



Experts taking care.

Development &
Manufacturing of Peptides
& Oligonucleotides

CPHI Japan, Tokyo
18th April 2018

www.cordenpharma.com

CordenPharma Overview

Your Full-Service CDMO Partner

- Full-Service CDMO Organized under 5 Technology Platforms
- €365 Million Total Sales (2016)
- 11 Manufacturing Facilities in Europe / US (9 GMP Plants, 2 R&D Labs)
- 1,670 Employees

Value Chain Positioning

Supply Chain Positioning



- CordenPharma covers the full GMP supply chain of pharmaceutical custom manufacturing (raw materials and non-GMP pharmaceutical intermediates partially sourced from WeylChem)
- API manufacturing accounts for c.62% of net sales and usually has a shorter ramp-up phase than respective Drug Product projects

Lifecycle Positioning



- CordenPharma focuses on all stages of a drug lifecycle with competitive advantages in clinical development and commercial production

CordenPharma - Value Proposition



**Peptides,
Oligonucleotides,
Lipids &
Carbohydrates**



**Highly Potent
& Oncology**



Injectables



**Small
Molecules**



Antibiotics

- **Serving Global Pharma & Biotech Customers**
- **Organized under 5 Distinctive Technology Platforms**
- **Broad Range of Expertise:**
 - **API's:** Small Molecules, Peptides, Oligonucleotides, Lipids, Carbohydrates, Highly Potent, Cytotoxics, Conjugates
 - **Drug Products:** Oral, Liquids, Injectables, Highly Potents, Anti-infectives / Antibiotics
- **Global Coverage Allowing for Flexibility**
- **Your Full-Service Provider from Clinical Development to Full-Scale Commercial Supply of APIs & Drug Products**

Compliance

| Market | Agency | Bergamo (IT) | Boulder (CO, US) | Brussels (BE) | Caponago (IT) | Chenôve (FR) | Colorado (US) | Latina (IT) | Liestal (CH) | Plankstadt (DE) |
|------------------------------------------------------------------------------------|---------------|--------------|------------------|---------------|---------------|--------------|---------------|-------------|--------------|-----------------|
|  | EMA, EU local | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
|  | FDA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
|  | PMDA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
|  | TGA | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ |
|  | Health Canada | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
|  | ANVISA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ |
|  | IMPROM TORG | | | | | | | ✓ | ✓ | ✓ |



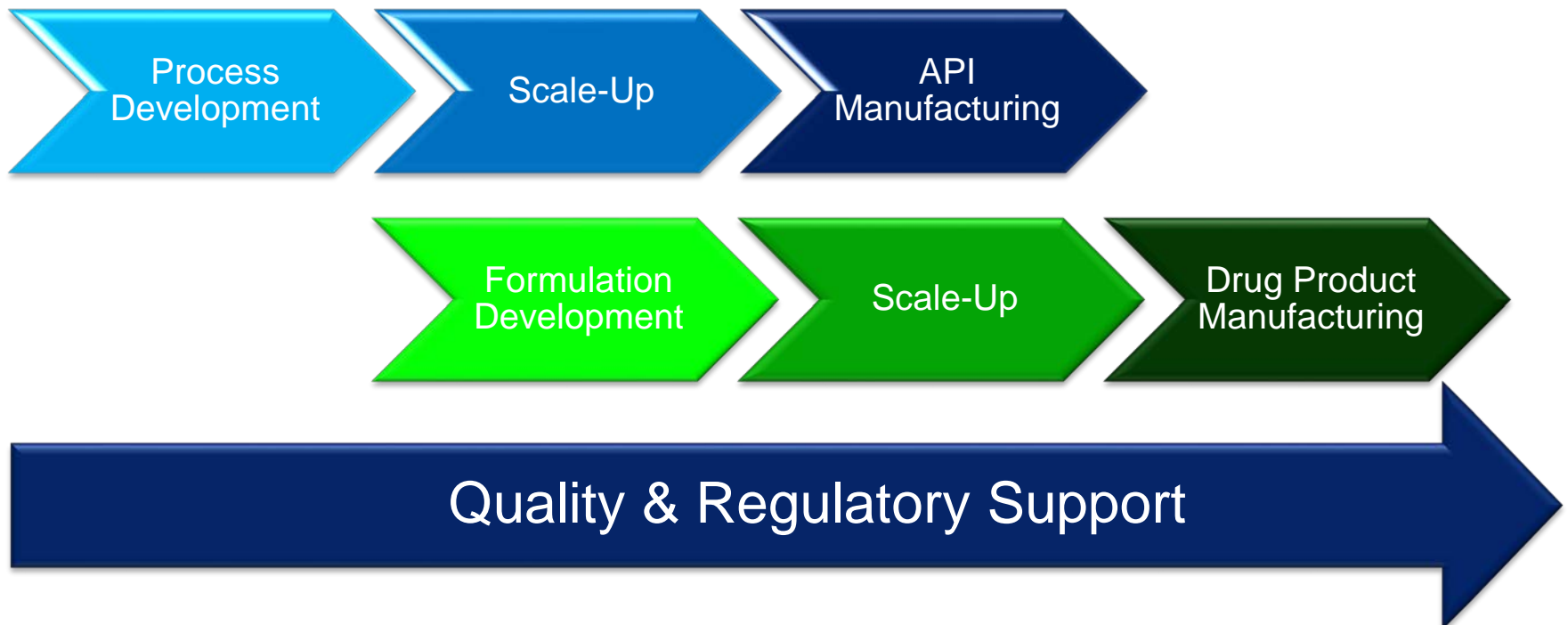
**Peptides, Oligonucleotides,
Lipids & Carbohydrates
Platform**

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Platform Unique Positioning

Fully Integrated Supply API and Drug Product: Short Time to Market

- One Partner: Straightforward Communication and Project Management
- Efficient Exchange between API and Drug Product Teams
- Shorten Timelines



Peptides Capabilities

Solid-Phase Peptide Synthesis

Solution-Phase Peptide Synthesis

HPLC Purification Capabilities

Small to Large Scale

Highly Potent Peptides (OEL 1 ng/m³)

Conjugations

Synthetic Vaccines

Peptide Overview

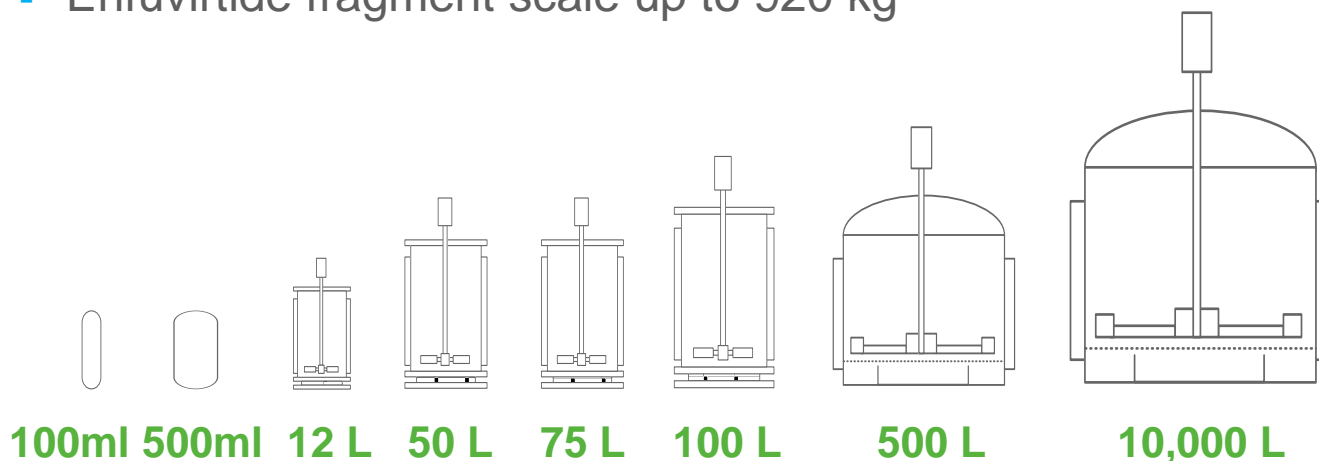
- A Broad Range of Technical Capabilities from **Process Design** and **Scale-Up** to **Commercial Manufacturing** – g-scale to 100's of kg production under full cGMP conditions
 - Complex Peptides & Peptidomimetics
 - Proprietary Process Technologies for cost-effective manufacturing
 - Peptide Conjugations (PEGs, Proteins, Lipids, Carbohydrates)
 - Cyclic Peptides & Peptides with multiple Disulfide Bridges
 - Short Peptides (up to 12 residues), often without HPLC purification
 - Arginine-rich Peptides
 - Long Sequences (>30-AA) at 100's kg
 - CMC Section: Process & Analytical Services (stability, test methods, validations, etc)
 - Filings: DMF Filing (e.g. USA, EU, Japan), IND, NDA, ANDA, IMPD

Solid-Phase Peptide Synthesis at any Scale



Solid-Phase Synthesis:

- Full range of synthesizer covering any scale at any stage of development
- Batch automation
- Large-volume solvent and waste-handling logistics
- Precipitation / isolation of fragments and final APIs
- Enfuvirtide fragment scale up to 920 kg



Solution-Phase Peptide Synthesis

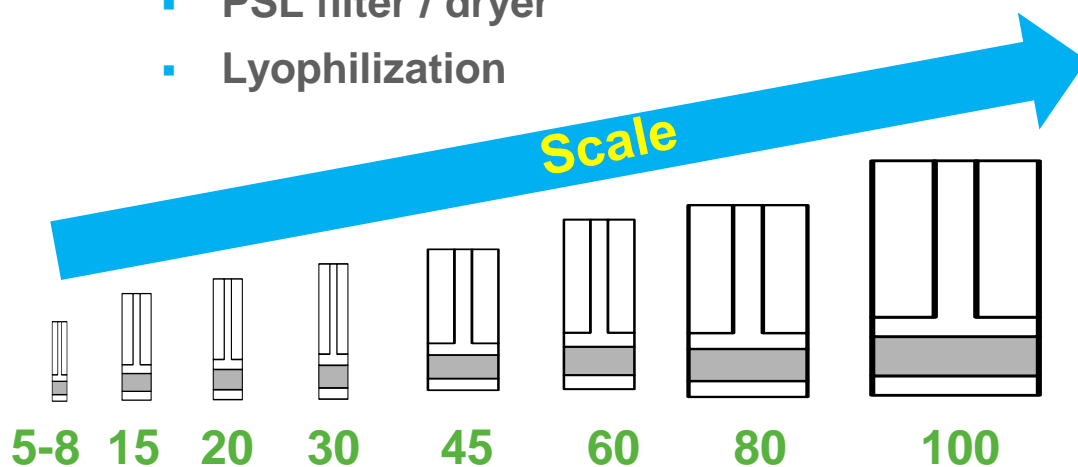
State-of-the-art Manufacturing Infrastructure:

- Corrosion-resistant Vessels (Hastelloy)
 - 2000 – 12,000 L pilot / commercial scale
- Wide range of reactor sizes
 - 20 L to 18,000 L vessels
- Precipitation, Isolation & Drying
 - Heinkel 600 & 800 centrifuges
 - AP 300 & 600 BHS Autopress
 - 20 L to 3 m³ filter / dryers
 - 50 L to 3000 L conical screw dryers



Peptide Purification Capabilities

- Full range of HPLC, LPLC Scale
 - Orthogonal chromatography capability
 - Continuous acetonitrile recovery
 - Diagnosis & control of gel formation
- Precipitation, Isolation & Drying
 - AP 300 BHS Autopress
 - PSL filter / dryer
 - Lyophilization



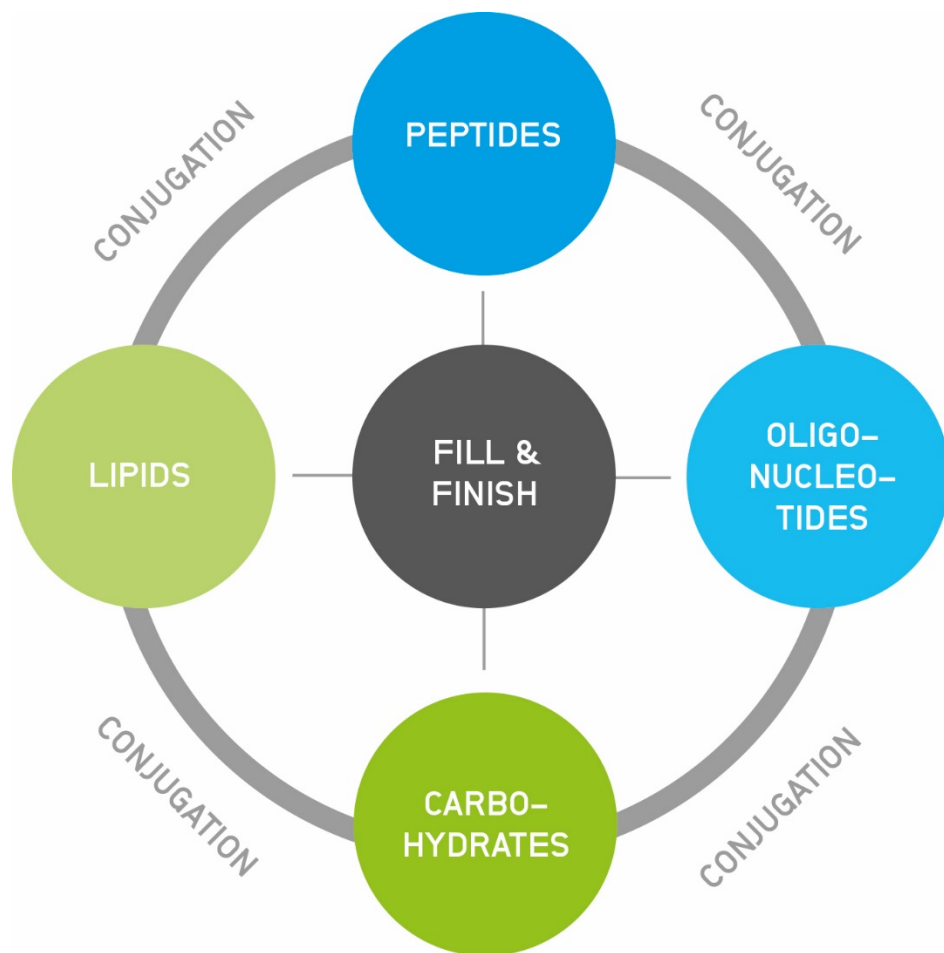


Peptides, **Oligonucleotides**,
Lipids & Carbohydrates
Platform

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Peptides, Oligonucleotides, Lipids & Carbohydrates Platform

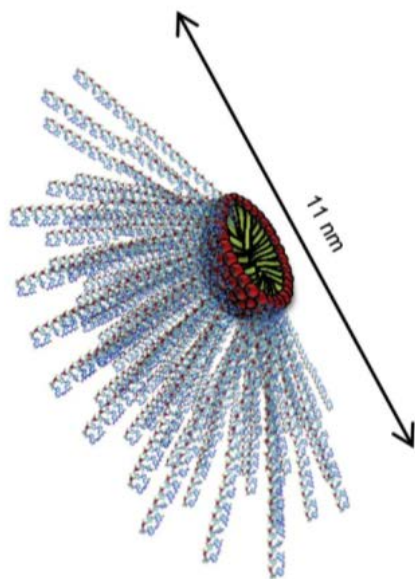
Your Expert Partner for Bio-Organic APIs



Areas of Indication

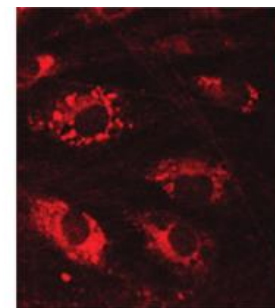
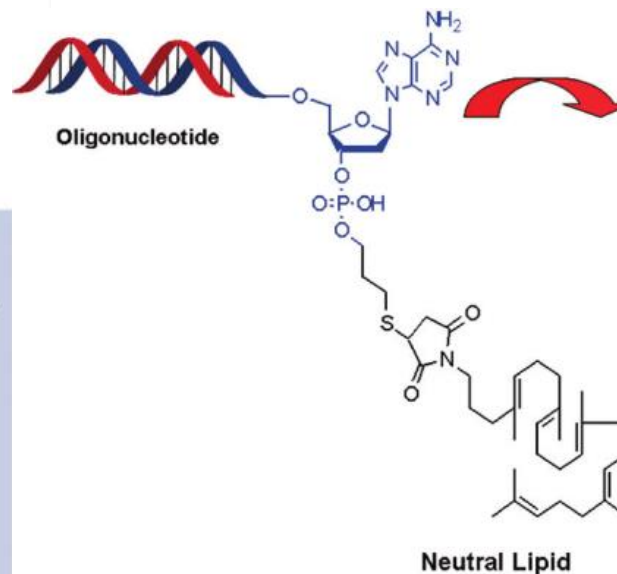
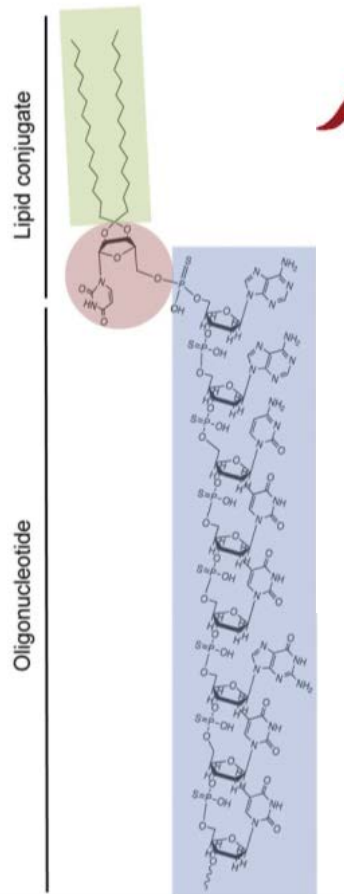
- APIs covering a wide range of therapeutic indications
- Vaccines
- Adjuvants
- Drug Delivery Systems
- Drug Targeting: Conjugations

Lipids > Targeting & Delivery Strategies



Nanomicelles

Journal of Controlled Release 258 (2017) 1–9

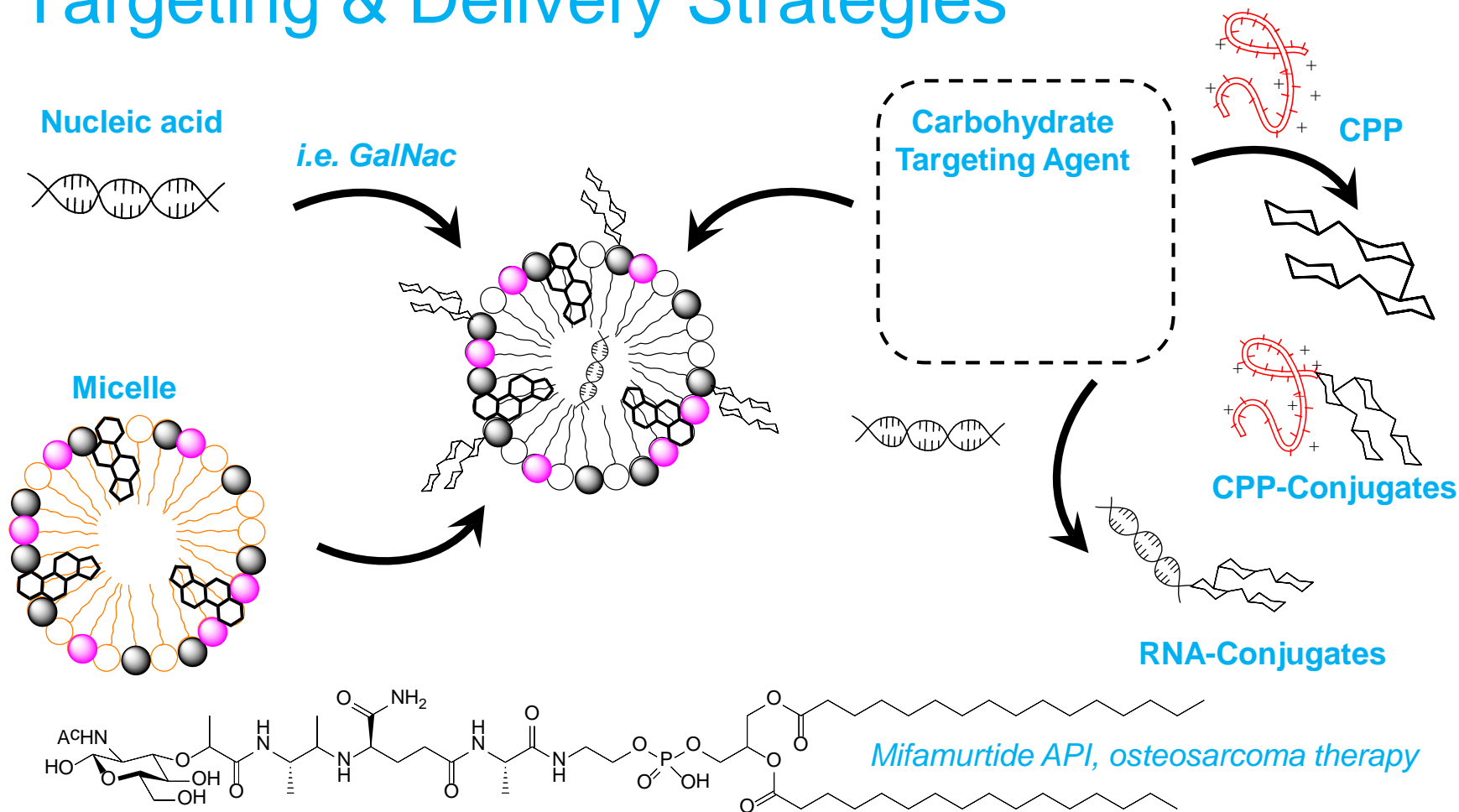


Cellular delivery

Natural Lipid

Bioconjugate Chem. 2012, 23, 1091–1104

Carbohydrates / Peptides Targeting & Delivery Strategies



Oligonucleotide Value Proposition - Summary

Building on Decades of Peptide Expertise

➤ **Integrated Supply Chain**

- Cationic lipids and carbohydrates for Oligo drug delivery (e.g. LNP and GALNAc chemistry)
- Drug product – liquid vials, pre-filled syringes, lyophilized product

➤ **Technology Synergies**

- Conjugation
- Solid phase and solution phase peptide synthesis
- MPLC and HPLC, RP & IEX
- Precipitation, Isolation and lyophilization

➤ **Manufacturing Scale & Expertise**

- Gram scale to >> 100 kg batch scale for peptide APIs
- Experience developing and scaling up peptide APIs for over 40 years

➤ **Quality & Regulatory**

- Quality system built for life cycle management from clinical through post process validation
- Excellent regulatory agency and customer inspection history

Custom DNA/RNA - Value Proposition – Life Cycle

Dharmacon™
A Horizon Discovery Group Company

CORDENPHARMA



| | ≤ 1 mg | 10 mg | 100 mg | 1 g | 10 g | 100 g | 1 kg | > 10 kg |
|--------------|--------|-------|--------|-----|------|-------|------|---------|
| Discovery | | | | | | | | |
| Research | | | | | | | | |
| Pre-clinical | | | | | | | | |
| Clinical | | | | | | | | |
| Commercial | | | | | | | | |

Custom DNA/RNA - API Manufacturing Services

| | 10 g | 100 g | 250 g | 500 g | 1 kg | > 10 kg* |
|---------------------|------|-------|-------|-------|------|----------|
| OligoPilot 100 iso | → | | | | | |
| OligoPilot 100 GMP* | → | | | | | |
| OligoPilot 400 GMP | → | | | | | |
| OligoProcess GMP** | | | | → | | |

- **OligoPilot 100:** 2-9 mmol scale (5 - 35g per run)
- **OligoPilot 400:** 4-60 mmol scale (15-120g of Oligo after DSP) per run
- **OligoProcess:** 100-4000 mmol scale (400g-16kg of Oligo after DSP) per run

* Additional OligoPilot 100 in 2018 for small scale GMP production

** Rolling out our first GMP Oligo Process in Q2 2018

Custom DNA / RNA - API Manufacturing Services

- Sugar modifications, i.e. 2'-OH, 2'-F, 2'-OMe,...
- Backbone modifications (sulfurization,...)
- Base modifications
- SiRNA duplex
- 3' and 5' modifications
 - GalNac
 - Amino linker
 - Cholesterol
 - PEG
 - Peptide
 - Lipids

Analytical Equipment Requirements (Pilot & Process Scale)

- Analytical instrumentation for raw material, process and final control includes (minimal & non-comprehensive list):
 - HPLC (SEC, Ion exchange & Ion pairing)
 - LC-MS (ESI, Ion Trap)
 - NMR (PAT for phosphoramidite coupling)
 - Micro calorimeter, DSC
 - UV-VIS (temperature controlled)
 - Q-tof
 - Sequencing
 - nnn

Experience & Expertise Q/A



- several non-GMP & GMP projects started so far
- Relation with Ionis
- Growing oligo team with specific expertise
- PhD MS expert with oligo experience
- Experienced in transferring methods from Waters to Agilent

Oligonucleotide - API Manufacturing Equipment

| Type | Item | Status |
|-------------------------|------------------------------------------------|---------------------------------------------|
| Oligo Synthesis | 2 x AKTA 100 OP 400 Oligo Process | Qualified Qualified Qualified Q2 2018 |
| Cleavage / Deprotection | 100L – 8,000L Hastelloy Reactors | Qualified |
| Chromatography | L/MPLC (cm) | Qualified |
| | 12 | |
| | 18 | |
| | 30 | |
| | 45 | |
| | 50 | |
| | 60 | |
| 80 | HPLC (cm) | |
| | 5 | |
| | 8 | |
| | 15 (3) | |
| | 45 | |
| | 80 | |
| | 100 | |
| UF | 6 m ² 30 m² | Qualified Planning |
| Lyophilization | 36L 90L+ | Qualified Planning |
| Bulk Solvent | 12 50K L tanks (6), 10-20K L tanks (~20) | Qualified |
| Solvent Recycling | Batch Distillation Continuous Distillation | Qualified |

Bold = to be placed in service

CordenPharma Colorado

- **Location: Boulder, Colorado USA**
- **Acquisition: September 2011**
- **Employees: 250**

- Integrated Resource for the Development & Manufacture of Advanced Intermediates and APIs for Global Pharmaceutical and Biotechnology Industries
- Development & Manufacture of Complex Synthetic Peptides, Oligonucleotides and Conjugates
- Development & Manufacturing of Highly Potent, Cytotoxic & Non-Cytotoxic APIs
- Excellent Track Record in Development from Early Stage to Launch
- SafeBridge® IV Certified



Core Competencies

- **Leader in Development & Manufacture of Synthetic Peptides**
- **Process Analytical Technology & Track Record in Regulatory Filing**
- **Development & Scale-up of Highly Potent & Oncology APIs**

THANK YOU

Contact

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