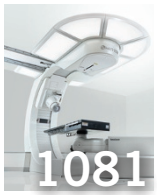

Proton vs. photon:
Proton therapy undergoes close scrutiny

Protein hunting:
Aptamer-based approach gains ground

Positive plan:
Organ transplants between people with HIV

Ice bucket challenge cash may help derisk ALS drug research

Until now, the funding landscape for amyotrophic lateral sclerosis (ALS) has been dominated mainly by the US National Institutes of Health (NIH), which provided over $39 million last year for projects to develop animal models, study genetic risk factors and test new therapies involving stem cells. But as *Nature Medicine* went to press, a social media phenomenon known as the Ice Bucket Challenge had raised more than $100 million toward solutions and increased awareness for this progressive and fatal neuromuscular disease that affects about 5 in every 100,000 people worldwide (see Editorial, page 1079).

The $100 million gained this summer by the Washington, DC–based Amyotrophic Lateral Sclerosis Association (ALSA), is more than 35 times the funds it received last year in July and August. And although the ALSA, which historically spends approximately 28% of its funds on research, has not made its plans for spending these funds public yet, the scientific community has a few ideas ready.

Many scientists have pointed to genetic therapies that might work for the disorder. Multiple gene mutations have been implicated in ALS. However, *SOD1*, the first gene linked to the disorder, and *C9ORF72*, a gene affected in familial ALS as well as some sporadic cases of the disorder, are currently the main focus of drug developers. Recently a phase 1 clinical trial, funded by Isis Pharmaceuticals of California, demonstrated the safety of an antisense oligonucleotide designed to silence an errant version of the *SOD1* gene in 32 patients with ALS who had this type of genetic abnormality. The clinical trial was a gamble in that it delivered the therapy into the central nervous system.

"Getting the therapy to the clinical trials was very difficult," says Don Cleveland, a neurobiologist at the University of California, San Diego School of Medicine, whose lab was a part of the group that conducted the early research in developing the antisense technology targeting *SOD1*. Cleveland, who did not study the therapy in humans, notes the clinical trial received funding from the NIH and the ALSA, but the giants of the pharmaceutical industry have not shown much interest so far in early-stage ALS trials, which can be expensive. He now hopes that the new funds from the Ice Bucket Challenge will fuel phase 1 research of genetic therapies.

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Challenge accepted: Cleveland's lab splashes out.

Getting pharma involved

The ALSA is now considering new types of mechanisms to involve pharmaceutical companies more directly with ALS drug development.

"One of things we are most interested in is to accelerate the early stage of de-risking clinical therapies," says Lucie Bruijn, the chief scientist at ALSA, who has been a major figure in directing the research agenda of the association. She points to the partnership between Isis Pharmaceuticals and research labs for the development of *SOD1* antisense technology as a model that the ALSA might support in the future.

Despite a number of genetic studies on ALS in the last decade, "the biggest challenge is determining the disease mechanism—and the funding for that is limited," Cleveland says. Currently, whole-genome sequencing costs approximately $1,200 per patient, making the cost for large-scale studies to identify genetic and environmental risk factors prohibitive. Large-scale genome-wide association studies haven't been done adequately in ALS, says Bryan Traynor, a neurologist at the US National Institute on Aging, who led the team that discovered the *C9ORF72* repeat in ALS. "If we have large amounts of money, we should definitely be going after genome-wide association studies [and] genome and exome sequencing studies that will help dissect the architecture of the disorder." With the new funds, Bruijn wants to get more people from industry interested in finding genetic markers for the disease: "biomarkers is an area where we want to develop a competitive landscape for the industry."

The previously unavailable extensive funds have also allowed ALSA to consider undertaking large-scale projects such as building patient repositories of genetic material that are more comprehensive that the current ones, which was previously too expensive. Orla Hardiman, director of the National ALS Clinic in Dublin and the Irish ALS Research Group, says that building such collections now, as well as building patient registries, would lay a stronger foundation for future clinical trials.

"One of the ways to utilize resources raised by the Ice Bucket Challenge would be to put a more robust footing for the resourcing of population-based longitudinal [patient] registries, so they are adequately funded till perpetuity, so that patients can be tracked," she says.

The Ice Bucket Challenge has produced more cash for ALS advocacy and research groups beyond US borders. For example, ALS Canada has raised more than C$14 million ($12 million) and the Irish Motor Neurone Disease Association has received €1.4 million ($1.8 million). The coming months will be a test of spending it wisely.

Manasi Vaidya