BIOGRAPHICAL SKETCH

NAME: Cerione, Richard A.

eRA COMMONS USER NAME (credential, e.g., agency login): RAC1CORNELL

POSITION TITLE: Distinguished Professor of Arts and Sciences in Chemistry

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Rutgers College, Rutgers University, New Brunswick, NJ	B.A./Ph.D.	05/1979	Biochemistry
Cornell University, Ithaca, NY	Postdoc. Fellow	05/1982	Chemistry
Duke University Medical Ctr., Durham, NC	HHMI Sr. Res. Assoc.	10/1985	Biochemistry

A. Personal Statement: A major goal of my research programs has been to understand the signal transduction pathways that regulate cell growth, differentiation, and development, and how when de-regulated, they contribute to cancer progression and other disease pathologies. My laboratories in the Department of Molecular Medicine, and the Department of Chemistry and Chemical Biology, at Cornell University have used a combination of biophysical, chemical, genetic and structural biology-based approaches in studying both G protein-coupled receptor-signaling using the vertebrate vision system as a model and growth factor receptor/tyrosine kinase-stimulated signal transduction. Our studies of signaling pathways triggered by the EGF receptor (EGFR) and related family members resulted in our finding that the Neu/ErbB2/HER2 tyrosine kinase is activated through a Heregulin-stimulated heterodimerization with the related family member ErbB3. Attempts to identify novel participants downstream from the EGFR led to our discovery of the human Cdc42 protein, a small GTPase, and to the identification of several Cdc42 signaling partners. We discovered that Cdc42 and related small GTPases signal the upregulation of metabolic activities essential for cancer progression. These include the recent discovery of the activation by Cdc42 of a novel mTOR complex, and the ability of Cdc42 and other small GTPases to promote the upregulation of members the family of glutaminase enzymes, necessary for satisfying the 'glutamine addiction' of cancer cells. These findings motivated our efforts to develop specific allosteric inhibitors that target these enzymes as anti-cancer drug candidates. Those efforts have benefitted from my involvement as the Principal Investigator of the NIH-funded Macromolecular Crystallography Center of the Cornell High Energy Synchrotron (MacCHESS) facility, which provides resources for standard macromolecular crystallography, small angle X-ray scattering (SAXS), and recently, serial room temperature crystallography as a new approach for rational drug design. These studies uncovered a connection between glutamine metabolism and the formation of extracellular vesicles, which are comprised of two large subfamilies, microvesicles and exosomes. My laboratory has made a major commitment to understand the biogenesis and function of these vesicles and helped to drive the field forward, as I co-organized (with Dr. Xandra Breakefield of Massachusetts General Hospital) the first Keystone meeting on Extracellular Vesicles (June 19-21, 2016) as well as co-organized the Workshop on Extracellular Vesicles in 2019 for the New York Academy of Sciences. We have shown that microvesicles shed by cancer cells can enhance the growth and survival of non-transformed cells, as well as stimulate tumor angiogenesis. We also identified roles for microvesicles and exosomes in embryonic development and stem cell biology. We are now working together with Howard Fine, the Director of the Brain Tumor Center at Weill Cornell Medical College, to test the importance of these and other recent discoveries in clinically relevant cerebral organoid models of aggressive brain cancer.

The research in my laboratory has been pursued by several postdoctoral associates, graduate students, and undergraduates (including a total of 60 PhD students and 40 postdoctoral fellows and associates). A great many of my trainees have gone on to have extremely rewarding careers in medicine, pharmaceutical, and academic research. Some examples include Kermit Carraway, a former graduate student who is now having a very successful career as Co-Director of the Breast Cancer Program at the University of California at Davis Cancer Center and Greg Hoffman, a former graduate student who is currently Vice President of Discovery and Platform at Arbor Biotechnologies in Cambridge Massachusetts. One of my former postdoctoral associates, Yi Zheng, is the Director of Hematology and Cancer Biology at the University of Cincinnati Medical Center, while Shubha

Bagrodia, a former postdoctoral associate is currently a research scientist at the Pfizer Oncology Unit in San Diego. Another example is Reuben Shaw, an honors-undergraduate in my group, who is Director of the Cancer Center at the Salk Institute. During the past five years, 9 graduate students have completed their training and have all secured excellent positions. They include Arash Latifkar, who was awarded a K99 predoctoral-F00 postdoctoral transition research award and is currently a postdoctoral fellow with David Bartel at MIT, Tien Nguyen, who is doing postdoctoral research with Peter Kim at Stanford, Yun Ha Hur, who did postdoctoral training with Elaine Fuchs at Rockefeller University and is now a Professor at Pohang University, and Yang Gao who after a short postdoctoral stint with Yiorgo Skiniotis at Stanford, is now a Professor at the Institute of Interdisciplinary Information Science at Tsinghua University.

Ongoing and recently completed projects that I would like to highlight include:
R35 GM152206
Cerione (PI)
01/01/24-11/30/28
Studies of Global Signal Transduction. These studies involve structural studies of multi-protein metabolic complexes assembled in response to Cdc42 in different biological contexts and efforts to define the structural features of the extracellular vesicles they generate.

P30 GM124166
Cerione (PI)
08/15/19-06/30/24
MacCHESS Synchrotron Source for Structural Biology. This is a facility to provide the necessary resources and technology to support X-ray crystallography and small angle X-ray scattering experiments by the structural biology community.

R01 CA201402
Cerione (PI)
12/04/15-4/30/25
The Unique Roles of the GTP-Binding Protein/Crosslinking Enzyme Transglutaminase and Signaling Partners in Aggressive Cancers. These studies involve examining the roles played by a unique signaling protein/crosslinking enzyme in aggressive cancers including its functions in shed extracellular vesicles, with an emphasis on glioblastoma.

R01 CA223534
Cerione (PI); Weiss (PI); Lin (PI)
04/01/19-03/31/24
Targeting the dependency of cancer cells on the sirtuin SIRT5. These studies involve examining the roles of SIRT5 in cancer metabolism and developing small molecule inhibitors targeting this protein.

R01 EY034867
06/01/23-05/31/27
Cerione (PI)
Probing the molecular mechanisms that regulate the key steps in the GPCR-sensory response pathway responsible for vision in dim light.

Citations:

1. Wang, J.B., Erickson, J.W., Fuji, R., Ramachandran, S., Gao, P., Dinavahi, R., Wilson, K.F., Ambrosio, A.L.B., Dias, S.M.G., Dang, C.V., and **Cerione, R.A.** (2010) Targeting mitochondrial glutaminase activity inhibits oncogenic transformation. *Cancer Cell* **18**, 207-219. *Cover Article.* PMCID: PMC3078749
2. Latifkar, A., Wang, F., Mullmann, J.J., Panizaa, E., Fernandez, I.R.,Lu, L., Miller, A.D., Fischbach, C.F., Weiss, R.S., Lin, H., **Cerione, R.A.***, and Antonyak, M.A. (2022) IGF2BP2 promotes cancer progression by degrading the RNA transcript encoding a v-ATPase subunit. *Proc. Natl. Acad. Sci. USA* **119** (45):e22000447719. *Corresponding author. PMID: 36322753.
3. Gao Y., Eskici, G., Ramachandran, S., Poitevin, F., Steve, A.B., Panova, O., Skiniotis, G., and **Cerione, R.A.** (2020) Structure of the visual signaling complex between transducin and phosphodiesterase 6. *Mol. Cell* **80**, 237-245. PMCID: PMC759677

4. Feng S, Aplin C, Nguyen TT, Milano SK, **Cerione RA**. (2024) Filament formation drives catalysis by glutaminase enzymes important in cancer progression. *Nature Communications **15**, 1971. doi:10.1038/s41467-024-46351-3* PMCID: PMC9949068

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-present Distinguished Professor of Arts and Sciences in Chemistry
2005-present Principal Investigator, Macromolecular Crystallography at the Cornell High Energy Synchrotron
2002-2021 Goldwin Smith Professor of Pharmacology and Chemical Biology, Cornell University
1998-present Full Professor, Department of Chemistry and Chemical Biology, Cornell University
1993-present Full Professor**,** Department of Molecular Medicine, Cornell University
1990-1993. Associate Professor, Department of Pharmacology, Cornell University
1985-1990. Assistant Professor**,** Department of Pharmacology, Cornell University
1982-1985. Senior Research Associate at Howard Hughes Medical Institute, Duke University Medical Center, with Robert Lefkowitz, Reconstitution of Adenylyl Cyclase systems
1979-1982. Postdoctoral Fellow, Cornell University, Professor Gordon G. Hammes, Department of Chemistry, Reconstitution studies of the Chloroplast H^+-ATP Synthetase

Other Experience and Professional Memberships

2023-present Scientific Advisory Board Revere Pharmaceuticals- Development of therapeutic strategies targeting the Rac GTPase
2021 Scientific Advisory Board SHY Therapeutics-Development of small molecule therapeutics for Ras and related small GTPases
2021 External Advisory Committee; Mass. General NCI Program Project Grant
2019-present Advisory Board, P01, Glioblastoma and Extracellular Vesicles, U. of Kentucky Cancer Center
2019 Review panel member, Tumor Cell Biology Study Section
2019 Scientific Organizer, New York Academy of Sciences Workshop on Extracellular Vesicles
2016 Scientific Organizer, Inaugural Keystone Meeting, Exosomes/Microvesicles: Novel mechanisms of cell-cell communication
2016-present Member of Editorial Board, Small GTPases
2013 Co-Director of the Cancer Signaling and Cell Biology Program of the Weill/Cornell Cancer Center
2007-2010 Member, National Institutes of Health Study Section, Molecular Integrative Signal Transduction
2006-2015 Member, Editorial Advisory Board, Biochemistry
2001-2008 Member, Scientific Advisory Board Gene Network Sciences
2000-2005 Member, Editorial Board, Molecular Biology of the Cell
1998 Review Committee for Laboratory of Molecular Biology, National Cancer Institute
1997 Visiting Professor, Louisiana State University Medical Center
1997 Visiting Lecturer, Scripps Research Institute
1996-2000 Member, National Institutes of Health Study Section, Cell Biology and Physiology
1996 Member, Study Section for Department of Defense Breast Cancer Program
1992-1996, 2001-2006 Member, Editorial Board, Journal of Biological Chemistry

Honors

2023 The Jeffrey L. Benovic Award for Excellence in Fundamental or Translational Research, Sidney Kimmel Cancer Center, Thomas Jefferson University
2023 Frontiers in Science Lecturer, Case Western University School of Medicine
2022 Member of the Nominating Committee for the VinFuture Prize in Life Sciences
2021 Keynote Speaker, Center for Extracellular Vesicle Research, Vanderbilt University
2018-2022 Invited Nominator for the Japan Prize
2016, 2022 Invited Nominator for the Nobel Prize in Chemistry
2013 Plenary Presenter: Workshop on Creativity and Innovation. University of Buffalo
2013 Chancellor's Award for Excellence in Scholarship and Creative Activities
2009 American Association for Advancement of Science Fellow
2000 Frontiers Lecturer, Case Western University Medical Center
1999 Eppley Institute Distinguished Lecturer in Cancer Research, Nebraska Medical Center
1986-1990 PEW Foundation Biomedical Scholar Award

1979-1982 National Institutes of Health Postdoctoral Fellow
1979 American Cancer Society Postdoctoral Fellowship Award

C. Contributions to Science

1. In attempting to identify new signaling partners for the EGF receptor (EGFR), we discovered and cloned the human Cdc42 GTPase. We then identified many of its key regulators. They include the product of the Dbl oncogene, which is the founding member of an important family of guanine nucleotide exchange factors for the Rho GTPases (oncogenic Rho GEFs), as well as the Cool (for Cloned-out of library)/Pix (Pak interactive exchange factor)/ARGEFH family of GEFs, and the negative regulator, GDP dissociation factor (RhoGDI). These efforts also led us to show that Heregulin activates Neu/ErbB2/HER2 by first binding to its receptor, ErbB3, which lacks detectable kinase activity but forms a Heregulin-promoted heterodimer with Neu/ErbB2, stimulating Neu/ErbB2 tyrosine kinase activity.

- **a.** Hart, M.J., Eva, A., Evans, T., Aaronson, S.A., and **Cerione, R.A.** (1991) Catalysis of guanine nucleotide exchange on the CDC42Hs protein by the dbl oncogene product. *Nature* **354**, 311-314. PMID:195638
- **b.** Hart, M.J., Maru, Y., Leonard, D., Witte, O.N., Evans, T., and **Cerione, R.A.** (1992) A GDP dissociation inhibitor that serves as a GTPase inhibitor for the Ras-like protein Cdc42Hs. *Science* **258**, 812-815. PMID: 1439791
- **c.** Carraway, K.L. III, Sliwkowski, M.X., Akita, R., Platko, J.V., Guy, P.M., Nuijens, A., Diamonti, A.J., Vandlen, R.L., Cantley, L.C., and **Cerione, R.A.** (1994) The erbB3 gene product is a receptor for heregulin. *J. Biol. Chem.* **269**, 14303-14306. PMID: 8188716
- **d.** Guy, P.M., Platko, J.V., Cantley, L.C., **Cerione, R.A.**, and Carraway, K.L.III (1994) Insect cell expressed p180erbB3 possesses an impaired tyrosine kinase activity. *Proc. Natl. Acad. Sci.* **91**, 8132-8136. PMCID: PMC44559

2. We then identified many signaling targets of Cdc42. They include the serine/threonine kinase PAK (p21-activated kinase)-3 which has been implicated in various biological processes, the γ–coatomer subunit of the COP1 trafficking proteins which work together with Cdc42 to promote oncogenic transformation, and mTOR which in response to Cdc42-signaling activates the RNA cap-binding complex and cap-dependent splicing in cancer cells, as well as ensures their survival during nutrient deprivation. We also discovered that the Cool proteins serve both as upstream activators and downstream signaling effectors for Cdc42, and significantly extend the signaling lifetime of the EGFR.

- **a.** Bagrodia, S., Taylor, S.J., Creasy, C.L., Chernoff, J., and **Cerione, R.A.** (1995) Identification of a mouse p21Cdc42/Rac activated kinase. *J. Biol. Chem.* **270**, 22731-22737. PMID: 7559398
- **b.** Bagrodia, S., Taylor, S.J., Jordan, K.A., Van Aelst, L., and **Cerione, R.A.** (1998) A novel regulator of p21-activated kinases. *J. Biol. Chem.* **273**, 23633-23636. PMID: 9726964
- **c.** Wu, W.J., Erickson, J.W., Lin, R., and **Cerione, R.A.** (2000) The γ-subunit of the coatomer complex binds Cdc42 to mediate transformation. *Nature* **405**, 800-804. PMID: 10866202
- **d.** Wu, W.J., Tu, S., and **Cerione, R.A.** (2003) Activated Cdc42 sequesters c-Cbl and prevents EGF receptor degradation. *Cell* **114**, 715-725. PMID: 14505571

3. Following the discovery of Cdc42 and its various regulators and downstream effectors, we undertook structural biology approaches to obtain images of Cdc42 and its various signaling partners. These include the X-ray structure for Cdc42 bound to RhoGDI which first showed how a geranyl-geranyl moiety attached to the C-terminal end of Cdc42 fits into a hydrophobic pocket, and the X-ray structure for the capped RNA-binding protein complex activated downstream of Cdc42 and mTORC1, bound to α- and β-importin. More recently, we extended these approaches to the use of cryo-EM to probe GPCR-G protein-effector complexes, using the phototransduction signaling pathway as a starting point.

- **a.** Hoffman, G.R., Nassar, N., and **Cerione, R.A.** (2000) Structure of the Rho family GTP-binding protein Cdc42 in complex with the multifunctional regulator RhoGDI. *Cell* **100**, 345-356. *Cover Article.* PMID: 10676816
- **b.** Dias, S.M.G., Wilson, K.F., Rojas, K.S., Ambrosio, A.L.B., and **Cerione, R.A.** (2009) The molecular basis for the regulation of the cap-binding complex by importins. *Nature Struct. Mol. Biol*. **16**, 930-937. PMCID: PMC2782468
- **c.** Gao, Y., Hu, H., Ramachandran, S., Erickson, J.W., **Cerione, R.A.***, and Skiniotis, G.* (2019) Structures of the Rhodopsin-Transducin complex: Insights into G-protein activation. *Mol. Cell* 75, 781-790. *co-Senior author PMCID: PMC6707884.

d. Aplin, C., Milano, S.K., Zielinski, K.A., Pollack, L., and **Cerione, R.A.** (2022) Evolving experimental techniques for structure-based drug design. *J. Phys Chem B*. **126**, 6599-6607. PMID: 3602922

4. While studying the roles of Cdc42 in cancer progression, we discovered a surprising connection between Rho GTPases and the upregulation of glutaminase C (GAC), a member of the glutaminase family of metabolic enzymes, that satisfies the glutamine addiction of cancer cells. This occurs through the activation of the transcription factor c-Jun and the actions of SIRT5 which protects GAC from degradation in cancer cells. These efforts were aided by our development of small molecule allosteric inhibitors of these metabolic enzymes that represent anti-cancer drug candidates and through the establishment of new methods in structural biology for rational drug design.

a. Lukey, M.J., Greene, K.S., Erickson, J.W., Wilson, K.F., and **Cerione, R.A**. (2016) The oncogenic transcription factor c-Jun regulates glutaminase expression and sensitizes cells to glutaminase-targeted therapy. *Nat. Commun.* **7**, 11321. PMCID: PMC483747233.

b. Lukey, M.J., Cluntun, A.A., Katt, W.P., Lin, M.J., Druso, J.E., Ramachandran, S., Erickson, J.W., Le, H.H., Wang, Z.E., Blank, B., Greene, K.S., and **Cerione, R.A.** (2019) Liver-type glutaminase GLS2 is a druggable metabolic node in luminal-subtype breast cancer. *Cell Reports* **29**, 76-88.e7. PMCID: PMC6939472

c. Greene, K.S., Lukey, M.J., Wang, X., Blank, B., Druso, J.E., Stalnecker, C.A., Zhang, C., Negrón Abril Y, Erickson J.W, Wilson K.F, Lin H., Weiss R.S., and **Cerione R. A. (**2019**)** SIRT5 stabilizes mitochondrial glutaminase and supports breast cancer tumorigenesis. *Proc. Natl. Acad. Sci. USA* **116**, 26625-26632. PMCID: PMC6936584

d. Milano, S.K., Huang, Q. Nguyen, T-T.T., Ramachandran, S., Finke, A., Kriksunov, I., Schuller, D., Szebenyi, M., Arenholz, E., McDermott, L.A., Sukumar, N., **Cerione, R.A.***, and Katt, W.P. (2022) New insights into the molecular mechanisms of glutaminase C inhibitors in cancer using serial room temperature crystallography. *J. Biol. Chem*. doi: 10.1016/j.jbc.2021.101535. Online ahead of print. *Corresponding author. PMID: 34954143

5. We determined that increased glutamine metabolism promotes the biogenesis of extracellular shed vesicles (microvesicles and exosomes). We showed that tissue transglutaminase crosslinks fibronectin and VEGF on the surfaces of microvesicles shed by cancer cells, enabling them to alter the tumor microenvironment and to stimulate tumor angiogenesis. We determined how SIRT1 downregulation in cancer cells results in the biogenesis of exosomes with unique cargo capable of promoting metastatic spread and identified a novel role for extracellular vesicles shed from embryonic stem cells in maintaining their pluripotent state.

a. Antonyak, M.A., Li, B., Boroughs, L.K., Johnson, J.L., Druso, J.E., Bryant, K.L., Holowka, D.A., and **Cerione, R.A.** (2011) Cancer cell-derived microvesicles induce transformation by transferring tissue transglutaminase and fibronectin to recipient cells. *Proc. Natl. Acad. Sci. USA* **108**, 4852-4857. PMCID: PMC3064359 *Highlight Article*

b. Feng, Q., Zhang, C., Lum, D., Druso, J.E., Blank, B., Wilson, K.F., Welm, A., Antonyak, M.A., and **Cerione, R.A.** (2017) A class of extracellular vesicles from breast cancer cells activates VEGF receptors and tumor angiogenesis. *Nature Commun.* **8**, 14450. PMCID: PMC5316898

c. Latifkar, A., Ling, L., Hingorani, A., Johansen, E., Clement, A., Zhang, X., Hartman, J., Fischbach, C., Lin, H., **Cerione, R.A.***, and Antonyak, M.A. (2019) Loss of Sirtuin 1 alters the secretome of breast cancer cells by impairing lysosomal integrity. *Dev. Cell* **49**, 393-408.e7. *Cover Article.* *Corresponding author. PMCID: PMC6519475

d. Hur, Y.H., Feng, S., Wilson, K.F., **Cerione, R.A.***, and Antonyak, M.A. (2021) Embryonic stem cell derived extracellular vesicles maintain ESC stemness by activating FAK. *Dev. Cell* **56**, 277-291. *Corresponding author. PMCID: PMC8005871

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/richard.cerione.1/bibliography/40596517/public/?sort=date&direction=ascending