BIOGRAPHICAL SKETCH

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NAME: Mocarski, Edward

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POSITION TITLE: Robert W. Woodruff Professor (Emory University)

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
Rutgers University, New Brunswick, NJ	A.B.	05/1974	Microbiology
The University of Iowa, Iowa City, IA	Ph.D.	05/1979	Microbiology
The University of Chicago, Chicago, IL	Postdoc	12/1982	Virology

A. Personal Statement

Dr. Mocarski has actively pursued research in virology and immunology for several decades, initially at Stanford University (1983-2006), where he served as Professor and Chair of Microbiology & Immunology (1994-1999) and Associate Dean of Research (2000-2001). He currently holds the position of Emeritus Professor at Stanford. He is Robert W. Woodruff Professor of Microbiology and Immunology at Emory University (2006-present) in the Emory Vaccine Center. Dr. Mocarski has a long-standing interest in vaccines, having served as a founding scientific advisory board SAB member of Aviron (now part of MedImmune), a company founded in the early 1990's that developed live human cytomegalovirus (CMV) vaccine candidates to reduce the burden of CMV-associated congenital disease. He has served as founding SAB of GlobeImmune, which sought to develop therapeutic vaccines, as well as the Scientific Advisory Committee of the International AIDS Vaccine Initiative (2014 - present). As Distinguished Fellow at MedImmune, LLC, Dr. Mocarski establishing new pipeline vaccine programs (2009-2011) while on leave from Emory. He is recognized as a world expert in herpesviruses, having edited the Human Herpesviruses (2007) and authored the chapter, *Cytomegaloviruses* in Fields Virology four times (2001 – present), most recently for the 6th Edition (2013). He has served as a director of graduate programs at Stanford as well as Emory, and has trained more than 60 graduate students and postdoctoral fellows now pursuing active careers in academia and industry.

Dr. Mocarski's early research career focused on CMV biology where he made numerous discoveries that brought to light key viral replication processes and highlighted the impact this virus has on host cells and animals leading to persistence and latency. Host and viral pathways contributing to the virus-host "stand-off" have been a major interest for over three decades. In the battle between host immune control and viral immunomodulation, cell death pathways stand out because these are not well understood but are evolutionarily conserved in rodents and humans, as well as in the CMVs that infect these hosts. The viral inhibitor of apoptosis (vMIA) and the viral inhibitor caspase 8 activation (vICA) are the only CMV-encoded immune modulators that are evolutionarily conserved in murine and human CMV. This research has unveiled novel antiviral host pathways that play out as alternatives to apoptosis in host defense, including an HtrA2 serine protease cell death and a receptor interacting protein kinase (RIP or RIPK)3 programmed necrosis pathway, called necroptosis. His contributions revealed the importance of necroptosis in host defense.

As a result of his research, RIPK3, caspase-8 (Casp8) and associated signaling components may be viewed as a pathogen supersensor complex that is activated by different innate immune signaling pathways to initiate alternate apoptotic and necrotic death outcomes. This capability evolved in order to facilitate elimination of virus-infected cells. In the course of these studies, the developmental lethality of Casp8 knockout mice was shown to be dependent on the kinase activity of RIPK3 and the perinatal lethality of RIPK1 knockout mice was shown to result from combined Casp8 and RIPK3 cell death at birth. These discoveries brought important features of Casp8-apoptosis and RIPK3-necroptosis to light.

B. Positions and Honors

Experience and Employment:

1975-1981 USPHS Predoctoral and Postdoctoral Trainee
1981-1983 Leukemia Society of America Special Fellow
1983-1989 Assistant Professor, Department of Microbiology & Immunology, Stanford University,
1989-1995 Associate Professor (with tenure)
1995-1999 Professor & Chair
2000-2001 Professor & Associate Dean of Research, President's Office, Stanford University
1995-2006 Professor
2006 (May) Professor Emeritus, Stanford
2009-2011 Distinguished Fellow, MedImmune LLC (a wholly owned subsidiary of AstraZeneca)
2006-pres Robert W. Woodruff Professor, Emory Vaccine Center, Emory University School of Medicine

Honors, Awards and Service:

1981-1983 Leukemia Society of America Special Fellow
1984 Agnes Axtell Moule Faculty Scholar and Andrew Mellon Fellow
1984-1990 American Cancer Society Faculty Research Award
1989 NIH-NIAID Board of Scientific Counselors
1989-1993 USDA Biotechnology Study Section
1990-1994 Member, NIH Experimental Virology Study Section
1991-2015 *Journal of Virology* Editorial Board
1991-2016 *Virology* Editorial Board
1992-1994 ASM Foundation for Microbiology
1993 NIH Wallace Rowe Lecture
1995-1996 Advisory Panel to Office of AIDS Research on Opportunistic Infections
1995-1996 SmithKline Beecham Fellow
2000-2003 9th District US Federal Court Judicial Scientific Advisor
2000-2001 Associate Dean of Research in the Provost's Office at Stanford University
2000-2015 Nebraska Center for Virology COBRE External Advisory Board
2001-2015 *Journal of Biological Chemistry* Editorial Board
2001 Pfizer Visiting Professor in Infectious Diseases, Univ of Oklahoma
2001-2004 Chair, Stanford University School of Medicine Conflict of Interest Committee
2002-2004 Stanford University Fellow
2002 NIH-NHLBI Program Review Panel
2002-2015 NIH Reviewers Reserve (*ad hoc* reviews performed in all years)
2003 Organizer, Keystone Conference, Pathogen:Host Standoff – Taos, NM
2004 NIH NIDCD Review Panel on CMV-related Hearing Loss
2004-2015 Louisiana Biomedical Research Network INBRE External Advisory Board
2005 Organizer, Keystone Conference, Pathogen:Host Standoff – Keystone, CO
2006-2007 United Kingdom MRC Virology Focus Strategy Review Group
2006-2011 Georgia Cancer Coalition Distinguished Cancer Scholar
2008 Hilleman Lecturer, University of Chicago
2009-2011 Distinguished Fellow, MedImmune,
2012 NCI-NIAID Joint EBV Vaccine Meeting
2012 NIH NCI Burkitt Lymphoma Workshop
2012 FDA-CDC-NIH Joint CMV Vaccine
2012 Fellow, American Academy of Microbiology
2012 Emory 1% Award
2013 NIH NCI Review Panel on Role of CMV in Glioblastoma
2014 Herpes Laison Award – Eastern Virginia Medical School
2014-2015 NIH Viral and Microbial Disease Study Section – ad hoc
2015 Weller-Smith Oration – CMV/Betaherpesvirus Workshop, Brisbane
2015 Nirit and Michael Shaoul Fellow (Visiting Professor), Tel Aviv University
2014 IAVI Scientific Advisory Committee

C. Contribution to Science

1. Cytomegalovirus Replication

Dr. Mocarski was first to identify CMV replication and regulation functions, pioneering genetic engineering of the large CMV genome to reveal the regulatory function of the major immediate early gene (1), the identify of the viral DNA replication origin (2) and specific transcription control of viral late gene expression (3). He showed the function of the major tegument phosphoprotein in virion assembly (4):

(1) Greaves, R. F., and E.S. Mocarski (1998) Low multiplicity growth defect and gene expression during infection by a human cytomegalovirus *ie*1 mutant. J. Virol. 72:366-379. PMC109384

(2) Masse, M.J., S. Karlin, G.A. Schachtel and E.S. Mocarski (1992). Human cytomegalovirus origin of DNA replication (oriLyt) resides within a highly complex repetitive region. *Proc. Natl. Acad. Sci. USA* 89:5246-5250.

(3) Omoto, S., and E. S. Mocarski (2013) Cytomegalovirus UL91 is essential for transcription of viral true late (γ2) genes. *J. Virol.* 87:8651-8664. PMC3719799

(4) Tandon, R. and E. S. Mocarski. (2011) Stabilization of nucleocapsids by cytomegalovirus pp150 is dependent upon pUL96 function. *J. Virol.* 85:7129-7141. PMC3126555

2. Cytomegalovirus Dissemination and Latency

Dr. Mocarski was the first to evaluate CMV replication in humanized mice, research that led to the importance of myeloid cell progenitors in CMV latency (5) and the enumeration of CMV genomes in natural latency (6). Studies with MCMV have revealed seminal knowledge of a virus-encoded chemokine that controls T cell immunity (7) as well as the ability of virus to disseminate into latency (8):

(5) Kondo, K., H. Kaneshima, and E.S. Mocarski. (1994) Human cytomegalovirus latent infection of granulocyte-macrophage progenitors. Proc. Natl. Acad. Sci. USA 91:11879-11883. PMC45339

(6) Slobedman, B., and E.S. Mocarski (1999) Quantitative analysis of latent human cytomegalovirus. J. Virol. 73:4806-4812. PMC112523

(7) Daley-Bauer, L. P., G. M. Wynn and E. S. Mocarski. (2012) Cytomegalovirus impairs antiviral $CD8^+$ T cell immunity by recruiting inflammatory monocytes. *Immunity* 37:122-133. PMC3412053

(8) Daley-Bauer, L. P., L. J. Roback, G. M. Wynn, and E. S. Mocarski (2014) Cytomegalovirus hijacks $CX3CR1^{hi}$ patrolling monocytes as immune-privileged vehicles for dissemination in mice. *Cell Host Microbe* 5:351-362. PMC3989205

3. Virus-encoded Inhibitors of Cell Death

Dr. Mocarski has characterized the function of virus-encoded cell death suppressors targeting mitochondria, Casp8 and RIPK3. He demonstrated the existence of a novel serine protease death pathway that is regulated by the mitochondrial cell death suppressor (9) and characterized the first virus-encoded inhibitor of necroptosis, a RHIM-signaling suppressor encoded by murine CMV (10,11) that naturally blocks DAI-RIPK3 signaling. He showed the importance of necroptosis in human host defense by identifying HSV-encoded inhibitors (12). The studies with virus-encoded inhibitors resulted in a series of remarkable observations on mammalian development, where apoptotic and necroptotic death can be prematurely unleashed. Germ line disruption of Casp8 in mice was found to be completely reversed by elimination of RIPK3 (13) or kinase inactive RIPK3 (15), that RIPK1 deficiency results in perinatal death due to combined necroptosis and apoptosis (14), and that pronecrotic RIPK3 protein kinase can unleash Casp8-dependent apoptosis via RHIM signal transduction (15):

(9) McCormick, A. L., L. Roback and E. S. Mocarski. (2008) vMIA control of intramitochondrial, HtrA2/Omi-dependent cytomegalovirus programmed cell death to terminate the replication cycle. PLoS Pathogens 4: e1000063 PMC2528007

(10) Upton J. W., W. J. Kaiser, and E. S. Mocarski. (2010) Viral inhibition of RIP3–dependent necrosis. *Cell Host Microbe* 22:302-313. PMC4279434

(11) Upton J. W., W. J. Kaiser, and E. S. Mocarski. (2012) DAI/ZBP1/DLM-1 complexes with RIP3 to mediate virus-induced programmed necrosis that is targeted by murine cytomegalovirus vIRA. *Cell Host Microbe* 11:290-297. PMC3531981

(12) Guo, H. S. Omoto, P. A. Harris, J. N. Finger, J. Bertin, P. J. Gough, W. J. Kaiser and E. S. Mocarski (2015) Herpes simplex virus suppresses necroptosis in human cells. *Cell Host Microbe* 17:243-251 PMC4382104

(13) Kaiser, W. J., J. W. Upton, A. B. Long, D. Livingston-Rosanoff, L. P. Daley, R. Hakem, T. Caspary and E. S. Mocarski. (2011) RIP3 mediates the embryonic lethality of caspase-8-deficient mice. *Nature* 471:368-372. PMC3060292

(14) Kaiser, W. J., L. P. Daley-Bauer, R. J. Thapa, P. Mandal, S. B. Berger, C. Huang, A. Sundararajan, H. Guo, L. Roback, S. H. Speck, J. Bertin, P. J. Gough, S. Balachandran, and E. S. Mocarski (2014). RIP1 suppresses innate immune cell death during mammalian parturition. *Proc. Natl. Acad. Sci. (USA)* 111:7753-7758 PMC4040608

(15) Mandal, P., S. B. Berger, S. Pillay, K. Moriwaki, C. Huang, H. Guo, J. D. Lich, J. Finger, V. Kasparcova, B. Votta, M. Ouellette, B. W. King, D. Wisnoski, A. S. Lakdawala, M. P. DeMartino, L. N. Casillas, P. A. Haile, C. A. Sehon, R. W. Marquis, J. Upton, L. P. Daley-Bauer, L. Roback, N. Ramia, C. M. Dovey, J. E. Carette, F. Chan, J. Bertin, P. J. Gough, E. S. Mocarski and W. J. Kaiser. (2014) RIP3 induces apoptosis independent of pro-necrotic kinase activity. Mol. Cell 56:481-495 PMC4512186

4. Vaccine Research and Development

Dr. Mocarski contributed to a hallmark report showing that HCMV loses genes and rearranges its genome during propagation outside the human host (16), leading directly to strategies employing recombinant live attenuated vaccine candidates that have been under clinical development for over 20 years (17). This research has lead to many reviews and is recognized as the conceptual underpinning leading to the evaluation of RhCMV 68-1 as a vaccine vector in macaques:

(16) Cha, T-A., E. Tom, G.W. Kemble, G.M. Duke, E.S. Mocarski and R.R. Spaete (1996) Human cytomegalovirus clinical isolates carry at least 19 genes not found in laboratory strains. J. Virol. 70:78-83. PMID:8523595

(17) Adler, S. P., A. M. Manganello, R. Lee, M. A. McVoy, D. E. Nixon, S. Plotkin, E. Mocarski, J. H. Cox, P. E. Fast, P. A. Nesterenko, S. E. Murray, A. B. Hill, and G. Kemble. (2016) A Phase 1 study of four live, recombinant human cytomegalovirus Towne/Toledo chimera vaccines in CMV-seronegative men. *J Infect Dis* Aug 11. pii: jiw365. [Epub ahead of print]

5. CMV Pathogenesis

Dr. Mocarski has contributed to the understanding of CMV strain variation, construction of live attenuated viral vaccine candidates, and the behavior of the virus in transplant recipients. He has shown that despite antiviral prophylaxis, an overwhelming majority of at-risk heart transplant recipients encounter active human CMV infection (18). Furthermore, studies using a rodent model have revealed role of the antiviral T cell response in systemic disease (19) as well as the modulation of that response by virus-encoded chemokine (7):

(18) Potena, L., C.T.J. Holweg, M.L. Vana, A. L. McCormick, L. Bashyam, J. Rajamani, J.P. Cooke, H.A. Valantine and E.S. Mocarski. (2007) Frequent occult infection with cytomegalovirus despite antiviral prophylaxis in cardiac transplant recipients. J. Clin. Microbiol. 45:1804-1810. PMC1933112

(19) Livingston-Rosanoff, D., L. P. Daley, A. Garcia, A. L. McCormick, J. Huang and E. S. Mocarski. (2012) Antiviral T cell response triggers cytomegalovirus hepatitis in mice. *J. Virol.* 86:12879-12890. PMC3497643

PublicBibliography:http://www.ncbi.nlm.nih.gov/sites/myncbi/edward.mocarski.1/bibliography/41345455/public/?sort=date&direction=ascending

D. Research Support

Ongoing:

Project Number: 5 RO1 AI020211-30 (Mocarski, PI) **Dates of Project:** 12/01/16-11/30/21
Source: NIH/NIAID **Title:** Cytomegalovirus DNA replication and inversion.
Major Goals: (1) Study cell death pathways controlling viral dissemination. (2) Investigate cell death pathways controlling latency and persistence. (3) Elaborate the contribution of cell death to innate and adaptive immunity.

Project Number: 2 R01 AI118853-01 (Mocarski, PI) **Dates of Project:** 6/01/15-7/31/19
Source: NIH/NIAID Directors Award **Title:** Innate activation and death signals in health and disease.
Major Goals: (1) Optimize allogeneic engraftment by manipulating cell death pathways by controlling cell death. (2) Enhance nuclear reprogramming by eliminating detrimental innate cell death. (3) Determine the contribution of apoptosis and necroptosis to inflammatory disease in mouse models.

Project Number: GSK Grant (Mocarski, PI) **Dates of Project:** 04/01/15-03/31/17
Source: GlaxoSmithKline **Title:** Combined elimination of Casp8 and RIP3 improves HCT engraftment
Major Goals: Determine the contribution of RIPK1 and RIPK3 kinase activity in**:** (1) allogeneic engraftment of bone marrow in mice, (2) tissue repair and regeneration, and (3) inflammatory disease models**.**

Project Number: Onyx/Emory Grant (Mocarski, PI) **Dates of Project:** 12/01/15-11/30/17
Source: Onyx/Amgen **Title:** Innate Immune Cell Death as an Adjunct to Proteasome Inhibition Therapy
Major Goals: A pilot study to gain mechanistic understanding of the anti-cancer cytotoxic properties of ONYX proteasome inhibitors together with innate cell death signaling via either of two pathways (TRIF and PKR), each of which sits as a biological complement to TNF-mediated death receptor signaling.

Project Number: 13SDG17340025 (Mocarski, mentor) **Dates of Project:** 7/01/2013 - 6/30/2017
Source: AHA **Annual Direct Costs**: $77,000
Title: Novel Regulators to Enhance Safer iPSC Derivation and Differentiation to Endothelial Cells.
Major Goals: The major goal of this project is to provide diagnostic approaches and small molecule intervention for vascular regeneration, specifically in patients suffering from peripheral artery disease.
Percent Effort: 1%

Robert W. Woodruff Professorship provides salary support for Prof. Mocarski.

Completed:

Project Number: 1 ROl GM112547-01 (Mocarski, PI) **Dates of Project:** 08/01/14-05/31/15
Source: NIH/NIGMS **Title:** Benefits of Eliminating Cell Death Pathways in Health and Disease
Major Goals: (Due to overlap, this grant was replaced by NIH Director's Award R01 AI118853)

Project Number: 1 R56 AI107295-01A1 (Mocarski, PI) **Dates of Project:** 04/01/14-03/31/15
Source: NIH/NIAID **Title:** Cell Death Pathways in Cytomegalovirus Pathogenesis and Control**.**
Major Goals: 1) Determine the functional contribution of caspase 8 and RIPK3 to virus-induced programmed necrosis. 2) Investigate the contribution of viral caspase 8 inhibition in unleashing necroptosis. 3) Determine the contribution of programmed cell death in monocyte lineage cells and during latency.