



Use of a Bacteriophage Cocktail for Eradication of *Klebsiella pneumoniae* in Primary Sclerosing Cholangitis

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Disclosure

BiomX employee

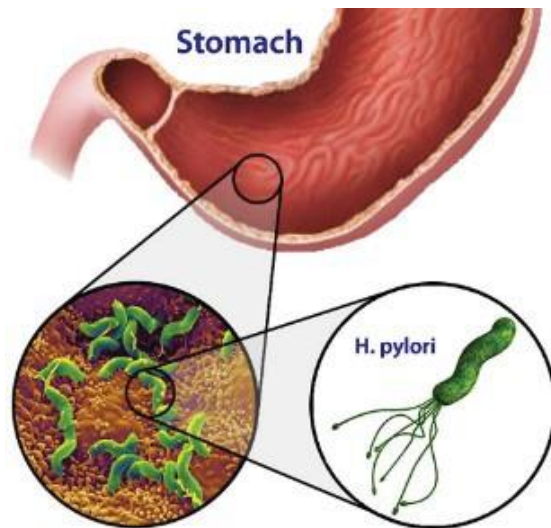
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Growing Evidence of Role of Harmful Bacteria in Chronic Diseases

Peptic Ulcers/Gastric Cancer – *H. pylori*

Proven to be directly linked to gastric cancer



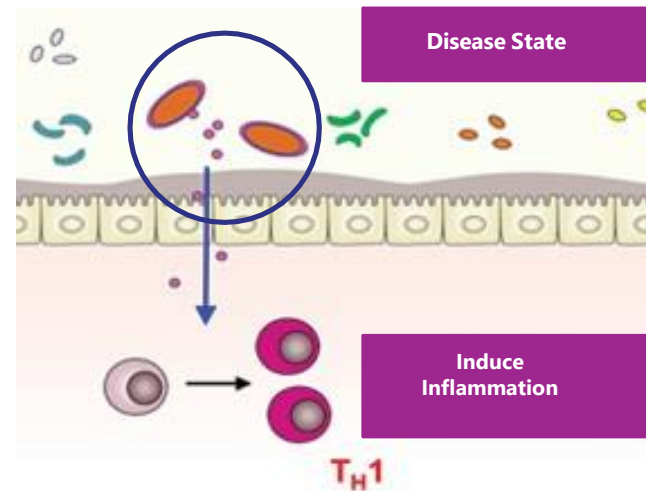
IBD – *K. pneumoniae*

Oct. 2017

Science
AAAS

MICROBIOTA

Ectopic colonization of oral bacteria in the intestine drives T_H1 cell induction and inflammation



Colon Cancer – *F. nucleatum*

Jan. 2018

CANCER

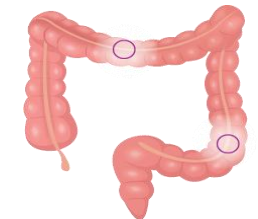
Science
AAAS

Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer

Oct. 2017

Cell

Fusobacterium nucleatum Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy



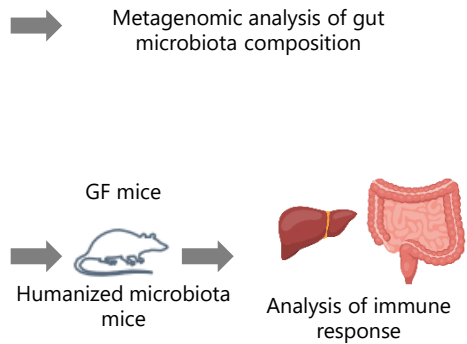
Klebsiella pneumoniae Identified as Novel Pathobiont in PSC

nature
microbiology

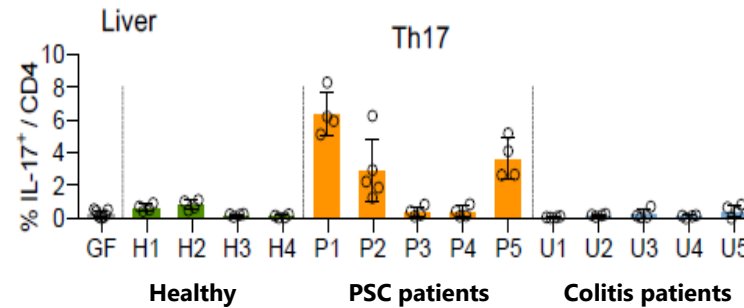
Discovery approach



Fecal samples
From PSC patients



Th17 is induced in livers of GF mice inoculated with fecal samples from PSC patients



KP isolated from mice's lymph nodes colonized with patient samples

	Liver	MLN	Spleen
SPF mice	ND		ND
HC-gnotobiotite	ND		ND
PSC/UC-gnotobiotite	ND		ND

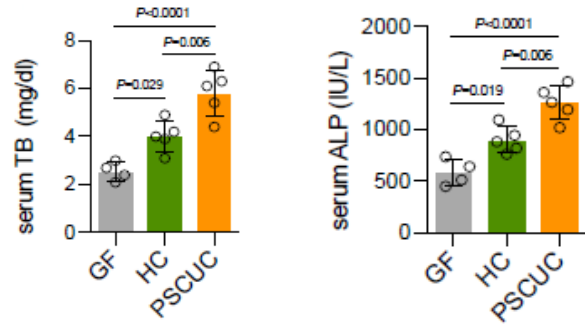
Klebsiella pneumoniae
plays a gating role

Klebsiella pneumoniae (KP) is a specific gut pathobiont of PSC that is an intestinal barrier disrupter and is pro-inflammatory ("leaky gut")

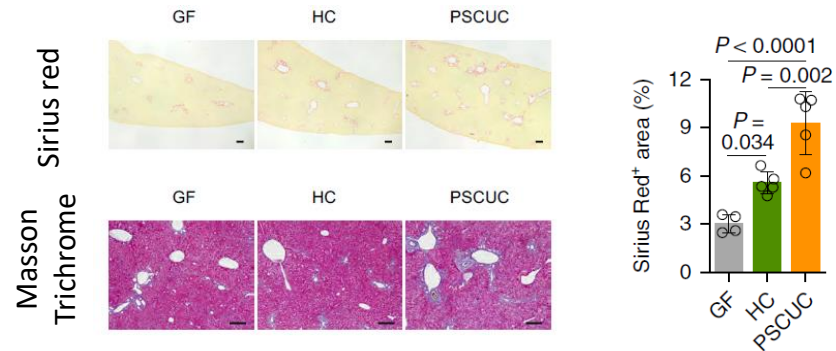
Hepatobiliary Damage in Colonized Mice

DDC-induced Hepatobiliary Injury *In-vivo*

Elevated liver markers

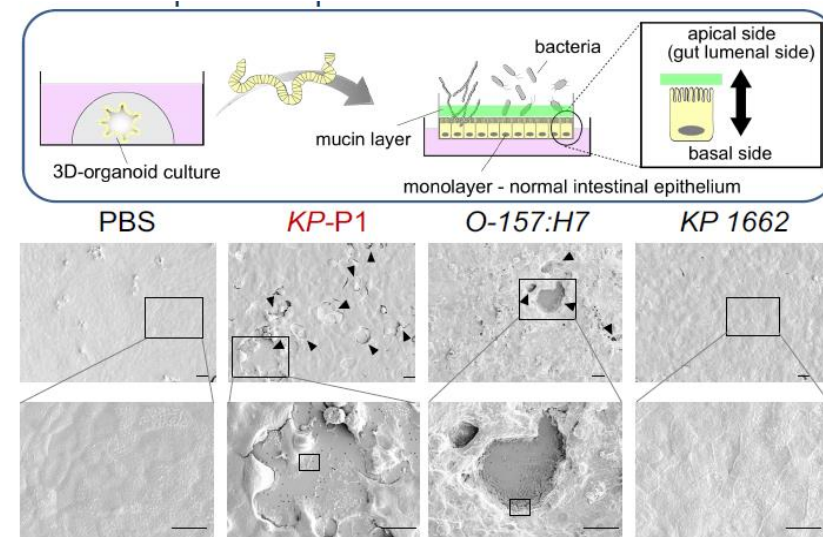


Enhanced fibrosis



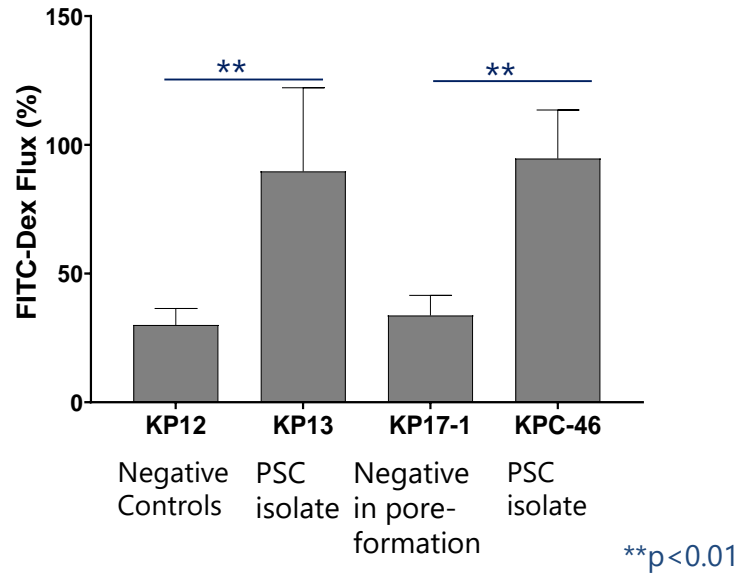
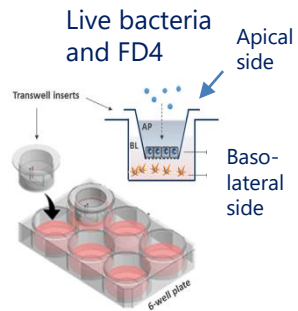
Mechanism of Action-Gut Permeability (Epithelial Pore formation)

Bacterial-human organoid co-culture system

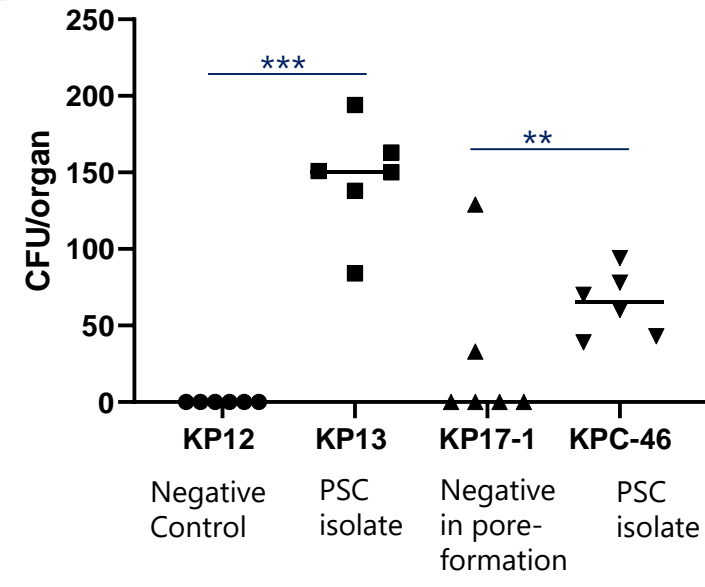


Confirmation of *Klebsiella pneumoniae* as a Pathobiont-Gut Permeability

In vitro- Caco2 Permeability Assay



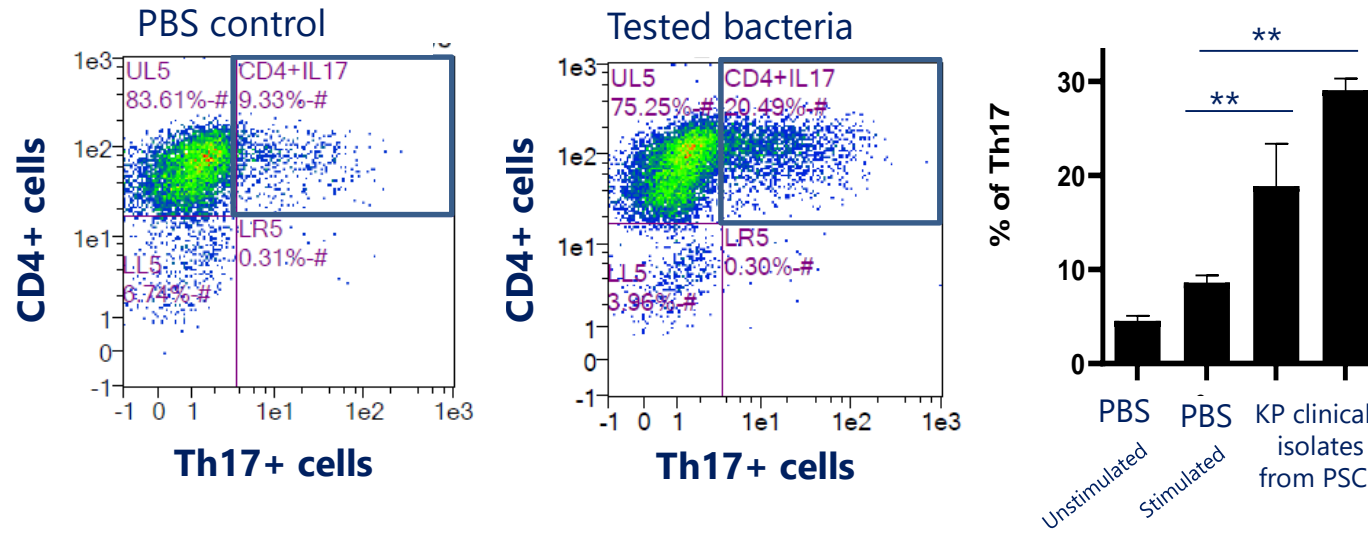
In vivo- Translocation to The Lymph Nodes



High correlation between *in vivo* bacterial translocation to the mesenteric lymph nodes and *in vitro* gut permeability

Confirmation of *Klebsiella pneumoniae* as a Pathobiont-Pro-Inflammatory Th17 Immune Response

Co-cultures of Naïve CD4 and CD11c with Clinical *Kp*



FACS analysis demonstrated a significant increase in the Th17+CD4+ cell population

High Prevalence and Abundance of *Kp* in PSC Patients Compared to Healthy Individuals

Cohort Analysis - Prevalence

Cohort	Healthy volunteers (N)	PSC patients (N)	% Healthy positive	% PSC positive	Detection method
Israel	30	35	66%	75%	qPCR*
France	29	49	55%	80%	MG**
Germany	119	68	60%	95%	MG***

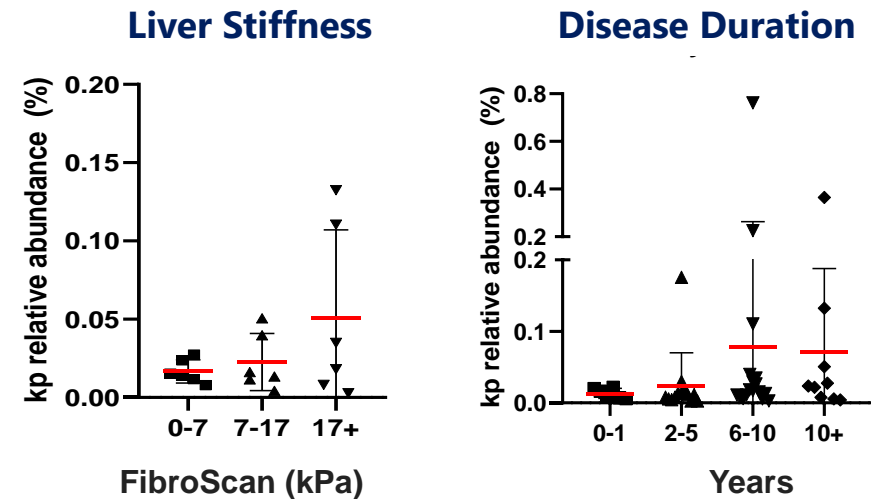
* qPCR-100ng DNA input, positive cutoff defined as > 10 copies

**50Gbp depth - positive cutoff defined as >0.01% *Kp* relative abundance

***5Gbp depth - positive cutoff defined as >0.01% *Kp* relative abundance

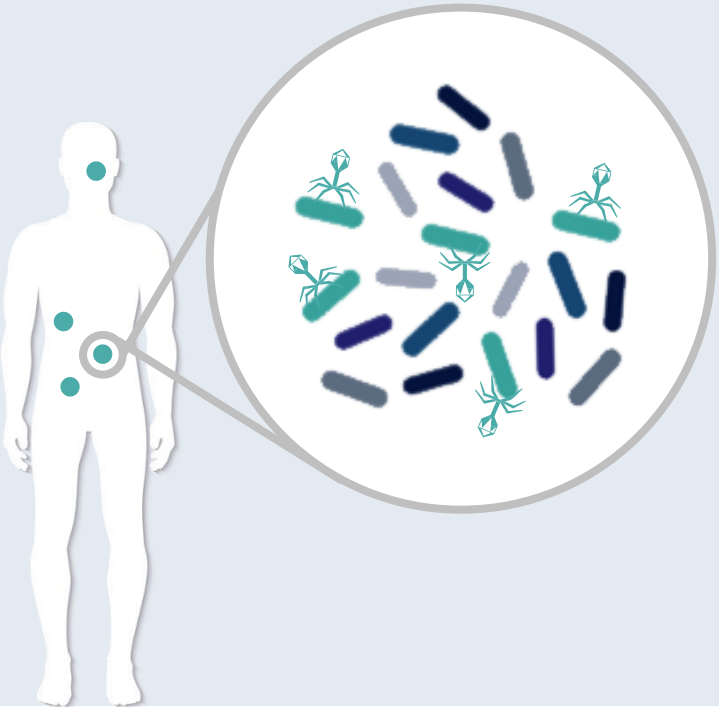
***Kp* abundance was also higher in PSC patients compared to healthy controls (qFDR = 3.64×10^{-07})**

Correlation to Fibrosis and Disease Duration



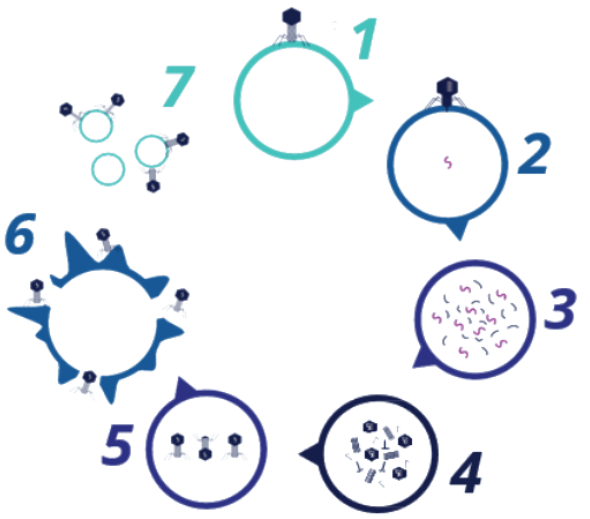
Phage • Nature's Precision Targeting Vector

Phage bind only to specific bacterial strains



Phage have an amplifying lifecycle

- 1 Locate
- 2 Inject
- 3 Infect
- 4 Multiply
- 5 Assemble
- 6 Eradicate
- 7 Seek



Phage Technology Platform – Designing a Phage Cocktail

Phage Hunting

- Sample sourcing
- Automated sample processing



Phage Engineering (SynBio)

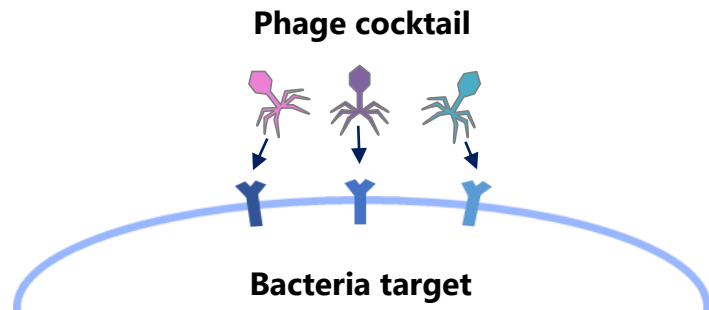
- Host range expansion
- Lysogenic to lytic
- Payload incorporation

Cocktail Optimization

Multi-dimensional optimization *in vitro* and *in vivo*: host range, biofilm, resistance, bioinformatic receptor analysis, toxic genes

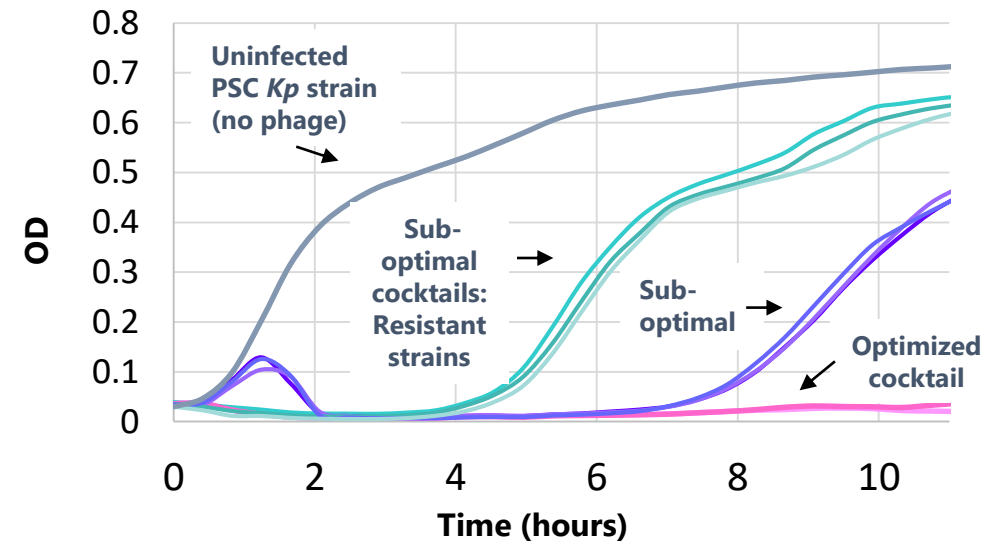
Designing a Phage Cocktail Targeting Pathobiont – *In-vitro* Results

How a Phage Cocktail Overcomes Resistance



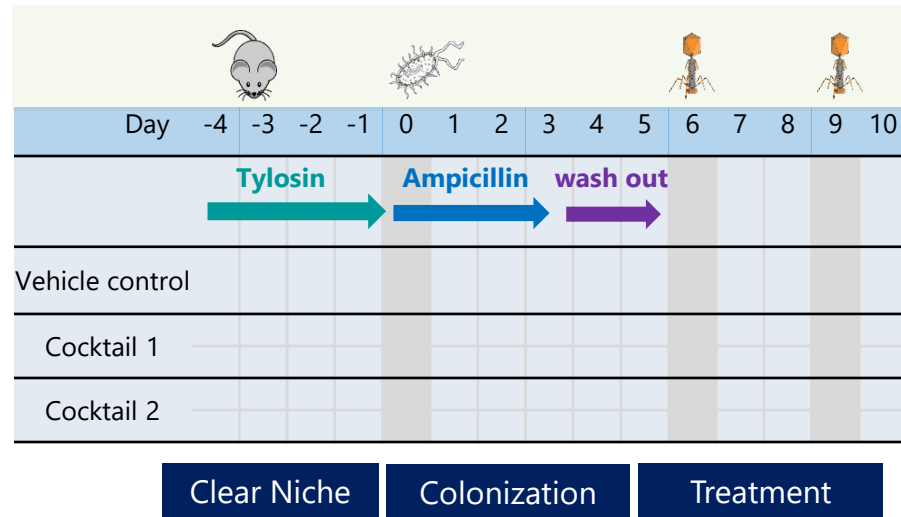
Phage cocktails are rationally optimized to prevent resistance by targeting multiple bacterial receptors and defense mechanisms

Infection Dynamics of Phage Cocktails (*in vitro*)

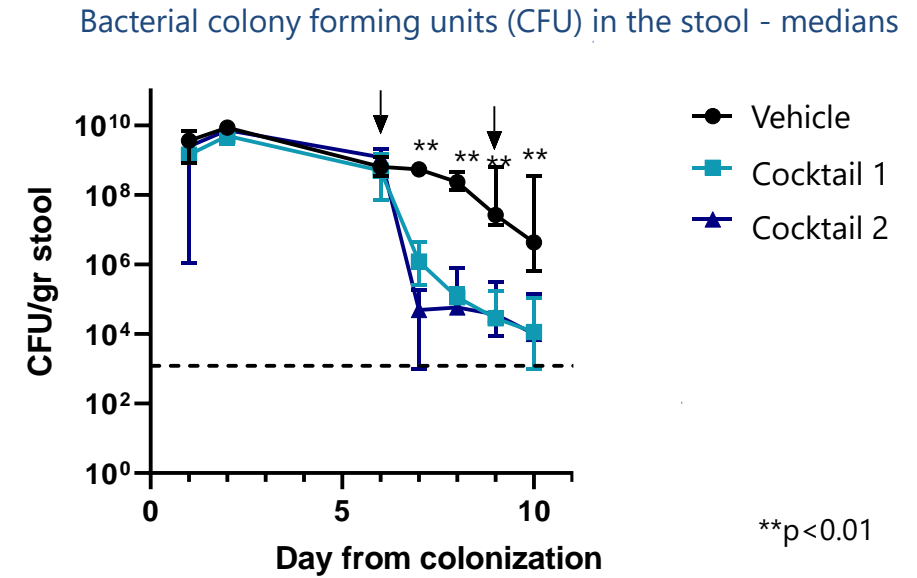


Phage Cocktails Efficiently Eradicated PSC *Kp* Strains *In-vivo*

Study Design



Results- Reduction of *Kp* bacterial colonies



Oral administration of phage reduced target bacterial load by 3-4 logs in the stool and by at least 2 logs in the mucosa of colonized animals and in the lymph-nodes

Conclusions

- *Klebsiella pneumoniae* confirmed as a novel pathobiont in PSC
- Clinical isolates of *Klebsiella pneumoniae* from PSC patients were found to be pro-inflammatory (Th17) and were able to induce epithelial barrier disruption
- *Klebsiella pneumoniae* is highly prevalent in PSC patients, and its presence is associated with increased severity and advanced stages of disease
- The *Kp* phage cocktail was effective in eradicating clinical *Kp* isolates in mouse models. The cocktail prevented the appearance of phage resistant mutant bacteria both *in vitro* and *in vivo*
- Collectively, these results support the role of *Kp* as a PSC pathobiont and establish the first steps in development of a rationally designed phage cocktail, which may provide a novel treatment approach for PSC patients

BiomX

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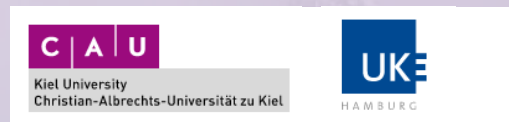
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Prof. Kanai
Prof. Honda



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Corinna Bang



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