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My name is Katharina Kaiser and I am a third year PhD student at the DDZ in Düsseldorf with the group of Prof. Hadi Al-Hasani.

My award winning project comprises the identification of causal genes for type 2 diabetes and obesity.

Our group uses crossbreedings of diabetes-susceptible New Zealand Obese (NZO) strains with lean, diabetes-resistant mice, in this case the 129P2/Ola strain. By genotyping with high density SNP panels and phenotyping for diabetes related traits like blood glucose, plasma insulin, body weight and other metabolic traits, risk loci for diabetes can be identified through linkage analysis.

This way we were able to identify a risk loci linked to elevated blood glucose and plasma insulin on chromosome 4 (*Nbg4*). To narrow down the number of possible candidate genes in this locus a recombinant congenic strain (RCS) was generated by breeding the proximal or distal region of this locus into the NZO background through introgression. These RCS were also genotyped and phenotyped for diabetic traits. Mice harboring the proximal region revealed the highest accordance with the parental lines. Gene expression and microarray analysis revealed *Alad* (aminolevulinate, delta-, dehydratase), *Svep1* (sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1) and *Ptpn3* (protein tyrosine phosphatase, non-receptor type 3) as possible candidate genes in gWAT.

The selected candidate genes were further investigated through knockdown or overexpression in 3T3-L1 adipocytes. To investigate their role in blood glucose control, functional assays including insulin-stimulated glucose uptake, Oil Red O staining and quantitative real time PCR were performed.

Si-RNA mediated knockdown of *Svep1* revealed a reduction in gene expression of adipogenic markers *Adipoq* and *Fabp4*, as well as lipolysis associated genes *Hsl* and *Atgl*. Retroviral Overexpression of *Ptpn3* led to decreased lipid accumulation quantified by Oil Red O staining. Also, the gene expression of the lipolysis associated marker *Plin1* was found to be reduced in 3T3-L1 adipocytes in response to *Ptpn3* overexpression. Si-RNA mediated knockdown of *Alad* showed an influence on glucose uptake of

adipocytes. Increasing knockdown efficiency correlates with a decreased insulin stimulated glucose uptake into the 3T3-L1 cells.

These findings indicate a possible role of *Alad*, *Svep1* and *Ptpn3* in glucose and lipid metabolism in adipocytes. All genes constitute novel candidates for diabetes-related traits and further experiments will determine their molecular function in fat cells in more detail.