



Fleming Prize Lecture Edze Westra

#whymicrobiologistsmatter





Evolution and Ecology of CRISPR-Cas

Edze Westra University of Exeter



CRISPR: A microbial adaptive immune system



Acquisition

Interference

CRISPR: A microbial adaptive immune system







E. coli BL21 overexpressing CRISPR-Cas

Infected with phage Lambda



Brouns et al Science 2008

The P. aeruginosa PA14 and phage DMS3 experimental system

DMS3 (Siphoviridae) temperate phage 36 kb genome (52 genes)





Zegans et al. JBac 2009

The P. aeruginosa PA14 and phage DMS3 experimental system

DMS3<u>vir</u> (Siphoviridae) temperate phage 36 kb genome (52 genes)





The P. aeruginosa PA14 and phage DMS3 experimental system

DMS3<u>vir</u> (Siphoviridae) temperate phage 36 kb genome (52 genes)





Zegans et al. JBac 2009

Part I – When do bacteria evolve CRISPR immunity ?







Theoretical model to explain observed effect of resource levels









A. Best





Force of infection drives differences in CRISPR vs sm evolution



Westra et al. Curr Biol 2015



Westra et al. Curr Biol 2015



Induced and constitutive fitness costs of SM & CRISPR



Westra et al. Curr Biol 2015



Part I – When do bacteria evolve CRISPR immunity ?



The effects of microbial community diversity



Alseth et al. Nature 2019

The effects of microbial community diversity



Alseth et al. Nature 2019

The effects of phage population diversity





Broniewski et al. ISME J 2019

The effects of phage population diversity







Semenova et al. PNAS 2011

The effects of phage population diversity





Broniewski et al. ISME J 2019

Part II – What are the coevolutionary consequences of CRISPR immunity ?



CRISPR drives phage extinct



CRISPR generates population-level diversity



Iranzo et al, J. Bacteriol. 2013; Childs et al PLoS One 2015

Why would diversity matter?

1. Evolutionary effect:



Why would diversity matter?



Experimental Test



- 1. Phage abundance
- 2. Relative Fitness
- 3. Phage evolution

Phage extinction increases with CRISPR allele diversity



Phage extinction increases with CRISPR allele diversity



Van Houte et al. Nature 2016




Van Houte et al. Nature 2016



Phage is unable to overcome diverse CRISPR alleles

targeted phage escape phage



Phage is unable to overcome diverse CRISPR alleles



targeted phage escape phage Part III – Phages use "anti-CRISPR" genes to overcome CRISPR immunity



Acr-phage shows partial infectivity on CRISPR-resistant host



Acr-phage shows partial infectivity on CRISPR-resistant host





Acr-phage initial density tips balance from extinction to epidemic



Acr-phage initial density tips balance from extinction to epidemic





Sylvain Gandon











Variation between Acrs in partial infectivity



Tipping point shifts when Acr is weaker





Partial infectivity decreases as host resistance increases



Tipping point shifts with host resistance levels



Multiplicity of infection (MOI)

Landsberger et al, Cell 2018



Experimental test for lasting immunosuppression



Relative transformation efficiency RTE = # pT transformants /# pNT transformants

Infection with Acr-phage leaves behind immunosuppressed host

Infection with Acr-phage leaves behind immunosuppressed host

Sequential infections allow Acr-phages to overcome CRISPR immunity

Part IV – Why do more than half of sequenced genomes lack CRISPR-Cas?

Rollie & Chevallereau et al. Nature 2020

Life cycle temperate phage

Life cycle temperate phage

50:50

WT / ∆cas7 + DMS3vir 1:100 1:100

Evolutionary and population dynamics of CRISPR-DMS3 interaction

Rollie & Chevallereau et al. Nature 2020

Genomes lysogens: Loss of CRISPR-Cas

Summary

1. Range of ecological factors (phage density, diversity, community context) impact the evolution of CRISPR immunity

2. CRISPR immunity alleles easy to overcome individually, but strong population-level immunity when mixed

3. Anti-CRISPR phages need to cooperate in order to overcome CRISPR immunity

4. CRISPR provides advantage when phage transmits horizontally, but costly when they transmit vertically



Special thanks



