How a nose at the bench can help a knee at the bedside

Ivan Martin
DBM: “The place to be” for translational research

Fundamental research developed in relationship to a clinical question / environment
Pathophysiology of osteoarthritis

Inflammatory processes

Enhanced catabolic activity

Synovial changes

Osmotic stresses

Chondrocyte hypertrophy

Subchondral bone changes

Mechanical stresses

Lianxu et al, Osteoarthritis Cartilage 2006
Attur et al, J Immunol 2008

Kawaguchi et al, Mol Cells 2008
Abramson et al, Arthritis Res Ther 2009
Cartilage injury is a strong risk factor for OA

How to prevent (or delay) degenerative joint disease?

Gelber et al., Ann Intern Med 2000
Current treatments for articular cartilage lesions

- Microfracture
- Drilling
- Tissue autografts or allografts
- Autologous chondrocytes implantation

No predictable and durable hyaline cartilage repair
Engineered nasal cartilage

Jakob et al., J Cell Biochem (2001)
Jakob et al., Connect Tissue Res (2003)

Kafienah et al., Tissue Eng (2000)

M. Jakob
A. Barbero
First-in-man

Regenerative surgery!

Engineered autologous cartilage tissue for nasal reconstruction after tumour resection: an observational first-in-human trial

Are nasal chondrocytes compatible with implantation in a joint?

Mechanical aspects
Candrian et al., Arthritis Rheum (2008)

Inflammatory aspects
Scotti et al., Tissue Eng-A (2012)

Developmental aspects

Pre-clinical studies
A developmental perspective for cartilage cells

Nasal chondrocytes
(ECTODERM)

Articular chondrocytes
(MESODERM)

HOX negative
HOX positive

Self-renewal and regenerative capacity
(Lee+, Cell 2006)

Hox-negative

Developmental plasticity
(LeDouarin+, Development 2004)

Pelttari et al., Sci Transl Med (2014)
Self-renewal & plasticity for adult human chondrocytes?

Nasal chondrocytes can form hyaline cartilage following serial cloning (more than 20 doublings)

Nasal chondrocytes can acquire an articular 'signature' upon implantation into a joint

Many questions still open

Pelttari et al., Sci Transl Med (2014)
Nasal chondrocytes in goat articular defects

Alcian Blue

GFP Staining

Mumme et al., Tissue Eng-A (2016)
Are nasal chondrocytes compatible with implantation in a joint?

**Mechanical aspects**
*Candrian et al., Arthritis Rheum (2008)*

**Inflammatory aspects**
*Scotti et al., Tissue Eng-A (2012)*

**Developmental aspects**
*Pelttari et al., Sci Transl Med (2014)*

**Pre-clinical studies**
*Mumme et al., Tissue Eng-A (2016)*
Janu Sirsasana
From the Nose to the Knee

Compositional quality of repair tissue (6 and 24 months):

- dGEMRIC → Significant increase with time in GAG content

\[ \Delta R1(\text{Native}) = 1 \]
\[ \Delta R1(\text{Repair}) = 1.38 \pm 0.19 \]
\[ \Delta R1(\text{ACI}) = 2.18 \]
\[ \Delta R1(\text{Microfracture}) = 3.39 \]

Trattnig et al., 2008
Nasal chondrocyte-based engineered autologous cartilage tissue for repair of articular cartilage defects: an observational first-in-human trial


Extension to a phase II study (98 patients treated)
What is possible?
Challenges to address

Manufacturing
Streamline processes in bioreactors => Cost-effectiveness?

Extension to degenerative settings
Can cartilage be restored in ‘early OA’ conditions?
Nose2Knee extension towards early OA?

Pre-clinical models:
- Resistance of nasal chondrocytes to OA settings
- Positive conditioning on cells from OA joints
- Repair of "chronic" chondral defects in a sheep model

Design of next generation treatment
- Combined approaches

Pilot clinical treatment of 3 individual cases
- QoL scores: 31 → 44 (8 months)
  31 → 88 (8 months)
  19 → 63 (2 years)
Next clinical step

Temporary authorization

Knee joint
Revision surgery, large defects
Kissing lesions

Other joints
Ankle revision surgeries
Shoulder cartilage lesions
Challenges to address

Manufacturing
Streamline processes in bioreactors => Cost-effectiveness?

Extension to degenerative settings
Can cartilage be restored in ‘early OA’ conditions?

Understanding of regenerative processes
Fundamental knowledge => Mode of action => IPC and Release Criteria
The mistery of nasal chondrocytes…


Epigenetic regulation of regeneration/plasticity?

Molecular reprogramming of cell subpopulations?

Synergy program with F. Rijli, FMI
Towards modeling human osteoarthritis

- Uniaxial stretching
- Confined compression

Collab. with M. Rasponi, Milan

Occhetta et al., Nat Biomed Eng (2019)
Osteochondral composites
Towards Joint on a Chip

A. Mainardi
F. Mariuzzo
Challenges to address

Manufacturing
Streamline processes in bioreactors => Cost-effectiveness?

Extension to degenerative settings
Can cartilage be restored in ‘early OA’ conditions?

Understanding of regenerative processes
Fundamental knowledge => Mode of action => IPC and Release Criteria

Robustness
Recapitulate developmental processes?
„Developmental Engineering“

Scotti, Tonnarelli et al., PNAS (2010)  
Scotti, Piccinini, Takizawa et al., PNAS (2013)

Occhetta et al., PNAS (2018)  
Chawla et al., J Cell Sci (2020)
Translation process

Patient

Clinician

Research Team
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SNF-NCCR: Molecular Systems Engineering
SNF-Div 3: Engineered extracellular matrices
SNF-IndoSwiss: Developmental engineering
SNF-Sinergia: Human omentum
Janu Sirsasana