RHAPSODY
for precision therapy and prevention of diabetes

The RHAPSODY project: Biomarkers in type 2 diabetes

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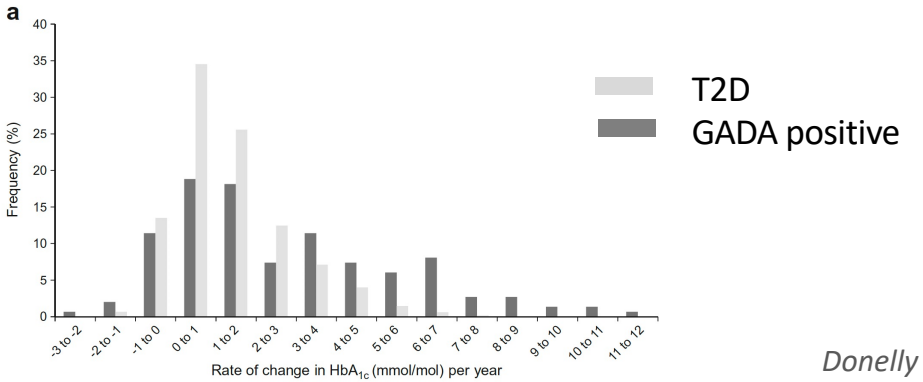
Development of type 2 diabetes: A stepwise process

Normal glycemic control → Prediabetes (Impaired Glucose tolerance /Impaired Fasting glycemia) → Type 2 diabetes → Diabetes deterioration

Rate of glycemic deterioration in T2D patients from the GoDarts cohort (HbA_{1C}/year)



Donelly LA, et al., Diabetologia, 2018

Development of type 2 diabetes: A stepwise process

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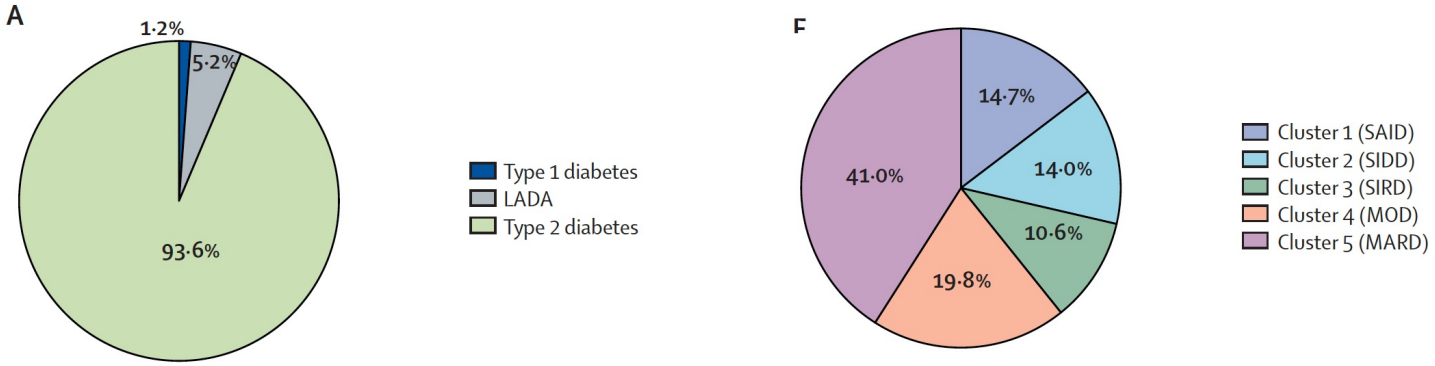
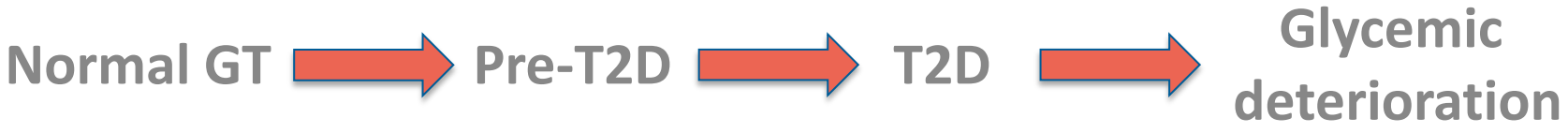


Ahlqvist E et al., The Lancet Diabetes Endocrinology, 2018

Identification of biomarkers



Specific Questions:

- Can we identify biomarkers that are prognostic of T2D susceptibility and T2D deterioration?
- Can such biomarkers predict dysfunctions in ß-cells or in insulin target tissues?
- Can we identify the tissues and metabolic pathways controlling the production of these biomarkers?

Biomarkers

- Molecules that can be objectively measured and evaluated as an indicator of normal biological or pathogenic processes, as well as pharmacological response to a therapeutic intervention

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

Plasma Biomarkers

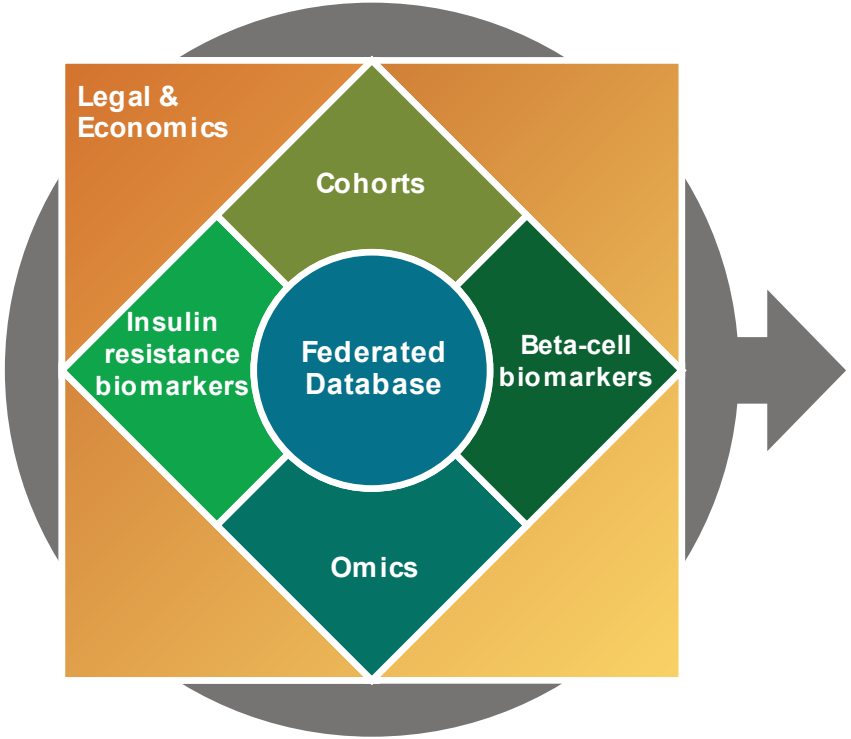
- Lipids
- Polar metabolites
- Proteins
- RNAs

Plasma Biomarkers

Requirements for biomarker discovery:

- Technological platforms for quantitative measurements of molecular species
- Patient cohorts with detailed phenotyping and biosamples (plasma)
- Preclinical models of prediabetes/diabetes
- Federated database for all data storage and analysis

RHAPSODY Plasma Biomarkers Strategy



Biomarkers for:

- ✓ Disease stratification
- ✓ Diagnosis
- ✓ Disease monitoring
- ✓ Innovative clinical trials

Use of preclinical models to identify biomarkers of diabetes susceptibility and of ß-cell dysfunction

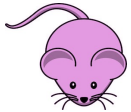
- Use of preclinical models to identify candidate biomarkers for the **progression to type 2 diabetes** and validation in human cohorts

- Use of preclinical models to identify plasma biomarkers **predictive of ß-cell function** and to identify the **metabolic pathways** involved in biomarker production

Use of preclinical models to identify biomarkers of diabetes susceptibility and of ß-cell dysfunction

6 mouse strains


C57Bl/6


A/J


Balb/c


AKR


129S2

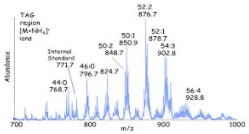

DBA/2J

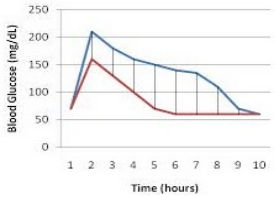

Weight


High Fat

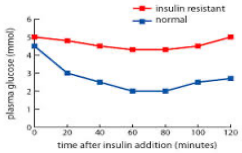

Regular

2, 10, 30 and 90 days

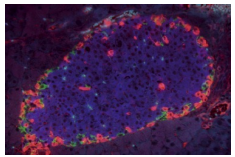

Lipidomics



Glucose Tolerance
Insulin secretion

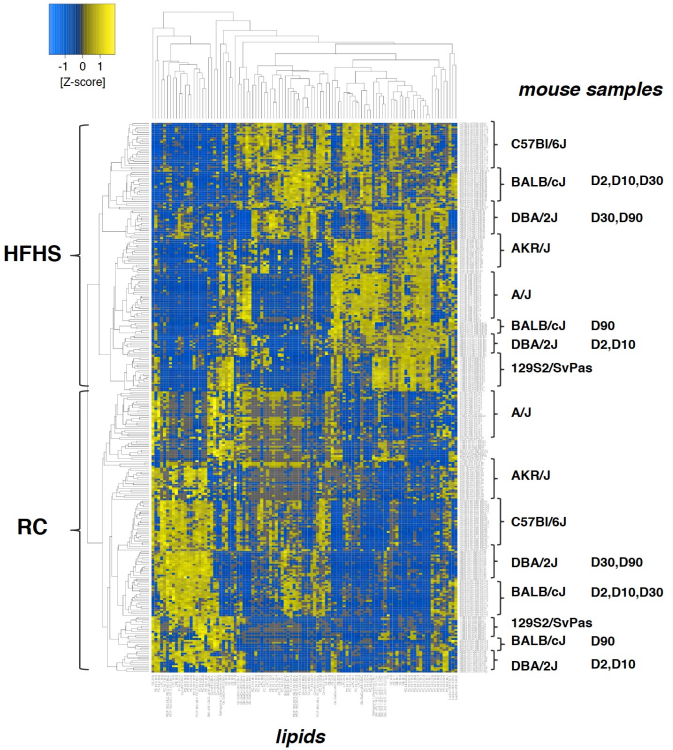


Insulin Tolerance


Islet morphology


RNA-Seq
Islets, liver, fat, muscle

Integrative analysis of plasma lipidomics with mouse physiological traits



Lipid profiles across all conditions (6 strains, 4 time points, 2 diets)

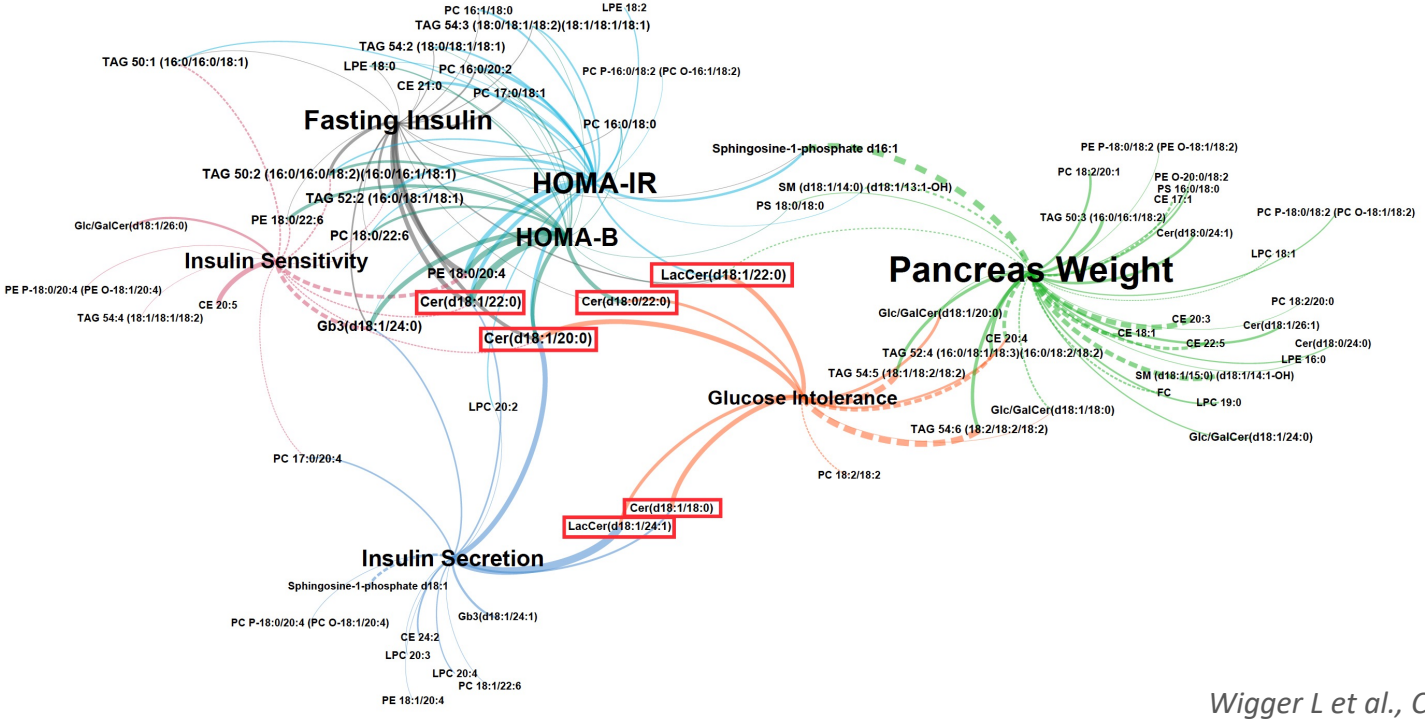
Correlation, hierarchical clustering

Modules of lipids with similar profiles

Correlation of module profiles with physiological traits

Investigation of trait-associated lipid modules

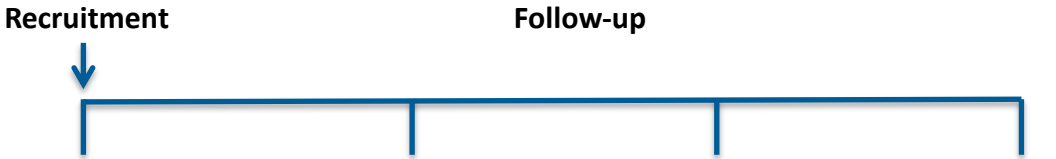
Ceramides are correlated to glucose intolerance and insulin sensitivity in metabolically challenged mouse strains



Wigger L et al., Cell Reports, 2017

Analysis of ceramides in the plasma of individuals from the DESIR cohort

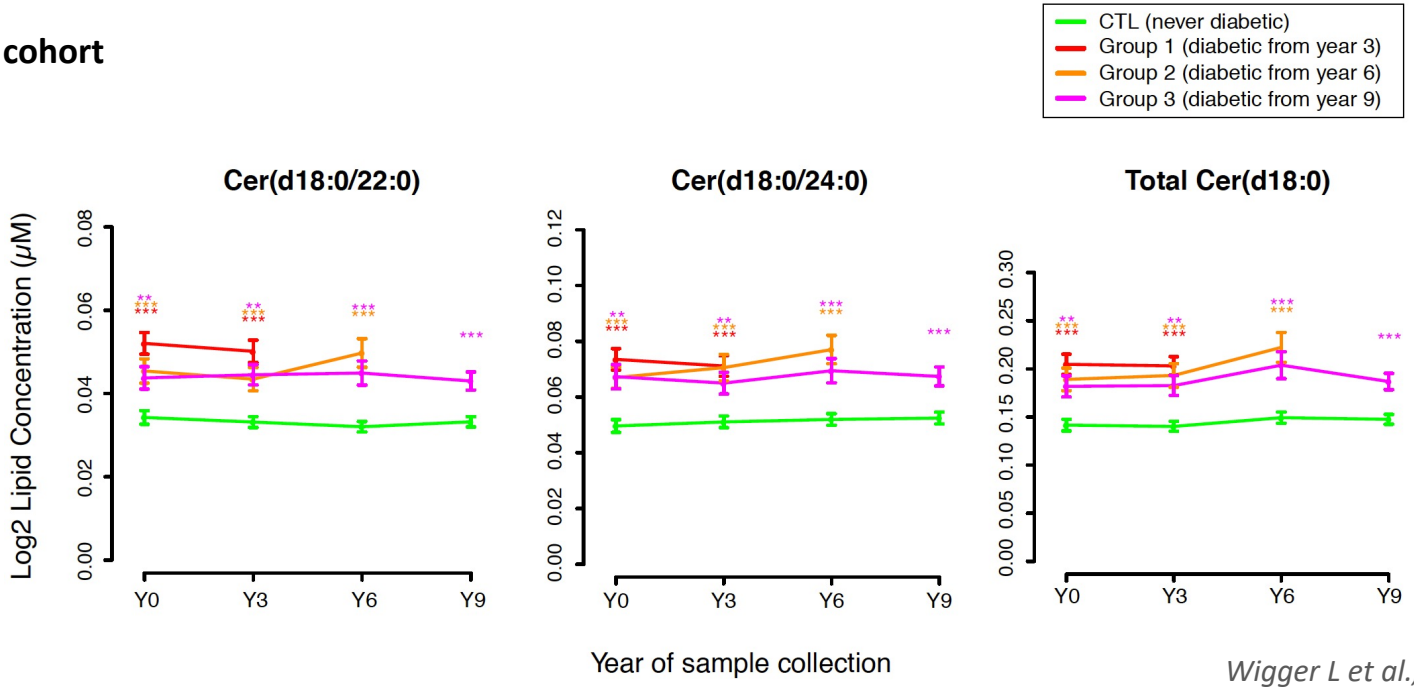
- Prospective cohort of > 5000 people followed for > 9 years
- **Summary of plasma analysis**



Group 1: 82 ND	82 T2D		
Group 2: 48 ND	48 ND	48 T2D	
Group 3: 62 ND	61 ND	61 ND	61 T2D
Control: 105 ND	102 ND	102 ND	97 ND

Dihydroceramides are enriched in the plasma of T2D patients up to 9 years before diagnostic

The DESIR cohort



Wigger L et al., Cell Reports, 2017

Use of preclinical models to identify biomarkers of diabetes susceptibility and of ß-cell dysfunction

- Use of preclinical models to identify candidate biomarkers for the progression to type 2 diabetes and validation in human cohorts

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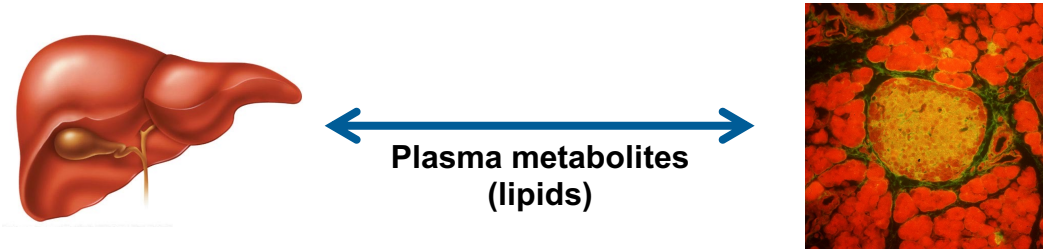
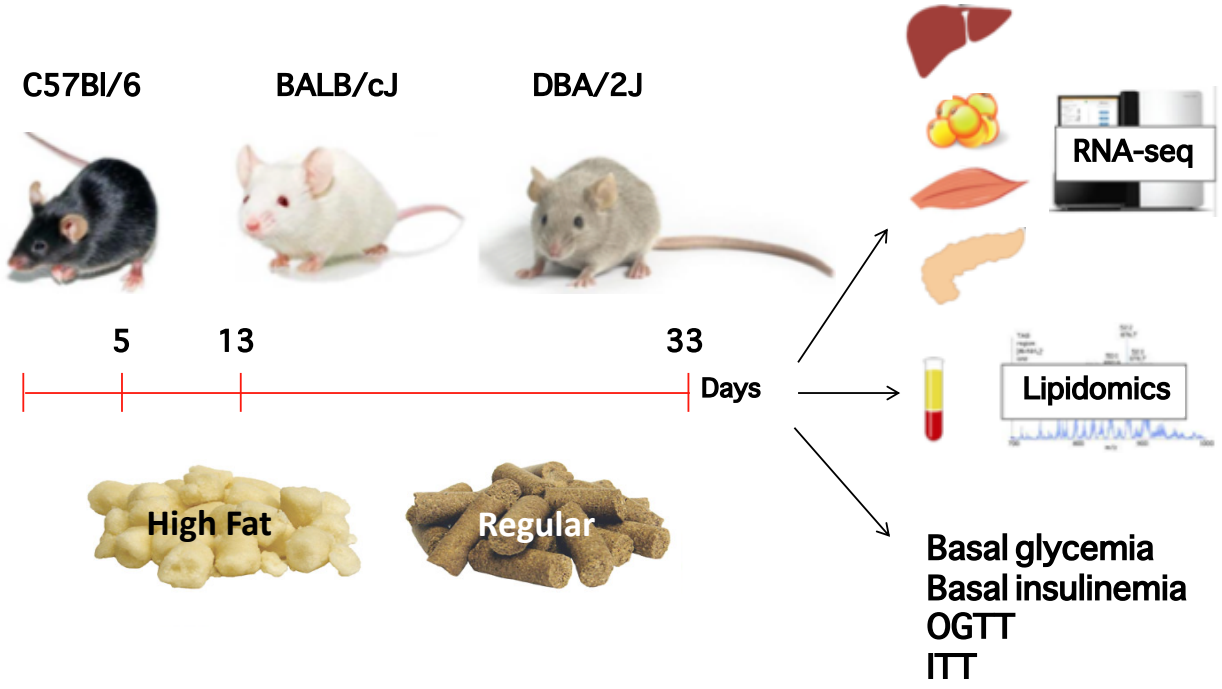
A systems biology analysis of the crosstalk between liver and pancreatic ß-cell function through plasma lipids

- Progressive loss of ß-cell secretion capacity over time

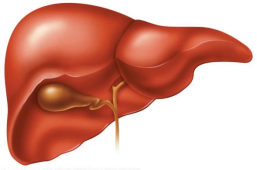


- **Questions**:
  - Can we find plasma biomarkers predictive of ß-cell function?
  - Can we identify the tissue and metabolic pathway that produce the biomarker?
  - Can we establish a link between a tissue metabolic pathway – plasma biomarkers – and ß-cell function?

Search for plasma lipids as potential biomarkers: experimental design



Plasma Triglycerides (TAGs) correlate with ß-cell insulin secretion genes and liver fatty acid degradation pathway

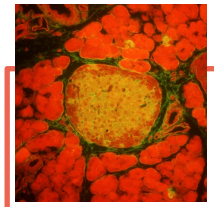


Fatty acid degradation (ß-oxidation)

-

TAGs

-



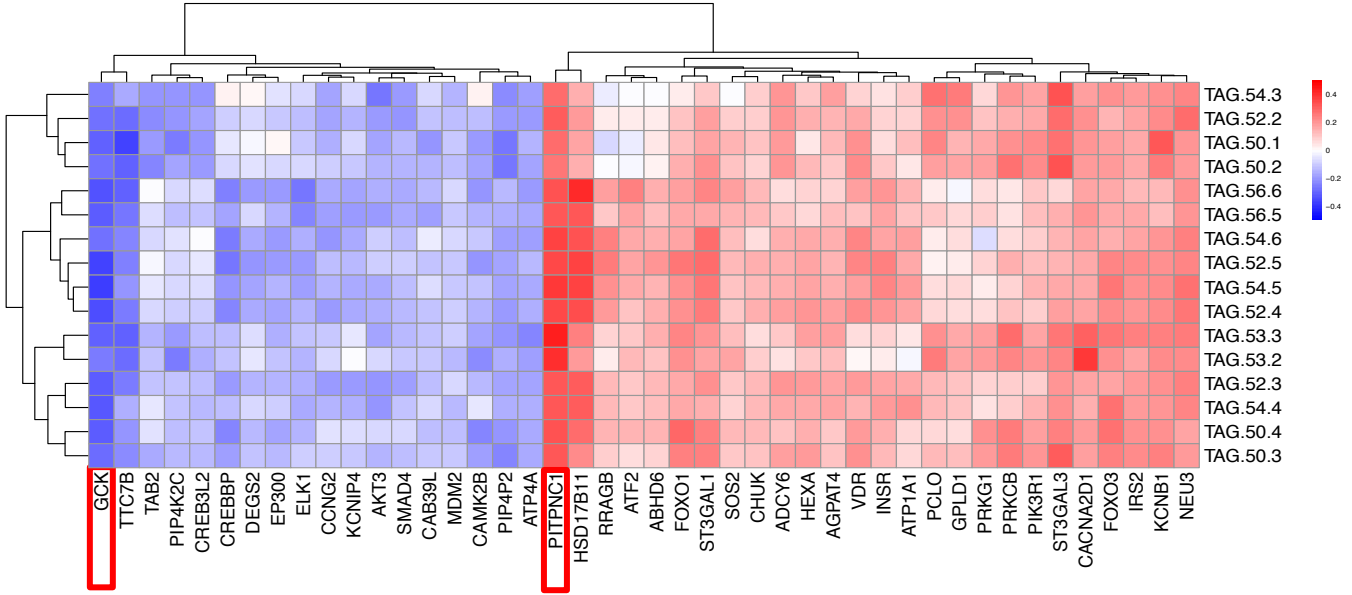
Glucose-stimulated insulin secretion (GSIS)

Rodriguez Sanchez-Archidona A. et al., submitted

IN HUMANS: Same correlation between plasma TAGs and insulin secretion genes as in mice

- Islets from partially pancreatectomized patients
- Plasma lipids from the same patients

Wigger L. (…) Solimena, M., Nat. Metabolism, 2021



➔ **Identification of PITPNC1 as a novel regulator of insulin secretion**

Rodriguez Sanchez-Archidona A. et al., submitted

Conclusions

- The use of preclinical models allowed to identify plasma biomarkers for type 2 diabetes susceptibility
- Such biomarkers were found to be prognostic biomarkers also in humans
- These biomarkers could be demonstrated to correlate with the function of pancreatic ß-cells
- Comparative analysis in mice and humans of the correlation between plasma TAGs and islet gene expression allowed to characterise a so far unknown regulator of insulin secretion

RHAPSODY biomarker identification in humans

(See presentation by R. Slieker)

- Biomarker discovery was assayed for:
  - Proteomics
  - Lipids
  - Polar metabolites

- **Phase 1: Discovery** of biomarkers of T2D progression using samples from the three RHAPSODY discovery cohorts (NT = 9900)

- **Phase 2: Replication** of biomarkers of T2D progression (NT= 4000)

- **Phase 3:** Establishment of a **biomarker shortlist**

Biomarker shortlist includes the same lipids identified in preclinical models

Lipidomics:

- TAG class (namely 50.1.0, 46.1.0, 46.2.0, 48.1.0, 51.1.0, 48.2.0, 48.3.0 and 49.1.0)

- Sphingomyelin (SM 42.2.2)

Next steps

Evaluate the utility of the biomarkers in a **prospective clinical trial** to assess their utility for:

- **Stratification of diabetic patients** - to more precisely identify high-risk subjects at baseline more likely to respond to a specific intervention

- **Monitoring of diabetes progression** - to improve understanding of the course of the disease, or specific symptoms of the disease

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Thank you for your attention!

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