BIOGRAPHICAL SKETCH

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NAME: LATTIME, EDMUND CHARLES

eRA COMMONS USERNAME (credential, e.g., agency login): lattime

POSITION TITLE: Associate Director for Education and Training

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
Gettysburg College, Gettysburg, PA	BA	01/1973	Biology
Rutgers University, Newark, NJ	PHD	07/1977	Immunology
Sloan-Kettering Institute, New York, NJ	Postdoctoral Fellow	07/1979	Immunology

A. Personal Statement

For more than 20 years, the focus of research in my group has been on the interaction of the immune response and tumors, addressing the question of immune escape mechanisms. Increasingly, our efforts have been studying mechanisms active in the tumor microenvironment (TME). Our preclinical studies have led to several translational trials in bladder cancer, melanoma, and most recently pancreas cancer. Our group pioneered the modulation of the tumor microenvironment via gene transfer using poxvirus vectors. We took our first-in-class oncolytic Vaccinia-GMCSF construct from preclinical to clinical studies and the resultant patents have been licensed by Jennerex Biotherapeutics and SillaJen with the agent (Pexa-Vec) including a Phase 3 trial for hepatocellular cancer. Our preclinical findings that a vigorous tumor specific T cell response in the tumor microenvironment (balanced by localized immune suppression by Treg and MDSC populations) coincided with systemic anergy to tumor and antigen-encoding vaccine led us to immunize via the TME using our recombinant poxviral vaccine platform with resultant systemic T cell response and antitumor activity. We translated these findings to NCI/CTEP- supported first-in-man Phase I trials of intravesical poxvirus-GMCSF in invasive bladder cancer demonstrating the ability to "immunize" at the bladder site and more recently intratumoral poxvirus vaccine in patients with locally advanced pancreatic cancer resulting in a demonstration of significant effectiveness in preventing liver metastasis. Clinically, we are finalizing the design of a neoadjuvant trial of intratumoral poxviral vaccine in resectable pancreatic cancer patients to determine if the antimetastatic effects seen in the locally advanced trial will translate to clinical benefit in earlier disease. Administratively, I serve as Associate Director for Education and Training at Rutgers Cancer Institute of New Jersey (Rutgers Cancer Institute). In this role, I have been responsible for overseeing the development of all Rutgers Cancer Institute Training Programs. Most recently, I have led the faculty mentoring and development initiative at Rutgers Cancer Institute. Extramurally, I serve as Chair of the ECOG (ECOG-ACRIN) Laboratory Science and Pathology Committee (Co-chair 2003-2019) and am the co-chair of the ECOG-ACRIN Immune Strategy Biomarker Group (ISBG). I am a member of the External Advisory Board of the Roswell Park Cancer Center.

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

827464 NET Foundation Peterson Accelerator Award
Libutti (PI), Role: Co-Investigator
01/03/2020-01/02/2024
The role of the B7x pathway in the progression of neuroendocrine tumors

R01CA243547
Ganesan/Lattime/White (MPI)
02/01/2019-11/30/2024
Impact of Mutation Burden on Cancer Growth and the Immune Landscape

R01CA247652-01A1
Chang, Zamboni (Contact PI), Libutti (MPI), Role: Co-Investigator
04/01/2021-03/31/2026
Minibeam Radiation Therapy Enhanced Delivery of Nanoparticle Anticancer Agents to Pancreatic Cancer Tumors

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2022	Member, NIH NCATS Review Panel for Training Grants
2020 -	Member, National Clinical Trials Network (NCTN) Core Correlative Sciences Committee
2002 -	Member, American Society of Clinical Oncology
1998 -	Professor (with tenure), Department of Surgery, Rutgers-Robert Wood Johnson Medical School
1998 -	Professor, Department of Biochemistry and Molecular Biology, (Previously Molecular Genetics, Microbiology, & Immunology), Rutgers-Robert Wood Johnson Medical School
1998 -	Associate Director for Education and Training Programs, Rutgers Cancer Institute of New Jersey
1986 -	Member, American Association for Cancer Research
1981 -	Member, American Association of Immunologists
1976 -	Member, American Chemical Society, Division of Medicinal Chemistry
2020 - 2021	Chair, NIH NCATS Review Panel Clinical and Translational Research Award (CTSA)
2020 - 2021	Program Leader, Cancer Metabolism and Growth, Rutgers Cancer Institute of New Jersey
2019 - 2019	Chair, NIH Mutant Mouse U42 Center Review Panel
2019 - 2019	Member, NCI UE5 Short Course Review Panel
2019 - 2019	Chair, NCI R21 Immunotherapy Special Emphasis Panel
2018 - 2018	Chair, NCI Biden Moonshot Review Panel, Immunology, and Immunotherapy
2017 - 2017	Member, NIH NCATS Review Panel Clinical and Translational Research Award (CTSA)
2017 - 2017	Co-Chair, NIH Oncological Sciences Fellowship Study Section
2016 - 2016	Chair, NCI CSR Special Emphasis Panel, Member Conflict Cancer Immunotherapy
2016 - 2016	Chair, NIH NCATS Review Panel Clinical and Translational Research Award (CTSA)
2016 - 2016	Chair, NIH IDeA States Pediatric Clinical Trials Network and Data Coordinating and Operations Center (DCOC) Special Emphasis Panel
2016 - 2016	Member, NIH Intramural Site visit team National Institute on Deafness and Other Communication Disorders
2016 - 2016	Member, NIH NCATS Special Emphasis Panel, Preclinical Research Based on Existing Repurposing Tools
2016 - 2016	Member, Site Visit Team, NCI Intramural Laboratory of Genitourinary Cancer Pathogenesis
2014 - 2016	Chair, NCI R21 Immunotherapy Special Emphasis Panel
2013 - 2015	Reviewer, AACR Special Grants Program
2014 - 2014	Member, NCI Intramural Program Review Laboratory of Tumor Immunology and Biology
2014 - 2014	Chair, NCI K01, K22 Study Section for Mentored and Transition Awards to Promote Diversity
2013 - 2014	Member, NCI R21 Immunotherapy Special Emphasis Panel
2011 - 2014	Member, National Cancer Institute Subcommittee F, Manpower, and Training Committee
2008 - 2014	Deputy Director, Rutgers Cancer Institute of New Jersey
1998 - 2014	Director, Surgical Oncology Research, Department of Surgery, Rutgers-Robert Wood Johnson Medical School
2013 - 2013	Chair, NIH U54 Rare Disease Clinical Research Consortia (RDCRC)
2013 - 2013	Member, NCI Lasker Clinical Research Scholars Program Review
2011 - 2011	Chair, National Cancer Institute Subcommittee F SEP, Institutional Training & Education Review
2010 - 2010	Ad hoc Member, National Cancer Institute Subcommittee A

2009 - 2010 Chair, NIH-NCRR COBRE Review Panel
2009 - 2009 Chair, NIH-NCRR Panel for mouse biorepositories
2009 - 2009 Senior Editor, NCI Challenge Grants
2008 - 2008 Ad hoc Site Visit Team, NCI, Centers Branch
2006 - 2008 Chair, NCI Cancer Immunopathology, and Immunotherapy (CII) Study Section
2007 - 2007 Chair, NIH Roadmap Interdisciplinary Research Consortium (U54) Review Special Emphasis Panel
2006 - 2006 Ad hoc, NCI Subcommittee F Manpower and Training Study Section
2003 - 2006 Ad hoc, NCI Cancer Immunopathology and Immunotherapy (CII) Study Section
2003 - 2005 Member, NCI/BRB Oversight Committee
1999 - 2003 Member and Chair, NIH SBIR Study Section in Oncology
1995 - 1999 Member, USPHS/NCI Experimental Therapeutics II (ET2) Study Section
1995 - 1999 Member, Am. Cancer Soc. Immunology, and Immunotherapy Study Section
1995 - 1998 Professor (with tenure), Department of Medicine, Division of Neoplastic Diseases, Thomas Jefferson Medical College
1995 - 1998 Professor, Department of Microbiology and Immunology, Thomas Jefferson University
1991 - 1998 Member, Jefferson Cancer Institute, Thomas Jefferson University
1990 - 1995 Associate Professor, Department of Microbiology and Immunology, Thomas Jefferson University
1989 - 1995 Associate Professor, Department of Medicine, Division of Neoplastic Diseases, Thomas Jefferson Medical College
1989 - 1989 Associate Laboratory Member, Immunology Program, Sloan-Kettering Institute for Cancer Research
1985 - 1989 Assistant Laboratory Member, Immunology Program, Sloan-Kettering Institute for Cancer Research
1979 - 1984 Research Associate, Cellular Immunology, Sloan-Kettering Institute for Cancer Research

Honors

1984 - 1989 Scholar Award, Leukemia Society of America
1979 - 1982 Young Investigator Award, National Cancer Institute

C. Contribution to Science

1. **The role of TNF and adaptive immunity in antitumor selection:** First as a postdoc with Osias Stutman and then as faculty at MSKCC collaborating with Stutman, my group focusing on the role of the innate and adaptive immune response in-vitro and in-vivo in antitumor activity and immune "selection". Osias had first identified an activity that he termed as due Natural Cytotoxic Cells (NC). Together, we further characterized their lineage (multiple) and activity later shown to be due to TNF. In collaboration, we further characterized the cells and activity in murine and then human cells and were the first to propose their mechanism(s) of recognition. These studies led us to our seminal finding that NC elicited TNF had significant activity in selecting for TNF resistance in vivo and importantly when comparing immunocompetent and nu/nu mice that in the presence of adaptive immunity led to selection for increased tumorigenicity (multiple logs). Together these studies paved the way for our major focus on the modulation of the tumor microenvironment in immune escape.

    a. **Lattime EC**, Stutman O. Tumor growth in vivo selects for resistance to tumor necrosis factor. J Immunol. 1989 Dec 15;143(12):4317-23. PubMed PMID: 2592776.
    b. **Lattime EC**, Stoppacciaro A, Khan A, Stutman O. Human natural cytotoxic activity mediated by tumor necrosis factor: regulation by interleukin-2. J Natl Cancer Inst. 1988 Sep 7;80(13):1035-8. PubMed PMID: 2457708.
    c. **Lattime EC**, Pecoraro GA, Stutman O. Natural cytotoxic cells against solid tumors in mice. III. A comparison of effector cell antigenic phenotype and target cell recognition structures with those of NK cells. J Immunol. 1981 May;126(5):2011-4. PubMed PMID: 7217680.

d. Stutman O, Dien P, Wisun RE, **Lattime EC**. Natural cytotoxic cells against solid tumors in mice: blocking of cytotoxicity by D-mannose. Proc Natl Acad Sci U S A. 1980 May;77(5):2895-8. PubMed Central PMCID: PMC349512.

2. **Characterizing and modulating the cytokine milieu in solid tumors:** In dissecting cytokine profiles in the tumor microenvironment as indications of the tumor-immune interaction, we found a significant overexpression of IL10 mRNA in 24/25 biopsies of patient melanoma and a similar fraction of locally advanced bladder cancer with significant IL10 protein production seen in explanted melanoma. We were the first to show this and it led to studies investigating the known properties of IL10 in the regulation of adaptive immunity. Using murine models of bladder cancer, we found that tumor associated IL10 produced a state of non-recognition of tumor and anergy to what was an effective systemic vaccine strategy in naïve mice. Further studies identified that the anergy was associated with a significant systemic inhibition of dendritic cell function and thus adaptive immunity. We demonstrated using IL10 knockout mice that this was restored with positive antitumor responses and the generation of systemic immunity. Given the pivotal role of DC maturation in the downstream sequellae of IL10, this and studies from others led us to hypothesize that a gene therapy approach to providing GM-CSF to the tumor microenvironment might recruit and activate DC and this be effective in reversing the IL10 based anergy.

    a. Yang AS, **Lattime EC**. Tumor-induced interleukin 10 suppresses the ability of splenic dendritic cells to stimulate CD4 and CD8 T-cell responses. Cancer Res. 2003 May 1;63(9):2150-7. PubMed PMID: 12727833.
    b. Halak BK, Maguire HC Jr, **Lattime EC**. Tumor-induced interleukin-10 inhibits type 1 immune responses directed at a tumor antigen as well as a non-tumor antigen present at the tumor site. Cancer Res. 1999 Feb 15;59(4):911-7. PubMed PMID: 10029084.
    c. Maguire HC Jr, Ketcha KA, **Lattime EC**. Neutralizing anti-IL-10 antibody upregulates the induction and elicitation of contact hypersensitivity. J Interferon Cytokine Res. 1997 Dec;17(12):763-8. PubMed PMID: 9452364.
    d. **Lattime EC**, Mastrangelo MJ, Bagasra O, Li W, Berd D. Expression of cytokine mRNA in human melanoma tissues. Cancer Immunol Immunother. 1995 Sep;41(3):151-6. PubMed PMID: 7553683.

3. **In-situ modulation of the immune tumor microenvironment using poxvirus vectors and antigen-specific vaccines:** Given the above findings, we evaluated approaches to modulate the tumor microenvironment using recombinant vector systems. We found that vaccinia had all the required and ideal features. Initial murine studies followed by a series of Phase I trials of vaccinia vector alone in patients with recurrent melanoma (intralesional) and bladder cancer (intravesical) demonstrated that viral vector could be given repeatedly with effective tumor infection/transfection seen despite growing neutralizing antibody titers. We then generated the first-in-class oncolytic virus expressing GMCSF using the vaccinia vector. Phase I study in patients with recurrent superficial melanoma demonstrated antitumor effects in both injected tumor and non-contiguous distant lesions consistent with the generation of a systemic tumor specific response. Awarded US patents (6,093,700; 6,177,076; & 6,475,999) were licensed to Jennerex/SillaJen, and the agent is being studied in Phase III liver cancer as Pexa-Vec. We expanded these studies to add tumor antigen to the viral construct and found that immunizing intratumorally with virally encoded antigen plus GMCSF overcame systemic anergy in both bladder and breast models and led to a first-in-man Phase I study of intratumoral antigen encoding pox in patients with locally advanced inoperable pancreatic cancer (NCI/CTEP-sponsored investigator-initiated trial NCT 00669734). Of note, 8/8 patients presenting with no liver metastases failed to develop metastasis, which is a hallmark of this stage disease. Intratumoral immunization also resulted in the generation of systemic tumor antigen specific T cell immunity.

    a. Portal DE, Weiss RE, Wojtowicz M, Mansour A, Monken C, Mehnert JM, Aisner JA, Kane M, Nishioka J, Aisner S, Peters S, Stein MN, Kim IY, Mayer TM, Shih W, Gulley J, Streicher H, Singer EA, **Lattime EC**. Phase I neoadjuvant study of intravesical recombinant fowlpox-GM-CSF (rF-GM-CSF) or fowlpox-TRICOM (rF-TRICOM) in patients with bladder carcinoma. Cancer Gene Ther. 2020 Jun;27(6):438-447. PubMed Central PMCID: PMC6923616.
    b. de Vries CR, Monken CE, **Lattime EC**. The addition of recombinant vaccinia HER2/neu to oncolytic vaccinia-GMCSF given into the tumor microenvironment overcomes MDSC-mediated immune escape and systemic anergy. Cancer Gene Ther. 2015 Apr;22(3):154-62. PubMed Central PMCID: PMC4397129.

c. Yang AS, Monken CE, **Lattime EC**. Intratumoral vaccination with vaccinia-expressed tumor antigen and granulocyte macrophage colony-stimulating factor overcomes immunological ignorance to tumor antigen. Cancer Res. 2003 Oct 15;63(20):6956-61. PubMed PMID: 14583497.
d. Mastrangelo MJ, Maguire HC Jr, Eisenlohr LC, Laughlin CE, Monken CE, McCue PA, Kovatich AJ, **Lattime EC**. Intratumoral recombinant GM-CSF-encoding virus as gene therapy in patients with cutaneous melanoma. Cancer Gene Ther. 1999 Sep-Oct;6(5):409-22. PubMed PMID: 10505851.

4. **Metabolism, autophagy, and tumor mutation status combine to effect the generation of antitumor immunity:** Building on our prior tumor microenvironment studies demonstrating requirements for appropriate antigen presentation and cytokine balance, we have continued to investigate the tumor microenvironment and its role in modulating antitumor responses. In collaborative studies we have focused on 2 areas of investigation, metabolism and tumor mutation burden and their effects on tumor and immune compartments. Tumor cells upregulate and require autophagy to support their metabolism and enhance their proliferation and malignancy, and host autophagy also promotes tumor growth by providing essential tumor nutrients such as arginine in the circulation or alanine in the local tumor microenvironment. In addition to its metabolic role, autophagy regulates immune cell homeostasis and function, and suppresses inflammation, which may also play a role in cancer. Recent studies from our group have demonstrated that although host autophagy does not promote a T cell anti-tumor immune response in tumors with low tumor mutational burden (LTMB), deletion of the essential autophagy gene *Atg7* induces a pro-inflammatory cytokine response and limits the growth of high tumor mutational burden (HTMB) tumors, which is rescued by $CD4^+/CD8^+$ T-cell depletion. Expression of immune-related genes is increased in tumors from $Atg7^{\Delta/\Delta}$ hosts in a T-cell dependent manner. Tumors from $Atg7^{\Delta/\Delta}$ hosts also have decreased T regulatory cells (Tregs), and depletion of Tregs phenocopies the reduced tumor growth observed in $Atg7^{\Delta/\Delta}$ hosts. Finally, loss of *IFN*γ restores growth of HTMB tumors on $Atg7^{\Delta/\Delta}$ hosts and in the context of tumors with HTMB, loss of host autophagy leads to an anti-tumor immune response induced by loss of Tregs, activation of T cells and production of *IFN*γ, which restricts tumor growth. These latter studies are associated with the content in our MPI R01 studying the *Impact of Mutation Burden on Cancer Growth and the Immune Landscape*.

a. Yuan Z, Gardiner JC, Maggi EC, Huang S, Adem A, Bagdasarov S, Li G, Lee S, Slegowski D, Exarchakis A, Howe JR, **Lattime EC**, Zang X, Libutti SK. B7 immune checkpoints as targets for the treatment of neuroendocrine tumors. Endocr Relat Cancer. 2021 Feb;28(2):135-149. PubMed Central PMCID: PMC8486311.
b. Poillet-Perez L, Sharp DW, Yang Y, Laddha SV, Ibrahim M, Bommareddy PK, Hu ZS, Vieth J, Haas M, Bosenberg MW, Rabinowitz JD, Cao J, Guan JL, Ganesan S, Chan CS, Mehnert JM, **Lattime EC**, White E. Autophagy promotes growth of tumors with high mutational burden by inhibiting a T-cell immune response. Nat Cancer. 2020 Sep;1(9):923-934. PubMed Central PMCID: PMC8409526.
c. Poillet-Perez L, Xie X, Zhan L, Yang Y, Sharp DW, Hu ZS, Su X, Maganti A, Jiang C, Lu W, Zheng H, Bosenberg MW, Mehnert JM, Guo JY, **Lattime E**, Rabinowitz JD, White E. Autophagy maintains tumour growth through circulating arginine. Nature. 2018 Nov;563(7732):569-573. PubMed Central PMCID: PMC6287937.
d. Panda A, Betigeri A, Subramanian K, Ross JS, Pavlick DC, Ali S, Markowski P, Silk A, Kaufman HL, **Lattime E**, Mehnert JM, Sullivan R, Lovly CM, Sosman J, Johnson DB, Bhanot G, Ganesan S. Identifying a Clinically Applicable Mutational Burden Threshold as a Potential Biomarker of Response to Immune Checkpoint Therapy in Solid Tumors. JCO Precis Oncol. 2017;2017 PubMed Central PMCID: PMC6016848.

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