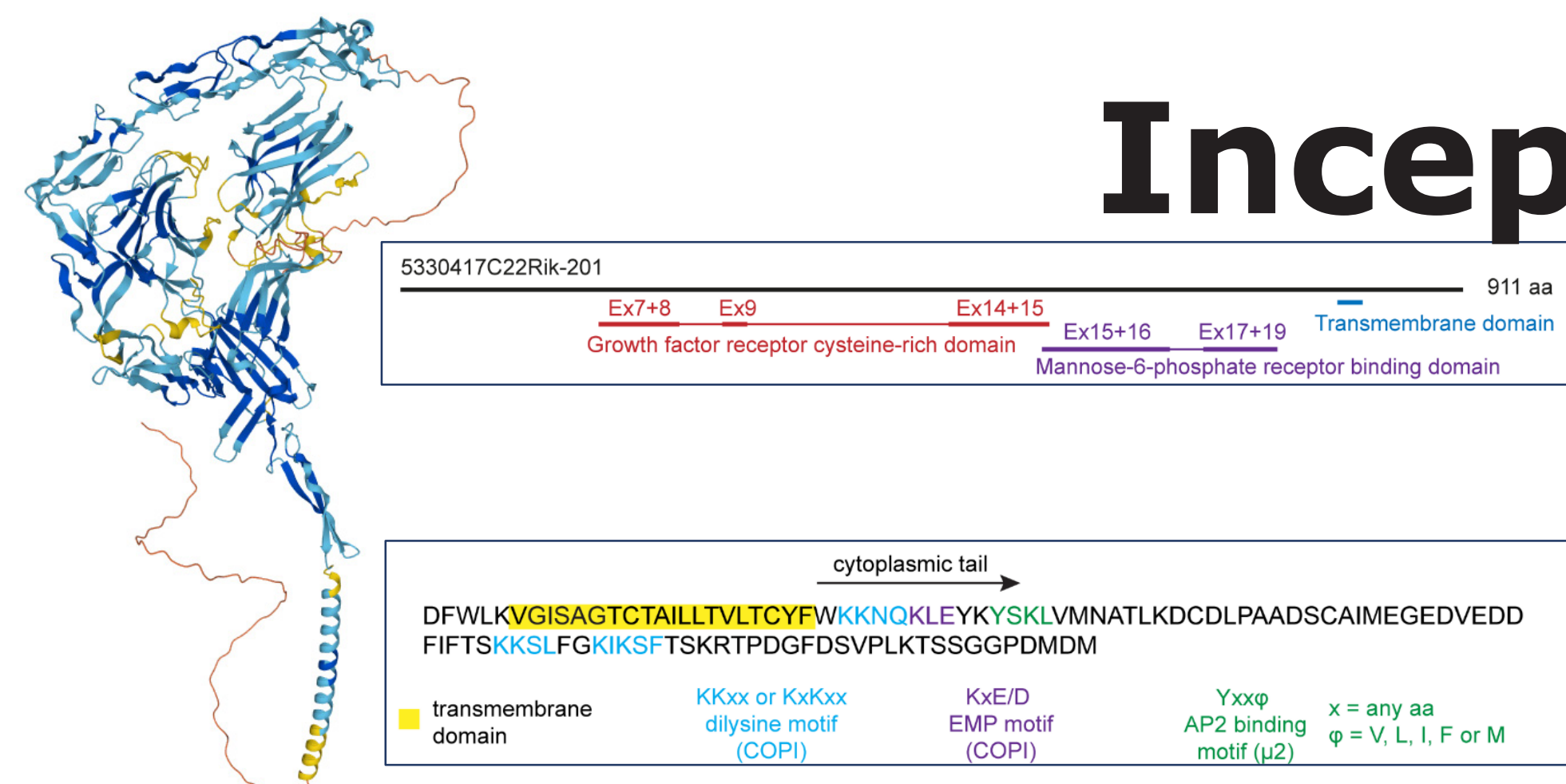
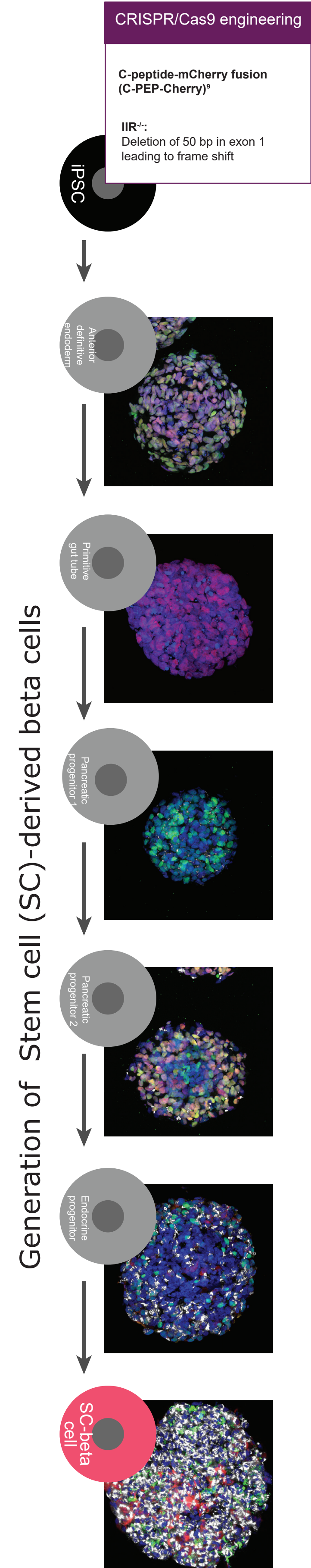


Inceptor Binds and Directs Insulin to Lysosomal Degradation in Beta Cells



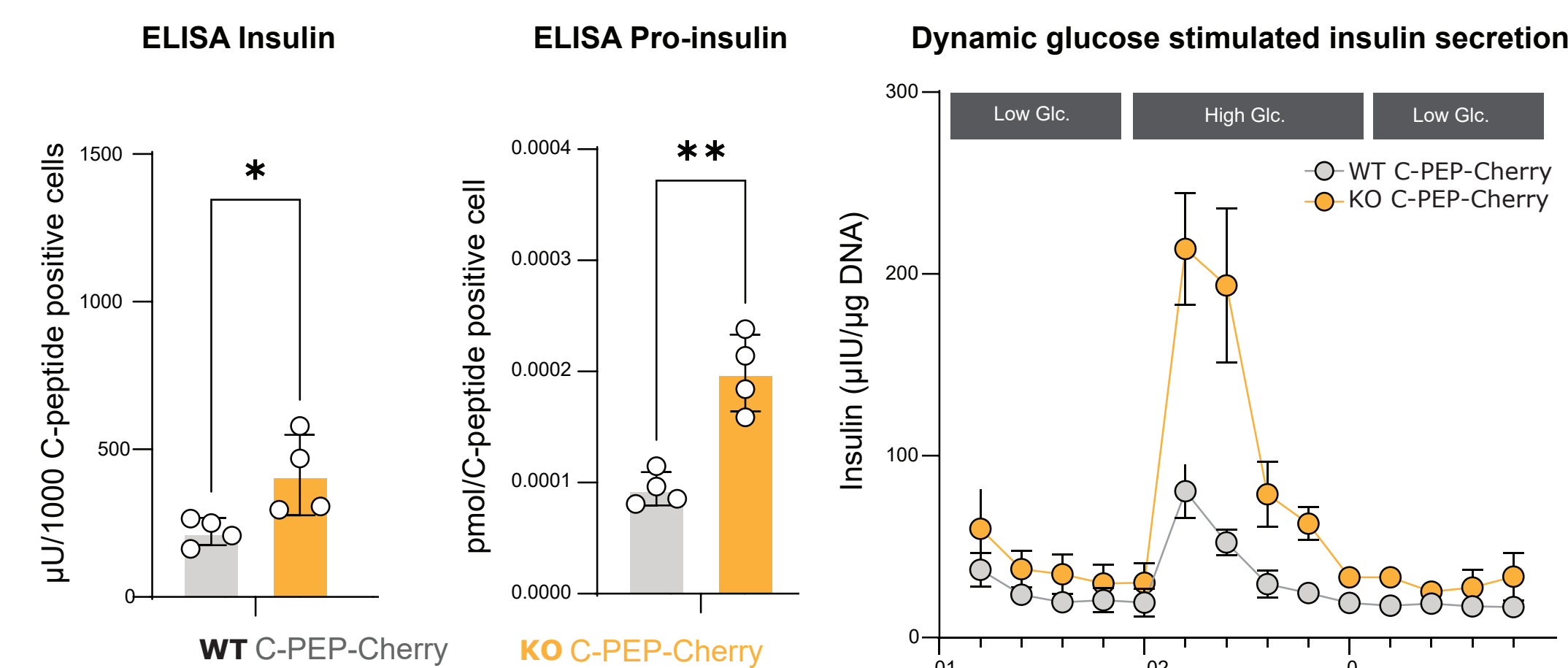
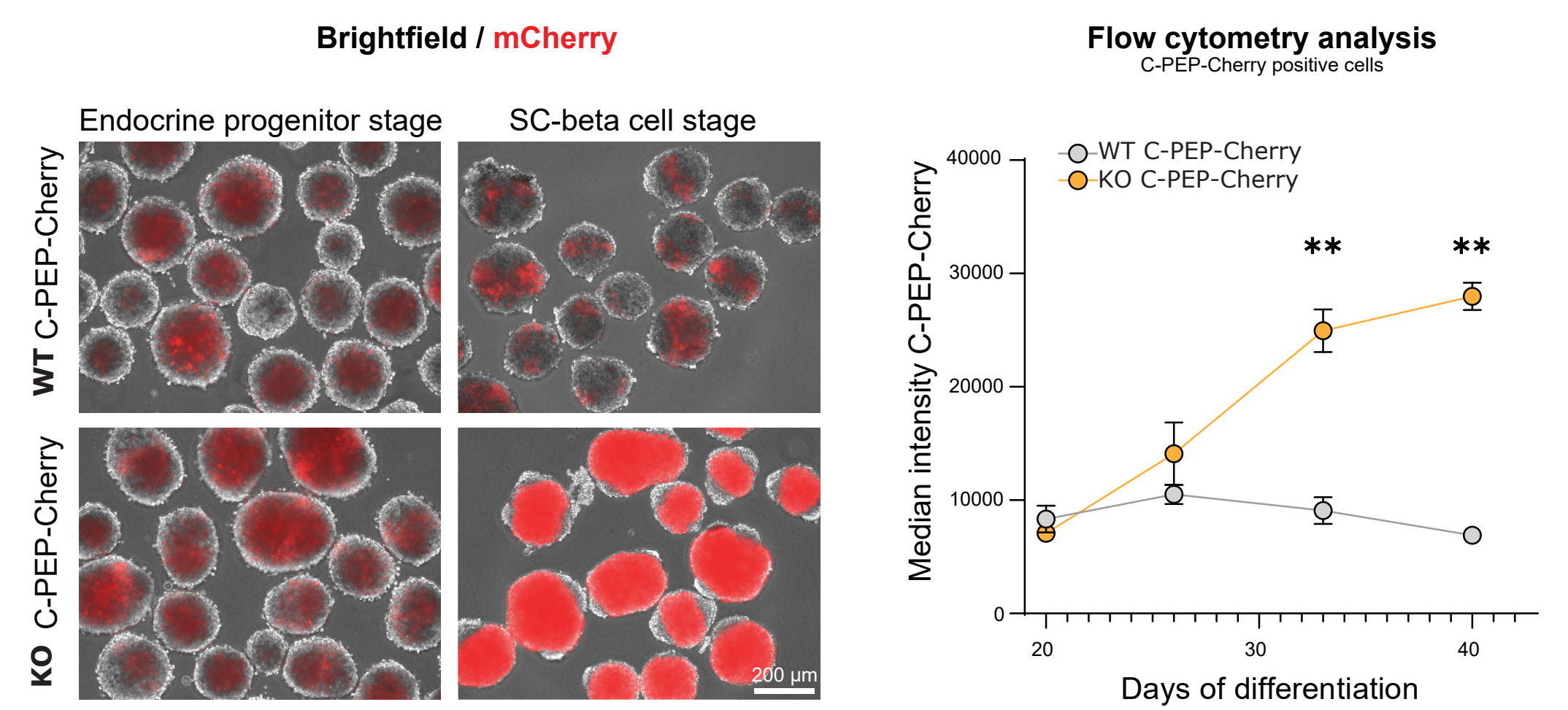
Johanna Siehler^{1,2,3,4}, Prisca Chapouton^{1,3,4}, Sara Bilekova^{1,3,4}, Federico Ribaudo^{1,3,4}, Sreya Bhattacharia^{1,3,4}, Chetna Malhotra^{1,3,4}, Thomas Kurth⁵, Ingo Burtscher^{1,2,3,4}, Heiko Lickert^{1,2,3,4}
 1- Institute of Diabetes and Regeneration Research, Helmholtz Center Munich, Neuherberg, Germany, 2- Institute of Stem Cell Research, Helmholtz Center Munich, Neuherberg, Germany 3- Technical University of Munich, Medical Faculty, Munich, Germany 4- German Center for Diabetes Research (DZD), Neuherberg, Germany 5- Center for Molecular and Cellular Bioengineering, Technology Platform, Technische Universität Dresden, Dresden, Germany

Inceptor in Alpha Fold



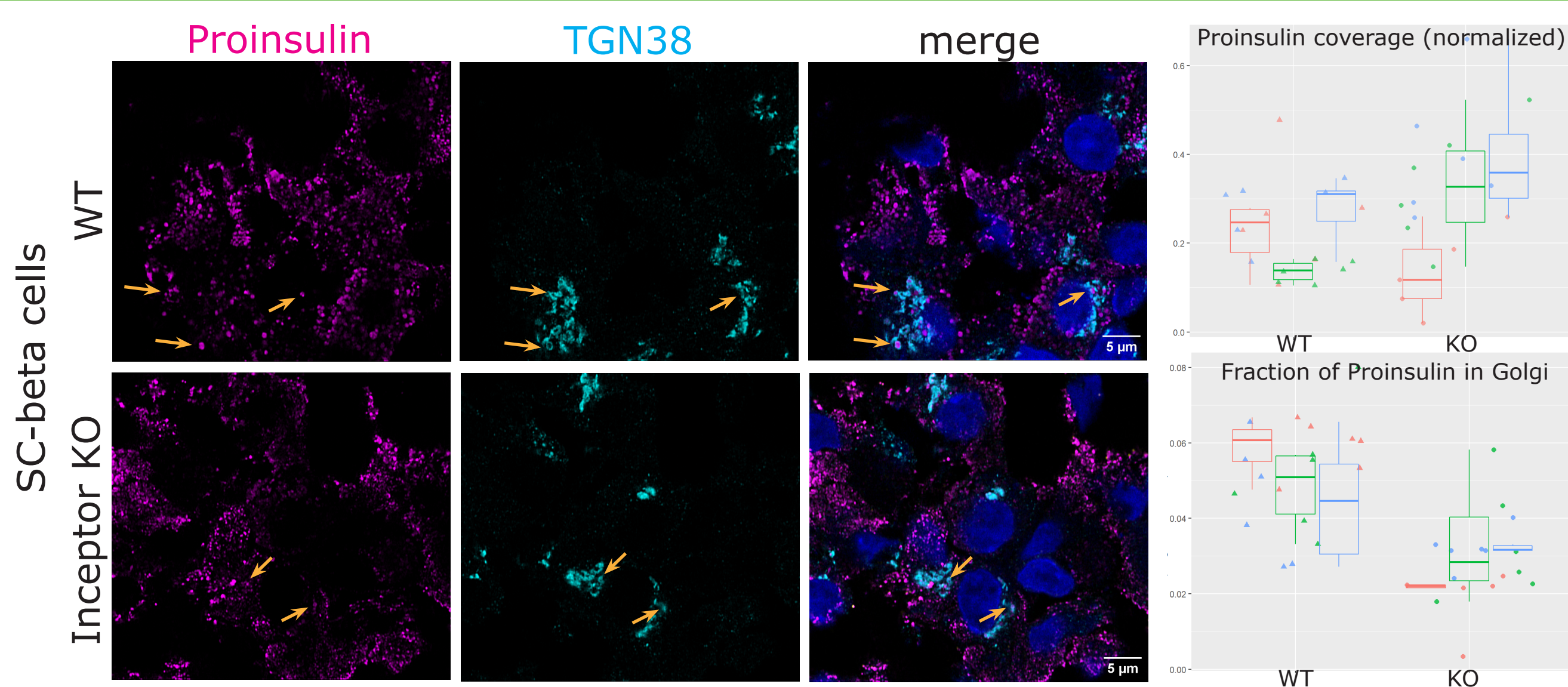
Beta cells are endocrine secretory cells of the pancreas that produce the hormone insulin via its precursor proinsulin, sorted from the Golgi into nascent secretory granules. C-peptide is excised out of proinsulin, giving rise to insulin. Besides insulin, inceptor (Insulin Inhibitory Receptor) is a major component of beta cells and its function at the plasma membrane in insulin receptor desensitization has been deciphered in Ansarullah et al., Nature, 2021. We are elucidating here further intracellular functions of inceptor at the the trans-Golgi-network and nascent secretory granules.

(Pro) insulin stores and insulin secretion are increased upon inceptor deletion in SC-derived beta cells



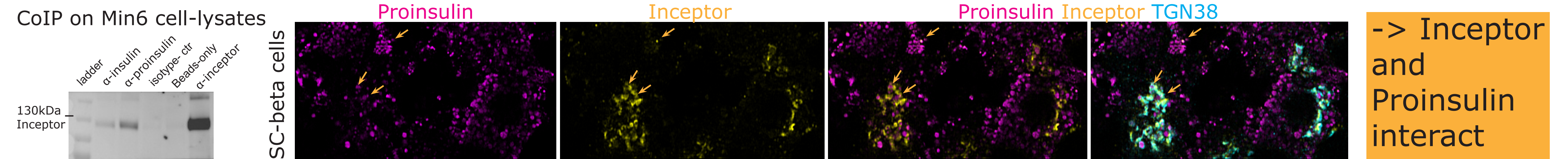
-> How does the Proinsulin increase come about?
 -> Not due to translation -> Which mechanism?

The fraction of Proinsulin localization at the Golgi is decreased upon inceptor deletion in SC-derived beta cells

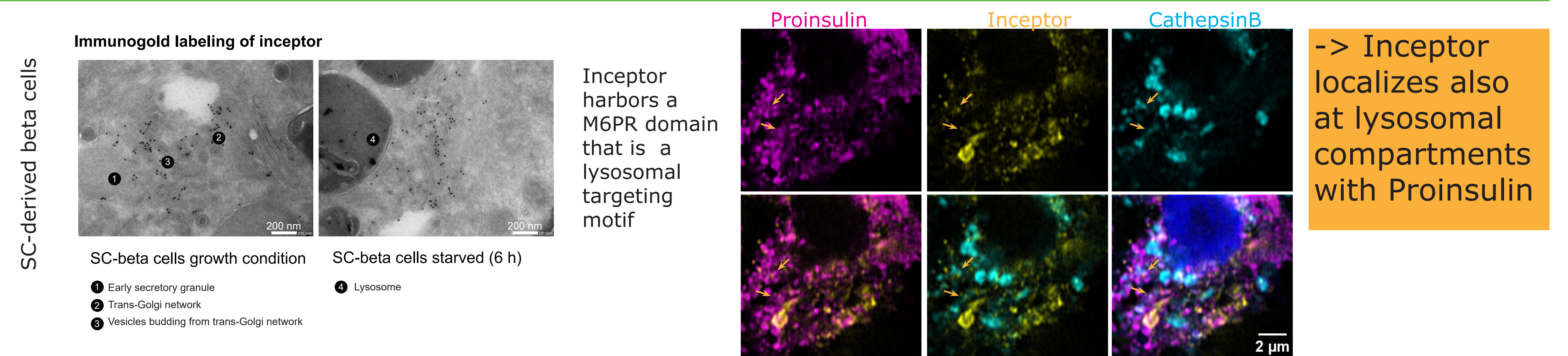


-> Where does Proinsulin accumulate? Could the degradation of Proinsulin become impaired in the absence of Inceptor?

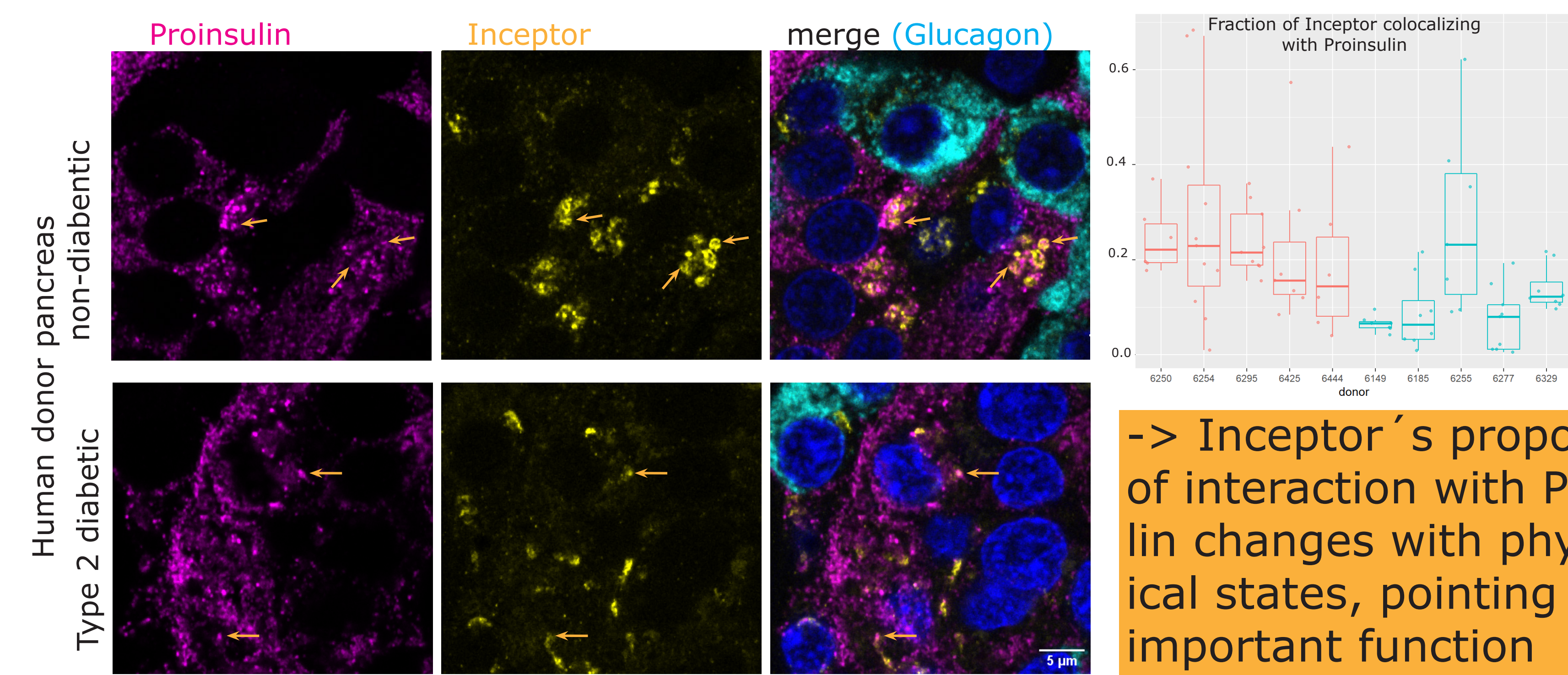
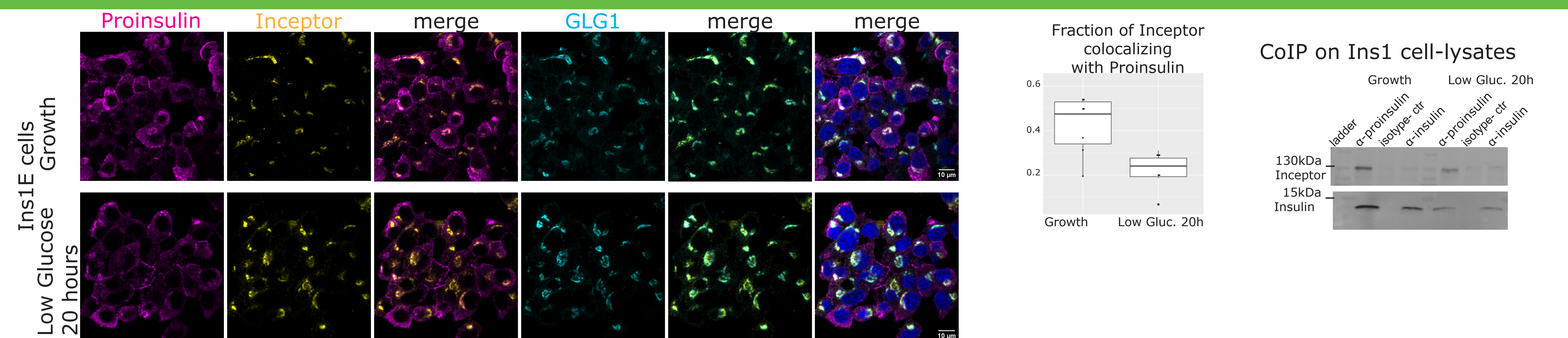
Inceptor co-immunoprecipitates with Proinsulin and they co-localize mainly at the TGN



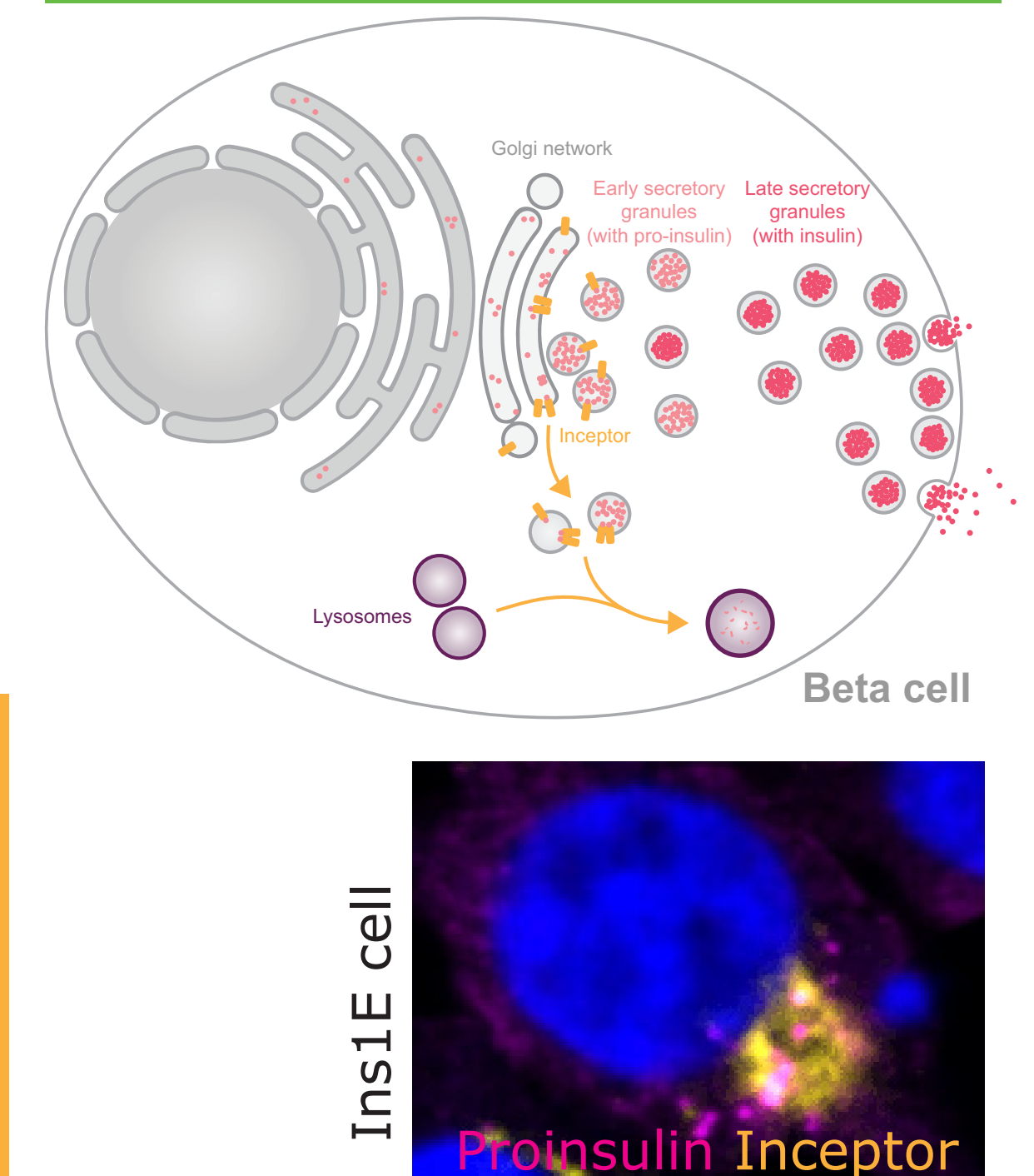
Inceptor, Proinsulin and the lysosomal marker Cathepsin localize closely



Inceptor interaction with Proinsulin is subject to modulations (Ins1 cell line and human pancreatic donor tissue)



Working Model



-> Inceptor's proportion of interaction with Proinsulin changes with physiological states, pointing to an important function