Growth Factors in Bone Regeneration

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CRANIOFACIAL BONE DEFECTS

- Congenital malformations
- Traumatic induced defects
- Surgical resection
- Periodontal disease
- Alveolar bone atrophy

MATERIALS & BIOLOGICS

Development

60's-70's

- fully edentulous
- undisturbed healing
- 2-stage approach

Exploration

80's-90's

- technological advances
- surface modifications
- bone grafting
THE “PERFECT MATERIAL”

- Biocompatible
- Mechanical properties similar to bone
- Osteogenic Selectivity
- Promote vascularity
- Degradation at similar rate to bone formation
- Controlled release of GFs

Modified from Block and Kent, JOMS 55;1997:1281-1286.

WHERE ARE WE NOW?

Osteoinduction
- Attraction, proliferation, differentiation of osteoprogenitors

Osteoconduction
- Support of bone growth providing scaffold for cellular activity

Osteogenesis
- Formation of bone, requiring viable osteoblasts

Desirability:
- Passive
- Active

Bone Grafting Materials

- Osteoconductive
  - Allograft (mineralized)
  - Xenograft

- Osteoinductive
  - Allograft (demineralized)
  - rhBMP-2 (ACS carrier)

- Osteogenic
  - Autogenous bone

Most important:
- Biocompatible
- Mechanical properties similar to bone
- Osteogenic Selectivity
- Degradation at similar rate to bone formation
- Controlled release of GFs
WHAT ARE THE ISSUES & CHALLENGES?

Wound Dehiscence
Hard AND Soft Tissue Defects
Long-term Stability
Ethical/Spiritual
Vascularity

Cost
Infection
Donor Site Morbidity
Resorption
Integration
Disease Transmission

WHERE ARE WE GOING?
CAN WE ADDRESS THESE ISSUES?

Aghaloo T and Le AD, 2004
Scaffolds
Vascularity
WHY GROWTH FACTORS?
- Recreate natural wound healing environment
- Orthopedic fracture healing
- Bone healing and regeneration
- Diabetic skin ulcers
- Soft tissue healing and vascularity
- Implant Dentistry
- Bone and soft tissue healing

HISTORY
- Biological sealants since 1970's
- Fibrin glue to decrease operative time
- Enhances coagulation and creates mechanical barrier

GROWTH FACTORS
- Platelet-derived Growth Factor (PDGF)
- Transforming Growth Factor-β (TGF-β)
- Vascular Endothelial Growth Factor (VEGF)
- Fibroblast Growth Factor-2 (FGF-2)
- Bone Morphogenetic Proteins (BMPs)
- Neural-like epidermal growth factor (Nell-1)

RH-PDGF
- Recombinant human platelet-derived growth factor
- First approved for treatment of diabetic ulcers
- Beta-Tricalcium Phosphate Carrier
- Approved bone void filler in orthopedics and periodontics
- 2005 FDA approved for intraosseous periodontal defects and associated gingival recession (Gem21S®)
- Case reports of xenograft blocks with PDGF for vertical ridge augmentation

RH-BMP-2
- 1965 Urist discovers DBM and induces bone in rat ectopic model
- 1971 Urist coins term bone morphogenetic protein (BMP)
- 1988 1st recombinant human BMP produced: rhBMP-2
- 2002 FDA approval for spinal fusion and non-union tibia fractures
- 2007 FDA approval for sinus and local alveolar ridge augmentation, BMP-2 on ACS (INFUSE®)
RHBMP-2 CLINICAL CASES
• Good preliminary results allowing implant placement with titanium mesh and bone plate
• May be improved with osteoconductive material added for space maintenance
• No complications in posterior mandible and able to place implants without further augmentation

RH-BMP-2 MANDIBULAR CONTINUITY AND VERTICAL AUGMENTATION

- Cost
- Compression of soft tissue onto ridge during healing
- Few studies
- Lack of long-term follow up

LIMITATIONS OF RHBMP-2
• Xenograft studies for GBR had higher implant success rate vs. autografts
• No difference in implant survival rate between iliac crest, intraoral autogenous, or xenografts for onlay grafting
• Largest number of studies that met inclusion criteria with xenografts than any other single material, except autogenous bone
• Trend toward increase survival with xenograft, both alone and when combined with adjunctive materials such as PRP, fibrin glue, etc.

GRAFTING MATERIALS

DIFFICULT CASES
HOW CAN WE USE GROWTH FACTORS WITHOUT HUGE COST?

PLATELET-RICH PLASMA (PRP)
- Anticoagulate collected blood
- Double spin cycle
- Significantly higher platelet counts than peripheral blood
- Increased concentration of growth factors
  - TGF-β, PDGF, FGF-2, VEGF, IGF-1, HGF
- ?Correlation between platelet counts and growth factor levels
- Platelet concentration >600,000
- Holds graft particles together
- ? Bone or soft tissue healing benefits

PLATELET-RICH FIBRIN (PRF)
- Small amount of blood
- No need for anticoagulation and recoagulation
- Autologous source
- Lower cost, simple and faster preparation
- Improved handling of graft materials

PRP IN ANIMALS AND HUMANS
- Conflicting literature regarding effects on bone healing and regeneration
- More soft tissue healing benefits
- Expensive and time consuming
- Requires large volume of blood
ONE low speed spin (15-27 RPM for 12-14 min) to separate lower rbcs, middle buffy coat (wbcs, platelets), poor plasma
Fibrin matrix with fibronectin and vitronectin
Growth factors
Platelet concentration
Monocytes, granulocytes, neutrophils
Anti-inflammatory cytokines
Utilized as a membrane
Soft tissue healing benefits

**PLATELET-RICH FIBRIN (PRF)**

- 64 yo male with implants placed 25 years ago
- Long span FPD tooth to implants
- Treatment plan?
CLINICAL OBSERVATION

- Less postoperative discomfort
- Less facial bruising
- Faster primary soft tissue healing
- Decreased intraoral wound dehiscence
- Shorter surgical time
- More condensed and consolidated graft
- Less bone grafting material required
- Less hematoma formation

WHAT IS THE FUTURE OF ORAL BONE AND SOFT TISSUE REGENERATION??

CLINICAL OBSERVATION

- All patients
- Compromised wounds
- Alveolar bone defects
- Osteonecrosis
- Radiation induced
- Antiresorptive induced
- Translational studies
- From “Proof-of-principle” to Clinical Trials

WHEN TO USE THESE TECHNIQUES

- Porcine amelogenin
- Accelerate soft tissue healing and regenerate acellular cementum
- Increased clinical attachment level and decreased probing depths

OTHER WOUND HEALING ENHANCERS ON THE MARKET?

- Porcine amelogenin
  - Accelerate soft tissue healing and regenerate acellular cementum
  - Increased clinical attachment level and decreased probing depths

ENAMEL MATRIX DERIVATIVE

- Porcine amelogenin
- Accelerate soft tissue healing and regenerate acellular cementum
- Increased clinical attachment level and decreased probing depths

OSTEOCEL PLUS

- Allograft cellular matrix with viable
- Cancellous bone and demineralized bone matrix
- Progenitor cells (AdMSCs), CD45- (hematopoetic cells)
- Regulated
- As a tissue bank, but if claim stem cells, should be regulated by FDA
- Sterilization and immune reactivity
- Single donor, treated with antibacterial and antifungal
- Freeze/thaw 5 times, devoid living cells and mostly consist of cancellous matrix
- Some markers of stem cells
**OSIRIS**
- Mesenchymal stem cell product from another human's bone marrow
- For hematologic malignancies, cardiac repair after MI or CHF
- Regeneration of meniscus after meniscectomy
- Not to have immunologic reactions
- Used for graft vs. host disease
- Undergoing FDA review and clinical trials

**TRINITY EVOLUTION**
- Demineralized allograft cortical
- Cancellous bone with viable osteogenic and osteoprogenitor cells
- Adult allogeneic MSCs
- Only 2 clinical references

**HARD & SOFT TISSUE CONSTRUCTS**
- Deficiencies ALWAYS combined
- Minimally invasive
- Improved healing
- Focus on precision
- Long-term stability
- Fewer surgeries
Need for More
Rigorous Research

And Clinical Innovation