ASYMCHEM



# OLIGONUCLEOTIDE SERVICES



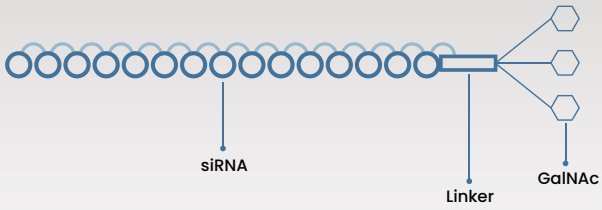

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# Oligonucleotide Platform Overview

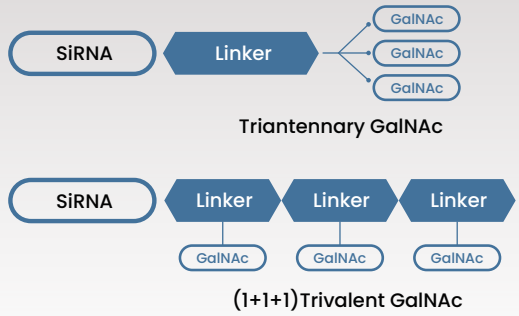
We offer custom synthesis and purification services ranging from 0.1 mmol to 1,000 mmol scale, supported by our state-of-the-art synthesis and analytical facilities. Leveraging our proprietary platform technologies, we handle both single-stranded and double-stranded oligonucleotides with precision. Our manufacturing plant maintains strict microbial controls while delivering production capacity of up to 1,500 kg annually.

## Oligonucleotide



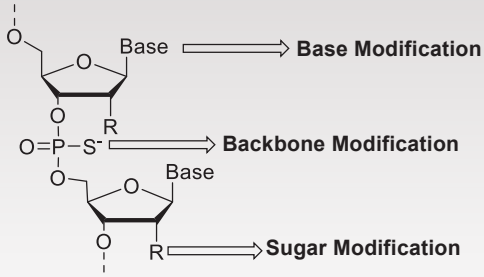

- ASO
- CpG
- siRNA, saRNA, miRNA, sgRNA
- Aptamer

## Conjugation



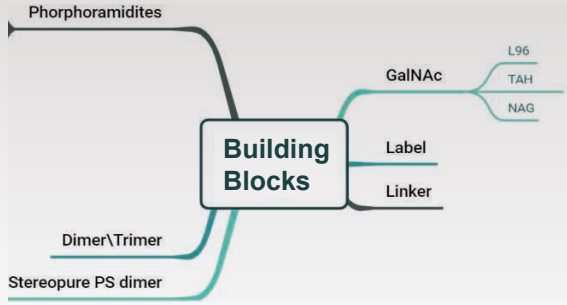

ApDC, AOC, POC, PPMO (e.g. GalNAc, PEG, Cholesterol)

## Modification




Backbone - PO, PS and PO-PS mixed
Sugar - 2-F, 2-O-Me, 2-MOE, PMOs, LNAs and cEt
Base - Various Modifications

## Key Raw Materials




- Phosphoramidites
- GalNAc
- Payload Linkers for ApDC and AOC, etc.

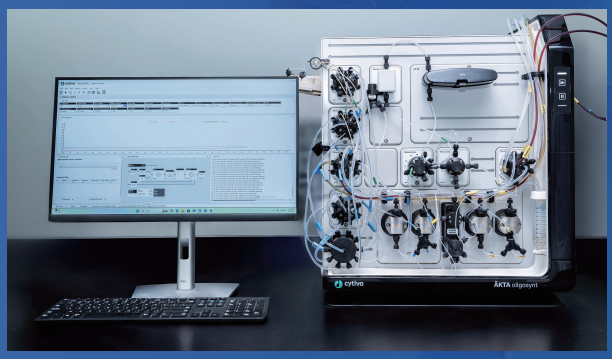
- 2,000 m² R&D Lab for Oligo Synthesis, Purification and Analysis; 9,500 m² GMP Plant
- 500+ Process and Analytical Chemists; 50% Ph.D and Master Degree Holders
- 6 PPQ; 100+ IND Enabling Work

# Oligonucleotide: Capability & Capacity

- **End-to-end service** from preclinical to commercial manufacturing for both DS & DP
- **Platform technology** for synthesis and analysis of oligonucleotide development and manufacturing
- **85%-90% purity for GLP** and **90-95% for GMP** batches and control of endotoxin up to 0.01 EU/mg
- Lead time of **4-6** months for IND filing
- Comprehensive approaches for PPQ projects
- **60** synthesizer sets, from OP100 to OligoProcess™, along with specialized equipment trains, enabling production of up to ~**1,500 kg per year**
- Dedicated analytical facility



OP100 (20mg-20g / batch)



OligoSynt™ (5g-30g / batch)



OligoPilot™ (30g-500g / batch)



OligoProcess™ (400g-10kg / batch)

# 4-6 Months Lead Time for IND Filing Package

## Oligonucleotides IND Filing: 4-6 Months for GMP Batch Delivery




| | |
|---|---|
| **Process Development** | • Preliminary study of RSMs specification<br>• Preliminary process development & optimization<br>• Preliminary study on fate & purge of key impurity<br>• Preliminary stress test of unit operation stress test<br>• Confirmation of reaction IPC and endpoints of unit operations<br>• Process safety assessment |
| **Analytical Method Development** | • Preliminary analytical method development & optimization<br>• Reference standard characterization<br>• Structural Elucidation (API)<br>• Preliminary analysis method validation (API)<br>• Preliminary cleaning test method development<br>• Stability study of API |
| **GMP Production** | GMP document preparation & GMP production |
| **Release** | • One day for laboratory sample release<br>• 1 week for GLP sample release<br>• 1-2 weeks for GMP sample release<br>• Endotoxin and microbial test |

# CMC Study Strategy in NDA Stage

## NDA Stage CMC Work Flow

### Process Optimization

- Production change assessment
- Review historical batch data to identify high-risk impurities.
- Enhance process robustness
- Starting material supplier selection, expensive material equivalent screening

### API Specification Study

- Set up specification of API based on regulatory (guidelines) or toxicological (clinical) experimental data, dosage cycle, daily dose, etc. and process impurities, degradation impurities, stability results

### RSM Specification Study

- Potential process impurities will be evaluated based on the synthesis route and process of the starting material.
- The actual impurities are studied according to the test results
- Setting reasonable limits through sample addition derived experiment
- All data will be used to support the rationality of RSM selection

### Intermediate Specification Study

- Confirmation of intermediate specification by PAR experiments, typical historical batch data, potential process impurity analysis, sample addition derivative experiments, and actual production control

### Impurity Study

- Analytical method development, validation, and detection will be supported by potential impurity assessment, actual impurity spectrum analysis, and synthesized impurities

### Genotoxic Impurities Study

- Derek Nexus and Sarah Nexus software were used to evaluate potential process impurities, by-products, involved materials, reagents, intermediates, etc
- Different research and control strategies for GTI were developed based on the evaluation results and ICH M7

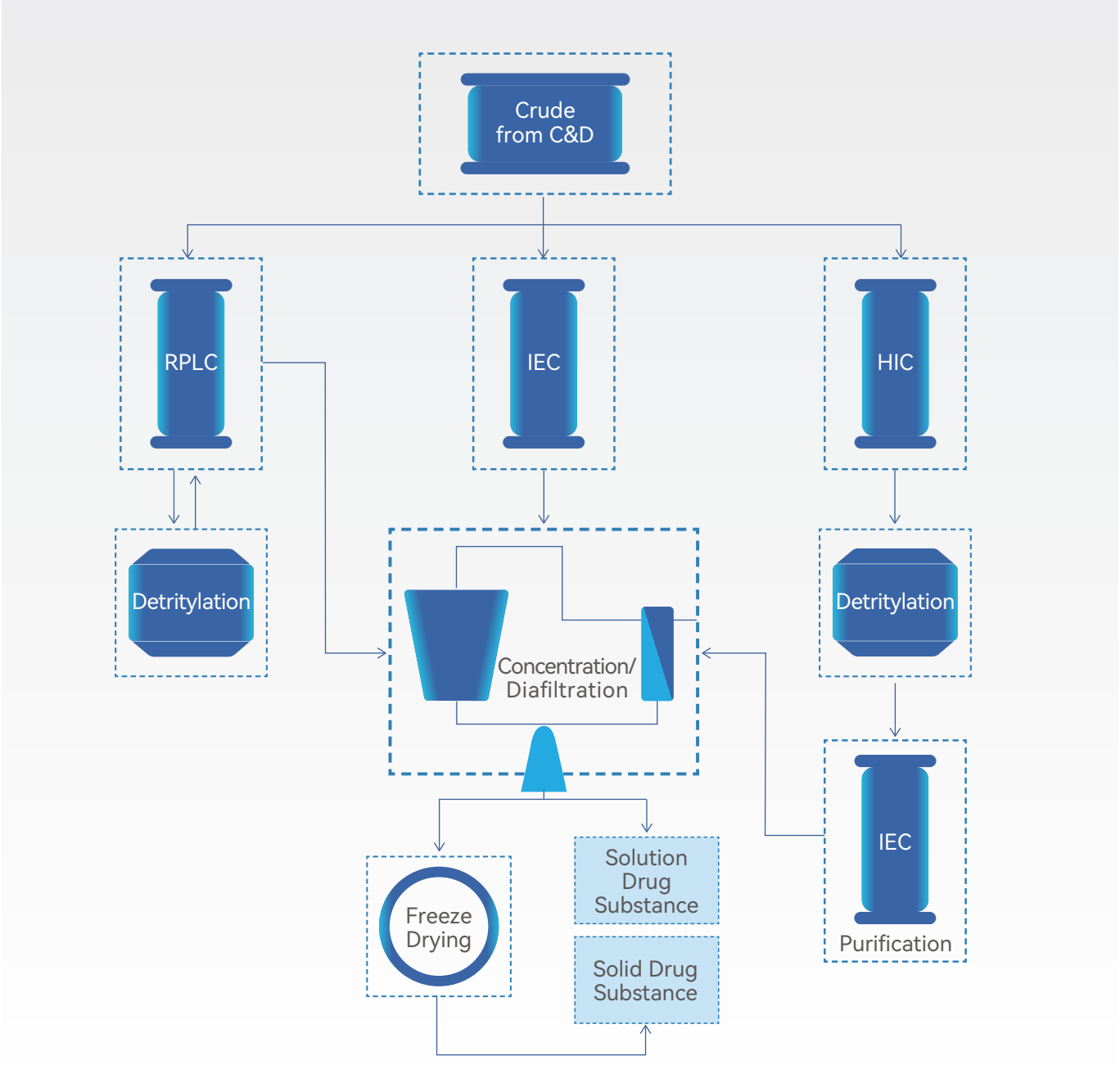
### PAR/CPP Study

- Select different experimental methods (DoE, OFAT, MFAT) based on the parameter risk to establish the PAR range of the parameters
- CPP confirmation based on actual production control

### Analytical Method Development & Validation

- Develop and optimize analysis methods for starting raw materials, intermediates, IPC, and final product release based on impurity evaluation results and actual process requirements
- Perform analytical method validation to demonstrate that the method meets the test requirements according to pharmacopeial guidelines

# Purification Capability



# Purification Capability

### Ion Exchange Chromatography (IEC) (most commonly used)

- Process Strategy: DMT-on (De-protected on column), DMT-off
- Functional group: Q, DEAE (PS/DVB, PMA, Agarose matrix)

### Reversed-Phase Liquid Chromatography (RP-LC)

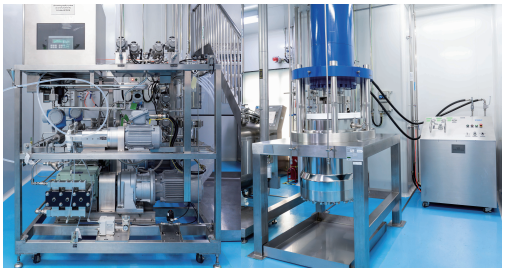
- Process Strategy: DMT-on, DMT-off
- Functional group: C18, C8, Phenyl (Silicone, polymer matrix)

### Hydrophobic Interaction Chromatography (HIC)

- Process Strategy: DMT-on
- Functional group: Phenyl/ Butyl/ Ethyl

### Two-Step Orthogonal Chromatographic Process

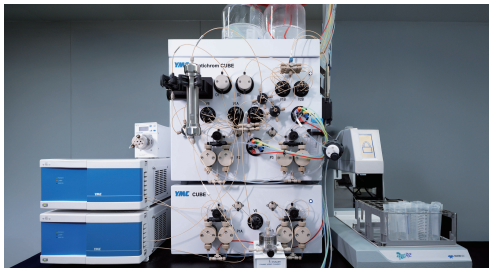
- RPC, IEX and HIC Orthogonal purification



YMC Prep-HPLC with DAC600



Bioprocess



YMC CUBE 100w

# Isolation Capacity

**Lyophilizers with isolators: 1-30 $m^2$**

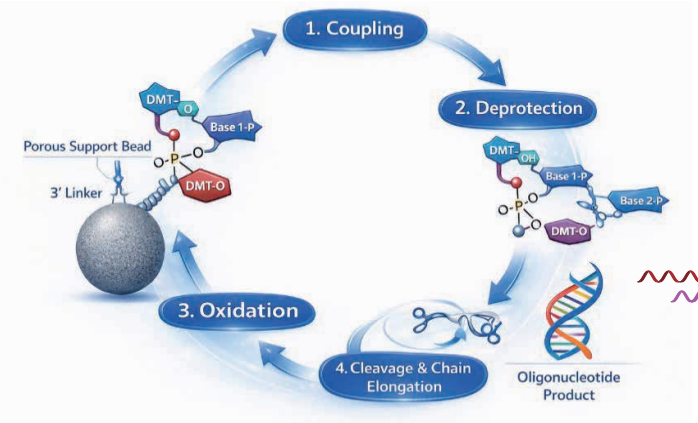


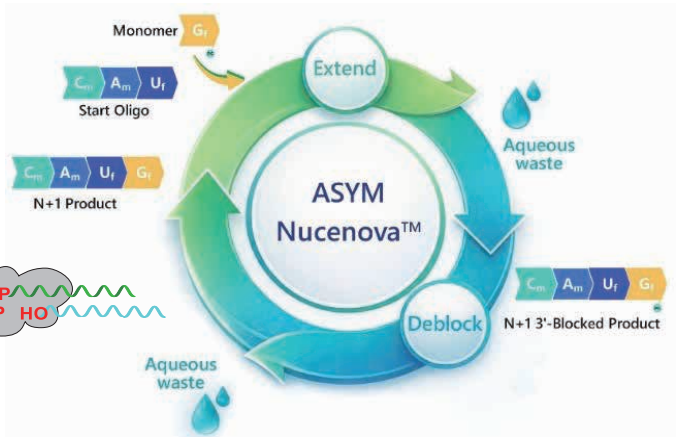
# Diverse Biosynthetic Technologies for Oligonucleotides

Oligo manufacturing is evolving from single-method chemistry toward integrated chemical and biological solutions.

## Nucleic Acid Synthesis Platforms

*From Solid-Phase to Enzymatic Solutions*




### Solid-Phase (Current baseline)

Robust chemical platform for high-quality oligonucleotide production

- High cost, high PMI, limited scalability
- Approaching inherent technical constraints

### Chemoenzymatic (Core platform)

Hybrid enzymatic platform for efficient oligonucleotide synthesis

- Lower cost, reduced PMI, and improved scalability compared with solid-phase synthesis
- Chemical efficiency + enzymatic precision
- Ideal for current manufacturing needs

### De Novo Enzymatic (Future direction)

Fully enzymatic platform for template-free synthesis

- Further reduction in cost and PMI
- Complementary to hybrid approach

# Enzymatic Ligation Platform for Flexible Manufacturing

| Versatile Ligation Modes | Comprehensive Product Portfolio | Engineered Enzymes |
|---|---|---|
| Suit diverse oligonucleotide synthesis requirements | Broad application scenarios | Directed evolution deliver superior catalytic performance |

## Workflow

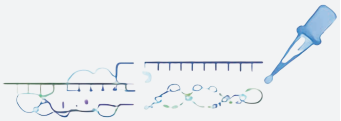
### Monomers




A | U | C | G

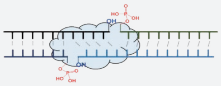
Modified NTPs

### Fragment Generation

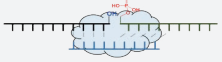


- SPOS
- LPOS
- De Novo

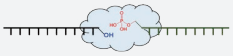
### Ligation



Double



Template-Assisted



Single

### Products



- siRNA
- miRNA
- sgRNA
- tRNA
- saRNA
- ASO
- Aptamer

## Enzyme portfolio

| Core Ligases | Engineered Variants |
|---|---|
|  Nucleic acid ligase library | • Improved yield<br>• Broad substrate compatibility<br>• Reduced side products |

# Analytical Capability

- Analytical Methods Development, Validation and Transfer
- Raw Materials, Intermediates and Final Products Release Testing and In-process Control
- Genotoxic Impurity Detection Methods Development, Validation and Testing
- Structure Elucidation and Physicochemical Testing
- Reference Standard Characterization
- Oligonucleotides Analysis
- Microbiological and Endotoxin Testing
- Cleaning Inspection and Environmental Monitoring
- ICH Stability Testing for IND / NDA / ANDA / Commercialization









# Analytical Instruments

## HPLC / UPLC

**200+** HPLC,

Detector: UV/CAD/DAD/RID/ELSD

**170+** UPLC

Detector: PDA/TUV/DAD/CAD

Brand: Thermo, Agilent , Waters

## GC / HS-GC

GC instrument

**10+** Agilent instruments GC + Headspace

**20+** Agilent instruments

## MS / NMR / XRD / ICP

**30+** LC-MS instruments

(Q-TOF, Q-E, UPLC-MS, LC-MS)

**5+** GC-MS

NMR: 400 MHz, 500 MHz, 600MHz

## Stability Chamber

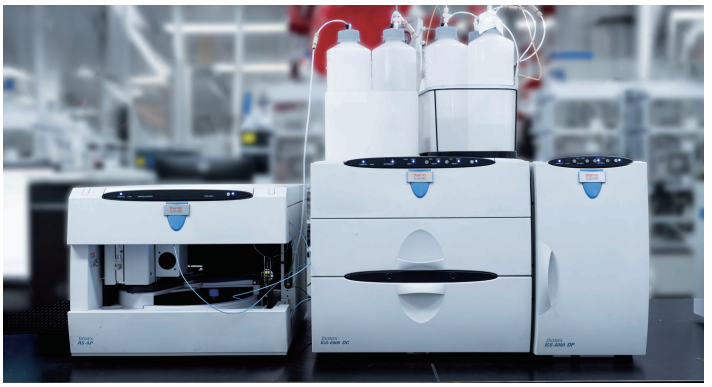
**15+** 25oC/60%R.H.

**5+** 30oC/65%R.H.

**5+** 40oC/75%R.H.

**60+** 2-8oC, -20oC, -80oC








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