BIOGRAPHICAL SKETCH

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NAME: Paul M. Guyre

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

POSITION TITLE: Vice President for Research and Discovery

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
Montclair State College	B.A.	06/1972	Biology
University of New Hampshire, Durham, NH	M.S.	06/1976	Microbial Genetics
University of New Hampshire, Durham, NH	Ph.D.	06/1979	Immunogenetics
Dartmouth Medical School, Hanover, NH	Post-doc.	01/1981	Physiology/Immunology

A. Personal Statement

The assembled team is fully qualified and experienced to successfully carry out the work described in this application. We are committed to developing a first-in-class monoclonal antibody that is engineered and optimized to efficiently neutralize *Sudan ebolavirus* (SUDV). We will declare success when a single dose of our antibody serves both the prophylactic and therapeutic needs of frontline medical staff. As PI on this application, my credentials include over three decades as a continuously NIH funded Professor of Microbiology and Immunology, a holder of 7 issued patents, and co-founder of Medarex – the company that developed the cancer immunotherapeutic antibodies ipilimumab/Yervoy (formerly MDX-010) and nivolumab/Opdivo (MDX-1106). Yervoy is the first therapy to prolong survival for patients with advanced melanoma, and was highlighted by the journal Science as the 2013 "Breakthrough of the Year". Relevant to this infectious disease work, Medarex also developed the even more recently approved bezlotoxumab/Zinplava (MDX-1388) for the treatment of *C. difficile*, the third Medarex-originated drug to be approved.

I have led research teams focused on mechanisms that regulate immunity to bacteria, cancer and viruses, as well as cross-functional and distributed teams focused on applied research and development.

My initial research involved culturing and quantifying antibiotic resistant bacteria from environmental sources. Subsequent directly relevant experience ranges from bacterial plasmid transfection, to the creation and testing of novel fusion proteins, to oversight of clinical trials using therapeutic candidates (bispecific antibodies) that were discovered and developed in my laboratory. As co-founder of Medarex, I was involved in many critical decisions that enabled new-to-world antibody therapies to advance through clinical trials and to FDA approval. Thus, I am very familiar with the promise as well as the challenges of translational research. Oncology was – until recently – resistant to new ideas, and immunotherapy for cancer was a revolutionary and widely disparaged concept. A similar revolution is needed to address new immunotherapeutic approaches to prevent and treat infection by the most serious viruses, including ebola.

With regard to my role as PI on this application, I believe I am very well qualified to successfully direct the work described herein. I have served as PI on numerous NIH-funded projects, on NIH study sections, and as primary mentor for undergraduate students, graduate students, and MD and PhD postdoctoral fellows. I was the founder of the Norris Cotton Cancer Center's first flow cytometry laboratory, and continue to be engaged as an advisor to Dartmouth's Immune Monitoring Laboratory. Until 2015, I was director of the immunology course for Dartmouth's Graduate Program in Experimental and Molecular Medicine. My mentees have gone on to

successful careers in industry and academia, and have won numerous awards, including a Presidential Fellowship. As an and active emeritus faculty member I continue to contribute to Dartmouth's graduate immunology courses, seminars and journal clubs. I therefore have ongoing access to the Faculty in one of the top ten NIH-funded immunology programs in the United States.

I have been advising and working with Drs. Fanger (CSO) and Reder (CEO) since they co-founded Celdara Medical in 2008, and am excited to now be fully engaged in an operational role as Vice President for Research and Discovery. My knowledge and expertise in antibody development combined with an underlying commitment to develop therapies to neglected tropical diseases will drive my personal effort on this program. This program is an exciting and novel approach with outstanding scientific merit and promise.

The current application builds logically upon facets of my prior experience that integrate microbiology, immunology and physiology-- as noted by publications listed below.

1. Yeager MP, Colacchio TA, Yu CT, Hildebrandt L, Howell AL, Weiss J, Guyre PM. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. Anesthesiology. 1995 Sep;83(3):500-8. PubMed PMID:7661350.
2. Howell AL, Guyre PM, You K, Fanger MW. Targeting HIV-1 to Fc gamma R on human phagocytes via bispecific antibodies reduces infectivity of HIV-1 to T cells. J Leukoc Biol. 1994 Mar;55(3):385-91. PubMed PMID: 8120455.
3. Fanger MW, Morganelli PM, Guyre PM. Bispecific antibodies. Crit Rev Immunol.1992;12(3-4):101-24. Review. PubMed PMID: 1476620.
4. Guyre PM, Zsigray RM, Collins WM, Dunlop WR. Major histocompatibility complex (B): effect on the response of chickens to a second challenge with rous sarcoma virus. Poult Sci. 1982 May;61(5):829-34. PubMed PMID: 6285325.

B. Positions and Honors

Positions and Employment

1981-1987	Assistant Professor of Physiology, Dartmouth Medical School, Hanover, NH
1981-1992	Founding Director, Flow Cytometry Laboratory, Dartmouth Medical School, Hanover, NH
1987	Cofounder, Medarex, Inc.
1987-1992	Associate Professor of Microbiology and Immunology, and of Physiology, Dartmouth Medical School, Hanover, NH
1992-2010	Co-Director, Herbert C. Englert Cell Analysis Laboratories, Norris Cotton Cancer Center, Hanover and Lebanon, NH
1992-2013	Professor of Microbiology and Immunology, and of Physiology, Dartmouth Medical School
2013-present	33% effort, Professor Microbiology and Immunology, Dartmouth Medical School
2013-present	67% effort, Vice President for Research and Discovery, Celdara Medical, LLC
2017-present	Vice President for Research and Discovery, Celdara Medical, LLC

Other Experience and Professional Memberships

1985	Society for Analytical Cytology
1981	American Association of Immunologists
1987	Society for Leukocyte Biology
1981-present	Primary mentor to 12 graduate students, 11 postdoctoral fellows, 12 junior faculty and 18 undergraduate students.

C. Contribution to Science

My most significant scientific contributions to date have focused on how steroid-cytokine interactions influence both antigen-presentation and effector functions of macrophages and dendritic cells. Research in my lab has elucidated key mechanisms relating to: (i) the regulation and function of human leukocyte receptors, primarily Fc-gamma and scavenger receptors; and (ii) how hormones and cytokines influence antigen uptake and

presentation as well as inflammatory processes involving monocytes, macrophages, dendritic cells, and neutrophils.

C.1. Cytokine and hormone regulation of human leukocyte Fc receptors. Early in my career I led studies identifying gamma interferon as the active Fc receptor augmenting factor that we had detected in supernatants of activated T cells. A surprising finding was that IFN-γ-induced upregulation of the high affinity Fcγ receptor CD64 was not inhibited by corticosteroids. This led to the overarching hypothesis that glucocorticoids can mediate either stimulation or inhibition of immune responses, depending upon both dose and timing. Our *Endocrine Reviews* article (reference d below) has now been cited over 2000 times.

a) **Guyre PM**, Crabtree GR, Bodwell JE, Munck A. MLC-conditioned media stimulate an increase in Fc receptors on human macrophages. J Immunol. 1981;126(2):666-8. PubMed PMID: 6450248.
b) **Guyre PM**, Morganelli PM, Miller R. Recombinant immune interferon increases immunoglobulin G Fc receptors on cultured human mononuclear phagocytes. J Clin Invest. 1983;72(1):393-7. PubMed PMID: 6192145; PMCID: PMC1129195.
c) Girard MT, Hjaltadottir S, Fejes-Toth AN, **Guyre PM**. Glucocorticoids enhance the gamma-interferon augmentation of human monocyte immunoglobulin G Fc receptor expression. J Immunol. 1987;138(10):3235-41. PubMed PMID: 2952714.
d) Munck A, **Guyre PM**, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev. 1984;5(1):25-44. doi: 10.1210/edrv-5-1-25. PubMed PMID: 6368214.

C.2. Monoclonal antibody production and early application to Immunotherapy. The first monoclonal antibodies to the high affinity Fcγ receptor were produced in my laboratory using a strategy that selected for antibodies binding outside the ligand-binding domain of CD64. This led to creation and testing of novel bispecific antibodies (BsAbs) that triggered phagocytosis and antibody-dependent cytotoxicity that was not inhibited by serum IgG. Although these BsAbs showed some promise in the clinic, they were abandoned due to manufacturing difficulties and the rapid progress toward production of clinical grade human monoclonals.

a) Anderson CL, **Guyre PM**, Whitin JC, Ryan DH, Looney RJ, Fanger MW. Monoclonal antibodies to Fc receptors for IgG on human mononuclear phagocytes. Antibody characterization and induction of superoxide production in a monocyte cell line. J Biol Chem. 1986;261(27):12856-64. PubMed PMID: 3017990.
b) Shen L, **Guyre PM**, Anderson CL, Fanger MW. Heteroantibody-mediated cytotoxicity: antibody to the high affinity Fc receptor for IgG mediates cytotoxicity by human monocytes that is enhanced by interferon-gamma and is not blocked by human IgG. J Immunol. 1986;137(11):3378-82. PubMed PMID: 2946759.
c) Graziano RF, Tempest PR, White P, Keler T, Deo Y, Ghebremariam H, Coleman K, Pfefferkorn LC, Fanger MW, **Guyre PM**. Construction and characterization of a humanized anti-gamma-Ig receptor type I (Fc gamma RI) monoclonal antibody. J Immunol. 1995;155(10):4996-5002. PubMed PMID: 7594506.
d) Valone FH, Kaufman PA, **Guyre PM**, Lewis LD, Memoli V, Deo Y, Graziano R, Fisher JL, Meyer L, Mrozek-Orlowski M, et al. Phase Ia/Ib trial of bispecific antibody MDX-210 in patients with advanced breast or ovarian cancer that overexpresses the proto-oncogene HER-2/neu. J Clin Oncol. 1995;13(9):2281-92. PubMed PMID: 7545221.

C.3. Discovery and Clinical Application of M2 Macrophage Scavenger Receptor CD163. The hemoglobin-haptoglobin scavenger receptor CD163 was originally identified as "p155" using monoclonal antibodies that were generated against human monocytes following differentiation in the presence of IFN-γ and dexamethasone. Many studies have now shown CD163 to be upregulated by IL-10, TGF-β □□□ glucocorticoids, and to be shed by metalloproteinases that are activated when macrophages are exposed to bacterial endotoxin. Macrophage CD163 is commonly cited as the most reliable "M2" macrophage marker, and over 150 reports cite elevation of soluble CD163 in serum to be a hallmark of many inflammatory diseases.

a) Morganelli PM, **Guyre PM**. IFN-gamma plus glucocorticoids stimulate the expression of a newly identified human mononuclear phagocyte-specific antigen. J Immunol. 1988;140(7):2296-304. PubMed PMID: 2450916.
b) Weaver LK, Hintz-Goldstein KA, Pioli PA, Wardwell K, Qureshi N, Vogel SN, **Guyre PM**. Pivotal advance: activation of cell surface Toll-like receptors causes shedding of the hemoglobin scavenger receptor CD163. J Leukoc Biol. 2006;80(1):26-35. doi: 10.1189/jlb.1205756. PubMed PMID: 16799153.
c) Goldstein JI, Goldstein KA, Wardwell K, Fahrner SL, Goonan KE, Cheney MD, Yeager MP, **Guyre PM**. Increase in plasma and surface CD163 levels in patients undergoing coronary artery bypass graft surgery. Atherosclerosis. 2003;170(2):325-32. PubMed PMID: 14612214.
d) Yeager MP, Pioli PA, Wardwell K, Beach ML, Martel P, Lee HK, Rassias AJ, **Guyre PM**. In vivo exposure to high or low cortisol has biphasic effects on inflammatory response pathways of human monocytes. Anesth Analg. 2008;107(5):1726-34. doi: 10.1213/ane.0b013e3181875fb0. PubMed PMID: 18931239; PMCID: PMC2819142.

C.4. Identification of Annexin 1 binding to human leukocytes. Annexin 1, previously known as lipocortin 1, is a glucocorticoid-induced protein with important antiinflammatory and immunomodulatory functions. Our early work has led to many studies identifying Annexin-A1 as a pivotal regulator of the innate and adaptive immune systems, and most recently as a glucocorticoid-inducible protein that modulates inflammatory pain.

a) Goulding NJ, **Guyre PM**. Glucocorticoids, lipocortins and the immune response. Curr Opin Immunol. 1993;5(1):108-13. PubMed PMID: 8452667.
b) Goulding NJ, Luying P, **Guyre PM**. Characteristics of lipocortin 1 binding to the surface of human peripheral blood leucocytes. Biochem Soc Trans. 1990;18(6):1237-8. PubMed PMID: 2150953.
c) Goulding NJ, Jefferiss CM, Pan L, Rigby WF, **Guyre PM**. Specific binding of lipocortin-1 (annexin I) to monocytes and neutrophils is decreased in rheumatoid arthritis. Arthritis Rheum. 1992;35(11):1395-7. PubMed PMID: 1445462.
d) Goulding NJ, **Guyre PM**. Lipocortin 1 binding to human leukocytes correlates with its ability to inhibit IgG interactions with Fc gamma receptors. Biochem Biophys Res Commun. 1993;192(2):351-8. doi: 10.1006/bbrc.1993.1422. PubMed PMID: 8484747.

C.5. Paradigm-shifting analysis of how glucocorticoids affect immune function. Glucocorticoids (GCs) are widely understood to suppress inflammation through their regulation of signaling pathways in leukocytes and other effector cells. Until recently, these potent and clinically important effects of GCs have obscured results from early research that documented GC stimulation of *in vivo* defense mechanisms. We have shown that a 6-hour *in vivo* exposure of healthy humans to cortisol levels that mimic the physiological stress-induced rise that follows a car crash or lion bite, induce a substantial increase in the pro-inflammatory response to a subsequent challenge with bacterial endotoxin. In those studies, "stress cortisol" pretreatment resulted in increased serum TNF-α and IL-6, as well as reduced serum IL-10 during subsequent endotoxemia.

a) Yeager MP, Rassias AJ, Pioli PA, Beach ML, Wardwell K, Collins JE, Lee HK, **Guyre PM**. Pretreatment with stress cortisol enhances the human systemic inflammatory response to bacterial endotoxin. Crit Care Med. 2009;37(10):2727-32. PubMed PMID: 19885996; PMCID: PMC2819133.
b) Yeager MP, Rassias AJ, Fillinger MP, Discipio AW, Gloor KE, Gregory JA, **Guyre PM**. Cortisol antiinflammatory effects are maximal at postoperative plasma concentrations. Crit Care Med. 2005;33(7):1507-12. PubMed PMID: 16003055.
c) Yeager MP, Pioli PA, **Guyre PM**. Cortisol exerts bi-phasic regulation of inflammation in humans. Dose Response. 2011;9(3):332-47. doi: 10.2203/dose-response.10-013.Yeager. PubMed PMID: 22013396; PMCID: PMC3186928.
d) Yeager MP, Pioli PA, Collins J, Barr F, Metzler S, Sites BD, Guyre PM. Glucocorticoids enhance the in vivo migratory response of human monocytes. Brain Behav Immun. 2016 May;54:86-94. doi: 10.1016/j.bbi.2016.01.004. PubMed PMID:26790757; PubMed Central PMCID: PMC4828285.

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