Drug discovery productivity has failed to improve markedly in recent years and a key issue is high attrition due to efficacy failures in initial proof-of-concept clinical studies. This reflects the fact that preclinical “target validation” studies do not always translate into man, where ultimate target validation must reside. Given these facts, it is easy to see the importance of results from those first clinical validation studies for overall target validation. There are various initiatives to promote the publication of clinical data, but many clinical results, particularly negative results, remain unpublished, are published in obscure places or are published after a considerable delay. This gives rise to the potential that vast sums of money could be spent on compounds for which the molecular target has essentially been invalidated, but the data are not publicly available. Pharmacology, Research and Perspectives has indicated that it will welcome publication of all data pertinent to target validation, particularly negative data (clinical and preclinical), and it will do so in a form that should be relatively rapid and easy to achieve.
There are various initiatives to promote the publication of clinical data, for example, from the European Medicines Agency and the Pharmaceutical Research and Manufacturers of America, although these are geared toward publication once a marketing authorization has been given. There are also initiatives led by the pharmaceutical companies themselves; for example, GlaxoSmithKline have declared their intention to publish the summary results on their database www.gskclinicalstudyregister.com. In addition, a group of large Pharma companies have founded the “Medical Publishing Insights and Practices (MPIP) Initiative” – a unique collaboration of pharmaceutical co-sponsors (Amgen, AstraZeneca, GlaxoSmithKline, Johnson & Johnson, Merck, Pfizer, Takeda) and the International Society for Medical Publication Professionals (MPIP). They have published on their website (http://www.mpip-initiative.org/) ten recommendations of which the second was ‘Make public all results, including negative or unfavorable ones, in a timely fashion, while avoiding redundancy’. However, it is still the case that many clinical results, particularly negative results, remain unpublished, despite their critical importance for target validation or invalidation purposes. Results are often not published for several years, published on company websites but hard to locate, or sometimes not published at all. It is especially important to publish clinical data on key targets because many companies will be working on these targets in parallel. This gives rise to the potential that vast sums of money could be spent on compounds for which the molecular target has essentially been invalidated but the data are not publicly available. Because most compounds (51%) do fail at Phase IIa (Arrowsmith 2011), spending large sums of money on compounds doomed to fail is to the commercial disadvantage of everyone.

The example of TRPV1 antagonists illustrates this point. There was considerable rationale from preclinical models that antagonists of the TRPV1 vanilloid receptor would make good analgesic drugs (Szallasi et al. 2007). In addition, early clinical experimental medicine models had shown that compounds such as SB705498 could antagonize capsaicin-induced hyperalgesia in Phase I volunteer studies (Chizh et al. 2007). Between 2006 and 2009, around nine clinical studies were carried out with TRPV1 antagonists in several different pain syndromes (see Table 1). For most of these studies, no data have been published; and where they have been published, it was generally 4 to 5 years later. We can assume that the compounds were either inactive or flawed owing to the hyperthermia seen with the early Amgen compound, since none have progressed. Yet a search of the Thomson Cortellis database in 2011 revealed that there were 35 compound entries for TRPV1 antagonists of which 4 were in Phase II, 6 in Phase I, and 13 in the Discovery Phase. Thus, these compounds were being progressed at a time when several clinical studies had been completed with a negative outcome. Indeed, even in 2014, there still appears to be companies pursuing this target.

Publication of all clinical data, including negative results, is very important, but it is not sufficient for target validation purposes. Compounds can fail in the clinic for a number of reasons: lack of efficacy/therapeutic index, lack of target engagement at the dose administered or lack of an appropriate clinical study design, for example, inappropriate exclusion or inclusion criteria. Ideally, clinical information needs to be accompanied by details on the selectivity, potency, and pharmacokinetics of the compound, plus any information on the level of target engagement at the dose used. Armed with such information, clinical failure can be confirmed as a failure of the target for that indication and not a failure of the molecule or the clinical trial design. A good example of sharing information on a target was given by Pfizer with their fatty acid amide hydrolase inhibitor, PF-04457845. This compound was shown definitively to be inactive in a clinical study on pain associated with osteoarthritis (Huggins et al. 2012); the negative result was published reasonably rapidly and was accompanied by data showing adequate target engagement at the dose tested in the clinic. This allowed an unequivocal conclusion that the target is unlikely to be of interest for treating osteoarthritis pain.

Table 1. Clinical studies carried out with TRPV1 antagonists.

| Company       | Compound | Trials carried out (date), plus effect seen | Publications               |
|---------------|----------|-------------------------------------------|----------------------------|
| Amgen         | AMG-517  | Phase 1, demonstration of hyperthermic effect | Gavva et al. (2008)        |
| AstraZeneca   | AZD-1386 | Dental pain (2008), transient effect Osteoarthritis (2009), no effect | Quding et al. (2013) Miller et al. (2014) |
| GlaxoSmithKline| GSK-705498| Migraine (2005), Dental pain (2006) Irritable bowel syndrome (2007) | No data published          |
| Merck         | MK-2295  | Dental pain (2008/7)                       | No data published          |
| Novartis      | SAF-312  | Dental pain (2009)                         | No data published          |
| Glenmark      | GRC-6211 | Dental pain (2007)                         | No data published          |

¹Data obtained from the Thomson Cortellis database or from www.clinicaltrials.gov.
In the past, companies may not have wanted to publish clinical data because it was perceived as giving sensitive information to competitors. Given the recognition that most compounds will fail and the need to improve overall attrition rates, this is probably no longer a key issue. However, there are still hurdles to publication. There can be difficulties in finding suitable journals which are willing to publish negative clinical data, although the MPIP initiative is hopefully a sign that this is changing. Another issue is that termination of a project within a company is often rapidly followed by redeployment of the people to other projects of higher priority, which can make writing a paper difficult. Pharmacology, Research and Perspectives (PR&P) has indicated that it will welcome publication of all data pertinent to target validation, particularly negative data (clinical and preclinical), and it will do so in a form that should be relatively rapid and easy to achieve. For further details, please see the PR&P website at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2052-1707/homepage/ForAuthors.html.

In conclusion, there is a positive move toward publishing all clinical data, both positive and negative, but we need to ensure that momentum is maintained. The issue should be given high priority, not just because of the potential for reducing costs for Pharma, improving future clinical trial design, or even because of the potential for reducing attrition rates, important though these are. But an even more important argument is the ethical one of not subjecting large numbers of patients to ineffective treatments and thereby increasing the pool of patients available for testing other, potentially effective treatments. Hopefully the increased availability of all trial data will become another weapon in the urgent battle to improve drug discovery productivity and hence facilitate the bringing to market of better medicines to improve patient care.

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Disclosure

None declared.