

- Despite recent outstanding advances in chemo-immunotherapy having shifted certain B-cell tumor subtypes from uniformly lethal to curable, most **mature B-cell malignancies** remain **incurable**.
- The use of therapies combining **direct B-cell targeting** and **immunotherapy** implementing T-cell anti-tumor responses by repression of Tregs may improve cure rates of B-cell malignancies.
- A ion carrier numbered as 17 (**IC17**) has been found as a **new target** for tumor immunotherapy. Blocking IC17 function exerts a **dual anti-tumor effect** on a large number of B-cell malignancies by:
 - direct targeting of tumor B cells that are forced to undergo apoptosis.
 - triggering of T-cell anti-tumor responses through decreasing T_{reg} numbers and potentiating effector T cells.
- **Indication:** B-cell malignancies (B-cell lymphoma, leukemia and multiple myeloma).

Novel Approach

- To establish a proof of principle for a new strategy to treat B-cell malignancies by blocking IC17 function.
- There are no similar dual therapy (potentiating T-cell mediated immunotherapy responses and directly induction of apoptosis) in cancer using a single molecule.

Target Identification

- Lymphocytes exhibit a network of ion channels and transporters in the plasma membrane that modulate intracellular concentration of ions which regulate intracellular pH (pHi). Higher pHi promotes proliferation whereas an acidic pHi favors apoptosis. Basal pHi values are higher in all B-cell lymphoma, leukemia and myeloma cells in comparison with non-tumoral B lymphocytes.
- Mice with targeted deletion of one of the master regulators of pHi, termed IC17, show lymphocytes with abnormal pHi, which was associated with reduced regulatory T cell (T_{reg}) numbers.
- IC17 has been identified as a T_{reg} function regulator and a potential target for tumor immunotherapy.

Target Validation

- **In vitro**, chemical probe: CM-1300, a molecule binding an extracellular loop of IC17, shows different effects on T cell subsets (decreased T_{reg} numbers and increased effector T cell numbers) and kills B-cell leukemia, lymphoma and myeloma cells.

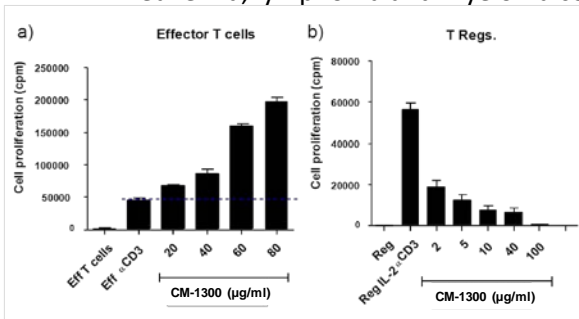


Figure 1. CM-1300 exerts opposite effects on T-cell subpopulations: it promotes proliferation of effector T cells and decreases survival of Tregs.

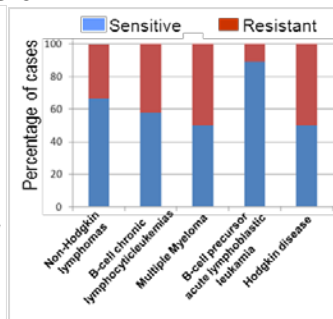


Figure 2. CM-1300 induces apoptosis in human derived B-cell leukemia, lymphoma and myeloma cell lines.

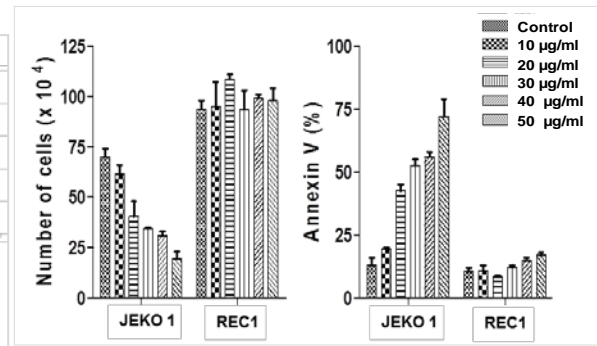


Figure 3. Dose-dependent decrease in cell proliferation and increase in apoptosis after CM-1300 exposure is observed in the sensitive lymphoma cells Jeko1 but not in resistant U266 cells.

- CM-1300 kills B-cell lymphoma cells by disrupting IC17 transport function.

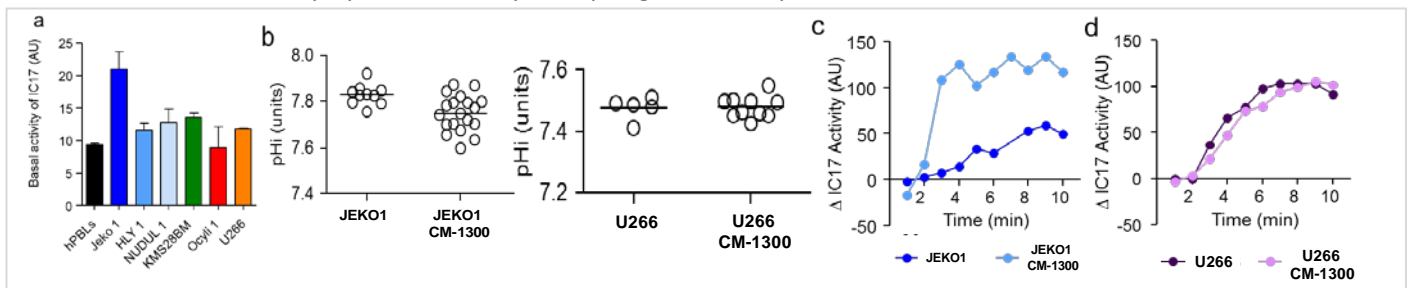


Figure 4. Effects of CM-1300 in sensitive lymphoma cells (Jeko1) and resistant myeloma cells (U266). a) Baseline, IC17 activity is higher in Jeko1 cells than in U266 cells. b) Basal Jeko1 pHi decreases upon CM-1300 incubation, whereas U266 pHi remains unchanged. c) and d) Measurement of IC17 activity upon pIC17 incubation, which increases in Jeko1 cells but not in U266 cells.

- **In vivo** studies are on-going.

Safety

Studies to determine therapeutic window are on-going.

Intellectual Property

Patent application to be filled.