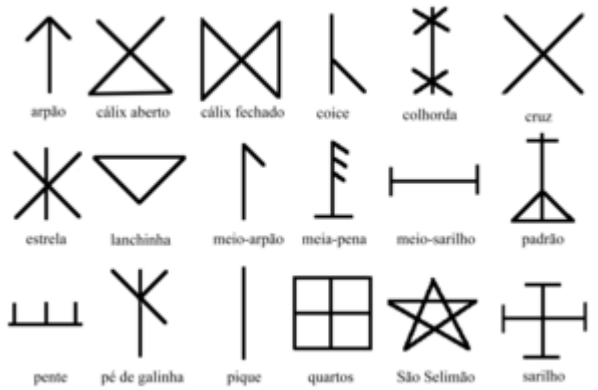
Transthyretin amyloidosis

Carlos Cordeiro

Ciências ULisboa

Scandinavia 850 AD



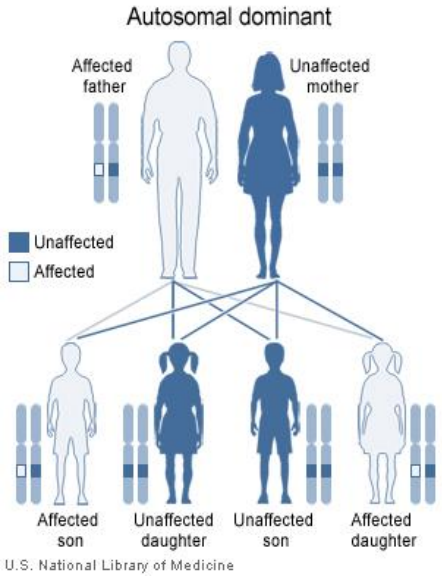
Japan XVI century

Trade, religion, firearms and... paramyloidosis

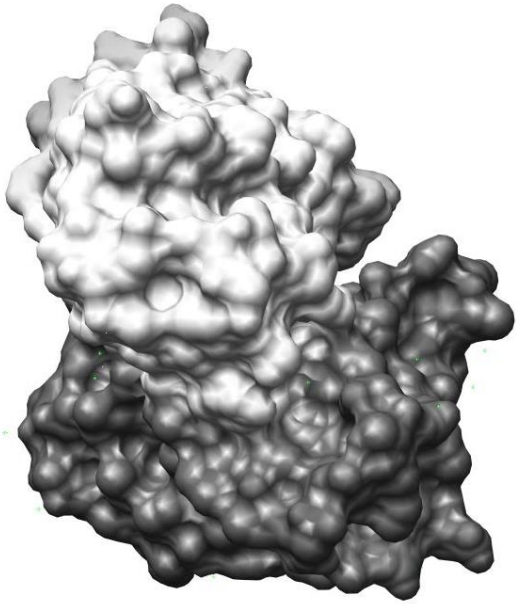
Póvoa de Varzim 1952

Corino de Andrade

Peripheral nervous system
Systemic
Amyloid deposits



Transthyretin



- Tetramer (14 KDa)
- Liver, brain
- Amyloid deposits

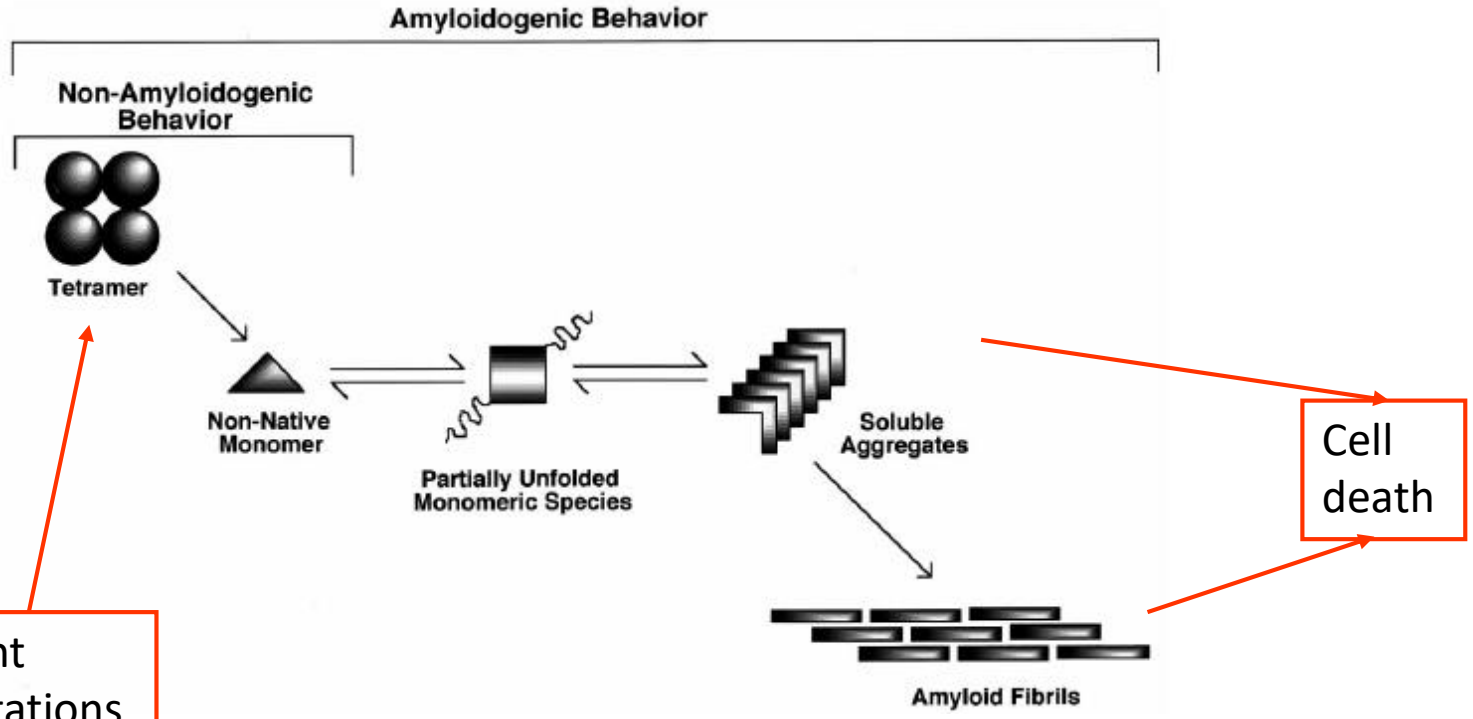
  Familial amyloidotic polyneuropathy

>100 Point mutations

V30M Portuguese type

L55P Early onset type

Molecular model



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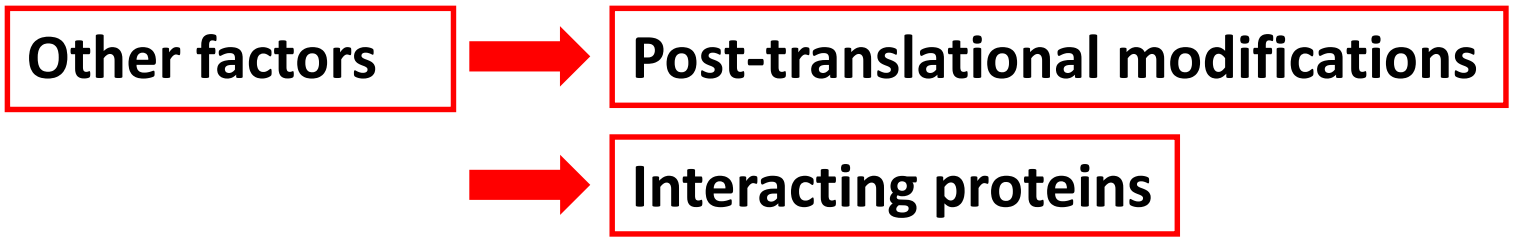
Tetramer Dissociation and Monomer Partial Unfolding Precedes Protofibril Formation in Amyloidogenic Transthyretin Variants*

Received for publication, February 2, 2001, and in revised form, April 10, 2001
Published, JBC Papers in Press, April 16, 2001, DOI 10.1074/jbc.M101024200

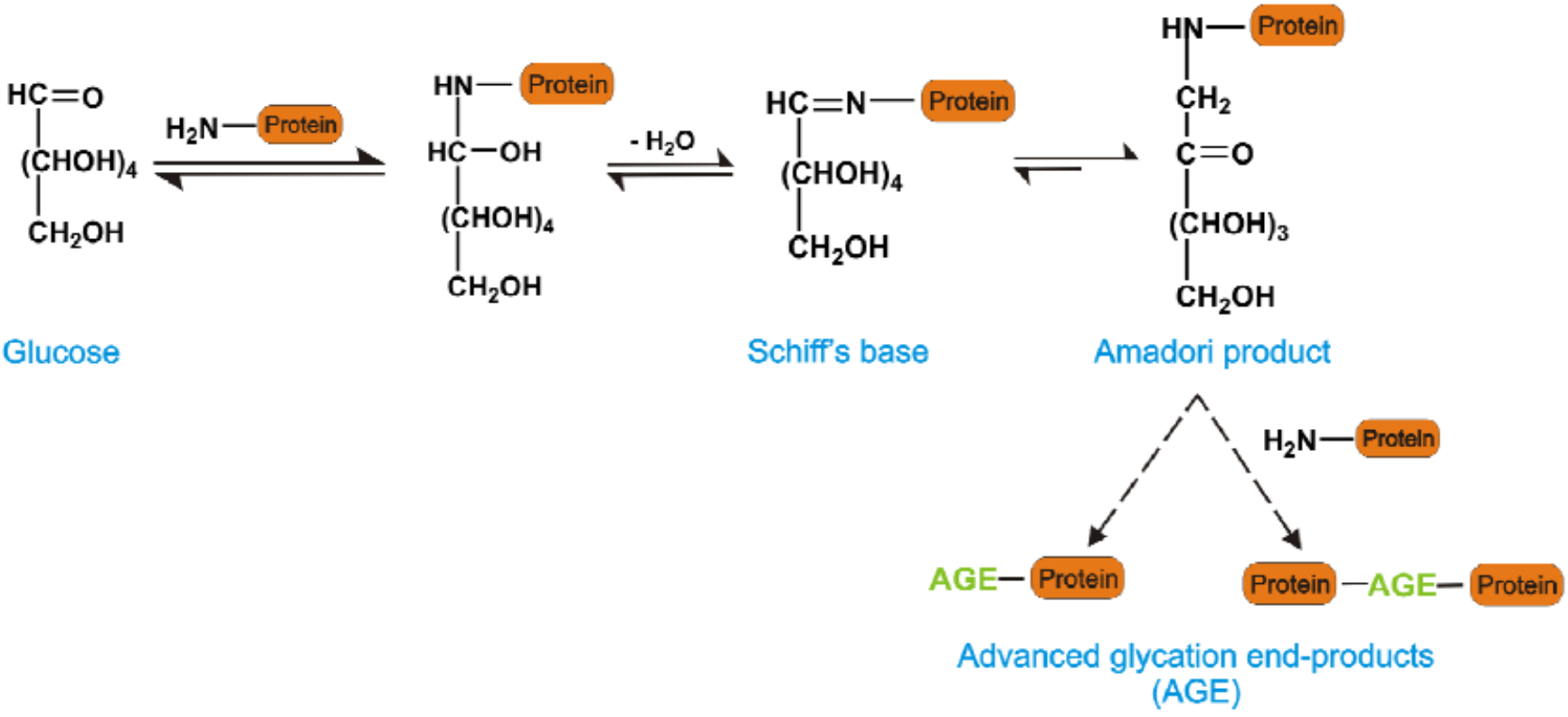
Alexandre Quintas‡§, Daniela C. Vaz‡, Isabel Cardoso¶, Maria João M. Saraiva¶, and Rui M. M. Brito‡‖**

Unexplained…

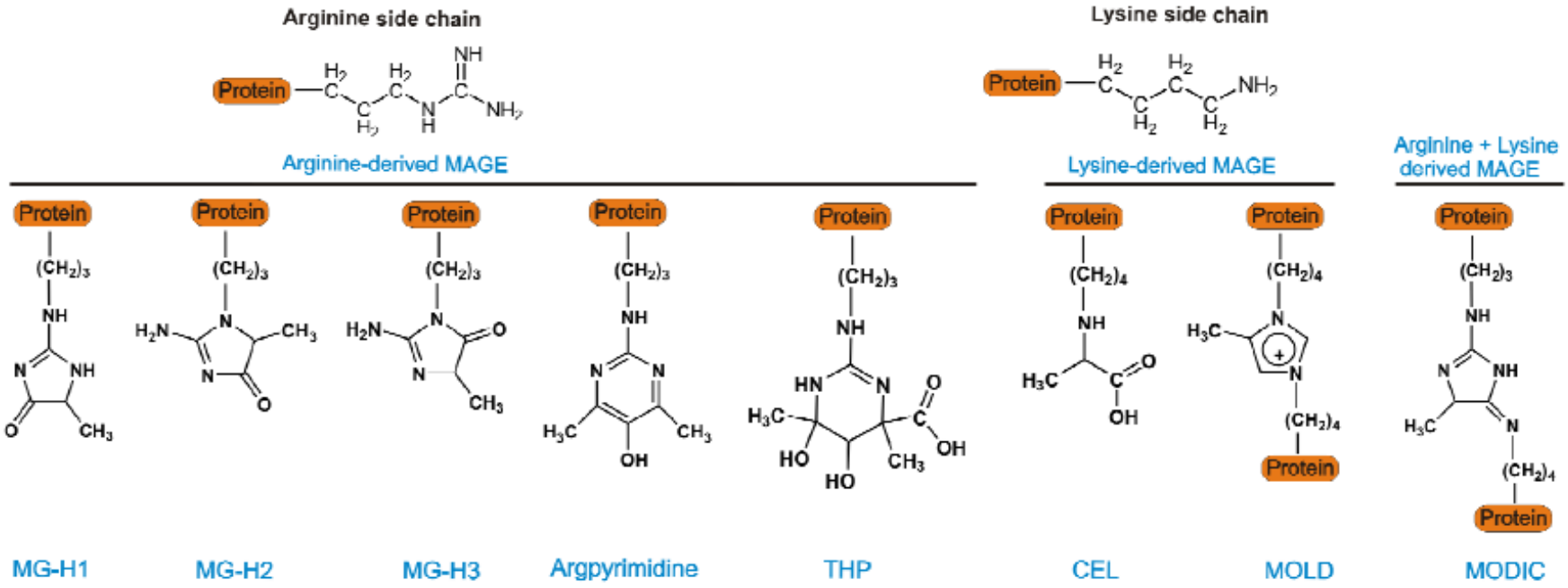
- Variable age at onset
- Asymptomatic cases
- Mutations not required
  - Sistemic Senile Amyloidosys
- Toxic effects of self-proteins
- High protease resistance

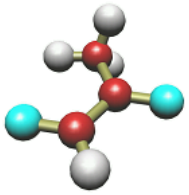


Why Protein Glycation ?



MAGE





Methylglyoxal
2-Oxopropanal

Biochem. J. (2002) **364**, 1–14 (Printed in Great Britain)

Assay of advanced glycation endproducts (AGEs): surveying AGEs by chromatographic assay with derivatization by 6-aminoquinolyl-*N*-hydroxysuccinimidyl-carbamate and application to N_ε-carboxymethyl-lysine- and N_ε-(1-carboxyethyl)lysine-modified albumin

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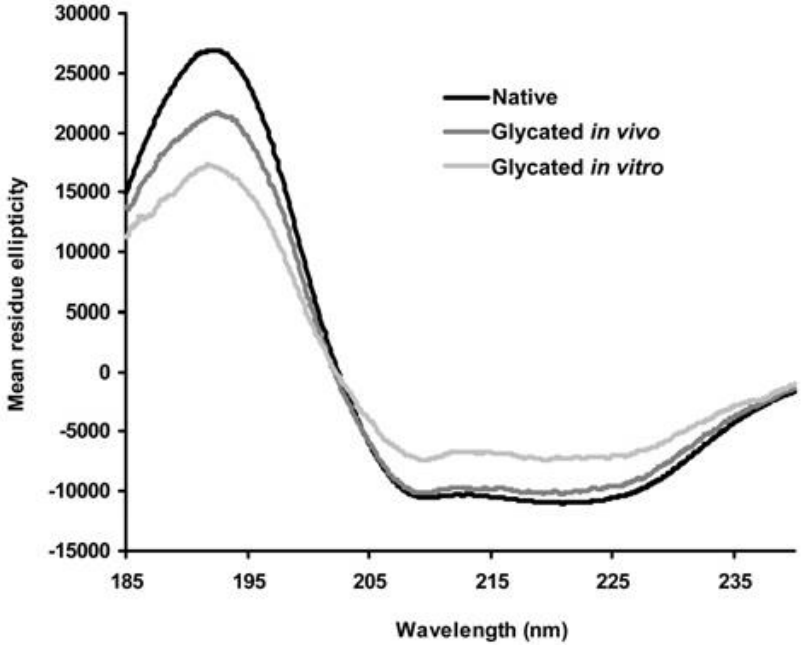
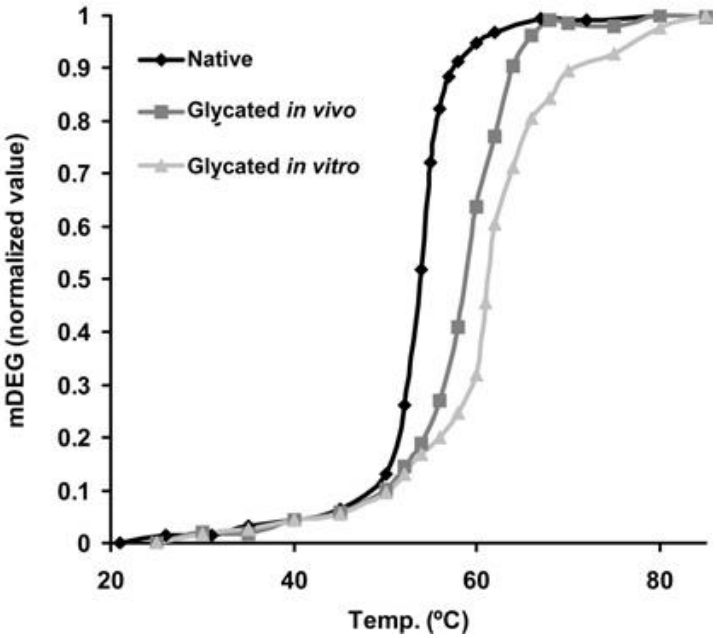
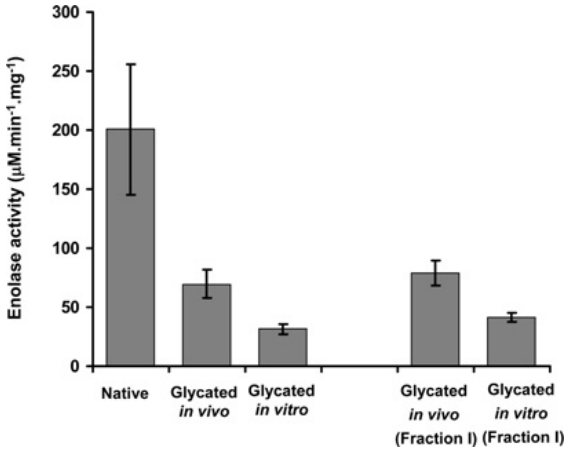
Department of Biological Sciences, University of Essex, Central Campus, Wivenhoe Park, Colchester, Essex CO4 3SQ, U.K.

Protein glycation *in vivo*

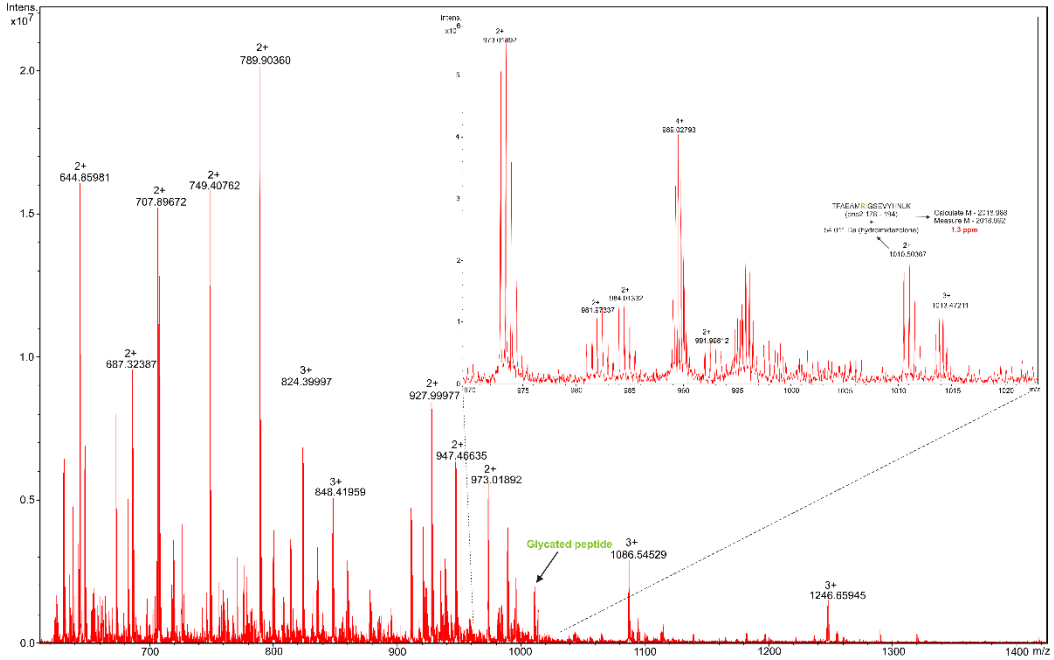


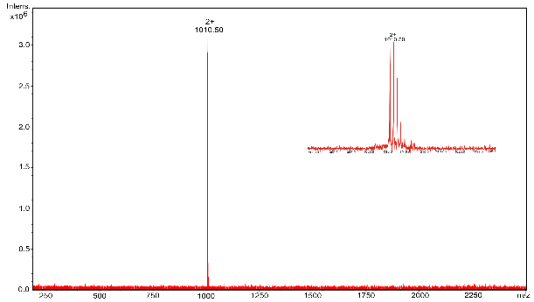


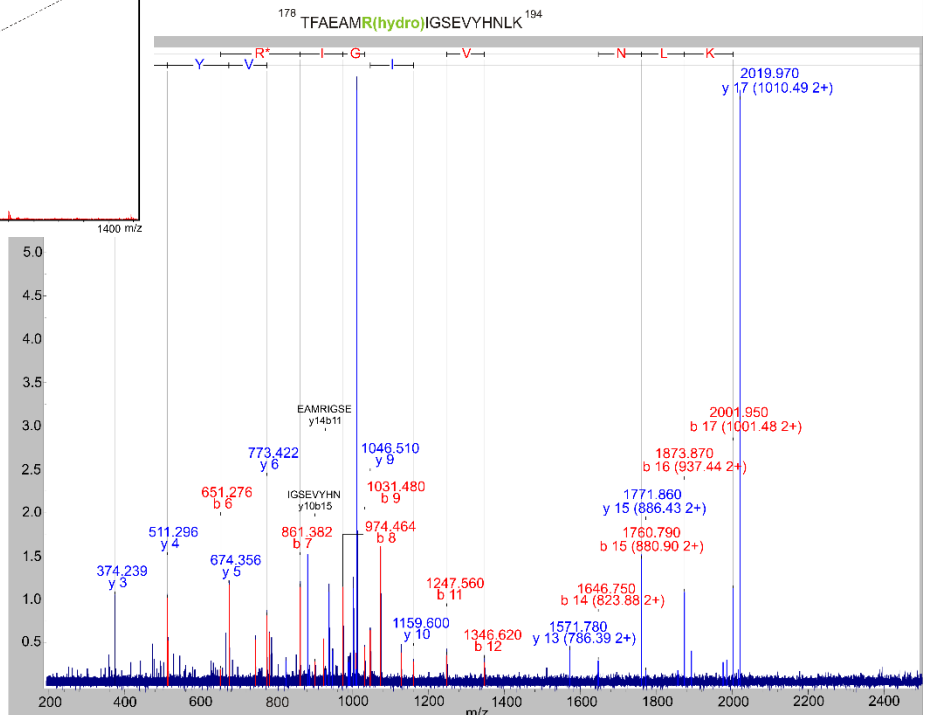


Enolase
Enzyme activity loss
Structural statibility decrease
Unfolding

Protein characterization (FT-ICR)

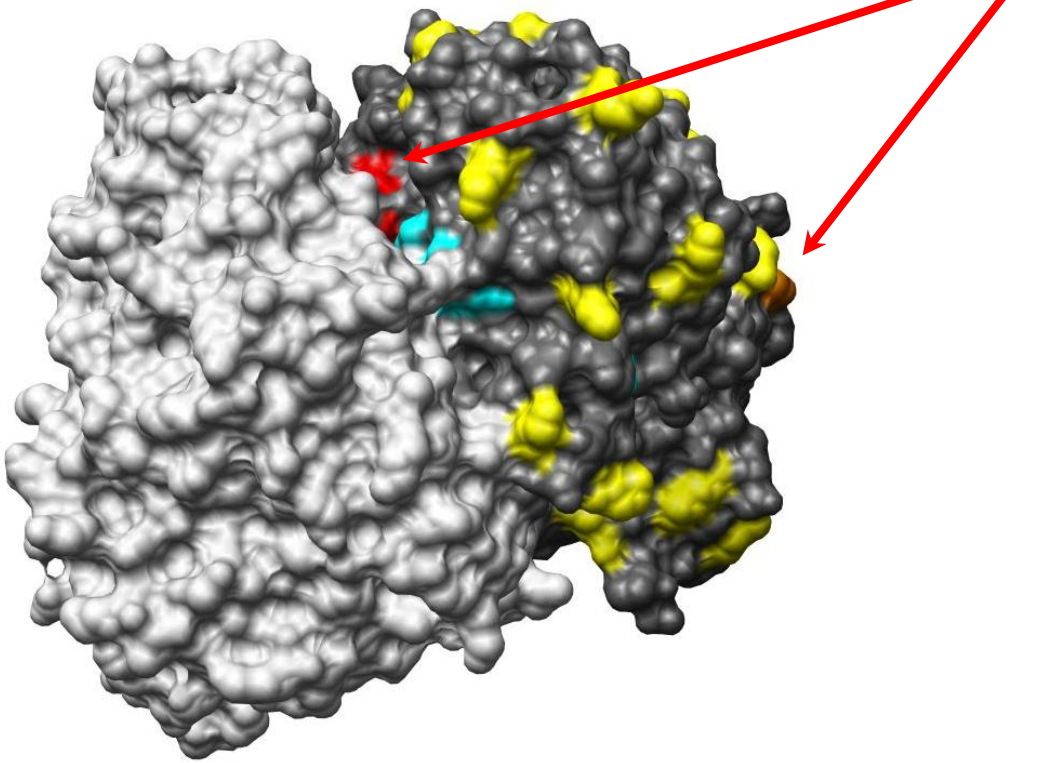






Peptide mapping
trypsin hydrolysis
Analysis of the peptide mix
60% sequence coverage

Enolase



Disruption of a salt bridge
Dimer dissociation
Unfolding...

Biochem. J. (2008) **416**, 317–326 (Printed in Great Britain) doi:10.1042/BJ20080632

Protein glycation *in vivo*: functional and structural effects on yeast enolase

Ricardo A. GOMES*, Luís M. A. OLIVEIRA*†, Mariana SILVA*, Carla ASCENSO†, Alexandre QUINTAS†, Gonçalo COSTA‡, Ana V. COELHO‡§, Marta SOUSA SILVA*, António E. N. FERREIRA*, Ana PONCES FREIRE* and Carlos CORDEIRO*[1]

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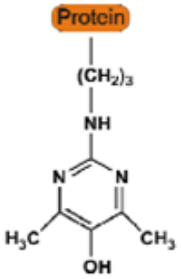
Glycation in ATTR



Argpyrimidine

Detection and quantification of argpyrimidine in FAP amyloid deposits

Biochem. J. (2005) **385**, 339–345 (Printed in Great Britain)

Argpyrimidine, a methylglyoxal-derived advanced glycation end-product in familial amyloidotic polyneuropathy

Ricardo GOMES*, Marta SOUSA SILVA*, Alexandre QUINTAS*, Carlos CORDEIRO*[1], António FREIRE†, Paulino PEREIRA†, Américo MARTINS†, Estela MONTEIRO†, Eduardo BARROSO† and Ana PONCES FREIRE*

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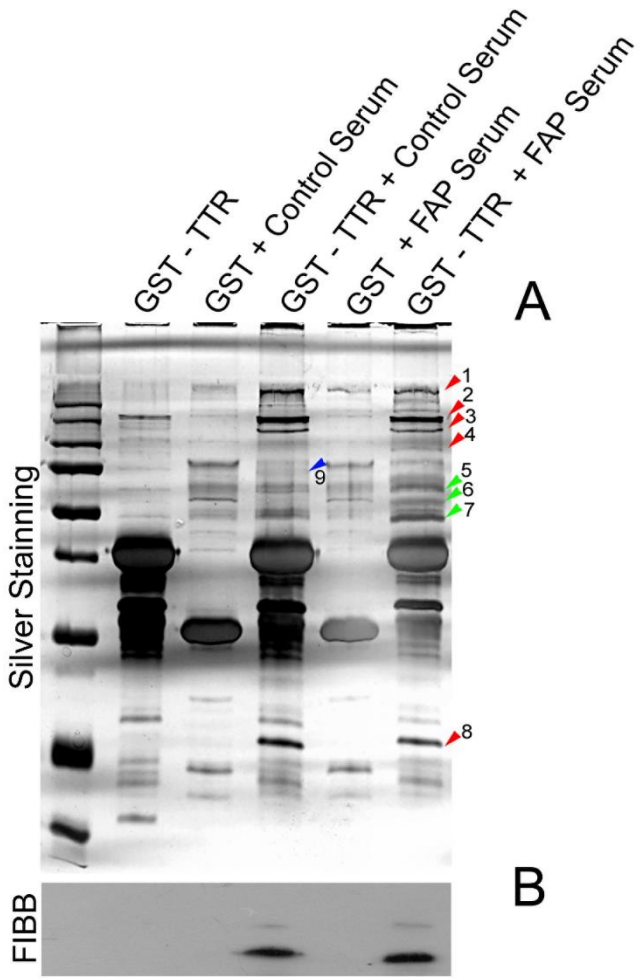
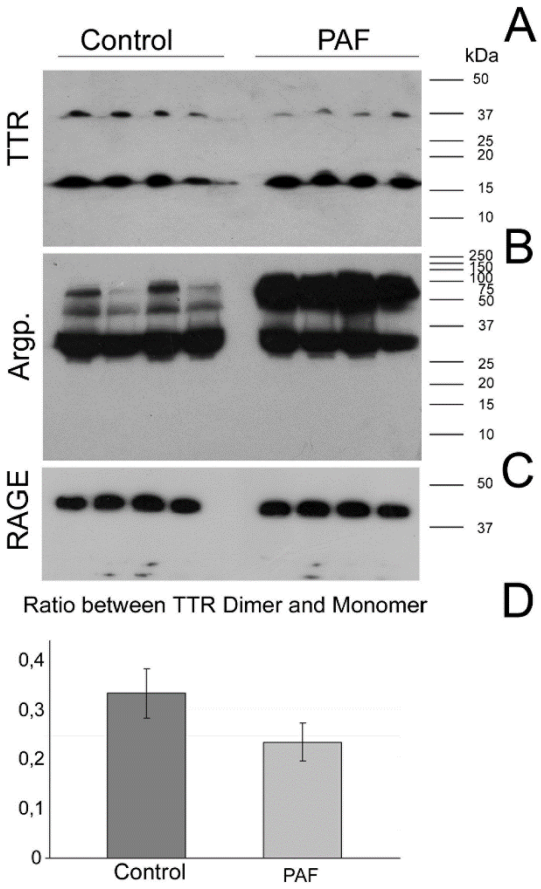
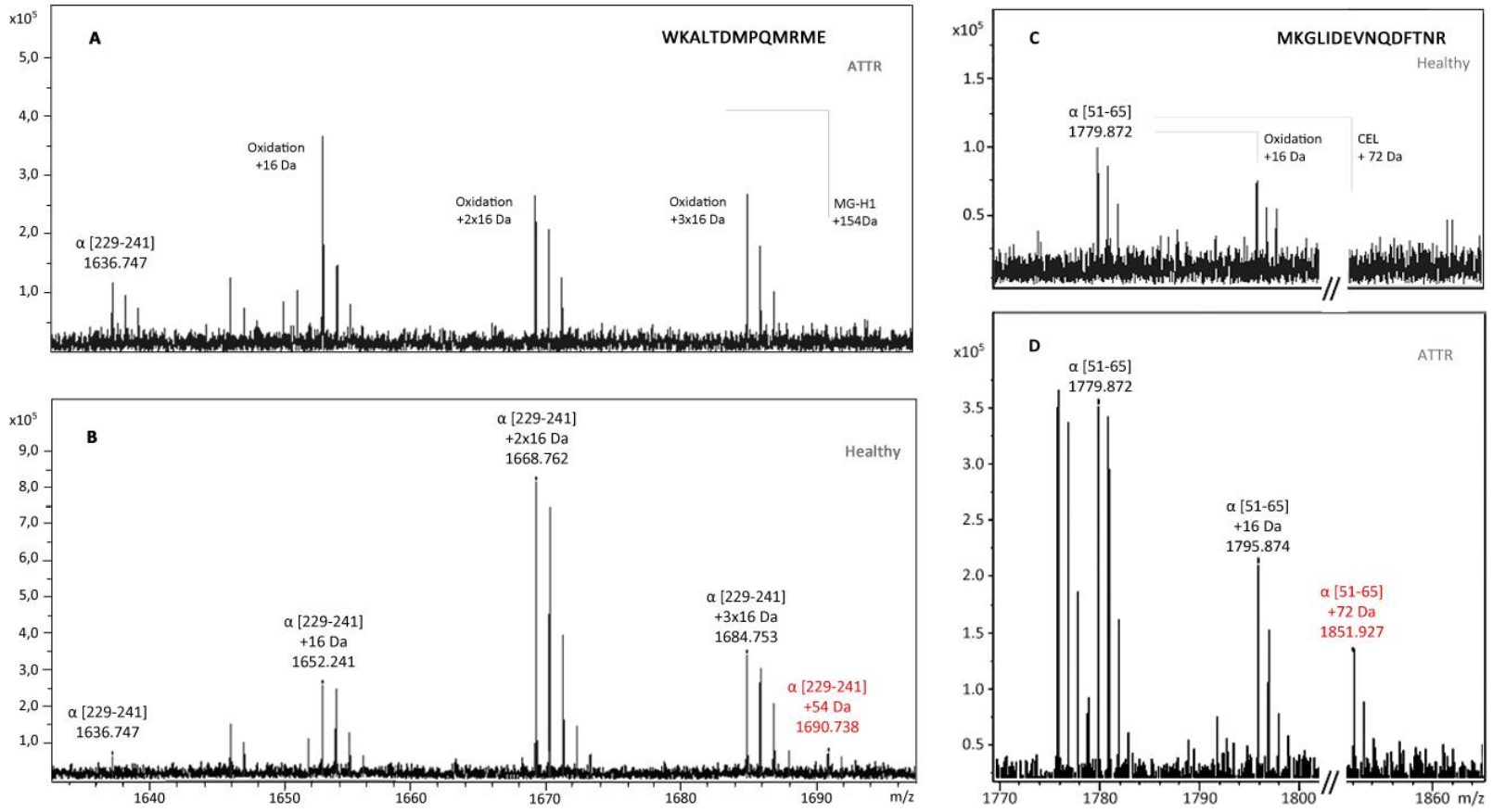
Finding partners & modifications



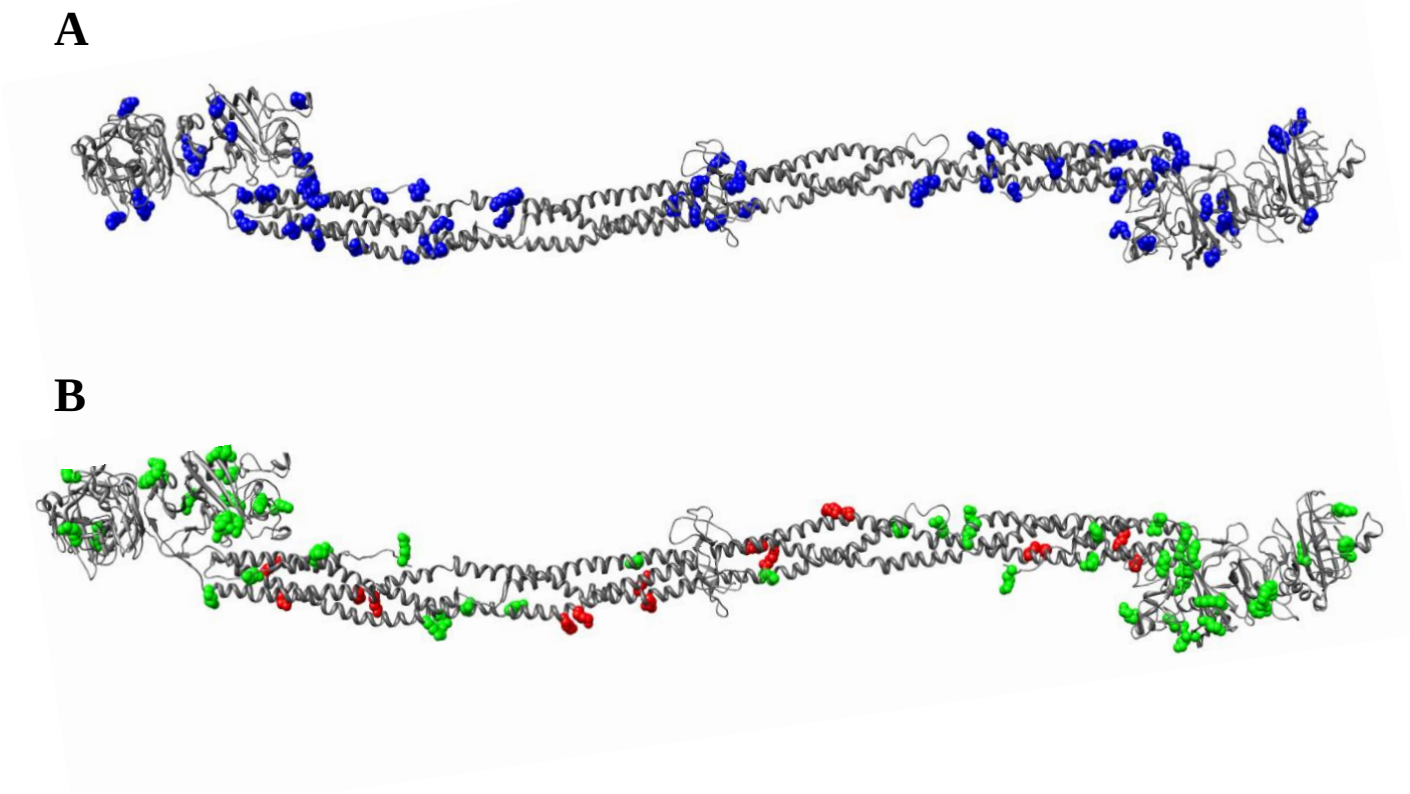
Fibrinogen
TTR partner
chaperone
glycated...

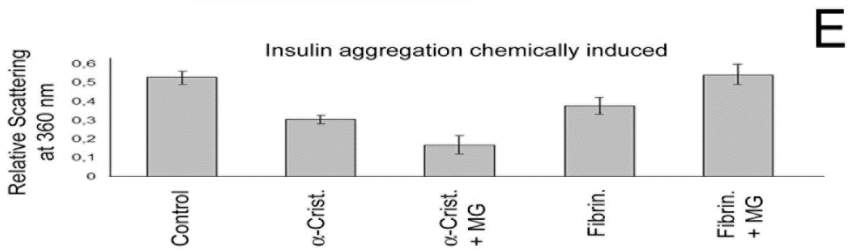


Finding needles in haystacks



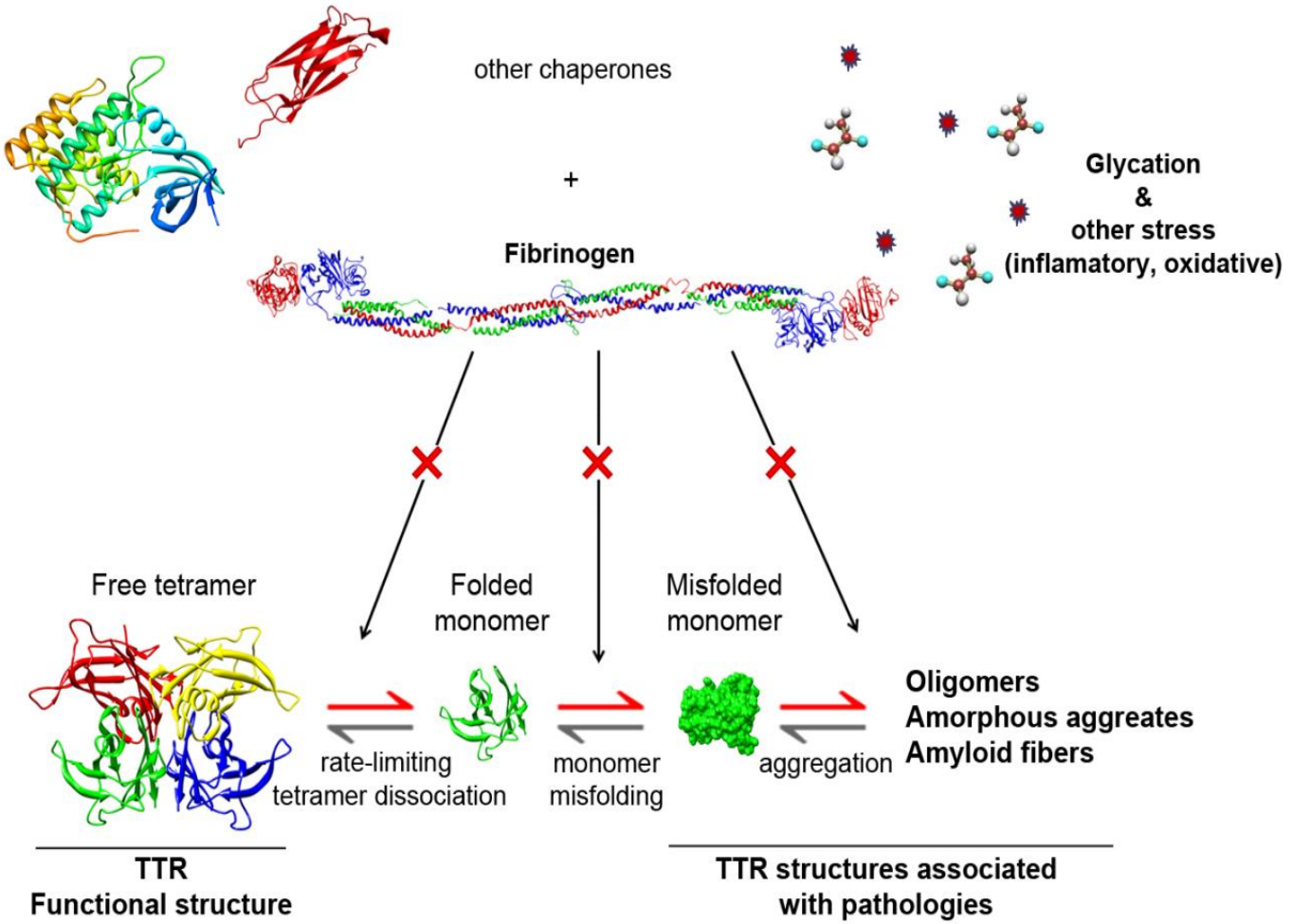
Fibrinogen glycation mapping



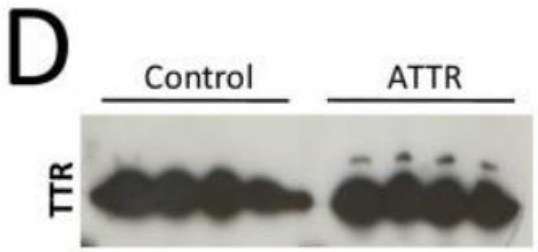


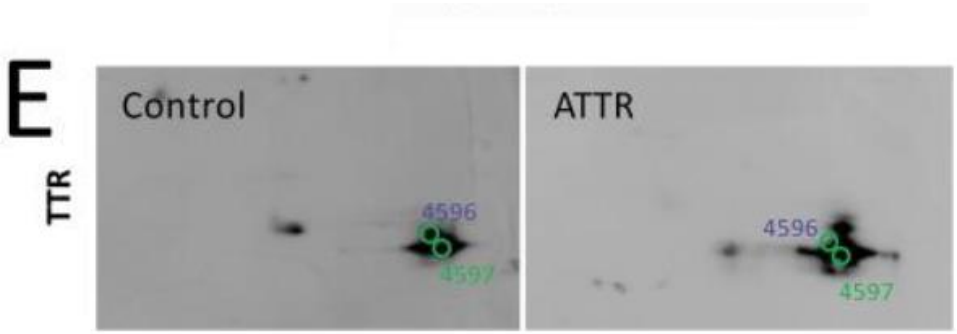
Glycation decreases chaperone activity (fibrinogen))

Molecular model of glycation effects



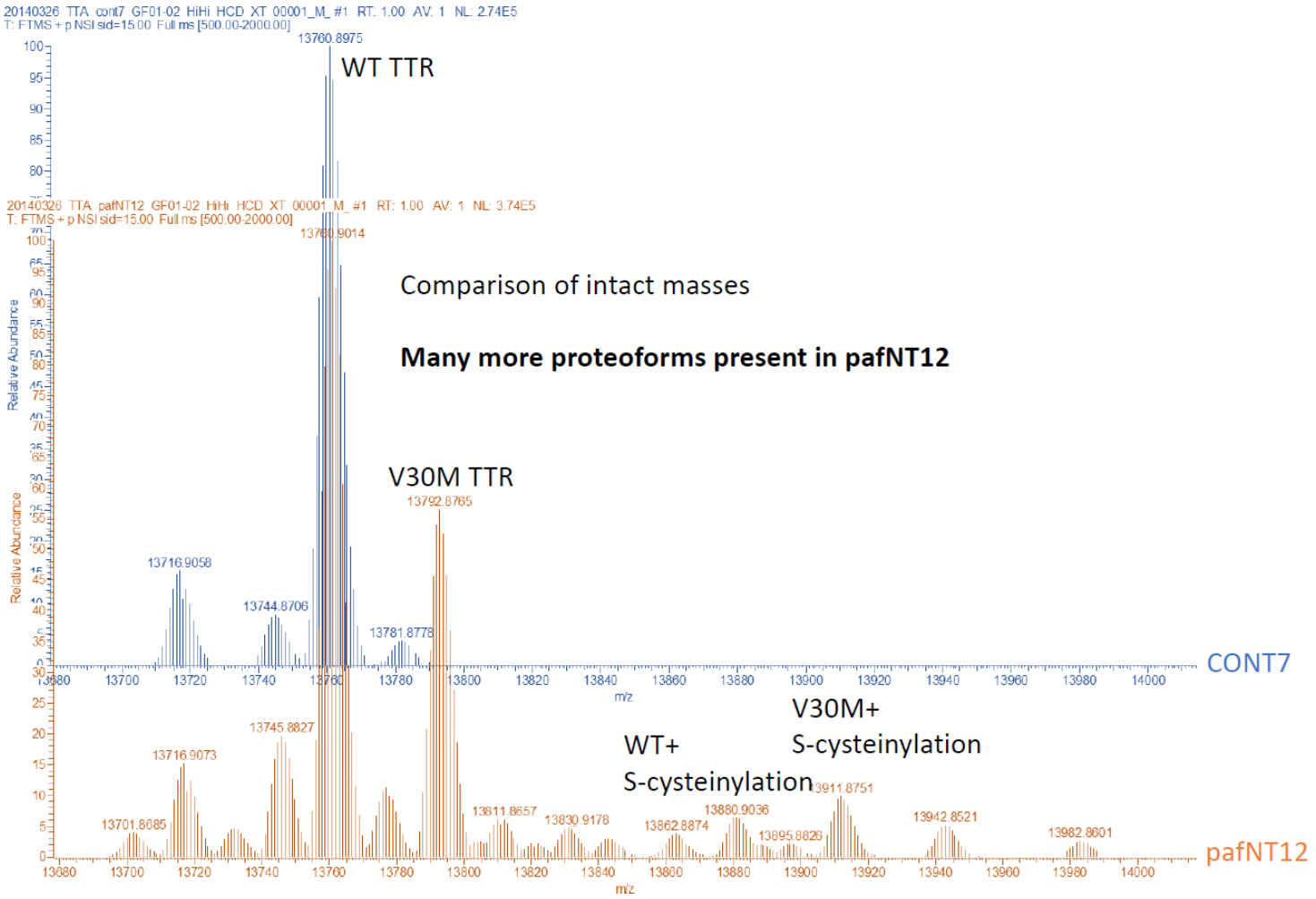
Is TTR modified?





Clear mass shift in ATTR (ubiquitin?)
Increased heterogeneity in ATTR

Top-Down analysis



Outlook

- Quest for TTR modifications
- Glycation and proteostasis
  - Missing link in amyloid diseases?
- Selective effects of glycation on chaperones
  - Activation
  - Inactivation