T-cell engagers: some lessons learned from a minimal mechanistic model of trimer formation.

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Abstract

T-cell engagers (TCEs) are a promising therapeutic strategy for solid tumours and haematological malignancies. They are a class of bispecific antibodies designed to act as a cross bridge between T-cells and target malignant cells, by engaging T-cell receptors (TCRs) on one arm and tumor-associated antigens (TAAs) on malignant cells with the other arm. It is agreed upon that TCE efficacy is related to the ability of the compound to stimulate T-cell effector function, which depends on the formation of trimers (often referred to as “trimeric synapses” or “ternary complexes”).

It is known that TCEs follow a bell-shaped relationship between antibody concentration and trimer concentration. If we assume that trimer formation is the main efficacy biomarker driving T-cell effector function, there is a point of diminishing returns beyond which efficacy is expected to plateau or even decrease at higher doses. Theoretical models can capture this dynamic which is further observed in vitro. This “hook effect” phenomenon can potentially arise for any bispecific molecule. The mechanistic rationale for it is that trimer formation can only occur if both an antibody-receptor dimer and an unoccupied receptor are simultaneously available. Excess TCE saturates all available tumor receptors or effector receptors, thus biasing the equilibrium towards dimers instead of trimers.

We present an exploratory analysis for a generic bispecific TCE, targeting CD3 on T-cells and a tumor-specific receptor on cancer cells, and discuss implications for compound design and clinical dosing. We utilised a minimalistic kinetic model of trimer formation, with the simplifying assumption that reactions occur in a well-mixed compartment. We used the model to investigate the interplay between drug exposure, target affinity, and target expression levels.

Target expression levels, which cannot be controlled, may differ among patients. We found that the exposure at which the efficacy plateau is predicted depends mainly on the relative affinities of the antibody for each target, but not on target expression levels. Therefore, the optimal exposure level may not be “patient-specific”, but rather “compound-specific”.