Discovery of SCO-267, a First-in-class GPR40 Full Agonist, as a Promising Candidate for the Treatment of Type 2 Diabetes Mellitus, Obesity, and NASH

Naoyoshi Noguchi, Ph.D. on behalf of the GPR40 PJ Team
Research Division, Drug Discovery Chemistry Laboratory
SCOHIA PHARMA, Inc.
Agenda

1. Introduction

2. Med. Chem. Campaign to Discover SCO-267

3. Pharmacological Efficacy of SCO-267
   - Single Dosing and Repeated Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)
   - Repeated Dosing Effects in DIO-rats (Obese Model)
   - Single Dosing and Repeated Dosing Effects in CDAHFD-fed Mice (NAFLD Model)

4. Summary
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4. Summary
Characteristics of GPR40

- **GPR40/FFAR1**
  - GPCR activated by endogenous ligands of medium-to-long chain fatty acids
  - Expressed in pancreatic islet cells and enteroendocrine cells

- **Partial agonist - Fasiglifam**
  - Markedly improved glycemic control by increasing insulin secretion in patients with T2DM
Characteristics of GPR40

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  - Markedly improved glycemic control by increasing insulin secretion in patients with T2DM

- **Full agonist**
  - Stimulates secretion of not only insulin, but also GLP-1, GIP, PYY, and glucagon

---

**Blood glucose ↓**

**Body weight ↓**

**Liver conditions ↑**

**Insulin ↑**

**Glucagon ↑**

**GLP-1 ↑**

**PYY ↑**

**GIP ↑**

**Pancreatic islet cells**

**Enteroendocrine cells**

**GPR40**

**Ca^{2+}↑↑**
Characteristics of GPR40

- **Full agonist**
  - Stimulates secretion of not only *insulin*, but also *GLP-1, GIP, PYY*, and *glucagon*

GPR40 full agonist is expected to be a new drug option for the treatment of *diabetes, obesity, and NAFLD/NASH*
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4. Summary
Exploration of New Lead Compound

Challenges of compound (S)-1

- Aromaticity (negative impact on overall physicochemical properties, DMPK profiles...)
- Insufficient agonistic activity

Previously reported GPR40 full agonist
(WO2013122029)

*All compounds are racemate unless otherwise noted*
**Exploration of New Lead Compound**

**Challenges of compound (S)-1**

- Aromaticity (negative impact on overall physicochemical properties, DMPK profiles...)
- Insufficient agonistic activity

**Initial SAR**

- The hydrophobic substituent and the terminal aromatic rings (A and C) are essential for potent agonistic activity

\[(S)-1\]

\[\text{hGPR40 EC}_{50}: 150 \text{ nM}\]

\[\text{clogP}: 7.1\]

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Exploration of New Lead Compound

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Molecular design and hypothesis

a. The central aromatic ring (B) of compound (S)-1 would serve as just a linker to keep the position and distance of terminal aromatic rings (A and C), therefore, would be replaced with a saturated ring system

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b. Fluorine-substituted position of compound (S)-1 would easily access the presumed hydrophobic pocket that the neopentyl alkyl chain of compound (S)-1 occupies

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Exploration of New Lead Compound

Molecular design and hypothesis

- a. The central aromatic ring (B) of compound \((S)\)-1 would serve as just a linker to keep the position and distance of terminal aromatic rings (A and C), therefore, would be replaced with a saturated ring system.

- b. Fluorine-substituted position of compound \((S)\)-1 would easily access the presumed hydrophobic pocket that the neopentyl alkyl chain of compound \((S)\)-1 occupies.

Rearrangement of the hydrophobic moiety on the central ring (B) to the terminal ring (A) retained agonistic activity.

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Exploration of New Lead Compound

Molecular design and hypothesis

a. The central aromatic ring (B) of compound (S)-1 would serve as just a linker to keep the position and distance of terminal aromatic rings (A and C), therefore, would be replaced with a saturated ring system

b. Fluorine-substituted position of compound (S)-1 would easily access the presumed hydrophobic pocket that the neopentyl alkyl chain of compound (S)-1 occupies

- 4-Methyl piperidine ether 3 was identified as a new lead compound which showed potent agonistic activity

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Flexible alignment of compounds (S)-1 (gray) and 2 (green) using Maestro.
Effect of Substituent on the Benzene Ring A

**Challenge of compound 3**

- Highly lipophilic property

![Chemical structure of compound 3](image)

- hGPR40 EC$_{50}$: **11 nM**
- clogP: **8.4**
- Cell viability ATP at 30 µM: **0.1%**

*All compounds are racemate unless otherwise noted*
Effect of Substituent on the Benzene Ring A

**Challenge of compound 3**
- Highly lipophilic property

**Molecular design**
- Introduction of a polar linker (X and/or Y) to decrease the lipophilicity and to improve the physicochemical properties

*All compounds are racemate unless otherwise noted*
**Effect of Substituent on the Benzene Ring A**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>hEC$_{50}$ nM</th>
<th>(E_{\text{max}})</th>
<th>clogP</th>
<th>Cell viability ATP % at 30 (\mu)M</th>
</tr>
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<tbody>
<tr>
<td>3</td>
<td></td>
<td>11</td>
<td>106%</td>
<td>8.4</td>
<td>0.1</td>
</tr>
<tr>
<td>4a</td>
<td></td>
<td>190</td>
<td>108%</td>
<td>7.6</td>
<td>0.1</td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td>97</td>
<td>112%</td>
<td>6.5</td>
<td>0.1</td>
</tr>
<tr>
<td>4c</td>
<td></td>
<td>1000</td>
<td>110%</td>
<td>4.0</td>
<td>80.7</td>
</tr>
<tr>
<td>4d</td>
<td></td>
<td>2200</td>
<td>96%</td>
<td>5.8</td>
<td>76.4</td>
</tr>
<tr>
<td>4e</td>
<td></td>
<td>100</td>
<td>107%</td>
<td>5.6</td>
<td>82.2</td>
</tr>
</tbody>
</table>

*Introduction of amide moiety as a linker led to the improvement of druggability especially for lipophilicity and cell viability (set the target clogP value: <6.0)*

*All compounds are racemate unless otherwise noted*
Effect of Substituents on the Amide Group

Challenge of compound 4e
- Insufficient agonistic activity

4e
hGPR40 EC<sub>50</sub>: 100 nM
clogP: 5.6
Cell viability ATP at 30 &mu;M: 82.2%

*All compounds are racemate unless otherwise noted.
Effect of Substituents on the Amide Group

**Challenge of compound 4e**
- Insufficient agonistic activity

**Molecular design**
- Introduction of aromatic ring onto the amide nitrogen to restrict the N-alkyl moiety to the presumed hydrophobic pocket

4e

hGPR40 EC$_{50}$: 100 nM
clogP: 5.6
Cell viability ATP at 30 μM: 82.2%

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Effect of Substituents on the Amide Group

**Challenge of compound 4e**
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- Introduction of aromatic ring on the amide nitrogen to restrict the N-alkyl moiety to the presumed hydrophobic pocket

**Conformational preference of N-methylbenzanilide**

The structure of N-methylbenzanilide derivatives place the aromatic ring in cis conformation to each other, and the methyl substituent on nitrogen is cis to the carbonyl group.

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Effect of Substituents on the Amide Group

**Challenge of compound 4e**
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- Introduction of aromatic ring on the amide nitrogen to restrict the N-alkyl moiety to the presumed hydrophobic pocket

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**Conformational preference of N-methylbenzanilide**

- 4e
- hGPR40 EC$_{50}$: 100 nM
- clogP: 5.6
- Cell viability ATP at 30 µM: 82.2%

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**Hypothesis**

Incorporation of suitable lipophilic moiety onto the nitrogen group of the benzanilide moiety would enhance the agonistic activity

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**Effect of Substituents on the Amide Group**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>hEC&lt;sub&gt;50&lt;/sub&gt; nM</th>
<th>E&lt;sub&gt;max&lt;/sub&gt;</th>
<th>clogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>4e</td>
<td></td>
<td>Me</td>
<td>100</td>
<td>107%</td>
<td>5.6</td>
</tr>
<tr>
<td>4f</td>
<td>Me</td>
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<td>4g</td>
<td>Me</td>
<td></td>
<td>180</td>
<td>105%</td>
<td>4.0</td>
</tr>
</tbody>
</table>

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Effect of Substituents on the Amide Group

<table>
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<th>hEC&lt;sub&gt;50&lt;/sub&gt; nM</th>
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<th>clogP</th>
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</thead>
<tbody>
<tr>
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<td>4f</td>
<td>Me</td>
<td></td>
<td>140</td>
<td>101%</td>
<td>5.5</td>
</tr>
<tr>
<td>4g</td>
<td>Me</td>
<td></td>
<td>180</td>
<td>105%</td>
<td>4.0</td>
</tr>
<tr>
<td>4h</td>
<td></td>
<td></td>
<td>26</td>
<td>110%</td>
<td>5.9</td>
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</table>

**Hypothesis**
- Incorporation of aromatic ring and suitable lipophilic moiety dramatically impacted agonistic activity

*All compounds are racemate unless otherwise noted*
### Effect of Substituents on the Amide Group

#### Hypothesis

*Incorporation of aromatic ring and suitable lipophilic moiety dramatically impacted agonistic activity*

*Introduction of a “magic methyl” group onto the pyridine ring led to a discovery of 4i with a good balance between agonistic activity and lipophilicity*

*All compounds are racemate unless otherwise noted*

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>hEC₅₀ nM</th>
<th>Eₘₐₓ</th>
<th>clogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>4e</td>
<td>Me</td>
<td>Me</td>
<td>100</td>
<td>107%</td>
<td>5.6</td>
</tr>
<tr>
<td>4f</td>
<td>Me</td>
<td>Phenyl</td>
<td>140</td>
<td>101%</td>
<td>5.5</td>
</tr>
<tr>
<td>4g</td>
<td>Me</td>
<td>Pyridine</td>
<td>180</td>
<td>105%</td>
<td>4.0</td>
</tr>
<tr>
<td>4h</td>
<td>Me</td>
<td>Pyridine</td>
<td>26</td>
<td>110%</td>
<td>5.9</td>
</tr>
<tr>
<td>4i</td>
<td>Me</td>
<td>Pyridine</td>
<td>17</td>
<td>109%</td>
<td>6.4</td>
</tr>
</tbody>
</table>
Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety

**Challenge of compound 4i**
- Slightly high lipophilicity (Target clogP value: <6.0)

hGPR40 EC\textsubscript{50}: 17 nM  
clogP: 6.4  
Cell viability ATP at 30 μM: 5.0%

*All compounds are racemate unless otherwise noted*
Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety

**Challenge of compound 4i**
- Slightly high lipophilicity (Target clogP value: <6.0)

**Molecular design**
- Replacement of the benzene ring (C) with a 2-alkoxy pyridine ring to reduce the lipophilicity

*Basic property is NOT tolerable for agonistic activity*

\[ 4i \]

hGPR40 EC\textsubscript{50}: 17 nM
clogP: 6.4
Cell viability ATP at 30 \( \mu \text{M} \): 5.0%

*All compounds are racemate unless otherwise noted*
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### Basic property is NOT tolerable for agonistic activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar</th>
<th>hEC&lt;sub&gt;50&lt;/sub&gt; nM</th>
<th>E&lt;sub&gt;max&lt;/sub&gt;</th>
<th>clogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>4i</td>
<td><img src="4i" alt="Ar" /></td>
<td>17</td>
<td>109%</td>
<td>6.4</td>
</tr>
<tr>
<td>5a</td>
<td><img src="5a" alt="Ar" /></td>
<td>39% at 10 μM</td>
<td>-</td>
<td>5.8</td>
</tr>
<tr>
<td>5b</td>
<td><img src="5b" alt="Ar" /></td>
<td>17</td>
<td>112%</td>
<td>5.8</td>
</tr>
</tbody>
</table>

**2,4-Disubstituted pyridine derivative 5b retained agonistic activity with decreased lipophilicity**

*All compounds are racemate unless otherwise noted*
Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar</th>
<th>hEC$_{50}$ nM</th>
<th>$E_{\text{max}}$</th>
<th>clogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td></td>
<td>39% at 10 μM</td>
<td>-</td>
<td>5.8</td>
</tr>
<tr>
<td>5b</td>
<td></td>
<td>17</td>
<td>112%</td>
<td>5.8</td>
</tr>
</tbody>
</table>

2,6-disubstituted pyridine (5a): presumed active conformer A is less stable than B

2,4-disubstituted pyridine (5b): presumed active conformer C is more stable than D

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Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar</th>
<th>hEC$_{50}$ nM</th>
<th>$E_{\text{max}}$</th>
<th>clogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td><img src="image" alt="aromatic ring" /></td>
<td>39% at 10 μM</td>
<td>-</td>
<td>5.8</td>
</tr>
<tr>
<td>5b</td>
<td><img src="image" alt="aromatic ring" /></td>
<td>17</td>
<td>112%</td>
<td>5.8</td>
</tr>
<tr>
<td>(S)-5b</td>
<td><img src="image" alt="aromatic ring" /></td>
<td>12</td>
<td>108%</td>
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<tr>
<td>(R)-5b</td>
<td><img src="image" alt="aromatic ring" /></td>
<td>84</td>
<td>109%</td>
<td>5.8</td>
</tr>
</tbody>
</table>

- (S)-5b was identified as an eutomer based on its agonistic activity
- (S)-5b (SCO-267) was selected for further evaluation

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Profiles of SCO-267

- **GPR40 agonistic activity**
  
human GPR40 EC<sub>50</sub>: 12 nM

- **Pharmacokinetic profiles in rat/mouse**
  
  Good oral bioavailability

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>F (%)</th>
<th>Intravenous (0.1 mg/kg)</th>
<th>Oral (1 mg/kg)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CL&lt;sub&gt;total&lt;/sub&gt; (mL/h/kg)</td>
<td>Vss (mL/kg)</td>
</tr>
<tr>
<td>SCO-267</td>
<td>rat</td>
<td>16</td>
<td>1478</td>
<td>3094</td>
</tr>
<tr>
<td></td>
<td>mouse</td>
<td>26</td>
<td>2584</td>
<td>1349</td>
</tr>
</tbody>
</table>

- **In vitro Tox assessment**
  
  Good cell viability profile (ATP: 92.1% at 30 μM), No risk of hERG inhibition and Ames test

- **In vivo Tox assessment**
  
  Wide safety margin (633- (male) to 776- (female) and 471- (male) to 421- (female) fold in the rat and dog 4-week studies, respectively), No concerns in the safety pharmacology studies
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4. Summary
Single Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)

**Male N-STZ-1.5 rats (25-week-old) Fasted**

- Vehicle (p.o.)
- SCO-267 (p.o.)
- Fasiglifam (p.o.)

Single oral dosing → OGTT (1.5 g/kg) 1 h after drug dosing

- Plasma insulin
- Plasma GLP-1 change

---

* Plasma concentration of 3 mg/kg fasiglifam ($C_{\text{max}}$: 6170 ng/ml) in N-STZ-1.5 rats is similar levels with clinically effective exposure of 50 mg fasiglifam ($C_{\text{max}}$: 5300 ng/ml) in T2DM patients

* $P<0.025$ and $\#P<0.025$ vs. vehicle by one-tailed Williams’ test and one-tailed Shirley-Williams test, respectively. Values are presented as mean ± S.D. ($n = 6$). Fasi, fasiglifam.

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**Single dosing of SCO-267 increased insulin and GLP-1 in N-STZ-1.5 rats in a dose-dependent manner**

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**J Pharmacol Exp Ther. 2019;370(2):172-181.**
0.3 mg/kg SCO-267 ($C_{\text{max}}$: 22.7 ng/ml) had a glucose-lowering efficacy comparable to that of 3 mg/kg fasiglifam ($C_{\text{max}}$: 6170 ng/ml).
Repeated Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)

- Male N-STZ-1.5 rats (27-week-old)
  - Vehicle (p.o.)
  - SCO-267 (p.o.)
  - Fasiglifam (p.o.)

Once daily dosing for 2 weeks → OGTT (1.5 g/kg) 1 h after drug dosing

2 weeks of repeated dosing of SCO-267 resulted in sustained glucose lowering, and the efficacy was much better than that of fasiglifam.

1 mg/kg (3-fold higher dose of MED) SCO-267 did not induce desensitization in N-STZ-1.5 Rats.

$\S$ and $\P<0.05$ vs vehicle by Dunnett’s test and Steel test, respectively. Values are presented as mean ± SD (n=6).

---

**Plasma insulin**

- Vehicle
- SCO-267 1 mg/kg
- Fasiglifam 10 mg/kg

**Plasma insulin AUC$_{0-60\text{min}}$**

- Vehicle
- SCO-267 1 mg/kg
- Fasiglifam 10 mg/kg

**Plasma glucose**

- Vehicle
- SCO-267 1 mg/kg
- Fasiglifam 10 mg/kg

**Plasma glucose AUC$_{0-120\text{min}}$**

$\S$ and $\P<0.05$ vs vehicle by Dunnett’s test and Steel test, respectively.
Repeated Dosing Effects in DIO-rats (Obese Model)

Male F344 rats (49-week-old)
High fat diet (M12451M)
Baseline BW: 487 g

- Vehicle (p.o.)
- SCO-267 (p.o.)

Once daily dosing for 2 weeks → measure GLP-1 and PYY 16 h after the 15th dosing

*P<0.025 vs. vehicle by one-tailed Williams’ test. Values are presented as mean ± S.D. (n = 6).

- Plasma GLP-1 and PYY levels remained high 16 h after the final dose of SCO-267
- These hormones contributed to the food intake reduction and body weight loss
- Efficacy on body weight control was durable
Single Effects in CDAHFD-fed Mice (NAFLD Model)

Male CDAHFD-fed mice (12-week-old) Non-fasting
Vehicle (p.o.)  •  SCO-267 (p.o.)

Values are presented as mean ± S.D. (n = 8).
†P<0.025 vs. vehicle by one-tailed Williams’ test.
‡P<0.025 vs. vehicle by one-tailed Shirley–Williams test.

Male CDAHFD-fed mice (12-week-old)
Non-fasting

Values are presented as mean ± S.D. (n = 8).
†P<0.025 vs. vehicle by one-tailed Williams’ test.
‡P<0.025 vs. vehicle by one-tailed Shirley–Williams test.

SCO-267 stimulated glucagon and GLP-1 secretion in a mouse model of NAFLD
Repeated Dosing Effects in CDAHFD-fed Mice (NAFLD Model)

- Vehicle (p.o.) - SCO-267 (p.o. BID)
- Alogliptin (p.o. BID) - Dapagliflozin (p.o. BID)

Male CDAHFD-fed mice (11-week-old) Non-fasting

Repeated administration for 4 weeks

Values are presented as mean ± S.D. (n = 8).

\*P<0.025 vs. vehicle by one-tailed Williams’ test.
Alo, alogliptin benzoate; Dapa, dapagliflozin.

- SCO-267 decreased liver weight, liver triglyceride content, liver collagen levels, and plasma ALT levels in CDAHFD-fed mice, a non-diabetic animal model of NAFLD.

- These effects were induced without any effects on glucose levels or body weight.
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4. Summary
New lead compound 3 was discovered by rearrangement of the lipophilic moiety onto the terminal aromatic ring (A) and replacement of central aromatic ring (B) with piperidine linker.

Introduction of amide linker, then incorporation of aromatic ring and suitable lipophilic moiety onto the amide nitrogen showed good balance between agonistic activity and lipophilicity.

Further optimization of terminal ring (C) to reduce the lipophilicity led to the identification of SCO-267.

SCO-267 exhibited potent GPR40 full agonistic activity, good oral bioavailability, and favorable in vitro/in vivo Tox profiles.

SCO-267 effectively improved glycemic control in N-STZ-1.5 rats (diabetic model), decreased body weight in DIO-rats (obese model), and improved liver parameters in CDAHFD-fed mice (NAFLD model).
Ph1 clinical study to evaluate safety, pharmacokinetics, and pharmacodynamic effect in healthy adults and people with impaired glucose tolerance is ongoing.
Acknowledgement

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Yasufumi Miyamoto
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Tsuyoshi Maekawa

CMC
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Toshitake Kobayashi

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Hikaru Ueno
Mitugi Ookawara
Shin-ichi Abe
Hirohisa Miyashita
Hitomi Ogino
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Thank you for your attention!

&

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