

Clinical Biomarkers: Novel Tools for Pharmacodynamic Applications

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Summary

Biomarkers are currently changing the way we diagnose and treat diseases. Today pharmacodynamic biomarkers are widely used in the industry elaborating optimal dosing of new drugs and predictive biomarkers have an enormous potential for companion diagnostics ⁽¹⁾.

Background

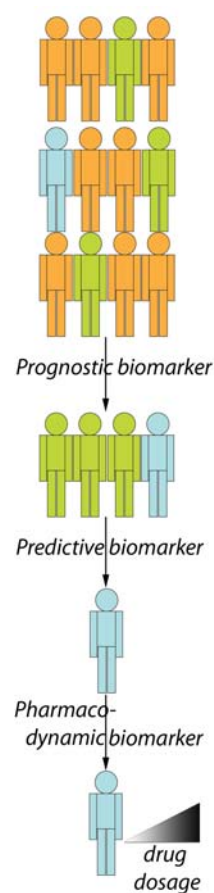


Fig.1 In a given population, the prognostic biomarker sorts the individuals with a likely course of a disease if untreated (blue and green). Predictive biomarkers identify subpopulations of patients who are likely to respond to a given therapy (blue). The drug dosage for responsive individuals is optimized by analysis of pharmacodynamic biomarkers.

Challenge 1: How to study base levels?

While elevated cytokine marker concentrations in patients are well documented, limited data are available for endogenous baseline concentrations for the majority of biomarkers ⁽²⁾. In clinically relevant study set ups several cytokine markers specific for inflammatory diseases were quantified in human biological matrix. The aim was to determine baseline cytokine concentrations in individual healthy human individuals.

Strategic consideration for biomarker quantification:

- For many inflammatory biomarkers base levels of healthy control groups have not yet been described. For regulatory approval of companion diagnostic tests, understanding of base levels is essential.
- Drugs affecting disease biomarkers can be very efficient. Only sensitive biomarker quantification platform allows monitoring the full PD-profile of these drugs.
- In early phases of companion diagnostic development little is known about physiological levels of biomarker candidates in different patient sub-groups and disease states. Sensitive biomarker quantification enables studying even ultra-low biomarker levels.

Results 1

Low fg/ml concentration limits of TNF-alpha in human serum was shown with Imperacer® in comparison to other standard ligand binding technology ⁽⁴⁾.

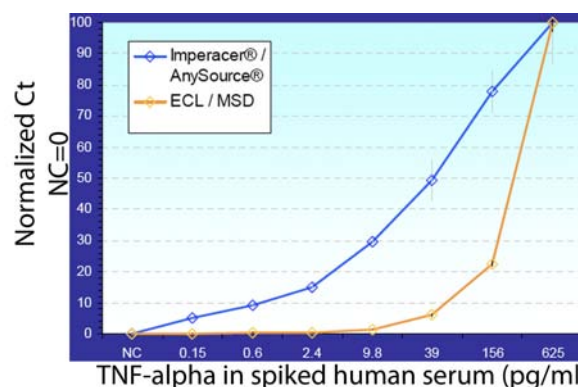


Fig. 2 Comparison of ligand binding technologies ⁽⁵⁾

Results 2

The ultra sensitive Imperacer® technology, quantifies fg/ml concentrations of several clinically relevant cytokines in human serum matrix. This low level quantification enables the detection of endogenous baseline concentrations as well as biomarker surveillance throughout several phases of a clinical study ⁽⁵⁾.

Cytokine	LOD Imperacer®	Matrix
IL-2	0,1 pg/ml	Serum
IL-6	0,1 pg/ml	Serum
IL-8	0,1 pg/ml	Serum
IL-11	0,8 pg/ml	Serum
IL-12	0,05 pg/ml	Serum
IL-17	0,02 pg/ml	Tissue culture
IL-23	0,17 pg/ml	Serum
INF-gamma	0,3 pg/ml	Cell lysate
TNF-alpha	0,01 pg/ml	Serum

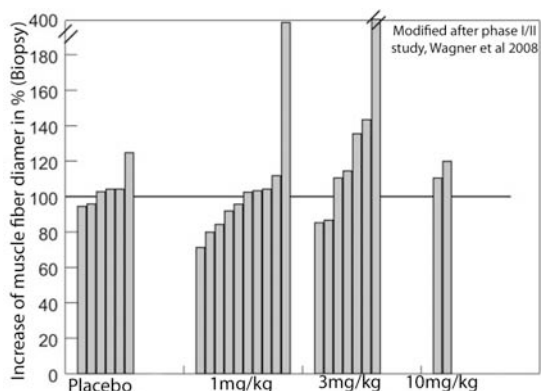
Tab.1 Ultra low quantification of several predictive and pharmacodynamic biomarkers⁽⁵⁾

Challenge 2: How to study pharmacodynamic profiles?

Blocking of the myostatin (MSTN) signaling pathway by inhibitors, e.g. MSTN neutralizing antibodies, result in drastic increase of skeletal muscle mass. Clinical studies focusing on diseases interfering muscle growth, e.g. muscle dystrophy, mostly generate data by muscle biopsies to analyze increase or decrease of muscle mass and muscle fiber diameter after treatment⁽⁶⁾. A less invasive strategy is to exploit molecular biomarkers for muscle growth e.g. myostatin propeptide (MYO-P) or follistatin to generate reliable clinical data on molecular basis from biomarker concentration in blood⁽³⁾.

Results 3

Based on clinical studies on MSTN inhibitors like neutralizing antibodies, further analysis has been reported by detection MSTN inhibitor concentrations in serum. MYO-P as well as follistatin is here detected in pg/ml concentration levels in blood serum⁽³⁾.



Treatment of individuals with myostatin neutralizing antibody
Fig.3 Response in muscle fiber diameter increase after treatment in individual patients⁽⁶⁾.

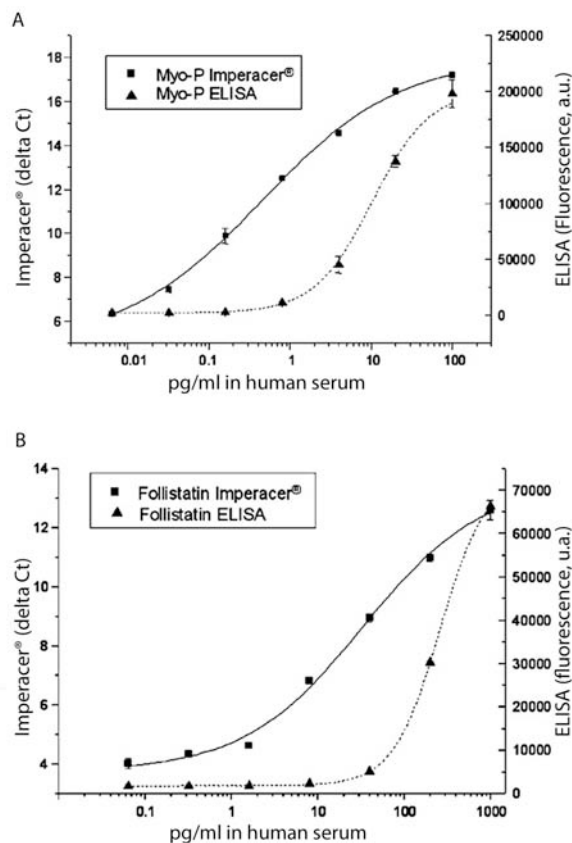


Fig.4A, 4B Broad dynamic range and sub pg/ml levels of MSTN inhibitors in blood serum compared to standard ELISA⁽³⁾.

Conclusion:

Imperacer® as prime technology in clinical studies enabled specific biomarker quantification in sub pg/ml detection limits and broad dynamic range.

Literatur:

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