PROFILE

Of Survival and Science

From street waif in war-torn Italy to "knocking out" the genes of mice—Mario R. Capecchi shows how genius springs from the most unlikely beginnings

In 1996 Japan's Inamori Foundation asked Mario R. Capecchi to review his life and work in an acceptance speech for the prestigious Kyoto Prize. Capecchi dutifully described his pathbreaking research on a precision method for insertion or deletion of genes in mice. The most compelling part of the talk, however, had nothing to do with mouse chimeras or positive-negative selection. Rather Capecchi recounted memories of a childhood with the makings of a script Italian actor/director Roberto Benigni might use as an encore for his Academy Award–winning *Life Is Beautiful.*

Capecchi is living evidence that scientific creativity and genius can spring from the most improbable circumstances. Little more than 15 years before he began doctoral studies under Nobelist James D. Watson, an eight-year-old Capecchi was using the same intellect to avoid death on the streets of war-ravaged Italy.

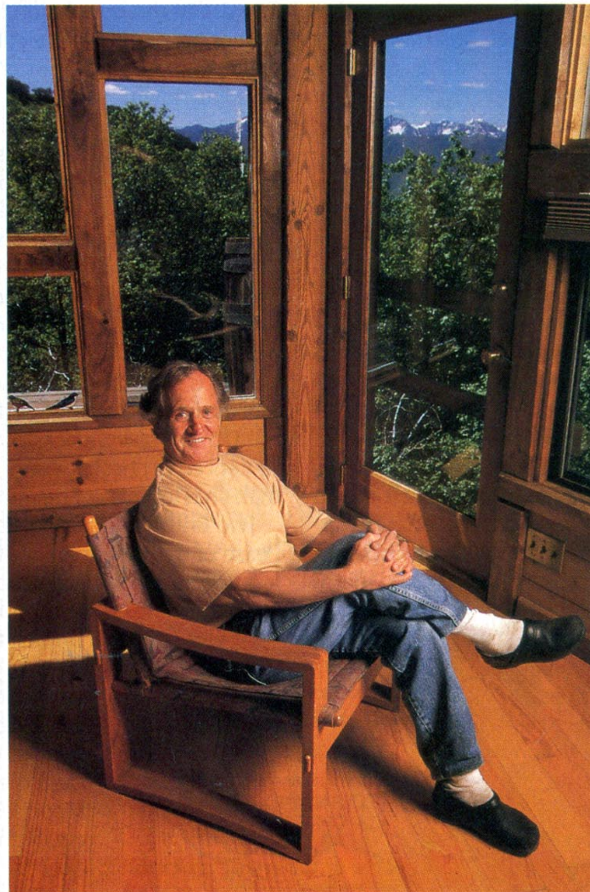
Capecchi was born on October 6, 1937, in the northern city of Verona, the offspring of a brief liaison between an Italian airman and an American poet. In 1941 the Gestapo arrested and sent his mother to the Dachau concentration camp. Hitler believed that like Jews, gypsies and homosexuals, the Bohemians, a group of artists who opposed the Nazis and Fascists, should be extirpated from society. In anticipation of being deported, Lucy Ramberg sold her possessions and gave the proceeds to a Tyrolean peasant family to care for the three-and-a-half-year-old Mario.

For a while, things went as well as they could in the middle of a war. On the farm, the boy watched the wheat harvest and would help crush wine grapes with his bare feet. One of his first direct encounters with the war came one afternoon when American airplanes strafed peasants in the field with machine-gun fire. Capecchi took a bullet in the leg, although the wound healed quickly.

After a year, his mother's money unexpectedly ran out, and the boy was put out on the street—Capecchi suspects that his father, an Italian fighter pilot, may have wrangled the remainder of the cash from his caretakers. Thus began a life-defining odyssey for the young boy, the effects of which persist to this day. The man who greets a visitor in his University of Utah office looking out onto the distant Oquirrh Mountains is five feet, four inches tall, perhaps eight inches or so shorter than he would be had he had enough to eat during those formative years.

From 1942 to 1946, Capecchi was in and out of orphanages, a hospital and the Balilla, Mussolini's youth army. These places, usually bereft of food and run by Dickensian masters, proved worse than simply fending for oneself on the street. So he spent most of his time plotting escapes. On the outside, he would live in bombed-out buildings and conspire with companions to steal bread and fruit from open-air shops. It was the best existence possible, despite having to protect himself with his fists and to witness frequent atrocities or their aftermaths, such as discovering a pile of body parts. At times he would live with his father, Luciano Capecchi, who would put up with him for a while and then throw him out. "He was a very loose soul," as Capecchi remembers.

On his ninth birthday, a woman he did not recognize showed up at the hospital where he was confined in the northern Italian city of Reggio Emelia. He had been relegated there because he suffered from malnutrition, yet the hospital itself served only a bowl of chicory coffee and a crust of bread once a day. The woman looked much older than his vague memory of his mother, but Capecchi didn't care whether she was his mother or not. He only knew that she represented a ticket to freedom. Life in the hospital was marked by endless days of lying naked on a bed staring at the ceiling, wracked by famine-induced fevers. Three weeks later—a period that gave him the assurance that his orphanhood had ended—mother and son left on a boat for America.



RAVELL CALL SABA

FLEEING A HARVARD PROFESSORSHIP, Mario R. Capecchi sought out Utah's wide open vistas.

In the course of just a few weeks, Capecchi went from a collapsed civilization to the highly moralistic environment of a Quaker commune, where he and his mother settled with his uncle and aunt, 20 miles north of Philadelphia. In contrast to the murderous rivalries that had fractured Europe, the commune harbored an ethnic melange that included Chinese, blacks and Jews.

His uncle, Edward Ramberg, a physicist who worked on electron optics during the day at the Princeton RCA Research Laboratory in New Jersey, was

a conscientious objector who refused to fight in the war or labor on projects that would help the military effort. The childless couple virtually adopted the boy, taking over parenting responsibilities from his mother, who was still scarred from her time at Dachau. "Their mission was to make me into a social being, and it was a struggle," Capecchi notes, his voice retaining the slightest trace of an Italian accent.

The child entered the third grade at the local public school not knowing a word of English nor how to read or calculate. The one thing the adopted Quaker communard did know was how to fight. "Initially what I did was beat up everybody. That established my own turf and gave me a social status," Capecchi recounts, his blue-jeaned leg draped over the arm of his desk chair, revealing a foot in a black clog.

Gradually, he sublimated his aggression into sports, particularly wrestling, and caught up academically with his schoolmates. At Antioch College he dropped his dalliance with athletics and began to pursue the simple elegance of the physical sciences, which held a great appeal for someone whose life had been shaped by the chaos of war. On a work-study program he grew excited over the new field of molecular biology. Later, during an interview for a graduate program at Harvard University, he shyly asked Professor Watson where he should do his graduate studies. "You would be f—ing crazy to go anywhere else," he remembers Watson telling him. He received his doctorate for doing protein synthesis work in Watson's laboratory and went on to a four-year stint as a faculty member in the department of biochemistry at Harvard Medical School.

Then Capecchi did something that seemed an act of madness to his colleagues but made sense in the larger context of his earlier experiences of entrapment and self-reliance. In 1973 he abandoned the claustrophobic, politicized atmosphere of the Harvard-M.I.T. biomedical-research complex. There researchers seemed to be suffering from a herding instinct in which each group would pursue closely related problems. Capecchi accepted a position at the University of Utah. The West's wide open spaces afforded a sense of release and a place where he could follow Watson's entreaty to concentrate only on the biggest and most important biomedical research problems. "I think that by being isolated you have the opportunity to do things much more long range," he says.

That desire for freedom extends to his personal life as well. Capecchi lives in a refashioned wooden geodesic dome on 18 acres of land in the Wasatch Mountains that he bought from a hippie in the late 1970s. He and his wife, Laurie Fraser, waited until years after the birth of their daughter, Misha, in 1984 before trading the outhouse for central plumbing.

This independent streak helped Capecchi weather the biggest crisis of his professional career. In 1980 a panel of reviewers from the National Institutes of Health classified his studies on targeted gene replacement (inactivating or modifying a gene in mouse embryos) as "not worthy of pursuit." The reviewers judged that it would be unlikely that a segment of DNA introduced into a cell could line up and replace a matching sequence from among the cell's billions of nucleotides and that if it did it would be all but impossible to detect.

Capecchi made the decision to use funds from another project to pursue this line of research. By 1984 he had amassed enough evidence to prove to NIH scientists that the technique was effective. Gene targeting gets around the tendency of a newly introduced gene to insert itself randomly into a cell's nuclear DNA. It takes advantage of a natural cellular process called homologous recombination, in which strands of nucleotides from a gene home in on matching sequences in a cell. If the newly inserted gene finds its target, it will line up with it and replace it, even when carrying altered sequences that turn off a gene or modify its activity.

This process occurs in only a small fraction of embryo cells. What made the technique effective was that the investigators found a way to detect gene insertions by killing off those cells that did not contain the gene or had inserted it in the wrong place. That year a critique done by the reviewing scientists of a new submission for funding from Capecchi's laboratory began by saying, "We are glad you didn't follow our advice."

The basic gene-targeting technique—pursued on a parallel track by Oliver Smithies of the University of North Carolina—has become the fundamental technology for testing the functional role of a particular gene in mammals. Scientists have published thousands of papers in which a mouse gene has been "knocked out" to assess resulting genetic defects—the triggering of a process that leads to cancer, for instance.

In recent years Capecchi's main interest has focused on using the suite of knockout techniques to trace neurological development in mice. His group, part of the Howard Hughes Medical Institute, is investigating how the set of homeobox genes involved in programming embryonic development can produce the thousands of types of differentiated neurons from a single set of brain cells. "What we're asking is how an embryo makes a brain. If you understand how to take it apart, you'll understand how it works," he says.

COURTESY OF MARIO R. CAPECCHI

***CAPECCHI'S MOTHER AND UNCLE** rescued the boy from the horrors of his war experiences.*

Capecchi does not foresee retirement for another 15 years. "My wife says I'm going to die in the laboratory," he notes. Even if his career ended now, his life story would remain a testament to a message that Capecchi tried to convey to his Japanese audience. Genius should be nurtured in places both high and low. Society must find ways to recruit and nurture its outcasts, even malnourished, illiterate street urchins. "No matter how good you think you are," he remarks, "you don't have the capability to predict who are the people who are going to bloom." Unlikely beginnings can produce extraordinary lives.

—Gary Stix in Salt Lake City