Cholesterol is a critically important substance for our bodies—it builds cell membranes and supports the production of hormones and vitamins. However, excess cholesterol can lead to serious health issues, including atherosclerosis, heart disease, and strokes. Although current cholesterol-lowering therapies effectively help many patients, they often fall short for some individuals or cause undesirable side effects. Moreover, elevated cholesterol frequently coexists with other metabolic disorders such as type 2 diabetes, obesity (excessive body fat), or lipodystrophy (abnormal distribution of fat tissue). Together, these conditions greatly elevate the risk of developing atherosclerosis, heart attacks, and premature death.

In our project, we aim to thoroughly investigate a recently discovered hormone named cholesin. This hormone is produced by cells in the small intestine in response to cholesterol-rich meals. Once released into the bloodstream, cholesin travels, among other places, to the liver, where it interacts with a receptor called GPR146. This interaction reduces the liver's cholesterol production, subsequently decreasing its blood levels. Discovered in 2024, this mechanism is not yet fully understood but holds significant promise for developing novel therapies for cardiovascular diseases.

Yet, cholesin's role appears to extend beyond just regulating cholesterol. Our preliminary research indicates that cholesin may also influence fat metabolism in adipose tissue, suggesting its broader systemic impact than previously thought. Additionally, we observed that other metabolic disorders, such as type 2 diabetes and the medications used to treat it, influence the functioning of the GPR146 receptor.

In this project, we plan to thoroughly investigate the mechanisms of action of cholesin and its receptor, GPR146—from the hormone's secretion and influencing factors through detailed molecular processes in human tissues, to the application of new chemical compounds to control receptor activity.

Using advanced laboratory techniques and computational simulations, we aim to precisely define how cholesin affects human health and the metabolic changes in individuals with various diseases. Our research will include blood analyses from patients with metabolic disorders, exploring the relationship between cholesin levels and key health indicators such as lipid profiles, glucose levels, and inflammation markers. Additionally, we will screen commercially available chemical libraries to identify compounds capable of modulating cholesin and GPR146 activity. This crucial step may lead to developing new, more effective therapies, especially valuable for individuals poorly responding to current treatments.

We expect our research to yield groundbreaking findings, enabling the development of more effective, safer, and personalized therapies for lipid disorders, significantly reducing the risk of severe cardiovascular diseases.