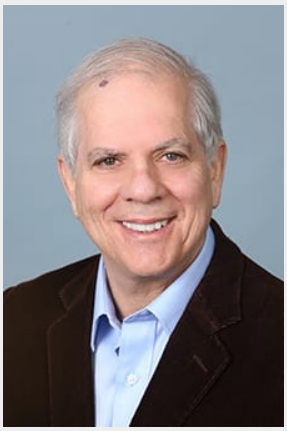
ENDPOINTS NEWS

# AACR: Bay Area biotech bets on antibodies armed with immuno-stimulant to fight checkpoint-resistant cancers

by Natalie Grover on April 1st, 2019

The scientist behind the first prostate cancer vaccine Provenge — once celebrated as a historic breakthrough, but now a fading star — has devised a type of armed antibody — loaded with an immuno-stimulant rather than a cytotoxic payload — to fight cancers resistant to the army of existing checkpoint inhibitors.



Ed Engleman

The researcher, Stanford's Ed Engleman, has built on his research into dendritic cells — which are considered 'sentinels' of the immune system as they are responsible for inducing immune T-cell responses — to develop this Immune-Stimulating Antibody Conjugate (ISAC) technology, which was unveiled by exclusive licensee Bolt Biotherapeutics at the American Association for Cancer Research (AACR) Conference on Monday.

"What Bolt has come up with is to wake up dendritic cells within the (tumor) microenvironment, and we were able to do this in a targeted way," said David Dornan, senior VP of research, in an interview with *Endpoints News* ahead of the conference.

Many patients are refractory to checkpoint inhibitors because there are a number of immunosuppressive factors present in their tumor microenvironment, and so researchers have been trying to harness different molecules to stimulate the immune system, one of which are toll-like receptor (TLR) agonists — specialized proteins that initiate an immune response to foreign pathogens or, in this case, cancer cells.

But the challenge of delivering these adjuvants is that they must be delivered intratumorally, because if they were administered systemically — say orally or intravenously — they can become toxic as immune cells across the body are activated and the impact is not targeted, Dornan emphasized.


David Dornan

Bolt's ISAC technology is therefore targeted — it conjugates an adjuvant on to a tumor targeting antibody in order to deliver this immune agonist directly to the tumor.


Grant Yonehiro

This is a logical evolution — originally, researchers were targeting the tumor with chemotherapeutics or antibody drug conjugates, then came the checkpoint inhibitors that were designed to prime the immune system to attack the tumor, Bolt's chief operating officer Grant Yonehiro said. "We do both, we're targeting the tumor with our antibody, but we're also turning on the immune system in the tumor."

But it's still early days. Bolt has so far conducted preclinical studies.

The data suggest that the tech can "reinvigorate the immune system to an extent that if the cancer came back you have a repertoire of T-cells that can find, start proliferating and then start to kill the cancer cells," Dornan said.

"We see profound tumor shrinkage in preclinical models, we see immunological memory — the ability for once when you clear a tumor, that if the cancer comes back — if we give the mouse the cancer cells, we don't have re-administer any therapy — the mouse's T-cells recognize the tumor and eradicate it. We've done these models in cancers that are largely refractory to standard-of-care therapies."

With the addition of a cytotoxic payload, the duration of response is the main hurdle — but adding on an immuno-stimulant can circumvent that, the executives underscored. Bolt's preclinical data has shown that the ISAC approach is arming the body with a repertoire of T-cells that even if the cancer tries to mutate around it, the patient has a fighting chance.

Bolt has several programs in its arsenal, and its lead program is likely going to be developed for use in breast cancer, gastric cancer and bladder cancer, Dornan said.

The 30-employee Bay Area company has raised $72 million so far, and hopes to be in the clinic by 2020. An IPO is also on the cards. “We’re still a little early for that, but we think there’s a lot of potential for an IPO down the line,” Yonehiro said.

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