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Dr Anthony Letai reflects on how a career spanning cancer biology, clinical oncology, and translational research is shaping his early priorities as Director of the National Cancer Institute. The conversation examines how NCI is navigating a shifting global research landscape while accelerating innovation, strengthening evidence-based decision-making, and reinforcing confidence across the cancer ecosystem. At its core, the interview offers a clear view of how scientific rigour, long-term investment, and patient impact remain central to NCI's mission.

What shaped your scientific career, and how is that background informing your approach as Director of the National Cancer Institute?

I spent more than two decades at Dana-Farber Cancer Institute and Harvard Medical School, practising as a medical oncologist with a clinical focus on blood cancers while leading a cancer biology laboratory. Our work centred on programmed cell death, particularly apoptosis, and on understanding how cancer cells evade this process through proteins such as BCL-2. That research helped serve as the basis for the development and clinical translation of venetoclax, a first-in-class BCL-2 inhibitor, which first received accelerated approval from the FDA in 2016 for relapsed or refractory chronic lymphocytic leukaemia, and later expanded into acute myeloid leukaemia through combination regimens.

Alongside that work, we developed sustained interests in precision oncology and immuno-oncology. In immunotherapy, our focus was not only on how immune cells recognise tumours, but on what determines whether that recognition actually leads to tumour cell death. The biology of the target cell, particularly its programmed cell death pathways, turns out to be just as important as the immune cell itself, and that insight has shaped how I think about cancer biology and therapeutic development more broadly.

Coming to my role as Director of the NCI, I was sworn in as on 29 September 2025. 48 hours later, the federal government entered a shutdown that lasted roughly six weeks and disrupted operations across the National Institutes of Health (NIH). That inevitably fragmented the early phase of my tenure, and the subsequent holiday period made it harder to build immediate operational momentum. We are now past that phase, and the Institute is fully back up to speed. From a leadership perspective, a central part of my approach is recognising the scale and complexity of the organisation and how much there is to learn. While the NCI is large, most of its impact comes through its extramural programme, which is the work that NCI funds at research labs across the country. I want to bring my experience as an extramural investigator, as well as a scientist and clinician, to make it as straightforward as possible for the best science to be funded. At the same time, I am focused on understanding the administrative structure and ensuring that taxpayer dollars are used effectively across both intramural research that takes place on the NIH campus and extramural research.

One of the most difficult issues is how we assess the quality and impact of research funding. It is challenging even in hindsight to determine which grants were most productive, and the harder task is identifying, prospectively, the characteristics that are most likely to define an excellent grant over time. That challenge is intellectually demanding, but it is also what makes the role engaging. The job is very different from what I did before, and that constant variety is a large part of what makes it stimulating.

As you step into the role at a time of renewed federal focus on cancer and chronic diseases, what priorities are guiding the NCI's agenda today?

It is still early in my tenure, but one area where I see an immediate opportunity for improvement is communication. There is a persistent gap between how cancer research actually works and how it is perceived outside the field. Almost every major cancer therapy or diagnostic that ultimately reaches patients can be traced back, often ten to twenty years earlier, to foundational research supported by NCI grants. Ideas originate in the laboratory, receive public funding, mature scientifically, and are then taken forward by biotech or pharmaceutical companies before receiving approval from the FDA. By the time a treatment reaches the clinic, that long chain of public investment is largely invisible.

We have a responsibility to make that pathway clearer. Taxpayers should be able to see how their investment in cancer research translates, over time, into real benefits for patients. That means being more proactive and more accessible in how we explain our role in the innovation ecosystem, and in how we connect today's therapies to the publicly funded science that made them possible. Alongside this, we need to engage more directly with the questions people have about cancer treatments. Many patients and families understand, at least in broad terms, how research leads to regulatory approval, but they are also exposed to claims that fall outside established oncology or FDA-approved pathways. In most cases, there are straightforward reasons why certain approaches are prioritised and others are not. Not everything can be a top priority, and when we focus resources on specific areas, it is because there is evidence to support that choice. The scientific method itself is not mysterious. We start with a question, develop a hypothesis, and test it. If a therapy does not

demonstrate consistent benefit, it is deprioritised unless new data emerge.

As clinicians and as an institution, we cannot rely on anecdotes, even when individual stories are compelling. A response in a single patient does not automatically translate into a treatment that works reliably for others. Our responsibility is to understand who is likely to benefit, who is not, and why, and that requires controlled clinical trials and predictive approaches. This logic is second nature to people working in cancer research, but it is not always obvious outside the field. Helping to bridge that gap, and to explain why evidence matters when it comes to treatment decisions, is an important part of how we set priorities and engage with the public.

How do you approach setting scientific priorities at an institution as large and diverse as NCI, while preserving the creativity of the broader research community?

We need to be careful about how tightly we define scientific priorities. One of the core strengths of the US cancer research ecosystem is the breadth of highly trained investigators pursuing their own ideas, and it would be a mistake to constrain that creativity with an overly rigid framework. At the institutional level, NCI has a responsibility to look across the landscape and identify areas that appear particularly promising, recognising that support does not always take the form of conventional research grants.

Immunotherapy is a clear example. Early in my career, immune-based approaches produced occasional and poorly understood responses, often with very low success rates. A small group of investigators persisted for decades, and that work ultimately led to checkpoint inhibitors and cellular therapies such as CD19-directed chimeric antigen receptor T cells, with important foundational contributions from the NCI intramural programme. That history makes it clear that immunotherapy needs to remain a central focus.

Where NCI can add particular value is not only through funding, but by helping to address structural bottlenecks. The human immune system is extraordinarily complex, and while *ex vivo* systems and animal models have traditionally been essential, they cannot fully capture how immunity behaves in patients. Many hypotheses only reveal their strengths or limitations when tested in humans. For that reason, a key priority is accelerating first-in-human studies so that promising ideas can succeed or fail more quickly. This means understanding where the barriers lie and identifying how NCI can help reduce them, whether through facilitating interactions with regulatory bodies, supporting good manufacturing practice capabilities, or providing shared technical expertise.

There is also an opportunity to strengthen common infrastructure. One area we are actively exploring is the development of more centralised biomarker capabilities within NCI, including at the Frederick National Laboratory for Cancer Research which the federal health agencies utilize for high risk-high reward research. Greater centralisation could help standardise assays, reduce duplication, and support earlier and more consistent biomarker evaluation in clinical studies. Decisions of this kind should be guided by expert input, so an important part of my role is convening investigators from both the extramural and intramural communities to advise on where NCI can be most effective.

Within immuno-oncology, there is renewed momentum around areas such as cancer vaccines, particularly personalised and therapeutic approaches, although these represent only one component of a much broader cellular immunotherapy landscape. Beyond vaccines, there is active work focused on improving CAR-T cell therapies, including durability, expansion, targeting strategies, and combination approaches, as well as growing interest in other immune cell types such as natural killer cells and myeloid cells.

Ultimately, the challenge is deciding where to place our bets. Resources are finite, and the goal is not to pursue every idea, but to focus on those with the greatest potential to address unmet needs, especially in solid tumours where progress has been most difficult. We see intriguing signals across immunotherapy, and our task over the coming years is to understand what drives those successes, test hypotheses rigorously, and create the conditions for the most promising approaches to move forward.

How does NCI work across the cancer ecosystem to ensure that innovation moves beyond major academic centres and reaches patients in community settings?

Collaboration with industry has long been integral to how we operate. The National Cancer Institute has an established track record of working with biotech and pharmaceutical partners, including through the Small Business Innovation Research programme, which provides non-dilutive federal funding to early-stage companies to help translate academic discoveries into viable cancer technologies. While SBIR periodically requires congressional reauthorisation, it has consistently remained a core mechanism for early innovation. More broadly, there is a practical reality that promising scientific ideas ultimately need to become products that can be manufactured, approved, and delivered to patients, and there are few viable pathways to achieve that without industry involvement.

As initiatives mature and grow in scale, industry engagement becomes even more important, not only for scientific input but also for financial participation. In many cases, we are helping to de-risk early development and move programmes closer to the clinic, and it is reasonable to expect industry to contribute as that process advances. One structure that has been particularly effective in facilitating these collaborations is the Foundation for the NIH, which was established by Congress to support public-private partnerships bringing together NIH, industry, academia, and, where appropriate, regulatory agencies such as the FDA. In parallel, licensing NCI-developed technologies remains another important route through which publicly funded research is translated into patient care.

Equally important is ensuring that innovation does not remain confined to a small number of academic centres. While many advances originate in comprehensive cancer centres, most patients receive care at their local hospital or in other community settings. From the outset, we need to think not only about how to develop the next effective therapy, but about how to make it accessible across the country. Some approaches will inevitably begin in specialised centres, particularly in early-stage testing, but once there is a clear signal of benefit, broader dissemination must follow.

Programmes such as the NCI Community Oncology Research Program are central to this effort. By extending clinical trials into community oncology practices and smaller hospitals, NCORP allows patients to participate in research closer to home and helps ensure that new advances are evaluated and adopted beyond academic centres. Equity of access is a core priority, and we place particular emphasis on technologies and approaches that can be delivered realistically across a wide range of clinical settings.

In a global landscape where countries such as China are investing heavily in biomedical research, what will it take for the United States to sustain leadership in cancer science beyond funding alone?

China made a deliberate strategic decision to prioritise biotechnology as part of its long-term national planning and has committed substantial, centralised resources to that goal. Over the past decade, it has advanced rapidly, moving from a limited domestic biotech base, through a strong contract research environment, to a position that now sits between fast follower and genuine innovator. The United States still leads at the cutting edge of innovation, but it would be a mistake to underestimate how close other countries have become.

The issue is not whether multiple nations can contribute meaningful scientific advances, which ultimately benefits patients worldwide, but whether the United States risks relinquishing its traditional leadership role. That leadership matters. If the US ceases to be seen as the place where the most ambitious science is done and where top talent wants to build careers, the consequences would extend beyond biotechnology. There is also a practical concern, as few Americans would be comfortable with a future in which major breakthroughs routinely become available elsewhere before reaching patients in the US.

We have to accept that countries such as China will continue to produce excellent scientists and important discoveries. The objective is not to prevent that, but to ensure that the majority of transformative innovation does not migrate away. From a drug development perspective, this shifts the focus from funding alone to efficiency. Countries like Australia offer useful examples of how to move from scientific concept to early clinical testing more quickly and predictably.

In the United States, translating a cancer idea into a first-in-human study typically involves clearing several essential steps, including IRB review and, for investigational products, an active IND application with the FDA. These safeguards are critical, but they can also introduce delays. While this is not something the National Institutes of Health can solve on its own, much of the process runs through the country's major cancer centres, where the National Cancer Institute does have a role. Our task is to work with cancer centres and other stakeholders to identify and reduce unnecessary friction between discovery and clinical testing, without compromising standards. That means thinking through the entire pathway, from trial initiation to patient accrual and execution. This is a shared challenge across the system, and one where closer coordination between NCI, academic centres, and regulatory partners can make a meaningful difference in sustaining US leadership in cancer research.

What does success in cancer care look like ten years from now, and how do you expect treatment and decision-making to evolve?

At its core, success means fewer people dying from cancer. We have already made substantial progress, with cancer mortality declining by roughly thirty percent over the past two to three decades, a gain driven in large part by prevention, particularly reductions in tobacco use. That remains one of the most significant public health achievements in oncology, and sustaining that momentum is essential, alongside continued advances in treatment.

Looking ahead, immunotherapy is likely to play an increasingly prominent role. We already see clear proof of principle in diseases where patients respond in settings where other options have failed. Those responses may be limited today, but they are real, and they justify continued, rigorous testing. Over the next decade, many of these approaches will be evaluated more systematically. Some will fall away, but others will succeed, and as that happens we will learn how to make them more effective and extend their benefit across a broader range of cancers. Immuno-oncology will be central to that progress.

In parallel, advances across immunotherapy, ADCs, and small molecules will increasingly depend on better predictive biomarkers. These therapies are expensive, and there is a shared interest among patients, clinicians, and health systems in identifying who is most likely to benefit while avoiding ineffective treatment. Precision medicine has delivered important successes through genomic biomarkers, from chronic myeloid leukaemia to EGFR-mutant lung cancer and BRAF-driven melanoma, and those advances have been transformative. However, genomics alone has not met all of its early expectations, and there remains a clear unmet need for better predictors of response.

That is where functional precision medicine becomes increasingly relevant. Rather than relying solely on models or genomic inference, this approach tests therapies directly on living tumour cells from patients using advanced ex vivo systems. These methods are now far more mature than many outside the field realise and can be applied both to drug discovery and to clinical decision-making. Over the next decade, I expect functional biomarkers to play a much larger role, including in immunotherapy, helping to identify vulnerabilities more directly and match treatments to patients more effectively. While challenges remain around reimbursement, logistics, and awareness, these are solvable, and early successes are likely to accelerate broader adoption.

As you look ahead, what legacy would you like to leave at the National Cancer Institute, and what perspective would you share with the global oncology community?

What I hope to leave behind is a strong, confident, and well-functioning cancer research ecosystem, particularly across the extramural programme. Over the past year there has been a great deal of unnecessary anxiety, fuelled by reporting that has often been more alarming than accurate. While some mechanisms and processes evolve, the fundamentals have not changed in any meaningful way. We continue to fund the best science through rigorous peer review, and our commitment to supporting early-career investigators remains firm. That next generation is essential to long-term scientific leadership, and restoring a sense of stability and confidence is an important part of my role.

Within the intramural programme, my ambition is for NCI to be recognised as a true centre of excellence. We have investigators here who have fundamentally changed clinical practice and driven innovation in areas such as cellular immunotherapy, much of which has its roots on this campus. The goal is not to compete broadly with universities, but to choose our areas carefully and be world class where we focus, in ways that are visible both to the scientific community and to patients who may benefit directly from that expertise.

More broadly, I believe oncology is moving through a period of unprecedented momentum. We are able to test ideas faster and more intelligently than ever before, supported by advances in data science and artificial intelligence, while still recognising that careful observation in patients remains irreplaceable. My message to the community is one of continuity and confidence. NCI stands firmly behind researchers and clinicians, with an unchanged commitment to reducing the burden of cancer, and that commitment will guide our work throughout my tenure and well beyond it.

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