The Challenge of Funding Research on Rare Malignancies

By Alison Palkhivala

In a funding climate where funding research for the most prevalent malignancies such as breast and colorectal cancers is already highly competitive, researchers working on rare malignancies such as myelofibrosis or soft-tissue sarcomas face an even bigger challenge.

Hundreds of cancers meet the criterion for a rare disease: a prevalence of less than 200,000 in the U.S. And researchers of these diseases are all reaching into the same pot for funding support, which can make for a mean competition. Just ask Ross Levine, M.D., an associate member at Memorial Sloan–Kettering Cancer Center in New York. Levine’s lab conducts research into the genetics of hematopoietic malignancies, particularly acute and chronic myeloid leukemia.

Unlike many of his rare-disease colleagues, Levine has obtained Research Project (R01) grants, the primary form of funding of health-related research from the National Institutes of Health. But that is never enough. “A large part of my effort, like all of my colleagues doing laboratory research, has been in identifying other sources of funding to supplement the federal funding we get,” he said. “It’s very difficult to predict success for any individual grant application. I think that’s why most of us have increased the number of applications we write for peer-reviewed funding.”

Private Foundations and Networking

For this additional funding, Levine relies on private foundations that sponsor leukemia research, such as the Leukemia and Lymphoma Society and the Myeloproliferative Neoplasm Research Foundation. Such patient-driven foundations often offer small grants for research focused on specific diseases. Applications are peer reviewed, and ideally, the best science wins the grant.

But the foundations do favor research with the most clinical promise. “There’s no doubt that doing translational research that involves studying patient samples and developing novel therapies are what the foundations are looking for,” said Levine. “That’s evidenced in their requests for applications. That’s in contrast to federal funding, where generally you just put in your best science and the overt translational value is not as absolutely requisite.”

Levine has become intimately involved with the foundations’ work. “I have given probably 10 talks to patient groups in the past year,” said Levine. “Patients are very hungry for information, and we are very eager to provide it to them because we believe that their involvement in the process is really a positive thing on many levels. It leads to more funding, but it also leads to more participation in clinical and research studies. It leads to more advocacy for what we all do, and in general it is a positive thing.”

Levine also makes a point of networking with the rare malignancy community. He works closely with Srdan Verstovsek, M.D.,
Ph.D., a staff physician in the leukemia department at the University of Texas M. D. Anderson Cancer Center in Houston. Verstovsek conducts clinical research on myeloproliferative neoplasms (MPNs), with a particular interest in myelofibrosis. As recently as 2004, he said, no drugs were approved in the community setting to treat some of the most aggressive MPNs. With only about 60 MPN patients being treated at M.D. Anderson, he could not even launch a properly-powered clinical trial.

Then in 2005, a januskinase 2 (JAK2) mutation was found to be associated with MPN, spurring Verstovsek to initiate a clinical trial with an investigative JAK2 inhibitor. To garner support, he developed a web page for MPN. “I engaged actively with patient [advocacy] groups [and] chat groups on the Web. I’m on the medical advisory board for one of the MPN foundations. My e-mail is always available to everybody.” He also exploited established leukemia networks, writing regular articles on MPN for their newsletters. He ran ads and contacted patients online through blogs and websites, finally accruing 157 for the largest clinical trial ever in myelofibrosis. Most important, he persuaded a small biotech startup to fund the study, using the prestige of M.D. Anderson as an incentive.

Levine’s efforts paid off. Initial clinical findings were positive: a phase III trial with the drug has just been completed, and Levine expects it to be approved by the end of the year. This success led to increased interest among other sponsors. Today, Verstovsek heads the largest MPN center in the world, treating about 250 patients every year. About 10 JAK2 inhibitors are in clinical development for MPN, and Verstovsek has helped develop all of them.

The importance of that first successful clinical trial is a lesson also learned by George Fisher, M.D., Ph.D., an associate professor of medicine in the department of oncology at the Stanford Cancer Institute. He works in rare gastrointestinal stromal and neuroendocrine tumors. Like Verstovsek, he was once faced with patients for whom no standard therapy was available.

“For really good science, there is almost always R01 grants, but the problem with these rare diseases is we don’t have good tumor models, so we don’t have tools to develop the good science. . . . With a lack of good laboratory models, most of the funding is going toward trying to develop models and not capitalizing on the models that we have.”

Fisher also turned to private foundations for support. “In the past 3–4 years, we’ve been successful in getting some national and international trials completed, which have actually been positive, and a positive trial always gets other [drug companies] interested in competing,” he said.

Other researchers, such as David G. Kirsch, M.D., Ph.D., an associate professor of radiation oncology at Duke University School of Medicine in Durham, N.C., are working on multiple research projects, which can open up their funding opportunities. Kirsch’s research focuses on soft-tissue sarcomas, as well as the biology of radiotherapy. “One thing I’ve done is to have a diverse portfolio of interests,” he said “So, I can get funding for my lab both for the sarcoma work and for radiation biology work.”

It also helps that he is now working on a hot topic: developing an animal model of disease. He obtained an R01 grant for research into developing a genetically-engineered mouse model of sarcoma metastasis. He also received an innovation award from the Damon Runyon Cancer Research Foundation to develop intraoperative molecular imaging technology in genetically engineered soft tissue obtained from a mouse model. “The technology for the foundation award is not necessarily sarcoma-specific, but we happened to be studying sarcoma,” he said. On that basis, he received a grant from the American Society of Clinical Oncology to translate that research into a phase I trial.

Federal Funding

In the past few decades, the federal government has stepped up efforts to support research into rare diseases. For that, thank the National Organization for Rare Disorders (NORD). Influence of public policy is NORD’s primary role, said Chief Medical Officer Timothy Coté, M.D., M.P.H. NORD also offers seed money to fund preliminary research in the hope it will act as a springboard to funding from other sources.

The U.S. Food and Drug Administration promotes research into rare diseases via its Office of Orphan Products Development (OOPD). Debra Lewis, O.D., M.B.A., is OOPD’s acting director. She said their biggest incentives are special designations for orphan drugs and devices, offering financial incentives that include tax credits, waivers from users’ fees, and marketing exclusivity.

But OOPD also set aside about $14 million annually to fund human clinical research into rare diseases. OOPD evaluates applications on technical merit. “Study design is very important to the FDA,” said Lewis. Evaluation involves input from an ad hoc peer review team as well as the FDA’s own review division. “The availability of that regulatory input can be valuable” for heading off any potential barriers to approval early on, she said. “Sometimes collaborations with investors come together well because they see that FDA is interested in investing in this and sees the technical merit.” This past year, their approval rate of applications has been as high as 15%–20%.
NIH is also on board via its Office of Rare Diseases Research (ORDR), headed by director Stephen C. Groft, Pharm. D. With an annual budget of about $18 million, ORDR grants are about $1.25 million per year for 5 years. According to Groft, ORDR encourages a broad range of research and activities that include multiple site and multiple disease trials; training of new investigators; involvement of patient advocacy; and the potential for collaboration among several NIH institutes, private foundations, and industry.

NIH works through its institutes to administer grants, with most rare tumor research falling under the auspices of the National Cancer Institute. Betsy Read-Connole, Ph.D., is program director of the Cancer Etiology Branch in the Division of Cancer Biology at the NCI, as well as its representative to the Trans-NIH Committee for Rare Diseases Research. Unsolicited grants, she explained, are peer reviewed, scored, and then ranked based on this score. Those with the highest rankings win funding.

“The main thing we look for is, do we think it’s an important question and do we think it’s feasible?” she said. “The importance [of the research] can sometimes be based on the investigator. Do they have the expertise to show on paper that they can actually undertake this study? Have they done similar studies?” Research that is novel or “out there” may be faced with skepticism about its feasibility, even if it sounds good on paper.

10 Tips for Getting Grants to Study Rare Malignancies

Trying to fund rare cancer research? Here is some advice from the experts:

1. Never wait for patients or funding sources to come to you. Be aggressive in pursuing patient groups, foundations, and industry. Find the funding sources that most closely match your research.
2. If you have multiple related research interests, use funding for one project to help boost work in another.
3. Engage activity with your patients, patient advocacy groups, and private foundations. Offer to give talks, sit on advisory boards, or just be available for advice.
4. Network with colleagues working in the same area or with other rare diseases. Develop strategic partnerships.
5. Take advantage of available resources, such as newsletters and websites. If these are lacking, develop them yourself.
6. Develop an animal or laboratory model of the disease you are studying if one is not available. Or work on developing a tissue bank, which will usually require collaboration with other centers.
7. If you work at a high-profile center, use its reputation to your advantage. Make sure others are aware of your prestigious affiliations.
8. Try to develop a center of excellence in your field.
9. Contact the federal agencies you wish to apply to early on. The OOPD can give you tips on study design, and ORDR can put you in touch with a program director who will help walk you through the grant application process.
10. Don’t forget the personal touch. “I personally always call back the referring doctor when I have a new patient,” said Verstovsek.