



Edward MocarSKI

Professor of Microbiology and Immunology, Emeritus
Microbiology & Immunology

 NIH Biosketch available Online

Bio

BIO

Edward S. MocarSKI, Jr.

Emeritus Professor of Microbiology and Immunology (2021 – present)

Emory University Vaccine Center

Emory University

Emeritus Professor following 15 years as Robert W. Woodruff Professor of Microbiology & Immunology in the Emory Vaccine Center, Emory University. Previously Professor and Chair of Microbiology & Immunology at Stanford University between 1983 and 2006. Distinguished Fellow at MedImmune, LLC, a division of AstraZeneca in 2009 and 2010 where he directed new pipeline vaccine research. His research interest is in the biology and pathogenesis of cytomegalovirus (CMV), and his group has made key contributions to the identification of replication functions, latent reservoir in myelomonocytic progenitors, immunomodulatory functions, and cellular response to viral infection. Most recently, study of viral functions that modulate host cell intrinsic activation and death pathways has brought understanding of cell death pathways in host defense and development.

ACADEMIC APPOINTMENTS

- Emeritus Faculty, Acad Council, Microbiology & Immunology
- Member, Cardiovascular Institute

HONORS AND AWARDS

- Robert W. Woodruff Endowed Professor, Emory University (2006 - 2021)
- Distinguished Fellow, MedImmune, LLC. (2009-2011)
- See Biosketch for full list, Various (2016)

PROFESSIONAL EDUCATION

- AB, Rutgers University , Microbiology (1974)
- PhD, University of Iowa , Microbiology (1979)
- postdoc, The University of Chicago , Virology (1982)

COMMUNITY AND INTERNATIONAL WORK

- Emory Vaccine Center, Atlanta, GA
- Vaccine Research and Development, Mountain View
- International AIDS Vaccine Initiative, New York, NY

- NIH NIAID Vaccine Research Center, Bethesda MD

LINKS

- Personal Web site: <http://cmgm.stanford.edu/micro/fac/mocarski.html>

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

Through 2021, my Emory laboratory had focused on the infected cell response to infection, mainly the contribution of regulated cell death pathways to host defense against viruses. A mechanistic understanding of cytomegalovirus (CMV)-encoded modulators of cell death enabled the discovery of alternate cell death pathways that are active in mammals. All large mammalian DNA viruses encode multiple suppressors of apoptosis that have been shown to play out via mitochondrial components or via cytosolic cell death machinery. Cell death suppressors encoded by human CMV are conserved in murine CMV. Direct studies of this species restricted virus in infected mice have helped to provide information on the natural role these suppressors play in human CMV pathogenesis. After identifying the CMV-encoded viral inhibitor of mitochondrial apoptosis (vMIA) and characterizing the caspase-independent cell death pathway that this suppressor blocked during infection, we described a second player, the CMV-encoded viral inhibitor of caspase 8 activation (vICA), capable of suppressing extrinsic apoptosis and necessary for either human or murine CMV replication in macrophage lineage cells from the respective species. A third cell death suppressor, viral inhibitor of receptor interacting protein RIP activation (vIRA) unveiled a second caspase-independent pathway, programmed necrosis. Suppression of caspase-8 activity by vICA unleashed this alternative (trap door) necroptosis, a pathway that is triggered by Z-nucleic acid binding protein (ZBP)1, mediated by RIPK3 and executed by a protein called mixed lineage-like (MLKL). The pathogen sensor ZBP1 (also called DAI) senses newly synthesized viral RNA, oligomerizes with RIPK3, and the murine CMV-encoded vIRA prevents this recruitment and oligomerization. We have established that vICA suppression of caspase 8 activity is an essential part of this process, and that, together, vICA and vIRA represent key modulators of potent host defense pathways. Through such investigations discovered that developmental death of caspase 8-deficient and receptor-interacting protein kinase (RIPK)1-deficient mice is due to alternate cell death pathways controlled by RIPK3 that evolved to control intracellular pathogens such as viruses. We were the first laboratory to demonstrate the importance of RIPK3-dependent necroptosis in innate host resistance to viral infection through the elaboration of necroptosis inhibitors encoded by CMV, herpes simplex virus and the poxvirus, vaccinia. This work has highlighted the importance of ZBP1 as a specialized pathogen sensor triggering RIPK3-dependent cell death and inflammatory pathways. We further demonstrated that mice lacking caspase-8 and RIPK3 as well as mice lacking RIPK1 caspase-8 and RIPK3 mount a robust immune response that controls virus infection despite the absence of cell death, attributed to the ability of other cell death-dependent and cell death-independent host defense pathways to control viral infection. Because CMV is such a master manipulator of the host response to infection, other individual viral gene products have provided us with high impact observations, such as the virus-encoded chemokine whose function assures CMV-susceptible myeloid cells are recruited to sites of infection as vehicles for dissemination as well as to downmodulate the CD8 T cell response to infection.

Teaching

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Cancer Biology (Phd Program)
- Microbiology and Immunology (Phd Program)

Publications

PUBLICATIONS

- **The RIPK3 Scaffold Regulates Lung Inflammation During *Pseudomonas Aeruginosa* Pneumonia** *AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY*
Lyons, J. D., Mandal, P., Otani, S., Chihade, D. B., Easley, K. F., Swift, D. A., Burd, E. M., Liang, Z., Koval, M., Mocarski, E. S., Coopersmith, C. M.
2023; 68 (2): 150-160
- **RIPK3 and caspase 8 collaborate to limit herpes simplex encephalitis.** *PLoS pathogens*
Guo, H., Koehler, H. S., Mocarski, E. S., Dix, R. D.

2022; 18 (9): e1010857

- **Multiple Autonomous Cell Death Suppression Strategies Ensure Cytomegalovirus Fitness** *VIRUSES-BASEL*
Mandal, P., Nagrani, L. N., Hernandez, L., McCormick, A., Dillon, C. P., Koehler, H. S., Roback, L., Alnemri, E. S., Green, D. R., Mocarski, E. S.
2021; 13 (9)
- **Vaccinia virus E3 prevents sensing of Z-RNA to block ZBP1-dependent necroptosis** *CELL HOST & MICROBE*
Koehler, H., Cotsmire, S., Zhang, T., Balachandran, S., Upton, J. W., Langland, J., Kalman, D., Jacobs, B. L., Mocarski, E. S.
2021; 29 (8): 1266+
- **TNF Signaling Dictates Myeloid and Non-Myeloid Cell Crosstalk to Execute MCMV-Induced Extrinsic Apoptosis** *VIRUSES-BASEL*
Mandal, P., McCormick, A., Mocarski, E. S.
2020; 12 (11)
- **Recognizing limits of Z-nucleic acid binding protein (ZBP1/DAI/DLM1) function** *FEBS JOURNAL*
Koehler, H. S., Feng, Y., Mandal, P., Mocarski, E. S.
2020; 287 (20): 4362-4369
- **Necroptosis-based CRISPR knockout screen reveals Neuropilin-1 as a critical host factor for early stages of murine cytomegalovirus infection.** *Proceedings of the National Academy of Sciences of the United States of America*
Lane, R. K., Guo, H., Fisher, A. D., Diep, J., Lai, Z., Chen, Y., Upton, J. W., Carette, J., Mocarski, E. S., Kaiser, W. J.
2020
- **Squalene-based adjuvants stimulate CD8 T cell, but not antibody responses, through a RIPK3-dependent pathway.** *eLife*
Kim, E. H., Woodruff, M. C., Grigoryan, L., Maier, B., Lee, S. H., Mandal, P., Cortese, M., Natrajan, M. S., Ravindran, R., Ma, H., Merad, M., Gitlin, A. D., Mocarski, et al
2020; 9
- **HIF1 β Regulates Early Metabolic Changes due to Activation of Innate Immunity in Nuclear Reprogramming.** *Stem cell reports*
Liu, C. n., Ruan, H. n., Himmati, F. n., Zhao, M. T., Chen, C. C., Makar, M. n., Chen, I. Y., Sallam, K. n., Mocarski, E. S., Sayed, D. n., Sayed, N. n.
2020; 14 (2): 192–200
- **Caspase-8 restricts natural killer cell accumulation during MCMV Infection** *MEDICAL MICROBIOLOGY AND IMMUNOLOGY*
Feng, Y., Daley-Bauer, L. P., Roback, L., Potempa, M., Lanier, L. L., Mocarski, E. S.
2019; 208 (3-4): 543-554
- **Caspase-8 restricts antiviral CD8 T cell hyperaccumulation** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Feng, Y., Daley-Bauer, L. P., Roback, L., Guo, H., Koehler, H. S., Potempa, M., Lanier, L. L., Mocarski, E. S.
2019; 116 (30): 15170-15177
- **Herpes simplex virus 1 ICP6 impedes TNF receptor 1-induced necrosome assembly during compartmentalization to detergent-resistant membrane vesicles** *JOURNAL OF BIOLOGICAL CHEMISTRY*
Ali, M., Roback, L., Mocarski, E. S.
2019; 294 (3): 991-1004
- **Remarkably Robust Antiviral Immune Response despite Combined Deficiency in Caspase-8 and RIPK3** *JOURNAL OF IMMUNOLOGY*
Feng, Y., Livingston-Rosanoff, D., Roback, L., Sundararajan, A., Speck, S. H., Mocarski, E. S., Daley-Bauer, L. P.
2018; 201 (8): 2244-2255
- **Species-independent contribution of ZBP1/DAI/DLM-1-triggered necroptosis in host defense against HSV1** *CELL DEATH & DISEASE*
Guo, H., Gilley, R. P., Fisher, A., Lane, R., Landsteiner, V. J., Ragan, K. B., Dovey, C. M., Carette, J. E., Upton, J. W., Mocarski, E. S., Kaiser, W. J.
2018; 9: 816
- **Caspase-8 Collaborates with Caspase-11 to Drive Tissue Damage and Execution of Endotoxic Shock** *IMMUNITY*
Manda, P., Feng, Y., Lyons, J. D., Berger, S. B., Otani, S., DeLaney, A., Tharp, G. K., Maner-Smith, K., Burd, E. M., Schaeffer, M., Hoffman, S., Capriotti, C., Roback, et al
2018; 49 (1): 42+
- **MLKL Requires the Inositol Phosphate Code to Execute Necroptosis.** *Molecular cell*

- Dovey, C. M., Diep, J. n., Clarke, B. P., Hale, A. T., McNamara, D. E., Guo, H. n., Brown, N. W., Cao, J. Y., Grace, C. R., Gough, P. J., Bertin, J. n., Dixon, S. J., Fiedler, et al
2018; 70 (5): 936–48.e7
- **Retinoic Acid Inducible Gene 1 Protein (RIG1)-Like Receptor Pathway Is Required for Efficient Nuclear Reprogramming** *STEM CELLS*
Sayed, N., Ospino, F., Himmati, F., Lee, J., Chanda, P., Mocarski, E. S., Cooke, J. P.
2017; 35 (5): 1197-1207
 - **Mouse cytomegalovirus M36 and M45 death suppressors cooperate to prevent inflammation resulting from antiviral programmed cell death pathways** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Daley-Bauer, L. P., Roback, L., Crosby, L. N., McCormick, A. L., Feng, Y., Kaiser, W. J., Mocarski, E. S.
2017; 114 (13): E2786-E2795
 - **A Phase 1 Study of 4 Live, Recombinant Human Cytomegalovirus Towne/Toledo Chimera Vaccines in Cytomegalovirus-Seronegative Men** *JOURNAL OF INFECTIOUS DISEASES*
Adler, S. P., Manganello, A., Lee, R., McVoy, M. A., Nixon, D. E., Plotkin, S., Mocarski, E., Cox, J. H., Fast, P. E., Nesterenko, P. A., Murray, S. E., Hill, A. B., Kemble, et al
2016; 214 (9): 1341-1348
 - **RIPK3 Activates Parallel Pathways of MLKL-Driven Necroptosis and FADD-Mediated Apoptosis to Protect against Influenza A Virus** *CELL HOST & MICROBE*
Nogusa, S., Thapa, R. J., Dillon, C. P., Liedmann, S., Oguin, T. H., Ingram, J. P., Rodriguez, D. A., Kosoff, R., Sharma, S., Sturm, O., Verbist, K., Gough, P. J., Bertin, et al
2016; 20 (1): 13-24
 - **T cell-intrinsic ASC critically promotes T(H)17-mediated experimental autoimmune encephalomyelitis** *NATURE IMMUNOLOGY*
Martin, B. N., Wang, C., Zhang, C., Kang, Z., Gulen, M. F., Zepp, J. A., Zhao, J., Bian, G., Do, J., Min, B., Pavicic, P. G., El-Sanadi, C., Fox, et al
2016; 17 (5): 583-?
 - **Caspase-8 as an Effector and Regulator of NLRP3 Inflammasome Signaling** *JOURNAL OF BIOLOGICAL CHEMISTRY*
Antonopoulos, C., Russo, H. M., El Sanadi, C., Martin, B. N., Li, X., Kaiser, W. J., Mocarski, E. S., Dubyak, G. R.
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 - **Manipulation of apoptosis and necroptosis signaling by herpesviruses** *MEDICAL MICROBIOLOGY AND IMMUNOLOGY*
Guo, H., Kaiser, W. J., Mocarski, E. S.
2015; 204 (3): 439-448
 - **Caspase-8 scaffolding function and MLKL regulate NLRP3 inflammasome activation downstream of TLR3** *NATURE COMMUNICATIONS*
Kang, S., Fernandes-Alnemri, T., Rogers, C., Mayes, L., Wang, Y., Dillon, C., Roback, L., Kaiser, W., Oberst, A., Sagara, J., Fitzgerald, K. A., Green, D. R., Zhang, et al
2015; 6
 - **Necroptosis: The Trojan horse in cell autonomous antiviral host defense** *VIROLOGY*
Mocarski, E. S., Guo, H., Kaiser, W. J.
2015; 479: 160-166
 - **Suppression of RIP3-dependent Necroptosis by Human Cytomegalovirus** *JOURNAL OF BIOLOGICAL CHEMISTRY*
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2015; 290 (18): 11635-11648
 - **The immunological underpinnings of vaccinations to prevent cytomegalovirus disease** *CELLULAR & MOLECULAR IMMUNOLOGY*
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2015; 12 (2): 170-179
 - **The A, B, Cs of Herpesvirus Capsids** *VIRUSES-BASEL*
Tandon, R., Mocarski, E. S., Conway, J. F.
2015; 7 (3): 899-914
 - **Herpes Simplex Virus Suppresses Necroptosis in Human Cells** *CELL HOST & MICROBE*
Guo, H., Omoto, S., Harris, P. A., Finger, J. N., Bertin, J., Gough, P. J., Kaiser, W. J., Mocarski, E. S.
2015; 17 (2): 243-251

- **MicroRNA miR-21 Attenuates Human Cytomegalovirus Replication in Neural Cells by Targeting Cdc25a** *JOURNAL OF VIROLOGY*
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2015; 89 (2): 1070-1082
- **TNFR1-dependent cell death drives inflammation in Sharpin-deficient mice** *ELIFE*
Rickard, J. A., Anderton, H., Etemadi, N., Nachbur, U., Darding, M., Peltzer, N., Lalaoui, N., Lawlor, K. E., Vanyai, H., Hall, C., Bankovacki, A., Gangoda, L., Wong, et al
2014; 3
- **RIP3 Induces Apoptosis Independent of Pronecrotic Kinase Activity** *MOLECULAR CELL*
Mandal, P., Berger, S. B., Pillay, S., Moriwaki, K., Huang, C., Guo, H., Lich, J. D., Finger, J., Kasparcova, V., Votta, B., Ouellette, M., King, B. W., Wisnoski, et al
2014; 56 (4): 481-495
- **Caspase-8 Modulates Dectin-1 and Complement Receptor 3-Driven IL-1 beta Production in Response to beta-Glucans and the Fungal Pathogen, Candida albicans** *JOURNAL OF IMMUNOLOGY*
Ganesan, S., Rathinam, V. A., Bossaller, L., Army, K., Kaiser, W. J., Mocarski, E. S., Dillon, C. P., Green, D. R., Mayadas, T. N., Levitz, S. M., Hise, A. G., Silverman, N., Fitzgerald, et al
2014; 193 (5): 2519-2530
- **Cutting Edge: RIP1 Kinase Activity Is Dispensable for Normal Development but Is a Key Regulator of Inflammation in SHARPIN-Deficient Mice** *JOURNAL OF IMMUNOLOGY*
Berger, S. B., Kasparcova, V., Hoffman, S., Swift, B., Dare, L., Schaeffer, M., Capriotti, C., Cook, M., Finger, J., Hughes-Earle, A., Harris, P. A., Kaiser, W. J., Mocarski, et al
2014; 192 (12): 5476-5480
- **RIP1 suppresses innate immune necrotic as well as apoptotic cell death during mammalian parturition** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Kaiser, W. J., Daley-Bauer, L. P., Thapa, R. J., Mandal, P., Berger, S. B., Huang, C., Sundararajan, A., Guo, H., Roback, L., Speck, S. H., Bertin, J., Gough, P. J., Balachandran, et al
2014; 111 (21): 7753-7758
- **Caspase-8 and RIP kinases regulate bacteria-induced innate immune responses and cell death** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Weng, D., Marty-Roix, R., Ganesan, S., Proulx, M. K., Vladimer, G. I., Kaiser, W. J., Mocarski, E. S., Pouliot, K., Chan, F. K., Kelliher, M. A., Harris, P. A., Bertin, J., Gough, et al
2014; 111 (20): 7391-7396
- **Highly Acidic C-Terminal Region of Cytomegalovirus pUL96 Determines Its Functions during Virus Maturation Independently of a Direct pp150 Interaction** *JOURNAL OF VIROLOGY*
Brechtel, T. M., Mocarski, E. S., Tandon, R.
2014; 88 (8): 4493-4503
- **Cytomegalovirus Hijacks CX3CR1(hi) Patrolling Monocytes as Immune-Privileged Vehicles for Dissemination in Mice.** *Cell host & microbe*
Daley-Bauer, L. P., Roback, L. J., Wynn, G. M., Mocarski, E. S.
2014; 15 (3): 351-362
- **True grit: programmed necrosis in antiviral host defense, inflammation, and immunogenicity.** *Journal of immunology*
Mocarski, E. S., Kaiser, W. J., Livingston-Rosanoff, D., Upton, J. W., Daley-Bauer, L. P.
2014; 192 (5): 2019-2026
- **Transcription of True Late (gamma 2) Cytomegalovirus Genes Requires UL92 Function That Is Conserved among Beta- and Gammaherpesviruses** *JOURNAL OF VIROLOGY*
Omoto, S., Mocarski, E. S.
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- **Natural antisense transcripts of UL123 packaged in human cytomegalovirus virions** *ARCHIVES OF VIROLOGY*
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Krause, P. R., Bialek, S. R., Boppana, S. B., Griffiths, P. D., Laughlin, C. A., Ljungman, P., Mocarski, E. S., Pass, R. F., Read, J. S., Schleiss, M. R., Plotkin, S. A.

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- **Apaf1 apoptotic function critically limits Sonic hedgehog signaling during craniofacial development** *CELL DEATH AND DIFFERENTIATION*
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- **Proapoptotic Chemotherapeutic Drugs Induce Noncanonical Processing and Release of IL-1 beta via Caspase-8 in Dendritic Cells** *JOURNAL OF IMMUNOLOGY*
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- **Toll-like Receptor 3-mediated Necrosis via TRIF, RIP3, and MLKL** *JOURNAL OF BIOLOGICAL CHEMISTRY*
Kaiser, W. J., Sridharan, H., Huang, C., Mandal, P., Upton, J. W., Gough, P. J., Schon, C. A., Marquis, R. W., Bertin, J., Mocarski, E. S.
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- **Viral modulation of programmed necrosis** *CURRENT OPINION IN VIROLOGY*
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Tandon, R., Mocarski, E. S.

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- **DAI/ZBP1/DLM-1 Complexes with RIP3 to Mediate Virus-Induced Programmed Necrosis that Is Targeted by Murine Cytomegalovirus vIRA** *CELL HOST & MICROBE*
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Mocarski, E. S., Upton, J. W., Kaiser, W. J.
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- **Viral infection and the evolution of caspase 8-regulated apoptotic and necrotic death pathways** *NATURE REVIEWS IMMUNOLOGY*
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