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CENTER FOR APPLIED MEDICAL RESEARCH
UNIVERSITY OF NAVARRA

Novel therapeutic strategy in B-cell malignancies: targeting a key microenvironmental ion carrier machinery

- 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.
- An 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 immune responses through decreasing T_{reg} numbers.
- **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, decreases T_{reg} numbers, increased effector T cells, and kills B-cell leukemia, lymphoma and myeloma cells.

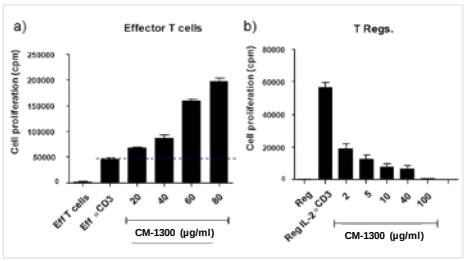

Figure 1. CM-1300 exerts opposite effects on T-cell subpopulations: it promotes proliferation of effector T cells and decreases survival of Tregs.

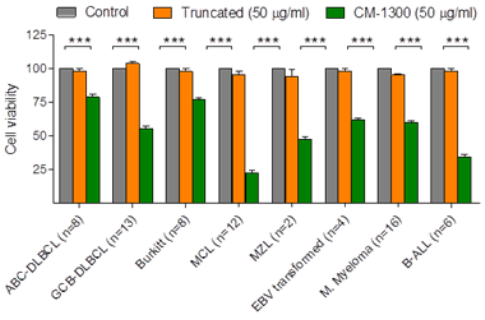

Figure 2. CM-1300 induces apoptosis in human derived B-cell leukemia, lymphoma and myeloma cell lines.

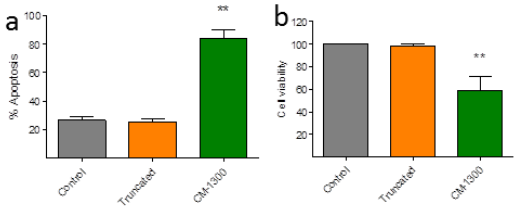

Figure 3. CM-1300 reduced cell viability (a) and promoted apoptosis (b) of primary samples obtained from patients with B-cell lymphomas (n=10).

- CM-1300 kills B-cell lymphoma cells by disrupting IC17 transport function.
- ***In vivo,*** xenograft model of B-cell lymphoma. Intratumoral injection of CM-1300 showed a reduction in tumor volume at high dosage in comparison to the control (truncated) peptide.

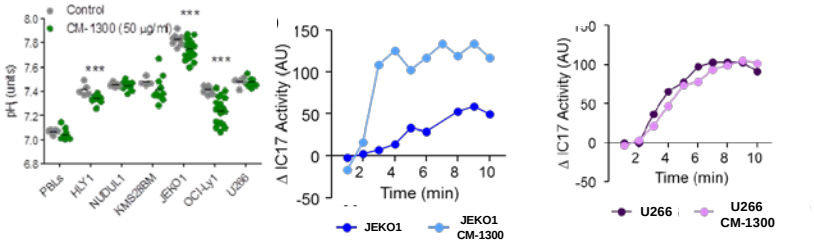

Figure 4. Effects of CM-1300 in sensitive lymphoma cells (JEKO1) and resistant myeloma cells (U266). a) Basal pHi decreases upon CM-1300 incubation in sensitive cells, whereas in resistant cell lines pHi remains unchanged. b) Measurement of IC17 activity upon CM-1300 incubation, which increases in JEKO1 cells but not in U266 cells.

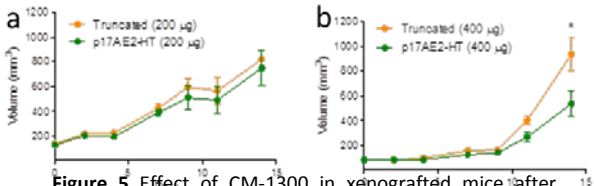

Figure 5 Effect of CM-1300 in xenografted mice after intratumoral injection. CM-1300 induced reduction of tumor size at a dosage of 400 µg (b), but not at 200 µg (a).

Safety	Studies to determine therapeutic window are on-going.
Intellectual Property	Patent application to be filed.

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