Amy Moore argues that people with lung cancer have a stronger voice when they act together.

GO2 FOUNDATION FOR LUNG CANCER

Drivers of change

Oncogene-specific advocacy groups are bringing a patient-centric perspective to studies of lung cancer.

By Elie Dolgin

Justin Gainor wanted to study rare forms of lung cancer caused by particular genetic alterations. But time and again, after submitting grant applications, he would get the same response from funding organizations. "The reviewers would say: 'It's a relatively niche patient population'," says Gainor, a lung cancer specialist at Massachusetts General Hospital in Boston. "And what commonly followed were questions about whether the research was feasible or generalizable because the cancers were so rare."

Research funding for lung cancer in general is hard to come by. In the United States, the disease accounts for roughly 13% of all new cancer diagnoses and 22% of cancer deaths, but only 7% of the US National Cancer Institute budget goes to lung cancer research. Similar discrepancies exist in the United Kingdom and China.

Even this figure only scratches the surface of the funding problem. Lung cancer is not a single disease but rather a collection of subtypes, each with its own molecular characteristics and mutations, and what little funding is available is not evenly distributed between them. The rarer subtypes that interest Gainor — numerous malignancies that each account for 1–2% of people with lung cancer — often receive no public research support at all.

Over the past five years, that has started to change — and patients have been the catalysts. People with lung cancer who share particular rare molecular abnormalities, such as mutations affecting the *ROS1* or *ALK* genes, have banded together to create online communities with names such as ROS1ders and ALK Positive. These oncogene-specific groups initially provided support and education to people with these particular lung cancers, but many now fund research with the goal of kick-starting the development of new life-saving medicines.

The stimulus for these patient groups to act was the availability of therapies targeted at specific genetic mutations. Each drug blocks the cancer-promoting functions of a particular oncogene (see page S10). The first such drugs to reach the market for lung cancer attacked mutated forms of the EGFR receptor. Then came drugs directed against the ALK and ROS1 pathways. The past few years have also seen the approval of therapies targeting abnormal versions of RET, MET and NTRK.

Oncogene-specific advocacy played little part in the arrival of those first-generation therapies. Doctors recognized the clinical need, drugmakers saw a market opportunity, and the emerging science of cancer genetics made it ripe for advances in precision medicine. Yet with each new drug class came a new group of patients, many living longer and with more vitality. Previously, the outlook for lung cancer was so dismal that few patients had the time or strength to enter the advocacy arena, but now many survivors are beginning to fight for the next generation of therapies, both for others and for themselves.

Many patients were experiencing the debilitating side effects of their drugs and wanted agents that offered a better quality of life. They also knew that their cancers would invariably develop resistance to the drugs, so they would need additional options down the line. And because the latest immune therapies offered little benefit for most people with driver-mutated disease, "there's really a need here for what comes next", says Ivy Elkins, one of the founding members of the EGFR Resisters.

More altruistically, Elkins and others wanted to make targeted therapies accessible to more patients, many of whom have metastatic lesions in the brain and cannot benefit from drugs that do not cross the blood–brain barrier (see page S14). But increased patient involvement brought friction, sometimes between different oncogene-specific groups and sometimes between advocates and researchers. Even so, most scientists, clinicians and industry partners welcome the push towards patient-centred research funding for rare oncogene-driven cancers, along with the critical patient perspectives that it brings.

"It's a good thing that we're seeing more of these groups arise," says Amy Moore, director of science and research at the GO2 Foundation for Lung Cancer, a non-profit body in Washington DC that partners with several oncogene-specific groups. "We need all hands on deck."

Making a difference

The ticking time bomb of drug resistance was a major motivator for Laura Greco to push clinicians and scientists to focus on her particular type of lung cancer. "I want to maximize the time I have on this Earth, and I want to maximize the odds of me and everyone else living," says Greco, whose own lung cancer contains both an ALK fusion and a MET amplification. In 2018, she spearheaded ALK Positive's first research grant and has since co-founded two other groups, ALKFusion and MET Crusaders.

These organizations do more than bankroll projects. Some groups have conducted patient outcome surveys. Others have procured tissue

samples to create patient-derived research tools. With each initiative, "they provide a direct-to-researcher sense of urgency", says Trever Bivona, a lung cancer specialist at the University of California, San Francisco.

Patient advocates often want immediate results but this can be at odds with the slow pace of scientific investigation. Yet clinicians and scientists who have collaborated with advocacy groups say they are an invaluable addition to the research ecosystem. "They're engaged in the research in a way that I haven't otherwise often experienced," says Christine Bestvina, a thoracic oncologist at the University of Chicago Medical Center in Illinois.

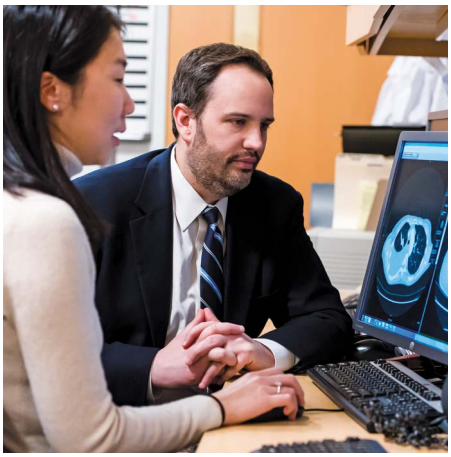
"I do not have a scientific background whatsoever, but when you get diagnosed with a disease like lung cancer, you get highly motivated," says Elkins. She and her fellow EGFR Resisters now routinely attend scientific conferences in the field. Seeing a dearth of EGFR-focused presentations, earlier this year they launched a programme in which patient advocates work with scientists and clinicians to award two-year, US$200,000 grants. Winners of the inaugural EGFR Resisters research award will be announced in January 2021.

Before deciding to fund external research, Elkins and other organizers of her group realized they needed to better understand the medical needs and treatment experiences of their community. So in 2018, they created a 130-question survey and, helped by Upal Basu Roy, vice-president of research at the LUNGevity Foundation in Chicago, they gained institutional review board (IRB) approval to gather data from hundreds of patients worldwide.

They found that nearly two-thirds of people taking EGFR inhibitors were hospitalized during their treatment, typically for side effects or symptoms related to the cancer. Many were also diagnosed with clinical depression, often accompanied by suicidal thoughts. These findings had not previously been reported in the scientific literature. Basu Roy applauds members of EGFR Resisters for crafting a "very powerful survey tool that really captures that patient's unique data", and he expects it to result in better disease and drug management.

Ups and downs

Not all advocacy efforts have gone smoothly. In 2016, members of ROS1ders teamed up with Manali Patel, an oncologist at Stanford University School of Medicine in California, and a precursor to the GO2 Foundation to run a similar survey for people with ROS1-altered tumours. Like Basu Roy, Patel credits the patient advocates with steering the project and devising survey questions that reflect knowledge gaps relevant to their community.



MASSACHUSETTS GENERAL CANCER CENTER

Justin Gainor (right) says it can be hard to get funding to study rare forms of lung cancer.

But over time, the objective became blurred and the various stakeholders had different expectations, particularly over issues of data access tied to IRB regulations. Patel eventually published the results in a 2019 paper[1] co-authored with several ROS1ders members. The study showed that delays in genetic testing often lead patients to receive chemotherapy before they can get more-effective ROS1-targeted agents. But the ROS1ders website makes no mention of the paper because "the project does not represent the transparency, collaboration or data sharing we'd hoped to achieve," says ROS1ders co-founder Janet Freeman-Daily.

By contrast, the group touts the success of its ROS1 Cancer Model Project, through which individuals can donate tumour tissue to help create new cell lines and mouse models. "It's hard to research a disease if you don't have a model to test it against," says Freeman-Daily. Now, thanks to the project's cell lines, researchers have probed mechanisms of resistance to ROS1-targeted therapies[2] and explored how different gene rearrangements modify the aggressiveness of ROS1-mutated tumours[3].

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The need for fresh specimens meant that only patients in North America were eligible to participate in the initial phase of the project. But Merel Hennink, a ROS1ders member living in the Netherlands, expanded access to Europeans. She established a non-profit organization (Merel's World), raised funds and teamed up with local academics to facilitate sample collection and cell-line derivation.

In Australia, patients can contribute tissue to a new national biorepository called Aurora focused on ROS1-mutated lung tumours, and there are plans to expand to other targetable mutations in the future. Lillian Leigh, a ROS1ders member living in Sydney, worked with her oncologist, Ben Solomon of the Peter MacCallum Cancer Centre in Melbourne, to design the biorepository and to secure seed funding to start tissue collection at ten hospitals across the country. "I don't have any doubt that her involvement helped us get the funding," Solomon says of Leigh, "but more importantly, I think it's shaping the project."

Stronger together

The growing number of people involved in oncogene-focused advocacy has led to internal divisions. In 2019, for example, Greco and six other members of ALK Positive started their own spin-off group called ALKFusion to focus solely on research-related activities.

One might imagine that such sectarianism would impede the goal of advancing research into lung cancer. But Rachel Kahn Best, a sociologist at the University of Michigan in Ann Arbor, says those fears are largely unfounded. "People have repeatedly raised the concern that dividing activism into specific disease categories was counterproductive, limiting overall fundraising," says Best, who has studied why some diseases attract more funding support than others. "But disease-specific activism has consistently been much more effective in inspiring donations and volunteerism."

Oncogene-dedicated patient groups can be highly collaborative, says Moore. For example, several are now joining forces to study the problem of histological transformation, in which tumours undergo changes in cell type that render them unresponsive to targeted agents, regardless of their mutational underpinnings. The groups come together under the umbrella of other organizations, such as the Lung Cancer Action Network, to lobby policymakers in their push for increased federal funding. And they have united with the GO2 Foundation, LUNGevity and others to provide updates on issues surrounding the COVID-19 pandemic that are relevant to the lung cancer community.

"There are times when it makes sense to divide and conquer," says Moore. "And there are times when it makes sense to come together."

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1. Parikh, D. A. *et al. JCO Oncol. Pract.* **16**, e183–e189 (2019).
2. McCoach, C. E. *et al. Clin. Cancer Res.* **24**, 3334–3347 (2018).
3. Neel, D. S. *et al. Cancer Res.* **79**, 546–556 (2019).