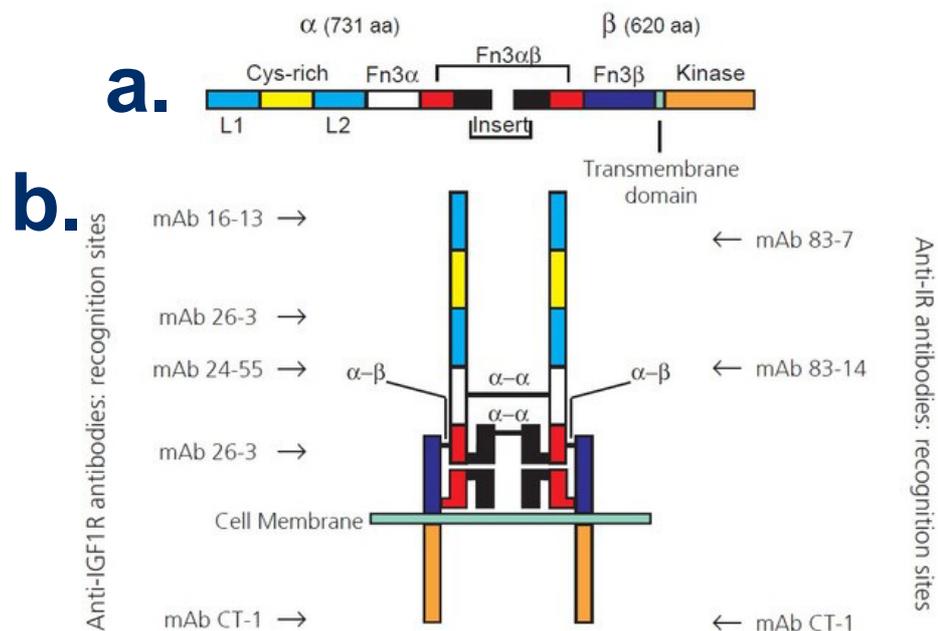


While the Type 1 IGF receptor (IGF1R) and the Insulin receptor (IR) are distinct and separate entities, they share many structural and functional similarities. Both are 420 kDa membrane glycoproteins, made up of the same structural domain components. Both are synthesized as single polypeptide chains and proteolytically cleaved to yield two distinct chains termed α and β , linked by disulphide bonds. The α chain is extracellular, whereas the β chain consists of an extracellular region, a single transmembrane segment and an intracellular tyrosine kinase domain which mediates signal transduction. The extracellular portion of the receptor consists of six structurally independent domains. The first three, namely L1, a cysteine-rich domain, and L2 form the minimal binding fragment of the Receptor and are responsible for the initial low-affinity ($K_d \sim 5 \text{ nM}$) ligand-binding event. C-terminal to the L2 domain are three extracellular fibronectin type 3 modules, one in the α chain (Fn3 α), one in the α - β linking module (Fn3 $\alpha\beta$) (Mulhern et al, 1998) and the third in the β chain (Fn3 β). This third extracellular fibronectin module links through the transmembrane domain to the intracellular tyrosine kinase domain. In hIR, the Fn3 β module contains the proteolytic processing site (residues 759-762) that splits the synthesised polypeptide chain into α and β chains.

The α and β chains form an $\alpha\beta$ heterodimer and two such heterodimers, linked by at least 2 disulphide bonds, associate to form the intact $(\alpha\beta)_2$ receptor (Figure 1). Both IGF1R and IR bind either insulin or the insulin-like family of growth factors on the α chain, but the receptors have greatest affinity for their homologous ligand. Ligand binding is central to receptor activation, regulation and function, and both receptors are involved in cell growth, transformation and apoptosis. The role of each receptor and ligand pair is complicated by the existence of hybrid tetrameric receptors made up of dimers of IR and IGF1R sub-units. De Meyts et al, 1995 and others have proposed that specificity of signalling may be controlled by ligand binding kinetics which affect the lifetime of the activated receptor. The observed range of biological responses undoubtedly reflect the net effect of a range of events at the cell surface and the inter-related cascades of intracellular signalling molecules that vary with cell type and physiological state. Further insights into the structure of these receptors are likely to provide new and exciting directions in the design of therapeutic agents for the treatment of diabetes and cancer.



a. The domain structure of the insulin-receptor family $\alpha\beta$ subunit
b. Diagrammatic representation of the intact Type 1 IGF Receptor and the Insulin Receptor showing the interchain α - α and α - β disulphide bridges. (After Mulhern, et al. 1998)

TECHNICAL BULLETIN #4

Type 1 IGF receptor and Insulin receptor

To help investigate the functions of the Type 1 IGF and Insulin receptors, GroPep have a range of monoclonal antibodies available, directed against different regions of each receptor.

Monoclonal antibodies to the Human Type 1 IGF Receptor (IGF1R):

Antibody	Epitope Recognised	Product Code	Effect on IGF-I Binding ^a
anti-IGF1R 16-13	aa 62-184	MAC1	↑↑
anti-IGF1R 24-55	aa 440-586	MAD1	↓
anti-IGF1R	aa 283-440 or 586-908	MAF1	↑↑
anti-IGF1R CT-1 (IGFR 1-2)	aa 1336-1351	MAJ1	NA

^a Soos, M. A., et al. (1992) J. Biol. Chem. 267, 12955-12963

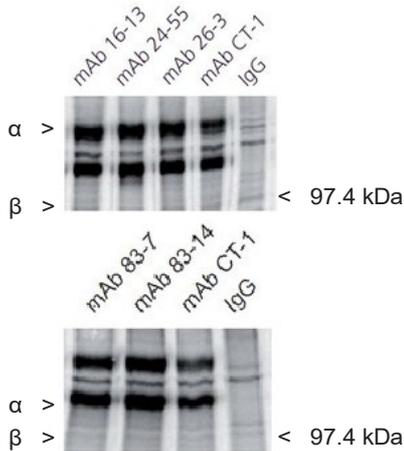
Monoclonal antibodies to the Human Insulin Receptor (IR):

Antibody	Epitope Recognised	Product Code	Effect on Insulin Binding ^b
anti-IR 83-7	aa 140-301	MAG1	↑
anti-IR 83-14	aa 469-592	MAI1	↓↓
anti-IR CT-1	aa 1337-1355	MAH1	NA

^b Soos, M. A., et al, (1986) Biochem. J., 235, 199-208.

- **Immunoprecipitation:** All antibodies (1/5000)
- 200 µg lyophilized aliquots
- **Immunoblotting:** Anti-IGF1R CT-1 & anti-IR CT-1 (1/5000)
- **Cross-reactivity with rat:** anti-IGF1R CT-1 & anti-IR CT-1
- **FACS:** Anti-IGF1R 24-55 (1/5000)

Anti-IGF1R monoclonal antibodies



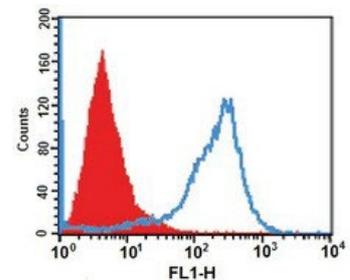
Immunoprecipitation and SDS-PAGE of the α and β receptor sub-units in rat p6 cell lysates.

Lysates made from 35S-labelled p6 cells

overexpressing stably transfected IGF1R (p6 cell line kindly supplied by R. Baserga).

Immunoprecipitation and SDS-PAGE of the α and β receptor sub-units in NIH 3T3 Balb lysates.

Lysates made from 35S-labelled NIH 3T3 HIR 3.5 cells overexpressing stably transfected IR (Whittaker, et al. 1987).



Fluorescence Activated Cell Sorting (FACS) of IGF1R

Analysis performed using anti-IGF1R 24-55 and rat p6 cells overexpressing stably transfected IGF1R (FACS Analysis by Mehrnaz Keyhanfar, University of Adelaide) (p6 cell line kindly supplied by R. Baserga).

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