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AnaptysBio and TESARO team up to develop novel immuno-oncology combinations

The partnership explores novel paradigms in T-cell checkpoint receptor inhibitor antibodies.

AnaptysBio, an antibody discovery company based in San Diego, California, and TESARO, an oncology drug development and commercialization entity in Waltham, Massachusetts, have joined forces to bring new immuno-oncology therapies to help treat cancer patients. The deal combines AnaptysBio's antibody discovery platform and preclinical R&D expertise with TESARO's clinical development expertise to rapidly develop novel antibody and small molecule combinations in the fast-moving field of immuno-oncology.

Recent advances in immuno-oncology have demonstrated that the immune system is a critical line of defense against cancer. However, tumor cells have developed ways of evading the body's natural defenses inducing a state of immunosuppression by co-opting what are called T cell checkpoint receptors—receptors that halt or place the brakes on a T cell response. Under normal conditions, healthy cells present ligands on their surfaces to engage checkpoint receptors, thus protecting the cells from attack by the immune system. Many tumors evolve to present checkpoint receptor ligands on their surface to engage these receptors, resulting in the inhibition of tumor-specific T cell activity.

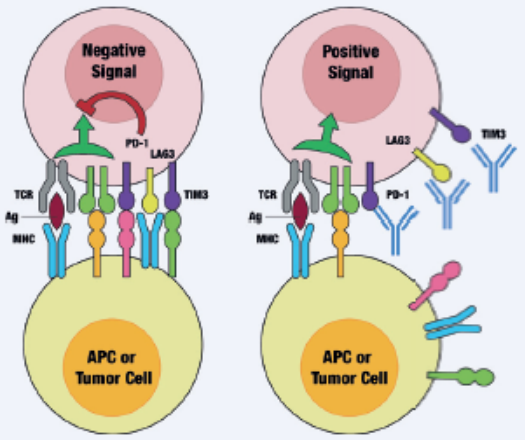
Antibodies that block checkpoint receptor–ligand interactions can release the brake and restore T cell activity, thus allowing the natural immune system to destroy the tumor cells. AnaptysBio has used its somatic hypermutation (SHM) technology to generate antibodies against three such T cell checkpoint receptors: programmed cell death 1 (PD-1), T cell immunoglobulin and mucin domain 3 (TIM-3), and lymphocyte activation gene 3 (LAG-3). Increased PD-1 ligand (PD-L1) expression has been found on many tumor types, and high PD-L1 expression has been linked to poor clinical outcomes in many different types of cancers[1]. Furthermore, treatment with anti–PD-1 antibodies has demonstrated durable responses in patients with metastatic melanoma, renal cell carcinoma and non–small cell lung cancer[2]. However, anti-PD-1 antibodies alone do not restore full T cell responsiveness, and only a subset of patients respond.

TIM-3 and LAG-3 are upregulated later in T cell activation and are often coexpressed with PD-1 on exhausted and dysfunctional T cells. Researchers at AnaptysBio and TESARO believe that concurrently targeting PD-1 and either TIM-3 or LAG-3 will result in an increase in immune response against tumor cells, representing a new cancer treatment paradigm. Indeed, a combination of anti-PD-1 and anti-TIM-3 has been shown to be more effective in inhibiting tumor growth than either agent alone in a mouse model of colon carcinoma[3]. An anti-PD-1 and anti-LAG-3 combination showed similar results in mouse models of fibrosarcoma and colon carcinoma[4].

Targeting checkpoint receptors more distal in the T-cell activation cascade has the theoretical potential to reduce side effects seen with the first T-cell checkpoint inhibitor to reach the market, Bristol-Myers Squibb's anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody ipilimumab (Yervoy). Ipilimumab was approved by the FDA in 2011 to treat metastatic or unresectable melanoma, but can cause severe inflammation-related side effects like colitis, hepatitis and toxic epidermal necrolysis. CTLA-4 is upregulated very early during T-cell activation, and ipilimumab results in T-cells attacking many types of healthy cells. Conversely, PD-1, TIM-3 and LAG-3 are upregulated later in the T-cell activation cascade, and antibodies against those receptors may result in a more specific immune response to tumors and be less toxic to patients.

On March 13, 2014, TESARO and AnaptysBio announced a collaboration and exclusive license agreement for AnaptysBio's antibodies against PD-1, TIM-3 and LAG-3, including monospecific and dual-reactive antibodies. The companies will jointly complete preclinical development of the antibodies, while TESARO will be responsible for all clinical development, regulatory, commercial and manufacturing activities.

The lead candidate from the immuno-oncology program is TSR-042, an anti-PD-1 antibody that is tenfold more potent than competitor PD-1-specific antibodies. The partners expect to begin clinical testing on TSR-042 in the second half of 2015 and have already selected an anti-TIM-3 clinical candidate. TESARO and AnaptysBio also expect to select an anti-LAG-3 clinical candidate by the third quarter of 2014 and PD-1/TIM-3 and PD-1/LAG-3 dual reactive antibody clinical candidates by the first quarter of 2015. In addition, the partners plan to investigate combinations of TSR-042 with other therapeutic candidates in TESARO's pipeline, namely the anaplastic lymphoma kinase/tropomyosin-related kinases (ALK/TRK) inhibitor TSR-011 and the poly (ADP-ribose) polymerase (PARP) inhibitor, niraparib. TSR-011 is currently in a phase 1/2 trial to treat non–small cell lung cancer and other tumors with mutations in ALK or TRK. Niraparib is currently in phase 3 trials to treat ovarian cancer and BRCA+ breast cancer and phase 1 testing to treat Ewing's sarcoma.



Therapeutic antibodies in development target checkpoint receptor–ligand interactions with receptors (PD-1, TIM-3 or LAG-3) to restore T cell activity against the tumor cell.

TESARO, whose business model is to in-license promising candidates and develop them through approval and commercialization, was attracted to AnaptysBio's ability to generate antibodies against targets that were previously thought to be intractable such as TIM-3. AnaptysBio's monoclonal discovery platform couples SHM *in vitro* with a novel mammalian cell display system, allowing simultaneous selection for potency, function, expression, stability and other biophysical features required for successful therapeutic antibody development.

References

1. Zou, W. & Chen, L. *Nat. Rev. Immunol.* **8**, 467–477 (2008).
2. Drake, C.G., Lipson, E.J. & Brahmer, J.R. *Nat. Rev. Clin. Oncol.* **11**, 24–37 (2014).
3. Sakuishi, K. *et al. J. Exp. Med.* **207**, 2187–2194 (2010).
4. Woo, S.-R. *et al. Cancer Res.* **72**, 917–927 (2012).

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