AN EXCLUSIVE INTERVIEW WITH:

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With the rise of novel molecules and immunotherapies, being able to optimize and validate a suitable preclinical model will help advance drug candidates into clinics. Kleo Pharmaceuticals, an up-and-coming biotech with proprietary platform specialized in NK cells and bispecific medium sized– antibody recruiting molecules (ARMs), has developed a unique toolbox to enable this advancement.

I have caught up with their Associate Director – Immunology, Anna Bunin, for her insight and journey in this space.

HW: Anna, would you be able to tell us a bit more about Kleo Pharmaceuticals' pipeline? The bispecific compounds for immuno-oncology therapy are very interesting.

Yes, definitely. Right now, the most advanced in Kleo's pipeline are bi-specific medium sized molecules called antibody recruiting molecules, or ARMs for short. Antibody recruiting molecules represent a new modality in immunotherapy of cancer.

These are bifunctional molecules composed of two active termini connected by a linker. One of the termini binds to a target molecule on a cancer cell. The other, a universal antibody binding terminus (uABT), recruits endogenous antibodies independent of their antigen binding specificity via a unique epitope that leaves the Fc receptor binding site free. As a result, the target cell is "opsonized" by antibodies, which then bring the immune effector cells to eliminate the target through various antibody-dependent destruction mechanisms.

HW: While both pharma and biotechs are now focusing on the possibilities and potential of targeted IO therapeutics, it's a lot more complicated in target validation and safety assessment. How do you tackle these challenges?

What we are trying to do in this case is put each drug candidate through rigorous testing in a variety of settings: in silico, in vitro, and in vivo. One needs to thoroughly understand the mechanism of action of the drug, and the biology of its target to be able to predict and avoid toxicity. Our efforts run in a continuum and are based on solid immunology, oncology and pharmacology. We carefully evaluate how our candidate agents bind various cellular or protein targets. This evaluation in addition to a clear pharmacokinetic profile, allow us to advance agents that are likely to be true to our proposed mechanism of action in a safe and efficacious manner.

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HW: Biotechs are now using more preclinical oncology modeling to help support translatability and predictability of clinical decisions. What are your thoughts?

I am glad to see the development and emergence of new exciting models that can be used in oncology. To build a translatable model one needs to keep in mind the biology of the disease. What is also of paramount importance is that many of these new models (e.g. PDX, humanized mice, etc.) require that we master basic disciplines that are sometimes minimized. Efforts like pharmacokinetics, bioanalytical work and appropriate tumor model selection and implantation are essential to properly translate novel discoveries into clinical candidates. Translational work is vital for our industry, but it is just as important to understand the limitations of each model we use in advancing new therapeutic agents.

HW: Kleo Pharmaceuticals has 3 proprietary platforms including ARMS, SYAMS and MATES – can you share a bit more about them, and how they could help accelerate drug discovery and development?

Similar to complex biologic drugs, Kleo's compounds recruit the immune system to destroy cancer cells, but unlike biologics, they're smaller and more

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versatile, leading to potentially improved safety and efficacy. Our three platforms are much faster and less costly to design and produce, particularly against novel targets. We are currently advancing several drug candidates based on these proprietary technology platforms, all of which are modular in design and can enable rapid generation of novel immunotherapies that can be optimized against certain cancers, or enhance the properties of existing immunotherapies.

As I have described above, ARMs are targeted antibody rescruiting molecules that are composed of a target binding moiety linked to a universal antibody recruiting molecule. This allows specific engagement of endogenous antibodies on the surface of malignant cells. Recruited antibodies in turn, bind immune cells such as NK cells and macrophages through the Fc receptors and activate their effector functions, leading to target cell killing.

Syams are bifunctional comounds which bridge together the target cancer cell and an immune cell of choice to facilitate execution of an effector function by the immune cell towards the target cancer cell.

Monoclonal Antibody Therapy Enhancers (MATEs) are synthetic compounds that are chemically conjugated with existing therapeutic monoclonal antibodies to enhance their ability to engage different components of the immune system.

HW: With more emphasis placed on optimizing preclinical model and target validation, what would be your top tip for fellow colleagues ahead of the 7th PREDiCT: Tumor Models Boston Summit?

There are a few things we would like to implement at Kleo and these apply throughout our industry.

First, don't forget the basics! A poorly planned experiment will not help anyone. Treat each study as if it were the pivotal experiment for your IND submission.

Second, advancing a novel target will be improved if it is done with the potential in vivo pre-clinical model in mind even at the discovery level. "Off-the-shelf" models offer a distinct advantage to the rapid development of a target in contrast to using a non-validated model to advance a new candidate.

Third, there is a wealth of resources out there. Kleo has engaged many outside entities including companies like Taconic and JAX. In the end, it is in our common interest to advance new treatment modalities - we very much believe in cooperation.

At the forthcoming **7th PREDiCT: Tumor Models Boston Summit**, **Anna Bunin**, Associate Director, Immunology and **Enrique Alvarez**, Director of Preclinical Development from **Kleo Pharmaceuticals** will jointly present the success story of:

How to Build a Translational Platform to Develop Effector Cell Centered Immuno-Oncology Agents

Download your full event guide here