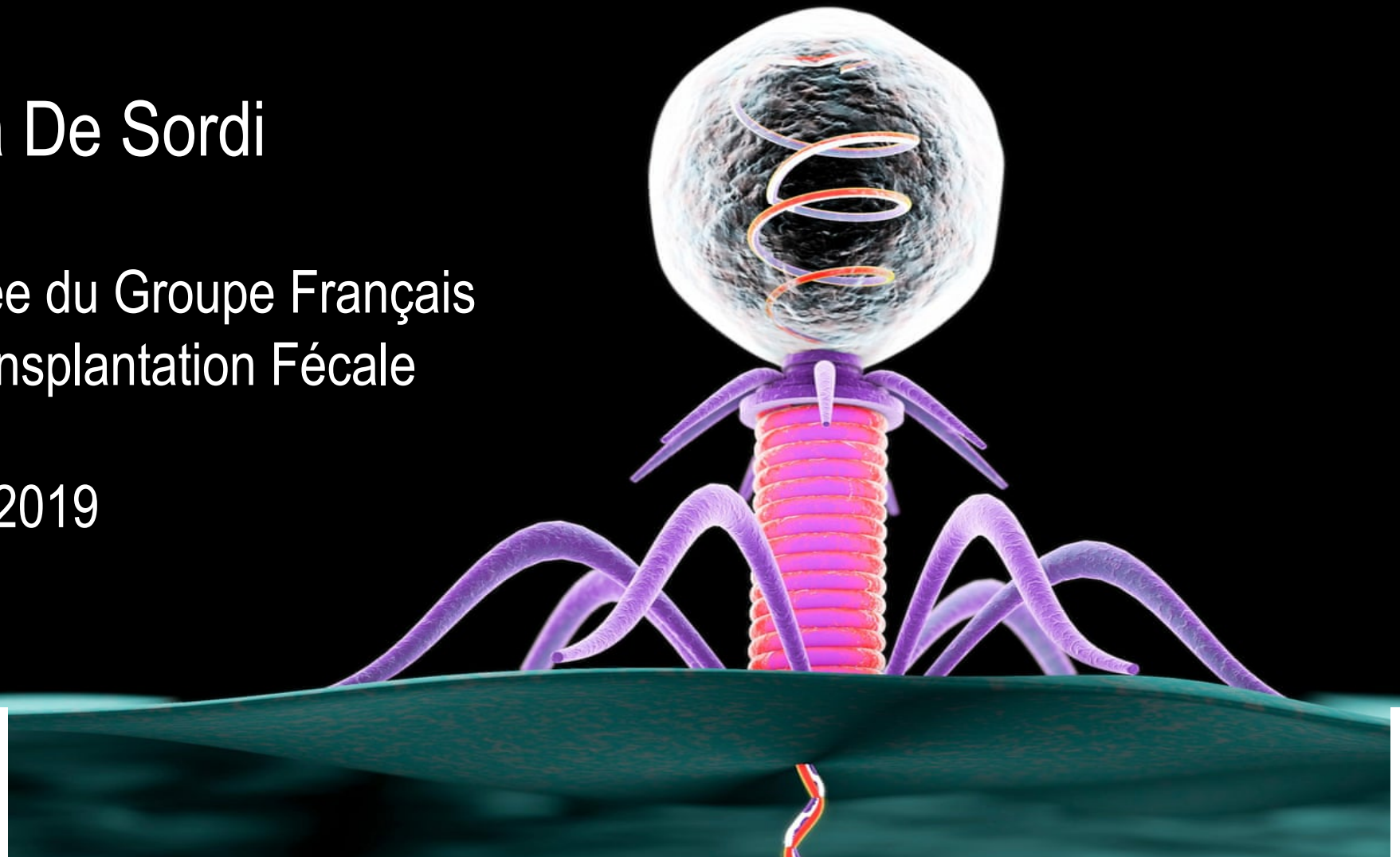
Mieux connaître les acteurs du microbiote:
RÔLE DES BACTÉRIOPHAGES

Luisa De Sordi

Journée du Groupe Français
de Transplantation Fécale

28/06/2019



SORBONNE UNIVERSITÉ

crsa

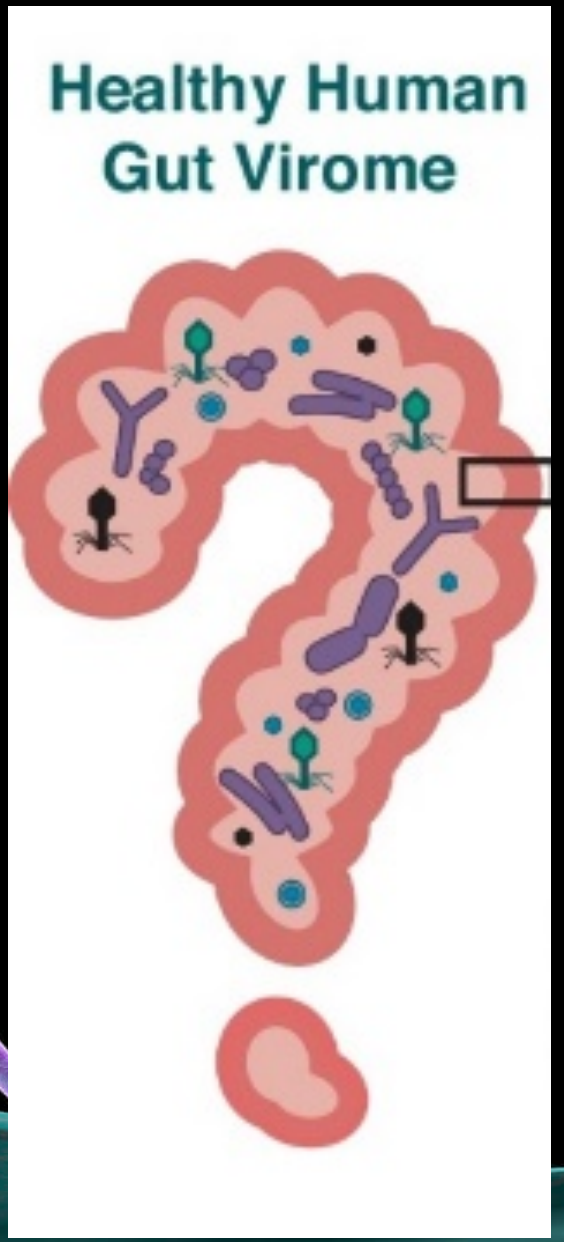
Mieux connaître les acteurs du microbiote: RÔLE DES BACTÉRIOPHAGES

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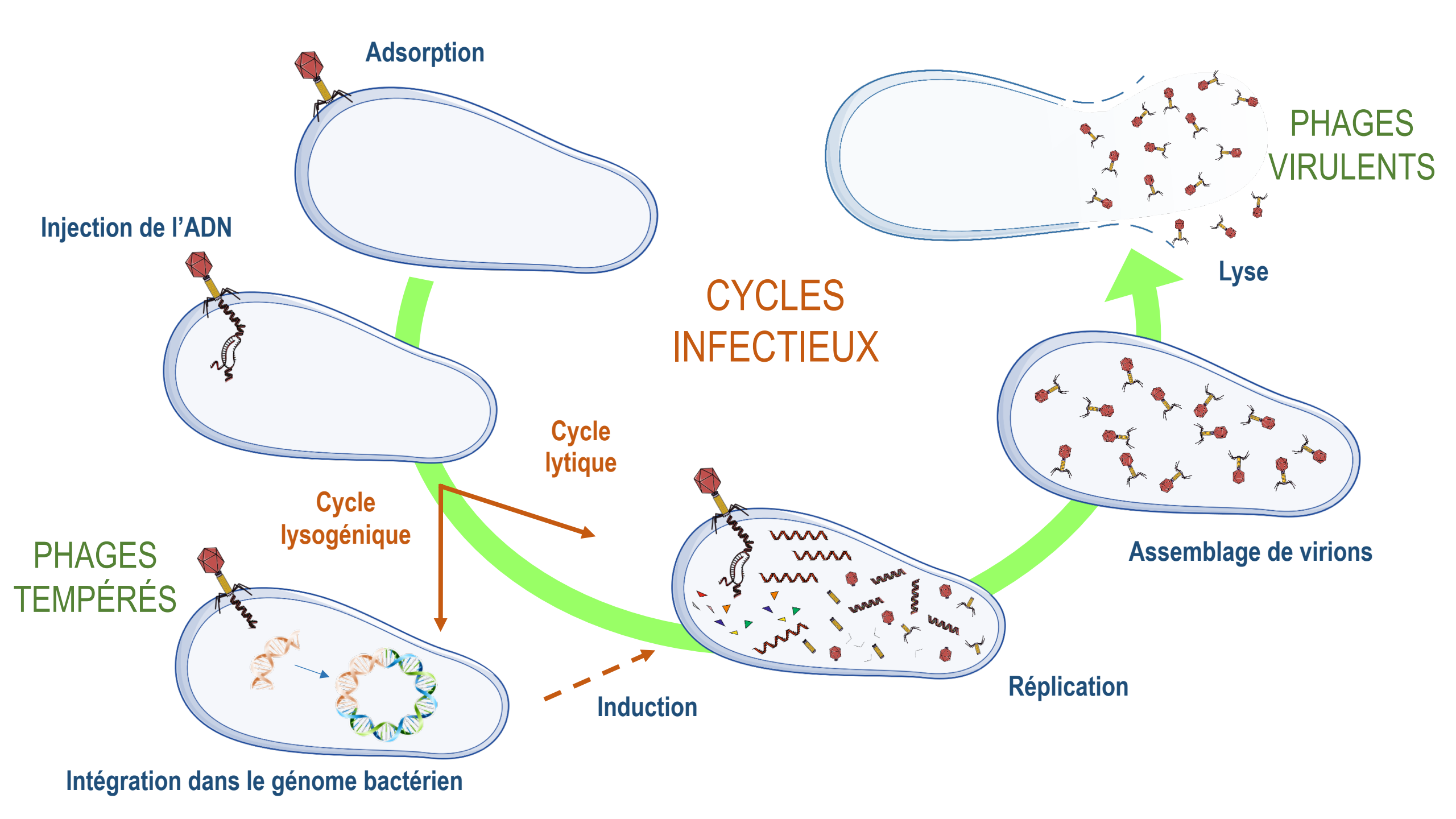


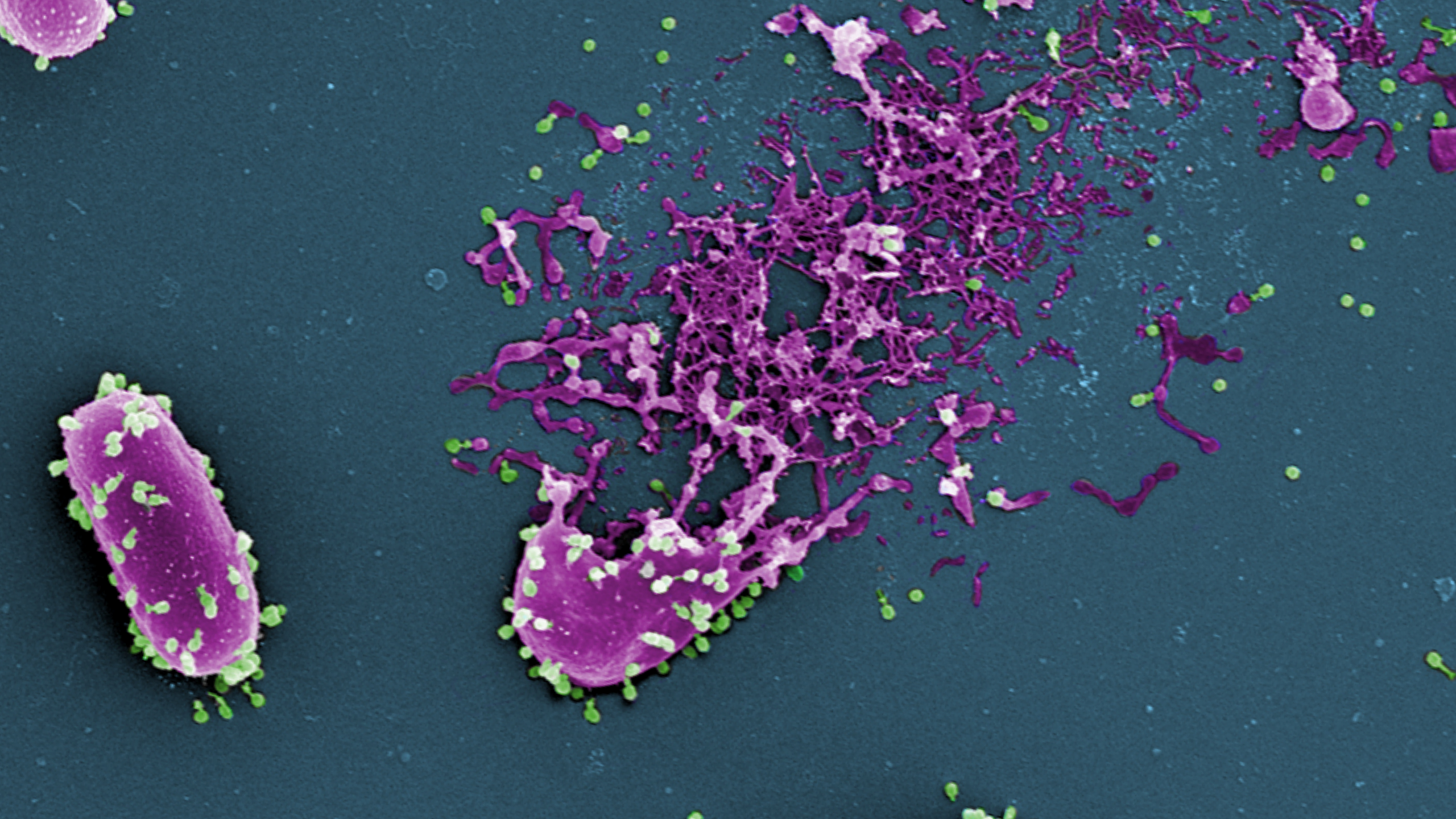
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BACTÉRIOPHAGES

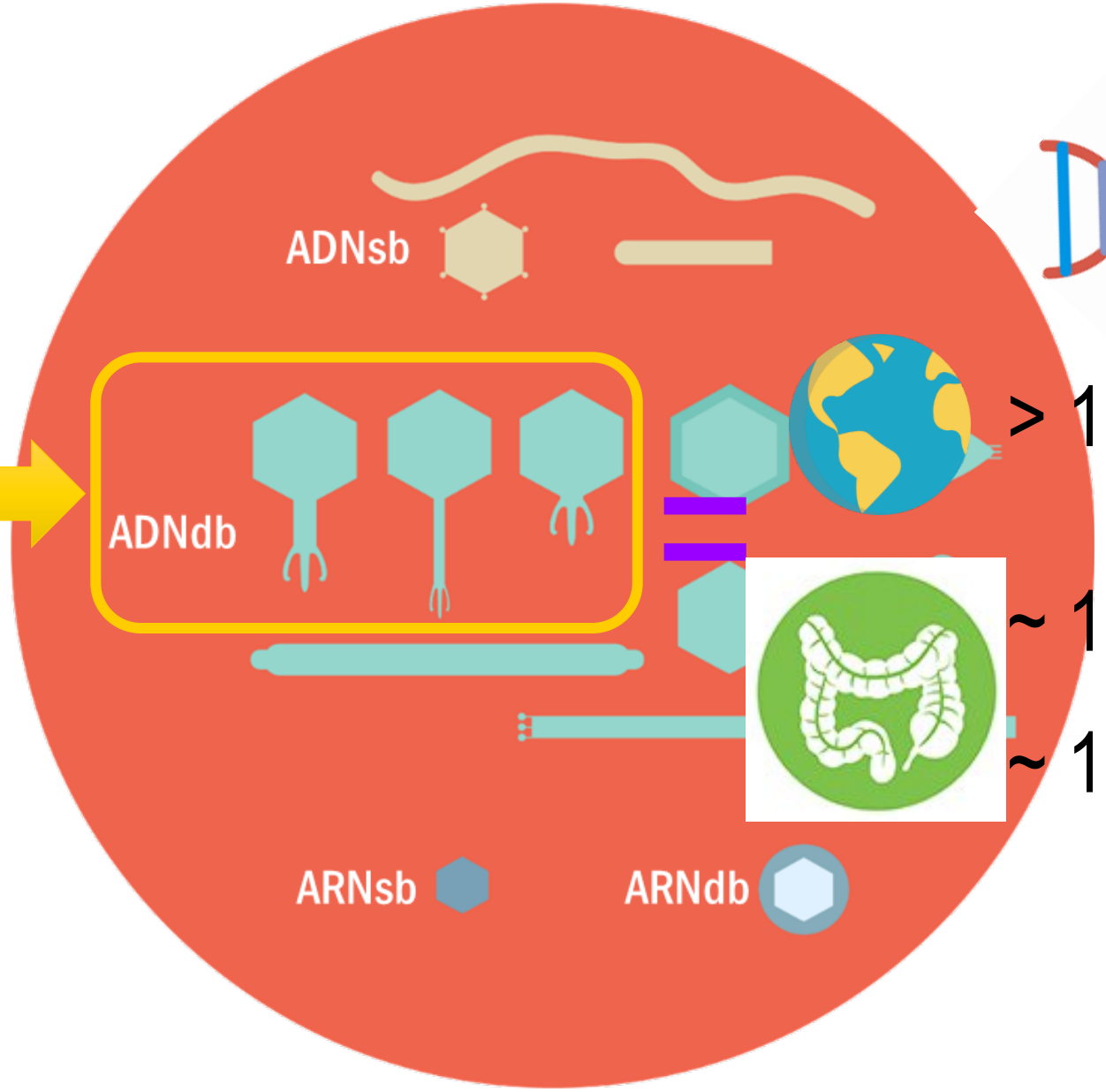


- virus qui infectent les bactéries
- très spécifiques (quelques souches d'une espèce)
- ubiquitaires


Adsorption
Injection de l'ADN
CYCLES INFECTIEUX
PHAGES VIRULENTS
Lyse
Cycle lytique
Cycle lysogénique
PHAGES TEMPÉRÉS
Assemblage de virions
Induction
Réplication
Intégration dans le génome bactérien



CAUDOVIRALES
97% des phages connus



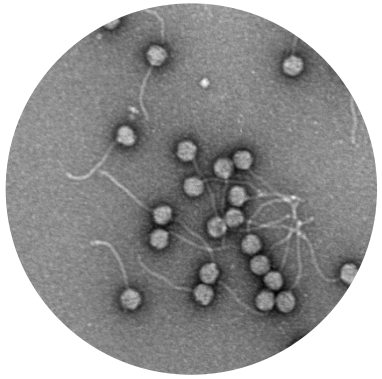


> 10^6 génotypes

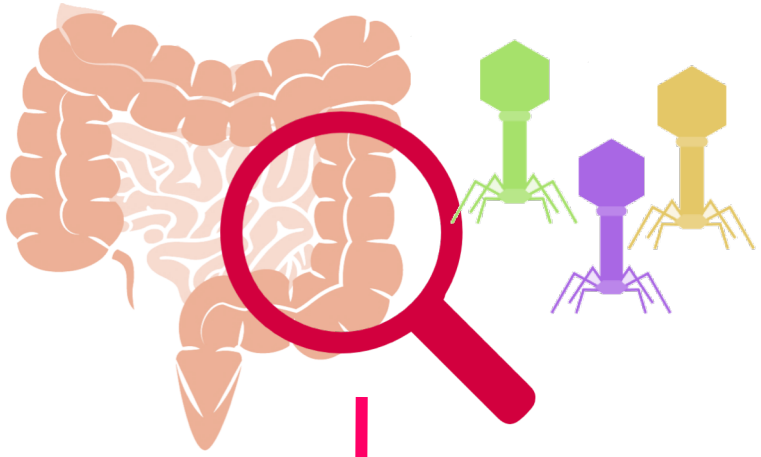
~ 10^2-10^3 génotypes

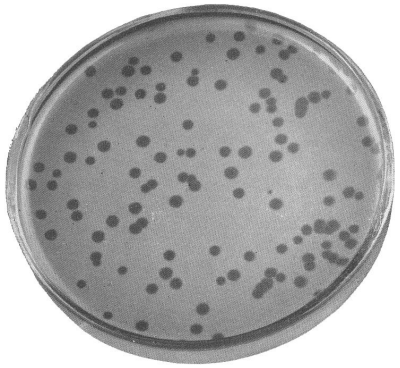
~ 10^{10} particules virales

ETUDE DES BACTÉRIOPHAGES INTESTINAUX (ET POURQUOI CE N'EST PAS ÉVIDENT)



MISCROSCOPIE





CULTURE

Diversité génomique
Taux de lysogénie



MÉTAGÉNOMIQUE

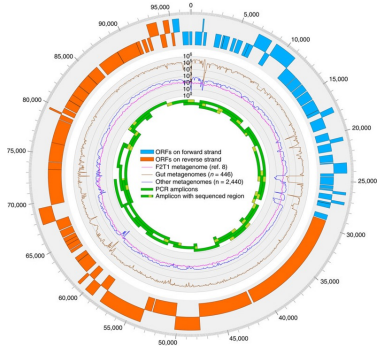
Classification
Association à un hôte

L'EXEMPLE CRASSPHAGE

2014 Nature Communications

A highly abundant bacteriophage discovered in the unknown sequences of human faecal metagenomes

Bas E. Dutilh[1,2,3,4], Noriko Cassman[3,†], Katelyn McNair[2], Savannah E. Sanchez[3], Genivaldo G.Z. Silva[5], Lance Boling[3], Jeremy J. Barr[3], Daan R. Speth[6], Victor Seguritan[3], Ramy K. Aziz[2,7], Ben Felts[8], Elizabeth A. Dinsdale[3,5], John L. Mokili[3] & Robert A. Edwards[2,4,5,9]

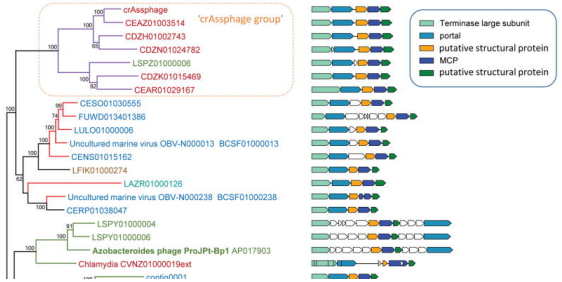


crAssphage:
Jusqu'à 90% des séquences virales intestinales
Plus de 80% des gènes sont inconnus

2017 Nature Microbiology

Discovery of an expansive bacteriophage family that includes the most abundant viruses from the human gut

Natalya Yutin[1], Kira S. Makarova[1], Ayal B. Gussow[1], Mart Krupovic[2], Anca Segall[1,3], Robert A. Edwards[3] and Eugene V. Koonin[1*]

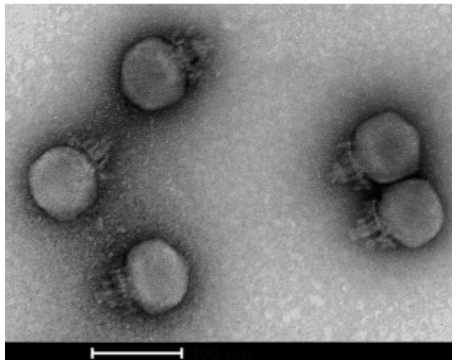


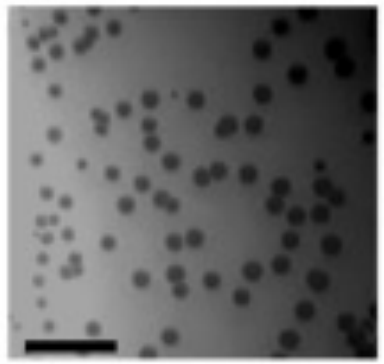
Classification
Hôte prédit: membre du phylum Bacteroidetes

2018 Nature Communications

ΦCrAss001 represents the most abundant bacteriophage family in the human gut and infects *Bacteroides intestinalis*

Andrey N. Shkoporov[1], Ekaterina V. Khokhlova[1], C. Brian Fitzgerald[1], Stephen R. Stockdale[2], Lorraine A. Draper[1], R. Paul Ross[1,2,3] & Colin Hill[1,4]

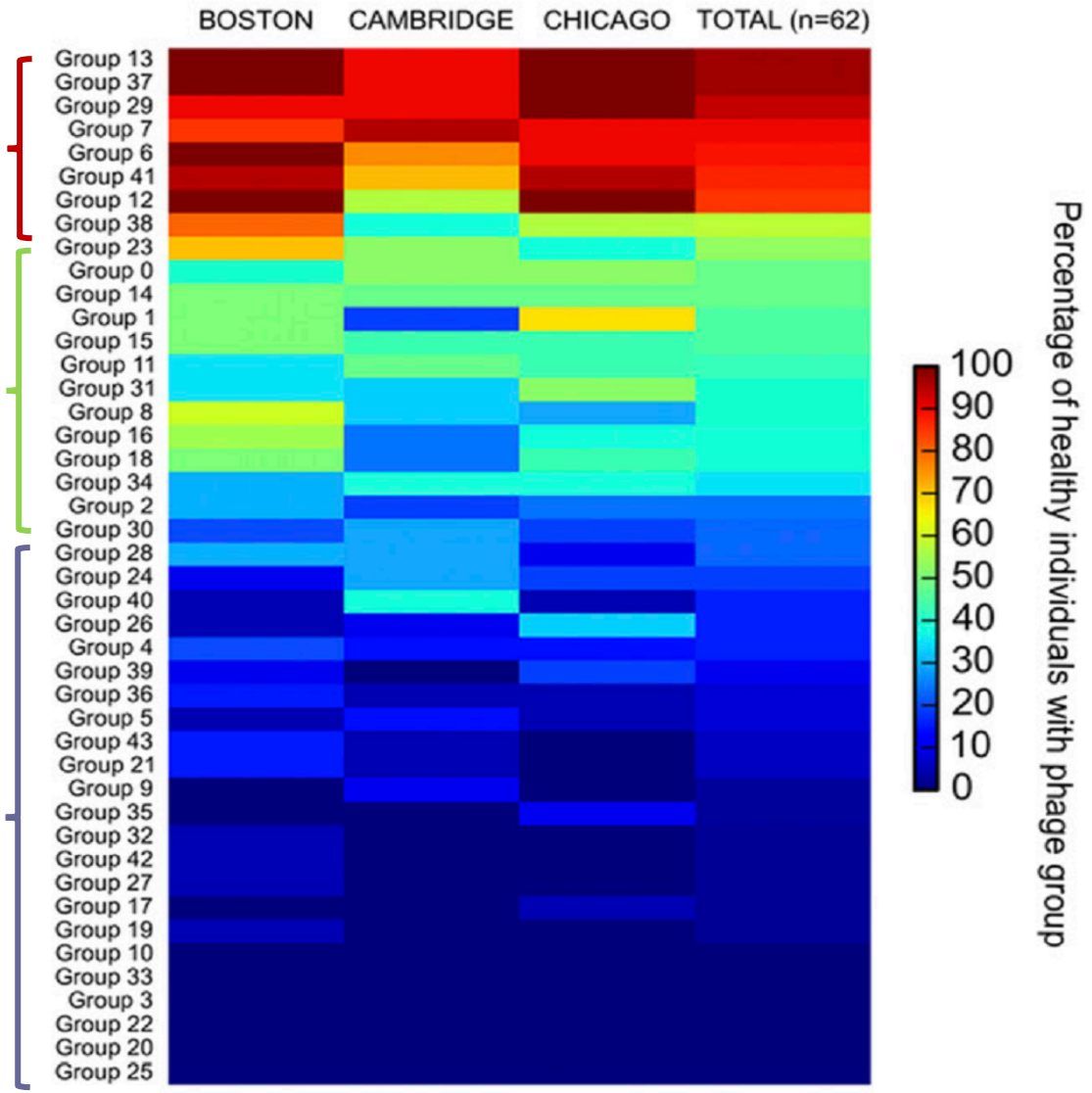




Isolement
Culture

LE PHAGEOME HUMAIN

- Composante virale plus abondante
- Spécifique à chaque individu
- Présence d'une signature de phages conservée chez les individus sains

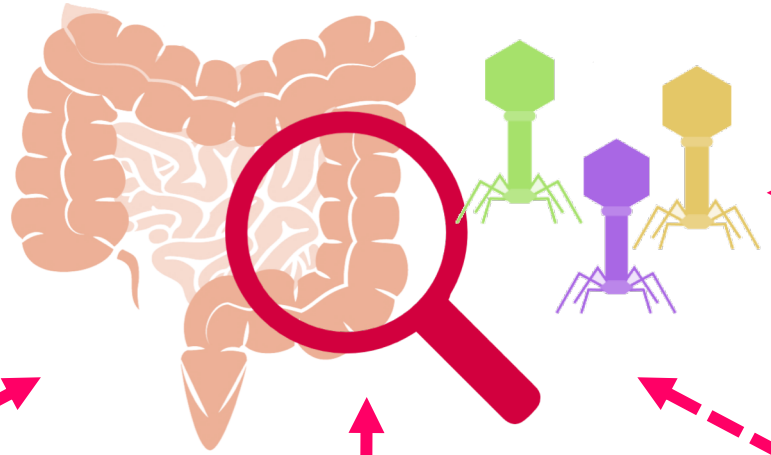


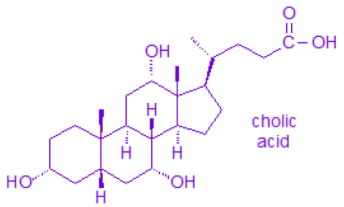
Manrique *et al.* 2016, PNAS

MODULATION DU PHAGEOME HUMAIN



ALIMENTATION
(métabolisme des AGCC)





SELS BILIAIRES

?

?

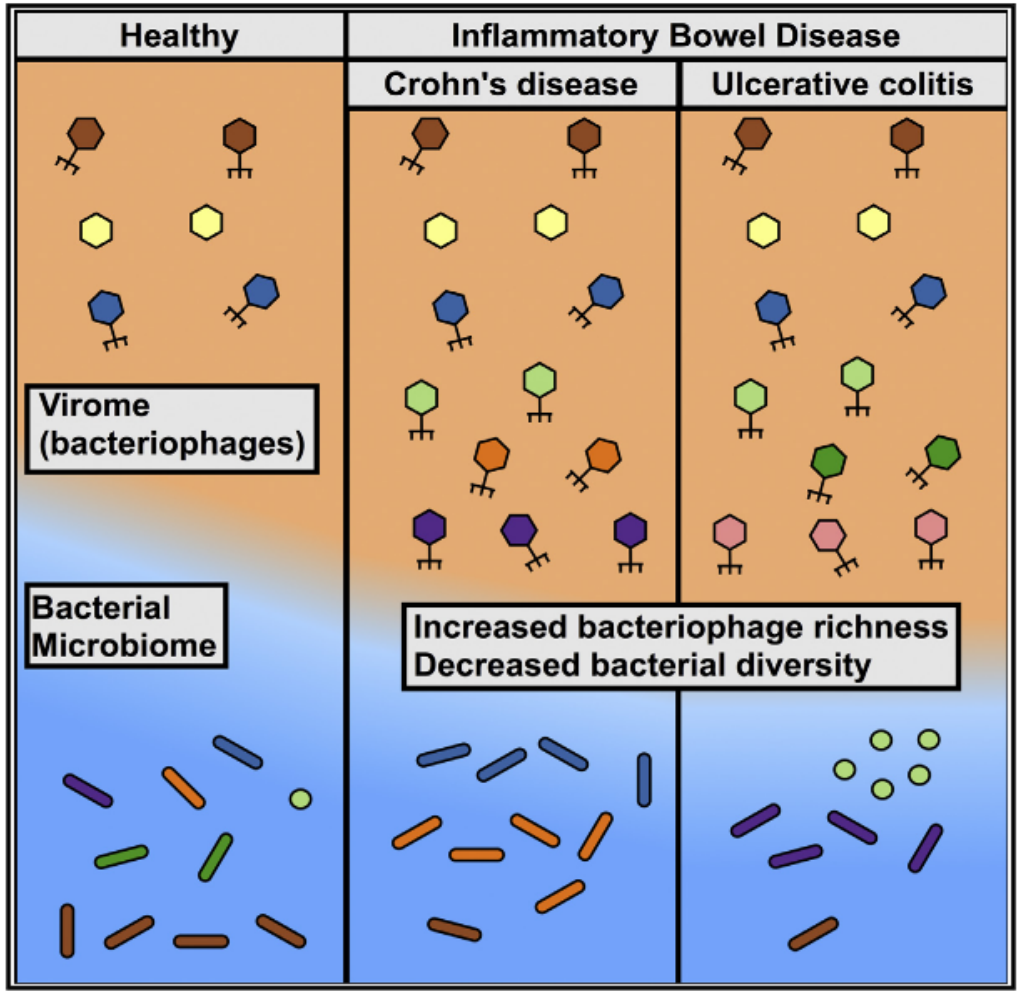
INFLAMMATION



+ phages

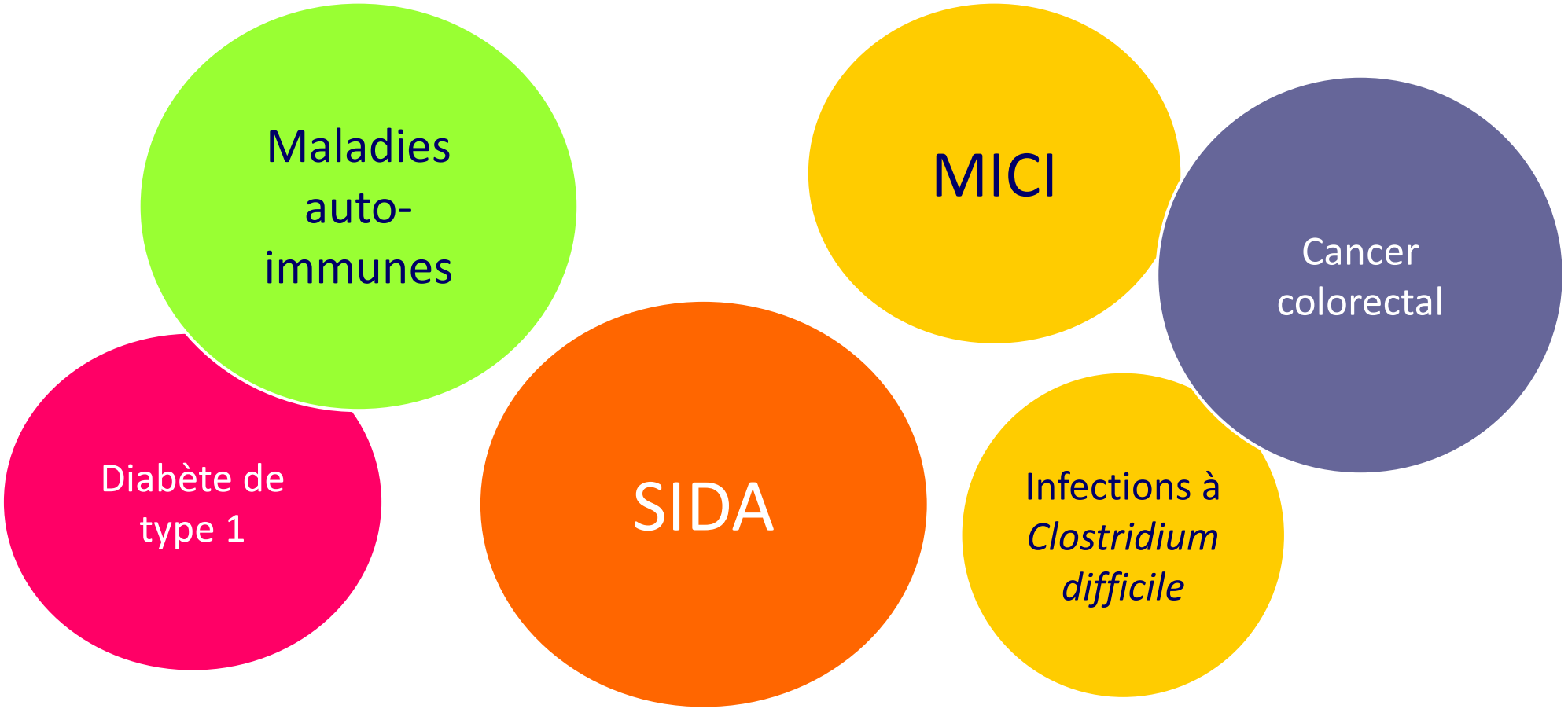
PHAGES ET INFLAMMATION

Expansion des séquence de phages chez les patients atteint de MICI



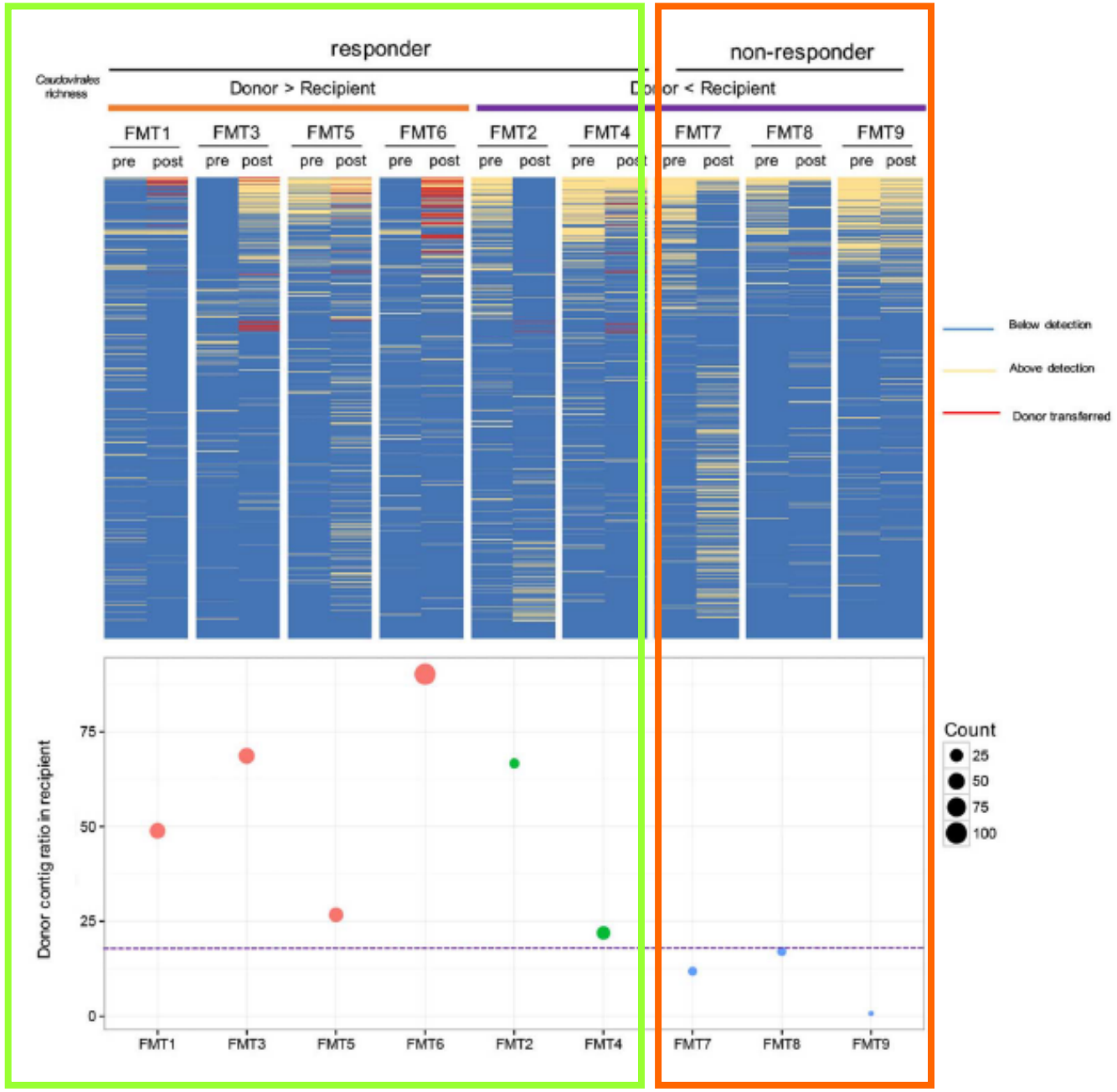
Norman *et al.* 2014, Cell

SIGNATURES MÉTAGÉNOMIQUES VIRALES DE MALADIE



TRANSFERT DES PHAGES PENDANT LA TRANSPLANTATION FÉCALE

- 20 sujets sains
- 24 patients CDI (plus d'abundance mais moins de diversité, richesse et distribution des phages Caudovirales)
- **Les patients qui ont répondu au traitement de TF portent des séquences virales du donneur.**



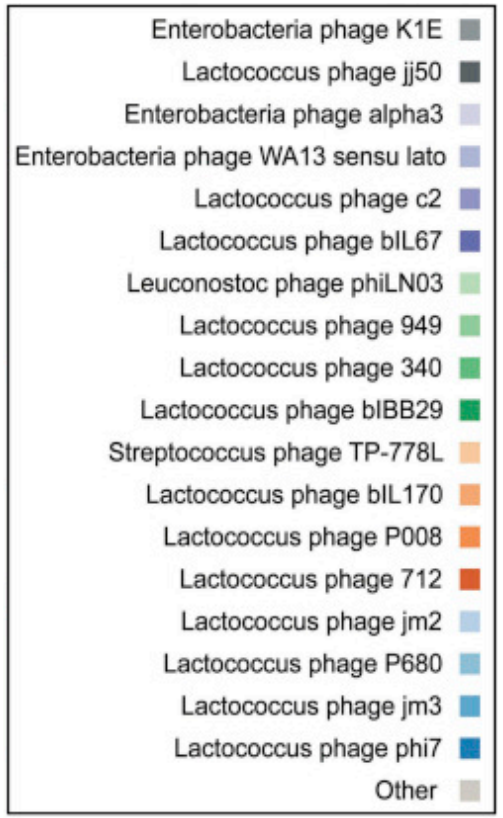
Zuo *et al*, Gut, 2018

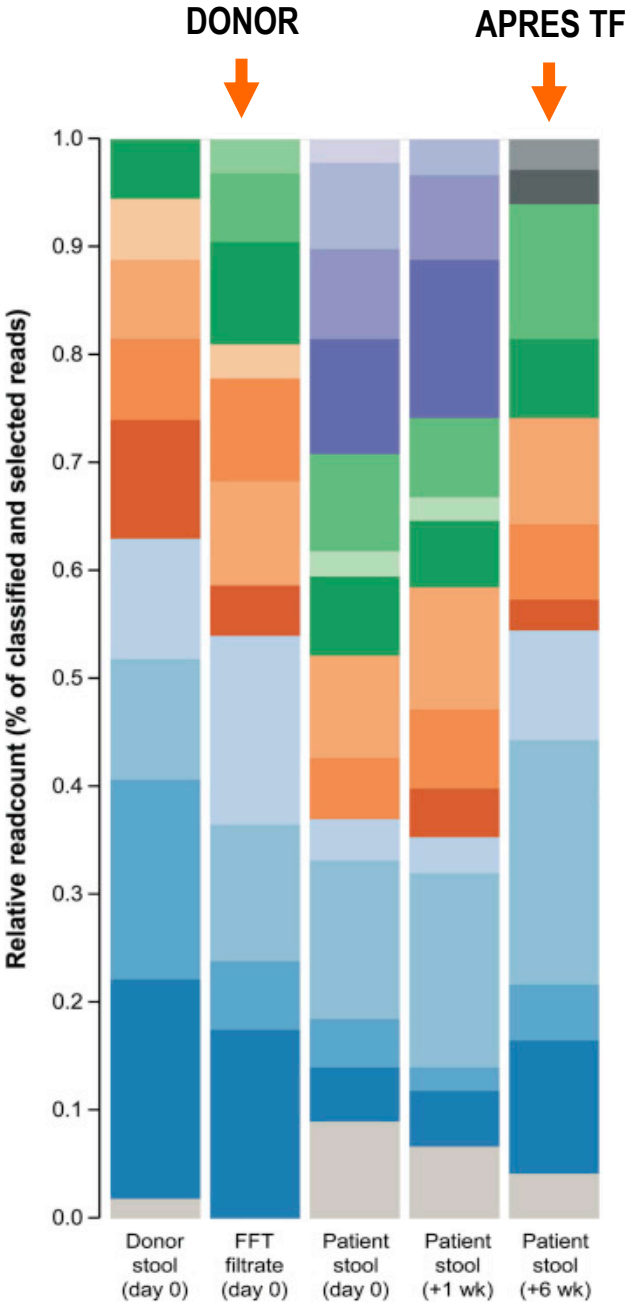
TRANSFERT DES PHAGES PENDANT LA TRANSPLANTATION FÉCALE STÉRILE

- 5 patients CDI
- Transplantation de matériel fécal filtré
- **Transfert de phages associé à la résolution des symptômes**

? COEXISTANCE PHAGE-BACTÉRIE

? ADAPTATION

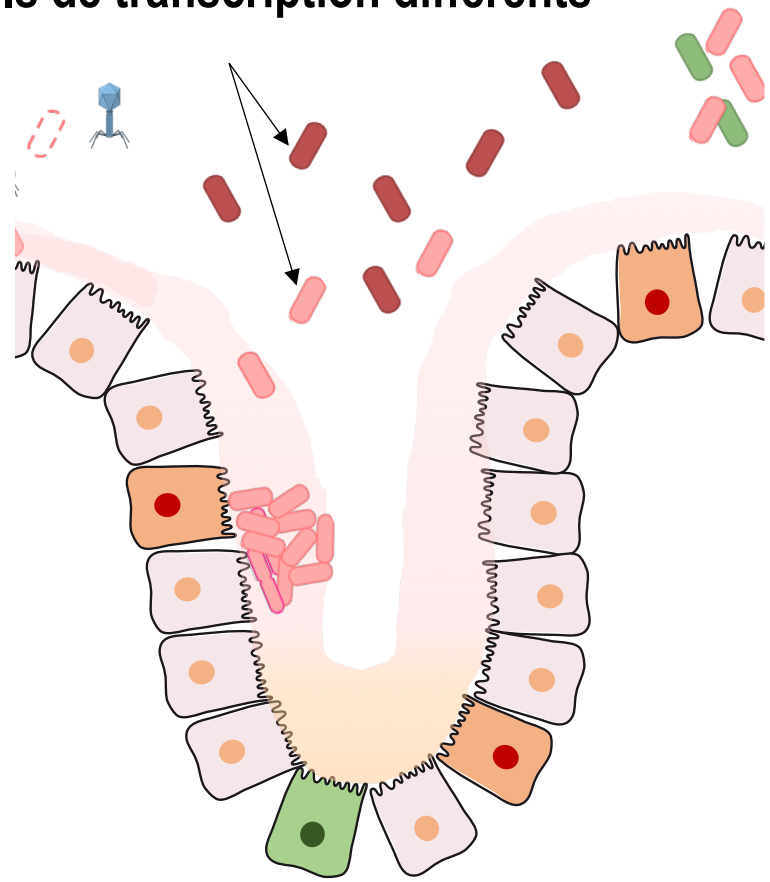




Ott *et al.* Gastroenterology 2017

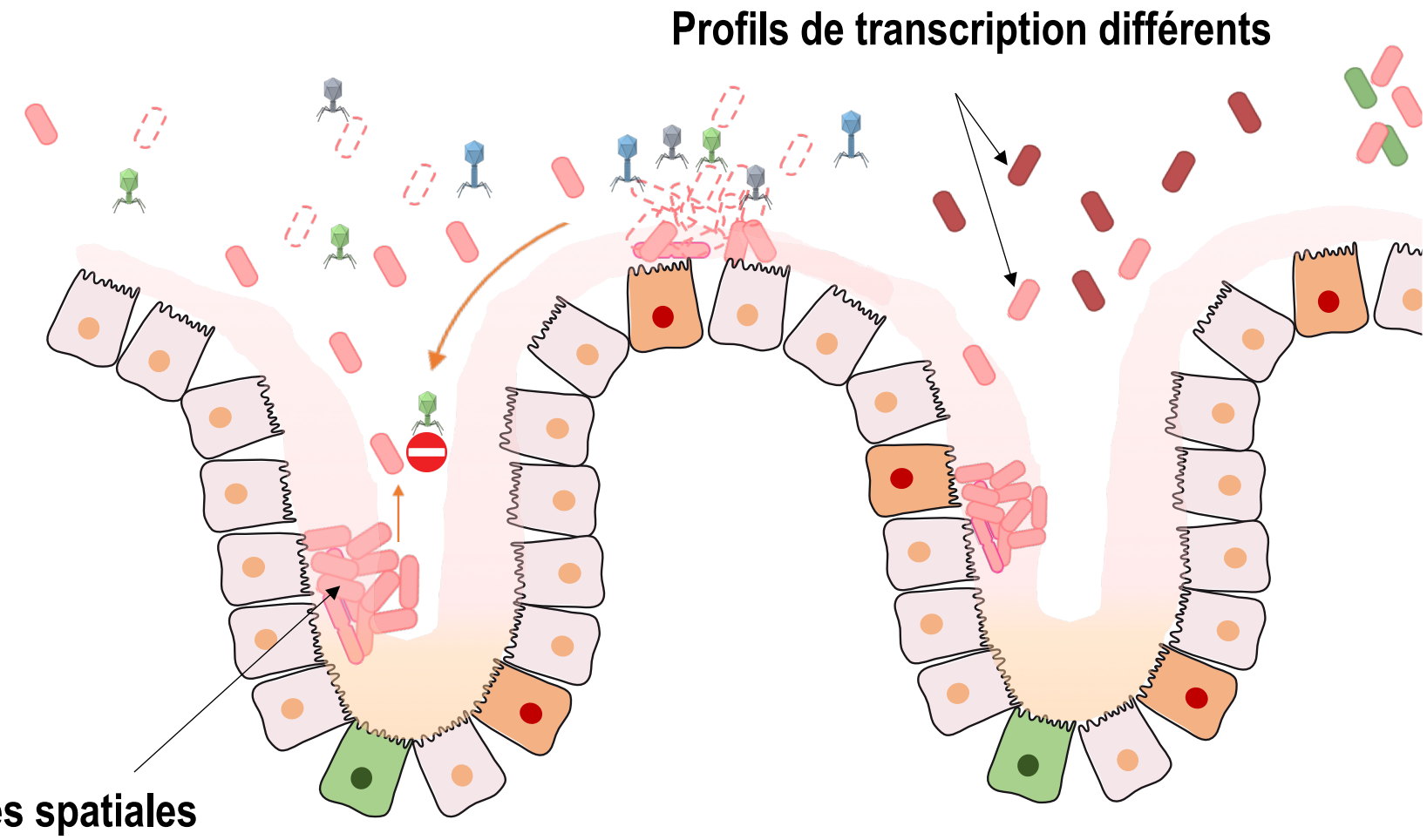
COEXISTENCE *IN VIVO*

Profils de transcription différents



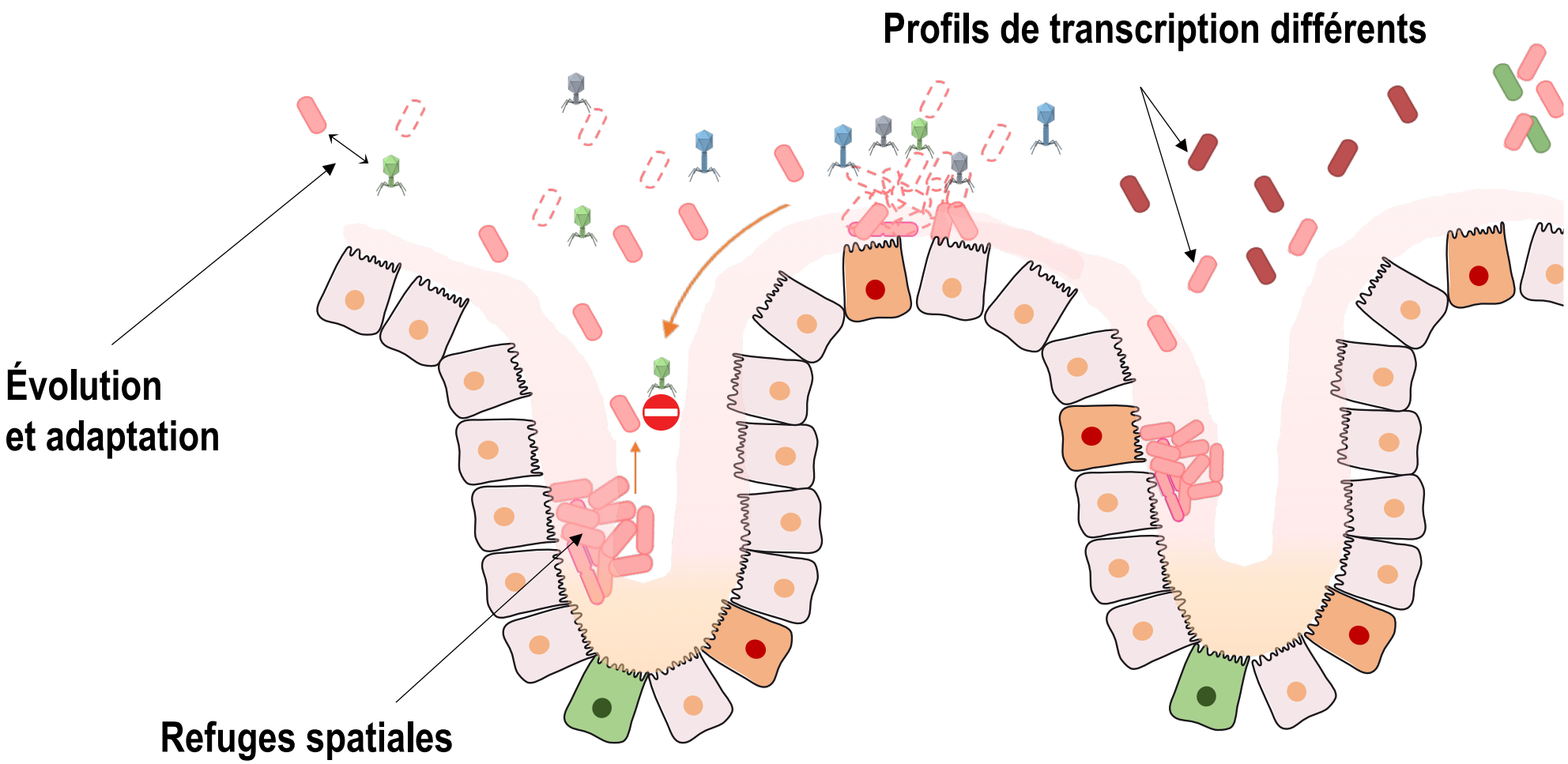
Adapted from De Sordi *et al*. *Cell Host Microbe*, 2019

COEXISTENCE *IN VIVO*



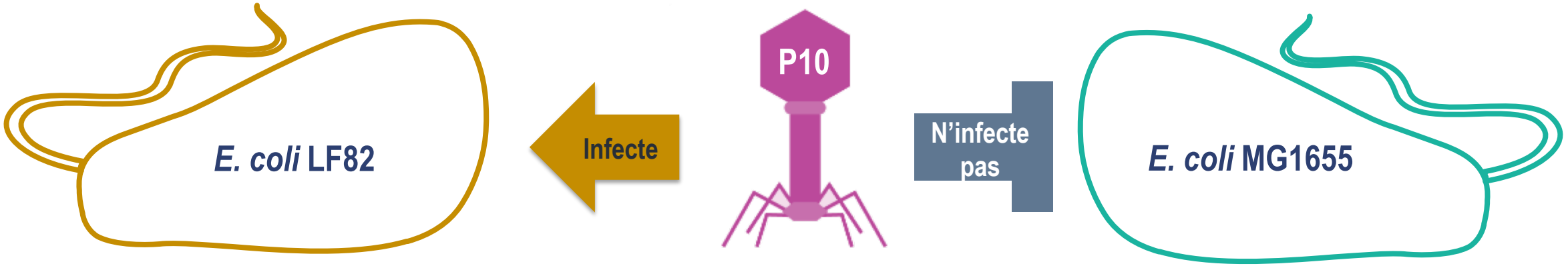
Adapted from De Sordi *et al*. *Cell Host Microbe*, 2019

COEXISTENCE *IN VIVO*



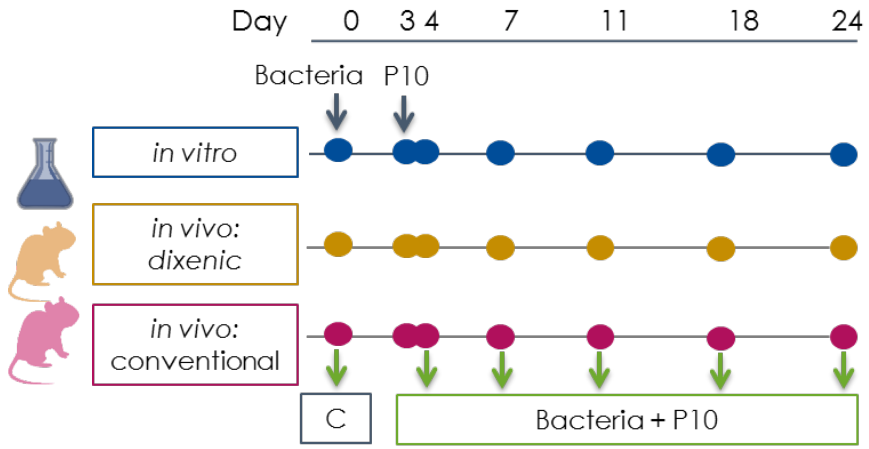
Adapted from De Sordi *et al*. *Cell Host Microbe*, 2019

ADAPTATION DES PHAGES INTESTINAUX

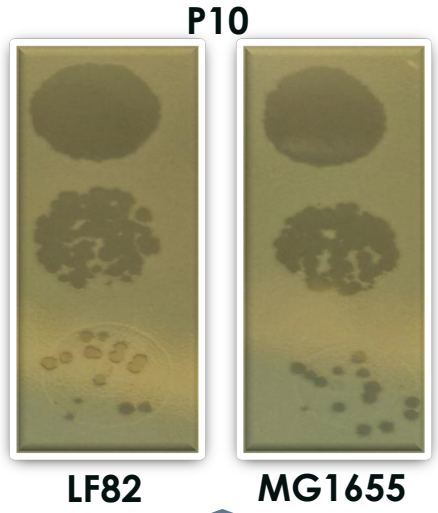


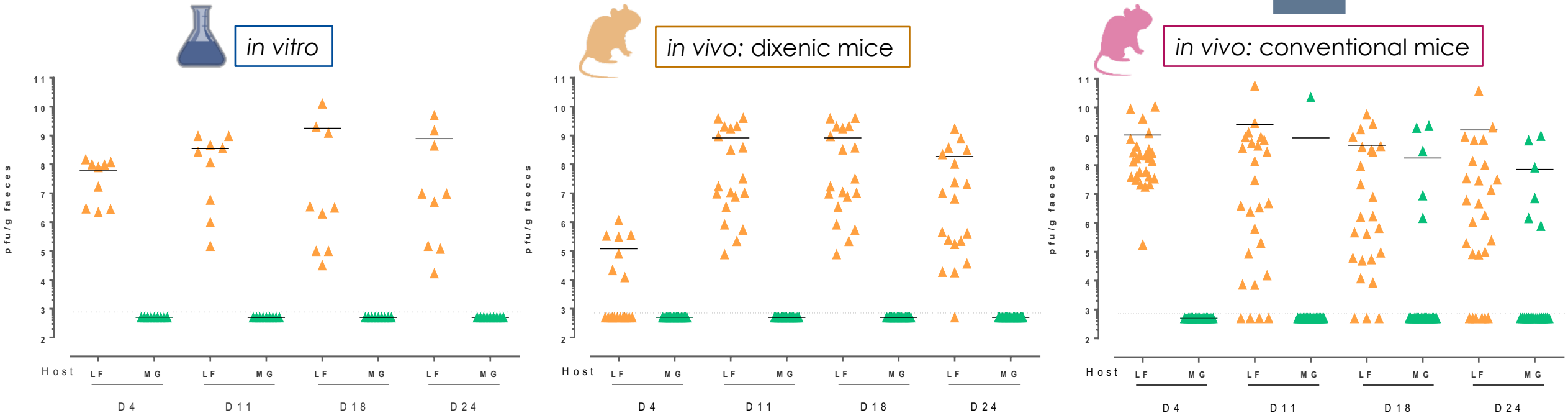
Adaptation à la souche MG1655 possible ?

L'ADAPTATION EST POSSIBLE SEULEMENT *IN VIVO*



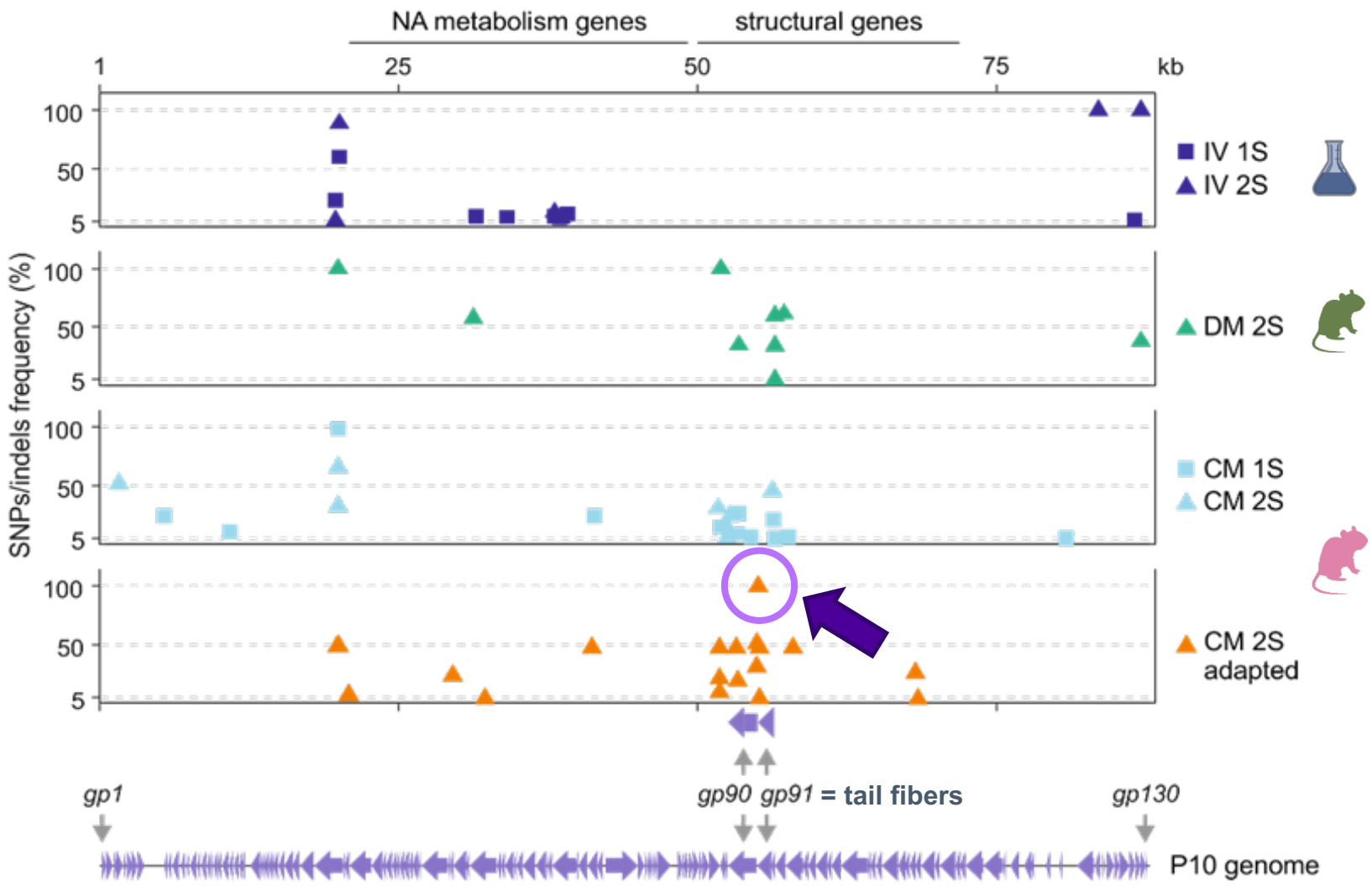
20% taux d'adaptation





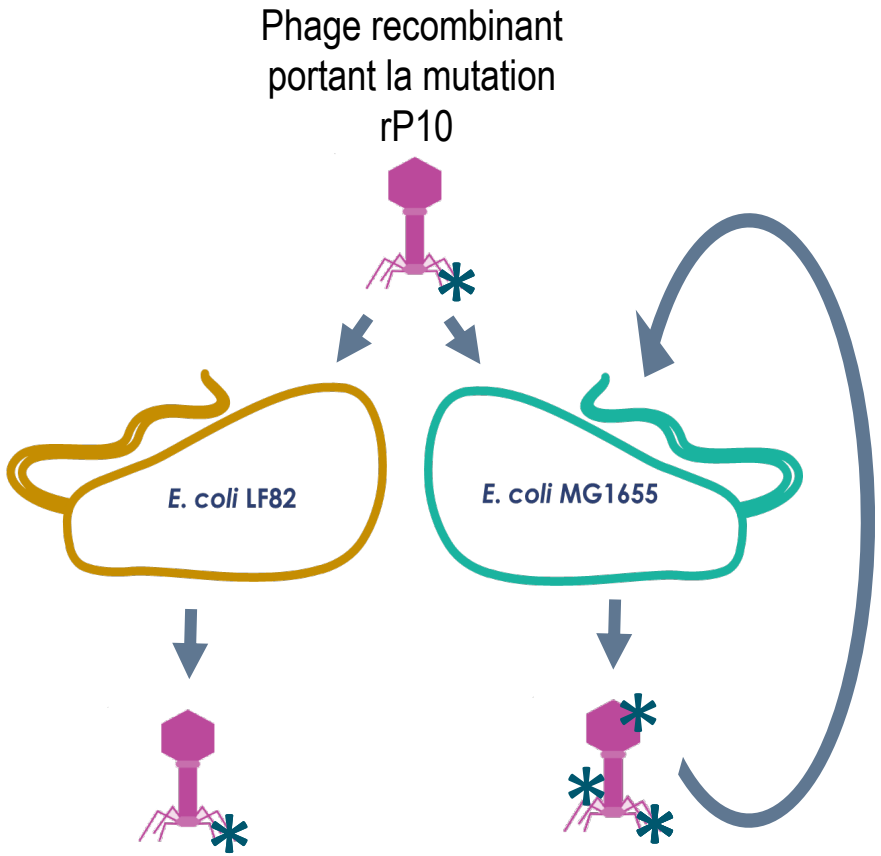
De Sordi *et al. Cell Host Microbe*, 2017

UNE MUTATION EST COMMUNE À TOUS LES PHAGES ADAPTÉS

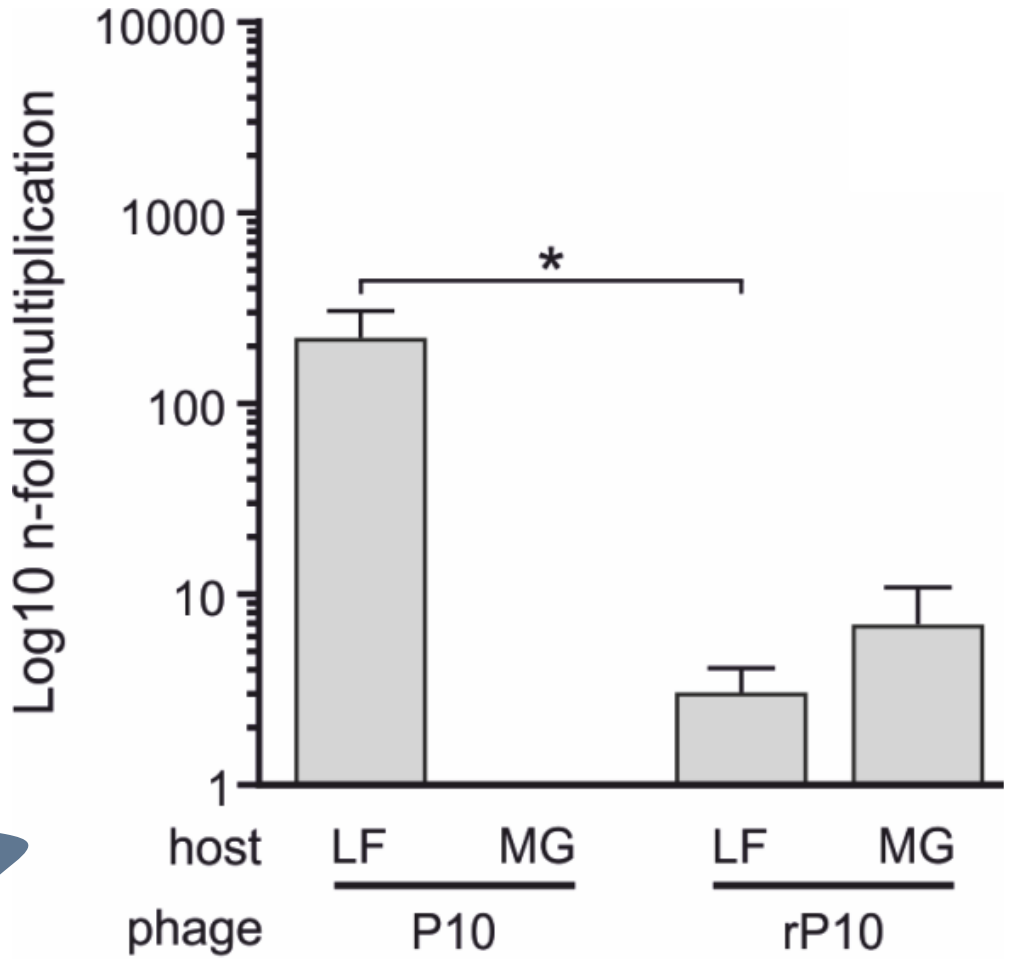


De Sordi *et al. Cell Host Microbe*, 2017

L'ADAPTATION A UN COUT DE SÉLECTION

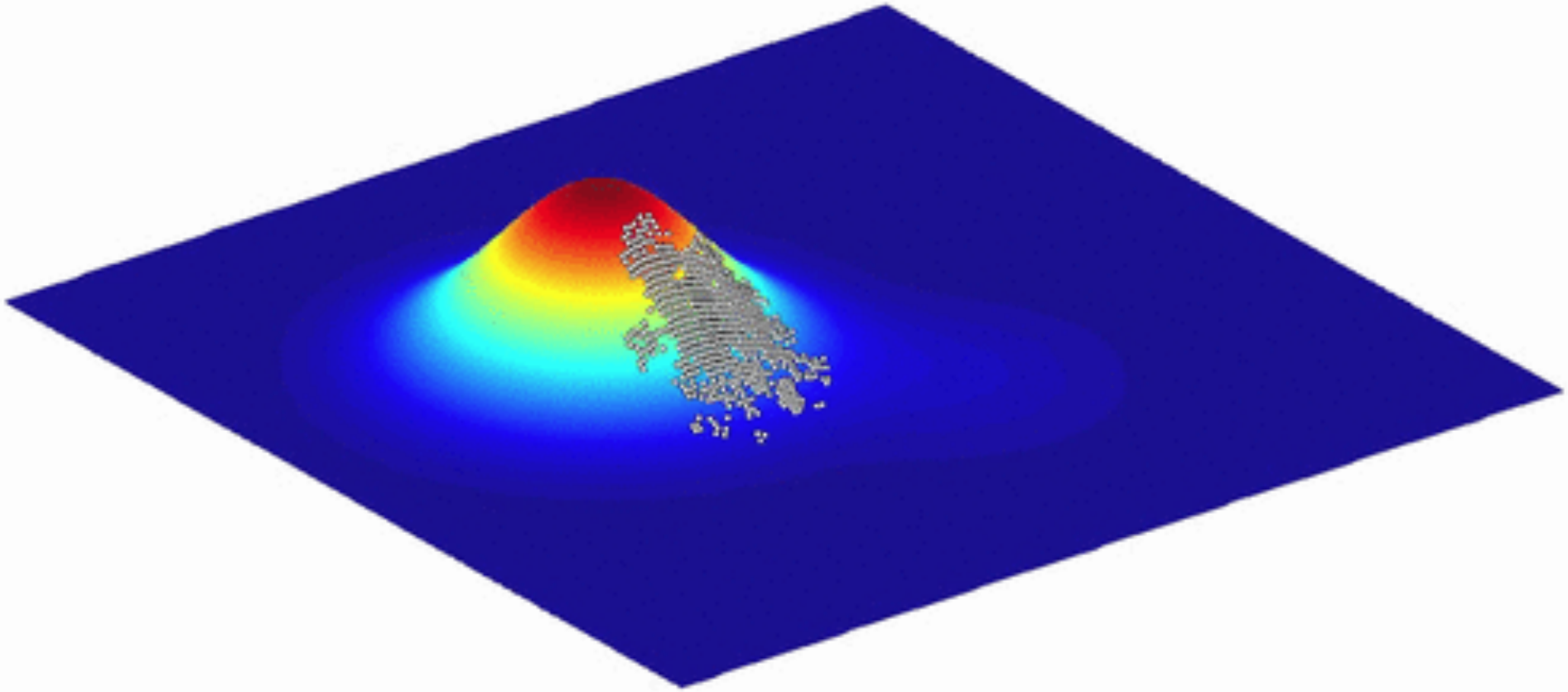


Les phages adaptés ont un avantage sélectif seulement en abondance du nouvel hôte



De Sordi *et al. Cell Host Microbe*, 2017

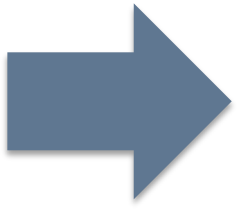
EVOLUTION DES POPULATIONS



© Randy Olson and Bjørn Østman

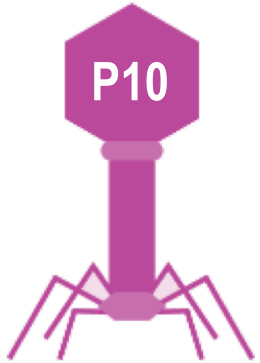
LE MICROBIOTE INTESTINALE FAVORISE L'ADAPTATION

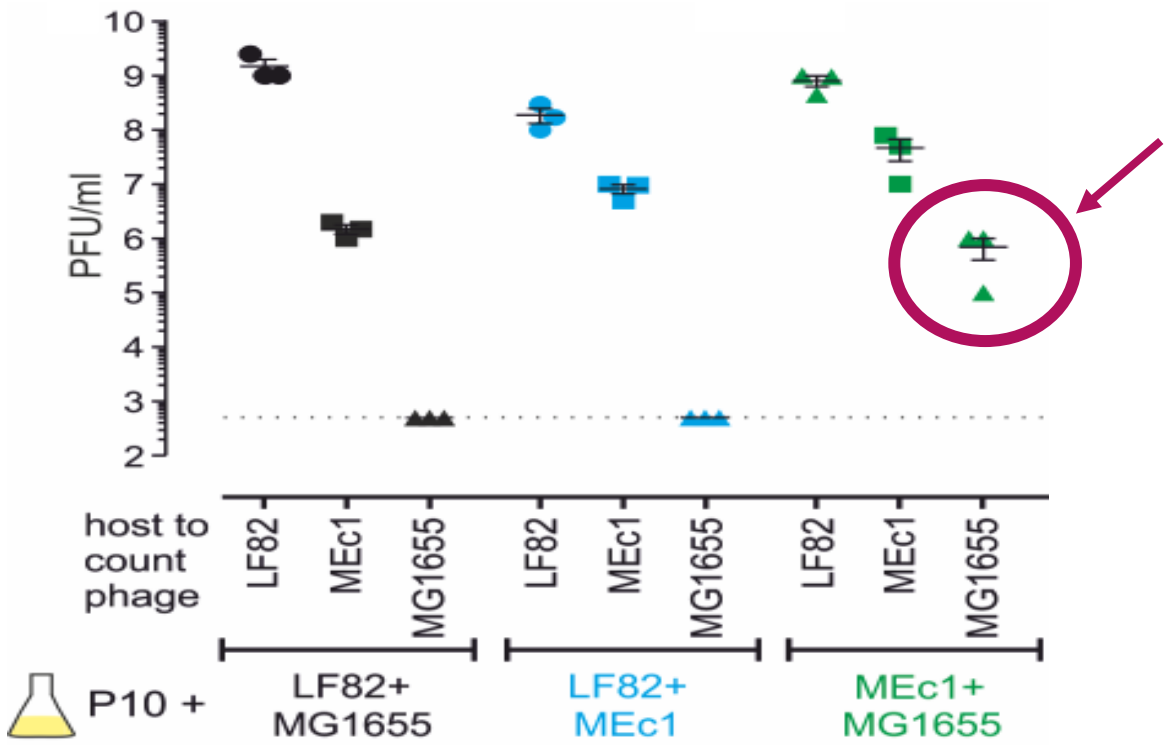








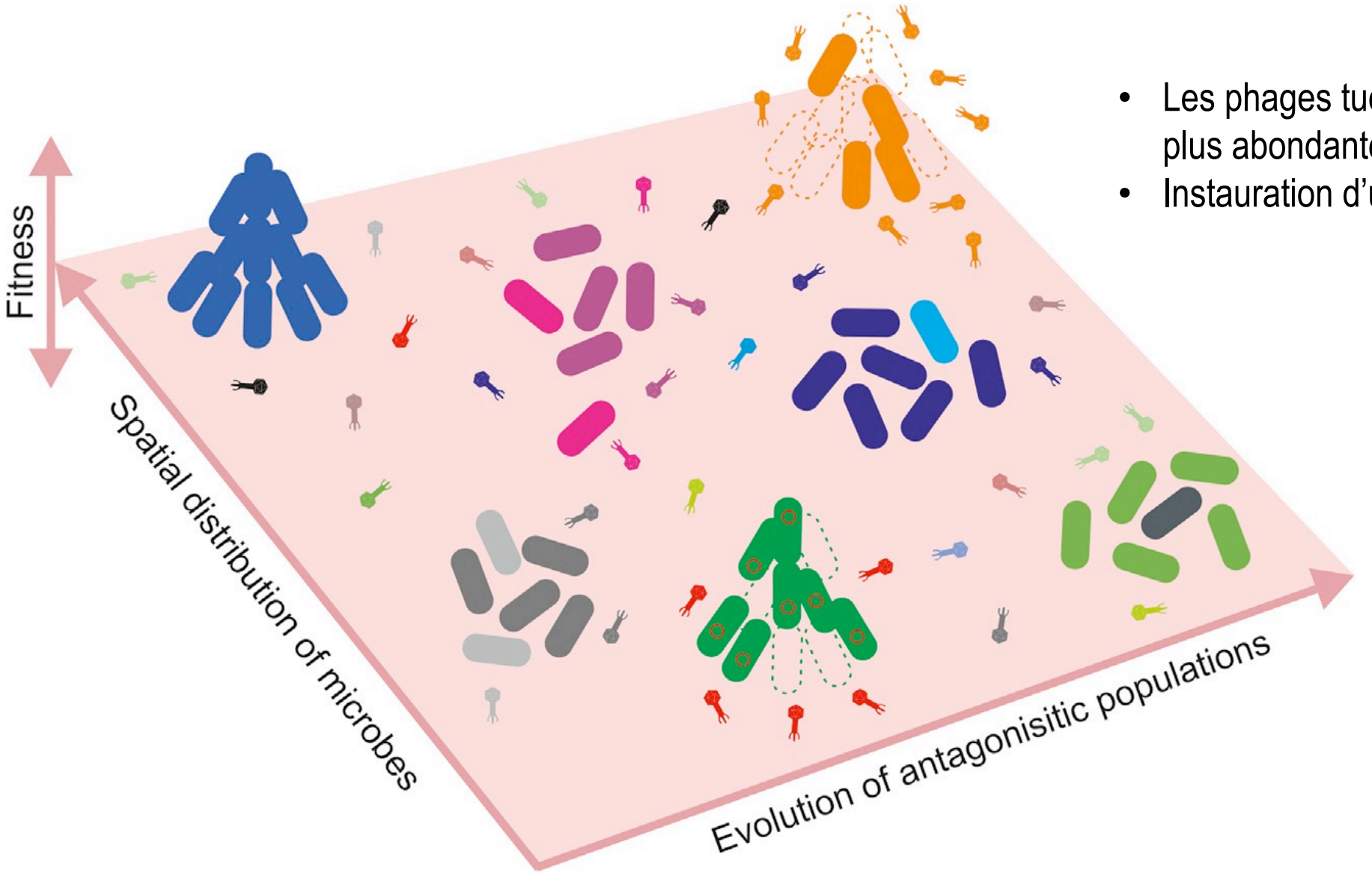




Adaptation *via* un hôte intermédiaire

De Sordi *et al*. *Cell Host Microbe*, 2017

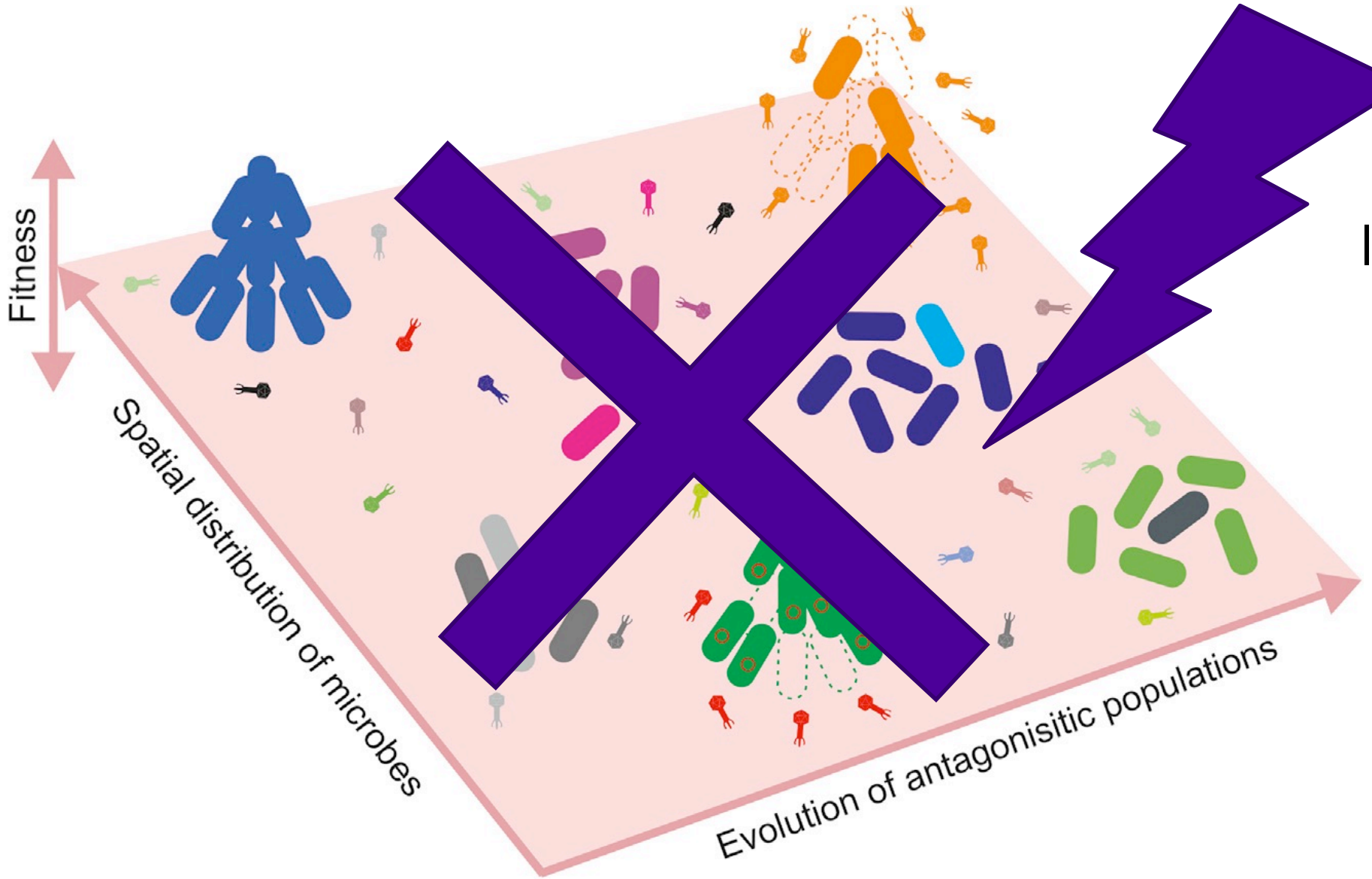
LA COEXISTENCE ENTRE PHAGES ET BACTÉRIES RÉGULE LA DIVERSITÉ ET L'ÉQUILIBRE DU MICROBIOTE



- Les phages tuent les populations les plus abondantes
- Instauration d'un équilibre dynamique

De Sordi *et al*. *Gut microbes*, 2018

DES CHANGEMENTS DANS L'ENVIRONEMENT INTESTINAL PEUVENT ALTÉRER CET ÉQUILIBRE



SIGNAL?

AGCC

INFLAMMATION

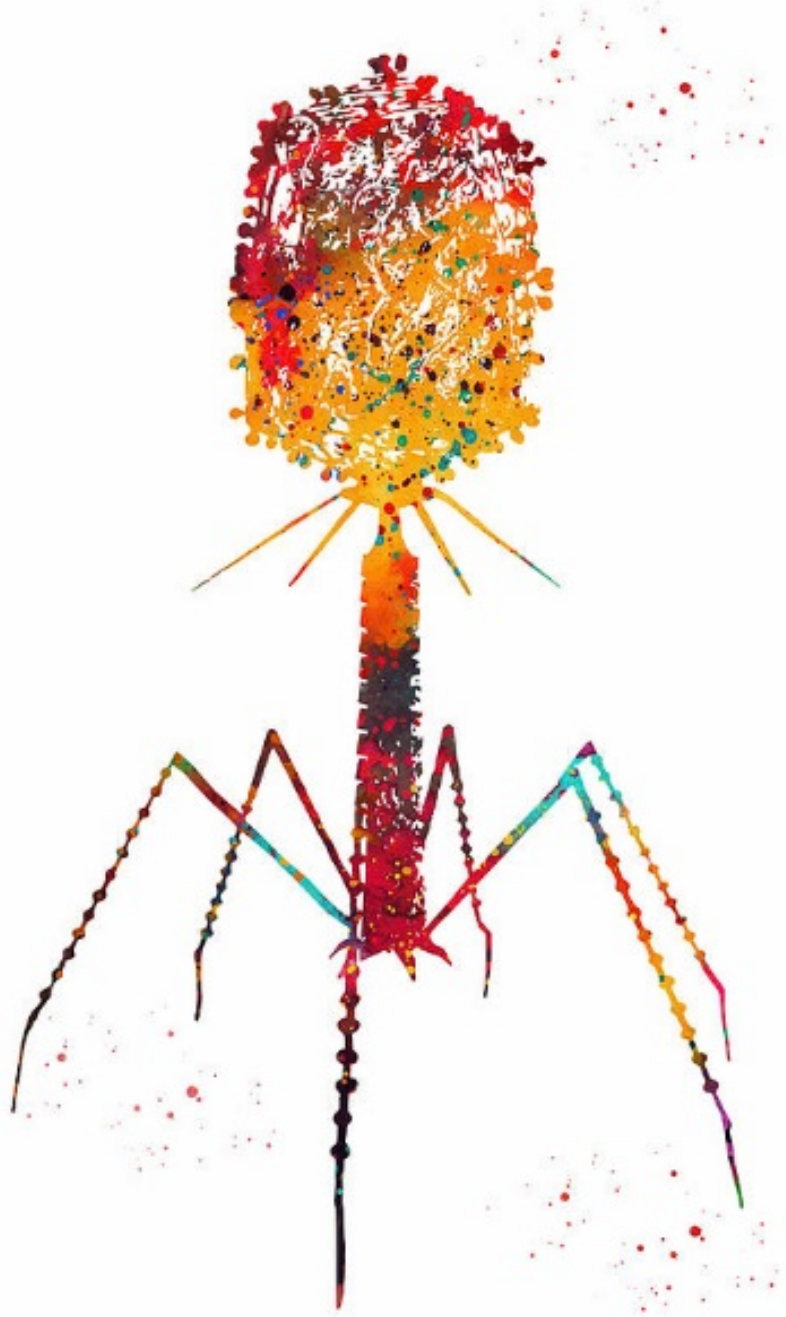
ANTIBIOTICS

INFECTIONS

Philippe Seksik
Harry Sokol

Laurent Debarbieux
Marta Mansos Lourenço

MERCI DE VOTRE ATTENTION



https://fineartamerica.com/featured/bacteriophage-erzebet-s.html