

Autoimmune Thyroid Diseases: Advances and Opportunities

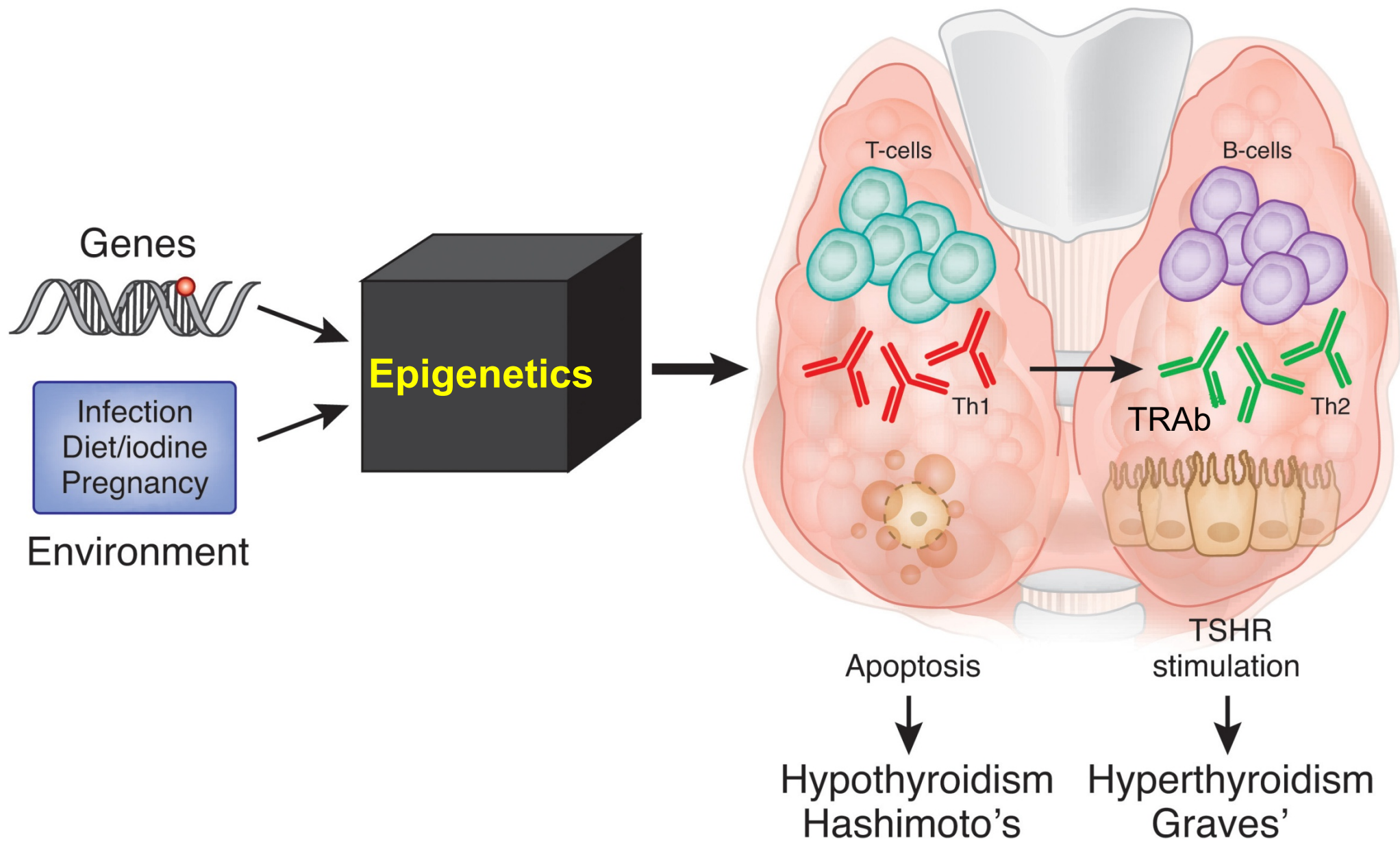
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Montefiore





- **Epidemiology**
- **The unmet need**
- **NIH-funded research driving new therapies**
- **The future of AITD research**

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Prevalence of Autoimmune Diseases

TABLE 44.1

Prevalence of Autoimmune Diseases

Autoimmune Disease	Organ	Weighted Mean Prevalence Rate/100,000	Weighted Mean Incidence Rate/100,000
Thyroiditis/hypothyroidism	Thyroid	1323.8	21.8
Grave disease/hyperthyroidism	Thyroid	1151.5	13.9
Rheumatoid arthritis	Joints, lung, heart, other	860.0	23.7
Vitiligo	Skin	400.2	
Type 1 diabetes	Pancreatic B cells	192.0	12.2
Pernicious anemia	Stomach	150.9	— ^a
Multiple sclerosis	Brain/spinal cord	58.3	3.2
Glomerulonephritis (primary)	Kidney	40.0	3.6
Systemic lupus erythematosus	Skin, joints, kidney, Brain, lung, heart, other	23.8	7.3
Glomerulonephritis (immunoglobulin A)	Kidney	23.2	2.4
Sjögren syndrome		14.4	— ^a
Addison disease	Adrenal	5.0	— ^a
Myasthenia gravis	Muscle	5.1	0.4
Polymyositis/dermatomyositis	Muscle, lung, heart, Joints, other	5.1	1.8
Scleroderma	Skin	4.4	0.8
Primary biliary cirrhosis	Liver bile ducts	3.5	0.9
Uveitis	Eye	1.7	18.9
Chronic active hepatitis	Liver	0.4	0.7

Coppieters, von Herrath et al. Fundamental Immunology 2013
 Jacobson et al. Clin Immunol Immunopathol 1997; 84: 223-243

The National Health & Nutrition Examination Survey (NHANES)

- Screened 16,533 people
- Prevalence of hypothyroidism – 4.6%
- Prevalence of hyperthyroidism – 1.3%
- Prevalence of thyroid antibodies ~ 11% Hollowell et al JCEM 2002; 87: 489-99

Translates to:

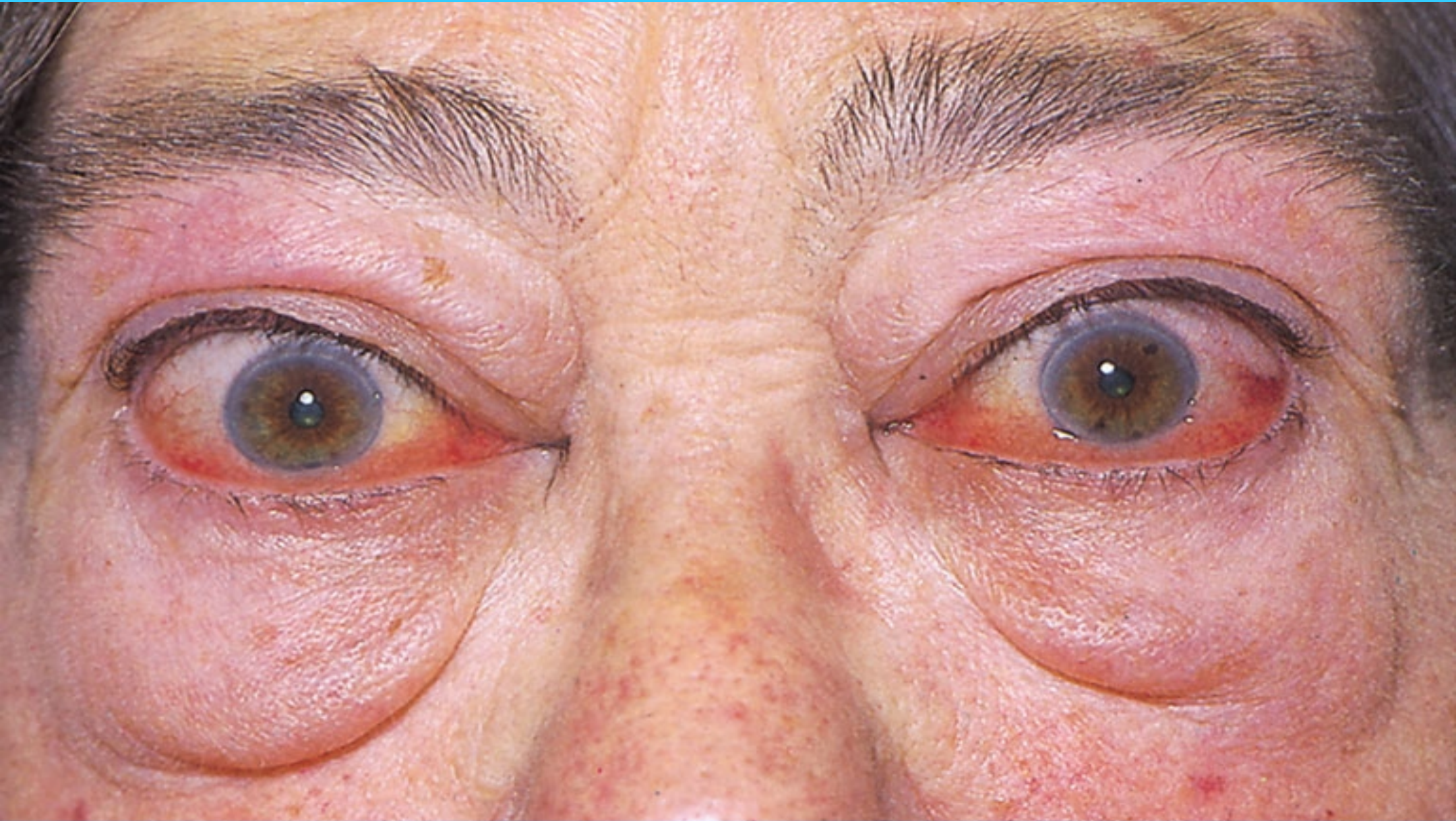
- **> 15 M** people in the US with hypothyroidism; 70-80% HT (**> 10 M**)
- **> 4 M** people in the US with hyperthyroidism; 80% GD (**> 3 M**)

The Colorado Thyroid Disease Prevalence Study

- Hypothyroidism 9.5%
- Hyperthyroidism 2.2%

- Epidemiology
- **The unmet need**
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Unmet Need in GD: Graves' Ophthalmopathy (20-30%)



Unmet Need: Graves' Dermopathy (Pretibial Myxedema)



Unmet Need in AITD:

Therapies Not Curative & Associated with Complications

- **Thionamides (PTU and Methimazole)**
Agranulocytosis, liver toxicity, vasculitis, birth defects (10%)
- **Radioactive Iodine**
Worsens GO, breast accumulation, TRAb increase - pregnancy complications
- **Thyroidectomy**
Vocal cord paralysis, hypocalcemia
- **T4 replacement in HT is challenging**
Inconsistent absorption & different bioavailability

> 50% patients are not euthyroid

Somwaru et al JCEM 2009; Flinterman Thyroid 2020

Hypothyroidism: Increased Mortality by 5% / 6 months

Hyperthyroidism: Increased Mortality by 18% / 6 months

TABLE 3. INCREASE IN MORTALITY PER SIX MONTHS OF THYROID DYSFUNCTION IN TREATED HYPOTHYROID INDIVIDUALS

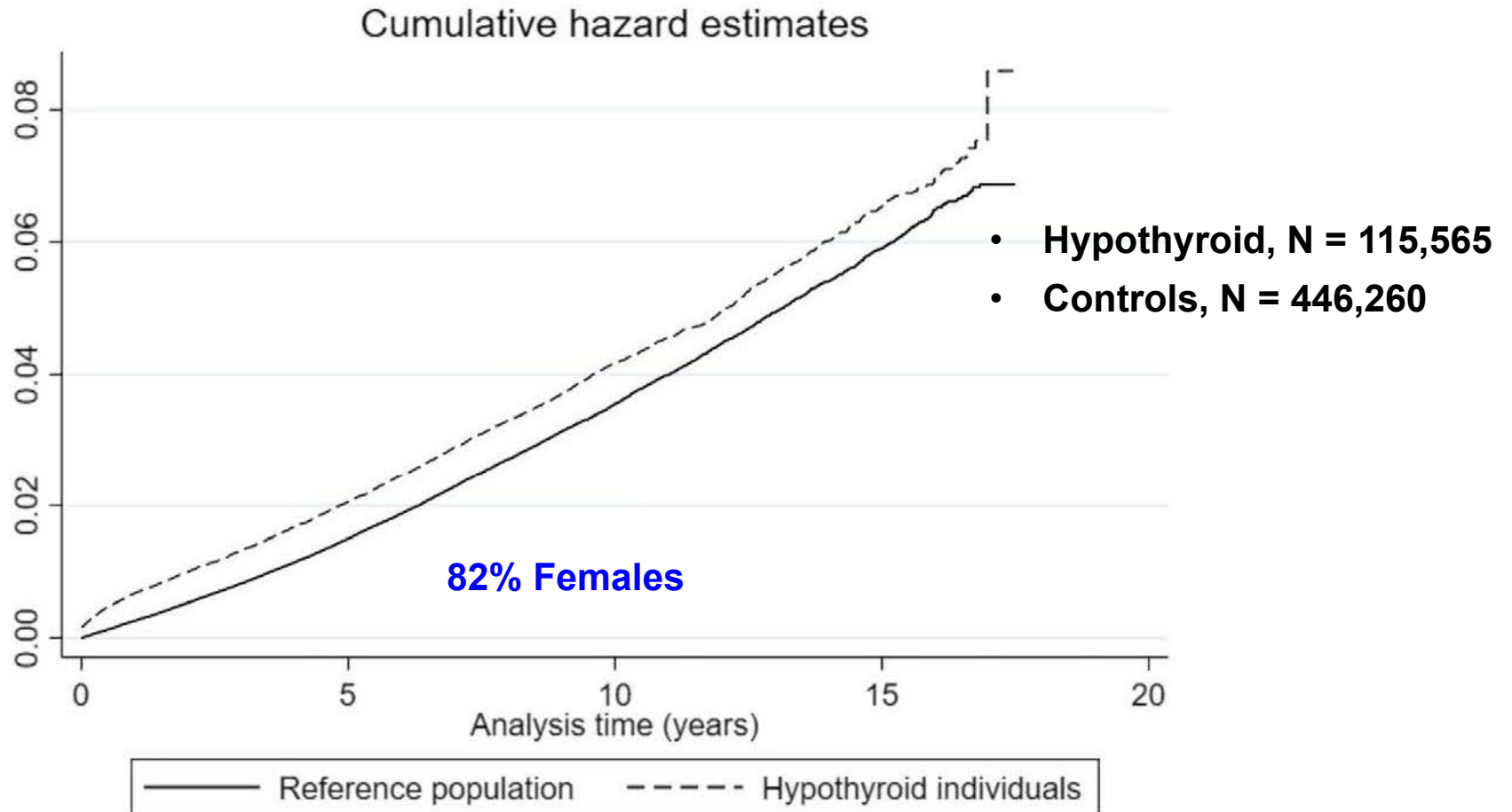
	<i>Entire hypothyroid group (n=2235) Treated vs. controls</i>	<i>Mild hypothyroidism (n=1224) Treated vs. controls</i>	<i>Marked hypothyroidism (n=1011) Treated vs. controls</i>
HR per 6 months of elevated TSH	1.05 [1.03–1.08]*	1.05 [1.03–1.08]*	1.05 [1.03–1.08]*
HR per 6 months of decreased TSH	1.18 [1.15–1.21]*	1.19 [1.16–1.22]*	1.18 [1.15–1.21]*

Data shown are HR with confidence intervals, adjusted for age, sex, and CCI.

* $p < 0.0001$.

The Unmet Need - Hypothyroidism:

Increased risk of dementia **12%** / 6 months



The Unmet Need:

Pregnancy Complications

- **Pregnancy loss** [Abalovich Thyroid 2002; Schneuer JCEM 2012; Casey Obst Gynecol 2007]
- **Gestational HTN** [Leung et al. Obstet Gynecol, 1993]
- **Pre-eclampsia (OR 1.7)** [van den Boogaard Hum Rep Update, 2011]
- **Low IQ** [Haddow NEJM 1999, Korevaar et al, Lancet Diabetes Endocrinol , 2016]
- **Autism Spectrum Disorder** [Andersen Thyroid , 2018]

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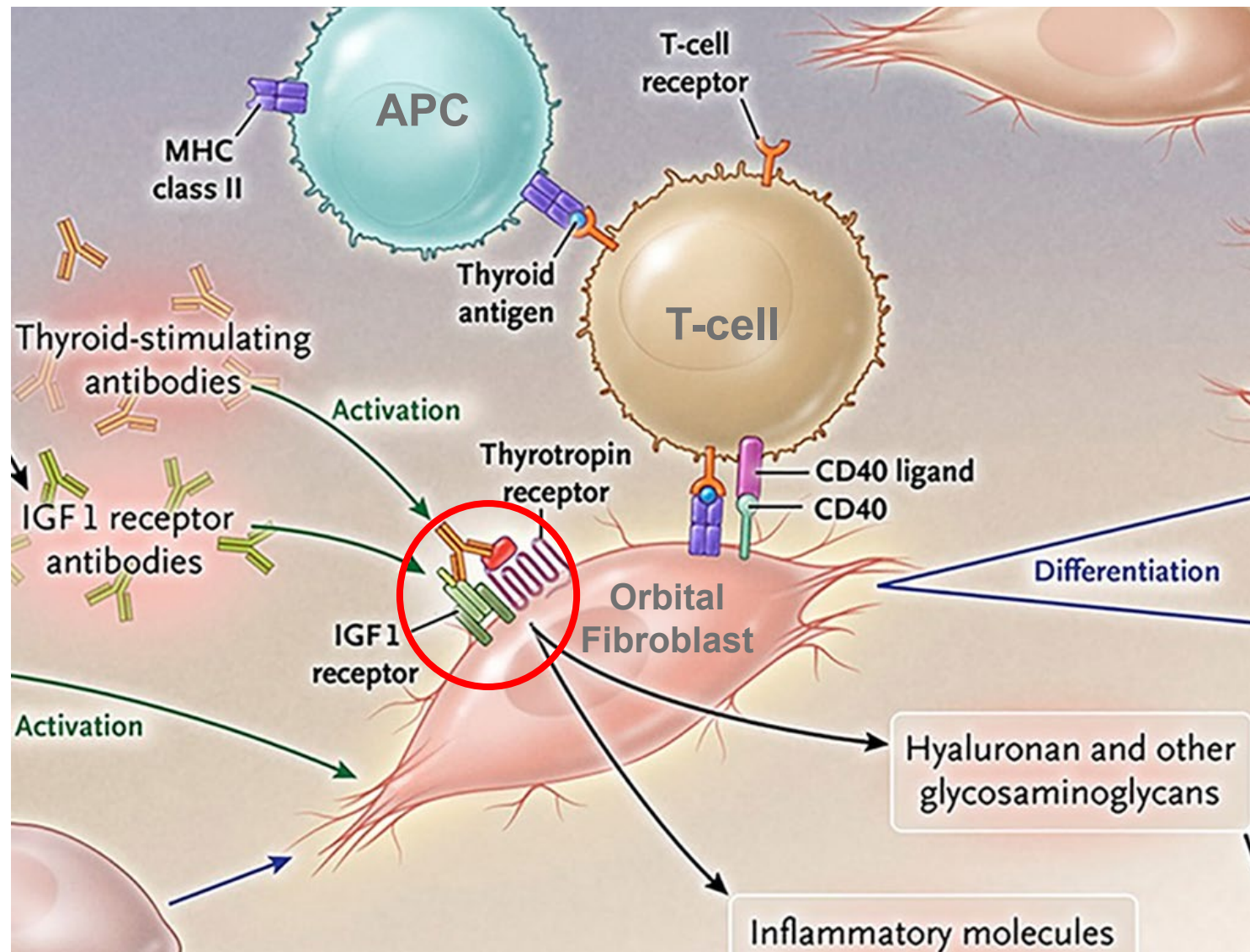
Examples of New Therapies Driven by Translational Research

- **Teprotumumab** – FDA approved MAb for Graves' ophthalmopathy
- **Iscalimab** – In clinical trials for Graves' disease
- **Cepharanthine** – in pre-clinical studies

Examples of New Therapies Driven by Translational Research

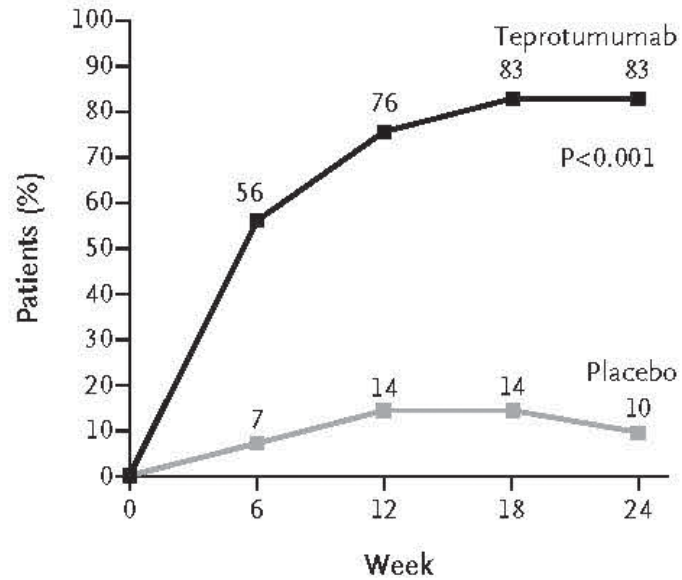
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A New Model for Graves' Ophthalmopathy

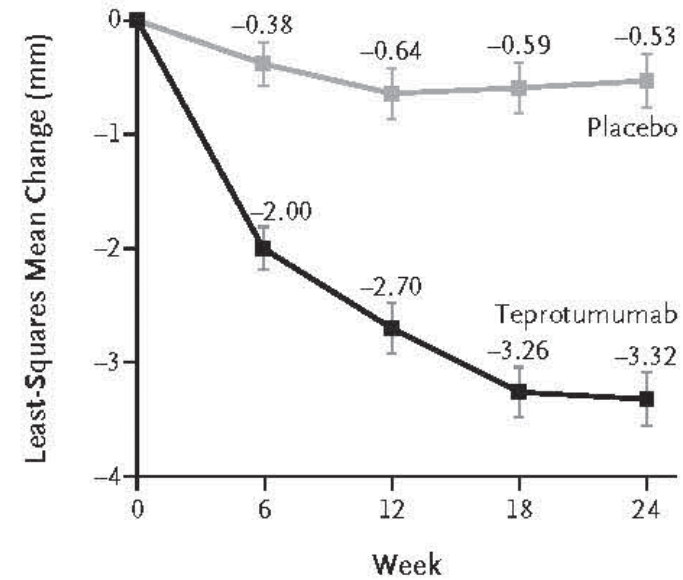


Modified from: Smith, & Hegedus. NEJM 2016; 375: 1552-1565

A Proptosis Response



B Change from Baseline in Proptosis



Baseline

24 Wk after Initial Dose

Placebo



B Clinical Photographs of a Patient in the Teprotumumab Group

Baseline

24 Wk after Initial Dose

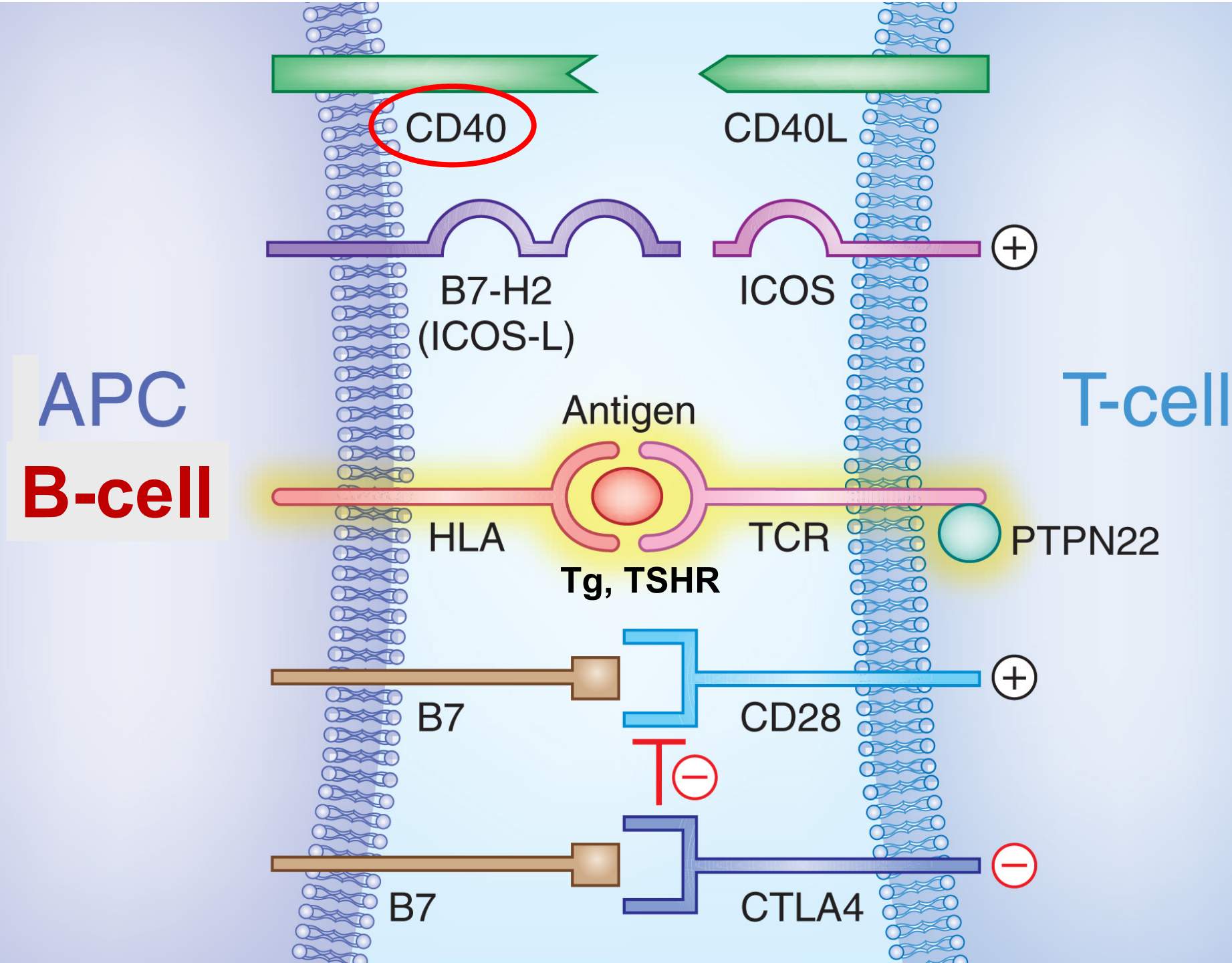


Teprotumumab

Douglas et al. NEJM
2020; 382: 341-352

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CD40 is a Key Graves' Disease Gene

- CD40 mapped as a Graves' disease gene (Tomer, 2002); Replicated by many groups in different populations (2003-2020)
- CD40 associated with RA (2008), MS (2008), SLE (2011), Psoriasis (2011)
- CD40 SNP is functional: risk allele drives higher CD40 expression (Tomer, 2005)
- CD40 SNP risk allele associated with higher CD40 expression in MS (2010), SLE (2011)
- Increased CD40 expression in thyroid accelerates Experimental Autoimmune GD (EAGD); KO of CD40 in thyroid suppresses EAGD (Tomer, 2012)

GD: Tomer, Thyroid 2002; Tomer, Am J Hum Genet 2003; Kim, Thyroid 2003; Houston, Thyroid 2004; Heward, Clin Endocrinol 2004; Kurylowicz, Thyroid 2005; Mukai, Endocr J 2005; Ban, Thyroid 2006; Jacobson, Genes Immunity 2007; Hsiao, Eur J Endocrinol 2008; Inoue, J Clin Immunol 2012; Wang, Eur Thyroid J 2013; Zhang, JCEM 2020

SLE: Vazgiourakis, Ann Rheum Dis 2011; Joo, Rheumatology 2013; Piotrowski, Lupus 2103

RA: Raychaudhuri, Nat Genet 2008; van der Linden, Arthritis Rheum 2009; Plant, Ann Rheum Dis 2010; Orozco, Ann Rheum Dis 2010; Criswell, Immunol Rev 2010

Multiple Sclerosis: MS Consortium, Nat Genet 2008; Blanco-Kelly, PLoS One 2010; Sokolova, PLoS One 2013

Psoriasis: Zervou, Hum Immunol 2011

Experimental Autoimmune Graves' Disease: Mouse Model of Graves' Disease

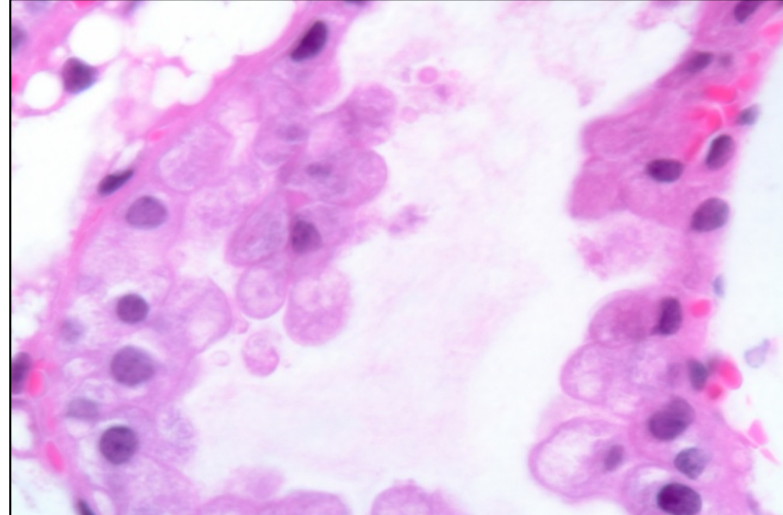
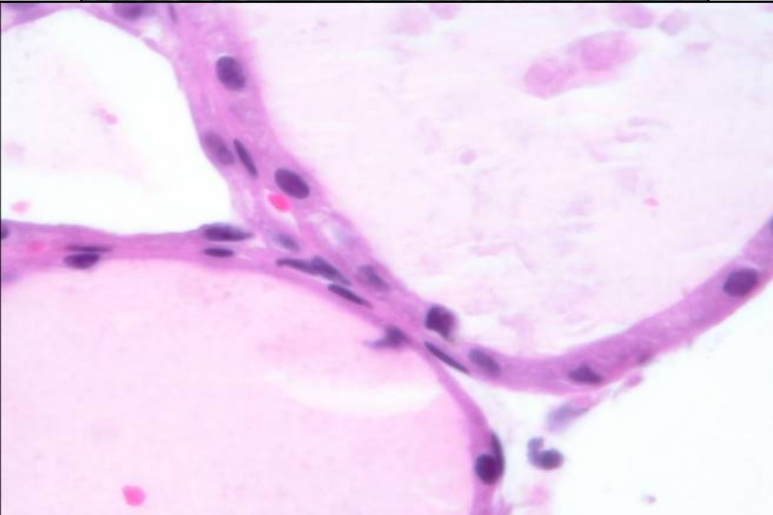
Normal



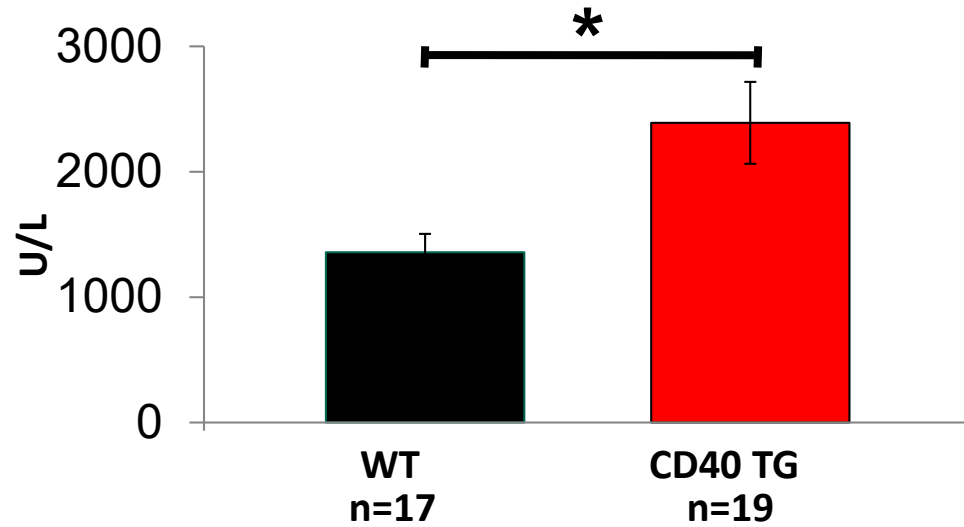
Graves' disease



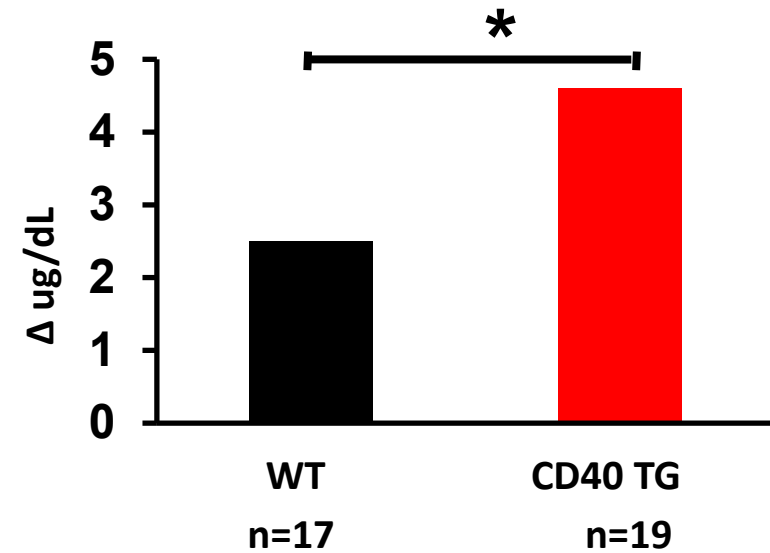
TRAb ↑
T4 ↑



TRAb & T4 Levels in EAGD mice



TSH Receptor Antibodies



Free T4 Levels

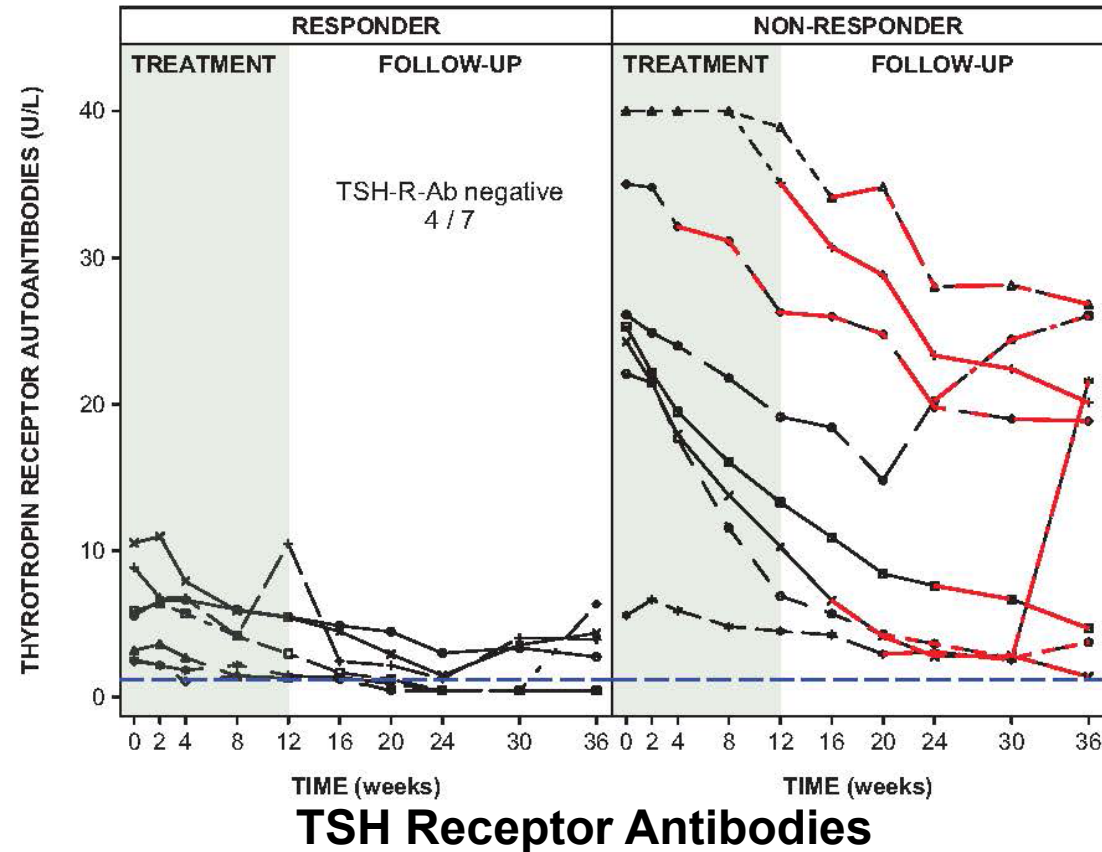
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- CD40 associated with RA (2008), MS (2008), SLE (2011), Psoriasis (2011)
- CD40 SNP risk allele associated with higher CD40 expression (2005)
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- Increased CD40 expression in thyroid accelerates Experimental GD (EAGD) and KO of CD40 in thyroid suppresses EAGD (2012)
- **Iscalimab – anti-CD40 MAb Clinical Trial (2020)**

Iscalimab Treatment in GD (n=15)

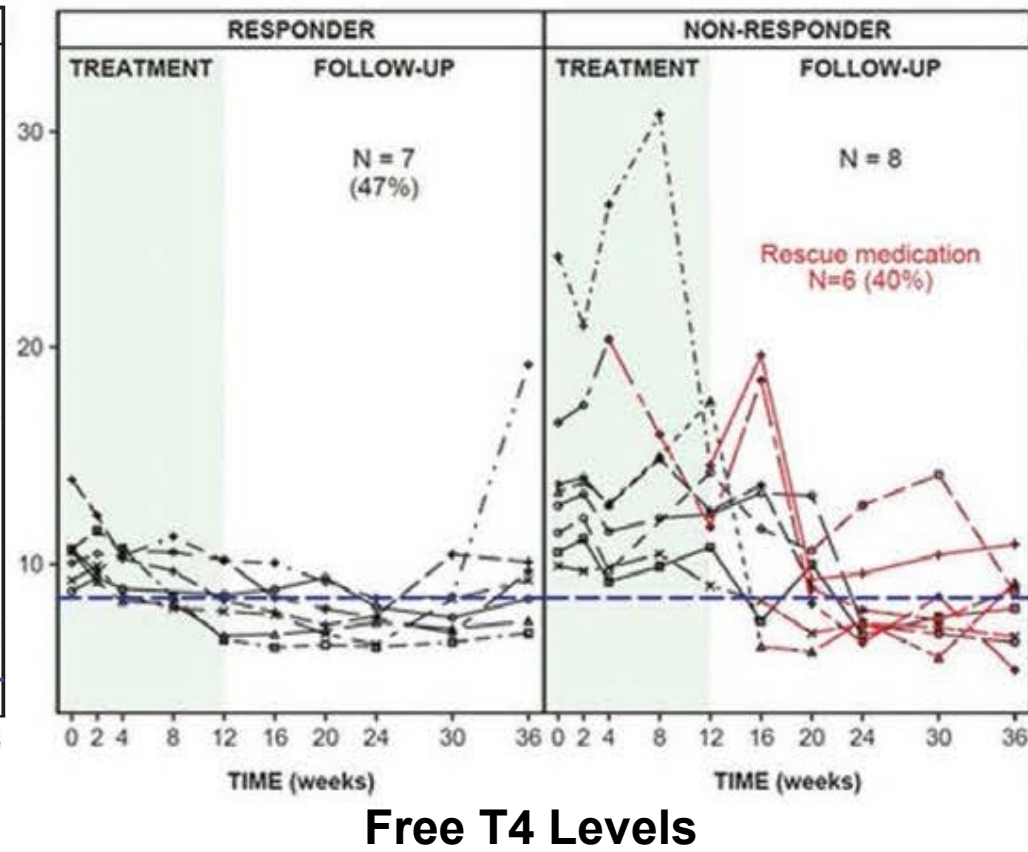
Responders (n=7)

Non Responders (n=8)



Responders (n=7)

Non Responders (n=8)



Kahaly et al. JCEM 2020; 105: 1-9

Response to Iscalimab may be determined by the CD40 SNP haplotypes

Tomer, unpublished

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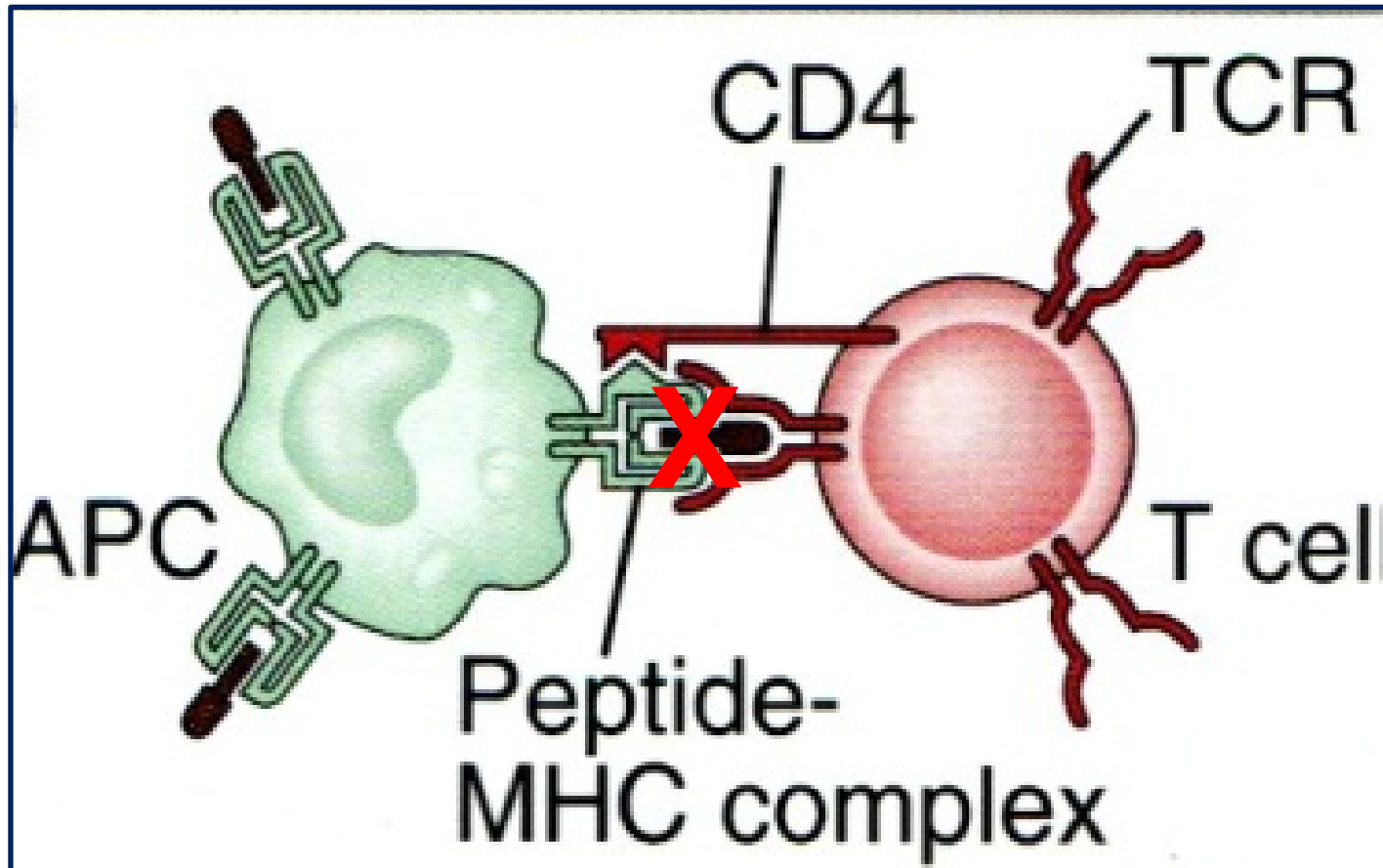
HLA-DRb1-Arg74 is The Key HLA-DR Pocket in AITD

- **HLA-DRb1-Arg74 identified as the key HLA-DR3 pocket in AITD (2004)**
- **Tg.2098 identified as the key T-cell epitope in AITD (2009)**
- **Cepharanthine identified as a compound that can block HLA-DRb1-Arg74 (2016)**
- **Cepharanthine can prevent EAT (model of HT) in DR3 humanized mouse (2016)**
- **Cepharanthine can prevent EAGD (model of GD) in DR3 mouse (2020)**

-
- Bech et al Acta Endocrinol 1977
 - Ban....Tomer Genes Immun 2004
 - Simmonds et al Am J Hum Genet 2005
 - Menconi....Tomer PNAS 2008

- Jacobson....Tomer JBC 2009
- Menconi....Tomer J Autoimmun 2010
- Li....Tomer JBC 2016
- Li....Tomer J Autoimmun 2020

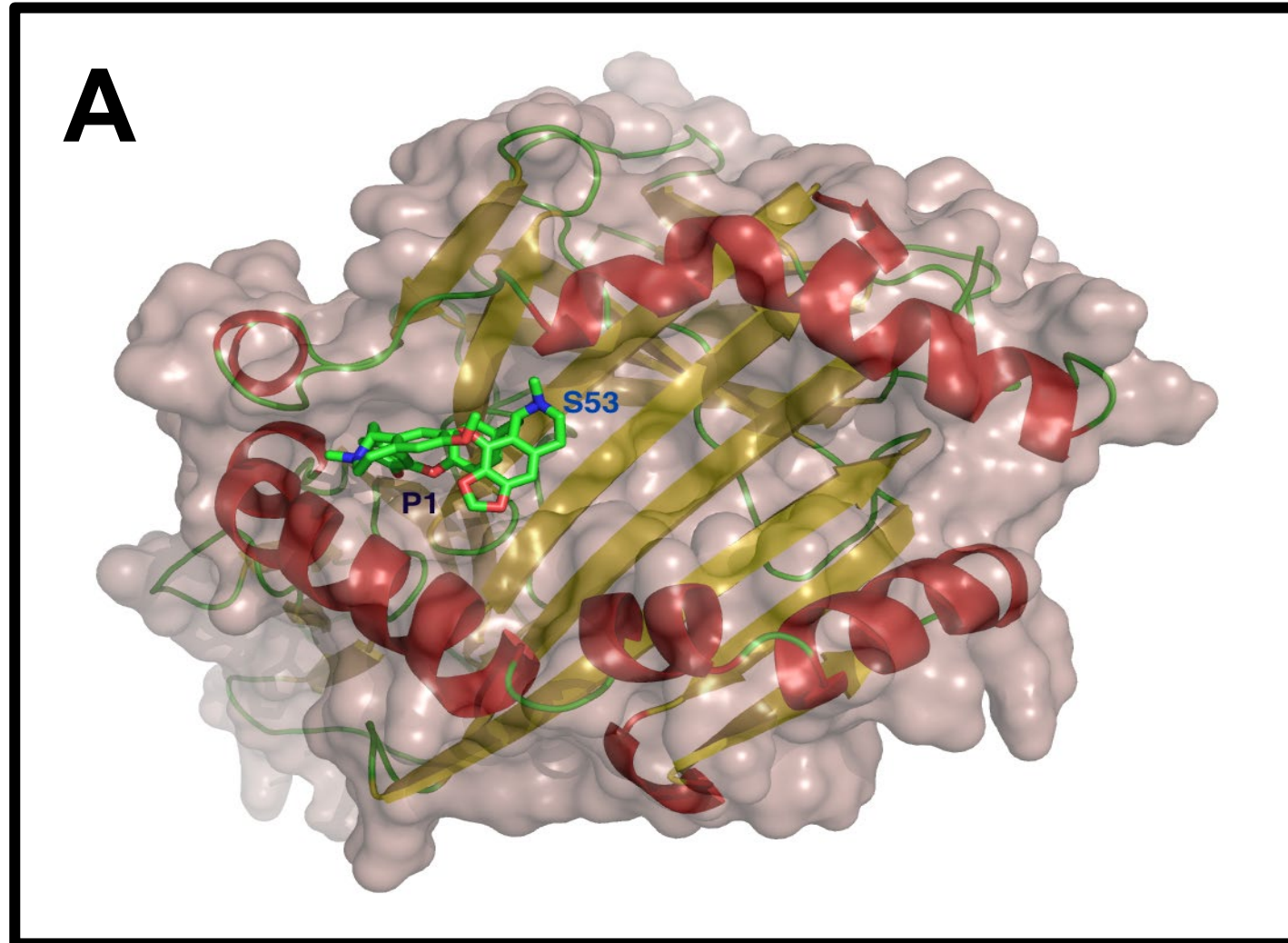
New Therapeutic Strategy for AITD: Blocking Peptide Presentation by DR β 1-Arg74



Adapted from Abbas, Cellular and Molecular Immunology, 5th Edition

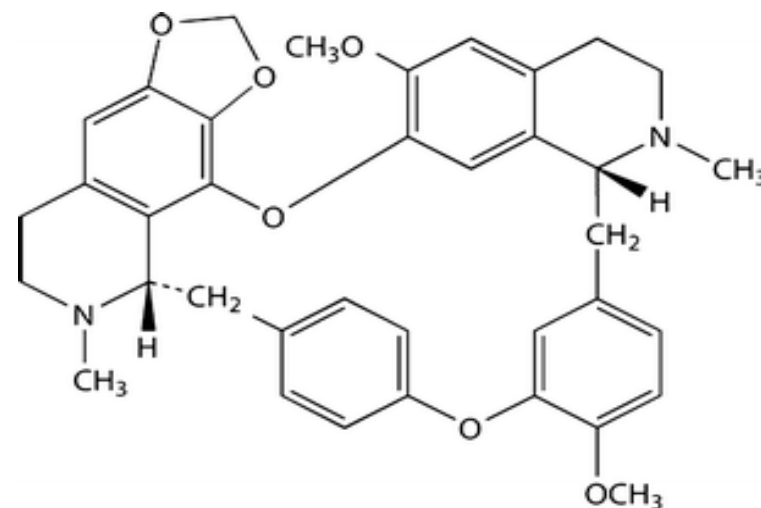
Such an approach is both specific and personalized

Cepharanthine Blocks HLA-DR3 And Prevents EAT (HT) and EAGD



Cepharanthine (S53)

- An alkaloid extracted from the plant *Stephania cepharantha* Hayata
- Used in Japan for > 40 years to treat many acute and chronic diseases
- Used to treat: **NOT AN ENDORSEMENT!**
 - ITP
 - Leukopenia & thrombocytopenia associated with chemotherapy
 - Immune thrombocytopenia associated with multiple myeloma



NOT FDA APPROVED FOR ANY INDICATION

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Opportunities in AITD Research

We are in a pivotal moment in AITD research

- Opportunities to discover new molecular mechanisms underlying AITD
- Opportunities to translate mechanisms into novel therapies
- Opportunities to identify mechanisms and therapies for other autoimmune diseases (e.g. Iscalimab, Cepharanthine)
- **Opportunities to alleviate suffering of AITD patients**

AITD Research Funding Opportunities

- **AITD research is completely dependent on NIH funding**
- No foundations support thyroid research (except ATA small grants)
- AITD: reviewed by endocrine Study Sections
- Require expertise in endocrinology and thyroidology:
 - Appreciation for the public health impact of AITD & unmet need
 - Thyroid specific factors: iodine, selenium
 - Thyroid is the key to its own demise
 - Overlap with non-autoimmune thyroiditis (e.g. ICI thyroiditis, COVID-19 thyroiditis)
 - Expertise is required in molecular thyroidology and endocrinology

2019



2020

