Small molecule drugs accelerate implant osseointegration

Npas2 modulating compounds to enhance implant osseointegration

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Overview

Titanium (Ti)-based biomaterials have been widely adopted in implantable medical devices for orthopedic and dental applications, yet the mechanisms of osseointegration remain unknown.

UCLA researchers have identified that the molecular circadian clock gene neuronal PAS domain protein 2 (Npas2) plays an important role in the establishment of osseointegration induced by Ti biomaterials with a complex surface modification.

These scientists have identified several Npas2 upregulating small molecule compounds that hold promise for accelerating and/or re-establishing implant osseointegration.
Biomaterial implants improve the outcomes of patients suffering from chronic conditions or traumatic injury.

These materials must be compatible with the body in order to allow for proper osseointegration— the direct, functional connection of a biomaterial with bone.

Researchers are seeking methods to increase osseointegration, and therefore the effectiveness, of biomaterial implants.

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Titanium alloy biomaterials have been applied to a wide range of implantable medical devices.

Ti-based biomaterials induce the least foreign body reaction, minimal fibrosis, and allow osseointegration without a layer of soft tissue encapsulation.

Surface functionalized Ti implants have been shown to improve and accelerate the osseointegration process.

The underlying mechanisms of surface functionalized Ti implant osseointegration are not fully understood.
Identifying the osseointegration mechanism.

UCLA RESEARCHERS HAVE ELUCIDATED THE MOLECULAR MECHANISM OF OSSEOINTEGRATION, AND IDENTIFIED NPAS2 MODULATING COMPOUNDS THAT CAN BE USED TO ENHANCE IMPLANT OSSEOINTEGRATION.
Team: Industry leaders in dental and orthopedic implants.

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Neuronal PAS domain protein 2 (Npas2) is required for osseointegration.

The molecular circadian clock gene Neuronal PAS domain protein 2 (Npas2) was found to be highly associated with the successful development of osseointegration.

Impaired osseointegration in Npas2+/− and Npas2−/− mice, demonstrated by decreased collagen fibers compared to WT.

Npas2 facilitates enhanced osseointegration through alternative neuroskeletal regulatory pathways induced by Ti biomaterials with a complex surface modification.

MORINAGA ET AL, BIOMATERIALS (2019)
Several compounds that upregulate Npas2 expression were identified to enhance osseointegration.
Market Opportunity
The generalized market for dental implants is predicted to reach $5 billion in 2023.

Dental disease is the most prevalent chronic disease on a global scale.

Global Market for Dental Implants, by Region, Through 2023
($ Millions)

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
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<tbody>
<tr>
<td>North America</td>
<td>1,020.0</td>
<td>1,074.2</td>
<td>1,151.9</td>
<td>1,221.8</td>
<td>1,297.8</td>
<td>1,378.9</td>
<td>1,537.9</td>
<td>7.4</td>
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<tr>
<td>Europe</td>
<td>1,530.0</td>
<td>1,599.3</td>
<td>1,671.1</td>
<td>1,745.5</td>
<td>1,832.7</td>
<td>1,937.9</td>
<td>1,984.4</td>
<td>4.4</td>
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<tr>
<td>APAC</td>
<td>442.0</td>
<td>522.1</td>
<td>590.0</td>
<td>677.7</td>
<td>762.4</td>
<td>840.8</td>
<td>917.8</td>
<td>11.9</td>
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<tr>
<td>RoW</td>
<td>408.0</td>
<td>425.4</td>
<td>443.4</td>
<td>462.1</td>
<td>481.2</td>
<td>500.8</td>
<td>521.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Total</td>
<td>3,400.0</td>
<td>3,621.0</td>
<td>3,856.4</td>
<td>4,107.1</td>
<td>4,374.1</td>
<td>4,658.4</td>
<td>4,961.2</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Analysis of the dental implant global market was performed with information from BCC Report HLC218A.
Any company utilizing Ti-based biomaterials for implants may take advantage of Npas2 enhancers for increased osseointegration, without the need for complex surface modification.

Market Share of Major Players in the Dental Implants, 2017 (%)

- Straumann Group: 23.0%
- Danaher (Nobel Biocare, MIS): 19.0%
- Henry Schein (Camlog, BioHorizons): 7.0%
- Dentsply: 15.0%
- Zimmer Biomet: 10.0%
- Others: 26.0%

Global Market for Dental Implants, by Material, Through 2023 ($ Millions)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Titanium dental implants</td>
<td>2,550.0</td>
<td>2,673.5</td>
<td>2,802.3</td>
<td>2,936.6</td>
<td>3,076.5</td>
<td>3,222.1</td>
<td>3,373.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Zirconium dental implants</td>
<td>850.0</td>
<td>947.5</td>
<td>1,054.1</td>
<td>1,170.5</td>
<td>1,297.6</td>
<td>1,436.3</td>
<td>1,587.6</td>
<td>10.9</td>
</tr>
<tr>
<td>Total</td>
<td>3,400.0</td>
<td>3,621.0</td>
<td>3,856.4</td>
<td>4,107.1</td>
<td>4,374.1</td>
<td>4,658.4</td>
<td>4,961.2</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Analysis of the dental implant global market was performed with information from BCC Report HLC218A.
Invention competition

- CaP
- BPs BMPs
- This technology

- Complex surface modification
- Machined implant surface

- High osseointegration
- Poor osseointegration

- 3M
- Straumann
- ProActive (Neoss)
- T3 (Zimmer)
- Swissplus (Zimmer)

- Implant adjuncts
- Implants
The market for dental and osteopathic implants is in a growth stage, and favorable for manufacturers entry.

Increasing oral diseases leading to tooth loss, a rising geriatric population, larger health care spending and disposable income, and the rapid development and advancement of dental technology are key market drivers.

There is a clear unmet need for enhanced osseointegration of implants.

Npas2 modulating compounds may be used not only for dental implants, but are applicable to other implantable biomaterials.

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Thank You
## Table: Validated compounds modulating *Npas2* expression

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Class</th>
<th>Action</th>
<th>Description and Relevant Functions</th>
<th>% Activity *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up01</td>
<td>Adenosine</td>
<td>Antagonist</td>
<td>Adenosine receptor antagonist with selectivity for A1 over A2 Block β adrenergic receptor-triggered cAMP signaling</td>
<td>104.0</td>
</tr>
<tr>
<td>Up02</td>
<td>K+ Channel</td>
<td>Inhibitor</td>
<td>Potent Kv1.3 potassium channel inhibitor Kv channel blockers inhibit cAMP-stimulated neuritogenesis</td>
<td>35.3</td>
</tr>
<tr>
<td>Up04</td>
<td>Cyclic Nucleotides</td>
<td>Inhibitor</td>
<td>Cyclic nucleotide phosphodiesterase catalyzes the hydrolysis of cAMP and cGMP</td>
<td>26.2</td>
</tr>
<tr>
<td>UP05</td>
<td>Serotonin</td>
<td>Antagonist</td>
<td>Semisynthetic ergot alkaloid. Competitive α1 adrenergic receptor blocker and partial α2 adrenergic receptor agonist</td>
<td>28.6</td>
</tr>
<tr>
<td>Up07</td>
<td>Biochemistry</td>
<td>Agonist</td>
<td>L-aromatic amino acid decarboxylase inhibitor α-2 adrenergic receptor agonist Decrease intracellular cAMP</td>
<td>18.1</td>
</tr>
</tbody>
</table>
Table: Validated compounds modulating *Npas2* expression

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
<th>Action</th>
<th>Activity (Fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down01</td>
<td>Cytoskeleton/ECM</td>
<td>Inhibitor of the Golgi apparatus</td>
<td>-45.4</td>
</tr>
<tr>
<td>Down03</td>
<td>Cytoskeleton/ECM</td>
<td>Prevents tubulin polymerization; Potentiates PGE1 stimulation of cAMP formation</td>
<td>-29.7</td>
</tr>
<tr>
<td>Down06</td>
<td>Hormone</td>
<td>Agonist of subtype selective retinoic acid receptor (RARα)</td>
<td>-25.1</td>
</tr>
<tr>
<td>Down08</td>
<td>Nitric Oxide</td>
<td>Inhibitor of endothelial nitric oxide synthase; Inhibits cell Redox metabolism; Accumulate cAMP</td>
<td>-18.6</td>
</tr>
<tr>
<td>Down10</td>
<td>Cytoskeleton/ECM</td>
<td>Antineoplastic glycoside; Inhibitor of microtubule assembly; Induce CREB activation</td>
<td>-15.6</td>
</tr>
<tr>
<td>Down11</td>
<td>Cytoskeleton/ECM</td>
<td>Disrupts microtubules by binding to beta-tubulin</td>
<td>-12.5</td>
</tr>
<tr>
<td>Down12</td>
<td>Intracellular Ca++</td>
<td>Potent, cell permeable, IP3-independent intracellular Ca++ releaser; Increase intracellular cAMP</td>
<td>-43.5</td>
</tr>
<tr>
<td>Down13</td>
<td>Kinase/Phosphatase</td>
<td>Broad spectrum protein tyrosine kinase inhibitor; Inhibits Src and FGFR kinases</td>
<td>-35.5</td>
</tr>
<tr>
<td>Down14</td>
<td>Kinase</td>
<td>Inhibitor of Src family kinases</td>
<td>-33.0</td>
</tr>
</tbody>
</table>

*Activity against negative controls in LOPAC screening*