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BIOGRAPHICAL SKETCH

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NAME: Gregory S. Barsh, M.D.Ph.D.

POSITION TITLE: Investigator, HudsonAlpha Institute; Professor of Genetics (active emeritus), Stanford University

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

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 California, Irvine | B.A. | 1977 | Biology |
| University of Washington | M.D. Ph.D. | 1984 | Human Genetics, Pathology |
| University of California, San Francisco | Postdoc | 1989 | Genetics |

**A. Personal Statement**

My graduate and medical school training was in the area of molecular and medical genetics of human Mendelian disease. As a faculty member at Stanford, my research group applied forward- and reverse-genetic approaches in laboratory mice to study gene action and interaction as it relates to human biology and common disease. Most of this work used color variation as a model system, and led to the discovery of a new set of paracrine mediators, new insight into the physiology of body weight regulation, novel aspects of membrane remodeling relevant to neurodegenerative disease, and an unexpected connection between the innate immune system and melanocortin receptor signaling. Between 1990 and 2005, I was also an active member of the Stanford Pediatric Genetics clinical service.

More recently, I have become interested in the opportunities provided by genome sequencing and genomic technology to study morphologic variation and disease in natural populations, including humans and domestic and companion animals. I accepted a position at the HudsonAlpha Institute in mid-2009, and maintain an active emeritus appointment at Stanford with a small mouse colony and laboratory. At HudsonAlpha, I also serve as project leader for the medical genetic component of our Clinical Sequencing Exploratory Research (CSER) award to identify de novo causes of intellectual disability by next-gen sequencing.

B. Positions and Honors

**Positions and Employment**

1984-1986 Resident, Internal Medicine, Harbor-UCLA Medical Center, Torrance, CA

1986-1989 Postdoctoral Fellow, Dept. of Pediatrics, University of California, San Francisco, CA

1989-present Assistant, Associate, and Full Professor, Stanford University School of Medicine

1990-2005 Investigator, Howard Hughes Medical Institute, Chevy Chase, MD

1996-1997 Acting Chief, Division of Pediatric Genetics, Interim Director, Prenatal Diagnosis Center

2002-2009 Director, Medical Scientist Training Program, Stanford University, Stanford, CA

2005-2008 Chair, Genetics of Health and Disease study section

2009-present Editor In Chief, PLoS Genetics

2009-present Investigator, HudsonAlpha Institute for Biotechnology, Huntsville, AL

2011-present Professor (emeritus, recalled to active duty), Stanford University, Stanford, CA

**Honors**

1999 Takeuchi Medal, International Society for Pigment Cell Research

2003 E Mead Johnson Award, Society for Pediatric Research

2005 Aaron B. Lerner Award, International Society for Pigment Cell Research

2008 Seiji Award, International Society for Pigment Cell Research

2010 American Skin Association Achievement Award

2014 Myron Gordon Award, International Federation of Pigment Cell Societies

**C. Contributions to Science**

**1. Biology of melanocortin signaling: As a junior faculty member at Stanford, I started my research program using mouse coat color mutations that affect the switch between melanin subtypes as a model system for studying how paracrine signaling triggers a cell biological switch. We identified Agouti signaling protein (Asip) as a novel endogenous antagonist of the melanocortin 1 receptor, and showed that neomorphic alleles of Asip elicit pleiotropic effects through ectopic action on other melanocortin receptors. We have continued to use mutations that affect pigment type-switching to show that Attractin (Atrn), a novel single transmembrane-spanning protein serves as an accessory receptor for Asip, and that beta-defensins function as neutral antagonists for melanocortin receptors. This work has provided fundamental insight into mechanisms whereby a hormone 7-TM receptor interaction triggers a cell biological switch.**

a) Duhl DM, Vrieling H, Miller KA, Wolff GL, and Barsh GS. (1994) Neomorphic agouti mutations in obese yellow mice. Nat Genet 8: 59-65, PMID: 7987393.

b) Ollmann MM, Lamoreux ML, Wilson BD, and Barsh GS. (1998) Interaction of Agouti protein with the melanocortin 1 receptor in vitro and in vivo. Genes Dev 12: 316-330.

c) He L et al. (2001) A biochemical function for attractin in agouti-induced pigmentation and obesity. Nat Genet 27: 40-47, PMID: 11137996.

d) Candille SI et al. (2007) A b-defensin mutation causes black coat color in domestic dogs. Science 318: 1418-1423, PMID: 1794754.

**2. Pigmentary genetics and human disease: We have also used color mutations in laboratory mice as a platform to investigate important aspects of mammalian physiology and pathophysiology. We showed that the ability of ectopic Asip to cause obesity was due to a homologous protein that we named Agouti-related protein (Agrp) and that acts as an endogenous antagonist for the melanocortin 3 and 4 receptors. We also discovered that Asip signaling through the Mc1r and Mc4r requires Atrn as well as an E3 ubiquitin ligase that we named Mahogunin (Mgrn), whose absence leads to spongiform encephalopathy. In a different line of investigation based on mutations that cause dark skin in mice, we discovered that loss of function alleles in Galphaq proteins causes dermal melanocytosis, leading to the discovery of an important human melanoma gene. More recently, we discovered that loss-of-function mutations in ribosomal protein genes causes epidermal melanocytosis, providing some of the first insight into the pathophysiology of so-called ribosomapathies.**

a) Ollmann MM et al. (1997) Antagonism of central melanocortin receptors in vitro and in vivo by agouti-related protein. Science 278: 135-138.

b) He L et al. (2003) Spongiform degeneration in mahoganoid mutant mice. Science 299: 710-712, PMID: 12560552.

c) Van Raamsdonk CD, Fitch KR, Fuchs H, de Angelis MH, and Barsh GS. (2004) Effects of G-protein mutations on skin color. Nat Genet 36: 961-968, PMID: 15322542.

d) McGowan KA et al. (2008) Ribosomal mutations cause p53-mediated dark skin and pleiotropic effects. Nat Genet 40: 963-970, PMID: 18641651.

**3. Developmental and evolutionary genetics of color patterns: The developmental and evolutionary genetic mechanisms that underlie color patterns in warm-blooded animals remain unsolved mysteries in biology. Using mutations in laboratory animals (mice) and natural populations (domestic cats, domestic dogs, wolves), we continue to chip away at some of these mysteries. We discovered that the position of the dorsal-ventral boundary depends on the interaction between a Tbox transcription factor (Tbx15) and . We also found that stochastic patterns in melanin subtype synthesis, the brindle pattern, is caused by an epigenetically unstable beta-defensin allele, and that natural selection for melanism in wolves represents introgression of a gain-of-function beta defensin allele acquired from domestic dogs. More recently, we identified a new component of periodic pattern that is responsible for tabby patterning in the domestic cat, Taqpep, and that may represent an entry point for a Turing-like mechanism that gives rise to regular spots and stripes in many different mammals.**

a) Candille SI et al. (2004) Dorsoventral patterning of the mouse coat by Tbx15. PLoS Biol 2: E3, PMID: 14737183.

b) Kerns JA et al. (2007) Linkage and segregation analysis of black and brindle coat color in domestic dogs. Genetics 176: 1679-1689, PMID: 17483404.

c) Anderson TM et al. (2009) Molecular and evolutionary history of melanism in North American gray wolves. Science 323: 1339-1343, PMID: 19197024.

d) Kaelin CB et al. (2012) Specifying and sustaining pigmentation patterns in domestic and wild cats. Science 337: 1536-1541, PMID: 22997338, PMCID: PMC3709578.

**4. National and international service:** I served for two terms as a regular member and then chair of the NIH study section on Genetics of Health and Disease. Since 2009, I have been an Editor-in-Chief (together with Greg Copenhaver) of PLOS Genetics.