

Product Design Specifications

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Problem Statement:

A method of treatment for various endocrine diseases incorporates the encapsulation of cells and tissues and the time-released delivery of chemical mediators. Presently, this method encounters a slew of problems, including a lack of biocompatibility, limited immunoprotective properties, and hypoxia. The client desires the development of microcapsules that would permit the successful release of hormones (namely, testosterone and inhibin) by encapsulated cells into animals, while avoiding the aforementioned problems.

Function:

Microcapsules should allow transplantation of hormone-releasing tissue without the use of immunosuppressant drugs by providing a mechanical barrier to immune system attack.

Client requirements:

- Microencapsulation of reproductive hormone-producing cells
- Must release molecules of interest (hormones) over time, while keeping harmful molecules (antibodies, etc.) out
- Biocompatible, immunoprotective, minimize mechanical, and chemical degradation

Design requirements:

Physical and operational characteristics

- Viability*: The encapsulation process may have adverse effects on initial cell viability in microcapsules. The proposed design should retain at least 75% cell viability measured 1 d post-encapsulation using a Live/Dead® assay.
- Hormone release*: Normal values of testosterone in human males is 2-12 ng/mL. Microencapsulated cell therapy should maintain serum testosterone concentrations of at least 2 ng/mL in patients, with contributions from both transplanted cells and patients' baseline testosterone secretion.
- Degradation*: The biomaterial should remain intact long enough to sustain a critical cell mass, such to provide adequate hormone release for at least 6 months.
- Capsule size*: Diameter of microcapsules should be such that 100 ± 20 μm describes 90% of the capsule distribution. Sufficient diffusion of gases and nutrients is limited beyond 100 μm (Murphy, 2005, personal communication).
- Molecular weight cutoff (MWCO)*: MWCO should be 75 kDa in order to allow diffusion of relevant molecules, specifically testosterone (300 Da), inhibin (32

kDa), activin, LH (30 kDa), FSH (36 kDa), but block antibody (150 kDa) diffusion.

- f. *Immune response*: Microcapsules must not allow the diffusion of antibodies (molecular weight ~150 kDa) or immune system cells by providing a sufficiently small mesh size.
- g. *Biocompatibility*: Biomaterial and its degradation products must be nontoxic and not cause inflammation within the body. Injected microcapsules must resist protein adsorption and fibroblast overgrowth. Previous designs suffer from fibroblast overgrowth resulting in cell graft death due to hypoxia (de Groot *et al.*, 2004). In addition, the microcapsule production process including droplet formation and biomaterial crosslinking (if required) should be sufficiently cytocompatible.
- h. *Life in service*: Therapy should sustain patient at minimum serum testosterone concentration (at least 2 ng/mL) for at least 6 months.
- i. *Production timeframe*: Microencapsulated cell therapy, at present, will be prepared from start to finish as needed by patient demand. Microencapsulated cells will be implanted soon after production. The microencapsulated cells should be sustainable *in vitro* for at least several days.
- j. *Operating environment*: *In vivo*, site of implantation to be determined. Subcutaneous and intraperitoneal injections are both possible (Machluf *et al.*, 2003).

Product characteristics:

- a. *Quantity*: Thousands to hundreds of thousands of microcapsules will be required per injection. The cell mass required to provide adequate hormone release is currently unknown, but likely on the order of 10^6 cells. Previous studies in rats used 5×10^6 cells in transplant therapies (Machluf *et al.*, 2003).
- b. *Sterility*: Final product must be sterile prior to implantation.
- c. *Target product cost*: Not specified.
- d. *Research costs*: A budget of approximately \$10,000 to \$20,000 has been reserved for research and development of working microcapsule designs.

Miscellaneous:

- a. *Standards and specifications*: FDA approval is required. University approval required prior to animal or human subject testing.
- b. *Competition*: Several patents regarding cell encapsulation exist and define specific production protocols. These are US Patent 5,762,959, US Patent 5,100,673, and US Patent 5,164,126. This study is not expected to infringe upon past technology as a novel capsule design is desired.