antibodies to TPO. Pre-existing antibodies were also detected for interferons in cancer and HIV patients.

Besides route of administration and product characteristics, other immunogenic determinants are dose and regimen, disease, and concomitant medications. Typically, larger proteins are more immunogenic than smaller ones. The effect of dose size on the antibody response is unpredictable, although cumulative dose may be more important than the daily dose. With interferons, for example, a higher cumulative dose resulted in less neutralizing antibodies. Time, more so than dosing frequency, is important, since any antibody response needs weeks to months to develop fully. In humans, IgM levels appear after 5–7 days, while IgG serum concentrations peak 3–4 weeks after dosing initiation. Patients with infectious diseases, presumably because of a stimulated immune system, showed higher antibody levels than cancer patients, who are typically immunosuppressed. Similarly, autoimmune disease state is a factor that might stimulate immunogenicity responses, while a lower response is possible in patients with kidney and liver disease. Immunosuppressants such as cyclosporin as concomitant medication may diminish the immunogenic response.

Because of the different possible effects of an immunogenicity response on the PK/PD of protein drugs, the study of an antibody response is very important in the drug development process. However, the presence of an immunogenic response in animal studies is rarely a prediction of a similar occurrence in humans. More importantly, the value of certain preclinical toxicology studies may be questioned when large titers of neutralizing antibodies are measured, because a lack of toxicity findings may be caused by the neutralization of the toxicodynamic effect. For the situation in humans, the measurement of antibody, and neutralizing antibody titers, in chronic clinical studies is important.

10. CONCLUSIONS AND IMPLICATIONS FOR PRECLINICAL DRUG DEVELOPMENT

In summary, the PK/PD of biotechnologically derived molecules is unique and amenable to mechanistic evaluations. These evaluations provide sound fundamental background for extrapolation across species and for prediction of outcomes under various dosing regimens.

Proteins, and chemically modified proteins—including glycoproteins—often possess similar absorption, distribution, and elimination mechanisms across species. Through understanding differences in physiology and anatomy of those species, systems analyses can be conducted to extrapolate findings into predicted human outcomes.

Similarly, when the PK/PD of these molecules have been characterized in humans, with the support of the preclinical database, one can predict outcomes when doses, routes of administration, and dose frequencies are