DECIPHERING hIAPP

A NOVEL WAY TO CURE DIABETES

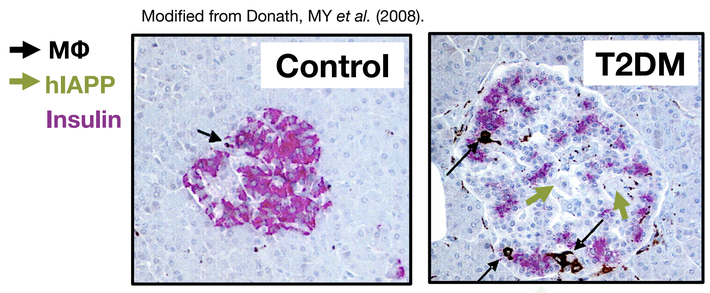
IÑIGO RUIZ LÓPEZ

Bachelor's Degree in Biotechnology

UAB Universitat Autònoma de Barcelona

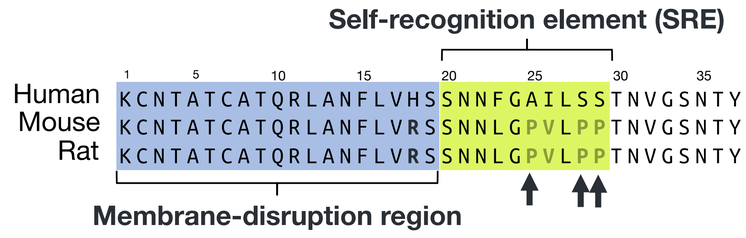
What is hIAPP?

Human islet amyloid polypeptide (hIAPP) is one of the major hormones produced by pancreatic β-cells and is involved in **type-II diabetes mellitus (T2DM)** pathogenesis. T2DM is a complex syndrome characterized by impaired insulin secretion and action. The loss of pancreatic β-cell mass is accompanied by the accumulation of amyloid deposits of hIAPP**.** The relationship between amyloidosis, cell-death and disease progression is extremely complex [1].



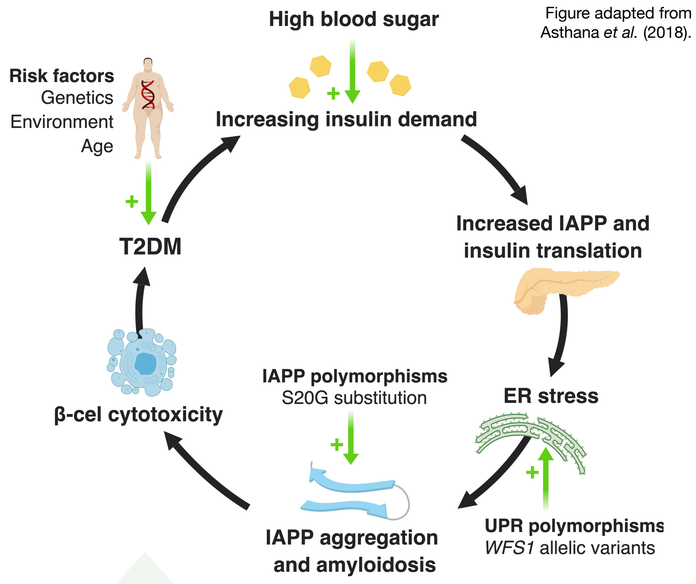
Amyloidosis in T2DM patients

Rodent IAPP (rIAPP) differs in three Pro in the SRE



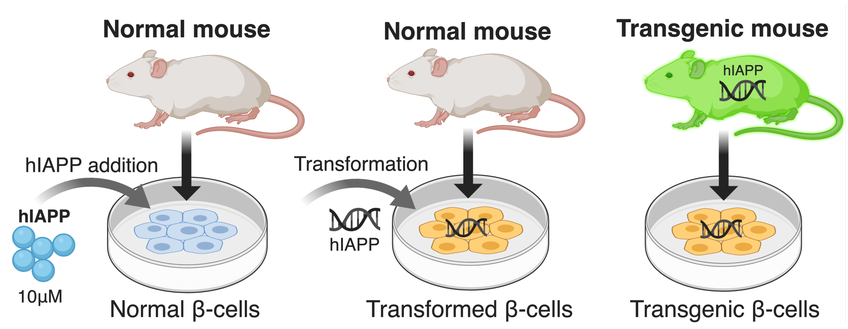
hIAPP participates in T2DM progression

Figure adapted from Asthana *et al.* (2018).



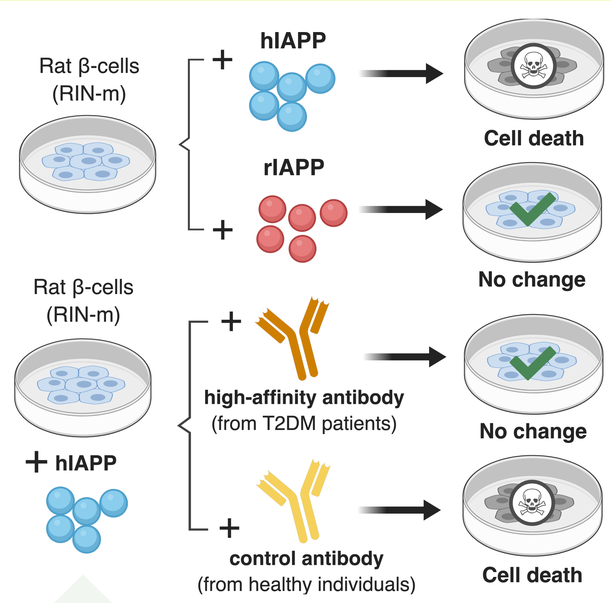
hIAPP contributes to T2DM in a positive feedback.

hIAPP reduces insulin secretion in β-cells



↓ Reduced insulin secretion ↓

hIAPP causes β-cell death

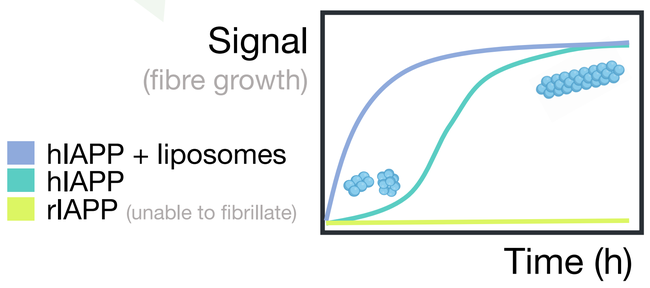


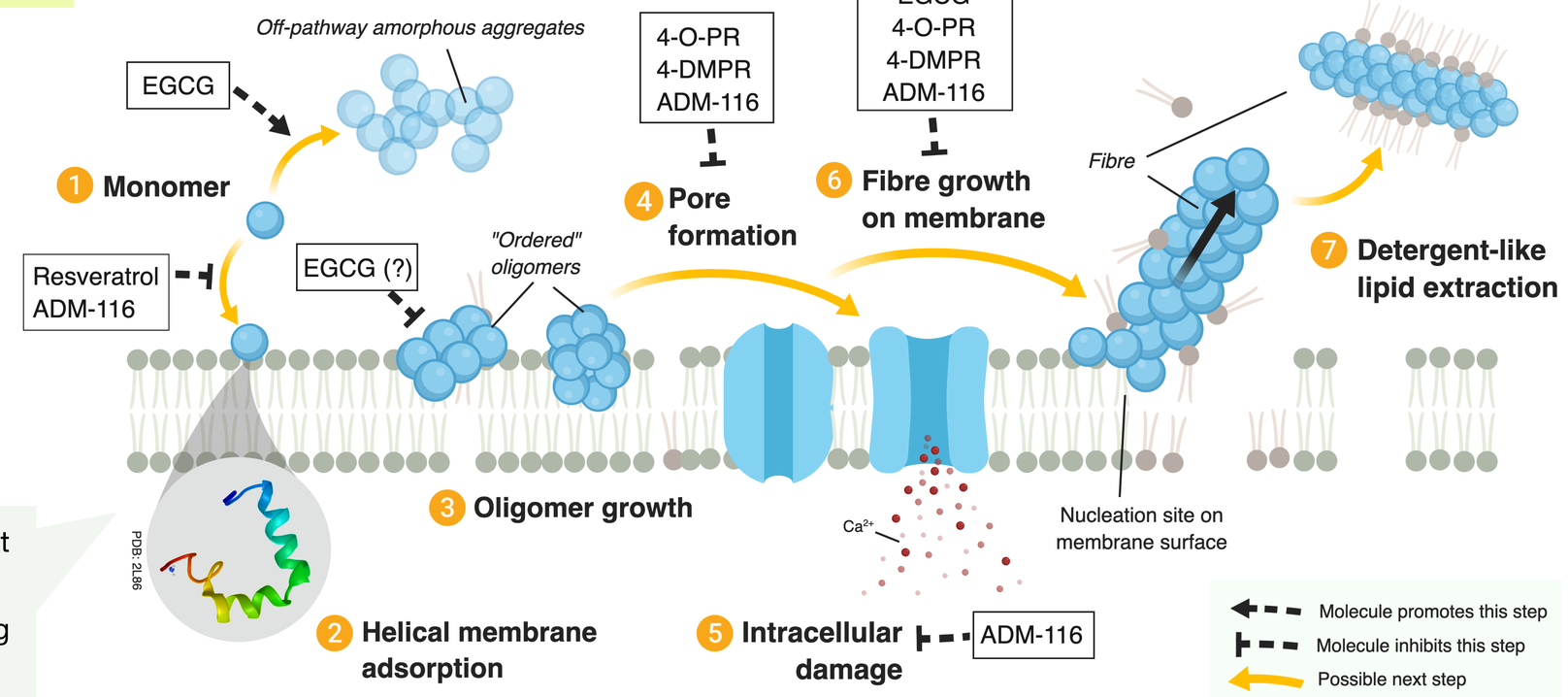
Cell viability is restored using high-affinity antibodies targeting hIAPP.

hIAPP is sufficient and necessary to develop T2DM

hIAPP associates with and destroys β-cell membranes

hIAPP fibrillation is enhanced in membranes in contrast with rodent IAPP (rIAPP) [2].

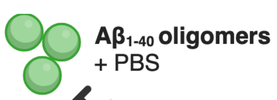




Integrative model for membrane disruption

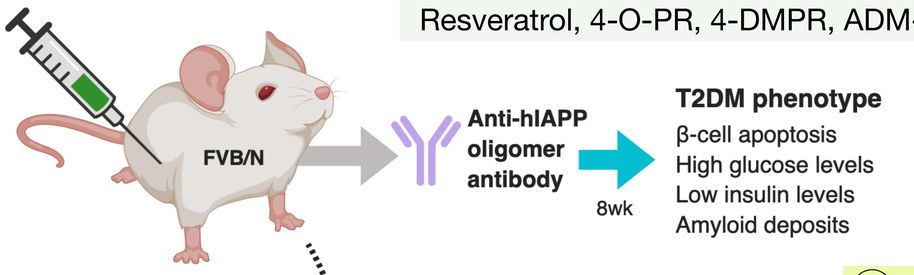
- Based on recent kinetic studies, I suggest that membrane interaction occurs in distinct stages.
- Small-molecules can prevent β-cell death acting on different steps of this cascade.

Which **therapeutic possibilities** are most **promising?**

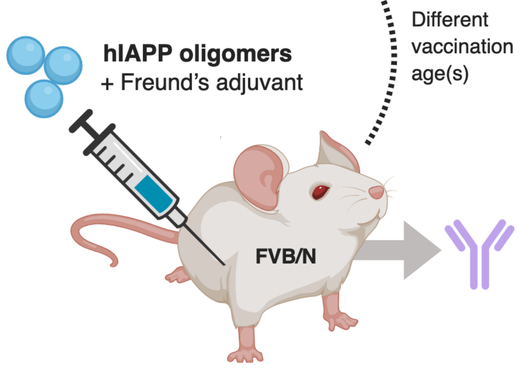


① Small-molecule inhibitors

Resveratrol, 4-O-PR, 4-DMPR, ADM-116, EGCG



② Vaccination



Vaccination of transgenic mice shows a nearly complete abolition of T2DM [3].

Future approaches: A personal contribution

Can we remove hIAPP from plasma?

[4]

- In Alzheimer, circulating amyloid (Aβ) associates with serum albumin.
- Plasmapheresis replaces albumin bound to Aβ with synthetic albumin.

- I propose that T2DM may be treated using the same strategy since hIAPP binds to albumin.

Conclusions

- Although the **molecular mechanisms are unclear**, hIAPP plays a **decisive role in T2DM**, this **role may vary** depending on the circumstances of the disease.
- **Therapies targeting IAPP** are a **promising possibility** to prevent T2DM or stop its progression. Removal of hIAPP from plasma is an **unexplored and interesting** approach.

Key references

[1] Asthana S *et al*. IAPP in type II diabetes: Basic research on structure, molecular interactions, and disease mechanisms suggests potential intervention strategies. *Biochim. Biophys. Acta - Biomembr.* 1860, 1765–1782 (2018).

[2] Divakara MB *et al.* Molecular mechanisms for the destabilization of model membranes by islet amyloid polypeptide. *Biophys. Chem.* 245, 34–40 (2019).

[3] Bram Y *et al*. Active Immunization Against hIAPP Oligomers Ameliorates the Diabetes- Associated Phenotype in a Transgenic Mice Model. *Sci. Rep.* 7, 3–8 (2017).

[4] Costa M *et al.* Treatment of Alzheimer disease using combination therapy with plasma exchange and haemapheresis with albumin and intravenous immunoglobulin... *Neurología* 31, 473–481 (2016).