bridgebio

hope through
rigorous science

R&D Day

September 29, 2020

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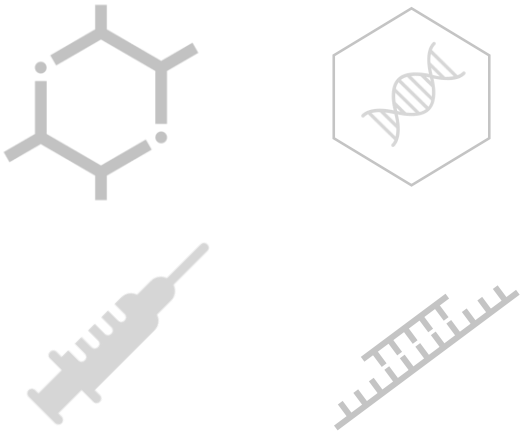
BridgeBio Pharma: Hope through rigorous science

Our mission: To **discover**, **create**, **test** and **deliver** transformative medicines to treat patients who suffer from genetic diseases and cancers with clear genetic drivers

BridgeBio corporate overview

Strategy

Platform

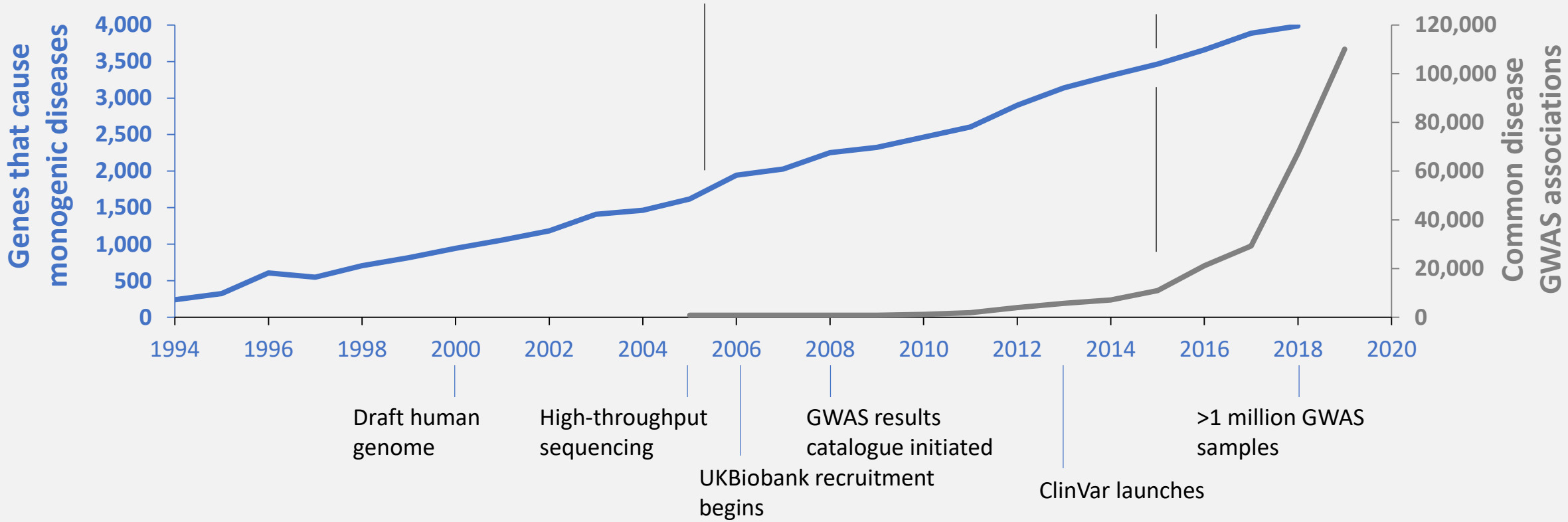


Products

We are at Day 1 in the era of genetic medicine

Hundreds of monogenic disease-causing variants are discovered every year…

…and common disease associations are increasing exponentially



Source: Claussnitzer *et al., Nature* 2020

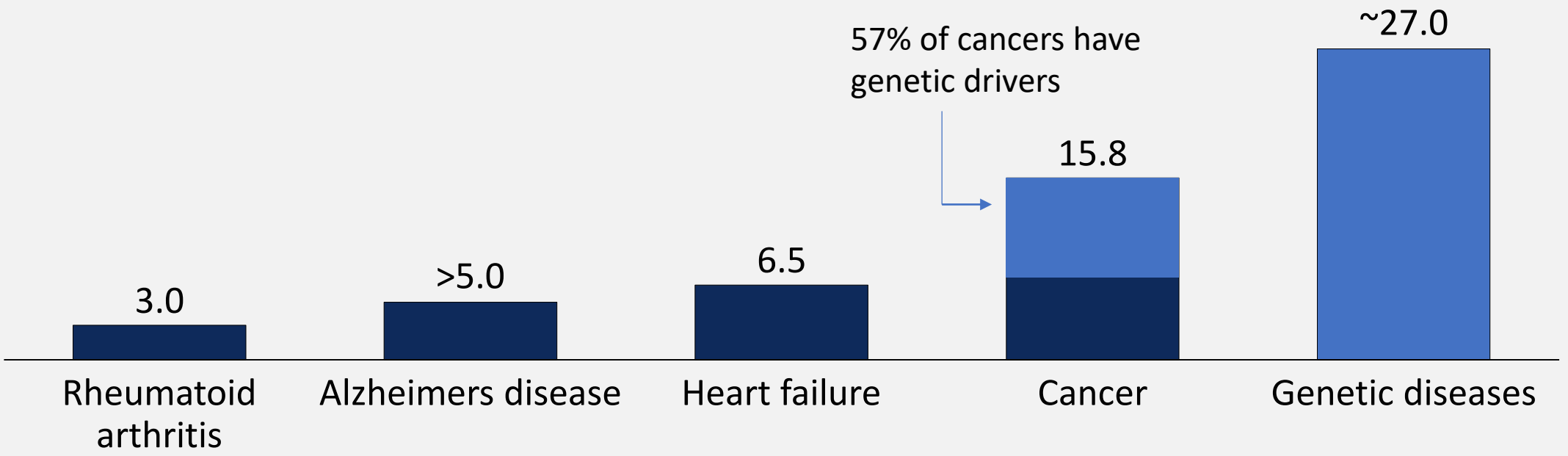
A vast opportunity to help patients

~27 million Americans are living with a genetic diseases

50% Of people affected are children

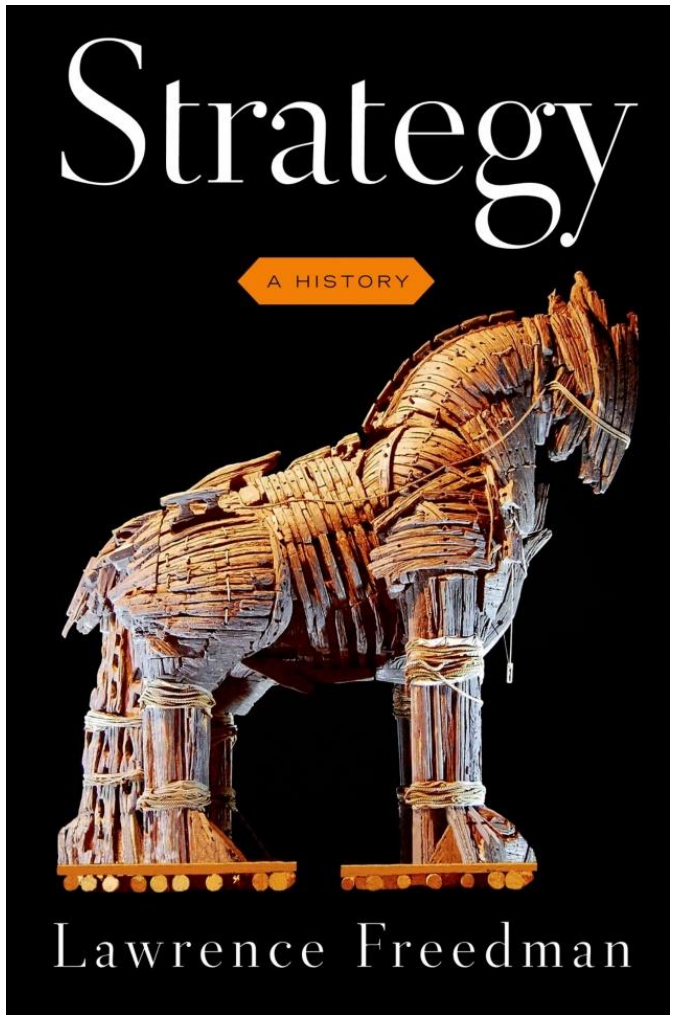
Only 5% Of these diseases have an approved therapy

US prevalence, mn



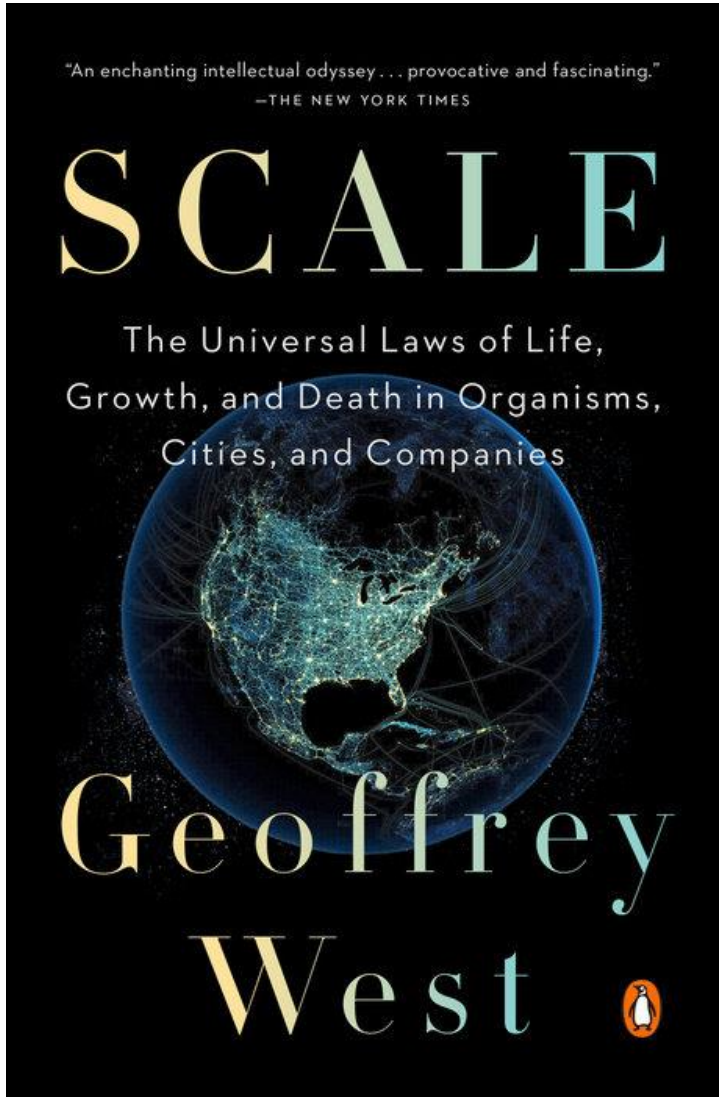
Source: Global Genes, American Cancer Society, American Heart Association, Alzheimer's Association, Arthritis Foundation, Bailey *et al., Cell* 2018

Our strategy is simple



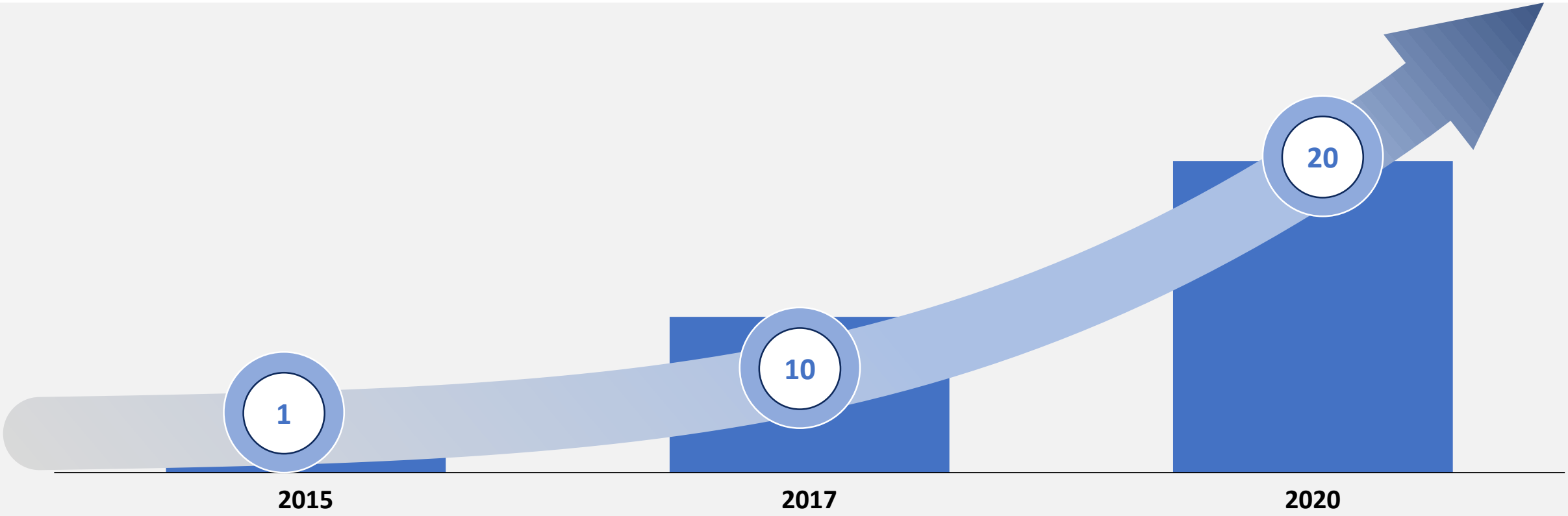
History teaches us about strategy:		BBIO applications:
1. Right playing field	→	1. Genetic disease
2. Right tenets	→	2. Beautiful science, NPV positive
3. Stay adaptive	→	3. No initial focus on TA, disease, or modality. Repeated application

Our organizational principles enable scale



History teaches us about growth:		BBIO applications:
1. Simple rules repeated at many levels	→	1. Simple rules – put patients first, think independently and let science speak, be efficient
2. De-centralized cities grow with *returns to scale*, centralized companies slow with economies of scale	→	2. De-centralized approach – small teams that focus and are incented at the level of each asset, scale that allows for rapid failure, learning

Result: Pipeline momentum



- BridgeBio founded
- 1 pipeline program

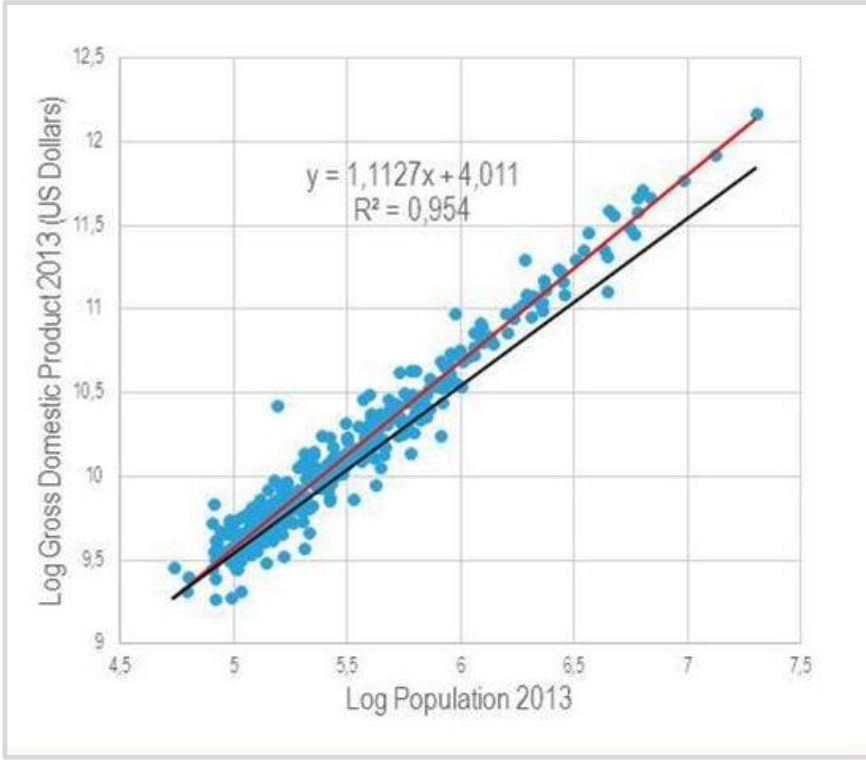
- 10 pipeline programs
- 3 clinical compounds

- 20+ programs
- Multiple $1B+ opportunities in Ph3
- Two NDA submissions
- >10 INDs in 5 years

Increasing returns to scale – BridgeBio since IPO

Achievement:

- NDA for MoCD Type A accepted, ODD & Fast Track received for 2L CCA program
- 7 INDs filed
- Six new clinical trials initiated (16 total), >350 trial sites across 25 countries
- 8 new programs, including LGMD2i and ADH1, both in the clinic
- TTR clinical data, DEB clinical data, CAH and Canavan pre-clinical data, achon pre-clinical data, TIO data



BridgeBio corporate overview

Strategy

Platform

Products

BridgeBio drug engineering basics: our platform

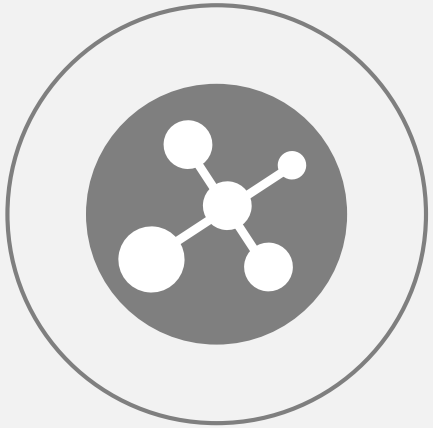
Discover

Novel genetic disease targets

Well described diseases than can be targeted at their source

Create

Medicines with industry-leading research capabilities



Tailored therapeutic technologies to create first or best-in-class medicines

Test

Our drugs through global development footprint

Broad clinical development capabilities across therapeutic areas and geographies

Deliver

Our products to patients through commercial infrastructure

Building the capabilities to deliver genetic medicines to patients globally

Discover

Capabilities to identify new genetic disease targets at scale

Our target identification engine is driven by three core areas of strength:

Computational genomics / statistical genetics

- Mining of large genotype-phenotype databases
- *De novo* target discovery
- Target validation
- Indication expansion

Systematic disease mapping

- Manual annotation and prioritization of the 7K known genetic diseases

Partnering with top academic researchers

- 15 current partnerships

Johns Hopkins University

The University of Texas MD Anderson Cancer Center — Making Cancer History®

Boston Children's Hospital — Until every child is well™

Cincinnati Children's™

Stanford University

Discover

Scientific insight and judgment from industry leaders with a proven track record

Charles Homcy, MD
Founder and Chairman of Pharmaceuticals

MyoKardia

GBT

Frank McCormick, PhD
Founder and Chairman of Oncology

ONYX PHARMACEUTICALS

UCSF

Richard Scheller, PhD
Chairman of R&D

Genentech

23andMe

Len Post, PhD
Advisor

BIOMARIN

LEAD THERAPEUTICS

Phil Reilly, MD, JD
Advisor

THIRD ROCK VENTURES

bluebirdbio

Create

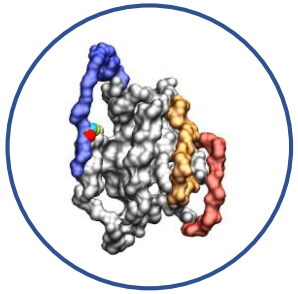
We select the optimal therapeutic modality to target each disease at its source

Industry-leading capabilities across 4 modalities:

Medicinal chemistry

- Molecular dynamics
- Reversible and irreversible chemistry
- Topical formulations

Optimal use: Inhibition of GOF or allosteric activation of LOF mutations



Gene therapy

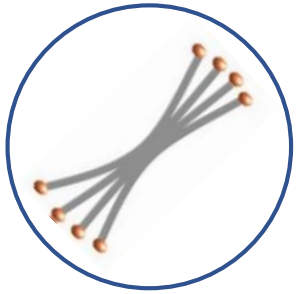
- Vector optimization
- Novel capsid engineering
- Analytical assay development

Optimal use: Replacement of intracellular protein in LOF diseases

Therapeutic proteins

- Large protein manufacturing
- Formulation expertise
- Comparability assay development

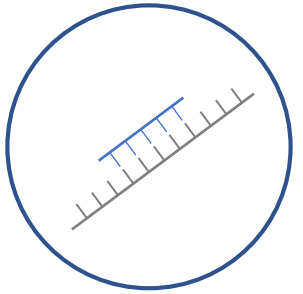
Optimal use: Replacement of extracellular protein in LOF diseases



Antisense oligonucleotides

- Target mapping with functional genomics
- Activity screening assay development
- Novel backbone and base chemistry

Optimal use: Inhibition of GOF or activation of WT allele in LOF diseases



GOF = gain-of-function, LOF = loss-of-function, WT = wild type

Create

Research leaders with a productive history developing novel therapeutics

Mendelian	Oncology	Gene therapy

Uma Sinha, PhD
Chief Scientific Officer

GBT
PORTOLA PHARMACEUTICALS

Robert Zamboni, PhD
Chemistry

MERCK FROSST

Eli Wallace, PhD
Chief Scientific Officer, Oncology

Peloton Therapeutics
ARRAY BIOPHARMA

Pedro Beltran, PhD
SVP, Biology

AMGEN
UNITY BIOTECHNOLOGY

Clayton Beard, PhD
SVP, Research and Development

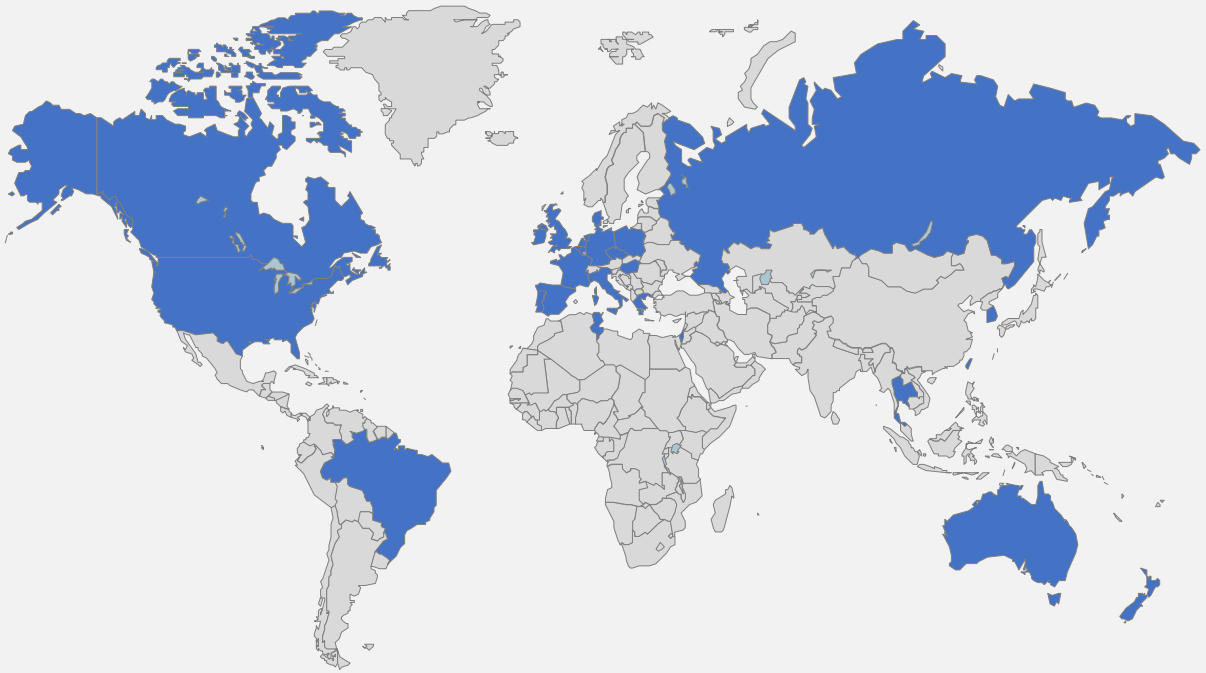
PRECISION BIOSCIENCES
NOVARTIS

Our global clinical development footprint

Test

- **16 ongoing trials** across 5 different therapeutic areas, >350 trial sites, and 25 countries
- **Creative clinical and regulatory strategy,** e.g., unique, nested Phase 3 trial design for acoramadis in ATTR
- **Central operations toolkit** for enrollment, protocol quality, site activation, CRO quality, regional performance
- **Expert, dedicated R&D teams** in each therapeutic area
  - **Cardio/renal:** Jonathan Fox, MD, PhD
  - **Oncology:** Susan Moran, MD
  - **Gene Therapy:** Adam Shaywitz, MD, PhD

Countries with BridgeBio trial sites



Deliver

Building capabilities to deliver our products to patients across the globe

- **Global commercial infrastructure** to leverage our drug and disease expertise
- **Diagnostic partnerships** to identify patients in need of our medicines
- **Disease awareness strategies** including close partnerships with patient advocacy groups
- **Country-specific Early Access Programs** (EAP) and patient assistance programs
- **Commercial partners in strategic geographies:**

FGFRi and SHP2i in China: LianBio

TTR in Japan: Alexion

MoCD type A in Israel: Medison Delivering Innovative Healthcare

Key people: Matt Outten (CCO), Jennifer Cook (BOD), Brent Saunders (BOD)

The platform is delivering

Discover
Novel genetic disease targets

20+
Disclosed programs in the pipeline

Create
Medicines with industry-leading research capabilities

>10
INDs since 2015

Test
Our drugs through global development footprint

16
Clinical trials across the globe

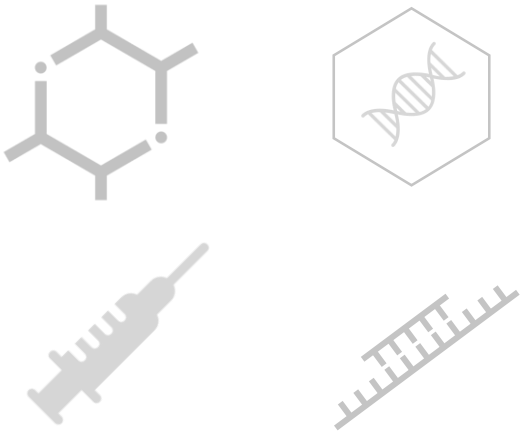
Deliver
Our products to patients through commercial infrastructure

2
Product launches expected in 2021

BridgeBio corporate overview

Strategy

Platform



Products

Our pipeline of 20+ development programs spans multiple therapeutic areas and drug modalities

Small molecule | Topical small molecule | Biologics | Gene therapy

Portfolio segment	Program	Drug mechanism	Diseases	Patient pop. (US+EU)	Modality	Preclinical: Discovery	Preclinical: IND-enabling	Clinical: Phase1	Clinical: Phase 2	Clinical: Phase 3
Mendelian	**Acoramidis**	TTR stabilizer	ATTR-CM	>400K	Small molecule					NDA filed
	Fosdenopterin	cPMP replacement	MoCD type A	100	Small molecule					NDA filed
	Infigratinib	Low-dose FGFR1-3i	Achondroplasia	55K	Small molecule					
	Encaleret	CaSR antagonist	ADH1 / HP	12K[1] / 200K	Small molecule					
	Zuretinol	Synthetic retinoid	IRD (RPE65 or LRAT)	3K	Small molecule					
	BBP-418	Glycosylation substrate	LGMD2i	7K	Small molecule					
	BBP-711	GO1 inhibitor	PH1 / FSF	5K / 1.5M	Small molecule					
	BBP-671	PanK activator	PKAN / OA	7K	Small molecule					
	BBP-761	Succinate prodrug	LHON	20K	Small molecule					
	BBP-472	PI3Kβi	PTEN autism	120K	Small molecule					
Genetic Dermatology	**Patidegib[2]**	Topical SMOi	Gorlin / BCC	120K	Topical small molecule					
	BBP-589	Recombinant COL7	RDEB	1.5K	Biologics					
	BBP-681	Topical PI3Kai	VM / LM	117K	Topical small molecule					
	BBP-561	Topical KLK 5/7i	Netherton	11K	Topical small molecule					
Targeted Oncology	**Infigratinib**	FGFR1-3i	FGFR+ tumors	37K	Small molecule					
	BBP-398	SHP2i	Multiple tumors	>500K	Small molecule					
	BBP-454	Pan-mutant KRASi	KRAS+ tumors	>500K	Small molecule					
	BBP-954	GPX4i	Multiple tumors	>500K	Small molecule					
Gene Therapy	**BBP-631**	21-OH gene therapy	CAH	>75K	Gene therapy					
	BBP-812	ASPA gene therapy	Canavan	1K	Gene therapy					
	BBP-815	TMC1 gene therapy	Genetic hearing loss	10K	Gene therapy					

1 US carriers; 2 We are party to an option agreement pursuant to which LEO Pharma A/S has been granted an exclusive, irrevocable option to acquire PellePharm, including the BBP-009 program. If the option is exercised by LEO Pharma A/S, we will no longer have rights to develop and commercialize BBP-009.

Four core value drivers over the next 12-24 months

Program	Opportunity size	Status	Upcoming event(s)
Acoramidis: TTR stabilizer for ATTR	>400K	ATTR-CM Ph3 ongoing	❑ Topline Ph3 part A data late-2021 / early-2022 ❑ Topline Ph3 part B data 2023
Low-dose infigratinib (FGFRi) for achondroplasia	55K	Enrolling Ph2 study	✓ Dose first child ❑ Phase 2 data 2021
Gene therapy for congenital adrenal hyperplasia (BBP-631)	>75K	GLP tox ongoing	❑ File IND ❑ Phase 1/2 data 2021
Encaleret: CaSR inhibitor for autosomal dominant hypocalcemia type 1 (ADH1)	12K	Ph2 ongoing	✓ FPI in Ph2 study ❑ Phase 2 data 2021

A pipeline with multi-blockbuster potential

$1B+
opportunities
in the pipeline

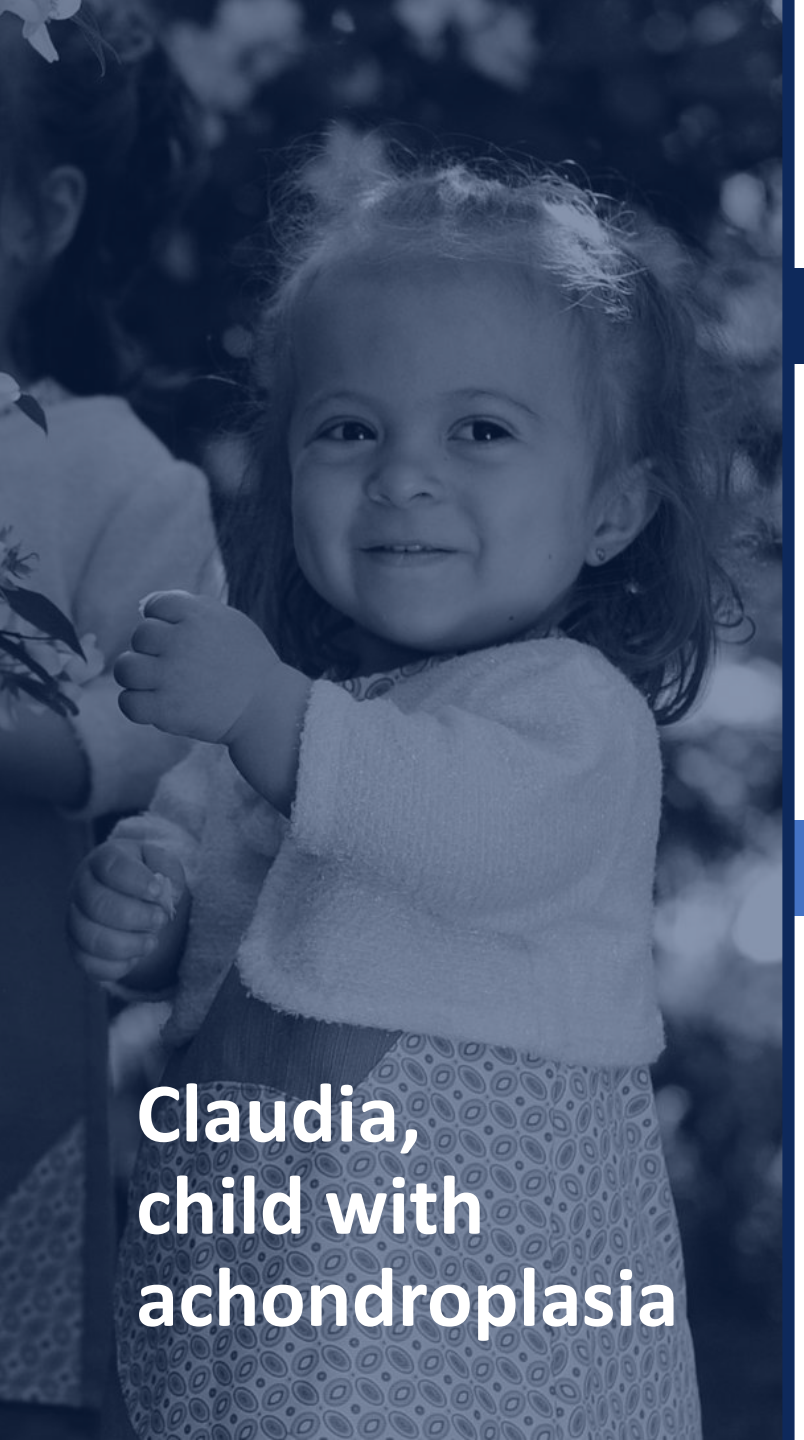
1) **Acoramidis** for ATTR CM and PN
2) **Low-dose infigratinib** for achondroplasia
3) **AAV5 gene therapy** for congenital adrenal hyperplasia
4) **High-dose infigratinib** for adjuvant urothelial carcinoma
5) **Pan-mutant KRAS inhibitor** for KRAS+ cancer
6) **SHP2 inhibitor** for RAS and kinase mutant cancer
7) **GPX4 inhibitor** for multiple tumor types
8) **GO1 inhibitor** for frequent kidney stone formers

Thank you to our speakers

Speaker	Related program
 **Ravi Saravirayan, MD, PhD** Professor and Group Leader, Murdoch Children's Research Institute Head of Clinical Genetics Services at the Victorian Clinical Genetic Services	Low-dose infigratinib (FGFRi) for achondroplasia
 **Julian Gillmore, MD, PhD** Head, Centre for Amyloidosis & Acute Phase Proteins, University College London	Acoramidis: TTR stabilizer for ATTR cardiomyopathy
 **Kyriakie (Kiki) Sarafoglou, MD** Associate Professor, University of Minnesota Medical School and College of Pharmacy	Gene therapy for congenital adrenal hyperplasia (BBP-631)
 **Michael Collins, MD** Chief of the Skeletal Disorders and Mineral Homeostasis Section, National Institutes of Health	Encaleret: CaSR inhibitor for autosomal dominant hypocalcemia type 1 (ADH1)
 **Frank McCormick, PhD** BridgeBio Chairman of Oncology Professor, Helen Diller Family Comprehensive Cancer Center University of California San Francisco	Oncology research, KRAS

Agenda

Program	Speakers
Low-dose infigratinib (FGFRi) for achondroplasia	Introduction: Dr. Susan Moran, M.D., M.S.C.E. Presenter: Dr. Ravi Savarirayan, M.D., Ph.D.
Acoramidis: TTR stabilizer for ATTR	Introduction: Dr. Jonathan Fox, M.D., Ph.D. Presenter: Professor Julian D. Gillmore, M.D., Ph.D.
Gene therapy for congenital adrenal hyperplasia (BBP-631)	Introduction: Dr. Eric David, M.D., J.D. Presenter: Dr. Kyriakie Sarafoglou, M.D.
Encaleret: CaSR inhibitor for autosomal dominant hypocalcemia type 1 (ADH1)	Introduction: Dr. Jonathan Fox, M.D., Ph.D. Presenter: Dr. Michael Collins, M.D.
Targeted oncology	Introduction: Dr. Eli Wallace, Ph.D. Presenter: Frank McCormick, Ph.D.
Q&A	Moderator: Christine Siu Speakers: All
Conclusion	Neil Kumar, Ph.D.



Claudia,
child with
achondroplasia

Low-dose FGFR inhibitor (infigratinib) for achondroplasia

Achondroplasia overview

Prevalence

55,000 (US+EU) –
one of the most common
genetic conditions

Genetic driver

FGFR3 activation

Pathophysiology

Up-regulation of STAT1 and MAPK in the growth plate cause cranial, spinal, and stature symptoms

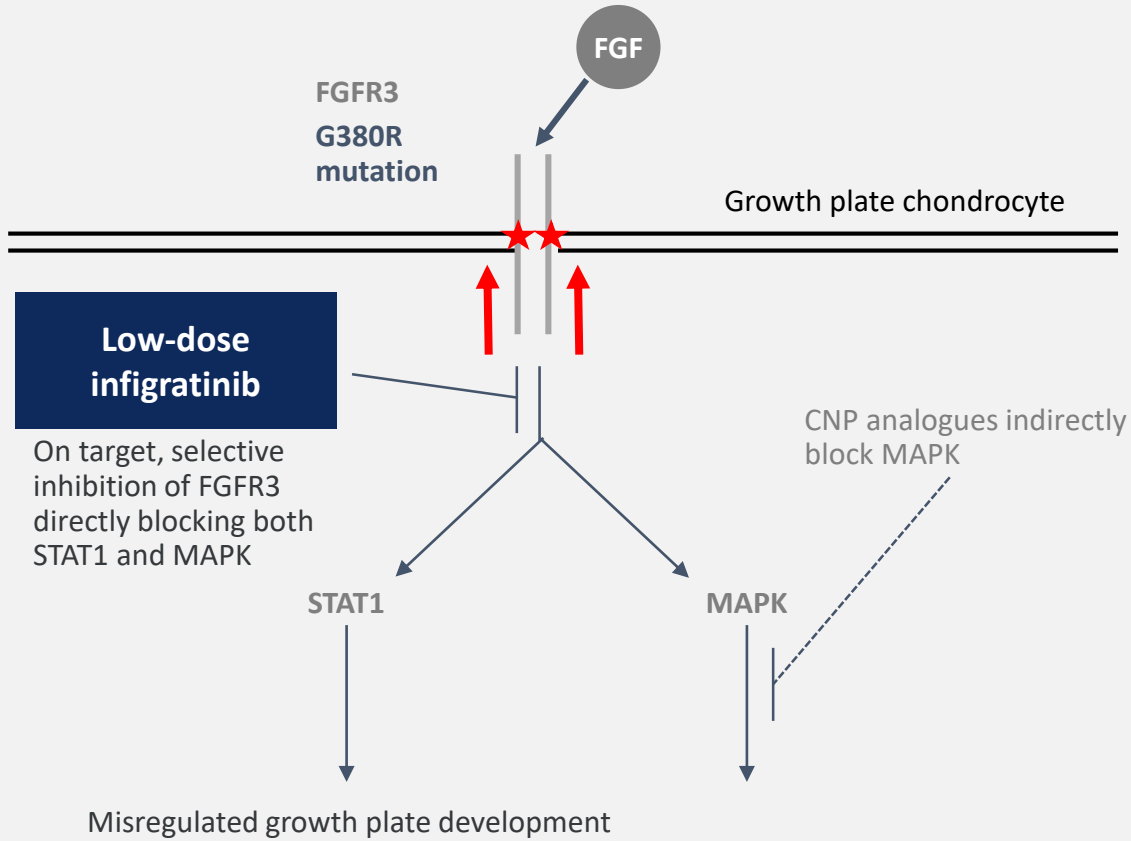
Features of a potential best-in-class medicine for achondroplasia

Direct targeting of FGFR3 and normalization of both STAT1 and MAPK signaling pathways

Potential to address all drivers of symptoms, including cranial, spinal and stature issues

Oral dosing, the most convenient solution for children with achondroplasia and their families

Potentially best-in-class approach targeting achondroplasia directly at its genetic source



ACH FGFR3 gain-of-function mutation causes:

- 2-3x over-activation of the receptor
- Up-regulation of downstream pathways STAT1 and MAPK
- Aberrant growth plate development, which causes cranial, spinal, and stature symptoms

Low-dose infigratinib has the potential to:

- Directly inhibit the causal gain-of-function mutation in FGFR3
- Normalize both the STAT1 and MAPK signaling pathways
- Reverse all key drivers of symptoms

Source: Ornitz DM et al. Developmental Dynamic 2017; Richette Joint Bone Spine 2007; Unger Curr Osteoporos Rep 2017, Hoover-Fong Am J Gen Med 2017

Low-dose infigratinib improves all the key drivers of clinical symptomology in validated ACH mouse model

FGFR3 WT
No treatment

FGFR3$^{Y367C/+}$
No treatment

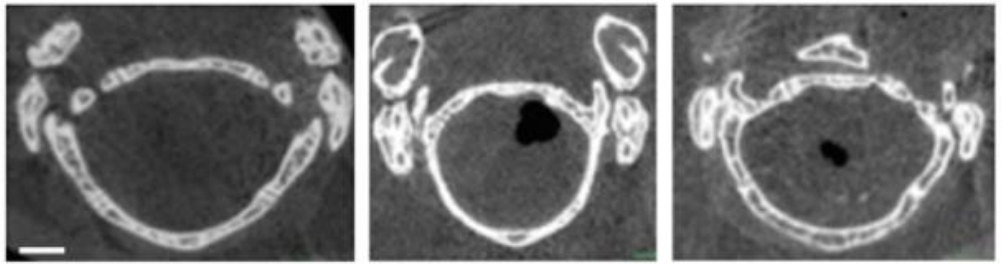
FGFR3$^{Y367C/+}$
Infigratinib tx

1 Cranial bone issues

17% increase in FM area

6% increase in AP skull length

May lead to **decrease** in **foramen magnum stenosis** and fewer surgeries

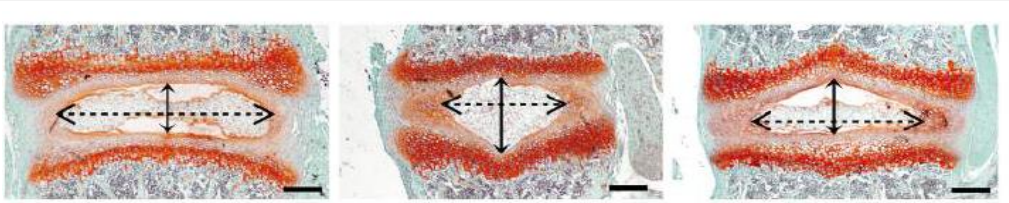


2 Disorders of the spine

12% increase in L4-L6 length

73% increase in disc width

May lead to **decrease** in **spinal stenosis**, possibly **reducing need for surgery**

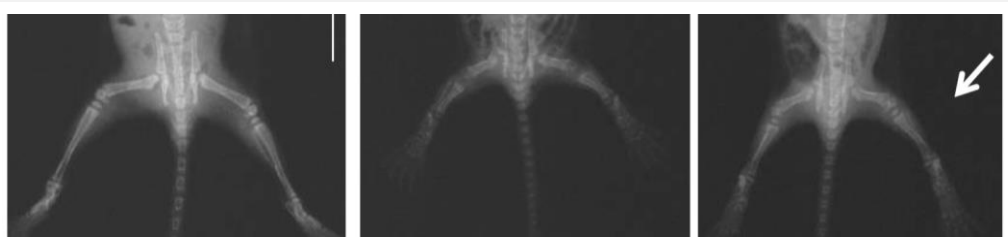


3 Disproportionate short stature

21% increase in femur length

33% increase in tibia length

May lead to **increased stature** and **proportionality**

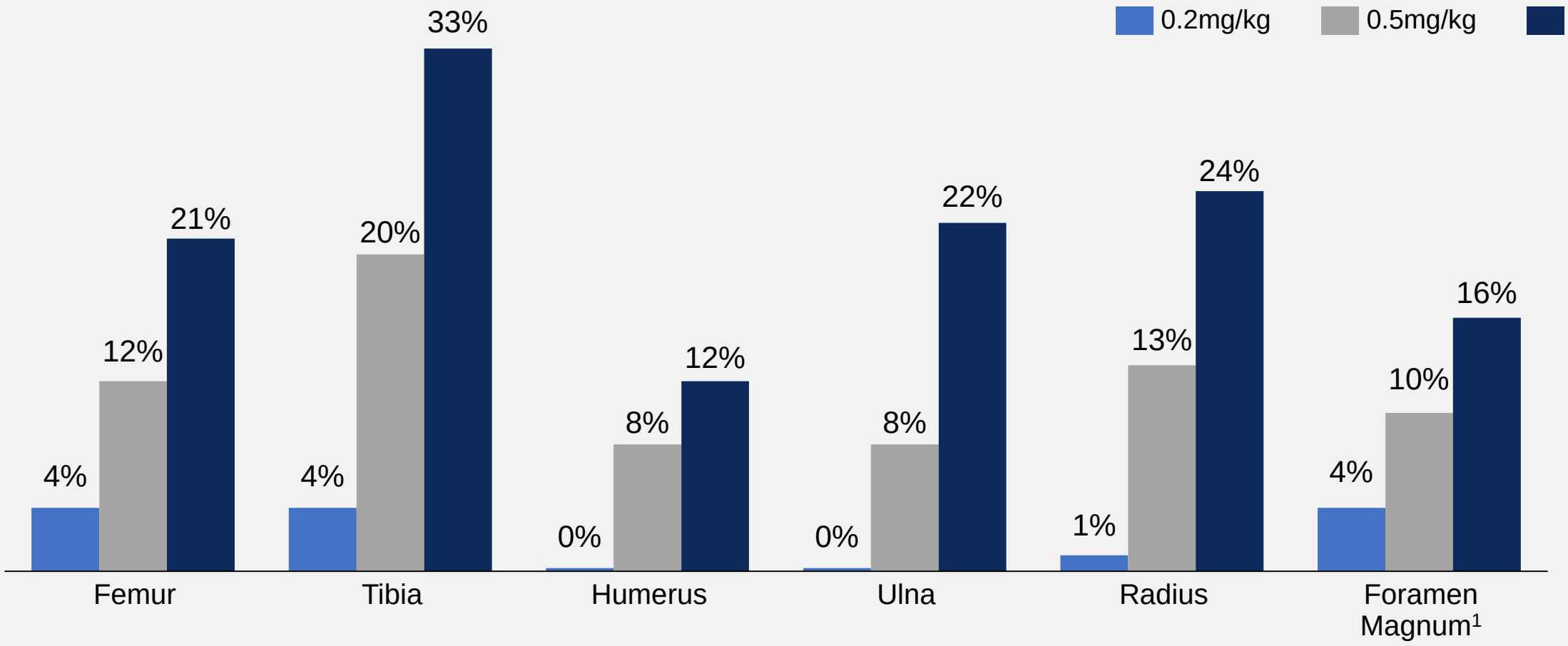


Source: Komla-Ebri et al. J Clin Inv 2016
Note: percent increase compared to vehicle treated FGFR3Y367C/+ mouse, infigratinib treatment with 2mg/kg subcutaneous dos

Preclinical data across multiple doses shows a robust dose-response relationship for infigratinib

Increase in length compared to non-treated mouse

%



1 Foramen magnum length
SOURCE: Komla-Ebri et al. J Clin Inv 2016, data on file
NOTE: subcutaneous doses, percent increase compared to vehicle treated FGFR3Y367C/+ mouse

Low-dose infigratinib showed potential best in-class preclinical profile in validated achondroplasia mouse model

Company/ Asset	MOA	Route	Status	Mouse model	Tibia length	Femur	Foramen magnum area	L4-L6 height
bridgebio Infigratinib	**Selective FGFR1-3i**	**Oral**	**Ph2**	**FGFR3^{Y367C}**	32.6%	20.9%	17.0%	12.1%
BIOMARIN Vosoritide (BMN111)	CNP analogue	Daily SQ	Pivotal (NDA filed)	FGFR3$^{Y367C/+}$	6.6%	5.2%	**No known publicly available data**	3.3%
ascendis pharma TransCon CNP[1]	CNP analogue	Weekly SQ	Ph2	FGFR3$^{Y367C/+}$	12.3%			
Pfizer Reifercept (TA-46)	FGFR3 decoy	Weekly SQ	Ph1	FGFR3^{ACH}	8.6%	6.2%		

Preclinical data from infigratinib and other investigational achondroplasia therapies

Percent increase compared to non-treated mouse

Source: Komla-Ebri et al. J Clin Inv 2016, Lorget et al. Am J Hum Genet 2012, Garcia et al. Science Trans Med 2013, Breinholt ENDO 2017
Note: subcutaneous doses, percent increase compared to vehicle treated FGFR3$^{Y367C/+}$, FGFR3$^{ACH/+}$ mouse as noted in "Mouse model" columns
Infigratinib treatment with 2mg/kg subcutaneous dose [1]Based on vosoritide continuous infusion; *Value estimated using DigitizeIt.

Ravi Savarirayan, MD, PhD

- Professor of Clinical Genetics and Group Leader of Skeletal Biology and Disease at Murdoch Children's Research Institute
- Foundation Director of the Southern Cross Bone Dysplasia Centre
- PROPEL Lead Principal Investigator

Clinical overview

Ravi Savarirayan, MD, PhD – Professor of Clinical Genetics, PROPEL Lead PI

Health and achondroplasia

- Some people with achondroplasia have no or minimal medical issues
- Some people do have a variety of medical problems (all have potential for medical issues)
- A small number have more serious problems
  - But the aim is to detect them early and intervene to treat them to stop more serious damage
- Disproportionate short statue can impact QoL and it matters (psych-social well being)
- New better tool to evaluate condition/ complications/ QoL
- Need to engage/ partner with short stature communities as treatments emerge

Achondroplasia: Medical complications

- Sudden death (SIDS-like in first year with 50x relative risk)
- Compression FM
- Sleep apnea
- Thoracolumbar kyphosis
- Spinal stenosis
- Hydrocephalus
- Orthopaedic limb deformity
- ENT/Dental
- Obesity
- Short stature and developmental impact
- Pain (impact on function)

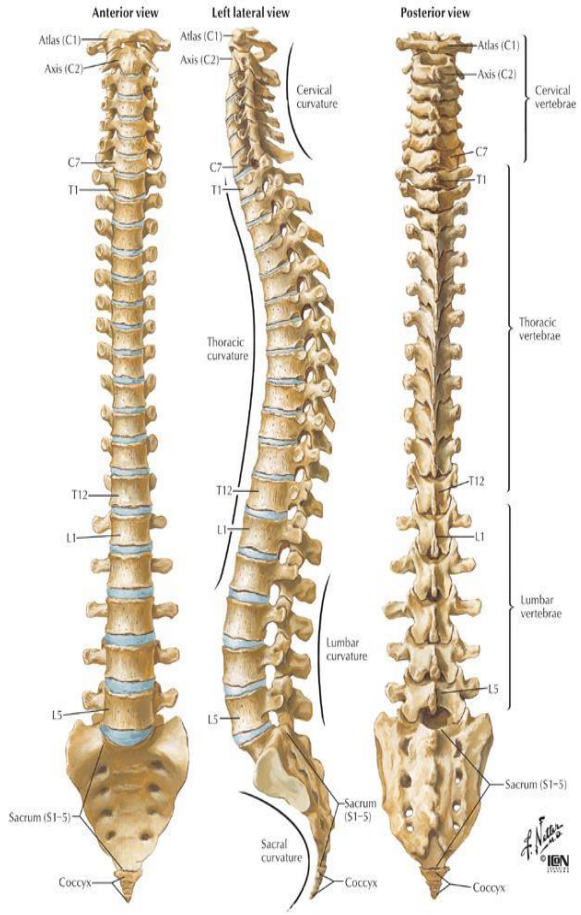
SOURCE: Savarirayan *et al*, Lancet 2020

Foramen magnum

- Major management and treatment issue
- No consensus on evaluation/management/markers
- Cause of higher infant mortality?
- Guidelines (*White, ...Savarirayan, 2015, AJMG*)

Spinal issues

- Thoraco-lumbar kyphosis
- Spinal stenosis (all levels)
- Chronic back pain
- Monitoring
- Assessment
- Treatment/ management



SOURCE: White, ..Savarirayan, 2020 OJRD

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Pain and function

How do pain and fatigue in conditions with disproportionate short stature impact function and mobility?

- Limited data on pain in SD
- Hoover-Fong *et al*., studied 361 people over 10 years with SD (cross sectional online survey via LPA)
- Chronic pain prevalence was 70.3%, highest in ACH and 20% with little/ no functional mobility to walk

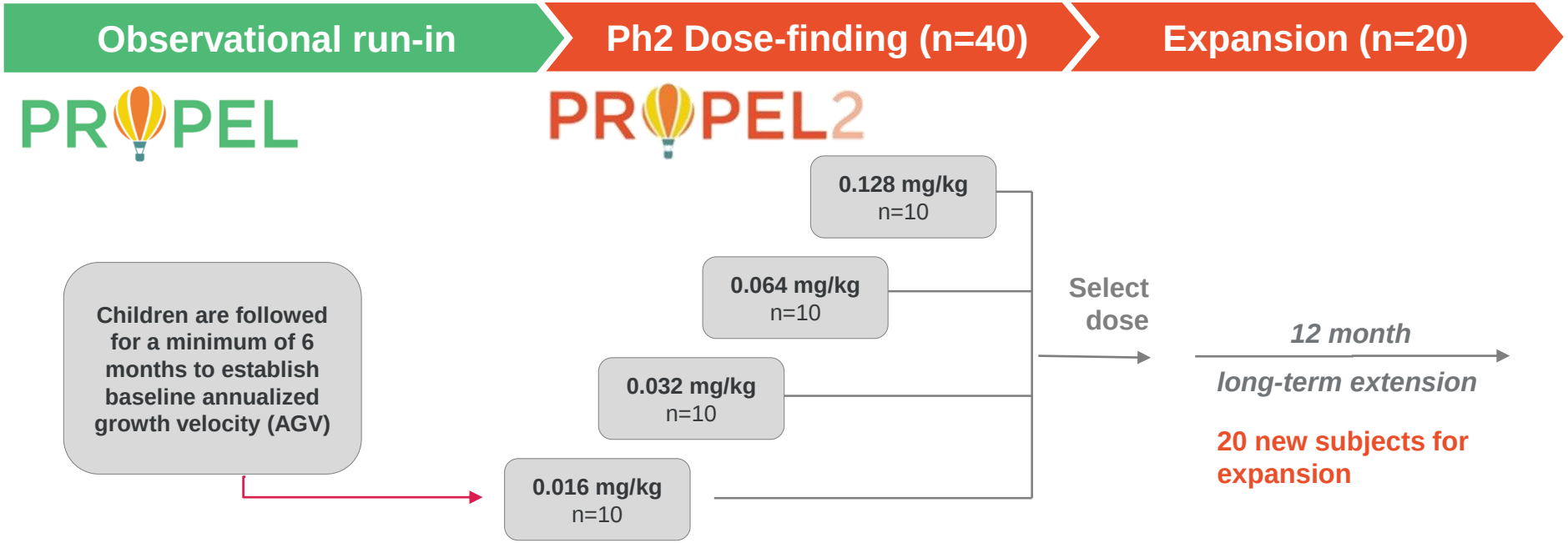
Psychosocial aspects of achondroplasia

- Impact for parents, siblings and child (teasing, “cyber-bullying”)
- Cultural issues of physical difference/short stature
- Resources:
  - Support groups
  - Genetic counsellors
  - Psychologists
- Awareness of impact of short stature at different ages (preschool, school, community)

Prioritizing functional outcomes

With permission

The PROPEL clinical program is enrolling and potential POC data expected in 2021



Key inclusion criteria

- Children 2.5 – 10 years old
- Clinical and molecular ACH diagnosis

Primary objectives

- Baseline annualized growth velocity (AGV)

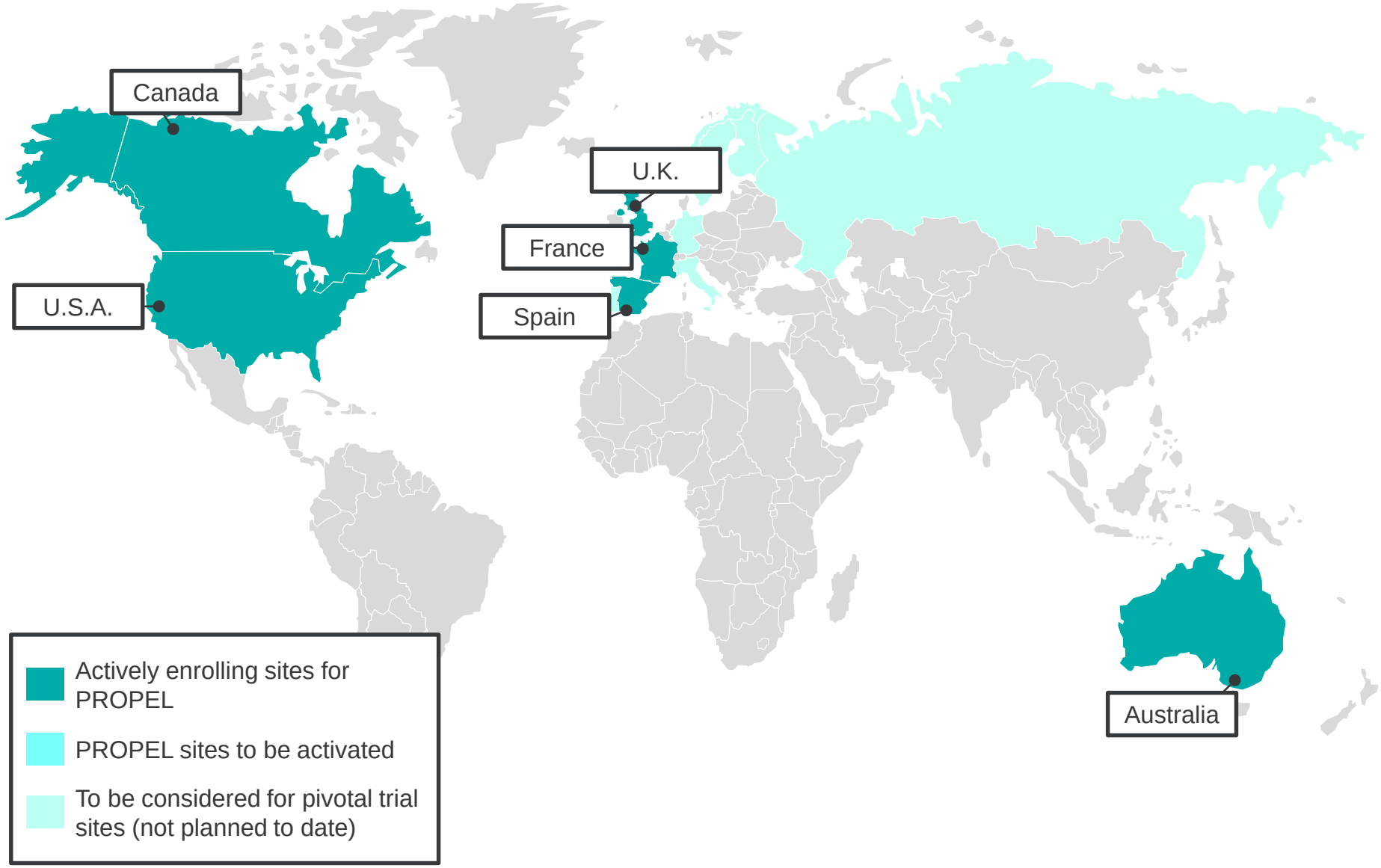
Primary objectives

- Identify safe therapeutic dose for expansion / pivotal study
- Safety and tolerability
- Change from baseline in AGV

Primary objectives

- Long-term safety and efficacy

PROPEL will have study sites in six countries around the world, with other regions to be considered for later trials



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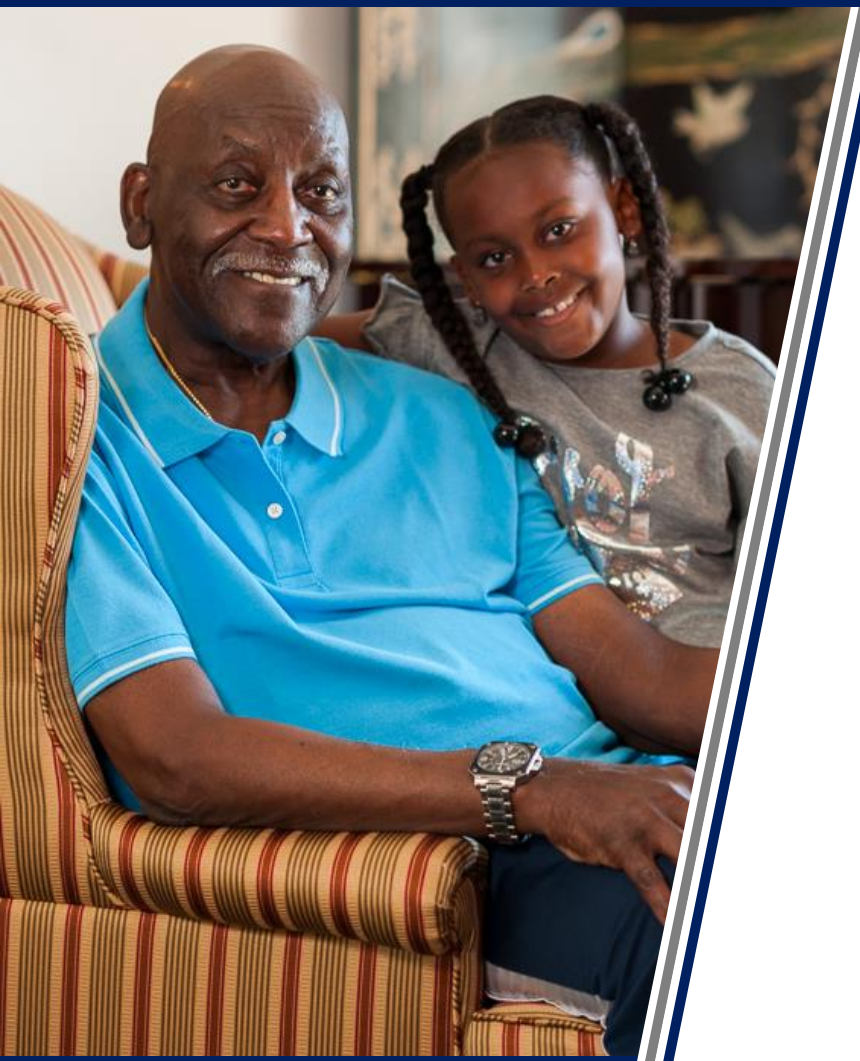
Thank you!

Agenda

Program	Speakers
Low-dose infigratinib (FGFRi) for achondroplasia	Introduction: Dr. Susan Moran, M.D., M.S.C.E. Presenter: Dr. Ravi Savarirayan, M.D., Ph.D.
Acoramidis: TTR stabilizer for ATTR	Introduction: Dr. Jonathan Fox, M.D., Ph.D. Presenter: Professor Julian D. Gillmore, M.D., Ph.D.
Gene therapy for congenital adrenal hyperplasia (BBP-631)	Introduction: Dr. Eric David, M.D., J.D. Presenter: Dr. Kyriakie Sarafoglou, M.D.
Encaleret: CaSR inhibitor for autosomal dominant hypocalcemia type 1 (ADH1)	Introduction: Dr. Jonathan Fox, M.D., Ph.D. Presenter: Dr. Michael Collins, M.D.
Targeted oncology	Introduction: Dr. Eli Wallace, Ph.D. Presenter: Frank McCormick, Ph.D.
Q&A	Moderator: Christine Siu Speakers: All
Conclusion	Neil Kumar, Ph.D.

Acoramidis (AG10) for transthyretin (TTR) amyloidosis (ATTR)



Art,
ATTR-CM patient

Seeking to address large and growing need in ATTR, a progressive and fatal disease affecting >400K patients

Designed to target the disease at its source by stabilizing TTR, a genetically and clinically validated mechanism

Advancing acoramidis, a potential best-in-class drug that mimics naturally occurring rescue mutation

Acoramidis has been **well-tolerated and demonstrated near-complete TTR stabilization** in Phase 1 and Phase 2 studies

Executing Phase 3 study with top-line data expected in late 2021 or early 2022

Acoramidis was designed to treat ATTR at its source

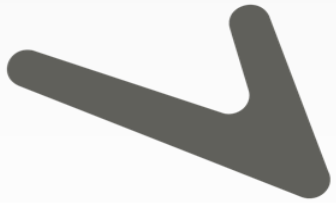
Disease mechanism

Native TTR circulates in blood as a tetramer

~130 known destabilizing mutations

Protective T119M mutation

Dissociation into monomers initiates pathogenesis



Monomers aggregate, causing disease

Therapeutic hypothesis

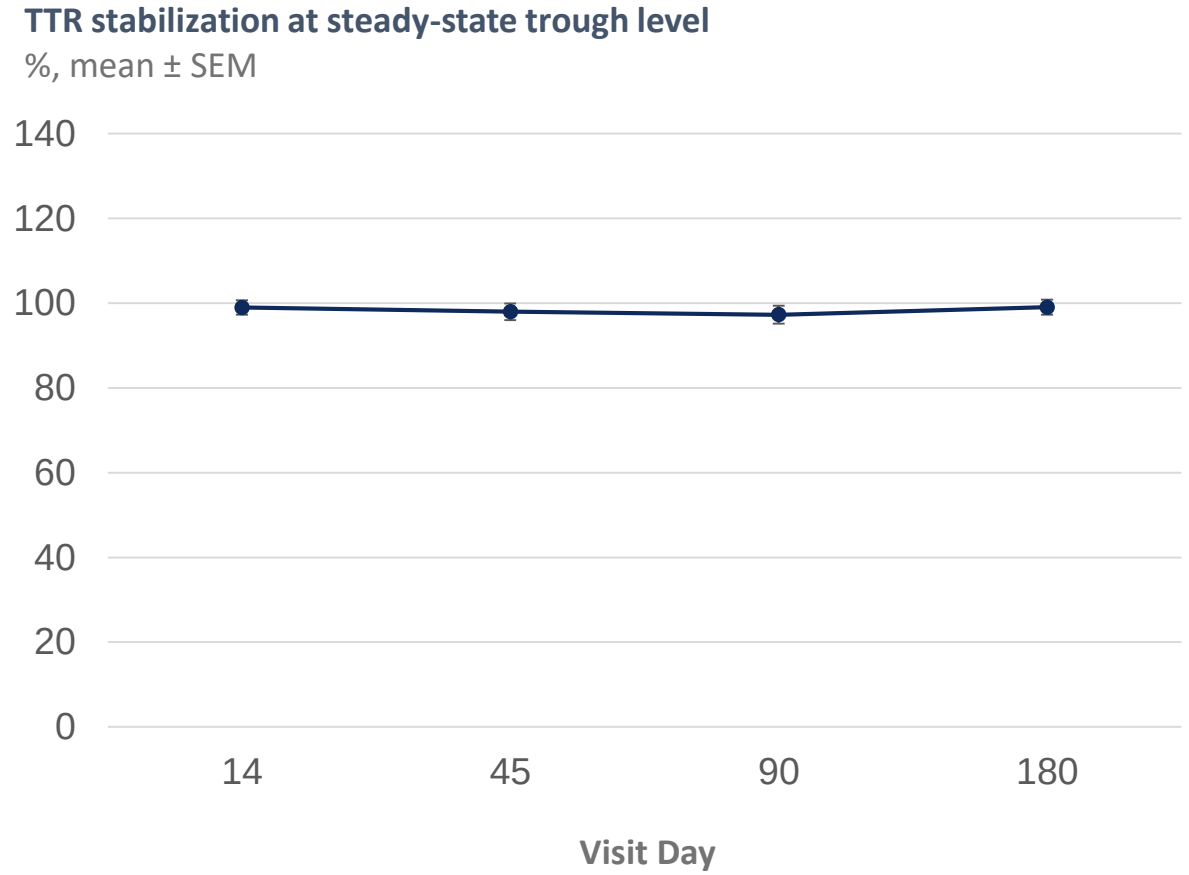
Acoramidis was designed to mimic protective T119M mutation by stabilizing TTR tetramers to slow or halt disease progression

Acoramidis has been well-tolerated and demonstrated near-complete TTR stabilization in pre-clinical, Ph1, and Ph2 studies

Phase 2 safety summary[1]

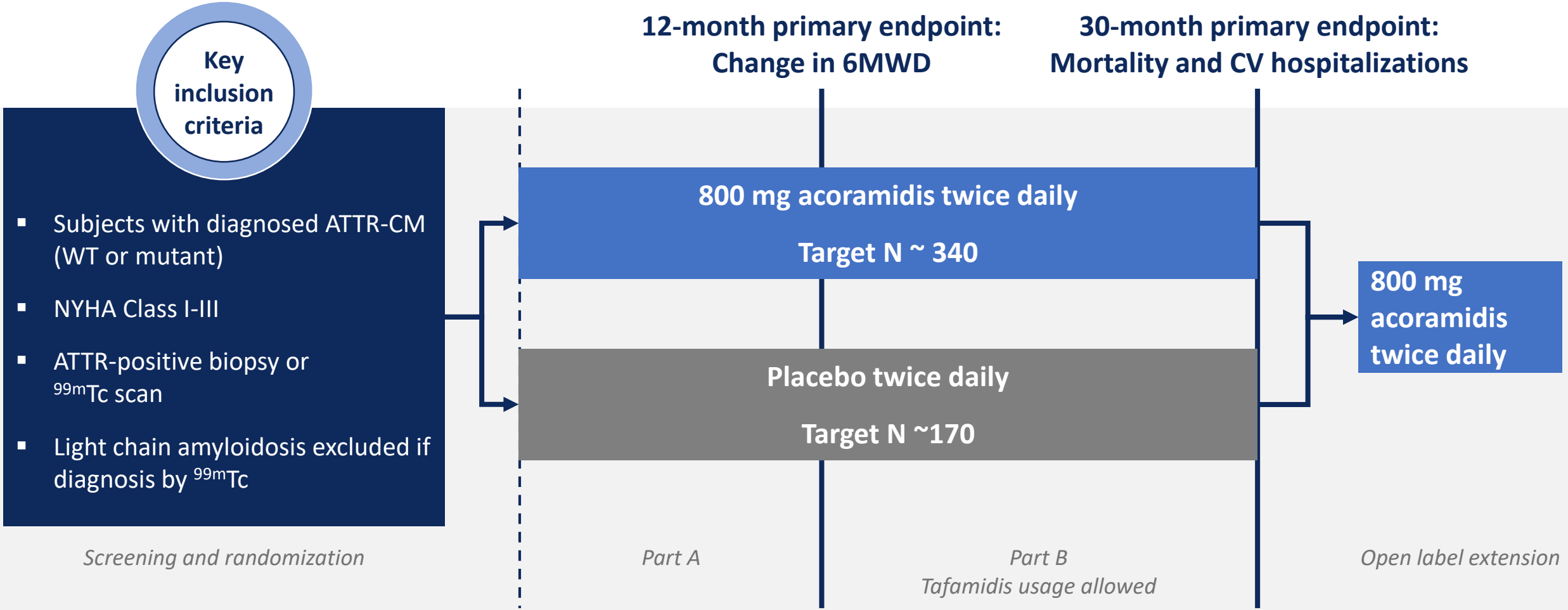
	Placebo N = 17	Acoramidis (pooled doses) N = 32
Any Adverse Event	**15 (88%)**	**21 (66%)**
Mild	6 (35%)	11 (34%)
Moderate	8 (47%)	9 (28%)
Severe	1 (6%)	1 (3%)
Any Serious Adverse Event	**2 (12%)**	**1 (3%)**
AF and CHF	1 (6%)[1]	0
Leg cellulitis	1 (6%)	0
Dyspnea	0	1 (3%)

Phase 2 TTR stabilization[2]



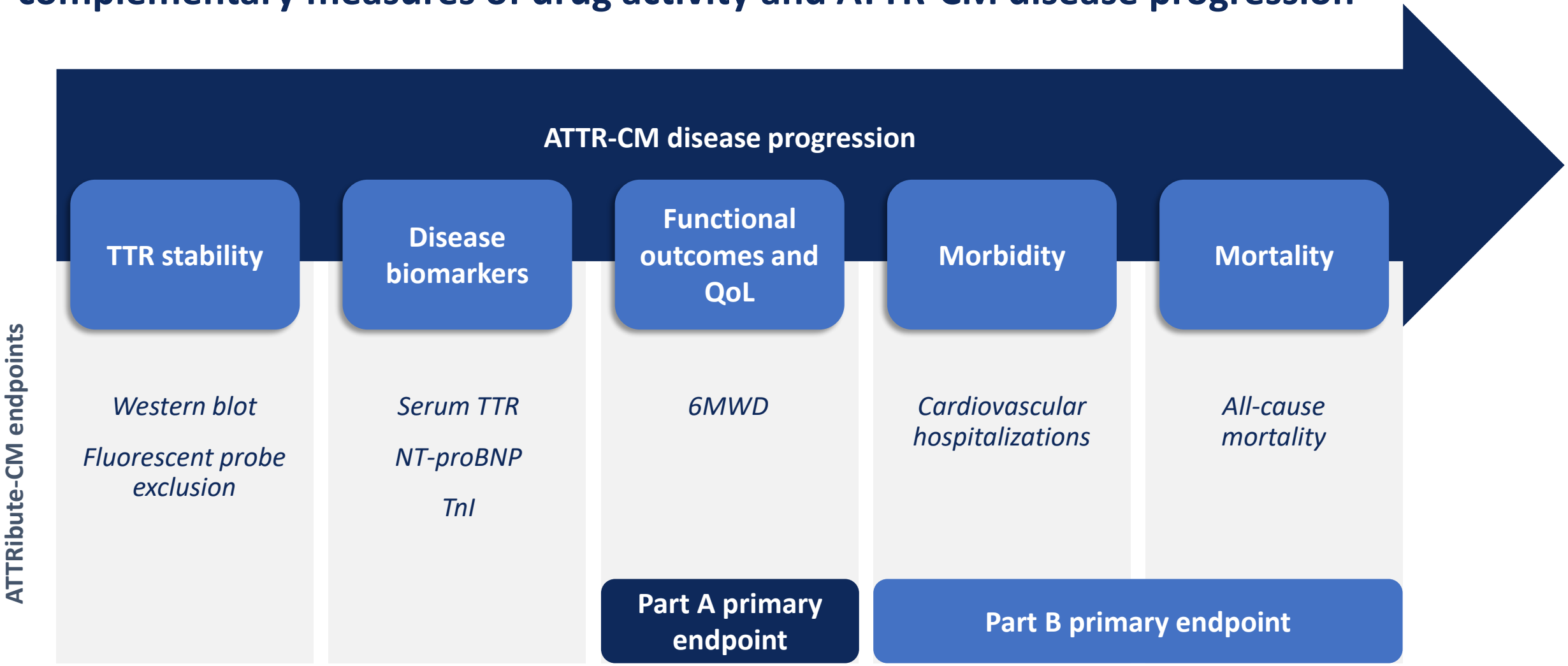
1 Judge, D.P. et al. JACC Vol. 74, No. 3, 2019:285 – 95
2 Judge, D.P. et al. American Heart Association 2019

ATTRibute-CM will provide 12-month functional outcome data and 30-month mortality and CV hospitalization data



6MWD = Six-minute walk distance; NYHA = New York Heart Association;
^{99m}Tc = Technetium labeled pyrophosphate (PYP) or bisphosphonate (e.g., DPD);
CV = cardiovascular-related

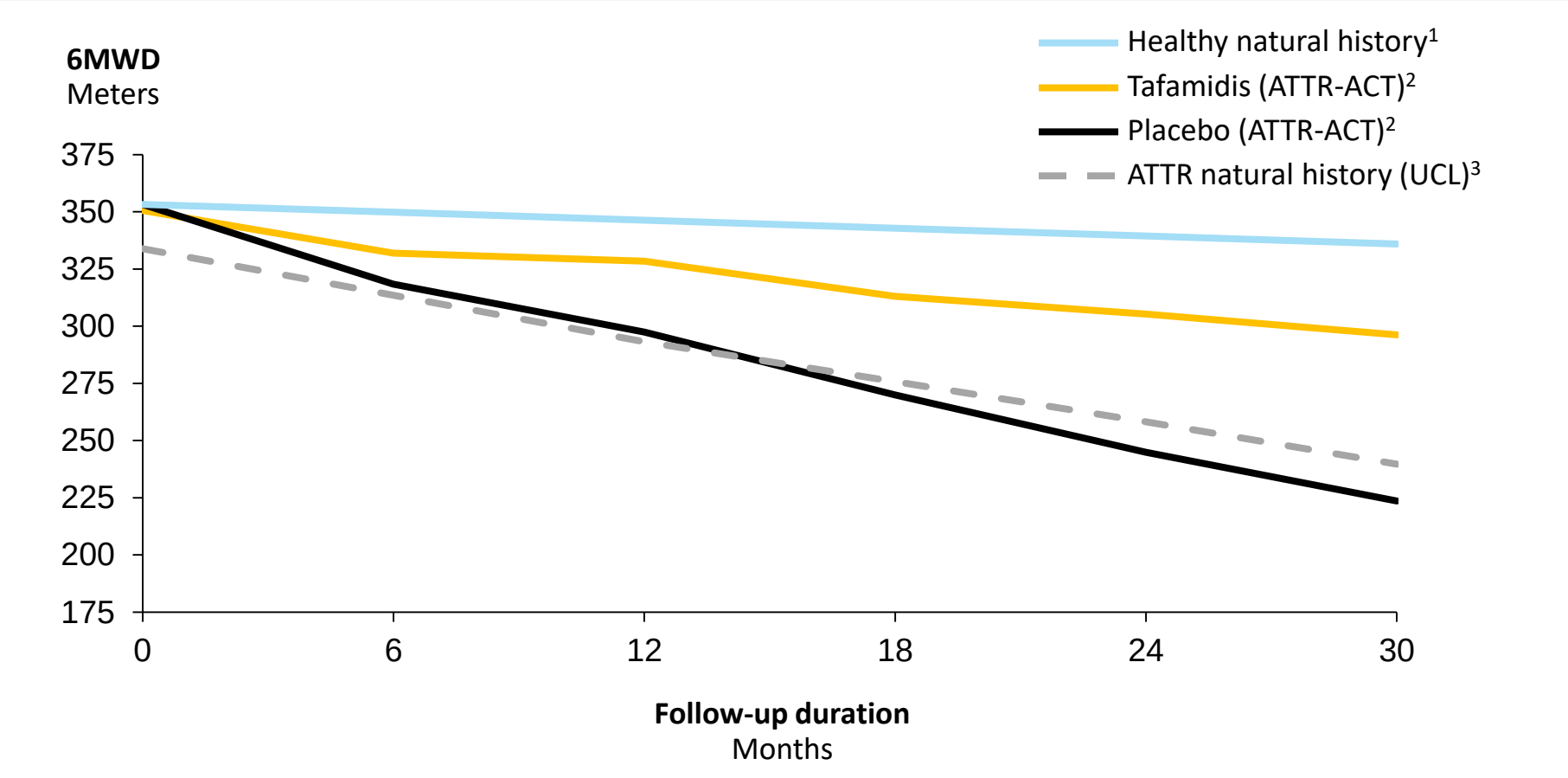
ATTRibute-CM is designed to evaluate safety and efficacy of acoramidis across complementary measures of drug activity and ATTR-CM disease progression



NT-proBNP = N-terminal pro b-type natriuretic peptide; TnI = Troponin I; 6MWD = Six-minute walk distance
QoL = Quality of life

Rapid functional decline in untreated ATTR-CM patients provides opportunity to demonstrate robust clinical benefit

Summary of 6MWD data in ATTR-CM and healthy cohorts

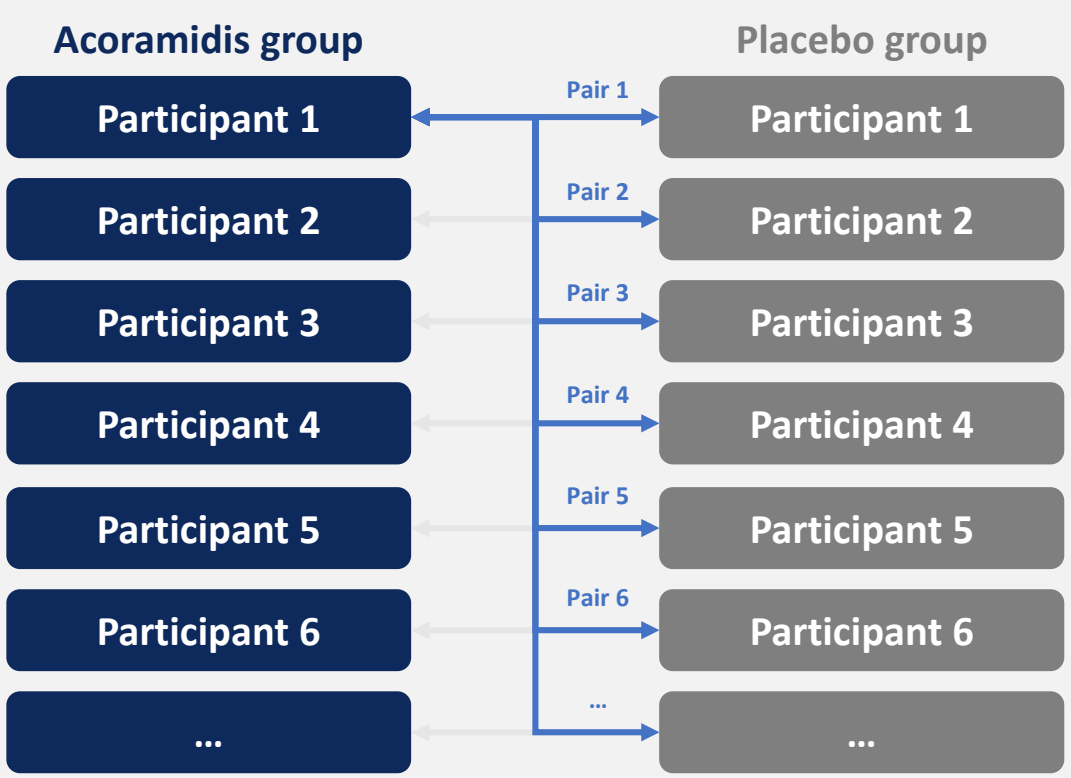


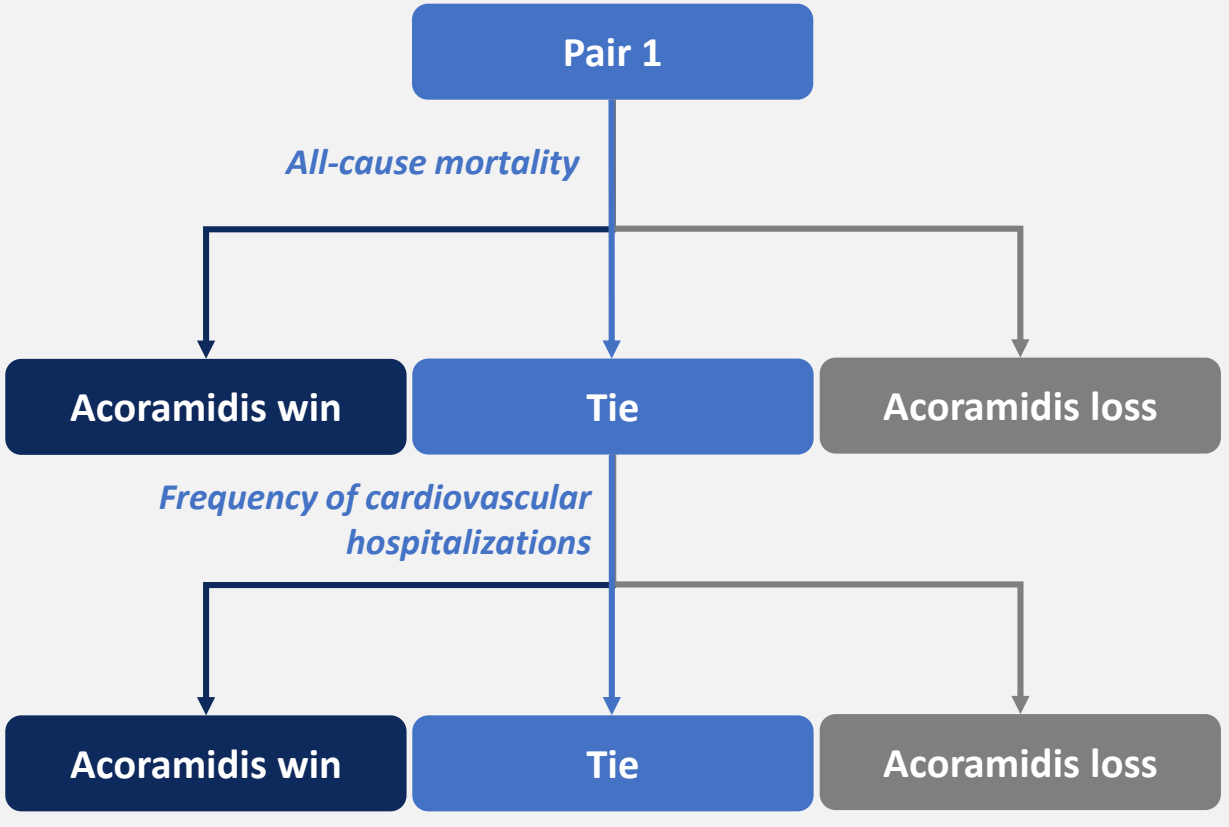
Optimal profile for acoramidis would markedly slow or halt decline in 6MWD in trial participants

1. Enright, P.L. et al. Chest 2003. N = 3333 healthy elderly adults, baseline set to match ATTR-ACT placebo group
2. Maurer, M.S. et al. NEJM 2018. N = 264 (tafamidis), N = 177 (placebo) ATTR-CM trial participants
3. Lane, T.L. et al. Circulation 2019. N = 1034 ATTR-CM patients

Part B endpoint will hierarchically compare mortality and cardiovascular hospitalizations between all pairs of trial participants

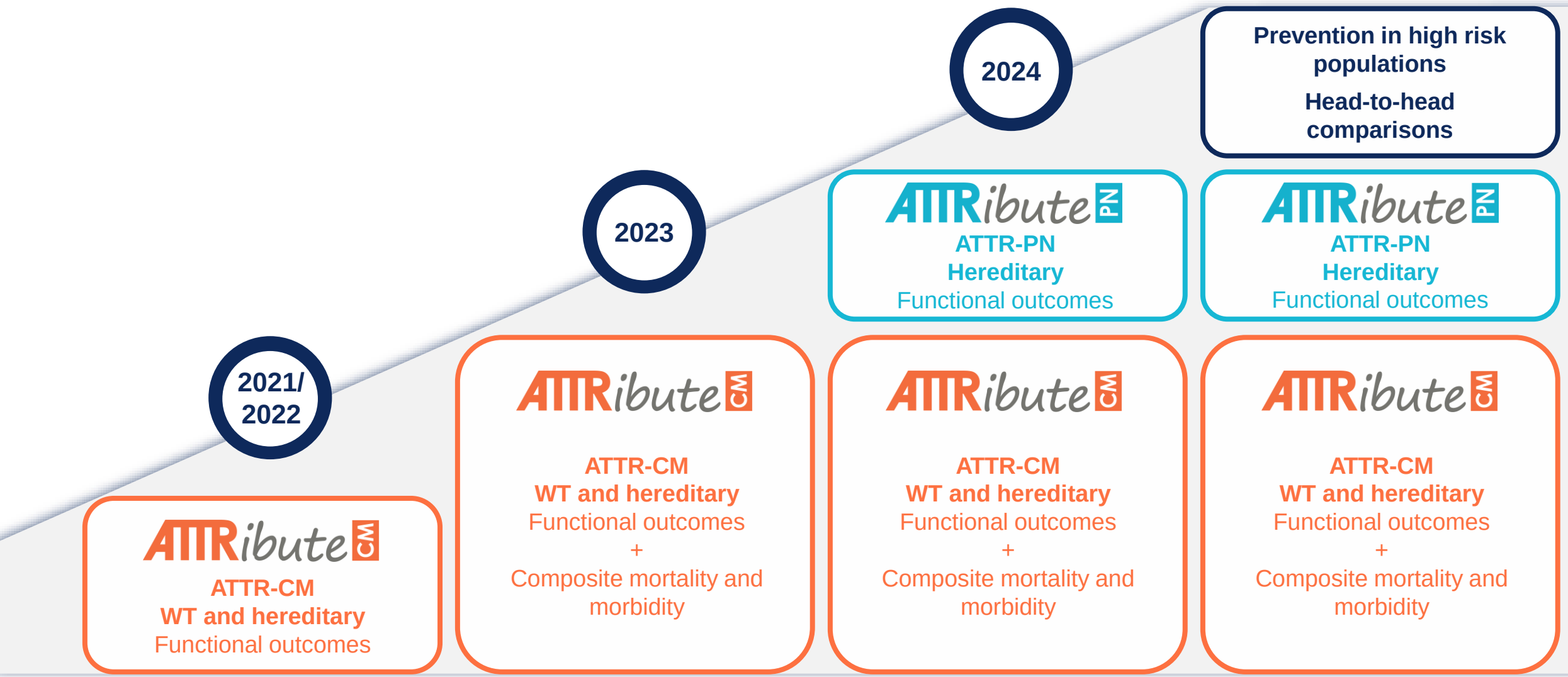
Schematic illustration of win ratio analysis[1]





1 Primary analysis of ATTRibute-CM will use a modified win ratio analysis (Finkelstein-Schoenfeld)

Ongoing and planned studies of acoramidis aim to continually expand clinical evidence and addressable patient population



Julian Gillmore, MD, PhD

- Centre Head at UCL's Centre for Amyloidosis & Acute Phase Proteins
- Research interests include pathogenesis, diagnosis and treatment of amyloidosis
- Co-author of 250+ peer-reviewed articles including numerous regarding ATTR
- Co-chair ATTRibute-CM Steering Committee

DIAGNOSIS, STAGING, EPIDEMIOLOGY & TREATMENT OF ATTR AMYLOIDOSIS

Professor Julian Gillmore
National Amyloidosis Centre
University College London

UCL

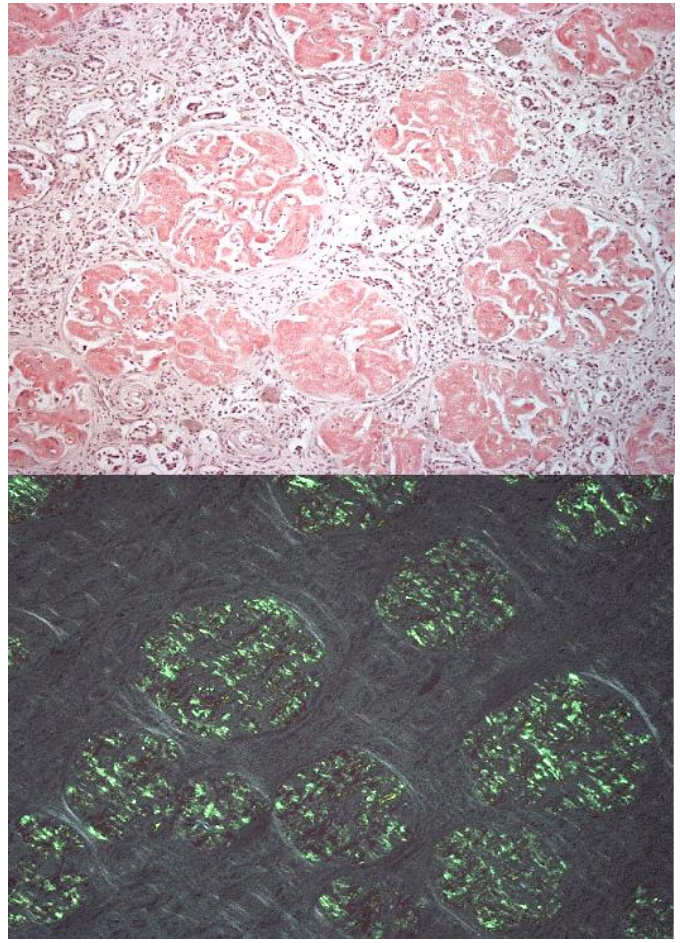
NHS
Royal Free London
NHS Foundation Trust

Outline

- Epidemiology & Clinical features of ATTR amyloidosis
- Diagnosis & Staging of cardiac ATTR amyloidosis
- Treatment principles in (ATTR) amyloidosis

Amyloid

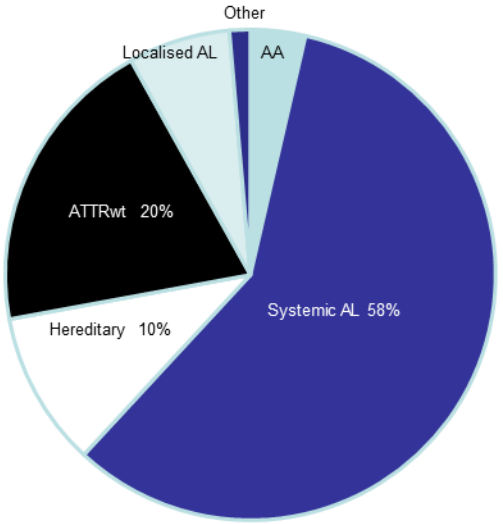
- Abnormal extracellular misfolded fibrillar protein deposit in tissues
- Pathognomonic green birefringence after Congo red staining
- >30 different amyloid fibril proteins



Merlini G. Hematology Am Soc Hematol Educ Program 2017;1:1–12
Sipe *et al.* Amyloid 2014;21:221–4

Amyloid fibril proteins/amyloid ‘types’

Amyloid type	Amyloid Fibril Protein (circulating)
• AL	**L**ight chain of immunoglobulin
• AA	**A**myloid A protein
• Wild-type ATTR (ATTRwt)	‘Normal’ (unmutated) transthyretin **(TTR)**
• Hereditary ATTR (hATTR)	‘Mutated’ transthyretin **(TTR)**



Why does amyloid type matter?

Different behaviour of disease

Different treatment of disease

Chemotherapy for AL amyloidosis

New drugs for ATTR amyloidosis

NAC Data 2018, unpublished

Wild-type ATTR amyloidosis

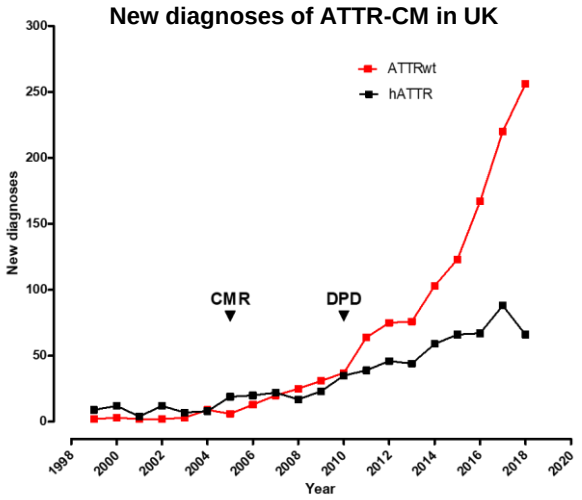
Amyloid fibril protein is wild-type (normal, unmutated) transthyretin (TTR)

- Wild-type ATTR amyloidosis (ATTRwt) is a cardiomyopathy
  - Increasingly recognised cause of heart failure in individuals >50 years (94% ♂)
  - Progressive and fatal with 3-10 years
  - Extra-cardiac features include CTS and lumbar canal stenosis
  - Autopsy studies indicate cardiac ATTR amyloid deposits are present in **~25% males over 80 years**
  - Majority not diagnosed with amyloidosis in life
    - ➢ Poor sensitivity of echocardiography
    - ➢ Clinical significance?

69 year old Caucasian gentleman
3 year history of dyspnoea, fatigue
Echocardiogram – thickened heart walls (21mm), restrictive physiology
Endomyocardial biopsy – amyloid (referred to NAC)
Immunohistochemistry – ATTR amyloid
TTR gene sequence – wild-type

- Final diagnosis – **wild-type ATTR amyloidosis**
- No disease-modifying treatment

The <u>only</u> new diagnosis of wild-type ATTR amyloidosis in 2000!



Lane T *et al,* Circulation 2019;140:16–26

Hereditary ATTR amyloidosis

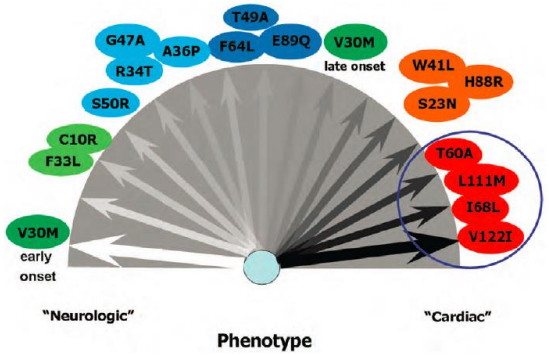
Amyloid fibril protein is variant (mutated) TTR

Spectrum of hereditary ATTR amyloidosis

- Dominantly inherited
- More than 130 amyloidogenic mutations of TTR
- Variable phenotype dominated by:
  - **amyloid cardiomyopathy (ATTR-CM)**
  - **peripheral & autonomic neuropathy (ATTR-PN)**

  } **ATTR-Mixed**

  vitreous & leptomeningeal amyloid



V122I TTR variant present in ~4% of African-Americans & Afro-Carribeans
T60A-associated ATTR amyloidosis most prevalent in British Caucasians (Irish)
V30M-associated ATTR amyloidosis (literature bias)

Reilly MM *et al*, J Neurol Neurosurg Psychiatry 1995;55:45-49
Carr AS *et al*, J Neurol Neurosurg Psychiatry 2016;87:620-627
Gillmore JD *et al*, New Engl J Med 2015; 372:1769

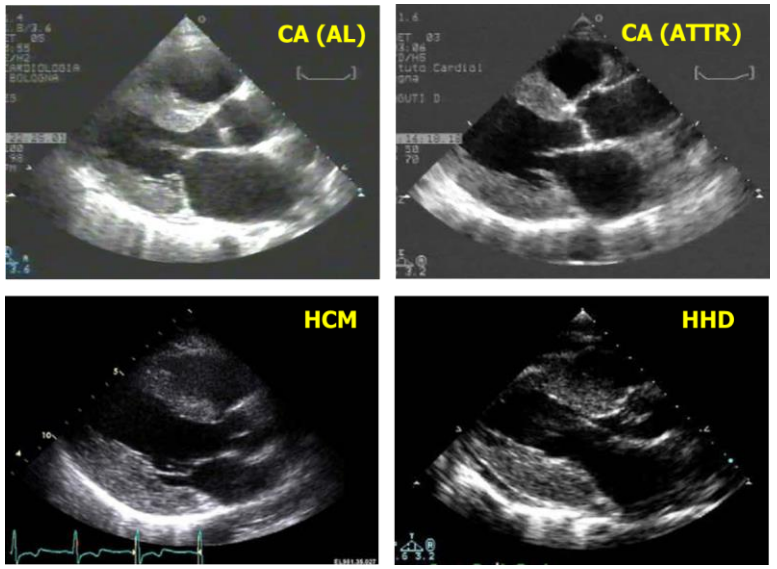
Diagnosis of amyloid

- ‘Traditionally’, biopsy and staining of affected organ with Congo red and antibody panel
  - Heart biopsy - has risk and is not routinely performed by cardiologists
  - Nerve biopsy – not routinely performed by neurologists

- Screening biopsy
  - Rectal
  - Abdominal fat aspirate
    - highly variable sensitivity

Amyloid type and load by SAP scan	FPFNA Sensitivity
AL amyloidosis	
Large burden	90%
Moderate burden	84%
Small burden	64%
ATTR amyloidosis	
ATTRv	30%
ATTRwt	15%

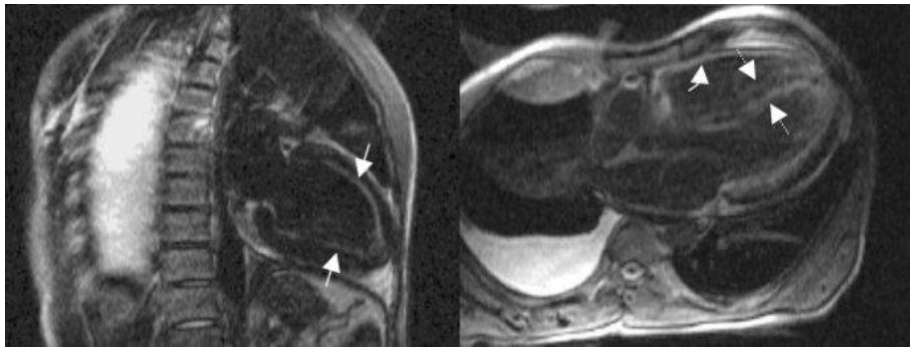
Echocardiography in cardiac amyloidosis

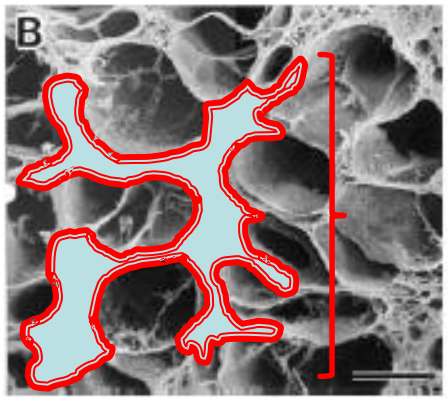


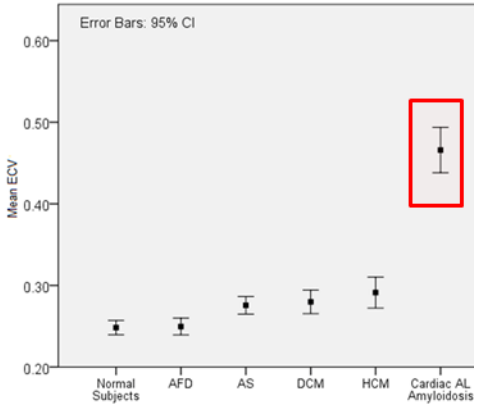
Van Gameren, Arth&Rheum 2006;54:2015
Ansari-Lari, Diagn Cytopathol 2004;30:178
Quarta, Eur Heart J 2017;38:1905-1908

Cardiac Magnetic Resonance (CMR) imaging in cardiac amyloidosis

- 29 patients (25 cardiac AL and 4 cardiac ATTR amyloidosis)
- Late gadolinium enhancement
- Rapid clearance of gadolinium from blood pool

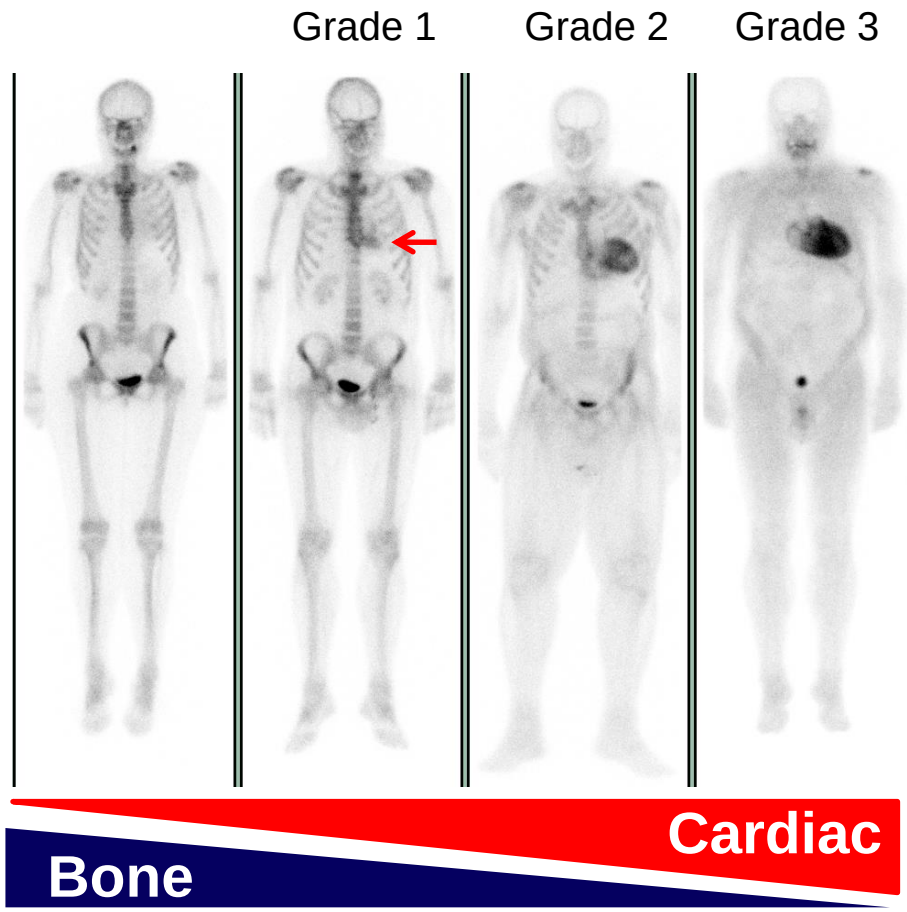






Maceira AM *et al*, Circulation 2005;111:186-93
Sado D *et al*, Heart 2012;98:1436-41
Fontana M *et al*, Circulation 2015;132:1570-9
Martinez-Naharro A *et al,* JACC Cardiovasc Imaging 2018;11:152-154

^{99m}Tc-DPD (or HMDP/PYP) scans in cardiac ATTR amyloidosis

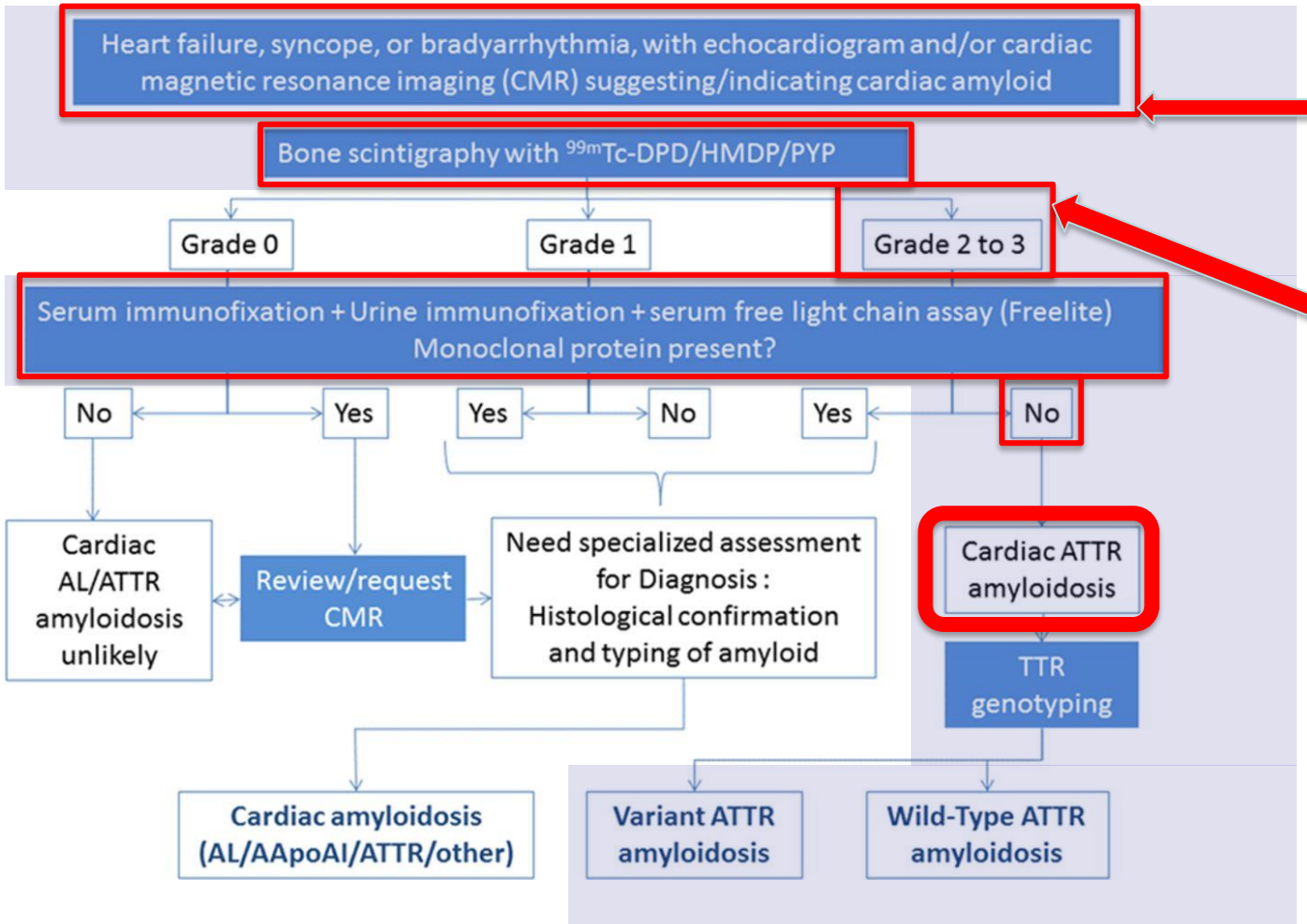


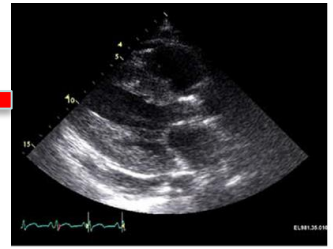
- **Grade 1** = Cardiac uptake less than or equal to bone uptake
- **Grade 2** = Moderate cardiac uptake greater than bone
- **Grade 3** = Strong cardiac uptake with little or no bone signal

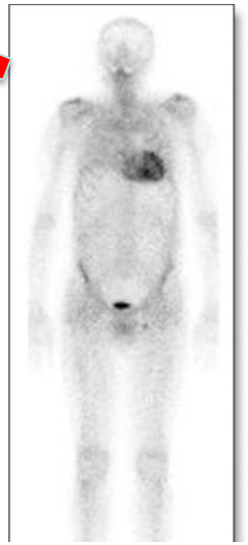
Cardiac ATTR amyloidosis
Positive - >99% sensitive
Grade 2/3 – 90% specific

Rapezzi *et al*, JACC Imaging 2011:659-70
Hutt *et al*, Eur Heart J 2014;15:1289-1298

Non-invasive diagnosis of cardiac ATTR amyloidosis (ATTR-CM)







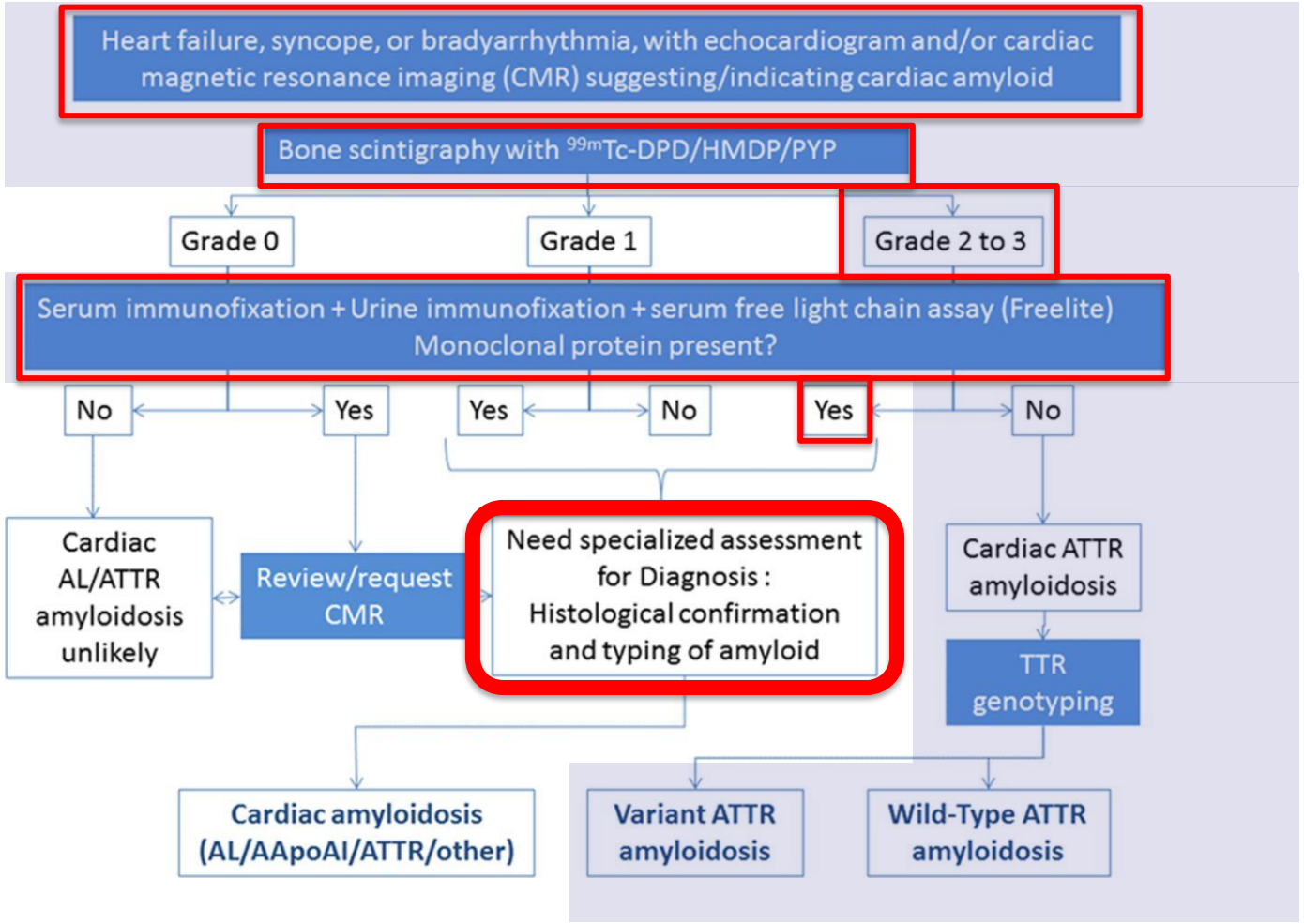
Gillmore JD *et al*, Circulation 2016;133:2404-12

Case

72 yr old male, referred to NAC with ‘cardiac AL amyloidosis’
HF with characteristic amyloid echocardiogram
Low level IgAλ paraproteinaemia

<u>At National Amyloidosis Centre</u>

HF, bilateral carpal tunnel decompressions
NT-proBNP 2865 ng/L, Troponin T 70 ng/L
Echocardiogram – **characteristic of cardiac amyloidosis**
CMR – **characteristic of cardiac amyloidosis**
Tc-DPD scan – **Perugini grade 2 cardiac uptake**
IgAλ pp 12g/L, κFLC 18.4mg/L, **λFLC 119.6mg/L, κ:λ 0.15**
TTR gene – wild-type sequence



Case

Differential Diagnosis - ?AL/?ATTR cardiac amyloidosis

Fat aspirate – no amyloid

Endomyocardial biopsy performed

Protein Group	Protein	Score	Match(Sig)	Seq(Sig)	Seq(Uniq+Sig)
Signature	SAMP_HUMAN	799	25	10	10
Signature	APOE_HUMAN	480	18	13	13
Signature	APOA4_HUMAN	352	17	15	15
Transthyretin (TTR)	TTHY_HUMAN	2243	60	12	12
Gelsolin	GELS_HUMAN	39	2	2	2

Diagnostic of ATTR amyloid

Final Diagnosis – wild-type ATTR amyloidosis

NO ROLE FOR CHEMOTHERAPY

Case

Tc-DPD scintigraphy in amyloidosis

- Diffuse cardiac uptake = cardiac amyloid
- No cardiac uptake ≠ no cardiac amyloid
- Grade 2/3 cardiac uptake ≠ cardiac ATTR amyloid

Case

Tc-DPD scintigraphy in amyloidosis

Diffuse cardiac uptake = cardiac amyloid

No cardiac uptake ≠ no cardi

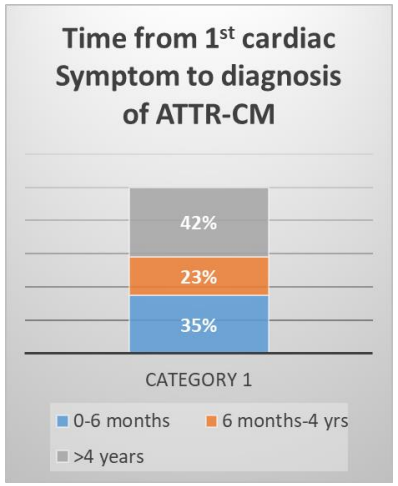
Grade 2/3 cardiac uptake ≠ cardiac ATTR amyloid

No DPD uptake in ~40% of cardiac AL amyloidosis

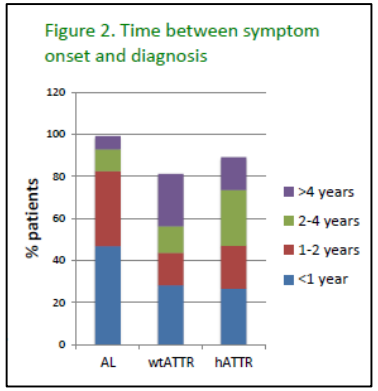
Grade 2/3 cardiac uptake in ~10% of cardiac AL amyloidosis

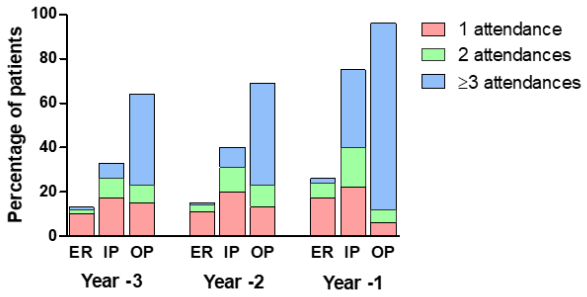
Diagnostic delay in cardiac ATTR amyloidosis but improving?

UK

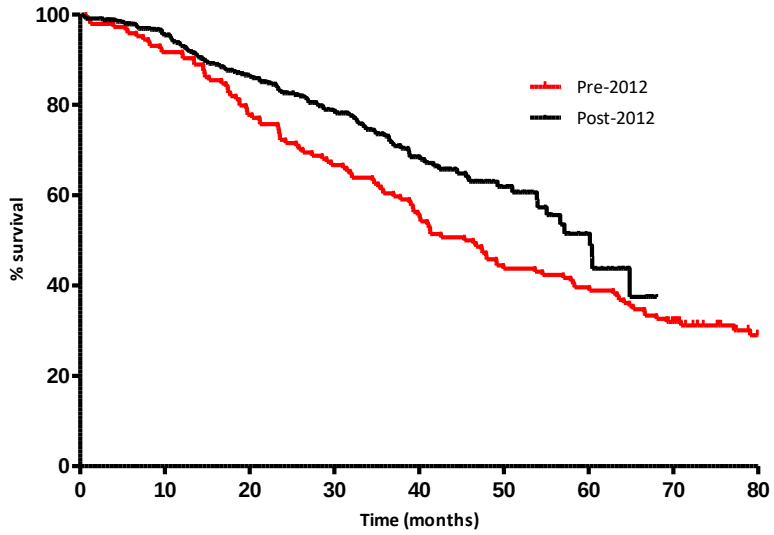


USA





Median 17 hospital attendances prior to diagnosis!
Median 3 hospital IP episodes prior to diagnosis



Pre-2012	Histological Diagnosis (usually EMB)	Median survival 46 months
Post-2012	~70% Non-Invasive Diagnosis	Median survival 60 months

Lane *et al,* Circulation 2019;140:16-26
Lousada, *et al. JACC* 2018;71:11(Abstract)

Avoiding misdiagnosis of a treatable hereditary neuropathy

49 of 150 hATTR amyloid patients misdiagnosed

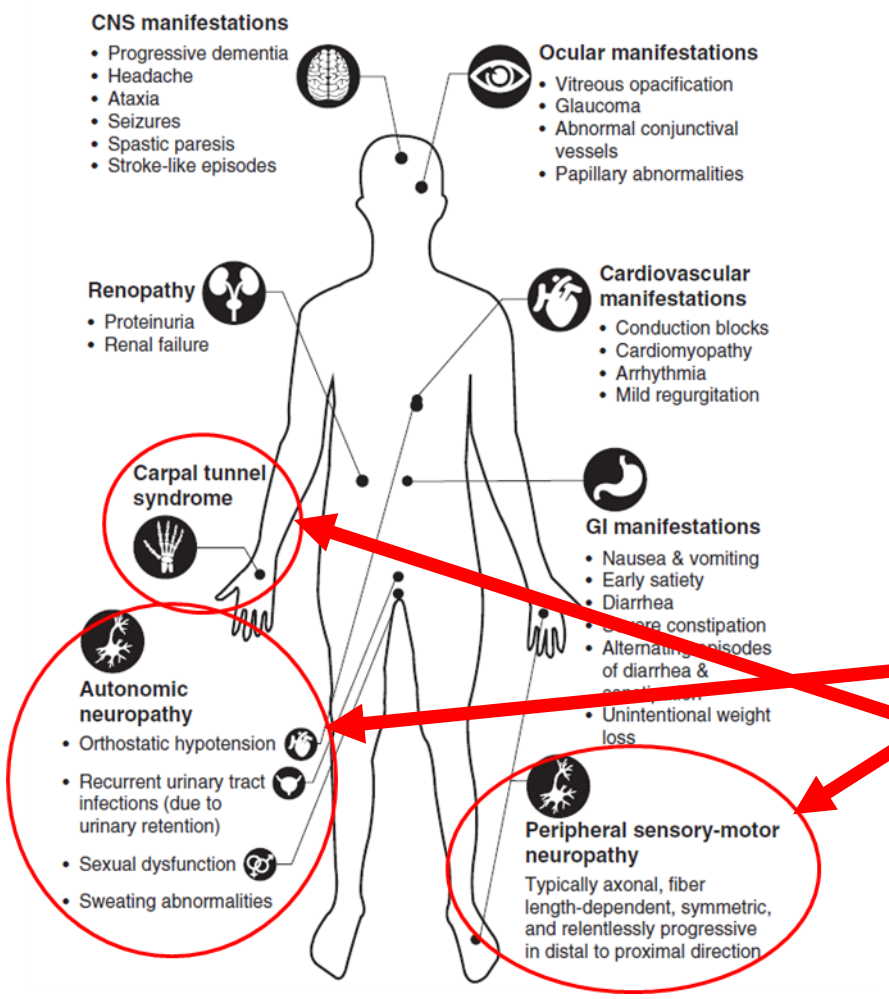
Average delay in diagnosis 2-6 years
Beware CIDP

Autonomic neuropathy
Cardiomyopathy
Family History
Irish origin

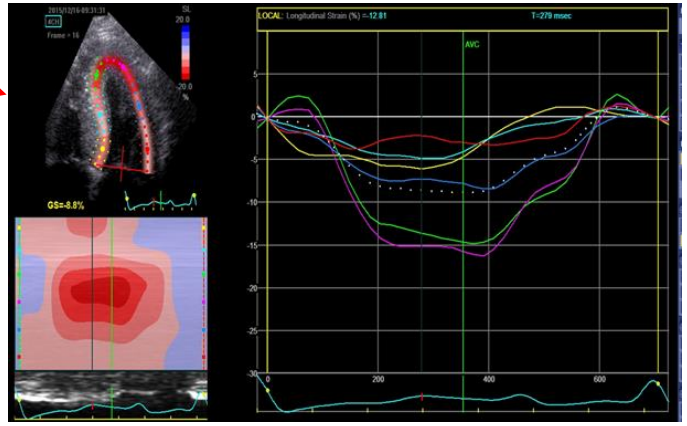
Plante-Bordeneuve V, Neurology 2007;69:693-698
Adams D *et al*, J Neurol 2020. doi: 10.1007/s00415-019-09688-0
Cortese A, J Neurol Neurosurg Psychiatry 2017;88:457-458

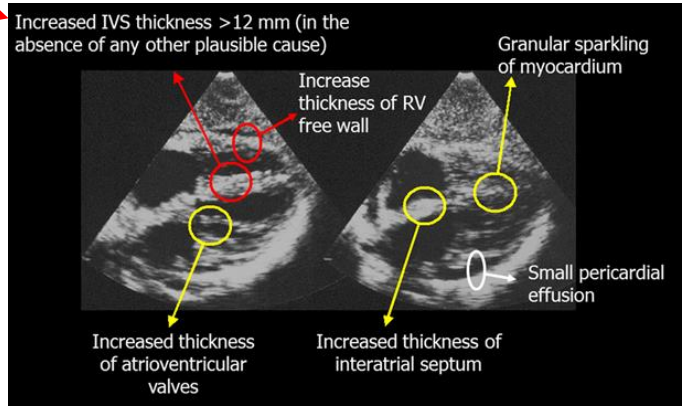
‘Red flags’ for early diagnosis of ATTR amyloidosis

Phenotypic spectrum of ATTR amyloidosis



- Reduction in longitudinal strain with apical sparing
- Discrepancy between left ventricular thickness and QRS voltage (with a lack of left ventricular hypertrophy on EKG)
- Atrioventricular block, in the presence of increased left ventricular wall thickness
- Echocardiographic hypertrophic phenotype with associated infiltrative features, including increased thickness of the atrioventricular valves, interatrial septum and right ventricular free wall
- Marked extracellular volume expansion, abnormal nulling time for the myocardium or diffuse late gadolinium enhancement on CMR
- Symptoms of polyneuropathy and / or dysautonomia
- History of bilateral carpal tunnel syndrome
- Mild increase in troponin levels on repeated occasions



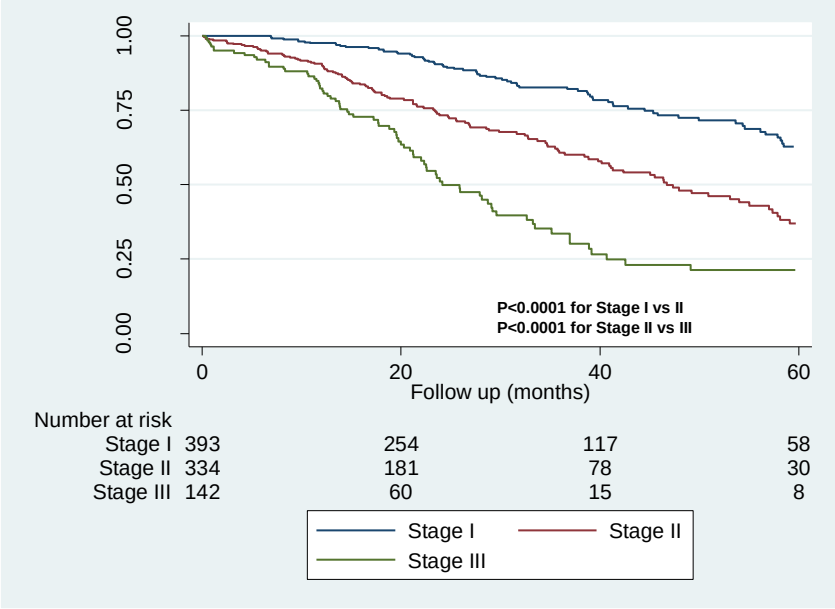


Conceição I, *et al.* J Peripher Nerv Syst 2016;21(1):5–9;
Witteles RM, *et al.* JACC Heart Fail 2019;7(8):709–716

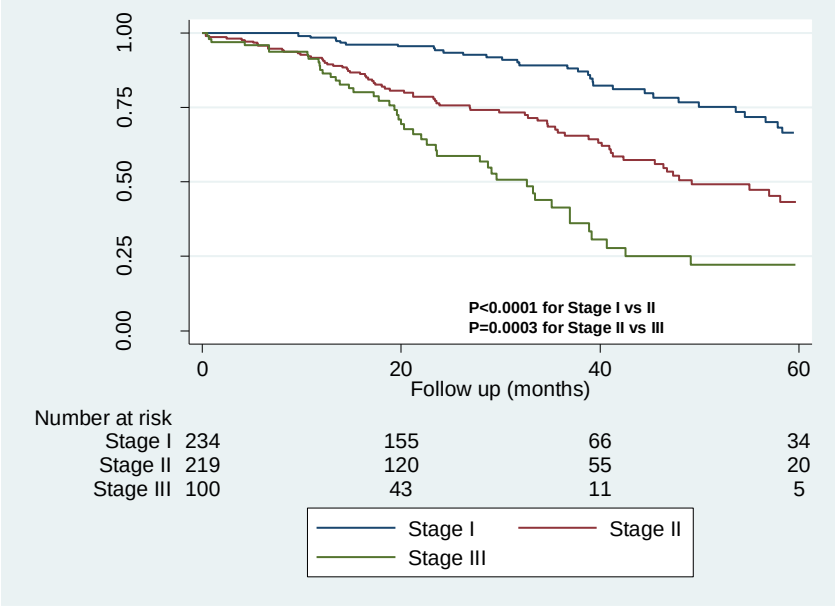
Staging of cardiac ATTR amyloidosis

NT-proBNP (3000ng/L) & eGFR (45ml/min)

All cardiac ATTR amyloidosis



Wild-type cardiac ATTR amyloidosis



	Stage I	Stage II	P value	Stage III	P value	Harrell's C
Number (Total = 869)	393 (45%)	334 (38%)		142 (16%)		
Median survival (months)	69.2	46.7		24.1		
Cox Regression: HR (95% CI)	1	2.05 (1.54-2.72)	<0.001	3.80 (2.73-5.28)	<0.001	0.69

	Stage I	Stage II	P value	Stage III	P value	Harrell's C
Number (Total = 553)	234 (42%)	219 (40%)		100 (18%)		
Median survival (months)	Indeterminable	49.2		32.7		
Cox Regression: HR (95% CI)	1	2.26 (1.51-3.36)	<0.001	4.37 (2.80-6.83)	<0.001	0.70

Gillmore JD *et al,* Eur Heart J 2018;39:2799–2806

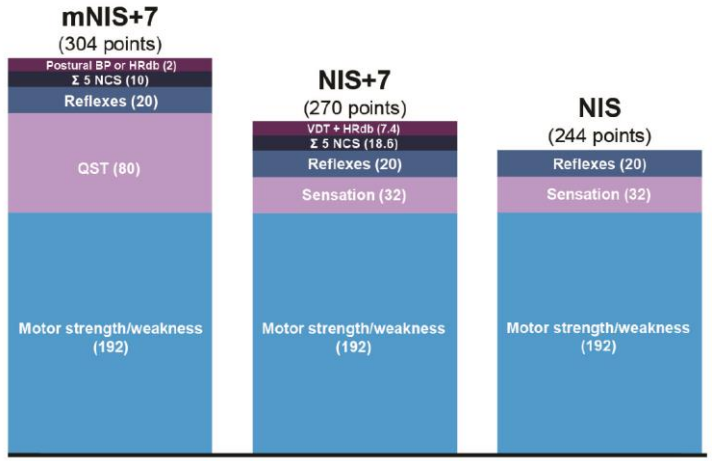
Staging Amyloid Neuropathy

Familial amyloid polyneuropathy (FAP) Stage (Coutinho *et al*, 1980)	**Polyneuropathy disability (PND) score** (Ando *et al*, 2013)
Stage 0: no symptoms	**Stage 0: no impairment**
Stage I: unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs	**Stage I**: sensory disturbances but preserved walking capability
	Stage II: impaired walking capability but ability to walk without a stick or crutches
Stage II: assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk	**Stage IIIA**: walking only with the help of one stick or crutch
	Stage IIIB: walking with the help of two sticks or crutches
Stage III: wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs	**Stage IV**: confined to a wheelchair or bedridden

- NIS and NIS-LL
  - *Sensory component minor (13%)*

- *NIS+7 and mNIS+7*
  - *Neurophysiology*
  - *Autonomic testing*

Clinical trials



Epidemiology of cardiac ATTR amyloid/amyloidosis

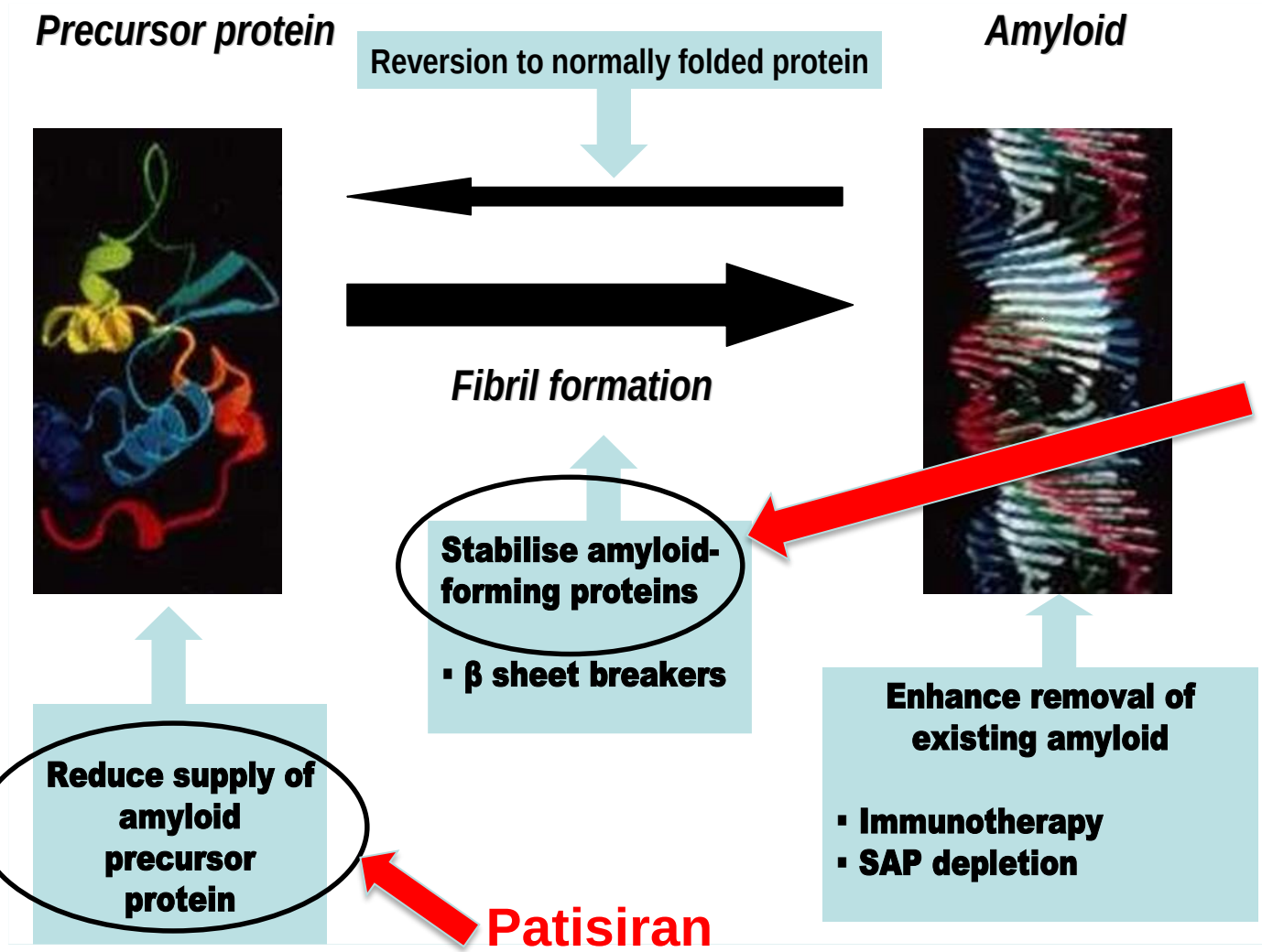
Recent/Emerging data…

Method of identification	Age	Percentage positive	Country
DPD positive	>30 years	<0.1%	South Korea[1]
DPD positive	>70 years	0.4%	South Korea[1]
Grade 2/3 DPD positive	>75 years	2.8% (4% males)	Spain[2]
Grade 2/3 DPD positive	>85 years	14%	Spain[2]
ATTR-CM among admissions with HF	>60 years	4%	Spain[3]
PYP +ve undergoing TAVR	All	16%	USA[4]

Note: Different methods of identification

[1]Kim HM *et al,* Int Heart J 2019;60:643–647
[2]Mohamed-Salem L *et al,* Int J Cardiol 2018;270:192–196
[3]Lopez-Sainz A *et al,* Amyloid 2019;26:156–163
[4]Castano A *et al,* Eur Heart J 2017;38:2879–2887

Disease-modifying treatment strategies in (ATTR) amyloidosis



Summary

- Cardiac ATTR amyloidosis (ATTR-CM) is an increasingly recognized cause of HF in individuals over age 50 years
  - True prevalence remains uncertain
- Non-biopsy diagnosis possible in ~70% patients with ATTR-CM
  - Diagnostic delays persist
  - Need earlier diagnosis (awareness & red flags!)
- ATTR-CM can easily be ‘Staged’ on the basis of eGFR and NT-proBNP
- Expanding treatment possibilities for patients with ATTR-CM

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Danny McCool

Histology
Janet Gilbertson

Genetics
Dorota Rowczenio
Hadija Trojer
Ania Zaremba

Statistics
Aviva Petrie

Agenda

Program	Speakers
Low-dose infigratinib (FGFRi) for achondroplasia	Introduction: Dr. Susan Moran, M.D., M.S.C.E. Presenter: Dr. Ravi Savarirayan, M.D., Ph.D.
Acoramidis: TTR stabilizer for ATTR	Introduction: Dr. Jonathan Fox, M.D., Ph.D. Presenter: Professor Julian D. Gillmore, M.D., Ph.D.
Gene therapy for congenital adrenal hyperplasia (BBP-631)	Introduction: Dr. Eric David, M.D., J.D. Presenter: Dr. Kyriakie Sarafoglou, M.D.
Encaleret: CaSR inhibitor for autosomal dominant hypocalcemia type 1 (ADH1)	Introduction: Dr. Jonathan Fox, M.D., Ph.D. Presenter: Dr. Michael Collins, M.D.
Targeted oncology	Introduction: Dr. Eli Wallace, Ph.D. Presenter: Frank McCormick, Ph.D.
Q&A	Moderator: Christine Siu Speakers: All
Conclusion	Neil Kumar, Ph.D.

Pipeline

BBP-631: AAV5 for CAH (IND-enabling)
IND anticipated in 2020

BBP-812: AAV9 for Canavan Disease
IND anticipated in 2020

BBP-815: AAV for TMC1 hearing loss

Multiple undisclosed discovery programs

BridgeBio's Gene Therapy Programs and Capabilities

- Collaborations with leading gene therapy pioneers
- In-house research vector manufacturing and optimization
- Best-in-class CMC, process development, and analytical development team
- Dedicated clinical/commercial manufacturing space at Catalent
- Leading clinical, non-clinical and regulatory team, with significant gene therapy experience

BBP-631: AAV5 gene therapy for congenital adrenal hyperplasia (CAH)

Program overview

Prevalence

75,000 (US+EU) – One of the largest known AAV gene therapy markets

Genetic driver

21-hydroxylase inactivation

Pathophysiology

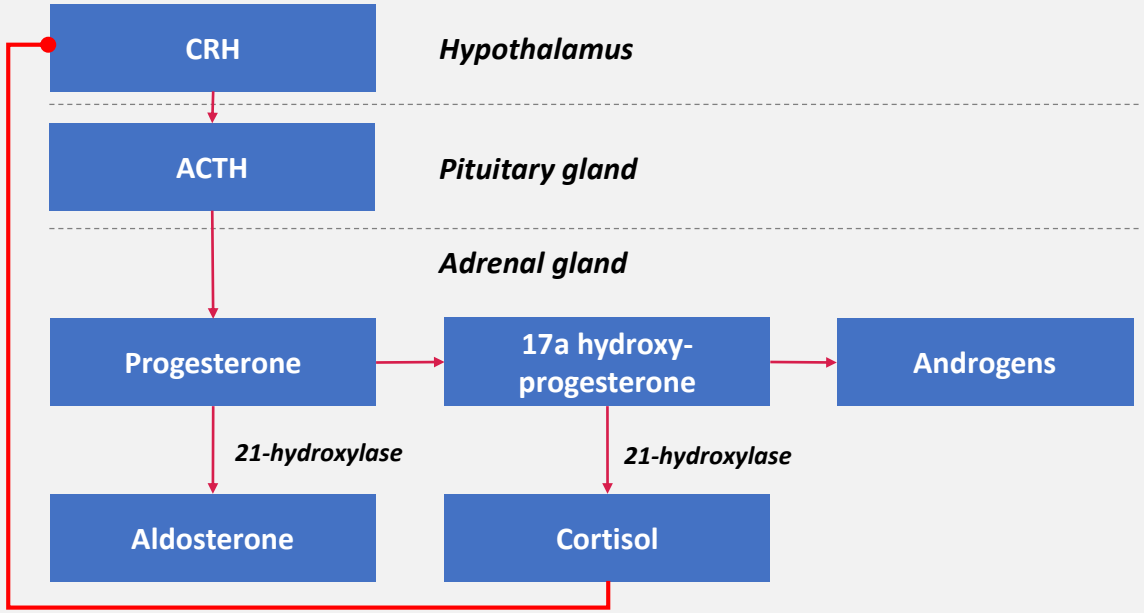
Inability to produce cortisol causes need for supraphysiologic doses of synthetic steroids, 3x increase in mortality risk, hirsutism, Cushingoid symptoms

We believe CAH is an ideal indication for AAV gene therapy:

- **Low threshold to correct phenotype**, validated by human clinical genetics (~5-10% of WT enzyme activity)
- **Only approach designed to induce endogenous cortisol and mineralocorticoid production**, potentially allowing steroid withdrawal
- **Durable transgene delivery to the adrenal gland of NHPs** with IV dosing of our construct
- **Preliminary Ph1/2 data anticipated in 2021** with endogenous cortisol production as a key endpoint

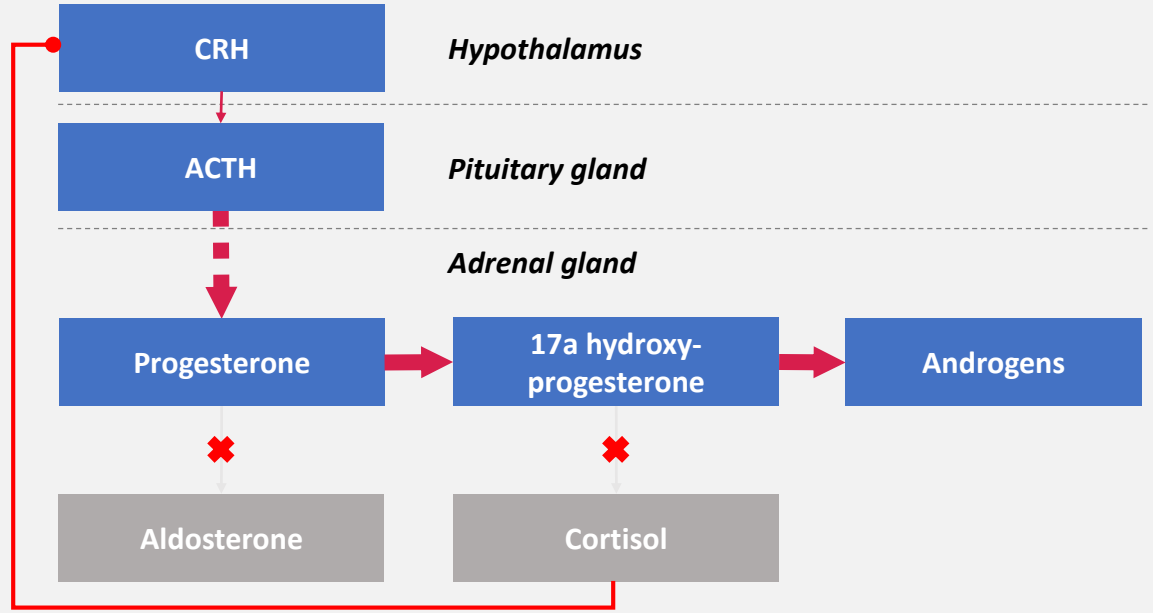
Gene therapy is the only modality designed to treat CAH at its source and allow for production of endogenous cortisol

Healthy Hypothalamic-Pituitary-Adrenal Axis



In a functional HPA system, cortisol and aldosterone are produced as needed by the body. Cortisol serves as a “brake” on the CRF/ACTH system

Hormonal dysregulation with 21OHD; no cortisol “brake” on ACTH, shunting of 17OHP to androgens

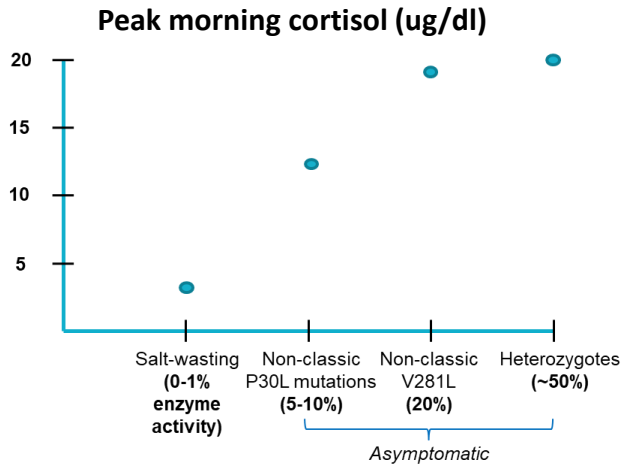


In CAH, cortisol and aldosterone are not able to be produced. The lack of a “cortisol brake” results in buildup of progesterone and 17OHP, leading to an excess of androgen production

CAH patients have 3-4X higher mortality than the general population, and suffer significant morbidity ranging across cardiovascular and metabolic disease, bone disease, infertility, chronic fatigue, and other disorders.

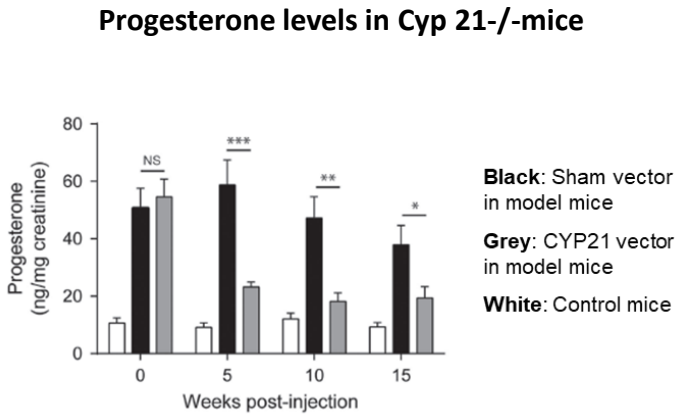
CAH: NHP study showed durable transgene expression; 5-10% of WT enzyme may be sufficient for clinical impact

Genotype-phenotype studies show that >5-10% of enzyme activity results in nonclassical CAH



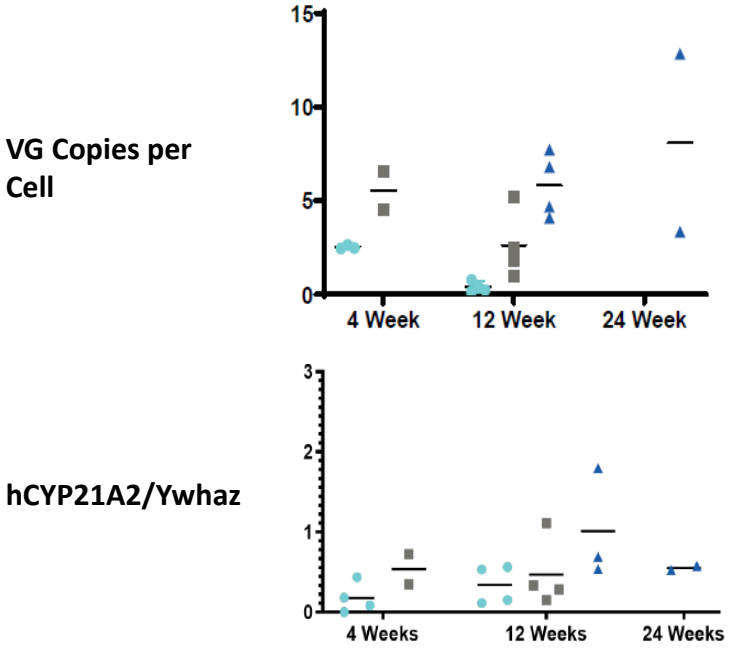
- Due to the high enzymatic efficiency/selectivity of 21-OHase, only a small amount of enzyme is required to rescue the phenotype

Mouse studies show a VGC of only 0.13 at 18 wks was sufficient for phenotypic correction



- At 15 weeks in treated mice, progesterone (the key substrate of 21OHase in mice) was significantly reduced vs untreated mice

NHP studies show sustained VGC and RNA out to 6 months

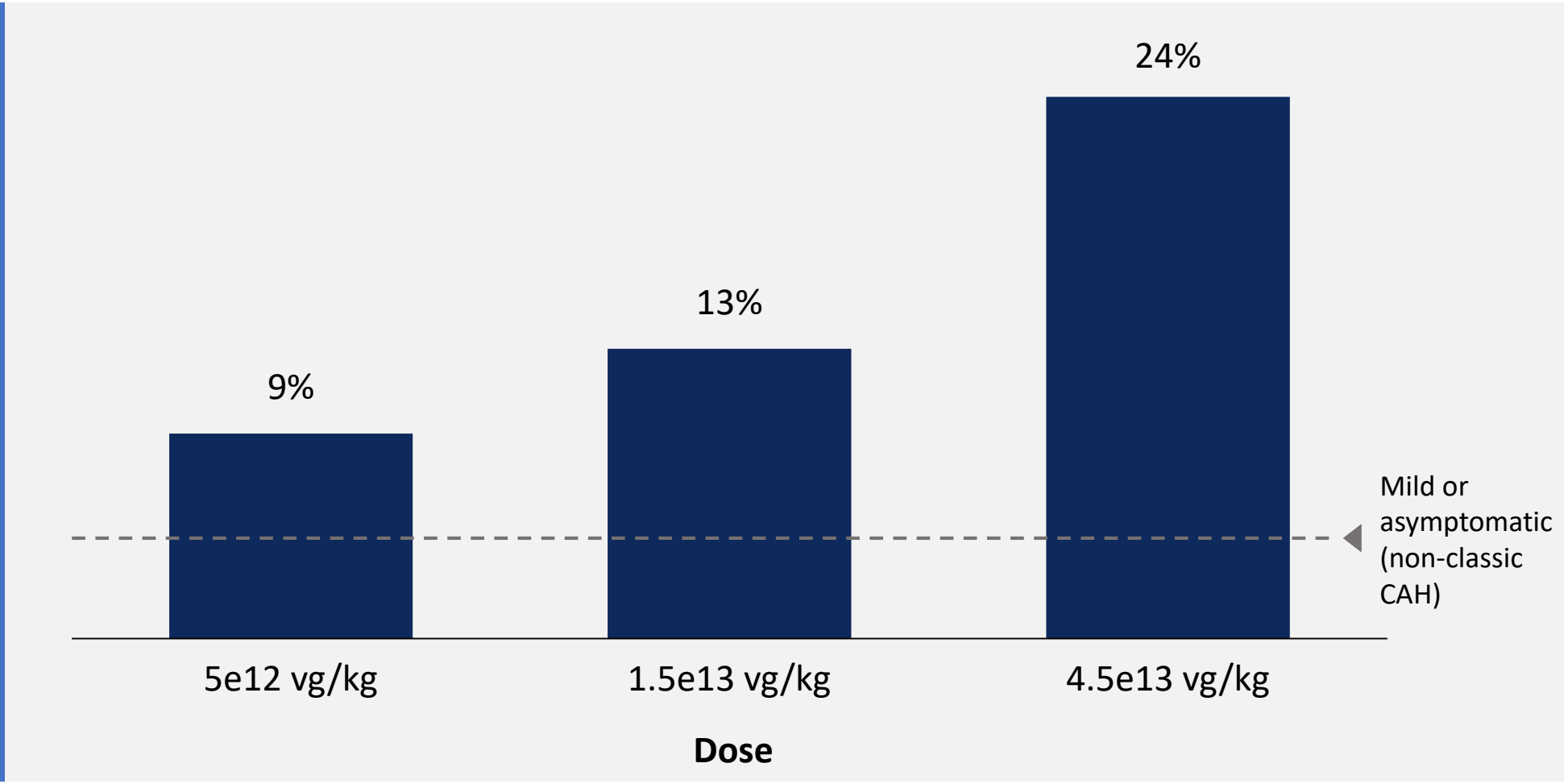


- Transgene expression is dose-dependent and stable out at 24 wks
- We can durably transduce the NHP adrenal gland with our construct at >20x the vector required to correct the CAH phenotype in mice

Source: Perdomini, Gene Therapy 2017; ESGCT 2019

NHP protein data using mass spec methods suggests potentially therapeutic levels of 21-hydroxylase enzyme

- We have developed mass-spec methods to quantify protein expression by identifying differential peptides between human and NHP 21-OH
- These data suggest dose-dependent enzyme expression in the adrenal cortex from 9%-24% of WT levels
- Genotype-phenotype relationship suggests as little as 5% of WT enzyme activity is associated with the mild/asymptomatic non-classic form of CAH



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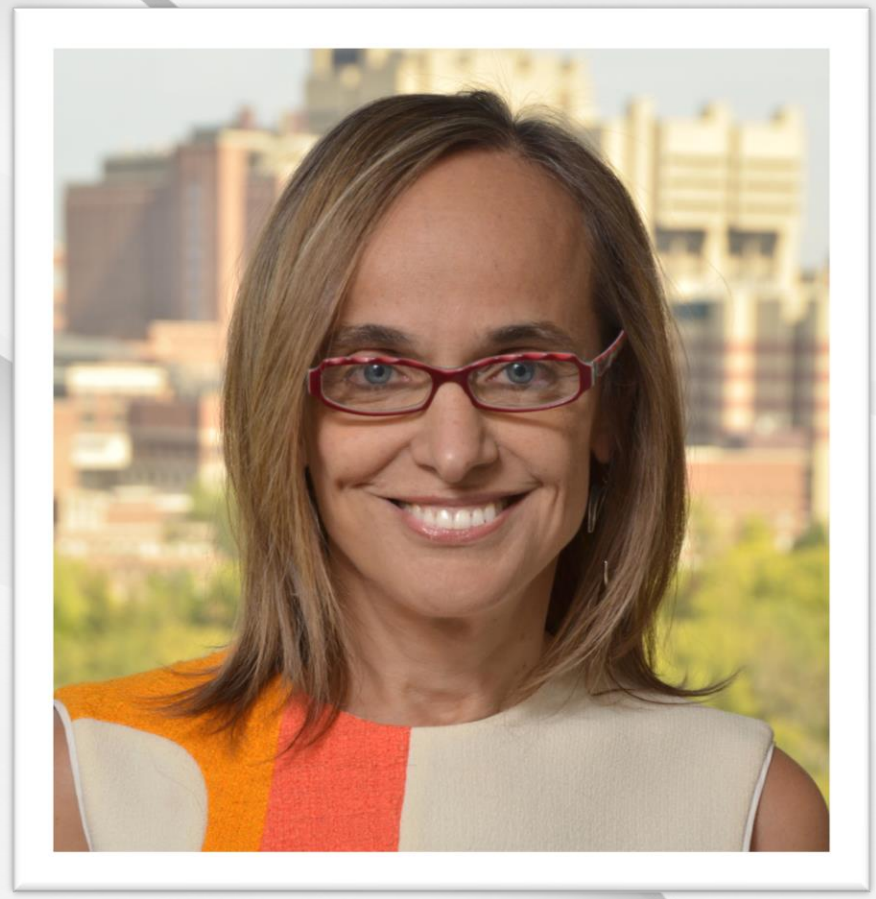


Kyriakie (Kiki) Sarafoglou, MD

- Associate Professor, Pediatrics, Endocrinology, Genetics & Metabolism at University of Minnesota Medical School, Experimental & Clinical Pharmacology at University of Minnesota College of Pharmacy
- Principal Investigator, BBP-631 CAH gene therapy trial
- Principal Investigator, crinecerfont adult and pediatric trials
- Principal Investigator, tildacerfont adult trials

BridgeBio R&D Day, September 29, 2020

Challenges in Treating Congenital Adrenal Hyperplasia: Opportunities For Improvement

Kyriakie Sarafoglou, M.D.
Associate Professor,
Dept. of Pediatrics - Divisions of Endocrinology and Genetics & Metabolism
Dept. of Experimental and Clinical Pharmacology | University of Minnesota

Director, Center for Congenital Adrenal Hyperplasia and Disorders of Sex Development | University of Minnesota Masonic Children's Hospital

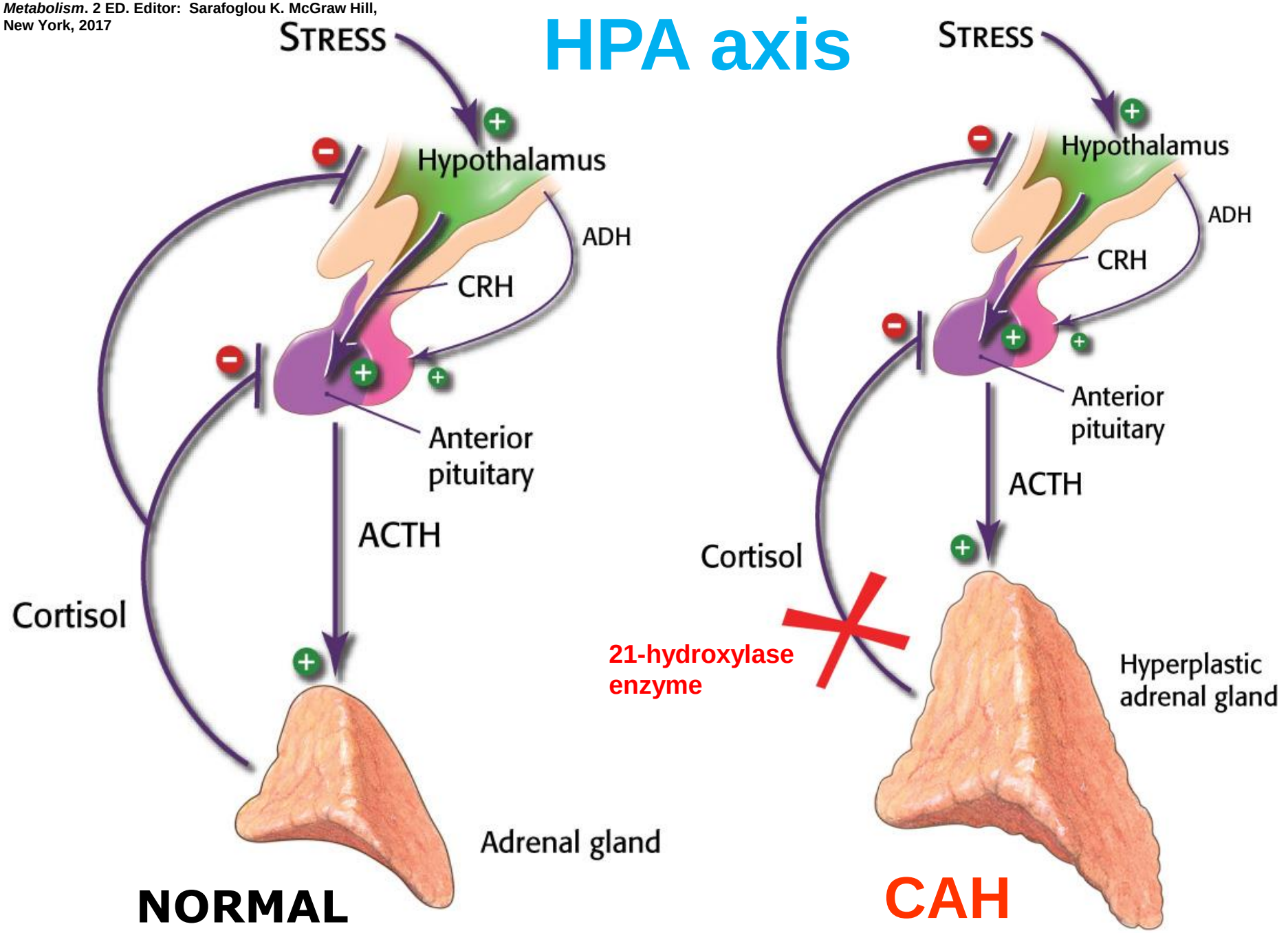
Congenital Adrenal Hyperplasia

TYPES OF CAH	OCCURRENCE	GENE	LOCUS
21α-Hydroxylase deficiency	90%	CYP21A2	6p21.3
11β-Hydroxylase deficiency	5%	CYP11B1	8q21
3β-Hydroxysteroid dehydrogenase II deficiency	Rare	HSD3B2	1p13.1
17α-Hydroxylase/17,20-lyase deficiency	Rare	CYP17	10q24.3
Congenital lipoid adrenal hyperplasia	Very rare	StAR, CYP11A	8p11.2
P450 oxidoreductase deficiency	Very rare	POR	7q11.2

Classic CAH due to 21-hydroxylase deficiency (21-OHD)

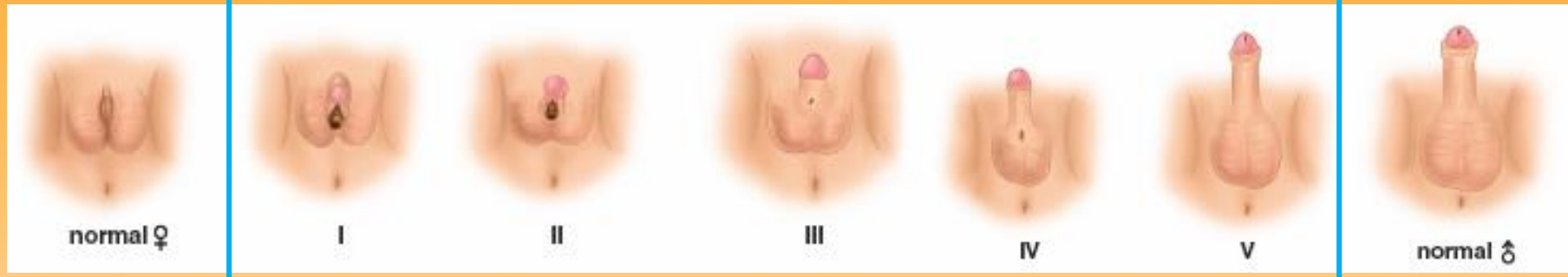
- Impaired cortisol synthesis
- Excess production of androgens
- Salt-wasting in 75% of cases of 21-OHD due to aldosterone deficiency

HPA axis



Degree of male appearing genitalia in female newborns with CAH

Typical Female



Typical Male

* © *Pediatric Endocrinology and Inborn Errors of Metabolism*. 2nd Edition. Editor: Sarafoglou K McGraw Hill, New York, 2017

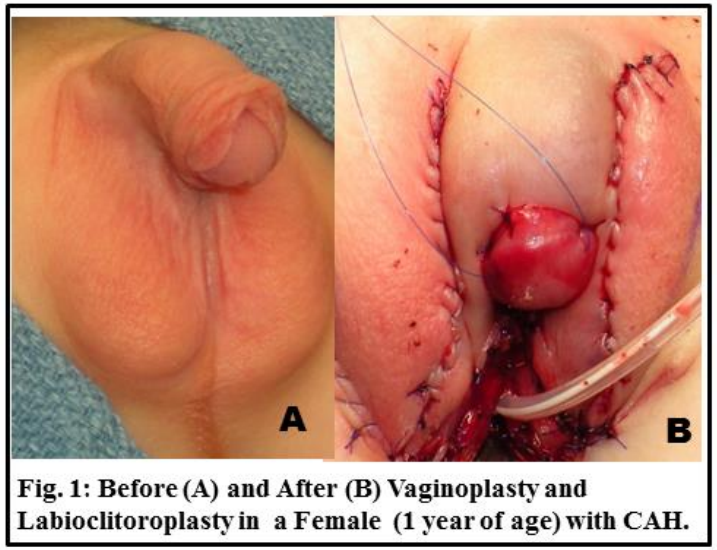


Fig. 1: Before (A) and After (B) Vaginoplasty and Labioclitoroplasty in a Female (1 year of age) with CAH.

CAH is the leading cause of atypical genitalia in the female newborn

Overview of CAH due to 21-OHD

- Classic forms (salt-wasting, simple-virilizing) requires life-long cortisol replacement with glucocorticoids
  - Mineralocorticoid treatment if salt-wasting present
- If untreated, classic CAH can lead to
  - Life threatening salt-wasting and/or adrenal crisis
  - Excess androgen production during newborn/childhood
    - Continued virilization in both sexes
    - Precocious puberty
    - Short stature due to early closure of epiphysis and growth plate
      - e.g. child stops growing at 8-9 years with an adult appearing physique

Diagnosis of CAH due to 21-OHD

- Classic form is typically identified by newborn screening
  - 4 million infants screened each year for CAH in U.S. by state newborn screening programs
- Diagnostic confirmation
  - If identified by NBS, diagnosis is confirmed by measurement of 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenendione (D4A) and testosterone.
- Molecular testing:
    - Excellent phenotype-genotype correlations

Current Treatment

- Childhood
  - Hydrocortisone
    - Short-acting glucocorticoid
    - Frequency: 3 times per day
    - Less negative effect on growth
- Adulthood
  - Long-acting steroids 1-2 times per day
    - Dexamethasone
    - Prednisone

Monitoring treatment in CAH

- **Treatment evaluated by measuring**
  - 17-hydroxyprogesterone (17OHP)
  - Androgens (androstenedione, testosterone)
  - Plasma renin activity *(in the salt-wasting form)*
  - Electrolytes *(in the salt-wasting form)*
  - Cortisol
  - Adrenocorticotropic hormone (ACTH)

Monitoring treatment of CAH

During childhood

- Weight gain
- Growth rate
- Skeletal maturation
- Signs of early puberty
- Blood pressure
- Genital virilization
- Sleep

During adulthood

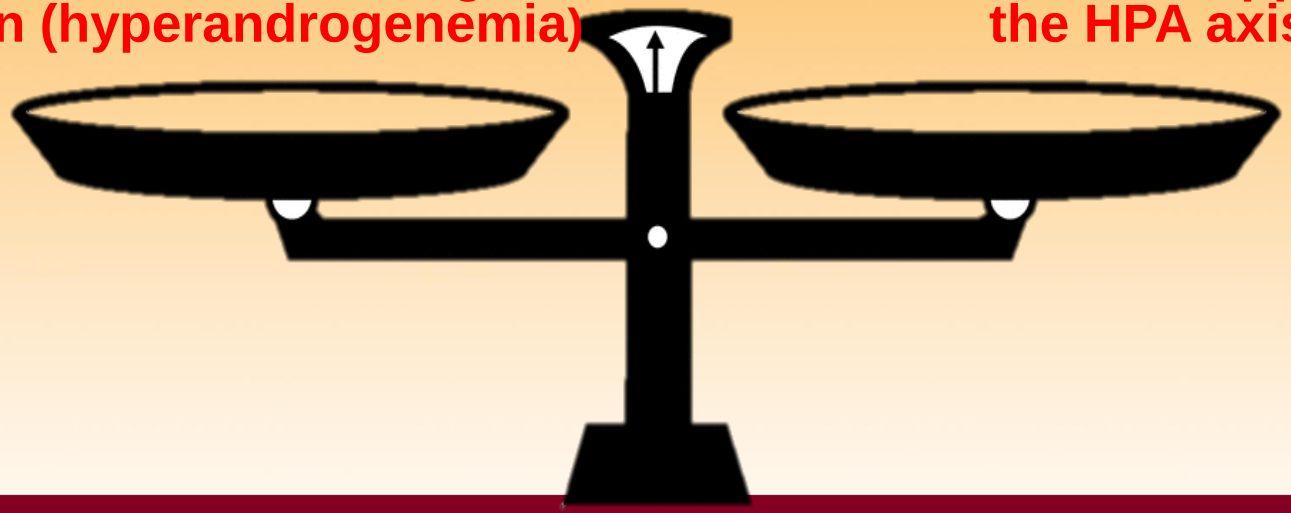
- Weight gain
- Blood pressure
- Quality of Life measures
- Adrenal rests
- Polycystic ovarian syndrome
- Infertility
- Insulin resistance
- Bone density

Challenges in Treatment of CAH

- Therapy has not advanced in 60 years
- All patients go through alternating periods of hypocortisolemia and hypercortisolemia every day
- Physicians struggle with balancing act to avoid

Undertreatment (hypocortisolemia) that leads to excess androgen production (hyperandrogenemia)

Overtreatment (hypercortisolemia) that leads to oversuppression of the HPA axis



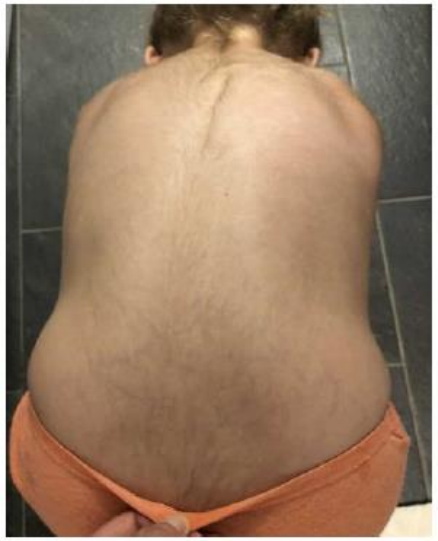
Challenges in Treatment of CAH

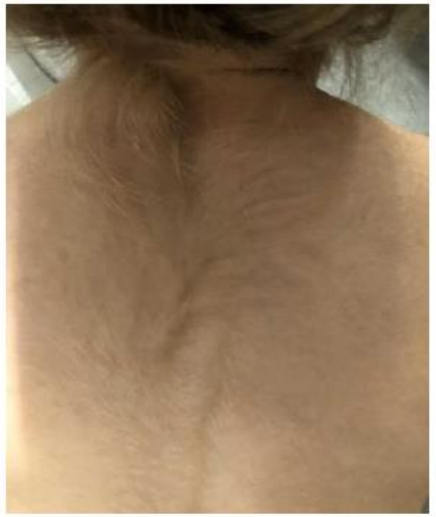
- Chronic **hypocortisolemia** can lead to:
  - Higher risk of salt-wasting and/or adrenal crisis
  - Excess production of androgens
  - Premature fusion of growth plates and short stature
  - Virilization
    - Increased body and face hair growth, acne
    - Genital virilization
  - Precocious puberty
  - Adrenal rests
  - Polycystic ovarian syndrome
  - Infertility
  - Insulin resistance
  - Endothelial dysfunction and cardiovascular disease

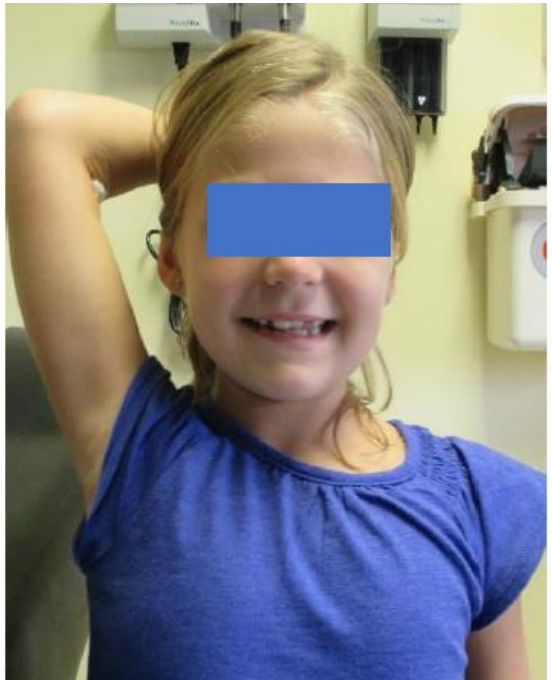
Challenges in Treatment of CAH

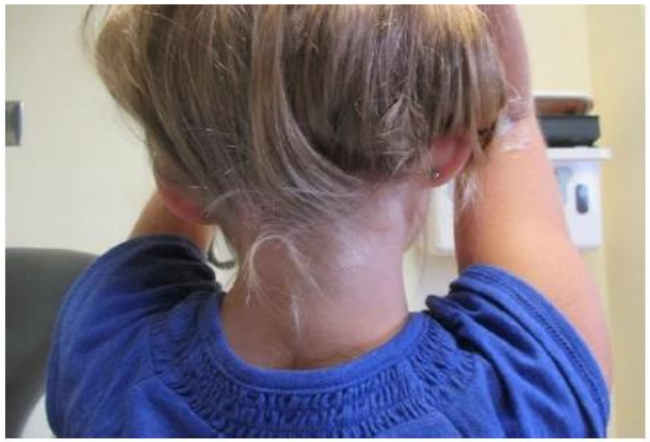
- Chronic **hypercortisolemia** can lead to:
  - Poor growth and short stature
  - Excess weight gain
  - Increased blood pressure
  - Decreased bone density
  - Cardiovascular disease
  - Increased morbidity
  - Depression
  - Iatrogenic Cushing syndrome

Overtreatment









Patient's previous treatment focused on suppressing androgens which caused glucocorticoid excess and iatrogenic Cushing syndrome.

Why is optimal treatment so hard to achieve?

- Current medication does not replicate physiological endogenous cortisol pulsatile secretion pattern
  - Circadian rhythm
  - Ultradian rhythm
- Hydrocortisone has a short half-life
- Long acting glucocorticoids can over suppress the HPA axis and lack pulsatility
- There is wide inter-individual variability of cortisol pharmacokinetics (PK) and the pharmacodynamic (PD) response to treatment.
- Keeping doses within cortisol's physiological range does not prevent adverse outcomes

Challenges in Treatment of CAH

- Hydrocortisone's short half life
  - Median elimination half-life in CAH children: 58 min (range: 41-105 min)
  - Most HC eliminated in 4-5 hours
- Sarafoglou K, Zimmerman CL, Gonzalez-Bolanos MT, Willis BA, Brundage R. Inter-relationships among cortisol, 17OHP and D4A exposures in the management of children with congenital adrenal hyperplasia. *Journal of Investigative Medicine*. 2015;63(1):35-41
  - Evening HC dose washes out over night resulting in unopposed ACTH-stimulated adrenal androgen production and significant hyperandrogenemia each morning
- Long acting glucocorticoids
  - Lack pulsatility and continuously deliver cortisol

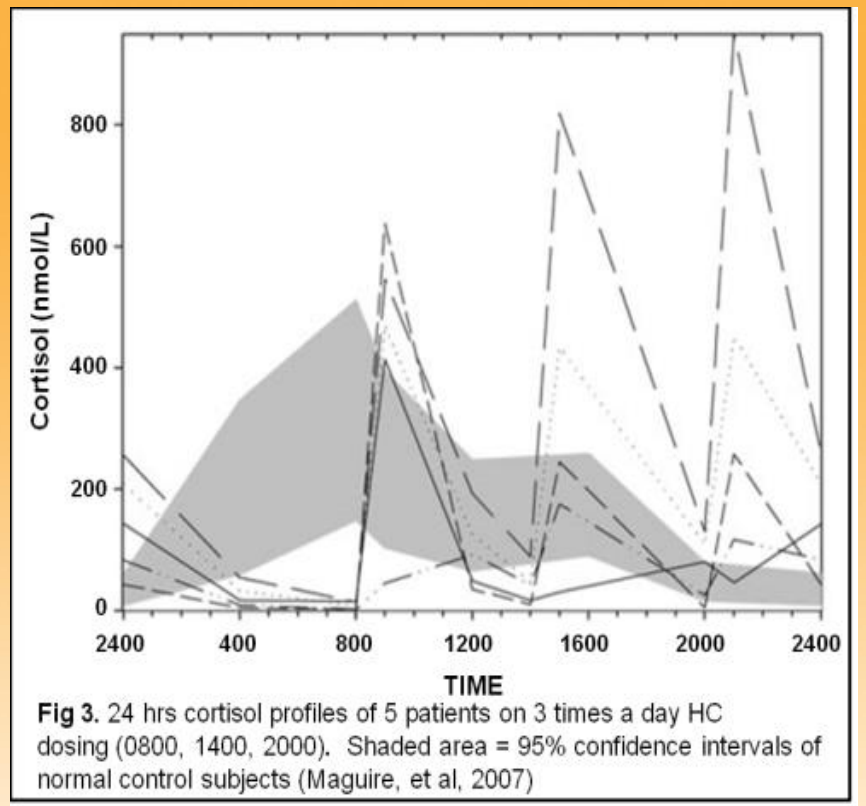
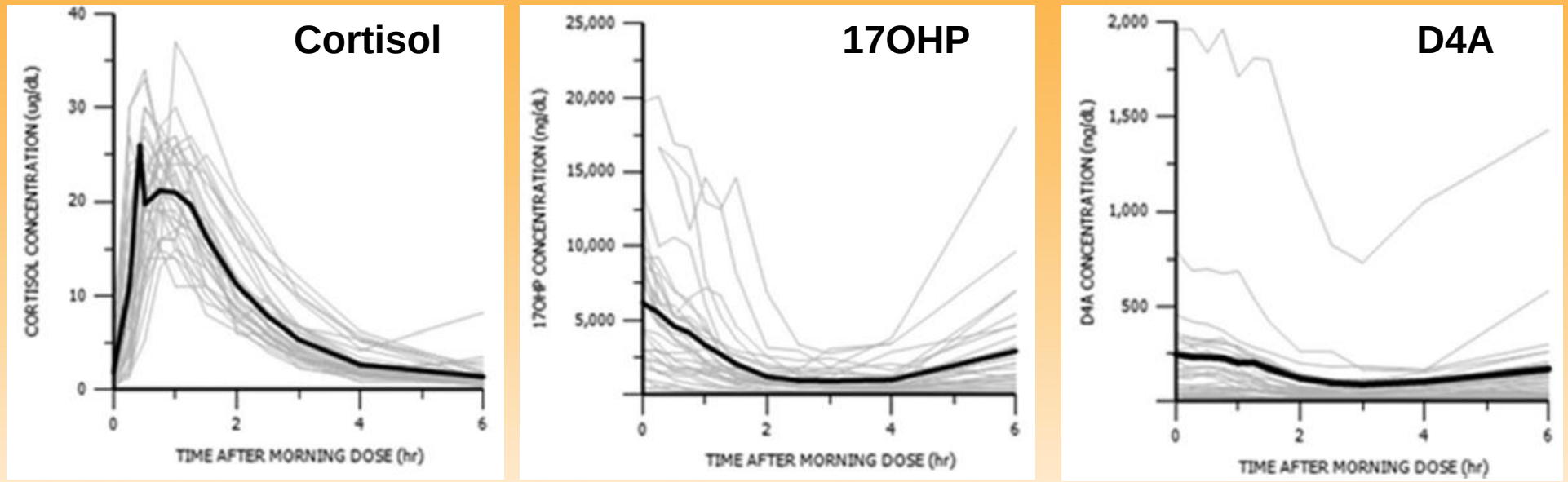


Fig 3. 24 hrs cortisol profiles of 5 patients on 3 times a day HC dosing (0800, 1400, 2000). Shaded area = 95% confidence intervals of normal control subjects (Maguire, et al, 2007)

Cortisol Pharmacokinetics – Pharmacodynamic Response



Pre and Post 6 hours after hydrocortisone dose

Sarafoglou K, Zimmerman CL, Gonzalez-Bolanos MT, Willis BA, Brundage R. Inter-relationships among cortisol, 17OHP and D4A exposures in the management of children with congenital adrenal hyperplasia. *Journal of Investigative Medicine*. 2015;63(1):35-41

Circadian and ultradian rhythms of cortisol secretion

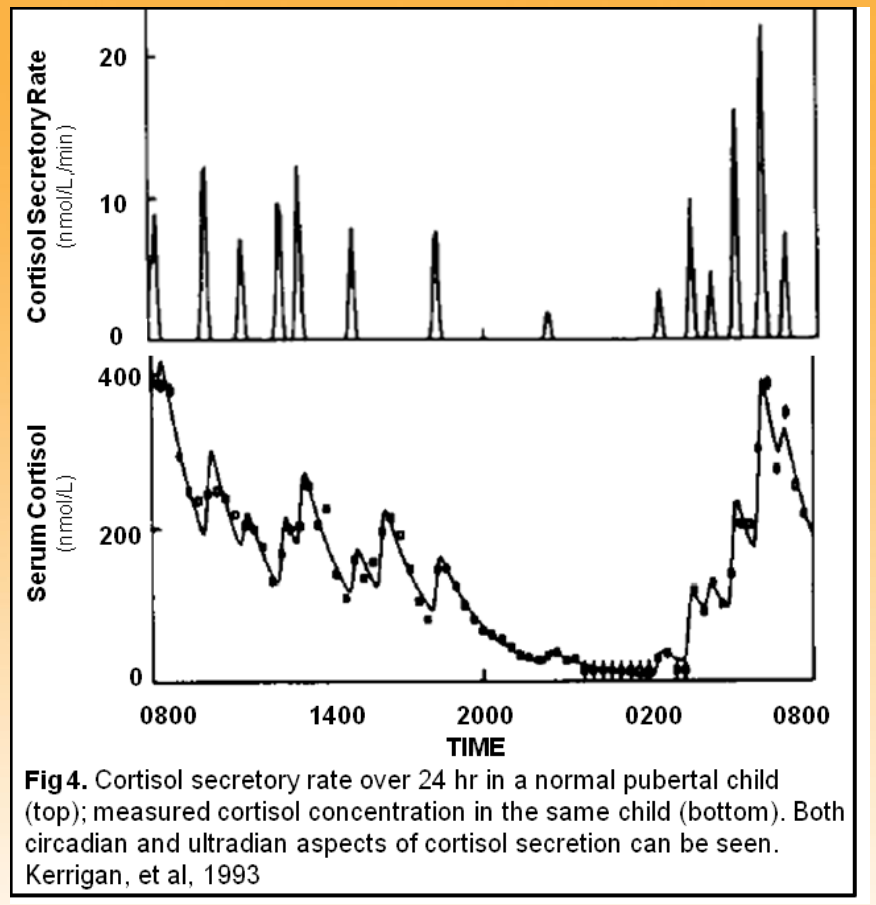


Fig 4. Cortisol secretory rate over 24 hr in a normal pubertal child (top); measured cortisol concentration in the same child (bottom). Both circadian and ultradian aspects of cortisol secretion can be seen. Kerrigan, et al, 1993

Endogenous cortisol secretion is **NOT** continuous

HPA axis is characterized by circadian rhythm derived by discrete pulses (ultradian rhythm) of ACTH and cortisol secretion every 80-110 mins.

Importance of endogenous cortisol pulsatility

- Gene regulation
- Non-genomic glucocorticoid signaling
- HPA axis regulation
- Endocrine and neuro behavioral responses
- Cardiovascular regulation
  - Stavreva DA, et al. Ultradian hormone stimulation induces glucocorticoid receptor-mediated pulses of gene transcription. Nature cell biology. Sep 2009;11(9):1093-1102.
  - Sarabdjitsingh RA, et al. Recovery from disrupted ultradian glucocorticoid rhythmicity reveals a dissociation between hormonal and behavioural stress responsiveness. Journal of neuroendocrinology. Aug 2010;22(8):862-871.
  - Russell GM, Lightman SL. Can side effects of steroid treatments be minimized by the temporal aspects of delivery method? Expert opinion on drug safety. Nov 2014;13(11):1501-1513.
- Pulsatile vs. continuous delivery of hormones have diametrically opposite results.
  - Pulsatile delivery of GnRH induces ovulation
  - Continuous delivery of GnRH results in anovulation and suppression of hypothalamic-pituitary-ovarian axis

Negative effect on growth even within physiological cortisol dosing

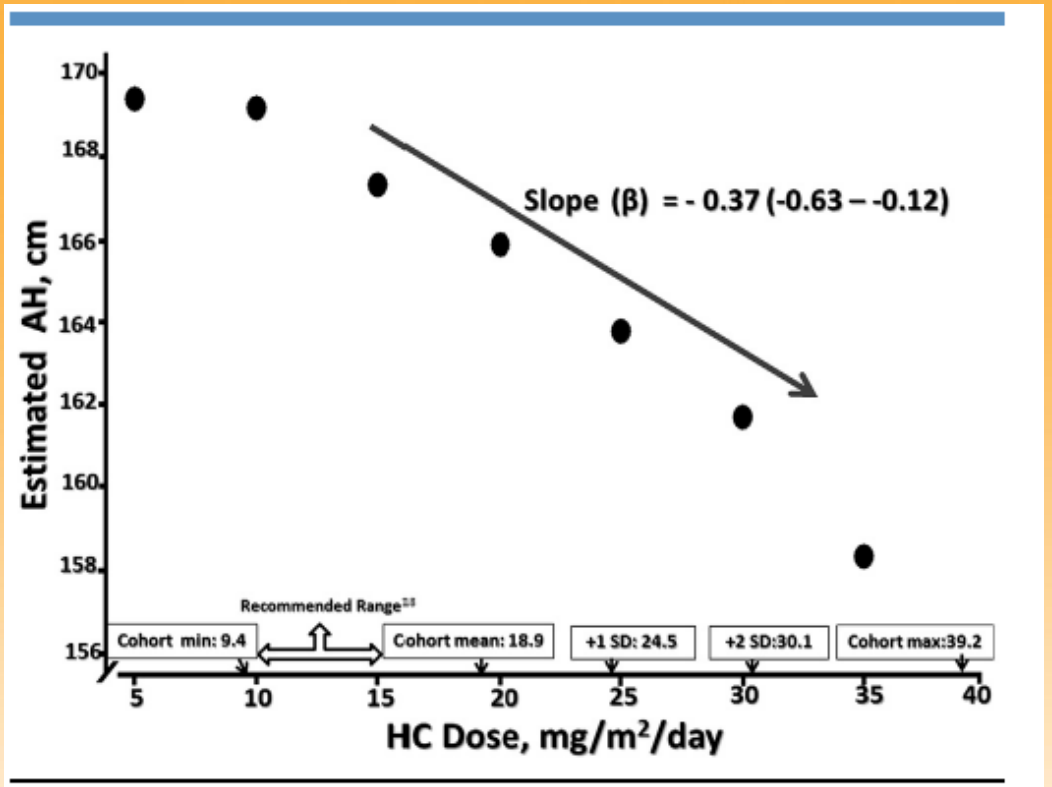
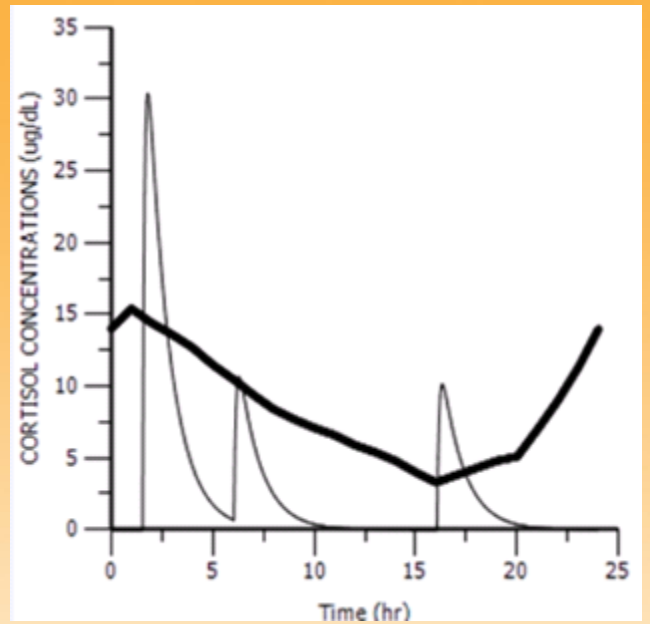


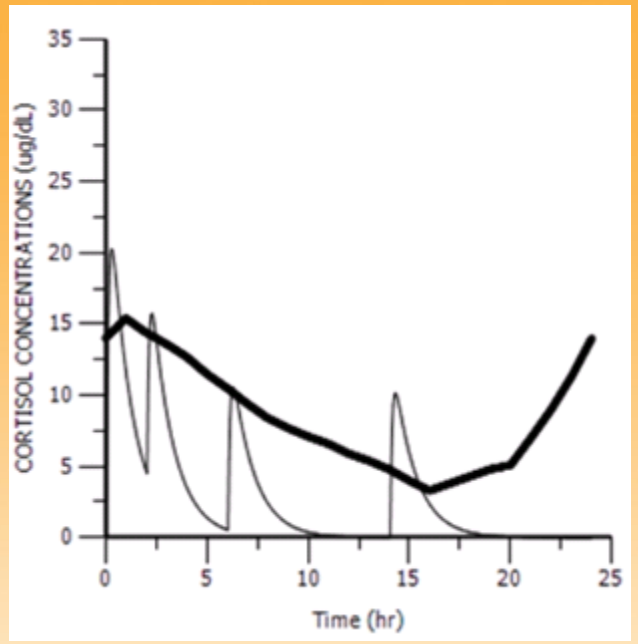
Figure. Association plots showing the dose-response relationship between growth period HC dose and PAH in the Minnesota CAH cohort (n = 104). Estimated PAH at minimum HC dose was ~169 cm. As the HC dose increased from 15 to 39.2 mg/m^2/day PAH progressively decreased from ~167.5 to 158 cm.

Sarafoglou K, Addo OY, Turcotte L, Otten N, Wickremasinghe A, Pittock S, Kyllo J, Lteif AN, Himes JH, Miller BS. Impact of hydrocortisone on adult height in congenital adrenal hyperplasia - the Minnesota cohort. *Journal of Pediatrics*. 2014 May;164(5):1141-1146

Increasing frequency of dosing still results in hypocortisolemia



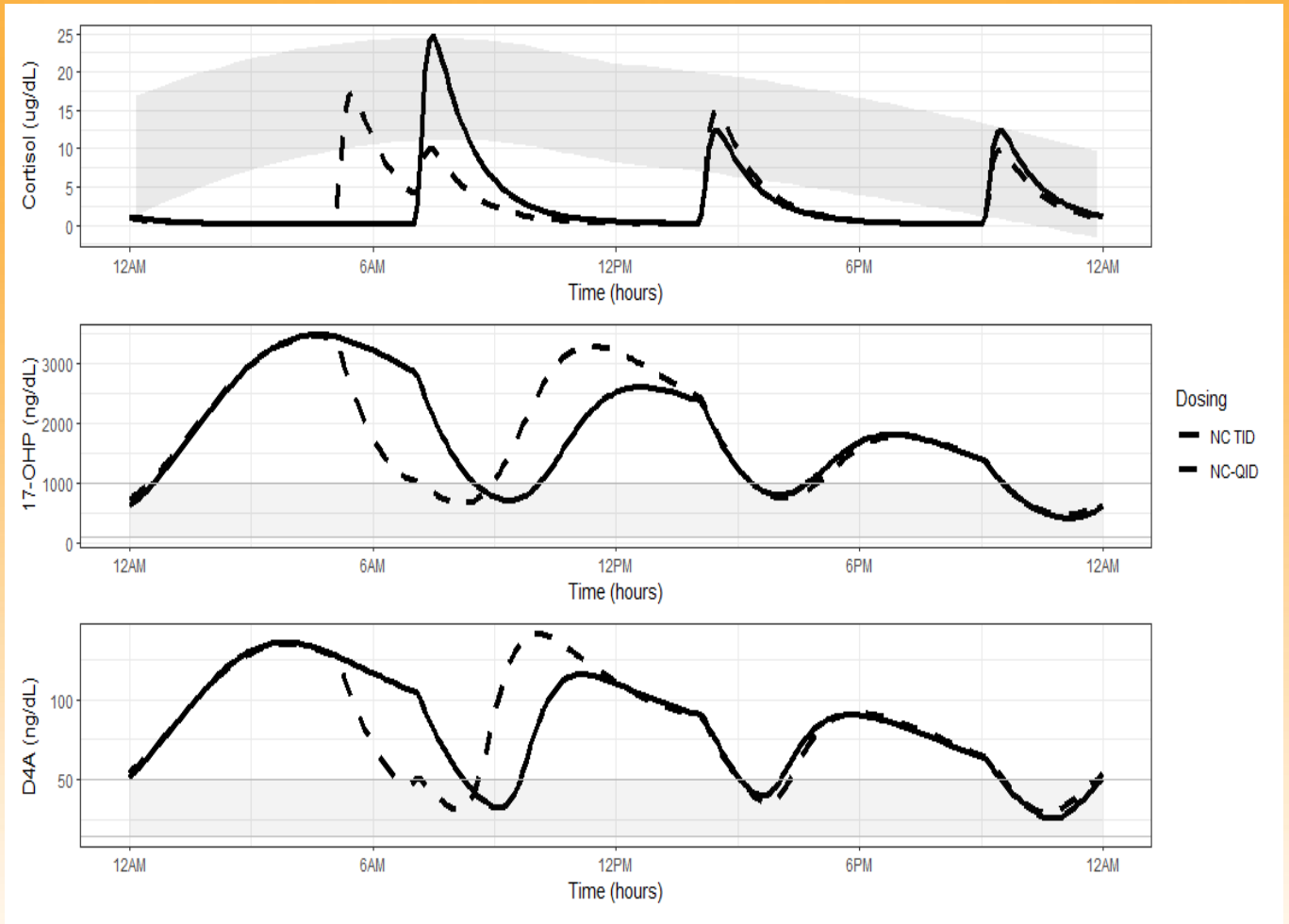
HC 3 x day



HC 4 x day
Split morning dose

Sarafoglou K, Zimmerman CL, Gonzalez-Bolanos MT, Willis BA, Brundage R. Inter-relationships among cortisol, 17OHP and D4A exposures in the management of children with congenital adrenal hyperplasia. *Journal of Investigative Medicine*. 2015;63(1):35-41

3-4 times a day dosing still results in elevated androgens throughout the day



Values simulated over 24 hours in 11 year old boy with physiologic HC dosing using PKPD modeling

Gray shade = normal ranges

Conclusion

- **Current therapy does not**
  - Reproduce endogenous cortisol production rates
  - Replicate circadian and ultradian cortisol secretion

- **Current therapy does**
  - Expose patients to alternating periods of hypo- and hypercortisolemia
  - Result in suboptimal short and long-term outcomes

Conclusion

- **What is needed to improve outcomes in CAH?**
  - Therapy that is based a patient's individual endogenous cortisol production rate
  - Therapy that takes into account a patient's individual glucocorticoid sensitivity
  - Therapy that replicates endogenous pulsatile and circadian cortisol secretion
  - Therapy that can increase endogenous cortisol production to respond to a patient's stress requirements during periods of illness, physical activity or trauma

Agenda

Program	Speakers
Low-dose infigratinib (FGFRi) for achondroplasia	Introduction: Dr. Susan Moran, M.D., M.S.C.E. Presenter: Dr. Ravi Savarirayan, M.D., Ph.D.
Acoramidis: TTR stabilizer for ATTR	Introduction: Dr. Jonathan Fox, M.D., Ph.D. Presenter: Professor Julian D. Gillmore, M.D., Ph.D.
Gene therapy for congenital adrenal hyperplasia (BBP-631)	Introduction: Dr. Eric David, M.D., J.D. Presenter: Dr. Kyriakie Sarafoglou, M.D.
Encaleret: CaSR inhibitor for autosomal dominant hypocalcemia type 1 (ADH1)	Introduction: Dr. Jonathan Fox, M.D., Ph.D. Presenter: Dr. Michael Collins, M.D.
Targeted oncology	Introduction: Dr. Eli Wallace, Ph.D. Presenter: Frank McCormick, Ph.D.
Q&A	Moderator: Christine Siu Speakers: All
Conclusion	Neil Kumar, Ph.D.

Encaleret for disorders of calcium homeostasis, including autosomal dominant hypocalcemia type 1 (ADH1)

Alexis and Jackson
ADH1 patients

Targets hypocalcemia/hypercalciuria by selectively antagonizing the calcium-sensing receptor (CaSR)

- Opportunity identified in collaboration with experts at the NIH

Prior clinical experience enables accelerated development

- Well tolerated in >1,200 human subjects excepting dose-dependent increases in serum calcium (target effect in ADH1 patients)
- Phase 2 study in ADH1 planned to initiate in 2020 with proof-of-concept data anticipated in 2021

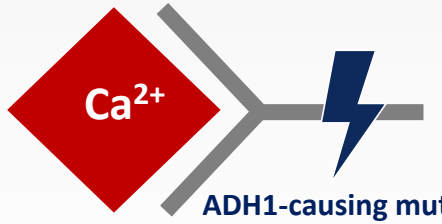
Potential 1st in class CaSR antagonist with differentiated profile for ADH1 and hypoparathyroidism

- Initial development in genetically-defined population of ADH1, driven by CaSR activating mutations (~12K carriers in US)
- Potential for expansion into post-surgical chronic hypoparathyroidism (~200K patients in US & EU)

Encaleret is designed to treat ADH1 at its source

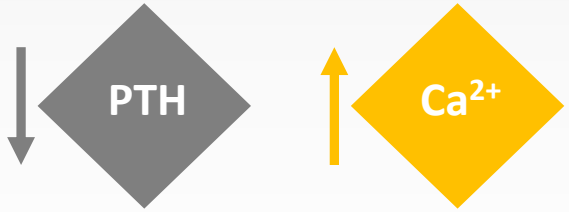
ADH1 disease mechanism

CaSR senses and regulates serum Ca levels

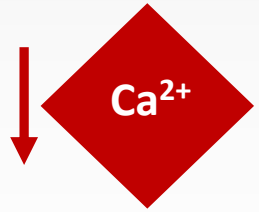


ADH1-causing mutations hyperactivate CaSR

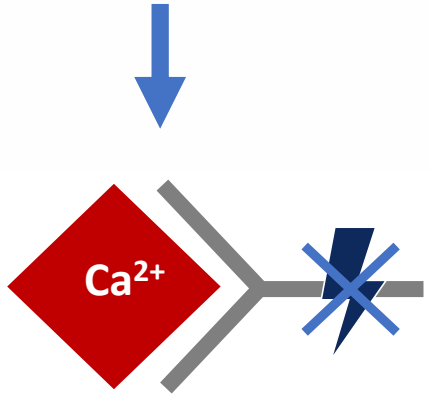
Hyperactive CaSR depresses PTH secretion and increases urinary Ca excretion



Serum Ca levels fall, requiring supplementation to prevent severe hypocalcemia



Therapeutic hypothesis



Encaleret is CaSR antagonist designed to stimulate PTH secretion, stabilize urinary Ca excretion, and increase serum Ca levels

The calcium sensing receptor (CaSR) primarily acts to regulate parathyroid hormone levels and renal calcium reabsorption

Illustration of parathyroid cell

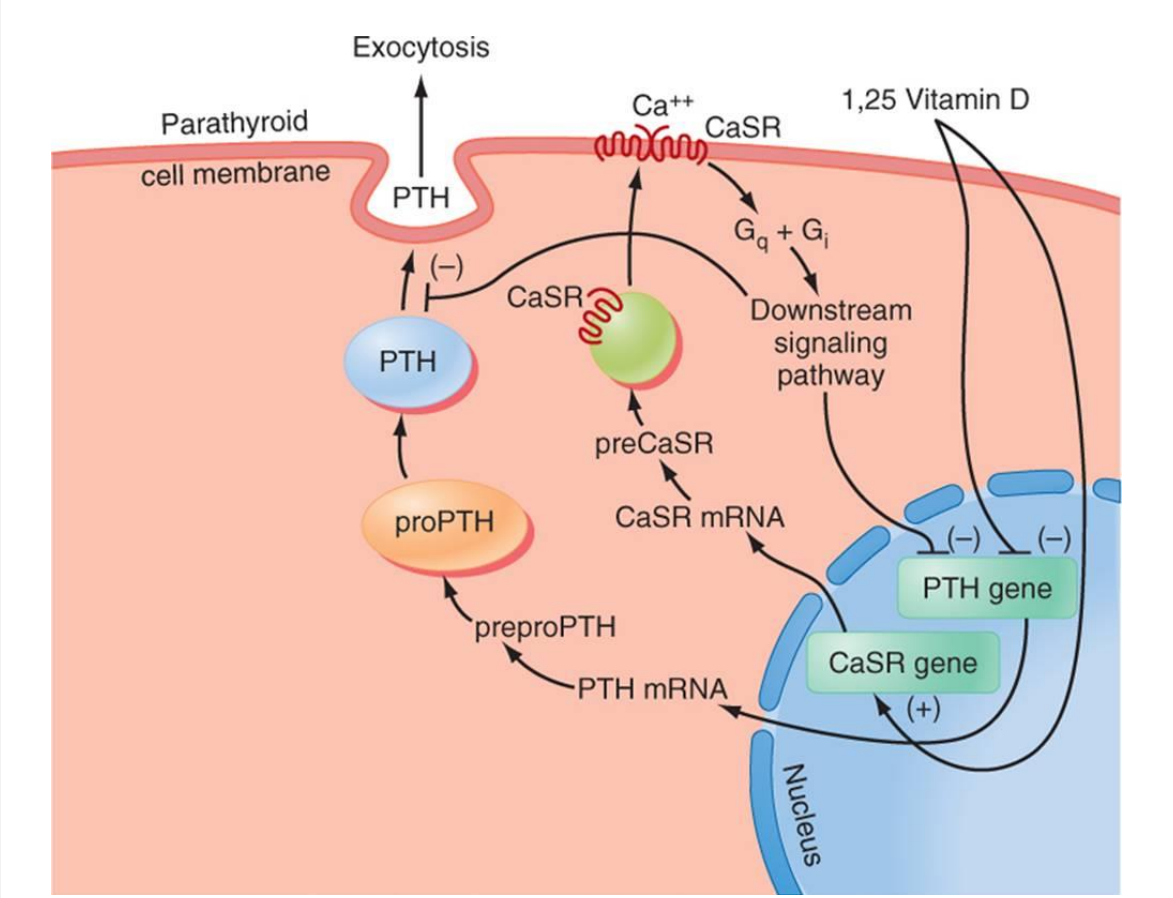
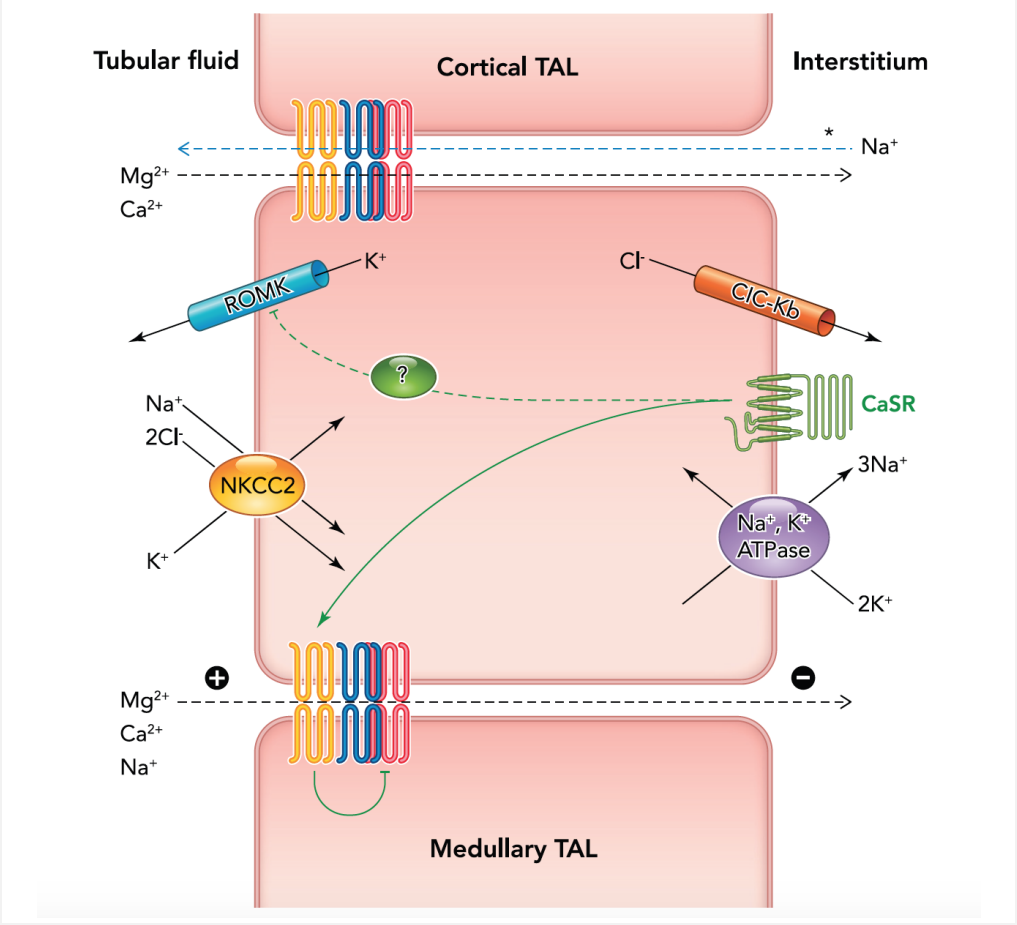


Illustration of renal tubule



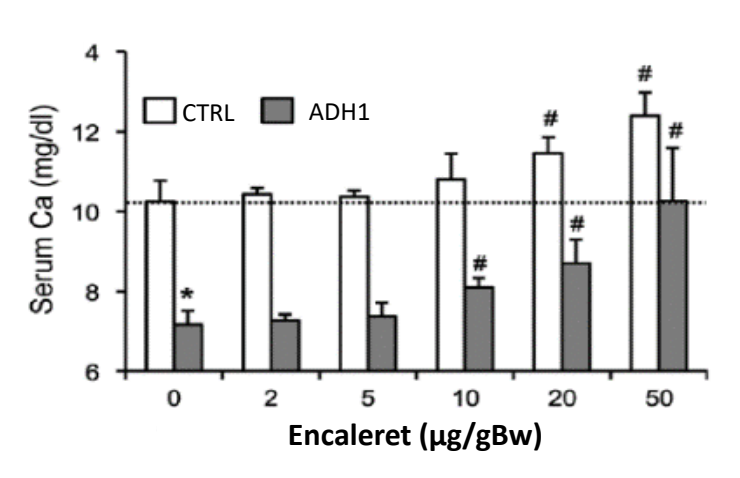
Source: 1 Berne and Levy Physiology, 6th ed. Chapter 39; 2 Toka, H.R., et al. Physiology. 2015.

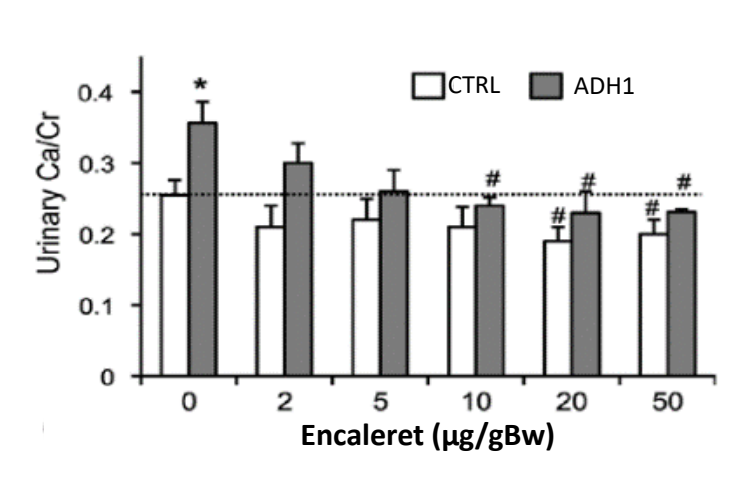
Encaleret is designed to target ADH1 at its source by normalizing hyper-active calcium sensing receptor

Rationale for studying CaSR inhibitor in ADH1

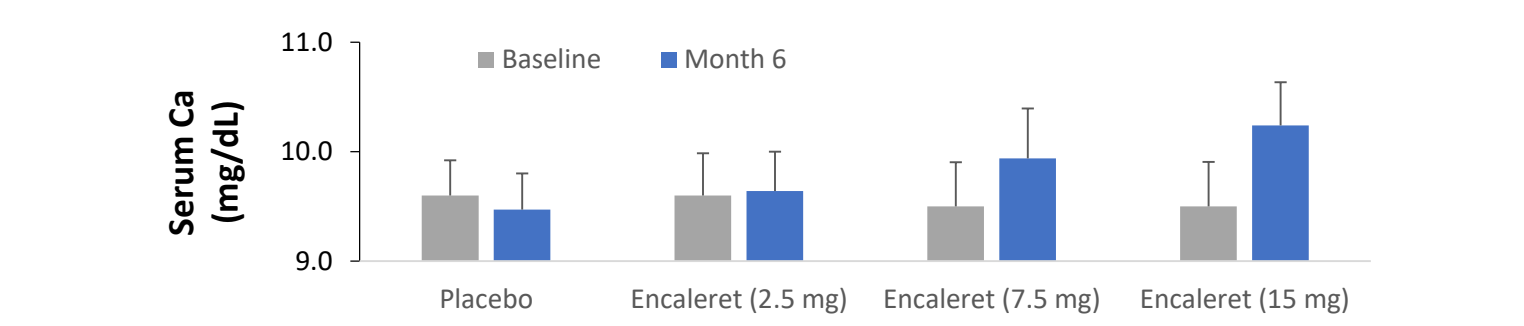
- ADH1 is caused by activating mutations in the CaSR leading to hypocalcemia and hypercalciuria
- Prior generation CaSR inhibitor partially addressed ADH1 phenotype despite limited exposure[1]

Encaleret normalized serum and urine calcium in a mouse model of ADH1[2]



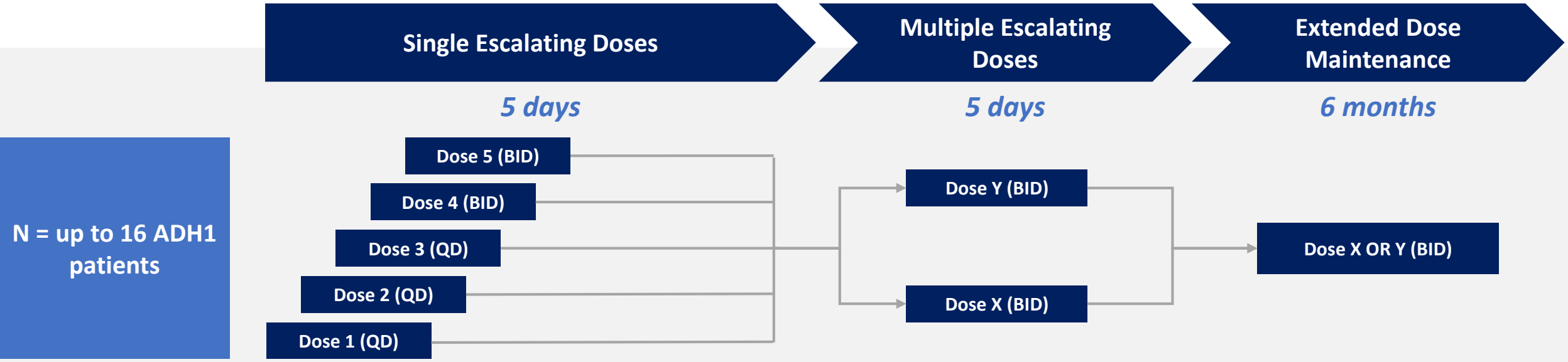


Encaleret increased serum calcium in clinical trials in patients with osteoporosis[3]



Source: 1 Roberts, M.S., et al. J Bone & Min 2019; 2 Dong B., et al. J Bone & Min 2015; 3 Data on file

Phase 2, open-label dose-ranging study will evaluate safety, tolerability, and efficacy of encaleret in ADH1



Top-line, proof-of-concept results of encaleret in ADH1 are anticipated in 2021

1 Pharmacodynamic measurements to be collected through duration of study

Michael Collins, MD

- Chief of the Skeletal Disorders and Mineral Homeostasis Section at the National Institutes of Health
- Research focused on the roles of PTH and FGF23 in bone biology and mineral homeostasis
- Corresponding author on publications of CaSR antagonists in the context of ADH1
- Encalaret clinical advisor and key collaborator

National Institute of Dental and Craniofacial Research

Encaleret for Autosomal Dominant Hypocalcemia Type 1

Michael T. Collins, MD

Skeletal Disorders and Mineral Homeostasis Section, NIDCR, NIH

National Institute of Dental and Craniofacial Research

Encaleret for ADH1

- Calcium regulation, the CaSR and CaSR diseases
- ADH1, the disease and the patients
- CaSR antagonists (calcilytics) for ADH1

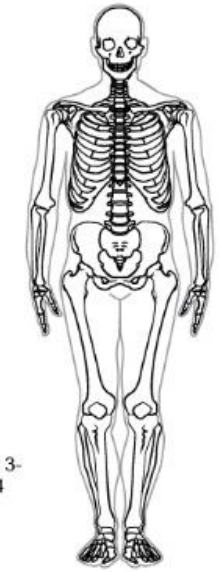
Importance of & Precision in Maintaining Blood Ca^{2+} levels

Tissues

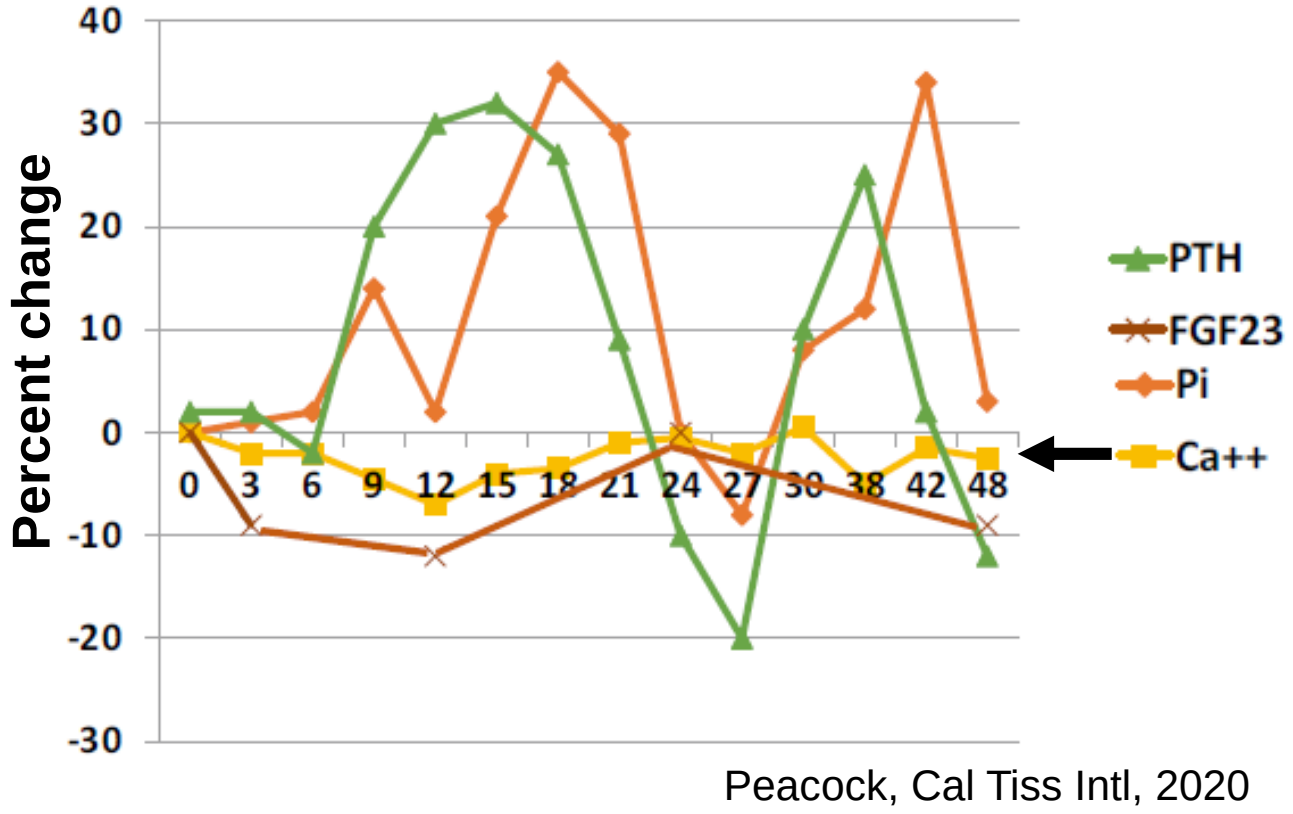
Calcium is critical for:

- Signaling
- Neurotransmission
- Cofactors
- Macromolecules

Skeleton



1.6 kg PO_4^{3-}
1 kg Ca^{2+}

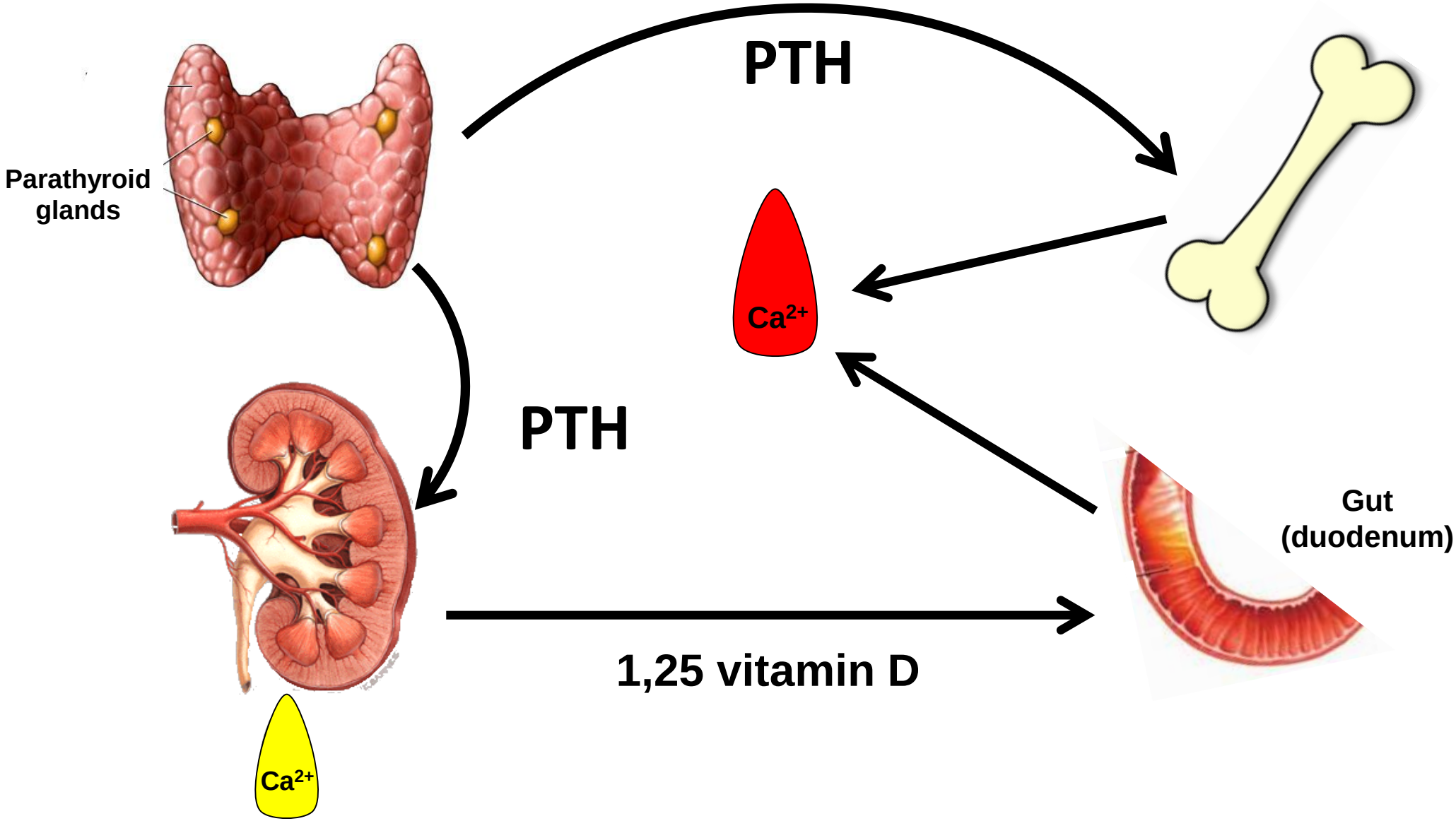


Peacock, Cal Tiss Intl, 2020

PTH = parathyroid hormone
FGF23 = fibroblast growth factor 23
Pi = inorganic phosphate

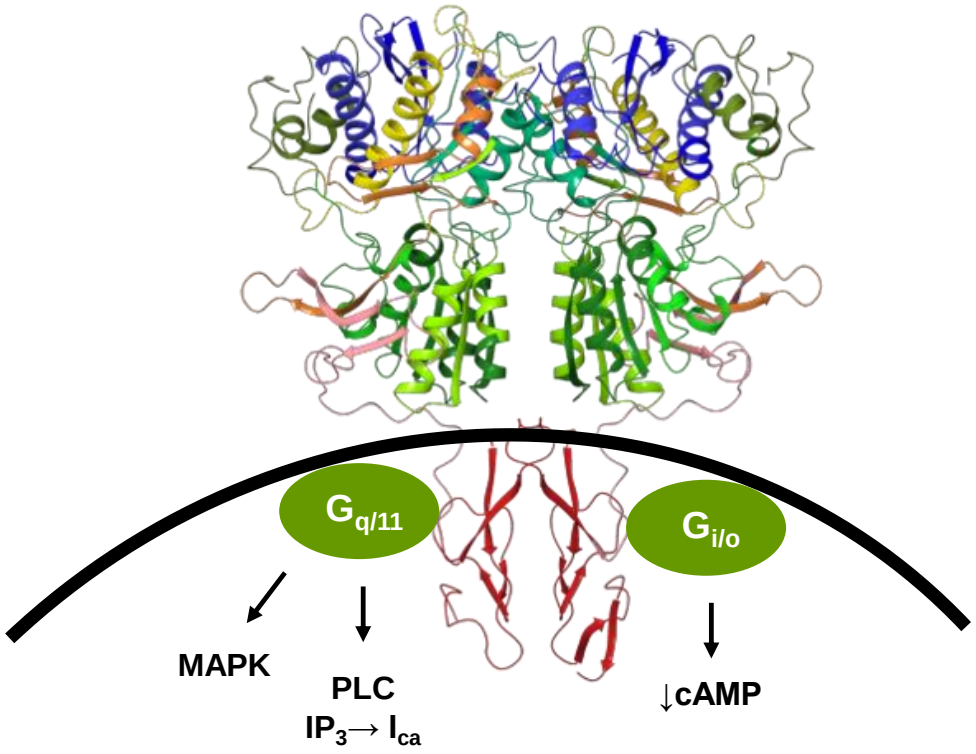
Blood Ca^{2+} is Maintained by Four Organs

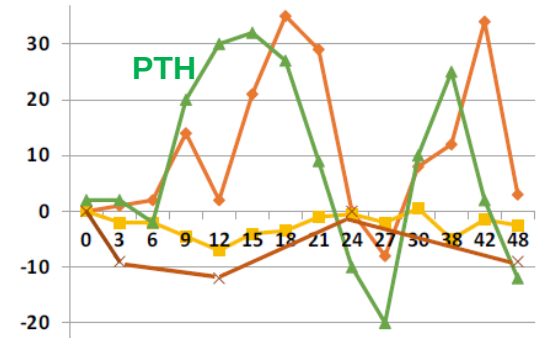
Primarily one hormone: PTH, with one job: maintain blood Ca^{2+}

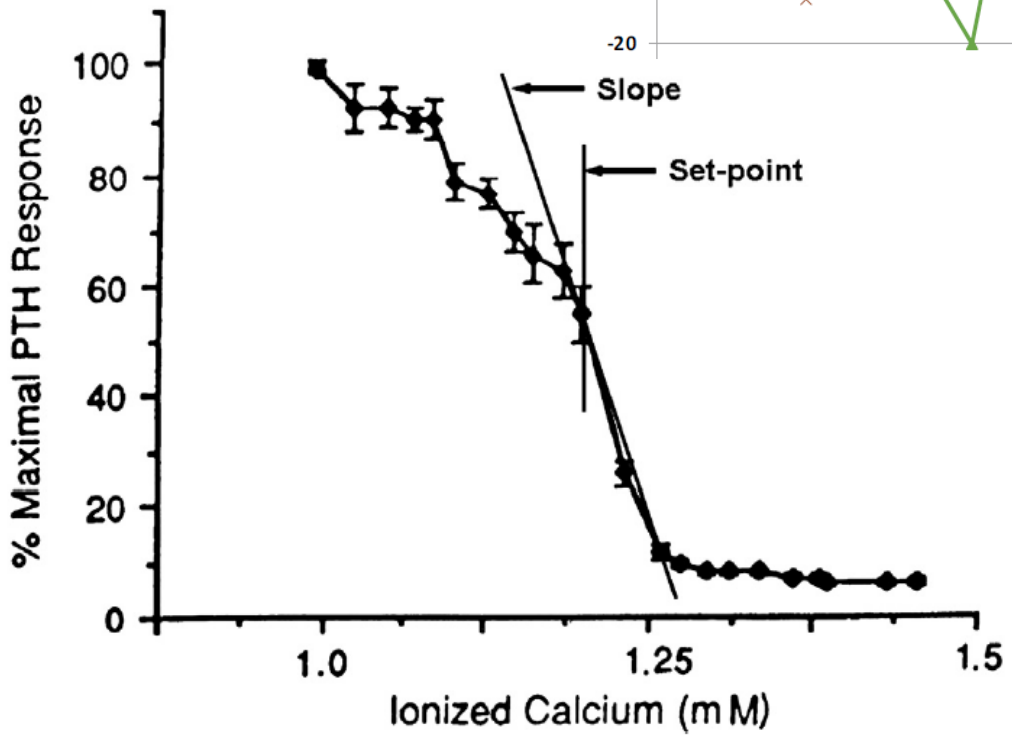


The CaSR: Master Regulator of Ca^{2+}

"Calciostat"



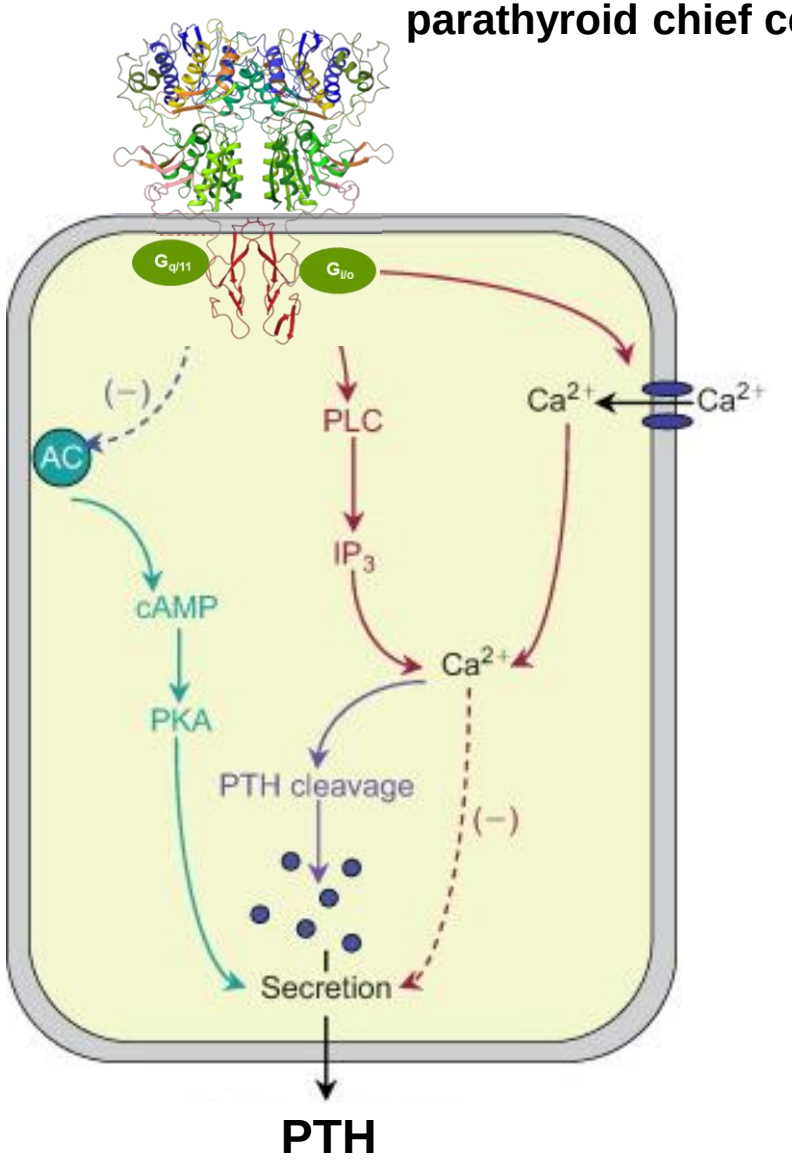




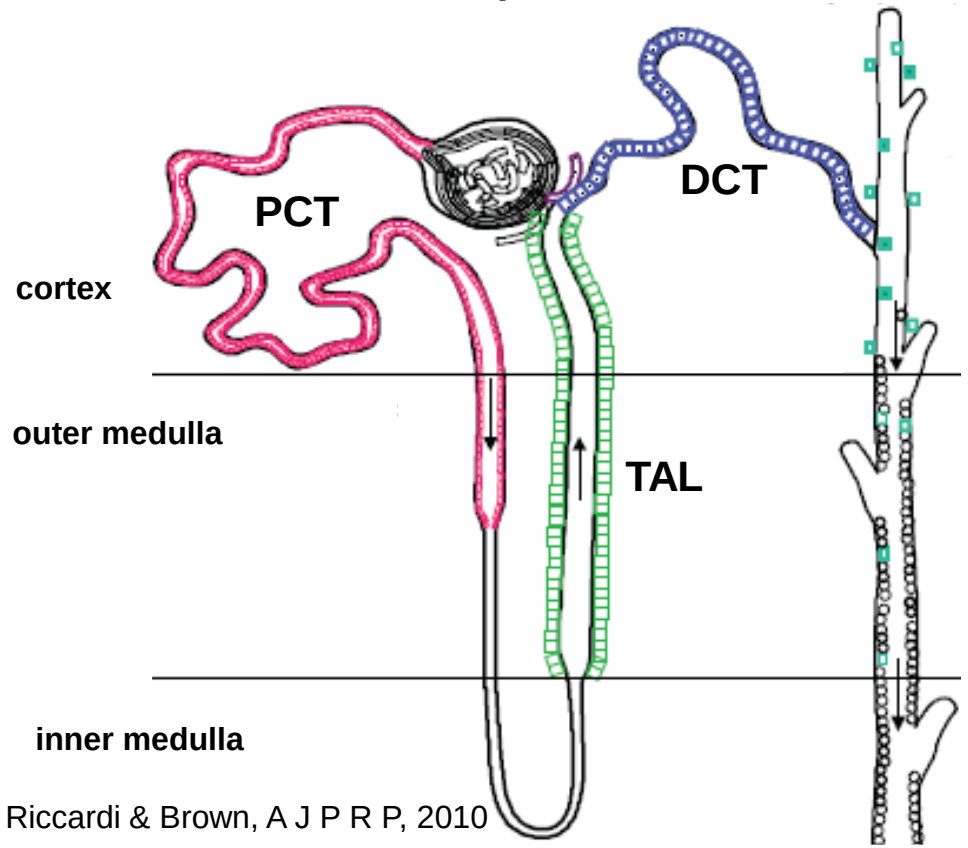
Ed Nemeth, FEBS Lett 1993
Brown, Nature, 1993

Two Tissues Primarily Express the CaSR; Responsible for Ca^{2+} Homeostasis

parathyroid chief cell

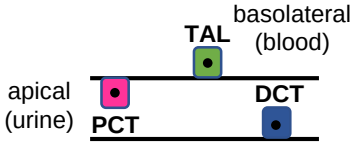


renal tubule CaSR expression

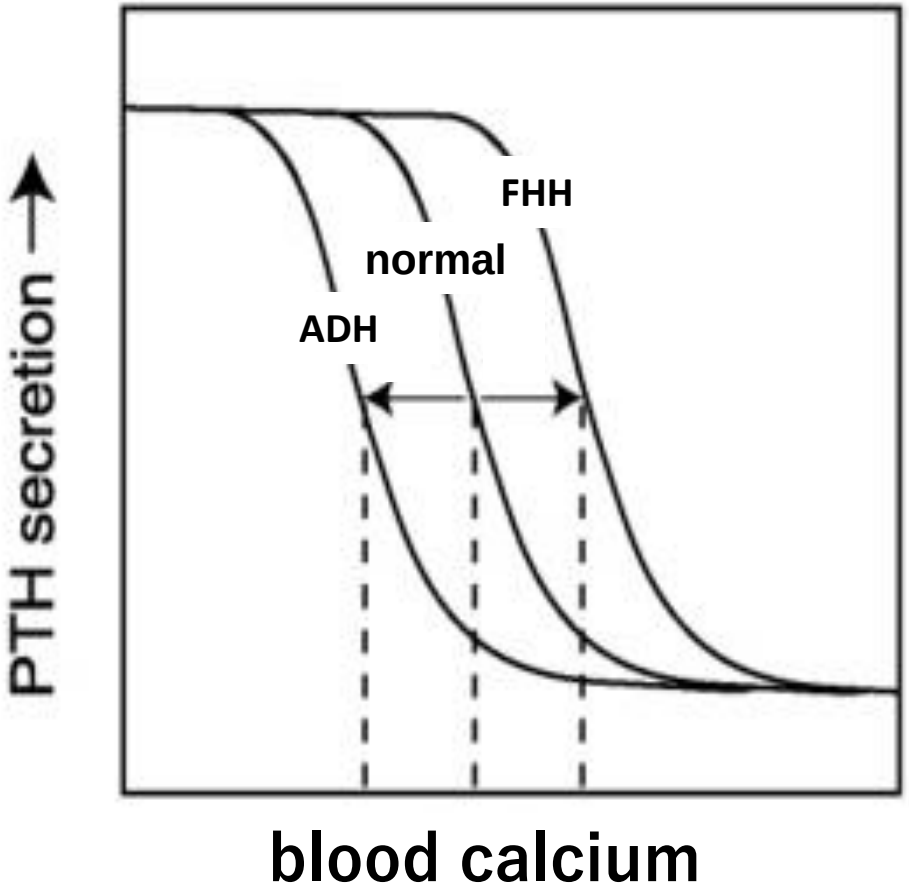


Riccardi & Brown, A J P R P, 2010

PCT: proximal convoluted tubule
TAL: thick ascending limb
DCT: distal convoluted tubule



Diseases of the CaSR



FHH: Familial hypocalciuric hypercalcemia

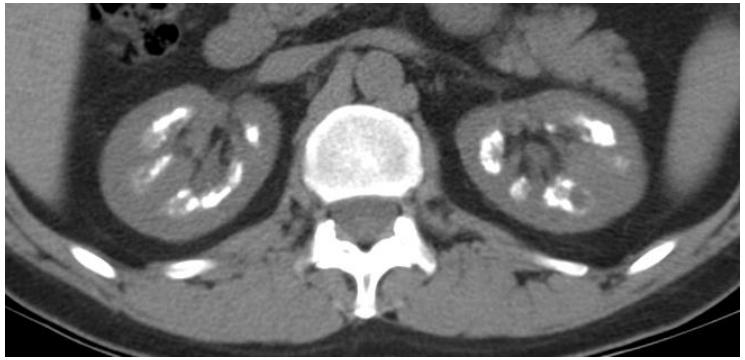
- Loss-of-function CaSR variant
- CaSR thinks blood Ca is low
- Dose/response right-shifted
- ↑ PTH, ↑ Blood Ca, ↓**urine Ca**

ADH: Autosomal dominant hypocalcemia

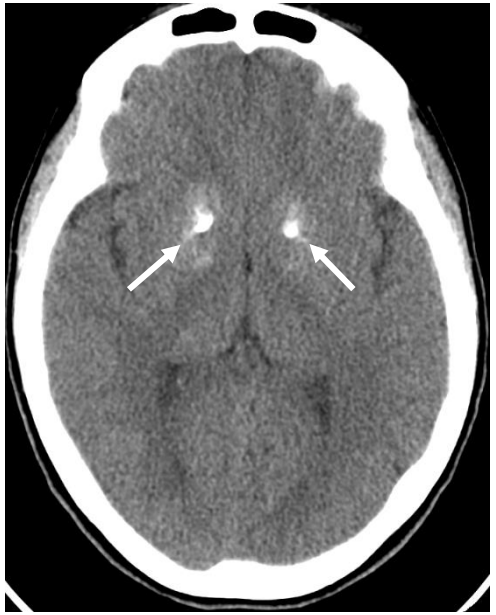
- Gain-of-function CaSR variant
- CaSR thinks blood Ca is high
- Dose/response left-shifted
- ↓ PTH, ↓ Blood Ca, ↑ urine Ca

Autosomal dominant hypocalcemia type 1

- 51 y.o. man, ADH1 seen at NIH x 13 y
- Diagnosed age 6 with ADH1, ↓ Ca noted during evaluationn for learning difficulties
- Ages 6-28 Rx calcium + calcitriol
- Frequent cramping, paresthesias, “foggy”
- nephrocalcinosis at 14; hospitalized for hypercalcemia at 20 (overtreatment)
- **Family:**
  - ♦ father diagnosed with patient
  - ♦ 2 siblings died in infancy, due to seizures, prior to patient’s and father’s diagnosis



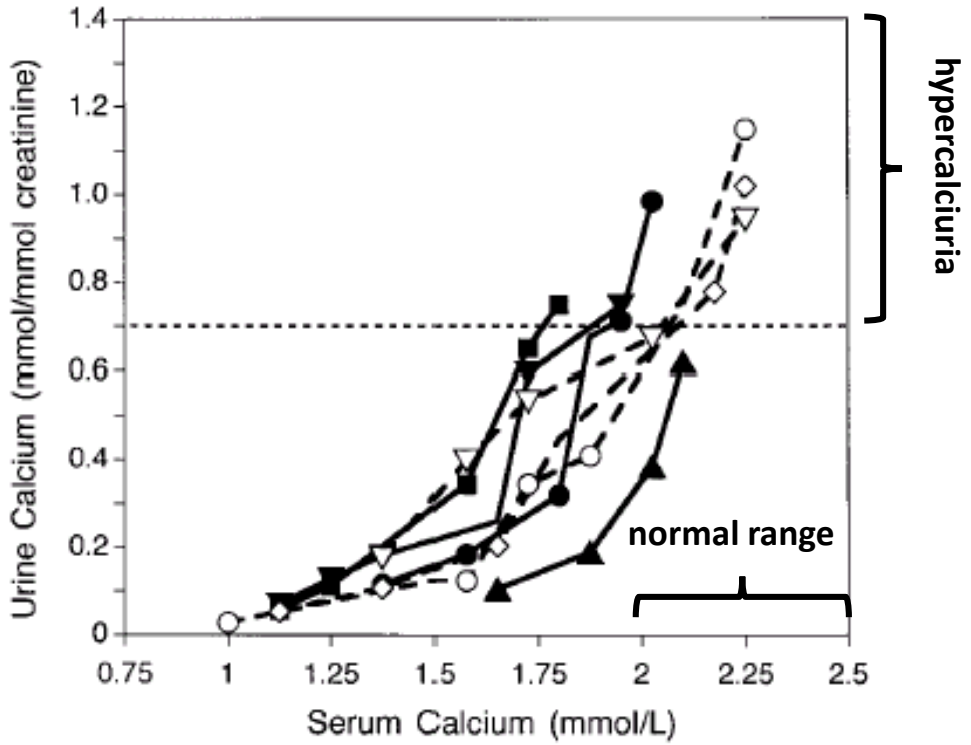
nephrocalcinosis – GFR 59, stage3 CKD



basal ganglia calcification

Hypoparathyroidism treatment leads to hyercalciuria

Double whammy in ADH1: loss of PTH *and* CaSR effect at kidney



Yamamoto et al (2000) *J Clin Endocrinol Metab* 85:4583

Keep blood calcium up

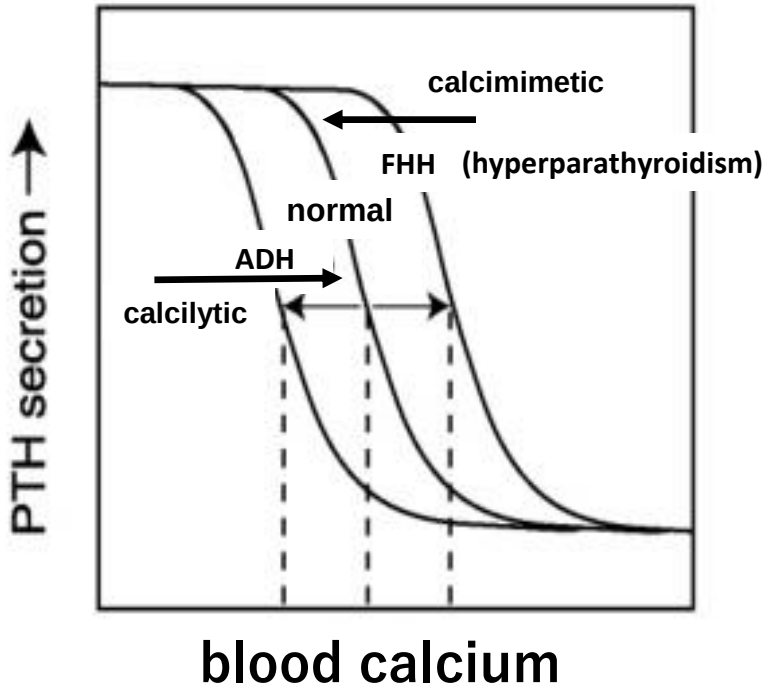
Keep urine calcium down

Treatment is a balancing act

Agonists and Antagonists of the CaSR

"Calcimimetics and Calcilytics"

- CaSR discovered in 1993 by Ed Nemeth and Ed Brown
- NPS R-568, first CaSR agonist (calcimimetic), Nemeth, Ped Nephrol, 1996
- NPS 2143, first antagonist (calcilytic), Gowen…Nemeth, Fox, JCI, 2000
- Shift the dose-response curve towards normal



Agonists and Antagonists of the CaSR

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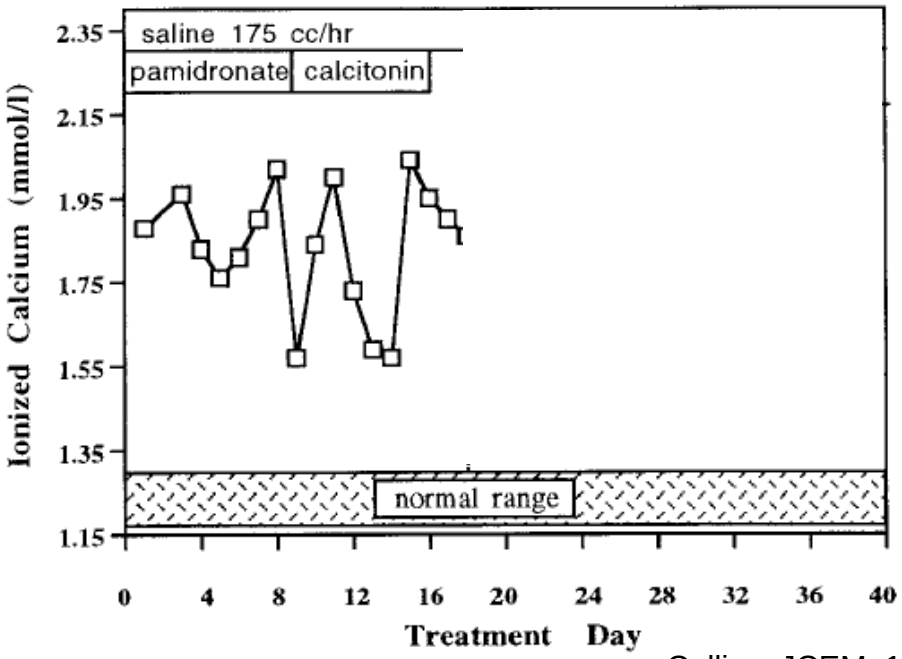
- NPS 2143, first antagonist (calcilytic), Gowen…Nemeth, Fox, JCI, 2000
- Shift the dose-response curve towards normal

- NPS licenses calcimimetics to Amgen; cinacalcet (Sensipar) approved for 2° hyperpara (2004), parathyroid CA (2011)

First Clinical Use of a Calcimimetic

- 1996, a 78-y.o. man widely metastatic parathyroid carcinoma
- Obtunded, unresponsive to conventional therapy
- Compassionate exemption for NPS R-568
- Immediately responsive
- Returned to work in NYC, Effectively treated 4 years
- Struck by car, died from complications



Collins, JCEM, 1998

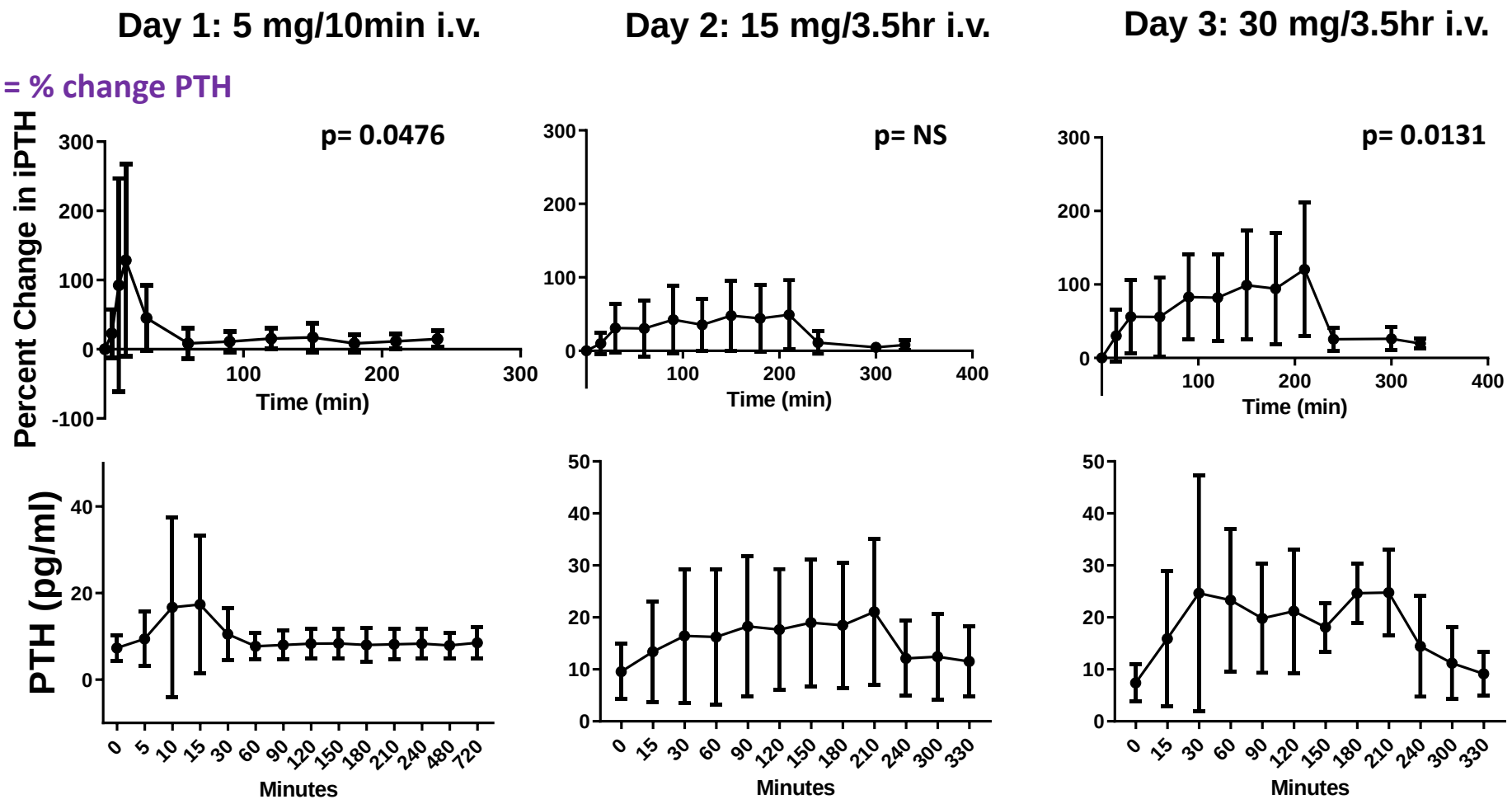
Calcilytics for ADH1 – Brief History – Bright Future

- **Calcilytics: precision medicine for ADH1!**
- **Calcilytics ↑ PTH; treatment for osteoporosis (ala teriparatide)?**
- **1993 NPS calcilytics licensed to GSK for osteoporosis; ronacaleret lead**
- **2007 NIDCR negotiate with GSK for POC study of ronacaleret for ADH1**
- **2008 Ronacaleret for osteoporosis failed in phase 2 study**
- **GSK abandoned calcilytics for bone and mineral disorders**
- **2011 NPS acquires calcilytics NPSP790 and 795 from GSK for ADH1**

Back in business!

Proof of Concept Calcilytic NPSP795 for ADH1

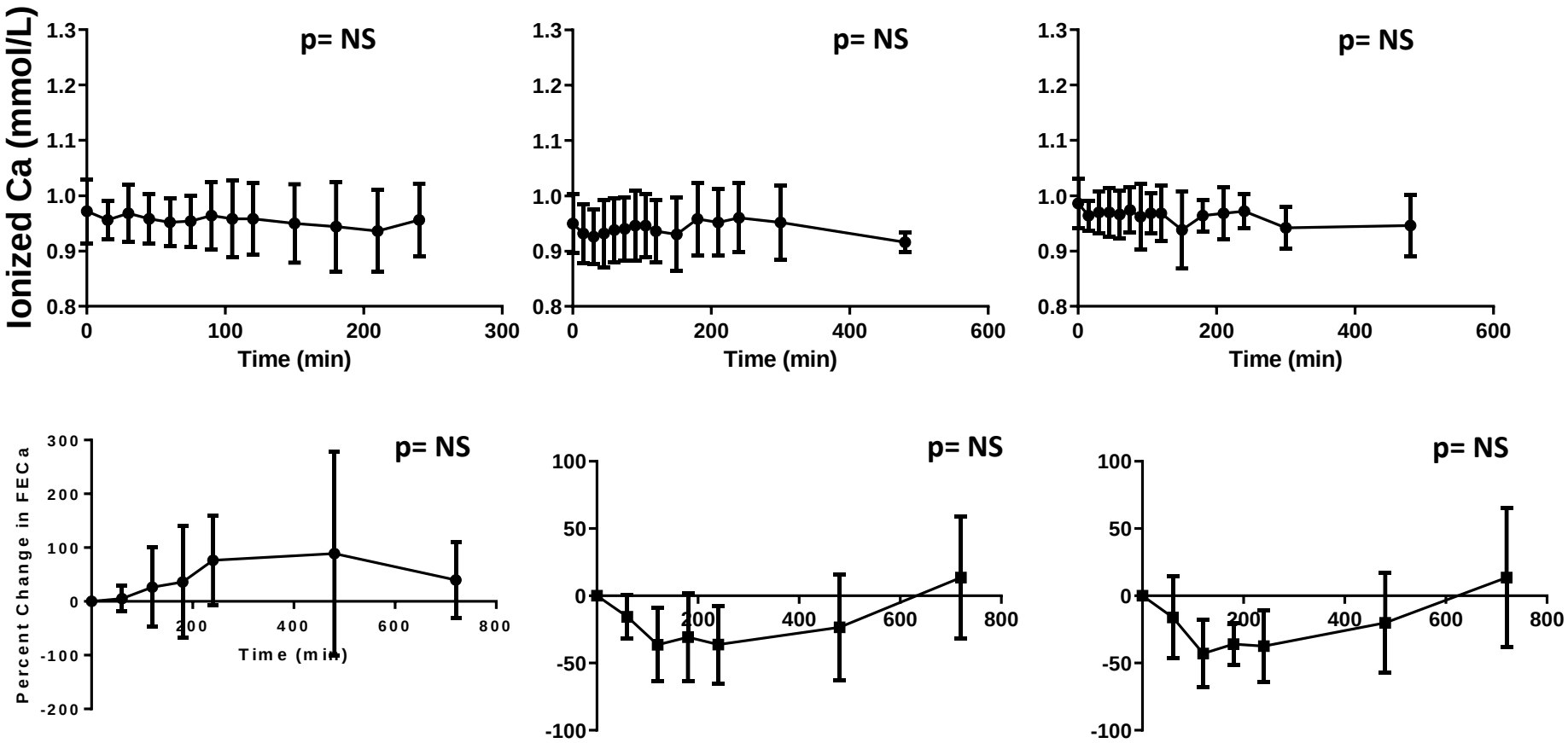
1° endpoint = % change PTH



n = 5; bar = 1 SD; p = mixed model repeated measures

Roberts, JBMR 2019

Exposure Inadequate to Change Blood/Urine Calcium



n = 5; bar = 1 SD; p = mixed model repeated measures

Roberts, JBMR 2019

Calcilytics for ADH1 – Future is Bright!

- **2015 Shire acquires NPS; calcilytic team leaves; interest is lost**
- **2019 Shire acquired by Takeda; future is dark ☹**
- **2018 BridgeBio acquired infigratinib from Novartis**
- **Includes NIDCR study for tumor-induced osteomalacia** (Hartley, NEJM 2020)
- **Calcilytics for ADH1 is suggested to Henderson team…**
- **BridgeBio/Michael Henderson to the rescue ☺**

Future Indications:

- **Postsurgical Hypoparathyroidism**
  - **↓ urinary calcium**
- **Idiopathic Hypercalciuria**
  - **convert to an FHH-like phenotype (↓urine Ca)**

Acknowledgments

National Institute of Dental and Craniofacial Research

NIH Team

Rachel Gafni, MD

Karen Pozo, BSN, RN

Beth Brillante, BSN, MBA

Iris Hatley, MD

Kelly Roszko, MD, PhD

Ed Nemeth, PhD

Stephen Marx

(NPS R-568)

Calcilytix Team

Michael Henderson

Eric Gomez

Jonathan Fox

Ramei Sani-Grosso

Ananth Sridhar

Lenny Katz

Dexter Kennedy

Agenda

Program	Speakers
Low-dose infigratinib (FGFRi) for achondroplasia	Introduction: Dr. Susan Moran, M.D., M.S.C.E. Presenter: Dr. Ravi Savarirayan, M.D., Ph.D.
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Q&A	Moderator: Christine Siu Speakers: All
Conclusion	Neil Kumar, Ph.D.

BridgeBio Oncology Research

World-class oncology team drives our discovery and development

Eli Wallace
CSO Oncology Research

ARRAY BIOPHARMA | Peloton Therapeutics

Pedro Beltran
SVP Oncology

AMGEN | UNITY BIOTECHNOLOGY

Frank McCormick
Chairman of Oncology

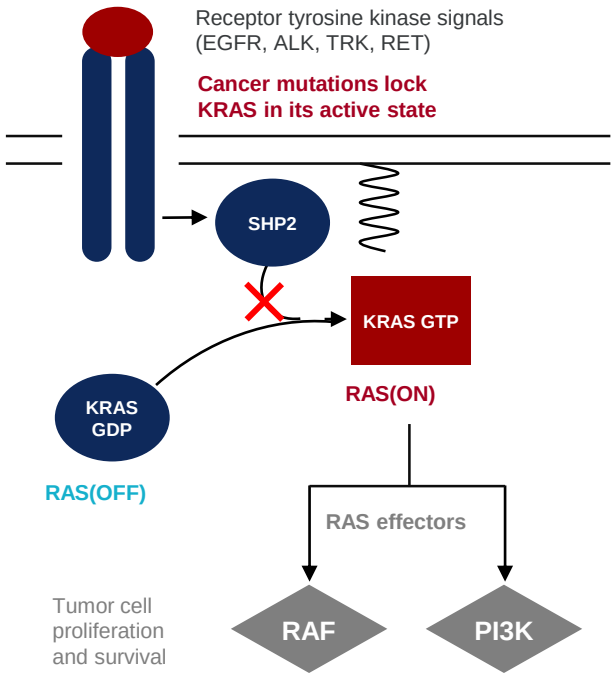
ONYX PHARMACEUTICALS | UCSF

Richard Scheller
Chairman of R&D

Genentech | 23andMe

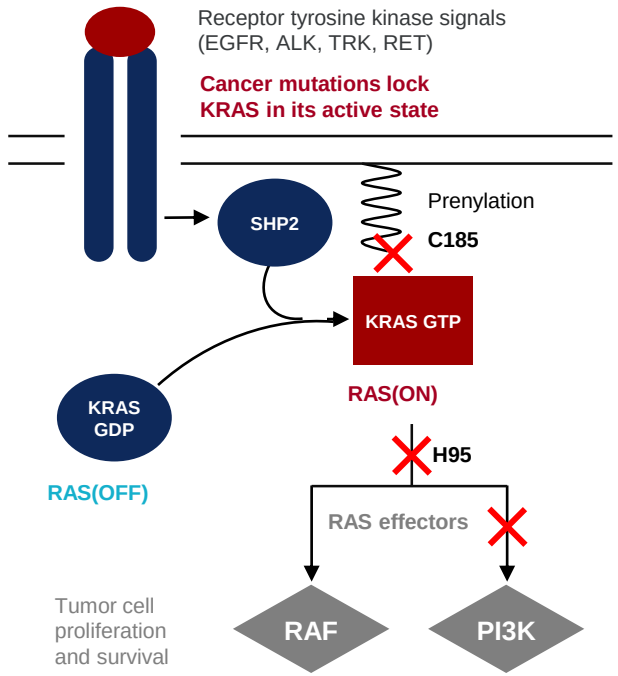
Three oncology research targets

SHP2 (BBP-398)



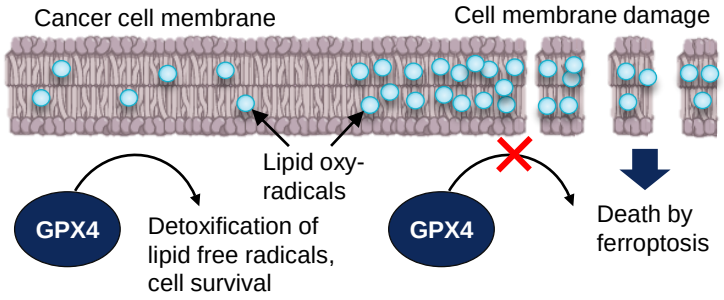
- Potential best in class oral compound
  - Optimized safety, PK and PD profile
  - Maximizes combination therapy potential
- IND cleared

KRAS



- Multiple unexploited sites
- Comprehensive pan-mutant targeting approaches

GPX4



- Potential first in class compound for novel cancer target
- In vivo monotherapy activity and combo potential

Partnerships afford us exceptional collaborators and resources

NIH NATIONAL CANCER INSTITUTE

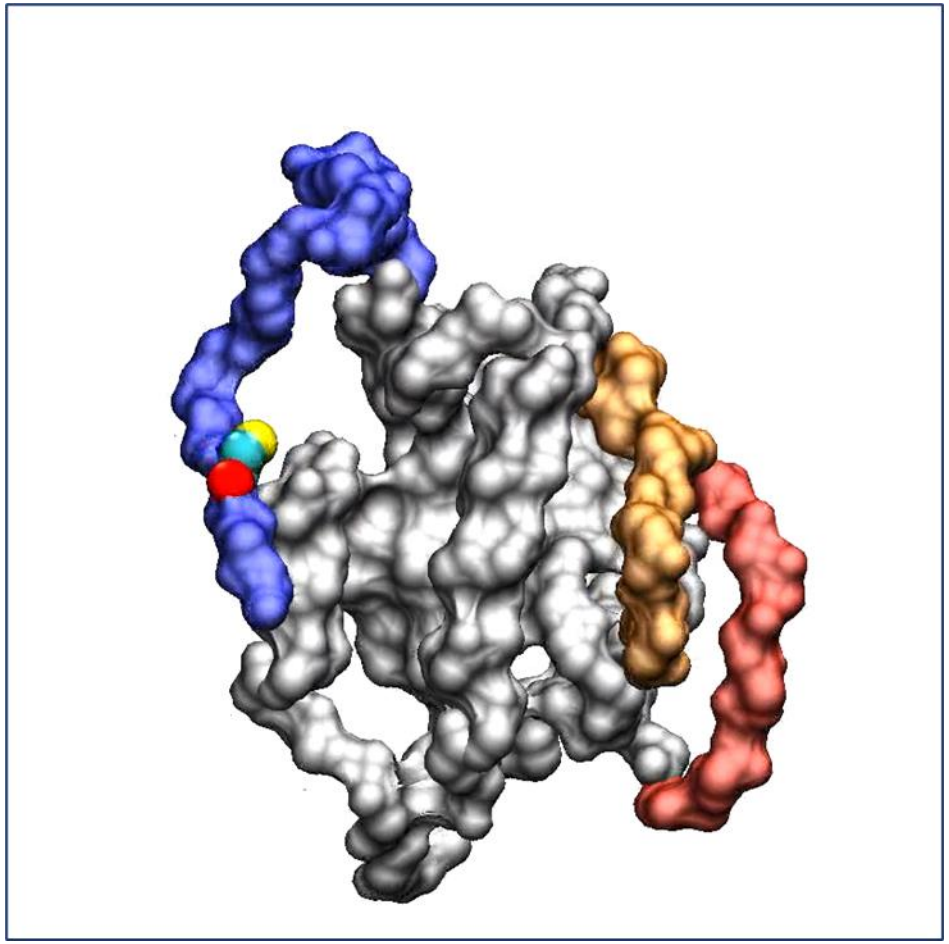
- Partnership with the National RAS Initiative, including 60 of the world's **foremost academic RAS researchers**
- Cutting edge RAS **structural biology expertise**
- Utilization of **cutting-edge instrumentation and techniques**, as well as the **expertise** to lead experiments

Lawrence Livermore National Laboratory

- Home to Sierra: the **world's 3rd fastest computing system**
- Enables **multi-microsecond molecular dynamics simulations** of protein complexes, and highly efficient *in silico* **docking simulations**
- This computing power, combined with RAS structural biology expertise at the NCI, delivers **unique insights that fuel our drug design**

Crystal structure enables a static understanding of the target …

KRAS4b model based on crystal



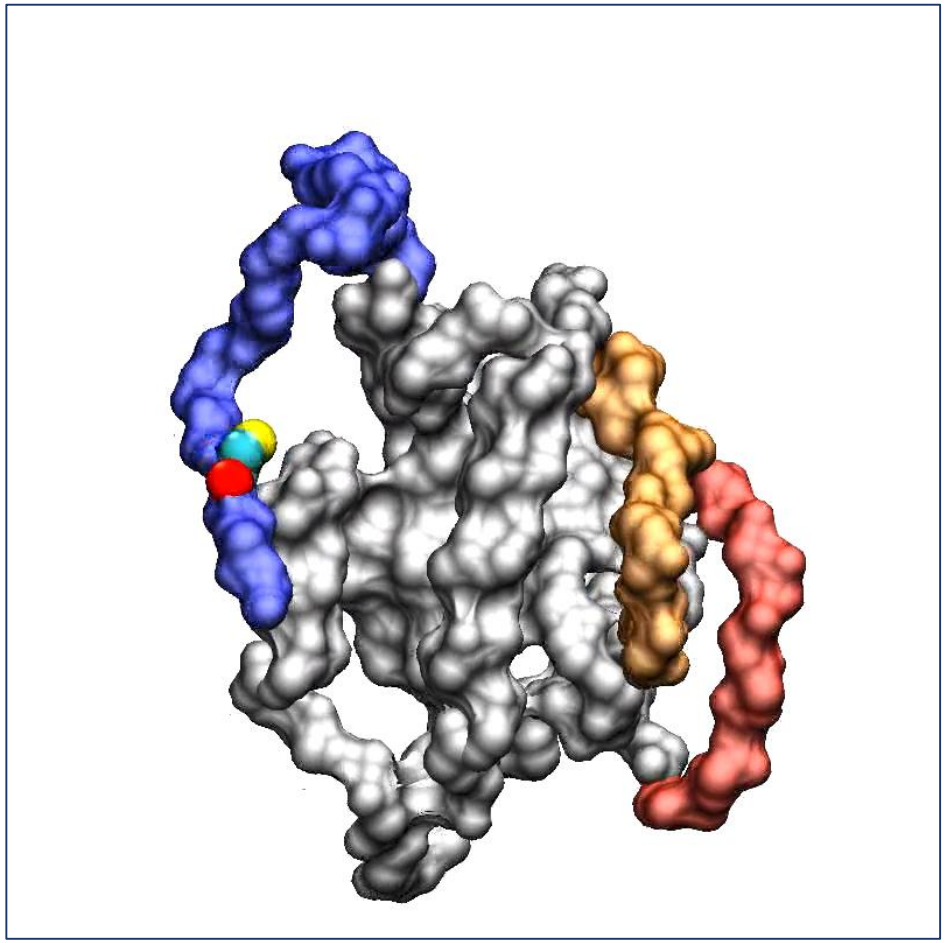
G-domain
G-domain switch I
G-domain switch II
Hypervariable region

One therapeutic approach is to inhibit KRAS4b **membrane localization** by targeting **hypervariable region**

Static model reveals only a **subset of potential binding sites** for pharmacological compounds

… whereas molecular dynamics simulation reveals transient conformations and interactions

KRAS4b simulation



G-domain
G-domain switch I
G-domain switch II
Hypervariable region

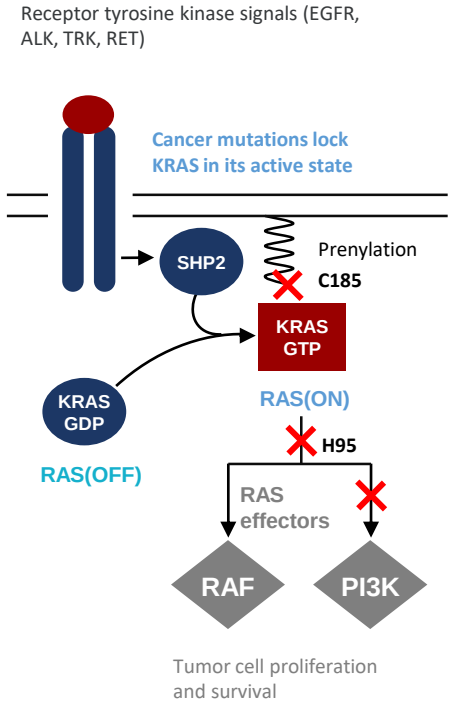
Reveals possible KRAS4b **HVR transient localization to G-domain**

Elucidates potential transient druggable pocket where **compounds could react covalently with C185**

Enables *in silico* SAR to **inhibit KRAS4b membrane localization**

KRAS: multiple shots on goal with our pan-mutant inhibitor programs – each with a unique MOA targeting a novel pocket

KRAS pathway in cancer



Program	MOA	Targets KRAS GTP	Pan-mutant	Crystal structure	Molecular Dynamics
Program 1: H95 targeting	▪ Directly binds activated KRAS through H95 ▪ Inhibits KRAS from signaling through effectors	✓	✓	✓	✓
Program 2: PI3K effector blocking	▪ Blocks specific interaction between KRAS and PI3Ka ▪ Blocks PI3K / AKT effector signaling	✓	✓	✓	✓
Program 3: C185 targeting	▪ Blocks KRAS from tethering ▪ Blocks conversion of inactive KRAS GDP to active KRAS GTP	✓	✓		✓

Our programs are designed to address all KRAS driver mutations, which occur in 30% of all cancers

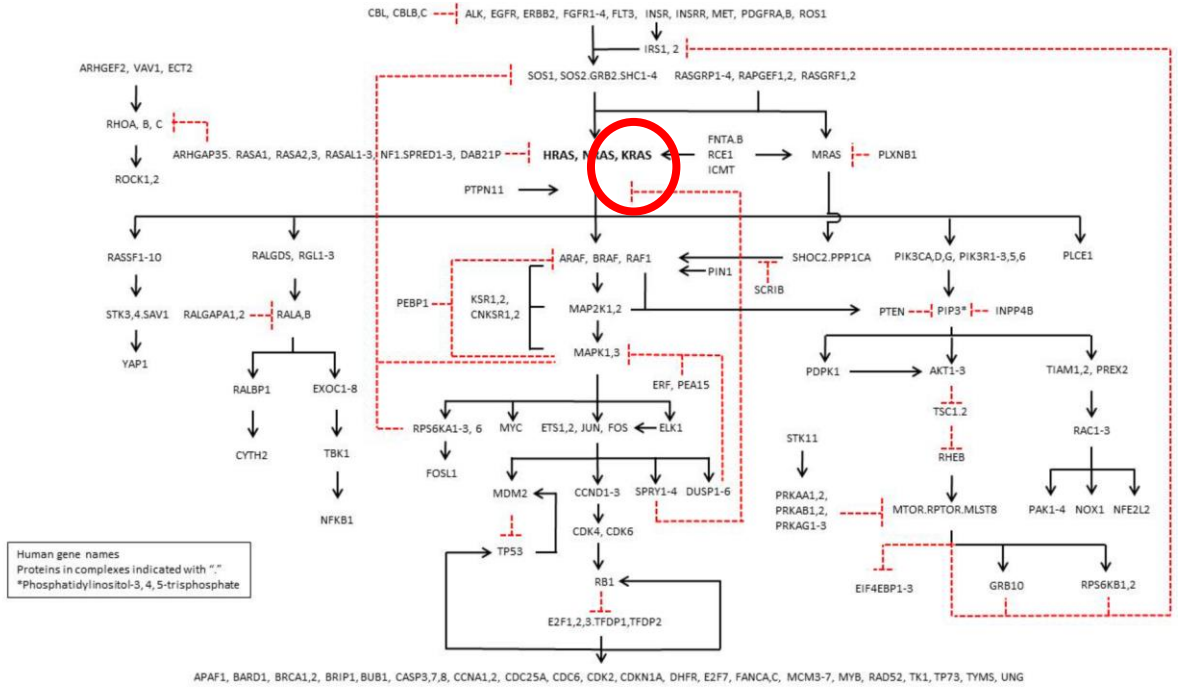
Frank McCormick, PhD

- BridgeBio Co-Founder and Chairman of Oncology
- Professor, University of California San Francisco, Helen Diller Family Comprehensive Cancer Center
- Founder of Onyx Pharmaceuticals

RAS mutations in human cancer

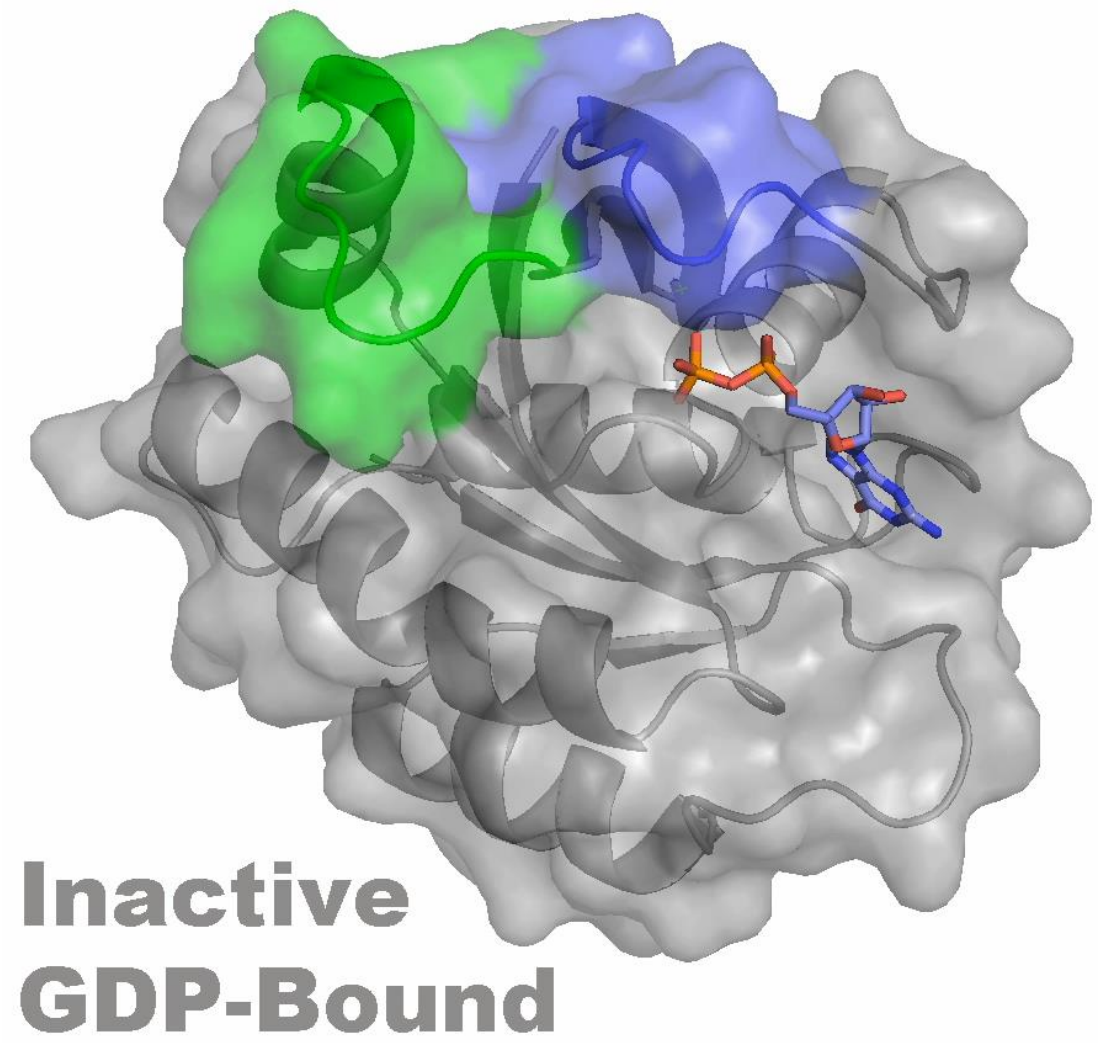
Pancreas	95%	KRAS
Colorectal	45%	KRAS
Lung	35%	KRAS
AML	30%	NRAS
Melanoma	15%	NRAS
Bladder Cancer	5%	HRAS
Thyroid Cancer	5%	HRAS

Challenges of targeting KRAS: complexity and redundancy

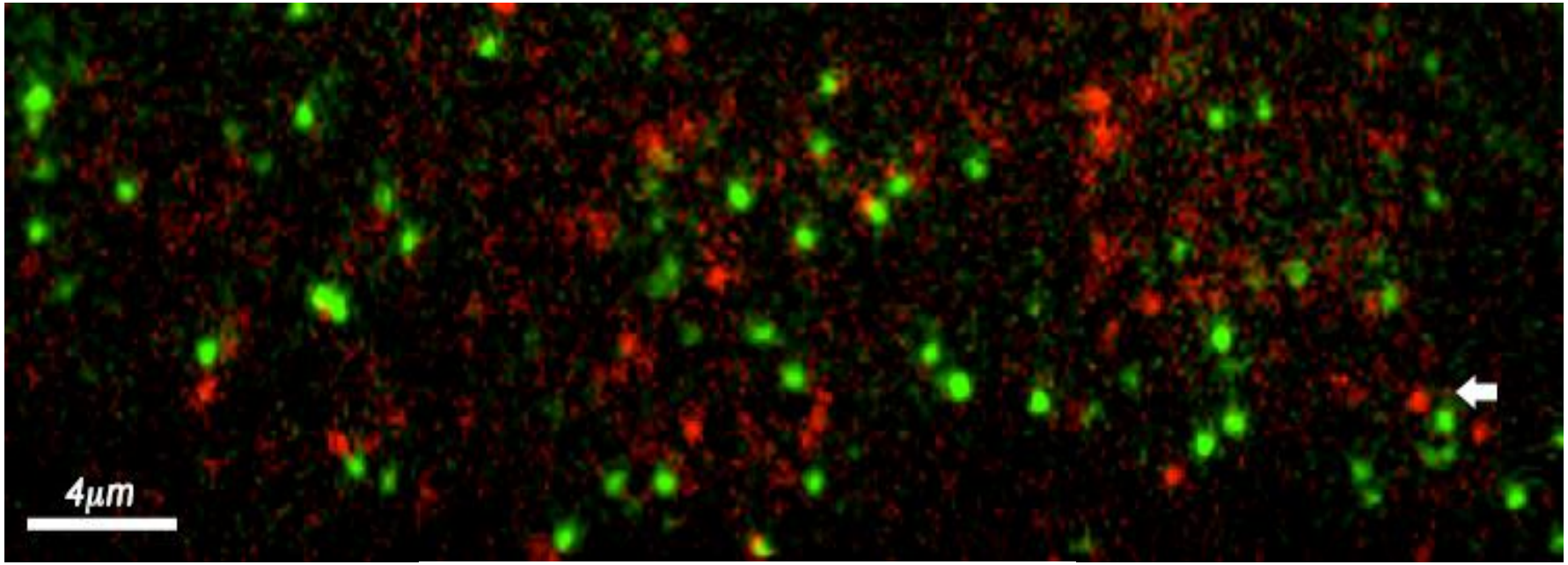


Ras	Rab	Rho	Arf	Rad	Ran	Rag
H-Ras	Rab1A	RhoA	Arf 1	Rad	Ran/TC4	RagA
K-Ras	Rab1B	RhoB	Arf 2	Gem		RagB
N-Ras	Rab2	RhoC	Arf 3	Rem		RagC
TC21	Rab3A	RhoD	Arf 4			RagD
R-Ras	Rab3B	RhoE	Arf 5			Gtr1
M-Ras	Rab4	RhoG	Arf 6			Gtr2
Rap1A	Rab5A	Rho6	Arl 1			
Rap1B	Rab5B	Rho7	Arl 2			
Rap2A	Rab6	Rac1	Arl 3			
Rap2B	Rab7	Rac2	Arl 4			
Rab2C	Rab8	Rac3	Arl 5			
RalA	Rab10	CDC42	Arl 6			
RalB	.	TC10	Arl 7			
Rheb	.	TTF	.			
Rit	.	Rop	.			
Rin	Rab41	.	.			
		.	Arl12			
		.				

Challenges of targeting KRAS: difficult drug target

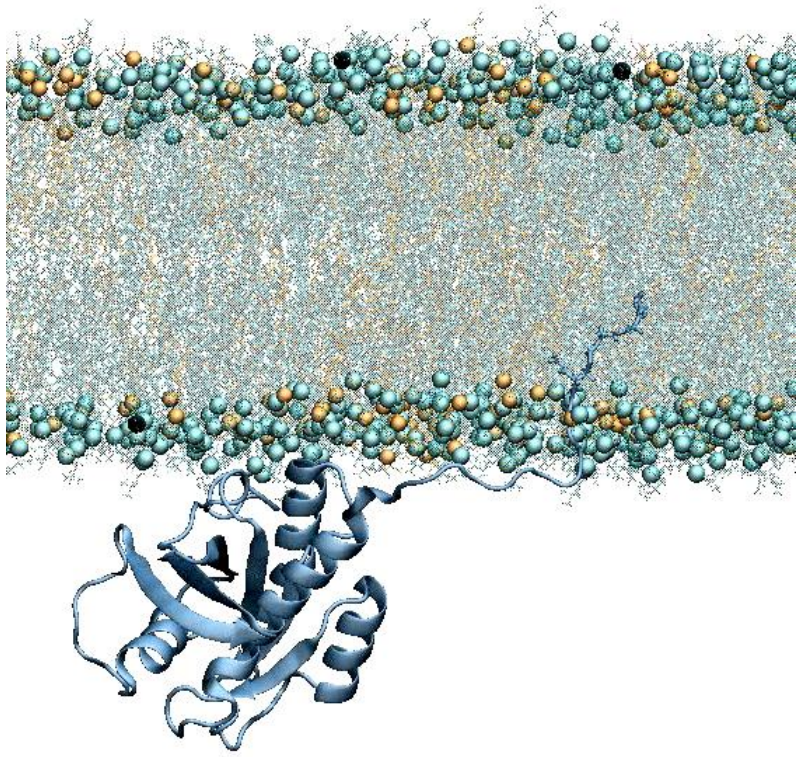


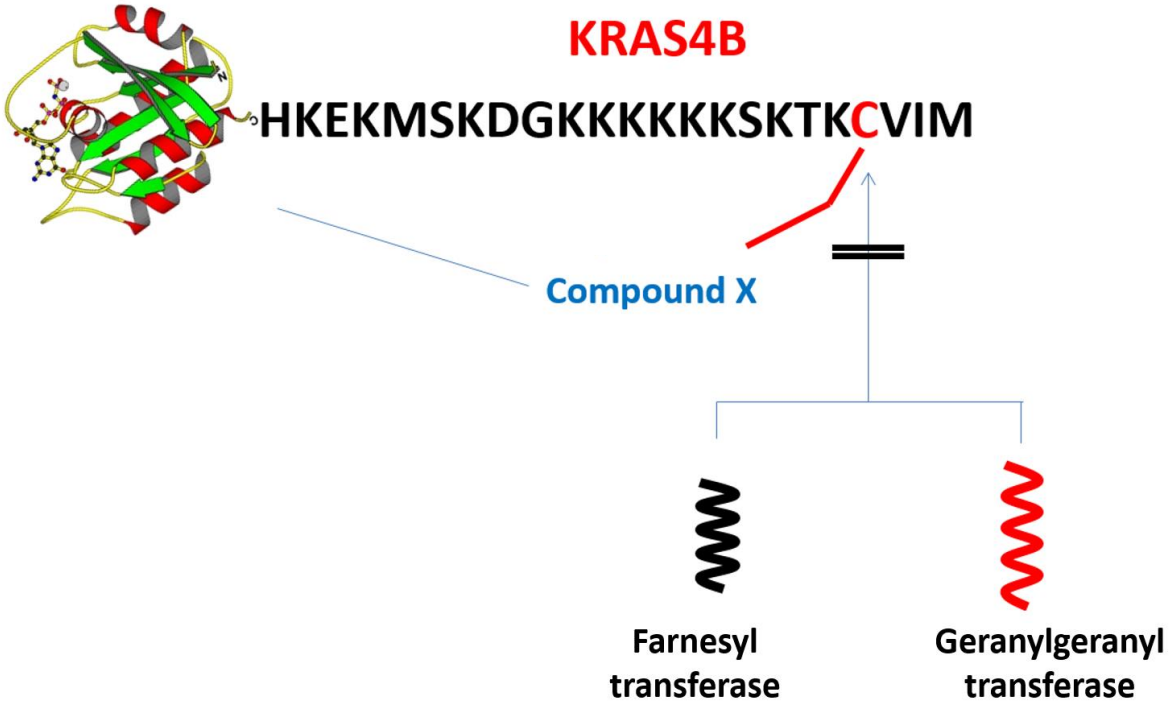
Ras proteins function in the plasma membrane



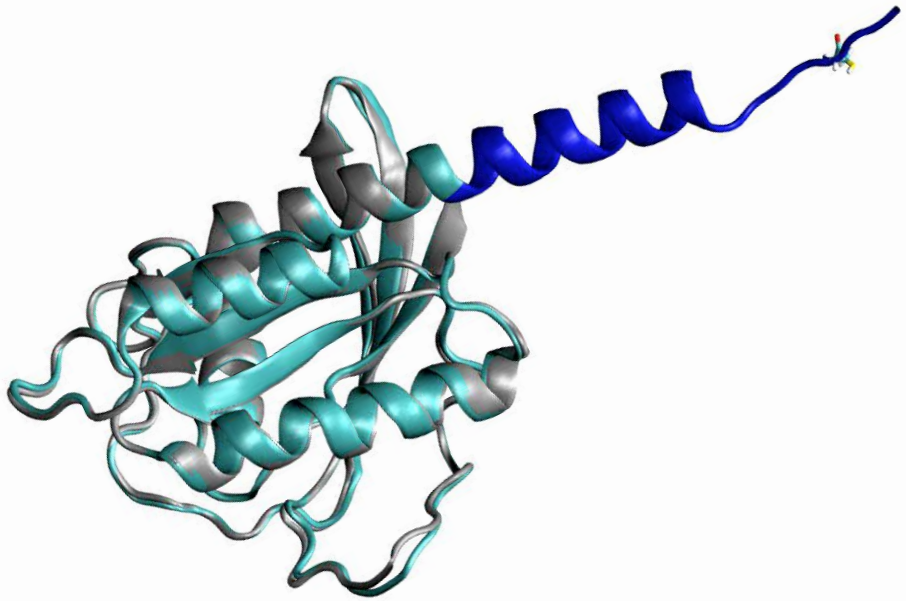
SNAP-Raf1+ Halo-KRAS4b

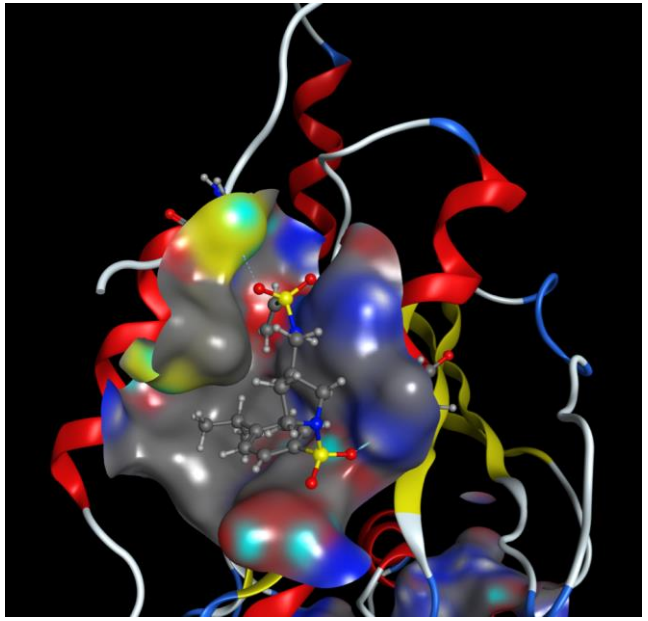
Targeting membrane processing



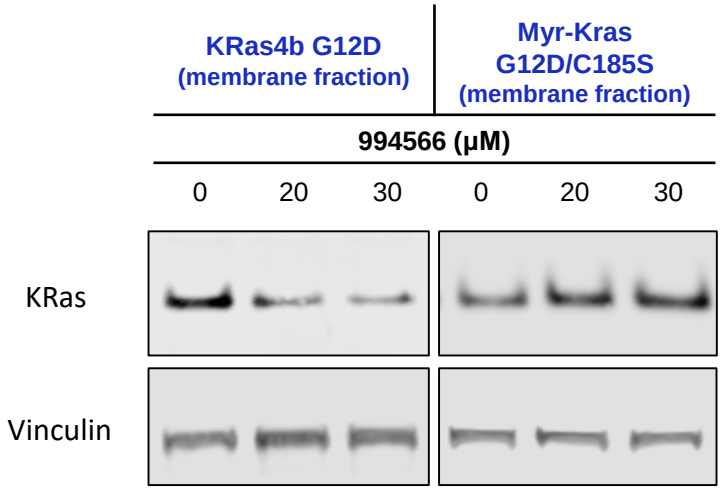


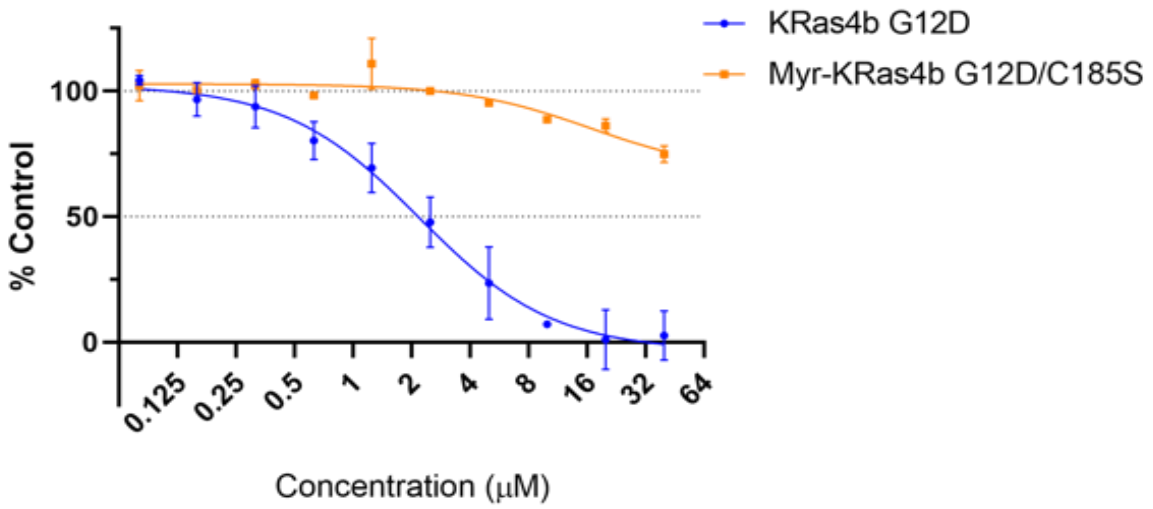
KRAS 4B HVR can interact with the G-domain



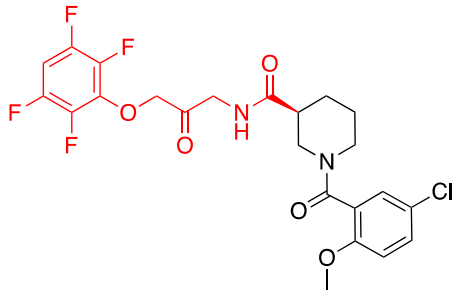


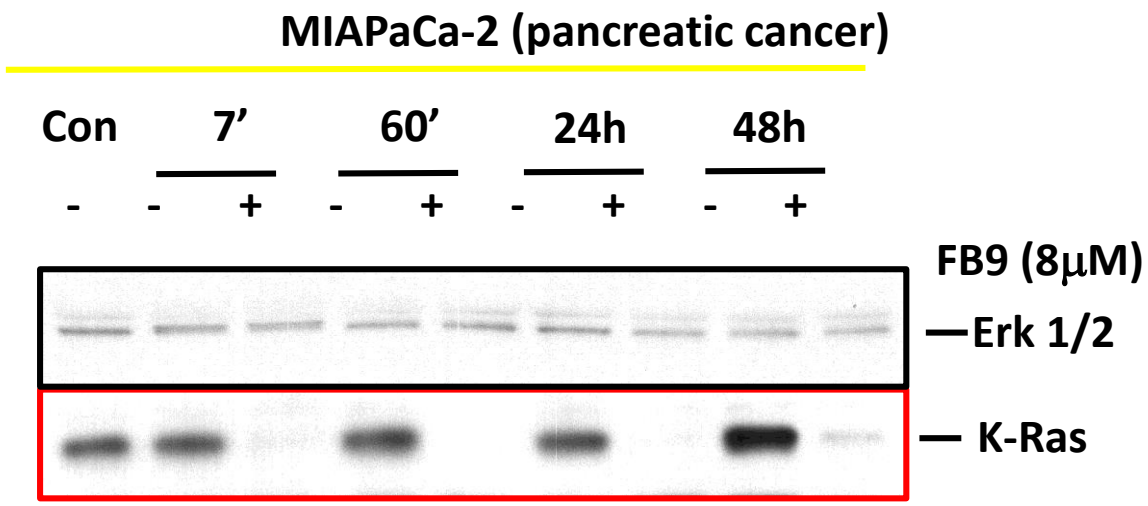
Blocking processing of newly synthesized K-Ras



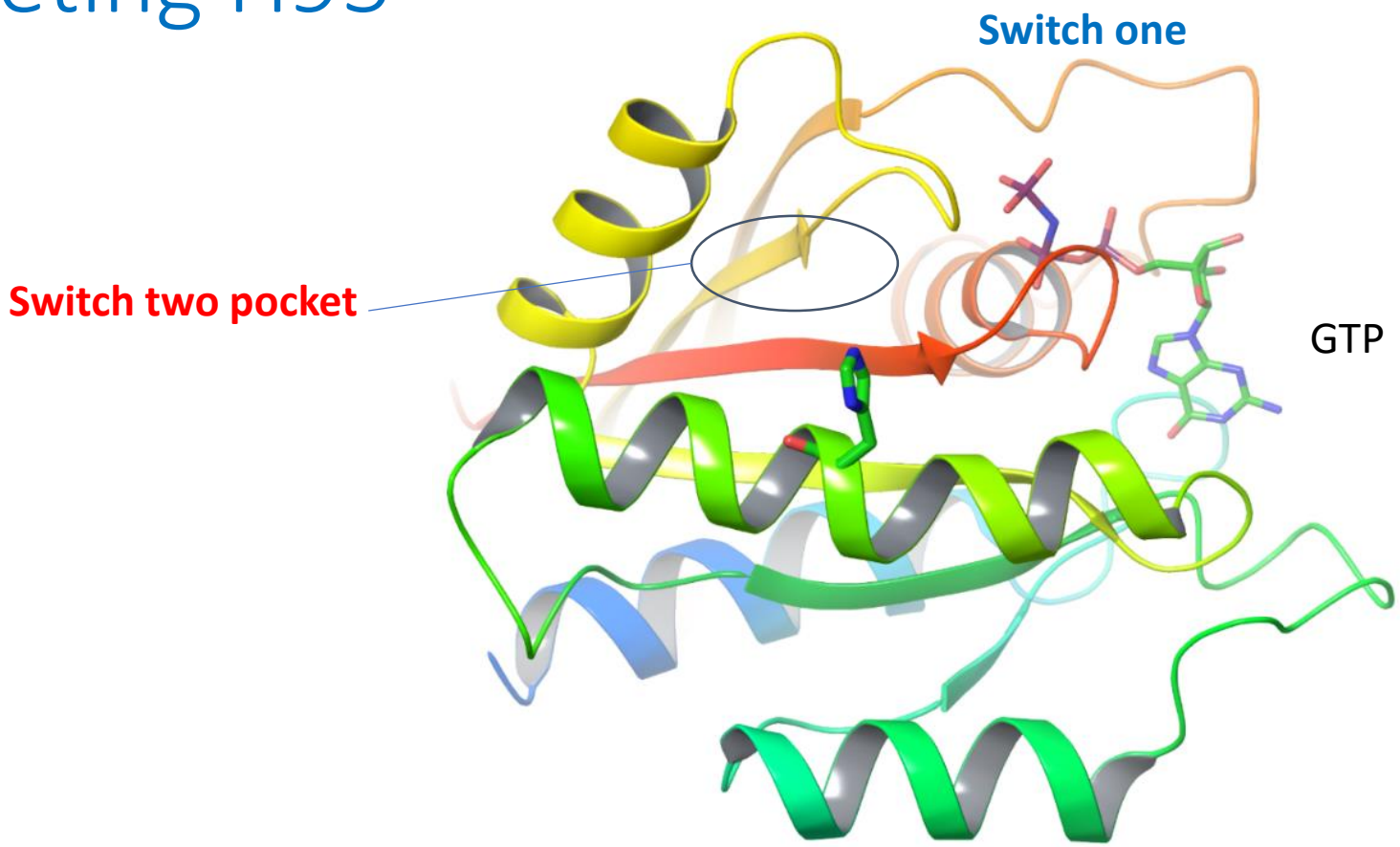


FB9 promotes degradation of K-Ras



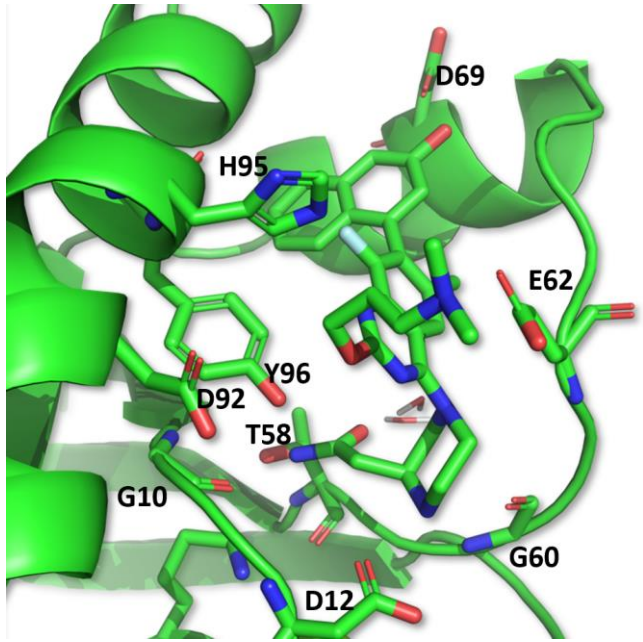


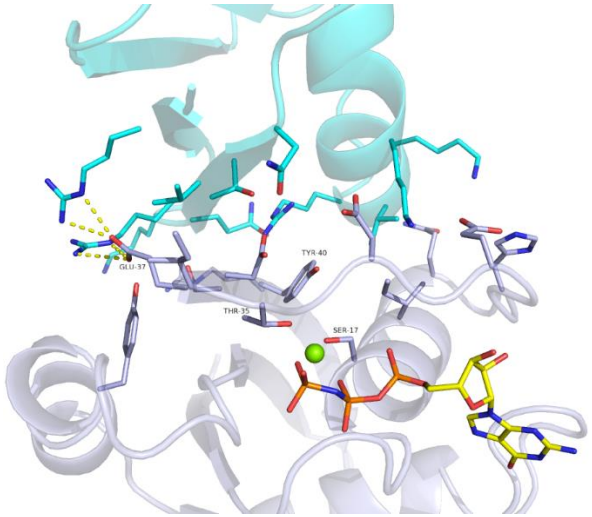
Targeting H95

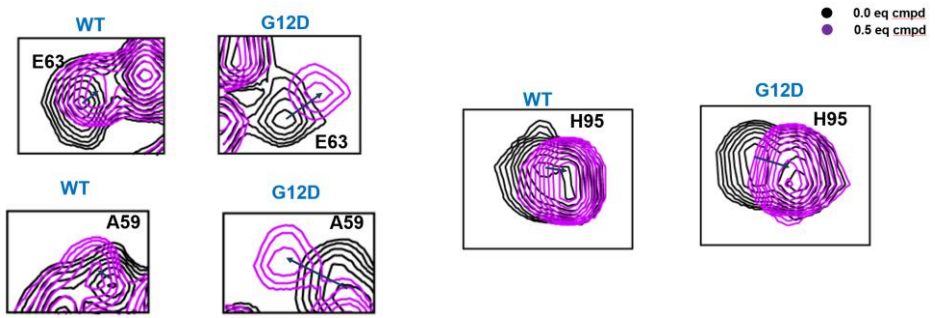


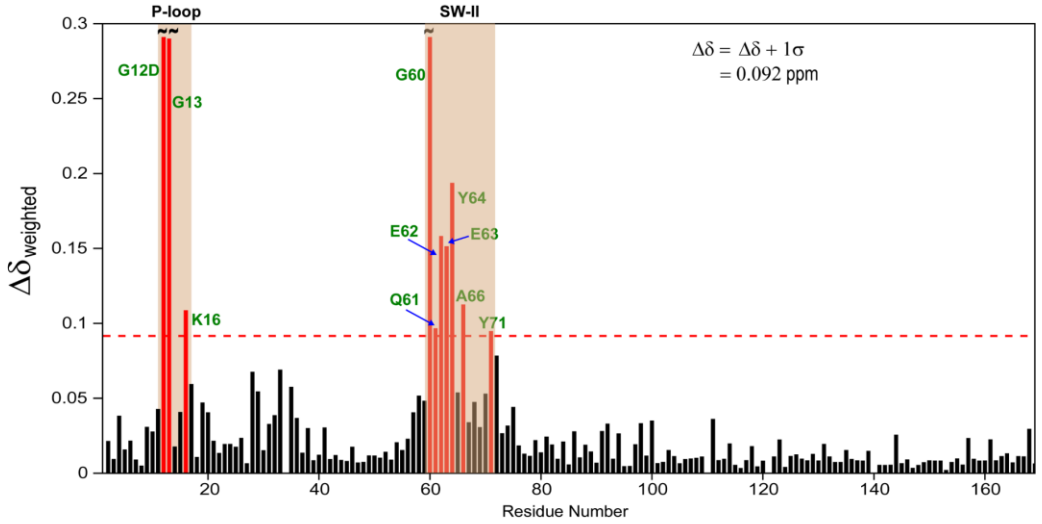
K-RASFAINNTKSFEDIHHYREQIKRVKD
H-RASFAINNTKSFEDIHQYREQIKRVKD
N-RASFAINNTKSFADINLYREQIKRVKD

Integrating structural biology, molecular dynamics and biophysics to target K-Ras H95









Agenda

Program	Speakers
Low-dose infigratinib (FGFRi) for achondroplasia	Introduction: Dr. Susan Moran, M.D., M.S.C.E. Presenter: Dr. Ravi Savarirayan, M.D., Ph.D.
Acoramidis: TTR stabilizer for ATTR	Introduction: Dr. Jonathan Fox, M.D., Ph.D. Presenter: Professor Julian D. Gillmore, M.D., Ph.D.
Gene therapy for congenital adrenal hyperplasia (BBP-631)	Introduction: Dr. Eric David, M.D., J.D. Presenter: Dr. Kyriakie Sarafoglou, M.D.
Encaleret: CaSR inhibitor for autosomal dominant hypocalcemia type 1 (ADH1)	Introduction: Dr. Jonathan Fox, M.D., Ph.D. Presenter: Dr. Michael Collins, M.D.
Targeted oncology	Introduction: Dr. Eli Wallace, Ph.D. Presenter: Frank McCormick, Ph.D.
Q&A	Moderator: Christine Siu Speakers: All
Conclusion	Neil Kumar, Ph.D.