

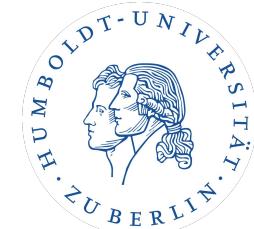


Resistance and tolerance against infections in hybrid mice

Using immune parameters to predict the impact of
hybridization on health

Fay Webster

Emanuel Heitlinger's Lab



Outline

1. Introduction

- a. The European House Mouse Hybrid zone
- b. Resistance and tolerance of hybrid mice

2. Research question

- a. Is tolerance modulating the fitness of hybrid host?
- b. How do we measure tolerance in the wild?

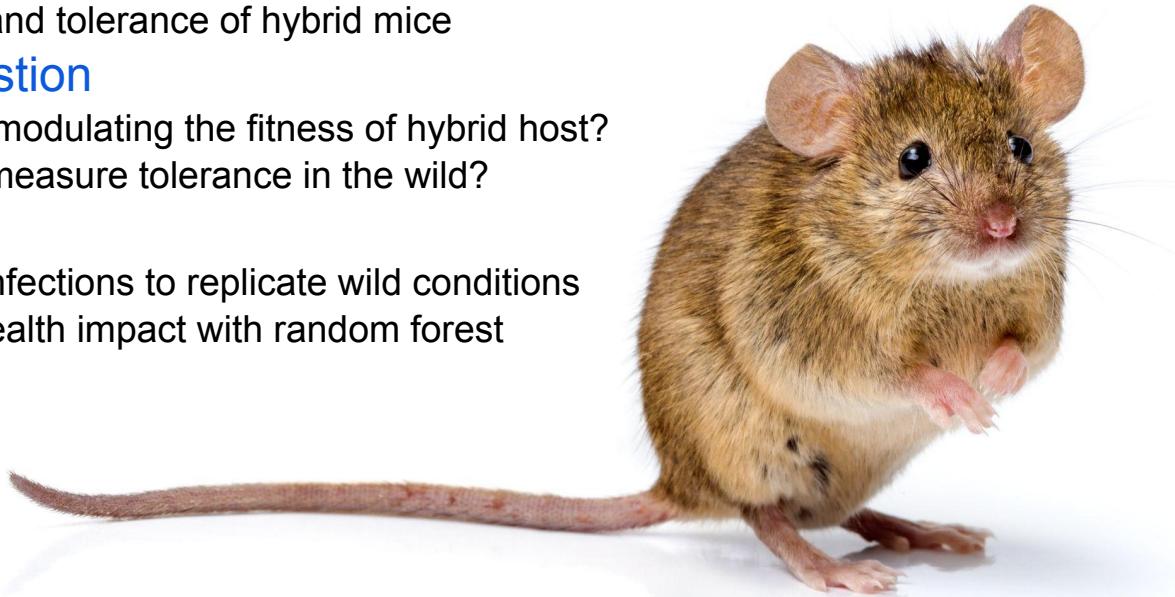
3. Methods

- a. Laboratory infections to replicate wild conditions
- b. Predicting health impact with random forest

4. Results

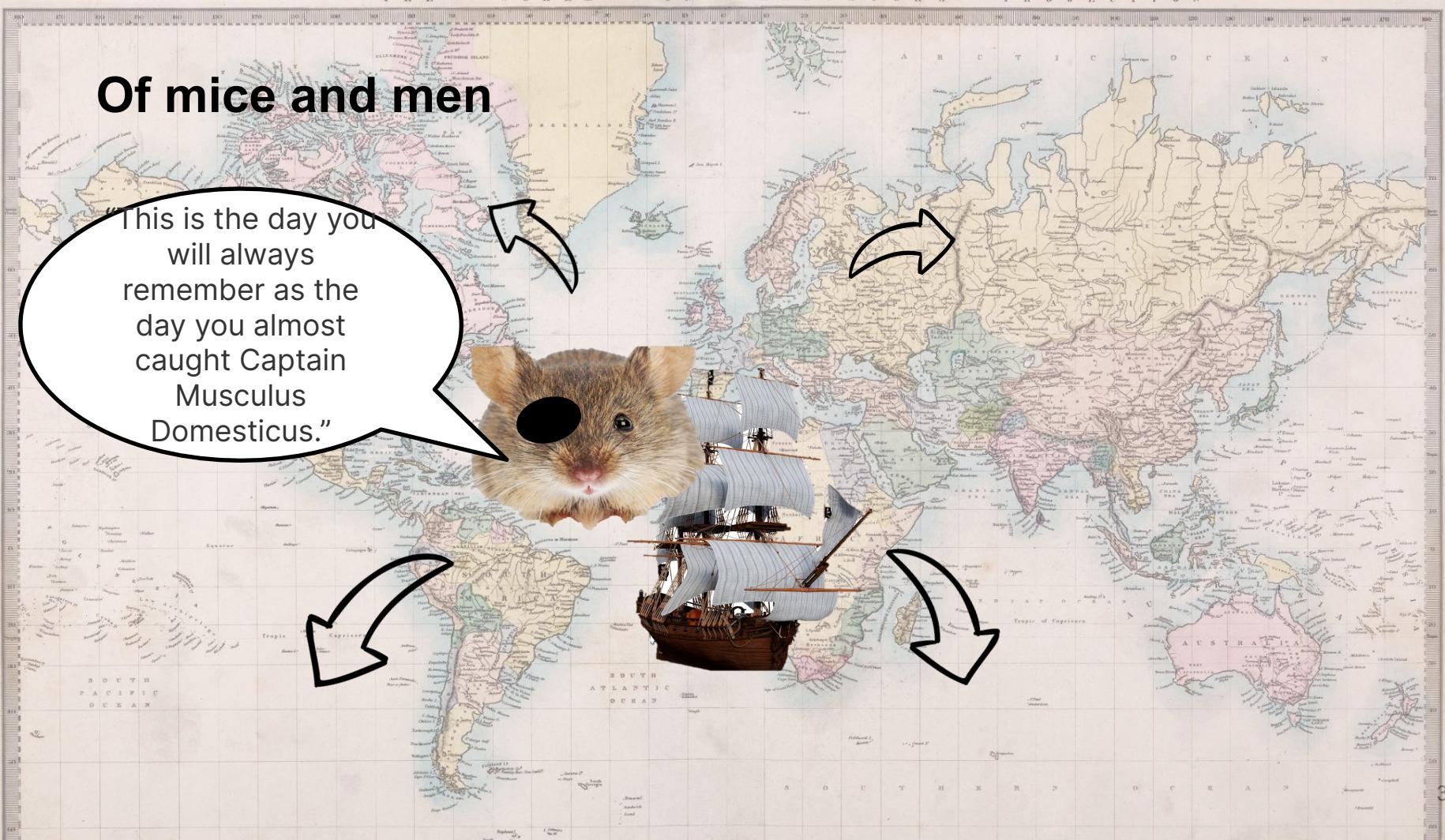
- a. No spoilers!

5. Discussion



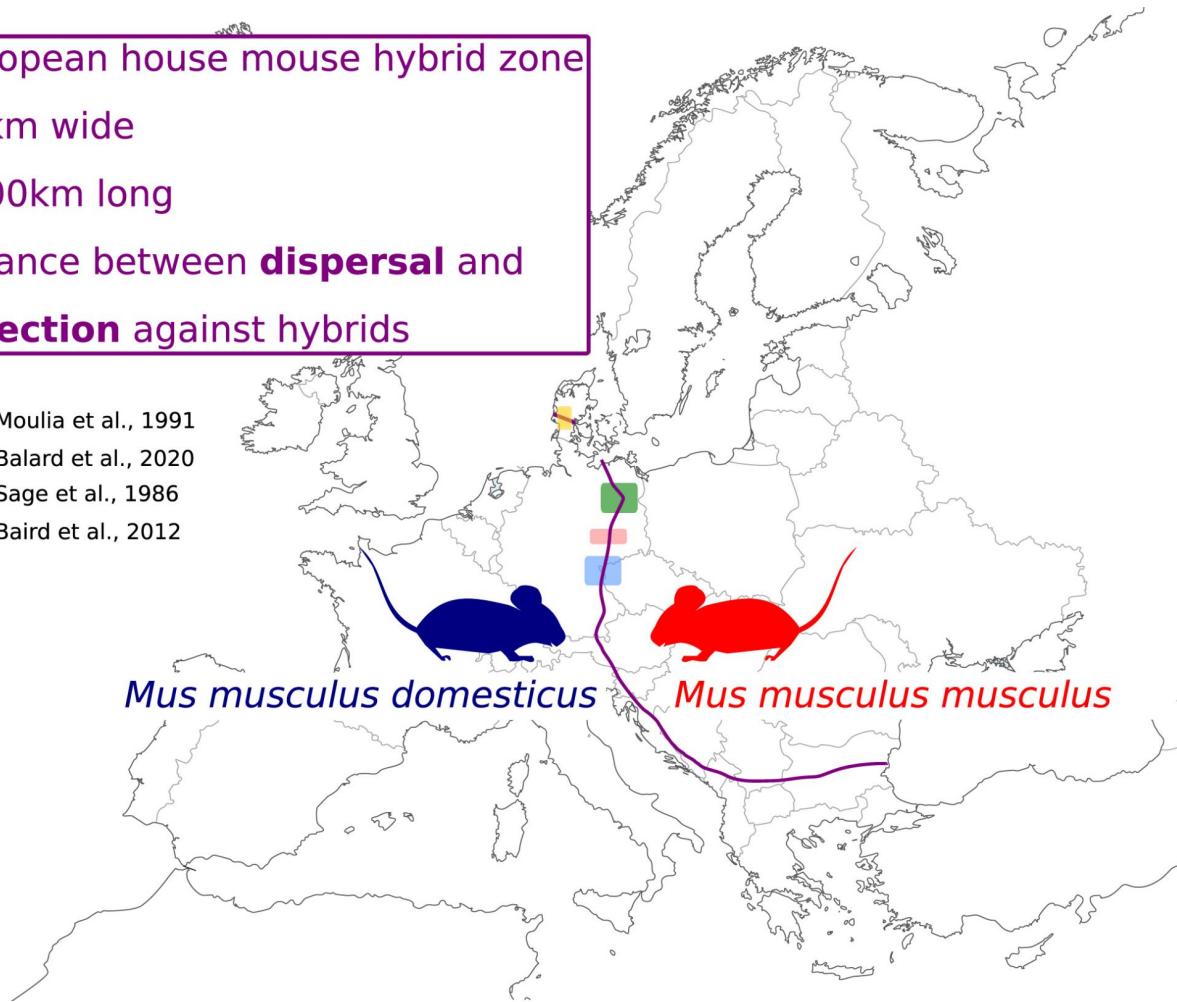
Of mice and men

"This is the day you will always remember as the day you almost caught Captain Musculus Domesticus."



European house mouse hybrid zone
20km wide
2500km long
Balance between **dispersal** and
selection against hybrids

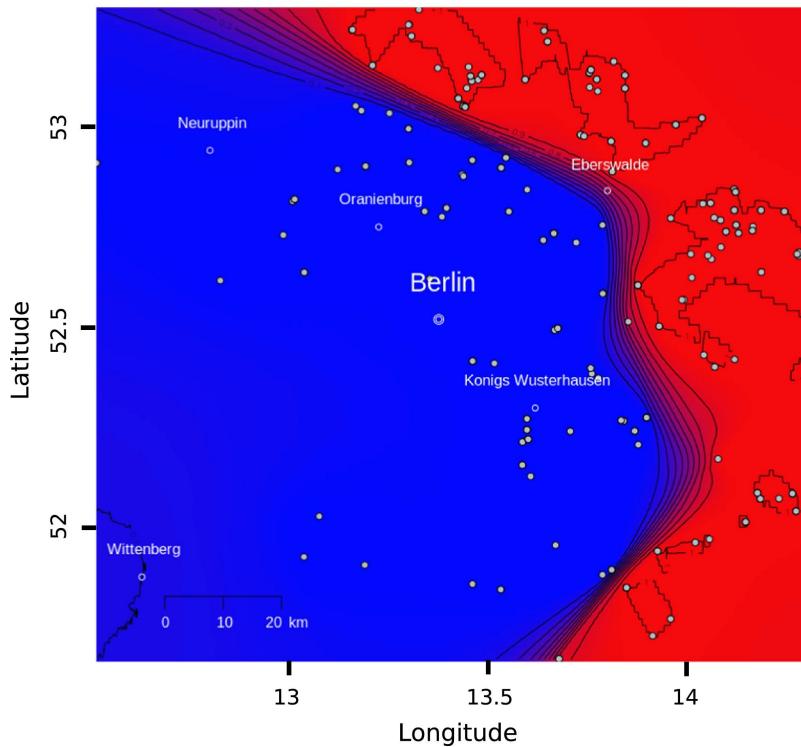
- Moulia et al., 1991
- Balard et al., 2020
- Sage et al., 1986
- Baird et al., 2012



Study area:

***M. musculus
domesticus***

Map of posterior probability to belong to Mmm

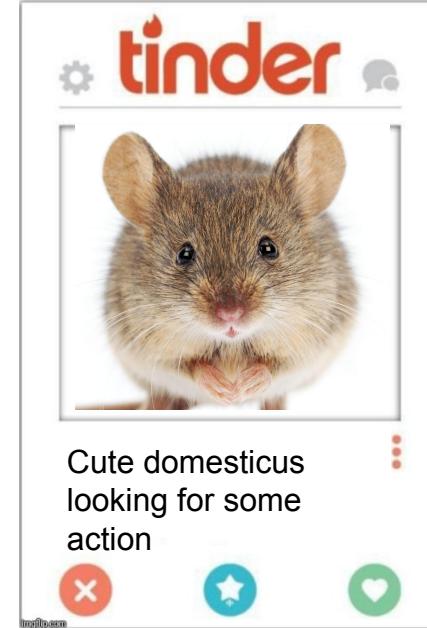


***M. musculus
musculus***

Balard et al., 2019

When you meet your tinder date ...

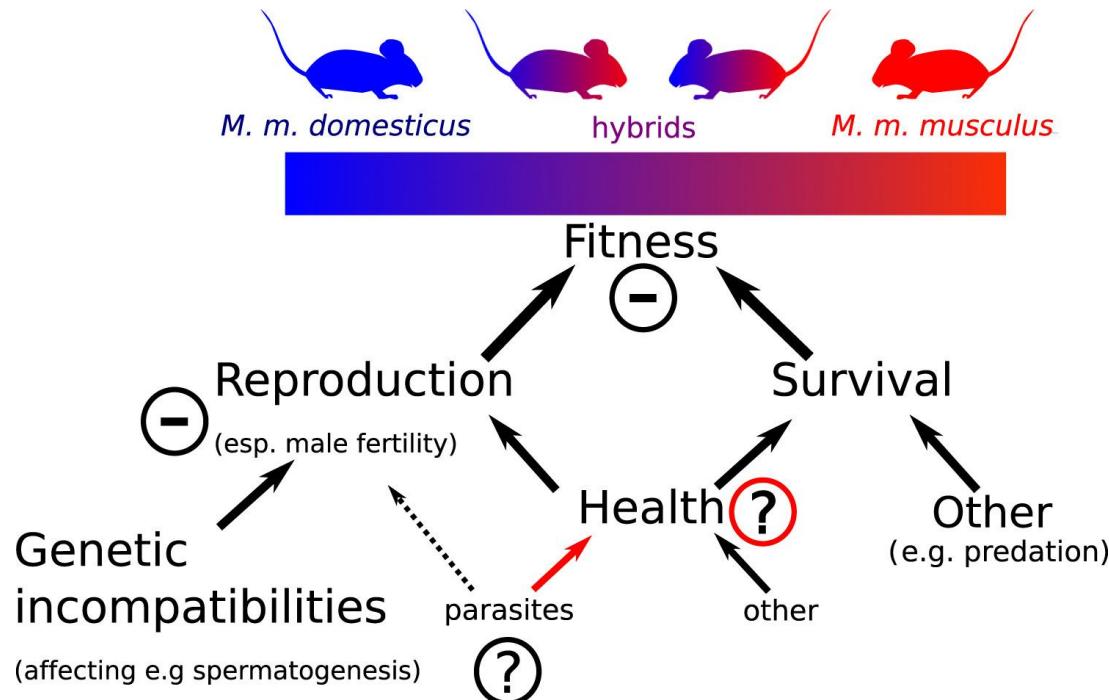
And it is a another species



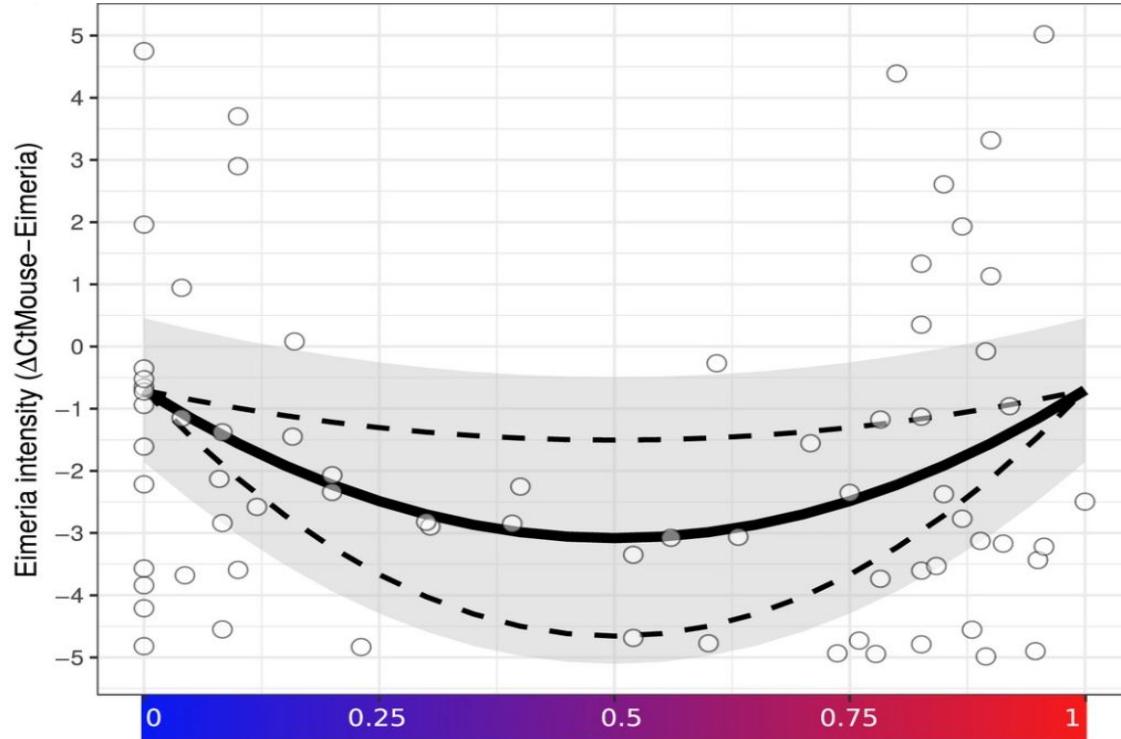
Hybrids: The Good, The Bad And The Ugly



Fitness components of hybrid mice



Intensity of infections with *Eimeria* are reduced in hybrids

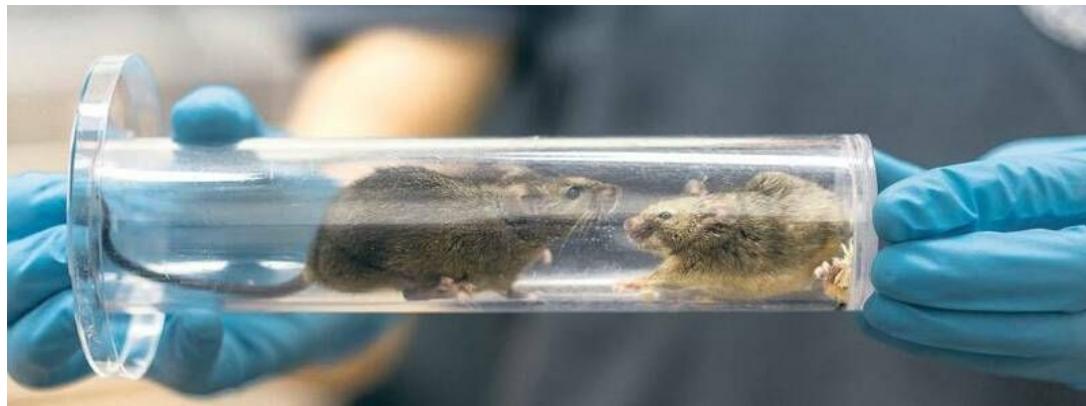


Graph: Balard et al., 2019

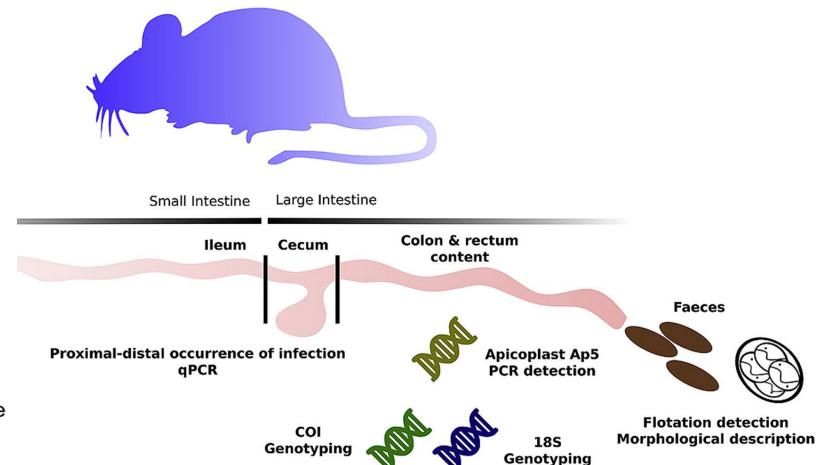
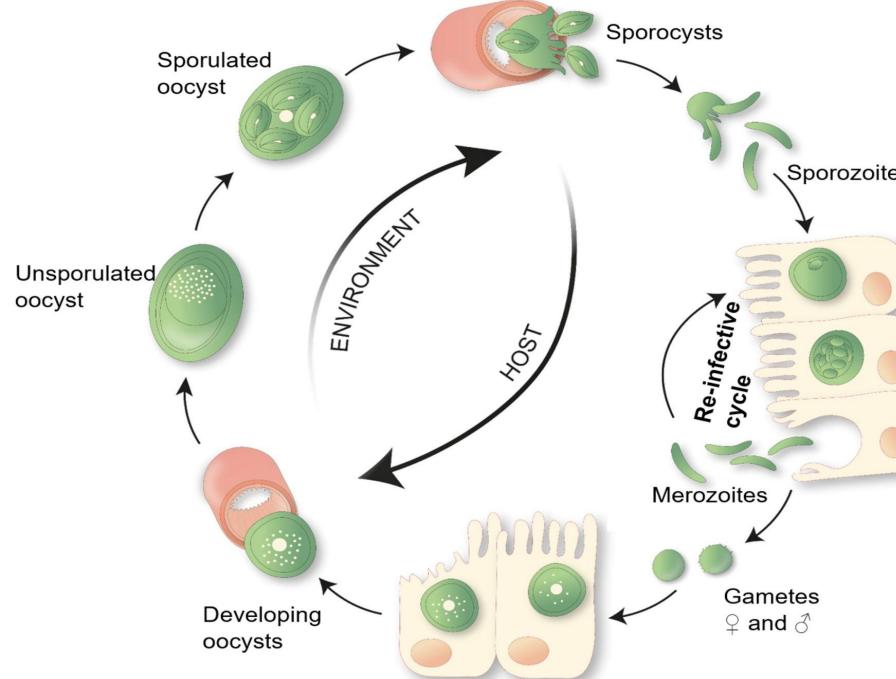
Method: Baird et al., 2012

Research question:

Is tolerance modulating the fitness of hybrids?



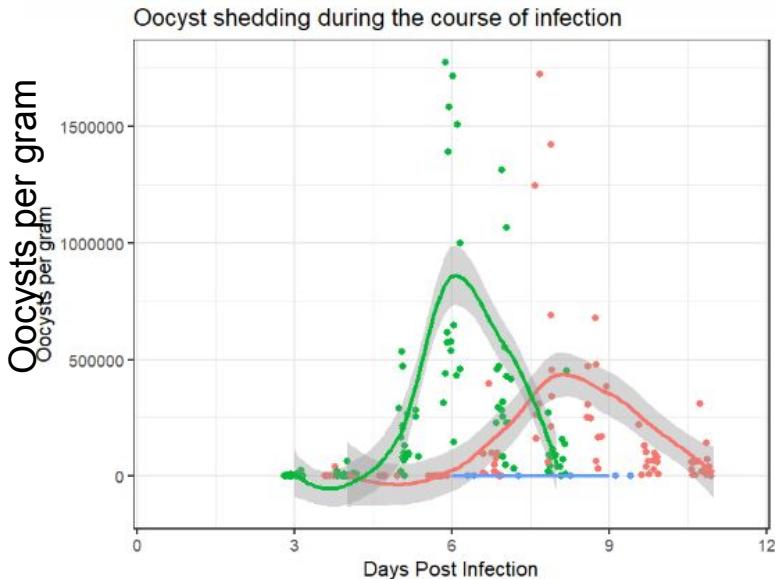
Life cycle of Eimeria



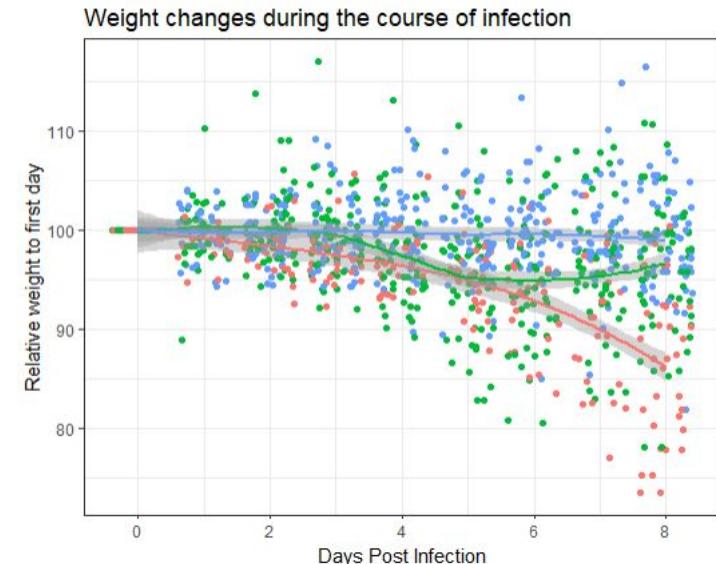
Life history differences between two *Eimeria* species



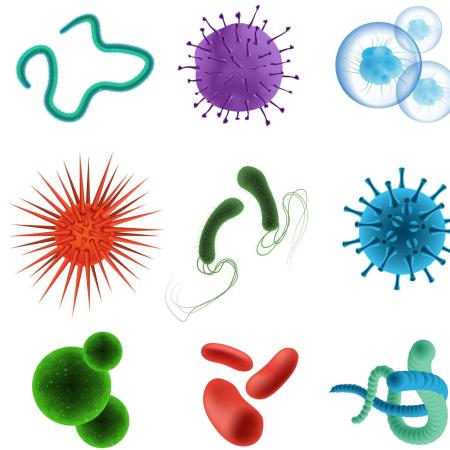
Oocysts shedding during the course of infection



Weight changes during the course of infection



Resistance and tolerance



Resistance

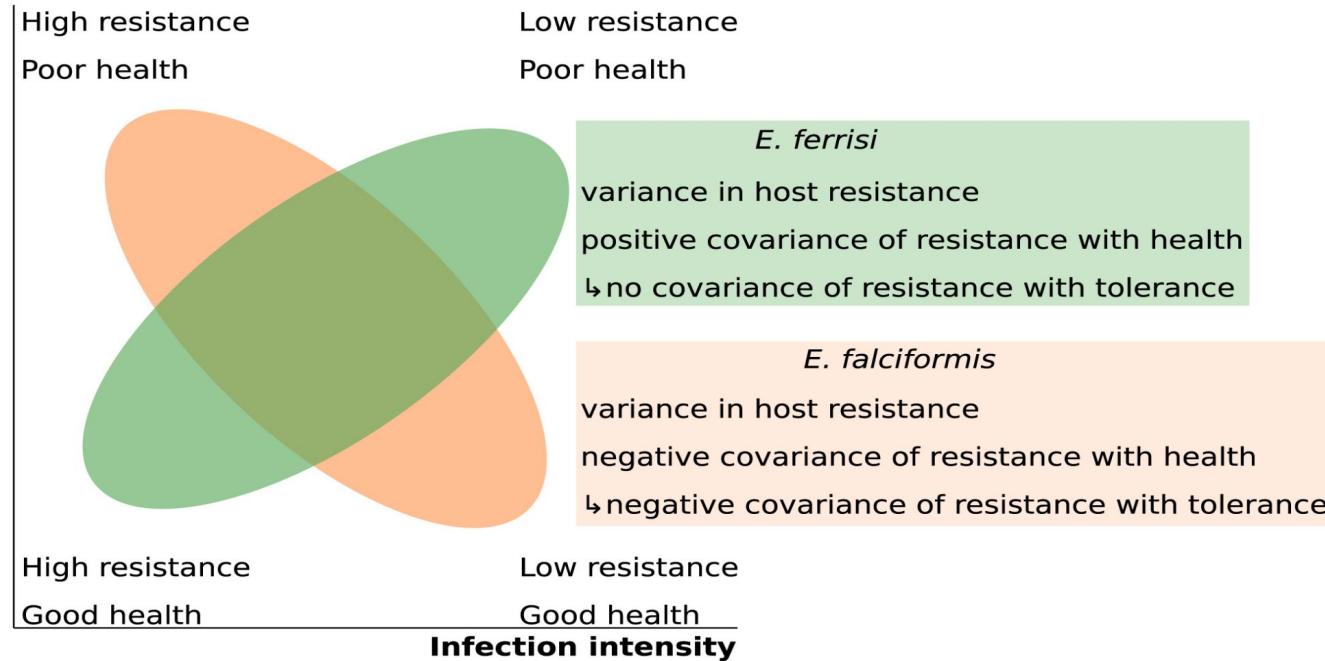


Tolerance



Resistance and Tolerance of *E. ferrisi* / *falciformis*

**Impact on
host health**



Summary

- Hybrid mice
 - lower infection intensities with *Eimeria* spp. = higher resistance
- *Eimeria ferririsi* and *Eimeria falciformis*
 - → different resistance tolerance relationships
- Hybridization effect on tolerance → ?

Objective:

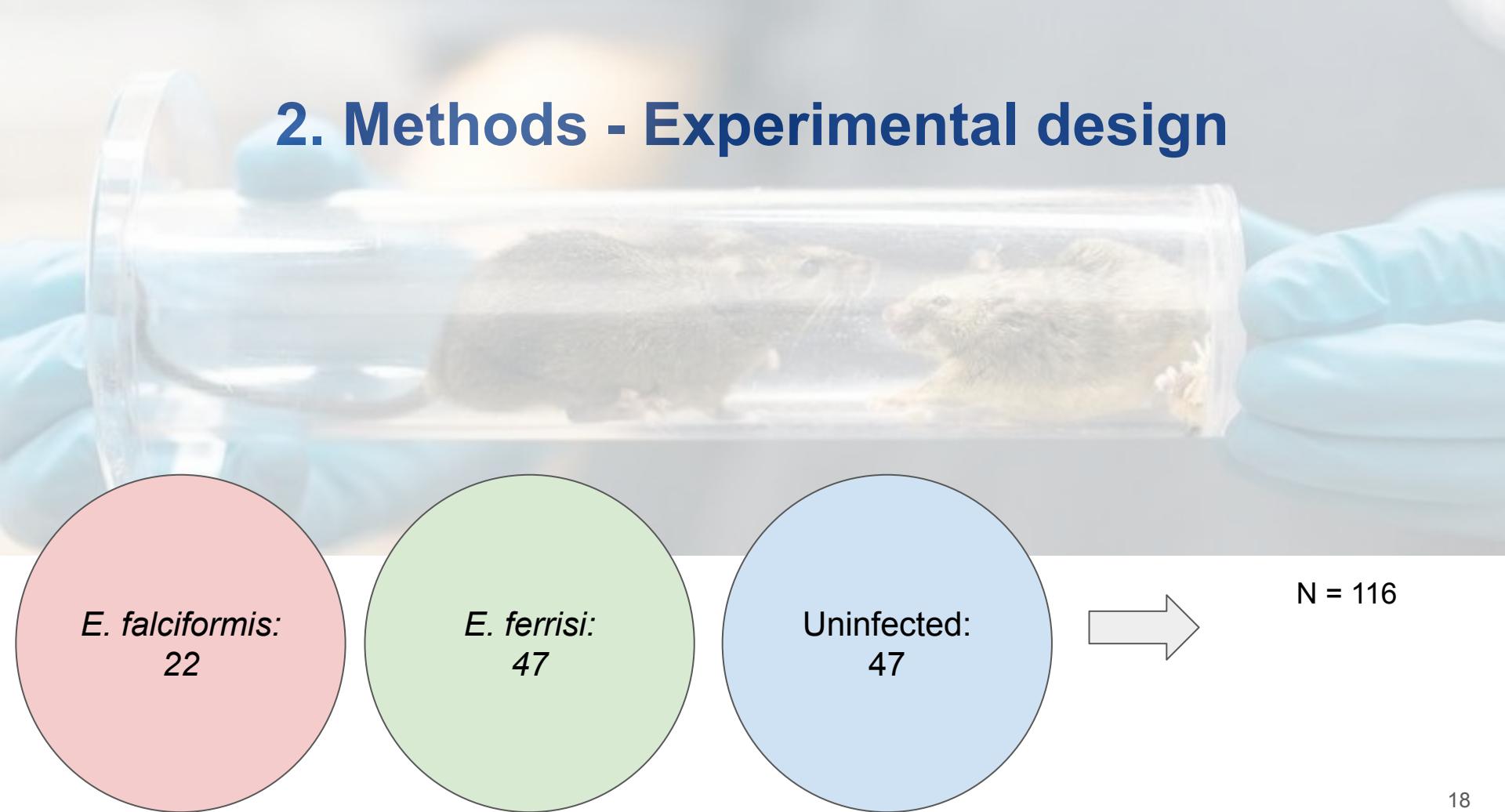
Predicting health impact:

An approach using
commonly used immune
parameters



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2. Methods - Experimental design



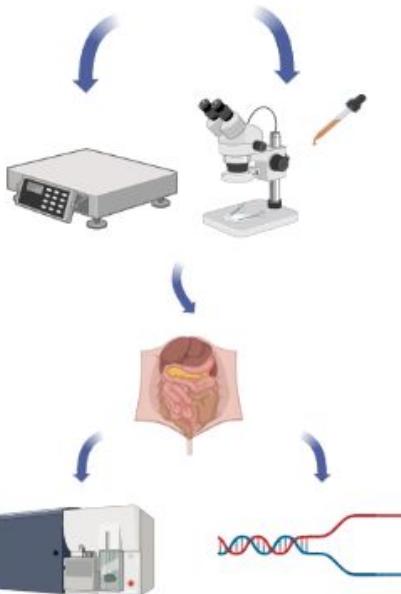
2. Methods: Experimental design

Day 0



Infection with 150 sporulated oocysts

Day 1 - 8

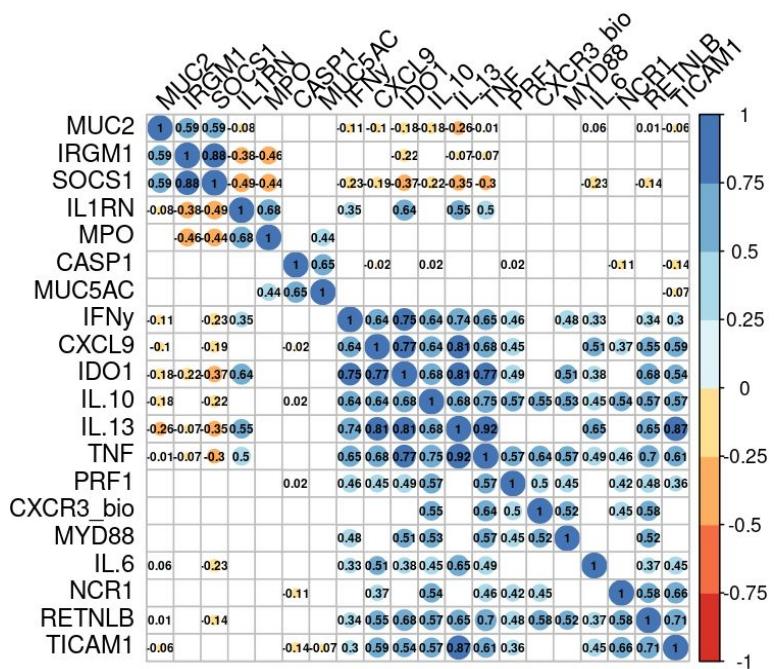


1. Weight changes
2. Flotation (OPG)

Day 8

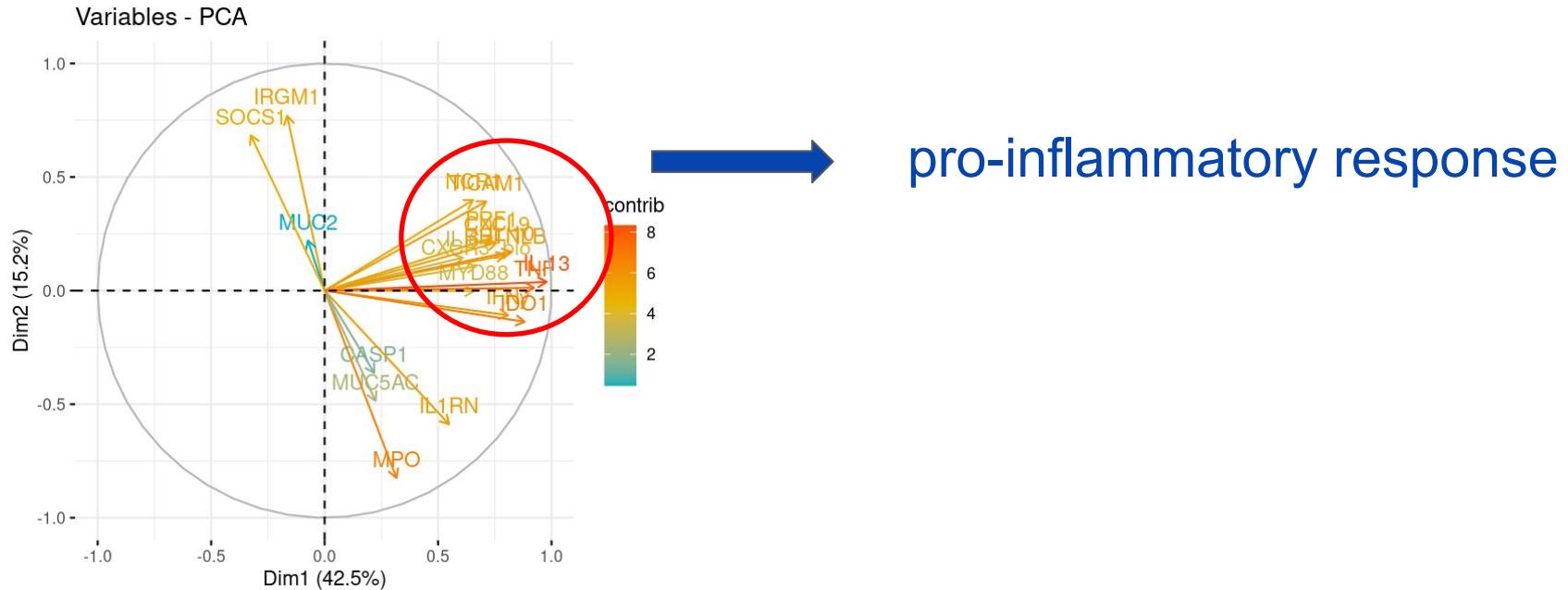
1. Cell sorting (FACS)
2. Immune gene expression Rt qPCR

2. Methods: Immune gene expression

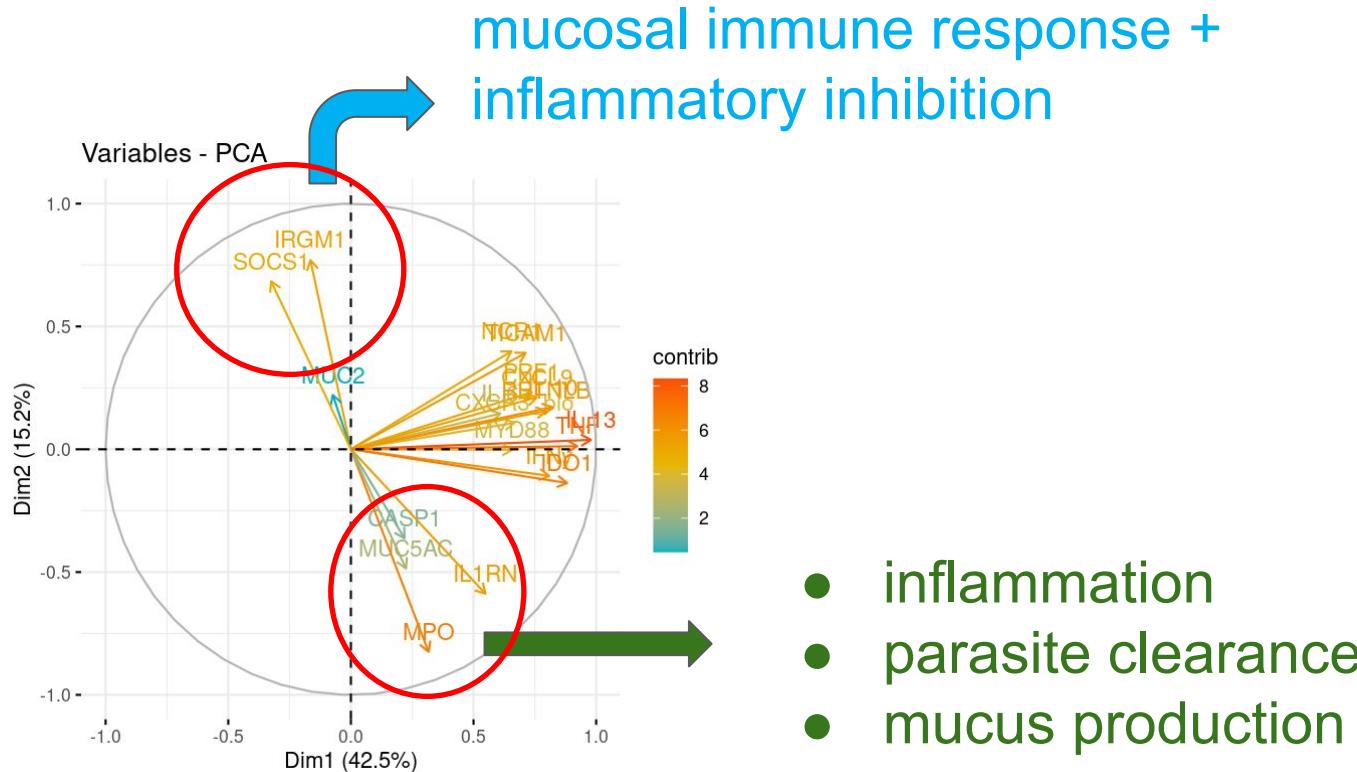


Can the immune measures predict the impact of the infection on host health?

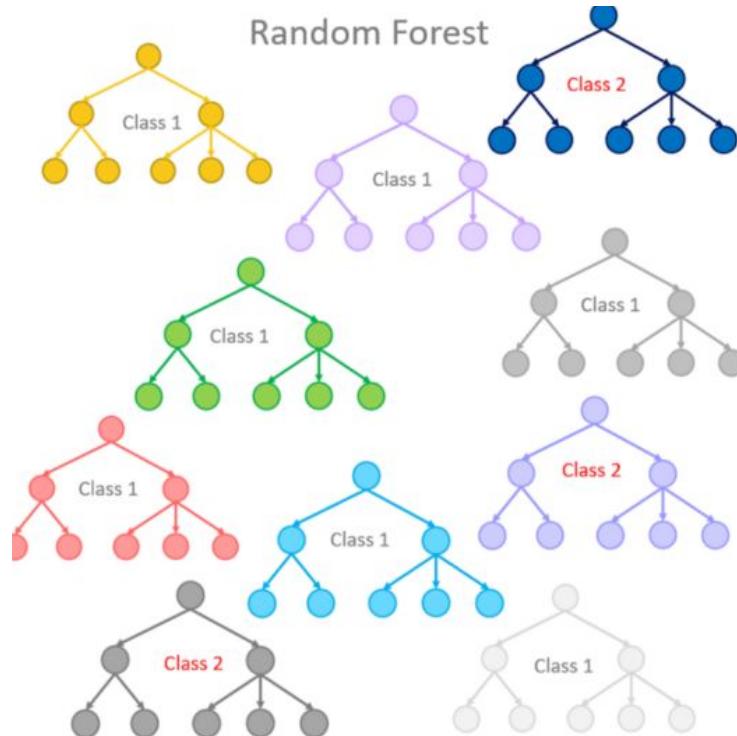
2. Methods: PCA of immune gene expression



2. Methods: PCA of immune gene expression



2. Methods: Random forest



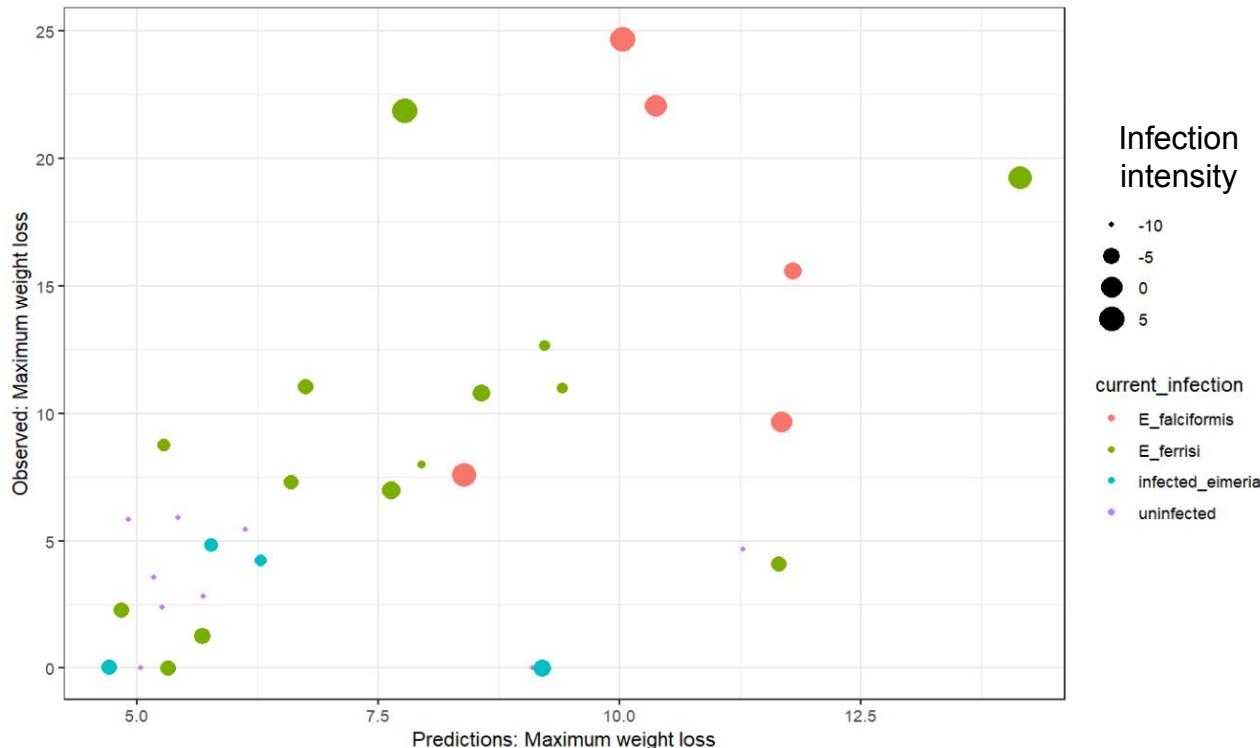
Random forest: Predicting health impact - lab data

Spearman's rank correlation

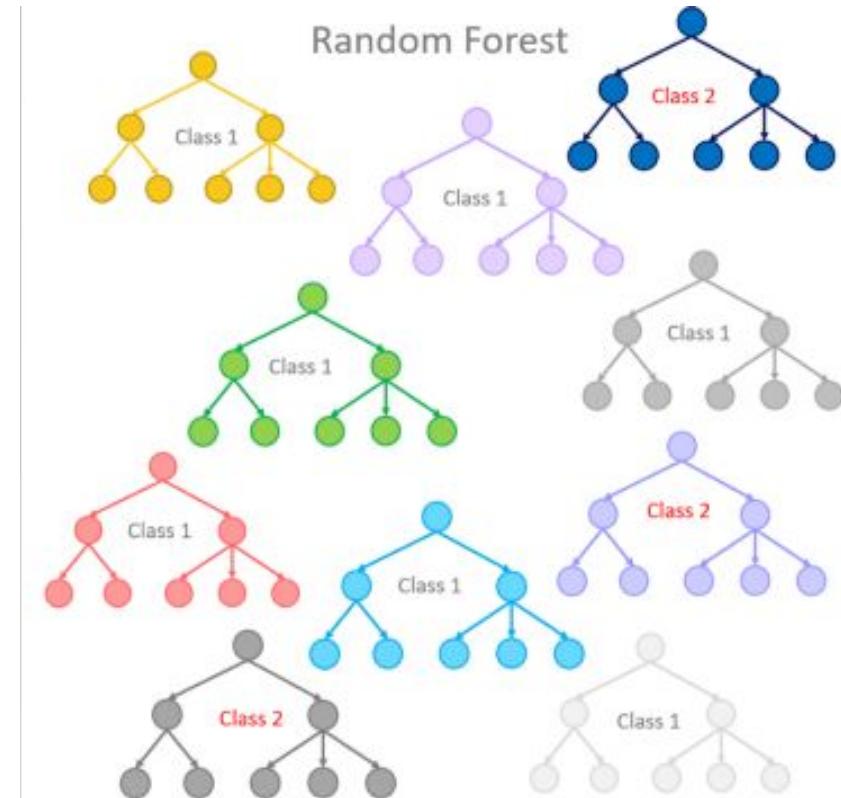
$S = 2346.1$

p-value = 0.0006603

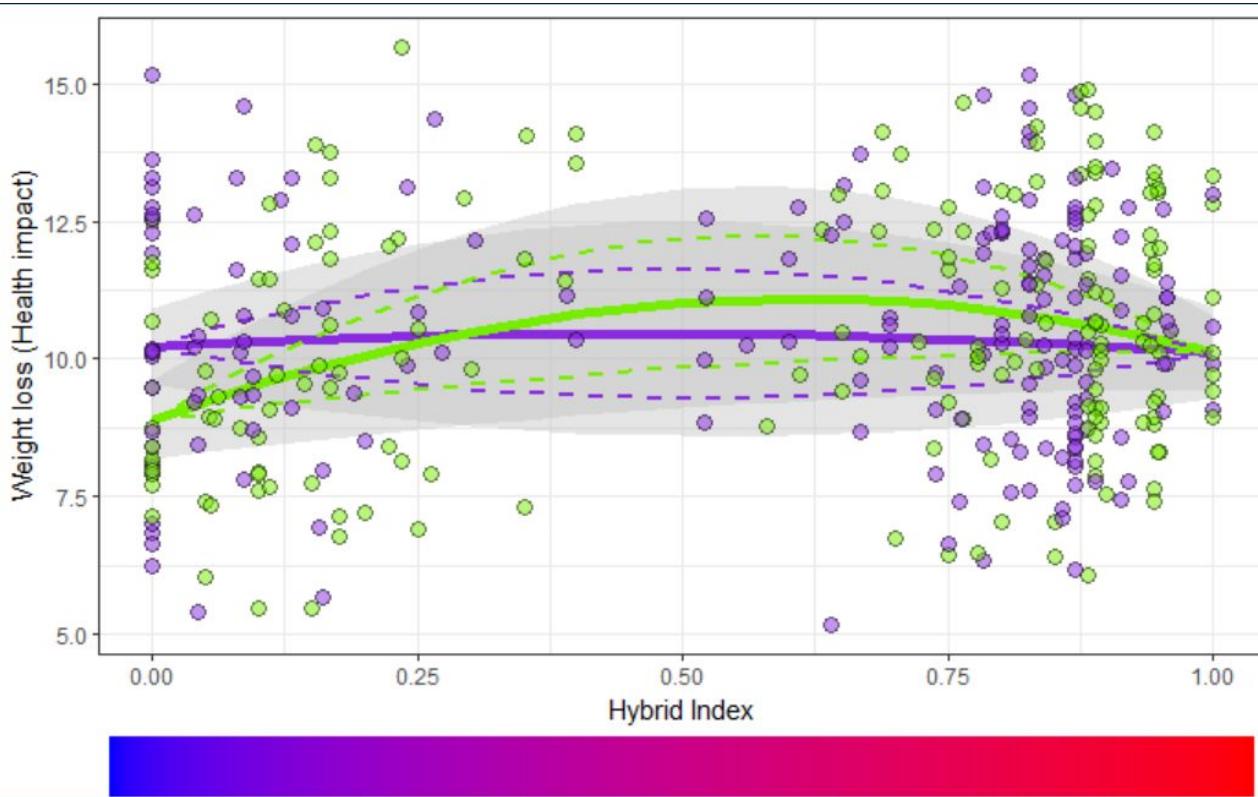
Rho: 0.5699874



Random forest: Predicting health impact in the field

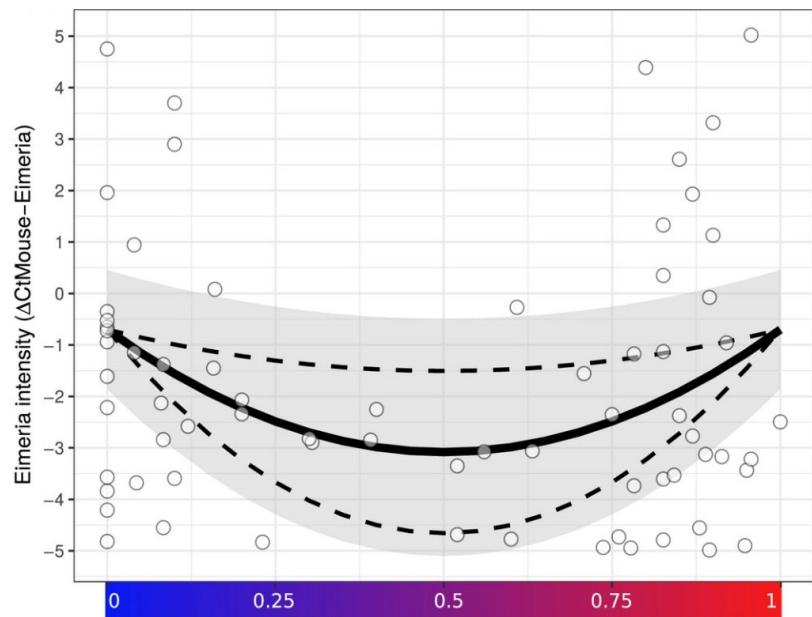


3. Results: Effect of hybridization on predicted health impact

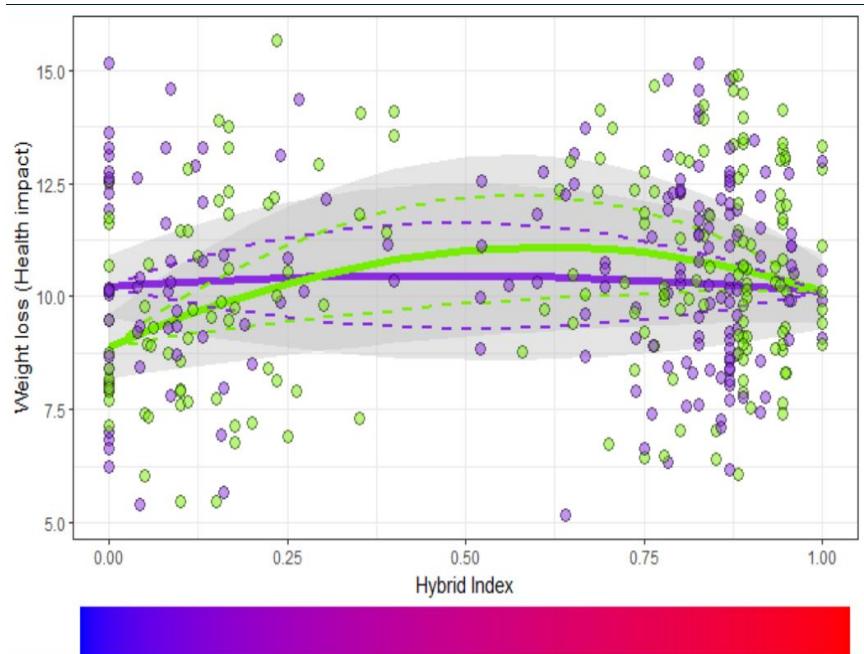


3. Results: Effect of hybridization on predicted health impact

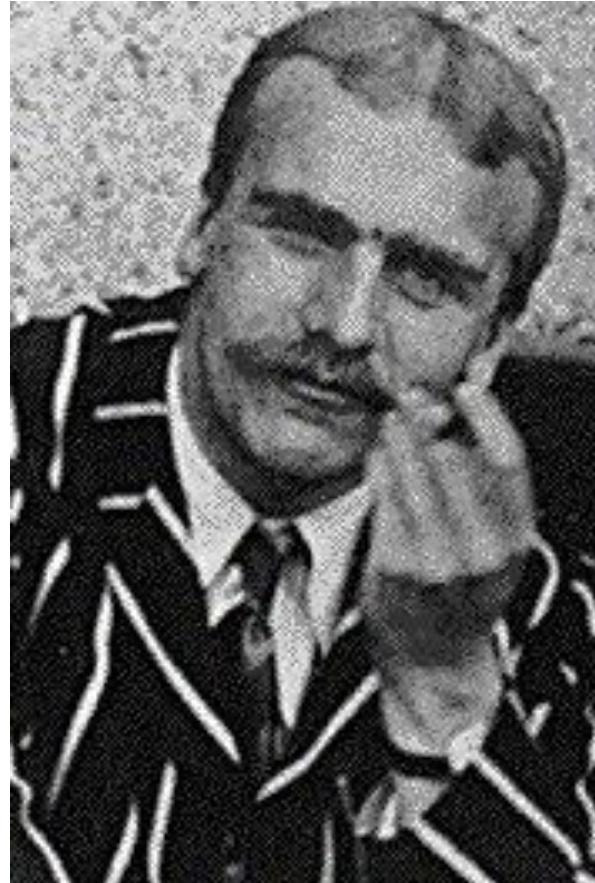
Resistance



Health impact

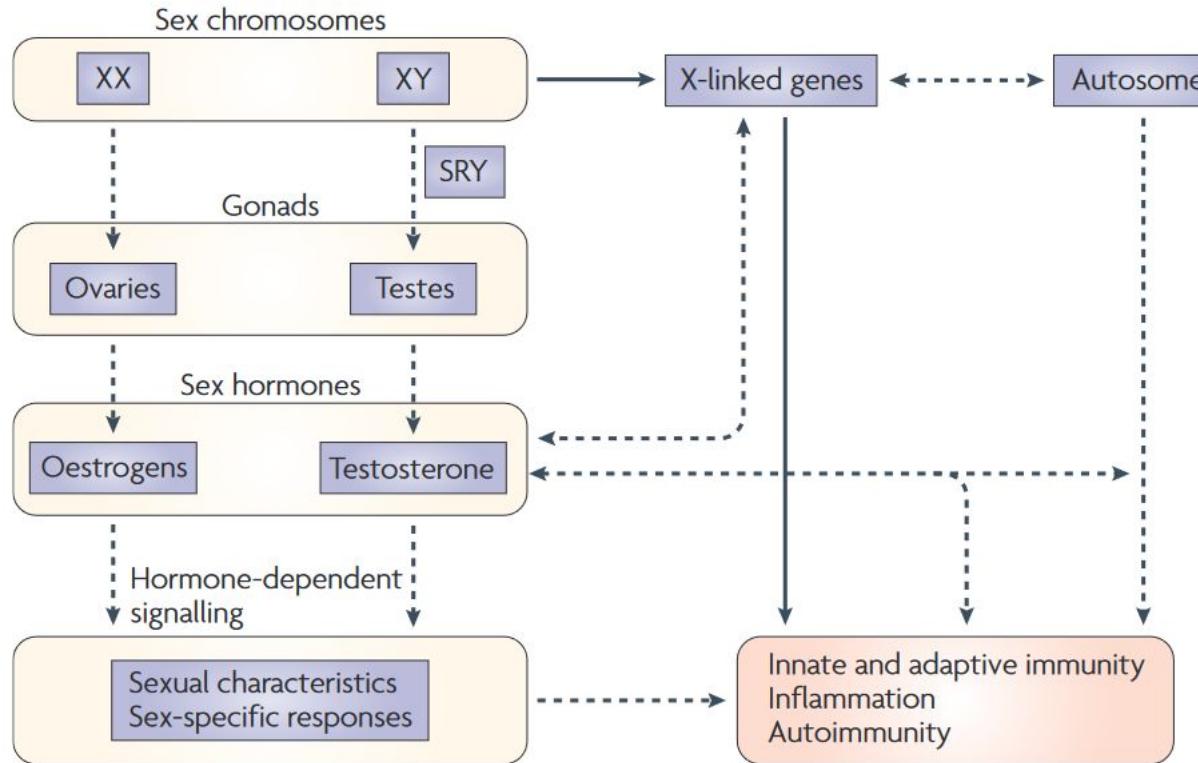


'When in the offspring of two different animal races one sex is absent, rare, or sterile, that sex is the heterozygous sex'



J. B. S. Haldane

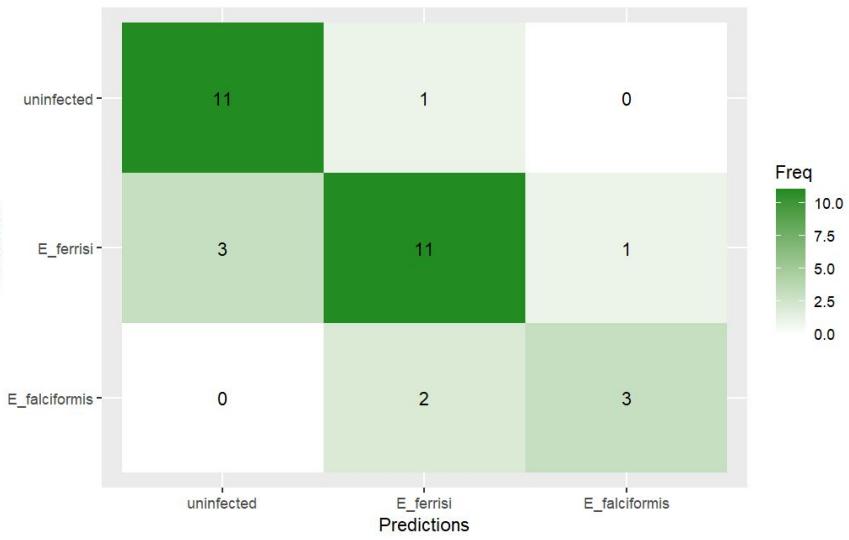
The X chromosome and immunity



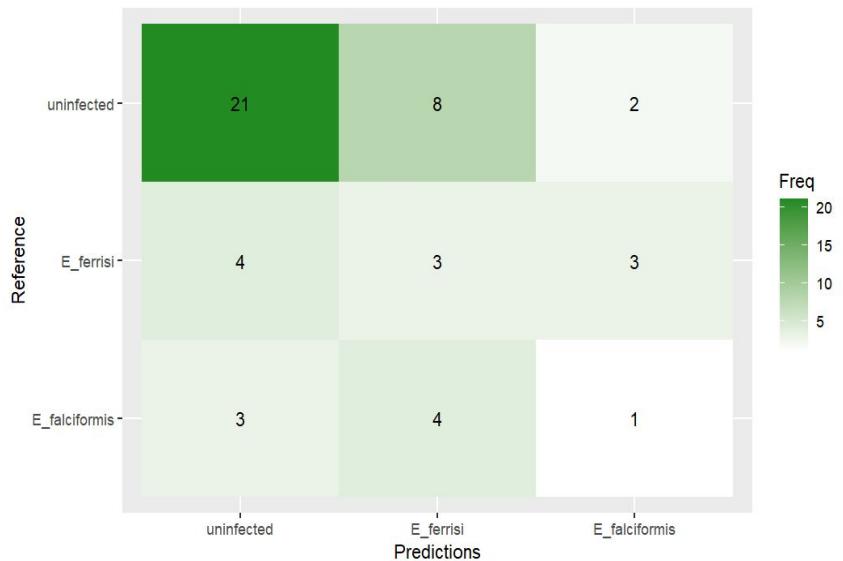
Libert et al., 2010

Random forest: Using immune parameters to predict current infection

Lab data: predicting infective parasite



Field data: application of random forest



Discussion

Acknowledgments

Berlin team:

- Emanuel Heitlinger
- Lubomir Bednar
- Finn Lobnow
- Victor Hugo Jarquín Díaz
- Alice Balard
- Sebastian Rausch
- Hongwei Zhang

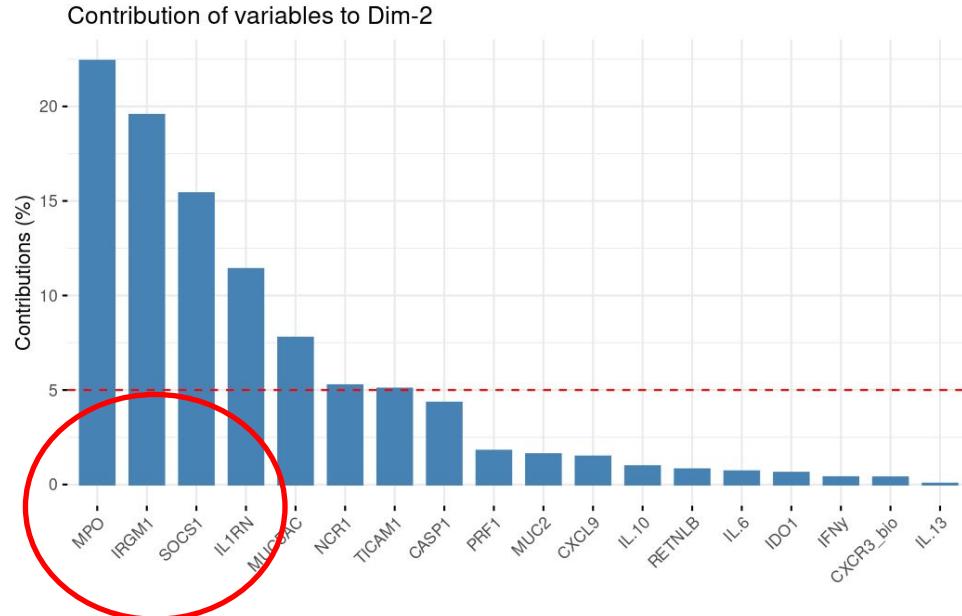


Czech team:

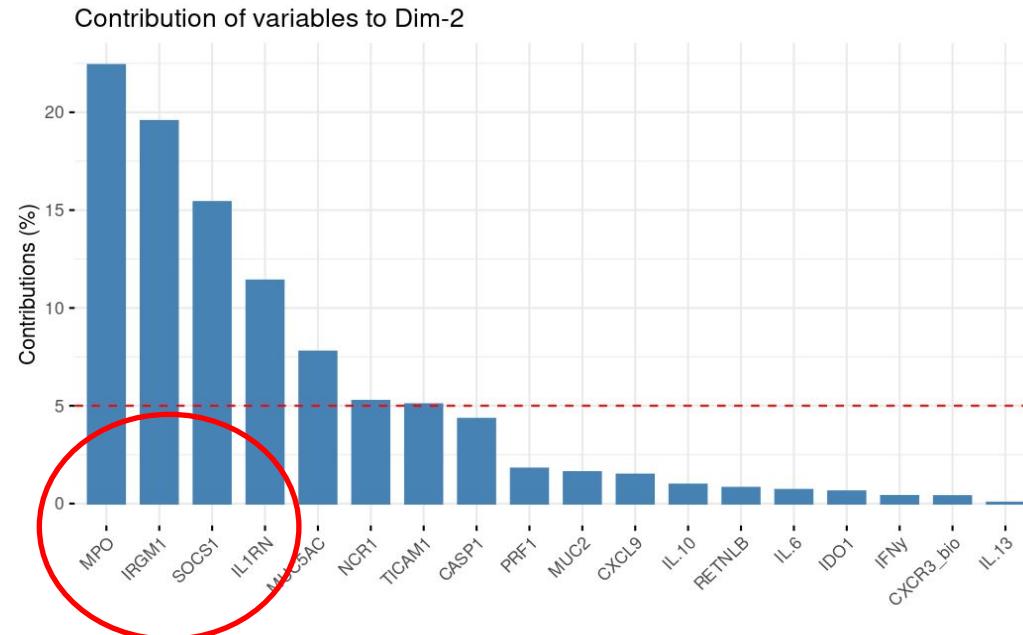
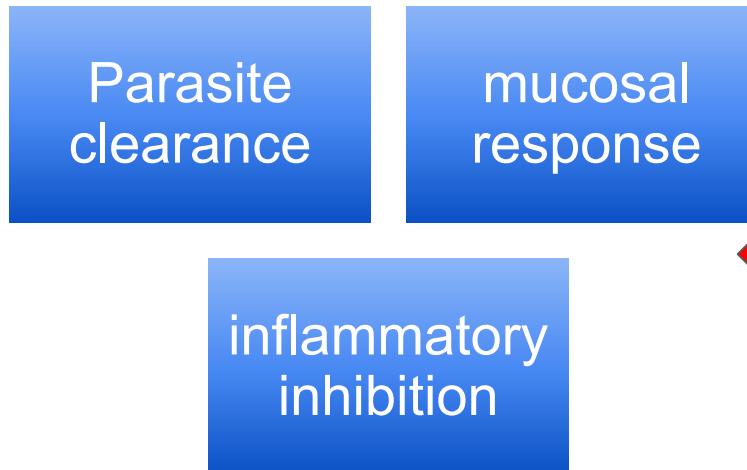
- Jaroslav Piálek
- Miloš Macholán
- Joëlle Goüy De Bellocq
- L'udovít Ďureje
- Iva Martincová

Which principle component better predicts weight loss?

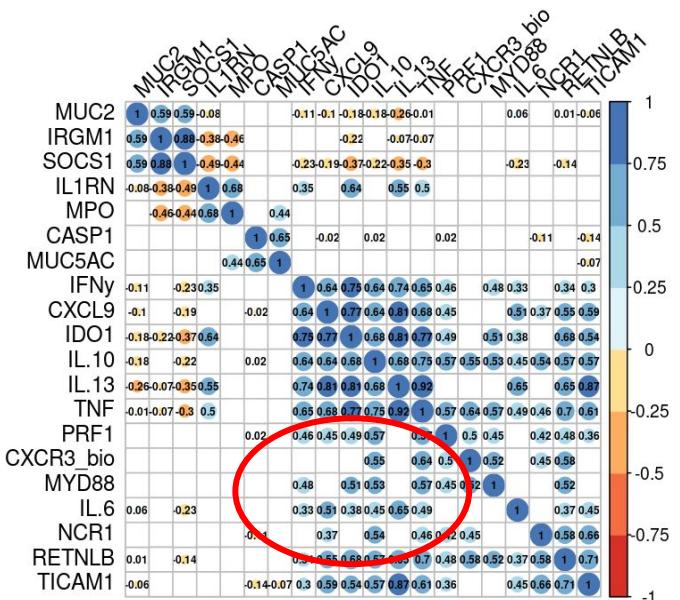
```
## Call:  
## lm(formula = max_WL ~ pc1 + pc2, data = imputed_expr)  
##  
## Residuals:  
##      Min        1Q    Median        3Q       Max  
## -16.913   -3.236    1.379    5.127   10.471  
##  
## Coefficients:  
##             Estimate Std. Error t value Pr(>|t|)  
## (Intercept) 92.3746     0.6006 153.811 <2e-16 ***  
## pc1         0.1702     0.2061   0.826  0.4107  
## pc2        -0.7501     0.3448  -2.175  0.0317 *  
## ---
```



Which principle component better predicts weight loss?



Inflammation, anti-fungal and microbial defense



PRF1

CXCR3

MYD88

IL.6

Field data

Accuracy : 0.5102

95% CI : (0.3634, 0.6558)

No Information Rate : 0.6327

P-Value [Acc > NIR] : 0.9713

Kappa : 0.1191

McNemar's Test P-Value : 0.6422

Statistics by Class:

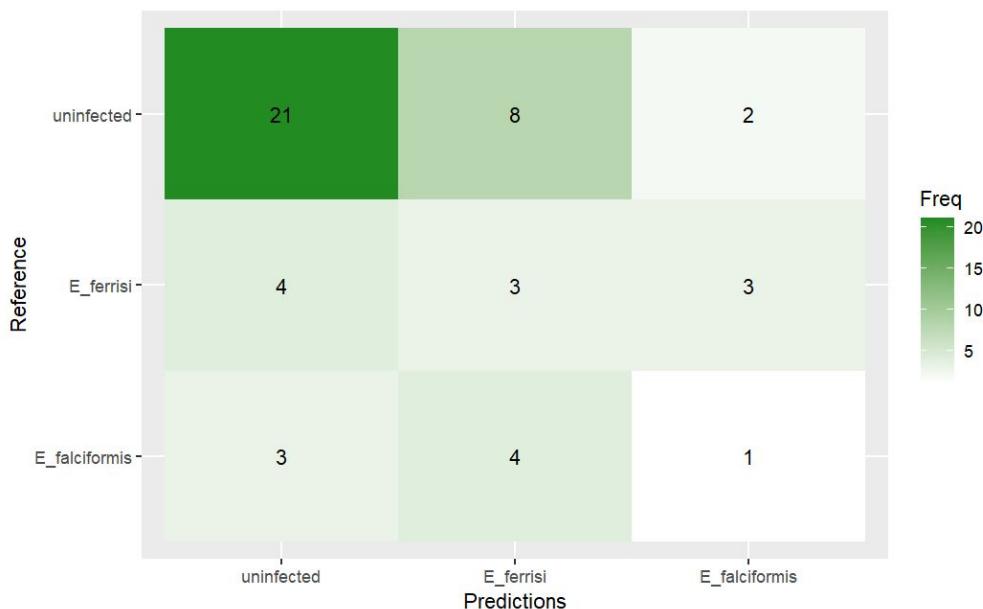
Class: E_falciformis Class: E_ferrisi Class: uninfected

Balanced Accuracy

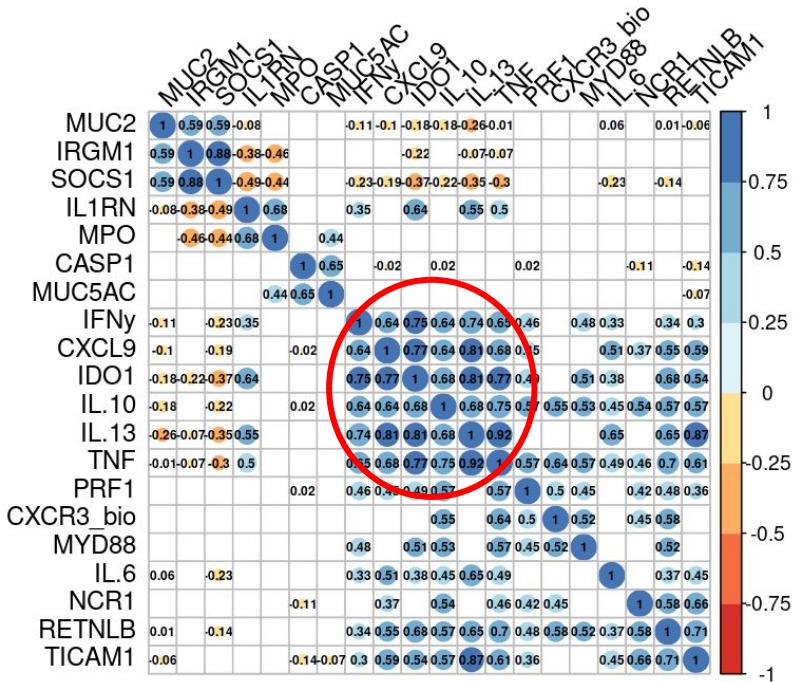
0.50152

0.49615

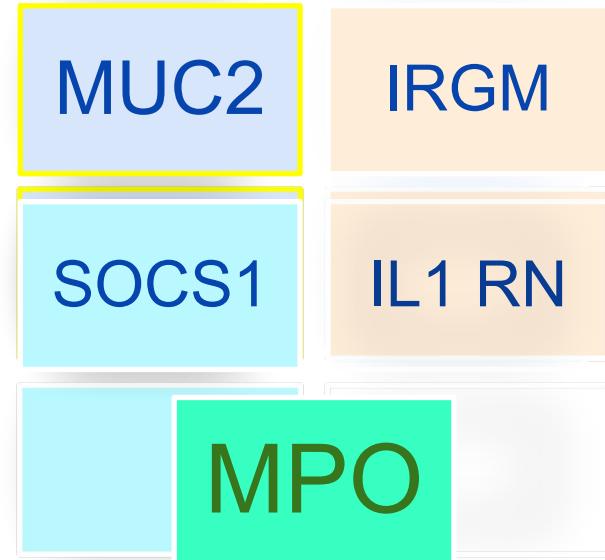
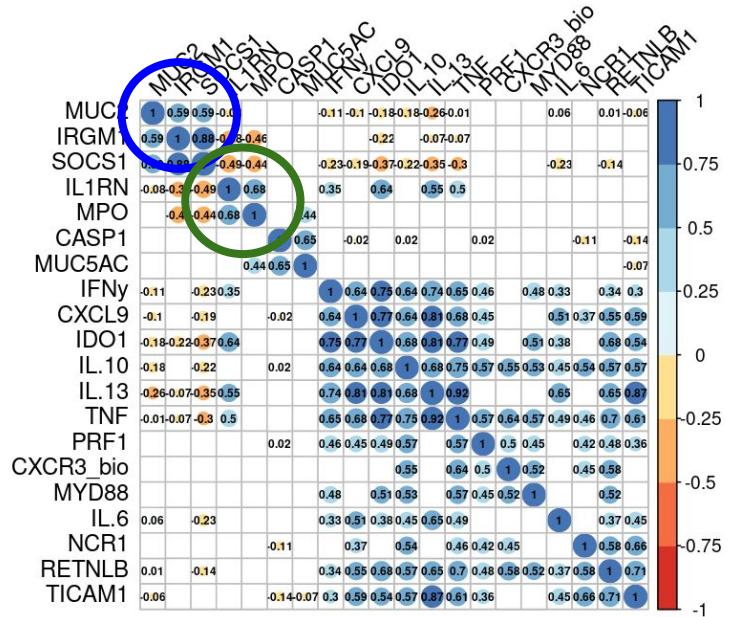
0.6443



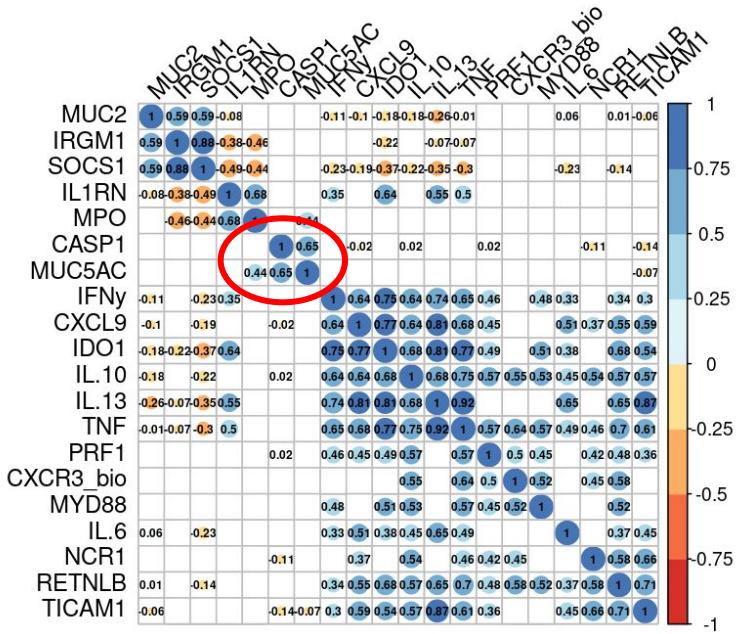
Pro-inflammatory response → parasite clearance, mucus production



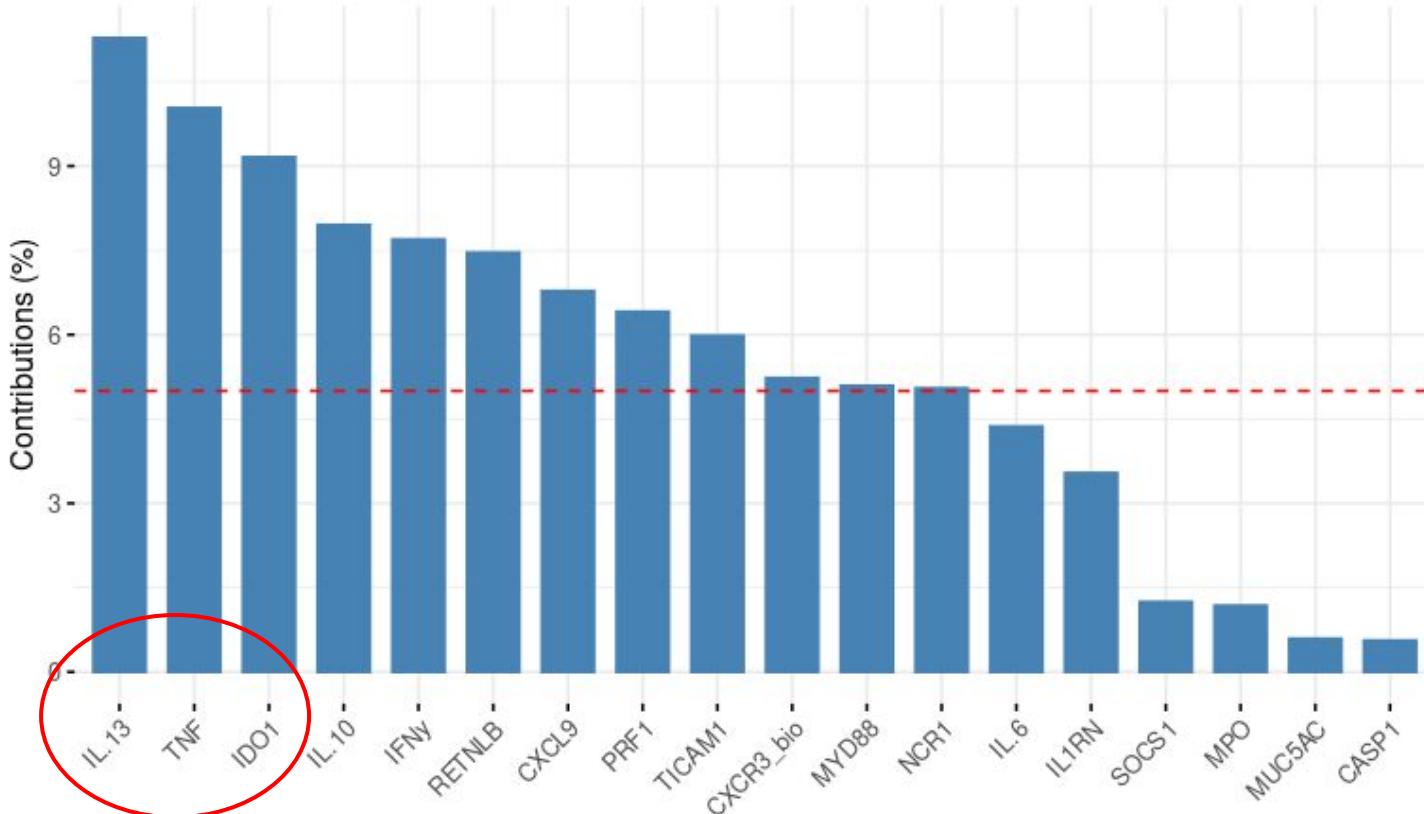
Mucosal immune response + inflammatory inhibition:



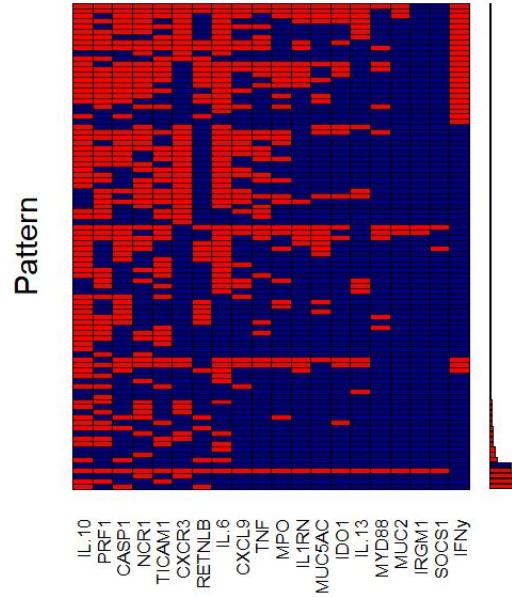
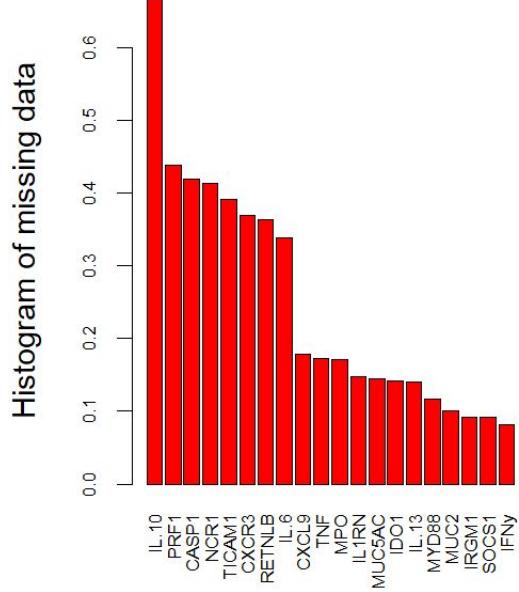
Parasite clearance, Mucus production



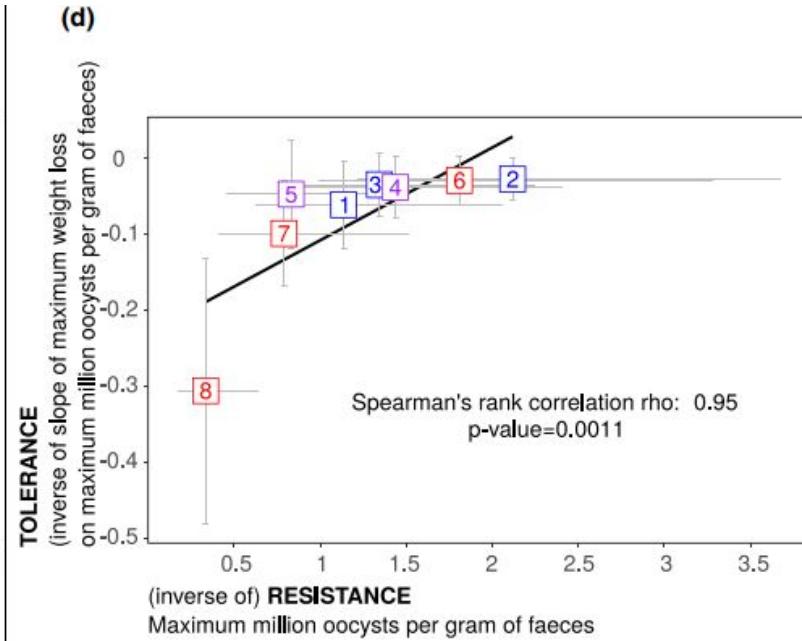
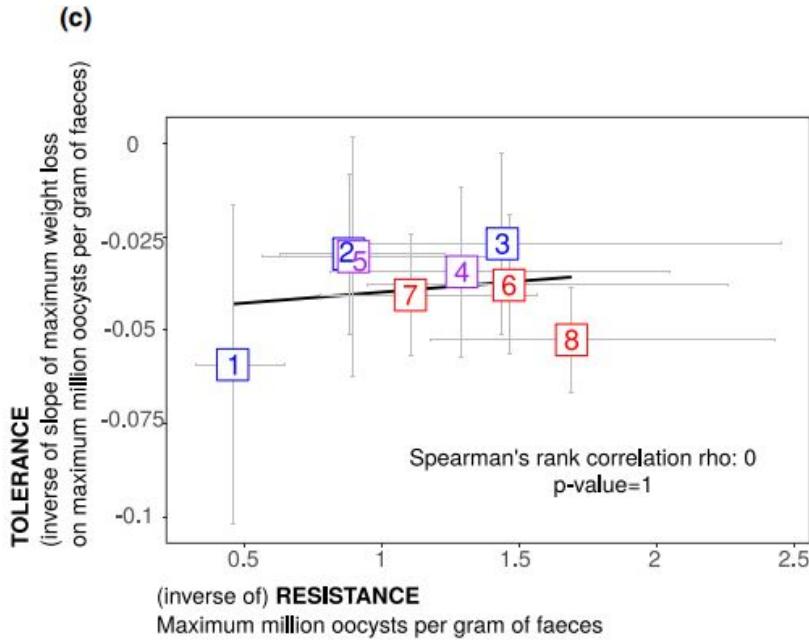
Contribution of variables to Dim-1



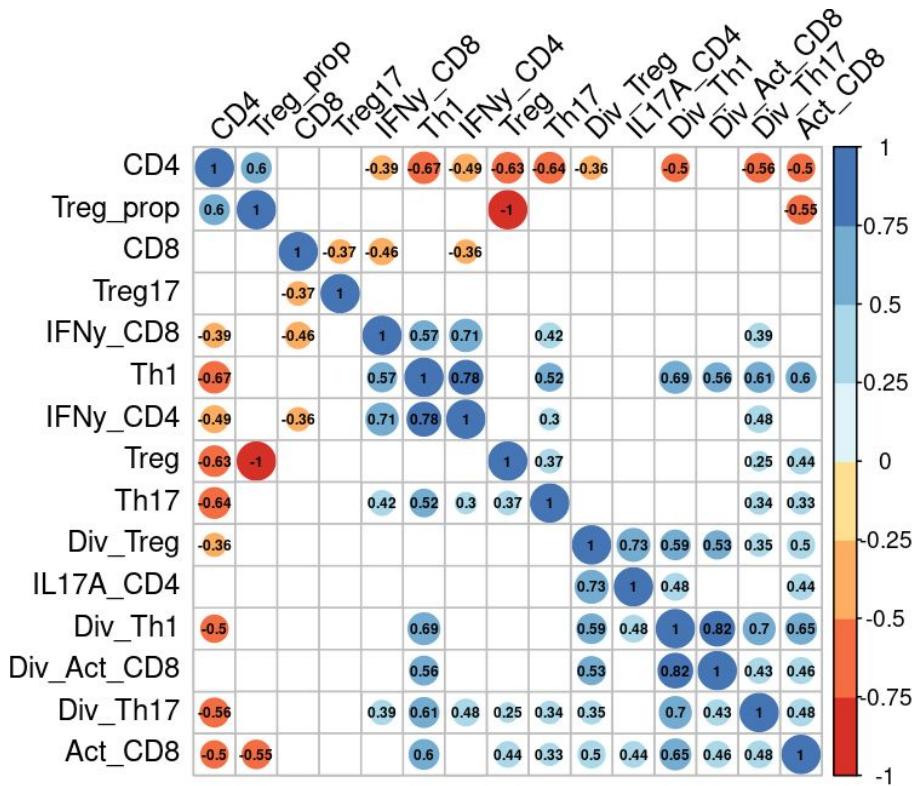
Imputation mice

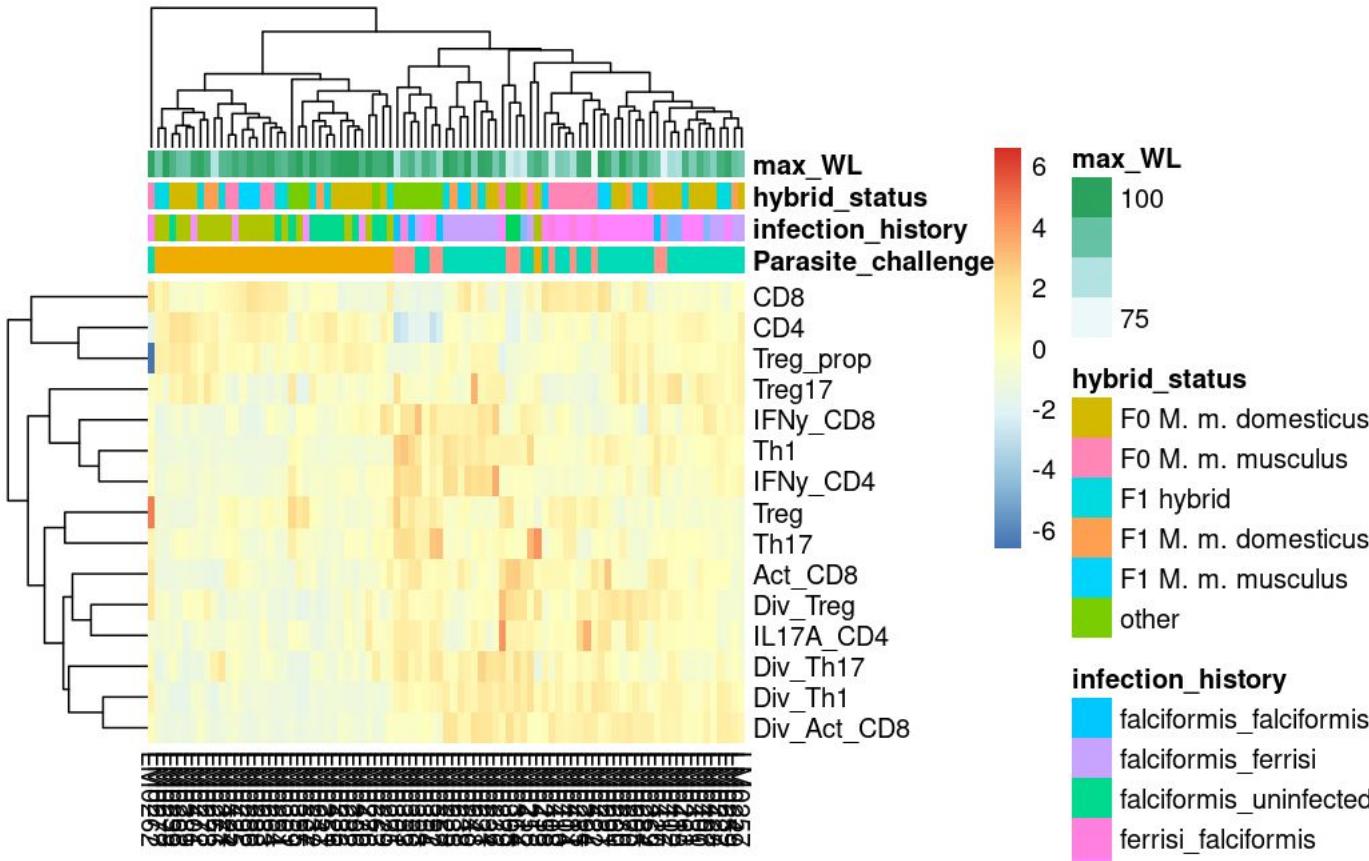


E. ferrisi and *E. falciformis*: How does resistance and tolerance correlate in each species?

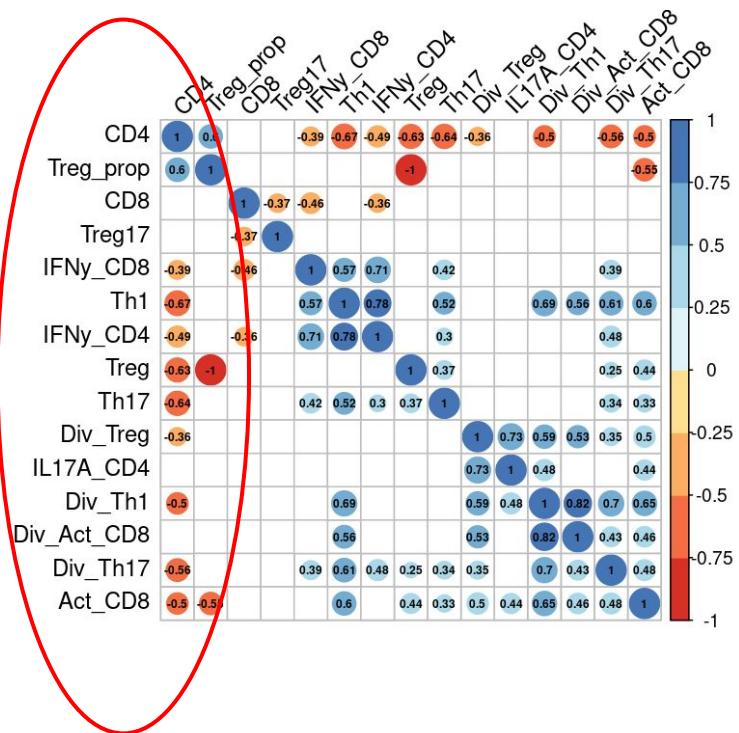


FACS



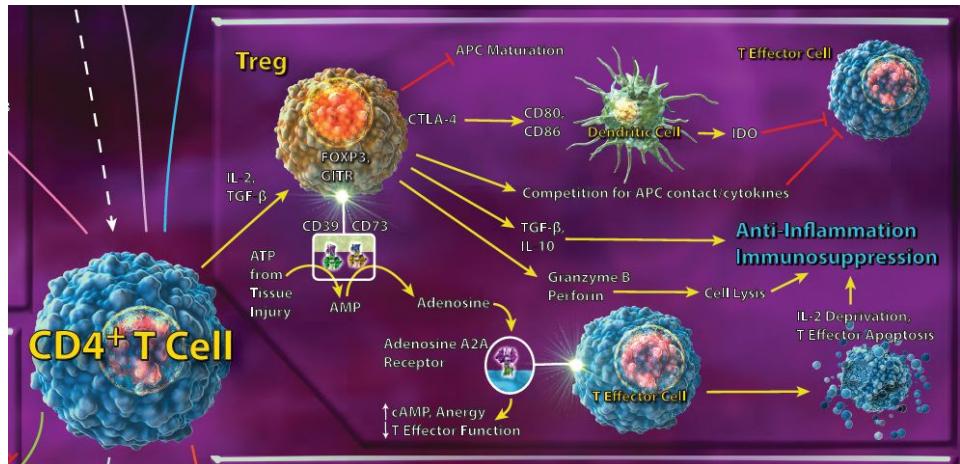


CD4

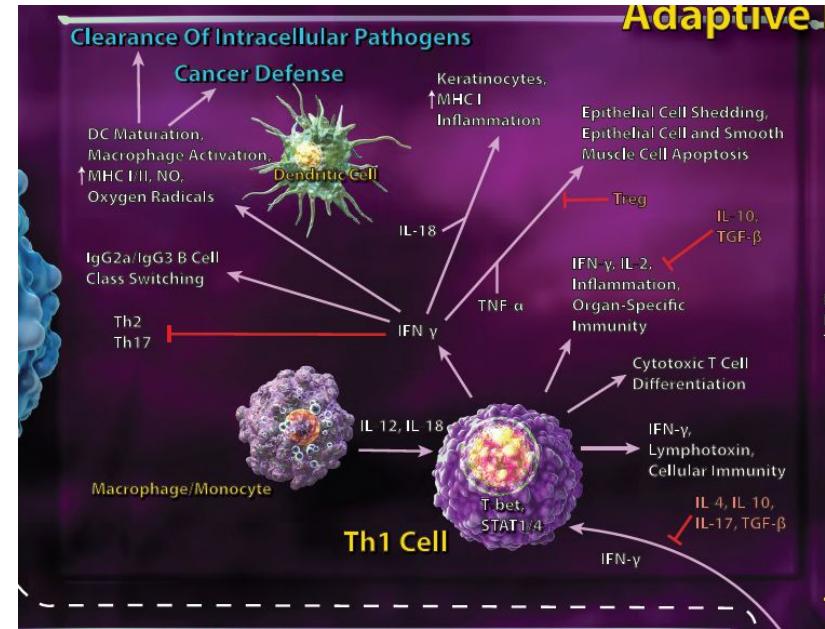
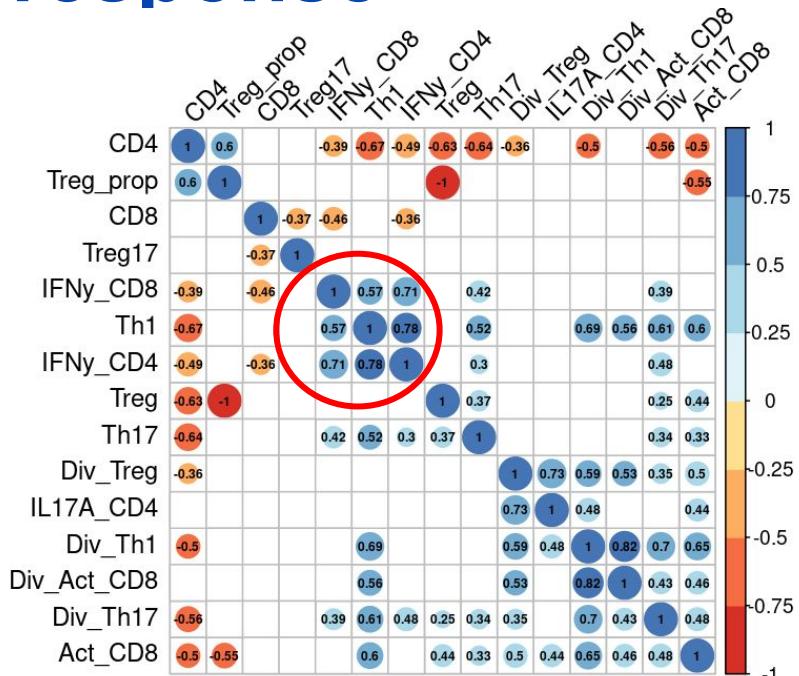


CD4+T:

- activation of the cells of the innate immune system
- critical role in the suppression of immune reaction

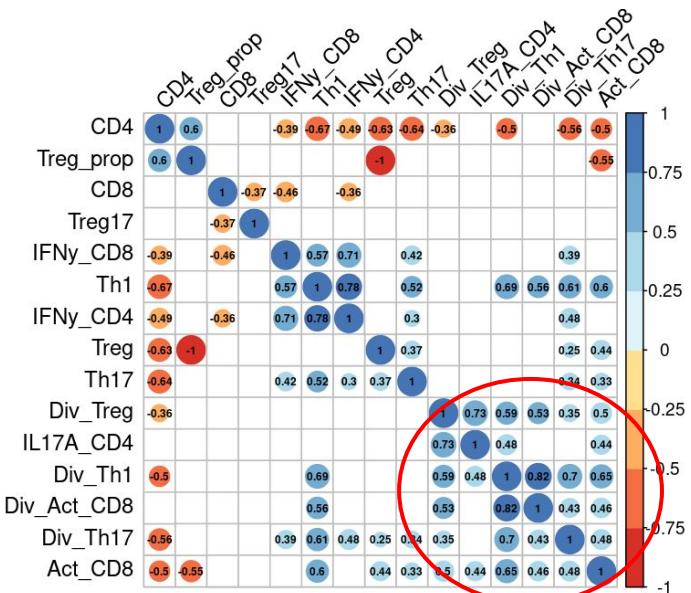


Pro-inflammatory response

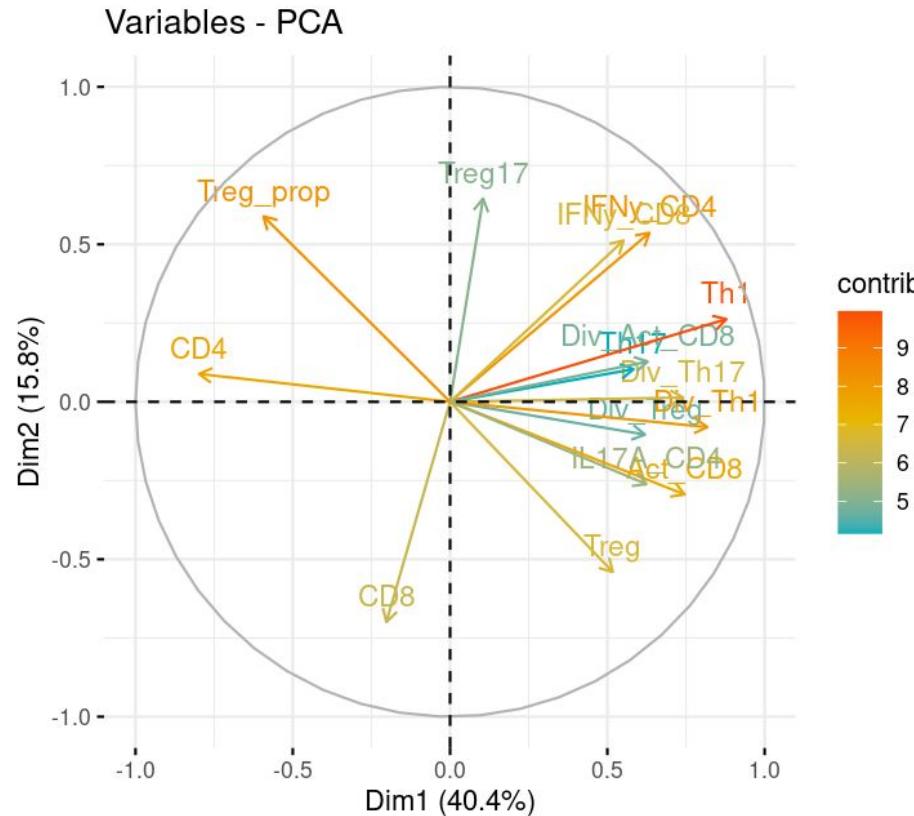


- **IFNy_CD8: pro - inflammatory IFNy**
- **IFNy_CD4: pro - inflammatory IFNy**
- **Th1: increased cell-mediated response**

Dividing cells



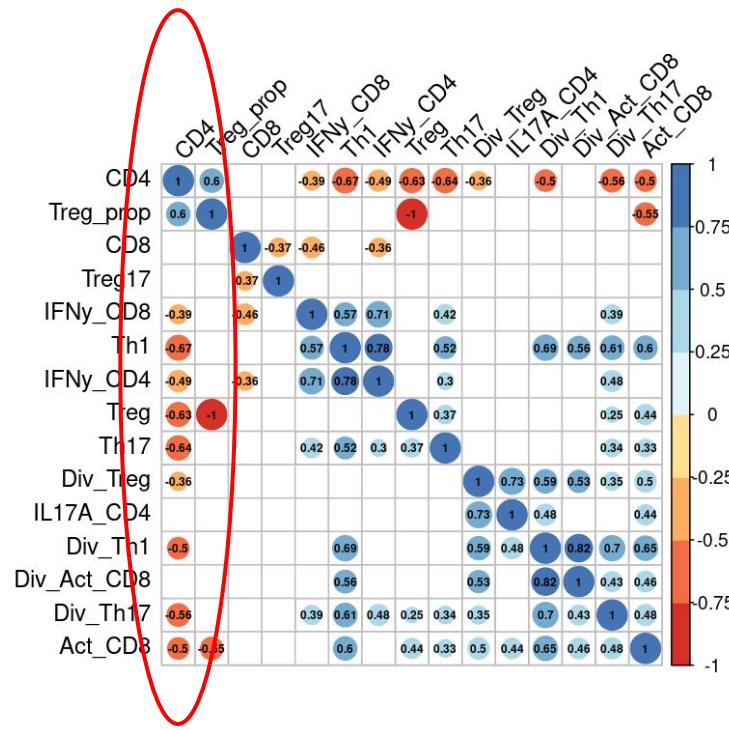
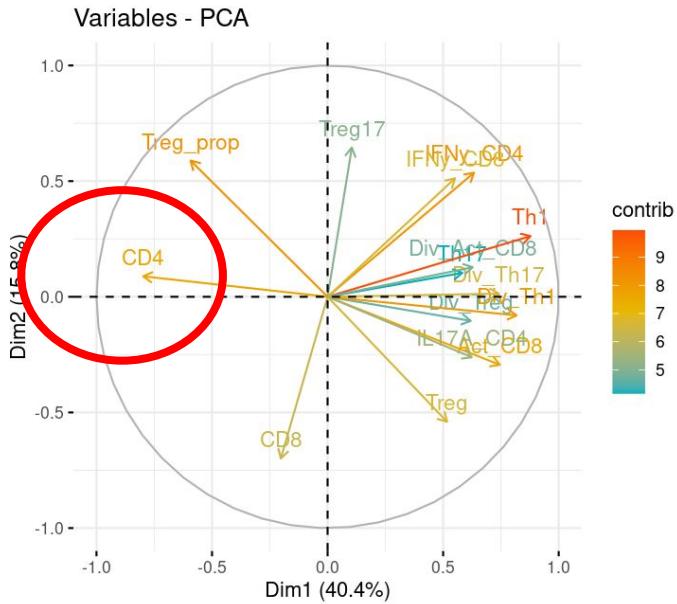
PCA of FACS data



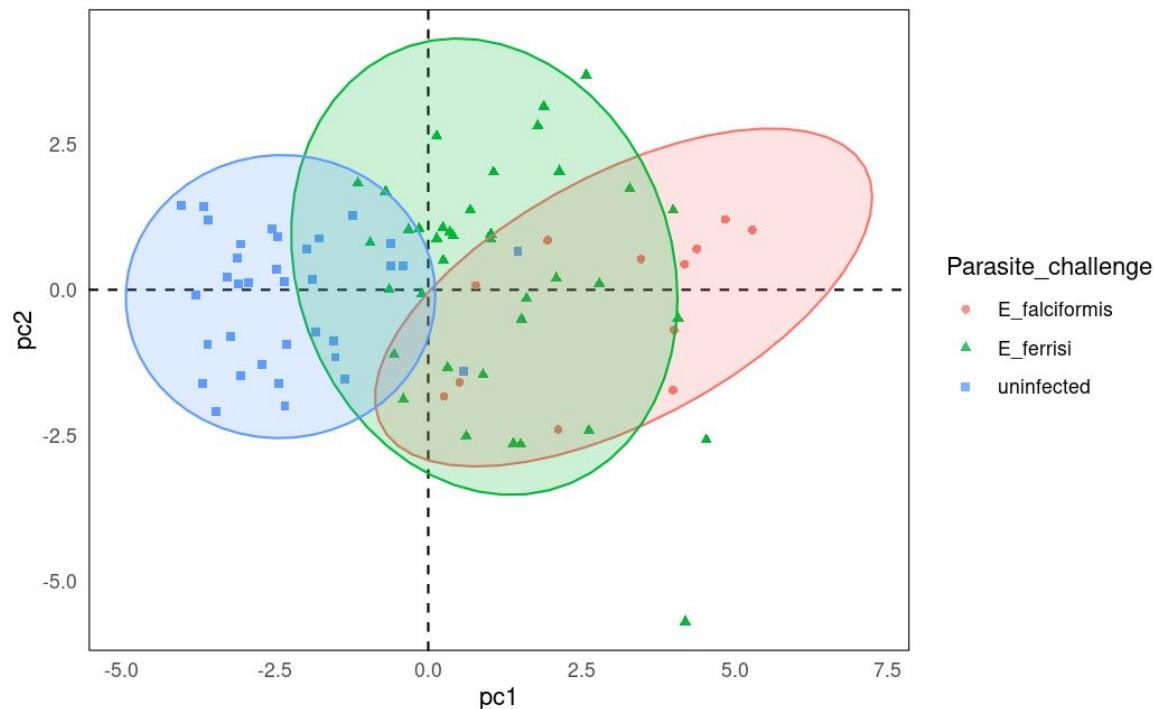
CD4

CD4+T:

- activation of the cells of the innate immune system
- critical role in the suppression of immune reaction

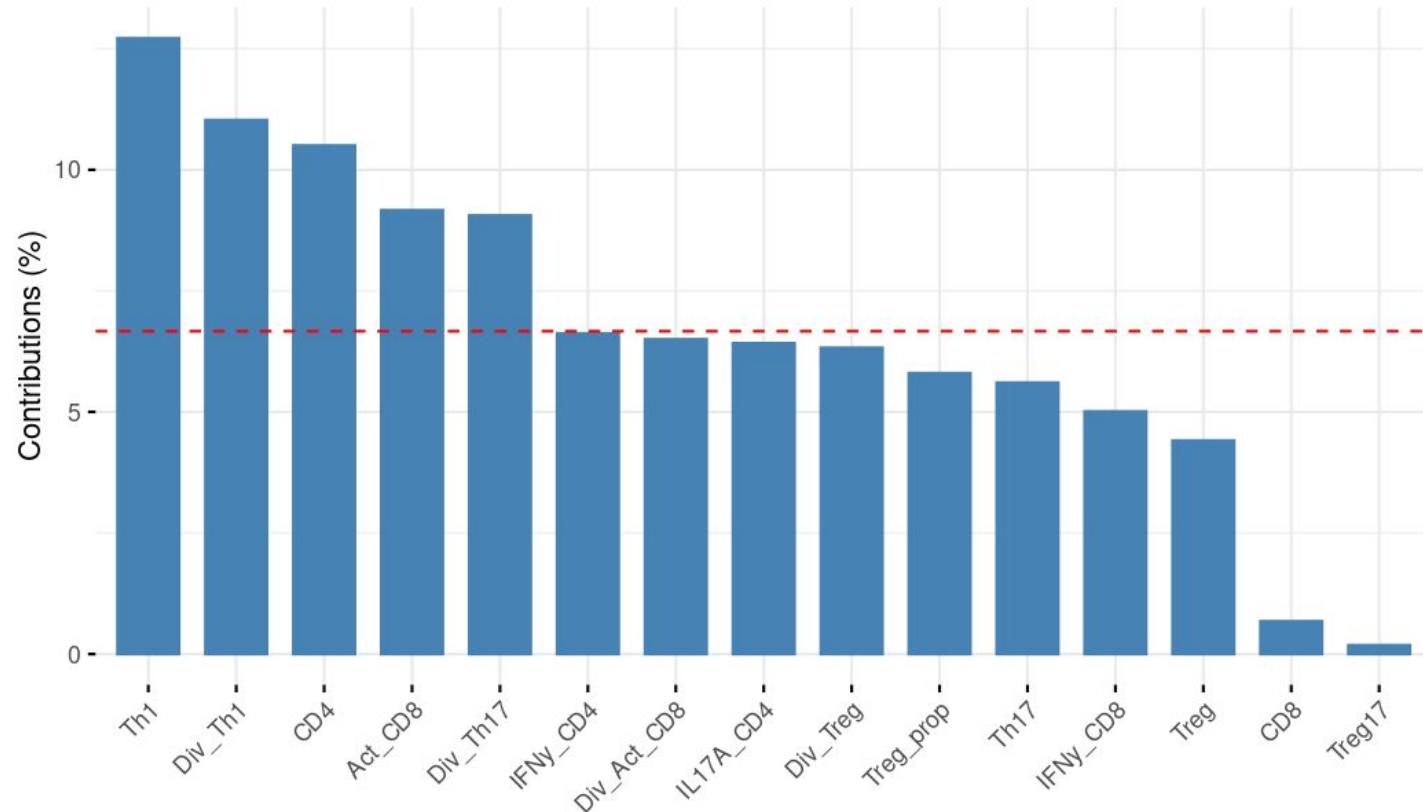


FACS



FACS

Contribution of variables to Dim-1



PCA of immune gene expression

