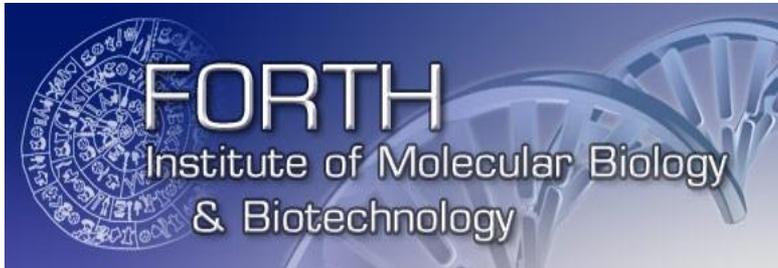
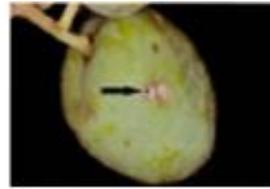


Η συμβολή της βιοτεχνολογίας στη μάχη εναντίον των εντόμων
και στην αντιμετώπιση της ανθεκτικότητας στα εντομοκτόνα

Γιάννης Βόντας



Molecular Entomology / Pesticide Science lab





Food and Agriculture Organization
of the United Nations



”Agricultural output has to double in the next 20-30 years, to feed the world’s population

Insect substantially decrease availability and cost of food: PESTICIDES (80% insect control market) save 50% agricultural outcome worldwide



“..malaria has halved since 2000, saving 660 million lives, with >50% of the reduction due to the use of **insecticides**, which are now under threat of resistance..”. Bhatt et al, *Nature* 527, 207 (2015).



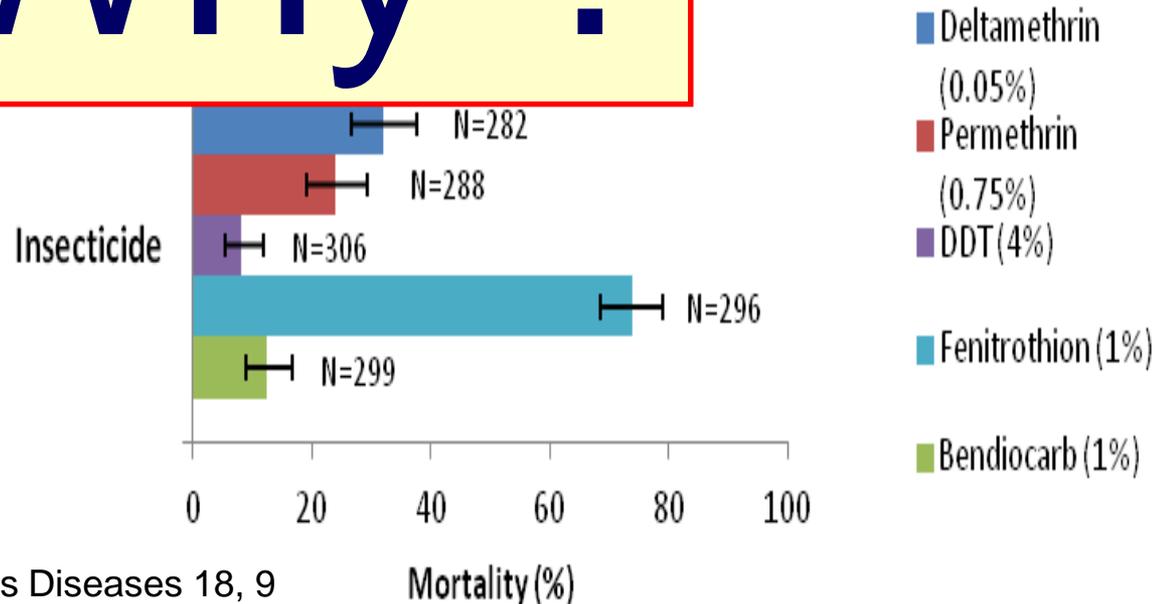
Urgent need to tackle insecticide resistance to secure the future of malaria prevention by insecticide based vector control

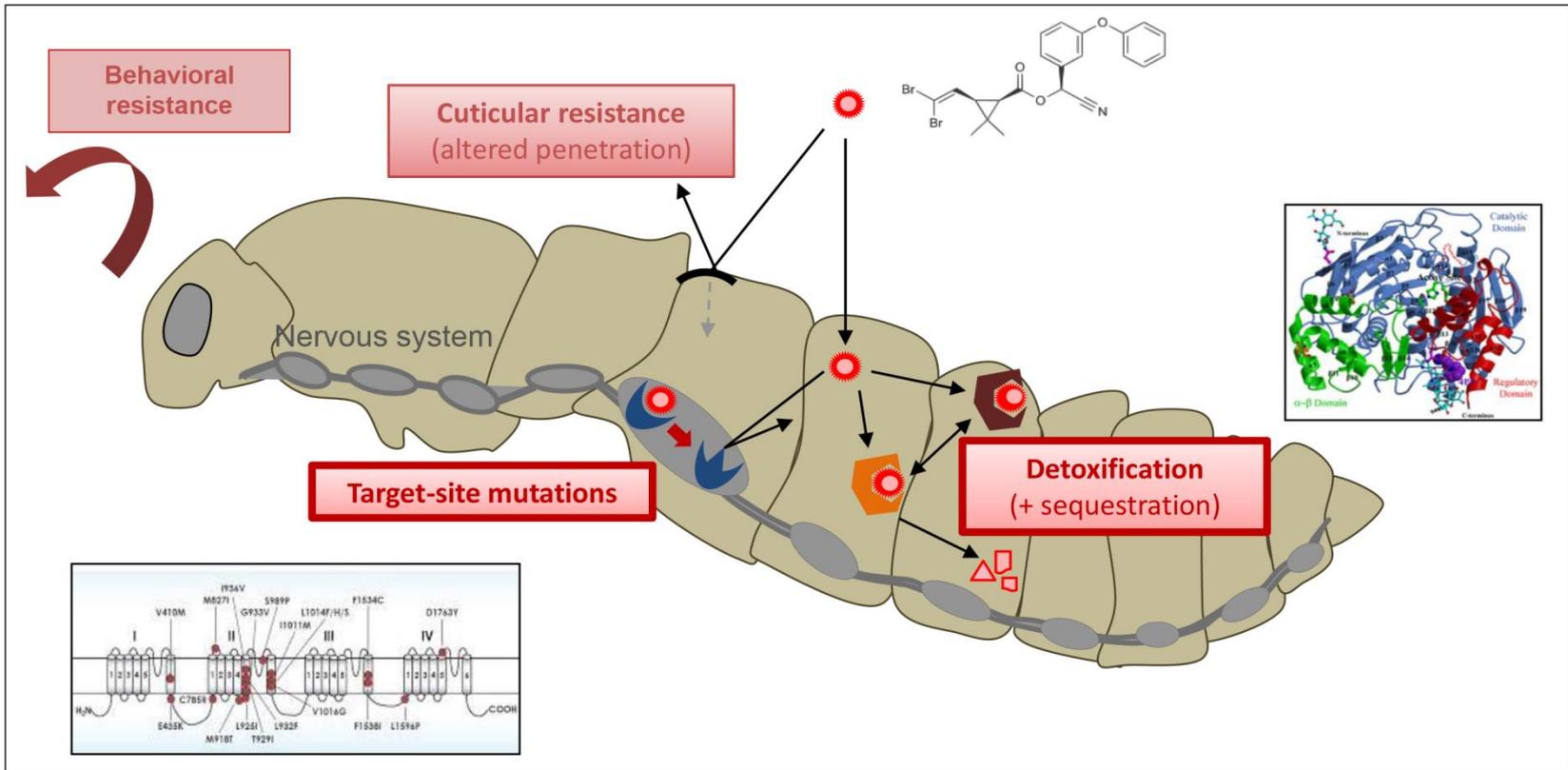
Striking resistance phenotypes evolving ..



Chemical	RR
Abamectin	1644
Fenb Oxide	>1700
Hexythiazox	>1500
Clofentezin	>1000
	426.0
	320.0

Why ?





Why are insects / mosquitoes SO resistant to insecticides ?

detoxification genes? mutations? Other mechanisms? ..

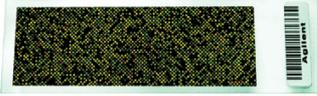
Insecticide Resistance research

- Identification of novel resistance mechanisms; regulation and coordination of different components (pathways)
- Functional characterization of enzymes and mutations involved in resistance and means to tackle the trait
- Molecular Diagnostics for early identification and management

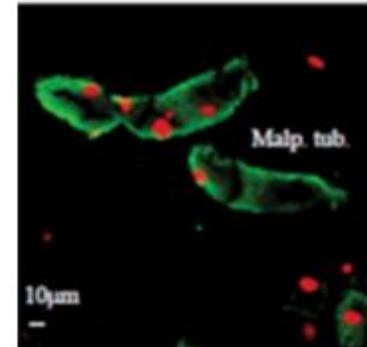
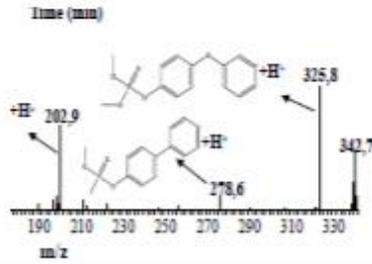
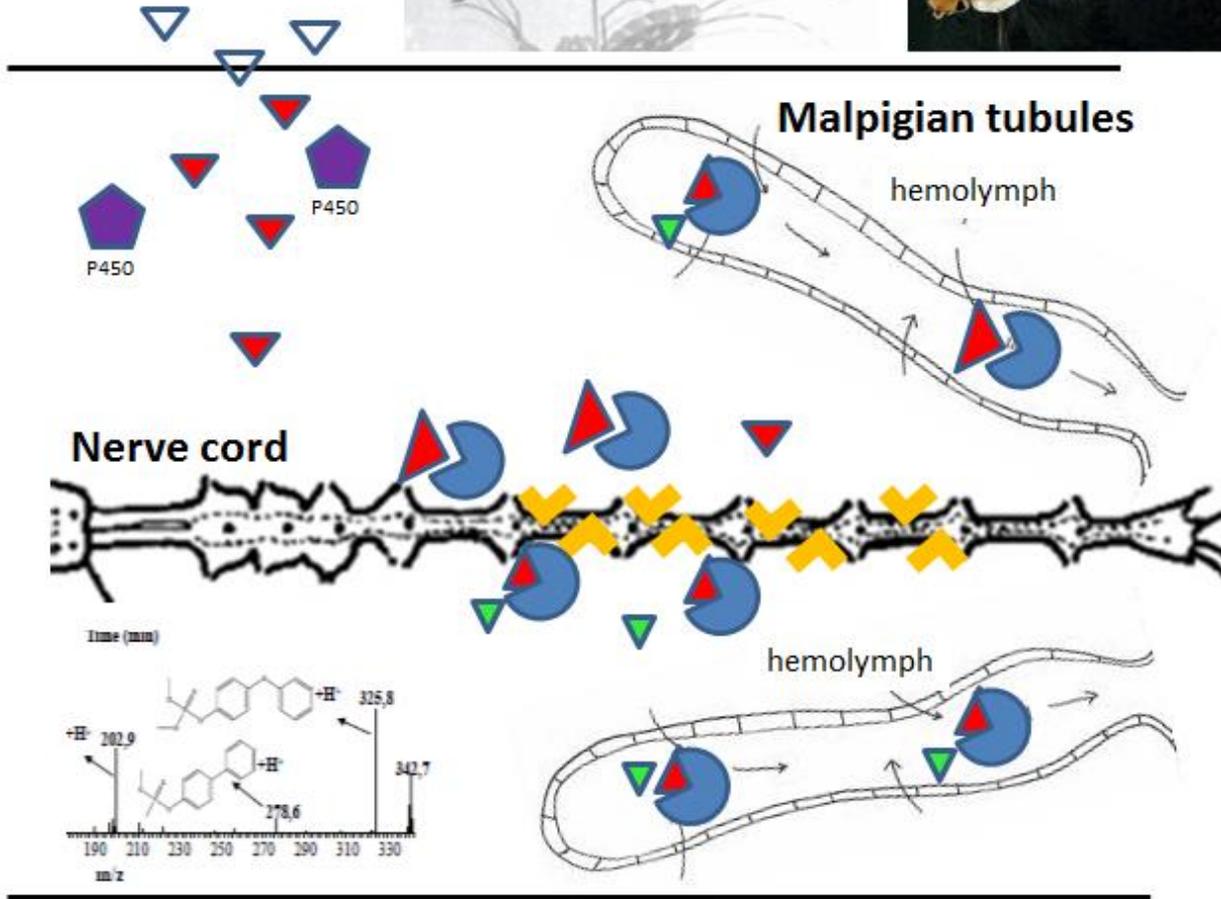
Novel insecticide target discovery

- Critical physiological roles – omic and cell based and functional (CRISPR/Cas9) approaches

Molecular analysis of temephos resistance in *Aedes albopictus*

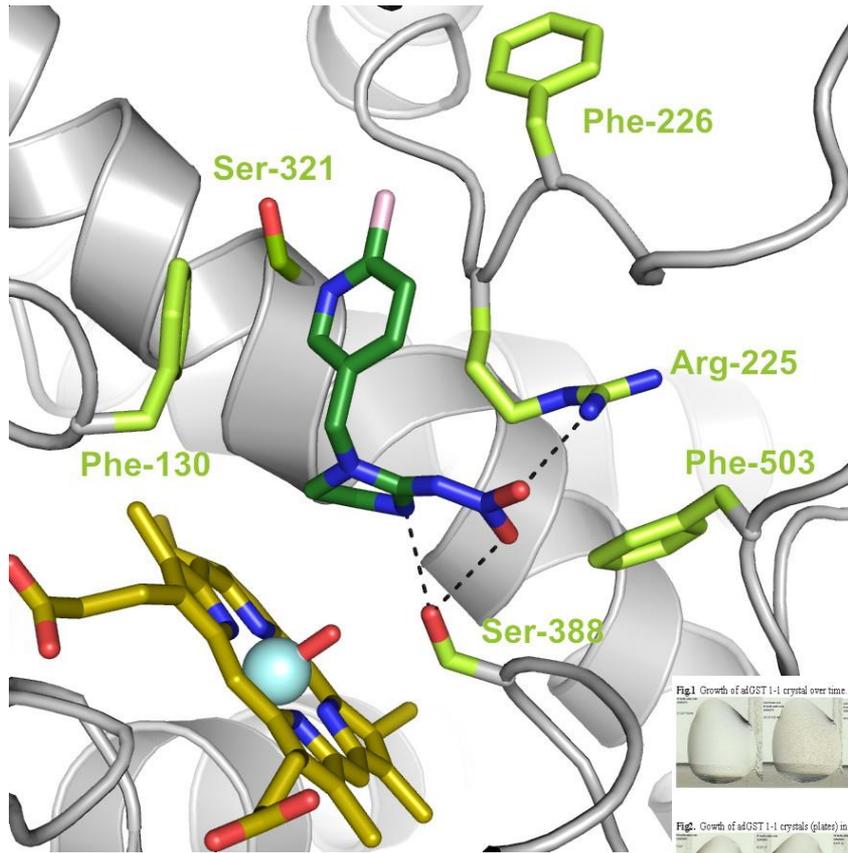


Linda



- ◆ AchE
- ▽ Temephos
- ▽ Temephos oxon
- CCEae3A
- ▽ P1 metabolite

Grigoraki et al., 2015 PlosNTD
 Grigoraki et al., (2016) IBMB 74, 61-67
 Grigoraki et al 2017



Identify molecular determinants of insecticide binding and metabolism



Rational design



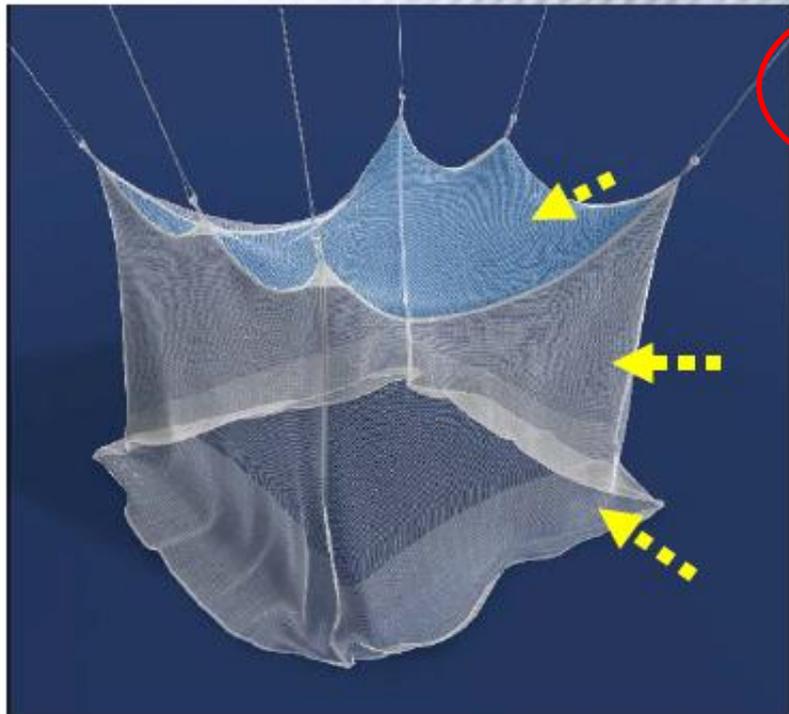
In silico prediction

Synergists -improved formulations (low toxicity, resistance breakers)

PermaNet[®] 3.0 Mosquito Net Combination



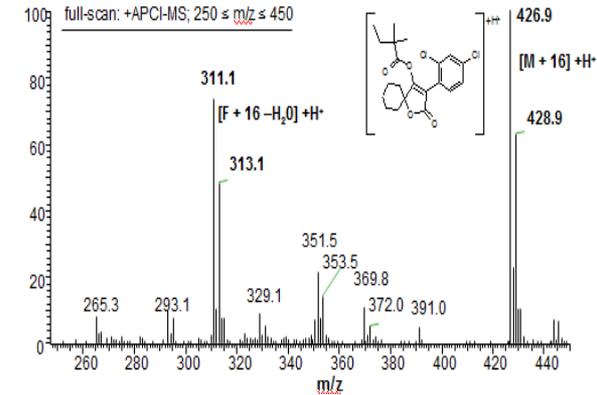
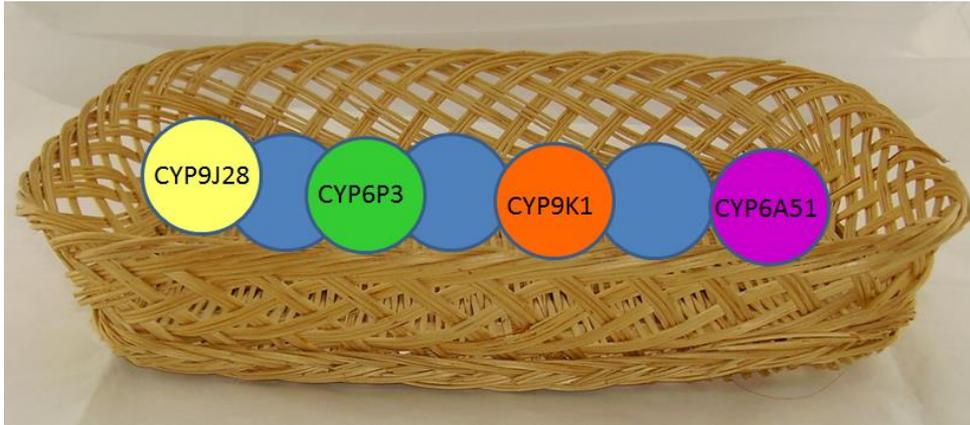
Developing innovative products and concepts and saving lives



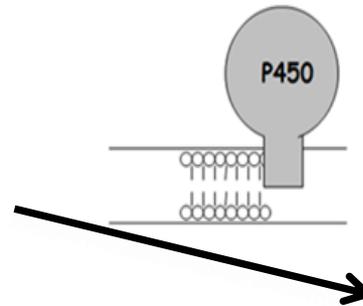
- The **roof** of PermaNet[®] 3.0 is polyethylene fiber with 100 Denier monofilament composite containing a "synergist" and Deltamethrina embedded within the filament.
- The **upper side** of PermaNet[®] 3.0 is a multifilament polyester fiber 75 Denier with a load of Deltamethrina of 85 mg/m², which offers a better long-term protection.
- The **lower side** PermaNet[®] 3.0 is a multifilament polyester fiber 75 Denier with a special design with the crown strengthened for added durability, with a cargo of 115 mg/m² Deltamethrina.

Tools for early screen of novel insecticides and synergists (plant/microbial metabolites..)

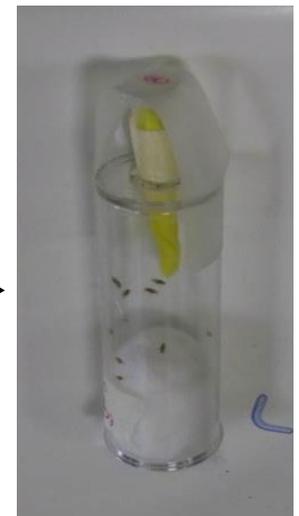
In vitro



In vivo



**Detox genes+
CRISPR/Cas9**

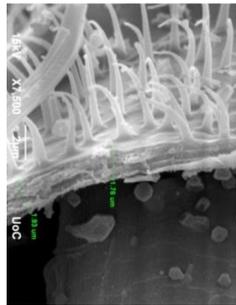
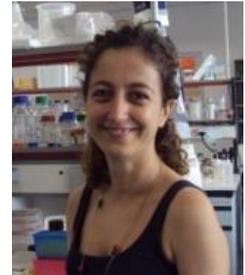
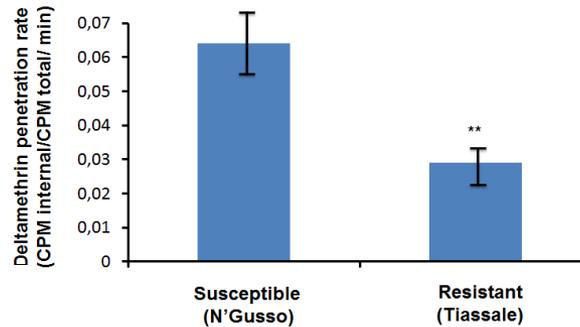


Cytochrome P450 associated with resistance catalyzes cuticular hydrocarbon production: a mechanism that slows the uptake of pyrethroids, contributing to resistance and broadening the phenotype



1

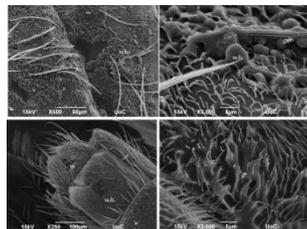
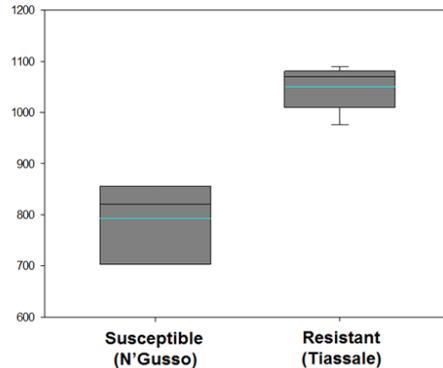
Substantially reduced insecticide uptake in resistance insects



2

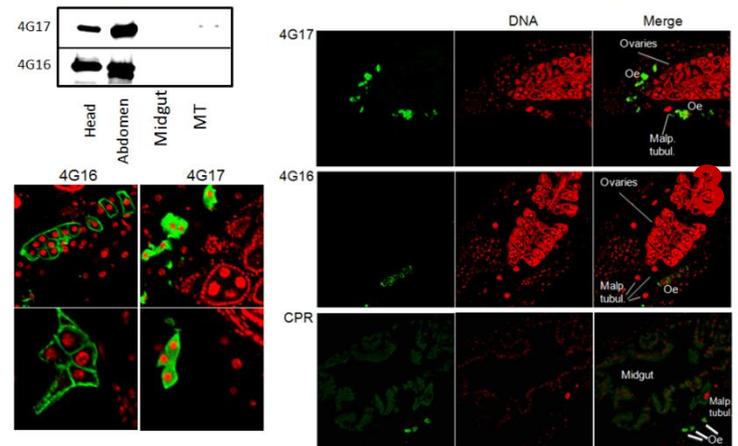
elevated epicuticular HCs

ng epicuticular HC/insect



CYP4G16/17 are over-expressed on the oenocytes of R mosquitoes and have decarboxylases activity (HC)

3



Improved insecticide “formulations” / delivery to bypass lipid layer ...

Electrostatic coating enhances bioavailability of insecticides and breaks pyrethroid resistance in mosquitoes

Rob Andriessen^{a,1}, Janneke Snetselaar^{a,1}, Remco A. Suer^a, Anne J. Osinga^a, Johan Deschietere^b, Issa N. Lyimo^c, Ladslaus L. Mnyone^c, Basil D. Brooke^{d,e}, Hilary Ranson^f, Bart G. J. Knols^a, and Marit Farenhorst^{a,2}

^aIn2Care BV, Wageningen 6709 PG, The Netherlands; ^bCTF2000, Zele 9240, Belgium; ^cEnvironmental Health and Ecological Sciences Thematic Group Health Institute, Ifakara, Tanzania; ^dWits Research Institute for Malaria, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; ^eVector Control Reference Laboratory, Centre for Opportunistic, Tropical and Hospital Infections, National Institute for Communicable Diseases, Johannesburg, South Africa; ^fCentre for Vector Borne Diseases, National Institute for Communicable Diseases, Johannesburg, South Africa

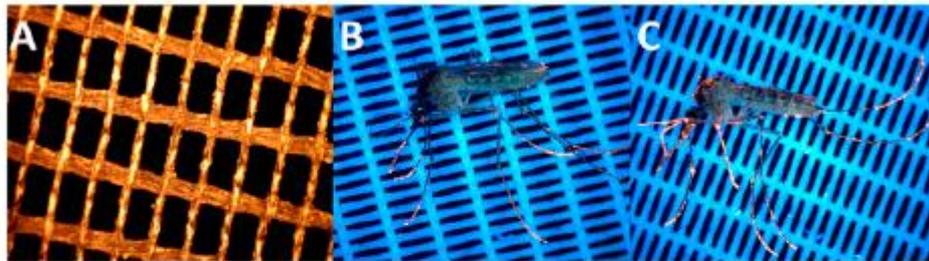
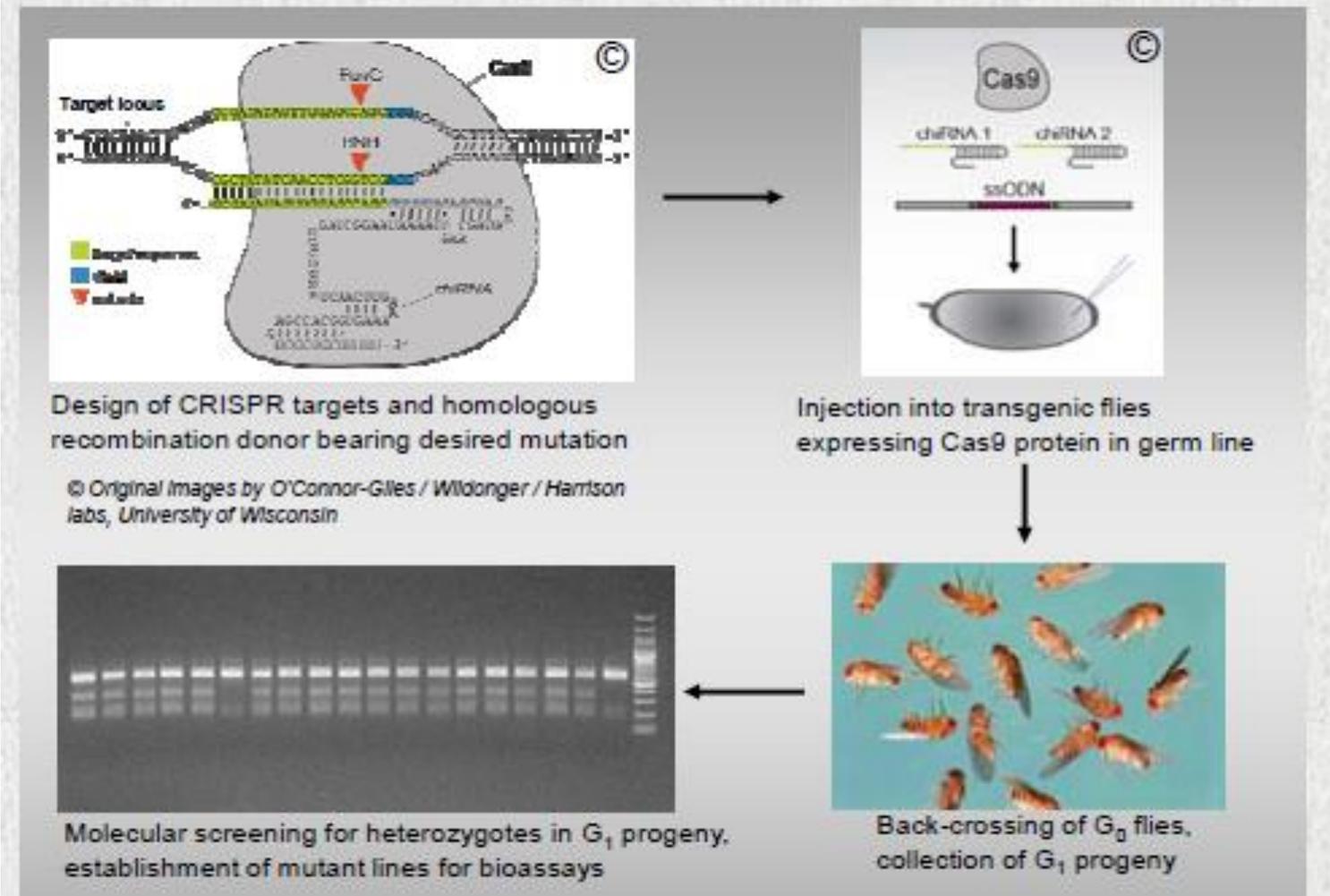


Fig. 2. (A) Photograph of electrostatic netting saturated with fluorescent dust particles lighting up orange under UV light at 50 \times magnification. (B) A *Culex* mosquito contaminated with fluorescent particles after a 5-s contact with the netting. (C) *Culex* female with fluorescent particles after 3-min contact with netting.

CRISPR/Cas9 to study the role of individual genes and mutations in resistance.



Analysis of resistance reveals the mode of action of insecticides with unknown MoA

.. including unexpected surprises ..



Significance

An old enigma in insect toxicology, the mode of action (MoA) of selective chitin biosynthesis inhibitors in arthropods, is resolved. Benzoylureas, buprofezin, and etoxazole share a MoA by directly interacting with chitin synthase 1. **The finding that a single mutation confers striking levels of insecticide resistance against three putative different MoAs has important ramifications on resistance management strategies and rational use of insecticides against major agricultural pests and vectors of human diseases.** Our results also show that CRISPR/Cas9-mediated gain-of-function mutations in single-copy genes of highly conserved target sites in arthropods provide opportunities for comprehensive insecticide resistance investigations across species boundaries and against several insecticide classes.

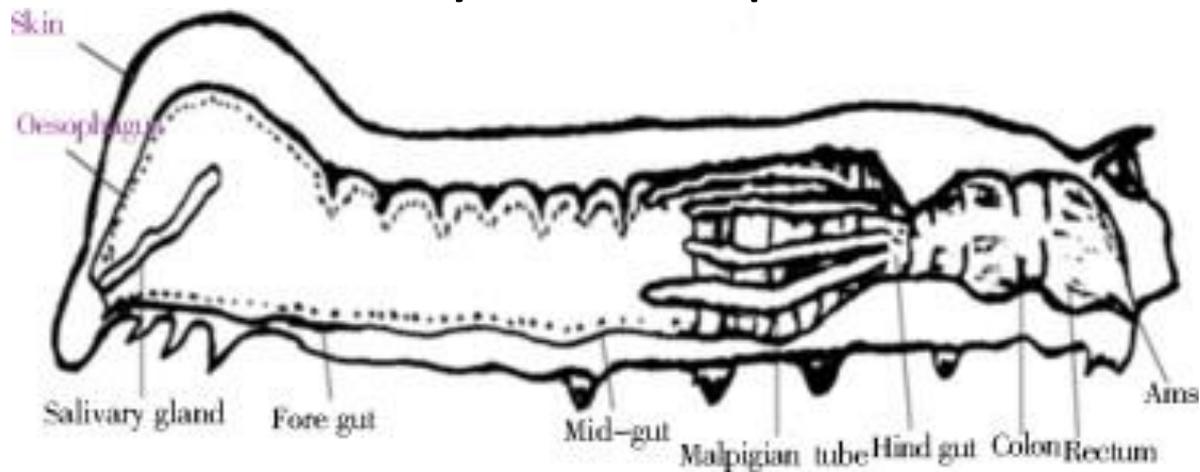
Resistance mutation conserved between insects and mites unravels the benzoylurea insecticide mode of action on chitin biosynthesis

Vassilis Douris^{a,b,1}, Denise Steinbach^{c,d,1}, Rafaela Panteleri^{a,b}, Ioannis Livadaras^a, John Anthony Pickett^{e,2}, Thomas Van Leeuwen^{f,g}, Ralf Nauen^{c,2}, and John Vontas^{a,h,2}

^aInstitute of Molecular Biology and Biotechnology, Foundation for Research and Technology Hellas, GR-70013 Heraklion, Crete, Greece; ^bLaboratory of Molecular Entomology, Department of Biology, University of Crete, GR-70013 Heraklion, Crete, Greece; ^cBayer CropScience AG, R&D Pest Control Biology, D-40789 Mannheim, Germany; ^dDevelopmental Biology, Department of Biology, Martin Luther University Halle-Wittenberg, 06120 Halle, Germany;

Identify novel specific insecticide targets

- aim at critical physiological roles
- The gut of lepidopterans is adjusted to digestion of plant material at very alkaline pH

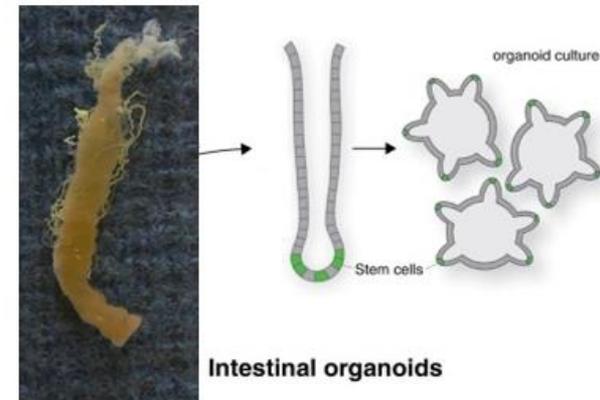
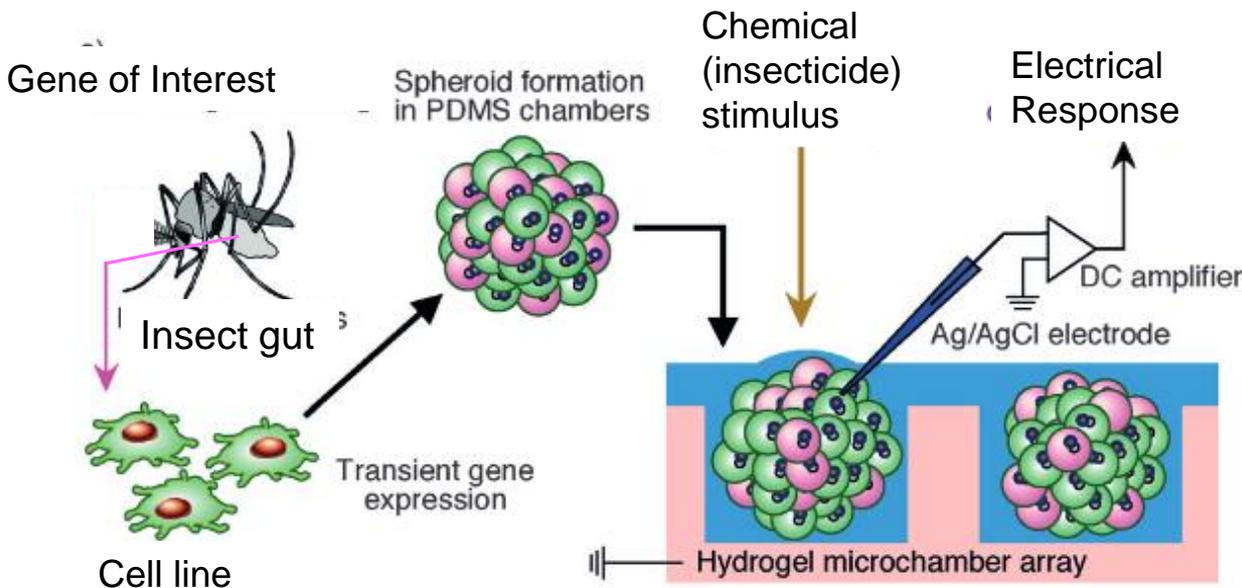


Enzymes, transporters, channels etc. that maintain physiological conditions and serve digestion and nutrient absorption in a specific manner **may serve as potential molecular targets**

In search of novel targets

- Comprehensive transcriptomic/proteomic study (spatial and temporal specificity)
- Validation by CRISPR/Cas9 mediated knock-outs (and/or high throughput RNAi)
- Development of cell-based screening assays

3D cell based approaches-insect cells: spheroids/organoids / hanging drops (Pharma models)



Bayer/IMBB launch insect control research programme

•14 Sep 2017

Bayer's Crop Science division has started a five-year research collaboration with the Greek Institute of Molecular Biology and Biotechnology (IMBB) to discover insect control solutions.



Bayer AG
Communications and
Public Affairs
51368 Leverkusen
Germany
Tel. +49 214 30-0
www.news.bayer.com

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ΤΟ ΕΣΤΑ
ΣΤΗΝ ΚΕΝΤΡΙΚΗ
ΜΑΚΕΔΟΝΙΑ

Η Περιφέρεια
στην πράξη!

ΠΕΡΙΦΕΡΕΙΑ
ΚΕΝΤΡΙΚΗΣ ΜΑΚΕΔΟΝΙΑΣ

ραδιό
φωνο
24/7
88.6



ON AIR:
00:00 - 02:00

 **ROUND MIDNIGHT**
Ιλάν Σολομών

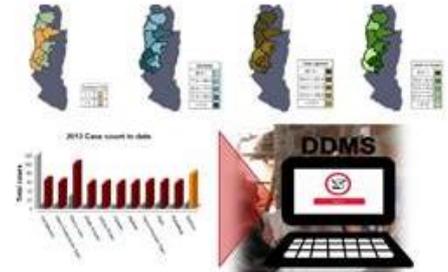
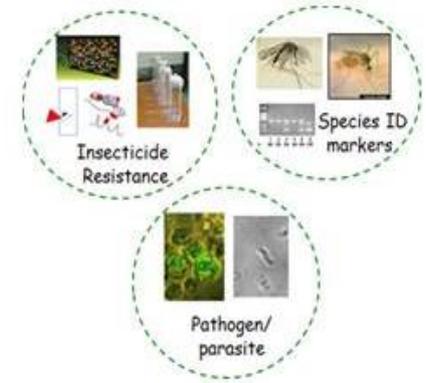
Μην τα χάσετε

 Το Έθνος'
επισκέφτηκε τον

Κρήτη: Συνεργασία του ΙΤΕ με τη Bayer για την καταπολέμηση των εντόμων



Markers for vector control and resistance management



Horizon 2020
2016-2019, 3.2 M Euro
Coordinator: FORTH-IMBB



LabDisk: “sample-to-answer” for monitoring the species ID, the infection status and the insecticide resistance profile of mosquitoes.

Lab - People



Collaborators



Swiss TPH



Institut Pasteur



Funding

