Are RIG-I-Like Receptors the Key to Understanding *Galliformes'* Susceptibility to Pathogens? Investigating the Role of MDA5 in Shaping the Interferon Response in Birds and Mammals.

Viruses pose one of the greatest threats to human health and the global economy. While we understand their impact on human health relatively well, our knowledge of host-pathogen interactions in other mammals and animal groups is less clear. Evolutionary differences and the diverse ecological niches of various species make it nearly impossible to transfer knowledge directly from humans to other animals. Given that a significant source of human protein is animal-based, understanding how animals defend against pathogens is essential for maintaining global food security.

The poultry industry, as the fastest-growing sector in animal agriculture, generates the highest revenues but faces substantial losses from disease outbreaks, such as avian influenza, Newcastle disease, and infectious bronchitis. All three diseases are caused by RNA viruses, which spread quickly through flocks, leading to high mortality, reduced egg production, and increased biosecurity costs. When a severe disease outbreak occurs in breeding birds, drastic measures such as culling are often recommended to contain the virus spread. Therefore, to reduce losses in the poultry industry and develop new biosecurity measures, it is crucial to understand how the avian immune system functions.

Innate immunity serves as the first line of defense against pathogens. RIG-I and MDA5 are members of the RIG-I-like receptor (RLR) family, which are essential for detecting viral RNA and activating the immune response. RIG-I specializes in detecting short viral RNAs with triphosphorylated 5’ ends, whereas MDA5 detects longer double-stranded RNAs. Interestingly, some animals, including the *Galliformes* family (e.g. chickens and turkeys), have lost RIG-I through evolution. This loss may make *Galliformes* more susceptible to viral infections compared for instance to *Anseriformes* (e.g. ducks), which have both RIG-I and MDA5. This hypothesis aligns with recent findings in human cells, where RIG-I plays a dominant role over MDA5 in activating innate immunity. However, recent research suggests that animals lacking RIG-I may undergo compensatory evolutionary changes in MDA5, enabling it to partially fulfill RIG-I’s function. This raises the question: why does innate immunity in some animals rely on RIG-I, while in others, MDA5 takes on the primary role?

While the antiviral role of RIG-I is well characterized, the function of MDA5 in activating the interferon response remains less understood, even in human cells. It is therefore unsurprising that our understanding of MDA5 function in birds remains very limited. This project aims to explore the role of MDA5 in triggering the antiviral response in avian cells, focusing on the initial stages of this process. Given that *Anseriformes* possess both RIG-I and MDA5, we will investigate whether the immune response in ducks is more similar to that in chickens or humans? Key questions include: Does the network of MDA5 interactions regulate its function across species, or does MDA5’s affinity for double-stranded ligands influence its antiviral efficacy?

To address these questions, the project will focus on three main research tasks:

- Analyze the MDA5 interactome in human and avian cells to look for species-specific key factors regulating MDA5 activity.
- Characterize the post-translational modification (PTM) profile of avian MDA5 to understand contribution of PTMs to mount proper interferon response.
- Compare the ability of human and avian MDA5 to trigger an effective interferon response to double-stranded RNA.

This project is expected to provide a more comprehensive understanding of immune pathway variations across species, facilitating the development of effective countermeasures in poultry farming to reduce the transmission of infectious diseases. Additionally, it will contribute to our knowledge of the long-term evolutionary arms race between viruses and host cells.