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COMMENTARY

The successes and limitations of preclinical studies in predicting the pharmacodynamics and safety of cell-surface-targeted biological agents in patients

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To improve drug development outcomes, it is important to review when preclinical pharmacodynamic and safety models have successfully predicted human responses and when they have not. In a recent issue of the *BJP*, Bugelski and Martin examined the concordance between preclinical and human data for biopharmaceuticals targeted to cell-surface proteins. The cases are interesting and several trends emerge. The pharmacodynamics of biopharmaceuticals in non-human primates is largely predictive; the use of surrogates in rodents may be similarly predictive, allowing for more conservative use of non-human primates. While overall concordance of preclinical toxicology data and clinical safety was poor, this is largely a reflection of the immunomodulatory biology of the majority of the biopharmaceuticals evaluated. The examples show that adverse effects in animals that were the result of direct and/or exaggerated pharmacology were modelled well, but that specific infections or other indirect outcomes of immunomodulation, along with cytokine-related events, were not modelled well in preclinical studies.

LINKED ARTICLES
To view Bugelski and Martin visit http://dx.doi.org/10.1111/j.1476-5381.2011.01811.x and to view Martin and Bugelski visit http://dx.doi.org/10.1111/j.1476-5381.2011.01812.x

The ultimate goals of preclinical studies are to accurately model, in animals, the desired biological effect of a drug in order to predict treatment outcome in patients (efficacy), and to identify and characterize all toxicities associated with a drug in order to predict adverse events in people (safety) for informed risk assessment. Currently, the outcomes of preclinical studies are more modest, and are better characterized as providing evidence for the desired biological effect of a drug (pharmacodynamics) and providing insight into potential toxicities to establish a human starting dose at which no serious adverse events are expected to occur and/or allow for monitoring of any undesired effects. As the ultimate goals of preclinical studies may never be fully achievable and the success rate for new drug approvals remains low due to failures of efficacy and safety (Kola and Landis, 2004; Reichert and Wenger, 2008), it is valuable to ask where have our preclinical models been successfully predictive and where they have not.

In two articles in a recent issue of *BJP*, Bugelski and Martin (Bugelski and Martin, 2012; Martin and Bugelski, 2012) examine the concordance between preclinical and human data for biopharmaceuticals. They provide an organized summary of the preclinical and human data on the 15 currently approved monoclonal antibodies and fusion proteins targeted to cell-surface proteins (Martin and Bugelski, 2012). In their overall analysis of the data, they found good and comparable concordance with human pharmacodynamics for mice receiving surrogate molecules or non-human primates receiving the cross-reactive human biopharmaceutical, but poor concordance of pharmacodynamics with genetically deficient mice and of all three models with human adverse effects.

It is not surprising that the pharmacodynamics of surrogates in rodents and the human pharmaceutical in non-human primates had good concordance with humans. Generally, the rationale for advancing a potential drug into the clinic relies on it having demonstrated the expected biological effect in animals. It is also not surprising that they are better predictors than engineered genetic deficiencies for reasons the authors note; that is, if the goal is target protein modulation then deletions may under- or over-predict the effect of the monoclonal antibody, or if the goal is to immunodeplete cells with target (e.g. rituximab) then knocking out the target protein would not be expected to produce a similar effect. The interesting conclusion from the analysis is that surrogates in rodents are comparably predictive to the human biopharmaceutical in non-human primates. This conclusion suggests that developing appropriate surrogates to evaluate the desired biologic effect in rodents is a worthwhile endeavour and provides support for the reduction in use of non-human primates in preclinical studies. As the surrogate rodent data set is limited and there are situations in which the surrogate or rodent model cannot mimic the human/primate conditions or responses, it may be premature to presume that rodent models alone would suffice in predicting human pharmacodynamics. Further, determining that a surrogate is an appropriate one requires careful characterization of its biological relevance to the clinical biopharmaceutical in order to extrapolate results. However, their conclusion certainly argues for justification of additional non-human primate use when a well-characterized, appropriate surrogate is available for rodents and careful consideration of experimental design when using non-human primates.

The authors found poor concordance with human adverse effects for mice receiving surrogate molecules or non-human primates receiving the cross-reactive human biopharmaceutical. This is perhaps a little surprising, given their own conclusion of good concordance for pharmacodynamics, as exaggerated pharmacology is generally the major toxicological effect of biopharmaceuticals and off-target effects are rare (Baldrick, 2011; Chapman *et al.*, 2012). However, this conclusion appears to be largely a reflection of the immunomodulatory biology of the majority of the cell-surface-targeted biopharmaceuticals evaluated in this paper. The authors point out that the mechanism of action and preclinical models suggest that many of the drugs would be immunosuppressive. In the cases of efalizumab and tocilizumab, serious infections were observed during clinical trials and included bacterial, viral, fungal and other opportunistic infections, which were not seen in the preclinical non-human primate or rodent studies (Bugelski and Martin, 2012). It is not surprising that preclinical models fail to predict the repercussions of immunosuppression, as the pathogens that a rodent or non-human primate is exposed to (or not) in controlled laboratory conditions is very different from that of human patients in a variety of environmental situations. Furthermore, human responses may be complicated by pre-existing immune system or haematological abnormalities, concurrent administration of additional immunosuppressive drugs and/or latent infections (e.g. John Cunningham virus inducing progressive multifocal leukoencephalopathy). Several monoclonal antibodies, such as muromonab, targeting lymphocytes induced a cytokine release syndrome in humans that was also not predicted by rodents or non-human primates. The best-documented example of a failure to predict cytokine release is the CD28-specific antibody TGN1412, which caused a life-threatening acute cytokine release syndrome in a phase I clinical trial, due to T-cell activation. This acute cytokine reaction did not occur in the non-human primate study (Suntharalingam *et al.*, 2006; Stebbings *et al.*, 2007). Follow-up *in vitro* experiments suggested that the failure of non-human primates to mimic the *in vivo* human response was due to differences in non-human primate and human white blood cell reactivity to TGN1412 (Stebbings *et al.*, 2007). Other monoclonal antibodies cause cytokine release by a non-target-specific activation mechanism in humans that is not predicted preclinically (e.g. cetuximab, rituximab), and which is sometimes referred to as an infusion reaction. The exact mechanism of effect is not clear but may be due to activation of immune cells by the Fc portion of target-bound antibody (Bugelski *et al.*, 2009); and therefore, predicting infusion reactions in preclinical studies is challenging given that human patient responses to a biopharmaceutical may be complicated by a pre-existing autoimmune condition or the tumour burden of a haematological malignancy.

This failure to predict outcomes of immunomodulation (immunosuppression and cytokine release) appears to be a primary reason for the discordance between the preclinical and clinical safety findings in the majority of biopharmaceuticals discussed in this paper. On this point, it is interesting to note that the four drugs (cetuximab, panitumumab, abciximab and trastuzumab) that are not immunomodulatory showed concordance of at least one of the preclinical models with clinical adverse effects.

Other causes of the poor concordance between preclinical toxicology and human safety may be the result of experimental limitations and the data set studied, and not the models *per se*. Preclinical toxicology studies are based on hazard identification and subtle effects noted by patients (headache, pain, fatigue, etc.) may not be identified in animals. In addition, any adverse event that is observed only rarely in patients is going to be very difficult to detect in preclinical studies due to the practical limitations on the size of the experiments, despite higher dose levels and longer durations of drug administration. Preclinical studies, particularly in non-human primates, are not powered to detect rare events. (It is important to note here that potential drugs that show a serious toxicity issue in non-human primates are not likely to advance to clinical trials and therefore remain untested in humans, so the concordance data are skewed to drugs with rare adverse effects.) Furthermore, preclinical studies generally utilize young, healthy animals, a contrast to the human patients being treated for inflammatory and oncology indications by the biopharmaceuticals. As already noted, this is part of the limitation of routine preclinical studies to accurately predict the human adverse effects of immunomodulatory drugs. It is also not surprising that studies in normal animals fail to detect some of the more serious adverse events seen in humans related to an interaction with a concurrent treatment, such as the increased risk of cardiac dysfunction in patients receiving trastuzumab following treatment with doxorubicin and cyclophosphamide (Chien and Rugo, 2010).

So what can we learn in order to design more efficient and successful drug development programs? We are beginning to

accumulate enough clinical data with cell-surface-targeted biopharmaceuticals to understand where our models may be more or less predictive. The pharmacodynamics of biopharmaceuticals in non-human primates is largely predictive; the use of appropriate surrogates in rodents may be similarly predictive, allowing for more conservative use of non-human primates. Preclinical adverse effects that are a direct result of exaggerated pharmacology appear to be largely predictive in humans, while opportunistic infections or other indirect outcomes of immunomodulation, along with cytokine release-related events, are less likely to be predicted from routine preclinical studies. Successful drug development programs will gather information from routine preclinical studies, assess when they may be less predictive, and consider novel and scientifically appropriate additional preclinical studies in order to make informed drug development decisions.

Conflicts of interest

The authors are employees of Genentech, which makes several of the drugs discussed in this commentary.

References

Baldrick P (2011). Safety evaluation of biological drugs: what are toxicology studies in primates telling us? Regul Toxicol Pharmacol 59: 227–236.

Bugelski PJ, Martin PL (2011). Concordance of preclinical and clinical pharmacology and toxicology of therapeutic monoclonal antibodies and fusion proteins: cell surface targets. Br J Pharmacol 166: 823–846.

Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E (2009). Monoclonal antibody-induced cytokine-release syndrome. Expert Rev Clin Immunol 5: 499–521.

Chapman KL, Andrews L, Bajramovic JJ, Baldrick P, Black LE, Bowman CJ *et al*. (2012). The design of chronic toxicology studies of monoclonal antibodies: implications for the reduction in use of non-human primates. Regul Toxicol Pharmacol 62: 347–354.

Chien AJ, Rugo HS (2010). The cardiac safety of Trastuzumab in the treatment of breast cancer. Expert Opin Drug Saf 9: 335–346.

Kola I, Landis J (2004). Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 3: 711–715.

Martin PL, Bugelski PJ (2011). Concordance of preclinical and clinical pharmacology and toxicology of monoclonal antibodies and fusion proteins: 1-soluble targets. Br J Pharmacol 166: 806–822.

Reichert JM, Wenger JB (2008). Development trends for new cancer therapeutics and vaccines. Drug Discov Today 13: 30–37.

Stebbings R, Findlay L, Edwards C, Eastwood D, Bird C, North D *et al*. (2007). 'Cytokine storm' in the phase I trial of monoclonal antibody TGN1412: better understanding the causes to improve preclinical testing of immunotherapeutics. J Immunol 179: 3325–3331.

Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD *et al*. (2006). Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. N Engl J Med 355: 1018–1028.