It was conceived after a yogurt company in 2007 identified an unexpected defense mechanism that its bacteria use to fight off viruses. A birth announcement came in 2012, followed by crucial first steps in 2013 and a massive growth spurt last year. Now, it has matured into a molecular marvel, and much of the world—not just biologists—is taking notice of the genome-editing method CRISPR, Science's 2015 Breakthrough of the Year.

CRISPR has appeared in Breakthrough sections twice before, in 2012 and 2013, each time as a runner-up in combination with other genome-editing techniques. But this is the year it broke away from the pack, revealing its true power in a series of spectacular achievements. Two striking examples—the creation of a long-sought “gene drive” that could eliminate pests or the diseases they carry, and the first deliberate editing of the DNA of human embryos—debuted to headlines and concern. Each announcement roiled the science policy world. The embryo work (done in China with nonviable embryos from a fertility clinic) even prompted an international summit this month to discuss human gene editing. The summit confronted a fraught—and newly plausible—prospect: altering human sperm, eggs, or early embryos to correct disease genes or offer “enhancements.” As a genetic counselor quipped during the discussion: “When we couldn’t do it, it was easy to say we shouldn’t.”

What sets CRISPR apart? Its competitors—designer proteins called zinc finger nucleases and TALENs—also precisely alter chosen DNA sequences, and several companies are already exploiting them for therapeutic purposes in clinical trials. But CRISPR has proven so easy and inexpensive that Dana Carroll of the University of Utah, Salt Lake City, who spearheaded the development of zinc finger nucleases, says it has brought about the “democratization of gene targeting.” Quoted in a recent issue of The New York, bioethicist Hank Greely of Stanford University in Palo Alto, California, compares CRISPR to the Model T Ford: far from the first automobile, but the one whose simplicity of production, dependability, and affordability transformed society. “Any molecular biology lab that wants to do CRISPR can,” says Harvard University’s George Church, whose lab was one of the first to show that it efficiently edits human and other eukaryotic cells.

Already, the nonprofit group Addgene has distributed about 50,000 plasmids—circlets of DNA—containing genetic code for the two basic components of CRISPR, the “guide RNA” used to target a specific DNA sequence and the DNA-cutting enzyme, or nuclease, usually one called Cas9. “It’s going to be like PCR, a tool in the toolbox,” says Jennifer Doudna of the University of California, Berkeley, whose group, in collaboration with one led by Emmanuelle Charpentier, now at the Max Planck Institute for Infection Biology in Berlin, published the first report...
CRISPR’s ability to edit DNA has helped scientists create a menagerie of genetically new organisms.

that CRISPR could cut specific DNA targets. Their work grew out of a surprising observation that bacteria could remember viruses. Researchers had found remnants of genes from past infections, sandwiched between odd, repeated bacterial DNA sequences—the “clustered regularly interspaced short palindromic repeats” that give CRISPR its name. The viral scraps serve as infection memory bank: From them, bacteria create guide RNAs that can seek out the DNA of returning viruses before chopping up the viral genes with a nuclease. Once this mechanism was understood, Doudna and Charpentier, among others, raced to adapt it to editing DNA in higher organisms.

A torrent of applications followed. One of them—the CRISPR-powered gene drive—is a case study in the power, and potential risks, of genome-editing technology. In 2003, Austin Burt, an evolutionary biologist at Imperial College London, envisioned attaching a gene for a desired trait to “selfish” DNA elements that could copy themselves from one chromosome spot to another. That would bias the offspring of a parent carrying the trait to inherit it, quickly spreading it throughout a population. Earlier this year, a U.S. team adapted CRISPR to just that purpose, succeeding well beyond the original vision.

In a method ominously dubbed “mutagenic chain reaction,” the researchers drove a pigmentation trait in lab-grown fruit flies to the next generation with 97% efficiency. They then teamed up with another research group to create a gene drive that, unleashed in a lab population of mosquitoes, spread genes that prevent the insects from harboring malaria parasites. Weeks later, working with another malaria-carrying mosquito, Burt and colleagues reported the same thing with genes that rendered the females infertile and could quickly wipe out a population. Debates are now erupting over the benefits and ecological risks of releasing such insects into the wild—and whether gene drives could also thwart invasive species such as Asian carp and cane toads, or combat other animal-borne pathogens such as the one causing Lyme disease.

In other labs, researchers harnessed the technique to create a growing menagerie of genetically engineered animals and plants: extra-muscular beagles, pigs resistant to several viruses, and wheat that can fend off a widespread fungus. Longer-lasting tomatoes, allergen-free peanuts, and biofuel-friendly poplars are all on the drawing board. Depending on how it’s wielded, CRISPR can do its work without leaving any foreign DNA behind, unlike earlier techniques for genetically modifying organisms, which poses a challenge for regulations based on the presence of foreign DNA.

There is much, much more. By making “dead” versions of Cas9, scientists eliminated CRISPR’s DNA-cutting ability but preserved its talent for finding sequences. Tack molecules onto Cas9 and CRISPR suddenly becomes a versatile, precise delivery vehicle. Several groups, for example, have outfitted dead Cas9s with various regulatory factors, enabling them to turn almost any gene on or off or subtly adjust its level of activity. In one experiment this year, a team led by another CRISPR pioneer, Feng Zhang of the Broad Institute in Cambridge, Massachusetts, targeted the 20,000 or so known human genes, turning them on one by one in groups of cells to identify those involved in resistance to a melanoma drug.

The biomedical applications of CRISPR are just starting to emerge. Clinical researchers are already applying it to create tissue-based treatments for cancer and other diseases. CRISPR may also revive the moribund concept of transplanting animal organs into people. Many people feared that retroviruses lurking in animal genomes could harm transplant recipients, but this year a team eliminated, in one fell swoop, 62 copies of a retrovirus’s DNA littering the pig genome.

And the international summit saw many discussions of CRISPR’s promise for repairing genetic defects in human embryos, if society dares to cross what many regard as an ethical threshold and alter the human germline.

In short, it’s only slightly hyperbolic to say that if scientists can dream of a genetic manipulation, CRISPR can now make it happen. At one point during the human gene-editing summit, Charpentier described its capabilities as “mind-blowing.” It’s the simple truth. For better or worse, we all now live in CRISPR’s world.

ON OUR WEBSITE
For more on the Breakthrough of the Year, including a video and a podcast, go to http://scim.ag/breakthru15.

People’s choice
Visitors to Science’s website voted on our 10 Breakthrough finalists. Their top picks:

1. Pluto 35%
2. CRISPR 20%
3. Lymphatic system in the central nervous system 15%
4. Ebola vaccine 10%
5. (Tie) Psychology replication/quantum entanglement 6%

For the second year in a row, the public weighed in through the Internet, voting for its top discovery while the Breakthrough team was hammering out its choices. High on the list, the results mirrored Science staffers’ own deliberations. CRISPR surged to an early lead, as high-profile meetings and magazine articles focused public attention on the genome-editing technique. Pluto, a media darling in July when the New Horizons probe swooped past it en route to points beyond, was a distant second.

But the dwarf planet rallied, as New Horizons scientists blasted Twitter with get-out-the-vote tweets. When the final returns were in, Pluto finished comfortably ahead of CRISPR in the popular vote.

Further down the list, it was a bad year for old bones. Homo naledi (a new human species!) finished in seventh place, and Kennewick Man, the ancient Native American whose DNA was recently sequenced, was dead last. Better luck next time, O my people.