BIOGRAPHICAL SKETCH

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NAME: Lewis, George

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

POSITION TITLE: Director, Division of Vaccine Research

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
University of Mississippi, Oxford, Mississippi	BS	06/1970	Biology
University of Mississippi, Oxford, Mississippi	PHD	06/1974	Immunology with Prof. Julius M. Cruse
University of California San Francisco, San Francisico, California	NIH training grant	06/1977	University of California San Francisco, San Francisico, California

A. Personal Statement

I am the Robert C. Gallo, MD, Distinguished Professor of Microbiology and Immunology and Translational Medicine, Deputy Director of the Institute of Human Virology (IHV), and Director of the IHV Division of Vaccine Research at the University of Maryland. Our team is pursuing the concept that antibody specificity contributes significantly to the potency of Fc- mediated effector functions. This work has led to a quantitative metric for assigning relative potency for antibodies that mediate ADCC, which led to the functional structural definition of a major ADCC hotspot on p120, Epitope Cluster A. I have a strong background in chemistry as well as biology that was essential for these studies. This body of work provided some of the earliest information about the B cell subsets responding to T-independent vs. T-dependent antigens as a function of antigen structure. In addition, we developed methods to map the specificities of antigen specific T cell responses using the synthetic immunogen azobenzenearsonate-L-tyrosine. My group also contributed new information on the genetic basis of antibody production by dominant B cell clones in this system. Shortly after the discovery of HIV-1 as the cause of AIDS, I shifted my research to HIV-1 vaccine development that continues to date. My group has maintained a long-standing interest in the nature of protective antibodies to HIV-1 and their cognate epitopes. We isolated and characterized some of the first monoclonal antibodies, mAbs, against the HIV-1 envelope glycoprotein, which have proven valuable for many groups over the years. We have followed these studies up with a renewed effort to understand the relationships among antibody specificity, neutralization, and Fc-mediated effector function. These efforts are detailed in our most recent publications. Most importantly, we contributed to the correlates of protection analysis in RV144 and are evaluating the structural basis of Fc-mediated effector function against epitopes that are apparent targets of protective antibodies, which continues to be our major research focus. I will participate in the structural and functional aspects of this project.

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

Grant# 30021141/3002114
Defense Threat Reduction Agency (US Military)
Lewis (PI)
02/01/2021-01/31/2024
Discovery And Development of Small Molecule and Antibody Therapeutics Using Artificial Intelligence And Machine Learning

1 P01 AI120756
Tomaras (PI), Role: Project 1, Co- Leader with Anthony L. DeVico (Leader)
05/01/2016-04/30/2022
Fc-gamma receptor function in humans and non-human primates.

Citations

1. Orlandi C, Deredge D, Ray K, Gohain N, Tolbert W, DeVico AL, Wintrode P, Pazgier M, **Lewis GK.** Antigen-Induced Allosteric Changes in a Human IgG1 Fc Increase Low-Affinity Fcγ Receptor Binding. Structure. 2020 May 5;28(5):516-527.e5. PubMed PMID: 32209433; PubMed Central PMCID: PMC7288244.
2. Tolbert WD, Gohain N, Veillette M, Chapleau JP, Orlandi C, Visciano ML, Ebadi M, DeVico AL, Fouts TR, Finzi A, **Lewis GK,** Pazgier M. Paring Down HIV Env: Design and Crystal Structure of a Stabilized Inner Domain of HIV-1 gp120 Displaying a Major ADCC Target of the A32 Region. Structure. 2016 May 3;24(5):697-709. PubMed PMID: 27041594; PubMed Central PMCID: PMC4856543.
3. Gohain N, Tolbert WD, Acharya P, Yu L, Liu T, Zhao P, Orlandi C, Visciano ML, Kamin-Lewis R, Sajadi MM, Martin L, Robinson JE, Kwong PD, DeVico AL, Ray K, **Lewis GK,** Pazgier M. Cocrystal Structures of Antibody N60-i3 and Antibody JR4 in Complex with gp120 Define More Cluster A Epitopes Involved in Effective Antibody-Dependent Effector Function against HIV-1. J Virol. 2015 Sep;89(17):8840-54. PubMed PMID: 26085162; PubMed Central PMCID: PMC4524080.
4. Guan Y, Pazgier M, Sajadi MM, Kamin-Lewis R, Al-Darmarki S, Flinko R, Lovo E, Wu X, Robinson JE, Seaman MS, Fouts TR, Gallo RC, DeVico AL, **Lewis GK**. Diverse specificity and effector function among human antibodies to HIV-1 envelope glycoprotein epitopes exposed by CD4 binding. Proc Natl Acad Sci U S A. 2013 Jan 2;110(1):E69-78. PubMed PMID: 23237851; PubMed Central PMCID: PMC3538257.

B. Positions and Honors

Positions and Employment

1977 - 1979 Assistant Research Immunologist, University of California San Francisco, Department of Microbiology and Immunology, San Francisco, CA
1979 - 1984 Assistant Professor in Residence, University of California San Francisco, Department of Microbiology and Immunology, San Francisco, CA
1984 - 1994 Associate Professor, University of Maryland School of Medicine, Department of Microbiology and Immunology, Baltimore, MD
1994 - Professor, University of Maryland School of Medicine, Department of Microbiology and Immunology, Baltimore, MD
1996 - Director, Division of Vaccine Research, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD
1997 - 2007 Professor, University of Maryland Biotechnology Institute, Baltimore, MD

Other Experience and Professional Memberships (selected)

1978 - Member, American Association of Immunologists
1996 - Member, American Society of Microbiology

Honors

1966 Faculty Scholar , University of Mississippi
1970 Member, Phi Kappa Phi, National Scholastic Honorary
1970 Graduate Fellowship, University of Mississippi
1974 Postdoctoral Fellowship (T32), National Institutes of Health
1977 Postdoctoral Fellowship (Individual), National Institutes of Health
1983 Faculty Research Award, FRA-254, American Cancer Society
1997 IDSRRC Study Section, Charter Member, National Institutes of Health
2000 AIDSRRC Study Section, Chairperson, National Institutes of Health
2003 MIDRC Study Section, Member, National Institutes of Health
2003 MIDRC Study Section, Chairperson, National Institutes of Health

2013 AIP Study Section, Member, National Institutes of Health
2016 AIDS Vaccine Research Subcommittee, NIAID, NIH
2017 The Robert C. Gallo, M.D., Professor in Translational Medicine, University of Maryland School of Medicine
2020 Chairperson, MHRP Scientific Advisory Board
2021 NIAID/NIH Vaccine Research Center Board of Advisors

C. Contributions to Science

1. In recent years my principal research interest has turned to the role of antibody specificity in Fc- mediated effector function. Our collaborative team provided the first rigorously controlled studies on the relationship between antibody specificity and Fc-mediated effector function. This work has led to some of the first physical chemical data on how differences antibody binding angles to a single epitope on target cells determines the potency of antibody-dependent cellular cytotoxicity (ADCC).

   a. Guan Y, Pazgier M, Sajadi MM, Kamin-Lewis R, Al-Darmarki S, Flinko R, Lovo E, Wu X, Robinson JE, Seaman MS, Fouts TR, Gallo RC, DeVico AL, **Lewis GK**. Diverse specificity and effector function among human antibodies to HIV-1 envelope glycoprotein epitopes exposed by CD4 binding. Proc Natl Acad Sci U S A. 2013 Jan 2;110(1):E69-78. PubMed PMID: 23237851; PubMed Central PMCID: PMC3538257.
   b. Acharya P, Tolbert WD, Gohain N, Wu X, Yu L, Liu T, Huang W, Huang CC, Kwon YD, Louder RK, Luongo TS, McLellan JS, Pancera M, Yang Y, Zhang B, Flinko R, Foulke JS Jr, Sajadi MM, Kamin-Lewis R, Robinson JE, Martin L, Kwong PD, Guan Y, DeVico AL, **Lewis GK**, Pazgier M. Structural definition of an antibody-dependent cellular cytotoxicity response implicated in reduced risk for HIV-1 infection. J Virol. 2014 Nov;88(21):12895-906. PubMed PMID: 25165110; PubMed Central PMCID: PMC4248932.
   c. Mengistu M, Ray K, **Lewis GK**, DeVico AL. Antigenic properties of the human immunodeficiency virus envelope glycoprotein gp120 on virions bound to target cells. PLoS Pathog. 2015 Mar;11(3):e1004772. PubMed PMID: 25807494; PubMed Central PMCID: PMC4373872.
   d. Gohain N, Tolbert WD, Acharya P, Yu L, Liu T, Zhao P, Orlandi C, Visciano ML, Kamin-Lewis R, Sajadi MM, Martin L, Robinson JE, Kwong PD, DeVico AL, Ray K, **Lewis GK**, Pazgier M. Cocrystal Structures of Antibody N60-i3 and Antibody JR4 in Complex with gp120 Define More Cluster A Epitopes Involved in Effective Antibody-Dependent Effector Function against HIV-1. J Virol. 2015 Sep;89(17):8840-54. PubMed PMID: 26085162; PubMed Central PMCID: PMC4524080.

2. Our group has published some of the earliest work on the poor durability of anti-p120 antibody responses. Interest in this problem began in 1989 when we first made murine monoclonal antibodies to gp120. I spent much of the early part of my career designing synthetic antigens and evaluating their immunogenicity in mice to define the rules of immunogenicity. This work provided excellent practical knowledge of the durability of murine antibody responses to strongly immunogenic proteins and synthetic antigens. When my group turned to HIV research in 1987, there were few anti-gp120 mAbs available, so we immunized mice with gp120 preparations to make hybridomas. We saw immediately that these antibody responses did not last as long as conventional immunogens. We found that wild-type cholera toxin improved the durability of anti-gp120 responses in mice and spent a number of years studying its ability to active human cells. Unfortunately, this effect did not extend to rhesus macaques and we continue to work on the problem in our clinical trials of the FLSC immunogen.

   a. Bagley KC, Shata MT, Onyabe DY, DeVico AL, Fouts TR, **Lewis GK**, Hone DM. Immunogenicity of DNA vaccines that direct the coincident expression of the 120 kDa glycoprotein of human immunodeficiency virus and the catalytic domain of cholera toxin. Vaccine. 2003 Jul 4;21(23):3335-41. PubMed PMID: 12804865.
   b. Bagley KC, Abdelwahab SF, Tuskan RG, **Lewis GK**. An enzymatically active a domain is required for cholera-like enterotoxins to induce a long-lived blockade on the induction of oral tolerance: new method for screening mucosal adjuvants. Infect Immun. 2003 Dec;71(12):6850-6. PubMed PMID: 14638772; PubMed Central PMCID: PMC308947.
   c. Bagley KC, Abdelwahab SF, Tuskan RG, **Lewis GK**. Calcium signaling through phospholipase C activates dendritic cells to mature and is necessary for the activation and maturation of dendritic cells induced by diverse agonists. Clin Diagn Lab Immunol. 2004 Jan;11(1):77-82. PubMed PMID: 14715548; PubMed Central PMCID: PMC321351.

d. **Lewis GK**, DeVico AL, Gallo RC. Antibody persistence and T-cell balance: two key factors confronting HIV vaccine development. Proc Natl Acad Sci U S A. 2014 Nov 4;111(44):15614-21. PubMed PMID: 25349379; PubMed Central PMCID: PMC4226080.

3. As a postdoctoral fellow, I published some of the first studies showing that different B cell subsets respond to T-dependent and T-independent antigens. This work provided key elements in the definition of B cell subsets for what are now T-dependent, TI-1, and TI-2 antigens.

   a. **Lewis GK**, Ranken R, Nitecki DE, Goodman JW. Murine B-cell subpopulations responsive to T-dependent and T-independent antigens. J Exp Med. 1976 Aug 1;144(2):382-97. PubMed PMID: 1085326; PubMed Central PMCID: PMC2190386.
   b. **Lewis GK**, Ranken R, Goodman JW. Complement-dependent and -independent pathways of T cell-B cell cooperation. J Immunol. 1977 May;118(5):1744-7. PubMed PMID: 323359.
   c. **Lewis GK**, Goodman JW. Carrier-directed anti-hapten responses by B-cell subsets. J Exp Med. 1977 Jul 1;146(1):1-10. PubMed PMID: 68986; PubMed Central PMCID: PMC2180734.
   d. **Lewis GK**, Goodman JW, Ranken R. Activation of B cell subsets by T-dependent and T- independent antigens. Adv Exp Med Biol. 1978;98:339-56. PubMed PMID: 309712.

4. As a young faculty member at UCSF, my group published the first studies of T cell antigen receptor fine specificity at the clonal level. These studies used CD4+ T cell clones isolated from inbred mice immunized with azobenzene-arsonate-L-Tyrosine, which was the only chemically characterized T cell epitope known at that time. Using a set of structural analogs we showed that T cell receptors could discriminate structures that differ by as little as a methyl group. Further, in collaboration with Joel Goodman, we mapped the structural subregion of ABA-Tyrosine that binds to Class IIMHC.

   a. Hertel-Wulff B, Goodman JW, Fathman CG, **Lewis GK**. Arsonate-specific murine T cell clones. I. Genetic control and antigen specificity. J Exp Med. 1983 Mar 1;157(3):987-97. PubMed PMID: 6187883; PubMed Central PMCID: PMC2186958.
   b. Godfrey WL, **Lewis GK**, Goodman JW. The anatomy of an antigen molecule: functional subregions of L-tyrosine-p-azobenzenearsonate. Mol Immunol. 1984 Oct;21(10):969-78. PubMed PMID: 6209567.
   c. Morita CT, Goodman JW, **Lewis GK**. Arsonate-specific murine T cell clones. II. Delayed-type hypersensitivity induced by P-azobenzenearsonate-L-tyrosine (ABA-Tyr). J Immunol. 1985 May;134(5):2894-9. PubMed PMID: 2580007.
   d. Morita CT, Godfrey WL, Goodman JW, **Lewis GK**. Arsonate-specific murine T cell clones. III. Correlation between clonotype expression and fine specificity for analogs of L-tyrosine-p- azobenzenearsonate. J Immunol. 1986 Oct 1;137(7):2139-44. PubMed PMID: 2428862.

Complete List of Published Work in MyBibliography:
http://1.usa.gov/1YfICV3