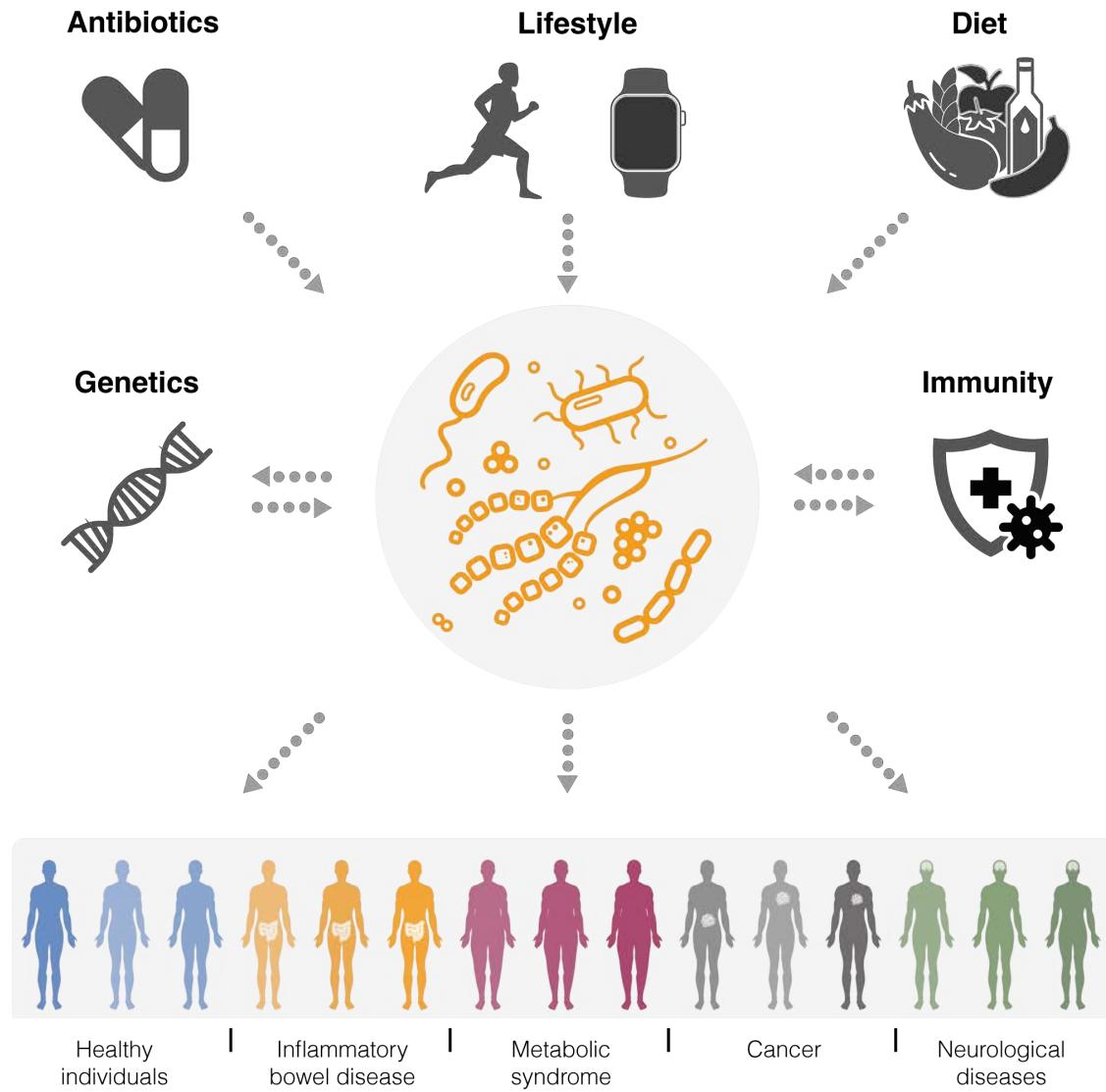


# ON THE MICROBIOME “SWEET-TOOTH”

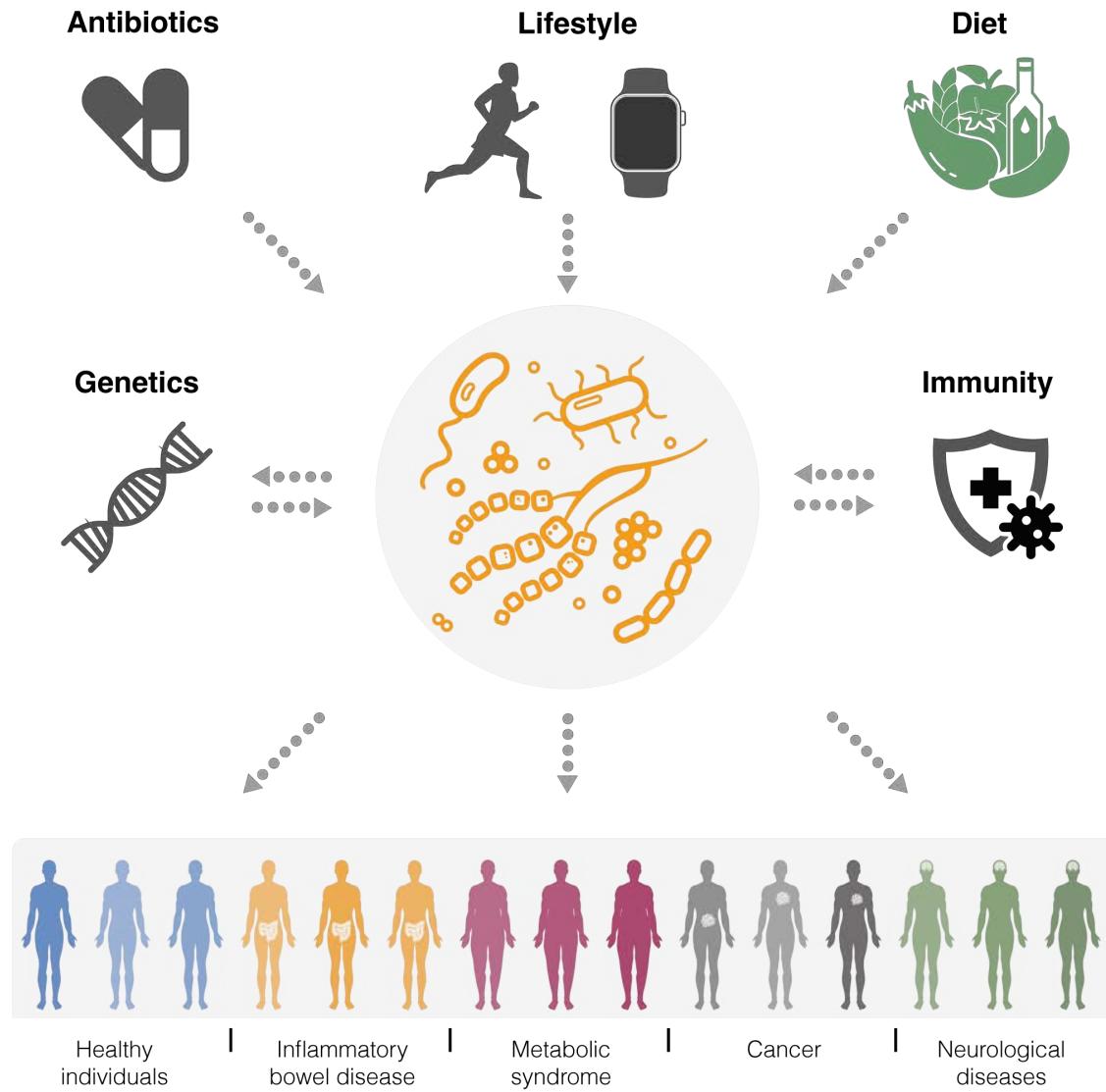


Rafael Valdés-Mas, Ph.D.  
Elinav Lab | Postdoctoral researcher

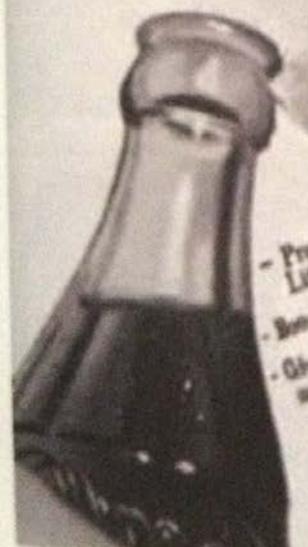
# MICROBIOME IS A SIGNALING HUB



# MICROBIOME IS A SIGNALING HUB



For a better start in life  
**start COLA earlier!**



### How soon Is too soon?

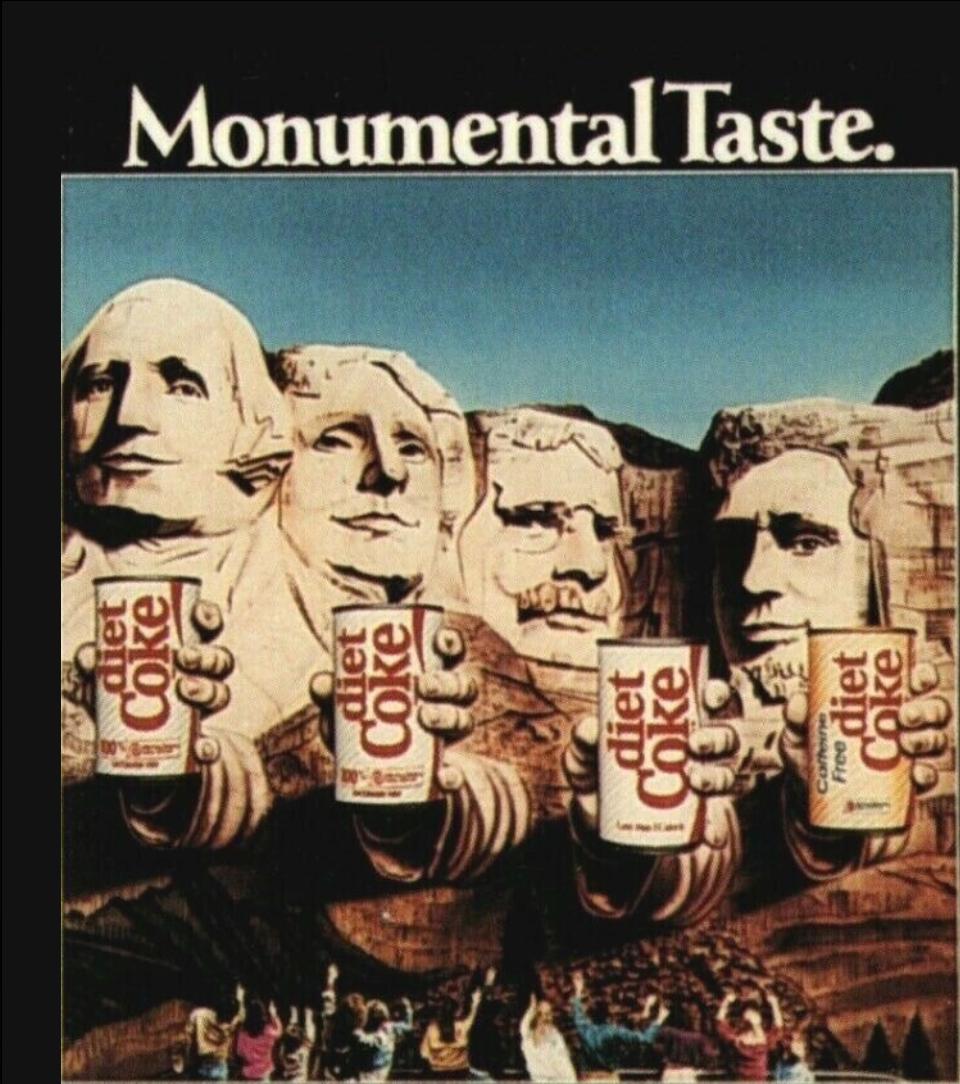
Not soon enough. Laboratory tests over the last few years have proven that babies who start drinking soda during that early formative period have a much higher chance of gaining acceptance and "fitting in" during those awkward pre-teen and teen years. So, do yourself a favor. Do your child a favor. Start them on a strict regimen of sodas and other sugary carbonated beverages right now, for a lifetime of guaranteed happiness.

The Soda Pop Board of America  
1515 W. Hart Ave., Chicago, Ill.

Fake ad (RJ White)

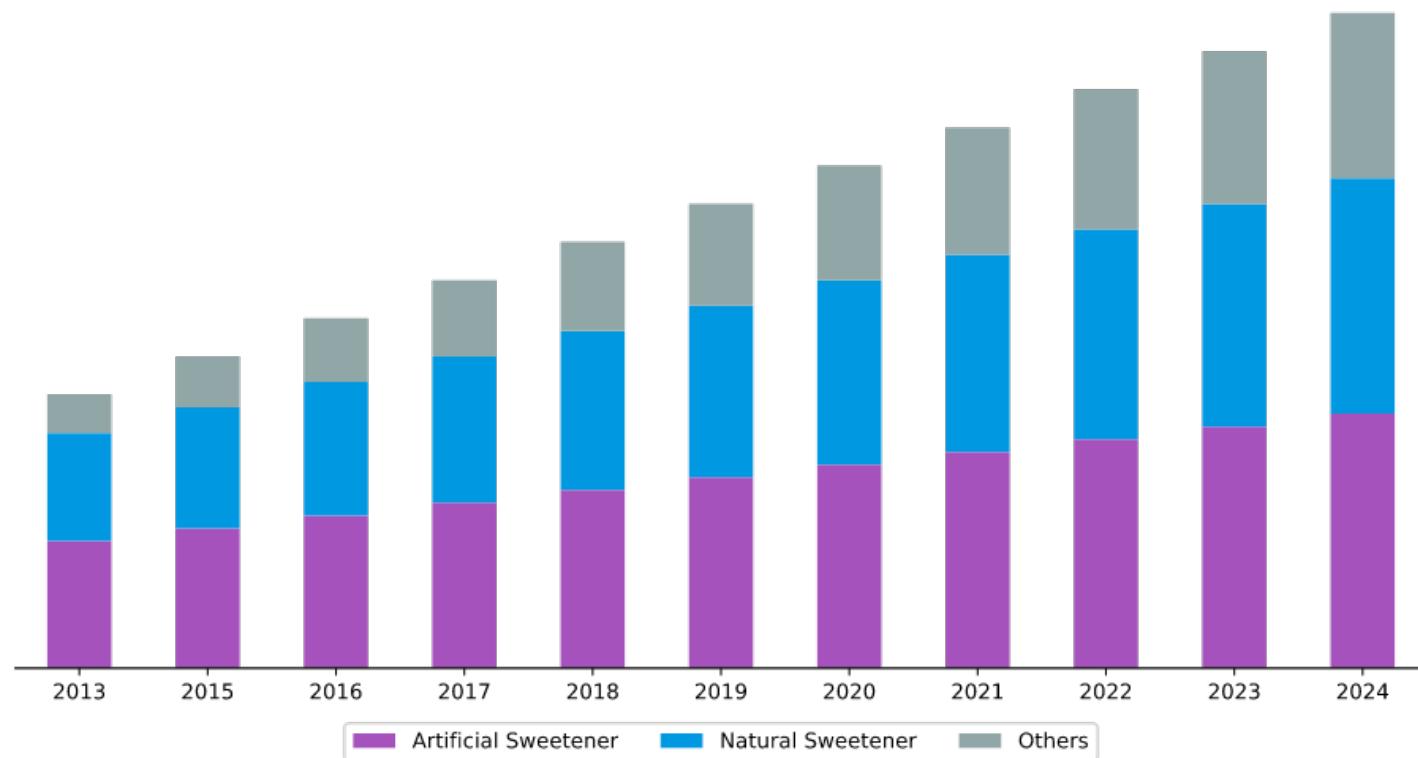


## NON-NUTRITIVE SWEETENERS (NNS)

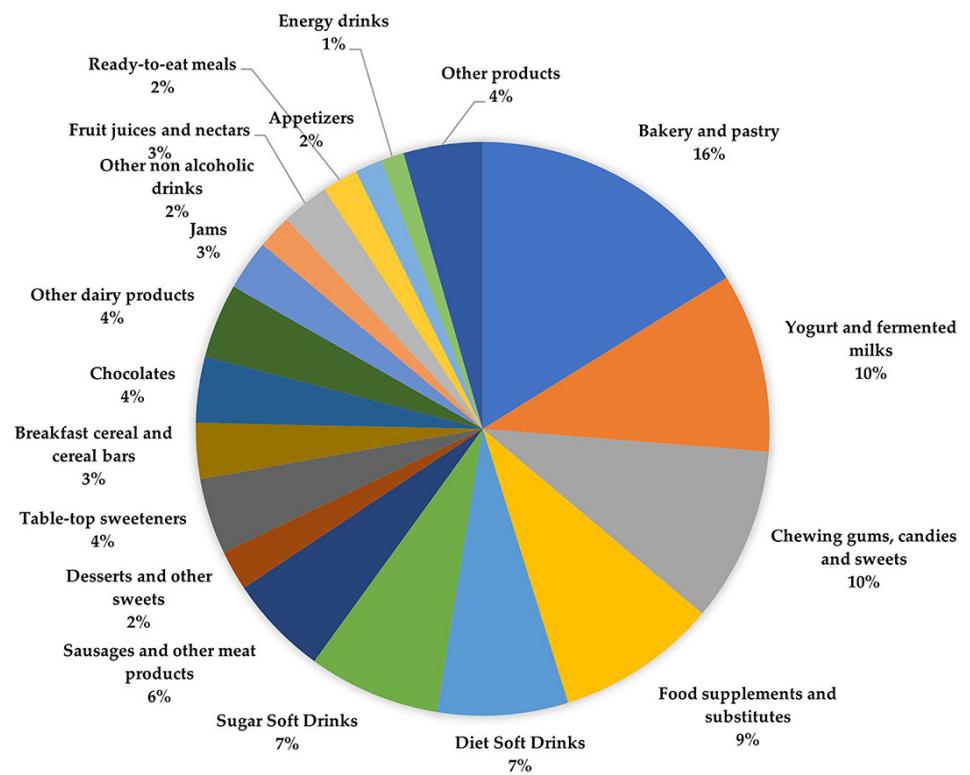


# NNS ARE HIGHLY POPULARIZED ACROSS THE WORLD

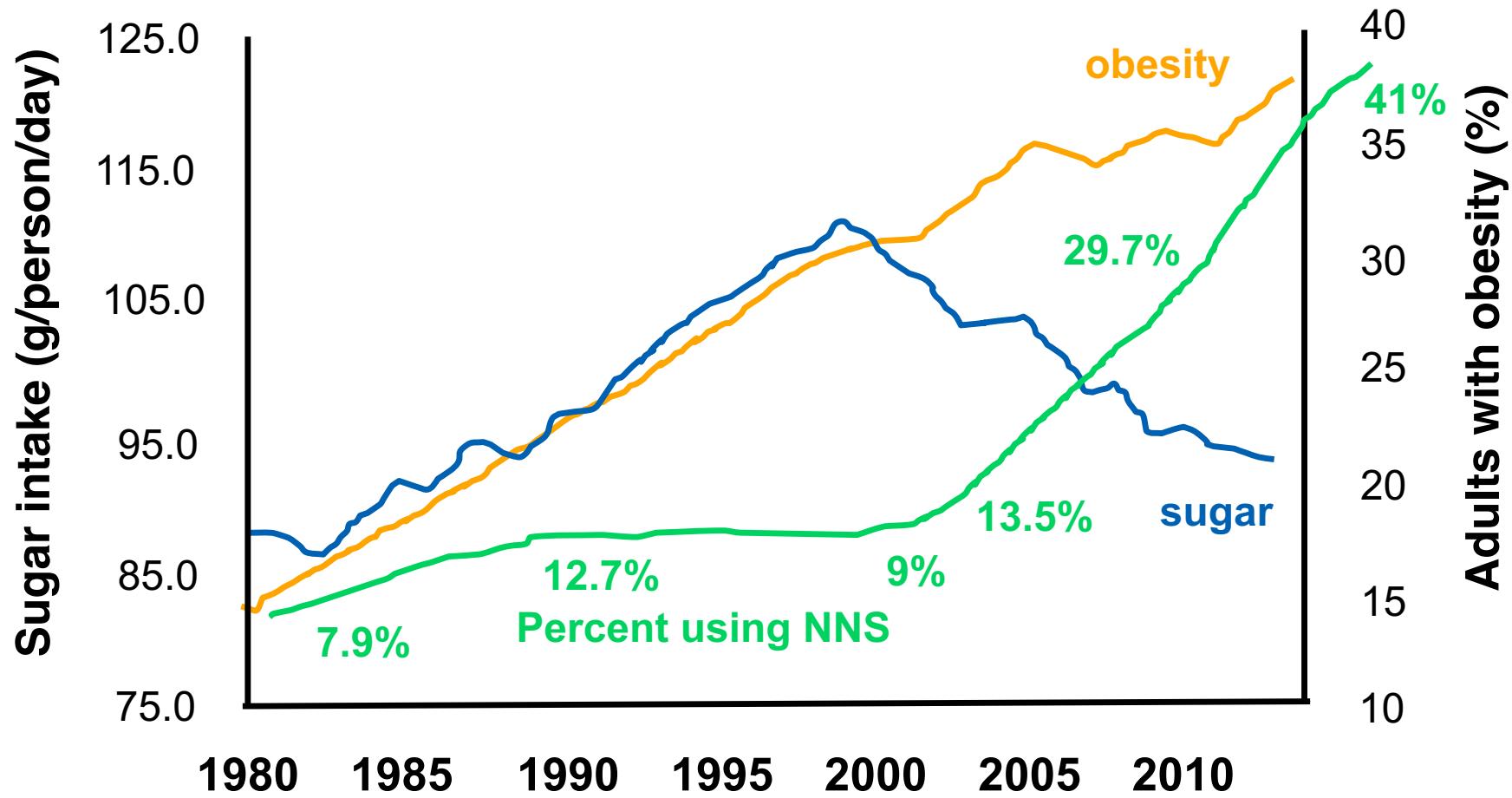
Market size | USD millions



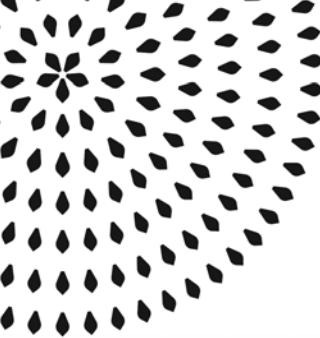
Integration into food



# NNS AND THE OBESITY EPIDEMIC



USDA Economic Research Service, CDC NHANES



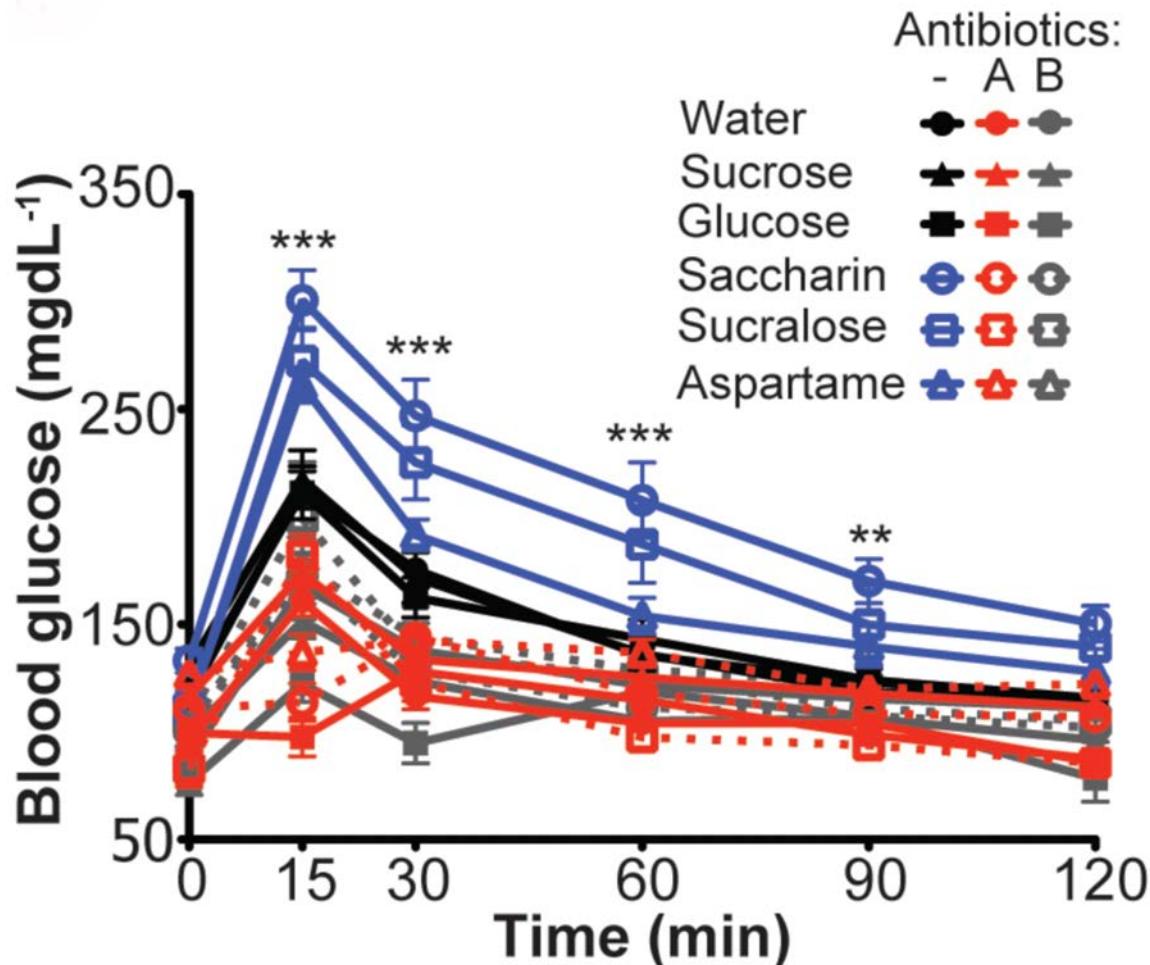
# **Do non-nutritive Sweeteners (NNS) modulate the gut microbiome to metabolically impact the host?**



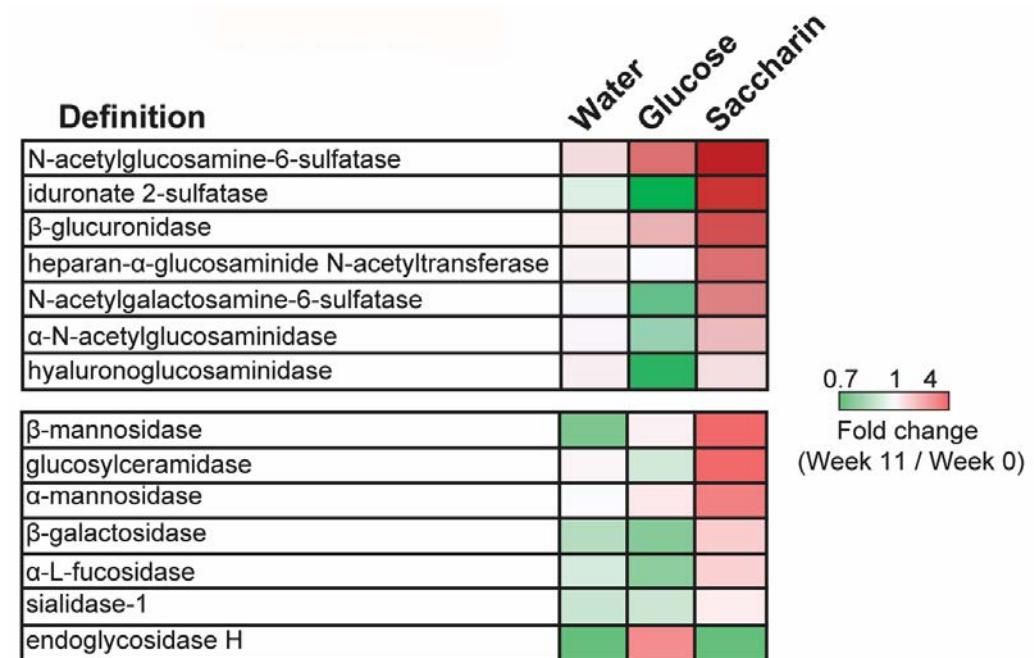
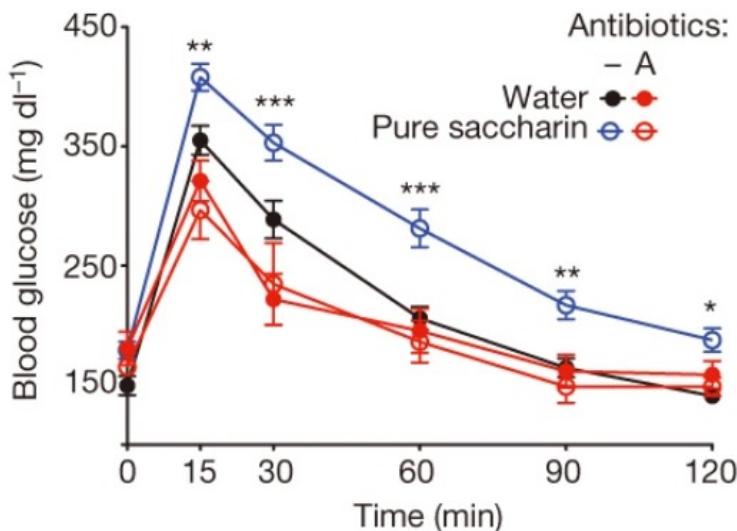
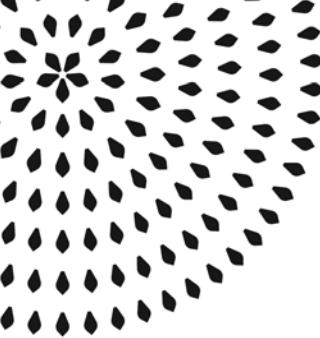
**Jotham Suez**

Suez et al, *Nature* 2014

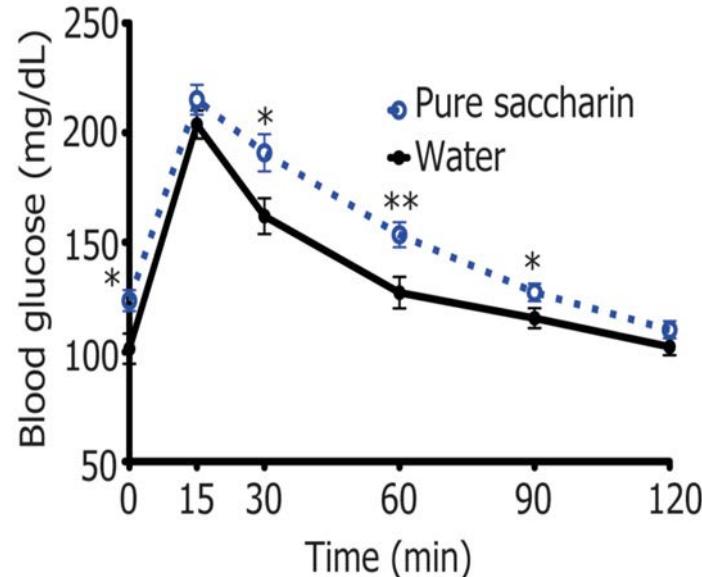
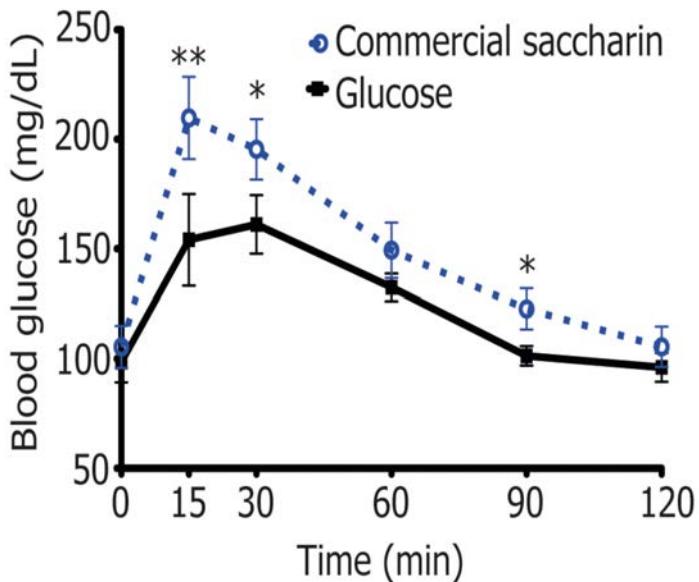
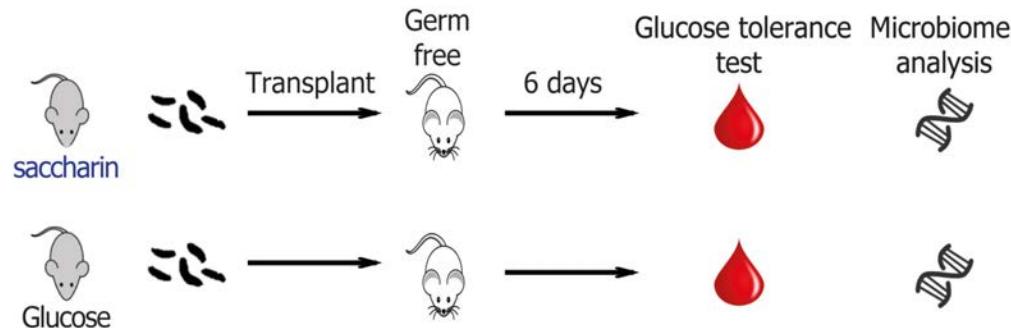
# NNS INDUCE A MICROBIOME-DEPENDENT GLUCOSE INTOLERANCE IN MICE



# SACCHARIN INDUCES A MICROBIOME-DEPENDENT GLUCOSE INTOLERANCE IN MICE

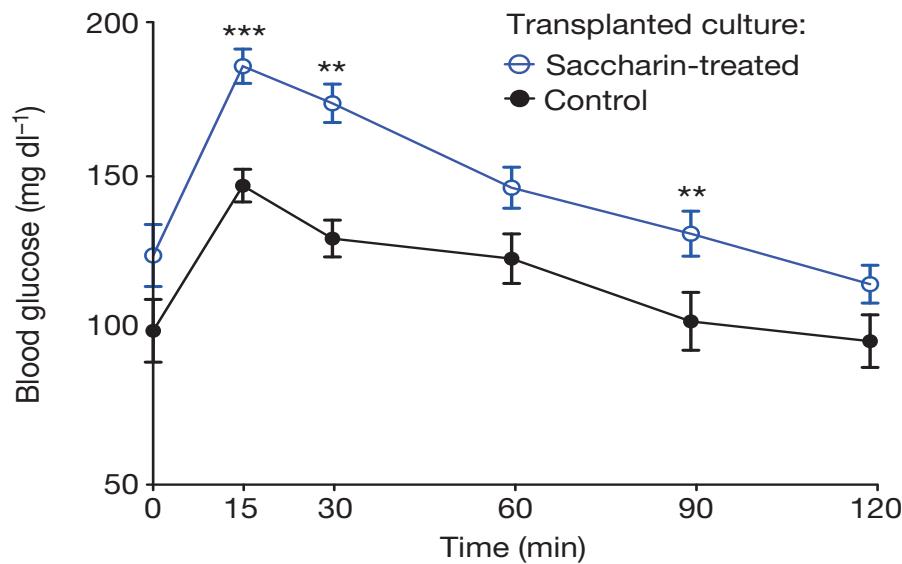
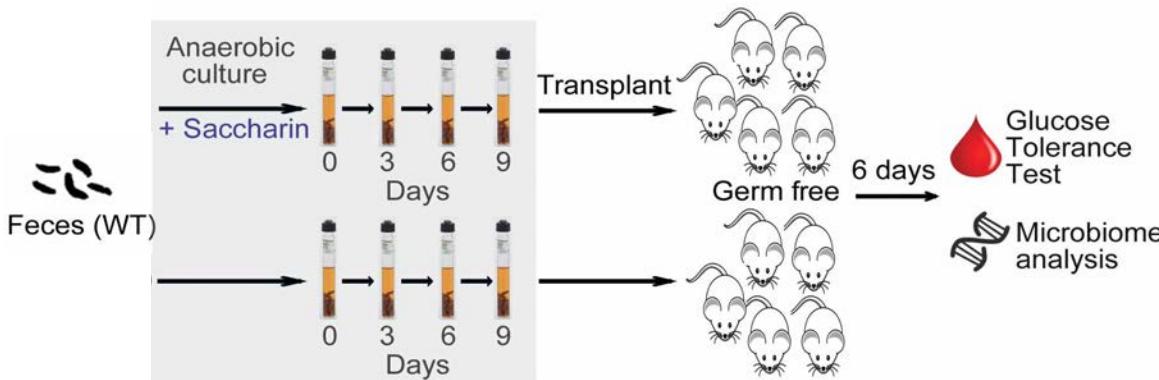


# SACCHARIN INDUCES A MICROBIOME-DEPENDENT GLUCOSE INTOLERANCE IN MICE



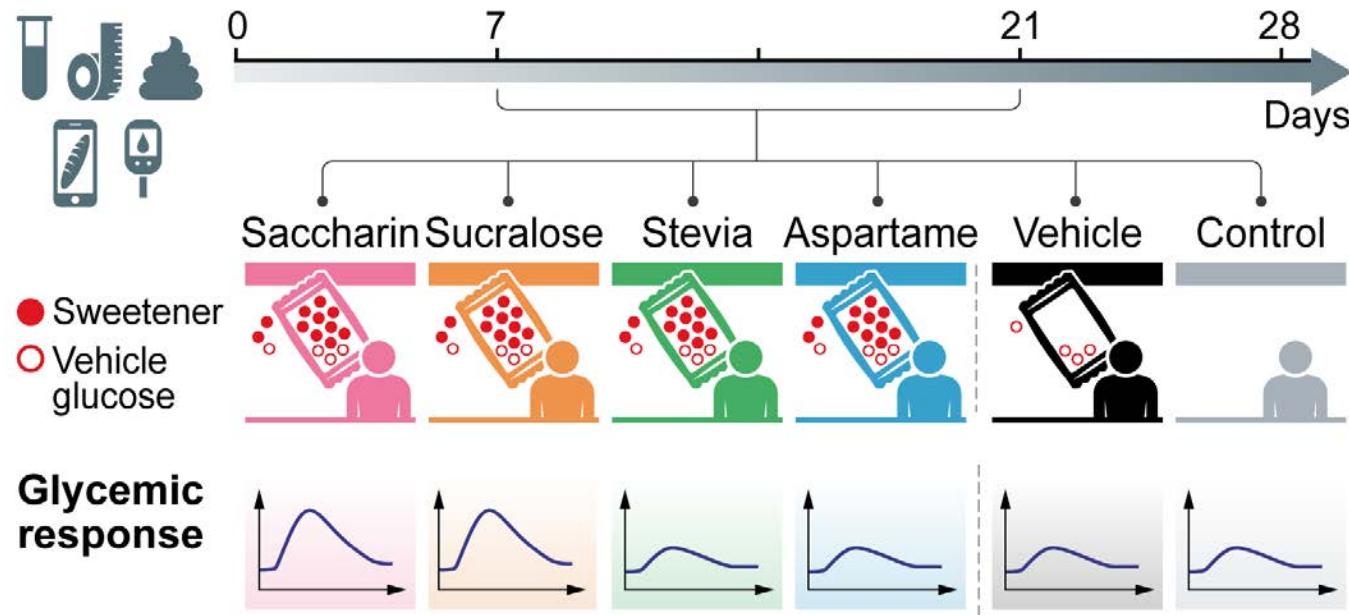
Suez et al, *Nature* 2014

# SACCHARIN INDUCES A MICROBIOME-DEPENDENT GLUCOSE INTOLERANCE IN MICE



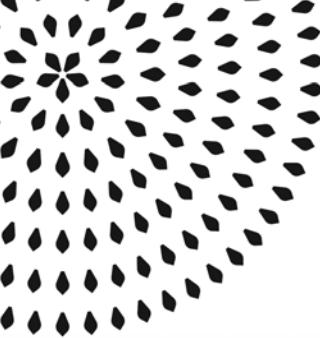


# AN INTERVENTIONAL RANDOMIZED CLINICAL TRIAL

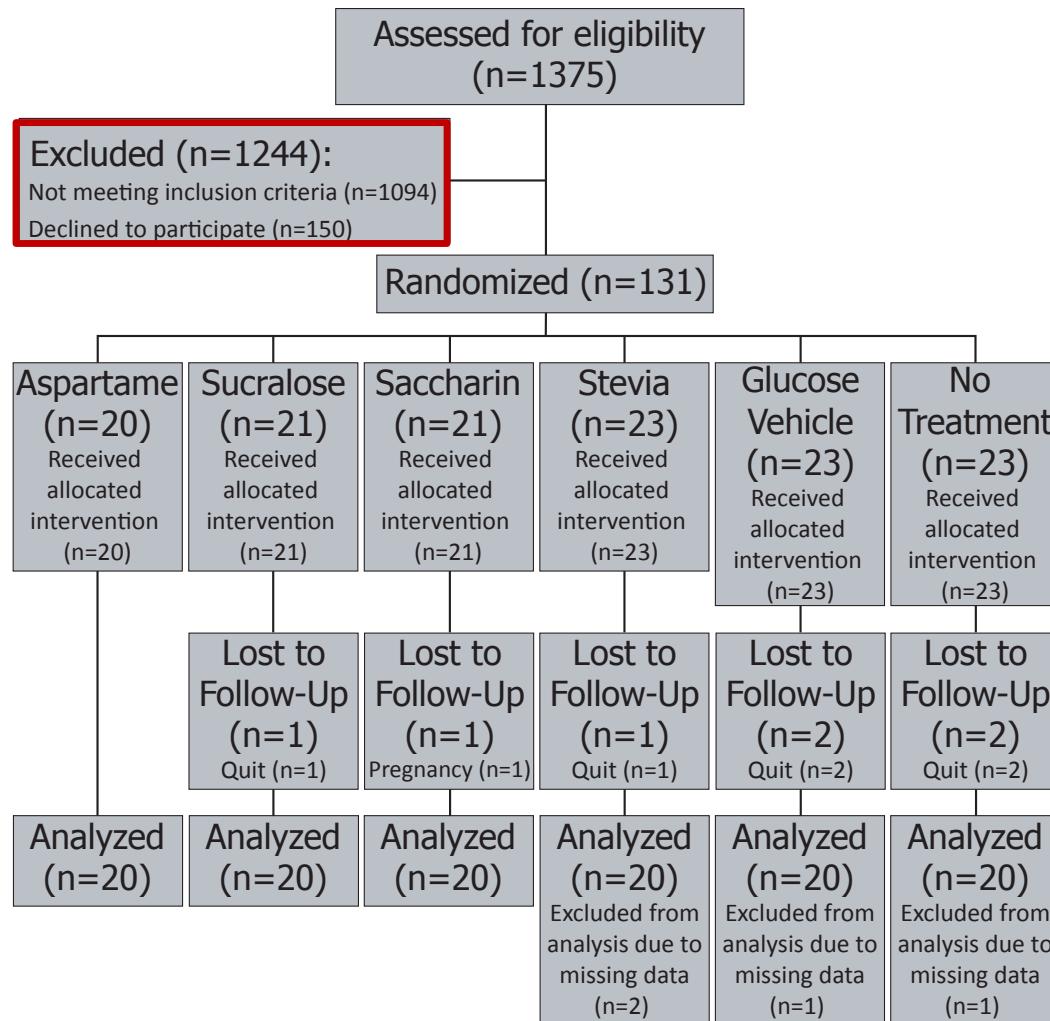


Study phase  
Day  
Glucose Tolerance Test  
Sweetener (except in NSC)  
Anthropometrics  
Food & activity logs  
Blood tests  
Plasma metabolomics  
Stool metagenomics  
Oral metagenomics  
Transplant to GF mice

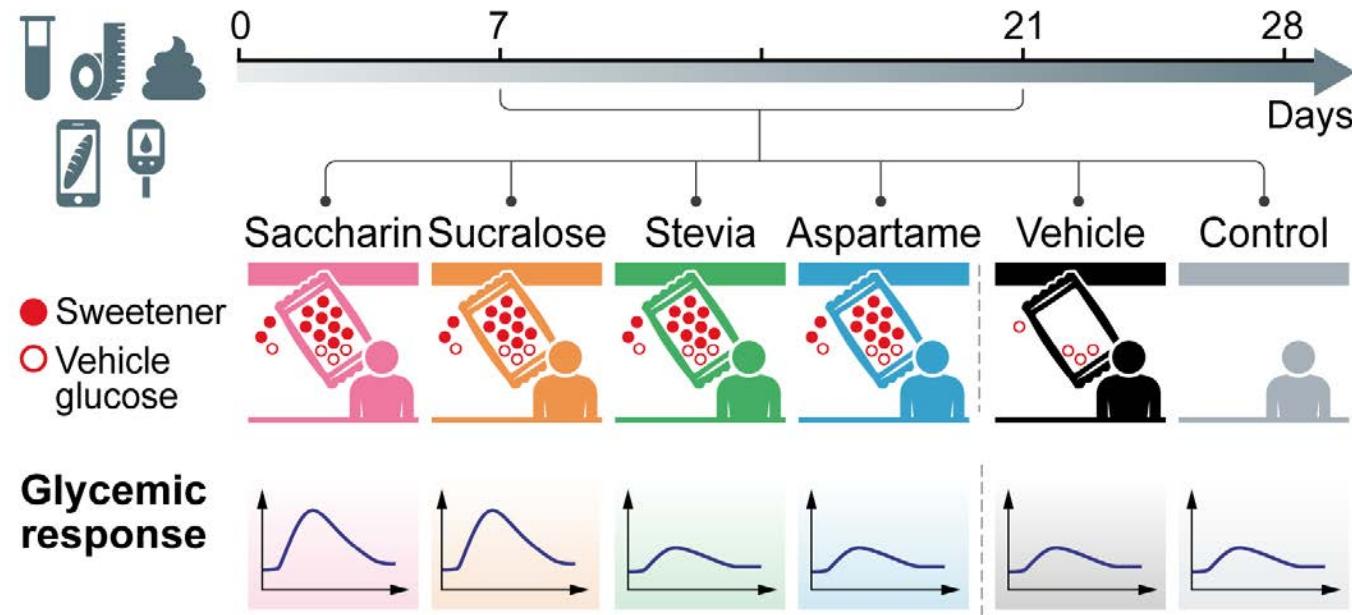
	Baseline							During 1							During 2							Follow-up							
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Glucose Tolerance Test	○	●	○	○	●	○	○	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Sweetener (except in NSC)	○	○	○	○	○	○	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Anthropometrics	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Food & activity logs	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood tests	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Plasma metabolomics	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Stool metagenomics	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Oral metagenomics	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Transplant to GF mice	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○



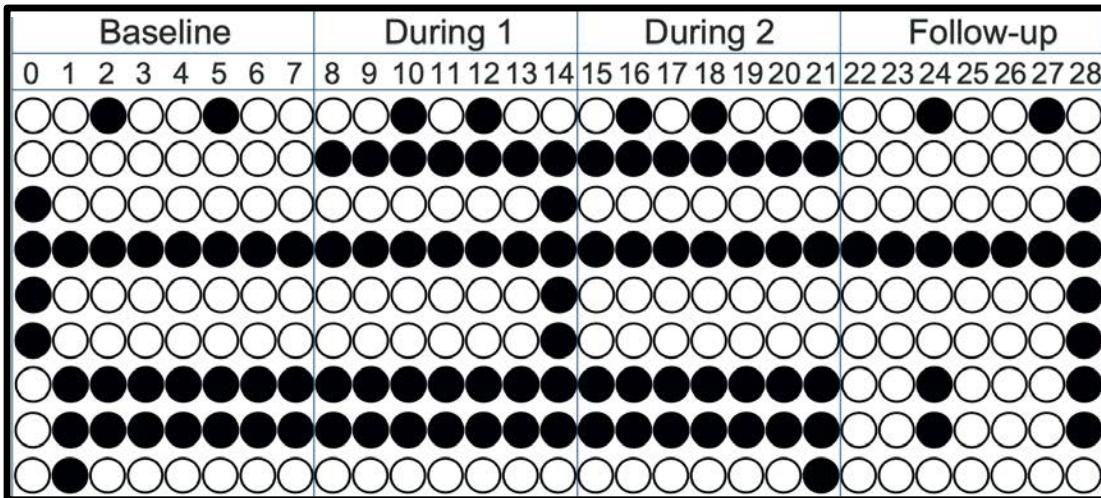
# A STRINGENT INTERVENTIONAL RANDOMIZED CLINICAL TRIAL



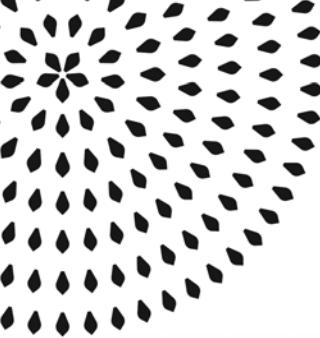
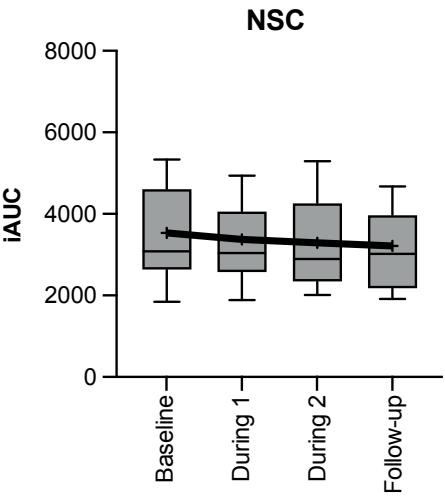
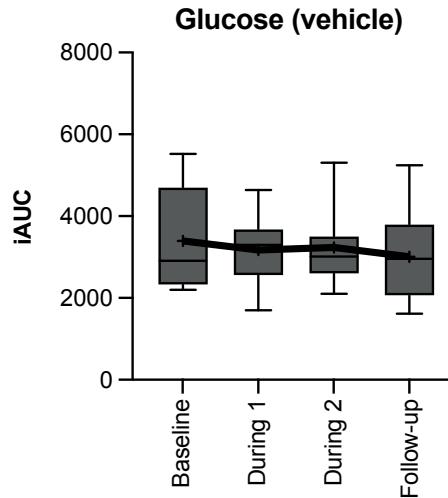
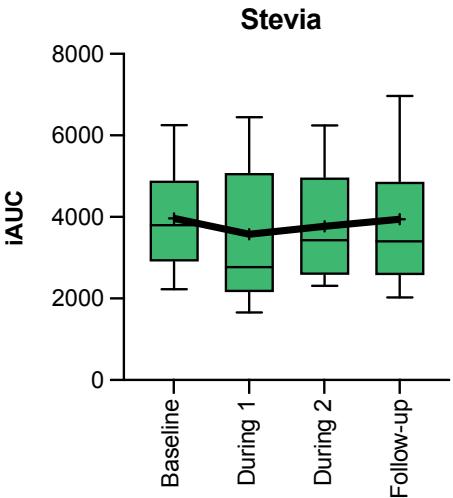
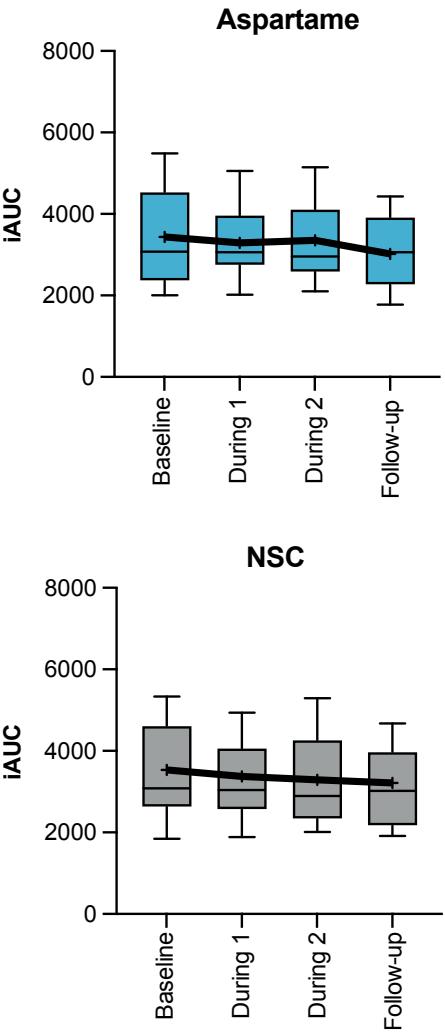
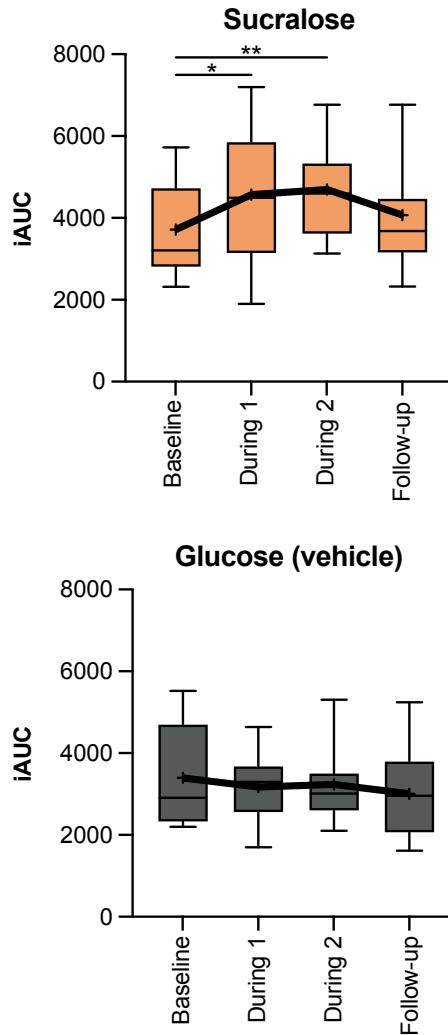
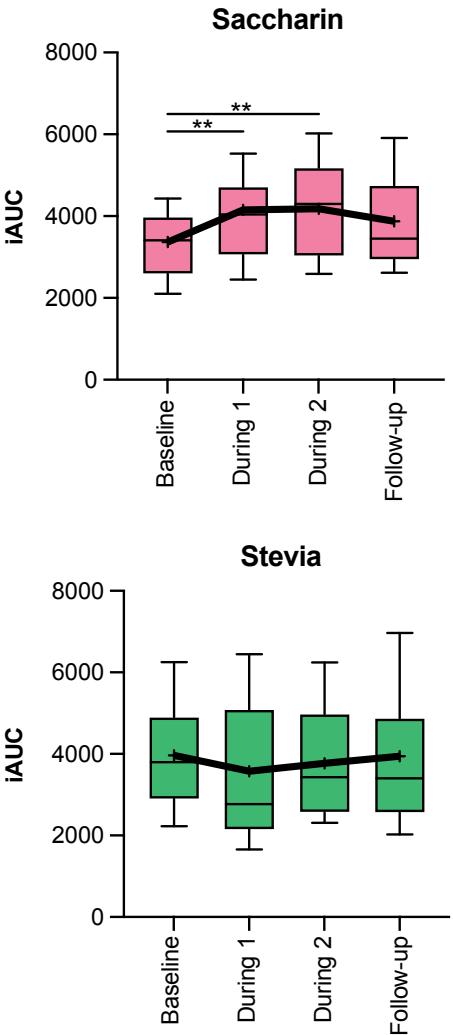
# AN INTERVENTIONAL RANDOMIZED CLINICAL TRIAL



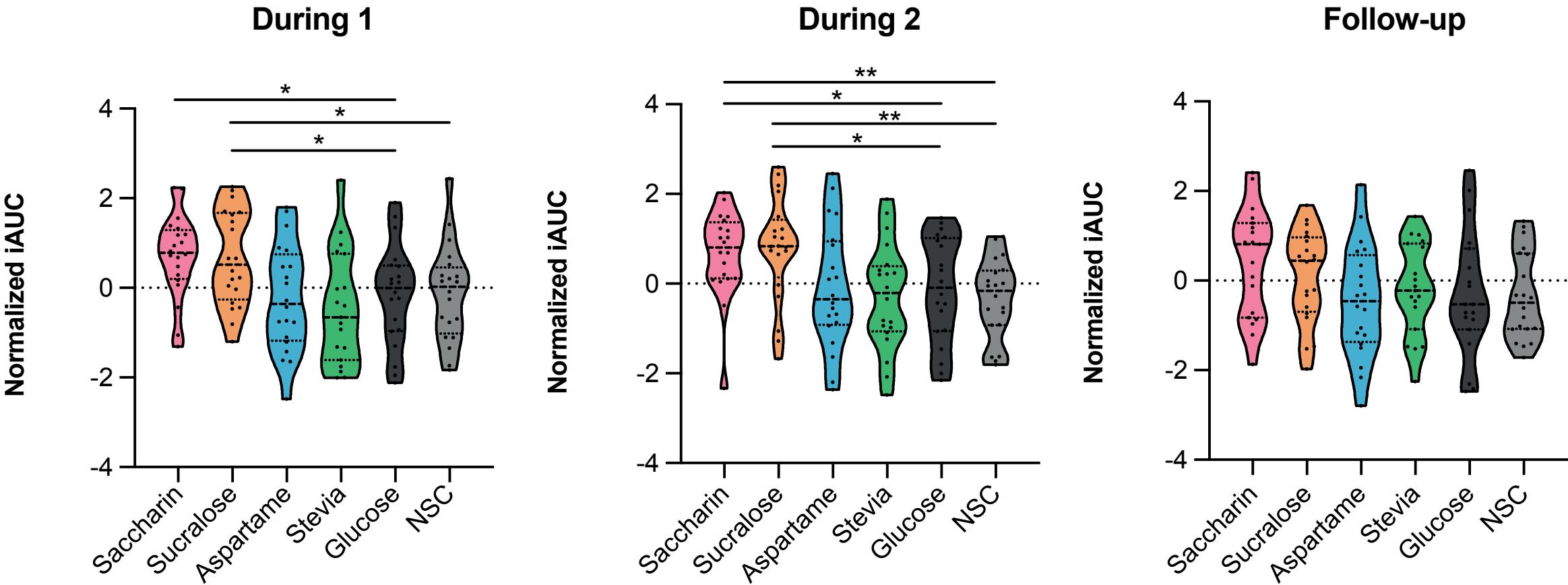
Study phase																													
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Glucose Tolerance Test	○	●	○	○	●	○	○	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Sweetener (except in NSC)	○	○	○	○	○	○	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Anthropometrics	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Food & activity logs	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood tests	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Plasma metabolomics	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Stool metagenomics	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Oral metagenomics	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Transplant to GF mice	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○

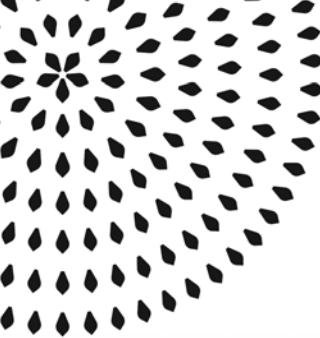


# SACCHARIN AND SUCRALOSE CONSUMPTION INDUCES GLYCEMIC ALTERATIONS



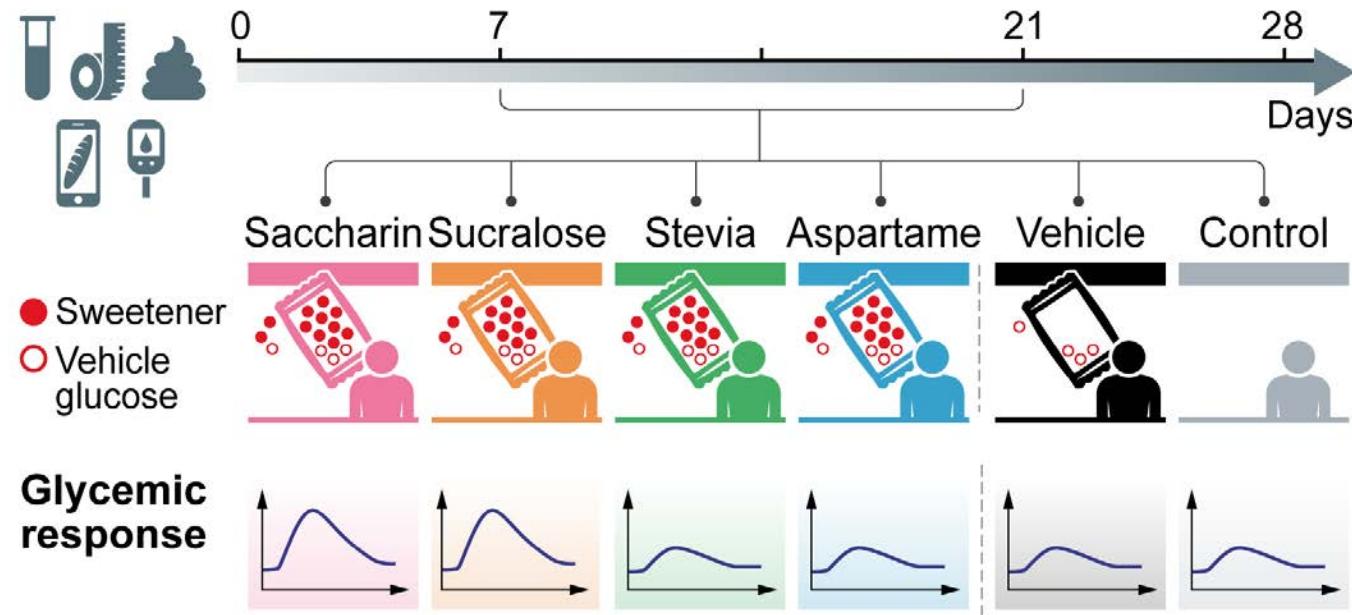
# SACCHARIN AND SUCRALOSE CONSUMPTION INDUCES GLYCEMIC ALTERATIONS





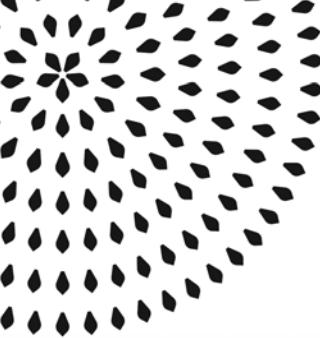
**Does human NNS consumption  
alter the gut microbiome and  
associated systemic metabolites?**

# AN INTERVENTIONAL RANDOMIZED CLINICAL TRIAL

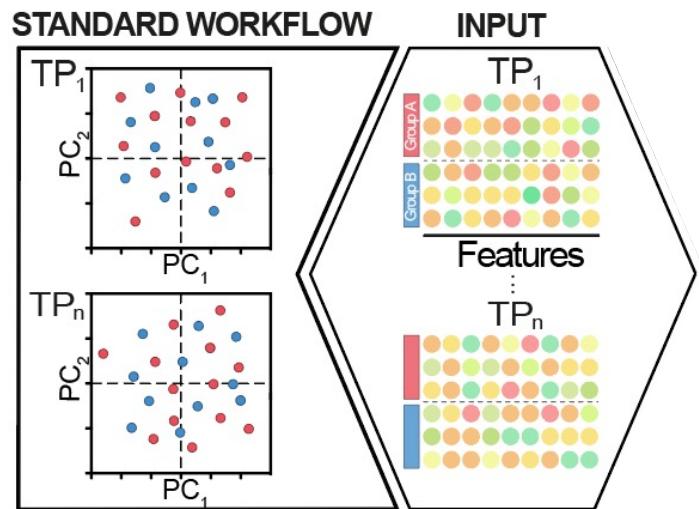


Study phase  
Day  
Glucose Tolerance Test  
Sweetener (except in NSC)  
Anthropometrics  
Food & activity logs  
Blood tests  
Plasma metabolomics  
Stool metagenomics  
Oral metagenomics  
Transplant to GF mice

	Baseline							During 1							During 2							Follow-up							
Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Glucose Tolerance Test	○	●	○	○	●	○	○	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Sweetener (except in NSC)	○	○	○	○	○	○	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Anthropometrics	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Food & activity logs	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood tests	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Plasma metabolomics	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Stool metagenomics	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Oral metagenomics	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Transplant to GF mice	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○



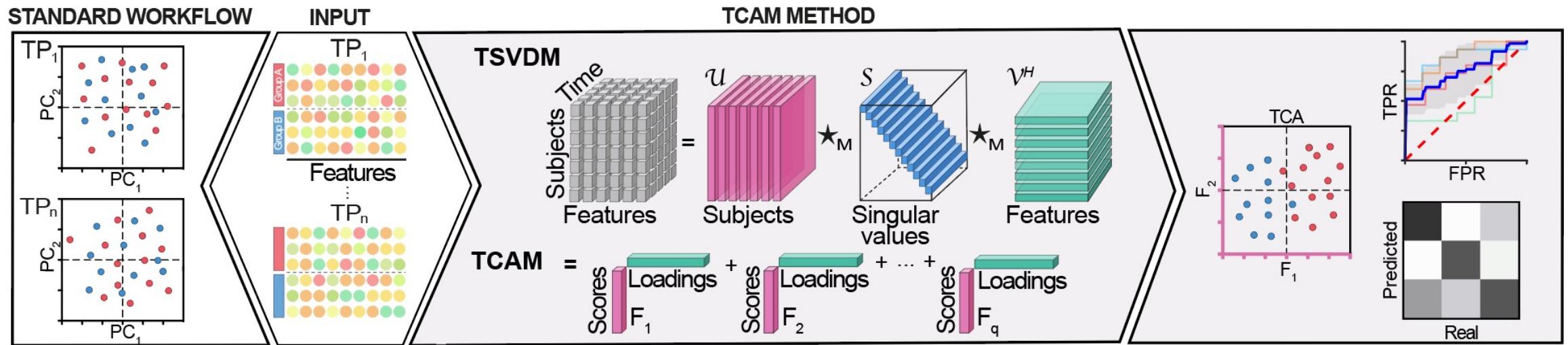
# TENSOR FACTORIZATION MICROBIOME ANALYSIS



**Uria Mor**

Mor et al, *PLOS Comp Bio* 2022

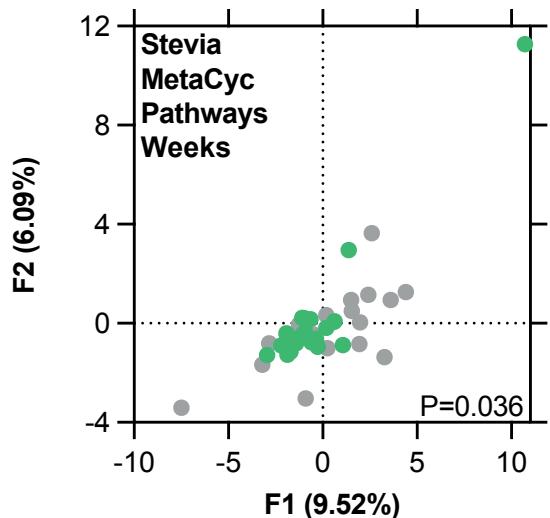
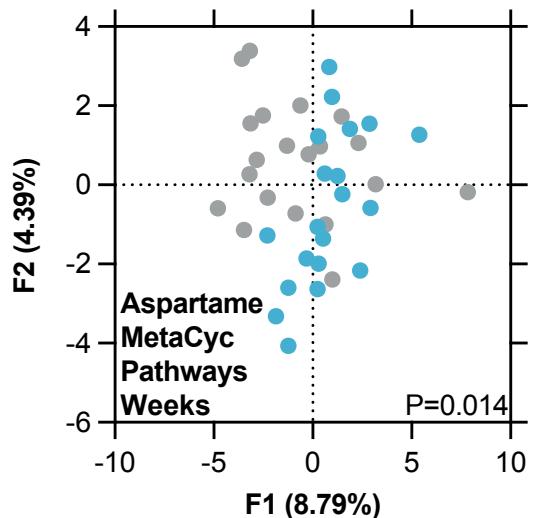
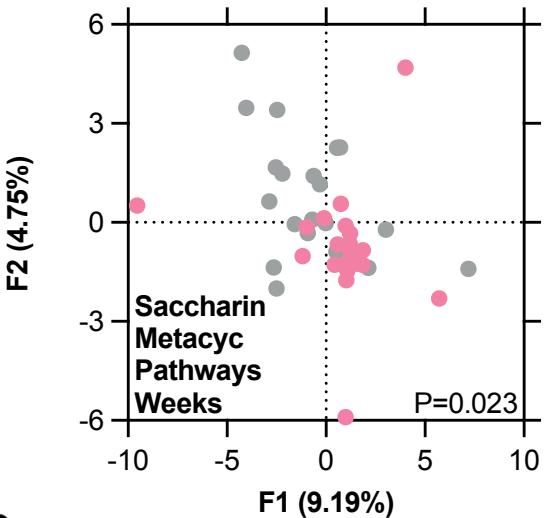
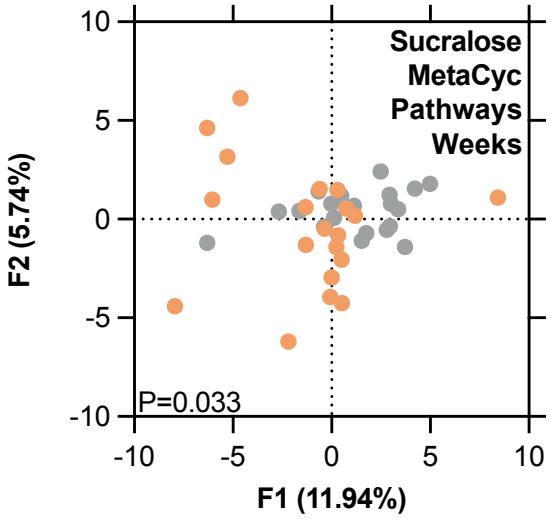
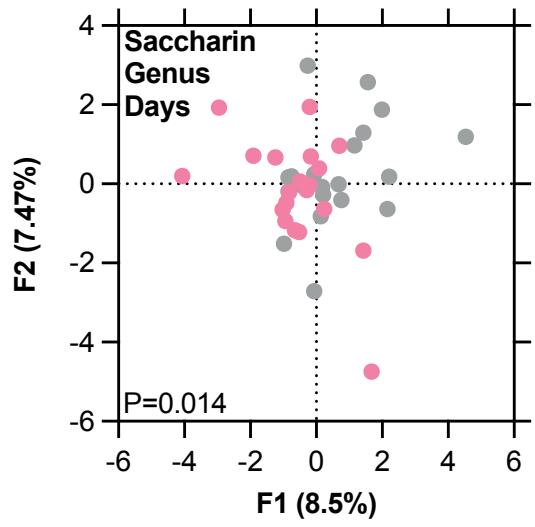
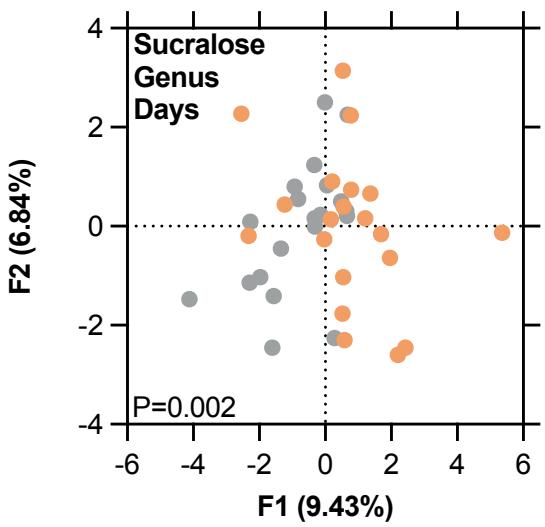
# TENSOR FACTORIZATION MICROBIOME ANALYSIS



**Uria Mor**

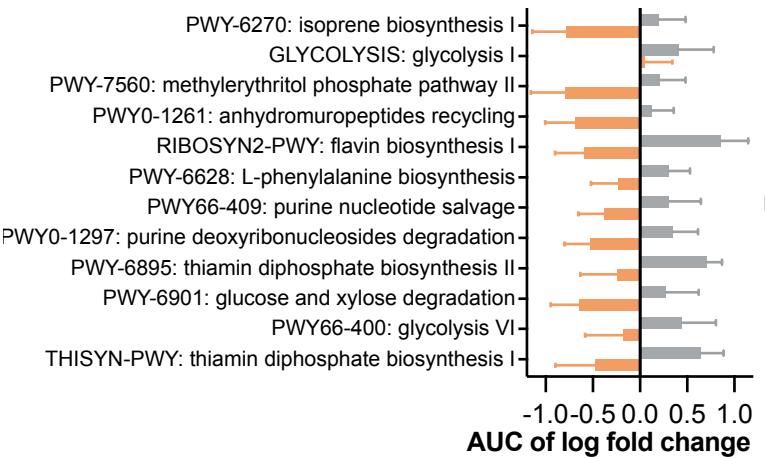
Mor et al, *PLOS Comp Bio* 2022

# NNS-CONSUMERS FEATURE DISTINCT GLOBAL GUT MICROBIOME CHANGES

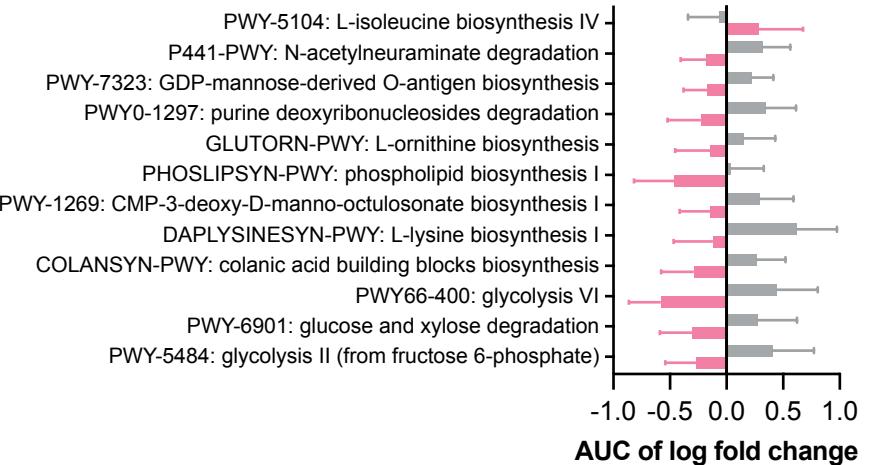


# NNS-CONSUMERS FEATURE DISTINCT GLOBAL GUT MICROBIOME CHANGES

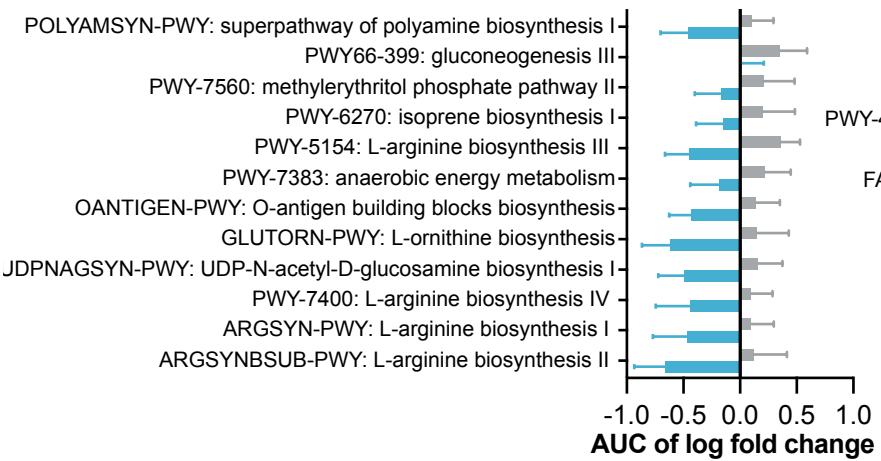
Sucratose



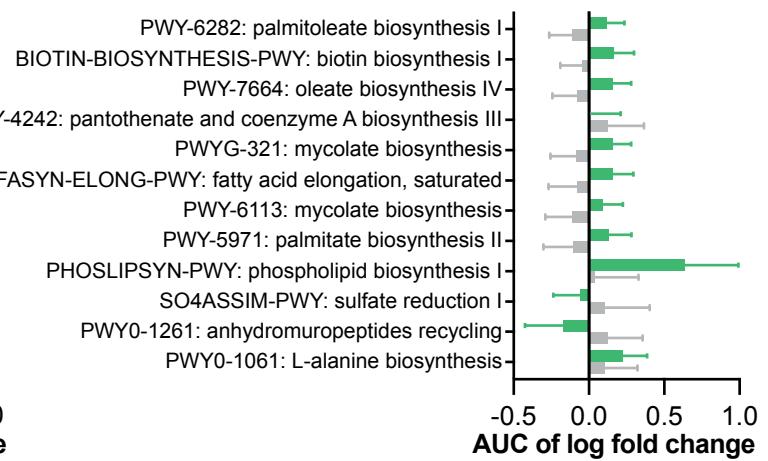
Saccharin

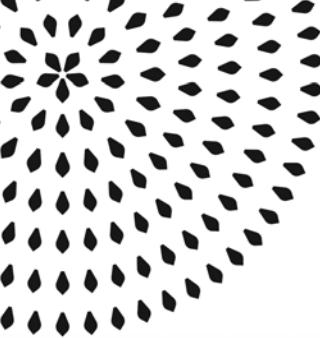


Aspartame

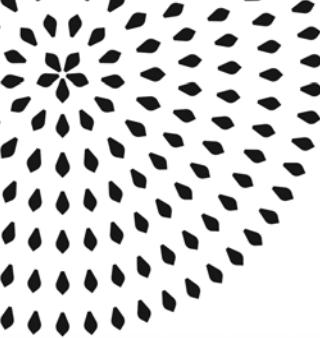


Stevia

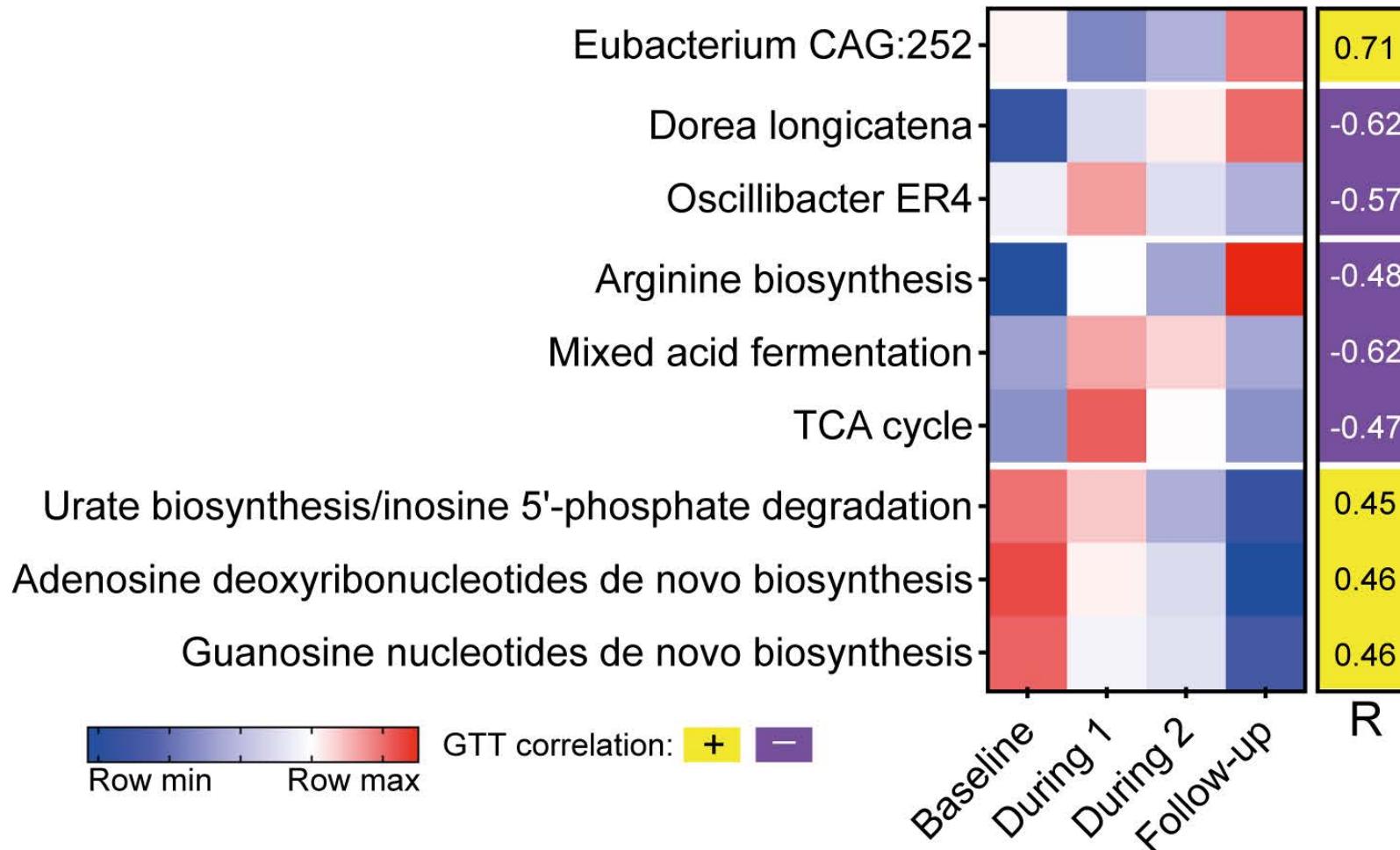




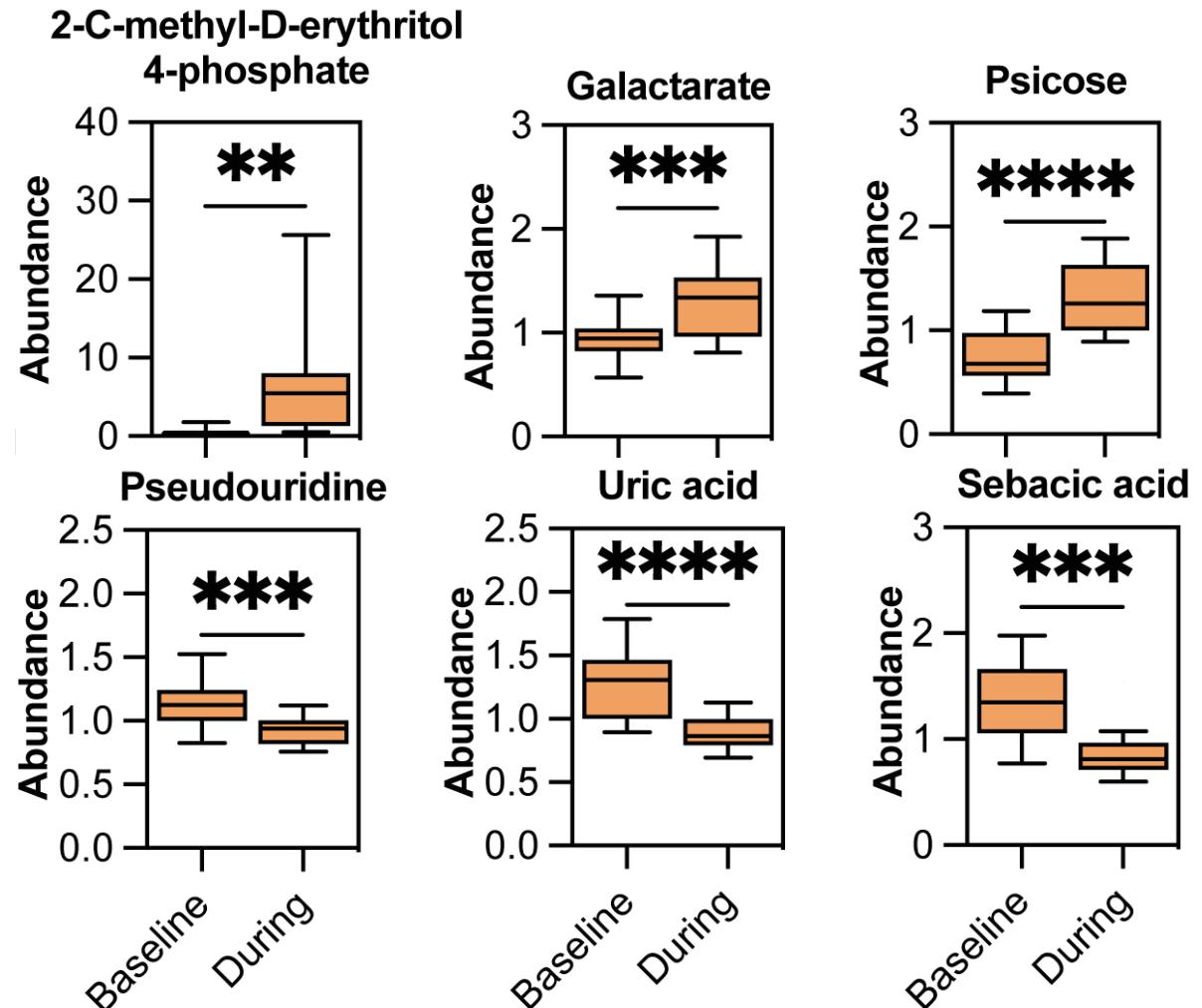
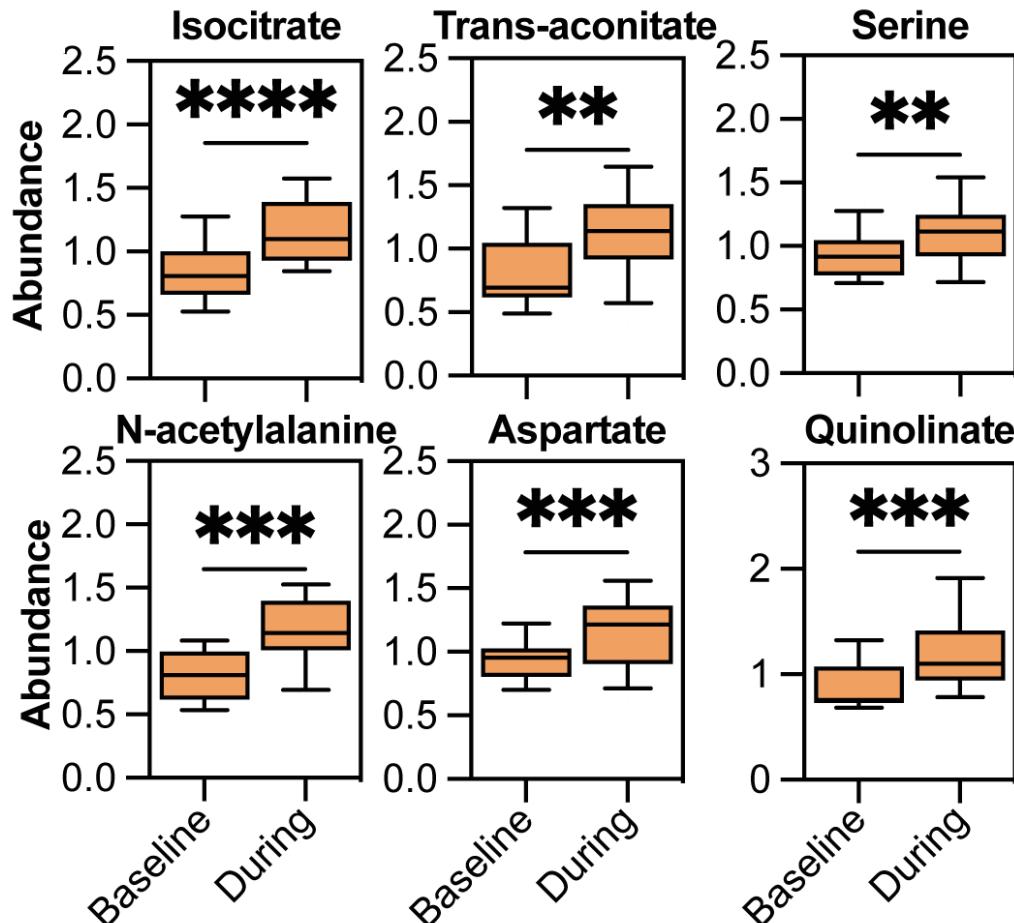
**Does NNS-induced dysbiosis  
associate with the changes  
in glycemic responses?**

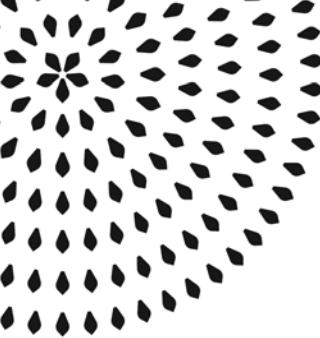


# SUCRALOSE-INDUCED MICROBIOME FEATURES CORRELATE WITH ALTERED GLYCEMIC RESPONSES



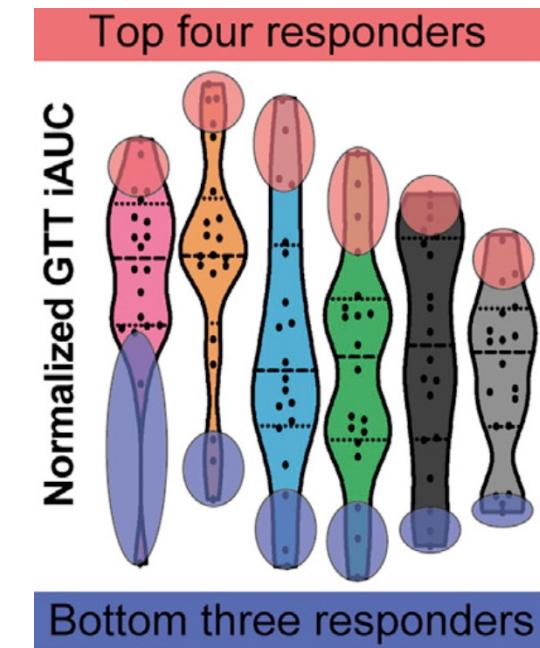
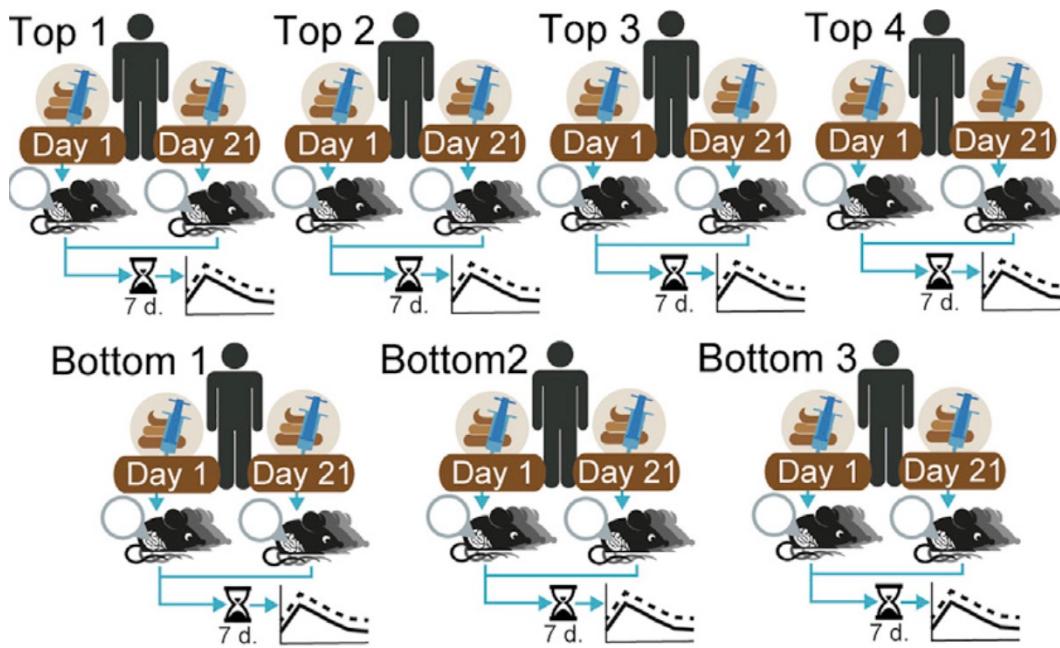
# SUCRALOSE-INDUCED MICROBIOME FEATURES CORRELATE WITH ALTERED GLYCEMIC RESPONSES



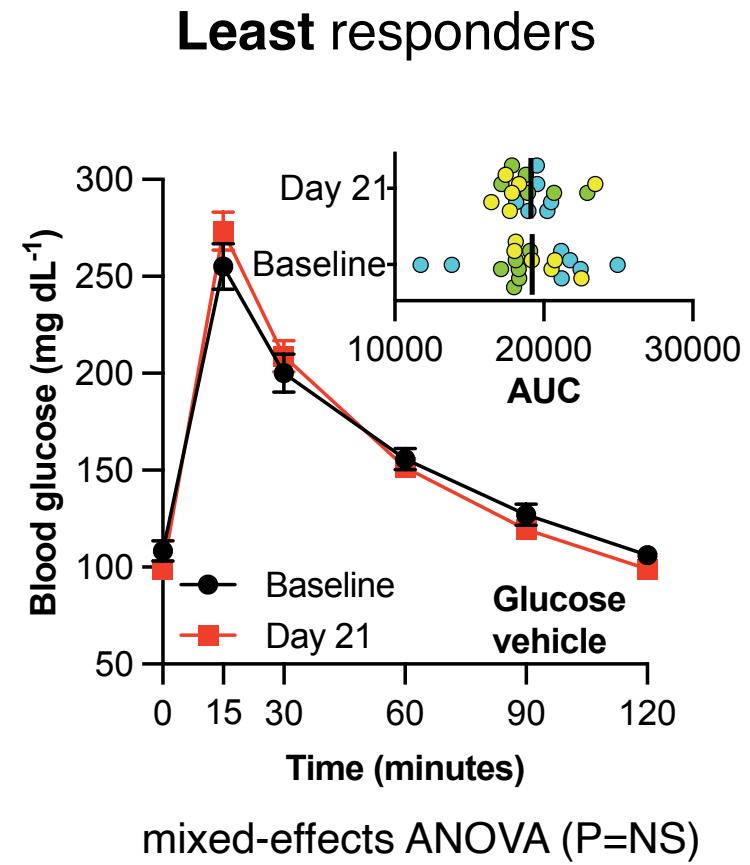
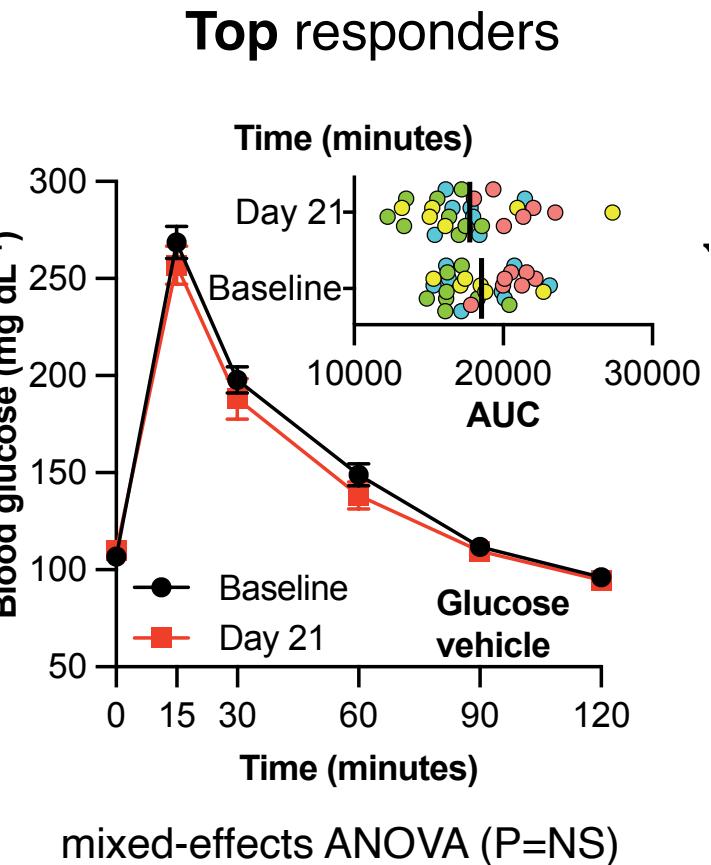
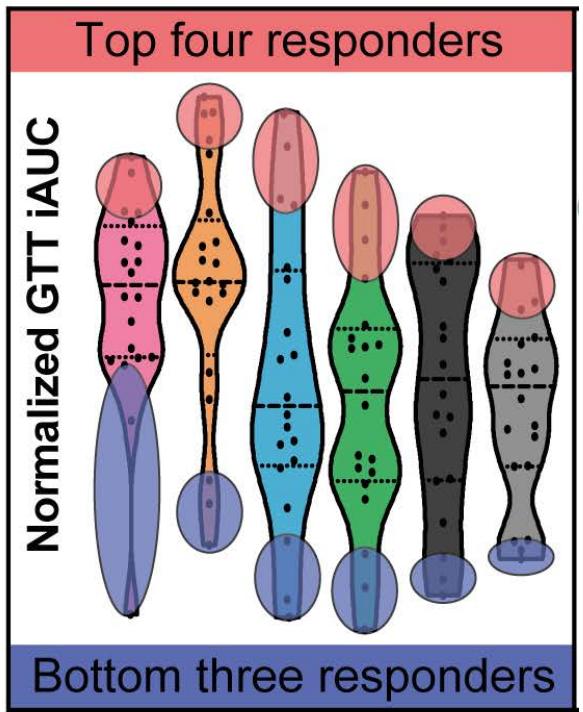


# **Do NNS-induced human microbiome alterations drive glycemic responses?**

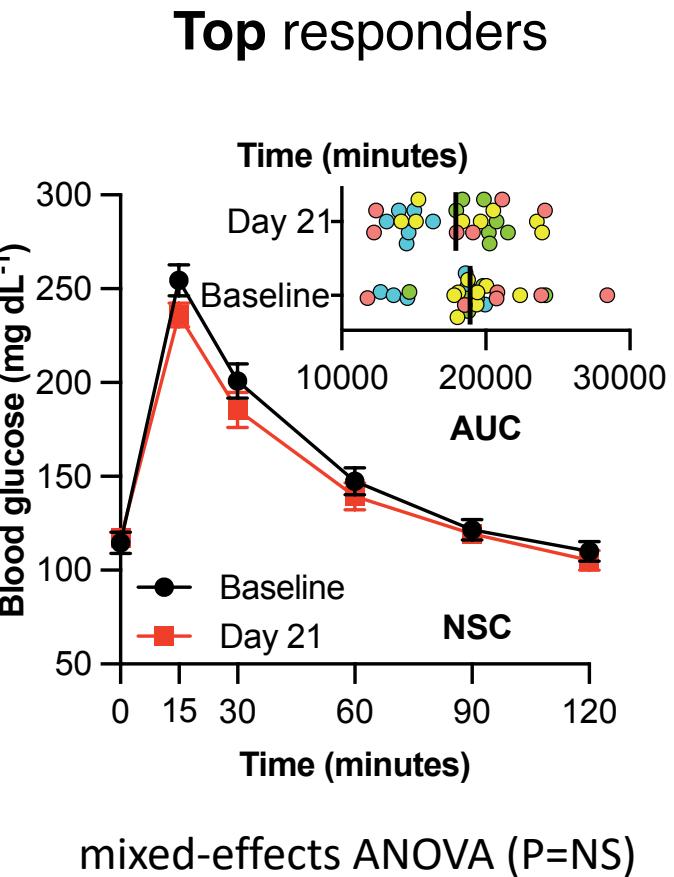
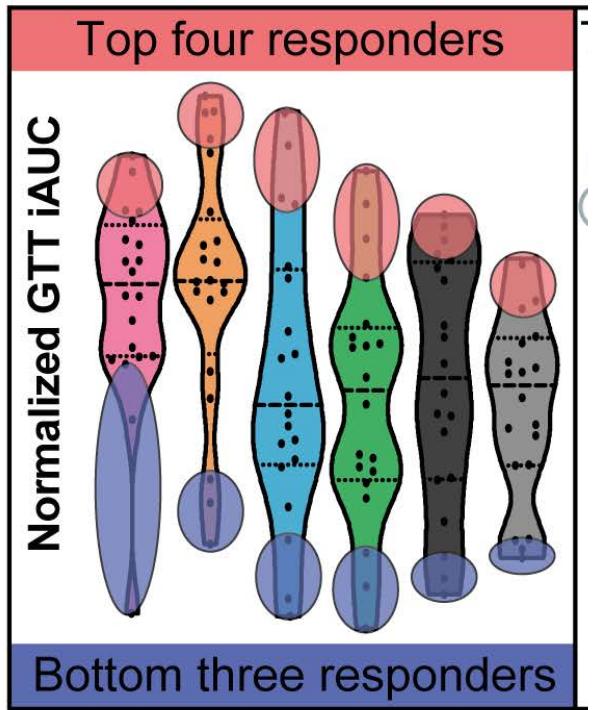
# FECAL MICROBIOME TRANSPLANTATION



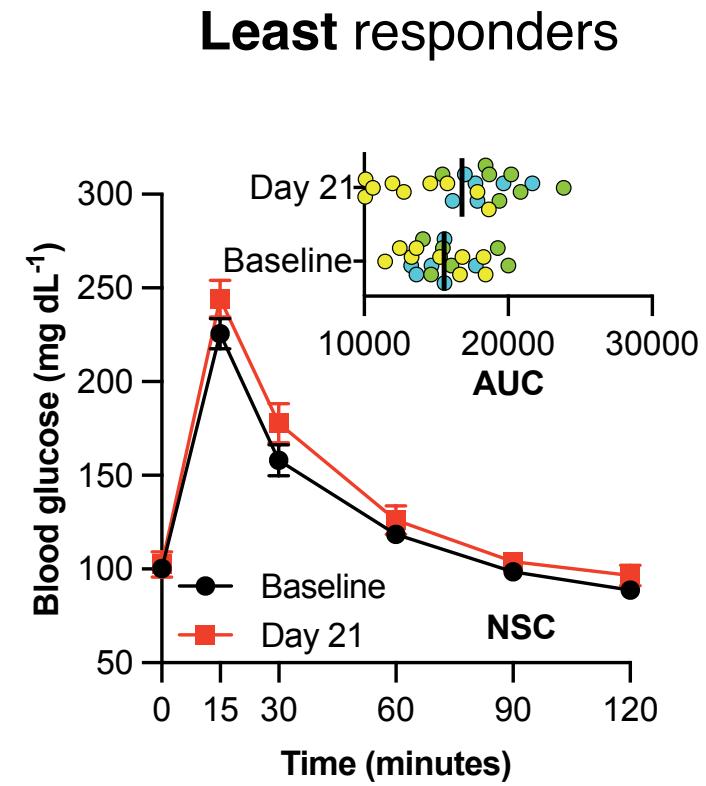
# GF RECIPIENTS OF 'RESPONDER' VEHICLE GROUP DO NOT DEVELOP GLYCEMIC ALTERATIONS



# GF RECIPIENTS OF 'RESPONDER' CONTROL GROUP DO NOT DEVELOP GLYCEMIC ALTERATIONS

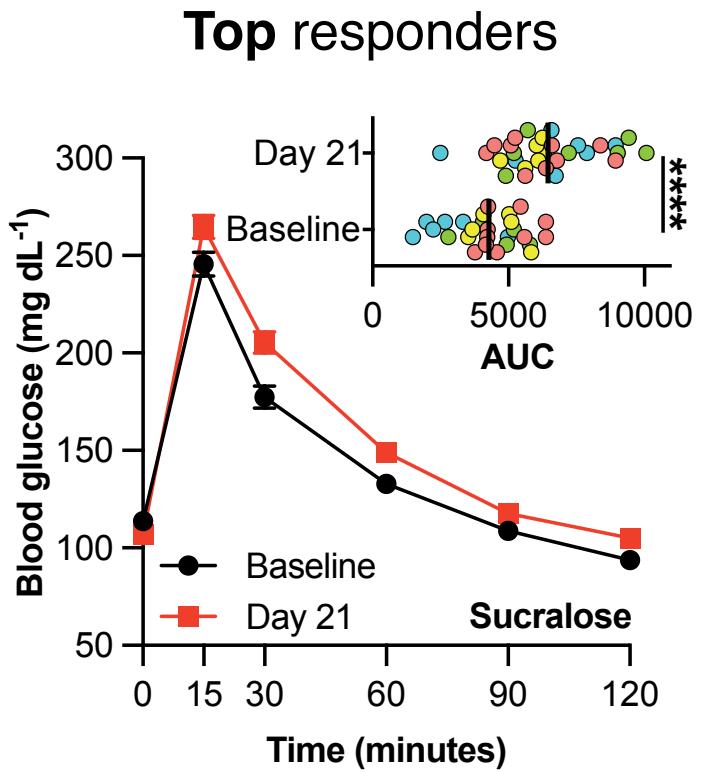
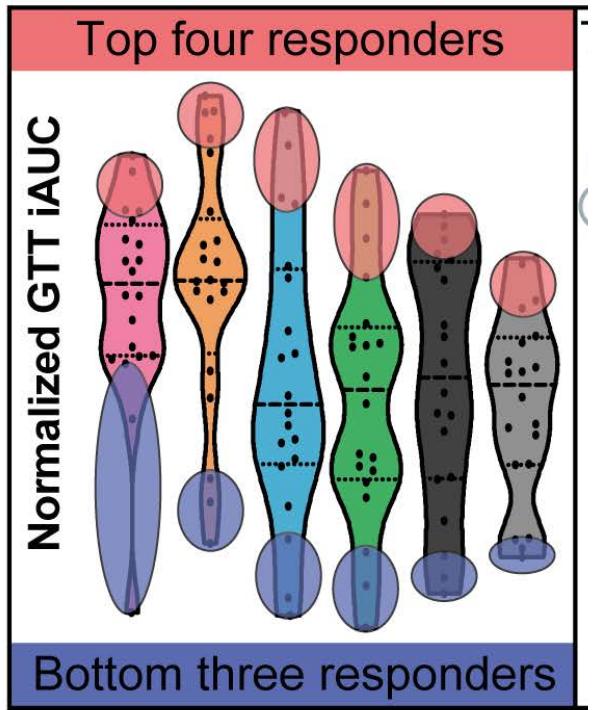


mixed-effects ANOVA (P=NS)

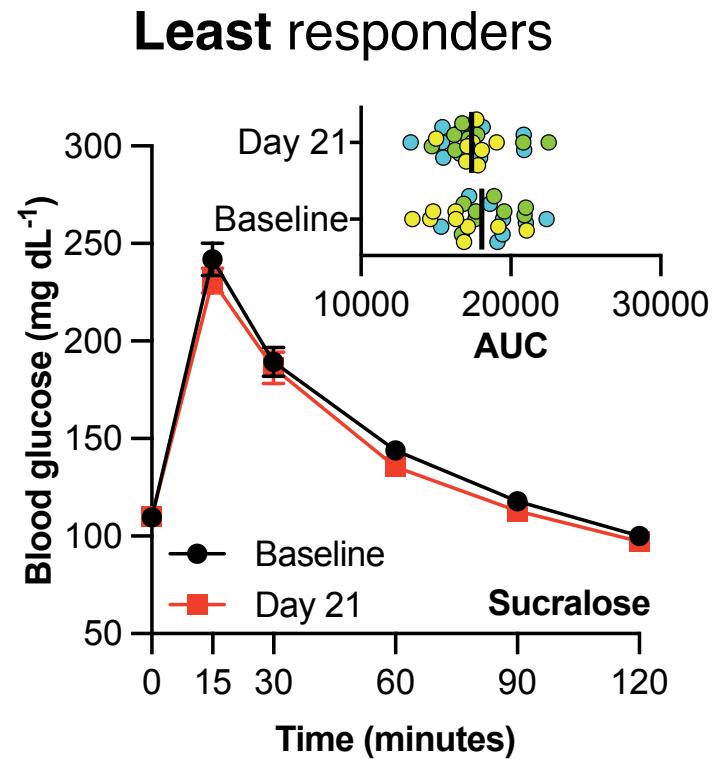


mixed-effects ANOVA (P=NS)

# GF RECIPIENTS OF TOP SUCRALOSE 'RESPONDERS' DEVELOP GLYCEMIC ALTERATIONS

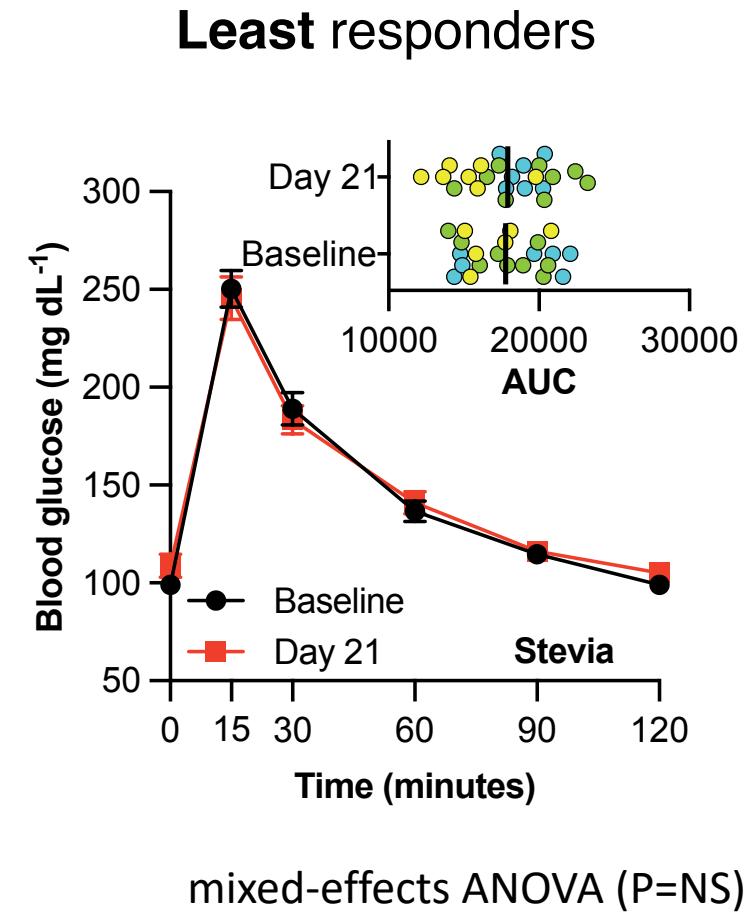
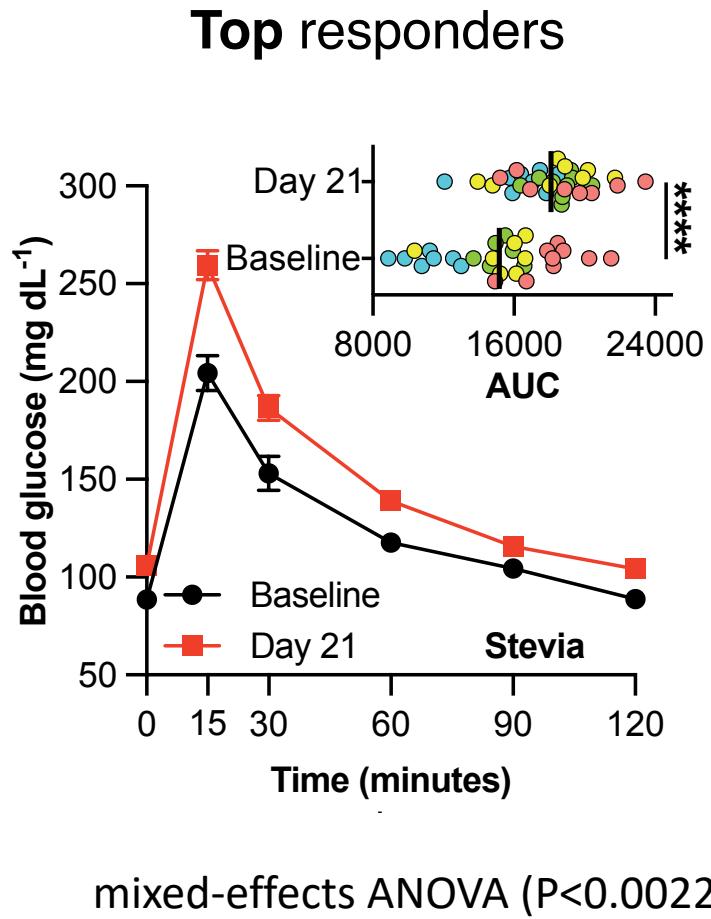
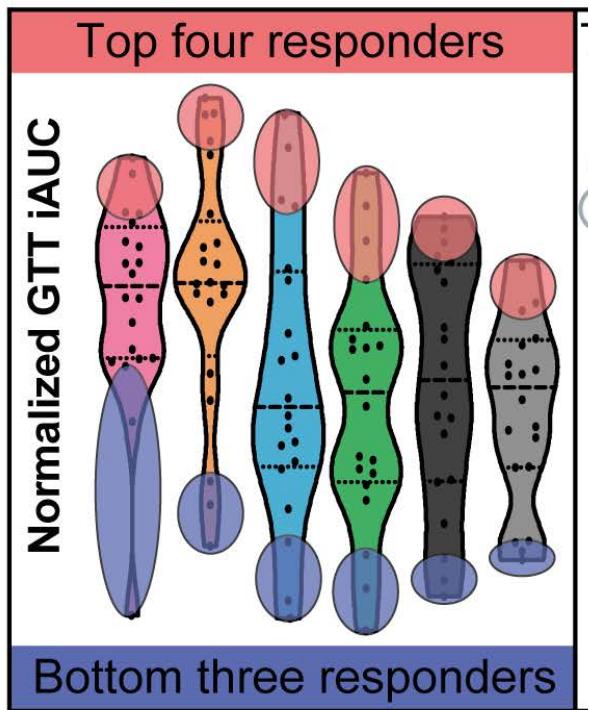


mixed-effects ANOVA ( $P < 0.0001$ )

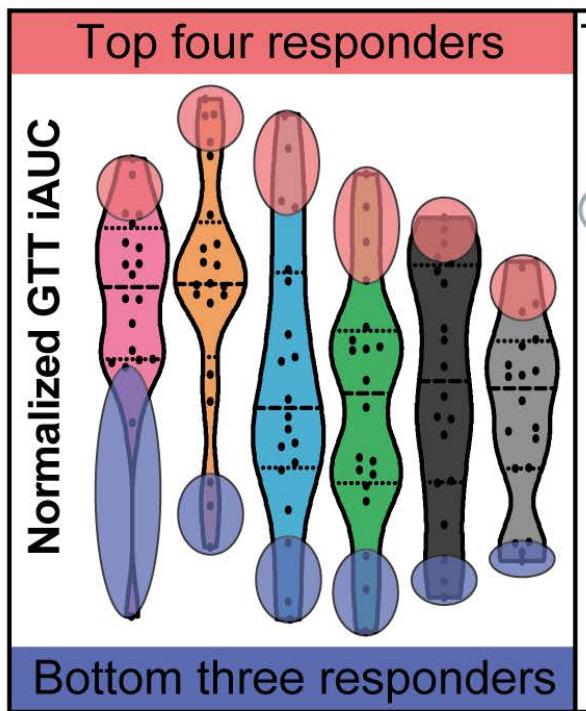


mixed-effects ANOVA ( $P = \text{NS}$ )

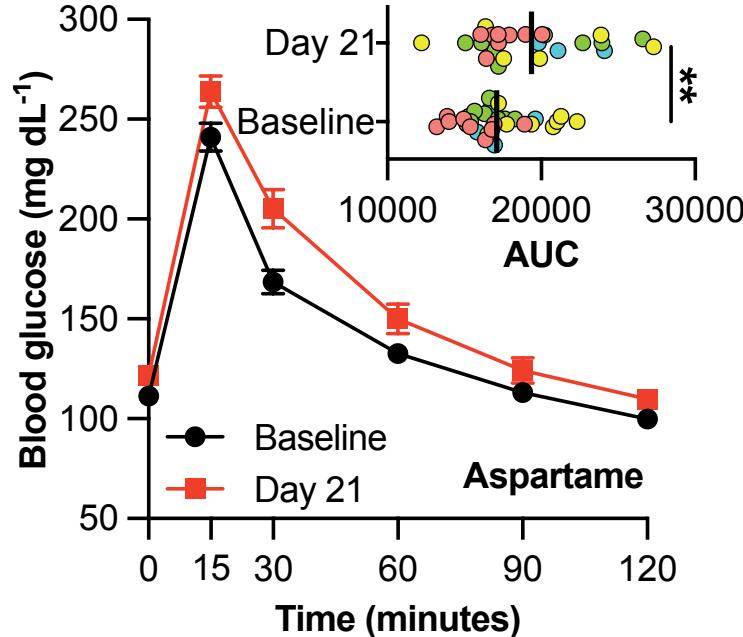
# GF RECIPIENTS OF TOP ASPARTAME 'RESPONDERS' DEVELOP GLYCEMIC ALTERATIONS



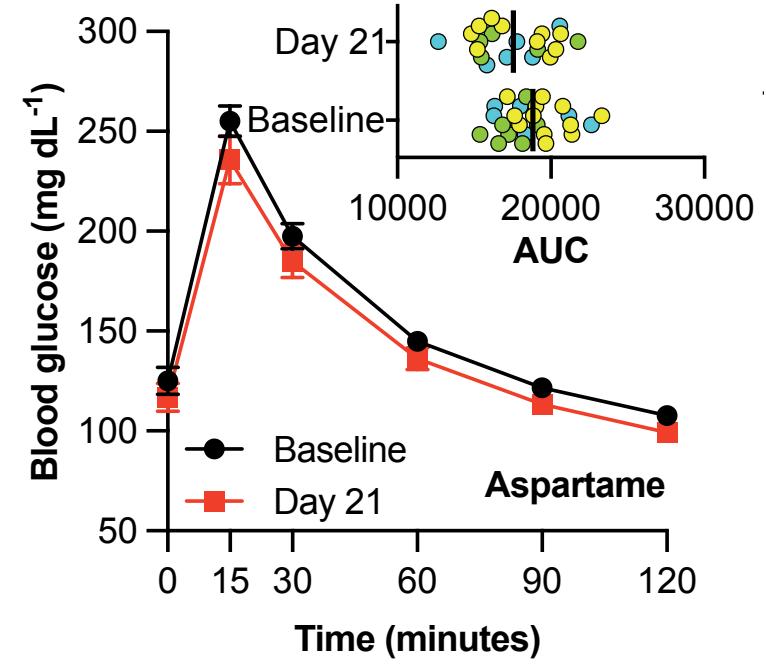
# GF RECIPIENTS OF TOP STEVIA 'RESPONDERS' DEVELOP GLYCEMIC ALTERATIONS



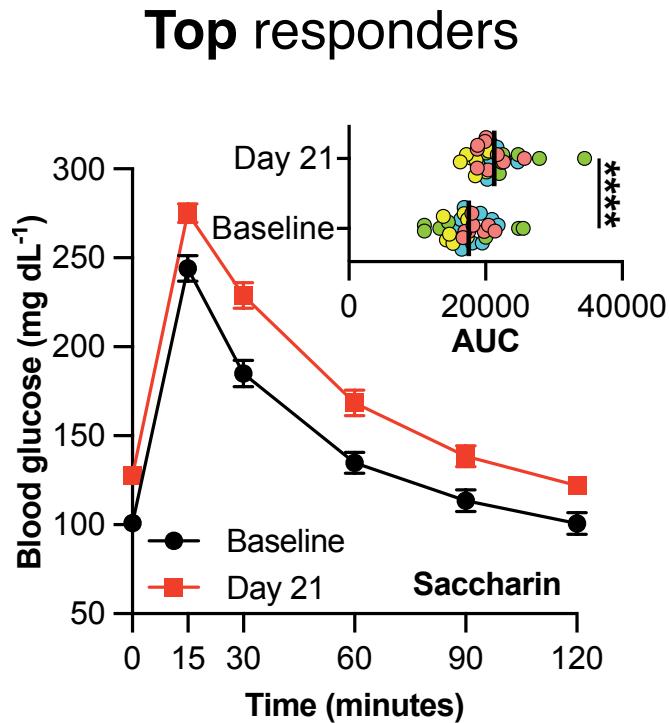
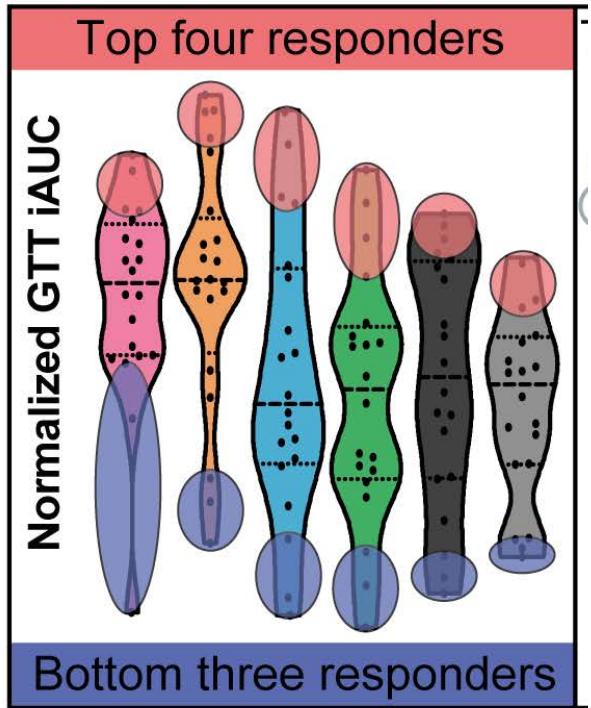
Top responders



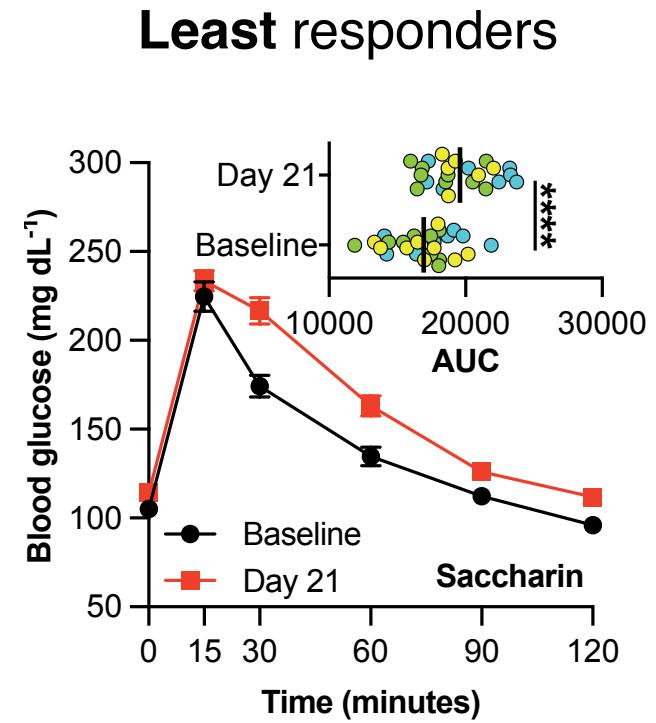
Least responders



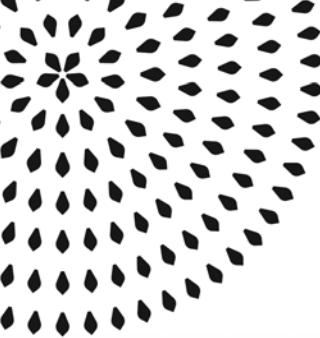
# GF RECIPIENTS OF TOP AND BOTTOM SACCHARIN 'RESPONDERS' DEVELOP GLYCEMIC ALTERATIONS



mixed-effects ANOVA ( $P<0.0001$ )

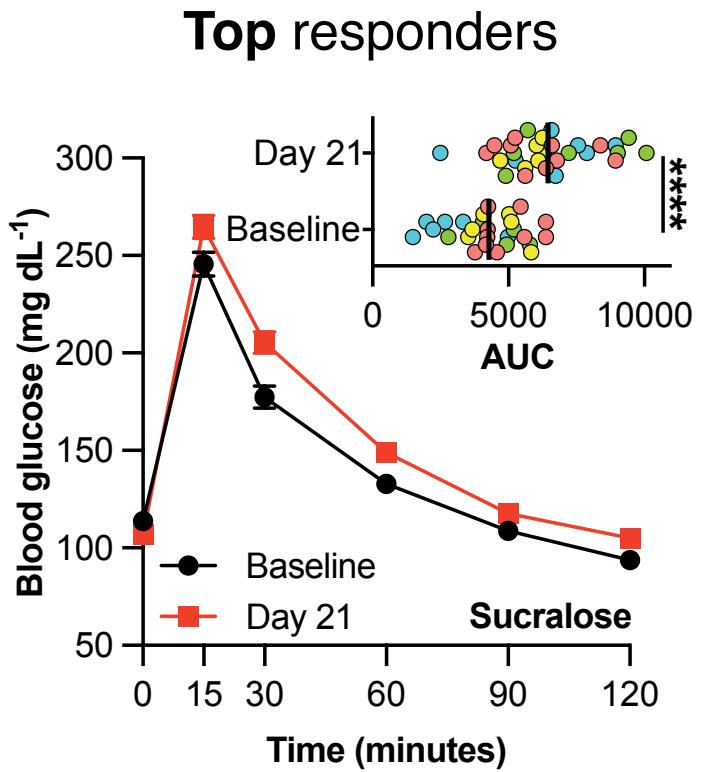
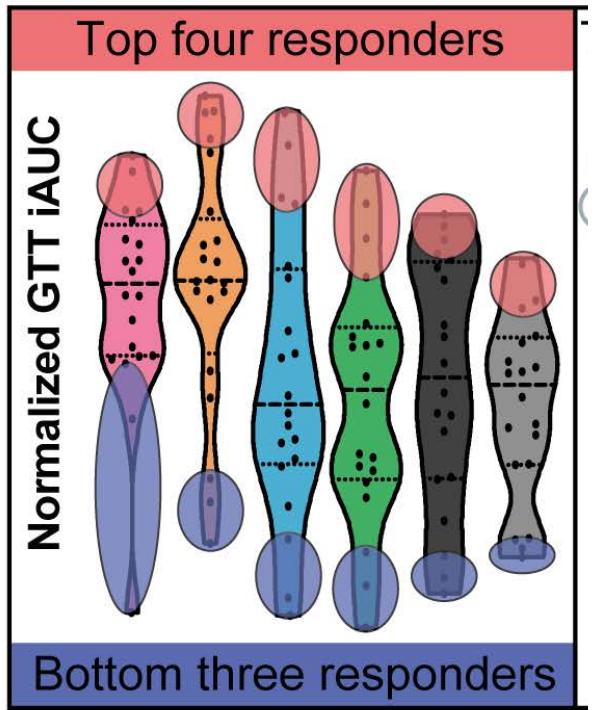


mixed-effects ANOVA ( $P<0.0003$ )

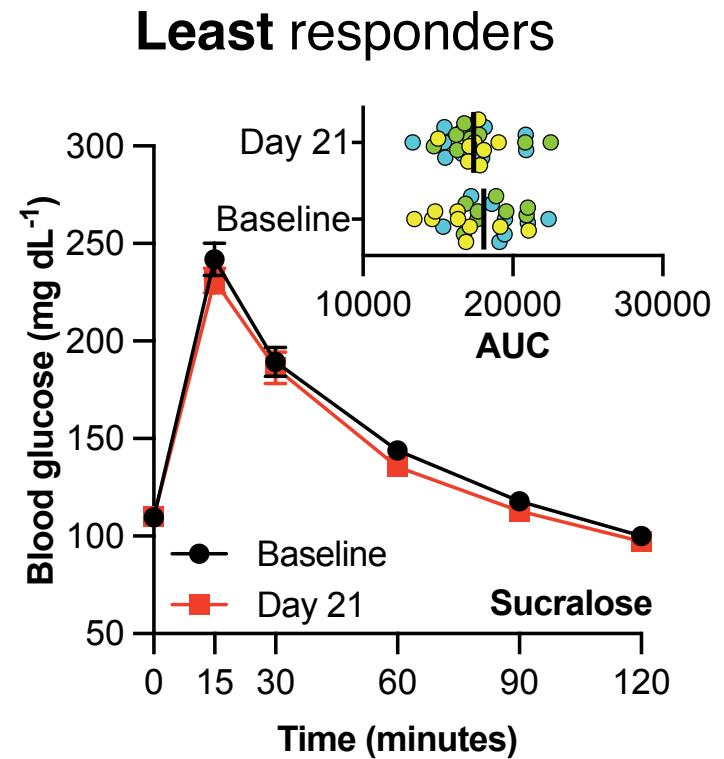


**Can baseline microbiome distinguish  
between top and least NNS responders  
(sucralose as an example)?**

# GF RECIPIENTS OF TOP SUCRALOSE 'RESPONDERS' DEVELOP GLYCEMIC ALTERATIONS

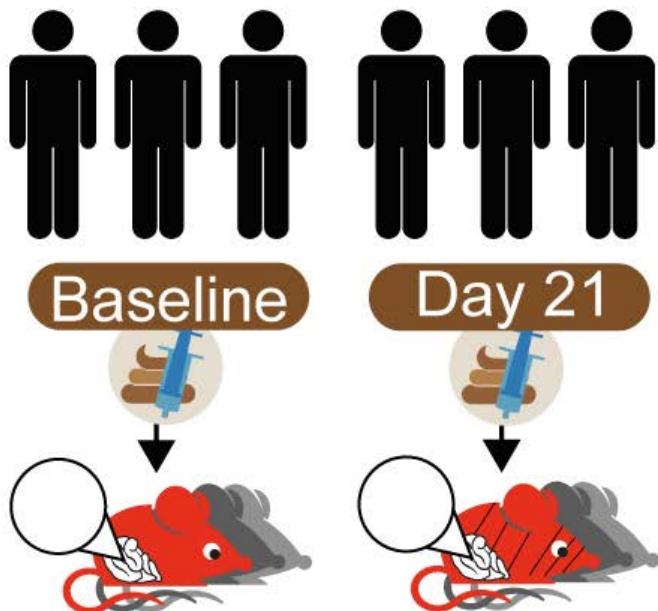


mixed-effects ANOVA ( $P<0.0001$ )

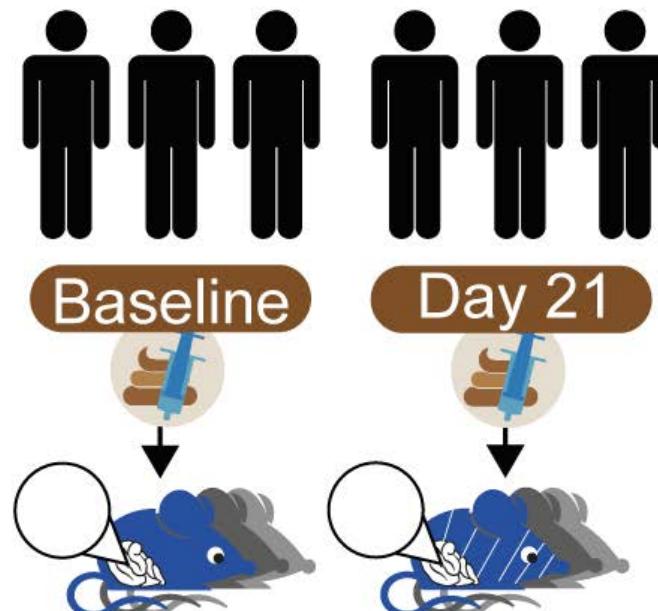


mixed-effects ANOVA ( $P=\text{NS}$ )

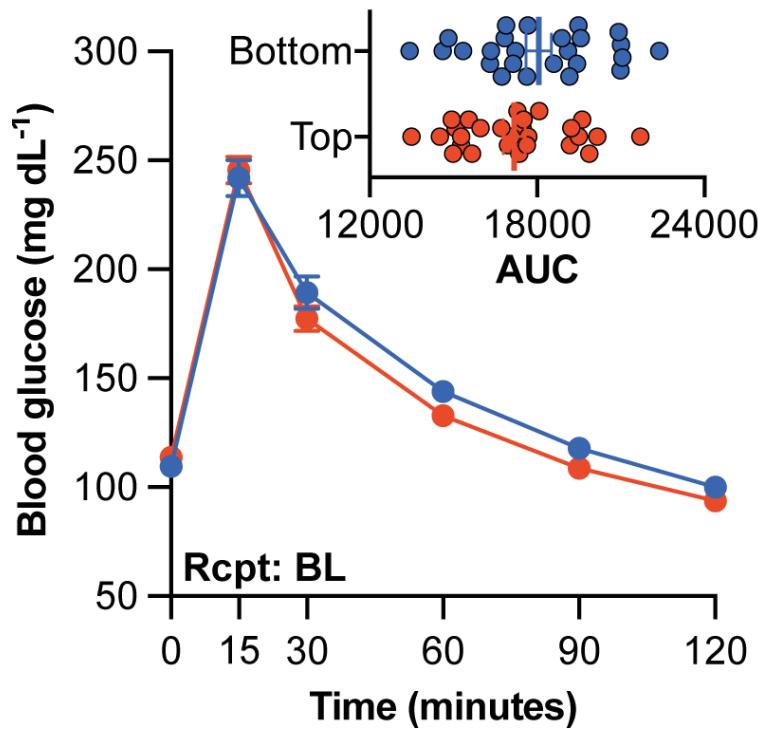
## Top Sucratose Responders



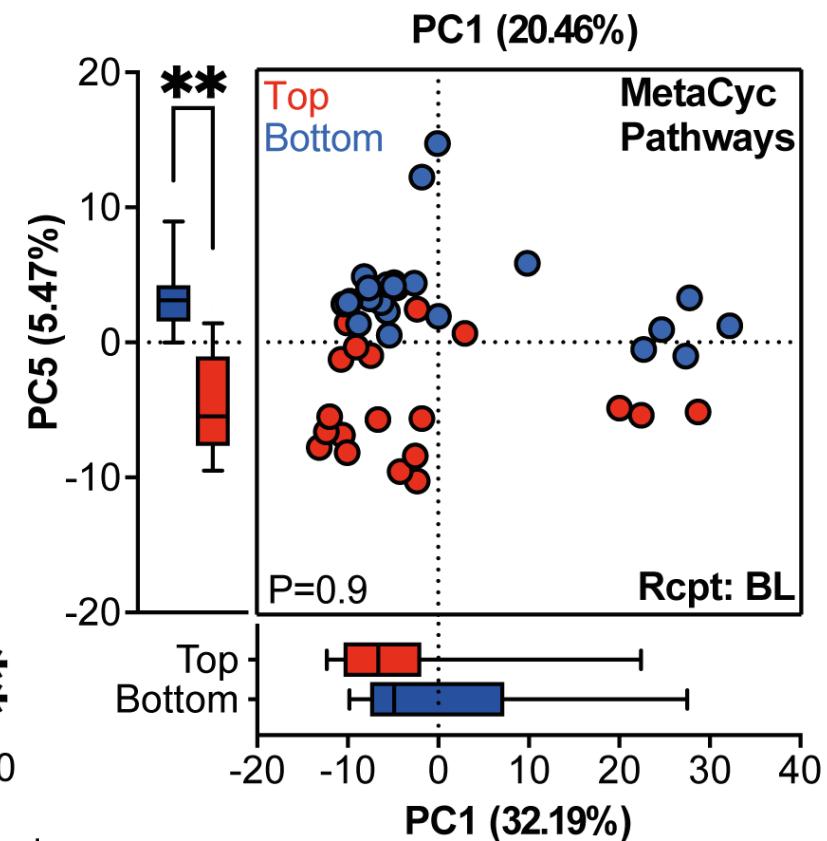
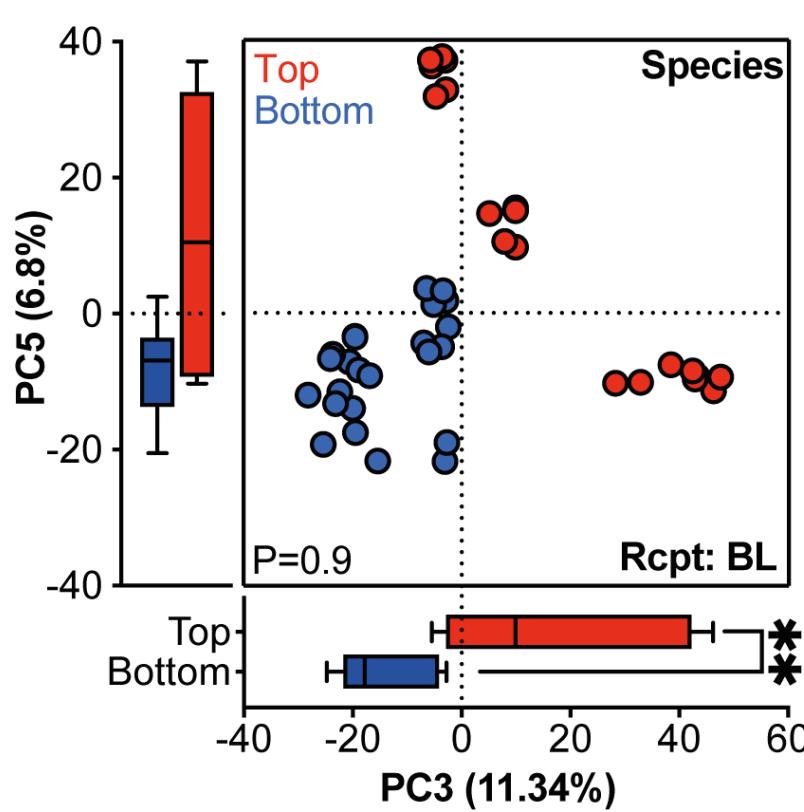
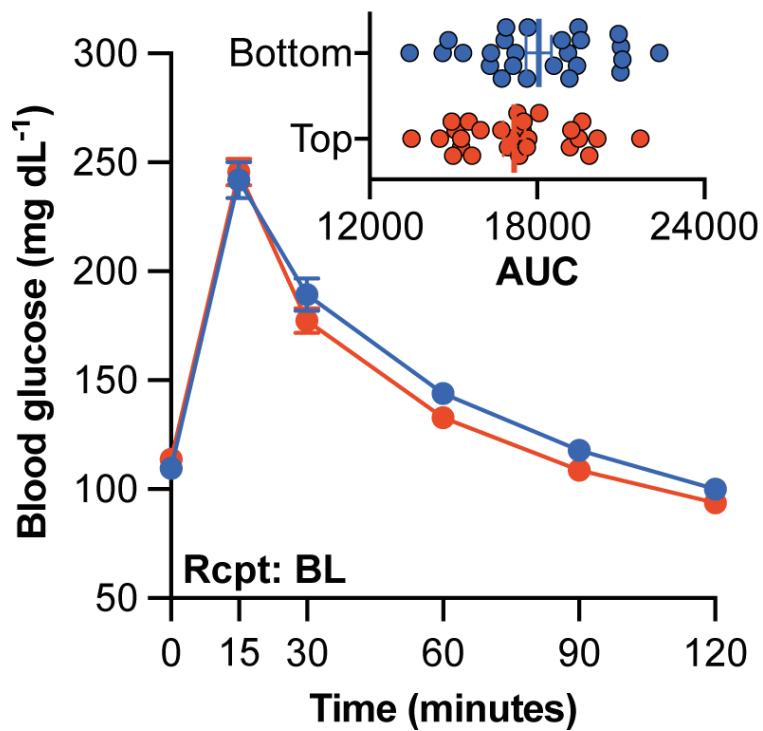
## Bottom Sucratose Responders



# BASELINE MICROBIOME DIFFERENCES BETWEEN MOUSE RECIPIENTS OF TOP AND LEAST RESPONDERS (SUCRALOSE)

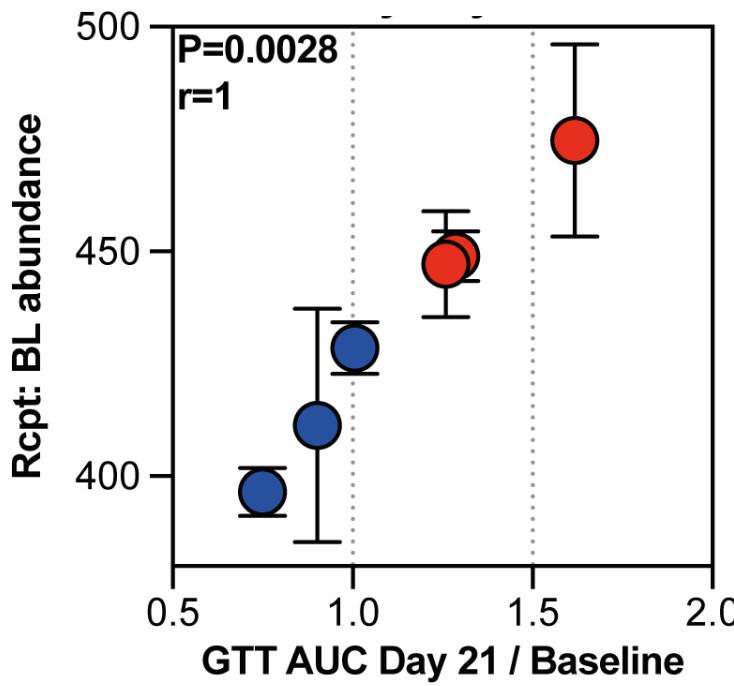


# BASELINE MICROBIOME DIFFERENCES BETWEEN MOUSE RECIPIENTS OF TOP AND LEAST RESPONDERS (SUCRALOSE)

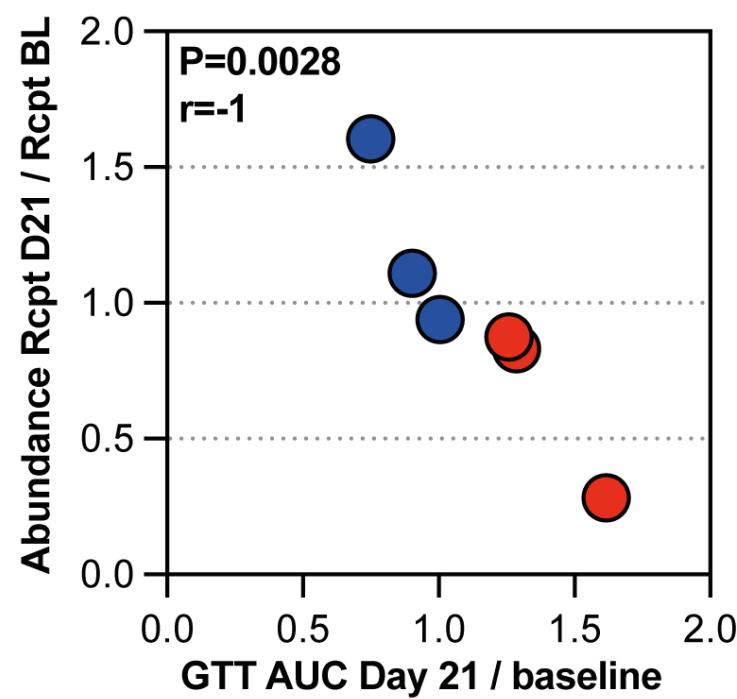


# BASELINE MICROBIOME DIFFERENCES BETWEEN MOUSE RECIPIENTS OF RESPONDERS AND NON-RESPONDERS (SUCRALOSE)

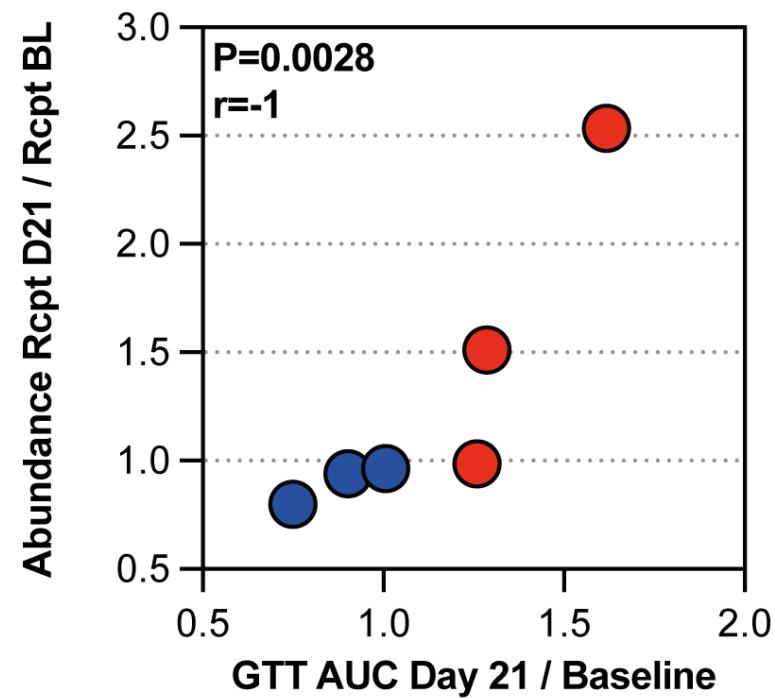
## Glycolysis

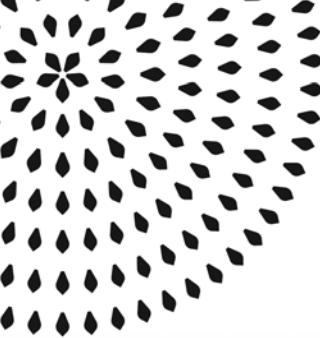


## Sucrose degradation



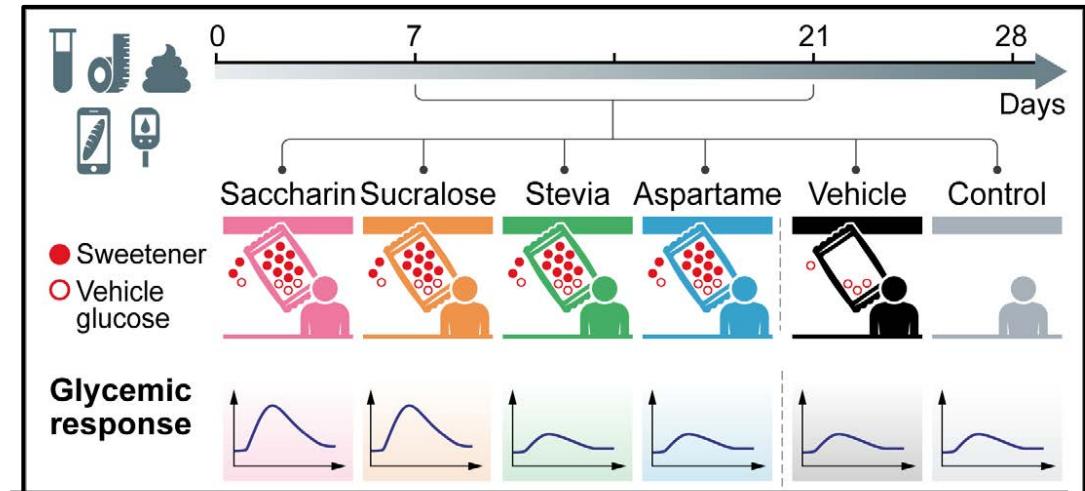
## Glycogen degradation

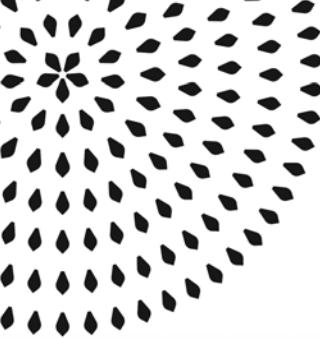




# OUR 'PERSONALIZED NNS' WORKING HYPOTHESIS

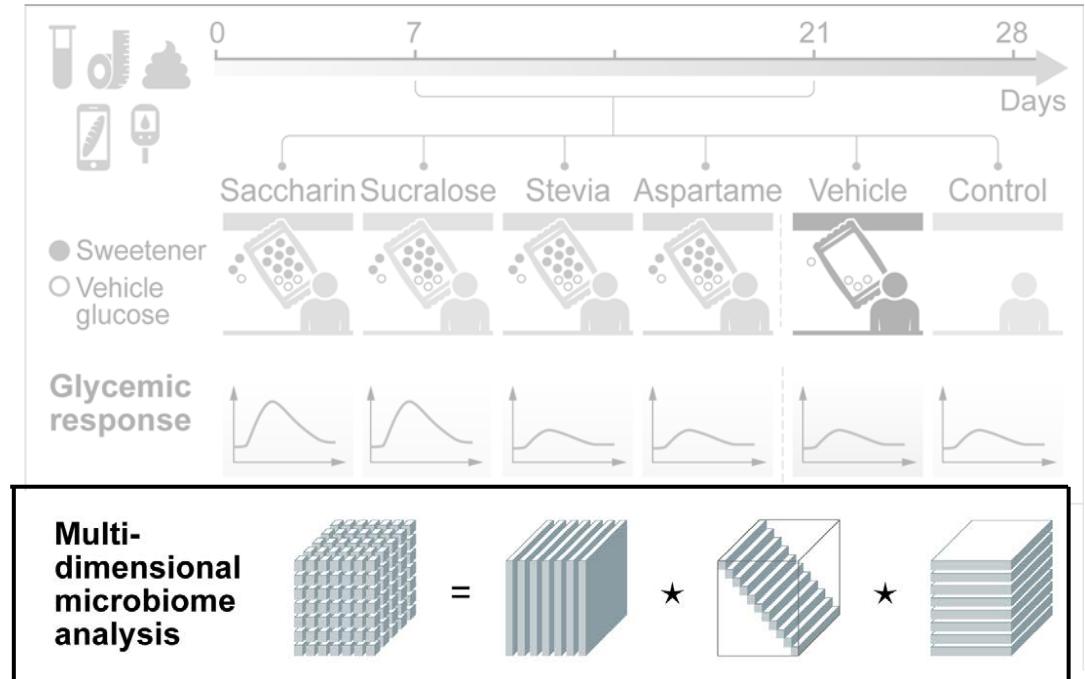
- NNS are not inert to the human body
- NNS may alter glycemic responses
- Saccharin/Sucralose>> Asp and Stevia





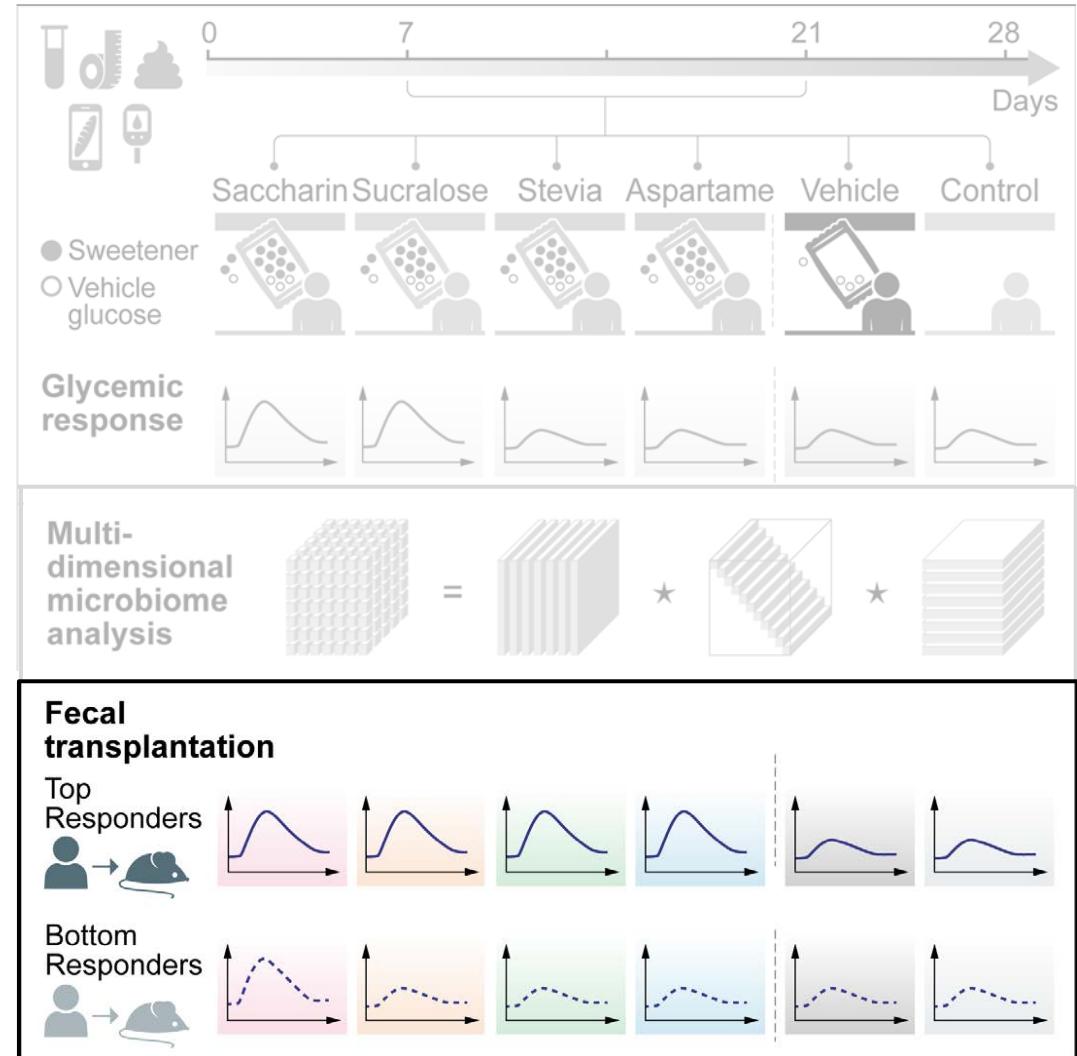
# OUR 'PERSONALIZED NNS' WORKING HYPOTHESIS

- NNS are not inert to the human body
- NNS may alter glycemic responses
- Saccharin/Sucralose>> Asp and Stevia
- **NNS alter the gut microbiome**
- **NNS alter the systemic metabolome**



# OUR 'PERSONALIZED NNS' WORKING HYPOTHESIS

- NNS are not inert to the human body
- NNS may alter glycemic responses
- Saccharin/Sucralose>> Asp and Stevia
- NNS alter the gut microbiome
- NNS alter the systemic metabolome
- **NNS-induced dysbiosis contributes to glycemic alterations**
- **Microbiome effects are personalized & may be predictable at baseline**





	Marharita Skvorodka
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	Dr. Mally Dori-Bachash
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	Tal Hevroni
	Dr. Dragos Ciocan
	Aurelie Bukimer

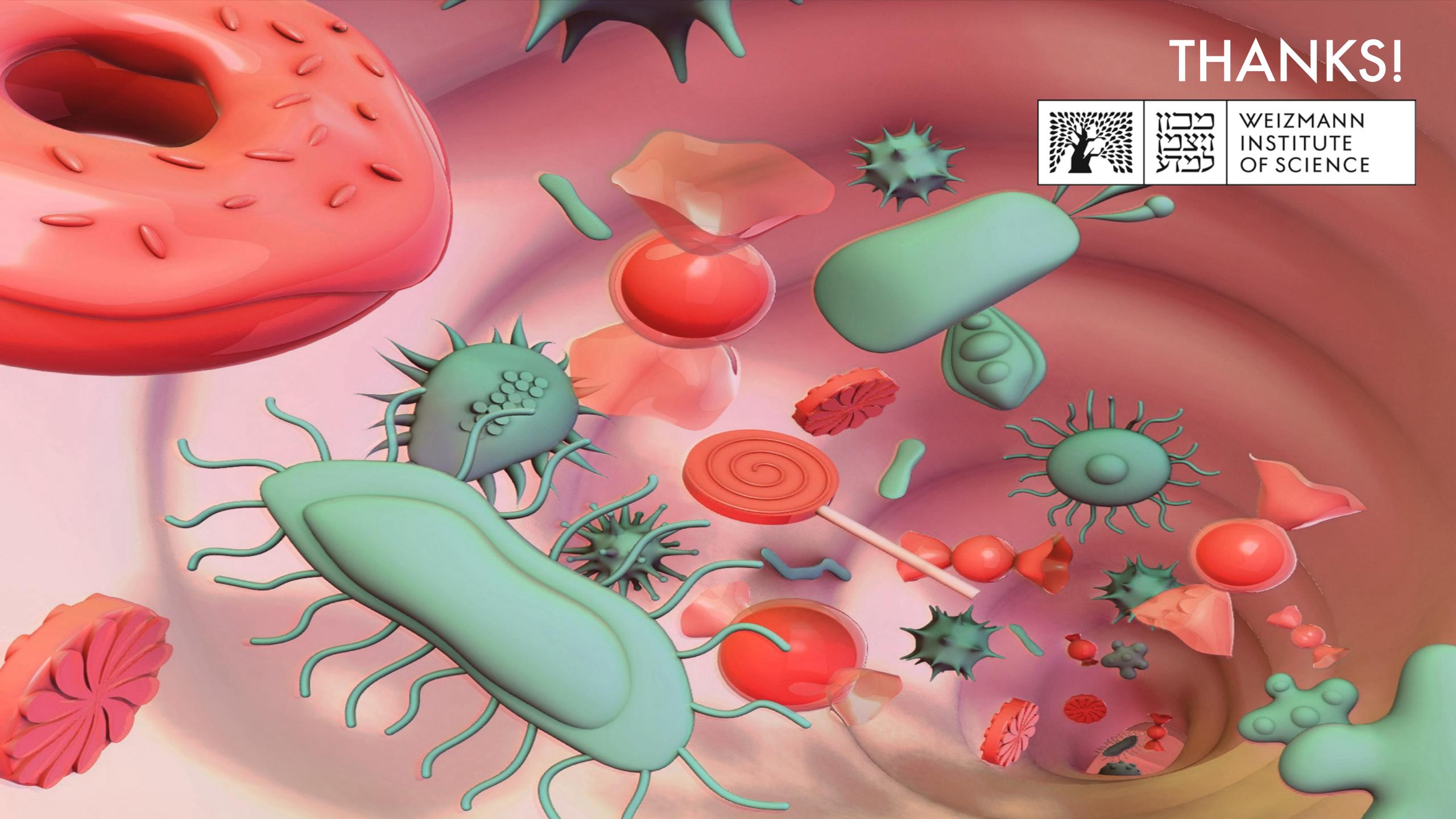
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# THANKS!



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