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SPEAKER INTERVIEW

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THERA technologies

As interest in ADCs and alternative conjugates continues to grow with impactful clinical readouts, licensing, and M&A dealmaking, what new innovations with conjugates are you most excited about?

ADCs have certainly revolutionized the approach to cancer therapy in the advanced setting. Novel approaches are always required to overcome resistance and to increase the therapeutic index of these agents to improve patient outcomes. That is why I am very excited about the alternative drug conjugates with their unique properties and MOA. For example, the sortilin-targeting PDCs developed by Theratechnologies provide a platform of agents that can be easily and rapidly manufactured with different payloads. These PDCs behave very differently from ADCs and have both a unique target (SORT1 receptor) and unique properties. Some of these properties are rapid internalization, stimulation of immune cell infiltration even in "cold" tumor models, inhibition of vasculogenic mimicry, targeting of chemotherapy-resistant cancer stem cells (CSCs), and activation of the cGAS/STING pathway, among other actions. Theratechnologies' PDCs can also be combined with other targeted agents, including chemo and checkpoint inhibitors (CPIs), due to their safety profile.

What are the biggest challenges to progress both ADCs and new conjugates to become SOC oncology treatments, and how can the industry overcome these challenges?

One of the key issues with ADCs in the clinical setting is the selective delivery of therapy. The bystander effect, the large size of the ADCs (preventing deep penetration of the tumor) and their long half-lives make it difficult to directly target tumor cells and avoid normal tissues. This has led to significant systemic and off-target toxicity for many patients (eg. cytopenias, interstitial lung disease, etc), which is difficult for the clinician to manage. It also makes it difficult for patients to stay on treatment for long periods of time. If there were biomarkers available to predict which patients would benefit most from these agents, the clinician could perform a better risk-benefit analysis when deciding upon treatment strategy. But no such biomarkers have been identified to date.

We all know that most anti-cancer regimens contain more than one agent for maximal efficacy, and it has been difficult to combine ADCs with other anti-cancer drugs due to toxicity issues.

Theratechnologies has developed a PDC platform that addresses some of these concerns. PDCs are small chemical entities with a unique, multimodal MOA that differs from that of an ADC. They can rapidly penetrate directly into the cytoplasm of the tumor cell via the SORT1 receptor, which is highly expressed in many solid tumors, by utilizing the transport function of this transmembrane receptor. Once inside, PDCs have a very short half-life, and are cleaved via the endosomal/lysosomal pathway. Very little of the drug gets into the systemic circulation (in the case of TH1902, <1%) and the safety profile is much improved over that of ADCs. We have generated a significant amount of preclinical data with different PDCs that demonstrate the ability to combine with many other agents, including other PDCs, immunotherapy agents, chemo and other targeted therapies.

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What are the key challenges in PDC development and what strategies are needed for rapid progression from bench to bedside?

Developing and introducing a PDC as a new chemical entity, in a category where ADCs have been well established for many years, is challenging. The benchmark for efficacy is constantly rising and has changed dramatically over the past 5-10 years. Compared to ADCs, PDC development is still in its infancy. Consequently, POC trial design, dosing strategies and optimal combinations are all ongoing challenges. As a small biotech company, it is challenging from a resource perspective to develop this important asset, so we are seeking a development partner. Many pharma companies are heavily invested in the development of ADCs, and it is difficult for them to pivot to a new platform and provide appropriate funding to scale-up the clinical trial program that is required to move forward.

What do you see as the next big breakthrough in this field?

Getting novel PDCs through clinical development will cement their place in anti-cancer therapy and provide an alternative strategy for clinicians who are treating advanced solid tumors.

Bispecific PDCs with different payloads are highly desirable, so that combinations of agents can be delivered directly to the tumor cell with minimal systemic circulation.

Radionuclides are a hot topic right now, and there is much interest from several companies in using PDCs to deliver this treatment. PDCs are ideally suited for radionuclide development, due to their rapid and targeted internalization into the tumor and their short half-lives. Radioactive ligands decay rapidly and need to be contained in the target tissue with minimal bystander effects. When attached to a PDC, these ligands can be rapidly internalized directly in the tumor tissues and the short half-life prevents them from entering the circulation, leading to a potentially improved safety profile overall.

What is the top benefit of attending World ADC San Diego, and what are you looking forward to?

I am excited to be here to share some of the newer data from our first asset in the SORT1+ TechnologyTM platform, TH1902, especially the safety profile. This is a PDC with a docetaxel payload and we have been investigating various dosing schedules in a phase I first-in-human trial in advanced cancers, particularly ovarian cancer. We are still working to optimize the dose, but the trial program has provided us with some very important information about the unique MOA, the efficacy and improved safety profile, which is very different from that of its payload and from other ADCs already approved for use. This may enable combinations with other anti-cancer agents, such as targeted agents, CPIs, and other PDCs/ADCs.

I look forward to networking with industry colleagues and to stimulating interest in investment in this broader program.

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