White paper

Performance Comparison of Assays Usable for FDA Project Optimus

Cytokine Analysis with Olink® Target 48

- Covers the most important pharmacodynamic pathways
- Offers exceptional data quality
- Results reported in standard pg/mL values

Background

The FDA Oncology Center of Excellence has launched Project Optimus, whose goal is to reform the dose optimization and dose selection paradigm in oncology drug development. The project's overall aim is to reduce toxicity without impact on efficacy.

Dual challenges of toxicity and pre-existing beliefs

Typically, achieving maximum efficacy is the largest hurdle in obtaining oncology drug approval (1). The need to obtain maximum efficacy in a short timeframe results in higher doses set in registration trials, while assessing for severe or life-threatening toxic effects to determine a maximum tolerated dose.

This 'more is better' thinking has resulted in several oncology drug approvals whose dose and/or schedules needed modification. One example is Ceritinib (brand name Zykadia® from Novartis) first approved for ALK-positive, advanced (metastatic) non-small cell lung cancer (NSCLC). The original dose was 750mg taken orally when fasting (results of ASCEND-1); later the dose was adjusted to 450mg to reduce gastrointestinal toxic effects (ASCEND-8). (1)

With Project Optimus, the FDA's Oncology Center of Excellence wants to dispel pre-existing beliefs: that lower doses are not as effective as higher ones. (2)

Selecting Pharmacokinetic (PK) and Pharmacodynamic (PD) metrics

In a white paper produced by the organization Friends of Cancer Research, selection of non-invasive blood- and imaging-based biomarkers for pharmacokinetic (PK) and pharmacodynamic (PD) metrics should be well-defined and use preclinical data to determine target saturation points and exposure timeframes. In addition, the dose-finding trial should be "randomized, compare at least two doses, and confirm dose selected maximizes benefit-risk by measuring efficacy across sizeable number of patients". (2) The usefulness of blood-based biomarkers raises the question of which biomarker platform to choose.

Comparable biomarker platforms

The overview in Table 1 compares the features and performance metrics for the major multiplexed biomarker measurement platforms.

Table 1. Overview comparison between existing blood-based biomarker platforms.

Measurement Platform	Olink	Luminex	Meso Scale Discovery
Cytokines measured	48	48	10
Sensitivity	***	*	**
Dynamic Range	***	**	*
Need for Replicates	None	Two or Three	Two
Sample Consumption	1 µL	50 µL	50 µL

* = Low ** = Medium *** = High

In collaboration with independent laboratories in the Uppsala-Stockholm area, Olink analyzed three identically-prepared sample plates, and a comprehensive comparative study was produced.(3)

In Figure 1 the lower and upper limit of quantification (LLOQ and ULOQ) are listed for selected biomarkers: IFN-γ, IL-6, EGF, TNF-α, CXCL-9, CXCL-10, CCL-3, CCL-4, IL-17, G-CSF, GM-CSF, IL-2 and IL-13. These markers were selected from the 45 cytokine or chemokine proteins in the Olink Target 48 biomarker list due to their typical use for monitoring pharmacological safety.

Example dilution series for three of the selected markers IFN-γ, IL-6, and TNF-α are shown in Figure 2. Six samples (three healthy controls, and one each of atopic dermatitis, Crohn's disease, and SLE) were diluted individually at a 1:2 dilution four times. Each sample is displayed with the same color, and visually the dilution series should be linear. Concentrations below the dotted line are under the lower limit of quantification (LLOQ). An extensive set of comparison data is available in reference (3).

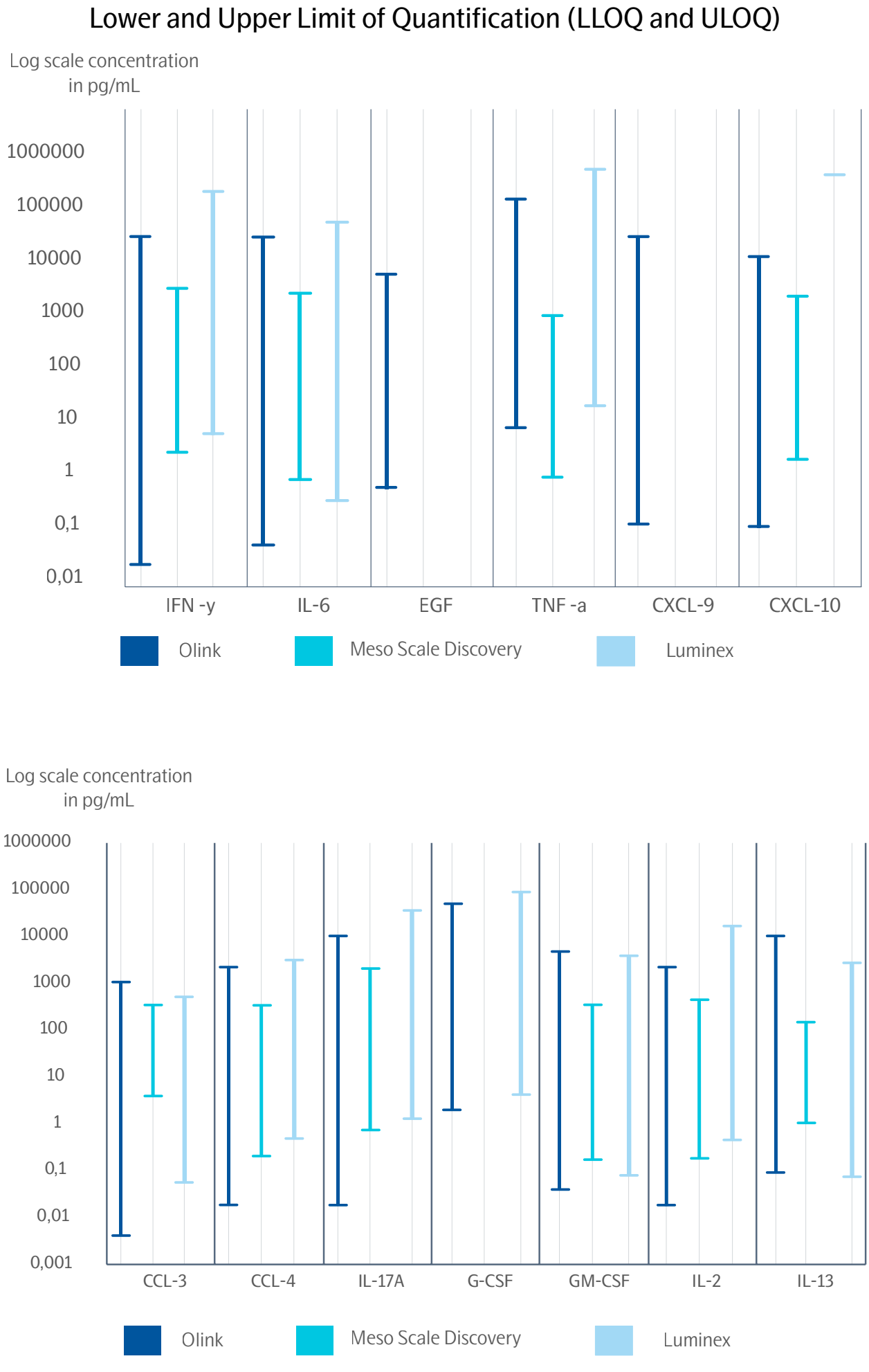

Figure 1. Bars represent Lower and Upper Limit of Quantification (LLOQ and ULOQ) for selected biomarkers across Olink Target 48, Meso Scale Discovery and Luminex

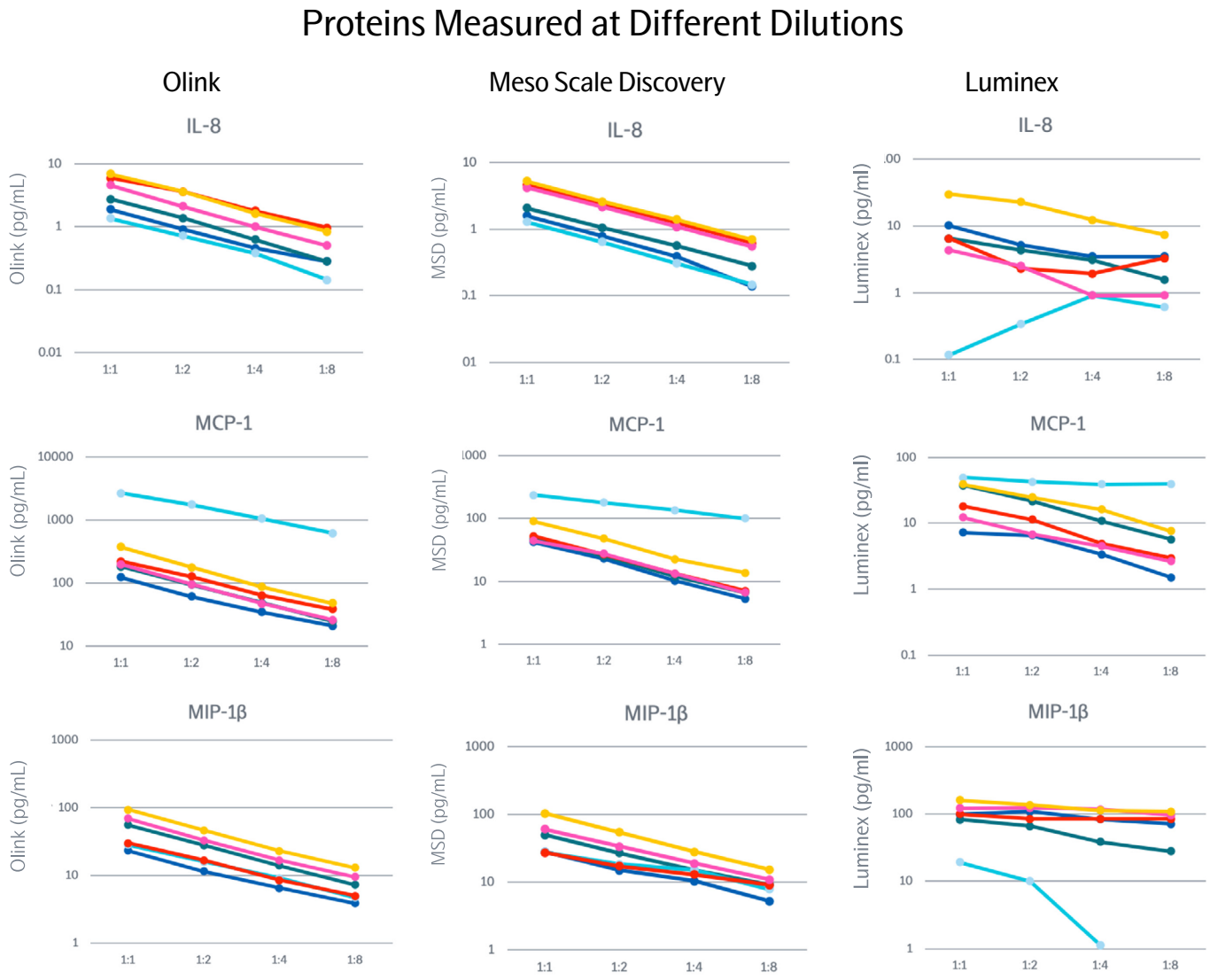

Figure 2. Six samples (3 pathological, 3 healthy) measured across all three measurement platforms at different dilutions, with each identical sample labeled with the same color in the plot throughout all charts. Concentrations below the dotted line are under the Lower limit of quantification (LLOQ)

Olink® Target 48 for your PK and PD studies

Existing platforms have been considered by many to be the "go-to" antibody-based technologies for multiplexed immune response monitoring. Olink offers a 45-plex biomarker panel with no compromise in performance. Olink results show excellent parallelism in a dilution series and reliable, consistent results without the need for replicates and with significantly lower sample volume requirements than other technologies. Contact us today for more information at info@olink.com or through our website at olink.com

References

1. Shah M and Pazdur R et al. N Engl J Med. (2021) 385(16):1445-1447. The Drug-Dosing Conundrum in Oncology - When Less Is More. doi:10.1056/NEJMp2109826.
2. Friends of Cancer Research Whitepaper, "Optimizing Dosage in Oncology Drug Development", Friend of Cancer Research Annual Meeting 2021. https://friendsofcancerresearch.org/wp-content/uploads/Optimizing_Dosing_in_Oncology_Drug_Development.pdf
3. Olink Whitepaper, "Multiplex Analysis of Inflammatory Proteins: A Comparative Study across Multiple Platforms". Files available here: Multiplex analysis of inflammatory proteins
   Olink Direct file links: https://www.olink.com/content/uploads/2021/09/olink-white-paper-a-comparative-study-across-multiple-platforms-v1.2.pdf
   and Appendix https://www.olink.com/content/uploads/2021/09/appendix-olink-white-paper-a-comparative-study-across-multiple-platforms-v1.1.pdf

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