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Faculty of Health and Medical Sciences



Structure, function and pharmacology of G protein-coupled receptors:
State-of-the-art and future challenges

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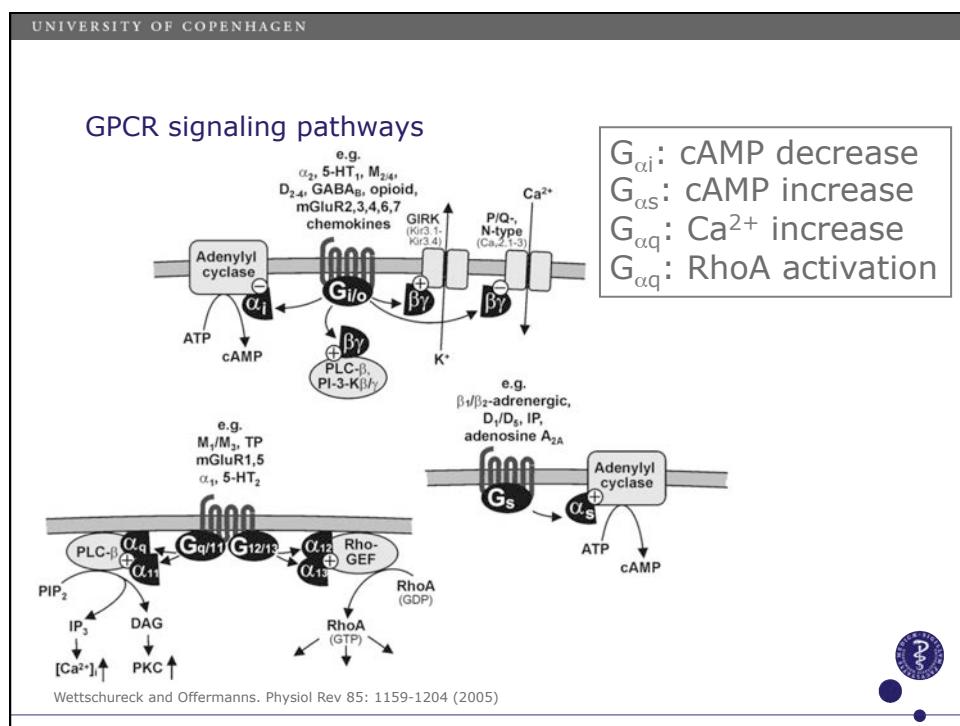
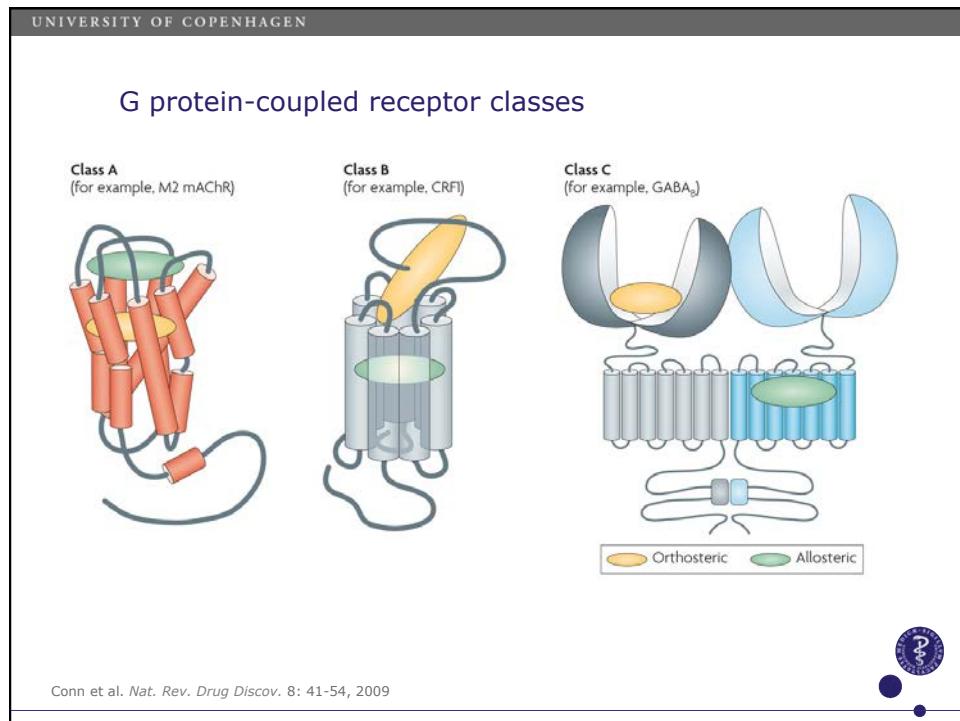
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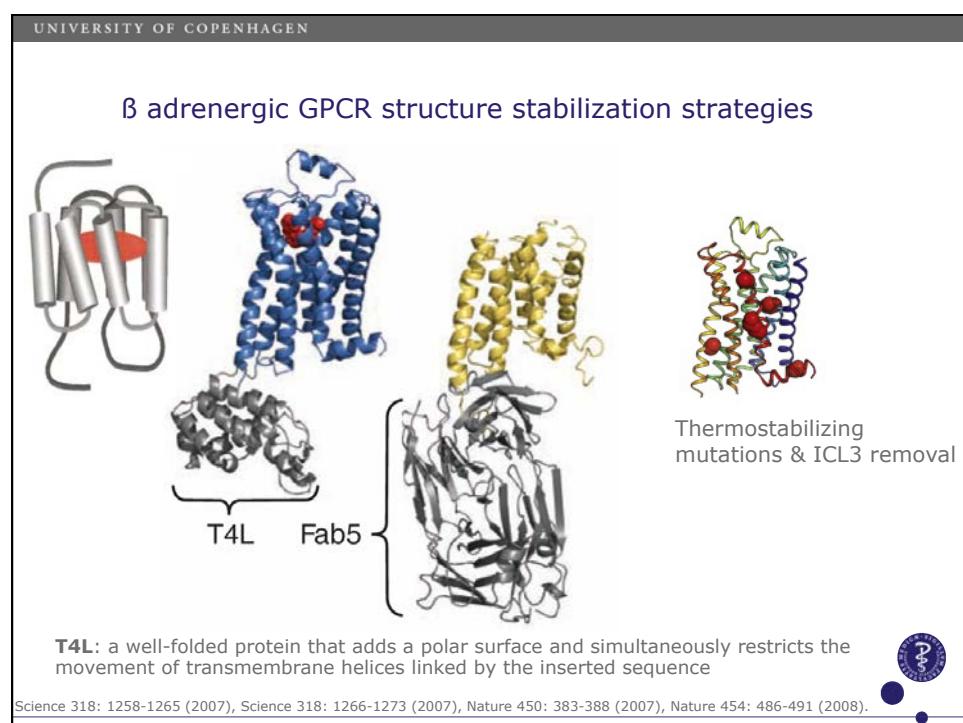
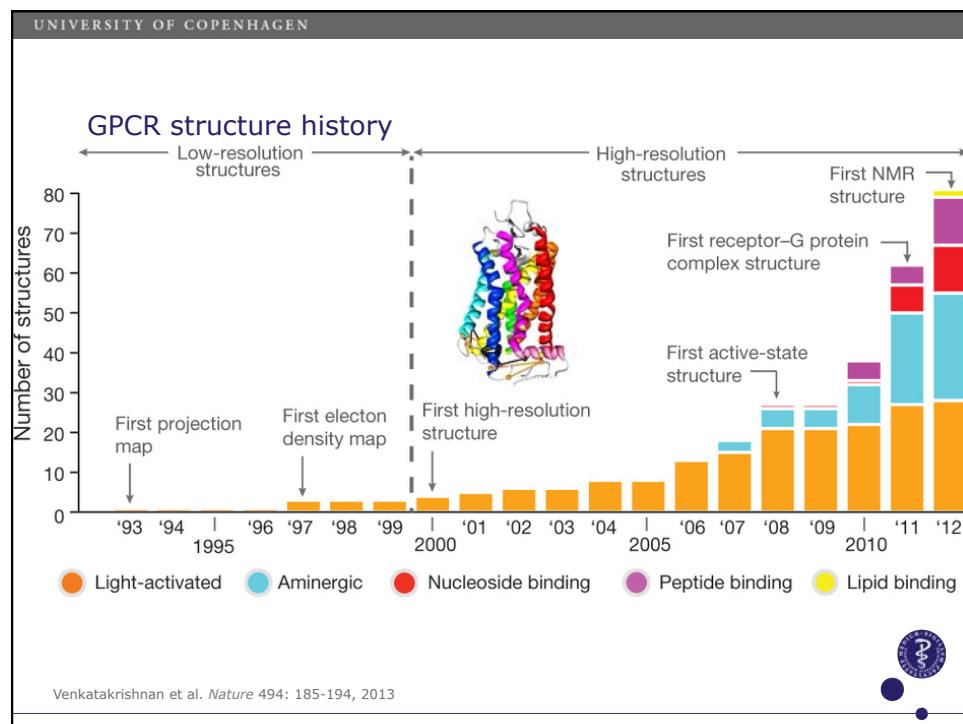
Overview

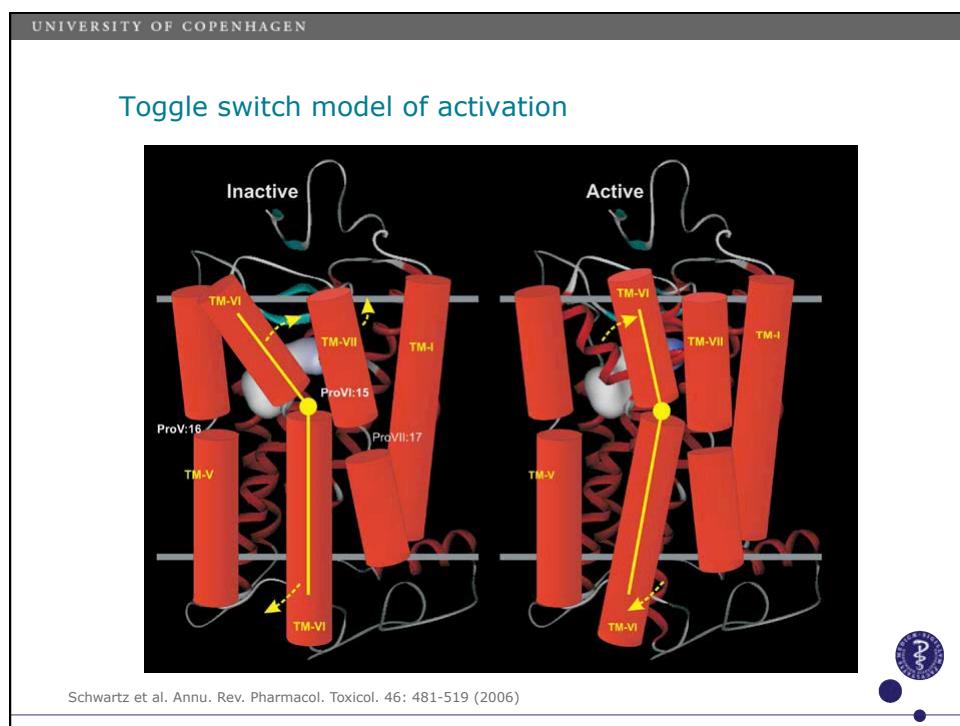
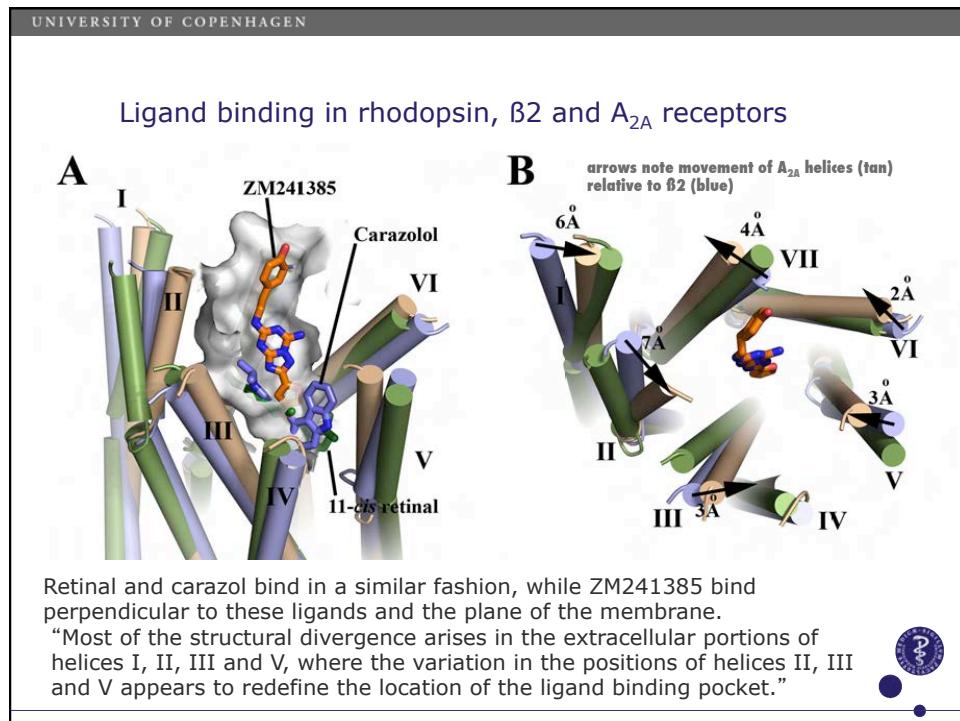
- GPCR structures
- Biased signaling
- Real-time receptor activation measurements
- Orphan receptors





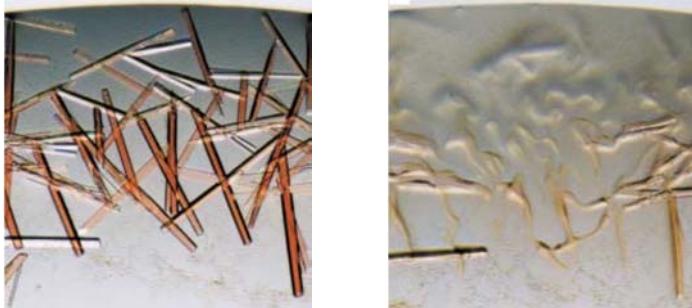






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GPCR structure - active conformation?



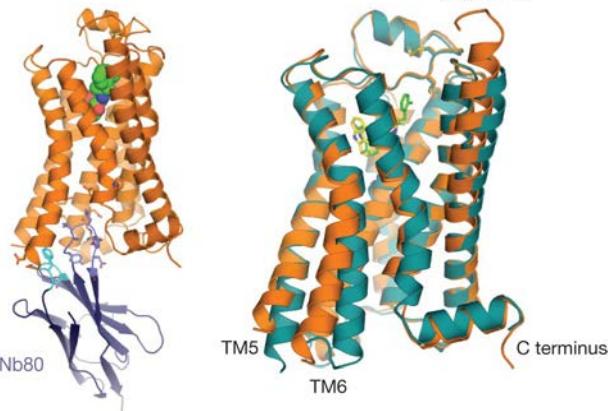
Crystals dissolve upon 1 min radiation with visible light.
Indicates conformational/structural change.

Okada and Palczewski. Curr. Opin. Struct. Biol. 11: 420-426 (2001)



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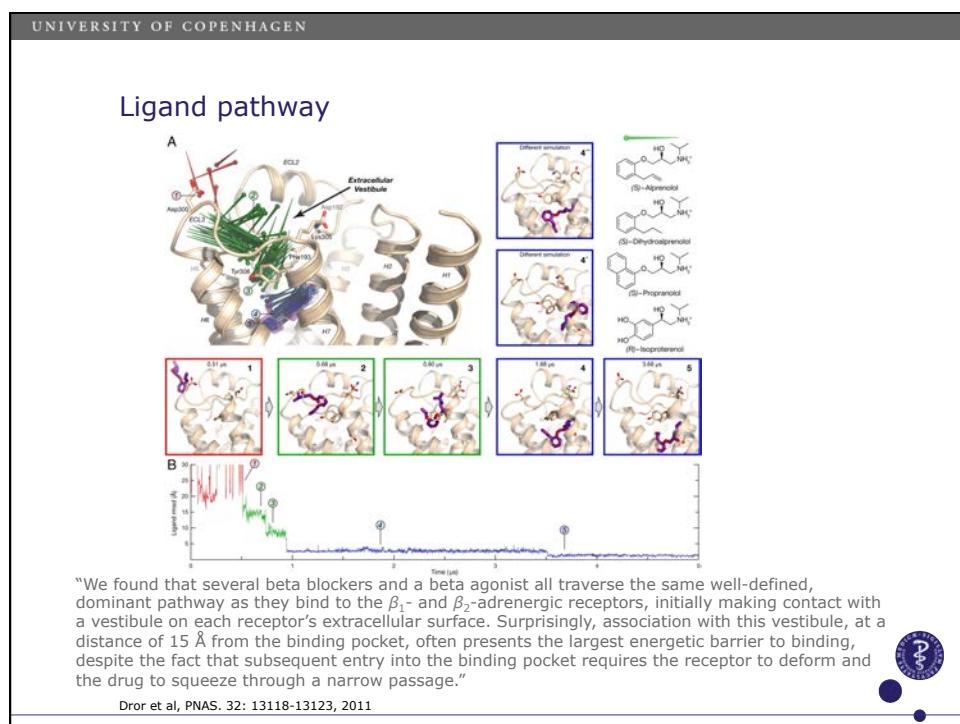
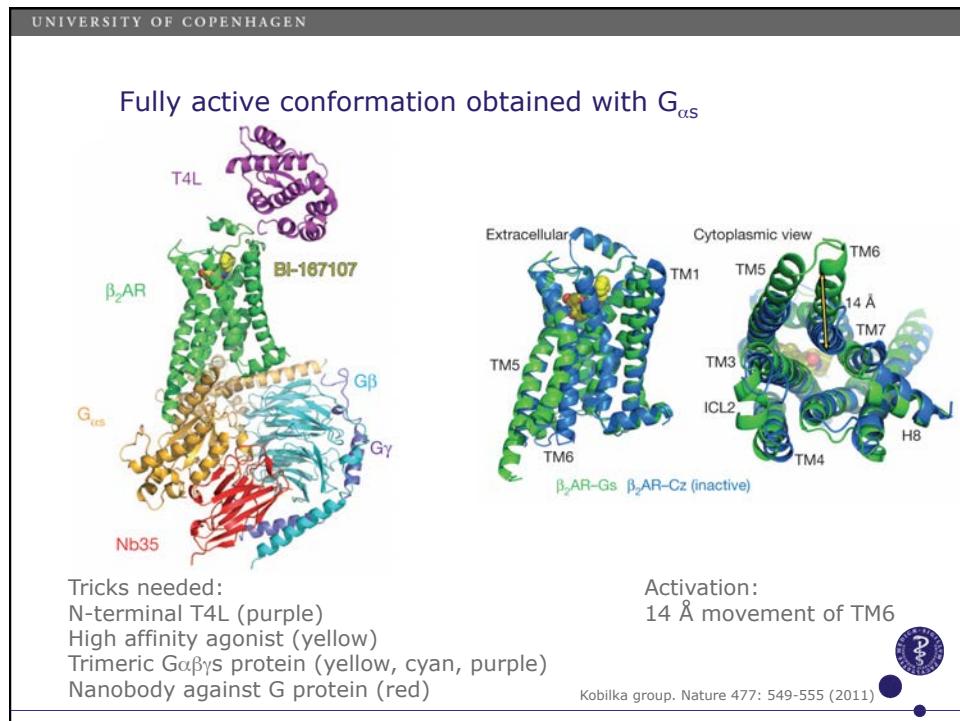
"Active" conformation by agonist and nanobody

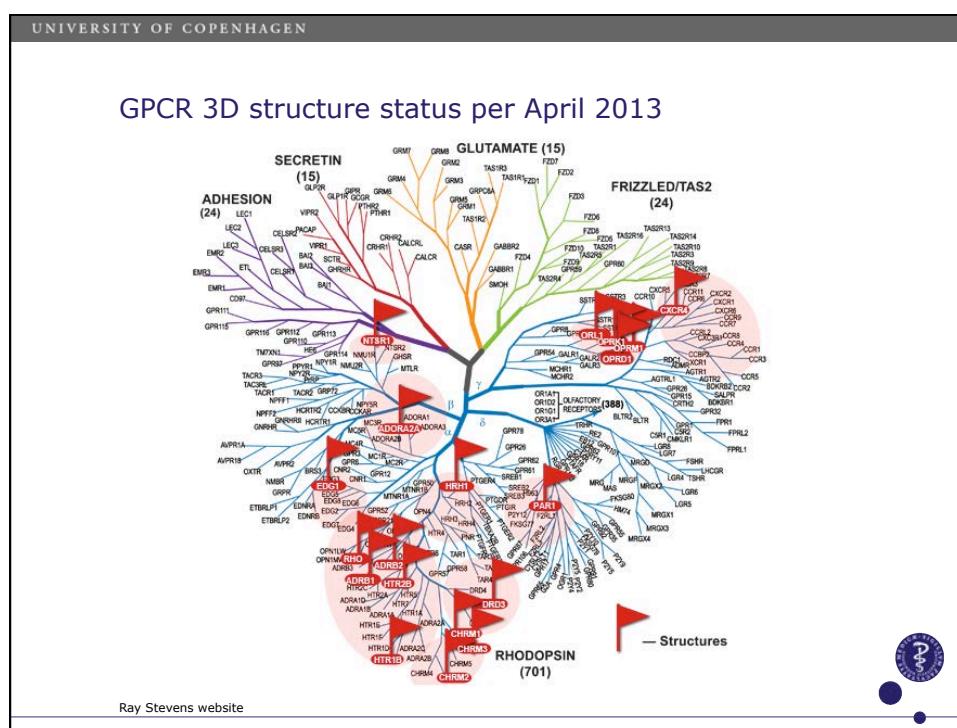
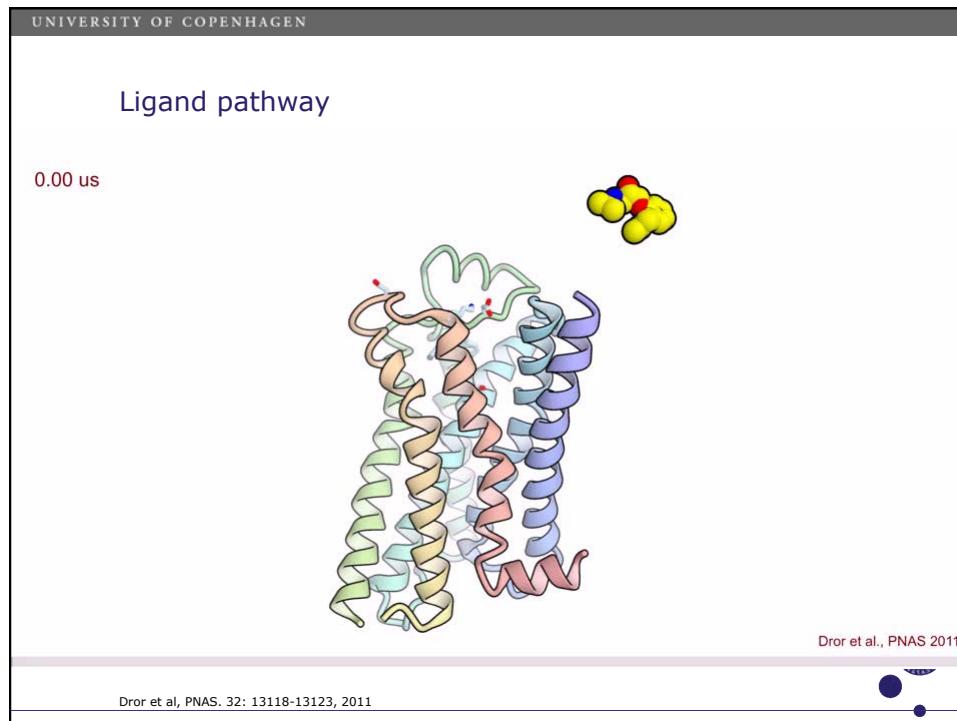


Orange: B2-T4L-Nanobody with full agonist (in green)
Cyan: B2-T4L with inverse agonist (in yellow)
Not possible to make agonist structure in the absence of nanobody.
TM5 top moves 2 Å inward, TM3-5-6-7 hydrogen bond network rearranged.
TM6 bottom moves 11 Å outward, TM5 & TM7 bottoms rearranged

Kobilka group. Nature 469: 175-180 (2011)



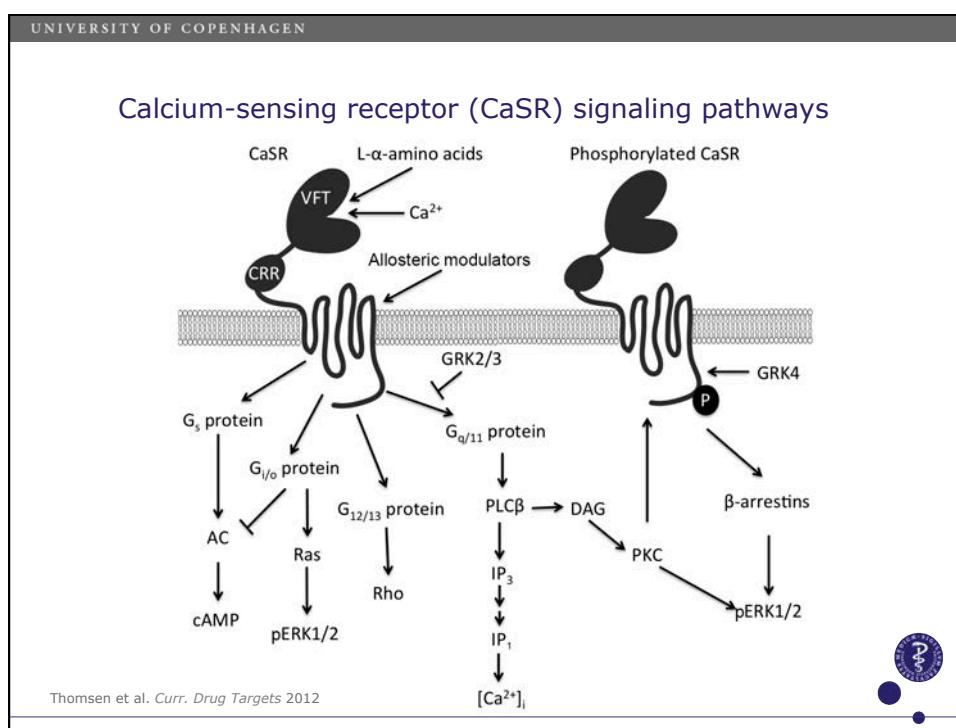


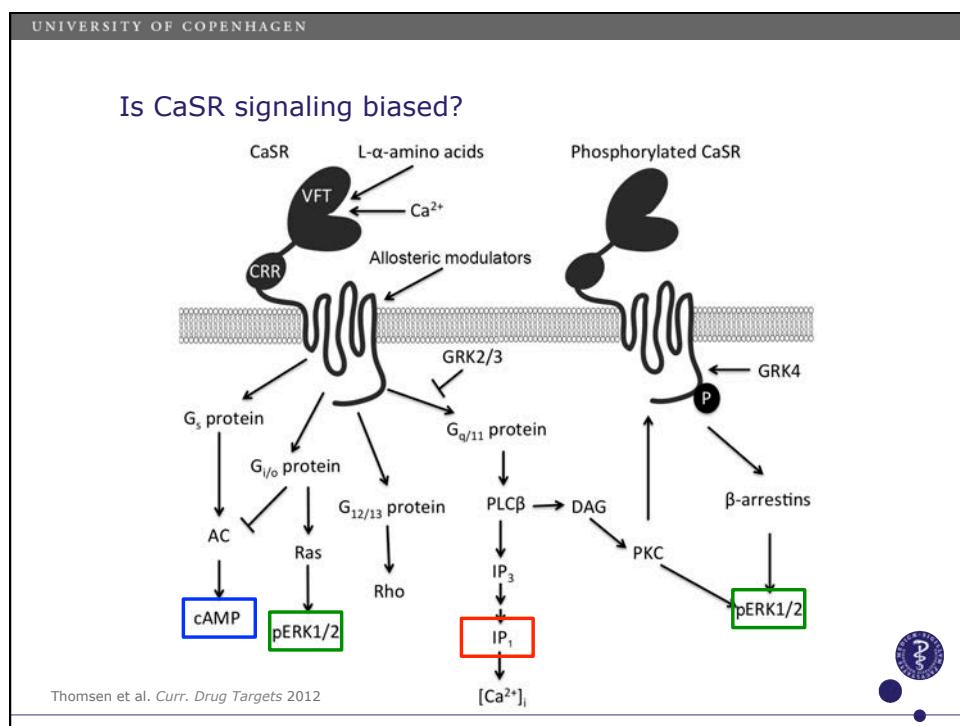
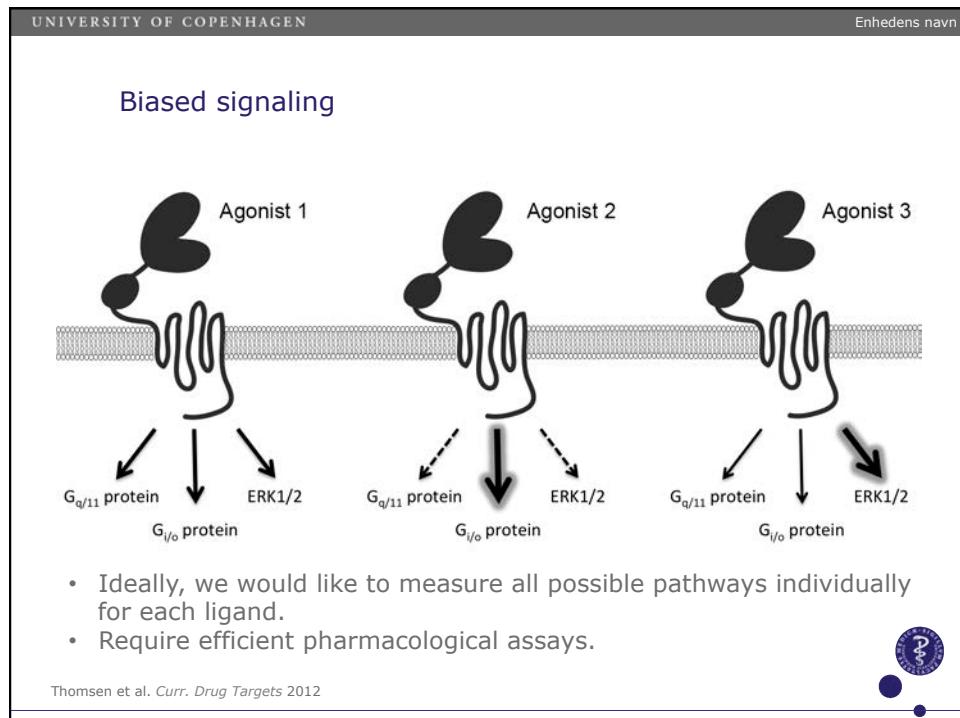


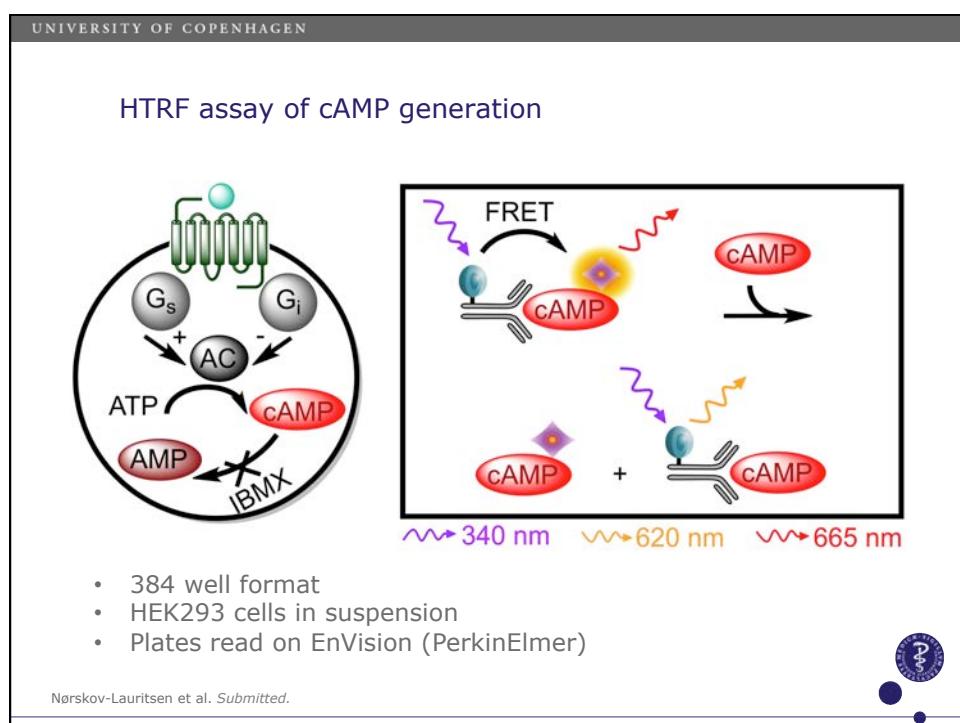
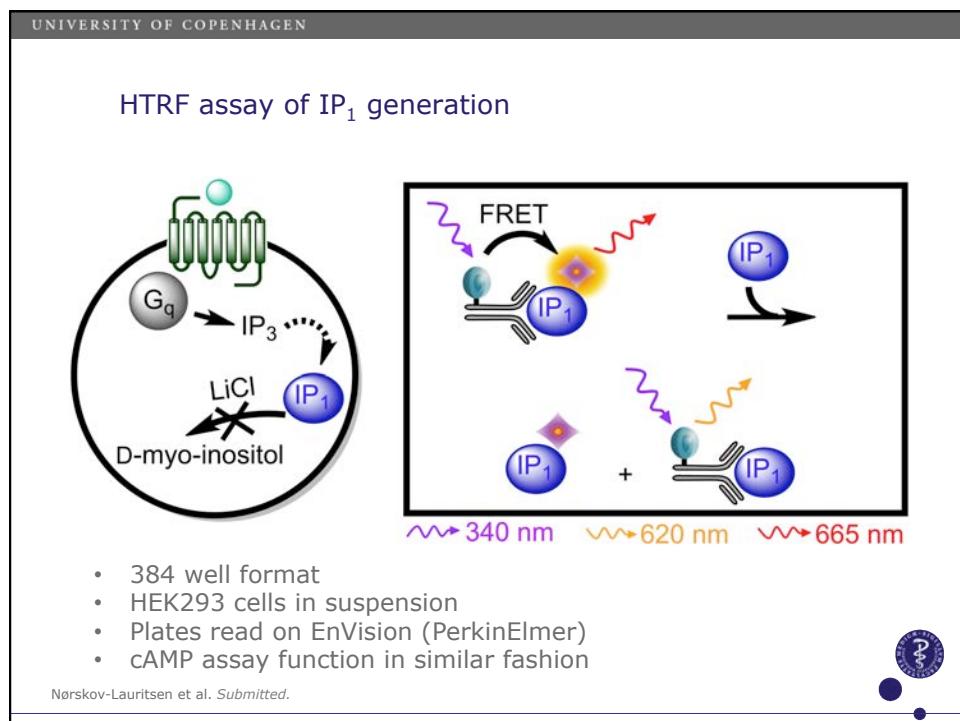
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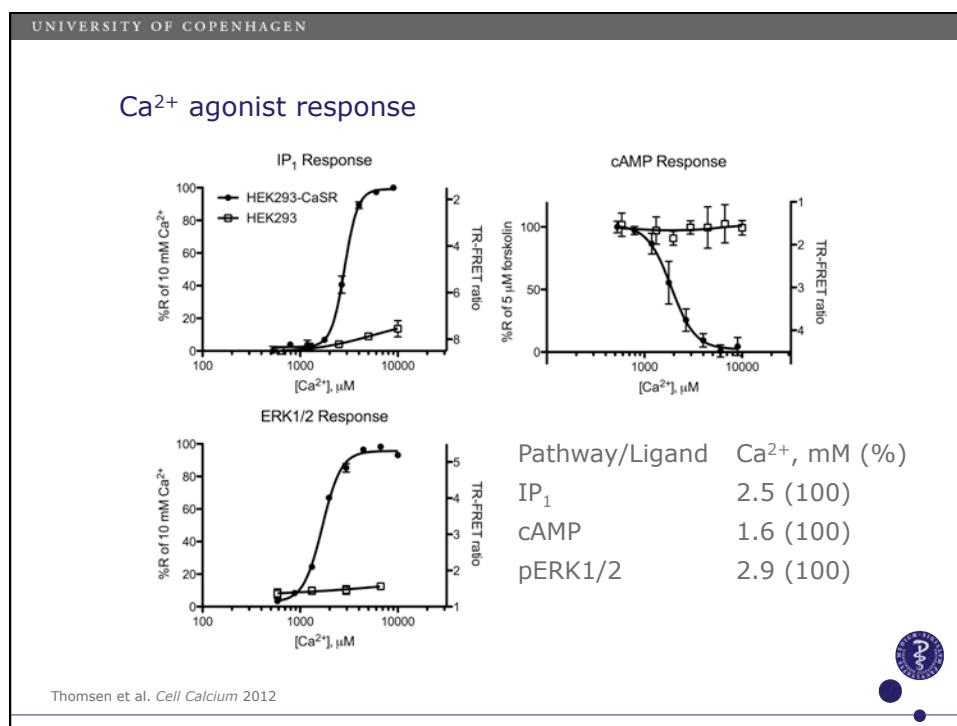
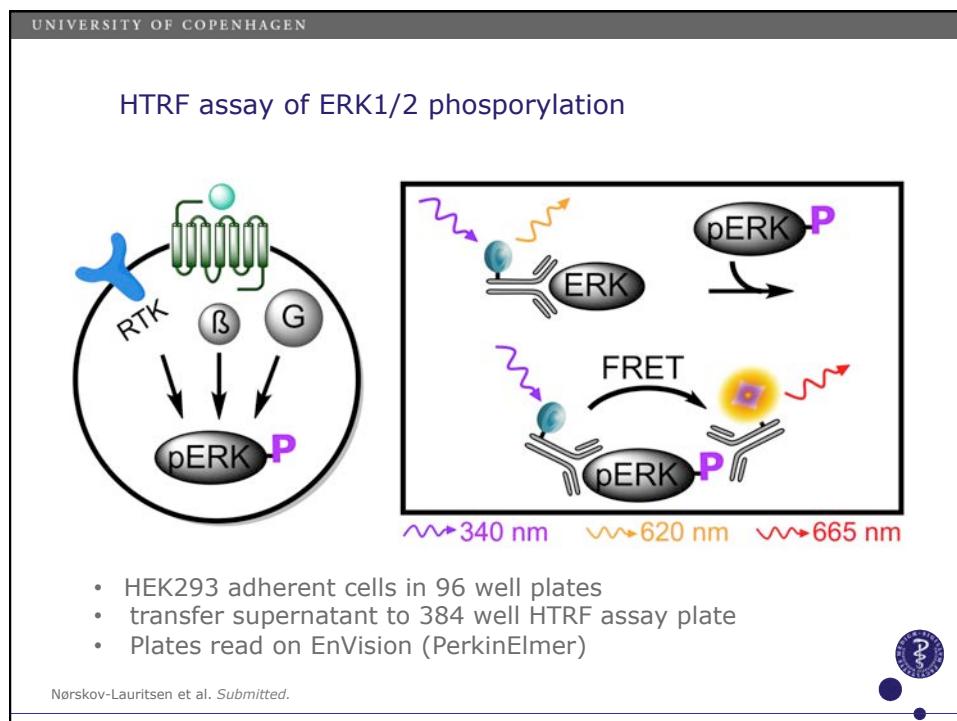
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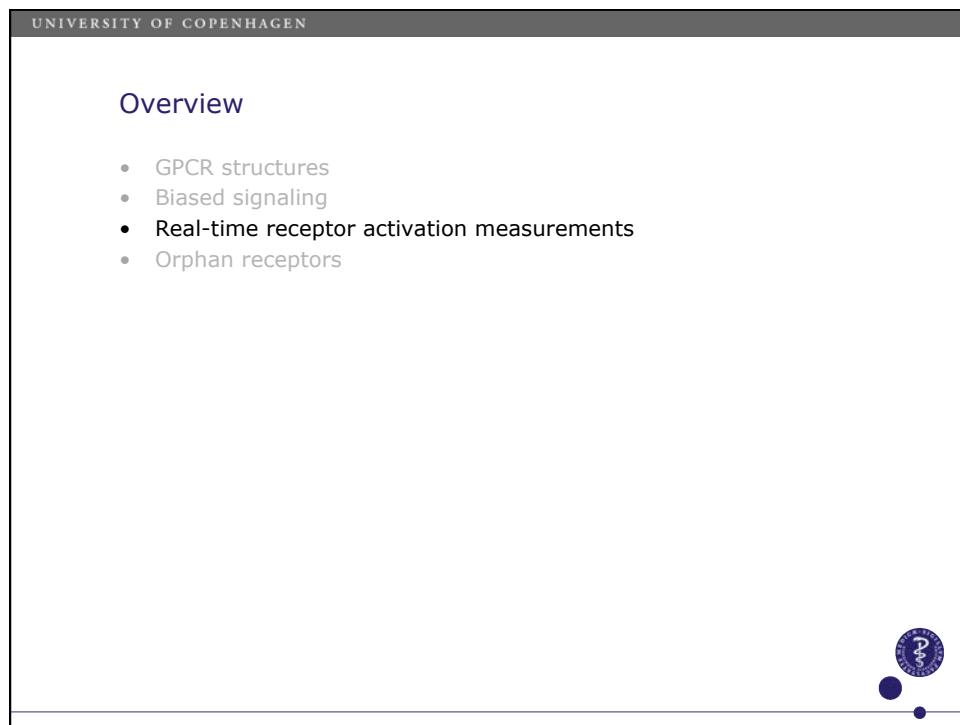
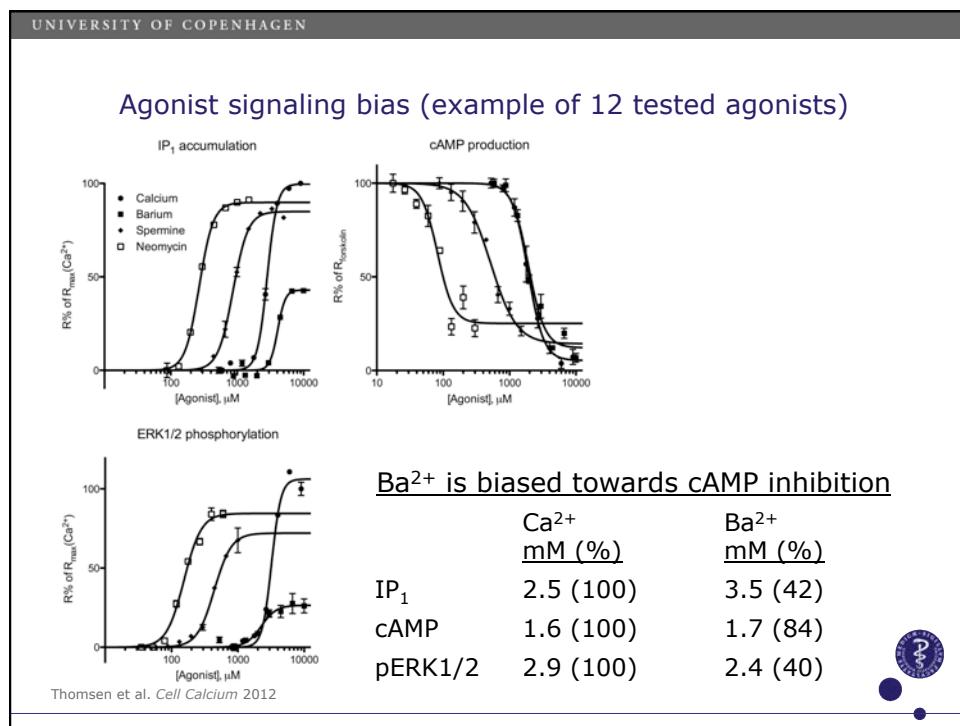
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- Online receptor activation measurements
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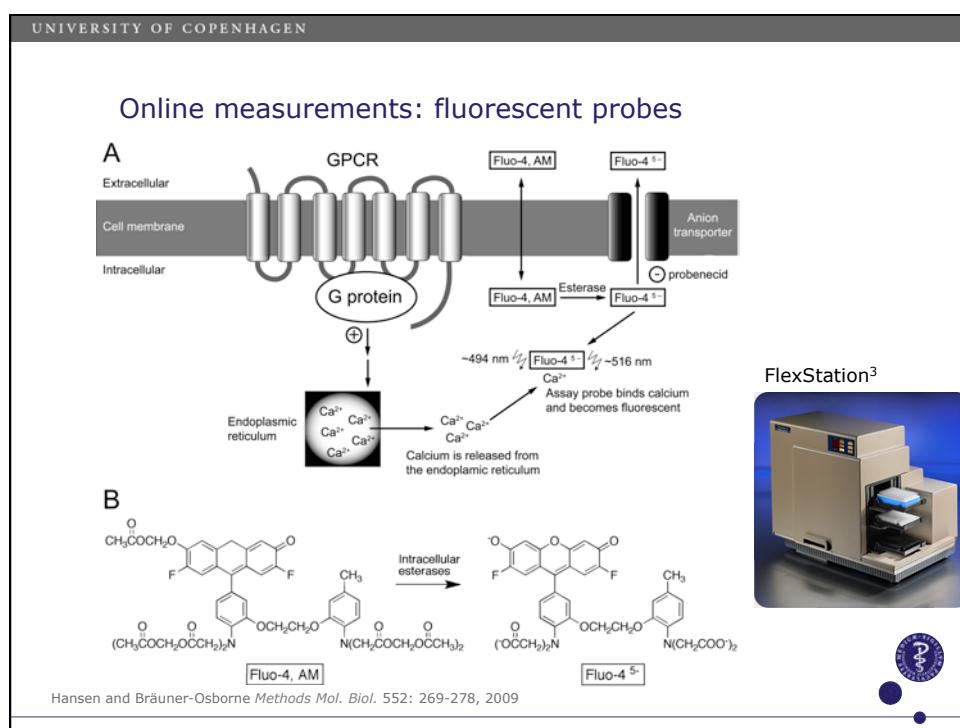
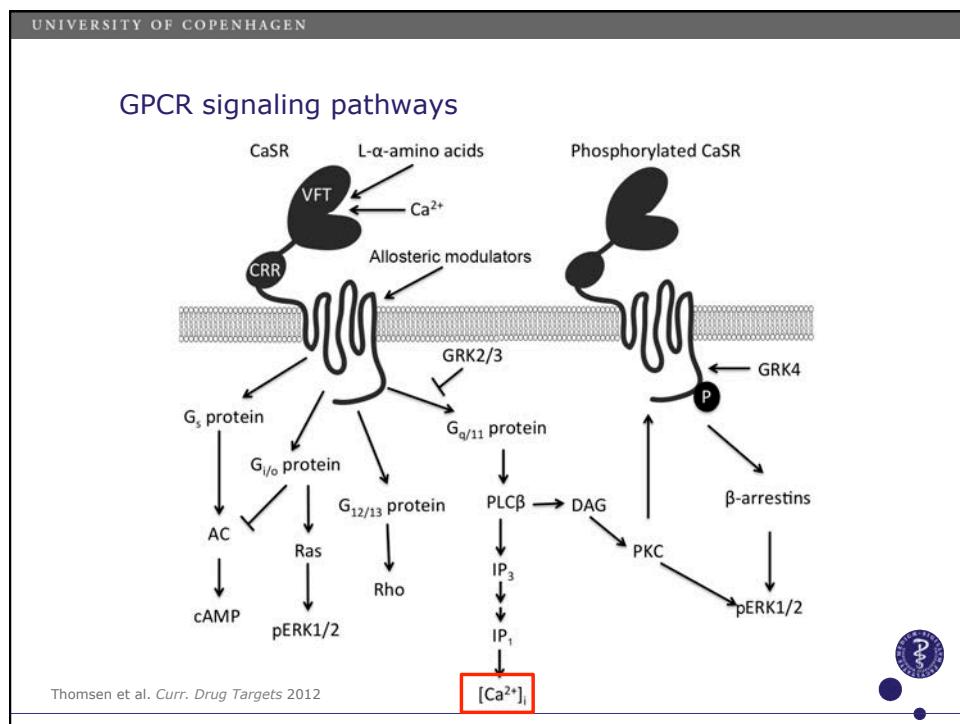



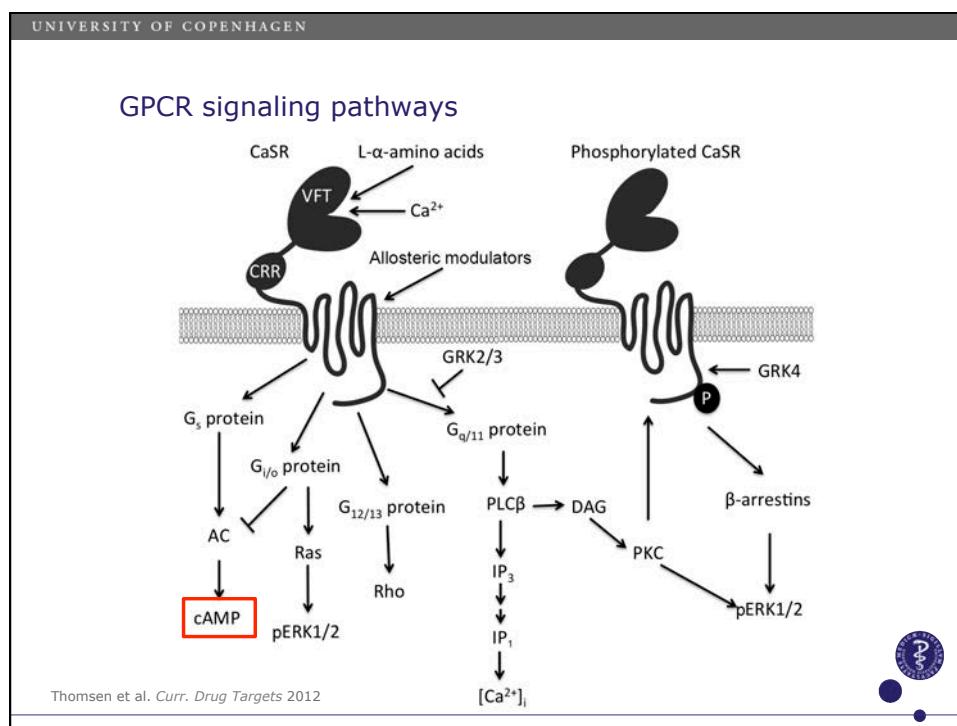
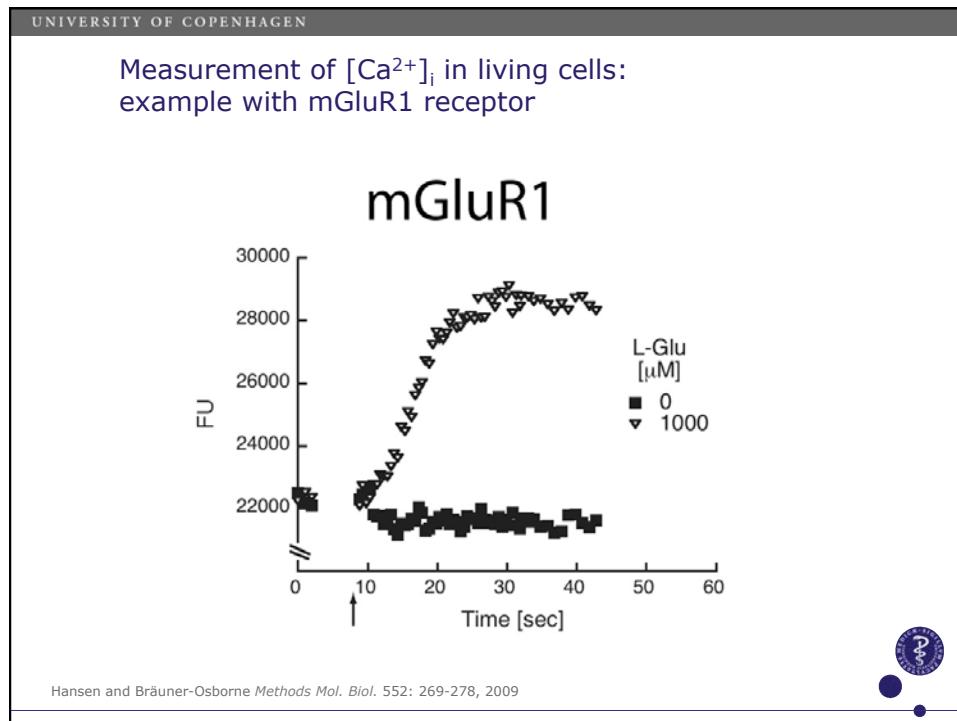


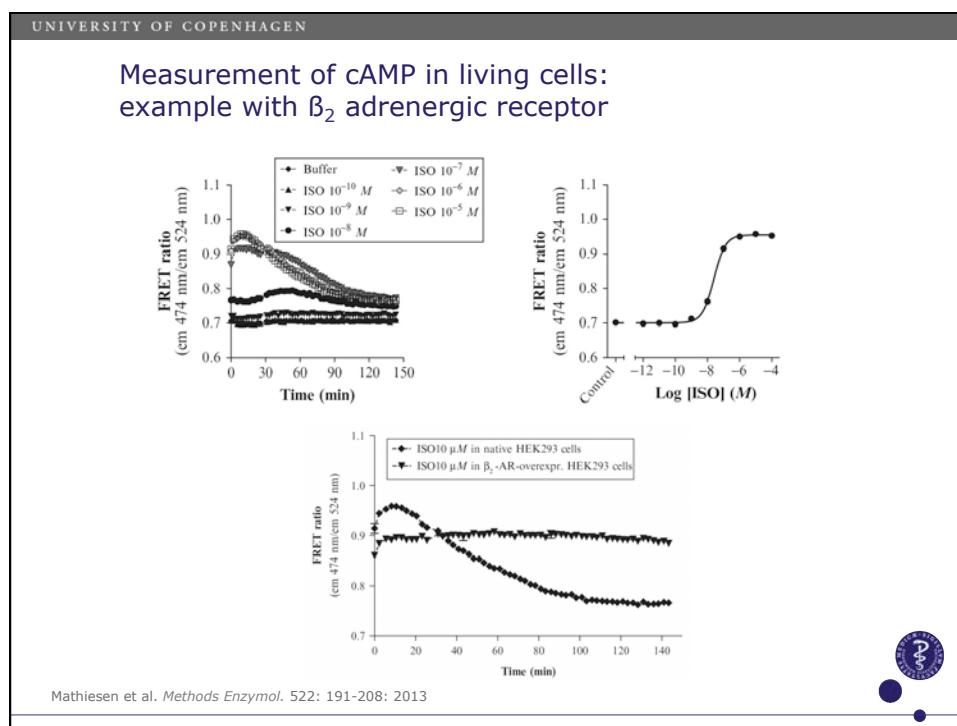
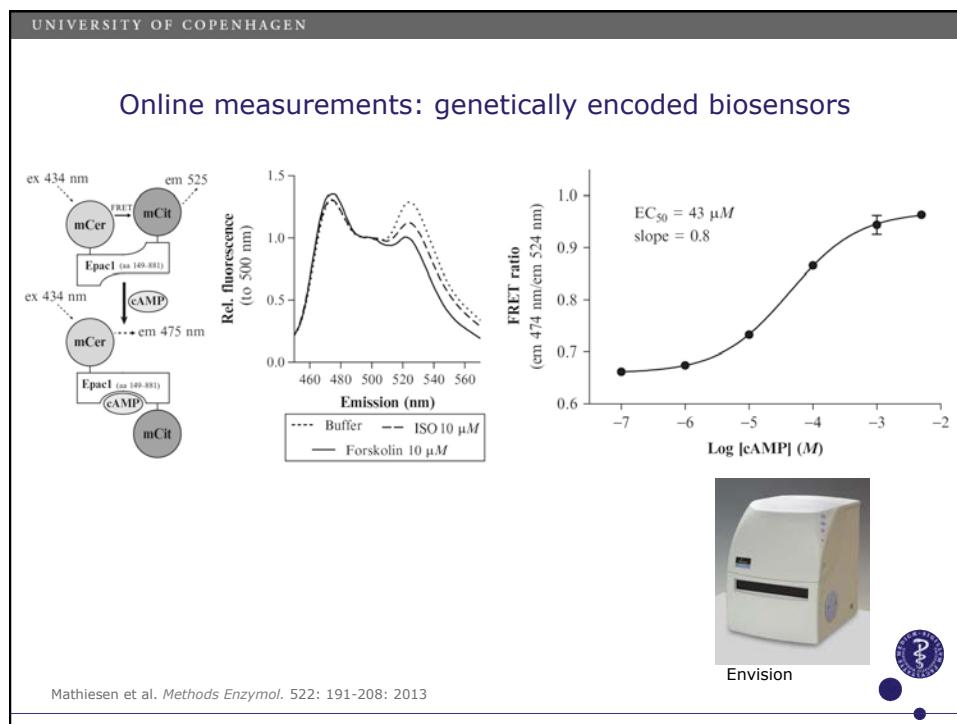


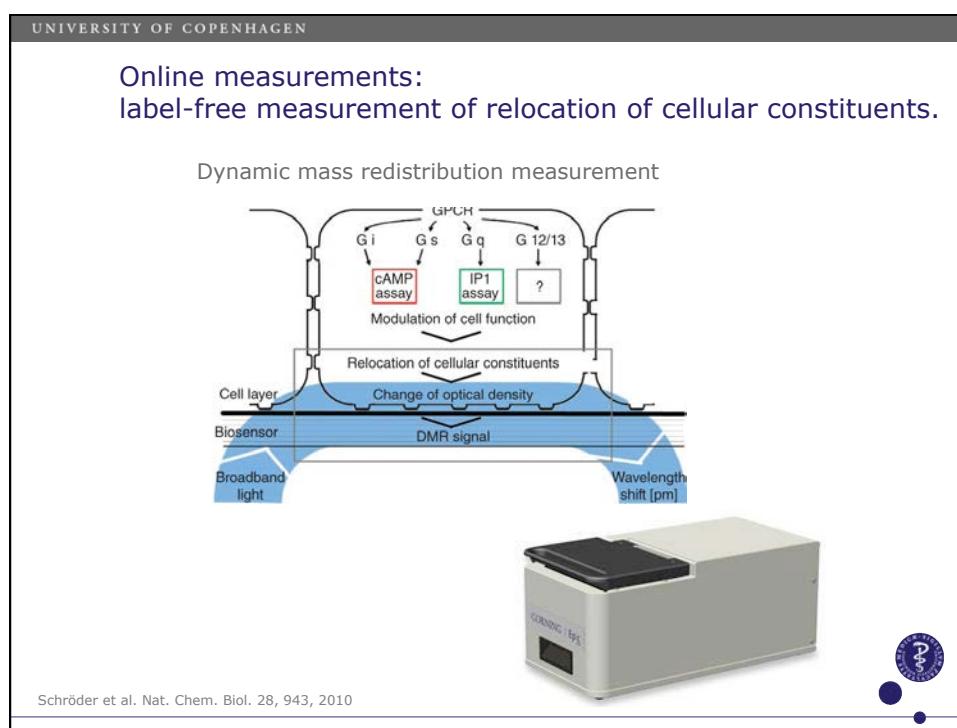
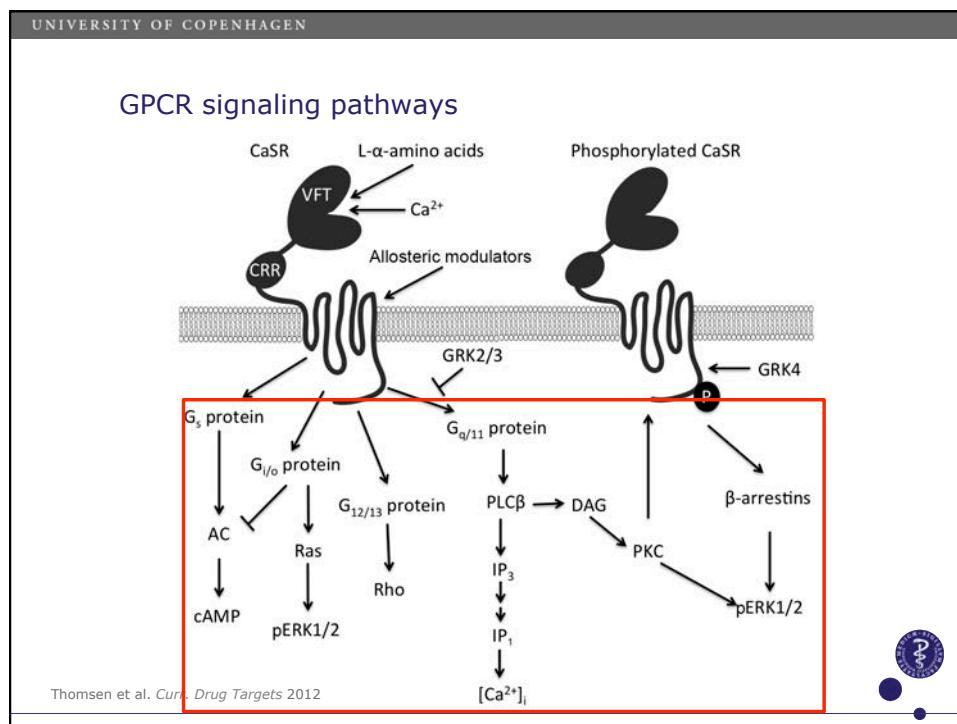


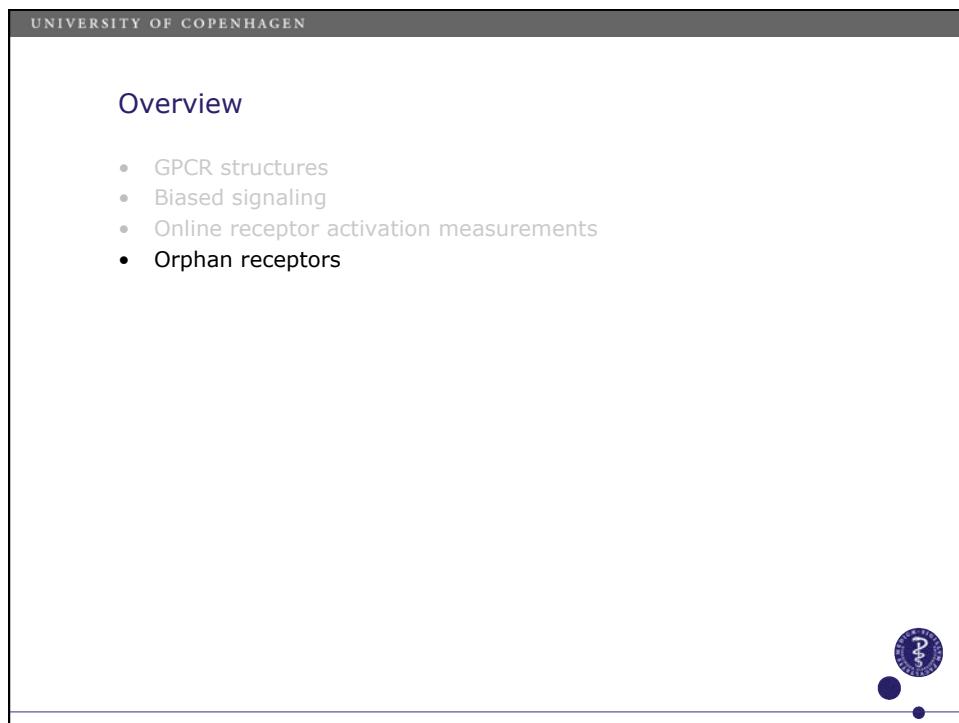
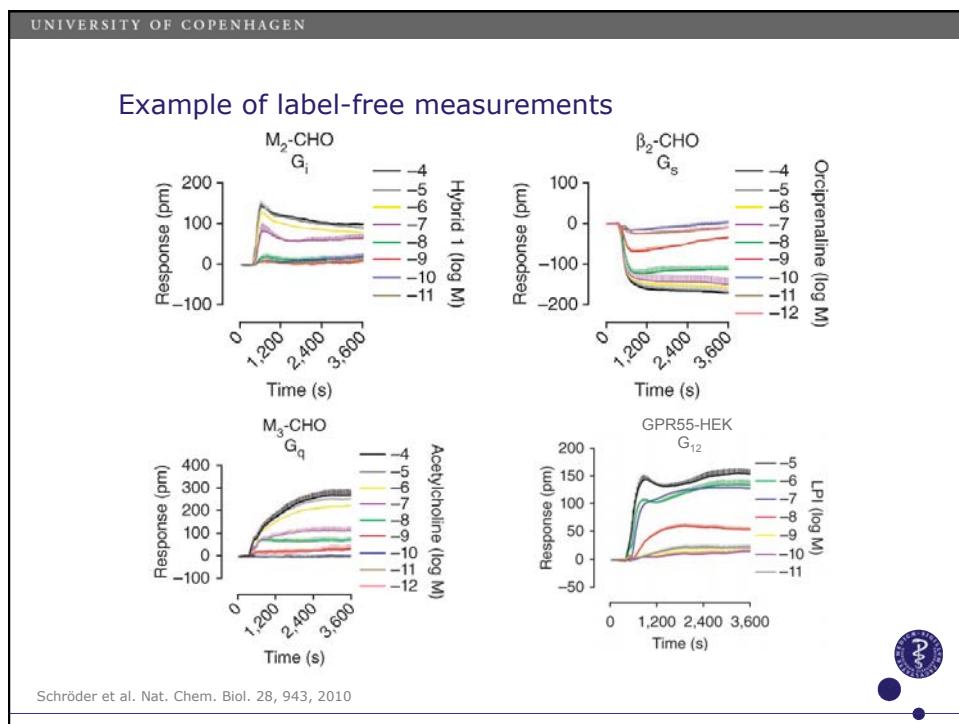


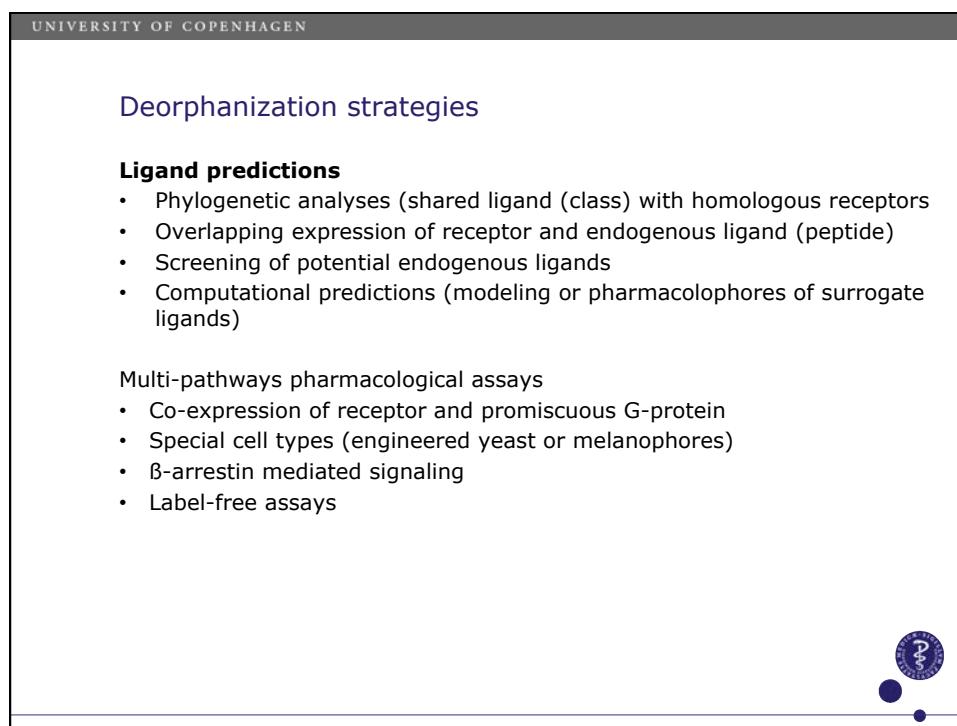
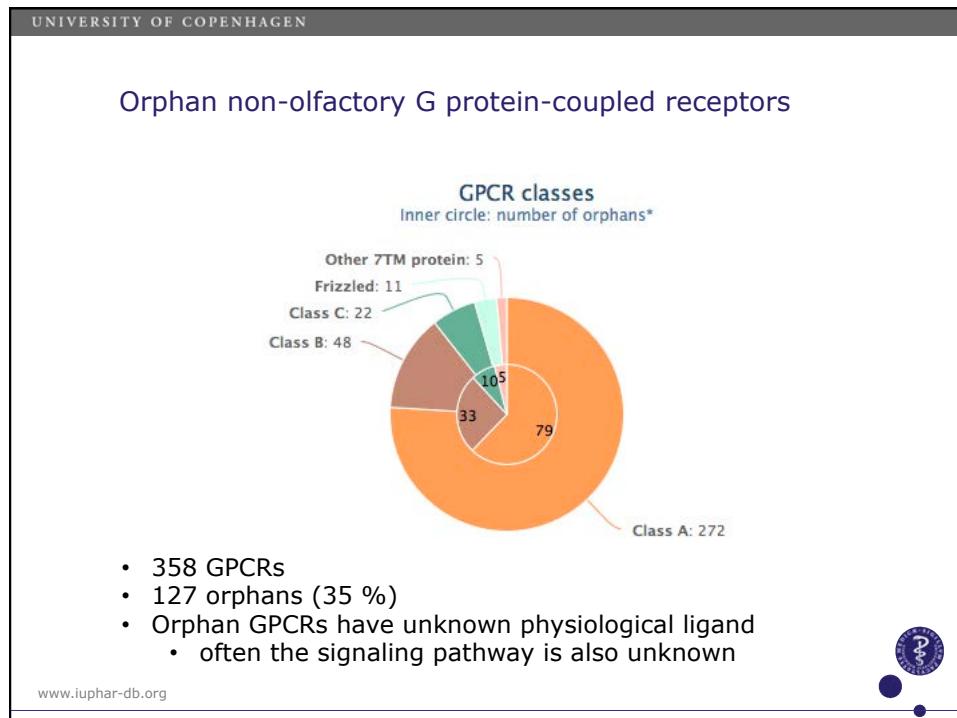


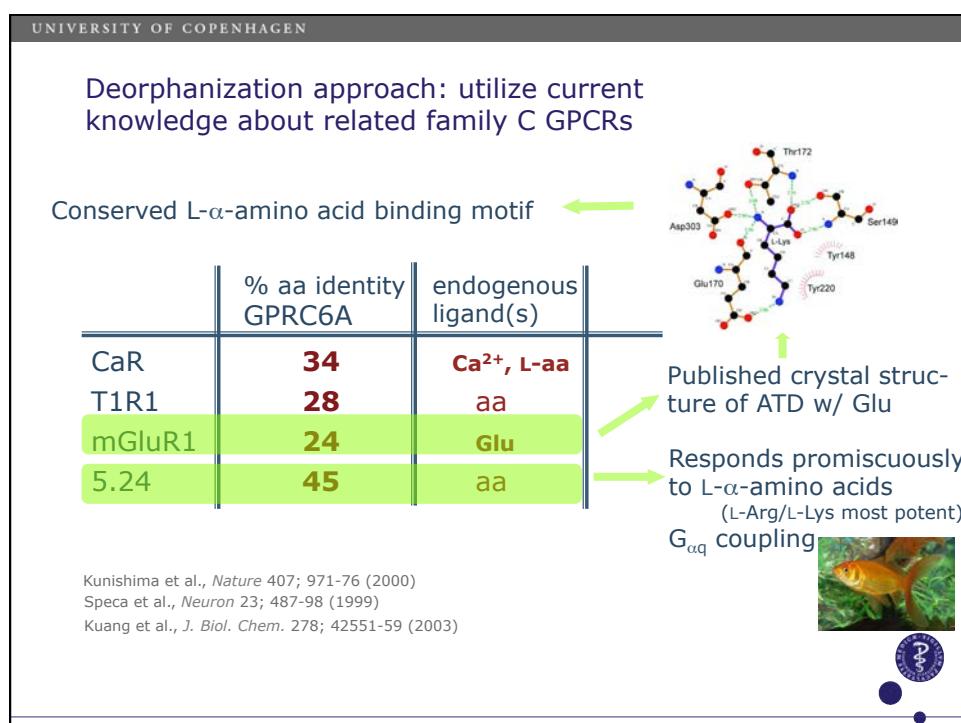
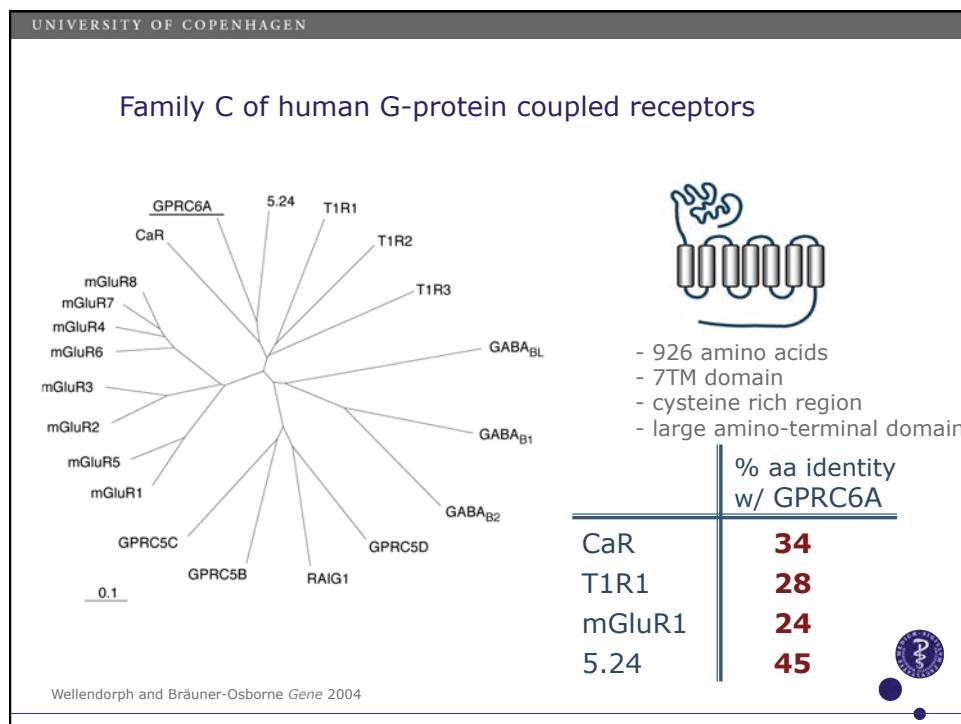












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Development of pharmacological assay

Problem:

- mammalian cell culture media contains high levels of putative agonists

Solution:

Expression in *Xenopus* oocytes

