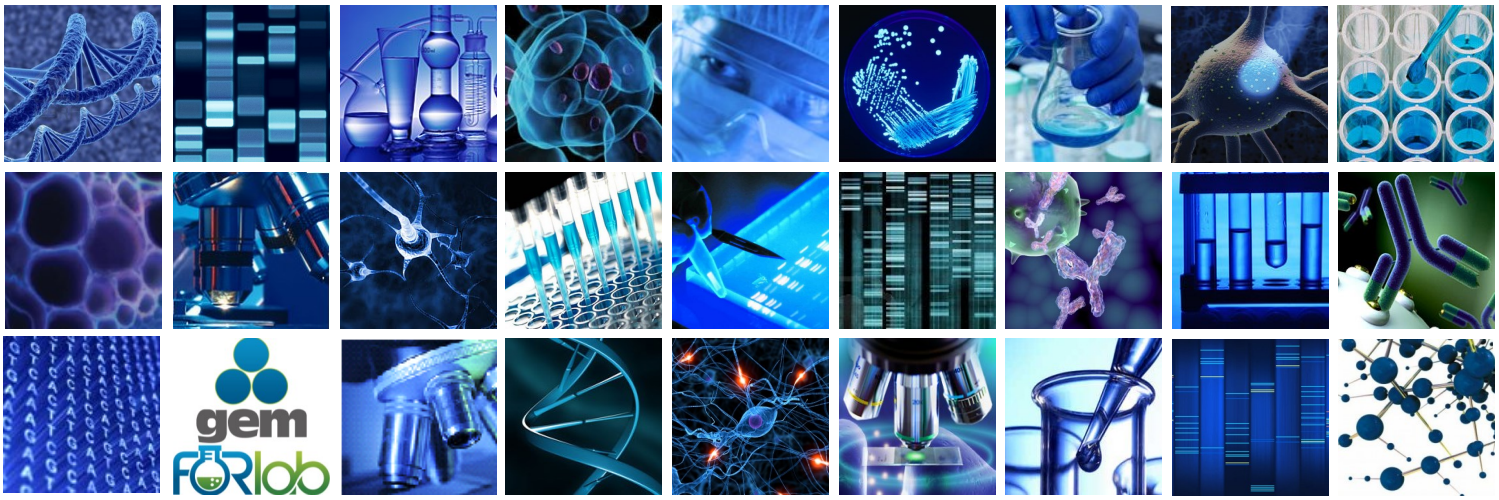

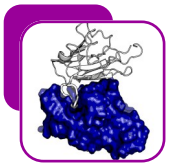

Biomarker quantification in patient serum dependent on drug binding

Aim of the study

Quantification of circulating biomarkers was affected by drug administration. A method was developed to measure both free and bound biomarkers in the serum of drug-treated patients.

Analyte

Circulating protein biomarkers

Methodology

ELISA methods applied for the measurement of biomarkers in clinical trials should be fit for purpose. It is strongly recommended that sources from relevant disease population be included in the validation of the method to cover disease induced Interferences on measured biomarkers. Moreover, it is important to consider possible drug-induced effects on circulating proteins, including binding of the drug to the measured biomarkers.

System Human serum

Therapeutic area Autoimmune and inflammatory disease

Development stage Clinical trial

Customer A multinational pharmaceutical company commercializing biological and antibody based drugs

Results

Quantification of two specific circulating biomarkers after drug administration to patients were consistently low. Mimicking samples, quantification of the biomarkers was shown to be inversely correlated with drug concentration in serum. Therefore, A method was set up to quantify both the free fraction of biomarker, as the total (free + bound) fraction of biomarker, in order to correctly assess correlation with disease progression after treatment. Samples, prior to direct sandwich ELISA, were subjected to acid dissociation varying time, concentration and type of acid, but biomarker levels were not reliably quantified since biomarker proteins were no more able to bind the antibodies of the ELISA. Therefore, biomarker and drug structure were studied and reduction of disulfide bridges of the antibody-based drug was tried to dissociate biomarkers from the drug. Although biomarkers were not destroyed with this method, quantification of total biomarker concentration was shown to be dependent on the concentration of drug in the samples. Thus, an excess of drug substance was added to each sample prior to analysis, a winning approach. Optimizing also reduction agent and concentration, total biomarker concentration was quantified, as assessed through quality controls of spiked biomarker in human serum in the presence of antibody-based drug.

Advantage of the methodology

Relevance of biomarker concentration can be undermined if drugs have direct effects on their binding to drug proteins other proteins induced in the drug response. Measurement of total biomarker concentration can be relevant for clinical correlation. Dissociation of bound circulating biomarkers for quantification of total biomarker in human serum can be necessary to obtain relevant information about disease state in patients.

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