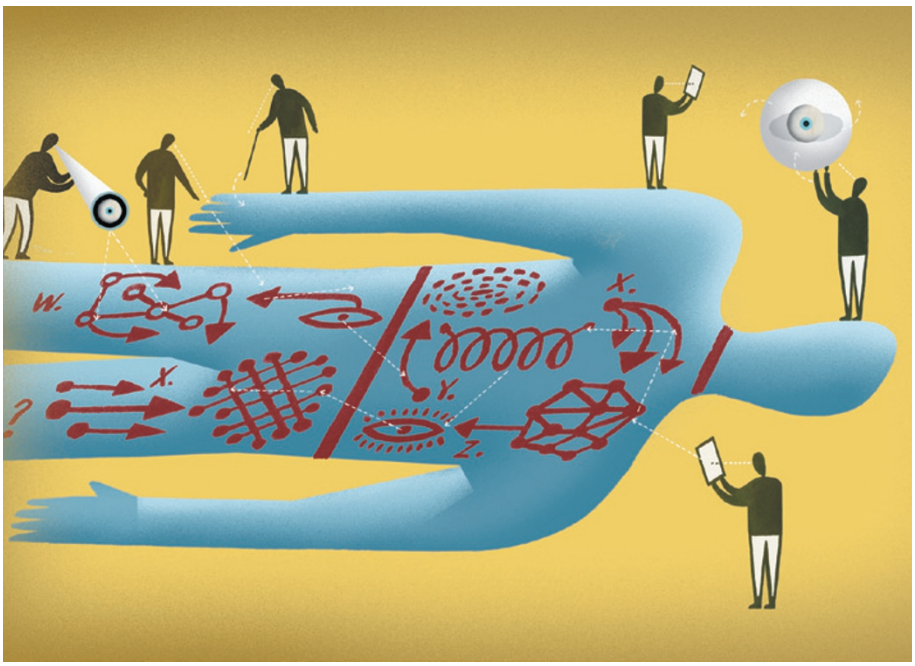
GENDER Conference committees with women enlist more female speakers **p.445**

SALARIES Prospective postgraduates ignore future salary outlook **p.445**

NATUREJOBS For the latest career listings and advice **www.naturejobs.com**



DRAWN IDEAS/IKON IMAGES/CORBIS

DISEASE RESEARCH

Rare insights

Scientists who specialize in uncommon diseases can find a research focus with a purpose.

BY HEIDI LEDFORD

Steven Gray used to spend long hours in the lab for the simple love of science. As a postdoctoral researcher, he was tinkering with a virus in search of ways to shuttle genes into nerve cells for gene therapy. Then, in 2008, his adviser sent him to a meeting held by a non-profit organization called Hannah's Hope Fund, and Gray found a new inspiration.

Hannah's Hope Fund is a charity based in Rexford, New York, that supports research on giant axonal neuropathy (GAN), a fatal nerve disorder. At the meeting, Gray met Hannah Sames, a clumsy four-year-old with tight curls and a sweet smile whose disease had inspired her parents to start the charity. He launched a GAN project after the meeting. "I looked at her and saw my own daughter," says Gray, whose child was then also four. "Now I'm focused on finding a treatment, almost as I would for my own child."

GAN is one of more than 6,000 rare, or 'orphan', diseases that affect humans worldwide. Such diseases typically strike fewer than 1 in 2,000 people, and present unique challenges to researchers and drug developers, who have access to limited numbers of participants for clinical trials and few resources such as animal models.

But for scientists who can overcome such challenges, the rewards can be tremendous. From a practical perspective, an increasing interest from industry and available government funds dedicated to rare diseases have brought new job options. "There are great opportunities for people in academia to interact with pharma and to access government funding," says Daniel Ory, who studies Niemann–Pick type C disease, a genetic neurodegenerative disorder, at Washington University in St. Louis, Missouri.

Rare-disease research also offers rich returns for scientists who thrive on interaction, adds Ory. Because of the small numbers affected and a dearth of information about most rare diseases, scientists must work closely with patients and their families. They also frequently collaborate with patient-advocacy organizations to gather tissue samples, learn more about symptoms and recruit subjects for clinical trials. Personal interaction presents challenges: many rare diseases are fatal, and they often affect children. "It really doesn't get any more raw or emotional," says Nick Leschly, president of biotechnology firm bluebird bio in Cambridge, Massachusetts, which is seeking treatments for several rare diseases.

HIRING OUTLOOK

Thanks mostly to the fervour of patient advocates, research into rare diseases is booming. Philanthropic donations have allowed universities to set up rare-disease centres, such as the University of Pennsylvania's Center for Orphan Disease Research and Therapy in Philadelphia, which has awarded more than US$4.1 million in grants to its researchers since it opened in 2011. In 2012, the US National Institutes of Health (NIH) awarded $3.6 billion for rare-disease research, including supporting dedicated initiatives such as its Therapeutics for Rare and Neglected Diseases programme. The European Commission's Seventh Framework Programme for research funding spent an estimated €530 million (US$720 million) on orphan diseases between 2007 and 2013, according to EURORDIS, an alliance of rare-diseases patient organizations based in Paris.

But it is in industry that the field has really taken off. Pharmaceutical companies that once shied away from developing drugs for small markets have learned from success stories such as Genzyme, an orphan-disease company based in Cambridge, Massachusetts. Genzyme built a booming business, compensating for the small market by charging high prices. (There are programmes to help patients to pay for their drugs, but the pricing remains controversial — see 'Cost conundrum'.) Other companies are now flocking to take advantage of regulatory incentives: in the United States, firms sometimes receive tax credits for clinical trials of orphan-disease drugs, and US and European regulators often streamline the approval of such medicines. One-third of the 39 drugs approved by the US Food and Drug Administration (FDA) in 2012 were for orphan diseases, and the global market for them is expected to grow from $86 billion in 2012 to $112 billion in ▶

2017, according to BCC Research, a market-research firm in Wellesley, Massachusetts.

As a result, orphan-drug development is teeming in small biotechnology firms such as bluebird bio, which almost doubled its staff by adding about 40 new employees this year, most of them scientists. Large pharmaceutical companies, including London-based GlaxoSmithKline (GSK), have developed specialized units that focus on rare diseases. Hans Schikan, chief executive of Prosensa, a rare-diseases company in Leiden, the Netherlands, was surprised when GSK approached him in 2009 about investing in his company's research, because he had not realized that GSK had any interest in rare diseases. The resulting partnership brought Prosensa $25 million, with added payments as the company hit milestones in its Duchenne muscular dystrophy projects. Since then, says Schikan, the field has blossomed. Other large pharmaceutical companies such as Novartis in Basel, Switzerland, have increased their focus on rare diseases, creating job opportunities. "It's still a fairly young space," says Schikan. "But it's growing."

MULTIPLE NICHES

There are many different kinds of orphan disease, and interested researchers can come from a variety of disciplines. Veterans in the field recommend that prospective researchers brush up on statistics because small sample sizes can require sophisticated analyses. Experience in the latest genome-sequencing techniques is a boon: the technology has unearthed the genetic basis for many rare diseases in recent years. "We're seeing many of the tools and technologies developed for common diseases now being applied for the first time in rare diseases," says Robert Steiner, executive director of the Marshfield Clinic Research Foundation in Wisconsin.

And orphan diseases provide an opportunity to carve out a niche and make contributions with little fear of being scooped, Steiner adds. "There is often less competition," he says. "And I've felt as if everything I was doing had the potential to add significant knowledge to an area where there was a real gap."

But carving out a niche can be isolating, as Josh Sommer learned first-hand. In 2006, as an undergraduate at Duke University in Durham, North Carolina, Sommer was diagnosed with chordoma, a rare spinal cancer. He later decided to work in a lab that studied the disease, and Duke, as it happened, was the country's only university with a federally funded chordoma lab. But it did not take long for Sommer to learn about the frustrations of rare-disease research. "We didn't have access to tissue samples, cell lines or mouse models," he says. "And we didn't have other labs to reach out to or collaborate with. It was lonely."

Sommer left the university after his third year to co-found the Chordoma Foundation, also based in Durham, where he remains executive director. One of his first initiatives was an annual workshop to bring together chordoma researchers and other scientists whose work may have a bearing on the disease. The foundation also sponsors $10,000 prizes for scientists who develop useful preclinical models. The cash is not much, says Sommer, but it has incentivized several laboratory technicians to develop chordoma cell lines and mouse models. So far, the foundation has distributed three cell lines to 60 labs and companies, and Sommer says that he stays in contact with more than 150 researchers whose work may be relevant to the disease.

Few preclinical models are available to rare-disease researchers, but this can be a chance to create high-quality models in one's own lab, says Steiner. His biggest worry is making the case for funding. Although the NIH supports a range of orphan-disease research, Steiner says that he and his colleagues still occasionally receive grant reviews questioning the importance of their work. "Some study sections for federal funding agencies are still focused on

AT WHAT PRICE?

Cost conundrum

One way in which companies have made a profit from orphan drugs is by charging high prices — a trend that can frustrate researchers intent on helping patients.

For example, the cystic fibrosis drug Kalydeco (ivacaftor), made by Vertex Pharmaceuticals of Cambridge, Massachusetts, can cost individuals a staggering US$373,000 per year. Drug companies say that they need to charge such high prices to recoup the cost of developing drugs for a tiny number of people. People with health insurance may not have to shoulder much of this cost, and many companies, including Vertex, have global financial-aid programmes to help those without insurance.

But physicians and researchers are voicing concerns about whether these programmes are sufficient for ensuring access, and question how sustainable the high prices are. Charging so much for the drugs disregards the contribution of academic researchers and clinical-trial participants to drug development, argues Carlos Milla, a paediatrician who studies rare diseases at Stanford University in Palo Alto, California. "It's more than just the company and the investors," he says. "There was a whole community that contributed to this effort." H.L.

STEVEN GRAY

Steven Gray (far right) was inspired to launch a project on giant axonal neuropathy, a rare disease.

the idea that the significance of a project is directly proportional to the number of patients affected," he says.

SECURING FUNDS

One method for boosting funding opportunities is to look for ways in which a rare disease overlaps with a more common one. Heather Bean, a chemist at Dartmouth College in Hanover, New Hampshire, is using a two-year postdoctoral fellowship from the Cystic Fibrosis Foundation in Bethesda, Maryland, to support her studies of bacterial lung infections associated with cystic fibrosis. But she hopes eventually to expand her funding opportunities by exploring overlaps between cystic fibrosis and a more common ailment, chronic obstructive pulmonary disease. "I'm still committed to looking at cystic fibrosis," she says. "But drawing those links to a bigger, more fundable disease is handy."

Some labs thrive by pulling in grants and fellowships from multiple foundations. Claudio Hetz, co-director of the Biomedical Neuroscience Institute at the University of Chile in Santiago, studies protein folding, which goes awry in several rare diseases including Creutzfeldt–Jakob disease, Huntington's disease and amyotrophic lateral sclerosis. Hetz was worried about finding funds when he left his postdoc in the United States to open his own lab. He applied to a slew of foundations, hoping to get an award from one. He received three grants. "It was the starting point for everything," he says. "It allowed me to build a solid lab really fast."

Hetz rattles off a list of five foundations that he works with, and says that he has forged personal relationships with people at each of them. Some, such as the Michael J. Fox Foundation for Parkinson's Research, based in New York, do more than just hand over money. Hetz says that he contacts a programme officer there when he encounters a technical stumbling block, and the officer works with him to find the right scientist to consult.

Yet there can be drawbacks to foundation grants. The awards are often smaller than government grants — Gray, who now runs his own laboratory at the University of North Carolina in Chapel Hill, says that the largest of his seven foundation grants is still just shy of $250,000 a year. His smallest have values of about $50,000 per year. And the grants often last only a year or two, creating a sense of instability. Furthermore, foundations rarely pay for full operational costs — such as building maintenance and administrative support — that universities typically take out of government grants. For that reason, universities say that they can lose money on the awards, and sometimes force staff to decline them. Researchers who are interested in competing for foundation money would therefore do well to check with their institutions to find out if they can accept the funds (see *Nature* **504,** 343; 2013).

Foundations also expect their grant recipients to remain focused on the goal of helping patients. Gray warns applicants to his lab that this will sometimes mean dropping scientifically interesting experiments if they do not obviously contribute to the project's main mission. "We really make sure that everything we're doing is in the best interest of the people that are funding us," he says.

Gray is comfortable with that compromise. Last year, he applied to the FDA for approval to conduct a GAN clinical trial. He counts several people with GAN and their families among his friends. His voice is strained when discussing the recent death of an adult with the condition whom he met at that original meeting. "It's tough," he says. "You're always trying to work a little harder." ■

Heidi Ledford *reports for* Nature *from Cambridge, Massachusetts.*

GENDER

Female speakers

Having at least one woman on the speaker-recruiting team for a scientific conference boosts the number of female speakers, finds a 7 January study (A. Casadevall and J. Handelsman *mBio* http://doi.org/qsh; 2014). The authors examined 460 symposia with a total of 1,845 speakers at two annual meetings sponsored by Washington DC's American Society for Microbiology in 2011–2013. They focused on 104 all-male convener teams and 112 with at least one woman. When at least one woman was on the team, the proportion of female speakers rose from an average of 25% to 43%. Co-author Arturo Casadevall, a microbiologist at the Albert Einstein College of Medicine in New York, says that early-career female scientists can benefit from volunteering to be speaker recruiters.

SALARIES

Living in the present

Prospective biomedical postgraduate students decide whether to enrol on the basis of current salaries rather than potential future earnings, says a study out on 23 December (M. E. Blume-Kohout and J. W. Clack *PLoS ONE* http://doi.org/qsq; 2013). Data for 1996–2010 showed that postgraduate enrolment for a given year rose by 2.9–3.9% when relative wages for biomedical-science posts rose by 1%. But enrolment in a given year did not correspond to salary changes six years later, around graduation time. Prospective students should consider effects on salary trends, such as dips in agency budgets, says co-author Meg Blume-Kohout, a senior research economist at the New Mexico Consortium in Albuquerque.

FEMALE RESEARCHERS

Ireland lines up grants

The Irish government plans to launch one- and two-year postdoctoral fellowships, worth up to €185,000 (US$252,000) each, to prompt early-career female researchers to stay in or return to the scientific workforce after childcare or other breaks. Science Foundation Ireland (SFI) in Dublin will announce the 20 or so Advance Fellowship grants by June, says Elena Martines, the SFI's scientific programme officer. Currently, 35% of SFI-funded Irish postdocs and 20% of SFI-funded academic researchers are women, says Martines. "This is a very bold programme," she says, noting that few similar initiatives exist.