CarboMet

Targeting Antimicrobial Resistance (AMR) with New Innovative Vaccine Therapies

European Commission

Metrology of Carbohydrates for Enabling European Bioindustries

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Background

CarboMet is a four-year Collaborative Support Action [‘CSA’] funded by the EC Horizon 2020 Future and Emerging Technologies initiative. The primary aim of the CSA is to mobilise the European academic and industrial community to identify generic measurement, data management and metrological challenges that must be met in order to advance and exploit carbohydrate knowledge and applications. The potential for exploitation of carbohydrates lies in their diversity and structural complexity – subtle changes in the three-dimensional structure of a carbohydrate profoundly affects (for example) its ability to protect against or fight infectious disease. However, these subtle structural differences present a challenge for their analysis. Sophisticated measurement and metrological capabilities for analysing carbohydrates are available but are nowhere near as advanced or as routinely used in other areas such as gene sequencing. Therefore as a first stage CarboMet has organised some open, Europe-wide workshops to identify key topics where our understanding needs to be advanced urgently, and where current limitations in our measurement, data management and metrological capabilities are hindering progress. The Workshops were also asked to recommend appropriate Work Programmes that should be supported by Horizon 2020 and its successor, Horizon Europe. One of these workshops addressed the topic of the role of carbohydrate molecules in vaccine technology. This paper reports on the technological challenges that were identified at this workshop and lists a set of recommended Work Programmes which have been designed to help solve measurement, data management and metrological needs.

Executive Summary

Antimicrobial resistance (AMR) is a global healthcare challenge with both social and economic implications. The increasing prevalence of AMR from the misuse of antibiotics in healthcare and in agriculture has exacerbated the problem resulting in increased morbidity and mortality rates in developed and developing countreis. Without the necessary intervention AMR will become the leading cause of death globally ensuing increased healthcare costs with devastating impact on the world economy. A new strategy is needed to combat AMR, one which offers a new mechanism of action and is not prone to resistance. Carbohydrate based vaccines has emerged as a highly promising alternative to antibiotics for the treatment of infectious disease with very minimal side-effects. This report highlights several crucial areas for funding to advance current technologies and to develop new innovative medicine as a first line of treatment against bacterial infection.

Introduction

Antimicrobial resistance (AMR) is one the biggest threats to global health and food security today. The improvident use of antibiotics in clinical settings and animal husbandry has been the major cause for the emergence of AMR and is a major concern for both developed and developing countries. The number of deaths due to infections resistant to antibiotics is projected to reach to 10 million deaths annually by 2050 – more than cancer. The increased resistance and infection rate equates to healthcare and hospital costs of EUR 1.5 billion per year and will surpass EUR 1 trillion by the year 2050.[1] As a result, several initiatives have been started by the World Health Organization (WHO) to raise awareness and to promote R&D to combat AMR.

What is AMR and why is it a global threat.

AMR is when micro-organisms such as bacteria, virus and fungi evolve resistance to antibiotics. This is a natural evolution process which normally occurs over a long time, however, the speed at which AMR is occurring is causing a major threat to the global population. As a result, drugs that were once effective in treating bacterial infection are losing efficacy. This means a simple surgical procedure can result in a life threatening bacterial infection.

AMR Key facts:[2]

- Resistance in *E.Coli* to one of the most widely used antibiotic (fluoroquinolone) to treat urinary tract infections (UTI)
- 10 countries have reported resistance to third generation cephalosporin antibiotic to treat gonorrhoea.
- Patients with methicillin-resistant *Staphylococcus aureus* (MRSA) are 64% more likely to die.

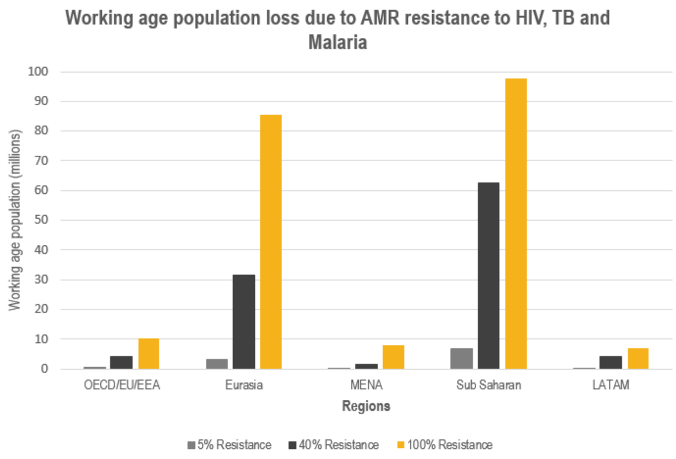

Exhibit 1. Loss of working age population per year due to AMR.

Social and Economic Impact

Perhaps the greatest impact will be felt financially and particularly in lower income countries but also in other developed and developing nations. The impact on human health will be enormous with increased rate of morbidity and mortality. If the current rate of resistance increases, the likelihood of contracting antibiotic resistant strains of bacteria will rise considerably over the next decade. This comes with a financial penalty of increase hospital stay bringing additional strain to the healthcare system. The indirect cost of losing patients prematurely will directly impact the workforce causing lower productivity and leading to stagnant economic growth. A recent study showed a loss of >10 million working age people per year in the EU/EEA member countries if AMR continues to rise in the next 40 years.[3] These impacts will resonate globally with GDP and world trade falling as much as 3.8%, healthcare costs rising to EUR 1 trillion by 2050 and even in the food sector where livestock will decrease between 2.6% and 7.5%.[4]

Challenges and Solutions

The increasing prevalence of AMR can be attributed to three key factors; the lack of public awareness, misuse of antibiotics and the enormous investment gap in the discovery and development of new interventions. It has been more than 30 years since the last class of antibiotics was discovered with many of the 'new' drugs being second and third generation antibiotics without a novel mechanism of action. Even these last resort antibiotics will be inefficient as new resistant strains emerge. The high cost of R&D and low return on investments is one of the major bottlenecks in the discovery process. Investments in fundamental research and new collaborative business models between academia and industry is needed to share costs and expedite development of new innovative therapies to tackle AMR.[5] Carbohydrate based vaccination offers a highly promising alternative solution for the treatment of infectious disease and have several advantages over antibiotics. The treatment is very specific with minimal side-effects, they are not prone to resistance and can be used to either prevent or fight off infections.

Vaccine

A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles antigenic proteins or carbohydrates of disease-causing microorganisms.

Active vaccines stimulate the body's immune system to recognize the agent as foreign, produce antibodies and destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

Passive vaccines consist of externally administered antibodies against the pathogen.

Under the 'One health' philosophy, both human and veterinary health should be prioritised, adopting the same programme and technologies with targets chosen from the global priority pathogens list (Global PPL) published by WHO in 2017. To accelerate the discovery process we identified several areas for investment to address this challenge.2

Advanced Sequencing of Carbohydrates

Highly targeted and effective carbohydrate-based vaccines can only be developed from a deep understanding of the molecular structure and conformation of the relevant cell surface polysaccharides. The identification of suitable sugar structures with days or hours is required by the clinic is a major bottleneck to rapidly assess and identify bacterial strains for treatment. Fast sequencing methodologies for DNA and proteins are available and have revolutionised modern medicine. A similar development and investment is needed for carbohydrate sequencing to enable faster analysis of cell surface structures and to aid development of new drugs.

Polysaccharide Production

Once the targets have been identified there is a need for industrial scale production of the vaccine. Three approaches have been identified which will be a core technology for carbohydrate based vaccines.

- Isolation of naturally occurring polysaccharides from microbes via fermentation processes: Biotechnological production from naturally producing organism or using gene technologies to optimise strain for increased and cleaner production of target antigen.

- Chemical synthesis: Automated synthesis of large complex polysaccharides carried out by expert academic groups and specialist SMEs in Europe.

- Enzymatic synthesis is being used increasingly and is often a more sustainable approach to traditional synthetic approaches. Recent examples demonstrate that the use of functionally optimized enzymes (engineered to apply product size control in the production process) enabling the synthesis of oligo- or polysaccharide antigens for vaccine development. Further development and large scale manufacturing requires access to new glycoenzymes with functional properties suited for industrial use.

Optimising Glycoconjugate / Adjuvant Design

The choice of carrier protein and conjugation method both have impact on the overall effect of the glycoconjugate vaccine on the immune response. These affect not just the effectiveness of the vaccine but also the stability and shelf life. Present conjugation method are laborious and expensive and require new methodologies and measurement capabilities for well-defined conjugate design. Currently there very limited number of carrier proteins available and therefore require development of novel carriers with dual carrier-adjuvant role to enhance vaccine efficacy.

Definitions

Carbohydrates: Are a class of organic compounds found in food and in every organism such as starch, cellulose and small sugars.

Polysaccharide: This is a carbohydrate where individual sugar molecules and linked together to make longer chain biopolymers. For example, starch, cellulose and glycogen are polysaccharides.

Improved and Robust vaccine

Further understanding of the exact and diverse role carbohydrates play in immunisation mechanisms will undoubtedly allow improved vaccine design. New and improved animal models are needed that will allow the study of bacterial diseases in humans, as well as the effect of antibiotics and how AMR arises. In addition to this, improved and more detailed mechanistic models that address fundamental understanding of the immune response are also required using advanced measurement techniques that can elucidate subtle details of the mechanistic processes.

Regulations, IP and ISO Standards

Regulatory guidance does exist for carbohydrate-based vaccines (USP). The WHO also produces guidelines on vaccines alongside other agencies including the European Medicines Agency and the Food and Drugs Administration (FDA). The challenge is to guide researchers from academia and industry particularly SMEs, to navigate effectively the regulatory landscape and to be comprehensively aware of, and meet, regulatory guidelines aimed at ensuring effective drug development.

How do carbohydrate based vaccines work

Polysaccharides on the surface of bacteria can be sequenced to elucidate the correct structure which are unique to the bacteria and foreign to the human immune system.

Once sequenced, the polysaccharides can be produced in large scale and attached to a protein carrier. This is injected into the patient which elicits an immune response as the body recognises the bacterial polysaccharide as foreign and therefore fighting off the infection.

Metrology / Informatics Data Integration

To manage glycoscience data and make the information accessible to the wider scientific community, a number of publicly available databases and modelling tools have already been developed. However there is a need to integrate the information into more centralised and dedicated platforms (as for DNA and protein research and technology development) and to develop this into a long term, permanent, stable, up-to-date and open platform to support discovery projects

New Business Models

Poor returns on investment for AMR research has necessitated the introduction of new business models. Cost sharing models for SMEs and incentives for large biopharmaceutical companies are required to facilitate antibiotic discovery. Require new collaborative framework between industry and academia to mitigate issues surrounding IP ownership. Open source innovation, collaborative partnership and fast track approval process will persuade public-private investments.

Conclusions

In conclusion, CarboMet draws attention to the huge potential of novel carbohydrate-based vaccines in fighting AMR as well as protecting both humans and animals from disease and epidemics. The global implication of these technologies is far-reaching and requires development of new analytical techniques to accelerate antigen discovery and vaccine production. This requires investment in novel carbohydrate measurement, metrology, synthesis and industrial scale production — an essential prerequisite for producing innovative carbohydrate-based vaccines. To achieve this, future funding calls must include topics discussed in the report as specific work programmes and draw expertise from industry in a public private partnership.

References

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