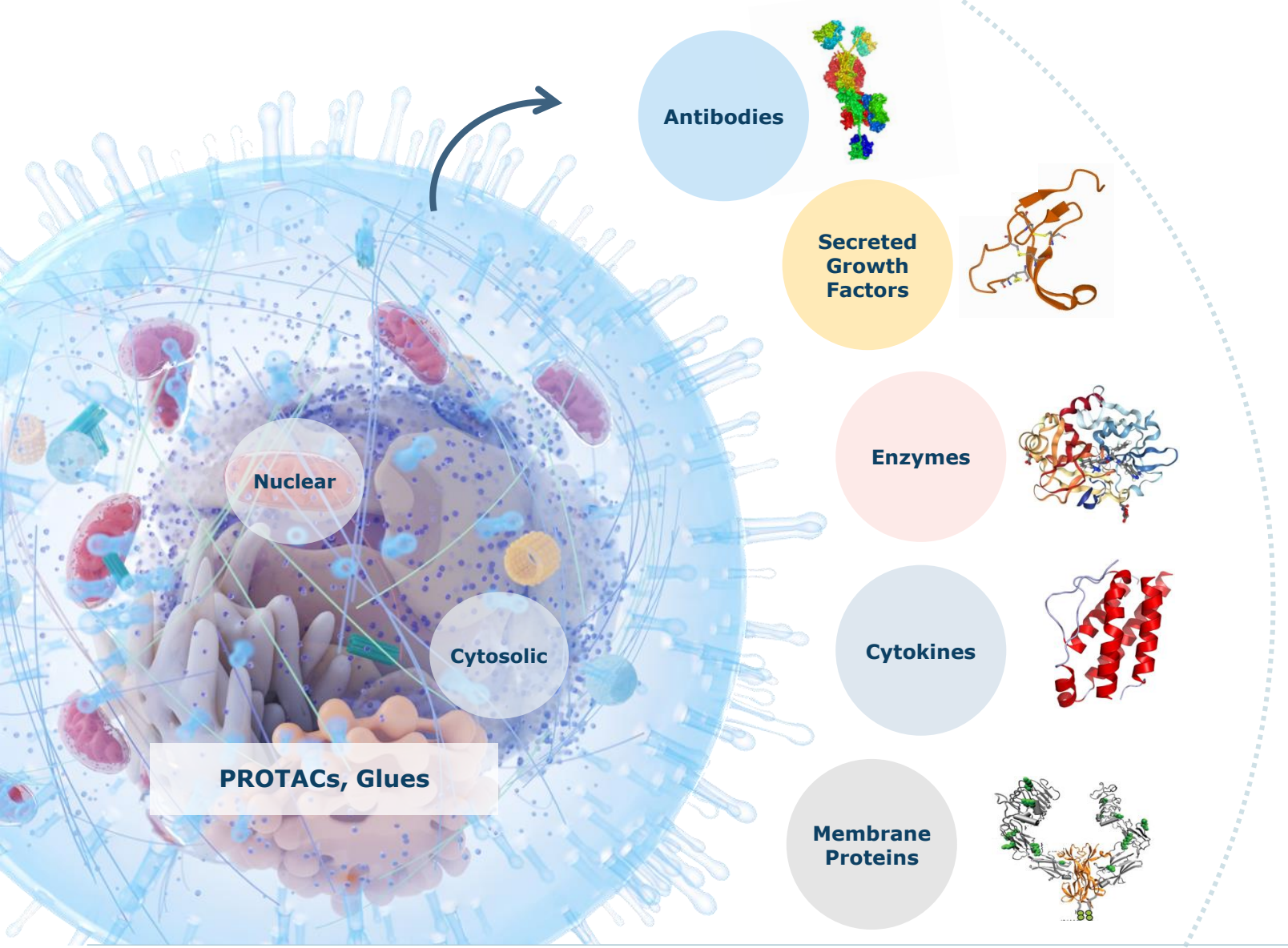
Targeted Degradation of Extracellular Proteins with ATACs (ASGPR Targeting Chimeras)

5th Annual
Targeted Protein Degradation Summit

Boston, MA
October 28, 2022

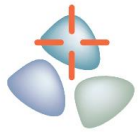
Universe of Extracellular and Membrane Proteins for Degradation



- First generation degraders target intracellular proteins
- Yet almost 40% of human proteins are extracellular (EC) or membrane-bound
- Multiple classes and hundreds with established role in pathogenesis of diseases
- Degradation of extracellular proteins would dramatically expand the "degradome"
- Avilar initial focus: validated yet poorly served EC targets where ATACs have advantage

https://www.proteinatlas.org/humanproteome/tissue/secretome

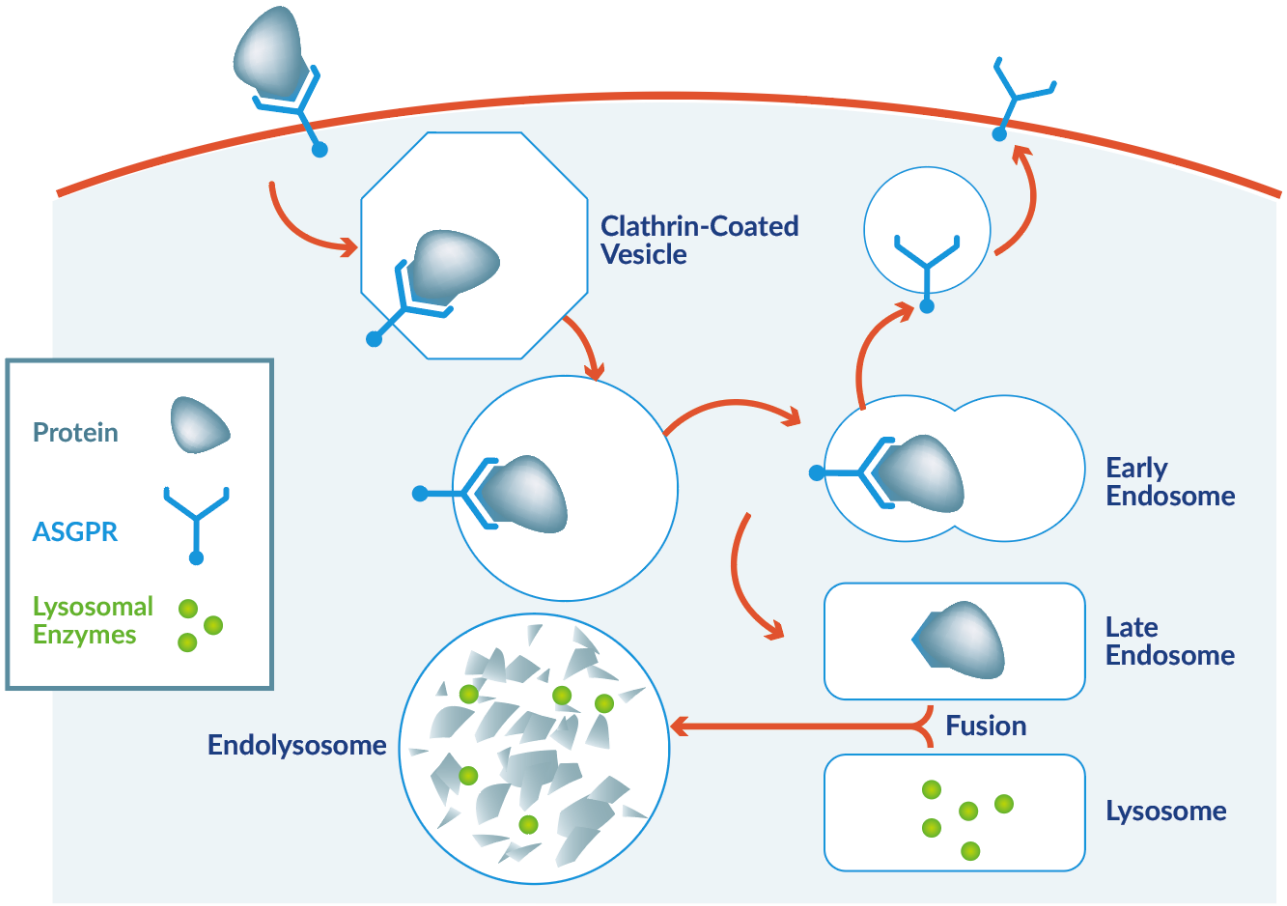
Novel Applications for ATAC Extracellular Protein Degraders

	**Drug Historically Undruggable Targets**	• Leverage ligands that bind but do not have – or need to have – functional activity to **degrade previously undruggable targets**
	**Degrade Very High Concentration Proteins**	• Degrade very high concentration proteins that would otherwise require **infeasibly or unattractively large doses of neutralizing mAb**
	**Selectively Target Relevant Proteins**	• Degrade **specific protein classes or subclasses** responsible for disease, while leaving other related proteins unaffected
	**Rapid Onset of Action**	• Rapidly degrade pathogenic protein to drive faster clinical benefit for **patients in crisis or in acute need**
	**Remove Pathogenic Complexes**	• Degrade **protein complexes** or necessary component elements of protein complexes causing diseases
	**Oral Degraders**	• Use small molecule ASGPR ligands + small molecule protein binders to create **oral ATACs** for proteins currently targeted by injectable biologics

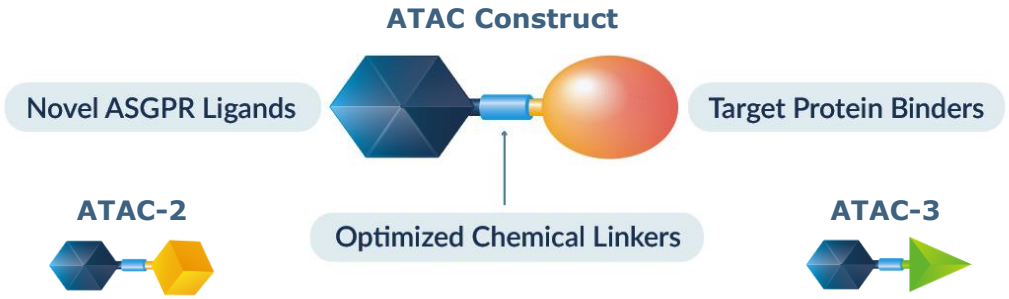
ASGPR Role in Body's Natural Cellular Degradation Machinery

- Cell surface receptor and part of natural cellular machinery for extracellular degradation (like E3 ligases in intracellular degradation)
- Mediates the endocytosis and degradation of various endogenous glycoproteins in endolysosome
- Highly expressed on hepatocytes (~1M receptors per cell in humans)
- Endocytosed and recycled from endosome back to plasma membrane every ~15 minutes

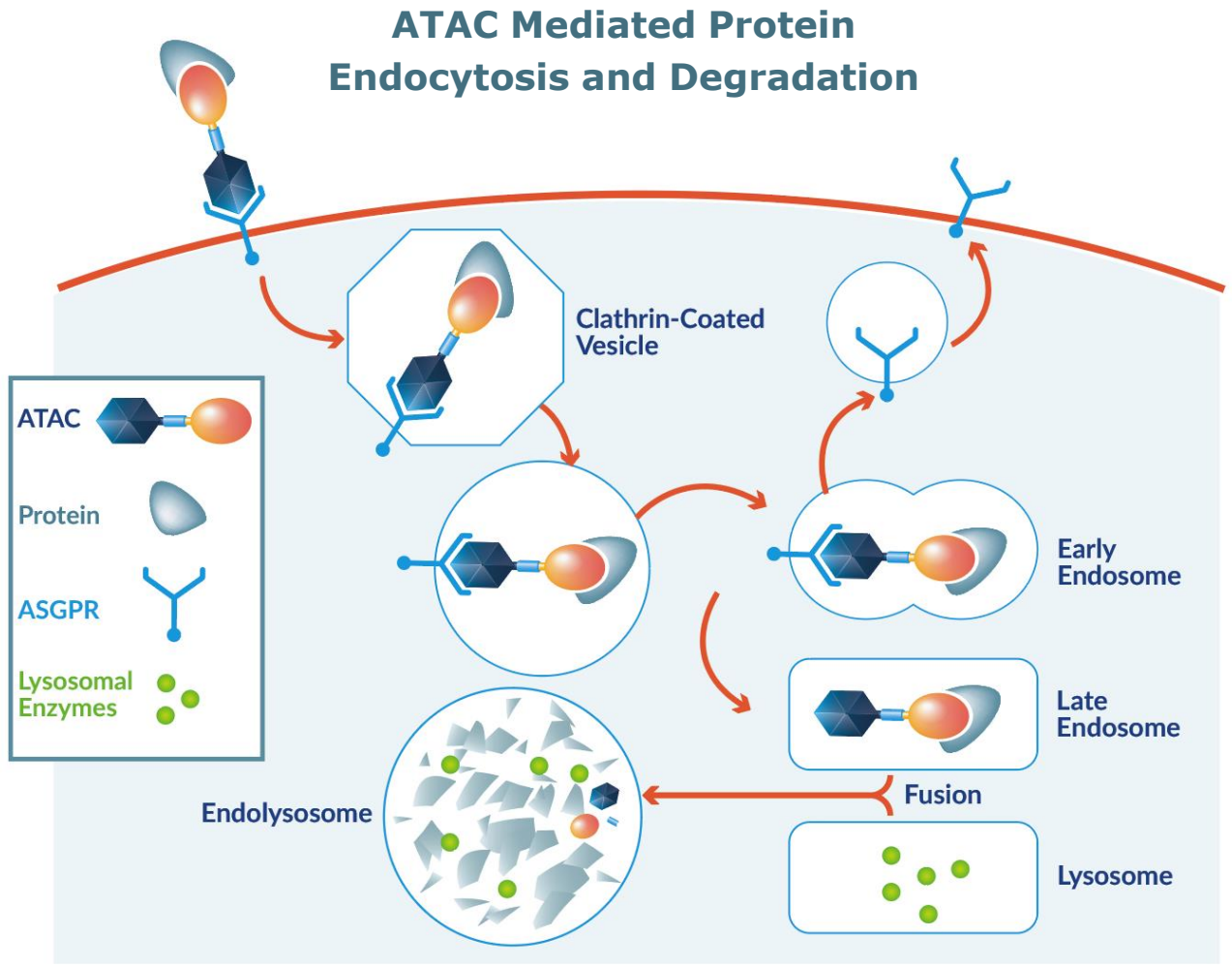
Natural Endocytosis and Degradation of Endogenous Proteins via ASGPR



ATACs Harness ASGPR Pathway to Degrade Extracellular Proteins

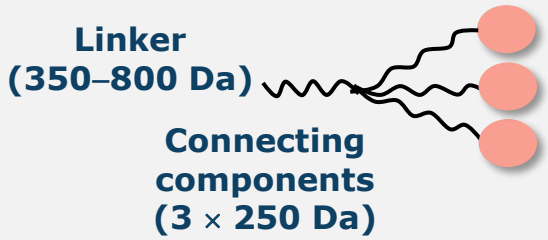


- Bi-functional molecules comprising ASGPR binder, specialized linker, and binder to a target protein
- Shuttle target protein from circulation to endolysosome for degradation
- Modular: proprietary ASGPR binders and linkers deployed in synthesis of ATACs with diverse protein targeting binders



Proprietary ASGPR Ligands with Significantly Improved Affinity

Conventional GalNAc Tridentate



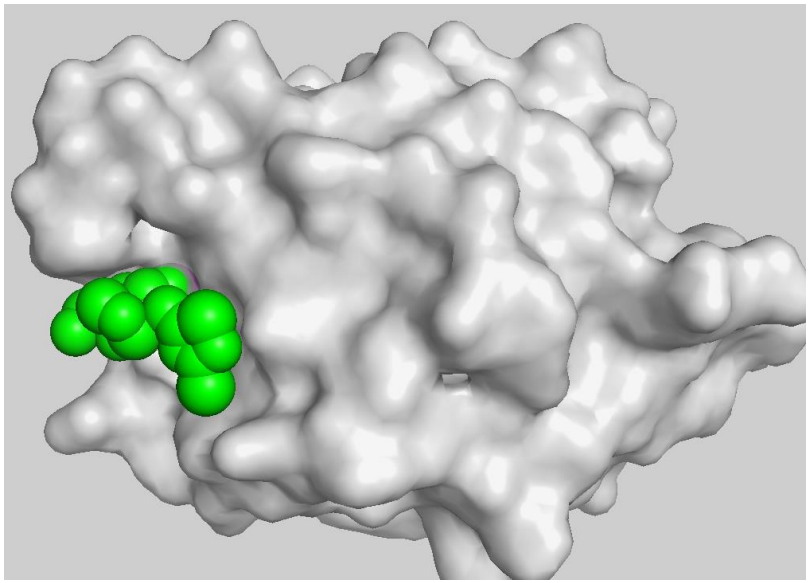
Total MW ~1,700–2,150 Da (3–4x > Avilar)

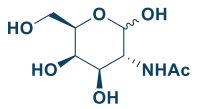
↑Affinity ↓Avidity ↓MW ↓Dose/Volume

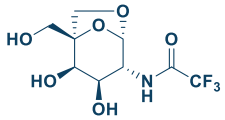
Avilar Monodentate

Total MW <550 Da

Structure-Guided ASGPR Ligand Design



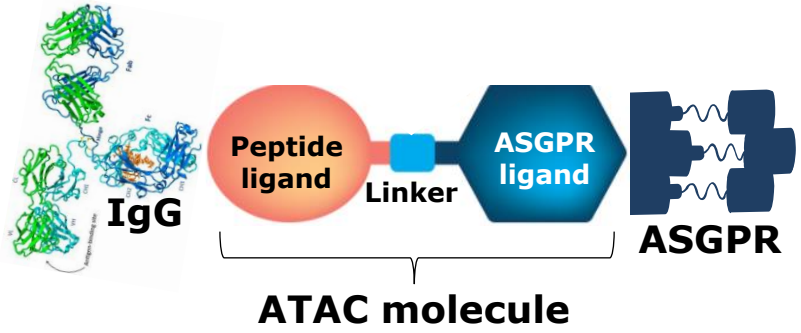




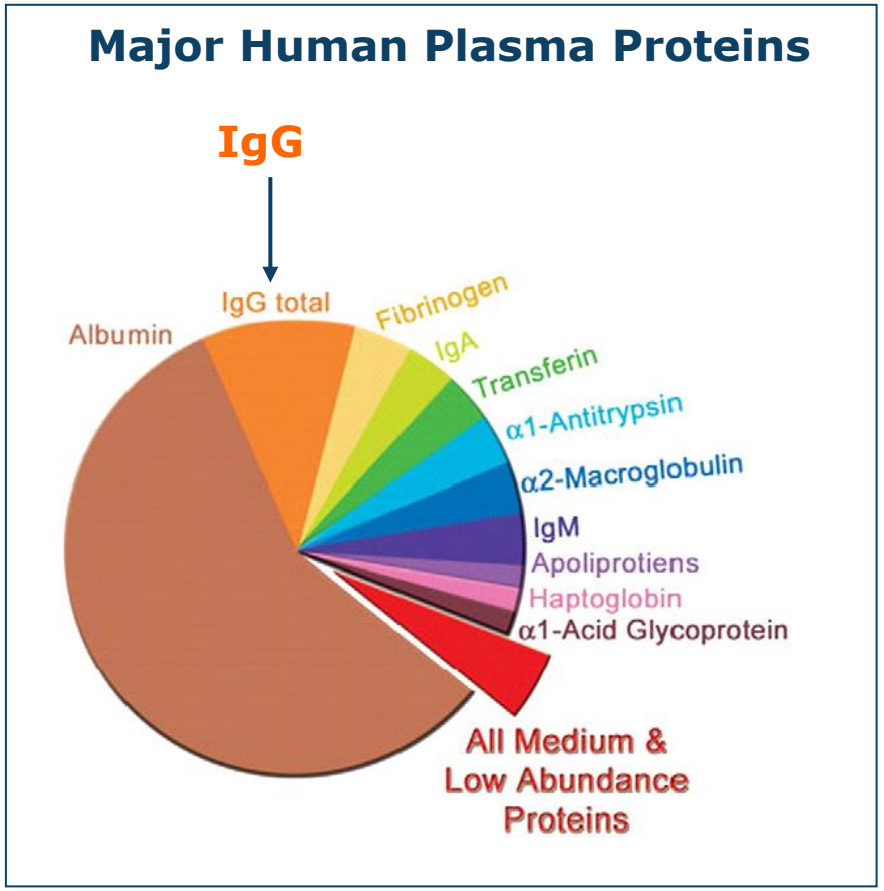
Compound ID	GalNAc	Pfizer	AVI-1	AVI-2	AVI-3
ASGPR K_D (SPR) (nM)	52,800	1,650	720	210	24
Increase in Affinity (X Fold)	1	32	73	251	2200

ATAC PoC Studies Demonstrating Degradation of IgG

- IgG is the most common antibody; 2nd most abundant plasma protein
  - High plasma concentration: 1.06 g/kg total body IgG or 74.2 g in 70 kg human
  - Long half life: 21 days in humans
  - Resynthesis rate: 32 mg/kg/day; ~3% of total IgG/day
- ATACs synthesized using a peptide ligand for IgG



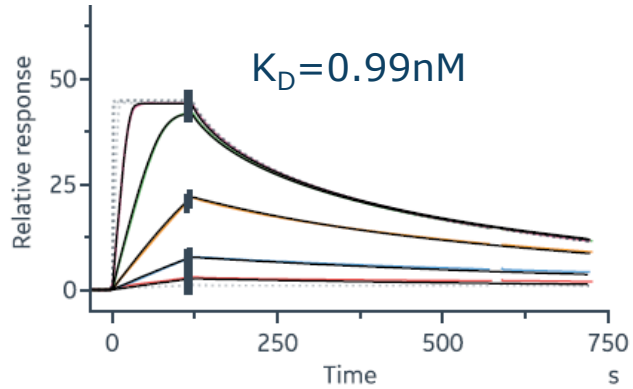
- Studies completed with ATACs targeting IgG:
  - Monodentate and bidentate ATACs, dosed IV and SQ
  - Single and repeat dose *in vivo* studies
  - MOA elucidation studies



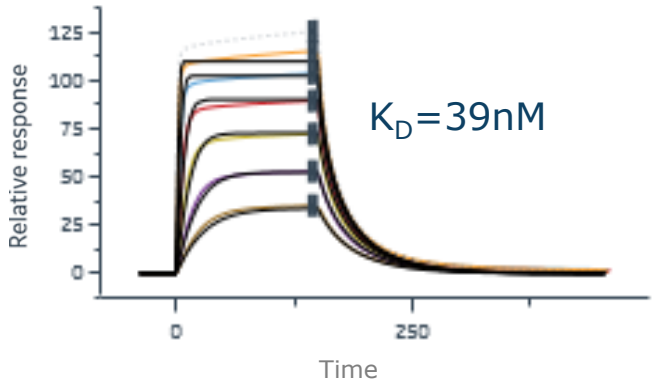
Monodentate ATAC-77 Binds IgG and ASGPR In Vitro

- Binary complexes: ATAC-77 binding to human IgG and ASGPR measured by SPR

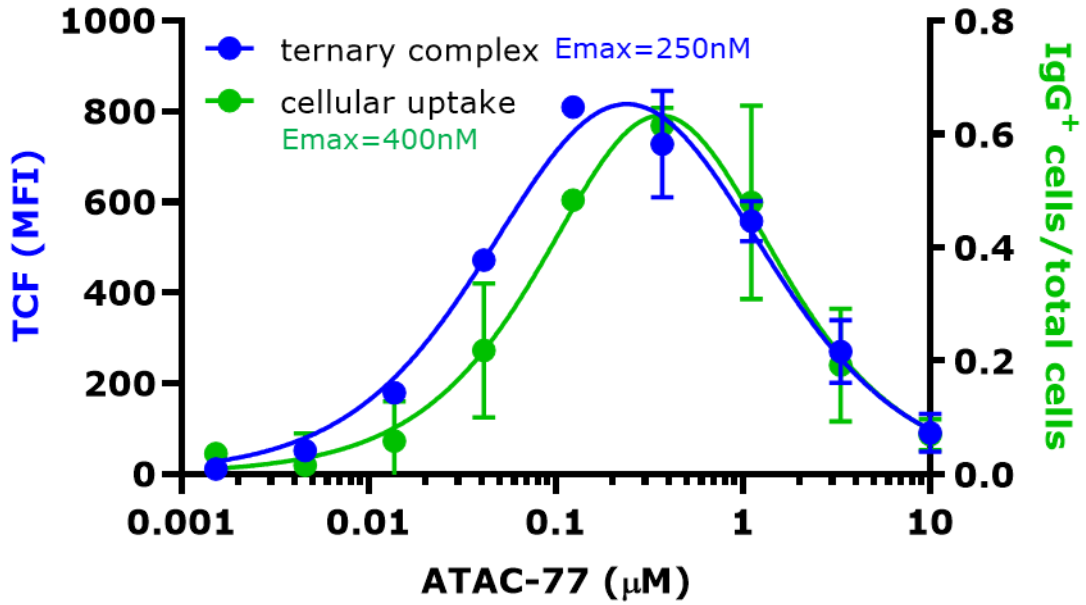
Binding to human IgG Fc



Binding to human ASGPR



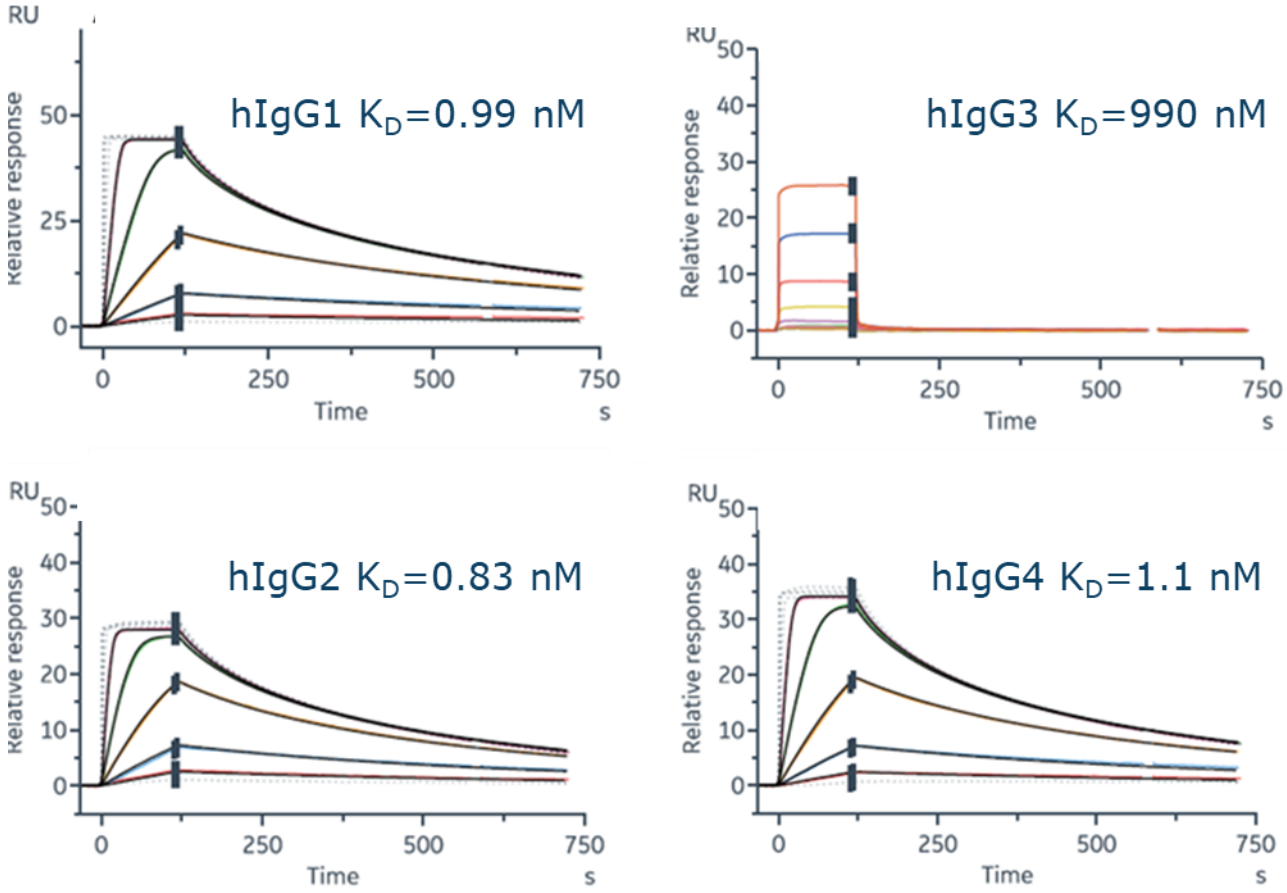
- Ternary complex formation and cellular uptake into HepG2 cells measured by flow



ATAC-77 Has Differential Binding Affinities to IgG Subclasses

- Four IgG subclasses (IgG1, 2, 3, and 4) exist in humans
  - IgG1 is most abundant (~60% of total IgG*)
- Each IgG subclass binding affinity was tested separately by SPR with both full-length and Fc IgG
- ATAC-77 shows potent in vitro binding affinities to Fc IgG1,2 and 4 and weak binding to IgG3
- Similar profile was obtained for full length IgG

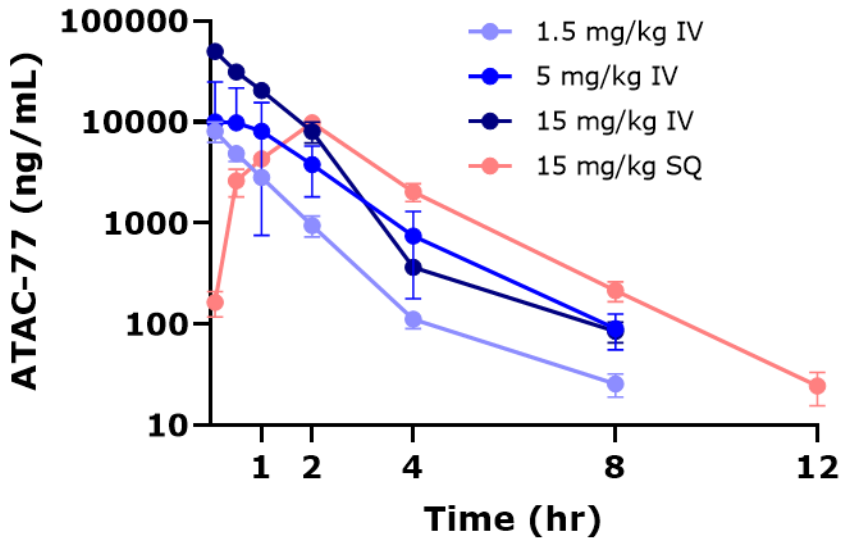
Binding to human Fc IgG1, IgG2, IgG3, and IgG4



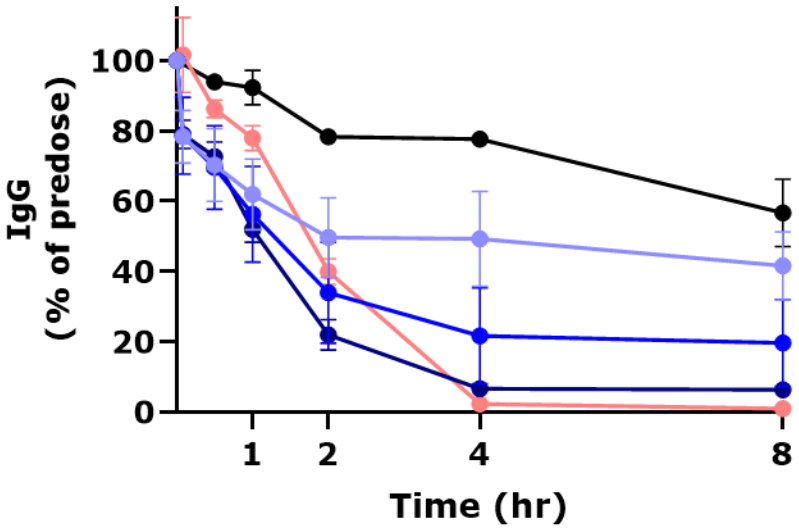
*Vidarsson 2014, Mayo Clinic 2022

ATAC-77 Degrades Human IgG in Rat PK/PD Model

ATAC-77 Plasma Exposure



ATAC-77 Degradation of hIgG



- Rats injected with 200 mg/kg of human IgG IV at T-1hr (ATAC-77 does not bind to rat IgG)
- ATAC-77 effectively degrades human IgG from rat plasma in a dose-dependent manner
- SQ dose results in degradation of ~22 μM IgG in 4 hrs despite ~2.3X lower AUC than IV dose

Expert Team of Biopharma Executives and R&D Leaders

Daniel Grau, MPhil
CEO & President

Effie Tozzo, PhD
Chief Scientific Officer

Phil Graham, PhD
Chief Development Officer

Adam Muzikant, PhD
Chief Business Officer

Jason Wiles, PhD
VP, Discovery & Preclin Sciences

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VP, Biology

Lisa Molz, PhD
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Sr Director, Biophysics

Alison Davis, PhD
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Srinivasa Karra, PhD
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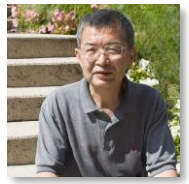

Hu Liu, PhD
Director, Medicinal Chemistry

Nanqun Zhu, PhD
Director, DMPK

Emilie Castonguay, PhD
Director, Strategy & Portfolio Dev

Paul Muir, PhD
Sr Manager, Strategy & Portfolio

Karen Goulet
Office Manager