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FORGING STABLE RELATIONSHIPS FOR ANTIBODY-DRUG CONJUGATES

A conversation with **ROBERT LUTZ**, PhD, Chief Scientific Officer of Iksuda Therapeutics

Iksuda Therapeutics develops next-generation antibody-drug conjugate (ADC) therapies to target cancers that are difficult to treat, or resistant to current treatments, without damaging healthy cells. Iksuda focuses on solid tumours including lung, ovarian, cervix, pancreatic and colorectal cancers. The company collaborates with academia, biotech and pharma to develop therapies utilising its PermaLink technology, a conjugation chemistry that improves ADC stability, in combination with an arsenal of cytotoxic payloads. Iksuda currently has four candidate drugs in early stage development, including one in preclinical studies, and aims to advance multiple candidates to clinical studies in 2021.

How do ADCs work?
ADCs are a class of biopharmaceuticals that target cancer cells while leaving healthy cells alone. They capitalize on the fact that specific proteins are often upregulated on a cancer cell's surface. These proteins act like a postcode, directing antibodies to the cell. People once thought that antibody binding was enough to kill the tumour cell, and in some cases, it can. But through the 1990s and early 2000s, we found that most antibodies weren't powerful enough to cause tumours to regress. So, researchers found ways to attach very potent cytotoxic molecules to the antibody, which would be delivered selectively to cancer cells, while reducing side-effects.

How do ADC payloads compare with standard chemotherapy?
Payloads are reminiscent of the kinds of chemotherapy we regularly use to treat cancer, but significantly more potent. Standard treatment floods a patient's body with chemotherapeutic agents so has to be milder. In ADC therapy, payload delivery relies on a selective antibody binding event. Think of ADC therapy as less like a sledgehammer and more like a scalpel.

What cancers do ADCs treat best?
Because antibodies are so large – around 150,000 Daltons – they can circulate in blood for a long time. This means an ADC can, over time, deliver more of its payload to cancer cells. But an antibody's size is also a limitation when it comes to penetrating solid tissue. ADCs treat solid tumours much more slowly than they do blood cancers. Most of the initial approvals have been for blood cancers because they don't have that barrier of delivery. The only ADC therapy currently approved for solid tumours, trastuzumab emtansine, is for a type of metastatic breast cancer, and it was approved in 2013. The challenge is getting the right balance of power and safety — and that is hardest when treating solid tumours. An early obstacle was the instability of some of the classic conjugation chemistries, which could lead to the payload falling off prematurely, before delivery.

How is Iksuda addressing ADC stability?
In ADC design, conjugation stability determines clinical utility by allowing the use of more potent payloads. Iksuda is building a therapeutic pipeline based on a bioconjugation technology called PermaLink. The vinyl part of PermaLink's vinyl-pyridine-based chemistry reacts with the thiol group on the amino acid cysteine. Cysteines are used to orient an antibody's heavy and light chains, so all antibodies, wild type or engineered, have sites where we can do the conjugation. There are no known reactions for the conjugation to go backwards, so we don't have to worry about our payload breaking free before it reaches its target.

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How does Iksuda source payloads?
Our goal is to build an extensive armoury of payloads allowing development of the most powerful ADCs for treating any cancer. While our portfolio will be centred around PermaLink, our payload choice will be matched to each indication. We're looking for more powerful payloads under development in academia or small biotech firms. They might have different mechanisms of action, or different chemistries, water-solubility, for example, so they are easier to work with. We have licence agreements and option agreements on new types of payloads.

Which ADCs is Iksuda developing in-house?
We have four ADCs in our pipeline. Our current lead, IKS01, targets folate receptor alpha, which is mainly expressed in ovarian and lung cancers. Our objective was to come up with something that could be used on moderate-expressing tumours. We already knew the target was sufficient to deliver the payload, so we conjugated the antibody with Femtogenix's highly potent FGX-2-62 payload. Preclinical tests show effective tumour regression, even in low-expressing tumour models. Our extended ADC pipeline will seek to address similar issues with other target antigens.

What is the outlook for ADCs?
Big pharma is interested. For example, take AstraZeneca's recent multi-billion-dollar deal for Daiichi Sankyo's ADC. And the industry is making a massive effort, with hundreds of ADCs in development. Instead of a few companies trying to figure this out, hundreds of companies are working on concepts — some on payloads, others on antibodis. The patients will be the ones who benefit from this energy. Now we can do the small molecule cytotoxin part relatively cheaply because that part of the chemistry world has evolved. The most expensive part of an ADC is the antibody, but that price has come down enormously over the last 20 years, because antibody-based therapies have become so popular.

IKSUDA THERAPEUTICS

Iksuda Therapeutics is a pre-clinical stage drug development company focused on advancing the next generation of antibody drug conjugates (ADCs) into the clinic to improve the lives of cancer patients.

Iksuda's approach is to combat difficult-to-treat solid tumours, including those that are resistant or refractory to current treatment regimens, using ADCs that are designed to provide superior therapeutic index when compared to current clinical approaches.

By leveraging the stability of PermaLink® conjugation chemistry, Iksuda is able to incorporate the latest generation of highly potent payloads into its ADCs. IKS01, Iksuda's lead ADC targets Folate receptor (FLR) and demonstrates complete or near complete regression of both ovarian and lung tumours at well tolerated doses. IND approval is anticipated in Q2 2021.

Pipeline

Target	Therapeutic Area	Discovery	Preclinical	Phase 1
Folate Receptor	Ovarian, Lung			
Undisclosed	Lung, Pancreatic			
Undisclosed	Colorectal, Lung			
Multiple Targets In Early Stage Evaluation / Discovery				

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