Pioneering a New Era of GPCR Drug Discovery

TD Cowen 45th Annual Health Care Conference

March 2025

Nasdaq: SEPN

Forward-Looking Statements

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Septerna: Pioneering a New Era of GPCR Drug Discovery with Oral Small Molecules

Native Complex Platform™ designed to unlock the full potential of GPCR therapies

Iterative structure-based drug design to rapidly optimize and validate programs in animal models

Portfolio strategy to drive value creation

Validated targets + early clinical readouts + multi-billion $ market opportunities

Well-capitalized with planned operating runway into at least 2H 2027

Lead Programs

PTH1R Agonists: Potential first-in-class oral small molecule for hypoparathyroidism; plan to select a next-generation candidate to accelerate toward clinical development later this year

SEP-631 MRGPRX2 NAM: Pipeline-in-a-product opportunity for mast cell diseases (e.g., CSU); Phase 1 initiation expected in 2025

Discovery Stage

TSHR NAM: Potential first disease-modifying treatment for Graves' disease and TED

Incretin Receptor Agonists: Opportunities for single- and multi-incretin receptor agonists for metabolic diseases (e.g., obesity and T2D)

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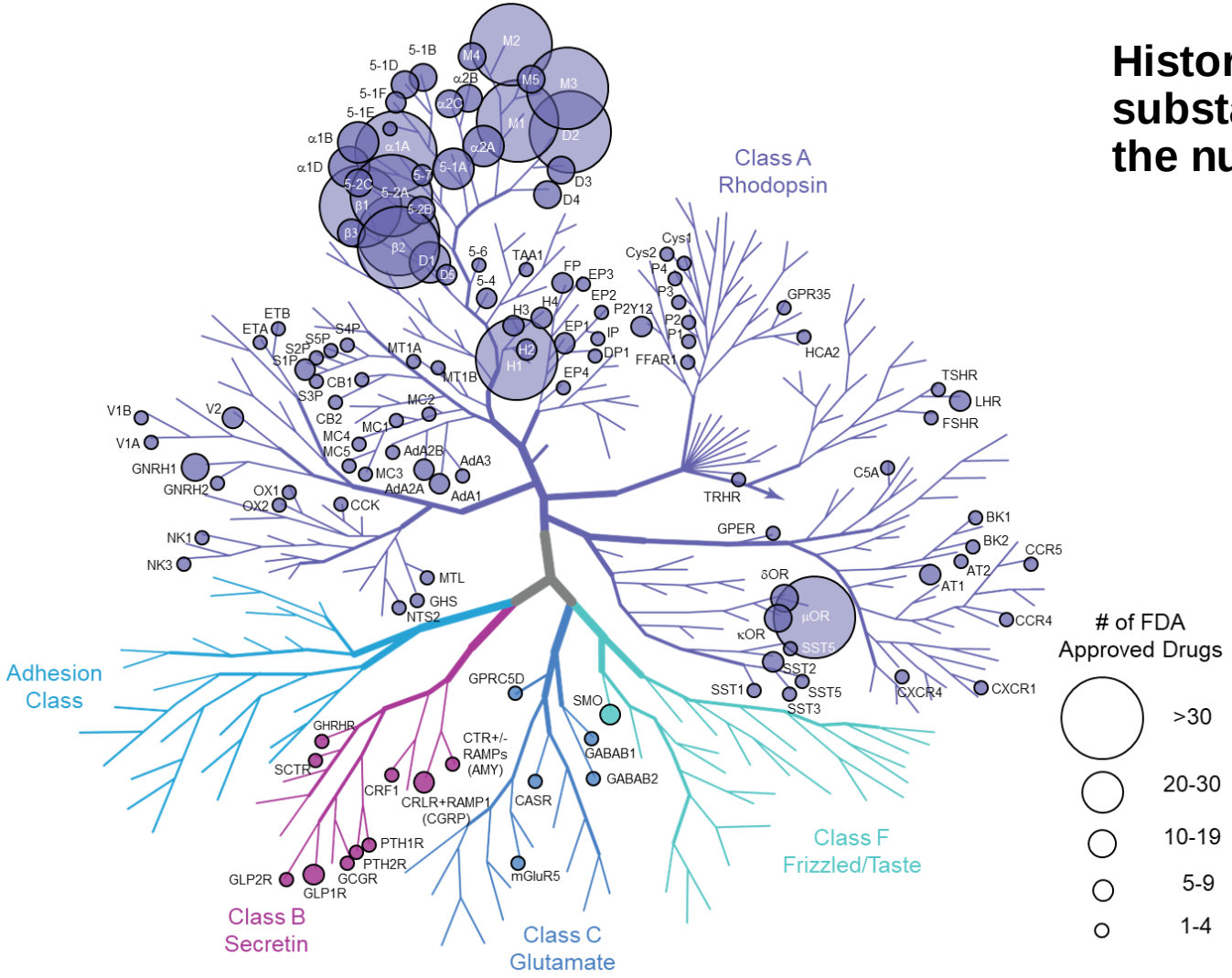
GPCR = G protein-coupled receptor; NAM = negative allosteric modulator; TED = thyroid eye disease; CSU = chronic spontaneous urticaria; T2D = Type 2 diabetes

GPCR Drug Discovery Success Has Been Highly Concentrated to a Small Fraction of GPCRs



Historically productive target class, yet substantial untapped opportunity to expand the number of druggable GPCRs

~1/3 of all FDA-approved drugs (~500 approved products) target GPCRs

>70% of GPCR drugs target 6 small subfamilies of GPCRs

~75% of potential GPCR targets remain undrugged

Our focus: Unlocking difficult-to-drug GPCRs with our Native Complex Platform™

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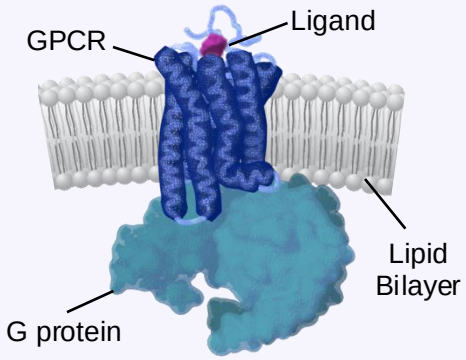
Proprietary Native Complex Platform™

Today's GPCR Drug Discovery Challenge

- Several new small molecule drug discovery technologies have largely been inaccessible to GPCRs
- Inability to isolate fully functional GPCR proteins significantly limits use of modern discovery tools

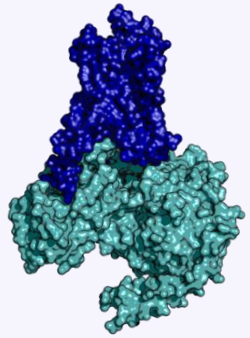
Native Complex Platform™: Industrialized Workflows to Unlock Difficult-to-Drug GPCRs

Native Complexes



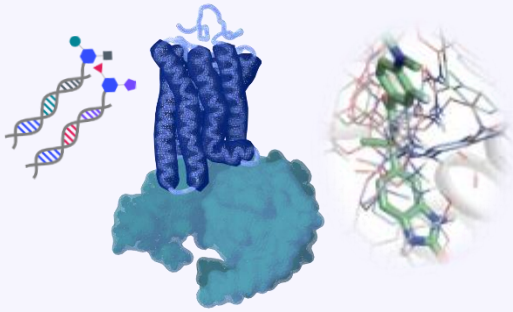
Retain GPCR natural structure, function, and dynamics

High-Resolution GPCR Structures



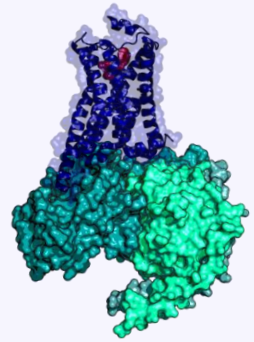
Novel binding pockets and new insights into GPCR modulation

Technologies to Screen Billions of Compounds



Discovery of new leads with relevant modes of action

Structure-Based Drug Design & Optimization



<1 year from initiation of med chem to activity in animal models for each program to date

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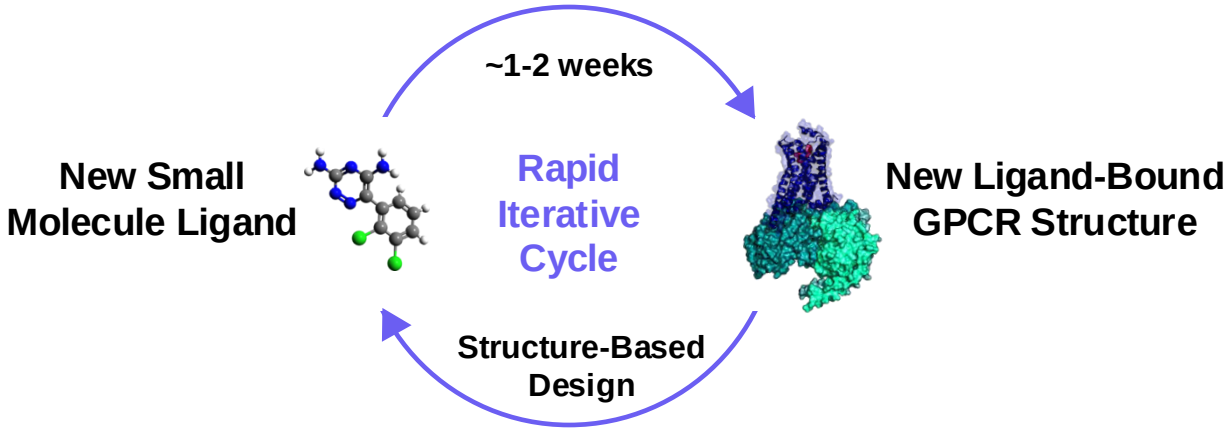
Native Complex Platform™ is a Highly Efficient Platform for GPCR Structure-based Drug Design

GPCR cryo-EM now achieving resolutions relevant for structure-based drug design

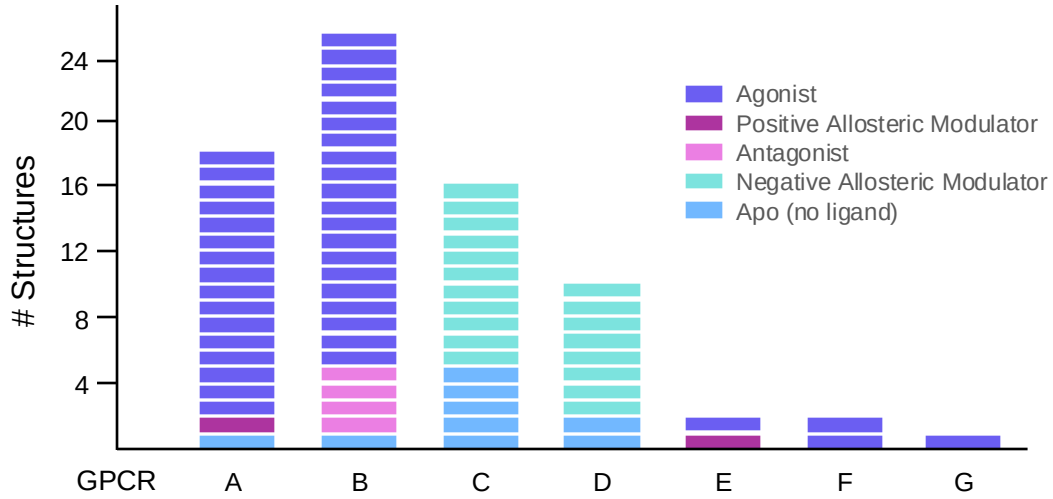
Native Complex cryo-EM enables rapid and iterative lead optimization

- Applies to a broad range of lead candidate modes of action (e.g., agonists, antagonists, allosteric modulators)

Native Complex Cryo-EM



Native Complex High-Resolution GPCR Structures



© 2025 SEPTERNA cryo-EM = cryogenic electron microscopy

Advancing a Deep Portfolio of Oral Small Molecule GPCR-Targeted Programs

Programs		Development Status		
Program / Target Mode of Action	Therapeutic Area Indications / US Patient Population	Discovery	IND-enabling	Phase 1
PTH1R Agonist	Endocrinology Hypoparathyroidism: ~70k			
SEP-631 (MRGPRX2) Negative Allosteric Modulator	Immunology and Inflammation CSU: ~1.5mm Other mast cell diseases			
TSHR Negative Allosteric Modulator	Endocrinology Graves' disease: ~2mm Thyroid eye disease: ~1mm			
GLP-1R, GIPR, GCGR Single- and Multi-Agonists	Metabolic Diseases Obesity and T2D: ~800mm (worldwide) Other metabolic diseases			

Other Therapeutic Areas of Interest / Focus:

Neurology, Women's Health, Cardiovascular Disease and Respiratory Disease

Note: Vertex acquired an undisclosed discovery-stage program in 2023 for $47.5M upfront

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PTH1R Agonist Program

Oral Small Molecule Targeting PTH1R for Hypoparathyroidism

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Hypoparathyroidism: Significant Unmet Need for an Oral PTH Replacement

Hypoparathyroidism: Low PTH leads to low blood calcium

- ~70K patients in US; ~140K patients in EU

Challenging patient symptoms

- Muscle cramps, tingling, brain fog
- Life-threatening complications: cardiac arrhythmias, seizures

Inadequate standard-of-care

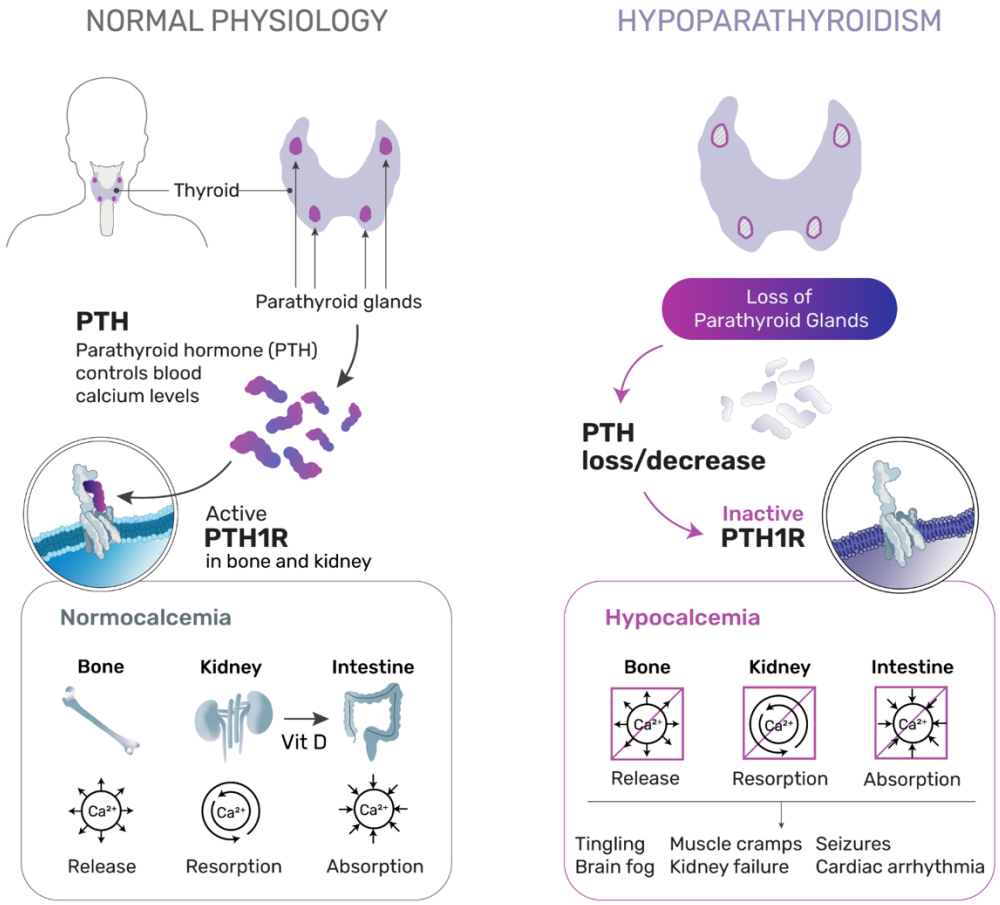
- Calcium supplements (high doses several times per day) and Vitamin D do not fully resolve symptoms, and lead to complications including calcifications and renal impairment

Injectable PTH therapies approved and in development

- Will require life-long injections

Our Strategy: Functionally replace PTH with oral small molecule PTH1R agonist to normalize serum calcium

PTH: Master Regulator of Blood Calcium



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PTH = Parathyroid Hormone

Discontinuation of SEP-786 Development to Focus on Advancing Next-Generation Oral Small Molecule PTH1R Agonist

Decision to discontinue SEP-786 Phase 1 SAD/MAD trial in healthy volunteers

- No Serious Adverse Events across all participants
- 2 unanticipated severe (Grade 3) events of elevated unconjugated bilirubin levels in MAD; believed to be SEP-786 off-target effect
- Both events were reversible and without liver injury (normal AST, ALT, GGT), cholestasis, or hemolysis
- No predicted risk of elevated bilirubin from all preclinical studies including 28-day GLP toxicology studies in rats and dogs

Non-clinical studies underway to investigate underlying mechanism of observed effects

Early signals of on-target pharmacology seen for SEP-786 prior to trial discontinuation

- Observed initial increases in serum calcium and decreases in endogenous PTH (as anticipated for healthy subjects)
- Favorable human PK profile consistent with preclinical predictions to support QD or BID dosing

Well-positioned to quickly pivot to next-generation oral PTH1R agonist

- Native Complex discovery efforts identified multiple chemically diverse PTH1R agonists
- Multiple candidate-quality leads with chemical structures unrelated to SEP-786, activity in animal models, and excellent pharmaceutical properties

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Native Complex Platform™ Identified Broad Portfolio of Chemically Distinct PTH1R Agonists

Native Complex Hit Identification

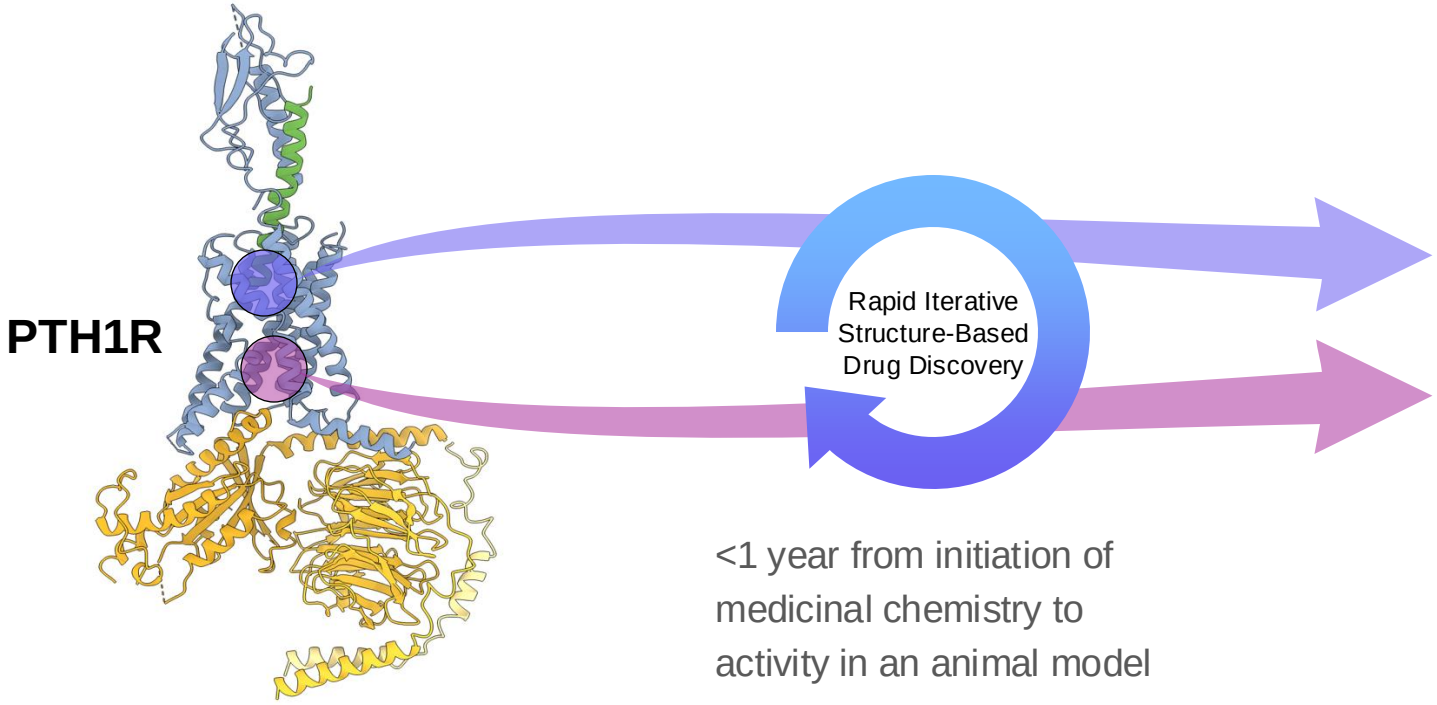
Multiple PTH1R agonists with distinct binding sites

Native Complex Structure-Based Design

Multiple PTH1R agonist series optimized in parallel

Optimization of Multiple Next-Generation Compounds

Multiple leads optimized toward development candidate selection



<1 year from initiation of medicinal chemistry to activity in an animal model

Next-Gen PTH1R Agonist Target Candidate Features

- Structurally unrelated to SEP-786
- Potent, selective, oral small molecule
- Normalizes serum calcium in preclinical animal models
- PK/PD projects full-day calcium control in hypoparathyroidism patients with QD or BID dosing
- Safe and well tolerated in preclinical toxicology studies

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QD = once-daily dosing BID = twice-daily dosing PK = pharmacokinetics PD = pharmacodynamics

Potent, Selective Next-Generation PTH1R Agonists Normalize Serum Calcium and Phosphate in Hypoparathyroidism Animal Model

Rat surgical model of hypoparathyroidism

Rat

↓ Surgery to remove parathyroid glands

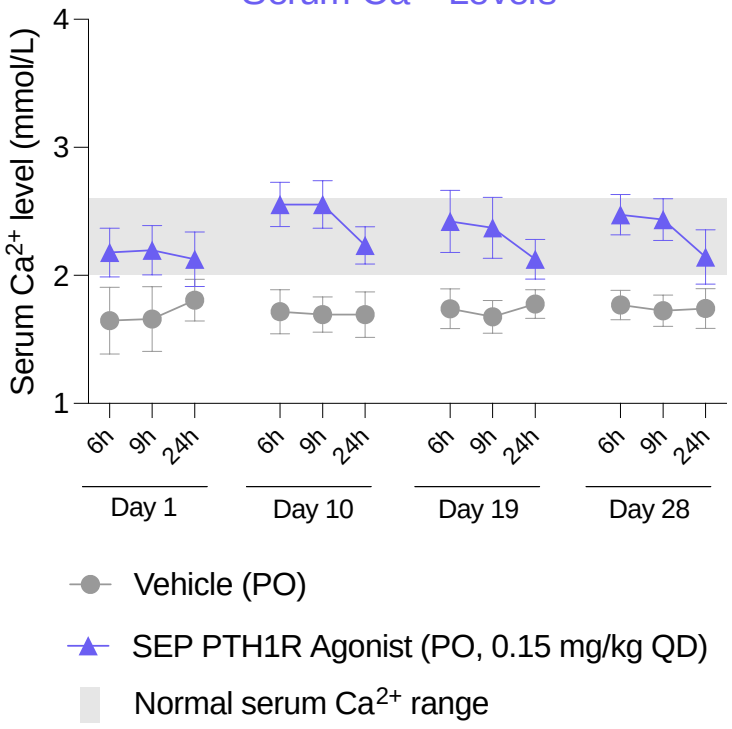
Decreased serum calcium (hypocalcemia)

↓ Oral small molecule PTH1R agonist

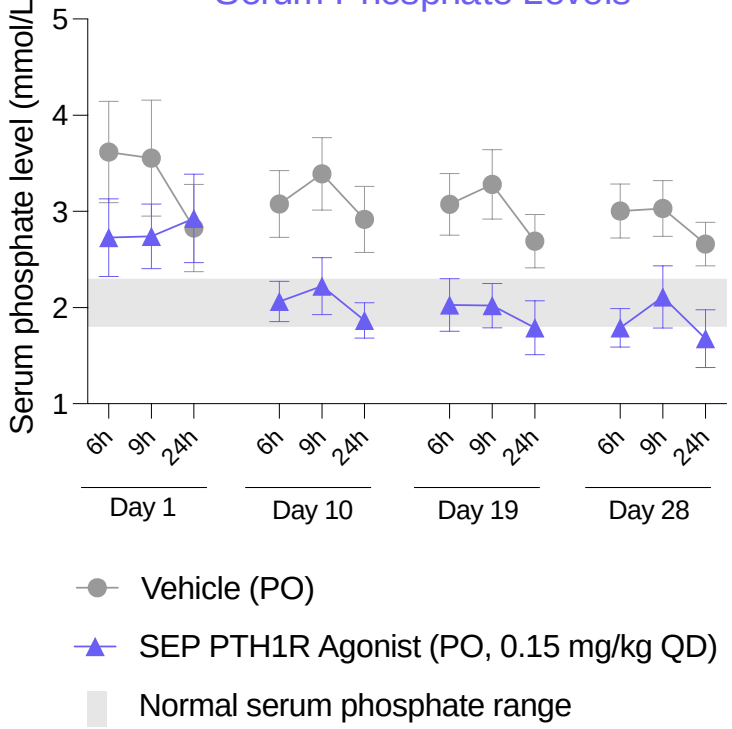
Normalize serum calcium

Example Next-Generation PTH1R Agonist: 28-day Dosing

Sustained Normalization of Serum Ca^{2+} Levels



Sustained Normalization of Serum Phosphate Levels



Next-gen PTH1R agonist: activity at 0.15 mg/kg QD comparable to SEP-786 at 3 mg/kg BID

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PO = oral dosing QD = once daily dosing BID = twice daily dosing

Multiple Next-Generation PTH1R Agonists with Distinct Chemical Structures and Favorable Pharmacokinetics Profiles

Example Next-Generation PTH1R Agonist PK Profiles

- PK studies in mice, rats, dogs, and cynomolgus monkeys support predicted human PK for QD or BID dosing

	Next-Gen PTH1R Agonist #1				Next-Gen PTH1R Agonist #2			
Parameter	Mouse	Rat	Dog	Cyno	Mouse	Rat	Dog	Cyno
Oral Bioavailability (%F)	91	56	88	68	90	93	77	56
PO Half-life (hr)	7.8	17	24	14	7.2	14	39	17

vs.

SEP-786			
Mouse	Rat	Dog	Cyno
54	26-50	40-60	44
4.6	4-8	5-7	8.2

Predicted Human PK	
PO Half-life	17-34 hours

Predicted Human PK	
PO Half-life	43-87 hours

vs.

Predicted Human PK	
PO Half-life	9-27 hours

Observed Human PK (Ph 1)	
PO Half-life	~18 hours

- Next-gen PTH1R agonists: human PK properties (e.g., oral bioavailability and half life) predicted to be superior to SEP-786
- Plan to select a next-generation candidate to accelerate toward the clinic later this year

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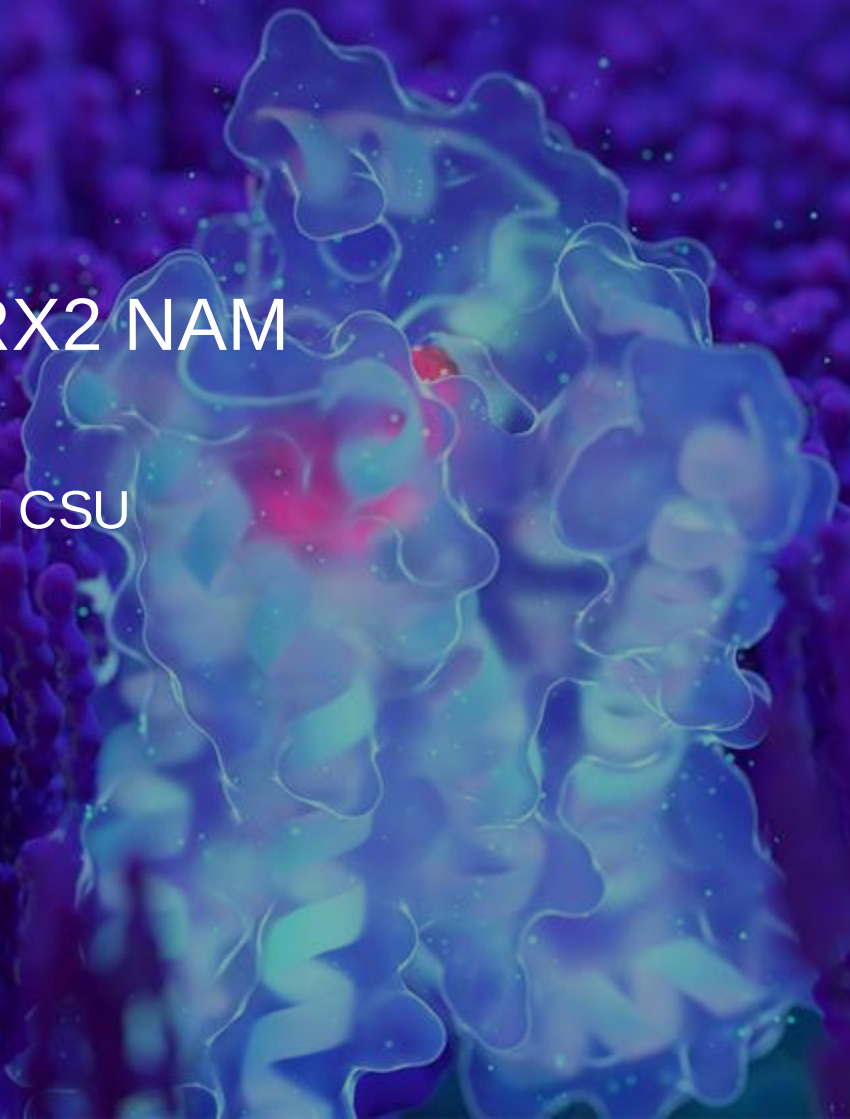
SEP-631: Oral Small Molecule MRGPRX2 NAM

Targeting MRGPRX2 for Mast Cell Disorders, Including CSU



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MRGPRX2: Emerging Target for Mast Cell-Driven Diseases

MRGPRX2

- Highly and uniquely expressed on mast cells
- Distinct from IgE / allergen pathway
- Multiple endogenous agonists

Mast Cell-Driven Diseases

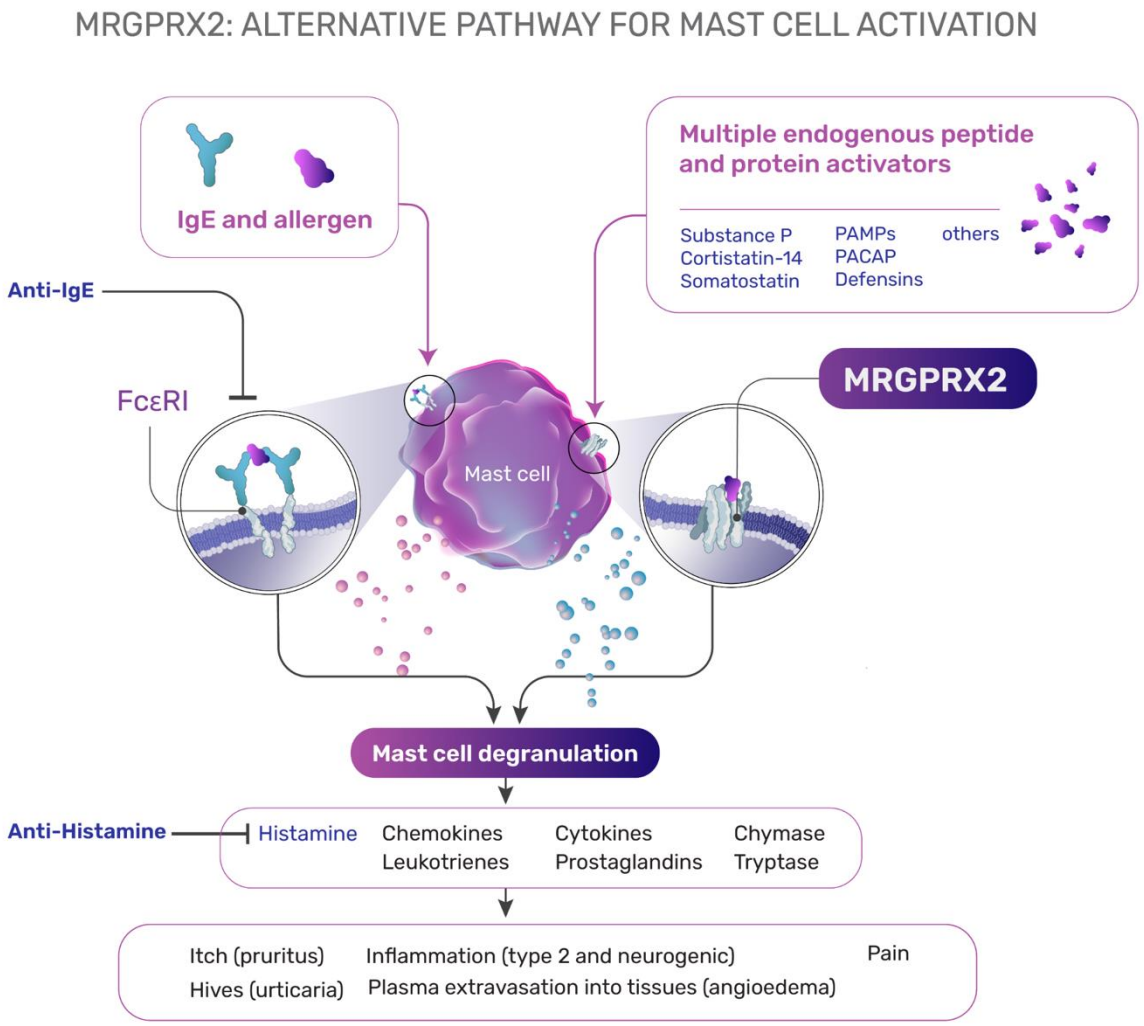
- CSU, atopic dermatitis, allergic asthma, and others

CSU: Significant Unmet Need

- ~1.5 million patients in US
- Itchy, painful hives and angioedema
- Chronic symptoms can impact quality of life
- First-line treatment: antihistamines; 37% refractory
- Second-line treatment: anti-IgE (Xolair); 64% refractory

Our Strategy: MRGPRX2 NAM

Inhibit mast cell activation by selectively blocking MRGPRX2



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NAM= Negative Allosteric Modulator

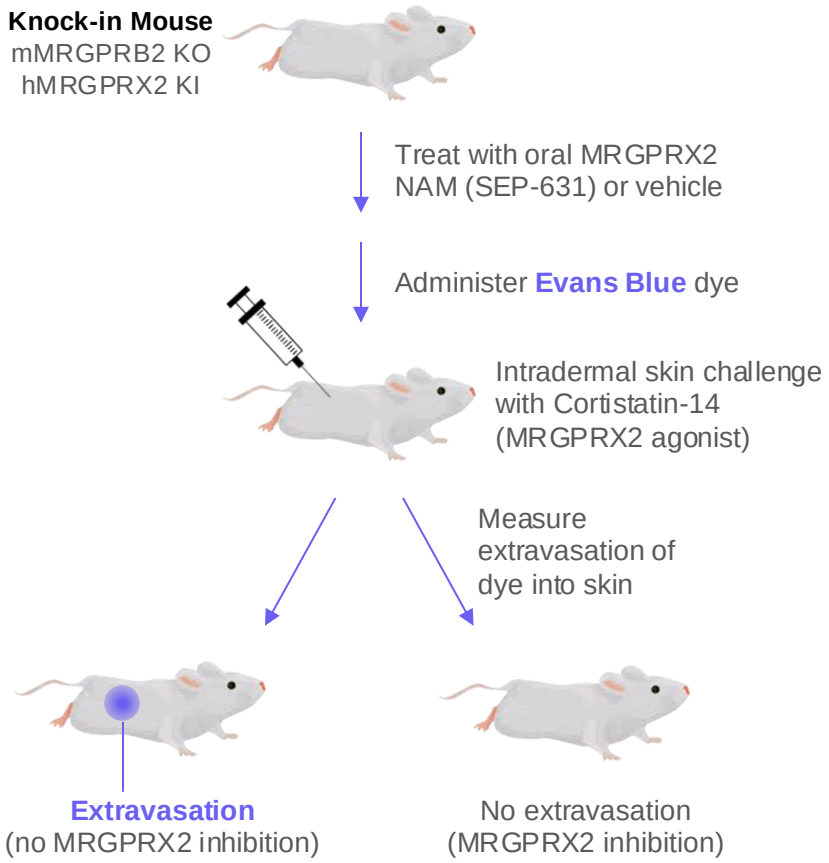
SEP-631: Oral Small Molecule MRGPRX2 NAM Designed to Stop MRGPRX2-Mediated Mast Cell Degranulation

SEP-631: Selective MRGPRX2 NAM

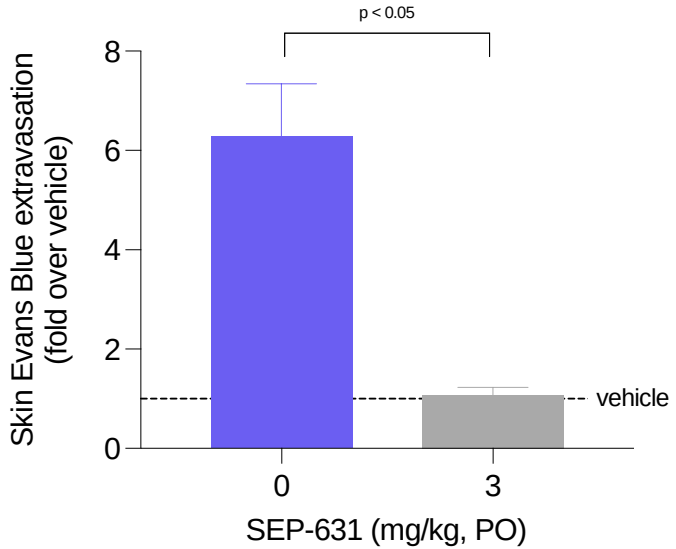
- Potent oral small molecule
- Blocked activation of all endogenous MRGPRX2 activators
- Showed insurmountable NAM profile with long-lasting inhibition

Effective in Preclinical Models

- Prevented skin extravasation in human MRGPRX2 knock-in mouse
- Potently inhibited degranulation of primary human mast cells
- Demonstrated good PK properties and has been generally well tolerated in preclinical safety models to date



SEP-631 Potently Inhibited Skin Extravasation in MRGPRX2 Knock-in Mouse Model



KO = gene knockout KI = gene knock-in

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SEP-631: MRGPRX2 NAM with Potentially Differentiated Profile

Key Criteria	SEP-631
High Potency ✓	Demonstrated in multiple functional and binding assays
Broad Inhibition ✓	Long residence time and insurmountable inhibition of multiple endogenous agonists
Good Oral PK ✓	Excellent oral bioavailability; PK profile across species supports QD oral dosing projection in humans
In vitro PD ✓	Activity in primary human skin mast cells
In vivo PD ✓	Activity in hMRGPRX2 knock-in mice
Favorable *in vivo* safety profile ✓	14-day non-GLP studies in rat and dog showed a generally favorable tolerability profile

IND-enabling studies ongoing to support advancement into Phase 1 clinical trial in 2025

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TSHR NAM Program

Oral Small Molecule Targeting TSHR for Graves' Disease and TED

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No Disease-Modifying Therapies for Graves' Disease and Thyroid Eye Disease (TED)

Graves' Disease & TED Pathophysiology:

- Autoantibodies activate TSHR in thyroid gland and in orbital fibroblasts behind the eyes

Graves' Disease

- >2M patients in US
- Standard-of-care: antithyroid drugs, radioactive iodine, thyroidectomy

TED

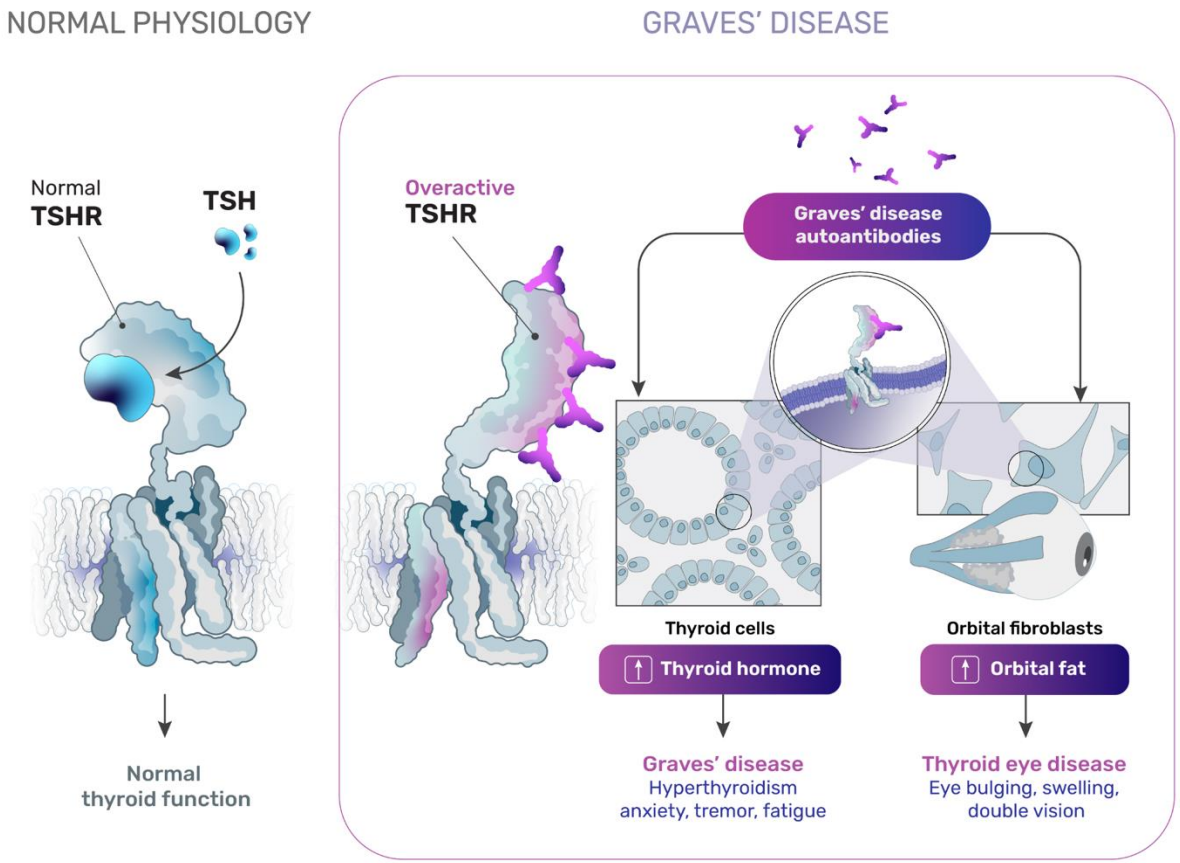
- Develops in ~50% of Graves' disease patients
- TEPEZZA® (anti-IGF-1R) decreases proptosis but requires multiple IV infusions; serious side effects (e.g., hearing loss)

Drug Discovery Challenge: Each Patient Has Unique Autoantibodies

- High-affinity, frequently polyclonal, high titer

Our Strategy: TSHR NAM

Oral disease-modifying treatment for all Graves' disease and TED patients



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NAM= Negative Allosteric Modulator

Oral Small Molecule TSHR NAMs Reversed Symptoms in Novel Graves' Disease Model

Selective TSHR NAMs

- Blocked activation of TSHR by patient-derived autoantibodies
- Demonstrate insurmountable profiles

Preclinical Leads Inhibited Diverse Patient Autoantibodies

- Fully inhibited several Graves' patient polyclonal serum samples in primary orbital fibroblasts

Reversed Graves' Animal Disease Model Effects

- Normalization of thyroid hormone T4
- Reduction in thyroid weight
- Reversal of proptosis

Mouse

TSHR Activating Antibody

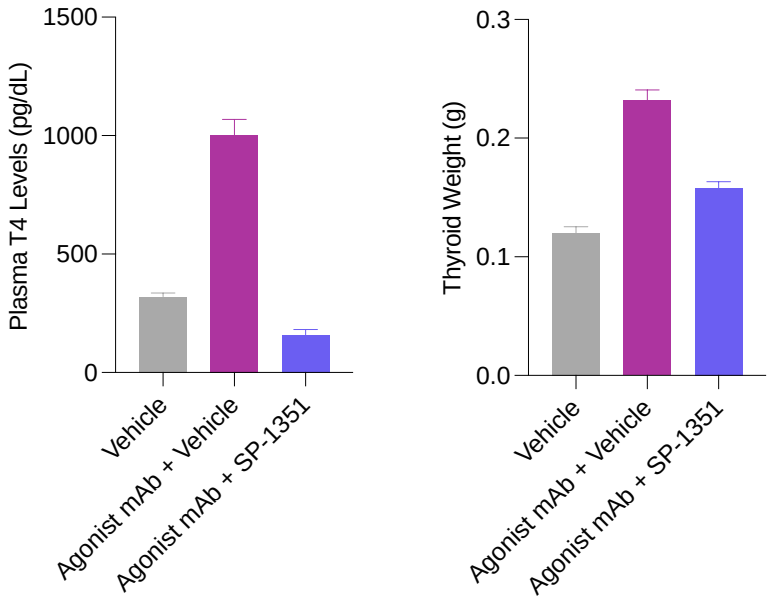
6 weeks

↑ Thyroid Hormone Levels
↑ Thyroid Size
↑ Eye Proptosis (bulging)

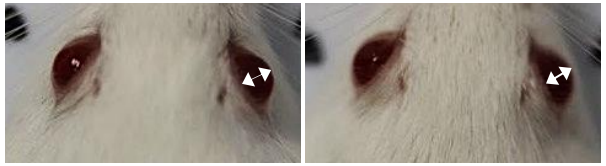
TSHR Activating Ab +TSHR NAM

1 week

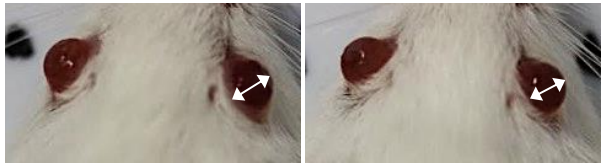
Reversal of Thyroid and Eye Manifestations



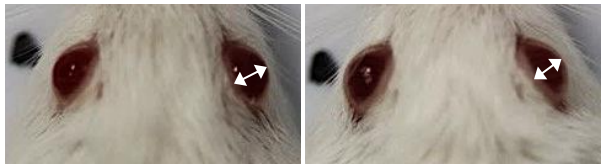
Isotype mAb control + Vehicle



Agonist mAb + Vehicle



Agonist mAb + SP-1351



mAb = monoclonal antibody

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Incretin Receptor Agonist Programs

Oral Small Molecule Single- and Multi-GLP-1R, GIPR, and GCGR Agonists for Metabolic Disorders, Including Obesity and Type 2 Diabetes

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Next-Generation Oral Incretin Receptor Agonists

Incretin peptide therapeutics have been transformative treatments for obesity and diabetes

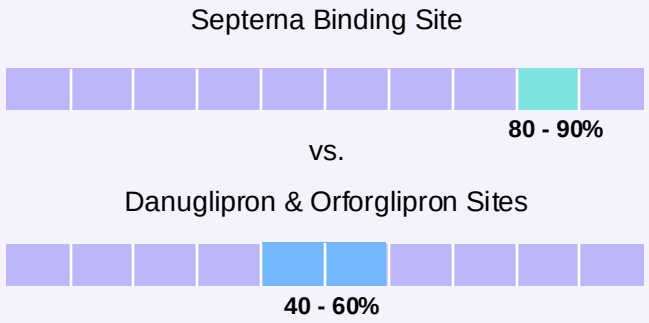
- Marketed GLP-1 and GLP-1/GIP products generated ~$36B in global sales in 2023
- Limitations: tolerability, injection administration, prolonged titration schemes

Our Strategy: Next-generation oral small molecule single- and multi-incretin receptor agonists that can be used as single medicines or in combination

Novel binding pocket identified with potential to develop both single- and multi-incretin receptor agonists

- Pocket has higher sequence similarity across GLP-1R, GIPR, GCGR than known binding sites occupied by clinical-stage GLP-1R small molecule agonists

Approximate % sequence similarity across GLP-1R, GIPR, GCGR



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Discovery of Oral Small Molecule Single- and Multi-Incretin Receptor Agonists

Identified Multiple Incretin Receptor Agonist Chemical Series

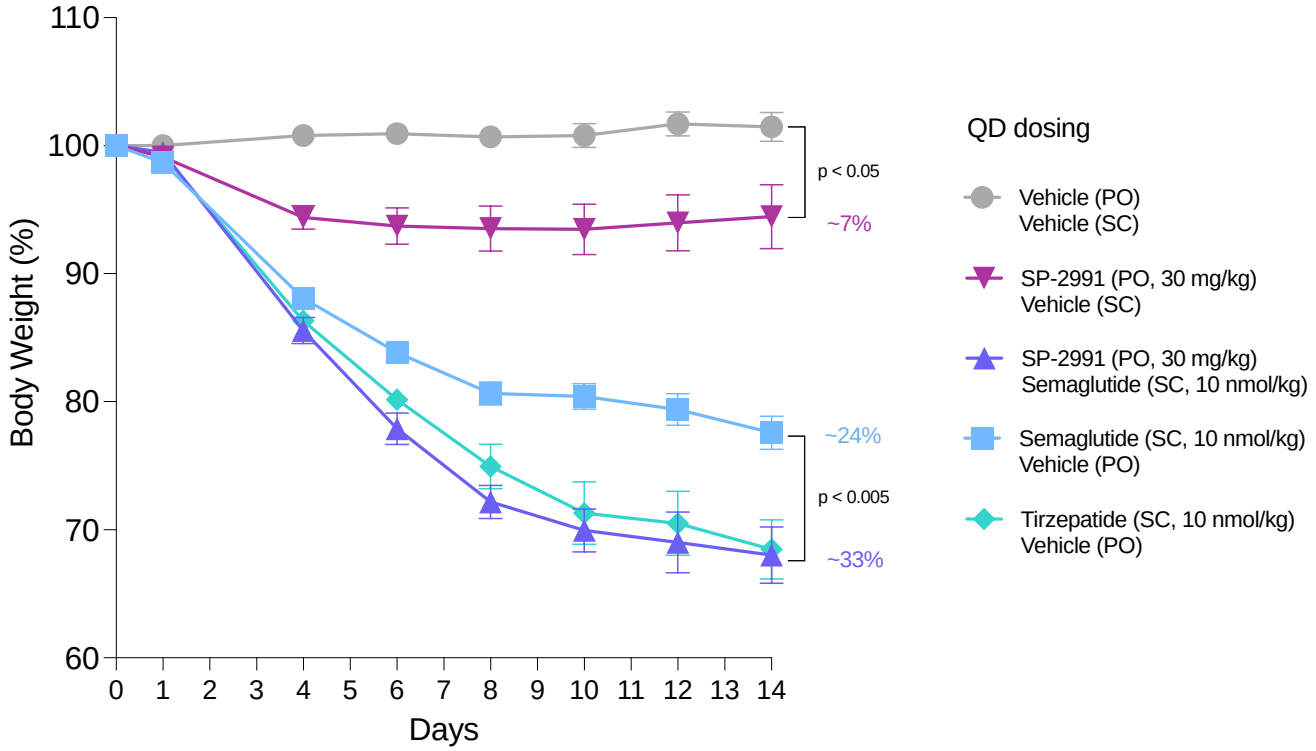
- Activity spans combinations of activities across GLP-1R, GIPR, and GCGR

Optimizing Both Single- and Multi-Incretin Agonist Leads Focused on:

- Mono-GIPR agonists
- Dual-GIPR / GCGR agonists
- Triple-GLP-1R / GIPR / GCGR agonists

Example: Selective mono-GIPR agonists demonstrated weight loss both alone and with additive activity in combination with a GLP-1 peptide

- Diet-induced obese (DIO) mouse model +/- semaglutide



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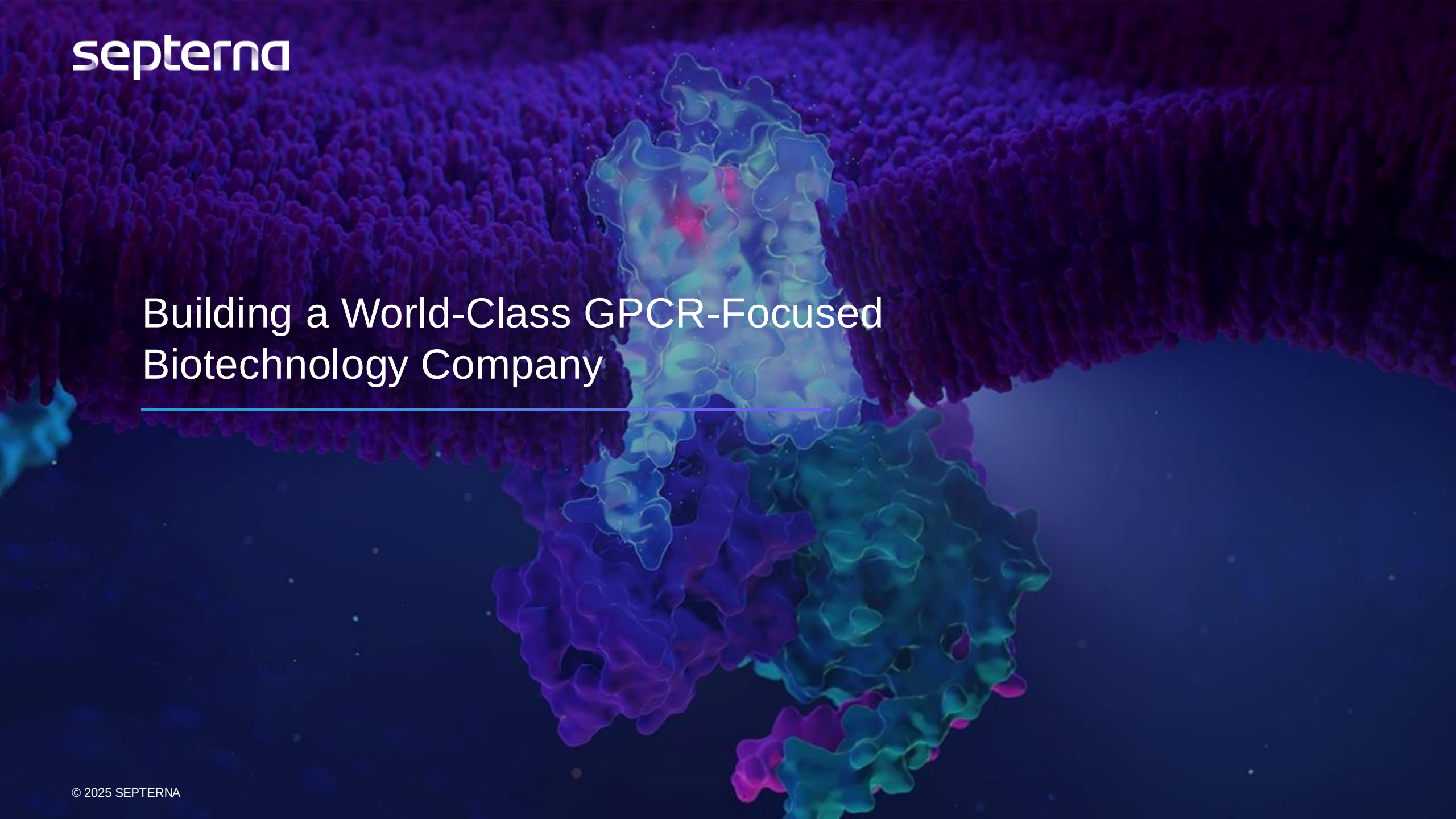
Building a World-Class GPCR-Focused Biotechnology Company



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Proven Leaders in GPCR Drug Development and Company Building

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Liz Bhatt, MS MBA
COO

Jae Kim, MD
CMO

Gil Labrucherie, CFA JD
CFO

Uwe Klein, PhD
SVP Biological Sciences

Dan Long, DPhil
SVP Drug Discovery

Samira Shaikhly
CPO

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- Arthur Christopoulos, PhD, Monash University
- Patrick Sexton, PhD, DSc, Monash University

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- John Lowe, PhD, formerly with Pfizer
- Craig Lindsley, PhD, Vanderbilt, formerly with Merck

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Septerna: Pioneering a New Era of GPCR Drug Discovery

- **Wholly owned portfolio of oral small molecule GPCR-targeted programs**
- **Multi-product pipeline, each with multi-billion $ market opportunity**
- **Native Complex Platform™ drives rapid compound identification and portfolio expansion**
- **Well-capitalized with operating runway into at least 2H 2027**

Program / Target Mode of Action	Therapeutic Area Indications	Discovery	IND-enabling	Phase 1
PTH1R Agonist	Endocrinology Hypoparathyroidism			
SEP-631 (MRGPRX2) Negative Allosteric Modulator	Immunology and Inflammation CSU and other mast cells diseases			
TSHR Negative Allosteric Modulator	Endocrinology Graves' disease and TED			
GLP-1R, GIPR, GCGR Single- and Multi-Agonists	Metabolic Diseases Obesity and T2D			

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Pioneering a New Era of GPCR Drug Discovery

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