# TGMs on the interaction of WT and Y329S GBE1 with membranes: Effects on GBE1 activity and APBD pathophysiology and therapy.

**Pablo Escribá**
University of the Balearic Islands, Palma, Spain

*Rafael Alvarez[a], Jesús Casas[a], David J. López[a], Maitane Ibarguren[a], Alexander Lossos[b], Xavier Busquets[a], Or Kakhlon[b] and Pablo V. Escribá[a]*

Adult Polyglucosan Body Disease (APBD) is triggered by GBE1 Y329 mutation and it is characterized by adult-onset neurogenic bladder, spasticity, weakness, sensory loss and more. Albeit being a soluble enzyme, we observed that protein-membrane interactions regulate GBE1 activity. Because soluble proteins can be in contact with a wide variety of cell membranes, we investigated the interactions of purified wild type and Y329S GBE1 proteins with different types of model membranes (liposomes). Moreover, the investigational drug triheptanoin (TH) and some of the triacylglycerol mimetics we designed and synthesized (TGM0 and TGM5) were able to induce marked and significant increases in GBE1 Y329S activity, which may suffice to achieve enough glycogen branching to reverse APBD symptoms. Our results indicate that the Y329S mutation causes exposure of a hydrophobic amino acid stretch whose interaction with cell membranes can either stabilize and *increase* its activity or alter protein-membrane interactions *reducing* the enzyme's activity. In addition, we observed that GBE1 activity is modulated by $Ca^{2+}$ and phosphatidylserine (PS), which could be associated with a metabolic mechanism to regulate energy consumption and storage. In summary, both TGM0 and TGM5 could have higher activity against APBD than TH, although only TGM5 can be developed as a food supplement. Given the (i) thermal stabilization produced by TGM5, (ii) the increase in GBE1 activity induced, and (iii) its omega-3 oil structure, this molecule has a great therapeutic potential for the treatment of APBD.