Motion and Antagonism of the Human Nuclear Xenobiotic Receptor PXR

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Departments of Chemistry,
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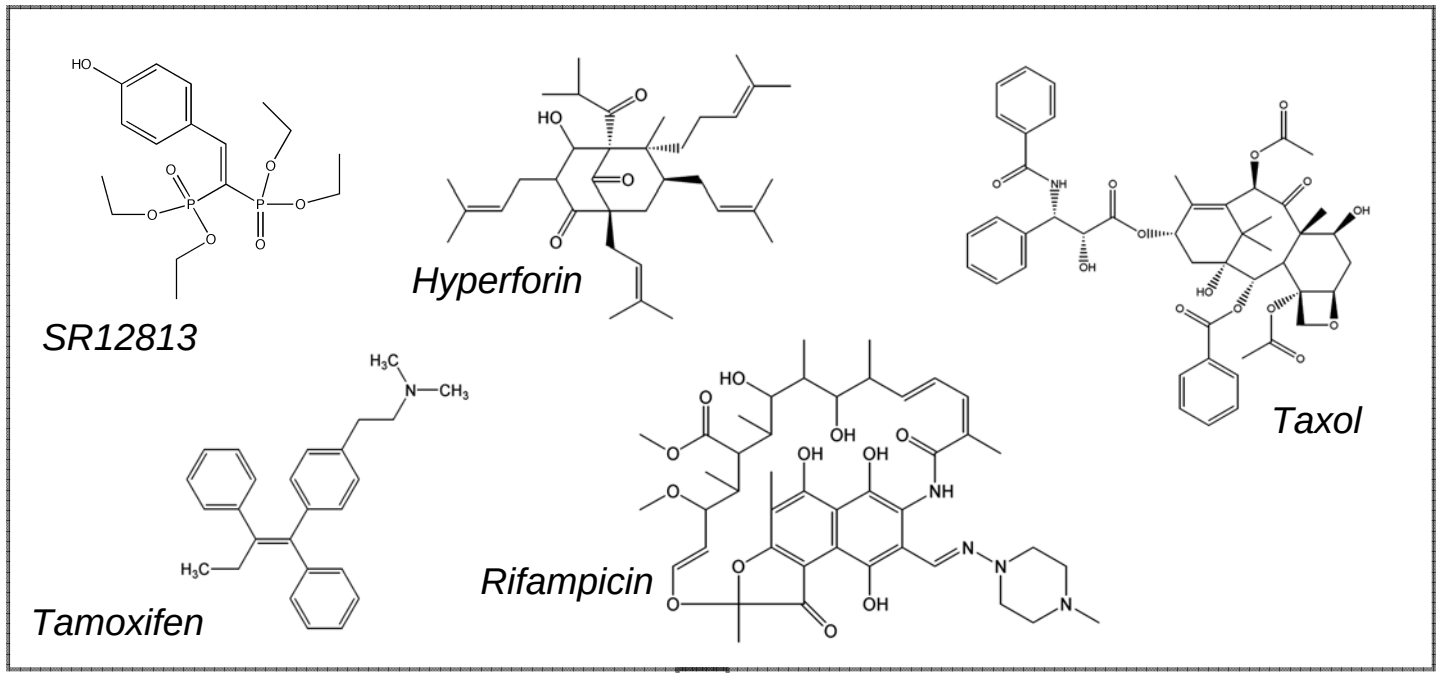
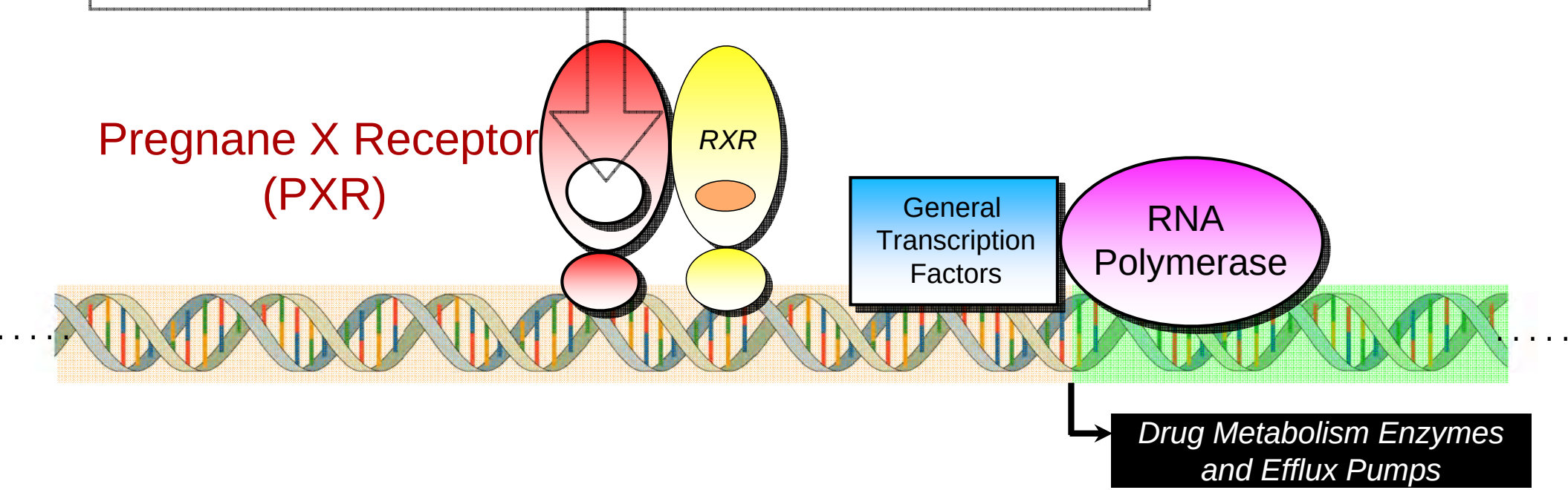
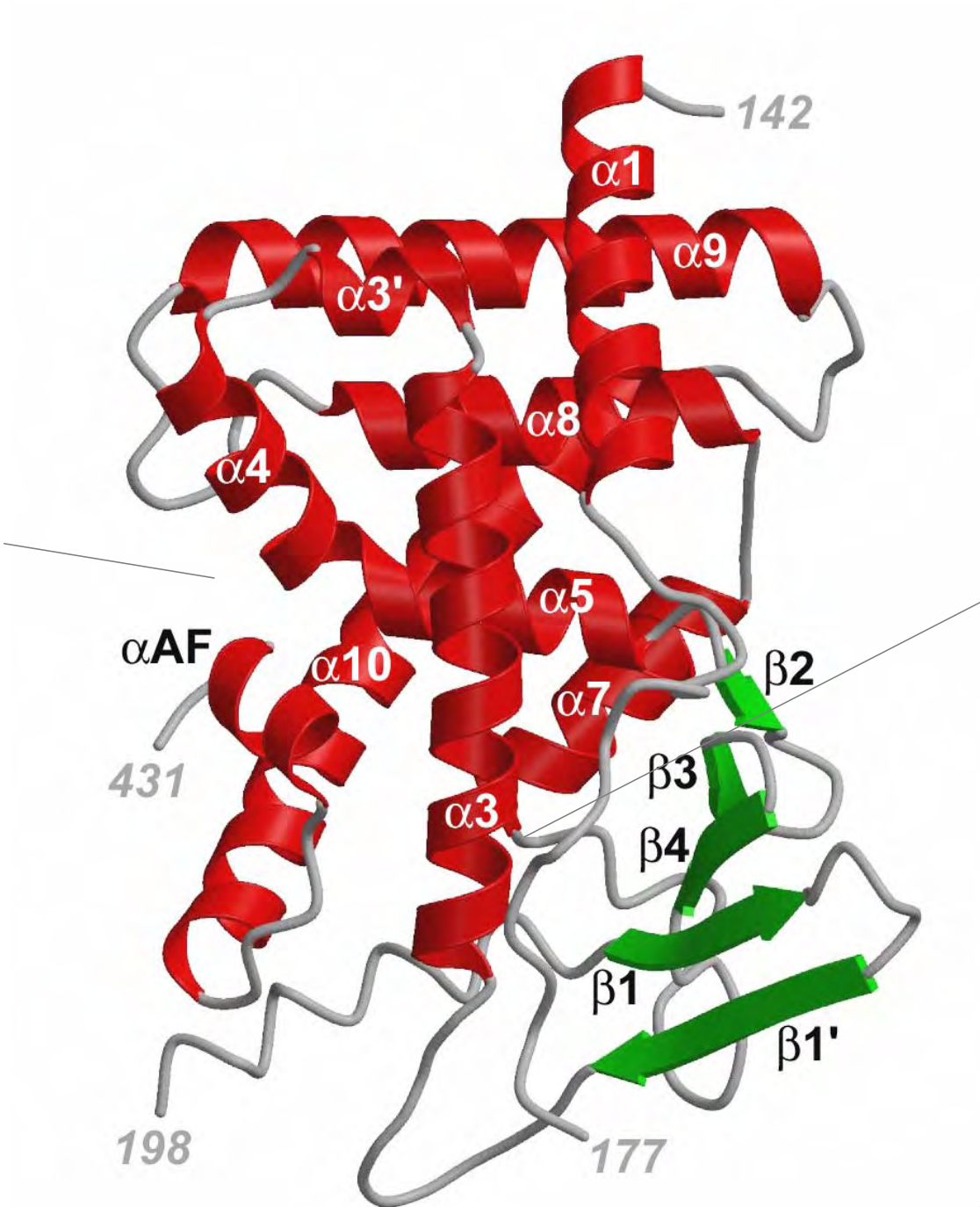
PXR: Promiscuous Control of Gene Expression



Xenobiotics



Crystal Structure of Human PXR Ligand Binding Domain



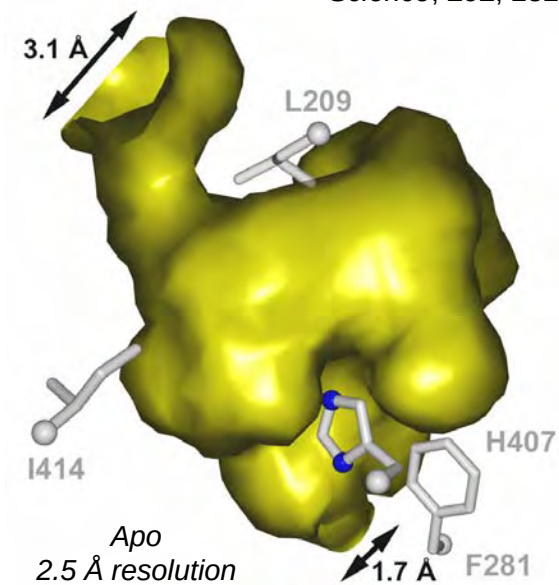
Ligand Binding Pocket

2.5 Å resolution

Watkins et al. (2001). *Science*, **292**, 2329.

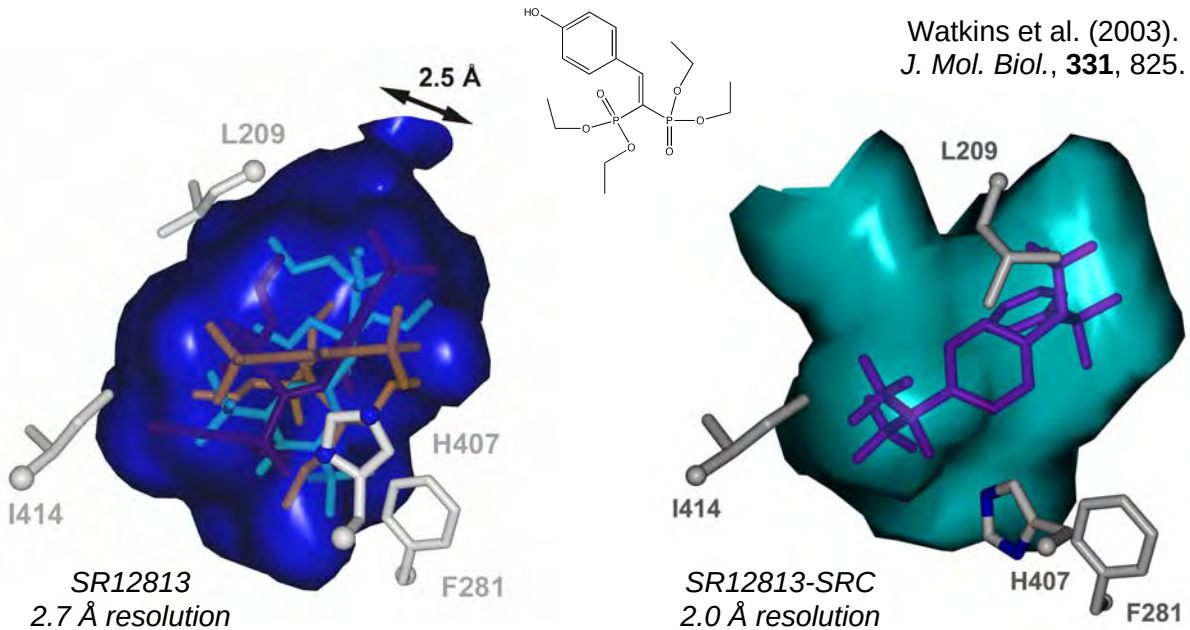
Recognizing Drugs: Change Your Tune

Watkins et al. (2001).
Science, **292**, 2329.



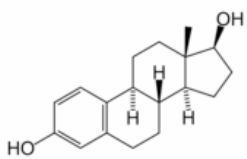
Apo
2.5 Å resolution

Watkins et al. (2003).
J. Mol. Biol., **331**, 825.

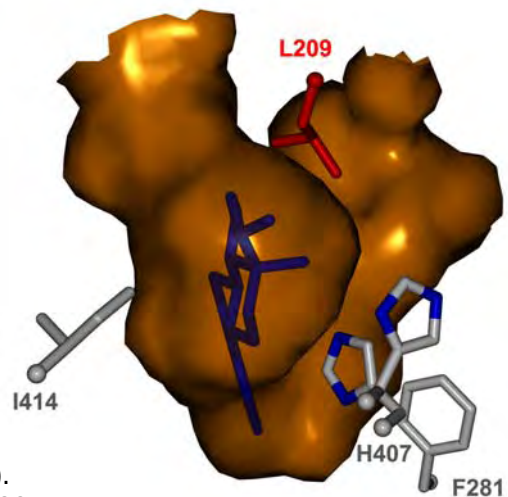


SR12813
2.7 Å resolution

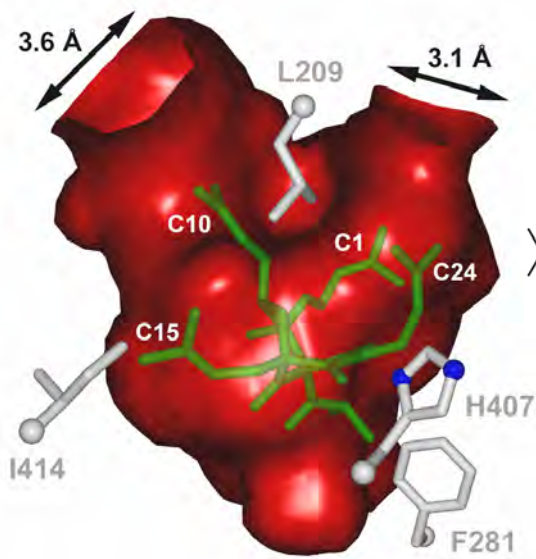
SR12813-SRC
2.0 Å resolution

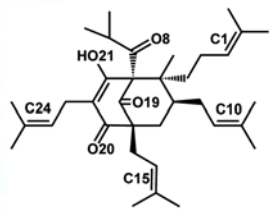


Estrogen
2.8 Å resolution



Xue et al. (2007).
Mol. Endo., **21**, 1028.

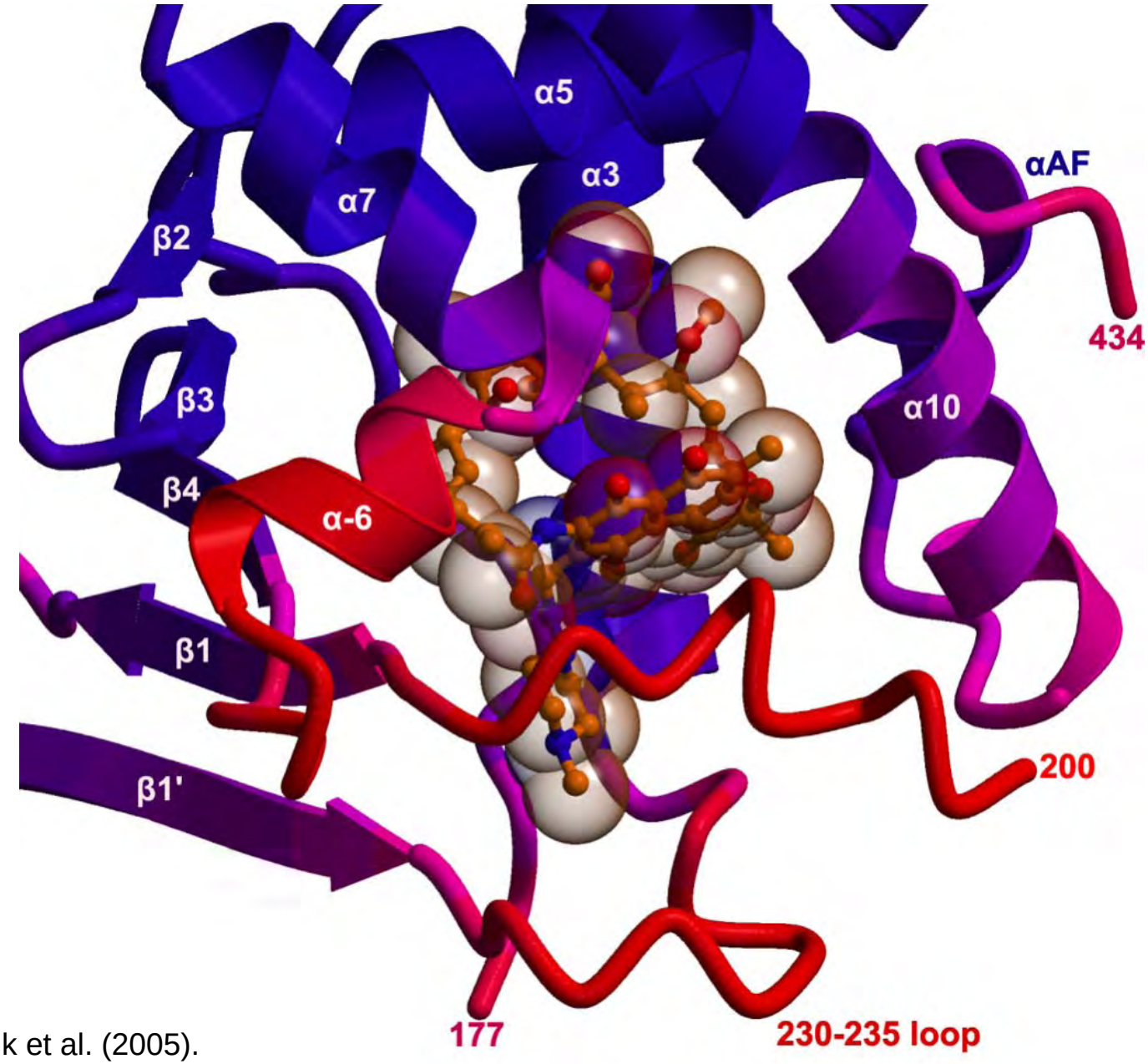




Hyperforin
2.1 Å resolution

Watkins et al. (2003).
Biochemistry, **42**, 1430.

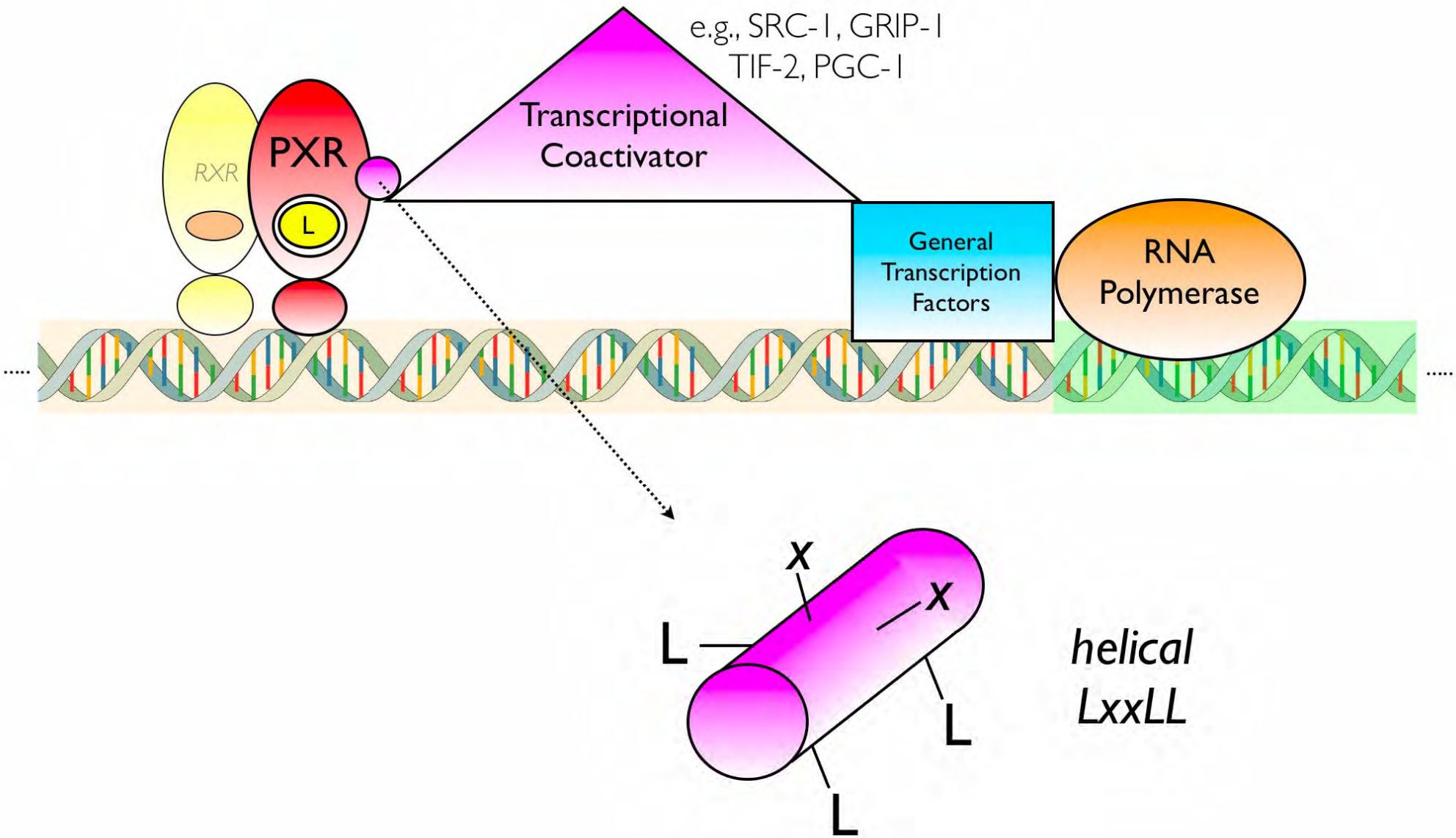
Don’t Pin Yourself Down: Using Loose Ends



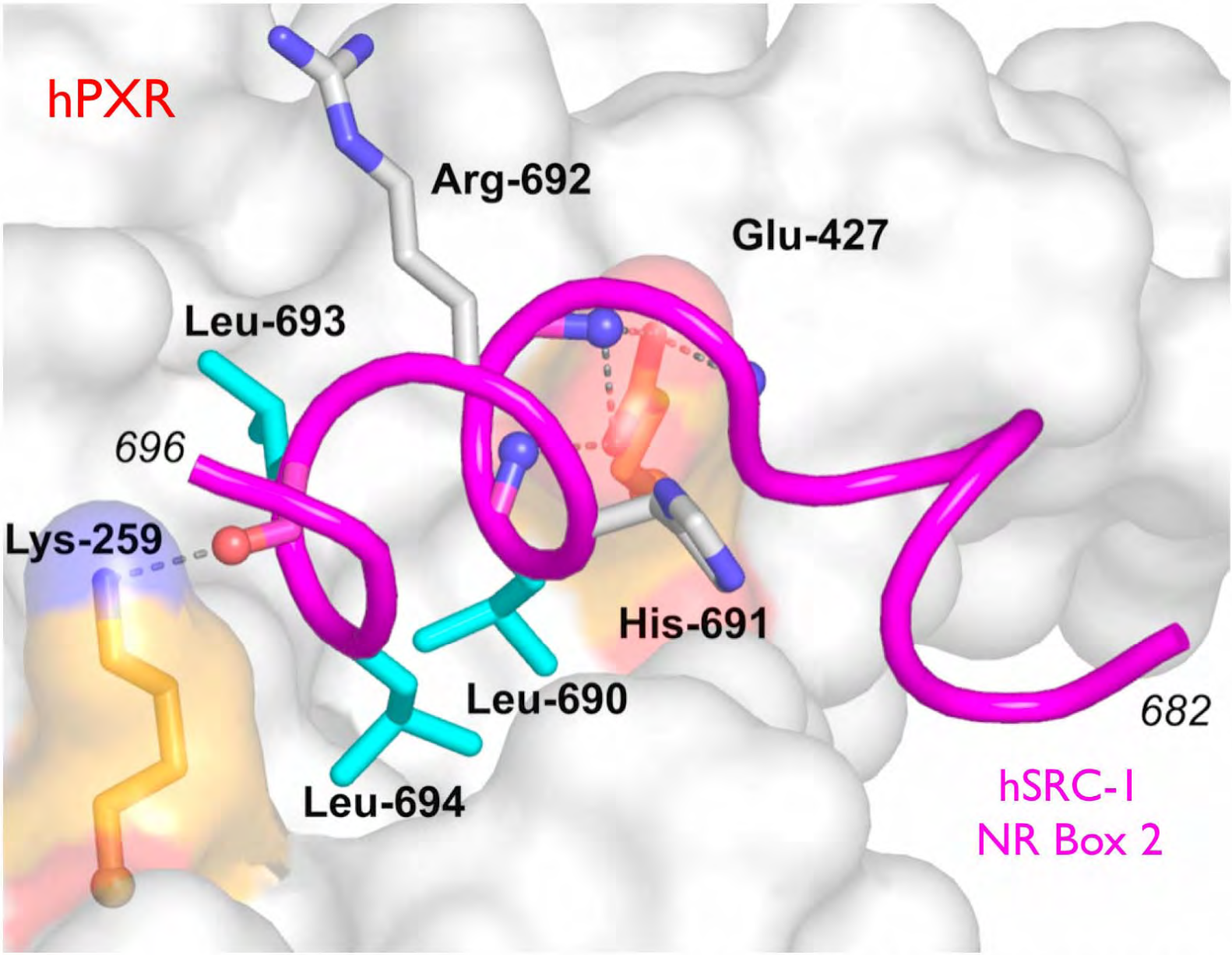
Chrencik et al. (2005).
Molecular Endocrinology, **19**, 1125.

Rifampicin
2.8 Å resolution

Transcriptional Coactivator Recruitment

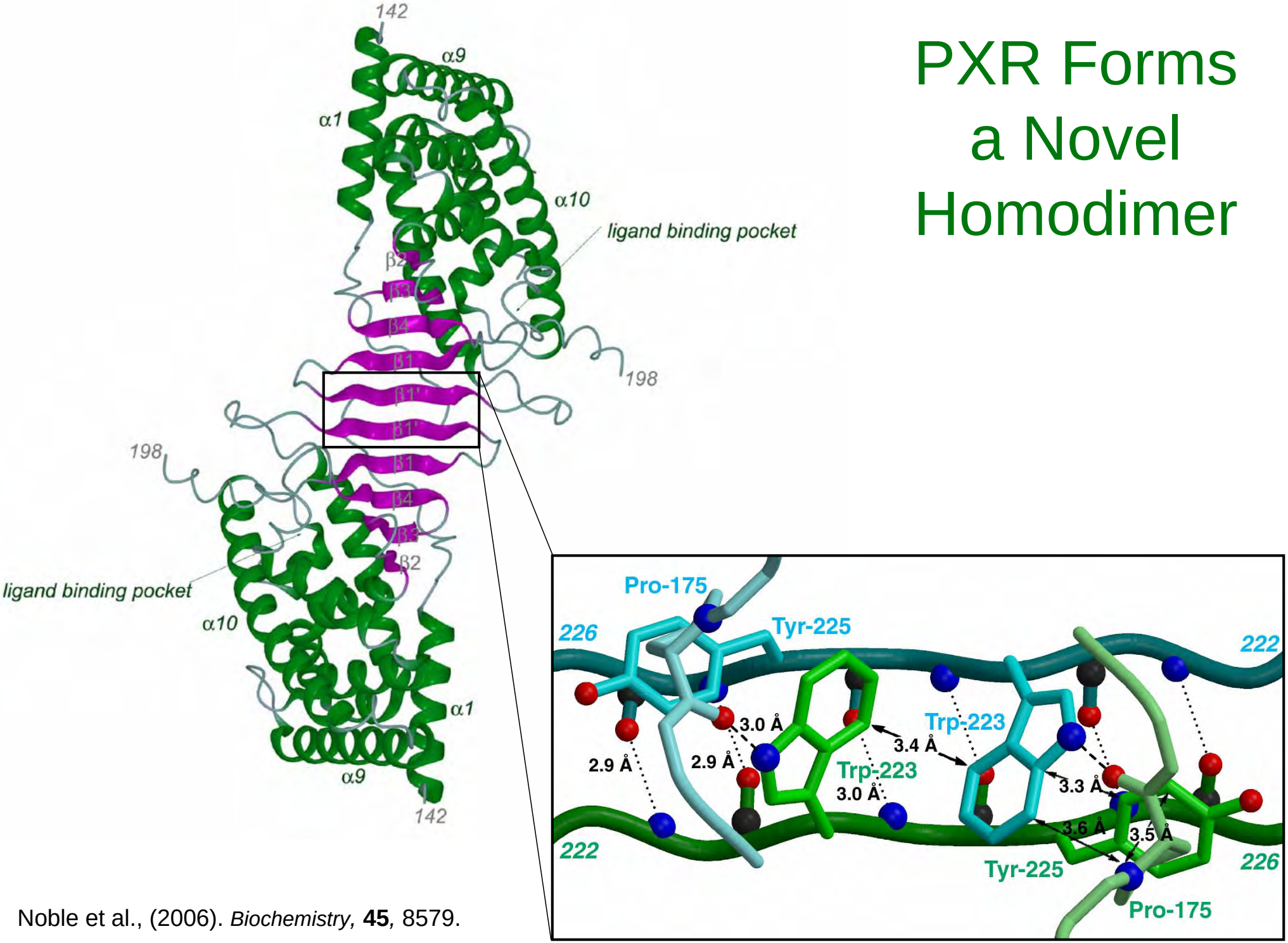


Canonical "Charge Clamp" Interaction

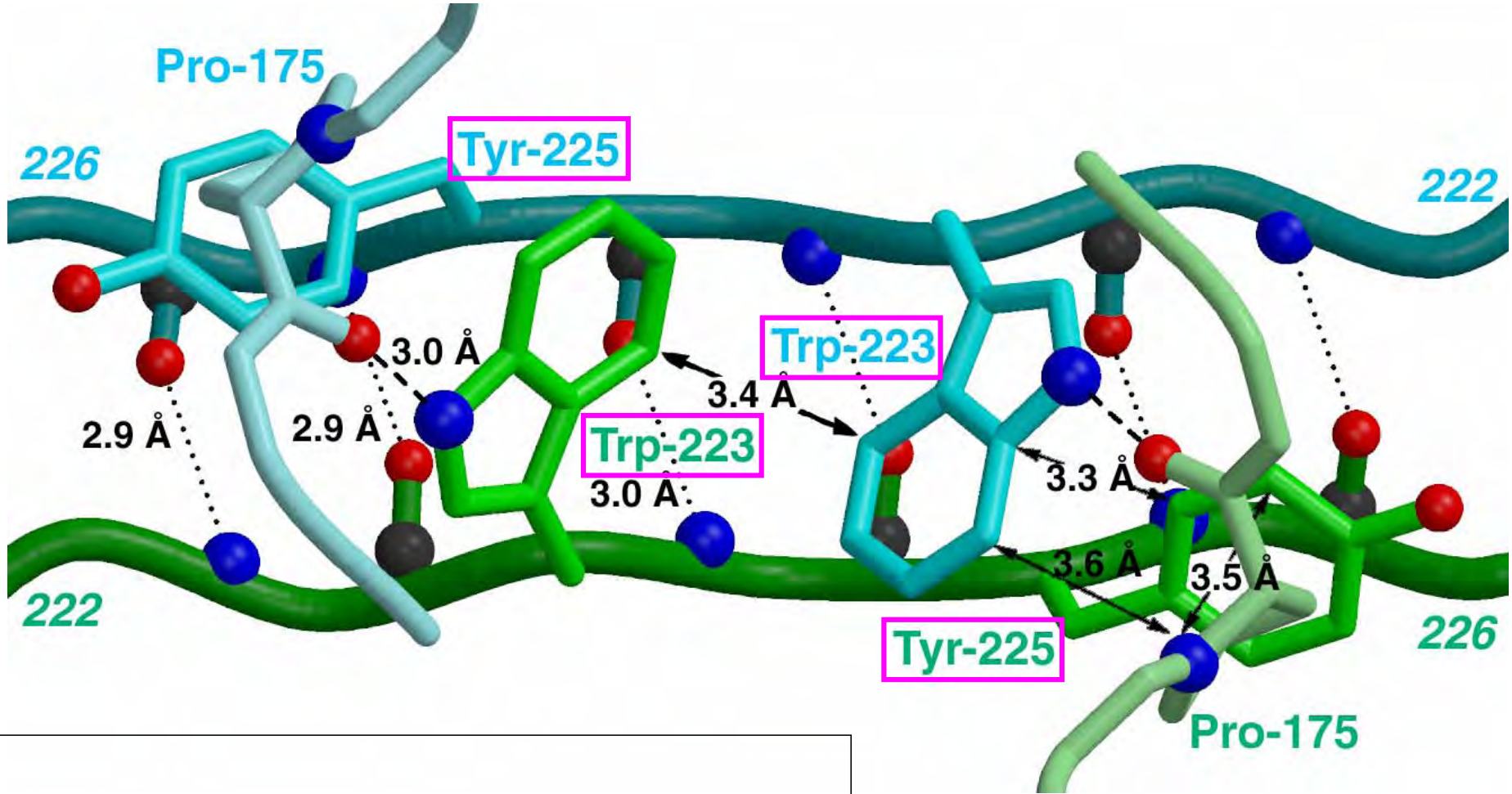


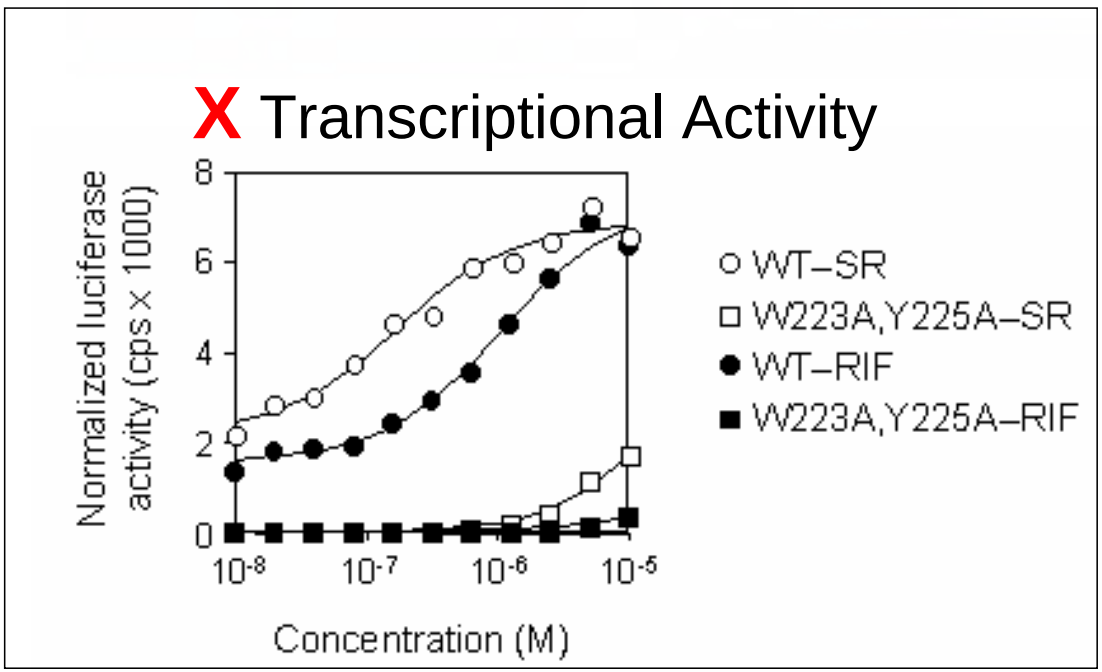
Watkins et al. (2003). *Journal of Molecular Biology*, **331**, 825.

PXR Forms a Novel Homodimer



Noble et al., (2006). *Biochemistry*, **45**, 8579.





√ DNA Binding

√ Nuclear Localization

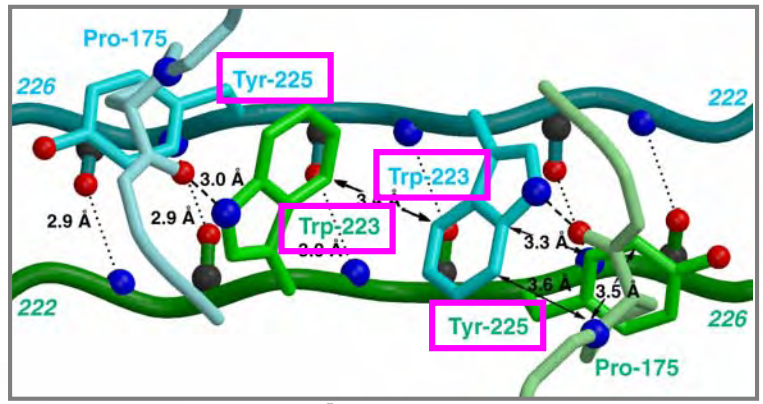
√ Ligand Binding

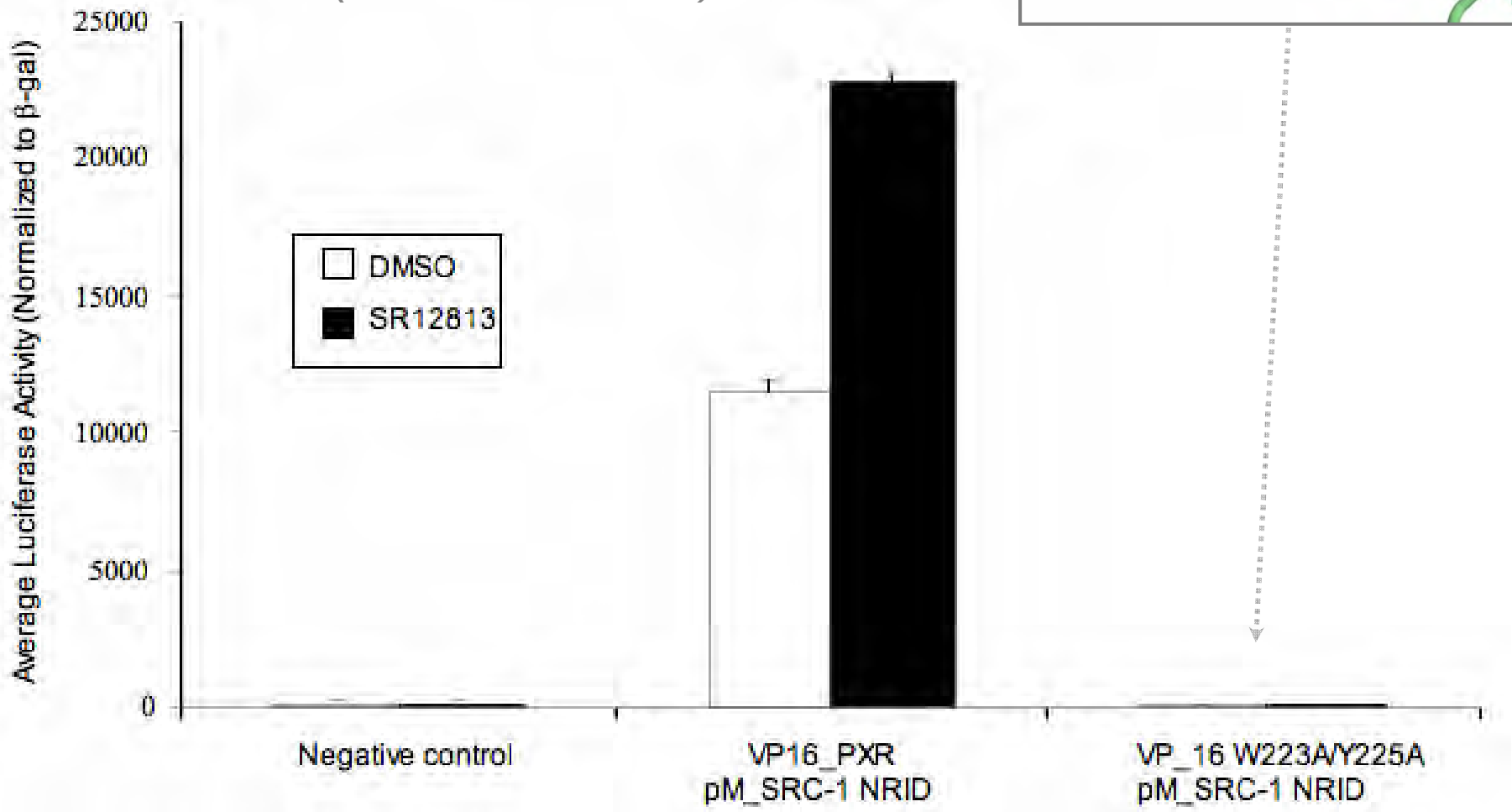
√ RXR Binding

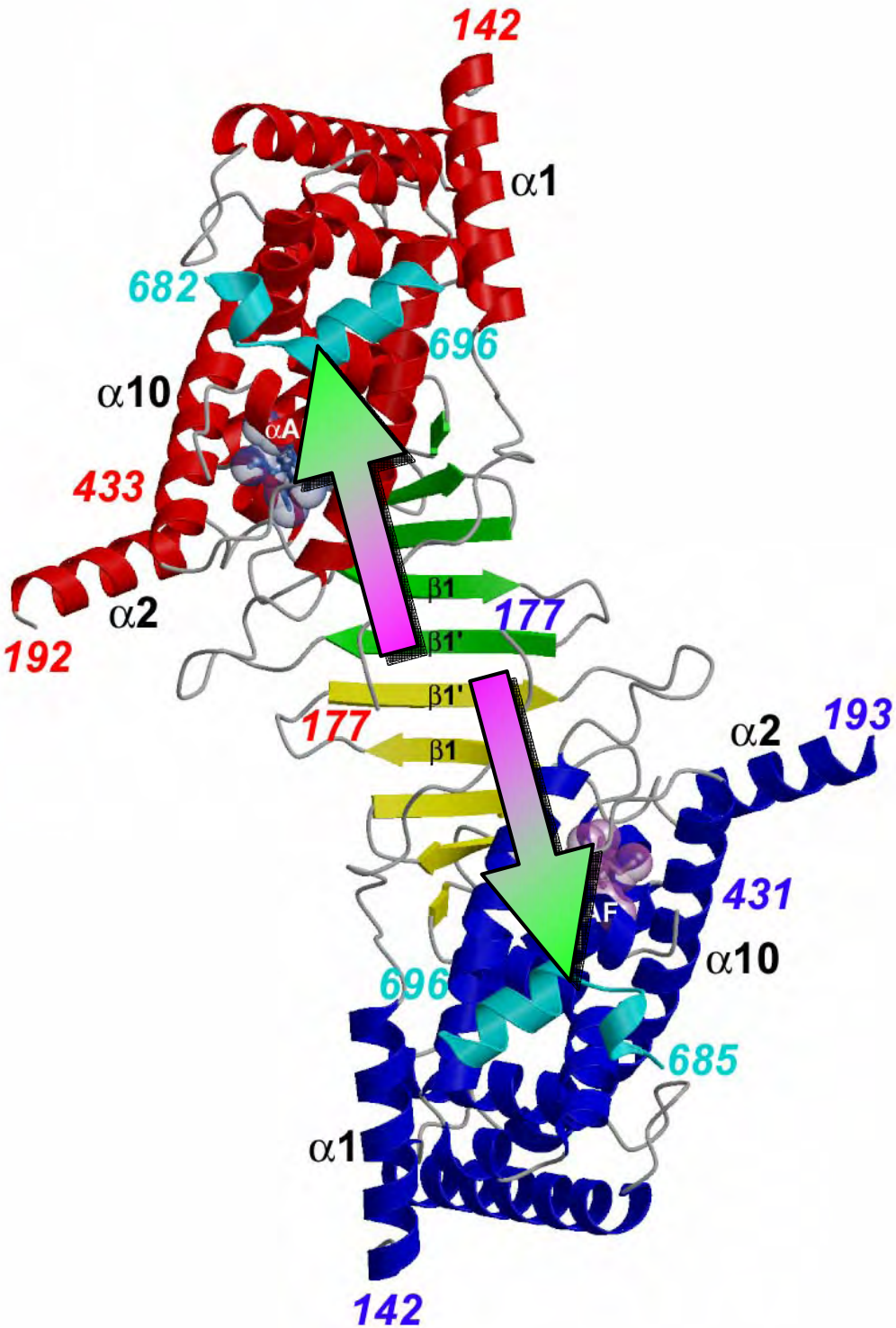
PXR Double-Mutant Incapable of Interacting with SRC-1

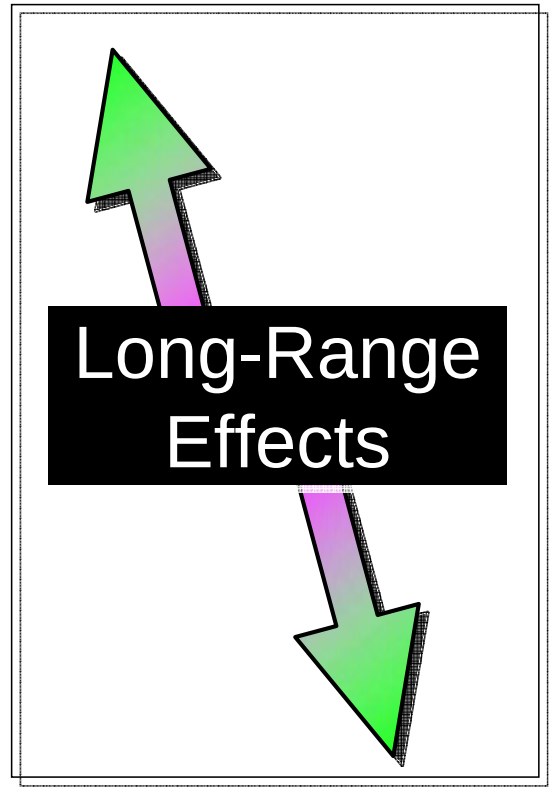
X Coactivator Recruitment

Mammalian Two-Hybrid (In Vitro Pull-Downs)

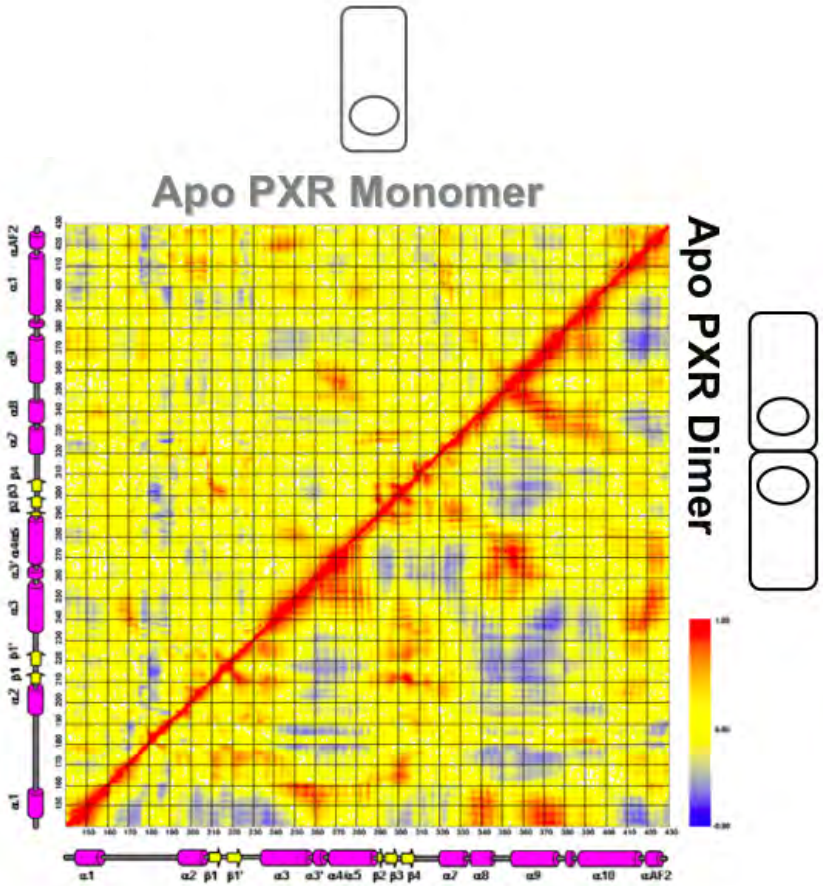


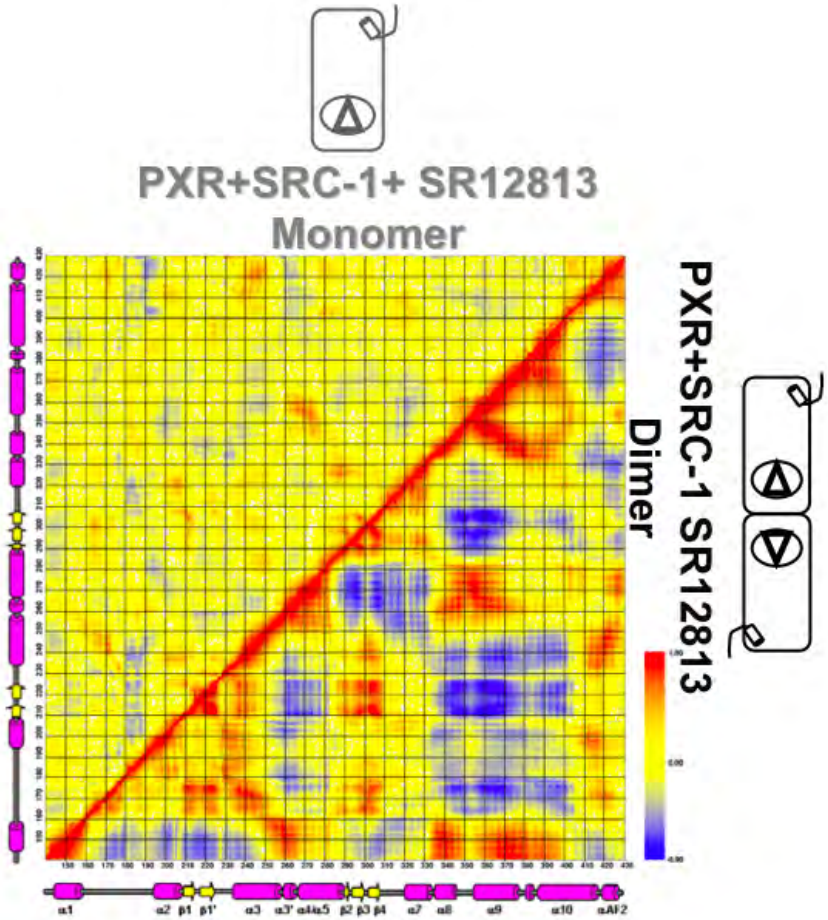



142
α1
682
696
α10
αA
433
β1
177
β1'
192
α2
β1'
177
β1
α2
193
431
AF
α10
696
685
α1
142


Long-Range
Effects

Molecular Dynamics

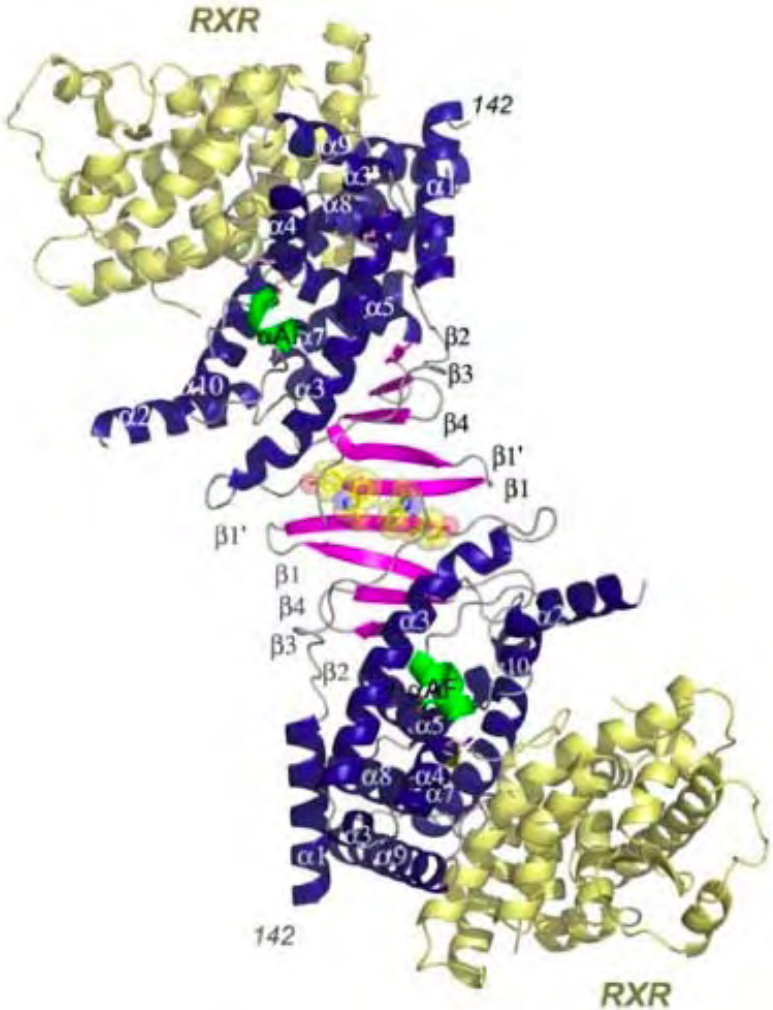


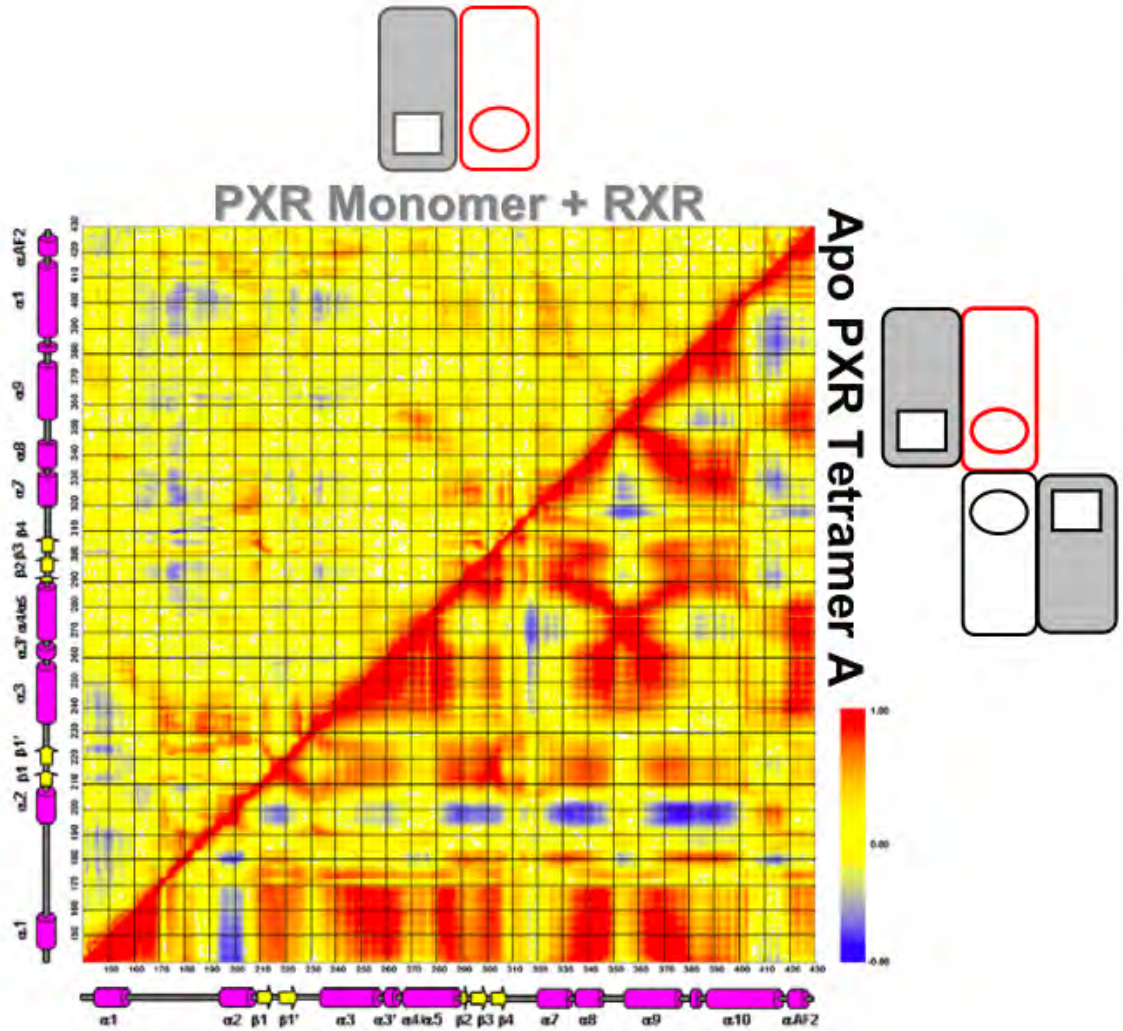


Correlated

Anticorrelated

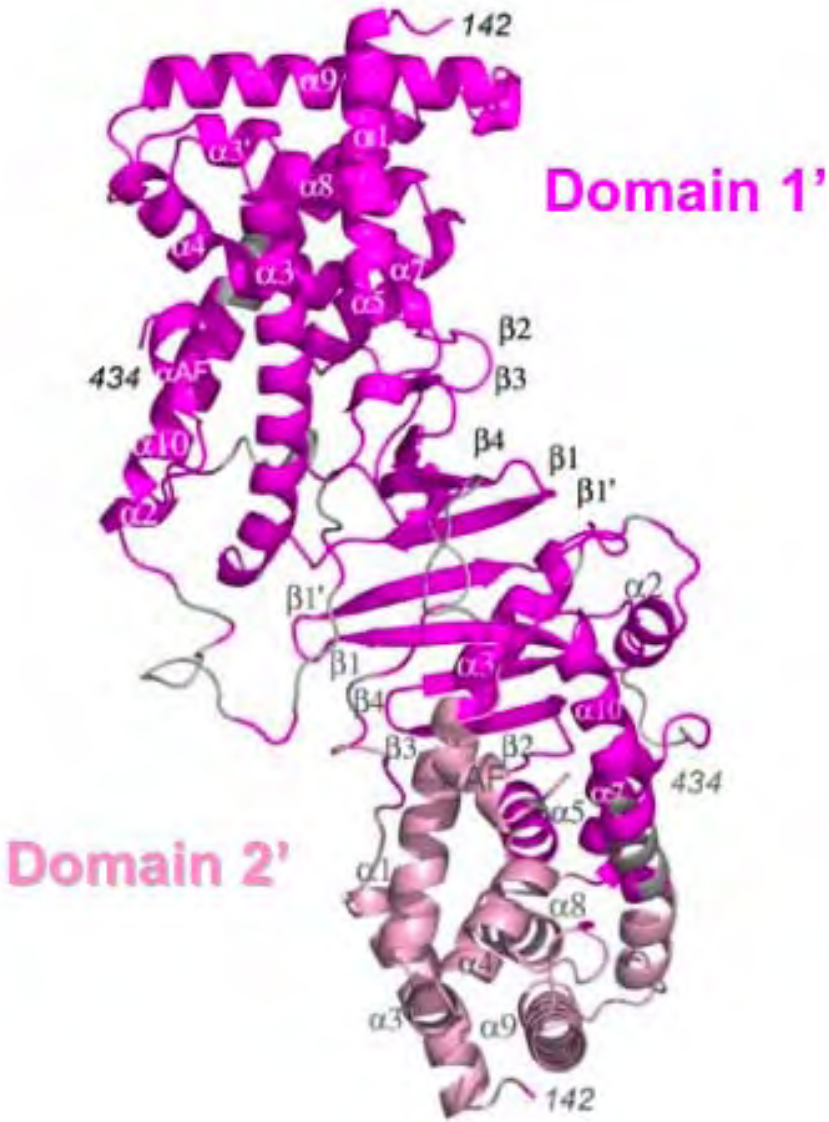
10 ns Trajectories

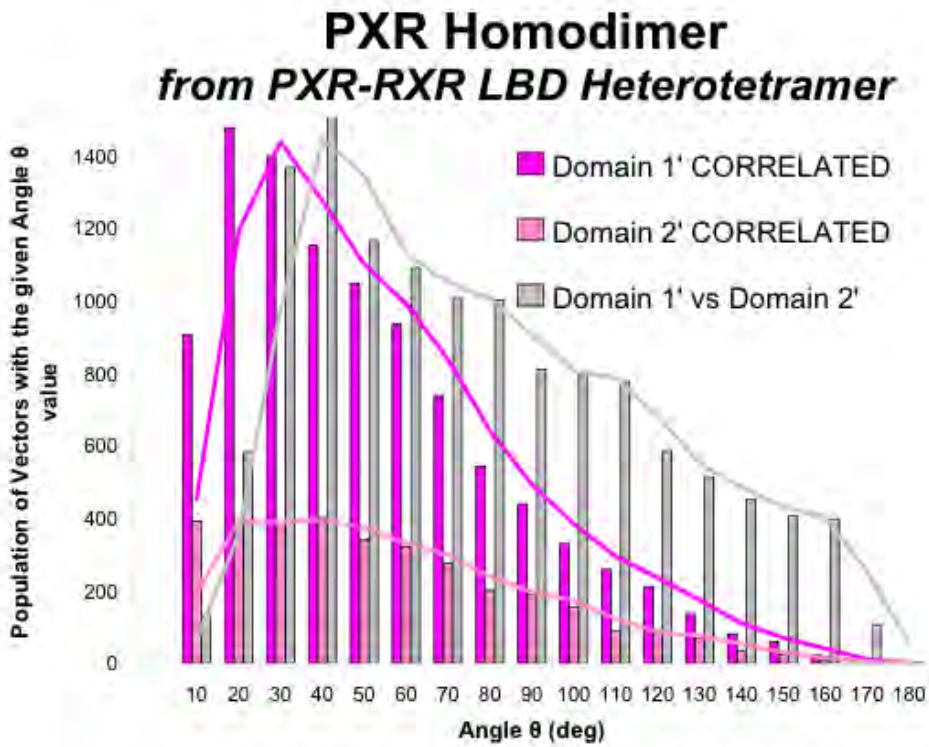


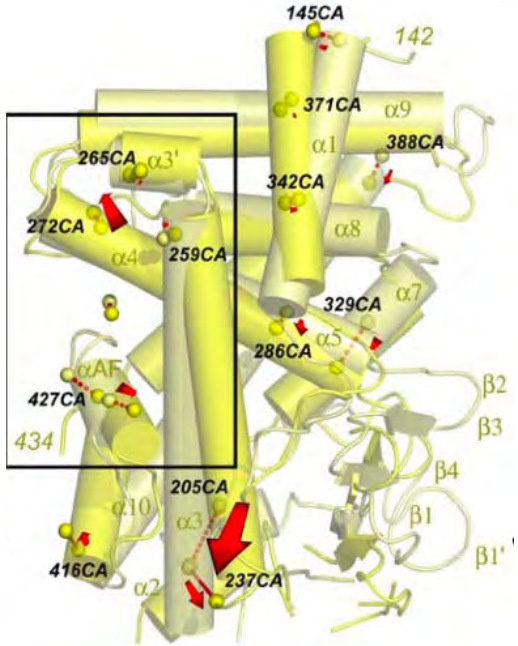


Correlated

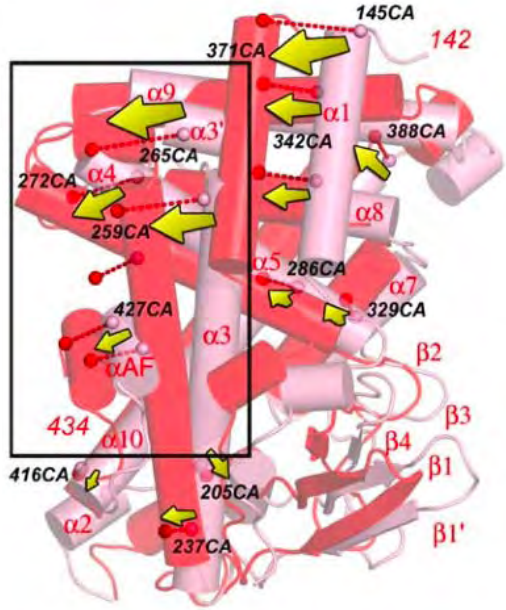
Anticorrelated


142
α9
α1
α3'
α8
Domain 1'
α4
α3
α7
α5
β2
434
αAF
β3
α10
β4
β1
β1'
α2
β1'
α2
β1
α3
β4
α10
β3
β2
AF
α2
434
α5
Domain 2'
α1
α8
α4
α3
α9
142

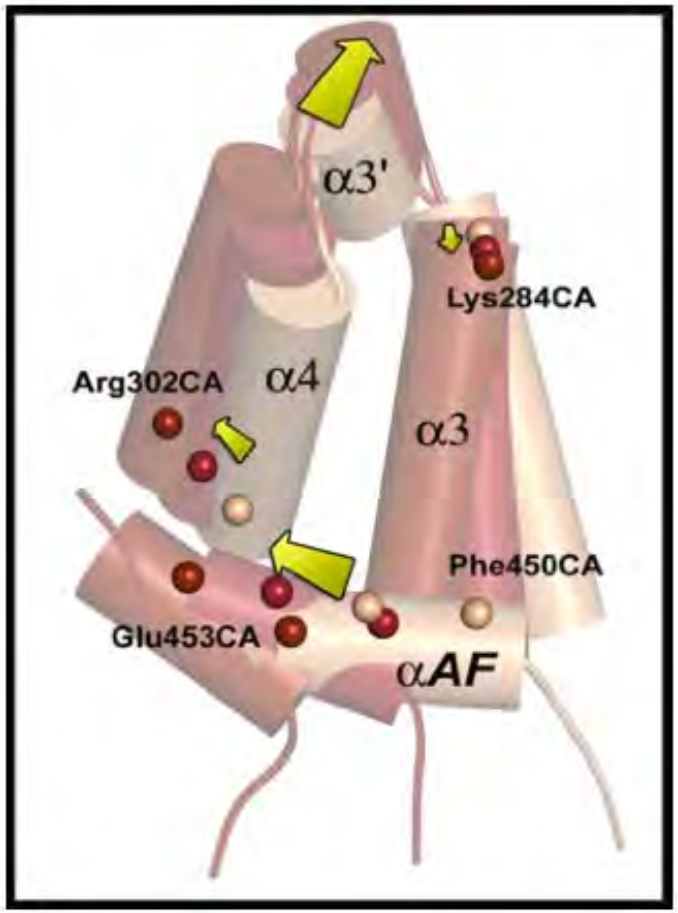

PXR Homodimer
from PXR-RXR LBD Heterotetramer
Domain 1' CORRELATED
Domain 2' CORRELATED
Domain 1' vs Domain 2'
Population of Vectors with the given Angle θ value
0
200
400
600
800
1000
1200
1400
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
Angle θ (deg)



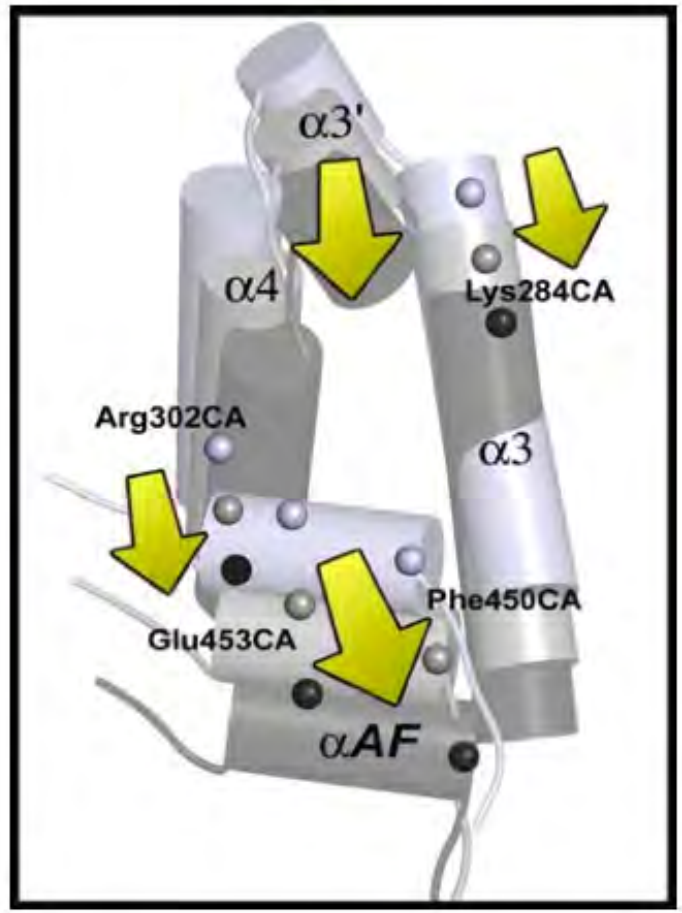
PXR Monomer
from PXR-RXR LBD
Heterodimer



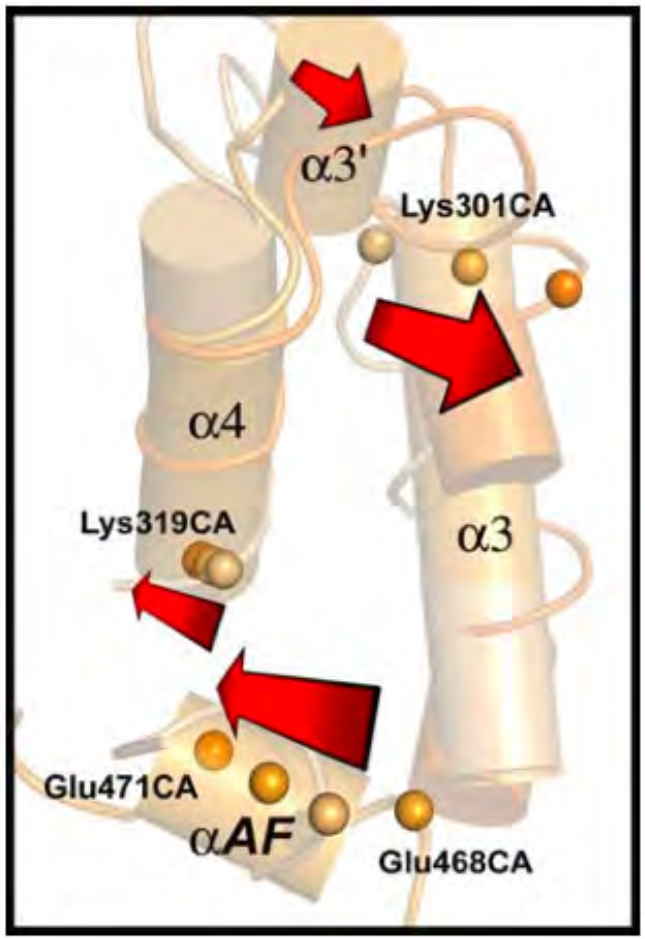
PXR Homodimer
from PXR-RXR LBD
Heterotetramer



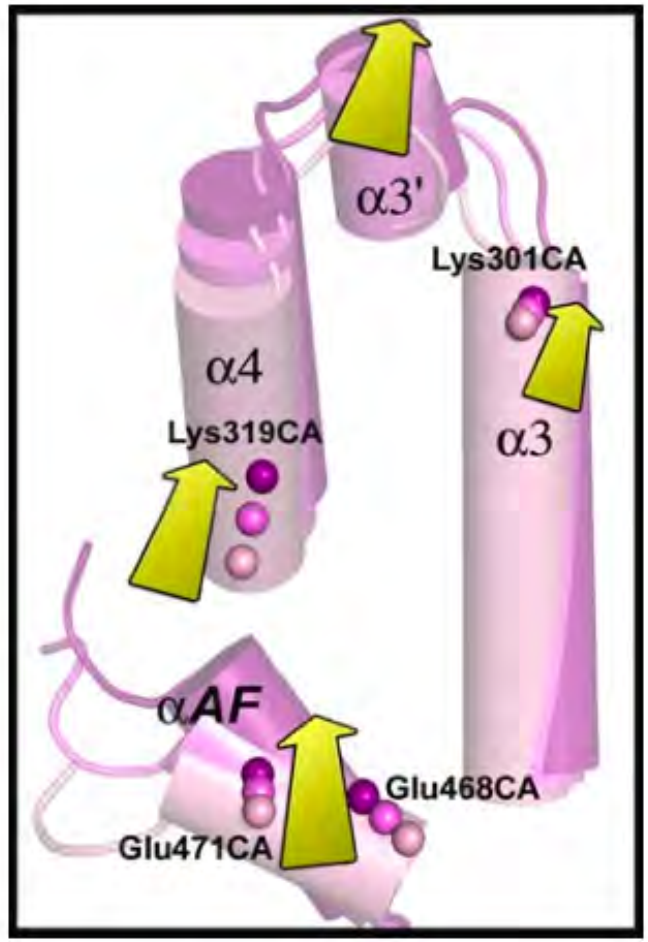
RXR
from PXR-RXR LBD
Heterodimer



RXR
from PXR-RXR LBD
Heterotetramer



PPARγ P467L

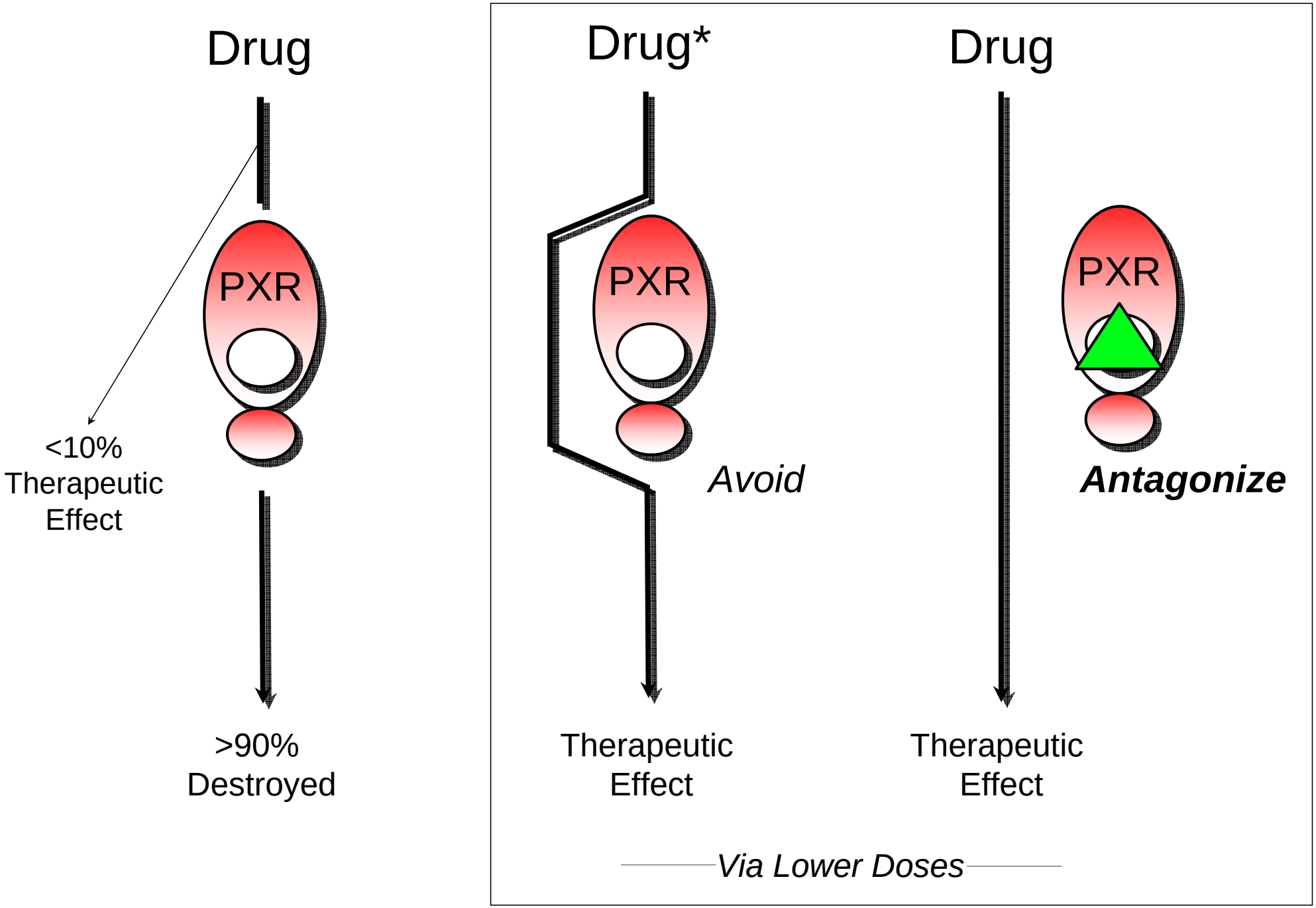


PPARγ + RXR

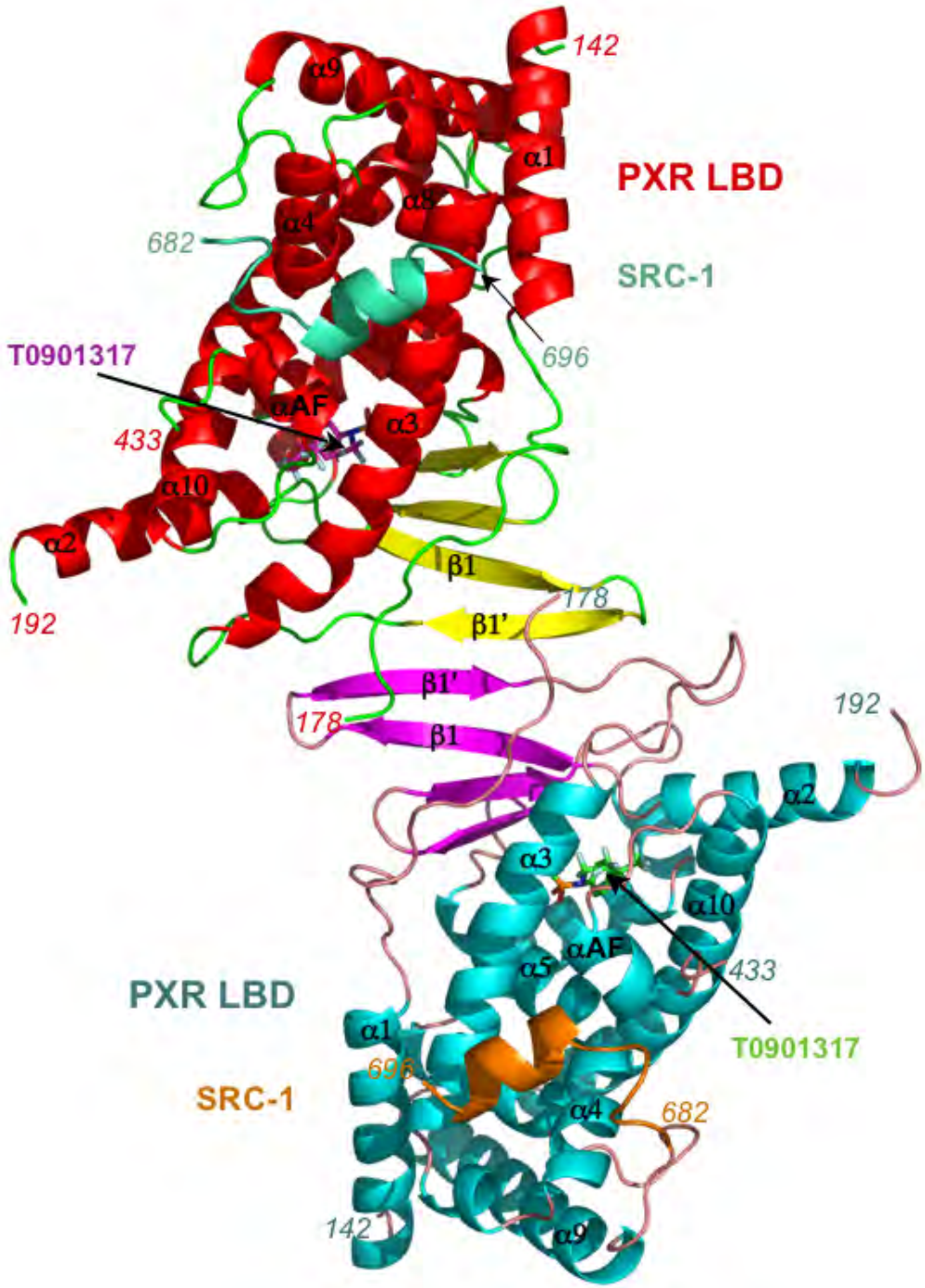
Inactive

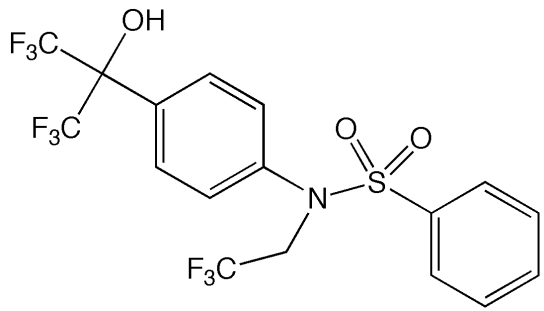
Kallenberger et al., (2003). Nature Structural Biology, 10: 136

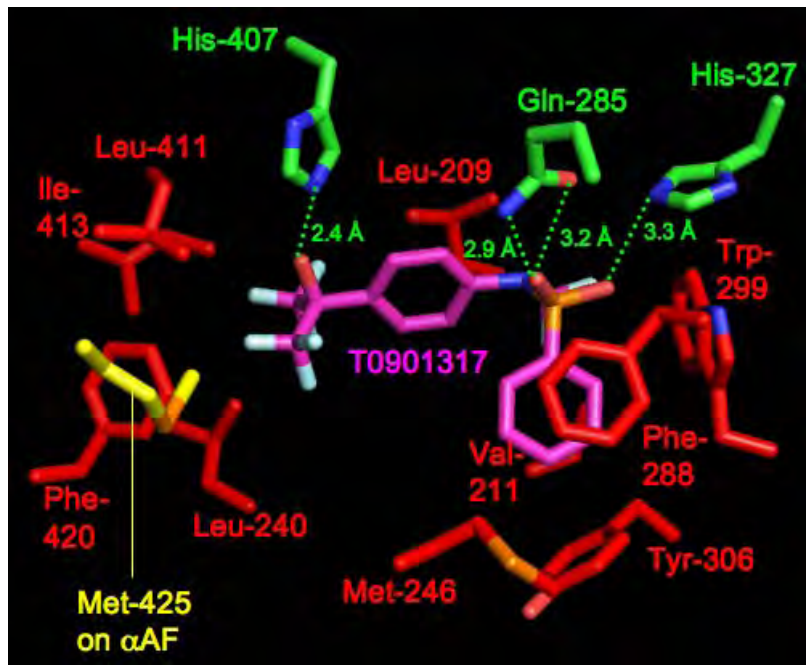
New Avenues to Control PXR?



PXR Antagonism via Ligand Binding Pocket



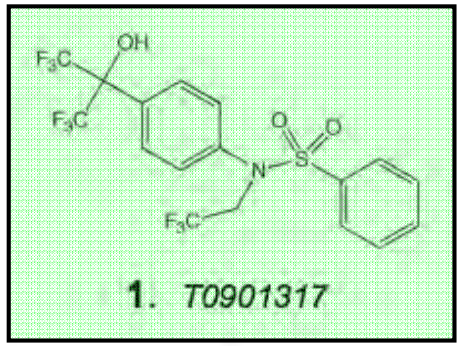


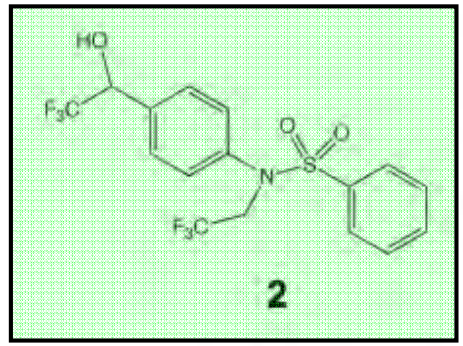


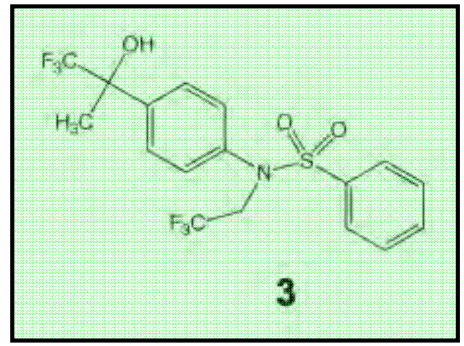
Xue et al. (2007). *Bioorg. Med. Chem.*, **15**, 2156.

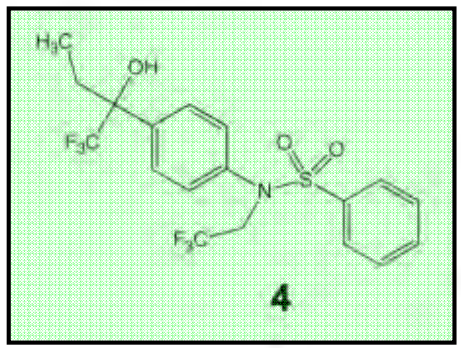
Agonist

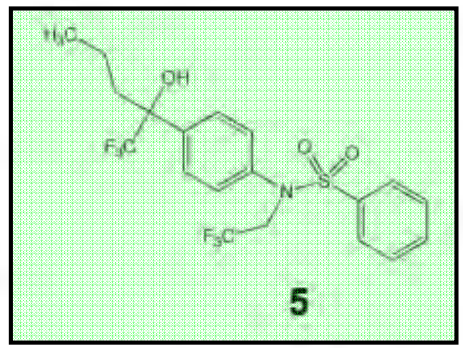
No Binding

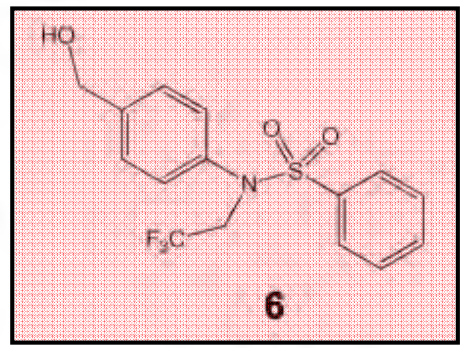


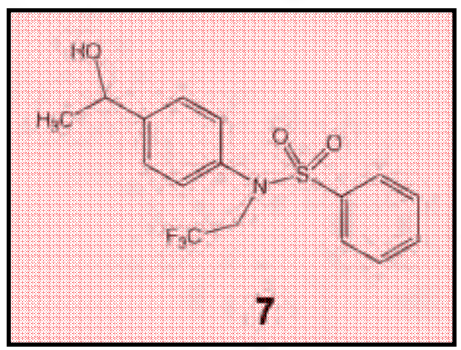


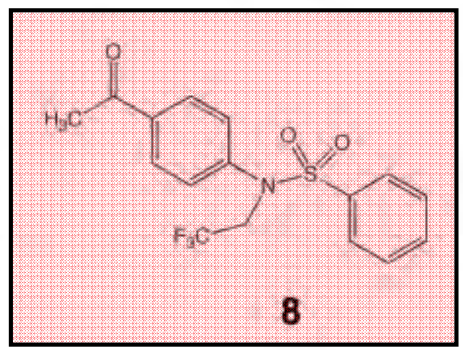


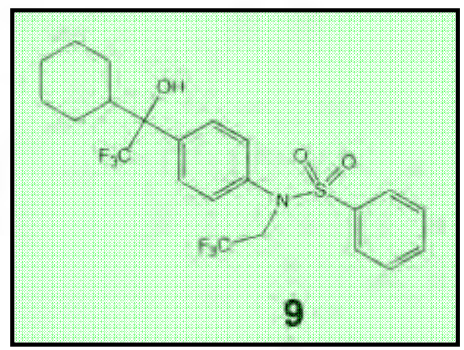


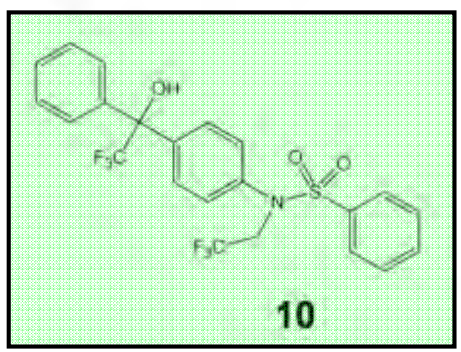


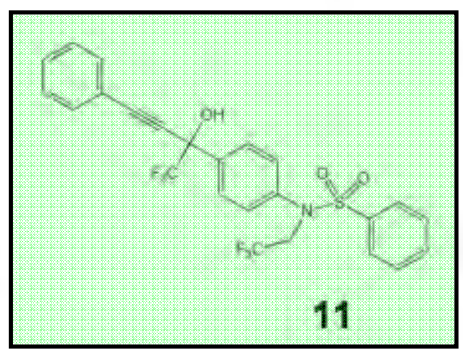


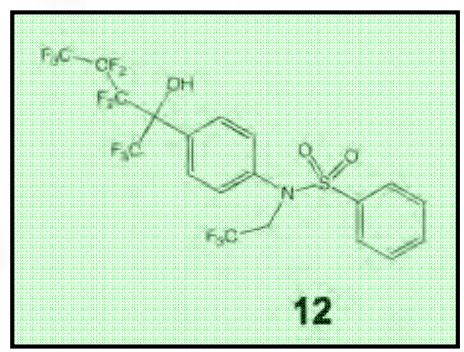




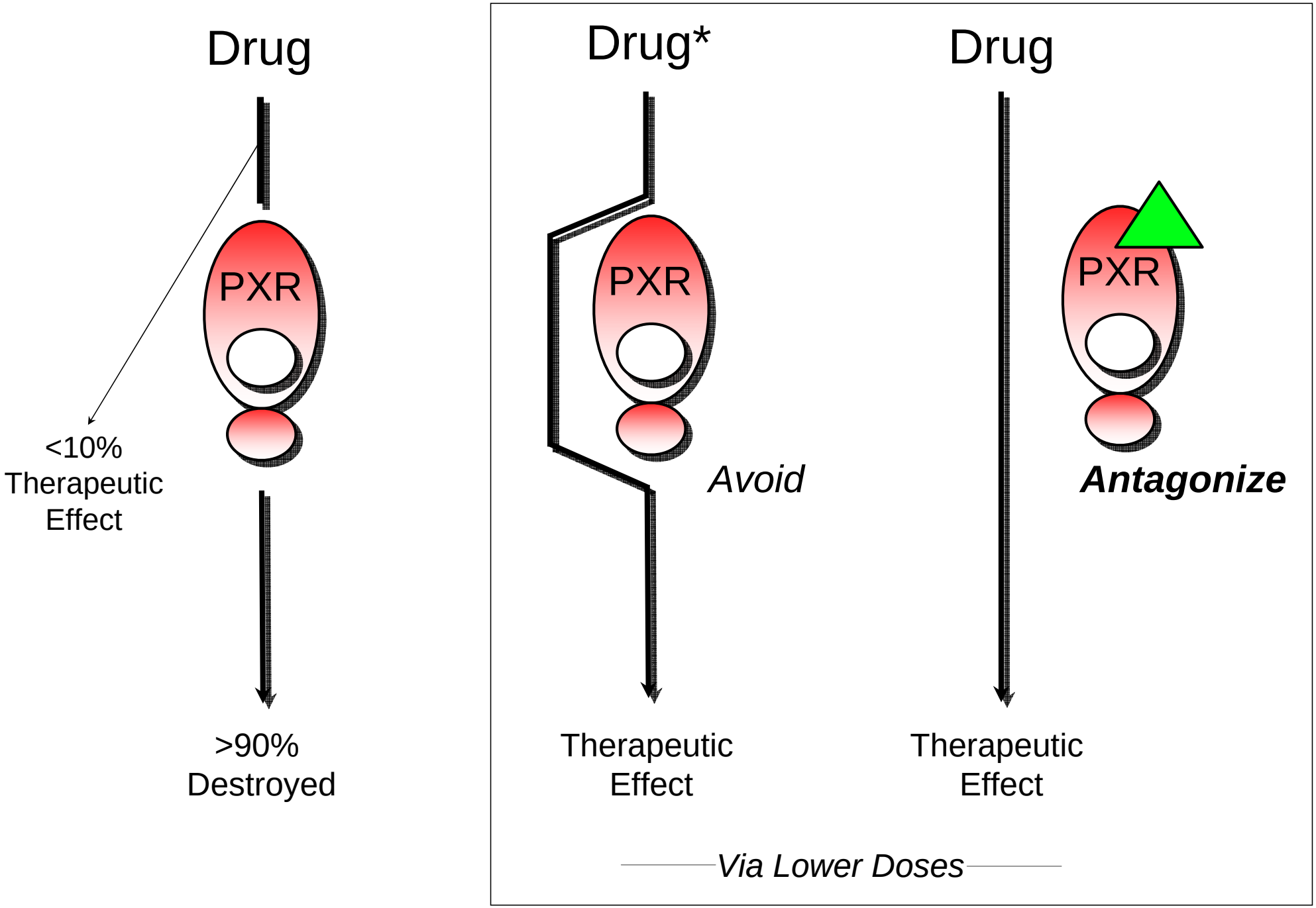






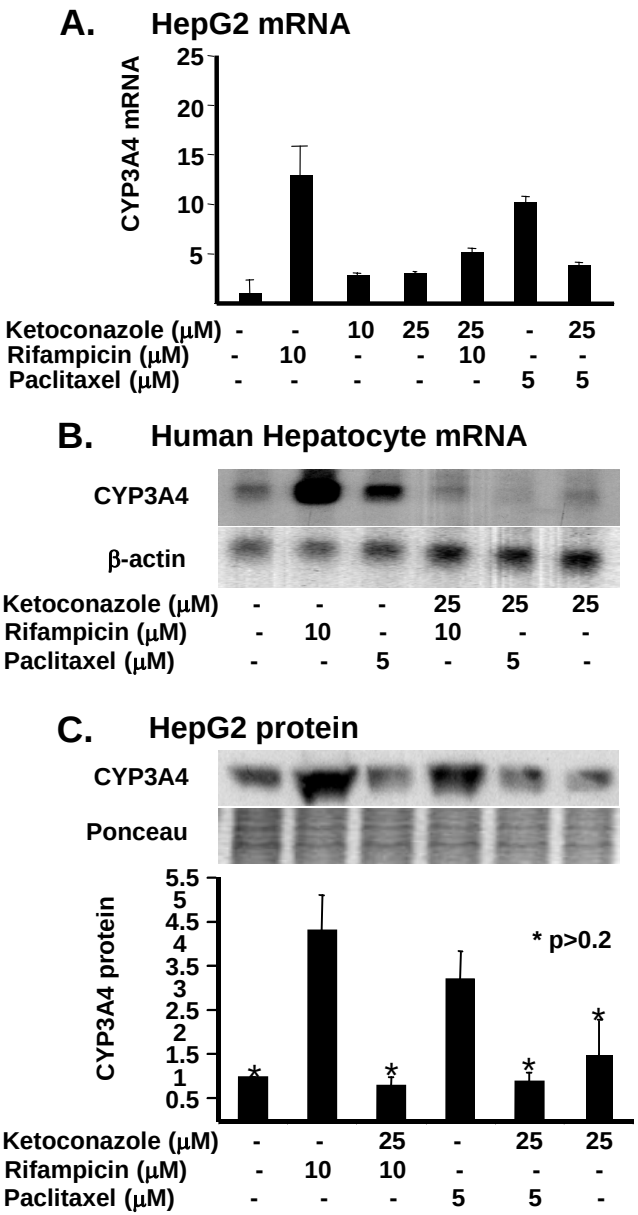


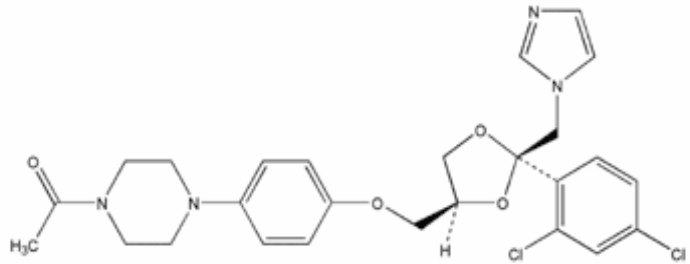
New Avenues to Control PXR?



Antifungal Drug Ketoconazole:

Ligand-Dependent PXR Antagonist





√ PXR

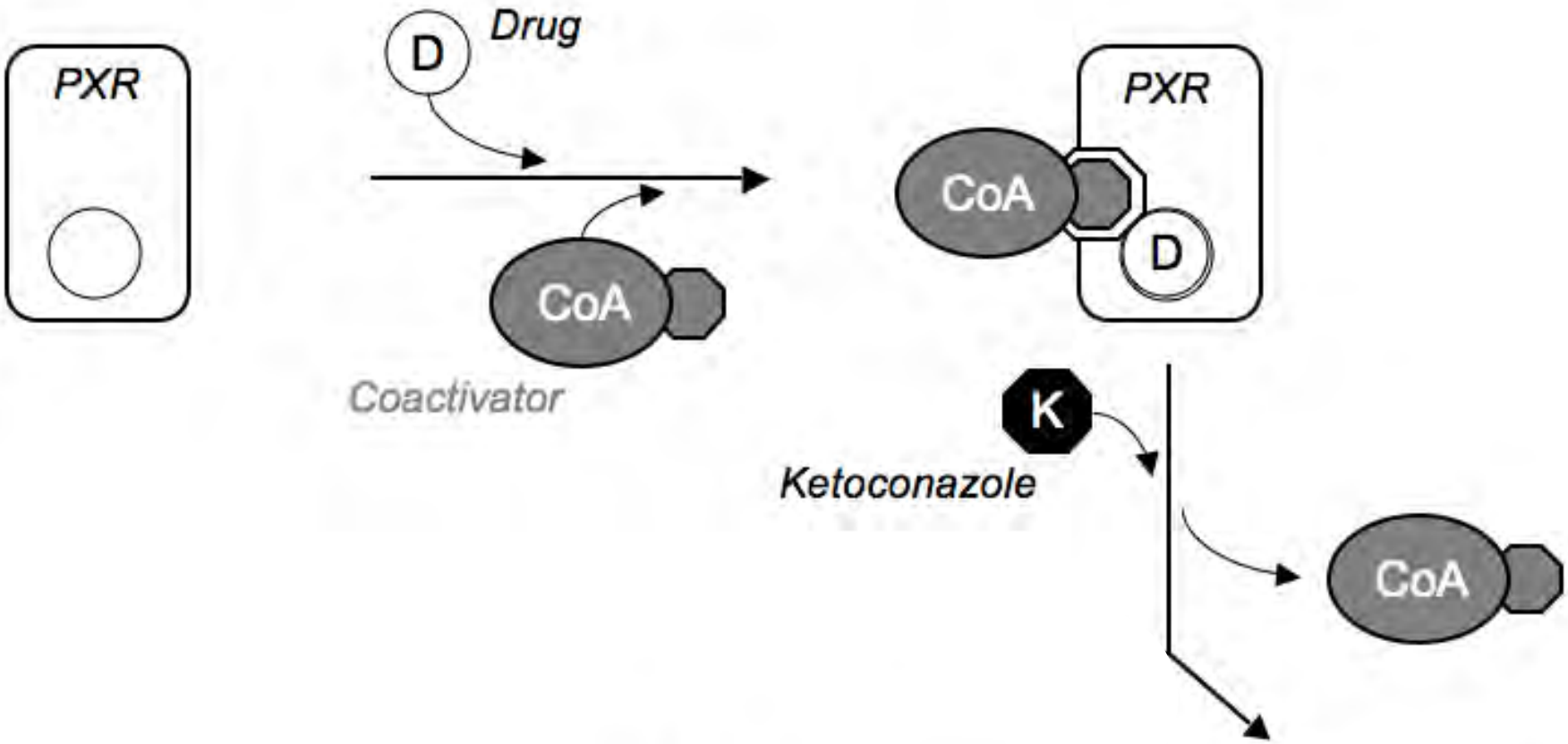
√ CAR

√ FXR

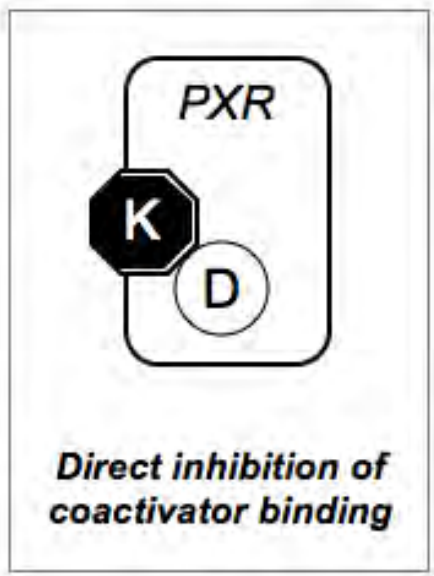
√ LXR

X ER

Huang et al., (2007). Oncogene, 26, 258.



Modulation of Drug Metabolism During Therapeutic Treatment



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Sarah Kennedy
Kim Lane
Joe Lomino
Scott Lujan
Michael Miley
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Jillian Orans
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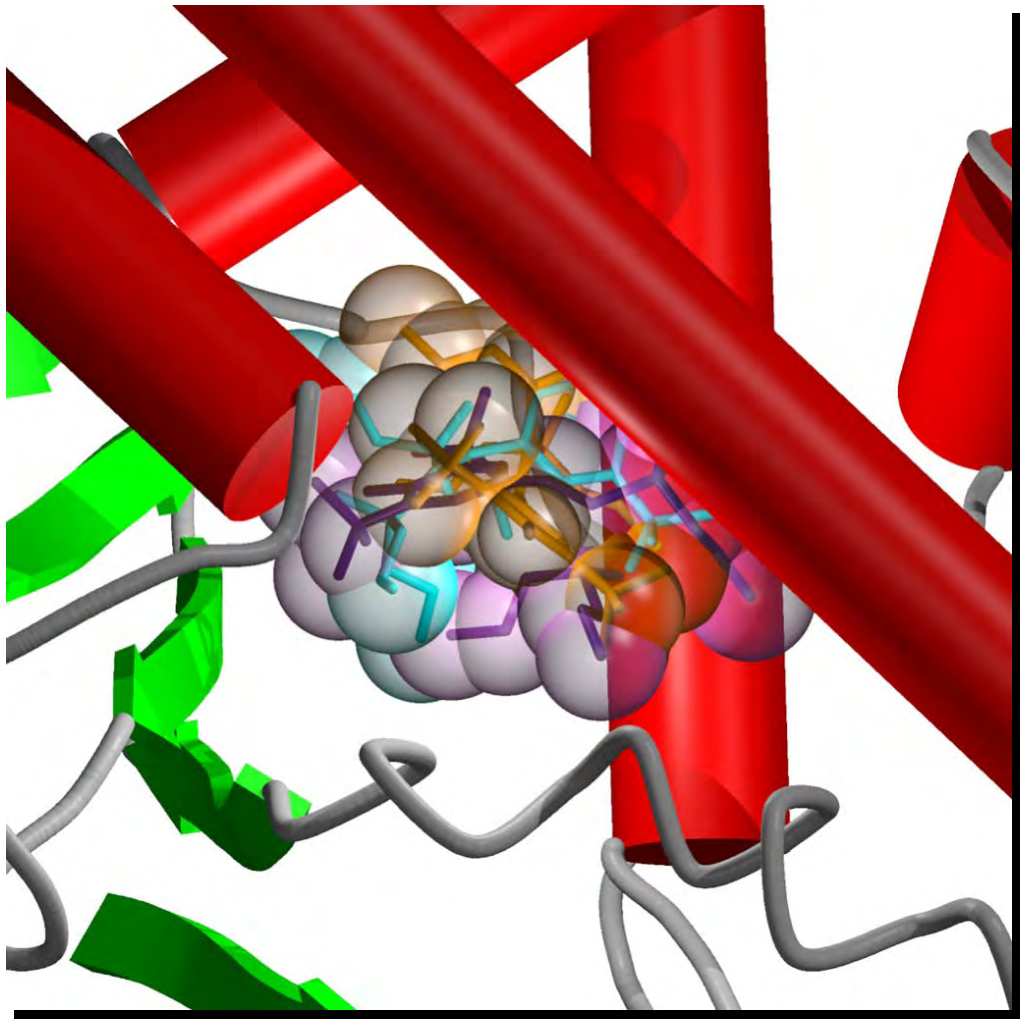
Isaac Solomon
Denise Teotico
Ryan Watkins
Yu Xue



National Institutes of Health
Burroughs Wellcome Fund
Endocrine Society

Steve Kliewer
Linda Moore
Bruce Wisely
Mill Lambert
Julie Stimmel
Olivia Ittoop
Tim Willson
Jon Collins

Brenda Temple

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