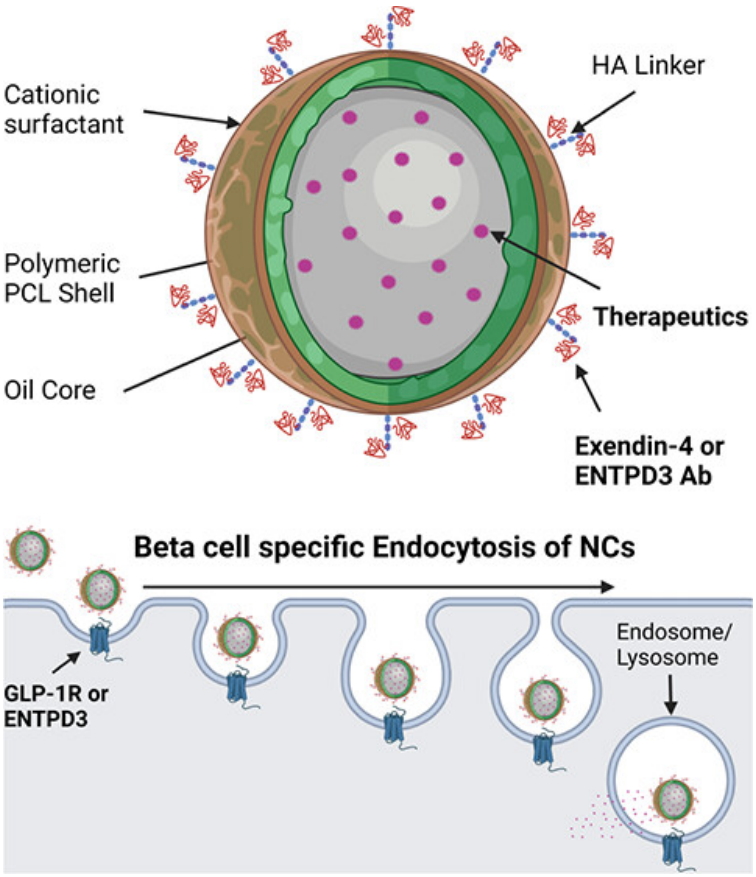
Peptide-Coated Polycaprolactone-Benzalkonium Chloride Nanocapsules for Targeted Drug Delivery to the Pancreatic *β*-Cell

Jillian Collins, Jessie M. Barra, **Keifer Holcomb**, Andres Ocampo, Ashton Fremin, Austin Kratz, Jubril Akolade, Julianna K. Hays, Ali Shilleh, Amit Sela, David J. Hodson, Johannes Broichhagen, Holger A. Russ, and Nikki L. Farnsworth*

ABSTRACT: Targeting current therapies to treat or prevent the loss of pancreatic islet *β*-cells in Type 1 Diabetes (T1D) may provide improved efficacy and reduce off-target effects. Current efforts to target the *β*-cell are limited by a lack of *β*-cell-specific targets and the inability to test multiple targeting moieties with the same delivery vehicle. Here, we fabricate a tailorable polycaprolactone nanocapsule (NC) in which multiple different targeting peptides can be interchangeably attached for *β*-cell-specific delivery. Incorporation of a cationic surfactant in the NC shell allows for the attachment of Exendin-4 and an antibody for ectonucleoside triphosphate diphosphohydrolase 3 (ENTPD3) for *β*-cell-specific targeting. The average NC size ranges from 250 to 300 nm with a polydispersity index under 0.2. The NCs are nontoxic, stable in media culture, and can be lyophilized and reconstituted. NCs coated with a targeting peptide were taken up by human cadaveric islet *β*-cells and human stem cell-derived *β*-like cells (sBC) in vitro with a high level of specificity. Furthermore, NCs successfully delivered both hydrophobic and hydrophilic cargo to human *β*-cells. Additionally, Exendin-4-coated NCs were stable and targeted the mouse pancreatic islet *β*-cell in vivo. Overall, our tailorable NCs have the potential to improve cell-targeted drug delivery and can be utilized as a screening platform to test the efficacy of cell-targeting peptides.



***Corresponding Author**

- Nikki L. Farnsworth− Department of Chemical and Biological Engineering, Colorado School of Mines, Golden, Colorado 80401, United States; orcid.org/0000-0002-9834-9168; Email: nfarnsworth@mines.edu

Authors

- Jillian Collins− Department of Chemical and Biological Engineering, Colorado School of Mines, Golden, Colorado 80401, United States
- Jessie M. Barra− Department of Pharmacology and Therapeutics, Diabetes Institute, University of Florida, Gainesville, Florida 32610, United States
- Keifer Holcomb− School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado 80045, United States
- Andres Ocampo− Department of Chemical and Biological Engineering, Colorado School of Mines, Golden, Colorado 80401, United States
- Ashton Fremin− Department of Chemical and Biological Engineering, Colorado School of Mines, Golden, Colorado 80401, United States
- Austin Kratz− Department of Pharmacology and Therapeutics, Diabetes Institute, University of Florida, Gainesville, Florida 32610, United States
- Jubril Akolade− Department of Chemical and Biological Engineering, Colorado School of Mines, Golden, Colorado 80401, United States
- Julianna K. Hays− Department of Chemical and Biological Engineering, Colorado School of Mines, Golden, Colorado 80401, United States
- Ali Shilleh− Centre for Diabetes, Endocrinology and Metabolism (OCDEM), NIHR Oxford Biomedical Research Centre, Churchill Hospital, Radcliffe Department of Medicine, University of Oxford, Oxford OX39DU, United Kingdom
- Amit Sela− Department of Chemical and Biological Engineering, Colorado School of Mines, Golden, Colorado 80401, United States
- David J. Hodson− Centre for Diabetes, Endocrinology and Metabolism (OCDEM), NIHR Oxford Biomedical Research Centre, Churchill Hospital, Radcliffe Department of Medicine, University of Oxford, Oxford OX39DU, United Kingdom
- Johannes Broichhagen− Leibniz-Forschungsinstitutfür Molekulare Pharmakologie, Berlin13125, Germany; orcid.org/0000-0003-3084-6595
- Holger A. Russ− Department of Pharmacology and Therapeutics, Diabetes Institute, University of Florida, Gainesville, Florida 32610, United States