

# Autoantibodies in Diabetes Mellitus Type 1

Insulin-dependent diabetes mellitus (IDDM) or type 1 diabetes mellitus (T1DM) is a T-cell mediated autoimmune disorder characterized by destruction of the pancreatic beta cells (Ziegler *et al.* 2013). Mostly starting in childhood, this leads to insulin deficiency and metabolic abnormalities, as impaired glucose homeostasis and symptomatic hyperglycemia (Pihoker *et al.* 2005). Patients require lifelong insulin treatment (Landin-Olsson *et al.* 1992).

In the 1970s it was described that beta cell destruction is associated with production of cytoplasmic autoantibodies to islet cells (ICAs) (Bottazzo *et al.* 1974). Using classic diagnostic ICA tests, polyclonal antibodies are detected in app. 85% of children with recently diagnosed T1DM (Winter *et al.* 2002).

In the early 1990s, new antigens were identified including 37/40 kDa tryptic fragments and the Glutamate decarboxylase (GAD) antigen (Borg *et al.* 1994; Passin *et al.* 1995).

GAD is a pyridoxal phosphate-dependent enzyme catalyzing irreversible decarboxylation of glutamate to form gamma-aminobutyrate (GABA). In humans, two genes encoding different GAD isoforms have been identified. Named according to their respective molecular weights, the pancreatic GAD65 isoform contains an N-terminal membrane-anchoring signal peptide and localizes in the proximity of the Golgi apparatus of islet cells and GABA-containing vesicles (Bu *et al.* 1992; Brilliant *et al.* 1990; Solimena *et al.* 1994). GAD65 autoantibodies appear in 70 – 80% of sera from recently diagnosed T1DM patients (Hagopian *et al.* 1993). However, they can also be present in nondiabetic individuals and are thus alone not strictly specific (Christie *et al.* 1994).

The 40 kDa antigen detected in 37/40 kDa tryptic fragments was considered to be another major target of autoimmune response in diabetes (Passin *et al.* 1995). The insulinoma-associated protein (IA-2), also called islet cell antigen 512 (ICA 512), is a catalytically inactive protein tyrosine phosphatase (PTP) (Bonifacio *et al.* 1995). It consists of an

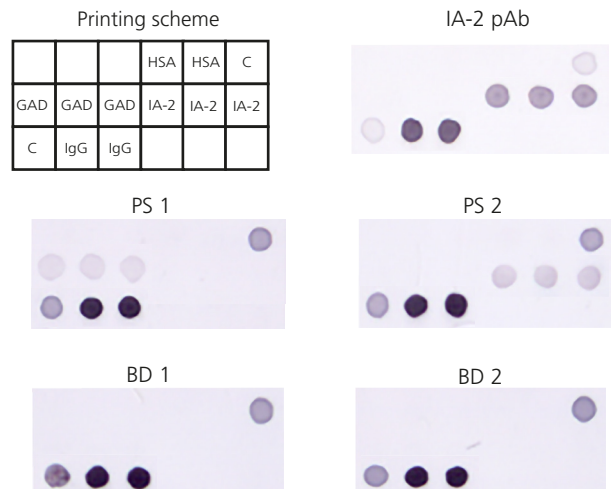


Figure: Immunodot analyses of GAD65 and IA-2 in triplicates using a polyclonal IA-2 antibody (pAb), samples from T1DM patients (PS1-2) and blood donors (BD1-2). As positive (serum) controls, goat anti-human IgGMA (C) and IgG were used. As negative control HSA was spotted on nitrocellulose membrane.

N-terminal extracellular signal sequence, a transmembrane domain and a long C-terminal intracellular tail, that harbors the majority of autoantibody epitopes (Lampasona *et al.* 1996). Similar to GAD it is expressed within secretory granules in neural, neuroendocrine and pancreatic islet cells (Solimena *et al.* 1996). Compared to GAD antibodies, IA-2 antibodies appear later and are therefore used as predictive value for upcoming T1DM onset in at-risk individuals (Achenbach *et al.* 2013). IA-2 autoantibodies are detected in 60 - 80% of sera from individuals with recent onset of the disease (Winter *et al.* 2011).

DIARECT's antigens GAD65 and IA-2 (ICA512) are produced in the baculovirus/insect cell system.

#### References:

Achenbach *et al.* (2013) *Diabetologia*. 56: 1615–1622  
 Bonifacio *et al.* (1995) *J Immunol*. 155(11): 5419–26  
 Bottazzo *et al.* (1974) *Lancet*. 2(7892):1279–83  
 Brilliant *et al.* (1990) *Genomics*. 6: 115-122  
 Bu *et al.* (1992) *PNAS*. 89: 2115-2119  
 Christie *et al.* (1994) *Diabetes*. 43: 1254-1259  
 Hagopian *et al.* (1993) *Diabetes*. 42: 631-636  
 Lampasona *et al.* (1996) *J Immunol*. 157: 2707–2711  
 Landin-Olsson *et al.* (1992) *Diabetologia*. 35: 1068–73  
 Passin *et al.* (1995) *PNAS*. 92: 9412-9416  
 Pihoker *et al.* (2005) *Diabetes*. 54: 52– 61  
 Solimena *et al.* (1994) *J Cell Biol*. 126: 331-341  
 Solimena *et al.* (1996) *EMBO J*. 15: 2102–2114  
 Winter *et al.* (2002) *Clinical Diabetes*. 20 (4): 183-191  
 Winter *et al.* (2011) *Clin Chem*. 57: 168–175  
 Ziegler *et al.* (2013) *JAMA*. 309: 2473–2479

In some countries the use of certain antigens in diagnostic tests may be protected by patents. DIARECT is not responsible for the determination of these issues and suggests clarification prior to use.

#### Ordering Information

13800	Glutamate Decarboxylase 65 kDa	0.1 mg
13801	(GAD65)	1.0 mg
30500	IA-2 (ICA 512)	0.1 mg
30501		1.0 mg

181218\_Rev04

