BioEclipse Therapeutics
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BioEclipse Therapeutics targeted biotherapy

Dual biotherapy may deliver a curative treatment for cancer

BioEclipse (formerly ConcentRx) is preparing to start clinical trials of its novel approach to immuno-oncology, which combines two monotherapies with a synergistic effect.

Transformative progress in cancer biology and the role of the immune system has disrupted the field, yet a cure remains elusive because of major problems with existing cancer therapies: cancer cells become resistant to chemical therapies and can evade the immune system, and ultimately the disease recurs. BioEclipse Therapeutics (formerly ConcentRx) is developing a novel, multi-mechanistic approach that circumvents the mechanisms used by tumor cells to evade the patient's immune system, making resistance less likely and leading to an immune response against multiple tumor antigens that precludes cancer recurrence.

Based in California, USA, BioEclipse is an emerging, clinical-stage biopharmaceutical company committed to delivering first-in-class curative immuno-oncology therapeutics to patients with cancer. "Even though the words 'cure' and 'cancer' are rarely used in the same sentence, we can now contemplate a cure," said Pamela Contag, CEO of BioEclipse. "We have combined two monotherapies that create a synergistic effect, acting together to target and kill cancer cells deep within the tumor, and leading to a durable immune response that enables our bodies to combat new tumor growth."

BioEclipse recently submitted an investigational new drug (IND) application to the US Food and Drug Administration for its cancer immunotherapy, which is patented by Stanford University, and manufacturing is in place for a phase 1/2 trial.

First-in-class dual biotherapy

The technology is a first-in-class targeted dual biotherapy comprising immune effector cells that carry a therapeutic payload of oncolytic virus. It utilizes the ability of these immune cells to migrate to tumors and bind directly to cancer cells, thereby facilitating the delivery of a lytic agent (virus) that preferentially replicates in tumor cells, but not in normal cells. Administered systemically, the combination therapy is effective because the replication of the oncolytic virus delivered deep into the tumor can de-bulk large tumors.

Immune effector cells called cytokine-induced killer (CIK) cells are activated *in vitro* before infection with an oncolytic virus. The mechanism of action is not major histocompatibility complex (MHC) restricted, so either the patient's own cells or donor cells can be used. Importantly, unlike immunotherapy approaches that rely on tumor-specific antigens for cell killing, these effector cells recognize the abnormal tumor vasculature, tumor secreted chemokines and a class of cellular-stress-associated ligands expressed on tumor cells, which offers the potential to treat numerous types of cancer[1].

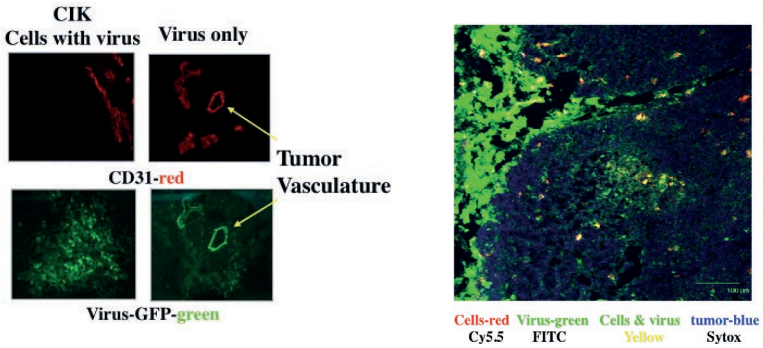

Figure 1: Image-guided histopathogy. The virus alone does not leave the vasculature, however immune cells are able to deliver the oncolytic virus deep into the tumor. Reprinted from *Science* **311**, 1780–1784 (2006) DOI: 10.1126/science.1121411.

The dual biotherapy relies on a complex set of interactions among immune effector cells, oncolytic virus, tumor cells and the body's immune response[2,3]. Cell-mediated delivery of the oncolytic virus serves to protect the viral payload from immune attack after administration. As the virus lies dormant for approximately 48 hours after infection of the effector cells, the majority of infected cells migrate to the tumor before releasing their payload, which results in greater on-target delivery of the lytic agent. Data from preclinical studies confirm that biodistribution within tumor tissue is enhanced compared with that observed after the administration of virus alone[3].

Synergistic effect

Once the biotherapy reaches the tumor, it launches an attack on several fronts[1–3]. Infected effector cells penetrate deep into the tumor and release multiple infectious viral particles in the tumor microenvironment, where they replicate and spread rapidly, producing a dramatic antitumor effect. At the same time, uninfected effector cells (which are also present in the dual biotherapy) target and kill tumor cells. Viral infection of the tumor induces a stress response that makes tumor cells more susceptible to effector cell therapy, thus further enhancing the tumor-killing process.

Results from animal models of human cancer show that the dual biotherapy is highly effective, offering a synergistic cancer-killing effect that is more efficacious than either therapy alone[1,3]. For example, a preclinical study using a xenograft mouse model of human ovarian cancer found that survival was 100% at 30 days after treatment with dual biotherapy, compared with 0% at the same time point in either of the two groups treated with a single therapy[3]. Preclinical models show that the combined therapeutic has a good safety profile with minimal viral infection of normal tissues. Studies of CIK cells in humans and the oncolytic virus used as monotherapies also demonstrate good safety profiles[1,4].

Durable immune response

BioEclipse's approach also has potential for host vaccination *in situ*, as there is evidence that a strong cytotoxic T lymphocyte response is initiated, which could help maintain the durable immune response observed in preclinical studies[2]. "First, the dual biotherapy is directed at the tumor microenvironment to kill the tumor cells," said Contag. "Then, a durable cytotoxic T cell immune response develops against specific tumor antigens from the lysed tumor cells."

BioEclipse's formulation is broadly applicable for several indications of solid and non-solid tumors. Patients can be treated multiple times for the same or different cancer.

"We have attracted a great team, have a scalable business model, and believe that results from our 2018 phase 1/2 trial will demonstrate that our pre-clinical efficacy can be translated to humans," said Contag.

1. Schmidt, T.L., *et al. Immunol. Res.* **58**, 300–306 (2014).
2. Thorne, S.H. & Contag, C.H. *Gene Ther.* **15**, 753–758 (2008).
3. Thorne, S.H. *et al. Science* **311**, 1780–1784 (2006).
4. Zeh, H.J. *et al. Mol. Ther.* **23**, 202–214 (2015).

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