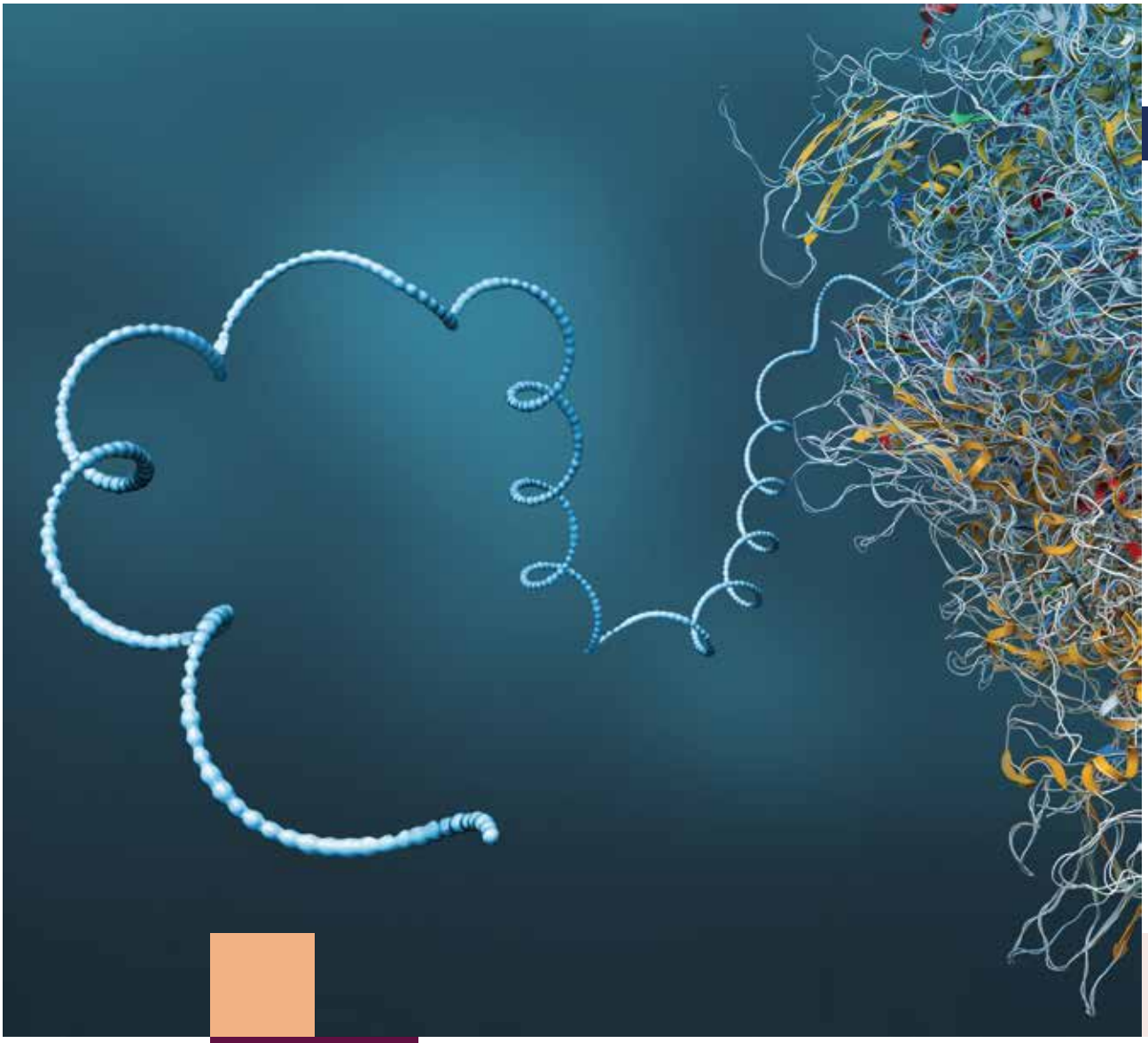
# Targeted Protein Degraders

CellCarta

## Untangle the complexities of TPD clinical development with expert biomarker services



MAPPING PRECISION MEDICINE

# TPDs: a promising modality with complex challenges

**Targeted protein degraders (TPDs) offer great promise in treating some of the most challenging diseases** thanks to their ability to degrade 'undruggable' disease-associated proteins. Consequently, **the field has grown rapidly, and continues to evolve at pace**, with the number of targets expected to climb substantially in coming years.

However, **TPD development involves complex biomarker challenges** — from confidently grasping a TPD's mechanism of action and discerning optimal dosing, to quickly understanding the causes of any TPD resistance.

To ensure TPD success, developers need a partner that deeply understands these challenges and has the expertise and tools to help confidently overcome them.

# CellCarta: your guiding partner to navigate TPD potency and resistance challenges

With significant scientific expertise and custom assay design experience, we steer you through the complexities of understanding TPD potency, dose adaptation, and resistance mechanisms, helping you increase your chances of TPD clinical development success.

### EXPERT-DRIVEN CLINICAL GUIDANCE

Our deep know-how combined with a comprehensive multi-omic approach and sample logistics support can help you to overcome the most challenging aspects of proving your therapy's potential in the clinic.

### COMPREHENSIVE CAPABILITIES

We offer a breadth of complementary techniques and technologies covering immune monitoring, genomics, proteomics, and histopathology, helping you better answer the most important questions about your TPD.

### EXPERTISE IN DECODING PATIENT RESISTANCE

We have the tools and knowledge to elucidate the complex mechanisms behind patient resistance to your TPD, so you can better overcome it.

### PRECISION IN POTENCY

Armed with specific and quantitative data, we can help you accurately assess potency and optimize dosing schedules.

# Confidently evaluate your TPD's potency for better dosing

Accurately ascertaining the potency of your TPD is critical. With CellCarta, you get a range of complementary assays and the know-how to make it possible.

## ACCURATELY MEASURE TARGET DEGRADATION AND DRUG SPECIFICITY WITH MASS SPECTROMETRY

**Confidently quantify target degradation over time** with our highly sensitive and specific multiple-reaction monitoring (MRM) platform. **From liquid biopsies, you can:**

- measure and compare the degradation kinetics, depth, and recovery of your target using different doses of your TPD therapy
- evaluate degradation of different isoforms of your target protein to ascertain your drug's specificity
- refine dosing and scheduling based on informed understanding of TPD potency

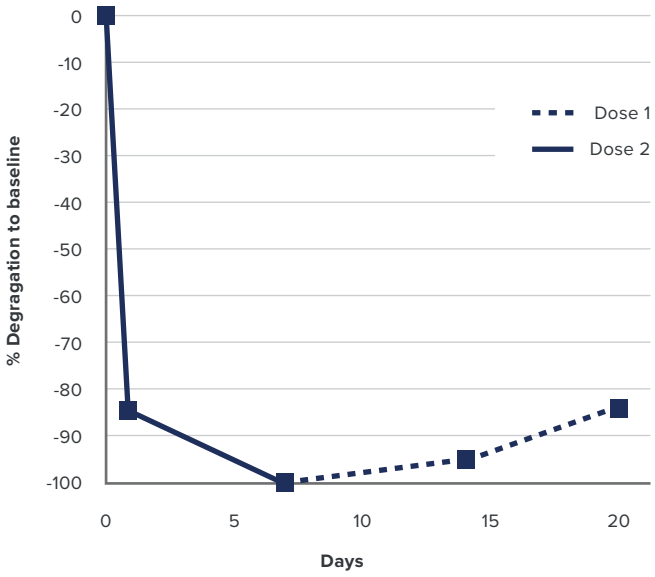


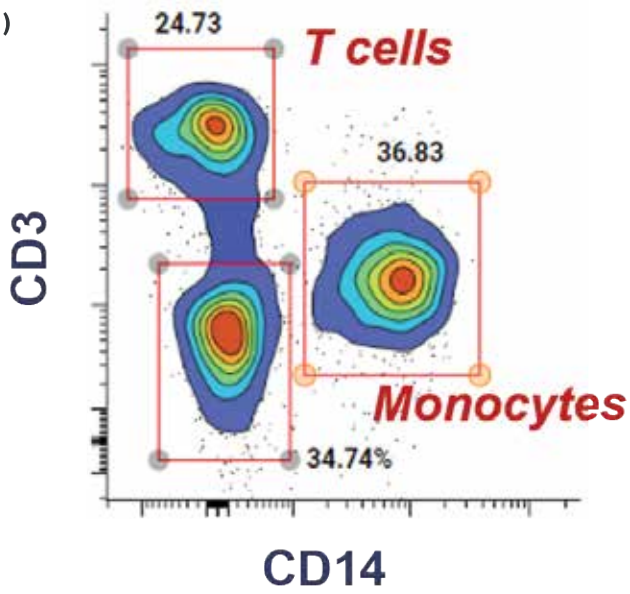

**Figure 1:** Graph showing the percentage (%) degradation to baseline over time for two different TPD therapy doses (dashed and solid lines) in PBMCs.

***With our MRM platform, you can measure a range of common TPD targets**, including IRAK4, STAT3, MDM2, BRAF, EGFR, IKZF1/3*, BTK, BRD9, KRAS‡, Tau, BRD4 and GSPT1.*

- **Experience:** >20 years' expertise in developing customer-specific bioanalytical solutions
- **Global presence:** Nine facilities spanning the US, Canada, Belgium, China, and Australia
- **Quality:** CAP accreditations/CLIA certifications and validation processes that meet the requirements for primary/secondary endpoints
- **Trust:** A track record of working with some of the biggest TPD developers

## MEASURE TARGET DEGRADATION IN SPECIFIC CELL POPULATIONS WITH FLOW CYTOMETRY

With CellCarta's multiparametric flow cytometry services, you can **accurately explore target degradation and drug specificity in specific cell populations**. And, given our assays offer "per cell" data, changes in cell number or relative abundance won't impact your results.




***Evaluate a range of common TPD targets with our flow cytometry platform**, including IRAK4, STAT3, MDM2, IKZF1/3*, BTK, SHP2, Myc, BCR-ABL and IKZF2†*

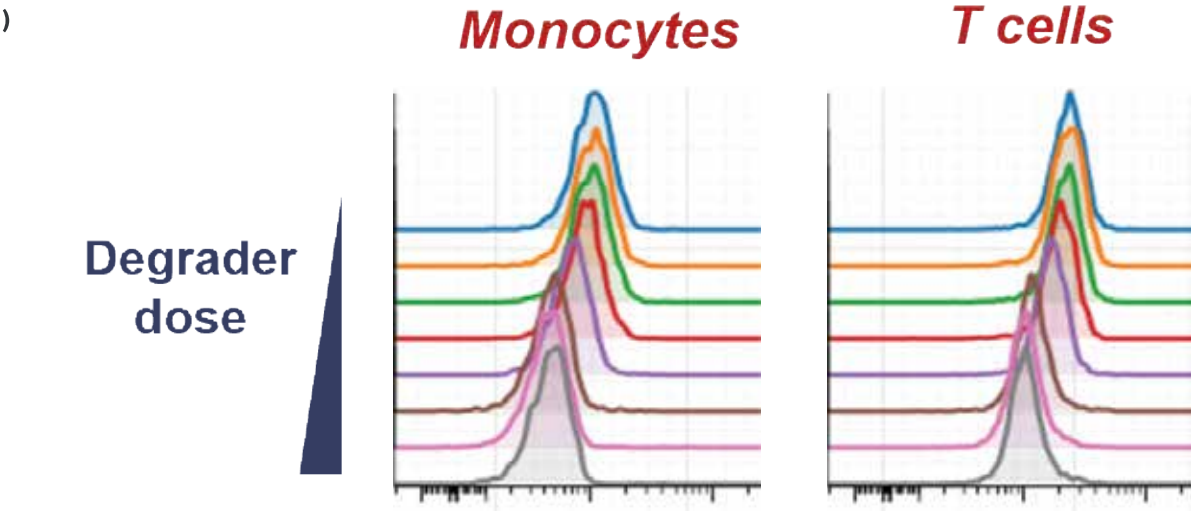



**Figure 2:** (A) Flow cytometry histogram showing the two cell populations (monocytes and T cells) in which target degradation is measured. (B) Graph showing target degradation over time (X axis) based on dosing (Y axis) for these cells.

## MEASURE TARGET DEGRADATION IN TISSUE USING IHC/IF AND MASS SPECTROMETRY

Take advantage of customized immunohistochemistry (IHC) and immunofluorescence (IF) assays to **gain spatial target degradation information to complement your mass spectrometry and flow cytometry data**.

(A) (B) (C)

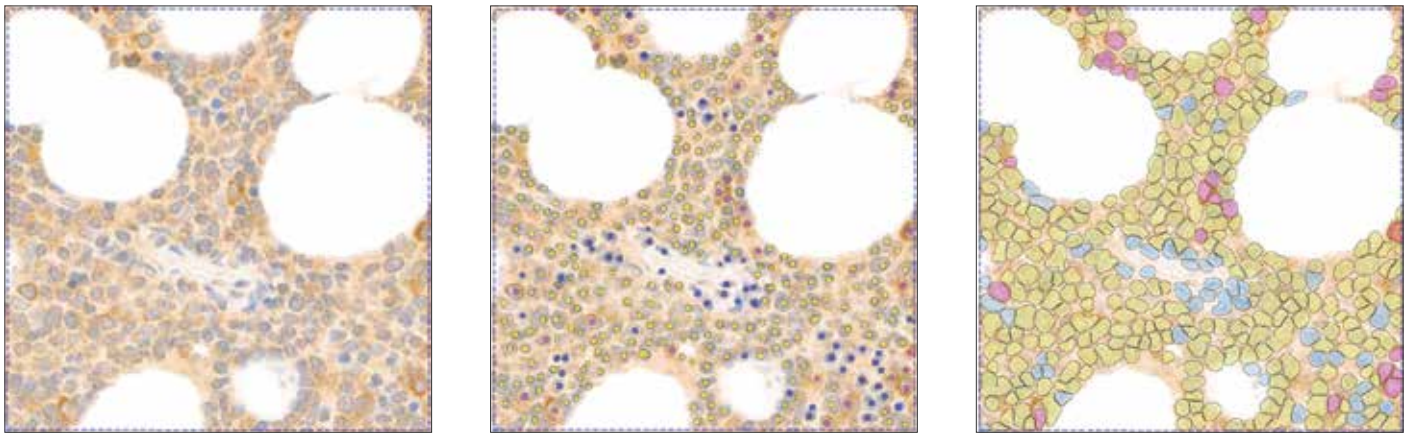


**Figure 3:** (A) TPD target staining of bone marrow biopsy. (B) Pathologist quantitative evaluation of the TPD target in the cytoplasm with a color code according to intensity. (C) Digital image analysis of TPD target using an AI-powered image analysis software to categorize cells based on intensity.

***Our IHC/IF assays enable you to interrogate a range of TPD targets,*** *including MDM2, BRAF, EGFR , BRD9, KRAS‡, Myc, AR and ER.*

**What's more, we can use mass spectrometry to measure target degradation in tissues, too (in addition to measuring in liquid biopsies).**

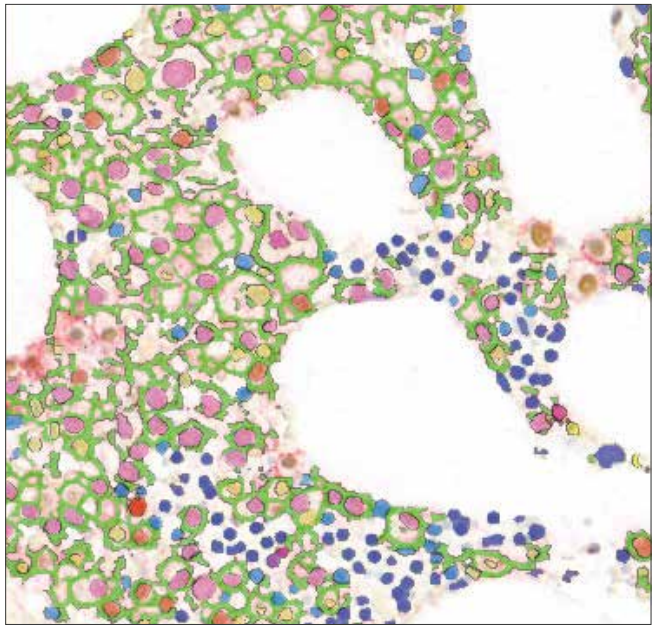


**Figure 4:** Image analysis performed within tumour cells of interest — in this case, plasma cells within a bone marrow biopsy. CD138 is used as a mask to define tumour cell populations, with target degradation colorcoded based on intensity level.

# Optimally select and monitor patients, and unravel the cause of TPD resistance

To demonstrate the promise of your TPD in clinical trials, you need to ensure that the patients you recruit will respond well to treatment. With a multi-omics approach and extensive clinical development expertise, we can help you better stratify and monitor patients, as well as unravel mechanisms of TPD resistance, maximizing your chance of clinical trial success.

## BETTER STRATIFY PATIENTS

Our advanced sequencing tools, IHC/IF assays, and deep knowledge of companion diagnostic (CDx) development enable you to:

- Ensure that key targets are expressed before enrolling trial participants
- Measure well-known mutations that could impact treatment, such as KRAS, BRAF, and EGFR
- Transition a biomarker assay from investigational clinical trial assay to CDx

In this way, we help you **ensure the patients most likely to benefit from treatment are included in your trial to minimize risk of side effects and improve patient outcomes.**

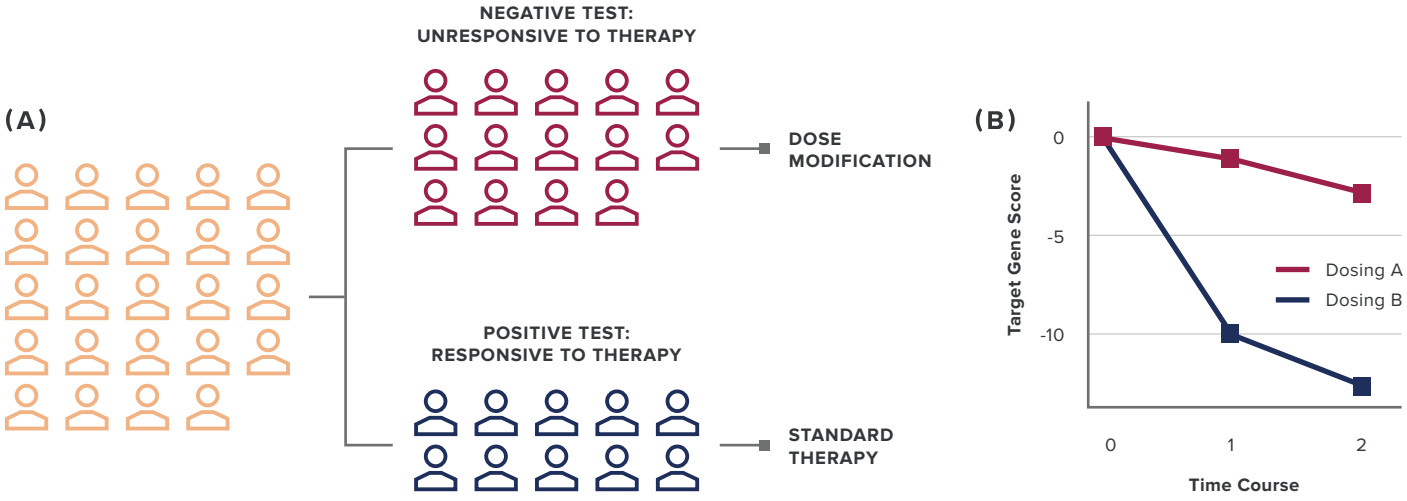



**Figure 5:** (A) schematic representation of patients, showing the two different doses tested (B) Time course RNA sequencing data showing expression of a target gene (y-axis) over time in patients sub-groups receiving two different dosing (blue and purple lines) at two different timepoints (x-axis).

## ENHANCED PATIENT MONITORING DURING TREATMENT

We have a variety of advanced tools to help you **generate more comprehensive data about your therapy, and better understand and monitor patient responses during clinical trials.**

- Non-invasive monitoring of circulating tumour cells using Rarecyte (Figure 6)
- Tracking target degradation over time using time-course RNA sequencing
- Precise and reliable sequencing of known mutations usin NGS (TSO500 panel)
- Monitoring for cytokine storms using our sensitive an specific multiplexed Meso Scale Discovery (MSD) platfor and the Olink® Proximity Extension Assay (PEA)

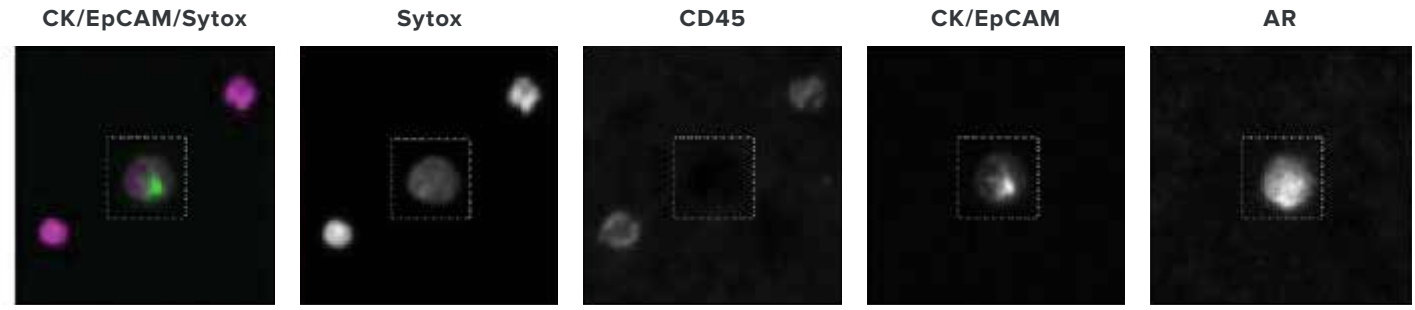



**Figure 6:** Circulating tumour cells (CTCs) analysis by RareCyte®. CTCs are immunophenotyped by automated IF assays using four markers: SytoxOrange, a nuclear dye for CTCs; CK/EpCam, a CTC epithelial markers; CD45, a white blood cell exclusion marker; and up to two investigational biomarkers (e.g., AR) for further phenotypic characterization over time.

## ELUCIDATE THE MECHANISMS OF TPD RESISTANCE

To maximize the therapeutic benefit of your TPD, it's critical to understand and overcome drug resistance.

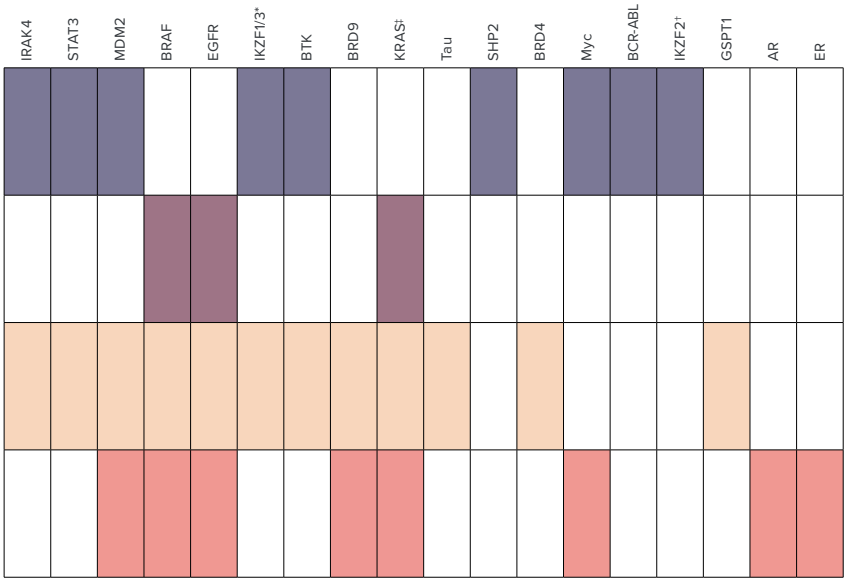
CellCarta can help you **decode complex TPD resistance pathways, and monitor for their activation, using a broad range of advanced technologies and methods**, such as next-generation sequencing (TSO500 panel, whole exosome sequencing, RNA sequencing) and NanoString™.

## CAPABILITIES THAT SPAN A RANGE OF TARGETS

Our multi-omics tools **unlock detailed insights into a vast and continually expanding range of targets.**

| Platforms | Capabilities |
|---|---|
| Immune Monitoring | • **Measure** target degradation in specific cell subtypes<br>• **Establish** dose level and frequency |
| Genomics | • **Map** genomes for mutations associated with response or resistance<br>• **Measure** gene expression (RNAseq, qPCR, Nanostring)<br>• **Develop** CDx for patient selection and stratification using DNA and/or RNA biomarkers |
| Proteomics | • **Measure** target engagement and degradation<br>• **Monitor** protein regeneration<br>• **Establish** dose level and frequency |
| Histopathology | • **Visualize** target degradation with IHC and multiplex IHC, and mRNA ISH<br>• **Measure/quantify** target degradation using digital pathology software<br>• **Immunophenotype** CTCs |

**Targeted Protein Degradation Targets**




TPD: targeted protein degradation, qPCR: quantitative PCR, CDx: companion diagnostics, cfDNA: circulating free DNA, IHC: immunohistochemistry, ISH: in situ hybridization, CTCs: Circulating tumor cells.

*Ikaros/Aiolos ‡KRAS G12D †Helios

## CELLCARTA: GUIDING YOU TO TPD CLINICAL DEVELOPMENT SUCCESS

With the right complementary multi-omics tools and expertise at hand, you can overcome the toughest challenges in TPD clinical development — from understanding potency and refining dosing to decoding TPD resistance.

### READY TO PROPEL YOUR TPD FORWARD?

**Contact our TPD experts** to find out how we can accelerate your routine to clinical development success.

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CellCarta

### ABOUT CELLCARTA

Leading provider of specialized precision medicine laboratory services to the biopharmaceutical industry. Leveraging its integrated analytical platforms in immunology, histopathology, proteomics and genomics, as well as related specimen collection and logistics services, CellCarta supports the entire drug development cycle, from discovery to late-stage clinical trials. The company operates globally with 9 facilities located in Canada, USA, Belgium, Australia and China.

## For more information on how CellCarta can partner with you, please contact us:

**www.cellcarta.com**
**Toll Free: + 1 877 776 3443**

### HEADQUARTERS

201 President Kennedy Ave., Suite 3900
Montreal, Quebec, Canada H2X 3Y7
Phone: + 1 514 360 3600