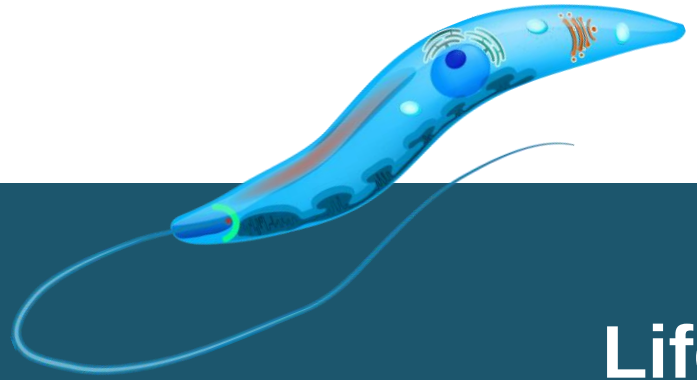
ERC-SyG-2022 - n° 101071613



DECOLeishRN

Life without transcriptional control in *Leishmania:* Genome instability and post-transcriptional regulation to the rescue

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Bar-Ilan University

Yitzhak Pilpel
Weizmann Institute of Science

Gerald Spaeth
Institut Pasteur

How it all started ?

In a meeting of our field a Gerald approached me with A question…why I see in my adpated parasites so many snoRNA genes?

We obtained funding

Israel Ministry of Science & Technology

The preliminary data suggested a new concpet Adaptation of paraistes to growth under different cues is regulated

ERC syng was submitted on Fall 2019
Gerald Spaeth (Pasteur Institute, Shualmit Michaeli (BIU)

We passed two stages…and all summer prepared for the Interview (zoom)

We selected excellent team at ISERD
Their questions were used ny us to correct the 2022 Submission

The Interview went well but at the end I knew will not get it..
The chair told us right away…it is a great idea but was not yet
Peer reviewed…(we did not publish!!)

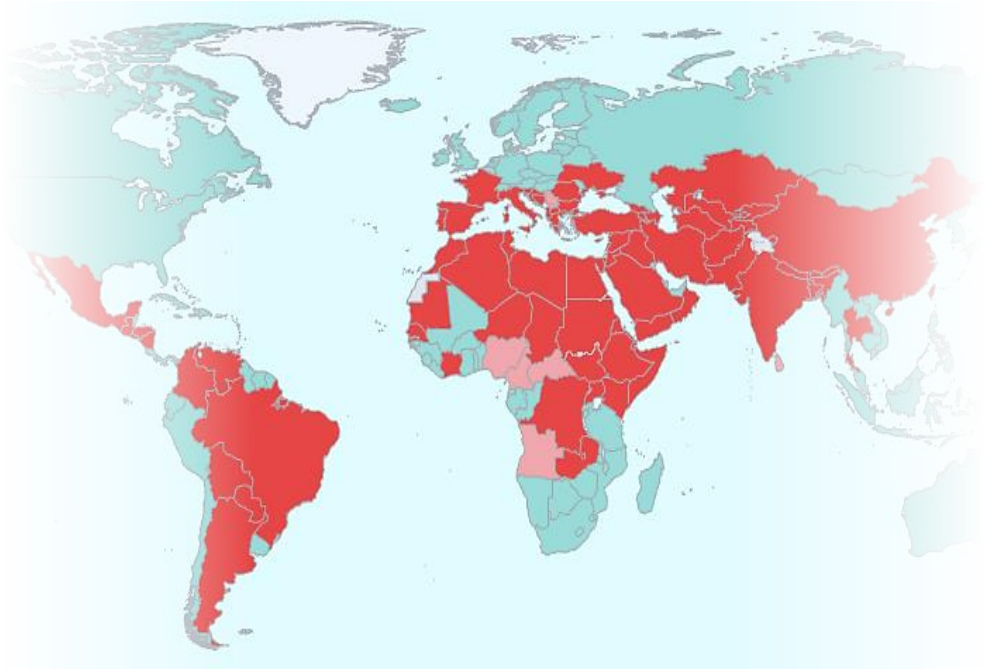
Add Yizhak Pilpel from the WIS to the team (was our exmaminer in 2019 by ISERD)
Remove the Aim 3
Publish two collaborative papers (PNAS 2021, PLoS pathognes, 2022)
Michaeli with PilPel (JBC 2022)

We re-wrote the grant with two big aims sharing the efforts
We prepared for the interview all summer!!

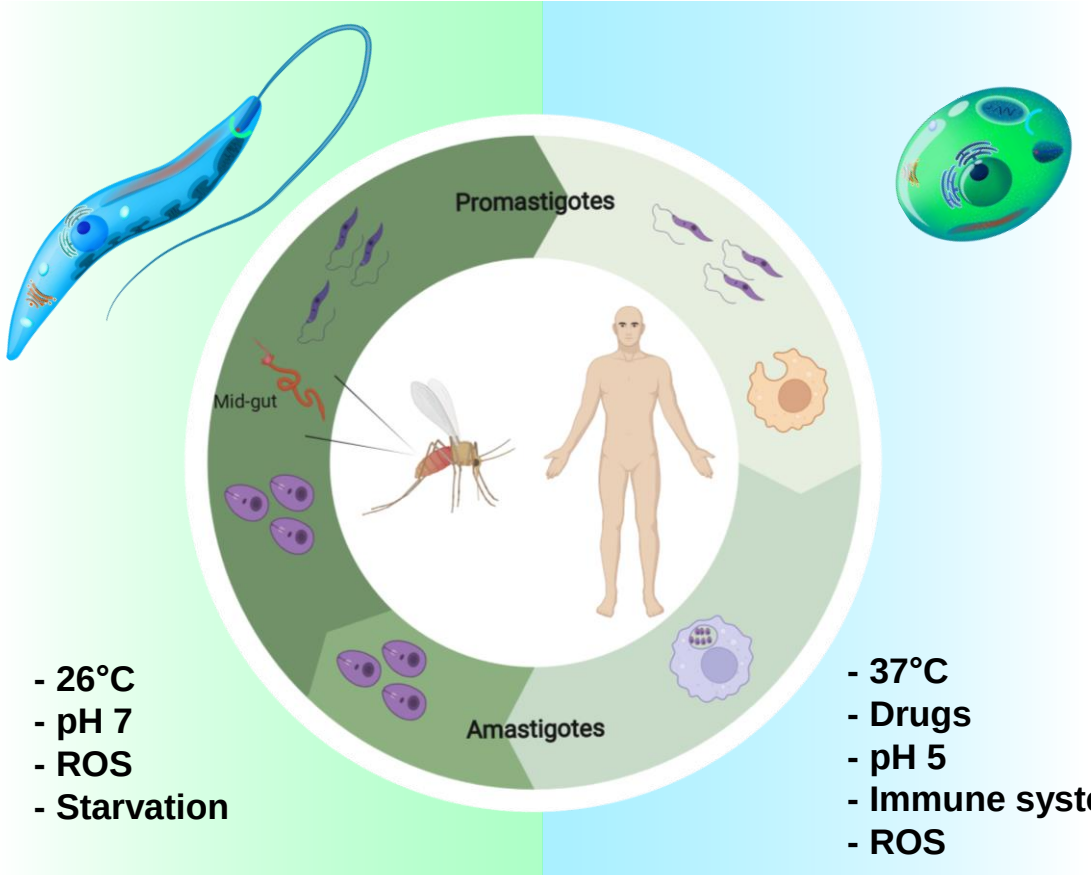
The protozoan parasite *Leishmania*

An important human pathogen

- 12M people infected
- 1 billion at risk
- Emerging in the EU

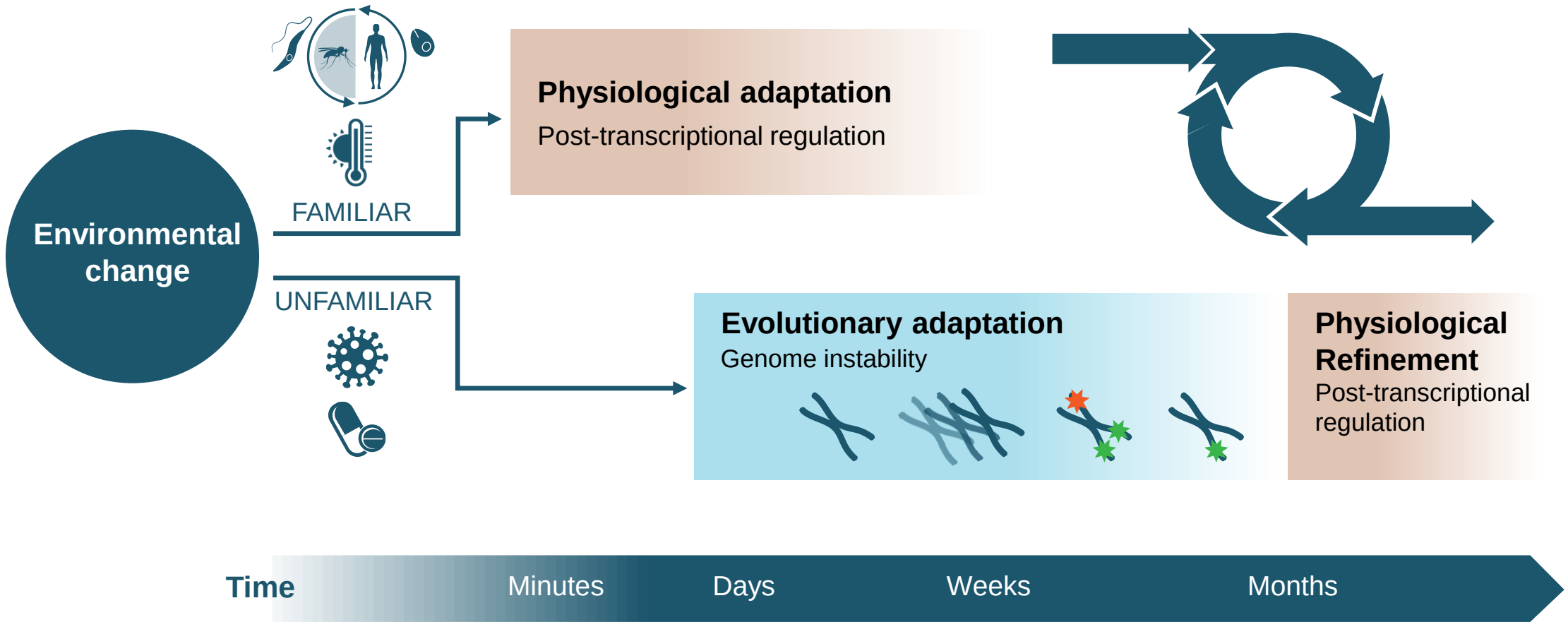


A life cycle that involves adaptation to two hosts



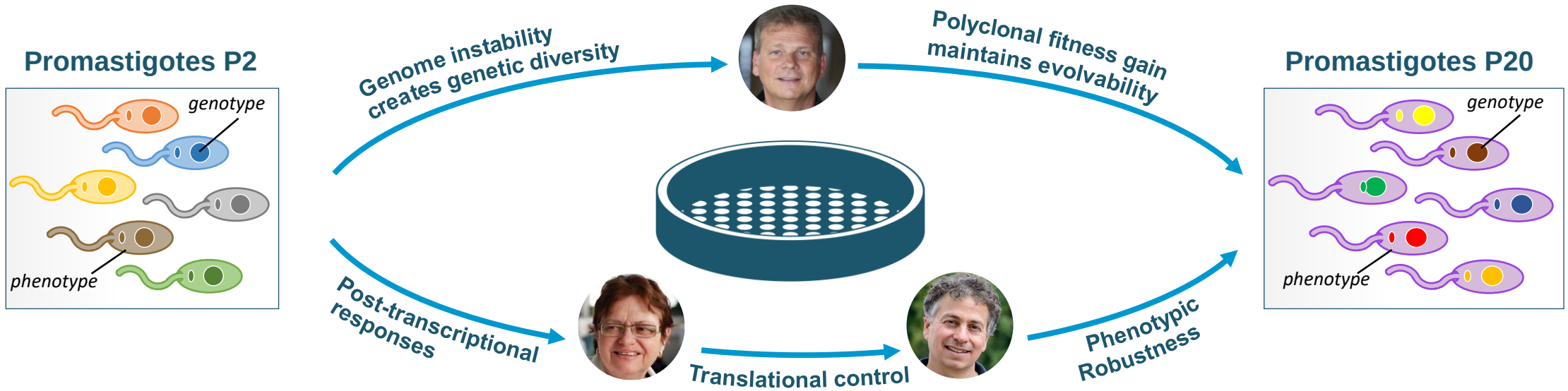
Life without transcriptional regulation

Innovation: intertwined physiological and evolutionary adaptation



Pilpel PNAS 2012 | *Pilpel Cell 2015* | *Michaeli Späth PNAS 2021* | *Michaeli Späth PLoS Path 2022*

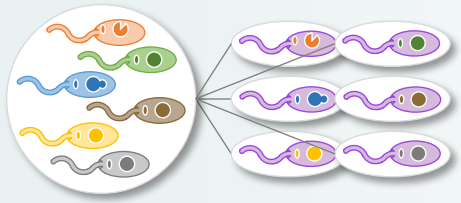
Pioneering experimental evolution (EE) in *Leishmania*



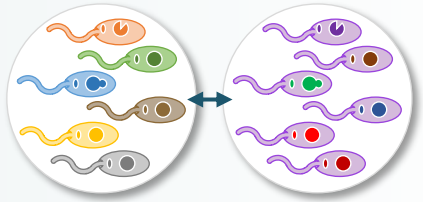
Pilpel PNAS 2012 | *Pilpel Cell 2015* | *Michaeli Späth PNAS 2021* | *Michaeli Späth PLoS Path 2022*

Revealing epistatic genome/RNome interactions driving *Leishmania* fitness

EE in hamsters/in culture



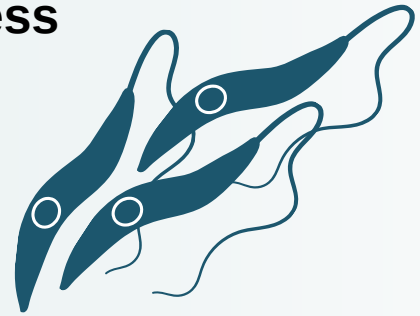
Within-population adaptation



In-between population adaptation

EE under stress

- Heat
- Starvation
- pH
- Drug



Sequencing libraries

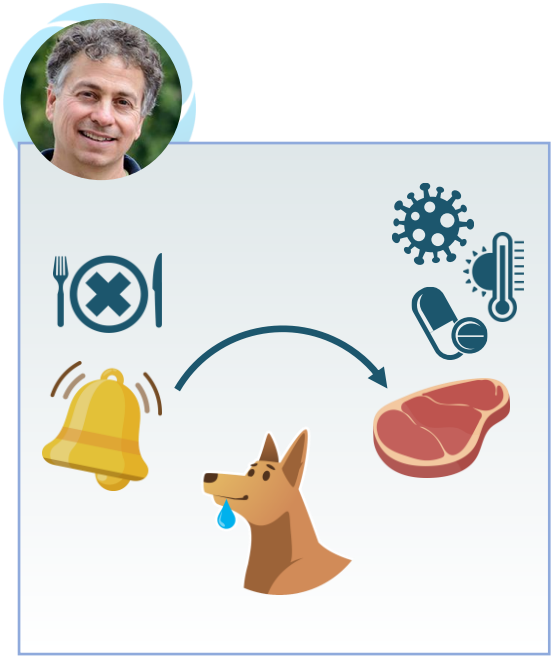
Iterations: evolution data analysis LOF/GOF

Candidate genes

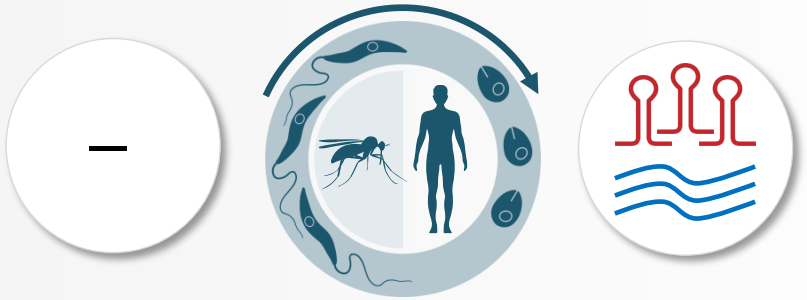
- Data analysis
- Network modelling
- Discovery of evolvability genes

Pavlovian adaptation:

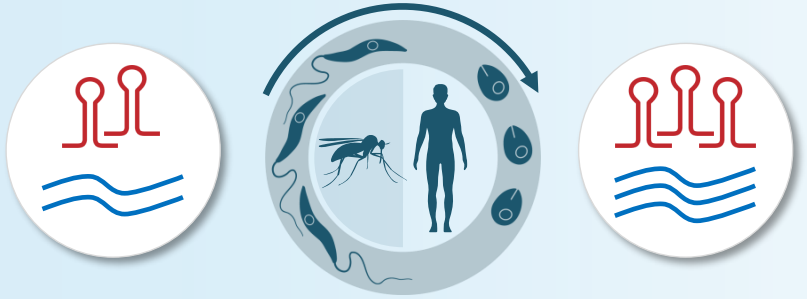
Can *Leishmania* predict and prepare in advance to the next condition?

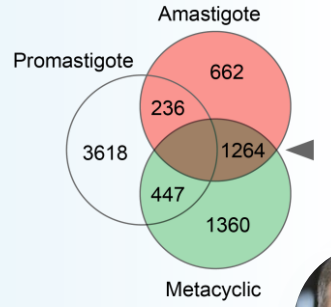


Direct regulation



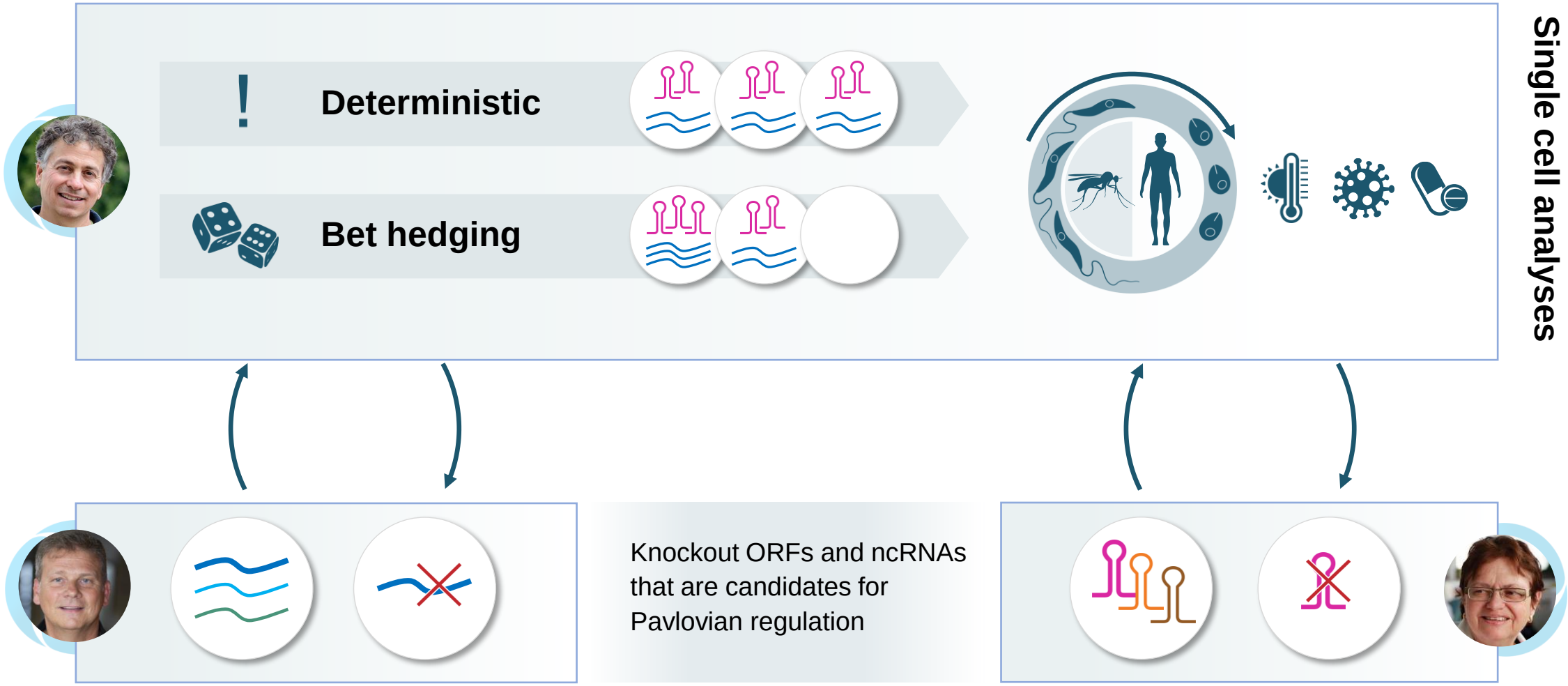
Predictive regulation



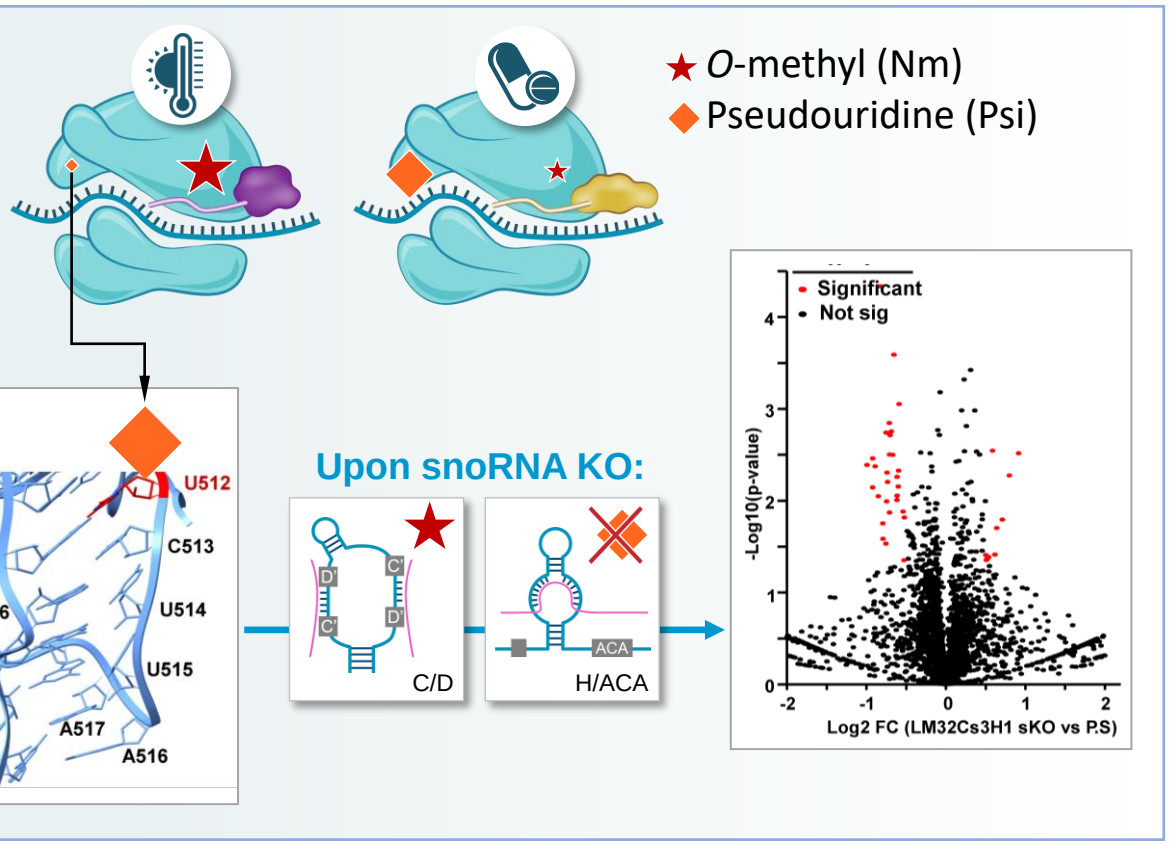


Pilpel Nature 2009 | Pilpel PNAS 2011 | Späth Michaeli Pilpel in preparation

How can Pavlovian predictive regulation work?

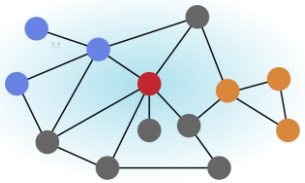


Functional genetic analyses of ncRNA and ribosome composition regulating translation



Examine specific KO and their specific role upon infection of the host

Post-transcriptional regulatory networks under stress

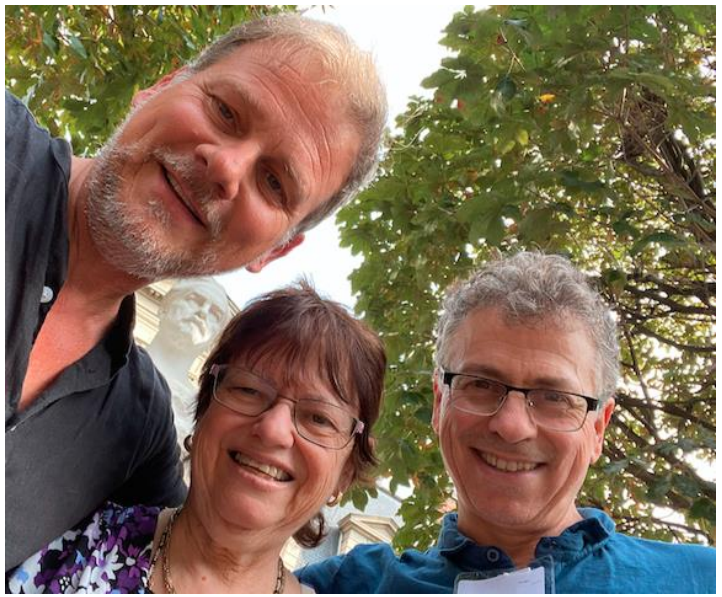


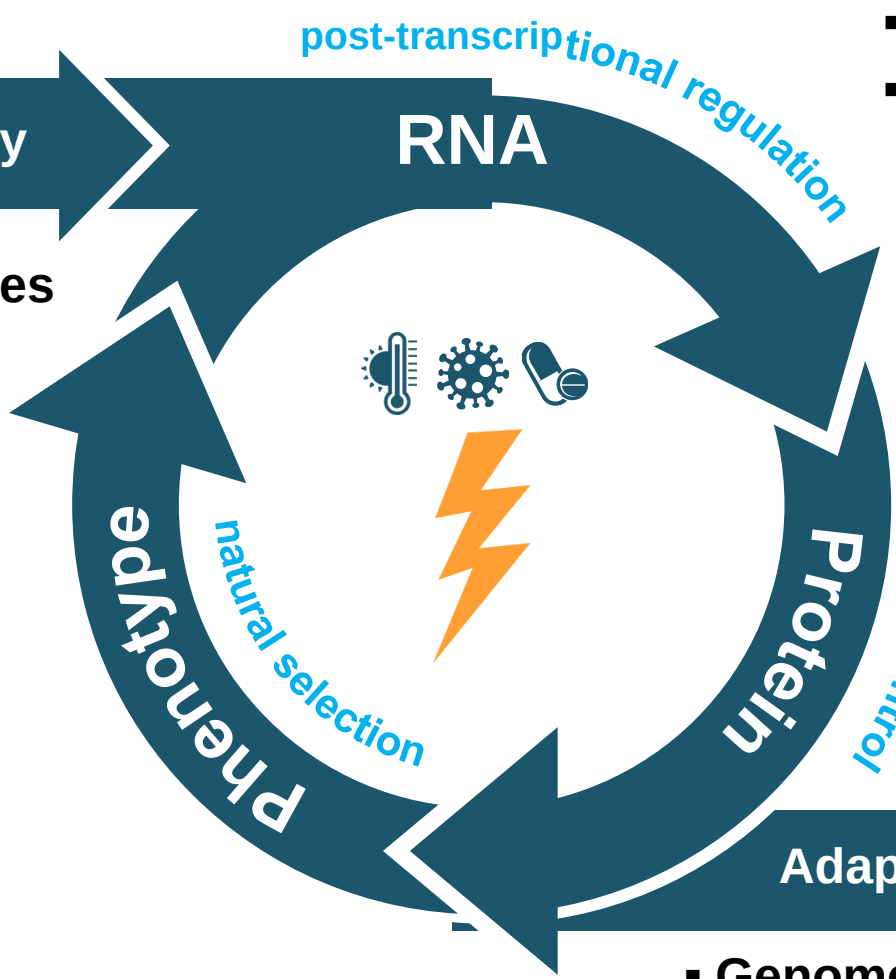
Michaeli, iScience 2020 | Michaeli & Figueiredo Science Adv 2022 | Späth & Michaeli, in preparation

Leishmania fitness gain is an emerging property

Genome instability

- Experimental evolution in parasites
- Infection model





- Non-coding RNA in parasites
- Ribosomal biogenesis

Adaptive networks

- Genome evolution
- Systems and computational biology

IMPACT

Pathogen evolution within a mammalian host

Genomic adaptation and phenotypic refinement

Stress-adapted ribosomes

The filter of genome instability
Combat parasitic pathogens