

Prospects and Challenges for Islet Regeneration as a Treatment for Diabetes: A Review of Islet Neogenesis Associated Protein

Alexander Fleming, M.D.¹ and Lawrence Rosenberg, M.D., Ph.D.²

Abstract

Diabetes mellitus results from inadequate insulin action, which can be viewed as a consequence of the limited ability to restore β cells after they are lost as the result of metabolic exhaustion, autoimmune destruction, or surgical insult. Arguably, a uniformly effective therapeutic pathway to address all forms of diabetes would be to reverse the restrictions on β -cell and islet regeneration. The development from progenitor cells of islets with normal endocrine function does occur in adult humans; it is referred to as islet neogenesis. The induction of islet neogenesis is an important, if not essential, therapeutic approach for curing type 1 diabetes mellitus (T1DM) and could be valuable in the treatment of type 2 diabetes mellitus (T2DM) as well.

Islet neogenesis associated protein (INGAP) is the first therapeutic candidate to be identified as the result of a purposeful search for an endogenous molecule with islet neogenic activity. It was found that partial obstruction of the pancreatic duct in hamsters induced islet neogenesis; under this condition, a neogenesis-promoting activity was identified and partially purified from a soluble tissue fraction. A 168-kDa protein product of the cloned gene was found to be responsible for the neogenesis activity. This molecule named INGAP contains an active core sequence of amino acids called INGAP peptide. Results from *in vitro*, animal, and human studies suggest that INGAP and INGAP peptide are neogenic in at least several vertebrate species, including humans. INGAP has since been found to be a member of the family of Reg proteins, which are found across and in multiple versions within species and are closely associated with embryonic and regenerative processes.

Clinical results suggest that INGAP peptide can be a suitable neogenesis therapy, but optimization of the therapy and more data are required to fully access this potential. Understanding of the signaling pathways of INGAP and other related Reg proteins is a promising means of advancing therapeutic development for people with T1DM and T2DM. The quest for the fundamental restorative approach to lost insulin secretion is an enticing target for drug development.

J Diabetes Sci Technol 2007;1(2):231-244

Author Affiliations: ¹Kinexum Metabolics, Inc., Harpers Ferry, West Virginia, and formerly Supervisory Medical Officer, Division of Metabolic and Endocrine Drug Products, Food and Drug Administration; and ²Department of Surgery, McGill University, and Centre for Pancreatic Diseases, Research Institute of the McGill University Health Centre, Montréal, Québec, Canada

Abbreviations: (CK+) cytokeratin positive, (DLS) duct-like structures, (FANs) focal areas of neogenesis, (GLP-1) glucagon-like peptide-1, (IGF-1) insulin-like growth factor-1, (INGAP) islet neogenesis associated protein, (ILS) islet-like structures, (NOD) nonobese diabetic, (PDX-1) pancreatic and duodenal homeobox gene-1, (T1DM) type 1 diabetes mellitus, (T2DM) type 2 diabetes mellitus

Keywords: INGAP, islet neogenesis, pancreatic plasticity, regeneration, diabetes, Reg

Corresponding Author: Lawrence Rosenberg, M.D., Ph.D., MEng, Montreal General Hospital C9-128, 1650 Cedar Avenue, Montréal, Québec, H3G 1A4, Canada; email address lawrence.rosenberg@mcgill.ca