



1st International
Conference of
TWAS Young
Affiliates Network



ACADEMIA
BRASILEIRA
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TWAS YOUNG
AFFILIATES/ALUMNI
NETWORK

Searching for anti-scrapie compounds using a biochemical and biophysical assay platform

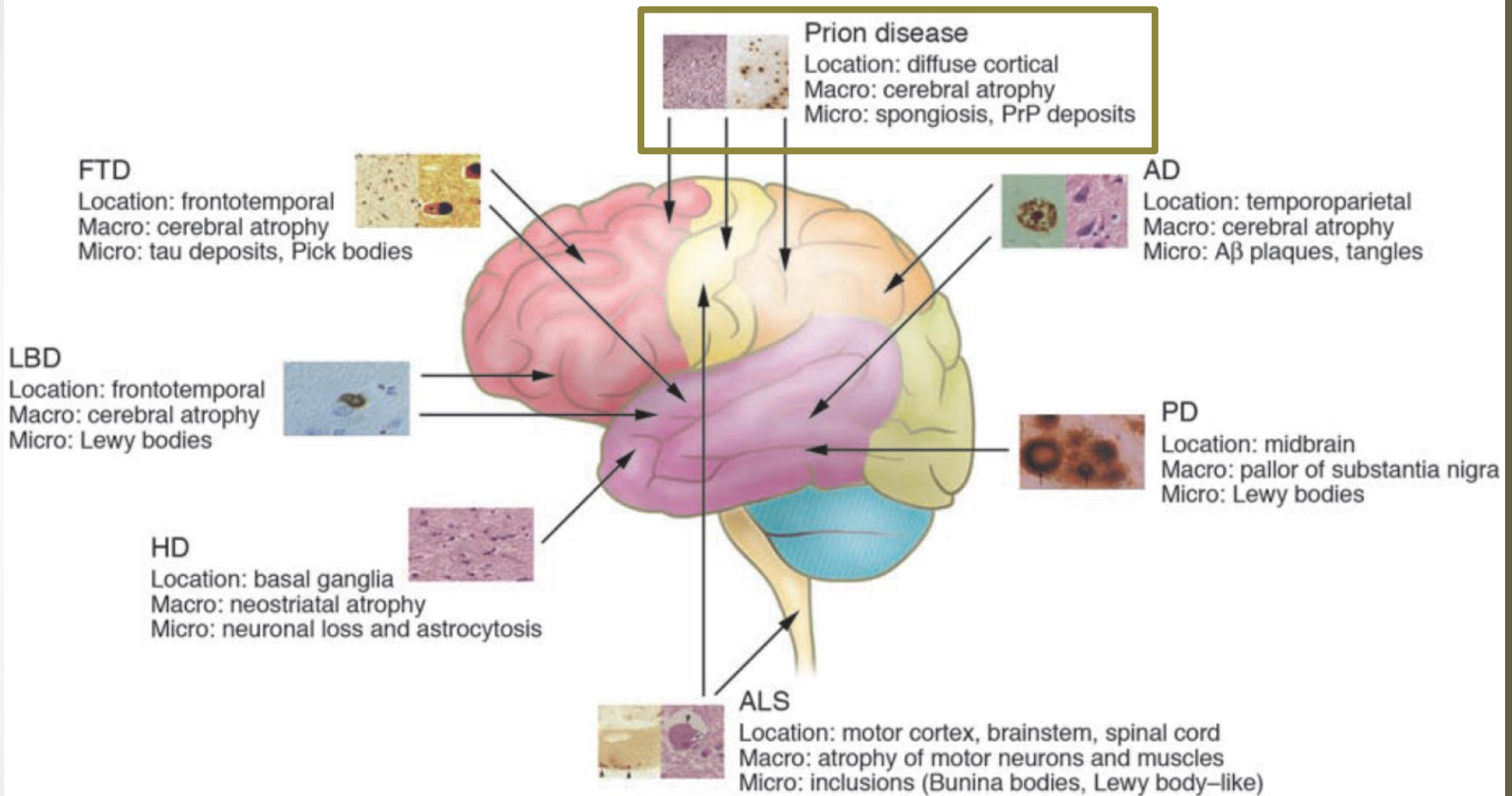
Yraima Cordeiro
Faculty of Pharmacy
UFRJ

Laβi

Laboratório de Biologia Molecular Estrutural

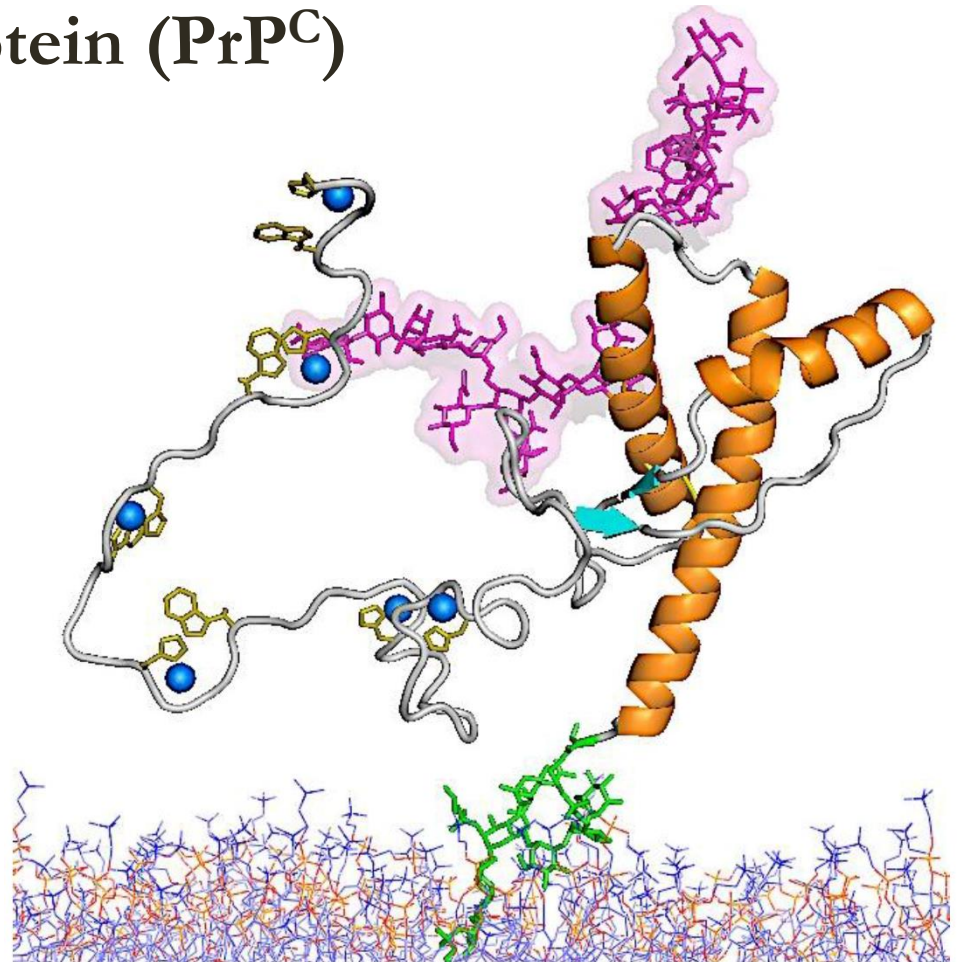


Protein misfolding/conformational diseases: *Neurodegenerative disorders*



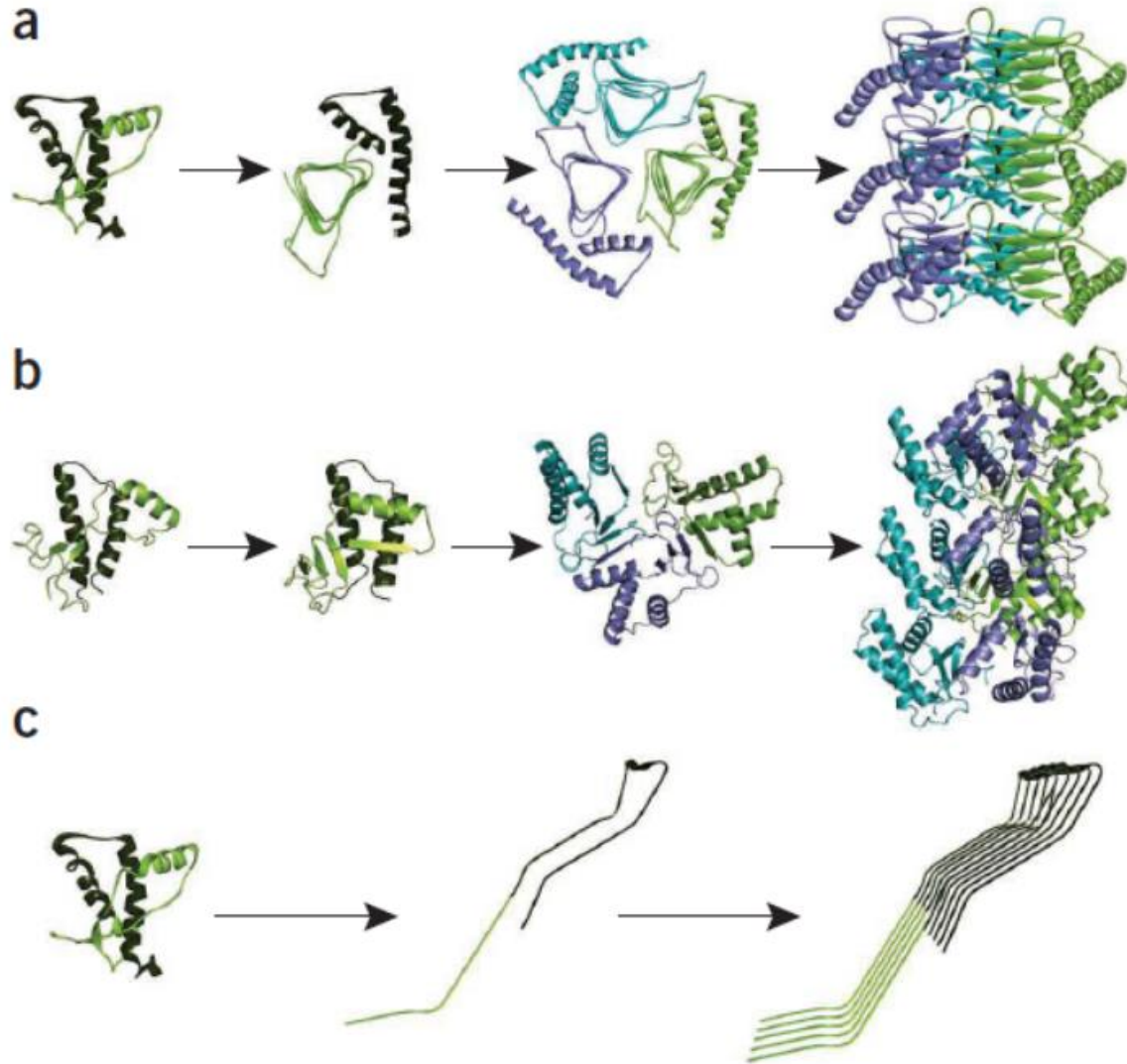
Transmissible Spongiform Encephalopathies (TSEs) and the Prion Protein

Cellular Prion Protein (PrP^C)



Prion diseases and the prion protein (PrP)

PrP^{C} \longrightarrow scrapie PrP (PrP^{Sc} / PrP^{Res})



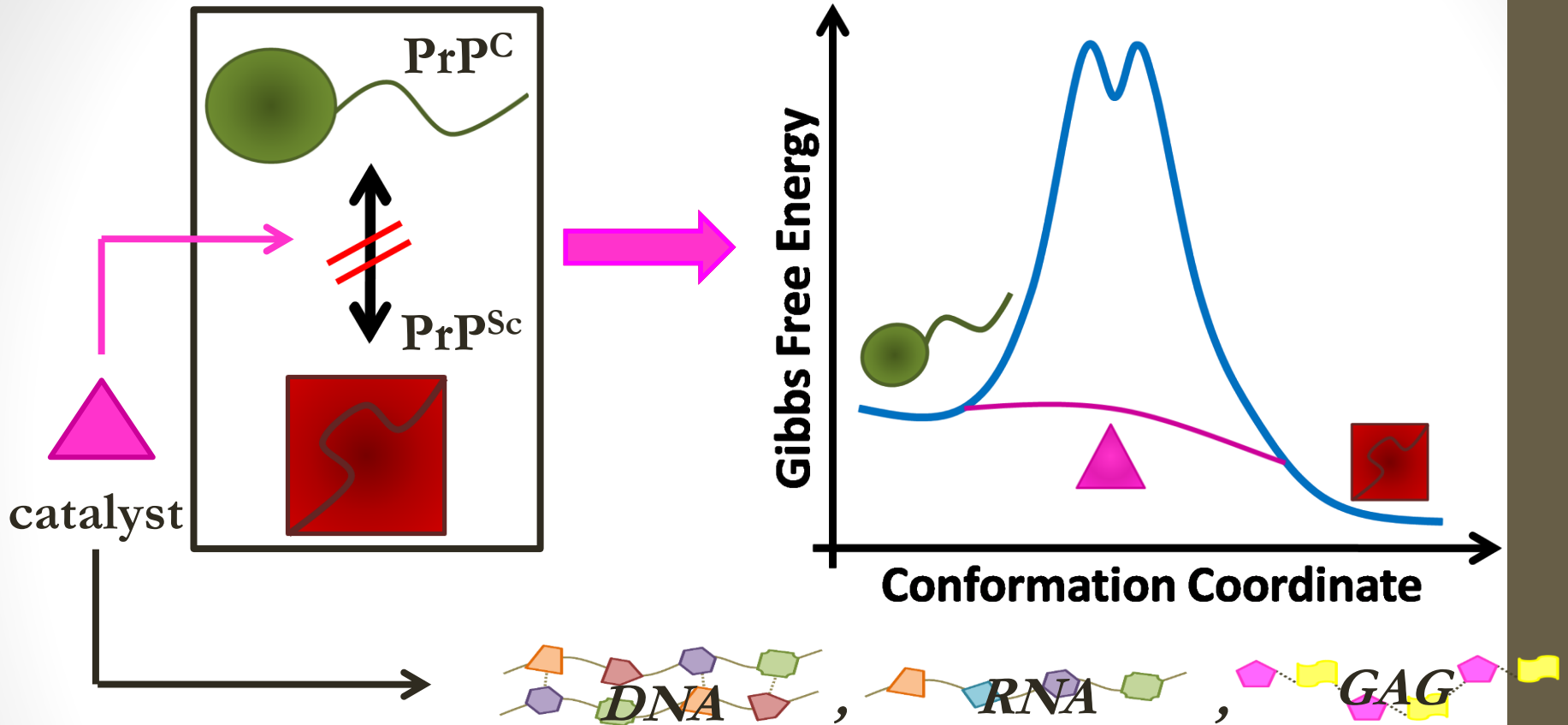
LaBiME interests:

- ✓ To understand the molecular mechanisms of PrP^C to PrP^{Sc} conversion;
- ✓ To evaluate the role of natural and synthetic ligands of PrP in physiology and disease;
- ✓ **To screen and identify organic compounds that might be useful for TSE therapy.**



Laboratório de Biologia Molecular Estrutural

PrP^C to PrP^{Sc} conversion: role of cofactors

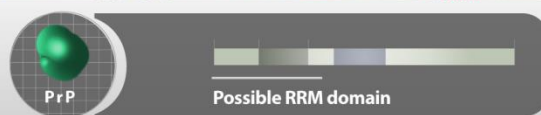
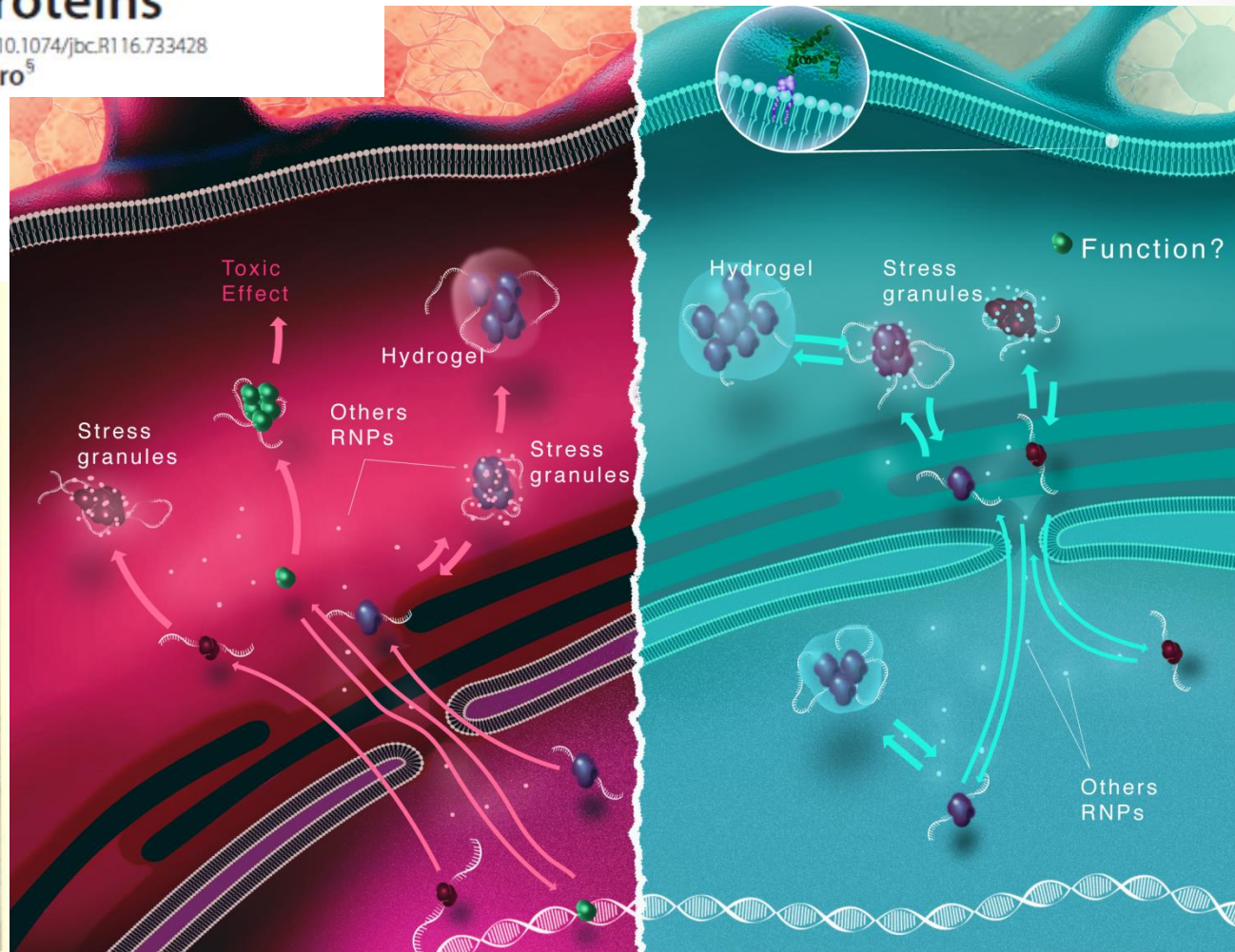
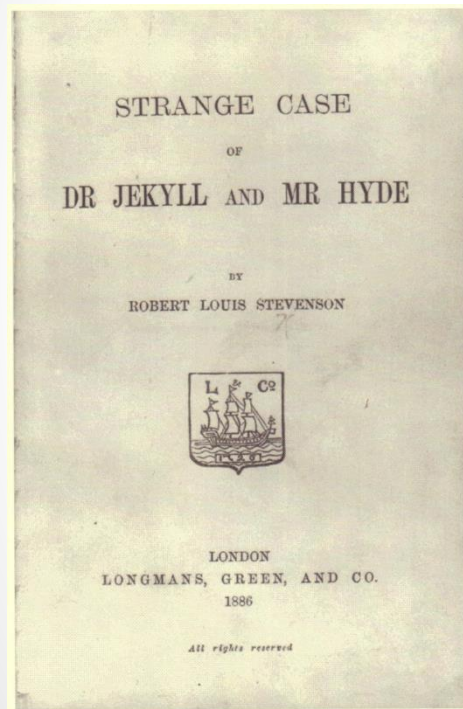


Cordeiro et al., *JBC* 2001; Cordeiro & Silva, *Prot. Pept. Lett.*, 2005; Lima et al., *Biochemistry* 2006; Silva et al. *Tibs* 2008; Gomes et al., *JBC* 2008; Vieira et al., *JACS* 2010; Silva & Cordeiro et al., *Acc. Chem. Res.* 2010; Macedo et al., *Biochemistry* 2012; Vieira et al., *FASEB J*, 2014; Cordeiro et al., *Biophys Rev.* 2014.

The "Jekyll and Hyde" Actions of Nucleic Acids on the Prion-like Aggregation of Proteins*

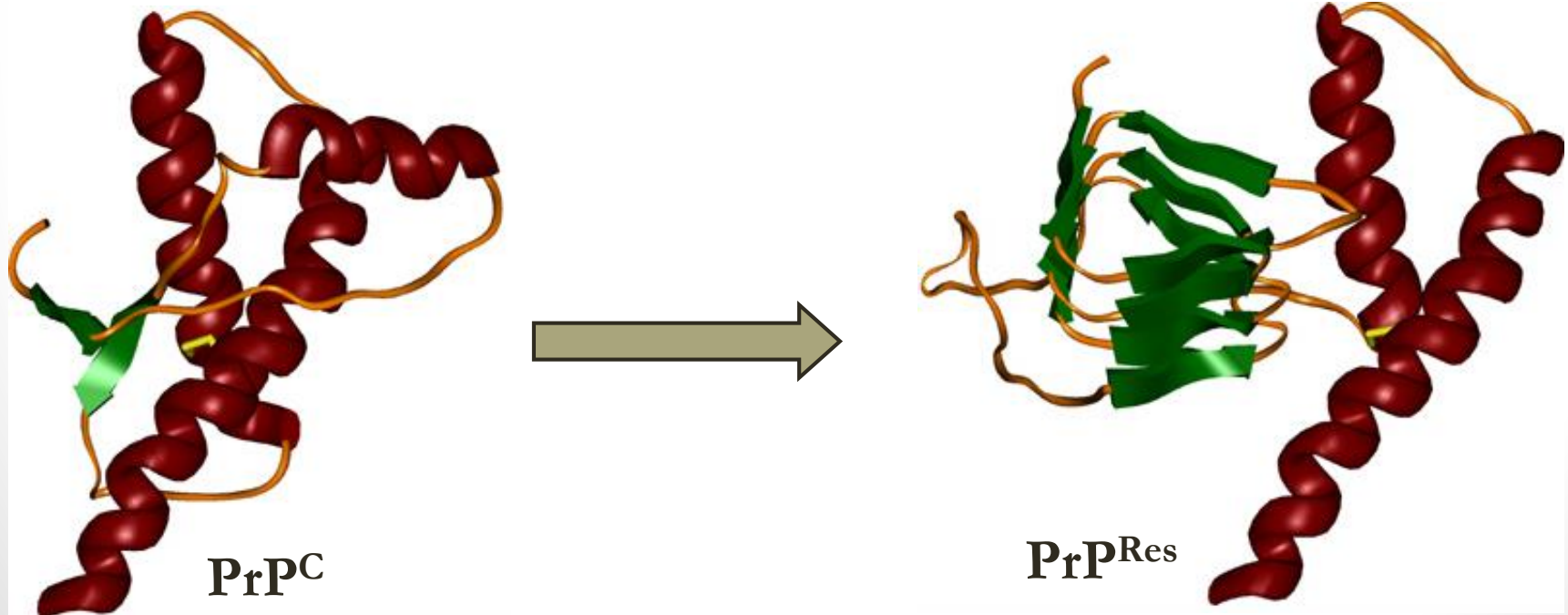
Published, JBC Papers in Press, June 10, 2016, DOI 10.1074/jbc.R116.733428

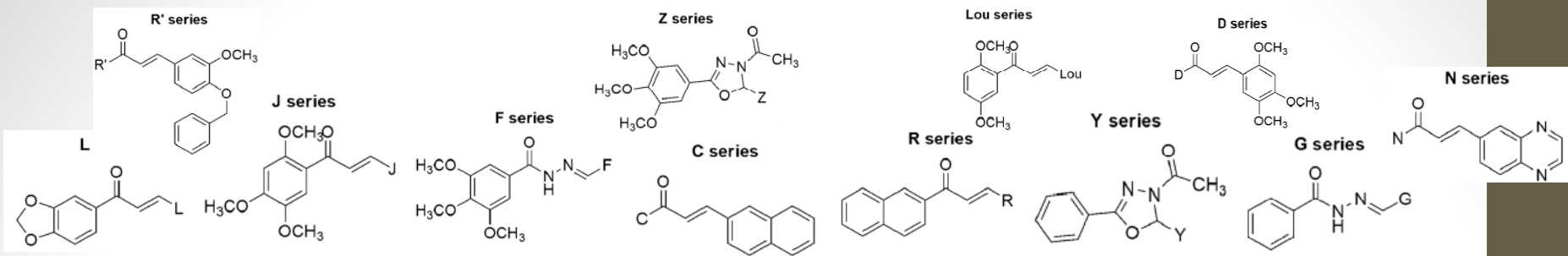
Jerson L. Silva^{†1} and Yralma Cordeiro⁵



Therapeutic strategies

- Control conformational conversion:
 - Stabilize PrP^C.
 - Modulate interaction with cofactors.
- Focus on the infectious species, PrP^{Sc}:
 - Allow abnormal PrP *clearance*.
 - Prevent aggregation.
 - Dissociate pre-formed aggregates.





Screening in PrP^{Sc}-infected cell lines

> 200

Cytotoxicity evaluation in non-infected cell lines

In silico evaluation of PK-PD properties

in vitro/ *in silico* approaches: mechanism of action

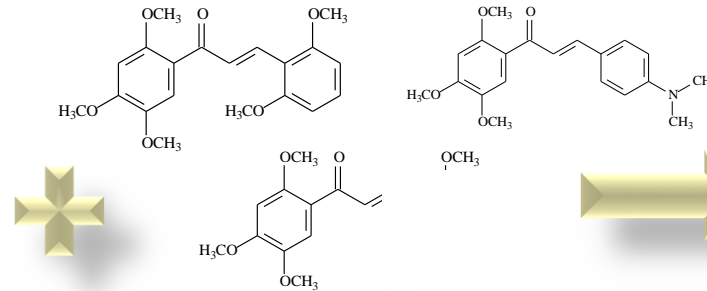
Efficacy/
toxicology
in vivo

2-4

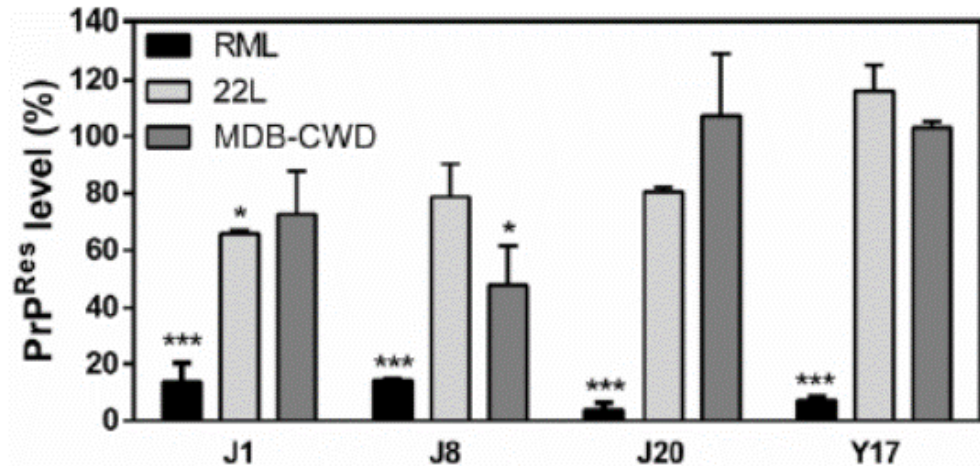
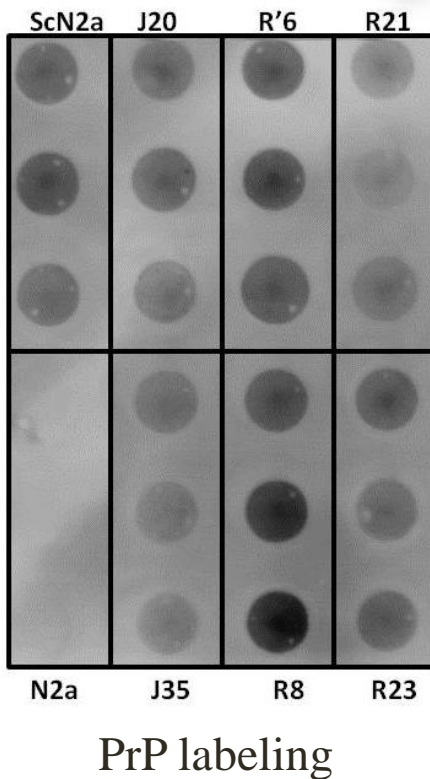


Rational drug design

Efficacy: PrP^{Res} clearance in scrapie-infected cell lines



Lysis and PK treatment



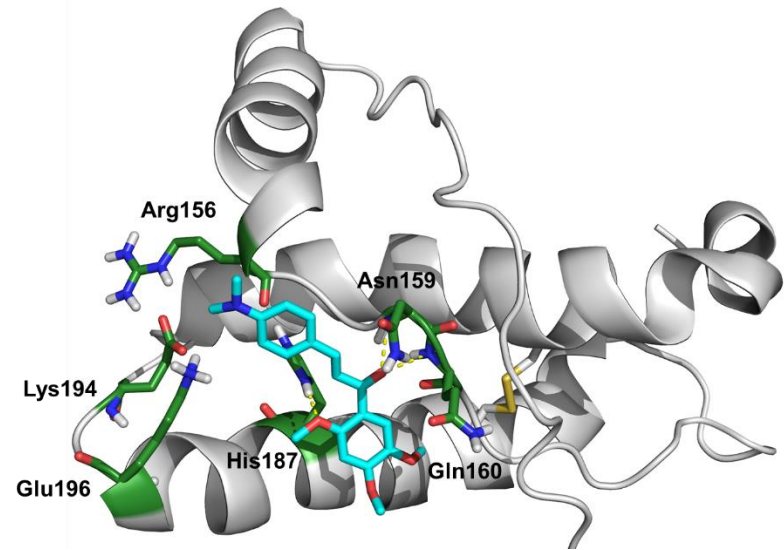
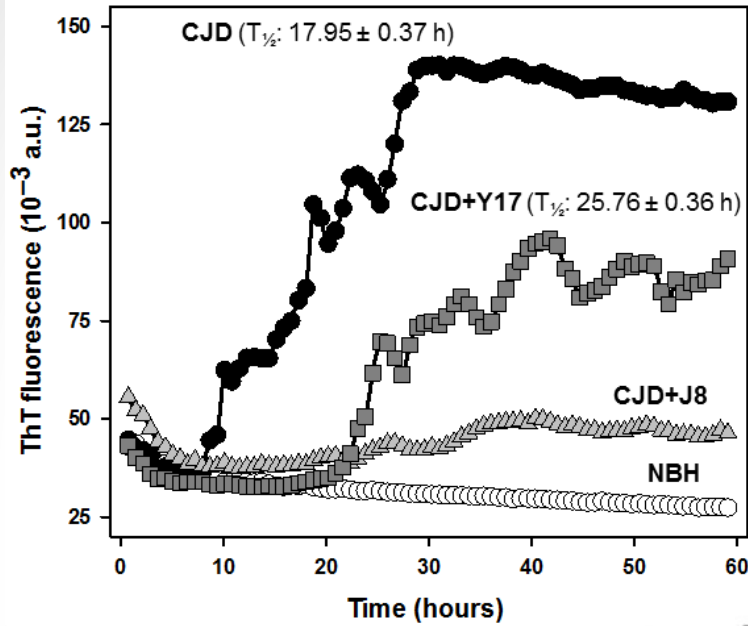
Different prion strains

Mechanism of action

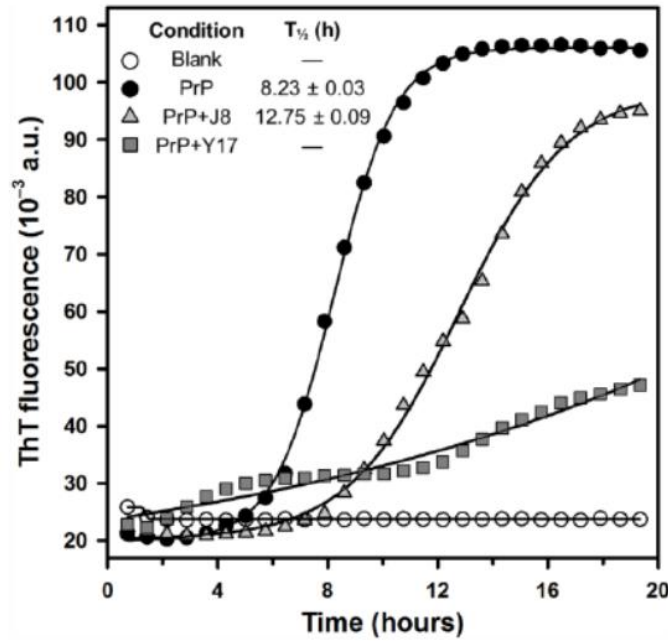
- Direct binding to PrP^C?
- Interaction with PrP^{Sc}?
- PrP^{Sc} depletion?
- Expression changes in PrP?
- Changes in PrP cellular location/traffic?
- Other molecular targets?

■ Direct binding to PrP^C?

In vitro × *in silico* approaches

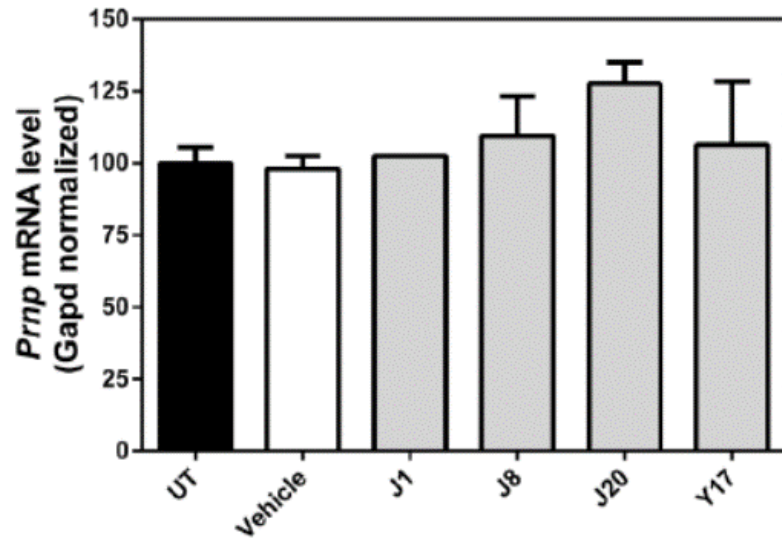


Cell-free conversion assay



Molecular docking

- Changes in PrP expression levels?

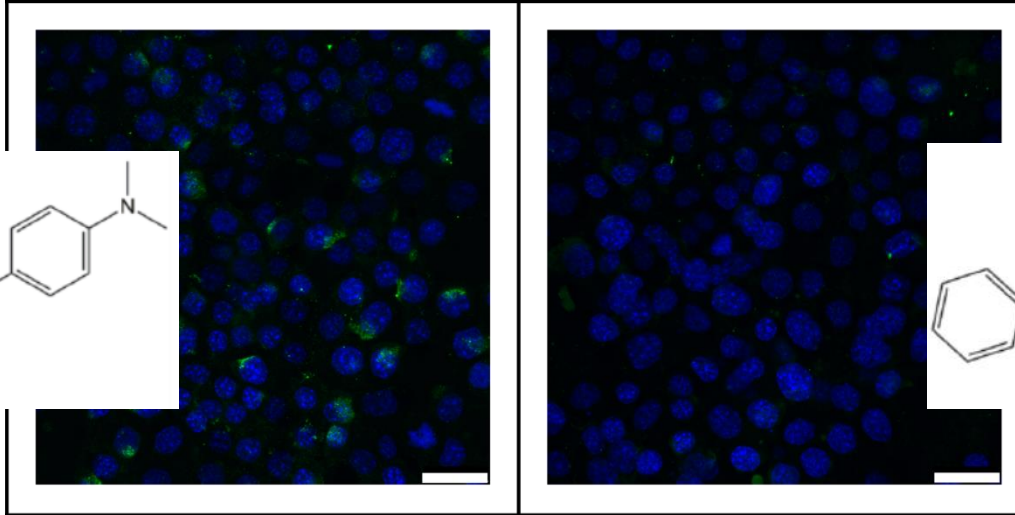
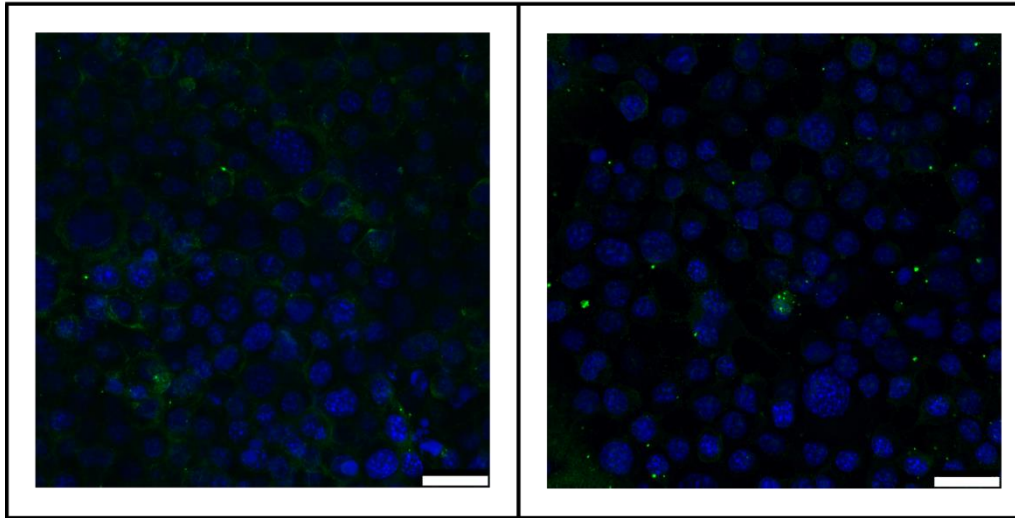


Real-time RT-PCR

- Changes in PrP cellular location/traffic?

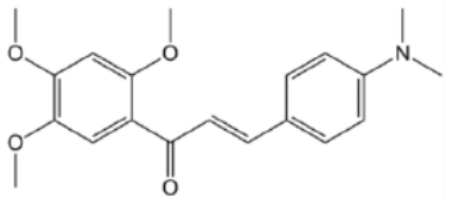
UT

PPS

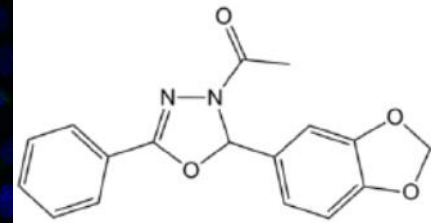


J8

Y17



J8



Y17

LaBiME contributions to the field:

Anti-Prion Activity of a Panel of Aromatic Chemical Compounds: *In Vitro* and *In Silico* Approaches *PLoS ONE* 2014

Natalia C. Ferreira¹, Icaro A. Marques¹, Wesley A. Conceição^{1,2}, Bruno Macedo¹, Clarice S. Machado¹, Alessandra Mascarello³, Louise Domeneghini Chiaradia-Delatorre³, Rosendo Augusto Yunes³, Ricardo José Nunes³, Andrew G. Hughson⁴, Lynne D. Raymond⁴, Pedro G. Pascutti², Byron Caughey⁴, Yraima Cordeiro^{1*}

Toxicological Evaluation of Anti-Scrapie Trimethoxychalcones and Oxadiazoles

CLAUDIA P. FIGUEIREDO¹, NATALIA C. FERREIRA¹, GISELLE F. PASSOS¹, ROBSON DA COSTA¹, FERNANDA S. NEVES¹, CLARICE S.C. MACHADO¹, ALESSANDRA MASCARELLO², LOUISE D. CHIARADIA-DELATORRE², PATRÍCIA D. NEUENFELDT², RICARDO J. NUNES² and YRAIMA CORDEIRO¹
Anais da Academia Brasileira de Ciências (2015) 87(2 Suppl.): 1421-1434

Synthesis and anti-prion activity evaluation of aminoquinoline analogues

Bruno Macedo^a, Catherine H. Kaschula^b, Roger Hunter^b, Juliana A.P. Chaves^a, Johannes D. van der Merwe^b, Jerson L. Silva^c, Timothy J. Egan^b, Yraima Cordeiro^{a,*}

^a Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Av Carlos Chagas Filho, Rio de Janeiro 21941-902, Brazil

^b Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa

^c Instituto de Bioquímica Médica, Universidade Federal do Rio de Janeiro, Rio de Janeiro 21941-590, Brazil

Eur J Med Chem, 2010

New Approaches for the Selection and Evaluation of Anti-Prion Organic Compounds *Mini Reviews in Medicinal Chemistry*, 2015

Yraima Cordeiro* and Natalia C. Ferreira

Virtual drug screening for prion diseases: A valuable step?

Yraima Cordeiro

EBioMedicine 9 (2016) 15–16

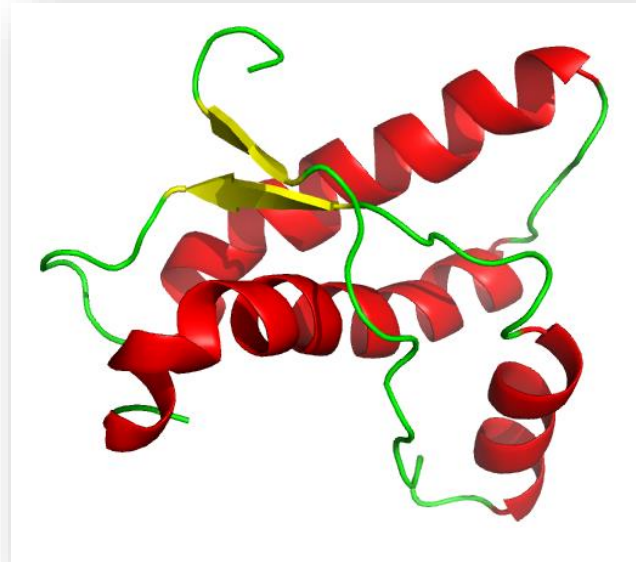
Faculty of Pharmacy, Federal University of Rio de Janeiro, Brazil

Platform to reveal targets of anti-prion compounds. Ferreira, Cordeiro et al. *AAC*, Under review, 2017.

Acknowledgments

LaBiME:

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Alessandra M. T. Souza
Rodrigo Martins

Byron Caughey (NIAID, RML)