https://doi.org/10.17952/38EPS.2026.P123

Macrocyclic Molecular Glues for the 14-3-3/ChREBP Interaction; Affinity and Cooperativity in an Inverse Relationship

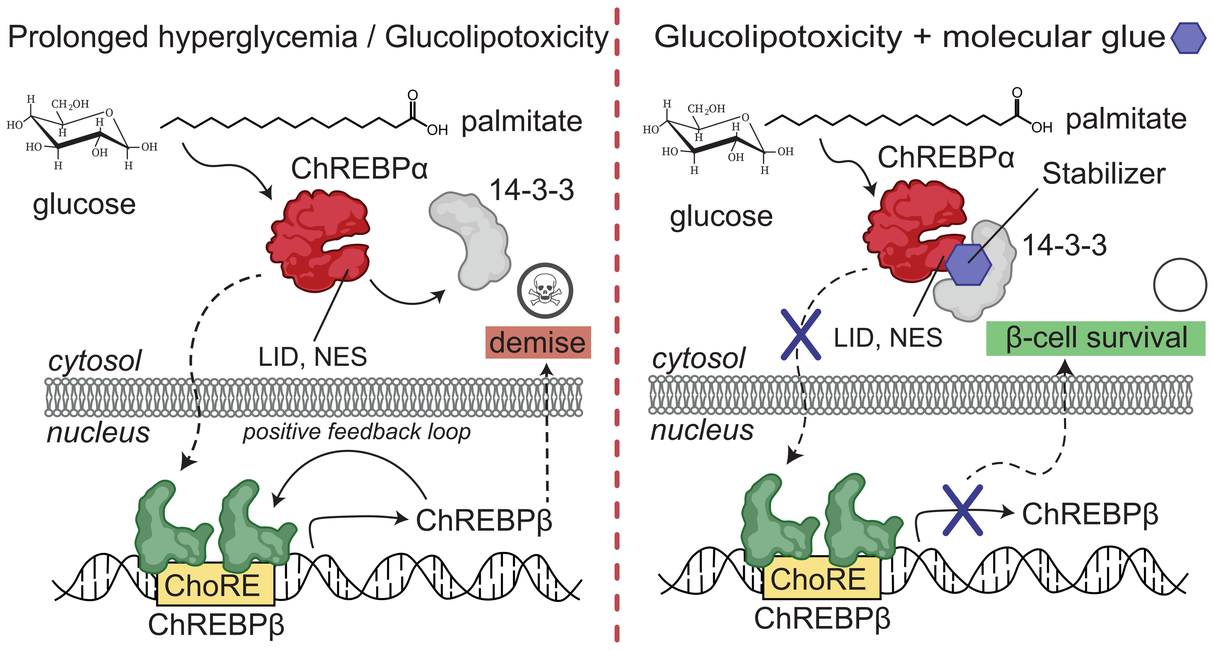
Merel A.W. van den Bosch,[a] Marloes A.M. Pennings,[a] Ansgar Oberheide,[a] Carlo J.A. Verhoef,[a] Christian Ottmann,[a] Albert J. Markvoort,[b] Galen P. Miley,[a] Luc Brunsveld*[a]



M.a.w.v.d.bosch@tue.nl

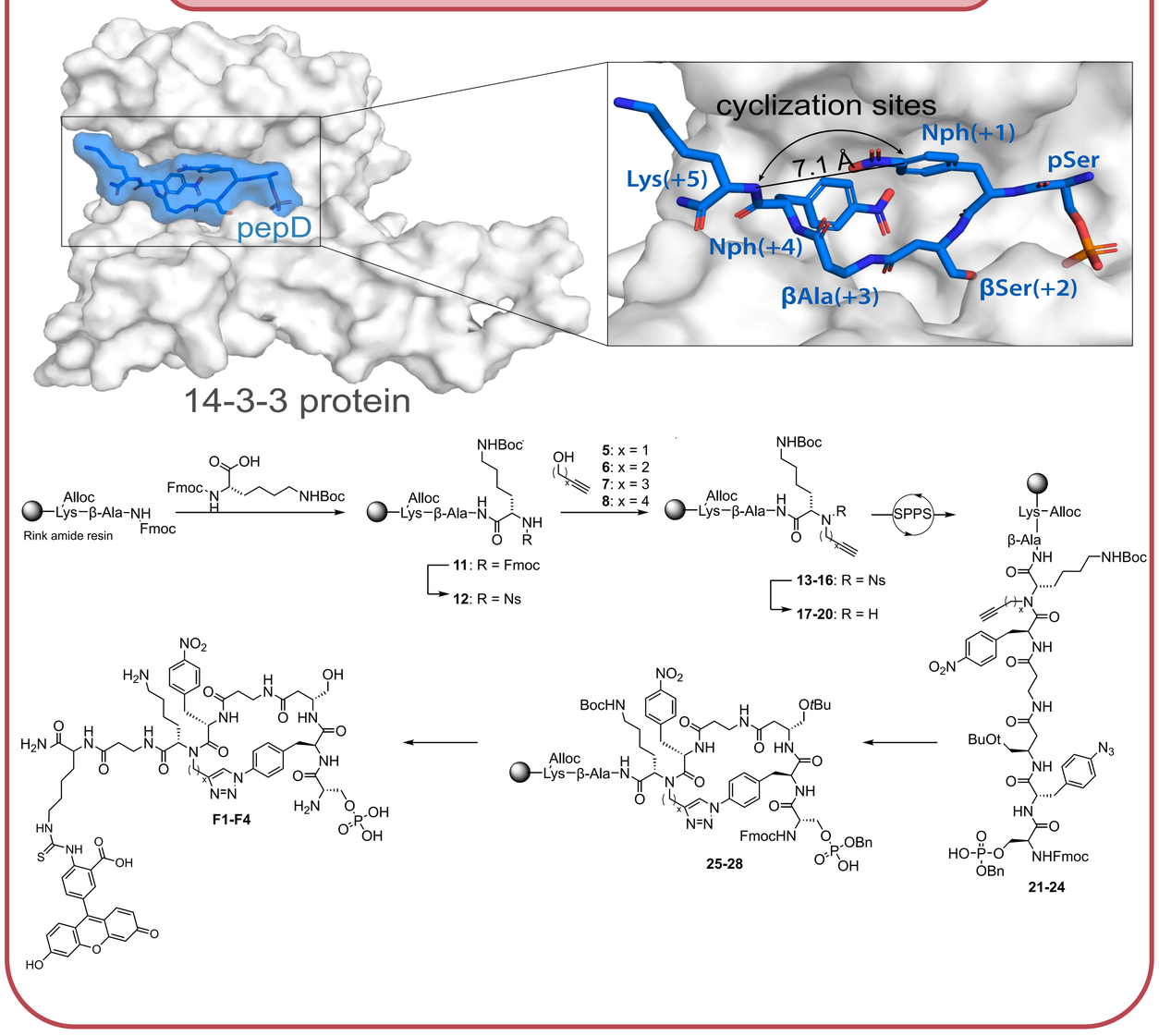
[a] Laboratory of Chemical Biology, Department of Biomedical Engineering and Institute for Complex Molecular Systems (ICMS), Eindhoven University of Technology, 5600MB, Eindhoven, The Netherlands
[b] Synthetic Biology Group, Department of Biomedical Engineering and Institute for Complex Molecular Systems (ICMS) Eindhoven University of Technology, 5600MB, Eindhoven, The Netherlands

1. The 14-3-3/ChREBPα interaction regulates β-cell fate

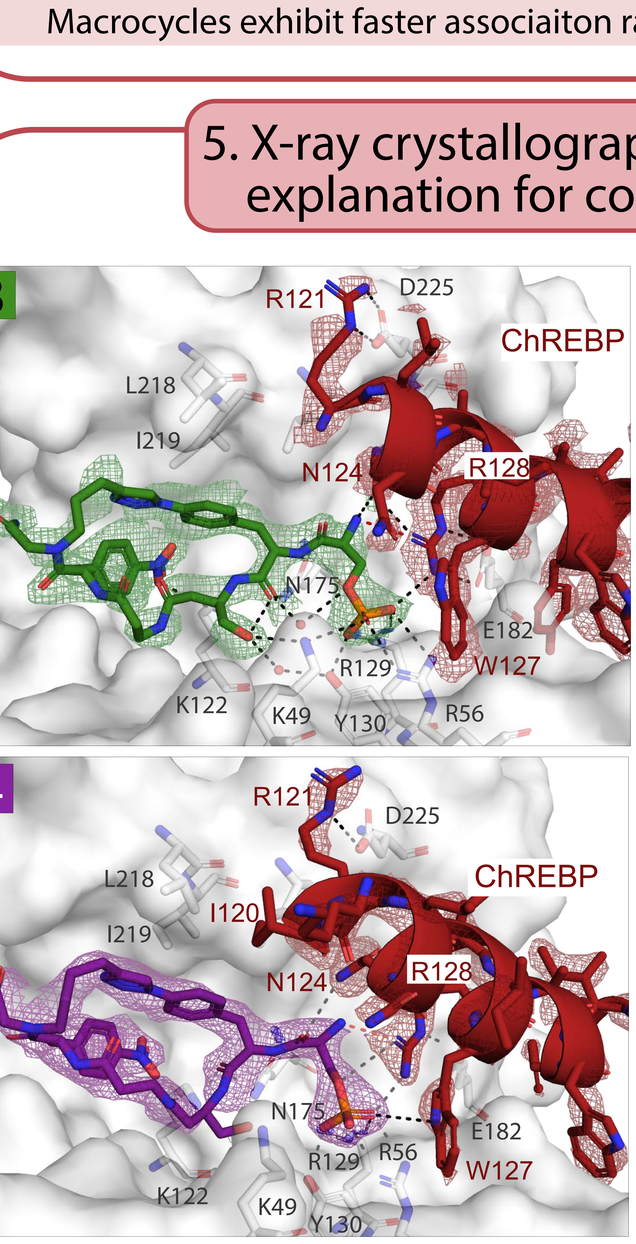


ChREBP as a glucose responsive transcription factor
Overexpression of ChREBPα leads to β-cell death
Stabilization of the 14-3-3/ChREBPα PPI rescues β-cells

2. Cyclization of previously discovered 14-3-3 peptidic molecular glue

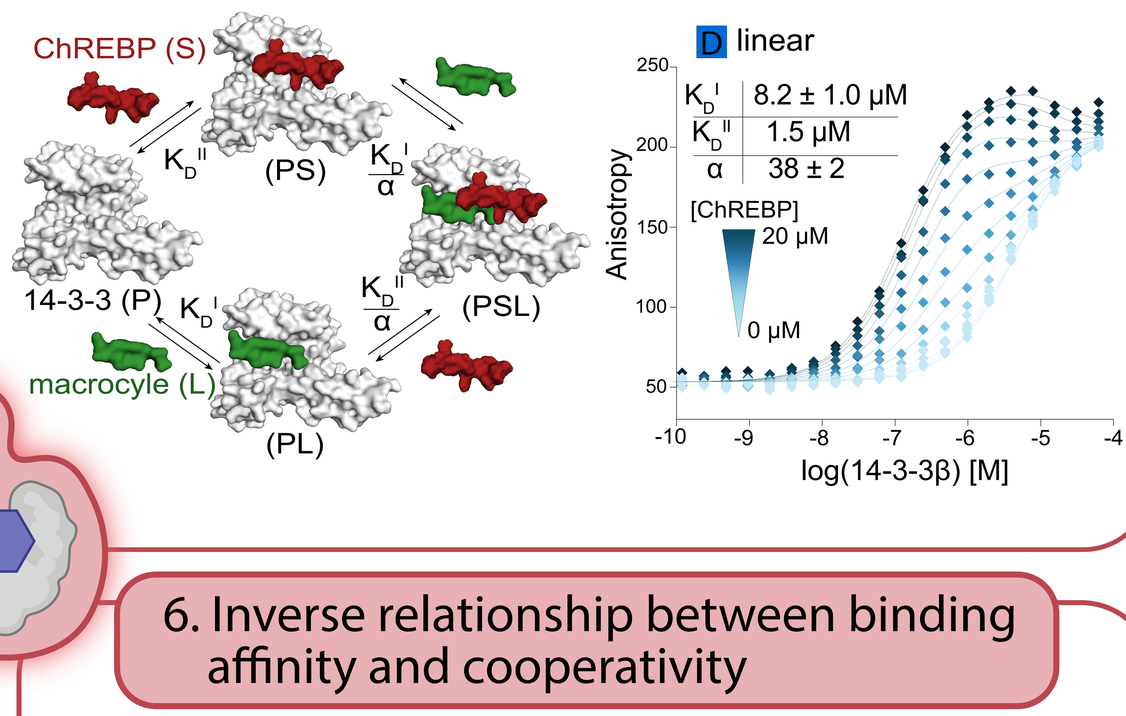


3. Cyclization leads to more favorable binding properties



Cyclization leads to more favorable entropy, leading to higher binding affinities
Macrocycles exhibit faster associaiton rates compared to linear peptide

4. Cooperativity as a measure for ternary complex formation

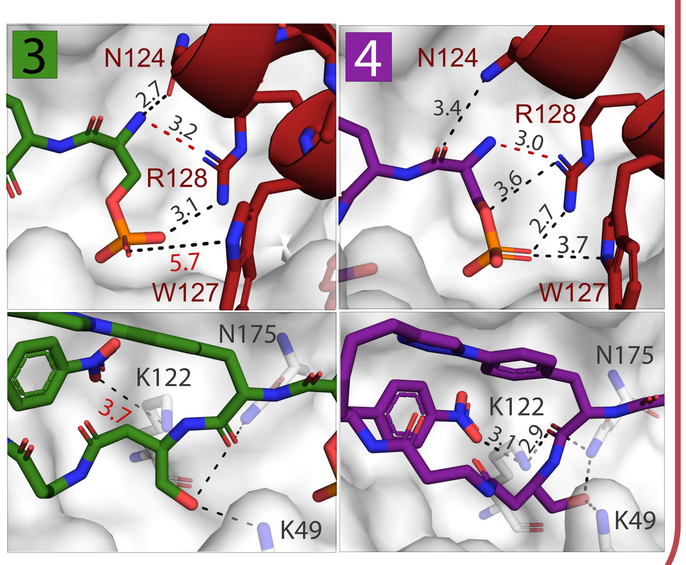


K_D^I	8.2 ± 1.0 μM
K_D^{II}	1.5 μM
α	38 ± 2

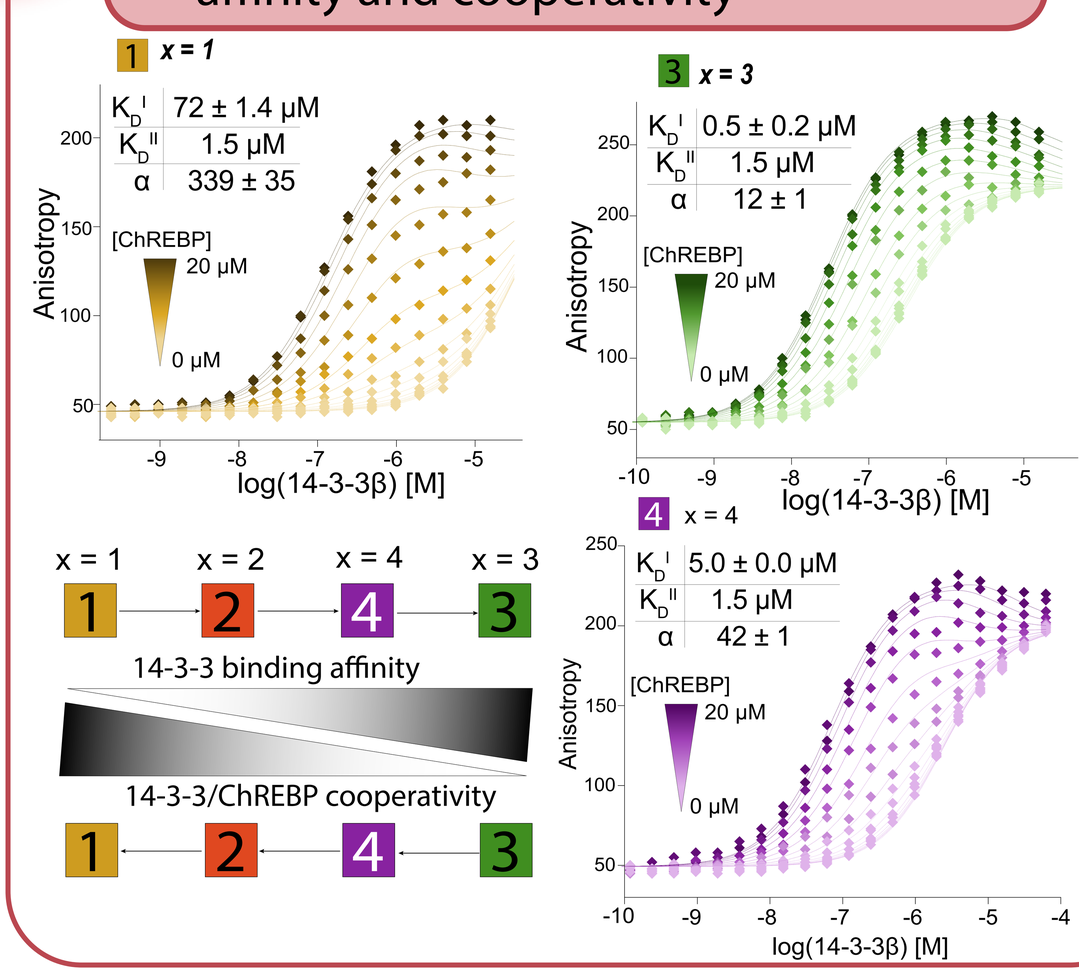
5. X-ray crystallography gives molecular explanation for cooperativity

Interactions at the macrocycle/ChREBP interface are the basis of cooperativity

Loss of hydrogen bonds in ternary complex gives structural explanation for higher cooperativity of macrocycle 4 compared to 3



6. Inverse relationship between binding affinity and cooperativity



K_D^I	72 ± 1.4 μM
K_D^{II}	1.5 μM
α	339 ± 35

K_D^I	0.5 ± 0.2 μM
K_D^{II}	1.5 μM
α	12 ± 1

K_D^I	5.0 ± 0.0 μM
K_D^{II}	1.5 μM
α	42 ± 1

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