

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Dohlman, Henrik Gunnar

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

POSITION TITLE: Sanford Steelman Distinguished Professor and Chair of Pharmacology

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
Wesleyan University, Middletown CT	BA	06/1982	Chemistry
Duke University, Durham NC	PhD	12/1988	Biochemistry
Duke University, Durham NC University of California, Berkeley CA	Postdoc	08/1989	Medicine/Cardiology
	Postdoc	02/1993	Molec. & Cell Biology

A. Personal Statement

My overall **research goal** is to identify new regulators of G protein signaling and desensitization. Listed below are selected review articles and patents related to these discoveries (**a-d**).

As a graduate student with Robert Lefkowitz, I coauthored a paper describing the first molecular cloning and sequencing of a G protein-coupled receptor (GPCR) (Dixon et al. Nature 1986). GPCRs respond to hormones and neurotransmitters, as well as sensory signals, and are the target of one third of all pharmaceuticals. As a post-doc with Jeremy Thorner I initiated molecular genetic studies of G protein signaling in yeast. My independent lab has since been conducting large-scale genomic, proteomic and (now) metabolomics analysis to identify mutants with altered signaling and desensitization properties. These mutants are then characterized biochemically in yeast and animal cells. This effort led to the identification of the first RGS protein (Dohlman et al. Mol Cell Biol 1996). RGS proteins inactivate G proteins by accelerating their intrinsic GTPase activity. *Thus, past contributions include identification of the first G protein activator and inactivator.*

Our investigations of desensitization have included novel post-translational modifications. My lab was the first to use mass spectrometry to map a site of protein ubiquitination in vivo (for Ga, Marotti et al. Biochemistry 2002), and the first to demonstrate signaling by G proteins at endosomes (**e**). *Thus, past contributions include ubiquitin-mediated trafficking to, and signaling at, endomembrane compartments.*

Later we showed that changes in pH (**i**) and the production of 2-hydroxy branched chain amino acids (**l**) serve as second messengers of glucose limitation and osmotic stress, respectively. 2-hydroxy branched chain amino acids are elevated in patients with maple syrup urine disease and cause defects in neurotransmitter function. *Thus, past contributions include novel second messengers of nutrient and osmostress signaling.*

A major **training goal** has been to mentor young scientists. I have consistently strived to recruit and maintain a diverse scientific team, which I believe will bring new ideas and new directions to the scientific endeavor. Including current members of the lab, I have sponsored more than 40 postdoc and doctoral students and nearly as many undergraduates. *In 2019 my efforts were recognized by the UNC Office of Graduate Education award for "Excellence in Basic Science Mentoring"*

My **leadership experience** has helped me to become a better scientist and a better mentor. As past Director of Graduate Studies I revamped existing course requirements and implemented an accelerated timeline to graduation, including a much earlier submission of the thesis research proposal. As past Director of the department's *Grant Writing* course (designed to prepare students for the qualifying exam and for NIH grant

submissions) I wrote a 60+ page course manual, which I have shared freely with other departments and institutions (*m*). As department Chair I have led RCR training focusing on plagiarism and image manipulation, and taken initiatives to address racial inequity and mental health concerns. As a long-standing member of the scientific community, I have contributed by serving as Chair of the *Molecular Pharmacology* division of ASPET, as chair of a Gordon Research Conference, as co-organizer of the first ASPET meeting on RGS proteins, as Associate Editor for the *Journal of Biological Chemistry*, and through service on NIH grant review panels.

I have used these experiences to help students publish, obtain fellowship funding and gain meaningful employment in the sciences.

I have had continuous **NIH grant support** for the period 1995-2026, and since 2016 has been through the R35 MIRA program.

- a. Wang, Y. and Dohlman, H. G., Pheromone signaling mechanisms in yeast: a prototypical sex machine. **Science** 306:1508-9, 2004. PMID: 15567849.
- b. Dohlman, H. G., Diminishing returns: Desensitization. **Nature** 418:591, 2002. PMID: 12167838.
- c. Dohlman, H. G., Thorner, J., Caron, M. G. and Lefkowitz, R. J., Model systems for the study of seven transmembrane-segment receptors. **Annual Reviews of Biochemistry** 60:653-88, 1991. PMID: 1652922
- d. Licensed U. S. Patents 5,482,835; 5,739,029; 6,168,927; 6,242,205; 6,482,603; 6,855,550; 7,413,876

B. Positions, Scientific Appointments, and Honors

10/16-	Professor and Chair of Pharmacology, University of North Carolina Chapel Hill
10/06-12/15	Vice Chair of Biochemistry & Biophysics, University of North Carolina Chapel Hill
8/05-9/06	Interim Chair of Biochemistry & Biophysics, University of North Carolina Chapel Hill
7/04-	Professor of Biochemistry & Biophysics, University of North Carolina Chapel Hill
6/01-6/04	Associate Professor of Biochemistry & Biophysics, University of North Carolina Chapel Hill
7/99-6/01	Associate Professor of Pharmacology, Yale University
3/93-6/99	Assistant Professor of Pharmacology, Yale University
9/89-2/93	Jane Coffin Childs Postdoc Fellow, University of California Berkeley

Other Experience and Professional Memberships

2017-18	Chair, Molecular Pharmacology Division of ASPET
2016-21	Editorial Board, <i>Molecular Pharmacology</i>
2013-23	Associate Editor, <i>Journal of Biological Chemistry</i>
2012-	Reviewer, NIH New Innovator (DP2) Award
2008-	Board of Reviewing Editors, <i>Science Signaling</i>
2002-09	Regular Member, NIH PHRA, HM, and MIST study sections
2007	Co-chair (with JoAnn Trejo), Gordon Research Conference, "Phosphorylation & G protein mediated signaling networks"
2002-09	Regular Member, NIH PHRA, HM, and MIST study sections

Honors

2021	Elected <i>Fellow</i> of the American Society for Biochemistry and Molecular Biology
2019	Office of Graduate Education <i>Excellence in Basic Science Mentoring Award</i>
2011	Elected <i>Fellow</i> of the American Association for the Advancement of Science
1998-01	American Heart Association <i>Established Investigator Award</i>

C. Contributions to Science

Past contributions to research:

As a graduate student, I contributed to the genetic identification of the β 2-adrenergic receptor, the first of the large and pharmacologically important family of G protein-coupled neurotransmitter receptors. That work

was cited in the 2012 Nobel Prize to Robert Lefkowitz. In 1995 I described the first of a new family of desensitization factors, called RGS proteins. Whereas receptors activate G proteins, RGS proteins inactivate G proteins, and do so by accelerating their GTPase activity. Human genetic studies have since revealed that RGS proteins are necessary for desensitization to light and other stimulants. More recently, we identified a number of new signaling and desensitization mechanisms. These findings include G protein signaling from an internal (endomembrane) compartment (**e**), the development of microfluidics methods and mathematical models to follow signaling in time and space (**f,j**), identification of new pathway regulators from a comprehensive screen of the essential genome (**g**), and a universal allosteric mechanism of G protein activation (**h**).

Newly discovered regulators have been characterized using integrated genetic, biochemical, computational, cell biological (including microfluidics and electron microscopy) and biophysical (including mass spectrometry, x-ray crystallography and NMR) approaches.

- e. Slessareva, J. E., Routt S. M., Temple, B., Bankaitis, V. A. and Dohlman, H. G., Activation of the phosphatidylinositol 3-kinase Vps34 by a G protein alpha subunit at the endosome. **Cell** 126:191-203, 2006. PMID: 16839886.
[See news articles by M. Koelle (*Cell* 126:25-7, 2006), by L. Bardwell (*Curr. Biol.*, 2006), in *Science STKE* (tw234, 2006) and in *Faculty of 1000*]
- f. Hao, N., Nayak, S., Behar, M., Shanks, R. H., Nagiec, M. J., Errede, B., Hasty, J., Elston, T. C., and Dohlman, H. G., Regulation of cell signaling dynamics by the protein kinase-scaffold Ste5. **Molecular Cell** 30:649-56, 2008. PMID:PMC2518723
[See news article in *Faculty of 1000*].
- g. Cappell, S. D., Baker, R., Skowyra, D. and Dohlman, H. G., Systematic analysis of essential genes reveals important regulators of G protein signaling. **Molecular Cell** 38:746-57, 2010. PMID: PMC2919228.
[See news articles by L. B. Ray (*Science Signal.* 3:ec191, 2010) and in *Faculty of 1000*]
- h. Knight, K. M., Ghosh, S., Campbell, S. L., Lefevre, T., Olsen, R. H. J., Smrcka, A. V., Valentin, H. V., Yin, G., Vaidehi, N., and Dohlman, H. G., A universal allosteric mechanism for G protein activation. **Molecular Cell**, 81:1384-1396, 2021.

Current contributions to research:

Current studies with my collaborator Tim Elston are aimed at defining the global (“systems level”) changes that occur in a stimulus-adapted cell (**f,j,k**). Our efforts benefit from genomic and proteomic technologies that were pioneered in yeast; these include comprehensive collections of gene knockout strains and libraries of yeast genes fused to GFP or affinity tags. These strain libraries are characterized using specialized microfluidic (“lab on a chip”) chambers capable of exposing cells to a precisely-controlled stimulus gradient or pulse (**f,j**). Our approach required the development of new image analysis approaches to map the relative distribution of signaling proteins. Through the integration of modeling and experimentation, we have discovered new systems-level principles such as ‘dose-to-duration encoding’ and ‘kinetic insulation’.

The integration of experimental and computational biology will be increasingly important in biomedical research, and these efforts represent an important training opportunity for my students and postdoctoral fellows.

- i. Isom, D. G., Sridharan, V., Baker, R., Clement, S. T., Smalley, D. M. and Dohlman, H. G., Protons as second messenger regulators of G protein signaling. **Molecular Cell** 51:531-538, 2013. PMID: PMC3770139.
[see news articles by K. Minton (*Nature Reviews Molecular Cell Biology*, 14:608-609,2013), in *Faculty of 1000*, and a perspective by S. Sprang (*Molecular Cell*, 51:405-406, 2013)]
- j. Dixit, G., Kelley, J. B., Houser, J. R., Elston, T. C. and Dohlman, H. G., Cellular noise suppression by the regulator of G protein signaling Sst2. **Molecular Cell** 55:85-96, 2014. PMID: PMC4142594.
- k. English, J. G., Shellhammer, J. P., Malahe, M., McCarter, P. C., Elston, T. C. and Dohlman, H. G., MAPK feedback encodes a switch and timer for tunable stress adaptation in yeast. **Science Signaling** 8:ra5, 2015. PMID: PMC4505820.
- l. Shellhammer, J. P., Morin-Kensicki, E., Matson, J. P., Yin, G., Isom, D. G., Campbell, S. L., Mohny, R. P. and Dohlman, H. G., Amino acid metabolites that regulate G protein signaling during osmotic stress. **PLoS Genetics** 13:e1006829, 2017. PMID: PMC5469498

Contributions to training and mentorship:

Over the past 28 years I have served on 75+ thesis committees and trained 40+ doctoral students and postdoctoral fellows. There are three central tenets of my training program: scientific writing (*m*), hands-on research training at the interface of experimental and computational biology, and individualized mentorship in career planning and professional development (*n,o*). Since starting my independent career I have served on multiple NIH grant review panels and I have benefitted from 25 years of uninterrupted grant support. I have used this experience to help junior investigators and trainees obtain grants of their own. In recent years I served as the director of our graduate student *Grant Writing* course (*m*). I continue to be an active mentor to undergraduate, graduate and postdoctoral researchers (*n,o*). The majority of lab alumni are now in academia and others have found success in medicine, biotechnology, the pharmaceutical industry, scientific publishing and intellectual property law.

These lab alumni represent a valuable professional resource for current and future trainees as they enter the job market (*o*).

- m. I have written a 60+ page course manual for my department's grant writing class. These materials have been adopted by other graduate programs at UNC and elsewhere. They are being distributed without cost or restriction (<http://tibbs.unc.edu/resources/funding-opportunities/>)
- n. Dohlman, H. G. (2012). PhDs: Acquired skills good for marketplace. **Nature** 485:41. PMID: 22552086. This article illustrates my advocacy for students pursuing a PhD, regardless of career goals and interests.
- o. The following lists recent trainees with present academic positions.

Postdoctoral trainees (selected from 22 total)

<u>Name</u>	<u>Dates</u>	<u>Present position</u>
Claire Gordy	2013-16	Professor, NC State Univ
Daniel Isom	2010-16	Professor, University of Miami
Jillian Hurst	2010-12	Professor, Duke University
Matthew Torres	2007-10	Professor, Georgia Tech

Doctoral trainees (selected from 21 total)

<u>Name</u>	<u>Dates</u>	<u>Present position</u>
Rachael Baker	2008-14	Professor, Calvin University
Justin English	2008-14	Professor, University of Utah
Steven Cappell	2005-11	Stadtman Investigator, NIH/NCI
Nan Hao	2001-06	Professor, UC San Diego

Undergraduate trainees (selected from 32 total)

<u>Name</u>	<u>Dates</u>	<u>Present position</u>
Ivan Kuznetsov	JHU 2016	MD/PhD student, University of Pennsylvania
Lauren Askew	UNC 2016	MD/PhD student, Emory University
Joshua Sheetz	UNC 2015	PhD student, Yale University
Vishwajith Sridharan	UNC 2014	MD/MBA student, Harvard University

Complete List of Published Work: <http://www.ncbi.nlm.nih.gov/pubmed/?term=dohlman+h>