CAELUS HEALTH

FMT-based discovery
From platform to product

DUTCH LIFE SCIENCES CONFERENCE 2018

MICROBIOME THERAPEUTICS

Oegstgeest, 29 November 2018

TOPICS

FMT-based discovery
Cardio-metabolic disorders
Diabetes Mellitus and NASH/NAFLD

Pipeline of microbiota-based products
Clinical evaluations
Metagenomics

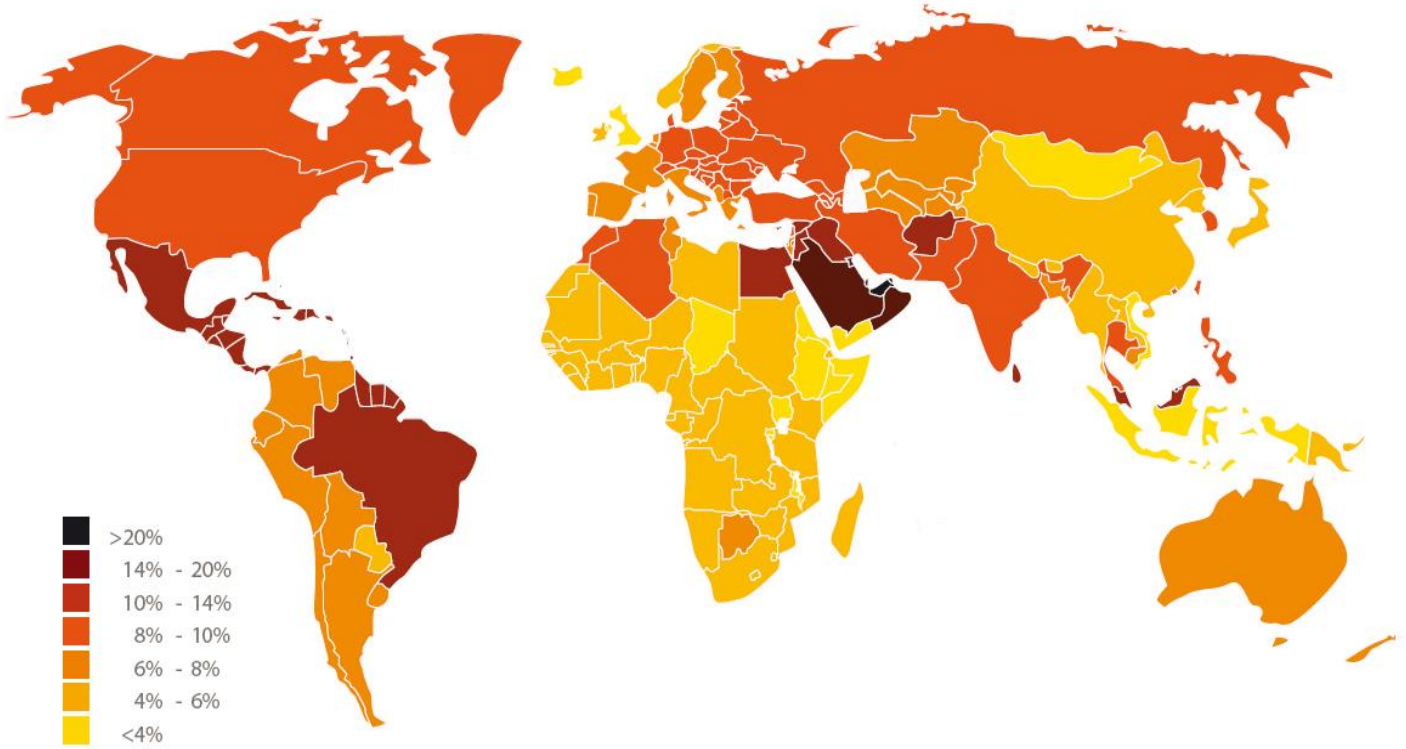
Platform approach
Reverse engineering
Leads from FMT-studies
Systematic in-vitro and in-vivo screening of new leads

First company with novel therapeutic strains to reduce cardio-metabolic disorders

Market data

- Global pandemic of obesity and Diabetes mellitus
- Huge burden for both subjects & society - health care budgets
- Strong need for early intervention

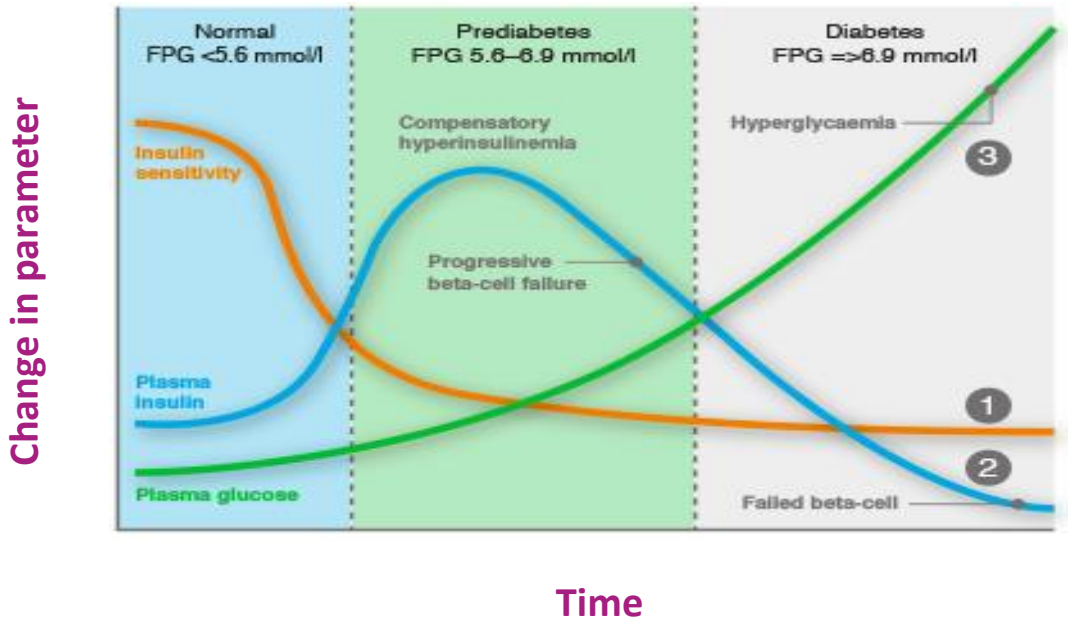
Prevalence estimates of diabetes, 2025



SOURCE: *DIABETES ATLAS THIRD EDITION*, © INTERNATIONAL DIABETES FEDERATION, 2006

Metabolic syndrome or pre-diabetes

- 1 out of 3 individual
  Syndrome develops
- Diabetes mellitus is
  disorders
- This needs to be str
- Preferrably by early
  treatment



1. Insulin resistance
2. Failed beta cells
3. Hyperglycemia

From platform to pipeline

LEAD DISCOVERY

- FMT - in cardiometabolic field (MetS, NASH)
- Biostatistics - Datamining

LEAD EVALUATION

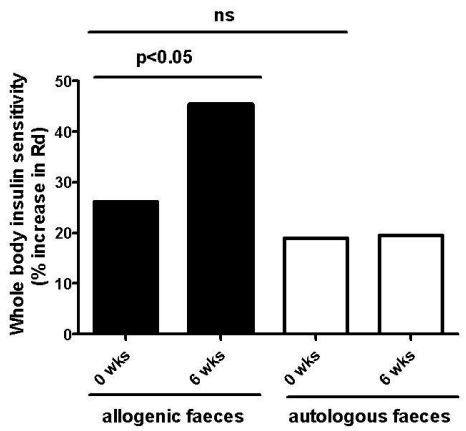
- Validated in-vitro & in-vivo models
- Genomics and metabolomics

PIPELINE

- MetS/Type 2 diabetes
- NAFLD/NASH

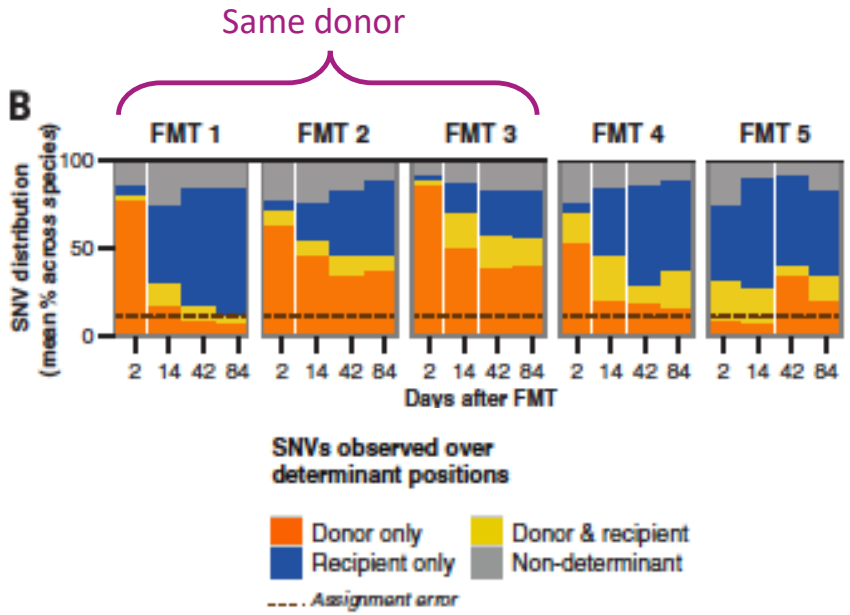
FMT from lean donor – improves insulin sensitivity

Whole body insulin sensitivity increased



Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome, Vrieze et al, Gastroenterology 2012

One stool does not fit all



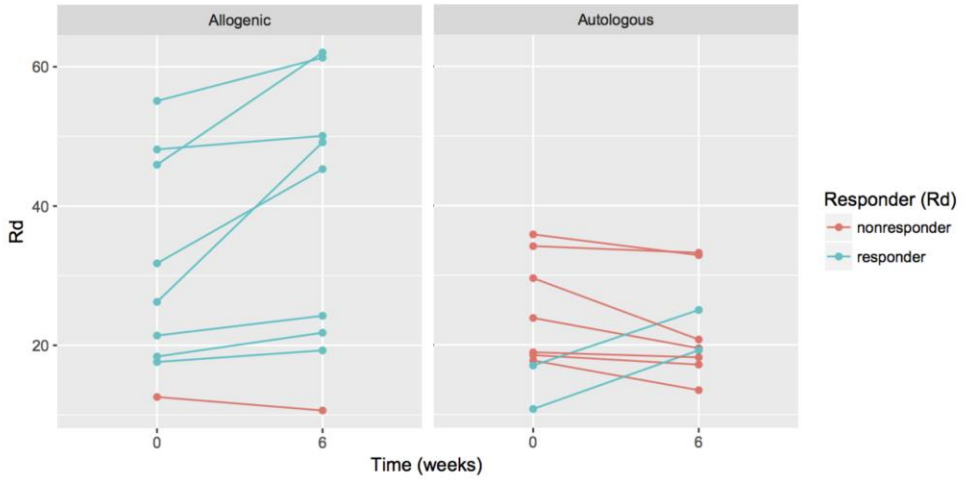
Retrieved from: Sciencemag.org

Durable Coexistance of Donor and Recipient Strains after Fecal Microbiota Transplantation, Simone S. Li et al, Science 2016

FMT from lean donor – improves insulin sensitivity

Whole body insulin sensitivity increased

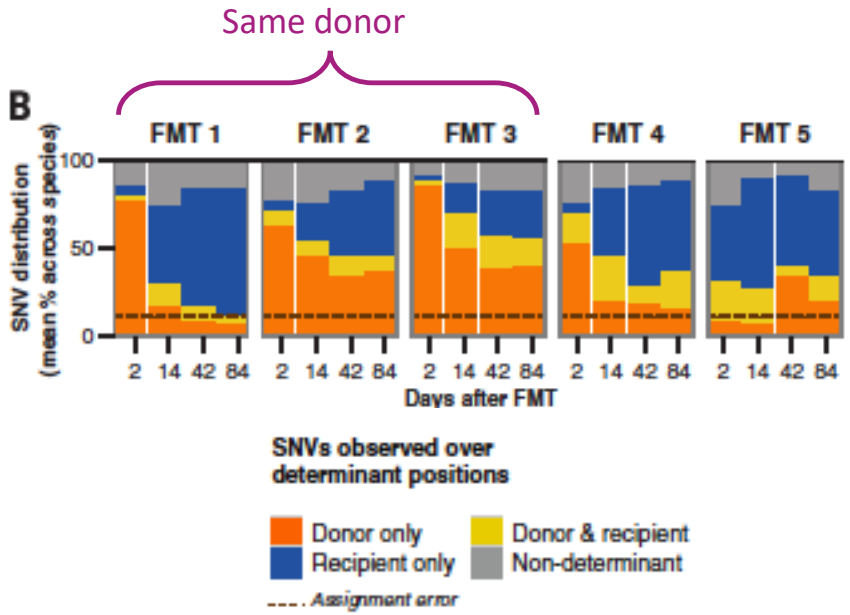
Figure 3: Rd values by patient over time



Increased Rate of Disappearance (Rd)

Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome, Vrieze et al, Gastroenterology 2012

One stool does not fit all



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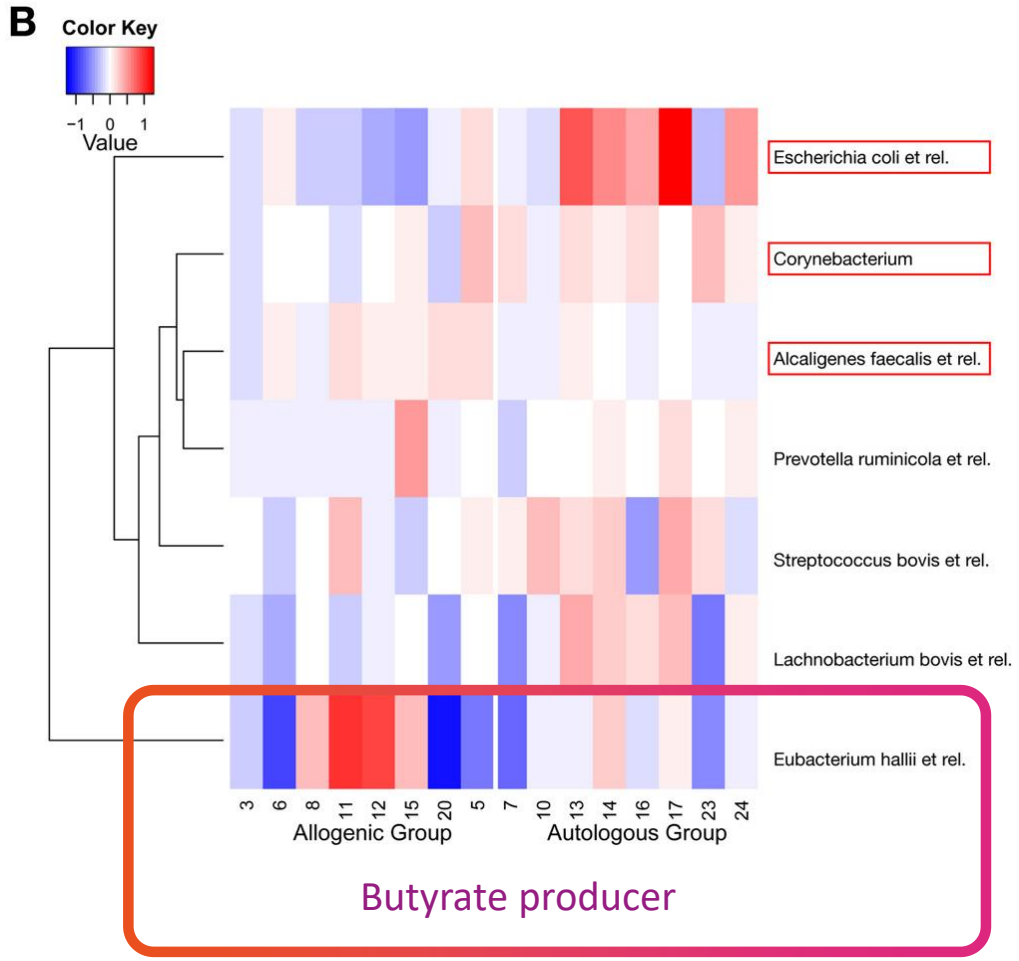
Beneficial changes in small intestinal *E. hallii* after fecal transplant

Remarkably high correlation of beneficial gene expression was linked to the abundance of relatives of *E. hallii*

The abundance of relatives of *E. coli* was linked to damaging gene expression

Demonstration of colonisation resistance versus new species

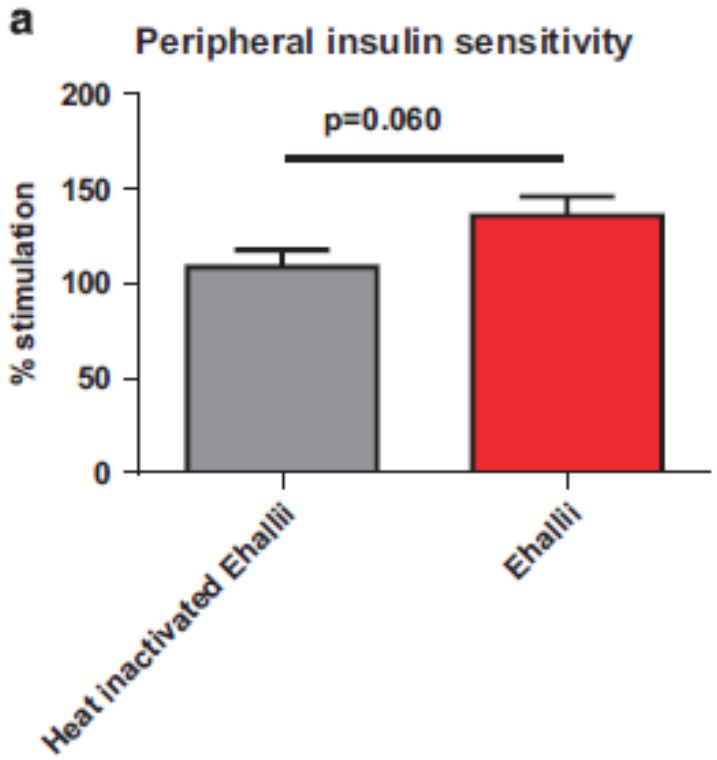


Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome, Vrieze et al, Gastroenterology 2012

Major change in insulin sensitivity after *E. hallii* treatment

An animal study in db/db mice comparing the effect of 4 week intervention with active ***E. hallii*** **led to a close-to-significant increase in the ability of insulin to stimulate Rd***
Rd = Rate of disappearance
measure of peripheral insulin sensitivity

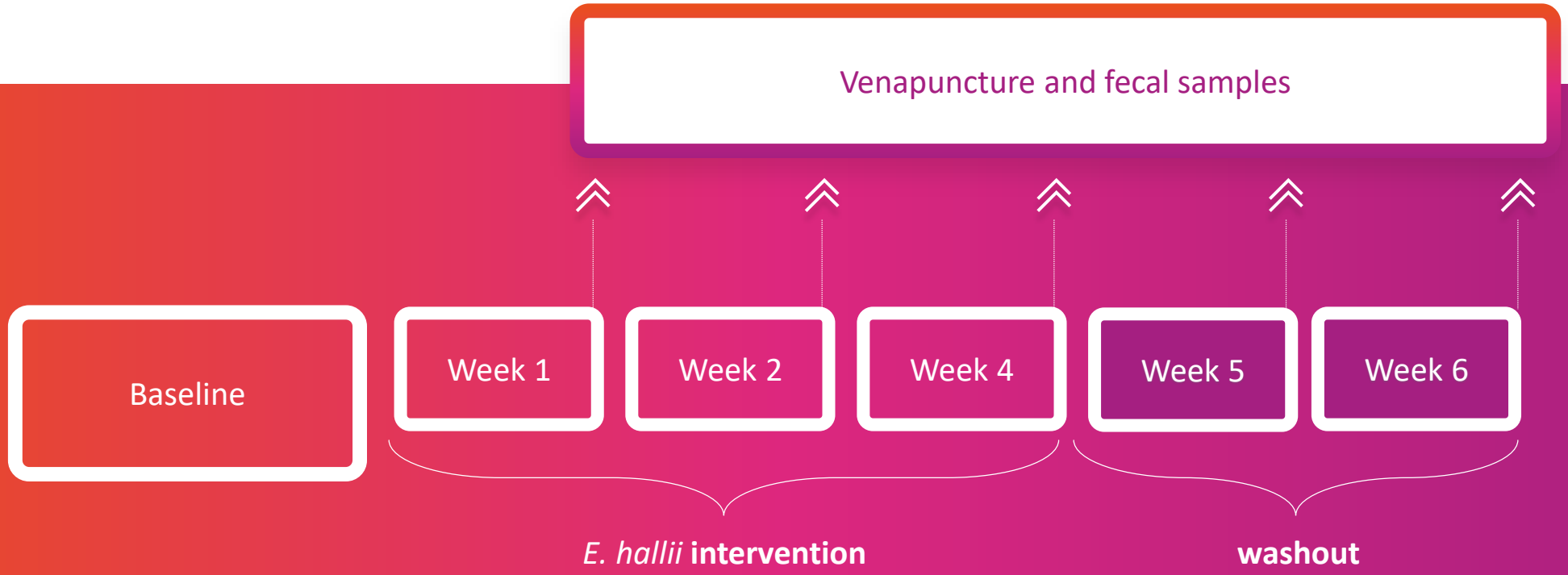
Significant dose-depending improvement of metabolic parameters in mice.



Udayappan et al, NPJ Biofilms 2016

DIME study - design

Dose-ranging study of 4 week intervention with *E. hallii* drink to assess safety and efficacy in male subjects with Metabolic Syndrome



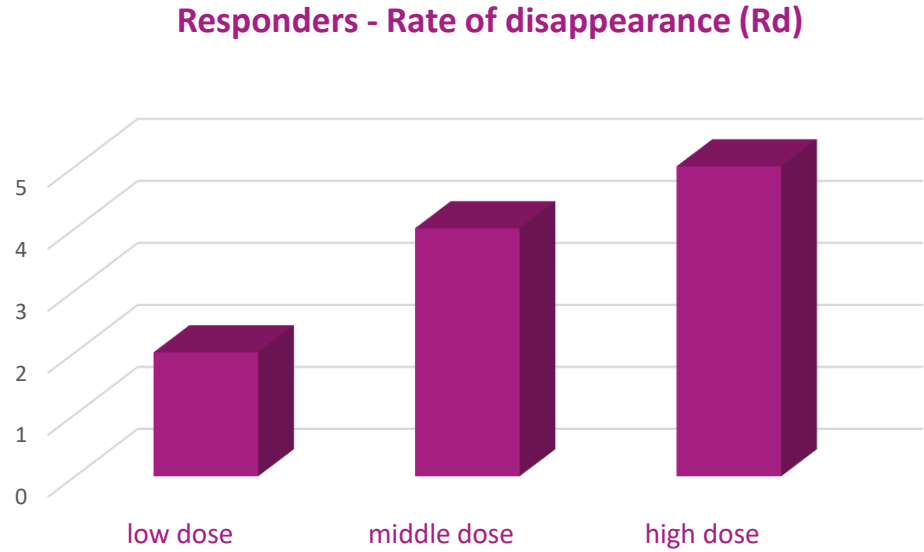
Key parameter:

Insulin sensitivity assessed by HOMA-IR and Hyperinsulinemic clamp

Study of increasing dose levels in male subjects with Metabolic Syndrome (n=9 per group)

DIME study – safety & efficacy #1

- Excellent safety profile
- No serious adverse events, no diarrhoea
- No significant changes in safety parameters (biochemistry, hematology and CRP)
- Average increase in peripheral insulin sensitivity of 23% in middle dose group



- Number of responders increased from low dose (2/9) to high dose (5/9).
- Implicates need for further selection of subjects in future studies and/or stratification for diversity and/or baseline levels of microbiota used as intervention.

DIME study – safety & efficacy #2

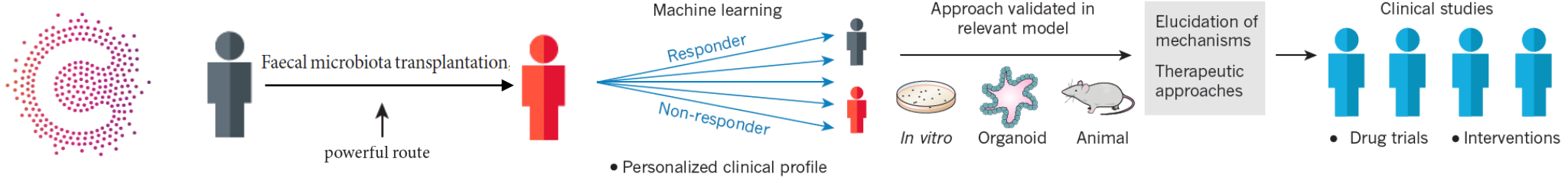
Clinical marker	Rho	P-value
Rd	0.41	0.044*
Rd change	0.39	0.061
Relative Rd change	0.40	0.055

Significant correlation of administered E hallii with change in peripheral insulin senstivity

Metagenomics analysis of the DIME study shows:

- **Significant increase in insulin sensitivity (Rd)**
- **Close to significant relative Rd change**

Development overview and current status



Development based on

- FMT as discovery tool (MetS/T2D, T1D, NAFLD)
  - FMT in Metabolic Syndrome -> first leads
- Screening leads @ WU & JLABS incubator lab

Registration and Commercialization

- Single strain: food supplements
- Combined/consortia: pharma products

Caelus product pipeline

		FMT-discosvery	in-vitro	in-vivo	clinical development
E. halllii	Metabolic syndrome	→			
Intestinimonas	Type 2 diabetes	→			
Microbiota intervention	Type 1 diabetes	→			

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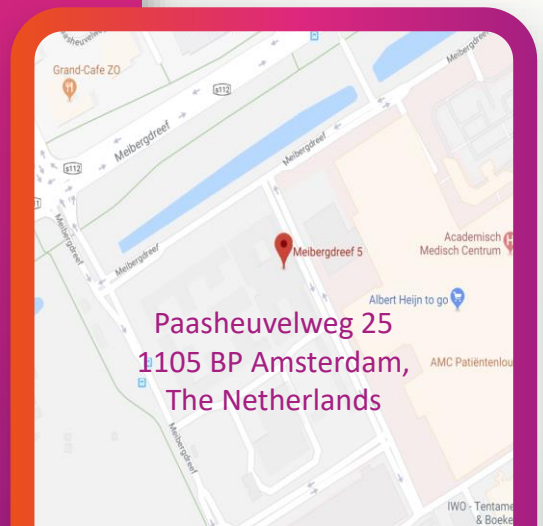

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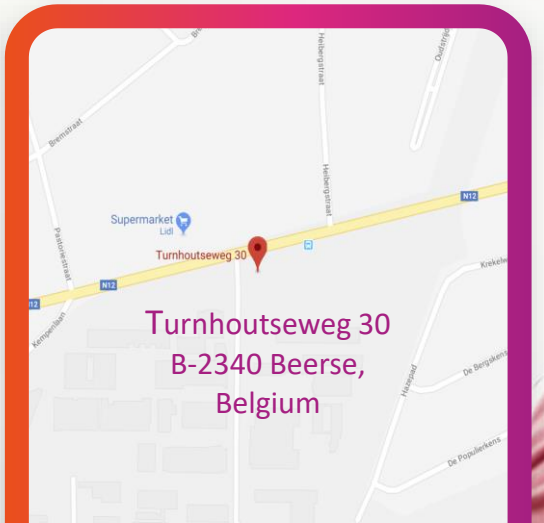

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