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IMMUNO-ONCOLOGY INSIGHTS

SPOTLIGHT ON
Novel targets and pathways

Guest Editor
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Spotlight

Tools and Technologies

Novel targets in I-O

Joe Dukes

"...it has quickly become appreciated that despite the efficacious outcome of generally 'releasing the brakes' of T cells to restore and enable tumor cell targeting, significant challenges remain."

FOREWORD

Immuno-Oncology Insights 2023; 4(8), 279–281

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A critical breakthrough in the last two decades for I-O was the clinical demonstration that a patient's immune system, specifically their T cells, can be manipulated as a powerful tool to overcome cancer and deplete malignant cells. The seminal evidence to support this came with the observation that the anti-CTLA4 antibody ipilimumab, conferred a significant survival benefit to a subset of patients with metastatic melanoma—a disease which at the time was considered a 'graveyard' of drug development [1]. Building on this, evidence quickly mounted that blocking checkpoints expressed on T cells such as PD-1, and their respective ligands on tumor cells, such as PD-L1, could provide striking clinical benefits to patients including durable complete responses in advanced disease [2].

Today, the historical perspective of 20 years ago is all but forgotten. T cell-focused

immunotherapy is front and center in the treatment of I-O. It continues to be one of the most promising fields for delivering the hope of curative treatment for cancer patients. However, it has quickly become appreciated that despite the efficacious outcome of generally 'releasing the brakes' of T cells to restore and enable tumor cell targeting, significant challenges remain. Namely, only a minority of patients experience maximal benefit and there is often a trade-off with immune-related side effects, that in many cases can lead to treatment discontinuation and risk of significant harm [3]. As such, the field has recognized the need for targeted immunotherapies that harness the potency of a T cell.

Given the powerful capacity of T cells to destroy target cells, T cells have been exploited generally in two different ways to advance targeted immunotherapies. Firstly, T cells can be modified to express a targeting domain that recognizes a cancer-specific or over-expressed target. Secondly, a protein-based therapeutic can be generated that has specificity for both a cancer target and to engage the T cell to 're-direct' its activity to the target, for example, bispecific T cell engagers. In both cases, the predominant challenge to address has been the target antigen itself. T cells are highly potent, thus the target must be either expressed exclusively on tumor cells or expressed on healthy tissues that are temporarily dispensable, for example, CD19 expressed on both malignant and healthy B-cells. One of the challenges with the latter approach to targets is that where antigen load is high, for example, tumor and B-cell compartment in the case of CD19, the T cell response is proportionate, leading to vast production of proinflammatory cytokines that can have other unwanted, and severe, side-effects such as cytokine release syndrome [4]. In addition, such targets to date have been restricted to hematological 'liquid' tumors. Given this and the paucity of targets, especially in the solid tumor setting, a significant challenge that remains for the field is the discovery of targets with an optimal expression profile for targeted immunotherapy.

In light of the challenges described for both general immunotherapy and targeted immunotherapy in cancer, there is a clear need for novel targets in the field. Thankfully, many academic groups and biopharma companies are pursuing this in earnest. This edition of Immuno-Oncology Insights seeks to address key considerations on antigens in I-O to provoke further progress in this area, by exploring the gaps, considerations for optimal targets and modalities for therapeutic application, and finally what the future could look like beyond novel targets in improving the patient benefit through overcoming escape mechanisms and maximizing efficacy.

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BIOGRAPHY

JOE DUKES is Chief Scientific Officer of Enara Bio, and joined the company in 2019 following leadership across research and early development of novel immunotherapies, having led molecules from early discovery and validation through to first-in-human clinical studies. Prior to joining Enara Bio, Joe spent eight years at Immunocore, developing novel T cell receptor (TCR)-based bispecific therapeutics. During this time, he established a bespoke, in vitro preclinical approach for generating safety data to de-risk TCR-based therapeutics. In his role as Head of Biology, Joe oversaw TCR discovery, characterisation, and preclinical screening of drug candidates. In addition, Joe was Program Leader for the second TCR-bispecific molecule to enter the clinic, candidates through preclinical and clinical development to successful IND/CTA submissions and first-in-human phase 1 studies. Joe also oversaw non-clinical studies and contributed authorship to the BLA for the first approved TCR-bispecific therapy, Kimmtrak (tebentafusp). Joe obtained a PhD in Cell Biology and a subsequent post-doctoral fellowship at the University of Bath, UK.

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VIEWPOINT

Optimal selection of tumor antigens

Sophie Papa

"We need new targets to continue to advance treatments and thankfully, recent advances in technologies underpinning antigen discovery are accelerating change."

VIEWPOINT

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CHALLENGES AND IMPERATIVES IN I-O DRUG DEVELOPMENT

Targeted I-O drug development requires antigens and we do not have enough of them. This limitation is both in number but also coverage of broad patient populations. Current targets were discovered as our understanding of cancer cell biology and the available tools for interrogation evolved which has resulted in multiple drug development efforts clustering around only a few suitable antigens.

We need new targets to continue to advance treatments and thankfully, recent advances in technologies underpinning antigen discovery are accelerating change.

The requirements of an immune therapy target vary depending on modality, from cell surface expression for antibody-based therapeutics, to robust presentation of a peptide in the human leucocyte antigen groove (pHLA) for T cell receptor (TCR) based therapies. There is much to be gained from stepping back from the antigens that we already have in hand to think about what a high-quality novel target would look like.

OPTIMAL CHARACTERISTICS FOR ADVANCED THERAPEUTIC IMPACT

At the tumor level, a target that is shared widely across patients will have the greatest potential for off-the-shelf drug development and resultant patient benefit. Ideally, this antigen will also be shared widely across tumor types. Tumor type matters as it contributes to risk as well as opportunity. We have seen significant success with immune therapies in certain diseases such as cutaneous melanoma, sub-sets of non-small cell lung cancer, and microsatellite unstable colorectal cancers with elusive impact in others, such as microsatellite stable colorectal cancer, pancreatic cancer, and ovarian cancers. Then there are the tantalizing exceptions, the preeminent of which is the impact of KIMMTRAK® in uveal melanoma [1]. A disease few would have singled out as likely to deliver such success with a T cell engager molecule. Having targets that enable a drug development plan that includes tumor types that are underserved and/or highly challenging with others where perhaps recruitment is a little easier and expectation of positive outcome higher would be optimal.

An ideal target should be found only in cancer and not in healthy tissue. For antibody-based therapeutics, where high cell surface density of the target is required for activity, a significant window of expression between cancer and normal can suffice to deliver safety and efficacy. For TCR therapeutics the unique ability of TCRs to recognize very low density of antigen emphasizes the need for clean cancer-specific presentation. Strategies are in development to try to overcome targeting non-cancer-restricted targets such as masking engineering and bivalency to enhance the impact on higher expressing tissues [2]. These approaches introduce complexity and are not yet proven to obtain their goals clinically.

ADDRESSING EARLY RESISTANCE AND ENSURING TARGET STABILITY

To mitigate the risk of early resistance having the greatest breadth of targetability through homogeneous expression is key. Linked to this is the stability of antigen expression across disease stages and after therapeutic intervention common to established treatment paradigms. This latter point is often overlooked in the initial validation of a promising new target, but it is vital for viable clinical impact.

For TCR-based therapies that target pHLA, resistance does not appear to be driven by loss of parent antigen in the clinical data we have seen to date, instead, it is mediated through abrogation of antigen presentation machinery [3–5]. This needs to be recognized as we discover new pHLA targets with an early eye to favoring novel targets that can be enhanced through rational therapeutic combination strategies and then testing these combinations early in clinical development.

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SOPHIE PAPA is Chief Medical Officer at Enara Bio and a Clinical Reader in Immuno-oncology at King's College London. Prior to joining Enara, she was a Consultant Medical Oncologist at Guy's and St Thomas' NHS Foundation Trust (GSTFT) in London specialising in skin cancers. She has extensive clinical trial experience as a principal investigator in the GSTFT early phase trials team. Central to this was Sophie's leadership of the solid tumour cell therapy clinical trial portfolio at GSTFT as program lead for cell therapy. Sophie's laboratory is focused on translational immune-therapy research. Sophie undertook medical training at the University of Oxford and Imperial College London and completed a PhD in CAR-T cell therapy from King's College London. She was awarded an MRC Clinician Scientist Fellowship in 2014 and became a Fellow of The Royal College of Physicians (London) in 2019. She has published over 50 academic papers.

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INTERVIEW

Navigating the complexities of immunotherapy: unraveling novel targets & pathways

Lauren Coyle, Editor, *Immuno-Oncology Insights,* interviews **Lars van der Veen,** Founder and CTO of iOnctura to discuss the evolving landscape of novel targets and pathways in the I-O space.

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Q What novel and emerging targets and pathways in I-O are currently showing the greatest potential and are there currently any challenges and gaps?

LV: Most efforts have historically focused on addressing the T cell component of the immune system. However, a notable gap exists when examining the tumor microenvironment, where numerous immune cells play crucial roles in tumor progression. To gain a comprehensive understanding of the contributions of various immune cells, along with the often-overlooked cancer-associated fibroblast, it is essential to comprehend how these cells

"To gain a comprehensive understanding of the contributions of various immune cells, along with the often-overlooked cancer-associated fibroblast, it is essential to comprehend how these cells work together."

work together. These collaborations either control or enable the tumor to exploit interactions, evading an anti-tumor immune response.

While new targets continually emerge, concentrating on singular aspects of tumor immunology, it is imperative to initially grasp the intricacies of crosstalk within the tumor. Subsequently, novel therapies can be developed to address some of the crosstalk. Rather than solely focusing on individual aspects of tumor immunology, efforts should be directed toward rectifying the imbalance within the immune system by targeting multiple crosstalk pathways. This approach can potentially enhance the natural immunity already present in most patients.

Patients typically possess T cells capable of recognizing the tumor, yet their response is hindered due to an immune imbalance within the tumor. The forefront of the next wave of immunotherapies should involve resolving these resistant mechanisms within the tumor. Although immune checkpoint inhibitors (ICIs) marked a significant breakthrough, subsequent therapies faced challenges as merely activating the immune system proved insufficient. Over-activation can lead to toxicities, a prominent issue with current ICIs. The focus should shift towards rectifying the tumor's imbalance, thereby devising more tumor-specific methods for resolution. This targeted approach may mitigate the general immune toxicities, representing the potential future of immunotherapies.

In the clinical landscape, there is a proliferation of bi-specific antibodies addressing specific facets of I-O. However, until the prevalent resistance mechanisms within tumors are resolved, the efficacy of these therapies remains limited. While these treatments may complement the effects of ICIs, a true breakthrough remains on targeting these resistance mechanisms. This pursuit forms the core of iOnctura's mission—identifying key resistant pathways enabling tumors to elude the immune system.

To further emphasize, a more profound understanding of crosstalk within the tumor immune system is imperative for optimizing these therapies. The emphasis should extend to exploring how therapies can be better combined, as a rational understanding of improvement goals is crucial for effective combinations.

Q How can the industry and academia better align the priorities around funding and balancing risk versus reward?

LV: In the industry, the trend seems to be chasing one hype after another, where companies and academics alike strive to be associated with success. There's a pervasive belief that jumping on the bandwagon of a successful endeavor guarantees success, however, this perspective is somewhat flawed. Disappointment sets in when achieving success proves more elusive than anticipated, leading many to give up.

What is truly needed, is a commitment to gaining a deeper understanding of the disease and its underlying biology which demands hard work and significant effort. Simply shifting from one focus to the next, driven by the allure of a new ICI, is counterproductive. It does little to enhance our comprehension of tumors, and the pursuit of knowledge about tumors should always be the foundation. Only then can we identify the right targets and develop the appropriate molecules to address them.

The prevailing issue in the industry is that programs often operate with limited funding, constrained timelines, and a finite number of years to prove their success. If a program falls short, it is typically terminated. However, it takes approximately 5 years to accumulate the necessary insights to refine and develop a more effective molecule. Embracing the possibility of failure in the initial attempts is crucial for eventual success, yet the current industry climate often does not allow for this necessary trial-and-error period.

This urgency is one reason we observe the resurgence of previously explored targets in the industry. Academics who maintain close ties to their targets over the years discover how to better utilize or address them, yielding more favorable responses in clinical settings. The key to unlocking the potential of these old targets lies in a thorough understanding of the associated pathways, coupled with the endurance required for a sustained, long-term effort.

Q What recent milestones and achievements have iOnctura reached in research and what are the most promising targets and pathways you are currently exploring?

LV: One of our most recent milestones involves the discovery that autotaxin plays a pivotal role in resistance to TGF-β. TGF-β, a significant player in tumor immunology, exhibits a dual nature, functioning both as a tumor promoter and suppressor. Despite being an intriguing target for quite some time, the industry has faced challenges in developing effective TGF-β inhibitors. However, our recent understanding of TGF-β inhibition reveals a complex interplay within tumors, akin to a waterbed effect wherein attempting to suppress one pathway prompts the tumor to counter-regulate, leading to the emergence of alternative pathways.

In our current research, we observe that inhibiting TGF-β results in heightened autotaxin pathway activity. Preclinically, we have demonstrated, and aim to validate in clinical trials, that combining TGF-β inhibition with an autotaxin inhibitor significantly enhances the anti-tumor activity. In preclinical models, this combined inhibition yielded impressive results, even suggesting the potential for curing pancreatic cancer in murine models. While the translation to human trials remains to be seen, these findings underscore the potential impact of rationally combining inhibitors to address different resistance mechanisms synergistically, effectively halting aggressive tumor growth.

Additionally, a noteworthy accomplishment involves our lead program, Roginolisib (IOA-244). We have demonstrated that PI3K-δ inhibition in solid

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"With confidence in the potential of clean molecules and a deep understanding of biologically effective doses, we believe that strategically combining these molecules holds the key to the future of oncology."

tumor patients is not only safe but also leads to clinical benefits. Patients treated with Roginolisib (IOA-224) show a substantial extension in overall survival with minimal reported side effects. This success highlights the importance of a deep understanding of the target and the underlying biology, emphasizing our ability to make a meaningful impact on patients.

Moreover, our experience with PI3K-δ inhibition has unveiled broader effects than initially anticipated. Through comprehensive analyses, considering all measurable biomarkers, and assessing the patients' immune systems, we have gained valuable insights. This knowledge not only aids in refining the development of the drug but also guides the exploration of new indications where the drug may be effectively deployed. Our learnings from the Roginolisib (IOA-244) program will serve as a foundation for further expansion in new clinical trials and additional preclinical research.

In our perspective, the primary emphasis lies in the identification and development of safe molecules, complemented by a robust pharmacodynamic marker. Our approach involves determining the biologically effective dose, a departure from the conventional method of identifying the maximum tolerated dose and developing the molecule just below that level. By pinpointing the relevant biologically effective dose during development, we ensure the production of a drug that can be optimally utilized.

Another crucial aspect of our strategy is the use of clean molecules, selectively targeting the intended pathways while minimizing off-target toxicity. Clean drugs, coupled with a comprehensive understanding of their biologically effective dose ranges, provide the foundation for developing more effective combinations. The goal is to enable the creation of combinations in the clinic that do not introduce additional toxicity and genuinely enhance efficacy.

This philosophy has yielded promising results in our programs, particularly with autotaxin inhibitors showing significant synergy with TGF-β inhibition and PI3K-δ inhibition. The potential for synergies extends beyond our programs, opening avenues for exploration with various other therapies. Currently, we are in the planning stages for our initial clinical studies to further validate these synergies. With confidence in the potential of clean molecules and a deep understanding of biologically effective doses, we believe that strategically combining these molecules holds the key to the future of oncology.

Our vision centers on identifying the right combinations of drugs for specific patients, minimizing toxicity while maximizing efficacy. This, we believe, is the path toward making a substantial impact on the survival outcomes of patients in the field of oncology.

Q How do you decide on which targets or pathways should take priority for further investigation?

LV: Our decision-making process revolves around a prudent allocation of our limited resources, given our current team size. The central criterion guiding our choices

is a focus on combinations that exhibit true synergy, where the combined effect of two drugs surpasses the sum of their individual impacts. This strategic approach maximizes the likelihood of achieving a meaningful and positive effect in clinical settings.

Our primary focus is on identifying those synergistic combinations within our existing pipeline, and we've already observed several promising examples. Additionally, we extend our exploration beyond our pipeline to assess where our drugs can be most effectively combined, especially with existing standard-of-care treatments. We prioritize areas where we anticipate a significant impact.

If novel targets or pathways emerge that align with our strategic goals and offer compelling synergy, we are certainly open to exploring these possibilities. At present, we find substantial potential for synergy within our pipeline combinations, particularly with our PI3K-δ compound, providing us with multiple avenues for further exploration and development.

Q How do novel and emerging approaches fit into the picture of combination therapy?

LV: In the evolving landscape of cancer treatment, we recognize that combination therapy is key. As we delve into novel and emerging approaches, such as vaccines, oncolytic viruses, and antibody-derived or antibody-drug conjugates, each of these therapies holds unique potential. The key lies in identifying the right combination of these agents tailored to specific tumor types. To achieve this, it is important to employ safe therapies—molecules with a clean off-target profile that can be seamlessly combined and selectively target pathways relevant to the tumor while sparing healthy tissue.

Looking forward, we anticipate that the major tumor indications will be subdivided into smaller, more specific sub-indications characterized by distinct molecular, immune microenvironment, or immune phenotypes. For each of these subtypes, specific combinations will be necessary to address the underlying mechanisms fueling tumor growth. This approach acknowledges that there is no one-size-fits-all solution in cancer treatment. The past misconception of attempting to combine everything with an ICI serves as a lesson, emphasizing the need for tailored combinations for specific tumors.

The future of combination therapy holds great promise, but it necessitates a deep understanding of primary resistance mechanisms. Achieving this understanding requires safe drugs that enable exploration and discovery. While combination therapy is undoubtedly the future, the path forward will demand diligent research to determine the specific combinations suitable for individual tumors. Despite the challenges, the evolving landscape offers hope and positive developments, signaling progress on the horizon, though we acknowledge that we have not yet reached our destination.

BIOGRAPHY

LARS VAN DER VEEN holds a PhD in Chemistry. As Chief Technology Officer at iOnctura he is primarily responsible for the non-clinical development activities. These include non-clinical safety and toxicology, manufacturing and project management. He is a medicinal chemist with over 20 years of experience in biopharma R&D, and delivered multiple clinical candidates and

lead compounds for different therapeutic areas including oncology. Prior to founding iOnctura he has held various positions in project management and project leadership spanning early discovery up to commercial products and dealing with both biologics and small molecules. Lars has previously worked at Solvay Pharmaceuticals, Organon, Boehringer-Ingelheim, and Merck.

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IMMUNO-ONCOLOGY INSIGHTS

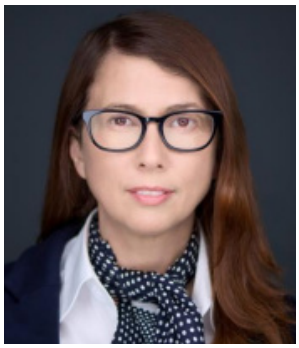
NOVEL TARGETS & PATHWAYS

SPOTLIGHT

INTERVIEW

Exploring the landscape of novel targets & pathways in immuno-oncology

Yvonne McGrath



Lauren Coyle, Editor, *Immuno-Oncology Insights*, speaks to **Yvonne McGrath,** Chief Scientific Officer, iTeos Therapeutics, about the current and emerging novel targets and pathways for the use of cancer therapy in the I-O field with a focus on small molecules and antibody targets.

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Q Could you briefly describe your past experiences in cancer research and your current role at iTeos Therapeutics?

YM: Immediately after completing my PhD in 2000, I joined the UK-based company Biovex which marked the start of my career in oncology. I started working on oncolytic viruses and dendritic cell vaccination strategies for seven years before moving to Immunocore. Here, I assumed the responsibility of re-engineering their initial

anti-CD3 T cell receptor bispecific, taking it to clinical development, and successfully advancing it to phase II studies. This drug, known as KIMMTRAK, has since been launched in the market, providing a therapeutic avenue for uveal melanoma patients.

I moved from the UK to Belgium where I spent six years as the Chief Scientific Officer at Complix, and during this time, we focused on advancing a novel platform technology. I then moved to iTeos Therapeutics in 2020 and as the Chief Scientific Officer, my role encompassed building and expanding the pipeline with promising drugs for clinical trials and also shaping the scientific strategy. Given our significant emphasis on translational medicine, a key aspect involves understanding how to deploy our drugs within diverse patient populations optimally.

Q Could you give background on the novel targets and pathways development platform at iTeos? How do these represent an advance on previous work?

YM: We play a significant role in the adenosine pathway, emphasizing our belief in the immunosuppressive effects of adenosine. Although widely acknowledged, the successful drugging of this pathway has been quite elusive. We believe that our unique insights, built upon prior knowledge, offer a new and different approach that holds promise for the benefit of patients.

Our key insights revolve around the concentration of adenosine in the tumor microenvironment (TME). Utilizing advanced techniques such as mass spectrometry, we have surpassed previous capabilities in measuring adenosine levels within tumor tissue. Our findings reveal substantially higher levels than previously recognized. In response, we have developed a novel drug, covered by a new patent, designed to operate effectively in these elevated adenosine concentrations, interacting specifically with the major adenosine receptor, the A2A receptor

Further, we have identified a new mechanism of action related to adenosine-mediated immunosuppression. We have developed a new drug for this as well, addressing this mechanism, currently in phase I dose escalation. While details remain confidential, we anticipate sharing more information publicly next year.

Additionally, we take pride in our TIGIT drug development. Our approach, involving a fully functional IgG1, has demonstrated Treg depletion in both peripheral and, more importantly, tumor tissues. Our translational medicine efforts have successfully translated into these findings, and we believe this will significantly benefit patients by eliminating immunosuppressive regulatory T cells.

Currently, these represent our major clinical focus areas, however, our commitment extends to continually seeking novel approaches to modify the TME. Our goal is to make it more receptive to both novel therapies and standard of care treatments.

Q Can you tell me more about the research and development pipeline that this work fuels?

YM: We approach our research in three key ways which can best be seen in a new endeavor currently underway at iTeos. Like most, we carry out *in vitro* work, supported by some *in vivo* work, to understand what the drugs are doing to the TME before progressing to patient trials. Substantial focus is also placed on translational medicine, where we analyze extensive datasets to identify patient populations suitable for testing the drugs.

A recent and exciting initiative at iTeos involves obtaining freshly resected tumor tissue from patients undergoing standard-of-care tumor resection which requires swift handling to maintain tissue viability. Though somewhat of an art, we have been making strides in perfecting this technique. Upon acquiring the tissues, they are sliced into smaller sections and novel agent or one of our clinic-ready drugs is applied to the tissue, and the reaction to this agent is measured.

This approach opens up numerous possibilities, one of which is exploring combinations to determine which elicits the most intriguing biological responses in the tumor tissue. Moreover, the responsive tumor tissues can be analyzed to decipher the characteristics influencing their reaction versus tissues that were less responsive. This information aids in extrapolating findings to identify individual patients who might benefit from either a new therapy or a specific combination. The technique proves powerful across various tumor types.

This growing initiative is poised to become the third pillar in drug discovery and development. It promises to bridge the gap between predictions derived from preclinical studies and the realities observed in clinical trials, enhancing the understanding and efficacy in drug development.

Q There's been an increased interest surrounding personalized medicine, do you think this will help with the development of personalized medicine?

YM: It undeniably provides a clear pathway for validating personalized medicine or even pioneering entirely new personalized medicine approaches. I-O, however, may not naturally align with the most specific and purest forms of personalized medicine, instead, it is viewed more in terms of patient groups or subgroups within indications.

The immune system within a particular tumor or indication may closely resemble that of a patient in a completely different indication. The perspective of iTeos is centered around tracking and mapping the TME across various patient groups. Nonetheless, this technique could serve as an incredible tool for eventually achieving and validating a pure personalized medicine approach.

Q What impact is being made by small-molecule targets and do you see any specific areas that require more focus?

YM: In the I-O space, the use of small molecules is not as widespread as antibodies, setting iTeos apart with the capability of employing both approaches. The in-house medicinal chemistry group, in collaboration with great suppliers, equips us to target a broad spectrum of entities that we deem crucial for modulating biology. This flexibility extends to intracellular as well as extracellular targets.

Previously, the focus in I-O has leaned toward cell-surface molecules, given the predominant role of ligand-cell-surface interactions in immunology. While this emphasis is understandable, it may have led to the underexploitation of intracellular signaling. There is potential value in delving into this, to better understand and address important biological aspects. There may be potential opportunities for developing more effective strategies to tackle specific biologies crucial in I-O.

Q Is there any progress in antibody targets, and how can they be further developed?

YM: For breakthroughs, it's essential to explore biology comprehensively and consider innovative ways to harness its complexity. While anti-PD-1 breakthroughs have been monumental, duplicating similar efforts may be an inefficient use of resources. Instead, the focus should be beyond PD-1 and CD8 T cells and more on the immune system components within the TME. The key is to develop antibodies, or even small molecules, that modify their biology, creating a TME conducive to patient benefit rather than tumor growth.

I believe that significant breakthroughs occur when approaches diverge from the conventional. Reflecting on my previous roles at Biovex and Immunocore, I contributed to the development of the first oncolytic viruses and engaged in dendritic cell vaccination strategies before I-O gained widespread attention. The Immunocore team slightly later to the game developing novel I-O agents in the form of T cell receptor-based bispecifics, two of which have reached the clinic and are actively treating patients, showcasing their novelty at the time.

The next wave of breakthroughs may emerge through similar diverse approaches, whether in the form of small molecules, large molecules, bispecifics, or other inventive methods. By exploring various novel approaches, we advance scientific understanding and increase the likelihood of developing drugs that genuinely benefit patients.

Q What challenges are currently facing the I-O field in terms of targeted therapies and how could these be addressed?

YM: The greatest challenge in the I-O space is the inherent complexity of its operation in conjunction with other drugs. Given the intricate nature of the immune system—comprising various cell types, each with subtypes expressing different receptors—the approach necessitates a comprehensive understanding. Recognizing the immune system as a

collective, where different components work together, highlights the importance of simultaneous targeting of various aspects. Achieving this involves combination therapies, a strategy filled with challenges in the clinical trial space.

Combinations are inherently difficult to execute and justify in terms of progression. Vision is crucial to proceed, especially when faced with unclear clinical data. The central challenge lies in advancing clinical development while navigating through extensive clinical trials. This challenge is then amplified when attempting to prove the added benefit of a new drug on top of what may be considered standard care.

In an ideal scenario, the next frontier would involve adding novel agents atop other novel agents. However, this presents even more significant challenges in clinical development. Within the framework of projects like Project Optimus, determining the optimal dose for each drug is essential. Simultaneously managing the intricacies of two novel agents, including understanding their specific toxicity profiles and potential interactions, further complicates matters. Overcoming these challenges anticipates the greatest benefit for patients.

Q Finally, what are some key goals and priorities for your role and iTeos as a whole in the future?

YM: Overall, my key priorities at iTeos involve a twofold approach. Firstly, in terms of our current clinical drugs, my focus is on determining the specific patient populations that will gain optimal benefits from these therapies. This necessitates a robust translational medicine approach, ensuring a thoughtful and comprehensive understanding. Recognizing that these drugs won't have universal efficacy, identifying which patients stand to gain the most from a particular treatment is crucial. It aligns with the goals of oncologists and ensures that patients are not only exposed to the right drugs but are also allowed to explore alternative, potentially more beneficial treatments.

In terms of clinical space, the challenge extends to deciphering the most effective combination strategies. This involves identifying the right placement of our drugs within combination therapies to maximize benefits for the patients.

On the other front, concerning our pipeline and its growth, my second goal involves strategically considering the best approaches and searching for groundbreaking changes in the TME that can genuinely benefit patients and make a significant difference. Identifying the most promising targets and developing drugs against them to be best-in-class and first-in-class is a priority. Constructing a pipeline with innovative, promising drugs is a continual challenge. This dual focus involves not only developing the pipeline but also discerning the optimal treatment approaches for specific patient groups that will derive the most significant benefits.

BIOGRAPHY

YVONNE MCGRATH joined iTeos in 2020 as Vice-President of R&D. With more than 20 years of international experience in oncology drug discovery and development, she has taken lead candidates from early stage research into clinical trials. Immediately prior to iTeos, she served as CSO and board member in Complix, a company developing novel biologics.

She has also lead R&D activities in UK based biotech companies including Immunocore and Biovex. Yvonne holds a PhD from the University of Wales, College of Medicine.

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IMMUNO-ONCOLOGY INSIGHTS

TOOLS & TECHNOLOGIES

Leveraging cutting edge tools and technology to advance I–O: tools of tomorrow

DECEMBER 2023
Volume 4, Issue 8

Evaluating organoid culture using live-cell analysis & RUO growth factors

Natasha Lewis, Senior Scientist, Sartorius

For organoids to reach their full potential within immuno-oncology, they require more effective quantification methods and increased reproducibility. This poster will discuss the use of the Incucyte® Organoid Analysis Software Module on a range of organoid types, and show how research use only (RUO) growth factors and cytokines can be used to promote and sustain organoid growth.

INTRODUCTION TO ORGANOIDS

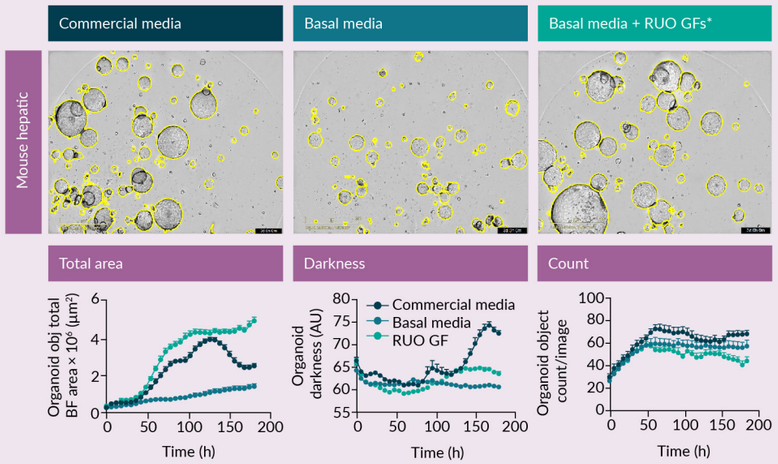
Organoids have huge potential in the field of immuno-oncology as they can accurately replicate both the architecture and function of their full-scale counterparts. However, their full potential is limited by a lack of standardization, poor reproducibility, and challenging quantification of phenotypic data. Live-cell imaging allows the acquisition of images throughout the culture period in a non-perturbing manner, allowing the preservation of precious material and comprehensive multiparametric analysis of growth dynamics.

INCUCYTE® LIVE-CELL IMAGING & ANALYSIS

Incucyte® Organoid workflows for culture and assays are designed to standardize the entire organoid workflow from generation, maintenance, and passaging to the final assay analysis with image-based, label-free measurement of organoid count, size, and morphology in a relevant environment.

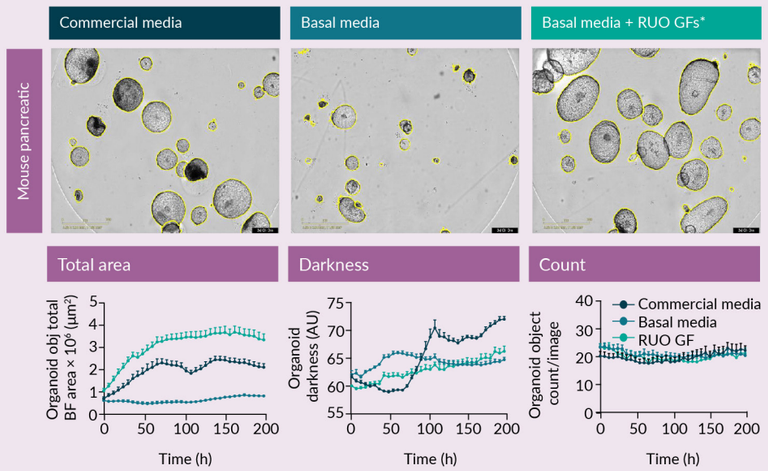
Once stem cells have been isolated and transferred into Matrigel®, they can then be manipulated, for example genetically modified or treated, and transferred into 96-well plates for assays. This can then be analyzed using the organoid software module.

Figure 1. Mouse hepatic organoid growth under varying media conditions.



*Media contains 50 ng/mL EGF, 100 ng/mL FGF10, 50 ng/mL HGF, 1 µg/mL Rspondin-1.

Figure 2. Mouse pancreatic organoid growth under varying media conditions.



*Media contains 50 ng/mL EGF, 100 ng/mL FGF10, 25 ng/mL Noggin, 1 µg/mL R-spondin1.

GROWTH FACTORS IN ORGANOID CULTURE

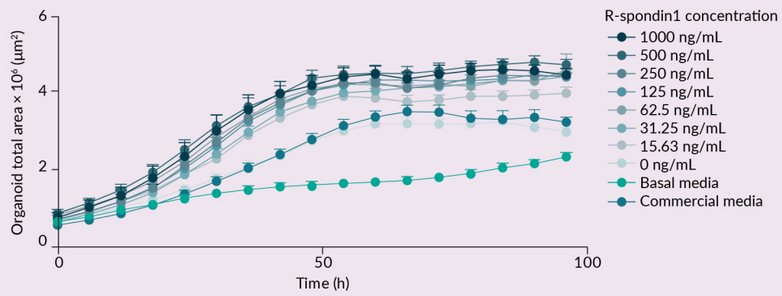
Growth factors (GFs) and cytokines are signaling molecules that cause cells to proliferate, migrate, and differentiate. They are used in cell culture to maintain cell growth or direct cells toward a desired cell fate. Sartorius supplies high-quality, protein-free, animal-free, RUO GFs and cytokines, shown to have the highest levels of purity and bioactivity.

As an example of where GFs can be used to culture organoids, mouse hepatic organoids were cultured in either commercially available organoid media, basal media without GFs, or with GFs (EGF, FGF10, HGF, and R-spondin1). Data shown in **Figure 1** highlights that alternative media with GFs shows improved hepatic organoid growth.

Similarly, mouse pancreatic organoids were cultured in either commercial media, basal media without GFs, or with GFs (EGF, FGF10, Noggin, and R-spondin1). Alternative media with GFs shows improved pancreatic organoid growth **(Figure 2)**.

An investigation of individual GF effects was performed with live-cell analysis. Mouse hepatic organoids were cultured with varying concentrations of R-spondin1 **(Figure 3)**. With increasing concentrations of R-spondin1, organoid growth increases accordingly, although >62.5 ng/mL the relationship between concentration and organoid growth is weaker.

Figure 3. R-spondin1 concentration-dependent response.



CELL & GENE THERAPY INSIGHTS

Immuno-Oncology Insights 2023; 4(8), 256; DOI: 10.18609/ioi.2023.036

In partnership with: SARTORIUS

IMMUNO-ONCOLOGY INSIGHTS

LEVERAGING CUTTING EDGE TOOLS & TECHNOLOGY TO ADVANCE I–O: TOOLS OF TOMORROW

CHANNEL CONTENT

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.

Immuno-Oncology Insights 2023; 4(8), 287–294

DOI: 10.18609/ioi.2023.42

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.

Q 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 becoming 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.

"Removing immune system brakes with checkpoints was a significant breakthrough, but there are other steps that limit the effectiveness of immunotherapy."

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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.

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"...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."

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.

Q 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.

Q 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.

Q 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.

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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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