

Legends of Allergy: Stephen J. Galli

Professor Stephen J. Galli's rigorous and innovative research in the field of allergy and immunology has truly made him a legend in the field (Figure 1). His accomplishments are many as are the awards and recognitions he has received. He and his team have published approximately 430 publications and 14 patents. He has chaired, organized, or co-organized 18 scientific meetings or symposia. Some of the major awards he has received are the MERIT award from NIAID/NIH (1995), Scientific Achievement Award from the International Association of Allergy and Clinical Immunology (1997), Scientific Achievement Award from the World Allergy Organization (2011), Rous-Whipple Award of the American Society for Investigative Pathology (2014), the Karl Landsteiner Medal of the Austrian Society of Allergology and Immunology (2014), and an honorary PhD in Clinical and Experimental Medicine from the University of Naples Federico II, Naples, Italy (2019). He has been elected to prestigious societies such as the National Academy of Medicine (2010), Collegium Internationale Allergologicum, of which he was president between 2010 and 2014, and the Accademia Nazionale dei Lincei, an organization that counts Galileo Galilei among its former members.

Through tireless scientific pursuit, Steve has made significant contributions to the field of immunology through his work on mast cells and basophils (Table 1). His work has given us a deeper understanding of the function and the complexity of these cells, showing us that these cells besides having a bad side (allergic reactions and anaphylaxis) also have a good side (defense against venoms and pathogens) to them. His interest in basophils began during his residency in pathology at Massachusetts General Hospital in Boston in the 1970s, in the laboratory of Harold Dvorak at Beth Israel Hospital, when he demonstrated that basophils make their own histamine from histidine.¹ He then went on to develop a basophil-depleting anti-serum. Basophils were known to accumulate at tick feeding sites. On using basophil-depleting anti-serum on guinea pigs, he demonstrated loss of basophils at tick feeding sites and abolished immunity to ticks, suggesting a protective role for basophils in guinea pig acquired immunity to ticks.²

When Yukihiko Kitamura reported *Kit*^{W/W^v} mice with profound mast cell deficiency in the late 70s and early 80s, Steve's interest in mast cells was sparked. He developed culture medium containing IL-3 to generate immature mast cells from mouse hematopoietic progenitor cells in vitro and showed that these immature cells could populate, mature, and resemble native mast cells when injected into the mast cell-deficient mice. This seminal study of "mast cell knock-in mice" was originally published in the *Journal of Experimental Medicine* in 1985 and republished in 2009³ as a "Pillars of Immunology" in the *Journal of Immunology*. In 2011, he generated another mouse model, *Cpa3-Cre;Mcl-1(fl/fl)*,⁴ which, unlike previous mouse models, had

normal *c-kit* (informally called "Hello Kitty" mice by Steve). His work with mice with impaired mast cell development due to loss of function of either *White spotting* (*W*) or *Steel* (*Sl*) locus led to the discovery of stem cell factor (SCF), a factor necessary for in vitro human mast cell growth and survival.⁵ While mouse mast cells can be generated in the presence of IL-3 or SCF, human mast cells can only be generated in vitro upon continuous stimulation of SCF. SCF-derived cultured human and mouse mast cells greatly benefited mast cell research. For more than 30 years, mast cell engraftment in mast cell-deficient mice has been widely used by many researchers studying mast cells. Mast cell knock-in approaches have greatly broadened our appreciation of mast cell contributions in health and disease, including allergy, asthma, anaphylaxis, and parasite resistance.

To further understand the "beneficial" side of mast cells, Steve's intrepid scientific curiosity took him to the venomous world of some of the most toxic creatures on the planet—the Israeli mole viper, the Gila monster, the Deathstalker scorpion, the Arizona bark scorpion, the North American pit vipers, the western diamondback rattlesnake and the southern copperhead. Steve and his team initially discovered that mast cells release proteases to degrade endothelin-1, one of the major toxins produced by the body during sepsis, thereby reducing its toxicity.⁶ When they further appreciated that endothelin-1 bore



FIGURE 1 Stephen J. Galli

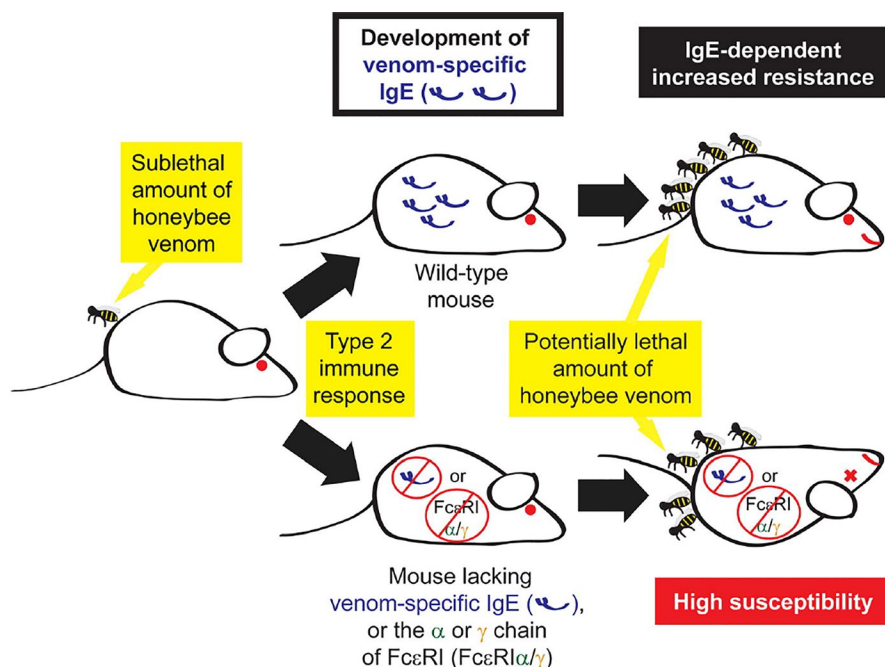


FIGURE 2 Protective role of IgE in bee venom toxicity. Reprinted from Marichal et al. A beneficial role for immunoglobulin E in host defense against honeybee venom. *Immunity*. 2013;39:963-75 with permission from Elsevier

a striking similarity to sarafotoxin 6b, the major toxin in the Israeli mole viper, they hypothesized that mast cells might also act to degrade sarafotoxins and reduce the toxicity of the Israeli mole viper venom. Later experiments confirmed this hypothesis, and he found that mast cells released an enzyme (carboxypeptidases A3), which could degrade and diminish the toxicity of sarafotoxin 6b and reduce the mortality of mice injected with sarafotoxin 6b or with the whole venom of the Israeli mole viper.⁷ In the case of the Gila monster, it was the mast cell chymase, MMCP4, rather than carboxypeptidases A3, that degraded helodermin, the toxin generated by the Gila monster.⁸ Using mast cell knock-in mice, he demonstrated that mast cell-derived proteases enhanced survival in mice injected with venoms from the honeybee, two species of scorpion, four species of poisonous snakes, or the Gila monster. He also demonstrated the protective role of IgE, by injecting mice with sub-lethal amounts of honeybee or Russell's viper venom. He showed that mice, as long

as they survive the first encounter and develop an IgE response to the venom, can tolerate larger amounts of the venom in subsequent exposures because IgE allows for extremely rapid activation of mast cells and subsequent degradation of the venom (Figure 2).⁹

Steve and his laboratory team were the first to provide evidence of mast cell generation of cytokine bioactivity via the detection of tumor necrosis factor (TNF) in mast cells. TNF produced during infection is tightly regulated in order to reduce bacterial burden and pathology and excess production of TNF can be detrimental, as seen in severe sepsis. He used the mast cell knock-in mouse models to tease out the beneficial vs. detrimental roles of mast cell-derived TNF in host defense in bacterial infection.¹⁰

After many years of dedication primarily to mast cell research, Steve's more recent work has shifted back to basophils. His laboratory has helped to standardize the protocol for basophil activation tests and develop a new avidin binding assay to monitor basophil activation in allergic patients to diagnose the severity of allergic reactions.¹¹

Steve is not only a world-renowned researcher and leader, but also a kind, generous, collaborative visionary (and poet) who cares deeply about all his laboratory staff, students, and collaborators. We can fully attest that our research and our lives would be less than full if it were not for the inspiration and involvement of Dr Stephen J. Galli.

Steve is currently Professor of Pathology and of Microbiology and Immunology & the Mary Hewitt Loveless, MD, Professor in the School of Medicine, Stanford University, Stanford, CA. From 1999 to 2016, he served as Chair of the Department of Pathology at Stanford University.

TABLE 1 Major research contribution of Stephen J. Galli, MD

Developed "mast cell knock-in" model to solve the riddle of the mast cells

Elucidated Stem Cell Factor (SCF) as the major growth factor for mast cell development and activation

Elucidated effector and immunoregulatory functions of mast cells in immune modulation

Elucidated beneficial roles of mast cells in maintaining tissue homeostasis by regulating levels of endogenous peptides and exogenous toxic substances

Elucidated beneficial functions of mast cells, IgE, and acquired immunity in responses to venoms

Elucidated the roles of mast cells and basophils in host defense against pathogens-showing importance of mast cell- and basophil-derived Tumor Necrosis Factor (TNF)

AUTHOR CONTRIBUTION

All authors contributed to the writing and editing of this manuscript.

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