BIOGRAPHICAL SKETCH

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NAME: Cerione, Richard A.

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

POSITION TITLE: Goldwin Smith Professor of Pharmacology and Chemical Biology

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	B.A., Ph.D.	05/1979	Biochemistry
Cornell University, Ithaca, NY	Postdoc	05/1982	Chemistry
Duke University, Durham, NC	Sr. Res. Assoc.	08/1985	Biochemistry

A. Personal Statement

The overall goals of our research program have been to understand the signaling cues that regulate cell growth, differentiation, and development. This began with our discovery of the human Cdc42 GTPase and many of its regulatory proteins and signaling targets, through efforts to identify novel participants downstream from the EGF receptor and other growth factor receptors. These goals have been pursued by a number of postdoctoral associates, graduate students, and undergraduates, with many of my trainees (including a total of 40 PhD students and 30 postdoctoral fellows and associates) having gone on to rewarding careers in medicine, and in pharmaceutical and academic research. Our 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 to study the signaling pathways activated by the two classical GTP-binding protein families, namely, heterotrimeric (large) G-proteins that are essential to the actions of G-protein-coupled receptors (GPCRs), and the Ras-related (small) G-proteins (also known as small GTPases). In our studies, we have taken great advantage of my involvement as the Principal Investigator at MacCHESS (Macromolecular crystallography at the Cornell High Energy Synchrotron), and the many resources provided by this facility in the areas of standard macromolecular crystallography, small angle X-ray scattering (SAXS) and now through the development of serial room temperature crystallography. Our studies of small G-proteins have primarily focused on Cdc42, related Rho GTPases and their downstream signaling targets. We have used X-ray crystallography and SAXS, in combination with cryoEM and biochemical methods, to delineate the mechanisms used to regulate these G-proteins and how they transmit signals to a host of biological targets and effectors. This led to our discovery of new biological outcomes that are mediated by these signaling proteins, including the identification of previously unappreciated roles for Cdc42 and other Rho GTPases in promoting elevated glutamine metabolism in cancer cells, as well as in the generation and shedding of a relatively new class of signaling vesicles by cancer cells (extracellular vesicles). These findings motivated us to use structural methods in combination with small molecule chemistry to design new candidate drug molecules that target metabolic enzymes (e.g. the glutaminases) that play critical roles in cancer progression. For the past several years, our laboratory has also been heavily invested in the study of signaling pathways triggered by GPCRs and large G-proteins that are responsible for sensory responses. A particular emphasis has been the Rhodopsin-Transducin-coupled phototransduction system operating in retinal rods that underlies the ability to see in dim light. In these studies, we are using a combination of X-ray crystallography, SAXS, and cryoEM to obtain structural pictures for the complex between light-activated Rhodopsin and its G-protein partner Transducin, as well as for Transducin bound to its biological effector, the cyclic GMP phosphoidesterase. *CryoEM has in fact become a major application for our studies and so we will greatly benefit from having access to the National Center for CryoEM Access and Training.*

Some representative examples of our work through the years is presented below, and further elaborated in Section C.

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

R35 GM122575
Cerione (PI)
05/01/17-04/30/22
New Frontiers in Extracellular Signaling.

P30 GM124166
Cerione (PI)
08/15/19-06/30/24
MacCHESS Synchrotron Source for Structural Biology.

R01 CA201402
Cerione (PI); Nakano (PI)
12/04/15-4/30/25
The Unique Roles of the GTP-Binding Protein/Crosslinking Enzyme Transglutaminase and Signaling Partners in Aggressive Cancers.

U54 CA210184
Fischbach (PI), Role: Co-Investigator
08/29/16-07/31/21
Center on the Physics of Cancer Metabolism.

R01 CA223534
Cerione (PI); Weiss (PI); Lin (PI)
04/01/19-03/31/24
Targeting the dependency of cancer cells on the sirtuin SIRT5.

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. PMCID: PMC3078749 *Cover Article*
2. 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
3. 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 authors PMID: 31300275
4. 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

B. Positions and Honors

Positions and Employment

2005-present Principal Investigator, Macromolecular Crystallography at the Cornell High Energy Synchrotron (MacCHESS)
2002-present 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
1973-1978 Graduate Teaching Assistant, Dept. of Biochemistry, Professor Theodore Chase, Rutgers Univ.

Other Experience and Professional Memberships

2021 Scientific Advisory Board SHY Therapeutics-Development of small molecule therapeutics for the Ras superfamily of small GTPases
2021 External Advisory Committee; Mass. General NCI Program Project Grant
2019-present Advisory Board, P01, Glioblastoma and Extracellular Vesicles, University of Kentucky (Markey 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
1991-1997 Member, Scientific Advisory Board of Cornell Biotechnology Institute

Honors

2014 Juror for Blavatnik Regional Awards for Young Scientists
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. Contribution to Science

1. Our initial efforts to identify new signaling partners for the EGF receptor resulted in the discovery of the human Cdc42 GTPase. We then identified many of its key regulators and signaling targets. These 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 a number of signaling partners and effectors, including the serine/threonine kinase Pak3, the Cool (for Cloned-out of library)/Pix (Pak interactive exchange factor) family of GEFs and signaling effectors, the gamma subunit of the coatomer complex (COP1), and mTORC1.
   a. Shinjo, K., Koland, J.G., Hart, M.J., Narasimhan, V., Johnson, D., Evans, T., and Cerione, R.A. (1990) Molecular cloning of the gene for the human placental GTP-binding protein, Gp (G25K): identification of this GTP-binding protein as the human homolog of the yeast cell-division-cycle protein CDC42. *Proc. Natl. Acad. Sci. USA* **87**, 9853-9857. PMCID: PMC55272
   b. 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: 1956381
   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. Endo, M., Druso, J.E., and Cerione, R.A. (2020) The two splice variant forms of Cdc42 exert distinct and essential functions in neurogenesis. *J. Biol. Chem*. **295**, 4498-4512. PMCID: PMC7136000

2. Following the discovery of Cdc42 and its various regulators and downstream signaling effectors including those involved in intracellular protein and RNA trafficking, as well as those responsible for elevated glutamine metabolism, we obtained X-ray crystal structures for many of these proteins or protein complexes. Some examples are the X-ray structure for Cdc42 bound to GDI, which for the first time showed how a geranyl-geranyl moiety attached to the C-terminal end of Cdc42 can fit into a hydrophobic pocket, the X-ray structure for the appendage domain of γ-COP, which exhibited striking similarities to a number of adaptors involved in clathrin-mediated endocytosis, the X-ray structure for the capped RNA-binding protein complex bound to α- and β-importin, and an X-ray structure for the metabolic enzyme glutaminase C.
   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. Hoffman, G.R., Rahl, P.B., Collins, R.N., and Cerione, R.A. (2003) Conserved structural motifs in intracellular trafficking pathways: Structure of the γCOP appendage domain. *Mol. Cell* **12**, 615-625. PMID: 14527408
   c. 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 the importins. *Nat. Struct. Mol. Biol.* **16**, 930-937. PMCID: PMC2782468
   d. Li, Y., Erickson, J.W., Stalnecker, C.A., Katt, W.P., Huang, Q., Cerione, R.A.*, and Ramachandran, S. (2016) Mechanistic basis of glutaminase activation: a key enzyme that promotes glutamine metabolism in cancer cells. *J. Biol. Chem.* **291**, 20900-20910. *Corresponding author. PMCID: PMC5076503

3. We also performed biochemical, biophysical, and mechanistic studies examining a number of the signaling partners for Cdc42 and related Rho GTPases. We made the surprising discovery that the Cool proteins serve both as upstream activators and downstream signaling effectors for Cdc42 and Rac, and that by binding both activated Cdc42, and the E3 ubiquitin ligase c-Cbl, Cool-1 significantly influenced EGF receptor signaling by extending its signaling lifetime. We then developed strategies to block downstream signaling outcomes stimulated by Cdc42 and other Rho GTPases. This led to our discovery of a rather unexpected connection between Rho GTPase-signaling and the up-regulation of the glutaminase enzymes that occurs in highly proliferative cells and to the development of small molecules that represent anti-cancer and anti-viral drug candidates.
   a. Wu, W.J., Tu, S., and Cerione, R.A. (2003) Activated Cdc42 sequesters c-Cbl and prevents EGF receptor degradation. *Cell* **114**, 715-725.
   b. Stalnecker, C.A., Ulrich, S.M., Li, Y., Ramachandran, S., McBrayer, M.K., DeBerardinis, R.J., Cerione, R.A.*, and Erickson, J.W. (2015) Mechanism by which a recently discovered allosteric inhibitor blocks glutamine metabolism in transformed cells. *Proc. Natl. Acad. Sci. USA* **112**, 394-399. *Corresponding author. PMCID: PMC4299208
   c. Stalnecker, C.A., Erickson, J.W., and Cerione, R.A. (2017) Conformational changes in the activation loop of mitochondrial glutaminase C: A direct fluorescence readout that distinguishes the binding of allosteric activators from inhibitors. *J. Biol. Chem*. **292**, 6095-6107. PMCID: PMC5391743.
   d. 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

4. We determined that an important consequence of Rho GTPase-signaling in transformed cells and cancer cell metabolism is the generation of extracellular shed vesicles (microvesicles and exosomes) that are generated and shed by aggressive cancer cells. We discovered that microvesicles markedly alter the signaling properties, as well as the proliferative and survival capabilities, of non-transfomed cells that they target. Extracellular vesicles are currently receiving a great deal of attention in both the basic research and pharmaceutical communities because of evidence from our laboratory and other groups showing that they contribute to a number of aspects of cell biology and diseases such as cancer.
   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. Li, B., Antonyak, M.A., Zhang, J., and Cerione, R.A. (2012) RhoA triggers a specific signaling pathway that generates transforming microvesicles in cancer cells. *Oncogene* **31**, 4740-4749. PMCID: PMC3607381
c. Desrochers, L.M., Bordeleau, F., Reinhart-King, C.A., Cerione, R.A.*, and Antonyak, M.A. (2016) Microvesicles provide a novel mechanism for intercellular communication by embryonic stem cells during embryo implantation. *Nat. Commun.* **7**, 11958. *Corresponding author. PMCID: PMC4912619
d. 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. *Nat. Commun.* **8**, 14450. PMCID: PMC5316898

5. We have a long-standing interest in the reconstitution and structure-function analyses of the principle components of the phototransduction signaling pathway responsible for vertebrate vision. This led us to make a sustained commitment toward obtaining structural information that has shed important light on the molecular basis for the coupling of Rhodopsin and Transducin, as well as insights into the mechanisms responsible for the activation of this G-protein and its ensuing regulation of its biological effector enzyme, PDE6.
   a. Mittal, R., Erickson, J.W., and Cerione, R.A. (1996) Uncoupling GTP binding from target stimulation by a single mutation in the transducin alpha subunit. *Science* **271**, 1413-1416.
   b. Singh, G., Ramachandran, S., and Cerione, R.A. (2012) A constitutively active Gα subunit provides insights into the mechanism of G protein activation. *Biochemistry* **51**, 3232-3240. PMCID: PMC3620018
   c. Gao, Y., Westfield, G., Erickson, J.W., Cerione, R.A.*, Skiniotis, G., and Ramachandran, S. (2017) Isolation and structure-function characterization of a signaling-active rhodopsin-G protein complex. *J. Biol. Chem.* **292**, 14280-14289. PMCID: PMC5572916 *Highlight Article* *Corresponding author.
   d. Milano, S.K., Wang, C., Erickson, J.W., Cerione, R.A*, and Ramachandran, S. (2018) Gain-of-function screen of α-transducin identifies an essential phenylalanine residue necessary for full effector activation. *J. Biol. Chem.* **293**, 17941-17952. PMCID: PMC6240874. *Corresponding author.

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