Almost all calorie uptake from ingested nutrients takes place in the intestine. Fats are the densest energy source and evolution has promoted the individuals of higher fat absorption efficiency thus increasing the chance to survive in the time of food deprivation. That robust capacity is ensured by enterocytes, absorptive cells of the small intestine epithelium, which equipped in specialized enzymatic machinery transfer dietary lipids in the form of lipoprotein particles known as chylomicrons that are secreted to the circulation to supply triglycerides to the peripheral organs. The same trait that provided survival to ancestors, currently is one of the factors for globally growing incidence of obesity. Change of lifestyle to more sedentary combined with high consumption of fat enriched diets contribute to current status of obesity as a disease that affects more people than malnutrition in almost every region of the world, according to WHO. However, the individuals do not respond equally well to dietetic interventions aimed at weight loss. This creates a need for searching for pharmacological therapies to combat obesity and its comorbidities (such as type 2 diabetes or non-alcoholic fatty liver disease). Minimizing intestinal absorption of fats, which are energy-densest nutrients, appears to be a logical choice. In our recently published study we identified Protein Kinase D2 (PKD2) as a promoter of intestinal fat absorption which genetic or pharmacological inhibition protects from diet induced obesity and improves metabolic profile via reduction of size (lipidation) of chylomicrons secreted to the circulation. My newest preliminary data indicate that PKD2 not only regulates the size of chylomicrons, but is relevant for their post-secretion transport in the intestine, which can be an additional mechanism of PKD2-dependent promotion of lipid absorption. In our project we are going to investigate the signaling pathways integrated by PKD2 and involved in chylomicron synthesis and transport. We belive that the outcomes of proposed research will not only result in identification of novel mechanisms mediating fat absorption in the intestine, but will also lead to the generation of new pharmacological strategies to treat obesity and related diseases in the next attempts.