
Emerging Forms of Evidence in
Assessing Regenerative
Medicine
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Definitions

- Tissue engineering uses principles of life sciences and engineering to develop biological substitutes and/or to stimulate tissue generation or self-repair, using cells, biologicals (factors, molecules, etc) and biomaterials
- "the design, specification and fabrication of cells, biomaterials or biomolecules to restore or modify the biological function of tissue" *(P. Johnson)*
- "the persuasion of the body to heal itself through the delivery to the appropriate sites of molecular signals, cells and/or supporting structures" *(D. Williams)*

- Cells from human sources (living, cadaver, fetal, embryo)
- Cells can be alive or dead
- Can be grown with or embedded in synthetic materials
- Can be ‘engineered’
- Can be acellular - stimulate tissue in body to grow with biomaterials
- Dependant on interactions: *this is systems biology, not molecular biology*
- Expertise from engineering, biology, materials science & more

- (Slides with photos or representations of TE products will be inserted here in presentation)

Problems of Evidence

- Shift away from efficacy proofs
- Substitution of predictive models for observational, empirical models
- Evidence through standards-setting

FDA Definition of Biological

- …any virus, therapeutic serum, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment or cure of diseases or injuries.

FDA Definition of a Medical Device

- "…apparatus…implant, in vitro reagent, including any component…or accessory…
- intended for the diagnosis, mitigation, treatment, or prevention of disease…
- or intended to affect the structure or function of the body…
- and does not achieve its primary intended purposes through chemical action within or on the body…and which is not dependent upon being metabolized to achieve its intended purposes"

FDA claims right to regulate tissue but there's an unclear regulatory pathway

So artificial skin (fibroblasts on a scaffold) could be classified as a device, while a cartilage product (bone morphogenic protein on a collagen sponge) could be a biological

Terminology and definitions determine designation and ultimately, reimbursement:

Does the product "initiate healing," act as a cover, act as a graft?

Office of Combination Products

- Office created in 2002 to vet applications
- TE products exhibit characteristics of more than one classification
- Classification determines how an entity is reviewed, how trials may proceed, how/if it will be reimbursed and whether product will ultimately be subject to liability litigation
- Classified according to its “primary mode of action”

Basis for determining classification

- EUROPE:
  - autologous vs allogeneic
- U.S.:
  - Mode of action of the “most relevant component” of the product

Regulatory context

- FDA under scrutiny
  - Gene therapy failures, post-market discoveries & lack of public trust
- Conflict between FDA divisions
  - Competition for resources

Regulatory context

- FDAMA (1997) – attempt to ‘downsize government’; turn to outside expertise
- National Tech Transfer and Advancement Act (1995)-- requires governmental agencies to use *privately developed* standards & validation
- HR 5651 (2002)--institutes user fees for devices

Why are standards important?

Reduce variability in the way materials are made and supplied

They create credibility, image of public accountability

But standards also set the rules of participation, determine who participates in market & governance

- **ASTM** – nonprofit org that validates standards. (industrial lubricants, consumer electronics, highways)

- **F04 – TEMPS (Tissue Engineered Medical Products)**
  - Committees= CDRH, CBER, industry reps
  - COI concerns

Outcomes of TEMPS process

- Harmonized procedures, but had effect of eliminating new entries to field & innovative materials
- Standards get modeled on ASTM templates for existing products
- Standards are written in a way to define TE products as devices,
- Standards are sold to other industries; become ‘translatable’ to other products

- Evidence is produced in a way to direct classification, redirect attention to safety and away from efficacy, is agnostic to function in patients
- Mismatch of processes and goals of technology assessment and regulatory review with actual practices