Lepton Pharmaceuticals LTD

Castling Technology Platform Overview

January 2022

Forward Looking Statements

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LN-Cast

- The Castling Technology (LN-Cast) is a proprietary, breakthrough technology:
  - manipulation/engineering of miRNA expression for enhanced efficacy and longevity (reduced exhaustion) of cell-based therapies
  - PCT patent application filed
- Proof of Concept of technology in CAR-T cells

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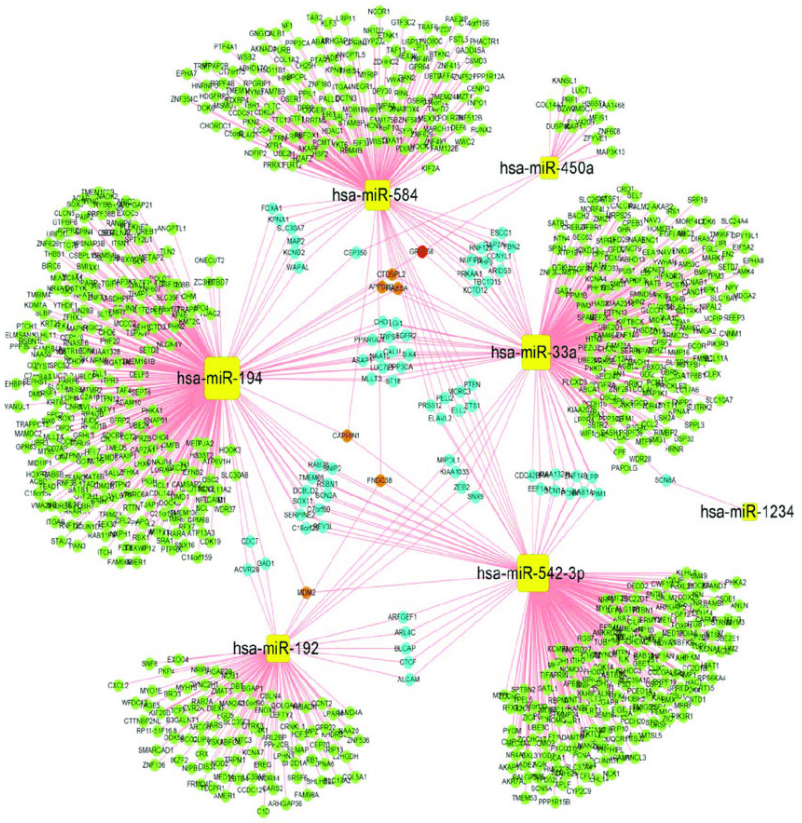
LN-Cast Takes Advantage of:

1. Broad and pivotal roles that microRNAs (miRNAs) play in cell biology
2. The pleiotropic effect that each individual miRNA has on multiple (up to hundreds) genes within a specific molecular pathway, thus regulating whole gene networks associated with a certain biological state of a cell, and
3. The available tools for gene editing (e.g., CRISPR/Cas or TALEN but not limited to those) as a technical platform.



From Lv et al. Oncotarget, Vol. 7, No. 32; p52270

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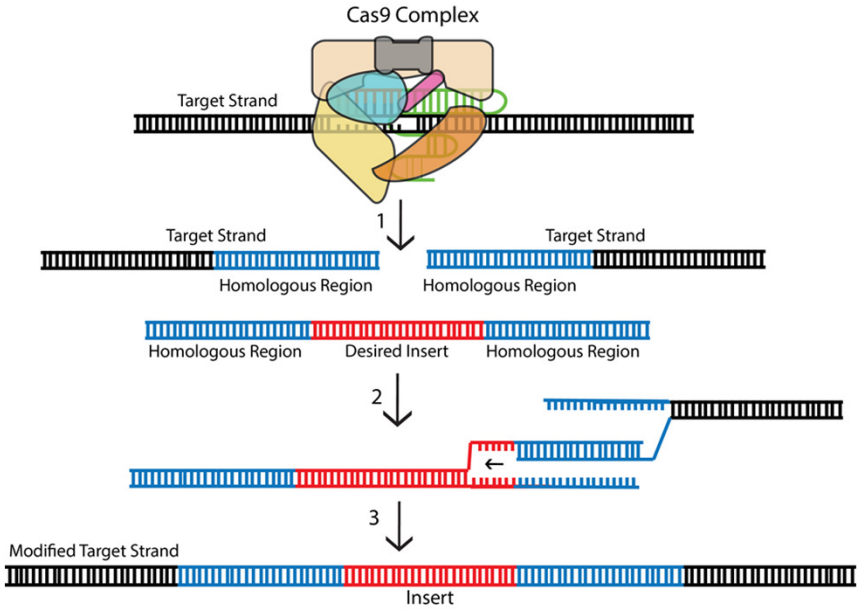
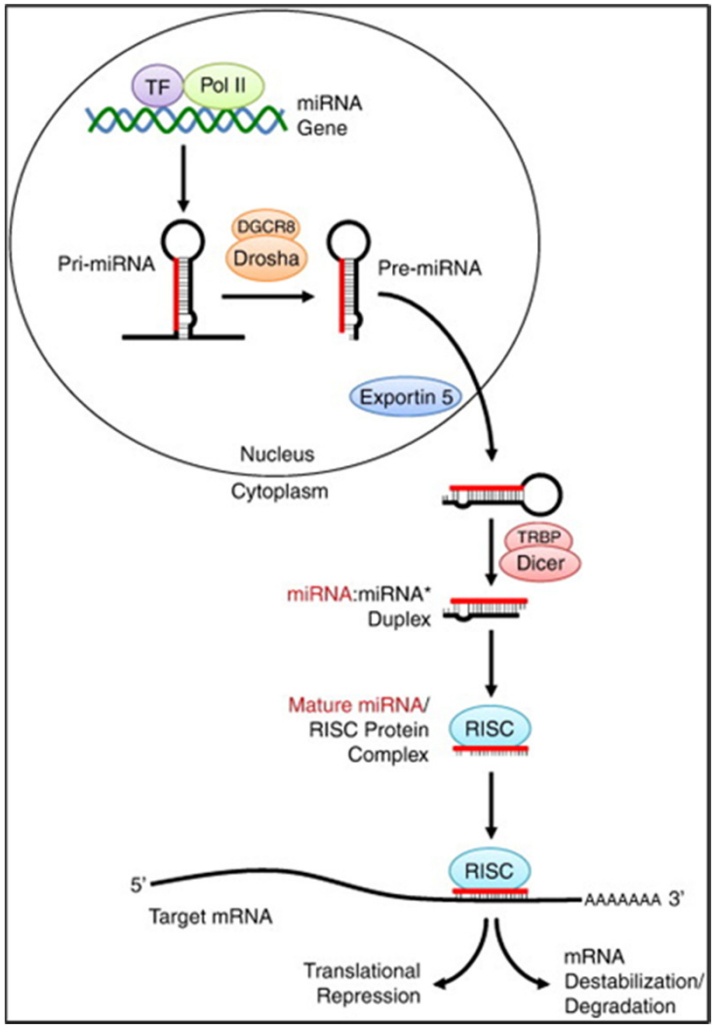


https://sites.tufts.edu/crispr/genome-editing/homology-directed-repair/

miRNA Function

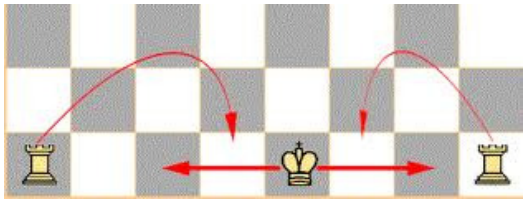
- miRNAs are small (~19–24 nucleotides) double-stranded, non-coding RNAs that control gene expression, either by promoting mRNAs degradation or by repressing their translation to proteins.



https://www.sciencedirect.com/science/article/pii/S002228361300154X

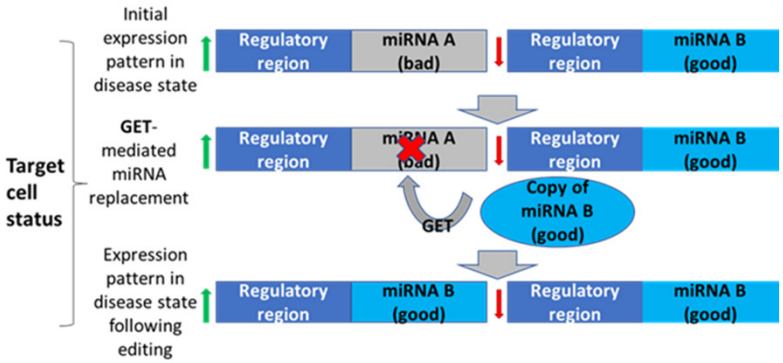
LN-Cast Consists of:

- Identification of miRNA pairs, in which
  - One pair member is transcriptionally induced in pathology and orchestrates activation of gene network(s) that mediate(s) the unwanted phenotype(s) (“harmful” miRNA), and
  - Another pair member is underexpessed or unchanged in pathology but, if upregulated ectopically, can activate gene network(s) that counteract(s) the unwanted pathological phenotype(s) (“beneficial” miRNA).
- Employing gene editing technologies **(GETs)** for placing “beneficial” miRNA sequence under the transcriptional control of actively expressed “harmful” miRNA, thus simultaneously achieving two goals:
  - Ectopic overexpression of “beneficial” miRNA, and
  - Inhibition of expression of “harmful” miRNA



Castling

LN-Cast



Note that theoretically “beneficial” miRNA can be also inserted within an actively expressed “harmful” coding gene (e.g., PD-1) while disrupting its protein synthesis.

Main Advantages of LN-CAST

Potential to reach higher efficacy compared to other approaches

- Castling introduces a “good” miRNA in the genomic region that by default is actively transcribed under conditions of “bad” pathological phenotype aimed for reversion, thus guaranteeing that the transgene will be also effectively transcribed within the given pathological epigenetic state (e.g., in a hostile to immunocytes tumor microenvironment).
- The resulting simultaneous and reciprocal impact on genetic networks regulated by two different miRNAs is expected to have more significant therapeutic effect compared to single/few gene manipulations typical for other cell engineering approaches.

Better safety compared to other approaches

- Castling is based on precise manipulation of two sequences, expression of each of which is specifically tuned in the desired direction without bystander effects on the neighboring genes.
- Castling-mediated changes in miRNA expression are manifested only upon transcriptional signals from the natural promoter that is activated under pathological condition(s) (e.g., by tumor microenvironment) that is (are) in the focus of the therapeutic intervention,.
- This is in contrast to other cell engineering technologies (especially those based on ectopic gene expression from the vector-derived promoters) that may suffer from safety sequelae associated with constitutive transgene expression or non-predictable bystander activation/inactivation of genes adjacent to vector integration site.

Cost effectiveness

- The Castling technology uses a single gene-editing manipulation to simultaneously introduce changes in the expression of two miRNAs, each of which regulates a network of hundreds of genes.
- In comparison, the common gene-engineering approaches, employed in the development of effective CAR-T cells, mostly manipulate the expression of a single gene at a time, thus requiring sequential gene manipulation, which is expensive and technically challenging.

Therapeutic Applicability of LN-Cast

- Provided involvement of miRNA in regulation of genetic networks in all cell types in the body, the technology is amenable for therapeutic modification of a variety of cell therapies used for treatment of cancer, autoimmune and inflammatory diseases:
  - Chimeric antigen receptor (CAR) T-cells (both autologous or allogeneic)
  - CAR-Natural Killer (NK) cells
  - CAR-macrophages
  - Tumor infiltrating lymphocytes (TILs)
  - Mesenchymal stem cells (MSC)
- We think that for safety reasons, cells of choice should act autonomously without structural integration in a tissue (as e.g., expected for stem cell therapies in regenerative medicines).

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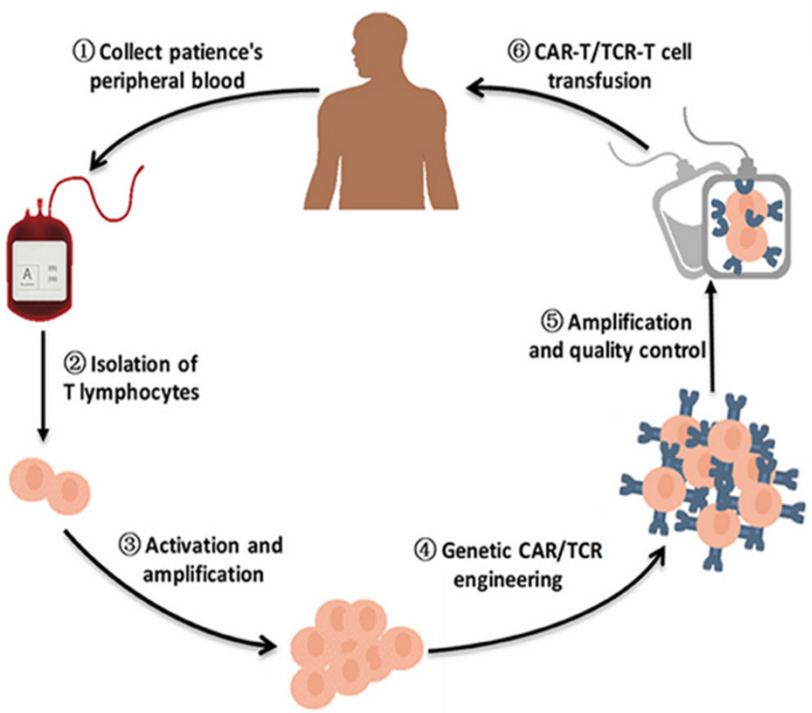
LN-Cast
Proof of Concept Studies in CAR-T cells

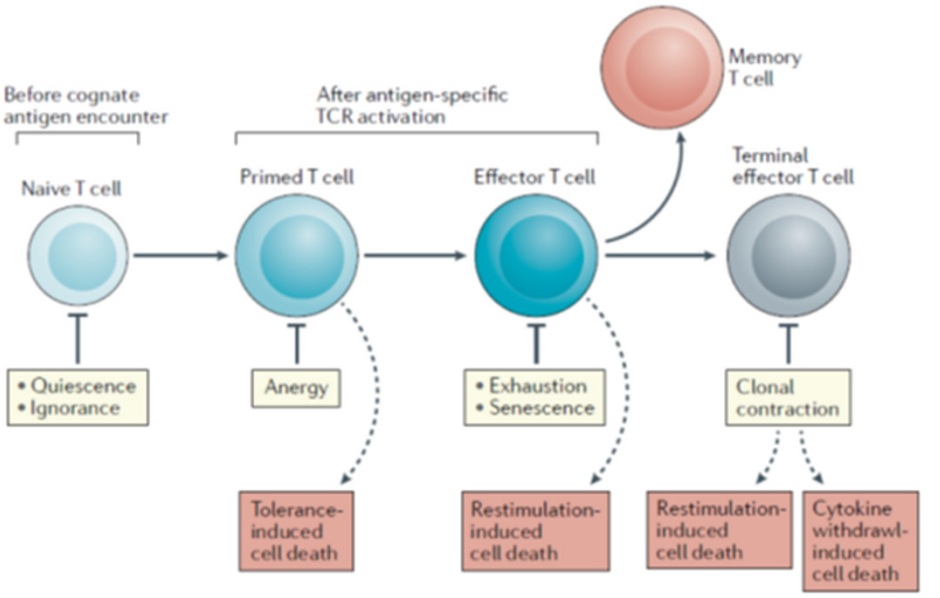
CAR-T Cells in Cancer Therapy



- Currently used for treatment of hematological cancers
- Main challenges
  - Economical
    - Simplifying logistics
    - Reducing cost of production
  - Biological
    - Improving efficacy
    - Improving safety
    - Expansion of use to treat solid tumors
    - Off-the-shelf CAR-T

Amenable for LN-Cast

Roadmap for Tolerance Development During T-cell Lifespan



From: El-Tanbouly&Noelle. Nat Rev Immunol 2021 Apr;21(4):257-267)

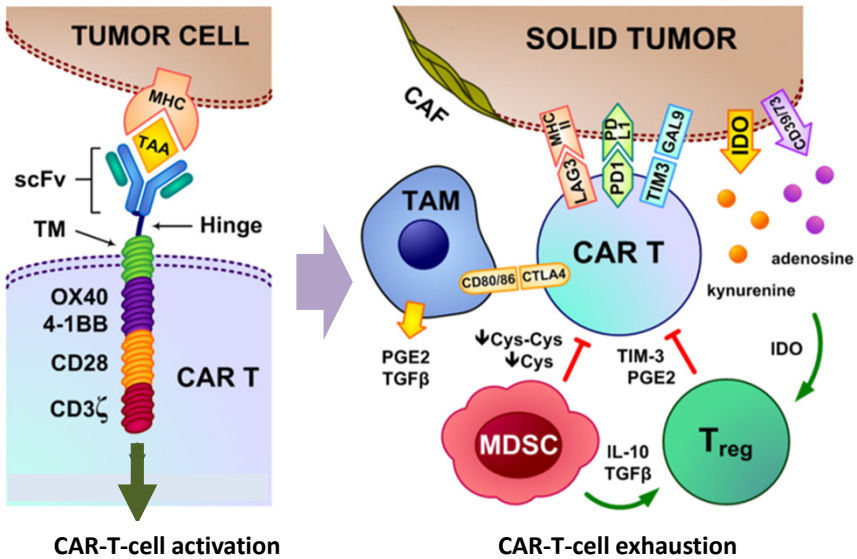
Development of T-cell tolerance
=
loss of cytotoxic function

that is crucial for their anti-cancer effect

T-cell and CAR-T cell Exhaustion and Loss of Cytotoxic Activity in Tumor Microenvironment (TME)

- T cells are activated upon the encounter of tumor cells antigens.
- Activation is directed by changes in gene expression profile and results in rapid proliferation and acquirement of effector (cytotoxic) functions.

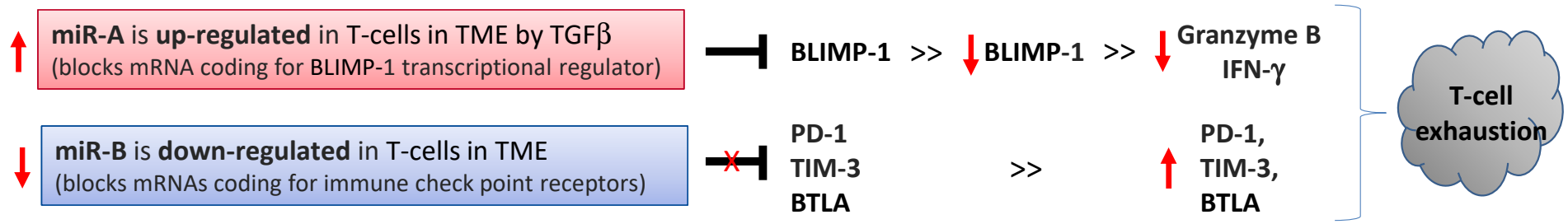
- **However, immune suppressive mechanisms employed by the tumor cells in the TME to escape the immune attack** (such as secretion of suppressive factors like TGFb and expression of immune checkpoint ligands), **lead to progressive loss of T-cell effector function owing to tolerance to tumor antigen/s, insufficient activation (anergy),** and **exhaustion.**
- Gene-expression profile in exhausted T-cells is different from that of functional effector T-cells and is characterized by elevated expression of inhibitory immune checkpoint receptors (PD-1, TIM-3, LAG-3, BTLA, CTLA-4).



From: Tang et.al., Cancer Rep Rev, 2020, Volume 4:1-5.

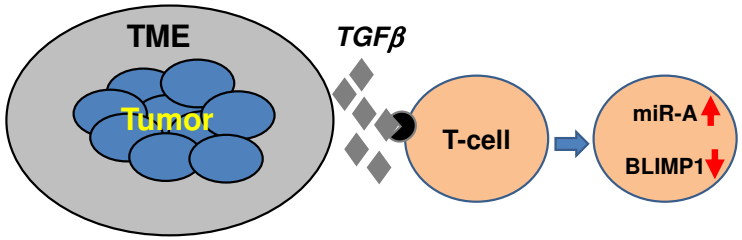
miRNAs affect T-cell / CAR-T-cells effectiveness and exhaustion

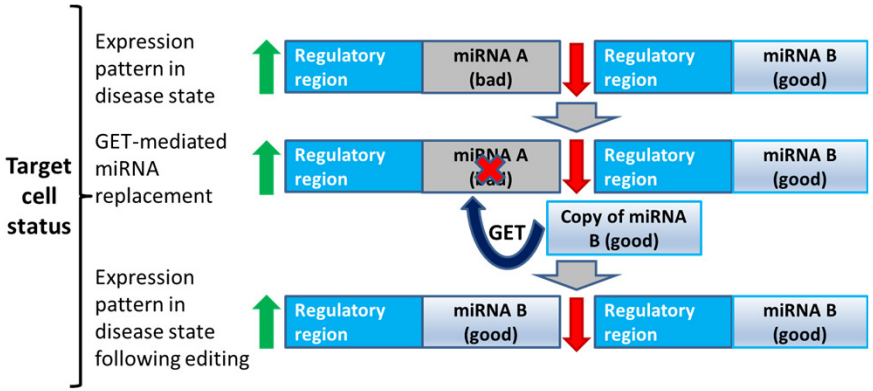
- miRNAs are involved in the regulation of T-cell activation and exhaustion (loss of effector function) processes, by targeting the mRNAs encoding for T-cell effector and tolerance-related proteins
- The expression profile of miRNAs in T-cells, changes in response to external (such as TME) and internal regulatory signals, resulting in the upregulation of some miRNAs and the downregulation of others, which eventually affect T-cell functional state (effective or exhausted)
- The example below depicts the expression profiles of specific miRNAs, which are affected by TME signals and in turn promote T-cell exhaustive (ineffective) state



BLIMP-1 – a key transcription regulator, essential for promoting CTL cytotoxicity
Granzyme B and IFN-γ - key cytotoxic mediators
PD1 - a protein on the surface of T-cells, which suppresses T cell inflammatory activity
TIM-3 - a T cell inhibitory receptor defined as immune checkpoint protein. Together with other inhibitory receptors (**PD1**, **BTLA** and **LAG3)** it mediates CD8+ T-cell exhaustion

Application of LN-Cast

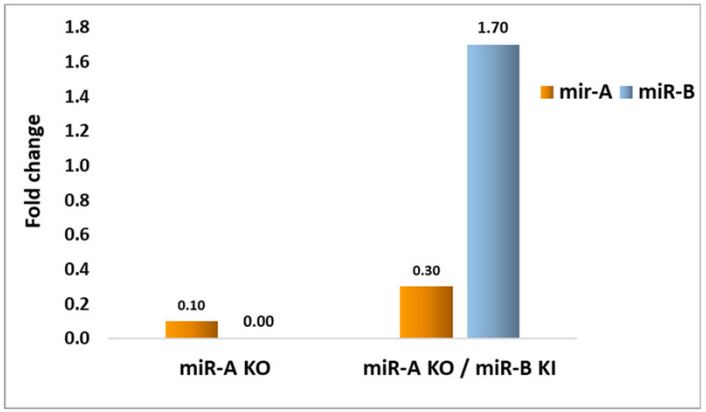


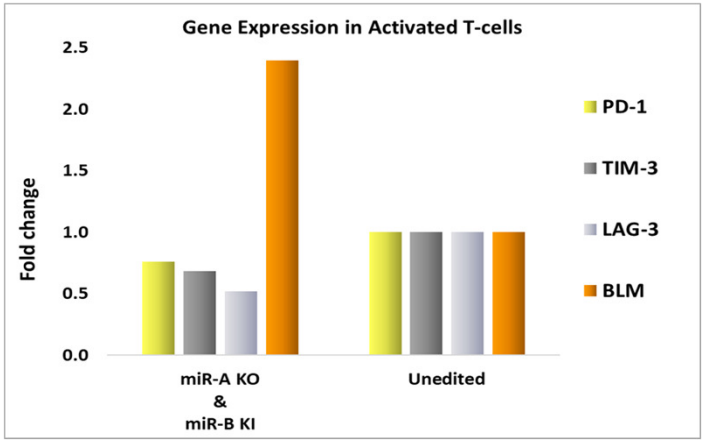


Upon activation of the "castled" T-cells under TME-mimicking treatment, we observe

- Increased levels of miR-B (knocked in) and decreased levels of the regulated checkpoint inhibitors PD1, TIM-3 and LAG-3
- Decreased levels of miR-A (knocked out) and increased levels of the regulated BLIMP-1 - a key transcription regulator, essential for promoting T-cell cytotoxicity

miRNA and target gene expression following T-cell treatment mimicking TME





BLM = BLIMP-1

Lepton's current business strategy calls for:

- One or more licensing/partnering agreements
- Technology collaboration / license that is disease area / miRNA or target cell specific / exclusive

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