Commentary

Antibiotic resistance

A never-ending challenge for drug research

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Do you also find it tiresome and disagreeable when tasks long-since done and dusted suddenly resurface, appear never to have been finished in the first place and now need your urgent attention? In drug research, the topic of antibiotics is a shining – and simultaneously appalling – example of this phenomenon, as the WHO's latest report on antimicrobial resistance has just confirmed.

The discovery of antibiotics in the first half of the 20th century has undoubtedly earned its place in the annals of the history of medicine. Beginning with the discovery of penicillin by Alexander Fleming and sulphonamides by Gerhard Domagk, a wide range of effective classes of antibiotics were launched on the market right up until the 1960s and are still in constant use today. This runaway success prompted US Surgeon General William H. Steward to declare "…that we essentially defeated infectious diseases and could close the book on them…".

A lack of new products

A fallacy, as it turned out – and one that severely underestimated pathogen adaptability. There were economic reasons, too, which argued against a strong business commitment to antibiotic research and development. Since new and innovative products were deployed only briefly for a period of a few weeks (at which point the patient was then healed) and were often utilised as an alternative treatment rather than a primary medication, antibiotics offered far less hope of strong sales and profits than other drugs that targeted chronic illnesses. For research, its very quality paradoxically proved to be its downfall. The high degree of translational predictability of in vitro systems and animal models for antibiotics leads to a high level of preclinical disqualification and, in turn, to rather sparsely populated pipelines. This is a disadvantage for a numbers-driven view of R&D productivity – which also fails to reward the high success rates of later clinical development. Over the last two decades, this low economic appeal and a medical need that was apparently adequately met have produced a sharp decline in antibiotic research and, as a consequence, to a dearth of new products.

Facing a rising tide of resistance

The pace of pathogen resistance development has not slackened, however. Since bacteria are constantly adapting

– via mutations or the acquisition of entire genes – many formerly effective antibiotics are becoming increasingly powerless, especially against the problem pathogens classified as the "ESKAPE panel". Research scientists warn us that if this trend continues, we face the spectre of a return to the dark days of the pre-antibiotic era, marked by a much higher rate of infection-related mortality.

This prognosis has led to retaliatory action from the stakeholders involved. Through measures such as the simplified "fast track" registration trials anchored in the GAIN (Generating Antibiotics Incentives Now) Act and extended terms for patents, the US Food and Drug Agency (FDA) has made the development of antibiotics more attractive in economic terms for businesses, not only for counter-cyclical biotech firms like Cubist but also for companies returning to the big pharma fold, such as Novartis, Sanofi or Roche. Increasingly, research is no longer the domain of isolated firms going it alone but is conducted by consortia such as the New Drugs for Bad Bugs (ND4BB) group created within the EU's Innovative Medicine Initiative (IMI). Germany has played its part with the formulation of the German Antibiotic Resistance Strategy (DARTS) and, in particular, the establishment of the German Centre for Infection Research (DZIF).

Integrated knowledge

The DZIF comprises 32 institutions, including universities, university hospitals, Leibniz and Max Planck institutes, Helmholtz centres and federal research units. This grand coalition of experts in the fields of fundamental research, epidemiology and clinical practice aims to master the primary challenges facing translational infection research. As long as these commitments are strong, sustainable and tenacious – just as pathogens themselves are – we will confront resistances successfully. For researchers, the excitement lies in guessing which of these innovative approaches – modernised, genome-based natural product research, for example, or pathoblockers such as quorum sensing inhibitors, toxin binders, immunomodulators or pathogen-specific antibiotics – will deliver truly novel (and not merely improved) products.

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