

**ÖSDG** 2022, Feldkirch



UNIVERSITÄTS**medizin.**  
MAINZ



Johannes Gutenberg  
University (JGU)  
Medical Center,  
Mainz, Germany

**George J. Kahaly**

# ENDOKRINE ORBITOPATHIE



# DISCLOSURES

George J Kahaly

The Johannes Gutenberg-University (JGU) Medical Center, Mainz, Germany has received research-associated funding from the JGU Medical Faculty, Byondis, Glycoera, Horizon Therapeutics, Immunovant, ISAR, Mediomics, Merck, Novartis, Quidel, Roche and Sling Therapeutics. GJK consults for Glycoera, Immunovant, ISAR, Merck, Novartis, Quidel and Sling Therapeutics

# **Psychosocial MORBIDITY**

## **▼ QUALITY OF LIFE** in 310 consecutive, unselected patients with Graves' Orbitopathy (GO)

Kahaly & al.,  
*American J Ophthalmology* 2011;  
152: 483-490

# PUBLIC HEALTH RELEVANCE

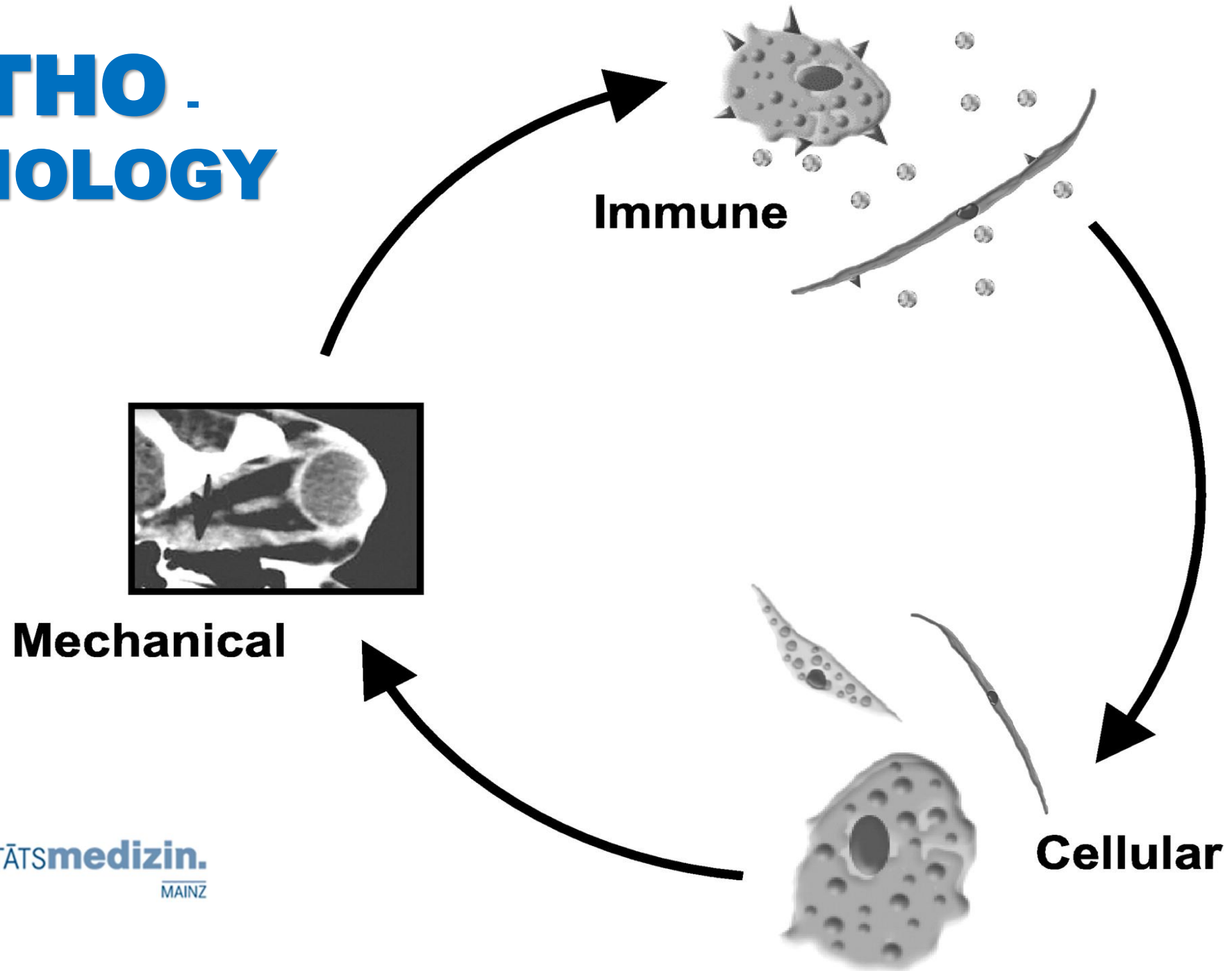
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- N = 680 consecutive subjects
- **Indirect costs: ~ 2,762,580,000 € / year**
- **Direct costs: 159,080,000 € / year**

Kahaly & al., *J Clin Endocrinol Metab* 2013; 98: 145-152



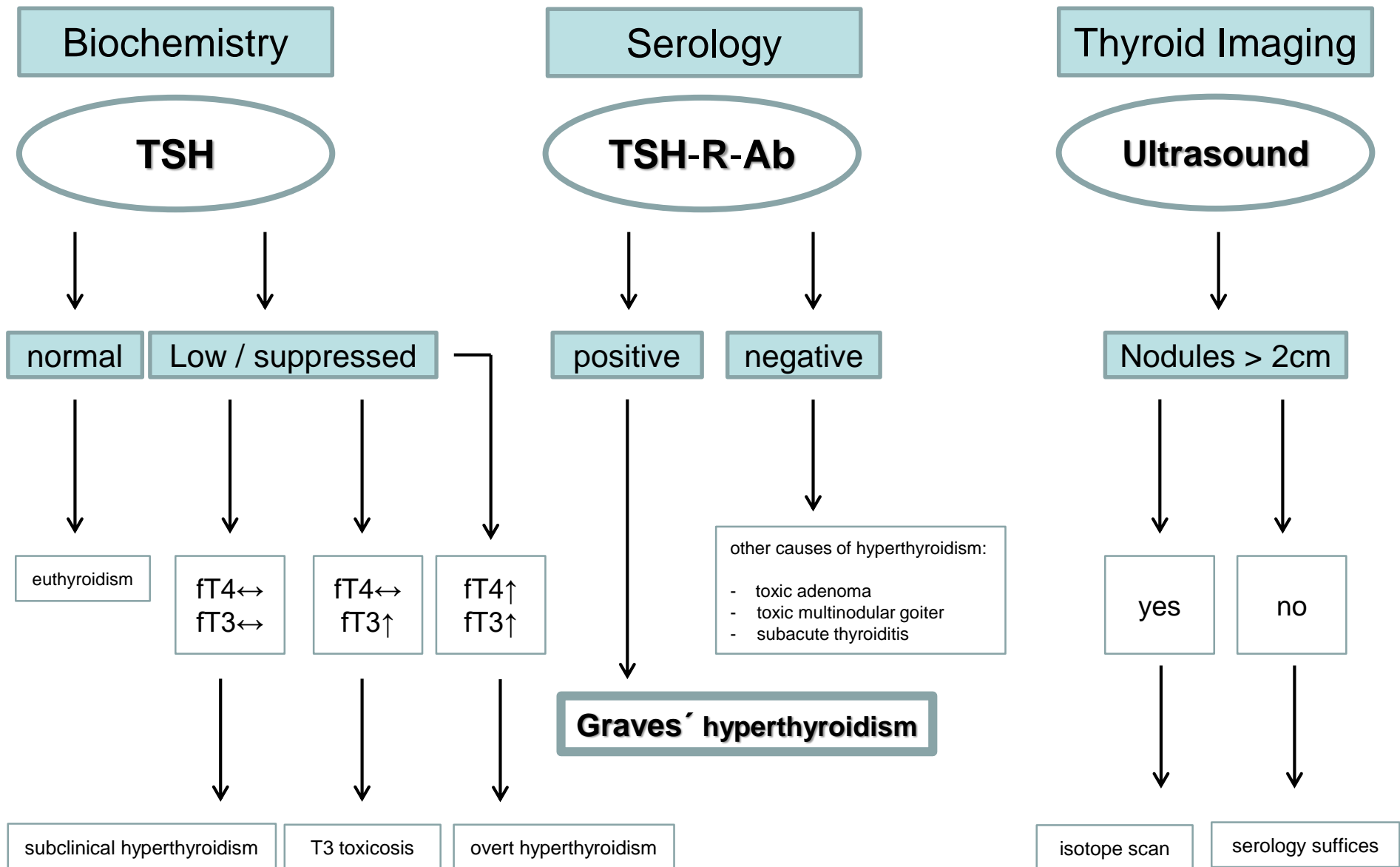
# **PATHO. PHYSIOLOGY**



# **SMOKING HURTS the **EYES****

Relative risk **8** for  
**Proptosis / Diplopia**





# TSH-R stimulating Ig (TSI): biomarker

TSI [SRR%]

Kahaly & al.

JCEM 2010, Thyroid 2011, Ophthalmology 2011,  
Ophthalmology 2012, JCEM 2014, JCEM 2016,  
Clin Exp Immunol 2017, **N Engl J Med** 2017,  
Ann Intern Med 2020, **N Engl J Med** 2020, **Nature**  
**Reviews Disease Primer** 2020, Front Endocrinol  
2021, J Autoimmunity 2021, Thyroid 2022

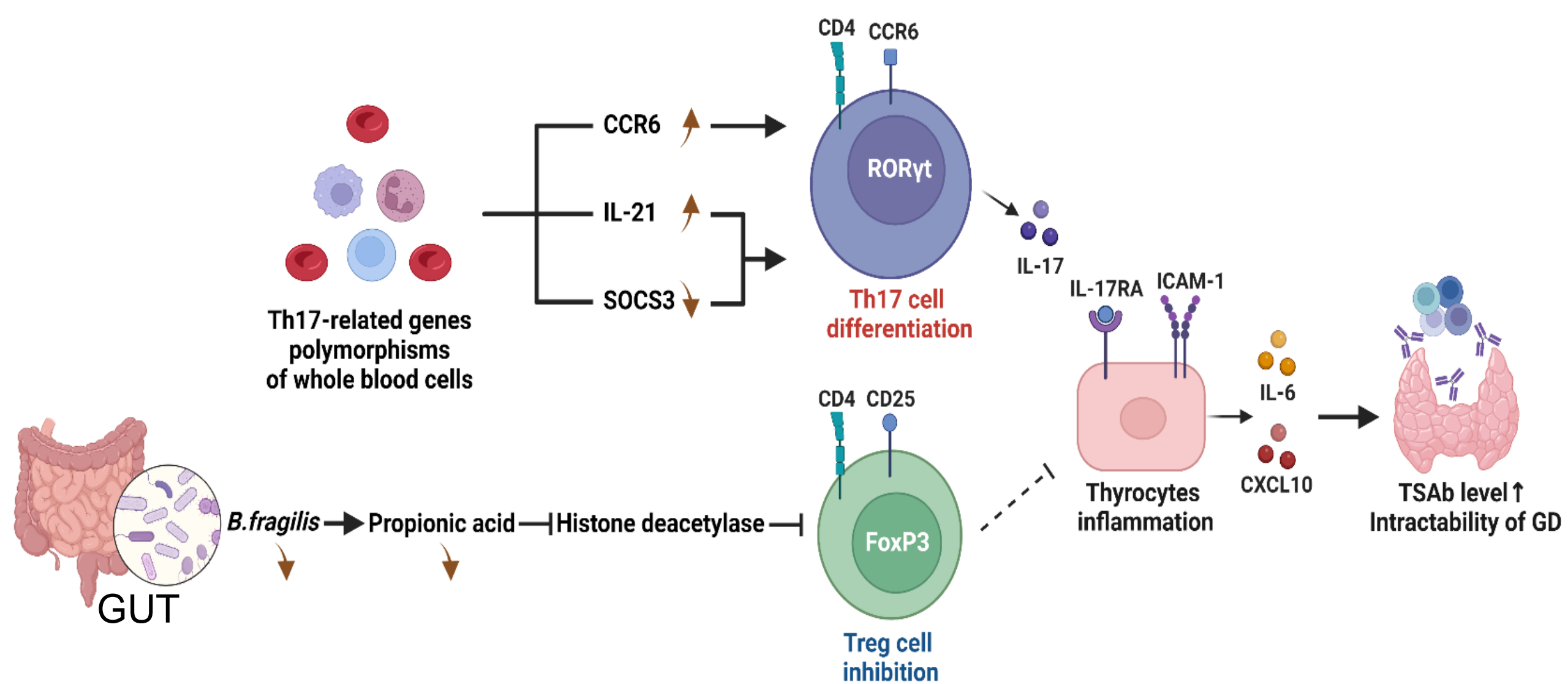
Mean  $\pm$  2SD

$P < 0.001$

no diplopia

diplopia

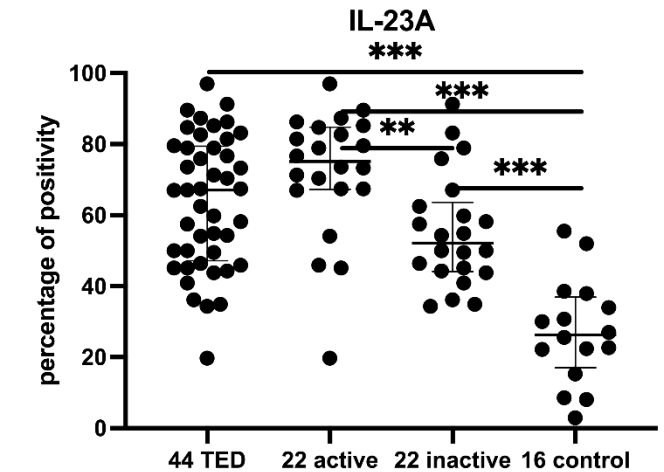
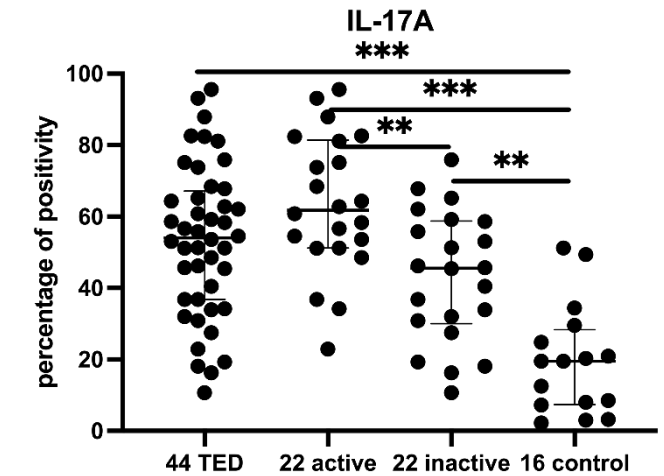
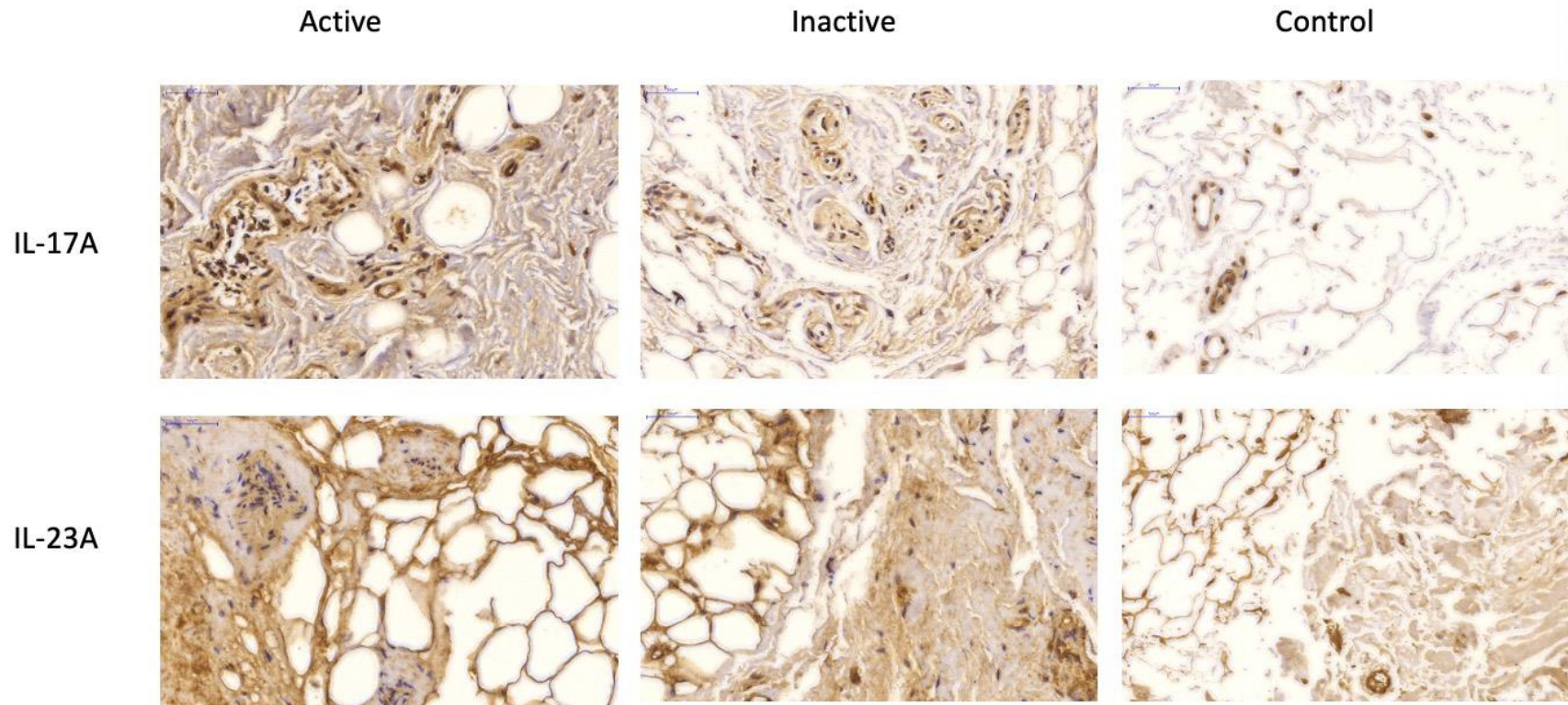




**PATHOGENIC ROLE of the MICROBIOME and INNATE (Th17) IMMUNITY**

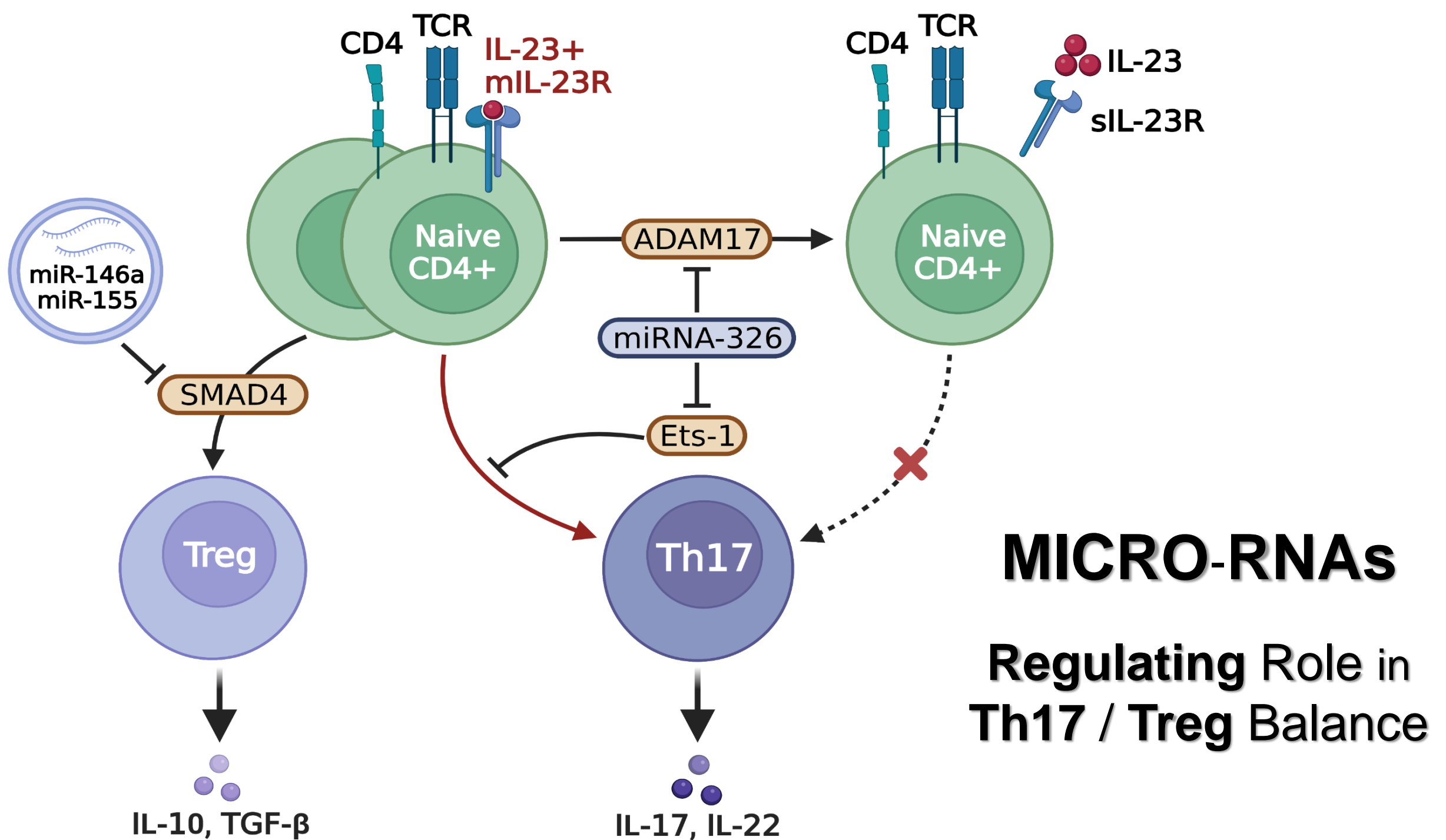


# INNATE IMMUNITY (Th17) in ORBITAL TISSUE



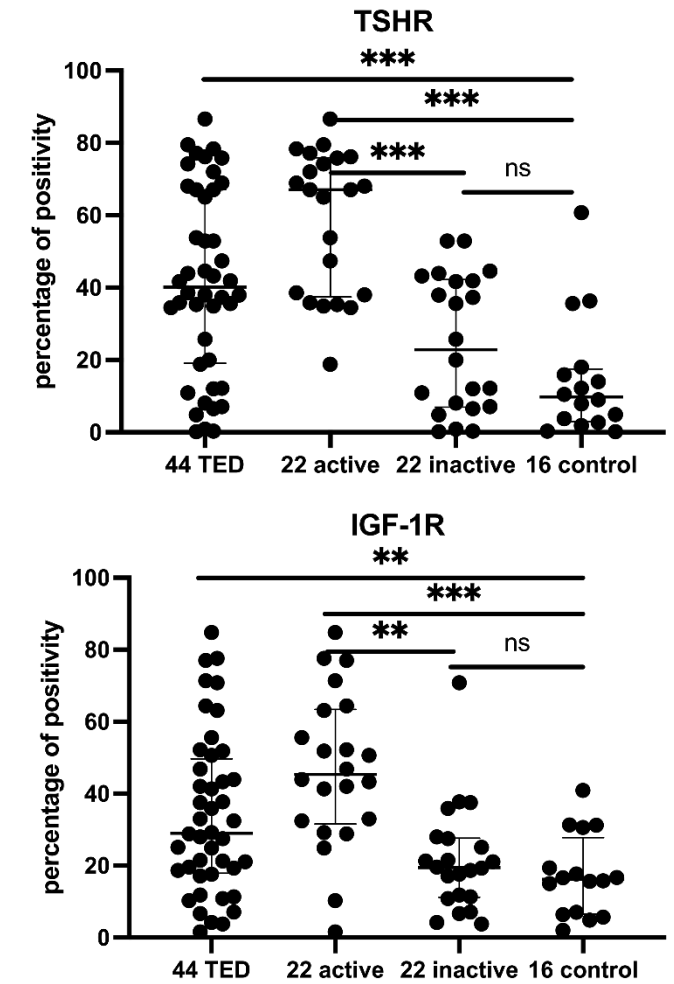
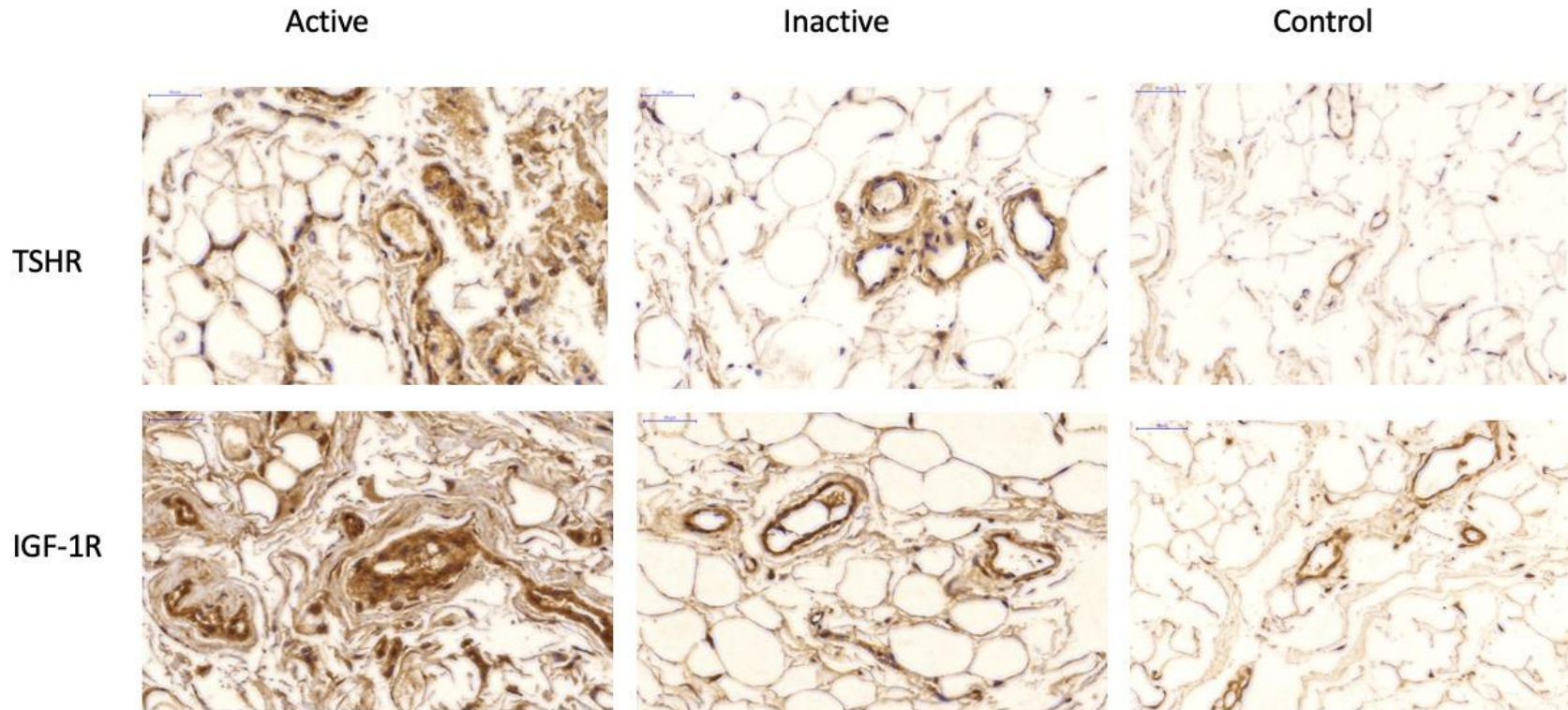
Multicenter, single-blind, case-control, immunohistochemical study of orbital tissue in GO

Kahaly & al., *Thyroid* 2022



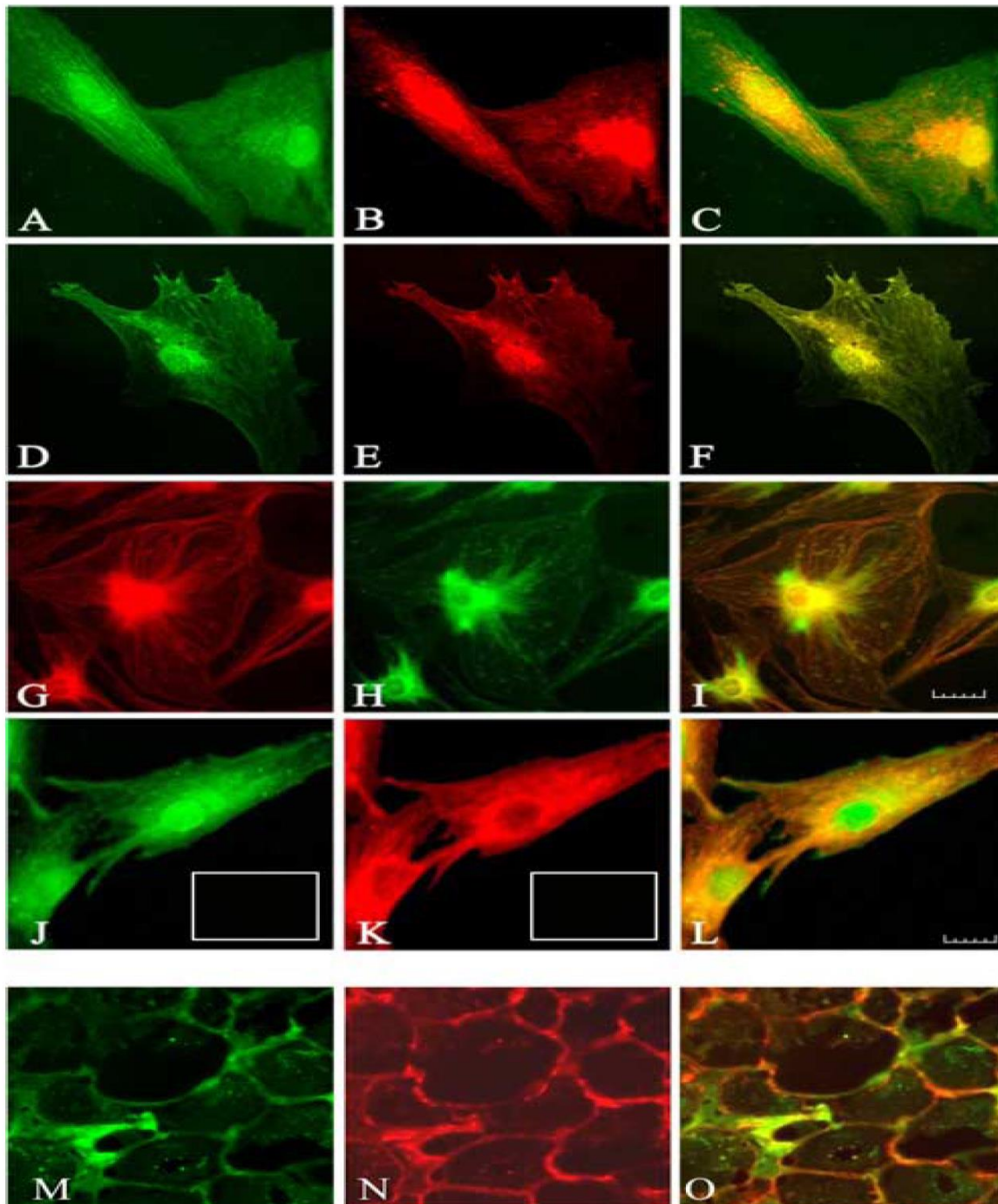


# TSH-R & IGF-1R Expression in Orbital Tissue



Multicenter, single-blind, case-control, immunohistochemical study of orbital tissue in GO

Kahaly & al., *Thyroid* 2022



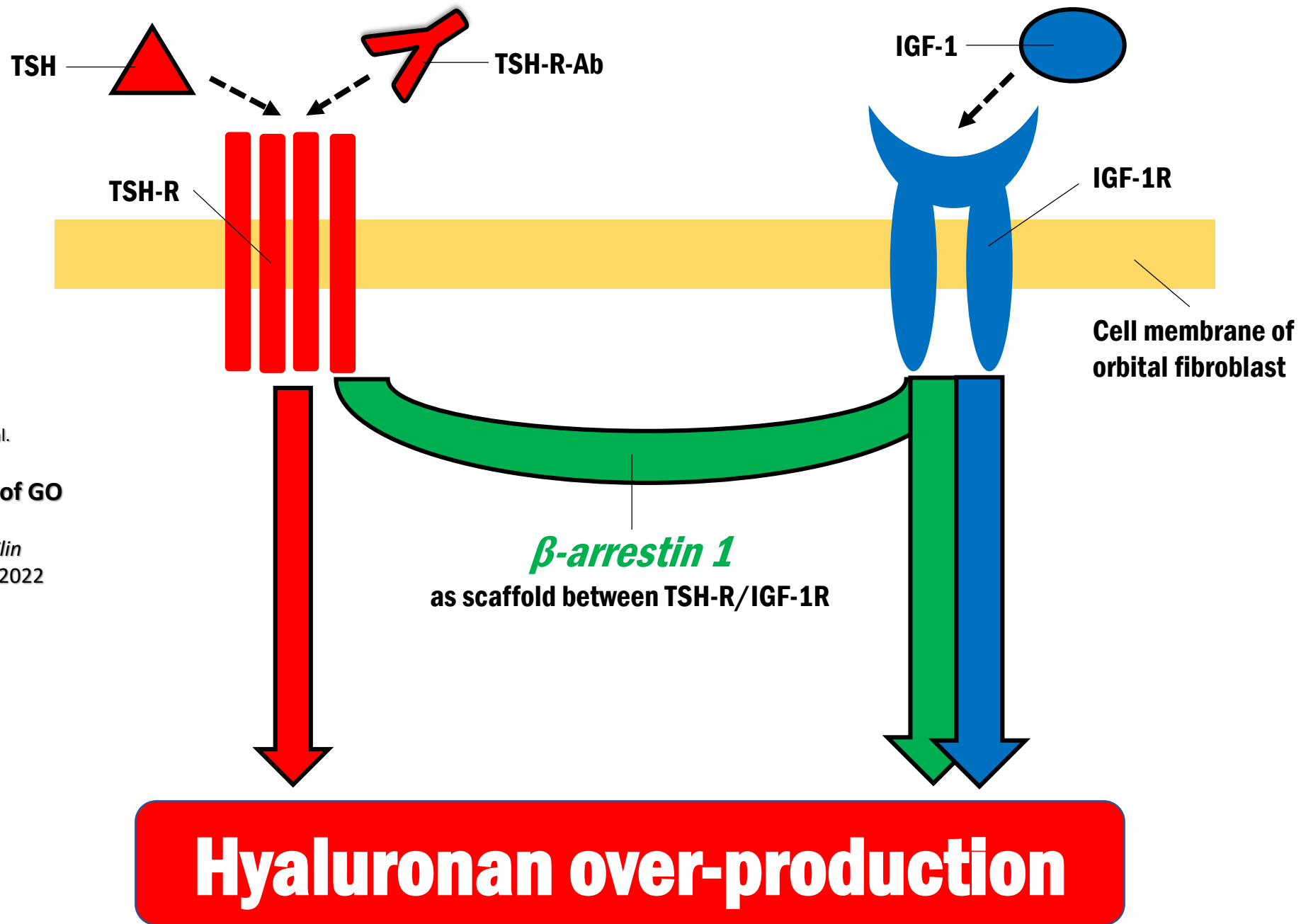
# TSH-R

and

# IGF-1R

## Colocalization

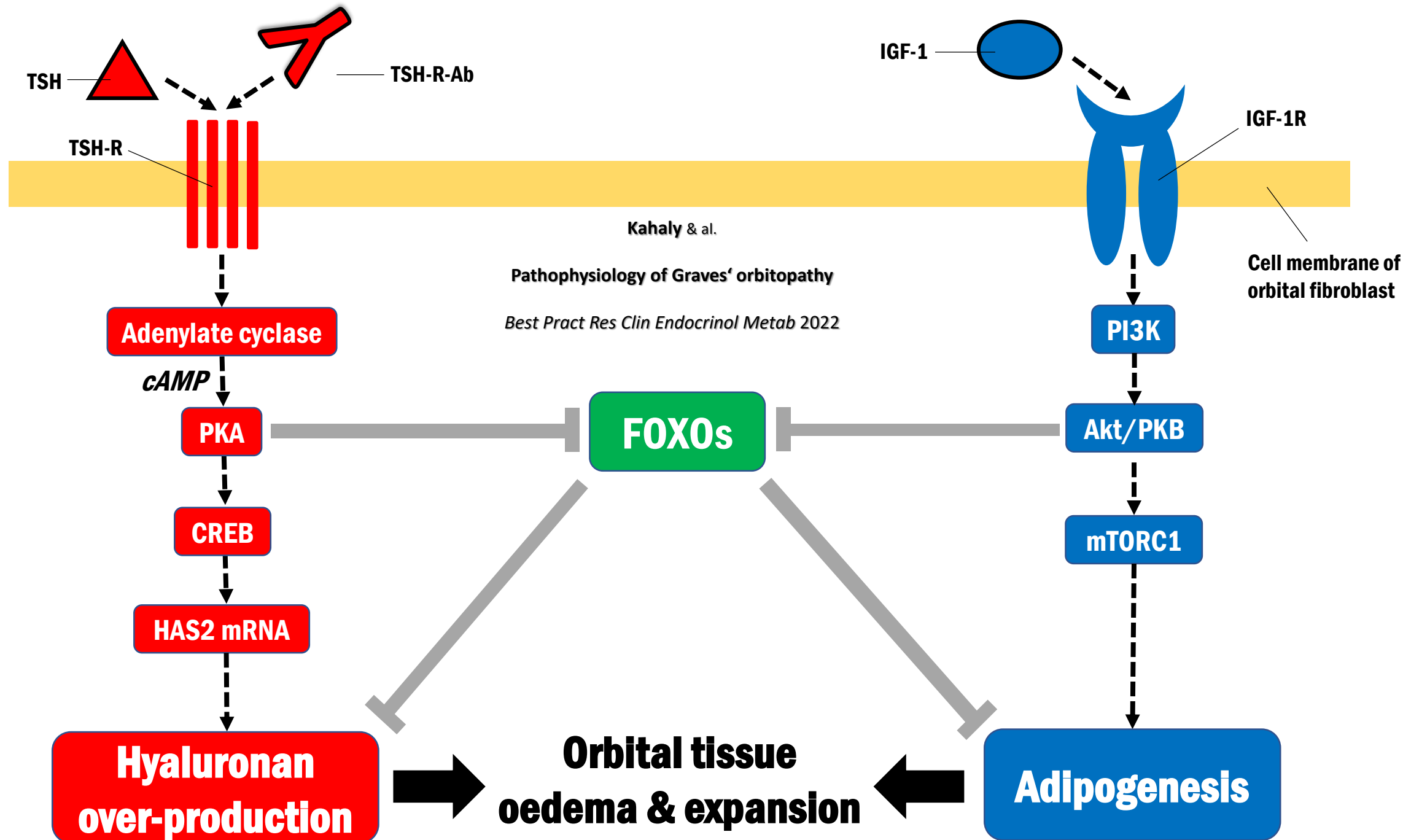
in **thyrocytes** and  
orbital **fibroblasts**



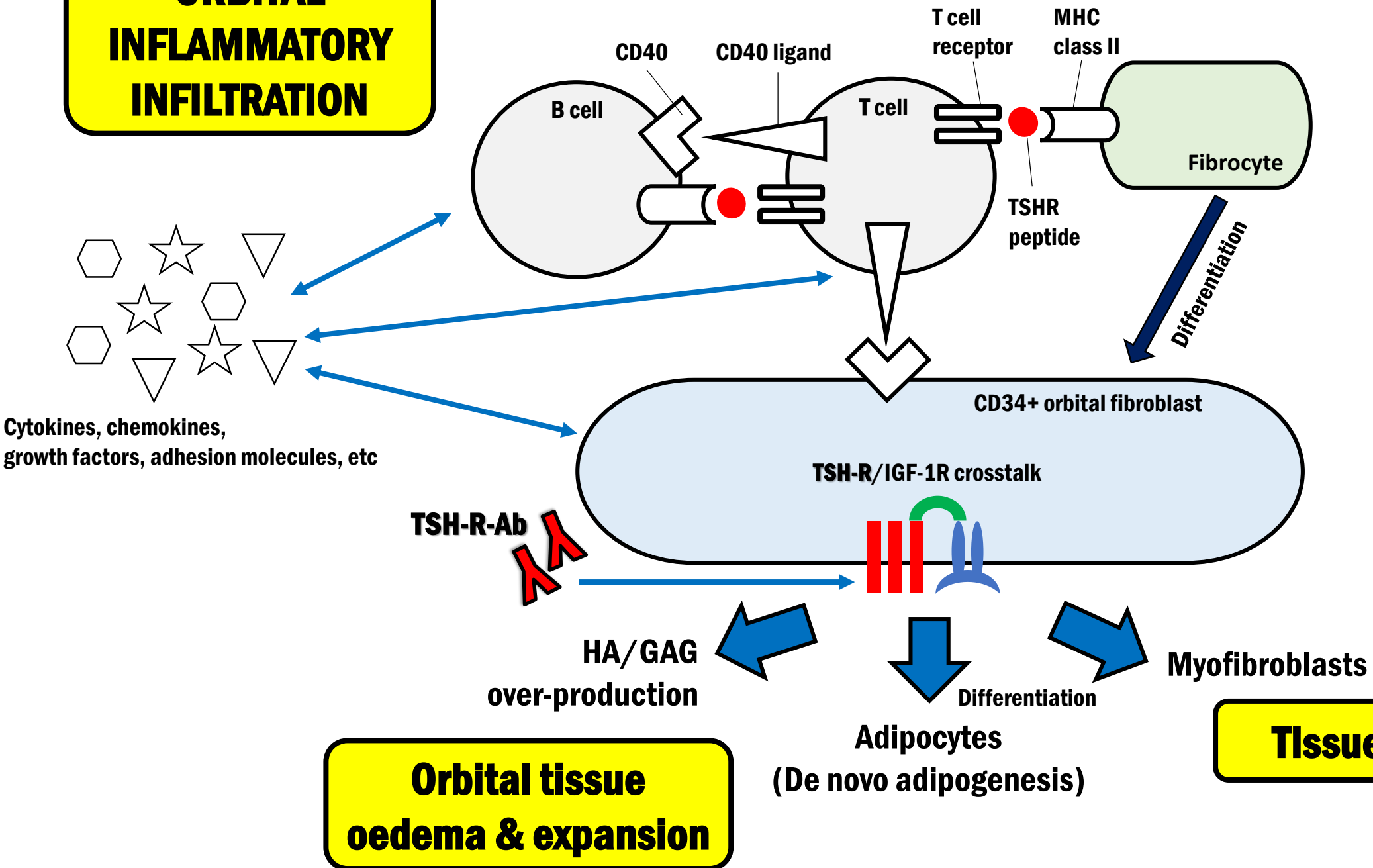
Kahaly GJ & al.

Pathophysiology of GO

Best Pract Res Clin  
Endocrinol Metab 2022



**ORBITAL  
INFLAMMATORY  
INFILTRATION**



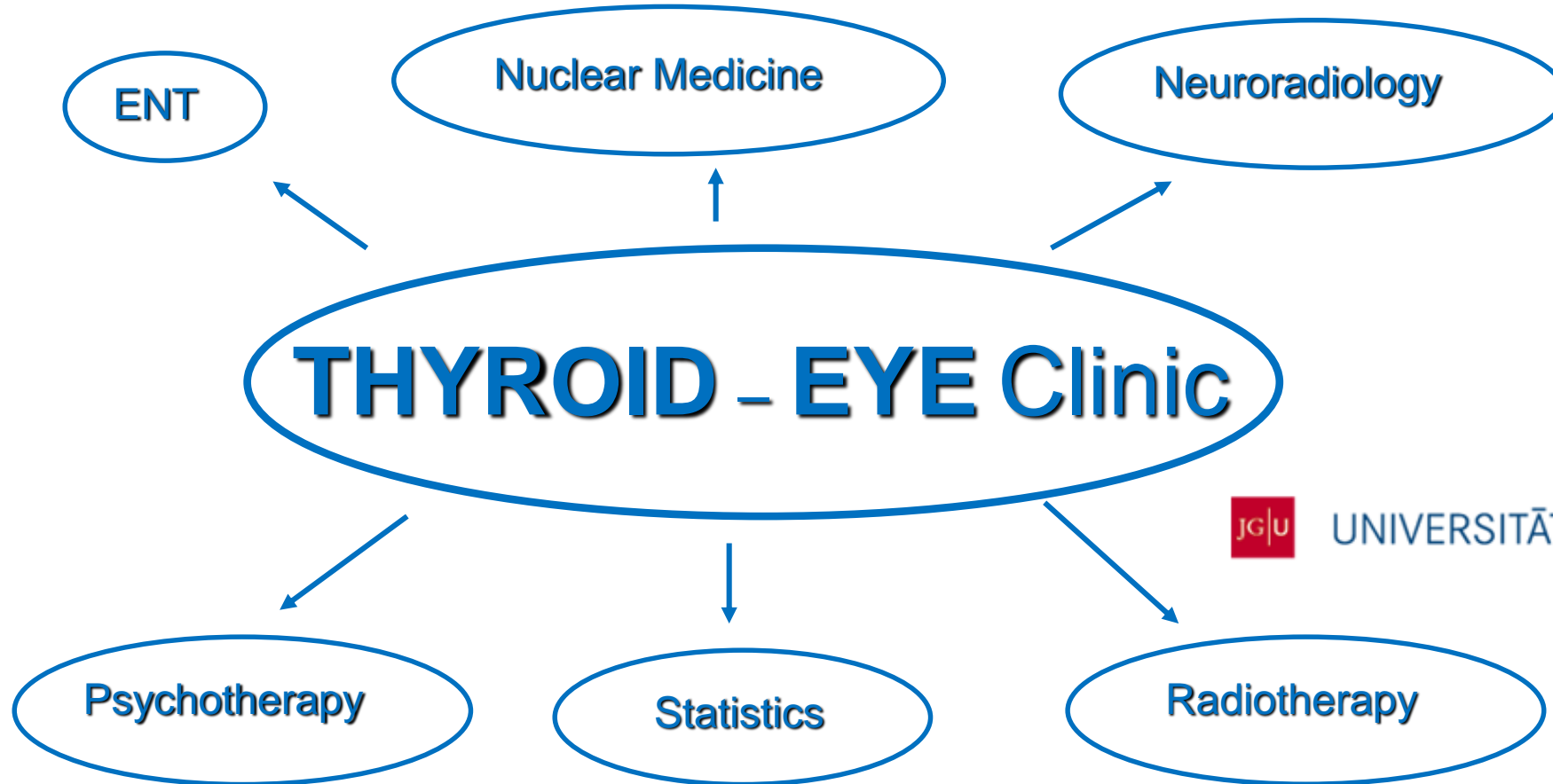
Kahaly GJ & al.

Graves' Orbitopathy

DeGroot Textbook of Endocrinology 2022



# JGU ORBITAL Center



## Multidisciplinary Network

# **The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy**

**L Bartalena<sup>1,\*</sup>, G J Kahaly<sup>2,\*</sup>, L Baldeschi<sup>3</sup>, C M Dayan<sup>4</sup>, A Eckstein<sup>5</sup>, C Marcocci<sup>6</sup>, M Marinò<sup>6</sup>, B Vaidya<sup>7</sup> and W M Wiersinga<sup>8</sup> on behalf of EUGOGO<sup>†</sup>**

<sup>1</sup>Department of Medicine and Surgery, University of Insubria, Varese, Italy, <sup>2</sup>Department of Medicine I, Johannes Gutenberg-University (JGU) Medical Center, Mainz, Germany, <sup>3</sup>Department of Ophthalmology, Cliniques Universitaires Saint Luc, Catholic University of Louvain, Brussels, Belgium, <sup>4</sup>Thyroid Research Group, Cardiff University School of Medicine, Cardiff, UK, <sup>5</sup>Clinic for Ophthalmology, University Clinic, Essen, Germany, <sup>6</sup>Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, <sup>7</sup>Department of Endocrinology, Royal Devon & Exeter Hospital and University of Exeter Medical School, Exeter, UK, and <sup>8</sup>Amsterdam University Medical Center, Amsterdam, the Netherlands

<sup>\*</sup>(L Bartalena and G J Kahaly contributed equally to this work and share first authorship)

<sup>†</sup>(List of EUGOGO members who collaborated for this Guideline is provided in the Acknowledgements section)

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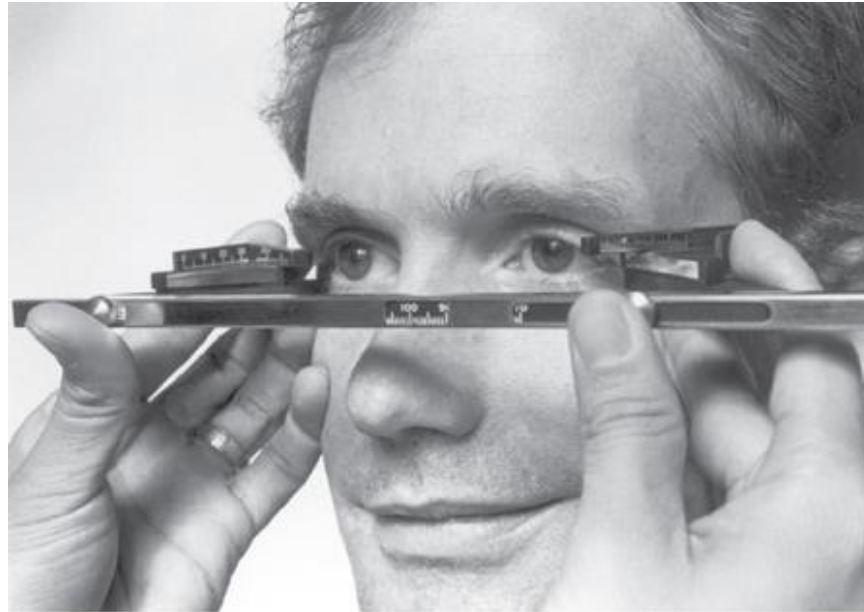
# Measures Utilized

## Clinical Activity Score (CAS)

*7-item CAS was used*

- 
- |   |  |
|---|--|
| 1 | Spontaneous orbital pain                                       |
| 2 | Gaze evoked orbital pain                                       |
| 3 | Eyelid swelling that is considered to be due to active GO      |
| 4 | Eyelid erythema  |
| 5 | Conjunctival redness that is considered to be due to active GO |
| 6 | Chemosis   |
| 7 | Inflammation of caruncle OR plica                              |

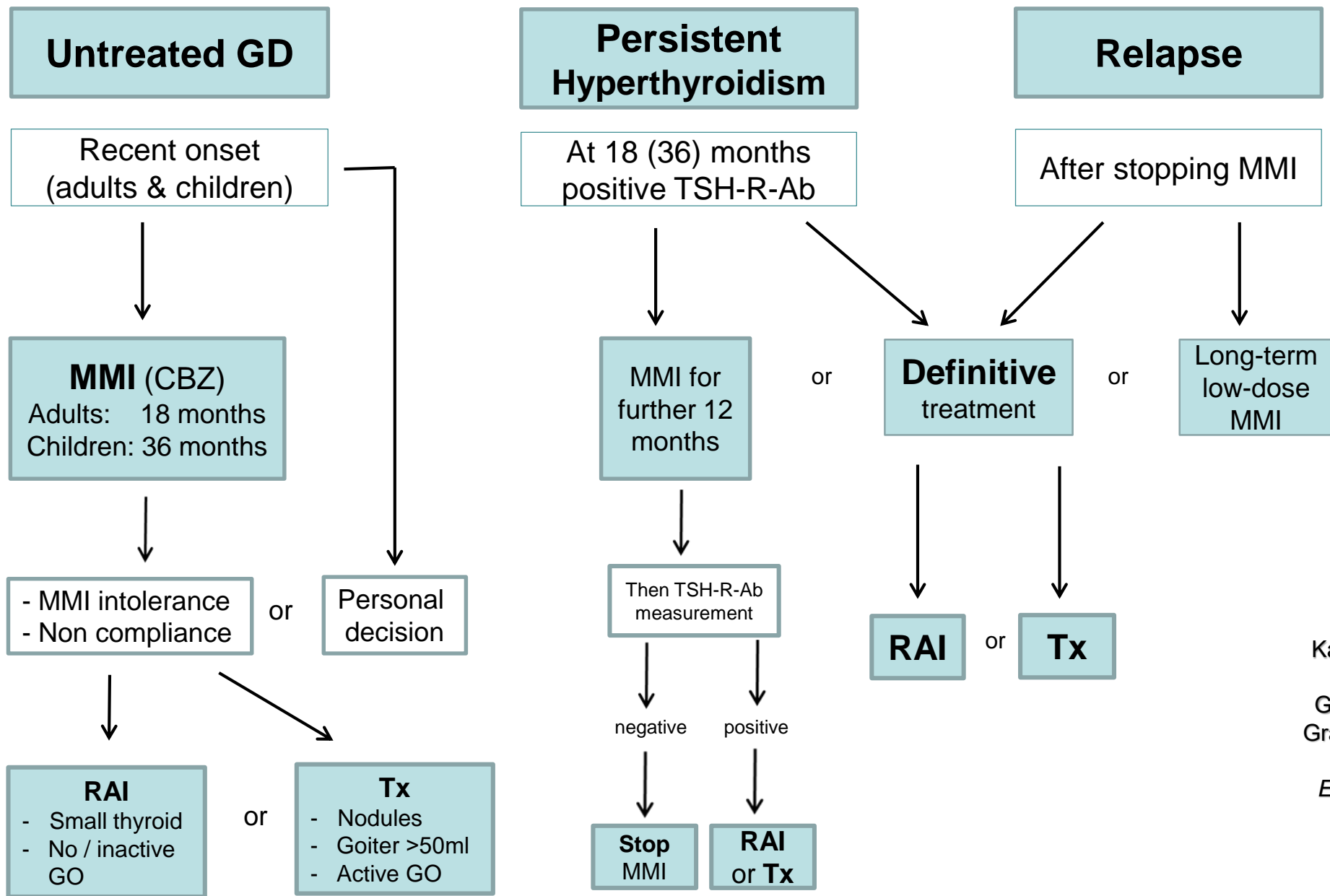
## Exophthalmometer - Proptosis



Source: Riordan-Eva P, Cunningham E: *Vaughan & Asbury's General Ophthalmology*, 18th Edition: <http://www.accessmedicine.com>

## Diplopia Score

- 
- |   |   |
|---|---|
| 0 | No diplopia   |
| 1 | <b>Intermittent</b> , i.e. diplopia in primary position of gaze, when tired or when first awakening |
| 2 | <b>Inconstant</b> , i.e. diplopia at extremes of gaze   |
| 3 | <b>Constant</b> , i.e. continuous diplopia in primary or reading position                           |



Kahaly GJ & al.,  
Guidelines for  
Graves' disease  
*Eur Thyroid J*  
2018

# Clinical **SEVERITY**

Wiersinga & Kahaly, Graves' Orbitopathy, 3d Ed. Karger 2017



**MILD** GO: Lid swelling, minimal upper right lid retraction, minimal proptosis



**SEVERE** GO: stare, severe lid retraction, proptosis, motility disturbance of the right eye with diplopia

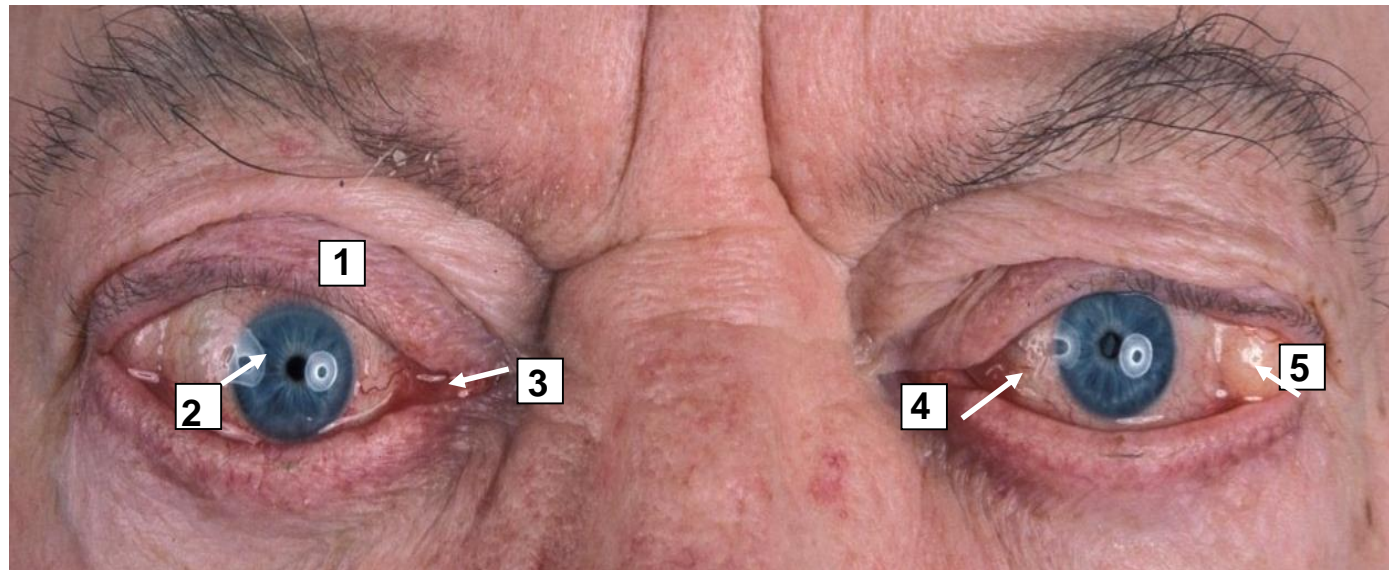


# Clinical ACTIVITY



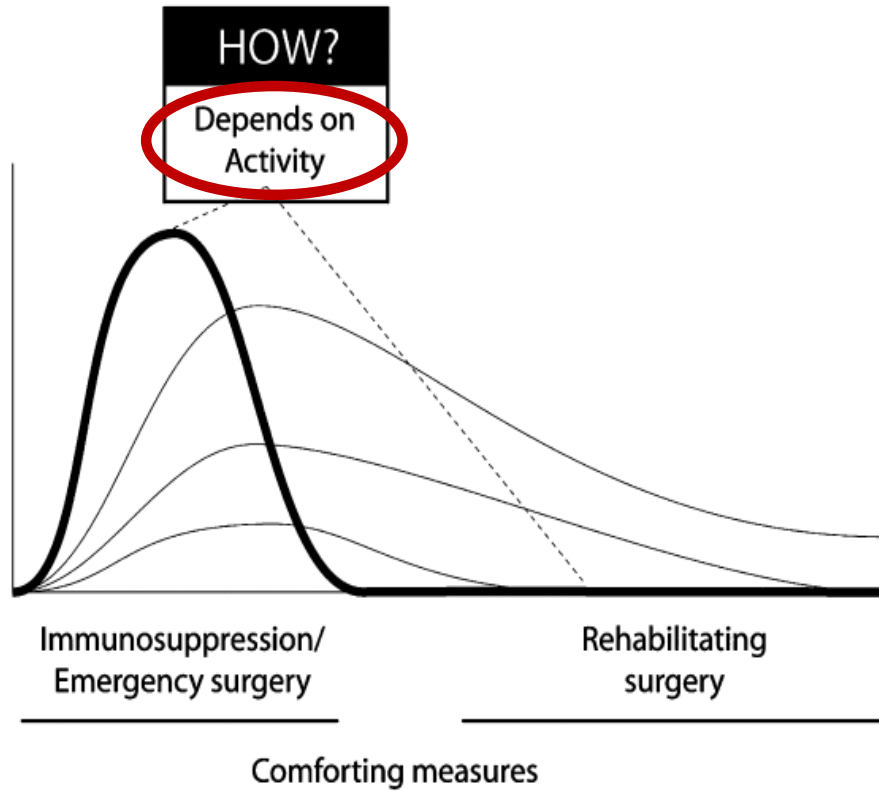
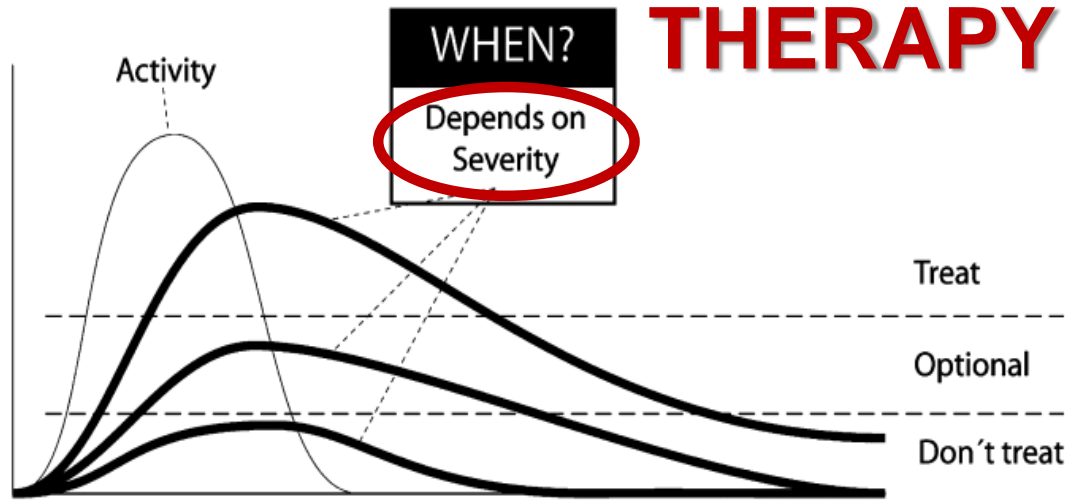
Wiersinga & Kahaly,  
Graves' Orbitopathy.  
3rd Ed. Karger 2017

**Inactive** GO. Mild lid swelling (1) and lid retraction left > right (2). CAS 1



**Active** GO. Lid swelling / redness (1), chemosis (2), swelling of plica and caruncle (3), conjunctivitis (4): CAS 5. Orbital prolapse of fat tissue (5)

# THERAPY



## MILD GO

### General recommendations

- Refrain from smoking
- Treat thyroid dysfunction (preferably with antithyroid drugs, especially if risk factors for deterioration/progression of GO are present (see below))
- Avoid iatrogenic hypothyroidism in treating patients with GD/GO
- Referral to thyroid-eye clinics if risk factors present (active GO, smoker, high TSHR-Ab, unstable / severe hyperthyroidism)
- Search for dry eye syndrome

### Management

#### Local treatment

- Artificial tears, especially when dry eye present
- Ophthalmic gels (cornea protection during the night)

#### Systemic adjunct therapy for active GO

- Selenium supplementation for six months (fasting intake)

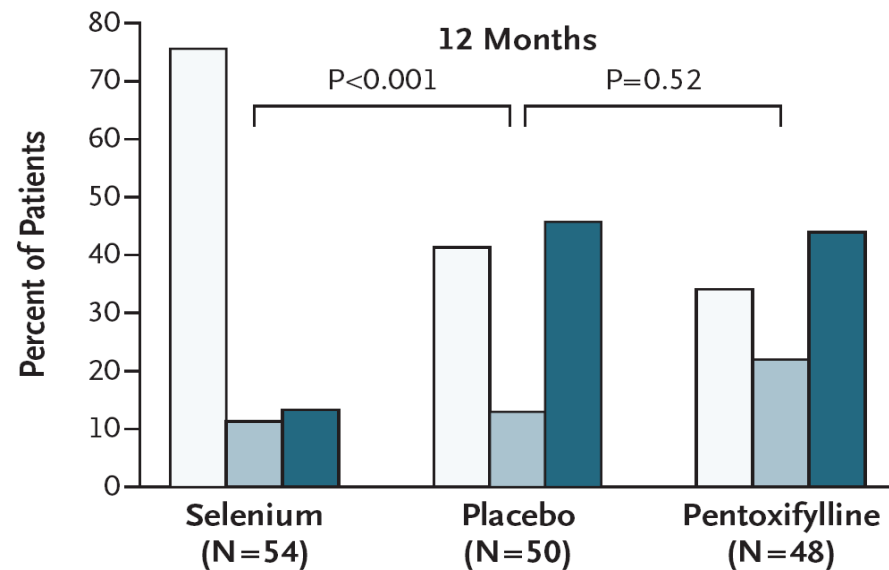
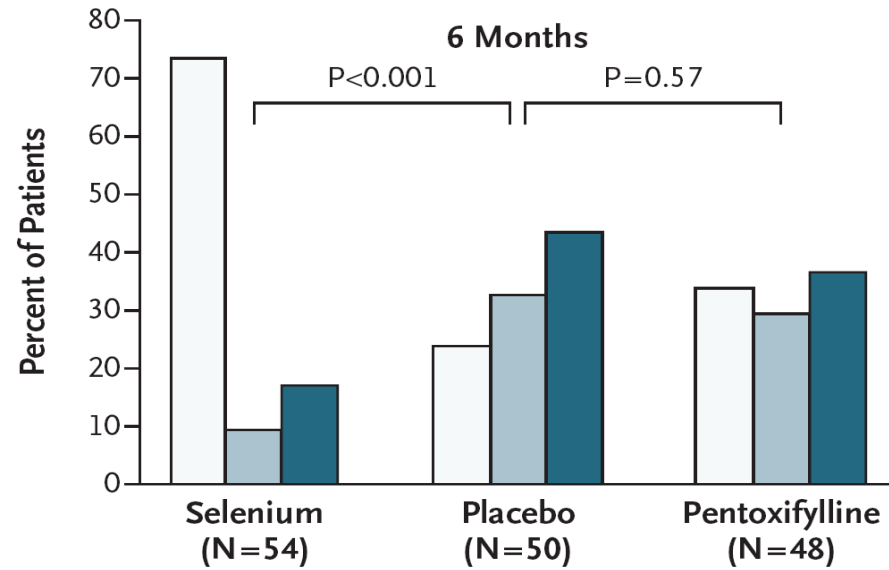
Quality of life markedly impaired



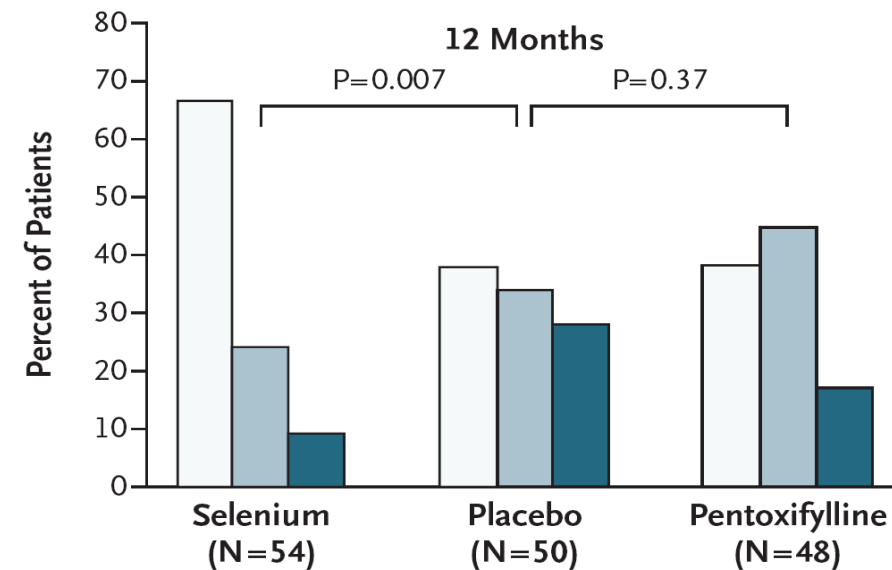
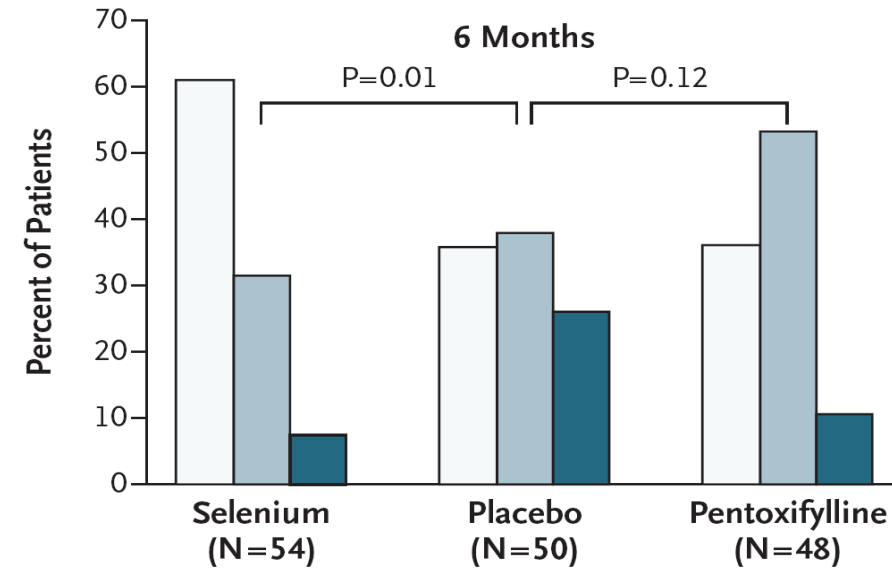
Discuss low dose immunomodulatory (active GO) or rehabilitative surgery (inactive GO) following extensive counseling and shared decision



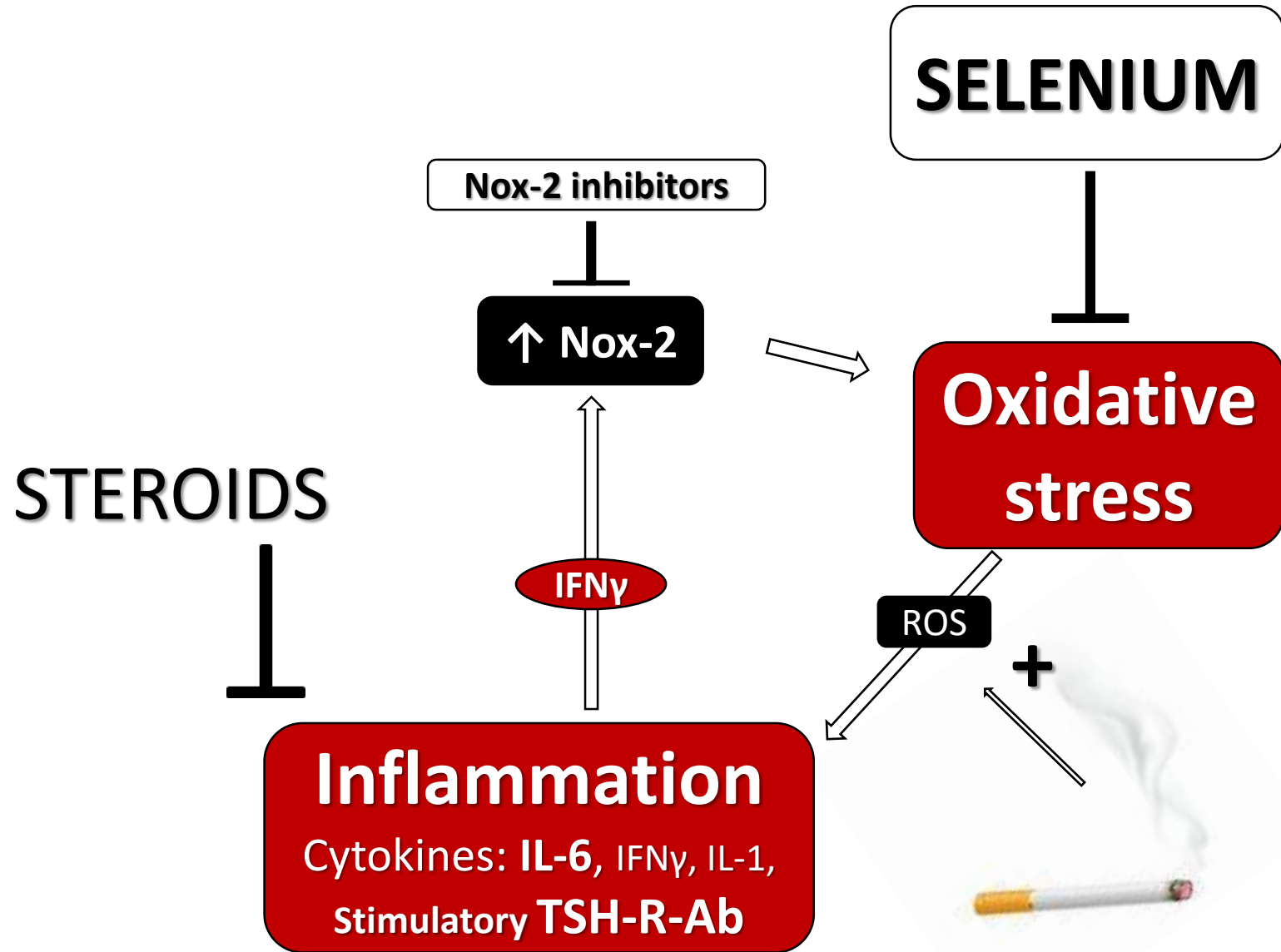
**A GO-QOL Score**



**B Overall Eye Evaluation in GO**

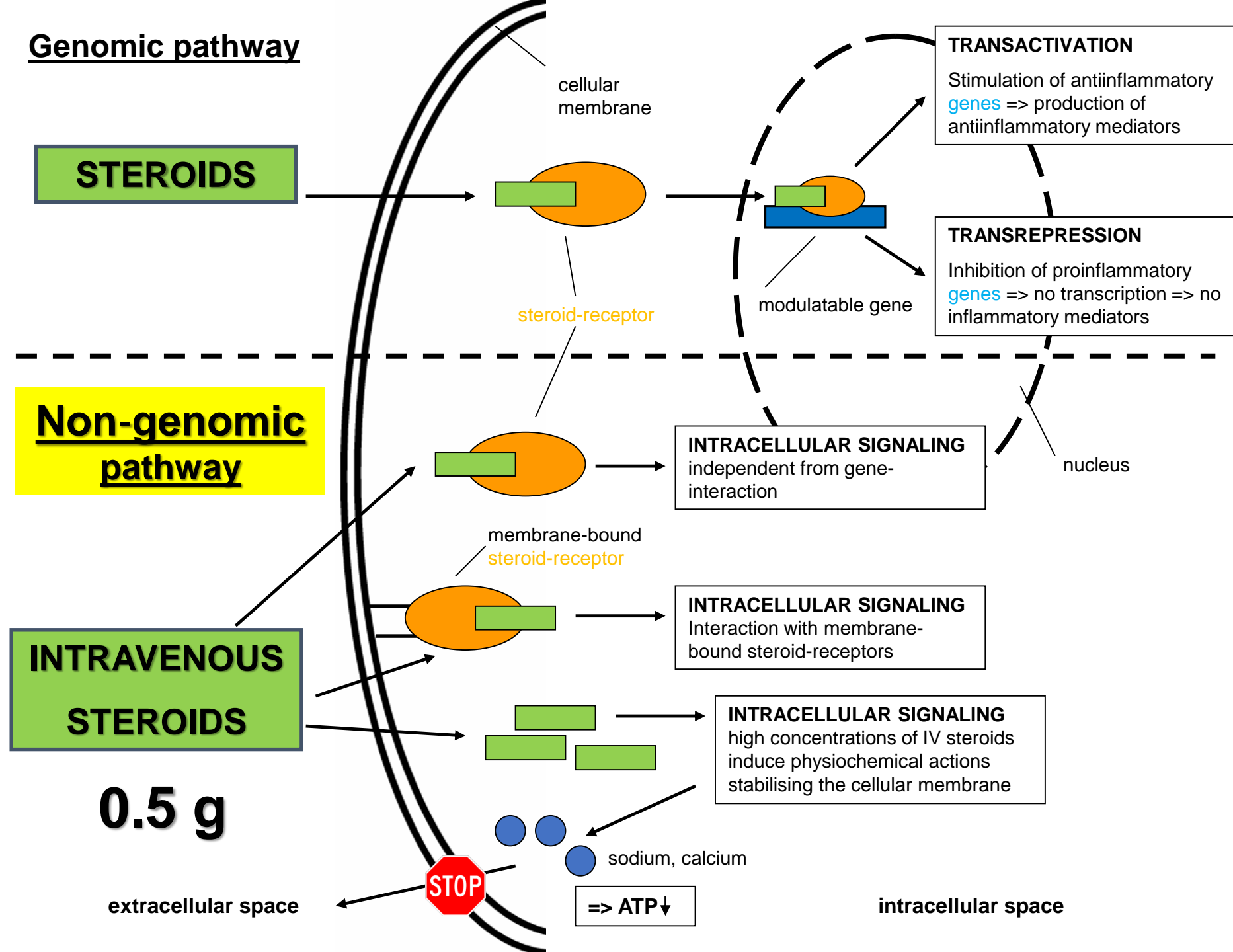






# **IV vs. oral steroids for active/severe GO**





Kahaly & al.

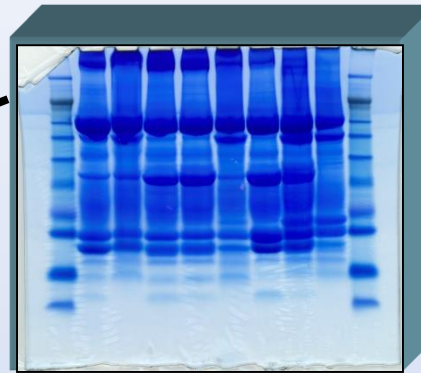
*Ther Adv Endo  
Metab 2020*

Schirmer strips  
– Elution



Fractionation with  
magnetic beads  
(C8, C18, WCX)

SDS - PAGE



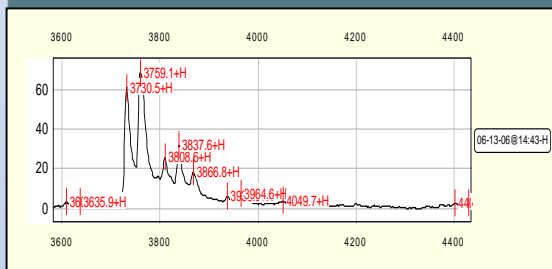
Cut out gel slices

Cut out gel slices

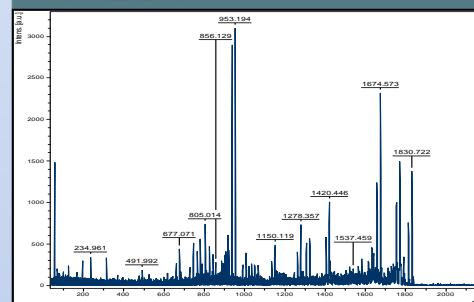
Protein extraction from a  
part of the gel slice

In-Gel Trypsin digestion  
(rest of gel slice)

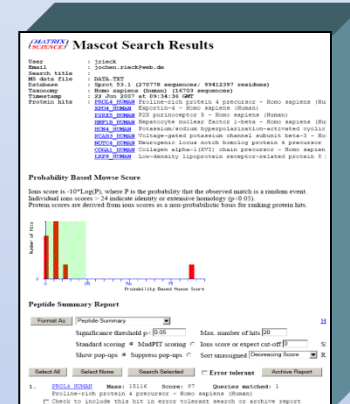
SELDI measurement



MALDI measurement



Data base  
validation



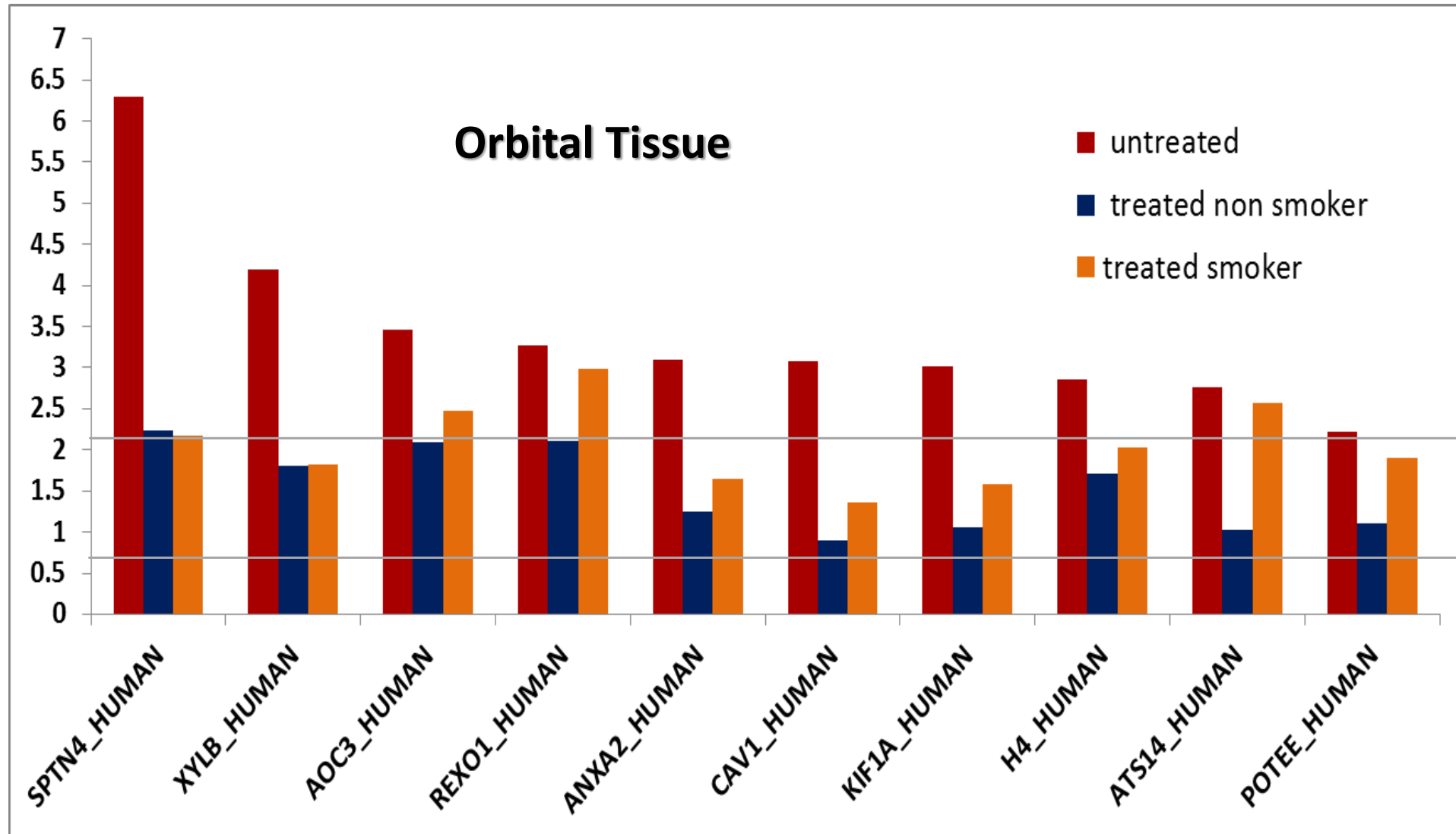
Kahaly & al.,

Thyroid 2012

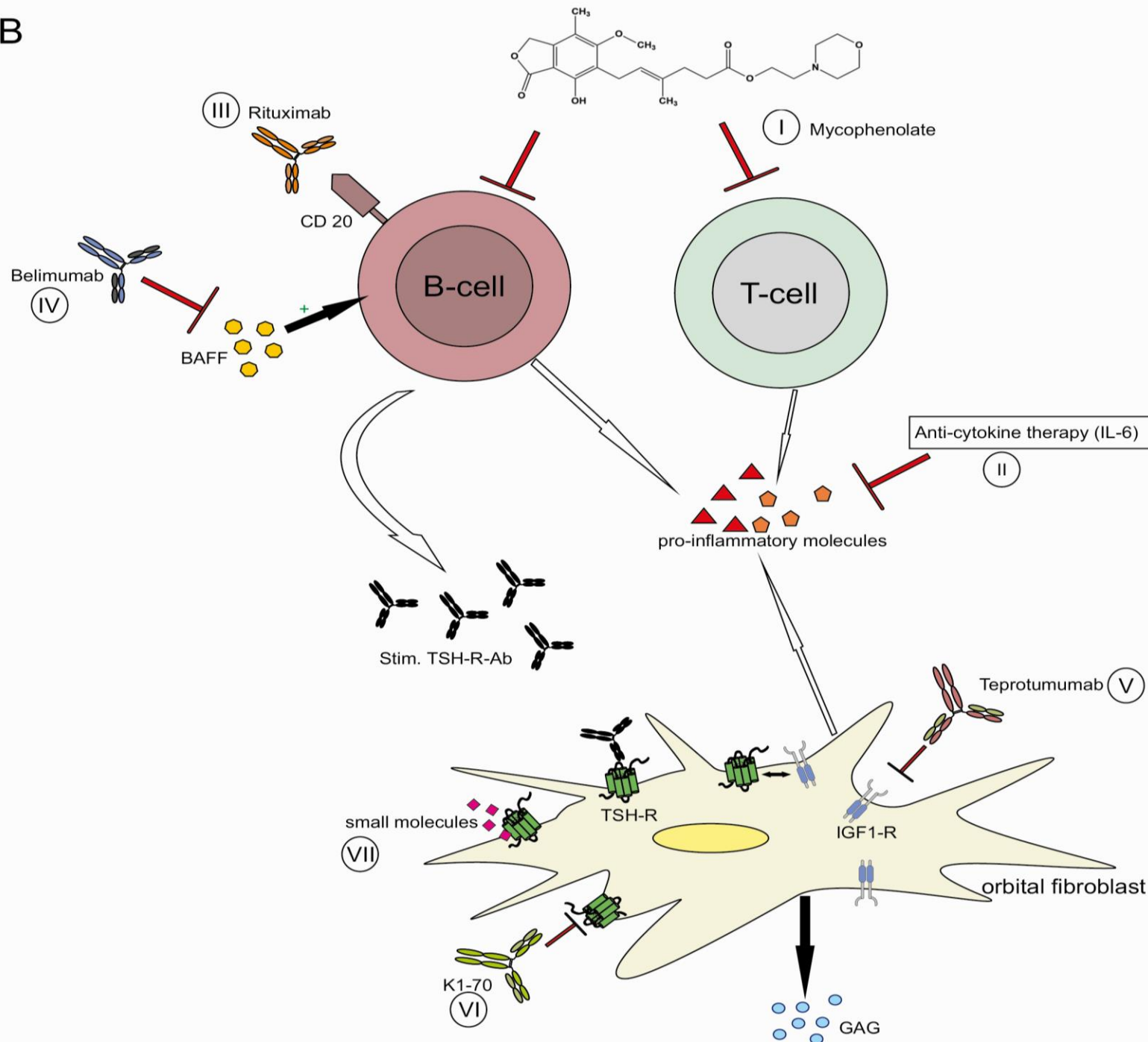
Invest Ophthalmol  
Visual Science 2015

JCEM 2015

# Proteomics in Graves' orbitopathy: IV steroids decrease upregulation of inflammatory proteins



B



## Sites of action of novel treatments for GO

Kahaly GJ

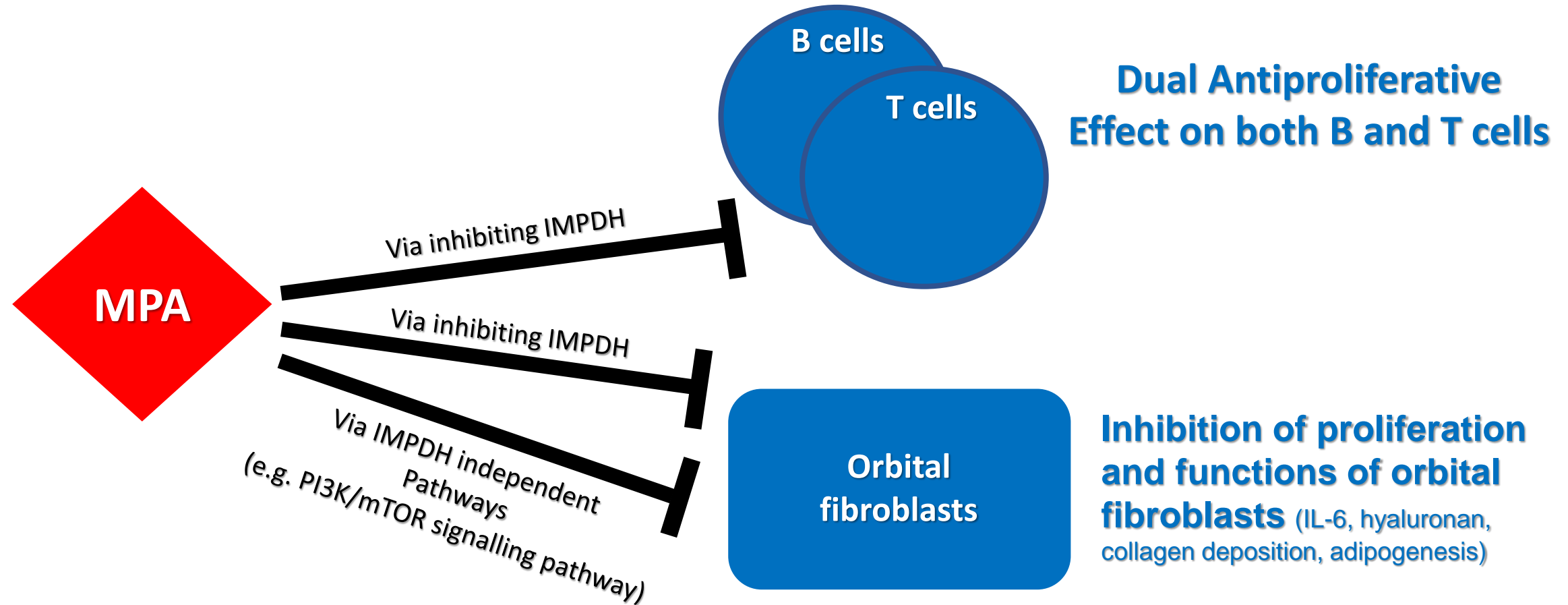
*J Clin Endocrinol Metab*, Volume 105,  
Issue 12, December 2020, Pages 3704–  
3720

<https://doi.org/10.1210/clinem/dgaa646>

ENDOCRINE  
SOCIETY

OXFORD  
UNIVERSITY PRESS

# Mycophenolate - Rationale





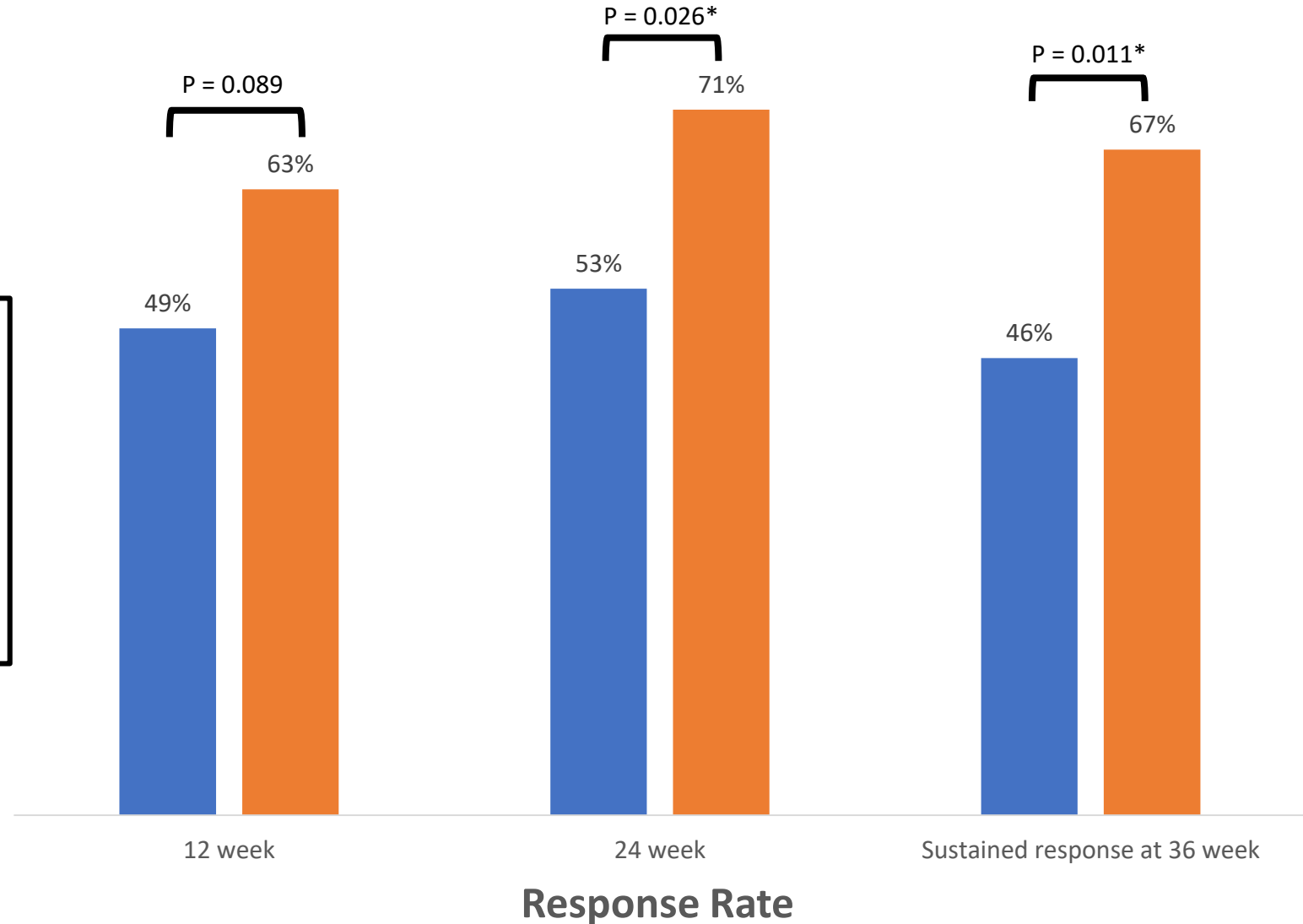
# Mycophenolate – RCT (**EUGOGO** Trial)

■ **IVMP (total 4.5g, n = 81)**

■ **IVMP + Mycophenolate sodium, MPS (360mg BD for 24wk, n = 83)**

Overall response defined as  $\geq 2$  measures of a composite index without any deterioration:

- 1) ↓ CAS by  $\geq 2$  points
- 2) ↓ Eyelid swelling
- 3) ↓ Proptosis by  $\geq 2$ mm
- 4) ↓ lid width by  $\geq 2$ mm
- 5) Improvement of  $\geq 8$  degrees in EOM motility
- 6) Improvement in diplopia



Kahaly GJ & al. *Lancet D&E* 2018

## MODERATE-TO-SEVERE AND ACTIVE GO FIRST – LINE TREATMENT

### General Recommendations

- Referral to thyroid-eye clinic for counseling and treatment plan shared with patient
- Stop smoking
- Treat thyroid dysfunction with antithyroid drugs
- Avoid iatrogenic hypothyroidism in treating patients with GD/GO

0.5 g intravenous Methylprednisolone  
/ week / 6 weeks  
+ Mycophenolate sodium 0.72 g / day / 6 wk.

Response /  
partial response

0.25 g intravenous Methyl-  
Prednisolone / wk. / 6 wk.  
+ Mycophenolate sodium  
0.72 g / day / 18 wk.

Response

Stop therapy

No response /  
Deterioration

Second–line  
treatment

0.75 g intravenous Methylprednisolone  
/ week / 6 weeks

Response /  
Partial Response

0.5 g intravenous Methyl-  
Prednisolone / wk. / 6 wk.

Response

Stop therapy

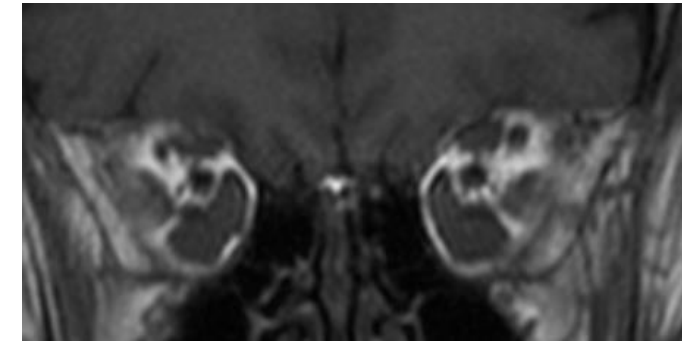
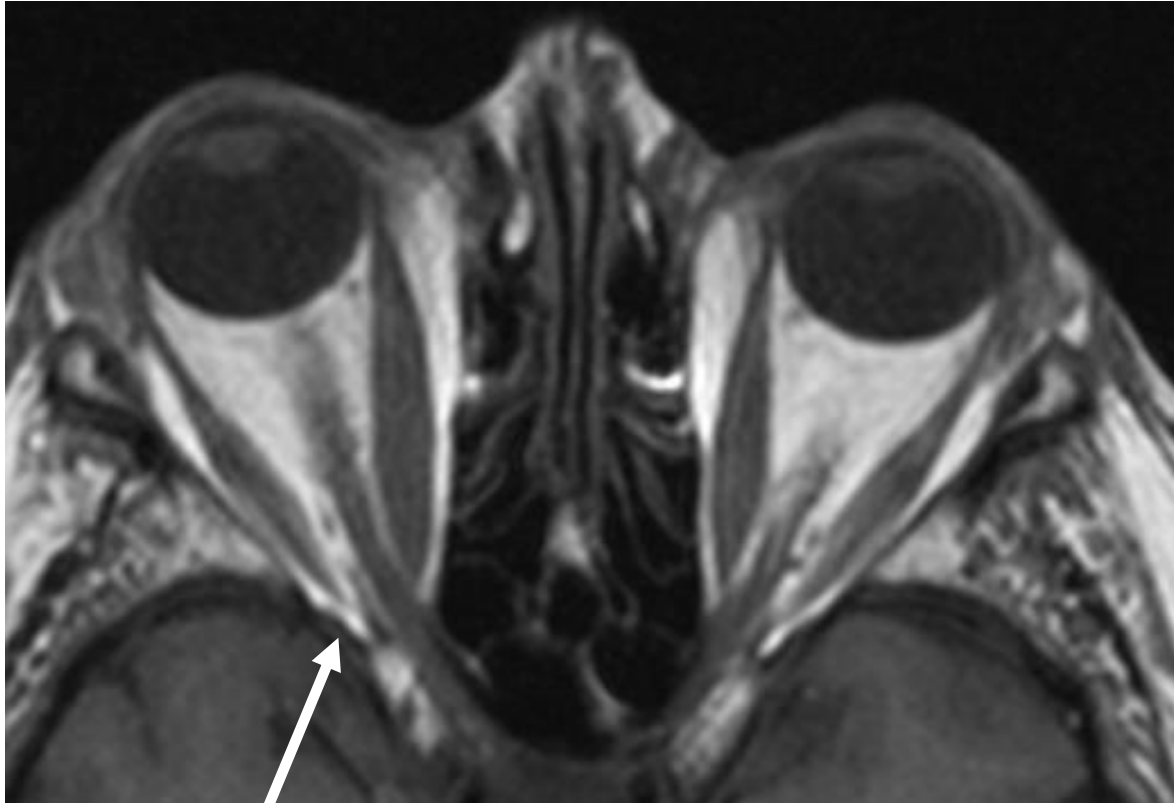
No response /  
Deterioration of  
ophthalmic signs

Second – Line  
treatment

INACTIVE GO

Rehabilitative surgery as needed or required by the patient

# Optic Neuropathy (MRI)



**IV Steroids 750mg**  
3x / wk / 2 wk

**Intracranial prolapse of orbital adipose tissue**  
→ Optic nerve compression and apical crowding

# SIGHT - THREATENING GO (Optic Neuropathy)

## General recommendations

- Immediate referral to thyroid-eye clinic
- Stop smoking
- Avoid radioactive iodine treatment
- Stabilize thyroid dysfunction with antithyroid drugs
- Avoid iatrogenic hypothyroidism in treating patients with GD/GO

## Specific Management

Intravenous methylprednisolone (0.5 – 1 gram, as single dose repeated on three consecutive or alternate days)



Daily monitoring of ophthalmic parameters



After one week, evaluation if therapy can be continued



Yes



Further with intravenous methylprednisolone as in week one



Response



0.5 g intravenous methylprednisolone 1x / wk. (cumulative dose <8 g / cycle)



Partial response



Urgent orbital decompression surgery (Imaging recommended)



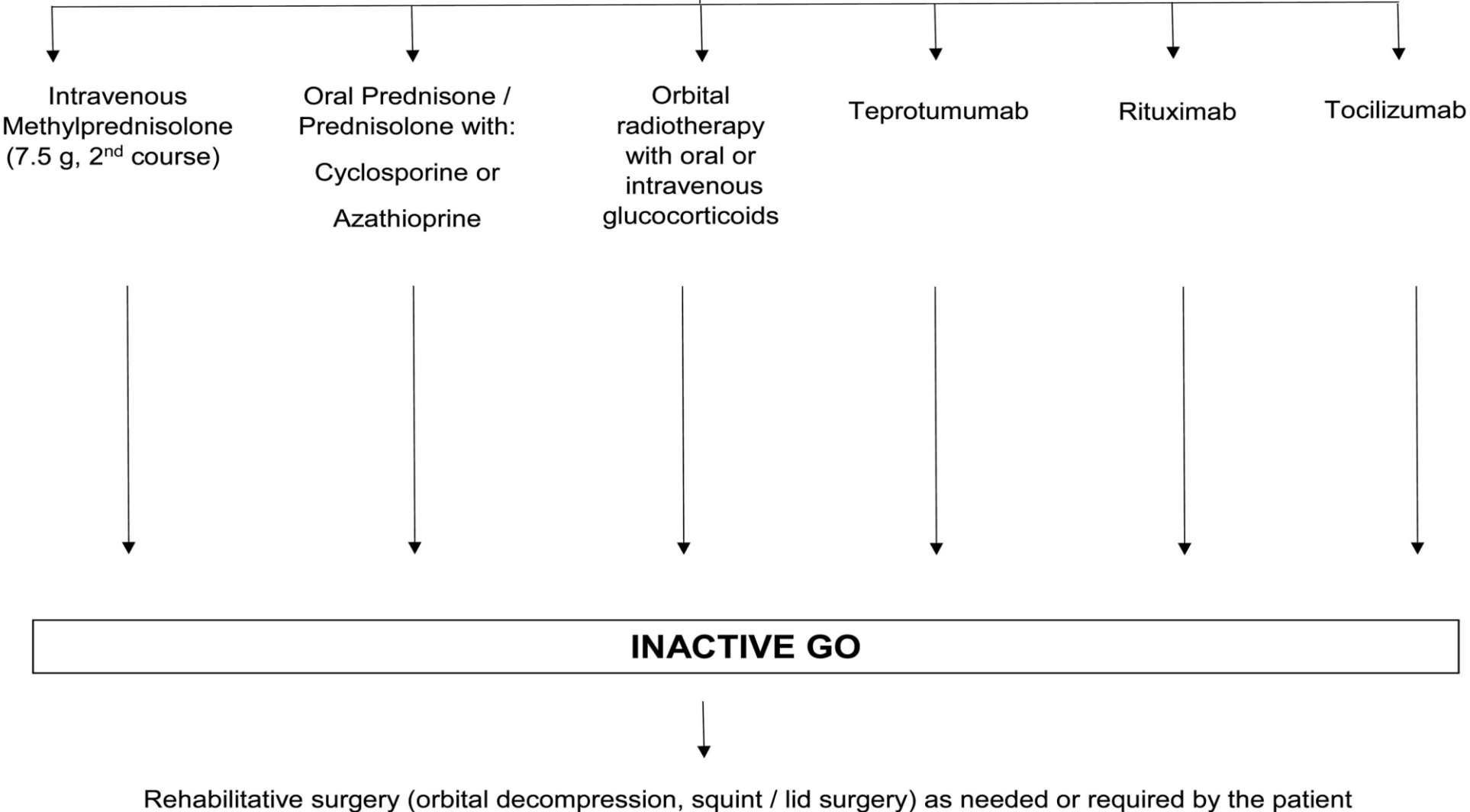
No response and/or deterioration of ophthalmic signs



MODERATE-TO-SEVERE AND ACTIVE GO  
SECOND – LINE TREATMENTS

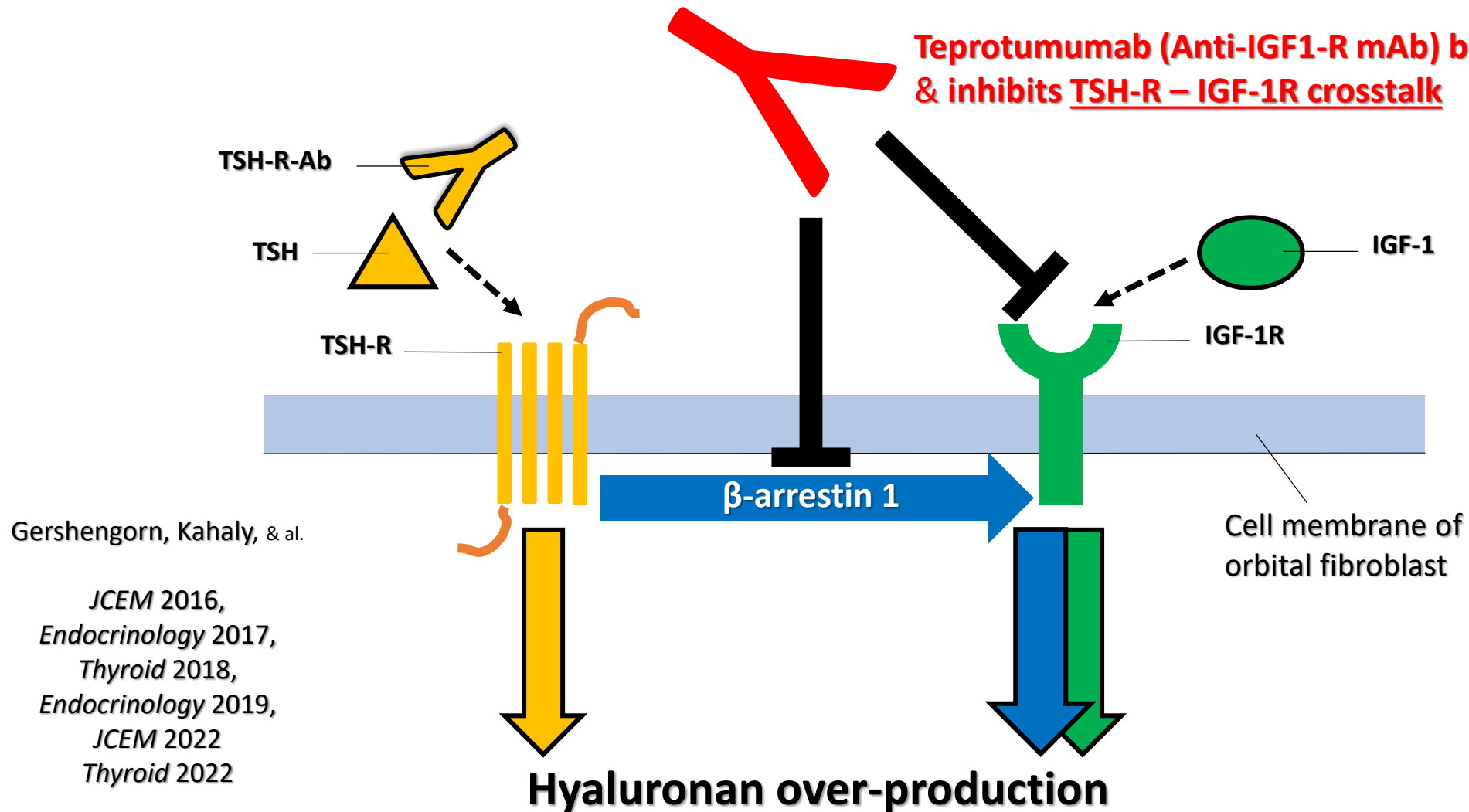
General  
Recommendations

- Referral to thyroid-eye clinic for counseling and treatment plan shared with patient
- Stop smoking
- Treat thyroid dysfunction with antithyroid drugs
- Avoid iatrogenic hypothyroidism in treating patients with GD/GO





# Teprotumumab - Rationale

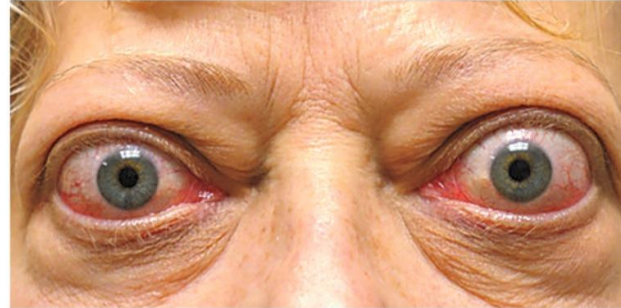


**A Clinical Photographs of a Patient in the Placebo Group**

Baseline



24 Wk after Initial Dose



**B Clinical Photographs of a Patient in the Teprotumumab Group**

Baseline

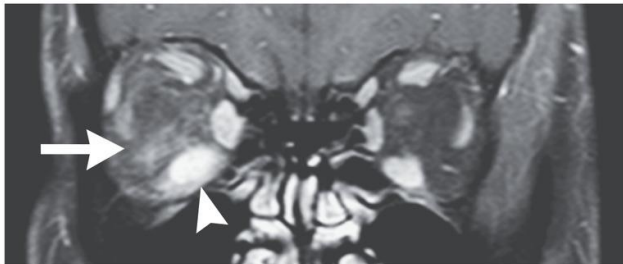


24 Wk after Initial Dose

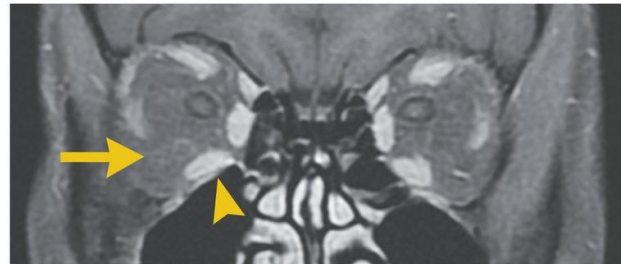


**C MRIs from a Patient in the Teprotumumab Group**

Baseline



24 Wk after Initial Dose



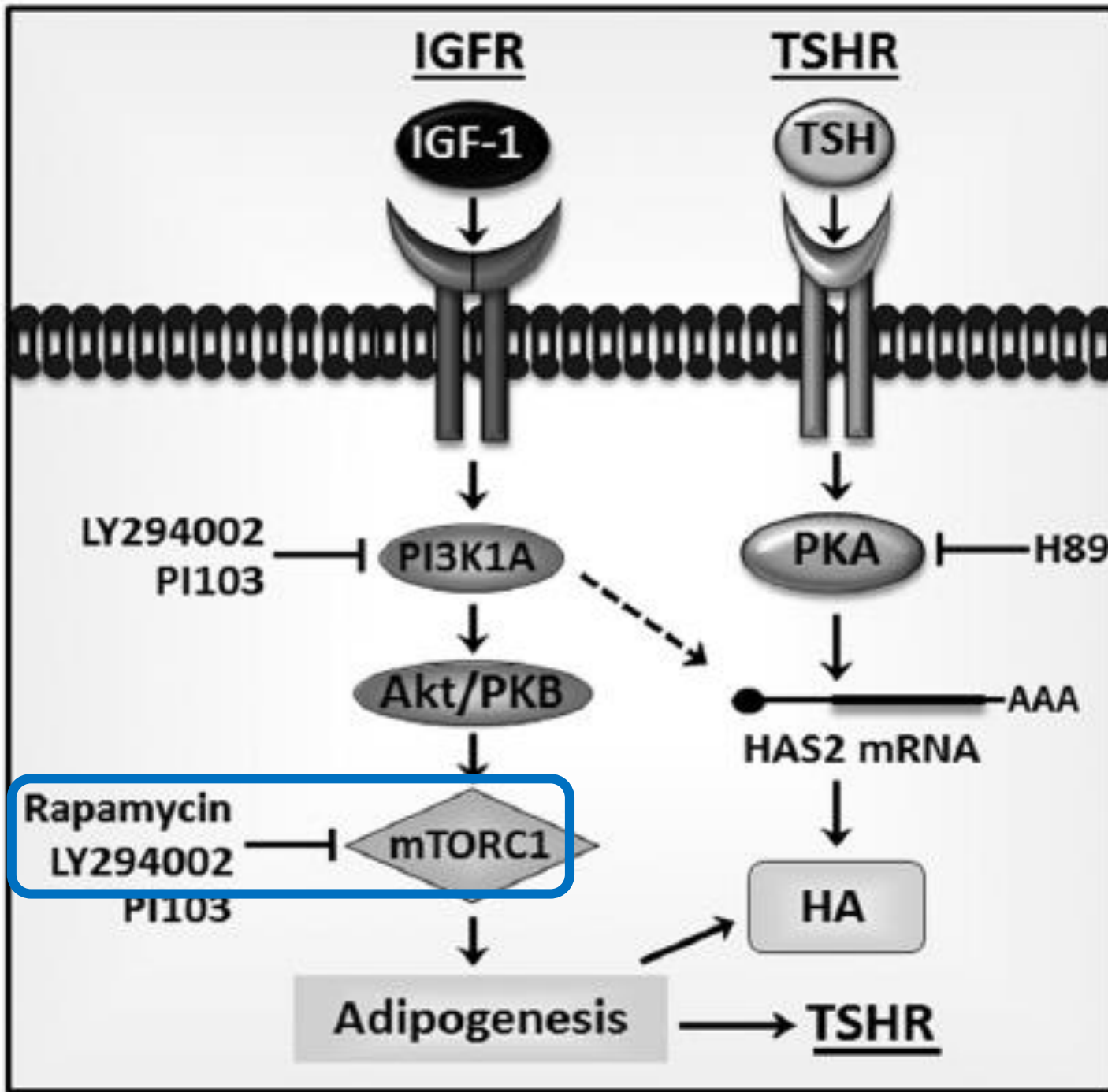
**TEPROTUMUMAB FOR  
THE TREATMENT OF  
ACTIVE GO**

Douglas, **Kahaly** & al.,

***N Engl J Med*** 2020;  
382:341-352

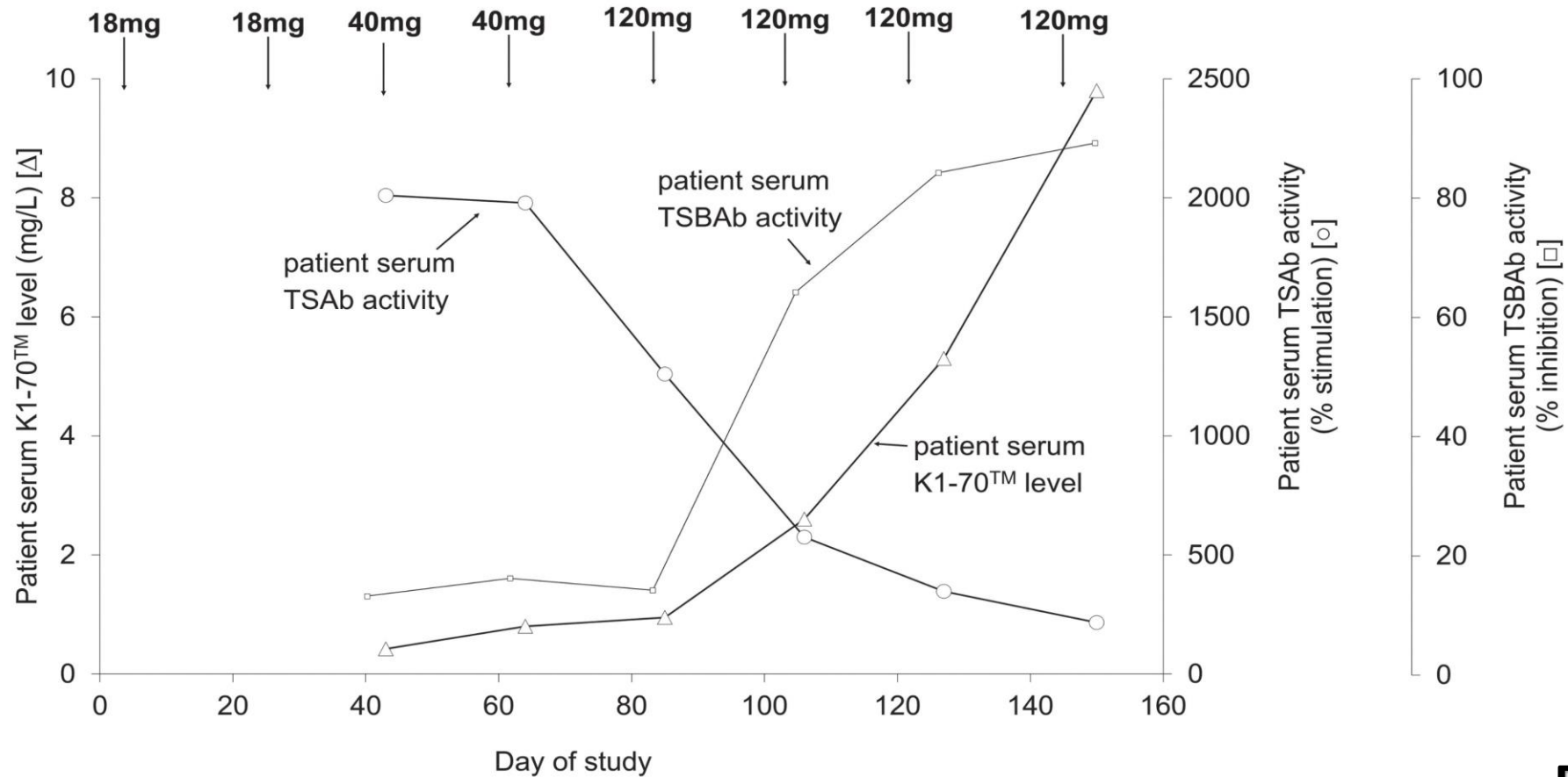


**Kahaly GJ** & al.  
***Lancet DE*** 2021

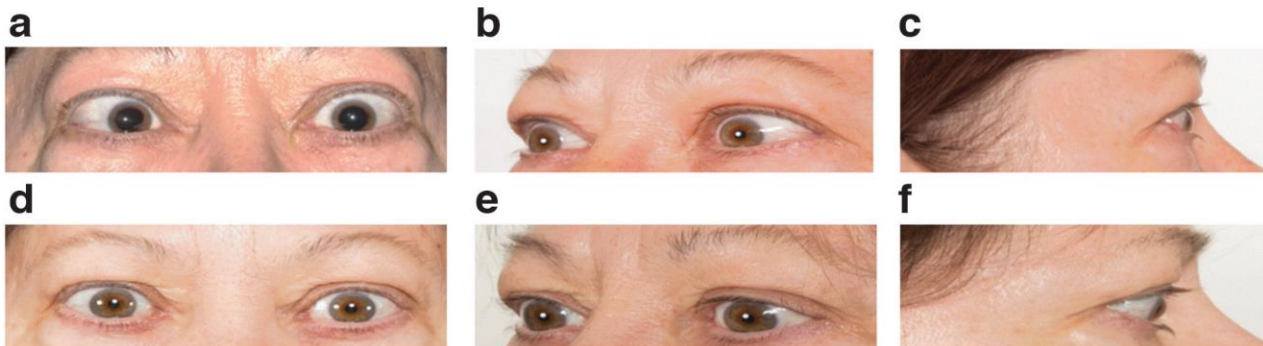


# SIROLIMUS for GO

- **mTOR inhibitor**
- **Inhibits T / B cell activation**
- **Antifibrotic effect**

**A****Dose of K1-70™ (i.m.)**

## Blocking the TSH-R with K1-70 in a Patient with GO

**B**

Ryder &amp; al.

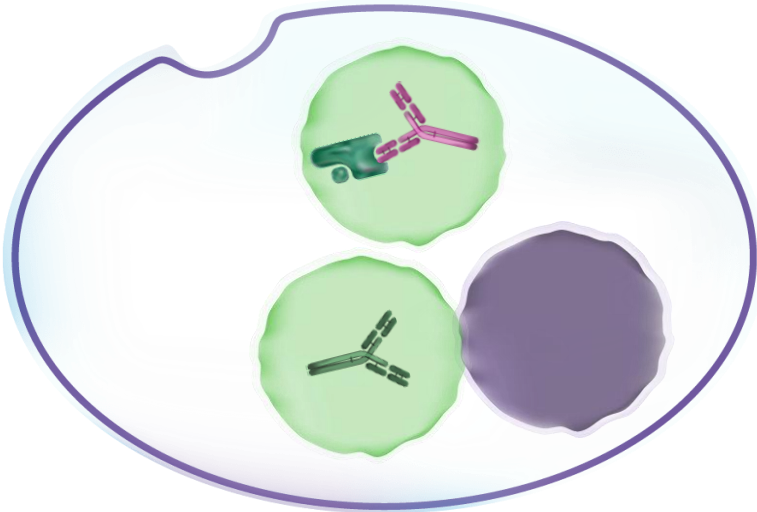
THYROID 2021; 31(10): 1597-1602



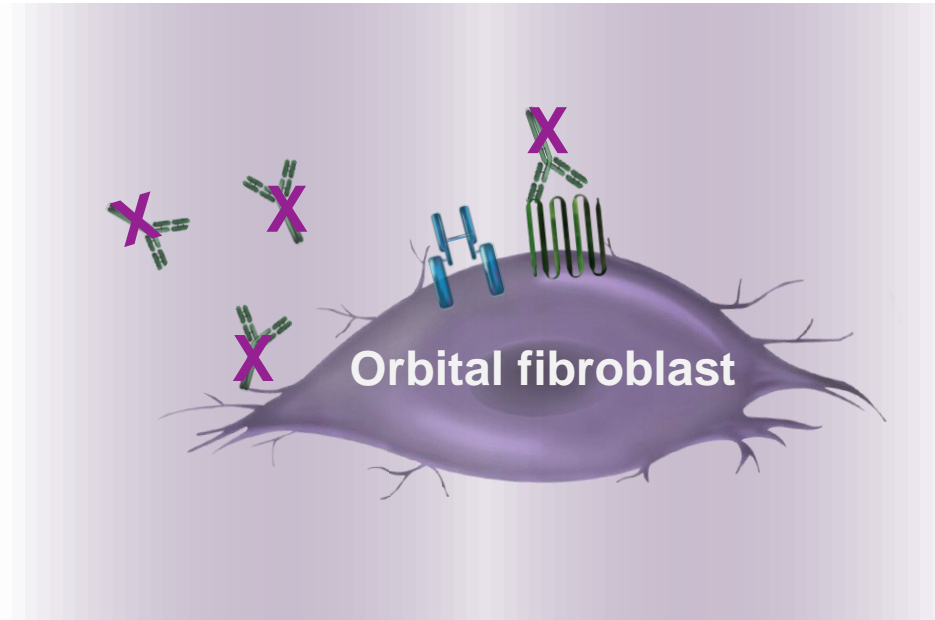
➤ **Batoclimab has the potential to provide clinical benefit for GO patients by reducing the level of pathogenic IgG anti-TSHR-Ab**

**Batoclimab**

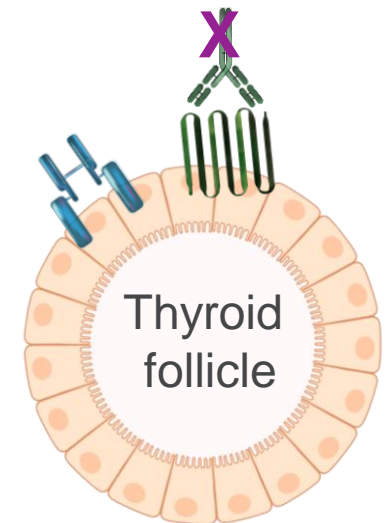
↓ IgG autoantibodies



**Orbit**



**Thyroid**



TSHR



IGF-1R



Anti-TSHR-Ab



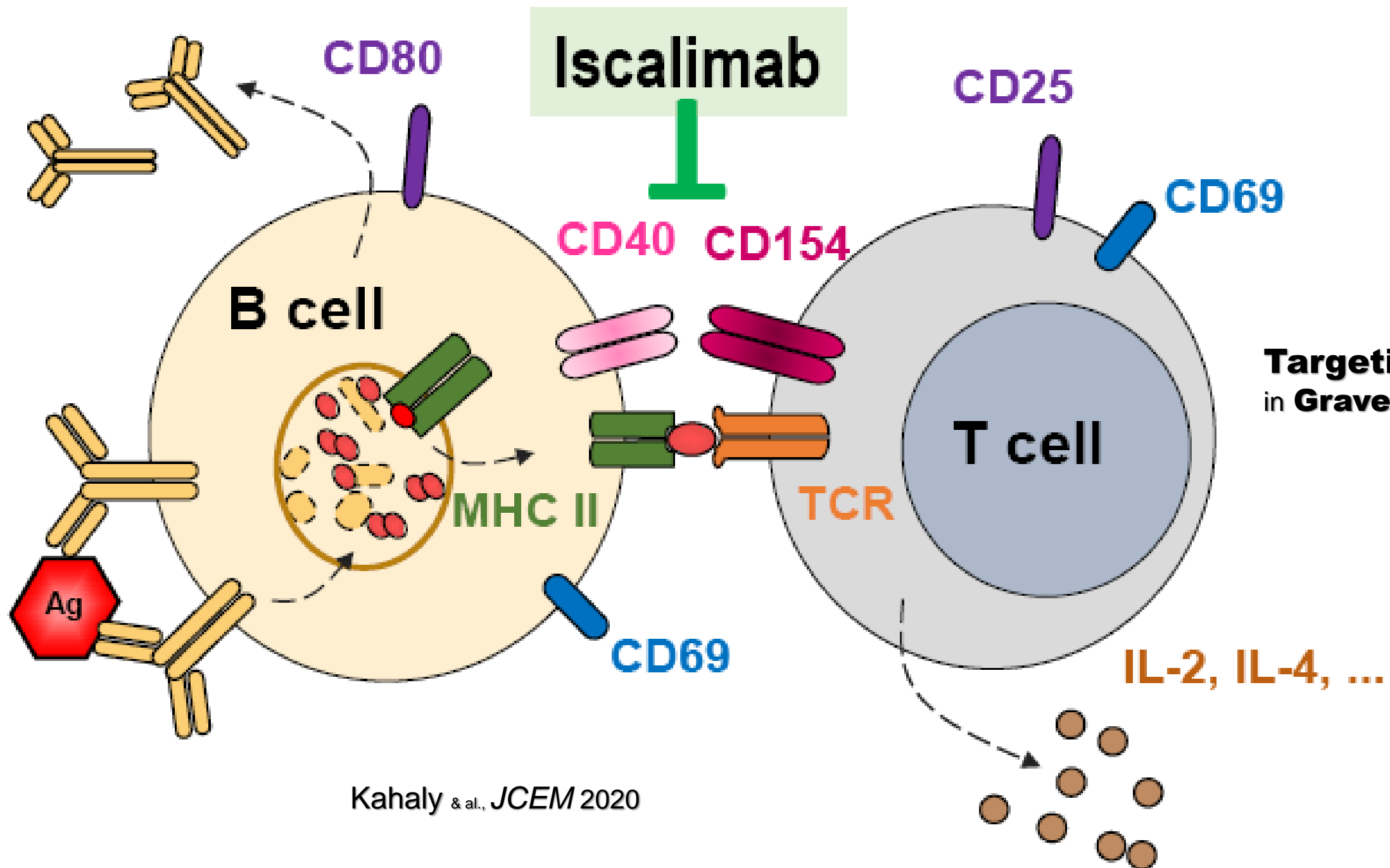
Batoclimab



FcRN

Kahaly & al.,  
ENDO 2022





Kahaly & al., *JCEM* 2020

# STATIN Trial

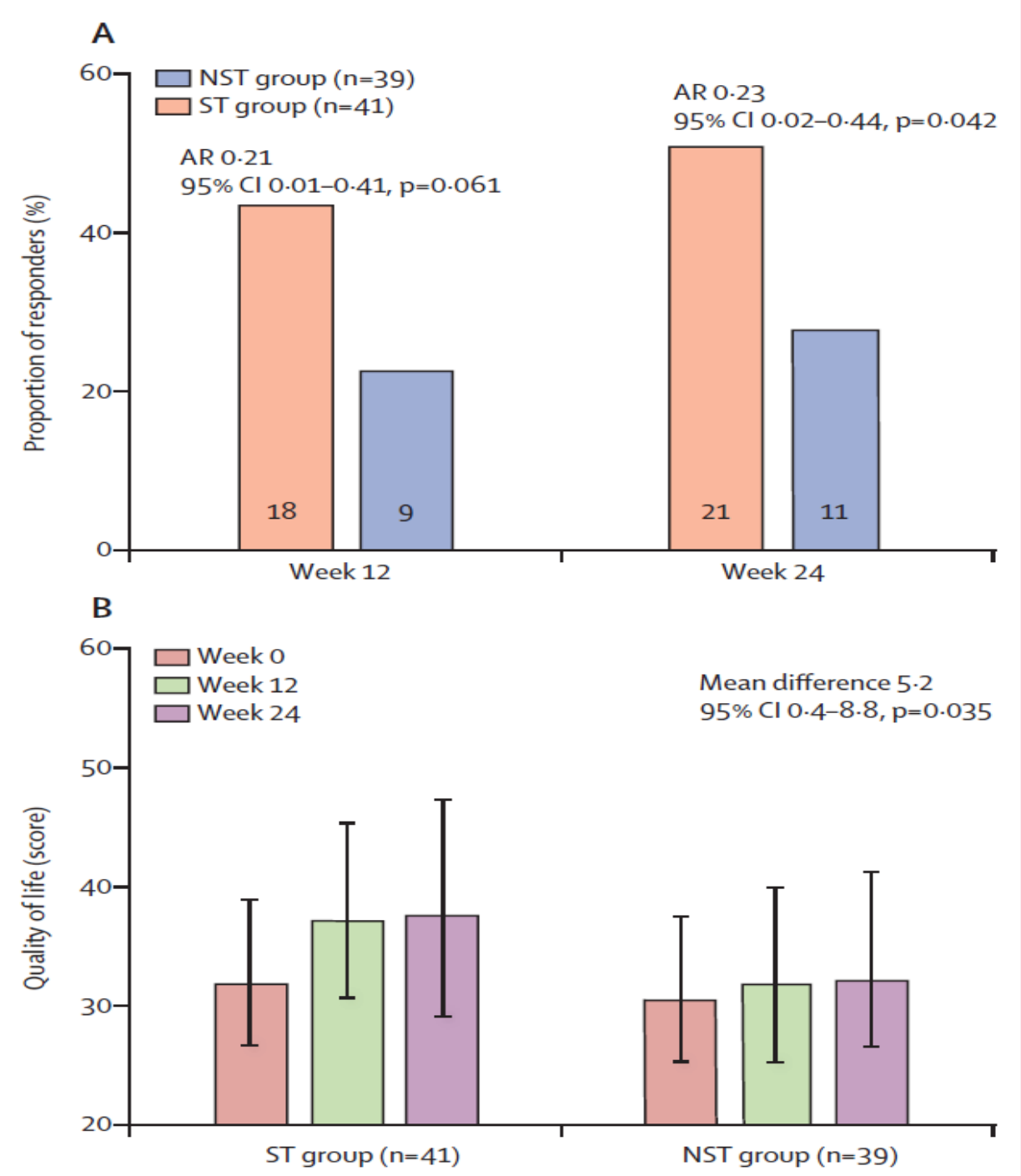
**IVMP 4.5g**

**IVMP 4.5g + atorvastatin (20mg  
QD / 24 wk)**

**STATIN group:**

- **Better overall response** at 24wk  
(51% vs 28%)
- **Greater QoL improvement**
- **No relapse** at 24wk (0% vs 15%)

Lanzolla & al., *Lancet D&E* 2021



# SUMMARY

- AUTOIMMUNE INFLAMMATORY ORBITAL DISEASE
- ASSOCIATED with AUTOIMMUNE THYROID DISEASE
- **TSH-R** AUTOANTIGEN / **TSH-R-Ab** BIOMARKER
- **IGF-1R** MAJOR PLAYER / CROSS-TALK with TSH-R
  - TREAT THYROID DYSFUNCTION
  - REFRAIN FROM **SMOKING** (risk factor)
  - **IV STEROIDS** (+ Mycophenolate): FIRST-LINE R/
  - TEPROTUMUMAB: effective, high costs, US only!