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RESULTS PACK ON ANTIBIOTIC RESISTANCE

New weapons to combat antibiotic resistance

EDITORIAL

NEW WEAPONS TO COMBAT ANTIBIOTIC RESISTANCE

One of the greatest challenges facing modern medicine is the unrestrained use of antibiotics, leading to antimicrobial resistance (AMR) and the growth of superbugs like Methicillin-resistant *Staphylococcus aureus* (MRSA) that have become highly resistant to antibiotics. Official figures show that annually, AMR is currently responsible for around 25 000 deaths in the EU and costs EUR 1.5 billion in healthcare expenditure and productivity losses.

However, the impact of AMR is felt elsewhere too. Drug resistance means people suffer infections for longer, resulting in disabling medical complications like amputation and damage to vital organs. Resistance also means repeated visits to doctors, longer hospital stays and treatment with more expensive drugs.

Combating AMR is therefore a key priority for the EU: through the FP7 and Horizon 2020 framework programmes, the EU is providing millions of euros in funding to innovative projects working to counter this threat. The aim is to strengthen research on AMR and enable the EU to actively promote global action and play a defining role in the fight against AMR.

Faster diagnosis — better drug delivery

This CORDIS Results Pack features 13 EU-funded projects that are spearheading AMR research. The ***RAPID*** *initiative created a gene-based test for* Klebsiella pneumonia*, a multidrug-resistant (MDR) bacterium common in hospital infections, while* ***PNEUMOSIP*** *developed a state-of-the-art device to analyse AMR and speed up pneumonia diagnosis.*

In addition, ***PNEUMONP*** *created a theragnostic system for the treatment of lung Gram-negative bacterial infections and nanocarriers for better drug delivery. The* ***CYCLON HIT*** *project also used nanoparticle drug delivery to tackle resistance to antibiotics of tuberculosis and bacteria species associated with hospital infections.*

Molecular mechanisms and personalised medicine

The ***TRANSLOCATION*** *project investigated cellular and molecular mechanisms behind influx and efflux processes in Gram-negative bacteria.* ***SYNPEPTIDE*** *generated variations of peptides with useful functions for the pharmaceutical industry. The structural analysis of antibiotic binding to ribosomes and pathogens was investigated by* ***NOVRIB*** *to create environmentally friendly drugs that combat antibiotic resistance.* ***DrugSense****, meanwhile, developed novel biosensors based on RNA molecules.*

Thanks to ***TAILORED-TREATMENT****, clinicians can now make better informed decisions.* ***R-GNOSIS*** *devised interventions to reduce the spread of MDR Gram-negative bacteria.* ***DRIVE-AB*** *will help ensure new antibiotics are used sustainably and meet the public's health needs. Finally,* ***AIDA*** *is re-evaluating the efficacy of old antibiotics from the past for use in the future.*

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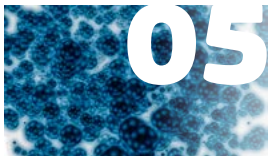


Old antibiotics – a new lease of life

In the wake of AMR, doctors are prescribing old off-patent antibiotics. The EU project AIDA has re-evaluated five major antibiotics in this class using current assessment and approval standards.

A combination of multiple drug resistance (MDR) in bacteria and lack of new antibiotics has fuelled the use of antimicrobials developed before the advent of a structured process for clinical efficacy and effectiveness assessment. The AIDA project worked to assess the effectiveness and optimal dosing of off-patent antibiotics for infections caused by MDR bacteria in three randomised controlled trials.

Five off-patent antibiotics subject to study

Researchers addressed the optimisation of treatment of infections caused by MDR pathogens that impose a major burden of disease on Europe and the rest of the world. Off-patent antibiotics are increasingly being used without clear evidence on their effectiveness, duration of therapy and issues of emerging drug resistance (EDR).

"We have been able to finalise three large clinical trials initiated by investigators at a fraction of the cost of the typical industry-initiated trials, including those currently supported by the Innovative Medicines Initiative (IMI)."

Importantly for patients, many of these antibiotics were licensed many years ago, when the rules were less stringent and we lacked the knowledge to determine optimal doses using pharmacodynamics. "As a result, the efficacy of many old drugs is not clearly established, nor is the dosing regimen," explains project coordinator, Dr Johan Mouton.

The AIDA project adopted a pharmacokinetic (PK) and pharmacodynamic (PD) approach alongside microbiological studies, thereby addressing the pressing issue of drug resistance. Looking at exposure-response relationships, PK/PD, they have established safe and effective dosing. "With EDR issues an essential element of the research project, these studies will interrelate synergistically with the clinical studies," Dr Mouton points out. Results will be used to refine exposure-response relationships, but also to study effects of exposure that are not readily observed in the trials.

Randomised trials for three serious real-life resistance scenarios

AIDA researchers chose microbial infections that were subject to potential inappropriate prescription for study, both in hospitals and in outpatients. Hospital-acquired pneumonia causes severe infections due to carbapenem-resistant Gram-negative bacteria in patients in intensive care units. The major outcome of a trial with 345 patients was that the combination therapy, using meropenem and colistin, although practised frequently, offered no benefit over colistin alone. The results were recently published in the journal *Lancet Infectious Diseases*.

Community-acquired lower urinary tract infections are common, and patients are increasingly at risk from MDR pathogens. The trial, involving more than 400 patients, compares the efficacy of the old antibiotics fosfomycin with nitrofurantoin, and the

results are expected to be published shortly. Together with the pharmacodynamic studies, these results provide a clear message on how to use these drugs.

MRSA, likewise often a community-acquired bacterium, causes skin and soft tissue infections. The AIDA randomised clinical trial has examined the effectiveness of minocycline plus rifampicin versus linezolid. Classed as a so-called reserve antibiotic, linezolid should be used sparingly in order to remain effective against potentially intractable infections.

Research impact and social significance

Emphasising what is possibly the key result in the project, Dr Mouton outlines, "We have been able to finalise three large clinical trials initiated by investigators at a fraction of the cost of the typical industry-initiated trials, including those currently supported by the Innovative Medicines Initiative (IMI)."

This assessment of the effectiveness of off-patent antibiotics means that the choice of antimicrobial as well as its dose can be optimised, resulting in an improved clinical outcome with possibly lower EDR and cost. "Indeed, the outcome of the trial in lower urinary tract infections provides a clear indication that the choice of therapy has a profound impact on clinical outcome in one of the most common infectious diseases, which will benefit a large number of patients," Dr Mouton stresses.

Project	**AIDA - Preserving old antibiotics for the future: assessment of clinical efficacy by a pharmacokinetic/pharmacodynamic approach to optimize effectiveness and reduce resistance for off-patent antibiotics**
Coordinated by	Erasmus Medical Centre, Netherlands
Funded under	FP7-HEALTH
Project website	http://www.aida-project.eu/

Nanoparticle drug delivery to tackle antibiotic resistance

There is a general consensus that drug-resistant microorganisms have emerged as an ecological consequence of the injudicious use of antimicrobial agents. To combat resistance, a European study has developed nanoparticles for the safer delivery of drugs.

Mycobacterium tuberculosis, the causative agent of tuberculosis, is an intracellular pathogen. When targeting such pathogens, the selected drug must be able to cross the eukaryotic cell membrane, to ensure therapeutic success. However, not all antibiotics achieve the therapeutic intracellular concentration, resulting in antibiotic resistance: this highlights the need for improved drug delivery systems capable of penetrating infected cells.

Nanocarriers based on biocompatible cyclic oligosaccharides known as cyclodextrins (CDs) are emerging as promising delivery vehicles for antibiotics. They exhibit excellent biocompatibility in humans, low toxicity and absence of immune stimulation, even at high dosages. Importantly, they can effectively incorporate a series of active molecules that protect them from degradation, thereby increasing drug bioavailability and decreasing treatment duration.

CD nanocarriers are being considered to treat tuberculosis as well as bacteria species most frequently implicated in hospital infections. With a focus on tuberculosis, the EU-funded CYCLON HIT project aimed to design, characterise and evaluate the efficacy of CD-based nanocarriers.

Nanoparticles for treating tuberculosis

Tuberculosis constitutes a major health issue, with millions infected worldwide. The misuse of first-line drugs may lead to multidrug-resistant tuberculosis, which is subsequently treated with chemotherapy or second-line drugs such as ethionamide (ETH). However, patients often find it difficult to comply with treatment regimens that require high doses of ETH.

Recent studies have discovered that certain 'booster' molecules significantly increase ETH efficacy, improving the clinical treatment of drug-resistant tuberculosis. "We wanted to investigate the simultaneous delivery of ETH and booster molecules using CD nanoparticles," explains project coordinator Dr Ruxandra Gref.

"The CYCLON HIT project trained the next generation of highly educated researchers to deal with the complex issues related to increasing antibiotic resistance."

Researchers focused on pulmonary administration of the nanoparticles, since lungs are the primary site of *M. tuberculosis* infection. This approach helped achieve higher drug concentrations at the target site and had fewer systemic side effects.

Following treatment in an animal model for tuberculosis, researchers observed a significant decrease in lung mycobacterial load. "Considering that the current regimen for tuberculosis consists of a cocktail of drugs, the CYCLON HIT approach could be employed to encapsulate synergic drugs, considerably simplifying the treatment and increasing patient compliance," continues Dr Gref.

The next era in antibiotic design

Drug resistance does not prevail in healthcare environments due to selection pressure or drug abuse alone. Resistance is increasing amongst community-acquired pathogens as well, owing to continuous exposure to low doses of antibiotics contained in foods, for example.

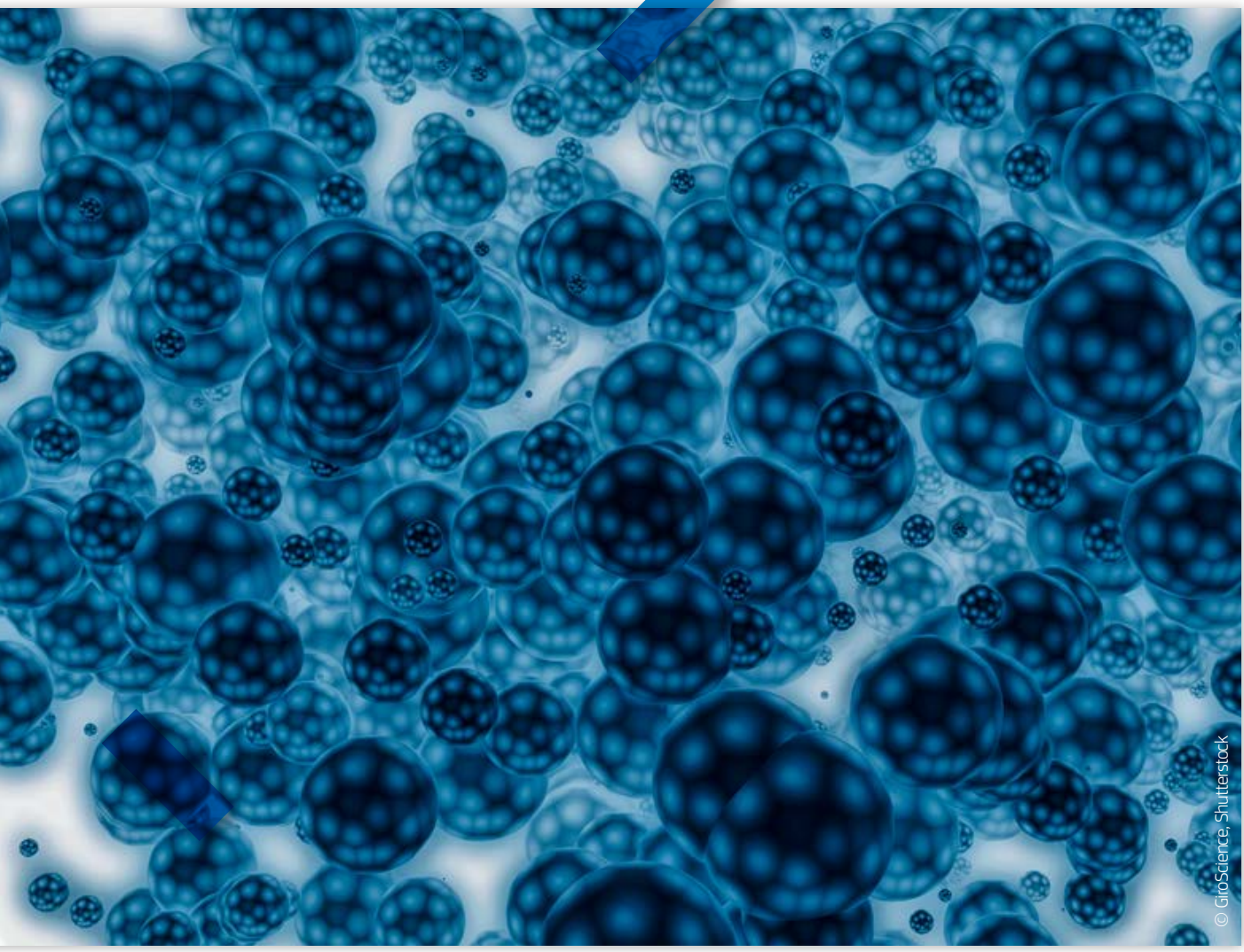
Given that bacteria respond to the selective pressure of antibiotics by continuously mutating and acquiring resistance genes, sustained research efforts are needed to deliver well-documented existing drugs in an optimised fashion.

Towards this goal, "the CYCLON HIT project trained the next generation of highly educated researchers to deal with the complex issues related to the increasing antibiotic resistance," outlines Dr Gref. Early stage and experienced researchers undertook interdisciplinary training in chemistry, nanotechnology, microbiology and *in vivo* studies.

The consortium also held three workshops, two summer schools and numerous outreach activities. The teams involved went beyond their initial objectives by organising a congress at the Pasteur Institute in Paris in 2015, and a 'brokerage and pitching' event in Orsay in 2018, bringing together several EU projects. Furthermore, Prof. Thorsteinn Loftsson and Dr Gref edited a special issue of a high-impact journal in the field (https://www.sciencedirect.com/journal/international-journal-of-pharmaceutics/vol/531/issue/2), where CYCLON HIT partners made significant contributions on the use of CDs to fight serious diseases.

Exploiting the most recent advances in the nanomedicine field, CYCLON HIT partners envision alternative therapeutic approaches for other resistant microorganisms besides *M. tuberculosis*. "Intelligent nanoparticles capable of delivering drugs to the site of infection with minimal side effects are certainly the choice of the future," claims Dr Gref.

Project	**CYCLON HIT – Nanocarriers for the delivery of antimicrobial agents to fight resistance mechanisms**
Coordinated by	National Centre for Scientific Research (CNRS), France
Funded under	FP7-PEOPLE
Project website	http://itn-cyclonhit.eu/



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Recommendations on driving antibiotic R&D and helping to fight AMR

Antibiotic resistance is one of the biggest threats to global health, and it's only getting worse. Innovation is lacking in this area because few big pharma companies are willing to invest in R&D, owing to the low returns and high risks.

It is estimated that antibacterial drug resistance costs the EU at least EUR 1.5 billion and about 25 000 lives every year. The development of new drugs to treat resistant infections is falling behind. New economic models offering incentives that directly support R&D and reward successful outcomes from R&D for the discovery and development of novel antibiotics are long overdue. These models will also need to reconcile such incentives with responsible antibiotic use and access.

The EU-funded project DRIVE-AB aimed to "transform the way policymakers stimulate antibiotic innovation, while ensuring that these new antibiotics are used sustainably and are equitably available to meet public health needs," says Judith Hackett, the project's coordinator. To build policy recommendations and incentivise antibiotic R&D, DRIVE-AB used a research-based multidisciplinary approach involving a broad range of stakeholders from academic institutions, research organisations and pharmaceutical/biotechnology industries.

Furthermore, project partners defined standards and metrics for responsible use of antibiotics, and identified antibiotic-related public health priorities. They also calculated the societal value of having new antibiotics available for these priorities. In addition, the project team developed and costed new economic models to promote the desired antibiotic innovation and sustainable use of the resulting novel antibiotics.

"By developing and testing new economic models for antibiotic development and use, DRIVE-AB will help reinvigorate investment in this area."

Incentives to revitalise antibiotic pipeline and boost innovation

DRIVE-AB assessed more than 30 different economic incentives. The project considered how each one of these would affect antibiotic innovation, sustainable use and equitable availability. One key incentive is the market entry reward, which aims to create an attractive market for investment in antibiotic R&D by attracting increased private sector funding and supporting sustainable R&D investment. A model developed by the project estimates that a market entry reward of at least EUR 850 million per antibiotic globally could quadruple the number of new antibiotics entering the market in the next 30 years.

Of all the incentives analysed, three additional models were found to be the most effective in stimulating R&D and ensuring that critical antibiotics continue to be accessible and can be used sustainably. Non-refundable research grants to academic institutions, companies and others is one model; paying for R&D, governmental or non-profit pipeline coordinators that identify and fill gaps in the global antibiotic pipeline is another. The final model is long-term supply continuity funding to ensure a predictable supply of generic antibiotics over time.

The project determines that EUR 680 million is needed annually to fund grants and pipeline coordinators. This represents an increase of about 50 % over the current public investments in antibiotic R&D made every year.

Novel incentives and models to maximise R&D

Each incentive is intended to stimulate specific phases of the R&D process. These models do not operate in isolation; they are designed to be complementary. Together, they form an incentive ecosystem to maximise their effectiveness in stimulating innovation while ensuring sustainable use and access.

"There's no 'one size fits all' solution to incentivising antibacterial innovation in a global market with varying unmet needs, healthcare systems and access requirements," explains Hackett. "A menu of incentives will ultimately be required that can be adapted to a local context and yet still achieve the goal of stimulating antibacterial innovation."

"By developing and testing new economic models for antibiotic development and use, DRIVE-AB will help reinvigorate investment in this area," concludes Dr Hackett. "Governments and policymakers must act now to implement these incentives and tackle one of the three biggest public health threats, according to the World Health Organization."

Project	**DRIVE-AB - Driving re-investment in R&D and responsible antibiotic use**
Coordinated by	Astrazeneca AB, Sweden
Funded under	FP7-JTI
Project website	http://www.drive-ab.eu/

Novel biosensors of antibiotics

Antibiotics have revolutionised modern clinical and veterinary medicine as well as agriculture. However, their injudicious use has driven a rapid spread of antibiotic resistance among pathogenic and commensal bacteria, with adverse health effects.

The health and safety risks imposed by the presence of antibiotics in food, drinking water, and environmental waters emphasise the need for continuous monitoring. According to EU regulations, food manufacturers must screen their products for traces of antibiotics.

Currently, screening of aquatic pollution by chemicals including antibiotics is performed by liquid chromatographic techniques combined with mass spectrometric analysis. However, antibiotic sensing requires more advanced sensors that would accurately, rapidly and inexpensively report on the presence of antibiotics in various environments.

Scientists of the EU-funded DrugSense project proposed to develop innovative sensors that rely on RNA molecules used by bacteria to switch on and off antibiotic resistance genes. RNA aptamers are increasingly being used in biosensor development to bind the analyte of interest with an excellent sensitivity, similar to the affinity exhibited by antibodies. Other approaches for antibacterial detection include functionalised gold nanoparticles or immobilised enzymes that break down specific antibiotics such as penicillin causing a change in the pH of the target sample.

Exploiting antibacterial mechanisms

"The DrugSense concept relies on the well-established mechanisms evolved in bacteria to overcome the antibiotic imposed pressure," explains project coordinator Prof. Rotem Sorek. These mechanisms include enzymatic degradation of antibiotic molecules, efflux from the cells via specific pumps or protection of antibiotic targets via appropriate chemical modifications.

"The DrugSense concept relies on the well-established mechanisms evolved in bacteria to overcome the antibiotic-imposed pressure."

However, antibiotic resistance often comes at a cost to bacterial fitness. As a result, bacteria employ regulatory mechanisms by which they sense the presence of antibiotics and selectively activate the expression of the relevant resistance genes only during antibiotic exposure. Growing evidence indicates that for gene regulation, in addition to classic transcription factors, bacteria employ cis-regulatory non-coding RNAs (ncRNAs) as antibiotic sensors.

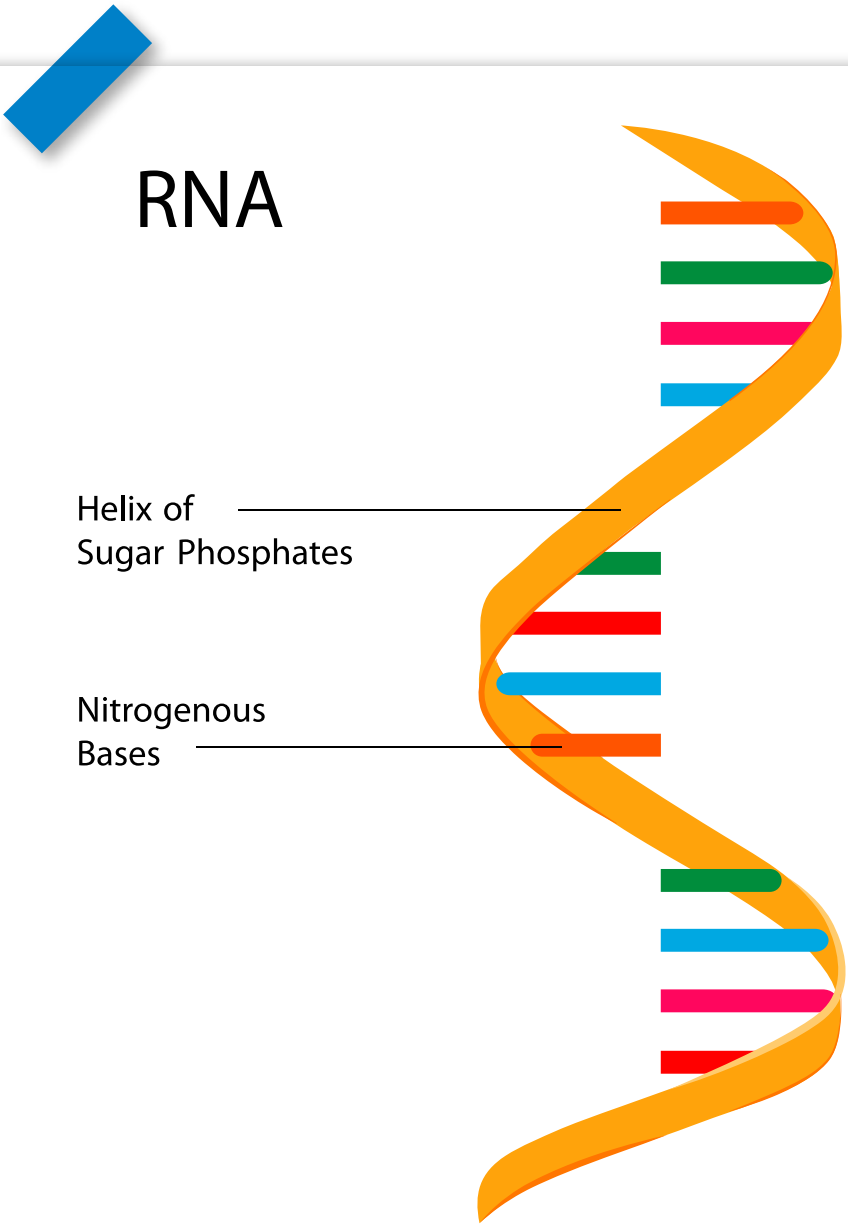
Through genome-wide studies, the DrugSense team had previously identified RNA molecules — known as ribo-regulators — that respond to the presence of antibiotics by stalling ribosomes, thus controlling the expression of antibiotic resistance genes. This mechanism seems to be functional in both pathogenic and commensal bacteria.

Innovative biosensors based on bacterial RNA molecules

"These ribo-regulators can thus function as efficient antibiotics sensors," outlines Prof. Rotem Sorek. "We will use them to develop a prototype for a highly sensitive biosensor, capable of rapid detection of trace levels of multiple antibiotics in food, water and other substances, in a cost-effective manner."

DrugSense scientists utilised their earlier discoveries to bioengineer the antibiotics sensor. At the same time, they performed comprehensive market research to identify the needs, map the competition and pinpoint market segments where the biosensor would offer certain advantages over existing products. In future, Prof. Sorek hopes to "achieve an intellectual property-protected proof-of-concept prototype that will attract further external investments, and help bring our technology to the market."

Project	**DrugSense - Ribo-regulators that sense trace antibiotics**
Coordinated by	Weizmann Institute of Science, Israel
Funded under	H2020-EU.1.1.



Treating infectious disease with the help of antimicrobial peptides

Against the backdrop of increasing antibiotic resistance, the FORMAMP project has trialled nanotechnology-based delivery systems and antimicrobial peptides (AMPs), to deliver new tools in the fight against infectious diseases.

It has been calculated that increased microbial resistance is responsible for an estimated 25 000 deaths per year, costing EUR 1.5 billion across the EU. In the quest for new therapies against infectious diseases, AMPs are touted as promising candidates, as they appear to induce less resistance.

The EU-funded FORMAMP project was established to explore how nanotechnology formulations and local delivery strategies could improve the stability and efficiency of AMPs when applied directly to the site of skin and burn wounds, and also to lung infections.

The project developed a completely new type of nanomaterial as well as generating a new approach for the treatment of tuberculosis, with promising strategies for biofilm degradation.

"The combination of new treatments such as ours, and increased public awareness of antimicrobial resistance, diagnostic tools and preventive actions against the spread of multiresistant strains, should bring us closer to a future where resistance can be reduced."

Developing smart formulation and delivery strategies

AMPs are a group of molecules functioning as part of the innate immune system in most organisms. As they are fast-acting against invading microorganisms and operate under non-specific mechanisms, bacteria struggle to develop resistance towards them. Despite holding out great promise for a new generation of therapeutic treatments, few AMPs have reached clinical trials, due to their sensitivity to degradation and high manufacturing costs.

The FORMAMP team evaluated various combinations of AMPs and nanocarriers for antibacterial effect against several types of strains (including multiresistant strains). The nanocarriers investigated included lipidic nanocapsules, lipid self-assembly systems, microgels, dendrimers and mesoporous silica nanoparticles. The team also succeeded in developing a completely new type of carrier system, with a patent pending.

Summarising the nanocarrier results, project coordinator Dr Lovisa Ringstad says, "Lipid-based systems were most successful for topical delivery. Whereas the mesoporous silica particles were shown to be highly successful for pulmonary delivery. The polymer-based systems were utilised both for pulmonary and topical application. For bacteria biofilm degradation, one type of lipid-based nanocarrier has been shown to act synergistically with the AMPs, which is highly exciting."

As for the drug delivery systems, a thermosensitive gel formulation was shown to be most promising for topical administration. For pulmonary delivery, inhalable powders were developed which were shown to distribute well within the lungs.

Biophysical characterisations were carried out continuously to understand the interactions between AMP and nanocarriers, as well as with the surrounding environment. Cell and tissue modelling (*in vitro* and *ex vivo*) were used to investigate the effect of the peptides, and at the final stage, mouse and rat models (*in vivo*) were used to assess effects. Additionally, the toxicity of the formulations was investigated.

Adding to the treatment toolkit

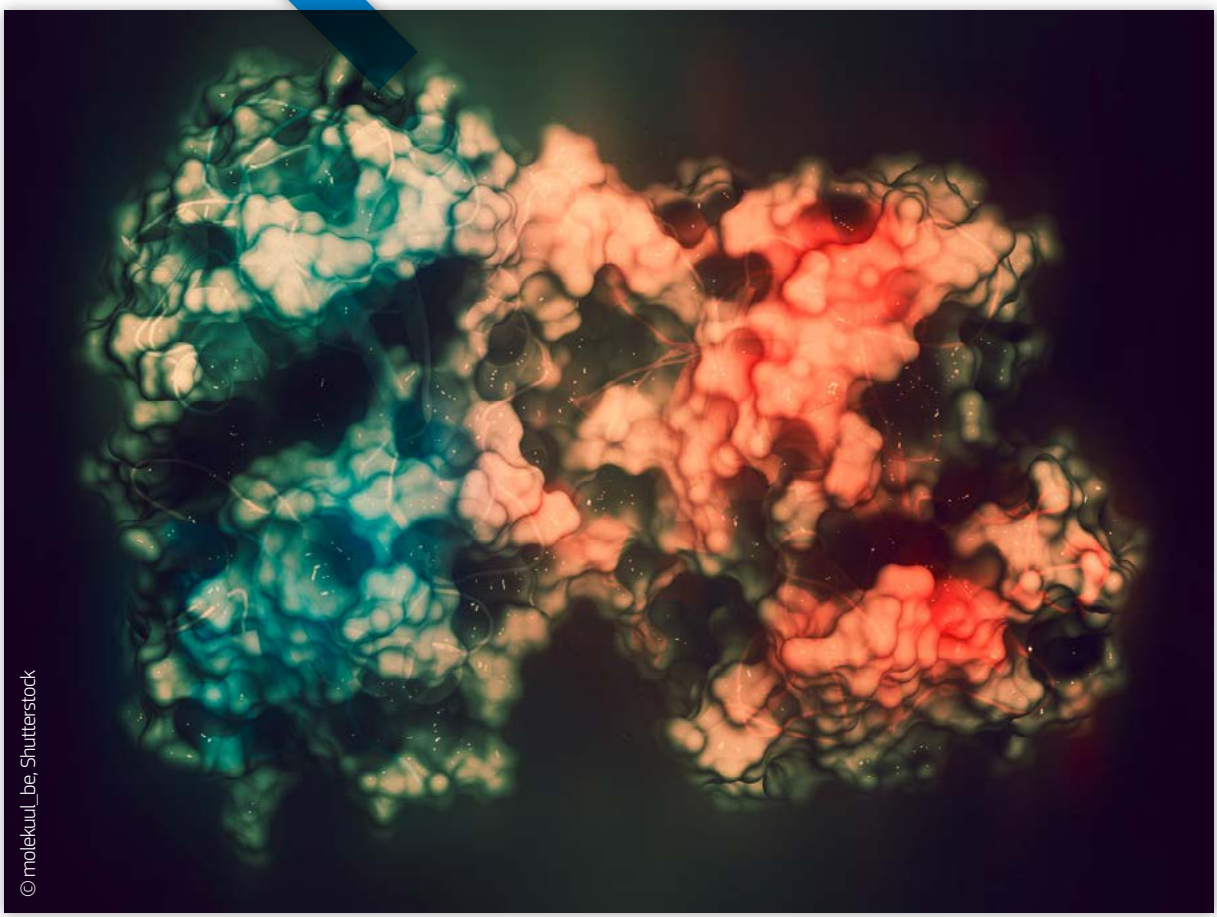
A number of tangible project results are already contributing to new treatments. For example, one of the consortium's small and medium-sized enterprises (SMEs) has signed a licensing agreement for further development of a peptide for the treatment of skin and soft tissue infections. Additionally, strategies to degrade biofilms, associated with several severe infections such as cystic fibrosis and burn wounds, have also been developed.

FORMAMP has also led to the development of a promising formulation for tuberculosis treatment. As Dr Ringstad elaborates, "Further development is planned for this treatment, where additional proof of concept in living organisms and a more detailed understanding of the precise mechanism is needed. Also, we need to fine-tune our formulation, which requires further manufacturing and quality control development."

The FORMAMP nanoformulations can also be further developed to serve as a platform for other applications delivering biologics as new therapies with fewer side effects for a range of diseases.

As Dr Ringstad says, "The combination of these new treatments, increased public awareness of antimicrobial resistance, diagnostic tools and preventive actions against the spread of multiresistant strains, should bring us closer to a future where resistance can be reduced."

Project	**FORMAMP - Innovative Nanoformulation of Antimicrobial Peptides to Treat Bacterial Infectious Diseases**
Coordinated by	Rise Research Institutes, Sweden
Funded under	FP7-NMP
Project website	http://formampproject.com/



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A fresh look at antibiotic design

The emergence of antibiotic resistance poses a significant health threat and hampers the effectiveness of many antibiotics used today. With many diseases on the verge of becoming untreatable, and negligible design of new antibiotics by pharma companies, there is an imminent need for basic research to discover novel antibiotics.

Most clinically useful antibiotics are natural compounds produced by microorganisms as defence against pathogens. To improve their potency, pharma companies chemically modify natural antibiotics or generate semi-synthetic analogues. However, pathogenic bacteria such as *S. aureus* respond to the pressure imposed by natural and improved antibiotics by developing resistance, thereby significantly hampering their effectiveness.

Intriguingly, AMR is a key survival tactic for many microorganisms, and antibiotic resistance genes existed before the clinical utilisation of the natural antibiotics. Resistance manifests through various molecular mechanisms such as activation of drug efflux pumps or mutations that modify the antibiotic binding pockets.

Scientists of the EU-funded NOVRIB project focused their research on antibiotics that target ribosomes, multiprotein-RNA assemblies that drive protein biosynthesis. Given their key role in life, ribosomes constitute a target for many antibiotics, which in essence inhibit protein synthesis in pathogenic microorganisms. As Chemistry Nobelist and project coordinator Prof. Ada Yonath outlines, "NOVRIB explored new potent selective compounds, keeping in mind not only to combat or decrease antibiotics resistance, but also to preserve the microbiome and the environment."

Advancing ribosomal antibiotics

Currently, antibiotic research mainly concentrates on underexplored microbial niches or the design of new chemical probes for improving the performance of existing antibiotics. The NOVRIB consortium proposed a different approach: they expanded the common search for establishing as yet unknown mechanisms of antibiotic function, selectivity and resistance by discovering novel antibiotic binding sites. These sites demonstrated high potential to become useful targets, for which lower levels of resistance are expected to appear soon.

Towards this goal, they determined the detailed structure of ribosomes from the pathogenic bacteria ***S. aureus*** by X-ray crystallography or the recently developed 3D electron microscopy. By comparing this structure to those of ribosomes from non-pathogenic bacteria they identified unique structural motifs that provide novel sites for the design of new pathogen-specific drugs. "This paved the way for designing novel selective antibiotics, less susceptible to resistance, thus dealing with the current acute resistance issues," continues Prof. Yonath.

The future of antibiotics

The emergence of multidrug-resistant strains, together with the very few new antibiotics presently in the drug discovery pipeline from pharma companies threaten to send us back to the pre-antibiotic era, where infections were untreatable. Looking into the future, Prof. Yonath is hopeful, but emphasises "the immediate necessity for novel antibacterial agents."

"NOVRIB explored new potent selective compounds, keeping in mind not only to combat or decrease antibiotics resistance, but also to preserve the microbiome and the environment."

Antibiotic toxicity — and the spreading of drug resistance — is linked to the chemical composition of many existing antibiotics which are non-biodegradable and indigestible by humans or animals. As a result, they contaminate the environment, and may enter agricultural irrigation systems, with direct implications for human and animal health. The novel antibiotics binding sites discovered by this study could also address this problem, since one can design according to preference compounds, with species specificity and minimal toxicity, thereby reducing the widespread antibiotics resistance while preserving the microbiome in an ecofriendly manner.

In brief, contrary to the current medical preference for broad-spectrum antibiotics, the NOVRIB structural analysis approach provides the means for the design of pathogen-specific antibiotics that display selectivity, biodegradability and minimal toxicity. "Environmentally friendly drugs should also help reduce antibiotic resistance," concludes Prof. Yonath.

Project	NOVRIB - Novel Insights into Multi-drug Resistance to Antibiotics and the Primordial Ribosome
Coordinated by	Weizmann Institute of Science, Israel
Funded under	FP7-IDEAS-ERC

New solutions for diagnosing and treating antibiotic-resistant bacteria

Infections caused by antibiotic-resistant bacteria are a widespread health problem. To help, the EU-funded PNEUMONP project has developed new ways to both diagnose and treat infections caused by antibiotic-resistant bacteria.

A patient suffering from a respiratory tract infection caused by a bacterium goes to the doctor for help. To treat him, the doctor tries several different types of antibiotics, none of which is successful. This is because the bacteria causing the patient's infection are resistant to the most common types of antibiotics available.

This by no means is an isolated case. Every year, millions of people suffer from infections caused by antibiotic-resistant bacteria. In fact, the problem is now so widespread that the World Health Organization (WHO) regards it as one of the major current global health crises.

In response to this crisis, the European Union has funded many research projects aimed at solving the problem, including PNEUMONP. "The objective of the PNEUMONP project was to develop a novel solution for diagnosing and treating infections caused by antibiotic-resistant bacteria," says project coordinator Iraida Loinaz.

A better diagnostic kit

One solution was the development of a diagnostic kit to identify the bacteria causing the infection within a single sample. Using polymerase chain reaction (PCR) technology, the PNEUMONP multiplex kit screens for more than 30 of the main antibiotic-resistant genes. Running on standard lab equipment, the kit has the added benefit of being relatively cheap to use.

Thanks to this kit, doctors can now easily get a diagnosis at a very early stage of the disease, immediately treat with the proper antibiotics and likely save a life. "Using the kit, a doctor can quickly identify whether a patient is infected with an antibiotic-resistant bacterium and prescribe the proper treatment — all within as little as just 3 hours, whereas conventional methods take up to 48 hours," explains Loinaz.

The diagnostic kit will receive clinical approval in 2018 and will then be released onto the market.

Coupling antibiotics with nanocarriers

But what about those bacteria that are extremely resistant to antibiotics, where no antibiotic is available to treat the resulting infections? Here, PNEUMONP researchers created new antibiotics.

For instance, the project explored the antibacterial properties of the M33 peptide, developing a specific form of the molecule that has proved effective against such infections as *Pseudomonas aeruginosa* and *K. pneumoniae*. Researchers also studied the AA139 molecule, another promising antimicrobial peptide.

To ensure the efficient and safe delivery of these new antibiotics, researchers also looked at coupling the M33 and AA139 molecules with nanocarriers. Nanocarriers are nanomaterials used as a mode of transporting another substance.

As a proof of concept, the new antibiotics in nanocarrier form were delivered as an aerosol and tested against an antibiotic-resistant bacterium responsible for serious respiratory tract infections. "Attaching antibiotics to nanocarriers allows for the delivery of various combinations of antibiotics without an increase in risk to the patient," says Loinaz. "Early tests of several combinations demonstrate that this approach does improve the performance of antibiotics, and there were no signs of resistance to the new antibiotics."

The project has also been developing a manufacturing process that will allow for scalable production of the nanosystems — crucial if these new antibiotics are to break into the highly regulated pharmaceutical sector.

"We are still far from having a new medicinal product in clinical trials, but we have generated knowledge on the systems, and we really think nanotechnology will help in the design of a new generation of drugs."

Overall, the PNEUMONP project successfully demonstrated the positive effect of coupling antibiotics with nanocarriers for treating multiresistant bacteria-based infections. "We are still far from having a new medicinal product in clinical trials, but we have generated knowledge on the systems and we really think nanotechnology will help in the design of a new generation of drugs," adds Loinaz.

Project	**PNEUMONP - Nanotherapeutics to Treat Antibiotic Resistant Gram-Negative Pneumonia Infections**
Coordinated by	Fundación CIDETEC, Spain
Funded under	FP7-NMP
Project website	http://www.labsexplorer.com/site/pneumonp_3

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State-of-the-art device speeds up pneumonia diagnosis

Community-acquired pneumonia (CAP), the most common type of pneumonia, is a leading cause of death globally, with an associated annual cost in Europe of about EUR 10 billion. Current diagnostic methods are too slow, and increasing antibiotic resistance makes CAP harder to treat.

CAP is the fourth most common cause of death in adults (90 % for those aged over 65) and the number one cause in children younger than 5. There are about 3.4 million cases reported annually in Europe. CAP is an enormous burden on the economy, because of patients who are diagnosed too late. It also puts a tremendous strain on healthcare resources.

Early diagnosis key to keeping pneumonia mortality rates down

To manage patients and reduce mortality, rapid diagnostic techniques with high capacity and sensitivity are in great demand. Existing methods to identify pneumonia are time-consuming, and are characterised by low sensitivity and specificity. They also fail to provide useful information for prescribing appropriate treatment in avoiding possible resistance to antibiotics.

"There's a clear and urgent need for a rapid, reliable, fully automatic and cost-effective method to properly diagnose the common causes of pneumonia in Europe."

The three main pathogens responsible for CAP in Europe are ***Streptococcus pneumoniae***, ***Haemophilus influenzae*** type b and respiratory syncytial virus. "There's a clear and urgent need for a rapid, reliable, fully automatic and cost-effective method to properly diagnose the most common causes of pneumonia in Europe," says Miguel Roncales, CEO of AlphaSIP, the company managing the EU-funded project PNEUMOSIP. "This method should also analyse antibiotic resistance, helping to prescribe the right treatment in the shortest possible time period."

To date, project partners have built a prototype point-of-care (PoC) system. With preclinical validation complete, they are starting with the clinical validation phase. Definitive results are expected in June 2018.

Quick and easy solution to properly diagnose pneumonia

The molecular diagnostic PoC device will provide a one-stop, automated sample-to-result solution for the speedy diagnosis of CAP infectious agents. The diagnosis is based on a patented procedure previously developed within the scope of the EU-funded CAJAL4EU project.

According to Roncales, the PoC device surpasses existing methods by reducing the time needed to obtain results, and gives information about the best line of treatment. It will serve as an accurate and immediate clinical management decision tool, by using a single sample to determine the occurrence and level of activity of the three different agents and their resistance to antibiotics.

The innovation is designed to help doctors confirm the existence of the disease in less than two hours, identify what is causing it and supply data to better select treatment options. "It will provide the right information for doctors to make the most informed decisions," explains Roncales. "As a result, patients will be treated faster and more reliably, thus helping to reduce mortality."

The system promises widespread reach due to its compact design and simple operation. It can be employed by a variety of professionals in most public and private hospitals, physician office laboratories, emergency units, primary care centres and even pharmacies in some particular regions. "They will all benefit from a rapid, measurable detection of biological agents and antibiotic resistance with high levels of accuracy at affordable prices," concludes Roncales.

Ultimately, PNEUMOSIP should improve the efficiency of Europe's healthcare system by allowing hospitals to do more work in less time, while reducing the overall costs associated with CAP testing, hospitalisation and improper treatment.

Project	**PNEUMOSIP**
Coordinated by	Laboratorios Alpha San Ignacio Pharma S.L. – ALPHASIP, Spain
Funded under	H2020-EU.2.3.1. & H2020-EU.3.1.
Project website	http://www.pneumosipdx.com/

Rapid detection of multidrug-resistant bacteria

A rapid, gene-based test has provided AMR profiles for one of the major multidrug-resistant bacteria common in hospital infections.

Emerging resistance to antimicrobials continues to whittle away the treatment options for opportunistic infections in patients undergoing treatment for other conditions. Equipment such as ventilators and catheters encourage invasion of these pathogens and patients remain at risk.

In spite of the initial enthusiasm and the extensive research literature, gene-detection based molecular methods have not yet had the impact on routine diagnostic microbiology that many had predicted. "To change this situation, clinical microbiology needs to provide more impact on the management of infectious diseases and should accommodate the general drive towards more cost-efficient medicine," outlines Prof. Susanne Häussler, RAPID project coordinator.

The EU-funded RAPID project has developed a cost-effective assay that could change the current model of culture-based microbial diagnostics and provide the surveillance necessary for detecting multidrug resistance.

Rapid, robust and reasonably priced resistance profiles

Currently, results from samples arriving in the lab are available after two full days. RAPID diagnostics, however, are ready after only one full day of testing, a significant improvement when appropriate antimicrobials could be administered to clear any infection. Reduction of the stay in hospitalisation and a hike in improvement in prognosis are just two massive benefits for patients and healthcare authorities.

"This enables timely and more detailed information on antimicrobial resistance profiles for more effective antibiotic treatment, and facilitates tracking of bacterial pathogen spread in the hospital setting."

Screening for 58 of the genetic resistance determinants in *K. pneumoniae* genome as well as for phylogeny informative sequence variations, the RAPID test is a gene-detection-based high-density molecular system. The test gives valuable information on the evolutionary relationships between the groups of microbes. "This enables timely and more detailed information on antimicrobial resistance profiles for more effective antibiotic treatment, and facilitates tracking of bacterial pathogen spread in the hospital setting," explains Prof. Häussler.

With the design of the assay now completed, more than 800 clinical *K. pneumoniae* isolates have passed through the RAPID screens. The sheer number of tests has validated its sensitivity and specificity to detect resistance.

Cost is affordable, at EUR 10 for materials, albeit slightly higher than the conventional cost of up to EUR 7. However, the real savings come with targeted, more effective therapies and possibly shorter stays in hospital. "Reduction of spread from patient to patient may well be of highest value in the hospital ward," points out Prof. Häussler.

Road from the lab to the clinic

RAPID has designed a robust molecular resistance detection assay with excellent technical performance when used with clinical *K. pneumoniae* isolates. "An important prerequisite for commercialisation, the next step will be to demonstrate that its broad use in the clinic will indeed improve management of multidrug-resistant bacteria and thus improve patient care," Prof. Häussler concludes.

Implementation of RAPID, a tailored and cost-effective diagnostic tool, in clinical microbiology laboratories could provide critical information for decision-making with respect to prudent antibiotic use. The test tackles multidrug-resistant opportunistic pathogens, an area which until now has remained underfunded.

Project	**RAPID – Rapid Antimicrobial susceptibility testing and phylogenetic Identification**
Coordinated by	Helmholtz Centre for Infection Research, Germany
Funded under	H2020-EU.1.1.

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Intervention strategies against antibiotic resistance

Europe faces a dramatic increase in infections caused by drug-resistant bacteria. With very few antimicrobial agents in the drug discovery pipeline, effective measures are urgently needed to contain resistance and limit the spread of these pathogens.

"Our aim was to develop prophylaxis strategies and optimise treatment against MDR-GNB, avoiding the detrimental consequences of these bacteria on patient outcome."

Multidrug-resistant Gram-negative bacteria (MDR-GNB) can cause serious infections that pose a threat to hospitalised patients, especially those in intensive care units (ICUs). The European Centre for Disease Prevention and Control and the European Medicines Agency estimated that nearly 200 000 patients were infected with MDR-GNB in 2007. With a striking lack of antimicrobial agents, new interventions are required to contain resistance and limit the spread of MDR-GNB.

Towards this goal, the EU-funded R-GNOSIS project brought together leading experts in the field who developed cutting-edge interventions against MDR-GNB. Using highly innovative microbiology, mathematical modelling and data management, researchers performed five pivotal clinical studies that tested the efficacy of various approaches. "Our aim was to develop prophylaxis strategies and optimise treatment against MDR-GNB, avoiding the detrimental consequences of these bacteria on patient outcome," explains project coordinator Dr Marc Bonten.

Approaches for containing drug resistance

The injudicious prescription of antibiotics is to blame to a large extent for the emergence of MDR-GNB species. Therefore, improving antibiotic prescription in primary care is believed to alleviate the issue. For this purpose, R-GNOSIS partners developed point-of-care testing (POCT) for optimising antibiotic prescription and prophylaxis before surgery.

Since bacteria are capable of transferring drug resistance genes, the scientific teams of R-GNOSIS worked to identify the most effective measures for controlling genetic transmission. In particular, they investigated the critical molecular aspects for persistence and transfer of resistance genes in the human gut. They used mathematical modelling to generate mechanistic and quantitative understanding of the ecological and evolutionary processes determining the dynamics of MDR-GNB in the host. Significant insight was also gained into how these organisms are transmitted in hospitals.

R-GNOSIS included a clinical study involving gut decolonisation followed by faecal microbiota transplantation (FMT) for intestinal carriers of MDR-GNB, such as extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae. The study showed encouraging preliminary results, although technical challenges prohibited recruitment of the necessary number of patients. Nonetheless, R-GNOSIS partners hope to continue these studies, exploring the use of FMT without prior use of antibiotics.

In a multicentre study, different patient isolation strategies were tested in an approach for reducing ESBL-Enterobacteriaceae acquisition among hospitalised patients, which is similar to what occurs with MRSA. This study revealed no difference between two strategies that differed in the intensity of isolation measures.

In another multicentre study, researchers tested various decontamination strategies for patients in ICUs as a means of eliminating bacteria from the airways and gut, and preventing hospital infections. This approach is standard care in Dutch ICUs, where the prevalence of antibiotic resistance is low. This study was based on 8 500 patients admitted to 13 ICUs in 6 European countries where the prevalence of antibiotic resistance was considerably higher than in Dutch ICUs.

Two of these strategies included antibiotics, and contrary to previous results obtained in Dutch ICUs, they demonstrated no beneficial effect compared to standard care. This constitutes a strong argument against the use of decontamination strategies with antibiotics in ICUs with moderate to high prevalence of antibiotic resistance.

The future of antibiotic resistance

Dr Bonten views drug-resistant bacteria as "a formidable enemy, equipped with sophisticated molecular methods to express and exchange resistance genes, capable of colonising multiple reservoirs and harbouring a bewildering array of virulence factors to infect any suitable host." He therefore emphasises the need for concerted efforts to improve diagnosis, antibiotic-prescribing practices and infection prevention strategies for tackling antibiotic resistance in the future. Recommendations derived from the R-GNOSIS results will undoubtedly contribute to all these, leading to better quality of patient care in Europe.

Project	**R-GNOSIS – Resistance in Gram-Negative Organisms: Studying Intervention Strategies**
Coordinated by	University Medical Centre Utrecht, Netherlands
Funded under	FP7-HEALTH
Project website	http://www.r-gnosis.eu/

Functional peptides for next-gen antibiotics

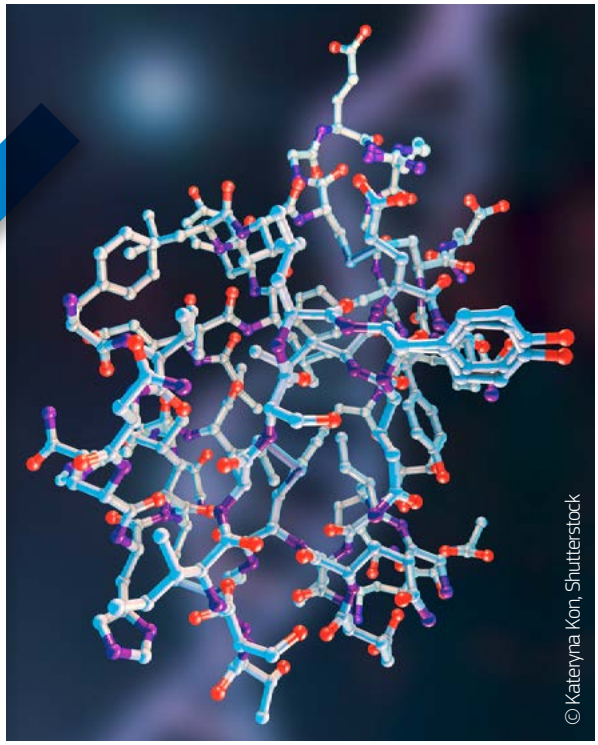
In the face of growing AMR amongst patients, pharmaceutical companies are looking for new compounds. Peptides provide them with thousands of options, but finding suitable candidates is tedious to say the least. An EU-funded project has come up with a method to facilitate their design and production.

Long considered as a no-go area for researchers because of some inherent disadvantages, peptide pharmaceuticals have been booming over the past few years: by 2024, their market value is expected to grow from USD 19.5 million to USD 45.5 million. This success can easily be explained: peptides benefit from greater efficacy, selectivity and specificity than synthetic drugs.

Over 7 000 naturally occurring peptides have been identified so far. The SYNPEPTIDE project aimed to generate variations of peptides with useful function for the pharmaceuticals industry, as well as endow them with new functionalities.

"We have found new molecules that show very interesting activities against certain Gram-positive bacteria that are currently a problem in clinics."

"We were looking for novel peptides with antibiotic activity," says Prof. Dr Sven Panke, coordinator of SYNPEPTIDE. "Antibiotic resistance, including multiple antibiotic resistances within the same bacterium, is spreading, so it is important to consider all options to keep treating bacterial infections. Some solutions revolve around optimising our way of administering antibiotics, whilst others focus on finding novel antibiotics. We are following the latter path, by screening bacterial peptide libraries for ideal candidates."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For Prof. Dr Panke and his team, these peptides were the obvious choice for producing the new molecules within a reasonable time frame. They focused on a specific group of peptides called lantibiotics — a portmanteau word combining the terms 'lanthionine' and 'antibiotic'. "Lantibiotic-like antibiotic molecules are too complicated for chemists to create rapidly — so we need bacteria to make them," Prof. Dr Panke explains.

The team used a method called directed evolution. They produced myriads of variants of a specific peptide at DNA level, and then inserted this DNA into bacteria. By doing so, they can use the bacteria to 'read out' the information and translate it into peptide structures.

"We give the DNA to the bacteria, and the bacteria make the peptide," Prof. Dr Panke summarises. "We do it in this way because it is much easier to manipulate DNA than peptides. But the process to get the information from DNA to peptide remains complicated. It requires transcription and translation, ribosomes, tRNAs, etc., and we need living cells for that."

Whereas companies focusing on chemical synthesis can often only create several peptide compounds at a time, SYNPEPTIDE's method allows for the production of dozens of thousands of variants.

Once the peptide has been produced, the team can introduce additional functionalities. Standard amino acids are inserted into the peptide, and once ready, the peptide is passed on to so-called post-translational modification enzymes which convert the standard amino acids into the special functions. "We need to make sure that our variants get modified, otherwise they will be inactive," Prof. Dr Panke points out.

After four years of research, the project's strategy works exactly as expected, as Prof. Dr Panke enthuses: "We can produce a broad range of novel peptide variants that get post-translationally modified and are active as antimicrobials. We have found new molecules that show very interesting activities against certain Gram-positive bacteria that are currently a problem in clinics. The next step would be to make more of it, test it in animal experiments, and conduct a variety of tests that show whether they are suitable for use in humans at all. I'd say we are 10 years away from selling them." The consortium is already looking into options to further exploit the project's results.

Until then, SYNPEPTIDE has already taken a huge step forward by providing leads for a novel class of antibiotics, as well as developing methods to look for them. Prof. Dr Panke hopes that, in this way, the project will eventually make an important contribution to fighting antibiotic resistance.

Project	**SYNPEPTIDE - Synthetic Biology for the production of functional peptides**
Coordinated by	Swiss Federal Institute of Technology in Zurich, Switzerland
Funded under	FP7-KBBE
Project website	http://www.synpeptide.eu/

Innovative method to help doctors tackle antibiotic resistance in patients

Antibiotics represent the most misused drugs in the world. An effective strategy is needed to help physicians make informed decisions about the need for and type of antimicrobial therapy required for individual patients.

Appropriate antibiotic prescribing is one of the key steps necessary to prevent the development and spread of antibiotic-resistant bacteria. However, a major hurdle to this goal is the fact that clinicians are currently unable to rapidly and accurately distinguish between a viral and bacterial infection. Patients suffering from a viral infection may not require antibiotics, but may be prescribed them if the clinician suspects a bacterial infection.

The issue with the two infections presents a dilemma. On the one hand, patients may die if they are not prescribed antibiotics when actually required. On the other, the indiscriminate use of antibiotics may lead to the development of AMR (reducing antibiotic treatment options in the future) and cause avoidable side effects for the patient.

The EU-funded TAILORED-TREATMENT project set out to "develop rapid and accurate diagnostics that would help clinicians tailor their antimicrobial prescribing practices to individual patients," says Dr John Hays, the project's coordinator.

Treatment regimens customised for the needs of children and adults

Project partners employed state-of-the-art molecular techniques to generate transcriptomic, proteomic, genomic and microbiome data. All these data were collected in a single database designed to identify novel interactions that would help distinguish patients with a particular type of bacterial or viral infection. The purpose

"We are one step closer to the development of rapid diagnostics that will allow for tailored antibiotic therapy by clinicians."

was to discover new biological markers (biomarkers) of infection, and develop new computer tools enabling clinicians to tailor their antibiotic therapy in an appropriate and effective way to patients.

Scientists conducting an extensive clinical study recruited 1 222 Dutch and Israeli patients, ranging from infants under 12 months to elderly patients suffering from respiratory tract infections and/or sepsis. Analysis indicated that the inappropriate use of antibiotics was found in 41 % of viral infections.

Protein- and RNA-based host response signatures were developed by computationally combining multiple biomarkers that can identify different types of infections while overcoming the challenge of patient diversity. The best performing single protein biomarker was TNF-related apoptosis-inducing ligand (TRAIL). The signature with the highest precision included both viral- and bacterial-induced proteins: TRAIL, interferon gamma-induced protein-10 and C-reactive protein.

Mass spectrometry (MS) was used to identify relevant protein biomarkers for use in bacterial species, strain and AMR identification. In addition, existing MS-proteomics methodologies were optimised for rapid pathogen detection and identification, and for analysis of the expression of AMR genes.

Lastly, a novel microbiota sequencing platform (MYcrobiota) was developed, that facilitates the implementation of microbiota diagnostics from the research environment into the clinical diagnostic laboratory.

"We are one step closer to the development of rapid diagnostics that will allow for tailored antibiotic therapy by clinicians," notes Dr Hays. "The quick identification of pathogens or pathogen types by rapid diagnostics can help prevent or even reverse the increasing incidence of worldwide antibiotic resistance."

Novel algorithms for patient diagnosis and disease monitoring

TAILORED-TREATMENT generated novel algorithms to help rapidly diagnose if a sick child or adult is suffering from a bacterial or viral infection, both or neither. "Such algorithms and their implementation in the clinic will allow clinicians to rapidly assess whether a patient requires antibiotics or not, therefore helping to reduce antibiotic overprescribing," concludes Dr Hays. "The effective implementation of rapid diagnostic testing will help reduce the 400 000 patients in the EU and the 2 million people in the United States who become infected with antibiotic-resistant bacteria each year."

A biomarker patent has been submitted. Biomarker combinations are currently being commercialised as diagnostic kits for use in emergency departments and hospitals.

Project	**TAILORED-TREATMENT - Development of tailored antimicrobial treatment regimens and novel host-pathogen insights for respiratory tract infections and sepsis**
Coordinated by	Erasmus Medical Centre, Netherlands
Funded under	FP7-HEALTH
Project website	http://www.tailored-treatment.eu/

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Discoveries on Gram-negative bacteria could give a new lease of life to antibiotics

EU-funded researchers shed new light on how molecules get into and out of bacteria as part of Europe-wide efforts to combat AMR.

A multidisciplinary team of European researchers has produced new knowledge about how molecules penetrate the cell walls of bacteria and how bacteria defend themselves by flushing them out. These findings from the TRANSLOCATION project can help select and optimise promising molecules which could be used to develop new antibiotic drugs.

TRANSLOCATION was a part of the wider New Drugs for Bad Bugs initiative. This platform is leading the EU's efforts to combat the increasing ability of bacteria to develop resistance to attack. This development is "becoming a public health emergency of yet unknown proportions," according to the WHO.

"People are becoming aware that there may come a time when we don't have enough drugs to fight bacterial infections," says Prof. Mathias Winterhalter, TRANSLOCATION project coordinator and professor of biophysics at Jacobs University Bremen in Germany.

Few incentives for new drugs

Just two new classes of antibiotics have been brought to market in the past 30 years. The weak business model for producing more means that only a few pharmaceutical companies remain active in the field. One of the barriers to developing new drugs is the lack of understanding of how molecules enter bacteria.

To look into this basic question of science, TRANSLOCATION built a 150-strong team of physicists, chemists and clinical microbiologists, and encouraged them to work together in an unusually open fashion. "Everyone has to be willing to tell everyone else what they are doing all of the time," says Prof. Winterhalter. "You need to trust people so they will not just keep their research secret until they publish."

"Having a high-resolution structure allowed us to use computer-modelling to draw a molecular picture of how antibiotics smuggle themselves inside porins."

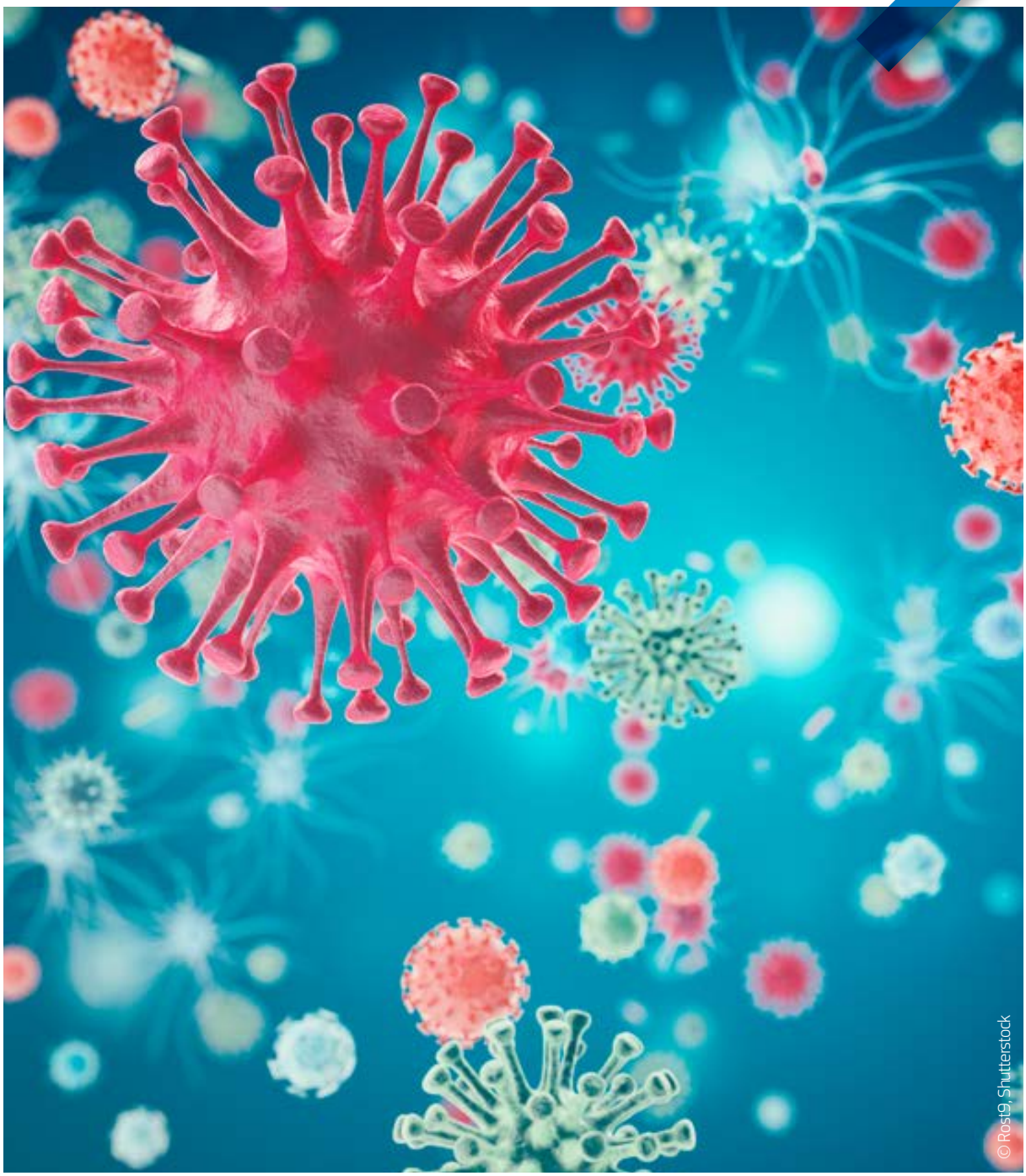
The Marie Curie fellows managed to solve several structures of porins for different Gram-negative bacteria, including *Campylobacter, Vibrio cholera* and *Enterobacter aerogenes.* Porins are membrane proteins which form a water-filled pore through a bacteria's outer cell wall. Exploring how they perform their sieving function — only allowing molecules up to a certain size into the bacteria — is a promising avenue of research. "Having a high-resolution structure allowed us to use computer-modelling to draw a molecular picture of how antibiotics smuggle themselves inside porins," comments Prof. Winterhalter.

Self-defence

Efflux pumps, the mechanism whereby bacteria defend themselves by expelling certain molecules, was a second area of research. The team focused on discovering how bacteria recognise these molecules. "We contributed to understanding how the efflux pump works for certain molecules, how the bacteria act on them with the eventual goal of being able to make a blocker," says Prof. Winterhalter. If scientists can find out how to prevent bacteria from expelling the right molecules, it could make existing antibiotics effective once more.

Making their findings available to other scientists was a third aim of the project. The team has used an electronic lab book describing their results and the methods employed to achieve them. All significant findings have been published in academic journals, but the team is now working on a database to make more detailed data freely available. "We have to be a lot more open because taxpayers want to know what they are paying for," concludes Prof. Winterhalter, "but also because, with the big problems, you need a really big picture in order to solve something and you need lots of people to contribute to this."

Project	**TRANSLOCATION - Molecular basis of antibiotic translation**
Coordinated by	Jacobs University Bremen, Germany
Funded under	FP7-PEOPLE
Project websites	http://www.translocation.eu/index.php http://www.itn-translocation.eu/wp/ https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb



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