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Taylor co-founded Shattuck Labs, is a member of the Board of Directors, and is the lead inventor of Shattuck's ARC technology platform.

How are researchers seeking to overcome the toxicity challenges associated with targeting the CD47/SIRPa axis?

The toxicity challenges associated with targeting CD47 are principally related to whether the agent in question binds Fc receptors, thus providing an 'eat me' signal, in addition to blocking the 'don't eat me' signal. In agents where 'don't eat me' and 'eat me' functions are coupled in the same therapeutic, which is the case with any antibody or fusion protein targeting CD47/SIRPa that contains an active Fc domain, indiscriminate phagocytosis of CD47 positive cells ensues.
Magrolimab, which contains a partially active IgG4 Fc domain, causes significant anemia in the absence of a clever priming regimen. TTI-621 which contains an active IgG1 Fc domain is reported to cause grade 3 thrombocytopenia and anemia. Even in the presence of an active Fc domain, clinical efficacy is largely dependent upon exogenous 'eat me' signals, either from molecules like calreticulin or ADCP-competent targeted antibodies.

Thus, the key to avoiding toxicity with CD47/SIRPa targeting is to uncouple the 'eat me' signal from the CD47/SIRPa blocking agent.

What impact are predictive biomarkers having in the clinic?

Whether or not a patient may benefit from CD47/SIRPa blockade is largely dependent upon the balance of anti-phagocytic signals (density of CD47/SIRPa blockade) and pro-phagocytic signals within a tumor. Because high-density CD47/SIRPa blockade can be determined during dose-escalation studies, a prospective understanding of the abundance of endogenous pro-phagocytic signals, including calreticulin, or the target antigens for ADCP competent antibodies (CD20, EGFR, Her2, CD38, etc.) is critical.

The paucity of anti-tumor activity in the clinical trial combining magrolimab with cetuximab in colorectal cancer is thought to be at least in part due to the low expression of EGFR, the target antigen for cetuximab. There is likely a strong correlation between the

density of certain pro-phagocytic signals in a tumor and clinical response to CD47/SIRPa blockade.

Are we more likely to see CD47/SIRPa + other target(s) succeeding in the clinic, compared to as a monotherapy?

Yes. There has been, and we believe there will continue to be, very limited single-agent activity with CD47/SIRPa blockade.I expect we will continue to see impressive overall survival benefit when agents like magrolimab or ALX-148 are combined with ADCP competent antibodies (in tumors where the target of those antibodies is abundantly expressed) and in combination with anthracycline based chemotherapy.

What other related areas of drug R&D are are showing promise?

CD47/SIRPa inhibition has the potential to initiate anti-tumor immune responses in tumors that are immunologically 'cold', where current immunotherapy including PD-1 blockade has limited clinical activity. While concurrent CD47/SIRPa and PD-1 blockade has not shown clinical activity, it is likely that PD-1 blockade may aid in the propagation of an anti-tumor immune response that has been initiated by combinations of CD47/SIRPa inhibitors and either immunogenic chemotherapy or ADCP competent tumor targeted antibodies.

What needs to happen for the work in this space to meet its full potential?

Macrophage gluttony is not the goal of CD47/SIRPa blockade, because macrophages are not the cell type that is responsible for reducing tumor burden – T cells are. Thus, therapies that coax macrophages to better display antigens from the tumor cells they have just phagocytosed are likely to provide synergy with CD47/SIRPa blockade. This hypothesis was the motivation for SL-172154, which combines CD47 blockade with a CD40 agonist.

What are you most looking forward to at the CD47/SIRPa Summit?

We believe CD47/SIRPa blockade has emerged as the most clinically validated immune checkpoint pathway since PD-1/L1. The field is advancing very rapidly, and the 'rules of engagement' are largely defined. This conference is a terrific opportunity to explore the recent learnings with key opinion leaders, so that the emerging data can expedite development of CD47/SIRPa therapeutics for the benefit of cancer patients.

You can hear more from Taylor on Day 2 of the Summit where is presenting and participating in a panel discussion.