The ECO Synthesis™ Platform & The Future of RNAi Therapeutics Manufacturing

Virtual Key Opinion Leader Event

December 8, 2023

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We engineer **enzymes**

Forward Looking Statements; Disclaimer

These slides contain forward-looking statements that involve risks and uncertainties. These statements relate to future events or our future financial or operational performance and involve known and unknown risks, uncertainties and other factors that could cause our actual results or levels of activity, performance or achievement to differ materially from those expressed or implied by these forward-looking statements. In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “could,” “would,” “expects,” “plans,” “anticipates,” “believes,” “estimates,” “projects,” “predicts,” “potential” or the negative of these terms, and similar expressions and comparable terminology intended to identify forward-looking statements. In addition, forward-looking statements include all statements that are not historical facts including, but not limited to, the evolving oligonucleotide manufacturing landscape and the potential for fully enzymatic oligonucleotide manufacturing technologies to drive improvements in sustainability metrics and green chemistry principles, including anticipated improvements in speed, product purity, yield, and energy efficiency of a fully enzymatic manufacturing process relative to SPOS, LPOS and ligation; the future regulatory framework applicable to enzymatic synthesis; the level of future supply and demand for RNAi therapeutics based on product candidates in development; our expectations regarding the successful execution and commercialization of our ECO Synthesis™ platform, including those regarding the platform’s potential to drive innovation in oligonucleotide therapeutic manufacturing; timing of the commercial launch of Codexis’ dsRNA ligase offering and its potential features and benefits; timing of news updates regarding the ECO Synthesis™ platform and Codexis’ achievement of key development, pre-commercial and commercial milestones; and Codexis’ generating positive cash flow around the end of 2026. These forward-looking statements represent our estimates and assumptions only as of the date hereof, and, except as required by law, Codexis undertakes no obligation to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise.

Actual results could differ materially from Codexis' current expectations for a variety of reasons, including due to the factors set forth in Codexis’ most recently filed periodic report, including under the caption “Risk Factors,” and Codexis’ other current and periodic reports filed with the SEC. If any of these risks or uncertainties materialize, or if Codexis’ underlying assumptions prove to be incorrect, actual results or levels of activity, performance or achievement, or any of the foregoing forward-looking statements, may vary significantly from what Codexis projected.

Today’s guest speakers are presenting on behalf of Codexis but are expressing their own independent perspectives as leaders in the space.

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Today's Guest Speakers

John Maraganore, PhD

Founder and Former Chief Executive Officer,
Alnylam Pharmaceuticals

David Butler, PhD

Chief Technology Officer,
Hongene Biotech Corporation

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Today's Agenda & Speakers

Welcome & Introduction

Stephen Dilly – President & Chief Executive Officer, Codexis

RNAi Therapeutics: a Growing Modality

John Maraganore – Founder & Former CEO, Alnylam Pharmaceuticals

The RNAi Therapeutics Manufacturing Landscape

David Butler – Chief Technology Officer, Hongene Biotech Corporation

ECO Synthesis™ Platform: Technical Overview

Stefan Lutz – SVP, Research, Codexis

Evolving Commercial Strategy & Upcoming Milestones

Kevin Norrett – Chief Operating Officer, Codexis

Q&A

Stephen Dilly – Moderator

John Maraganore, PhD

Founder and Former Chief Executive Officer,
Alnylam Pharmaceuticals

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Disclosure

- John Maraganore is founding CEO of Alnylam Pharmaceutics
  - Retired from Alnylam at end-2021 after building company for ~20 years
  - Remains a significant shareholder
- Maraganore is currently CEO and Principal of JMM Innovations, LLC, committed to advancing novel medicines to patients
  - Serves as advisor to a number of investment groups, including: ARCH Ventures; Atlas Ventures; Blackstone Life Sciences; RTW Investments
  - Serves as a Board Director of a number of public and private biopharmaceuticals, including: Beam Therapeutics; Kymera Therapeutics; ProKidney Corp; Takeda Pharmaceuticals; Aera Therapeutics; Aerium Therapeutics; Aitia; HeMab Therapeutics; Orbital Therapeutics
  - Serves as strategic advisor for a number of public and private biopharmaceutical companies, including Codexis
  - Serves as Director/Advisor for a number of non-profit organizations and patient advocacy groups, including: Ariadne Labs; BIO; MGH Research Advisory Council; N-Lorem; Nucleate; Termeer Foundation

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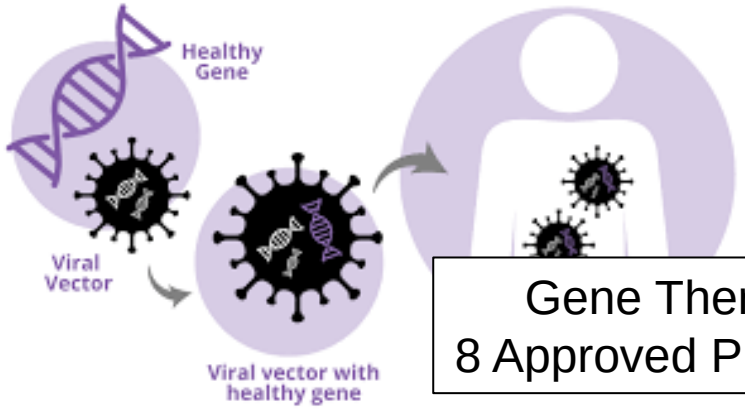
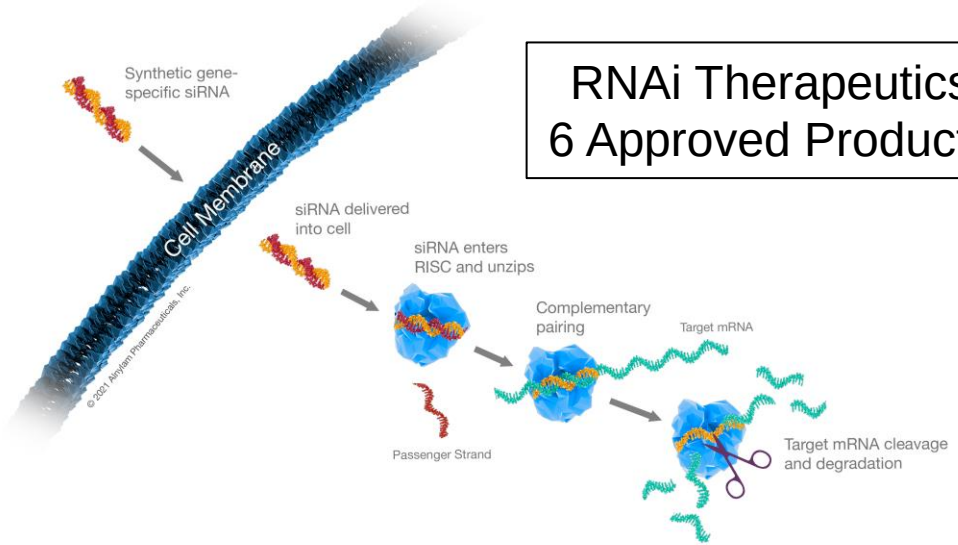
Genetic Medicines Coming of Age

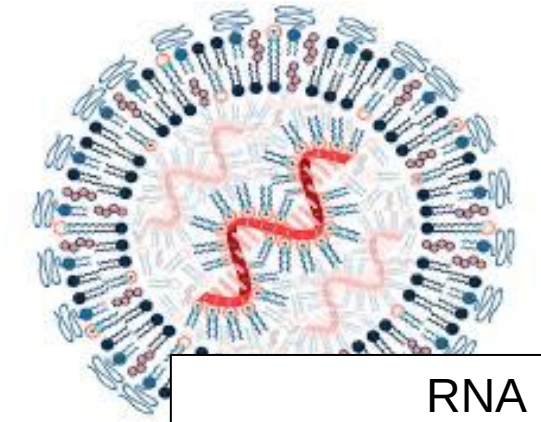
Examples of Categories with Approved or Pending Approvals



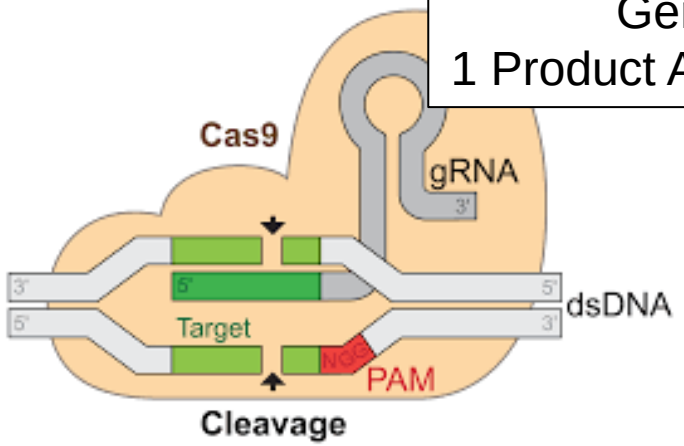
Gene Therapy
8 Approved Products



RNAi Therapeutics
6 Approved Products



RNA Medicines
COVID Vaccines (Multiple Approvals)



Gene Editing
1 Product Approved (MHRA)

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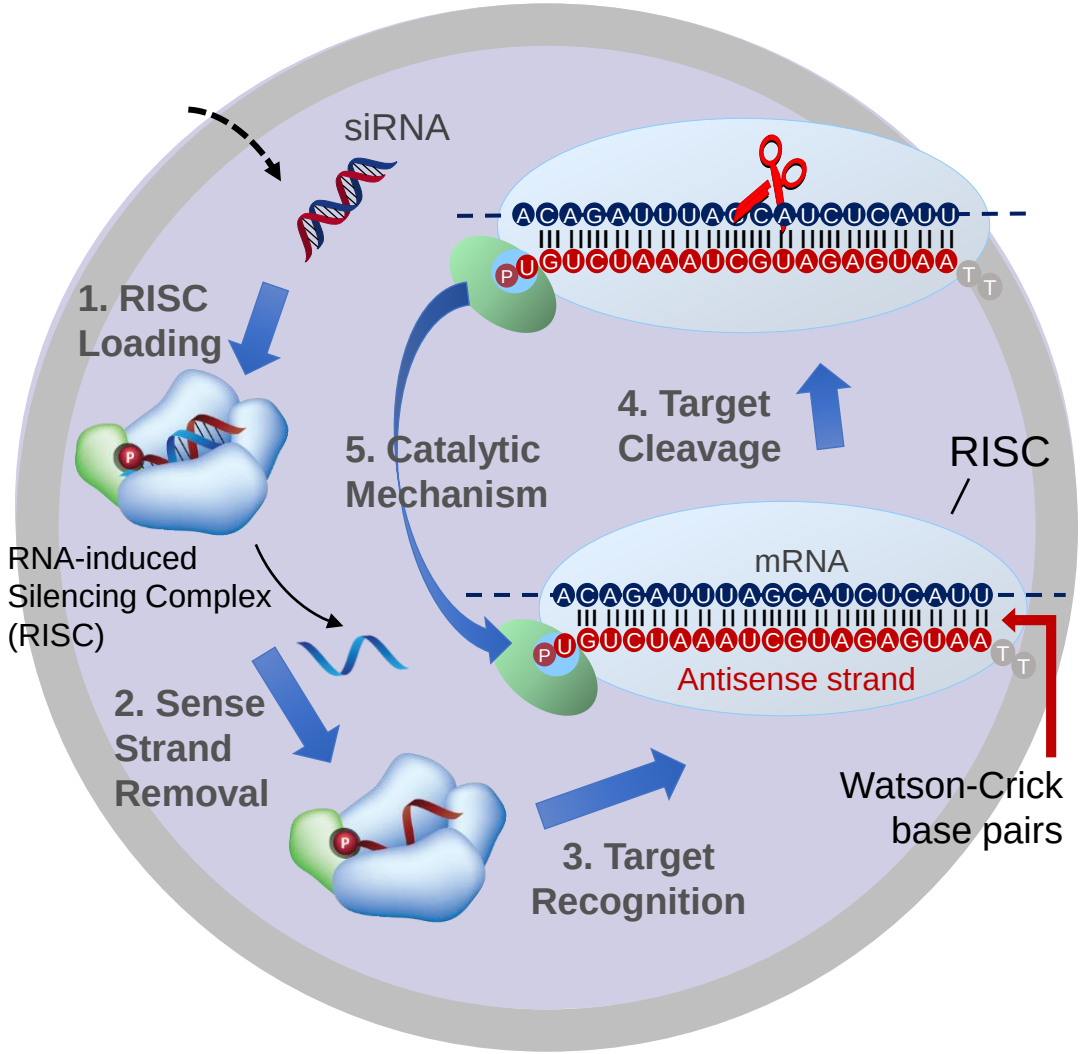
RNA Interference (RNAi) Pathway

Naturally Occurring Mechanism to Regulate Gene Expression



- Ability to harness an endogenous pathway
- Catalytic mechanism
- Ability to silence ***ANY*** gene in genome
- Ability to act upstream of today's medicines
- Potential for whole new class of medicines: RNAi therapeutics

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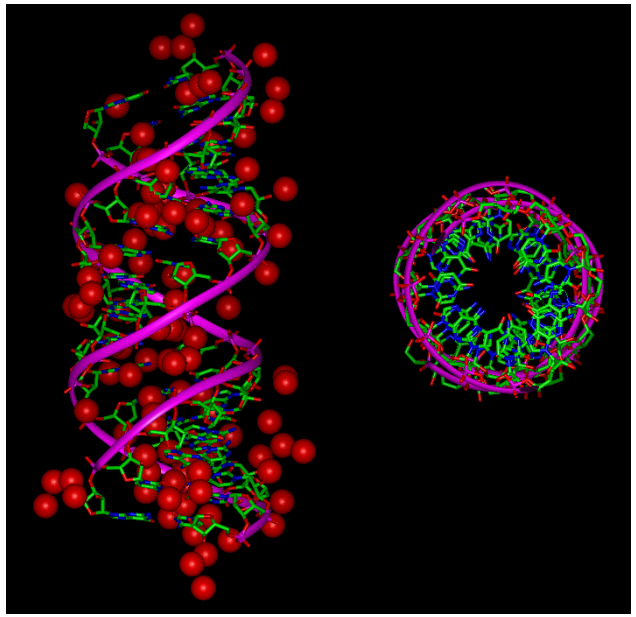
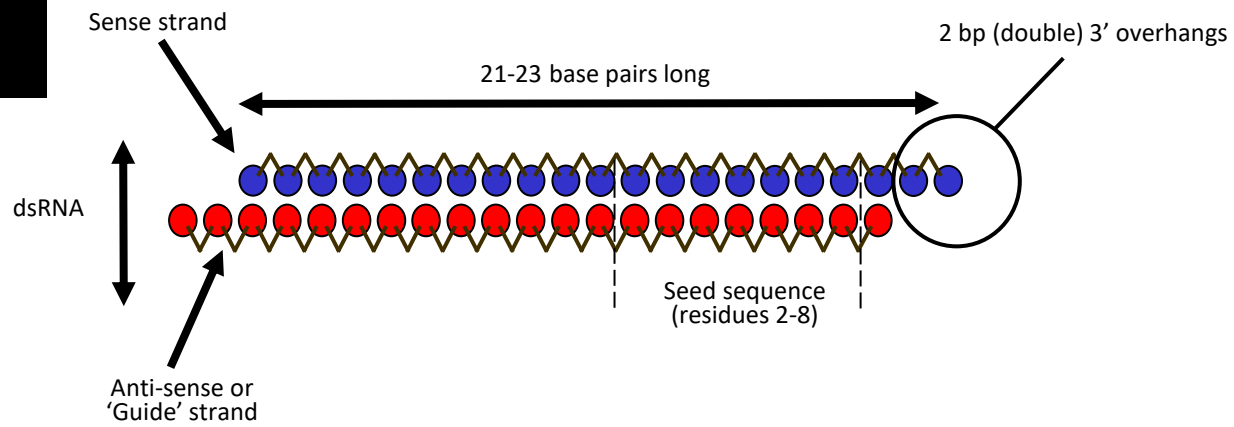
Making Drugs Out of siRNA

The Challenge



Characteristics

- M.W 12,000-14,000
- Size: 2 turns of helix
- 40 negative charges
- Hydrophilic
- Hydrated heavily
- ca. 5.5 nm X 2 nm
- Biostability



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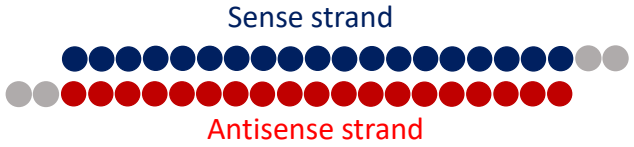
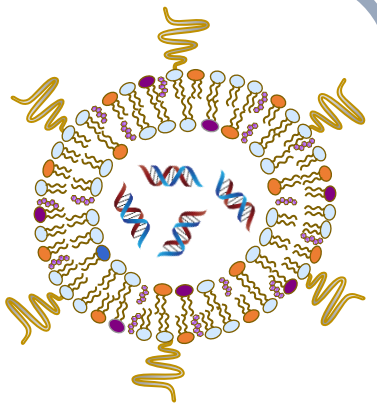
Addressing Delivery Challenge

Solutions Achieved Enabling RNAi Therapeutics Development and Commercialization

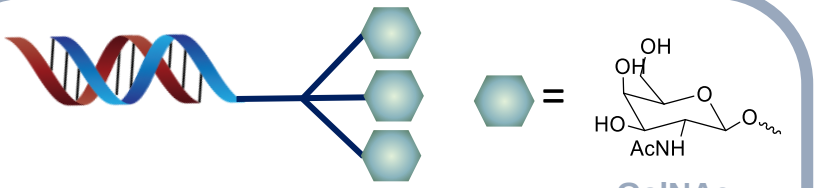


Lipid Nanoparticles (LNPs)

- Multi-component lipid formulation (~100 nm in size)
- Encapsulated siRNA
- Highly efficient for targeted delivery to liver
- Administered intravenously (IV)
- Clinically validated



Patisiran



GalNAc

GalNAc-siRNA Conjugates

- Single chemical entity
- GalNAc ligand conjugated to extensively modified siRNA
- Targeted delivery to liver
- Administered subcutaneously (SC)
- Clinically validated

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A Whole New Class of Medicines

Five RNAi Therapeutic Medicines Approved from 2018-2022

2018

2019

2020

2021

2022

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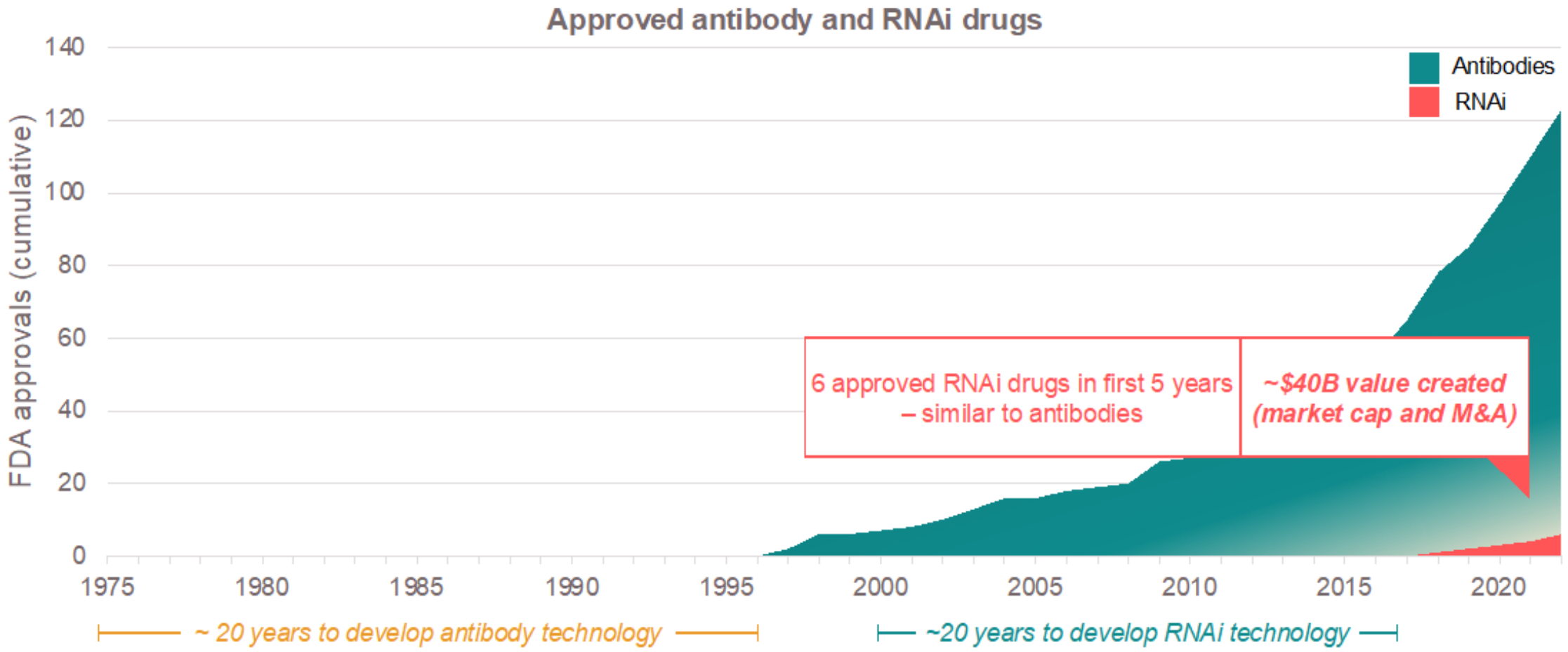
RNAi Therapeutics – The Next Mab Modality?



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Key Trends in RNAi Therapeutics

1. Rare to Prevalent Disease Opportunities
2. Liver to Extra-hepatic Delivery
3. Pharma Coming Back

1. Rare to Prevalent Disease Opportunities

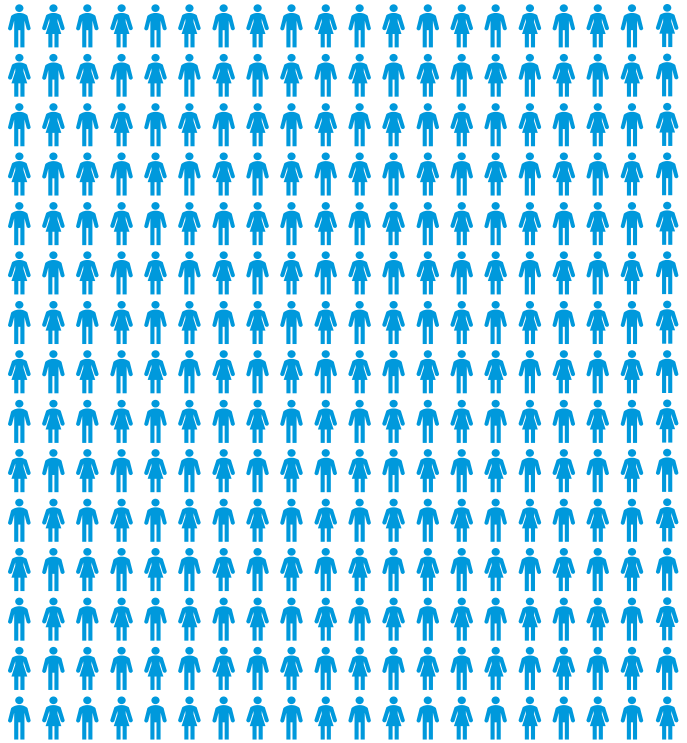
- Durability
- Clamped pharmacology
- Established safety profile
- Improved access

RARE

ONPATTRO: hATTR-PN
GIVLAARI
OXLUMO
AMVUTTRA: hATTR-PN
Fitusiran
Belcisiran
ALN-APP
ALN-HTT

SPECIALTY

AMVUTTRA: ATTR-CM
Cemdisiran



PREVALENT

Leqvio® (inclisiran)
ALN-HBV02 (VIR-2218)
Zilebesiran
ALN-HSD
ALN-INH
ALN-KHK

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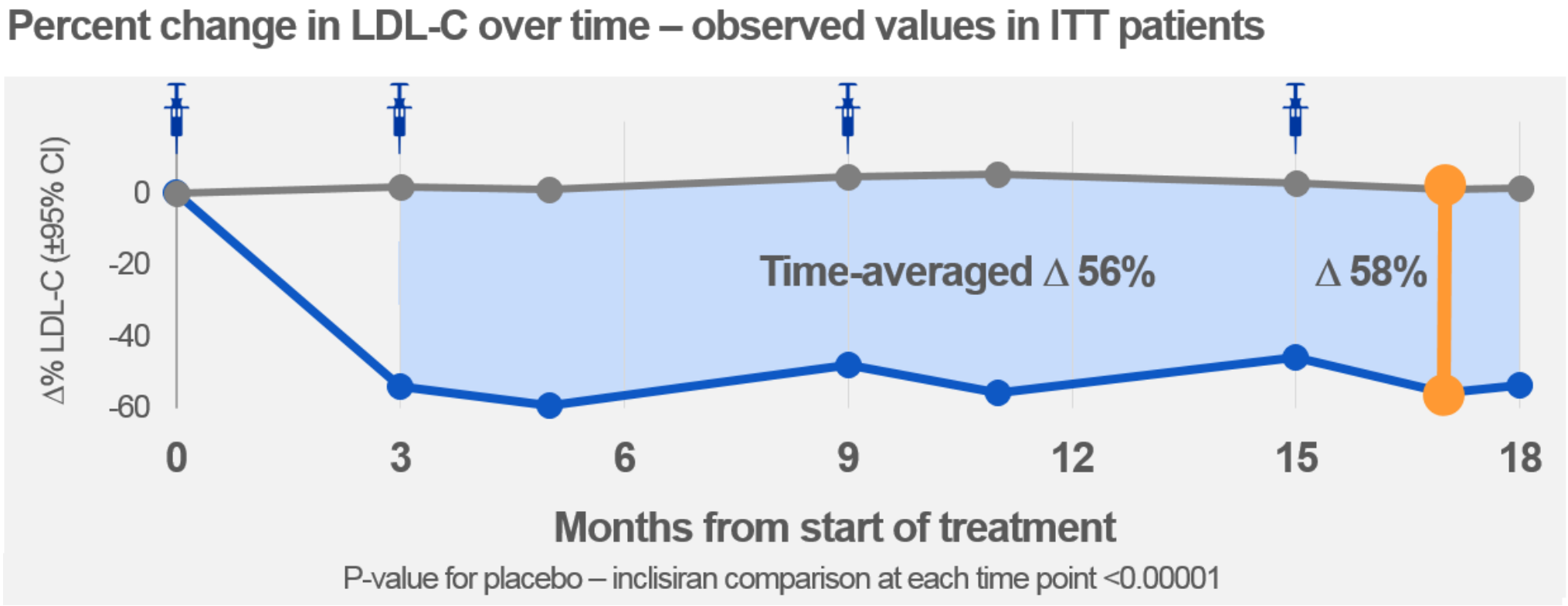
Inclisiran ORION 10+11 Results

Durable, Potent, and Consistent LDL-C Lowering with Encouraging Safety Profile



- Inclisiran safety profile similar to placebo, with no adverse changes in laboratory markers
- Injection site events 2.6-4.7% - predominantly mild and none persistent
- ORION-10+11: Numerically fewer CV events reported for inclisiran than placebo (exploratory endpoint)

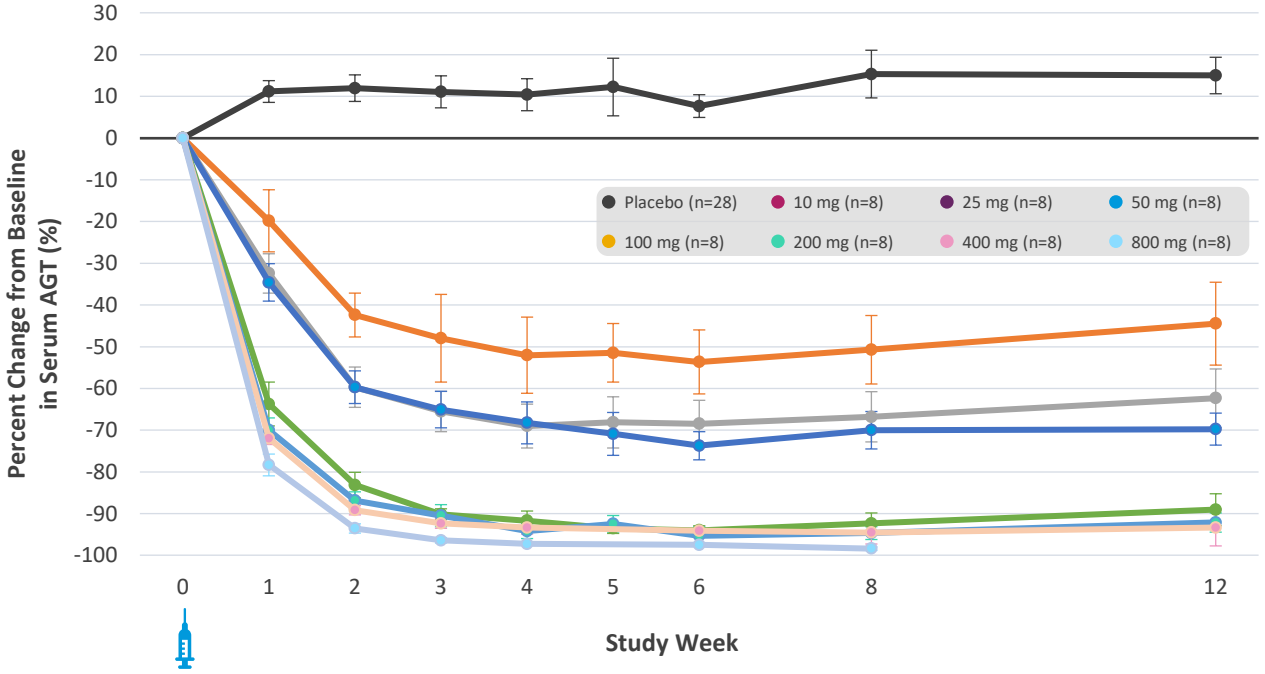
Wright et al., AHA 2019; Ray et al., ESC Congress 2019
All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

Zilbesiran Phase 1 Study Results

Durable, Potent, and Consistent AGT and BP Lowering with Encouraging Safety Profile

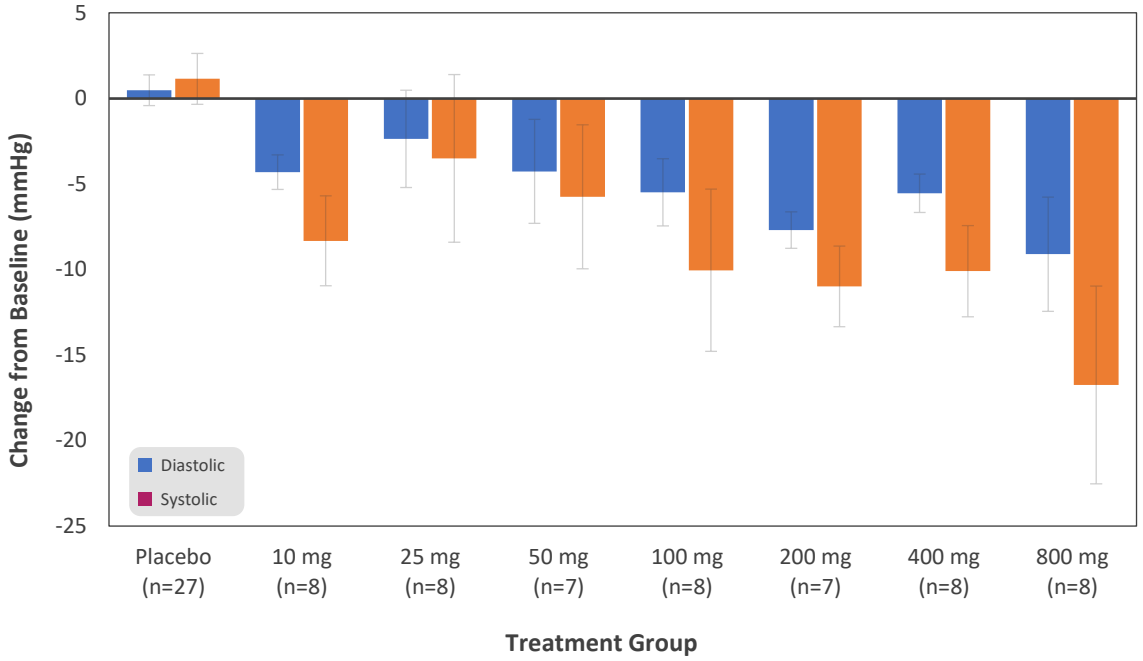
Dose-Dependent AGT Lowering[1]

>95% AGT Knockdown following Single Injection



Dose-Dependent Reductions in SBP and DBP[2]

>15 mmHg Systolic BP Reduction at Week 8 following Single Injection



- Encouraging safety and tolerability profile
- AEs mild or moderate in severity

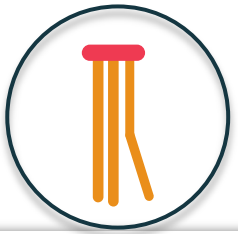
[1] Data transfer date: 08 Dec 2020

[2] Data access date: 19 Nov 2020; SBP: systolic blood pressure; DBP: diastolic blood pressure

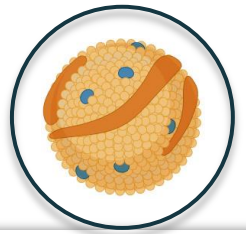
RNAi Therapeutic Programs in Prevalent Diseases

Hypercholesterolemia
Inclisiran
86 M U.S. Patients

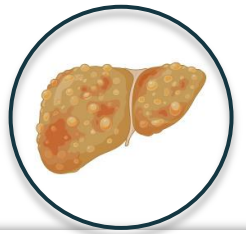
Hypertension
Zilebesiran
120 M U.S. Patients



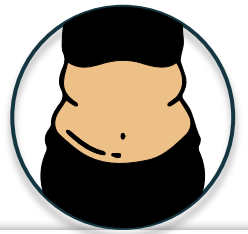
Hypertriglyceridemia
Plozasiran
57 M U.S. Patients



Elevated Lp(a)
Olpasiran (Amgen), Lepodisiran (Lilly)
64 M U.S. Patients



NASH/MASH
ALN-HSD
9 M U.S. Patients



Obesity
ALN-INH, WVE
138 M U.S. Patients

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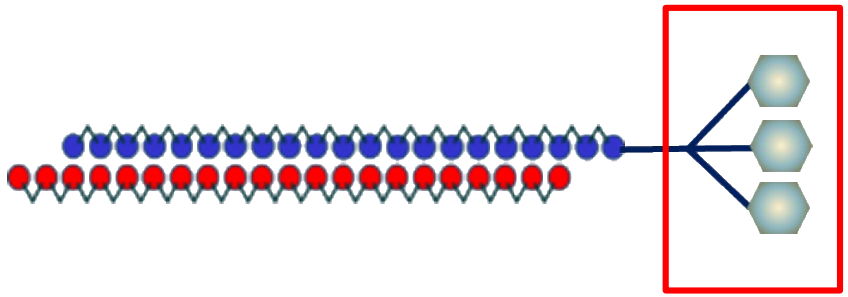
2. Liver to Extra-hepatic Delivery

GalNAc Conjugate



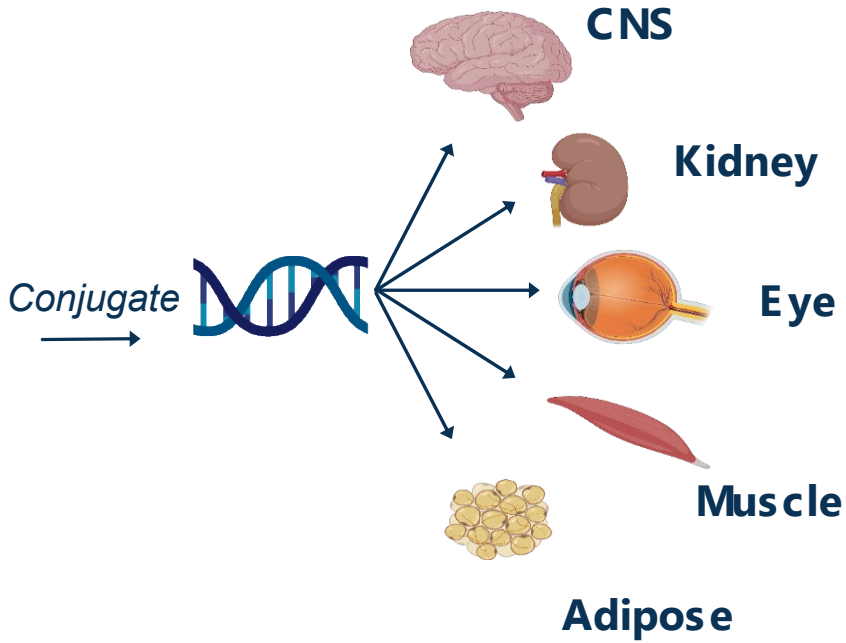
New Ligand Approaches

Protein

Peptide

Lipid

Small molecule



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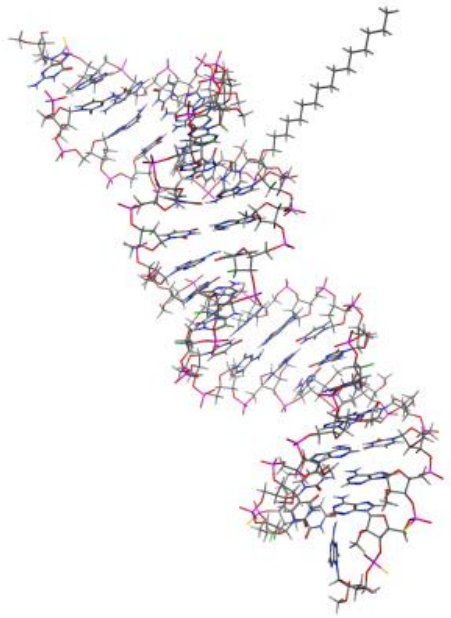
Alnylam CNS Delivery Platform

Potential for C16 Conjugates

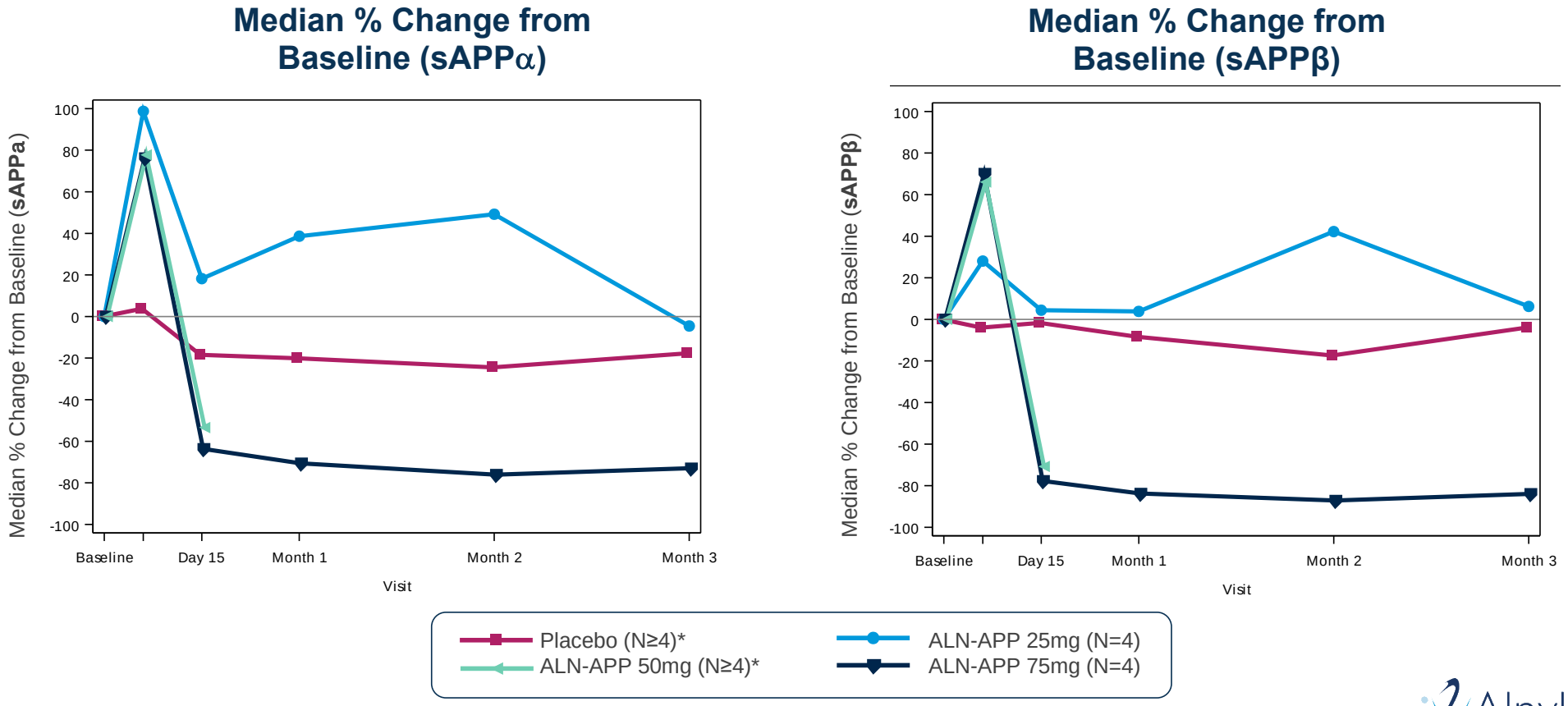
- **High potency**
- **Wide biodistribution in CNS**
- **Long duration of action**
- **Favorable risk / benefit profile**



C16 Conjugate

Initial Phase 1 Results for ALN-APP – 1st Human POC in CNS

RNAi Therapeutic Targeting Amyloid Precursor Protein for Alzheimer's Disease



* Cohort (N≥4). Exact number of subjects is masked to prevent unblinding in ongoing clinical trial.

Alnylam®

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3. Pharma Coming Back

Drugmakers' Fever for the Power of RNA Interference Has Cooled

By Andrew Pollack

Feb. 7, 2011

Recent Major Pharma RNAi Deals

~$17B in Deals in Last 5 Years

NOVARTIS

$9.7B acq. MDCO (2019)
$1B acq DTx (2023)

Takeda

$300M u/f deal ARWR (2018)

Lilly

$200M u/f deal DRNA (2018)

Roche

$200M u/f deal DRNA (2019)
$310M u/f deal ALNY (2023)

novo nordisk®

$3.3B acq. DRNA (2021)

GSK

$1B deal ARWR/J&J (2023)

REGENERON

$800M u/f deal ALNY (2019)

Boehringer Ingelheim

$200M u/f deal DRNA (2017)

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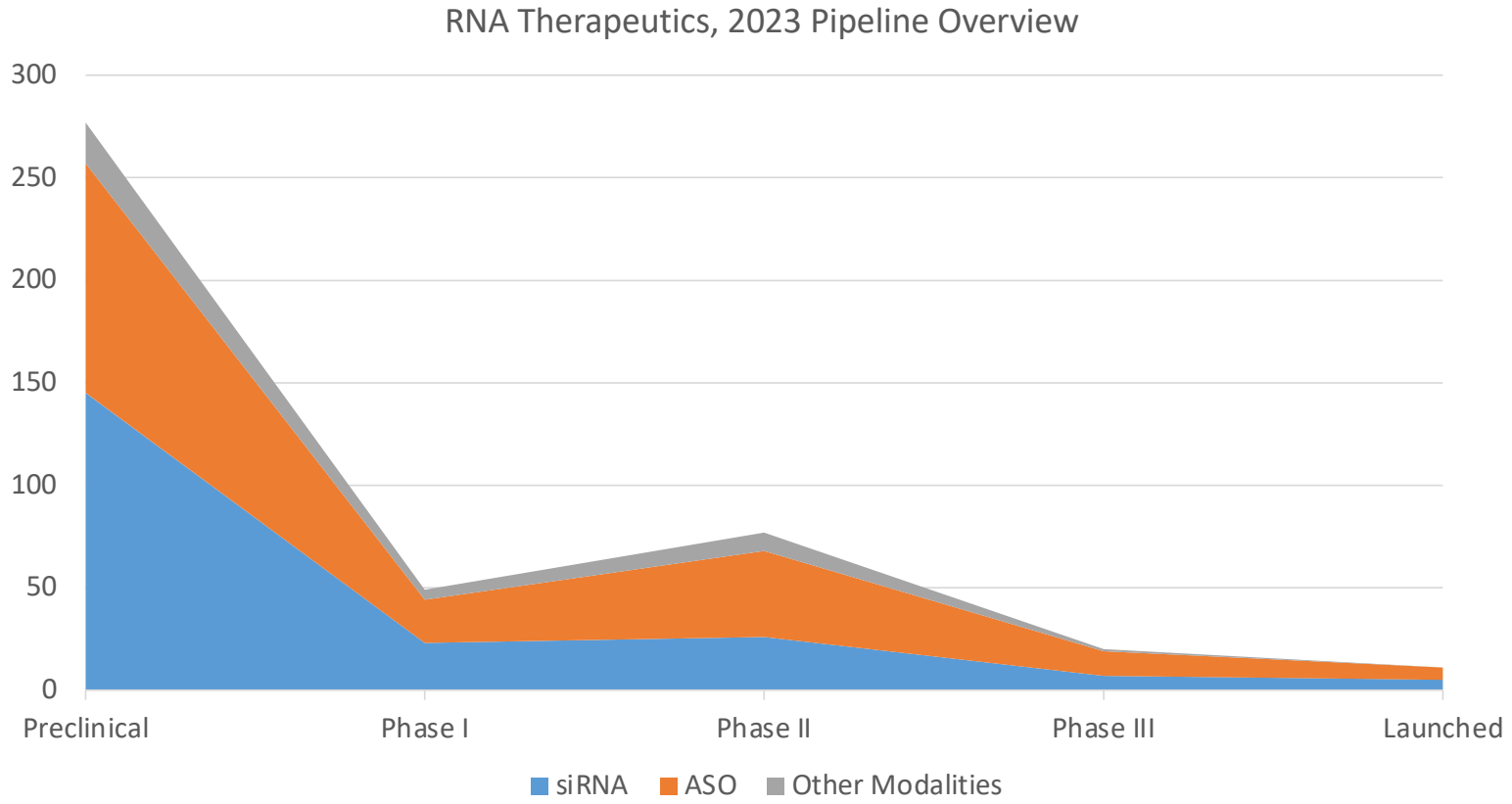
Key Trends in RNAi Therapeutics

1. Rare to Prevalent Disease Opportunities
2. Liver to Extra-hepatic Delivery
3. Pharma Coming Back

Significant Need for Increased RNA Manufacturing Capacity

Growing Development Pipeline of Oligo Rx

>100 Programs in Clinical Development



Source: Cortellis database, pipeline status as of June 2023

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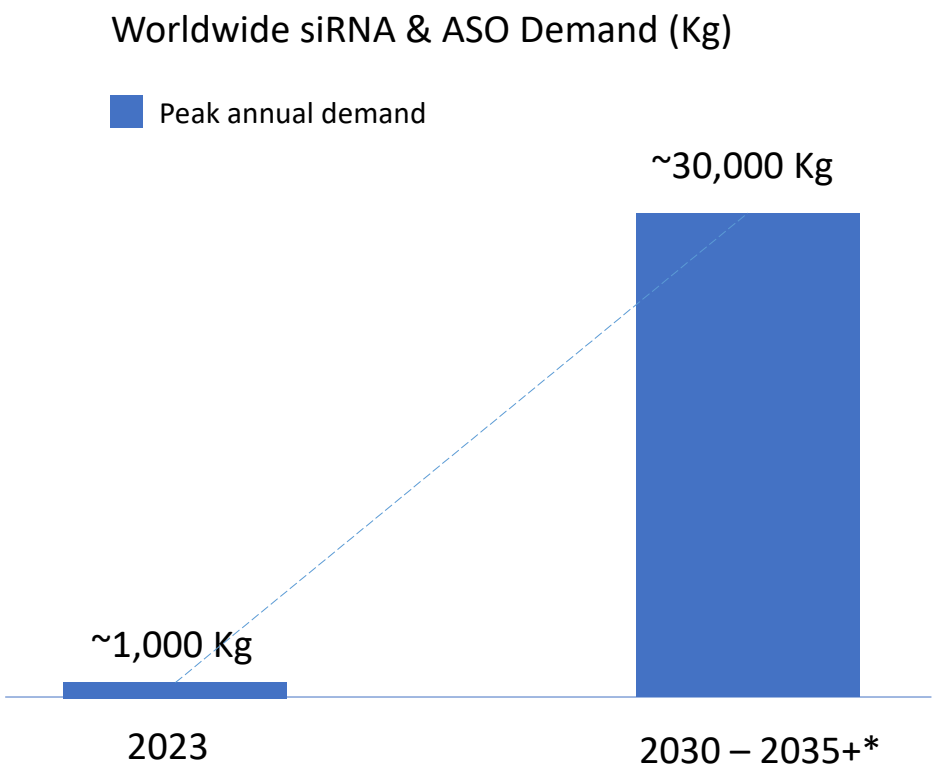
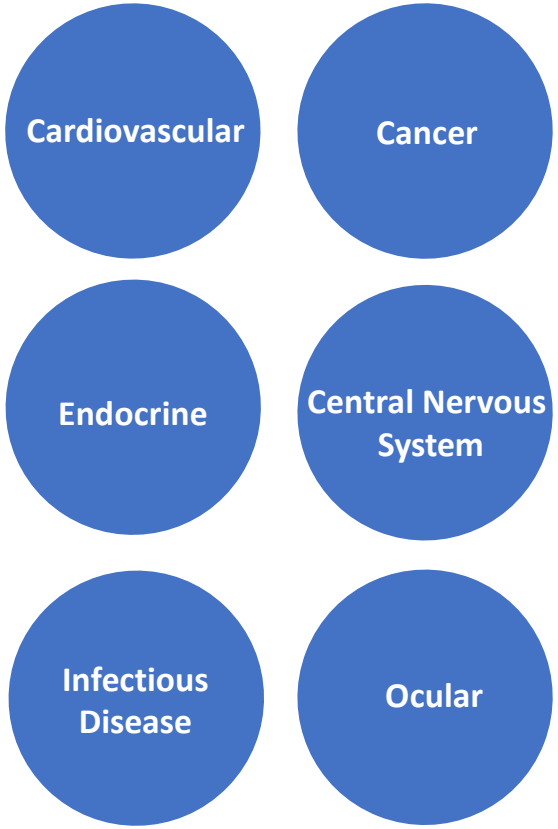
Estimated Growth in Oligo Manufacturing Demand

Risk-Adjusted Estimates



Key Disease Areas in Clinical Development



*Assumes 35% of assets currently in Phase 2/3 clinical trials are approved by 2030; assumed rate of approval is based on data from Wong & Siah, *Biostatistics* (2019)

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Reflections on Alnylam's Manufacturing

My parting words to Alnylam SVP, Process Development:
"Lubo, the future of RNAi rests in your hands!"

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David Butler, PhD

Chief Technology Officer,
Hongene Biotech Corporation

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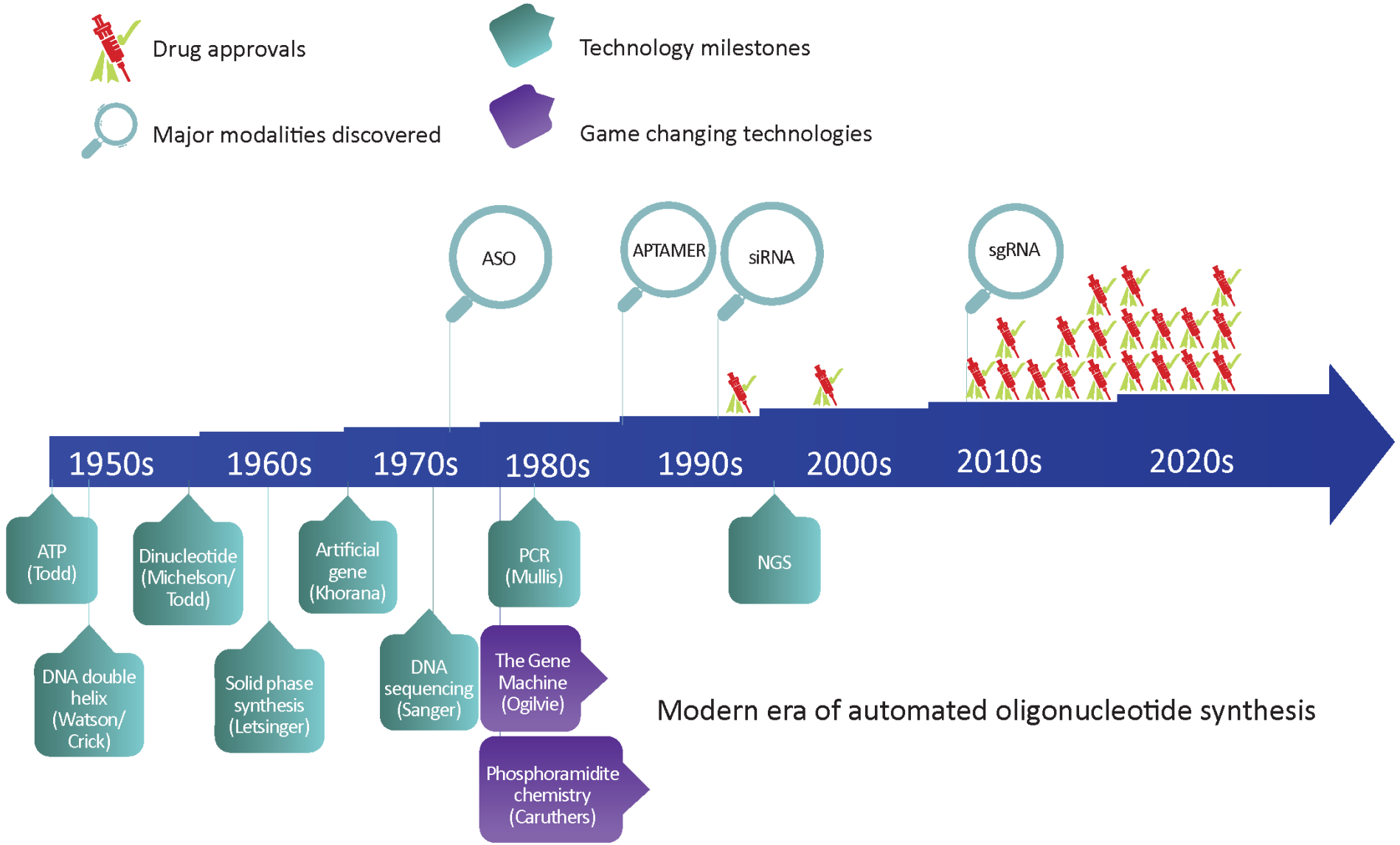
Disclosures

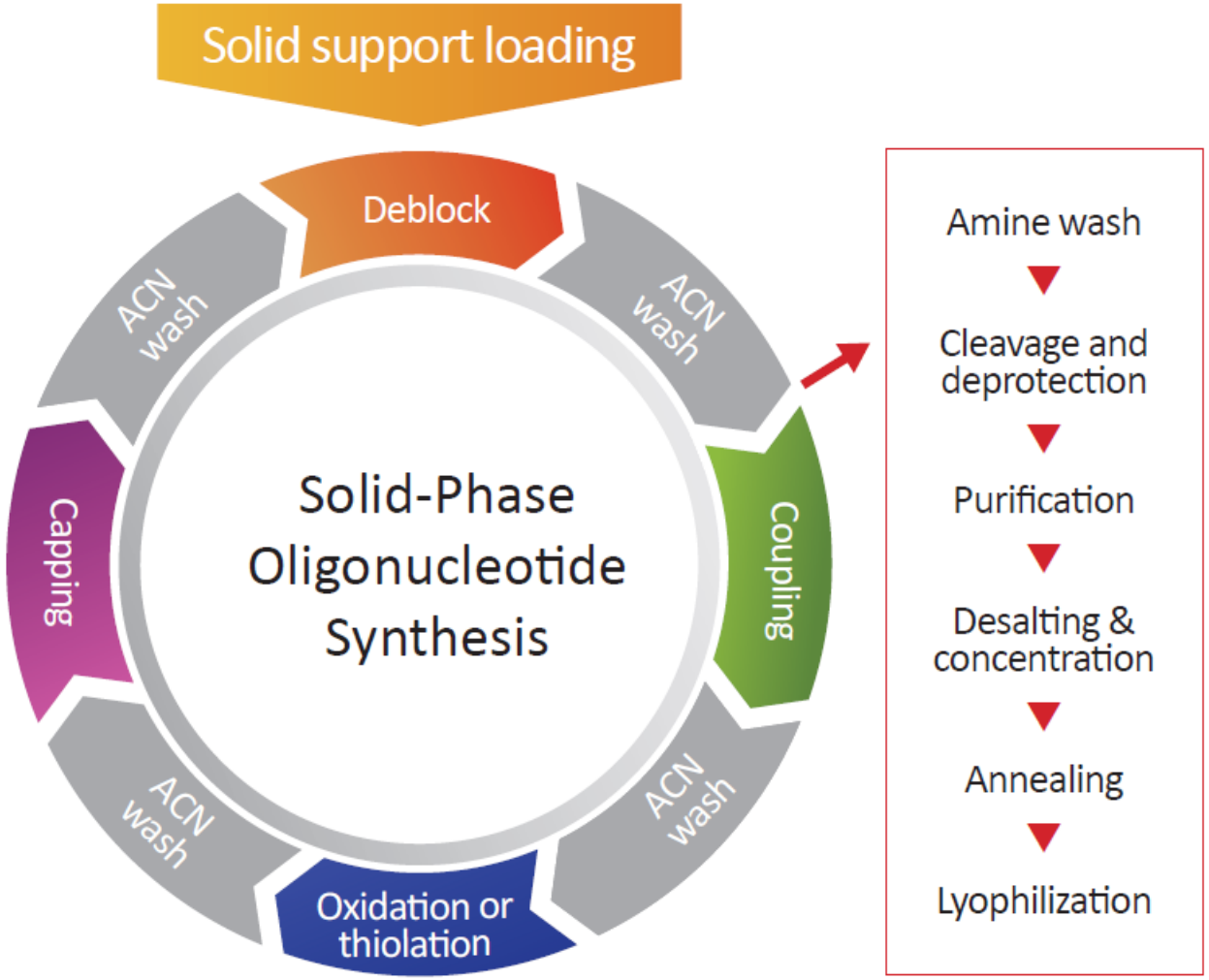
- Presenting today on behalf of Codexis; compensated as an independent consultant.
- The content within this presentation is my own and was developed independently of Codexis.
- I serve as a Board Director for Akte Therapeutics.

A Glimpse Through Time: The Saga of Oligonucleotides



Manufacturing by Solid Phase Oligonucleotide Synthesis (SPOS)

- Solid support with reagents flowing over the synthesis bed
- Linear synthesis consisting of 160+ steps for a 21mer siRNA duplex
- Yield depends on modality ~50% for siRNA, purities ~90%, amazing achievement
- Suitable for meeting market demands of rare disease indications, more challenging for widespread disease indications
  - **~60% of drugs in current oligo pipelines are for non-rare disease indications**
- Decades of process improvements now achieving diminishing returns



Pain Points of Conventional SPOS

- Cost
  - Process mass intensity (PMI) typically >4,000
  - Expensive raw materials
  - Expensive equipment and lengthy process
  - Low yield and efficiency
  - 1 kg API typically >$1M
- Scalability
  - Column-based synthesis process limits **scaling up** to ~5kg per batch
  - 1 ton of API requires **scaling out** 200 x 5 kg batches
- Environmental impact
  - Low atom efficiency (0.25 – 0.36)
  - Raw materials are generally not recycled
  - Non-renewable hazardous solvents and reagents
  - High carbon footprint
- Quality concerns for longer oligos such as sgRNA
  - Inconsistent quality
  - Low overall purity and yield

3035-7023 Kg

Raw materials required to synthesize 1 Kg of

Oligonucleotide API using phosphoramidite chemistry[1]

[1]Andrews et al, 2021, *J. Org. Chem.*

Oligonucleotide CDMO Landscape

- Demand for oligo therapeutics anticipated to hit **~30K kg of demand by ~2030-2035+**
  - Will there be sufficient capacity at these CDMOs?
- Oligo CDMO expansion to meet anticipated increase in market demand
  - Established companies are investing heavily
  - New players are emerging
- Leading oligo biopharma building in-house capabilities
  - Pipeline growth and CDMO capacity constraints
- Improved manufacturing technologies
  - Liquid phase oligonucleotide synthesis (LPOS)
  - Stirred bed reactors
  - Ligation
  - Reliant on same reagents as SPOS
  - Improved COGS and scalability

Company	Status	Region	Oligo API Est.	Technology
Nitto Avecia	Established	NA	1997	SPOS
Agilent	Established	NA	2006	SPOS
Biospring	Established	EMEA	2007	SPOS
ST Pharm	Established	APAC	2003	SPOS
Wuxi TIDES	Emerging	APAC	2019	SPOS
Corden Pharma	Emerging	NA	2023	SPOS
EuroAPI	Emerging	EMEA	2021	SPOS
RiboBio	Emerging	APAC	2012	SPOS
AxoLabs/ LGC	Emerging	EMEA	2000	SPOS
Biosearch/ LGC	Emerging	NA	2017	SPOS
Ajinomoto	Emerging	APAC; EMEA	2019	SPOS, LPOS, ligation
Bachem	Emerging	EMEA	2017	SPOS, stirred bed
Asymchem	Emerging	APAC	2022	SPOS
Exactmer	Emerging	EMEA	2023	LPOS
Hongene	Emerging	APAC	2021	SPOS, ligation

Perception of Enzymatic Oligo Synthesis within the Field

- **TIDES survey[1] on sustainability practices in oligonucleotide manufacturing**
  - Conducted survey from August 23 – September 5, 2023
  - Received **110 completed responses** from those employed in a role involving the development and/or manufacture of oligonucleotide therapeutics

Selected survey results:

52%
very concerned about environmental impact of acetonitrile (ACN) as a waste product of oligonucleotide manufacturing

59%
at least somewhat familiar with advancements in enzymatic synthesis

44%
of respondents' organizations likely to invest in ACN recycling technologies

71%
believe liquid or enzymatic synthesis will overtake SPOS within 10 years

[1]Informa and Asahi Kasei, 2023, *Sustainability Practices in Oligonucleotide Manufacturing*, Online Survey

Comparative Analysis of Anticipated Performance of Full Enzymatic vs. SPOS vs. LPOS vs. Ligation

Parameter	SPOS	LPOS	Ligation	Full Enzymatic[1]
Total synthesis time				
Product yield				
Scale per batch				
Chemical modifications				
Equipment complexity				
Raw materials costs				
Product purity				
Purification costs				
Waste disposal costs				
Safety				

[1]Assessment based on publicly-available information provided by the Company

12 Principles of Green Chemistry[1]

Comparative Analysis of Anticipated Performance of Full Enzymatic vs. SPOS vs. LPOS vs. Ligation

Principle	SPOS[2]	LPOS	Ligation	Full Enzymatic[3]
Waste prevention				
Atom economy				
Less hazardous chemical synthesis				
Designing safer chemicals				
Safer solvents and auxiliaries				
Design for energy efficiency				
Use of renewable feedstocks				
Reduce derivatives				
Catalysis				
Design for degradation				
Real-time analysis for pollution prevention				
Safer chemistry for accident prevention				

[1]Anastas et al, 1998, *Green Chemistry: Theory and Practice*
[2]Andrews et al, 2021, *J. Org. Chem.*
[3]Assessment based on publicly-available information provided by the Company

Considerations for CDMOs Moving to Enzymatic Manufacturing

- **Investment and Cost Analysis**
  - Understand the financial implications of a switch, including CapEx and operating costs
- **Engineering**
  - Can the current site accommodate batch reactors; single-use vs stainless?
  - Can controlled non-classified standards be employed?
  - Understand how volumes of materials and waste liquid move from one operation to the next
- **Workforce**
  - Retraining and/or hiring for skills in enzymatic manufacturing processes
- **Supply Chain**
  - Sourcing high quality enzymes, starting materials and other raw materials
  - Establishing relationships with and qualifying new suppliers
- **Quality Control**
  - Establishing robust analytics and IPC for reaction monitoring and final QC

Considerations for Drug Sponsors Moving to Enzymatic Manufacturing

- **Stickiness for current processes**
  - Need very good reasons to switch from established SPOS processes
- **Identifying an oligo CDMO services partner that meets expectations**
- **Regulatory**
  - Requirements for bridging studies
  - CDER or CBER (if enzymatic synthesis is considered a biological process)
  - Requirements for GMP raw materials?
- **Quality control**
  - Impurities arising from raw materials and the process will be different compared with a chemical process
  - Product specifications that test for residual enzyme
- **Phosphorothioate backbone stereochemistry**
  - Diastereomeric composition will be different

Requirements and Future of Enzymatic Technology

- **Requirements for technology adoption**
  - COGS and quality comparable with SPOS and competing processes
  - Sufficiently stable raw material inputs
  - Solve for all relevant chemical modifications (e.g. 2’-F, 2’-OMe, GalNAc, others for siRNA)

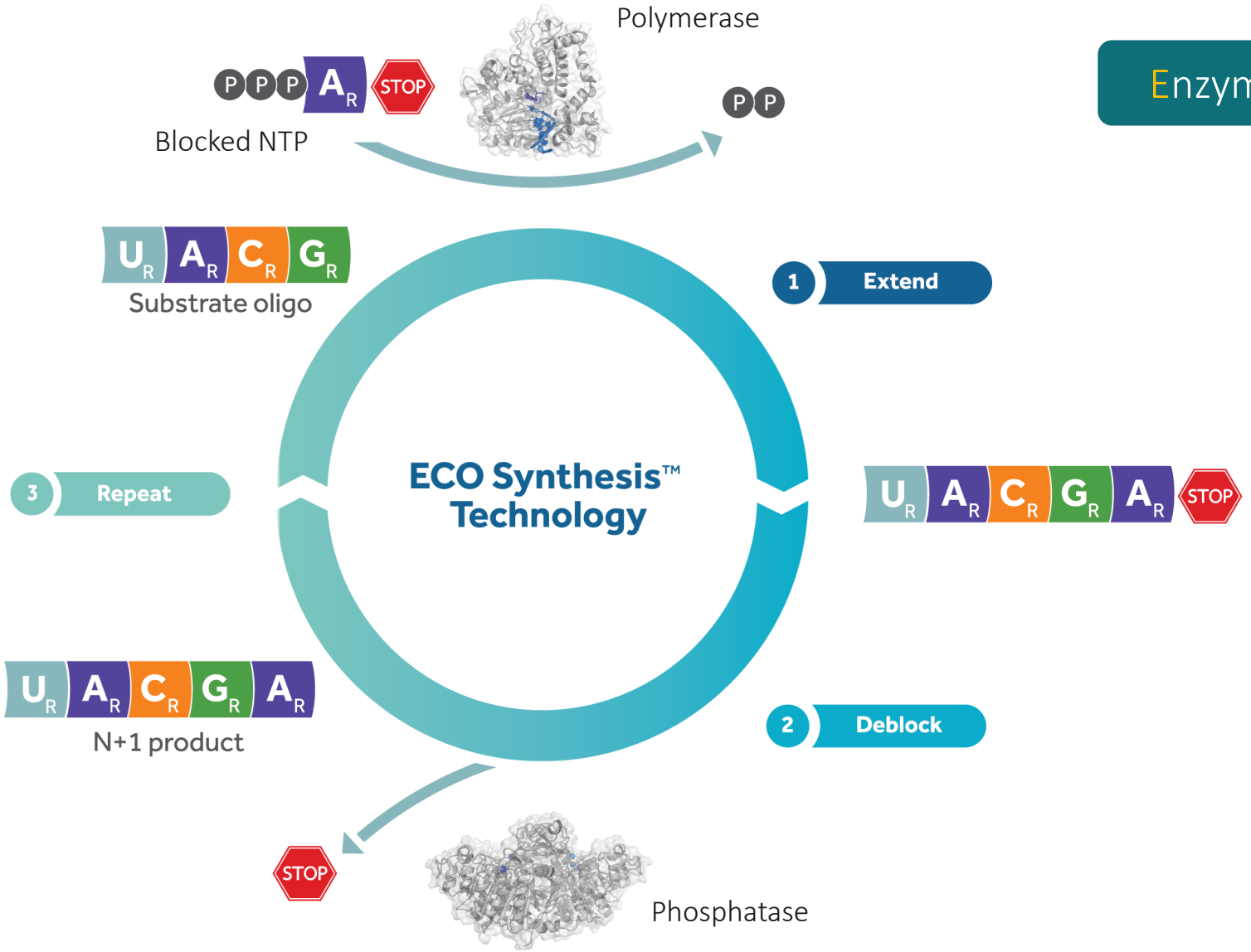
- **Research Trends**
  - Enhancements of enzymes, processes, convergence of AI and directed evolution
  - Expiration of foundational siRNA patents leading to expanded adoption
  - Investments spurred by gene-editing technology advances

- **Industry Shift**
  - Technology adoption when market conditions and requirements are met
  - Biopharma increasingly leveraging high volume siRNA assets
  - Development of improved sgRNA manufacturing processes

Stefan Lutz, PhD

SVP, Research
Codexis

Codexis ECO Synthesis™ Technology



Enzyme Catalyzed Oligonucleotide Synthesis

Core process:

Extend – Deblock … Repeat

- Oligonucleotide synthesis by iterative, single nucleotide extension:

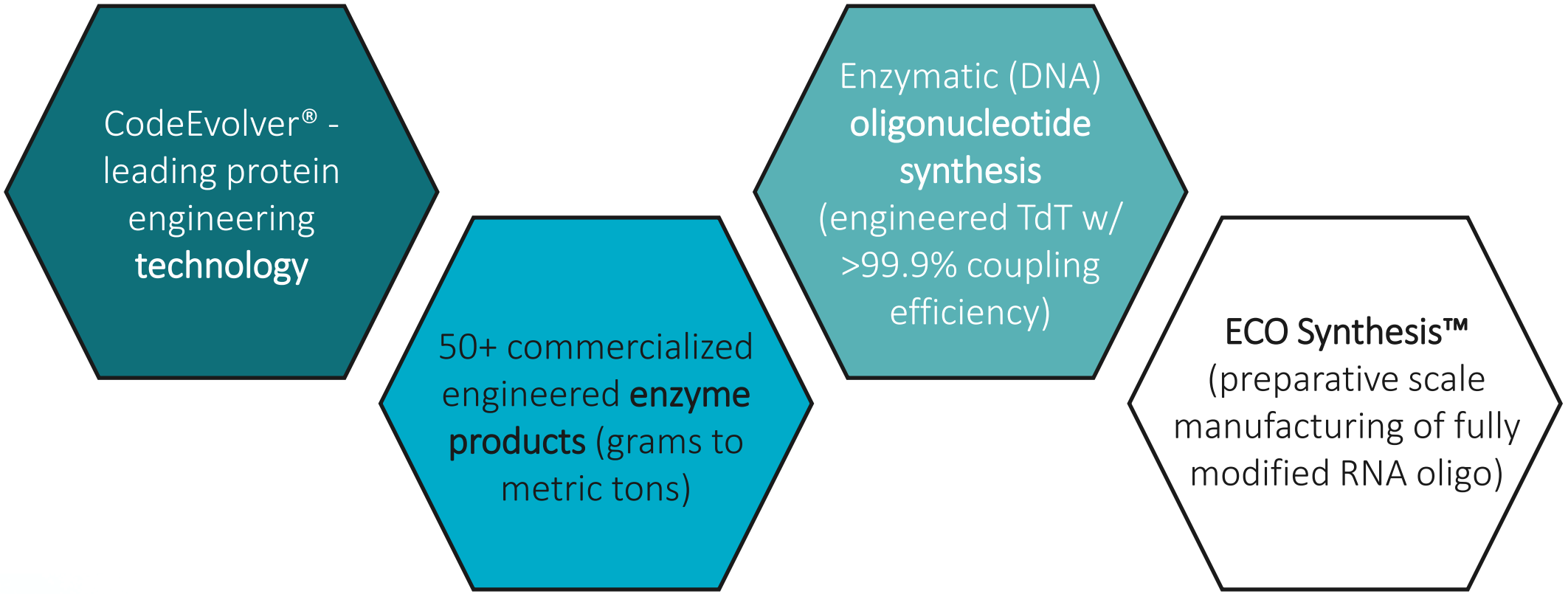
Supply processes:

- Biocatalytic production of modified, 3’-phosphate blocked ribonucleotides (NQPs)
- Enzymatic synthesis of substrate oligonucleotide (starter)

CODEXIS

ECO Synthesis™ Technology – (r)evolution in Progress

Set up for success based on two decades of expertise and experience in biocatalysis

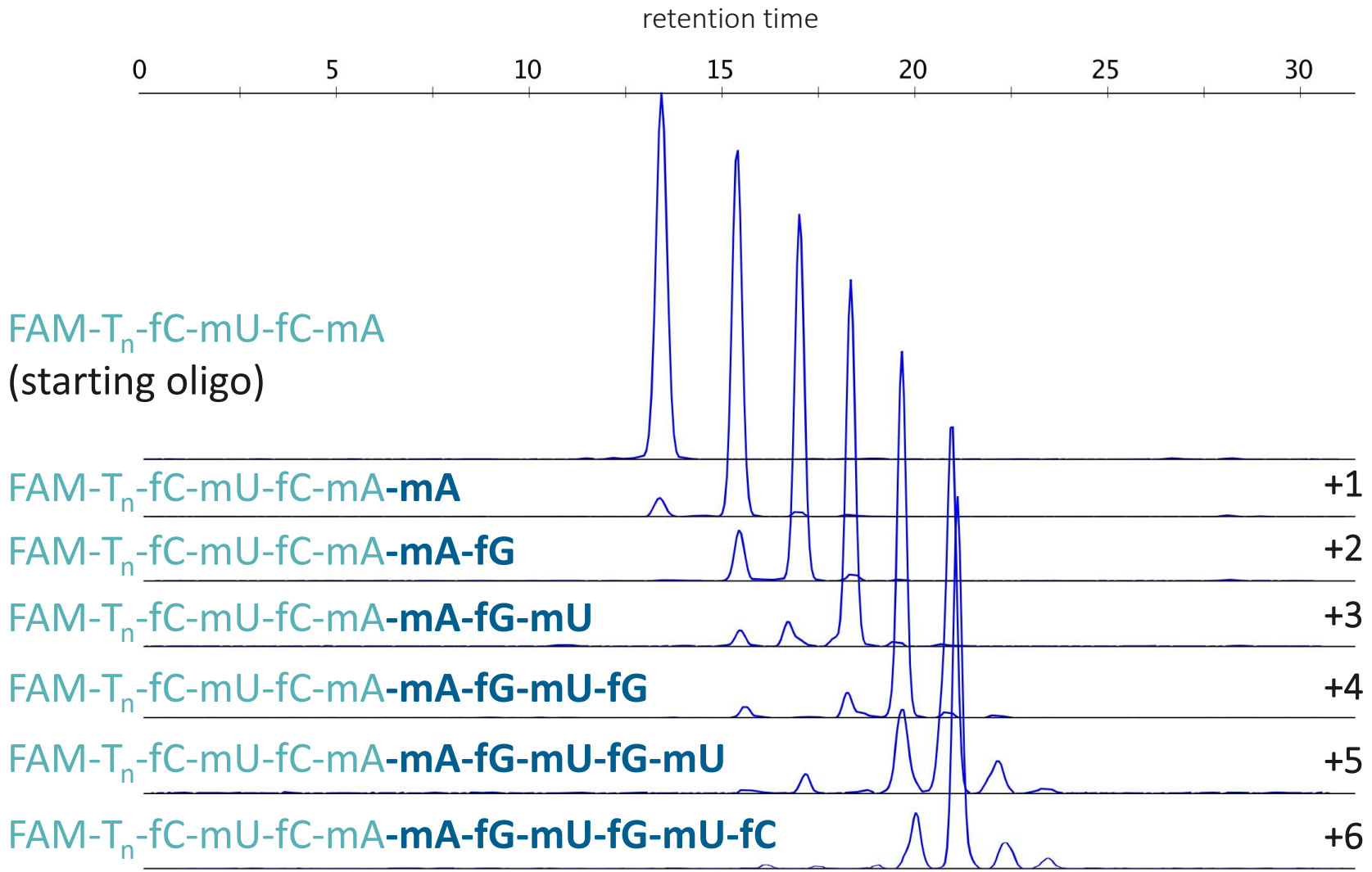


CODEXIS

Iterative Oligonucleotide Synthesis with ECO Synthesis™ Platform

Platform performance

- 6+ extension cycles
- Oligo in solution, enzyme immobilized
- Modified NQPs & fully modified oligonucleotide
- Average incorporation efficiency ~92%
- *Further enzyme engineering & process optimization ongoing*



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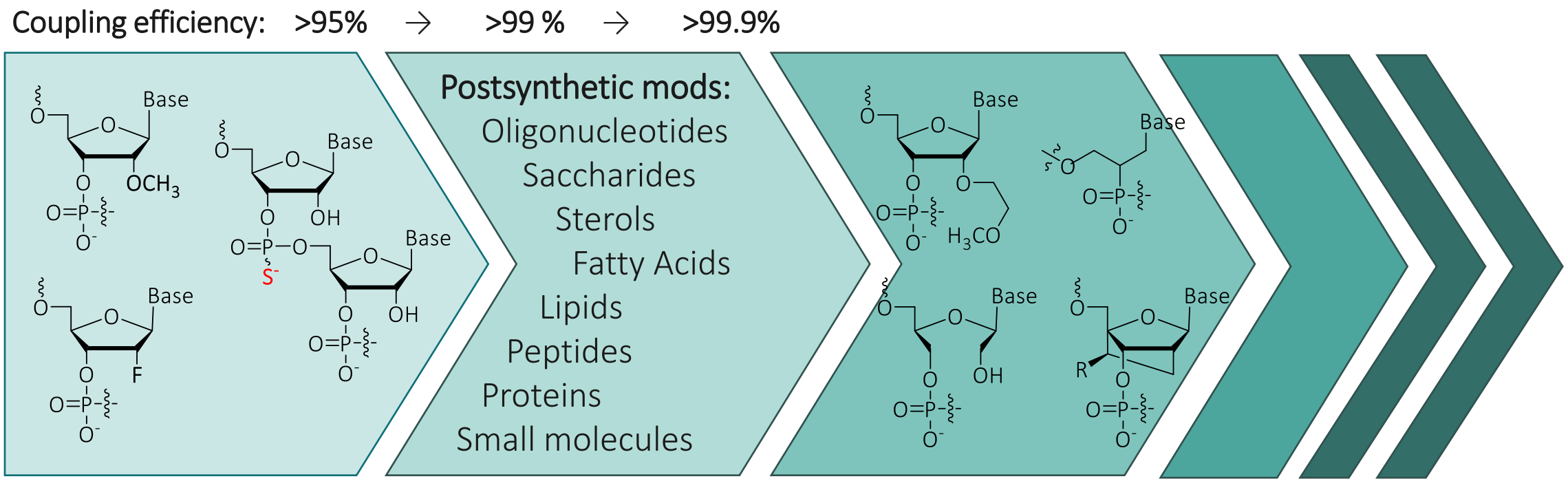
ECO Synthesis™ Technology – What's Next?

A (Launch) Platform for Future Innovation in RNAi Therapeutics Manufacturing



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Kevin Norrett, MBA

Chief Operating Officer,
Codexis

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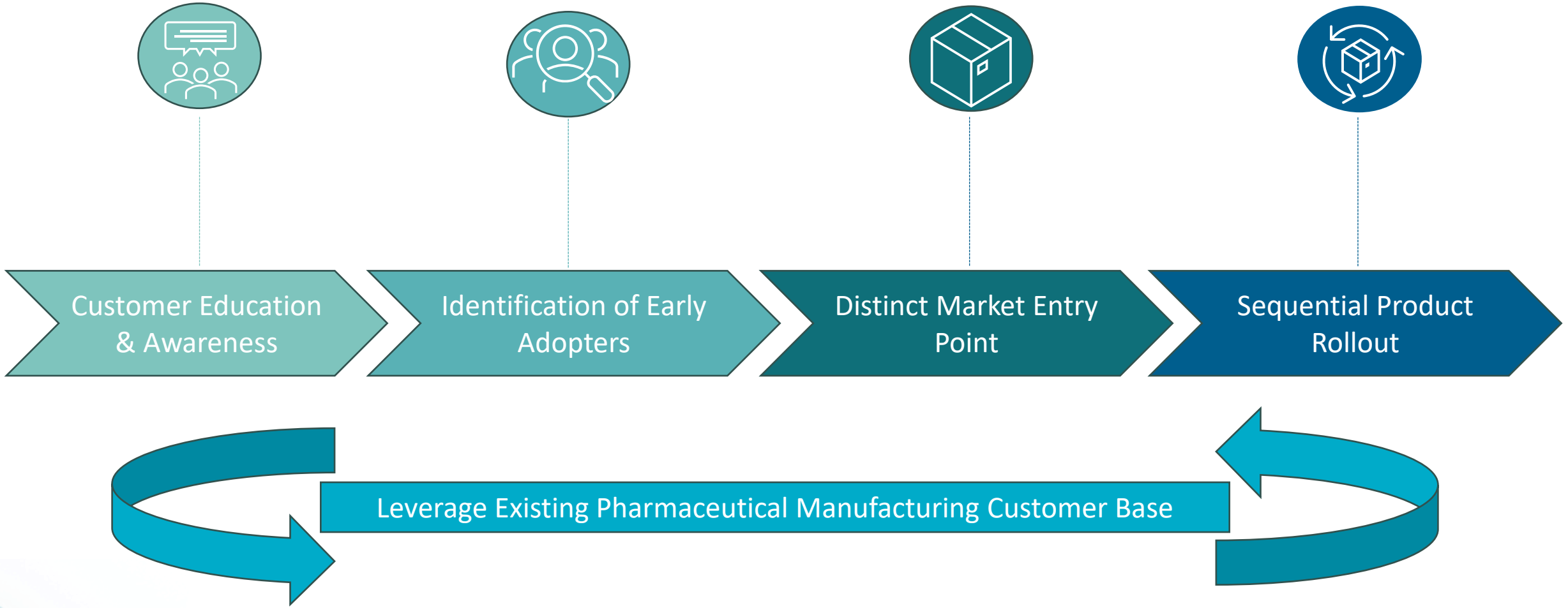
ECO Synthesis™ Platform: Key Elements of Our Commercial Strategy



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Anticipated News Flow for ECO Synthesis™ Platform

2023	• Demonstrate gram-scale synthesis with ECO Synthesis™ technology
2024	• TIDES USA • Validation of ECO Synthesis™ technology through pre-commercial testing with select customers and partners • Double-stranded RNA (dsRNA) ligase widely available for customers
2025	• Early commercial licenses to ECO Synthesis™ technology
2026	• ECO Synthesis™ technology and process widely available for customers

Key Milestones Approaching & Projected Runway to Positive Cash Flow Around End of 2026

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Q&A

Thank You

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