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IMMUNO-ONCOLOGY INSIGHTS

SPOTLIGHT ON
Combination therapy development

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SPOTLIGHT

Unraveling combination therapies in lung cancer: oncogenic drivers, ICI resistance, and predictive biomarkers

"To predict resistance…there is a need for robust and novel predictive biomarkers, and combining different biomarkers simultaneously will become essential."

VIEWPOINT

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On February 23, 2024, **Lauren Coyle**, Commissioning Editor, *Immuno-Oncology Insights*, spoke to **Paul Hofman**, Head of the University-Hospital Institute RespirERA and of the Department of Pathology at Nice Côte d'Azur University, France, about refining combination therapies to enhance lung cancer treatment, addressing the issues surrounding immune checkpoint inhibitor resistance and implementing predictive biomarkers. This Viewpoint article is based on that conversation.

ONCOGENIC DRIVERS AND PERSONALIZED MEDICINE IN NSCLC

Non-small cell lung cancer (NSCLC) has become a paradigm for personalized medicine, where identifying disease subtypes through oncogenic driver mutations has led to the development of molecularly targeted therapies.

The impact of driver oncogenes on the immune tumor microenvironment (TME) has profound implications for the effectiveness of immune check point inhibitors (ICIs). For instance, NSCLC patients with BRAF mutations or KRAS and TP53 co-mutations tend to benefit more from ICIs, while those with EGFR mutations or ALK/ROS1 rearrangements often exhibit lower tumor PD-L1 levels and mutational burdens, leading to resistance. Understanding factors contributing to ICI resistance is crucial for developing approaches to sensitize tumors to these therapies.

A comprehensive grasp of NSCLC genomics and immunophenotypes could aid patient stratification for ICI-based therapies, with combination strategies targeting oncogenic signaling-related immune-inhibitory mechanisms enhancing tumor immunogenicity.

Advancements in ICIs, particularly antagonistic antibodies targeting the PD-L1–PD-1 axis in thoracic oncology, have rapidly progressed. However, major oncogenic drivers of NSCLC are often linked to intrinsic resistance to ICIs. Patients with oncogene-driven subtypes responsive to targeted therapies may benefit from immunotherapy, posing challenges in understanding the optimal combination of ICIs and oncogene-directed therapies.

UNDERSTANDING IMMUNE CHECKPOINT INHIBITOR RESISTANCE

Developments in understanding immune checkpoint blockade resistance involve the interplay of tumor-intrinsic and tumor-extrinsic factors. Tumor-intrinsic mechanisms encompass genetic and epigenetic modifications hindering neoantigen processing and T cell action within the TME. Tumor-extrinsic factors include non-cancerous stromal or immune cells and systemic influences promoting resistance.

Primary resistance is associated with genetic mutations, epigenetic changes, interferon-γ signaling pathway alterations, and PD-L1 expression levels. Acquired resistance, shared with primary resistance, involves T cell dysfunction, changes in the mutational landscape, induced expression of alternative immune checkpoints, and metabolic alterations promoting immunosuppression through extracellular adenosine.

Secondary resistance mechanisms include therapy-induced alterations in the TME, exemplified by a combination of anti-angiogenic and anti-PD-1 agents in NSCLC. While dual inhibition mediates anti-tumoral effects, adding PD-1 leads to relapse.

The mechanisms of acquired resistance to ICIs exhibit significant overlap with primary resistance and are intricately interconnected. Pseudo-progression, occurring in the initial or late stage of treatment, complicates the identification of resistance mechanisms. These resistance mechanisms may vary not only by tumor types but also by patient-specific factors, reflecting the unique genetic and clinical backgrounds of each individual.

The complexity of resistance mechanisms becomes apparent when considering different solid tumor types. High PD-L1 expression in melanoma does not necessarily predict a favorable response to ICIs, while in lung cancer, it tends to serve as a reliable biomarker for response in a majority of the cases. The association between high tumor mutation burden (TMB) and a positive response to ICIs is quite clear in melanoma, but in lung cancer, the relationship with high TMB is less evident and presents discrepancies among solid tumor types.

As the impact of gene mutations on the response to targeted therapy combined with

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immunotherapy varies across solid tumor types, understanding the mechanism of resistance necessitates considering the specific histological type of these solid tumors. While some advocate for a transversal view of different resistance mechanisms across various tumor types, others argue for a vertical view specific to the solid tumor type. Balancing both perspectives emphasizes the importance of comprehensive research that considers the general genomic profile of the TME alongside specific views tailored to individual solid tumor types.

The challenge in overcoming these resistances lies in integrating data from genomics, epigenomics, proteomics, microbiomics, clinical records, and radiomics into a unified database. This multi-omic or 'panomic' approach requires meticulous data management and high-quality data. Despite the challenge, future advancements involve associating biomarkers from different fields and monitoring patients' responses to different ICIs. Adapting these challenges to daily practice in smaller healthcare settings remains an ongoing hurdle for optimal patient care.

The need to understand different resistance mechanisms to ICIs in thoracic oncology, especially in oncogene-addicted NSCLC, is urgent. This could be achieved by combining ICIs with chemotherapy, targeted therapy, radiotherapy, anti-angiogenesis therapy, ADCs, or adoptive cell therapy (ACT) to enhance immunomodulatory effects on T cells.

The advent of ICI therapy has revolutionized medical oncology, yet the significant challenge of acquired resistance in a considerable proportion of patients persists. The true landscape of acquired resistance remains uncertain, necessitating the establishment of uniform definitions and evaluation criteria.

Multifaceted approaches and higher-resolution investigations may uncover new resistance mechanisms and predict synergistic combinations. Ongoing research into the underlying biology of acquired resistance predicts therapeutic combinations to overcome it, benefiting more patients. Human bioinformatic analysis and genome sequencing advancements will undoubtedly extend the benefits of integrated and individualized immunotherapies to more patients.

OVERCOMING RESISTANCE AND IMPROVING COMBINATION THERAPIES

There is an urgent need to address obstacles hindering clinical advancements in I-O, including the development of accurate preclinical models mimicking human immunity and understanding molecular and cellular determinants of primary and secondary resistance. The design of effective combinations of personalized immune-based therapies is crucial for individual patient treatment.

Combination therapies, such as immunotherapy plus chemotherapy, have shown promise in improving patient outcomes. Chemotherapy inhibits immunosuppressive immune cell generation, promoting a more inflammatory immune infiltrate. Ongoing clinical trials aim to validate the efficacy of atezolizumab in combination with chemotherapy in NSCLC patients. Direct intervention in the TME, including combining anti-VEGF bevacizumab with immunotherapy, stabilizes tumor vasculature and enhances immunotherapy effectiveness. Synergistic activity is observed when ICIs are combined with adoptive cell therapy and cancer vaccines. Clinical trials are underway to investigate these combinations in various cancer types.

Overcoming resistance with ICIs, particularly when PD-L1 expression is low, involves the addition of molecules such as CD73, CD39, and purinergic receptors, or targeting the α-adrenergic receptor. New clinical trials focus on combining molecules targeting PD-L1 and other immune checkpoint molecules, as well as combining targeted therapy with immunotherapy and chemotherapy. Although more toxic, combining immunotherapy and chemotherapy has proven more efficient. Emerging on the market are new

ADCs for these combinations, including for example anti-cMet, anti-CEACAM5, anti-Trop-2, anti-HER2, anti-HER3, anti-Nectin-4, and anti-B7-H3.

Supported by clinical trials, these innovative approaches show potential in enhancing cancer immunotherapy, offering more effective and personalized solutions for patients. Beyond refining therapeutic strategies, there is a crucial need to improve patient selection for immunotherapy by excluding those unlikely to respond or prone to significant side effects.

Systematic analysis through obtaining tumor tissue before and after treatment initiation could hold potential. This approach, involving serial assessment of tumor specimens and the development of minimally invasive biomarkers, aims to comprehensively understand the mechanisms of response and resistance to ICIs. The dynamic nature of this approach surpasses traditional static time points research, aiming to identify superior diagnostic biomarkers by analyzing responses to ICIs over time.

IMPLEMENTING PREDICTIVE BIOMARKERS TO IMPROVE TREATMENT

The narrative surrounding biomarkers has evolved over the past few decades, moving beyond PD-L1 and TMB. To predict resistance, particularly in advancing combination therapies, there is a need for robust and novel predictive biomarkers, and combining different biomarkers simultaneously will become essential.

Next-generation sequencing provides abundant information about genomic aberrations, including KEAP1, STK11, MTAP, NOTCH, and SMARCA4. Analyzing this network of genomic alterations alongside PD-L1 expression, CD8 expression, and other factors is certainly crucial for predictive accuracy.

There is an urgent need to standardize companion/complementary biomarker tests for routine clinical practice. Despite the promise of biomarkers, research is in the early phase of development, requiring time for global acceptance through large-scale collaborative efforts. Currently, no clinically validated biomarker of resistance to ICIs exists for daily practice use.

While the field of I-O is thriving and promising, overcoming detection, stratification, and resistance obstacles demands significant efforts. Thoroughly understanding the mechanisms behind effective anti-tumor responses, including cell-intrinsic and -extrinsic tumor factors leading to primary, adaptive, and acquired immunotherapy resistance, is crucial. Unveiling these pathways will guide future approaches to effectively address immunotherapy resistance.

Effective implementation requires advanced bioinformatics tools and robust data management, along with a sufficient patient cohort. Considering aging's impact on immunotherapy response, biomarkers associated with senescence, such as telomere length, become significant. Future advancements will likely involve combining various biomarkers for a comprehensive predictive approach. The challenges in implementing biomarkers extend beyond ICI resistance, exemplified by the example of EGFR mutation assessment for EGFR TKI treatment.

The primary challenge lies in developing an easy, robust, sensitive, specific, and cost-effective biomarker that is universally applicable, and is not limited to large centers but accessible in small clinics worldwide. Ensuring equal opportunities for all patients, regardless of location, demands addressing logistical and financial barriers. This requires collaborative efforts from different stakeholders to ensure equitable access to effective cancer management worldwide.

LOOKING TO THE FUTURE

The future goals for improving immunotherapy's benefits in lung cancer encompass a holistic approach to better predict ICI

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responsiveness and potential biomarkers of toxicity. This approach integrates signatures from at least genomic, epigenomic, transcriptomic, and proteomic data, utilizing AI tools for routine clinical practice. However, potential barriers and bottlenecks need to be acknowledged.

Clinical trials, though promising, encounter challenges in exploring ICI resistance mechanisms. ctDNA, CRISPR screens, single-cell RNA sequencing, and spatial multi-omics offer new avenues for comprehensive resistance monitoring. While immunotherapy remains promising for cancer treatment, translating these advancements into clinical applications requires swift efforts. Future considerations include the cost and reimbursement of therapeutic molecules and associated companion diagnostic tests. In the pursuit of personalized cancer management, the integration of AI tools holds promise for predicting ICI resistance and optimizing combination therapies. Finally, future efforts must focus on preventive and screening programs, especially for lung cancer.

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IMMUNO-ONCOLOGY INSIGHTS

COMBINATION THERAPY DEVELOPMENT

SPOTLIGHT

Exploring the potential of combination radio-immunotherapy for a comprehensive cancer treatment

"Radiotherapy emerges as a valuable tool for managing life-threatening disease, ensuring patients can endure the necessary time for immunotherapy to take effect."

VIEWPOINT

On February 26, 2024, **Lauren Coyle**, Commissioning Editor, *Immuno-Oncology Insights*, spoke to **Zachary Morris**, a radiation oncologist and Vice Chair of the Department of Human Oncology, University of Wisconsin, about the landscape of cancer treatment through the combination of immunotherapy and radiation therapy, highlighting their distinct yet complementary roles through preclinical evidence, clinical considerations, and future directions. This Viewpoint is based on that conversation.

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COMBINATION RADIO-IMMUNOTHERAPY

Immunotherapy and radiation therapy have evolved rapidly over the years, and while both have been integral in cancer treatment for an extensive period, their recent advancements have gained significant attention.

Immunotherapies have largely replaced traditional treatments for many diseases, becoming a frontline choice for metastatic disease and increasingly employed in locally advanced cases. On the other hand, radiation therapy, having proven itself as a standard of care due to its long-standing presence, plays a critical role in curative combined modality treatments.

Radiotherapy, in the metastatic setting, serves as a crucial method for providing palliation to symptomatic lesions, enhancing the quality of life for patients. Additionally, it is increasingly utilized to target spatial resistance in cases where metastatic sites are unresponsive to systemic treatments. Together, these modalities present two distinct yet complementary approaches to cancer treatment.

Examining the historical integration of chemotherapy plus radiotherapy, it became clear that combining these treatments often led to synergistic effects, providing greater efficacy than when administered separately. Similarly, there is promising preclinical and clinical data suggesting that the combination of radiation and immunotherapies may offer enhanced outcomes compared to their individual applications.

Radiotherapy, with its ability to be delivered throughout the body, has the potential to address areas of immune privilege, where the immune system may not be as active. Immunotherapies, effective in settings with less bulky disease, could benefit from radiation's ability to target larger tumors, either debulking or eliminating them, allowing the immunotherapy to exert more significant effects on smaller, microscopic sites.

Considerations for patients undergoing immunotherapy reveal challenges, particularly in cases where disease progression is rapid. Radiotherapy emerges as a valuable tool for managing life-threatening disease, ensuring patients can endure the necessary time for immunotherapy to take effect.

Conversely, radiation therapy's limitation lies in its dependence on visualizing the tumor for accurate targeting. Immunotherapy, capable of addressing microscopic disease throughout the body, complements this constraint. Together, they present a promising avenue for comprehensive cancer treatment, capitalizing on each other's strengths.

While there is substantial preclinical evidence demonstrating the impact of radiation on immune susceptibility and the tumor microenvironment (TME), comprehensive investigation into the immunologic effects of radiation in the context of tumors is still underway. Understanding these effects is crucial for effectively harnessing radiation to promote immune responses.

One intriguing phenomenon, the abscopal effect, where radiation to one tumor site induces a response in distant sites, has been observed, albeit rarely. The emerging concept of the *in situ* vaccine effect of radiation is captivating, wherein radiation transforms a treated tumor into a personalized vaccine against cancer elsewhere in the body. While challenges remain, ongoing research aims to optimize this effect and explore strategies for activating it reliably in patients.

Efforts to enhance the immunobiology of radiation involve addressing potentially detrimental effects on the TME. Targeting specific cell lineages that may contribute to suppressive environments, especially following radiation, offers a potential avenue for refining the synergistic effects of combined radio-immunotherapy.

CLINICAL CONSIDERATIONS AND INTEGRATION

It is crucial to emphasize the need for increased investment in research for radiotherapy plus immunotherapy. Testing is the

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key, and this necessitates comprehensive preclinical evaluations.

A noteworthy opportunity lies in exploring our approaches in companion canine species. This involves providing free treatment to pet dogs afflicted with cancer, an unfortunate situation where treatment is often unaffordable. This could potentially offer a more clinically relevant model compared to traditional mouse models.

Engaging with this canine population allows a better understanding before transitioning to the clinic, ensuring that only the most promising approaches are advanced. However, the subsequent step requires meticulous clinical investigation.

The importance of collaboration becomes apparent when we strive to involve expertise from both preclinical research and clinical trials. This collaborative approach is instrumental in identifying the right patient populations, designing appropriate clinical endpoints, and establishing pertinent core pathologic endpoints. Understanding the molecular and cellular dynamics, whether the study shows a clinical effect or not, is equally crucial. This comprehension guides our subsequent efforts, allowing us to refine our strategies.

The overarching goal of research extends beyond assessing whether a treatment benefits the patient, it also aims to discern the molecular and cellular responses. In instances where the treatment does not yield the expected results, it is imperative not to prematurely discard these concepts. Instead, there should be considerations for adjustments to dosing or other parameters. This nuanced approach ensures that potential therapies are not dismissed prematurely, allowing for their refinement based on thorough clinical correlate data.

Designing effective clinical trials poses a significant challenge, and it is crucial to acknowledge this reality. An unfortunate but notable observation is that many clinical trials do not lead to revolutionary advancements in cancer care. However, these trials represent essential, incremental steps in the iterative process of developing transformative trials.

To achieve this, it is imperative to incorporate a robust scientific component into the trial design. This ensures a comprehensive understanding not only of the clinical outcomes, but also of the molecular, cellular, and immunologic levels.

Recognizing the complexity of radiation as a tool, there is still much to learn about its effective utilization in conjunction with immunotherapies. The field finds itself at a crucial juncture, necessitating significant consideration of factors such as patient selection, radiation type, and target locations, incorporating the evolving wealth of data to optimize these approaches.

While acknowledging gaps in our understanding and the potential for unforeseen challenges, the key lies in building on observed phenomena. Opening trials that strategically deliver radiation to immune-suppressive locations, utilizing dose heterogeneity, and considering timing relative to immunotherapy are steps towards refining our approach.

Hypofractionated courses of radiation may prove more effective in combination with immunotherapy, though ongoing research is needed to fully grasp these dynamics. Early phase studies, meticulously examining both clinical and biologic immunologic signals, pave the way for appropriately powered clinical studies that can elucidate benefits.

It is essential for the clinical science community and patients alike to appreciate that the absence of proof is not proof of absence. The complex interplay between radiation therapy and immune checkpoint blockade requires careful consideration, patience, and continuous scientific assessment.

Looking beyond the current landscape, future directions involve not only combined radiation with immune checkpoint blockade, but also exploring additional components of immunotherapy tailored to enhance favorable effects or mitigate detrimental ones. For instance, ongoing work on CAR-T cells highlights the need for nuanced approaches

depending on the specific goals and mechanistic interactions with radiation. This understanding informs the design of preclinical and clinical studies, ensuring that radiation is utilized optimally to demonstrate its potential therapeutic effects.

RADIOPHARMACEUTICALS TO ADVANCE COMBINATION THERAPIES

Currently, the clinical role of radiopharmaceuticals in combination therapies has not been clearly defined or established to show a distinct benefit over sequential monotherapy approaches. This is a common trajectory in drug development, where monotherapies are typically evaluated first before exploring combination approaches. However, there is significant potential for radiopharmaceutical combinations, and there's reason to believe that they may exhibit enhanced efficacy when used in tandem with other therapies.

This expectation is rooted in a mechanistic understanding of how radiopharmaceuticals may impact the tumor or TME, potentially facilitating the activity of other agents and vice versa. Two specific areas with substantial research activity and promising potential are the combination of radiopharmaceuticals with agents targeting DNA damage repair, whether they be chemotherapeutics or molecular targeted therapies.

One compelling aspect of combining radiopharmaceuticals with agents targeting DNA damage repair is the temporal factor involved in radiation distribution. This creates an opportunity to use radiosensitizers and predominantly affect the tumor rather than off-target normal tissues. Unlike external beam radiation, where the dose is delivered instantaneously to both the tumor and surrounding normal tissues, radiopharmaceuticals often have off-target effects on organs involved in excretion or distribution. By strategically timing the delivery of a radiosensitizer after the drug has cleared from off-target organs, one can sensitize the tumor to radiation while minimizing effects on normal tissues, presenting a unique opportunity for research and potential clinical trials.

Another area of exploration involves combining radiopharmaceuticals with immunotherapy. Radiopharmaceuticals, due to their impact on tumor cells and the TME, have the potential to influence responses to immunotherapy. While the complex radiobiology and immunobiology of radiopharmaceuticals require extensive research, there is an opportunity to leverage molecular targeting of immunotherapies to shift the balance between immunogenic and immune-suppressive effects. This could lead to using immunotherapies to enhance the immunologic effects of radiopharmaceuticals or vice versa, offering another avenue of significant potential.

In terms of current practice, these combinations remain experimental. However, there is hope that careful research and investigation will reveal their potential benefits. It is essential to manage expectations and recognize that the enthusiastic exploration of these combinations must be grounded in thorough scientific inquiry. The path toward establishing the efficacy of these combinations will likely take years of meticulous research to ensure their safety and effectiveness are well-understood.

LOOKING TO THE FUTURE

The overall goal is to witness more consistent successes in the treatment of cancer patients with metastatic disease. Ideally, the aim is for outcomes where either patients are cured, or they have access to a sufficient number of therapeutic options to manage their disease over many years, akin to a chronic condition. While strides have been made in this direction, there still is a substantial need for further progress to achieve our overarching goals.

The areas of significant interest are those involving the activation and development of the patient's own immune response. Immunotherapy, based on this immune-driven response, stands out as a promising avenue. The dynamic nature of the immune

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response evolving over time in tandem with the patient's tumor offers a unique advantage. Traditional approaches often face challenges due to the diverse nature of tumor cells, leading to resistance. In contrast, an active immune response exhibits adaptability over time. As we deepen our understanding of the molecular and cellular foundations of anti-tumor immune responses, there is a vast opportunity for continual enhancements in the treatment of metastatic disease.

The ability to reactivate an immune response against a tumor multiple times provides optimism for managing cancer as a chronic condition or achieving curative outcomes. However, it is essential to acknowledge that potent immune responses may have off-target effects on normal tissues, resulting in severe autoimmune side effects. Addressing and improving the management of these toxicities will be critical for enhancing the overall quality of life for patients undergoing such treatments.

The path forward involves embracing combination approaches. While testing agents in monotherapy makes sense initially, a more efficient and effective long-term strategy involves exploring combination therapies. With each new agent, the therapeutic toolbox expands, and it becomes increasingly likely that these agents will show improved efficacy in combination or target mechanisms that only manifest in conjunction with other agents.

Encouraging and empowering studies that focus on combination therapies will be pivotal to moving away from a singular drug approach and addressing the inherent complexity of cancers through simultaneous targeting of multiple mechanisms. These hold the promise for considerable progress in the future of cancer treatment.

BIOGRAPHY

ZACHARY MORRIS is an Associate Professor and Vice Chair of the Department of Human Oncology at the University of Wisconsin School of Medicine and Public Health. He completed undergraduate studies at Ripon College and two masters' degrees as a Rhodes Scholar at Oxford University before obtaining his MD and PhD from Harvard Medical School. He completed a residency in Radiation Oncology at the University of Wisconsin. Clinically he specializes in the treatment of patients with melanoma and sarcomas. His research laboratory has been examining the mechanisms of therapeutic interaction between radiation therapies and immunotherapies. A prior recipient of the NIH Director's Early Independence Award, he has been co-PI of an NIH Cancer Moonshot Initiative U01 and an NIH P01. He serves as co-Chair of the NIH/NCI Radio-Immunotherapy Working Group.

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IMMUNO-ONCOLOGY INSIGHTS

COMBINATION THERAPY DEVELOPMENT

SPOTLIGHT

INTERVIEW

Developing novel radioimmunotherapy combinations for lung cancer treatment

Lauren Coyle, Commissioning Editor, *Immuno-Oncology Insights*, speaks to **Joe Chang**, Clinical Thoracic Oncologist, MD Anderson Cancer Center, University of Texas, who discusses his team's pioneering work in combining radiation therapy with immunotherapy for lung cancer treatment. He highlights the challenges and promises of optimizing radioimmunotherapy combinations, emphasizing the importance of personalized treatment approaches and collaboration across disciplines to improve patient outcomes.

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Q Can you provide a brief overview of your background and experience in the field of combination radioimmunotherapy, and what sparked your interest in this area?

JC: I am a physician-scientist focused on clinical research. I have a medical degree, a PhD in Cancer Biology, and a MSc in Immunology. For the past two decades, I have worked

as a radiation oncologist for lung cancer. As we all know, immunotherapy is changing the landscape of lung cancer management.

As a radiation oncologist, I have seen how evolving technology has changed the way we treat lung cancer. We can now deliver much higher doses for lung cancer, improve local control, and minimize toxicity more than ever. The question now is how we combine these two modalities to improve patient outcomes. This is why I began paying attention to lung cancer immunotherapy treatment and started to think about combining this with radiation therapy. I am one of the pioneers of stereotactic radiation therapy for lung cancer, specifically early-stage lung cancer.

Stereotactic radiation therapy for lung cancers achieves high local control of ≥95%. However, cancer can still recur in a different region after treatment. To reduce the recurrence of secondary lung cancer, I began working on combining this treatment with immunotherapy. The goal now is to explore these combinations for stage 3 and 4 lung cancers.

Q How do you approach the selection of specific radioimmunotherapy combinations, and what factors do you consider in designing these protocols?

JC: Immunotherapy for lung cancer began as a treatment for stage 4 lung cancer, for which it has shown promising impacts on progression-free survival and overall survival. Gradually, our focus has turned to stage 3 lung cancer. PACIFIC study with concurrent chemoradiation therapy followed by adjuvant immunotherapy for stage 3 lung cancer significantly improves progression-free survival and overall survival. This treatment achieves 43% 5-year survival, marking an important milestone for lung cancer.

Now, we want to move into early-stage lung cancer. Historically, some people have felt that immunotherapy may have less of an impact here in terms of clinical outcomes. I do not agree with this idea because we have such great local control, so immunotherapy may help improve clinical outcomes. If immunotherapy takes care of other recurrences such as regional, distant, or even secondary malignancies, the outcome could be even better. This is why we decided to use a combination of immunotherapy with stereotactic radiation therapy in early-stage lung cancer.

Q What are the current challenges associated with radioimmunotherapy, considering potential synergies and conflicts between these treatment modalities, and what promises are there to overcome these?

JC: The greatest challenge is in the optimization of combinations. One plus one does not necessarily larger or equal two when you combine two modalities. Toxicity can increase in this way, but efficacy-wise, optimization is critical to achieve the outcome that you want. In the literature for stage 3 lung cancer, the PACIFIC study is promising and has shown outstanding outcomes. However, in PACIFIC-2, concurrent immunotherapy with chemoradiotherapy did not show improved results for stage 3 lung cancer. The data published for stage 4 disease has been mixed, with some showing an improved clinical outcome and some showing

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"As a radiation oncologist, I have seen how evolving technology has changed the way we treat lung cancer. We can now deliver much higher doses for lung cancer, improve local control, and minimize toxicity more than ever."

no improvement, particularly the recently published randomized studies. The question now is how to optimize the combination.

I am a believer that radiation therapy is not just a single drug. Its effects depend on the dose, the treatment regimen, the indication site, biology, and stage, as well as the patient's immunological background. It is critical that all these factors are considered for us to develop an optimized combination of immunotherapy and radiation therapy.

Q Can you share insights into how combination therapies have impacted patient outcomes in your research?

JC: We combine programmed death-ligand 1 immunotherapy with stereotactic operative radiation, which is also known as stereotactic ablative radiotherapy therapy (SABR), in early-stage lung cancer. SABR has been the standard of care for medical inoperable early-stage lung cancer and has been shown to have better overall survival and progression-free survival compared with previous standard forms of radiation treatment. However, 30% of patients recur either distantly, regionally, or experience a secondary lung cancer, at roughly 2–3% per year.

We want to reduce that recurrence. We published data on SABR +/- immunotherapy last year in *The Lancet,* which showed event-free survival was significantly improved with an impressive hazard ratio of 0.38. This is the first time that published data has shown that immunotherapy combined with SABR works well in early-stage lung cancer. As mentioned, historically people have doubted whether immunotherapy could be helpful at all for early-stage lung cancer. Our paper is the first published study to prove that it works.

Q Collaboration is often essential in research. How do you collaborate with other professionals to enhance the effectiveness of combination therapies?

JC: We are experts in radiation therapy, but we work closely with medical physicists to develop novel technology like stereotactic radiation therapy, tumor motion management, and particle therapy. We also work closely with our medical and surgical oncologist, immunologist, and biologist colleagues, who all contributed to our paper published in *The Lancet*. Currently, we are collaborating with immunologists to develop bio or immunological markers to guide our individualized treatment.

We also work with AI experts to develop modeling to identify the patients who will benefit the most from immunotherapy and who may not need immunotherapy. For early-stage lung

cancer, about 50% of patients never recur after SABR. This group does not need immunotherapy, and as immunotherapy is expensive and not without toxicity, we want to minimize the number of patients who receive it. To identify them, we work with our AI and immunologist colleagues to develop modeling for this individualized approach.

Q How do you stay updated on the latest advancements in the field and integrate these into your research?

JC: Our goal is to set a new standard of care for using immunotherapy and radiation therapy in early-stage lung cancer and extend it to metastatic disease. To do this, we need to use the lessons learned from work in stage 1 and stage 3 cancers and apply these to our work in stage 4. Currently, the positive randomized study data for combined immunotherapy and radiation therapy comes from stage 1, 2, and 3 cancers. For stage 4 lung cancer, the data is still quite controversial. Some data reports positive results while some data reports negative results, although these are all smaller randomized studies.

The key lesson we learned from stages 1–3, in my view, is that we needed to deliver a comprehensive ablative dose or definitive dose to maximize both the immuno-stimulation effect and the cytoreduction effect of radiation therapy. We know the cytoreduction effect by itself is important for curing cancer to reduce the tumor burden and release the immunosuppression for stage 4 lung cancer. We should further explore validating the concept of the ablative/definitive dose combined with immunotherapy, whenever possible, for stage 4 lung cancer. Much more work needs to be done for lung cancer and of course other types of cancer too.

Q What are the key goals and priorities for your work in the upcoming years?

JC: This year we are working to develop AI modeling and biomarkers to guide individualized treatment. We are developing AI modeling combined with clinical, radiomic, and biomarker features to help make predictions for individualized treatment.

This way, in the future, patients will be assessed for clinical, radiomic, and immunological features to help us decide who needs immunotherapy and who does not. We are also applying the concept of developing individualized treatment for stage 4 lung cancer, with combined radiation therapy plus immunotherapy.

Q Lastly, what is one piece of wisdom you would like to share with the field at large?

JC: Most people consider radiation therapy to be a single drug that either works or does not. However, as radiation oncologists, we know that different doses of radiation therapy using different techniques to treat different patients with different histology and immunostatus lead to different efficacies and toxicities. We should not view radiation therapy as a simple drug; it is a diverse drug that highly depends on the clinical setting, like immunotherapies or

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chemotherapies. If for one type of cancer, one kind of radiation dose does not work, this does not mean that radiation does not work. It is still worth exploring other settings and situations.

BIOGRAPHY

JOE CHANG holds a tenured Texas 4000 Distinguished Professorship at the MD Anderson Cancer Center. He is honored as Fellow of American Society of Radiation Oncology (ASTRO) and Fellow of American College of Radiology (ACR). He has also been recognized with the Best Doctors of America award. He is a voting committee member of NCCN thoracic guidelines, Board Director of International Association for the Study of Lung Cancer (IASLC) and Clinical Scientific Program Chair for Particle Therapy Cooperative Group (PTCOGF). As one of the pioneers in the field of stereotactic ablative radiotherapy (SABR), proton therapy and immunotherapy for lung cancer, he has published more than 300 peer-reviewed articles in prestigious journals, including *The Lancet*, *Nature*, *JAMA*, *Journal of Clinical Oncology*, *Journal of Thoracic Oncology*, and various others.

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We hope you enjoyed reading this interview.
You can also listen to the recorded podcast here:

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COMBINATION THERAPY DEVELOPMENT

SPOTLIGHT

INTERVIEW

The evolving landscape of combination therapies in lung cancer

Lauren Coyle, Commissioning Editor of *Immuno-Oncology Insights*, speaks with **Heather Wakelee**, Chief of the Division of Oncology at Stanford University, about the advancements on lung cancer treatment with targeted therapies and immunotherapy combinations. Their conversation also covers notable clinical trials with CTLA-4, TIGIT, and ADCs and the best strategies to optimize personalized medicine.

Immuno-Oncology Insights 2024; 5(2), 57–63

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Q Can you briefly describe your career so far and what you are currently working on?

HW: I have been taking care of lung cancer patients for over two decades, starting from the era of limited chemotherapy options and progressing into targeted therapy. Currently, we are excited to have immunotherapy as an additional option for our patients. Throughout my career, I have been involved in a variety of areas of research, but

a recurring theme has been exploring treatments effective in metastatic disease and adapting them for patients diagnosed with earlier stages of the disease.

My focus includes investigating whether chemotherapy can improve outcomes both before and after surgery and explore the possibility of incorporating other novel agents. While some past trials with chemotherapy did not yield positive results, current research predominantly involving immunotherapy—examining its effectiveness after surgery or in combination with chemotherapy before surgery has demonstrated clear improvements in survival. While this has been a major focus, I am also actively engaged in research with targeted therapy agents, spanning from earlier stages to advanced stages of the disease and recent trials with targeted agents given after surgery have also been positive.

Q In what ways have recent advancements in combination therapies contributed to the progress of treatment options and strategies, specifically for lung cancer?

HW: When discussing the use of immune checkpoint inhibitors (ICIs), we primarily refer to programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) targeted agents. These agents have demonstrated particular effectiveness in tumors exhibiting elevated levels of PD-L1 expression and lacking a driving mutation. However, for patients with driver mutations, efforts have been made to combine targeted therapies with immunotherapy, but results have shown increased toxicity. This emphasizes the distinction between these approaches as addressing different diseases.

When discussing with my patients, I emphasize that their diagnosis might involve treatment with chemotherapy, and especially if their cancer is associated with a driver mutation, a range of options with targeted therapies. Alternatively, if no targeted mutation is present, immunotherapies, specifically ICIs, become a viable option alone or frequently in combination with chemotherapy. For instance, for a patient with a tumor with high PD-L1 expression, particularly in individuals with a history of smoking-induced lung cancer, immunotherapy can be highly effective. To improve efficacy, we are also exploring combining ICI agents.

Chemotherapy remains a compelling option in cases with no or low PD-L1 expression on the tumor and combining it with ICIs has shown promising results. Notably, cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors, a distinct type of ICI, when combined with PD-1 or PD-L1 therapies, have demonstrated exciting outcomes. These combinations show promise, including in scenarios where the PD-L1 biomarker is absent, indicating potential efficacy when single-agent ICI therapy may not work.

In addition to these developments, exploration of other agents such as those that target other immune targets such as T cell immunoreceptor with Ig and ITIM domains (TIGIT) and lymphocyte-activation gene 3 (LAG-3), have revealed hints of activity, though progress has been slower compared to cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors and not as rapid as PD-1 or PD-L1 ICIs in conjunction with chemotherapy.

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"Combining different agents tends to increase toxicity, and with certain ICI combinations, this heightened toxicity can be particularly profound."

More recently, there has been promising data emerging from the use of antibody–drug conjugates (ADCs). These drugs are a combination of chemotherapy and incorporate an immune component through their linkage with an antibody. Their single-agent activity is somewhat superior to chemotherapy, particularly in cases lacking a clear biomarker. However, their combinations with ICIs have shown considerable promise, presenting another area of excitement and exploration.

Q Further to that, what challenges have arisen from this and how can these be effectively tackled in the future?

HW: Initially, when we observed compelling data with PD-1 and PD-L1 inhibitors, there was a sense that we had cracked the code. There was an anticipation that subsequent ICIs would follow suit, leading to a sequence of breakthroughs that could revolutionize cancer treatment. The initial ICIs have made a huge impact in care, but unfortunately, the reality proved to be more complex in regard to the next steps. Developing effective alternative ICIs has proven to be a considerable challenge. This challenge is compounded by the difficulty in identifying biomarkers associated with these inhibitors and their activity.

Additionally, there is the issue of toxicity, especially when combining ICIs. Combining different agents tends to increase toxicity, and with certain ICI combinations, this heightened toxicity can be particularly profound. This presents another critical area that requires careful consideration moving forward.

Q Can you discuss any notable clinical trials that have investigated the effectiveness of these combination therapies and their key outcomes?

HW: Combinations involving CTLA-4 and PD-1 drugs, specifically nivolumab and ipilimumab, as well as durvalumab and tremelimumab have emerged as particularly exciting, with more mature data highlighting their effectiveness. Notably, in the case of nivolumab and ipilimumab, and durvalumab and tremelimumab, we have observed promising outcomes. Of particular note is the efficacy seen with the combinations in patients

with tumors with low PD-L1, a group where the PD-1 and PD-L1 checkpoint inhibitors used alone are not usually active. This development has been particularly exciting.

Additionally, in more recent trials involving several ADCs, we are witnessing encouraging data. Although we have not yet reached definitive results that would mark a practice-changing milestone, the outcomes thus far are promising and warrant attention. These combinations hold potential for reshaping treatment approaches.

In the realm of newer drugs such as TIGIT and LAG-3, preliminary indications from Phase 2 and Phase 3 data are emerging. However, we are still awaiting conclusive results to further inform our understanding of their effectiveness and potential impact.

Q Given the complexity and the expense of combination trials, how can resources be best deployed to maximize efficiency and success in clinical development?

HW: It is crucial to maintain a steadfast focus on finding biomarkers. Recognizing the diversity within lung cancers is essential; the notion of a universal treatment applicable to all was a dream from the chemotherapy era, and we have progressed beyond that. Rather than opting for a one-size-fits-all approach, it is vital to refine our understanding of which groups benefit most from a particular treatment. Instead of broadly administering a treatment that works best for a specific subgroup to everyone, we should identify and prioritize the groups where it is most effective.

The ongoing emphasis on biomarker development is imperative, although we acknowledge its inherent challenges. Particularly with ADCs, where we understand the target of the antibody, correlating the levels of that specific target with responses is not always straightforward. Despite these challenges, the realization is that not every treatment is universally effective. Our continued efforts should focus on discerning the scenarios in which various agents prove effective, determining the need for combinations, and understanding that each new agent introduces additional toxicity. The main goal is to ascertain the minimum necessary intervention to achieve the best possible outcome for each individual patient.

Q Do you think that the work we are seeing in biomarkers can lead to more personalized medicines and will this have an improved impact?

HW: The trajectory in lung cancer treatment is increasingly moving towards maximizing personalization. This is evident in cases where we can identify driver mutations and employ targeted therapies, not only for the initial treatment but also for addressing resistance mechanisms with other targeted therapies.

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"We have already made great strides with targeted therapy with personalization and are moving there with immune-based approaches."

However, in the realm of immunotherapy, our understanding of the immune system remains incomplete. Despite the simplified belief that high PD-L1 expression guarantees efficacy, it does not consistently deliver optimal results. The complexity becomes even more evident with the variable responses observed in patients to CTLA-4 and PD-1 combinations, which do not always correlate neatly with expected outcomes. The challenge persists in determining biomarkers for emerging treatments like those targeting TIGIT, LAG-3, and most classes of ADCs, and progress in this area has been challenging.

The potential for true personalization lies in deciphering these intricate biomarkers. It is not always a straightforward correlation with the anticipated target, but rather an exploration of other pathways or unique aspects of the patient's metabolism and tumor biology. The more we can unravel these complexities and identify reliable biomarkers, the closer we come to achieving a level of personalization that can significantly improve the impact of cancer treatments. We have already made great strides with targeted therapy with personalization and are moving there with immune-based approaches.

Q How do you navigate the integration of different modalities such as ICIs and ADCs, to achieve optimal therapeutic outcomes?

HW: The key lies in tailoring the approach for each individual patient, aiming to identify the combination that minimizes toxicity while maximizing efficacy. Typically, the assessment involves weighing efficacy against toxicity, but it is also crucial to consider the patient's simultaneous concerns about both aspects. Navigating this terrain becomes particularly challenging when dealing with a newly diagnosed adenocarcinoma of the lung, lacking a driver mutation, and featuring a PD-L1 level that is neither very low nor very high (i.e., 1–49%). The array of available options can be overwhelming, making it difficult to determine the most effective strategy.

Cost considerations also come into play on the list of evaluations. Although this aspect may not be as prominent in the US due to insurance coverage, it remains a significant consideration. The ensuing discussion with the patient entails presenting the available options, discussing the likelihood of effectiveness, potential toxicity, associated costs, and outlining the treatment schedule. Patients harbor varying aversions to different toxicity risks, further complicating the decision-making process. Engaging patients in these discussions is paramount due to the intricate and multifaceted nature of the decision-making process.

When considering immune therapies, ADCs, and antibodies, it is crucial to recognize that an ADC is essentially a refined form of chemotherapy. This refined form demonstrates efficacy,

especially when combined with immune therapy. Determining its utility in other contexts requires careful consideration. While PD-L1 levels serve as a biomarker for PD-1/PD-L1 ICI effectiveness, it is far from a perfect biomarker. The decision-making process involves gathering as much information as possible about the tumor, the individual's metabolism, and tolerance, and understanding the patient's preferences regarding the associated risks of various therapeutic approaches.

Q How do you envision the evolving landscape of combination therapies contributing to the overall success of immunotherapy in the long run?

HW: With only a small percentage of patients experiencing long-term responses to single-agent PD-1 or PD-L1 ICIs, the remaining majority require more than a singular drug. Understanding the dynamics of combinations and developing the ability to discern which patients will benefit most from specific combinations is crucial.

Combinations involving CTLA-4 may show potential, particularly in cases with lower PD-L1 expression, but as mentioned, it comes with a higher risk of toxicity. Chemotherapy is recognized as a beneficial additive, and there is ongoing exploration into the potential superiority of ADCs, though conclusive evidence is still pending.

The key lies in delving deeper into biomarkers, gaining a more comprehensive understanding of how different combinations interact with the unique factors inherent to both the individual patient and their specific tumor. This evolving landscape holds the promise of tailoring therapies more precisely, ensuring that the chosen combination is genuinely the best fit for each individual based on their distinct characteristics.

Q Finally, what are your key goals and fears for the next few years?

HW: The ultimate goal is to reach a point where we can effectively cure lung cancer. However, concerns arise where numerous agents, although relatively similar, consume substantial resources—both financial and in terms of patient engagement. The competition among pharmaceutical companies to establish drug superiority for market share can potentially divert focus from genuine innovation and hinder progress in understanding the intricacies of optimal treatment strategies.

The shift towards personalized medicine and identifying the best biomarker for each individual patient is vital. Rather than pursuing a one-size-fits-all approach, the emphasis should be on uncovering innovative solutions tailored to individual patient needs.

Despite these concerns, there is significant potential for progress. The current era is undeniably exciting, especially when compared to the earlier stages of lung cancer treatment, where chemotherapy was the primary option. Now, we are delving into the specifics of each patient's

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cancer, exploring driver mutations, assessing the potential of immune therapy, and devising strategies to enhance its effectiveness. The landscape is dynamic, and the opportunities for advancement are substantial.

BIOGRAPHY

HEATHER WAKELEE is a Professor of Medicine and Chief of the Division of Oncology at Stanford University and Deputy Director of the Stanford Cancer Institute. She is past President of the International Association for the Study of Lung Cancer (IASLC) and is a Fellow of the American Society of Clinical Oncology (FASCO). Wakelee graduated from Princeton University and Johns Hopkins University School of Medicine and has been at Stanford University since internship. As an experienced investigator, Wakelee has authored or co-authored more than 300 medical articles on lung cancer and thymic malignancies and is involved in dozens of clinical trials involving adjuvant therapy, immunotherapy (particularly use of immunotherapy in the perioperative setting for NSCLC), and anti-angiogenesis agents. Her research additionally is focused on many specific lung cancer subtypes defined by mutations in genes such as *EGFR*, *ALK*, *ROS1*, *RET*, *BRAF*, as well as broad translational efforts.

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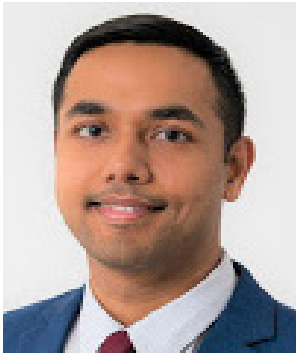
COMBINATION THERAPY DEVELOPMENT

SPOTLIGHT

INTERVIEW

Advancing combination therapies: a discussion on trials, challenges, and future goals



Lauren Coyle, Commissioning Editor of *Immuno-Oncology Insights,* speaks with **Aakash Desai,** Medical Oncologist, O'Neal Comprehensive Cancer Center at UAB, about the advancements in I-O combinations and the challenges with trial design, biomarker integration, and managing synergistic toxicities.

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Q Can you tell us a bit about your career so far and what you are currently working on?

AD: My journey in medical oncology began with my fellowship training at Mayo Clinic in Rochester, where I developed a keen interest in drug development and thoracic oncology. Throughout my first year of training, I naturally gravitated towards these areas and received focused training in both aspects.

My work has primarily revolved around immunotherapies and immuno-oncology, particularly in the context of thoracic malignancies. Since completing my training, I have had the

privilege of assuming a faculty role, where I now mentor students. Mentorship has played a pivotal role in my personal career growth, and I believe it is now my turn to give back.

There is a lot of excitement in the oncology field with many young minds expressing interest. I hope to provide them with guidance similar to what I received at their stage, hopefully shaping their careers and futures positively.

Q How have recent IO combination developments helped to advance treatment options or strategies for thoracic cancer?

AD: Over the past decade, the introduction of PD-1/PD-L1 immune checkpoint inhibitors (ICIs) has brought about significant outcomes for patients with non-small cell lung cancer. Initially, most data were observed in metastatic or advanced cancer stages, however, these benefits are now being incorporated into the early-stage setting as well.

Despite these positive developments, it is essential to acknowledge that not all patients respond to these treatments. This highlights the need to explore novel therapies with one aspect being the exploration of combinations with ICIs. Beyond PD-1/PD-L1, researchers are investigating other immune checkpoints in lung and thoracic cancers, such as CTLA-4, LAG-3, TIM-3, TIGIT, and various molecules. These combinations aim to enhance the effectiveness of current immunotherapies and improve outcomes for patients with thoracic malignancies.

In a recent review, we assessed the landscape of novel immune checkpoint targets and different molecules. This is an exciting aspect of the field, with researchers actively seeking the next frontier and aiming for advancements comparable to, if not surpassing, the strides made in the last decade with PD-1/PD-L1 checkpoint inhibitors.

Q Further to that, what challenges have arisen in this space, and how could these be tackled moving forward?

AD: As I mentioned, the plethora of novel ICIs and targeted molecules presents a unique challenge—determining the optimal approach and identifying the right patient for the right treatment at the right time. The most challenging aspect lies in refining our approaches by utilizing biomarkers to help identify potential treatments that are likely to elicit a response.

This challenge extends beyond biological considerations; it also poses logistical difficulties. Designing clinical trials now requires the inclusion of more biopsies to test these biomarkers, creating challenging situations within the context of clinical care for patients.

Moving forward, addressing these challenges may involve leveraging alternative approaches beyond standard pathological methods. Incorporating technologies like multiplex immunohistochemistry and exploring multiomics platforms, including RNA sequencing and proteomics,

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"...trial designs must be tailored for real-world applicability, ensuring a seamless transition to the patients we serve."

could prove beneficial on two fronts. Firstly, some of these approaches are already part of our clinical workflow, potentially easing the logistical barriers. Secondly, these technologies operate at a more profound level than current techniques, offering the potential to provide answers that elude us now.

Q There has been a rise in clinical trials for combination immunotherapy and traditional chemotherapy. What are the key considerations for optimizing trial design, and what unique challenges do these pose?

AD: The landscape is witnessing a significant number of combination immunotherapy trials and the primary consideration for these lies in identifying optimal combinations. As mentioned, incorporating a biomarker-based clinical trial design could play a pivotal role in the field. Trials must move towards being more reflective of real-world scenarios to become less burdensome for patients, clinical trial staff, investigators, and regulatory bodies alike.

To achieve this optimization, trial designs must be tailored for real-world applicability, ensuring a seamless transition to the patients we serve. However, to navigate this transition, certain challenges need to be addressed to shift from the norm. Implementing these changes is crucial for optimizing trial designs, and some of these adjustments are already underway. In the coming years, we hope to witness trials that more accurately represent real-world patients and utilize techniques mentioned earlier to identify the patients most likely to benefit from these combination treatments.

Q Can you discuss safety considerations and approaches being taken during these trials to minimize the risk of synergistic toxicity in patients?

AD: While PD-1/PD-L1 ICIs have proven highly efficacious, they do come with immune-related adverse events (irAEs) that we have learned to manage effectively. As we examine adding various other molecules or drugs to the existing landscape of immunotherapies, there is a legitimate concern regarding synergistic toxicities.

Many of these new molecules represent novel targets, and we are still in the process of understanding both on-target, off-target and off-tumor toxicities associated with them. To address

"...equipping ourselves with enhanced management strategies for known toxicities will better prepare us to design trials that are safer for our patients."

this, there must be an enhancement of our proficiency in managing the baseline toxicities associated with PD-1/PD-L1 ICIs. By refining our understanding and developing improved guidelines and algorithms for these known toxicities, we can establish a foundation to minimize potential irAEs when testing new molecules with unknown profiles.

While some level of synergistic toxicity may only become apparent during trials, equipping ourselves with enhanced management strategies for known toxicities will better prepare us to design trials that are safer for our patients. This proactive approach ensures that the trials conducted are well-informed where patient safety remains the main consideration.

Q Are there any promising novel tools or biomarkers that could be used in trials to gauge combination therapy development, specifically with ICIs in thoracic cancer?

AD: A biomarker-based approach is crucial for the development of immunotherapy in thoracic cancer and incorporating tools beyond traditional immunohistochemistry is essential. Exploring techniques such as RNA sequencing, proteomics, and other advanced technologies can provide a molecular-level understanding of the expression of novel ICIs on cancer cells. This would allow for the identification of specific overexpressed proteins in certain cancers, leading to tailored treatments based on individual patient profiles.

Being intentional and selective in our therapies by identifying cohorts of patients who are most likely to benefit maximally is significantly important for combination therapy development. This approach ensures that we move beyond a one-size-fits-all paradigm, offering more personalized and effective treatment strategies in clinical trials.

Q Lastly, what are your main goals and aspirations for the future, both in terms of your career and for your research?

AD: From a career perspective, my primary goal is to play a significant role in shaping the next frontier of immunotherapy and the development of antibody-based molecules. With the emergence of ADCs, bispecific antibodies, and various other innovative technologies, I aspire to be at the forefront of conducting impactful clinical trials for my

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patients. My focus lies in understanding the mechanisms of these molecules and their impact on treatment outcomes.

From a research standpoint, my goal is to advance biomarker-based approaches for trial design while making clinical trials more reflective of real-world scenarios, ensuring practical enrollment of patients, and making a tangible impact on their care and outcomes. My main aspiration is to bridge the gap between research and pragmatic, patient-centered advancements in cancer treatment.

BIOGRAPHY

AAKASH DESAI serves as an Assistant Professor of Medicine at the O'Neal Cancer Center, University of Alabama at Birmingham, specializing in thoracic oncology and experimental therapeutics. His expertise spans evidence-based oncology, clinical trials, novel drug development, and improving cancer care quality. Desai embarked on his medical journey at BJ Medical College, India, followed by a master's in public health from the University of Texas Health Science Center, Houston. His postgraduate training includes a residency in internal medicine at the University of Connecticut and a fellowship in oncology and hematology at Mayo Clinic, Rochester. Desai's significant contributions to medicine are recognized through numerous awards, such as the Conquer Cancer Foundation ASCO Young Investigator Award and the International Association for the Study of Lung Cancer Early Career Award, among others. His dedication to patient education and advocacy is evident in his role as a patient education ambassador for the Cancer GRACE Foundation. Focused on lung cancer and mesothelioma, Desai is committed to advancing cancer treatment through research on novel drugs, addressing health disparities, and enhancing the quality of cancer care. His work epitomizes a blend of clinical excellence and a profound commitment to patient well-being.

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COMBINATION THERAPY DEVELOPMENT

SPOTLIGHT

INTERVIEW

Combination therapies: a journey into personalized vaccine immunotherapeutics for early-stage cancers

Lauren Coyle, Commissioning Editor, *Immuno-Oncology Insights*, speaks with **Stephen Johnston**, CEO, Calviri, about the shift in the I-O space to preventative treatment in combination for early-stage cancers.

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Q Can you tell us a bit about your career and what you are working on right now?

SJ: The company that I head, Calviri, is focused on a project I initiated around 20 years ago where the goal is the development of a preventative cancer vaccine. Further, I aim to make conversations about curing cancer irrelevant.

We have been consistently working on this project, and the platform we have created has broader implications for both therapeutic vaccines and diagnostics. We have published extensively in the I-O area, demonstrating our expertise.

My main goal in my career is to create solutions. The cancer field, even two decades ago, appeared stagnant, primarily focusing on treating late-stage tumors with increasingly complex and expensive treatments. Recognizing this as a potential dead end, I observed a worldwide increase in cancer incidence, with 70% of all cancer deaths occurring in low- and middle-income countries. Realizing that most treatments would not reach most affected people, we decided to approach cancer as an infectious disease and develop a preventive vaccine.

Fortunately, there has been good news in this regard. Around 5 years ago, we initiated an 800-dog clinical trial to assess the vaccine. The trial is concluding in May, and the results are clear: the vaccine is effective. We are successfully preventing tumors and tumor-related deaths in healthy dogs. This outcome demonstrates the feasibility of developing such a vaccine.

Q Could you provide an overview of the current landscape of combination immunotherapies, (both I-O/I-O or I-O/other) in early-stage cancers?

SJ: The advent of checkpoint inhibitors, particularly, has revolutionized cancer treatment and our understanding of the interaction between tumors and the patient's immune response. While there have been remarkable successes with immunotherapeutics, especially in achieving cures, their application is starting to plateau with a lower percentage of patients showing response.

Response rates are peaking at around 20%, prompting the exploration of combination therapies to enhance these rates. The concept behind combining I-O therapies with each other, chemotherapeutics, radiation, and other agents led to the initiation of thousands of trials. However, despite some successes, most trials failed, resulting in a limited expansion of the immunotherapeutic space.

A recent apparent success involves combining I-O therapies with vaccines. Reports from Moderna and BioNTech suggest that combining a checkpoint inhibitor with a personalized cancer vaccine can significantly increase response rates and effective therapies. However, these are still personalized vaccines, adding to the already excessive cost of immunotherapy, ranging from US$100,000–300,000 per treatment course. These cost implications may limit the widespread application of such combinations.

Another avenue being explored is the expansion of these therapeutics to early-stage cancers, as most applications so far have been in late-stage tumors. While some late-stage cancers respond well, others, like breast cancer, have responded poorly. There seems to be a biological limitation, and companies are now exploring cancer screening to detect cancers at an early stage.

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"One unexplored possibility is whether vaccines alone could be effective in early-stage cancers, although this remains an open question."

Despite the attractiveness of early cancer detection, current technologies struggle to detect stage one tumors effectively. The idea of using immunotherapeutics at earlier stages, even stage one, faces challenges. Published research indicates that immunotherapy may not add significant benefits to early-stage tumor treatments due to biological reasons, such as fewer neoantigens.

Additionally, these therapeutics come with adverse events, and recent information suggests potential long-term ill effects after prolonged use. Considering the adverse event profiles, pushing immunotherapies into early stages may be challenging, and there is a need for safer alternatives. One unexplored possibility is whether vaccines alone could be effective in early-stage cancers, although this remains an open question.

Q How do the opportunities and challenges differ for combination therapies versus monotherapies?

SJ: The initial hope was that combining a checkpoint inhibitor like Keytruda with another agent, such as PDL-1 or CTLA-4 inhibitors, or even chemotherapy, would enhance responses in specific cancers. For instance, in lung cancer, where certain genotypes and cancer types respond better to a combination of immunotherapy and a drug, there was an increase in the response rate from 20 to 50%. However, such instances are few, and finding effective combinations for different cancers remains a challenge.

Another major challenge is the lack of a reliable method to predict response, leading to the necessity of conducting clinical trials to explore potential combinations. This approach is both costly and time-consuming, with patients undergoing treatments that may prove futile. Despite the widespread belief in the transformative power of AI, a definitive formula for predicting synergistic responses has not yet emerged.

The current approach is essentially trial and error, seeking combinations that might expand therapeutic options. Despite considerable effort, the gains in terms of expanding therapeutics have been limited. Subsequently, there is a new trend emphasizing bispecific or antibody-dependent drugs. These drugs use antibodies not to suppress the immune system but to directly kill cells, offering a potential shift in cancer therapy.

The bispecific approach involves enhancing specificity by incorporating two binding sites on the antibody, making it more targeted to tumors. This specificity allows for the attachment of drugs or even radiation to kill tumor cells. Although promising, the efficacy of bispecific drugs in opening new avenues for cancer therapy remains to be seen.

It is noteworthy, however, that these advancements primarily focus on treating late-stage tumors. While innovative, there is a recurring concern that interventions are occurring after the disease has progressed significantly, resulting in substantial financial costs. Addressing this limitation remains a significant challenge.

Q In your opinion, what are some of the most promising combination approaches for early-stage cancer, and can you explain the hypothesis behind them?

SJ: Addressing early-stage cancer presents a unique challenge as current treatments are predominantly designed for late-stage cases. Traditionally, surgical procedures, radiation, and chemotherapy have been applied to early-stage cancer, but there is a growing inclination to move away from these methods due to their invasive nature. The emphasis is shifting towards early detection, but the question remains whether existing late-stage treatments can effectively transition to early-stage.

Immunotherapeutics, in their current construction, may not seamlessly fit into this space, alone or in combination. However, there is hope that vaccines, designed to work without combination, could be a potential solution. Notably, cancer vaccines have shown safety over the years, even during a prolonged period of failure. If these vaccines prove effective for early-stage treatment, it could be a breakthrough, especially considering their demonstrated safety profile.

One obstacle is that personalized vaccines, which require sequencing the tumor and creating a unique vaccine for each patient, remain expensive and impractical for widespread early-stage cancer treatment. There is a need for alternative, more cost-effective forms of treatment, whether mono- or combination therapies, to address the unique challenges of early-stage cancer effectively.

The hypothesis revolves around finding treatments that align with the early detection trend, moving beyond the conventional invasive approaches, and exploring the potential efficacy of vaccines, while keeping the treatments economically viable for broader application.

Q Further to that, what key challenges have you seen, and what are the promising approaches for solving these?

SJ: For early-stage cases, one of the key challenges lies in the demand for therapeutics, whether they are immunotherapeutics or drugs, to possess exceptionally safe profiles. This is crucial as these treatments will be applied to essentially healthy individuals, and often to a large number of them.

The emphasis has shifted towards prioritizing safety and minimizing side effects more than ever before. In this context, vaccines emerge as the most promising candidates. However, a

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"Predicting responses and adverse events would be invaluable, especially concerning immunotherapeutics."

significant obstacle remains—the personalized nature of current vaccines. Crafting individual vaccines for each patient is both time-consuming and expensive.

A potential solution is to develop off-the-shelf vaccines that individuals can readily access at an early stage. While this approach is not guaranteed to succeed, it presents a viable and practical pathway. The feasibility of this idea is an open question, but if successful, it would represent an ideal scenario for early-stage cancer treatment. The emphasis is on finding solutions that balance safety, accessibility, and effectiveness in the early-stage therapeutic landscape.

Q Are there any areas that should be prioritized to improve measuring response to combination therapies for early-stage cancers?

SJ: Currently, there is a need to enhance both the measurement and prediction of responses to early-stage cancer therapies. Ideally, we would like to conduct individual assays on patients with a tumor and accurately predict which combination or therapy would yield the most effective response, or even foresee potential adverse events.

In an ideal scenario, researchers often envision the most comprehensive solutions and then work towards practical implementation. Predicting responses and adverse events would be invaluable, especially concerning immunotherapeutics. However, at present, there is not a widely adopted, simple method to take a pre-treatment blood sample and predict the patient's response, for example, to a checkpoint inhibitor.

We lack a commercially available solution for this need. Interestingly, we have developed a technology that performs these predictions effectively. Learning from this, for early-stage treatments, it would be beneficial to develop the diagnostic hand-in-hand with the therapeutic, as companion products. This approach could ensure that predictive diagnostics are available and aligned with the therapeutic development, facilitating a more integrated and effective approach to early-stage cancer treatment.

Q Lastly, what are your key goals and priorities for the future?

SJ: Our primary focus is to expedite the commercialization of the preventative vaccine for dogs within our company. Simultaneously, we are eager to advance it into human clinical trials as swiftly as possible. The overarching goal is that in our next conversation,

the dialogue will shift from discussing immunotherapeutics to highlighting vaccines as a groundbreaking approach for cancer prevention.

BIOGRAPHY

STEPHEN JOHNSTON is the current Founder and CEO of Calviri where their goal is to eradicate cancer worldwide. To do so, they are developing therapeutic and preventative cancer vaccines and early-stage diagnostics while testing a preventative cancer vaccine in an 800-dog clinical trial. Johnston has been involved in the creation of a wide range of methods and devices including pathogen-derived resistance, gene gun, DNA vaccines, organelle transformation, TEV system, and immunosignatures. Prior to founding Calviri, Johnston was a professor at Duke University, UT-Southwestern MC and the Biodesign Institute at Arizona State University.

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INTERVIEW

A deep dive into generative AI applications in I-O

André Freitas

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INTERVIEW

A deep dive into generative AI applications in I-O

Lauren Coyle, Commissioning Editor, *Immuno-Oncology Insights*, speaks with **André Freitas**, Senior Lecturer (University of Manchester) and Research Group Leader (Idiap Research Institute/National Biomarker Centre), about the intersection of generative AI and experimental cancer treatments, with a focus on clinical trials, regulatory considerations, and leveraging emerging technologies for a transformative impact in I-O.

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Q Can you tell us briefly about your background in generative AI?

AF: I am a research group leader at the Idiap Research Institute (Switzerland), a Senior Lecturer in the Department of Computer Science at The University of Manchester (UK). I also hold a role at the Cancer Research UK National Biomarker Centre, where I lead an AI group focusing on oncology.

My background primarily involves building models to support complex scientific inference using contemporary AI techniques, facilitating scientific discovery and inference at an advanced level. Most of my experience is around natural language processing and more recently applications in the oncology context.

Q Can you explain the concept of generative AI and how this differs from other types of machine learning?

AF: Generative AI, like other machine learning methods, relies on being data driven. Traditionally, people conceptualize machine learning models by considering specific data they want to learn from, as seen in biomedical applications where a cohort of patients is used to predict certain outcomes. However, this paradigm shifts when we look at Large Language Models (LLMs) like ChatGPT or computer vision models like DALL-E.

These large generative models undergo a learning or pre-training phase on large-scale datasets, such as web text corpora. For example, in the case of language, a clever mechanism involves masking words and predicting the next word based on context. What sets this approach apart is its self-supervised nature, eliminating the need for annotated data. This 'language game' can be played at a scale, allowing the model to learn intricate language representations.

This approach deviates from traditional machine learning, where the learning is task specific. After learning about language and general commonsense knowledge, the model goes through a fine-tuning phase for a specific problem, transferring knowledge to a particular task using annotated data if necessary.

Generative AI implies operating under this regime, facilitated by the scalability provided by deep learning models. Once trained, these large models can be specialized for various tasks.

The term generative refers to a class of models that can be contrasted to discriminative models. While delving into these technicalities might not be crucial at this point, the fundamental features of generative models contributes to the efficacy of their learning and inference capabilities.

Considering the oncology context, we extend the discussion to data modalities beyond language and images, such as molecular-level data and multiomics data. Although the scale of available data may vary when compared to language and imaging, the paradigm of generative models is being explored in other data modalities, such as multiomics, with potential high-impact applications in oncology.

The concept here revolves around moving beyond a narrower focus on learning over a specific disease or answer type. Instead, the approach begins pre-training the model over heterogeneous molecular patterns for example using single cell RNA-Seq data (over different cell types and disease settings). These identified motifs serve as a foundation to interpret omics patterns in a more specific setting (a target disease type). This follows a well-established paradigm: the foundational model is then fine-tuned aiming at addressing specific biomedical questions for that disease setting.

Q How can generative AI be employed to enhance the analysis of diversities, specifically in the I-O space?

AF: Examining various problems within the context of precision medicine reveals distinct analytical limits and fundamental issues when interpreting data. These challenges stem from the expanding dimensionality of patient data, driven by the ability to collect complex multiomics data. While there is a wealth of data per patient, the number of patients within a study may not proportionately increase. This hinders the application of conventional statistical inference frameworks, and the application of traditional machine learning models,

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"Another active area of our research involves supporting the interpretation and discovery of novel biomarkers. Understanding the variation in patient response to treatment and refining patient stratification are constant pursuits."

thus the deep learning/generative AI paradigm may provide a pathway to address the fundamental tension.

Another fundamental tension that is paradigmatic is integrating the abundance of observational real-world data with rigorously controlled randomized clinical trial data. Integrating these contextually different types of evidence presents another crucial tension that generative AI methods can address.

A third dimension involves an abundance of reported evidence and studies (expressed in scientific publications and clinical trial reports), opposed to lack of access to high-quality individual-level patient data. Generative AI, in particular specialized LLM-based infrastructures can play a vital role in making sense of these reported studies within the context of specific biomedical questions.

These are examples of analytical tensions where the typical statistical paradigms are limited in addressing, and that generative AI would help. To illustrate this concept in the context of I-O, the challenge of attempting to build predictive models for severe adverse events and toxicity should be considered. In the context of toxicity events for patients undergoing I-O treatment, particularly cytokine release syndrome, there is limited access to large cohorts of patients, meaning that there are significant barriers for building a predictive. One way this can be addressed is by systematically selecting and structuring evidence from previous literature, studies to provide the evidential basis for such an inference.

This strategy revolves around reducing barriers to access prior background knowledge, making it instrumental in the context of predictive modeling. While acknowledging the associated assumptions (for example, significant differences of context across these different pieces of evidence), there is a benefit in maximizing the utilization of this prior knowledge. This is achieved through the application of LLMs, employing a specialized pipeline to efficiently select and extract information for the diverse cytokine level ranges and their associated context. While in the past, this may have been a resource intensive task, with specialized LLM-based pipelines, this becomes viable.

Another active area of our research involves supporting the interpretation and discovery of novel biomarkers. Alongside conventional bioinformatics pipelines and statistical analyses, LLMs can play a crucial role in improving dialogue with external evidence. Alongside conventional bioinformatics pipelines and statistical analyses, LLMs can play a crucial role in improving dialogue with external evidence.

Upon identifying specific signatures that explain differences between patient subgroups, the next step typically involves contrasting and enriching these findings with evidence from high-quality, curated datasets such as civic and cosmic. Integrating evidence from the literature further enriches the interpretation of results, particularly for weaker signals that may not be statistically strong enough for conclusive outcomes.

The challenge lies in integrating these diverse external databases seamlessly within the biomedical interpretation process, a task often compromised due to its complexity. LLMs offer the ability to expand this integration, enabling a more comprehensive, integrated and resource-efficient dialogue with literature and databases, thereby strengthening the interpretative pipeline.

"There are other generative AI applications being explored within our research group with collaborators' support. For instance, creating digital twins for specific synthetic arms in clinical trials, and enhancing the prediction of toxicity effects are areas of current work."

These examples highlight the potential of generative AI in enhancing the analysis of the diversity of responses and the underlying biological mechanisms in the I-O space.

Q What are other potential applications of generative AI in the context of experimental cancer medicine?

AF: As mentioned, our collaboration extends to groups focused on biomarker discovery, patient stratification, and tumor subtyping. We aim to deliver mechanisms that enable oncologists to generate and explore new biomedical hypotheses. Although subsequent validation through controlled experiments is necessary, this approach fosters increased confidence in the hypotheses.

Building on this, another relevant area is the improvement of clinical trial design. Composing and designing specific trials often involves extensive dialogue with existing background knowledge, requiring time-consuming searches and curation. One ongoing project aims to systematize this process, integrating the maximum available evidence within the clinical trial design.

There are other generative AI applications being explored within our research group with collaborators' support. For instance, creating digital twins for specific synthetic arms in clinical trials, and enhancing the prediction of toxicity effects are areas of current work. Leveraging existing observational data and information within electronic health records, particularly clinical notes in natural language, further contributes to this effort.

Addressing semantic variability in patient descriptions is crucial. We are working on models to bridge the gap between all available treatments and patient descriptions, supporting clinicians within their situation awareness on the available treatments (by matching complex patient descriptions to a large database of clinical trials). This is particularly valuable in ensuring accessibility to a broader range of treatments, especially when clinical trial information may not be universally visible across the whole healthcare system. Overcoming complexities in interpreting eligibility criteria through natural language models and other methods is a key aspect of overcoming these barriers.

Additionally, we explore opportunities to enhance understanding and outcomes of clinical trials. This involves optimizing screening, reducing patient dropout, and mapping protocol deviations based on accessible evidence and clinical notes. Again, this is in effort to leverage observational evidence in the clinic.

Finally, there are significant opportunities in the earlier phases of drug discovery pipelines. This includes identifying opportunities for drug repurposing, improving the biological understanding behind groups of responders and non-responders, and linking these insights to specific drug assets available within a pharma context.

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Q Further to that, can you discuss the role of generative AI in optimizing and personalizing treatment strategies for cancer patients participating in clinical trials?

AF: When considering the current landscape of available technologies, it becomes evident that there are multiple intervention points where generative AI can be effectively applied. Looking at this, one can strategically intervene in various parts of the workflow to optimize both the management of the clinical trial itself and the interpretation of patient cohorts and responses. Anticipating events that may impact the clinical trial and the overall quality of life for patients becomes a key focus.

There are clear high-value intervention points within the pipeline, and it is essential to highlight that numerous opportunities exist for optimization. The common substrate of technologies enables this, although it is important to note that these technologies require adaptation efforts for integrating into the clinical or biomedical discovery workflow. This foundational infrastructure, once adapted, opens significant intervention points at different phases of the clinical trial.

Q What considerations should be taken when developing generative AI models in the context of I-O?

AF: The development of generative AI models in I-O and oncology in general demands careful consideration. When interfacing state-of-the-art AI with biomedical problems and experts, a nuanced approach becomes essential.

Firstly, it is crucial to recognize that the integration of these AI infrastructures within a biomedical workflow is a typically multi-disciplinary endeavor, which requires the harmonization of understanding across AI experts, oncologists, bioinformaticians, among other types of expertise. Understanding the intricate details and granularity required for optimal and critical application should be at center stage. The vast, dynamic, and rapidly evolving nature of both AI and biomedicine adds layers of complexity, emphasizing the need for caution and a thorough understanding of the expertise required for applying these infrastructures.

Approaching AI applications in I-O requires awareness and reflection on potential gaps in local expertise in terms of AI, data science, and specialized software engineering. Seeking external assistance such as advisors or collaborators becomes crucial, especially when starting to build an in-house AI team. Recruitment efforts should be aligned with obtaining balanced capabilities to navigate the complexity and specific expertise required.

Secondly, recognizing that many AI technologies are experimental, and complex is crucial. Out-of-the-box solutions may not be readily available in most cases, requiring the construction of specialized infrastructure. Crossing the gap from standard AI usage to developing expert models in biomedicine requires significant cross-disciplinary and specialized expertise, as mature tools specifically for biomedical experts are still being developed.

Lastly, understanding the position of distinct groups in the technology adoption cycle is key. Whether they aim to be pioneers, early adopters, or late adopters, internal context and conditions should guide this decision. While waiting for technology to mature might be necessary in some cases, being involved early can confer a competitive advantage. Acknowledging and

assessing the effort and investment required, along with navigating the complex technological landscape, is crucial and are commonly underestimated aspects.

Q What challenges have arisen so far, and how should these be addressed moving forward?

AF: From an analytical perspective it is vital to acknowledge that the general capabilities of generative AI represent a transformative change. However, these technologies, already proven in non-biomedical fields, face a necessary lag in adapting to the complexities of expert-level biomedical inference. This complexity is notably heightened when compared, for example, to the straightforward assistance provided by ChatGPT to a high school student.

Addressing these challenges requires a nuanced understanding. These models demand adaptation, investment, and the construction of necessary infrastructures. The convergence between a certain biomedical expertise and generative AI models represents a major opportunity for building specialized products and services and for improving outcomes for patients. The key is to consider how to tailor these models to embed specific expertise areas, building specialized infrastructures around their capabilities.

In contrast with the common discourse of complete automation, the emphasis lies in improving understanding, managing greater complexity, and delivering better treatments. For those with a biomedical background, the opportunity lies in building their own infrastructure, onboarding their expertise and data assets into these models, and creating AI workflows that are not only specialized but also add value on top of their existing knowledge.

This implies that an investment in constructing the necessary specialized pipelines is required. However, these challenges can be viewed as exciting and positive as they represent an opportunity to blend innovative AI capabilities with domain-specific expertise, advancing the field and delivering tangible value in biomedical applications.

Q What regulatory challenges and considerations should be considered when implementing generative AI?

AF: Addressing the regulatory landscape for implementing generative AI involves navigating through separate phases, each with its unique challenges and considerations. In the initial stages, particularly in the discovery phase, there are immediate and largely unproblematic uses, in the context of supporting the discovery of new hypotheses. For instance, enriching the biomarker analyses or enhancing interpretation over multiomics inference can better inform and position further interventional studies. However, even in these phases, formal ethical considerations and approvals should be at center stage.

Moving beyond the initial uses, a pre-regulatory layer emerges, marked by experimentation with technology solutions built around generative AI models. This phase is expected to grow, with organizations formalizing technological clinical trials to evaluate the efficacy of these technologies. The goal is to establish a robust evidence corpus that will eventually shape the regulatory landscape.

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"...the complexities of expert-level biomedical inference... [are] notably heightened when compared, for example, to the straightforward assistance provided by ChatGPT to a high school student."

Strictly regulatory elements come into play further downstream, particularly as organizations aim to onboard generative AI models at the status of a medical device. At this stage, the evidence built through technological clinical trials becomes crucial.

Importantly, it is essential to recognize that each AI system requires a cross-cutting assessment of safety, transparency, fairness, ethical implications, and security. These areas are highly technical and specialized, and as the use of generative AI models in biomedical applications evolves, more specialized certification authorities are expected to emerge. These groups will provide formal validation and certification, offering an independent assessment of safety and fitness for broader clinical use.

The evolving ecosystem suggests that the trajectory of these technologies will involve specialized validation groups providing certifications in alignment with the current regulations. Behind this evolution lies the ongoing transformation of the regulatory landscape, shaped by insights gained from studies and advancements in generative AI technologies. As the field progresses, it is crucial to be aware of the emerging and evolving regulatory requirements to ensure a smooth alignment to these regulations.

Q Lastly, what do you see as the future trends and advancements in generative AI for supporting experimental cancer medicine? What emerging technologies could contribute to this?

AF: It is important to first recognize that a significant foundation in AI has been established. The emphasis moving forward is on consolidating and integrating these foundational AI elements into the I-O space with a line of sight towards using them for answering value-delivering biomedical questions.

There are several key elements that can summarize the strategic landscape, with the first being LLMs. These stand out as a cornerstone technology for integrating and interpreting diverse evidence at scale, operating effectively over both unstructured and structured data with appropriate adaptations. Similarly, foundation models tailored for multiomics analysis represent a strategic focus—though still in initial stages, they hold promise for accelerating advancements in this area.

Generative AI models offer a unique fit for representing complex tumor states, spanning molecular to tissue-level integration. Integrating diverse datasets, accounting for batch effects, and building digital twins/chimaeras present exciting opportunities to model disease trajectories and gain a higher resolution understanding of patient and tumor states.

Beyond LLMs, variational autoencoders, diffusion models, and other emerging architectures serve as foundational tools for building molecular and tissue-level omics models, reflecting an increase of modelling possibilities. Integrating pathway data and CRISPR-based interventions

represents another strategic trend, enabling joint mechanistic-statistical inference and enhancing our understanding of underlying biological mechanisms.

Maximizing the value of observational data available in hospitals, integrating clinical records, and leveraging emerging technologies for data analysis and interpretation further enriches the landscape of generative AI in cancer medicine.

Moving forward on this strategic landscape would require significantly close collaboration between AI and biomedical experts, focusing on adapting, maturing, and specializing AI models for the intricacies of experimental cancer medicine.

In summary, the future of generative AI in experimental cancer medicine lies in consolidation, dialogue between experts, infrastructure development, and the continuous evolution of tools and solutions. Early translation of these advancements into tangible benefits for patients and experts alike remains a primary objective in driving forward the transformative potential of generative AI in cancer research and treatment.

BIOGRAPHY

ANDRÉ FREITAS is a Senior Lecturer (Associate Professor) at the Department of Computer Science at The University of Manchester, UK, an AI Group leader at the National Biomarker Centre, CRUK Manchester Institute, and a Research Group Leader at the Idiap Research Institute, Switzerland. He leads the Neuro-symbolic AI Group. His main research interests are in enabling the development of AI methods to support complex and controlled inference to support scientific discovery, with a particular emphasis on oncology. Some of his research areas in oncology include the use of contemporary AI methods to support biomarker discovery, the development of AI foundations for digital twins in oncology, expert-based systems supported by LLM, the development of AI systems for patient-treatment matching, and clinical trials management.

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Myeloid cells: unveiling their secrets as biomarkers through next-generation sample preparation

Chyan Ying Ke

FASTFACTS

Myeloid cells: unveiling their secrets as biomarkers through next-generation sample preparation

Chyan Ying Ke, Director of Bioapplications, Curiox Biosystems

The Curiox Laminar Wash™ technology provides improvements in myeloid cell characterization, fostering future research in advanced flow cytometry, single-cell analysis, and personalized medicine. These advancements aim to unravel myeloid cell complexity, identify biomarkers, enhance disease perspectives, analyze extensive data, and customize immune checkpoint inhibitor therapy for optimal efficacy with minimal side effects.

COMPARATIVE DATA OF TRADITIONAL CENTRIFUGATION AND THE CURIOX LAMINAR WASH™

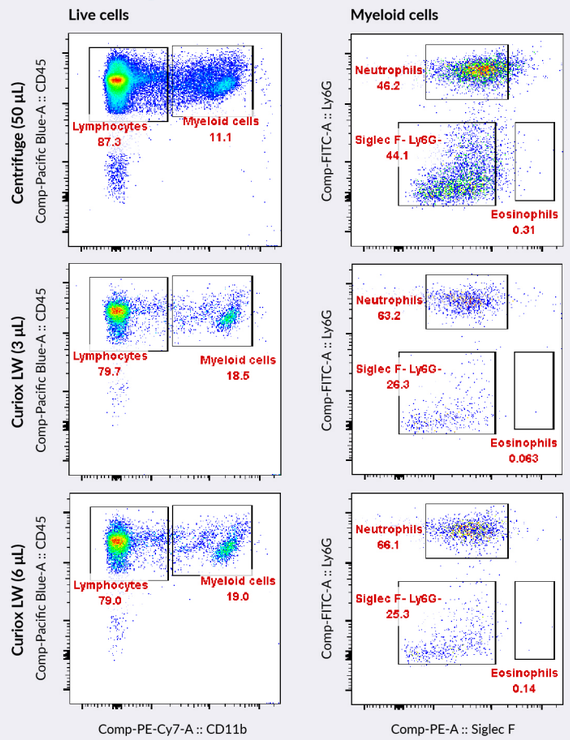
Next-generation sample preparation advancements, such as the Curiox Laminar Wash (Curiox LW) technology, are essential for accurately measuring biomarkers in cancer treatment, including various types of myeloid cells. Curiox LW excels as a gentle process that uses laminar flow and liquid handling robotics to efficiently remove debris and dead cells, offering a clear advantage over the traditional centrifugation methods. **Figure 1** visually compares the outcomes of these two approaches.

UNVEILING WITH HIGHER THROUGHPUT

Deciphering the role of myeloid cells in cancer and immunology hinges on robust analysis methods. Curiox LW, when compared to traditional centrifuge-based techniques, achieved a 7–8% increase in CD11b+ myeloid cell detection from minuscule murine blood volumes (3 or 6 µL vs 50 µL). This translates to significant gains in neutrophil identification through Ly6G and Siglec-F markers.

This further allows for better identification of neutrophils using specific markers and facilitates high-throughput analysis in both *in vivo* and *ex vivo* studies. It preserves more viable myeloid cells, crucial for immune checkpoint blockade research **(Figure 2)**, and optimizes sample preparation, enabling groundbreaking findings in myeloid cell biology.

Figure 1. 14-color flow cytometry analysis using a gating strategy that starts with All Events and focuses down to CD8+ T cells. Mouse blood samples were prepared using either centrifugation or Curiox LW.



Centrifuge=50 µL of blood lysed in bulk (twice in 10× volume); LW 3 µL/6 µL=3 µL/6 µL blood lysed on LW plate (once in total 60 µL)

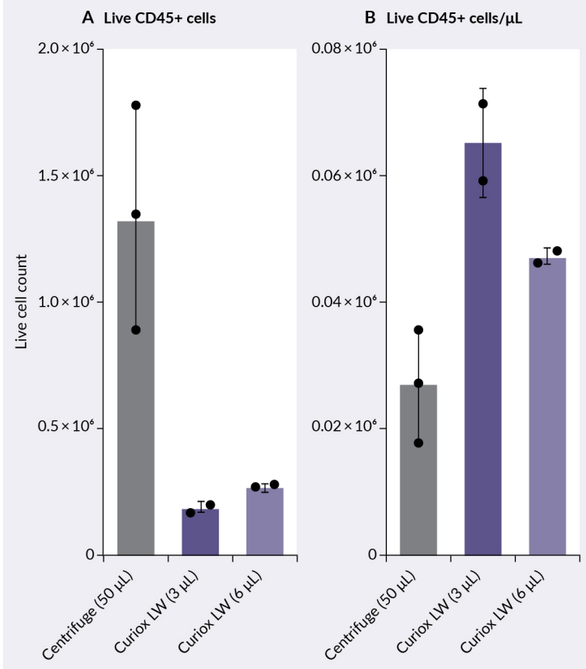
BEYOND THROUGHPUT: UNCOMPROMISED ANALYSIS FROM LIMITED SAMPLES

Limited and precious tissue samples are a constant hurdle in myeloid research. **Figure 2** illustrates Curiox LW's superior efficacy as it delivers high-throughput analysis with live CD45+ cell counts when compared with traditional centrifugation. Even with significantly smaller blood volumes, Curiox LW maintains significant cell retention and lysis efficiency. This translates to no compromise in data quality from minimal samples. Additionally, Curiox LW automates analysis, enabling high-resolution, improving precision, and streamlining workflows across human and mouse studies, enhancing signal-to-noise ratios for more reliable and groundbreaking discoveries.

SUMMARY

Curiox LW enhances the study of precious tissue samples by enabling higher throughput capabilities. Even when using smaller volumes, it consistently achieves higher relative cell retention and comparable lysis efficiency. This becomes particularly valuable for studies involving limited sample volumes, such as mouse models and other tissues, ensuring data quality is not compromised by reduced sample volumes. Furthermore, the Curiox LW systems boast a significant degree of automation, facilitating efficient and routine operations for achieving high resolution and tight clustering.

Figure 2. (A) The count of live CD45+ cells from samples that were prepared by centrifugation and the Curiox LW at different volumes. (B) The data is normalized using linear titration for clear comparison.



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