



IL-1 α (INTERLEUKIN 1, ALPHA)

The Singulex IL-1 α assay is sensitive enough to quantify IL-1 α concentration in plasma from healthy, normal human subjects with previously unattainable levels of accuracy and precision. It enables differentiation between IL-1 α concentrations in healthy and diseased states, allowing efficient preclinical and clinical study design.

BIOLOGY AND DISEASES

Interleukin-1 alpha and beta (IL-1 α and IL-1 β) are pro-inflammatory cytokines involved in immune defense against infection, and are part of the IL-1 superfamily of cytokines. Both IL-1 α and IL-1 β are produced by macrophages, monocytes and dendritic cells.

IL-1 is involved in various immune responses with a primary role in inflammation, making it a target for Rheumatoid Arthritis (RA). IL-1 α and IL-1 β are produced as precursor peptides, which are proteolytically processed and released in response to cell injury, and thus induce apoptosis. IL-1 β production in peripheral tissue has also been associated with hyperalgesia (increased sensitivity to pain) associated with fever.

THERAPIES

A synthetic form of the human IL-1 receptor antagonist (IL-1Ra) is marketed as Kineret (anakinra). IL-1Ra blocks the biologic activity of IL-1 α and IL-1 β by competitively inhibiting IL-1 from binding to the IL-1 type I receptor (IL-1RI), which is expressed in a wide variety of tissues and organs. IL-1Ra inhibits the biological activities of IL-1 both *in vitro* and *in vivo*, and has been shown to be effective in animal models of septic shock, RA, graft versus host disease, stroke, and cardiac ischemia. Also, a phase II clinical study is underway to assess long-term safety of treating RA with a fully human monoclonal antibody (AMG 108) that targets inhibition of the action of IL-1.

UNMET NEED

Elevated levels of IL-1 α will continue to be a diagnostic target for inflammatory diseases like RA. Thus, there is a need for assays with sensitivity to quantify low levels of IL-1 α in healthy subjects to differentiate between healthy and diseased states. Evaluation of IL-1 α as a drug target presents a need to detect the velocity of decreases in elevated levels of IL-1 α to evaluate effectiveness and dosing of potential therapies. This may prevent adverse events like neutropenia that develop after co-administration of drugs targeted to inflammatory cytokine pathways, like Kineret (IL-1Ra antagonist) and Entercept (TNF α antagonist). To meet these goals, it is essential to have an assay that can detect IL-1 α to below normal levels in human plasma.

SINGULEX ANSWER

The Singulex IL-1 α assay increases the utility of IL-1 α by allowing quantification at very low levels and differentiation between small changes in concentration that can provide insights into drug efficacy or disease progression. The IL-1 α assay has an LLoQ of 0.14 pg/mL and a reading range of 0.07–2000 pg/mL, enabling accurate quantification of IL-1 α in human plasma with a broad dynamic range. The Singulex IL-1 α Assay has also been validated for use in serum.

This assay will allow investigators to:

1. Measure the efficacy and dosing of therapeutics designed to interfere with the IL-1 mediated inflammatory response, such as Kineret.
2. Design more robust clinical and preclinical studies when IL-1 α concentration can be used as a therapeutic endpoint, as in the clinical trial of AMG 108.
3. Understand how IL-1 α levels change in patients as they transition from healthy to diseased states.

ERENNA TECHNOLOGY ACCESS PROGRAM.

Through the Erenna Technology Access Program (ETAP), Singulex offers an interactive, results-driven solution to biomarker challenges faced by the pharmaceutical industry during product development. Singulex assists the development programs of our ETAP collaborators by developing customer-driven assays and access to a menu of fully-validated assays. Participants in ETAP gain access to the Singulex Erenna Immunoassay System, our proven expertise developing high-value immunoassays and our world-class customer support. Together with Singulex, our ETAP collaborators are expanding the utility of protein biomarkers and using them as tools to measure disease progression, drug efficacy and toxicity.

TABLE 1: Analytical sensitivity of the Singulex IL-1 α assay.

Lower Limit of Detection (LoD)	0.07 pg/mL
Lower Limit of Quantification (LLoQ)	0.14 pg/mL
Reading Range	0.07-2000 pg/mL

Erenna® System



TABLE 2: IL-1 α assay low-end standard curve data.

[IL-1 α] pg/mL	Detected Events	Std Dev	CV
4.38	2841	201	7%
2.19	1513	29	2%
1.09	920	83	9%
0.55	649	32	5%
0.27	397	4	1%
0.14	310	5	2%
0.07	247	26	11%
0.00	253	20	8%

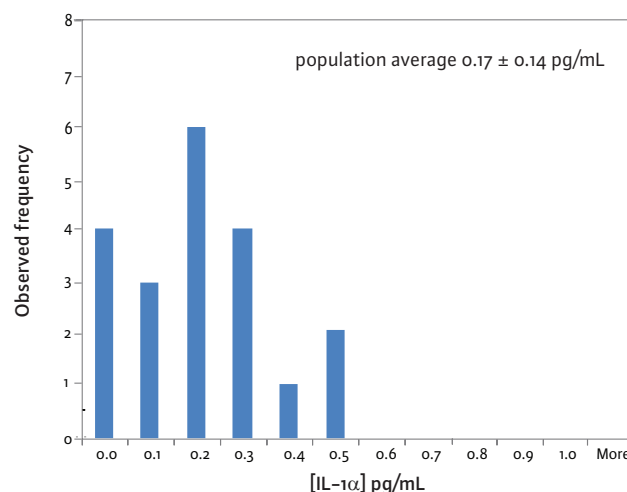


FIGURE 1: Plasma IL-1 α concentration in healthy human subjects.

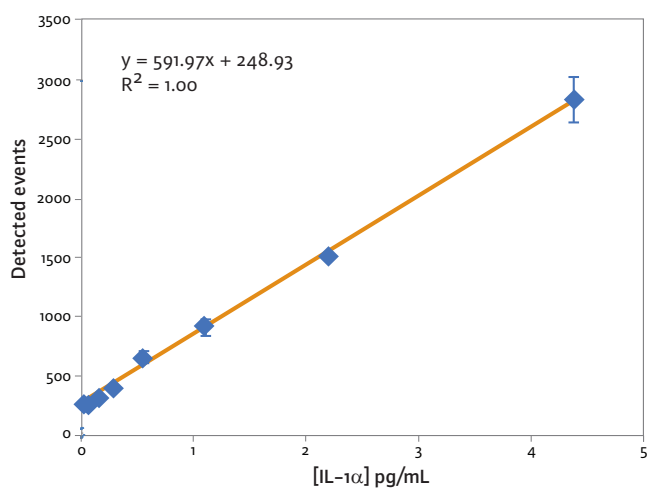


FIGURE 2: IL-1 α low-end standard curve signal.

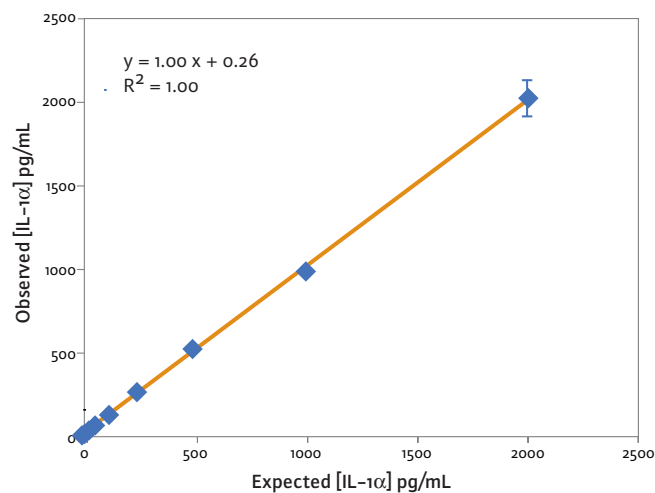


FIGURE 3: IL-1 α assay curve fit.

These standard curves are for representational purposes only. A standard curve must be run with each assay.

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