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Diversity in the binding interactions of nicotinic ligands to the nAChRs and associated conformational fluctuations: Insights into the core motif dictating antagonism (JMC 2019, Poster)

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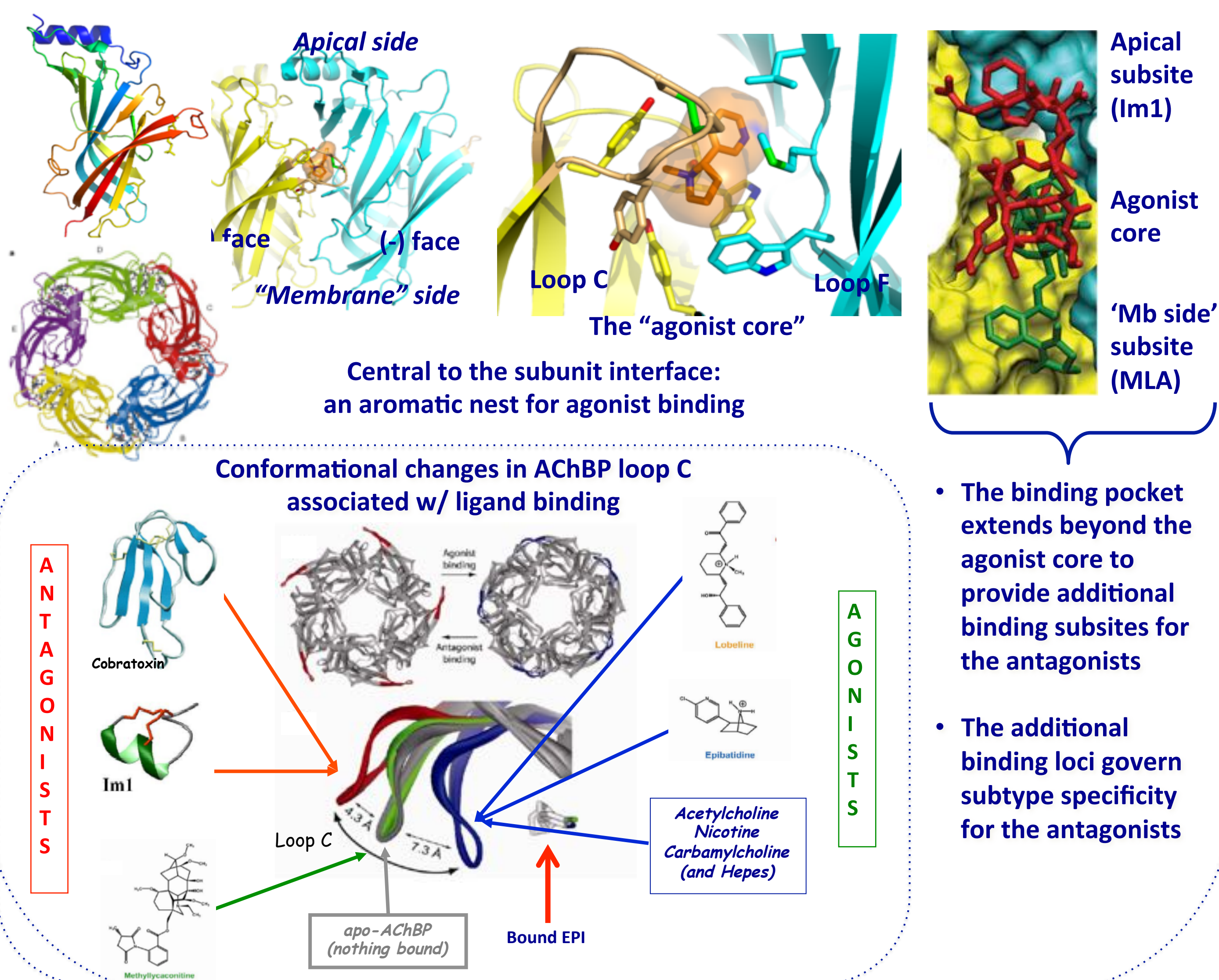
Diversity in the binding interactions of nicotinic ligands to the nAChRs and associated conformational fluctuations: Insights into the core motif dictating antagonism

Bourne Y¹, Sulzenbacher G¹, Radić Z², Chabaud L³, Aráoz R⁴, Benoit E⁴, Zakarian A⁵, Servent D⁴, Guillou C³, Taylor P², Molgo J⁴, & Marchot P¹



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1- Binding of nicotinic antagonists and agonists to the soluble, homopentameric nAChR surrogate, AChBP



2- Marine phycotoxins from dinoflagellate organisms

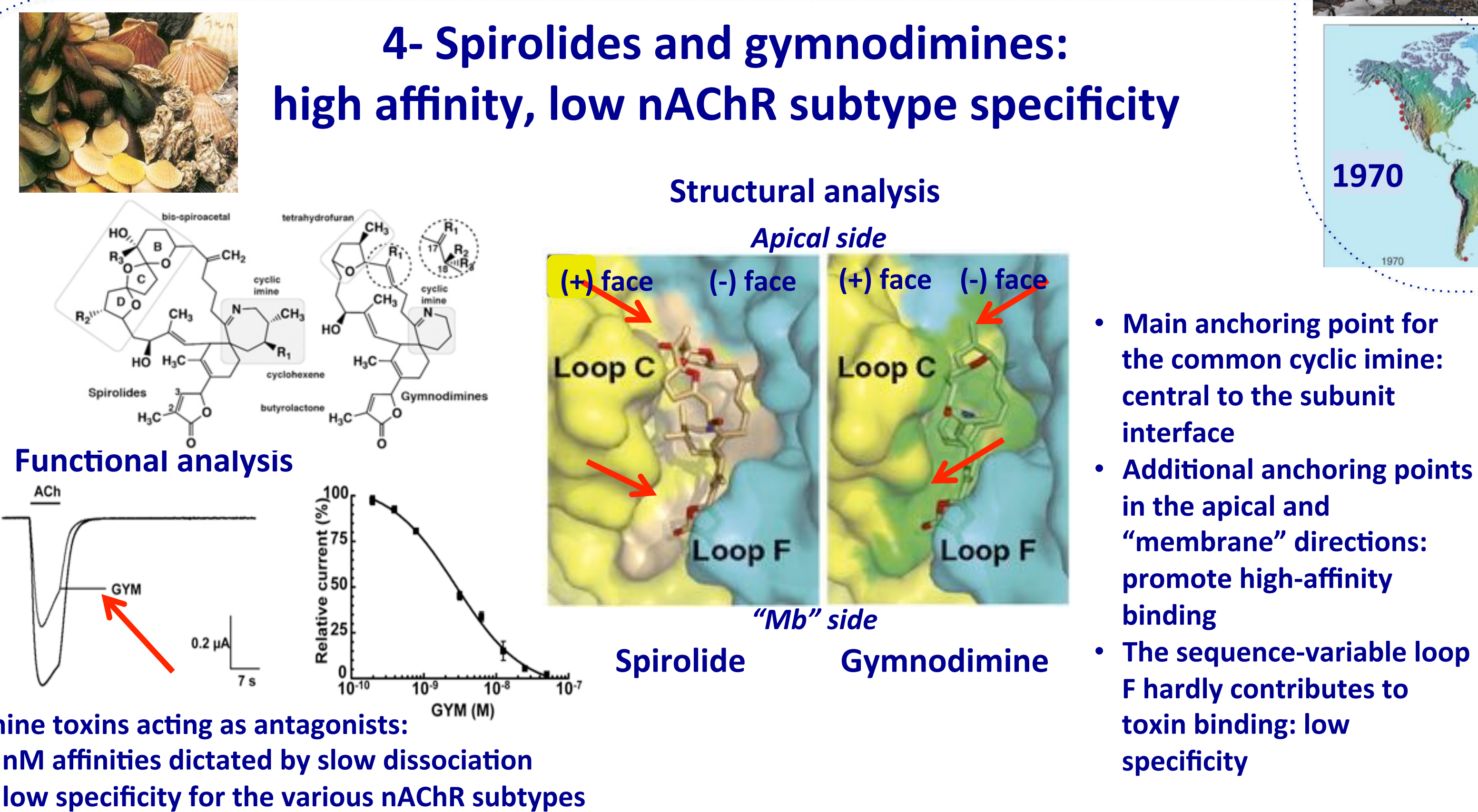


3- A combination of experimental approaches

- Synthesize toxins and analogs with controlled (+/-) and (R/S) properties
- Define mode of action, affinity, and subtype specificity for nAChR subtypes* in the membrane state (transfected oocytes), using voltage-clamp electrophysiology
- Record affinity and subtype specificity by competition binding at equilibrium to nAChR subtypes* in the membrane state (transfected HEK cells)
- Record kinetics and affinities for binding to soluble AChBP subtypes and mutants
- Crystallize (by hand!) the preformed AChBP complexes and solve their crystal structures

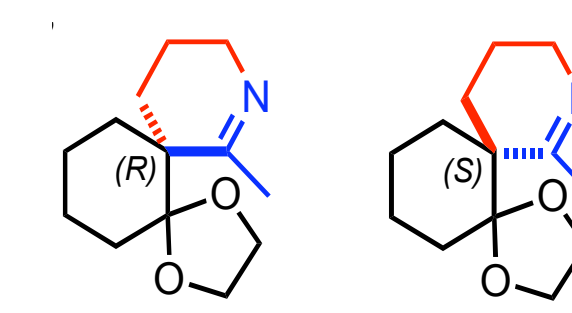
*muscle-type $\alpha_1\beta\gamma\delta$ and neuronal α_7 , $\alpha_4\beta_2$, $\alpha_3\beta_4$

4- Spirolides and gymnodimines: high affinity, low nAChR subtype specificity

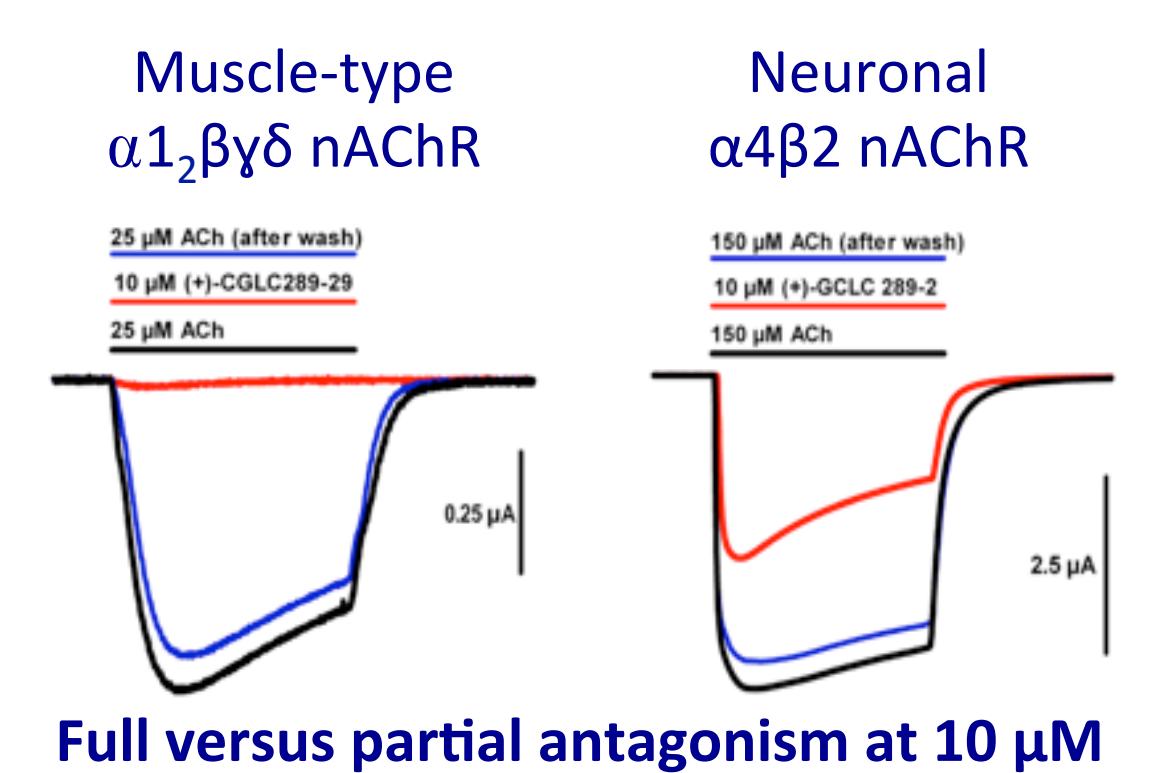


6- Is the imine core found in the macrocyclic toxins sufficient for dictating nicotinic antagonism?

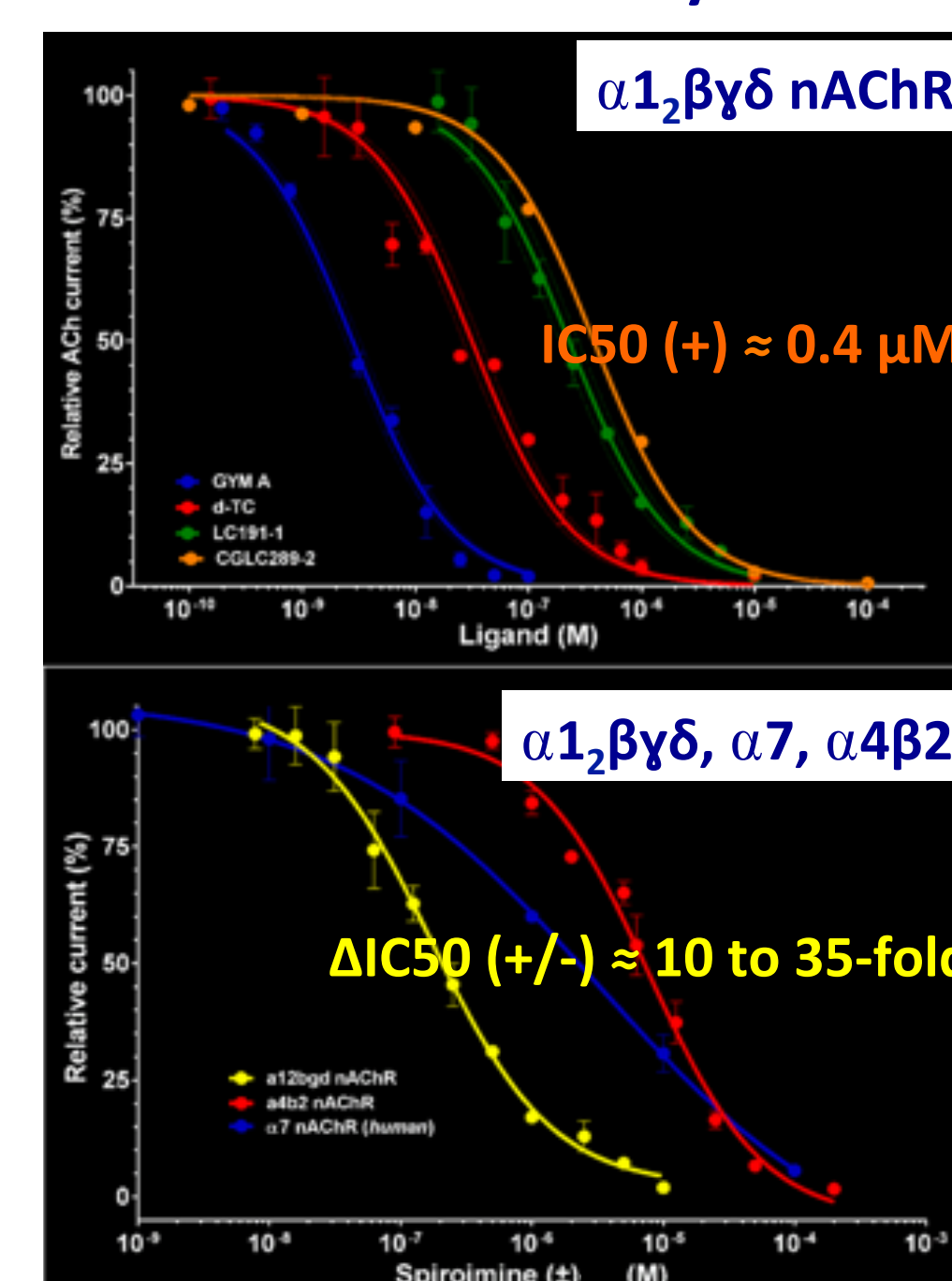
(R)-(+)- and (S)-(-)- spiroimine



Inhibition of ACh-evoked currents

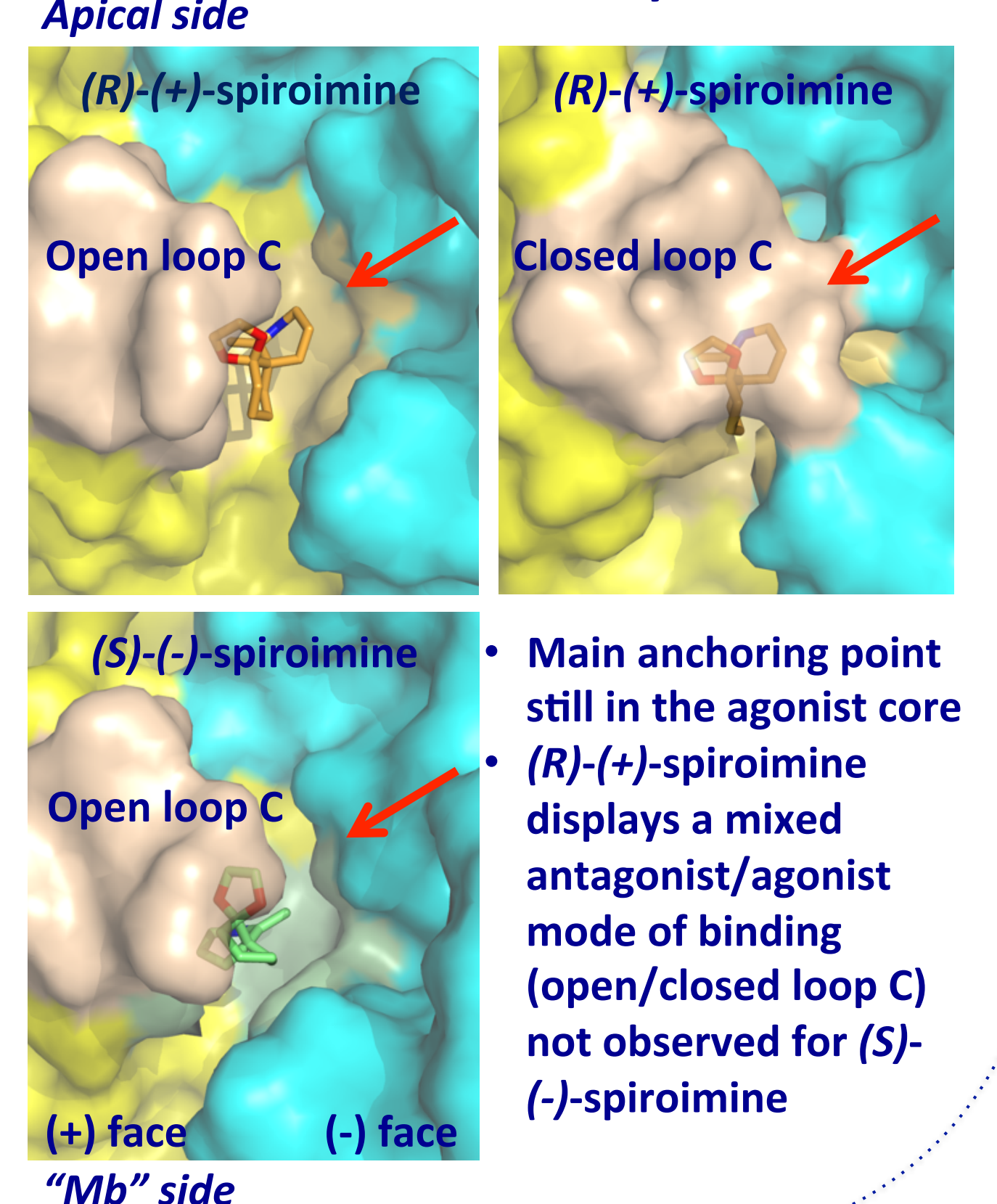


Functional analysis



- Compared with the macrocyclic imines:
- much lower affinity for the nAChRs and AChBPs, associated with limited interaction networks
 - moderate nAChR subtype specificity
 - longer term antagonistic properties

Structural analysis



5- Pinnatoxins: high affinity, high nAChR subtype specificity

