Allogeneic anti-PTK7 CAR-T cells for the treatment of solid tumors

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Abstract

Protein Tyrosine Kinase 7 (PTK7), also known as colon carcinoma kinase 4 (CCK-4), is a highly conserved citospedically reactive tissue kinase with inherent signaling activity. PTK7 is a member of the Fyn subfamily and thought to function in cell proliferation, adhesion, migration and apoptosis. PTK7 has been shown to be highly expressed in certain cancer types including breast, lung, pancreatic, and ovarian. Downregulation of PTK7 by shRNA has been shown to reduce tumor growth and metastatic development in xenograft mouse models. Furthermore, high PTK expression in principle negative breast and A498 patients has been linked to poor prognosis. PTK7 therefore appears to be an attractive target for solid cancer therapeutic intervention and has been targeted clinically with an Antibody Drug Conjugate (PF-06647020). However, the protein is also expressed in normal adult tissues, particularly in the stromal compartment of the uterus, and in immunocompromised mouse xenograft models of breast, lung, colon, pancreatic and ovarian cancer. However, consistent in vivo xenograft models, transient acute toxicity (indicated by a drop in body weight) was observed 5-7 days on study (blue arrow at right). All mice rapidly recovered to above baseline. Latent toxicity that was more variable amongst the xenograft experiments was also observed. Understanding and developing appropriate mitigation strategies to address the observed toxicity is required to develop further a safe and efficacious allogeneic anti-PTK7 CAR-T cell therapy for solid cancer treatment.

Figure 1: PTK7 has high expression in a variety of solid human cancers

Figure 2: Allogeneic anti-PTK7 CAR-T cells are generated efficiently using CRSPR/Cas9

Figure 3: Anti-PTK7 CAR-T cells show efficacy across a variety of in vivo xenograft models, but appear to induce acute and latent toxicity

Figure 4: On-target/off-tumor toxicity is visible in mice because anti-PTK7 CAR-T cells exhibit maruxine reactivity

Figure 5: A “modified” anti-PTK7 CAR mitigates on-target/off-tumor toxicity in vivo while maintaining efficacy

Conclusions from Preclinical Studies

- PTK7 is highly expressed in many different solid tumor cancer types and to a lesser extent in some normal tissues.
- Anti-PTK7 CAR-T cells are efficacious in vivo against a variety of solid tumor cell lines.
- Acute and latent toxicity in vivo, observed as loss of body weight, occurs due to species crossreactivity of the anti-PTK7 CAR-T cells.
- We developed a mitigation strategy to address the on-target/off-tumor toxicity through spatial control of modified CAR-T cells within the TME.
- Modified anti-PTK7 CAR-T cells successfully mitigate both the acute and latent toxicity while maintaining high efficacy in vivo.