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 of life-threatening diseases. At the start of my career, after establishing the Stanford Blood Center, I generated the first monoclonal antibodies to human CD4 and anti-CD8, enabling me and others to isolate CD4 and CD8 T cells and analyze their functions. I used these antibodies to 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* in patients with cancer. This work led to the development of Sipuleucel-T (Provenge) that was approved by the FDA in 2010 for the treatment of advanced prostate cancer. In 2015, my lab discovered a strategy that reprograms immunosuppressive tumor associated DCs into immunostimulatory antigen presenting cells, *in situ*, that entered clinical trials in 2021. During the past 10 years, my research has focused on understanding the cellular and molecular basis of **immune tolerance**. Toward this goal we recently completed a major effort to decipher the impact of lymph node metastasis on tumor immune tolerance and distant tumor spread. In addition to investigating ways to overcome immune tolerance for the treatment of cancer, I have collaborated with my Stanford colleagues to develop a therapy that targets lymphoid tissues with low doses of radiation to *induce* alloantigen-specific immune tolerance, enabling transplant recipients to retain their allografts without requiring immunosuppressive drugs. This therapy is now in a multicenter clinical trial for kidney transplantation. Beyond my research endeavors, 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 Mount 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, Steven Foung, Professor and Associate Chair of Pathology, Stanford University School of Medicine, Matthew Spitzer, Assistant Professor of Immunology at the University of California, San Francisco, and Nathan Reticker-Flynn, who was recently appointed Assistant Professor of Otolaryngology - Head and Neck Surgery at Stanford.

Ongoing and recently completed projects that I would like to highlight include:

P30 CA124435
Artandi (PI) Role: Co-director, Tumor Immunotherapy Research Program
06/01/22-05/31/27
Stanford University Cancer Institute

R01 CA251174
Engleman (PI)
04/01/21-03/31/26
Targeting Lymph Node Dependent Immune Tolerance in Cancer

5 P01 HL075462
Strober (PI) Role: Project Leader, Co-investigator
04/01/16-03/31/22
Blood Stem Cell Transplantation as Immunotherapy

Citations:

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, 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]
3. Ackerman, S.E., Pearson, C.I., Gregorio, J.D., Gonzalez, J.C., Kenkel, J.A., Hartmann, F.J., Luo, A., Ho, P.Y., LeBlanc, H., Blum, L.K., Kimmey, S.C., Luo, A., Nguyen, M.L., Paik, J.C., Sheu, L.Y., Ackerman, B., Lee, A., Li, H., Melrose, J., Laura, R.P., Ramani, V.C., Henning, K.A., Jackson, D.Y., Safina, B.S., Yonehiro, G., Devens, B.H., Carmi, Y., Chapin, S.J., Bendall, S.C., Kowanetz, M., Dornan, D., **Engleman, E.G.**, and Alonso, M.N. Immune-stimulating antibody conjugates elicit robust myeloid activation and durable antitumor immunity. **Nature Cancer** 2:18-33, 2021.
4. Reticker-Flynn, NE, Zhang W, Basto P, Bejnood A, Martins M, Kenkel J, Linde I, Bagchi S, Yuan R, Cheng, Tolentino L, Choi O, Wu N, Chang S, Gentles AJ, Sunwoo JB, Plevritis S, **Engleman EG.** Lymph node colonization induces tumor-immune tolerance, promoting distant metastasis. **Cell** 185, 1–19, May 26, 2022; Elsevier Inc. https://doi.org/10.1016/j.cell.2022.04.019.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2005-Present	Co-Leader, Stanford Cancer Institute Research Program in Cancer Immunotherapy
1990-Present	Professor of Pathology and Medicine, Stanford University School of Medicine.
1984-1990	Associate Professor of Pathology and Medicine, Stanford University School of Medicine.
1979-Present	Founding Director, Stanford Blood Center, Stanford University School of Medicine.
1978-2004	Attending Physician in Immunology and Rheumatology, Stanford University Medical Center.
1978-1984	Assistant Professor of Pathology and Medicine, Stanford University School of Medicine.
1976-1978	Postdoctoral Fellow in Immunogenetics and Rheumatology (H.O. McDevitt, Chief), Stanford University School of Medicine, Stanford, CA.
1973-1976	Research Associate, Laboratory of Biochemistry (ER Stadtman, Chief), NHLBI, NIH, Bethesda, MD.
1971-1973	Intern and Resident in Medicine, University of California Hospitals, San Francisco.

Honors
Recipient, Columbia University Gold Medal for Outstanding Achievements in Medical Research (2022)
Recipient, CABS K Fong Prize in Life Sciences (2017)
Recipient, Outstanding Inventor Award, Stanford University (2004)
Member, Association of American Physicians (1998)
Member, Pluto Club (Association of University Pathologists) (1984)
Member, American Society for Clinical Investigation (1982)

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 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). By demonstrating that the immunosuppressive environment could be overcome, this vaccine helped to open the way to a new era in which immunotherapies are increasingly becoming a standard component of cancer treatment. In 2015, we discovered a novel mechanism that enables arming and activating DC *in situ* in tumor-bearing hosts, based on the simultaneous delivery to tumors of tumor- binding antibodies and DC stimulating molecules. By directly linking these molecules to the tumor-binding antibodies, these immune stimulating antibody conjugates can be delivered to tumors via systemic administration. This approach is currently in a clinical trial.

    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. 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]
    c. Kenkel JA, Tseng WW, Davidson MG, Tolentino LL, Choi O, Bhattacharya N, Seeley ES, Winer DA, Reticker-Flynn NE, **Engleman E.G.** An immunosuppressive dendritic cell subset accumulates at secondary sites and promotes metastasis in pancreatic cancer. **Cancer Res.** 77:4158-4170, 2017. [PMCID: PMC5550516].

d. Ackerman, S.E., Pearson, C.I., Gregorio, J.D., Gonzalez, J.C., Kenkel, J.A., Hartmann, F.J., Luo, A., Ho, P.Y., LeBlanc, H., Blum, L.K., Kimmey, S.C., Luo, A., Nguyen, M.L., Paik, J.C., Sheu, L.Y., Ackerman, B., Lee, A., Li, H., Melrose, J., Laura, R.P., Ramani, V.C., Henning, K.A., Jackson, D.Y., Safina, B.S., Yonehiro, G., Devens, B.H., Carmi, Y., Chapin, S.J., Bendall, S.C., Kowanetz, M., Dornan, D., **Engleman, E.G.**, and Alonso, M.N. Immune-stimulating antibody conjugates elicit robust myeloid activation and durable antitumor immunity. **Nature Cancer** 2:18-33, 2021.

3. **Probing the role of the immune system in obesity associated diseases.** For the past fifteen years, my lab has been investigating the role of the immune system in obesity associated type 2 diabetes. We 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 by our discovery that B cells and autoantibodies also play a key role in the development of obesity-associated diabetes. 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. Most recently, we have begun to study the role of innate immune cells in adipose tissue inflammation and the development of obesity associated diabetes. Separately, we are also studying the mechanisms responsible for obesity associated cancers.

   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 TLI induced immune tolerance.** In collaboration with the Strober, Negrin and Myer labs 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. This work began with the discovery that conditioning mice or humans with total lymphoid irradiation (TLI) can induce 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. Subsequently, we discovered that tolerance induction results from complex cascade of cellular interactions starting with host dendritic cells (DCs), and including Tregs, natural killer T cells and Gr-1+CD11b+ myeloid cells, each of which is required for donor-host immune cell chimerism and sustained tolerance. This approach is now being evaluated in advanced clinical trials at Stanford and other centers, where more than 40 recipients of HLA-matched kidney allografts have been tapered off all immunosuppressive drugs without rejection episodes or serious toxicity over a median five year follow up period. The current proposal seeks to develop a deep understanding of the events that induce and mediate DC dependent tolerance induction with the goal of developing a more potent but still safe protocol that can induce tolerance in recipients of HLA-mismatched allografts.

   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. 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]

c. Busque S, Scandling JD, Lowsky R, Shizuru J, Jensen K, Waters J, Wu H-H, Sheehan K, Shori A, Choi O, Pham T, Fernandez Vina MA, Hoppe R, Tamaresis R, Lavori P, **Engleman EG,** Meyer E, Strober Mixed chimerism and acceptance of kidney transplants after immunosuppressive drug withdrawal. **Sci Transl Med** 12:10.eaax8863, 2020. Doi: 10.1016/scitranslmed.aax8863
d. Zhang X, Zheng P, Prestwood TR, Zhang H, Carmi Y, Tolentino LL, Wu N, Choi O, Winer D, Strober S, Kang E-S, Alonso MN, **Engleman EG**. Human regulatory dendritic cells develop from monocytes in response to signals from regulatory and helper T cells. **Frontiers in Immunol** 11:1982, 2020. [PMCID: PMC7461788]

Complete List of Published Work in MyBibliography:
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