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STUDY OF THE IMMUNE RESPONSE OF DROSOPHILA MIMICKING CYSTIC FIBROSIS TO INFECTIONS BY PATHOGENS PREVALENT IN PATIENTS

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In collaboration with the neighboring EPIM team from U1173 (INSERM-UVSQ), we have established *Drosophila* as a host for systemic infections by bacteria prevalent in patients with cystic fibrosis (*Staphylococcus aureus* and *Burkholderia cepacia*), and in particular *Mycobacterium abscessus* (Touré et al., 2023a, 2023b, 2024). The latter is a fast-growing opportunistic mycobacterium that is resistant to antibiotic and anti-tuberculosis treatments. Cystic fibrosis is a genetic disease caused by the loss of activity of an anion channel called CFTR, which negatively regulates the epithelial sodium channel (ENaC). Cell phenotypes reminiscent of those of the disease have been described in flies whose enterocytes are depleted of Cftr transcripts and in flies lacking the microRNA miR-263a,

which negatively regulates the levels of transcripts encoding ENaC subunits (Kim et al., 2017, 2020, Touré et al., 2023c).
We recently reported that these *miR-263a* mutant flies also exhibit hypersusceptibility to systemic infection by *M. abscessus*, *S aureus*, or *B. cepacia*, associated with a reduction in the levels of transcripts encoding antimicrobial peptides and enzymes involved in the synthesis of the steroid hormone ecdysone. These phenotypes are suppressed by adding the active form of ecdysone to the food of infected mutant flies (Touré et al., 2025).

We wish to:
identify the tissue(s) responsible for these phenotypes,develop new *Drosophila* models of cystic fibrosis by depleting *Drosophila* Cftr gene transcripts and expressing mutated alleles of the human CFTR gene in the miR-263a expression domain and in the tissues responsible for the phenotypes of interest.
test whether comparable phenotypes are observed in flies whose transcripts of the gene encoding Drosophila Cftr are depleted in the miR-263a expression domain,
develop new *Drosophila* models of cystic fibrosis by depleting *Drosophila* Cftr gene transcripts and expressing mutated alleles of the human CFTR gene in the *miR-263a* expression domain and in the tissues responsible for the phenotypes of interest.
We should thus validate at least one new model of cystic fibrosis that is susceptible to systemic infections by at least three pathogens prevalent in patients with the disease.
This model will allow us to explore the hormonal control of *Drosophila* innate immunity and determine whether the prevalence of infections in patients is due to the nature of the CFTR gene mutations they carry.
This approach could contribute to resolving the controversy surrounding the association between CFTR and ENaC in the context of cystic fibrosis.

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