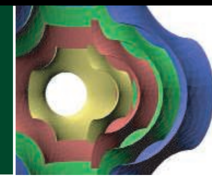


LETTERS

edited by Etta Kavanagh

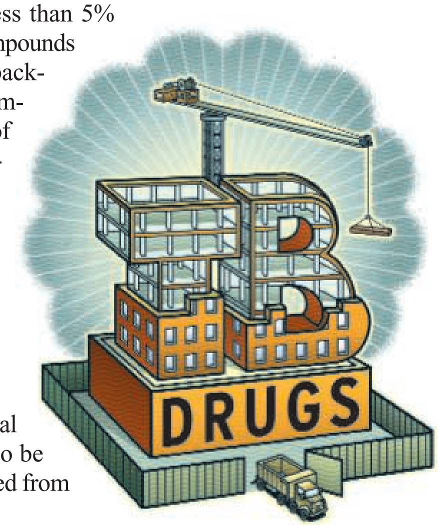
Developing Drugs for Tuberculosis

IN THEIR POLICY FORUM "A PORTFOLIO MODEL OF DRUG DEVELOPMENT FOR TUBERCULOSIS" (3 Mar. 2006, p. 1246), S. W. Glickman *et al.* conclude that achieving 95% confidence of at least one new tuberculosis (TB) drug takes 12 years and up to $400 million, and that there is a less than 5% chance of a new TB drug by 2010.

Their first Monte Carlo simulation is based on only 11 of the 27 compounds in the global portfolio (confusingly, still labeled the "global TB drug portfolio" in the first diagram). The policy relevance of such subportfolio simulation is unclear.

The finding of a less than 5% chance may be a bit on the low side, too. Gatifloxacin and moxifloxacin—the two drugs listed as Phase II/III in Glickman *et al.*'s reference (*8*)—are previously licensed anti-infectives for other purposes, now being re-indicated for anti-TB activity. Gatifloxacin is already in Phase III and moxifloxacin is about to enter Phase III with the TB Alliance, U.S. Centers for Disease Control, and Bayer. Both come from the same subclass of fluoroquinolones, and evidence suggests that their anti-TB efficacy is likely to be similar. Given extensive prior clinical experience and proven safety records, the likelihood of success of these two compounds is better and more predictable, and development time and costs lower, than for any of the other compounds should any of them reach Phase III.

The second simulation, still generating a less than 5% chance, "doubled the number of phase I and II compounds in the [first] portfolio." Yet diagram 2 and the background paper refer to "double the number of compounds in preclinical and clinical tests." Which of these did the authors do? What is the policy relevance? Building up to "optimal" portfolio size inevitably creates a cost bulge with little immediate outcome.



The third simulation, and the $400 million figure, is based on 30 phase I compounds only. How this relates to the current 27-compound global portfolio is not fully explained, although any funding shortfall depends on it.

And is the 11% per year cost of capital nominal or real (i.e., adjusting for inflation)? It seems to be treated as nominal, although the figure it is derived from (*1*) is real.

The point is to build a portfolio that will generate a rolling supply of new TB drugs and not only the chance of the first one. According to the transition probabilities used by Glickman *et al.*, the 30-compound portfolio generates on average 2.925 drugs. If the $400 million is right, this means $136.75 million each, which compares favorably with current funding into TB drug development. Policy-makers, and funders, need to hold their nerve (*2*).

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References

1. J. A. DiMasi, R. W. Hansen, H. G. Grabowski, *J. Health Econ.* **22**, 151 (2003).
2. See www.economics.ox.ac.uk/members/andrew.farlow/FarlowTBPortfolio.pdf for more details on these issues.

Response

WE APPRECIATE THE LETTER BY FARLOW ON OUR Policy Forum, and we reiterate that the TB Alliance's support and facilitation are immeasurable contributions toward the success of bringing new antituberculosis drugs to market. One goal of our analysis was to focus attention on the critical need for new antituberculosis drugs in the developing world by quantifying the gap between what is being spent and what needs to be spent to bring new drugs to market. Whether it will take 10 years or 20 years to develop the next effective antituberculosis drug is not certain. What is certain is that the need for such drugs is growing, and greater resources would help to shorten the development time. Since our Policy Forum was published, an outbreak of extensively drug-resistant tuberculosis has been reported (*1*), further highlighting the urgency of the problem. Therefore, we join in calls for increased support of antituberculosis drug development.

The first simulation model described in our Policy Forum is based on all 11 compounds in the global antituberculosis drug portfolio that were in preclinical or clinical testing at the time of our analysis. We derived this information from a report by the Stop TB Partnership (*2*). The remaining 16 compounds in the global portfolio were in discovery phase. The time required to bring any of these 16 compounds to market was well beyond the timeline of our analysis (through 2019), and their inclusion in the portfolio model would have simply inflated development costs without providing precise estimates around the eventual timing or likelihood of their development. Our model did include gatifloxacin and moxifloxacin, compounds that were in phase II testing for use in antituberculosis regimens at the time of our analysis. Phase III testing of gatifloxacin was in planning stages (*3*). To our knowledge, there was no publicly available information about phase III testing of moxifloxacin at that time. We are pleased to learn that the drug may soon enter phase III clinical trials.

We conducted two additional exercises to illustrate the magnitude of the challenges that policy-makers face in antituberculosis drug development efforts. In one exercise, we repeated the first simulation but doubled the number of compounds in preclinical and clini-

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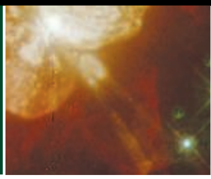

Supernova birthday

1086

Solving crystal structures

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cal testing. In another exercise, we examined how increasing the number of phase I compounds affects drug development timeline and costs. Despite large increases in the number of compounds in these hypothetical portfolios, our findings indicate that substantial challenges remain in bringing new antituberculosis drugs to market in a manner that is timely and not cost-prohibitive. Resources would ideally be directed toward compounds in late stages of development. However, given the limited number of such compounds in the current portfolio, resources should be devoted to increasing the number of compounds in early clinical testing.

As described in our Supporting Online Material, we used a 4% annual cost of capital, not 11%. Our choice of 4% reflects our belief that this is an appropriate (risk-free) discount rate for projects that are intended to generate social benefits, rather than the higher discount rate typically assumed by the pharmaceutical industry for profit-maximizing purposes.

We believe that the model accurately reflects the drug development process from the perspective of a public-private partnership, but could be improved with more reliable and timely input. We would welcome an opportunity to contribute to dialogue and planning for antituberculosis drug development by expanding the model to include all public and nonpublic information about potential therapies for tuberculosis. Such a model would allow the TB Alliance and the funding community to better understand the status of public-private partnerships in antituberculosis efforts and to assess the full range of unmet needs.

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References

1. N. R. Gandhi *et al., Lancets* **368**, 1575 (2006).
2. Working Group on New TB Drugs, Stop TB Partnership, *Strategic Plan: Prepared for the Global Plan to Stop TB: 2006-2015* (www.stoptb.org/wg/new_drugs/documents.asp).
3. World Health Organization, New tuberculosis therapy offers potential shorter treatment (press release) (www.who.int/mediacentre/news/releases/2005/pr71/en/index.html).

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 3 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

A Way to Deal with Image Enhancement

THE PROBLEMS RAISED IN THE NEWS FOCUS article "Don't pretty up that picture just yet" (J. Couzin, 22 Dec. 2006, p. 1866) on image editing in scientific publications can be ameliorated in the near term. For every published image, authors should be required to add the original, unaltered image to their supporting online data. First, this will allow the authors to gussy up their images for clarity and emphasis of specific points without being disingenuous. If they wish, aficionados in the field and other interested readers will be able to view the "raw data" and judge scientific validity. Second, by imposing the requirement for all images, regardless of the amount or type of editing, ambiguity as regards "literary license" is removed. Duplicity is not addressed, but unintentional missteps would be minimized.

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Recognizing William Bateson's Contributions

IN THEIR REPORT "A COMPLEX OSCILLATING network of signaling genes underlies the mouse segmentation clock" (8 Dec. 2006, p. 1595), M.-L. Dequéant *et al.* expand on Pourquié's (*1*) work demonstrating that the precursors of vertebrae (somites) are rhythmically produced from the presomitic mesoderm (PSM), specifically, how "during the formation of each somite [the gene coding for the transcription factor], *Lfng* is expressed in the PSM as a wave that sweeps across the tissue in a posterior-to-anterior direction" (p. 1595).

Historically, however, the idea of a rhythmical element in the development of repeated or meristic parts, such as somites and vertebrae, belongs to William Bateson. By 1888, Bateson had become consumed by studying variation in plants and animals as differences of expression of repeated parts. In September 1891, Bateson wrote to his sister that his "vibratory theory of repetition of parts" (also called the "Undulatory Hypothesis") explained "all the *patterns* and *recurrence* of patterns in animals and plants" In *Materials*, Bateson suggested that as waves of differing intensities create different numbers and spacings of sandy furrows, so, too, will developmental waves of differing intensities determine the expression and number of elements in series of repeated structures (*2*).

Although scientists usually concentrate on recent literature, the work of past scholars may still sometimes enlighten. In addition to translating into English Mendel's sole article and expanding Mendelism to include animals, Bateson struggled with issues such as the origin of species and of the features that distinguish them. His thoughts on alterations of development as the basis of evolutionary or specific novelty may have its roots in Victorian saltationism, but his appreciation of the achievement of difference through alteration of the developmental mechanisms underlying repeated parts foreshadowed by almost a century the current incarnation of developmental biology and the theoretical field of "evo-devo" (*3*).

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References

1. O. Pourquié, *Science* **301**, 328 (2003).
2. W. Bateson, *Materials for the Study of Variation, Treated with Especial Regard to Discontinuity in the Origin of Species* (Macmillan, New York, 1894).
3. J. H. Schwartz, *Sudden Origins: Fossils, Genes, and the Emergence of Species* (Wiley, New York, 1999).

CORRECTIONS AND CLARIFICATIONS

Reports: "Electric field–induced modification of magnetism in thin-film ferromagnets" by M. Weisheit *et al.* (19 Jan., p. 349). The first affiliation was incorrect. It should be [1]Institut Néel, CNRS/Université Joseph-Fourier, 25 Avenue des Martyrs, Boite Postale 166, F-38042 Grenoble Cedex 9, France.

Perspectives: "Negative refractive index at optical wavelengths" by C. M. Soukoulis *et al.* (5 Jan., p. 47). In the figure, the scale for the green panel should have been 200 nm, and the scale for the blue panel should have been 500 nm.