# Antibiyotikler ve Mikrobiyom

Prof Dr Hakan Abacıoğlu

İzmir Ekonomi Üniversitesi Tıp Fakültesi



http://www.fireboxmedia.com/illustration/

*Pediatrics International* (2005) **47**, 267–273

Original Article

# β-lactam antibiotic resistance in aerobic commensal fecal flora of newborns

MURAT DUMAN,[1] HAKAN ABACIOGLU,[2] MERAL KARAMAN,[2] NURAY DUMAN[1] AND HASAN ÖZKAN[1]

*Departments of [1]Pediatrics and [2]Microbiology, Faculty of Medicine, Dokuz Eylül University, Izmir, Turkey*

The only risk factor for colonization with ESBL-producing bacteria after discharge from the hospital was failure to feed breast milk (relative risk [RR], 7.6; 95% confidence interval [CI], 1.24–47.58; $P = 0.028$).

**Table 4** Risk factors for colonization with ESBL-producing microorganisms

| Risk factors | RR | 95%CI | *P* |
|---|---|---|---|
| Gestational age | – | – | 0.750 |
| Birthweight (<1500 g) | 22.02 | 1.60–309.90 | 0.021 |
| Vaginal delivery | 3.52 | 1.25–9.92 | 0.017 |
| Sex (male) | 2.61 | 1.08–6.28 | 0.031 |
| Failure to feed breast milk | – | – | 0.818 |
| Maternal antibiotic usage | 3.81 | 1.07–13.50 | 0.038 |
| Antibiotic usage of infant | 14.05 | 1.19–164.62 | 0.035 |
| Intravenous application | – | – | 0.647 |
| Total parenteral feeding | – | – | 0.834 |
| Nasogastric feeding | 0.05 | 0.004–0.064 | 0.021 |
| Ventilatory therapy | – | – | 0.862 |
| Premature rupture of membrane | 7.41 | 1.19–45.90 | 0.031 |
| Duration of hospitalization (>5 days) | – | – | 0.744 |
| Groups | | | |
| Control group (references) | | | |
| Neonatal ward group | – | – | 0.544 |
| NICU group | – | – | 0.804 |

MetaHIT

2010

Vol 464|4 March 2010|doi:10.1038/nature08821 nature

ARTICLES

# A human gut microbial gene catalogue established by metagenomic sequencing

HMP

NIH HUMAN MICROBIOME PROJECT

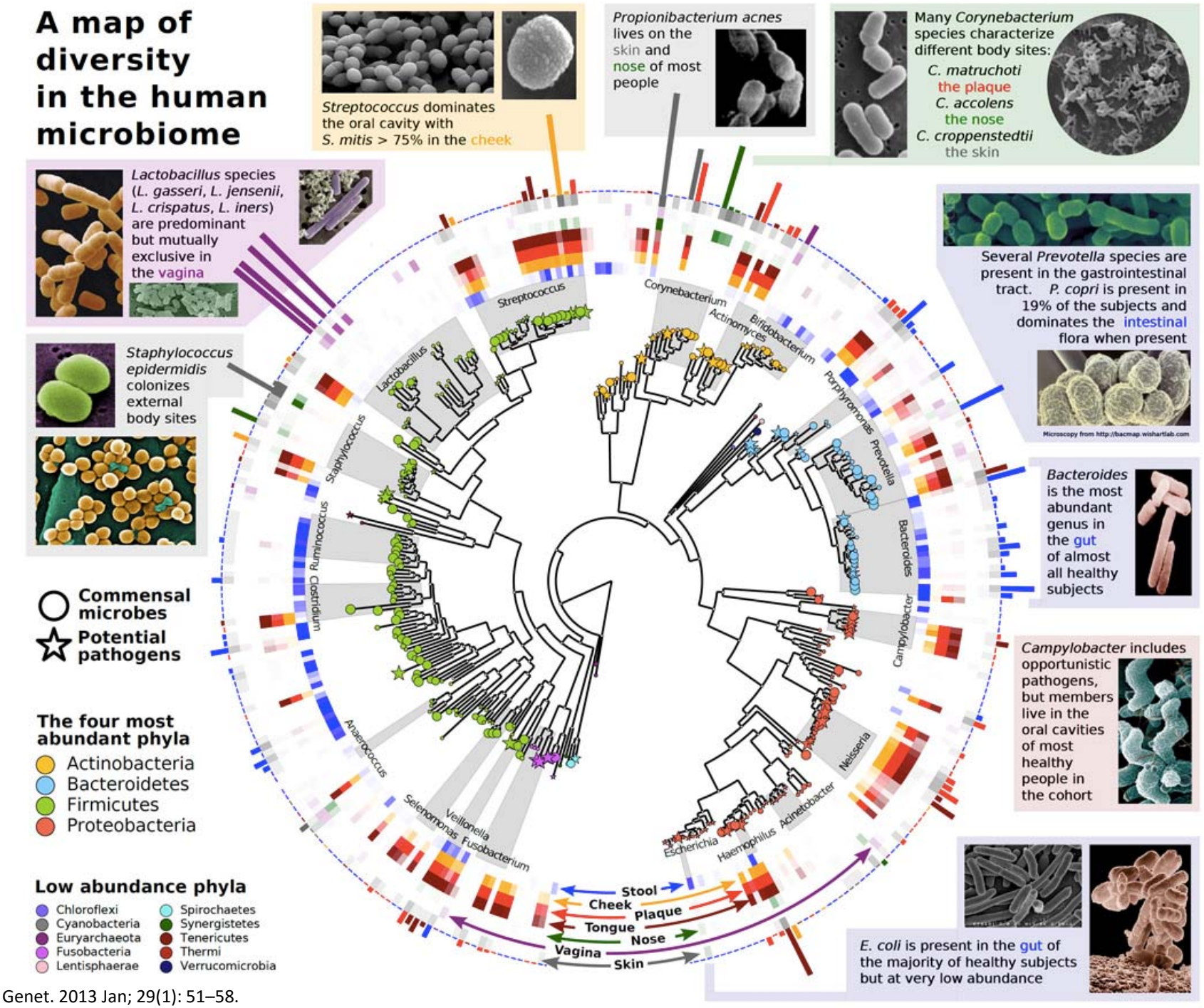
2012

ARTICLE

doi:10.1038/nature11209

# A framework for human microbiome research

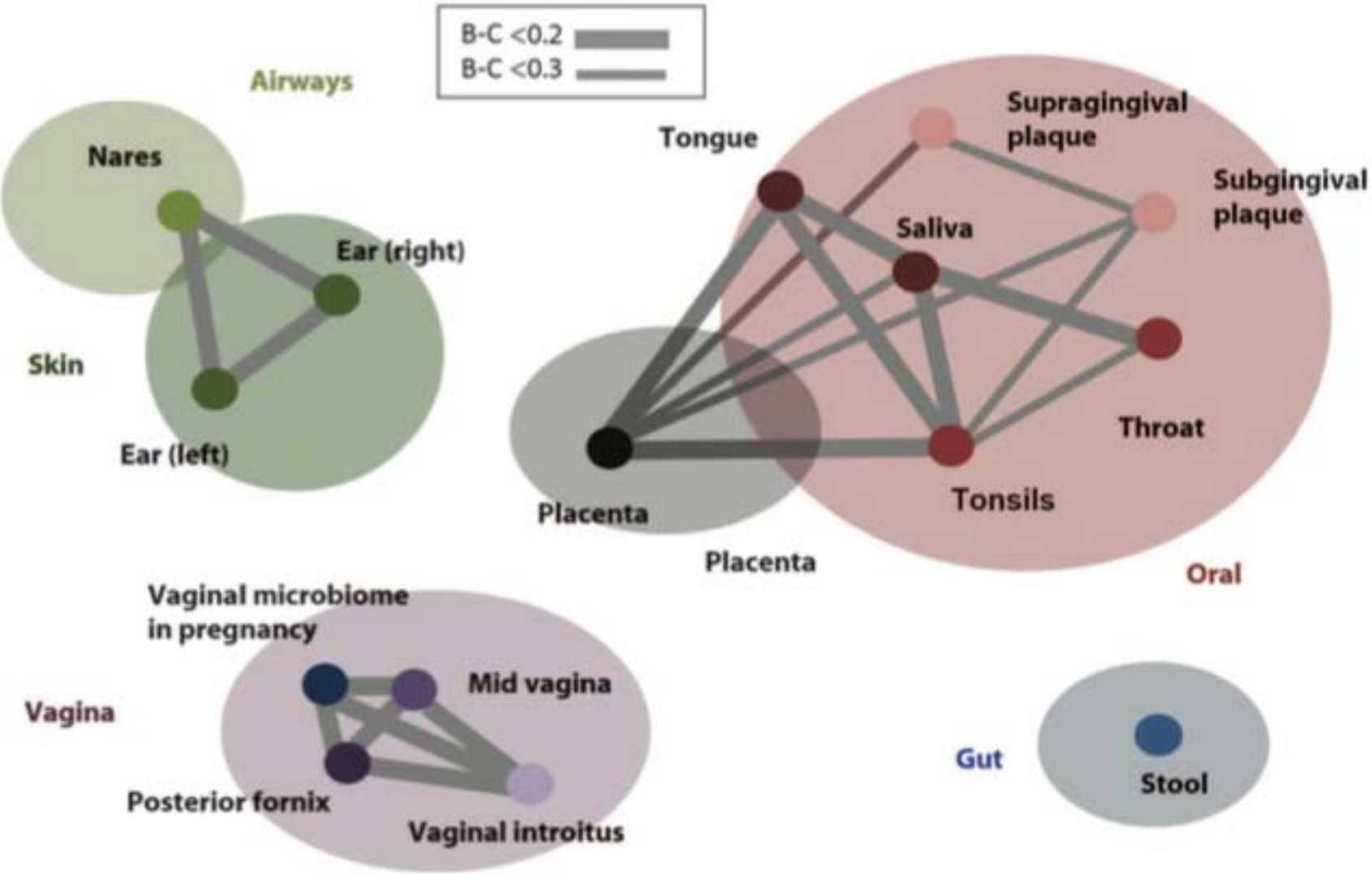
The Human Microbiome Project Consortium*




Trends Genet. 2013 Jan; 29(1): 51–58.

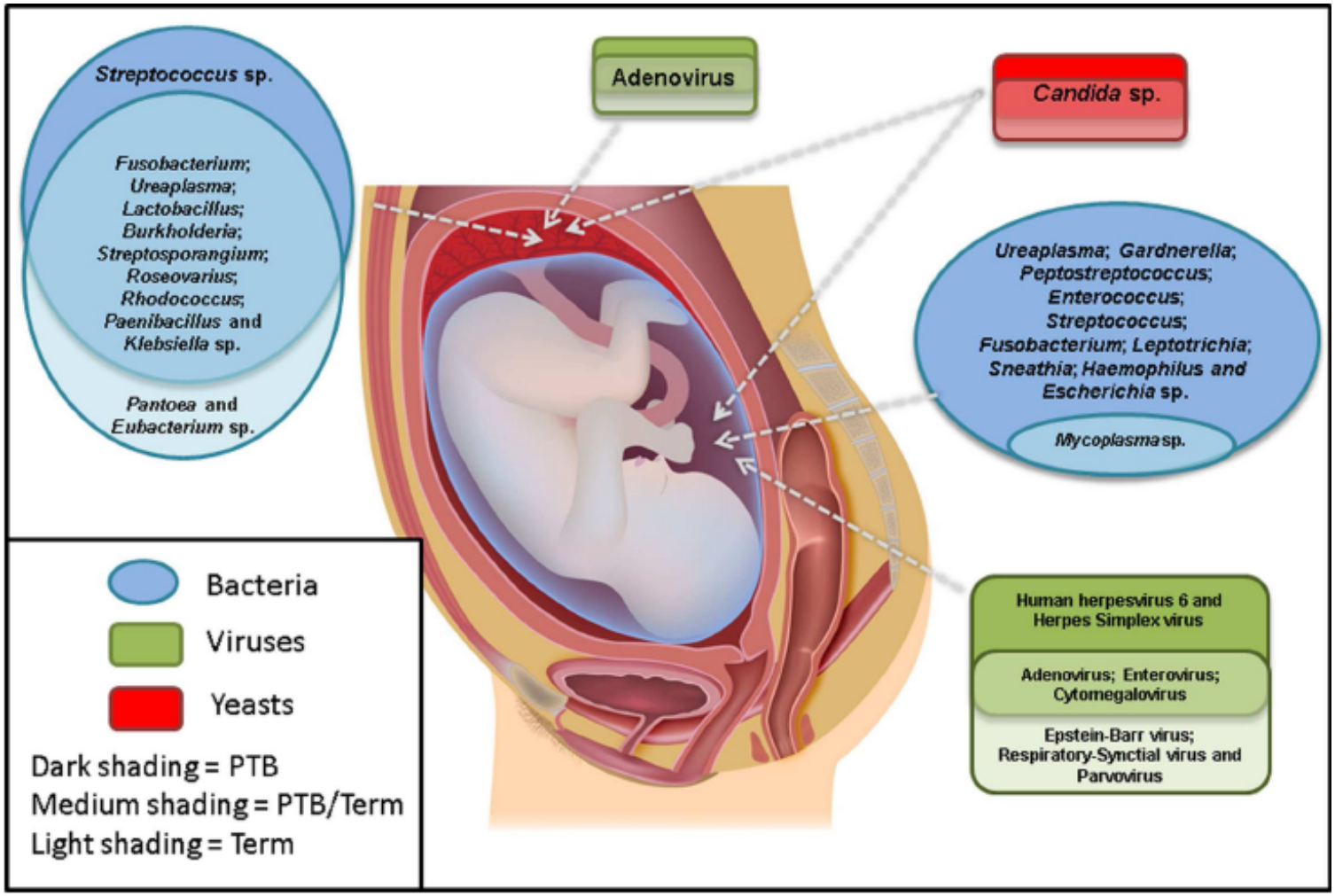
# The Placenta Harbors a Unique Microbiome

Kjersti Aagaard,[1,2,3]* Jun Ma,[1,2] Kathleen M. Antony,[1] Radhika Ganu,[1] Joseph Petrosino,[4] James Versalovic[5]



# Exploring preterm birth as a polymicrobial disease: an overview of the uterine microbiome

*Matthew S. Payne* and Sara Bayatibojakhi*




Front Immunol 2014;5: 595

http://med.stanford.edu/news/all-news/2015/12/new-technique-reveals-gut-bacteria-diversity.html

Stanford MEDICINE | News Center

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# Stunning diversity of gut bacteria uncovered by new approach to gene sequencing devised at Stanford

## The many microbes living in our intestines are far more diverse than once suspected, a new genomic technique reveals.

DEC 14
**2015**

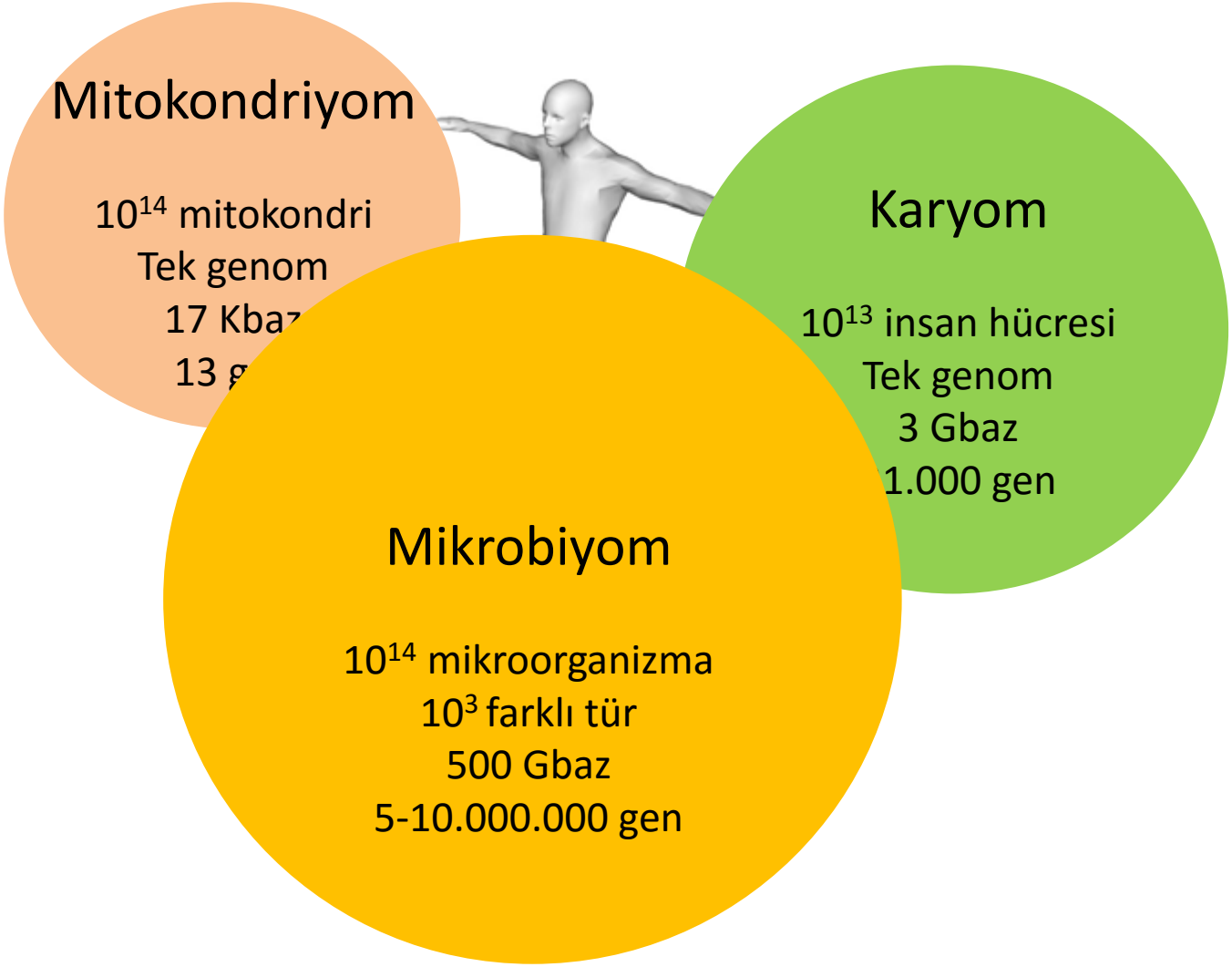
A collaboration between computer scientists and geneticists at Stanford has produced a novel technique for mapping the diversity of bacteria living in the human gut.

The new approach revealed a far more diverse community than the researchers had anticipated. "The bacteria are genetically much more heterogeneous than we thought," said Michael Snyder, PhD, professor and chair of genetics.

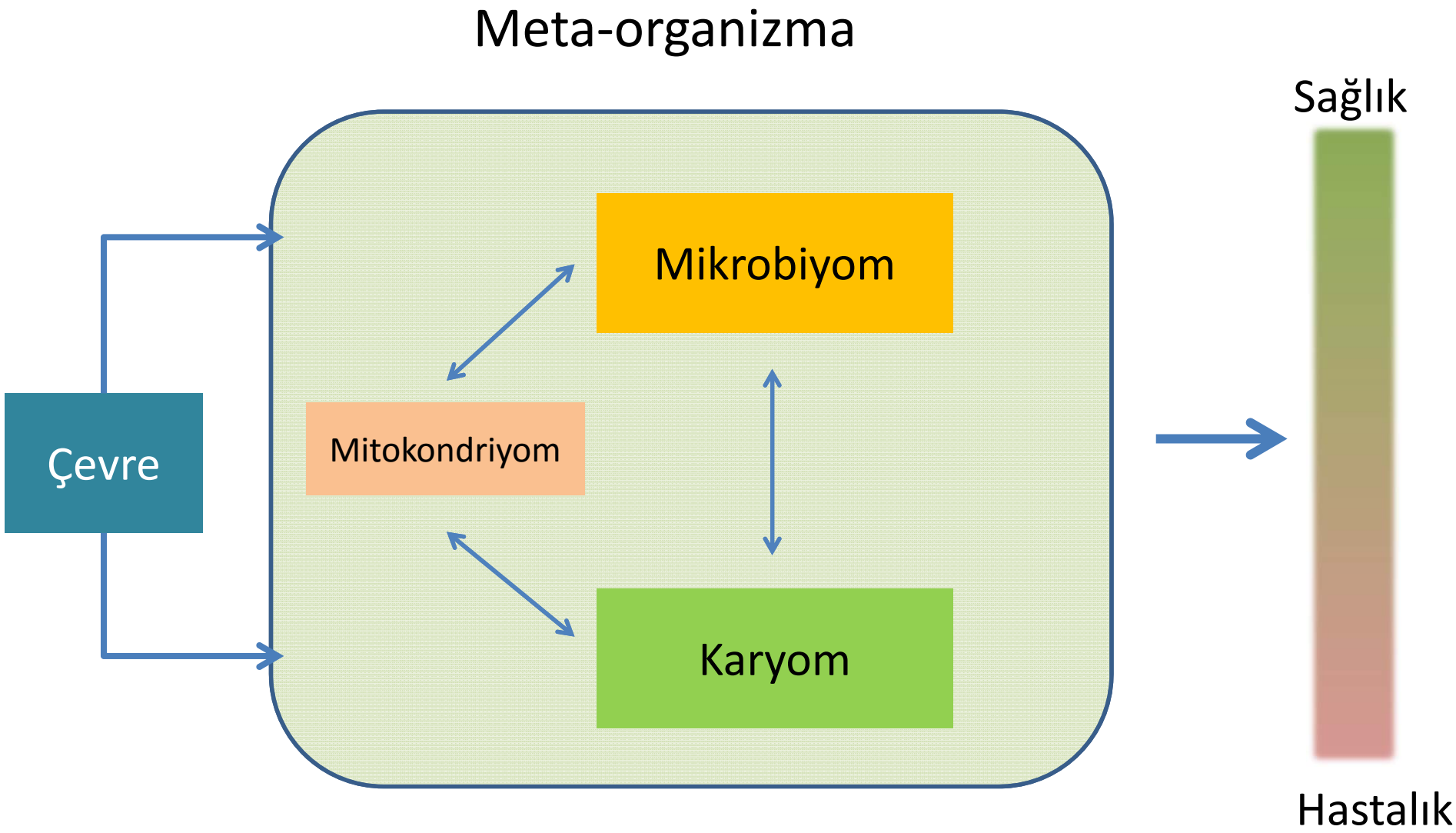
Any two humans typically differ by about 1 in 1,000 DNA bases, whereas bacteria of the same species may differ by as many as 250 in 1,000,

Synthetic long-read sequencing reveals intraspecies diversity in the human microbiome. Kuleshov V, Jiang C, Zhou W, Jahanbani F, Batzoglou S, Snyder M. Nature Biotechnology. 14 December 2015. 10.1038/nbt.316.

# Öteki genomlarımız?



# Simbiyotik etkileşimler




*Nature Reviews Microbiology* **11**, 639–647 (2013) den geliştirilerek yeniden çizilmiştir.

# Simbiyoz

- Benzer olmayan iki organizmanın birlikte yaşaması
    - Anton de Bary 1878

- İki organizma arasında *kalıtsal değişim potansiyeli* taşıyan etkileşimler
    - Francis Patrick Ryan 2016

# Kalıtımı değiştirmenin tek yolu mutasyon değildir.

| Değişim mekanizması | Genetik dizide değişim | Değişimin doğası | Seçilimin etkili olduğu düzey | Çevresel etkilenim |
|---|---|---|---|---|
| Mutasyon | Evet | **Rastlantısal**<br>Birikici | Gen<br>Organizma | Hayır (?) |
| Epigenetik | **Hayır** | Rastlantısal değil<br>Birikici | Epigenetik kalıtım sistemleri | **Evet** |
| Simbiyogenez | Evet | Rastlantısal değil<br>**Hızlı** | Holobiyont düzeyi | Hayır |
| Hibridogenez | Evet | Rastlantısal değil<br>Hızlı | Hibrit genom düzeyi | Hayır |

APMIS 2016; 124: 11–19.

Crisp et al. Genome Biology (2015) 16:50
DOI 10.1186/s13059-015-0607-3

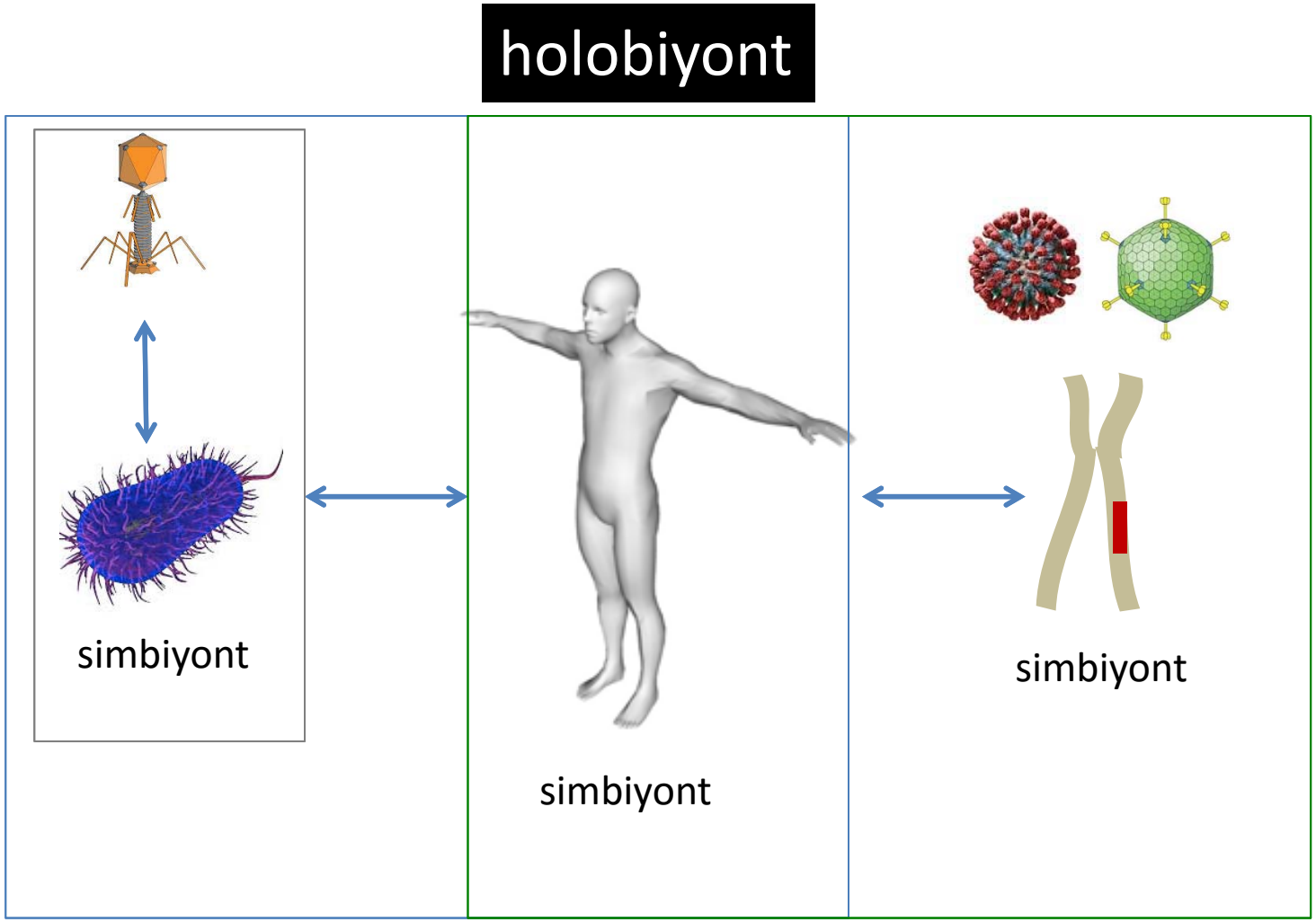
Genome Biology

RESEARCH Open Access

# Expression of multiple horizontally acquired genes is a hallmark of both vertebrate and invertebrate genomes

Alastair Crisp[1†], Chiara Boschetti[1†], Malcolm Perry[1,2,3], Alan Tunnacliffe[1*] and Gos Micklem[2,3*]

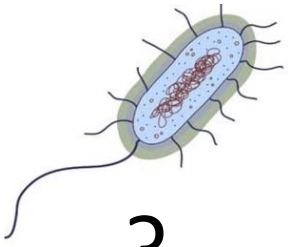
# Simbiyont ve Holobiyont




APMIS 2016; 124: 11–19.

# İnsanın tarihinde üç önemli *holobiyontik* olay

mikrobiyota

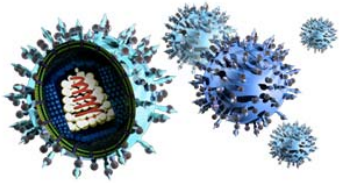


?

mitokondri

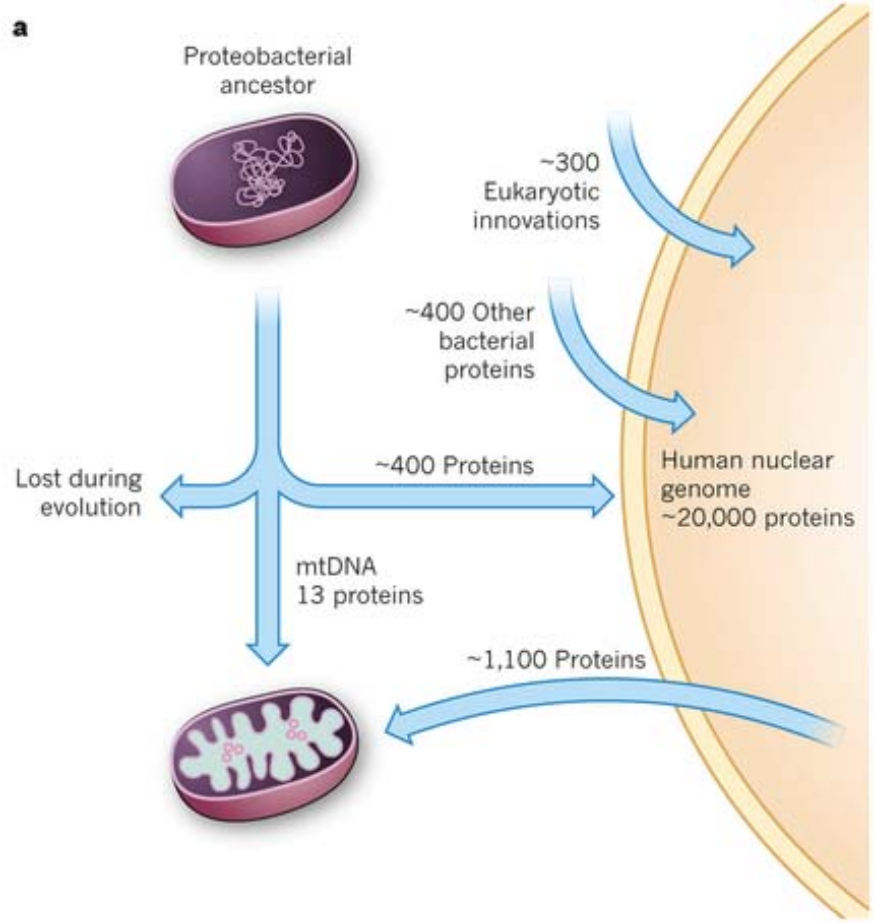
2-3 milyar yıl önce

endojen retrovirüsler

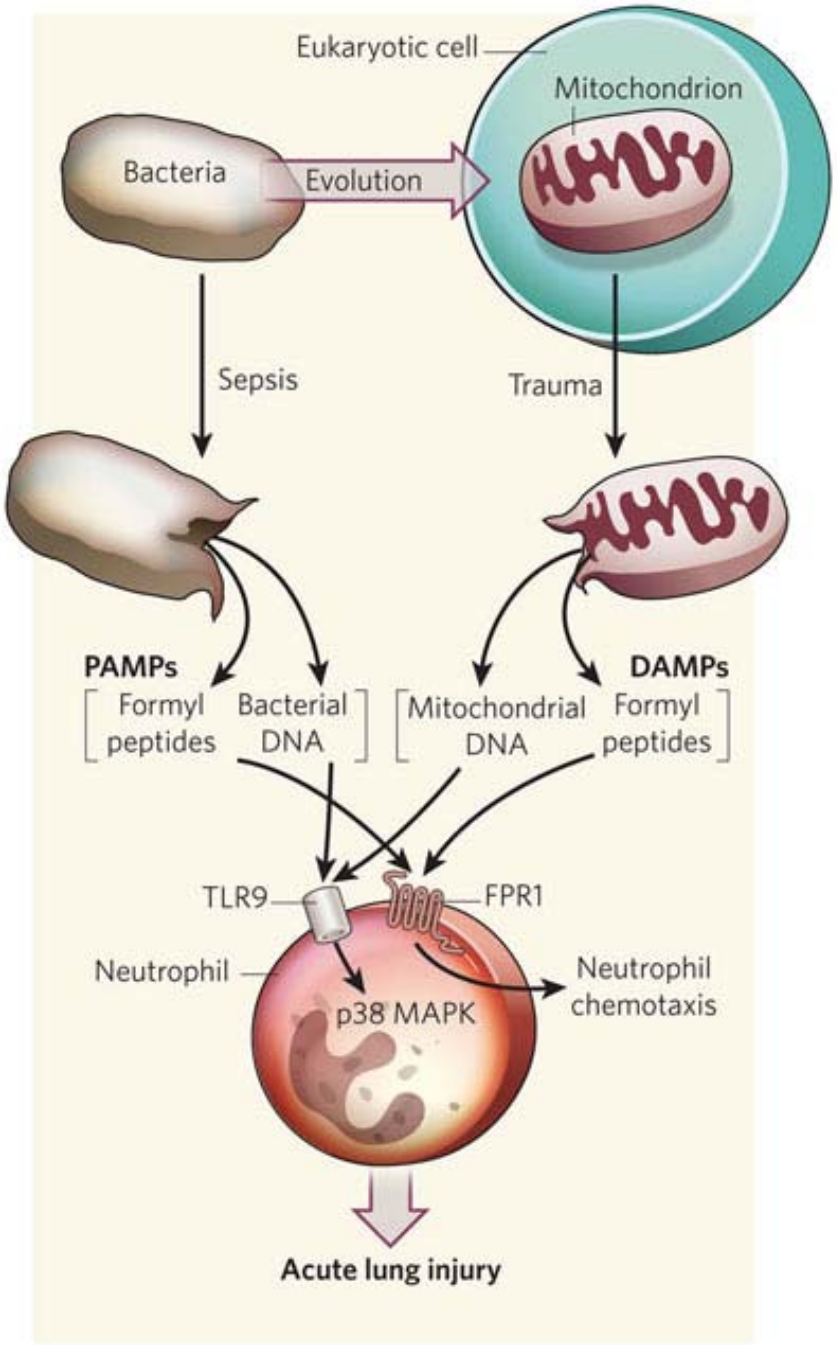


100-150 milyon yıl önce

# Mitokondrinin öyküsü



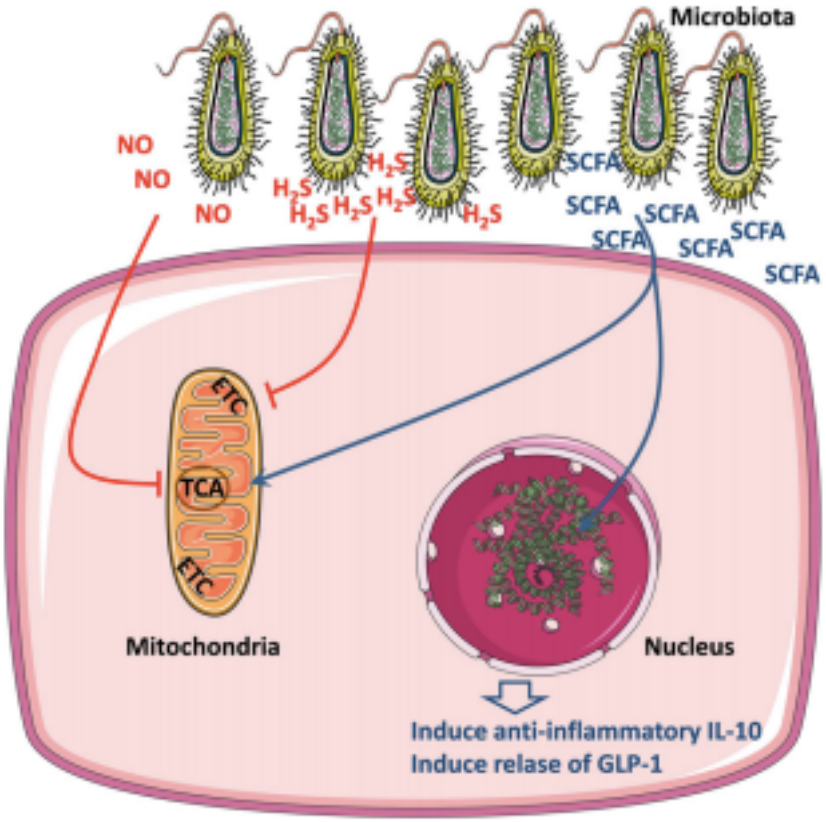

- Endosimbiyoz kuramı (2-3 milyar yıl önce)
- Mozaik yapı
  - Çembersel DNA
  - prokaryotik ribozom
  - Faj kökenli DNA polimeraz

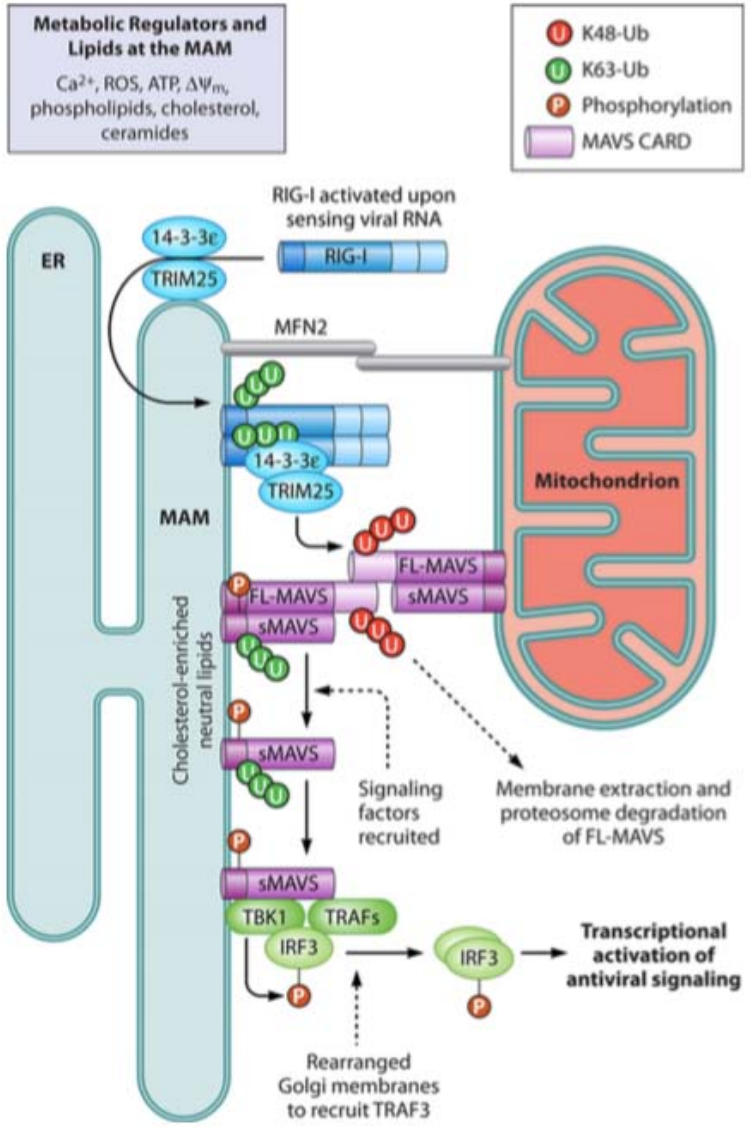



- Doğal bağışık yanıtların başlatılması
  - PAMP (mikroplar)
  - DAMP (mitokondri)

Nature 464, 41–42 (2010).

# Mikroplar *mitokondri* ile etkileşir




FEMS Pathogens and Disease, 2016, Vol. 74, No. 1

Vazquez C, Horner SM. 2015. MAVS coordination of antiviral innate immunity. J Virol 89:6974 –6977. doi:10.1128/JVI.01918-14.

ANTIBIOTICS

# Bactericidal Antibiotics Induce Mitochondrial Dysfunction and Oxidative Damage in Mammalian Cells

Sameer Kalghatgi,[1]* Catherine S. Spina,[1,2,3]* James C. Costello,[1] Marc Liesa,[3] J. Ruben Morones-Ramirez,[1] Shimyn Slomovic,[1] Anthony Molina,[3,4] Orian S. Shirihai,[3] James J. Collins[1,2,3]†

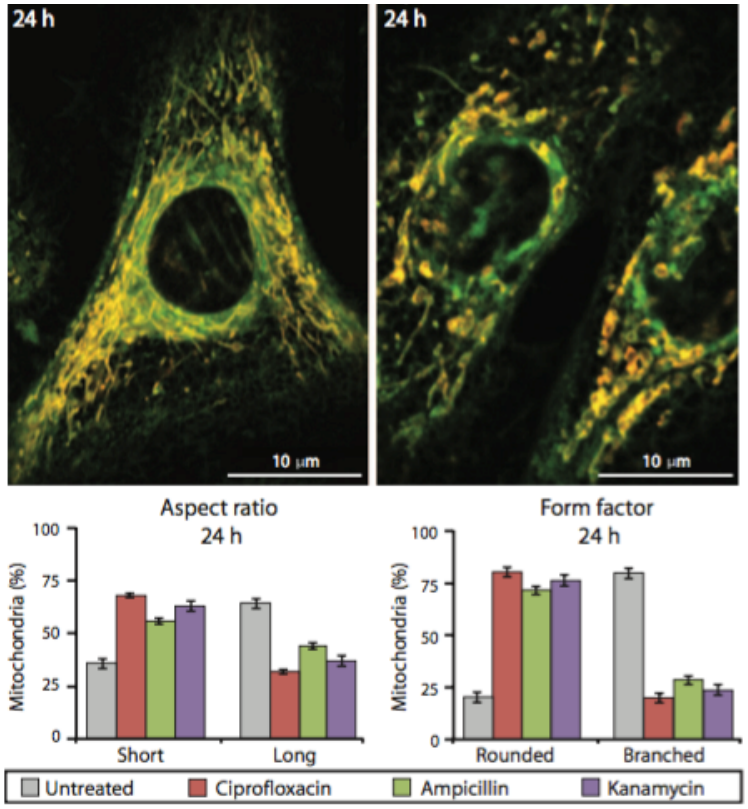



**Fig. 3. Mitochondria in bactericidal antibiotic–treated cells show an abnormal, profission state.** Mitochondrial morphology was measured

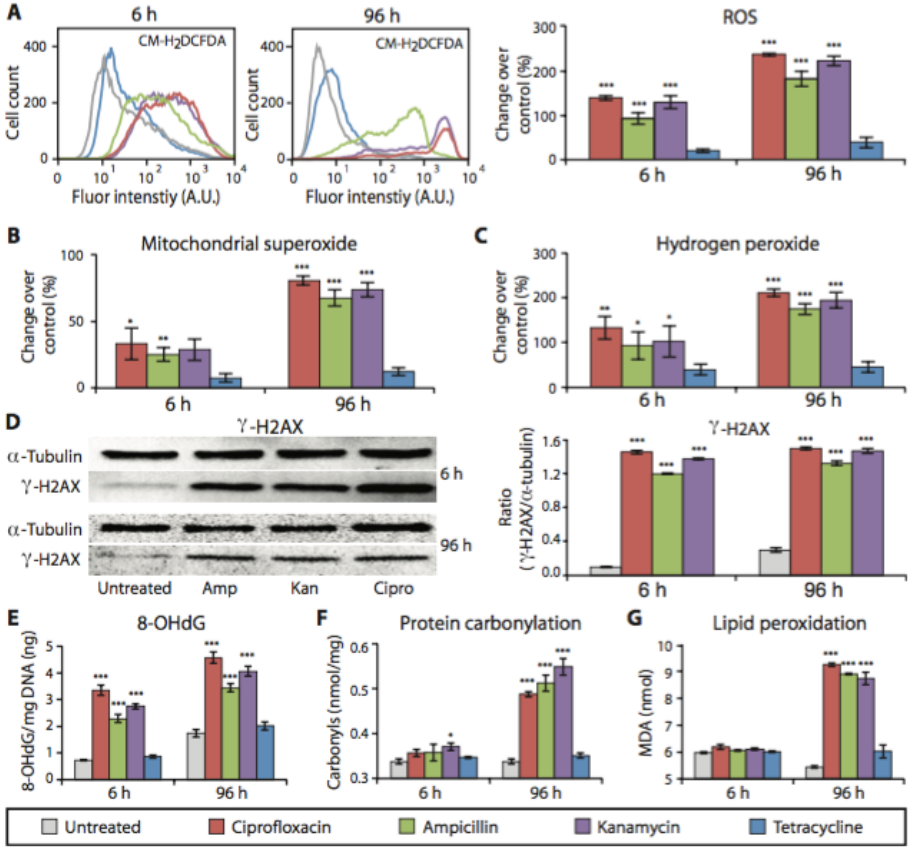
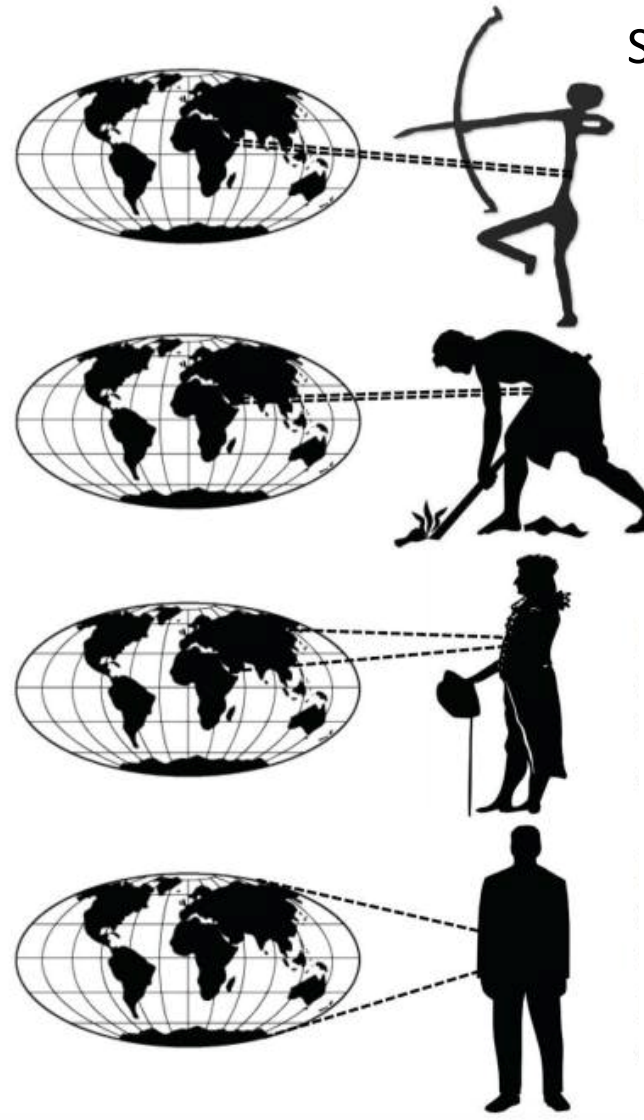



**Fig. 1. Bactericidal antibiotics cause oxidative damage to mammalian cells.** ROS and oxidative

# Mikrobiyota üzerindeki seçici baskılar



Seçici baskı

Diyet

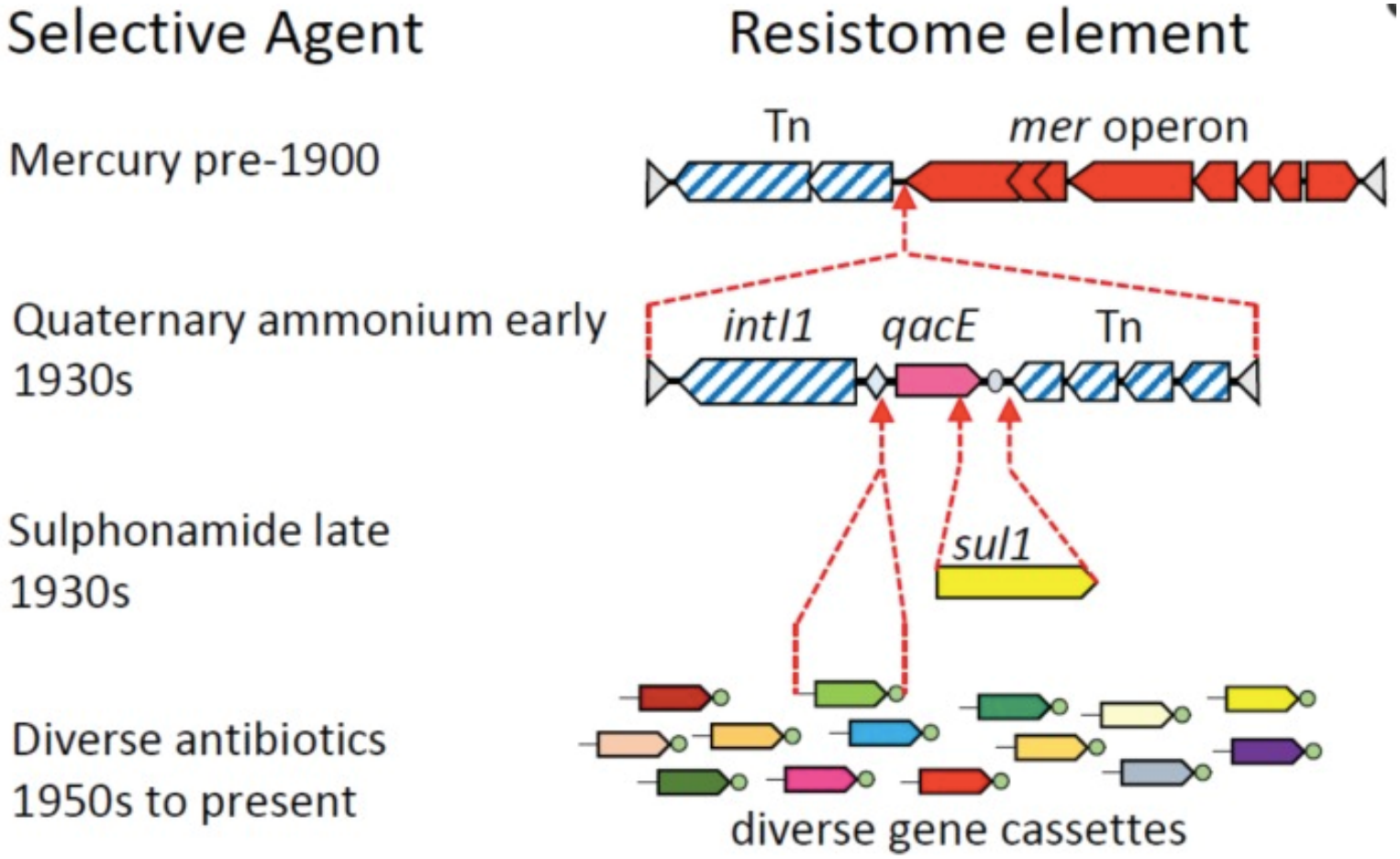
Diyet

Diyet
Ağır metaller
Arsenik

Diyet
Ağır metaller
Dezenfektanlar
Antibiyotikler

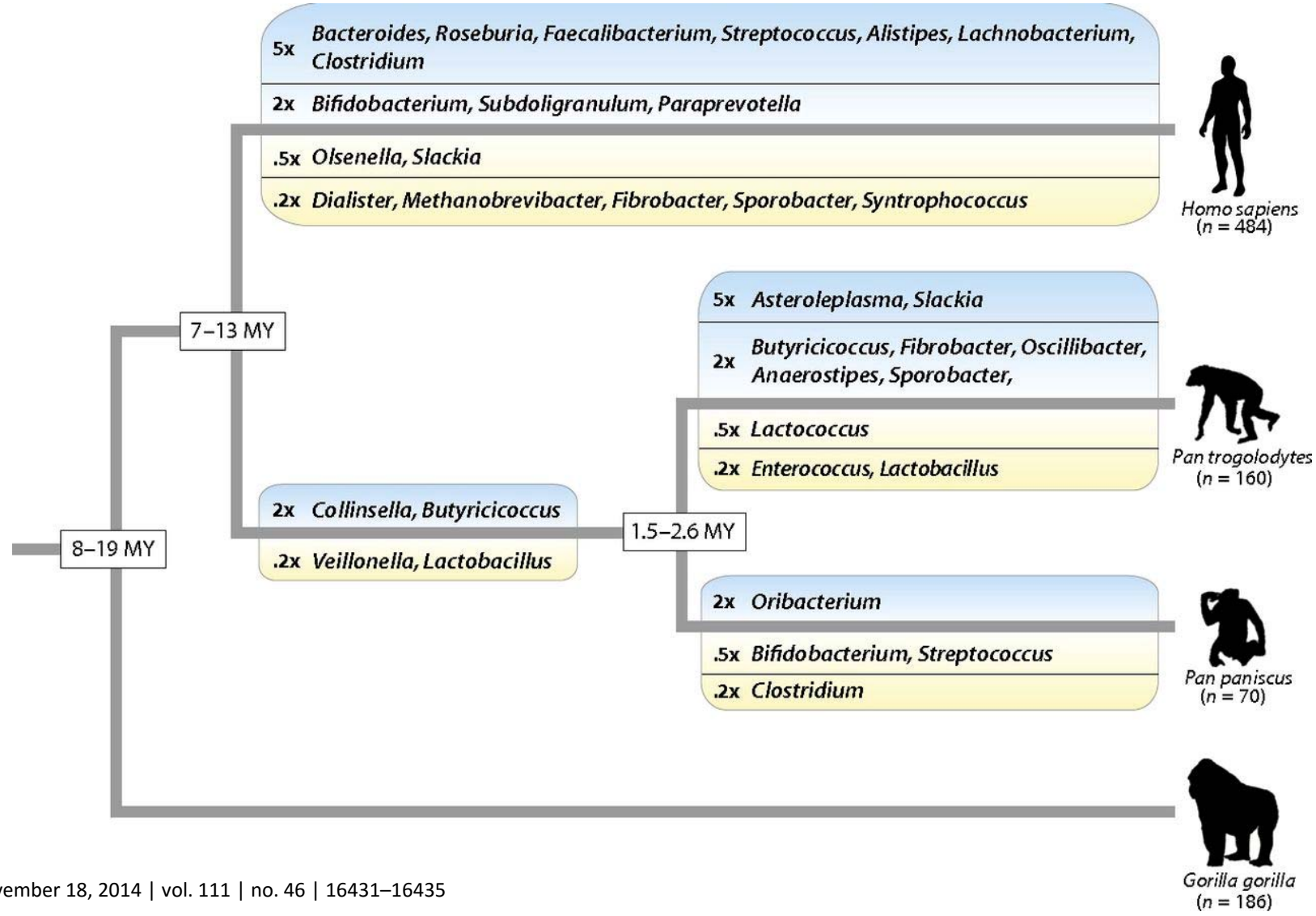
Genes (Basel). 2015 Sep; 6(3): 841–857

# *Tn*21'in evrimi




Genes (Basel). 2015 Sep; 6(3): 841–857

# Atasal çeşitliliği kaybediyoruz…



MICROBIAL ECOLOGY

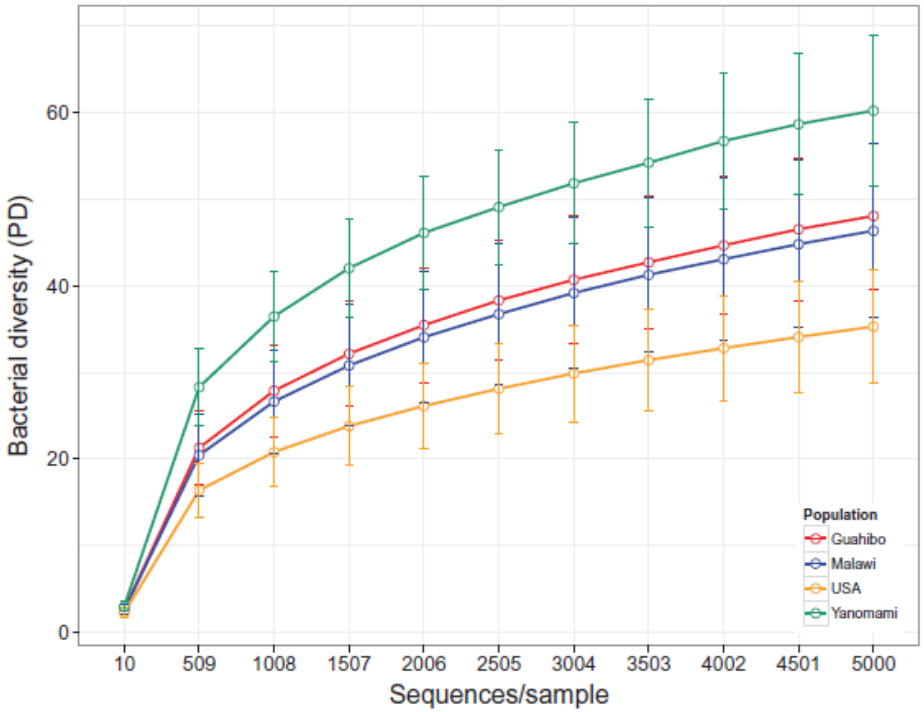
# The microbiome of uncontacted Amerindians

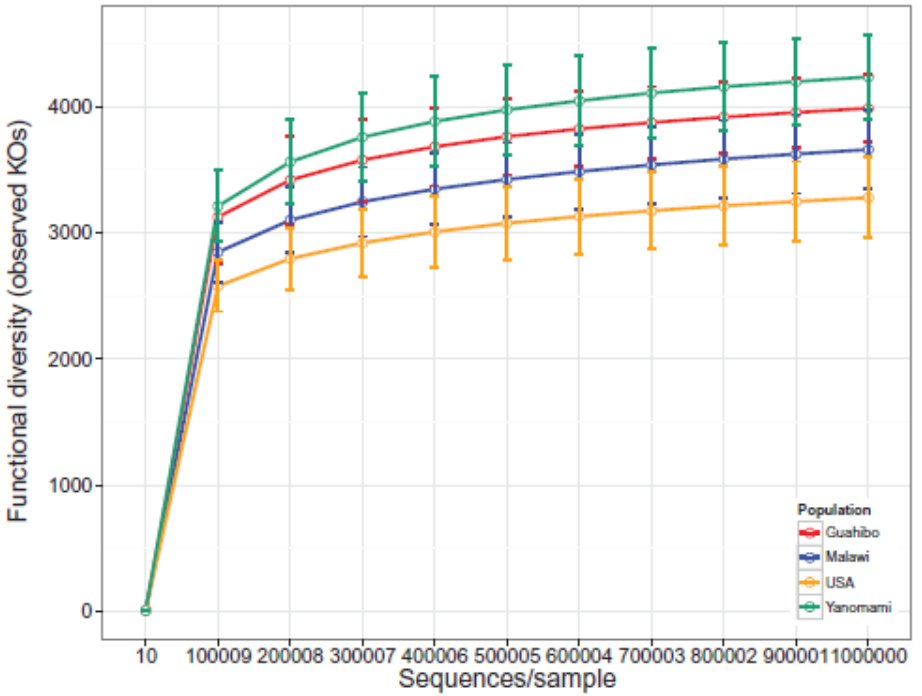
Clemente et al. Sci. Adv. 2015;1:e1500183 17 April 2015


CARLOS GARCIA RAWLINS/REUTERS/NEWSCOM

# Yanomami'lerin şaşırtıcı zenginliği

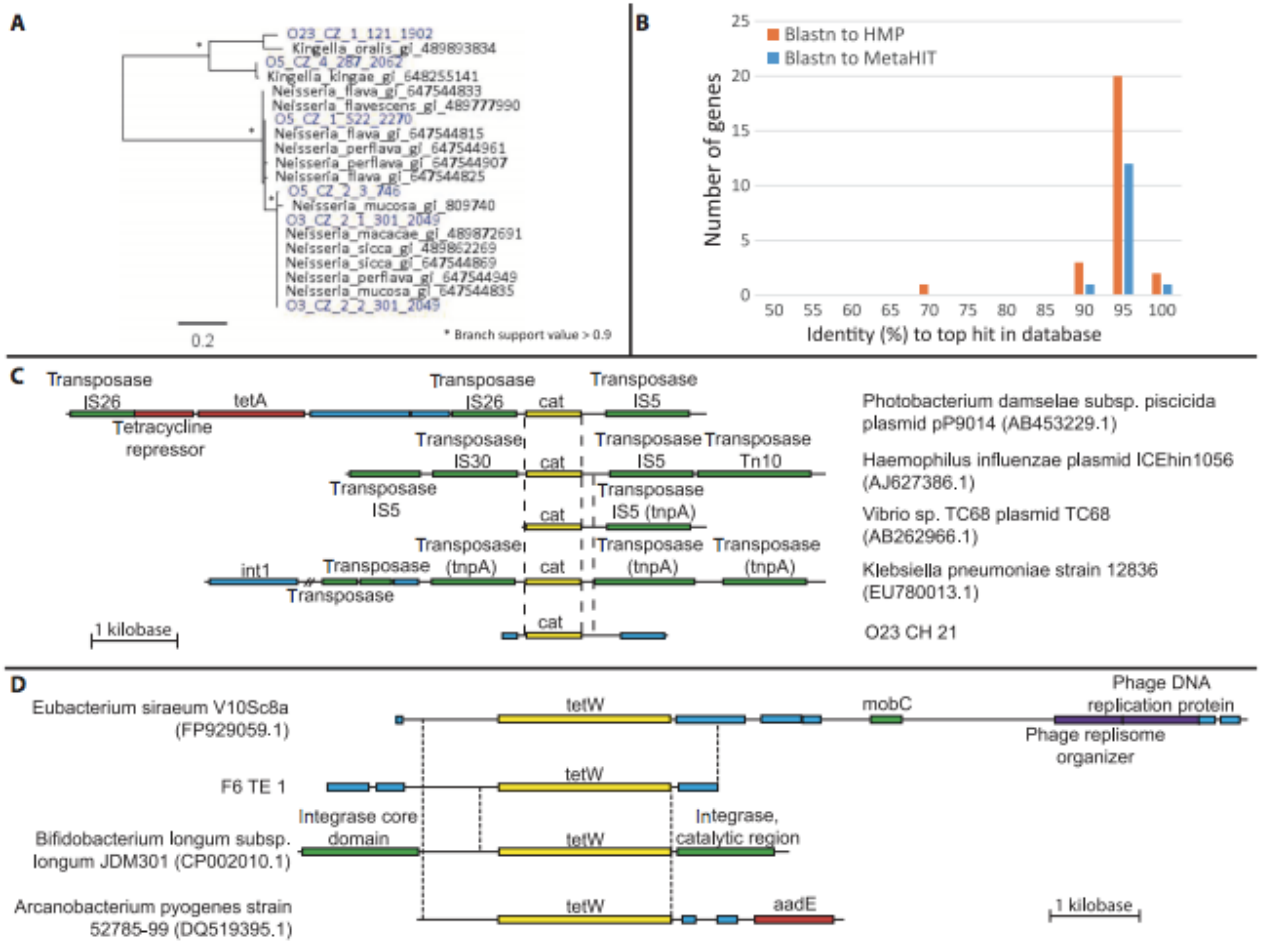
## bilinen en yüksek filogenetik ve işlevsel çeşitlilik




Clemente et al. Sci. Adv. 2015;1:e1500183 17 April 2015

# Mikrobiyomdaki antibiyotik direnç genleri




**ig. 3. Representative AR genes captured through functional metage-omic selection of Amerindian oral and fecal microbiota.** (**A**) Maximum kelihood (ML) tree of ceftazidime-resistant PBPs from Amerindian oral mi-robiota (blue) and their top blastx hits in NCBI nr (black). (**B**) Identity (%) of ne 28 AR genes to their top hits in HMP and MetaHIT (blastn). Fourteen ligned to MetaHIT, all isolated from fecal microbiota. (**C**) Chloramphenicol acetyltransferase (*cat*) from O23_CH_21 and homologs in NCBI nt (nucleotide database). Dashed lines indicate 99% identical sequences. Dashes indicate omitted sequence (8487..25716). (**D**) *tetW* from F6_TE_1 and homologs in NCBI nt. Dashed lines indicate 98 to 99% identical sequences. Sequences are to scale. Yellow, AR gene; red, other resistance genes; green, mobile genetic elements; purple, bacteriophage genes; blue, other.

Clemente et al. Sci. Adv. 2015;1:e1500183 17 April 2015

# Antibiyotiklerin tarihi ya da antibiyotikler neden var?

- Milyarlarca yıldır var (Microbiol. Mol. Biol. Rev. 2010; 74, 417-433, Trends Microbiol. 2012; 20, 157–159. )
- Doğal ortamda kısıtlı kaynaklara erişim açısından üreticisine seçici avantaj sağlıyabilir?
- Hücreler arası sinyal iletiminde rolü vardır? (PNAS 2006; 103: 19484-19489)
  - Örnek: Biyofilm oluşumu

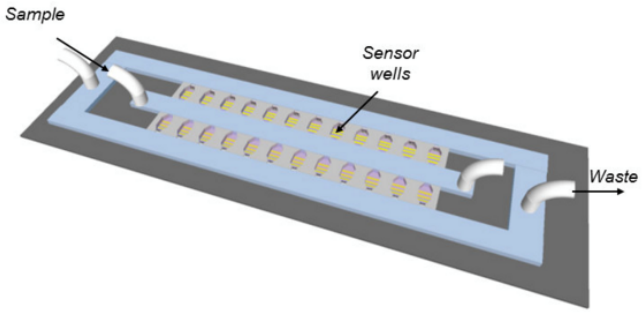
# Toprak: *biyoaktif moleküllerin kaynağı*

## A new antibiotic kills pathogens without detectable resistance

Losee L. Ling[1]*, Tanja Schneider[2,3]*, Aaron J. Peoples[1], Amy L. Spoering[1], Ina Engels[2,3], Brian P. Conlon[4], Anna Mueller[2,3], Till F. Schäberle[3,5], Dallas E. Hughes[1], Slava Epstein[6], Michael Jones[7], Linos Lazarides[7], Victoria A. Steadman[7], Douglas R. Cohen[1], Cintia R. Felix[1], K. Ashley Fetterman[1], William P. Millett[1], Anthony G. Nitti[1], Ashley M. Zullo[1], Chao Chen[4] & Kim Lewis[4]

**Antibiotic resistance is spreading faster than the introduction of new compounds into clinical practice, causing a public health crisis. Most antibiotics were produced by screening soil microorganisms, but this limited resource of cultivable bacteria was overmined by the 1960s. Synthetic approaches to produce antibiotics have been unable to replace this platform. Uncultured bacteria make up approximately 99% of all species in external environments, and are an untapped source of new antibiotics. We developed several methods to grow uncultured organisms by cultivation *in situ* or by using specific growth factors. Here we report a new antibiotic that we term teixobactin, discovered in a screen of uncultured bacteria. Teixobactin inhibits cell wall synthesis by binding to a highly conserved motif of lipid II (precursor of peptidoglycan) and lipid III (precursor of cell wall teichoic acid). We did not obtain any mutants of *Staphylococcus aureus* or *Mycobacterium tuberculosis* resistant to teixobactin. The properties of this compound suggest a path towards developing antibiotics that are likely to avoid development of resistance.**

iCHIP






APPLIED AND ENVIRONMENTAL MICROBIOLOGY, Apr. 2010, p. 2445–2450

# Direnç genlerinin (DG) kökeni

- Direnç genlerinin tarihi de **çok eskilere** dayanır.
  - "Serin β-laktamazlar" 2 milyar yıldan uzun süredir var (Drug Resist Updates 2004; 7: 111-123)
  - Bering bölgesinde 30,000 yıllık donmuş sedimentlerde β-laktam, tetrasiklin ve glikopeptit antibiyotiklere karşı direnç genleri (Nature 2011;477: 457-466)
  - OXA β-laktamazlar plazmitler üzerinde milyonlarca yıldır taşınıyor (J. Mol. Evol. 2002; 55, 314–321)

# Direnç genleri *neden* var?

- Üretici (producer) hipotezi
  - Antibiyotik üreten mikroorganizmalar kendilerini korumak için direnç geliştirir (PNAS 1973; 70:2276-2280)
- Dirence neden olan genler orijinal konağında tümüyle farklı bir işleve sahip?
  - *Providencia stuartii*'deki 2-N'-asetiltransferaz normal işlevi peptidoglikan modifikasyonu ancak aminoglikozitleri de parçalıyor (Front. Biosci. J. Virtual Libr. 4, D132 – D140).

# Context matters — the complex interplay between resistome genotypes and resistance phenotypes

Gautam Dantas[1,2] and Morten OA Sommer[3,4]

Current Opinion in Microbiology 2012, 15:577–582

**Definitions**

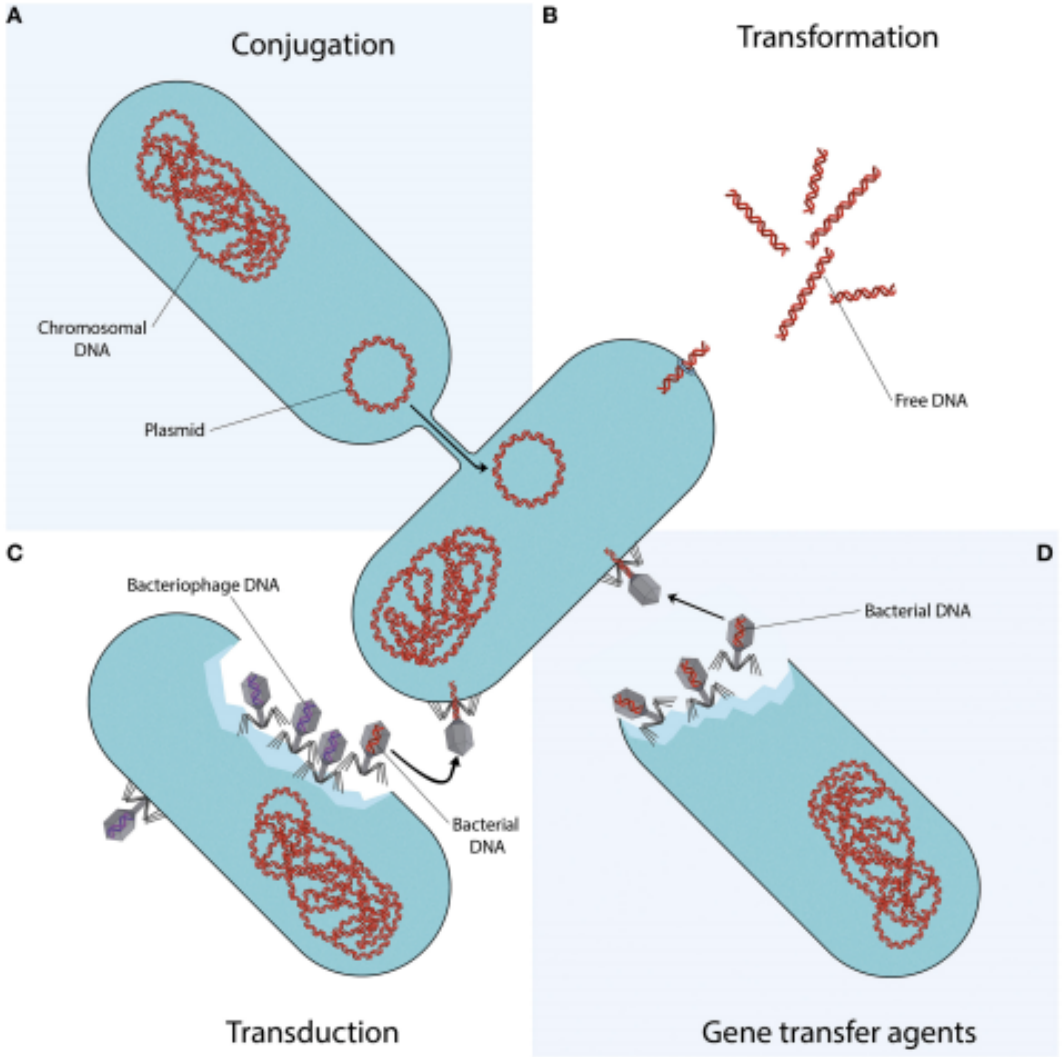
Antibiotic resistance: A phenotype, which is related to the ability of an organism to grow in the presence of an antibiotic.

Antibiotic resistome: A collection of genes, that is capable of conferring resistance towards antibiotics when expressed in a susceptible organism.

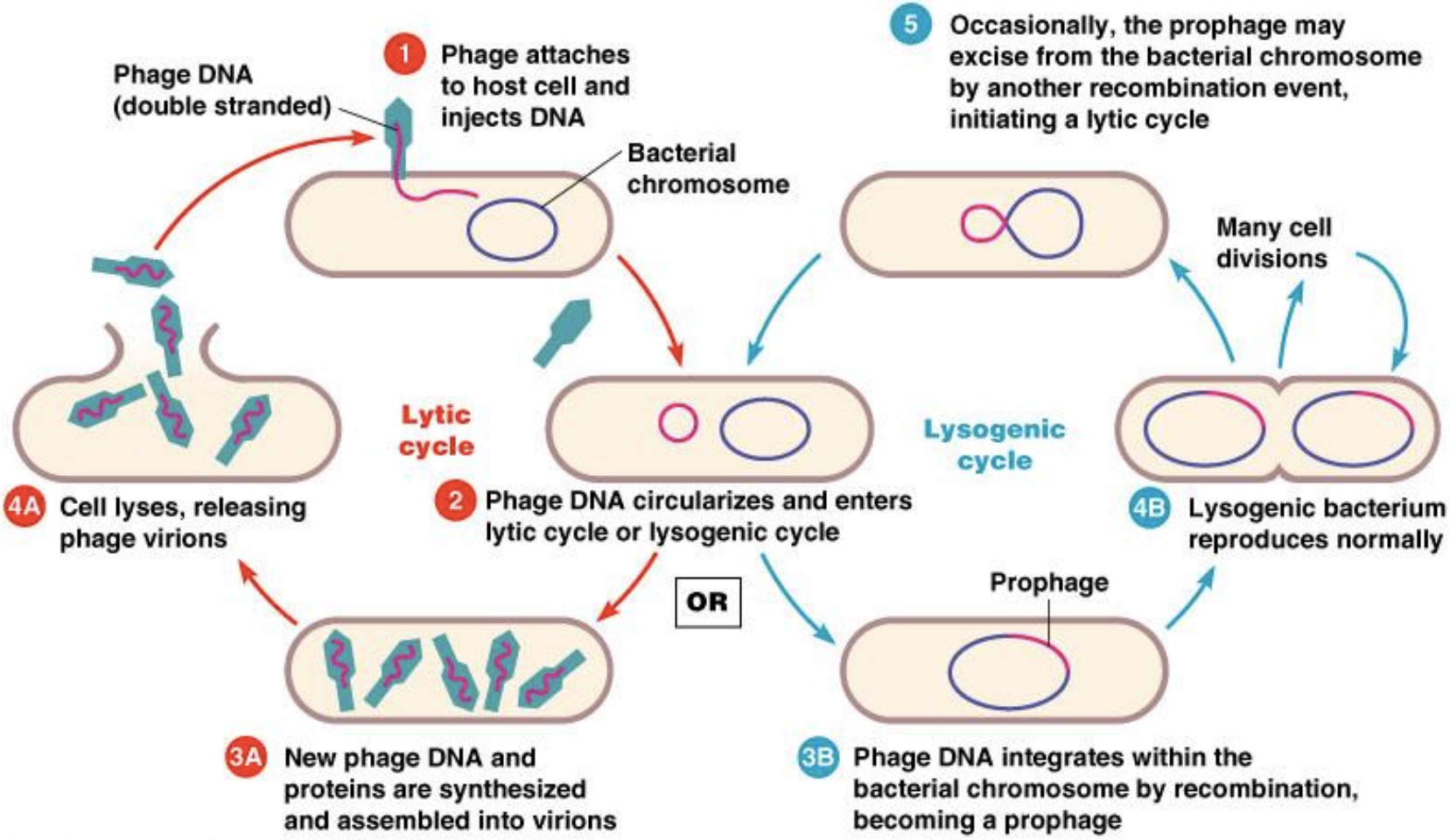
Silent resistance gene: A gene, which does not confer resistance to its native host, yet is capable of conferring resistance when expressed in other hosts


*Yatay gen aktarımı*

# Yatay gen aktarımı



# Barsak viromundaki fajların çoğu ılımlı fajlardır.



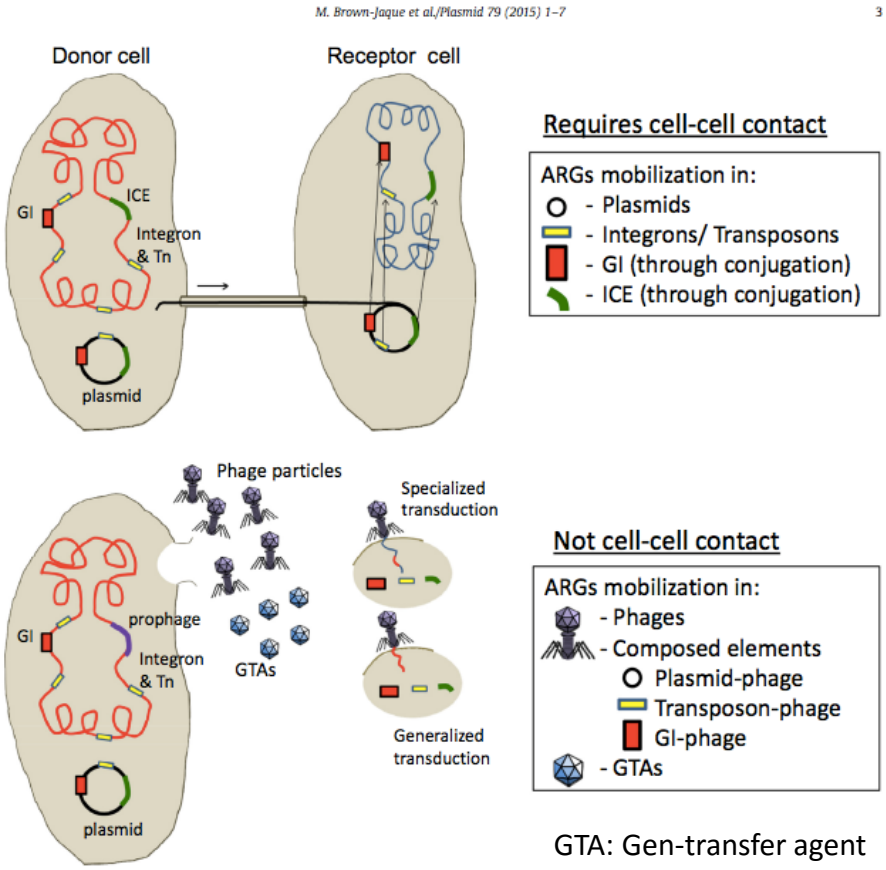
# Faj-mikrobiyota etkileşimleri

- Bakteri populasyon büyüklüğünü/dağılımını kontrol eder.
- Konakçılarının çevresel koşullara uyumunu arttırır/sağlar.
- Antibiyotik direnç genlerinin biriktiricileridir.

# Konakçılarının çevresel koşullara uyumunu arttırır/sağlar.

- Karbohidrat ve aminoasit metabolizmasında görev alan çok sayıda gen kodlarlar.
  - Örnek: musin ile etkileşen BACON domeyni
- Kriptik profajlar bakterilerin olumsuz koşullara dayanmalarını sağlar.
  - Örnek: antibiyotik, ozmotik, oksidatif stres, vb

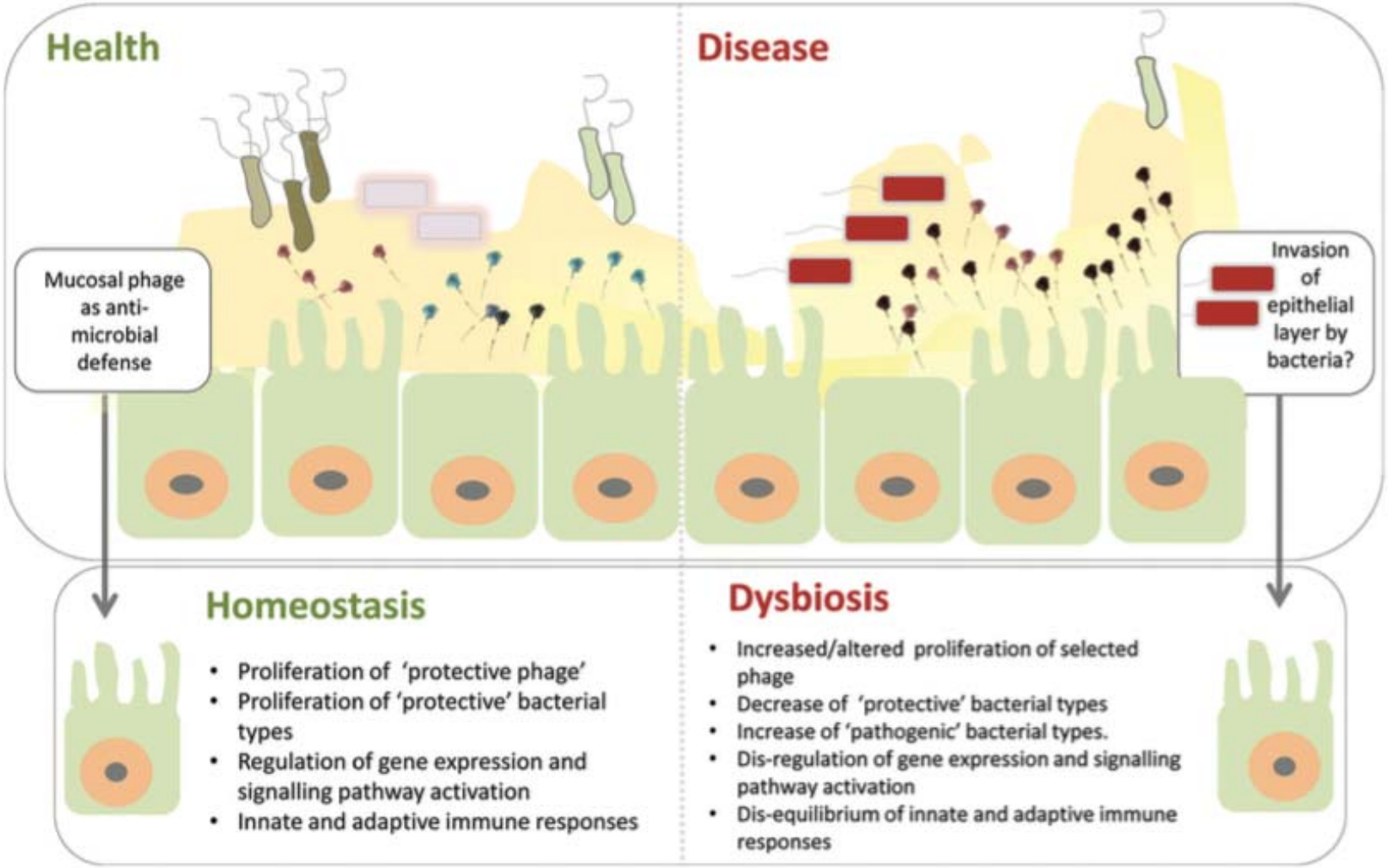
# Antibiyotik direnç genleri, fajlar ve faj-ilişkili elemanlar




GTA: Gen-transfer agent

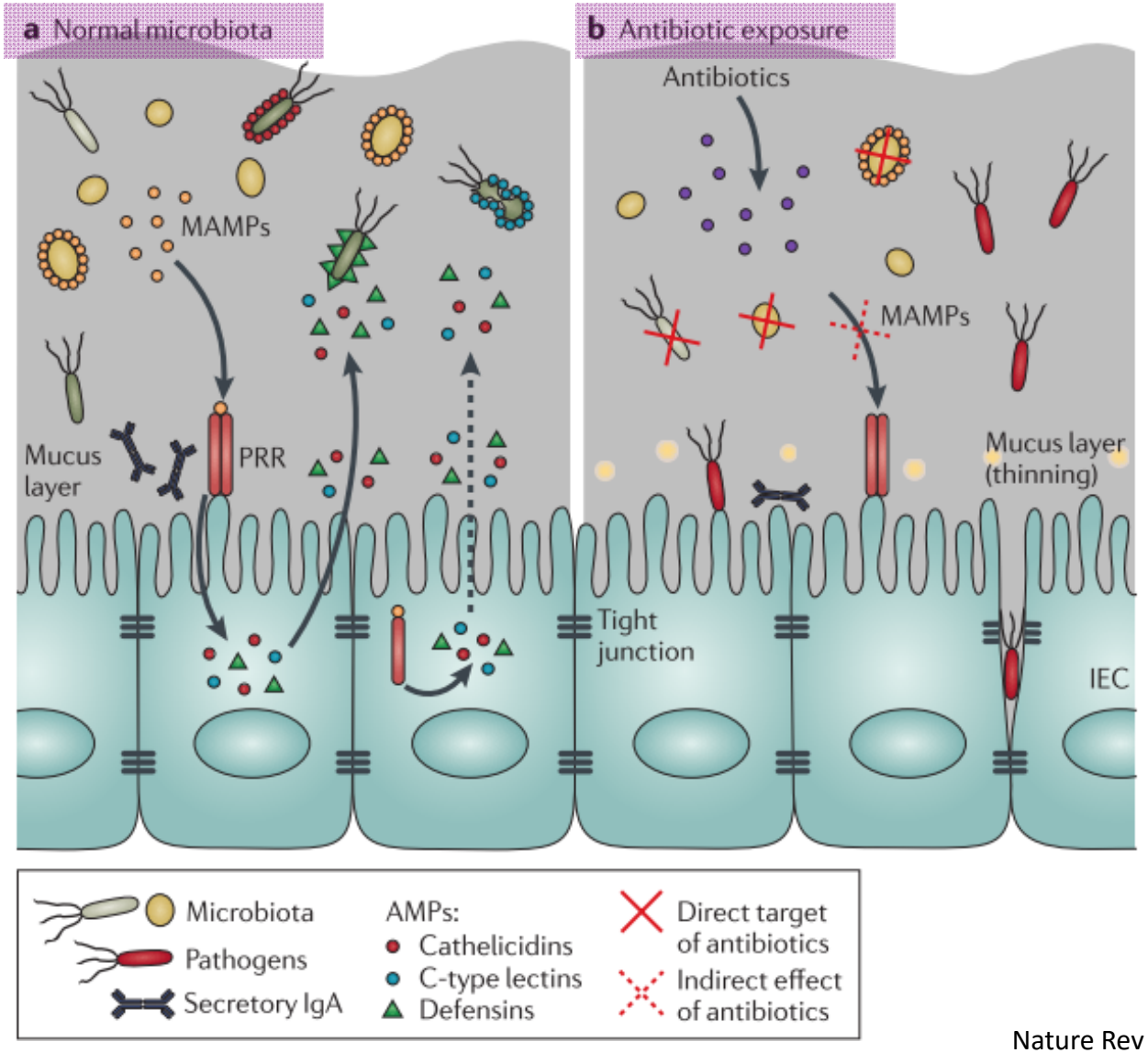
- Plazmid-faj
  - *P. aeruginosa* – AP 1 ve AP 12
    - imipenem/aztreonam/seftazidim direnci
- Genomik ada-faj
  - *S. aureus* fajı - SSCmec
- Transpozon-faj
  - *A. actinomycetemcomitans* da bulunan ve tetrasiklin direnci kodlayan transpozon

# Homeostaz-disbiyoz ve fajlar



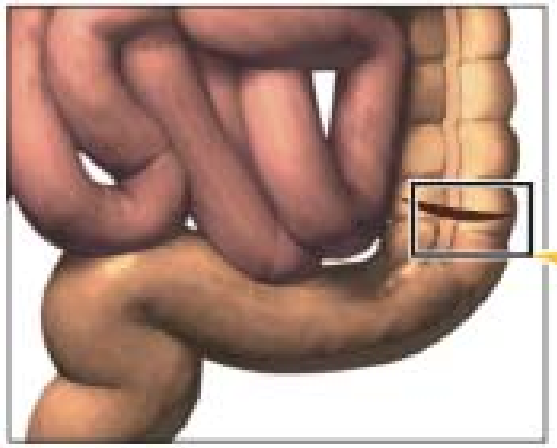
# Shifting the balance: antibiotic effects on host–microbiota mutualism

*Benjamin P. Willing*[*§], *Shannon L. Russell*[*‡§] and *B. Brett Finlay*[*‡]

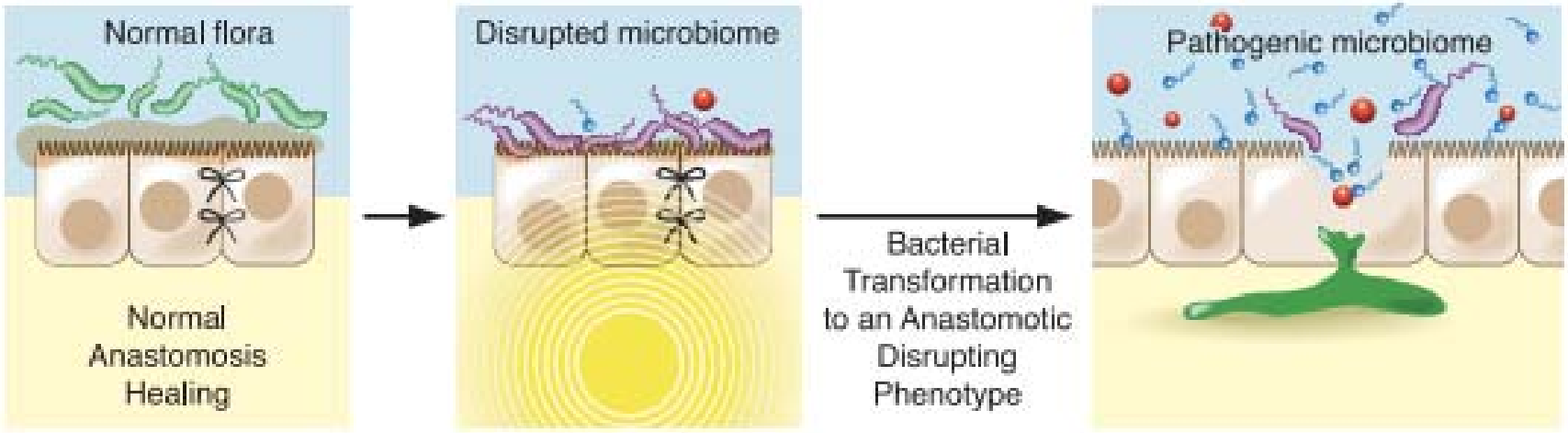



Nature Rev Microbiol 2011;9: 233

# Bağlam önemli!



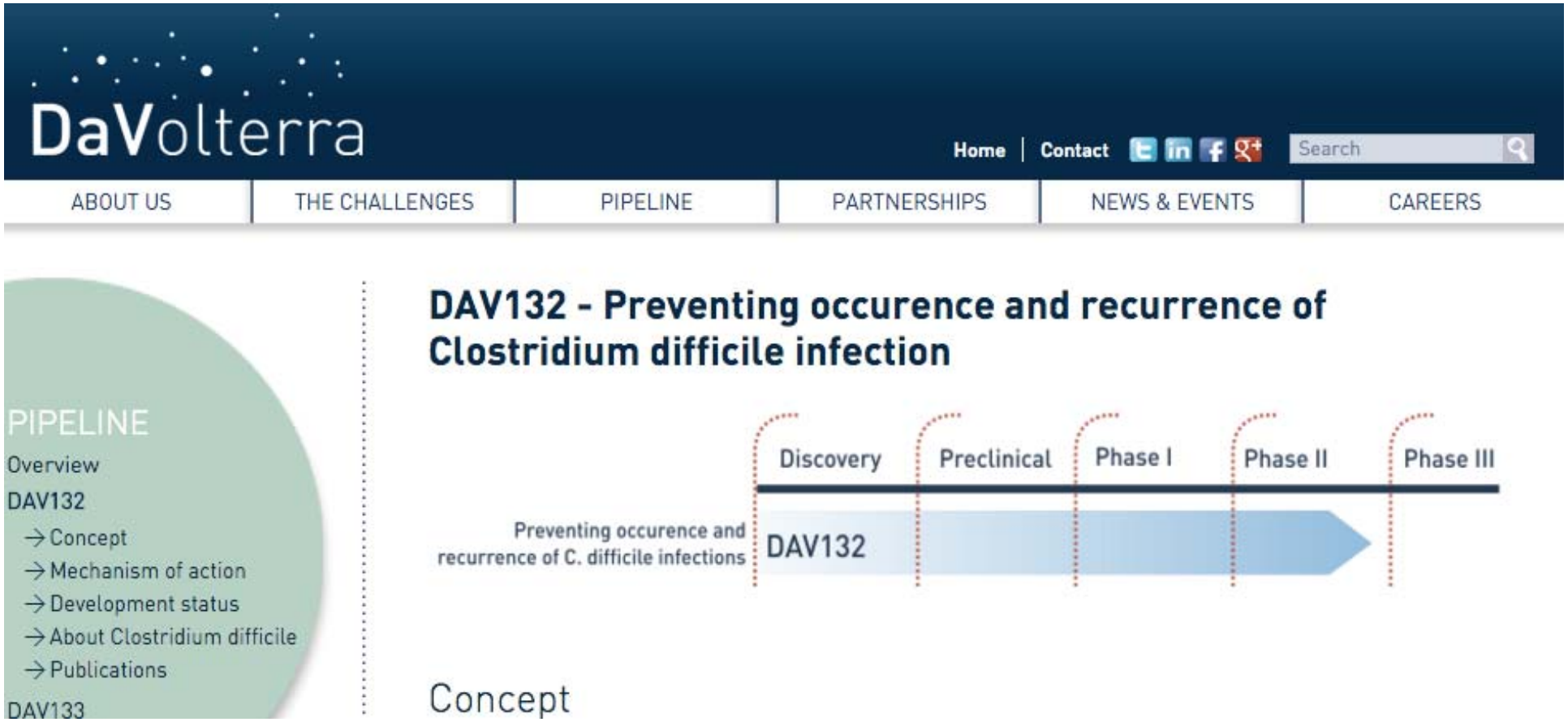
- Operasyon sırasında barsak oksijene maruz kalıyor
- Post-op hasta aç bırakılıyor
- Bakteriler fosfat gibi besin maddelerinden yoksun kalıyor
- Kollajen indirgeyen enzimler aktive oluyor




**Curing an anastomotic leak.**

Microbe—Volume 11, Number 1, 2016

# Yeni yollar…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## Table 2. Pathogen Directed Agents Under Development

| CDC classification | Target Pathogen | Compound | Sponsor | Type of molecule | Development Stage | Direct or Adjunctive Therapy | Single pathogen specificity | Target/mechanism of action | Novel class |
|---|---|---|---|---|---|---|---|---|---|
| Urgent Threat | **Carbapenemase-Resistant Enterobacteriaceae (CRE)** | Carbavance | The Medicines Company (with funding from BARDA) | Combination of meropenem & novel boron based b-lactamase inhibitor, RPX7009 | Phase 3, Tier B | Direct & Adjunctive | No | Cell wall biosynthesis (inhibition of PBPs and class A carbapenemases) | Yes |
| | | Plazomicin (ACHN-490) | Achaogen (with funding from BARDA) | Novel aminoglycoside | Phase 3, Tier B | Direct | No | Protein synthesis (ribosome) | No |
| | **Metallo-β-lactamase-expressing Enterobacteriaceae** | ATM-AVI | Allergan & AstraZeneca (with funding from BARDA & the IMI) | Combination of aztreonam & avibactam | Phase 2/3, Tier C | Direct & Adjunctive | No | Cell wall biosynthesis (inhibition of PBP3 in strains that express class B b-lactamases) | No |
| | ***Clostridium difficile*** | Bezlotoxumab | Merck | Anti-toxin B monclonal antibody | Registration | Adjunctive | Yes | Toxin B neutralization | Yes |
| | | SER-109 | Seres Therapeutics | Encapsulated Firmacute Eubacterial Spores | Phase 2/3, Tier C | Adjunctive | No | Microbiome (repopulate with beneficial bacteria) | Yes |
| | | CRS3123 (REP3123) | Crestone (with funding from NIAID) | Thienopyridinone | Phase 1 | Direct | No | Protein synthesis (Met tRNA synthetase) | Yes |
| | | Avidocin | Avidbiotics (with funding from NIAID) | Engineered bacteriocin | Preclinical | Direct | Yes | Membrane disruption | Yes |
| | ***Neisseria gonorrhoeae*** | Solithromycin | Cempra | Fluoroketolide | Phase 3, Tier B | Direct | No | Protein synthesis (ribosome) | No |
| | | Zoliflodacin (ETX0914) | Entasis (with funding from NIAID) | Spiropyrimidinetrione | Phase 2 | Direct | No | GyrB subunit of DNA topoisomerases | Yes |
| | | Gepotidacin (GSK2140944) | GlaxoSmithKline with funding from BARDA) | Acenaphthene (NBTI) | Phase 2 | Direct | No | GyrA subunit of DNA topoisomerases | Yes |
| | | P300847 | PTC Therapeutics | Novel aminoglycoside, ACHN-490 | Preclinical | Direct | Yes | Undisclosed | Yes |
| Serious Threat | ***Pseudomonas aeruginosa*** | POL7080 (RG7929) | Polyphor | Macrocycle (peptidomimetic) | Phase 2 | Direct | Yes | Membrane disruption (LptD) | Yes |
| | | MEDI3902 | MedImmune | Bispecific, opsonic monoclonal antibody | Phase 2 | Adjunctive | Yes | Psl (adhesion),PcrV (virulence), opsonophagocytic | Yes |
| | | AR101 | Aridis (with funding from NIAID) | Anti-LPS monoclonal antibody | Phase 2 | Adjunctive | Yes | Serotype O1 strains | Yes |
| | | Ampliphage | AmphiPhi Biosciences (with funding from Cystic Fibrosis Foundation) | Bacteriophage cocktail | Preclinical | Direct | Yes | Membrane disruption | Yes |
| | | M64 | Spero Therapeutics | Benzamide- benzimidazole | Preclinical | Adjunctive | Yes | Virulence inhibitor (MvfR) | Yes |
| | | Anticalin | Pieris/Sanofi | Tetraspecific engineered lipocalin | Preclinical | Adjunctive | Yes | Siderophore production | Yes |
| | **Methicillin-resistant *Staphylococcus aureus* (MRSA)** | MEDI4893 | MedImmune | Anti-alpha toxin monoclonal antibody | Phase 2 | Adjunctive | Yes | Alpha toxin neutralization | Yes |
| | | AR301 | Aridis (with funding from NIAID) | Anti-alpha toxin monoclonal antibody | Phase 2 | Adjunctive | Yes | Alpha toxin neutralization | Yes |
| | | SASPject PT1.2 | Phico Therapeutics (with funding from Wellcome Trust) | "Nano-delivered" DNA binding protein | Phase 2 | Direct | Yes | DNA replication | Yes |
| | | Debio 1450 (AFN-1252) | DebioPharm | Aryl acrylamide | Phase 2 | Direct | Yes | Fatty acid biosynthesis (FabI) | Yes |
| | | CG40059 | Crystal Genomics | Alkoxypyridinone | Phase 2 | Direct | Yes | Fatty acid biosynthesis (FabI) | Yes |
| | | ASN100 | Arsanis (with funding from FFG) | Combination of two anti-toxin monoclonal antibodies | Preclinical | Adjunctive | Yes | Neutralization of six cytolysins | Yes |

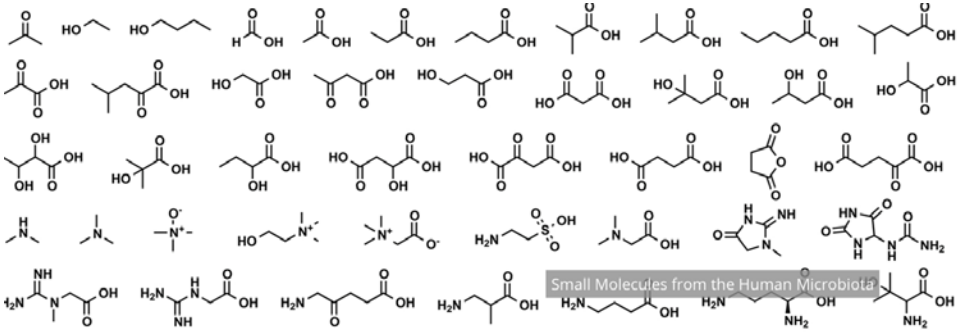
# Barsak mikrobiyotası yeni *biyoaktif moleküllerin* kaynağı olabilir.

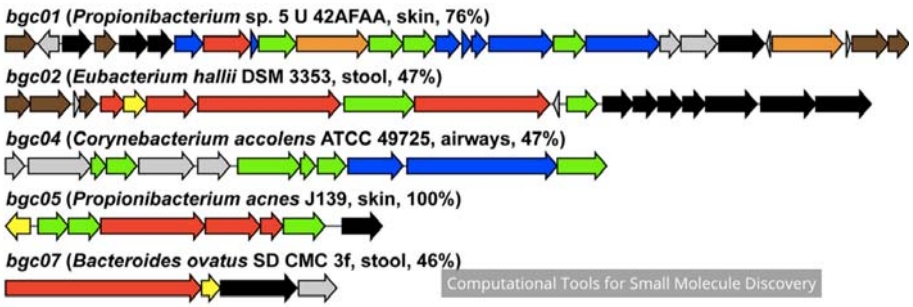
- Tiyopeptit antibiyotikler, polifenoller, gallik asit ve pirogallol, vb

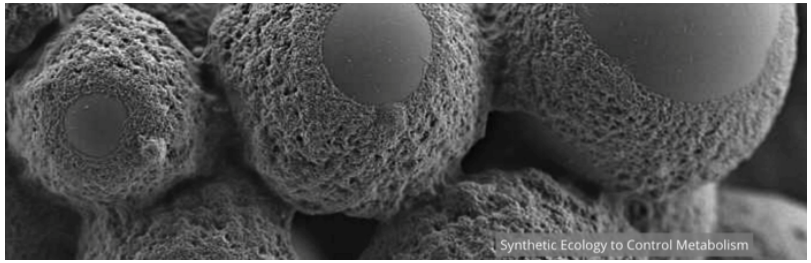
The New York Academy of Sciences. Advances in Human Microbiome Science: Intestinal Diseases. Academy eBriefings. 2015. Available at: www.nyas.org/Microbiome2015-eB

Journal of Nutritional Biochemistry 24 (2013) 1415–1422

Front Microbiol. 2014 Dec 5;5:684. doi: 10.3389/fmicb.2014.00684. eCollection 2014.

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# Son söz


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