Industry Insights

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What is our current level of understanding of CD47/SIRPa?

We know that the CD47/SIRPa interaction is a critical immune checkpoint. It regulates macrophage phagocytosis of cancer cells—acting as a "don't eat me" signal on tumors. Blocking this interaction stimulates macrophages to attack many different types of cancer. However, we have also learned that other myeloid immune cells, such as neutrophils and dendritic cells, can also be stimulated by CD47/SIRPa-blocking therapies. Furthermore, by activating the innate immune system, CD47/SIRPa-blocking therapies may stimulate antigen presentation and activate adaptive immune responses.

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

There are a number of strategies to overcome toxicity associated with targeting the CD47/SIRPa interaction. First, toxicity profiles may be different based on targeting CD47 on cancer cells versus SIRPa on immune cells. When targeting CD47, the choice of Fc has tremendous importance for toxicity, with Fc domains that are better able to engage Fc receptors corresponding to greater toxicity. Agents that contain Fc domains with reduced or eliminated effector functions may overcome this toxicity. Another strategy to mitigate toxicity has been to use a low "priming dose" as the first treatment with subsequent doses at much higher levels.

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

The data suggest that although CD47/SIRPa blockade may be effective as a monotherapy in some settings, the combination approach produces the greatest anti-tumor effects. Particularly promising is combination with monoclonal antibodies that

mark cancer cells for destruction by the immune system, for example, rituximab. However, there is emerging evidence that CD47/SIRPa-blocking therapies may be effective when combined with other immune checkpoint inhibitors or conventional chemotherapy drugs. These principles have been supported by the results of the initial clinical trials.

What lessons have been learned from targeting CD47/SIRPa that are impacting other "Don't eat me signals"?

In most cases, blocking the CD47/SIRPa interaction lowers the threshold for macrophage phagocytosis of cancer, but it is not sufficient to stimulate anti-tumor effects by macrophages. I expect this to be true for other macrophage immune checkpoints. We are also starting to learn that macrophage immune checkpoints are not only relevant to cancer, but could be important for other indications such as bone marrow transplant, infectious disease, and atherosclerosis.

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

For CD47/SIRPa-blocking therapies to reach their full potential, we must answer a number of questions. Are there certain types of tumors that respond best? Are there certain patients that respond best? Can we identify biomarkers that predict responses to CD47/SIRPa-blocking therapies? What are the best opportunities for therapeutic combinations—tumor-binding antibodies, immune checkpoint inhibitors, or conventional chemotherapy

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

The CD47/SIRPa Summit is a unique event that assembles the key leaders from industry and academia around this critical immune checkpoint. I am most looking forward to interacting and learning from the participants to help advance this field together for the benefit of patients.

You can hear more from Kipp Weiskopf on the 4th November 2020 at the CD47-SIRPa Sumit, EDT Timezone, where he will be opening the virtual Summit as Day 1 Chair.