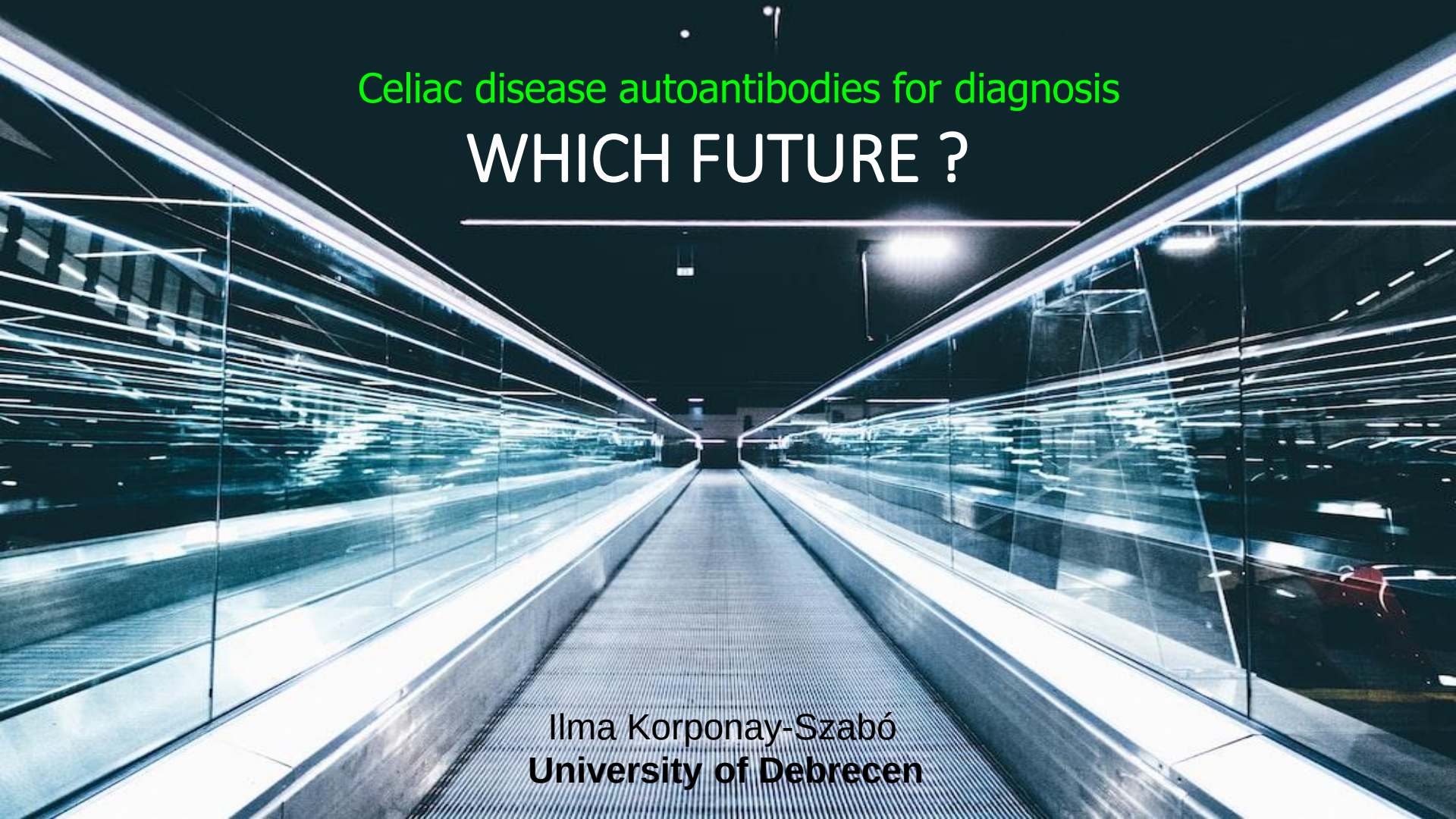




Celiac disease autoantibodies for diagnosis

WHICH FUTURE ?

Ilma Korponay-Szabó
University of Debrecen



Celiac autoantibodies to type-2 transglutaminase (TGA) are
highly accurate
non-invasive biomarkers
of celiac disease

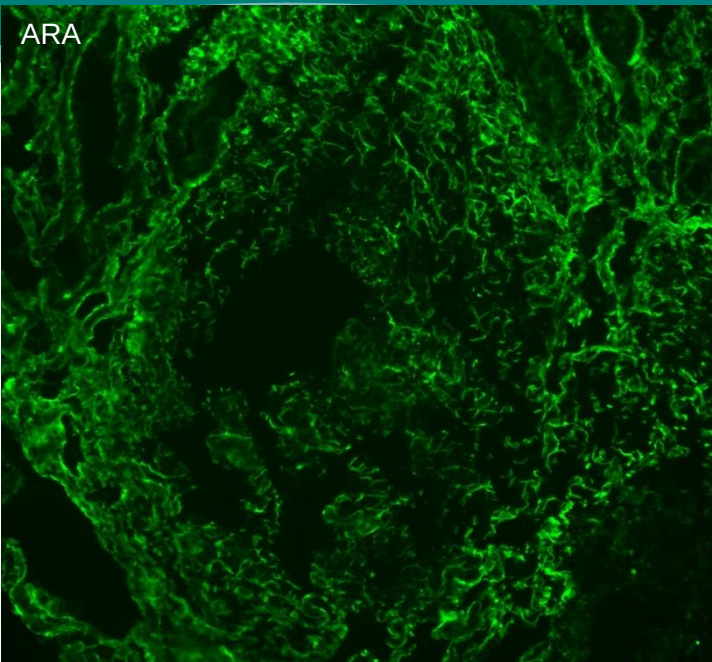
ORIGINAL ARTICLES | [VOLUME 298, ISSUE 7726, P681-682, SEPTEMBER 25, 1971](#)

ANTI-RETICULIN ANTIBODIES IN CHILDHOOD CÆLIAC DISEASE

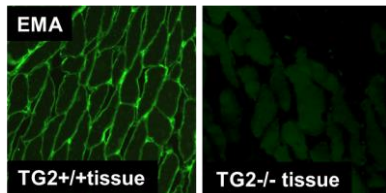
[P.P. Seah](#) • [Lionel Fry](#) • [MaryA. Rossiter](#) • [A.V. Hopfbrand](#) • [E.J. Holborow](#)

Published: September 25, 1971 • DOI: [https://doi.org/10.1016/S0140-6736\(71\)92248-3](https://doi.org/10.1016/S0140-6736(71)92248-3)





Both reticulin and endomysial antibodies target transglutaminase 2



Korponay-Szabo 2003

ORIGINAL ARTICLES | [VOLUME 298, ISSUE 7726, P681-682, SEPTEMBER 25, 1971](#)

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Evaluation of a serum IgA-class reticulin antibody test for the detection of childhood celiac disease

[M.D. Markku Mäki](#) • [M.D. Olavi Hällström](#) • [M.D. Timo Vesikari](#) • [M.D. Jarmo K. Visakorpi](#)

DOI: [https://doi.org/10.1016/S0022-3476\(84\)80074-8](https://doi.org/10.1016/S0022-3476(84)80074-8)

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Research Article

Comparison of IgA-class reticulin and endomysium antibodies in coeliac disease and dermatitis herpetiformis. **FREE**

[O Hällström](#)

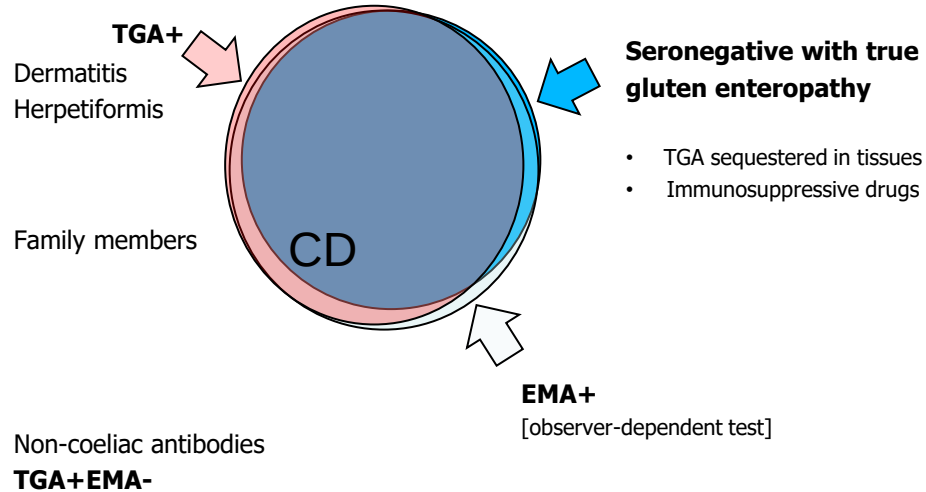


Characteristics of celiac autoantibodies

- They are specific for a few conformational epitopes of TG2 (mostly epitope 1 and epitope 2)
- Mucosal triggering results in IgA class production (more predictive than IgG)
- *TGA antibodies bind to TG2 in tissues*
- TGA antibodies are disease activity markers, dependent on gluten consumption and HLA-DQ2/DQ8 mediated presentation
- Predict forthcoming mucosal structural deterioration



Autoantibodies in coeliac disease

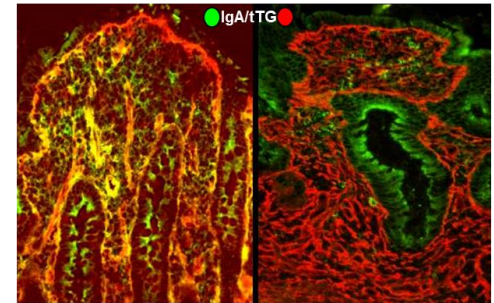


Autoimmune and malignant diseases
Some hepatic disorders
Down's syndrome
Psoriasis
Some cardiac diseases
Some infections (EBV)

RARE

Always consider possible sample mix-up !

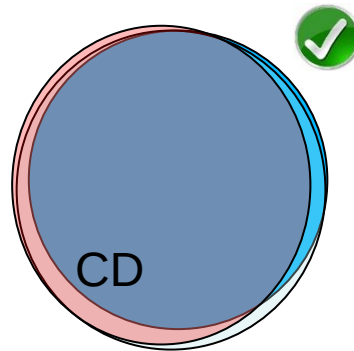
Coeliac disease **Autoimmune enteropathy**



Marsh III

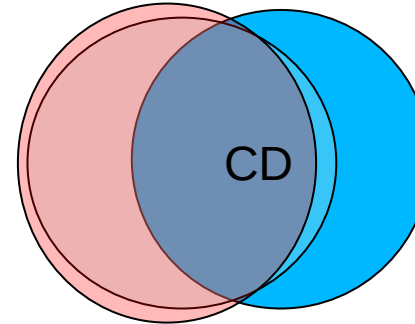


Autoantibodies in coeliac disease



Serology

Histology

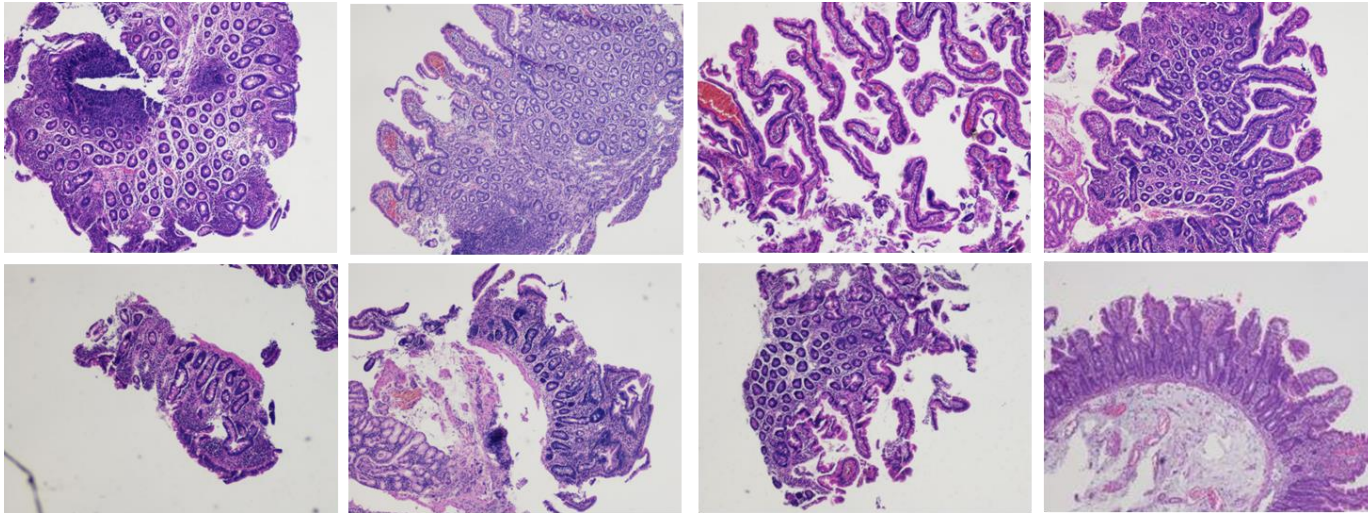


1. Not the appropriate test is used
or not at the right time

2. Technical errors



ORIENTATION problems are more frequent than previously considered



ProCeDE

79/83 samples received for morphometry
36 patients had non-evaluable histopathology



Achievements

- High accuracy of commercial TGA-IgA tests for initial diagnosis
- Decrease of non-specific positive results and background (human TG2 antigens of good shape)
- Proven performance in the screening of asymptomatic risk persons, population

→ ***Non-invasive diagnosis for children with $\geq 10 \times \text{ULN}$ high TGA seropositivity and EMA+ result from a 2nd sample***
ESPGHAN guidelines 2020

- Short turnaround time & cheap rapid testing
- Automated platforms & telemedicine solutions



Comparison of predictive values of IgA TGA antibodies and biopsy

Positive likelihood ratio (LR+): True positives / false positives

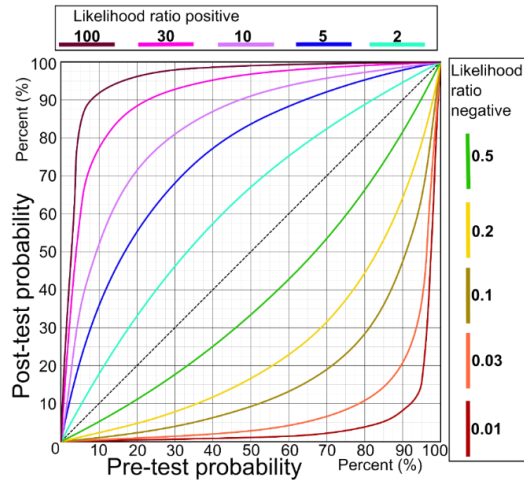


Table 3 Association between 'flat mucosa' at first biopsy and eventual diagnosis of coeliac disease

	No	%
All patients:		
Patients suspected of having coeliac disease with a 'flat mucosa'	3293	100
Eventual diagnosis of coeliac disease	3138	95.3
Other diagnoses	155	4.7

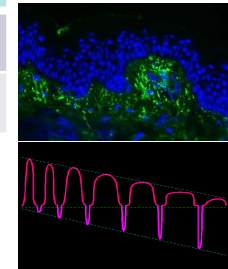
LR+ 20.3

Guandalini et al. Arch Dis Child 1989;64:1320-1325

LR+ for CD diagnosis	Duodenal histology dependent	Duodenal histology independent
TGA	21.8 (11-41)	127
EMA	31.8 (19-839)	127

Giersiepen, 2012

Dahlbom, 2010





Assumptions / expectations not fulfilled

- Adding IgG to IgA celiac TGA antibody detection would give more reliable results (except for proven IgA deficient cases)
- Adding DGP to IgA celiac TGA antibody detection would detect more true celiacs



Antibodies to native (NGP) and deamidated gliadin peptides (DGP) do not predict celiac disease in TGA-negative cases

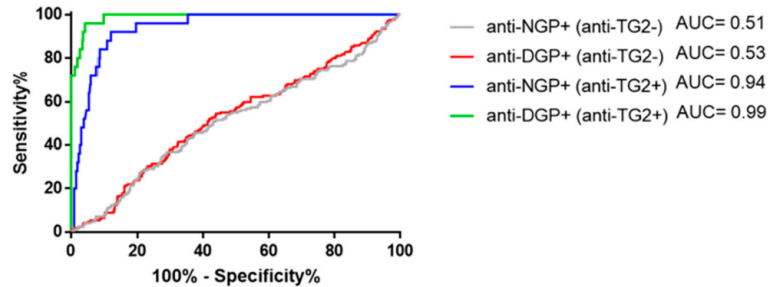
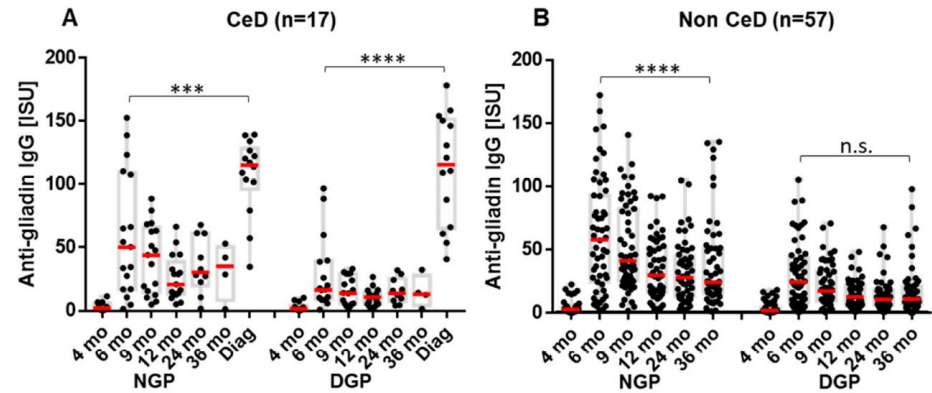


Figure 5. Antibodies to non-deamidated (NGP) or deamidated (DGP) gliadin peptides have no prediction for later celiac disease in the absence of anti-transglutaminase antibodies. Receiver operating characteristic curves for serum IgG antibody-positive samples at any age with gluten consumption to NGP or DGP in the absence or presence of concomitant IgA transglutaminase antibody (anti-TG2) positivity (>3.9 ISU). AUC, area under the curve. The graph is based on values of 562 samples obtained from the 122 children during gluten consumption.





Assumptions / expectations not fulfilled

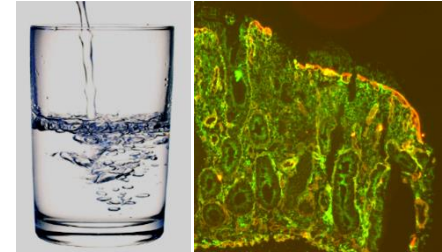
- Adding IgG to IgA celiac TGA antibody detection would give more reliable results (except for proven IgA deficient cases)
- Adding DGP to IgA celiac TGA antibody detection would detect more true celiacs
- Automated results would make observer-dependent methods (EMA) unnecessary
- Automated results would make ,medical thinking' unnecessary





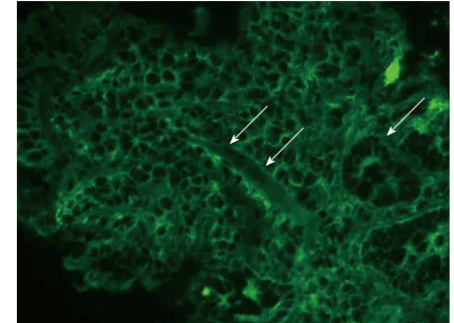
Unmet needs

- Increase of sensitivity (seronegative cases, diet monitoring)
- Standardisation of quantitation and calculation of results
- Non-invasive diagnosis for adults and patients with low positive TGA antibodies



Deposited IgA (green)
Salmi Gut 2006

Deposited IgA after 2 weeks gluten



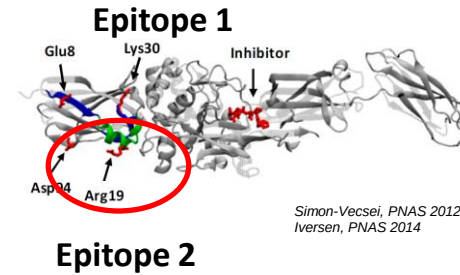
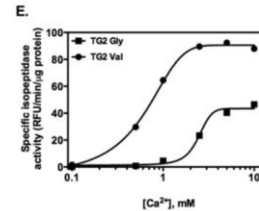
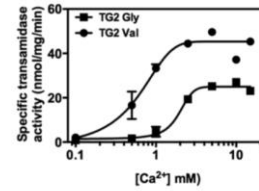
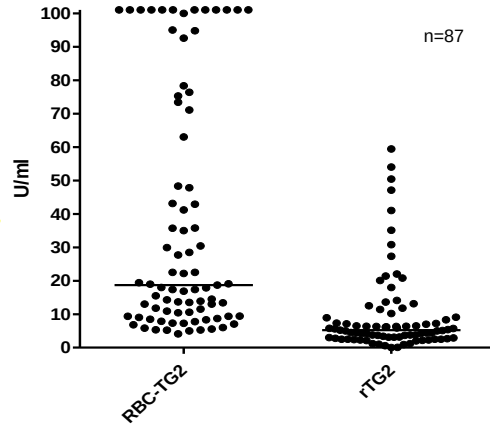
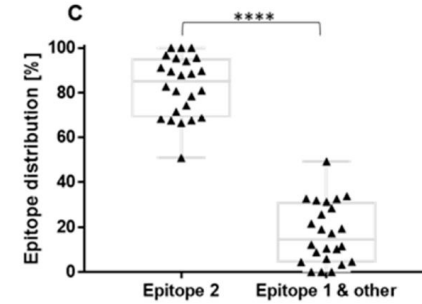
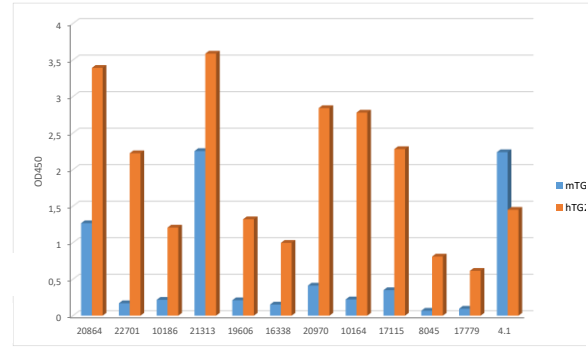
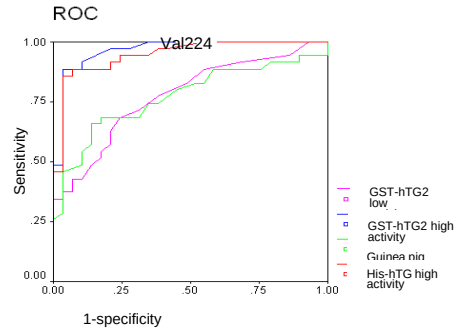
Tack W J Gas 2013

Mutant tTG



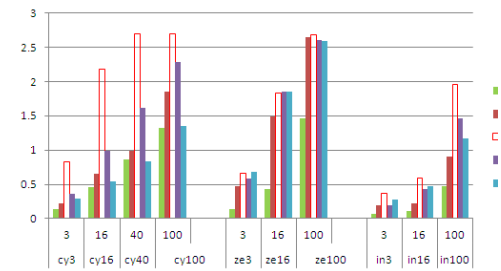
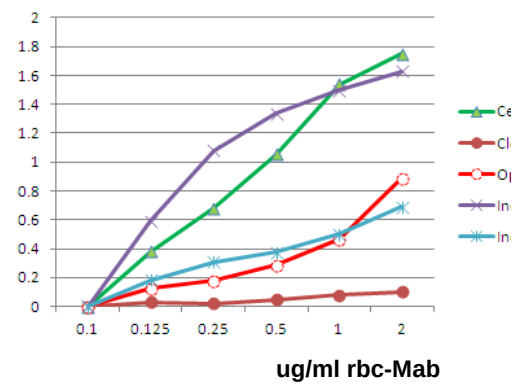
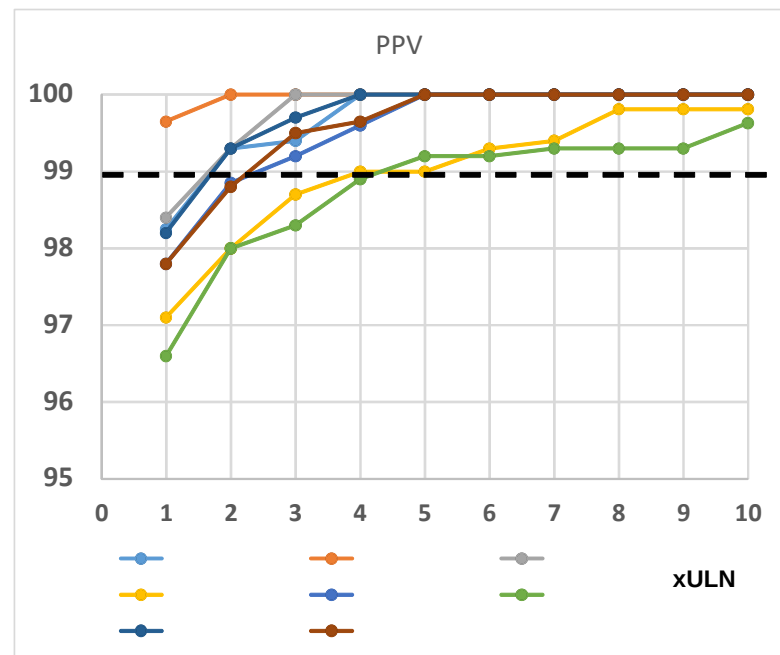
Inhibitors/
Activators



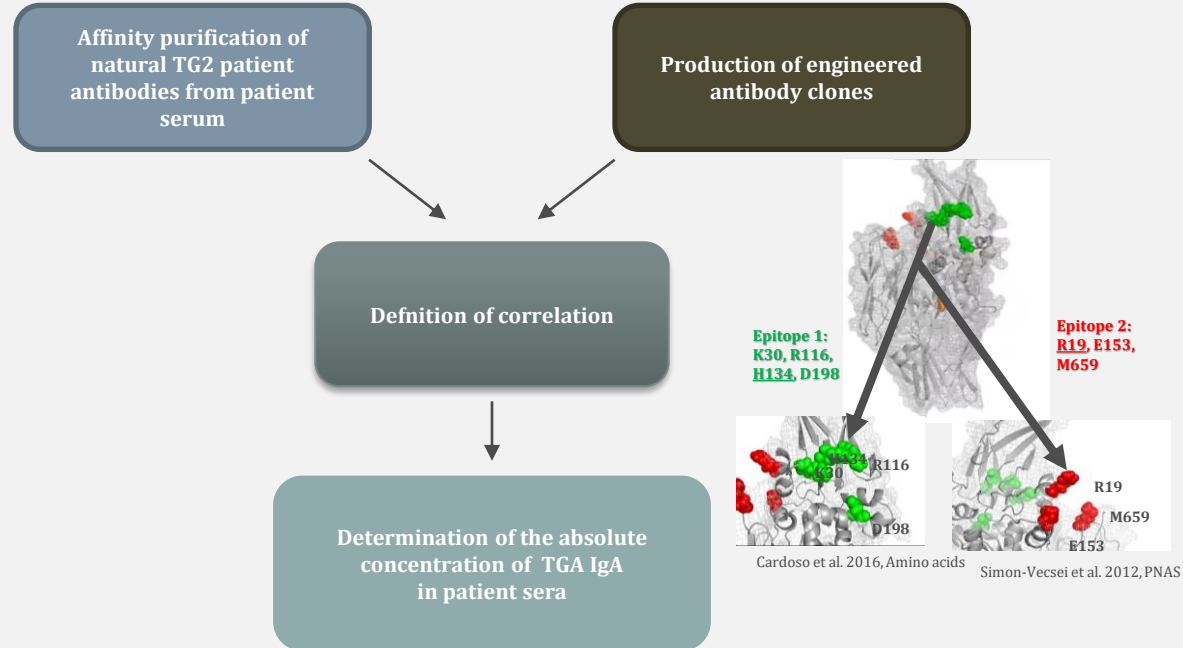
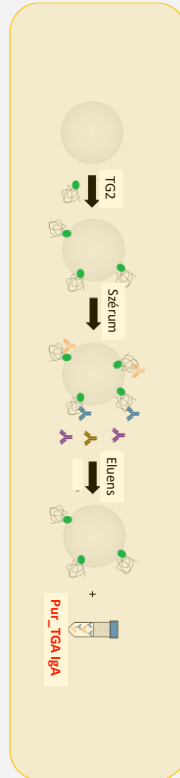


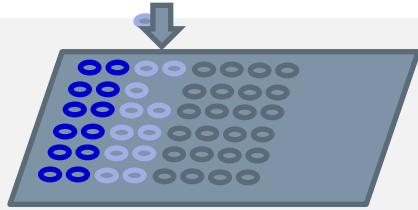
Simon-Vecsei, PNAS 2012
Iversen, PNAS 2014

ProCeDE

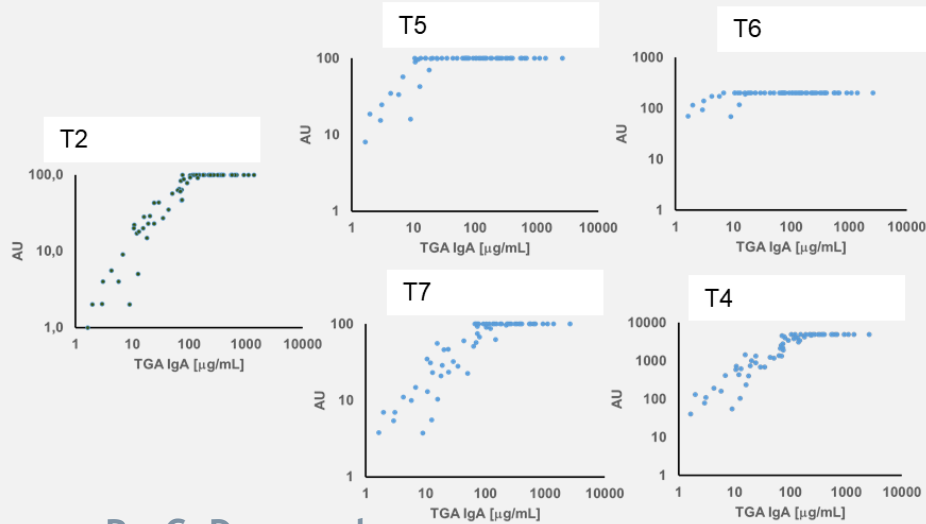


Calibrator development workflow

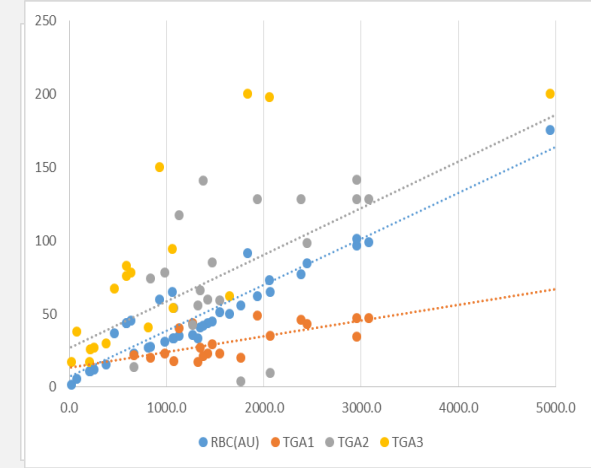
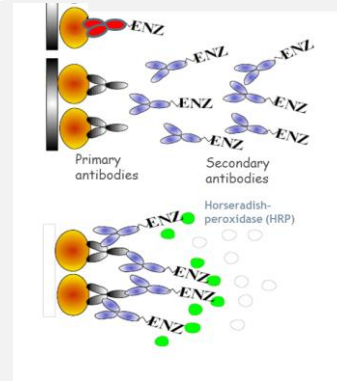




Comparison of different serology tests by the use of calibrators



ProCeDe samples



Interreg clinical samples





FUTURE ?



UniDebreceen



Contents lists available at ScienceDirect

Journal of Pharmaceutical Analysis

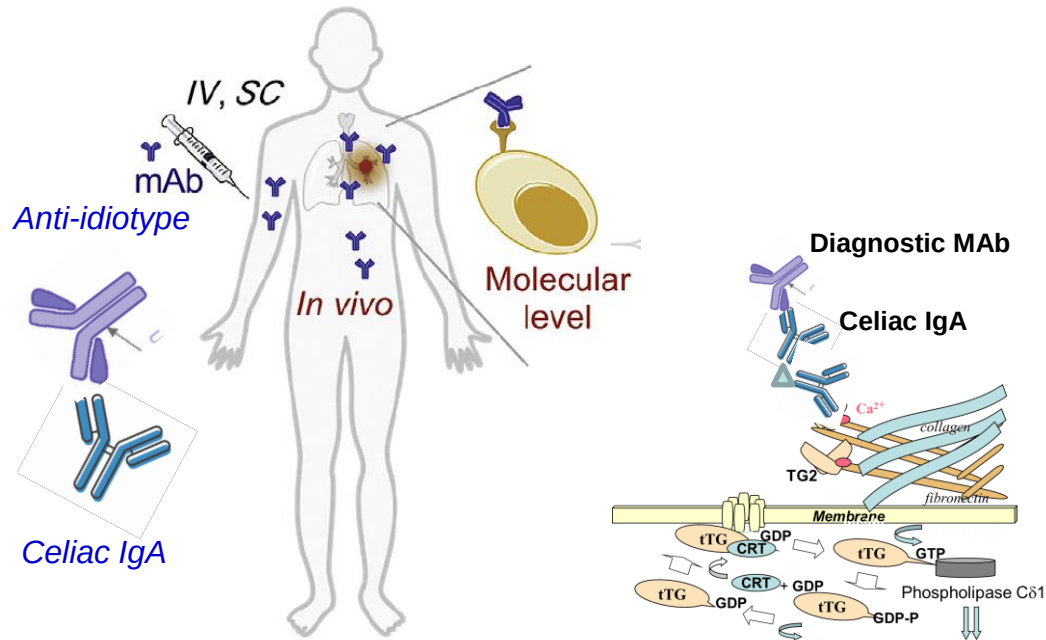
journal homepage: www.elsevier.com/locate/jpa

Review paper

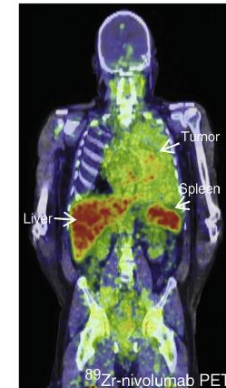
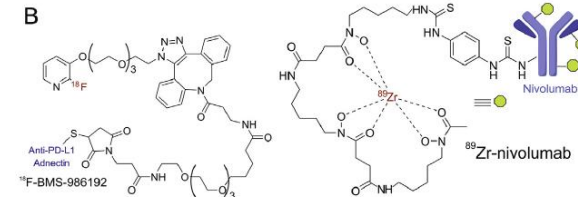
Recent progress in the molecular imaging of therapeutic monoclonal antibodies

Kaifeng He, Su Zeng, Linghui Qian*

Journal of Pharmaceutical Analysis 10 (2020) 397–413



B



FUTURE ?

K. He, S. Zeng and L. Qian

Journal of Pharmaceutical Analysis 10 (2020) 397–413



PLOS ONE

RESEARCH ARTICLE

Bloodstream-To-Eye Infections Are Facilitated by Outer Blood-Retinal Barrier Dysfunction

Phillip S. Coburn¹, Brandt J. Wiskur², Frederick C. Miller^{3,4}, Austin L. LaGrow¹, Roger A. Astley¹, Michael H. Elliott^{1,2,5}, Michelle C. Callegan^{1,2,6*}

PLoS One. 2016;19;11(5):e015456

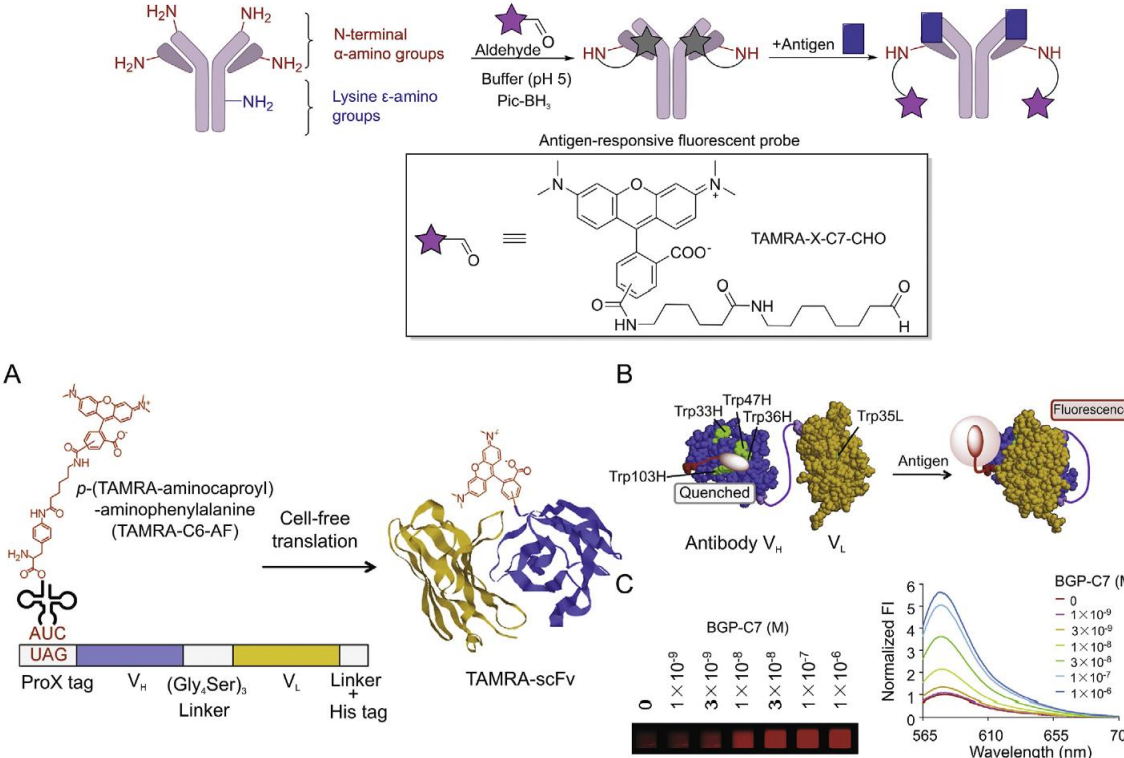
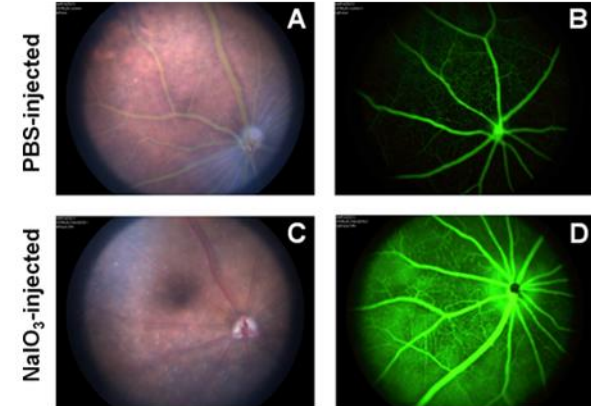
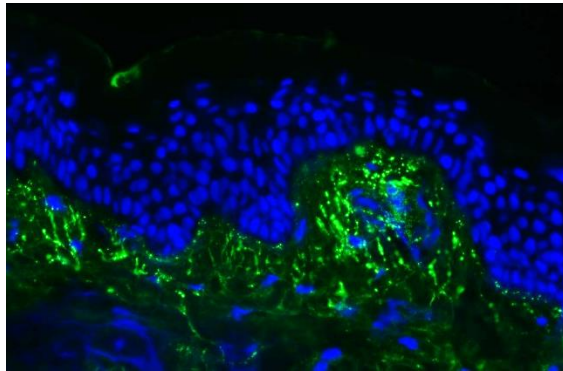


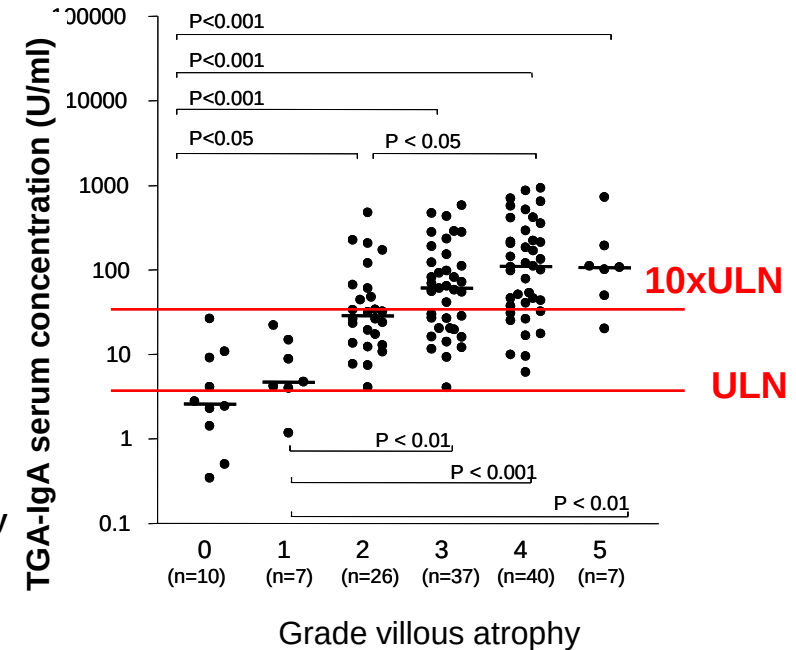
Fig. 15. (A) Incorporation of TAMRA-C6-AF into scFv in response to a UAG codon in a cell-free translation system. (B) The reaction model of TAMRA-scFv towards antigen. Trp residues, Trp33H, Trp36H, Trp47H, Trp103H, and Trp35L are colored green. (C) Antigen-dependent fluorescence enhancement of TAMRA-labeled anti-BGP scFv upon reaction with BGP-C7. The figure was reproduced with permission from Ref. [106].



Serum TGA concentrations strongly correlate with villous flattening

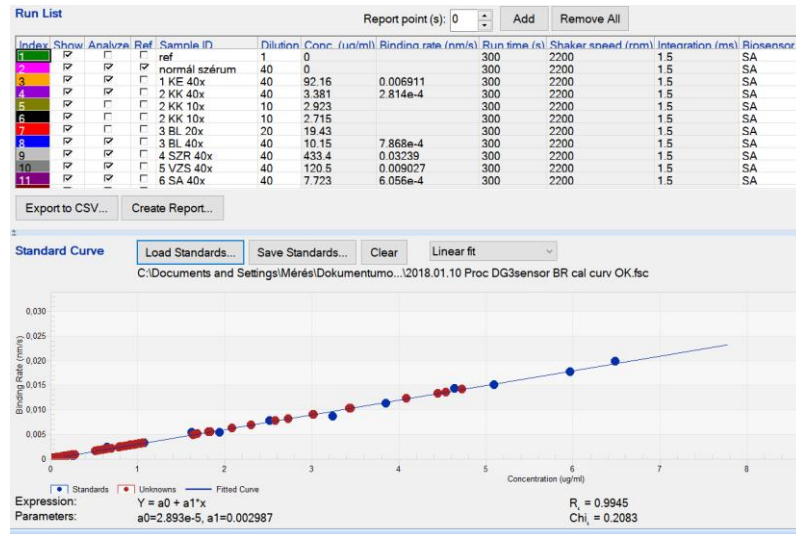
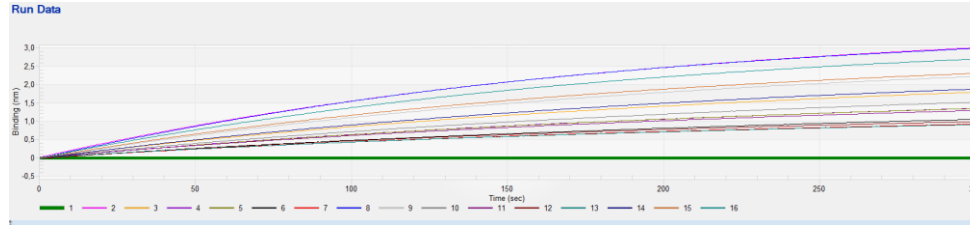


DH n=134
Positive
diagnosis from skin biopsy

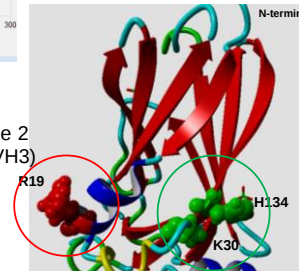




Quantitative transglutaminase antibody biosensor



Epitope 2
(VH3)



Epitope 1
(VH5)

