

Philippa Marrack

An obsession with immunology and a gritty approach has guided Philippa Marrack through the mysteries of T cell biology. Along the way, she has managed to solve more than a handful of the puzzles.

One summer Saturday in 1997, a group of teenage boys was loitering on the National Jewish Medical and Research Center campus in downtown Denver. The three boys asked immunologist Philippa Marrack if they could use the bathroom inside, but after a few minutes of goofing off, they stole her keycard and made a run for it. Undaunted, Marrack—dressed in jogging attire, with her hair dyed green and a manuscript in hand—chased them for half a mile into a rough neighborhood.

“I didn’t stop when they started throwing rocks, but then they pepper-sprayed me and I held up the manuscript as a shield,” Marrack now says casually. That incident, in part, prompted Thomas Mitchell, a former postdoctoral fellow, to give Marrack a movie poster of John Wayne’s *True Grit*. In her direct manner, Marrack says true grit also means you can’t crumble under a reviewer’s comments. “You only get a day to scream and kick the walls,” she says. “Then you have to get up and go on.”

Known to colleagues as Pippa, Marrack is described alternately as gracious, opinionated, self-effacing and tenacious. A Howard Hughes investigator since 1986, Marrack freely admits to an obsession with immunology and is credited with, among other things, discovering the $\alpha\beta$ T-cell receptor, the mechanism of T-cell tolerance and how superantigens directly stimulate T cells.

“Pippa is unrelenting in her pursuit of answers,” says Susan Swain, Marrack’s longtime colleague and president and director of the Trudeau Institute in Saranac Lake, New York. “If she wants to find out something, it doesn’t leave her mind. Even if a question lingers for many years, she finds something to answer it.”

Marrack traces her fixation on immunology back to an eccentric branch of the family tree. Her great uncle John Marrack, who she says was “irascible, abrasive, but smart,” proposed the lattice hypothesis of antibody-antigen interaction in the 1930s. Figuring her genetic connection to immunology might add character to his group, Alan Munro invited her to join his Cambridge University lab in 1967. From that point on, she says, immunology became “just a bad habit.”

When Marrack began her graduate work, T cells had only been known for about six years. But in the decades since, she has never shifted focus. “I had no reason to go and work on something else because it was always rewarding,” she says. “They have never been boring in all those years.”

Marrack shares the credit for many of her accomplishments with her husband John Kappler. The couple met in 1971 as postdoctoral fellows at the University of California in San Diego and launched a joint lab with their first jobs at the University of Rochester. Kappler is a whiz at protein chemistry and new technologies. Marrack matches that with a deep knowledge of the field and an attention to detail. Their complementary approach has made their lab a powerhouse for the past 30 years.

From the beginning, the pair set ground rules to avoid any domestic strain: they would publish all papers together and the primary driver of a study would take lead authorship. Still, “sometimes they had fantastic arguments about data in lab meetings,” recalls Mitchell. “It was really stimulating to see them air their scientific differences.”

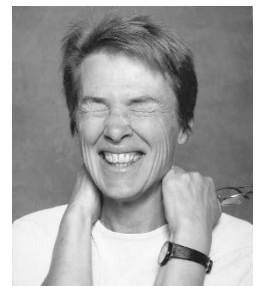
One of the lab’s hallmark achievements was the discovery in 1987 of how T cells become tolerant to the body’s own tissues—and the lab stumbled on to it by accident.

A 1950s hypothesis had proposed that immature T cells that inappropriately recognize ‘self’ would be deleted in the thymus before maturing into circulating immune cells. While screening antibodies for the various types of T cell receptors, the lab discovered that a whole subpopulation of T cells is missing in certain mice. When the missing T cells showed up only in the immature pool in the thymus, Marrack says, the team immediately realized the implications for proving the tolerance hypothesis. One of the most satisfying moments in research, Marrack says, is when “biology gives you an answer to a question you didn’t even ask.”

Colleagues say Marrack and Kappler are also particularly adept at designing elegant experiments to test hypotheses. For example, one set of experiments was meant to test if a viral superantigen passed from mother to offspring through milk. Catching newborn mice before they first suckle is tricky—mice often give birth in the middle of the night. So Marrack built a cage in which the mice gave birth sitting on chicken wire, and the babies dropped safely below to nurse from a surrogate mother.

A third, and perhaps their best-known, discovery also came from a simple, yet effective, experiment: fusing two T cells together to show that T cells use a single receptor with two chains to recognize antigens bound to the major histocompatibility complex protein. “Their work pushed the field forward tremendously to look for that kind of receptor,” says Swain.

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Marrack also leads by example and works alongside her students, not above them, say lab members. Although Marrack is a “tough broad with a quick mouth,” Kappler adds, she is the first person people go to when they are in trouble personally or professionally. She is also known for being unremittingly generous.

Former lab member Tony Vella recalls that at a conference in Montréal in July, Marrack hosted about 80 past lab members and their families at an expensive French restaurant. As people began to sit with their friends, Vella says, Marrack made them reshuffle to mingle with new faces.

Once a year, Marrack also leads lab members up 14,000-foot peaks in the Rocky Mountains with her two lovable chocolate Labradors. She also makes time every day to play her grand piano. These days, she’s working on her Beethoven. Perhaps not surprisingly, Kappler is a blues guitarist.

For their work in the lab, the couple have been honored by numerous awards. In 2003, Marrack received the American Association of Immunologists’ Lifetime Achievement Award. “The awards are nice, but they are not the point,” Marrack says. “It is satisfying when even the little things in lab work.”

Mitchell notes that that attitude is key to Marrack’s success. “She doesn’t need fancy experiments, she just goes straight for it,” he says. Not all her pursuits are successful: Marrack never did get her stolen keycard back, for example. Still, Mitchell says, the incident is a perfect illustration of her determination. “She went booking after them ... she’s just indefatigable.”

Kendall Powell, Denver