who was the first to crystallize rhodopsin[2], agrees that the work is "a tremendous accomplishment". But he is concerned that the engineered and antibody-stabilized proteins used in Kobilka's study might not be a perfect match for the structure found in nature. Kobilka, however, says that his functional assays show that the engineered proteins behave like the natural proteins.

Researchers already knew that inactive G proteins are bound to a molecule of guanosine diphosphate (GDP) — a complex that Sunahara likens to a Pac-Man with something in its mouth. When a GPCR receives a signal, the receptor forces the G protein to spit out the GDP, allowing a molecule of guanosine triphosphate to swoop in and switch the G protein on.

The structure now reveals how the activated receptor contorts to make this happen. Most surprisingly, it also shows that the G protein's mouth splays wide open when the GDP departs. X-ray crystallography provides static images, so the exact sequence of events is unclear. "But now that we know it happens, it's something we can study," says Kobilka.

The discovery could provide unexpected clues to the molecular mechanism of the cholera toxin. The toxin forces G proteins to stay on all the time and continuously activate signalling pathways in intestinal cells. The affected cells release much of their water, leading to diarrhoea and vomiting. But the site that the toxin modifies is buried deep inside the G protein, which was "sort of puzzling", says Sunahara. "How does it get to that buried site? Our structure showed us that the Pac-Man opens wide enough that it exposes the site. And if that's the way cholera works, it's probably the way a lot of things interact with G proteins."

"Brian's struggled for this for such a long time," says structural biologist Tracy Handel at the University of California in San Diego. "Thank God he got it, because, boy, he deserved it." ■

NATURE.COM
Listen to more about this story on the Nature podcast
go.nature.com/nfqq2j

Scan the tag above with the free app from gettag.mobi

1. Rasmussen, S. G. F. *et al. Nature* http://dx.doi.org/10.1038/nature10361 (2011).
2. Palczewski, K. *et al. Science* **289,** 739–745 (2000).
3. Rasmussen, S. G. F. *et al. Nature* **450,** 383–387 (2007).
4. Rosenbaum, D. M. *et al. Science* **318,** 1266–1273 (2007).
5. Cherezov, V. *et al. Science* **318,** 1258–1265 (2007).
6. Shimamura, T. *et al. Nature* **475,** 65–70 (2011).
7. Xu, F. *et al. Science* **332,** 322–327 (2011).
8. Wu, B. *et al. Science* **330,** 1066–1071 (2010).
9. Chien, E. Y. *et al. Science* **330,** 1091–1095 (2010).

SCOTTS MIRACLE-GRO COMPANY

Glyphosate-resistant Kentucky bluegrass has outgrown US rules on genetically modified crops.

BIOTECHNOLOGY

Transgenic grass skirts regulators

Technological advances remove basis for government oversight of genetically modified crops.

BY HEIDI LEDFORD

When the US Department of Agriculture (USDA) announced this month that it did not have the authority to oversee a new variety of genetically modified (GM) Kentucky bluegrass, it exposed a serious weakness in the regulations governing GM crops. These are based not on a plant's GM nature but on the techniques used for its genetic modification. With changing technologies, the department says that it lacks the authority to regulate newly created transgenic crops.

The grass, a GM variety of *Poa pratensis*, is still in the early stages of development by Scotts Miracle-Gro, a lawn-care company based in Marysville, Ohio. The grass has been genetically altered to tolerate the herbicide glyphosate, which would make it easier to keep a lawn weed-free. On 1 July, secretary of agriculture Tom Vilsack wrote to the company to say that the variety "is not subject" to the same regulations that govern other GM crops. The decision allows Scotts to bypass the years of environmental testing and consultation typically required by the regulators for GM plants, although the company says there are no plans to market this particular variety.

The grass can evade control because the regulations for GM plants derive from the Federal Plant Pest Act, a decades-old law intended to safeguard against plant pathogens from overseas. Previous types of GM plants are covered because they they were made using plant pathogens. The bacterium *Agrobacterium tumefaciens* — which can cause tumours on plants — shuttled foreign genes into plant genomes. Developers then used genetic control elements derived from pathogenic plant viruses such as the cauliflower mosaic virus to switch on the genes.

By revealing similar elements in plants' DNA, genome sequencing has liberated developers from having to borrow the viral sequences. And *Agrobacterium* is not essential either; foreign genes can be fired into plant cells on metal particles shot from a 'gene gun'. Scotts took advantage of both techniques to construct the herbicide-resistant Kentucky bluegrass that put the USDA's regulatory powers to the test.

"The Plant Pest Act was completely inappropriate for regulating biotech crops, but the USDA jury-rigged it," says Bill Freese, science-policy analyst at the Center for Food Safety in Washington DC. "Now we can foresee this loophole getting wider and wider as companies turn more to plants and away from bacteria and other plant-pest organisms." The USDA has not made public any plans to close the loophole and has also indicated that it will not broaden its definition of noxious weeds, a class of plants that falls under its regulatory purview, to facilitate the regulation of GM crops.

Nevertheless, *Agrobacterium* is still industry's tool of choice for shuttling in foreign genes, says Johan Botterman, head of product research at Bayer BioScience in Ghent, Belgium. The technique is well established for many crops, and particle bombardment is less predictable, often yielding multiple, fragmented insertions of the new gene.

But *Agrobacterium* isn't suitable for some new techniques. Many companies are developing 'mini-chromosomes' that can function in a plant cell without needing to be integrated into the plant's genome. Last summer, agribusiness giant Syngenta, based in Basel, Switzerland, conducted the first field trials of maize (corn) containing engineered mini-chromosomes, and showed that the mini-chromosomes, which carried multiple genes for insect and herbicide resistance, were stable in the field. "I would expect that by the end of the decade, this technology will be well used by many as a way to deliver large stacks of genes to plants," says Roger Kemble, head of technology scouting for Syngenta.

Other techniques under development insert foreign genes into designated sites in the genome, unlike the near-random scattering generated by *Agrobacterium*. In 2009, researchers at Dow AgroSciences in Indianapolis, Indiana, and Sangamo BioSciences in Richmond, California, announced that they had used enzymes called zinc-finger nucleases to insert a gene for herbicide resistance at a specific site in the maize genome (V. K. Shukla *et al. Nature* **459,** 437–441; 2009). Bayer is interested in harnessing other enzymes called 'meganucleases' to do the same type of targeted engineering, a strategy that Botterman says may make it possible to introduce multiple new traits into existing GM crops.

Regulators need to adapt to these new techniques, or run the risk of over- or under-regulating GM plants, says Roger Beachy, a plant biologist at Washington University in St Louis, Missouri, and former head of the USDA's National Institute for Food and Agriculture. The Kentucky bluegrass decision drives this point home, he says: "It really speaks to the importance of reviewing the regulatory process periodically to ensure that it is keeping up with the advances in technology." ■ SEE EDITORIAL PAGE 265

PHILANTHROPY

Charities seek cut of drug royalties

Non-profits that support medical research are angling for a share of the proceeds and intellectual-property rights.

BY HEIDI LEDFORD

Early next year, a drug for cystic fibrosis is expected to come before the US Food and Drug Administration for approval. It is a moment that the Cystic Fibrosis Foundation (CFF) will have waited 12 years and invested US$75 million to witness. Approval of the drug, VX-770 — developed by Vertex Pharmaceuticals of Cambridge, Massachusetts, with support from the foundation — would provide a new treatment for patients, and a revenue stream for the charity.

The CFF, based in Bethesda, Maryland, has a stake in the intellectual property underlying VX-770, and is entitled to royalties from sales of the drug. Such 'venture philanthropy' is increasing among charities. Like venture capitalists, non-profit groups are managing research projects, making funding dependent on the projects reaching predetermined milestones and potentially reaping a financial return. They are also keeping control over the fruits of their investment in case the journey from lab to treatment encounters obstacles.

"The charities are providing funds at the time when the risk is the very highest. But yes, they expect a return."

"Philanthropies are looking to have more of a hand in managing intellectual property," says Timothy Coetzee, chief research officer of the National Multiple Sclerosis Society in New York, and former president of Fast Forward, the society's venture-philanthropy arm. Philanthropic donations for medical research are increasing (see 'Growing influence'), even as government granting agencies tighten their purse strings and venture capitalists cut back on biotechnology investments. As a result, non-profits have more bargaining power than ever before — especially for early-stage, high-risk projects that tend to be unattractive to private and federal investors.

"The charities are providing funds at the time when the risk is the very highest," says Ken Schaner, an attorney at Schaner & Lubitz — a law firm in Bethesda, Maryland, that specializes in working with non-profit organizations. "But yes, they expect a return." The CFF is not alone: charities including the ALS Association in Washington DC, the Muscular Dystrophy Association in Tucson, Arizona, and the Wellcome Trust in London have also demanded royalties from some projects. Schaner says that the value of the return often depends on the size of the investment — for example, a foundation might be entitled to six times its input. In some cases, Schaner estimates that the payout could be as much as $1 billion.

But organizations aren't interested only in generating revenue for their charitable work. Their involvement also helps to ensure that therapies reach the people who need them, in case anything happens to the drug companies with which they are collaborating.

In 2000, Schaner worked with the CFF to carve out a deal with Aurora Biosciences in San Diego, California — a pharmaceutical company that was later sold to Vertex — to develop the drug that was to become VX-770. The deal was one of the first examples of venture philanthropy.

But Schaner says that he couldn't sleep the night after the deal was signed. "I started thinking about what would happen if Aurora lost interest in the project. It could just sit there on the shelf untouched," he says. So he created an 'interruption licence' that is now used widely to give charities the intellectual-property rights behind a project if a company abandons it. ▶

GROWING INFLUENCE

Donations from charities to US biomedical research have tripled in the past decade.

SOURCE: FOUNDATION CENTER