**The Immunotherapy Revolution's Path To Precision**

Since the approval of the first immune checkpoint inhibitor (ICI) more than a decade ago, immunotherapy has transformed oncology. The first CTLA-4 antibody, ipilimumab, was approved in 2011 and demonstrated durable survival gains in metastatic melanoma. Subsequent approvals of PD-1/PD-L1 inhibitors in 2014 extended these benefits to multiple tumor types. Together, these advances firmly established immunotherapy as a first-line treatment option in many cancer settings.

Predictive biomarkers were important for this evolution. PD-L1 expression, microsatellite instability (MSI) status, and tumor mutational burden (TMB) now guide treatment decisions across an expanding range of indications, including tumor-agnostic approvals for tumors with high MSI and TMB treated with pembrolizumab. It became clear that once it became possible to identify the likely responders, outcomes improved, and unnecessary toxicity was reduced. Artificial intelligence is accelerating this progress. For instance, deep learning models can already infer MSI status directly from routine histology, which allows for easier screening of ICI candidates without additional genetic or immunohistochemical tests. In gastrointestinal cancers, this approach has shown robust performance across cohorts, suggesting a scalable path to expand access to effective therapy where additional testing is unavailable.[1] In parallel, transcriptome-based algorithms such as TIDE integrate signatures of T-cell dysfunction, offering superior predictive power for checkpoint blockade response compared with single biomarkers.[2]

Despite this momentum, unintended immune activation remains a major challenge. The same mechanisms that cause anti-tumor immunity can also trigger systemic inflammation, cytokine release, or autoimmune reactions. These immune-related adverse events may appear unpredictably, so managing this risk requires more than standard safety monitoring. To understand the adverse immune stimulation mechanistically, we ideally need to measure the immune responses during early-phase drug development and in real time.

At CHDR, we address this challenge through comprehensive early immune profiling of novel drug candidates, integrating in vivo, ex vivo, and in vitro approaches. Controlled immune challenge models, such as lipopolysaccharide (LPS), keyhole limpet hemocyanin (KLH), imiquimod (IMQ) and UVB exposure, allow researchers to observe the immune system’s dynamic behavior under regulated conditions. When combined with advanced biomarkers, such as cytokine profiling, complement activation assays, and transcriptomics, these models enable assessment of both desired pharmacodynamic effects and potential adverse immune responses.

A key principle in modern immunotherapy development is that, unlike traditional chemotherapeutics, dosing should be guided not by the maximum tolerated dose but by a pharmacologically active dose: the level at which mechanistic biomarkers confirm target engagement and balanced immune activation. Incorporating these pharmacodynamic insights early, through studies in healthy participants or translational models, allows developers to de-risk patient trials, refine dose selection, and better understand immune mechanisms before exposing patients to novel drug candidates. Low-dose or short-exposure studies in healthy participants also remove confounding effects of comorbidities and concomitant medications, while accelerating recruitment. This creates ideal conditions to establish clear relationships between exposure, target engagement and biological effects prior to transitioning into target patient populations.

**References**

1. Kather, J.N., Pearson, A.T., Halama, N. et al. Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer. Nat Med 25, 1054–1056 (2019).

2. Jiang, P., Gu, S., Pan, D. et al. Signatures of T cell dysfunction and exclusion predict cancer immunotherapy response. Nat Med 24, 1550–1558 (2018).