GLOBAL ANTIBIOTIC RESEARCH AND DEVELOPMENT (GARD) PARTNERSHIP

Developing new antibiotic treatments, promoting responsible use, and ensuring access for all

SCIENTIFIC CONSULTATION SUMMARY

A joint WHO/DNDi initiative incubated by DNDi in support of the Global Action Plan for Antimicrobial Resistance

Institut Pasteur, France / 29 February 2016

DNDi Drugs for Neglected Diseases *initiative*

World Health Organization

Institut Pasteur

Background

Following recommendations made during the technical consultation meeting in November 2015 at the World Health Organization, GARD rapidly undertook an informal process of scoping for potential initial project proposals. A set of general selection criteria was established and a basic template was circulated to GARD's scientific contacts and networks. This was not a broad call for proposals as GARD is currently at the very early stages of incubation and would require greater resources in order to manage such a process. The template is now online.

This process, which began late December 2015 and is still ongoing, rendered 10 project proposals that were discussed during the meeting after briefings with each of the project proposers as the projects were being developed.

The aim of this initial scientific consultation was to help GARD evolve from the initial scientific strategy articulated in the initial and revised GARD concept notes, determine priority areas and short- to medium-term projects to be launched within one year. Longer-term (upstream) projects will also be considered as GARD builds its R&D pipeline.

Summary of discussions

The following aims to provide a summary of the discussions of the 29 February meeting. Introductory presentations were made in order to provide a common context in which the projects were to be discussed, including the respective roles of DND*i* and WHO in GARD, the work of WHO, the emphasis on embedding conservation and access in each project from the outset, and the need to consider diagnostics in the R&D equation.

Presentations can be broadly grouped in the following categories:

- Transversal projects / streams:
  - combinations and improving usage of existing antibiotics, or combinations with non antibiotic compounds
  - Reformulations: polymyxins, tebipenem, co-amoxiclav
- Disease specific projects: melioidosis, neonatal sepsis, gonorrhea, typhoid fever
- Upstream research projects

Combinations and improving usage of existing antibiotics, or combinations with non-antibiotic compounds

One of GARD's main aims is to fill gaps in the existing R&D landscape for antibiotic treatments. The two broad fields of combinations and improving usage of old antibiotics should be explored and would serve as a transversal basis on which most of the short- to medium-term projects could be built.

Although antibiotic-resistant gram-positive infections such as MRSA are not to be overlooked, the major focus should be on gram-negative pathogens of the ESKAPE group. While currently considered mostly as hospital associated, several gram-negative pathogens cause community acquired infections that are highly drug resistant. While new classes of antibiotics are being developed to fight such infections, it is

necessary to explore strategies to provide a 'bridge to new drugs', in particular by revisiting the use of existing (*old*) antibiotics, as well as their use in novel combination, either with another existing antibiotic or an approved drug. The latter approach aims at identifying compounds that could restore activity of a given antibiotic lost due to resistance or potentiate its activity (concept of 'antibiotic resistance breaker').

Antibiotic combinations are used in clinical practice but often without sufficient evidence to ensure clear clinical benefits. By engaging into a systematic exploration of antibiotic combinations to identify synergistic additive, or even antagonist effects, it is highly plausible to unravel potent new combinations capable of overcoming certain resistance patterns. Whereas in vitro high throughput methods can readily be set up to identify such combinations, it has to be complemented with thorough PK/PD and in vivo experiments to validate their possible benefit over existing regimens. Indeed, suitable animal models will be an integral part of the proposed platform so as to increase predictive capacity of new combinations and formulations.

Efforts should also be exerted on revisiting PK/PD of old antibiotics, as many of them have been developed and registered with scarce and incomplete PK/PD analysis, as compared to the current standards. This can lead to a reformulation or new regimens of such old drugs, with the aim to obtain the best efficacy while minimizing the emergence of resistance due to underdosage or inappropriate regimens. Such data will guide the development of alternative/improved formulations or regimens if they provide a clear therapeutic advantage over the old formulations or regimens.

The HTS combinatorial screening and the PK/PD-in vivo platforms proposed will complement each other. In addition, a geographically diverse consortium of experts (built on existing networks) will be constituted to participate in the development of the platforms through to clinical trials, establish harmonized protocols in order to ensure coherence of data across participating laboratories and clinical sites. Data generated should be made readily available to the scientific community through the creation of an open data hub.

It is envisaged to run experiments in a few centres already equipped with the technology suitable to conduct such experiments, hence the importance of protocol harmonization.

The platforms should also help in defining stewardship and treatment guidelines.

Reformulations (product specific): polymyxins, tebipenem, co-amoxiclav

Other 'bridges to new drugs' which can contribute to more effective use of existing antibiotics, include drug-specific reformulation projects, and are notably important in rendering key drugs (more) accessible in areas of need. Several projects were discussed along these lines.

Tebipenem was presented as one of the very few oral antibiotics active against ESBL-producing *E. coli* causing upper urinary tract infections (fosfomycin, for example is indicated for uncomplicated lower UTIs). Studies in Thailand demonstrated that tebipenem is also active against *N. gonorrhoeae* and *Burkholderia pseudomallei*. However, this drug is currently only marketed in Japan in a paediatric formulation, and it would be valuable to have such a drug made available in adult formulations. As the drug can be administered orally, the conservation strategy will be a key issue to study. More data is required to explore its potential further.

Polymyxins are used against XDR gram-negative bacteria and while promising new drugs are currently in the pipeline, polymyxins should be explored for ways to increase the dosage for greater efficacy, while decreasing toxicity either through new (for example liposomal) formulations or combinations.

Co-amoxiclav is a vital paediatric antibiotic combination against pneumonia and severe infections of soft tissue, of bones and articulations. However, in low resource settings, the drug is neither available in the most efficacious and safe ratio of 14:1, nor is it available in the most stable formulation (dispersible tablets) at this ratio. Given the instability of clavulanic acid at high temperatures, there is a high likelihood that the treatment is not being given at appropriate dosing, which is why the potential for developing a heat-stable, dispersible formulation at the appropriate ratio should be explored.

Such available drugs should be considered as a priority, with the objectives of optimizing their efficacy and toxicity profile (improving PK/PD data, exploring new regimens), developing adapted formulations to address dosing and stability, and subjecting these activities to a conservation and access plan. Whether taken on as individual projects, or as part of the work of the proposed platforms, all represent important existing drugs in need of optimization.

Antibiotic strategies targeting specific clinical infection syndromes

Specific diseases/conditions deserving attention were presented, providing another point of entry for the identification of short- to medium-term projects to which GARD could contribute.

Neonatal sepsis, notably high MDR serious bacterial infections, is a very serious global problem with a very high mortality, especially in LMICs. In many countries the problem is now recognized as both a hospital-acquired infection and a community-acquired infection. The initial choice of antibiotic has to be empiric, given the fast progression of the disease and its fatal outcome if left untreated. However, very high rates of resistance to the current WHO standard regimen of ampicillin and gentamicin are now reported in all global regions. A holistic approach is needed: rapid diagnostics to also allow treatment at the point of care rather than in reference hospitals, revisiting older antibiotics such as fosfomycin, alone or in combination, formulations that are stable (do not require a cold chain), and easy to administer for this vulnerable age group. A much better understanding of resistance patterns in the community as well as in hospital settings (which can be significantly different) is urgently needed to guide the development of suitable treatments and their appropriate usage.

Melioidosis has very poor treatment outcomes, as the intracellular pathogen has intrinsic resistance to most antibiotics. Poor treatment outcomes are also due to lack of a rapid diagnostic test and rapid disease progression (which is also one of the reasons the disease is considered a bio-threat in addition to the possibility of aerosol infection at very low inoculum). Treatment involves initial IV administration followed up with 12 to 20 weeks treatment with oral drugs to ensure eradication. A proposed strategy for melioidosis includes identification of a rapid diagnostic kit (*B. pseudomallei* is very poorly identified by microbiology labs, even in endemic regions), identification of an oral-only treatment option based on close to market drugs to allow potentially for community-based treatment, possible reformulations and combinations (maybe including a non-antibiotic). Exploring further currently available antibiotics could extend therapeutic options, work that has not been fully carried out. For example, moxifloxacin has shown activity, yet this drug is generally used for gram-positive infections. Formulation work could improve further their capacity to penetrate the host cell, *i.e.* using nanocarriers. Finally, there is some evidence for combining classic antibiotics with drugs having an indirect effect on *B. pseudomallei*. An important assessment remains to be undertaken to determine which type of intervention (new

antibiotics, oral availability, rapid diagnostic) should be prioritized to reduce the high death toll of melioidosis. BARDA has, in addition, developed relevant animal models that would be very useful to test.

Gonorrhoea has widespread drug resistance and is a global public health threat and a significant unmet medical need. Treatment with ceftriaxone is not ideal, as the injectable formulation is problematic for treating sexual partners and in addition, the rising drug resistance will eventually lead to the drug no longer being recommended. Rates of resistance to extended spectrum cephalosporins are rising rapidly worldwide. Strategies are needed to address the growing concern of *N. gonorrhoeae* include reviving old antibiotics, as well as exploring new compounds when available.

Zoflodacin is such a novel antibiotic, well tolerated, with no pre-existing resistance. Phase II enrolment is complete and readouts should be available in the coming months. Subject to partnering, phase III could begin early next year. There are no preclinical signals to suggest genotoxicity or mutagenicity. In vitro, as many as possible strains were tested, and these tests may need to be repeated with updated data from the 2016 reference panel with high strains of resistance.

Oral fosfomycin was proposed as a possible way to address growing resistance, provided that additional in vivo animal data are produced. As this drug has also been highlighted in the perspective of neonatal sepsis, clear synergies between projects can be envisioned

Typhoid (enteric) fever, caused by *Salmonella enterica* serovars Typhi and Paratyphi, is restricted to humans, and as such has the potential to be eradicated. It is currently poorly diagnosed and treated. Typhoid fever is prevalent in many lower income countries. Treatment is suboptimal both because of resistance to many previously effective antibiotics, including the current first-line agents; and because regimens have never been fully optimized through adequate clinical trials. Lack of sensitive and specific diagnostic tests compounds the difficulty of treating appropriately as well as gathering reliable information on incidence and antibiotic susceptibility. In the most recent typhoid treatment trial, in Nepal, resistance to fluoroquinolones was alarmingly high. Although no recent trials have been carried out elsewhere, evidence suggests significant antibiotic resistance throughout Southeast Asia and Africa. Typhoid vaccines are available, including a new conjugate vaccine about to be marketed, but even if vaccine coverage increases, diagnosis and effective treatment will play a key role in typhoid control and urgently need to be improved. Treatment effectiveness should consider not only symptom resolution, but also the elimination of the intestinal carriage responsible for maintaining transmission. New antibiotic trials should be based on adequate PK/PD studies to optimize dosing. R&D approaches include: evaluating PK/PD, including intracellular activity; well-designed treatment trials for clinical effectiveness and eradication of intestinal carriage using existing antibiotics alone and in combinations, as well as novel drugs for Gram-negative infections. Finally, as in the case of melioidosis, improving intracellular uptake of antibiotics through nanoparticles and other new technologies could be explored.

Easy-to-use, reliable and affordable rapid diagnostic tests are also needed to avoid the need for lengthy and costly blood culture and guide adequate treatment. Many tests are available and under development, and a strict comparison of these would greatly improve disease management.

Upstream research projects

Some of the previous examples including melioidosis and typhoid fever have shown the challenges of addressing intracellular pathogens. Another example of such a problem is *H. pylori* infection. *H. pylori* is

one of the few bacterial infections which intrinsically requires a drug combination because it occurs in the stomach – generally a triple therapy. One approach is to develop new therapeutic strategies by targeting the cell wall machinery, and to be used in combination. Using a structural approach, compounds inhibiting *in vitro* the assembly of essential membrane components have been identified. Such a project could provide tools to address the ESKAPE group in the future.

Comments

The projects presented during the meeting show that the potential scope of GARD projects is large, that there are numerous unmet needs that need to be addressed in a timely manner, and for which there may not be sufficient actors engaged. Even if far from comprehensive, this first round of project exploration confirmed that GARD has a role to play in the efforts being deployed to address AMR. Other similar consultations will be organized in other regions to continue to assess priority areas, R&D gaps, and potential projects to build the GARD project portfolio.

Although projects differed a great deal in terms of focus and approach, synergies among projects were clearly already evident:

- Most of the diseases presented need a suitable diagnostic approach, from the 'simple' discrimination between viral and bacterial infection to specific rapid test to identify the pathogen.
- Several old antibiotics are of great interest to cope with current resistance. However, they need improved PK/PD data to develop the appropriate regimen and formulation.
- Combinations are used in the clinic often without sufficient understanding of their benefit. Moreover, unexpected findings on known antibiotics demonstrate the need for systematic exploration (through HTS settings) of combinations, and not only of known antibiotics against each other but also against known drugs, as this could lead to improved treatment and restoration of activity on resistance strains.
- The same 'old antibiotic' is sought to treat conditions as different as neonatal sepsis and gonorrhoea (fosfomycin), prompting a need for immediate cross-fertilization.

At this stage, most of the projects will require additional work to further develop the details and to bring them forward as projects to potential funders. Importantly, given the potential synergies between the projects, it will be critical to ensure constant exchanges among those experts already involved. GARD is engaged to work closely with the project proposers and other experts to take the ideas forward in the coming months. While no projects have been selected at this stage, the aim is to have two projects ready for launch by the end of the year, and bring in additional projects thereafter.

Meeting contacts:

Jean-Pierre Paccaud jppaccaud@dndi.org

Gabrielle Landry glandry@dndi.org

Cover photo: copyright Swiss TPH