

W0523

Scaffolding Protein Islet-brain 1 Homodimerization. Michael Gajhede¹, Sylvie Guenat², Imran Dar¹, Jette S. Kastrup¹, Christophe Bonny², Ole Kristensen¹, ¹Biostructural Research, Dept. of Medicinal Chemistry, The Danish Univ. of Pharmaceutical Sciences, Universitetsparken 2, DK-2100 Copenhagen, Denmark, ² Unit of Molecular Genetics, University Hospital of Lausanne (CHUV), Falaises 1, 1011 Lausanne, Switzerland.

Islet-brain 1 (IB1 or JIP-1) is a scaffold protein that interacts with components of the JNK signal-transduction pathway. IB1 is expressed at high levels in neurons and in pancreatic β -cells, where it controls expression of insulin-secretory components and secretion. We have shown that IB1 homodimerizes through a novel and unique set of SH3-SH3 interactions¹. X-ray crystallography studies show that the dimer interface covers a region usually engaged in PxxP-mediated ligand recognition, even though the IB1 SH3 domain lacks this motif. The highly stable IB1 homodimer can be significantly destabilized *in vitro* by three point-mutations directed against key residues involved in dimerization. Taken together with *in-vivo* results this indicates that IB1 homodimerization through its SH3 domain has pleiotropic effects including regulation of the insulin secretion process.

1. Kristensen, O., Guenat, S., Dar, I., Allaman-Pillet, N., Abderrahmani, A., Ferdaoussi, M., Roudit, R., Maurer, F., Beckmann, J. S., Kastrup, J. S., Gajhede, M., & Bonny, C. (2006). *EMBO J.* **25**, 785-97