BNG 331 – Cell-Tissue Material Interactions

Biocompatibility
Course update

• LBL 6 **next Monday**; schedule otherwise the same
• Ethics discussion – The use of animals in biomedical research – Wednesday & Friday
  – Wednesday discussion facilitated by Maggie Tongue
• Attendance is mandatory for final five classes!
• Today: Biocompatibility
  – Introduction
  – Methods to test biocompatibility
    • *in vitro* studies
    • Animal models
  – Clinical trials
Happy Memorial Day!

- Schenectady Veterans Park – State and Nott Streets
Biocompatibility: general points

• Biocompatibility must be established & approved by appropriate regulatory agencies before any biomedical device can be marketed and used clinically

• **All** biocompatibility tests must be conducted according to carefully constructed protocols that include controls
For perspective...

• **Biocompatibility**, as a concept and term, is:
  - **ambiguous**; here are various definitions:
    - “The ability of a material to perform with an appropriate host response in a specific application”
    - “The quality of not having toxic or injurious effects on biological systems”
    - “The capability of a prosthesis to exist in harmony with tissue without causing deleterious changes”
  - **new** (graph on next slide)
  - Rather than endorsing any definition outright, we will examine some of the considerations involved; you can choose your favorite definition!
For perspective...

Annual number of published articles in peer-reviewed journals with the word “biocompatibility” in them between 1970 (first year ever) and 2007

What is the distinction between biocompatibility and bioactivity?
Examples of non-bioactive biomaterials

titanium bone screws

contact lenses

However, these materials must still be biocompatible
Medical devices versus drugs

• In this course we are concerned with medical devices

• Please review the FDA definition (google “Is the Product a Medical Device FDA”)
  – Different classes of devices (will see this later in the lecture)

• Beginning of the definition:
  – “an instrument, apparatus...or other similar or related article...which is...”
Medical devices versus materials

• Generally, the definitions given refer to a material (e.g., a certain type of metal or polymer)
• However, most medical devices are made of multiple materials
• Much of the pre-clinical testing phase is carried out using the material rather than the whole device
The FDA Development Process: Application Review

<table>
<thead>
<tr>
<th>Pre Clinical</th>
<th>Phase II</th>
<th>Phase III</th>
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- Pre-Clinical Research
- Synthesis and Purification
- Animal Testing
- Short-Term
- Long-Term
- Institutional Review Boards
- NDA Review
- Clinical Studies

- Phase 1
- Phase 2
- Phase 3

- Accelerated Development/Review
- Treatment IND
- Parallel Track

- IND Submitted
- NDA Submitted
- Review Decision

- Sponsor/FDA Meetings Encouraged
- Early Access: Subpart E
- Advisory Committees
- Sponsor Answers Any Questions From Review
Test prerequisite to evaluation

- *In vitro* characterization of material and of the functional performance of device prototypes are prerequisites
- must characterize properties of the raw materials
- Compare these results with the results at the end of manufacturing, sterilization, packaging, storage, and any other handling process/stage that may detrimentally affect stability & intended use of device
Methods for testing and evaluating

- Consists of a sequence of tests and includes:
  - *in vitro*: using cells and tissues
  - *ex vivo*: whenever applicable, done for a few hours up to 24 hours
  - animal models
  - clinical trials
In vitro testing

- Used successfully to screen materials and devices for biocompatibility

- Advantages
  - Reasonable cost
  - Small to reasonable capital investments in lab facilities and equipment
  - Relatively fast processing of large # of materials and prototypes

- Can you think of some disadvantages?
**In vitro testing**

- Common test in **blood compatibility** of materials and devices using **anticoagulated blood** and evaluating formation of **blood clots**
- Can conduct blood compatibility under **static or flow conditions**
- Advances in **cell culture techniques** have provided exceptionally versatile and useful in **in vitro** models
  - Automated cell culture system, Diamond Lab @ Upenn:
    https://www.youtube.com/watch?v=wHlxKhCSbpA
Animal models

- Used to determine *in vivo* compatibility of materials and devices
  - Negative results mean system is unacceptable
  - Positive results do not necessarily prove compatibility in humans
- Non-human primates are most desirable because of homology to humans
- Should only be considered after successful completion of:
  - Prerequisite material characterization tests
  - Appropriate computer simulation models
  - Pertinent *in vitro* models
Animal models

• Must recognize need to provide humane care & prevent their exposure to unnecessary pain and suffering

• Choose appropriate species, carefully plan experiments using smallest # of animals that will yield statistically useful information and avoid unnecessary duplication of studies

• Animal Welfare Act of 1985 addresses care and use of lab animals

We will discuss animal research further W/F!
Implant retrieval

• Information can be obtained by evaluating materials, devices, and surrounding biological tissue by retrieving implant at the end of the recipient’s life

• Remember that devices are usually designed based on data from healthy individuals
  – Why is this not ideal?

• Goal is to retrieve as many implants as possible (both failed and non-failed)

• Retrieved animal implants are important for FDA
  – Investigational Device Exemption (IDE) required for clinical trial and for the FDA premarket approval (PMA)
Classes of medical devices

The three classes

<table>
<thead>
<tr>
<th>CLASS</th>
<th>PREMARKET</th>
<th>CONTROLS</th>
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<tbody>
<tr>
<td>I</td>
<td>Does not support or sustain human life and has a significant history of safety and effectiveness</td>
<td>Most exempt from 510(k) clearance</td>
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<tr>
<td>II</td>
<td>Has a similar intended use and a safety and effectiveness profile of a device already on the market; risk requires special controls</td>
<td>Most require 510(k) clearance</td>
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<tr>
<td>III</td>
<td>Supports or sustains life or high risk of injury; typically requires clinical studies demonstrating safety and effectiveness</td>
<td>Nearly all require premarket approval (PMA)</td>
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Generally also requires clinical trials
Implant retrieval

• Prospective cohort study of a well-defined intervention
  – Different than a retrospective case review, in which patients have either received or not received the intervention and one studies the differences
  – Example of each type of study on the next two slides →
A Prospective Cohort Study

The Cohort
117,000 Nurses without cancer or CVD

After time has elapsed, investigators use the prospectively collected data to answer many questions.

We need to understand determinants of heart disease in women.

Enroll & assess exposures at the beginning.

Obese
Lean

Compare incidence of heart attack

Follow-up

The study is planned & designed to answer questions in a specific area. Non-diseased subjects meeting eligibility criteria are enrolled. Detailed baseline information on lifestyle & exposures is collected from each & they are followed over time.
A Retrospective Cohort Study

The Cohort
Employees of a tire manufacturing company.

Do chemicals used in tire manufacturing increase risk of death?

Get employee health records.

Exposed
Not exposed
Compare incidence death

This study was not preplanned. The investigator has to go back to pre-existing data that was not necessarily acquired in a precise, predetermined way. Follow up may have been incomplete.
Clinical trials – essential features

1. Prospective cohort study of a well-defined intervention
   - Different than a retrospective case review, in which patients have either received or not received the intervention and one studies the differences
   - Versus a retrospective study, Problems? Advantages?

2. Studies a population carefully defined by inclusion and exclusion rules
   - Key standards prospective participants must meet, e.g., age or weight requirements
Clinical trials – essential features

3. The use of a control group in addition to an experimental group
   – For medical devices, the control group can be a concurrent group receiving a standard intervention to which the intervention is compared
   – Could also be an earlier group that did not receive the intervention

4. Subjects assigned to groups randomly

5. Double-blinded studies – what does this mean?

https://www.youtube.com/watch?v=aSP2OMiFxhg
Clinical trials – essential features

6. Adequate size to determine if well-defined end points are found more often in one group

7. Has been approved as ethical in advance by an independent review process
   − Carefully monitored during the trial by an independent review process
   − If trials are run in more than once center, data may emerge about safety or efficacy
   − Want group to have NO vested interest in the continuation of the trial
Clinical trials – ethical issues

• Commencing a clinical trial
  – Limited window in which to commence trials
  – Heart of the problem is defining the window of opportunity for an ethically legitimate clinical trial
  – Freedman says trial should commence when experts disagree despite the evidence
  – Meier model says one should consider/image oneself as a prospective subject and ask whether one would be willing to volunteer to be in the trial
  – “BNG-331 model”?

• Defining study population
  – Can bring individual subjects benefits as well as burdens
  – Underrepresentation of women and minorities
Clinical trials – ethical issues

• Selection of the control group
  – Concurrent control group is preferred, but there are times when it would be unethical to have one and only can use historical controls
  – Equivalence testing vs determining if something is better
  – Special context of running clinical trials of inexpensive but promising therapies in less developed countries when there already exists an expensive successful therapy available is developed countries
Clinical trials – ethical issues

- The AMA is discouraging the use of placebo control groups for trials concerning illnesses that produce severe or painful symptoms when there are effective treatments available.
- There are some cases where it is ethical to use a placebo-control group and withhold the control group from an established treatment:
  - such as cases where the established therapy has significant side effects,
  - or the disease process being treated is not that important.