



**University of  
Nottingham**

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**New AChE inhibitor  
reduces amyloid  
aggregation in a  
Drosophila Alzheimer's  
model**

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University of Nottingham**

**10<sup>th</sup> APS International  
PharmSci Conference  
University of Greenwich,  
London**



## What is Alzheimer's disease?

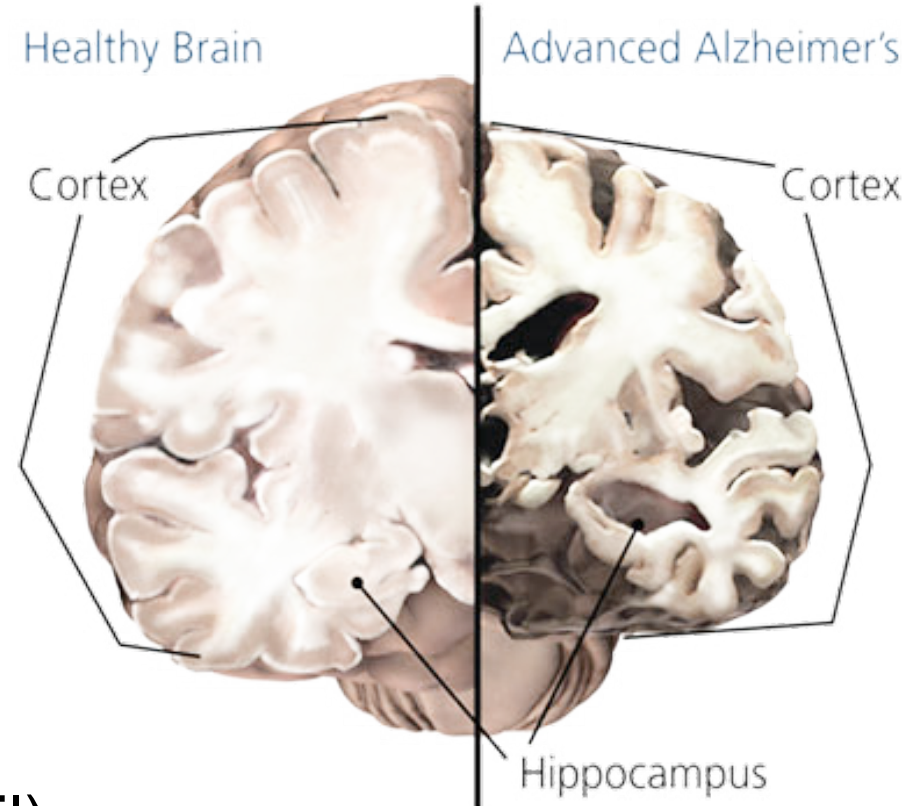
- 36 million people affected

## Aetiology

- Aggregation of  $\beta$ -peptide in plaques
- Tau hyperphosphorylation to form neurofibrillary tangles
- Loss of cholinergic markers

## Alzheimer's therapies?

- Acetylcholinesterase inhibitors (Donepezil)
- NMDA receptor antagonist (Memantine)



Source: [www.brainfacts.org](http://www.brainfacts.org)

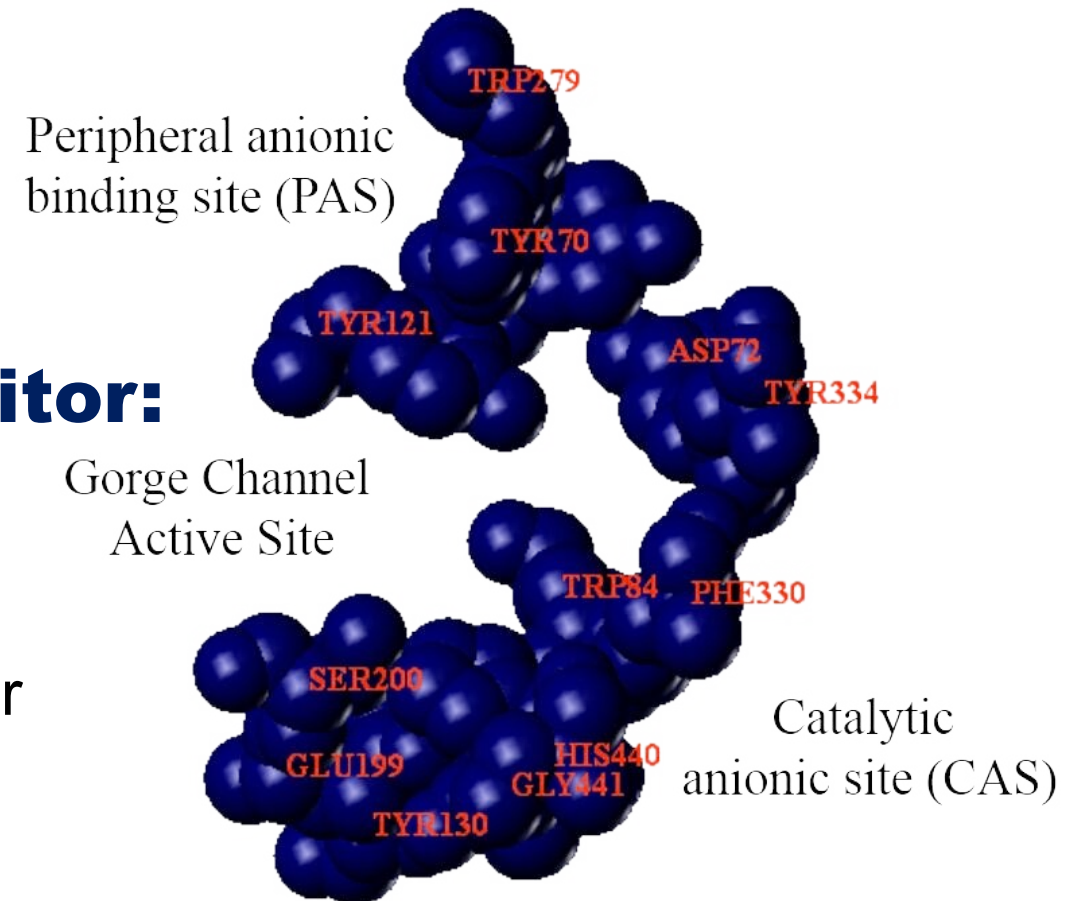


## Cholinergic replacement therapy:

- Acetylcholinesterase inhibition
- Aim to increase acetylcholine
- Improve psychiatric symptomatology

## Our newly synthesized AChE inhibitor:

- Dual binding activity for both peripheral anionic site and catalytic anionic site.
- Higher specificity to Acetylcholinesterase over Butyrylcholinesterase

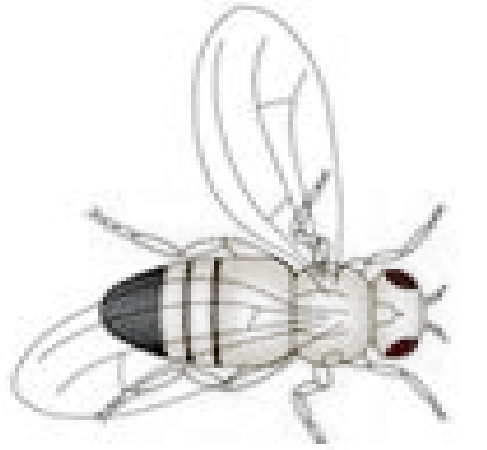


Source: More et al. Pharmaceutical Journals (2018)



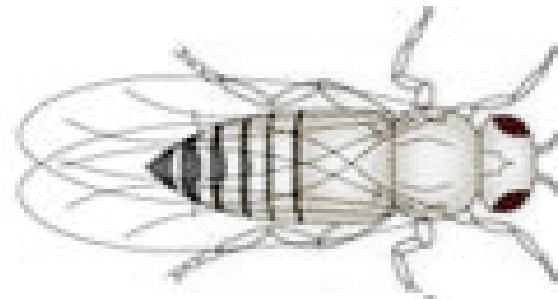
# *Drosophila* as Alzheimer's model

Enhancer-trap GAL4

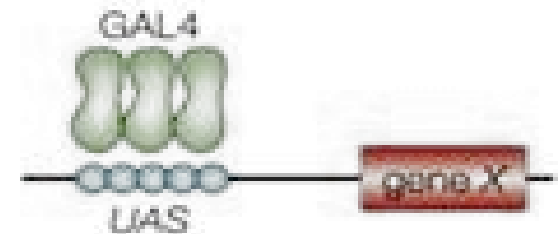


x

UAS-gene X

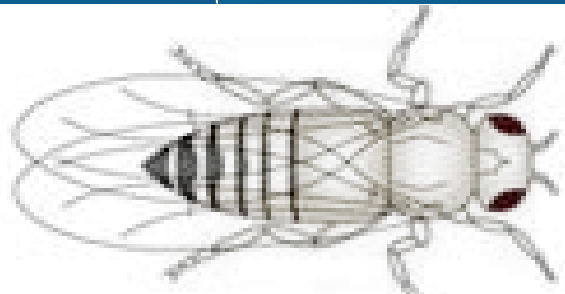


Tissue-specific expression  
of GAL4



Transcriptional activation  
of gene X

- Reduced lifespan
- Locomotive defects model
- Induce amyloid aggregation



**Develop an Alzheimer model using APP-Arctic mutation transgene**



**Characterisation**



**Evaluate efficacy of novel AChE Inhibitor**

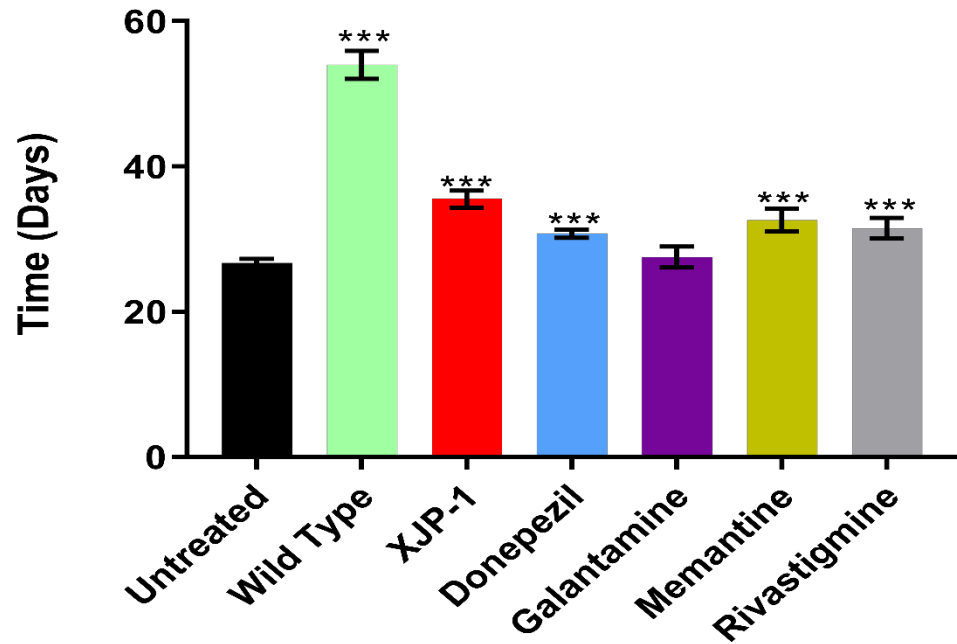


- Life span
- Climbing performance
- Amyloid plaque

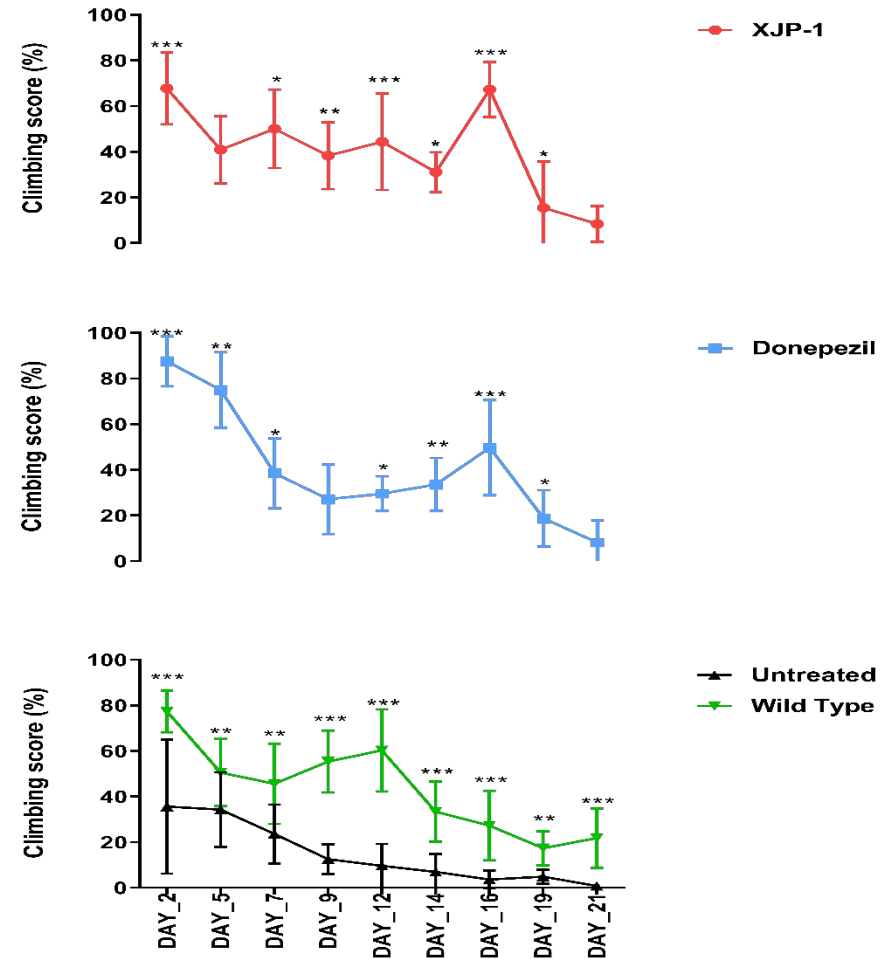


- Effect on survival time
- Locomotive functions
- Amyloid accumulation

## Lifespan

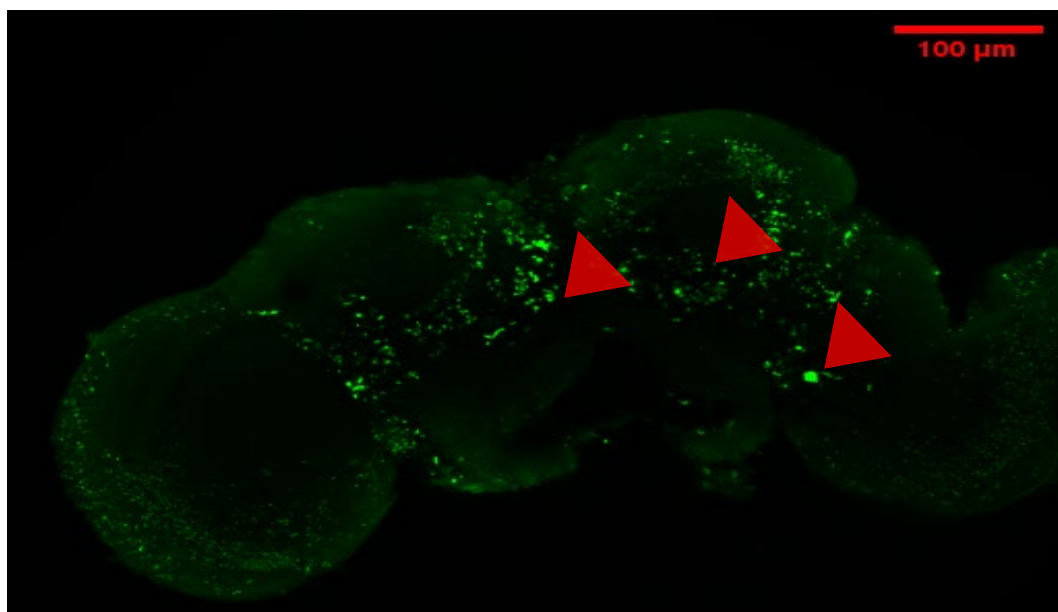


## Locomotive functions

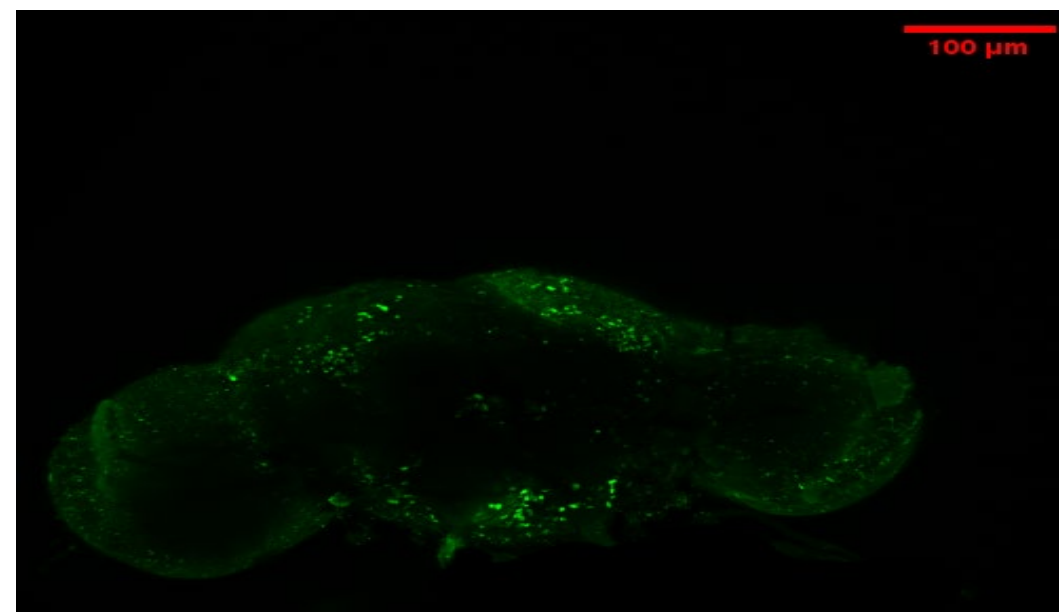




## DAY-10 Untreated



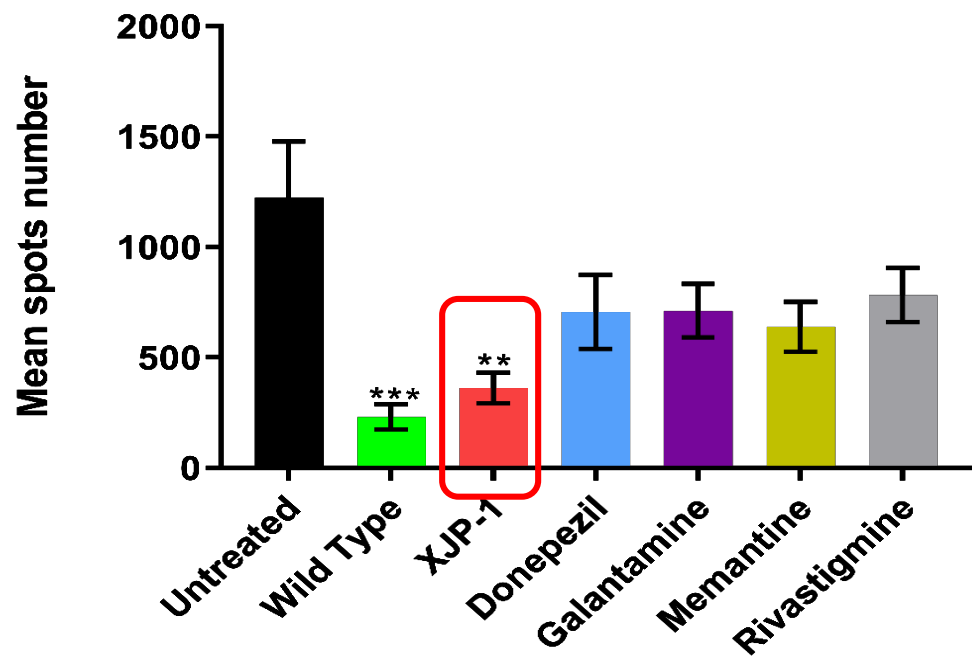
## DAY-10 with novel AChE Inhibitor



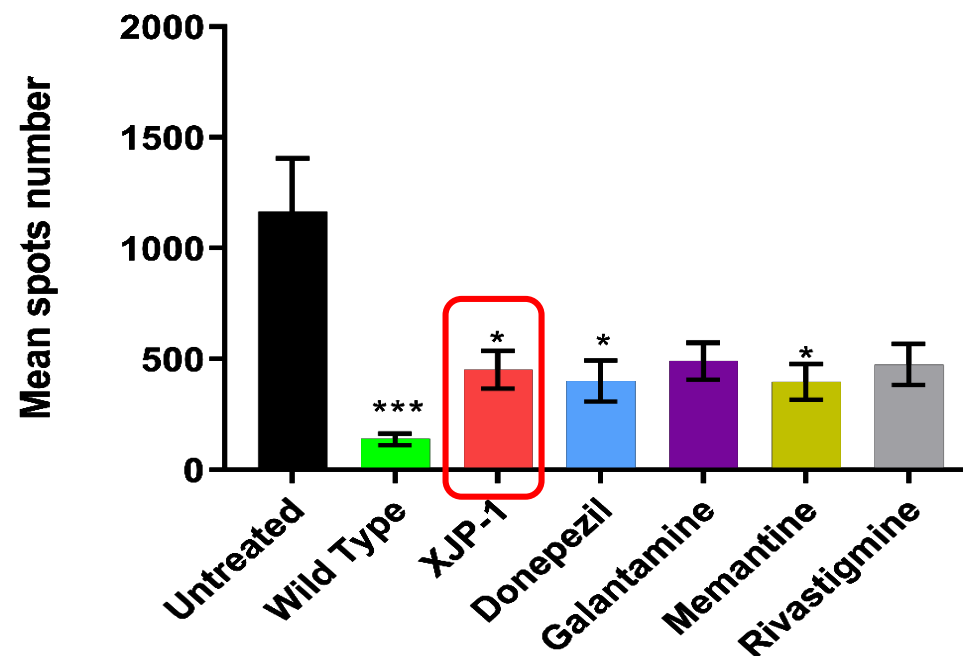
Confocal image of *Drosophila Melanogaster* brain  
Magnification: 20x  
Primary Antibody: mRb anti-A $\beta_{42}$   
**Arrow** indicates amyloid plaque



### Amyloid Spots Analysis DAY-10



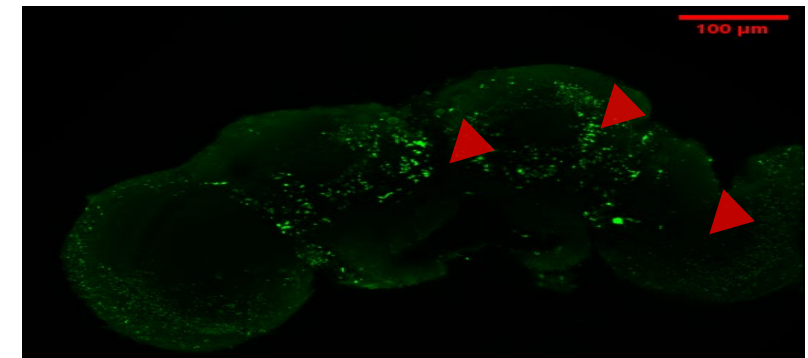
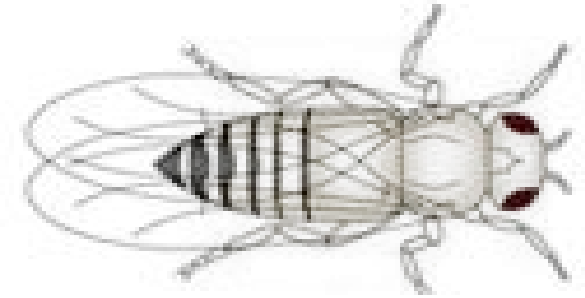
### Amyloid Spots Analysis DAY-20







- Novel AChE Inhibitor (**XJP-1**) shows improved efficacy compared to untreated group.
- Transgenic flies treated with XJP-1 had a significant improvement of their locomotive functions.
- XJP-1 is able to reduce the amyloid aggregation.





# Aknowledgments

- Dr. Zheyang Zhu, University of Nottingham
- Prof. Stephanie Allen, University of Nottingham
- Dr. Marios Georgiou, University of Nottingham
- Dr. Natalie Mack, University of Nottingham
- Alessia Manca, University of Sassari
- Akmal Bin Sabri, University of Nottingham





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# Aknowledgments

The background of the slide is a blue-tinted photograph of a modern building with large windows, likely a university building. In the foreground, there is a large, intricate sculpture of a fly or insect, made of thin, dark lines, with red accents on its head and thorax. The text "THANK YOU" is centered in large, white, sans-serif capital letters.

# THANK YOU

**10<sup>th</sup> APS International PharmSci Conference**  
**University of Greenwich, London**