Industry Insights

Undruggable LEADERS FORUM

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What are the biggest challenges facing 'undruggable' today?

We have to start with what we have viewed as ideal therapeutic targets traditionally, and then how we want to view targets moving forward. In oncology, therapeutic development targets have always been identified based on two key criteria – their role in tumor biology, and whether or not they have a high level of expression in tumors while also having a low level of expression in normal tissue.

The problem is that these criteria are extremely limiting because many promising targets we see in cancers are also very common and highly expressed in normal, healthy tissue. If we truly want to develop new treatment options for patients, and options that are safe and efficacious, we need to find new ways to expand our library of druggable targets by exploring alternative methods to make the undruggable, druggable. This is exactly where our platform can deliver, by exploiting the tumor microenvironment to activate our Probodies.

CytomX is leading the charge to develop and bring these conditionally activated molecules to the clinic.

How are CytomX currently tackling the 'undruggable'?

At CytomX, we are tackling the problem of how to solve for undruggable targets by redefining what is possible.

We have created a versatile therapeutic platform that allows biologic therapies, whether they are antibodies, antibody-drug conjugates (ADC), T-cell bispecific antibodies (TCB) or even cytokines, to remain virtually inert until they are conditionally activated by enzymes called proteases, which are abundant in cancerous tumors. Our Probody® platform is based on a technology that utilizes a peptide mask to cover and block the cellular binding region of our therapies, and a protease cleavable linker is used to hold the mask in place.

This technology, when applied to an antibody, is designed to prevent binding until the protease linker is cut away by proteases, releasing the mask and thereby allowing access to the target. It has been known for some time that proteases are highly active in cancer as they are necessary to break down surrounding tissue to allow tumors to grow

and invade other tissues. While proteases are present in normal tissue, their activity is tightly controlled to remain inactive. Thus we are able to transform cancer's dependence on proteases for growth and metastasis into its Achilles' heel.

For example, CD71, the transferrin receptor, has been a very attractive target to develop an antibody-drug conjugate against for a variety of reasons, with two in particular: it is highly expressed on tumors, and it is an extremely efficient internalizer of antibodies typically within minutes of binding.

However, CD71 remained undruggable because it is also highly expressed in normal tissue. In fact, a naked antibody can cause anemia in mouse models, and we showed that very low doses of an ADC to CD71 is lethal to non-human primates. As a result, CD71 was a quintessential undruggable target, until the development of CX-2029 at CytomX, which utilizes our Probody masking platform.

With CX-2029, we were able to safely dose non-human primates at expected therapeutic levels and recently completed a dose-escalation Phase 1 clinical study, in partnership with AbbVie, where we saw signs of anti-tumor activity in patients with squamous non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC).

What is the main limiting factor with therapeutic antibodies and how are CytomX working to overcome this?

The current limitations for unmasked, antibody-based treatments in oncology are that there are a finite number, and few, targets available. As a result, a massive amount of investment is going towards a small group of targets, like HER2. But there is a whole library of potential therapeutic targets just waiting to be explored if we can break though the limitations that make them undruggable.

There are other factors, aside from expression patterns, that limit prolonged dosing and that our masking platform could potentially alleviate. For example, immuno-oncology therapies carry the risk of severe and dose-limiting immune-mediated toxicities from 'over stimulation' of the immune system due to systemic activation of T cells. Even though these side effects may not be common, for patients they can be debilitating, can limit further treatment, and can last a lifetime.

Part of the promise of our conditionally activated Probody platform is that it can also be applied to current treatments, including antibody-based immuno-oncology approaches. If systemic activation of T cells can be diminished with a Probody approach, then it is possible that these immune-mediated adverse events could occur less often, or with less severity or both. Indeed, we have shown that treatment with our Probody to PD-L1,

pacmilimab, also known as CX-072, results in anti-tumor activity and the tolerability profile appears favorable. The opportunity to take approved treatments and mask them with our Probody technology may make them safer or better tolerated for longer periods of time.

What do the next 5 years look like for CytomX and what developments would you like to see across the industry?

The next five years for CytomX will be extremely exciting, with readouts starting to come in this year from Phase 2 studies, we could potentially be initiating pivotal clinical trials in 2022, assuming the data is positive. So in five years, we are really looking at the potential for regulatory submissions and possibly approvals of the therapies we are studying in our lead programs today. While these clinical trials are focused on relapsed and refractory cancers, we also believe that our conditionally activated platform may be equally or even more valuable in earlier lines of therapy, and we will be looking at those opportunities very closely as our data matures and we gain a better understanding of the potential benefit for patients. We will also be advancing new programs into the clinic including the first applications of our Probody technology to cytokines.

Outside of CytomX's work in this space, what area of 'undruggable' are you most excited about and why?

When we first started, there really wasn't anyone else in the industry that was exploring the potential for conditionally activated therapies like CytomX. When I look at the industry today, I am very excited and proud to see a number of other companies that have now chosen to start dedicating their own resources to this area of research.

I think it is a testament to the science that CytomX pioneered, and our unique platform that we are now validating in the clinical setting. Competition breeds innovation, and we need to continually innovate if we want to get the upper hand on cancer.

What are you most looking forward to at the Undruggable Leaders Forum in September?

I am excited to share some of the learnings we have had with our work at CytomX, but the real benefit of this forum for me will be to hear from the other leaders in this space and the exchange of new ideas.

To hear more from Amy Peterson, tune in to Day 1 of the virtual Undruggable Leaders Forum.

Amy is giving a talk titled "Reinventing Therapeutic Antibodies for the Treatment of Cancer" at 11:30 am EST on Wednesday September 15th.