LCA-0321 is a Novel Targeted Protein Degrader Designed to Specifically and Rapidly Eliminate TSHR Autoantibodies for the Treatment of Graves' Disease

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Designing a Lysosome Targeting Chimera (LYTAC) Degrader for the Treatment of Graves' Disease

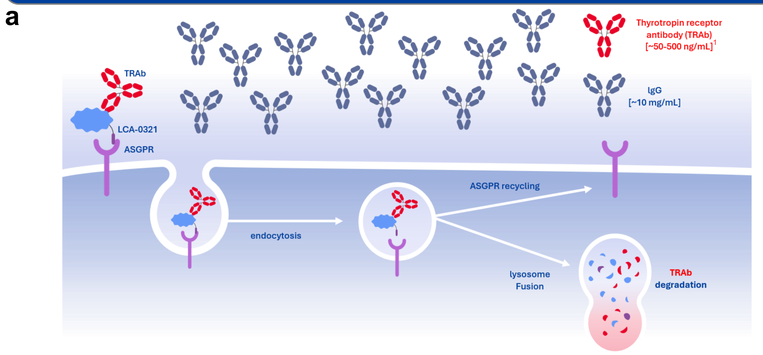


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Differentiated LCA-0321 Design Principles

- Designed to **directly target and eliminate the root cause** of Graves' disease (TRAbs)
- **Sparing broader IgG pool** may lead to improved dosing and lower immunosuppression
- Leverages **clinically validated pathway**[2] via ASGPR for elimination in hepatocytes
- Potential for **greater depth of TRAb depletion**, which is correlated with thyroid function improvement
- Does not impact TSH binding to TSHR, **minimizing risk of inducing hypothyroidism**

Design Principles of LCA-0321

a) LYTACs induce proximity between a target (TRAbs) and an internalizing receptor (ASGPR) resulting in target delivery to the lysosome and subsequent degradation.

b) Key LCA-0321 design features and differentiation. TSHR ECD = Thyroid stimulating hormone (thyrotropin) receptor extracellular domain. ASGPR = Asialoglycoprotein receptor. HSA = Human serum albumin

LCA-0321 Binds TRAbs and ASGPR while Sparing TSH

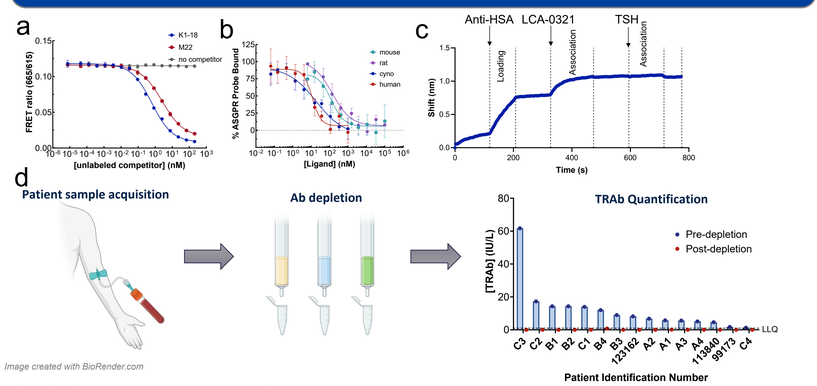


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LCA-0321 biochemical binding studies

a,b) Displacement binding assays measuring binding of LCA-0321 to two patient-derived TRAbs, K1-18[3] and M22[4] (a) and ASGPR from various species (b). Mean +/- SD (n=3 biological replicates)

c) Biolayer interferometry sensorgram showing undetectable binding of LCA-0321 to TSH (75 nM).

d) Serum from 15 individuals with GD with TRAb levels ranging from 1.7-61.7 IU/L (left). Samples were applied to an amine-coupled LCA-0321 resin and the flow through was evaluated for TRAb levels using a 3rd generation TRAb ELISA kit (RSR Limited) (middle). TRAbs were depleted from all serum samples below LLQ for the assay (0.8 IU/L) (right). Serum samples A-C were generously provided by Mario Salvi (Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Endocrinology Department)

LCA-0321 Promotes ASGPR-dependent TRAb Uptake and Degradation In Vitro

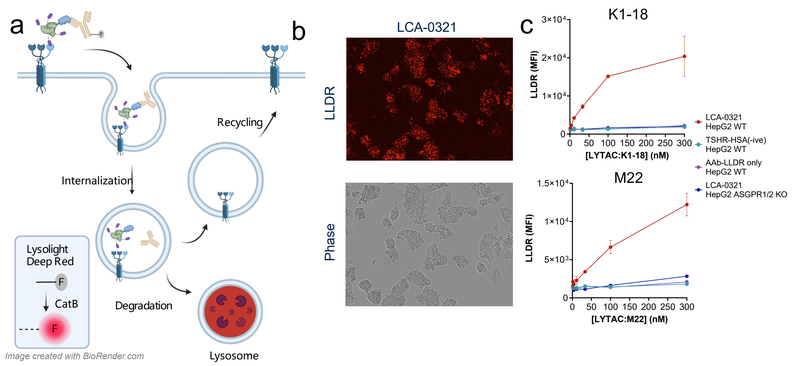


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TRAb uptake and degradation in vitro

a) Schematic showing in vitro assay to evaluate internalization and lysosomal degradation of TRAbs labeled with the cathepsin cleavable quenched probe LysoLight Deep Red (LLDR).

b) HepG2 (ASGPR+) cell line treated with LCA-0321 (100nM) and LLDR labeled K1-18 (100 nM) for 24 hrs and imaged at 20X magnification on an Incucyte S3 instrument.

c) HepG2 wild type (WT) and ASGPR1/2 knockout (KO) cell line treated with LYTAC and the indicated TRAb across dose range. TSHR-HSA conjugated to a non-ASGPR binding stereoisomer (TSHR-HSA(-ive)) is a negative control for ASGPR binding. Mean +/- SD (n=3 biological replicates).

LCA-0321 Directs TRAbs to Hepatocytes In Vivo

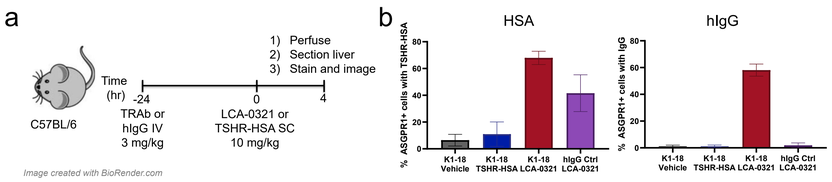
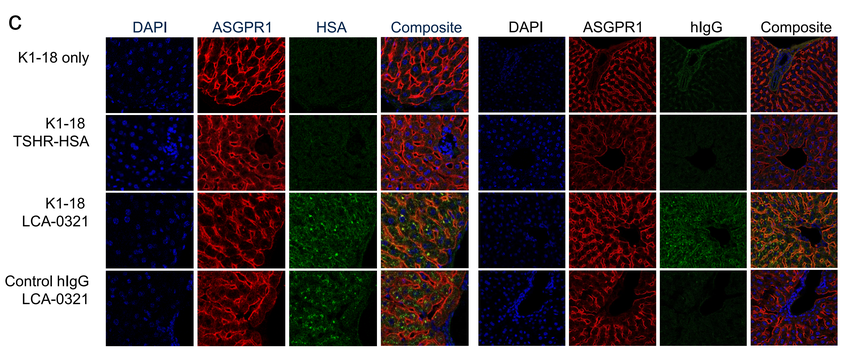


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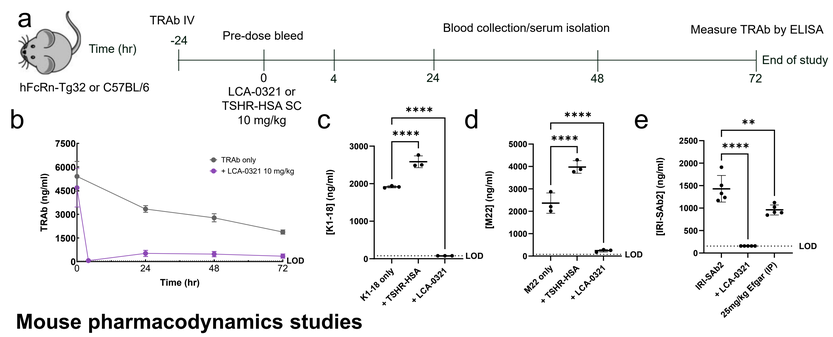
In vivo LCA-0321 and TRAb liver distribution

a) Schematic showing dosing strategy for biodistribution studies. IV = intravenous. SC = subcutaneous.

b) % of ASGPR+ cells containing internalized IgG (TRAb) or HSA (LCA-0321 and TSHR-HSA). Mean +/- SD from an average of 75,000 cells/mouse and n=3 mice/group.

c) Representative images related to the quantification shown in b. Images were acquired on a Leica STELLARIS confocal microscope at 20X magnification. Images represent a single Z plane and are representative of 3 individual liver sections.

LCA-0321 Demonstrates Rapid and Deep Depletion of TRAbs In Vivo



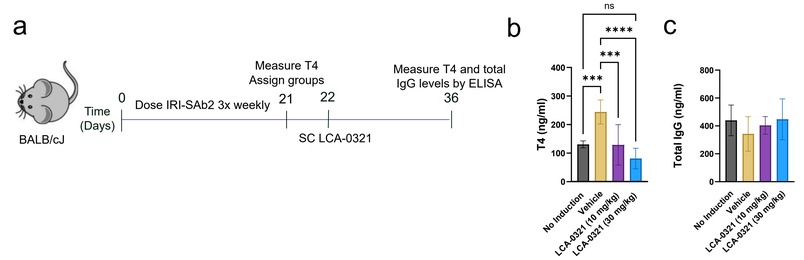
Mouse pharmacodynamics studies

a) Schematic illustrating dosing strategy for mouse pharmacodynamics studies.

b) Time course showing TRAb (K1-18) serum levels following a single SC administration in hFcRn-Tg32 mice. Mean +/- SD (n=3 mice/group)

c-e) Levels of 3 TRAbs (K1-18, M22 and mouse TSHR cross-reactive IRI-SAb2[5]) measured at 4 hours following a single SC administration in C57BL/6 mice. Mean +/- SD. Statistical analysis: One-way ANOVA with Tukey's multiple comparison test; n=3-5 mice/group. Efgar = Efgartigimod

LCA-0321 Renormalizes T4 Levels in a Mouse Model of Graves' Hyperthyroidism



Passive Immunization Model of Graves' Hyperthyroidism

a) Schematic illustrating mouse model of TRAb-induced hyperthyroidism and dosing.

b) T4 levels in uninduced or IRI-SAb2 induced mice and following a single SC dose in induced mice. Mean +/- SD. Statistical analysis: One-way ANOVA with Tukey's multiple comparison test; n=6-8 mice/group.

c) As in b except measuring total IgG levels. Mean +/- SD.

Preclinical studies demonstrate a differentiated profile for LCA-0321 as a treatment for Graves' Disease

LCA-0321 selectively **eliminated TRAbs** and restored a **euthyroid** state without impacting normal **TSHR signaling** or **total IgG**

These studies provide preclinical rationale for the ongoing Phase 1 trial of LCA-0321 in participants with Graves' Disease.

For more information visit our booth #50A

References

1) Nakatake N, et al. Thyroid. 2006;16:1077-1084. 2) Springer AD, et al. Nucleic Acid Ther. 2018;28:109-118. 3) Evans M, et al. Clin Endocrinol. 2010;73:404-412. 4) Sanders J, et al. Lancet. 2003;362:126-128. 5) Costagliola S, et al. Mol Endocrinol. 2004;18:3020-3034.