NEW TECHNOLOGIES: BIOMATERIALS, BIOMECHANICS, BIOPRINTING

Lisa Ferrara, Ph.D.

OrthoKinetic Technologies, LLC
&
OrthoKinetic Testing Technologies, LLC

DISCLOSURES

- OKT – Strategic Planning & Regulatory Consulting
- OKT² – ISO 17025 A2LA Accredited Test Facility

OVERVIEW

- What's new in biomaterials
- Mechanotransduction
- Combining Biomaterials, Nanostructures & Surfaces
- New & Exciting Technology

BIOMATERIALS

- A material intended to interface with biological systems to augment, treat, or replace damaged tissue

What's new in Biomaterials

PEEK

- Conventional
- HA PEEK
- HA Coated
- Titanium Coated
  - plasma spray, molded, printed inserts
- Coated
  - Many different Configurations
  - Endplates or Total Coverage
  - Printed, machined endplates, inserts
- Porous
  - Grown
  - Printed
  - Formed

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POROUS PEEK

- DUKE & Georgia Tech.
- PEEK scoria grown directly from the bulk PEEK on surface
- Surface treatment Vertera Spine's COHERE system.

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HA PEEK – InVibio – 10 Weeks Post-OP

Courtesy of Meditech Advisors foro the Talos-C

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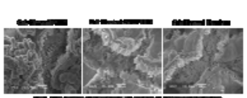
HA COATED PEEK (BIOMIMETIC)

- Short half life of HA, Debonding issues
- Increase surface roughness on PEEK, CFR-PEEK – biomimetic process
- Simulated Body Fluids / CO2 supply vs. Plasma Sprayed HA
- Increased Alk Phos. Activity
- Increased osteogenic differentiation



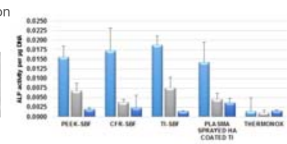


Figure 2. ALP expression normalized by the amount of DNA in each sample at day 7,14 and 21.

A biomimetic hydroxyapatite coating on polyetheretherketone
Sara Ajami[1], Gordon Blunn[1] and Melanie Coathup[1]
•[1] University College London, Institute of Orthopaedics and Musculo-Skeletal Science, United Kingdom

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WHAT IS ADDITIVE MANUFACTURING?

- Process of joining materials to make objects from 3D models
- Not subtractive – AM adds material in layers
- Builds layer upon layer onto substrates
- Value added
  - Can build complex structures that are difficult to machine
  - Characterized by rough surface quality – improved cellular response
  - Designed, controlled, interconnected porosity
  - High purity – restricted presence of O_2
  - High power processing velocity – rapid serial production of implants
  - Customize fit to patient anatomy

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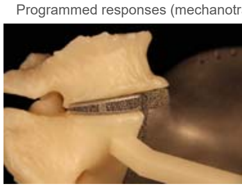
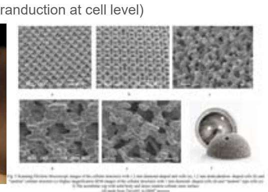
3D PRINTING - ADDITIVE MANUFACTURING

- Vehicle to fabricate open, complex structures for improved interface responses
- Microstructures, working on perfecting nanosizes
- Design custom porosities - graded porosities & structures
- Build Nanostructures & Nanoscaffolds
- Different material = different mechanical stimuli & response
- Programmed responses (mechanotranduction at cell level)





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Additive Manufactured Implants

- Biomaterial + Manufactured Process
  - Titanium Structures
  - CoCr
  - PEEK
  - Ceramics
- Provides a VEHICLE for fabricating complex devices, osseointegrative surfaces, graded materials w/o bonding processes

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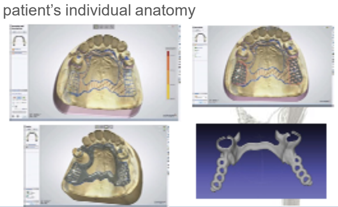
PEEK & CAD CAM

- Additive Manufacturing
- Early Stage
- PEEK partial denture frameworks
- Strong & lightweight improved patient comfort;
- Digital design matches the patient's individual anatomy
- Taste-neutral
- Fabricate restorations



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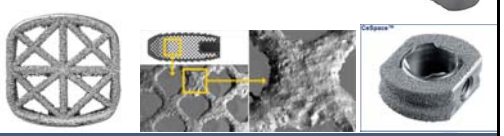
Titanium: Printed Coated or AM

- AM or 3D Printing is not the holy grail
- Mechanical behavior that is the **key**
  - Stress transfer
  - Strain behavior
  - LOCAL MODULUS vs. BULK MODULUS
- Failure Mode - IMPORTANT



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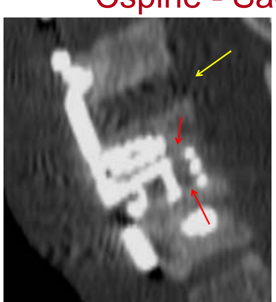
Cspine - Sagittal View



- No evidence of graft material at the levels with PEEK cage (yellow arrows)
- Partial consolidation and graft maturation at 4-Web level (blue arrows)
- 1 year out
- Courtesy of Dr. Camissa & 4Web

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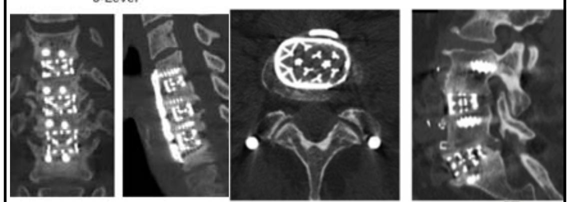
Multi-Level – Cspine / LSpine

3-Level



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COMBINING BIOMATERIALS WITH INNOVATIVE DESIGN & SURFACE TREATMENTS

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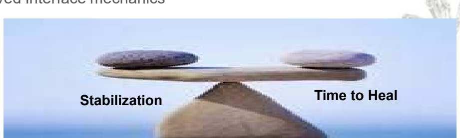
IMPROVING INTERFACE MECHANICS

- Why?
- Balance between Time & Stabilization -Earlier Stabilization = Earlier Fusion
- Increase time to heal = increase risk of failure
- Earlier stabilization = Decreased time to heal & Failure risk
- Improvements in materials & surfaces
- Improved Interface mechanics



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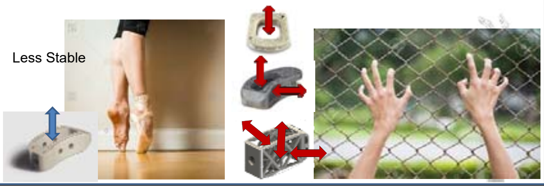
INTERFACE MECHANICS

- Improve designs - Multi-directional bone exchange = better biomechanical stability
  - Full open, multiplanar
  - Large windows, multiple directions
  - Surface textures – endplates or entire device
  - Materials that promote osseointegration, osteoinduction, osteoconduction
- Improved stability allows for further ingrowth towards center- throughout implant
- Greater area of bone contact, greater fusion footprint – better stress distribution



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Programmable Structures: Scaffolds, Trusses & Surface Modulation

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IMPORTANT VARIABLES

- Delivery
  - Cell Suspensions
  - Tissue-like constructs (scaffolds)
- Chemical properties
  - Growth factors
  - Degradation particles
  - ECM surface
- Physical properties
  - Structure
  - Topography
  - Rigidity
  - Mechanical Loading

→ Modify Cell Behavior
Survival
Organization
Migration
Proliferation
Differentiation

↓

Optimize Cellular Response

Can Tissue Regeneration be 'programmed'?

GEOMETRICAL FACTORS-

OPTIMAL POROSITIES FOR BONE GROWTH

- Bone tissue penetration – pore sizes 200-900µm (ideal 300-500µm)
- Enhanced cell penetration through pores
- Enhanced extracellular matrix production

- Vertical pores 300µm
- Horizontal pores 200-400µm
- Surface Posts - 10µm x 10µm / 10µm spacing
  - Kim et al. - Enhanced growth for CTPs

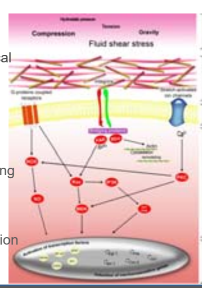
} **3D Scaffold + Surface Microtexture**

Surface Textures - Mechanotransduction

- Induce mechanotransduction
- Guide cellular growth
- Increased cell proliferation – or -
- Increased cell efficiency
- On Metals: use of surface textures
  - Increase fatigue performance of implant
  - Careful not to compromise strength
  - Titanium = improve osseointerdigitation

MECHANOTRANSDUCTION PROCESS

- Process where cells sense & respond to mechanical stimuli
- Cells convert energy to electrical & biochemical signals that elicit response.
- Stem cells sense mechanical loading thru membrane-anchored mechanosensors
- Converted to biochemical signals
- Trigger multi-step activation in array of signaling cascades in cytoplasm
- Activation of transcription factor
- Translocate to nucleus and modulate expression of mechanosensitive genes



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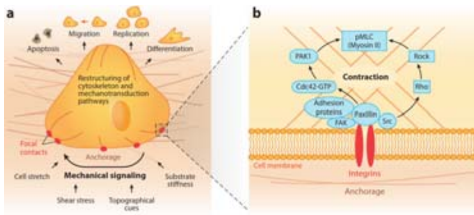
OVERVIEW



- Cells sense mechanical forces -convert into biological responses by triggering restructure of cytoskeleton
- FEEDBACK SYSTEM
- Cells respond

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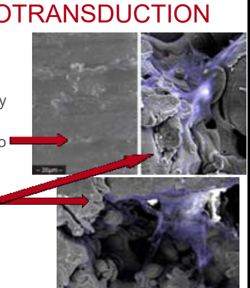
EXAMPLE OF MECHANOTRANSDUCTION

- Ti Coated
- Centinel Spine - ACTIVE™
- Cell migration of cultured cells studied by scanning electron microscopy (SEM).
- PEEK- absence of any cell attachment to surface.
- Ti-ACTIVE™- coated device shows cell attachment
- Ti-ACTIVE™ - cell migration seen by cytoplasmic expansions of cultured cells (purple)



http://www.centinelspine.com

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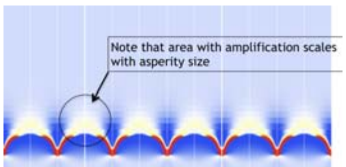
DIFFERENTIATION MSCs INTO SPECIFIC CELL PHENOTYPES

- Mechanical Forces
  - Varied/controlled stiffness of substrate
  - Differentiate with different stiffnesses
- MSCs respond to hydrogenated amorphous carbon nanotopographics with groove or grid surfaces
  - Groove structures demonstrated dynamic effect assoc. w/ stem cell alignment + elongation.
- Surface topography – Nanogrooves
  - Width/spacing – 40/30μm – optimal
  - Induced hMSCs -acquire neuronal characteristics in absence of differentiation agents.
- Mechanics = differentiation

Mechanotransduction: use the force(s)
Paluch *et al. BMC Biology* (2015) 13:47
DOI 10.1186/s12915-015-0150-4

SURFACE STRAIN

- Surface roughness had micro & nano structures that form peaks / valleys - strain responses during loading – micro and nanostrains measured
- Study showed that optimal biological responses to specific surface geometries
  Lending to different strain patterns



SCAFFOLD STRUCTURES - VARIABLES AFFECT CELL RESPONSES

- Surface chemistry
- Matrix topography
  - Cell organization, alignment
  - Fiber alignment -> tissue development
- Rigidity
- Porosity
  - Large interconnected
  - small disconnected

MICRO-NANO SCAFFOLDS CELL DIFFERENTIATION

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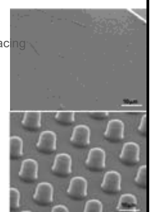
MICROTEXTURED POLYMERS

- MEMS structures – soft lithographic process
- Assessed osteogenesis- proliferation, differentiation
- Connective tissue progenitor cells [CTPs] – Human Bone Marrow
- Cultured 60 days
  - Smooth PDMS
  - Microtextured w/Posts PDMS - 10µm dia/ 6µm height / 10µm spacing
- DNA quantification
- Western Blot Analysis – for Integrin α5 expression
- Real time RTP chain rxn – alk phosphatase gene expression



Post microtextures accelerate cell proliferation and osteogenesis

Eun Jung Kim, Cynthia A. Boehm, Alvaro Mata, Aaron J. Fleischman, George F. Muschler, Shuvo Roy

Acta Biomaterialia 6 (2010) 160–169

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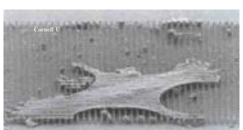
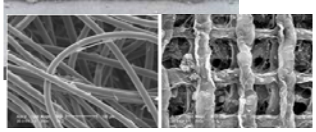
TEXTURED SURFACES -TISSUE SCAFFOLDS

- Disc & ligament regeneration
- Organized / programmed growth
- Respond to mechanical, chemical, electrical stimuli



Directed growth of a fibroblast that responds to mechanical stimuli



Astrocyte cells grown on (a) non-woven PET fiber matrix

(b) microfabricated PLGA scaffold

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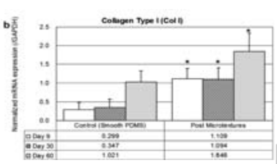
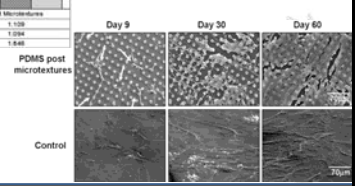
RESULTS



- Gene Expression for Collagen Type I



- Cell Proliferation & Growth Orientation

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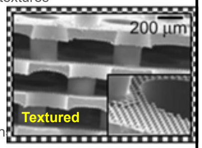
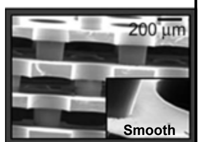
BIOACTIVE SURFACE TOPOGRAPHIES

- 3D Microstructure – defined microarchitecture + microtextures
- Provide specific physical cues to cells / tissue
- Precisely engineered architecture
- Tailored surface topography
  - Optimized for cell type
  - Microfabrication + Soft Lithography to build scaffolds
- Connective tissue progenitor cells [CTPs] – 3 Patients
- Cultured **9** days under osteoblast phenotype condition
  - Smooth PDMS 3D structure
  - Microtextured w/Posts PDMS - 10μmX10μm
  - 66% Porosity
  - 5 layered scaffolds – 3D





Biomaterials 30 (2009) 4610–4617

A three-dimensional scaffold with precise micro-architecture and surface micro-textures

Alvaro Mata, Eun Jung Kim, Cynthia A. Boehm, Aaron J. Fleischman, George F. Muschler, Shuvo Roy

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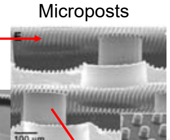
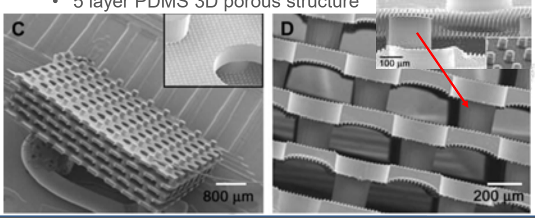
3D SCAFFOLD + MICROPOSTS

- 5 layer PDMS 3D porous structure





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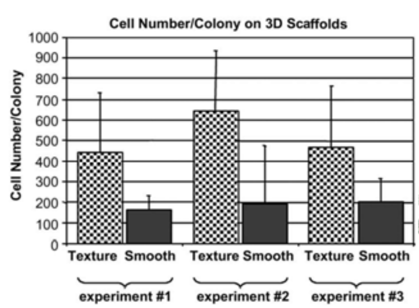
RESULTS



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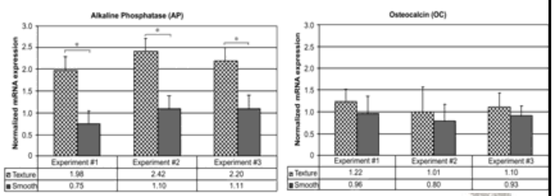
RESULTS



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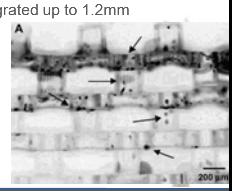
FINDINGS - 3D TEXTURE & 3D SMOOTH

- Cells attached, proliferated, migrated vertically betw layers, differentiated
- All 3 dimensions on different features of scaffold
- Cells grew top down to 4 layers deep
- Cells grew top/ bottom of each layer, walls of pores, columns
- Vertical direction, cells proliferated and migrated up to 1.2mm
- Colonies reached 3mm dia.horizontally
- Cytoskeleton grew within & around posts



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THE FUTURE

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SMART SCAFFOLDS

- Can create repeatable & predictable MICRO and NANO architectures for optimized cellular responses
- Can modulate, differentiate cells – surface textures and structures
- Can layer for smart scaffold – multilayer organized growth
- Mechanical behavior of scaffold / substrate material can dictate cellular response and organization (stiffness)
- Multiplanar stress transfer – optimized interface mechanics
- Create 'passively smart' structures for cell differentiation and tissue regeneration

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  - High power processing velocity – rapid serial production of implants
  - Customize fit to patient anatomy

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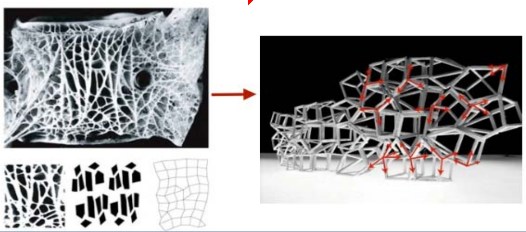
AM PROCESSES & BIOMIMICRY

- Can build structures & functions that mimic biology & complex shapes of tissues
  - Bone → Truss structures



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BIOPRINTING

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BIOPRINTING

Morphing new technologies to obtain impactful innovation

Regenerative Medicine – Next Wave

3D Bioprinting + Nanotechnology + Stem Cells >>> INNOVATION

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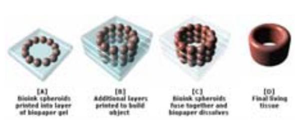
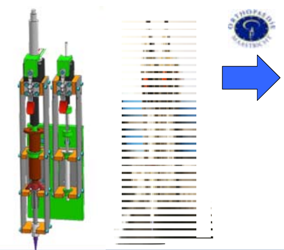
BIOPRINTING USING AM

- ORGANS / FACIAL PRINTING / TISSUE SCAFFOLDS
  - Artificially constructs living tissue / organs
  - Spheroids contain aggregate of tens of thousands of cells
  - Builds layer-upon-layer of living cells from the patient's own body
  - Reduces rejection to almost zero.
  - Organovo + Invetech created commercial bioprinter - NovoGen MMX. Loaded with bioink spheroids w/cells, substrated collagen / protein matrix etc.…
  - December 2010, Organovo created first blood vessels bioprinted using cells cultured from a single human.



3D PRINTED TISSUE

- 3-D printed CaP bone substitute
- 3D of Bone



3D PRINTED SKIN & CARTILAGE

- Print skin directly onto burn victims
- BIOPRINTING - computer-controlled machine assemble biological matter using organic inks and super-tough thermoplastics.
- HUMAN CARTILAGE - flexible mats of electrospun synthetic polymer combined, layer-by-layer, with cartilage cells from rabbit ear deposited by ink jet printer.
- The constructs were square with a 10cm diagonal and a 0.4mm thickness.
- Synthetic materials ensure the strength of the construct and natural gel materials provide an environment that promotes cell growth.

3D PRINTED ORGANS

- **Scientists Have 3D-Printed Mini Human Livers for the First Time Ever**
- New mini livers – live 40 days
- Great approximations of real deal - producing the proteins that carry hormones & drugs throughout body, cholestoral, and the major detoxification enzymes that let you consume reasonable amounts of alcohol without dying.
- **Organovo** plans to move on to the normal-sized organs

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Evolution of Technology & Medicine

- Continue to innovate
- Improve outcomes, quality of life, longevity
- Continue to progress – good & bad

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THANK YOU

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DIC – Measure Real-time Microstrain, Forces