

The Engineered T-Cell Receptor in Fusion Proteins, Antibodies & Cells: Emerging Opportunities for the Biopharmaceutical Industry

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Abstracts

A comparative analysis and assessment of TCR technologies, pipelines and companies from an industry perspective

Therapeutic monoclonal antibodies have become an increasingly successful treatment modality with sales of US\$ 65 bln in the year 2012 and with an average (continuous) annual growth rate from 2006 to 2012 of 18.9%. While antibody technologies are steadily evolving, the spectrum of druggable targets for monoclonal antibodies has remained limited to extracellular antigens, albeit including proteins, carbohydrates and glycolipids.

Access to druggable, IP-protected and validated new targets is a major bottleneck in the biopharmaceutical industry. Technologies which can deliver both new targets and the corresponding treatment modality, can expect significant financial acknowledgement.

The T-cell receptor (TCR) has recently emerged as a means to target peptide antigens derived from intracellular proteins, however, in a major histocompatibility complex (MHC)-restricted manner. The first companies have overcome significant technical hurdles in putting together a library of viable new TCR-targeted antigens and establish the corresponding standardized protein- and cell-based therapeutic frameworks.

This report entitled **The Engineered T-Cell Receptor in Fusion Proteins, Antibodies & Cells: Emerging Opportunities for the Biopharmaceutical Industry** published in October 2013 describes chances and pitfalls in exploiting the opportunities which offers the engineered T-cell receptor as integral part of fusion proteins, antibodies and cellular products. The key success factors are highlighted, the technical challenges described

and solutions presented.

Benefits from the report:

Identify players in the field, from industry and academia;

Find out which TCR technologies are valued by Big Pharma and Biotech;

Understand the value of intracellular antigens targeted by the TCR;

Recognize the challenges of TCR-based therapeutics and their solutions;

Learn which TCR-based therapeutics are attractive for partnering;

Find out which TCR therapeutic approaches are not yet tapped.

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About

CAR-Modified T-cells for Cancer

Quite a number of review articles have been published describing CAR design, T-cell production and dose, prior chemotherapy conditioning regimens, and tumor burden (e.g. Sadelain, 2013; Han, 2013; Curran, 2012; Zhang, 2013; Davila, 2013). CAR T-cell therapy is one modality of adoptive cell transfer, i.e. the treatment of patients with cell populations that have been expanded ex vivo (Restifo, 2012).

Background of CAR-Modified T-Cells

Some say that the chimeric antigen receptor is an artificial T-cell surface receptor that simulates the physiological function of the native T-cell receptor (Zhang, 2013). However, different from TCRs, CARs relay excitatory signals to T-cells in a non-MHC-restricted manner and can target non-protein antigens, e.g. carbohydrates and glycolipids. The CAR is composed of an extracellular antigen recognition domain, a spacer, a transmembrane domain and an intracellular (cytoplasmic) T cell activation domain. Commonly, the extracellular antigen recognition domain contains a single chain fragment variable (scFv) derived from a monoclonal antibody against a tumor-associated antigen (TAA) on the tumor cell surface. Early scFv constructs were derived from mouse monoclonal antibodies and should be humanized to avoid immunogenic reactions in immunocompetent hosts resulting in inhibition of the function of CAR-modified T-cells ((Zhang, 2013). Using gene transfer technologies, T cells can be genetically modified to stably express the CAR on their surface. The CAR combines the advantages of an antibody's tumor specificity and a T cell's effector function. Upon binding to a TAA, CARs can trigger T cell activation in a manner similar to that of endogenous TCRs.

Tumor targeting of CARs via a non-MHC-dependent mechanism in contrast to TCRs confers the advantage to overcome the tumor's ability to escape immunodetection by down-regulation of HLA molecules on the cell surface (Curran, 2012). Furthermore, it does not limit the number of patients by the HLA type.

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