Profile of Margaret J. McFall-Ngai

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At the 152nd annual meeting of the National Academy of Sciences (NAS) in 2015, newly elected NAS member Margaret McFall-Ngai told attendees, "I happen to be in the right place at the right time as microbiology takes center stage in biology." The charismatic professor and director of the Pacific Biosciences Research Center, School of Ocean and Earth Science and Technology, at the University of Hawaii at Manoa was referring, in part, to technologies like low-cost, high-throughput gene sequencing that have facilitated greater insight into the identity and function of microbes.

When McFall-Ngai's scientific career began in 1978, microbes were primarily viewed as pathogens or agents of decomposition. Since then, her work using a binary squid–bacterial symbiosis system to characterize animal microbiomes has contributed to expanding the once-narrow view of the microbial world. For example, McFall-Ngai and her team have shown that bacterial symbionts can induce host-animal development and drive circadian rhythms. Her Inaugural Article (1) advances such work by describing the biophysical mechanisms by which a host selects bacteria.

Interest in Animal–Bacterial Symbiosis

Raised in Southern California, McFall-Ngai attended Immaculate Heart High School in Los Angeles during the late 1960s. "It is a phenomenal college-preparatory girl's high school where students are taught that there is no limit to what they can dream about doing in their careers," she says. "I will forever be grateful to the faculty there for giving me wings."

McFall-Ngai next attended the University of San Francisco, where she earned her Bachelor of Science in biology in 1973. After returning to Southern California for graduate studies with James Morin at the University of California, Los Angeles (UCLA), McFall-Ngai began to explore how animals and bacteria collaborate in symbiosis. McFall-Ngai traveled to the central Philippines, where she investigated the biochemical basis of reflectivity and transparency in the tissues of fish that use bacterial bioluminescence. She says, "This experience began a lifelong interest in two areas: animal–bacterial symbiosis and the 'design' of tissues that interact with light, principally light organs and eyes."

Margaret McFall-Ngai. Image courtesy of Kent Nishimura (photographer).

Discovery of Squid Reflective Tissue Proteins

After earning her doctorate in biology and UCLA's Graduate Woman of the Year award in 1983, McFall-Ngai became a postdoctoral fellow at the university's Jules Stein Eye Institute. There, she studied under protein biochemist and biophysicist Joseph Horwitz, with whom she has collaborated on various projects. A University of California President's fellow from 1986 to 1988, McFall-Ngai undertook a second postdoctorate with biologist George Somero. On the side, McFall-Ngai began to investigate a mutually beneficial association that she had first heard about at UCLA: the Hawaiian bobtail squid (*Euprymna scolopes*)–*Vibrio fischeri* symbiosis. "This symbiosis was unusual, as one could obtain newly hatched animals and study, experimentally, how a symbiosis gets started with each generation," she says. "In collaboration with Edward Ruby, who studies the bacterial side of the squid–*Vibrio* symbiosis, I have been studying this model ever since."

From 1989 to 1994, McFall-Ngai was an assistant professor of biological sciences at the University of Southern California, where she also served as associate professor. To better study *E. scolopes*, she moved to Hawaii and became an associate professor and then professor at the Pacific Biomedical Research Center at the University of Hawaii. McFall-Ngai was

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 9510.

www.pnas.org/cgi/doi/10.1073/pnas.1713158114

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named a fellow of the American Academy of Microbiology in 2002.

In 2004, with Horwitz and other colleagues, McFall-Ngai discovered reflectins, which are proteins of squid reflective tissues (2). "These proteins, which are highly unusual in amino acid composition and structure, have been exploited by biotechnology [laboratories] in the government and private industry, specifically for infrared camouflage and as an electrical conductor," says McFall-Ngai.

Bacterial Symbionts Inducing Animal Development

During the same year, McFall-Ngai and her colleagues also observed that symbiont molecules signaling the presence of microbes (microbe-associated molecular patterns, or MAMPs) act in synergy to drive symbiont-induced development of the host animal (3). Before this work, MAMPs, which reside on the surface of bacteria, were linked primarily to pathogenesis in animals. The new findings demonstrated that host interpretation of these bacterial signal molecules is context-dependent, with differences leading to either inflammation and disease or to the establishment of a mutually beneficial animal–microbe association.

A subsequent study identified hundreds of *E. scolopes* genes affected by *V. fischeri* and its MAMPs, including some known to play a role in human responses to bacteria (4). The research additionally highlighted several genes corresponding to those previously determined to facilitate symbiotic relationships with gut bacteria in fish and mice. The evidence suggests that symbiotic microbe–host interactions may be similar across the animal kingdom. The papers were inspired, in part, by the work of microbiologist Everett Peter Greenberg, now a professor at the University of Washington.

Rethinking Immune System Functions

From 2004 to 2015, McFall-Ngai worked as a professor in the Department of Medical Microbiology and Immunology at the University of Wisconsin–Madison before accepting her current position at the University of Hawaii at Manoa. During this period, she developed a new theory, summarized in a *Nature* essay (5), concerning the evolution of the vertebrate immune system. The theory holds that the principal evolutionary selection pressure on the adaptive immune system is for the maintenance of a complex microbiome. As such, the vertebrate immune system is not stronger than that of invertebrates but is instead more permissive.

McFall-Ngai's hypothesis continues to be informed by her research on animal–microbe interactions. As she says, "Until recently, the prevailing view of the immune system held that its principal function is as a nonself-recognition system that protects the animal from pathogens. Although not an immunologist, I understand well the patterns of occurrence of microbial partners with animals."

Hawaiian bobtail squid (*Euprymna scolopes*). Image courtesy of Chris Frazee (University of Wisconsin–Madison, Madison, WI).

Circadian Rhythms and Host Recruitment of Bacteria

Abiotic forces, principally environmental light, were once thought to be the sole drivers of central and peripheral circadian rhythms. McFall-Ngai, Ruby, and their colleagues were the first to show that coevolved bacterial partners can also drive the circadian rhythms of the tissues with which they associate (6).

The researchers found that *E. scolopes* undergoes a daily remodeling of its symbiotic tissues, which is underlain by changes in gene expression and protein activity. "Such activities present a daily succession of growth substrates to the symbionts, which respond with metabolic rhythms supported by a cycling in transcription," McFall-Ngai says. Subsequent articles by other teams have reported that the microbiome also helps to drive circadian rhythms in mammals (7). For this and other achievements, McFall-Ngai was elected as a member of the American Academy of Arts and Sciences in 2012 and received a doctor honoris causa in 2015 from the Ecole Polytechnique Federale de Lausanne in Switzerland.

In her Inaugural Article, McFall-Ngai and her colleagues describe the mechanisms by which bacteria are recruited into a host animal's microbiome (1). Using the squid–*Vibrio* system, the researchers found that long cilia beat in waves along the host's mucous membranes to drive bacterial-sized particles into an area where colonization occurs. Once in that region, the bacteria interact with short cilia that have random motion and whose behavior, as suggested by mathematical modeling, mixes fluids. McFall-Ngai says, "We know that the host exports into that area chemicals that induce the symbiont to colonize host tissues, so we think that these short cilia promote the mixing of these biomolecules in the region where the symbionts are gathering, so that they can better detect the presence of these biomolecules."

Integrating Macrobiology and Microbiology

McFall-Ngai, Ruby, and their teams continue to investigate the biochemical and biophysical mechanisms by which specific bacteria are selected to form symbiotic associations with an animal host. They are

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also further studying the mechanisms by which such bacteria modify host gene expression and the host's microbiome, and are continuing to define the molecular and cellular underpinnings of symbiont-induced circadian rhythms.

An overarching goal is to integrate macrobiology and microbiology into a single, unified field, with microbiology at the base. McFall-Ngai says, "Such an effort involves a conceptual shift in the field, as well as a change in biology education. I am involved in both efforts." She was awarded a Guggenheim Fellowship in 2010 to explore how the change in conceptual framework would alter the view of the biological world. A portion of that funding was devoted to a workshop held at the National Evolutionary Synthesis Center in 2012 that resulted in a publication the following year outlining the new life sciences imperative (8). McFall-Ngai also contributed to laying the groundwork for the National Microbiome Initiative, which launched in 2016.

Symbiosis happens on a personal level in McFall-Ngai and Ruby's squid–*Vibrio* laboratories, which are distinct yet inextricably joined. Like the luminescent Hawaiian bobtail-squid and *Vibrio* system, the two researchers offer glowing appraisals of each other as well as their students and postdoctorates.

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2 Crookes WJ, et al. (2004) Reflectins: The unusual proteins of squid reflective tissues. *Science* 303:235–238.

3 Koropatnick TA, et al. (2004) Microbial factor-mediated development in a host-bacterial mutualism. *Science* 306:1186–1188.

4 Chun CK, et al. (2008) Effects of colonization, luminescence, and autoinducer on host transcription during development of the squid-*Vibrio* association. *Proc Natl Acad Sci USA* 105:11323–11328.

5 McFall-Ngai M (2007) Adaptive immunity: Care for the community. *Nature* 445:153.

6 Wier AM, et al. (2010) Transcriptional patterns in both host and bacterium underlie a daily rhythm of ultrastructural and metabolic change in a beneficial symbiosis. *Proc Natl Acad Sci USA* 107:2259–2264.

7 Thaiss CA, et al. (2015) A day in the life of the meta-organism: Diurnal rhythms of the intestinal microbiome and its host. *Gut Microbes* 6:137–142.

8 McFall-Ngai M, et al. (2013) Animals in a bacterial world, a new imperative for the life sciences. *Proc Natl Acad Sci USA* 110:3229–3236.

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