDA approved immunotherapy – the Sipuleucel-T (Provenge) vaccine that was approved in 2010 for the treatment of advanced prostate cancer. In 2015, my lab discovered a promising strategy that reprograms immunosuppressive tumor associated DCs into immunostimulatory antigen presenting cells, *in situ*, and is expected to enter clinical trials later this year in several different cancers. In addition to investigating ways to manipulate the immune system for the treatment of cancer, we helped develop a therapy that induces organ-specific immune tolerance, enabling transplant recipients to retain their allografts without requiring immunosuppressive drugs. Recently, to enable investigation of immune cells in multiple tissues throughout an organism, we developed an advanced analytical approach based on high dimensional mass cytometry and novel informatics. Although we initially used this approach to identify the locations, functions and cell types required for effective immunotherapy of cancer, we are now using it to dissect the role of the immune system in a wide range of diseases. Beyond my research contributions, I am particularly proud of having trained more than 90 graduate and postdoctoral students, many of whom have gone on to distinguished academic careers. Examples include Miriam Merad, Professor of Oncological Science and Medicine at Mt. Sinai School of Medicine, Lawrence Fong, Professor of Medicine and Director of Cancer Immunotherapy at University of California, San Francisco, Jeffrey Bender, Professor of Medicine and Immunobiology, and Director, Cardiovascular Research Center, Yale University School of Medicine, Jeffrey Lifson, Director of the AIDS and Cancer Virus Program at Frederick National Laboratory for Cancer Research and Steven Foung, Professor and Associate Chair of Pathology, Stanford University School of Medicine.

Selected Recent Publications:

1. Carmi Y, Spitzer M, Linde IL, Burt BM, Prestwood TR, Perlman N, Davidson MG, Kenkel JA, Segal E, Pusapati GV, Bhattacharya N, **Engleman EG**. Allogeneic IgG combined with dendritic cell stimuli induces

anti-tumor T cell immunity. **Nature** 521:99-104, 2015; doi:10.1038/nature14424, published online 29 April 2015. [PMCID: PMC4877172]

2. Spitzer MH, Gherardini PF, Fragiadakis GK, Bhattacharya N, Yuan RT, Hotson AN, Finck R, Carmi Y, Zunder ER, Fantl WJ, Bendall SC, **Engleman EG***, Nolan, GP*. An interactive reference framework for modeling a dynamic immune system. **Science** 349(6244):1259425, 2015. doi: 10.1126/science.1259425. *co-senior authors [PMCID: PMC4537647]
3. Bhattacharya N, Yuan R, Prestwood TR, Penny HL, DiMaio MA, Reticker-Flynn NE, Krois CR, Kenkel JA, Pham TD, Carmi Y, Tolentino L, Choi O, Hulett R, Wang J, Winer D, Napoli JL, **Engleman EG**. Normalizing microbiota-induced retinoic acid deficiency stimulates protective $CD8^+$ T-cell-mediated immunity in colorectal cancer. **Immunity** 45:641-655, 2016. doi: 10.1016/j.immuni.2016.08.008. Epub 2016 Aug 30. [PMCID: PMC5132405]
4. Spitzer MH, Carmi Y, Reticker-Flynn NE, Kwek SS, Madhireddy D, Martins MM, Gherardini PF, Prestwood TR, Chabon J, Bendall SC, Fong L, Nolan GP, **Engleman EG.** Systemic immunity is required for effective cancer immunotherapy. **Cell** 168:487-502.e15, 2017. doi: 10.1016/j.cell.2016.12.022. Epub 2017 Jan 19. [PMCID: PMC5312823]

B. Positions and Honors

Positions and Employment

1971-73 Intern and Resident in Medicine, University of California Hospitals, San Francisco.
1973-76 Research Associate, Laboratory of Biochemistry (ER Stadtman, Chief), NHLBI, NIH, Bethesda, MD.
1976-78 Postdoctoral Fellow in Immunogenetics and Rheumatology (H.O. McDevitt, Chief), Stanford University School of Medicine, Stanford, CA.
1978-84 Assistant Professor of Pathology and Medicine, Stanford University School of Medicine.
1978- Attending Physician in Immunology and Rheumatology, Stanford University Medical Center.
1979- Director, Stanford Blood Center, Stanford University School of Medicine.
1984-90 Associate Professor of Pathology and Medicine, Stanford University School of Medicine.
1990- Professor of Pathology and Medicine, Stanford University School of Medicine.
2005- Co-Leader, Stanford Cancer Institute Program in Tumor Immunology and Immunotherapy

Journal Editorial Boards and Editorships

Hybridoma (1980-87)
Journal of Immunology (1982-90); Section Editor, Cellular Immunology (1985-90)
Journal of Clinical Immunology (1983-87, 1993-96)
Clinical Immunology and Immunopathology (1988-98)
Biotechnology Therapeutics (1988-98)
AIDS Research and Human Retroviruses, Section Editor, Immunovirology (1990-2006)
Cancer Immunology Research (2013-present)

NIH Committees

Immunobiology Study Section (member, 1988-92)
Immunology and Virology Study Section for Small Business Innovative Research (member, 1994-2003)
Cancer Immunopathology and Immunotherapy Study Section (ad hoc member, 2017, 2018, 2019)

Honors

Member, American Society for Clinical Investigation
Member, Pluto Club (Association of University Pathologists)
Member, Association of American Physicians
Recipient, Outstanding Inventor Award, Stanford University (2004)
Recipient, CABS K Fong Prize in Life Sciences (2017)

C. Contributions to Science

1. **Defining the role of human T cell subsets and surface markers.** When my career began, there was little knowledge of the cellular components of the human immune system. In an effort to begin to address

this fundamental question, I generated a series of mouse monoclonal anti-human leukocyte antibodies and used these antibodies to identify and characterize subsets of human T cells. These antibodies became widely used standards in the field and I later used them as the basis for the first screening test for the AIDS carrier state in blood donors as well as probe the mechanism by which HIV enters and kills susceptible cells after binding to its cell surface receptor, CD4.

a. **Engleman, E.G.**, Benike, C.J., Glickman, E., and Evans, R.L. (1981). Antibodies to membrane structures that distinguish suppressor/cytotoxic and helper T lymphocyte subpopulations block the mixed leukocyte reaction in man. **J. Exp. Med.** 153:193-198.
b. **Engleman, E.G.**, Benike, C.J., Grumet, F.C., and Evans, R.L. (1981). Activation of human T lymphocyte subsets: Helper and suppressor/cytotoxic T cells recognize and respond to distinct histocompatibility antigens. **J. Immunol.** 127:2124-2129.
c. Lifson, J.D., Reyes, G.R., McGrath, M.S., Stein, B.S., and **Engleman, E.G.** (1986). AIDS retrovirus induced cytopathology: Giant cell formation and involvement of CD4 antigen. **Science** 232:1123-1127.
d. Stein, B.S., Gowda, S.D., Lifson, J.D., Penhallow, R.C., Bensch, K.G., and **Engleman, E.G.** (1987). pH-Independent HIV entry into CD4-positive T cells via virus envelope fusion to the plasma membrane. **Cell** 49:659-668.

2. Analyzing the properties of dendritic cells and how to harness these cells for the treatment of cancer. Beginning in 1990 I became interested in the biology and functions of dendritic cells (DCs). After developing a method for isolating human DCs from blood and demonstrating that these cells alone could present antigens to naïve T cells in vitro, I designed and led the first clinical trials to evaluate the potential utility of antigen-loaded DCs for tumor immunotherapy - in patients with malignant lymphoma, prostate and colon cancer. Our methods for isolating and arming human DCs with tumor antigens provided the basis for the Sipuleucel-T (Provenge) vaccine for the treatment of metastatic prostate cancer, the first active immunotherapeutic agent to be approved by the FDA (in 2010). Although this technology is now being superseded by newer approaches, by demonstrating that the immunosuppressive environment could be overcome, this vaccine opened the way to a new era in which immunotherapies are increasingly becoming a standard component of cancer treatment. In 2015, my group reported a potent approach to arming and activating DC *in situ* in tumor-bearing hosts, based on the combined delivery of tumor binding antibodies and DC stimuli. This approach is expected to enter clinical trials in 2019. To enable in-depth assessment of the effects of any therapy or disease on immune cells in tissues throughout the body, we recently developed a high-throughput method based on time of flight cytometry (CyTOF) and novel algorithms.

a. Markowicz, S. and **Engleman, E.G.** (1990). Granulocyte-macrophage colony-stimulating factor promotes differentiation and survival of human peripheral blood dendritic cells in vitro. **J. Clin. Invest.** 85:955-961.
b. Fong, L., Hou, Y., Rivas, A., Benike, C., Yuen, A., Fisher, G.A., Davis, M.M., and **Engleman, E.G.** (2001). Altered peptide ligand vaccination with Flt3 ligand expanded dendritic cells for tumor immunotherapy. **Proc. Natl. Acad. Sci. USA** 98:8809-8814.
c. Merad, M., Manz, M.G., Karsunky, H., Wagers, A., Peters, W., Charo, I., Weissman, I.L., Cyster, J.G., and **Engleman, E.G.** (2002). Langerhans cells renew in the skin throughout life. **Nature Immunol.** 3:1135-1141.
d. Kenkel JA, Tseng WW, Davidson MG, Tolentino LL, Choi O, Bhattacharya N, Seeley ES, Winer DA, Reticker-Flynn NE, **Engleman EG.** An immunosuppressive dendritic cell subset accumulates at secondary sites and promotes metastasis in pancreatic cancer. **Cancer Res.** 77:4158-4170, 2017. [PMCID: PMC5550516].

3. Probing the role of the immune system in obesity associated diseases. For the past ten years, my lab has been investigating the role of the immune system in obesity associated type 2 diabetes. In the first of two related studies, my collaborators and I showed that T lymphocytes infiltrating the visceral fat of diet induced obese (DIO) mice can both induce and protect against the development of diabetes. This study was followed two years later by our discovery that B cells and autoantibodies also play a key role in the development of obesity-associated diabetes. Surprisingly, we found that insulin resistance in obese humans is linked to a unique profile of IgG autoantibodies, thus repositioning this disease into an entirely new and unexpected category of pathology, autoimmunity. Subsequently, we showed that the pro-

inflammatory effects of B cells in obesity associated diabetes are mediated by B-2 cells, while a small population of IL-10-secreting regulatory B cells, that normally helps maintain a state of insulin sensitivity, is deficient in obese insulin resistant mice. We expanded on these findings by performing deep sequencing of the immunoglobulin repertoire from DIO mice and found that their antibody repertoire is significantly altered in the intestine and visceral adipose tissue relative to control mice on a regular diet. These findings demonstrate an immunological relationship between adipose and gastrointestinal tissues, and their role in molding the humoral immune system in response to diet.

a. Winer, S., Chan, Y., Paltser, G., Truong, D., Tsui, H., Bahrami, J., Dorfman, R., Wang, Y., Zielenski, J., Mastronardi, F., Maezawa, Y., Drucker, D., **Engleman, E.**, Winer, D., and Dosch, H.M. (2009). Normalization of obesity-associated insulin resistance through immunotherapy: CD4+ T cells control glucose homeostasis. **Nature Med.** 15:921-929. [PMCID: PMC3063199]
b. Winer, D.A., Winer, S., Shen, L., Wadia, P.P., Yantha, J., Paltser, G., Tsui, H., Wu, P., Davidson, M.G., Alonso, M.N., Leong, H., Glassford, A., Caimol, M., Tedder, T.F., McLaughlin, T., Miklos, D.B., Dosch, H.M., and **Engleman, E.G.** (2011). B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies. **Nature Med.** 17:610-617. [PMCID: PMC3270885]
c. Shen, L., Chng, M.H.Y., Alonso, M.N., Yuan, R., Winer, D.A., and **Engleman, E.G.** (2015). B-1a Lymphocytes Attenuate Insulin Resistance. **Diabetes** 64:593–603. [PMCID: PMC4303967]
d. McLaughlin, T., Ackerman, S.E., Shen, L., and **Engleman, E.** (2017). Role of innate and adaptive immunity in obesity associated metabolic disease. **J. Clin. Invest.** 127:5-13. Epub 2017 Jan 3. [PMCID: PMC5199693]

4. Analyzing the cellular and molecular basis for immune tolerance in the setting of organ transplantation. In collaboration with the Strober laboratory at Stanford, we have been seeking to understand how immune cells and the factors they produce can be manipulated for the purpose of inducing immune tolerance to organ allografts. Together we discovered that conditioning mice or humans with total lymphoid irradiation (TLI)) induces a tolerogenic microenvironment in host lymphoid tissues that enables complete withdrawal of immunosuppressive drugs following transplantation of allogeneic organs in combination with bone marrow from the organ donor. We further discovered that tolerance induction results from complex interactions between host dendritic cells, natural killer T cells, Tregs, and Gr-1+CD11b+ myeloid cells, each of which is absolutely required for donor-host immune cell chimerism and permanent tolerance. This approach is now being evaluated in advanced clinical trials at Stanford and other centers, where more than 30 recipients of kidney allografts have been tapered off all immunosuppressive drugs without rejection episodes or serious toxicity over a median five year follow up period.

a. Scandling, J.D., Busque, S., Shizuru, J., Engleman**, E.G.** and Strober, S. (2011). Induced immune tolerance for kidney transplantation. **New England J. Med.** 365:1359-1360. [PMCID: PMC3334358]
b. Scandling, J.D., Busque, S., Dejbakhsh-Jones, S., Benike, C., Sarwal, M., Millan, M.T., Shizuru, J.A., Lowsky, R., **Engleman, E.G.**, and Strober, S. (2012). Tolerance and withdrawal of immunosuppressive drugs in patients given kidney and hematopoietic cell transplants. **Am. J. Transplant.** 12:1133-1145. Epub 2012 Mar 8. [PMCID: PMC3338901]
c. Scandling, J.D., Busque, S., Shizuru, J.A., Lowsky, R., Hoppe, R., Dejbakhsh-Jones, S., Jensen, K., Shori, A., Strober, J.A., Lavori, P., Turnbull, B.B., **Engleman, E.G.**, and Strober, S. (2015). Chimerism, graft survival, and withdrawal of immunosuppressive drugs in HLA matched and mismatched patients after living donor kidney and hematopoietic cell transplantation. **Am. J. Transplant.** 15:695-704. [PMID: 25693475]
d. Hongo, D., Tang, X., Zhang, X., **Engleman, E.G.**, and Strober, S. (2017). Tolerogenic interactions between CD8+ dendritic cells and NKT cells prevent rejection of bone marrow and organ grafts. **Blood** 129:1718-1728. [PMCID: PMC5364338]

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/edgarg..engleman.1/bibliography/41166126/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

R01 AI118884 Engleman/Strober (Co-PI) 09/01/15-08/31/20
National Institutes of Health
Role of Dendritic Cells in Mixed Chimerism and Tolerance
The goal of this project is to understand the contribution of dendritic cells to TLI/ATG induced allograft tolerance in mouse models.
Role: Co-PI

1 U54 CA209971-01 Plevritis (PI) 08/01/16-07/31/21
National Institutes of Health
Modeling the Role of Lymph Node Metastasis in Tumor-Mediated Immunosuppression
The goal of this project is to analyze interactions between tumor cells and immune cells in tumor draining lymph nodes that promote tumor metastasis.
Role: Project Leader

1 R01 CA222969 Engleman (PI) 06/01/18-05/31/23
National Institutes of Health
Targeting Dectin-2 on Tumor-associated Macrophages for the Treatment of Cancer
The major goal of this project is to analyze the immunological and anti-tumor effects of natural and synthetic Dectin-2 agonists in mouse models of cancer.

5 P30 CA124435 Mitchell (PI) 06/01/15-05/31/20
NIH/NCI
Stanford University Cancer Institute
The Institute supports basic, clinical and translational studies into the biology of cancer and the factors that contribute to its onset and growth.
Role: Co-Leader, Program on Immunology and Immunotherapy of Cancer

5 P01 HL075462 Strober (PI) 04/01/16-03/31/21
NIH/NHLBI
Blood Stem Cell Transplantation as Immunotherapy
The objective of my project is to evaluate the role of multiple immune cell types in tolerance induction.
Role: Project Leader; Core Leader

1R21HD098688-01 Engleman (PI) 04/10/19-03/31/21
National Institutes of Health
Effects of Maternal Obesity on Offspring Immune System
The major goal is to study the effects of diet induced parental obesity on the phenotype and functions of fetal monocytes.

1R01CA233958 Engleman (PI) 07/01/19-06/30/24
National Institutes of Health
Effects of FLASH Radiation on Cancer and the Immune Response
The goal of this project is to compare the immunological and therapeutic effects of focused high intensity (FLASH) tumor irradiation with conventional tumor irradiation in mouse cancer models.