Company Overview

Tokyo Stock Exchange, Mothers  4571

Ichiro Nakatomi, Ph.D.
President & CEO
NanoCarrier Co., Ltd.
Japan

January 9, 2019
This presentation contains “forward-looking statements” within the meaning of Section 27A of the Securities Act and Section 21E of the U.S. Securities Exchange Act of 1934, as amended. These statements appear in a number of places in this presentation and include statements regarding the intent, belief or current expectations of the management of NanoCarrier Co., Ltd. (the “Company”) with respect to the Company’s business, results of operations and financial condition. In many cases, but not all, such words as “anticipate,” “believe,” “estimate,” “expect,” “forecast,” “intend,” “may,” “outlook,” “plan,” “probability,” “project,” “risk,” “seek,” “should,” “target,” “will” and similar expressions are used here in relation to the Company or its management to identify forward-looking statements. You can also identify forward-looking statements by discussions of strategies, plans or intentions. These statements reflect the Company’s current views with respect to future events and are subject to risks, uncertainties and assumptions. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, the company’s actual results may vary materially from those the Company currently anticipates. The Company disclaims any obligation to update, or to announce publicly any revision to, any of the forward-looking statements contained in this presentation to reflect future actual events or developments except as required by applicable law.
Company Overview

Core Technology
Clinical Pipeline
Next Generation and Next Application
Business Development
NanoCarrier Co., Ltd.

**MISSION**
We develop new drug products by using nanotechnology and contribute to improvement of human healthcare and quality of life.

**VISION**
We aim to become “FIRST ONE”, an oncology-focused innovative pharmaceutical company

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**2000**: Establishment of research activity in Kashiwa-city  
**2008**: Listing at Tokyo Stock Exchange (TSE) Mothers Market  
**2010**: Commencement of cosmetic business  
**2018**: Clinical trials of own projects involving global phase III trials
# Company Profile

<table>
<thead>
<tr>
<th>Founded</th>
<th>June 14, 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listed market</td>
<td>Listed on the Mothers Section of the Tokyo Stock Exchange on March 5, 2005</td>
</tr>
</tbody>
</table>
| Location         | Head Office and Lab: Wakashiba, Kashiwa, Chiba Prefecture  
Tokyo Office: Kyobashi, Chuo-ku, Tokyo  
iCONM Lab: Tonomachi, Kawasaki, Kanagawa Prefecture |
| Subsidiaries     | NanoCarrier U S: Medford, MA |
| Capital          | 1,115 million yen as of Aug. 31, 2018 |
| Total issued stocks | 46,193,584 shares as of Aug. 31, 2018 |
| Employees and Management | 58 |
| Directors        | President and CEO: Ichiro Nakatomi, Ph.D.  
CSFO: Tetsuhito Matsuyama  
Outside Directors: Teruo Okano, Ph.D. (Professor, Tokyo Women’s Medical University)  
Akira Ohashi, MD, Ph.D. (Clinical Doctor) |
| Auditors         | Kanshiro Noguchi  
Tadashi Morishima (Representative, Morishima CPA Office)  
Mieko Nakayama (Partner, Haruka Sogo Law Firm) |
| Scientific Advisor | Kazunori Kataoka, Ph.D. (Director General, iCONM/Project Professor, The University of Tokyo)  
Yukio Nagasaki, Ph.D. (Professor, University of Tsukuba)  
Nobuhiro Nishiyama, Ph.D. (Professor, Tokyo Institute of Technology) |
Highlights

Company Overview

Core Technology

Clinical Pipeline

Next Generation and Next Application

Business Development
# Drug Design System

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NanoCap™</strong></td>
<td></td>
</tr>
<tr>
<td>- Physical entrapment</td>
<td></td>
</tr>
<tr>
<td>- NK105(Paclitaxel) cosmetics</td>
<td></td>
</tr>
<tr>
<td>- Electrostatic bonding</td>
<td></td>
</tr>
<tr>
<td>- Protein, siRNA</td>
<td></td>
</tr>
<tr>
<td>- Improves drug’s solubility and retention in bloodstream</td>
<td></td>
</tr>
<tr>
<td><strong>Medicelle™</strong></td>
<td></td>
</tr>
<tr>
<td>- Chemical conjugation</td>
<td></td>
</tr>
<tr>
<td>- NC-6004 (Cisplatin)</td>
<td></td>
</tr>
<tr>
<td>- NC-4016 (DACH-Platinum)</td>
<td></td>
</tr>
<tr>
<td>- NC-6300 (Epirubicin)</td>
<td></td>
</tr>
<tr>
<td>- Improves drug’s retention in bloodstream</td>
<td></td>
</tr>
<tr>
<td><strong>ADCM (Antibody/Drug-Conjugated Micelle)</strong></td>
<td></td>
</tr>
<tr>
<td>- Sensor drug-conjugated micelle (Active Targeting)</td>
<td></td>
</tr>
<tr>
<td>- Sensor: antibody, peptide etc.</td>
<td></td>
</tr>
<tr>
<td>- Enhances amount of drugs effectively targeted to specific locus</td>
<td></td>
</tr>
</tbody>
</table>

**Polyethylene Glycol** (Hydrophilic, outside of micelle)

**Polyamino acid** (Hydrophobic, inside micelle)

*Average particle diameter: 30-100nm*
NanoCarrier - All in One Delivery Technology

Enhanced solubility
Dissolve the hydrophobic drug in water

<table>
<thead>
<tr>
<th>Drug (mg/mL)</th>
<th>Itraconazole</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>&lt;0.001</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Micelle</td>
<td>&gt;2</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Solubility (Micelle/water)</td>
<td>2000 times or more</td>
<td>500 times or more</td>
</tr>
</tbody>
</table>

Controlled release
Superior controlled release (improved stability and safety) and improved retention in bloodstream

Enhanced Targeting
Nanomicelles accumulate in cancerous tissue by taking advantage of characteristics of cancer cells

Normal tissue
●: Conventional drugs
**: Nanomicelle

Cancerous tissue

Enhancements:
- Superior controlled release
- Improved solubility
- Enhanced targeting

Plasma level
- Toxic level
- Efficacy level

Time:
- Conventional drugs
- No-efficacy level
- Efficacy level
Mechanism of Overcoming Multi-drug Resistance

abc transporter (e.g. P-glycoprotein)

Tumor cell

anti-cancer drug

Micellar nanoparticle

Conventional drugs unevenly exist close by membrane.

After continuous drug exposure...
Advantages of Micellar Nanoparticle Anti-cancer Agents

Development of high added value drugs

- Controlled released
  Drug release is controlled

- Targeting
  Drug is delivered to site of lesions

- Improved bioavailability\(^1\)
  Solubility of poorly soluble drugs is enhanced

Imagination of improved patient QOL

- Greater therapeutic effect
  Drug is delivered to target cells

- Reduction of adverse reactions
  Toxicity is reduced through controlled drug release

- Greater convenience
  No need for hospitalization, fewer adverse drug reactions and lower medical costs

Note: \(^1\)Bioavailability: Index that shows fraction of drug that enters systemic circulation and its efficacy
Highlights

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Core Technology
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## Clinical Pipeline

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>BR</th>
<th>PC</th>
<th>ph1</th>
<th>ph2</th>
<th>ph3</th>
<th>Develop Area</th>
<th>Alliance Partner</th>
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<tbody>
<tr>
<td>NC-6004 Cisplatin micelle</td>
<td>Pancreatic cancer</td>
<td>Co-Development</td>
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<td></td>
<td></td>
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<td>Japan/Asia</td>
<td>Orient Europharma Co., Ltd.</td>
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<td></td>
<td>Lung (NSCL), Bladder,</td>
<td>In-House</td>
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<td></td>
<td></td>
<td></td>
<td>USA/EU</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biliary tract cancer</td>
<td>Development</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Head and neck cancer</td>
<td>Co-Development</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>USA/EU/Asia</td>
<td></td>
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<tr>
<td>NC-6300 Epirubicin micelle</td>
<td>Soft tissue sarcoma</td>
<td>In-House</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>USA</td>
<td></td>
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<tr>
<td>NC-4016 Dach-platinum micelle</td>
<td>Solid cancer</td>
<td>In-House</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>USA</td>
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<tr>
<td>NK105 (Out-Licensed)</td>
<td>Breast cancer</td>
<td>Out-Licensed</td>
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<td>Japan</td>
<td>Nippon Kayaku</td>
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<tr>
<td>Paclitaxel micelle</td>
<td>Gastric cancer</td>
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<td></td>
<td>Japan</td>
<td>VBL therapeutics</td>
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<tr>
<td>Non-replicating Adeno 5</td>
<td>under examination</td>
<td>Operation by</td>
<td></td>
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<td></td>
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<tr>
<td>vectors</td>
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<td>VBL</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Japan</td>
<td>CEOLIA</td>
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</table>
Development of Major Clinical Pipeline

**NC-6004**

- **Phase III: Pancreatic cancer**
  - ✔ Resumed patient enrolment (August 2017)

- **Phase II: Basket design trial  (biliary tract, NSCLC, bladder)**
  - ✔ Granted orphan drug designation from the US FDA for the indication of biliary tract cancer
  - ✔ Completed the enrolment for biliary tract cancer

- **Phase II: Head and neck cancer**
  - ✔ In combination with the immune checkpoint inhibitor (KEYTRUDA®)
  - ✔ Prepared to start the multinational clinical trial in the US, EU and Asia
  - ✔ Filed IND application (US) (October 2018)

**NC-6300**

- **Phase I/II: Soft tissue sarcoma**
  - ✔ Granted orphan drug designation from the US FDA.
  - ✔ Completed Phase I part
  - ✔ Ongoing the preparation of Phase II part
NC-6004 (Cisplatin Micelle)

- Sustained Rerelease of Drugs in Blood
- Enhance Efficacy
- Reduce Side Effect
- Improve Accessibility

Phase I

- Reduced Cisplatin specific side effects (nephrotoxicity, nausea & vomiting)

Plasma Level of Cisplatin and NC-6004 in human

<table>
<thead>
<tr>
<th>Time after administration (hr)</th>
<th>Plasma Level (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Cisplatin)</td>
</tr>
<tr>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>20</td>
<td>0.1</td>
</tr>
<tr>
<td>40</td>
<td>1.0</td>
</tr>
<tr>
<td>60</td>
<td>10.0</td>
</tr>
</tbody>
</table>

- Platinum level of drugs released from the micelle when 90mg/m² of NC-6004 was dosed
- Platinum level of drugs when 80mg/m² of conventional Cisplatin was dosed

NC-6004 (Phase I result)

Cisplatin (Literature data)
Efficacy of NC-6004 in Phase Ib

- H&N responded to NC-6004
- NC-6004 was efficacious to platinum treated patients
A New Clinical Study for Head & Neck Cancer

1. Anti-cancer activity to patients with Head and Neck Cancer was observed in Phase I study conducted in US and Taiwan

2. Immune checkpoint inhibitors were already approved for Head and Neck Cancer (monotherapy)

3. Efficacy of the combination therapy of cisplatin with immune checkpoint inhibitor was approved for NSCLC in the US.

4. Possibly effective on patients with recurrent/refractory to platinum-based treatment

**Anticipate Probability of Success, Development Speed and Marketability**

Mechanism of potential synergistic effect of NC-6004 in combination with immune checkpoint inhibitor
(Cancelation of suppression/evasion of cancer immunotherapy)

**Immune checkpoint inhibitors**

Tasuku Honjo, distinguished professor at Kyoto University, has won the 2018 Nobel Prize in physiology and medicine. Professor Honjo has discovered a protein named PD-1 which brakes immune activity. Immune checkpoint inhibitor, which shows anti-cancer activity by removing such immune suppression by PD-1 pathway, has been spotlighted as novel immune-oncology therapy and has been developed actively in worldwide.
Difference of the effect size (↑) in add-on study is expected to be larger than head-to-head study.

Larger difference of effect size decreases sample size of the study and enables to get the result faster.

The Result of 1\textsuperscript{st} line ICI study is presently not available.
NC-6300 (Epirubicin Micelle)

Application of System to Enhance Functionality

- Sustained Release by Sensing Intracellular pH
- Enhance Efficacy
- Reduce Side Effect
- Improve Accessiibyi

Endocytosis: energy-using process by which cells absorb molecules (such as foreign matters, proteins, nutrition) by engulfing them
Endosome: Membrane-bound compartment created by endocytosis

- Results of First-in Human Study of NC-6300 in Japan
  - The recommended dose: 170 mg/m² (used in standard of care, i.e., 60 mg/m² or 100 mg/m²)
  - Major adverse events of epirubicin, such as vomiting and Myelosuppression, had a tendency to decrease
  - No clinically significant decrease in cardiac function was observed even in cases who were received NC-6300 administration for more than 12 months
  - No cardiac failure was observed in 4 cases treated with 900 mg/m² in Phase I data in Japan, which is the maximum accumulated dose of conventional epirubicin in lifetime to avoid risks of cardiac failure.

- Phase I/II Clinical Study Undergoing in US (PI part completed)
  - Granted orphan drug designation from the US FDA.
Phase I Part
No. of Patients: 29
Indication: Advanced solid tumors, including soft tissue sarcoma

1. Maximum tolerated dose of NC-6300 monotherapy was determined to be 185 mg/m².
2. Observed adverse events were similar to the conventional epirubicin.
3. Incidence rate or severity of adverse events are lower or milder than conventional epirubicin.
4. No clinically significant cardiac toxicity was observed.
5. Enrolled 2 angiosarcoma subjects responded to NC-6300.
6. Long SD was observe in a melanoma subject who was refractory to anti-PD-1 mAb and anti-PD-1 mAb +anti-CTLA-4 treatments.
NC-6300 Clinical Study for Soft Tissue Sarcoma

Considering indication for Phase II Part

**Soft tissue sarcoma**
- Malignant tumor that develops in the soft tissue such as the subcutaneous tissue or muscle
- Orphan drug (US: 12,000 pts per year)
- Development of new drugs is desired, as treatment options are limited.

**Aims of development**
1. Epirubicin is approved anthracycline anticancer agent
2. Not many drug candidates and relatively less competition (Efficacy of immune checkpoint inhibitors is limited)
3. Possibility of application of the FDA Accelerated Approval Program
In combination with Olaratumab (Lartruvo™)

Olaratumab: Antibody therapeutic approved for the treatment of soft tissue sarcoma in 2016
Blocks PDGF-alpha receptors and improves tumor microenvironment

Aim: Olaratumab will facilitate the penetration of NC-6300 and enhance its antitumor activity

Manufacturer: Eli Lilly
Indication: Malignant soft tissue tumors (approved October 2016)
Usage: Used in combination with Doxorubicin
Sales: 22.9 billion JPY (2017 forecast)*

*Global antibody therapeutics market size 2018 (TPC Marketing Research Corp.)
Highlights

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Business Development
Next Generation of our Technology

**ADCM**  （Antibody-Drug Conjugated Micelle）

A large quantity of payload can be delivered to target cells.

**Advantages of ADCM**

1. ADCM can carry 100-300 molecules of payload per Mab.
2. ADCM is equal or more active for sensitive tumors.
3. ADCM is significantly active for resistant tumors.
4. ADCM is more effectively internalized in the tumors.
5. ADCM shows a continuous drug release in the tumors.
The drug was found to be localized in epidermis *in vivo* permeation study.

Control (Fluorescent in water)  Encapsulated Fluorescent in micellar nanoparticles

S.C.  Epidermis  Basal layer  Hair follicles

Drug permeation

Epidermis  Dermis  Hypodermis
A Track Record of Cosmetic Products

2013
eclafutur:
co-development with ALBION
marketing by ALBION

2016
Depth:
hair growth set
for men

2016
EXCIA AL:
co-development with ALBION
marketing by NanoCarrier

2017
Depth for share:
hair growth set
for women

2018
eclafutur d:
co-development with ALBION
marketing by ALBION

2010
e‘clafutur-W essence:
own development/
own marketing
Cosmetics Business

Nanocesta, a micellar nanoparticle for delivering cosmetic ingredients, is powered up through the electrostatic interaction.

- Positively charges the nanoparticle surface
- Binds negatively charged cell membrane

Improves the skin penetration

New eclafatur d ®

Launched in department stores and beauty salon on October 18, 2018
High Permeation of Hydrophobic Drug in Skin

30-40% of total applied drug was penetrated into the skin

Free Solution vs Micellar Nanoparticles

<table>
<thead>
<tr>
<th>Amount of indomethacin in the skin (µg/g of skin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free Solution</td>
</tr>
<tr>
<td>Micellar Nanoparticles</td>
</tr>
<tr>
<td><img src="chart1.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

P<0.05

Oil-based Formulation vs Micellar Nanoparticles

<table>
<thead>
<tr>
<th>Amount of indomethacin in the skin (µg/g of skin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W/O Cream</td>
</tr>
<tr>
<td>O/W Cream</td>
</tr>
<tr>
<td>Micellar Nanoparticles</td>
</tr>
<tr>
<td><img src="chart2.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

P<0.05

Indomethacin: 100µg/g

Dermatological Advantage of Technology

- Improves the skin permeability of hydrophobic compounds
- Improves the water solubility of hydrophobic compounds
- Improves the thermal and light stabilities of hydrophobic compounds
- Improves the sustainability of compound activity
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## Business Developments

### License and Joint development for our Pipeline

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orient Europharma</td>
<td>NC-6004</td>
</tr>
<tr>
<td>Nippon Kayaku</td>
<td>NK105</td>
</tr>
</tbody>
</table>

### Joint research of ADCM Technology

<table>
<thead>
<tr>
<th>Company</th>
<th>Research Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPG Biologics</td>
<td>Optimization of sensor molecules</td>
</tr>
<tr>
<td>JCR Pharmaceuticals</td>
<td>Brain delivery</td>
</tr>
<tr>
<td></td>
<td>Combination of ADCM with J-Brain cargo</td>
</tr>
<tr>
<td>Gene Techno Science</td>
<td>Exploration of new sensor molecules, etc.</td>
</tr>
</tbody>
</table>

### License-in cancer filed and Joint development in other field

- **Enhancement of the late stage pipeline for early generation of revenue**
  - VBL Therapeutics: Introduction of systemically administered gene therapy in Japan
  - Ceolia Pharma: Moves to acquire joint development and sales network for pharmaceuticals in ENT field
Unique Drug Delivery Technology Opening Up for New Possibility of Therapy

Discovery of any compounds to meet unmet needs

Partners

- Existing drugs
- New drug candidates
- Compounds abandoned at development stage
- Cosmetic products

Seeking to enhance performance through unique formulation technologies

- Sustainability
- Solubility
- Pharmacodynamics
- Stability
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Initiatives Ongoing
Future on NanoCarrier

✓ Develop new products by using **NANOTECHNOLOGY** and contribute to improvement of human healthcare and **QOL**

✓ Aim to become “**FIRST ONE**”, as for the innovative company

✓ Moving towards a **SPECIALITY PHARMA** for new drugs with high unmet needs
Thank you very much

Contact
NanoCarrier Co., Ltd.
CEO Office
E-mail: info@nanocarrier.co.jp