**INTERVIEW**

Advancing immunotherapy and data-driven research

Lauren Coyle, Editor, *Immuno-Oncology Insights*, interviews Jill O’Donnell-Tormey, CEO and Director of Scientific Affairs at the Cancer Research Institute, to discuss the latest developments in data-driven technology for the I-O space.

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**Q** What is your role within the Cancer Research Institute?

**JOT:** I am the CEO and Director of Scientific Affairs at the Cancer Research Institute (CRI) where I oversee the entire organization and serve as a spokesperson. We are a nonprofit organization that raises its operating budget each year, and I’m heavily involved in overseeing various fundraising efforts from individuals, foundations, and corporations.

I am also deeply involved in the scientific side of our work and one of the highlights of my role is working closely with our Scientific Advisory Council, which boasts some of the most prominent figures in the field of cancer immunology.

Additionally, I oversee the entire grants process, which involves evaluating applications from individuals and organizations seeking our support and distributing funds to advance cancer research.
How would you describe the current state of the I-O space?

**JOT:** Over the past decade, we’ve seen concrete evidence that the immune system can effectively control and even cure cancer in some cases; however, we also know that immunotherapy is not yet effective in the majority of patients.

One of the key advantages of having clinical evidence that immunotherapy can be successful is that it allows us to ask questions that were previously unasked. One of the most pressing is to understand the mechanisms behind innate or acquired resistance to immunotherapies.

The field experienced a surge of enthusiasm and activity with the introduction of checkpoint inhibitors and CAR-T cells. However, after the initial FDA approvals for various therapies, progress in the field has been somewhat slow. The introduction of anti-CTLA-4 and anti-PD1 checkpoints and, more recently, anti-LAG-3 has been the extent of notable progress.

The initial expectations have been challenged and there is a risk that people and resources will drift away. After seeing the initial rapid approvals in a variety of different cancer types, some people may have naively thought that it was going to be easy to expand that success, but unfortunately that hasn’t proved to be the case.

My hopes lie with understanding that the immune system is a highly intricate and multifaceted system, involving various cell types and molecular interactions. Mechanistic understanding is crucial, and this is where CRI’s focus currently lies.

We are fortunate to have access to patient samples, enabling us to analyze why some patients respond to immunotherapy while others don’t. Further to this, technological advancements, including multi-omics and spatial technologies, provide the means to explore the significance of the tumor microenvironment.

In the past decade, we’ve recognized the importance of the tumor microenvironment, the need for effector T cells, and the complexity of activation and suppression mechanisms. It has become clear that there will not be a one-size-fits-all approach to immunotherapy; instead, it should be personalized. We categorize patients into three broad groups based on their tumor’s characteristics: inflamed, immune-excluded, or devoid of T cells. This framework helps us understand the differences between the groups and develop therapies that can activate a productive immune response in each group.

While monotherapy checkpoints have been remarkably effective in several cancer types, it’s apparent that achieving a productive immune response involves a multi-step process. Removing immune system brakes with checkpoints was a significant breakthrough, but there are other steps that limit the effectiveness of immunotherapy. Our current focus is on identifying and addressing these limitations to enhance the response in various patient groups.

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While progress in the field may not have been as rapid as we initially hoped, I remain hopeful. By delving into the science, understanding the underlying mechanisms, and developing new therapies, we can make immunotherapy more effective for a broader range of patients.

Q Does multi-omics analysis have importance in incorporating deep correlative science into clinical trials?

JOT: I firmly believe that this is the only path toward true understanding and progress. It is no longer a matter of administering treatment and hoping for a response. Thanks to the advancement of multi-omic technologies and the availability of invaluable patient samples, we can now conduct in-depth analyses and start identifying biomarkers that predict treatment responses.

For instance, consider the PRINCE Trial, which we funded for metastatic pancreatic cancer. In this trial, patients were randomly assigned to receive either standard chemotherapy with a PD-1 checkpoint inhibitor, or standard-of-care chemotherapy with a CD-40 agonist immune modulator or standard-of-care chemotherapy with both anti-PD-1 and the CD-40 agonist. Preliminary studies, often murine models, suggested that the four-drug combination would be the most effective. However, when the clinical trial was conducted in patients, it turned out that patients receiving chemotherapy/PD-1 inhibitor combination met primary endpoints and achieved response rates nearly double the historical standards for chemotherapy alone.

Through a deep analysis of correlated data, we were able to identify a blood-based genomic signature at patient baseline prior to treatment. This signature predicted which patients would respond favorably to this specific treatment regimen. This is a good example of what we could expect more of in the future. Rather than a one-size-fits-all approach, we can determine which combination therapy is most likely to work for each patient with a simple blood draw. This personalized approach holds the promise of significantly improving response rates. I firmly believe that the future of medicine lies in the fusion of small-scale trials with multi-omic analysis, guiding the development of treatments tailored to individual patients.

Q How important is basic research in drug development?

JOT: It’s vital to establish a two-way street, where the successes achieved in clinical settings feeds back into deep analysis and correlative research, and insights into what is happening at the molecular level should be relayed back to the laboratory. This dynamic dialogue should involve clinicians, scientists, academics, and biopharma professionals.

Over the past decade, the consensus in the field has solidified: we must grasp the underlying mechanisms. It is no longer a matter of haphazardly combining any drug with a PD-1 inhibitor and expecting it to work. There must be a robust scientific foundation and rationale behind the development and pairing of therapeutic agents.
We are currently at a pivotal time, leveraging the cutting-edge technologies at our disposal to ask questions and conduct analyses that were previously inconceivable. These technologies open up new horizons in mechanistic understanding, which is indispensable in the development of more efficient and effective therapies. This, in turn, will enable us to provide relief to a broader spectrum of patients in a timelier manner.

Q What is the significance of new biomarkers, such as circulating tumor (ct)DNA?

JOT: A report was recently published in *Nature Medicine* detailing a trial that the CRI supported. This trial focused on metastatic non-small cell lung cancer patients who were receiving standard-of-care checkpoint blockade treatment, specifically pembrolizumab. What made this trial unique was the utilization of ctDNA. By taking blood samples and measuring the levels of ctDNA, the goal was to determine if it could provide better insights into a patient’s response to immunotherapy.

Traditionally, the response to treatment has been assessed through radiographic imaging, typically done around the 12-week mark. However, this trial involving approximately 50 patients demonstrated that ctDNA levels in the blood correlated with the results of radiographic analysis and it could identify treatment failure earlier than radiographic imaging. What is more, ctDNA exhibited a stronger correlation with overall survival within the patient population compared to radiographic imaging.

Building on these promising findings, we are now funding the second phase of this study, involving 150 patients, to further explore the impact of this approach. This innovative use of ctDNA is not only exciting but also has the potential to significantly improve the management of non-small cell lung cancer treatment by providing early insights into treatment effectiveness, allowing for more aggressive interventions when necessary. It’s a very promising development in the I-O field.

Q How do programs such as the CRI Immuno-Informatics Fellowship and the Bioinformatics Bootcamp contribute to advancing the I-O space?

JOT: The CRI Immuno-Informatics Fellowship and the Bioinformatics Bootcamp emerged from discussions with our Scientific Advisory Council. In the current era of extensive multi-omic analyses, the volume of data generated from clinical trials and animal laboratory studies is phenomenal. It now requires individuals with backgrounds in data science and bioinformatics who can effectively analyze this wealth of data.

While universities and medical centers possess individuals with these competencies, there has been a growing realization among immunologists that data analysis should not occur in isolation from an understanding of the immune system. There’s a genuine need for individuals trained both as immunologists and data scientists. Recognizing this need, CRI has taken proactive steps, similar to how we funded postdoctoral fellows in immunology many years ago.
We’re now offering Immuno-Informatics Fellowships that enable individuals with a degree in data science to undertake their postdoctoral research in an immunology lab, or vice versa. These dual-trained individuals will play a pivotal role in shaping the future of immunotherapy, as their unique competencies are highly valuable across academia and pharmaceutical labs.

In addition, we conducted a survey among the postdoctoral fellows we currently fund. These young scientists are spread across the globe, and our survey aimed to gauge their interest and competence in data science analysis. The results revealed that around 70% of them were keen on receiving training in this field.

As a response, in spring of 2024, we will be launching the Bioinformatics Bootcamp. This week-long immersion program will bring our fellows together to learn how to analyze various types of data, including whole-exome DNA and RNA sequencing, and single-cell analyses. Our goal is to emphasize the critical integration of data and biology, and we believe that this represents the future of research. It’s a niche that demands attention, and we are eager to meet this need.

We plan to continue offering such programs in the future, and we hope that as time progresses, training in both data science and biology will become a standard part of education. For now, there appears to be a significant demand that we aim to address.

What is CRI’s iAtlas, and how does it facilitate the collection and analysis of immunogenomics data?

JOT: As part of the evolution of our programs towards a more data-focused approach, we’ve invested in what we call the CRI iAtlas over the past seven years. This initiative represents an interactive web platform along with a set of analytical tools designed for studying the interactions between tumors and the immune microenvironment. Importantly, it is open science, meaning it’s accessible to anyone. The tools within the iAtlas enable researchers to explore associations between a wide range of genomic characteristics of the immune response, clinical outcomes, germline genetics, and responses to immunotherapy.

As we have recognized the need to expand our research programs into the realm of data, we are now supporting the integration of single-cell and spatial data alongside whole-exome data. The objective is to be a repository for immunogenomics data, fostering open access for all who wish to explore, compare, and develop hypotheses. While this program is still in the process of development, my vision for it is to become the go-to open immunogenomic repository for the field.

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How can researchers and institutions leverage the iAtlas to advance their own studies and collaborations?

**JOT:** One notable feature of the iAtlas is its user-friendliness; you don’t need to be a data scientist to take advantage of the platform’s various features. We are genuinely excited about the potential of this initiative and look forward to witnessing its growth and increased adoption by researchers and immunologists in the field.

We have recognized that valuable immunogenomics data is often published but remains inaccessible. Our vision is that when people publish this data, they will make it available for others to benefit from. We are starting to make data from our funded CRI clinical trials accessible through the iAtlas. Additionally, we’ve initiated a program known as the Clinical Innovator, supporting investigator-initiated clinical trials with a strong focus on correlative science. As part of the terms and conditions, we encourage data updates.

Our goal is to see this initiative grow over time, and we believe that the larger the dataset we can compile, the more impactful it will be in addressing crucial questions. Initially, the iAtlas was based on data from 10,000 tumor samples spanning 33 different cancer types. We are also working on incorporating data from the Human Tumor Atlas Network, making it large enough and highly accessible.

To facilitate this effort, we are funding a team of scientists at Sage Bionetworks and the Institute for Systems Biology, Seattle to build and enhance the iAtlas. The quality and utility of the iAtlas will rely on the datasets it contains, so the more organizations we can collaborate with to encourage open access data contributions, the more valuable this resource will become.

Finally, what are your key priorities over the foreseeable future?

**JOT:** Our primary goal remains the same—to fund research that will pave the way for more effective immunotherapies, offering hope to a broader spectrum of patients. Being a not-for-profit organization provides us with the flexibility to pivot and adapt to the evolving needs of the field. We pride ourselves on being responsive, enabling us to create programs that are often more daring and adventurous than what pharmaceutical companies might undertake.

I view our partnerships as a means to sustain and foster the continuum of academic research, spanning from the laboratory to translation and clinical trials. This support is instrumental in fueling what biopharmaceutical companies do when they take these discoveries into drug development. However, we recognize that as a nonprofit, our capabilities are held back by resources. To overcome this, we are actively seeking new partnerships and collaborations. I’m exploring ways to engage with pharmaceutical companies in a manner that allows us to leverage our role in supporting scientists and academic research, which, in turn, drives drug development.

Our organization has cultivated a reputation as a trusted source of support and information within the field. My goal is to build upon this reputation and discover new avenues that enable us to expand our impact and fund even more critical research in the pursuit of more effective immunotherapies.
BIOGRAPHY

JILL O’DONNELL-TORMEY leads the CRI, a global nonprofit organization dedicated to investing in the most promising areas of cancer immunotherapy research to harness the power of the immune system to conquer and cure all cancers. O’Donnell-Tormey joined the organization in 1987 as Director of Scientific Affairs and began serving as its Chief Executive in 1993. During her tenure at CRI, she has helped to create catalytic and novel research programs that span the laboratory and the clinic. She has guided over US$500 million in funding to these programs, which enable the research and scientific discoveries changing the course of cancer treatment today. O’Donnell-Tormey began her career as a Postdoctoral Fellow in the Laboratory of Cellular Physiology and Immunology at The Rockefeller University and proceeded to work as a research associate in the Department of Medicine at Cornell University Medical College. She received a BSc degree in Chemistry, summa cum laude, from Fairleigh Dickinson University, and a PhD in Cell Biology from the SUNY Downstate Medical Center. She sits on the boards of The Staten Island Foundation where she serves as Secretary; The City University of New York; Richmond University Medical Center; and the Heath Research Alliance, Research Triangle Park, NC, and Coherus Biosciences, Redwood City, CA. She also serves on the Cancer Immunotherapy Advisory Board of the Focused Ultrasound Foundation, Charlottesville, VA, and the Editorial Advisory Board of Immuno-Oncology Insights. In 1998, O’Donnell-Tormey was named one of Irish America magazine’s ‘Top 100’ Irish Americans. She is the recipient of the 2002 Fairleigh Dickinson University Pinnacle Award, the highest honor bestowed on its alumni; the 2013 CRI-Frederick W. Alt Award for New Discoveries in Immunology; and the 2020 Tara Withington Public Service Award from the Society for Immunotherapy of Cancer.

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