

Challenges and prospects for the use of synergistic agents in mosquito control

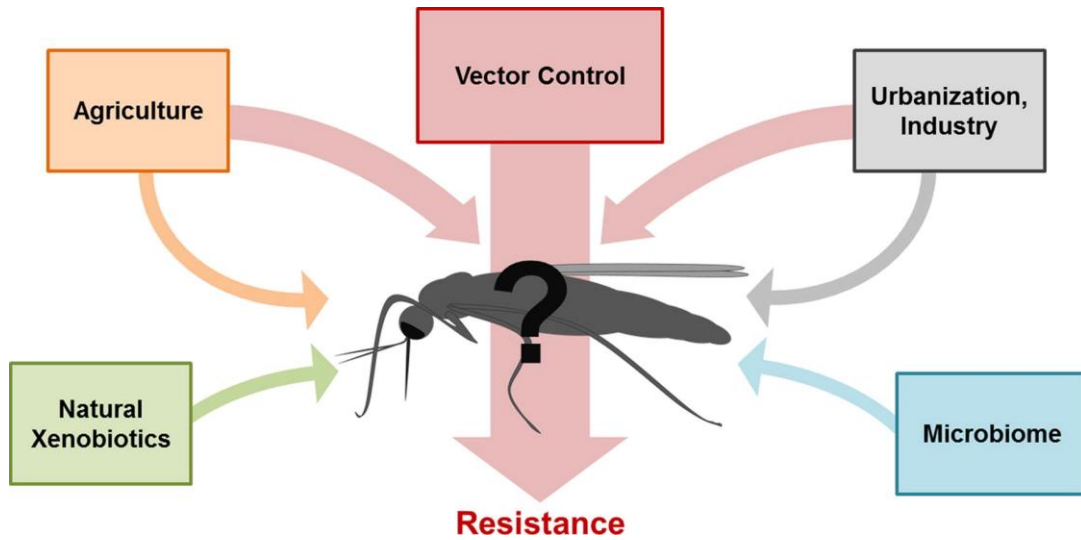
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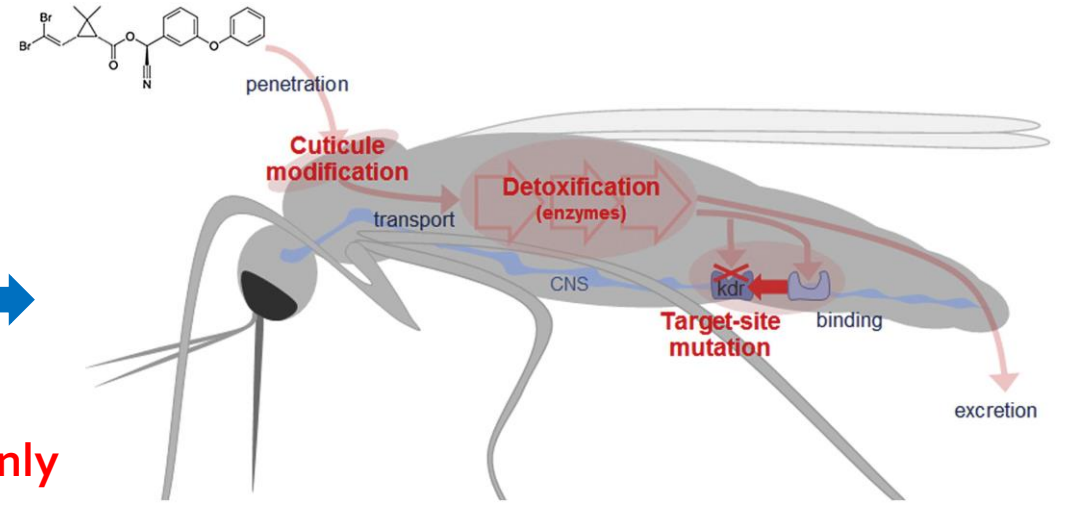
Research context



Impact of environmental parameters on pyrethroid resistance

Nkya TE, Akhouayri I., Kisinza W. David JP. *Insect Biochem. Mol. Biol.* 2013, 43

Not only



Additional parameters

Compensatory mechanisms in resistant *Anopheles gambiae* KdrKis modulating insecticide-based mosquito control

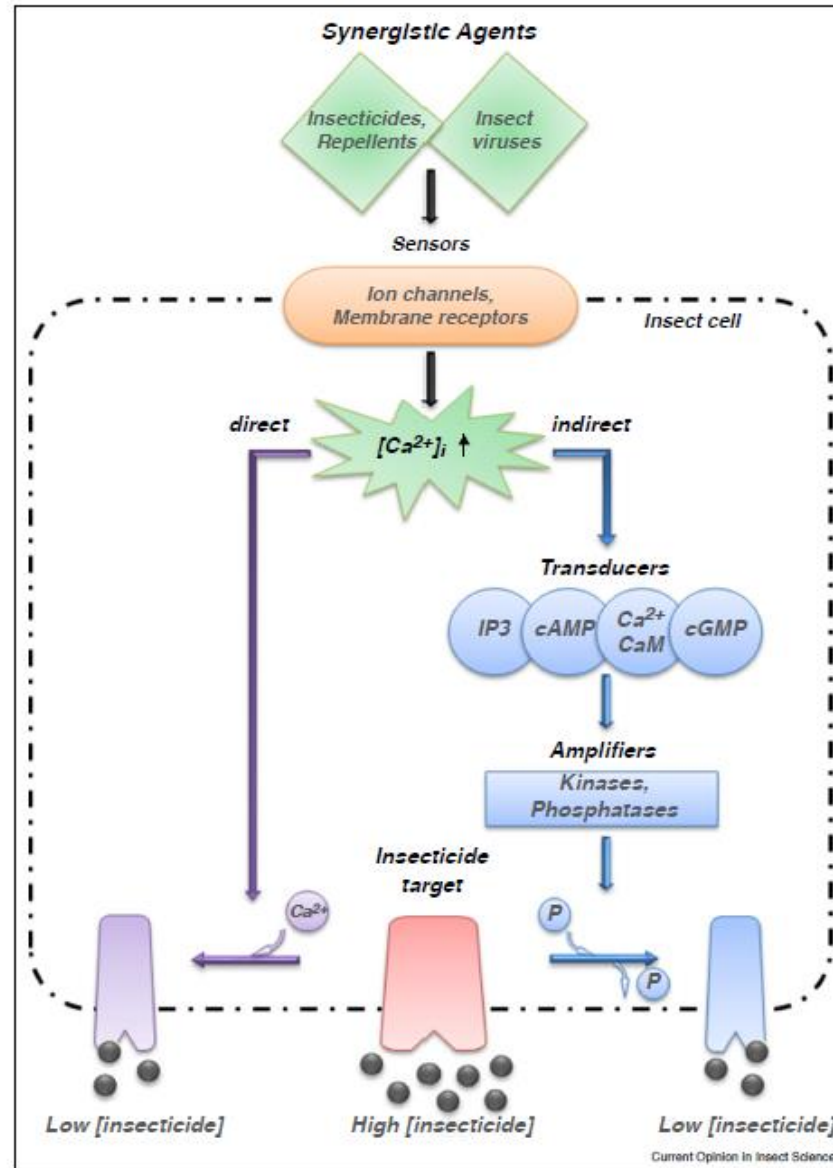
Cholinergic system = nicotinic AChR

Perrier S., Moreau E., Deshayes C., El-Adouzi M. Goven D., Chandre F. & Lapied B. *Comm. Biol.* 2021, 4

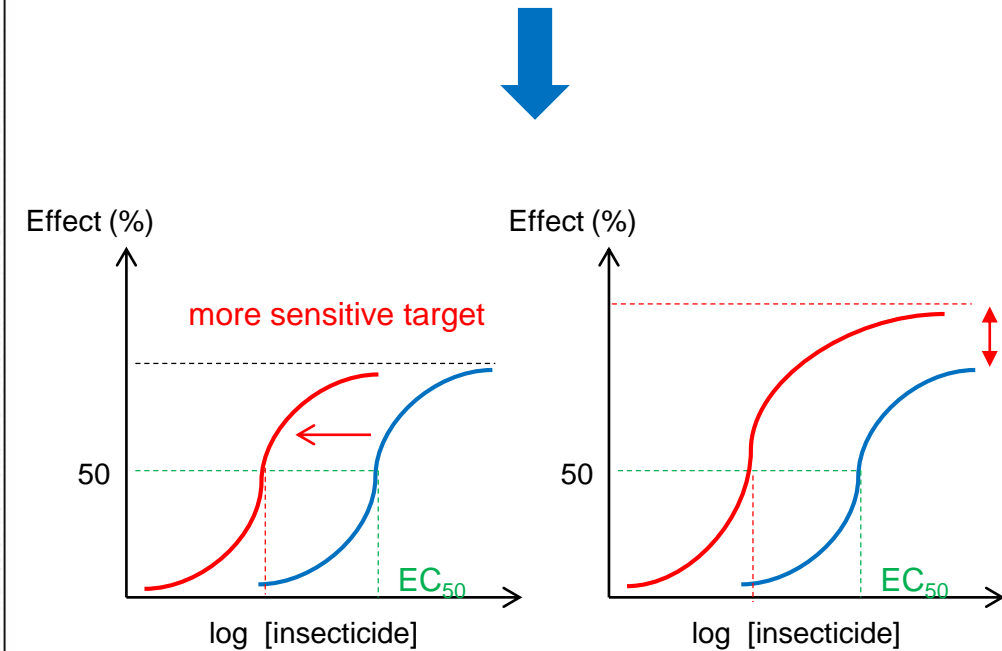
A synergistic agent **is not** a synergist

At non-toxic concentrations, a synergistic agent acts by **activating certain calcium-dependent intracellular signalling pathways**

Deshayes C., Moreau E., Pitti-Caballero J., Froger JA., Apaire-Marchais V. & Lapied B. Curr. Opin Insect Sci., 2018, 30.

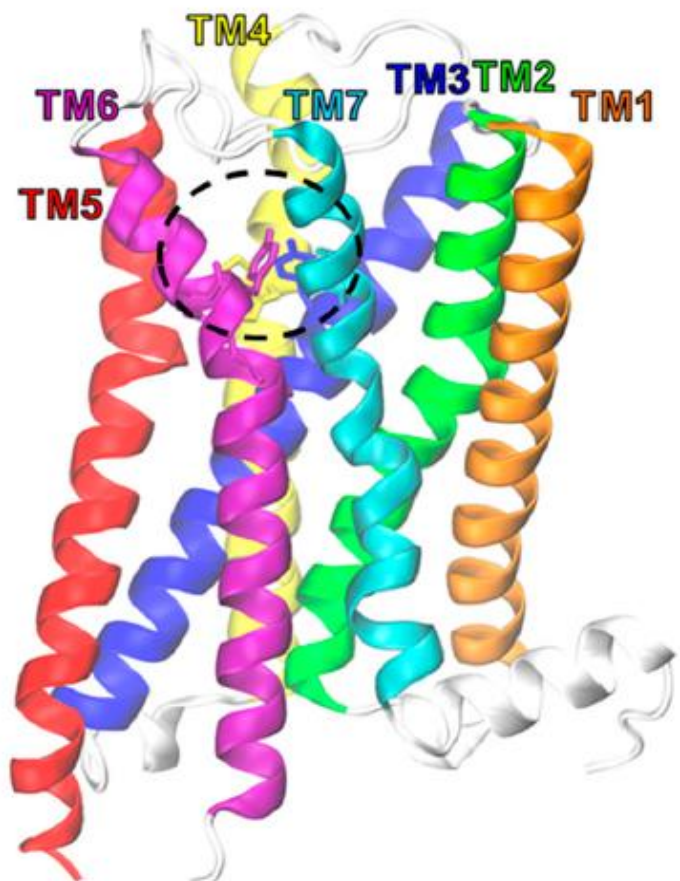


A synergistic agent is a chemical that **indirectly enhances the effectiveness of several class of insecticides**, although they usually have no effect or only a limited effect themselves.



This leads to sensitization of the insect thus **increasing the efficacy of the treatment.**

A product that is designed in order to prevent contact with or repel biting insects or arthropods.



Interaction of the repellent with the orthosteric site of the insect **GPCR**

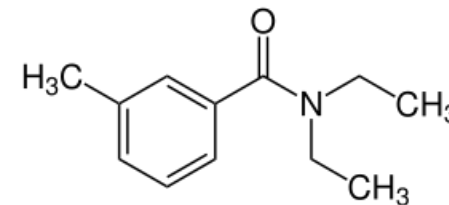
Insect repellent



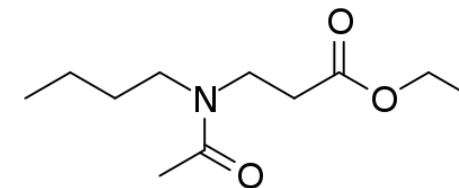
In ancient Roman religion and myth, **Janus** is the god with two faces



Niklas B, Lapied B. & Nowak W. molecules, 2022, 27



DEET



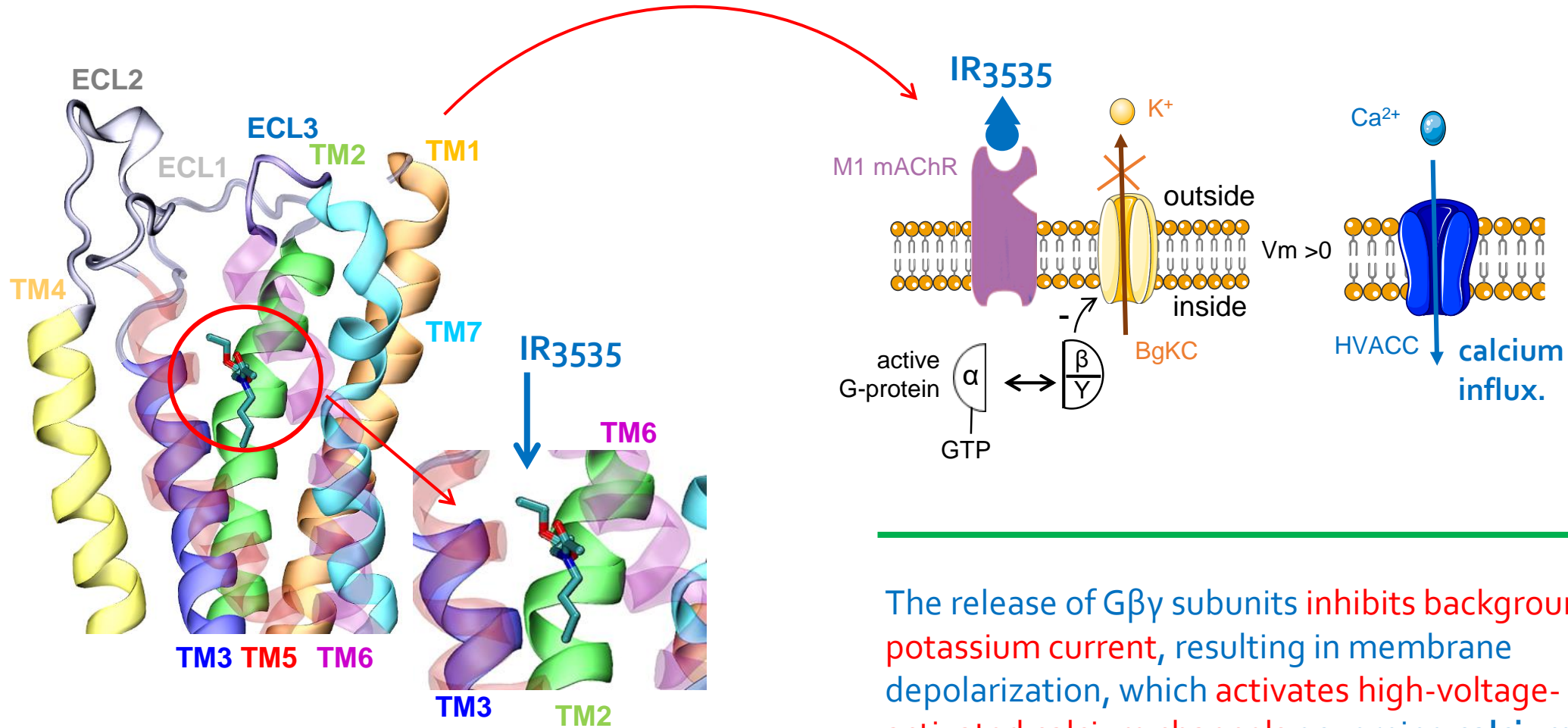
IR3535

The insect repellents as synergistic agent to potentiate insecticide effect



Unexpected membrane target site
G-Protein Coupled Receptor
intracellular calcium rise

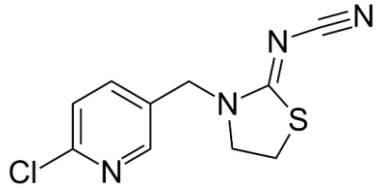
Orthosteric muscarinic receptor activation by IR3535



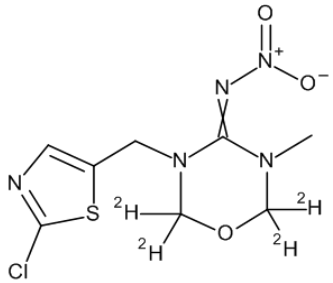
Moreau E., Mikulska-Ruminska K., Goulu M., Perrier S., Deshayes D., Stankiewicz M., Apaire-Marchais V., Nowak W. & Lapied B. *Sci. Rep.*, 2020, 10

The release of Gβγ subunits **inhibits background potassium current**, resulting in membrane depolarization, which **activates high-voltage-activated calcium channels** governing **calcium influx**.

In vitro evaluation



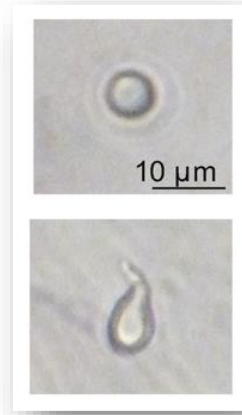
Thiacloprid
Cyanoimine (NCN, IRAC 4A)



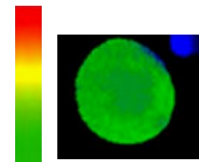
Thiamethoxam
Nitroimine (NNO₂, IRAC 4A)

Two types of neonicotinoid insecticides acting on distinct nicotinic receptor sites producing synergistic effects

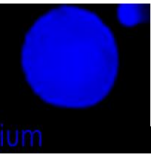
Casida JE, *Annu. Rev. Entomol.* 2018, 63



high calcium

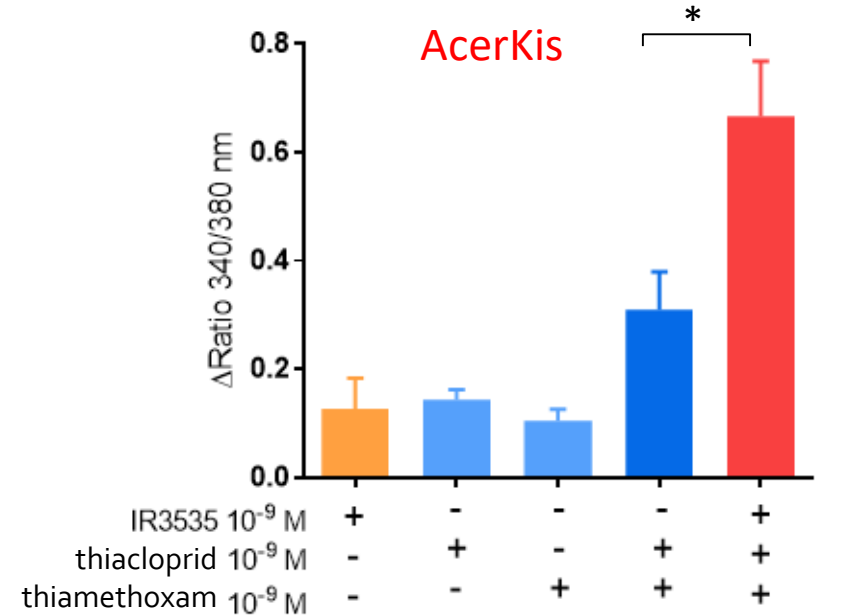
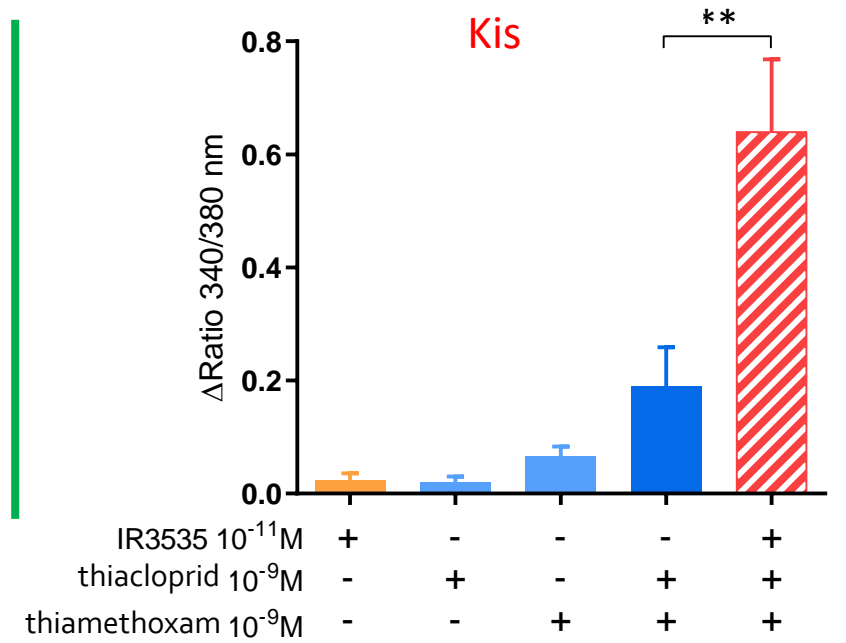
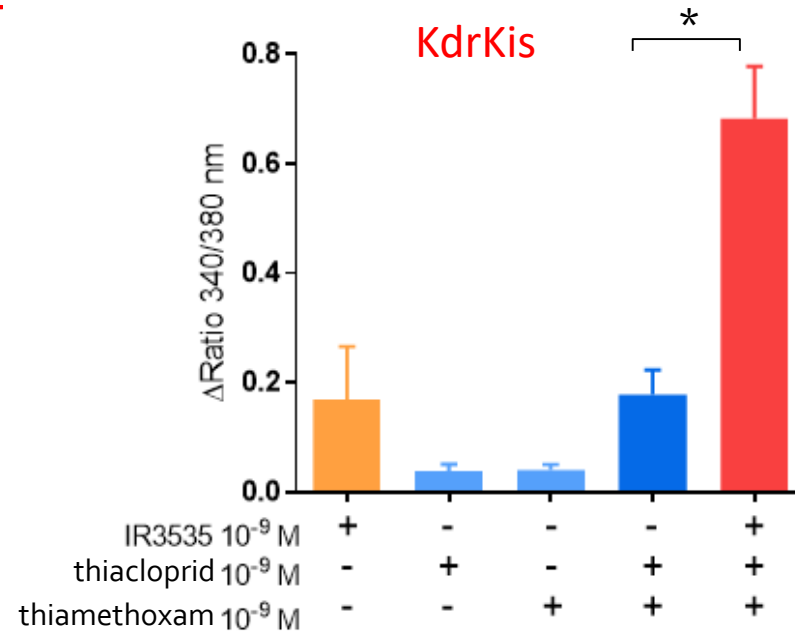


low calcium



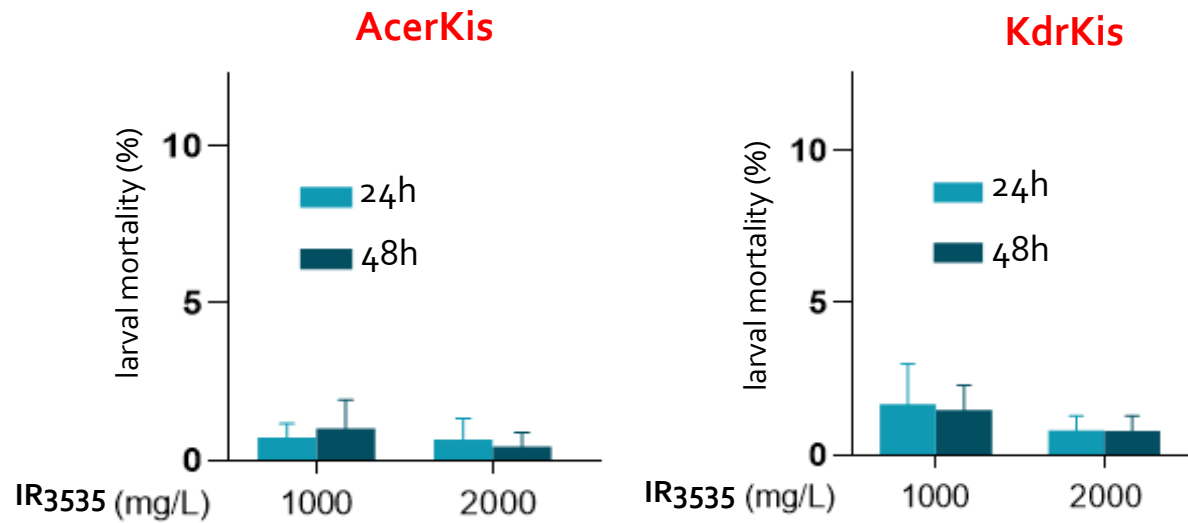
Calcium imaging
Isolated neuron
from *Anopheles gambiae* (n=6-9)

Lavialle-Defaix C., Apaire-Marchais V., Legros C., Pennetier C., Mohamed A., Licznar P., Corbel V. & Lapied B. *J. Neurosci. Meth.*, 2011, 200



In vivo evaluation

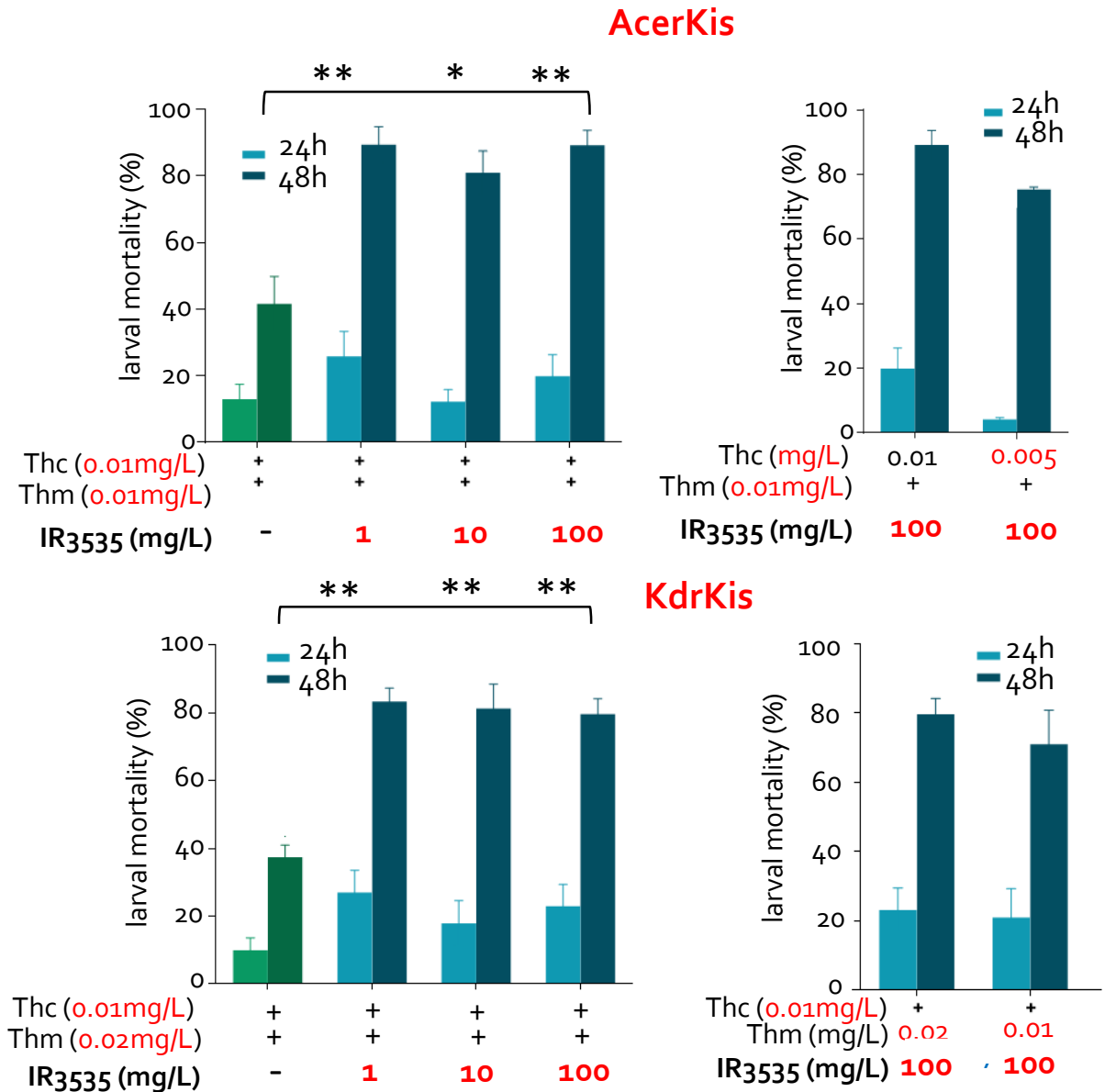
Larval susceptibility of *Anopheles gambiae* **AcerKis** and **KdrKis** to IR3535 combined with thiacloprid and thiamethoxam



Evaluation of the toxicity of IR3535 alone at relatively high concentration

Increasing insecticide effect while reducing the concentration

International application
PCT/EP2021/067833

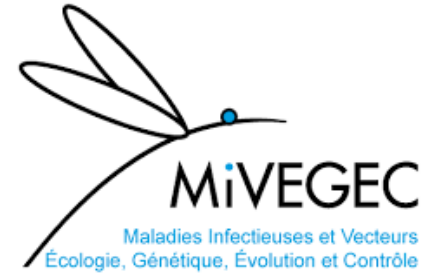




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*Fabrice Chandre
Carole Ginibre*

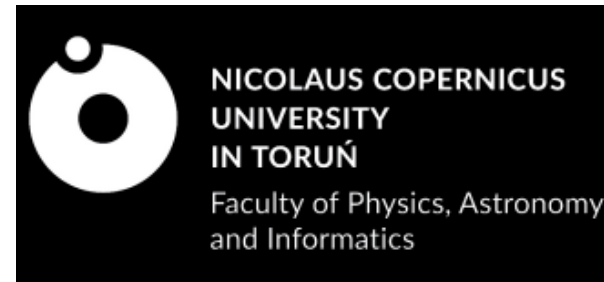
**Thank you
for your attention !**



Stéphane Perrier



CE PROJET EST COFINANCÉ PAR
LE FONDS EUROPÉEN DE DÉVELOPPEMENT RÉGIONAL



*Beata Niklas
Karolina Mikulska-Rumin
Wieslaw Nowak*

