Method for assessing the efficacy of immunmodulatory drugs

Reference No: B74042

CHALLENGE

Immunomodulatory drugs (**IMiDs**), such as **thalidomide** and its derivatives **lenalidomide and pomalidomide**, are key treatment modalities for **hematologic malignancies** like multiple myeloma (MM) and del(5q) myelodysplastic syndrome (MDS). Cereblon (**CRBN**), a substrate receptor of the CRL4 ubiquitin ligase complex, is the **primary target by which IMiDs mediate anticancer and teratogenic effects.** However, the physiological functions of CRBN are mostly unknown and the mechanisms by which IMiDs mediate their plethora of different antitumor and teratogenic effects have remained elusive.

INNOVATION

This technology **discovered the mechanism** by which CRBN mediates ubiquitin-independent maturation and stabilization of the CD147–MCT1 complex, and demonstrates that **IMiDs compete with CD147 and MCT1 for CRBN binding** to exert versatile anti-tumor effects. CRBN mediates the folding and maturation of the CD147 and MCT1 proteins and thereby allowes activation of the CD147-MCT1 transmembrane complex. The CD147-MCT1 complex is of vital importance for the regulation of cellular metabolism - particularly glycolysis, a major source of energy production in cancer cells. Notably, **expression of CD147 and MCT1 is upregulated in multiple myeloma (MM),** and both proteins have been critically implicated in the proliferation and survival of MM cells. All three established IMiDs (thalidomide, lenalidomide and pomalidomide) **destabilize CD147 and MCT1**, indicating the general drug-class-specific effect. The technology shows that destabilization of CD147 and MCT1 is **predictive of a therapeutic response to IMiDs**, and that this could be **used as a biomarker**. Moreover, given the location of the CD147–MCT1 complex at the cell surface and its functions, these proteins may represent accessible **therapeutic targets in both IMiD-responsive and IMiD-resistant tumors.**

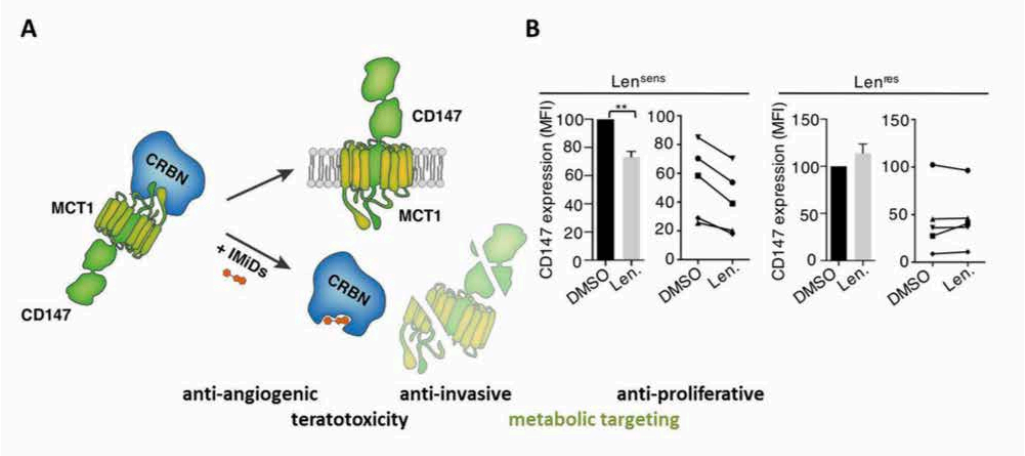

Figure: A) IMiDs mediate their biological effects by destabilizing CD147 and MCT1. B) Destabilization of CD147 is predictive of a therapeutic response to IMiDs.

COMMERCIAL OPPORTUNITIES

- Using CD147/MCT1 destabilization as **biomarker** to:
  - reduce **unneccesary treatment of IMiD-resistant patients** and
  - reduce **healthcare costs and drug-related toxicity**
- Previously **hard-to-treat patients** could benefit from CD147/MCT1-targeting therapies
- Potentially extendable to **other IMiD-sensitive or -resistant malignancies**

DEVELOPMENT STATUS

Proof of concept.

REFERENCE:

1 (1) Eichner et al, Nat Med. 2016 Jul;22(7):735-43. doi: 10.1038/nm.4128

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