UCLA Technology Development Group

Small molecule drugs accelerate implant osseointegration

Npas2 modulating compounds to enhance implant osseointegration

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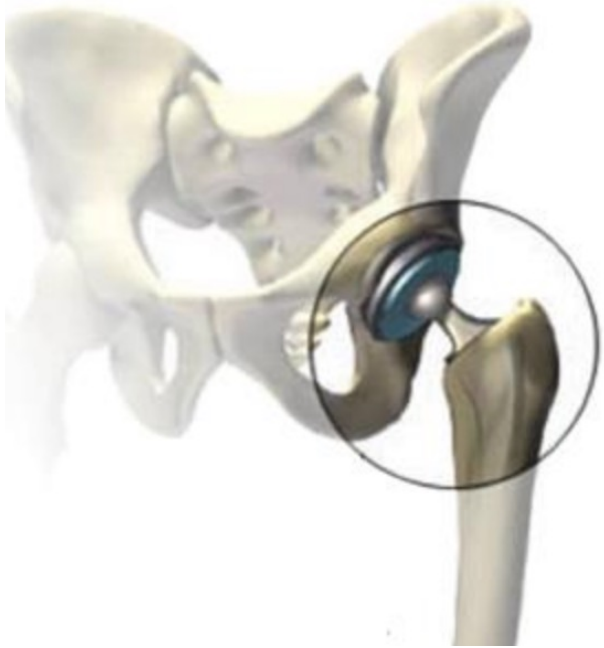
Overview

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.

Biomaterials interface with living tissue for a therapeutic, medical purpose.



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Biomaterial implants improve the outcomes of patients suffering from chronic conditions or traumatic injury.

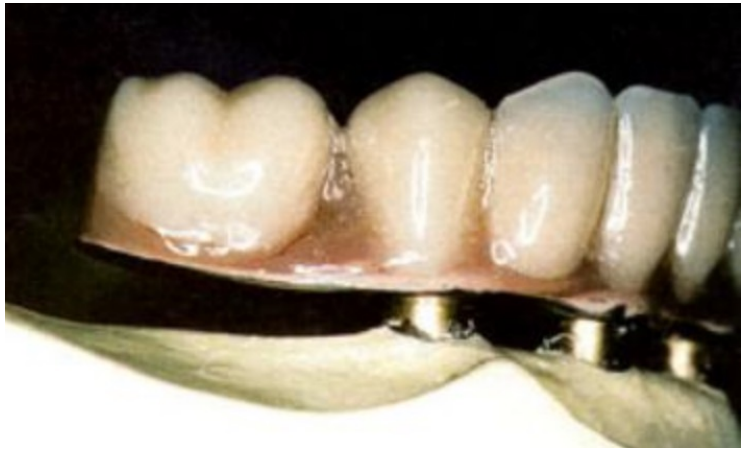
These materials must be compatible with the body in order to allow for proper osseointegration– the direct, functional connection of a biomaterial with bone.

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

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.



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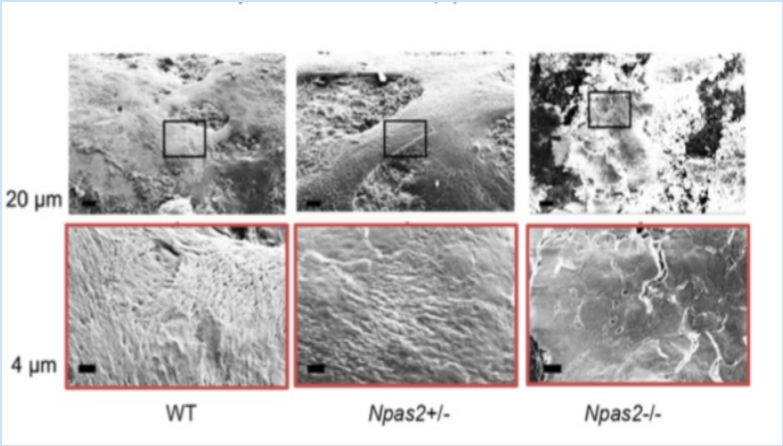
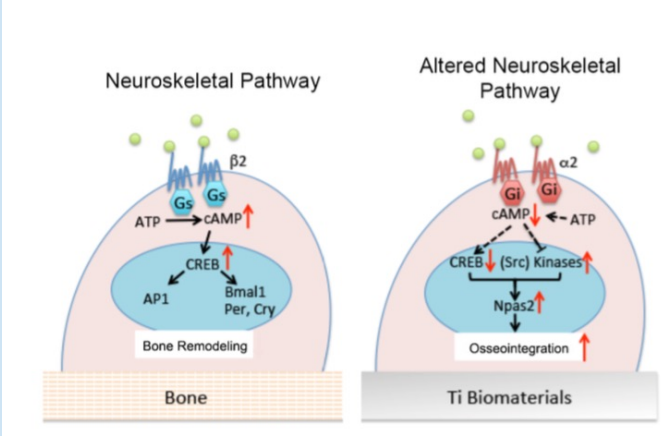
Neuronal PAS domain protein 2 (Npas2) is required for osseointegration.

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



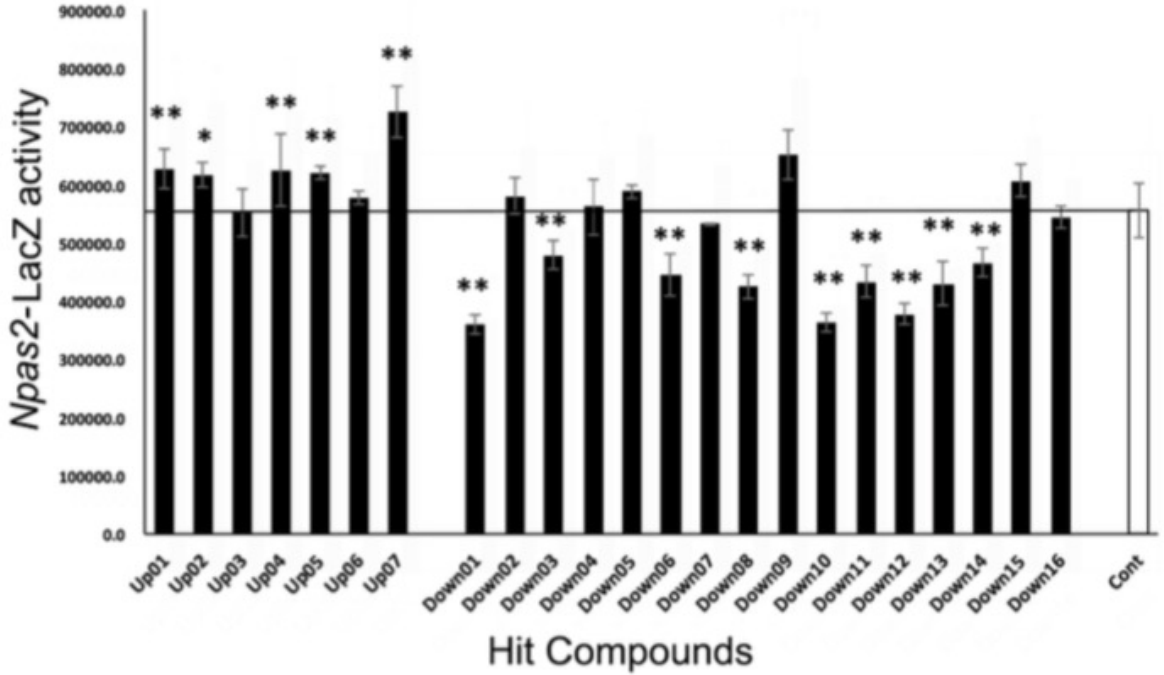
Impaired osseointegration in *Npas2*+/- and *Npas2*-/- mice, demonstrated by decreased collagen fibers compared to WT.



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.



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Market Opportunity

The generalized market for dental implants is predicted to reach $5 billion in 2023.

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

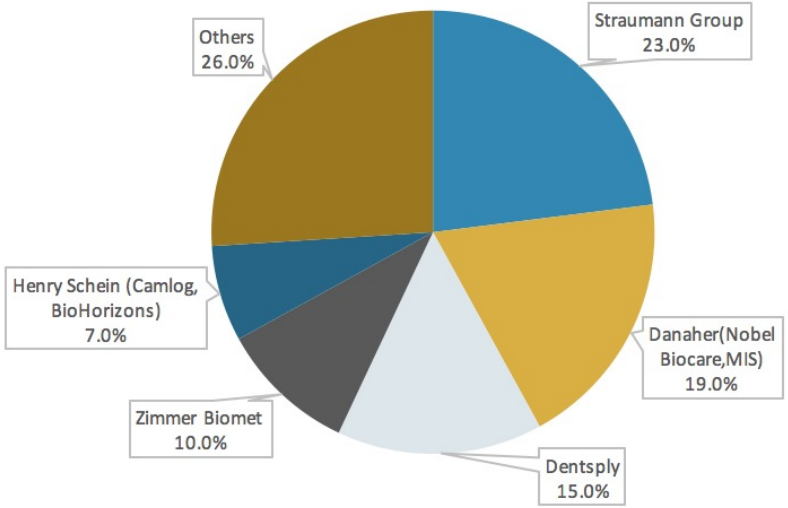
Global Market for Dental Implants, by Region, Through 2023
($ Millions)

Region	2017	2018	2019	2020	2021	2022	2023	CAGR% 2018-2023
North America	1,020.0	1,074.2	1,151.9	1,221.8	1,297.8	1,378.9	1,537.9	7.4
Europe	1,530.0	1,599.3	1,671.1	1,745.5	1,832.7	1,937.9	1,984.4	4.4
APAC	442.0	522.1	590.0	677.7	762.4	840.8	917.8	11.9
RoW	408.0	425.4	443.4	462.1	481.2	500.8	521.1	4.1
Total	3,400.0	3,621.0	3,856.4	4,107.1	4,374.1	4,658.4	4,961.2	6.5

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
(%)

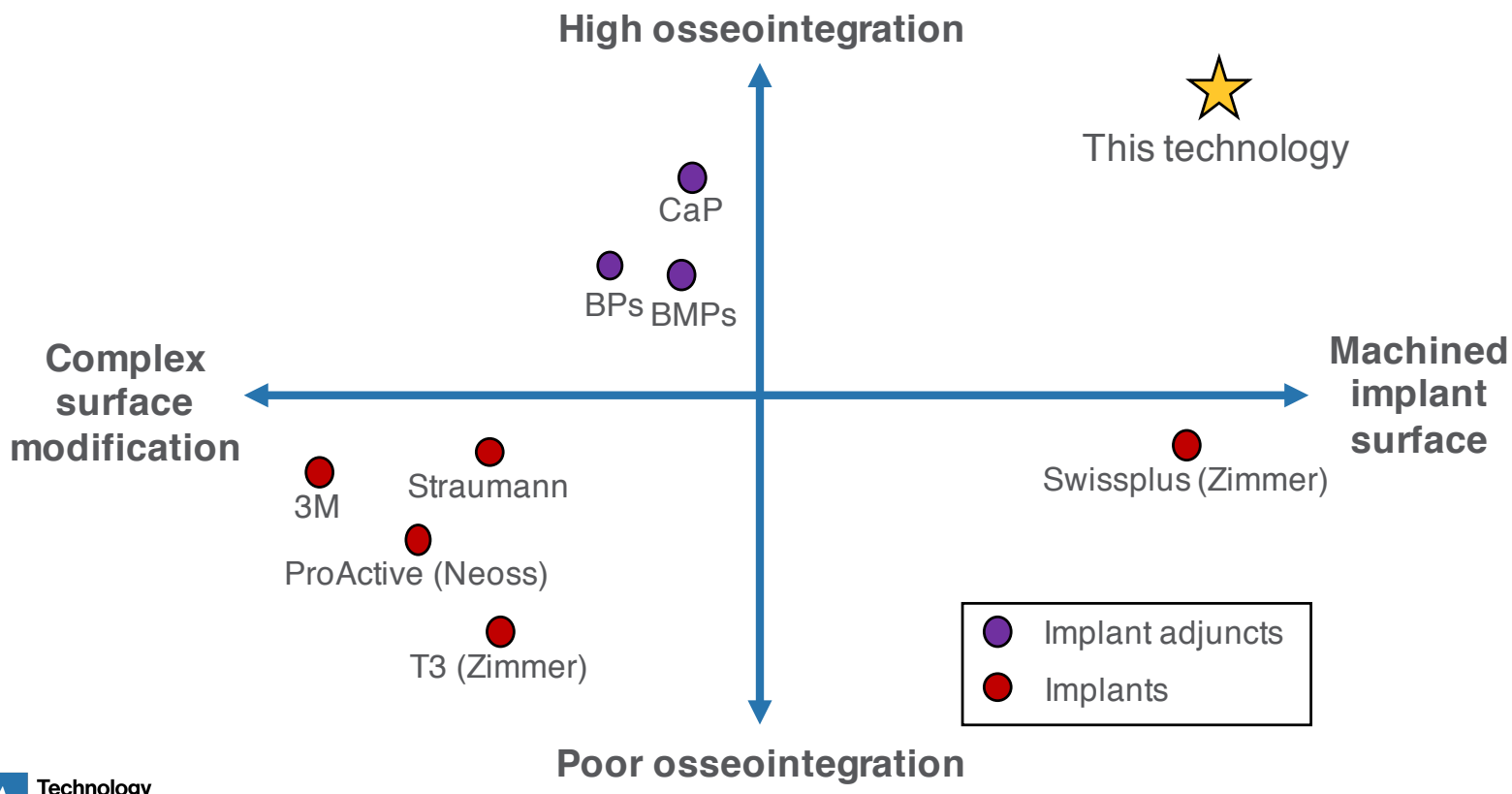


Global Market for Dental Implants, by Material, Through 2023
($ Millions)

Material	2017	2018	2019	2020	2021	2022	2023	CAGR% 2018-2023
Titanium dental implants	2,550.0	2,673.5	2,802.3	2,936.6	3,076.5	3,222.1	3,373.6	4.8
Zirconium dental implants	850.0	947.5	1,054.1	1,170.5	1,297.6	1,436.3	1,587.6	10.9
Total	3,400.0	3,621.0	3,856.4	4,107.1	4,374.1	4,658.4	4,961.2	6.5

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

Invention competition

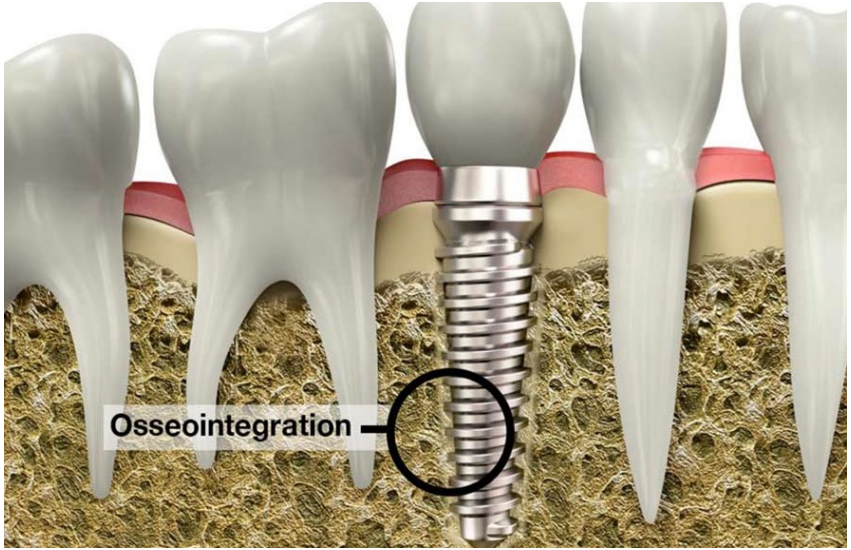


The market for dental and osteopathic implants is in a growth stage, and favorable for manufacturers entry.

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

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Table: Validated compounds modulating *Npas2* expression

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

MORINAGA *ET AL*, **BIOMATERIALS** (2018)

Table: Validated compounds modulating *Npas2* expression

***Npas2* down regulation**				
Down01	Cytoskeleton/ECM	Inhibitor	Fungal metabolite that disrupts the structure and function of the Golgi apparatus	-45.4
Down03	Cytoskeleton/ECM	Inhibitor	Prevents tubulin polymerization Potentiate PGE1 stimulation of cAMP formation	-29.7
Down06	Hormone	Agonist	Potent, cell permeable, subtype selective retinoic acid receptor (RARα) agonist	-25.1
Down08	Nitric Oxide	Inhibitor	Endothelial nitric oxide synthase inhibitor Inhibit cell Redox metabolism; Accumulate cAMP	-18.6
Down10	Cytoskeleton/ECM	Inhibitor	Antineoplastic glycoside; inhibitor of microtubule assembly Induce CREB activation	-15.6
Down11	Cytoskeleton/ECM	Inhibitor	Disrupts microtubules by binding to beta-tubulin	-12.5
Down12	Intracellular Ca++	Releaser	Potent, cell permeable, IP3-independent intracellular Ca++ releaser; Increase intracellular cAMP	-43.5
Down13	Kinase/Phosphatase	Inhibitor	Broad spectrum protein tyrosine kinase inhibitor Inhibit Src and FGFR kinases	-35.5
Down14	Kinase	Inhibitor	Inhibit Src family kinases	-33.0

*Activity against negative controls in LOPAC screening

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