BIOGRAPHICAL SKETCH

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NAME: **Patton, James G.**

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

POSITION TITLE: Stevenson Professor of Biological Sciences

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
University of St. Thomas, St. Paul, MN	BA	06/1980	Chemistry
Mayo Clinic and Graduate School, Rochester, MN	PhD	06/88	Molecular Biology and Biochemistry
Harvard Medical School, Children's Hospital, Boston	Post-Doc	12/92	Molecular Biology

A. Personal Statement

My research has been devoted to understanding the regulation of gene expression at the RNA level for over 25 years. Most recently, I have focused on the function of miRNAs during vertebrate development and retina regeneration using zebrafish as a model organism. With the discovery of miRNAs and other noncoding RNAs in exosomes, we have also begun a new area of research to study the role and biogenesis of extracellular RNA using a colorectal cancer model.

I have a long-standing commitment to education and training of both undergraduate and graduate students. I teach Introductory Biology at Vanderbilt and serve as Director of the Honors Program in Biological Sciences, Director of Vanderbilt's Interdisciplinary Graduate Program, PI of the Cellular, Biochemical, and Molecular Sciences (CBMS) T32 training grant, and PI of an R25-supported summer program offering research opportunities for students underrepresented in science.

B. Positions and Honors

1980-1983 Research Assistant, Atherosclerosis Research Lab, Mayo Clinic
1983-1988 Graduate Student, Mayo Clinic
1988-1992 Post-Doc, Harvard Medical School and Children's Hospital, Boston
1993-1999 Assistant Professor, Department of Molecular Biology, Vanderbilt University
1999-current Director, Interdisciplinary Graduate Program, Vanderbilt University
2002-current Director, Vanderbilt Summer Minority Research Program
2000-2005 Associate Professor, Department of Molecular Biology/Biological Sciences, Vanderbilt
2004-current Director and PI, Cellular, Biochemical and Molecular Sciences Training Program, Vanderbilt
2005-current Professor, Department of Biological Sciences, Vanderbilt University
2009-current Stevenson Professor of Biological Sciences, Vanderbilt University
2011 Chancellor's Research Award, Vanderbilt University
2013 Fellow, American Association for the Advancement of Science for Distinguished Contributions to RNA Biology and Leadership in Graduate Education

C. Contributions to Science

1. Regulation of Alternative Splicing

I began my graduate career studying U1 snRNP assembly and then expanded that interest into the regulation and mechanisms of alternative splicing for my post-doc and the first ~15 years of my own lab. My contributions included definition of regulatory splicing signals that regulate splice site selection with an

emphasis on proteins that bind the polypyrimidine tract and regulate 3' splice site selection. I biochemically identified, characterized, and cloned PTB (Polypyrimidine Tract Binding Protein), PSF (PTB-Associated Splicing Factor) and SRrp86, a member of the SR protein superfamily of splicing regulators. I also cloned U2AF (U2 Auxiliary Factor) which is required for the recruitment of U2 to the branch point. My work contributed substantially to the prevailing model whereby regulated alternative splicing is controlled in a combinatorial manner with multiple RNA sequences providing variable strength binding sites for specific splicing regulators. Combinations of positive and negative factors bind to these sequences to allow for precise control of alternative splicing.

Patton, J.G., Mayer, S.A., Tempst, P., and Nadal-Ginard, B. (1991) A polypyrimidine binding complex necessary for pre-mRNA splicing: Identification, characterization, and molecular cloning of the 57kD subunit. Genes and Development 5: 1237-1251.

Zamore, P.D., Patton, J.G., and Green, M.R. (1992) Cloning and domain structure of the mammalian splicing factor U2AF. Nature 355: 609-614.

Patton, J.G., Porro, E.B., Galceran, J., Tempst, P. and Nadal-Ginard, B. (1993) Cloning and characterization of PSF, a novel pre-mRNA splicing factor. Genes and Development 7: 393-406.

Perez, I., Lin, C-H., McAfee, J.G. and Patton, J.G. (1997) Mutation of PTB Binding Sites Causes Misregulation of Alternative 3' Splice Site Selection In Vivo. RNA 3: 764-778. PMCID: PMC1369523.

Barnard, D.C. and Patton, J.G. (2000) Identification of a serine-arginine rich protein that antagonizes the effect of SR proteins on alternative splice site selection. Molecular and Cellular Biology 20: 3049-3057. PMCID: PMC85584

2. RNA and Disease

Closely related to our work on alternative splicing, my lab collaborated with Dr. John Phillips, a pediatric geneticist at Vanderbilt to mechanistically explain how patient mutations induce Isolated Growth Hormone Deficiency, Type II (IGHD II). We showed that aberrant skipping of exon 3 in the human growth hormone gene generates a dominant negative isoform due to disruption of intronic splicing enhancer elements. The extent of skipping of exon 3 is directly proportional to long bone growth and stature, and leads to progressive destruction of the anterior pituitary. Using allele-specific RNAi, we were able to rescue a mouse model of IGHD II. The overall significance of this work was to uncover how seemingly innocuous mutations in introns can disrupt splicing to cause disease. This was informative both from a human genetic variation perspective as well as understanding the mechanisms that regulate splice site choice. The ability to rescue a genetic defect with allele specific RNAi was novel.

Ryther, R.C.C., McGuiness, L.M., Phillips, J.A. III, Moseley, C.T., Magoulas, C.B., Robinson, I.C.A.F., and Patton, J.G. (2003) Disruption of Exon Definition Produces a Dominant Negative Growth Hormone Isoform that Causes Somatotroph Death and IGHD II. Human Genetics 113: 140-148.

Ryther, R.C.C., Flynt, A.S., Harris, B. D., Phillips, J.A. III, and Patton, J.G. (2004) Splicing of GH1 is regulated by multiple enhancers whose mutation produces a dominant-negative GH isoform that can be degraded by allele-specific siRNA. Endocrinology, 145: 2988-2996.

Shariat, N., Ryther, R.C.C., Robinson, I.C.A.F., Phillips III, J.A., and Patton, J.G. (2008) Rescue of Murine IGHD II by Delivery of Short Hairpin RNAs. Endocrinology, 149: 580-586. PMCID:2219309

3. miRNAs and Development

I made a deliberate mid-career switch and changed my research interest from splicing to miRNA function and also decided to learn how to use zebrafish as a model system to study miRNA function during vertebrate development. miRNAs are highly conserved between fish and humans and the genetic and experimental tools in fish allow dissection of miRNA function at specific developmental times and places. Before commercial

approaches were available, we printed our own microarrays to characterize global miRNA expression patterns during early development and then picked specific miRNAs to determine their functions and targets during development. We have shown that miRNAs play crucial cell- and developmental-specific roles regulating muscle development, left/right asymmetry, osmotic stress, planar cell polarity, craniofacial development, synaptic activity, and regeneration. Our published and ongoing work has demonstrated that miRNAs are not just "tweakers" of gene expression; if captured at the right time and place, they play key roles in cell specification, differentiation and development.

Flynt, A.S., Thatcher, E.J., Li, N, Solnica-Krezel, L., and Patton, J.G. (2006) Zebrafish miR-214 modulates Hedgehog signaling to specify muscle cell fate. Nature Genetics, 39:259-263. (See News and Views perspective by Philip Ingham, Nature Genetics 39: 145-146.). PMCID: PMC3982799

Flynt, A.S., Thatcher, E.J., Burkewitz, K., Li, N., Liu, Y., and Patton, J.G. (2009) miR-8 miRNAs Regulate the Response to Osmotic Stress in Zebrafish Embryos. J. Cell Biology 185: 115-127. PMCID: PMC2700511

Li, N., Wei, C. and Patton, J.G. (2011) Regulation of Endoderm Formation and Left-Right Asymmetry by *miR-92* During Early Zebrafish Development. Development, 138: 1817. PMCID: PMC3074454

Wei, C., Thatcher, E.J., Olena, A.F., Perdigoto, A.L., Marshall, A., Carter, B.D., Broadie, K., and Patton, J.G., (2013) *miR-153* regulates SNAP-25, Synaptic Transmission, and Neuronal Development. PLOS One 8: e57080. PMCID: PMC3581580

Kara, N., Wei, C., Commanday, A., and Patton, J.G. (2017) *miR-27* regulates chondrogenesis by suppressing Focal Adhesion Kinase during pharyngeal arch development. Developmental Biology, in press.

4. Retina Development and Regeneration

Zebrafish are remarkable in their ability to repair and replace damaged tissues and organs. We first showed that miRNAs are required for caudal fin regeneration and that *miR-203* must be repressed to initiate regeneration and re-expressed to terminate regeneration. In contrast to mammals, zebrafish are capable of spontaneous retina regeneration, despite the fact that the cells, architecture, and key genes are highly conserved. We showed that *miR-203* is again a key player regulating proliferation of neuronal progenitor cells derived from Müller glia and have identified several miRNAs that regulate distinct steps during retina regeneration (including the focus of this grant on *miR-216a* and Dot1l. We also discovered a novel feed forward regulatory network involving three transcription factors (Tbx2b, Nr2e3, and Flh) that control rod and cone photoreceptor specification and differentiation. We are studying these factors in the zebrafish pineal organ to simplify the approach but the goal is to apply lessons learned to understand how rods and cones are specified during regeneration.

Thatcher, E.J., Paydar, I., Anderson, K.A., and Patton, J.G. (2008) microRNAs are Required for Vertebrate Regeneration. PNAS 105: 18384-18389. PMCID: PMC2587605

Rajaram, K., Harding, R., Hyde, D.R. and Patton, J.G. (2014) *miR-203* regulates progenitor cell proliferation during adult zebrafish retina regeneration. Developmental Biology 392: 393-403. (See highlight in Science, 346: 437). PMCID: PMC4104251.

Rajaram, K.*, Harding, R.L.*, Bailey, T. Patton, J.G.#, and Hyde, D.R.# (2014) Dynamic miRNA Expression Patterns During Retina Regeneration in Zebrafish: Loss of Dicer Inhibits Regeneration. *Co-first authors. #Co-corresponding authors. Developmental Dynamics, 2443: 1591-1605. PMCID: PMC4237695

Olena, A.F., Rao, M., Thatcher, E.J., and Patton, J.G. (2015) *miR-216a* regulates *snx5*, a novel Notch signaling pathway component, during zebrafish retinal development. Development Biology, 400: 72-81. PMCID: PMC4361363.

Khuansuwan, S., Clanton, J.A., Dean, B.J., Patton, J.G., and Gamse, J.T. (2015) A transcription factor network controls cell migration and fate decisions in the developing zebrafish diencephalon. Development, 143: 2641-2650.

Rao, M., Didiano, D., and Patton J.G. (2017) Initiation of Retinal Regeneration by a Conserved Mechanism of Adult Neurogenesis. Stem Cell Reports, 8: 831-842.

5. Extracellular RNA (exRNA)

The idea that RNA might serve as an extracellular signaling molecule is contrary to years of research that assumed that RNA functioned in a cell autonomous manner. In a collaboration involving the Coffey, Weaver, and Patton labs, we were awarded one of 5 U19 exRNA grants to study the biogenesis of extracellular RNA and to test whether RNA can be transferred between cells. We are studying this in the context of colorectal cancer initially using cell lines that differ only in KRAS status. We recently showed that miRNAs can be functionally transferred to effect changes in gene expression in recipient cells. Ongoing experiments are designed to understand the mechanisms of transfer, uptake, and release in recipient cells.

Cha, D.J., Franklin, J.L. Dou, Y., Liu, Q., Higginbotham, J.N., Demory Beckler, M., Weaver, A.M., Vickers, K., Prasad, N., Levy, S., Zhang, B., Coffey, R.J., and Patton, J.G., (2015) *KRAS*-Dependent Sorting of miRNA to Exosomes. eLife 2015;10.7554/eLife.07197; DOI: http://dx.doi.org/10.7554/eLife.07197 PMCID: PMC4510696.

Patton, J.G., Franklin, J.L., Weaver, A.M., Vickers, K., Zhang, B., Coffey, R.J., Ansel, K.M., Blelloch, R., Goga, A., Huang, B., L'Etoille, N., Raffai, R.L., Lai, C.P., Krichevsky, A.M., Mateescu, B., Greiner, V.J., Hunter, C., Voinnet, O., and McManus, M.T. (2015) Biogenesis, Delivery, and Function of Extracellular RNA. J Extracellular Vesicles, 4: 27494. PMCID: PMC4553266.

McKenzie, A.J., Hoshino, D., Cha, D.J., Franklin, J.L., Coffey, R.J., Patton, J.G., and Weaver, A.M. (2016) KRAS-MEK signaling controls Ago2 and miRNA sorting into exosomes. Cell Reports 15, 978-987. PMCID: In Process.

Dou, Y., Cha, D.J., Franklin, J.L., Higginbotham, J.N., Jeppesen, D.K., Weaver, A.M., Prasad, N., Levy, S., Coffey, R.J., Patton, J.G., and Zhang, B. (2017) Circular RNAs are down regulated by mutant KRAS in colon cancer and can be transferred to exosomes. Scientific Reports 6:37982 DOI: 10.1038/srep37982.

List of publications in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/james.patton.1/bibliography/41149299/public/?sort=date&direction=descending

D. Research Support

Current Funding

RO1 EY024354-03 Patton (PI) 4/1/14-3/31/17
NIH/NEI
A newly discovered feed forward mechanism controls photoreceptor fate

RO1 EY024354-02S1 Patton (PI) 4/1/14 –3/31/17
NIH/NEI Diversity Supplement for Matthew Kent
A newly discovered feed forward mechanism controls photoreceptor fate

6U19 CA179514-04
NIH/NCI Coffey, Weaver and Patton 9/1/13-8/31/18
Secreted RNA during CRC progression: Biogenesis, Function and Clinical Markers

U01 EY027265-01
NIH/NEI Patton, Levine Calkins, Multi-PIs 9/116-8/31/19
Novel Activators of Regeneration ion Muller Glia

5 T32 GM008554-20 Patton (PI) 7/1/12-6/30/17
NIH/NIGMS

Cellular, Biochemical, and Molecular Sciences Training Grant

R25 HL 118679-04 Patton (PI) 4/26/13-1/31/18
NIH/NHLBI
Short Term Research Training to Increase Diversity in Health-Related Research

Completed
R21EY019759 Patton (PI) 7/1/09-6/31/13
NIH/NIE
Analysis of miRNA Function During Eye Development and Retinal Regeneration

RO1 GM 075790 Patton (PI) 7/1/05-6/31/13
NIH/NIGMS
Identification and Characterization of Zebrafish microRNAs.
Role: PI

RO1 DK35592 Phillips (PI) 4/1/05-3/31/10
NIH/NIDDK
GH Alternative Splicing: Mechanisms and Diseases
Role: Co-PI

RO1 GM62487 Patton (PI) 8/01/02-1/31/10
NIH/NIGMS
Mechanisms and Regulation of Alternative pre-mRNA Splicing
Role: PI