Modulation of Host Response by Anti-inflammatory Drugs to Improve the Efficacy of Immuno-isolated islets in Diabetes Therapy.

Tram T. Dang[1,2,3], Anh V. Thai[1,3], Joshua Cohen[5], Jeremy E. Slosberg[1,3], Karolina Siniakowicz[5], Joshua C. Doloff[1,3], Minglin Ma[1,3], Jennifer Hollister-Lock[5], Katherine Tang[1,3], Zhen Gu[1,3], Hao Cheng[1], Gordon Weir[5], Robert Langer[1] and Daniel G. Anderson[1].

(1) Massachusetts Institute of Technology. (2) Brigham & Women's Hospital, Harvard Medical School. (3) Department of Anesthesiology, Children's Hospital Boston. (5) Joslin Diabetes Center, Harvard Medical School.

Statement of Purpose: Foreign body response leads to the formation of fibrotic cell layers which can impair essential functions of implantable medical devices. Anti-inflammatory drugs have the potential to overcome this challenge and improve device durability. This study aims to identify small molecule anti-inflammatory agents to be incorporated in hydrogel microcapsules encapsulating pancreatic islets for improved efficacy in diabetes therapy.

Methods: PLGA particles with or without anti-inflammatory drugs were fabricated using a water-in-oil emulsion method. Each formulation of drug-loaded particles was subcutaneously injected on the back of immunocompetent SKH1E mice as shown in the injection scheme (Fig. 1A). At selected time points during the first 14 days, each mouse was imaged in a Xenogen IVIS spectrum system after administration of Prosense-680 or luminol. These mice were sacrificed on day 28 and the polymer microparticles were retrieved for histological analysis. Hybrid alginate microcapsules co-encapsulating selected drugs and pancreatic rat islets were fabricated using an electrostatic droplet generator. These capsules were transplanted via a lapratomy into C57B6J streptozotocin-induced diabetic mice. These mice were monitored daily for blood glucose levels and were eventually sacrificed after two months to retrieve the encapsulated islets for fibrosis assessment.

Results: We performed *in vivo* screening of 16 small molecule anti-inflammatory drugs encapsulated in PLGA microparticles (each drug at three different loadings) by subcutaneous injections in immunocompetent hairless mice. Parallel non-invasive fluorescent and bioluminescent imaging of these mice during the acute inflammation phase showed that several steroidal drugs effectively inhibited the activities of inflammatory proteases (Fig. 1B) while a polyphenol drug significantly decreased the presence of reactive oxygen species (Fig. 1C) secreted by early immune cells. Histology analysis also showed that several steroidal drug formulations reduced cellular infiltration into the polymer microparticles for up to 4 weeks post-injection while the polyphenol compound also minimized the host response for up to 2-3 weeks. Next, we designed hybrid alginate hydrogel capsules co-encapsulating pancreatic rat islets and the selected drugs (Fig. 1D-F) and evaluate their efficacy in comparison with conventional capsules, using a mouse model of chemically-induced type I diabetes. Islets co-encapsulated with the polyphenol drug were able to maintain better glycemic control and prolonged graft survival in diabetic mice (approximately 30 days compared to 15 days for the control capsules). These capsules also had a significant reduction in the formation of fibrotic cell layers.

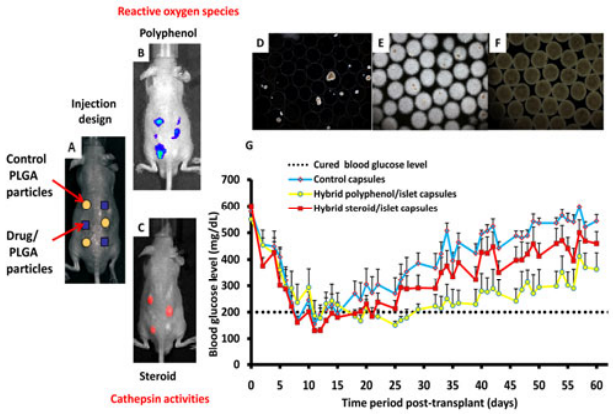

Figure 1. Anti-inflammatory drugs inhibit subcutaneous foreign body response and improve the efficacy of encapsulated islets in diabetes therapy. (A) Injection pattern showing sites of PLGA particles without (●) and with (■) drug. (B): Inhibition of reactive oxygen species by a polyphenol drug. (C): Inhibition of cathepsin activity by a steroidal drug. (D-F): Alginate microcapsules without any drug (D), with a steroidal drug (E) and a polyphenol drug (F). (G): Improved glycemic control and prolonged graft function by islets co-encapsulated with a polyphenol drug.

Conclusions: In this study, we identified promising anti-inflammatory drugs which inhibit the activities of inflammatory proteases as well as reactive oxygen species secreted from early immune cells. These drugs also decreased subsequent cellular infiltration and fibrosis formation surrounding subcutaneously injected polymeric microparticles. We further demonstrated that the selected drug can reduce fibrotic response against encapsulated islets and improve their efficacy in diabetes therapy. The drugs identified from our *in vivo* screening also have potential applications for a broad range of medical devices such as implantable glucose sensors and encapsulated cells for the treatment of neurodegenerative diseases and growth hormone deficiency.