Post Doc workshop 2 prep

Please come in with notes prepared on the following prompts. This should take about 45 minutes. After the prompt in this document, I have prepared an example to help guide you through answering these prompts. Please try to answer to the best of your ability and use market reports to try and answer marketing questions. Marketing report databases can be found on the Clemson library website and work exactly like web of science, pubmed, or other journal databases we use for our own literature reviews.

- Detailed description of how your research can be used to better the lives of a target end user
  - Who is your end user?
  - What problem do these end users have?
  - What exists already to solve this problem? How do users deal with the problem now?
  - Detailed description of functions and features of a solution necessary to solve your target user’s problem. **No solutions should be presented here, only qualitative descriptions of necessary features or functions an arbitrary solution should have to solve that target user’s problem.**
  - How is your research exactly going to help the user in fulfilling these functional requirements from the question above? Use detail here. Envision an embodiment (product or service) and how the user physically interacts/accesses this product or service and gets continued value.
  - How do your target users obtain your solution? How do they discard after use? How does your solution maintain itself?
  - How many target users are there in the next 5 years? What are the industry dynamics (regulatory, revenue model, existing big companies, etc.) that are going to increase time to market?

- Detailed experimental design to test solution against controls. Should contain all protocols, timelines, and item lists with prices.
- Detailed description of how your research can be used to better the lives of a target end user

Our laboratory has developed a novel treatment method to make more durable cardiovascular materials. We are focused on using our fabrication method to make more durable heart valve replacements.

- Who is your end user?

Our end users are heart valve replacement recipients. There are three types of heart valve recipients – Elderly patients (75+ yrs old), young patients (20-55 yrs old), and pediatric patients (below 20 yrs of age). Each end user has different needs based on durability due to the expected physical activity of the given end user.

- What problem do these end users have?

Heart valve replacements are necessitated due to a plethora of conditions. Over 300,000 heart valve replacements occur domestically every year. In elderly patients, valve stenosis caused by calcification of the valves or normal degenerative valve disease as a person ages is a common cause necessitating intervention. Younger patients can also develop these disease states early or have early deterioration of the valve necessitating replacement. Damage due to over stressed cardiovascular systems due to conditions like congestive heart failure also result in heart valve replacement. In developing countries, rheumatic fever and other disease states that attack the collagen types in heart valve materials also necessitate heart valve replacements. Pediatric patients needing heart valve replacements often have congenital conditions that have compromised the native heart valve or have been ill with rheumatic fever.

Elderly patients experience compromised heart valve replacements within 10-15 years due to restenosis (valve recalcifies) and structural degradation (valves start to fall apart). These require reoperation which the patient is often not able to do because heart valve replacements require open heart surgery.

Young patients heart valve replacement recipients experience much more accelerated calcification and structural degradation than elderly patients (within 3-5 years) simply due to more activity and competent immune systems. Though a young patient can survive an open heart surgery for successive heart valve replacements, each surgery gets riskier and riskier for an implant that lasts half or a third as long in an elderly patient. Young patients are also eligible for a mechanical heart valve replacement that is much more durable however requires lifelong anticoagulants. Anticoagulants are blood thinners and are the same active ingredients in rat poison (warfarin or Coumadin) and essentially bars you from physical activity. You’re essentially giving yourself hemophelia.

Pediatric patients heart valve recipients often have congenital disease or have suffered from rheumatic fever. Their heart valve replacements cannot grow with them nor these heart valve replacements survive past 3-5 years.

- What exists already to solve this problem? How do users deal with the problem now?
There are two types of heart valve replacements currently on market. The preferred market gold standard is bioprosthetic heart valves that comprise of chemically crosslinked bovine pericardium formed into a shape of a native heart valve. These valves mimic native valve behavior well and do not require lifelong anticoagulants. However, these valves tend to heavily calcify and structurally degrade after several years ending in catastrophic failure.

Another option is mechanical heart valves. Mechanical heart valves are comprised of a completely synthetic, man-made materials that will last long past the expected lifespan of the patient. However, these mechanical valves require lifelong anticoagulants which will compromise the patient in about the same time frame as a bioprosthetic valve degrades itself.
- Detailed description of functions and features of a solution necessary to solve your target user’s problem. **No solutions should be presented here, only qualitative descriptions of necessary features or functions an arbitrary solution should have to solve that target user’s problem.**

A new, alternative solution to heart valve replacements should do the following:

**Must haves:**
- Mimic native-like valve behavior
- Be biocompatible – it must not adversely affect the biology, resist calcification, and chemical degradation
- Be structurally durable – it must not succumb to cyclic loading
- Be able to be implanted into the human body – no toxic chemicals or leechables or materials easily degraded by the body
- No anti-coagulants required
- Must be clinician approved
- Must have 16 month shelf life in sterilization agent
- Must be transported over long distances

**Nice to haves:**
- Fits current surgical procedures and clinician workflow
- Uses current instrumentation clinicians are familiar with
- Fits current manufacturing processes and can be easily adopted by manufacturer

**How is your research exactly going to help the user in fulfilling these functional requirements from the question above? Use detail here. Envision an embodiment (product or service) and how the user physically interacts/accesses this product or service and gets continued value.**

Our novel treatment method is a sequential, stepwise series of immersing bovine pericardium to crosslink it. Current manufacturing processes can be used and all surgical protocols and instrumentation can be used. The entire value chain of getting a heart valve replacement to the hospital and implanted into a patient stays the same.

**How do your target users obtain your solution? How do they discard after use? How does your solution maintain itself?**

Target users obtain heart valve replacements through normal means – diagnosis and referral from a doctor for valve replacement. Users do not discard after use – it is a permanent, implanted device. The heart valve replacement is self sustaining.

**How many target users are there in the next 5 years? What are the industry dynamics (regulatory, revenue model, existing big companies, etc.) that are going to increase time to market?**
300k replacements each year in US. 600k internationally. Expected to rise next 15 years due to cardiovascular disease. Over 2.1 million young adults and children due to rheumatic fever currently needing a heart valve replacement that cannot obtain one because they do not live in a country that sells heart valve replacements.

A heart valve replacement is a medical device and thus heavily regulated by FDA. Once FDA approval is obtained, reimbursement codes for health insurance will need to be obtained before the valve can be sold to hospitals. Hospitals buy the heart valves from the manufacturer and the hospitals are reimbursed for the valve after a replacement occurs through a patient’s health insurance company.

There are currently three major producers of heart valve replacements – Edwards life sciences, Medtronic, and st jude. Because they own so much of the market share in a highly regulated market, we will most likely have to partner with one of them to push a heart valve replacement solution to market.

- Detailed experimental design to test solution against controls. Should contain all protocols, timelines, and item lists with prices. Example data is an abbreviated form.

**Specific Aims**

- Obtain manufactured TRI bovine pericardium from a verified supplier to other tissue based heart valve replacement producers
- Verification studies comparing market standards to manufactured TRI bovine pericardium
  - Small animal biocompatibility studies
  - In vitro mechanical testing for creep and mechanical properties
  - Preliminary data to test for cytotoxicity in line with 10993 testing

**General outline of project plan**

- **Specific Aim 1**
  - Disseminate treatment protocol to manufacturing partner
  - Incorporate treatment protocol into manufacturing process
  - Manufacture uniform batch of TRI material
- **Specific Aim 2**
  - Obtain commercially available materials → 60 days total; $50k
    - Glutaraldehyde crosslinked tissue based bovine pericardium; 30 days; $40k
    - Polymer heart valve replacement materials → 21 days; $10k
  - Subaim 2.1
    - 90 day calcification study in juvenile rats comparing (GLUT, TRI, Polymer) → 101 days total; $30k
    - Analyze samples for calcification and biocompatibility → 21 days total; $10k
      - ICP - quantification of calcification → 4 days; $1k
      - microCT - visualize localization of calcification on whole implant → 1 day; $2k
      - Alizarin red - visualization of calcification through cross section → 6 days; $1k
      - HE for gross anatomy and general biocompatibility → 6 days; $1k
      - Leccheables → 14 days; $1k
• Subaim 2.2
  • Suture pull out test → durability → 2 days; $1k
  • Biaxial tensile testing → mechanical properties → 7 days; $2k
  • Creep test → permanent geometric deformations → 41 days; $5k
• Subaim 2.3
  • In vitro contact studies → 60 days; $5k
  • In vitro leechables studies → 60 days; $5k
  • In vitro blood compatibility studies → 5 days; $5k
  • Small animal data from subaim 2.1
  • Degradation products?