Team develops new technology platform for cancer immunotherapy

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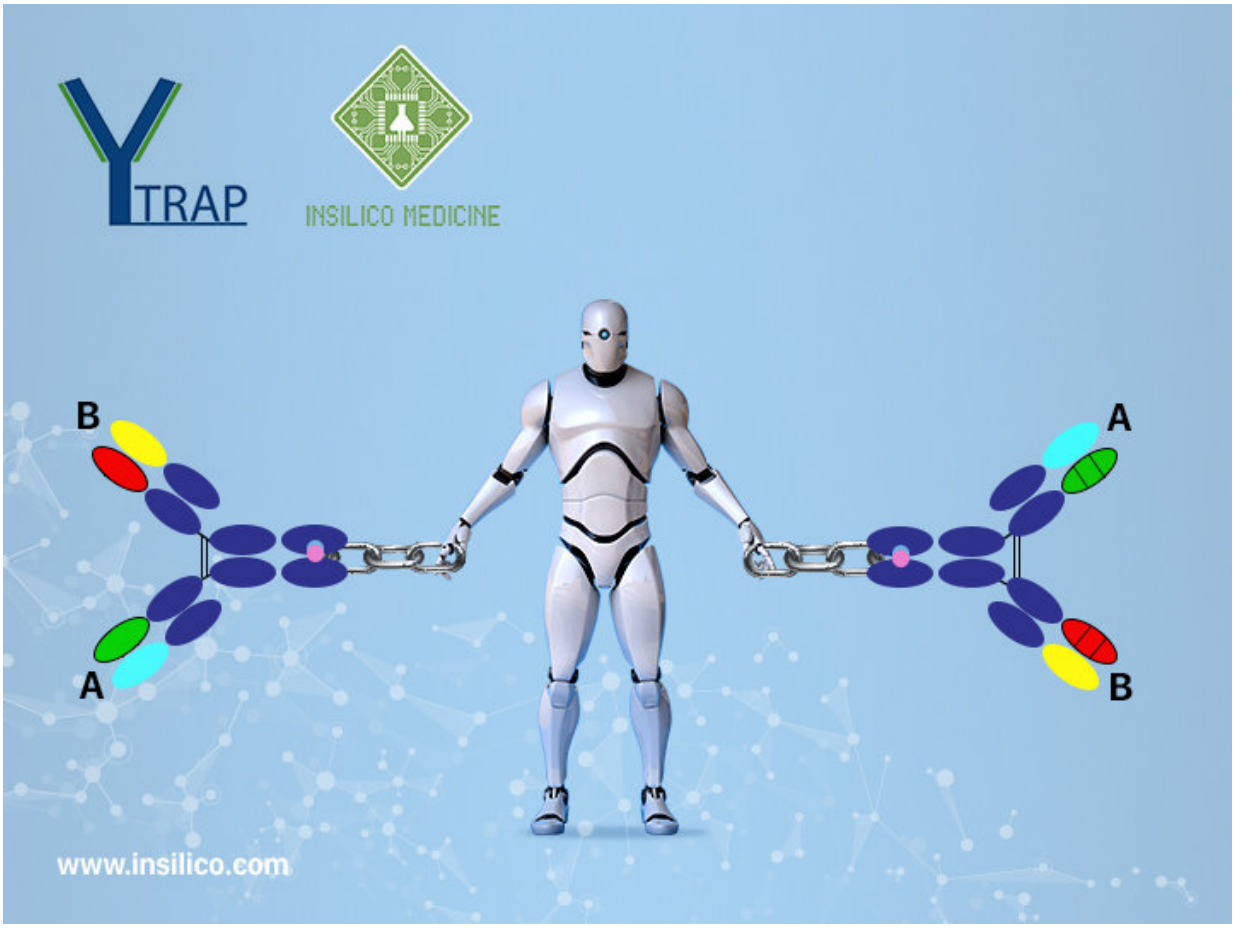

Y-traps is unleashing the immune system to treat Cancer. Credit: Insilico Medicine

Johns Hopkins researchers have invented a new class of immunotherapeutic agents that are more effective at harnessing the power of the immune system to fight cancer. Their approach results in significant inhibition of tumor growth, even against cancers which do not respond to existing immunotherapies used in the clinic. In collaboration with Insilico Medicine, a Baltimore-based leader in artificial intelligence for drug discovery, the team reports their results this week in *Nature Communications*.

Virtually all cancers—including the most common cancers, from lung, breast, and colon cancers to melanomas and lymphomas—evolve to defeat immune surveillance by amplifying natural mechanisms of immune suppression. Current clinical immunotherapy relies on using antibodies to disable specific molecules, such as CTLA-4 and PD-1/PD-L1, which function as natural brakes to suppress immune cells. Antibodies that counteract these checkpoints can unleash the immune system to attack cancer cells. While they produce lasting responses in some cases, these therapies are not effective in the vast majority of patients.

The researchers find that a major reason for the failure of immune checkpoint inhibitors is the ability of tumors to produce transforming growth factor-β (TGFβ). TGFβ plays a key role in immune regulation and development of immunosuppressive regulatory T cells (Tregs). Using Insilico Medicine software, the researchers found that TGFβ pathway activation in various cancers is highly correlated with FOXP3, the signature of Tregs. Tumors are frequently infiltrated by Tregs, and this is strongly correlated with poor outcome in multiple cancer types.

To address this challenge, the researchers invented Y-traps, a new class of bifunctional immunotherapeutic agents consisting of a targeting antibody (shaped like a "Y"), fused to a "trap" that disables an immunosuppressive molecule. To sequester TGFβ, they engineered a

trap based on the natural receptor to TGFβ. They created two different types of Y-traps: one consisting of a CTLA-4 antibody fused to a TGFβ trap, and another consisting of a PD-L1 antibody fused to a TGFβ trap.

The researchers used the CTLA4-targeted Y-trap to specifically turn off and delete Tregs. "This Y-trap not only disables CTLA-4 function, but disrupts the TGFβ feedback loop that is necessary for induction and maintenance of Tregs in the tumor," says Atul Bedi, M.D., associate professor at Johns Hopkins University School of Medicine and senior author of the study.

While the clinically-used CTLA-4 antibody, ipilimumab, could not decrease Tregs in these tumors, the CTLA4-targeted Y-trap was strikingly effective at reducing Tregs and activating antitumor immunity. Most significantly, the Y-trap was remarkably effective at inhibiting the growth and spread of tumors that were unresponsive to treatment with ipilimumab and pembrolizumab, a PD-1 antibody used in the clinic.

Antibodies to another immune checkpoint, PD-1, or its ligand (PD-L1) are approved for treatment of many advanced cancers. However, fewer than 20% of patients respond in most tumor types. "We hypothesized that TGFβ limits the efficacy of antibodies against PD-L1, so we designed a Y-trap that simultaneously counteracts both these axes of immune suppression in the tumor," Bedi says.

Indeed, Bedi and colleagues demonstrated that the PD-L1 targeted Y-Trap is significantly more effective in inhibiting tumor growth compared to clinically-used PD-L1 antibodies, atezolizumab and avelumab. Moreover, the PD-L1-targeted Y-trap was able to curtail the growth of tumors that do not respond to PD-L1 or PD-1 antibodies.

These first-in-class molecules are just the beginning. Bedi's team has already invented a family of multifunctional molecules based on the Y-

trap platform. The patented technology has been licensed from Johns Hopkins to Y-Trap, Inc., a company that is advancing its development for different cancer treatment scenarios.

"Since these mechanisms of immune dysfunction are shared across many types of cancer, the Y-trap approach could have broad impact for improving cancer immunotherapy," says Bedi.

"This approach appears to be an innovative strategy, and an exciting technical accomplishment to target multiple suppressive mechanisms in the tumor microenvironment," says Robert Ferris, MD, PhD, professor of oncology at the University of Pittsburgh, who was not connected with the study. "I look forward to seeing its translation into the clinic."

Bedi envisions using Y-traps not only for treatment of advanced, metastatic disease, but also in the neoadjuvant setting to elicit a vaccine effect— that is, giving them to patients before surgery to prevent recurrence of the disease.

More information: Rajani Ravi et al, Bifunctional immune checkpoint-targeted antibody-ligand traps that simultaneously disable TGFβ enhance the efficacy of cancer immunotherapy, *Nature Communications* (2018). DOI: 10.1038/s41467-017-02696-6

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