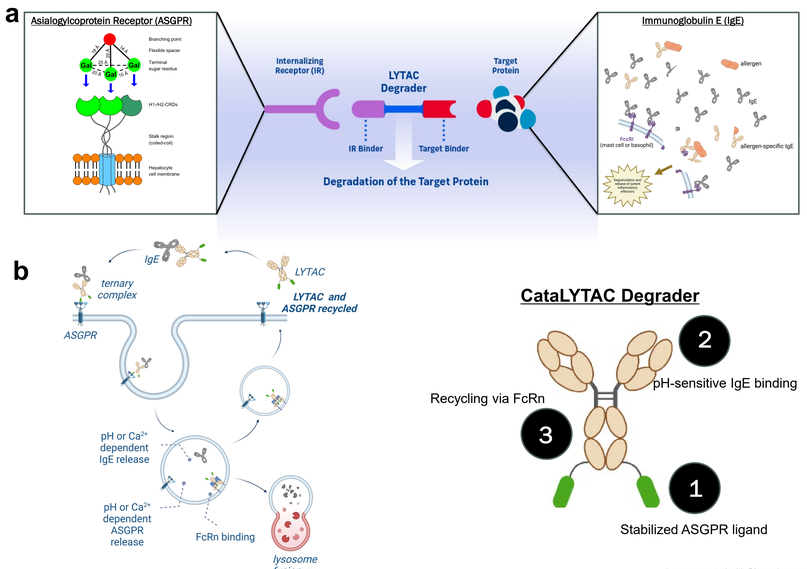
Catalytic Degradation of Circulating Targets by FcRn-mediated Cycling LYTACs

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Designing Catalytic Lysosome Targeting Chimeras (CataLYTAC) Degraders

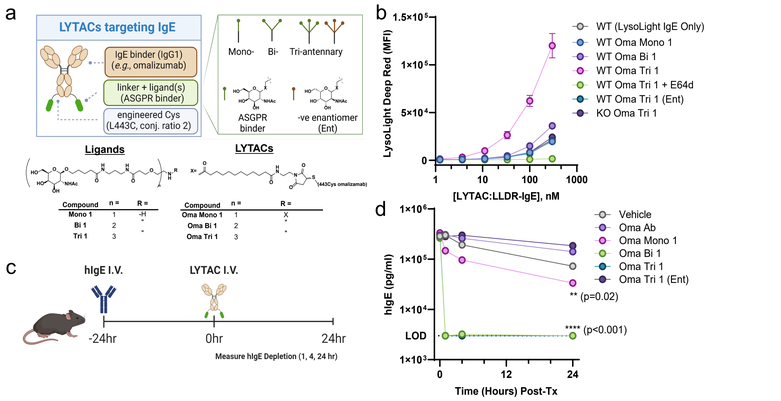


Design Principles of IgE CataLYTAC Degraders

a) LYTACs are heterobifunctional molecules that induce proximity between a target (IgE) and an internalizing receptor (ASGPR) resulting in target delivery to the lysosome and subsequent degradation.

b) Schematics illustrating key cellular events to enable catalytic activity (left) and relevant cataLYTAC degrader design features (right)

Rapid and Deep Depletion of IgE by Early Generation LYTACs



In vitro and in vivo activity of omalizumab-based LYTACs with non-stabilized ligands

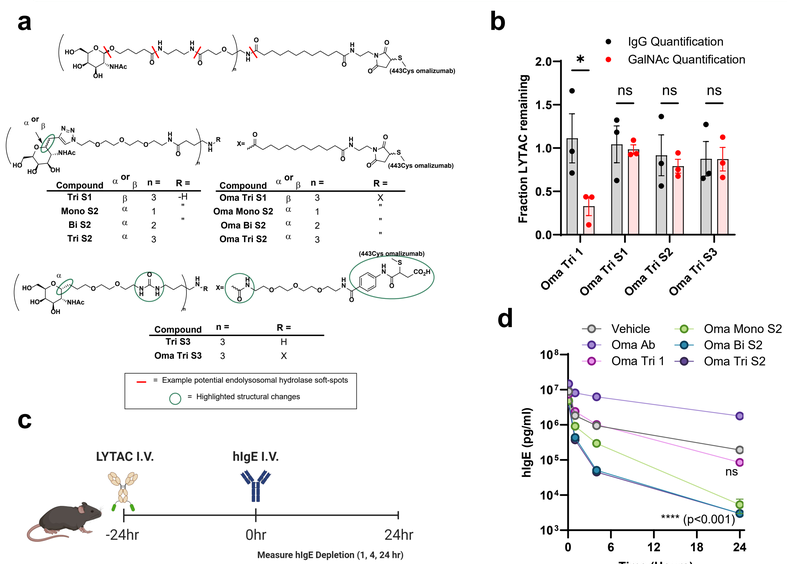
a) Schematic illustrating IgE targeting LYTAC and ligand designs.

b) In vitro uptake and lysosome catabolism of Lysolight Deep Red-labeled IgE in ASGPR WT or KO HepG2 cells.

c) C57BL/6 mice were dosed with 1 mg/kg human IgE intravenously 24 hours before being dosed with 5 mg/kg LYTACs intravenously.

d) In vivo clearance of human IgE by LYTAC molecules (n=3/group; 2-way ANOVA).

Stabilizing ASGPR Ligands for Endosome Recycling



In vitro and in vivo activity of stabilized ASGPR ligands

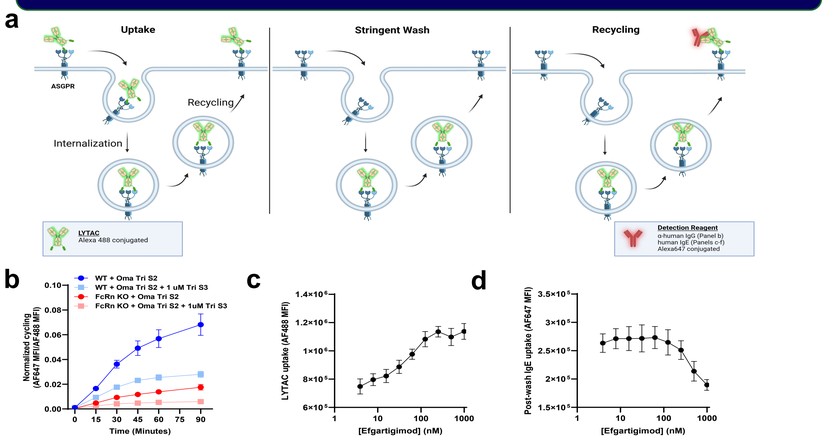
a) Potential ASGPR ligand hydrolase cleavage sites (red) and substitutions (green).

b) LYTACs were incubated with tritosomes for 0 or 3 hours, and concentrations were measured using a-IgG or ASGPR ELISAs. Fraction of LYTAC remaining after 3 hours, quantifying both IgG and GalNAc concentrations are shown.

c) Inverse dosing study - mice were dosed with 5 mg/kg LYTAC intravenously 24 hours before being challenged with 1 mg/kg hIgE intravenously.

d) In vivo clearance of human IgE by LYTAC molecules (n=3/group; 2-way ANOVA).

Stabilized LYTACs Recycle via FcRn



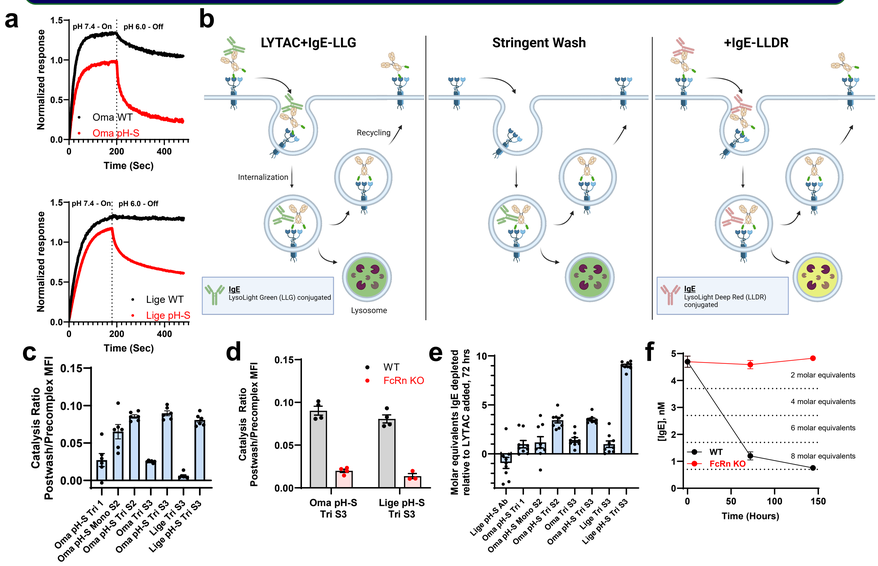
In vitro recycling of LYTACs with stabilized ASGPR ligands and role of FcRn

a) Schematic of recycling assay using anti-human IgG (b) or hIgE (c,d) for detection.

b) Recycling (normalized to uptake) over a 90 min post-wash time course in WT or FcRn-KO HepG2 cells.

c,d) Uptake (c) and recycling (d) in the presence of the FcRn inhibitor efgartigimod.

Requirements for Catalytic LYTAC Activity



Catalytic and super-stoichiometric depletion activity of cataLYTACs

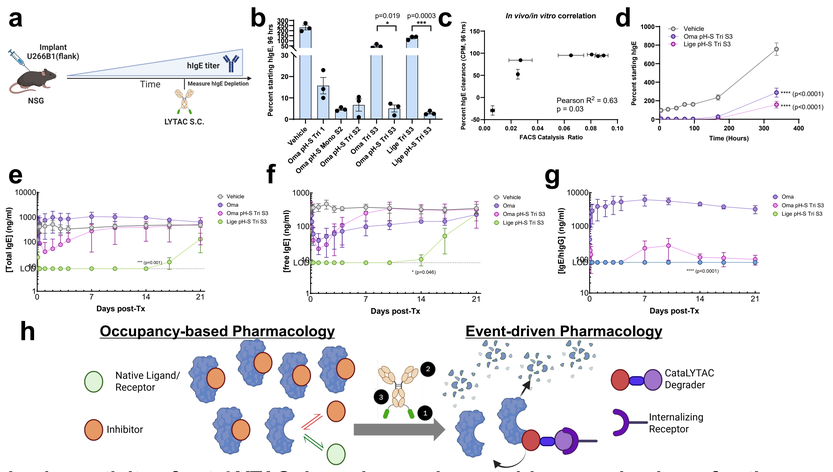
a) Binding of WT and pH-sensitive (pH-S) omalizumab (top) and ligelizumab (bottom) variants to IgE at pH 7.4 (association) and pH 6.0 (dissociation).

b) Schematic of catalysis assay.

c,d) Catalysis ratio (LLDR/LLG) of indicated LYTACs in WT and FcRn-KO HepG2 cells.

e,f) Depletion of super-stoichiometric quantity of IgE:LYTAC in WT and FcRn-KO HepG2.

Deep and Durable Elimination of IgE by CataLYTAC Degraders In Vivo



In vivo activity of cataLYTAC degraders and event-driven mechanism of action

a) In vivo constant hIgE contant production mouse model.

b,c,d) hIgE levels at 96 hrs following 10 mg/kg LYTAC dose (b) in vitro/in vivo correlation (c) and sampling timecourse for omalizumab and ligelizumab-based cataLYTACs (d).

e,f,g) Total IgE (e), Free IgE (f) and Ig:IgE (g) complex levels following cataLYTAC dosing in cynomolgus monkeys (5 mg/kg subcutaneously, n=3; 2-way ANOVA).

h) Occupancy-based (e.g., traditional inhibitors) vs. event-driven (e.g., degraders) MOAs.