

CURRICULUM VITAE

DOUGLAS ALLEN ANDRES, Ph.D.

Professor and Vice-Chair
Department of Molecular and Cellular Biochemistry
University of Kentucky College of Medicine
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Lexington, Kentucky 40536
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EDUCATION:

- 1981-1985 University of Wisconsin, Madison, Wisconsin,
B.S. in Chemistry.
- 1985-1990 Purdue University, West Lafayette, Indiana.
Advisor, Dr. Jack E. Dixon
Ph.D. in Biochemistry.
"Characterization of the Carboxyl-terminal Sequences Responsible
for Protein Retention in the Endoplasmic Reticulum"

PROFESSIONAL EXPERIENCE:

- 1990-1993 Postdoctoral Fellow
Advisors, Drs. Michael S. Brown and Joseph L. Goldstein
Department of Molecular Genetics
Univ. of Texas, Southwestern Medical Ctr., Dallas, Texas
Research Area: Protein isoprenylation and biochemical characterization of CAAX and
Rab prenyl transferase enzymes.
- 1993-Present UNIVERSITY OF KENTUCKY COLLEGE OF MEDICINE
Department of Molecular and Cellular Biochemistry
Position: Assistant Professor 1993-1999
Associate Professor 1999-2005
Professor and *Vice-Chair* 2005-present

SCIENTIFIC, HONORARY AND PROFESSIONAL SOCIETIES:

- 1990-present American Association for the Advancement of Science
1993-present Sigma Xi
1997-present American Society for Biochemistry and Molecular Biology
2002-present The Society of Neuroscience
2003-present American Heart Association

RESEARCH INTERESTS:

Ras-related GTP-binding Proteins, Signal Transduction, Cellular Transformation, Neuronal Growth and Differentiation, Calcium Channel Regulation, Protein Isoprenylation.

HONORS AND AWARDS

- 1984 Summer Research Fellowship, American Diabetes Association,
Indiana Affiliate
- 1985 Arnold Kent Balls Award - Outstanding Graduate Student,
Purdue University
- 1991-1993 Fellow of the Jane Coffin Childs Memorial Fund for Medical
Research, University of Texas, Southwestern Medical Center
- 1993-present Grant Awards (Section, ante)
- 1993-present Member of Sigma Xi (Purdue Chapter)

TEACHING EXPERIENCE

- 1994-present Seminar in Biochemistry (BCH 618/619)
(1995 *Co-Director*, 1996-97 *Director*, 01-02 *Director*)
Graduate course, University of Kentucky
- 1995 General Biochemistry (BCH 502)
Presented 12 lectures on amino acid/nucleotide biosynthesis
Graduate course, University of Kentucky
- 1995 Biochemistry of Lipids and Membranes (BCH 610)
Presented 9 lectures on Lipid Modification/Signaling
Graduate course, University of Kentucky
- 1995 Molecular Biology and Genetics (BCH 615)
Presented 2 lectures on Ras Signal Transduction
Graduate course, University of Kentucky
- 1996-02 Fundamentals of Biochemistry (BCH 401G)
Present 15-18 lectures/year. General survey
Undergraduate and Graduate course, University of Kentucky
- 1997 Independent Work in Chemistry (CHE 395),
Student: Chicola M. Whitfield
- 1997-99 Biochemistry of Cellular Signaling (BCH 780)
Present 2-6 lectures/year Ras GTPases and tyrosine phosphatases
Graduate course, University of Kentucky
- 1998-99 Independent Work in Chemistry (CHE 395),
Student: Brian Allen

- 1999 Molecular Cell Biology (MI 710)
6 lecture hours/year: Microtubules; Rac/Rho GTPases
Graduate Course, University of Kentucky
- 2001 Cellular Signaling (IBS 604)
5 lecturehours/year
Graduate Course, University of Kentucky
- 2002 Cellular Signaling (IBS 604)
10 lectures
Graduate Course, University of Kentucky
- 2003-present Cellular Biology (IBS 603)
5 lectures
Graduate Course, University of Kentucky
- 2003-present Cellular Signaling (IBS 604) *Course Director*
12 lectures
Graduate Course, University of Kentucky

SELECTED PROFESSIONAL ACTIVITIES

Extramural:

- 1996 Ad-hoc Reviewer, *Biochimica et Biophysica Acta*
- 1997-present Ad-hoc Reviewer, *Journal of Biological Chemistry*
- 1997-present Ad-hoc Reviewer, *Journal of Neuroscience*
- 1999-present Ad hoc Reviewer, *American J. of Pathology*
- 1999-present Ad hoc Reviewer, *Oncogene*
- 1999-present Ad hoc Reviewer, *Journal of Neurochemistry*
- 2000 Ad hoc Reviewer, *PNAS*
- 2002-present Ad hoc Reviewer, *Molecular Biology of the Cell*
- 2002-present Ad hoc Reviewer, *Biochemistry*
- 2002 Ad hoc Reviewer, *Biochemical Pharmacology*
- 2004 Ad hoc Reviewer, *Circulation*
- 2004 Ad hoc Reviewer, *Cancer Research*
- 2004-2006 *Editorial Board Member*, *The Journal of Biological Chemistry*

Study Sections:

- 1999-00 American Cancer Society: Tumor Biology and Endocrinology Section Ad-hoc
- 1999-00 UKMC Grant Ad-hoc Reviewer
- 1998-01 American Heart Association (Southern 5B) Study Section, Member
- 2002-present American Cancer Society: Tumor Biology and Endocrinology Section, Member
- 2001-present United States-Israel Bi-national Science Foundation
- 2002 Wellcome Trust Ad-hoc Reviewer
- 2003 Biotechnology and Biological Sciences Research Council, UK Ad-hoc reviewer

2003 Signal Transduction and Cellular Regulation, National Science Foundation Ad-hoc
 2004-present Developmental Neurosciences, National Science Foundation Ad-hoc
 2005-07 **Vice-Chair** Southeast/Ohio Valley AHA Affiliate Peer Review Committee
 2005-07 **Vice-Chair**, American Cancer Society: Tumor Biology and Endocrinology Section

University of Kentucky Activities:

1994-present Summer Student Undergraduate Advisor
 Sophie Picot (1999)
 Nathan Lucardie (1998)
 Marc Russell (1997)
 Stephen Koh (1995)
 Matthew Beaudet (1994)

1994-present Graduate Student Advisor
 Chunyan Pang Chemistry 8/05-present
 Jennifer Rudolph Biochemistry 6/03-present
 Nathan Correll Biochemistry 6/03-present
 Mike Spencer Biochemistry 6/99-11/02 Ph.D.
 Haipeng Shao Biochemistry 8/95-6/00 Ph.D.
 Brian Finlin Biochemistry 8/94-9/99 Ph.D.

1994-present University Student Committee Member
 Xiao-jie Yuan Biochemistry 2/94-4/00 Ph.D.
 Deqin Ma Biochemistry 3/94-1/98 Ph.D.
 Lisa Quinn Gothard Biochemistry 11/95-4/97 M.S.
 Paula Lemons Biochemistry 11/95-6/99 Ph.D.
 Nancy Webb Immunology 10/96-5/99 Ph.D.
 Kareem Chehade Biochemistry 6/97-6/02 Ph.D.
 Brian Thompson Biochemistry 10/97-10/98 M.S.
 Kristen Morey Biology 3/98-6/02 Ph.D.
 Tara Rutledge Biochemistry 6/99-3/04 Ph.D.
 Kirk Williams Biochemistry 6/99-6/00 M.S.
 Jake Issacs Biochemistry 6/99-8/03 Ph.D.
 Rongwen Xi Biology 5/00-11/02 Ph.D.
 Wangsun Choi Biochemistry 7/03-present
 Shannon Whitman Biochemistry 7/03-present
 Jason Ren Biochemistry 7/03-present
 Mark Wurth Biochemistry 7/03-present
 Divya Srinivasan Pharmacology 7/04-present
 Chiranthani Sumanasekera Biochemistry 7/04-present
 Nathan Vandeford Biochemistry 7/04-present

1994-present Directed Graduate Student Laboratory Rotations
 Marion Novak 2006
 Shawn Crump 2006
 Vishal J. Sindhava 2005

Weikang Cai	2005
Siva Gandhapudi	2004
Jianing Yang	2004
Divya Srinivasan	2004
Sarah Beth Martin	2003
Chiranthani Sumanasekera	2003
Richard Singiser	2003
Nathan Vandeford	2003
Jennifer Rudolph	2003
Nathan Correll	2003
Salim El-Amouri	2001
Mike Sheehan	2000
Kallol Ray	1999
Tara Rutledge	1999
Mike Spencer	1998
Deborah Sullivan	1998
Nan Guo	1998
Kris Jones	1997
Brian Thompson	1997
Kareem Chegade	1996
Jun-Tao Guo	1995
Haipeng Shao	1995
Brian Finlin	1994

- 1994-1995 Member, Biochemistry Department New Faculty Search Committee
- 1994-1995 Selection Committee for Summer Undergraduate Research Students
- 1995-present *Chairman*, Biochemistry Department Equipment Committee
- 1996 Summer Employment Research Apprentice Program.
Student Preceptor: Chicola M. Whitfield.
- 1996 Howard Hughes Medical Institute (HHMI) Summer Internship Mentor:
Loris E. Sherman (Instructor: Somerset Comm. College)
- 1996 Member of THRI/College of Agriculture Faculty Search Committee
- 1996-1997 Post Doctoral Fellow Advisor
Dr. Keiko Kadono-Okuda
Currently a faculty member: National Institute of Sericulture and Entomological Science,
Genome Research Team. Tsukuba, Japan.
- 1996-1999 Member College of Medicine Student Progress and Promotions Committee
8/96-7/99
- 1998 Member, Biochemistry Departmental Graduate Curriculum Subcommittee

- 1998 Member, Biochemistry Departmental Signal Transduction Faculty Search Committee
- 1999 Outside Member of Doctoral Thesis Examination
Liyue Huang Toxicology 9/99
- 1999 Member Microbiology/Immunology Department 6 year Review Committee
- 1999 IBS 604, Cell Biology and Signaling II, Course Committee
- 2000 Member, Departmental Graduate Recruitment Committee
- 2001-present Member, Departmental IBS Recruitment Committee
- 2001-2003 **Director**, Biochemistry Department Summer Undergraduate Program
- 2001 Outside member of Doctoral Thesis Examination
Bruce A. Waldrop Pharmacy 10/01
- 2002-present IBS 604, *Course Director*
- 2003 Outside member of Doctoral Thesis Examination
Brent Meier /03
- 2003 **Chairman**, Biochemistry Departmental/Aging Center Faculty Search Committee
- 2003-present Member, Curriculum Committee, Integrated Biomedical Sciences (IBS) Graduate Program
- 2004 Member, New Building Planning Committee
- 2005-08 Member, UK Senate Hearing Panel (Privilege and Tenure)
- 2005 Outside member of Doctoral Thesis Examination
Dr. Tun-Lan Huang 11/05
- 2005 **Chairman**, Department of Molecular and Cellular Biochemistry Faculty Search Committee
- 2005 **Vice-Chair**, Department of Molecular and Cellular Biochemistry

Postdoctoral Fellows:

Keiko Kadono-Okuda 1995-96 GTP Overlay Assay/Novel Ras Family GTPases
 Brian Finlin 1999-present RGK Family GTPases
 Grant (Geng-Xian) Shi 2003-present Rit and Rin GTPase Signaling

Michael J. Roberts 2003-present Novel Prenyl Compounds: RFIs
Tomoko Sengoku 2004-present Rit/Rin GTPases in Neuronal Survival

GRANT SUPPORT

Present:

1. **Principal Investigator**, “Regulation of Neuronal Survival by Ras-like GTPase”. NIH R01 2003-2007 NINDS045103.
2. **Principal Investigator**, “Regulation of Calcium Channel Function by the Rem GTPase”. NIH R01 2003-2007 HL072936.
3. Co-P.I. H. Peter Spielmann (PI), “Synthetic Probes of Protein Prenylation”. NIH R01 2002-2006 GM66152.
4. Co-P.I. J. Satin (PI), “Mechanisms of long-term Cardiac Ion Channel Regulation”. NIH R01 2003-2007 HL074091.
5. Predoctoral Fellowship (Sponsor) “Regulation of Cardiac L-type Calcium Channel Function by the Rem GTPase”. Southeast/Ohio Valley AHA Affiliate 2004-2006 0415107B

PATENTS

U.S. Patent #6,284,910
FARNESYL PYROPHOSPHATE ANALOGS
Inventors: Drs. D.A. Andres and H.P. Spielmann

PUBLICATIONS

1. Andres, D.A., Dickerson, I.M., and Dixon, J.E. (1990) Variants of the Carboxyl-terminal KDEL Sequence Direct Intracellular Retention. **Journal of Biological Chemistry**, 265, 5952-5955.
2. Andres, D.A., Rhodes, J.D., Meisel, R.L., and Dixon, J.E. (1991) Characterization of the Carboxyl-terminal Sequences Responsible for Protein Retention in the Endoplasmic Reticulum. **Journal of Biological Chemistry**, 266, 14277-14282.
3. Chen, W. -J., Andres, D.A., Goldstein, J.L., Russell, D.W., and Brown, M.S. (1991) cDNA Cloning and Expression of the Peptide-Binding β -Subunit of Rat p21^{ras} Farnesyltransferase, the Counterpart of Yeast DPR1/RAM1. **Cell** 66, 327-334.
4. Chen, W.-J., Andres, D.A., Goldstein, J.L., and Brown, M.S. (1991) Cloning and Expression of a cDNA Encoding the α subunit of Rat p21^{ras} Protein Farnesyltransferase. **Proceedings of the National Academy of Sciences USA**, 88, 11368-11372.
5. Andres, D.A., Goldstein, J.L., Ho, Y.K., and Brown, M.S. (1993) Mutational Analysis of the α -Subunit of Protein Farnesyltransferase. **Journal of Biological Chemistry** 268, 1383-1390.

6. Andres, D.A., Milatovich, A., Wenzlau, J., Ozcelik, T., Brown, M.S., Goldstein, J.L., and Francke, U. (1993) cDNA Cloning of the Two Subunits of Human CAAX Farnesyltransferase and Chromosomal Mapping of FNTA and FNTB Loci and Related Sequences. **Genomics** 18, 105-112.
7. Andres, D.A., Seabra, M.C., Brown, M.S., Armstrong, S.A., Smeland, T., Cremers, F., and Goldstein, J.L. (1993) cDNA Cloning of Component A of Rab Geranylgeranyl Transferase and Demonstration of its Role as a Rab Escort Protein. **Cell** 73, 1-20.

Since coming to the University of Kentucky

8. Crick, D.C., Waechter, C.J., and Andres, D.A. (1994) Utilization of Geranylgeraniol for Protein Isoprenylation in C6 Glial Cells. **Biochemical Biophysical Research Communications**, 205, 955-961.
9. Crick, D.C., Suders, J., Kluthe, C.M., Andres, D.A., and Waechter, C.J. (1995) Selective Inhibition of Cholesterol Biosynthesis in Brain Cells by Squalestatin. **Journal of Neurochemistry**, 65, 1365-1373.
10. Crick, D.C., Andres, D.A., and Waechter, C.J. (1995) Farnesol is Utilized for Protein Isoprenylation and the Biosynthesis of Cholesterol in Mammalian Cells. **Biochemical Biophysical Research Communications**. 211, 590-599.
11. Crick, D.C., Waechter, C.J., and Andres, D.A. (1996) Geranylgeraniol Restores Cell Proliferation to Lovastatin Treated C6 Glial Cells. **SAAS Bulletin**. 9, 37-42.
12. Crick, D.C., Andres, D.A., and Waechter, C.J. (1997) Geranylgeraniol Promotes Entry of UT-2 Cells into the Cell Cycle in the Absence of Mevalonate. **Experimental Cell Research**, 231, 302-307.
13. Finlin, B. and Andres, D.A. (1997) Rem: A New Member of the Rad and Gem/Kir Ras-Related GTP-binding Protein Family Repressed by Lipopolysaccharide Stimulation. **Journal of Biological Chemistry** 272, 21982-21988.
14. Andres, D.A., Shoa, H., Crick, D.C., and Finlin, B. (1997) Expression Cloning of a Novel Farnesylated Protein, RDJ2, Encoding a DnaJ Protein Homologue. **Biochemical Biophysical Research Communications** , 346, 113-124.
15. Kadono-Okuda, K. and Andres, D.A. (1997) An Expression Cloning Method to Identify Monomeric GTP-Binding Proteins by GTP Overlay. **Analytical Biochemistry**, 254, 187-191.
16. Crick, D.C., Andres, D.A., and Waechter, C.J. (1997) Novel Salvage Pathways Utilizing Farnesol and Geranylgeraniol for Protein Isoprenylation. **Biochemical Biophysical Research Communications** , 237, 483-487.
17. Crick, D. C., Andres, D. A., Danesi, R., Macchia, M., and Waechter, C. J. (1998) Geranylgeraniol Overcomes the Block of Cell Proliferation by Lovastatin in C6 Glioma Cells. **Journal of Neurochemistry**, 70, 2397-2405.
18. Finlin, B. S. and Andres, D. A. (1999) Phosphorylation-dependent Association of the Ras-Related GTP-binding Protein Rem with 14-3-3 Proteins. **Archives of Biochemistry and Biophysics**, 368, 401-412

19. Shao, H., Okuda, K, Finlin, B.S., and Andres, D.A. (1999) Biochemical Characterization of the Ras related GTPases Rit and Rin. **Archives of Biochemistry and Biophysics**, 371, 207-219.
20. Andres, D. A., Crick, D. C., Finlin, B. S., and Waechter, C. J. (1999) Rapid Identification of Cysteine-Linked Isoprenyl Groups By Metabolic Labeling with [³H]Farnesol and [³H]Geranylgeraniol. In: Protein Lipidation Protocols, Methods in Molecular Biology Vol. 116, 107-123. Ed. Gelb, M. H.
21. Finlin, B.S., Kadono-Okuda, K., Guo, N., and Andres, D.A. (2000) Rem2 a New Member of the Rad/Gem/Kir Family of Ras-related GTPases. **Biochemical Journal**, 347, 223-231.
22. Chehade, K.A.H, Andres, D.A., Morimoto, M., and Spielmann, H.P. (2000) Synthesis and Transfer of Farnesyl Pyrophosphate Analogs to Ras by Protein Farnesyltransferase. **Journal of Organic Chemistry**, 65, 3027-33.
23. Andres, D. A. (2000) Expression cloning to identify monomeric GTP-binding proteins by GTP overlay. **Methods in Enzymology**. 332, 203-210.
24. Andres, D. A. (2000) Expression cloning of novel prenylated proteins. **Methods in Enzymology**. 332, 195-202.
25. Rusyn, E.V., Reynolds, E.R., Shao, H., Grana T.M., Chan, T.O., Andres, D.A., and Cox, A.D. (2000) Rit, a non-lipid-modified Ras-related protein, transforms NIH3T3 cells without activating the ERK, JNK, p38 MAPK or PI3K/Akt pathways. **Oncogene**. 19, 4685-4694.
26. Shao, H. and Andres, D. A. (2000) A Novel RalGEF-like Protein, RGL3, as a Candidate Effector for Rit and Ras. **Journal of Biological Chemistry**, 275, 26914-26924.
27. Than, C., Morimoto, H., Williams, P.G., Chehade, K. A. H., Andres, D.A., and Spielmann H. P. (2001) Preparation, NMR Characterization and Labeling Reactions of Tritiated Triacetoxy Sodium Borohydride. **Journal of Organic Chemistry**, 66, 3602-3605.
28. Finlin, B.S., Gau, C-L, Murphy, G.A., Shao, H., Kimel, T., Seitz, R.S., Chiu, Y-F., Botstein, D., Brown, P.O., Der, C.J., Tamanoi, F., Andres, D.A., and Perou, C.M. (2001) RERG is a novel Ras-related, estrogen-regulated and growth-inhibitory gene in breast cancer. **Journal of Biological Chemistry**, 276, 42259-42267.
29. Micali, E, Chehade, K.A.H., Isaacs, R.J., Andres, D.A., and Spielmann, H.P. (2001) Protein farnesyltransferase isoprenoid substrate discrimination on isoprene double bonds and branched methyl groups. **Biochemistry**. 40, 12254-12265.
30. Andres, D. A., Crick, D. C., Finlin, B. S., and Waechter, C. J. (2002) The Metabolic Labeling and Analysis of Isoprenylated Proteins. In: Protein Purification Handbook 2nd Edition, Chapter 95. Ed. Walker, J. M.
31. Spencer M., Shao, H., Tucker, H.M., and Andres D.A. (2002) Nerve growth factor-dependent activation of the small GTPase Rin. **Journal of Biological Chemistry** 277, 17605-17615.

32. Spencer, M., Shao, H. and Andres, D.A. (2002) Induction of neurite outgrowth in pheochromocytoma cells by the Rit GTPase. **Journal of Biological Chemistry**, 277, 20160-20168.
33. Chehade, K. A. H., Kiegiel, K., Isaacs, R. J., Pickett, J. S., Bowers, K. E., Fierke, C. A., Andres, D. A. and Spielmann, H. P. (2002) Photoaffinity Analogs of Farnesyl Pyrophosphate Transferable by Protein Farnesyl Transferase, **Journal of the American Chemical Society**, 124(28), 8206-8219.
34. Hynda, D.L., Spencer, M.L., Andres, D.A., and Snow, D.M. (2003) Rit promotes MEK-independent neurite branching in human neuroblastoma cells **Journal of Cell Science**,116(10),1925-1935.
35. Finlin, B.S. Crump, S., Satin, J., and Andres, D.A. (2003) Regulation of Voltage-gated Calcium Channel Activity by the Rem and Rad GTPases. **Proceedings of the National Academy of Sciences USA**, 100(24), 14469-14474.
36. Andres D. A. (2004) Nonradioactive Methods for Detecting Activation of Ras-related Small G Proteins. **Methods in Molecular Biology**, 284, 163-173.
37. Troutman, J. M., Chehade, K. A., Kiegiel, K., Andres, D. A., and Spielmann, H. P. (2004) Synthesis of acyloxymethyl ester prodrugs of the transferable farnesyl transferase substrate farnesyl methylenediphosphate. **Bioorganic and Medicinal Chemistry Letters**, 14(19), 4979-4982.
38. Kim, I.-J., Drahushuk, K. M., Kim, W.-Y., Gonsiorek, E. A., Lein, P., Andres, D.A., and Higgins, D. (2004) Extracellular Signal-Regulated Kinases Regulate Dendritic Growth in Rat Sympathetic Neurons. **Journal of Neuroscience**, 24(13), 3304-3312.
39. Shi, G. -X and Andres, D.A. (2004) Rit Contributes to NGF-Induced Neuronal Differentiation via Activation of B-Raf-ERK and p38 MAP kinase Cascades, **Molecular and Cellular Biology**, 25(2), 830-846.
40. Harrison, S.M.W., Rudolph, J.L., Spencer, M.L., Wes, P.D., Montell, C., Andres, D.A., and Harrison, D.A. (2005) Activated RIC, a small GTPase, genetically interacts with the Ras pathway and calmodulin during Drosophila development. **Developmental Dynamics**, 232(3), 817-826.
41. Finlin, B. S., Mosely, A. L., Crump, S. M., Correll, R. N., Ozcan, S., Satin, J., and Andres, D.A. (2005) Regulation of L-type Ca²⁺ Channel Activity and Insulin Secretion by the Rem2 GTPase. **Journal of Biological Chemistry**, 280(51), 41864-41871.
42. Shi, G. -X., Han, J., and Andres, D.A. (2005) Rin GTPase Couples Nerve Growth Factor Signaling to p38 and b-Raf/ERK Pathways to Promote Neuronal Differentiation. **Journal of Biological Chemistry**, 280(45), 37599-37609.
43. Troutman, J.M., Roberts, M.J., Andres, D.A., and Spielmann, H.P. (2005) Tools to Analyze Protein Farnesylation in Cells. **Bioconjugate. Chemistry**,16(5), 1209-1217.
44. Subramanian, T., Wang, Z., Troutman, J.M., Andres, D.A., and Spielmann, H.P. (2005) Directed Library of Anilinoogeranyl Analogues of Farnesyl Diphosphate via mixed Solid- and Solution-phase Synthesis. Accepted: **Organic Letters**, 7(11), 2109-2112.

45. Andres, D.A., Crump, S. M., Correll, R. N., Satin, J., and Finlin, B. S. (2005) Analyses of Rem/RGK Signaling and Biological Activity. Accepted: **Methods in Enzymology** Vol. 407.
46. Andres, D.A., Rudolph, J.L., Sengoku, T., and Shi, G.-X. (2005) Analysis of Rit Signaling and Biological Activity. Accepted: **Methods in Enzymology** Vol. 407.
47. Key, M.D., Andres, D.A., Der, C.J., and Repasky, G.A. (2005) Characterization of RERG: An Estrogen-regulated Tumor Suppressor Gene. Accepted: **Methods in Enzymology** Vol. 407.

BOOK CHAPTERS

Andres, D. A., Crick, D. C., Finlin, B. S., and Waechter, C. J. (1999) Rapid Identification of Cysteine-Linked Isoprenyl Groups By Metabolic Labeling with [³H]Farnesol and [³H]Geranylgeraniol. In: Protein Lipidation Protocols, Methods in Molecular Biology Vol. 116, 107-123. Ed. Gelb, M. H.

Andres, D. A. (2000) Expression cloning to identify monomeric GTP-binding proteins by GTP overlay. Methods in Enzymology. 332, 203-210.

Andres, D. A. (2000) Expression cloning of novel prenylated proteins. Methods in Enzymology. 332, 195-202.

Andres, D. A., Crick, D. C., Finlin, B. S., and Waechter, C. J. (2002) The Metabolic Labeling and Analysis of Isorenylated Proteins. In: Protein Purification Handbook 2nd Edition, Chapter 95. Ed. Walker, J. M.

Andres, D. A. (2003) Non-radioactive Methods for Detecting Activation of Ras-related Small G Proteins. In: Signal Transduction Protocols, 2nd edition, Methods in Molecular Medicine. Ed. Dickson, R.C. and Mendenhall, M.D.

MANUSCRIPTS SUBMITTED FOR PUBLICATION

Crump, S. M., Schroder, E.A., Finlin, B.S., Andres, D.A., and Satin J. (2006) The L-type Calcium Channel Alpha-subunit and Protein Kinase Inhibitors Modulate the Rem-Mediated Regulation of Current. Manuscript submitted to *American Journal of Physiology*.

Shi, G.-X. and Andres, D.A. (2006) A Novel cAMP-dependent Epac-Rit Signaling Pathway Contributes to PACAP38-mediated Neuronal Differentiation. Manuscript submitted to *Molecular and Cellular Biology*.

Lein, P.J., Guo, X., Shi, G.-X., Moholt-Siebert, M., and Andres, D.A. (2006) The Novel GTPase Rit Regulates the Balance between Axonal and Dendritic Growth. Manuscript submitted to *J. Neuroscience*.

INVITED LECTURES (selected)

2000 Ras proteins, Signal Transduction and Cancer. Nephrology/Bone-Mineral Metabolism Division, University of Kentucky, February 2.

- 2001 Rem GTPase: A Regulator of Angiogenesis? Department of Genetics, Cell Biology, and Development, University of Minnesota, February 13.
- 2001 Regulation of Angiogenesis by the Rem GTPase. Conference on Invasion and Metastasis, International Institute of Anticancer Research, Kapandriti Greece, June 15.
- 2001 Role of the Rit GTPase in transformation and differentiation. 6th World Congress on Advances in Oncology, Hersonissos, Crete, Greece, October 19.
- 2002 Regulation of Neuronal Survival and Differentiation by the Rit GTPase. Indiana University School of Medicine, Indianapolis, IN, September 23, 2002.
- 2003 Regulation of Neuronal Survival and Differentiation by the Rit GTPase. Case Western Reserve University Department of Physiology and Biophysics, School of Medicine, Cleveland, OH, April 28, 2003.
- 2003 Rem GTPase Regulates Cardiac Ca Current Expression. American Heart Association National Meeting, Orlando, FL, November 11, 2003.
- 2004 RGK GTPases: Novel Regulators of Calcium Channel Function. National Institute on Aging, National Institutes of Health, Baltimore, MD, November 2004.
- 2004 Analysis of a Ca²⁺ Channel β -Subunit, AID, and Rem GTPase Regulatory Complex. American Heart Association National Meeting, New Orleans, LA, November 8, 2004.
- 2005 The Rit GTPase Regulates Neuronal Survival via Activation of B-Raf-ERK and p38 Kinase Cascades, CROET, Oregon Health & Science University, Portland, OR, May 2005.
- 2005 Regulation of L-type Ca²⁺ Channel Activity and Insulin Secretion by the Rem2 GTPase. American Diabetes Association National Meeting, San Diego, CA, June, 11, 2005.
- 2005 The small GTPase Rit Differentially Regulates Axonal and Dendritic Growth in Sympathetic and Hippocampal Neurons. Society for Neuroscience National Meeting, Washington D. C., November 2005.

Research Overview

Cells are highly responsive to signals from their environment. These signals include growth factors, hormones, or even neuronal firing. The sensing and processing of these signals are carried out by molecular circuits within the cell which detect, amplify and integrate these environmental cues into a specific response. Ras-related GTP-binding proteins function as GTP/GDP- regulated “switches” and are widely utilized in the cellular response pathways. Ras family proteins respond to extracellular stimuli by exchanging GTP for bound GDP, thereby triggering intracellular signaling cascades through their GTP-dependent interaction with a variety of target molecule(s) to produce a characteristic cellular effect. My laboratory is interested in deciphering the role of Ras GTPases in various cellular paradigms, as Ras family G-proteins play key roles in the ontogeny of cancer, diabetes, and heart disease as well as the processes of neuronal survival and axonal growth. Because we have studied the function of several GTPases in some detail, I will review some of our findings in this area and briefly outline our current research interests.

Regulation of Neuronal Survival by the Rit and Rin GTPases.

Aberrant cell death (apoptosis) contributes to various neurodegenerative disorders including stroke, epilepsy, and Alzheimer's disease. Elaborating the signal transduction mechanisms that regulate neuronal survival is thus important for understanding both basic biology and for therapeutic intervention. Neurotrophins (nerve growth factors) potently stimulate neuronal survival in part by activating members of the Ras small GTP-binding protein family, which function to translate and direct neurotrophin-initiated signals into multiple signaling pathways. We have discovered a novel, evolutionarily conserved group of Ras-related proteins (Rit and Rin) that are regulated by neurotrophins and direct neural pro-survival signaling cascades. Through the combined use of biochemistry, molecular biology, and genetic approaches, we continue to examine the function of these unique regulators of neuronal survival with the goal of applying this knowledge toward the treatment of neurodegenerative disease.

Spencer M., Shao, H., Tucker, H.M., and **Andres D.A.** (2002) NGF-dependent activation of the small GTPase Rin. *J. Biol. Chem.* 277, 17605-15.

Spencer, M., Shao, H. and **Andres, D.A.** (2002) Induction of neurite outgrowth in pheochromocytoma cells by the Rit GTPase. *J. Biol. Chem.* 277, 20160-68.

Hynds, D.L., Spencer, M.L., **Andres, D.A.**, and Snow, D.M. (2003) Rit promotes MEK- independent neurite branching in human neuroblastoma cells. *J. Cell Sci.* 116(10), 1925-35.

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Regulation of Calcium Channel Function by the Rem/Rem2 GTPases.

Voltage-dependent calcium channels (VDCCs) regulate the flow of Ca²⁺ ions across cellular membranes as a function of membrane potential. This calcium influx serves to regulate a variety of cellular functions, including muscle contraction, endocrine secretion, and synaptic transmission. Because of this, their regulation is of critical importance to the control of cellular activity. This is highlighted by the finding that calcium dysfunction accompanies disease progression such as in cardiac hypertrophy and diabetes. We have recently identified a novel mechanism for regulating voltage-dependent calcium channel function. These data provide evidence that the Ras-related GTPase Rem regulates calcium channel activity in cardiac and skeletal muscle to regulate contraction while the Rem2 G-protein functions to control both insulin secretion from pancreatic β -islet cells and neural transmission in the brain. These studies indicate that Rem and Rem2 proteins play a critical role in

regulating calcium channel function, and that modulating Rem/Rem2 activity may provide a unique approach to treating diseases as diverse as heart failure and diabetes.

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Characterization of a novel breast cancer tumor suppressor.

Breast cancer is one of the most common malignancies in the United States, affecting one in nine women. The high mortality rate associated with the disease is related to the ability of breast cancer cells to metastasize beyond the mammary gland and invade distant sites while the primary tumor is small and undetected. The progression of carcinogenic breast cells to a metastatic phenotype is typified by both genetic alterations but also by changes in gene expression that result in loss of normal cellular regulation. We have used gene microarray analysis to identify a unique Ras-superfamily gene, termed RERG whose expression is down regulated or lost in a significant percentage of primary breast tumors with a metastatic phenotype and a poor clinical prognosis. Importantly, elevated RERG expression in human breast tumors is associated with a slow rate of proliferation and a better prognosis for these cancer patients. In addition, we have demonstrated that expression of RERG in breast carcinoma cells results in a significant inhibition of cell growth and tumor formation. Taken together, these studies indicate that RERG acts to suppress uncontrolled cell proliferation, and that the loss of RERG contributes to breast cancer through the loss of a critical negative regulator of tumor cell growth. Our long-term goal is to understand the molecular details of how RERG controls breast tumor growth. We expect that these studies will provide fundamental insight into the progression of breast cancer and may eventually lead to novel treatment strategies.

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Design and evaluation of anti-cancer therapeutics.

In an ongoing collaboration with Dr. Peter Spielmann (Univ. Kentucky), we are involved in drug discovery efforts to target the protein Ras for cancer treatment. Whereas normal Ras function is required for proper cell growth, deregulated activity is linked to uncontrolled cell proliferation. Indeed, Ras genes are the most commonly mutated oncogenes in human cancer, and their malfunction is a critical mechanism driving over half of all human cancers. Ras proteins must be attached to the cell membrane in order to function, and this attachment requires modification by an unusual lipid called a farnesyl isoprenoid. Although the basis for this requirement in Ras protein function is not yet completely understood, a recent exciting development is that the enzyme responsible for the attachment of this lipid, farnesyl transferase (FTase), has become the target for a novel class of potential anticancer chemotherapeutic agents called FTase inhibitors. The mechanism of action for these drugs has turned out to be unexpectedly complex. We are involved in the design of a series of novel FTase inhibitors, and are characterizing the basis for their tumor inhibitory properties.