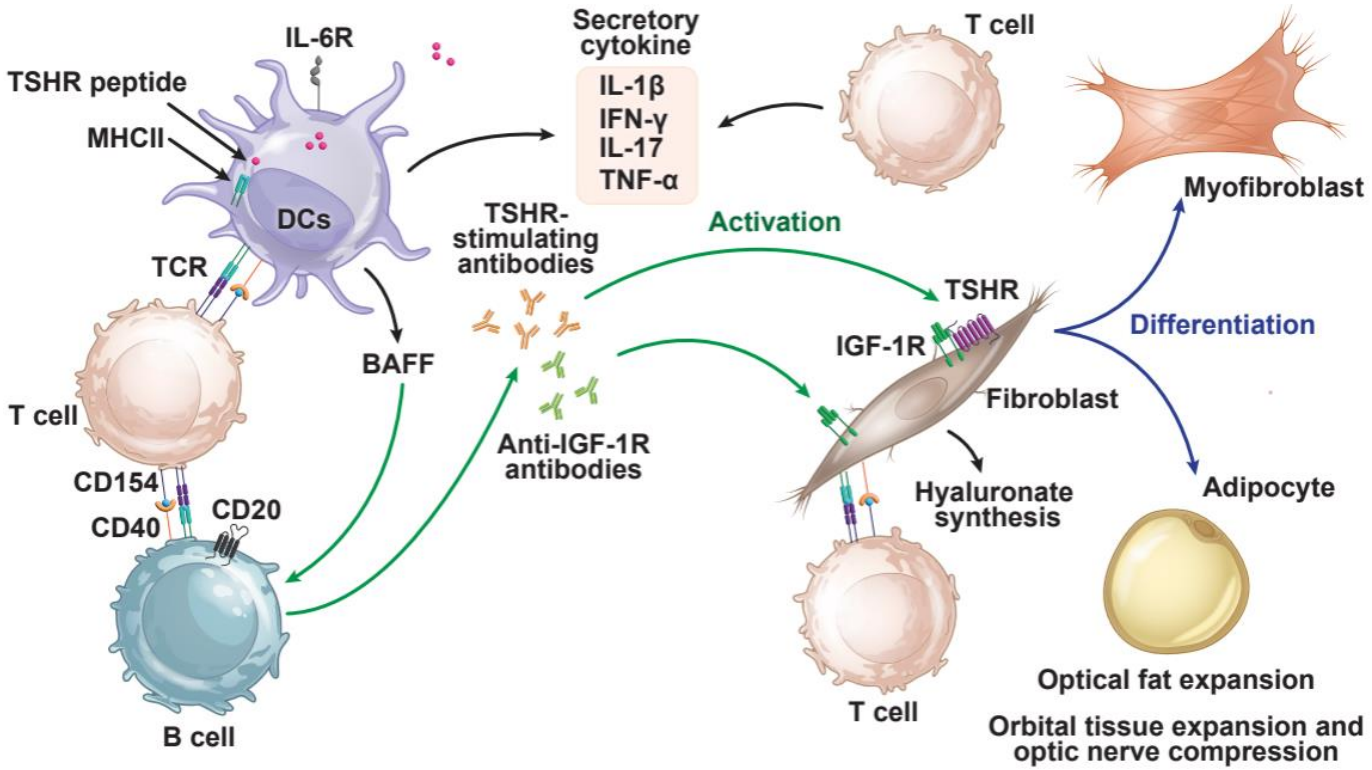
Teprotumumab Mechanism of Action

IGF-1R/TSHR Signaling Complex Activation Triggers Inflammatory Response Leading to Tissue Expansion and Remodeling

- TSHR and IGF-1R are overexpressed in orbital tissue[1,2]
- **IGF-1R and TSHR form a signaling complex on orbital fibroblasts**
  - Activation by autoantibody binding leads to production of proinflammatory cytokines, activation of B and T cells, production of hyaluronate and expansion of orbital fat[2,3]
- **There is subsequent expansion and remodeling of orbital tissues[1,2]**
- Damage can occur in the absence of visible signs[2,4,5]



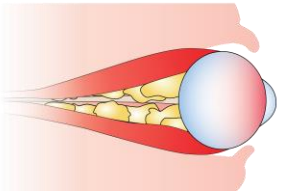


Figure modified from Zhang X, et al. *Front Pharmacol.* 2023;14:1217253.
BAFF, B-cell activating factor; CD, cluster of differentiation; DC, dendritic cell; IFN, interferon; IGF-1R, insulin-like growth factor 1 receptor; IL, interleukin; IL-6R, IL-6 receptor; MHCII, major histocompatibility complex class II; TCR, T-cell receptor; TED, thyroid eye disease; TNF, tumor necrosis factor; TSHR, thyroid-stimulating hormone receptor.
1. Bahn RS. *N Engl J Med.* 2010;362:726-738. 2. Smith TJ et al. *N Engl J Med.* 2016;375:1552-1565. 3. Tsui S et al. *J Immunol.* 2008;181:4397-4405. 4. Kilicarslan R, et al. Br J Radiol. 2015;88(1047):20140677. 5. Villadolid MC, et al. J Clin Endocrinol Metab. 1995;80(9):2830-2833.

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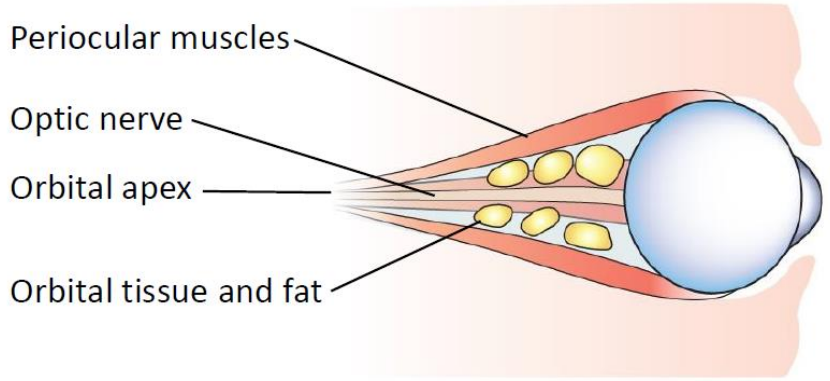
Thyroid Eye Disease (TED) Is an Autoimmune Inflammatory Eye Disease

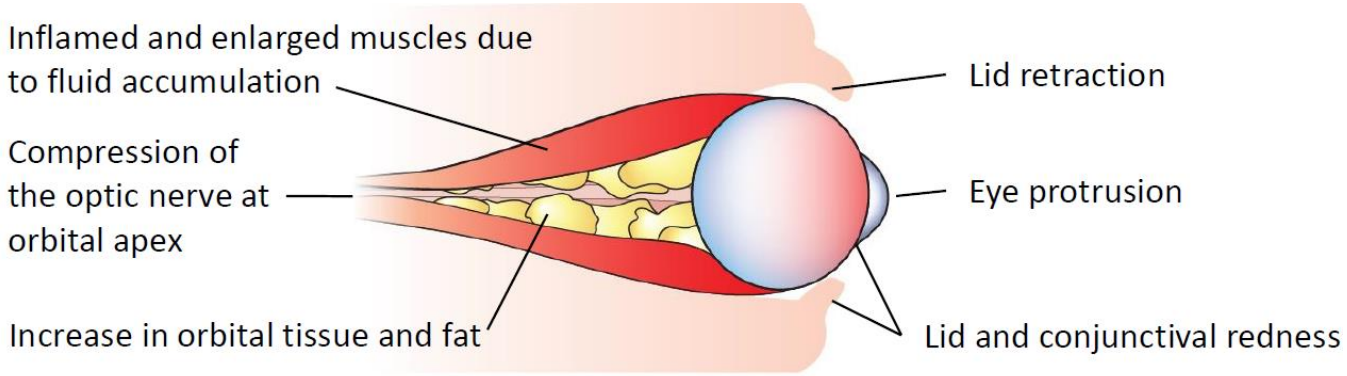
- While the exact autoimmune triggers for TED are unknown, autoantibody activation leads to inflammation and tissue expansion/remodeling in the eye[1,2]

Healthy Eye and Orbital Tissue[3]



- Eye is well protected by lid
- Thin periocular muscles
- Optic nerve can easily pass through apex
- Orbit contains a small amount of tissue and fat

In Presence of Moderate to Severe TED[3]



TED, thyroid eye disease

1. Smith TJ, et al. *N Engl J Med*. 2016;375(16):1552-1565. 2. Wang Y, et al. *Ther Clin Risk Manag*. 2019;15:1305-1318. 3. Perros P, et al. Nat Rev *Endocrinol*. 2009;5: 312–318.

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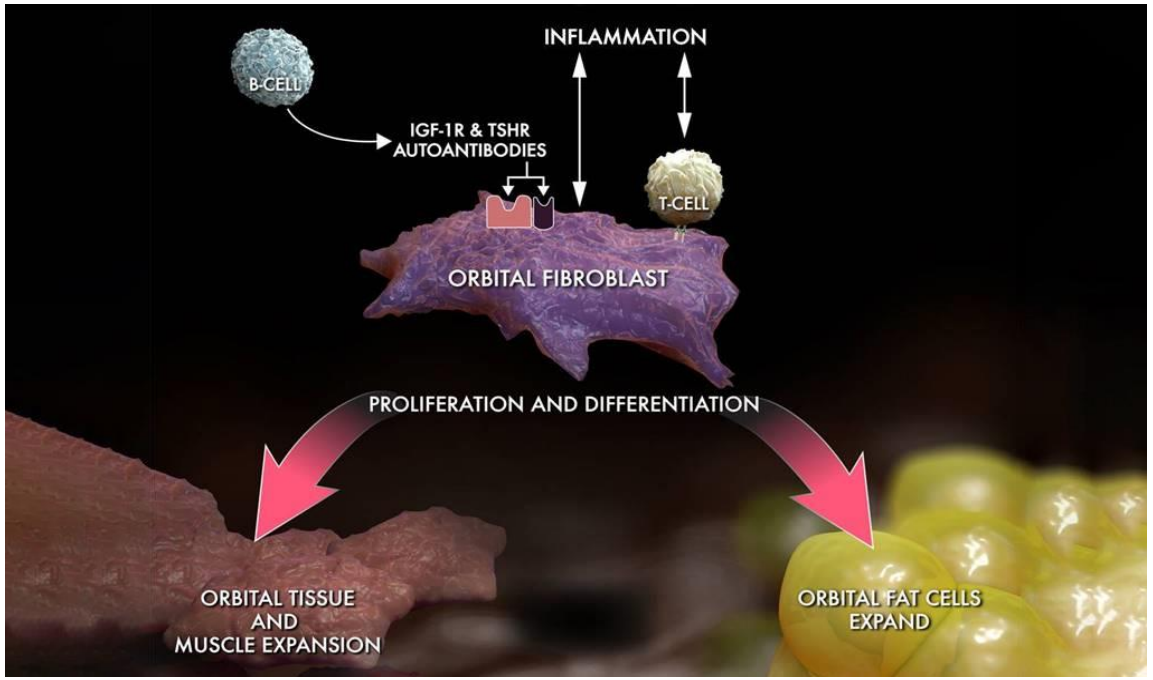
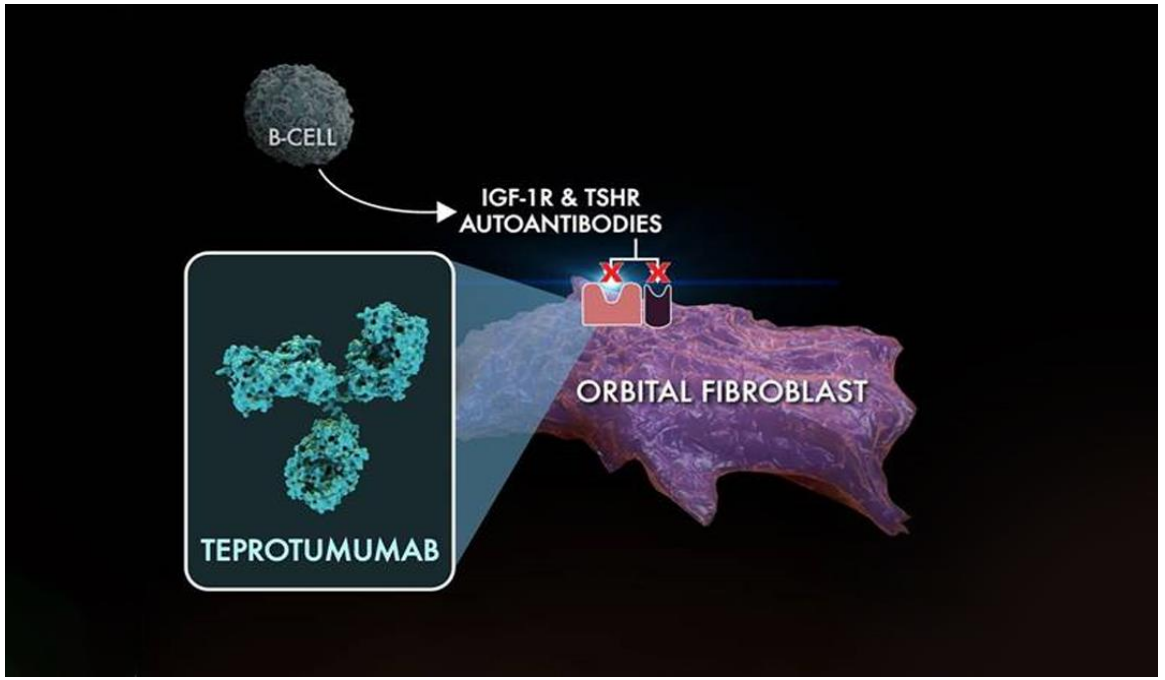
Teprotumumab Targets Underlying Pathophysiology of TED

Teprotumumab binds to IGF-1R and blocks its activation and signaling.[1] This prevents fat and muscle remodeling and reduces tissue expansion behind the eye that cause the signs and symptoms of TED.[2-4] The mechanism of action of teprotumumab has not been fully characterized.[1]



Activation of the complex by TED autoantibodies can lead to inflammation and expansion of tissue, muscle, and fat cells behind the eye[5,6]



Teprotumumab addresses the underlying pathophysiology of TED through targeted inhibition of IGF-1R. The resulting inactivation of IGF-1R/TSHR signaling complex, reduces orbital tissue expansion and inflammation of orbital muscle and fat. [2-4]

IGF-1R, insulin-like growth factor-1 receptor; TED, thyroid, eye disease, TSHR, thyroid-stimulating hormone receptor

1. Teprotumumab prescribing information approved by ANVISA on February 10, 2025. 2. Patel A, et al. *Am J Ophthalmol*. 2019;208:281-288. 3. Wang Y, et al. *Ther Clin Risk Manag*. 2019;15:1305-1318. 4. Douglas RS. *Eye (Lond)*. 2019;33(2):183-190. 5. Bahn RS. *N Engl J Med.* 2010;362:726-738. 6. Smith TJ, et al. *N Engl J Med.* 2016;375:1552-1565.

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Summary

- TED is a **progressive autoimmune disease**.[1-4]
- The binding of autoantibodies **activate the IGF-1R/TSHR signaling complex**, activating orbital fibroblasts.[2,3]
- Orbital fibroblasts proliferate and cause **expansion of fat and muscle tissue behind the eye**.[3,7]
- **Teprotumumab**, a fully human IgG1 monoclonal antibody, **binds to IGF-1R, blocking activation of the IGF-1R/TSHR signaling complex**. This inhibition prevents fat and muscle remodeling and reduces tissue expansion behind the eye, addressing the underlying cause of TED.[1,3,5,6]

TED, thyroid eye disease; IGF-1R, insulin-like growth factor-1 receptor; TSHR, thyroid-stimulating hormone receptor; IgG1, Immunoglobulin G1

1. Patel P, et al. *Ophthalmic Plast Reconstr Surg*. 2015;31(6):445-448. 2. Patel A, et al. *Am J Ophthalmol*. 2019;208:281-288. 3. Bahn RS. *N Engl J Med*. 2010;362(8):726-738. 4. Wang Y, et al. *Ther Clin Risk Manag*. 2019:15:1305-1318. 5. Douglas RS. *Eye (Lond)*. 2019;33(2):183-190. 7. Ugradar S, et al. *Eye*. 2021;35(9)2607-2612.

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