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editorial

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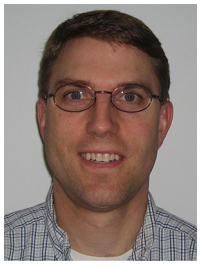

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Minding the gaps in tuberculosis research

There is a growing need for new therapeutics for treating tuberculosis and responding to drug resistance. The last decade has seen an increase in phenotypic high throughput screening for *Mycobacterium tuberculosis*. The next challenge is how to translate these hits into *in vivo* active compounds in the mouse. Analysis of seventy years of drug screening in mouse models of tuberculosis has created a database that reveals a significant 30-year 'valley of death' for research characterized by a gap between *in vivo* and *in vitro* testing. This suggests a rethink of approaches is required in drug discovery and development to meet the global health need for new therapies. We propose we should be learning from the historic data from the validated *in vivo* mouse model used over the past 70 years with existing TB treatments.

Mycobacterium tuberculosis (*Mtb*) is the causative agent of tuberculosis (TB) that has infected approximately 2 billion people, and kills 1.3 million people annually [1]. Efforts to discover and develop new therapeutics for TB are making very slow progress [2] and the pipeline is suboptimal, which is not surprising given the limited financial incentives and resources and the general uncertainties surrounding clinical trial success. We assert that we should learn from past efforts in TB drug discovery and return to a strategy that is simple yet has proven to be effective.

Today's predominant method for identifying compounds active against *Mtb* is to use whole-cell phenotypic high-throughput screening (HTS). These hits are then optimized to leads in an attempt to attain small molecules with *in vitro* (efficacy, cytotoxicity, Absorption-Distribution-Metabolism-Excretion and Toxicity (ADMET)) and *in vivo* (pharmacokinetic, tolerability) profiles worthy of progression to *in vivo* efficacy studies. We estimate upwards of 5 million compounds have been screened for *in vitro* efficacy over the last 10 years, with GlaxoSmithKline and Novartis each screening *ca*. 2 million compounds. To date we estimate *ca*. 1500 *in vitro Mtb* hits have been derived from one laboratory alone [3], while GlaxoSmithKline has recently published another 177 promising *in vitro* actives [4]. At least a further 21 studies between 2009 and 2013 have also described 66 hits (Supplemental Table 1 [15–17]) some of which are or have been under consideration for advancement and already have *in vivo* data. However, the infrastructure to provide a clear understanding of the position of each of these compounds or any others in the pipeline is essentially lacking.

1359-6446/06/$ - see front matter http://dx.doi.org/10.1016/j.drudis.2014.06.022

The next logical step would be to progress some of these or other lead compounds into an *in vivo* efficacy model. Mouse models are commonly the first and only *in vivo* model used for comparative assessment of new *Mtb* drugs and combinations, as well as optimization of dosing regimens [5]. Considerable development of acute [6] and chronic mouse models [7] has been achieved. Outside the scope of this opinion are debates as to which of the current mouse models is most relevant to human infection and whether the mouse is the best animal for *in vivo* infection studies due to differences in xenobiotic metabolism and tissue pathology [8]. Regardless, the correlation between treatment outcomes in mice and infected humans cannot be ignored.

A recent analysis of publications over a 12 year period reported a five-fold increase in the publication of TB mouse model studies from 1997 to 2009 [9]. Despite their economy compared to larger animal models, mouse models constitute an important bottleneck in screening and rank-ordering compounds for further preclinical development. And yet with over 70 years of use of this model there have been no efforts until recently to create a centralized database that curates the reported structure and efficacy of all compounds tested against *Mtb in vivo*.

Curating historic mouse *in vivo* data for TB and analysis

To represent better the current use of murine models within its historical context, we have collated and summarized published

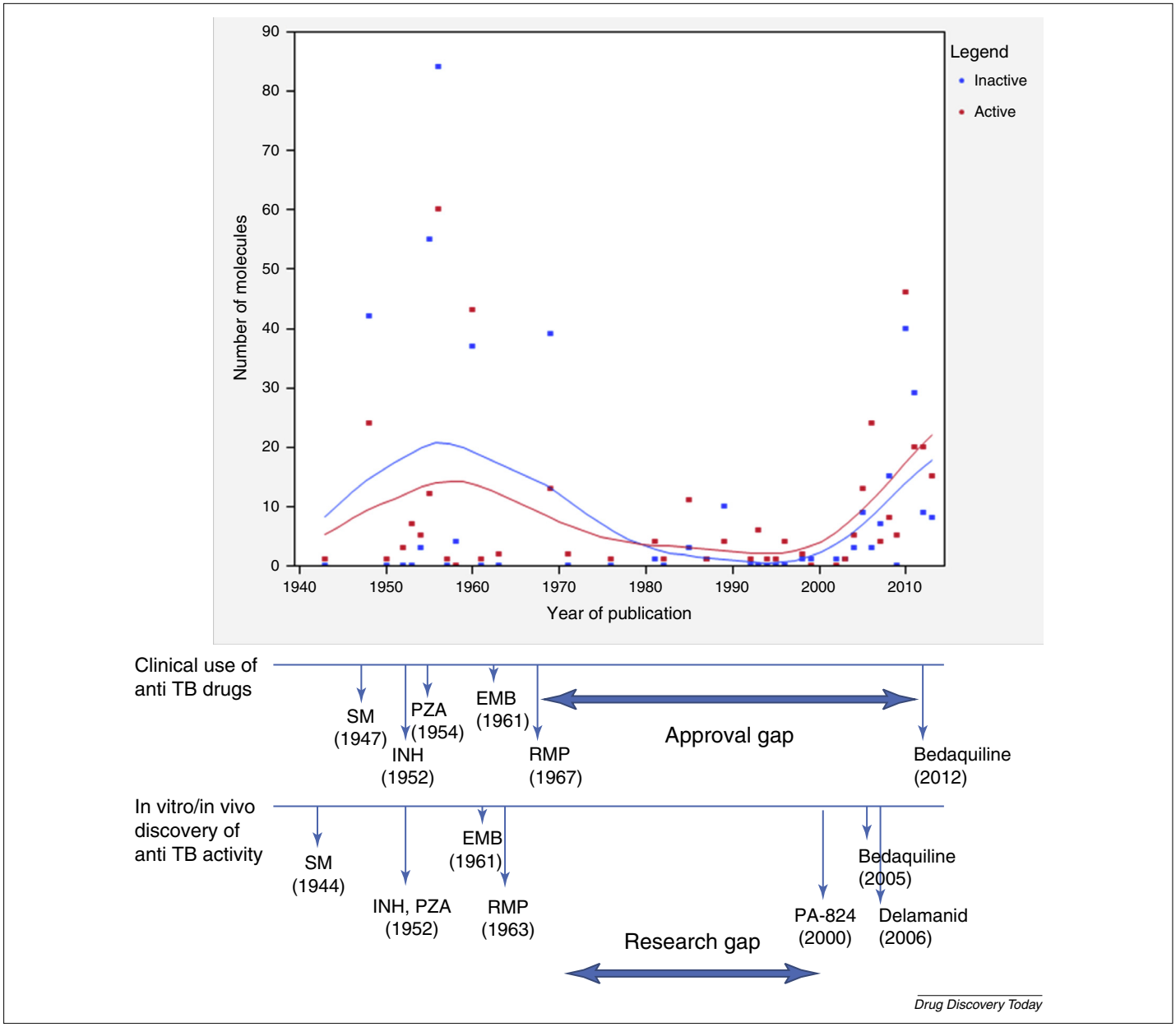

FIGURE 1

Gaps in TB drug discovery discovered from over 70 years of testing compounds in the mouse *Mtb in vivo* model. The solid lines show the trends in the data. Overlayed are the dates of *in vitro* or *in vivo* discovery of key drugs for TB and their first use in the clinic or approval date. It is worth noting that in the 1950s–1960s, thousands of compounds were tested *in vitro*, while from 2002 onward over 5 million have been tested and yet the number of compounds tested *in vivo* does not appear to have increased accordingly. SM: streptomycin; INH: isoniazid; PZA: pyrazinamide; EMB: ethambutol; RMP: rifampicin.