Differentiated CD38-CD3 bionic to treat AML

Brief Deck

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Overview

- **City of Hope has developed bispecific molecules (“bionics”) directed against CD38 and CD3 to target CD38-overexpressing cancers such as AML.**
- **The molecules show significant advantages over conventional daratumumab therapy including that**
  - they kill AML cells w/o affecting human peripheral blood viability
  - they specifically kill CD38+ cancer cells
  - They engage with CD4 positive cells, leading to high levels of IFN-g production
  - Local IFN-g induced CD38 on leukemic stem cells and their subsequent destruction
  - they do not kill human NK or T cells in co-culture assays
  - they exhibit favorable therapeutic/manufacturing properties (improved melting temp, high expression, single chain expression)
  - extensive biochemical, in vitro and in vivo data (multiple animal models) are available under confidentiality
- **The bionic technology is a platform that can be expanded to other antigens/bispecifics.**
- **City of Hope is seeking a licensee who continues the preclinical and IND-enabling work with this compound.**

AML - Proposed Disease Indications and Population Size

- **Lead indication AML relapsing patients independently from their cancer cells genetic abnormalities:**
  - Every year approximately 20,000 people in the United States are diagnosed with AML. An estimated 11,000 deaths occur on a yearly basis because of the disease
  - The five-year overall survival rate for AML is 28% (NCI SEER data)
  - There is only one antibody therapy for AML approved by the FDA (gemtuzumab ozogamicin, an antibody drug conjugate against CD33) but produces many side effects
- **Unmet medical need:**
  - Develop antibody base therapies to combine with backbone therapies for the treatment of AML is considered an unmet medical need
- **Other diseases:**
  - Targeted therapy of CD38-expressing cancers such as myeloma, B cell lymphoma, T-ALL and prostate cancer

Target Rationale

➢ Target background – CD38

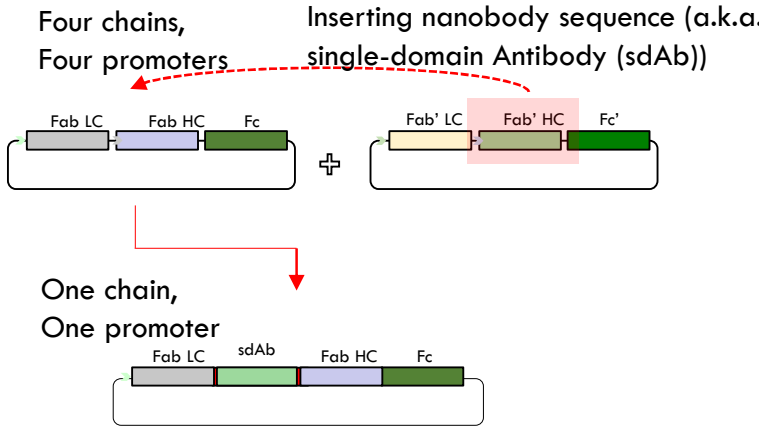
- CD38 is an ectoenzyme able to metabolize nicotinamide adenine dinucleotide (NAD+) regulating extracellular nucleotide homeostasis and calcium homeostasis, which influence immune cell functions.
- CD38 is highly expressed in the marrow of AML patients
- CD38 also interacts with its known ligand CD31, which is expressed on microenvironmental endothelial cells, stromal cells and macrophages and contributes to cancer cell survival
- CD38 is also express in immune effector cells and its targeting is associated with NK cell immune activation
- CD38 is highly and homogeneously expressed both on leukemia blasts
- A subset of AML CD38+ blasts has been shown to be highly resistant to treatment and has leukemia-initiating capacity

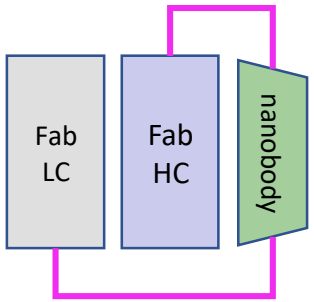
➢ Evidence of target validation

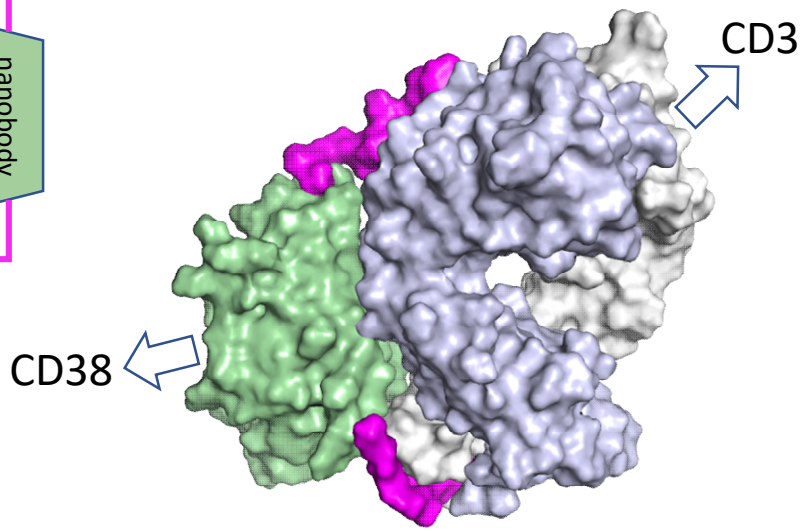
- In pre-clinical models and in two reported clinical cases the CD38-targeting mAb Daratumumab was found highly effective for the treatment of T-cell acute lymphoblastic leukemia
- In an *in vivo* human AML BM-like scaffold (huBMsc) patient-derived xenograft (PDX) model, targeting CD38 on the surface of AML cells with daratumumab was shown to reduce tumor burden in both high and low CD38 expressing cells
- AML cells resistant to therapeutic intervention can become CD34 negative but maintain CD38 expression on their surface

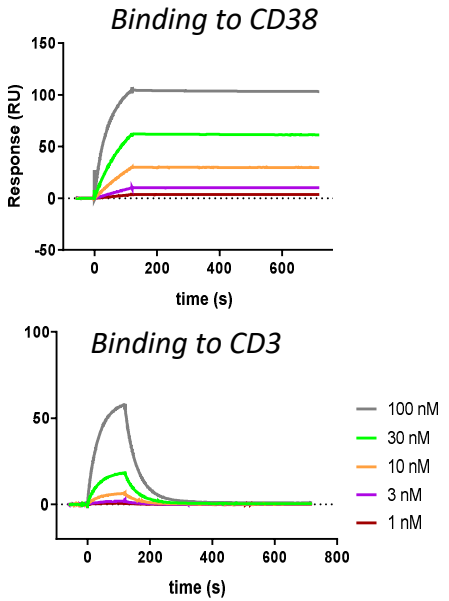
City of Hope's Bionic™ Technology

Biologics Nested Inside Chains or BIONICs™ involves the insertion of a second targeting domain ("nanobody") between the light and heavy chains of a Fab – in the example below, a Fab encoding CD3 and a nanobody encoding CD38.









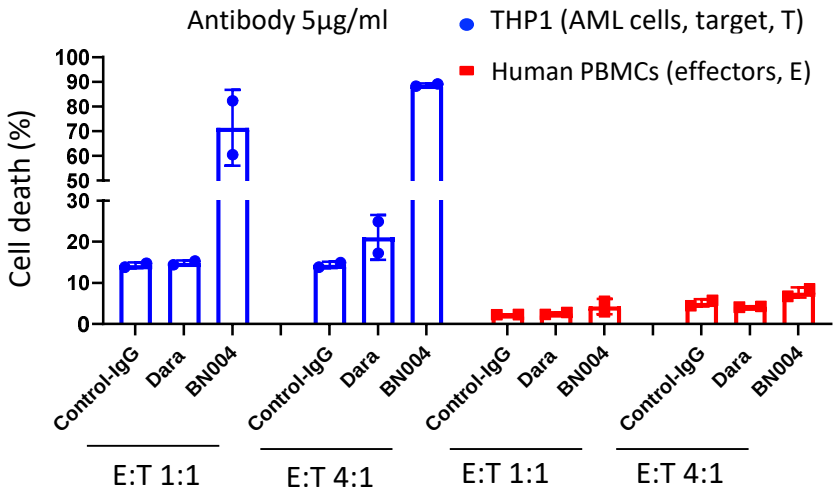
Advantages:

- Efficient - single peptide chain - No chain pairing issues
  - High yields
  - High stability
- Compact - potential to strengthen the immunological synapse, leading to improved killing efficiency
- High monovalent affinity to CD38 antigen
- Low affinity to CD3 for improved biodistribution (e.g., T cells don't act as a sink).

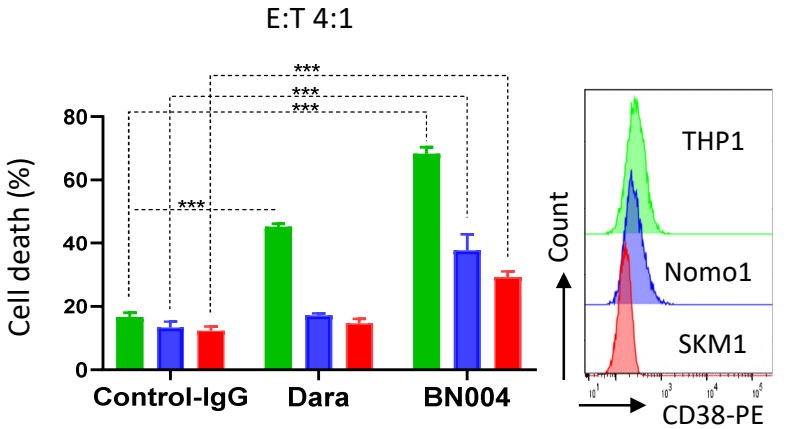
CD38-CD3 BIONICS show favorable therapeutic properties in vitro

- example compound “BN004” -

Bionics kill AML cells w/o affecting human peripheral blood viability

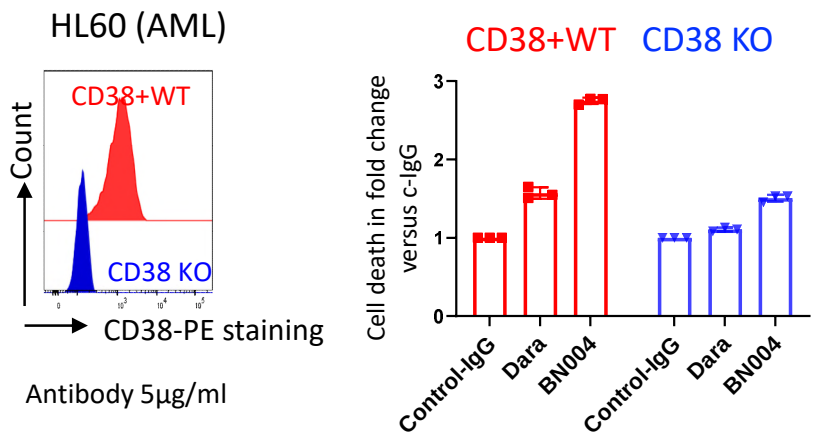


Bionics sensitive to antigen density

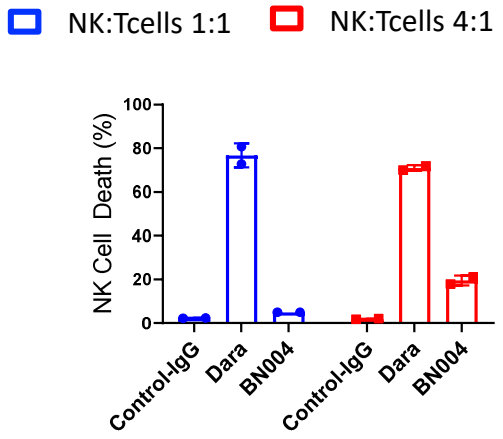


Graph demonstrates proportionality of cell death to CD38 content

Bionics specifically kill CD38+ cancer cells



Bionics do not kill human NK cells in co-culture assays



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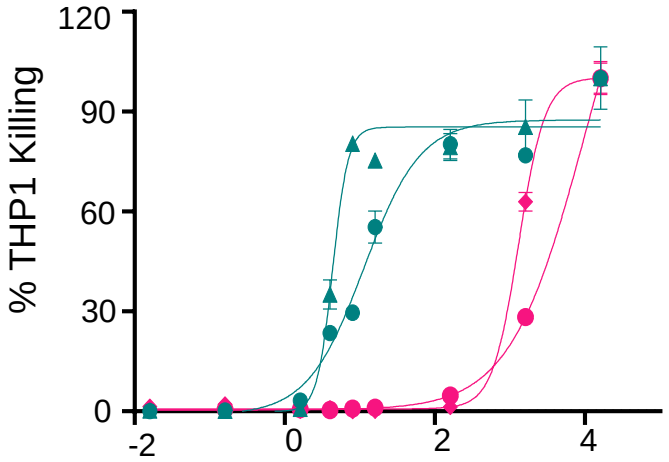
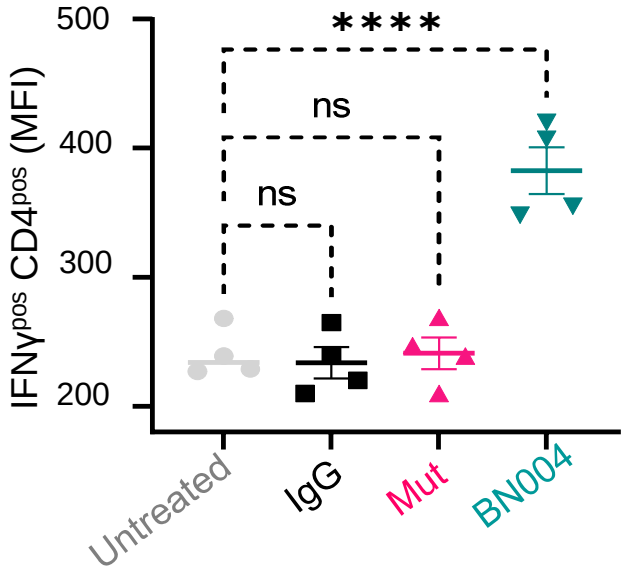
CD38-CD3 BIONICS activates both CD4+ and CD8+ T cells inducing high level of IFN-gamma release*

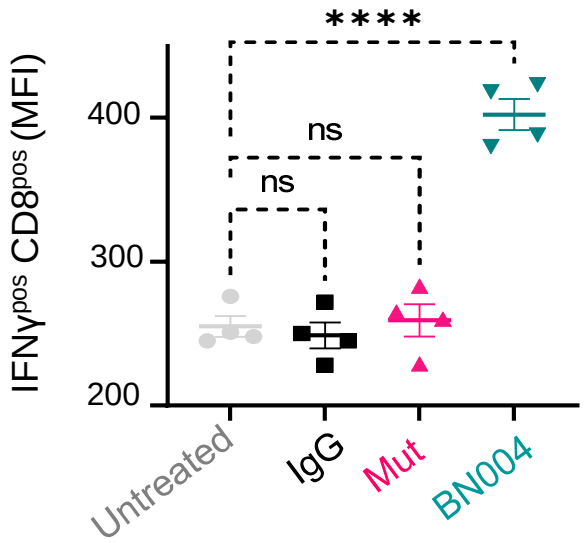
- example compound “BN004” -

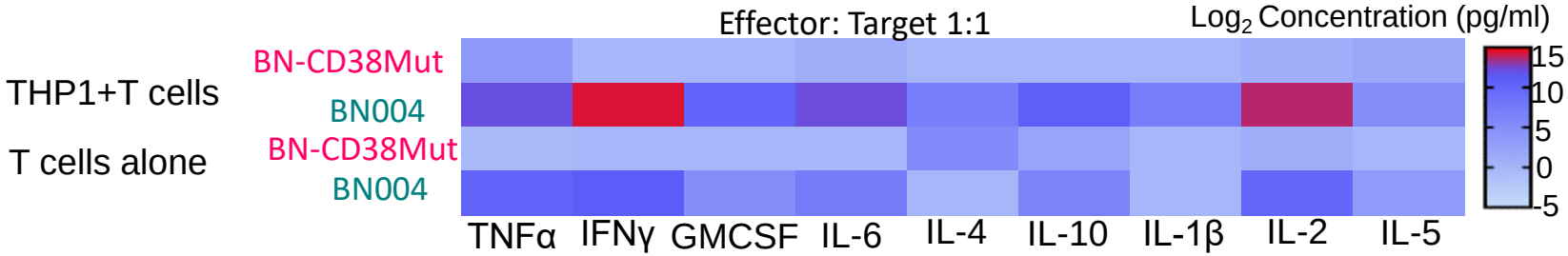
BN004+ CD4+ (IC50=0.3 ng/ml) BN-CD38Mut + CD4+ (IC50=980ng/ml)

BN004+ CD8+ (IC50=0.8ng/ml) BN-CD38Mut + CD8+ (IC50=600ng/ml)









IFN-γ released: 23ng/ml

*in the presence of tumor target cells (upper half of figure)

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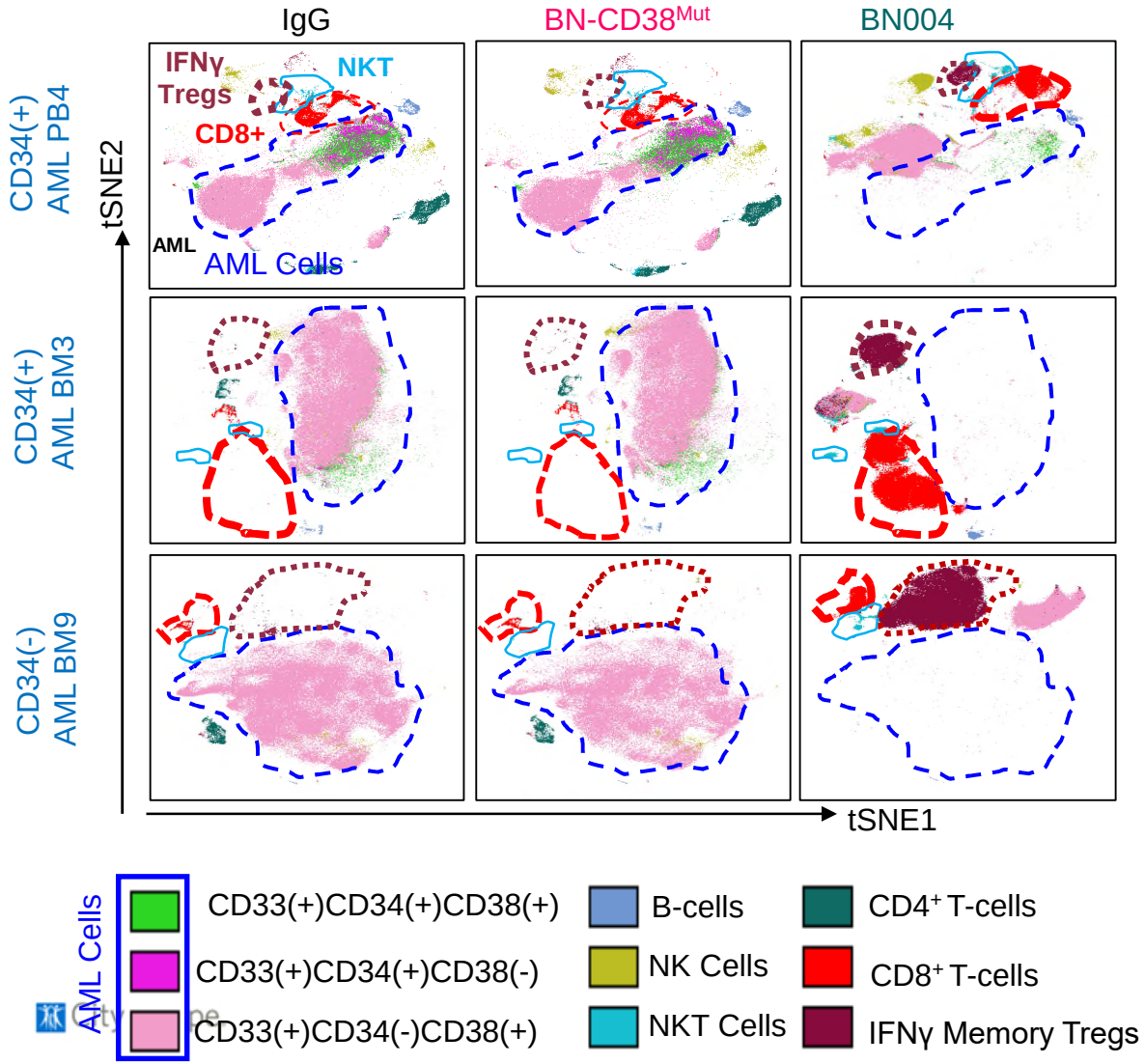
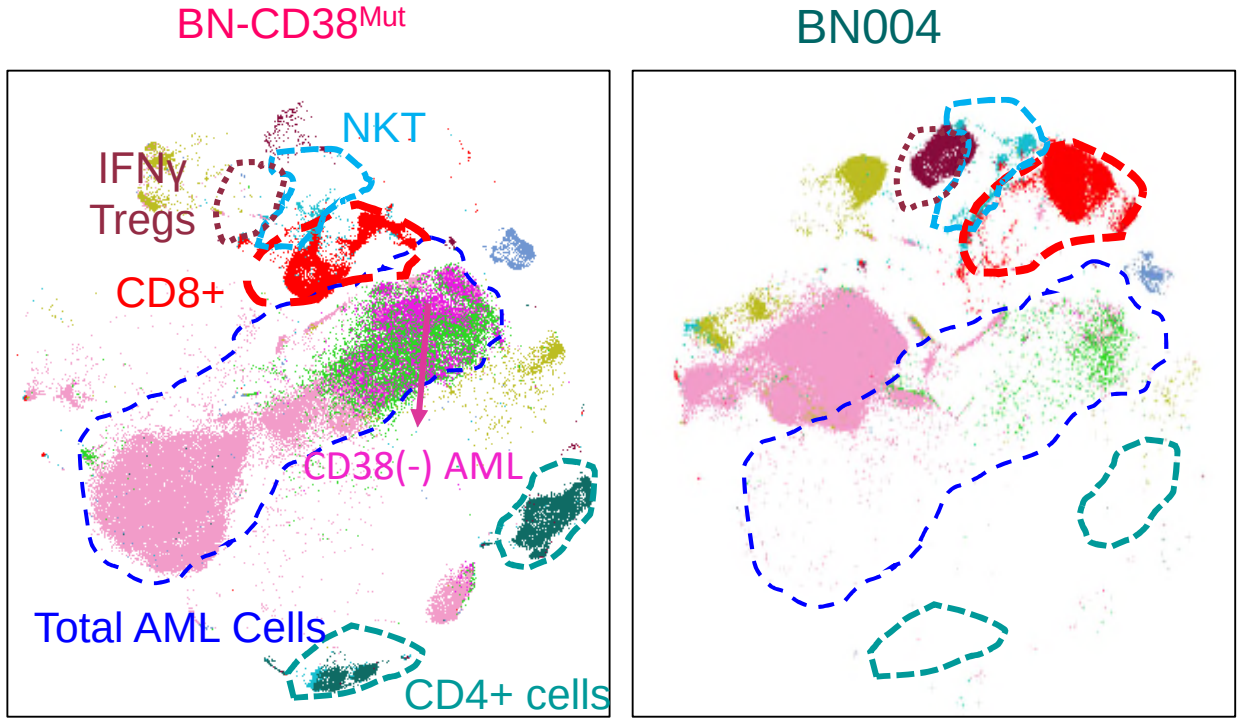
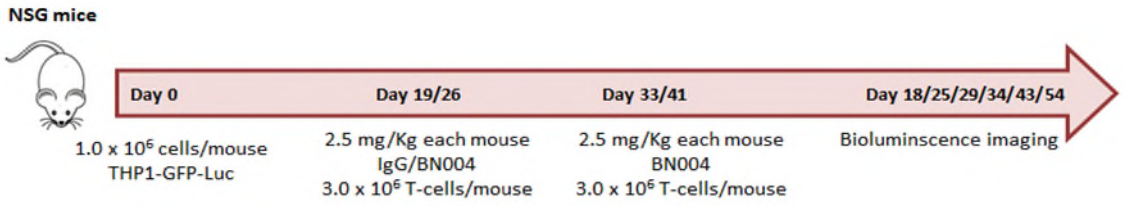
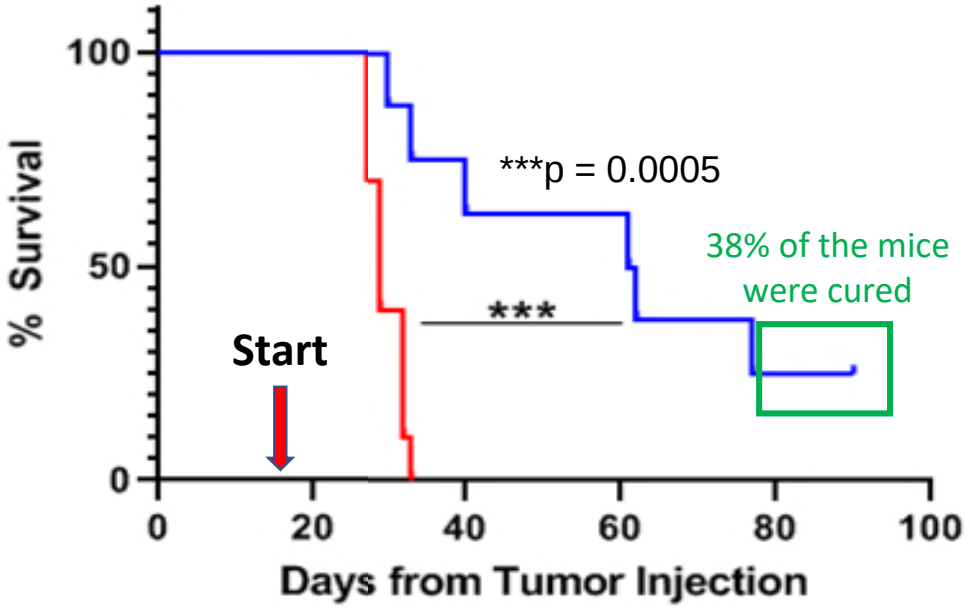
CD38-CD3 bionics kills total total AML cells but not non-CD38+ immune cells





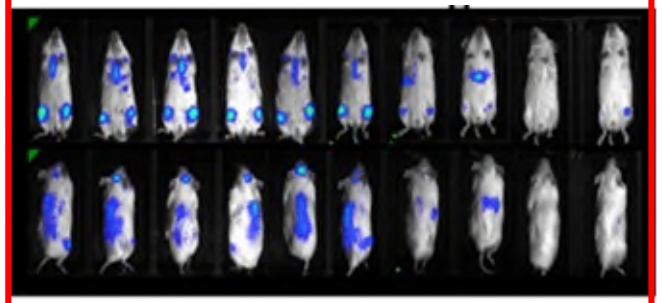
CD38-CD3 BIONIC has strong preclinical activity in AML models



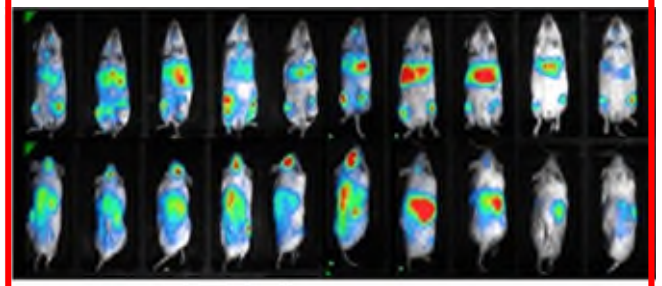


Control IgG

Before Treatment



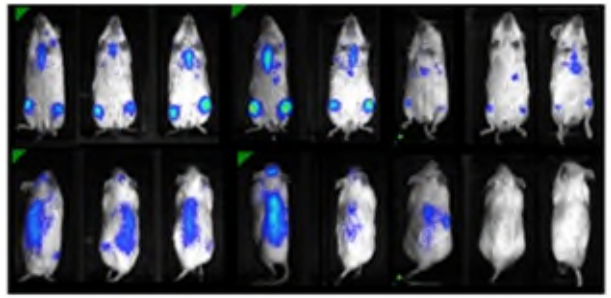
1 week of Treatments



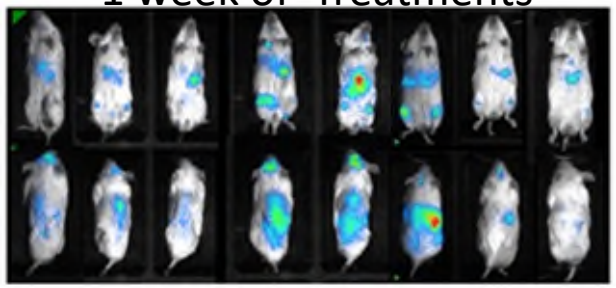
6 weeks of Treatment

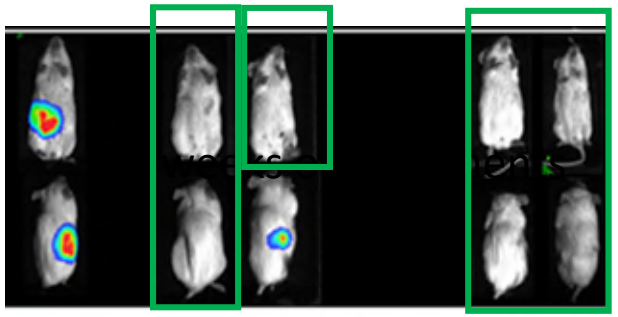
BN004

Before Treatments



1 week of Treatments





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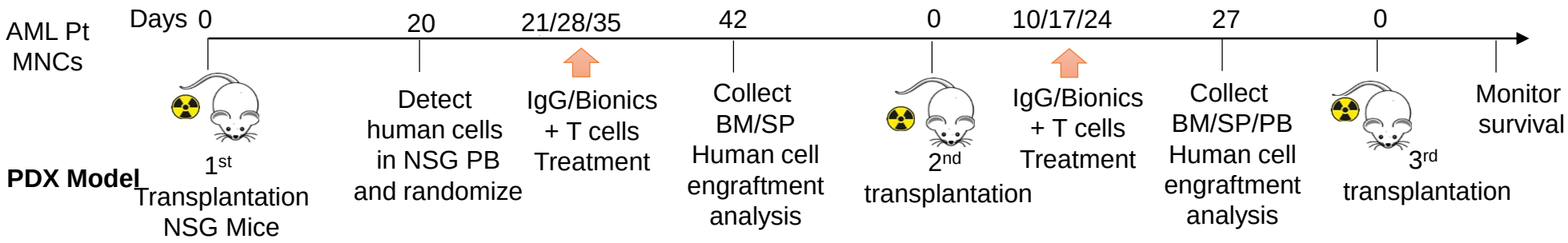
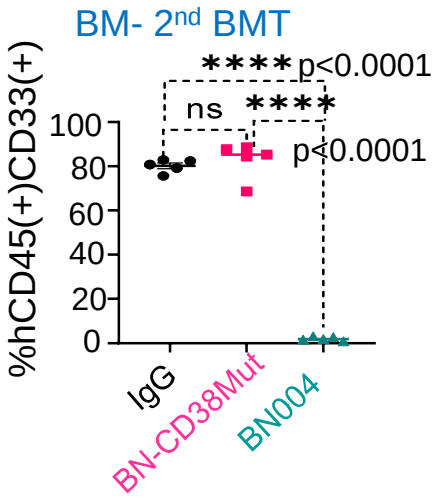
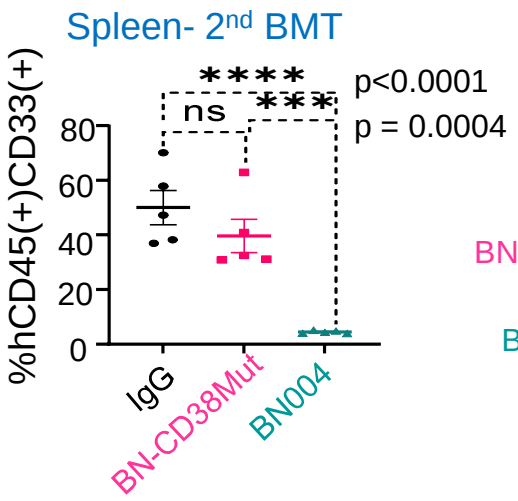
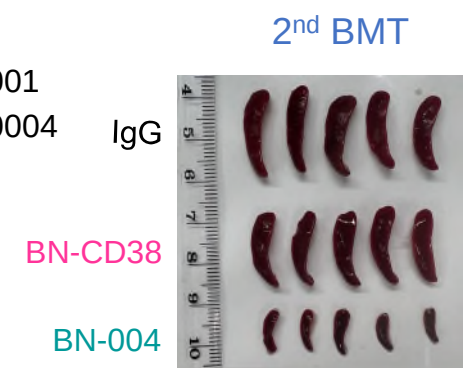
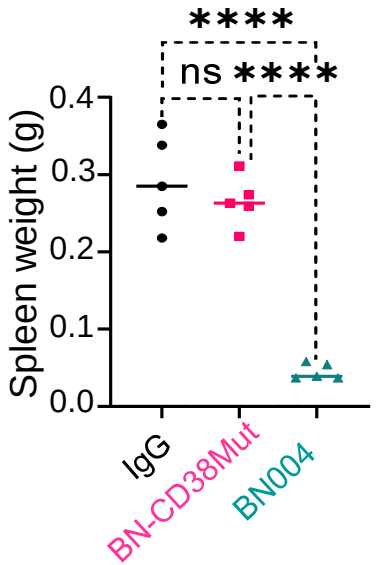
CD38-CD3 bionic eradicates AML in pdx mouse models

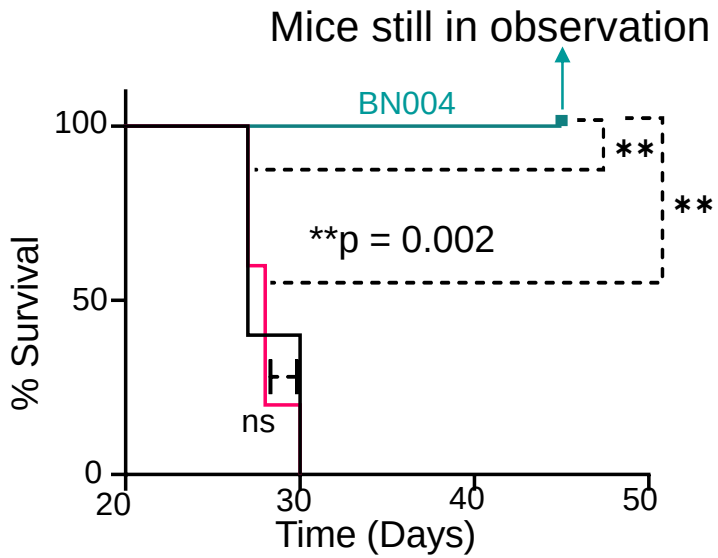












Commercialization/Business Potential

- **CD38 is ubiquitously highly expressed in cancer cells**
  - Hematopoietic: AML, MM, lymphoma and T-ALL
  - Solid tumors: prostate cancer

- **CD38-CD3 Bionics are expected to show single agent activity but could be explored in combination**

- **AML market is $1.46B in 2019**, expected to reach $3.65B in 2027.

  The MM market is expected to reach $20.9B in 2020 but decline to $17B in 2026.

  T-ALL was $132.2M in 2017

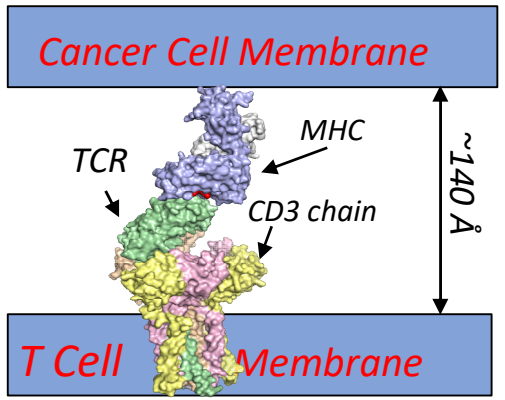
Summary

- Highly innovative molecular architecture, can be expanded to other antigens, other ‘bispecifics’
- Highly effective in vitro and in vivo, kills leukemic stem cells
- IP secured – Bionic Format and cyno/human cross-reactive, humanized aCD3 mAbs, T cell epitope depleted.
- Favorable therapeutic/manufacturing properties (improved melting temp, high expression, single chain expression)
- Extensive biochemical, in vitro and in vivo data (multiple animal models)

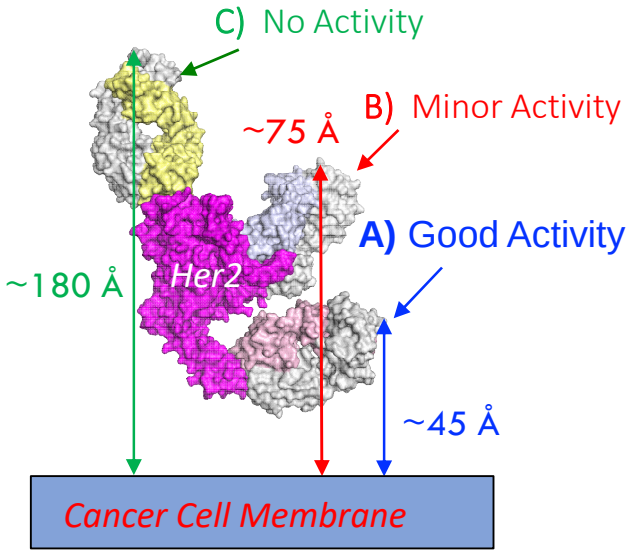
Appendix

Rationale of Design – membrane proximity leads to higher activation

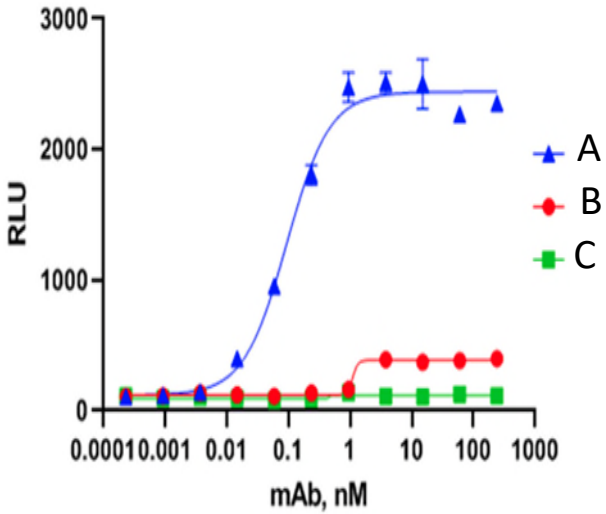
TCR/CD3 Complex
Involved in T Cell activity



Geometry is critical to
achieve effective T cell activation



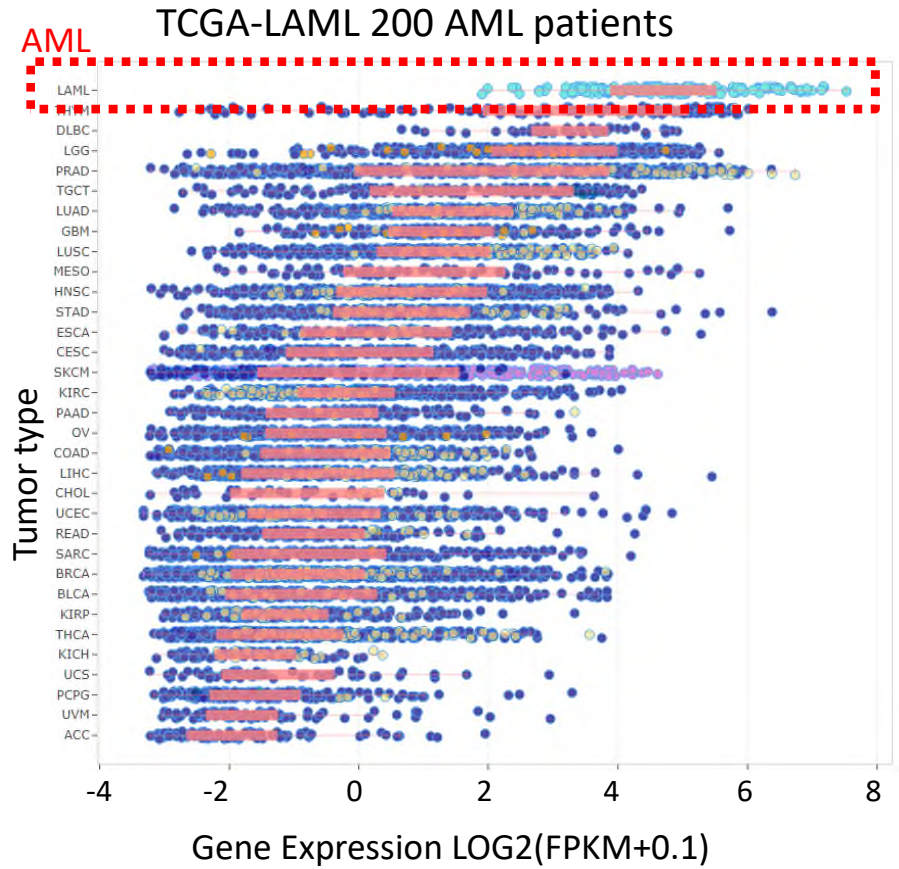
T Cell Activation Assay



Illustrative example on the role of distance to the membrane and T cell activity

Rationale of Antigen – CD38 is highly expressed in AML

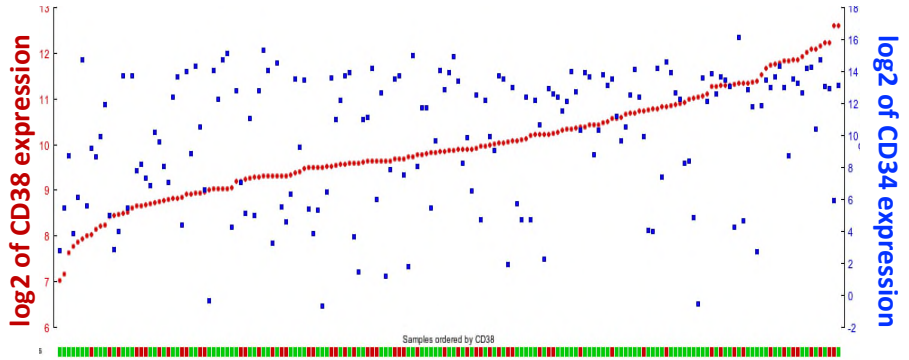
CD38 is the most abundant AML marker



CD38 expression correlates with CD34, one of the most abundant AML markers

Acute Myeloid Leukemia –TCGA-173
Cytogenetic risk groups: favorable, intermediate and poor
Samples obtained from 173 AML patients

CD34 transcript
CD38 transcript



Linear correlation value between CD38 and CD34 is R=0.285
p value=1.47e-04

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