High Priority Questions and Emerging Areas in Regenerative Engineering and Medicine

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UCONN HEALTH

Regenerative Engineering

- Convergence of Advanced Materials Science, Stem Cell Science, Physics, Developmental Biology and Clinical Translation for the regeneration of complex tissues and organ systems.

- "Regenerative engineering combines advanced bio-engineering with the development of advanced materials compatible with the body. Wearable bioreactors could be designed to enable tissue regrowth, and 3D printing of living cells might be used to produce new tissues. The goal is to dramatically improve quality of life for wounded military personnel, aging seniors, and all those with damaged or dysfunctional body parts. **Already techniques to re-grow torn ligaments and tendons are in clinical trials. The distant promise is to re-grow more complex tissues, such as a limb or a whole knee.**"

Convergence: The Future of Health. Cambridge MA (2016)

The Grand Challenge

- Beyond replacing individual tissue types
  - Multicomponent tissues
- Added challenges when restoring tissue of more than one tissue type
  - Interfaces are a challenge
- Grand Challenge
  - Whole joint, whole limb regeneration
  - HEAL
    - Hartford Engineering a Limb Project
    - The ultimate “complex tissue regeneration” project

Space Flight and Physiological Challenges

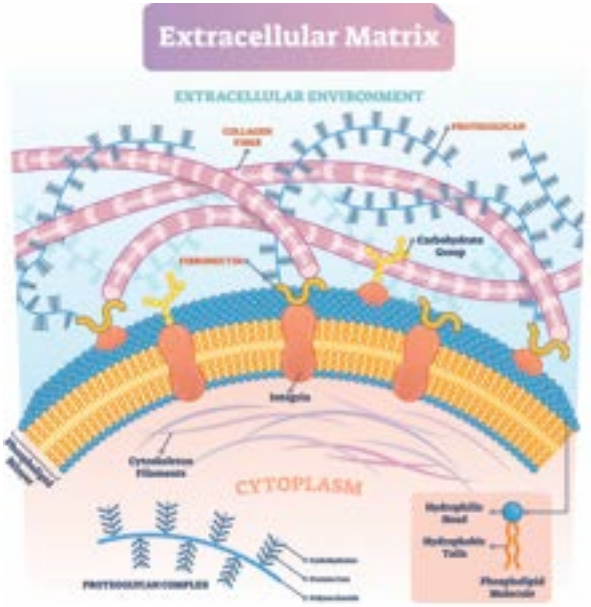
- Immune System
  - Functional Immune Alterations, Latent Herpesvirus Reactivation, Physiological Stress and Clinical Incidence Onboard the International Space Station (Functional Immune)
- Neuronal
  - Radiation Exposure
  - Anatomical effects on the brain, visual problems
  - Cognitive effects
  - Biological effects on the brain, cytoskeletal effects
- Musculoskeletal System
  - Muscle
  - bone

Critical and Emerging Issues

- Musculoskeletal tissue maintenance and regeneration
  - Bone tissue
  - Muscle tissue
- The impact of microgravity on stem cells
  - Stem cell maintenance and differentiation
  - Response of blastema to microgravity
- The role of mechanical forces on stem cell maintenance and differentiation
  - Microgravity
  - Substrate stiffness
  - Applied physical forces
  - 2-D vs 3-D cell culture

Musculoskeletal Tissue Maintenance

- Challenges
  - Bone and muscle respond to applied physical forces
  - Reduction in forces changes cellular behavior
  - Bone and muscle resorb/atrophy
    - Possibly via fewer available stem cells



Microgravity and Stem Cells

- Challenges
  - Stem cells have reduced/inhibited ability to differentiate in microgravity
  - When returned to normal gravitational environment their differentiation potential is magnified

Proliferation	Differentiation
Substrate stiffness	Substrate stiffness
Enhanced traction forces	Soft substrates
Mechanical strain	Mechanical strain
Uniaxial stretch	Localized stresses
	Malleable topography
	Substrate elasticity
	Cyclic stretch/compression

Adapted from Vining KH, Mooney DJ. Nature Reviews, 18, (2017)

Mechanical Forces and Cell Behavior

- Challenges
  - Applied forces, or lack of forces, greatly impact the behavior of cells
    - Forces arise from gravity (the weight of the cell), fluid flow, substrate materials, external forces
    - Cellular environment dramatically influences cell response
      - 2-D culture vs 3-D culture

Challenges to Study

- Complications created by density-gradient-driven flows
  - Passive diffusion through 3-dimensional structures
- Complications created by the weight of the system being studied
  - How does the weight of a cell impact its cytoskeletal elements and functions
  - how does the absence of this weight impact the same elements and functions

Opportunities Presented

- Failure to differentiate
  - Strategies to maintain stem cell cultures for extended period of time
- Lack of full gravitational effects
  - Control the application of forces (type and magnitude)
  - Control when and how stem cells differentiate
- Apply forces selectively
  - Choice of substrate materials
  - Location-specific application of mechanical forces
    - Transdermal acoustic radiation force

Summary

Challenge	Opportunity
• Musculoskeletal tissue maintenance	• Testbed for bone and muscle atrophy, and strategies to attenuate atrophy
• The impact of microgravity on stem cells, blastema	• Ideal environment to study and control the impact of forces (and lack thereof) on stem cell maintenance, differentiation, blastema in microgravity
• The alteration of environmental forces on cell behavior in microgravity	• Ideal environment to study cell-substrate relationship, application of controlled external forces, and the relationship to tissue regeneration

The Big Question

- How does microgravity influence large scale tissue regeneration, and how can it be used as a tool, specifically by evaluating and exploiting:
  - the impact of mechanical forces on stem cell survival and differentiation
  - The ability to impart appropriate mechanical forces on targeted stem cell/blastema populations within material-based constructs
  - The impact of substrate/environmental forces on stem cell survival and differentiation

Thank You

Questions