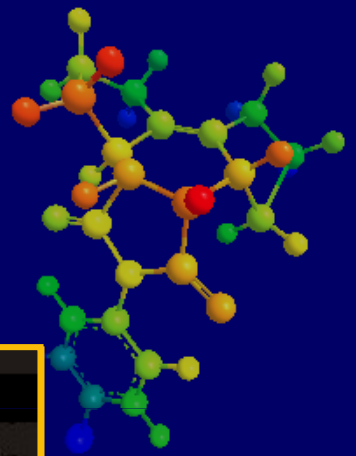
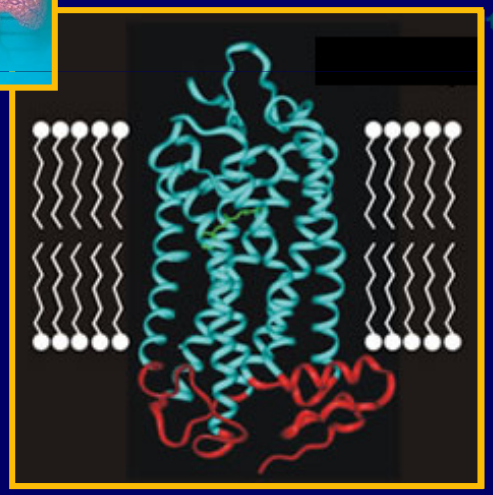
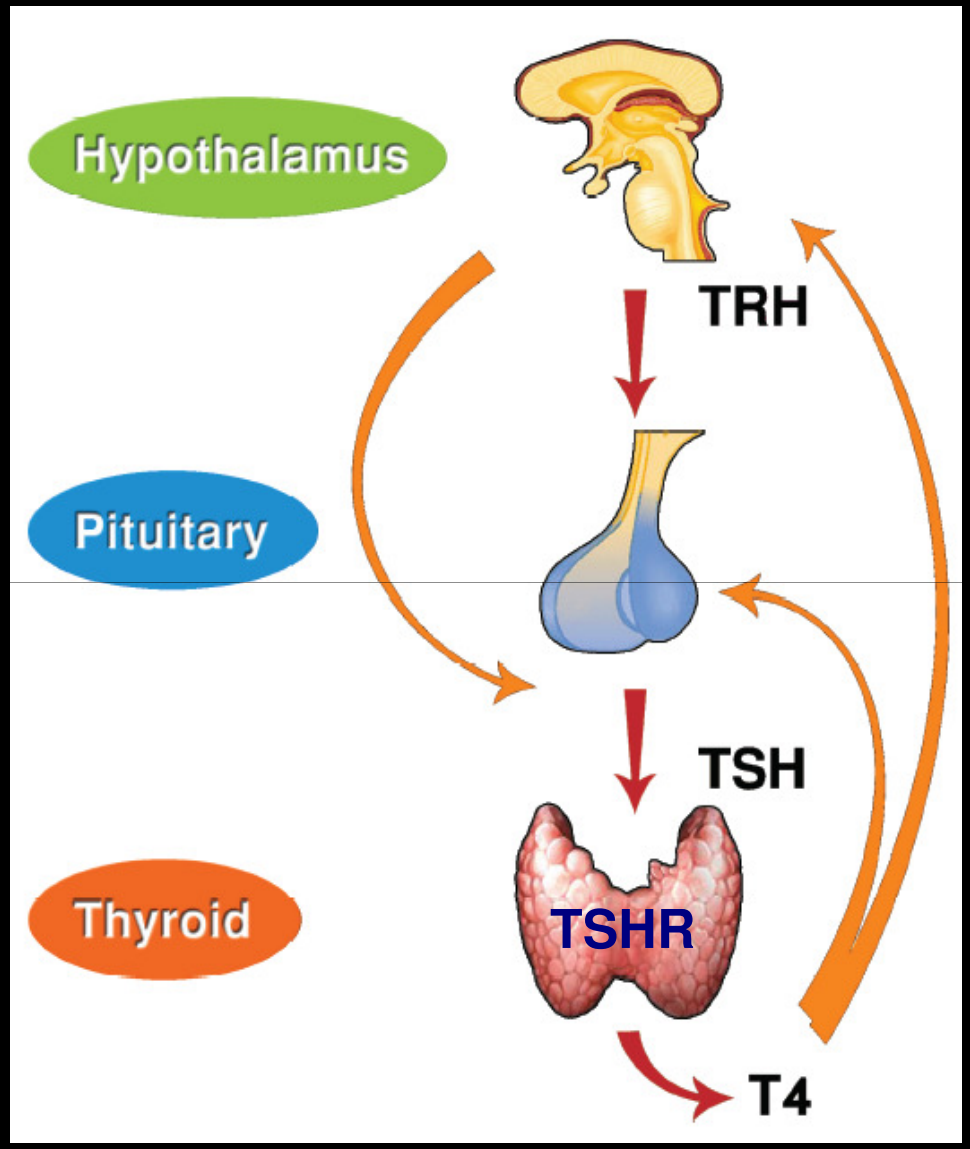
TSH Receptor Small Molecule "Drug-like" Antagonists

Susanne Neumann

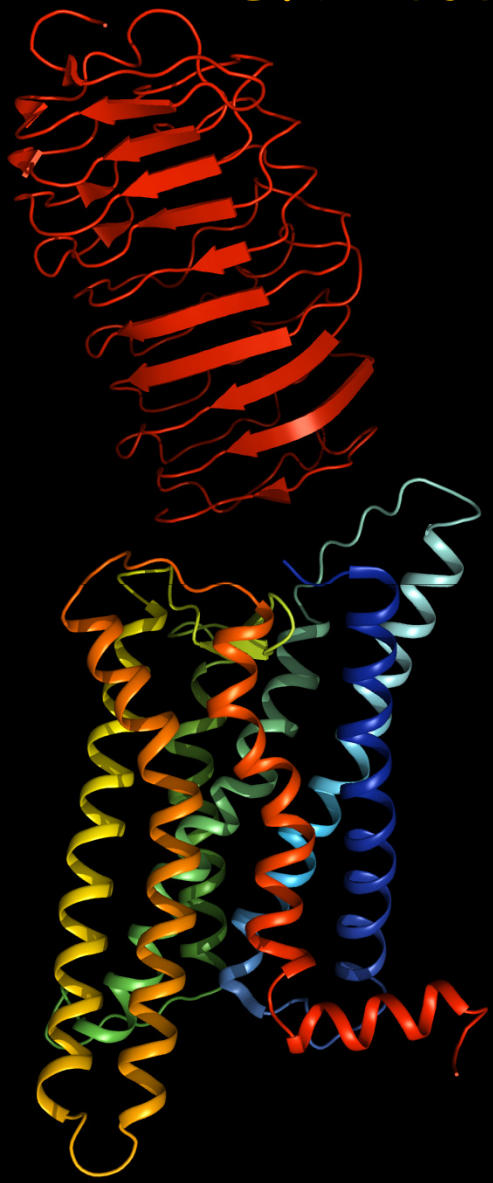




National Institute of
Diabetes and Digestive
and Kidney Diseases

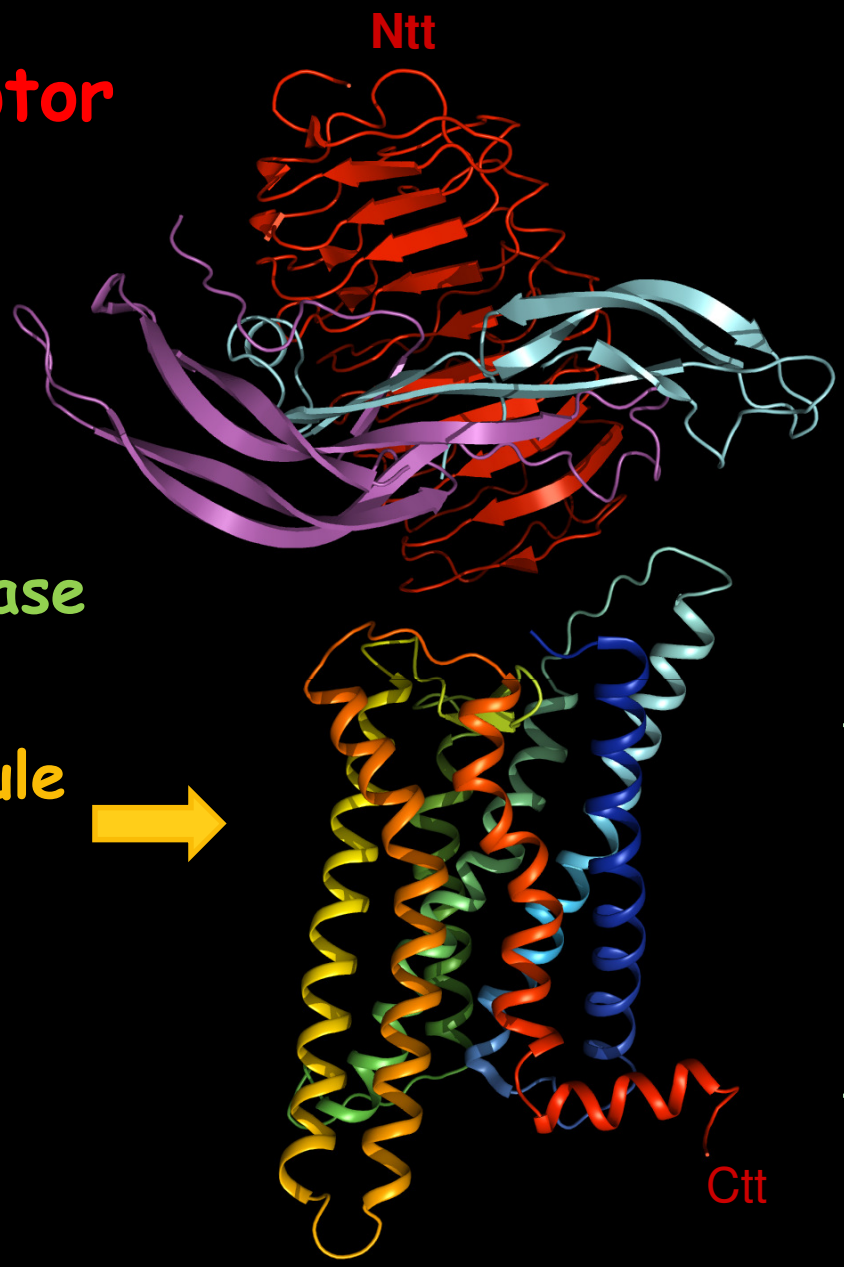


TSH Receptor



http://www.ssfa-gphr.de

TSH Receptor



TSH

TSABs
Graves'Disease

Small molecule
ligands

Extracellular

Transmembrane

Intracellular

http://www.ssfa-gphr.de

Graves' Disease (GD)

- Prevalence – approximately 1% of US population
  (Women:Men - between 5:1 and 10:1)
- is the underlying cause of 50 to 80% of hyperthyroidism
- caused by stimulating antibodies that activate the TSHR

Graves' Orbitopathy

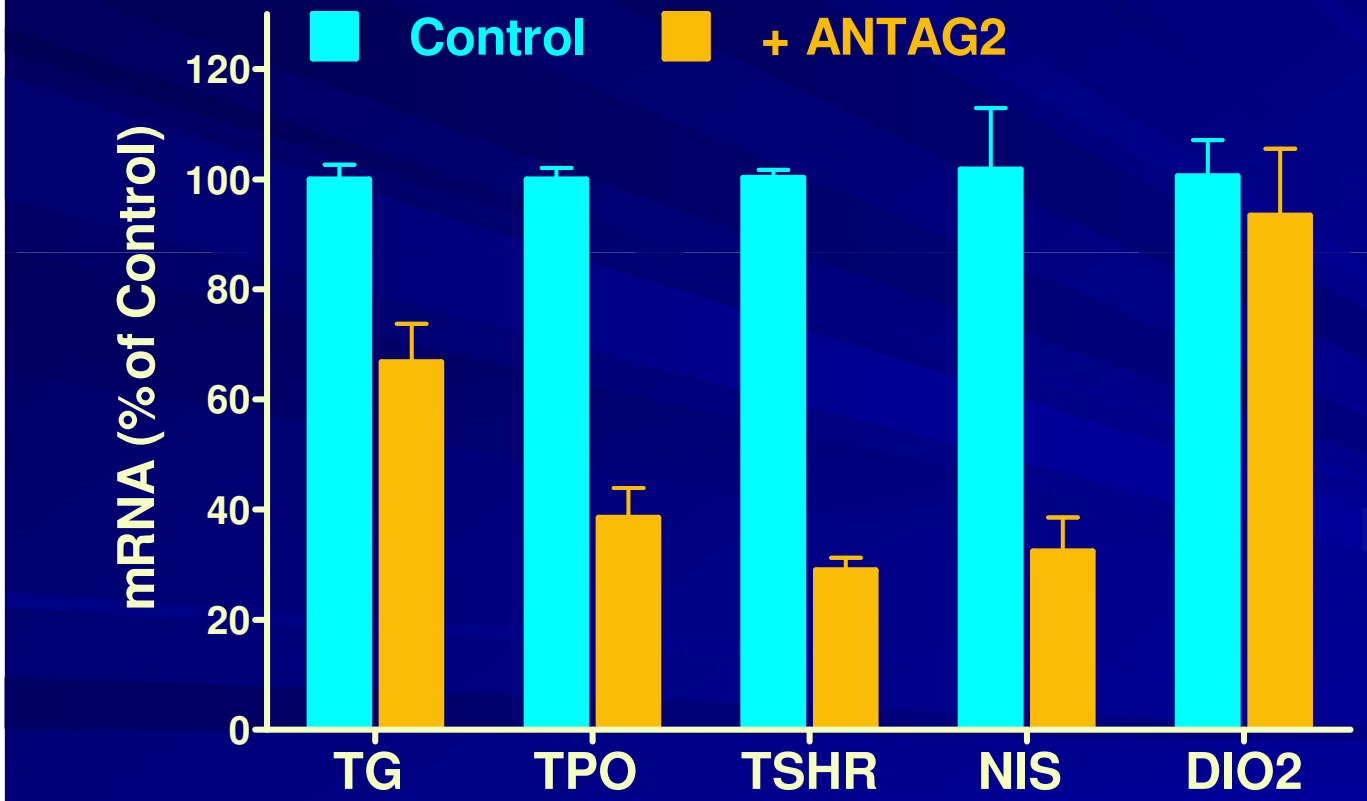
- Autoimmune inflammatory disorder affecting the orbit around the eye
- Clinically evident in 30% - 50% of GD patients

Brent, N Engl J Med 358, 2008

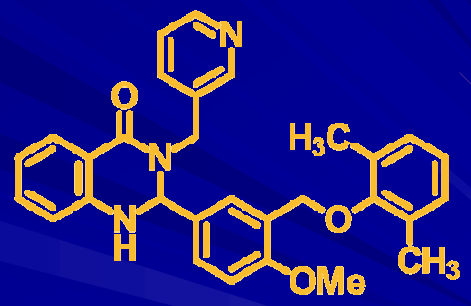
A Small Molecule TSH Receptor Antagonist

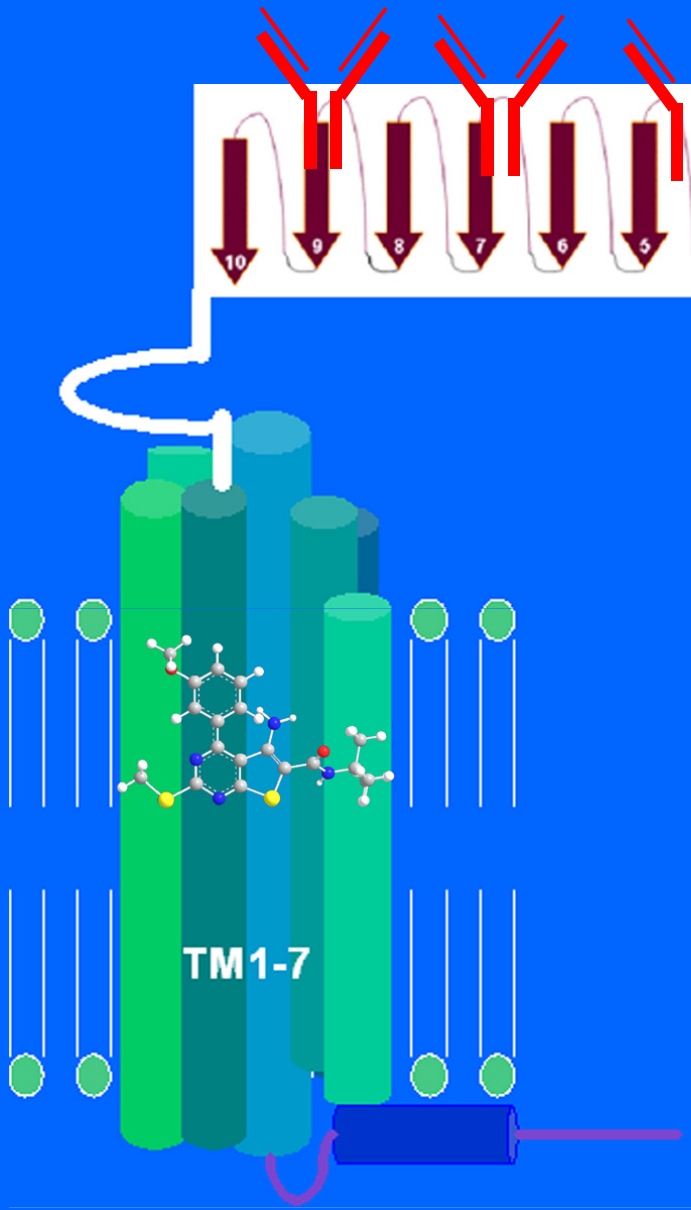
may have therapeutic potential
to block stimulating antibodies
in Graves' hyperthyroidism and
Graves' Orbitopathy

Inhibition of basal mRNA expression of thyroid specific genes in human thyrocytes



ANTAG2



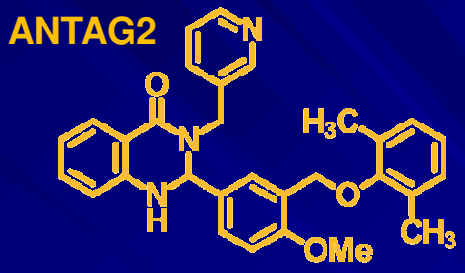


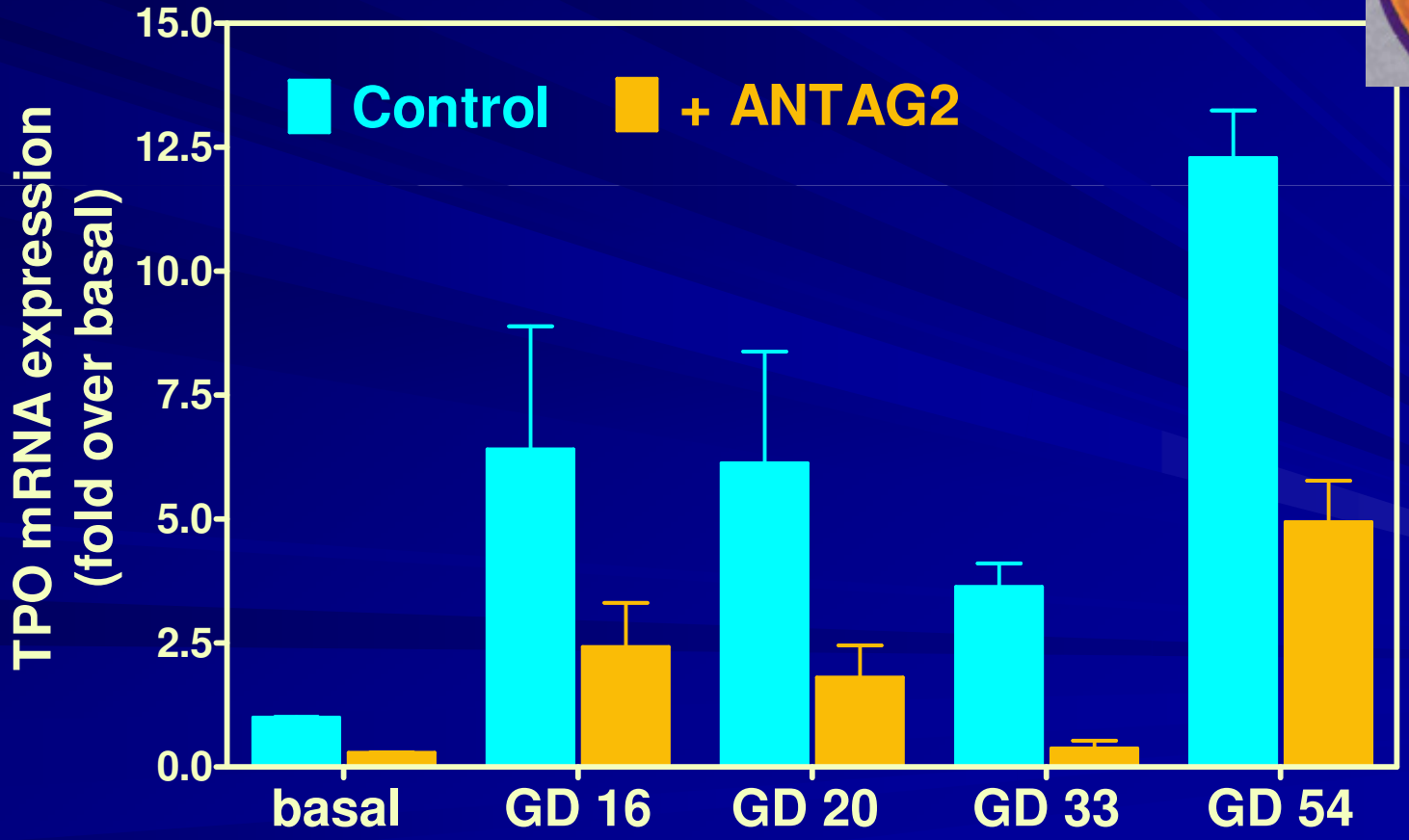
As therapy for Graves' Disease

- hyperthyroidism
- orbitopathy

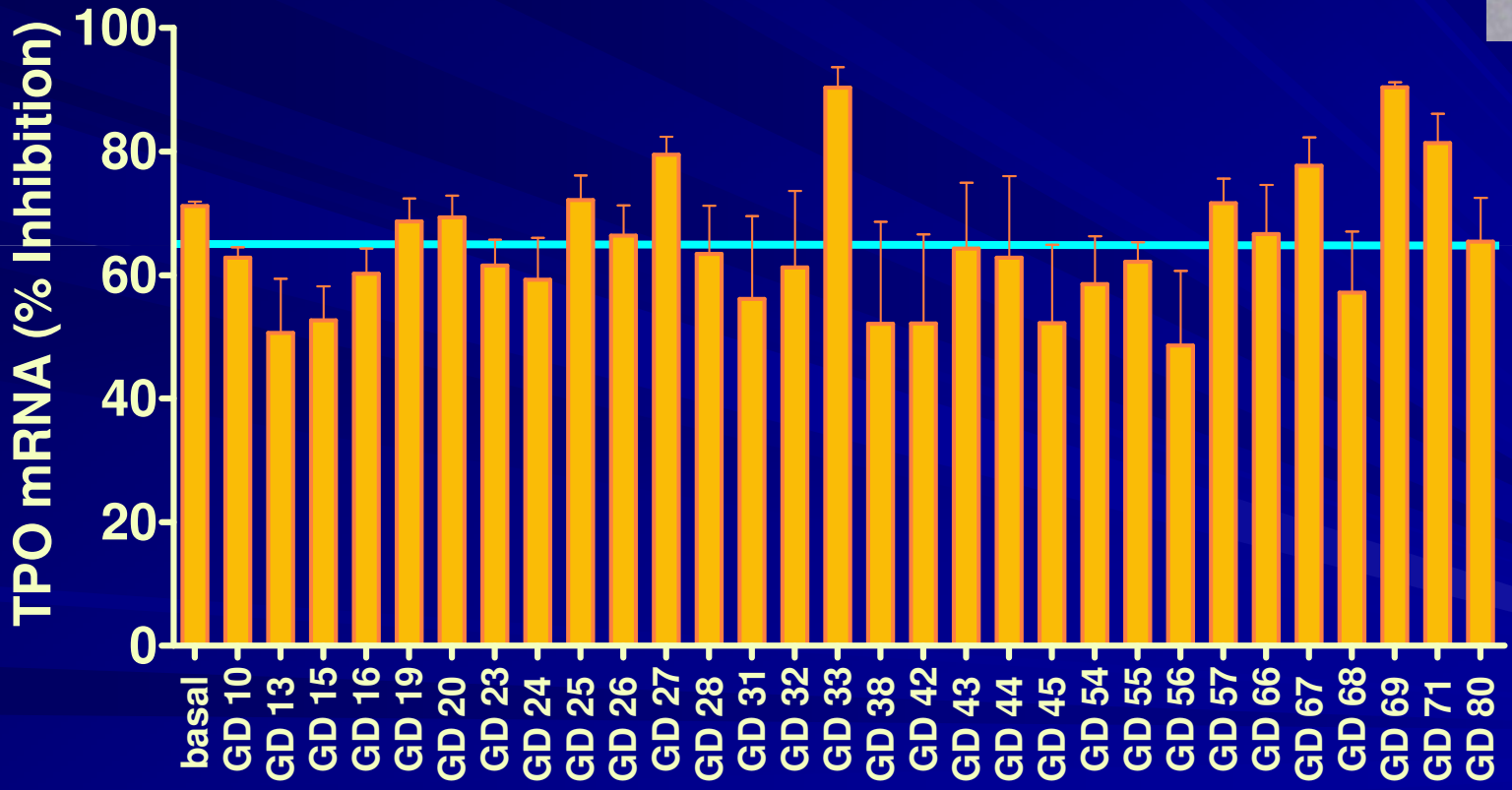
it would be important
that an antagonist
inhibits TSHR activation
by the majority of TSAbs

Inhibition of Graves' disease sera-induced up-regulation of TPO mRNA expression in human thyrocytes



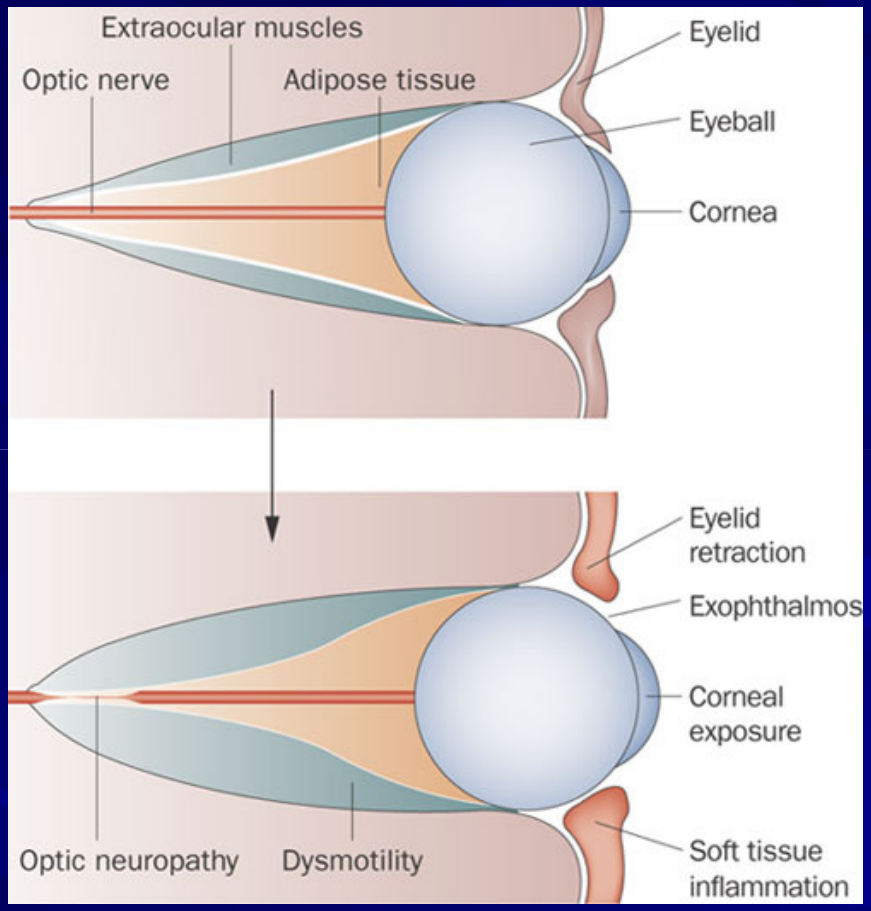


Inhibition of Graves' Disease sera-stimulated up-regulation of TPO mRNA expression in human thyrocytes



Inhibition of TPO mRNA levels by 65%

Graves' Orbitopathy



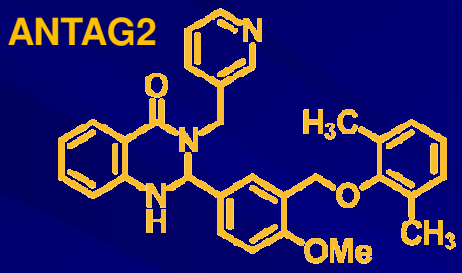
nature REVIEWS ENDOCRINOLOGY

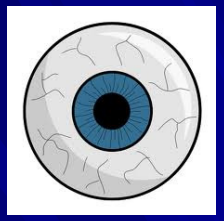
Perros &Krassas (2009)

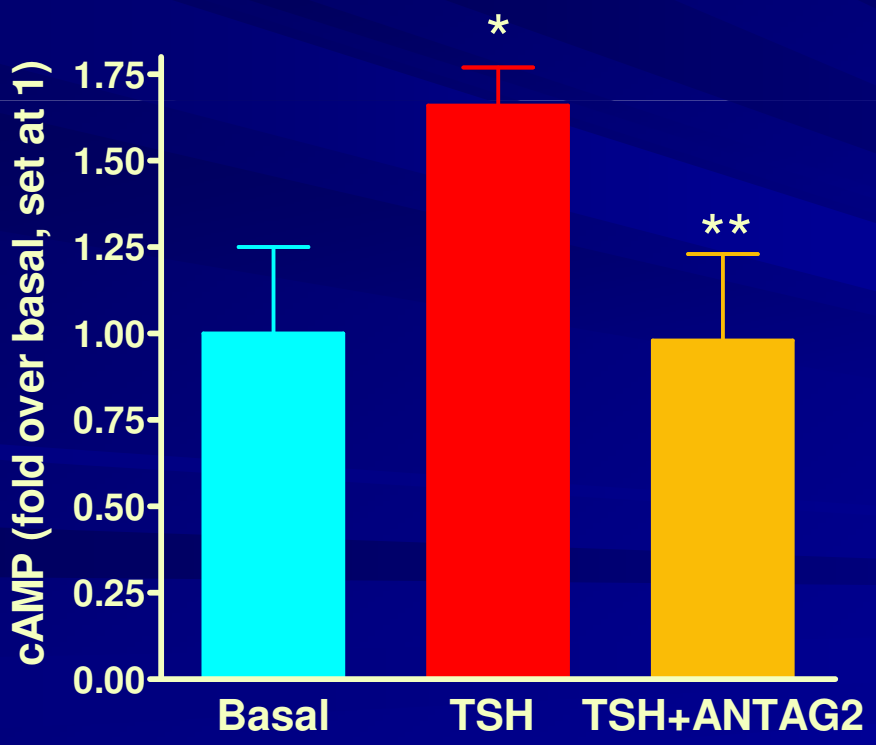
Changes in the Orbit

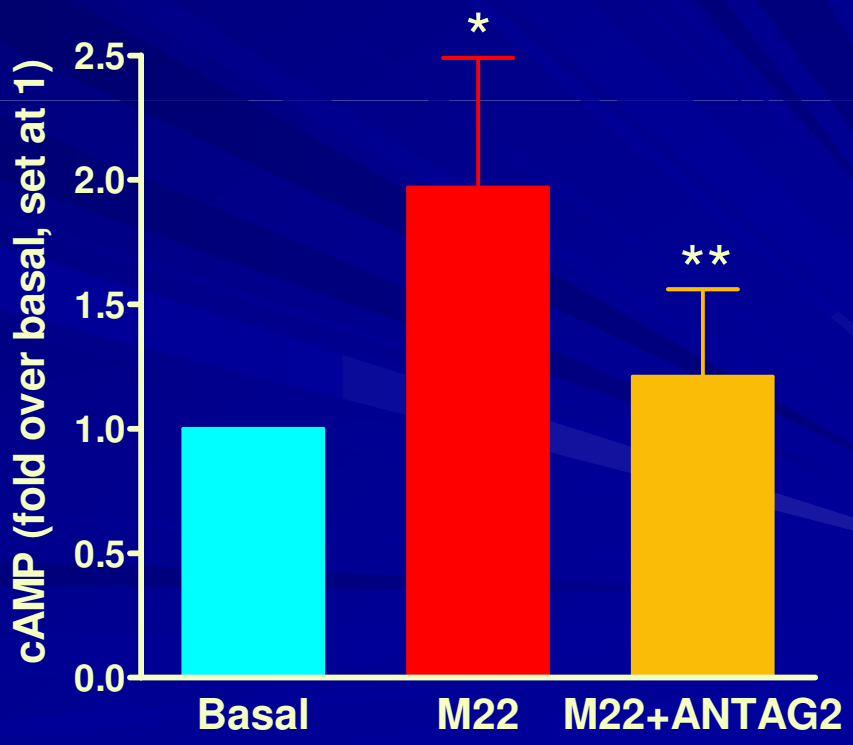
- Inflammation of orbital tissues
- Swelling in the orbital tissues causes the eye to be pushed forward, creating bulging of the eyes
- Connective tissues are extensively remodeled with enlargement of the extra-ocular muscles and orbital adipose tissues
- Excessive production of hyaluronic acid and new fat cell development

ANTAG2 reduces TSH- and TSAb-induced cAMP production in primary cultures of human Graves' orbital fibroblasts

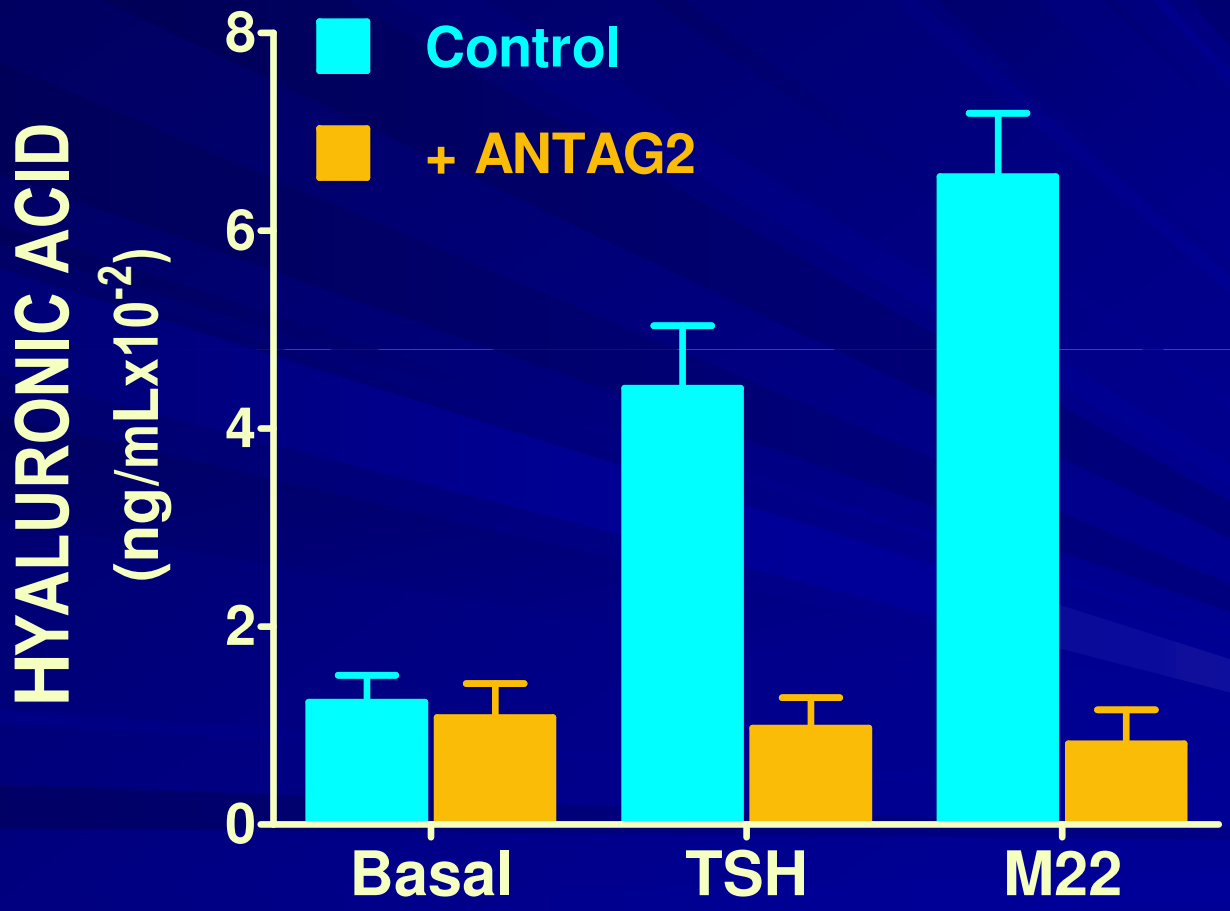








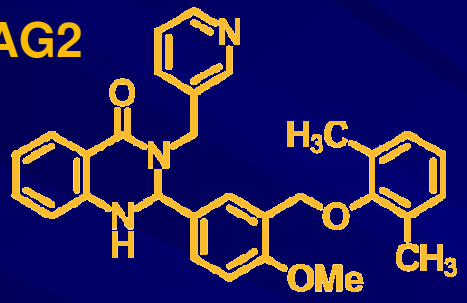
Inhibition of TSH- and M22-induced hyaluronic acid secretion by ANTAG2 in primary cultures of Graves' orbital fibroblasts

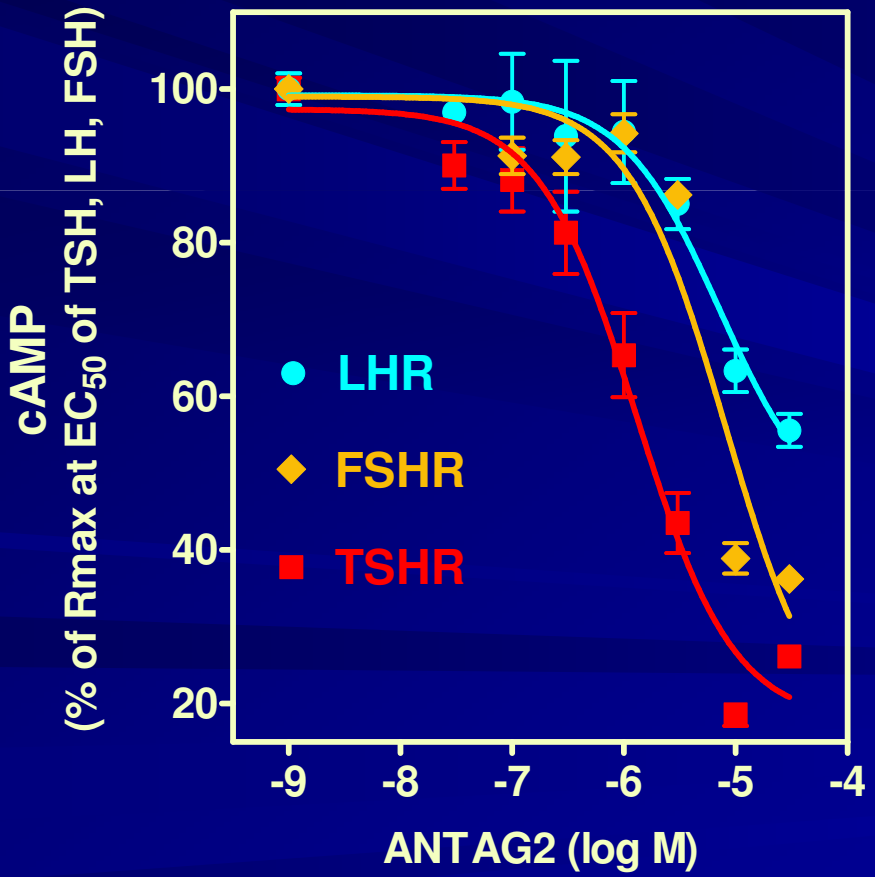


Krieger C et al. 2014. JCEM in revision

Selectivity of TSHR antagonists towards TSHR

ANTAG2





Selectivity of TSHR antagonists towards TSHR

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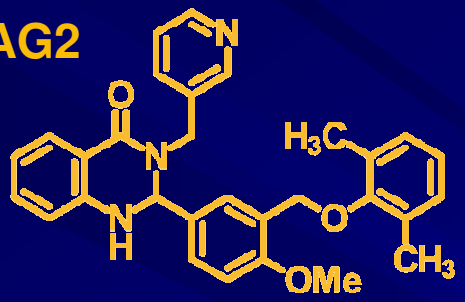

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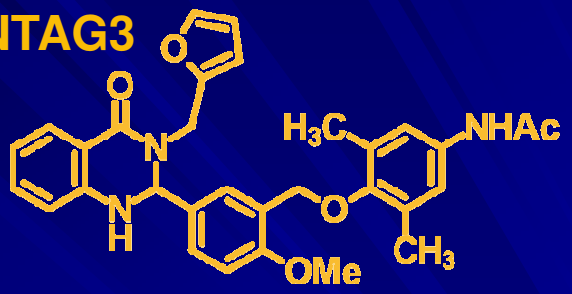
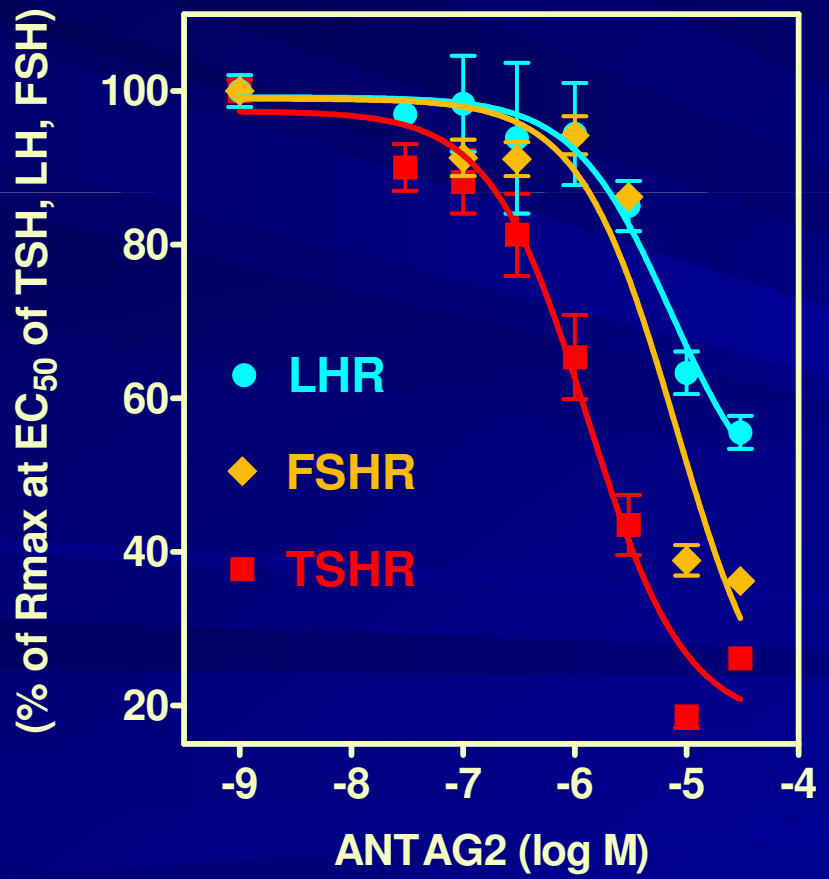
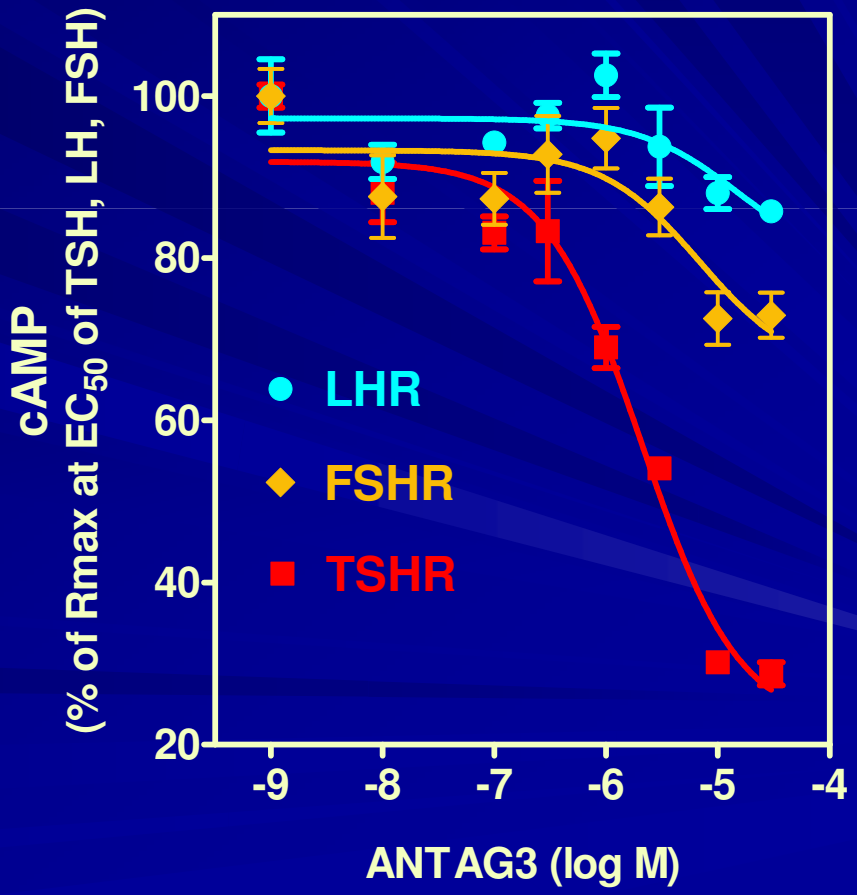
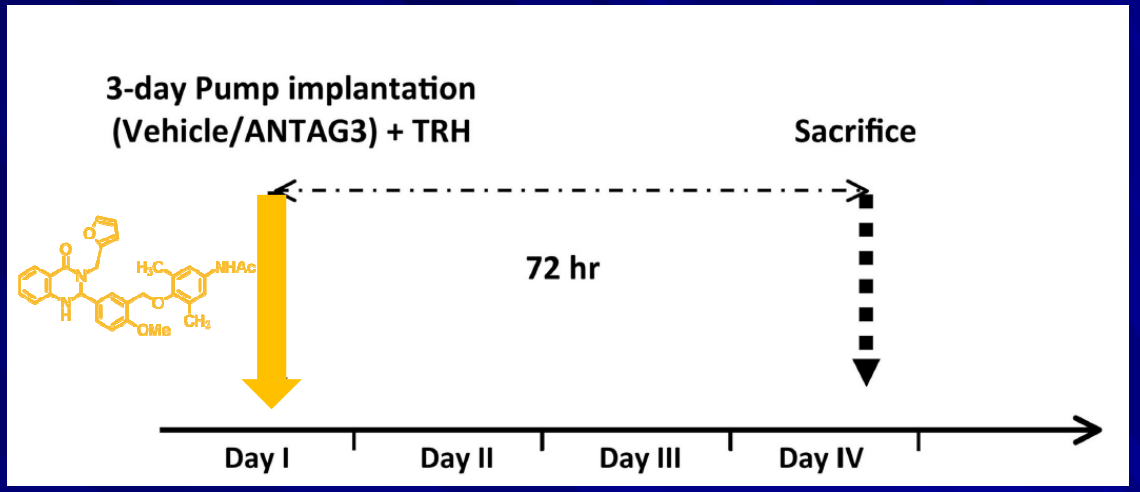






ANTAG3 lowers serum FT4 levels and thyroidal mRNAs for TPO and NIS in mice continuously stimulated by TRH



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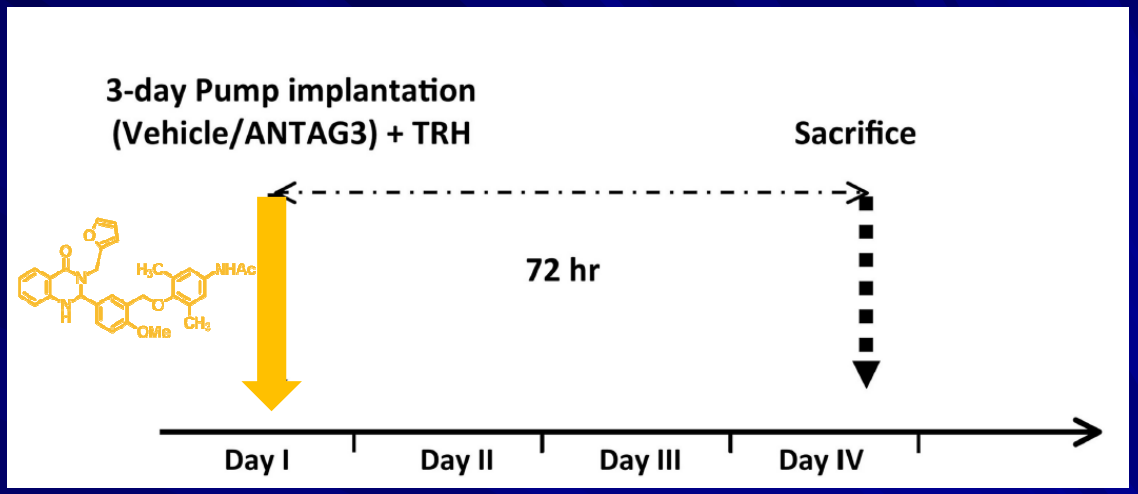
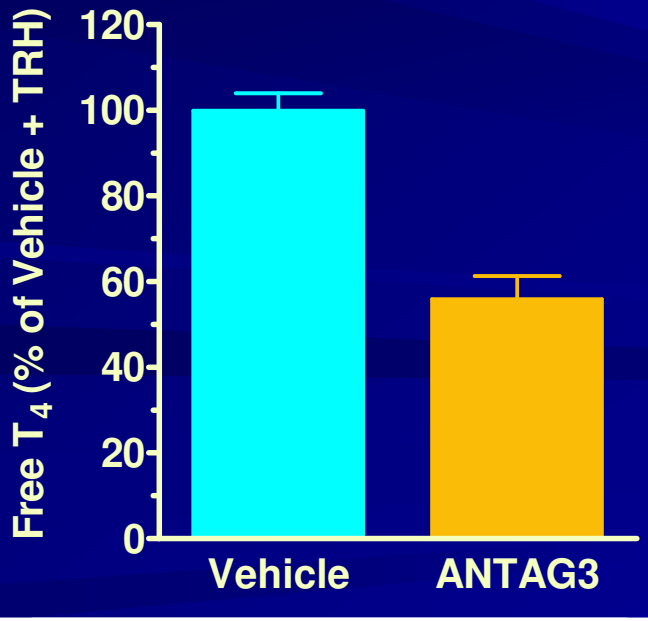
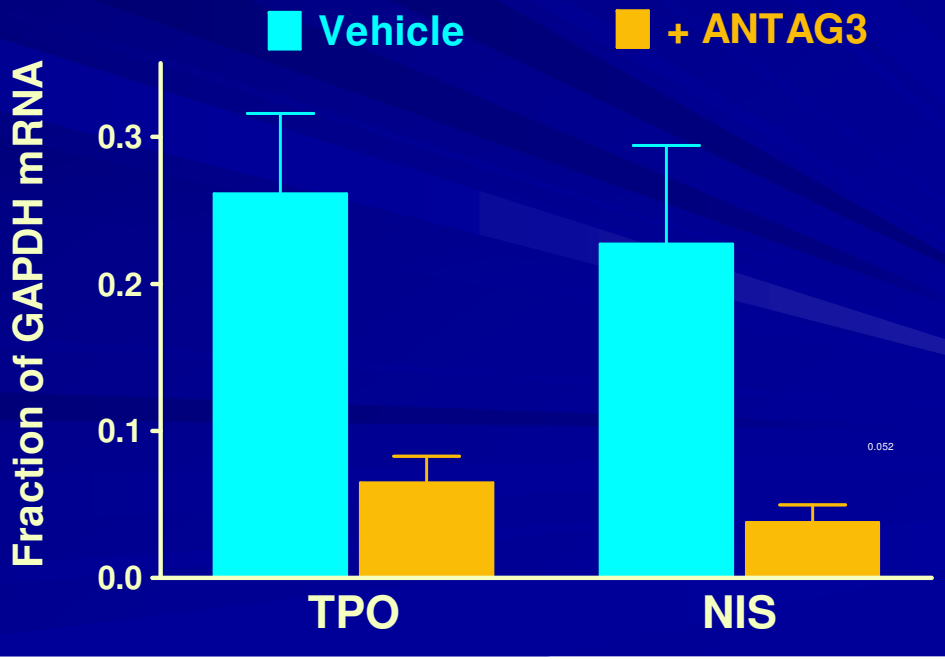


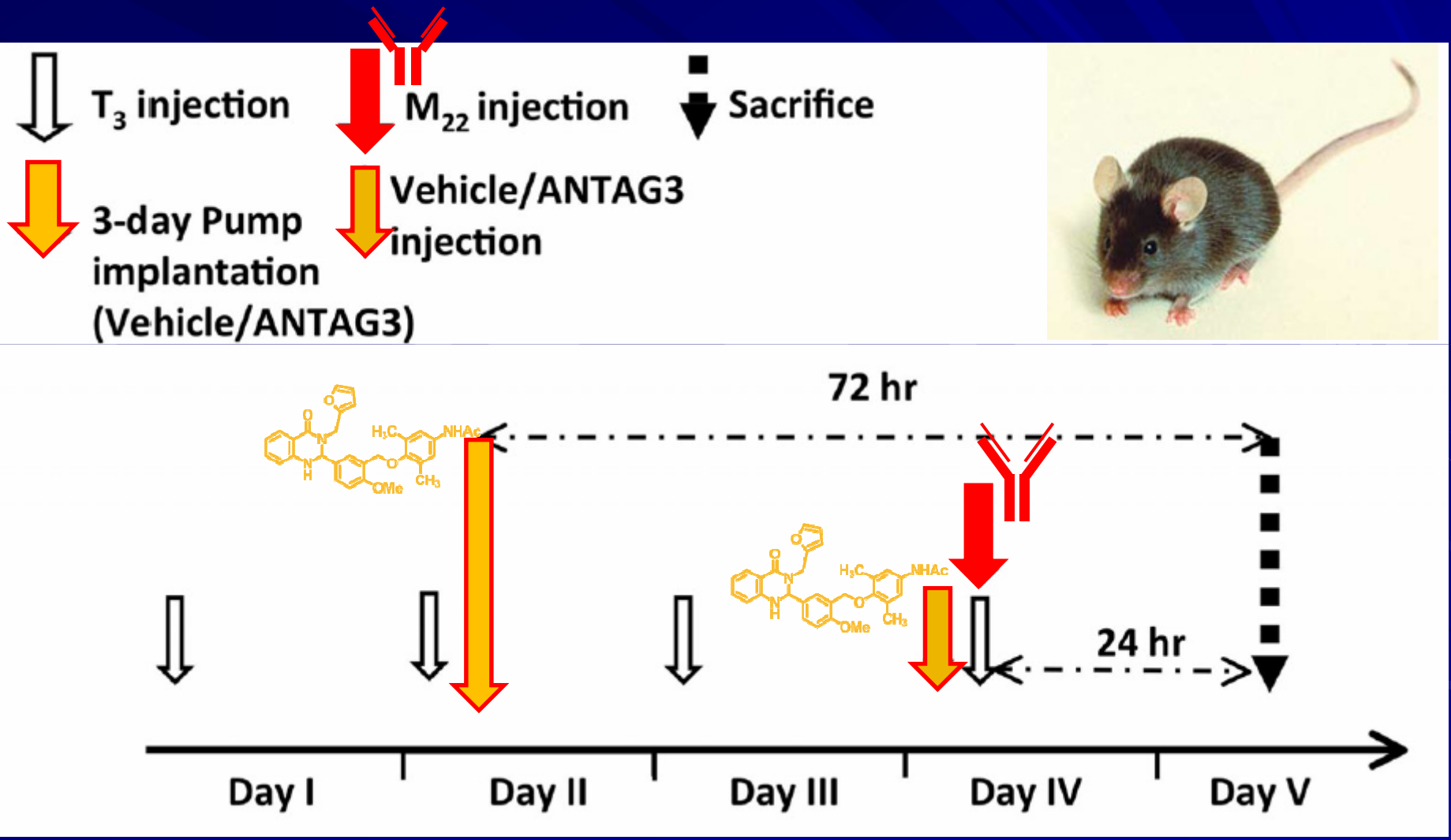
Free T4



mRNA expression



ANTAG3 lowers serum FT4 levels and thyroidal mRNAs for TPO and NIS in mice stimulated by a single injection of M22



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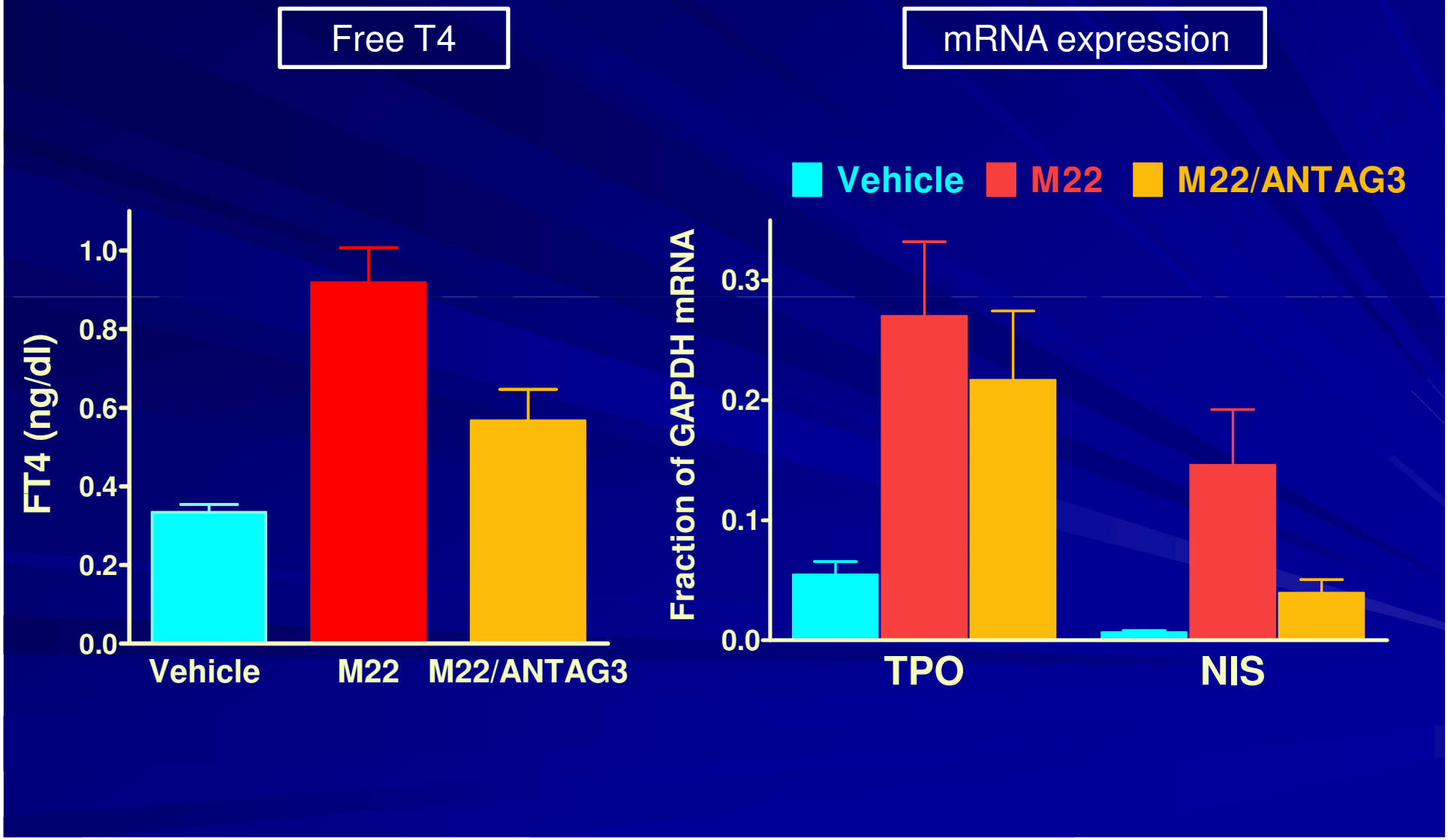

In summary,

- we have discovered/developed the first small molecule antagonists for the human TSHR

- we developed a selective TSHR antagonist that is effective *in vivo* in mice

In conclusion, we think these ligands are leads for the development of drugs to treat patients with Graves' Disease and Graves' Orbitopathy.

NIDDK

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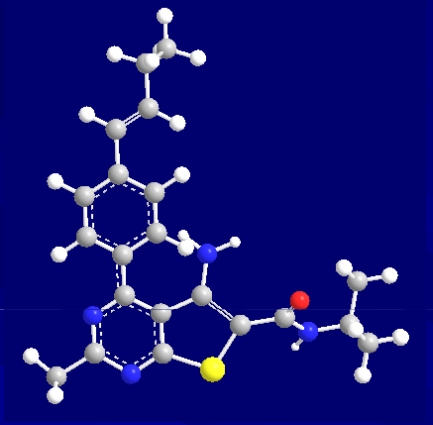

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