Mechanism of Action

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www.bonalive.com
BonAlive® granules (S53P4) composition:

- 53% Silicate (SiO\textsubscript{2})
- 23% Sodium (Na\textsubscript{2}O)
- 20% Calcium (CaO)
- 4% Phosphate (P\textsubscript{2}O\textsubscript{5})
Unique *bacterial growth inhibiting* bone graft substitute

Non-antibiotic based technology

- Based on physical-chemical reactions on granule surface

Stimulates bone formation and remodels slowly into bone

20-year clinical history

- Over 20 peer-reviewed published clinical articles
- More than a decade of human prospective randomised clinical data
References

Mechanism of action

Mechanism of action (osteostimulation*)


Inhibition of bacterial growth


References

Orthopaedics & trauma

Trauma surgery


Benigne bone tumour surgery


Chronic osteomyelitis surgery


Preclinical publications


Frontal sinus surgery


Mastoid surgery


Surface reaction cascade

Starts immediately after the granules are moistened

Bioactive glass inhibits bacterial growth

1. Increase of pH (alkaline environment)
   - Release of Sodium (Na), formation of NaOH
   - Bacteria cannot adhere and colonize on surface

2. Increase of osmotic pressure/salt concentration
   - Release of Sodium (Na), Calcium (Ca), Phosphate (P), Silicate (Si)

Na, Ca, P, Si are elements that exist naturally in the body
Surface reaction cascade
< 1 day in contact with body fluids

Silica-gel layer forms on granule surface

- Negatively charged surface
- Attracts Ca and P that have released from the granule surface

The Silica-gel layer acts as a template for CaP precipitation
Surface reaction cascade
< 1 week in contact with body fluids

CaP crystallizes to natural hydroxyapatite (HA)

- Ca and P will form CaP that precipitates to the silica gel
- The CaP-layer mineralizes to the natural hydroxyapatite
- The natural hydroxyapatite will bond to the surrounding bone

The HA layer bonds to bone & promotes osteointegration
Bone formation cascade
Scanning electron microscopy images

Hydroxyapatite starts to form on BonAlive® granules surface

Hydroxyapatite covers BonAlive® granules surface

BonAlive® granules bonds to bone and stimulates new bone formation (osteostimulation*)

*non-osteoinductive

1 day
1 week
6-12 weeks

Collagen fibres

BonAlive® granules surface

16.8.2014
Version 91318f/1
Bone formation cascade

Histological image

Dense tissue formation

- Reaction layer on the surface of BonAlive® granules
- Cells attach to granules surface

Histological 20 µm-thick section from the mastoid area at three months after obliteration with BonAlive® granules (human biopsy)
Osteostimulation* is a more active process than osteoconduction and thus anticipates an enhanced tissue response at molecular and cellular level. Osteostimulation* activates osteoblast proliferation and differentiation that leads to new bone formation in osseous defects. *non-osteoinductive

BonAlive® granules has been shown in-vivo to:

- stimulate the recruitment and differentiation of osteoblasts
- enhance osteoblast activity
- increase the remodelling rate of new bone

“The current study confirms that the BG (bioactive glass) surface is not only conductive but also osteoproductive in promoting migration, replication, and differentiation of osteogenic cells and their matrix production.”

Virolainen P. et al., 1997
Osteoconduction and osteostimulation*

*non-osteoinductive

Image showing the bonding between reaction layers of the bioactive glass and new bone

Scaffold structure and new bone formation around the bioactive glass

Image showing the bonding between reaction layers of the bioactive glass and new bone
BonAlive® granules *inhibits bacterial growth*

**Bacteria cannot grow on BonAlive® granules surface**

- Bacteria adhere and grow in the hydroxyapatite bone graft substitute mass
- Bacteria cannot adhere and grow on BonAlive® granules bone graft substitute surface

Aggregation test with pigmented *P. gingivalis*
BonAlive® granules *inhibits bacterial growth*

**Inhibits bacterial growth through physical and chemical reactions**

- Results show clear inhibition of all tested species

29 aerobic and 17 anaerobic clinically important bacterial species tested

### Aerobic species

<table>
<thead>
<tr>
<th>Gram positive</th>
<th>Growth inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. epidermidis</em></td>
<td>Effective</td>
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<tr>
<td><em>S. aureus</em></td>
<td>Effective</td>
</tr>
<tr>
<td><em>S. aureus (MRSA)</em></td>
<td>Effective</td>
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<tr>
<td><em>E. faecalis</em></td>
<td>Effective</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
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### Anaerobic species

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### Aerobic species

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<thead>
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<tr>
<td><em>E. coli</em></td>
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<tr>
<td><em>P. aeruginosa</em></td>
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</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>Effective</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
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*Munukka et al. 2008*

*Leppäranta et al. 2008*
Conclusions on BonAlive® granules

Biomaterial that inhibits bacterial growth
- Occurs through the surface reactions
  - *Increase of pH*
  - *Osmotic pressure*

Stimulates new bone formation
- Natural hydroxyapatite (HA) bonds to bone
- Resorbs and remodels to bone
- Increases the remodelling rate of new bone
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