



BAKTERİYOFAJLAR KLEBSİELLA

Bülent BOZDOĞAN

Aydın Adnan Menderes Üniversitesi

Tıp Fakültesi Tıbbi Mikrobiyoloji AD

Rekombinant DNA ve Rekombinant Protein Merkezi

REDPROM

KLİMİK KONGRESİ 26 NİSAN 2025

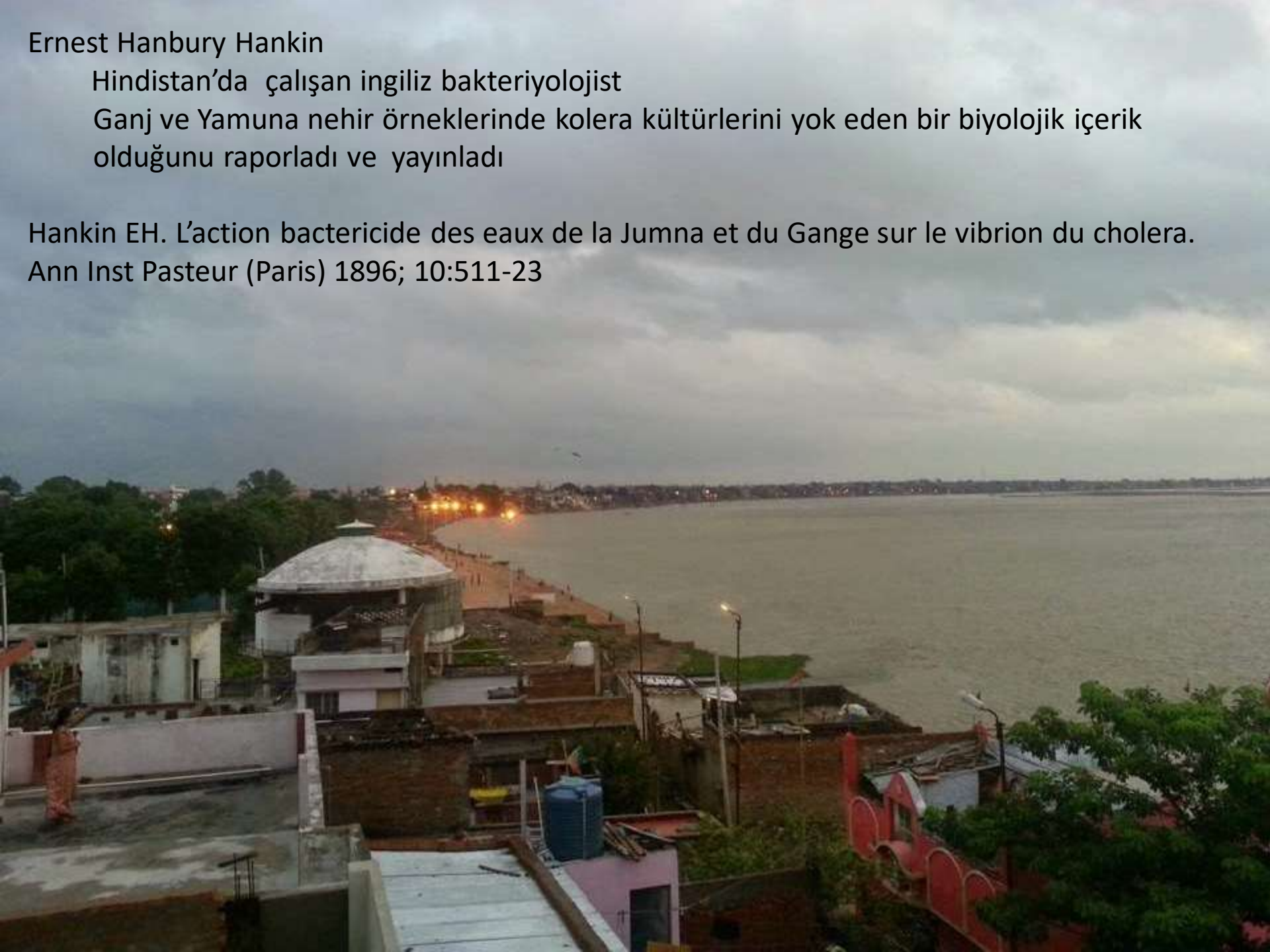
Ernest Hanbury Hankin

Hindistan'da çalışan ingiliz bakteriyolojist

Ganj ve Yamuna nehir örneklerinde kolera kültürlerini yok eden bir biyolojik içerik olduğunu raporladı ve yayınladı

Hankin EH. L'action bactericide des eaux de la Jumna et du Gange sur le vibron du cholera.

Ann Inst Pasteur (Paris) 1896; 10:511-23



- 10 Eylül 1917,
- Félix Hubert d'Herelle,
- *Comptes rendus de l'Academie des sciences*
- Yeni bir mikrop, bakterinin zorunlu hücre içi paraziti



d'Herelle F. Sur un microbe invisible antagoniste des bacilles dysentériques.
C R Acad Sci Paris 1917; 165:173-5

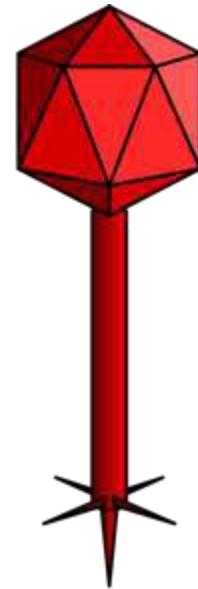
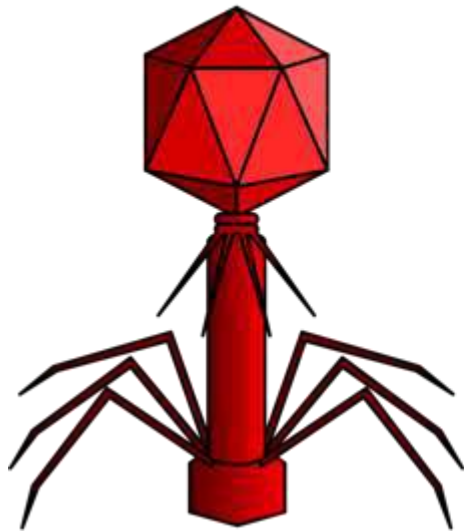
- 1927 yılında Asya'da kolera salgını
- Pencap'ta nüfusu 2000-3000 olan birkaç köyde profilaksi çalışması
 - 2 yöntem
 - Uygun dozu kişilere vermek
 - Su kaynaklarına uygulamak
 - Salgın 48 saatte sonlanır
- 8 kez NOBEL adayı
- 1934 – 1936 yılları arasında 3 şehirde faj üretim laboratuvarı
 - Kiev
 - Kharkov
 - Tiflis
- Antibiyotiklerin keşfi fajlara ilgiyi azaltır

Antibiyotik Direnci

- Günümüzde ilaç direnci nedeniyle ölüm 700 000/y
- Çoklu dirençli tüberküloza bağlı ölüm 230 000/y
- Artan sıklıkla tedavi edilemeyen enfeksiyonlar
 - Solunum sistemi enfeksiyonları
 - Cinsel yolla bulaşan enfeksiyonlar
 - İdrar yolu enfeksiyonları
- Önlem alınmazsa 2050 de 10 milyon/yıl ölüm

SINIFLANDIRMA

- Caudovirales Takımı (%96)
 - Myoviridae (%24,5)
 - Podoviridae (%13,9)
 - Siphoviridae (%61,7)



Bakteriyofajların Yaşam Döngüsü

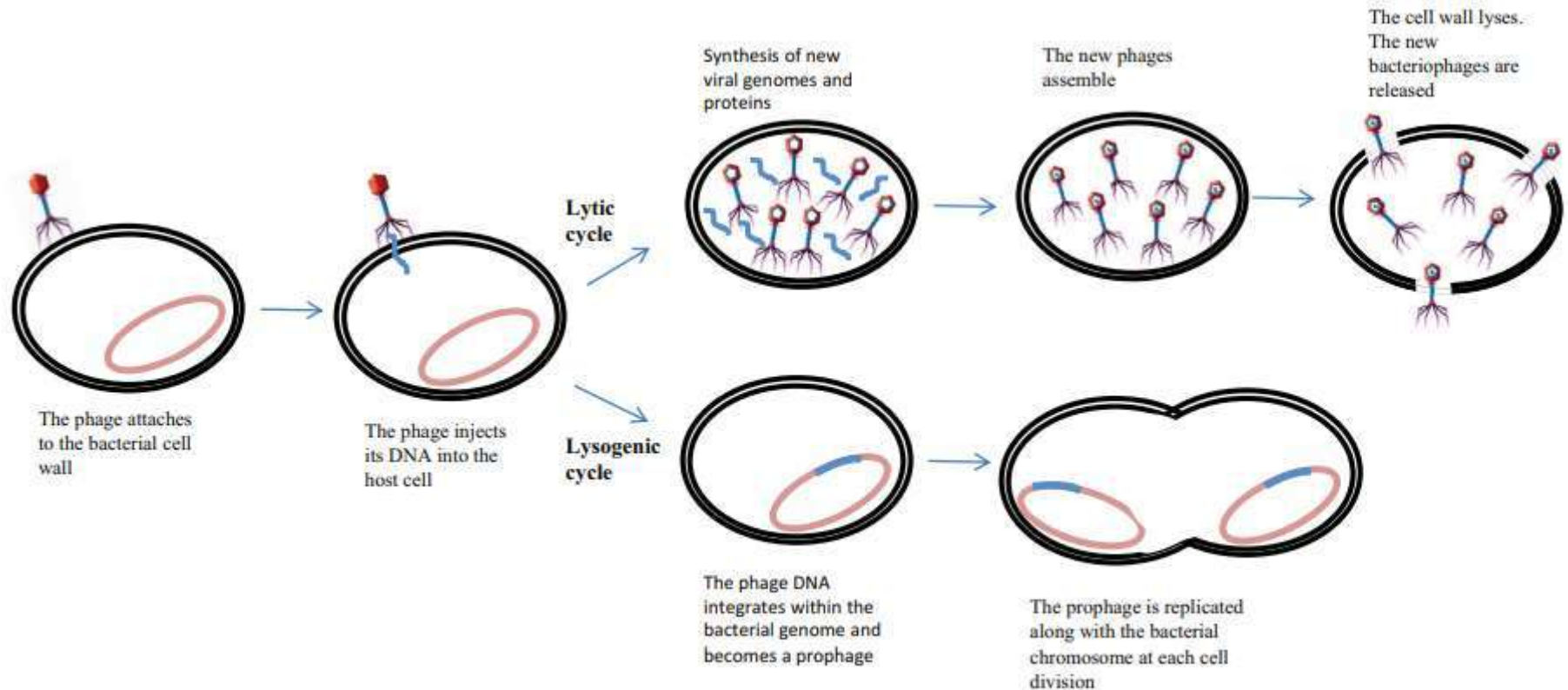
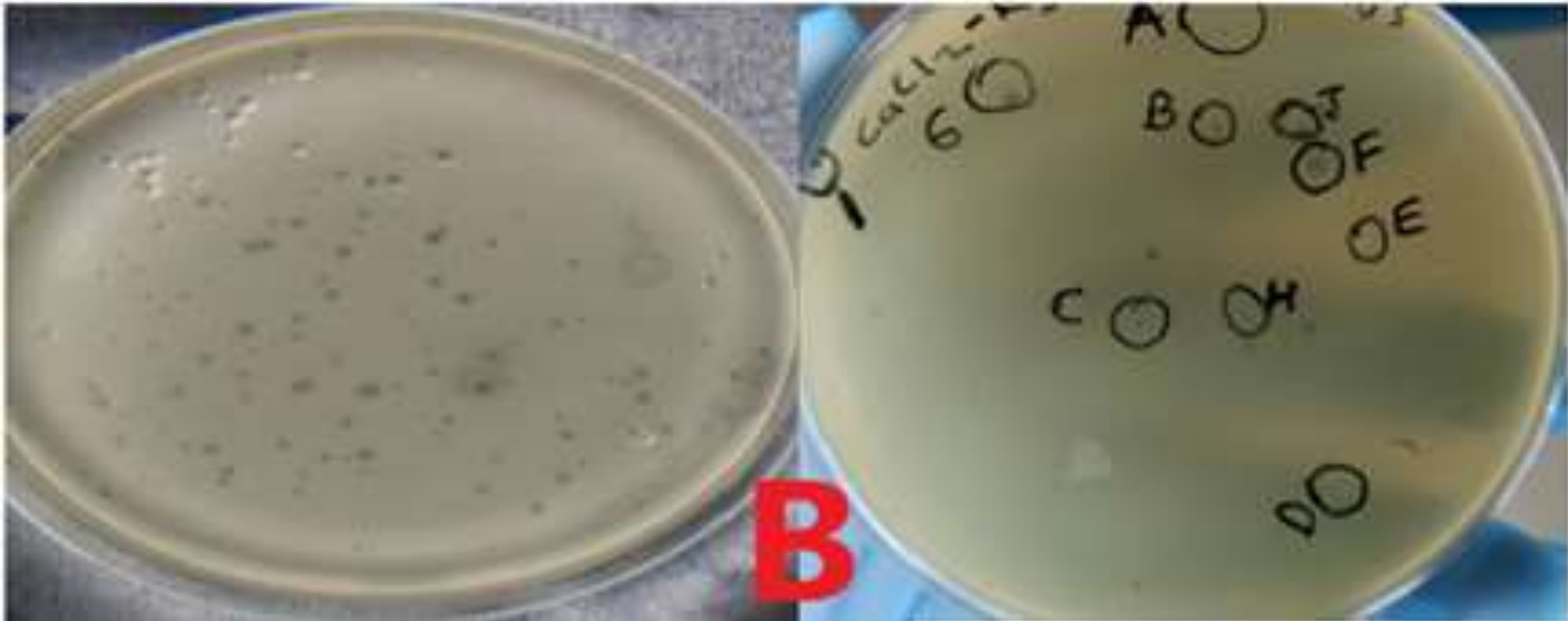
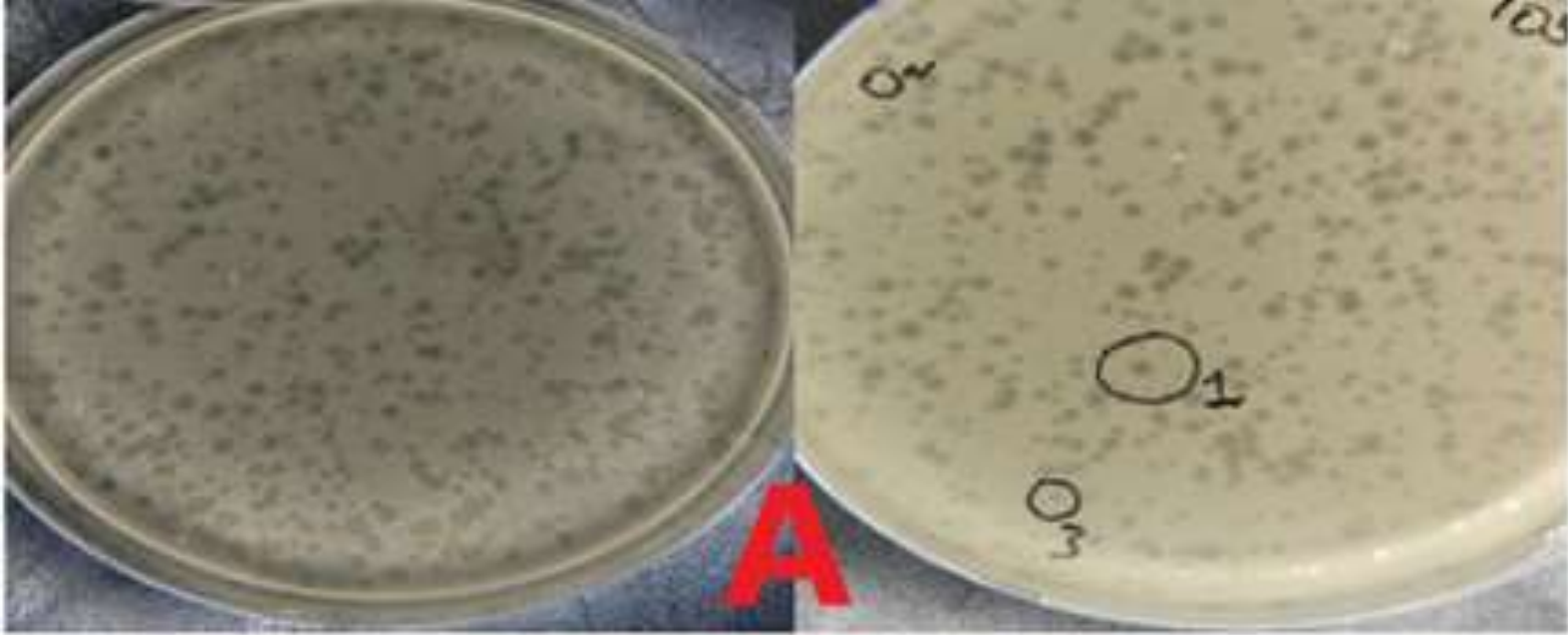
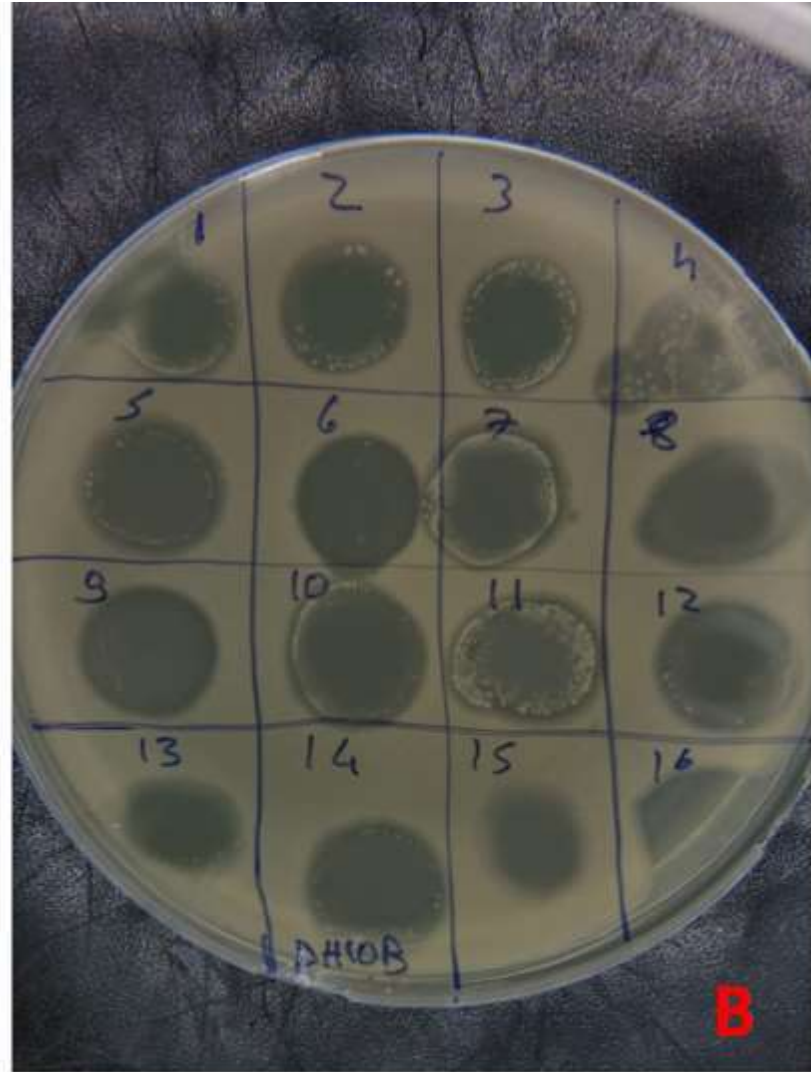
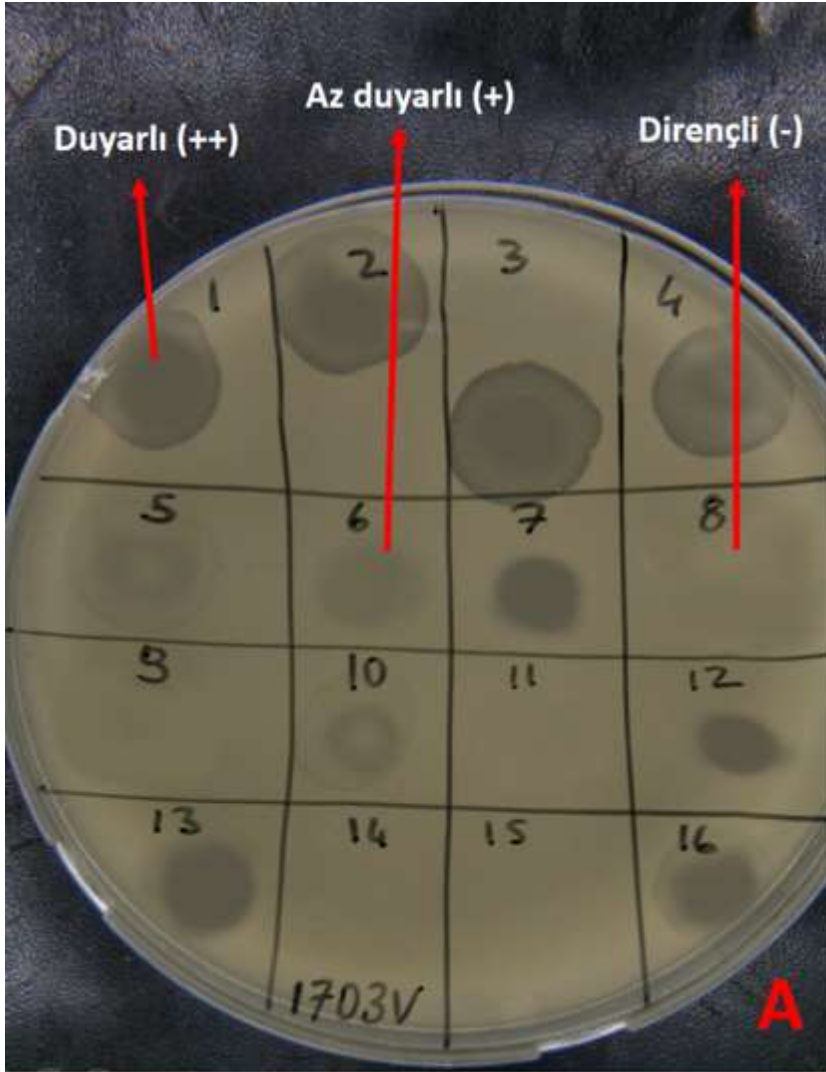


Fig. 1. Overview of the main differences between the lytic and the lysogenic bacteriophage life cycle.

FAJ ÇALIŞMALARI: İkili Agar



Phagogram



Spot Test Sonucu Bakteriyofajların Oluşturduğu Plaklar. Kerim Karaynir Tez

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Steffanie Strathdee: 'Phages have evolved to become perfect predators of bacteria'

Zoë Corbyn
Sat 15 Jun 2019 16:00 BST

f t e 343 114



▲ Steffanie Strathdee and her husband, Thomas Patterson. His picture shows the superbug that nearly killed him; hers the phage that saved his life. Photograph: Courtesy of Steffanie Strathdee / UC San Diego Health

Akut pankreatit, etken *Acinetobacter baumannii* ABD'de ilk IV faj tedavi uygulaması

<https://www.theguardian.com/science/2019/jun/15/steffanie-strathdee-phage-therapy-interview-perfect-predator>

Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant *Acinetobacter baumannii* Infection

Robert T. Schooley, Biswajit Biswas, Jason J. Gill, Adriana Hernandez-Morales, Jacob Lancaster, Lauren Lessor, Jeremy J. Barr, Sharon L. Reed, Forest Rohwer, Sean Benler, Anca M. Segall, Randy Taplitz, Davey M. Smith, Kim Kerr, Monika Kumaraswamy, Victor Nizet, Leo Lin, Melanie D. McCauley, Steffanie A. Strathdee, Constance A. Benson, Robert K. Pope, Brian M. Leroux, Andrew C. Picel, Alfred J. Mateczun, Katherine E. Cilwa, James M. Regeimbal, Luis A. Estrella, David M. Wolfe, Matthew S. Henry, Javier Quinones, Scott Salka, Kimberly A. Bishop-Lilly, Ry Young, Theron Hamilton

TABLE 3 Composition and details of administration of each phage cocktail

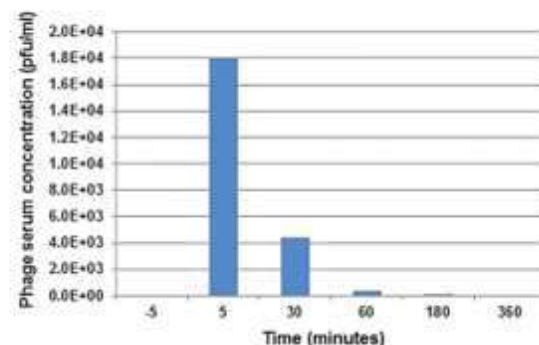
Phage cocktail	Cocktail composition	Route of administration	Duration of administration	Therapeutic dose
ΦPC	AC4, C1P12, C2P21, C2P24	Intracavitary ^a	18 wks, beginning day 109	NA ^b
ΦIV	AB-Navy1, AB-Navy4, AB-Navy71, AB-Navy97	Intravenous	16 wks, beginning day 111	5 × 10 ⁹ PFU
ΦIVB	AB-Navy71, AbTP3Φ1	Intravenous	2 wks, beginning day 221	5 × 10 ⁹ PFU

^aThrough percutaneous catheters draining the pseudocyst cavity, the gallbladder, and a third intra-abdominal cavity.

^bNA, not applicable (used for intracavitary washes).

TABLE 1 Bacterial isolates from this study

Strain	Isolation date	Site of isolation	Phenotype
TP1	10 March 2016	Pancreatic drainage of patient	Capsulated, susceptible to ΦIV
TP2	21 March 2016	Pancreatic drainage of patient	Capsulated, reduced susceptibility to ΦIV
TP3	23 March 2016	Pancreatic drainage of patient	Unencapsulated, resistant to ΦIV



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Phage therapy: 'Viral cocktail saved my daughter's life'

By James Gallagher
Health and science correspondent, BBC News

Q 8 May 2019



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Bacteria-killing viruses known as phages offer hope of solution to antibiotic resistance

Hannah Devlin *Science correspondent*

@hannahdev

Wed 8 May 2019 18.05 BST



3,066



▲ Jo Holdaway (L) with her daughter Isabelle who almost died after a lung transplant left her with an intractable infection. Photograph: Graham Fiddall/The Guardian

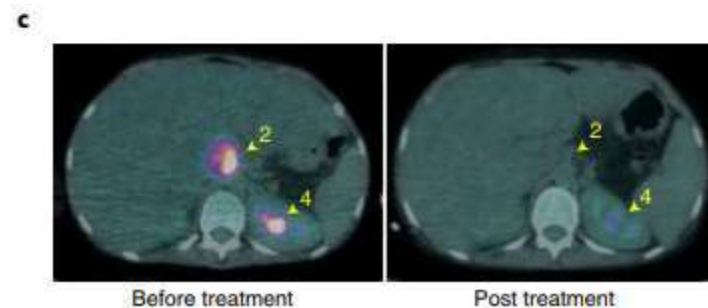
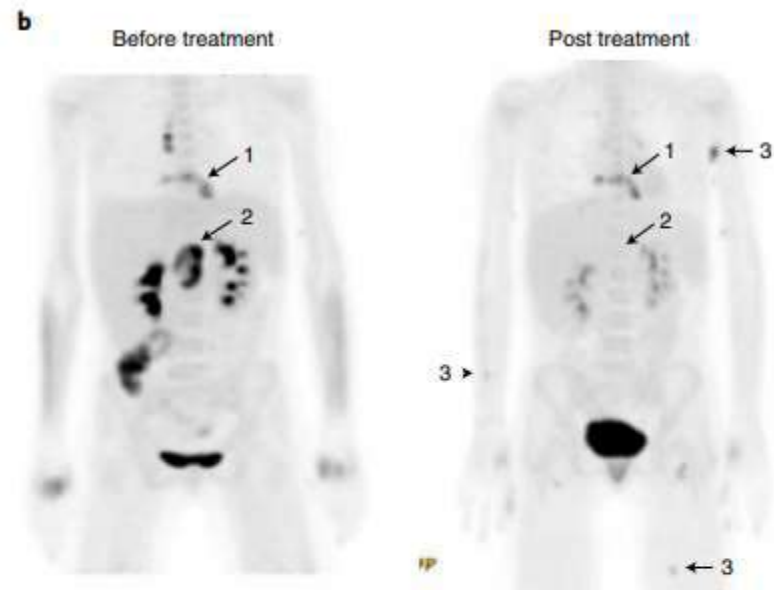
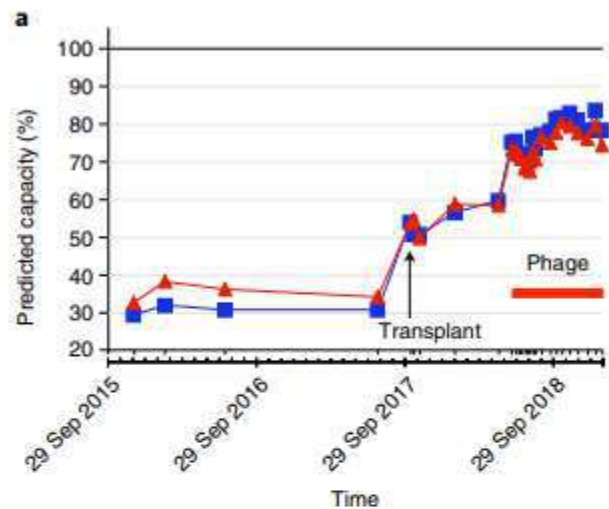
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Bacterial inoculation
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*Proteus
mirabilis*



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aeruginosa*



*Staphylococcus
spp.*



Selection
and bulk production
of bacteriophages

Application
of a bacteriophage
to the wound





Case Report

Resolving Digital Staphylococcal Osteomyelitis Using Bacteriophage—A Case Report

Randolph Fish ¹, Elizabeth Kutter ^{2,*}, Daniel Bryan ², Gordon Wheat and Sarah Kuhl ⁴



(a)



(b)



11 Mayis 2015

23 Mart 2015

Figure 1. Images of the patient's ulcer on presentation. (a) Top view of foot. (b) View of ulcer at the distal tip.

Etken MSSA

Eliava faj kokteyli

Antibiotics 2018, 7, 87; doi:10.3390/antibiotics7040087

Case Report: Arthroscopic “Debridement Antibiotics and Implant Retention” With Local Injection of Personalized Phage Therapy to Salvage a Relapsing *Pseudomonas Aeruginosa* Prosthetic Knee Infection

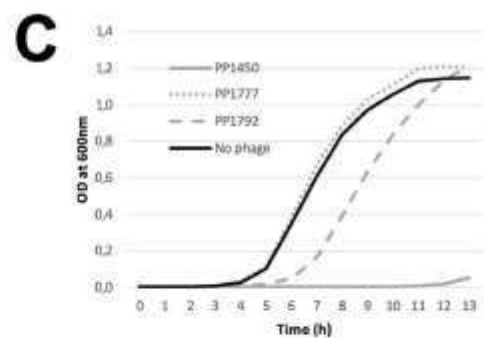
Frontiers in Medicine, 05 May 2021
| <https://doi.org/10.3389/fmed.2021.569159>

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Richard V. Goering,

Tristan Ferry^{1,2,3,4*}, Camille Kolenda^{2,3,4,5}, Cécile Batailler^{2,3,6}, Romain Gaillard^{3,6},
Claude-Alexandre Gustave^{2,3,4,5}, Sébastien Lustig^{2,3,6}, Cindy Fevre⁷, Charlotte Petitjean⁷,
Gilles Leboucher⁸, Frédéric Laurent^{2,3,4,5} and the Lyon BJL Study group



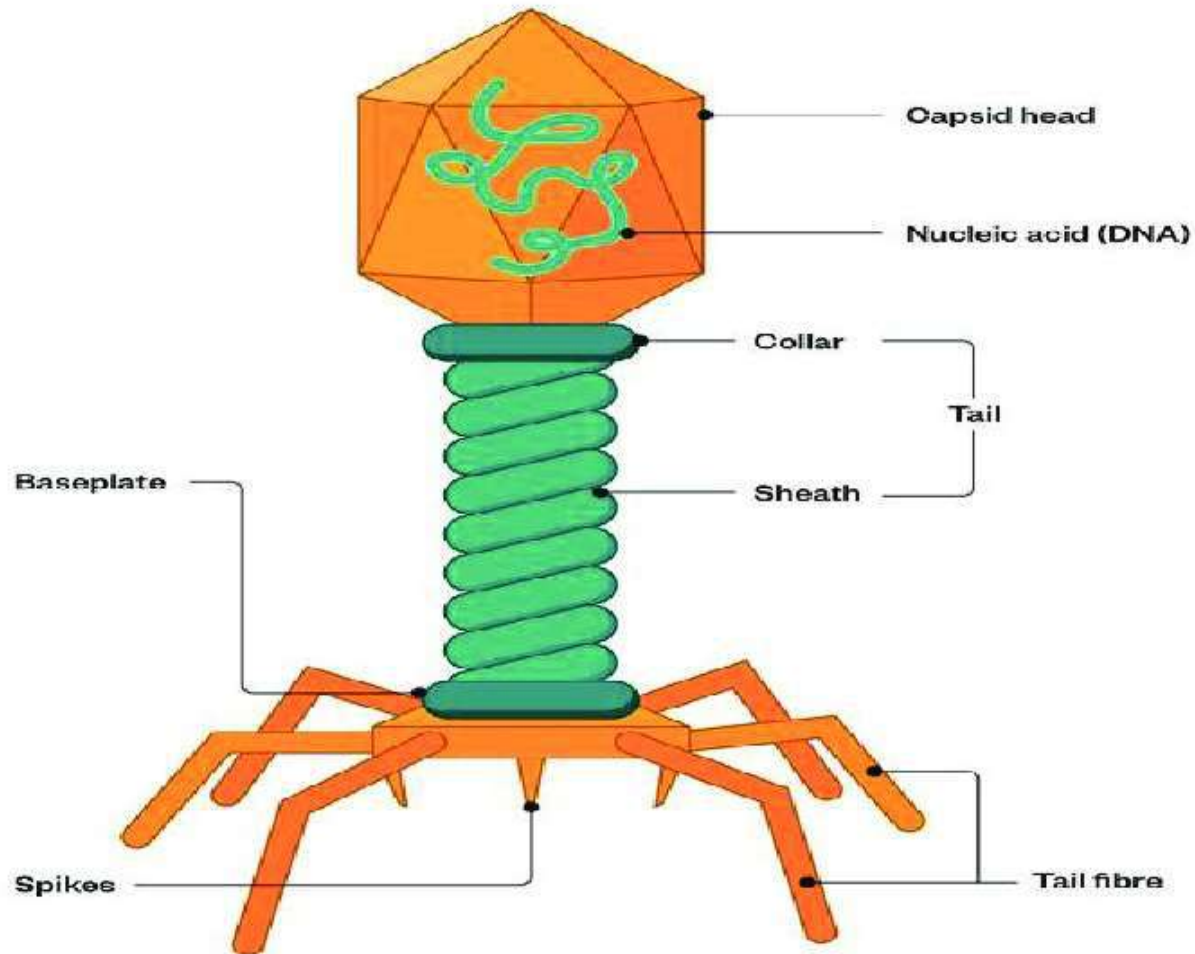
D

	PP1450	PP1777	PP1792
EOP	2.0×10^{-6}	4.0×10^{-6}	0
MCL _{PP1450}	1.0×10^7	1.7×10^8	9.3×10^8



88 yaşında tekrarlayan
diz protez enfeksiyonu
Kokteyl 3 faj 10^9 pfu/ml
Artroskopiyle 33cc

- Antibiyotik tedavisi
- 1 yıl sonra total iyileşme



Ozcan et al. 2023 Bacteriophage induction and application in aquatic products in book PROGRESS IN AQUACULTURE Orient Publications



Metagenomic analysis of wastewater phageome from a University Hospital in Turkey

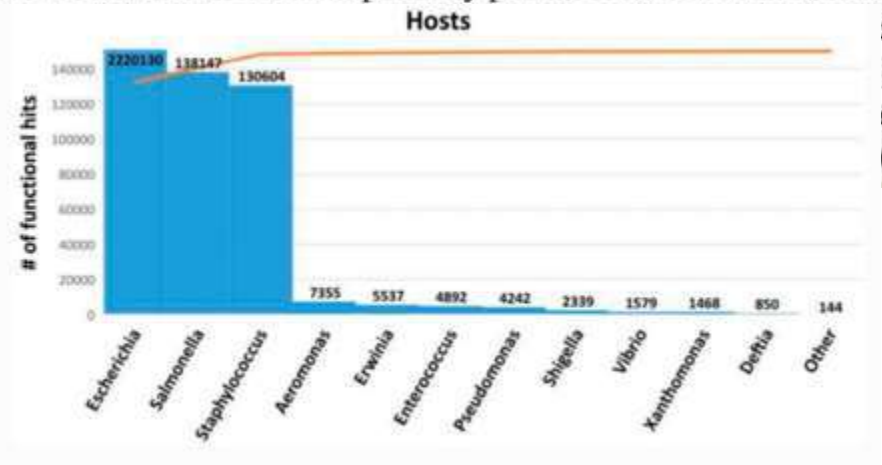
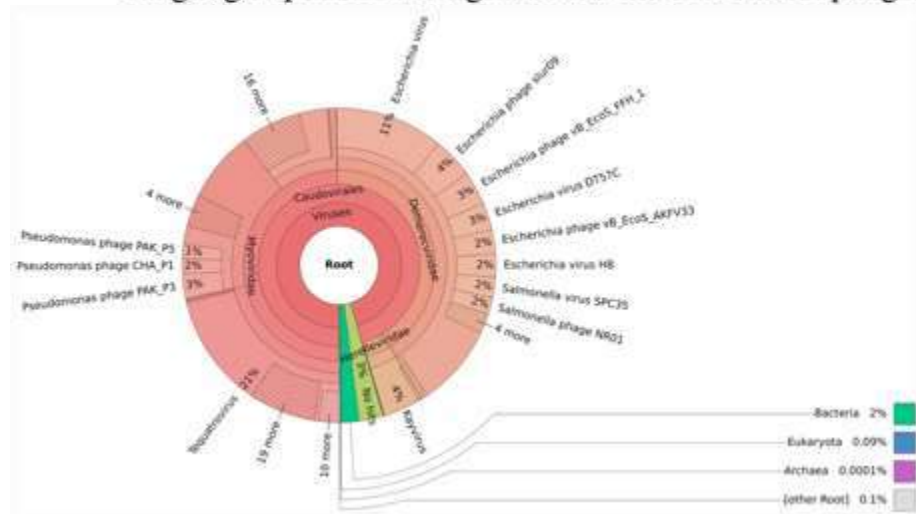
Hanife Salih¹ · Abdulkarim Karaynir¹ · Melis Yalcin¹ · Erman Oryasin^{1,2} · Can Holyavkin³ · Gamze Basbulbul^{1,4} · Bulent Bozdogan^{1,5}

Received: 17 March 2022 / Accepted: 8 May 2022 / Published online: 30 May 2022

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Abstract

Phage DNA analysis gives opportunity to understand living ecosystem of the environment where the samples are taken. In the present study, we analyzed phage DNA obtained from wastewater sample of university hospital sewage. After filtration, long high-speed centrifugation was done to collect phages. DNA was extracted from pellet by phenol chloroform extraction





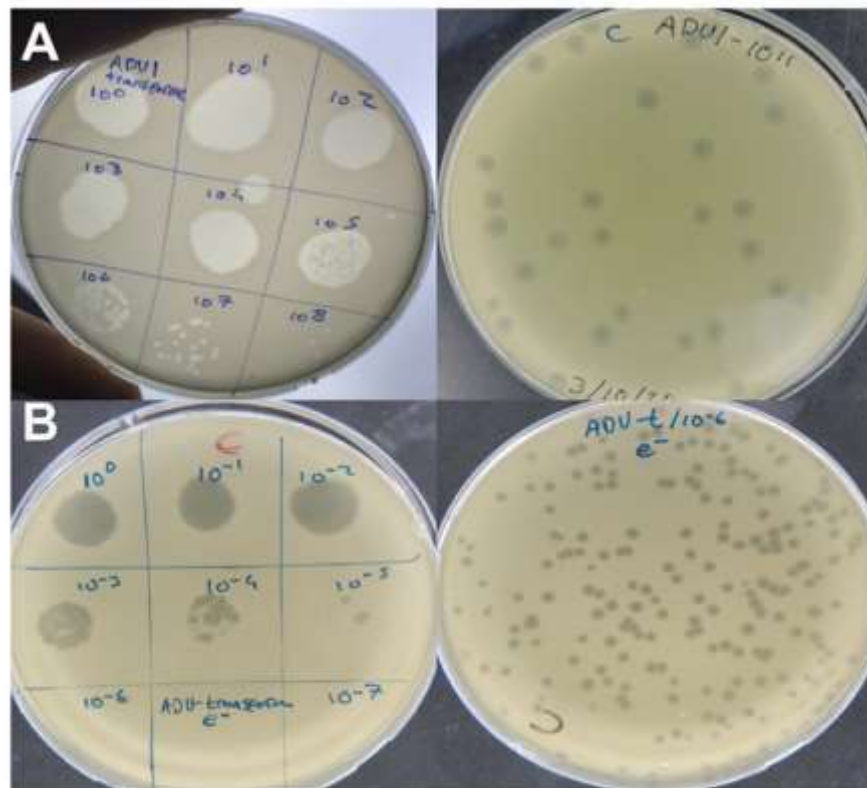
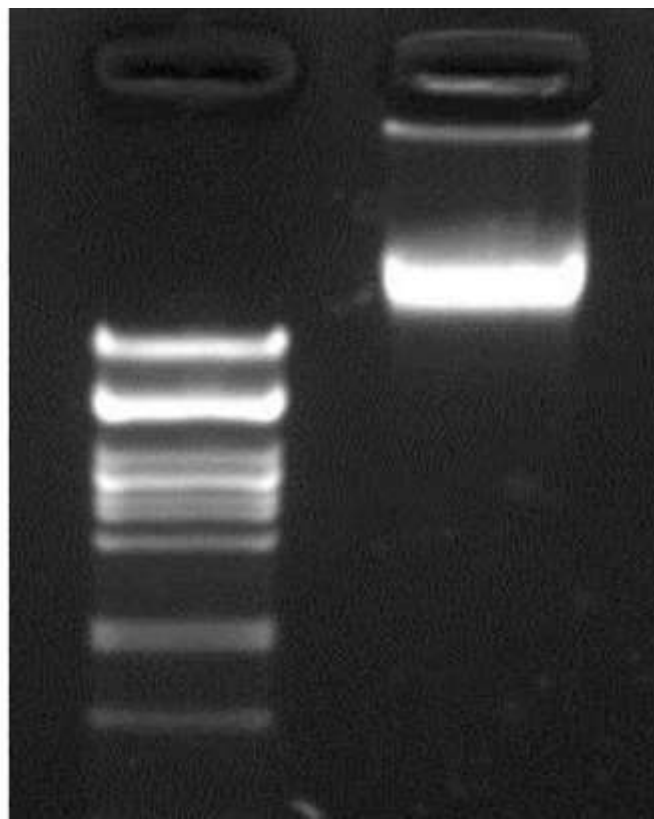
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Environmental DNA transformation resulted in an active phage in *Escherichia coli*

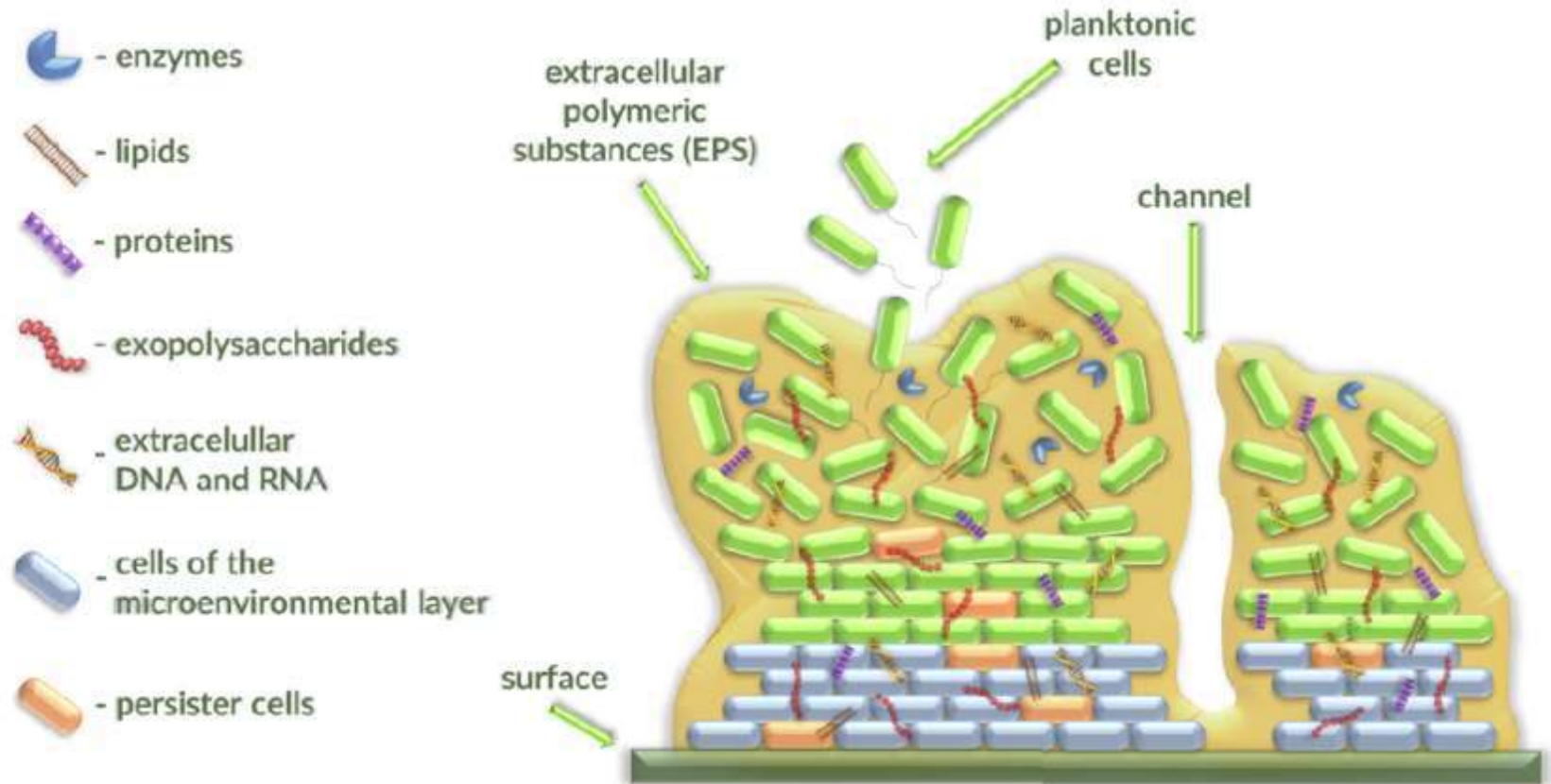
PLOS ONE |
<https://doi.org/10.1371/journal.pone.0292933>
October 13, 2023

Abdulkerim Karaynir¹, Bülent Bozdoğan^{1,2}, Hanife Salih Doğan^{1*}

1 Recombinant DNA and Recombinant Protein Center (REDPROM), Aydın Adnan Menderes University, Aydın, Türkiye, **2** Medical Faculty, Department of Medical Microbiology, Aydın Adnan Menderes University, Aydın, Türkiye



Phage and Biofilm



DNA, RNA, protein, lipid, enzymes in biofilm structures. *Extracellular polymeric substances (EPSs)*. From Topka-Bielecka et al *Antibiotics* 2021, 10(2), 175

Strategies to fight against biofilms



Opinion

Improving Phage-Biofilm In Vitro Experimentation

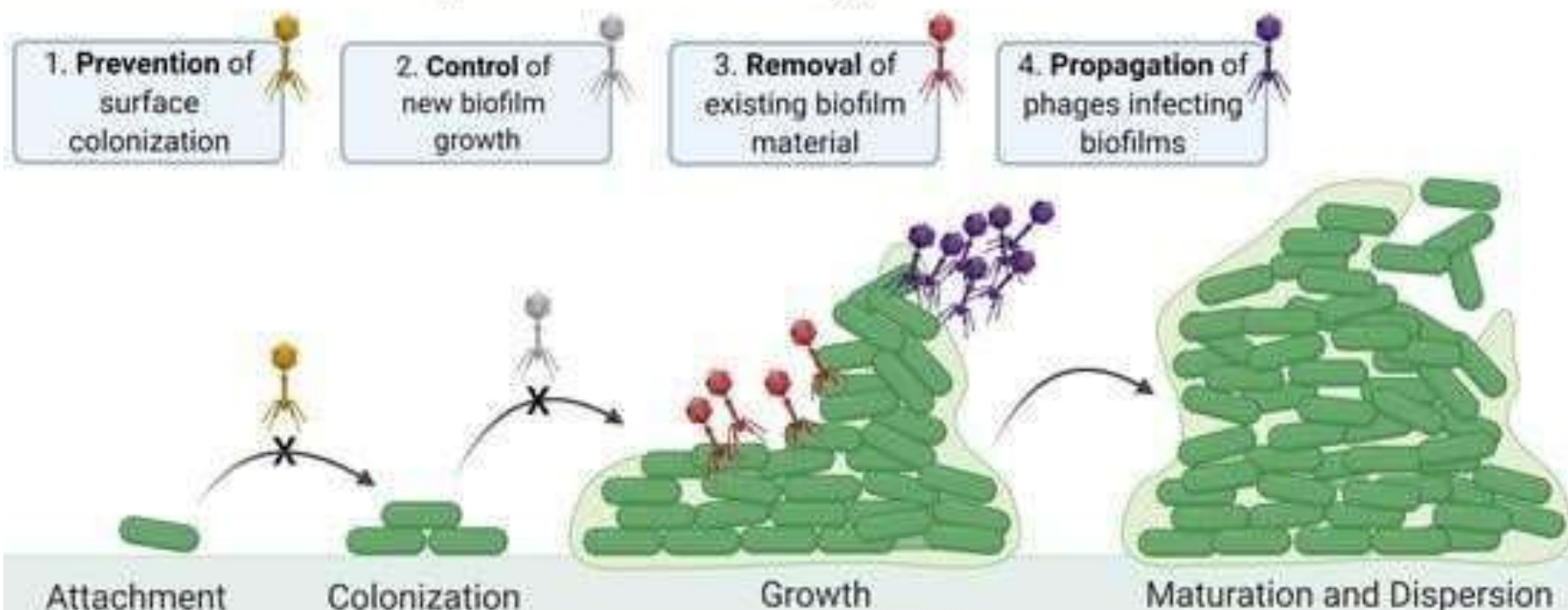
Stephen T. Abedon ^{1,*},, Katarzyna M. Danis-Włodarczyk ^{2,†}, Daniel J. Wozniak ^{1,2} and Matthew B. Sullivan ^{1,3}

¹ Department of Microbiology, The Ohio State University, Columbus, OH 43210, USA; wozniak.1@osu.edu (D.J.W.); sullivan.948@osu.edu (M.B.S.)

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³ Department of Civil, Environmental and Geodetic Engineering, The Ohio State University, Columbus, OH 43210, USA

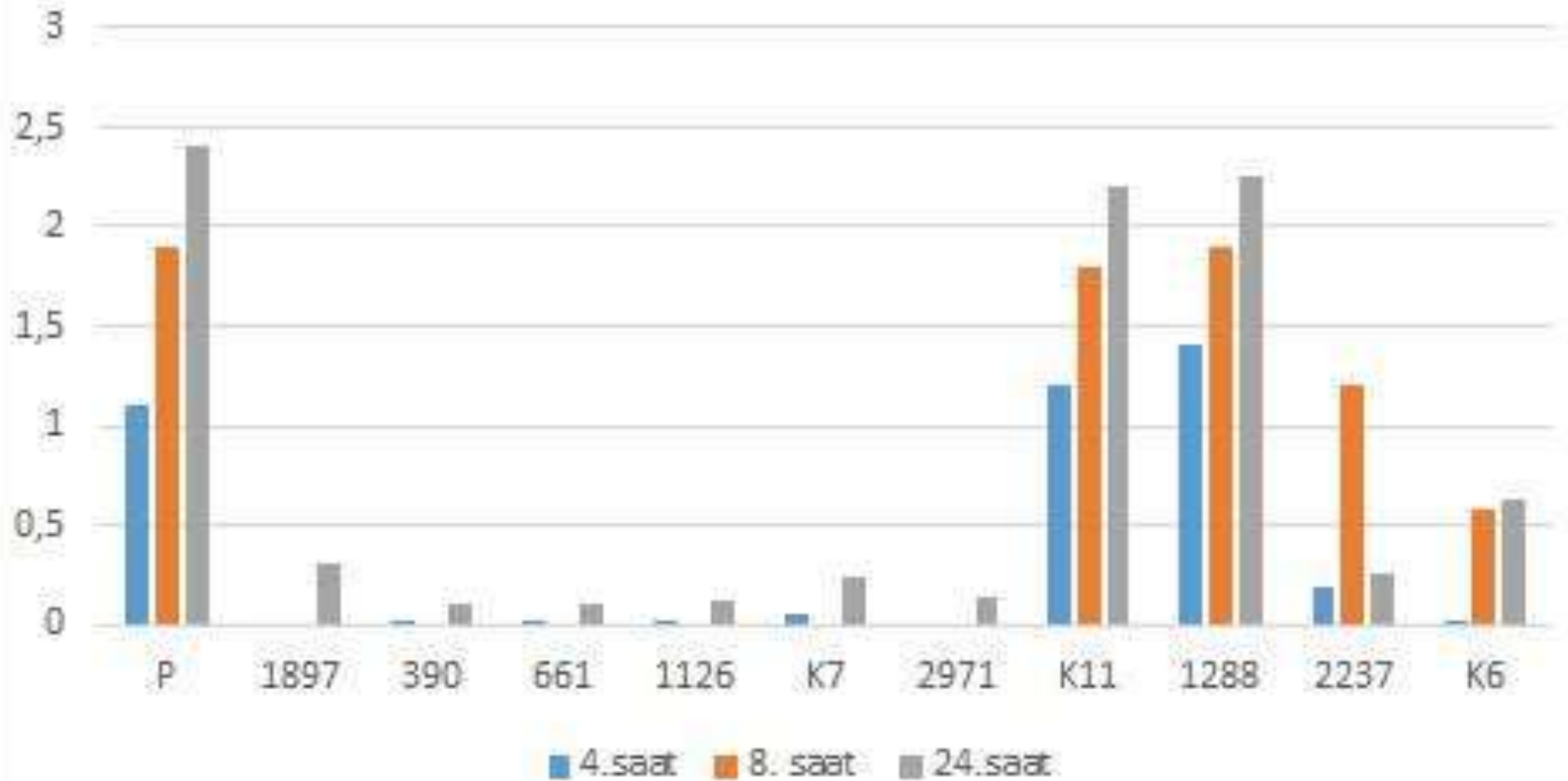
Different Aspects of Phage-Biofilm Interactions



Different Aspects of Biofilm Development

Pseudomonas Phages and Biofilm

PPA4





Isolation and characterization of Brochothrix phage ADU4

Abdulkerim Karaynir^a, Hanife Salih^a, Bülent Bozdoğan^{a,b}, Özgür Güçlü^{a,c}, Dilek Keskin^{a,d,*}

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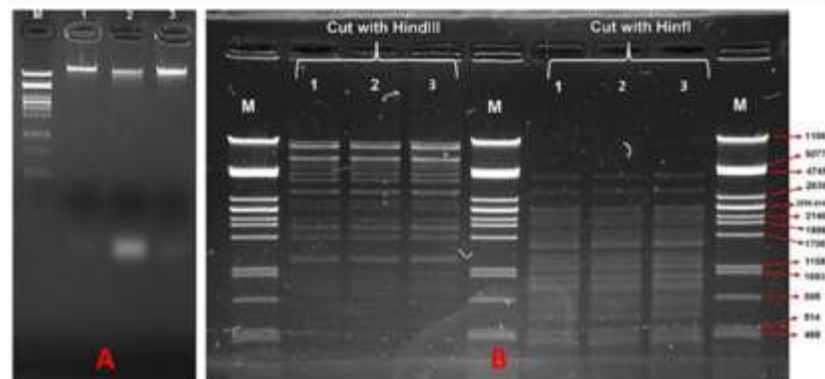
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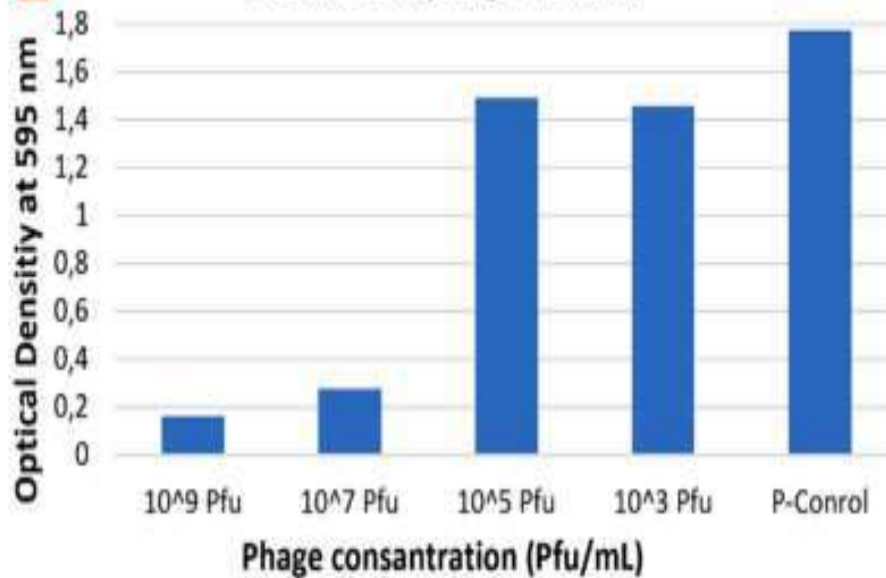
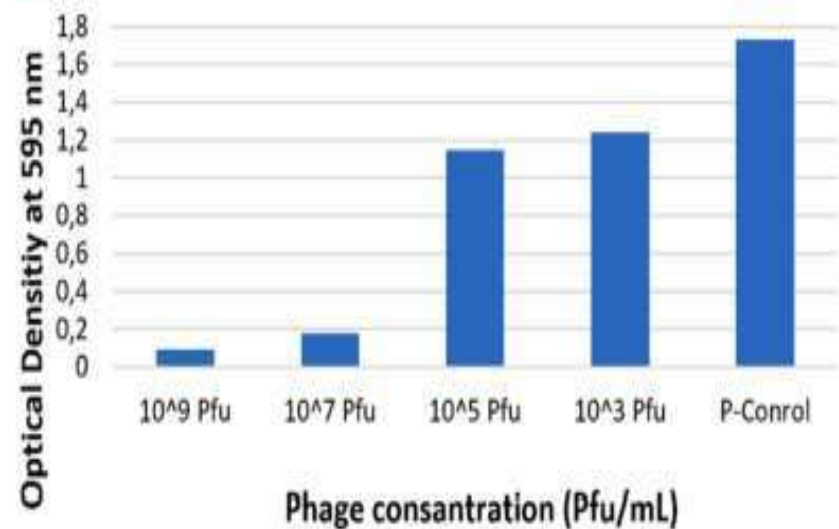
Keywords:

Brochothrix thermosphacta
Bacteriophage

ABSTRACT

B. thermosphacta is a psychrotrophic bacterium that often forms the predominant part of the spoilage microflora of aerobically and anaerobically stored meats. Bacteriophages are natural enemies of bacteria and their potential for use in environmentally friendly biocontrol of specific pathogens in food is being intensively studied. In this



B**Biofilms on phage-treated****C****Biofilm Prevention**



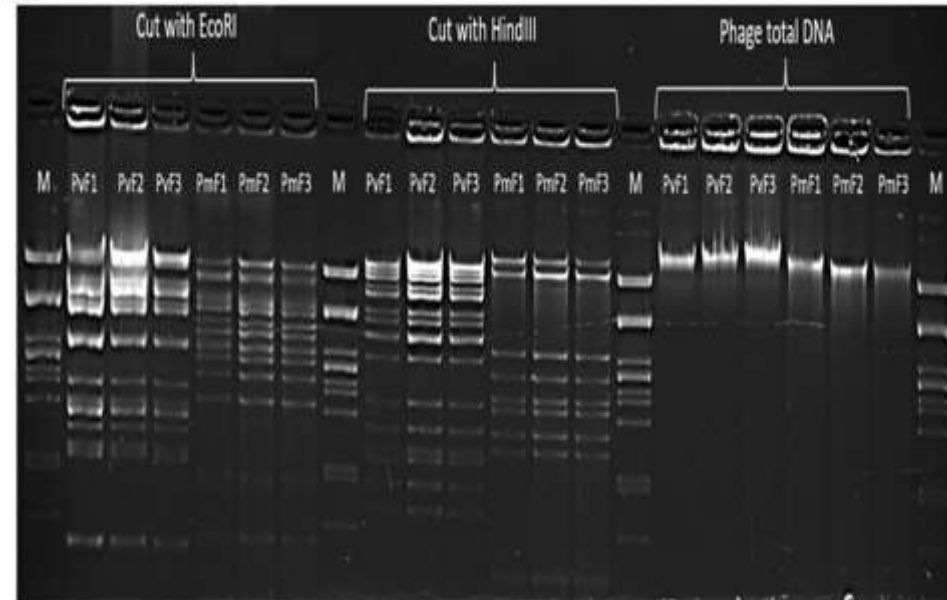
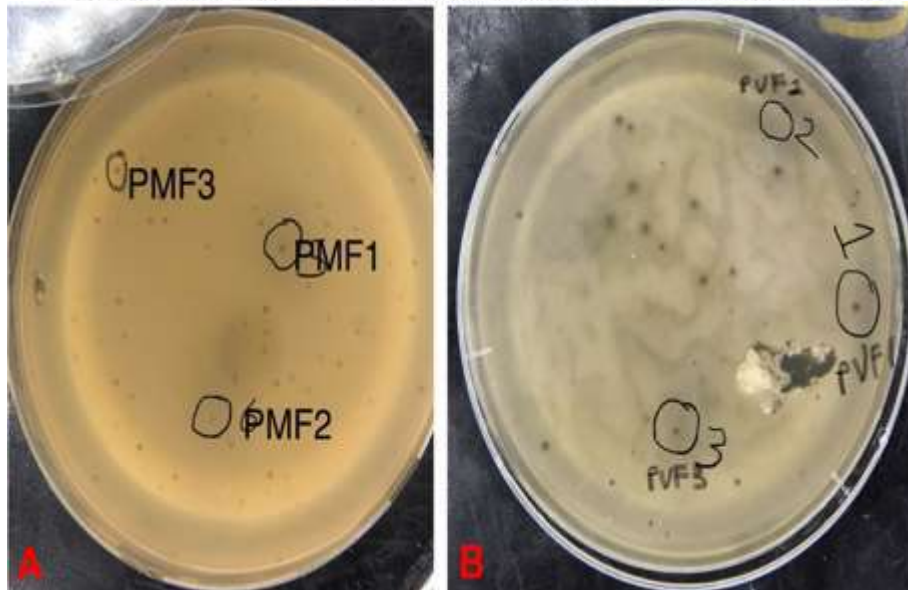
Characterization, genome analysis and antibiofilm efficacy of lytic *Proteus* phages RP6 and RP7 isolated from university hospital sewage

Sahd Ali^{a,*}, Abdulkerim Karaynir^{a,1}, Hanife Salih^a, Serkan Öncü^b, Bülent Bozdoğan^{a,c}

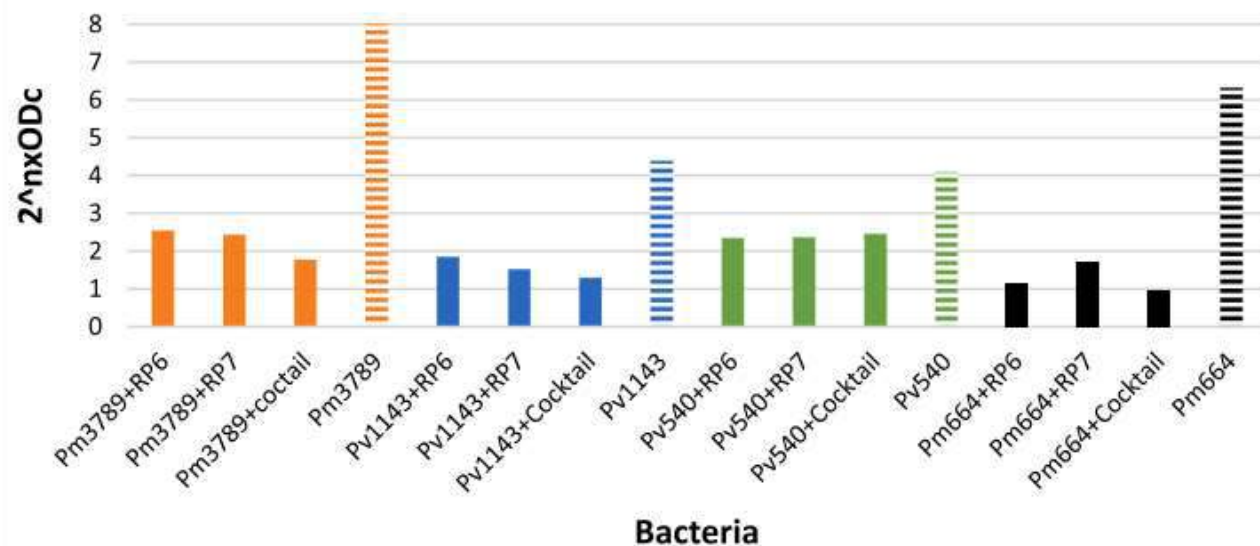
^a Recombinant DNA and Recombinant Protein Center (REDPROM), Aydın Adnan Menderes University, Türkiye

^b Medical Faculty, Department of Infectious Diseases and Clinical Microbiology, Aydın Adnan Menderes University, Türkiye

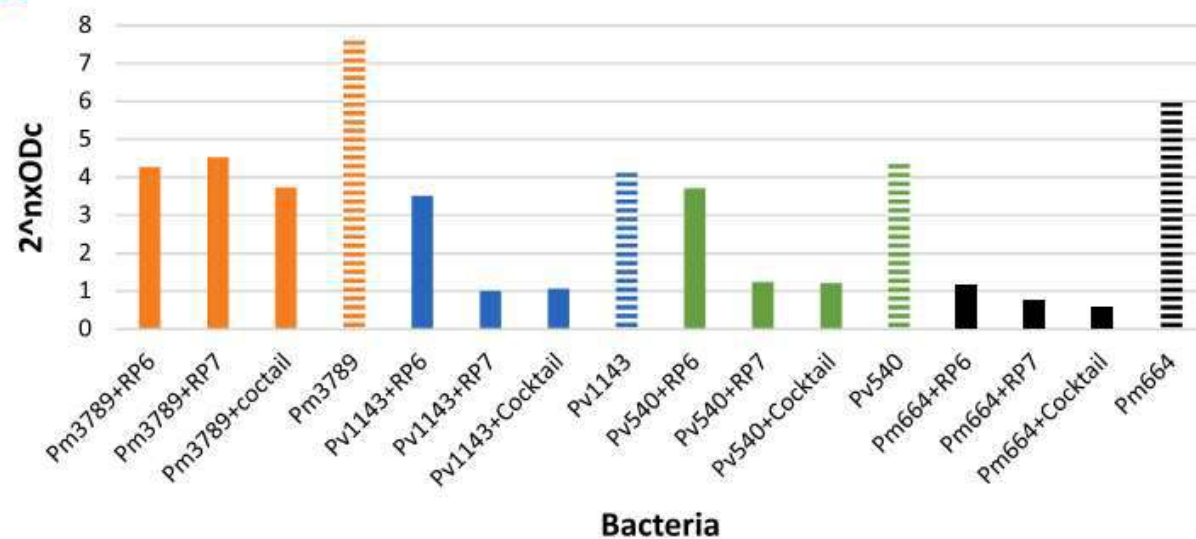
^c Medical Faculty, Department of Medical Microbiology, Aydın Adnan Menderes University, Türkiye



A Biofilm-Prevention



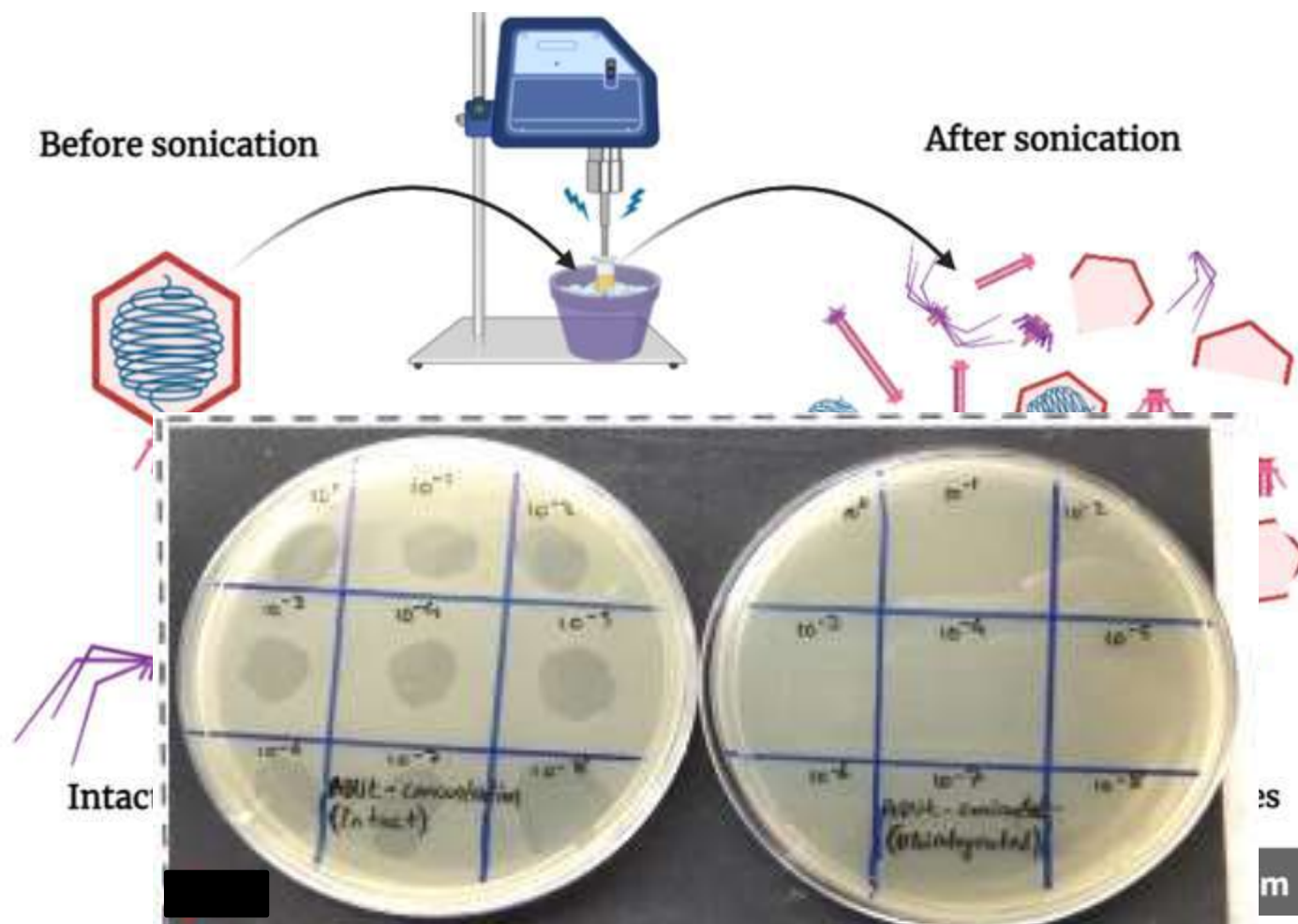
B Biofilm-Eradication





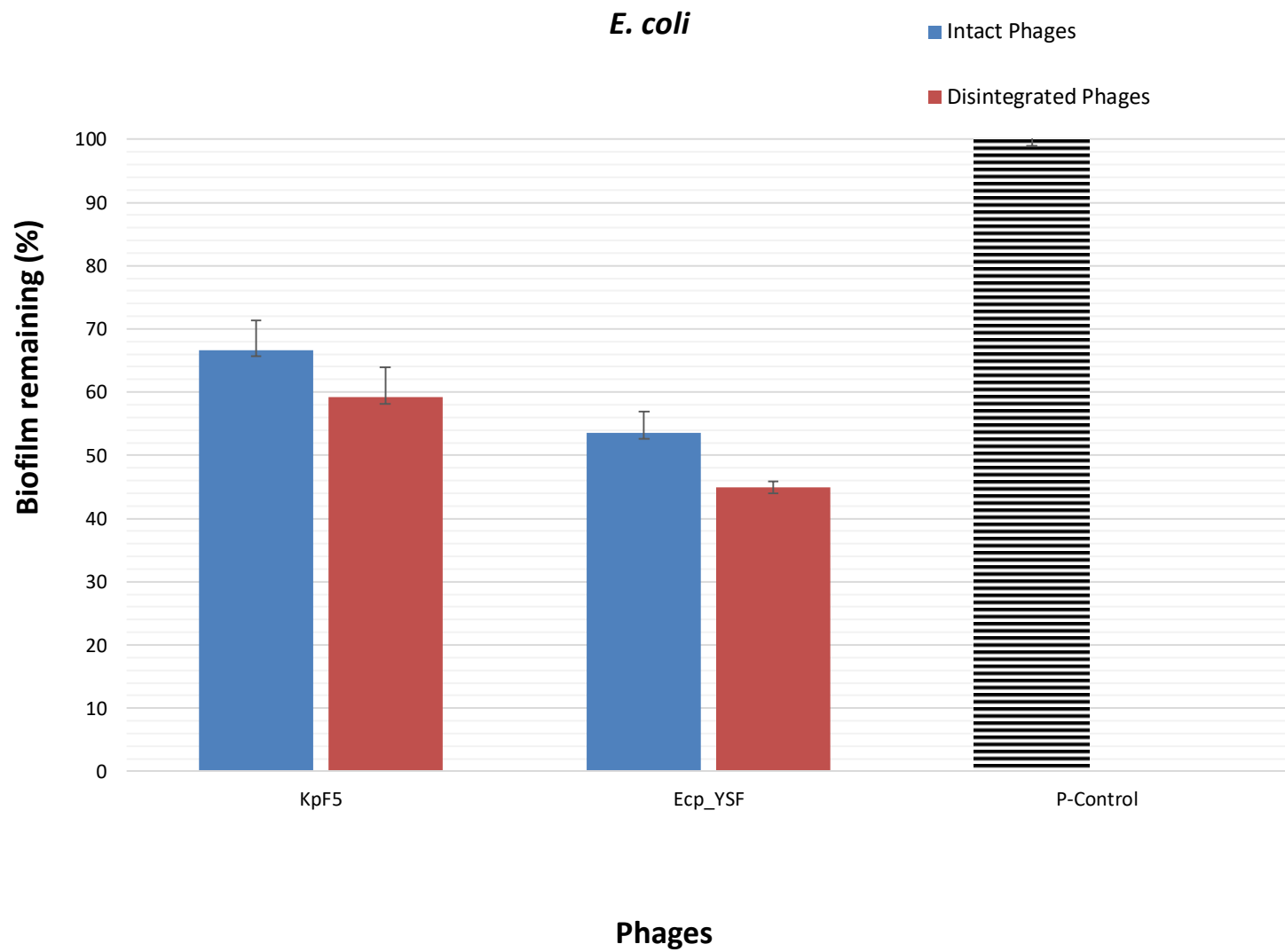
Degradation of Preformed Gram-Positive and Gram-Negative Bacterial Biofilms Using Disintegrated and Intact Phages

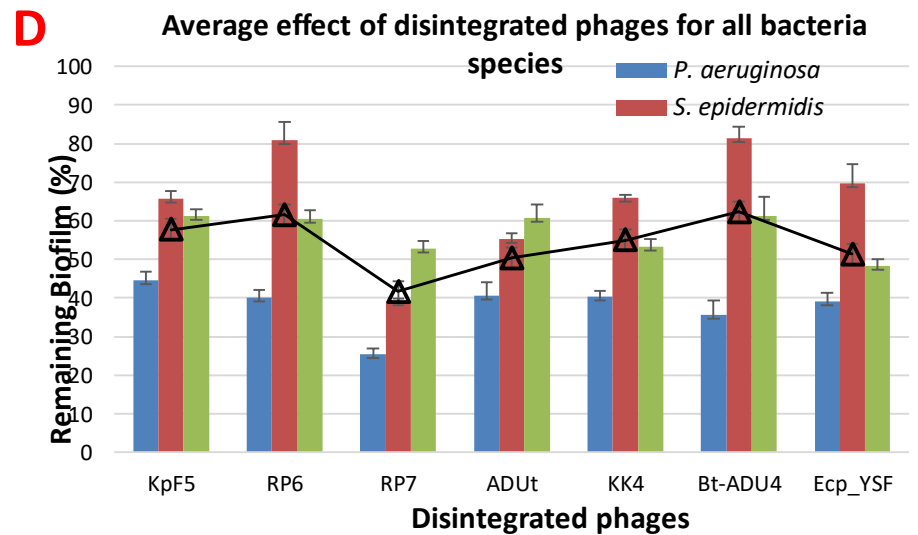
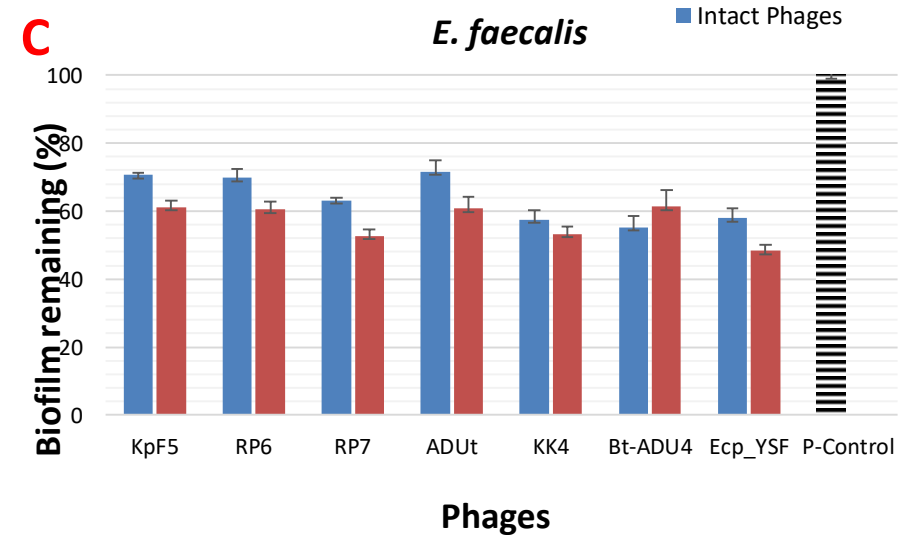
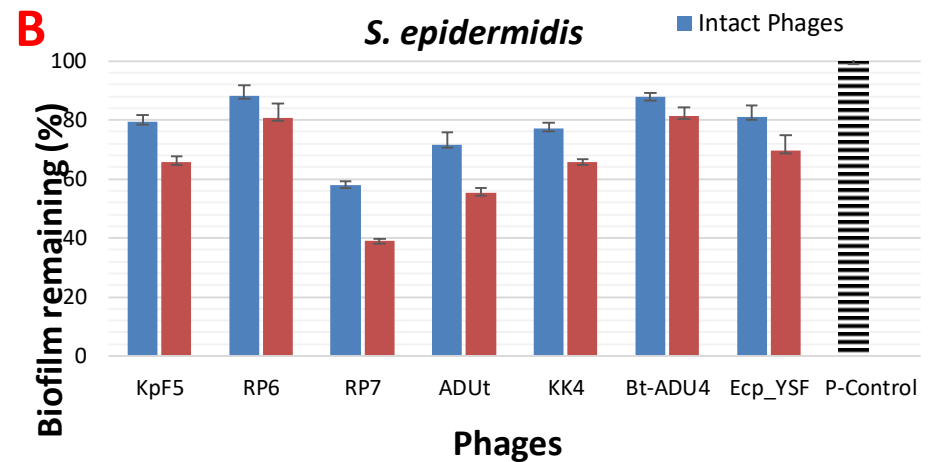
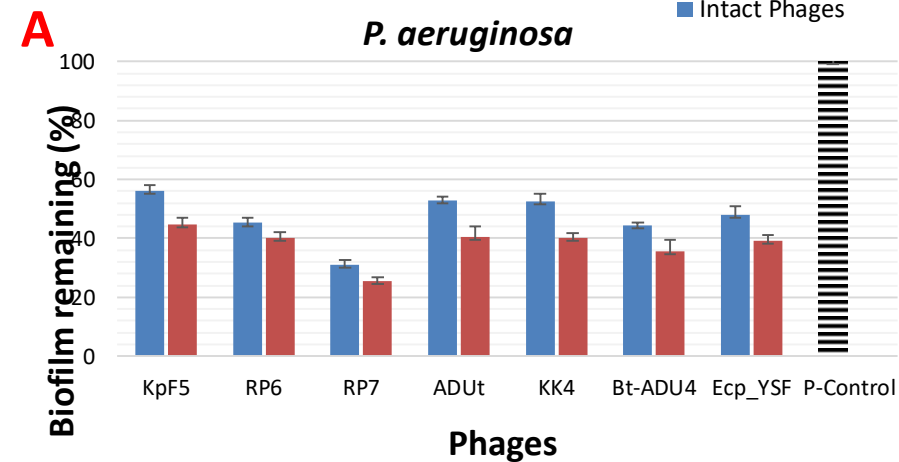
Sahd Ali, MSc,^{1,*} Abdulkerim Karaynir, MSc,^{1,*} Hanife Salih Doğan, PhD,^{1,†} Ramesh Nachimuthu, PhD,² Kingsley Badu, PhD,³ and Bülent Bozdoğan, MD, PhD^{1,4}



ES

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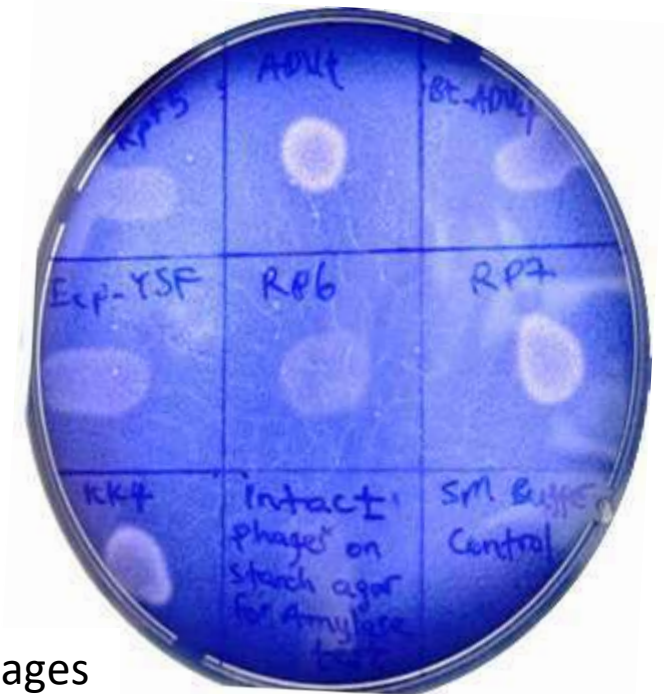


Yapısal proteinlerin Etkilerinin araştırılması

- DNase test (DNase Agar)
- Proteinase test (Skim milk)
- Lipase test (Tween 20 Agar)
- Amilase test (Starch agar)



Disintegrated Phages



Intact Phages

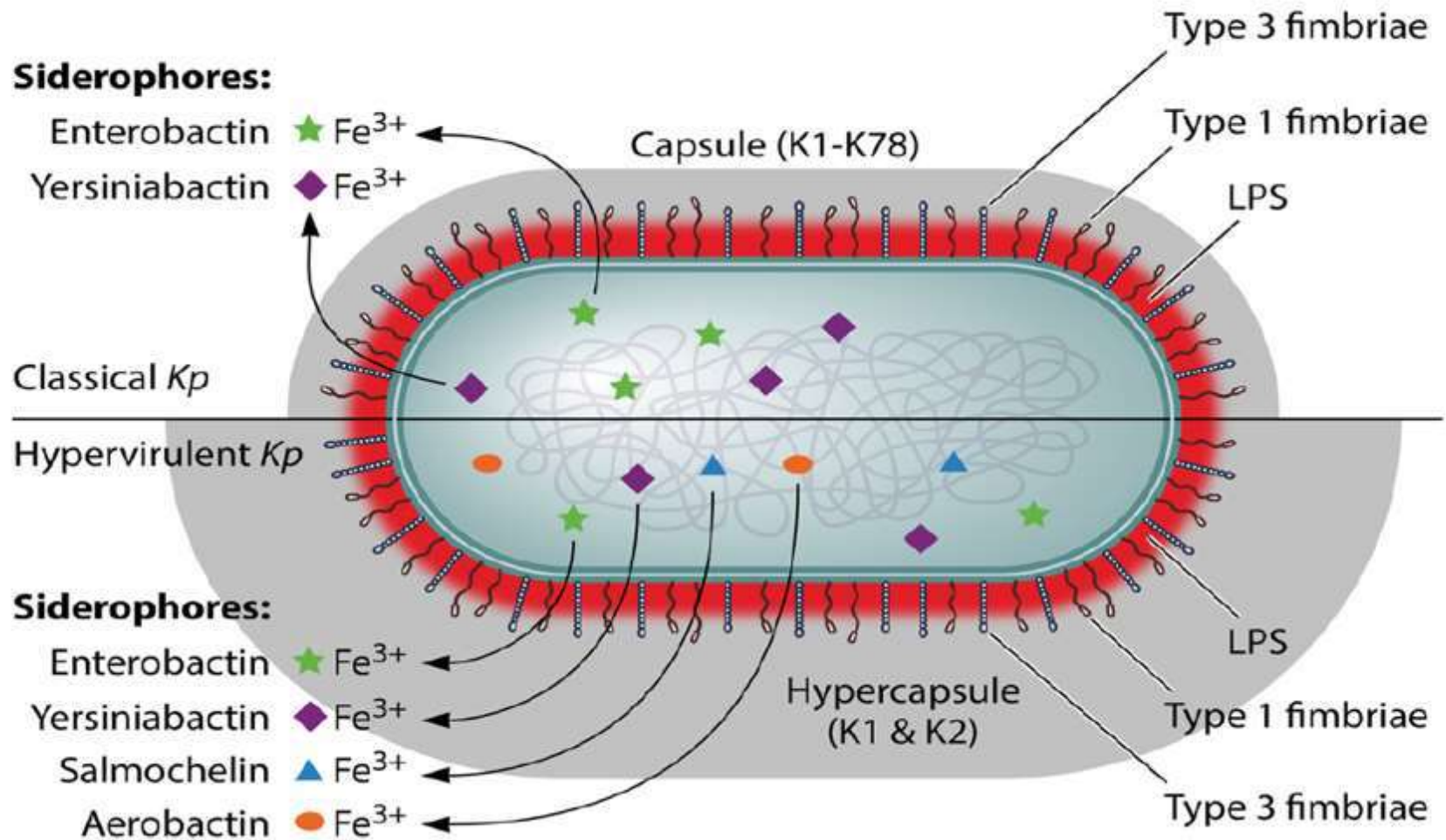
Table 2 Predicted proteins with sugar degrading enzymatic activities in the phage genomes. The prediction of protein domains and functions were analyzed among the tested 5 phage genomes. Two of tested phages had no genes with sugar degradation activities.

Phage	Protein	Homologue	Domain	Enzymatic function
KpF5	Gp4		Glyco_hydro_108 and Peptidoglycan_binding_3	Lytic transglycosylases and Amidase
Ecp_YSF	Gp31	Tail tube initiator protein	Lyz-like superfamily	Lytic transglycosylases
KK4	Gp47	Baseplate hub and tail lysozyme	Phage lysozyme	Lytic transglycosylases
	Gp72	Baseplate hub structural protein	Phage lysozyme	Lytic transglycosylases
ADU4	Gp35	Endolysin	Amidase_2	Amidase
	Gp200	Tail protein with lysin activity	Glucosaminidase	Glucosaminidase
RP7	Gp155	Cell wall hydrolase	Hydrolase_2 superfamily	Lytic transglycosylases



Klebsiella pneumoniae: Going on the Offense with a Strong Defense

Michelle K. Paczosa,^a Joan Meccas^b



Two novel phages, *Klebsiella* phage GADU21 and *Escherichia* phage GADU22, from the urine samples of patients with urinary tract infection

Original Paper | Published: 18 January 2024

Volume 60, pages 208–221, (2024) [Cite this article](#)



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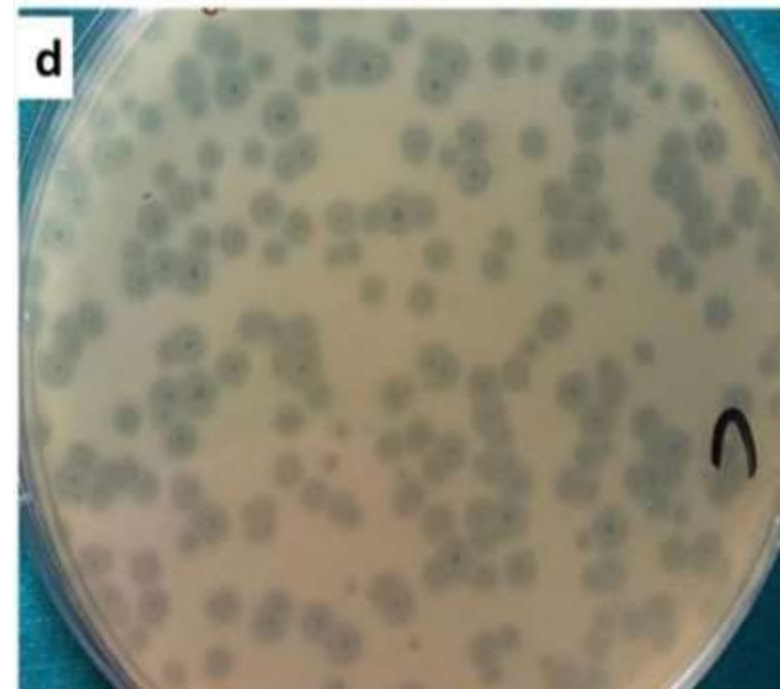
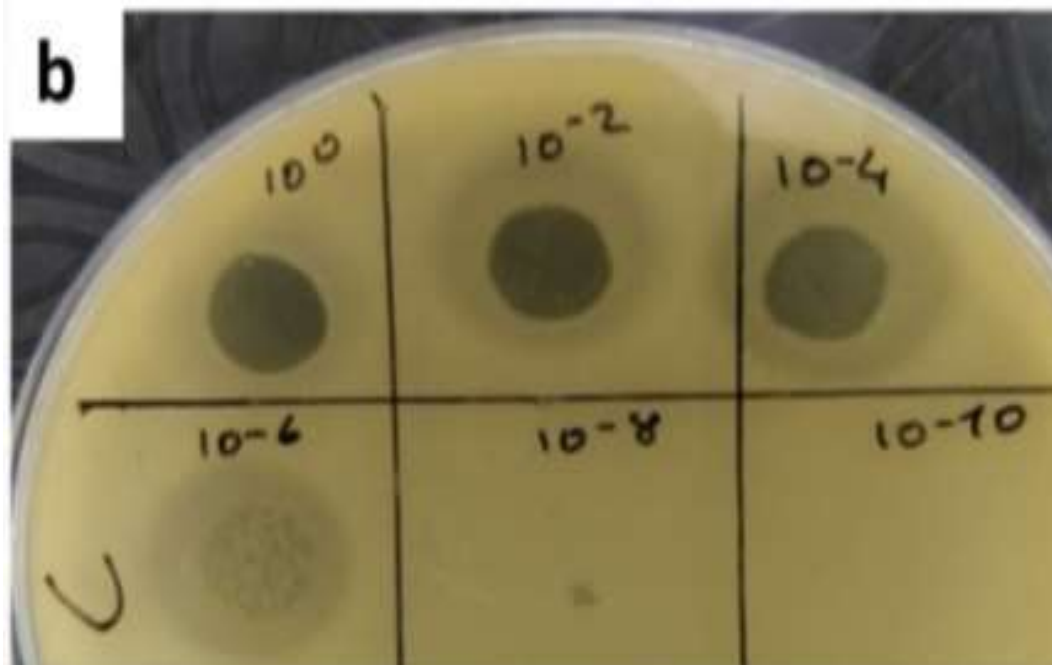
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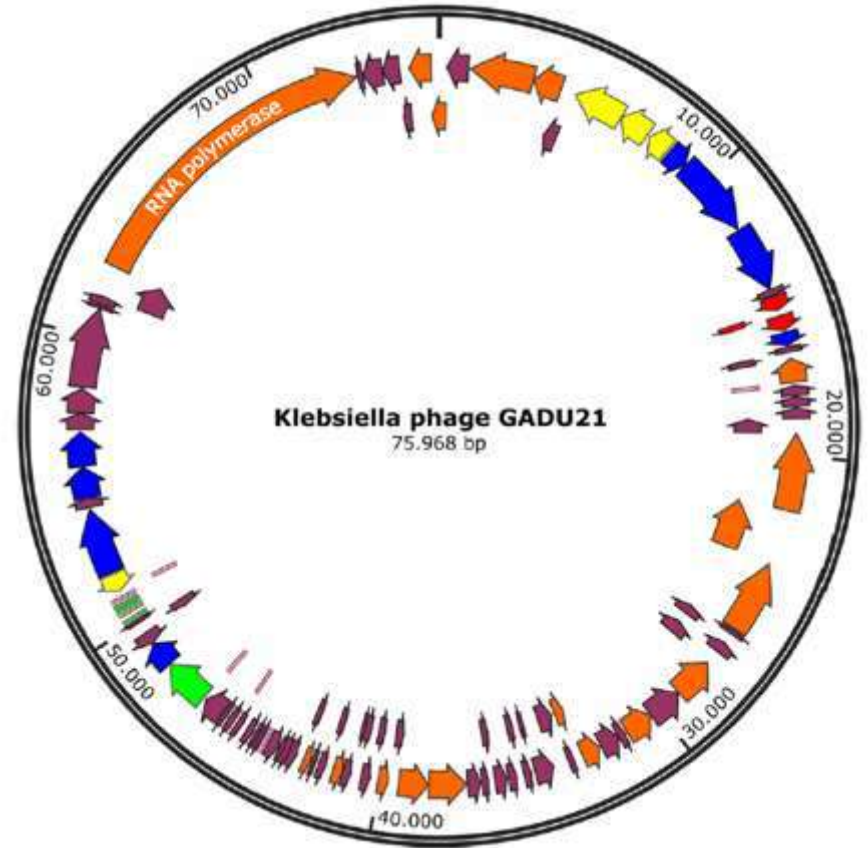
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- *K. pneumoniae* phage GADU21
- İdrar örneğinden izole



GADU21 Fajı

<i>K. pneumoniae</i>	Kp2933	—	—
	Kp1421	—	—
	Kp-154256	—	+++
	Kp1152	—	—
	Kp1022	—	++
	Kp19-101	—	—
+%55	Kp19-24	—	++
	Kp19-115	—	+++
	Kp19-31	—	—
	Kp19-2	—	+
	Kp19-99	—	+++
	Kp19-90	—	+
	Kp19-3	—	++
	Kp19-51	—	+++
	K1	—	—
	K2	—	—
	K3	—	+++
	K4	—	—
	K5	—	—
	E2	—	+++



Klebsiella fajı vB_KpP_FBKp27'in %88'i il
%95.61 benzerlik

Phage-encoded novel DP21 enzyme, a polysaccharide depolymerase, prevents and destruct biofilms of various species

P3624



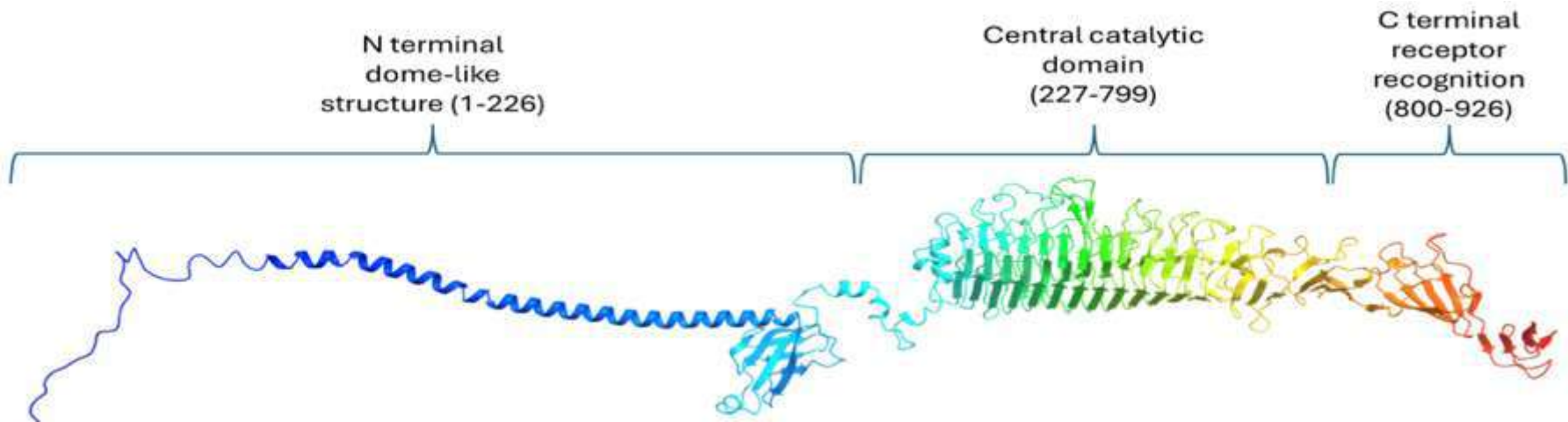
H. Salih Doğan^{1*}, G.A. Orbayoğlu¹, Y. Doğan¹, A. Karaynır¹, B. Bozdoğan^{1,2}

¹Recombinant DNA and Recombinant Protein Center (REDPROM), Aydın Adnan Menderes University, Türkiye

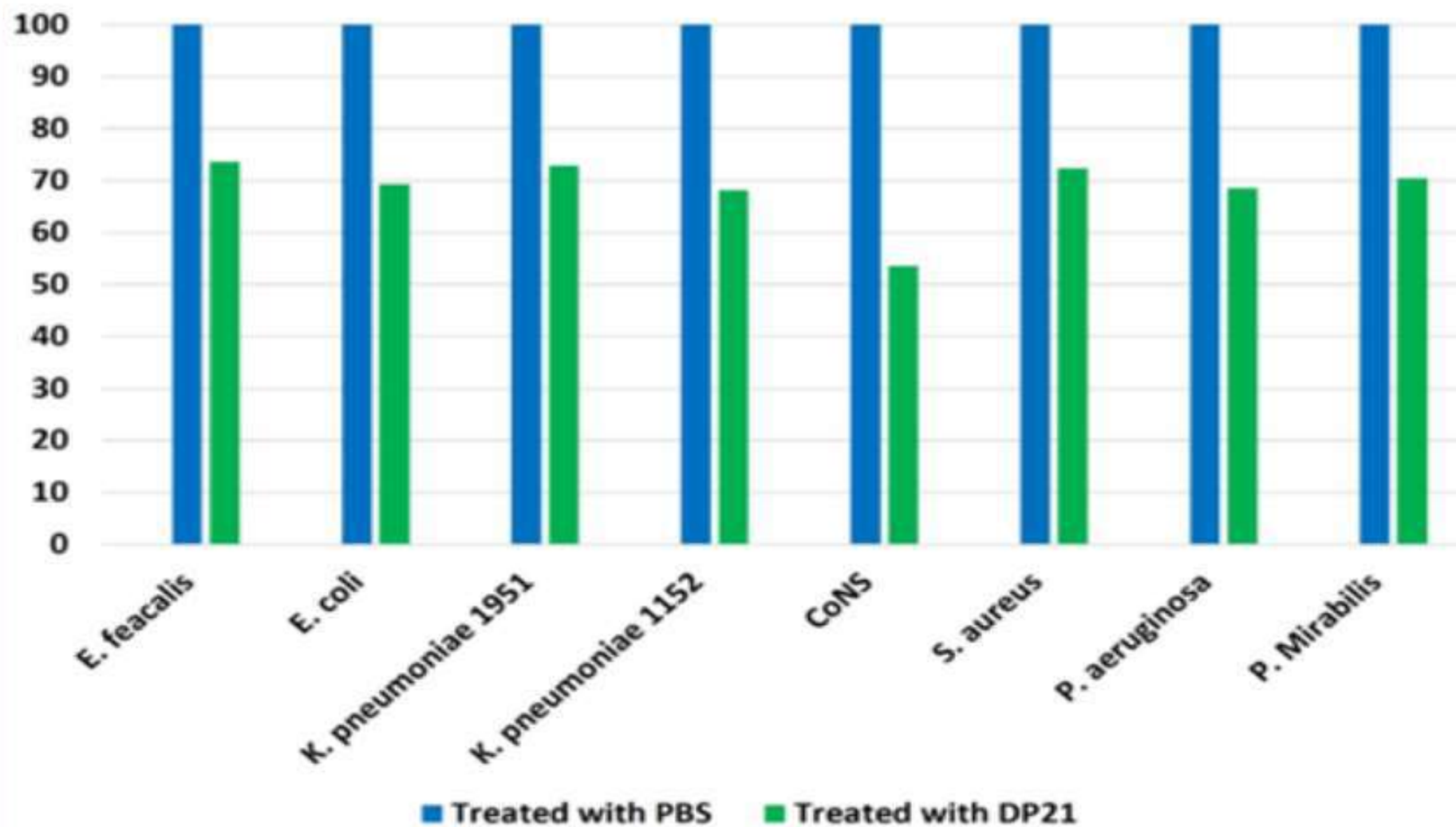
²Medical Microbiology Department, Medical Faculty, Aydın Adnan Menderes University, Aydın, Türkiye



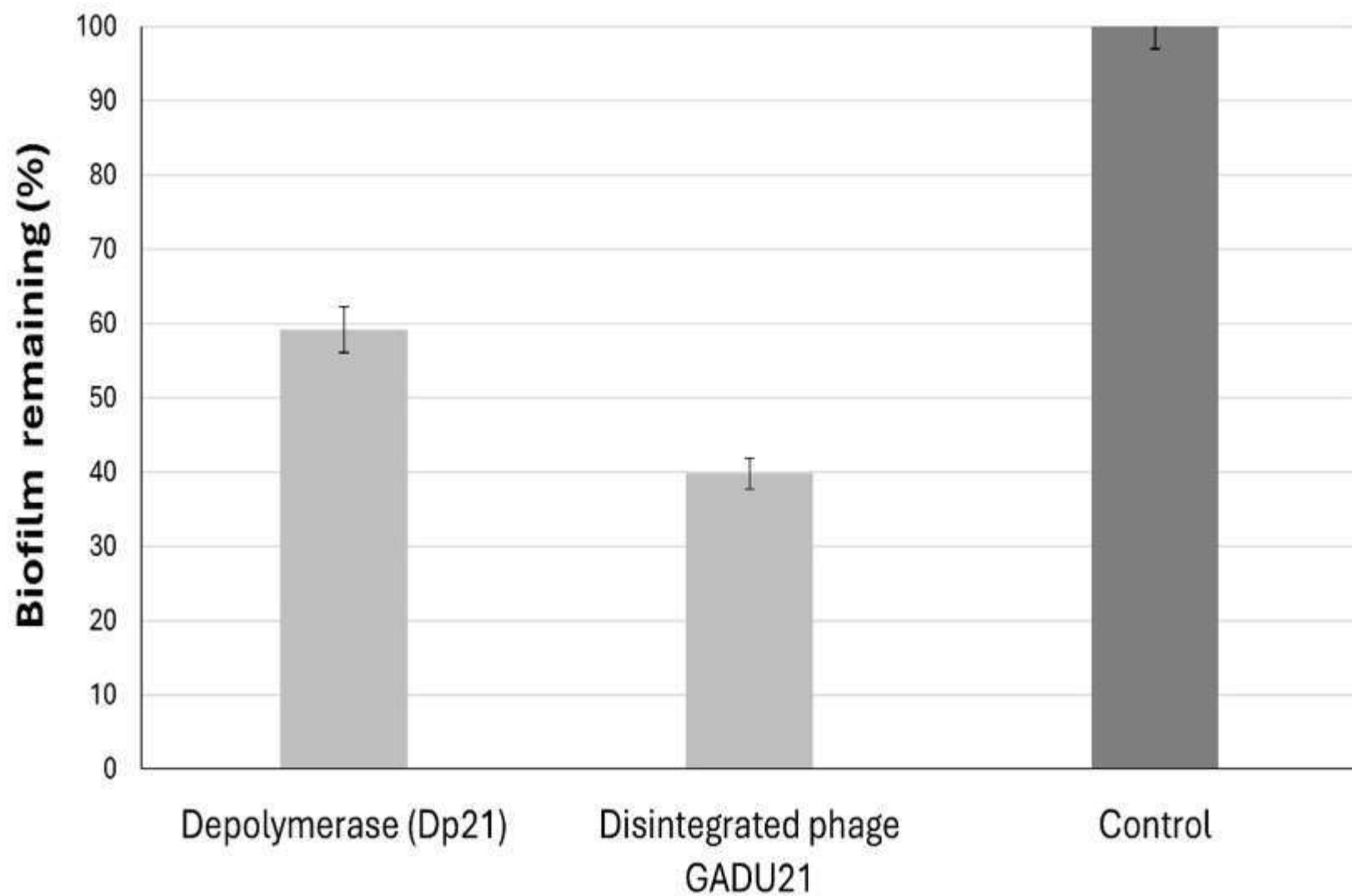
- *K. pneumoniae* phage GADU21
- İdrar örneğinden izole
- Genom sekansı: *dp21* geni, 926 aa protein
- PCR ile amplifikasyon, pET30a klonlama, *E. coli* BL21 sentez
- IMAC saflaştırma



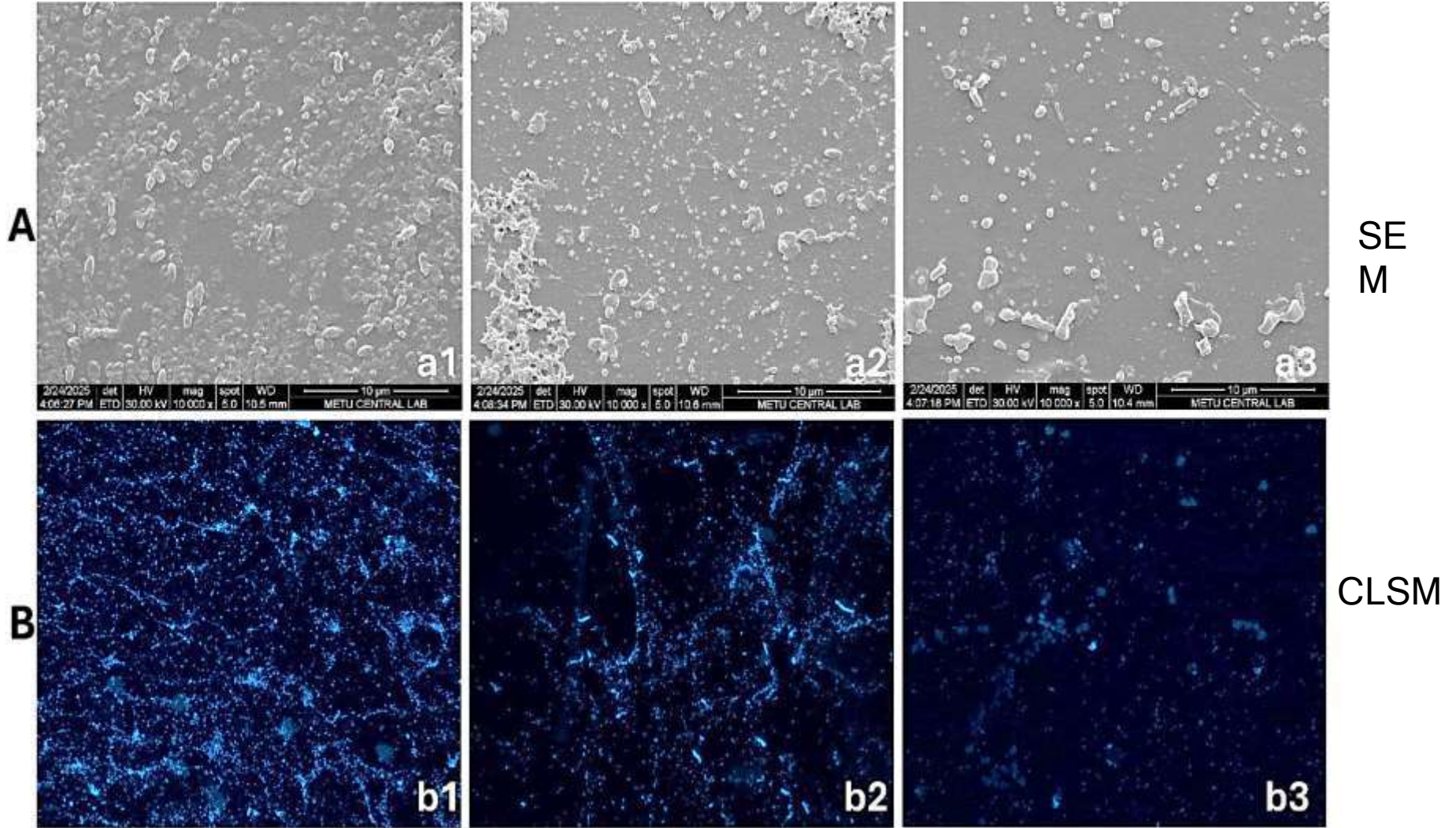
Biofilm-Destruction



Pseudomonas aeruginosa PAO1



P. aeruginosa PAO1 biyofilmi



Kontrol

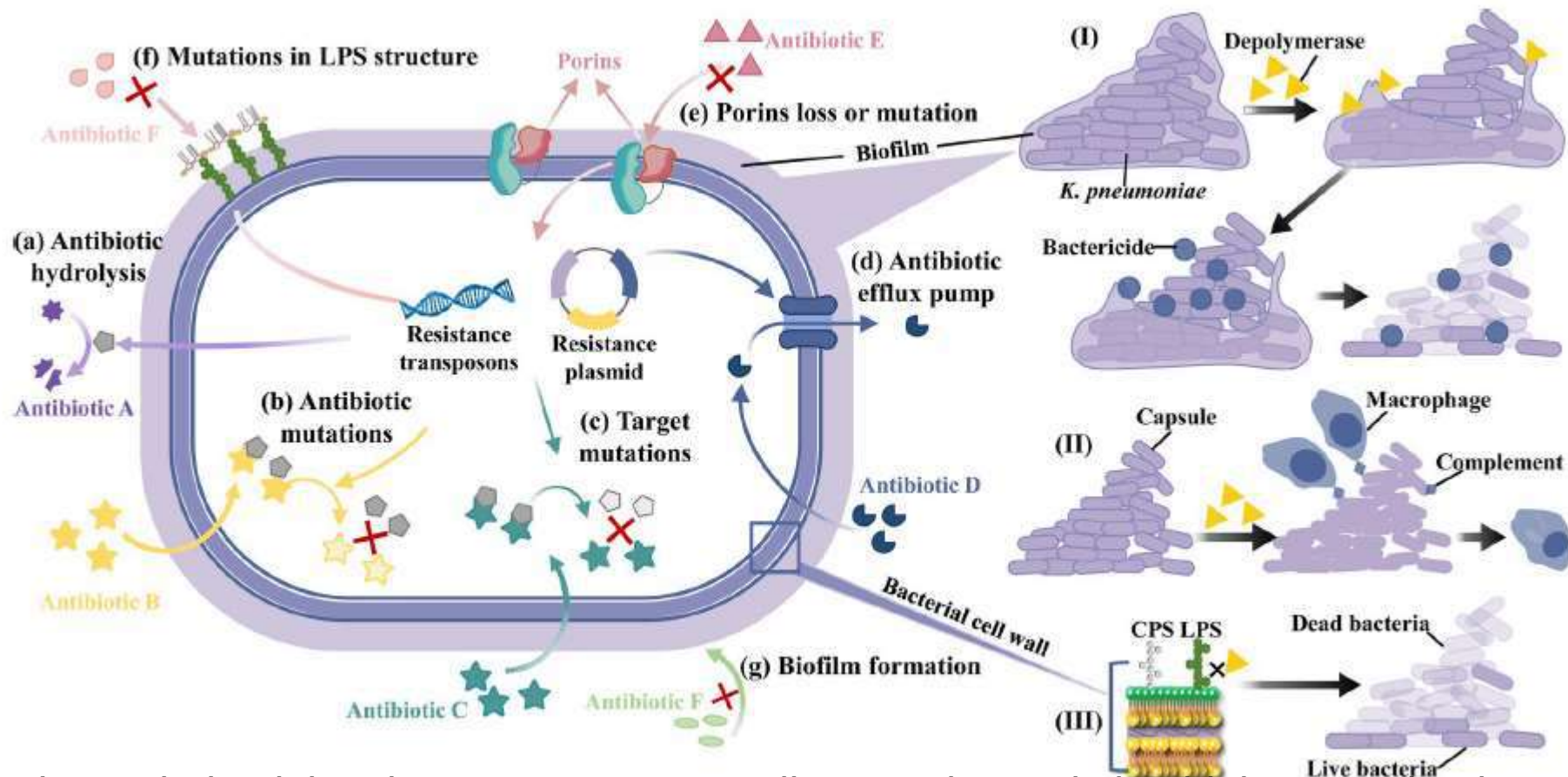
Dp21 enzimi

Parçalanmış
faj



Bacteriophage-derived depolymerase: a review on prospective antibacterial agents to combat *Klebsiella pneumoniae*

Xin Jiao¹ · Menglu Wang¹ · Yanxia Liu^{1,2} · Shuqi Yang¹ · Qianhui Yu¹ · Jinjuan Qiao^{1,3}



Phage-derived depolymerases are naturally occurring antimicrobial agents that have demonstrated potent antimicrobial effects against *K. pneumoniae* by inhibiting biofilm formation and degrading mature biofilms.

SONUÇ

Post-antibiyotik çağı yakın

Fajlar eski bir umut, kişiye özgü tedavi

Fajlar yalnızca bakteri parçalayıcı değil

Aynı zamanda mobil enzimler

Klebsiella fajları antibiyotik etkisini artırır mı?

Fajların sınırları bakterilerin ötesinde



Zeynep ERDEM-AYNUR



Abdulkerim KARAYNİR



Hanife SALİH DOĞAN

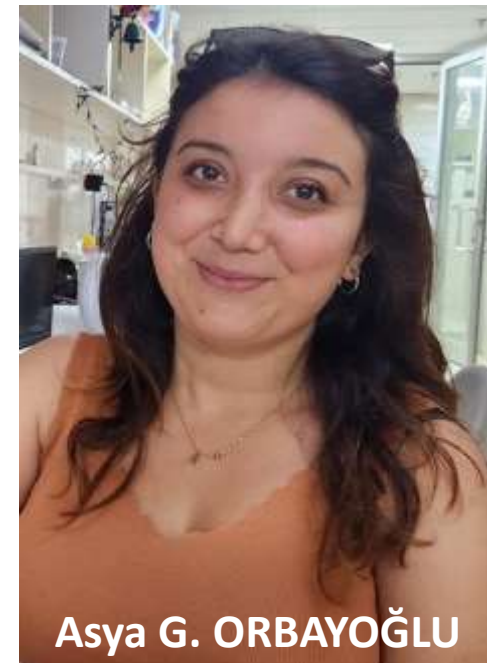


Sahd ALI



Melis YALÇIN

Rümeysa Gülsu ÖZKAN



Asya G. ORBAYOĞLU