abstract

Curing Allergy by Specifically Eliminating Human IgE-Producing B cells

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The prevalence of IgE-mediated allergic disorders (~5-10% of the worldwide population) has been rising markedly in industrialized societies, posing significant clinical and socioeconomic challenges, estimated at an annual cost of dozens of billions of dollars globally. These disorders are characterized by hypersensitivity reactions that range from acute, life-threatening anaphylaxis to chronic debilitating conditions, such as allergic asthma and autoimmune chronic urticaria. Despite advances in therapeutic strategies, the benefits obtained by existing treatments are either allergen-specific, or transient, making them inherently incapable of providing definitive cures. This is because these therapies only eliminate the free IgEs in the bloodstream, but do not eradicate their source - the rare subset of B cells that produce IgEs. Here, we present a novel chimeric antigen receptor (CAR)-T cell therapy targeting M1', the extracellular domain that is unique to the IgE B-cell receptor (BCR) on IgE producing cells. This domain, absent from secreted IgE, offers an unparalleled opportunity for selective targeting of IgE-producing cells. Our CAR construct, dubbed Q-CAR, demonstrated robust cytotoxicity against primary human IgE-secreting cells, and significantly reduced IgE production *in vitro*. In an NSG mouse model, Q-CAR inhibited the growth of IgE-expressing tumors and extended survival (p value=1.6E-05). By circumventing the limitations of

previously reported CAR designs that inherently targeted free IgE in addition to their producing B-cells—our strategy provides a novel framework for the development of cellular cures for allergic diseases. Zelig Therapeutics is now launching a pipeline of therapeutic programs, harnessing both in vivo and autologous formats, for a multitude of devastating allergic disorders. We ultimately aim to lead a revolution in the management of allergies, introducing one-and-done cures.