

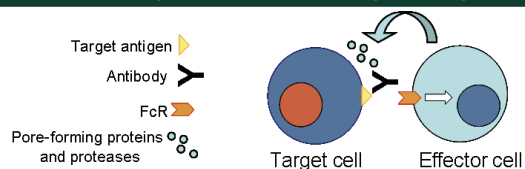
# SEA technology: a novel strategy for enhancing antibody effector function

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## 1. Background

The activity of monoclonal antibodies (mAbs) can be enhanced by a number of chemical and genetic strategies. We describe a novel strategy, Sugar Engineered Antibody (SEA) technology, for enhancing antibody-dependent cellular cytotoxicity (ADCC) through modification of the mAb carbohydrate. A series of small molecule fucose analogs were added to mAb-expressing Chinese hamster ovary (CHO) cells, with the resulting mAbs showing a significant reduction in their carbohydrate fucosylation. We demonstrate that these mAbs show markedly increased ADCC activity and improved CD16 binding. The fucose analogs inhibit GDP-mannose dehydratase (GMD), the first enzyme in de novo synthesis of GDP-fucose, and lead to global depletion of intracellular GDP-fucose. We also demonstrate that this strategy yields mAbs with significantly reduced fucosylation in large scale CHO cell culture and is broadly active across a variety of mAbs and expression systems. Since genetic modification of the mAb-producing cell line is not required, SEA technology can be readily applied from the mAb screening to manufacturing stage to generate effector function enhanced therapeutic antibodies.

## 2. Antibody-Dependent Cellular Cytotoxicity



Antibody-dependent cellular cytotoxicity (ADCC) is an important component of antibody efficacy. Antigen-bound mAbs engage CD16 on the surface of effector cells (NK and macrophages), which release pore-forming proteins and proteases to lyse the target cell. ADCC activity can be improved through a variety of techniques, including removing the fucose residue from the mature, biantennary mAb carbohydrate.



## 3. Unexpected Activity of Fucose Analogs

