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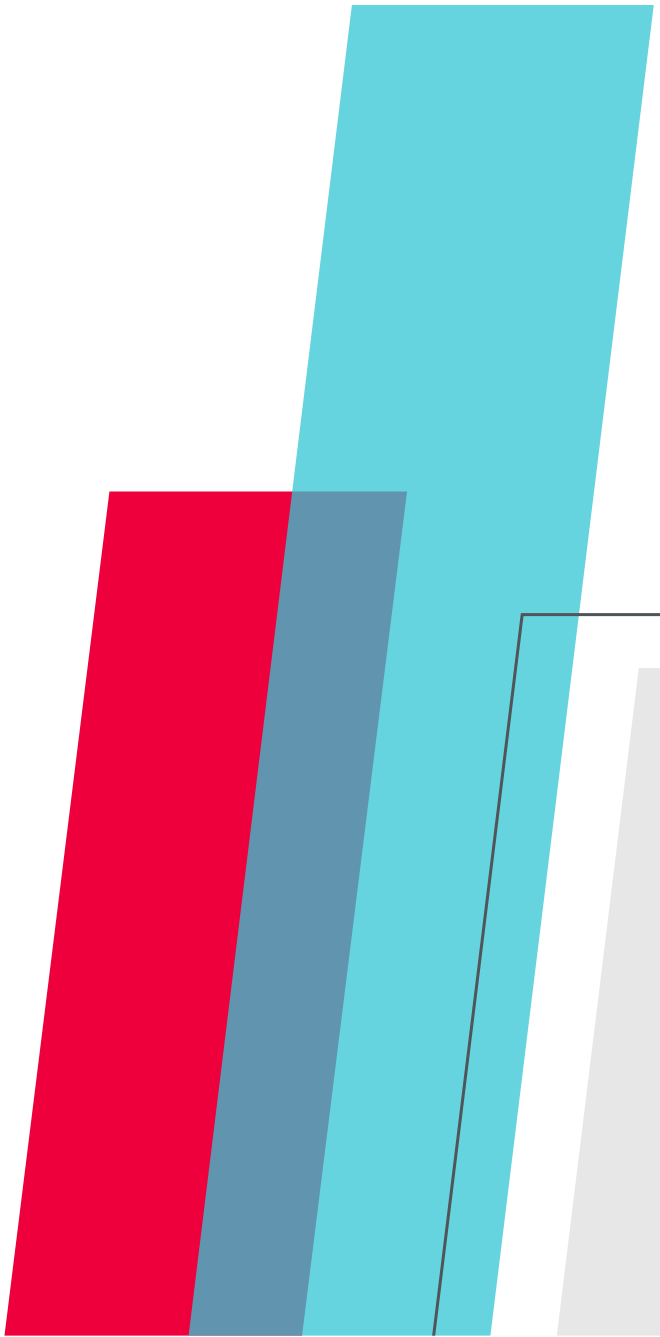
HFSP CASESTUDY

Research Grant: Mosquito Immunity

Exploring the concept of adaptive immunity to viruses in mosquitoes



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Client
Human Frontier Science Program Organization (HFSPO)

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Project Title	**Exploring the concept of adaptive immunity to viruses in mosquitoes**
Starting Year	2017
Principal Investigator	Mariangela Bonizzoni
Collaborators	Jayme Souza-Neto, Ronald van Rij
Countries	Italy, Brazil, Netherlands
Disciplines	Biologist/Zoologist, Molecular/Cell Biologist, Virologist
Task	Testing a specific hypothesis of adaptive immunity in mosquitoes to viruses
Key output	Improved understanding of adaptive immunity in mosquitoes and the evolutionary path leading there, mapping of mosquito genomes regarding immunity bestowing integrations and of different mosquito populations

In addition to the cited documents, interviews with the researchers and HFSP data were used as sources. Furthermore, quantitative analyses were carried out using the Dimensions Database.

1 Overview

The case study presents an intercontinental, interdisciplinary project that sets out to test a specific hypothesis concerning the adaptive immunity of mosquitoes, namely that it is mediated by non-retroviral endogenous viral elements. The project investigated how fragments of viral genomes become embedded in mosquito DNA and give rise to small RNAs that target viruses. The team mapped genomic signatures that distinguish the human-specialized yellow fever mosquito Aedes aegypti (Aaa) from its African ancestor form (Aaf). In this context, human specialization means that these populations are adapted to coexisting with human populations and, among other things, (can) use humans as a primary food source. It turned out that the integration of viral sequences did not exhibit the hypothesized correlations. The project subsequently shifted its focus to mapping whole mosquito genomes and different mosquito populations. The scientific work was coordinated across continents and disciplines, pairing

population sampling and genome sequencing with analytical pipelines and complementary assay capacity at partner sites. The aim was not simply to catalog variants, but to assemble a coherent picture of how genomic change and small-RNA biology shape vector competence and human specialization.

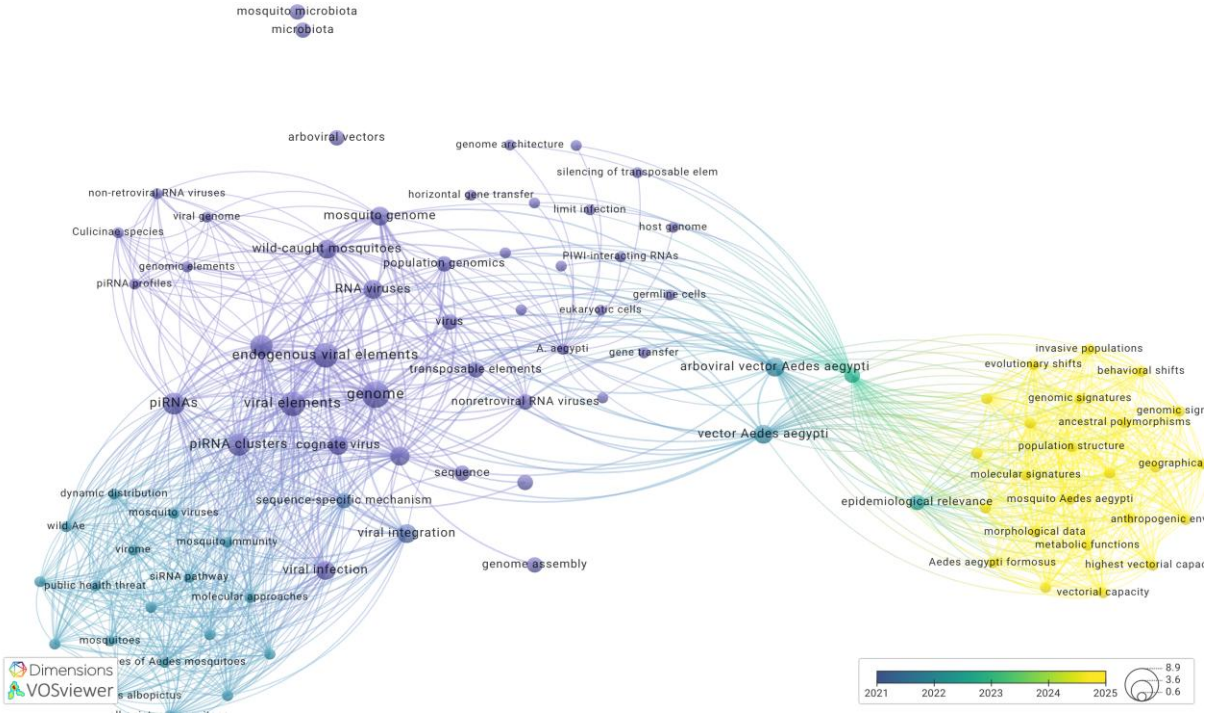
2 The Project

The project built on prior observations that mosquito genomes contain viral fragments. It was hypothesized that these fragments could represent an adaptive mechanism that helps mosquitoes strengthen their immunity to viruses. This, in turn, would have implications for the evolutionary development of this mechanism and of mosquito populations.

The team began by mapping the location, prevalence and stability of viral integrations and characterizing their small RNAs in order to evaluate a potentially heritable antiviral layer in mosquitoes. This was only possible because of the intercontinental collaboration, which greatly facilitated the collection of mosquitoes and their DNA in Brazil and elsewhere, while simultaneously providing the necessary testing and sequencing capacities. Partner sites were also involved and provided valuable contributions. The case study is therefore an example of how HFSP enables international projects that otherwise would have been infeasible, or feasible only with great difficulty.

Early analyses confirmed that viral integrations in mosquitoes are common yet dynamic, varying by geography and through time, and they revealed practical challenges in distinguishing stable signals from noise in highly variable genomes. The results did not support the initial hypothesis regarding the adaptive mechanism behind the mosquito's immunity to viruses. In parallel, the team recognized growing activity by other groups in adjacent areas, which reinforced the decision to pivot toward comparative and evolutionary analyses while continuing to pursue the question of what specific insertions and genes functionally do. The following figure clearly illustrates this pivot, with more recent publications (in yellow) differing markedly in thematic focus from the earlier ones.

Figure 1: Topics and thematic Cluster of HFSP-Publications of the Principal Investigator



Source: HFSP Data and Dimensions Data Base

The project identified robust, globally replicable genomic signatures that distinguish the domestic, human-seeking Aaa ecotype from the African forest form Aaf, thereby making human specialization genetically tractable and comparable across populations. This was possible because integrations are widespread and geographically structured. Thus, they can be used as identifiers. The project established a descriptive foundation for viral integrations and their small RNAs in Aedes aegypti and documented hundreds of adaptive variants that reliably differentiate Aaa from Aaf, with enrichment in chemosensory, neuronal, metabolic and regulatory functions. This supports the view that genetic adaptation contributes to human specialization and transmission potential.

Progress benefited from complementary laboratory competencies, a culture of engaging with uncertainty, early investment in analytical tooling and the deliberate decision to keep strands integrated so that insights could cross-fertilize. Constraints arose from lab start-up demands and tool maturation, pressure on staff capacity and the need to balance parallel funding lines. It was essential that HFSP allowed the team to reorient their project once the original direction had proved unviable. This underscores that high-risk research in particular requires flexibility to cope with setbacks and failures.

3 Outcomes and Impact

In addition to the project's direct results, it pioneered an approach to mapping genes and populations that was subsequently adopted by others for different species. The project thus served as a proof of concept and generated leverage extending beyond its immediate scientific findings.

These findings are, of course, also of intrinsic importance. Mosquitoes constitute a highly relevant species, particularly because, as disease vectors, they represent the deadliest animal for humans and are continuing to spread because of global warming. There are ongoing considerations to curb mosquito populations through genetic manipulation. The project's findings lay an important foundation for understanding the fundamental mechanisms underlying the evolution and genetic adaptation of mosquito populations and open the door to options for using this knowledge to restrict such populations. Translational reality would require careful functional validation, ecological safety, governance and financing.

In addition, the project helps to identify and track specific mosquito populations that are particularly anthropophilic and therefore especially dangerous. By linking host preference, urban adaptation and vector competence to concrete genomic features, public-health actors can design interventions with greater ecological and evolutionary realism, and they can monitor whether control efforts inadvertently select for re-domestication from wild populations.

4 Role of HFSP and Conclusion

The investigators describe HFSP as the only funder that would have backed the project in its high-risk form. In their words, HFSP funded "my crazy project". They also stressed that the international collaboration was essential and would not have been possible in this form without HFSP. The grant enabled the team to pursue a single integrated program, rather than splitting into safer sub-projects tuned to local infrastructure with slower progress and fewer reusable outputs for others. The unified project allowed long-read genomics, population comparisons and small-RNA profiling to move in concert. It was also emphasized as particularly important that the project could be refocused without major bureaucratic effort, which in turn made it possible to generate the results and impacts described above.

The case study illustrates several core aspects of HFSP and how these make scientific projects and success possible. The funding of high-risk frontier research, the enabling of intercontinental collaboration, and the trust placed in the researchers ultimately allowed the project to be scientifically successful, even though the original project objectives were not achieved. It also shows the role that basic research can play: as a driver of methodological developments that can spill over into other scientific fields, and as the foundation for practically relevant measures and interventions. What these measures and interventions will be, and how successful they will prove,

cannot yet be foreseen, but it is clear that the project has expanded the space of possibilities within which they will occur.

5 Sources

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