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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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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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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AUTHORSHIP & CONFLICT OF INTEREST

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