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
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...
“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.”

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.

AFFILIATION

Lars van der Veen PhD
Chief Technology Officer,
iOnctura

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given his approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: van der Veen L received an EIC Accelerator grant for the autotaxin program. iOnctura has an evolving patent portfolio around its pipeline assets. van der Veen L holds stock options in iOnctura SA.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

ARTICLE & COPYRIGHT INFORMATION

Copyright: Published by Immuno-Oncology Insights under Creative Commons License Deed CC BY NC ND 4.0 which allows anyone to copy, distribute, and transmit the article provided it is properly attributed in the manner specified below. No commercial use without permission.

Attribution: Copyright © 2023 van der Veen L. Published by Immuno-Oncology Insights under Creative Commons License Deed CC BY NC ND 4.0.

Article source: Invited; externally peer reviewed.

Revised manuscript received: Nov 17, 2023; Publication date: Nov 29, 2023.