



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



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



Pipeline of microbiota-based products
Clinical evaluations
Metagenomics



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

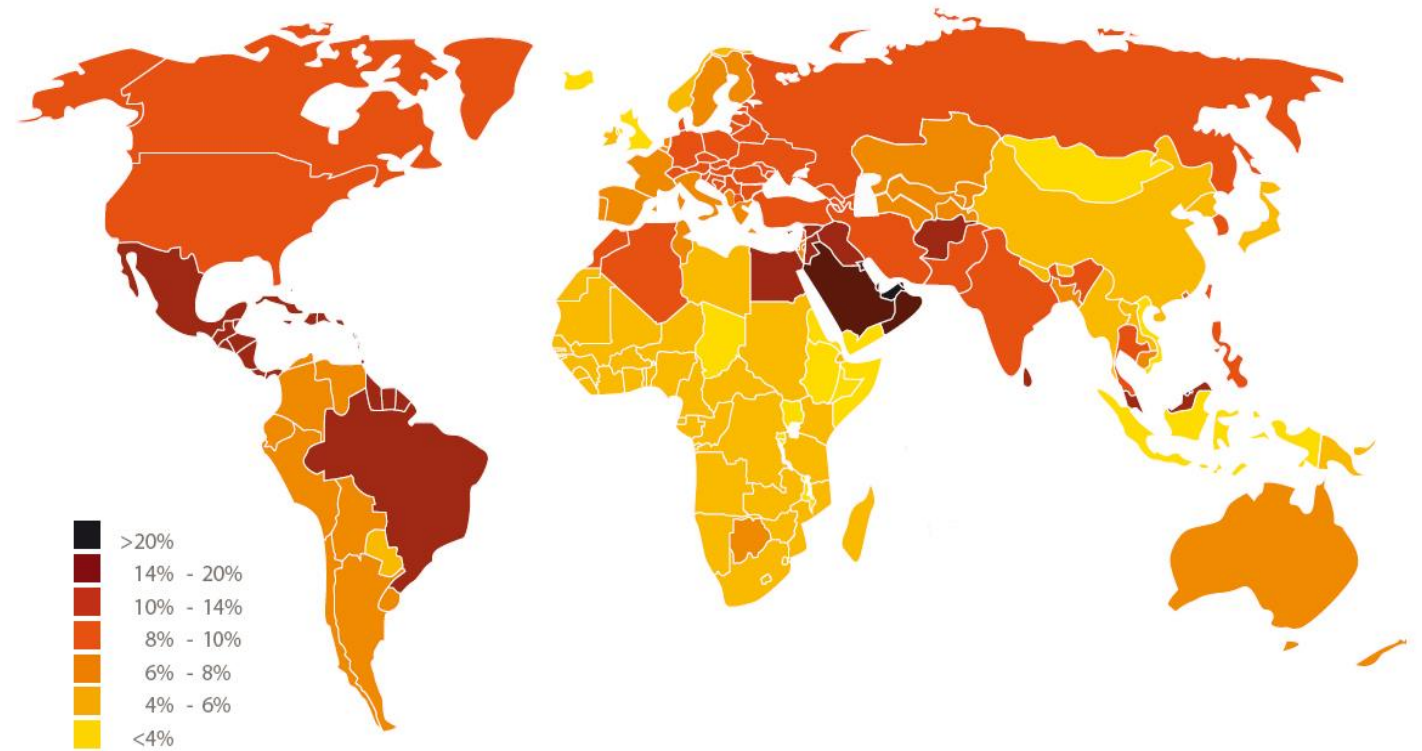
Market data

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

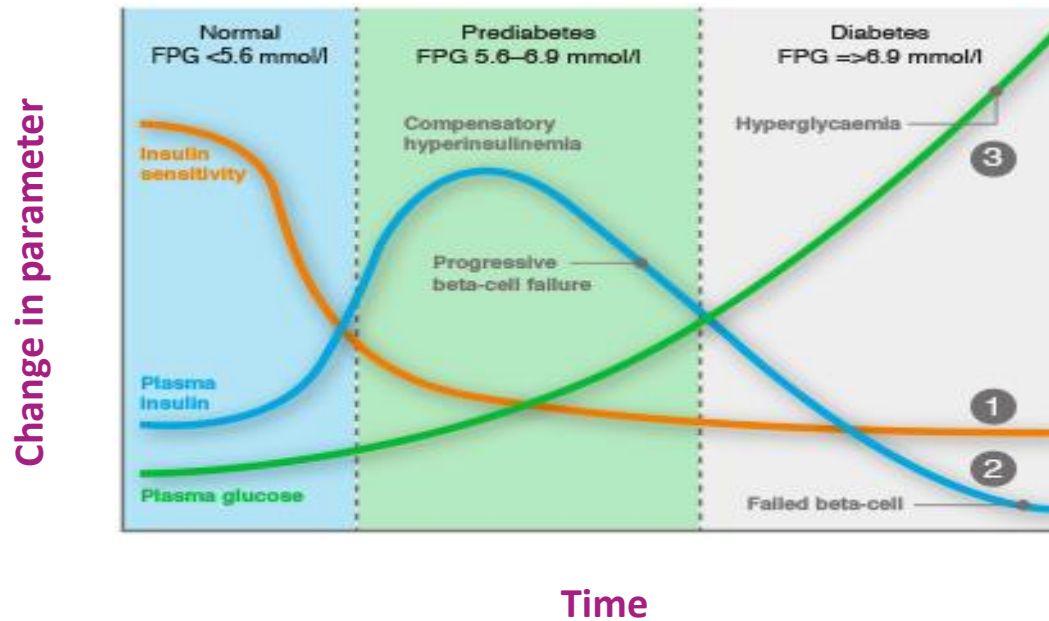
Metabolic syndrome or pre-diabetes

1 out of 3 individuals
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

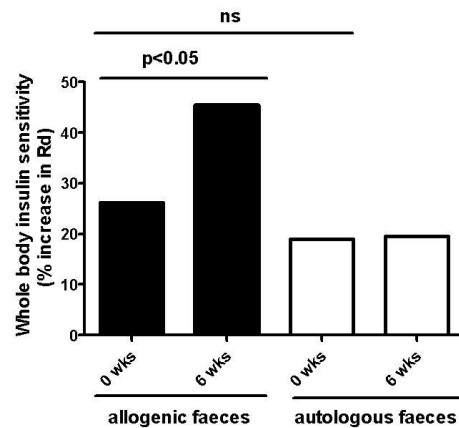
- Validated in-vitro & in-vivo models
- Genomics and metabolomics

PIPELINE

- MetS/Type 2 diabetes
- NAFLD/NASH

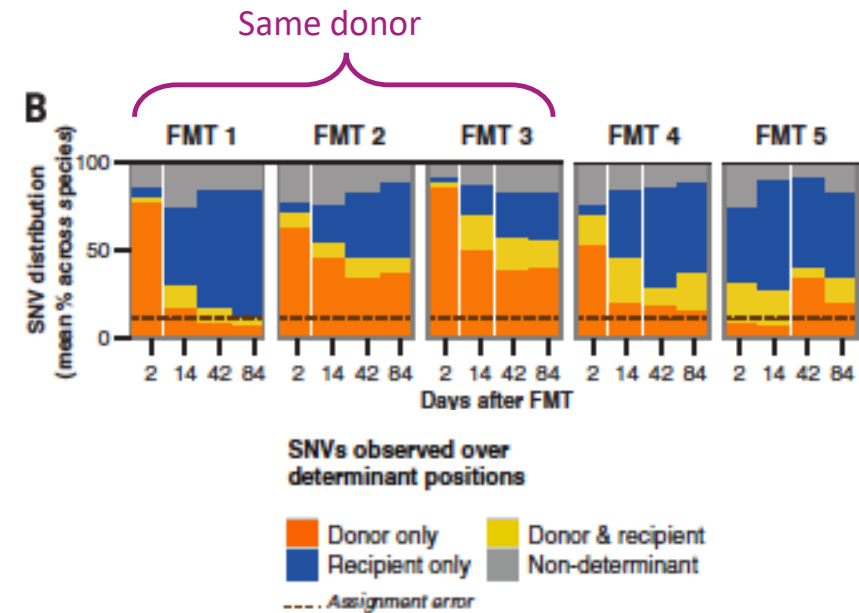
FMT from lean donor – improves insulin sensitivity

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

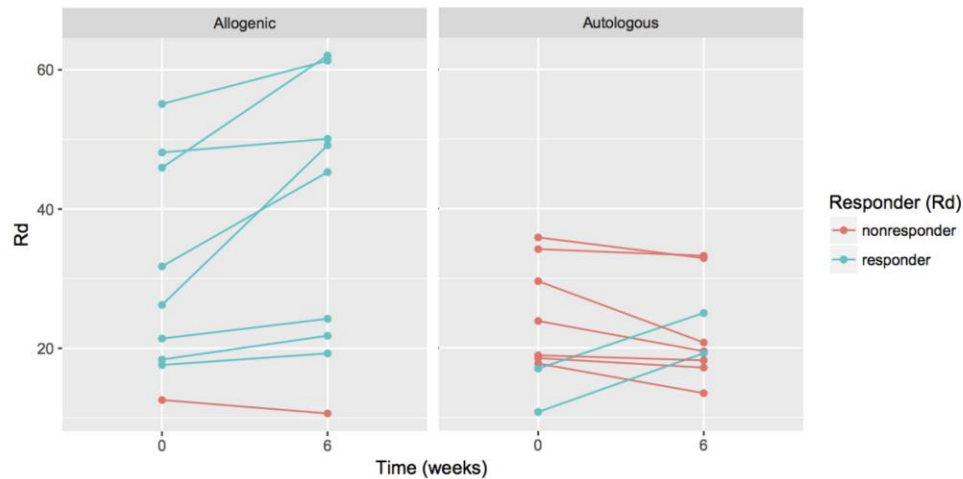


Retrieved from: [Sciencemag.org](https://www.sciencemag.org)
Durable Coexistence of Donor and Recipient Strains after Fecal Microbiota Transplantation, Simone S. Li et al, Science 2016

FMT from lean donor – improves insulin sensitivity

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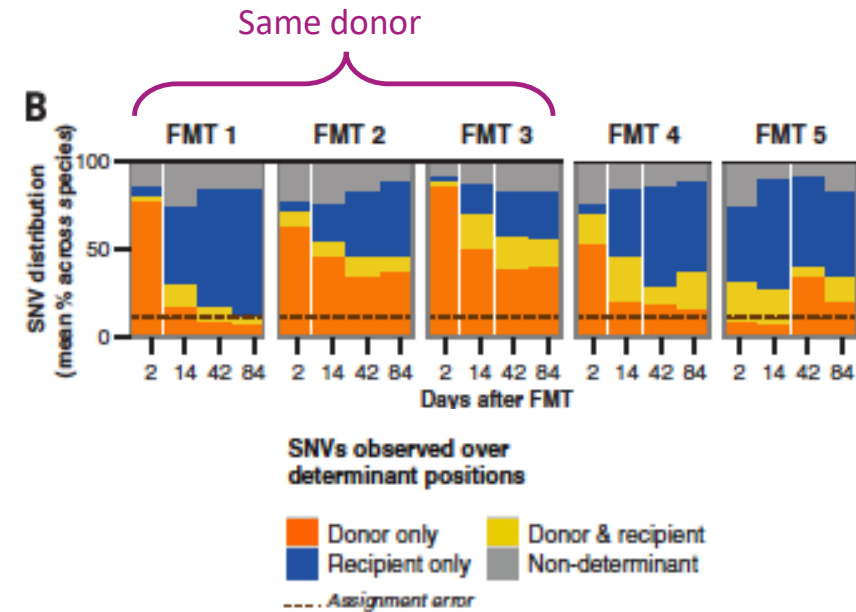
Figure 3: Rd values by patient over time



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



Retrieved from: Sciencemag.org

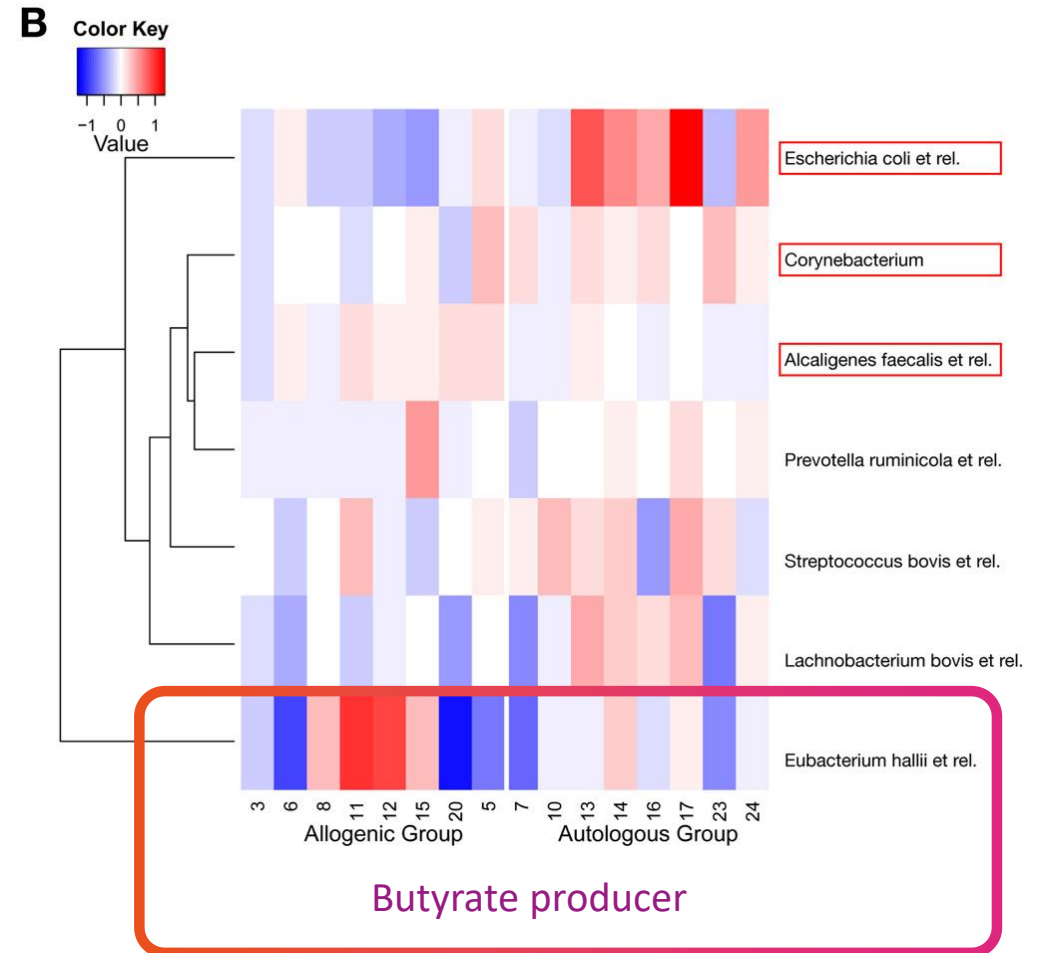
Durable Coexistence of Donor and Recipient Strains after Fecal Microbiota Transplantation, Simone S. Li et al, Science 2016

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



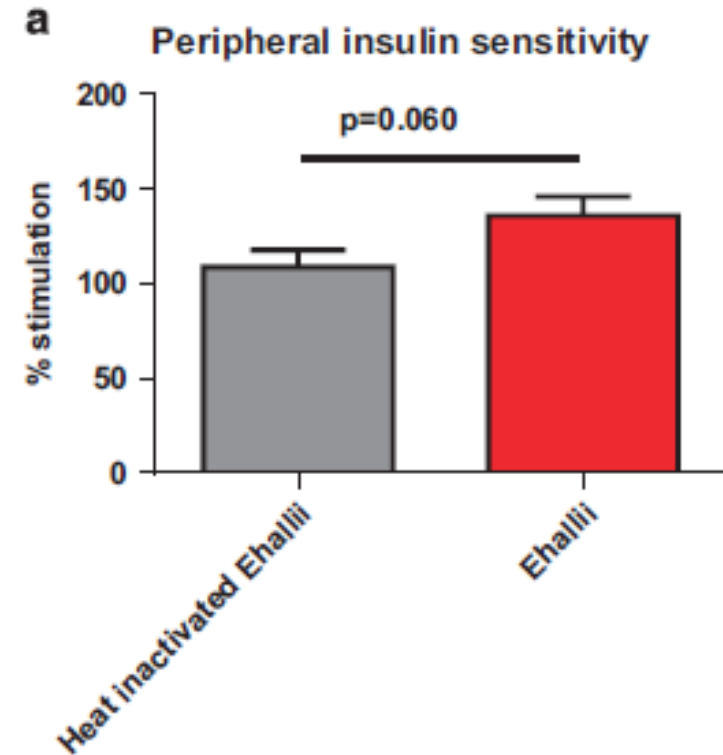
Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome, Vrieze et al, Gastroenterology 2012

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***

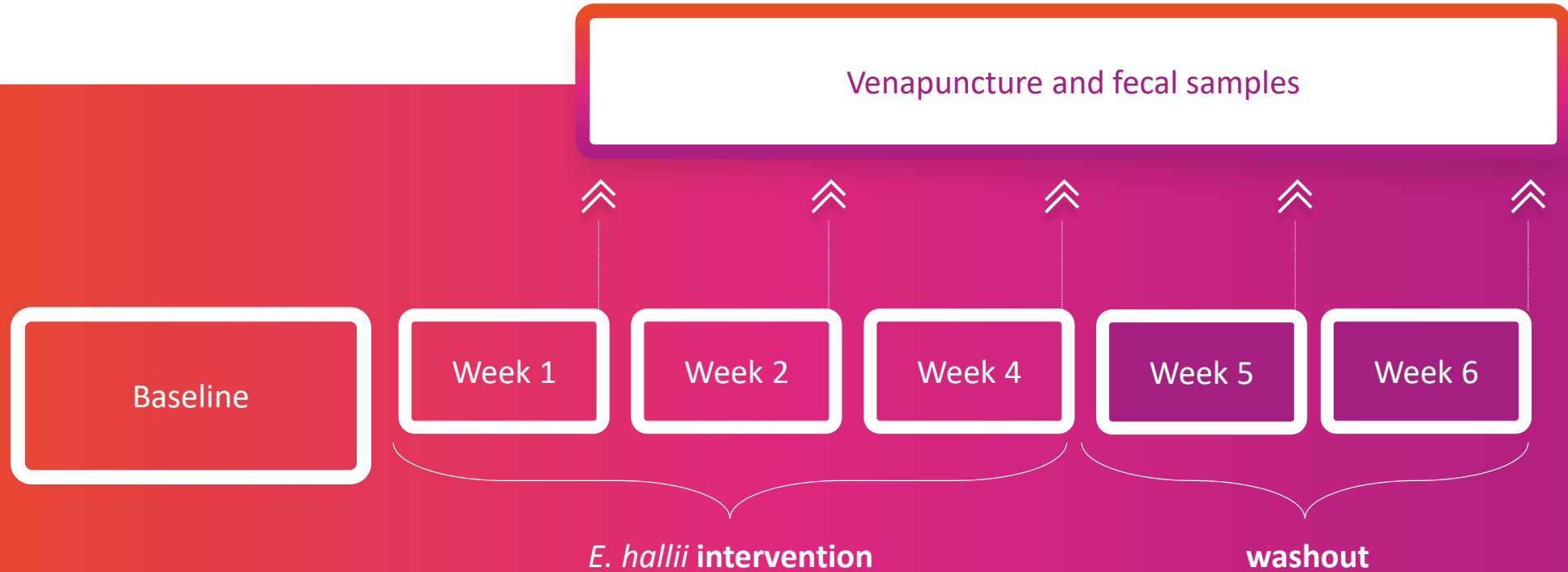
Rd = Rate of disappearance
measure of peripheral insulin sensitivity

Significant dose-depending improvement of metabolic parameters in mice.



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

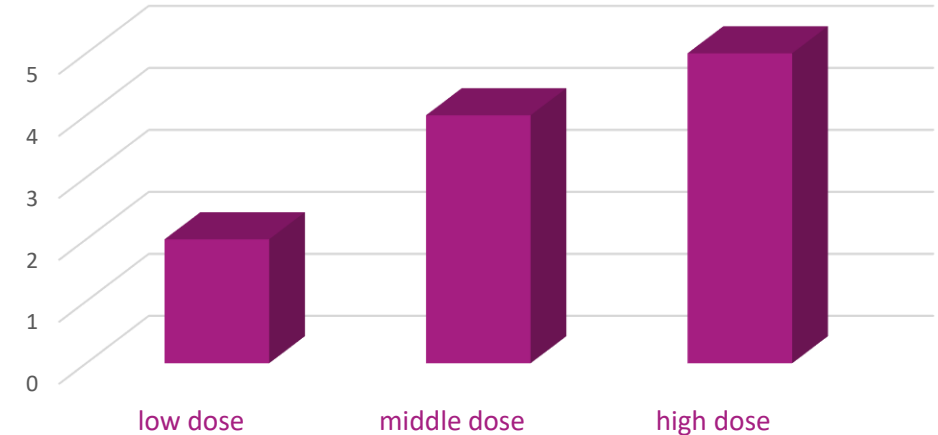
Excellent safety profile

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

Responders - Rate of disappearance (Rd)



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 sensitivity

Metagenomics analysis of the DIME study shows:

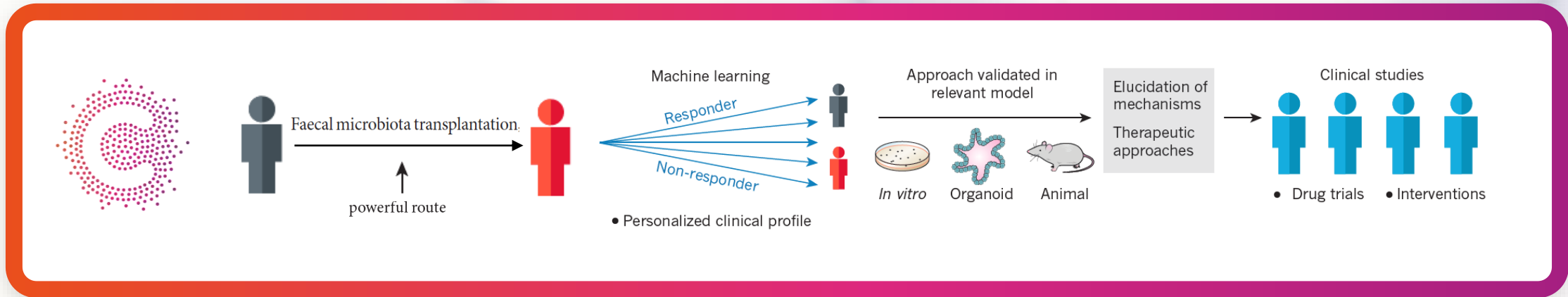


Significant increase in insulin sensitivity (Rd)



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-discovery	in-vitro	in-vivo	clinical development
E. hallii	Metabolic syndrome	—————→			
Intestinimonas	Type 2 diabetes	—————→			
Microbiota intervention	Type 1 diabetes	—————→			



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