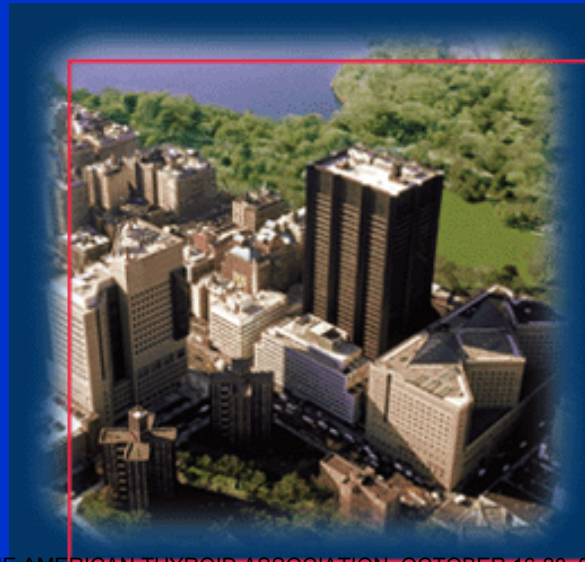


Triggering Thyroid Autoimmunity: Genes, Viruses, and Epigenetics

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**Mount
Sinai**

Nothing to Disclose

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Yaron Tomer)

Genes

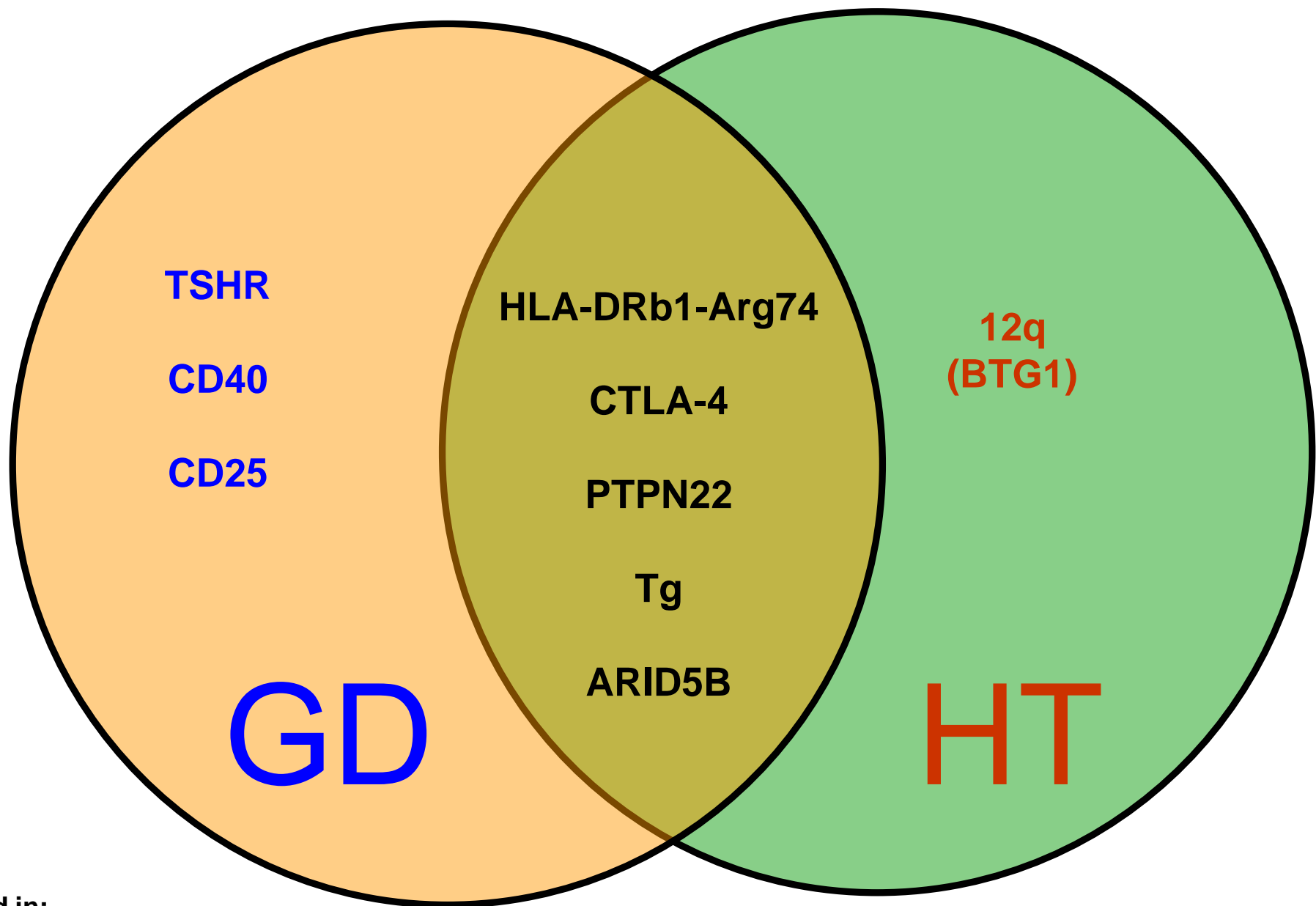
Viruses

Interactions

Genes

Viruses

Interactions



Reviewed in:

Tomer. Thyroid 2010; 20: 715-725

Huber, et al. Endocr Rev 2008; 29: 697-725

Brand, Gough, Curr Genomics 2011; 12: 526-541

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Genes

Viruses

Interactions

Hepatitis C and Thyroiditis

Country	Year	Patients		Controls		P-value	Study
		No.	%TAb's	No.	%TAb's		
France	1993	72	12.5	60	1.7	0.02	Tran
Japan	1994	109	9.2	--	--	--	Watanabe
Spain	1995	96	5.2	96	8.3	NS	Boadas
Italy	1995	75	10.7	--	--	--	Carella
UK	1997	111	4.5	99	11.1	NS	Metcalf
Italy	1999	86	9.3	1147	17.1	NS	Loviselli
France	2000	97	13.4	97	3.1	0.02	Ganne-Carrie
Italy	2004	630	21	389	12	0.0001	Antonelli

Reviewed in: Mandac, Chaudhry, Sherman, and Tomer. Hepatology; 2006; 43: 661-672

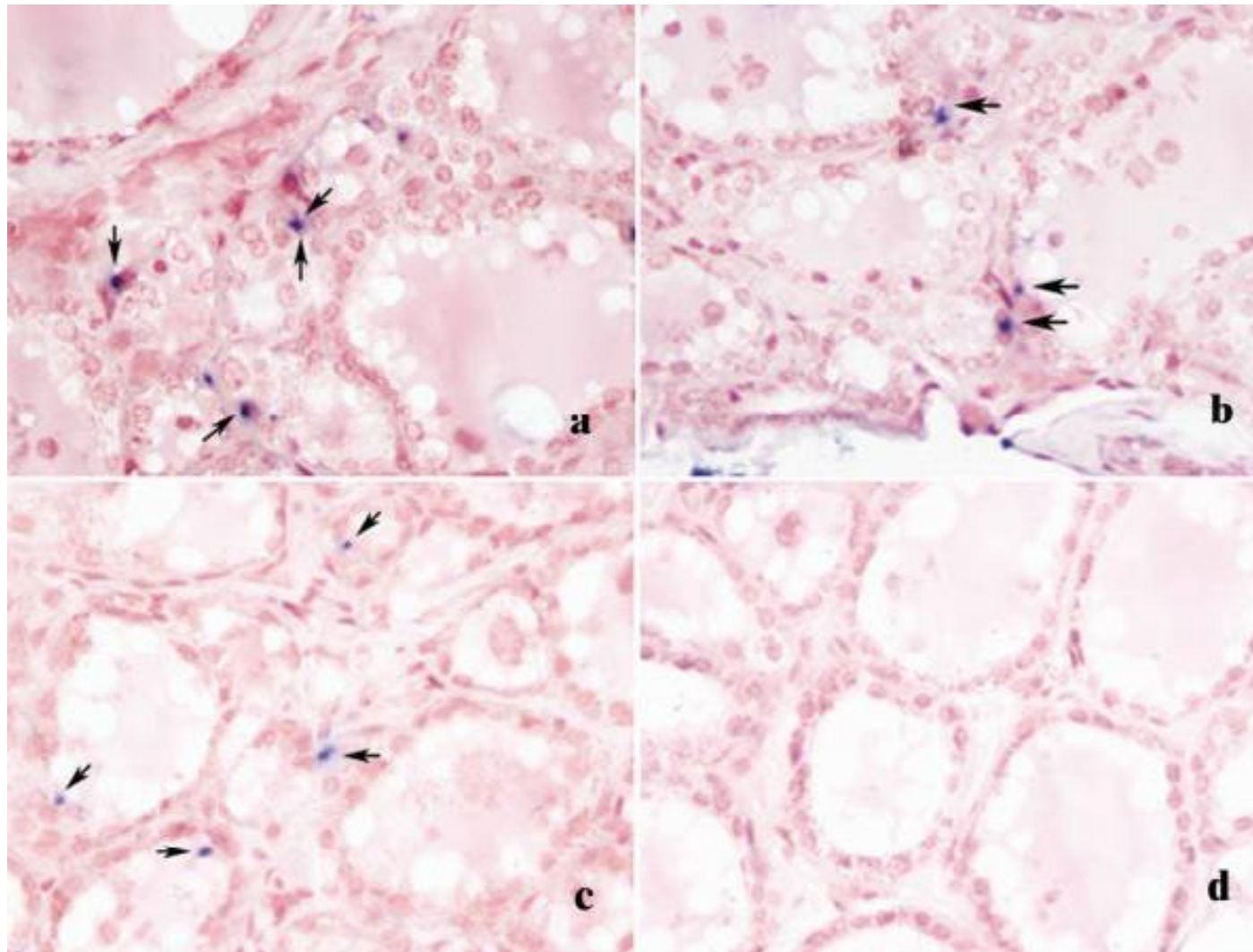
PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Yaron Tomer)

How can HCV infection trigger thyroiditis?

Non-specific effects of the virus

Can HCV infect human thyroid cells

Detection of HCV-RNA in the thyroid by in-situ hybridization



Bartolome et al J Med Virol 2008; 80: 1588-1594

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295 bp ↓ **ML-1**

295 bp ↓ **Huh7.5**

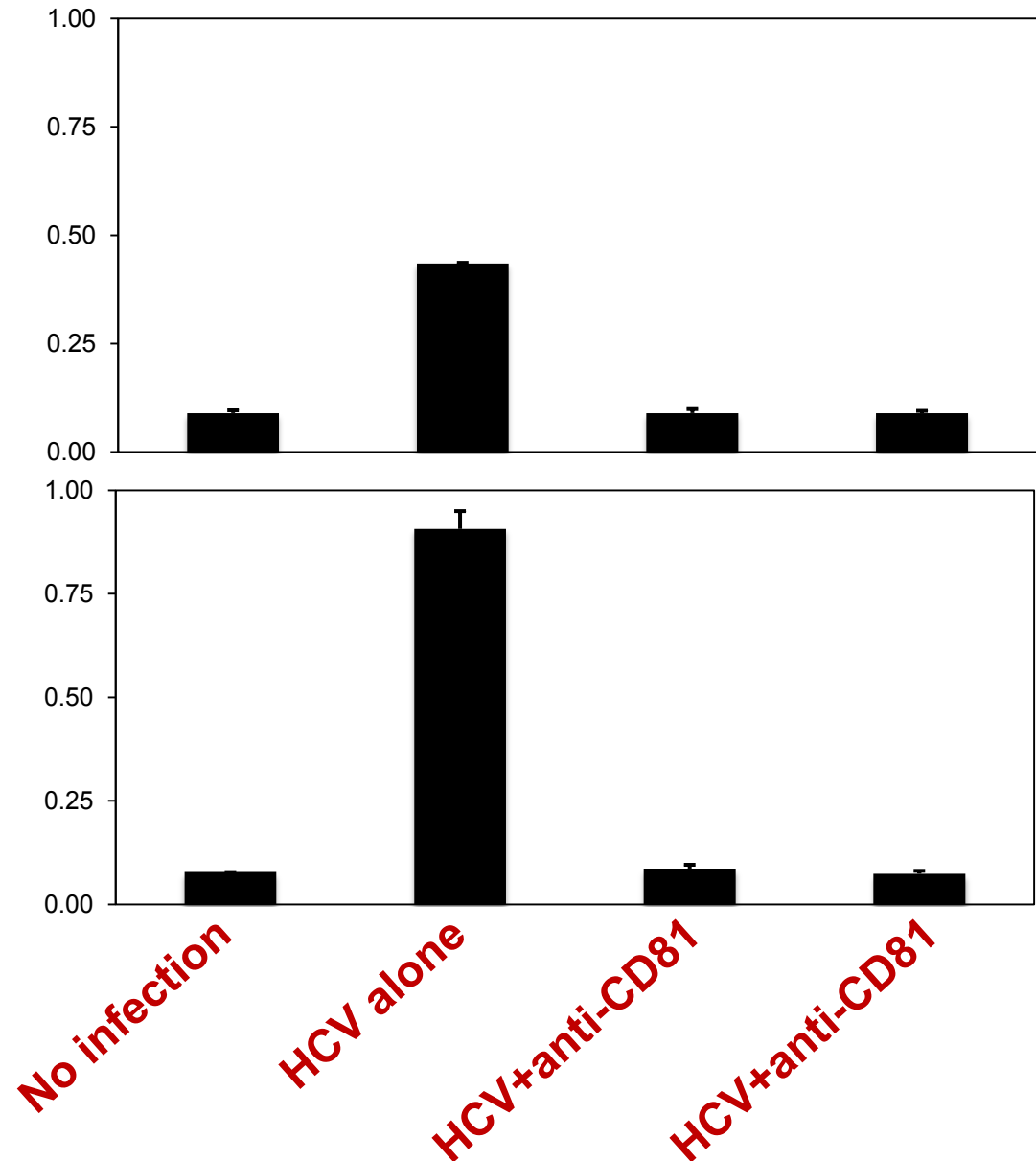
- ← Control – **PS** cells
- ← Control – **PS** supernatant
- ← Control – **NS** cells
- ← Control – **NS** supernatant
- ← **NS sup: uninfected**
- NS supernatant: infected**
- ← **NS cells: uninfected**
- NS cells: infected**
- ← **PS sup: uninfected**
- PS sup: infected**
- PS cells: uninfected**
- PS cells: infected**

Blackard et al.
Thyroid 2013;
23: 863-870

HCV Infection in the Presence or Absence of anti-CD81

Huh 7.5

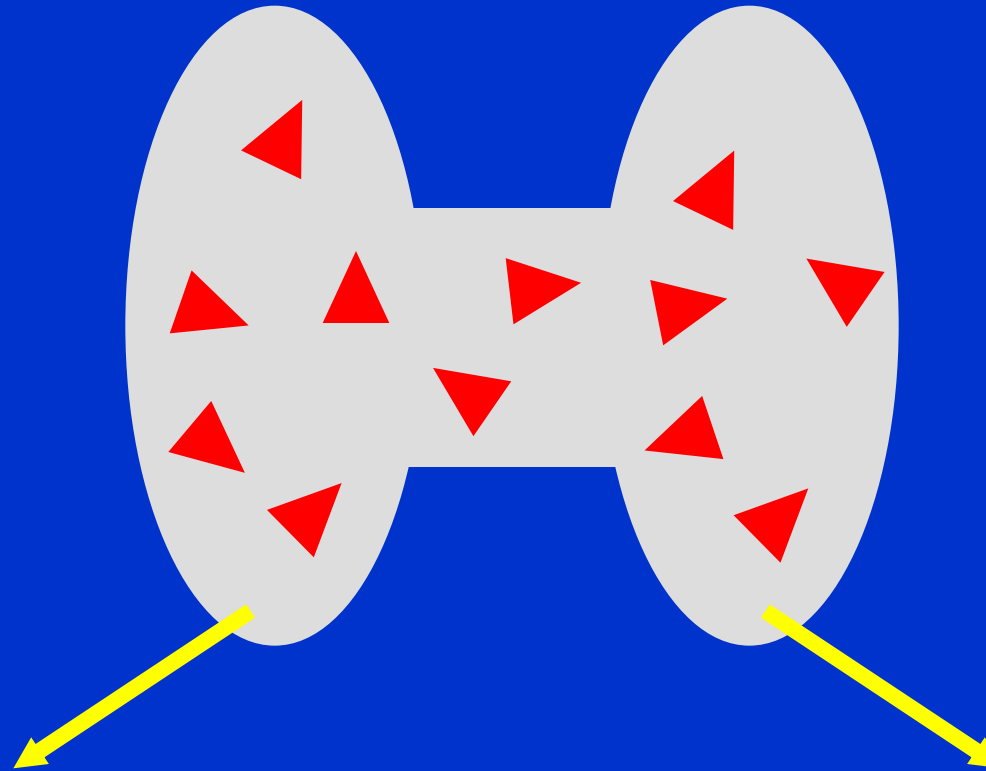
ML-1



Blackard et al. Thyroid 2013; 23: 863-870

Mechanisms of induction of Thyroiditis by HCV:

Bystander Activation



Inflammatory response
Secretion of cytokines (IL-8)

Exposure of cryptic Ag's
Alteration of self Ag's

Genes

Viruses

Interactions

Epigenetics: Definition

Non-coding effects on gene expression/function that are mitotically stable (i.e. long lasting)

- **DNA methylation**
- **Histone modifications**
- **microRNA activation**

Epigenetics: Definition

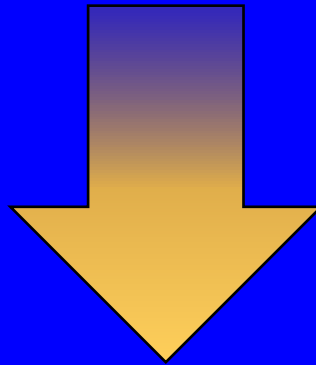
Non-coding effects on gene expression/function that are mitotically stable (i.e. long lasting)

- DNA methylation
- **Histone modifications**
- microRNA activation

Which environmental factor triggers epigenetic changes in thyroid cells?

Interferon α and AITD

- IFN α is a key cytokine secreted during infections
- IFN α therapy has been associated with autoimmunity – AITD, type 1 DM, SLE
- Transgenic mice expressing IFN α in thyroid develop thyroiditis



IFN α is a Key Cytokine Triggering AITD

Stewart . Science 1993; 260: 1942-1946

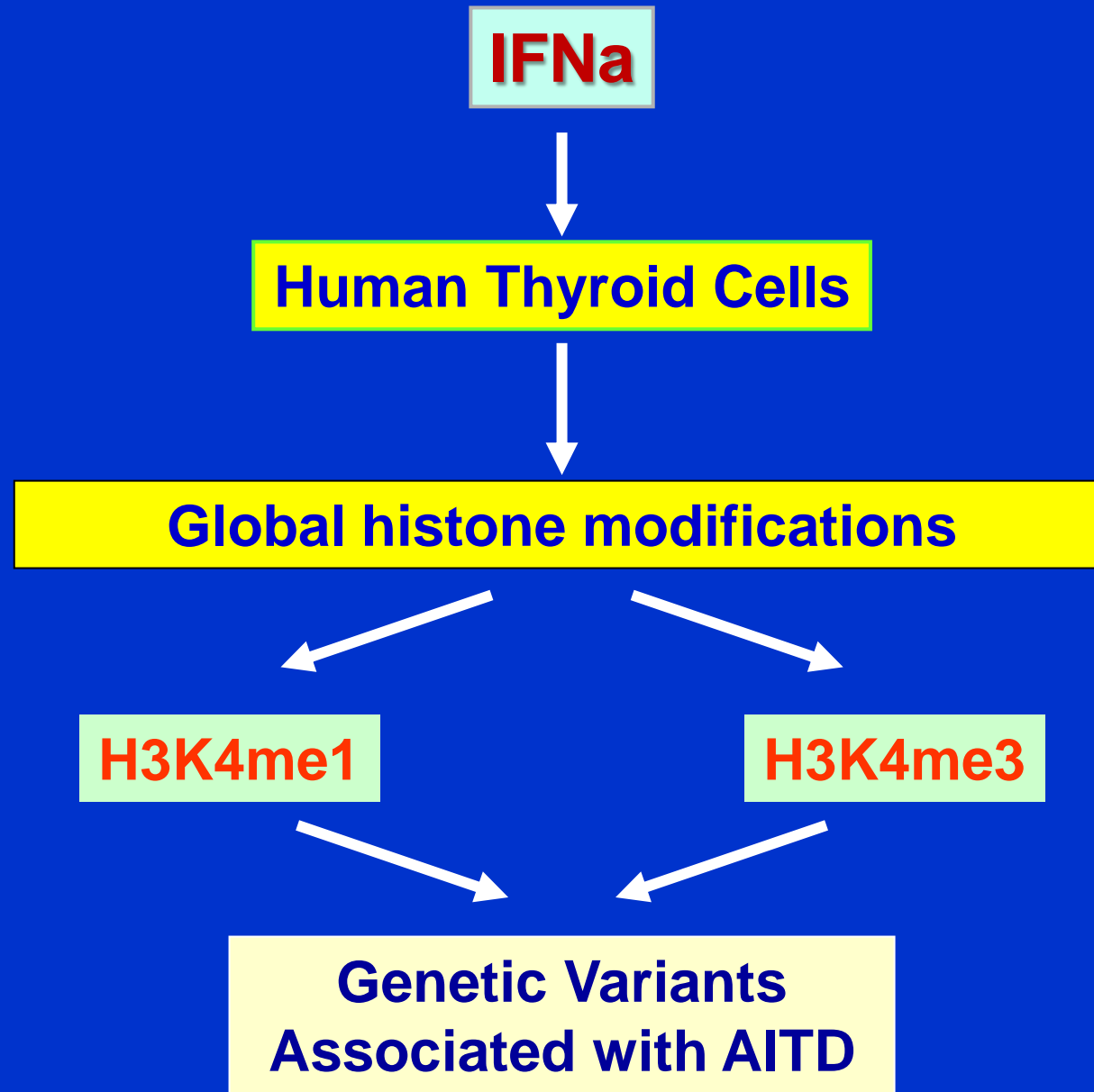
Akeno. J Immunol 2011; 186: 4693-4706

Eisenbarth. Clin Immunol 2004; 111: 225-233

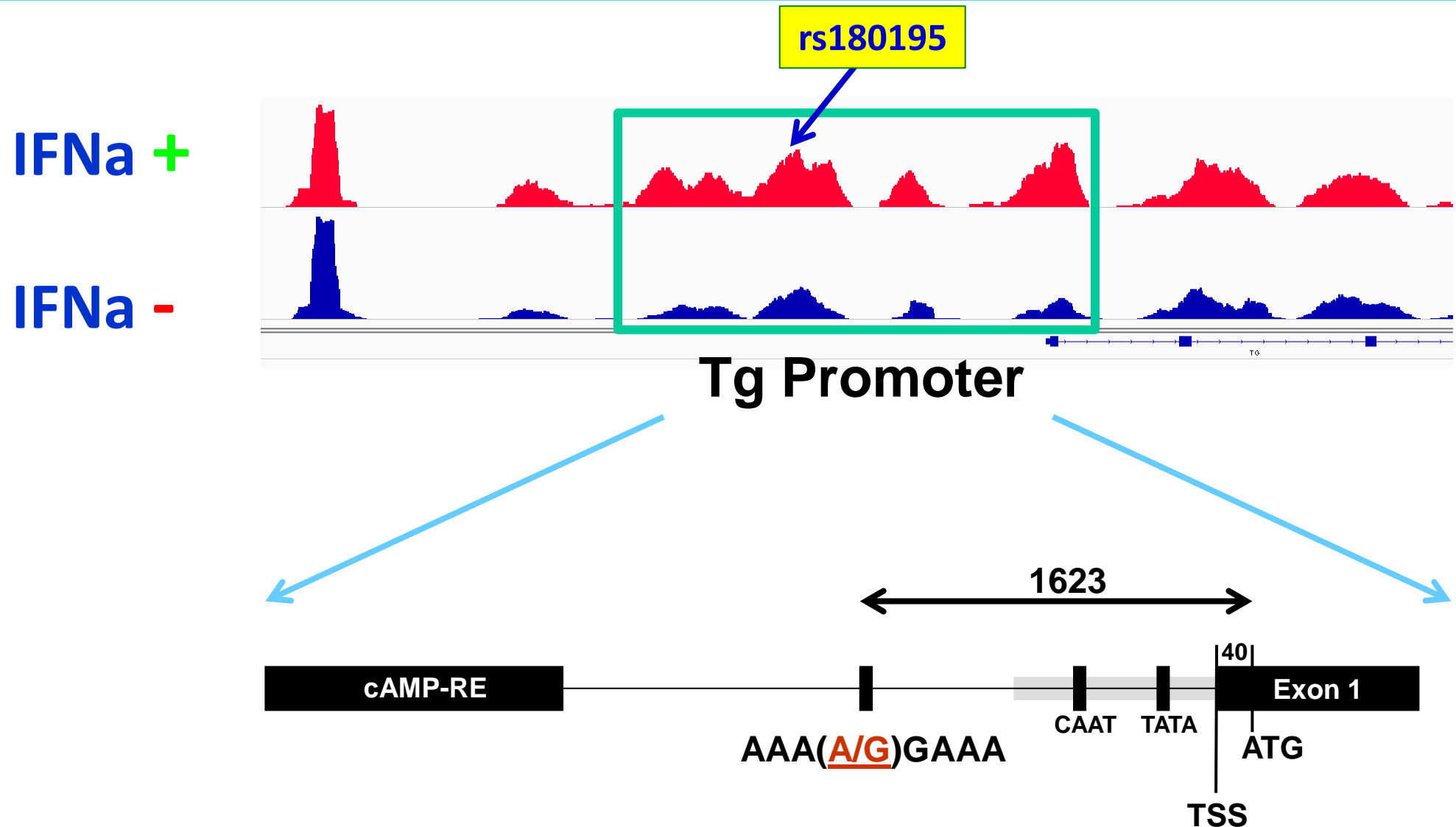
Tomer. J Autoimmun 2010; 34: J322-J326

Diana. Nat Med 2013; 19: 65-73

Epigenetic Effects of IFNa



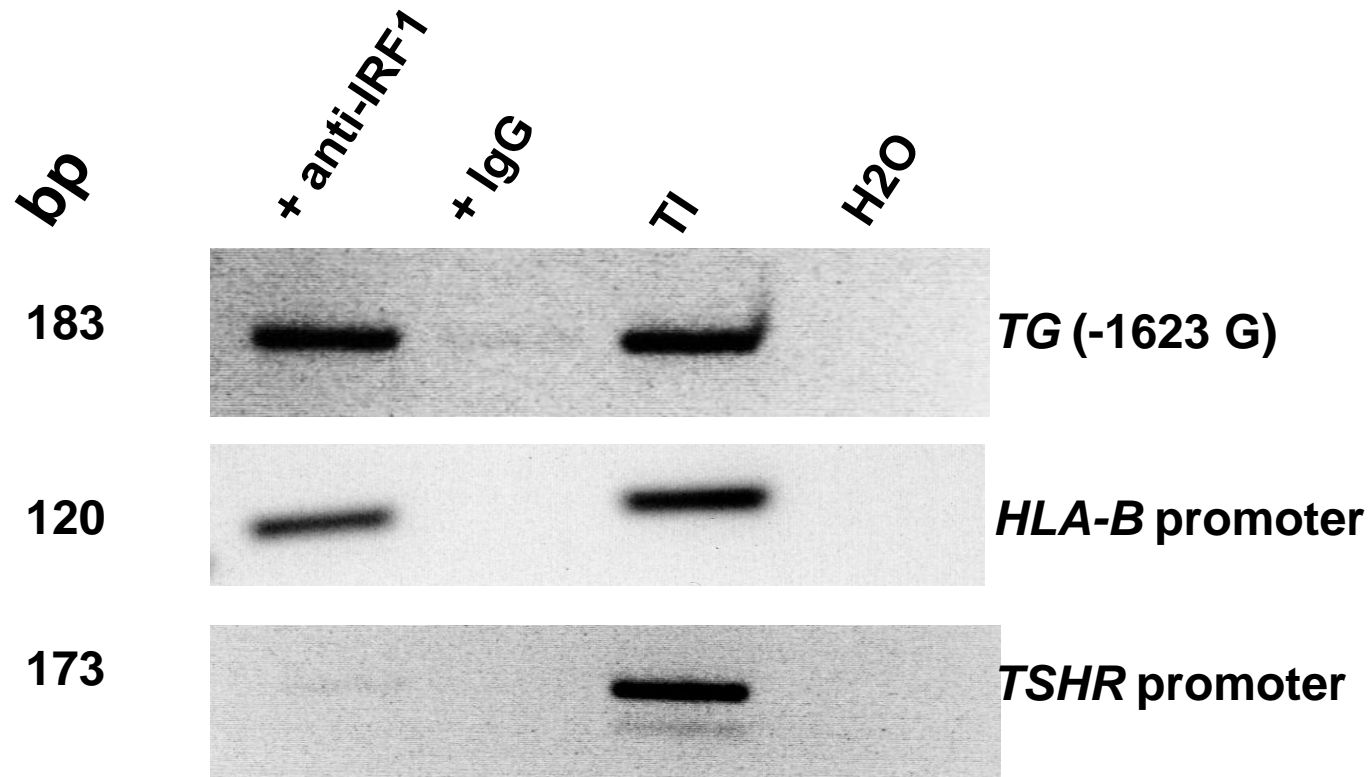
A Tg Promoter SNP That is Associated with AITD Shows Enrichment in H3K4me1



Stefan et al. JBC 2011; 286; 31168-31179

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Yaron Tomer)

Tg Promoter -1623 G Allele Binds IRF-1

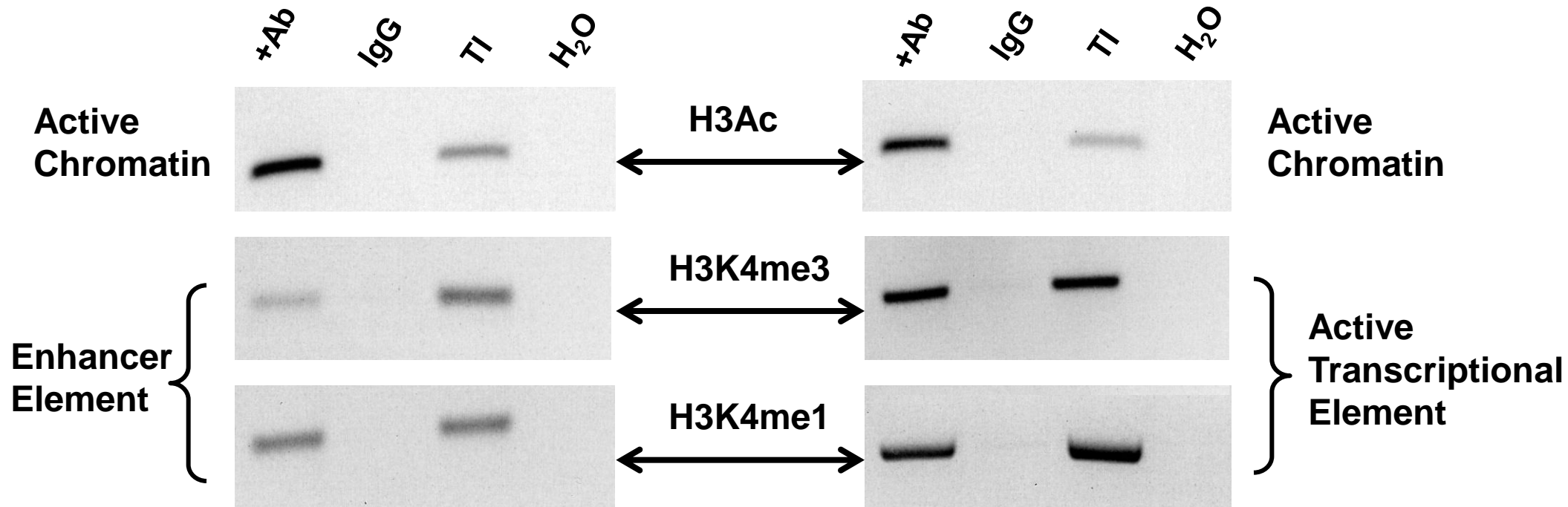


Stefan et al. JBC 2011; 286; 31168-31179

Binding of IRF-1 to the -1623 G-Allele Induces Epigenetic Changes Driving TG Transcription

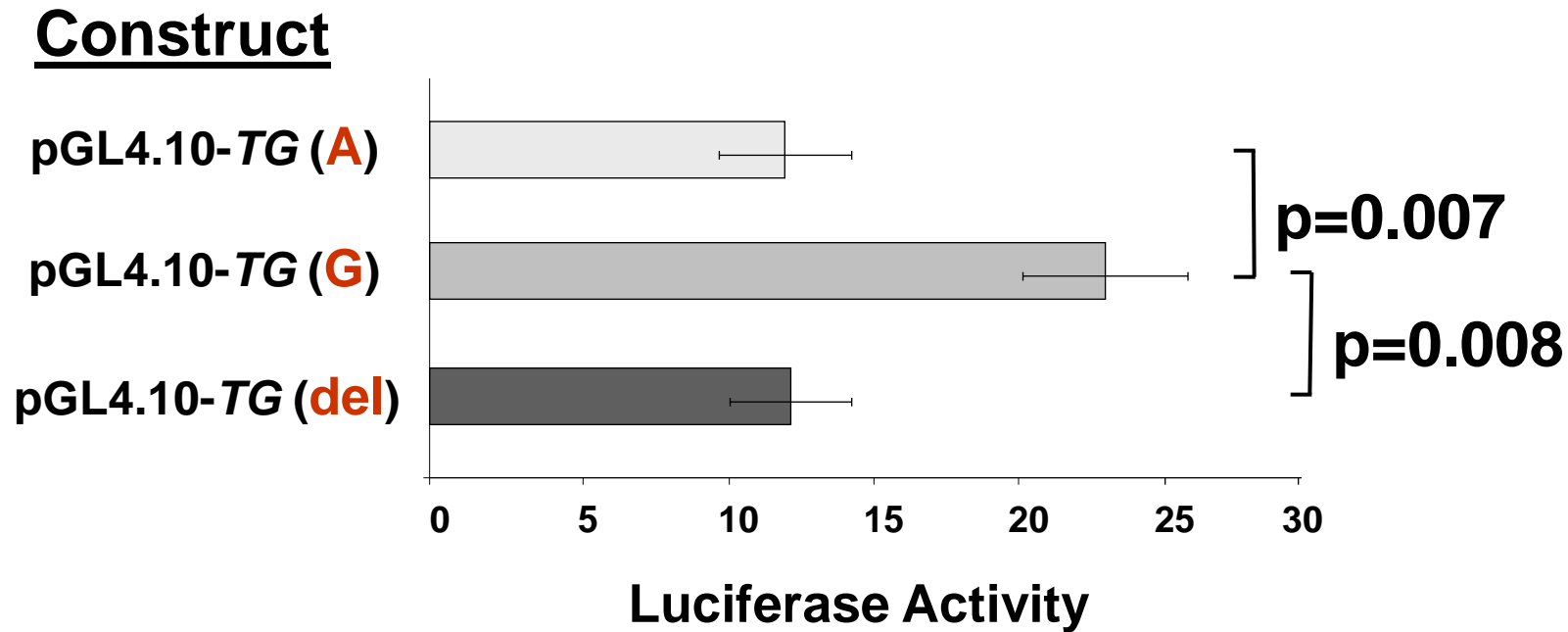
TG -1623 G

TG proximal promoter

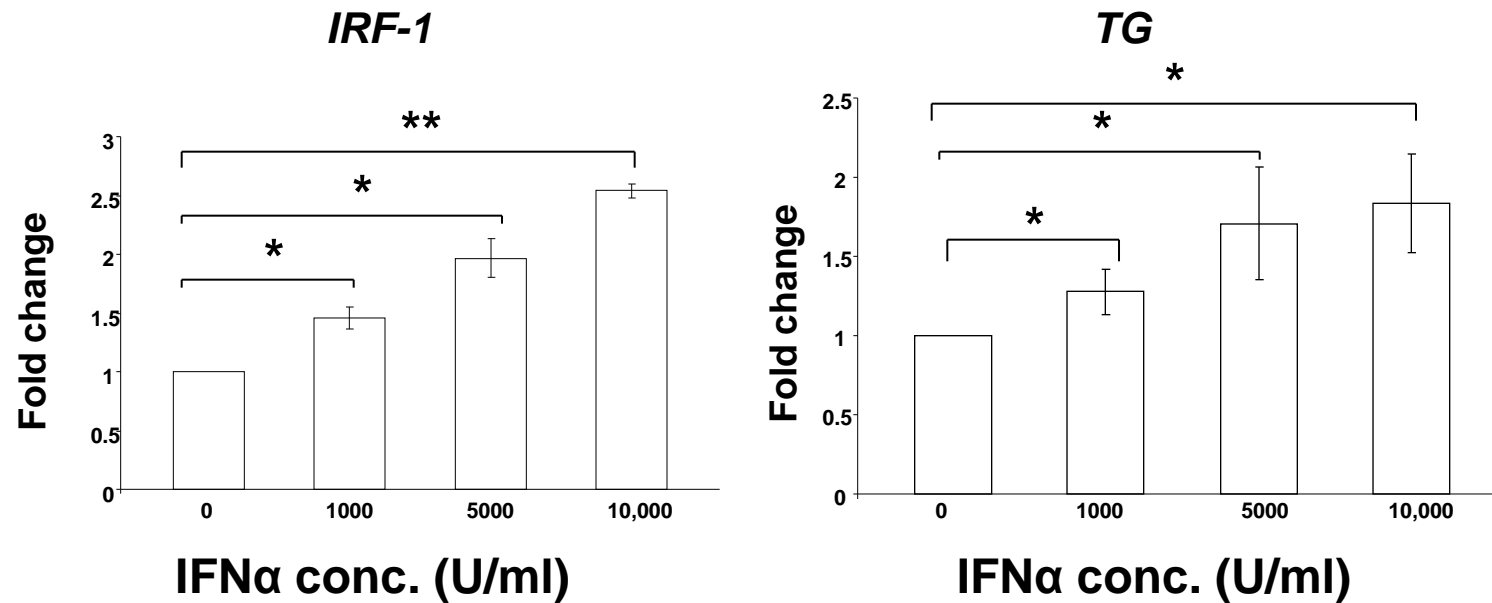


Stefan et al. JBC 2011; 286: 31168-31179

Tg Promoter -1623 G Allele Increases Promoter Activity

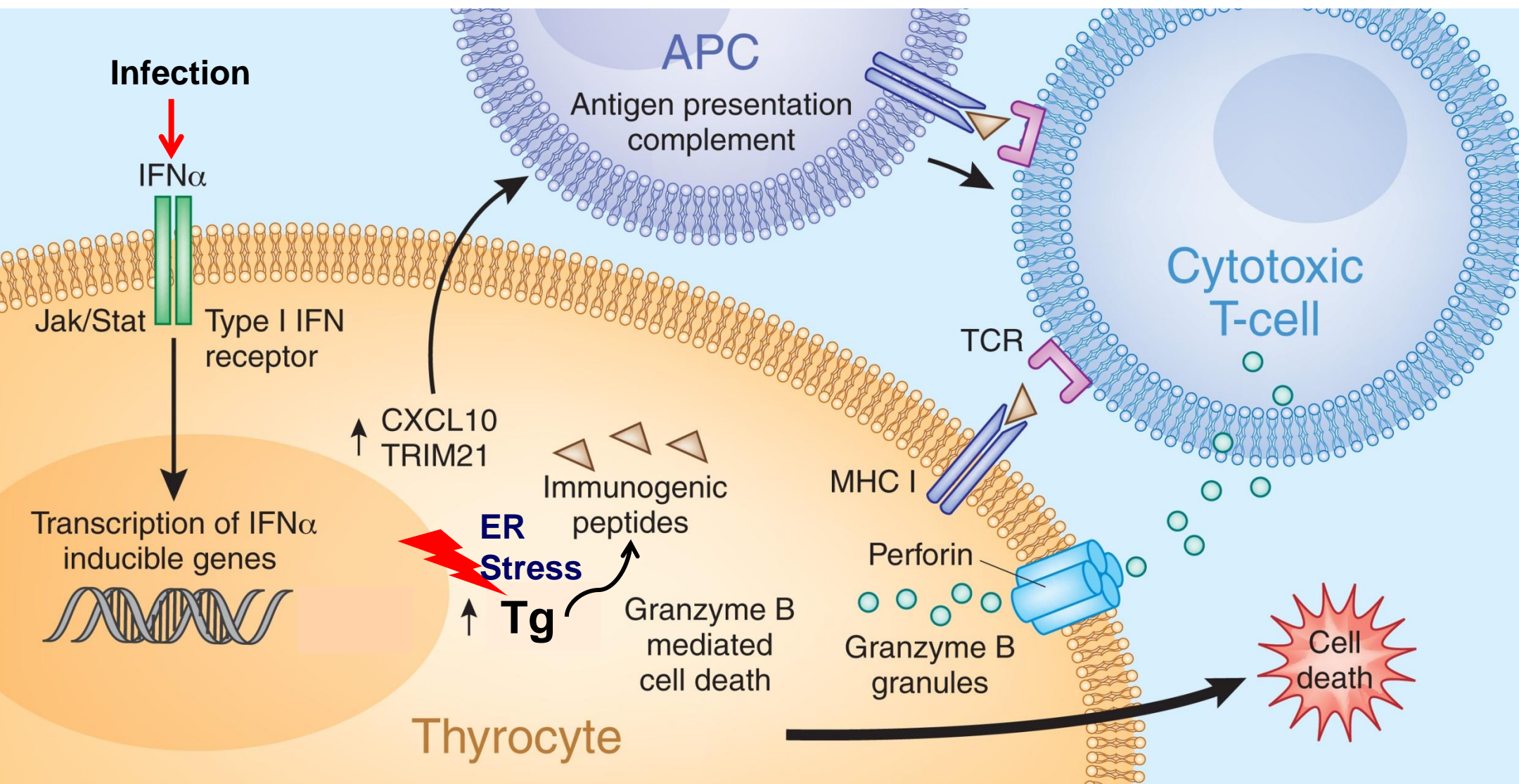


Interferon α Induces Tg Expression in Thyroid Cells



How can upregulation of Tg trigger AI TD?

MECHANISM



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Cheuk Wun Li
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Next gen Sequencing, Genotyping

Mehdi Keddache

Small molecule screening

Dan Felsenfeld

