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Mayo 2015

Web project

http://laurasanbeni.wix.com/antimicrobianos

Popular science for scientists

Universitat Autònoma de Barcelona
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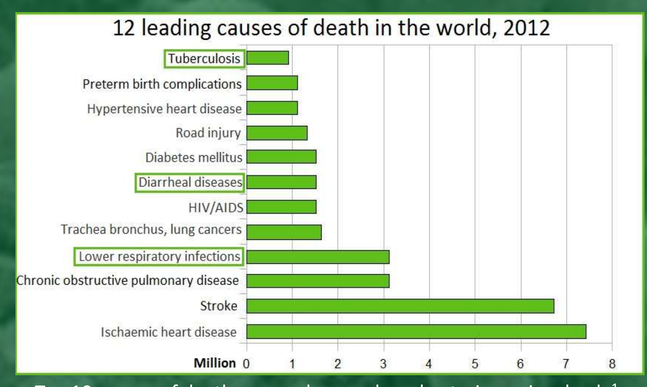
Discovering new antimicrobials

Bacterial infections have always been one of the main reasons of death in the world population. The graph shows some cases in which bacteria are involved, still currently generating havoc in humanity.

Seeing the importance of combating bacterial infections due to the damage generated in the world's population, it is vital to encourage scientific research in this field. This fact urges them to use all their ingenuity and creativity to counter the adaptive and infectious ability of bacteria. Thus, scientists can make it possible for their research saved thousands of lives.

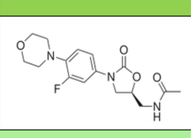
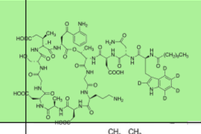
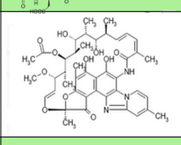
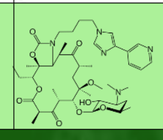
Moreover, it is a sector that has a broad market. It is the largest after the drugs for the central nervous and cardiovascular system market. On the world market, antimicrobials represented 42 billion dollars in 2009, which means 5% of the global pharmaceutical market. In 2014, it has been estimated that represents 66 billion.



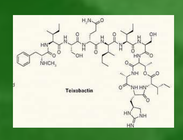
Top 10 causes of death, green shown where bacteria are involved. [1]

This website aims to collect information on about the status of investigations against most current antimicrobials as well as their applications. Being able to thereby provide an overview on this field and encouraging interested research groups to form projects. This webpage let these research groups search for new methods and compounds to mitigate bacterial infections.

There are almost no new molecules for over 30 years.
Although among them we can find:

New drug	Descripction	Mechanism of action	Resistance reported	Molecule
Linezolid (2-Oxazolidone)	The first antibiotic marketed of the group of the 2-oxazolidone.	Protein synthesis inhibitor, targeting an early step involving the binding of N-formylmethionyl-tRNA to the ribosome.	Yes	
Daptomycin	Lipopeptide antibiotic.	Gram-positive. Disrupting multiple aspects of bacterial cell membrane function.	Yes, but rare	
Rifaximin	Semisynthetic antibiotic based on rifamycin.	Interferes with transcription by binding to the β-subunit of bacterial RNA polymerase.	Yes	
Telrithromycin	Ketolide antibiotic (Derived from erythromycin).	Binds to the subunit 50S of the bacterial ribosome, interfering with their protein synthesis.	Yes	

TEIXOBACTIN (2015)



Teixobactin inhibits cell wall synthesis by binding to precursor of peptidoglycan and precursor of cell wall teichoic acid. The researchers 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. [2, 3]

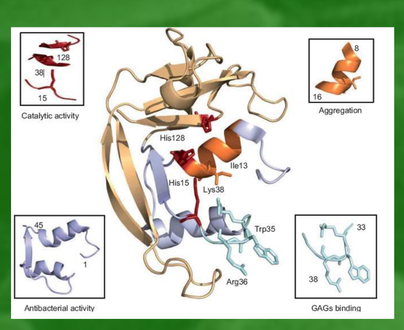
ICHip:
It allows culturing cells in their natural environment. Thanks to this device, Teixobactin was isolated in a soil bacterium (*Elephtheria terrae*).

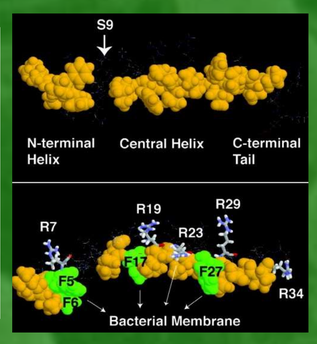
Spanish National Network for the discovery of new antibiotics

In statewide (Spain) it has been the great importance of research into new antibiotics, and this past 2014 it was created the "*Red Nacional Española para el Descubrimiento de Nuevos Antibióticos (AD-SP)*" network. This was made to combat the shortage of innovation in this field and dealing the rise of multi-resistant bacteria.

Antimicrobial peptides have retained their effectiveness against bacteria, avoiding resistances, as acting on a design feature, the microbial cell membrane, which distinguishes them from plants and animals.

There are two important families of human antimicrobial peptides for their antimicrobial activity. These are human ribonucleases and cathelicidins





Dimensional structure of human RNase; ECP (Eosinophil Cationic Protein) and human cathelicidin LL-37, where are shown the various regions involved in their activity. [4, 5]

Product	Description	Indication	Phase	Company (location)
Magainin peptide	22-amino-acid linear antimicrobial peptide, isolated from the skin of frog (*Xenopus laevis*)	Diabetic foot ulcers	3	Dipexium Pharma (White Plains, New York) MacroChem/Genaera
Omiganan	Synthetic cationic peptide derived from indolicidin	Rosacea	2	BioWest Therapeutics/Maruho (Vancouver)
OP-145	Synthetic 24-mer peptide derived from LL-37 for binding to lipopolysaccharides or lipoteichoic acid	Chronic bacterial middle-ear infection	2	OctoPlus (Leiden, The Netherlands)
Novexatin	Cyclic cationic peptide, 1.093 daltons	Fungal infections of the toenail	1/2	NovaBiotics (Aberdeen, UK)
Lytixar (LTX-109)	Synthetic, membrane-degrading peptide	Nasally colonized for Methicillin-resistant *Staphylococcus aureus*	1/2	Lytix Biopharma (Oslo)
NVB302	Lantibiotic (peptide antibiotic)	*Clostridium difficile*	1	Novacta (Welwyn Garden City, UK)
MU1140	Lantibiotic (peptide antibiotics)	Gram-positive (*Clostridium difficile*, Methicillin-resistant *Staphylococcus aureus*)	Preclinical	Oragenics (Tampa, Florida)
Arenicin	21 amino acids; rich in arginine and hydrophobic amino acids	Multiresistant Gram-positive bacteria	Preclinical	Adenium Biotech Copenhagen
Avidocin and purocin	Modified R-type bacteriocins from *Pseudomonas aeruginosa*	Narrow spectrum antibiotic for human health and food safety	Preclinical	AvidBiotics (S. San Francisco, California)
IMX924	Synthetic 5-amino-acid peptide innate defense regulator	Synthetic 5-amino-acid peptide innate defense regulator	Preclinical	Iminex (Coquitlam, British Columbia, Canada)

This table shows antimicrobial peptides in treatment and development (2013). [6]

A biofilm is a population of cells growing in a surface and encapsulated in a matrix of exopolysaccharides. Due to its characteristics, biofilms are notoriously difficult to eradicate and are a source of many recalcitrant infections. biofilms are involved as much in dental infection as cystic fibrosis, may even invade water pipes. Thanks to its versatility, they can be applied in very different treatments:

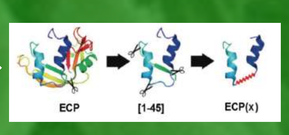
Therapy against biofilms integrity:

Coating agent	Coating method	Mechanism
Antibiotics	Non-covalent, covalent bonding	Bactericidal/Bacteriostatic
Silver	Plasma deposition, sol-gel coating, wet-chemical coating	Bactericidal
Furanones	Physical adsorption, covalent bonding	Bactericidal/Bacteriostatic
Quaternary Ammonium (QAS)	Covalent bonding	Inhibition of bacterial adhesion and viability
Silica nanoparticles with QAS	Covalent bonding	Bactericidal/Bacteriostatic
Trimethylsilane	Plasma coating deposition with covalent bonding	Anti-adhesion
Poly(l-lysine)-grafted-poly(ethylene glycol) (PLL-g-PEG)	Physical adsorption & covalent coupling	Anti-adhesion
Poly- carboxybetaine methacrylate	Zwitterionic surfaces grafted via radical polymerization	Anti-adhesion
Silica colloids/Silane xerogel	Synthesis of superhydrophobic coating	Anti-adhesion
Submicron surface textures	Physical surface roughness modification	Anti-adhesion
Selenocyanatodiacetic acid	Covalent bonding	Anti-adhesion
Polymer brush coatings	Surface grafting	Anti-adhesion

This table shows the prevention strategies (2013). [7]

Preventive therapy:

Creating a peptide from ECP, a human Rnase.



ECP (x) has given very encouraging results:

	(%max)			
Proteína o péptido	Dispersión del *Biofilm*	Mortalidad Bacteriana	Permeabilización de membrana	Despolarización de membrana
ECP	63.29 ± 4.08	67.31 ± 0.79	39.4 ± 2.88	46.11 ± 3.21
ECP(x)	100.00 ± 5.00	96.40 ± 2.41	64.26 ± 5.44	73.51 +- 1.94
GL13	33.28 ± 1.07	N.d.	N.d.	N.d.
LL-37	35.54 ± 1.13	64.05 ± 3.33	24.21 ± 3.71	31.85 +- 1.15
WY12	38.36 ± 2.36	39.67 ± 8.93	18.91 ± 2.23	32.58 +- 1.87
CEME	53.03 ± 1.46	54.32 ± 5.51	23.01 ± 1.13	39.09 +- 2.46

This figure contains the results of biofilm dispersion tests and antibacterial activity; permeation and membrane depolarization of different peptides including ECP (x) in % against P. aeruginosa biofilm formed. These trial were carried out by the Department of Biochemistry and molecular biology at the *Universitat Autònoma de Barcelona*. [8]

Conclusions

A lot of resources has been invested in the discovery of new antimicrobials. After proving that bacterial infections are no trifle and far of wreak ravages only in the third world, it is very interesting that the scientific community is involved and bet on this area. It is being achieved more broadly encompass the bacterial world. Not only focusing on finding a new miraculous conventional antibiotic, but attempts to diversify the problem. This issue may include since planktonic bacteria to biofilms, being counteracted both antibiotics and antimicrobial peptides.

References: **1.** WHO report: **The top 10 causes of death. 2.** LL Ling, T Schneider, AJ Peoples, AL Spoering et all. A new antibiotic kills pathogens without detectable resistance. *Nature* (2015)517:455–459 **3.** H Ledford. Promising antibiotic discovered in microbial 'dark matter'. *Nature News.* 07 January 2015 **4.** M Torrent, D Pulido, J Valle, MV Nogues, D Andreu and E Boix. Ribonucleases as a host-defence family: evidence of evolutionarily conserved antimicrobial activity at the N-terminus. *Biochem. J.* (2013);456:99–108 **5.** G Wang , Mishra B, RF Epand, RM Epand R. High-quality 3D structures shine light on antibacterial, anti-biofilm and antiviral activities of human cathelicidin LL-37 and its fragments. *Biochim Biophys Acta* (2014); 1838:2160-72 **6.** JL Fox. Antimicrobial peptides stage a comeback. *Nature Biotechnology* (2013); 31:379–382 **7.** M Chen, Q Yu, H Sun. Novel Strategies for the Prevention and Treatment of Biofilm Related Infections. *Int. J. Mol. Sci.* (2013); 14,9:18488-18501 **8.** D. Velázquez. *Estudio de la Proteína Catiónica de Eosinófilos (ECP), como agente antimicrobiano contra biofilms de origen bacteriano. (2014) Tesina – UAB.*