Checkpoint Inhibitor Combinations in a Human Mixed Leukocyte Reaction

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Overview

1. Review of the mixed leukocyte reaction (MLR).
2. Measuring anti-CD73 activity in the MLR.
3. Screening combinations in the MLR.
A Key Role for Adenosine in Tumor Biology

After Leone et al., 2015

Adenosine as “smog”…

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Anti-CD73 Enhances Leukocyte Clustering

- Mixed leukocyte clusters contain APCs.
- NB: No exogenous AMP or ADO added....
MEDI9447 Enhances a Two-Way Mixed Lymphocyte Reaction

- Timing and extent of PBMC clustering are increased.
- Dendritic cells are found at cluster centers.
Mixing PBMCs Increases Lymphocyte Populations

Response is consistent with an allogeneic reaction.
MLR Combinations Reflect Animal Data

An in vitro assay reflects in vivo data.

Allar et al, 2013
A Subset of Lymphocytes Proliferates

Response is consistent with an allogeneic reaction.
Dose-dependent Th1 Cytokine Secretion with MEDI9447

IL1-β response is suggests involvement of myeloid compartment.
Synergy Targeting CD73 and Other Targets

- Targeting both CD73 and other modulators in a “mixed” setting shows synergy.
- Consistent with literature for various syngeneic models and signaling pathways
When is Synergy Significant?

Classic Bliss: No Statistics

Novel Bliss: 95% CI

Drug A  Drug B

Anti-CD73

Statistical confidence minimizes bioassay false positives: informed decision making.

A New Bliss Independence Model to Analyze Drug Combination Data

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Anti-CD73 With Other Immune Modulators

Cytokine Secretion (fold control)

**MLR:** An opportunity for medium/high throughput combination screening.
Combination Effects Across Multiple Donor Pairs

Synergy generally reproducible and statistically significant.
Summary

Conclusions:

• The mixed leukocyte reaction mimics aspects of in vivo biology.

• Combinations of immuno-oncology targets can be screened using the MLR

Next Steps:

• Screen additional combinations.

• Extend MLR principle to autologous setting.
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