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 exterminated 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 feeding 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 Emilia. 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, wrecked 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.

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 responsibili-
ties from his mother, who was still
scared 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 cal-
culate. The one thing the adopted Quak-
er 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 aggres-
sion 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 pro-
gram 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 re-
ceived his doctorate for doing protein
synthesis work in Watson’s laboratory
and went on to a four-year stint as a fac-
ulty member in the department of bio-
chemistry at Harvard Medical School.

Then Capecchi did something that
seemed an act of madness to his col-
leagues but made sense in the larger
context of his earlier experiences of
entrapment and self-reliance. In 1973 he
abandoned the clausrophobic, politi-
cized 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 big-
gest and most important biomedical re-
search 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 Ca-
pecchi weather the biggest crisis of his
professional career. In 1980 a panel of
reviewers from the National Institutes
of Health classified his studies on tar-
geted 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 se-
quence 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 ten-
dency of a newly in-
troduced gene to
insert itself randomly
into a cell’s nuclear DNA. It takes ad-
vantage 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 re-
place it, even when carrying altered se-
quences 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 investi-
gators found a way to detect gene inser-
tions 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 Capec-
chi’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 Car-
olina—has become the fundamental
technology for testing the functional role
of a particular gene in mammals. Scien-
tists have published thousands of pa-
pers in which a mouse gene has been
“knocked out” to assess resulting ge-
netic defects—the triggering of a process
that leads to cancer, for instance.

In recent years Capecchi’s main inter-
est has focused on using the suite of
knockout techniques to trace neurolog-
ical development in mice. His group,
part of the Howard Hughes Medical
Institute, is investigating how the set of
homeobox genes involved in program-
ming embryonic development can pro-
duce the thousands of types of differenti-
tated neurons from a single set of brain
cells. “What we’re asking is how an
embryo makes a brain. If you under-
stand how to take it apart, you’ll un-
derstand how it works,” he says.

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 malnour-
ished, illiterate street urchins. “No mat-
ter how good you think you are,” he
reminds, “you don’t have the capability
to predict who are the people who are
going to bloom.” Unlikely beginnings
can produce extraordinary lives.

—Gary Sist in Salt Lake City