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The importance of being generous

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What have been the defining moments in your career so far?

LC: What got me started was recognizing that inflammation was present in premalignant lesions when I was a postdoc in Doug Hanahan's lab. We had started looking at benign hyperplasias and dysplasias in transgenic mouse models, which at the time were very new tools that provided our first glimpses of premalignant biology, something that wasn't possible when cancer research was restricted to tumor cell lines. Recognizing that in addition to the effects of activated oncogenes within epithelial cells, there was a dramatic response involving fibroblasts, matrix remodeling enzymes and a remarkable presence of immune cells blew me away. I had not ever been trained in immunology, and Doug, at the time, had not ever investigated inflammation in his own science, so a defining moment for me was how supportive he was when I explained that I wanted to study this phenomenon, and to also reach out to collaborators for help. One of these collaborators was Zena Werb, who not only was willing to provide guidance even though I was not in her lab, but became as much of a mentoring PI to me as Doug was. Another defining experience was that on one hand, Zena didn't have to offer her time and wisdom to me and yet she did; and on the other hand, Doug wasn't threatened by her but rather welcomed her insight. At her memorial after her death a few years ago, he acknowledged that her science made him a better scientist. The generosity of both of them completely transformed the way I approach mentoring: it caused me to be very generous with my own time and kind with people who need my help. I believe this has made me a better PI.

What has been the biggest change you've experienced in how we study, understand and treat cancer during your career?

LC: It has to be the remarkable recognition that the immune system plays a role in cancer and is an equal partner to the somatic mutations regulating critical signaling pathways in neoplastic cells. When I first started, there was no tumor immunology field per se, aside from research involving T cells. Mainstream cancer researchers were still deeply immersed in the idea that oncogenes and tumor suppressor genes controlled all aspects of cancer. Our research bucked that dogma. The *Cell* paper in which we knocked out a matrix remodeling protease that was expressed only by immune cells and significantly impacted neoplastic progression, and then demonstrated that its reconstitution through bone marrow transfer recovered the tumor phenotype in vivo, still serves as a paradigm that it is not only the neoplastic cells that are important, but myeloid cells also play key roles. That research led us to study inflammation in general and then to recognize that myeloid-inflamed microenvironments not only drive numerous pro-tumorigenic biologies, but also suppress anti-tumor activities of T cells, as we published in a *Cancer Discovery* paper that remains highly cited to this day. So, from a career point of view, embracing the immunobiology of solid tumor development has been very important.

More generally for the cancer field, I believe that in very short order, there will not be a patient who isn't treated with a combination of a cytotoxic or targeted agent, and some sort of immune-modulating therapy, likely approaches that neutralize pro-tumor myeloid aspects, in concert with those that drive T cell anti-tumor activity. We just have to learn how to combine and deliver these treatments to patients in the safest and most efficacious sequence, and learn how to monitor therapeutic response and resistance, because there will always be resistance. Recognizing this early and moving the patient to the next appropriate therapy before their tumors become completely resistant is an important component of modern clinical decision-making.

What are your goals for the future and your major aims as President of the AACR for 2022–2023?

LC: My goal is to continue to pay it forward. Much of my time used to be devoted to my own lab, but now I also run a department and help to oversee the basic science portfolio of the cancer center. Both involve mentoring many junior faculty and providing support to programs that assist their mentees. This year as President of the AACR my responsibilities have increased. Thus, I am more absent from my own lab than I used to be, but my lab members and all those people that I help have been very generous in supporting me in all the other things that I do. I am very appreciative of that and it has been a great reminder that being generous is very important.

As President of the AACR, I've staked out two major goals. One is to utilize the bullhorn I have to improve funding of the research pipeline, recognizing that some of the mass exodus out of the workforce that we're witnessing is driven by finances. Even though the National Institutes of Health (NIH) budget has doubled, the amount of funding to labs has not, and it's the early-career workers that need more support. For example, initiatives to expand the funding portfolio for undergraduate STEM trainees, graduate students, postdoctoral

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fellowships internationally, and for junior faculty whose labs have been hit the hardest by the effects of the COVID-19 pandemic are a high priority. During lockdowns, early-career investigators still had to pay salaries without a return on investment with regard to productivity. The worry is that they're going to run out of startup funding before they have completed and published some of the big research projects that they would need to garner major funding. Just last week at an industry roundtable with the major supporters of the AACR, we made a big pitch for increasing the funding to these sorts of programs, and fortunately, our industry sponsors were very supportive and requested proposals — so that will be the next step.

A big issue related to success in bolstering the workforce is paying attention to the diversity aspect of the workforce. It's become easier to balance gender, but it is still remarkably difficult to balance the representation from underserved communities, people of color and multidisciplinary expertise within the workforce. In recent conversations with Dr. Sanya Springfield, Director of the National Cancer Institute (NCI)'s Center to Reduce Cancer Health Disparities, who conceived and implemented the Continuing Umbrella of Research Experiences (CURE) program, I've asked for her help. I think she's going to be a mentor for me, as I have a lot to learn about how to help add diversity to the existing pipeline of workers and how to build a new, improved and stronger pipeline.

My other major agenda item involves helping to address the problem of storage, management and sharing of the big data sets that many academic labs are generating, most specifically data sets from multiplex tissue imaging. These are difficult to share and cannot be stored perpetually in individual institutions, but they are huge resources for the community. Helping colleagues close Zena's lab after her death articulated this point, especially with regard to what happens to our data once we're gone. It's ridiculous to think that all of our imaging or sequencing data sets would simply be lost upon my death and lab closure; thus, I became much more motivated to work with others and the NCI to help with common sense solutions to enable long-term data storage and sharing for the community.

With regard to large multiplex imaging data sets like those that my lab has been generating, the NIH now mandates that we share these, but at present, that is near impossible. The data sets live on private or institutional servers, behind firewalls, making it difficult to even share them with collaborators. The only way to achieve sharing openly is to put them in a common place, but that resource doesn't exist yet, and there are no community-wide standards or quality control for what would need to be uploaded. The first Cancer Moonshot led to the formation of the Human Tumor Atlas Network (HTAN), and one of the major goals of the HTAN and many of the Moonshot's grants was to think about standards needed to harmonize data sets. We've been working with the HTAN and have had a few publications with Peter Sorger's group focused on harmonizing analytics, quality control and so on. We're now also discussing with Monica Bertagnoli, the new Director of the NCI, and others at the NCI how best to utilize the NIH's cancer data commons sites as depositories to achieve openly available, harmonized data sets, much like The Cancer Genome Atlas (TCGA). Building TCGA was hard, but now it's a mainstay of cancer research across the world. The hope is that we can learn from TCGA about how to create a platform with general agreement on quality control that makes it possible for these data sets to be shared and to be mined. Once there is a place to put them, meeting funders' and publisher's data sharing mandates will be less difficult.

You mentioned that gender balance in the workforce has improved, but in other ways we're not there yet. What should we do to improve diversity, equity and inclusion in the cancer research workplace?

LC: We're absolutely not there yet. We need to improve representation from communities of color, people who are first in their families to go to higher education and those from impoverished or under-served communities. Improving funding and access to these groups is critical — keeping kids interested in science from junior high and high school is key, but they're only going to stay interested in science if they have access to interesting programs, have role models and see career prospects that are intriguing to them. If kids have no experience of how fun science can be, or don't have role models or mentors, they're unlikely to pursue science or biomedical research as a career. This is especially true in economically disadvantaged communities in the USA, where funding of science education in public schools has been reduced. My hope is that with the AACR and industry partners, we can improve funding for summer undergraduate programs and funding allowances to high school teachers, so that a modern curriculum can be expanded in high schools that have faced budget cuts. These types of efforts can help schools keep science programs current and build appropriate curricula to keep their students excited about science and provide them with mentoring and role models, so that they can appreciate the value of going to college, studying science, and how a career in biomedical research could positively impact their entire family. I can't see better ways to make a difference, but we have to reach kids early, because if we only focus on the pipeline at the graduate student or undergraduate level for summer internships, it might be too late.

What were the negatives and the positives for cancer research in 2022, and what are your big hopes for 2023?

LC: The biggest negative was the impact of the COVID-19 pandemic. Many patients with cancer failed to seek care early, and as a result, clinicians are seeing a higher proportion of late-stage disease that will likely result in an increase in cancer deaths, as documented in the AACR Report On The Impact Of COVID-19 On Cancer Research And Patient Care that was published in early 2022.

A second negative was the lost productivity from labs across the world during lockdowns, and the fact that funding portfolios were diminished without accelerating new research. As a result, I think we're going to lose a major component of the younger generation who may have become disillusioned during the tough years of the pandemic.

Among the positives were the Food and Drug Administration (FDA) approval of another checkpoint inhibitor against LAG-3, and the many myeloid-targeted agents moving through clinical trials, which is simply remarkable. I don't anticipate that these will be efficacious as monotherapy; my hope is that clinical researchers and biopharma will pay attention to the preclinical biology and recognize that efficacy is likely to be best achieved when these agents are judiciously combined and appropriately sequenced with cytotoxic therapies alongside drivers of T cell activity. My hope is that in 2023 we'll see some clinical successes with myeloid-based therapies, and they will move to larger phase III trials to start demonstrating clinical benefit.

Given these setbacks and advances and thinking of President Biden's call to "end cancer as we know it" when he relaunched the Cancer Moonshot earlier this year, what do you think are the biggest opportunities for progress and the biggest challenges that we need to overcome?

LC: There are many issues remaining to be addressed if we are to eradicate cancer and death from cancer. The biggest opportunity I see right now is ensuring that state-of-the-art medicine and clinical trials reach the entire population and not just white and privileged groups, because right now our efforts are missing most patients. Outreach into diverse communities is essential, especially underserved communities, such as communities of color, rural communities or those that are underrepresented because of political or economic factors. We have the most to gain, and we have the possibility of making the most substantial improvements if we can deliver standard-of-care medicine, and clinical trials into communities that have limited or no access.

Fostering trust in science is also very important. Unfortunately, there's a huge lack of trust in medicine and science outside of privileged white communities. Doing a better job with outreach and access to information and care will be a major step toward improving cancer outcomes and health equity.

Cancer research has become very interdisciplinary. What are your thoughts about the increased complexity this brings to the continuum of fundamental, translational and clinical research?

LC: I think the biggest disservice anyone moving into cancer science can do to themselves, whether that be wet or dry laboratory work or clinical research, is to not learn multiple scientific languages. Gone are the days when we worked as solo scientists. No one lab can afford all of the technologies that are needed to address the complexities of cancer, and completing studies for publication increasingly requires sophisticated technologies that are becoming standard, even though they're still expensive. However, not all cancer centers and institutions provide supportive services for the computational biology and data science needed to decipher data resulting from these new technologies. As a result, the whole notion of collaborative team science has never been more important, and with that comes the need to be able to communicate with people who speak an entirely different scientific language than you do.

I think scientists, especially from the younger generations, need to embrace not only the biology, but also new technologies that help to decipher the complexities of disease, while also learning the fundamentals of big data methodologies and analyses. If they understand multiple scientific languages and know best practices, they will be able to delve deeper and troubleshoot when needed. Having some understanding of different scientific languages is also very important for PIs from older generations, who may rely more on collaborating with experts they trust, as they need to be able to communicate with their collaborators on a scientific level, and mentor their lab members as they engage in such methodologies.

Continuing on this topic, how can we improve integration of the different disciplines to better support investigators and increase clinical translation of basic findings?

LC: One of the things I've learned by having collaborations with data scientists and also putting the postdocs and students in my laboratory through relevant courses is that these data sets are so rich and deep that you can get a bit lost in data analysis. The important thing is to remember your initial hypothesis and utilize the data to figure out whether your hypothesis is accurate or not. The same is true with translational and clinical work: thinking about a biological hypothesis means that the clinical trial is set up not just to assess efficacy, but to address a hypothesis so that we can learn about the underlying biology, make a course correction if we need to or add another therapy as the biology indicates.

What advice would you give those young people who are considering a career in academia?

LC: I think young students should have diversity in education and should try not to be too myopic in their course load. Balancing medicine or life sciences disciplines with an area relevant to data science — for example, combining biology or chemistry and computer science, or biology in physics and mathematics — will be increasingly important as these areas become more integrated.

Given the current realities of the job market and the availability of funding, what advice would you offer young researchers considering their career options in academia and industry?

LC: There are opportunities in both sectors, because of a general trend of fewer people entering the science workforce. I think one has to weigh the pros and cons of both. For example, I never wanted to be told what to study, so academia was the only option for me, even though reviewers of grants do shape how you think to some degree. In biopharma, scientists still think independently, but have to be willing to pivot more quickly from one research area to another, because marketing decisions drive the company's portfolio. From my perspective, those are the major differences, because the two sides are quite similar on the practical side of conducting research: proposals still have to be written, budgets still have to be provided and a research program still has to be justified.

To young investigators in academia, at least here in the USA, I would stress the importance of aligning themselves with a professional society in which they can participate and contribute. It is an investment in their careers, and I think disseminating this message to the younger generation is very important. This is what Zena taught me early in my career and that's how I eventually found my place in the AACR community. Belonging to a community is crucial, so that you can have the support you need, from knowing who you can turn to with a difficult question, to how to get help when you are in a hard spot. Societies can also help with funding and career development, and with furthering research ideas and collaborations through their working groups. Moreover, service to a society through reviewing grants or going through abstracts for a meeting can improve communication and writing skills. This goes back to learning to speak multiple languages: learning how to explain to the layperson why your research matters, and how it could impact them, is essential. Even more so nowadays when diversifying your funding portfolio beyond the major government grants is critical for success, and philanthropy from private sources provides a lot of support for research.

As a final thought, how can we better support and mentor the new generation of cancer researchers?

LC: I think it's important to be real with our mentees. We shouldn't shield them too much from the bad or the good things, but we should remember that words matter and should temper our messaging in an appropriate way. If you only complain to your students about how hard this job is, why would they want to follow such a career? I also come back to the concept of generosity. If with the support of others you were able to move up the career ladder, you have a responsibility to also help those who are following you, so that they also achieve their dreams.

Interviewed by Alexia-Ileana Zaromytidou

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