Crinetics® Pharmaceuticals

RESEARCH & DEVELOPMENT DAY

June 26, 2025 – New York

Safe Harbor Statement

This presentation contains forward-looking statements. Crinetics Pharmaceuticals, Inc. ("Crinetics," the "company," "we," "us," or "our") cautions you that all statements other than statements of historical facts contained in this presentation are forward-looking statements, including, but not limited to, statements regarding: the potential for any of our ongoing clinical trials to demonstrate safety or efficacy, plans and timing for CRN09682 trials targeting the treatment of patients with NETs, the potential expansion to further indications and complementary treatment with paltusotine; the potential clinical benefits of our TSHR antagonist, CRN12755, in patients across multiple indications, and the plans for advancement of such program, including future updates and potential studies; the potential benefits, safety and tolerability of our SST3 agonist, CRN10329, for autosomal dominant polycystic kidney disease, and the plans for advancement and growth of such program, including potential future public updates, studies, approval timeline, and expansion of treatment; development plans for our SST2 nonpeptide drug conjugates platform; development of possible new therapeutic options for neuroendocrine neoplasms; the anticipated timing of upcoming milestones of our development programs, clinical trials and registration applications of our product candidates; and the direction or trajectory of the Company's potential future growth, and our expected plans and timing for commercialization of paltusotine and other product candidates pending regulatory approval. In some cases, you can identify forward-looking statements by terms such as "may," "believe," "anticipate," "could," "should," "estimate," "expect," "intend," "plan," "project," "will," "predict," "forecast," "continue," "lead to," "designed to," "goal," "target," and similar terms or the negatives thereof. These statements speak only as of the date of this presentation, involve known and unknown risks, uncertainties, assumptions, and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, without limitation: topline and initial data that we report may change following a more comprehensive review of the data related to the clinical studies and such data may not accurately reflect the complete results of a clinical study, and the FDA and other regulatory authorities may not agree with our interpretation of such results; the risk that interim or preclinical results of a clinical trial do not necessarily predict final results and that one or more of the clinical outcomes may materially change as patient enrollment continues, following more comprehensive reviews of the data, and as more patient data become available; the possibility of unfavorable new clinical data and further analyses of existing clinical data; potential delays in the commencement, enrollment and completion of clinical trials and the reporting of data therefrom; our dependence on third parties in connection with product manufacturing, research and preclinical and clinical testing; the success of our clinical trials and nonclinical studies for paltusotine and our other product candidates; regulatory developments in the United States and foreign countries; unexpected adverse side effects or inadequate efficacy of our product candidates that may limit their development, regulatory approval and/or commercialization; our ability to obtain and maintain intellectual property protection for our product candidates; we may use our capital resources sooner than we expect; and other risks described under the heading "Risk Factors" in documents we file from time to time with the Securities and Exchange Commission. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. All forward-looking statements are qualified in their entirety by this cautionary statement, which is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and, except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Speakers

SCOTT STRUTHERS, Ph.D.
Founder and
Chief Executive Officer

STEPHEN BETZ, Ph.D.
Founder and
Chief Scientific Officer

RICK GRIMES
Global Product
Leader, TSH

STACEY HARTE
Global Product
Leader, NDC

DAVID C. METZ, MBBCH
Professor of Medicine (retired)
Neuroendocrinologist

AGENDA

INTRODUCTION

- **Strategic Focus**
- **Discovery Overview**

SESSION 1

- **CRN12755: TSH**
  Grave's Hyperthyroidism, Graves' Orbitopathy (TED)
- **CRN10329: SST3**
  Autosomal Dominant Polycystic Kidney Disease (ADPKD)

BREAK

SESSION 2

- **CRN09682: SST2 + NDC**
  - Non-Peptide Drug Conjugate (NDC) Platform and CRN09682
  - Neuroendocrine Tumors (NETs) and Carcinoid Syndrome

CLOSING

Q&A

INTRODUCTORY REMARKS

Scott Struthers, Ph.D.

Founder & Chief Executive Officer

Serving our Patients

Our mission is to build the world's leading endocrine company that consistently pioneers new therapeutics to help patients better control their disease and improve their daily lives.

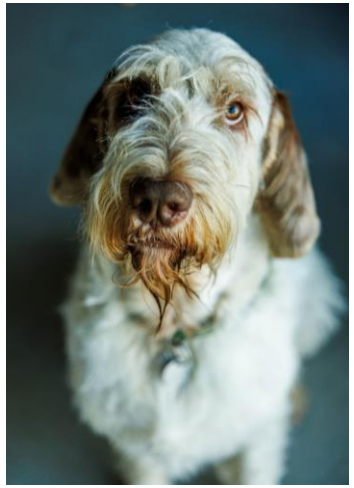
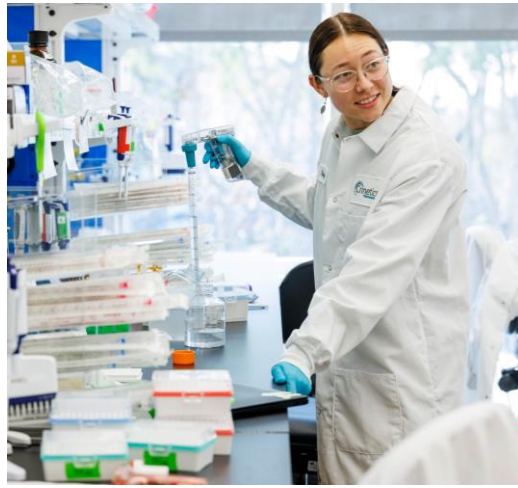
We made a **commitment** to the acromegaly community
And we stand by it

Traci
Acromegaly Patient




Our Passion for This Work Runs Deep



A Brief History of Crinetics

Opened Laboratories

Series A Venture Round

IPO

Founding of Radionetics Oncology

Bootstrapping Era
(Technology Creation)

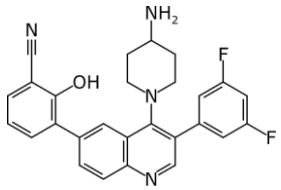
Private Financed Era
(Initial Pipeline Creation)

Modern Era
(Pipeline Advancement & Expansion)

2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025

Company Founded November

Four Founders

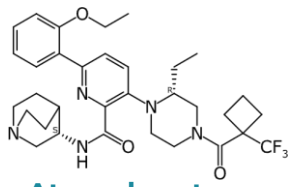


Paltusotine (CRN00808)

Paltusotine Phase 1 Data

Paltusotine Phase 2 Data

Atumelnant Phase 1 Data



Atumelnant (CRN04894)

Paltusotine Acromegaly Phase 3 Readouts

Paltusotine CS Phase 2 Data

Atumelnant Phase 2 Data

Paltusotine Sep. 2025 PDUFA DATE

PATHFNDR[1] pathfndr2

CS: Carcinoid Syndrome

Crinetics is Well-Positioned to Advance Standards of Care With Endocrine Science

First anticipated commercial **launch** this year

Deep pipeline with **2** late-stage programs in **4** indications

World-class R&D capabilities, **4** candidates in preclinical

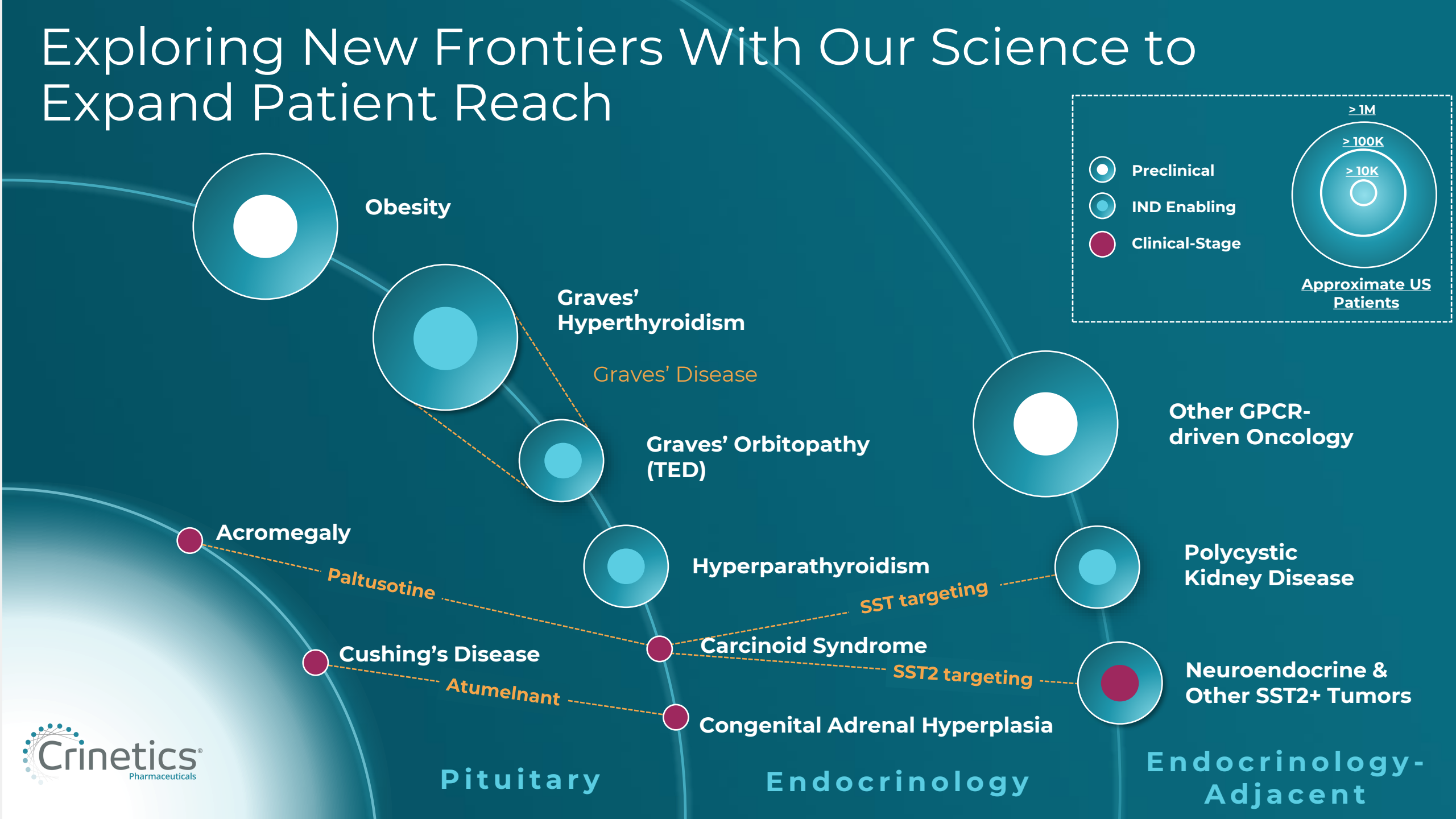
IP rights into 2040s

$1.3B of cash, cash equivalents & investments

Extensive internal **endocrinology expertise**

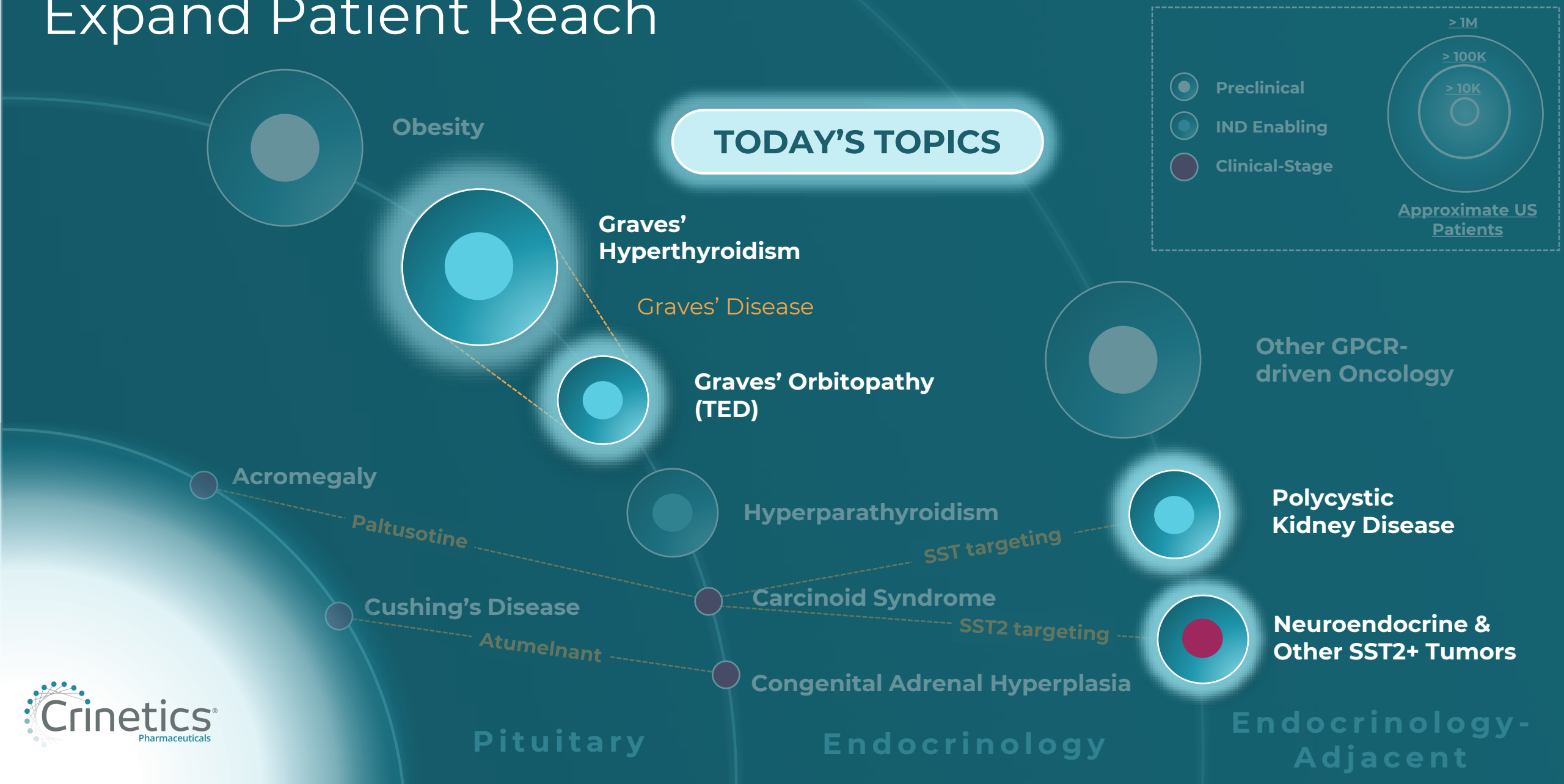
Culture dedicated to **patients** and **science**

Exploring New Frontiers With Our Science to Expand Patient Reach



Crinetics® Pharmaceuticals

Exploring New Frontiers With Our Science to Expand Patient Reach



Crinetics® Pharmaceuticals

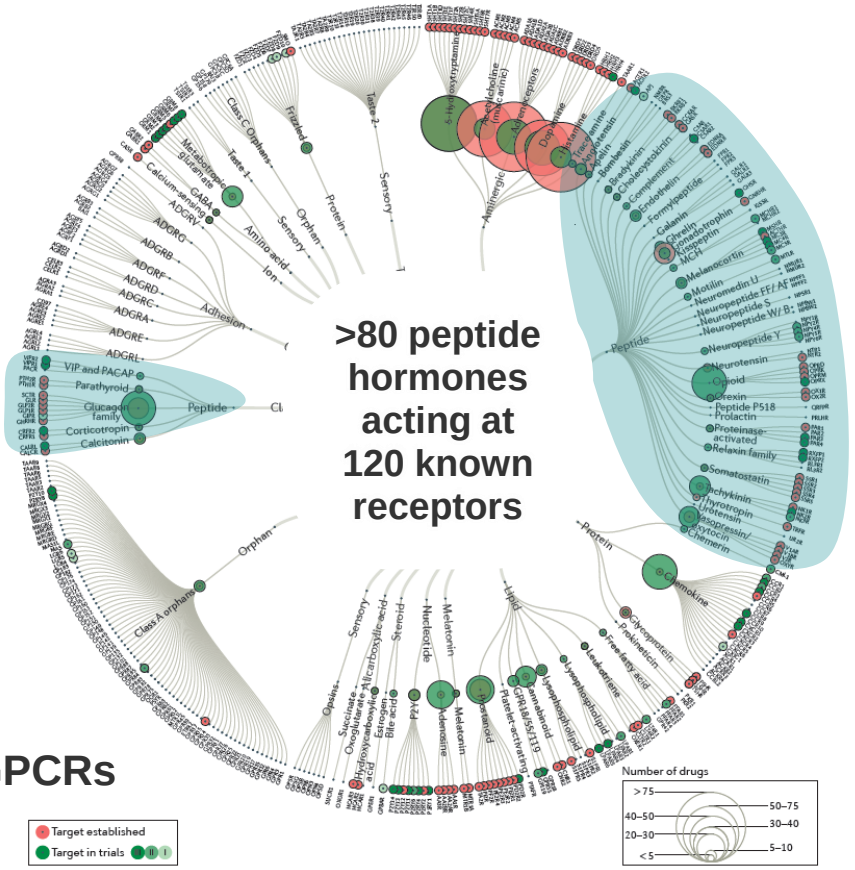
DISCOVERY OVERVIEW

Stephen Betz, Ph.D.

Founder & Chief Scientific Officer

Crinetics' Target Selection Focuses on the Intersection of Endocrinology and Peptide Hormone GPCR Pharmacology

The GPCR Superfamily



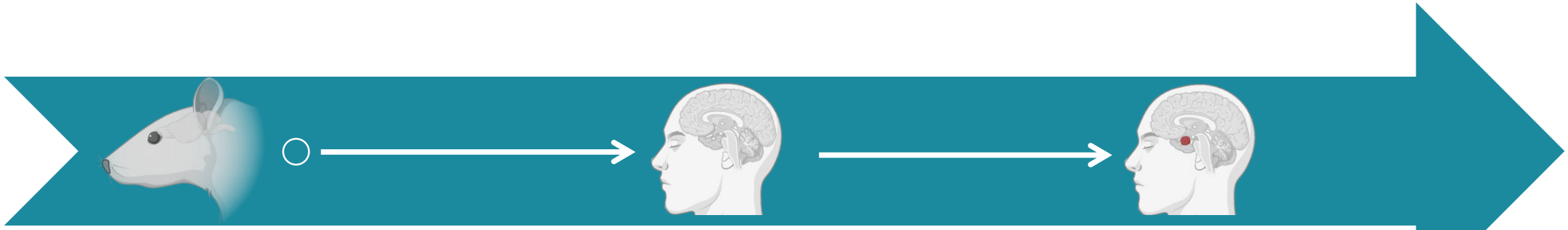
>800 Human GPCRs

Crinetics Current Indications

- Acromegaly
- Carcinoid Syndrome
- Congenital Adrenal Hyperplasia
- ACTH-dependent Cushing's Syndrome (ADCS)
- NETs & Other SST2+ Tumors
- Polycystic Kidney Disease
- Graves' Disease (including Graves' Hyperthyroidism and Graves' Orbitopathy)
- Hyperparathyroidism
- Obesity

Hauser et al, Nature Reviews, Drug Discovery 2017

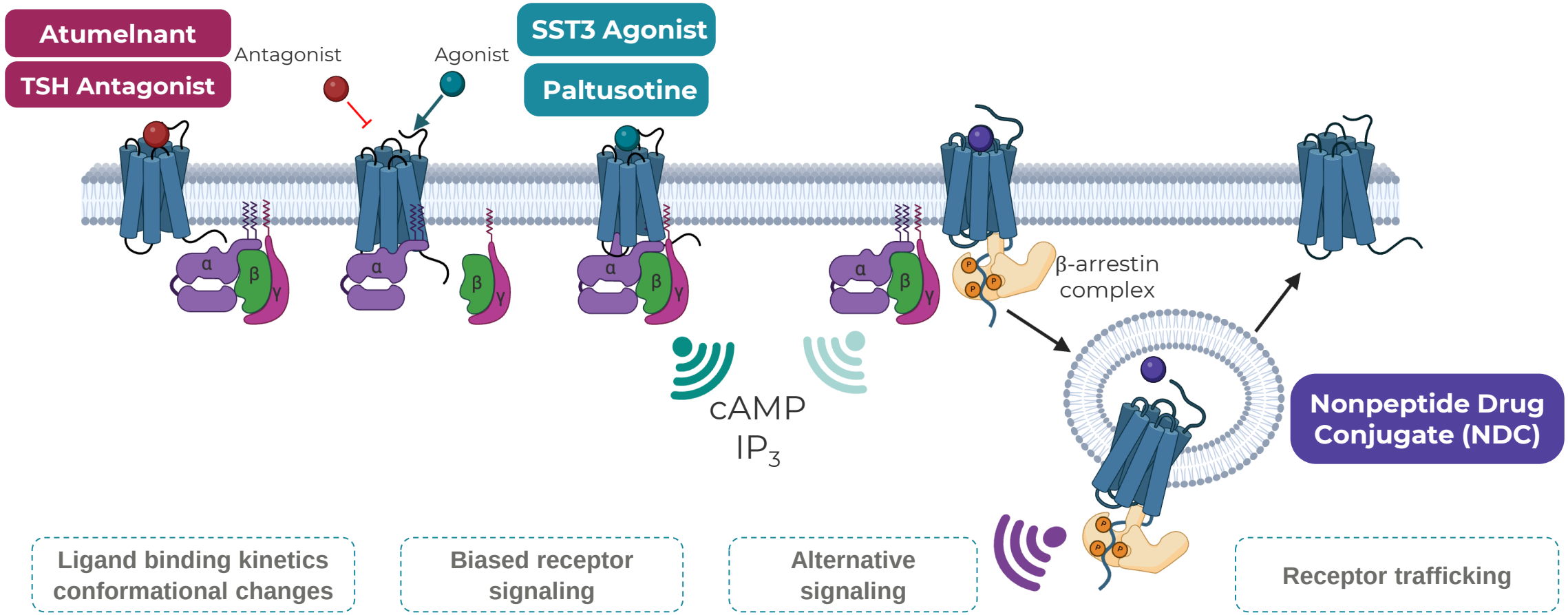
Our Strategy: Early Derisking with Biomarker Validation from Discovery through Approval



Preclinical Models POC	**Phase 1 (Healthy Volunteers) Safety, POC**	**Phase 2/3 (Patients) Safety, Disease Efficacy**
ΔHormones PK, Safety	ΔHormones PK, Safety	ΔHormones PK, Safety PROs

POC: Proof-of-Concept, PK: Pharmacokinetics, PROs: Patient Reported Outcomes

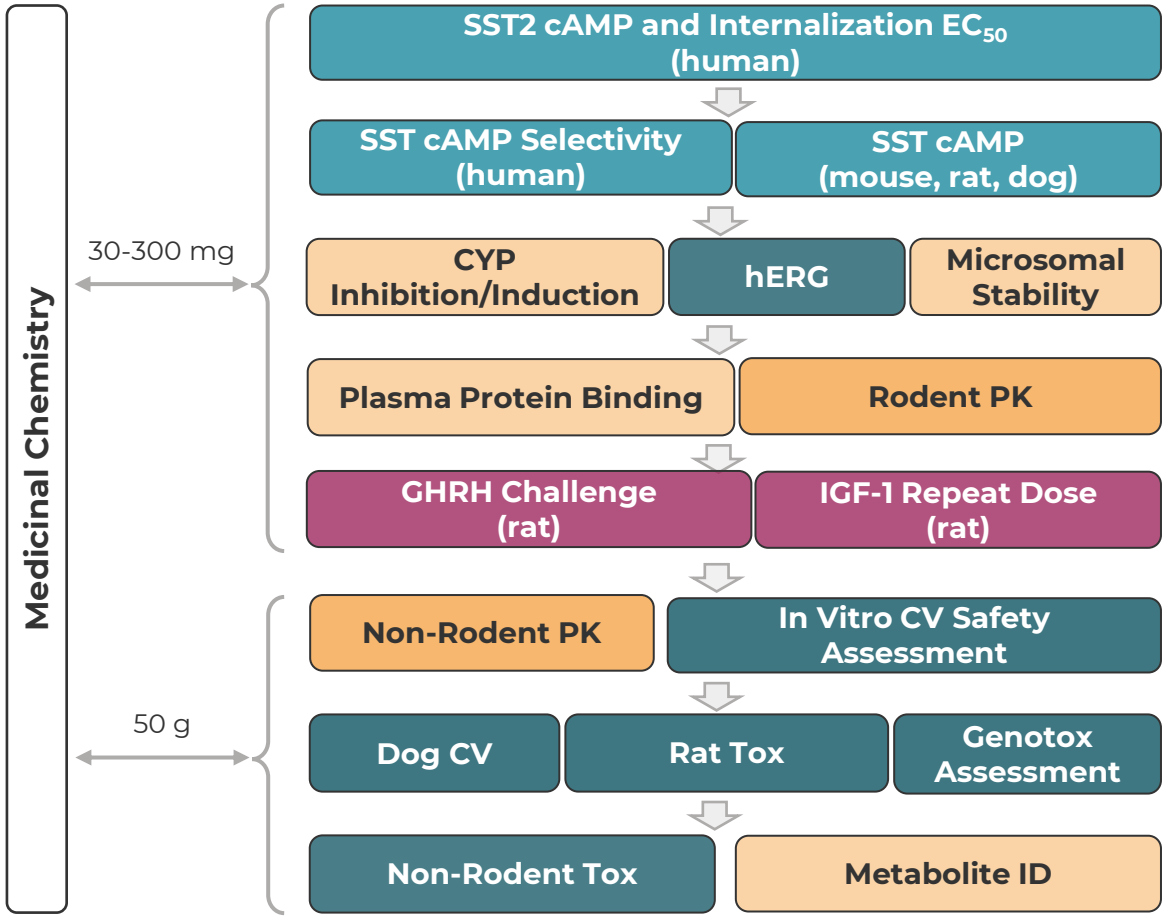
Our Approach: Tailor Ligands to Regulate Dynamic GPCR Behaviors to Ultimately Improve Patient Outcomes



Our understanding of complex GPCR signaling pathways enables us to develop product candidates that target specific GPCR dynamic behaviors

Despite Similarities, Every Assay Cascade Must Be Optimized for Receptor Specifics and Desired Drug Characteristics

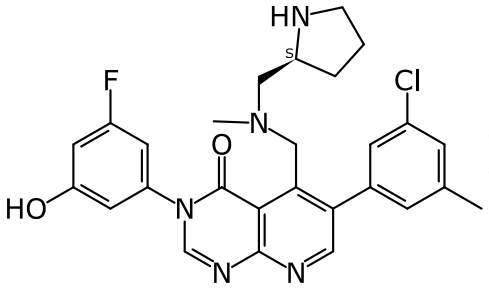
SST2 Agonist Assay Cascade



Properties		Criteria
Chemical Structure		New IP
In Vitro Pharmacology		Potent and SST2-selective Bias for cAMP over internalization
In Vitro ADME Profile		Acceptable drug-like properties
Brain Penetration		Minimal
Pharmacokinetics	Species PK	Acceptable exposures for PD / tox studies
	Predicted Human PK	Half-life compatible for QD dosing
In Vivo Efficacy		Suppression of growth axis
Rodent and Non-Rodent Toxicity		Acceptable NOAEL
Genotoxicity		Negative
Cardiovascular Toxicity		Acceptable NOAEL

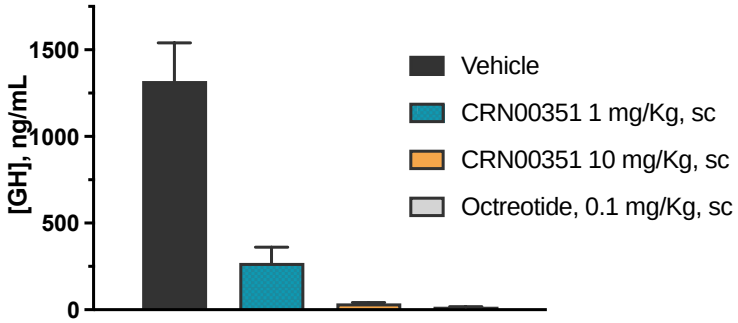
Early Leads Show the Way to Finding Clinical Class Compounds

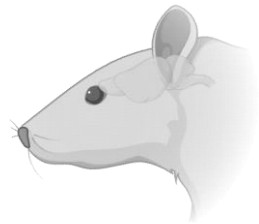
Early Lead



CRN00351
hSST2 EC_{50}=0.45 nM
hSST4 EC_{50}=0.47 nM

Rat GHRH Challenge

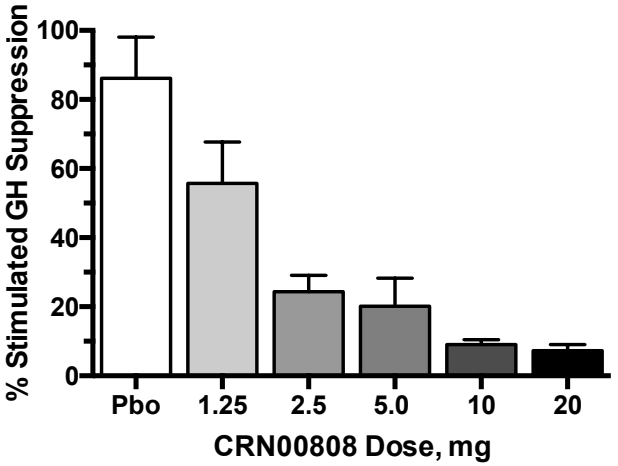


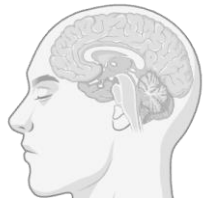


Ongoing Discovery

CRN00808

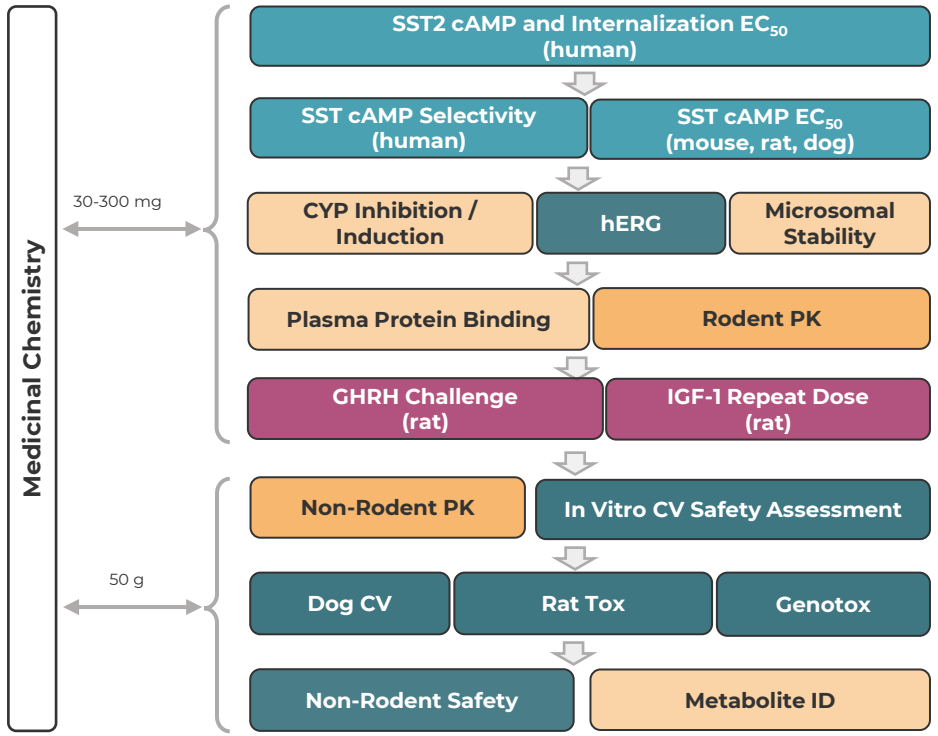
Healthy Volunteer GHRH Challenge

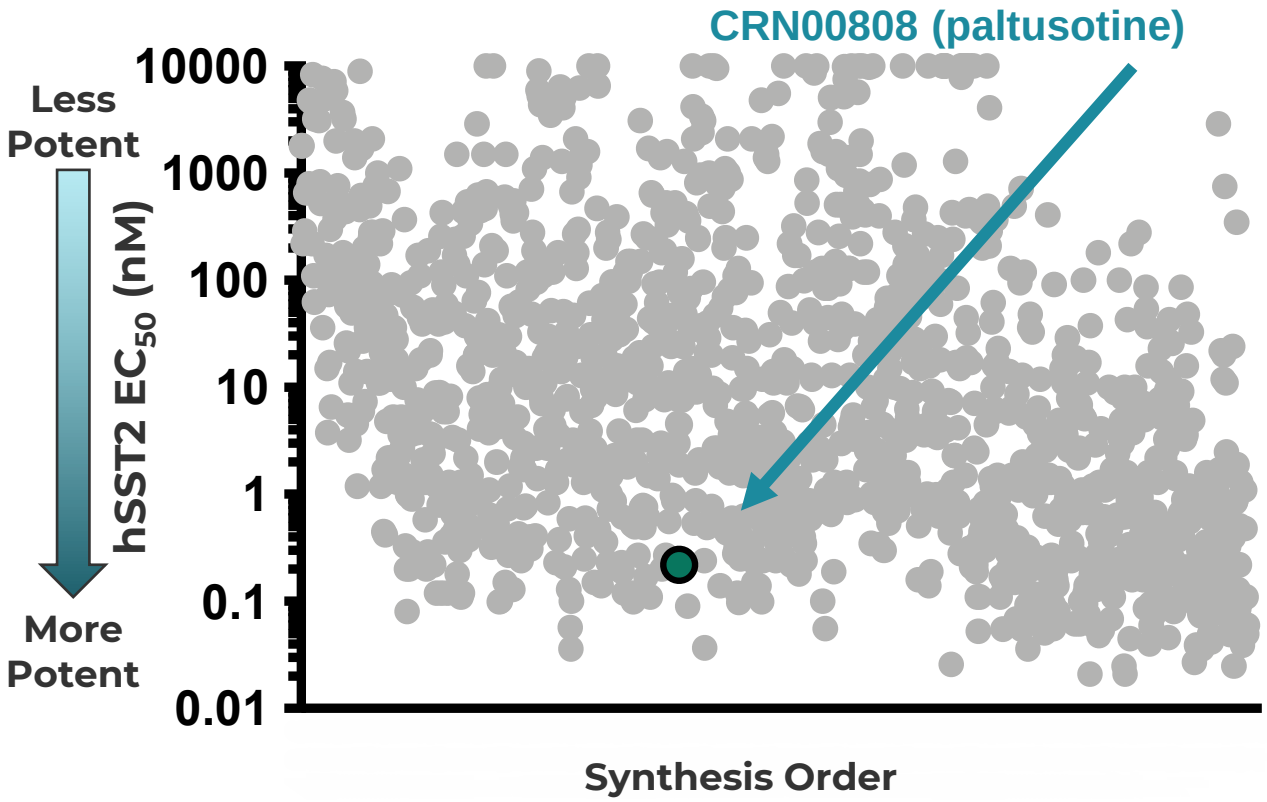




Every molecule Crinetics moves into the clinic is designed to exceed a high bar for selectivity, drug exposure and drug-like properties

The Ultimate Clinical Compound Is a Balance of Multiple Inputs and Evaluations



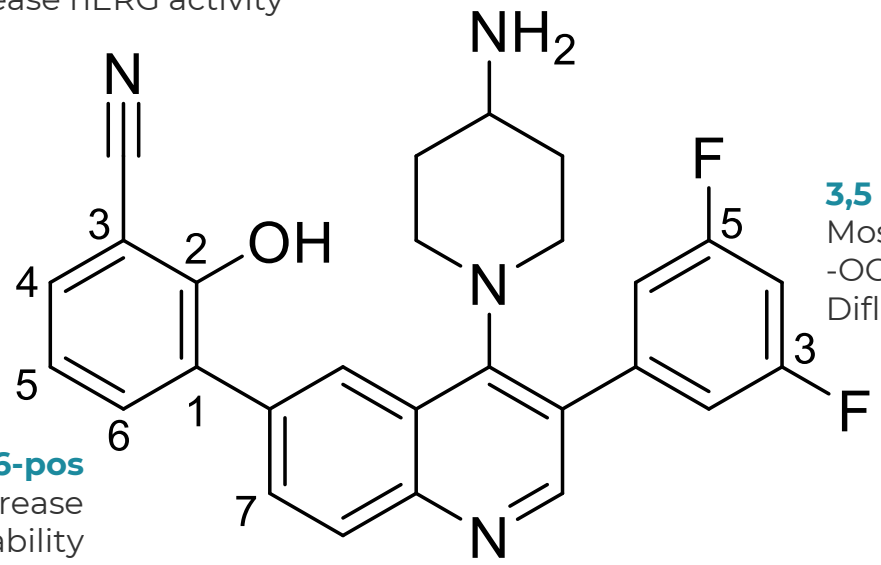


Zhao J, et al. *ACS Med Chem Lett.* 2023;14(1):66-74. Madan A, et al. *Pituitary.* 2022;25(2):328-339. Madan A, *Endocr Abstr.* 2020;70:AEP627.

Every Atom in Paltusotine (CRN00808) Was Optimized For Pharmacologic and Pharmaceutical Properties

2-OH, 3-CN combo
Removes hERG activity
Synergistic SST2 potency
-F, -Cl increase hERG activity

"Top" Diamine
Defines SST2 selectivity
Symmetry reduces chirality and conformational issues



5-pos
SST2 activity increase
Poorer SST selectivity
Increased hERG activity

3,5 substitution
Most potent and selective for SST2
-OCH_3, -CH_3 increases CYP and hERG activities
Difluoro = optimal drug-like properties

6-pos
SST2, SST3, and SST4 activity increase
Typically lowers metabolic stability

7-pos
Substitution lowers SST2 potency

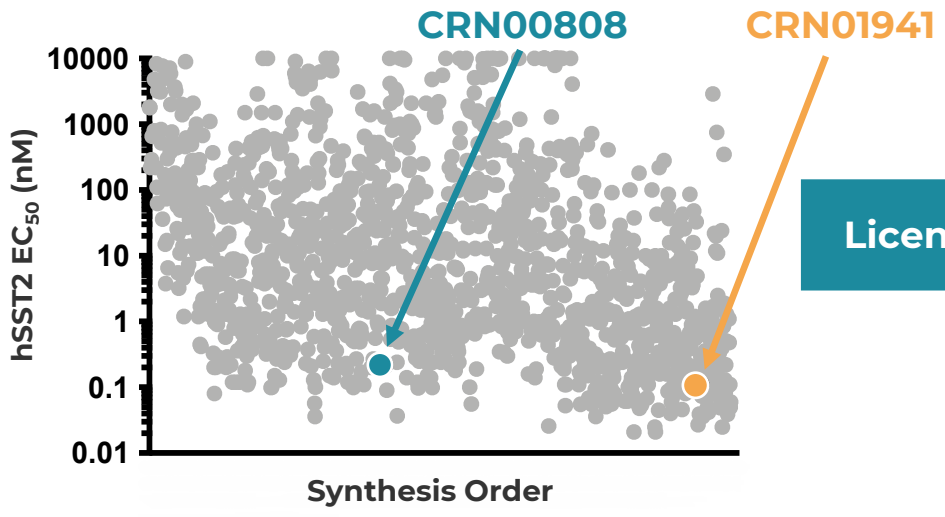
Quinoline core
N improves SST2 potency
Good synthetic accessibility
Overall acceptable bioavailability
Overall acceptable stability

Zhao et al. (2022) ACS Medicinal Chemistry Letters,
https://pubs.acs.org/doi/full/10.1021/acsmedchemlett.2c00431

Discovery Is (Almost) Never a One-and-Done Process

Backup Molecules Provide Insurance and Opportunity

SST2 Agonist



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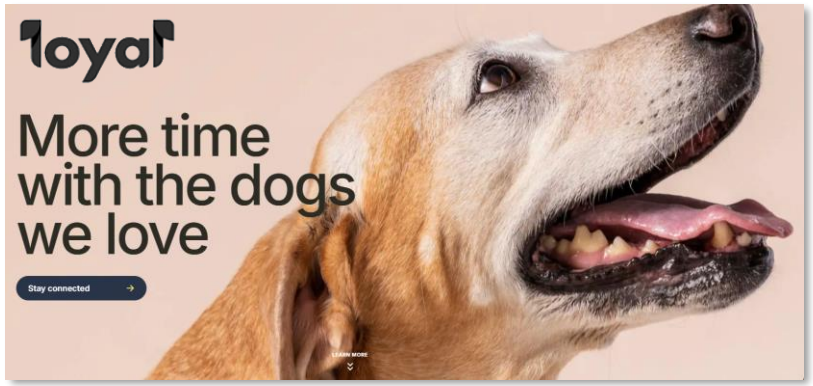


ACTH Antagonist

Initial Candidate CRN04599

Pivot to CRN04894

CRINETICS ANNOUNCES POSITIVE TOPLINE RESULTS FROM PHASE 2 TRIAL OF ATUMELNANT IN CONGENITAL ADRENAL HYPERPLASIA (CAH)

Substantial, Rapid and Sustained Statistically Significant Reductions of Key Biomarkers Achieved Across Doses, Including up to 80% Mean Reduction of Androstenedione

Meaningful Improvements Demonstrated in Multiple Clinical Signs and Symptoms of CAH Affecting Patient Health

Safety and Efficacy Data Support Initiation of Phase 3 Clinical Trial

Patients Play a Fundamental Role in Discovery and Development

We engage in **patient advocacy** starting in the Discovery phase

Feedback on patient journey is **incorporated into** overall **strategy and trial designs**

Early input optimizes enrollment and positions candidates for success to **address unmet need**

Awareness initiatives **build network**, develop insights, and support communities

Acromegaly Awareness Day
November 1, 2019

Patient engagement is in our DNA, with nearly two decades of relationship building that began well before our work in the clinic

TSHR ANTAGONIST

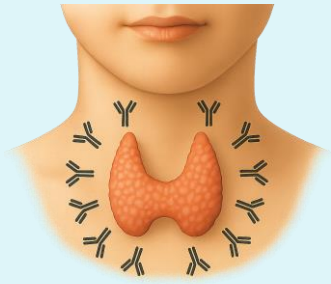
GRAVES' DISEASE:
- Graves' Hyperthyroidism
- Graves' Orbitopathy (Thyroid Eye Disease, TED)

Rick Grimes

Global Product Leader, TSH

Graves' Hyperthyroidism and Orbitopathy (TED) Have Significant Negative Effects on Patients

Graves' Hyperthyroidism



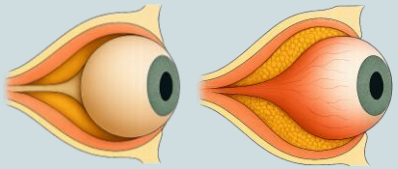
- Graves' disease is one of the most common endocrine diseases, affecting **~3 million individuals in the U.S.**[1]
- Symptoms include irritability, tremor, fatigue, weight loss, dyspnea and heat intolerance
- Major complications include atrial fibrillation, heart failure and thyroid storm

Significant Impact on Patients

- Emotional, mental and physical fatigue
- Anxiety
- Difficulty concentrating due to "brain fog"
- Reduced performance on daily living and work activities

Graves' Orbitopathy (TED)

Healthy Eye **TED Eye**



- **~500,000 prevalent patients in the U.S.**[2]
- Causes inflammation and damage to the tissues around the eye, including muscles, fatty tissue, and connective tissue
- Typically follows a biphasic course: active inflammatory phase (1-3 years) followed by a chronic, fibrotic phase
- Can lead to vision loss and blindness

Significant Impact on Patients

- Significant physical discomfort including ocular pain, double vision and proptosis
- Can lead to psychosocial distress, such as anxiety and depression
- Difficulty with daily tasks such as driving, reading and social interactions

1. Lee et al. 2023
2. Bartalena et al. 2020

Graves' Hyperthyroidism: Standard of Care Has Been Stagnant for Decades and Has Significant Limitations

ATDs have become the highly preferred 1L treatment in the US (~90%) due to risks associated with ablative therapies

Antithyroid Drugs (ATDs)

MOA

- Inhibits thyroid hormone synthesis in the thyroid gland

Limitations

- **Does not prevent or treat Graves' Orbitopathy**
  - 30-50% of Graves' patients develop TED[1]
  - Typically develop TED within 18 months of onset of Graves' Hyperthyroidism
- Potential for **serious side effects** including **liver injury (~3%)[2] and agranulocytosis (~0.3%)[3]**
- Other adverse effects including Itching, rash, hives, arthralgias, arthritis, fever, abnormal taste sensation, nausea, or vomiting in up to 13% of patients[2]

Ablative Therapy

MOA

- Ablation of thyroid function, either with
  - **Radioactive iodine (RAI),** which destroys the thyroid cells
  - **Thyroidectomy** (surgical thyroid removal)

Limitations

- **Permanent hypothyroidism** and **lifelong thyroid hormone replacement** therapy
- Thyroidectomy **risks parathyroid gland and laryngeal nerve damage**
- RAI has **risk of radiation thyroiditis** or **secondary malignancies**
- RAI has **increased risk of incidence or exacerbation of TED**

1. Chin et al. 2020
2. Sundaresh et al. 2013
3. Watanabe et al. 2012

Graves' Orbitopathy (TED): Anti-IGF-1R Has Changed the Treatment Paradigm but There is a Need for a Safer Therapy

Teprotumumab (anti-IGF-1R mAb)

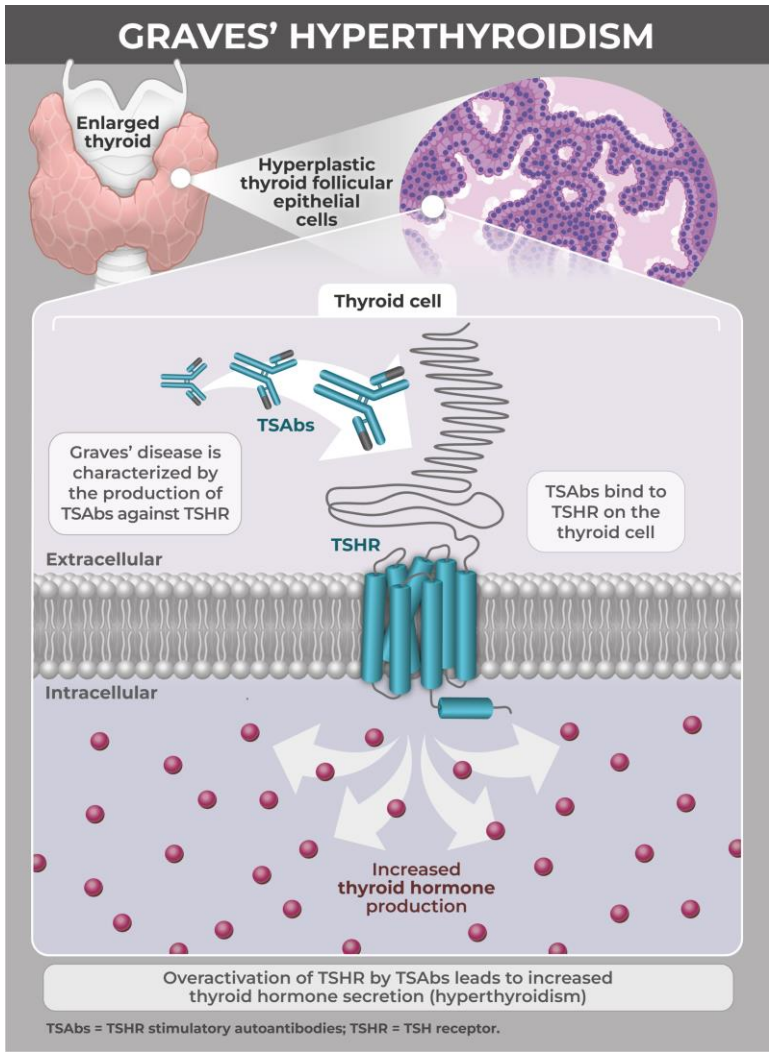
- Inhibition of IGF-1R improves proptosis associated with TED
- Teprotumumab reduces proptosis with up to 80% response[1] but **many experience relapse** (>30%)[2]
- Risks of therapy include:
  - **On target risk of hearing impairment (10-20%)[3,4] and hyperglycemia (10%)[3,5]**
  - **Other safety risks** including muscle spasms (32%), alopecia (15%), nausea (12%) and fatigue (10%)[6]
- Requires burdensome IV dosing in an infusion center
- **Not suitable for all patients** – precautions for those with inflammatory bowel disease, diabetes and pre-existing hearing conditions

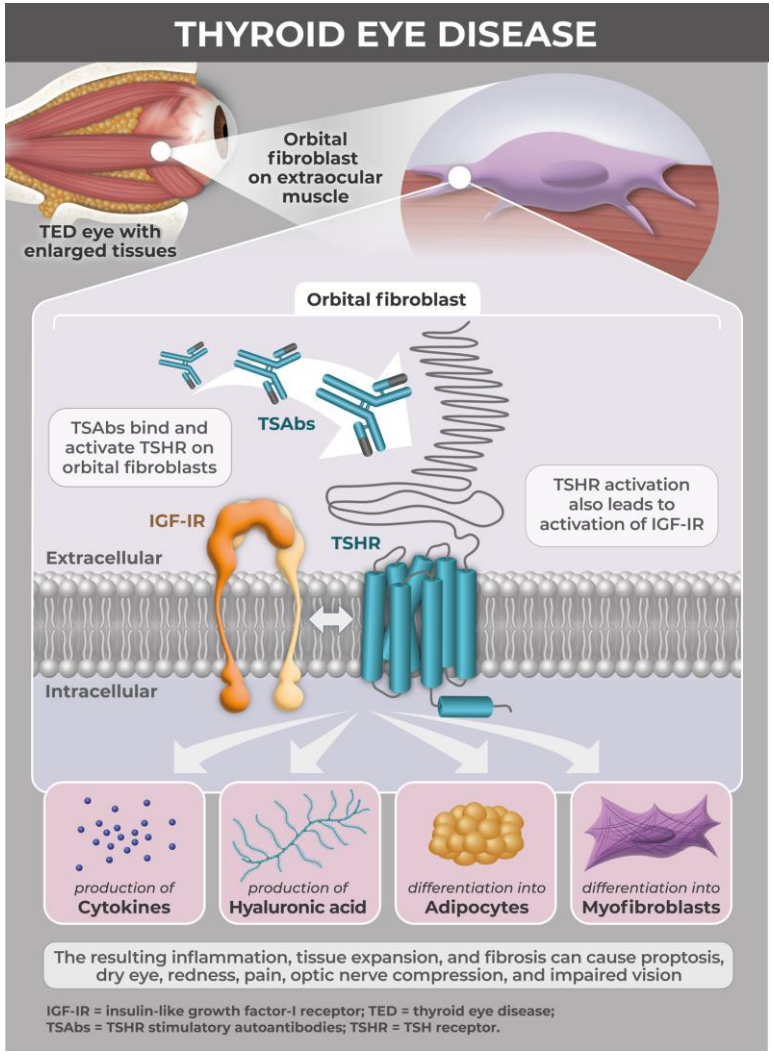
1. Douglas et al. 2020
2. Couch 2022
3. Kahaly et al. 2021
4. Douglas et al. 2023
5. Smith et al. 2024
6. Teprotumumab FDA briefing document Dec. 13, 2019

The Core Driver of Both Graves' Hyperthyroidism and Orbitopathy (TED) is Over-Stimulation of TSHR by TSHR Stimulating Auto-Antibodies (TSAbs)

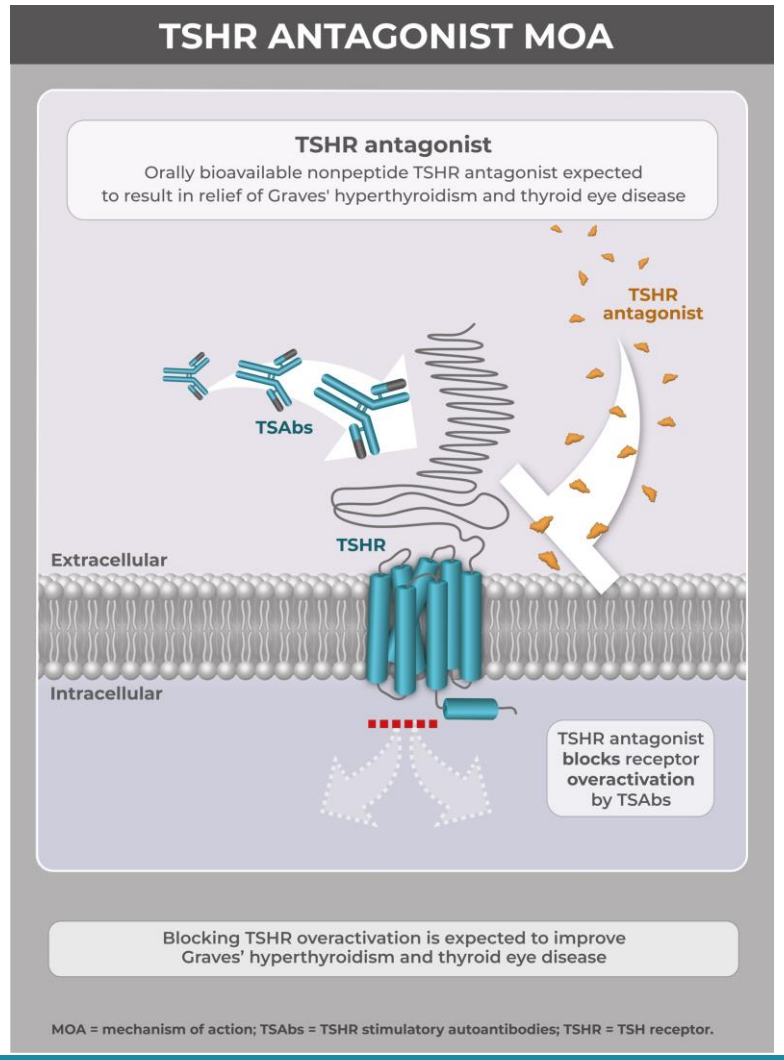
Graves' Disease has two major manifestations:

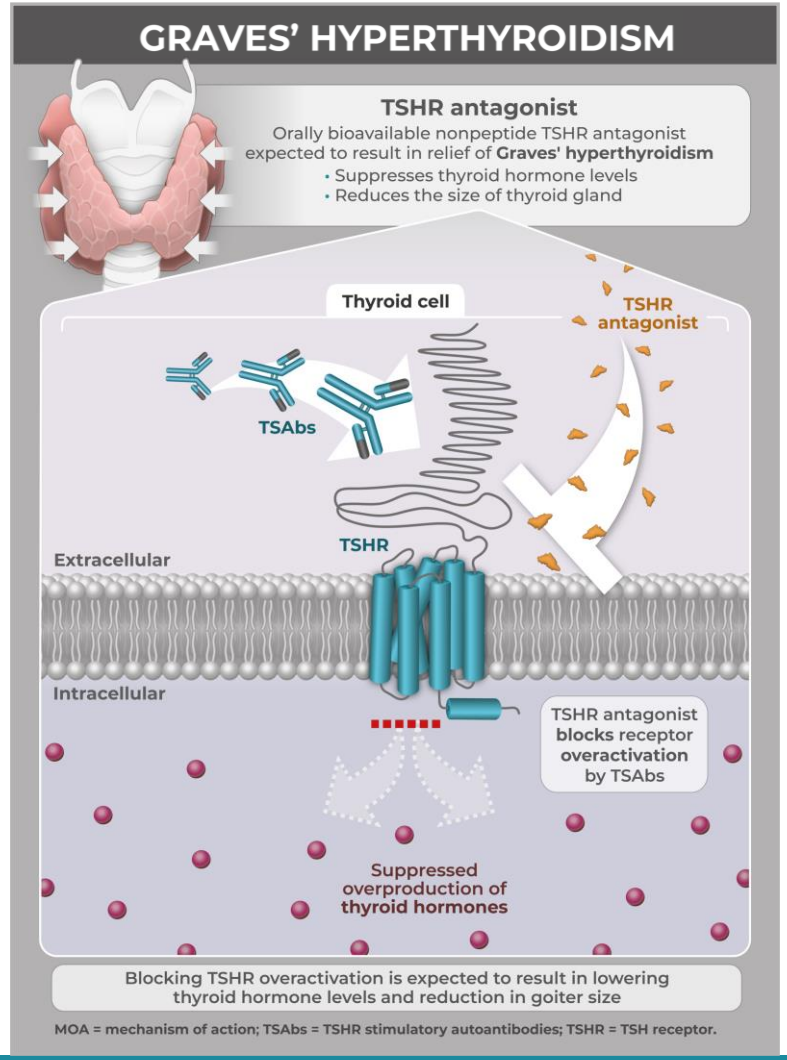
- Hyperthyroidism
- Orbitopathy (also known as Thyroid Eye Disease or TED)

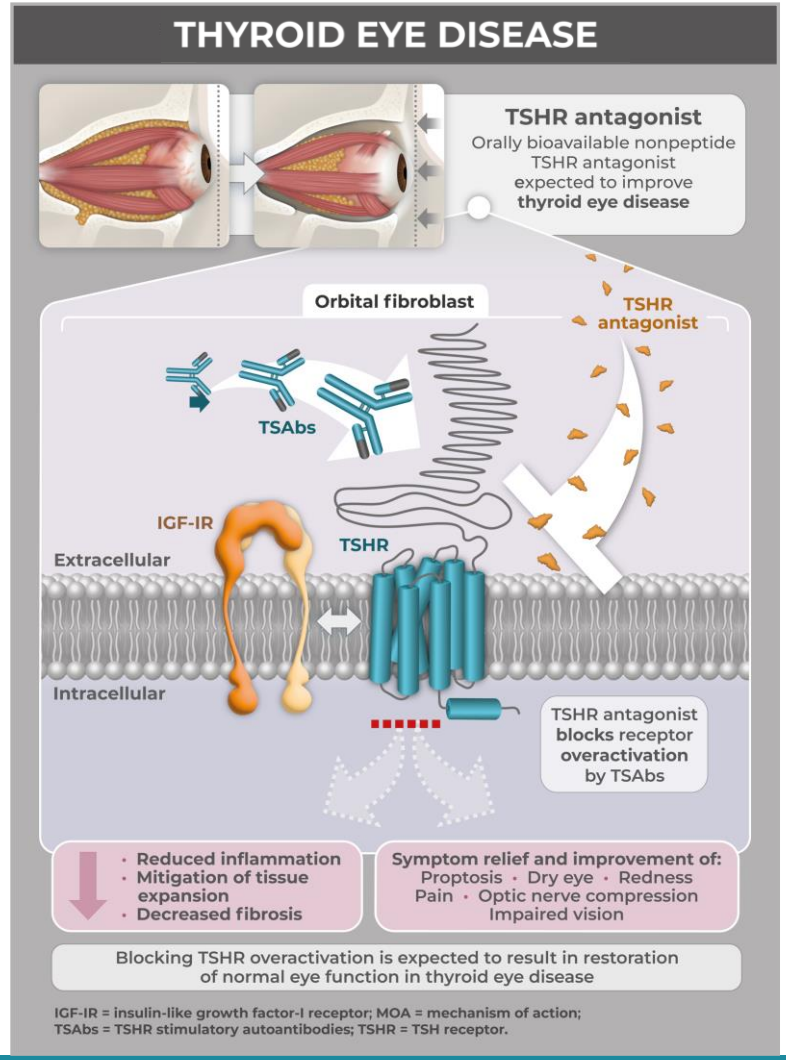




TSHR Antagonism: A Targeted, Novel Mechanism to Treat Both Major Manifestations of Graves' Disease







Crinetics Has Developed Potent and Selective Small Molecule, TSH Receptor Antagonists

CRNX TSHR Antagonists

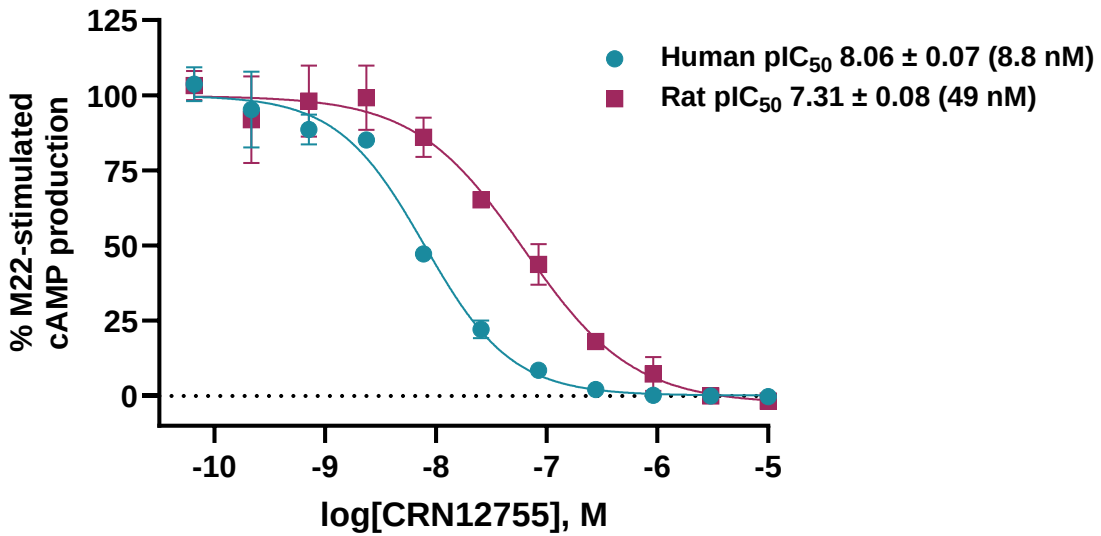
- Structurally diverse
- Potent and selective for TSHR
- Good ADME properties

CRN12755

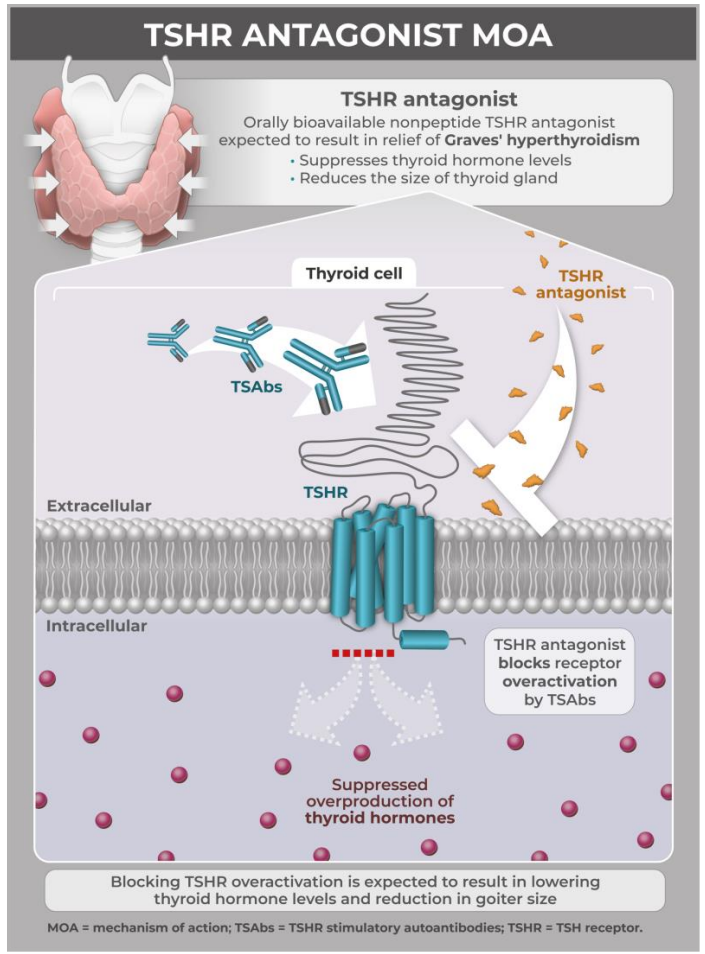
(leading development candidate)

- Predicted human PK to support QD dosing
- Efficacious in Graves' Hyperthyroidism rat model
- Inhibits TSAb stimulation in human Graves' patient orbital fibroblasts
- IND-enabling safety studies in progress

CRN12755 Is Potent Functional Antagonist of Human TSHR

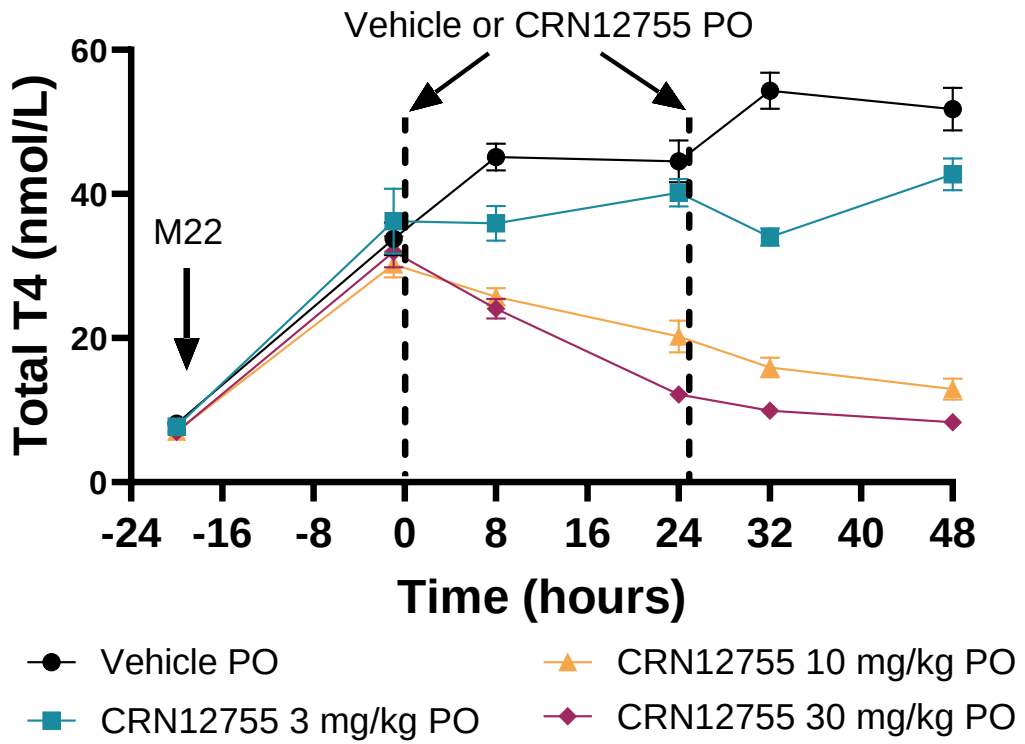


Graves' Hyperthyroidism: CRN12755, a TSHR Antagonist, Reduced Thyroid Hormone Levels in a Stimulated Rat Hyperthyroidism Model



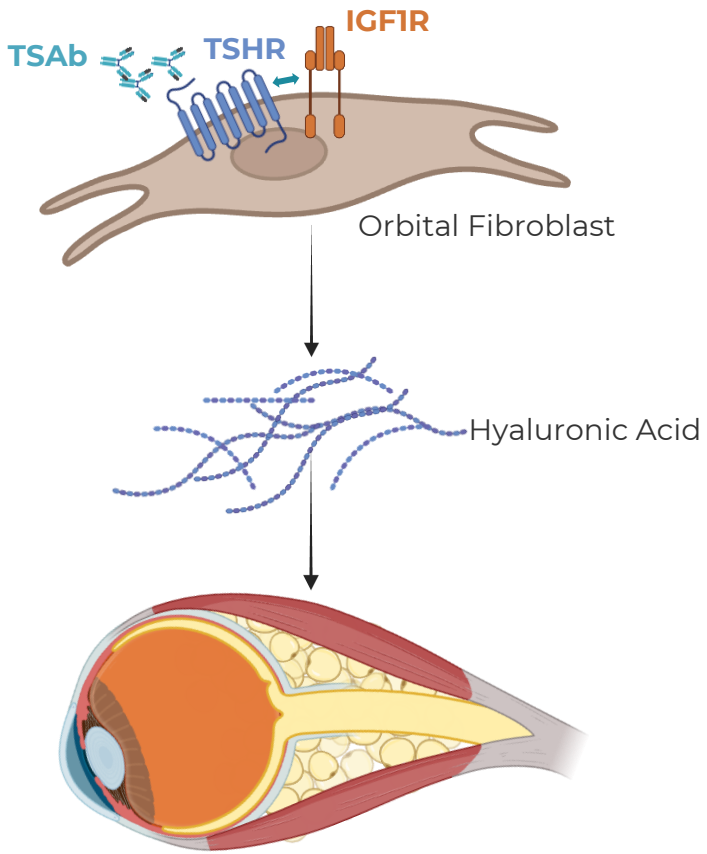
RAT HYPERTHYROIDISM MODEL

Oral administration of CRN12755 dose dependently reduced TSAb (M22) stimulated thyroid hormone (T4) levels



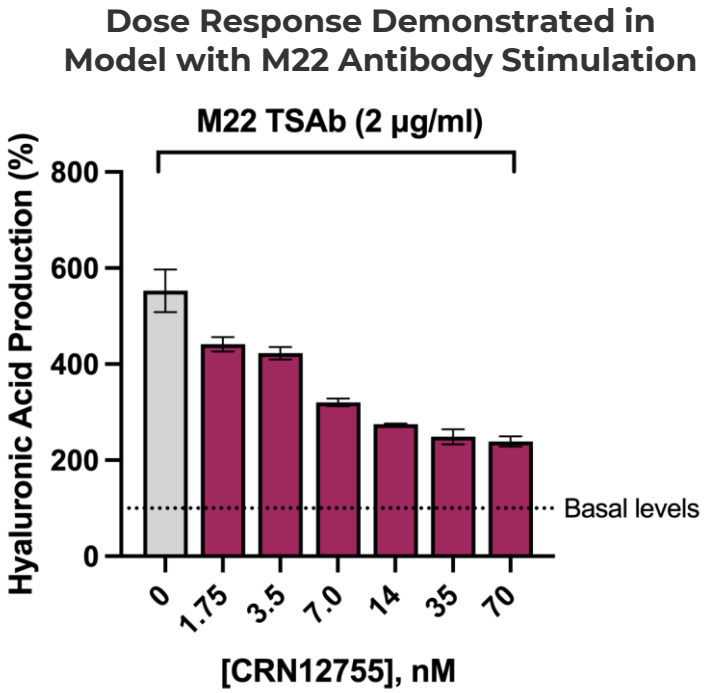
M22: TSAb derived from Graves' patient

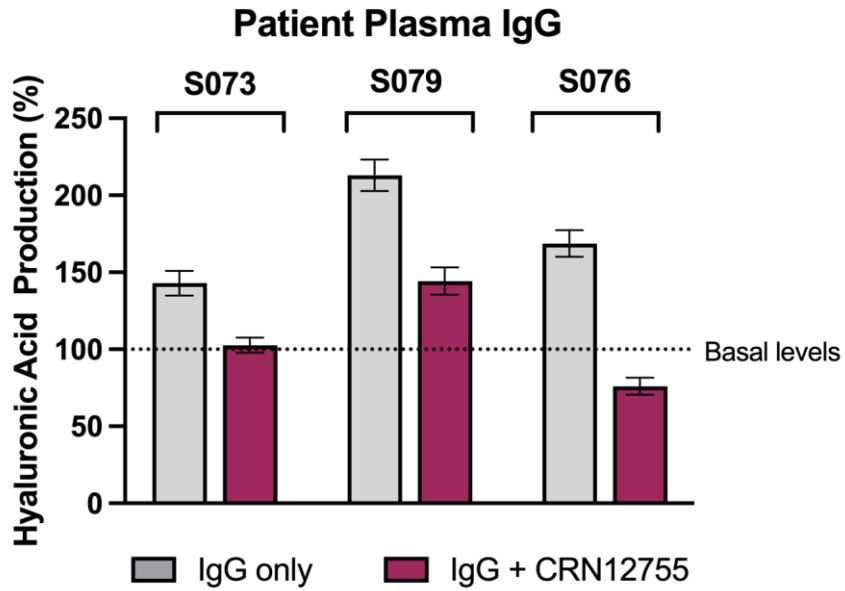
Graves' Orbitopathy (TED): CRN12755 Suppressed TSAb-Stimulated Hyaluronic Acid Production in TED Patient-Derived GOFs



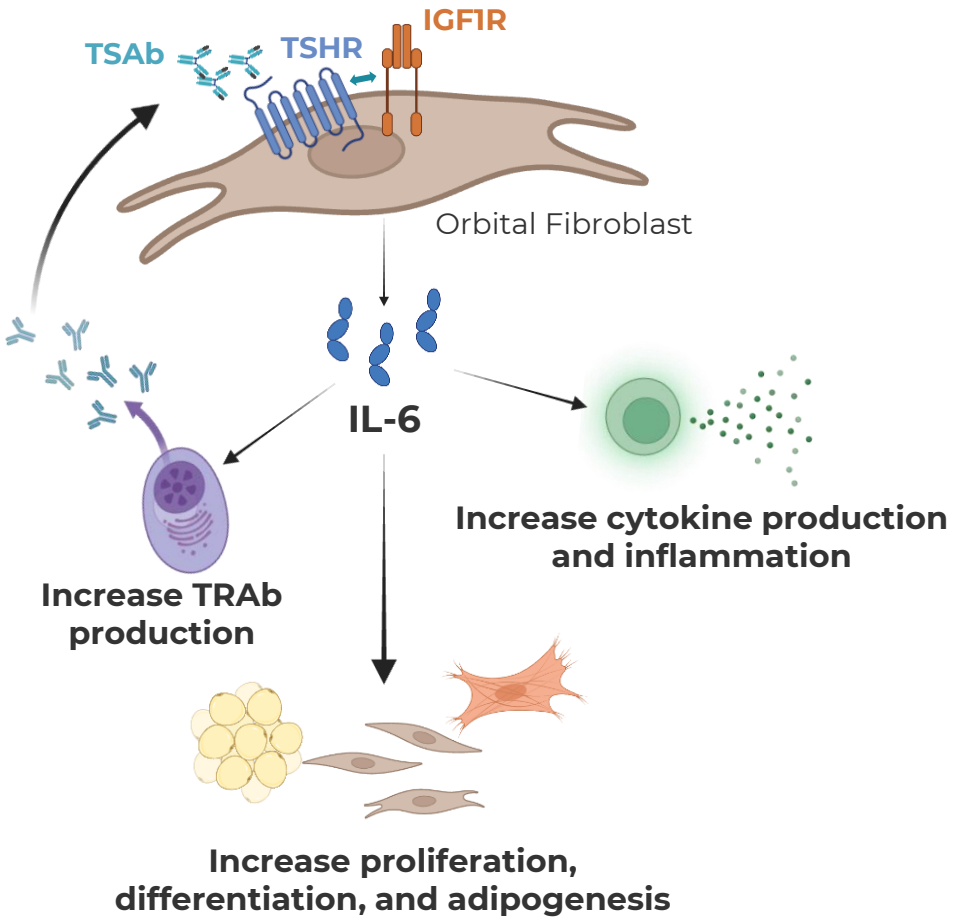
Hyaluronic acid attracts and binds to water, increasing the volume of orbital tissue

Graves' orbital fibroblasts (GOFs) are obtained from TED patients undergoing orbital decompression surgery and differentiated into orbital adipocytes

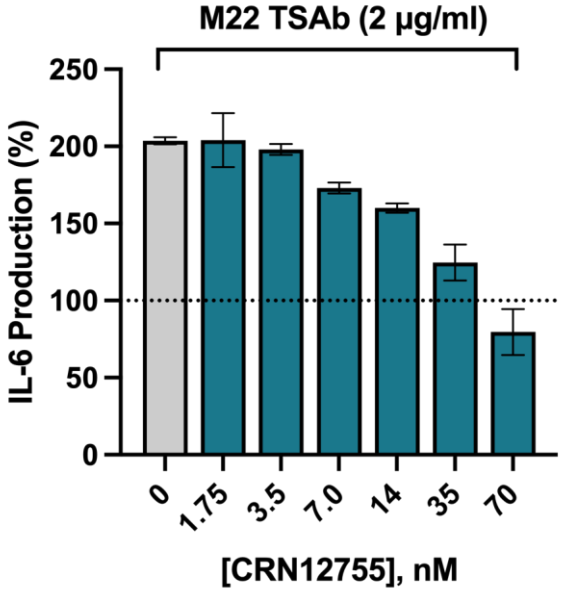


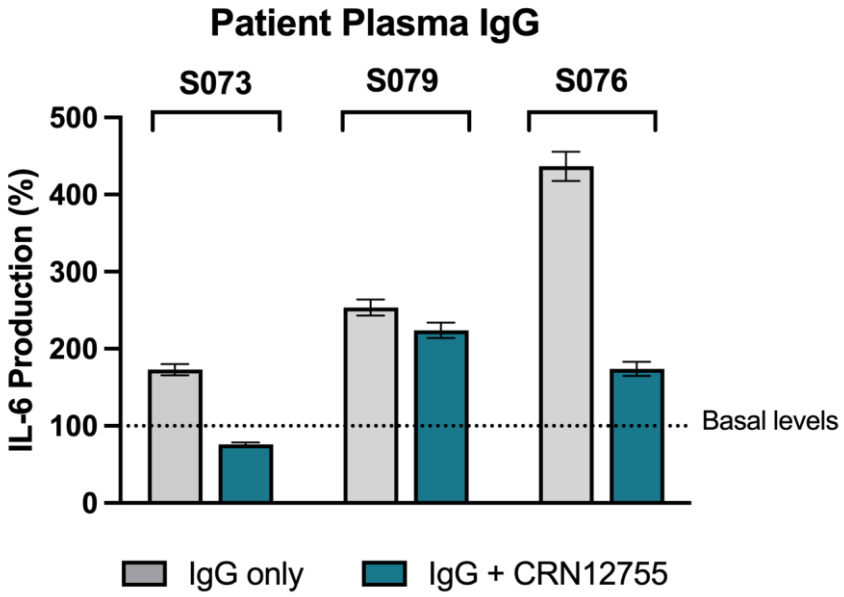


Graves' Orbitopathy (TED): CRN12755 Suppressed TSAb-Stimulated Production of IL-6 in TED Patient-Derived Orbital Adipocytes



Graves Orbital Fibroblasts (GOFs) from TED patients are differentiated into orbital adipocytes and stimulated with TSAbs





Fowler, M. (2025)

TSHR Antagonist: Has Potential to Be a Single, Oral Therapy to Treat Graves' Hyperthyroidism and Treat/Prevent Orbitopathy (TED)

Product Vision

Graves' Hyperthyroidism

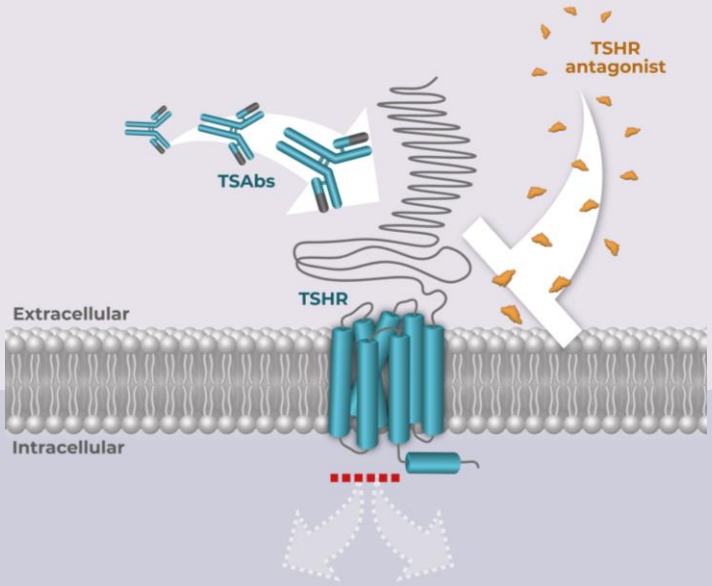
- Oral, once daily
- Rapid control of hyperthyroidism and symptoms
- Simultaneous treatment and prevention of orbitopathy
- No risks associated with ATDs
- Thyroid preservation

Prevent Orbitopathy

Graves' Orbitopathy (TED)

- Oral, once daily
- Equivalent or better efficacy than approved IGF-1R mAb
- Improved safety
  - No hearing impairment or hyperglycemia
  - Enabling a more durable treatment

A TSHR Antagonist Has Potential Advantages Over Emerging New Therapies



TSHR Antagonist Product Vision
A single, oral therapy to treat Graves' Hyperthyroidism and treat/prevent Graves' Orbitopathy

TSHR Antagonist Potential Attributes

- Oral, once daily
- Rapid control of hyperthyroidism with thyroid preservation
- Simultaneous treatment and prevention of orbitopathy
- No adverse effects of ATDs or anti-IGF-1R and no non-specific immunomodulation

2nd Generation IGF-1R Inhibitors (SC or oral)

- Treat TED only
- Early data suggest subcutaneous are more efficacious than oral
- On-target side effects remain a concern (full data still pending)

Anti-FcRn mAbs & Small Molecule Bispecific Degraders

- Reduce levels of TSAbs by promoting degradation
- Broad IgG degradation, not TSAb specific
- May require large reductions in IgG (>70%)
- High dose, once weekly subcutaneous injections

ROA: route of administration.

Large Patient Population in the US in Both Graves' Hyperthyroidism and Orbitopathy (TED) with High Unmet Need

GRAVES' HYPERTHYROIDISM

>3M prevalent patients[1] *

Up to ~1.2M with active Graves' hyperthyroidism[2]

Addressable patient population

up to ~170k incident[3]

GRAVES' ORBITOPATHY (TED)

~500,000 prevalent patients[4] *

~30k incident[4,5]

~325k Mild (55-75%)	**~150k Moderate-to-severe** (20-40%)[6,7]	**~25k Sight-threatening** (<10%)

Addressable patient population

~9k moderate to severe incident

*Theoretical prevalence

1. Lee et al. 2023
2. Hallowell et al. 2002
3. Smith et al. 2016
4. Bartalena et al. 2020
5. Bartley et al. 1994
6. Dosiou et al. 2021
7. Muralidhar et al. 2020

Next Steps for the TSH Antagonist Program

ENDO 2025: Poster Presentation

IND Submission

Phase 1 Healthy Volunteer Study

Early Proof-of-Concept in Phase 1 with Thyroid Biomarkers (TSH, T3, and T4)

IND: Investigational New Drug; POC: proof of concept.

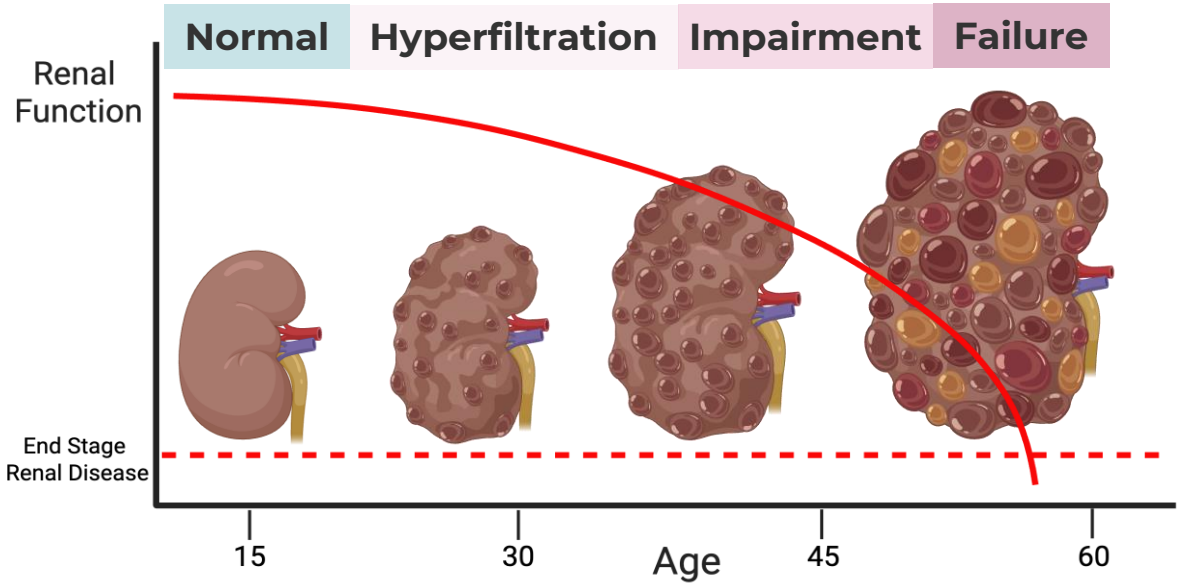
SST3 AGONIST

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

Stephen Betz, Ph.D.

Founder & Chief Scientific Officer

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a Genetic Disease That Significantly Impacts Quality of Life



Most common inherited kidney disorder (~145K diagnosed patients in the US)

- Abnormal primary cilia function triggers cystogenesis, fluid-filled cysts that gradually enlarge

Leads to kidney failure and dysfunction

- 50% of patients develop end stage kidney disease (ESKD), requiring dialysis or kidney transplant

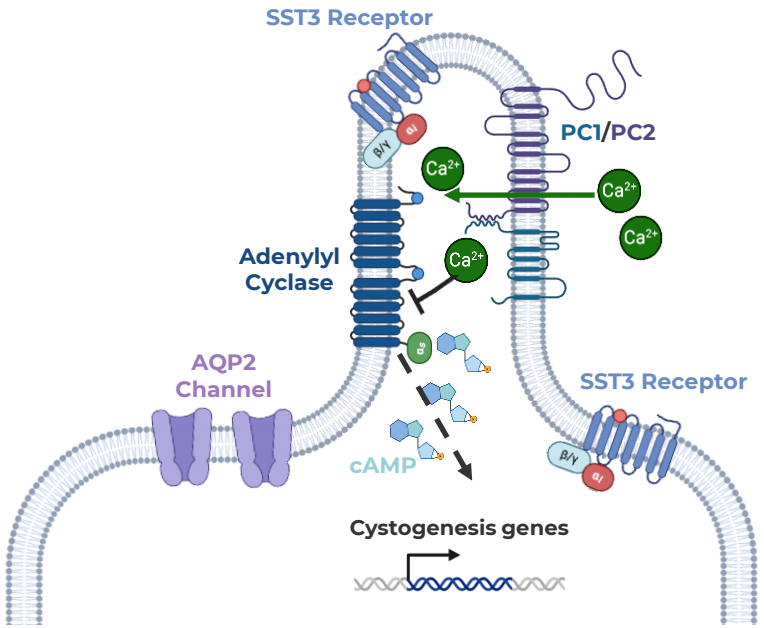
Tolvaptan (current standard-of-care) only used by <10% of patients:

- Modest efficacy
- Boxed Warning: Acute liver injury
- Key adverse effects (mechanism-dependent):
  - **Increased frequency of urination**
  - Thirst
  - Dehydration

Willey C et al. Kidney Disease 2019; Sim et al. 2021

ADPKD is a Disease of Disrupted Ca^{2+} and cAMP Ciliary Signaling

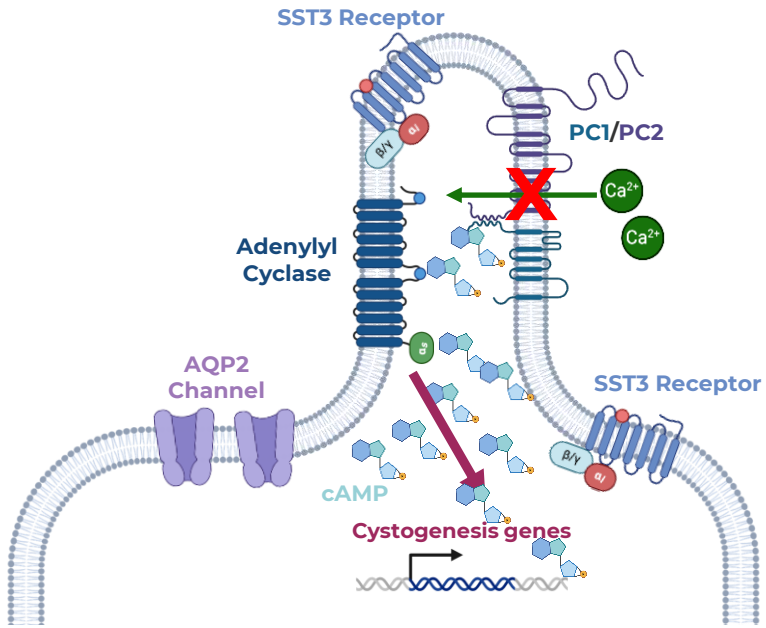
Healthy Human Kidney



PKD1 enables ciliary **Ca^{2+} influx**
- Inhibits adenylyl cyclase and reduces cAMP

Low ciliary cAMP levels → No cystogenic signal

ADPKD Patient Kidney

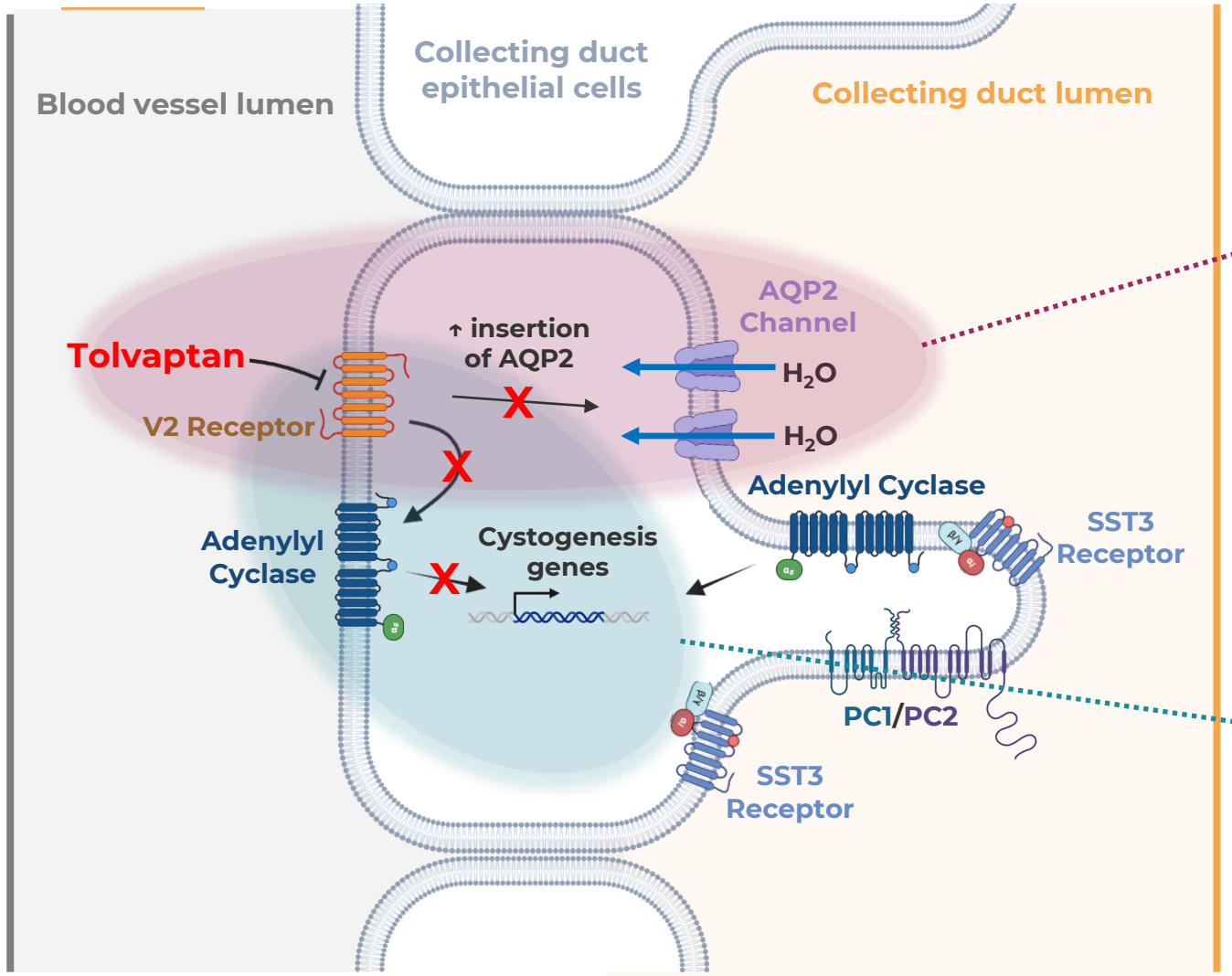


Calcium unable to enter cell to reduce cAMP

High ciliary cAMP levels → Cystogenic genes induced

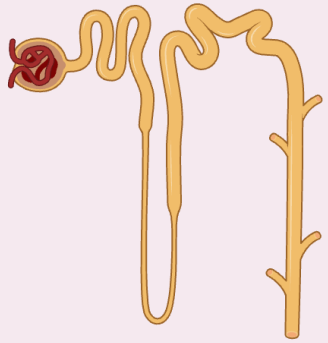
Hypothesis: Reducing ciliary cAMP levels is a novel approach for reducing cystogenesis

Tolvaptan Improves Kidney Function in ADPKD, but Causes Increased Urination and Hypernatremia



Risks

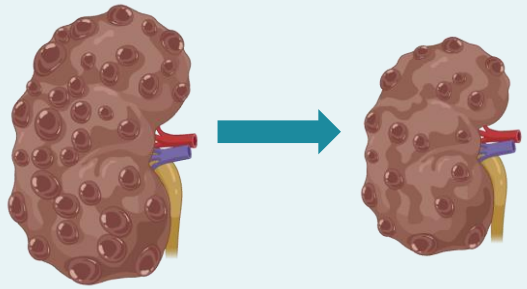
Decreases insertion of AQP2



- Decreased urine osmolality
- Increased water excretion
- Increased serum sodium (hypernatremia)

Benefit

Reduces adenylyl cyclase activity, decreasing expression of cystogenesis genes



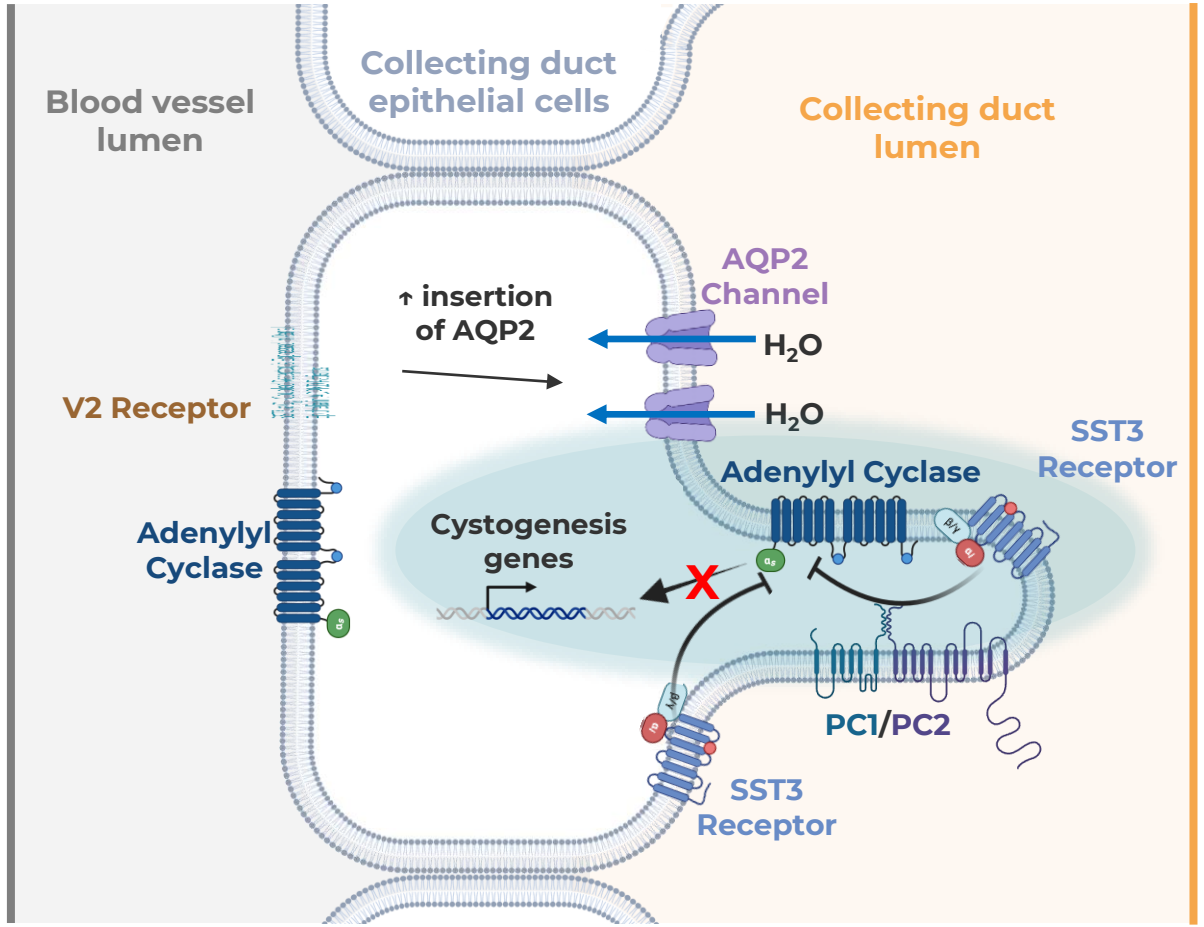
Decreased cystogenesis

Reduced kidney function decline

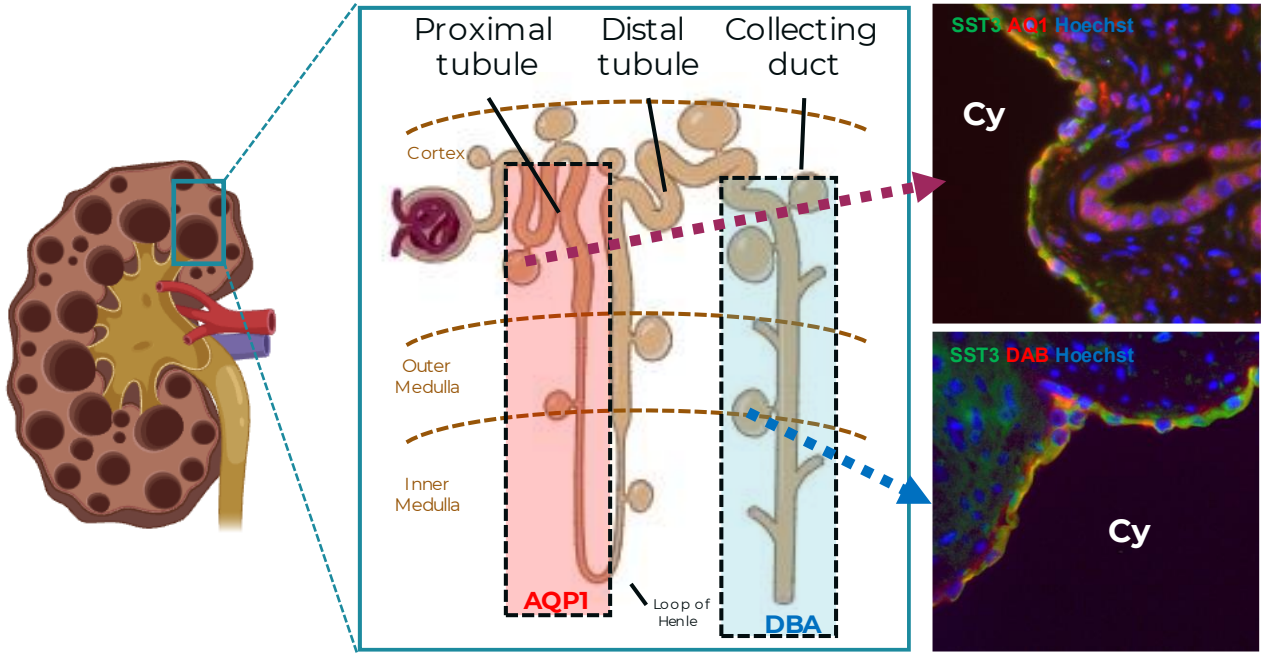
AQP2: aquaporin-2

SST3, a $G_{\alpha i}$-Coupled Receptor, is Expressed in Renal Epithelia in ADPKD Patients

Activation of SST3 localized in cilia and apical membrane of cyst-lining cells decreases cAMP and cystogenesis



SST3 is expressed in cysts emerging from both proximal tubules and collecting ducts

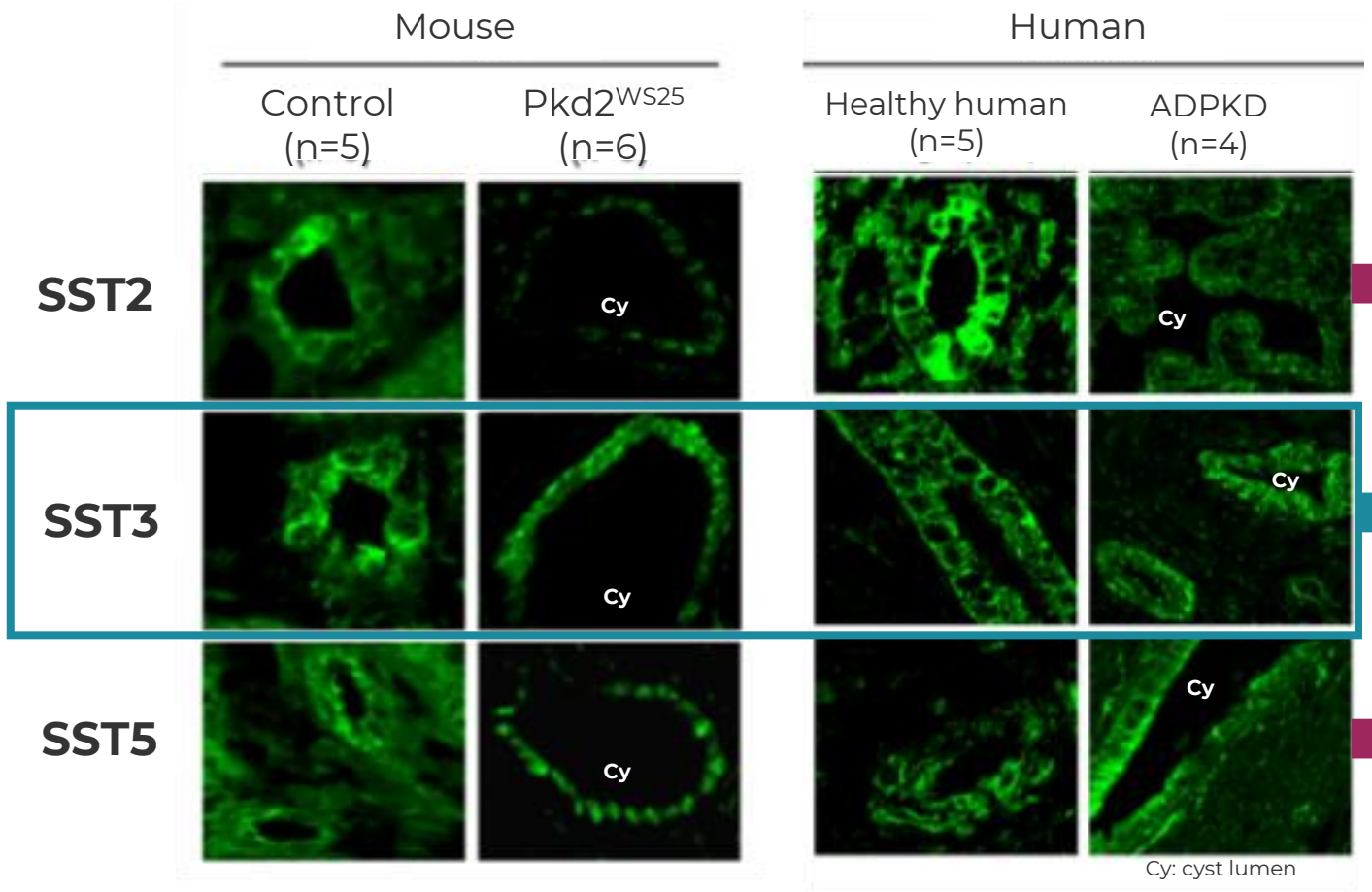


Cy: cyst lumen

- Tolvaptan acts only on cysts originating from collecting duct
- **SST3 agonist should impact expansion of cysts originating from tubules and collecting duct**

SST3 Agonism Represents an Effective Somatostatin-Targeted Strategy in ADPKD

SST3 is highly and consistently expressed in cyst-lining cells in ADPKD



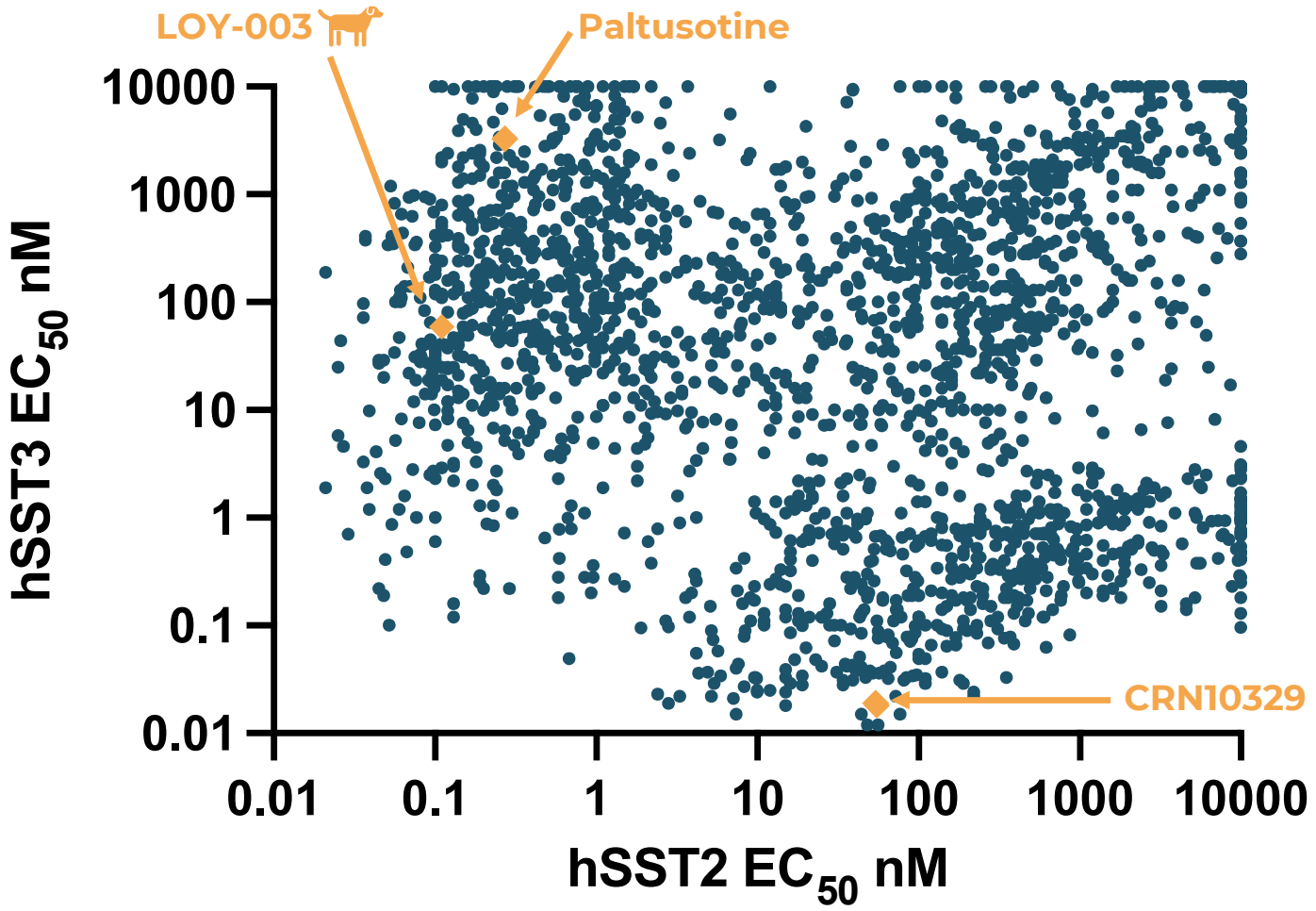
Waning efficacy: SST2 agonists have shown some efficacy in ADPKD trials

Consistent expression in healthy and ADPKD kidneys

Hyperglycemia with SST5 activation

Lancet 2013; 382: 1485–95; PLoS Med 16(4): e1002777; JAMA, 2018; 320 (19)
Hepatology 2013; 58(1), 409-421

Crinetics Has Developed Potent and Selective SST3 Small Molecule Agonists



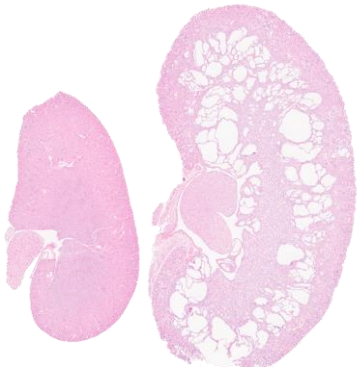
CRNX SST3 Agonists

- Structurally diverse
- Potent and selective at hSST3
- Good ADME properties

CRN10329 (Leading Development Candidate)

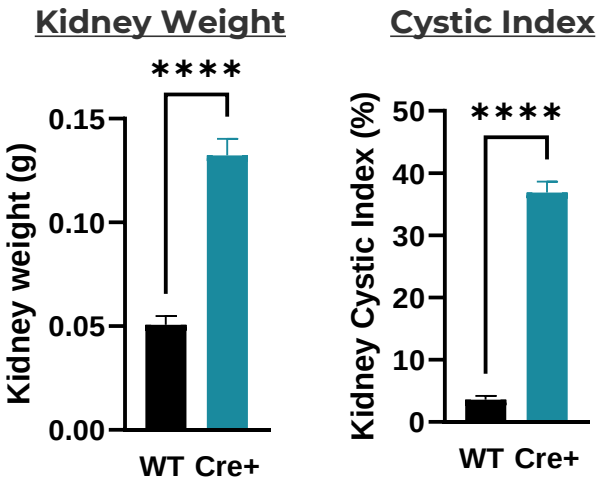
- Predicted human PK supports QD dosing
- Efficacious in ADPKD mouse model
- IND-enabling safety studies ongoing

Aggressive Conditional PKD1-KO Mouse Model of ADPKD Allows for Rapid Compound Evaluation

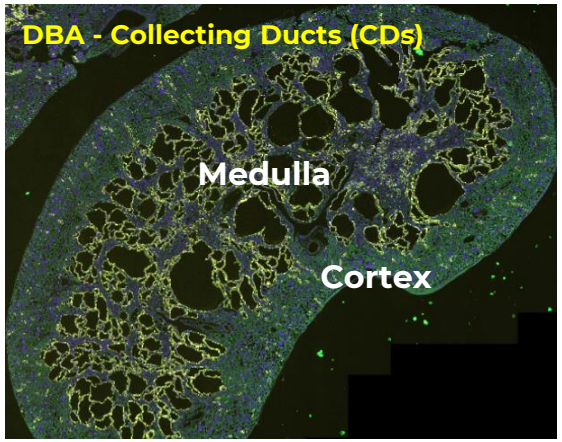


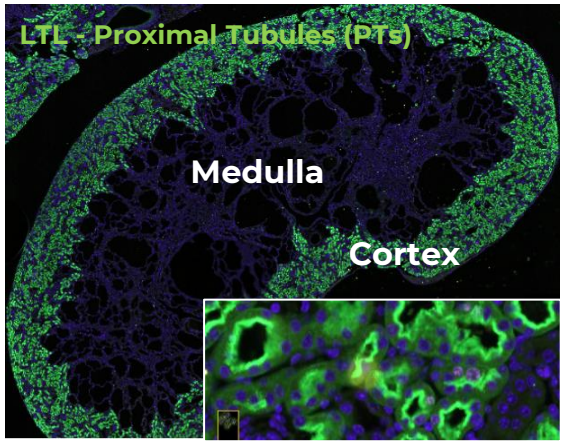
WT CreERT2^{-}; Pkd1$^{fl/fl}$

ADPKD CreERT2^{+}; Pkd1$^{fl/fl}$



Localization and segment identity of renal cysts in ADPKD mouse model



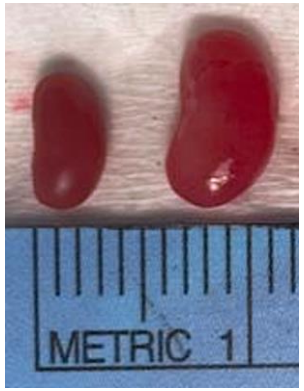
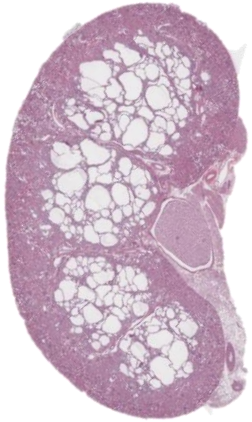
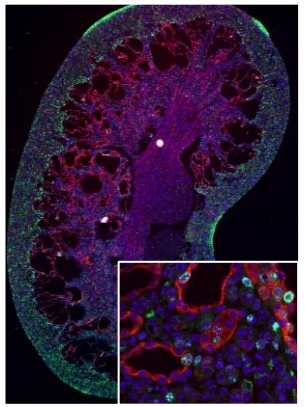
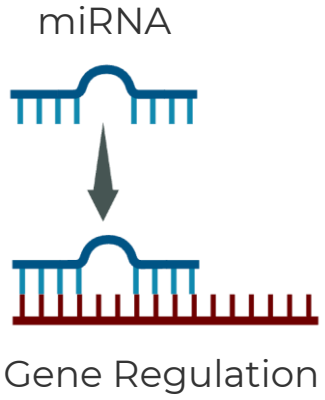


Cysts derive from collecting ducts in medulla and from proximal tubules in cortex

DBA: dolichos biflorus agglutinin
LTL: lotus tetragonolobus lectin

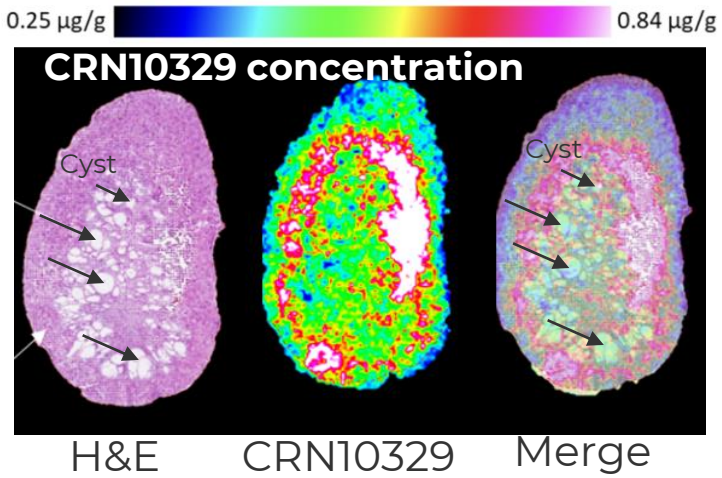
A Multi-level Approach to Characterize Efficacy in ADPKD Mouse Model

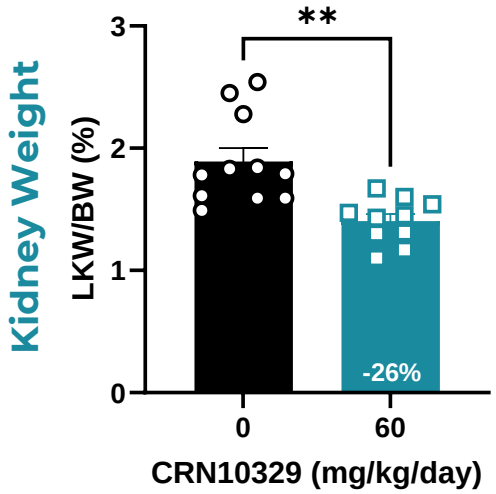
Biomarkers used to interrogate efficacy of advanced SST3 agonists

Level	Organ	Tissue	Cellular	Molecular
				
Biomarker	**Kidney Weight**	**Cyst size**	**Proliferation markers**	**RNA pathway profile**

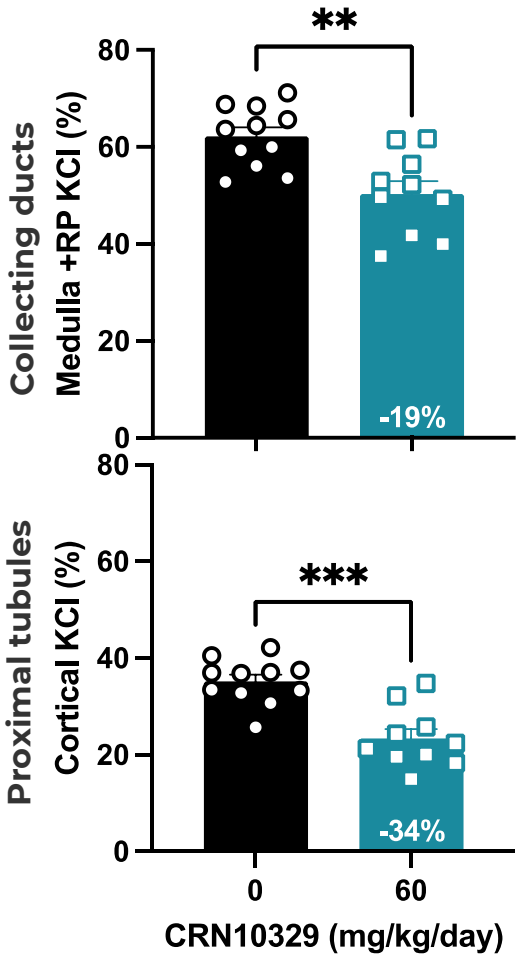
miRNA: microRNA

Exposure to CRN10329 Inhibits Cyst Growth and Decreases Proliferation in an Aggressive Mouse Model of ADPKD

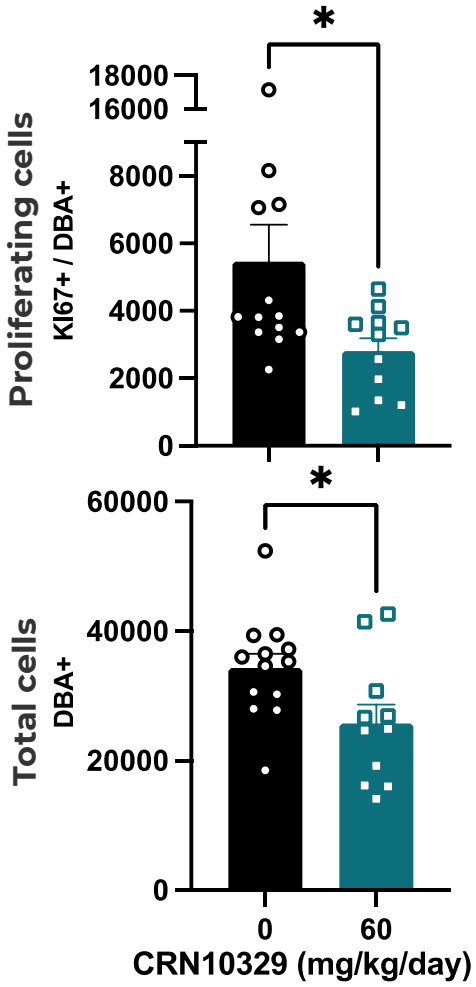




Cystic Index Decreased



Cellular Proliferation Decreased



LKW: left kidney weight; BW: body weight.

CRN10329 Corrects Aberrant Expression of Renal Tubular Injury Markers

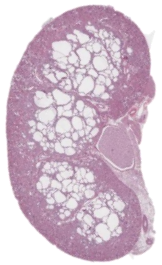
PKD1 KO

Periostin

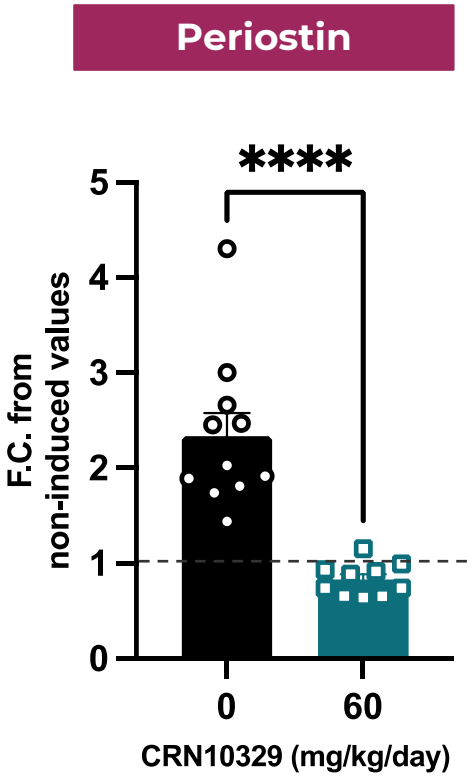
miR30a

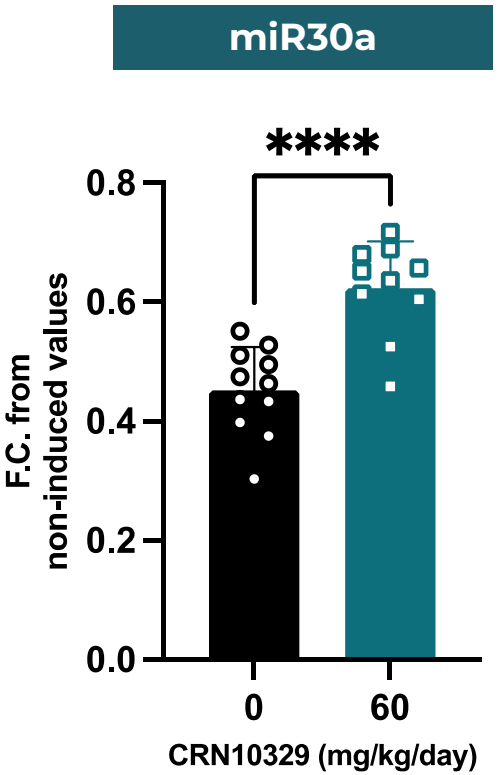
Cell Proliferation

Cyst Growth



CRN10329 Treatment





Kidney Int. 2014 Apr;85(4):845-54; Am J Physiol Renal Physiol. 2018 Dec 1;315(6):F1695-F1707; Nephrol Dial Transplant (2012) 27: 2702–2711; Ren Fail. 2020; 42(1): 1166–1172; Int J Oncol. 2016 Mar;48(3):1155-64

CRN10329 has the Potential to be Standard of Care for ADPKD

TPP Comparison	Tolvaptan V2R antagonist *Current SOC*	miRNA 17 inhibitor *Ph2/3*	**CRN10329** SST3 agonist *Preclinical*
Target Indication	ADPKD at risk of rapid progression	ADPKD at risk of moderate to very rapid progression,	ADPKD at any risk of progression
Efficacy	~50% reduction in total kidney volume (TKV) growth, only in first year of treatment	Potential for impact on TKV to be more effective than tolvaptan	Potential for impact on TKV to be more effective than tolvaptan
	~33% reduction in eGFR decline	Potential for impact on eGFR to be more effective than tolvaptan	Potential for impact on eGFR to be more effective than tolvaptan
Tolerability/Safety	Black Box Warning: Requires continual liver monitoring Hypernatremia, dehydration and hypovolemia, polyuria and nocturia significantly impact patients' lives	Mild to moderate AEs including injection site reaction, headache, and sinus infection	Expected to be well tolerated
Dosing	Oral BID, requires titration	SC, Q2W, no expected titration	Oral, QD, no titration expected

QD: Once daily
BID: Twice daily
Q2W: Once every two weeks
SC: Subcutaneous

SST3 Agonist: First-In-Class Novel Therapy for the Majority of ADPKD Patients and Beyond

Product Vision

To be the **first-in-class, oral, once-daily**, SST3 agonist that provides long-term **kidney function protection**, **improves** the **quality of life**, and becomes the **standard of care** for people living with ADPKD

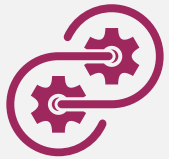
Strategies

1. Provide a new, superior SOC: Establish efficacy, improve safety/tolerability, first approval in ADPKD at high risk of rapid progression (Stage 2-3A)

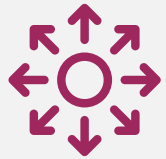
2. Accelerated approval based on Phase 2 endpoint (TKV): Efficient clinical development plan to enable accelerated approval based on TKV endpoint

3. Expand to earlier, younger patients with superior safety / tolerability: Lifelong protection of kidney function to stop or delay renal function impairment (Stage 1)

4. Expand to more advanced patients (superior efficacy): The first treatment to stop or delay progression to ESRD (Stages 3B-4)



5. Exploit combination potential: Evaluate emerging preclinical and clinical data to identify potential additive or synergistic combination therapies



6. Indication expansion: Explore in polycystic liver disease (PLD) and non-functioning pituitary adenomas (NFPAs)

Next Steps for the SST3 Agonist Program

IND Enabling Studies and Activities

IND Clearance

Phase 1 Healthy Volunteer Study

NONPEPTIDE DRUG CONJUGATES (NDC) PLATFORM

Stephen Betz, Ph.D.

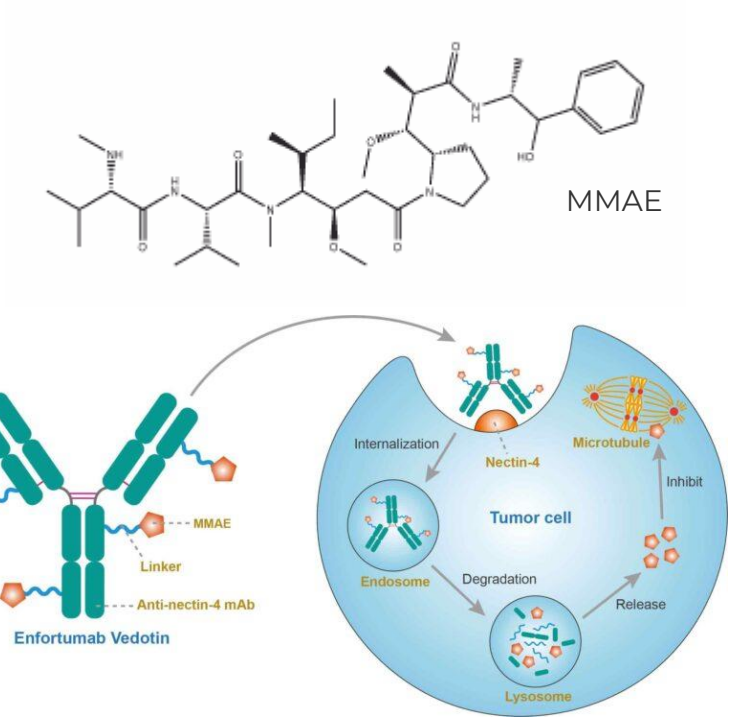
Founder & Chief Scientific Officer

Crinetics' Unique SST2-NDC Approach Integrates Two Validated Strategies in Oncology

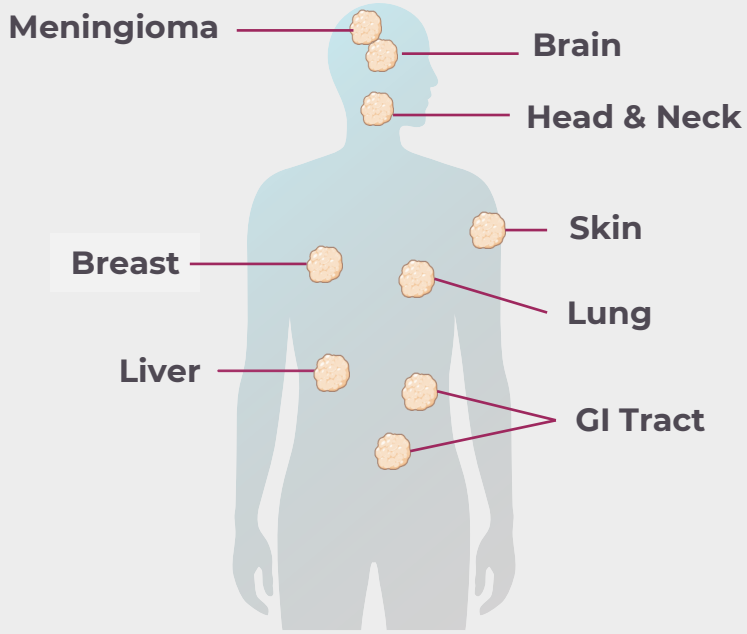
SST2 is a well-established target for imaging and PRRT

^{64}Cu-dotatate PET scan of a patient with intestinal NET and multiple metastases

MMAE is a well-established, effective, and easily sourced anti-tumor payload



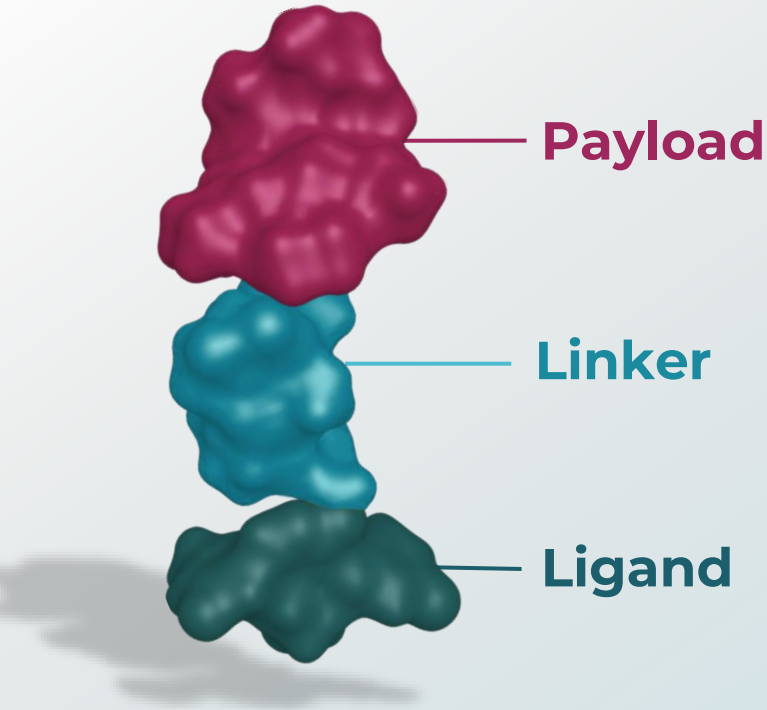
Broad Indication Potential



Pauwels (2018) Am J Nuc Med 8, 311-331

PET: positron emission tomography, NET: neuroendocrine tumor, PRRT: peptide receptor radionuclide therapy

NDCs Are Designed to Selectively Target and Deliver Cytotoxic Payloads to Cells of Interest



Payload

- Non-cytotoxic when linked
- Highly potent when free
- ***Interchangeable payload for future development***

Linker

- Stable in plasma
- Cleaved intracellularly

Ligand

- High affinity and selectivity
- Optimized internalization
- Low molecular weight
- Traditional chemical synthesis
- ***Designed for substitution with other GPCR-targeting small molecules***

Applicability across multiple endocrinology and endocrine-adjacent therapeutic areas including oncology and immunology

Differentiation vs. Current Modalities

Anticancer Agents
(Chemotherapies)

- X Not tumor specific
- X Unfavorable PK/ADME
- X Narrow therapeutic index

Antibody-Drug Conjugates

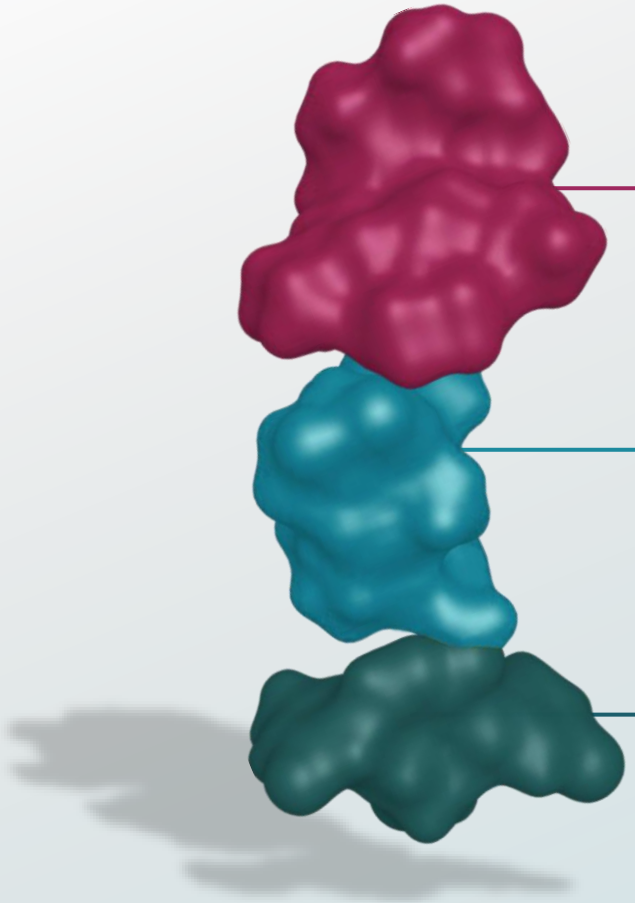
- X Long half-life
- X Poor tumor penetration
- X Unspecific uptake

Radioligand Therapies

- X Limited number of cycles
- X Radionuclide supply
- X Treatment logistics
- X Radiation safety

MMAE: monomethyl auristatin E; tubulin inactivator; PROTAC: proteolysis-targeting chimeras; PK: pharmacokinetics; ADME: absorption, distribution, metabolism, excretion.

CRN09682 is the First of Many Potential NDCs from this Platform



MMAE

Linker

SST2 Agonist

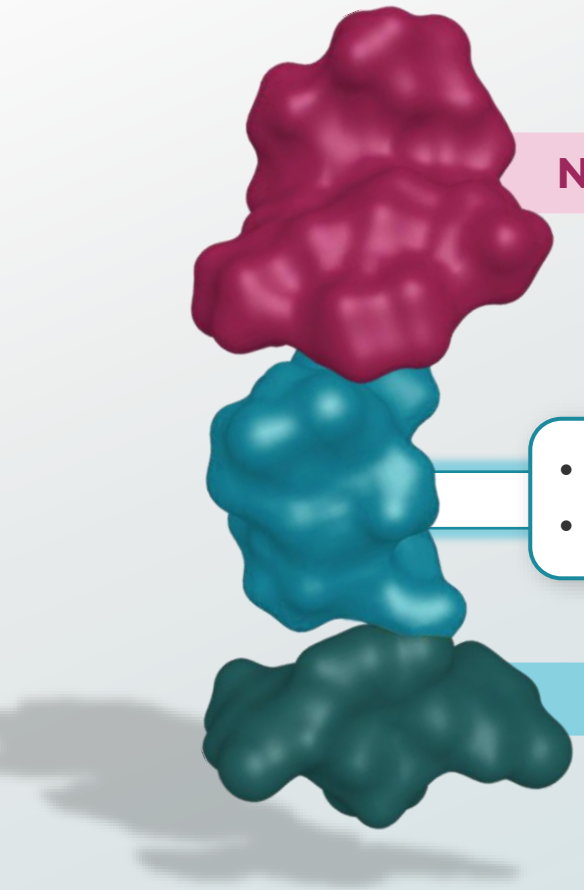
Each Component is Optimized

- Known to kill cells of interest
- Not toxic when conjugated
- Long in-tumor stability

- Stable in plasma
- Rapidly and specifically cleaved when internalized
- Does not interfere with pharmacology

- Potent SST2 agonist
- Selective for SST2
- Optimized for internalization
- Stable in plasma

Next Steps for the Crinetics NDC Platform: Leverage Tailoring of Components for Specific Patient Needs



New Payloads

- Novel payloads
- Multiple payloads per molecule
- Complementary with current therapies

- Tailored half life
- Optimal tissue distribution

New Targets

Other GPCRs in endocrinology and oncology

Next Gen NDC Opportunities

Wide array of specifically tailored molecules for areas of high unmet needs

NENS
NEUROENDOCRINE NEOPLASMS

DAVID C. METZ, MBBCH

Professor of Medicine (retired)

Neuroendocrinologist

Neuroendocrine Neoplasms (NENs): Rare Tumors Arising from Neuroendocrine Cells Throughout the Body

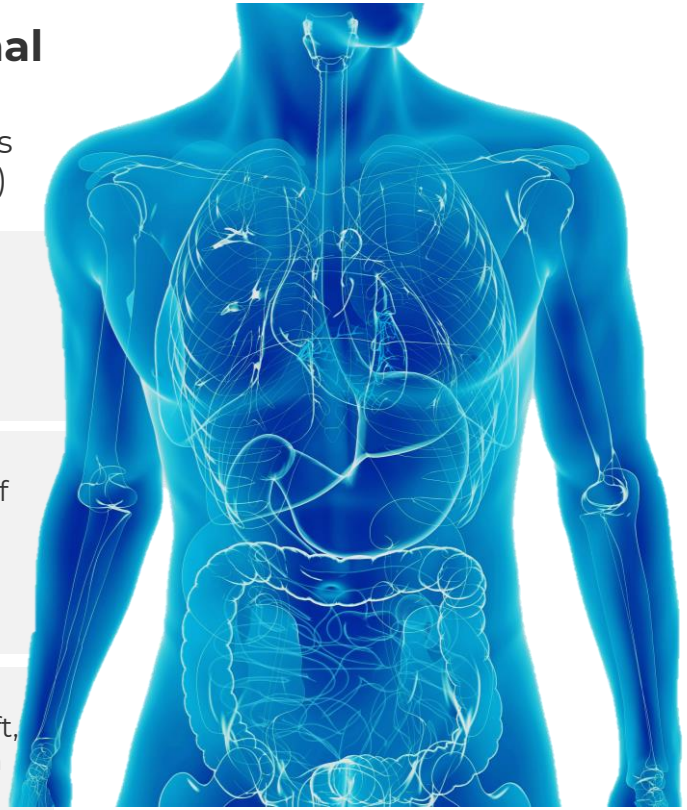
- NENs originate in wide range of organs
- **SST2 expressed on ~80%** of tumors[1]
- Spectrum of disease from **well-differentiated**, indolent neuroendocrine tumors **(NETs)** to **poorly-differentiated**, highly aggressive neuroendocrine carcinomas **(NECs)**, including small-cell lung cancer (SCLC)
- Often present at advanced, incurable stage with **>50% metastatic** typically to liver[2]
- Clinically, **nonfunctional or functional** based on symptoms of hormone hypersecretion (e.g. **carcinoid syndrome**)

Gastrointestinal (GI) NETs
(also referred to as carcinoid tumors)

Foregut
- Lungs
- Stomach
- First part of duodenum

Midgut
- Second part of duodenum
- Jejunum
- Ileum
- Right Colon

Hindgut
- Transverse, left, sigmoid colon
- Rectum



Pancreatic NETs
(functional/non-functional)

Most common primary sites:

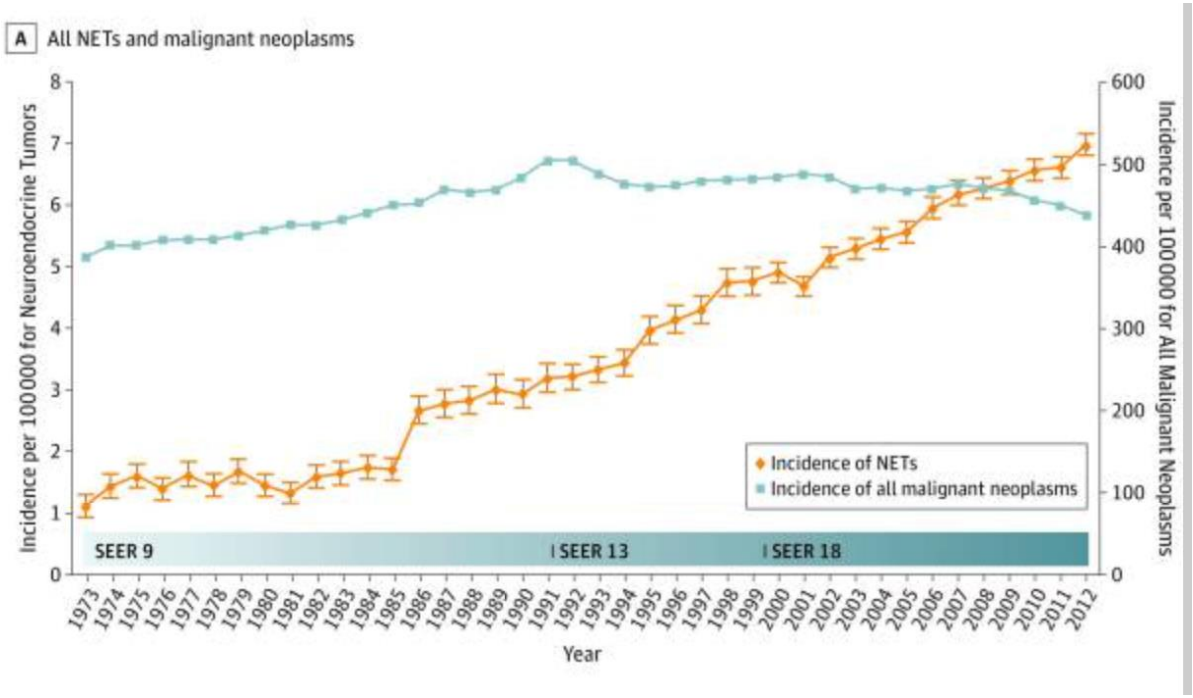
Extra-pulmonary
- Pancreas
- GI tract
- Lungs

Extra-pancreatic

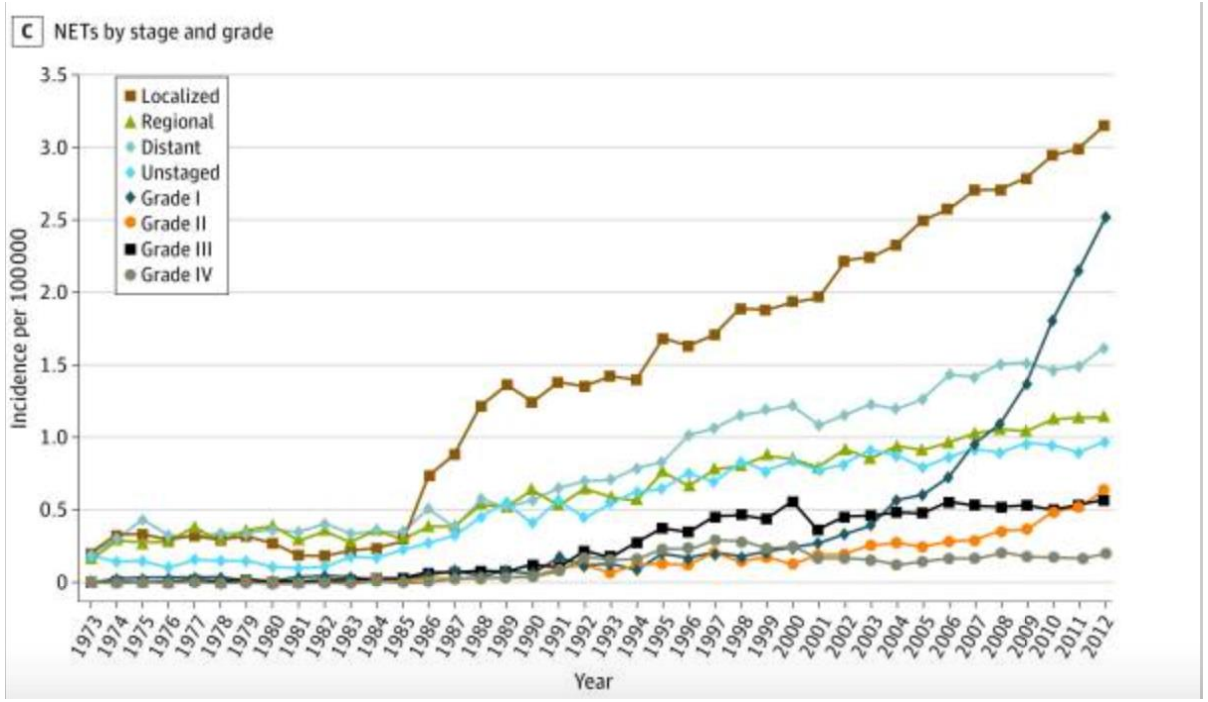
1. Baldelli R. et al. Somatostatin analogs therapy in gastroenteropancreatic neuroendocrine tumors: current aspects and new perspectives. doi: 10.3389/fendo.2014.00007; 2. Singh S et al. Patient reported burden of NET diagnosis: results from the first global survey of patients with NETs. J Glob Oncol. 2016; 2:43-53.

Incidence of Neuroendocrine Tumors is Increasing Over Time

NETs Incidence has Increased Faster than Other Malignancies

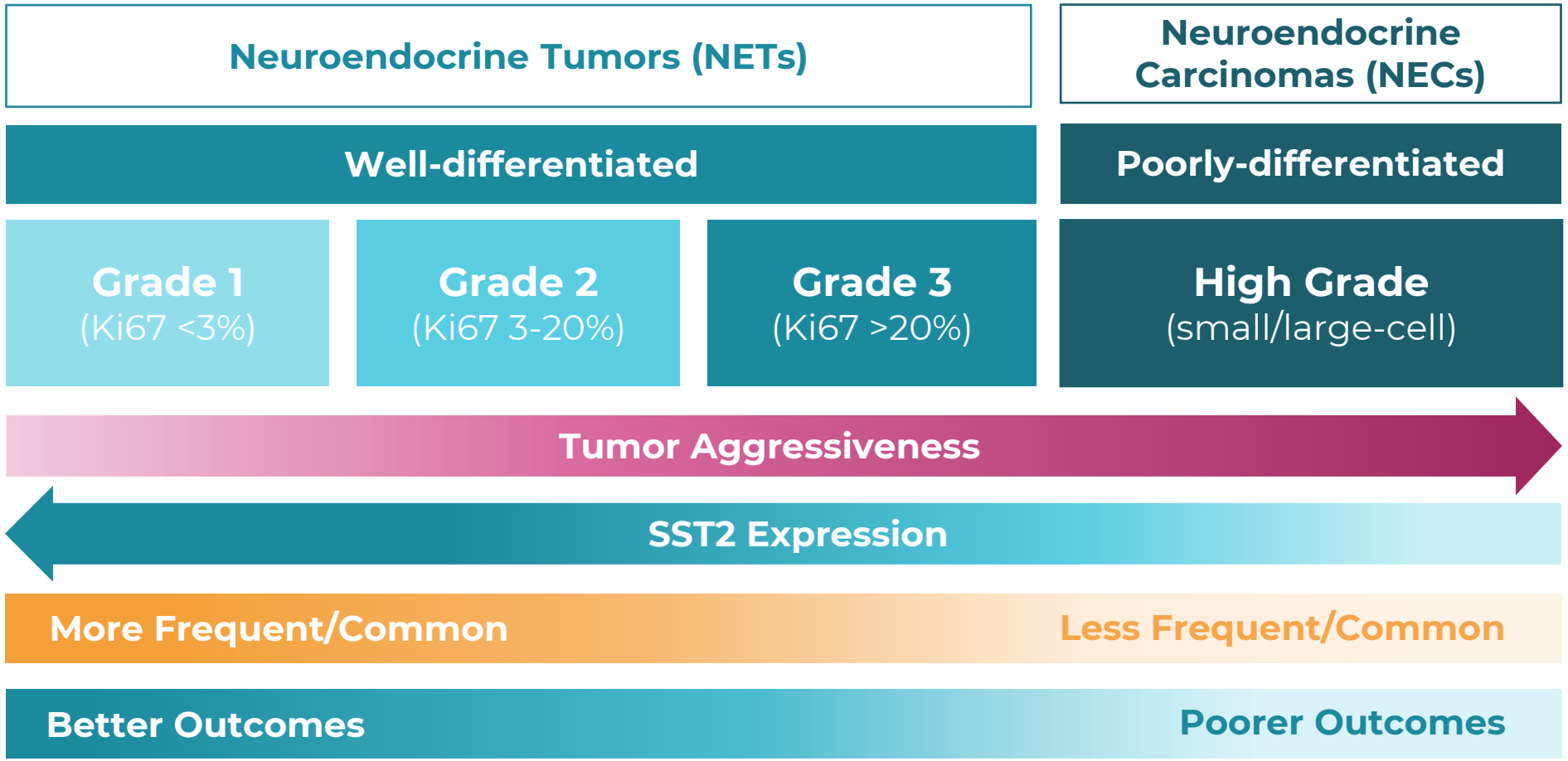


The Increase Affects All Grades and Stages



Dasari A, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017;3:1335-1342.

NENs are Rare, Heterogenous and Treated Based on the Tumor Grade & Differentiation



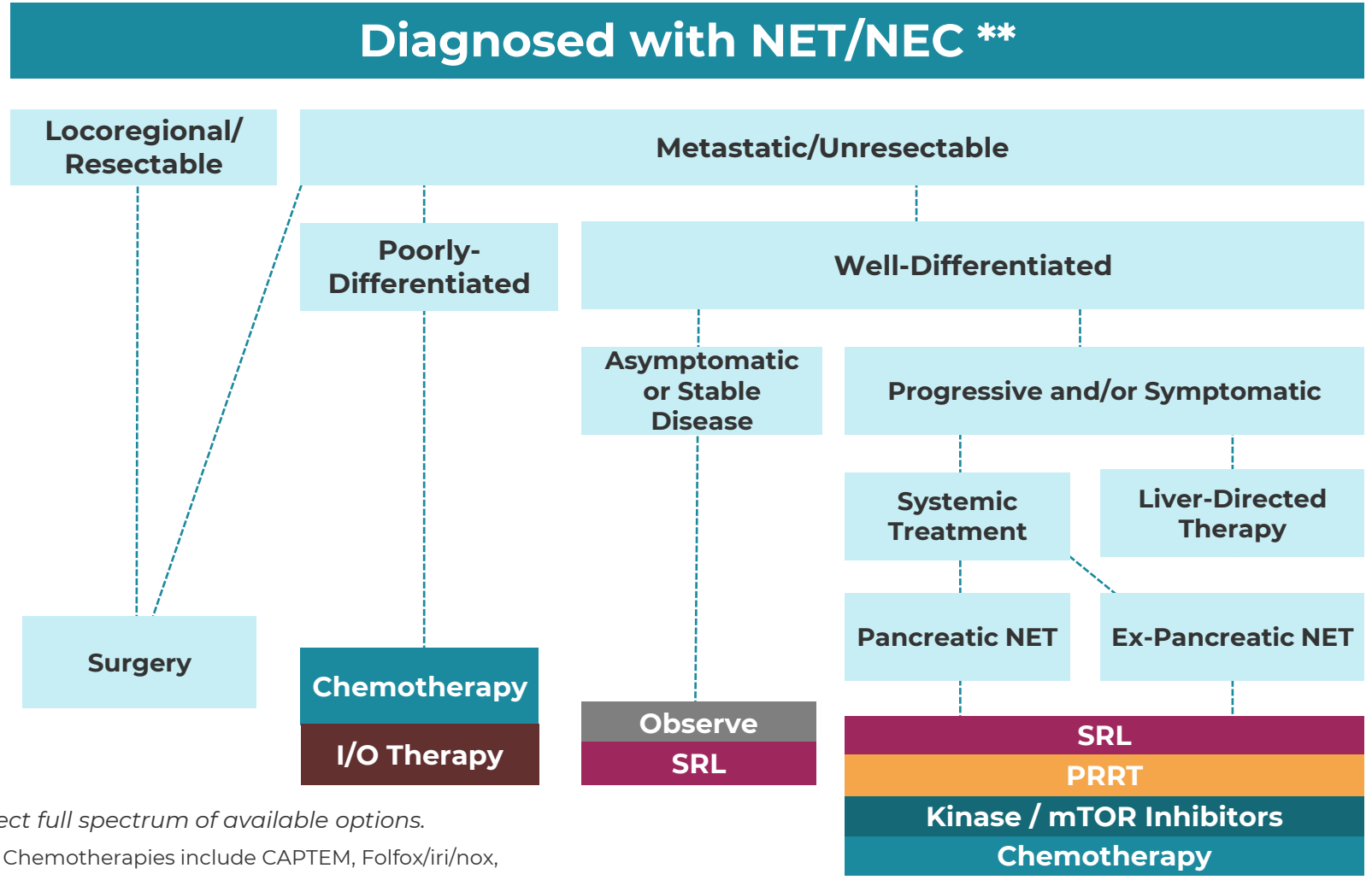
Klimstra DS, et al. Digestive System Tumours. In: WHO Classification of Tumours. 5th edition. Vol 1. IARC, Lyon, 2019.

NEN Treatment Algorithm is Complex

There is no consensus on order of treatments for advanced metastatic disease

Major Outcome Predictors*:

- Stage (extent of disease)
- Grade and differentiation
- Primary tumor site
- Patient age (<50 yo vs. ≥50 yo)



Treatments represent most commonly used but do not reflect full spectrum of available options.

Kinase / mTOR inhibitors include Cabozantinib, Everolimus, Sunitinib. Chemotherapies include CAPTEM, Folfox/iri/nox, platinum/etoposide, Lurbinectedin, I/O: Immunotherapies

* *Borbath I. The ENET registry: A tool to assess the prognosis of NENs. EJ Cancer 2022;168:80*

** Figure adapted from: Kunz P, J Clin Oncol 33:1855-1863, 2015 & Mohamed A, ERC (2024)31 e240025; Weaver JMJ, Cancers (2023)15, 4951; McGarrah PW, Pancreas (2020)49, 529; Chan J, NEJM. 2025;392:653-665; Lee L. Expert Opin Pharmacother. 2018 May 24;19(8):909–928; Strosberg J N Engl J Med 2017;376:125-135. , Horn L. N Engl J Med 2018;379:2220-9. Mountzios G. DOI: 10.1056/NEJMoa2502099, June 2, 2025. SRL = Somatostatin Receptor Ligand

Neuroendocrine Neoplasms (NENs) are Incurable When Metastatic, Regardless of Grade

Expected Treatment Outcomes

Somatostatin Receptor Ligand (SRL)	Peptide Receptor Radionuclide Therapy (PRRT)	Kinase / mTOR Inhibitors	Cytotoxic Chemotherapy
Tumor Stability	Some Tumor Regression	Some Tumor Regression	Good Tumor Regression
Well-Tolerated	Moderately Well-Tolerated	Moderate Side Effects	Moderate/ Severe Side Effects
Variable DOR	Longest DOR	Variable DOR	Variable DOR




A significant opportunity exists for a new therapy that....

- ✓ Kills tumor cells rapidly and effectively
- ✓ Improves efficacy for higher grade disease
- ✓ Addresses PRRT intolerance and cycle limitations
- ✓ Provides better benefit/risk profile after SRL use
- ✓ Improves quality of life and survival

Treatments represent most commonly used, but do not reflect full spectrum of available options
DOR: duration of response

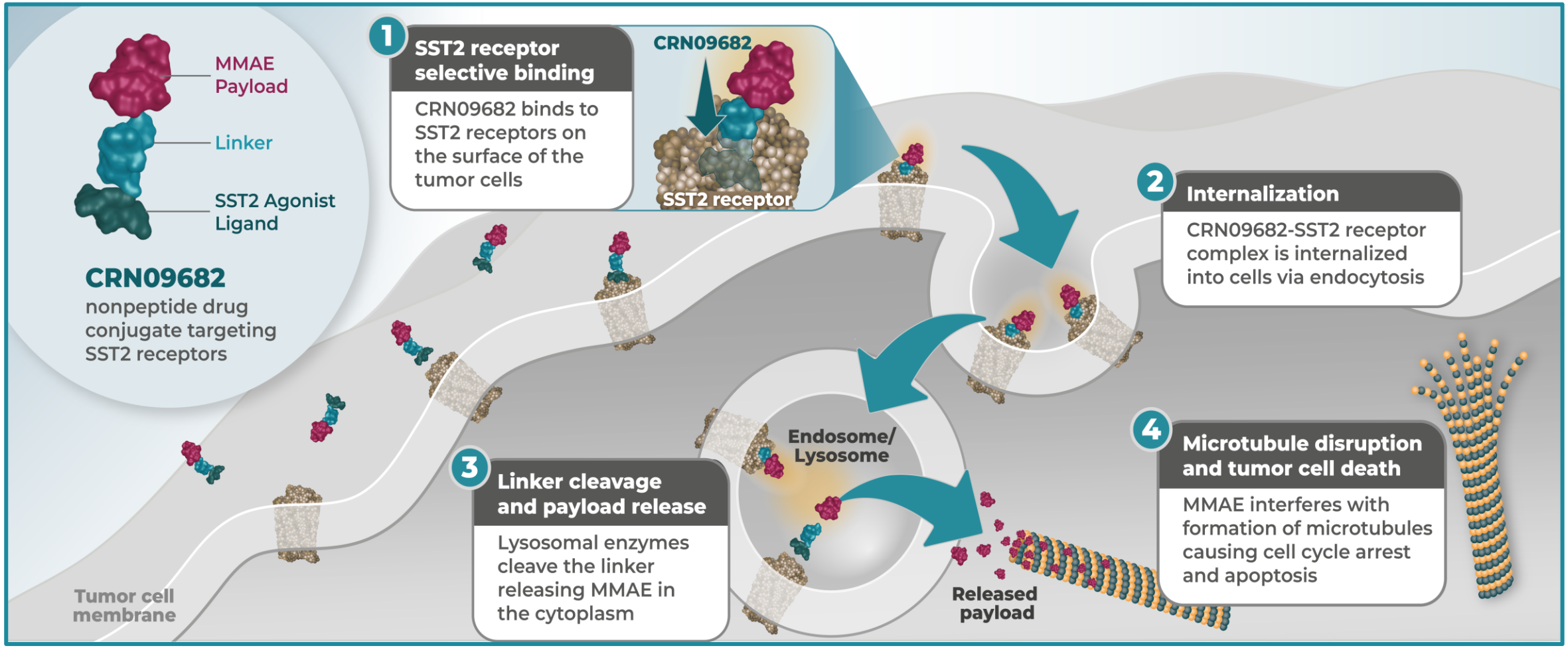
CRN09682

SST2+ CANCERS:
Neuroendocrine Tumors and Beyond

Stacey Harte

Global Product Leader, CRN09682

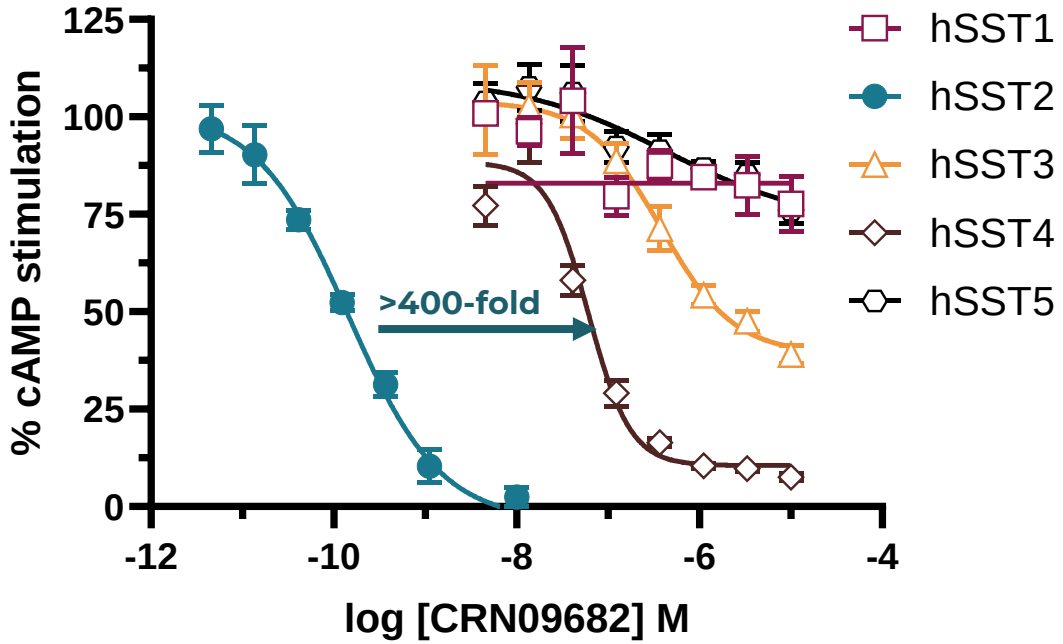
CRN09682 is a First-in-Class Therapy Designed to Selectively Target and Deliver MMAE to SST2-Expressing Tumor Cells



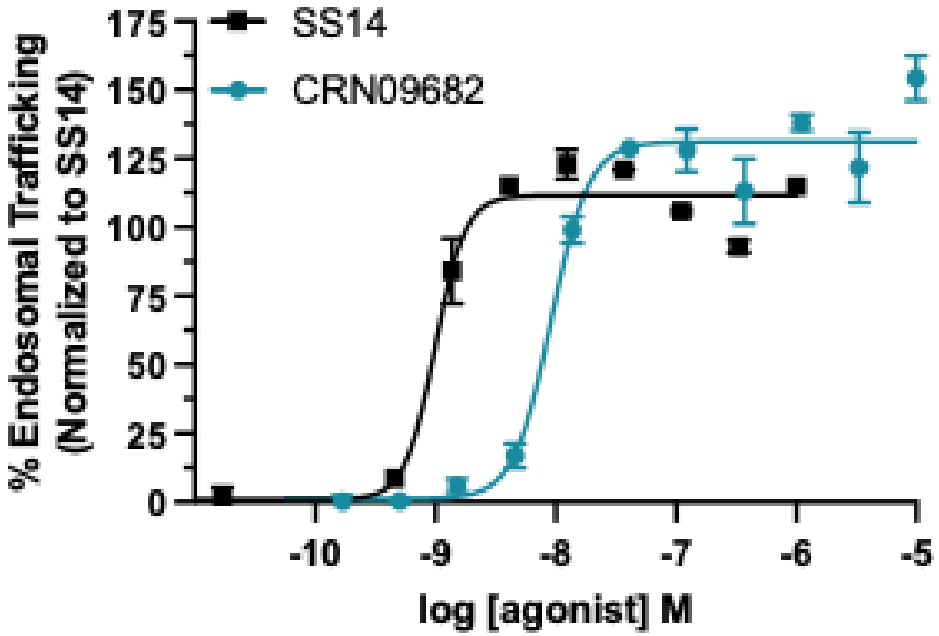
MMAE: monomethyl auristatin E, tubulin inactivator; NDC: non-peptide drug conjugate; SST2: somatostatin receptor 2

CRN09682 was Purposefully Designed to be Selective for and Internalized by SST2

Potency and Selectivity
cAMP production assay



SST2 Internalization
Endosomal trafficking assay

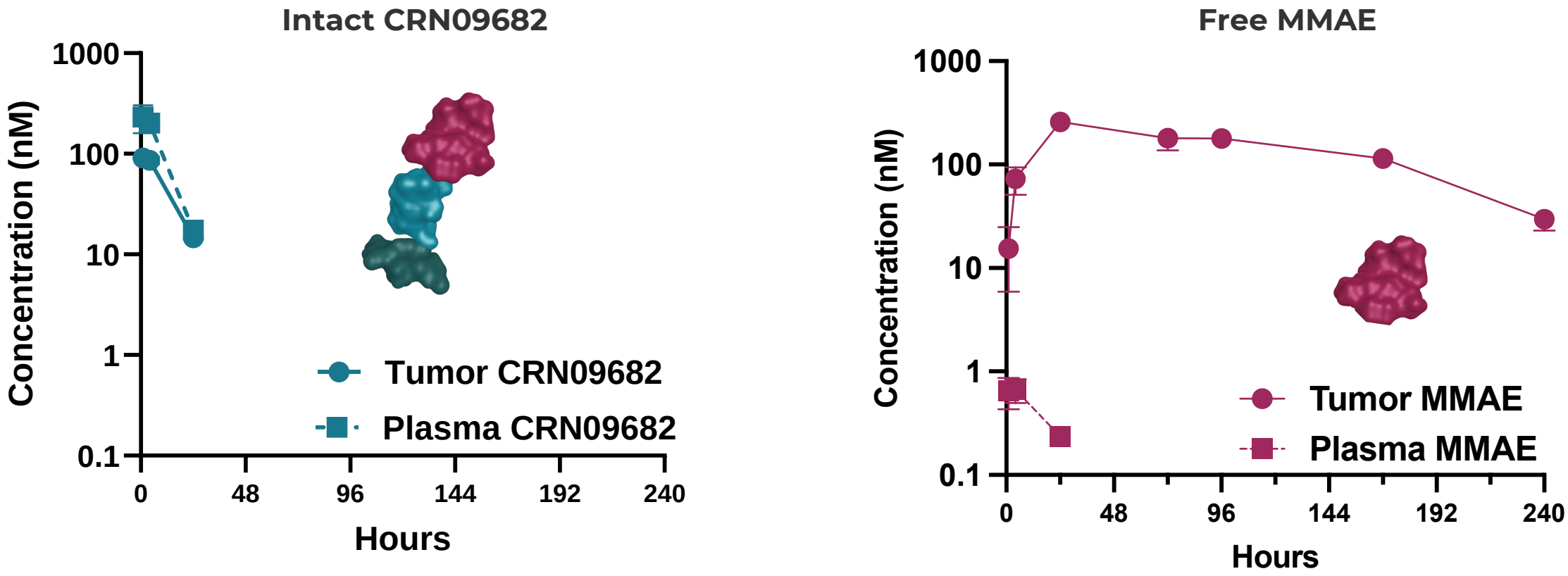


SS14 is native somatostatin, peptide hormone agonist of SST2

Assays performed in SST-expressing CHO cells

CRN09682 Selectively Delivered MMAE into SST2+ Tumors with Minimal Systemic Exposure to Free MMAE

Tumor PK in Nude Mice Bearing SCLC SST2-Expressing NCI-H524 Tumors

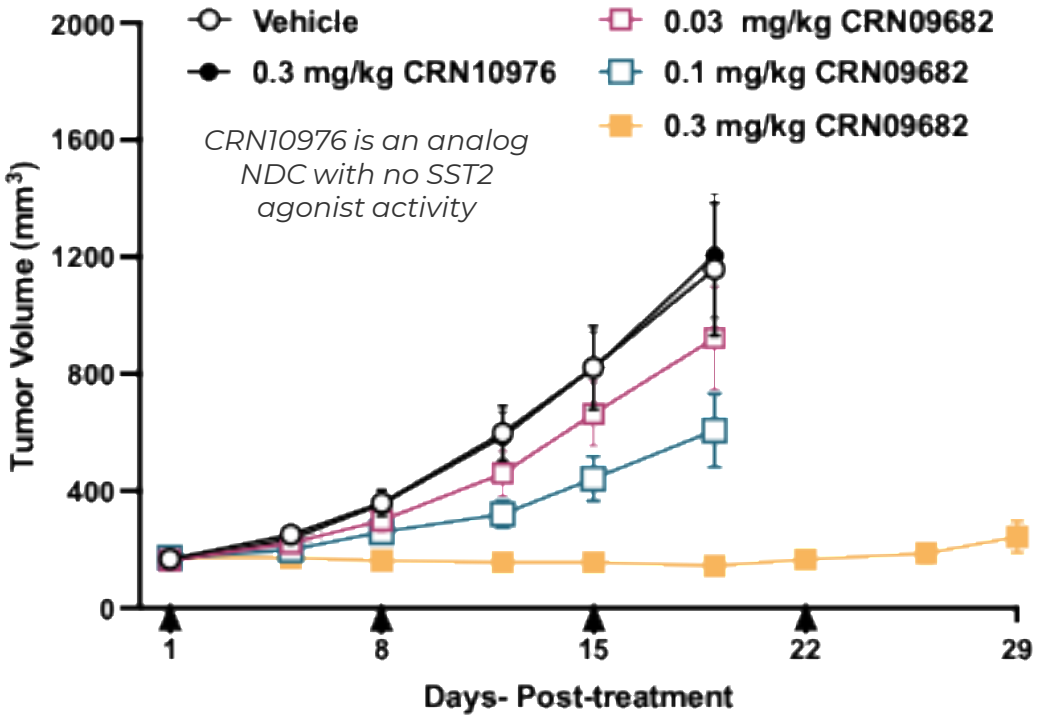


Single IV dose of CRN09682 0.3 mg/kg administered to CDX mice

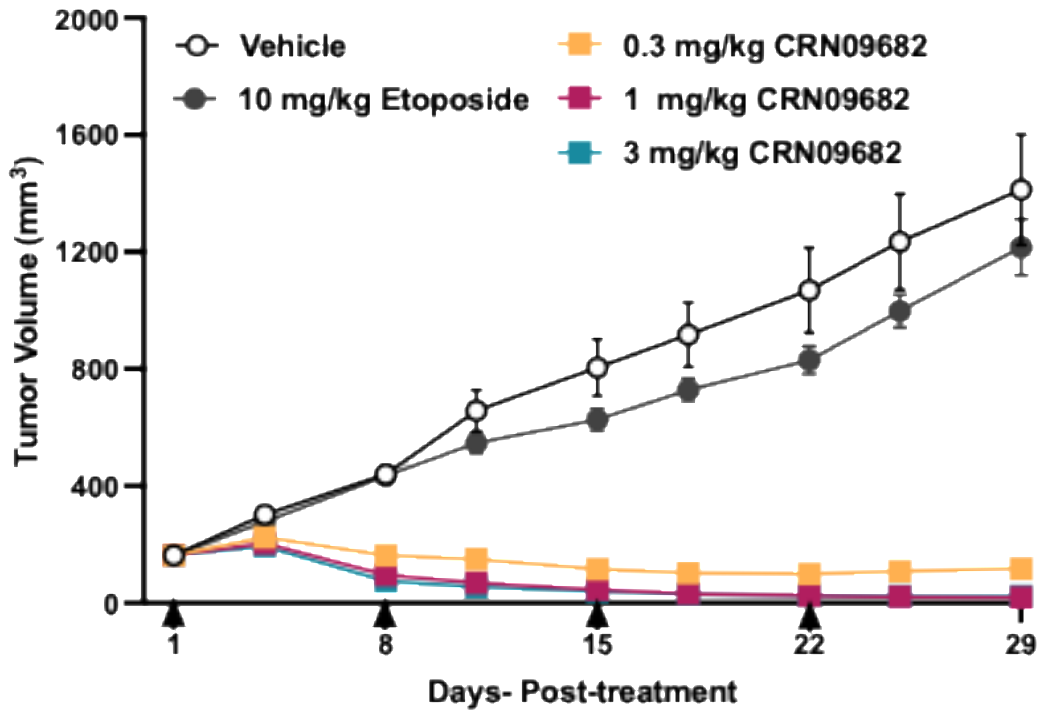
CDX: cell derived xenograft; SCLC: small cell lung cancer, MMAE: monomethyl auristatin E.

CRN09682 Inhibited Tumor Growth in Two SCLC SST2 Expressing CDX Mouse Models in a Dose-Dependent Manner

CRN09682 Efficacy Study in NCI-H524 Tumor Model



CRN09682 Efficacy Study in NCI-H69 Tumor Model



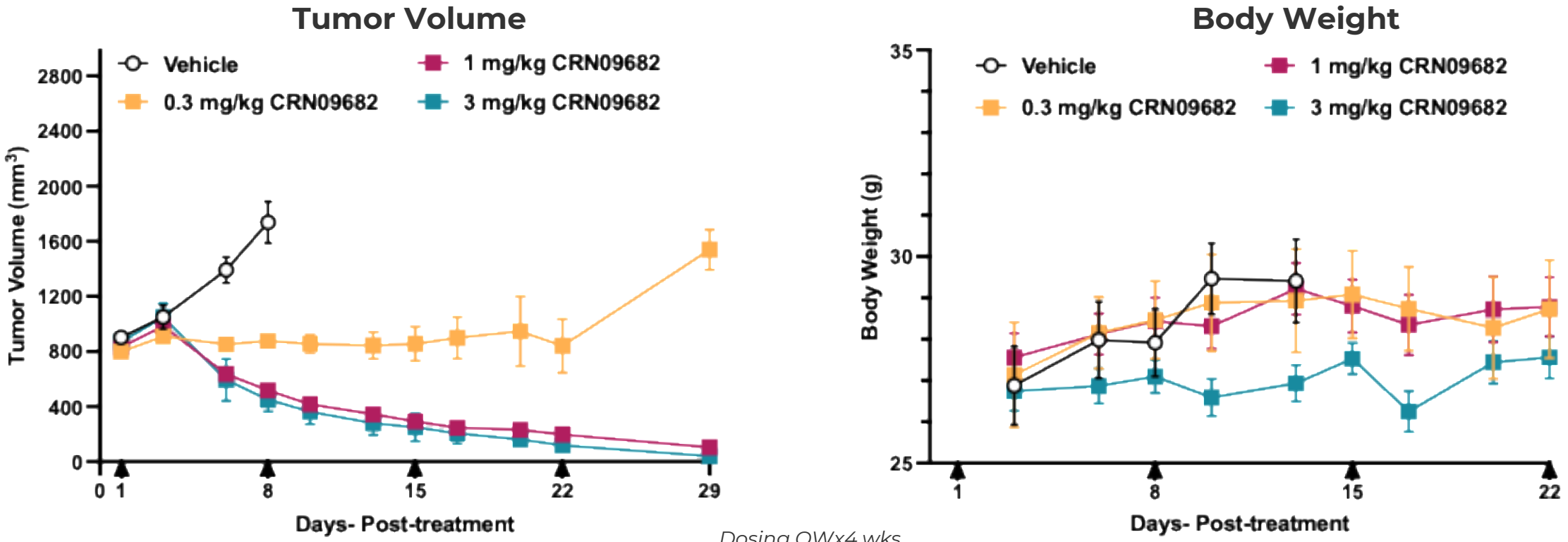
Dosing QWx4 wks in both studies.

- CRN09682 demonstrated anti-tumor activity in both models and induced tumor regression in NCI-H69 model
- CRN09682 had no effect on BW in NCI-H524 and induced minimal BW loss at 3 mg/kg in NCI-H69 model

BW: body weight; CDX: cell derived xenograft QW: every week; SCLC: small cell lung cancer; SST2: somatostatin receptor 2

CRN09682 Induced Rapid Tumor Regression in SCLC CDX Mice Bearing Large Tumors

CRN09682 Efficacy Study & Body Weights in NCI-H524 Tumor Model



Dosing QWx4 wks.

- CRN09682 demonstrated anti-tumor activity and induced tumor regression at 1 and 3 mg/kg
- Complete regression observed in 3/10 mice at 1 mg/kg and 7/10 mice at 3 mg/kg
- CRN09682 had no effect on BW loss in NCI-H524 model

BW: body weight; CDX: cell derived xenograft;; SCLC: small cell lung cancer; SST2: somatostatin receptor 2

CRN09682 Phase 1/2 Study

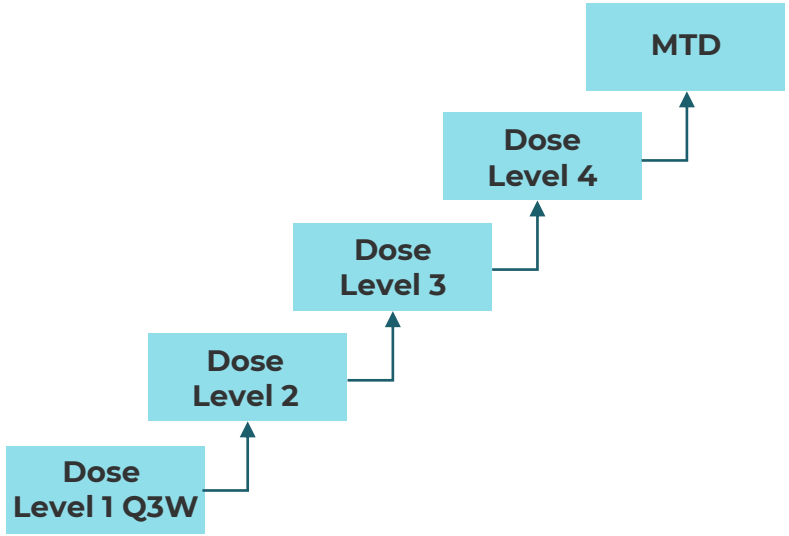
BRAVESST2 STUDY

Key Eligibility Criteria:

- Metastatic or locally advanced inoperable NETs, NECs or other solid tumors
- Tumor progression on or after last line of therapy
- Positive SSTR expression by FDA approved SSTR PET/CT
- No carcinoid syndrome

Ph 1: Dose Escalation

- Bayesian Optimal Interval design, n=3-6/cohort



FDA cleared starting dose

Ph 2: Dose Expansion*

- n=approximately 25/cohort

Recommended Expansion Dose

- **Cohort 1: Pancreatic NET Well-differentiated**
- **Cohort 2: ex-Pancreatic NET Well-differentiated**
- **Cohort 3: NEC Poorly Differentiated (includes SCLC)**
- **Cohort 4: Other Solid Tumors (e.g. Breast, Head-Neck)**

*representative of potential cohorts

Key Endpoints

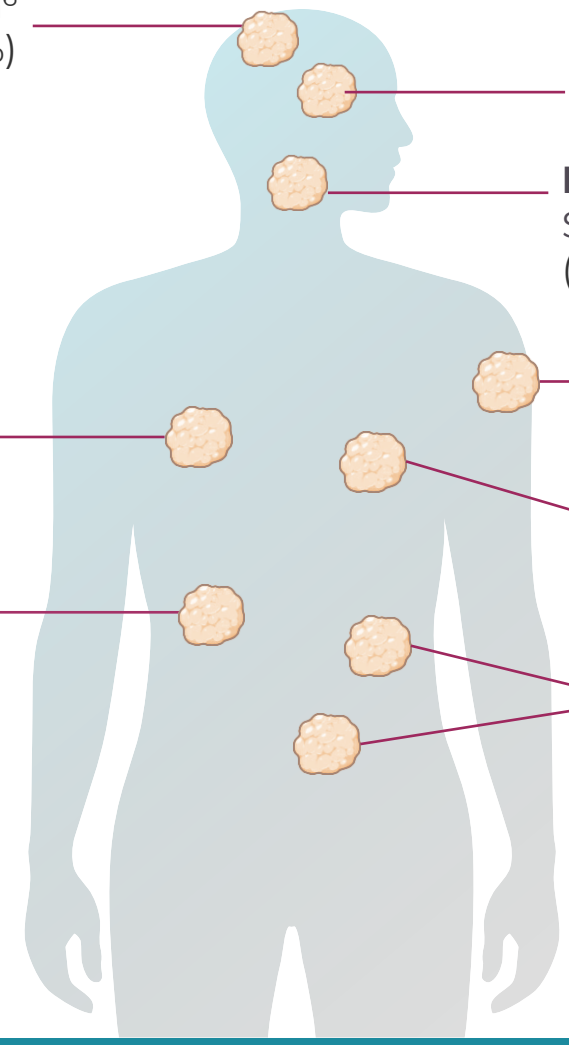
- Safety & tolerability of CRN09682
- Define DLT/MTD and select Expansion Dose
- PK of CRN09682 and MMAE

Efficacy Endpoints

- Measure preliminary anti-tumor activity of CRN09682: ORR, DOR, PFS by RECIST v1.1

DLT: Dose limiting toxicity; DOR: duration of response; MTD: Maximum tolerated dose; MMAE: monomethyl auristatin E; NEC: Neuroendocrine carcinoma; NET: Neuroendocrine tumor; ORR: objective response rate; PFS: progression free survival; PK: pharmacokinetics; Q3W: every 3 weeks; SCLC: small cell lung cancer); SSTR: somatostatin receptor; WD: well-differentiated

Expanding CRN09682 Opportunity into a Broad Set of Indications by Targeting SST2+ Tumors



Meningioma[6] (92%)

Glioblastoma[2] (89-100%)

Head & Neck Squamous Cell Carcinoma (inc. NPC)[3] (97-100%)

Metastatic Melanoma[5] (45-61%)

ER+/HER2- Metastatic Breast[7] (30%)

ES Small Cell Lung Cancer[8] (48-83%)

Hepatocellular Carcinoma[4] (38% (IHC))

GEP-NEC[1] (38%)

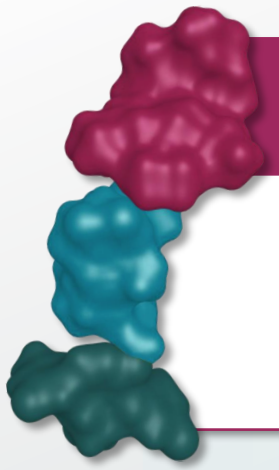
(Approximate Percent of Tumors Expressing SST2)

** SST2 expression measured by SST2 Dotatate unless noted.*

Sources in notes.

ER+: estrogen positive; ES: extensive stage; GEP: Gastroenteropancreatic; IHC: immunohistochemistry; NPC: nasopharyngeal carcinoma NEC: neuroendocrine carcinoma; SST2: somatostatin receptor 2

Paltusotine and CRN09682 Have the Potential to be Distinct, Complementary Treatment Options for NETs Patients



CRN09682
Progressive Disease

Triggers rapid cell death leading to tumor regression

Anti-Tumor Response

Paltusotine
Carcinoid Syndrome/Functional Tumors

Provides rapid and consistent symptom control

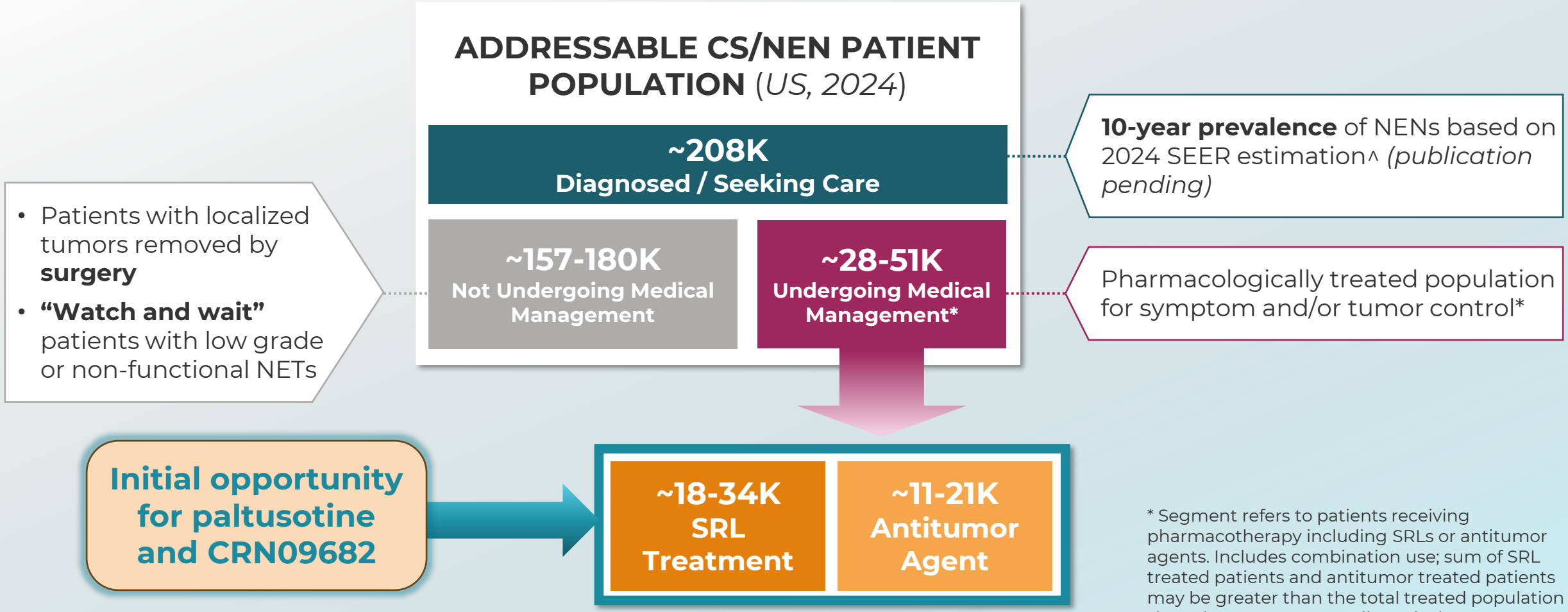
Disease Control

Together, they may offer additional benefit through co-administration, potentially broadening therapeutic impact.

Crinetics' Strategy Unlocks the Full Potential to Treat the Broadest Set of NETs Patients

Paltusotine is an investigational compound.

Availability of Additional Treatment Options May Expand the Limited Pharmacotherapy Use in NENs



* Segment refers to patients receiving pharmacotherapy including SRLs or antitumor agents. Includes combination use; sum of SRL treated patients and antitumor treated patients may be greater than the total treated population since they are not mutually exclusive.

^Source: SEER 17 & SEER 8 (Surveillance, Epidemiology, and End Results) Health Advances analysis, data on file.

NEN/Ts: neuroendocrine neoplasms/tumors; SRL: somatostatin receptor ligand

Next Steps for the CRN09682 Program and NDC Platform

Enrolling Patients in Phase 1/2 Study

BRAVESST2 STUDY

Data from Dose Escalation Portion of Phase 1/2 Study

Exploring Additional Tumor Types with CRN09682 Beyond NETs

Expansion of Crinetics NDC Discovery Pipeline

CLOSING REMARKS

Scott Struthers, Ph.D.

Founder & Chief Executive Officer

Continued Value Creation with Deep Pipeline of Transformative Drug Candidates

Program	Discovery	IND-Enabling	Phase 1	Phase 2	Phase 3	Registrational	Upcoming Milestones
Paltusotine (SST2 agonist)	**Acromegaly (US)**						PDUFA Date (September 2025)
	Acromegaly (EU)						CHMP Opinion (1H 2026)
	Carcinoid syndrome						Phase 3 (2H 2025)
Atumelnant (ACTH antagonist)	**Congenital adrenal hyperplasia (adult)**						Phase 3 in Adult (2H 2025)
	Congenital adrenal hyperplasia (pediatric)						Phase 2/3 in Pediatric (2H 2025)
	ACTH-dependent Cushing's syndrome						Phase 2/3 (2H 2025)
CRN09682 Nonpeptide drug conjugate	**NETs and SST2-expressing solid tumors**						Phase 1/2
TSH antagonist	**Graves' disease & TED**						IND
SST3 agonist	**ADPKD**						IND
PTH antagonist	**Hyperparathyroidism**						IND
Oral GLP-1 nonpeptide	**Obesity**						Candidate Selection
Oral GIP nonpeptide	**Obesity**						Candidate Selection

Partners:

SANWA KAGAKU KENKYUSHO CO., LTD.
Japan Development and Commercialization Partner for Paltusotine

Radionetics Oncology
Licensee of targeted, nonpeptide radiopharmaceuticals

loyal
Licensee of CRN01941 for veterinary use

SST: somatostatin receptor type; ACTH: adrenocorticotropic hormone; NETs: Neuroendocrine tumors; TSH: thyroid-stimulating hormone; TED: thyroid eye disease; ADPKD: Autosomal dominant polycystic kidney disease; PTH: parathyroid hormone; GLP-1: glucagon-like peptide-1 receptor agonists; GIP: gastric inhibitory polypeptide; IND: Investigational New Drug Application; PDUFA: Prescription Drug User Fee Act; CHMP: Committee for Medicinal Products for Human Use

Crinetics of Tomorrow: A Premier, Endocrine-Focused Global Biopharmaceutical Company

World Class R&D
Strong Balance Sheet

Sales Funded Growth
Pipeline Expansion

Crinetics® Pharmaceuticals

Thank You