Alnylam Engine for Sustainable Innovation: Leadership in RNAi Platform and Human Genetics

RNAi ROUNDTABLE 2022

October 21, 2022

Alnylam@20

Agenda

Welcome
- Joshua Brodsky – Senior Director, Investor Relations & Corporate Communications

Introduction
- Vasant Jadhav, Ph.D. – Senior Vice President, Research

Targeted Delivery of RNAi Therapeutics to Extrahepatic Tissues
- Kevin Dooley, Ph.D. – Associate Director, Research

Alnylam Human Genetics Overview
- Paul Nioi, Ph.D. – Vice President, Research

Case Study: Leveraging Human Genetics to Identify a Novel Target for Abdominal Obesity
- Aimee Deaton, Ph.D. – Associate Director, Human Genetics

Q&A Session

Reminders

Event will run for approximately 60 minutes

Q&A session at end of presentation

- Questions may be submitted at any time via the ‘Ask a Question’ field on the webcast interface

Replay, slides and transcript available at https://capella.alnylam.com

Alnylam Forward Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, including but not limited to expectations regarding our aspiration to become a leading biotech company and the planned achievement of our "*Alnylam P^{5}x25*" strategy, our ability to attain financial self-sustainability, the potential opportunity for RNAi therapeutics in prevalent diseases, and the potential of our engine for sustainable innovation, including the potential for improved product profiles to emerge from our IKARIA and GEMINI platforms, the potential for extrahepatic delivery approaches and our ability to leverage human genetics to accelerate our drug discovery and development efforts. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; the potential impact of the January 2022 leadership transition on our ability to attract and retain talent and to successfully execute on our "*Alnylam P^{5}x25*" strategy; our ability to discover and develop novel drug candidates and delivery approaches, including using our IKARIA and GEMINI platforms, and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates, including vutrisiran and patisiran; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including vutrisiran and patisiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO, AMVUTTRA and OXLUMO in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

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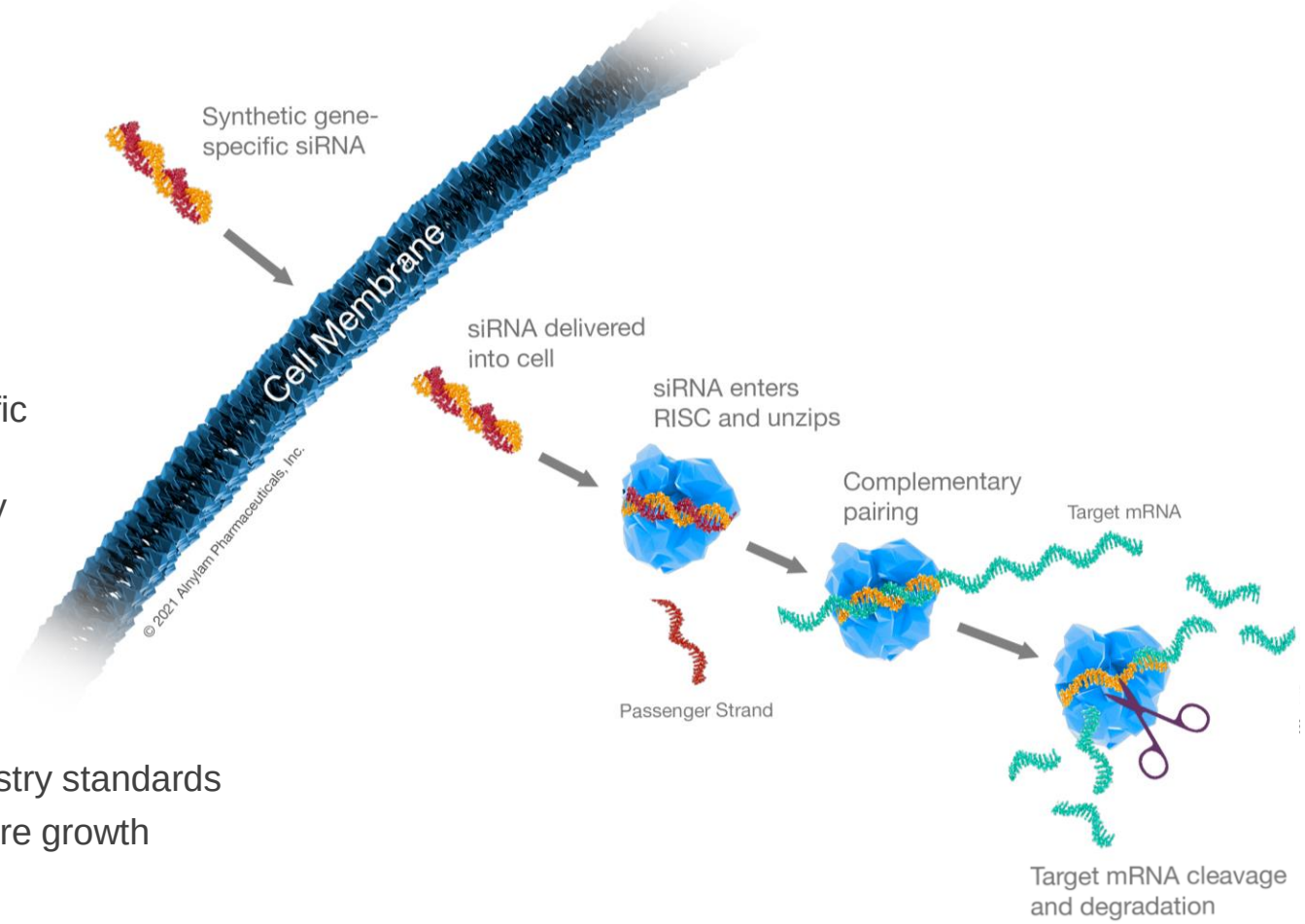
Alnylam Poised to Become a Top-Tier Biotech

Leader in RNAi Therapeutics

- Pioneered new class of innovative medicines
- 5 medicines approved in < 4 years
- Robust clinical pipeline across rare and prevalent diseases
- Global footprint with strong commercial capabilities
- Leading IP estate with fundamental, delivery, and product-specific patent protection
- Strong balance sheet, on path toward financial self-sustainability

Highly differentiated with proven track record and derisked platform

- Modular and reproducible approach to drug development
- Historic probability of clinical success multiples higher than industry standards
- Organic product engine capable of sustaining innovation for future growth
- Track record of setting and exceeding 5-year goals



Multiple Drivers of Future Growth

- TTR Franchise Leadership
- Expansion into Prevalent Diseases
- Engine for Sustainable Innovation

Multiple Drivers of Future Growth

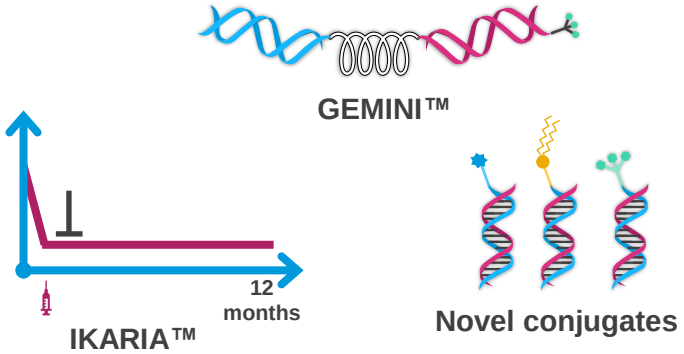
TTR Franchise Leadership

Expansion into Prevalent Diseases

Engine for Sustainable Innovation

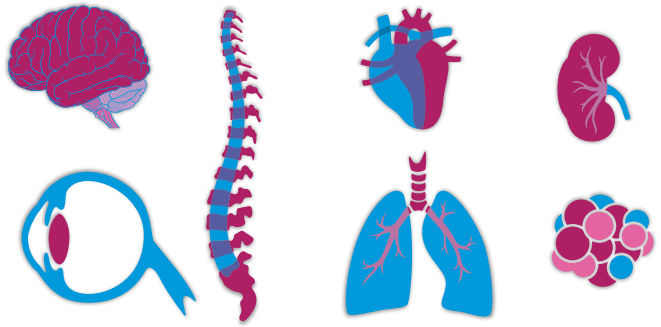
Sources of Sustainable Innovation

Platform Innovation



- Two-decade track record of industry leadership in RNAi
- GEMINI™ combines siRNAs for simultaneous silencing of two transcripts
- IKARIA™ enables robust target knockdown with annual dosing potential
- Novel conjugates with variety of ligands for delivery beyond liver

Extrahepatic Delivery



- Potential for delivery to range of organs
- C16 conjugate provides robust CNS knockdown with wide biodistribution and long duration of action
- Peptide and antibody-based approaches being explored for targeted siRNA delivery to new tissues

Human Genetics

+ Our Future Health

biobank uk

- Sourcing novel, genetically validated targets
- Secured access to large PheWAS databases
- Proven ability to uncover novel gene targets (e.g., *HSD17B13, INHBE*, and more)

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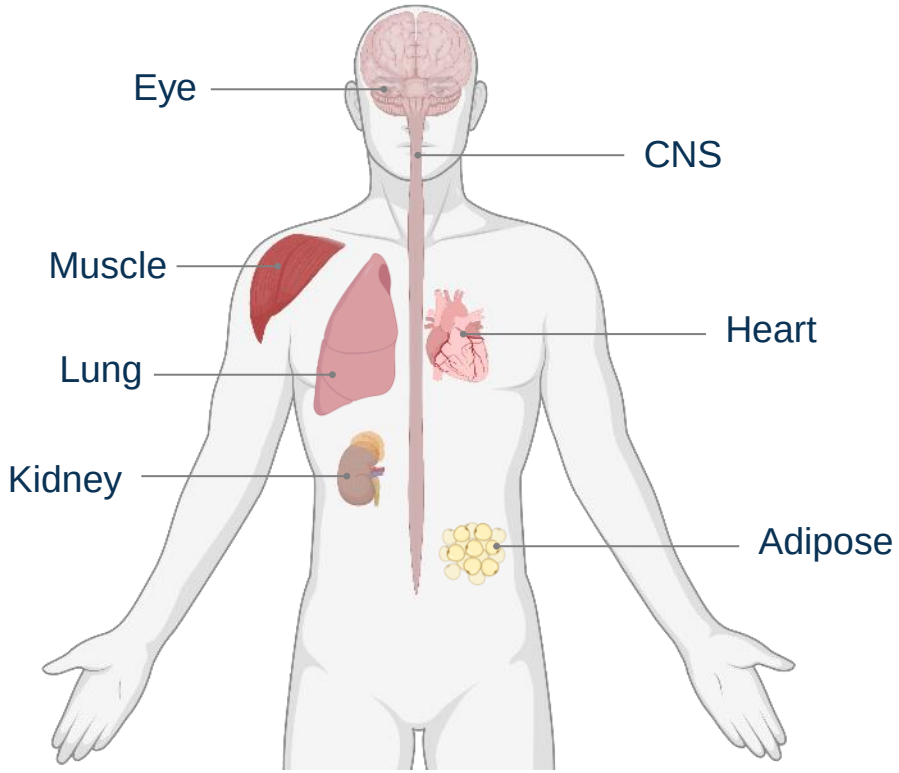
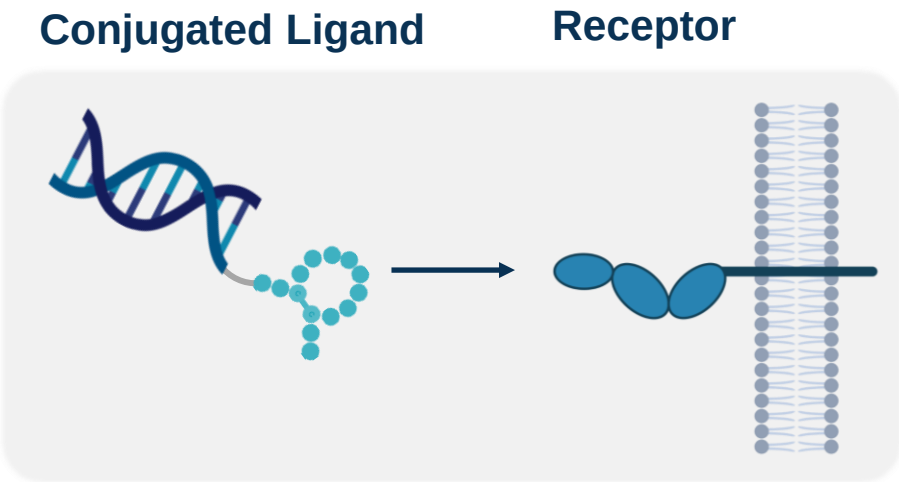
Targeted Delivery Has Potential to Expand Reach of RNAi Therapeutics Beyond Liver

Discovering the Next GalNAc/ASGPR

Priority tissues for targeted delivery



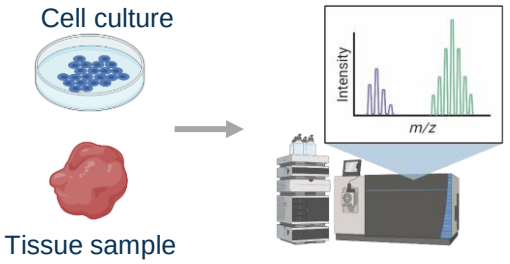


Identification of new receptors and targeting ligands are discrete efforts

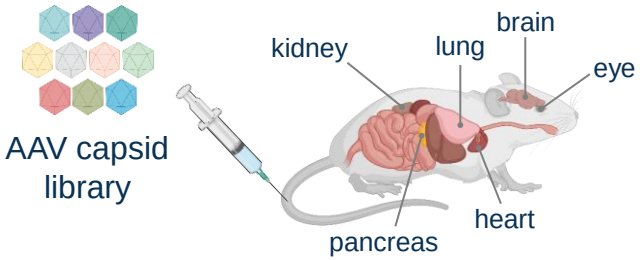
Broad Efforts Ongoing to Identify New Receptors and Ligands for Targeted Delivery

Receptor ID

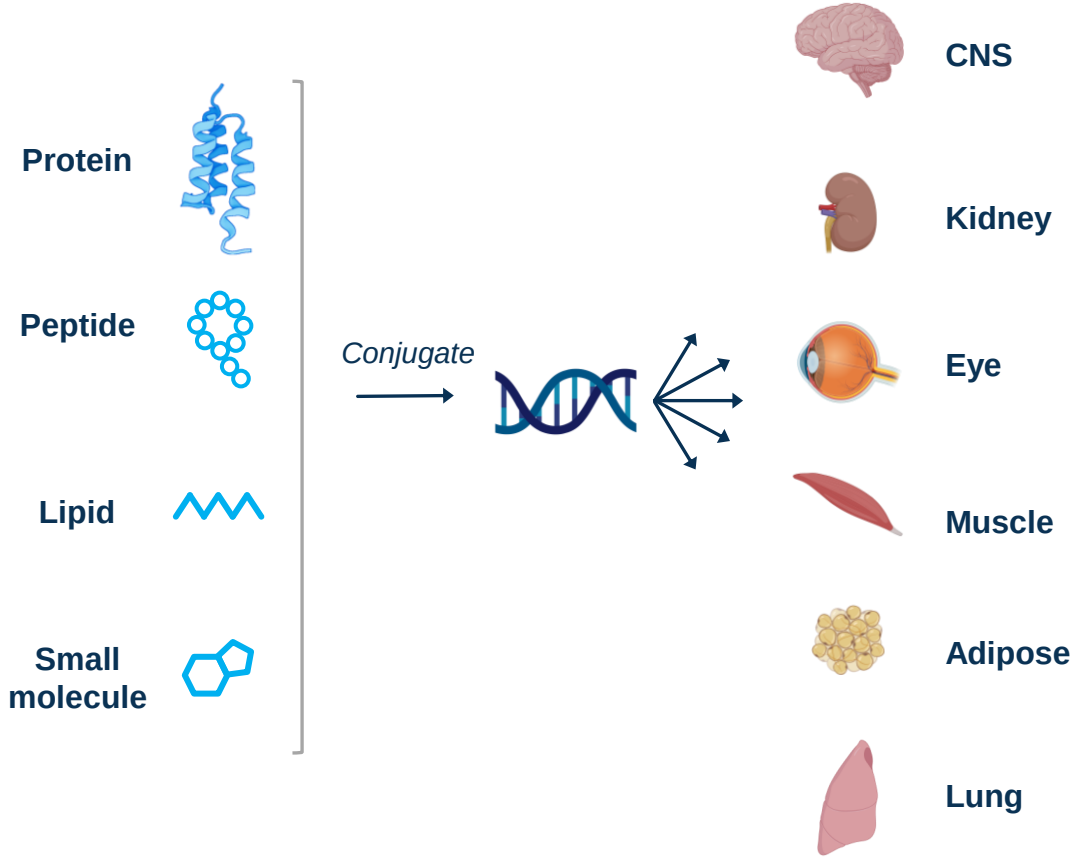
Proteomics/Transcriptomics



Unbiased Discovery

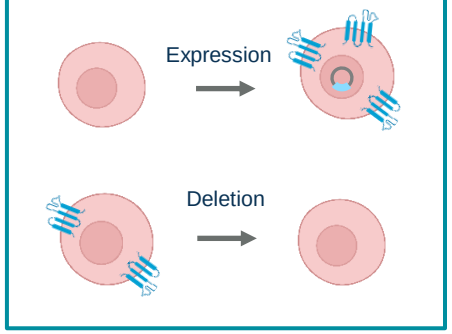


Ligand ID & Validation

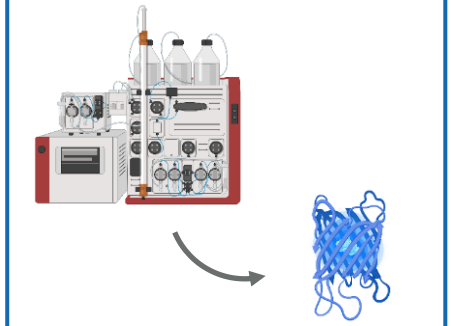


Core Capabilities Established to Identify and Characterize Novel Ligand-Receptor Pairs for Extrahepatic siRNA Delivery

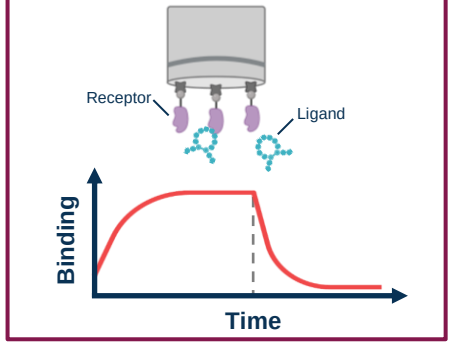
Cell Line Engineering



Protein Production

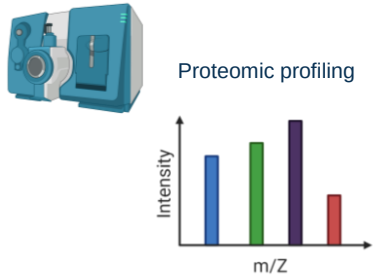


Receptor ↔ Ligand

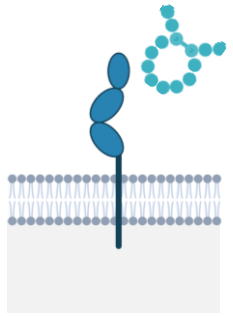


Conjugation

Receptor ID

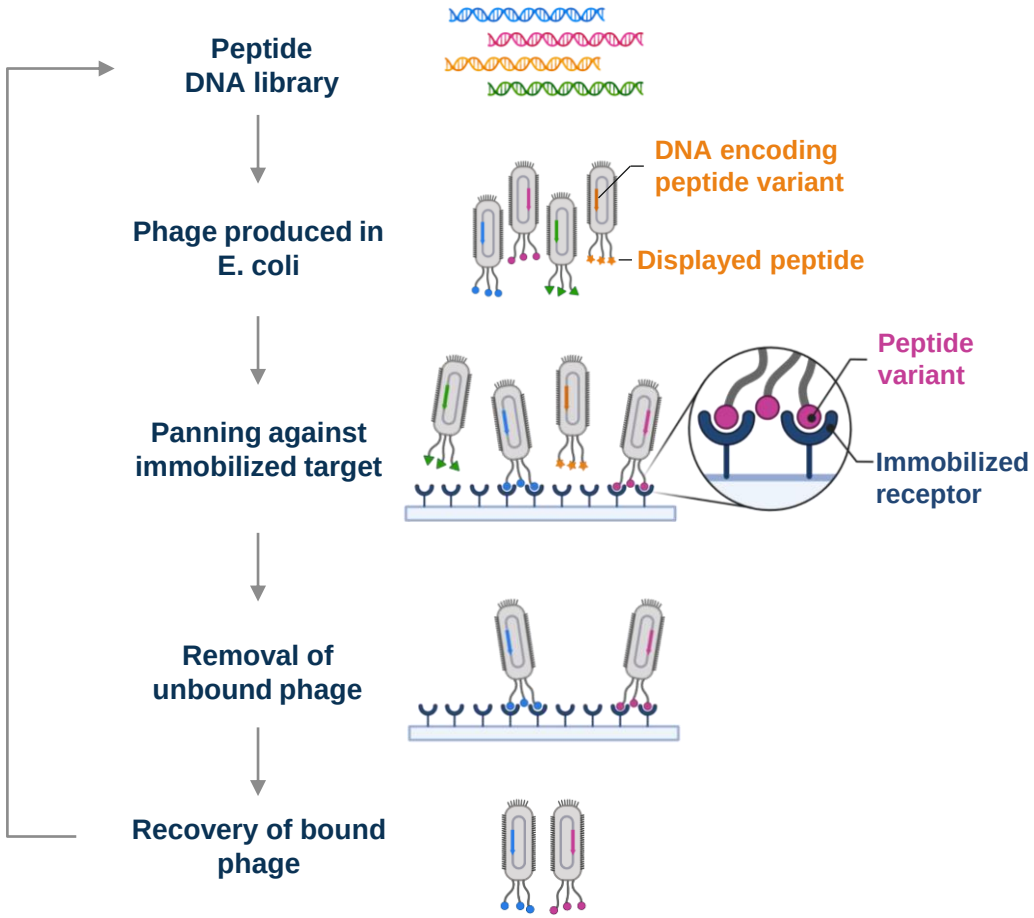


Ligand Discovery

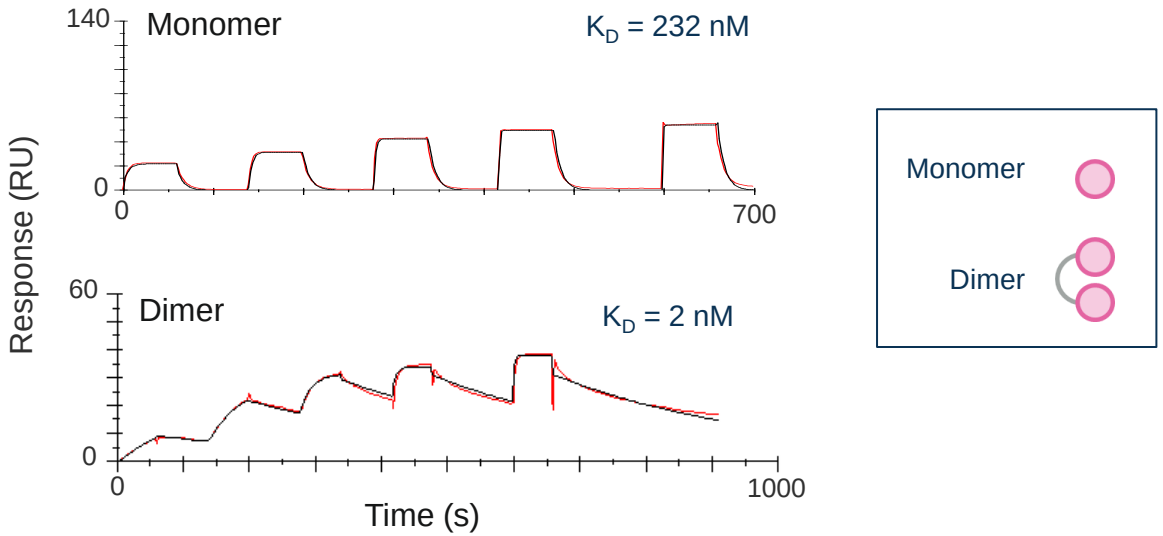


Phage Display Identified High-Affinity Peptide Binder for High-Value Cell Surface Receptor

Phage Display Cycle



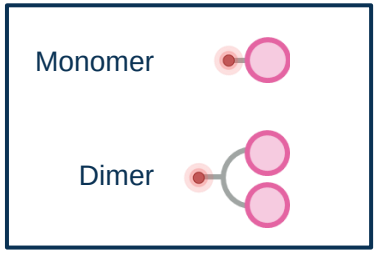
Peptide Characterization

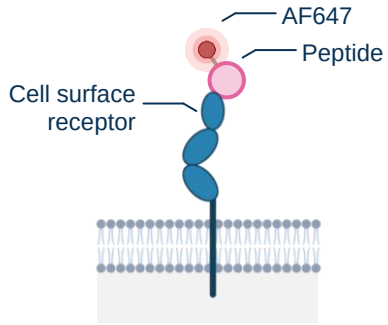


Dimerizing top peptide identified from phage display enhanced apparent affinity >100-fold as measured by SPR

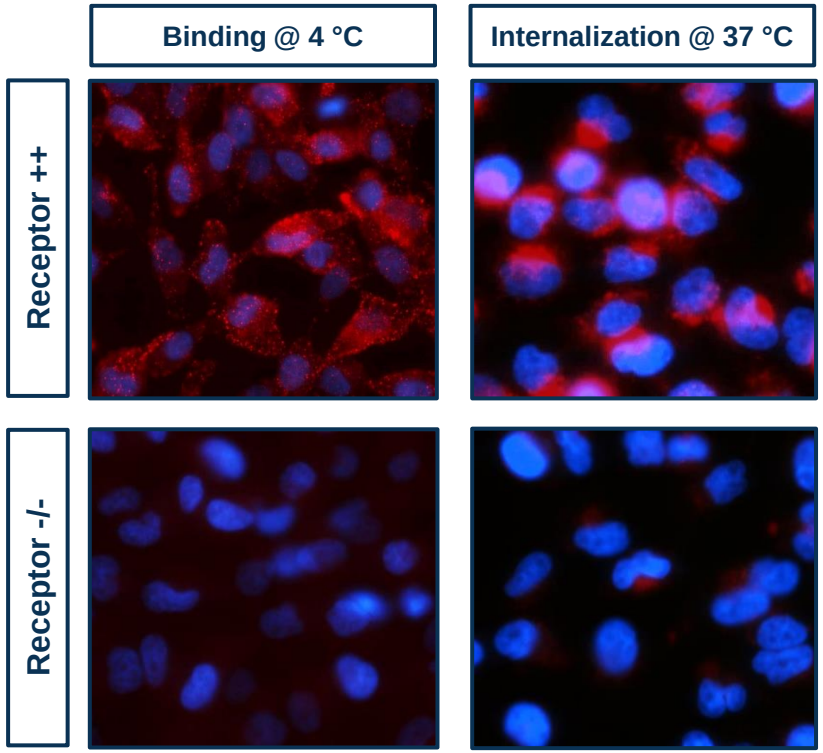
Monomeric and Dimeric Peptides are Specific for Cell Surface Receptor and Rapidly Internalize into Cells

Top peptide from phage display

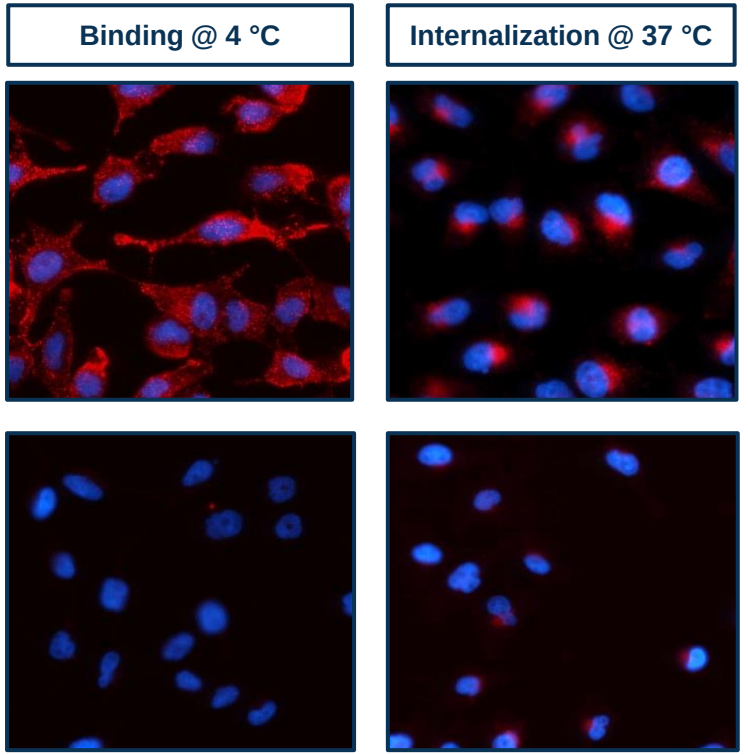




Monomer



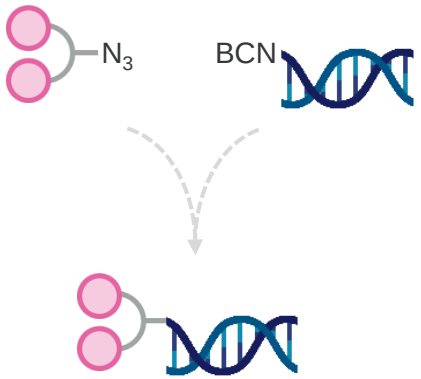
Dimer



Peptide Retains High-Affinity Binding for Target Receptor Upon Conjugation to siRNA

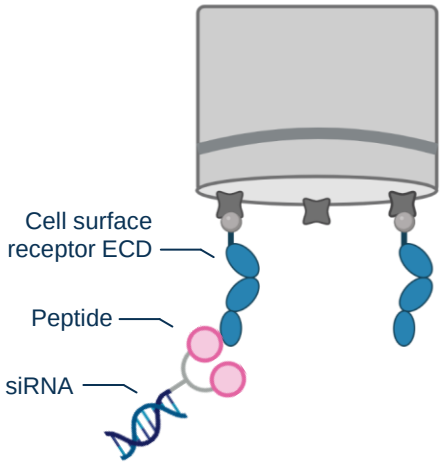
1

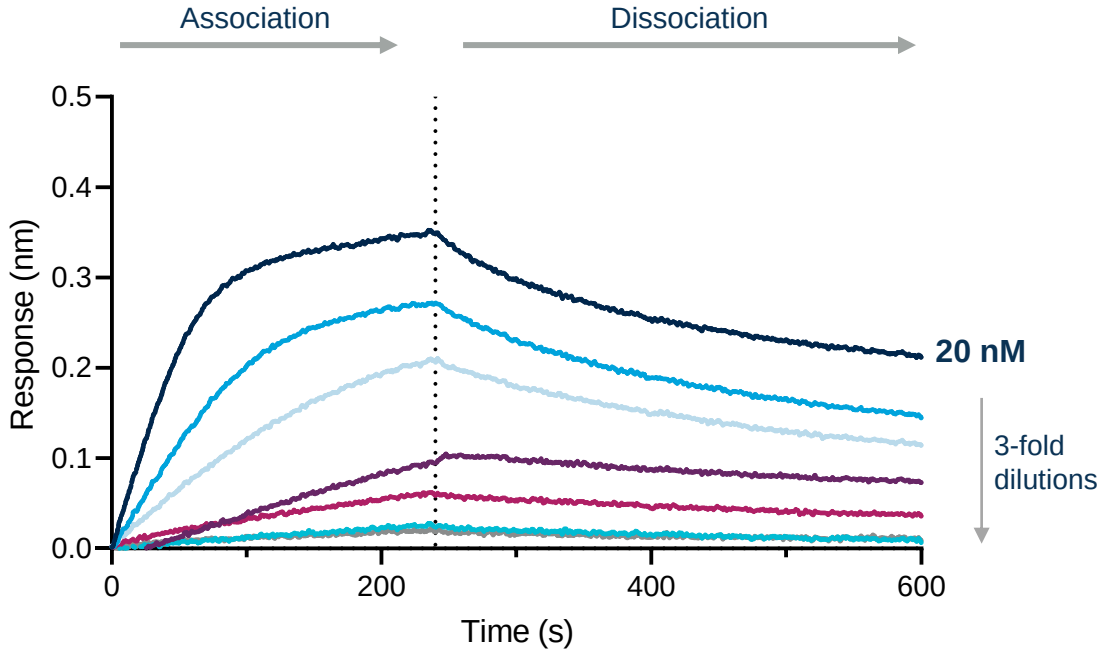
Peptide conjugated by click chemistry



2

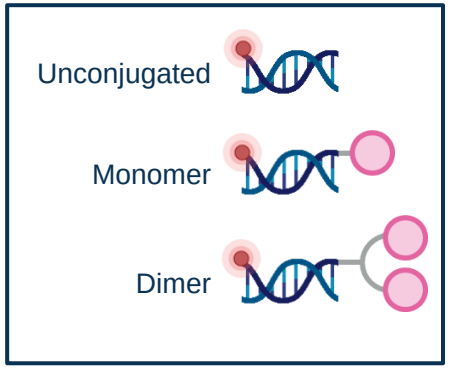
Binding affinity assessed by biolayer interferometry

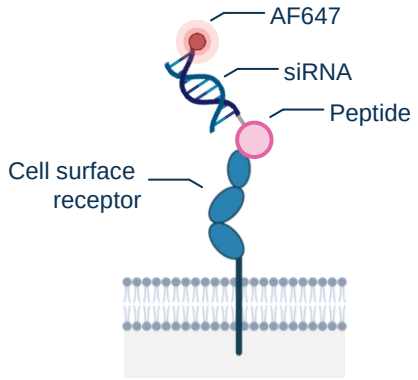


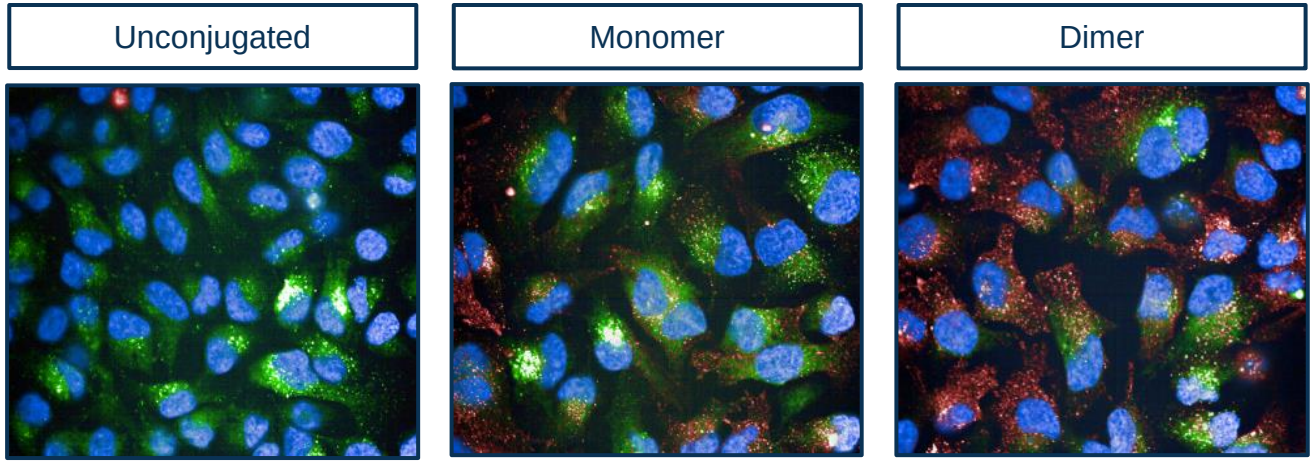


Calculated K_D	k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})
1.6 nM	9.8×10^{5}	1.6×10^{-3}

Confocal Microscopy and Flow Cytometry with Labeled Duplexes Confirm Binding and Internalization in Receptor-Expressing Cells

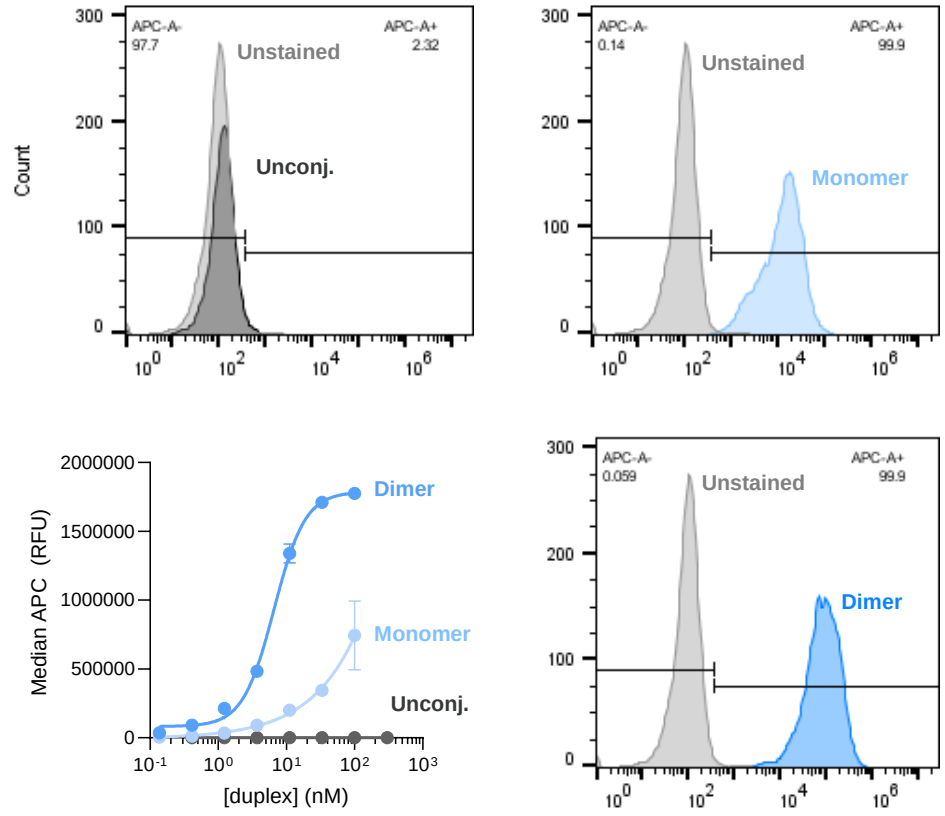




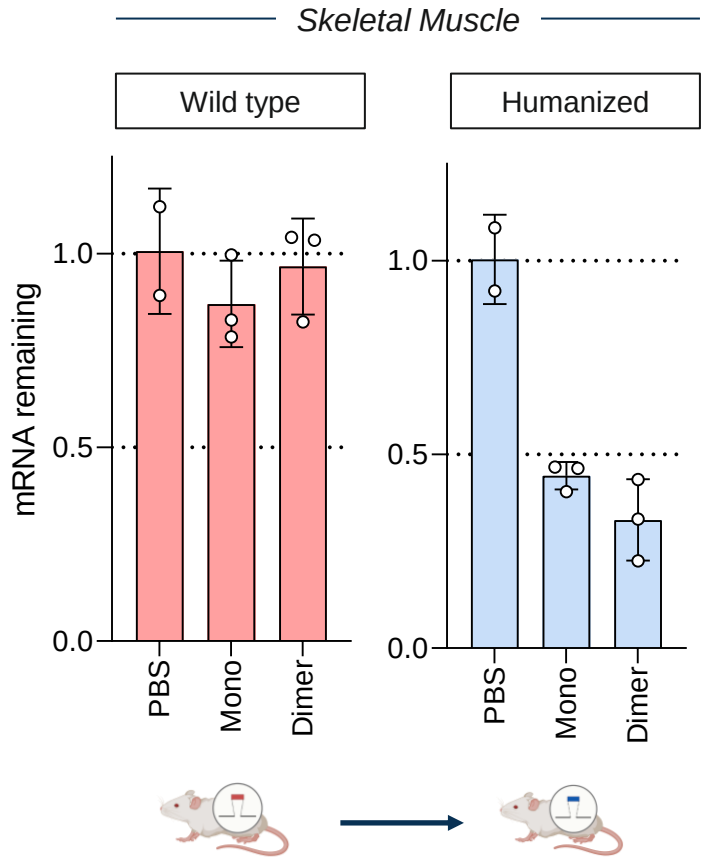


DAPI
Lysotracker
AF647 (siRNA)

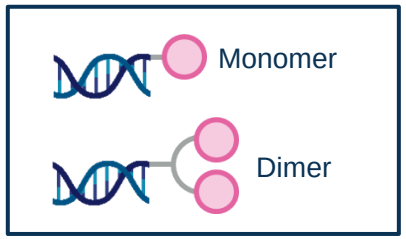
Histograms at 400 pM duplex



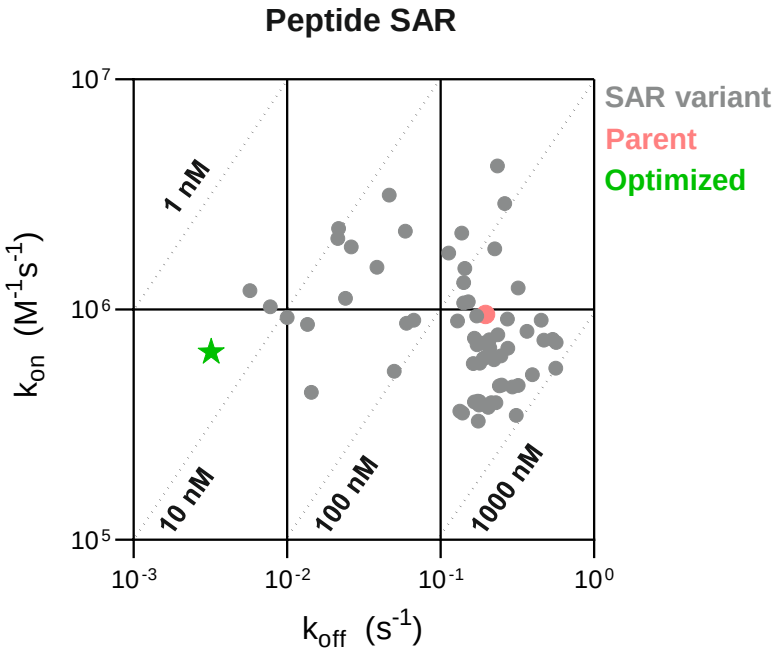
Single Dose of Peptide Conjugate Elicits Knockdown in Skeletal Muscle in Humanized Mouse Model Expressing Target Receptor



Extracellular domain of mouse receptor replaced with orthologous human sequence



Lack of knockdown in WT mice demonstrates targeting ligand specificity for human receptor and negligible off-target activity in skeletal muscle



Monomeric peptide optimization identified variants with >40-fold higher affinity for target receptor

Summary: Targeted Delivery of RNAi Therapeutics to Extrahepatic Tissues

- Systematic efforts ongoing to identify targeted delivery solutions for extra-hepatic RNAi in tissues of interest
- Established key collaborations to evaluate wide range of ligands and high value receptors
- Identified peptide-based ligands for targeted delivery to skeletal muscle and other tissues

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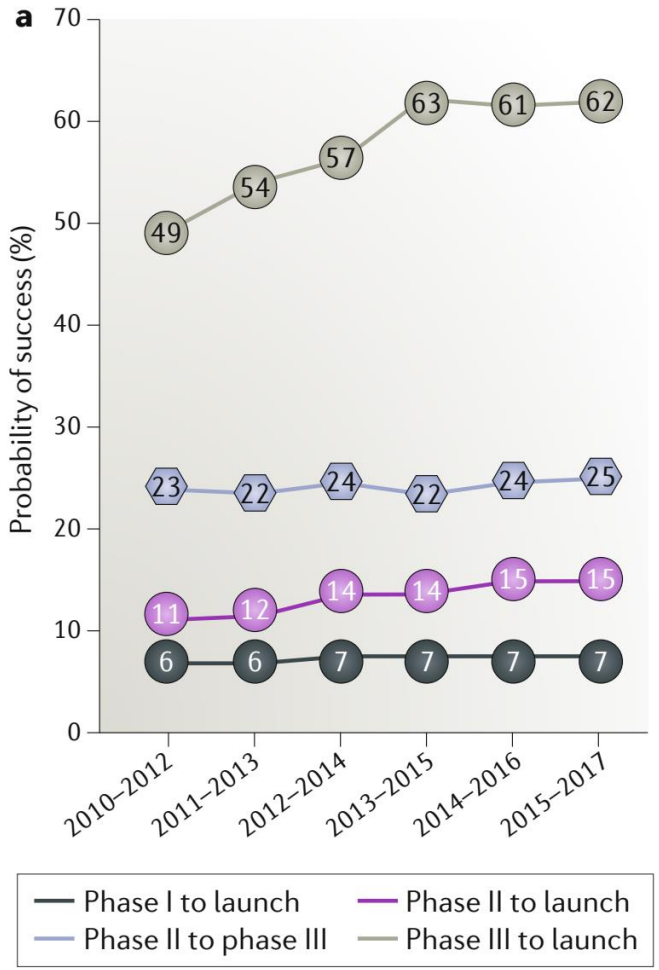
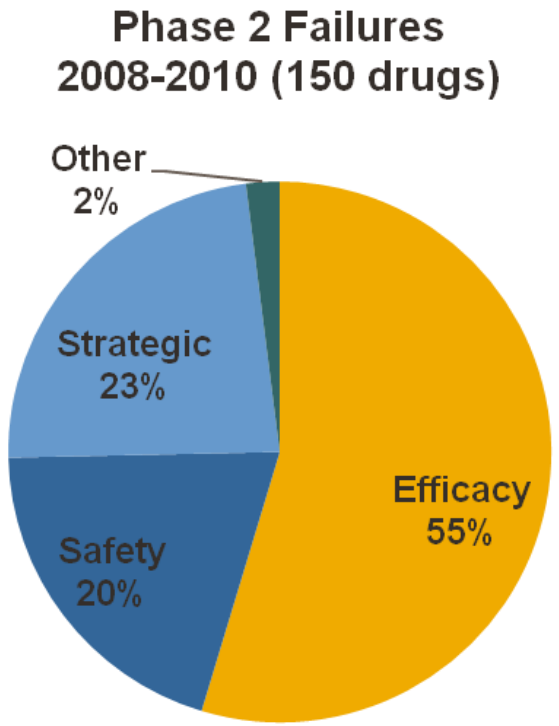
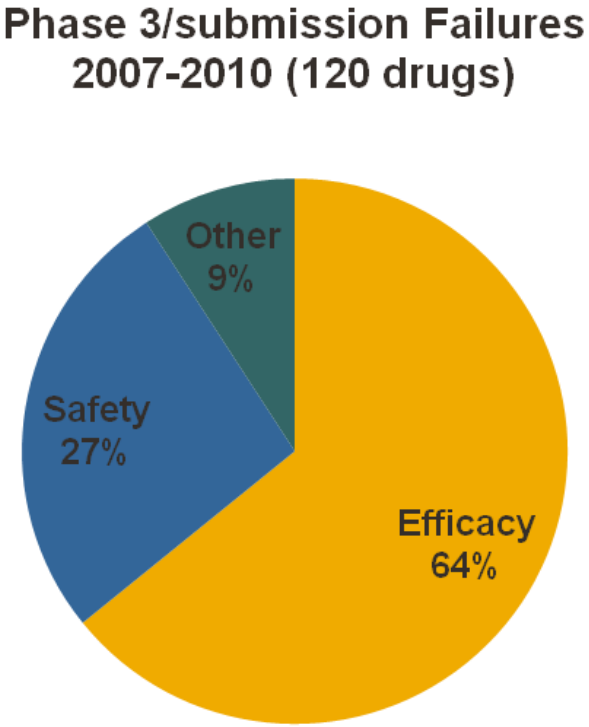
Drug Development Has a High Rate of Failure







Sources: Dowden and Munro (2019) Nat. Rev. Drug Disc. 18, 495-496, Hay et al. (2014) Nat. Biotech. 32:40-51, Arrowsmith & Miller (2013) Nat. Rev. Drug. Disc. 12:569

Traditional Target Discovery Has Had Challenges

Lack of Understanding of Disease Mechanisms in Humans

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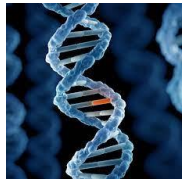
Human Genetically Validated Targets More Likely to Lead to Approved Drugs



Mutation in gene encoding drug target

Phenotype that matches drugs' indication

Medicines are 2x more likely to be approved if target is genetically validated

Progression	*p*(progress|genetics) / *p*(progress|no genetics)
Phase I to Phase II	1.2 (1.1-1.3)
Phase II to Phase III	1.5 (1.3-1.7)
Phase III to Approval	1.1 (1.0-1.2)
Phase I to Phase III	1.8 (1.5-2.1)
Phase I to Approval	2.0 (1.6-2.4)

Nelson et al., Nat Gen. 2015,47:856-60.

Investing to Discover Next Wave of Genetically Validated Targets

Alnylam HUMAN GENETICS

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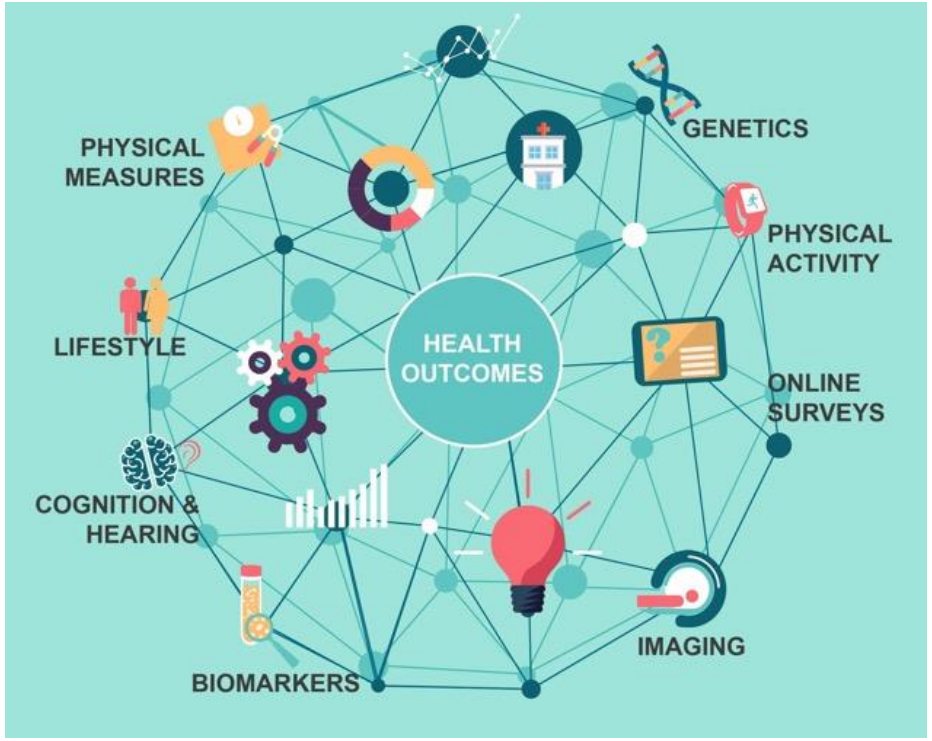
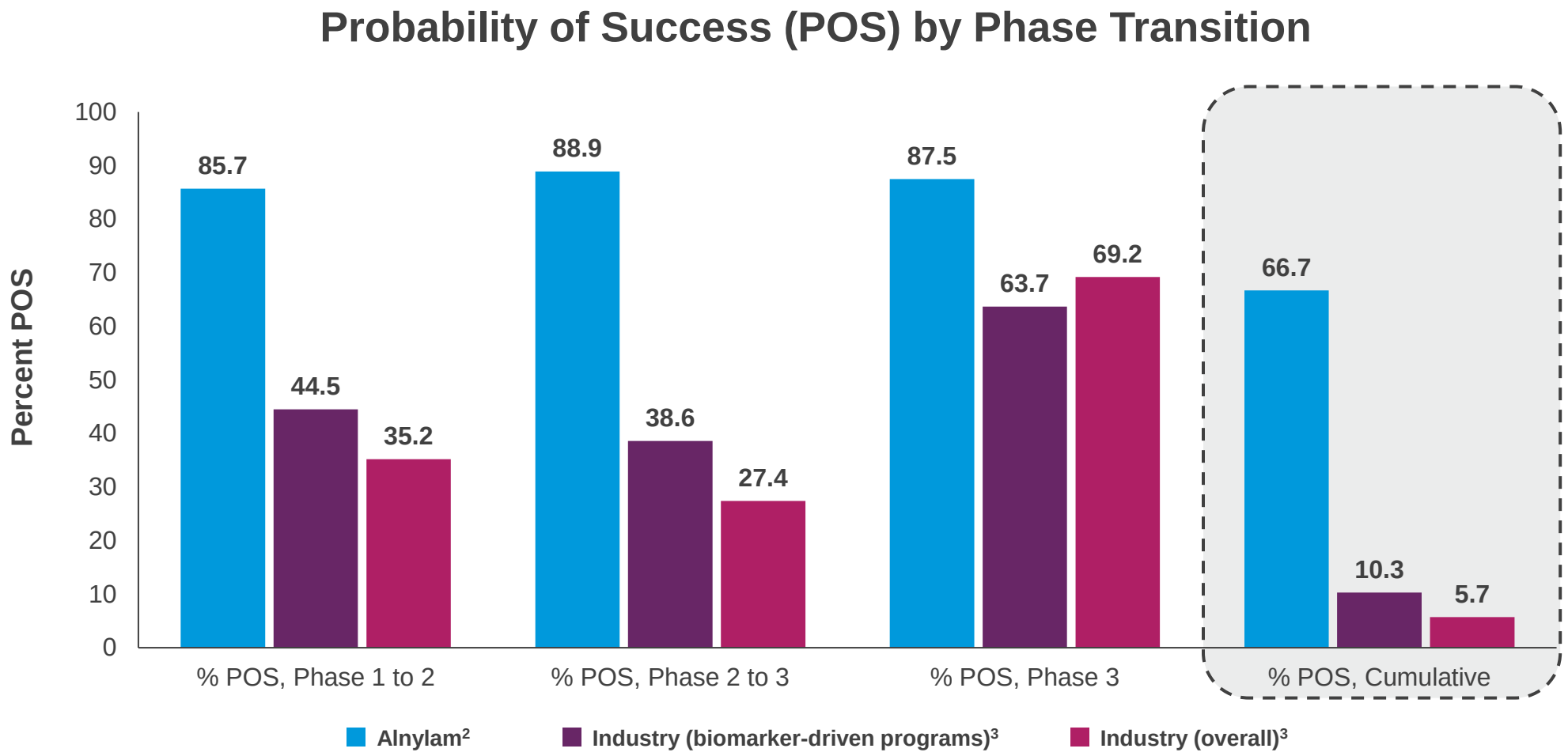


High-Yield Productivity of Alnylam RNAi Therapeutics Platform

Comparison of Historical Industry Metrics to Alnylam Portfolio[1]



[1] Analysis as of August 2022; Past rates of Alnylam and industry respectively may not be predictive of the future

[2] Alnylam programs biomarker-driven at all stages of development (100%); figures include Alnylam-originated molecules now being developed by partners

[3] Wong et al., Biostatistics (2019) 20, 2, pp. 273–286

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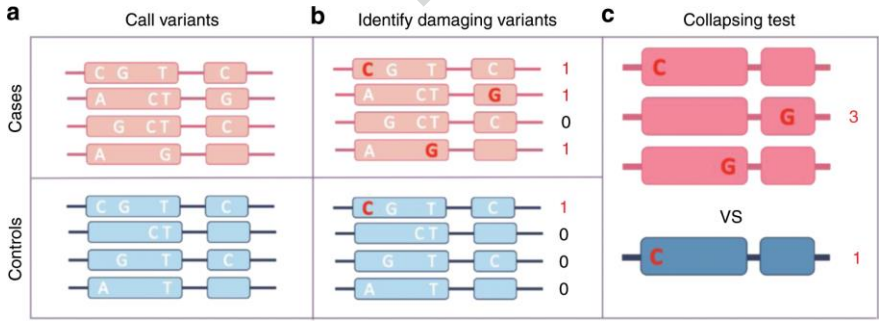
Finding Drug Targets Using Genetics

UK Biobank
Genetics: exome sequencing
Phenotypes:
- Diseases
- Biomarkers
- Traits causally related to disease (from Mendelian Randomization)

Gene-level tests



Loss of function + damaging missense variants

INHBE loss of function and lower waist-to-hip ratio

Graphic modified from Cirulli et al., Nat Comm 2020
https://doi.org/10.1038/s41467-020-14288-y

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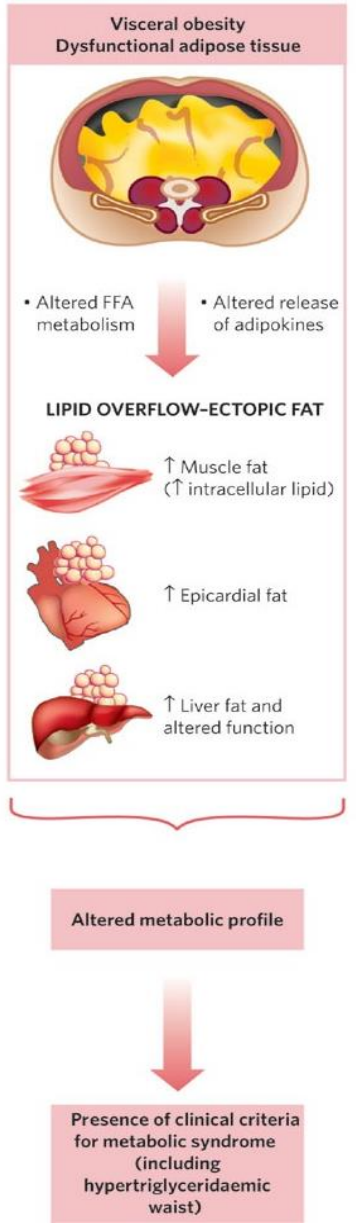
Rare loss of function variants in the hepatokine gene *INHBE* protect from abdominal obesity

Abdominal Obesity Contributes to Cardiometabolic Disease

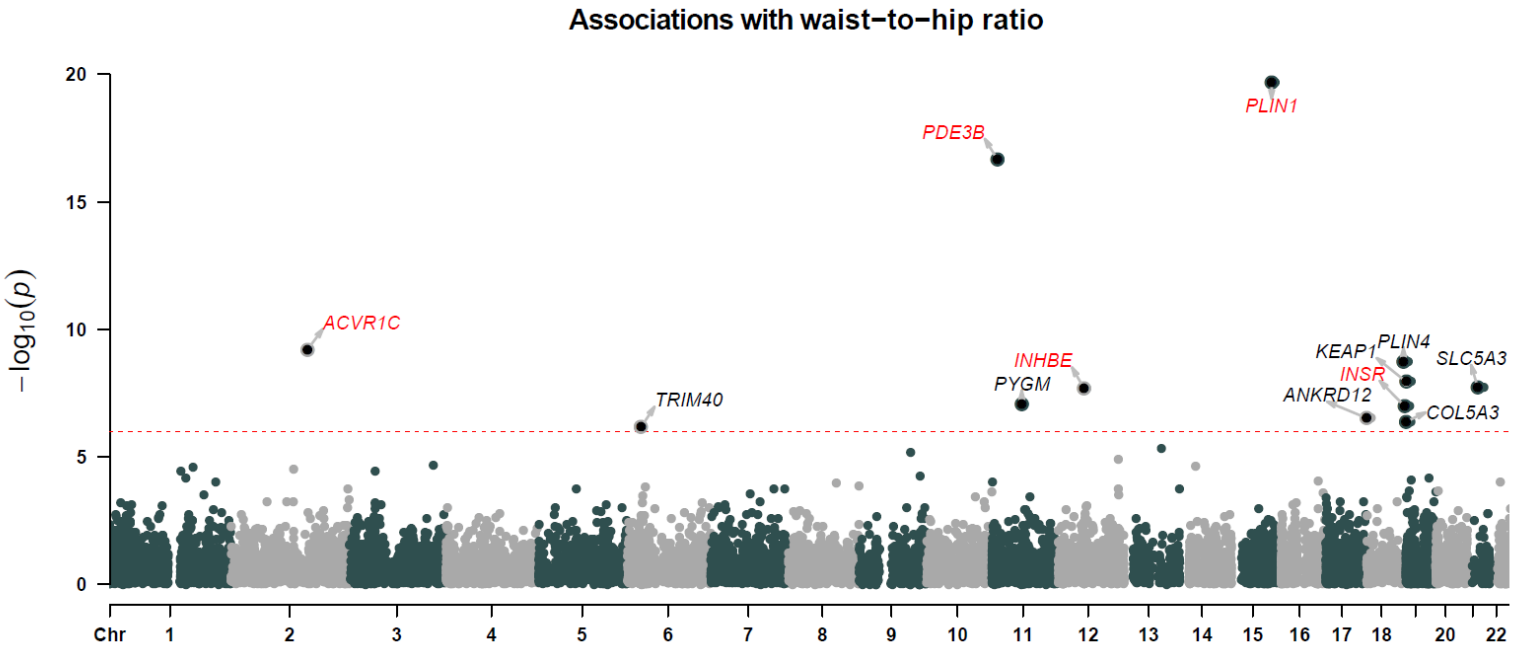
- Abdominal obesity is most prevalent manifestation of metabolic syndrome [1]
- Abdominal fat is contributor to cardiovascular disease and metabolic risk beyond BMI [2,3]
- **Waist-to-hip ratio** corrected for BMI (WHR) correlates with direct imaging of abdominal fat
- Mendelian Randomization shows increased WHR leads to increased risk of **type 2 diabetes** and **coronary heart disease** [4,5]
- Genetic analysis of WHR can identify new targets for cardiometabolic disease that are **mechanistically distinct** from current therapies

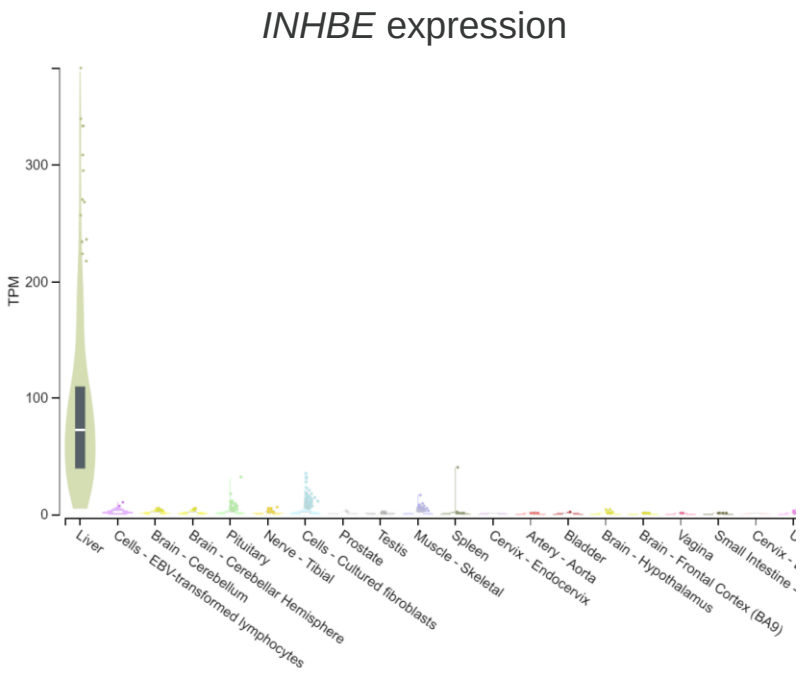


1. Despres et al., Nature 2016 https://doi.org/10.1038/nature05488
2. Neeland et al., Lancet Diabetes Endocrinol 2019 https://doi.org/10.1016/S2213-8587(19)30084-1
3. Scheja et al., Nat Rev Endocrinol 2019 https://doi.org/10.1038/s41574-019-0230-6
4. Emdin et al., JAMA 2017 https://doi.org/10.1001/jama.2016.21042
5. Dale et al., Circulation 2017 https://doi.org/10.1161/CIRCULATIONAHA.116.026560

Prioritizing Genes Associated with Waist-to-Hip Ratio

- Gene-level tests on predicted loss of function (pLOF), damaging missense and pLOF+missense variants



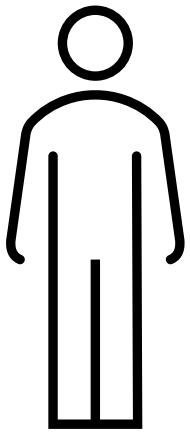


- Criteria for a good RNAi target
  1. Protective loss of function
  2. No pathologic phenotypes
  - ➢ *INHBE, ACVR1C, PDE3B* and *PLIN1*
- ***INHBE*** is the only one of these genes which is **liver-enriched** (hepatocyte-specific)

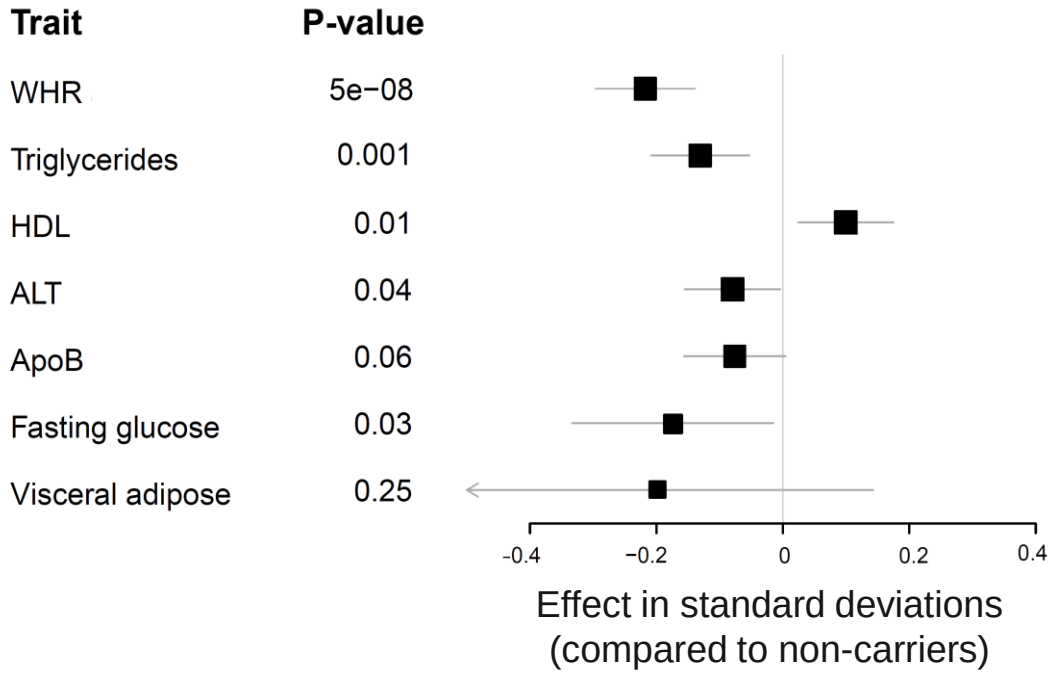
Deaton et al., Nat Comm 2022 https://doi.org/10.1038/s41467-022-31757-8

INHBE pLOF Carriers Have Favorable Metabolic Profile

- Replicated association of *INHBE* pLOF with WHR in independent cohort (AMP-T2D-GENES)
- Carriers have lower triglycerides, higher HDL cholesterol, lower alanine transaminase levels (suggesting better liver health), lower fasting glucose, fewer metabolic syndrome traits



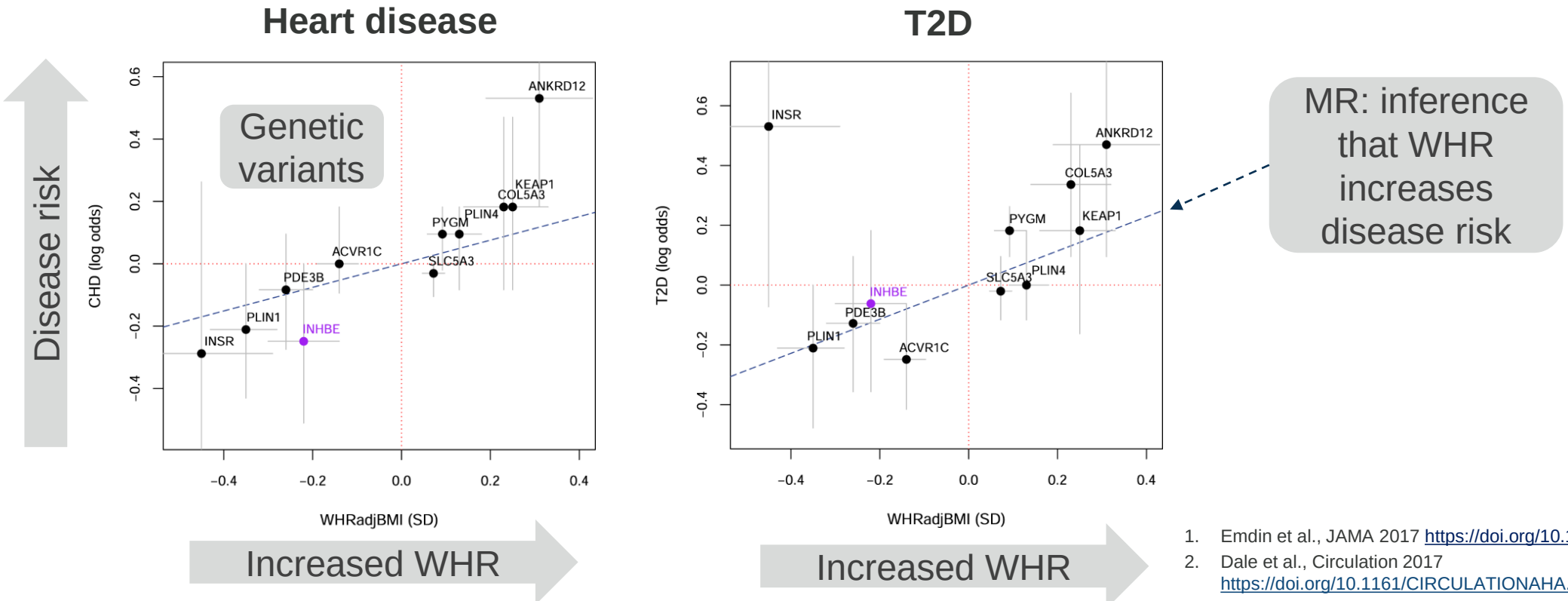
Genetic decrease in INHBE (~50%)



- Did not detect any associations suggesting adverse effects of *INHBE* pLOF

Fewer Cases of T2D and Heart Disease for *INHBE* pLOF Carriers

- Causal relationship between WHR and cardiometabolic disease risk has been established [1,2]
- Fewer cases of coronary heart disease and type 2 diabetes (T2D) for *INHBE* pLOF carriers compared to non-carriers
  - Effects on disease proportional to effect on WHR based on estimates from Mendelian Randomization (MR)[1]

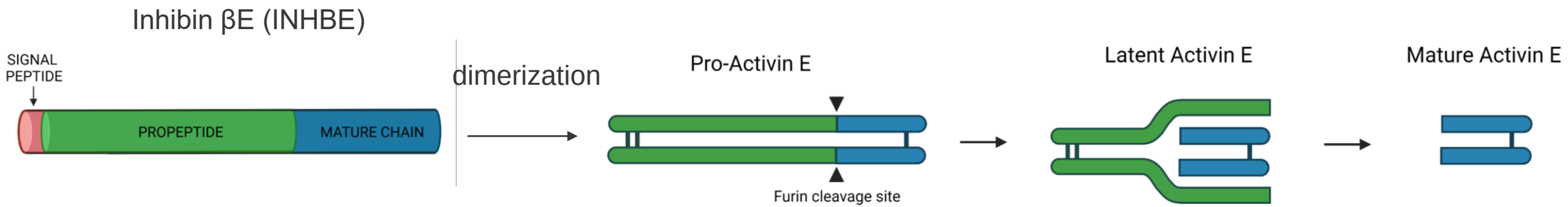


1. Emdin et al., JAMA 2017 https://doi.org/10.1001/jama.2016.21042
2. Dale et al., Circulation 2017 https://doi.org/10.1161/CIRCULATIONAHA.116.026560

INHBE Encodes Subunit of Activin E

Structural Similarity to TGFβ Superfamily

- *INHBE* encodes inhibin βE subunit which likely dimerizes to form **activin E**, a secreted protein
- Produced as pro-protein which dimerizes and is processed into mature protein prior to receptor binding[1]

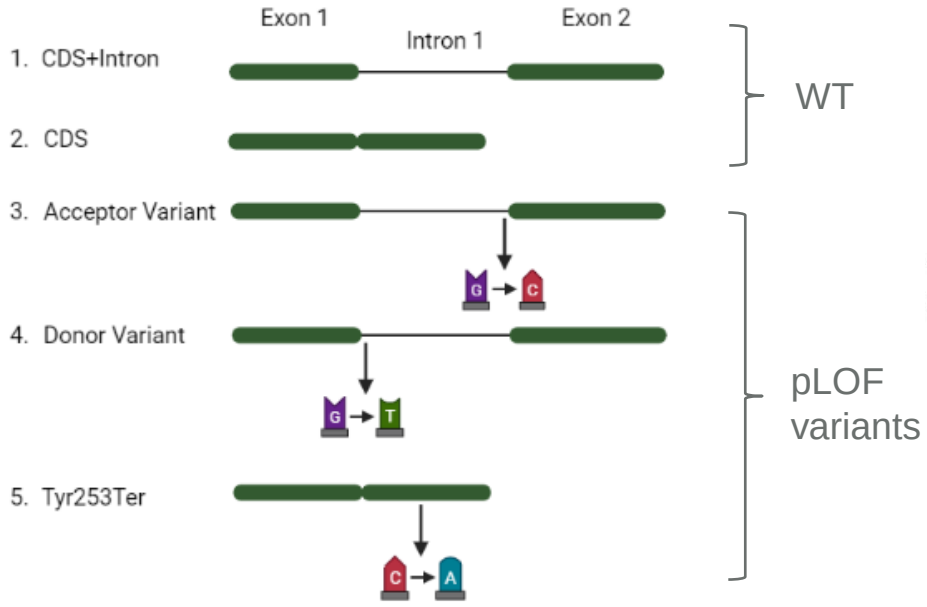


1. Lodberg et al., Cytokine and Growth Factor Rev 2021 https://doi.org/10.1016/j.cytogfr.2021.04.001; Schematics created with BioRender.com

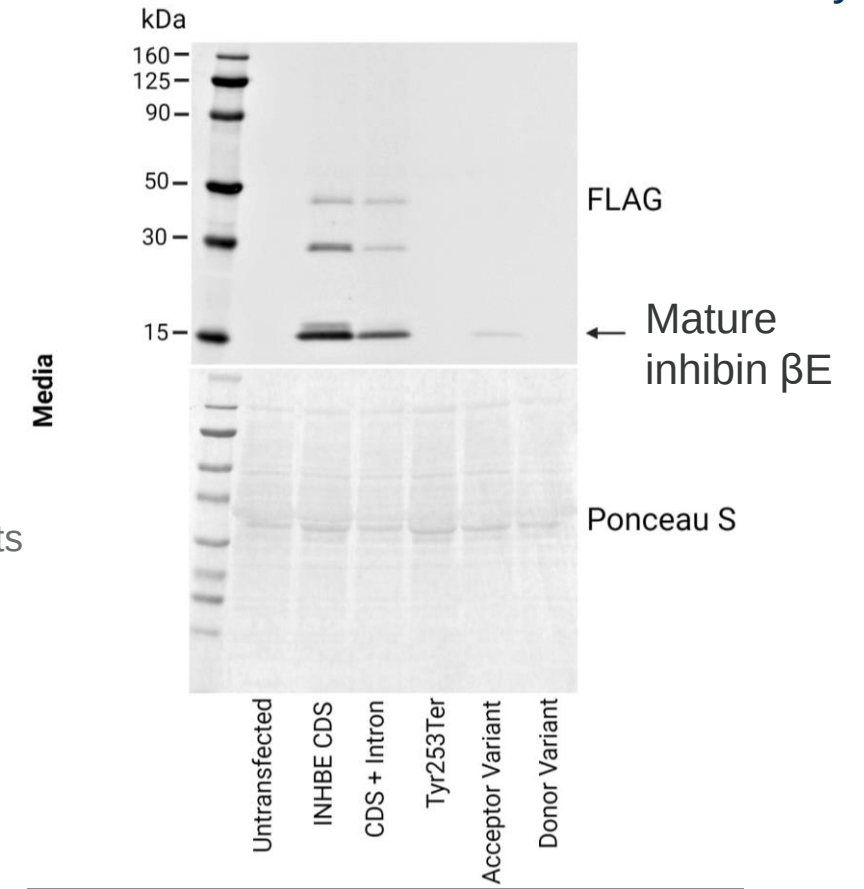
INHBE pLOF Variants Reduce or Eliminate Secreted Activin E

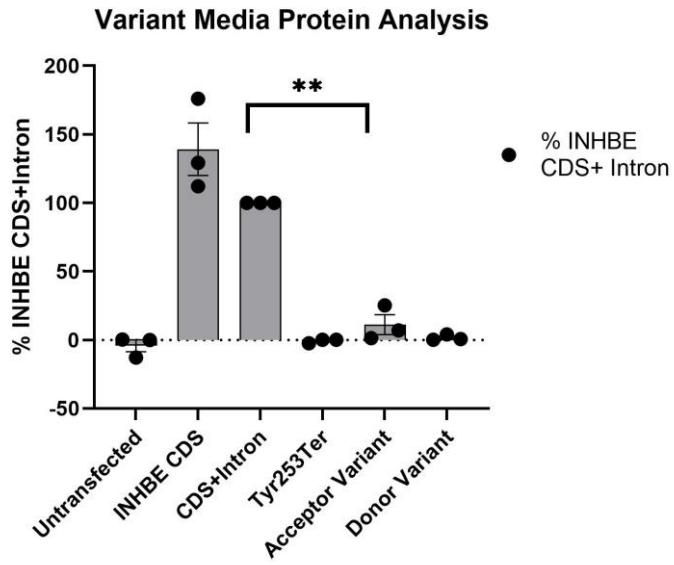
- Do *INHBE* pLOF variants really result in loss of function?
  - Splice acceptor, splice donor and stop gain variant (Tyr253Ter)

1. Overexpressed FLAG-tagged WT or variant *INHBE* in HEK293T cells



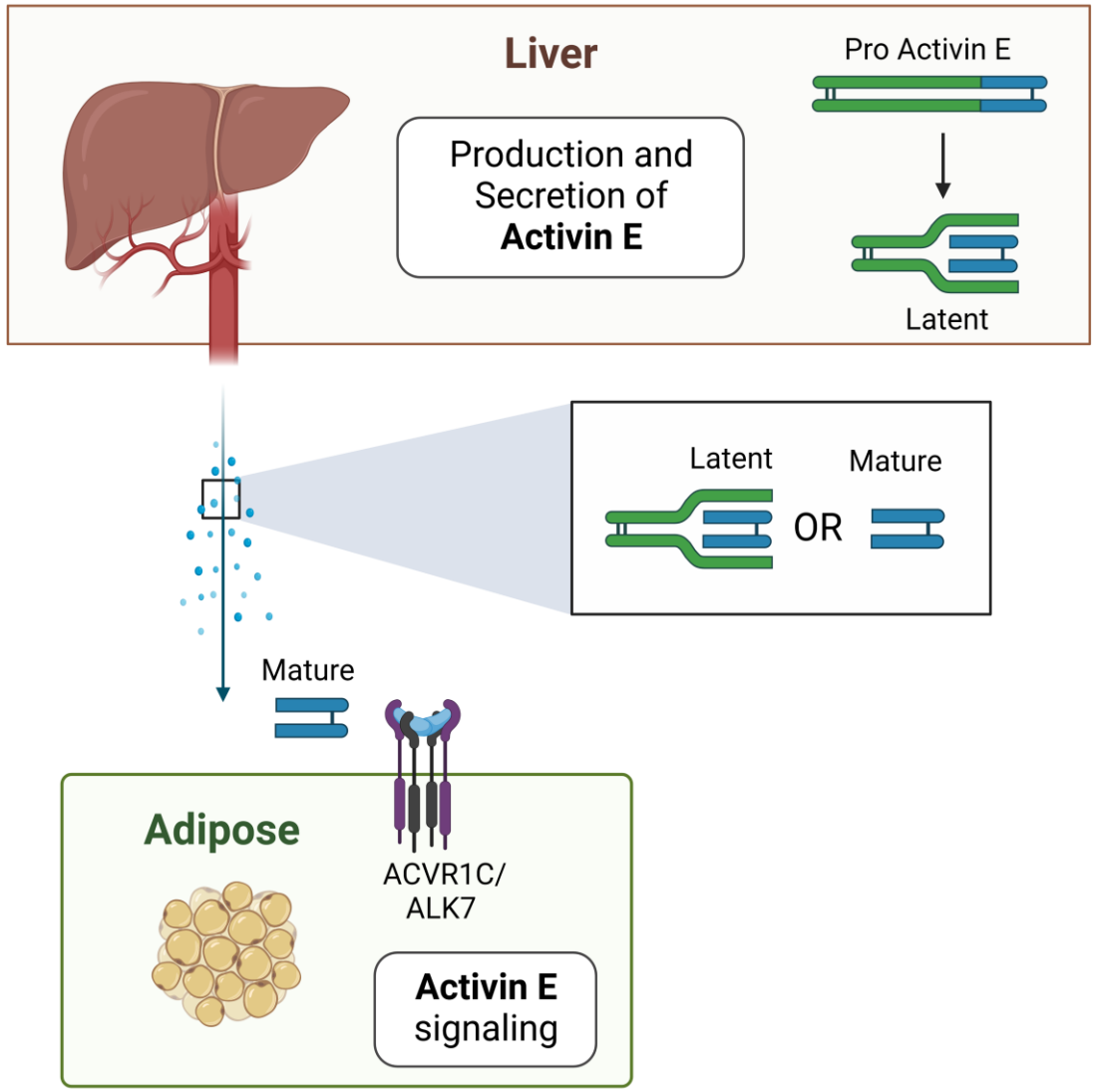
2. Protein in the media reduced 90% or more by pLOF variants





Activin E May Function as Hepatokine Modulating Abdominal Fat

- Activin E secreted from liver and likely binds to receptors on adipose tissue
- Activin E receptors and signaling are not understood
- ALK7 (encoded by *ACVR1C*) is a candidate type 1 receptor for activin E (its genetics "phenocopy" *INHBE* pLOF)



Created with BioRender.com

Genetics Support Development of RNAi Therapeutic Targeting INHBE

- Abdominal obesity and metabolic syndrome impact more than 20% of adults worldwide and have causal relationship with cardiometabolic disease
- Association of *INHBE* pLOF with lower WHR and favorable metabolic profile support potential of INHBE to be evaluated as novel therapeutic target for treatment of cardiometabolic disease
- Currently pursuing development candidate for RNAi therapeutic targeting INHBE using IKARIA platform

Agenda

Welcome
- Joshua Brodsky – Senior Director, Investor Relations & Corporate Communications

Introduction
- Vasant Jadhav, Ph.D. – Senior Vice President, Research

Targeted Delivery of RNAi Therapeutics to Extrahepatic Tissues
- Kevin Dooley, Ph.D. – Associate Director, Research

Alnylam Human Genetics Overview
- Paul Nioi, Ph.D. – Vice President, Research

Case Study: Leveraging Human Genetics to Identify a Novel Target for Abdominal Obesity
- Aimee Deaton, Ph.D. – Associate Director, Human Genetics

Q&A Session

Upcoming RNAi Roundtables

CNS Delivery and ALN-APP, in Development for the Treatment of Alzheimer's Disease and Cerebral Amyloid Angiopathy

Tuesday, November 1, 11:00 am ET

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company's website, https://capella.alnylam.com

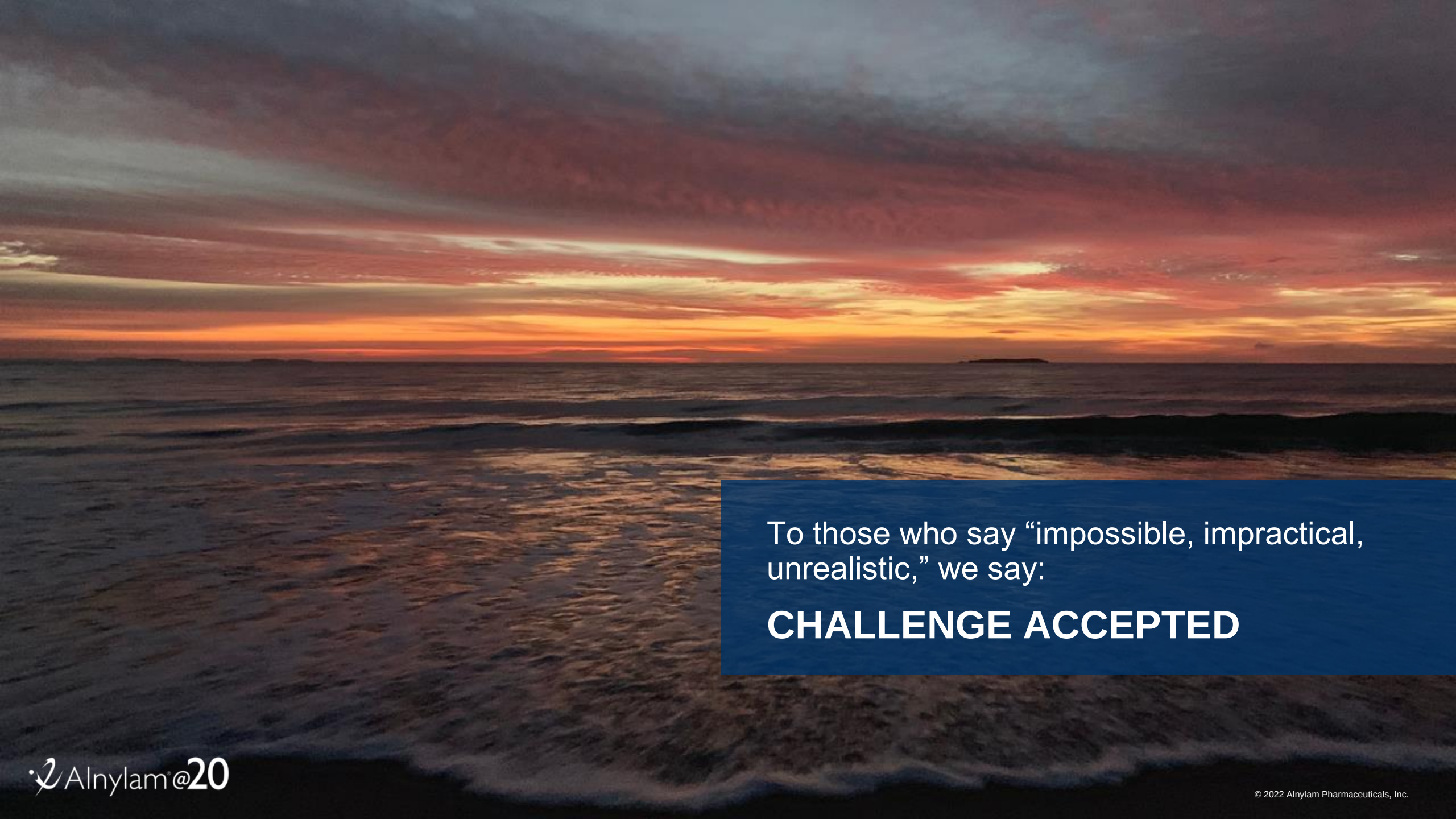
Save the date!

Alnylam® R&D Day

December 15, 2022

A VIRTUAL EVENT

Registration information coming soon.



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