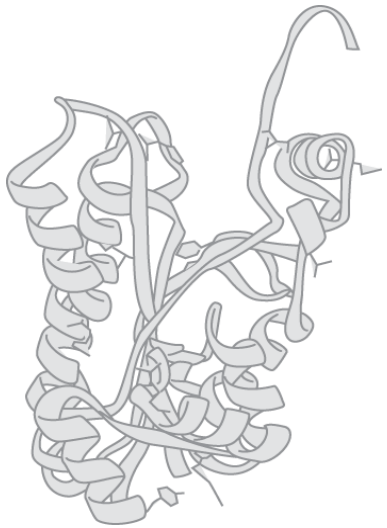
Engineered Enzymes to Overcome Scalability and Sustainability Challenges of Nucleic Acid Therapeutics Manufacturing

CODEXIS®

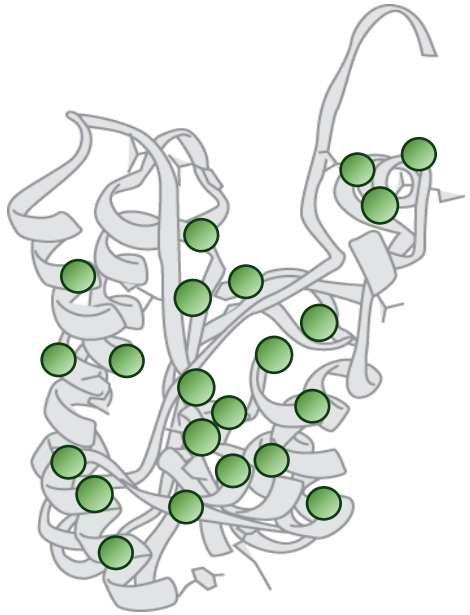
Codexis core business pillars

Based on CodeEvolver® platform to accelerate enzyme discovery and commercialization



Enzymes
from Nature

CodeEvolver®



Commercially
Relevant Enzyme

Value
Creating
Products

Biotherapeutics

enzymes as oral drugs;
engineered transgenes and
capsids for gene therapy

Pharmaceutical Manufacturing

enzymes for small molecule
production

Life Sciences

enzymes for NGS applications
and DNA/RNA synthesis

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ECO Synthesis™ Technology

(**E**nzyme-**C**atalyzed **O**ligonucleotide Synthesis)

RNAi: High Demand / Constrained Supply

Demand Drivers

RNA delivering on promise of personalized medicines
(10+ FDA approved therapies have reached market in past 5yrs)

RNAi therapeutics as a modality is growing rapidly with >450 assets in pipelines

RNAi therapies are treating the previously untreatable diseases

Production & Supply Challenges

Chemical RNA synthesis produces **Millions** of liters of chemical waste… and growing!

Phosphoramidite synthesis will be challenged to meet demand of 1,000s kg of RNAi p.a. by 2030

Critical solvent supply constraints likely (Acetonitrile)

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Enzymes are poised to spur innovation and disrupt RNAi manufacturing

Scalability

Enzyme catalytic activity enables multiple cycle use

Purity & Yield

Evolution targets >99% incorporation efficiency

Sustainability

Aqueous waste streams & lower solvent use

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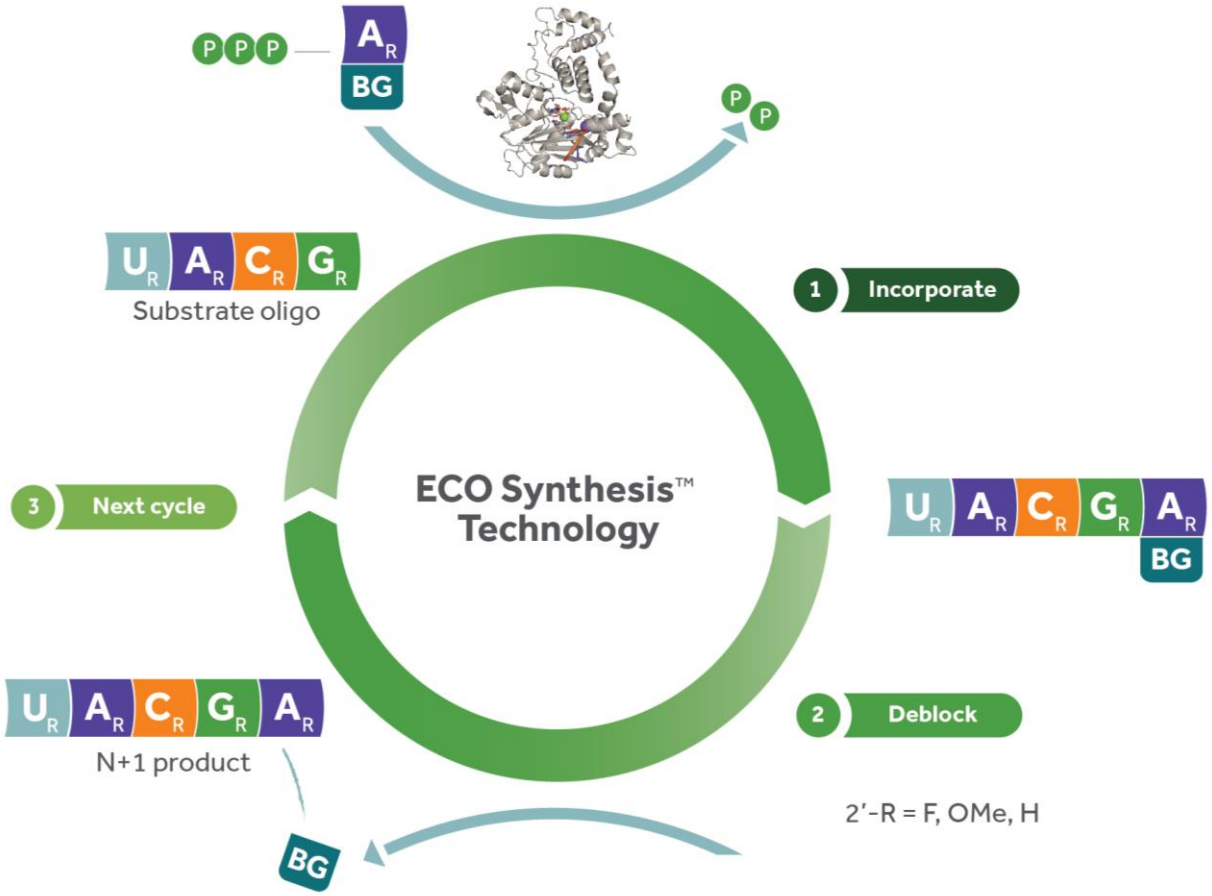
Codexis ECO Synthesis™ Technology

Enzyme-Catalyzed Oligonucleotide Synthesis for RNAi therapeutics



ECO Synthesis™ Technology

- Controlled addition of modified RNA bases (TdT)
- Deblocking of 3'blocking group (phosphatase)
- Supply of 3'blocked NTP substrates (multiple enzymes)

Final process in development

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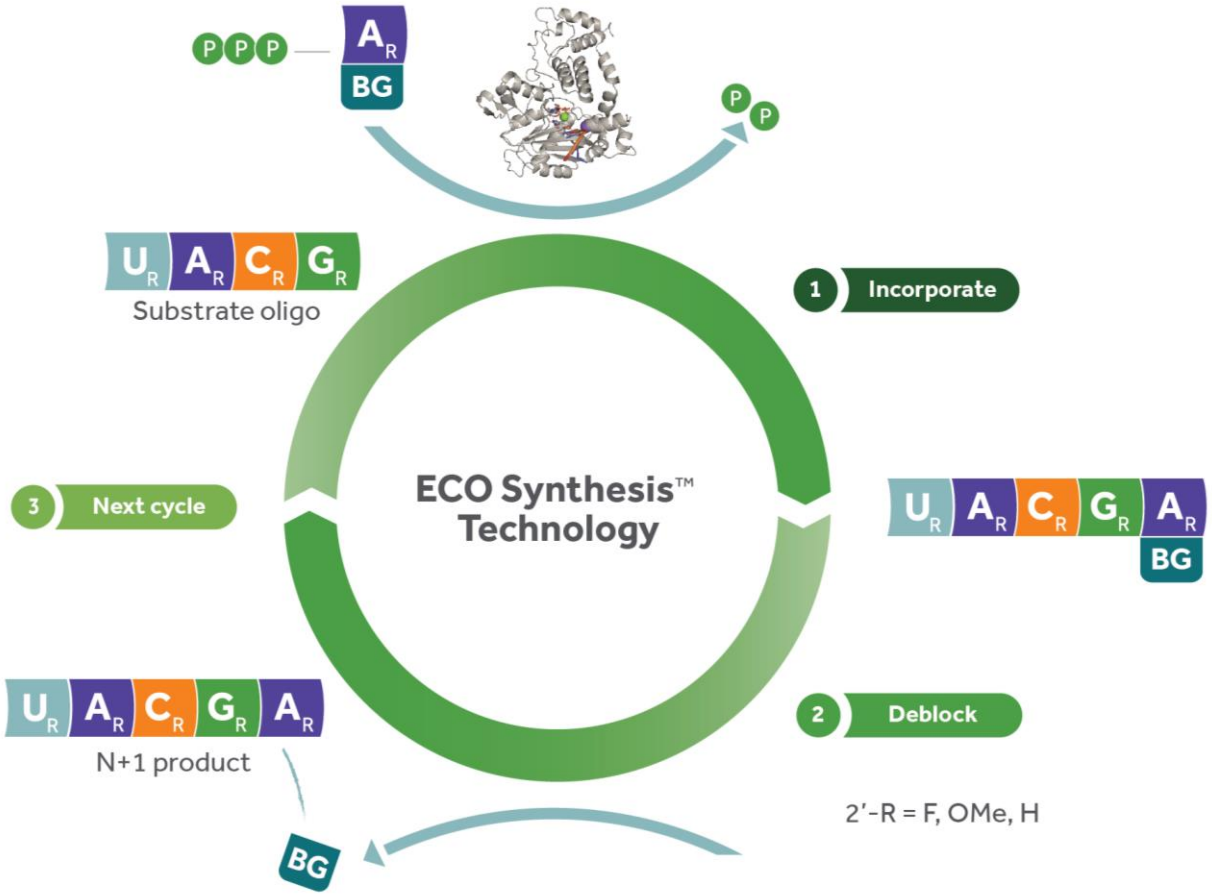
Codexis ECO Synthesis™ Technology

Enzyme-Catalyzed Oligonucleotide Synthesis for RNAi therapeutics



Enzyme Performance

- High incorporation efficiency (>99%)
- No sequence bias

At-Scale Process Requirements

- Controlled addition of monomers
- Low impurity production
- High volumetric productivity

Scalable & Economical Enzyme Manufacturing

- High manufacturing yields
- Scalable supply of nucleotide triphosphates

Final process in development

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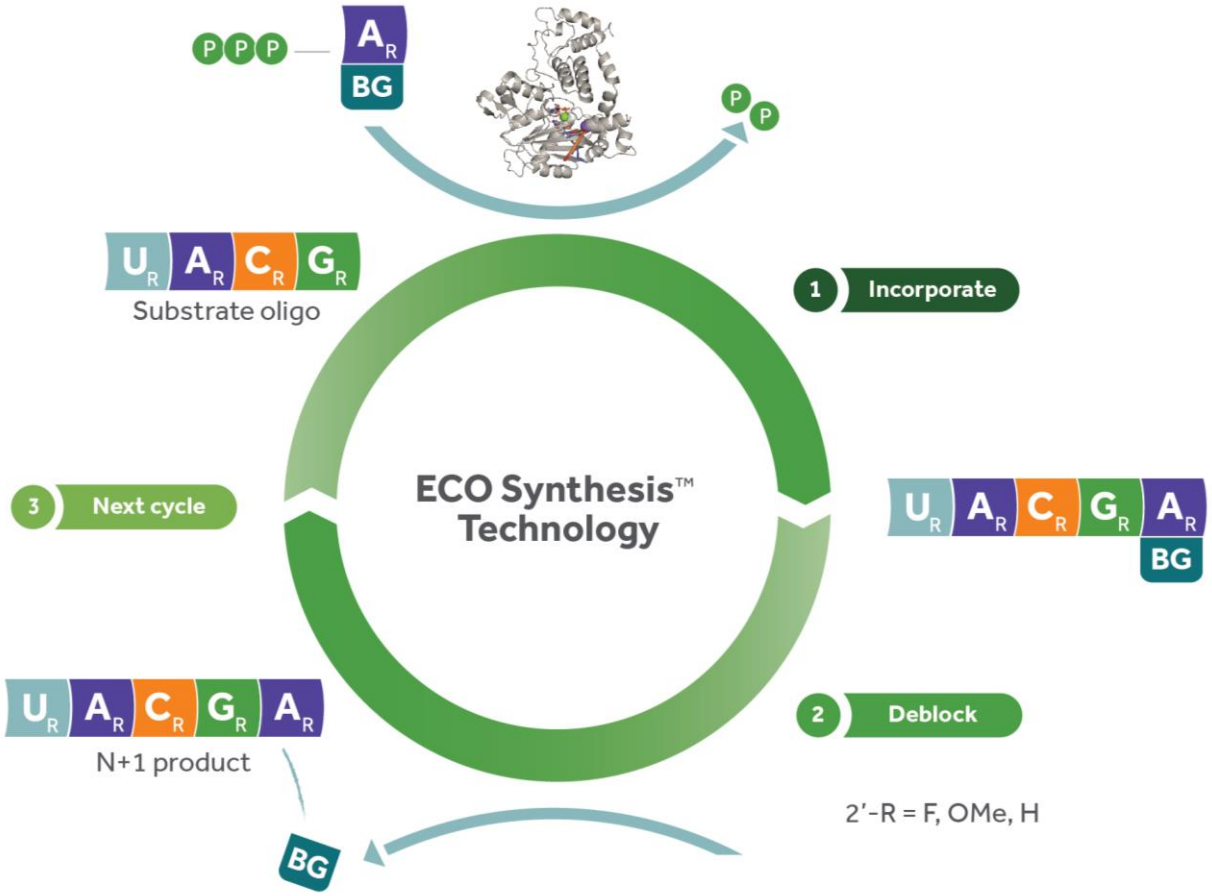
Codexis ECO Synthesis™ Technology

Enzyme-Catalyzed Oligonucleotide Synthesis for RNAi therapeutics



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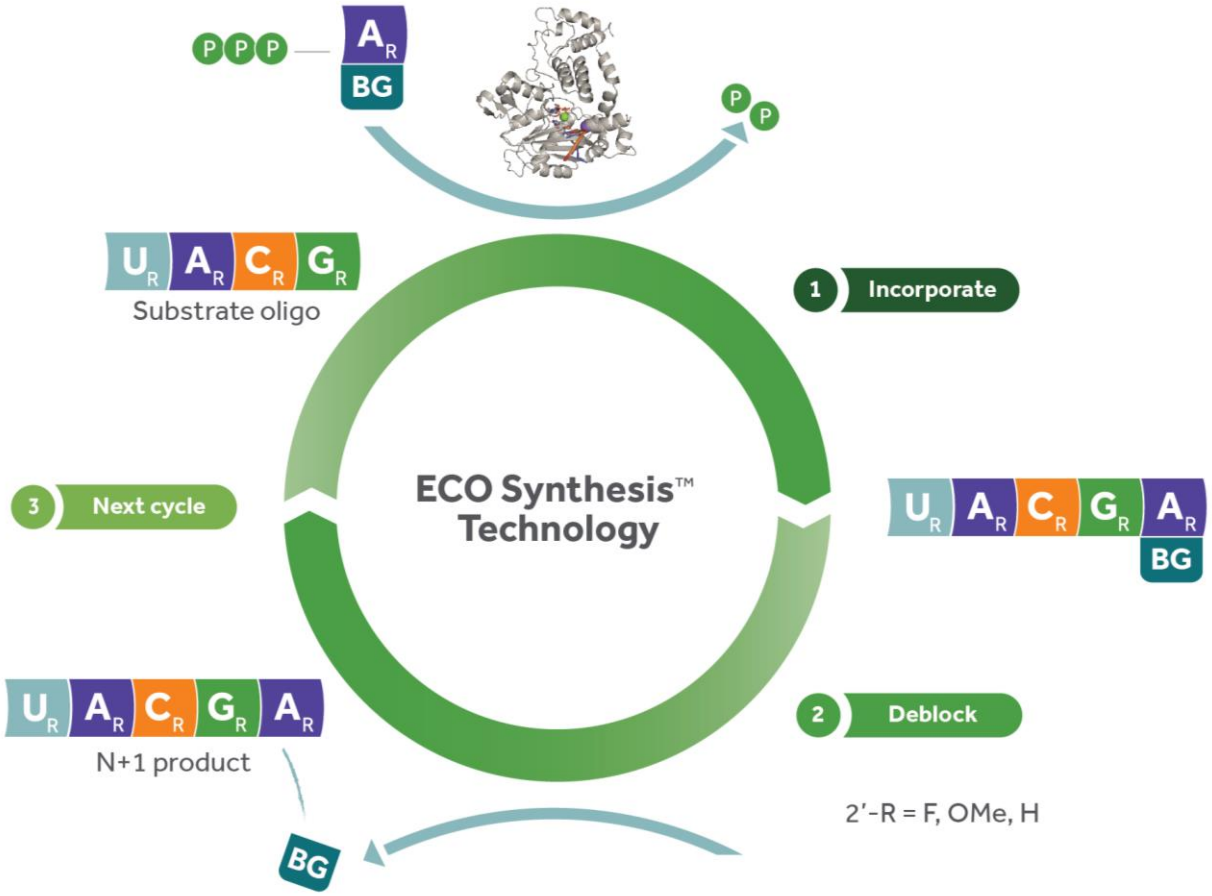

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Scalable & Economical Enzyme Manufacturing

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Final process in development

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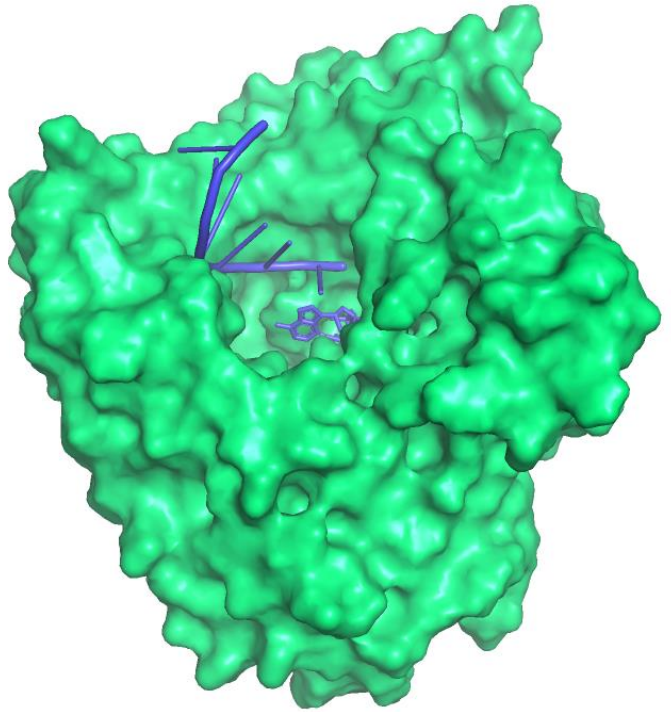
Enzyme Performance: A highly engineered TdT

Key Enzyme Challenges

- Does not naturally recognize modified RNA
- Poor soluble expression and stability
- Enzymes function close to physiological conditions
- Manufacturability for large scale enzyme needs



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Enzyme Performance: A highly engineered TdT

% Incorporation efficiency of N+1 additions over multiple rounds of evolution

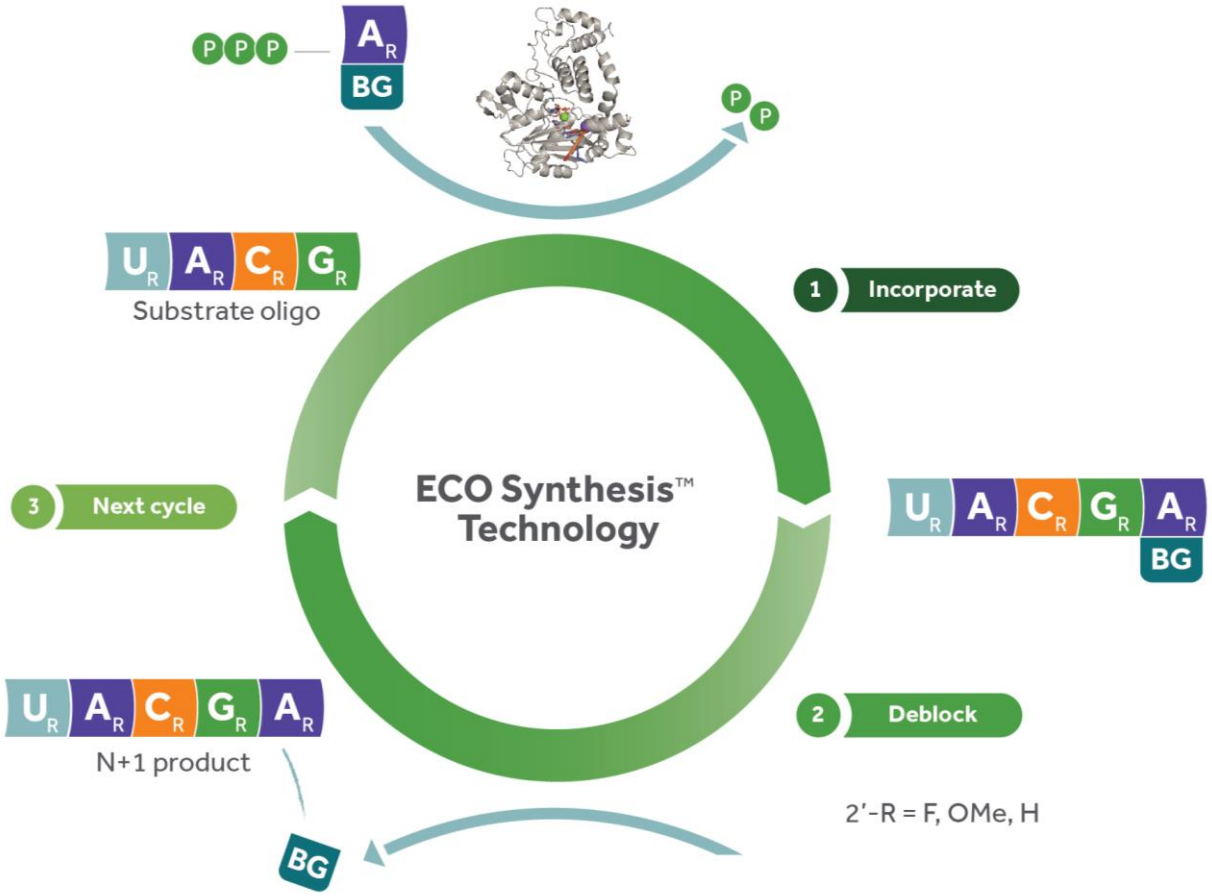
3'-Terminus Sequence	NTP	Starting TdT	Iterative Rounds of Evolution						
mAmCmU	fATP-3P	0	0	0	0	1	54	91	94
	fUTP-3P	0	0	0	0	1	56	93	94
	mCTP-3P	0	0	0	0	1	54	91	89
	mGTP-3P	0	0	0	0	1	24	87	78
	mATP-3P	0	0	0	0	1	39	88	66
	*mGTP-3P	0	0	0	0	0	0	2	55
	*mUTP-3P	0	0	0	0	0	0	19	24
mGmAmC	fUTP-3P	0	0	0	0	2	33	74	92
	mATP-3P	0	0	0	0	1	16	60	90
	fATP-3P	0	0	0	1	2	34	77	88
	mCTP-3P	0	0	0	0	0	13	66	86
	*mUTP-3P	0	0	0	0	0	0	11	79
	*mGTP-3P	0	0	0	0	0	0	3	64
	mGTP-3P	0	0	0	0	0	0	2	55
AT*mG	mATP-3P	4	1	4	49	75	82	47	56
AmU*mG		0	0	0	12	46	77	75	41
mAmU*mG		0	0	0	0	5	69	82	68
mAmUfG		0	0	0	0	0	2	1	66
mUmGmA	mATP-3P	0	0	0	1	2	38	82	86
mAfUCmC		0	0	0	0	4	58	88	86
mAmG(MOE)C		0	0	0	0	0	4	14	84
mC*mG*mA		0	0	0	0	2	39	75	75
mCmUmG		0	0	0	0	4	82	86	72
mAmUmC		0	0	0	0	2	57	84	63
mAmUfU		0	0	0	0	0	0	0	59
*mA*mA*mC		0	0	0	0	1	30	54	57
mAmUfC		0	0	0	0	0	1	1	51
mCmGmA	fATP-3P	0	0	0	1	4	82	93	92
*fAfGmA		4	2	4	19	50	79	85	85
mC*mG*mA		0	0	0	1	3	47	81	82
*fA*fAfG		0	0	0	0	0	44	56	70
fCfGfA		0	0	0	3	26	50	55	65
mU*fA*fA		0	0	0	0	3	11	17	34
fGmAfU		6	5	6	3	12	42	52	30
fC*fG*fA		0	0	0	0	4	14	30	14

So far…

- ✓ Incorporation of relevant 2’-modifications with 3’ phosphate blocking group
  - ✓ 2’-deoxyfluoro and 2’-methoxy
- ✓ Incorporation of α-PS bonds
- ✓ Recognition of modified initiator sequences
- ✓ Improving incorporation efficiency of each nucleotide (goal >99%)

Note: All incorporating nucleotides contain 3’-blocking group; “*” denotes alpha PS-bond; “m, r, f” denotes 2’-OMe, 2’-OH, or 2’-F modifications, respectively

ECO Synthesis™ Technology: Controlled addition of monomers



Target Sequence:

5’ – Biotin/FAM…mA mU mA mA mG mA fA – 3’

- ✓ 4 Cycles for proof of concept
- ✓ Feasibility demonstrated for modified RNA synthesis

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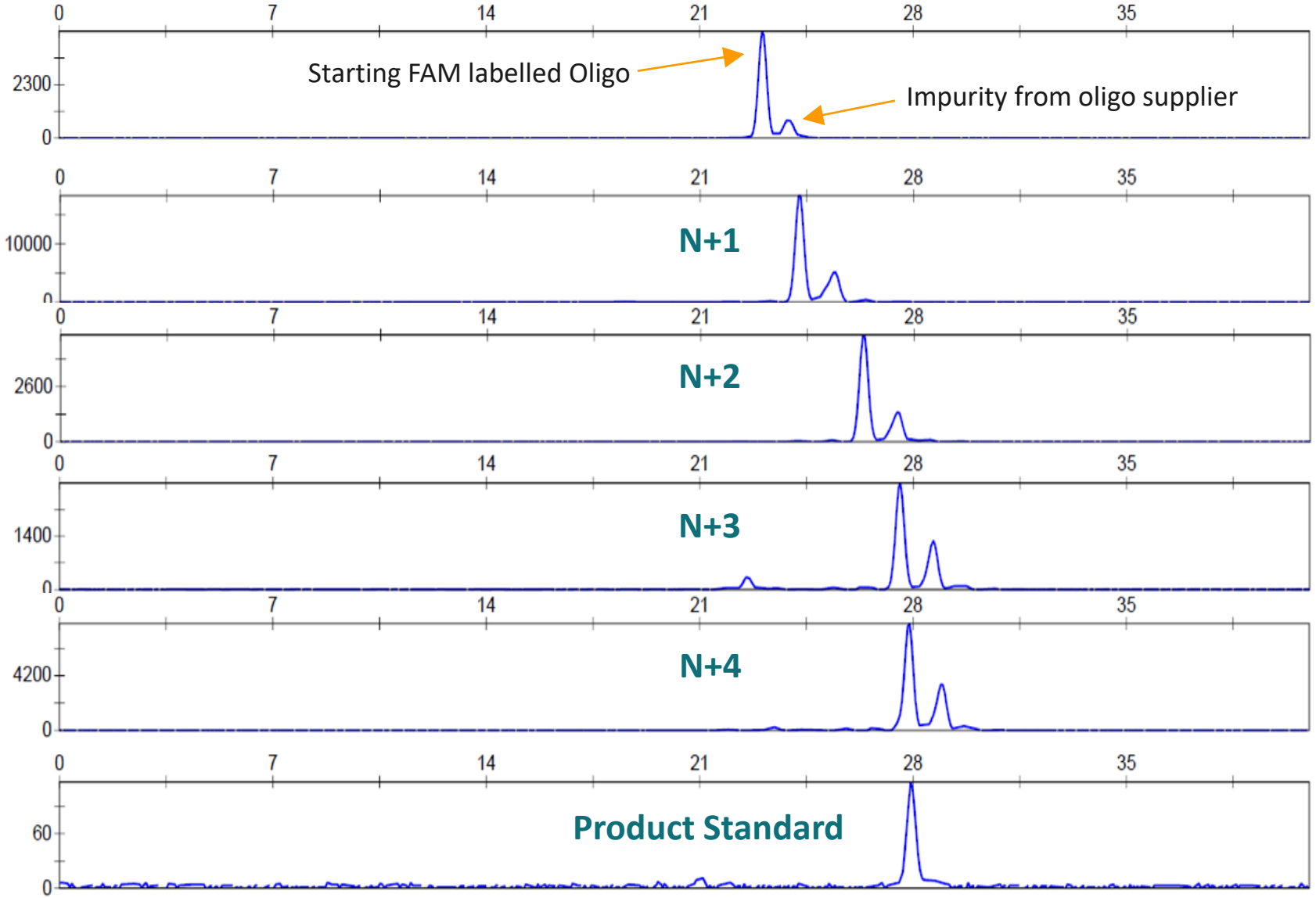
ECO Synthesis™ Technology: Controlled addition of monomers

Addition and deblocking with 5'-biotynilated-FAM…mAmUmA



5' …mA mU mA

5' …mA mU mA mA

5' …mA mU mA mA mG

5' …mA mU mA mA mG mA

5' …mA mU mA mA mG mA fA

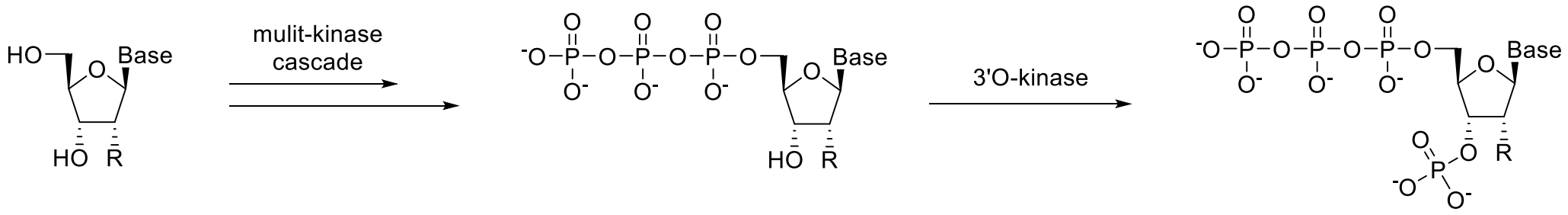
5' …mA mU mA mA mG mA fA

Not final process conditions

Coming soon…enzymatically-activated monomer supply

Demonstrated…

✓ Nucleoside → NTP conversion → 3’Blocked-NTP



“Two-step-one-pot” synthesis of 3’-blocked nucleotides

Provides scalable, sustainable, economic supply of required ECO Synthesis™ monomers

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ECO Synthesis™ Technology: A vision for sustainable RNA synthesis

Accomplished to date

- ✓ Progress on critical TdT performance
- ✓ Proof of Concept for iterative nucleotide addition
- ✓ Concept for enzymatically-derived source of 3’-blocked nucleotides

Next Steps

- ❑ Increase % monomer incorporation to reduce impurities
- ❑ Sustainable & scalable supply of nucleotides
- ❑ Scale-up to process-relevant conditions
- ❑ Achieve gram-scale synthesis of modified RNA

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