Nanometrik Partiküller

Dr. Oral ÖNCÜL
Istanbul Tıp Fakültesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji ABD

Sunum Planı

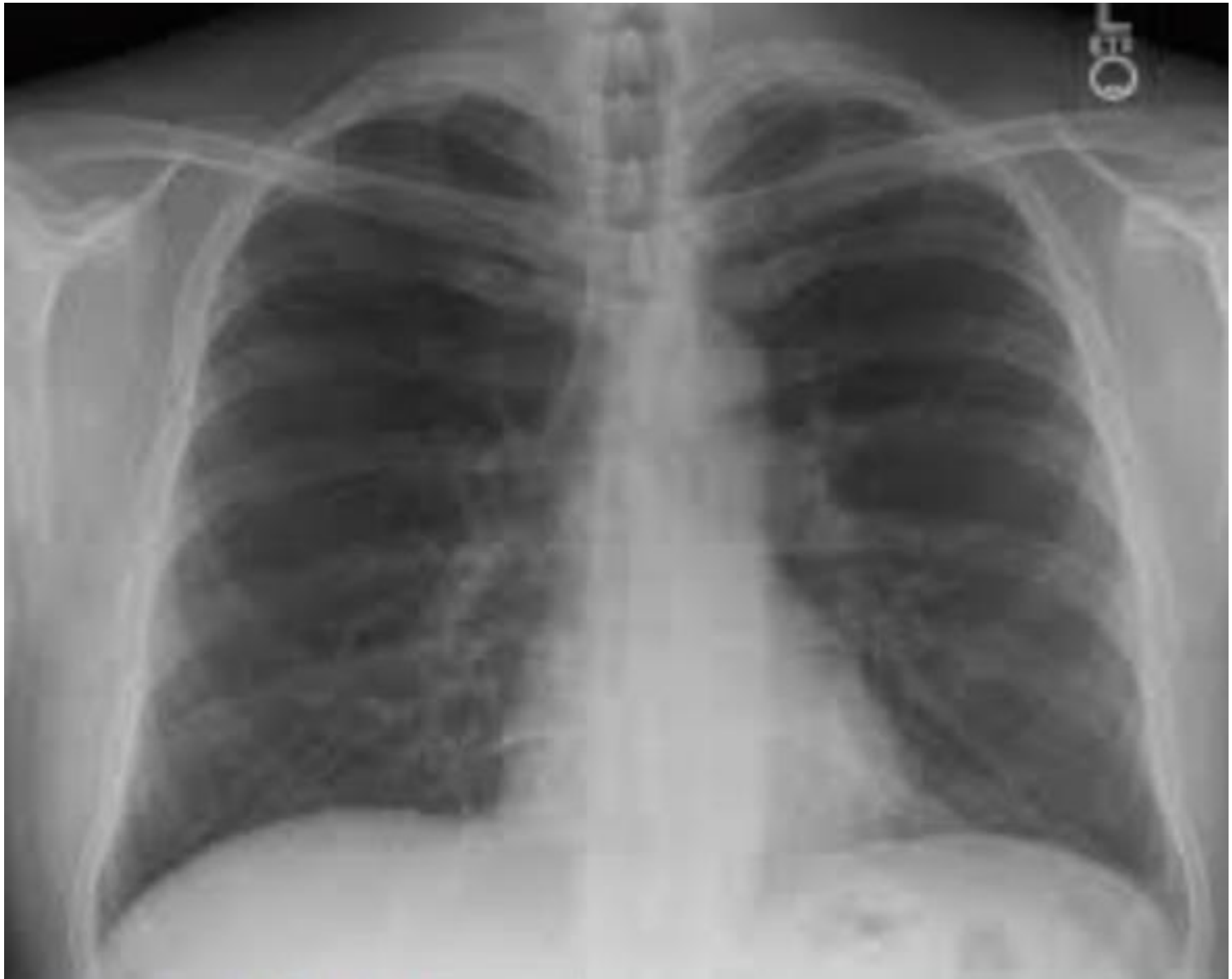
- Olgu sunumu
- Antibiyotikler ve yeni arayışlar
- Nanopartiküler sistemin tanımı
- Nano sistem içerisinde antibiyotikler
- Gelecek..

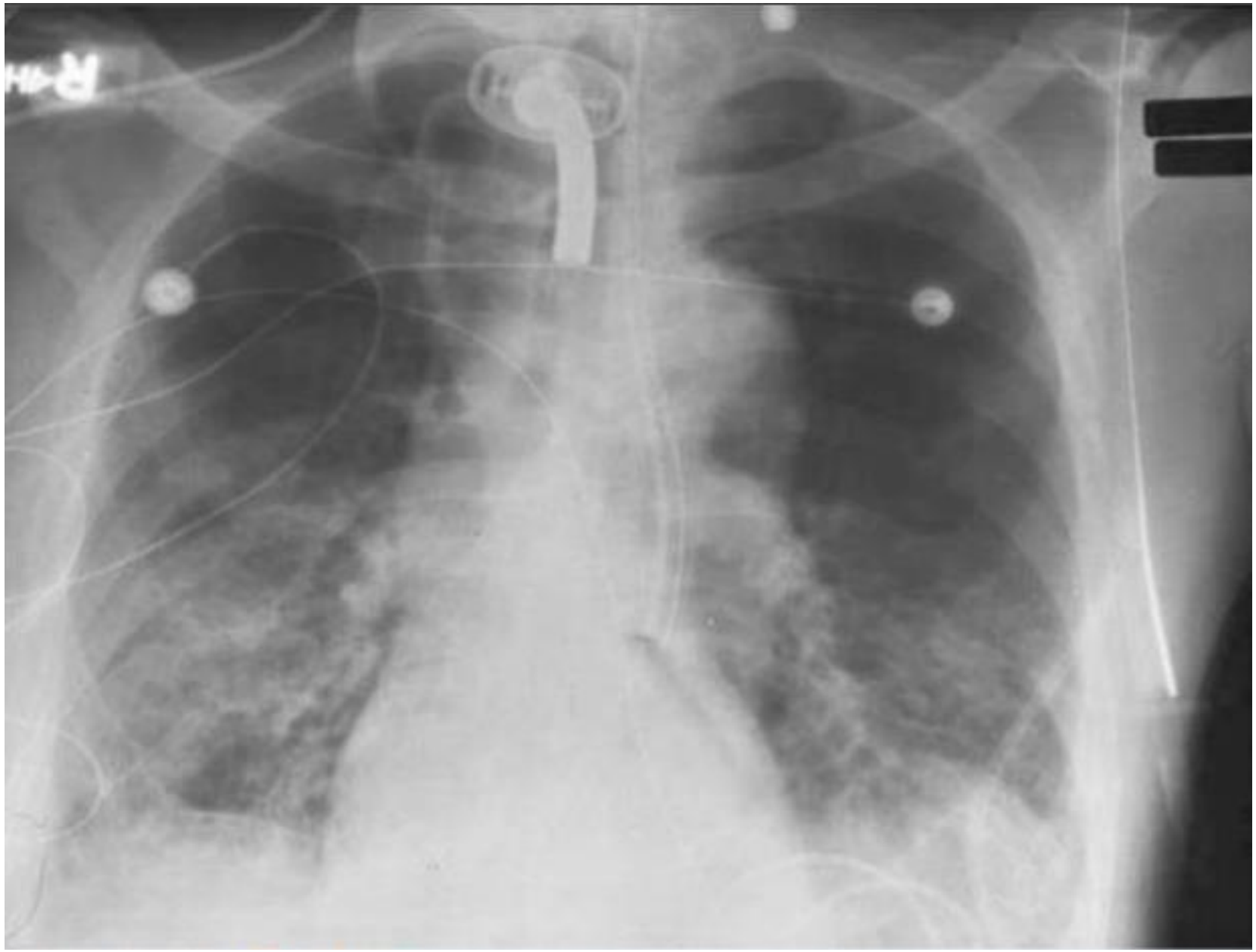
Olgu

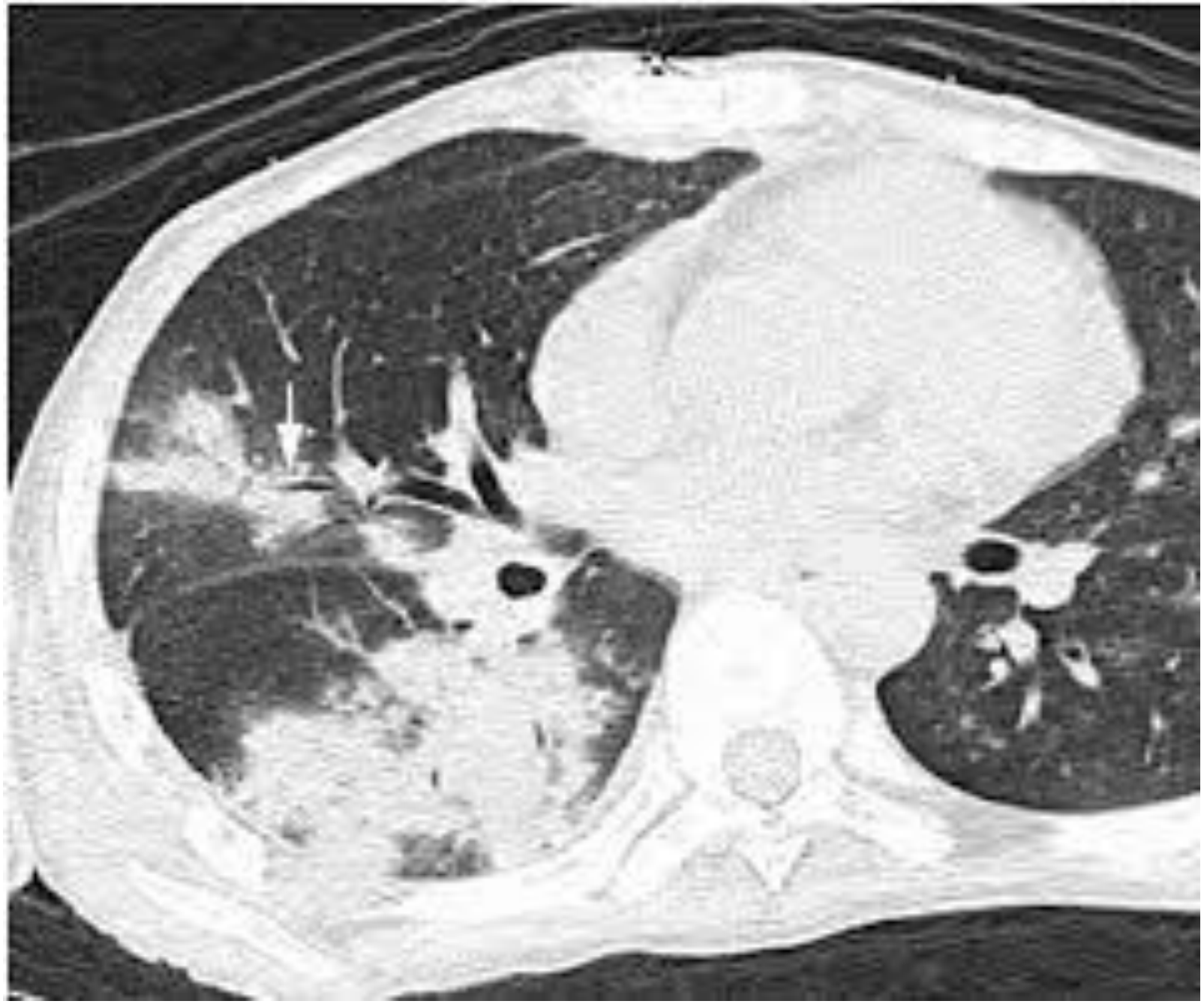
- 73 yaşında kadın
- Bilinen HT ve regüle DM hastası
- Ani şuur kaybı nedeniyle acil servisten YBÜ'sine yatış
- Beşinci gün şuur açılmaya başlıyor, halen entübe
- Yedinci gün O_2 saturasyonunda azalma,
- Solunum sekresyonunda artış ve koyulaşma
- Ateş: 37.8^{o}C, CRP'de üç kat artış, BK: 10.200/mm^3

Olgu

- Aynı gün ETA kültürü ve kan kültürü alınmış
- Ampirik olarak hastaya PIP/TAZ (3X4.5 gr/gün IV) ve levofloksasin (1x750 mg/gün IV) başlanmış.
- Sekizinci gün ateş: 38.6^{o}C ve BK sayısı: 16.000/mm^{3}
- Kan kültürü tekrarlanmış.
- Diğer kültürlerde
  - Kan kültüründe henüz üreme yok
  - ETA kültüründe Klebsiella pneumoniae izole edilmiş.







Olgu

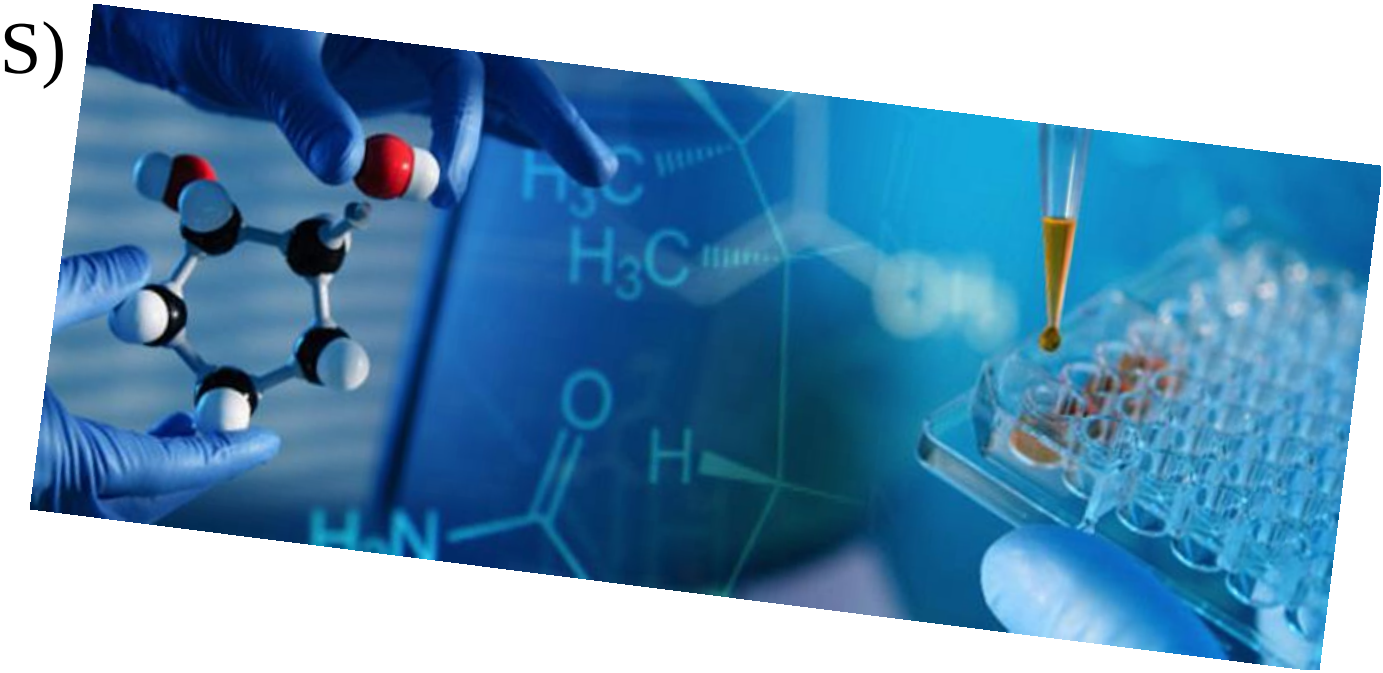
- *Klebsiella pneumoniae* suşunun karbapenemlere dirençli olduğu saptandı.
- Tedavi değişikliği yapıldı.
- Kolistin 300 mg yükleme dozu, 3 x 150 mg IV
- Kolistin 2 x 75 mg inhaler
- Meropenem 3 x 1 gr IV
- Tedaviye rağmen hastanın genel durumu düzelmedi
- Tedavinin 11. günü hasta solunum ve dolaşım yetmezliğiyle kaybedildi.

Olgu

- Uygun tedaviye rağmen hastanın kaybedilme nedenleri:
- Antibiyotik dirençli bakteri infeksiyonu
- Biyofilm oluşumu
- Antiyotiklerin düşük doku konsantrasyonu
- Diğer risk faktörleri

Virulansı ve Biyofilm Oluşumunu Engelleyici Yeni Yaklaşımlar

- Anti-quorum sinyaller (Anti-QS)
- Anti-toksinler
- Antibiyotik kaplı yüzeyler
- Nanoteknolojik yöntemler



Nanoteknoloji Nedir?

Günümüzde hemen her alanda kısa sürede yaygınlaşan önemli bir teknoloji

Maddelerin atomik ve moleküler düzeylerde kontrol ve işlem görebilir forma dönüştürülmesidir

Kullanılabilirlik için ideal boyut 100 nm ve altında olması arzulanır

Birçok farklı alanda kullanımı söz konusudur.

Nanoteknoloji

- Fizik, kimya, biyoloji ve mühendislik alanlarıdna kullanılan birçok madde, alet ve makinenin çok küçük fonksiyonlarda çalışmasını sağlayan bir alandır.

Nanoteknolojinin Kısa bir Hikayesi

29 Aralık 1959

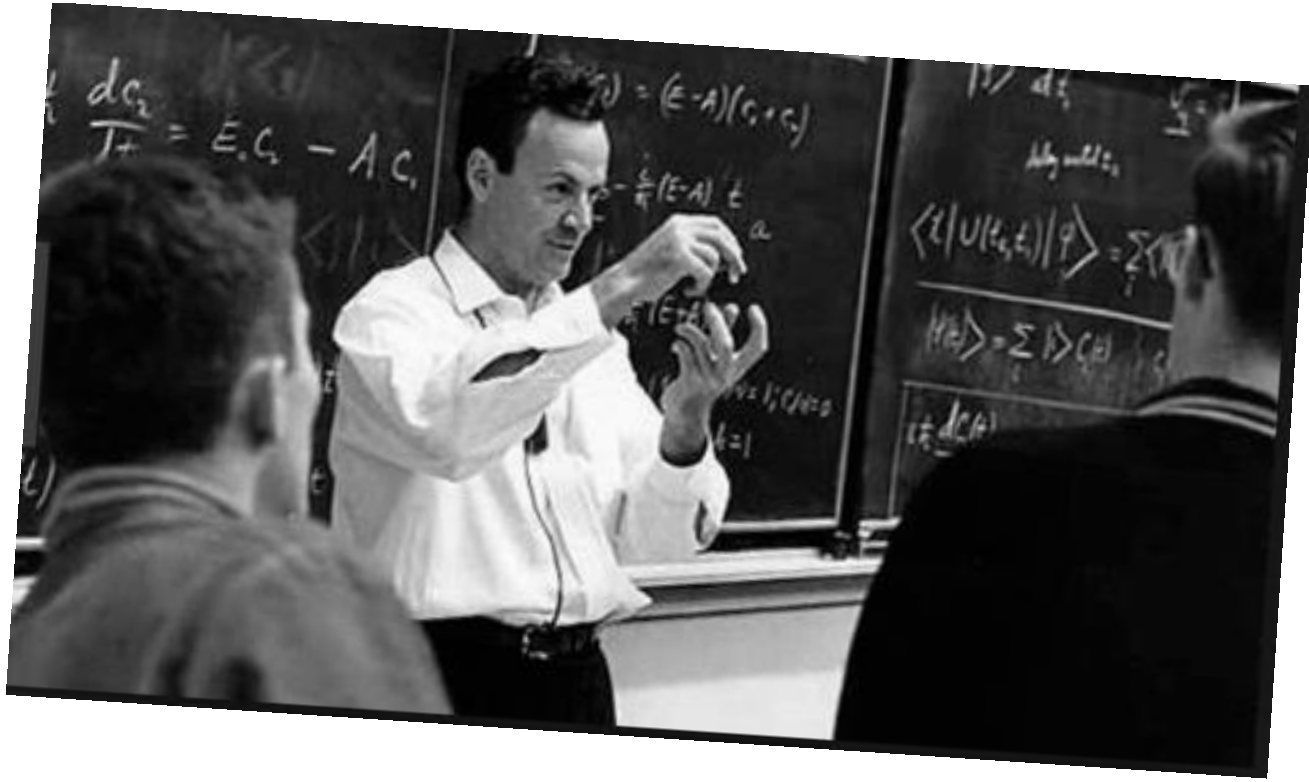
Richard Feynman

American Physical Society Meeting

“There’s Plenty of Room at the Bottom”

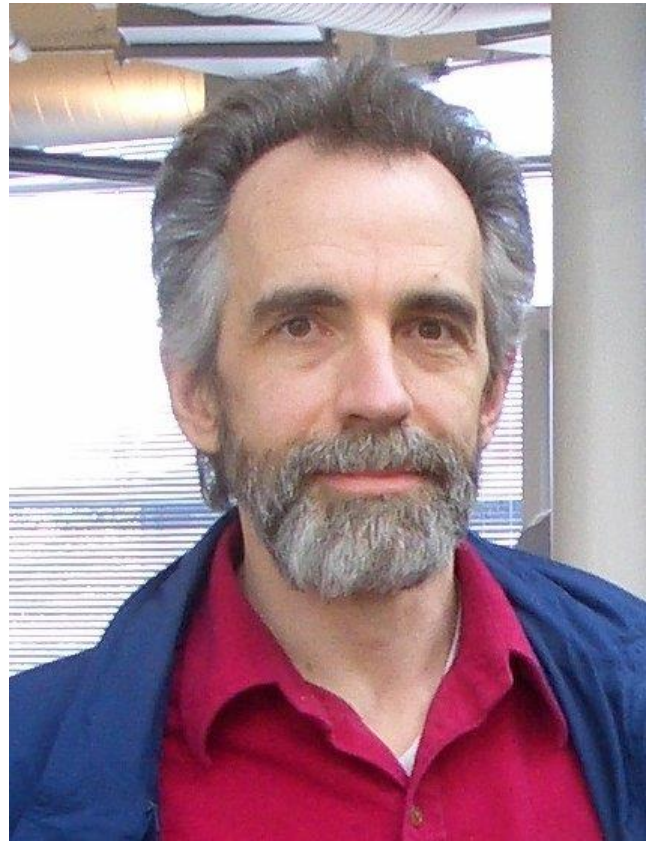
Maddelerin nano boyutunda manüplasyonu

Nanoteknoloji fikrinin ilk kez ortaya çıkışı



Nanoteknoloji ve Endüstriyel Uygulamaları

- Kaliforniya Foresight Enstitüsü Başkanı
- Dr. Eric Drexler
- Massachusetts Teknoloji Enstitüsü (MIT)
- Biyolojik sistemlerden esinlenerek moleküler düzeyde makinaların yapılabileceği görüşü
- Nanoteknoloji terminolojisinin ilk olarak ortaya çıkışı.

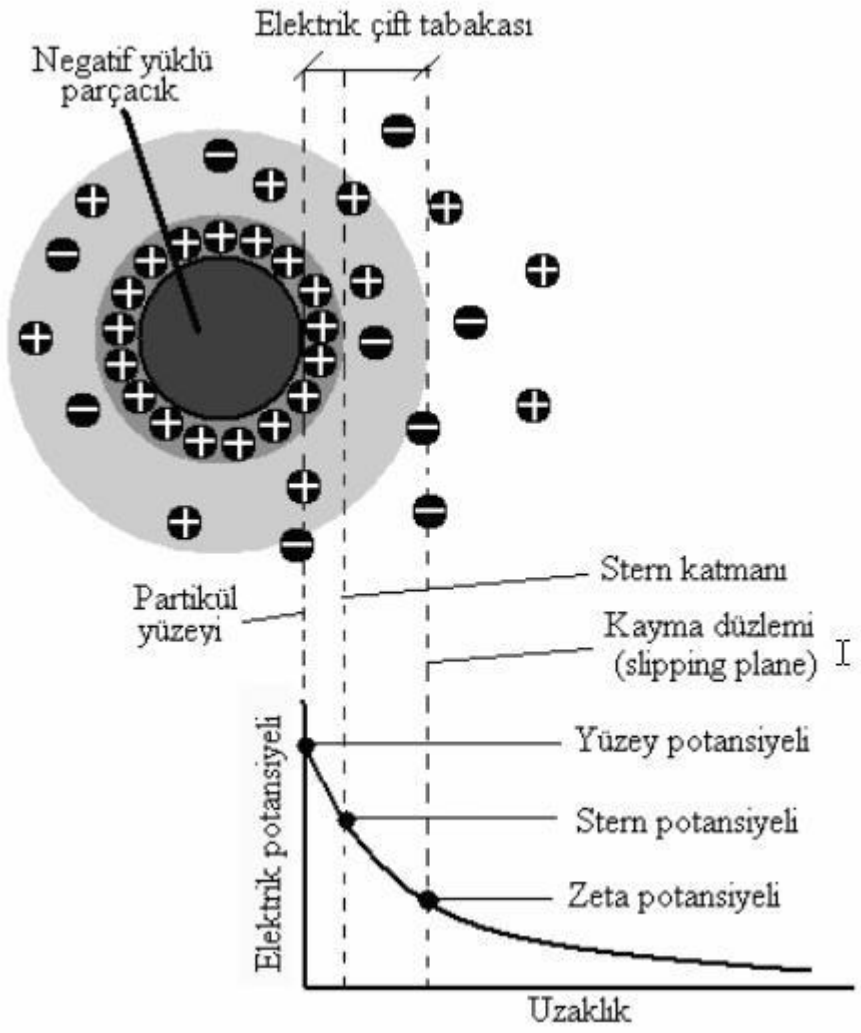


Nanoteknoloji ve Endüstriyel Uygulamaları

- Nano (Yunanca) '*nannos*' kelimesinden gelir
- *'Küçük yaşlı adam'* ya da '*cüce'* anlamına gelir.
- Günümüzde nano:
  - Metre $1/10^{9}$
  - Santimetre $1/10^{7}$
  - Milimetre $1/10^{6}$

Nanopartiküllerde Etkinliği Artıran Faktörler

- Kimyasal yapısı
- Partikül büyüklüğü,
- Partikülün şekli
- Zeta potansiyali



Nanoteknoloji ve Endüstriyel Uygulamaları

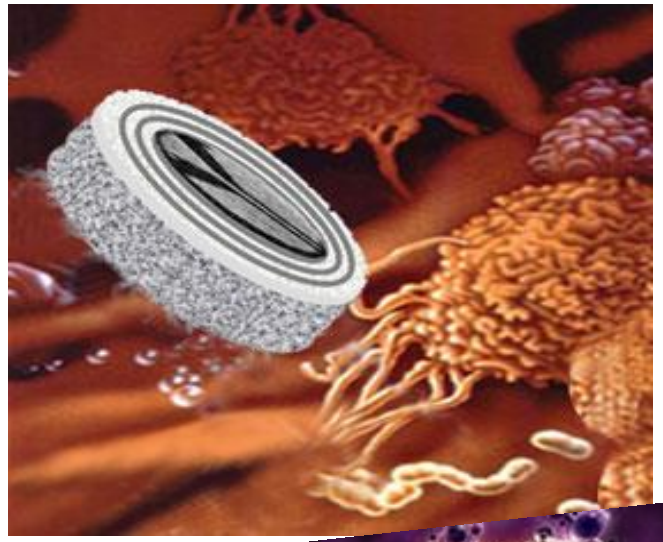
- Tıp ve sağlık sektörü
- Nano Elektronik ve Bilgisayar Teknolojileri
- Malzeme ve İmalat Sektörü
- Havacılık ve Uzay Araştırmaları
- Çevre ve Enerji
- Biyoteknoloji ve Tarım
- Savunma Sektörü

Nanoteknolojinin Sağlıkta Kullanım Alanları

- İlaç sektöründe
- Moleküler tanılarda
- Kanser tedavisinde
- Gen uygulamalarında
- Diş bakımında ve tedavisinde
- Ortopedik uygulamalar ve tedavilerinde
- Kalp hastalıklarının tedavisinde
- İnfeksiyon hastalıklarının tedavisinde

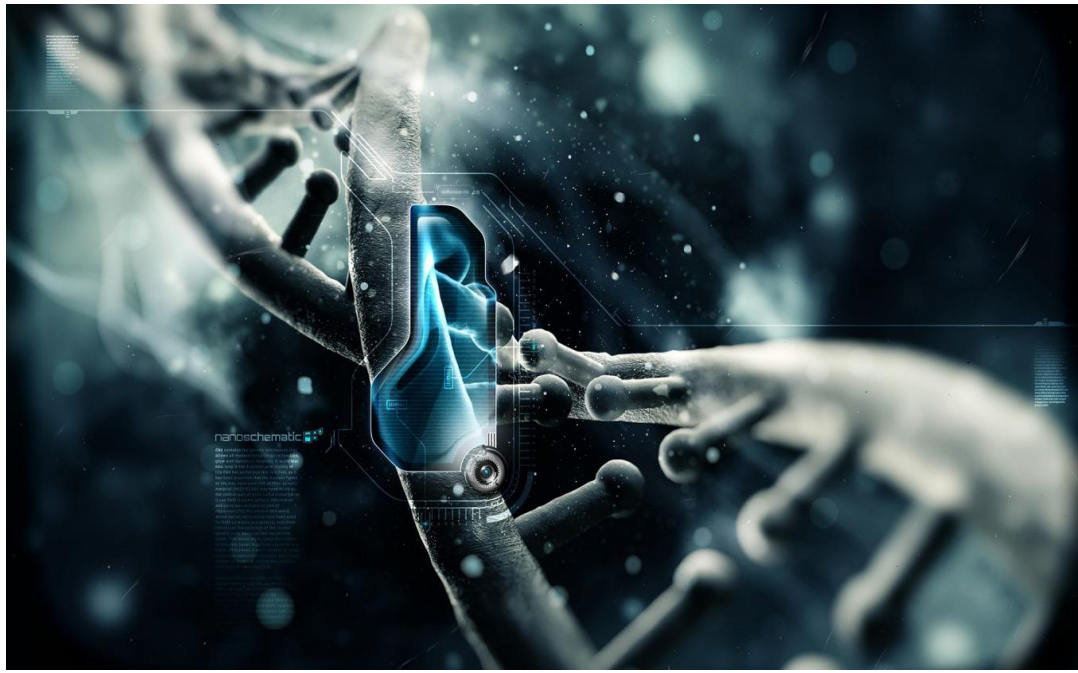
İlaç Sektöründe Nanoteknoloji

- Üzerinde nanopartiküller yüklenmiş ilaçlar
- Doğrudan hedef dokuya taşınma
- Doğrudan etkileşim
- Albümine bağlanmadan sağlanan etki
- Farmakodinamik etkide artış
- Biyoyararlanımda artış
- Güçlü biyolojik aktivite..



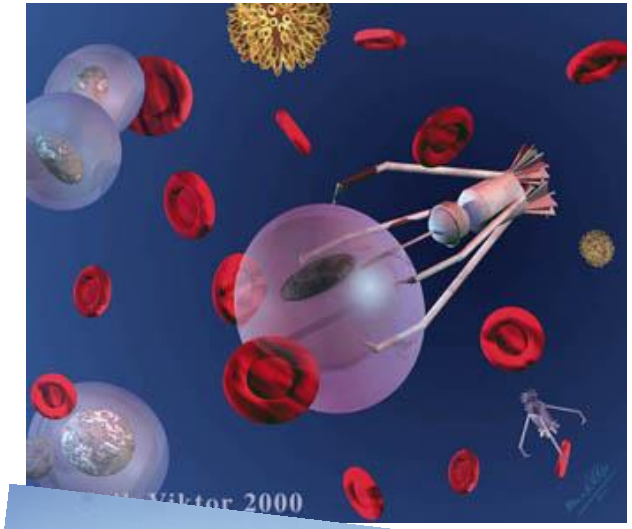
Gen Uygulamalarında Nanoteknoloji

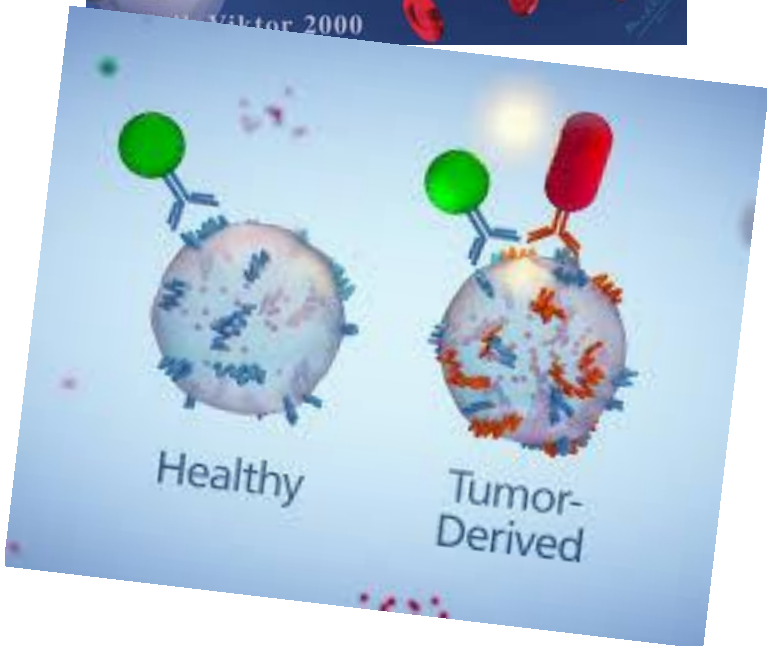
- Hasarlı genlerin düzeltilmesi
- Kalıtsal hastalıkların önlenmesi amacıyla ortaya çıkan bir tedavi yöntemidir.
- Nanoteknoloji, gen yapılarına ulaşma ve etki etme potansiyelini kazandırmıştır.



Kanserlerin Tedavisinde Nanoteknoloji

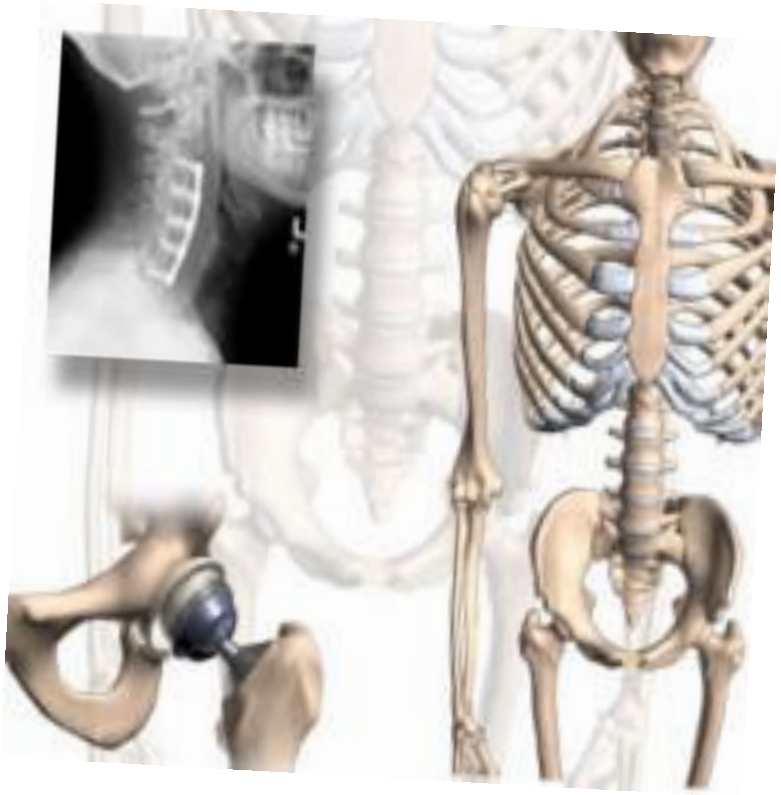
- Nanopartiküller ve nanorobotlar ile tümör hücre etkileşimi
- Nanorobotlar ilacı hedef tümör dokusuna taşır
- Beraberinde yeni odakları saptar
- Böylece kanserli hücreler diğer hücrelere zarar vermeden yok edilir.





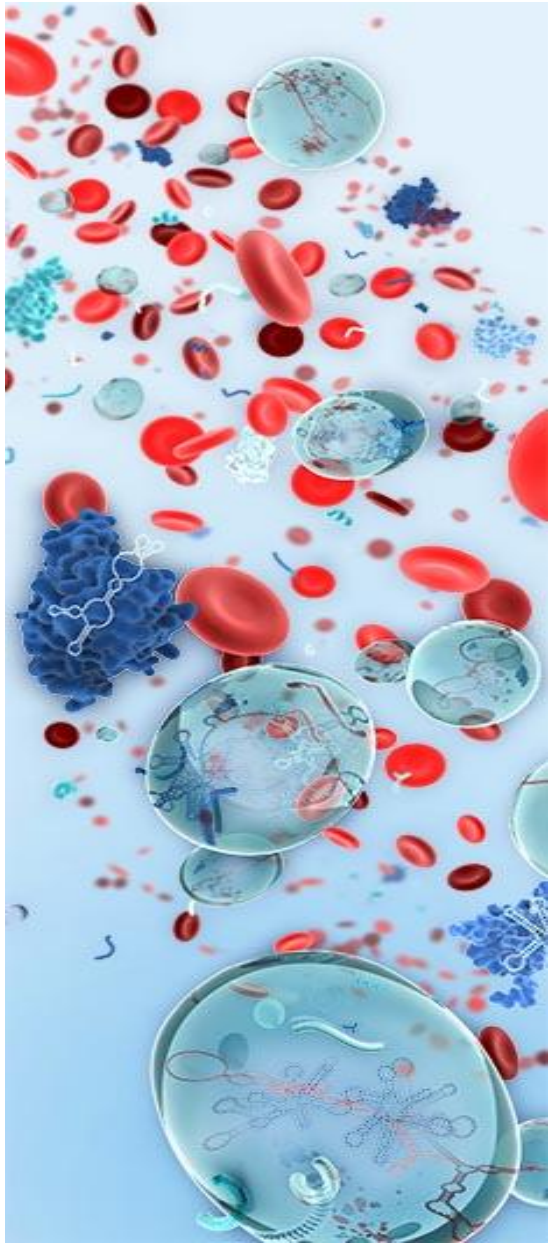
Ortopedi Tedavisinde Nanoteknoloji

- Kemik hücrelerinin defektlerinin saptanması,
- Kemik greftleriyle düzeltilmesi
- Protez tedavilerinde kullanılır
- Protezlerde mikro seviyede hareket sağlar.



Nanopartiküller ve Ökaryotik Hücreler

- İn vivo kullanımda potansiyel antibakteriyel etki?
- Ökaryotik hücrelerde sitotoksik etki
- Konsantrasyon ayarı ve yalnızca bakteri ölümü..
- Bu amaçla kullanılabilecek nanopartiküller:
  - ZnO
  - Gümüş içerikli nanopartiküller



International Journal of Nanomedicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Antimicrobial applications of nanotechnology: methods and literature

This article was published in the following Dove Press journal:
International Journal of Nanomedicine
5 June 2012
Number of times this article has been viewed

Justin T Seil
Thomas J Webster

Laboratory for Nanomedicine Research, School of Engineering, Brown University, Providence, RI, USA

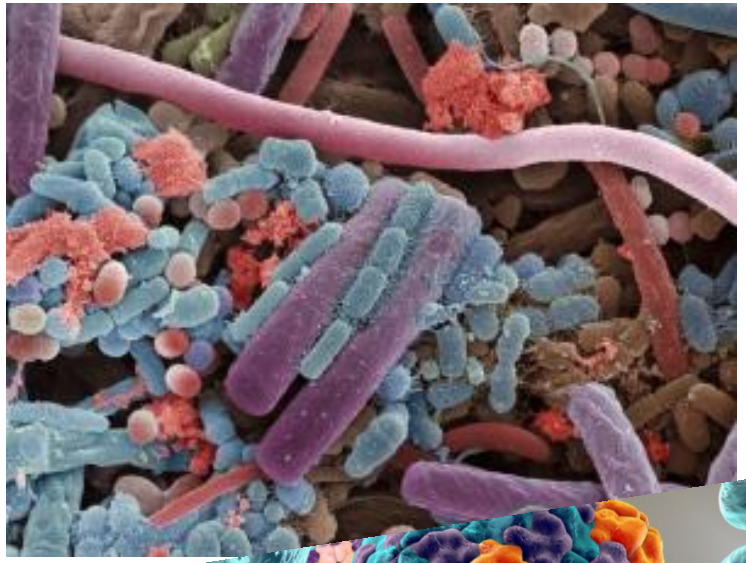
Abstract: The need for novel antibiotics comes from the relatively high incidence of bacterial infection and the growing resistance of bacteria to conventional antibiotics. Consequently, new methods for reducing bacteria activity (and associated infections) are badly needed. Nanotechnology, the use of materials with dimensions on the atomic or molecular scale, has become increasingly utilized for medical applications and is of great interest as an approach to killing or reducing the activity of numerous microorganisms. While some natural antibacterial materials, such as zinc and silver, possess greater antibacterial properties as particle size is reduced into the nanometer regime (due to the increased surface to volume ratio of a given mass of particles), the physical structure of a nanoparticle itself and the way in which it interacts with and penetrates into bacteria appears to also provide unique bactericidal mechanisms. A variety of techniques to evaluate bacteria viability, each with unique advantages and disadvantages, has been established and must be understood in order to determine the effectiveness of nanoparticles (diameter $\leq$100 nm) as antimicrobial agents. In addition to addressing those techniques, a review of select literature and a summary of bacteriostatic and bactericidal mechanisms are covered in this manuscript.

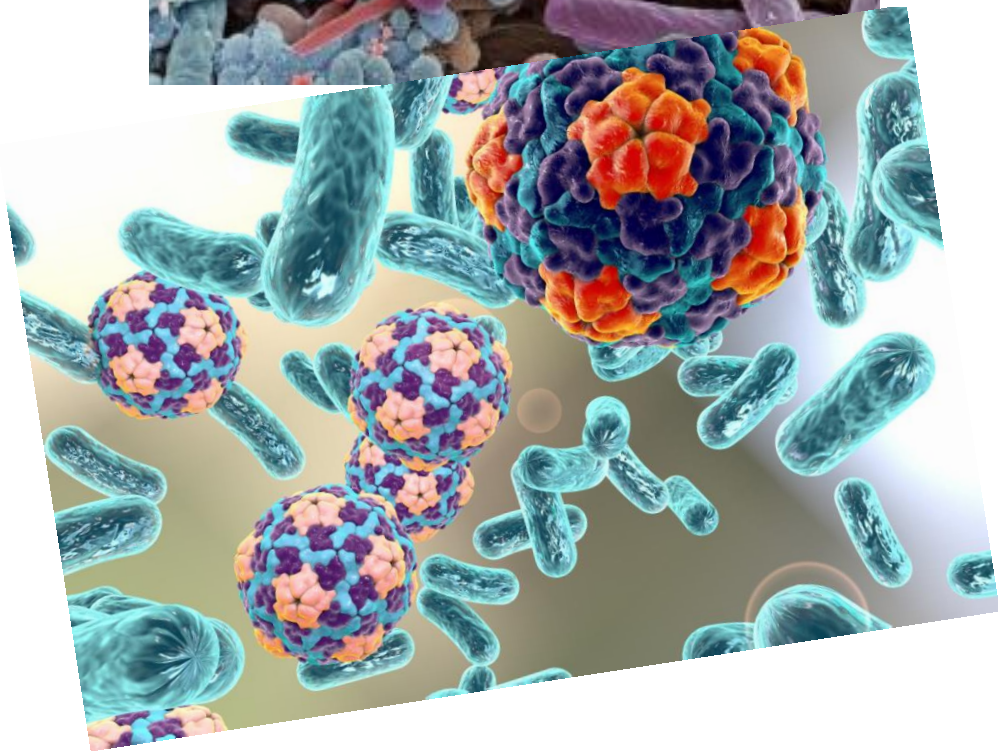
Keywords: nanomaterial, nanoparticle, nanotechnology, bacteria, antibacterial, biofilm

The need for novel antibiotics

Antibakteriyel Nanopartiküller

- Nanopartiküllerde antibakteriyel etkinlik araştırılmıştır
- Bazı metaller (çinko, gümüş ve bakır) antibakteriyel etki..
- Demir oksit doğrudan antibakteriyel etki göstermez, ancak nanopartiküler formun antibakteriyel yönlerini sergiler.



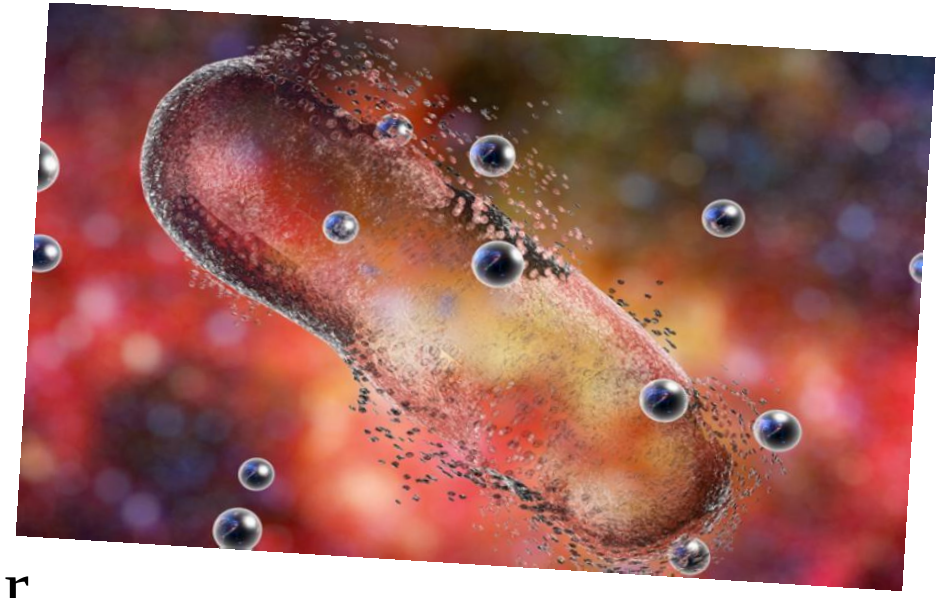


Antibakteriyel Nanopartiküller

- Antibakteriyel aktivite mekanizması tam olarak bilinmiyor
- Aktivite nanopartikülden nanopartiküle değişebiliyor
- Değişik etkiler mevcut
  - Membran hasarlandırıcı etkiye sahip olan nanopartiküller
  - Nanopartikül yüzeyinden antibakteriyel metal iyon salanlar

Antibakteriyel Nanopartiküller

- Çinko, gümüş gibi doğal antibakteriyel materyaller
- Partikül yüzeyinde fazla depolama ile
- Artan antibakteriyel etkinlik..



..

- Bakterinin hücre duvar penetarsayonuna
- Bakterinin membran hasarına neden olurlar

Table 2

Summary of select studies concerning the antimicrobial effects of nanoparticles

Chemistry	Size (average)	Zeta potential	Organism tested	MIC	Proposed mechanism	Reference
ZnO	13 nm	N/A	*Staphylococcus aureus*	Reduced 95% at 80 μg/mL	ROS inhibition	Reddy[10]
ZnO	60 nm	N/A	*S. aureus*	Reduced 50% at 400 μg/mL	ROS inhibition	Jones[2]
ZnO	40 nm	Positive (no value)	*S. aureus, Escherichia coli*	Both species reduced 99% at 400 μg/mL	Membrane disruption	Nair[11]
ZnO	12 nm	N/A	*E. coli*	Reduced 90% at 400 μg/mL	Membrane damage due to particle abrasiveness	Padmavathy[12]
ZnO ions	N/A	N/A	*Pseudomonas aeruginosa, S. aureus, Candida albicans*	Reduced 100% at 1917, 9, and 39 μg/mL, respectively	ROS inhibition	McCarthy[13]
Silver	21 nm	N/A	*E. coli, Vibrio cholerae, Salmonella typhi, P. aeruginosa*	All reduced 100% at 75 μg/mL	Membrane disruption, Ag ion interference with DNA replication	Morones[18]
Silver	Triangles (50 nm)	Positive (no value, cationic surfactant)	*E. coli*	Reduced 99% with 0.1 μg/mL added to agar surface	Membrane disruption, Ag ion interference with DNA replication	Pal[20]
Silver	12 nm	Negative (no value)	*E. coli*	Reduced 70% with 10 μg/mL in agar	Membrane disruption, Ag ion interference with DNA	Sondi[3]

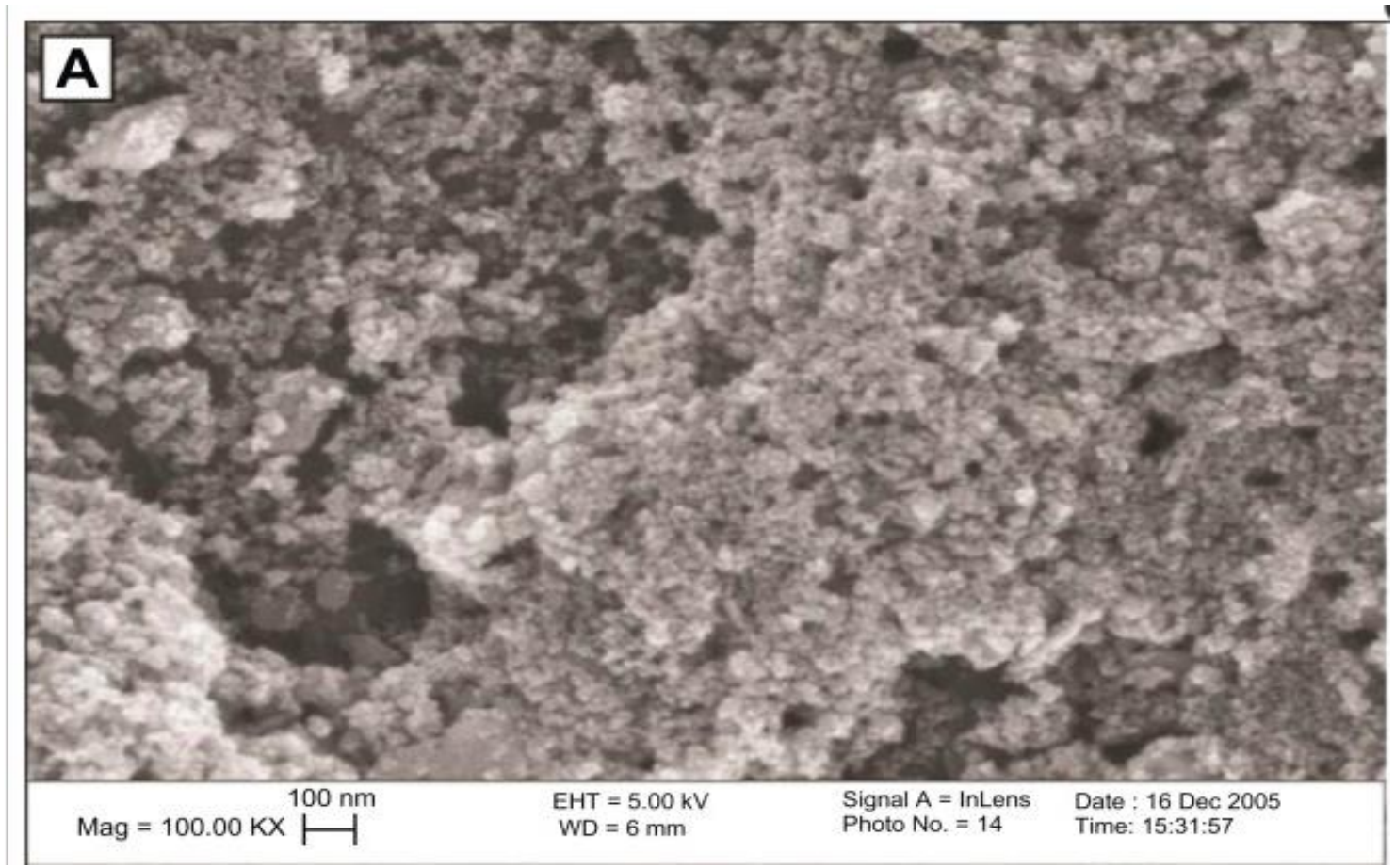
International Journal of Nanomedicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Antimicrobial applications of nanotechnology: methods and literature



Zinc oxide (ZnO) nanoparticles (**A**), *Escherichia coli* bacteria prior to exposure to ZnO nanoparticles (**B**), and *E. coli* bacteria after exposure to ZnO nanoparticles (**C**). Membrane irregularities were observed in bacteria exposed to ZnO nanoparticles. With kind permission from Springer Science+Business Media: *Journal of Nanoparticle Research*. Investigation into the antibacterial behaviour of suspensions of ZnO nanoparticles (ZnO nanofluids). 9(3), 2007, page 483. Zhang L. Figure 2.8

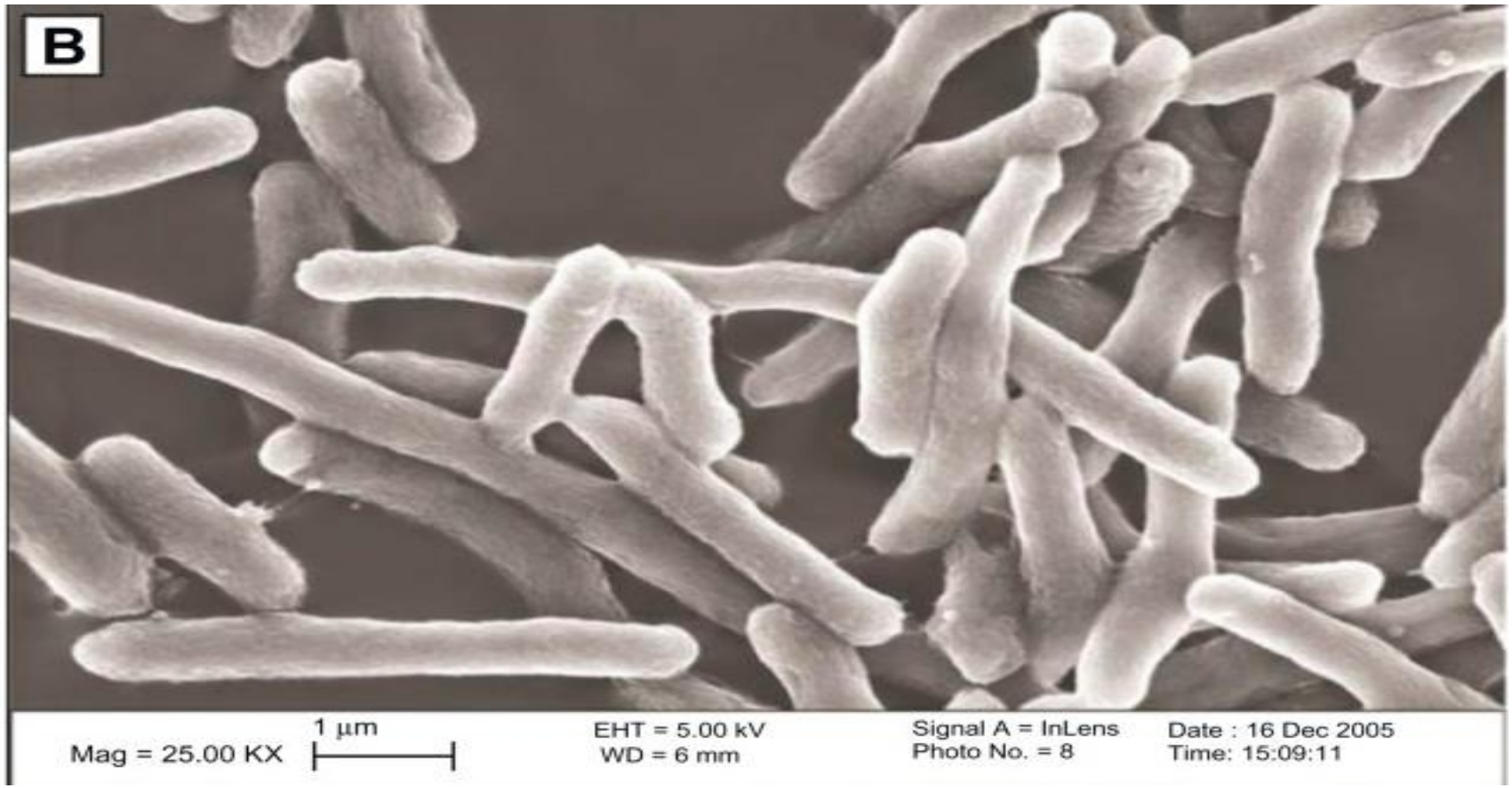
International Journal of Nanomedicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Antimicrobial applications of nanotechnology: methods and literature



Zinc oxide (ZnO) nanoparticles (**A**), *Escherichia coli* bacteria prior to exposure to ZnO nanoparticles (**B**), and *E. coli* bacteria after exposure to ZnO nanoparticles (**C**). Membrane irregularities were observed in bacteria exposed to ZnO nanoparticles. With kind permission from Springer Science+Business Media: *Journal of Nanoparticle Research*. Investigation into the antibacterial behaviour of suspensions of ZnO nanoparticles (ZnO nanofluids). 9(3), 2007, page 483. Zhang L. Figure 2.8

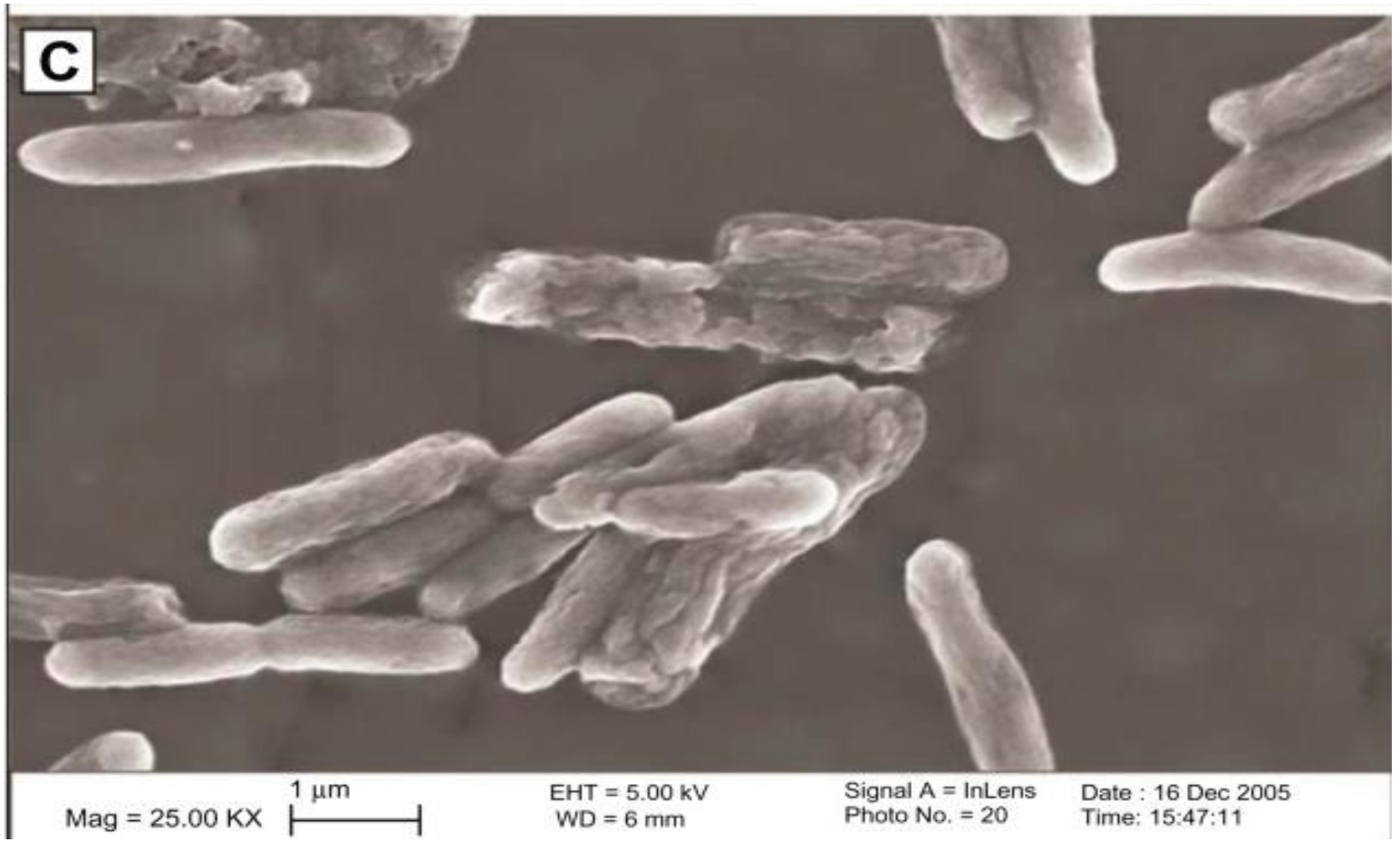
International Journal of Nanomedicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Antimicrobial applications of nanotechnology: methods and literature



Zinc oxide (ZnO) nanoparticles (**A**), *Escherichia coli* bacteria prior to exposure to ZnO nanoparticles (**B**), and *E. coli* bacteria after exposure to ZnO nanoparticles (**C**). Membrane irregularities were observed in bacteria exposed to ZnO nanoparticles. With kind permission from Springer Science+Business Media: *Journal of Nanoparticle Research*. Investigation into the antibacterial behaviour of suspensions of ZnO nanoparticles (ZnO nanofluids). 9(3), 2007, page 483. Zhang L. Figure 2.8

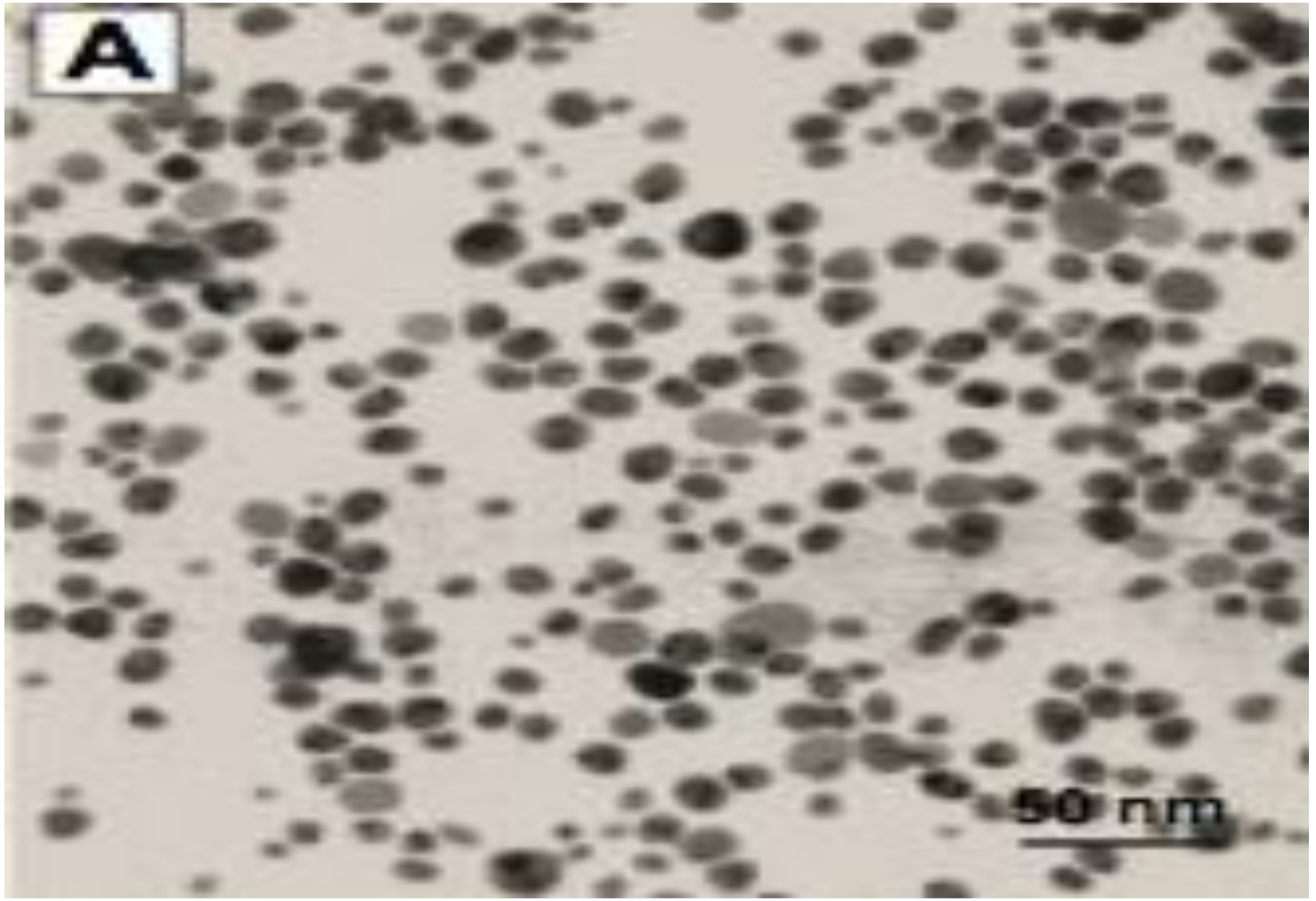


Figure 2 Transmission electron microscope images of silver nanoparticles used (**A**). Scanning electron microscope image of *Escherichia coli* control group (**B**) and *E. coli* exposed to 50 μg/mL of silver nanoparticles in lysogeny broth medium for 4 hours (**C**). Transmission electron microscope image of *E. coli* exposed to 50 μg/mL of silver nanoparticles in lysogeny broth medium for 1 hour at low magnification (**D**) and high magnification (**E**). Reprinted from *Journal of Colloid and Interface Science*, 275(1). Sondi I, Salopek-Sondi B. Silver nanoparticles as antimicrobial agent: a case study on *E. coli* as a model for Gram-negative bacteria. 177–182. Copyright © (2004), with permission from Elsevier.[3]

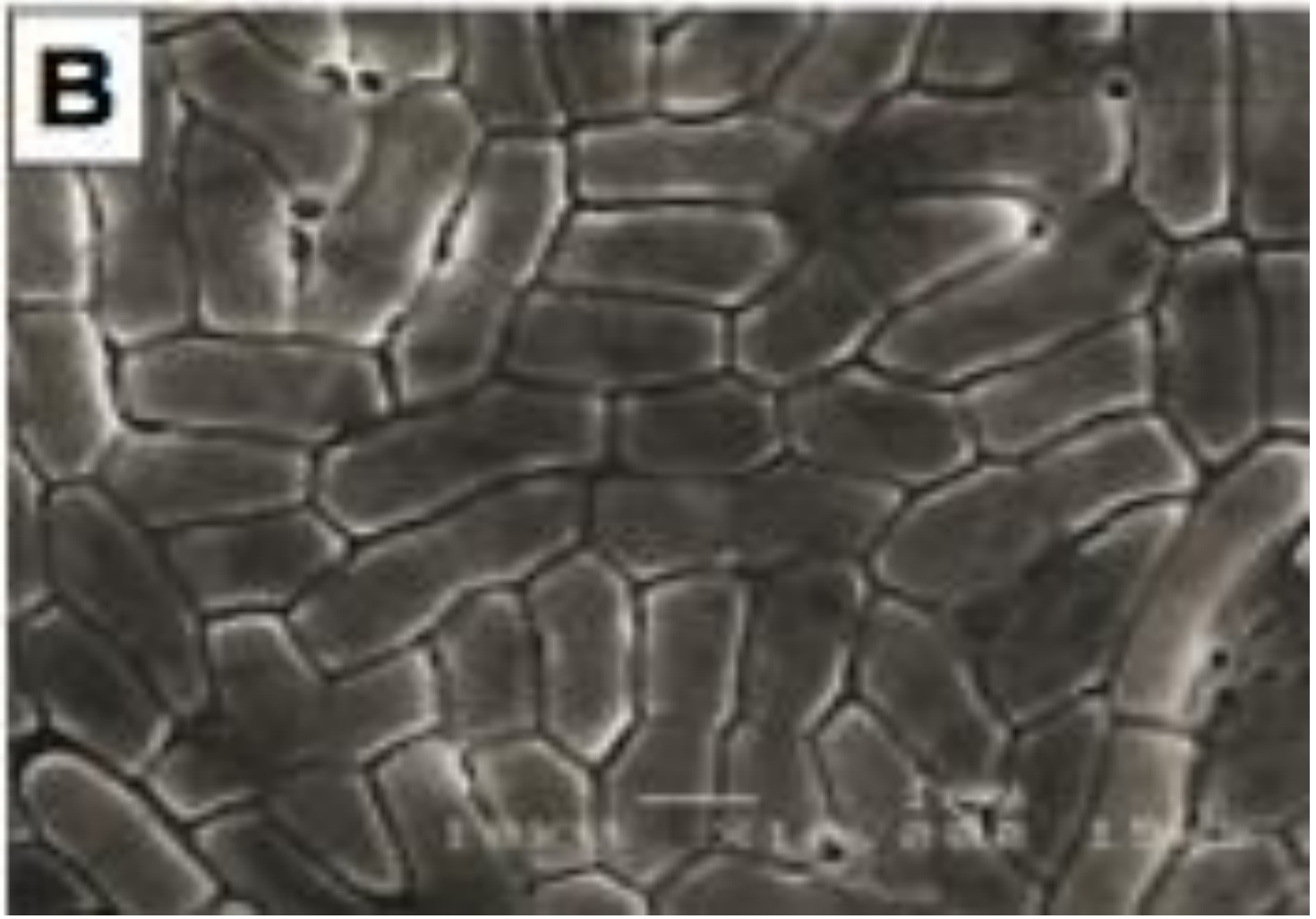


Figure 2 Transmission electron microscope images of silver nanoparticles used (**A**). Scanning electron microscope image of *Escherichia coli* control group (**B**) and *E. coli* exposed to 50 μg/mL of silver nanoparticles in lysogeny broth medium for 4 hours (**C**). Transmission electron microscope image of *E. coli* exposed to 50 μg/mL of silver nanoparticles in lysogeny broth medium for 1 hour at low magnification (**D**) and high magnification (**E**). Reprinted from *Journal of Colloid and Interface Science*, 275(1). Sondi I, Salopek-Sondi B. Silver nanoparticles as antimicrobial agent: a case study on *E. coli* as a model for Gram-negative bacteria. 177–182. Copyright © (2004), with permission from Elsevier.[3]

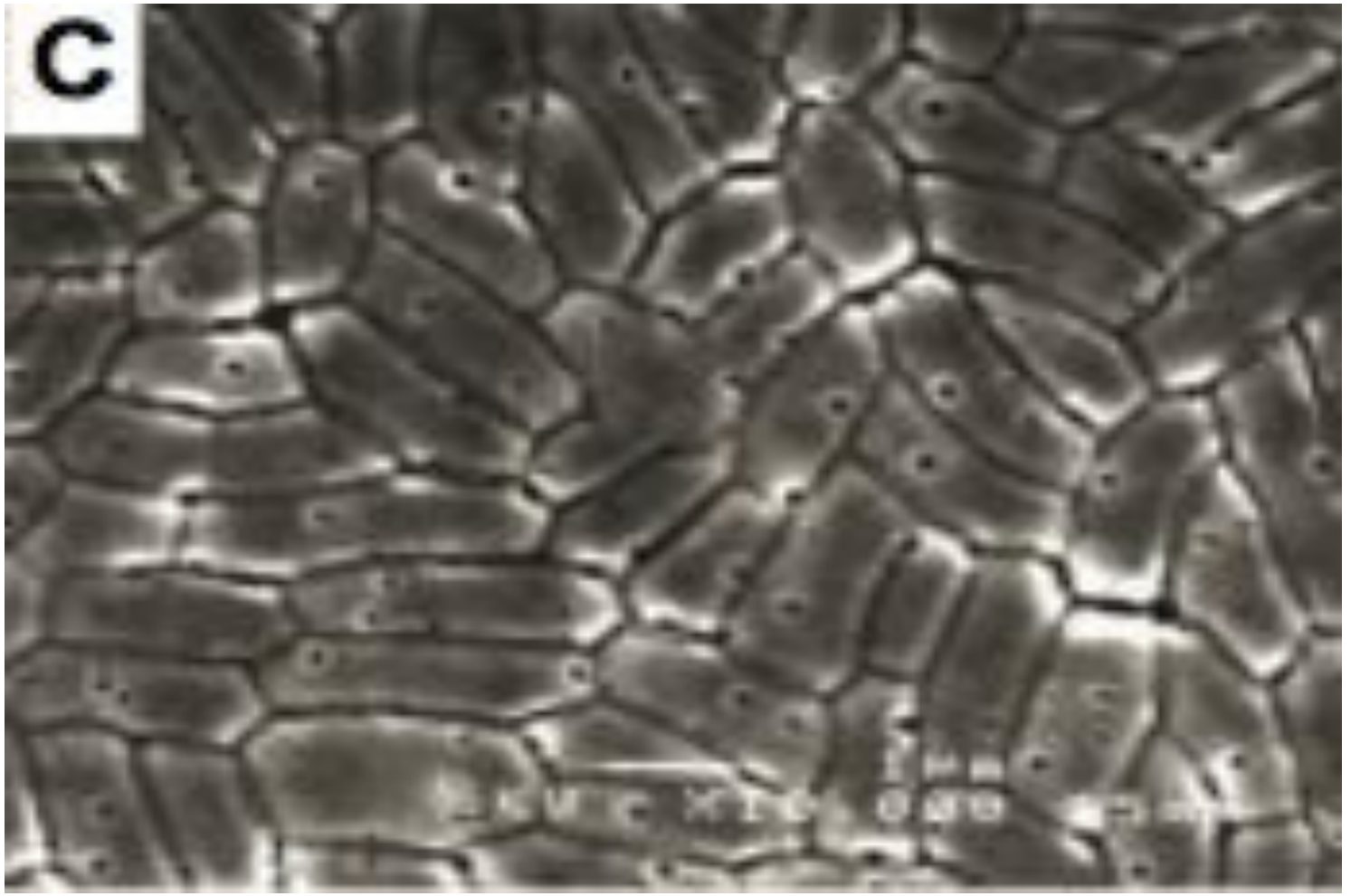


Figure 2 Transmission electron microscope images of silver nanoparticles used (**A**). Scanning electron microscope image of *Escherichia coli* control group (**B**) and *E. coli* exposed to 50 μg/mL of silver nanoparticles in lysogeny broth medium for 4 hours (**C**). Transmission electron microscope image of *E. coli* exposed to 50 μg/mL of silver nanoparticles in lysogeny broth medium for 1 hour at low magnification (**D**) and high magnification (**E**). Reprinted from *Journal of Colloid and Interface Science*, 275(1). Sondi I, Salopek-Sondi B. Silver nanoparticles as antimicrobial agent: a case study on *E. coli* as a model for Gram-negative bacteria. 177–182. Copyright © (2004), with permission from Elsevier.[3]

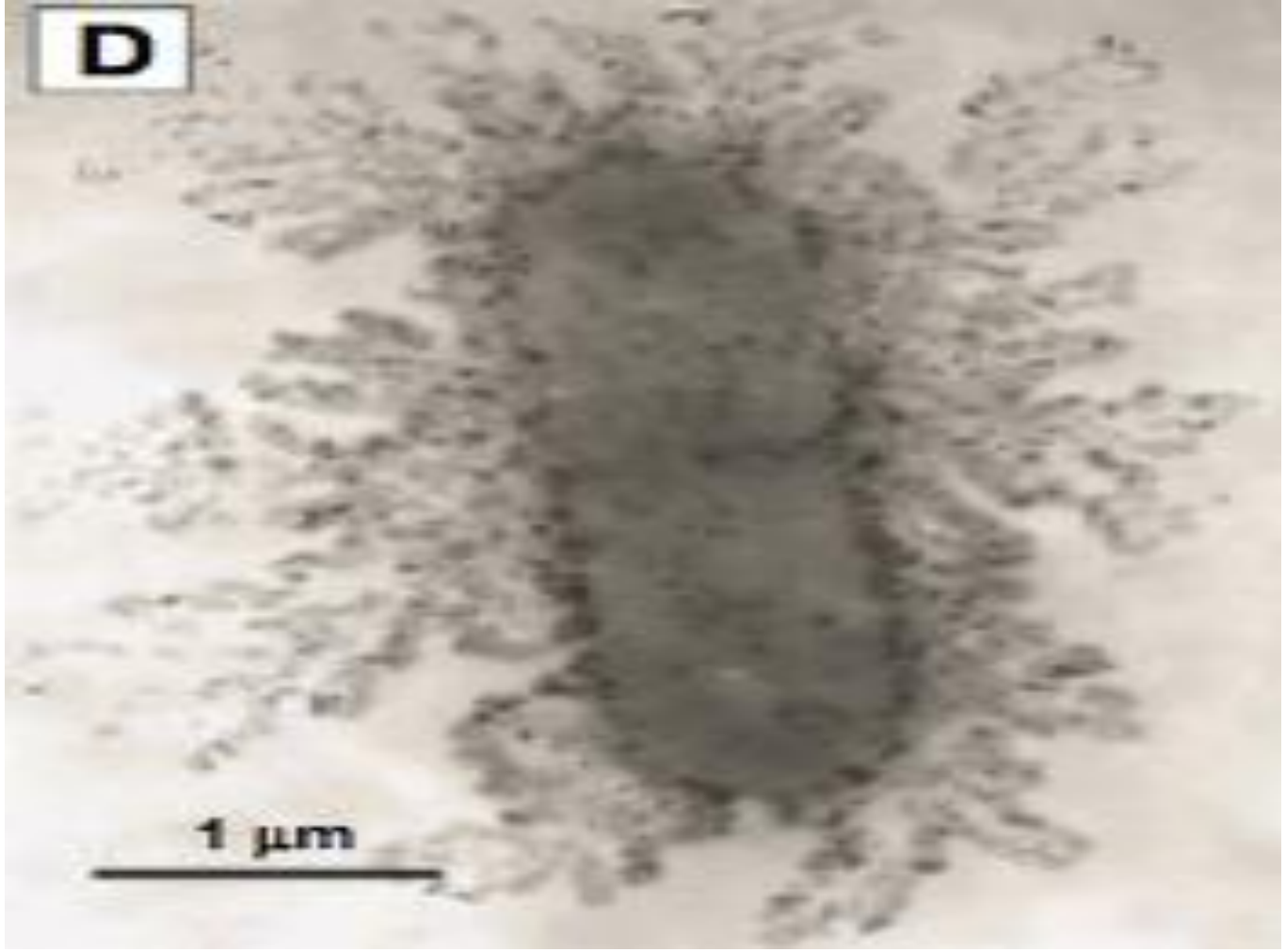


Figure 2 Transmission electron microscope images of silver nanoparticles used (**A**). Scanning electron microscope image of *Escherichia coli* control group (**B**) and *E. coli* exposed to 50 µg/mL of silver nanoparticles in lysogeny broth medium for 4 hours (**C**). Transmission electron microscope image of *E. coli* exposed to 50 µg/mL of silver nanoparticles in lysogeny broth medium for 1 hour at low magnification (**D**) and high magnification (**E**). Reprinted from *Journal of Colloid and Interface Science*, 275(1). Sondi I, Salopek-Sondi B. Silver nanoparticles as antimicrobial agent: a case study on *E. coli* as a model for Gram-negative bacteria. 177–182. Copyright © (2004), with permission from Elsevier.[3]

Fig

used (**A**). Scanning electron microscope image of *Escherichia coli* control group (**B**) and *E. coli* exposed to 50 µg/mL of silver nanoparticles in lysogeny broth medium for 4 hours (**C**). Transmission electron microscope image of *E. coli* exposed to 50 µg/mL of silver nanoparticles in lysogeny broth medium for 1 hour at low magnification (**D**) and high magnification (**E**). Reprinted from *Journal of Colloid and Interface Science*, 275(1). Sondi I, Salopek-Sondi B. Silver nanoparticles as antimicrobial agent: a case study on *E. coli* as a model for Gram-negative bacteria. 177–182. Copyright © (2004), with permission from Elsevier.[3]

Nanoyapılı Kaba Yüzeyler ve Antimikrobiyal Etki

- Kaba nanopartiküler yüzey
- Kimyasal ve topografik işlemler
- Bakteriyel adezyon ve biyofilm oluşumunun önlenmesi
- Özellikle tıbbı cihaz ve kateterler için kullanılıyor.

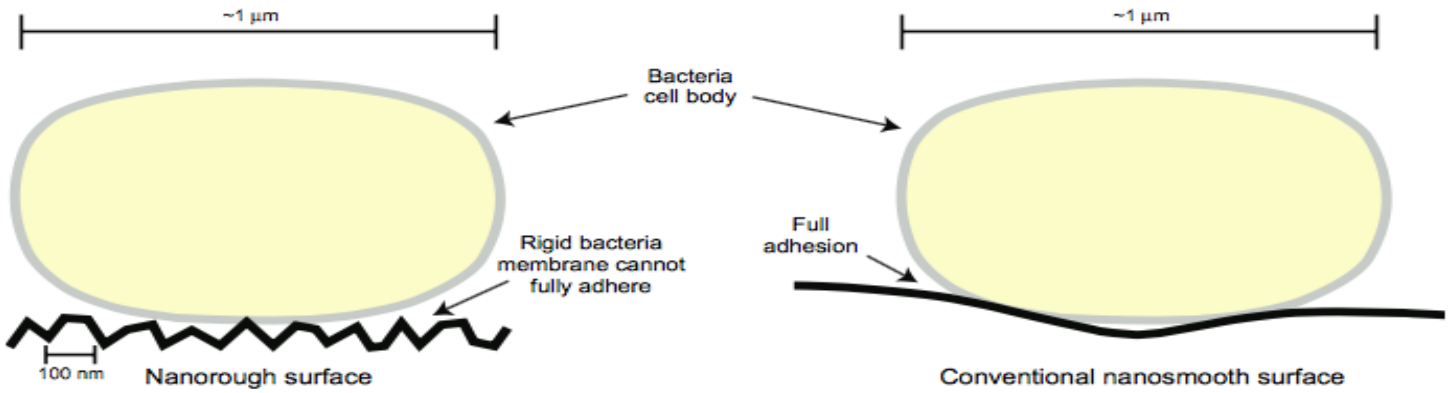


Figure 3 Illustration comparing bacteria surface interactions with nanorough surfaces and conventional nanosmooth surfaces. Due to the high degree of roughness on nanomaterials, rigid bacteria cell membranes cannot lay flush against the material surface. This may inhibit the preliminary steps which lead to bacteria adhesion. As a result, bacteria activity on a nanomaterial surface may be reduced.

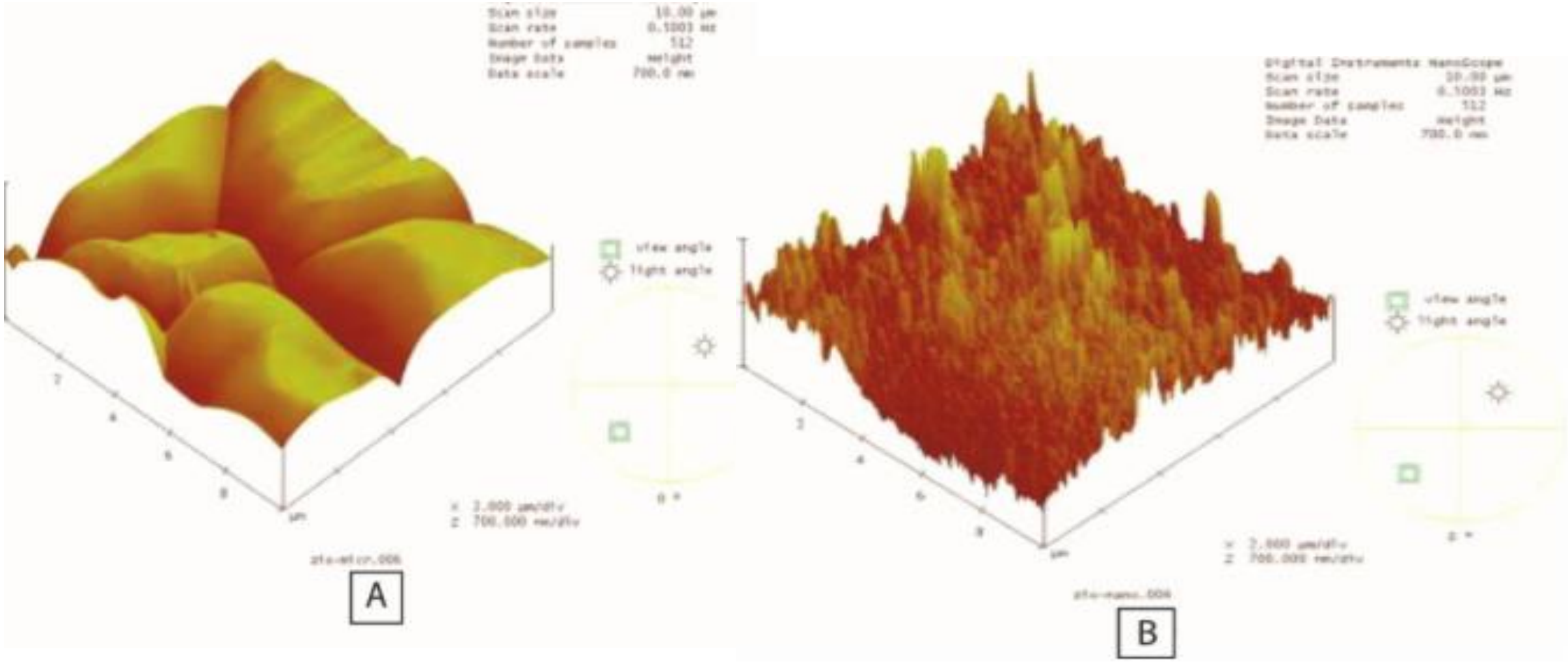


Figure 4 Atomic force microscopy images of particle compacts of microphase zinc oxide (ZnO) (**A**) and nanophase ZnO (**B**). Analysis indicated that compacts of nanophase ZnO had a 25% increase in surface area. Copyright © 2006, John Wiley and Sons. Adapted with permission from Colón G, Ward BC, Webster TJ. Increased osteoblast and decreased Staphylococcus epidermidis functions on nanophase ZnO and TiO2. *J Biomed Mater Res A*. 2006;78(3):595–604.[7]

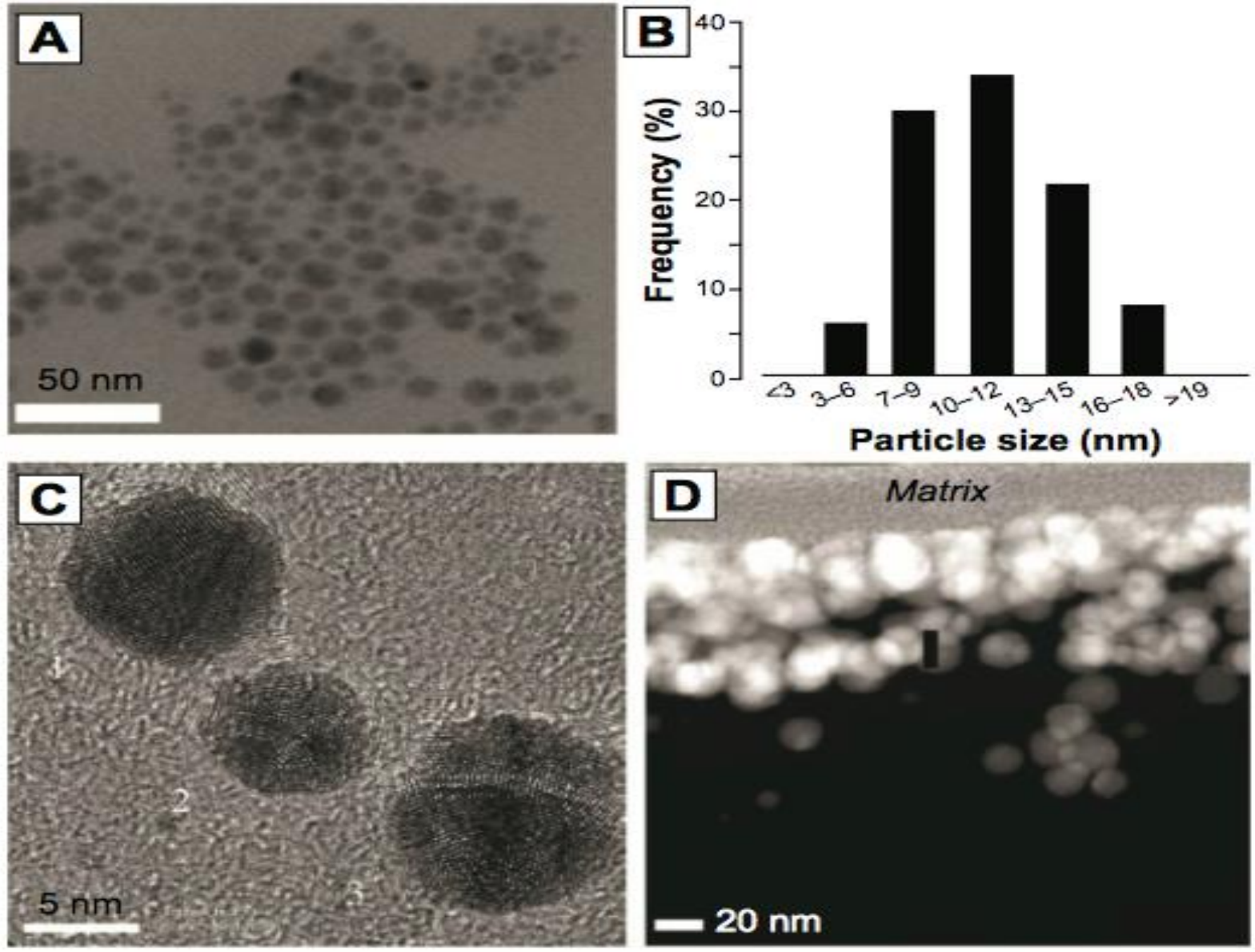
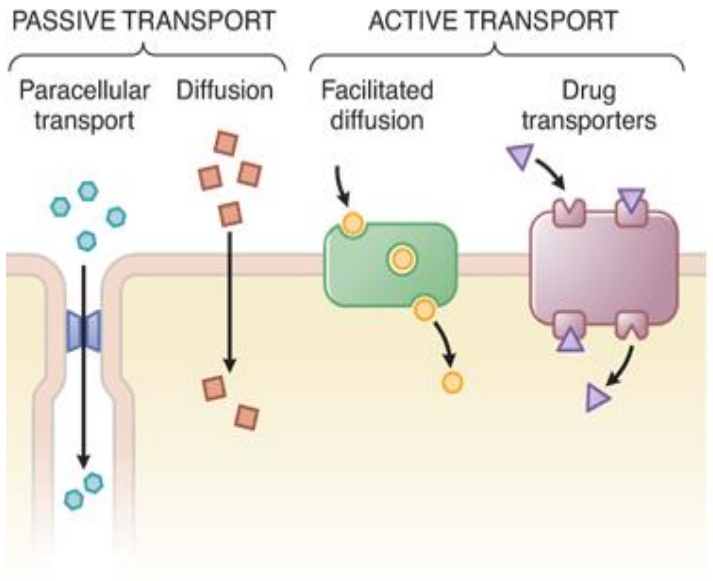


Figure 5 X-ray electron microscopy image of silver nanoparticles (**A**) and a particle size distribution histogram (**B**) of those particles. Higher magnification reveals polyhedral structure (**C**). Nondisruptive electron transmission microscopy reveals an 80–120 nm coating of silver nanoparticles on the surfaces of a polymer catheter (**D**).

Nanoteknolojinin Antibiyotikle İlişkili Kullanımı

- En yaygın kullanım alanı ilaç dağılım sistemi üzerinedir,
- İlaç dağılımındaki başlıca sorunlar:
  - İlacın erime sorunları
  - Yetersiz biyoyararlanım



Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com

Nanoteknolojinin Antibiyotik Etkinliğine Katkısı

- Kapsüllendirme yöntemiyle ilacın eriyebilme kapasitesinin artırılması
- İlacın membran premeabilitesinin artırılması
- Sirkülasyonda daha uzun süreli kalışının sağlanması
- İlaç etkinliğinin artırılması

Antimikrobiyal Ajanlar Olarak Nanopartiküller

- **Antibiyotikli Nanopartiküllerin Sinerjik Uygulaması:**
- Küçük moleküllü antibiyotiklerin nanopartiküllerle konjugasyonu sinerjik etki sağlar ve direnç sorununu giderebilir.
- Kolloidal gümüş konjugatları Amoksisilin, eritromisin ve vankomisinde kullanılır ve gram pozitif bakterilere karşı oldukça etkilidir.

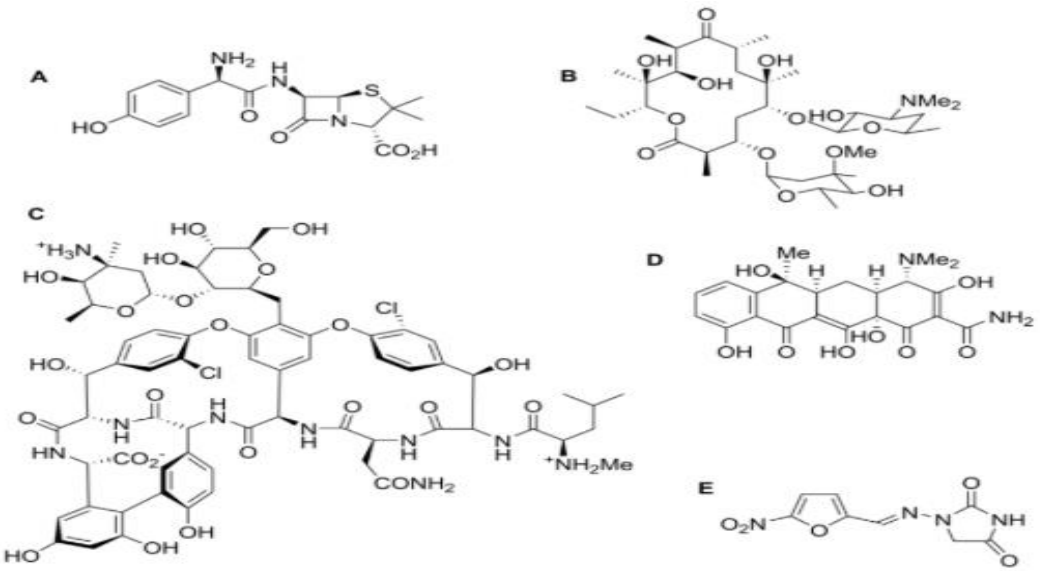
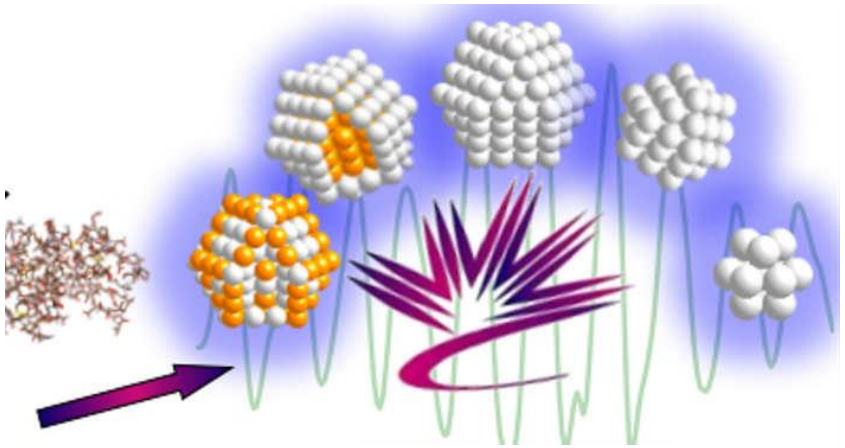


Figure 4. Chemical structures of (**A**) amoxicillin; (**B**) erythromycin; (**C**) vancomycin; (**D**) tetracycline and (**E**) nitrofurantoin.

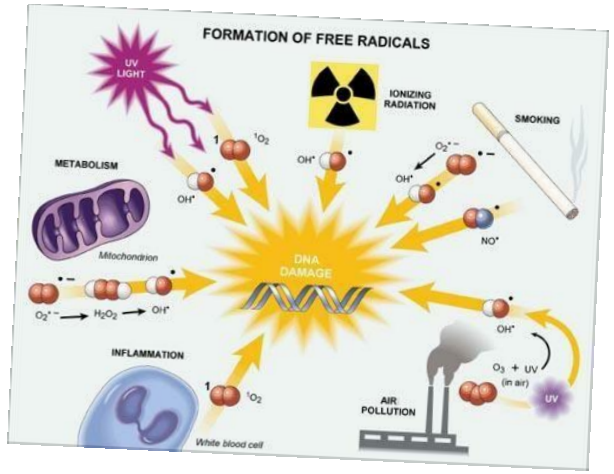
Nanopartikül-Anitibiyotik Örnekleri

- Tetrasiklin + Gümüş nanopartiküller: *S.typhimurium*
- Siprofloksasin + Çinko oksit: *S.aureus* ve *E.coli*
- Amoksisiln ve Nitrofurontain + Çinko oksit: *E.coli* ve *S.aureus*'lara etkisiz

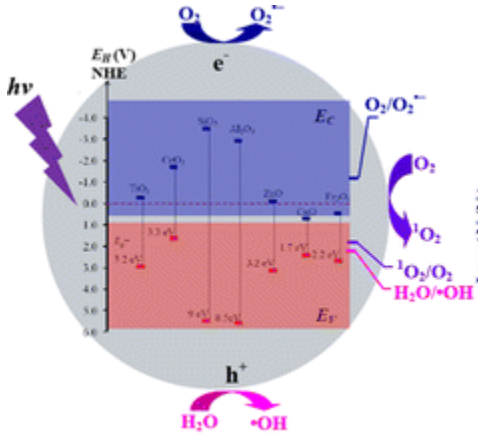


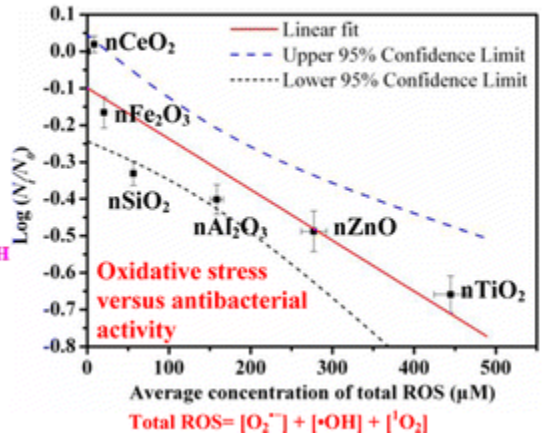
Nanopartikül İçerikli Antibiyotikler ve Antibakteriyel Etki

- **Serbest Oksijen Radikallerinin Oluşturulması:**
- Aerobik solunum ve UV ışınlarına maruziyet sonucu SOR oluşur
- Hidrojen peroksit, süperoksit ve hidroksil radikalleri



- Prokaryotlarda Nükleotid ve Lipid yapılara zarar verir
- *Süperoxide dismutase*, bakterinin korunma sistemi
- Divalan Metal İyonları ile Fenton Reaksiyonu
- Hidroksil radikal gelişimi ve DNA yapısının bozulması





Mechanism of Photogenerated Reactive Oxygen Species and Correlation with the Antibacterial Properties of Engineered Metal-Oxide Nanoparticles

Yang Li,[†,‡,§] Wen Zhang,[‡,§] Junfeng Niu,[†] and Yongsheng Chen[‡,*]

[†]State Key Laboratory of Water Environment Simulation, School of Environment, Beijing Normal University, Beijing 100875, People's Republic of China and [‡]School of Civil and Environmental Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332, United States. [§]The first and second authors contributed equally to this work.

ARTICLE

- Li ve ark
- Çinko oksit ve titanyum oksit nanopartikülleri
- Süperoksit, hidroksil ve SOR oluşur
- Oksidatif stres ve antibakteriyel etki..

Pharmaceutical Biology

http://informahealthcare.com/phb
ISSN 1388-0209 print/ISSN 1744-5116 online
Editor-in-Chief: John M. Pezzuto
Pharm Biol, 2014; 52(11): 1388–1397
 DOI: 10.3109/13880209.2014.893001

informa
healthcare

ORIGINAL ARTICLE

Antimicrobial activity of zinc oxide (ZnO) nanoparticle against *Klebsiella pneumoniae*

Lanka Shalini Reddy, Mary Magar Nisha, Mary Joice, and P. N. Shilpa

Department of Biotechnology, Sathyabama University, Chennai, Tamil Nadu, India

Abstract

Context: Zinc oxide nanoparticles (ZnO Nps) have potential application in piezoelectric nanogenerator and in biotechnology.
Objective: The antibacterial activity of ZnO Nps on *Klebsiella pneumoniae* (ATCC 70068) and mode of action of ZnO Nps was investigated.

Keywords

Agar diffusion assay, growth curve, HEp-2 cells, lipoploysaccharride, metal oxide nanoparticle, minimum inhibitory concentration, outer membrane protein

- Reddy ve ark
- Çinko nanopartikülleri ile SOR aktivasyonu
- Katalaz enzim sentezinde azalma
- Bakterinin oksidatif stresten korunma mekanizmasının azalması
- Antibakteriyel etki..

Figure 3. Minimum inhibitory concentration test of ZnO Nps against *K. pneumoniae*. Values represent mean ± SD of triplicate experiments.

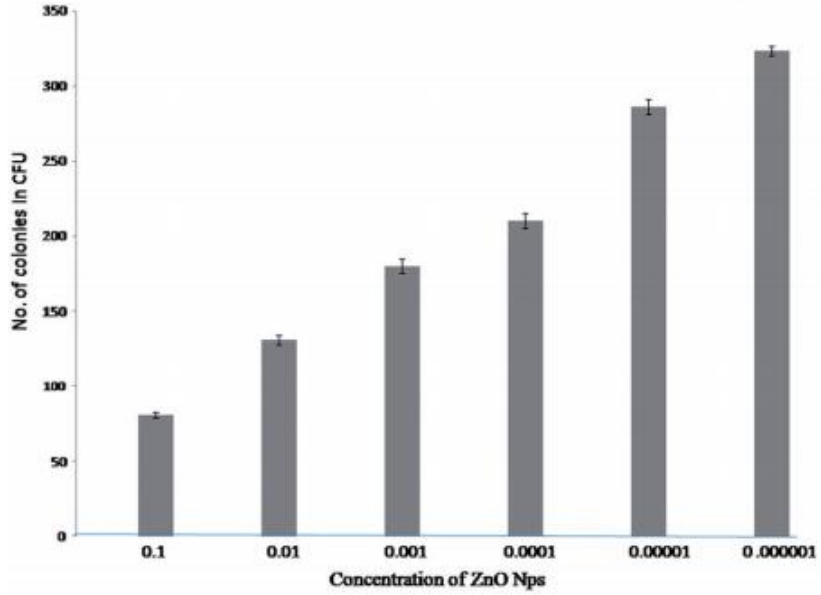
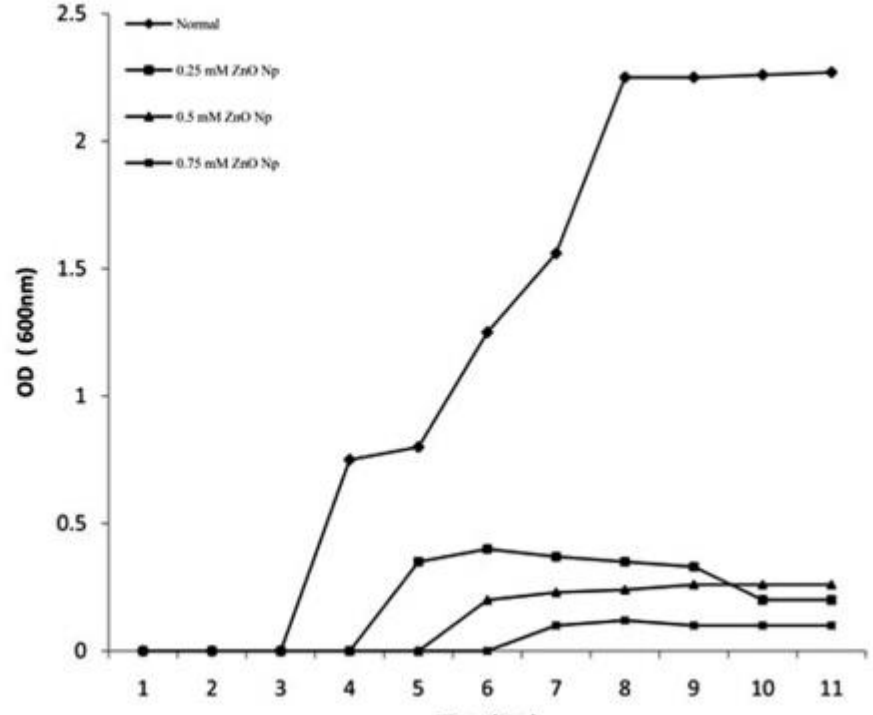


Figure 4. Growth curve of *K. pneumoniae* treated with ZnO Nps.



OPEN ACCESS Freely available online

PLOS | ONE

Reactive Oxygen Species Mediated Bacterial Biofilm Inhibition via Zinc Oxide Nanoparticles and Their Statistical Determination

Sourabh Dwivedi[1], Rizwan Wahab[1]*, Farheen Khan[2], Yogendra K. Mishra[3], Javed Musarrat[4], Abdulaziz A. Al-Khedhairy[1]

1 Department of Zoology, College of Science, King Saud University, Riyadh, Saudi Arabia, 2 Department of Chemistry, Aligarh Muslim University, Aligarh, India, 3 Functional Nanomaterials, Institute for Materials Science, University of Kiel, Kiel, Germany, 4 Department of Agricultural Microbiology, Faculty of Agricultural Sciences, Aligarh Muslim University, Aligarh, India

Abstract

The formation of bacterial biofilm is a major challenge in clinical applications. The main aim of this study is to describe the synthesis, characterization and biocidal potential of zinc oxide nanoparticles (NPs) against bacterial strain *Pseudomonas aeruginosa*. These nanoparticles were synthesized via soft chemical solution process in a very short time and their structural properties have been investigated in detail by using X-ray diffraction and transmission electron microscopy measurements

- Çinko nanopartikülleri ve *Pseudomonas aeruginosa* etkileşimi
- SOR artışı
- Çinko molekülleri *P.aeruginosa* dış membranıyla etkileşir
- Sonra çinko nanopartikülleri hücre içine girer ve bakteri hasarı oluşur

OPEN ACCESS Freely available online

PLOS | ONE

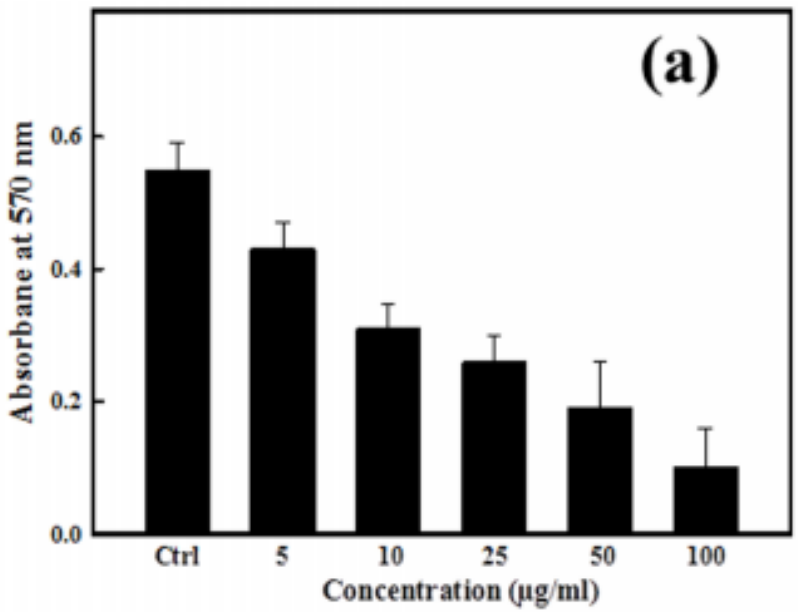
Reactive Oxygen Species Mediated Bacterial Biofilm Inhibition via Zinc Oxide Nanoparticles and Their Statistical Determination

Sourabh Dwivedi[1], Rizwan Wahab[1]*, Farheen Khan[2], Yogendra K. Mishra[3], Javed Musarrat[4], Abdulaziz A. Al-Khedhairy[1]

1 Department of Zoology, College of Science, King Saud University, Riyadh, Saudi Arabia, **2** Department of Chemistry, Aligarh Muslim University, Aligarh, India, **3** Functional Nanomaterials, Institute for Materials Science, University of Kiel, Kiel, Germany, **4** Department of Agricultural Microbiology, Faculty of Agricultural Sciences, Aligarh Muslim University, Aligarh, India

Abstract

The formation of bacterial biofilm is a major challenge in clinical applications. The main aim of this study is to describe the synthesis, characterization and biocidal potential of zinc oxide nanoparticles (NPs) against bacterial strain *Pseudomonas aeruginosa*. These nanoparticles were synthesized via soft chemical solution process in a very short time and their structural properties have been investigated in detail by using X-ray diffraction and transmission electron microscopy measurements



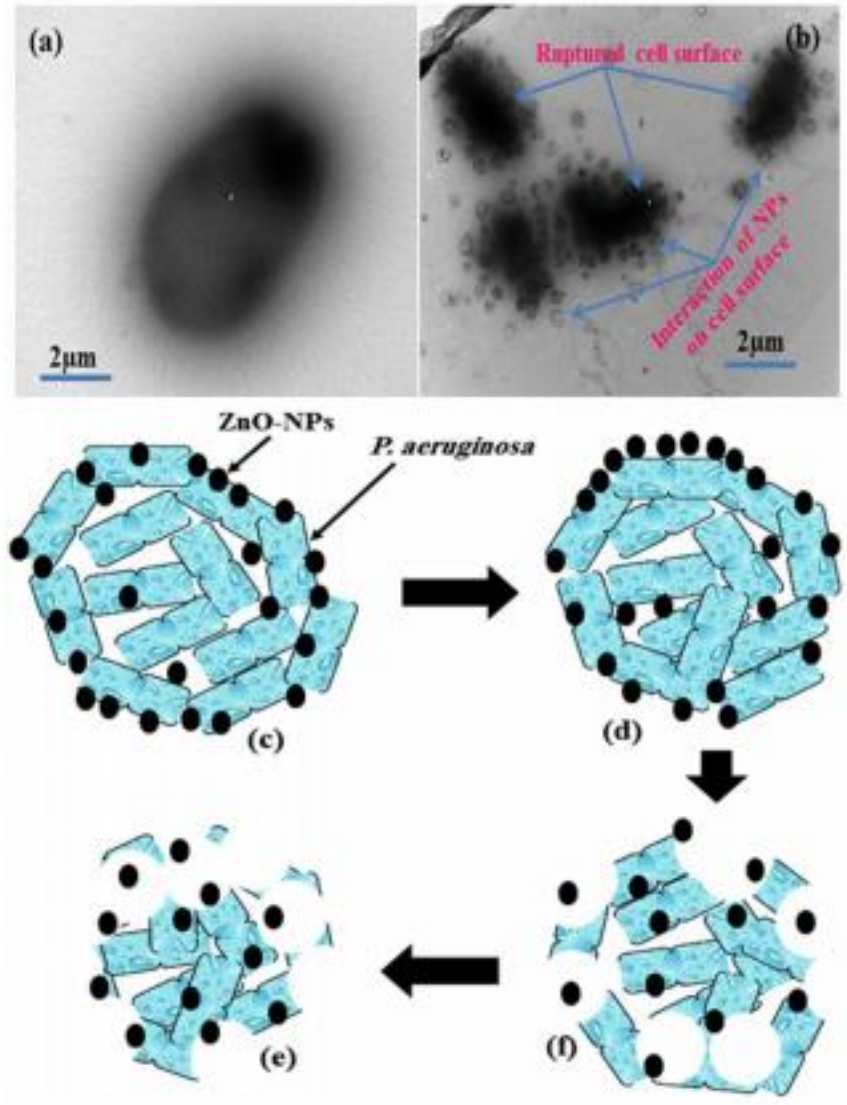


Figure 3. Bio-TEM images of: (a) *P.aeruginosa* (b) *P. aeruginosa* with ZnO-NPs. (c-f) Possible proposed pictorial mechanism.
doi:10.1371/journal.pone.0111289.g003

IOP Publishing Nanotechnology
Nanotechnology 25 (2014) 135101 (12pp) doi:10.1088/0957-4484/25/13/135101

Mechanism of antibacterial activity of copper nanoparticles

Arijit Kumar Chatterjee, Ruchira Chakraborty and Tarakdas Basu

Department of Biochemistry and Biophysics, University of Kalyani, Kalyani-741 235, West Bengal, India

E-mail: tarakdb@yahoo.com

- Bakır nanopartikülleri ve *E.coli* arasında etkileşim
- Lipit peroksidasyon gelişimi
- Peroksidasyon ile bakteri zarında doymamış yağların oksidatif parçalanması
- Bakteri hemostazı sonucu bakteri ölümü
- Bakteri zarının parçalanması

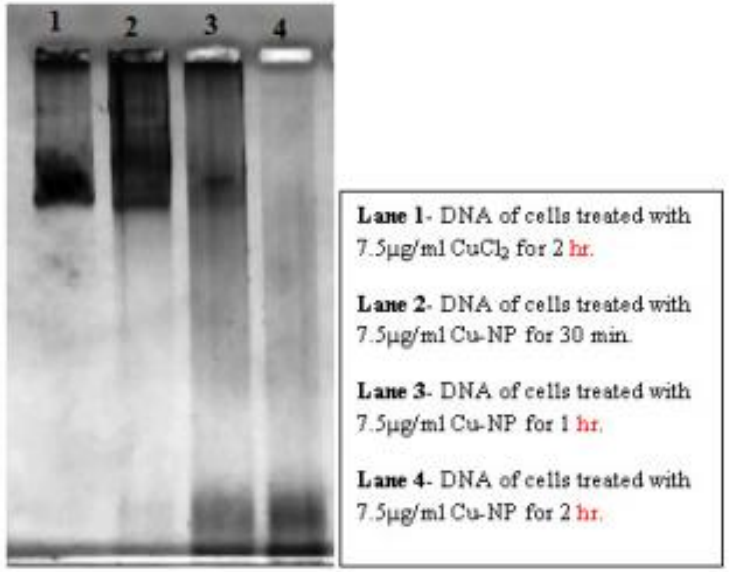
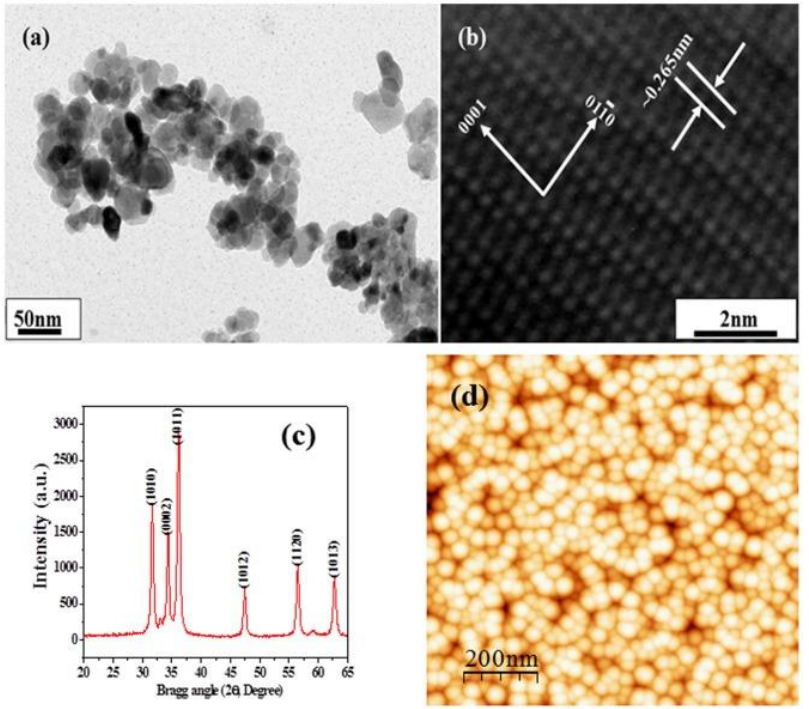


Figure 5. Agarose gel electrophoretic pattern of the chromosomal DNA isolated from the Cu-NP-treated *E. coli* cells.

Padmavathy ve ark.

- Çinko oksit nanopartikülleri SOR artışına neden olur
- Bakterinin DNA yapısını..
- Hücresel proteinlerin hasarlanmasına neden olur
- Ayrıca nanopartiküller bakterinin hücre duvarındaki lipid yapısını ayrıştırır
- Hücre yapısına zarar verir
- Bakteri homeostaz ve proliferasyonu için gereken lipid yapısını bozar



Bakterilerin Nanopartikül ile Tedavisi

Table 1. Examples of nanoparticles exhibiting anti-bacterial properties and their mechanism of action.

Bacterial Species	Gram Stain of the Species	Nanoparticle(s) with Anti-Microbial Activity	Mechanism of Action	Reference
Staphylococcus aureus	Gram-positive	Ag	Cell wall damage	[46]
Campylobacter jejuni	Gram-negative	ZnO	Growth inhibition by ROS	[47]
Escherichia coli	Gram-negative	Cu IONPs	Growth inhibition by ROS ROS generation	[48,49]
Pseudomonas aeruginosa	Gram-negative	Ag Zn	Enzyme inhibition in respiratory chain complex ROS generation	[43,50]
Klebsiella pneumoniae	Gram-negative	ZnO	Growth inhibition	[42]
Bacillus subtilis	Gram-positive	Ag IONPs	DNA degradation ROS generation	[49,51]

Applied Microbiology and Biotechnology
https://doi.org/10.1007/s00253-018-8776-0

MINI-REVIEW

Strategies to prevent the occurrence of resistance against antibiotics by using advanced materials

Arnau Bassegoda[1] · Kristina Ivanova[1] · Eva Ramon[1] · Tzanko Tzanov[1]

Received: 28 November 2017 / Revised: 4 January 2018 / Accepted: 6 January 2018

Abstract
Drug resistance occurrence is a global healthcare concern responsible for the increased morbidity and mortality in hospitals, time of hospitalisation and huge financial loss. The failure of the most antibiotics to kill "superbugs" poses the urgent need to develop innovative strategies aimed at not only controlling bacterial infection but also the spread of resistance. The prevention of pathogen host invasion by inhibiting bacterial virulence and biofilm formation, and the utilisation of bactericidal agents with different mode of action than classic antibiotics are the two most promising new alternative strategies to overcome antibiotic resistance. Based on these novel approaches, researchers are developing different advanced materials (nanoparticles, hydrogels and surface coatings) with novel antimicrobial properties. In this review, we summarise the recent advances in terms of engineered materials to prevent bacteria-resistant infections according to the antimicrobial strategies underlying their design.

Keywords Antibiotic resistance · Antibiofouling · Antimicrobial peptides · Quorum sensing · Virulence factors · Nano-antimicrobial materials

Introduction

Today, antimicrobial resistance (AMR) infections are responsible for 700,000 deaths annually with an economic burden of, only in the USA, over 20 billion dollars per year, and estimations reveal a devastating future by 2050 with ten million deceased per year, unless solutions are found (de Kraker et al. 2016). In the last decade, AMR infections have spread from predominantly hospital and care settings environments towards the wider community, endangering the healthcare advances. Antibiotics are crucial in the modern medicine and the loss of effectiveness jeopardises not only the fight against microbial infections such as pneumonia, tuberculosis and malaria, but also turns simple wounds or straightforward surgical procedures into a real menace to life (Jasovský et al. 2016). Current answers to AMR infections result in higher doses of drugs, treatments with toxic side effects, longer hospital stays and increased mortality (Lee et al. 2013; Ventola 2015). For instance, colistin, an antibiotic avoided for many years due to renal and neurological damage, is administered as a last resort treatment for patients with resilient Gram-negative bacterial infections (Karaaslan et al. 2016).

The appearance of antibiotic resistances is a naturally occurring phenomenon via natural selection. The antibiotic induces the environmental pressure and those bacteria able to survive and replicate will be the ones with genes that confer antibiotic resistance. Due to the high bacterial replication rate and the ability to acquire foreign genetic material coding for resistance determinants through horizontal gene transfer, bacteria can rapidly evolve and adapt to the selective antibiotic pressure with a variety of mechanisms including (i) degradation of antibiotics (e.g. beta-lactamase inactivation of penicillins), (ii) modification of the drug target (e.g. mutation of the protein rpsL of the 30S ribosomal subunit, which confers resistance to streptomycin), and (iii) expression of efflux pumps (e.g. AcrAB-TolC pumps which confer resistance to multiple

Arnau Bassegoda, Kristina Ivanova and Eva Ramon contributed equally to this work.

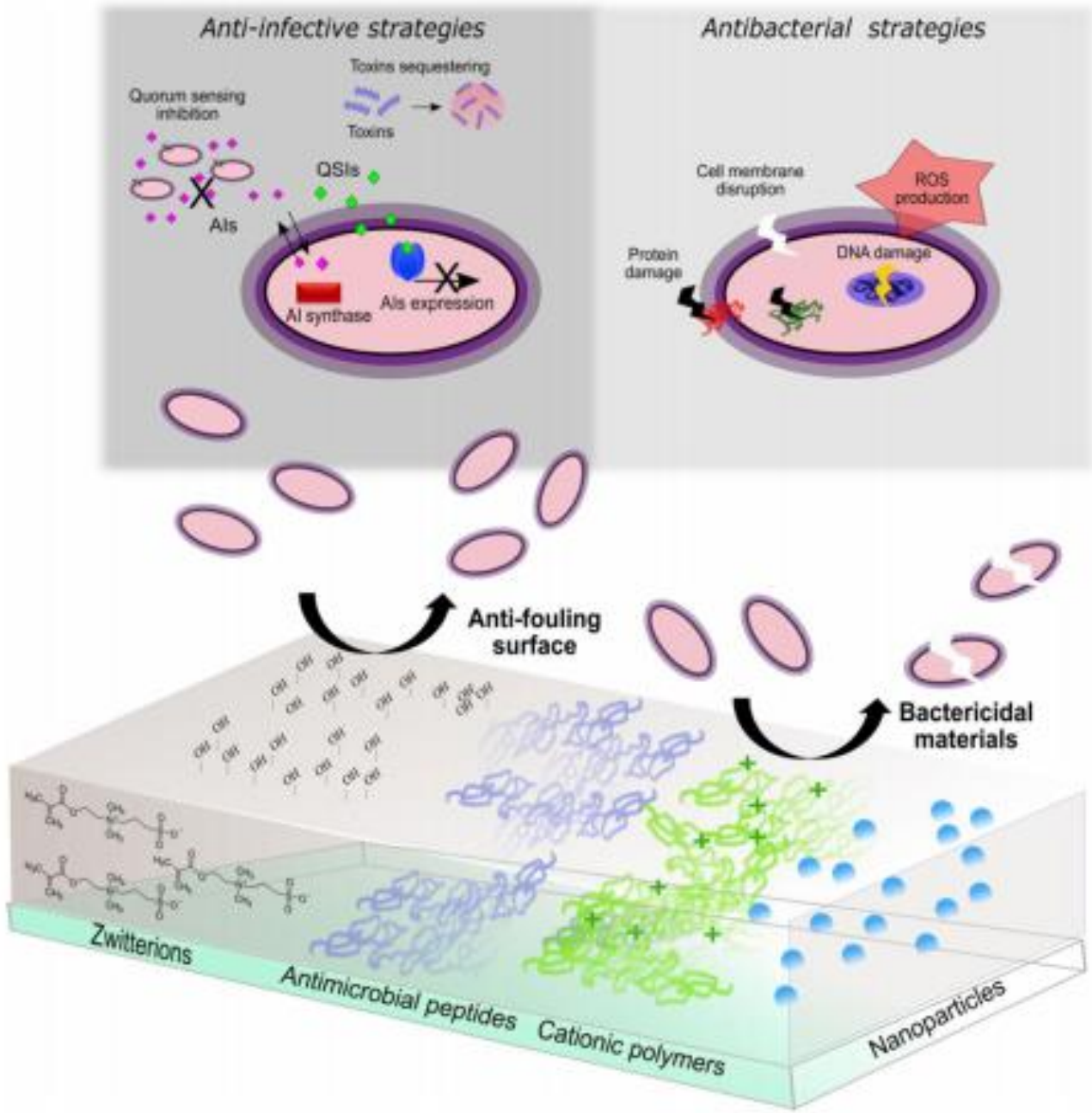


Fig. 1 Strategies to prevent AMR precluding the design and development of different advanced materials. Anti-infective strategies to suppress the expression of virulence factors and prevent biofilm growth can be divided into anti-quorum sensing, antitoxins and antibiofouling (left side). Novel antibiotic alternatives aimed at killing pathogens via nonspecific mechanisms related to membrane damage, oxidative stress and interaction with genetic material and protein, reducing the possibility of inducing resistance in bacteria (right side). QSI stands for quorum sensing inhibitors, AIs for autoinducers, DNA for deoxyribonucleic acid and ROS for reactive oxidative species

Table 1 Advanced anti-infective and antibacterial strategies

Approach	Actives	Target	References
Anti-infective strategies			
Antiquorum sensing	QQE: acylase and lactonase	Gram-negative bacteria	Johansen et al. (1997) Craigen et al. (2011) Ivanova et al. (2015a) Grover et al. (2016)
	Autoinducers analogues	*S. aureus*	Kratochvil et al. (2015)
	β-Cyclodextrin functionalised NPs	*V. fisheri*	Miller et al. (2015)
	Heterocyclic organic furanones: free form and encapsulated	*S. liquefaciens*, *P. mirabilis*, *E. coli* and *S. aureus*	Givskov et al. (1996) Gram et al. (1996) Ren et al. (2001) Cheng et al. (2012) Cheng et al. (2015)
	Synthetic furanones	*P. aeruginosa* and *S. epidermidis*	Wu et al. (2004) Hume et al. (2004)
Toxin sequestering materials	Polymer NPs coated with red blood cell membrane	*S. aureus*, *E. coli*, *S. pneumoniae*	Henry et al. (2014) Wang et al. (2015) Thamphiwatana et al. (2017)
Antibiofouling and antibiofilm surfaces	Silver and titanium oxide nanofilms	*S. mutans*	Ghasemi et al. (2017)
	Fluoroalkylsilane	*S. epidermidis*	Tang et al. (2009)
	Negatively charged surfaces	Gram-negative and Gram-positive bacteria	Boudou et al. (2010)
	Zwitterionic polymers	*E. coli*, *P. mirabilis*, *P. pseudomonas*, *S. aureus*	Cheng et al. (2009) Chen et al. (2010) Zhang and Chiao (2015) Guo et al. (2015) Diaz Blanco et al. (2014) Alves et al. (2016)
	Deoxyribonuclease I	*P. aeruginosa* and *S. aureus*	Baelo et al. (2015) Alves et al. (2016)
	Disersin B	*S. epidermidis*	Pavlukhina et al. (2012)
Antibacterial strategies			
Antibacterial enzymes	Cellobiose dehydrogenase	Gram-positive and Gram-negative bacteria, including multidrug-resistant strains	Walker et al. (2007) Ge et al. (2012) Nyanhongo et al. (2013) Thallinger et al. (2014) Lipovsky et al. (2015)
	Horseradish peroxidase	*E. coli* and *S. aureus*	Amitai et al. (2009)
	Glucose oxidase	*E. coli* and *S. aureus*	Amitai et al. (2009)
	Lysostaphin	*Staphylococci* genus	Yeroslavsky et al. (2015)
	Lysozyme	Gram-positive and Gram-negative bacteria	Minier et al. (2005) Muszanska et al. (2011) Yuan et al. (2011)
Antimicrobial peptides	Cateslytin functionalized HA	*S. aureus* and *C. albicans*	Cado et al. (2013)
	Tet213	*S. aureus* and *P. gingivalis*	Shi et al. (2015)
	Cecropin-melittin NPs	*E. coli*, *S. aureus*, *P. aeruginosa*, *Klebsiella pneumoniae*, multidrug resistant *E. coli* and *Staphylococcus haemolyticus*	Rai et al. (2016)
	Defensin-based AMP	*S. aureus*, *S. epidermidis* and *P. aeruginosa*	Townsend et al. (2017)
Cationic polymers	Chitosan	Clinically relevant *E. faecalis strains*, *P. aeruginosa*	Bratskaya et al. (2007) Wang et al. (2012)
		Gram-positive and Gram-negative bacteria	Shirvan et al. (2014)
	Quaternary ammonium salt of chitosan	*E. coli* and *S. aureus*	Graisuwan et al. (2012)
	Triblock polycarbonate polymer combined with PEG and a tethering or adhesive functional block	*E. coli* and *S. aureus*	Voo et al. (2015)
	Polycarbonate/PEG hydrogels	Clinically isolated multidrug-resistant bacteria	Liu et al. (2012)

Table 1 Advanced anti-infective and antibacterial strategies

Approach	Actives	Target	References
Anti-infective strategies			
Antiquorum sensing	QQE: acylase and lactonase	Gram-negative bacteria	Johansen et al. (1997) Craigen et al. (2011) Ivanova et al. (2015a) Grover et al. (2016)
	Autoinducers analogues	*S. aureus*	Kratochvil et al. (2015)
	β-Cyclodextrin functionalised NPs	*V. fisheri*	Miller et al. (2015)
	Heterocyclic organic furanones: free form and encapsulated	*S. liquefaciens*, *P. mirabilis*, *E. coli* and *S. aureus*	Givskov et al. (1996) Gram et al. (1996) Ren et al. (2001) Cheng et al. (2012) Cheng et al. (2015)
	Synthetic furanones	*P. aeruginosa* and *S. epidermidis*	Wu et al. (2004) Hume et al. (2004)
Toxin sequestering materials	Polymer NPs coated with red blood cell membrane	*S. aureus*, *E. coli*, *S. pneumoniae*	Henry et al. (2014) Wang et al. (2015) Thamphiwatana et al. (2017)
Antibiofouling and antibiofilm surfaces	Silver and titanium oxide nanofilms	*S. mutans*	Ghasemi et al. (2017)
	Fluoroalkylsilane	*S. epidermidis*	Tang et al. (2009)
	Negatively charged surfaces	Gram-negative and Gram-positive bacteria	Boudou et al. (2010)
	Zwitterionic polymers	*E. coli*, *P. mirabilis*, *P. pseudomonas*, *S. aureus*	Cheng et al. (2009) Chen et al. (2010) Zhang and Chiao (2015) Guo et al. (2015) Diaz Blanco et al. (2014) Alves et al. (2016)
	Deoxyribonuclease I	*P. aeruginosa* and *S. aureus*	Baelo et al. (2015) Alves et al. (2016)
	Disersin B	*S. epidermidis*	Pavlukhina et al. (2012)
Antibacterial strategies			
Antibacterial enzymes	Cellobiose dehydrogenase	Gram-positive and Gram-negative bacteria, including multidrug-resistant strains	Walker et al. (2007) Ge et al. (2012) Nyanhongo et al. (2013) Thallinger et al. (2014) Lipovsky et al. (2015)
	Horseradish peroxidase	*E. coli* and *S. aureus*	Amitai et al. (2009)
	Glucose oxidase	*E. coli* and *S. aureus*	Amitai et al. (2009)
	Lysostaphin	*Staphylococci* genus	Yeroslavsky et al. (2015)
	Lysozyme	Gram-positive and Gram-negative bacteria	Minier et al. (2005) Muszanska et al. (2011) Yuan et al. (2011)
Antimicrobial peptides	Cateslytin functionalized HA	*S. aureus* and *C. albicans*	Cado et al. (2013)
	Tet213	*S. aureus* and *P. gingivalis*	Shi et al. (2015)
	Cecropin-melittin NPs	*E. coli*, *S. aureus*, *P. aeruginosa*, *Klebsiella pneumoniae*, multidrug resistant *E. coli* and *Staphylococcus haemolyticus*	Rai et al. (2016)
	Defensin-based AMP	*S. aureus*, *S. epidermidis* and *P. aeruginosa*	Townsend et al. (2017)
Cationic polymers	Chitosan	Clinically relevant *E. faecalis strains*, *P. aeruginosa*	Bratskaya et al. (2007) Wang et al. (2012)
		Gram-positive and Gram-negative bacteria	Shirvan et al. (2014)
	Quaternary ammonium salt of chitosan	*E. coli* and *S. aureus*	Graisuwan et al. (2012)
	Triblock polycarbonate polymer combined with PEG and a tethering or adhesive functional block	*E. coli* and *S. aureus*	Voo et al. (2015)
	Polycarbonate/PEG hydrogels	Clinically isolated multidrug-resistant	Liu et al. (2012)

Sonuç..

Nanopartikül yapılı antibiyotikler yakın gelecekte yerini alacak..

Biyofilm sorunu?

Direnç sorunu?

- Teşekkürler..