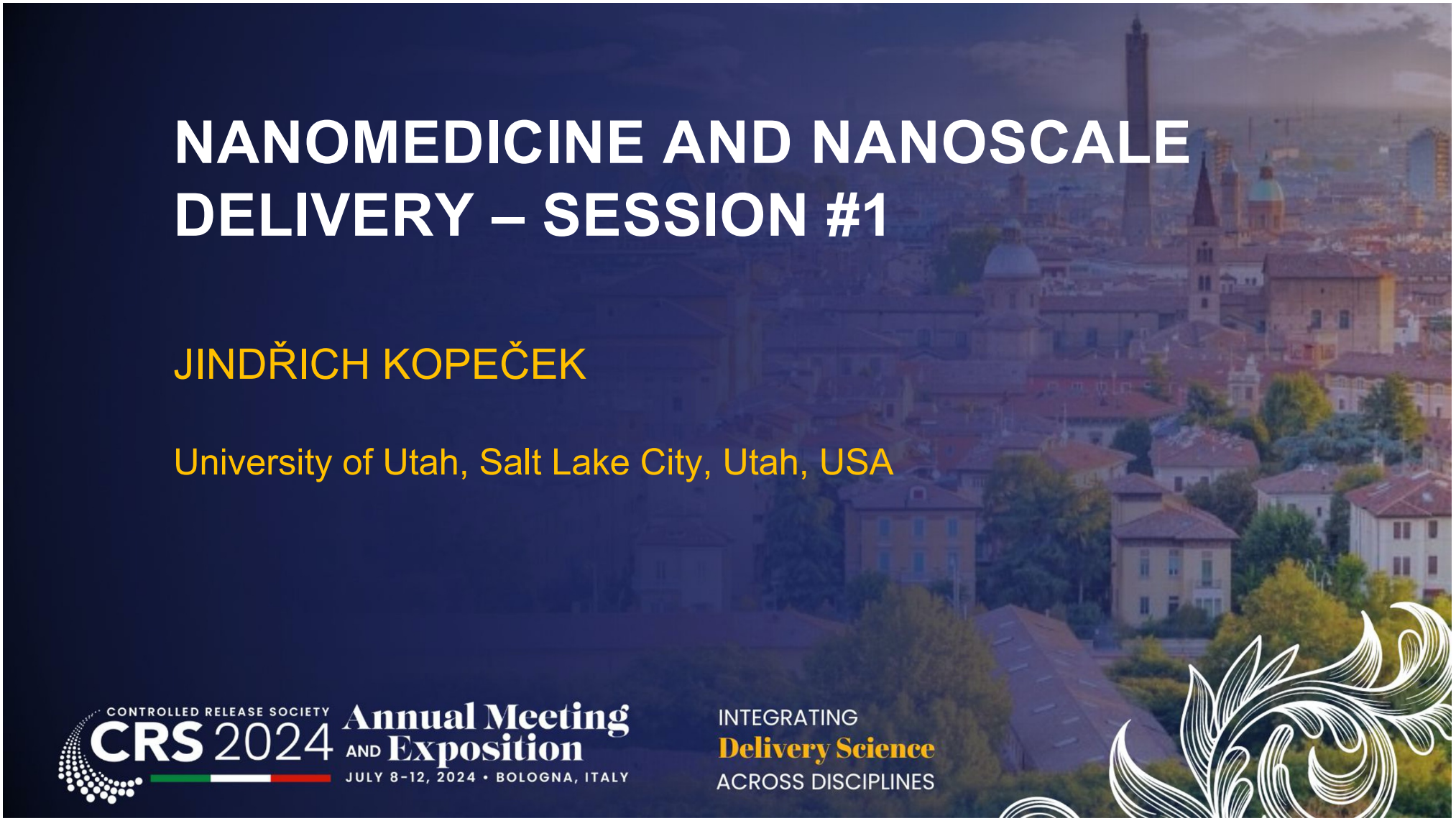
NANOMEDICINE AND NANOSCALE DELIVERY – SESSION #1

JINDŘICH KOPEČEK

University of Utah, Salt Lake City, Utah, USA



DRUG-FREE MACROMOLECULAR THERAPEUTICS

MULTI-ANTIGEN T CELL HYBRIDIZERS

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DRUG-FREE MACROMOLECULAR THERAPEUTICS: A NEW FRONTIER IN NANOMEDICINE

- **BACKGROUND**

  The Emergence of Drug-free Macromolecular Therapeutics

- **DEVELOPMENT OF DFMT**

  Bispecific engager: Fab'$_{B\ cell}$-motif1
  Crosslinking effector: HSA-(motif2)$_x$

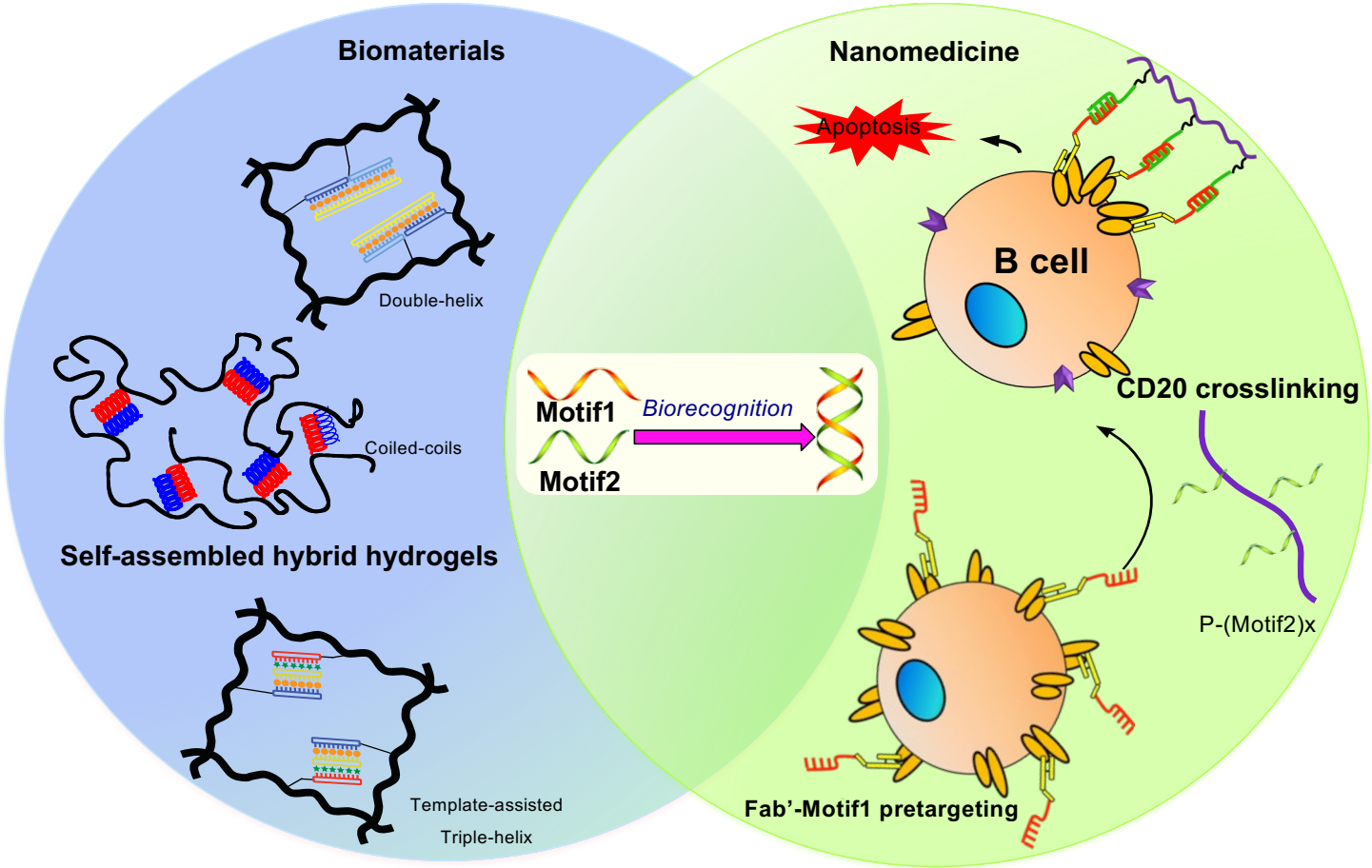
- **MULTI-ANTIGEN T CELL HYBRIDIZERS (MATCH)**

  Fab'$_{B\ cell}$-MORF1 +Fab'$_{T\ cell}$-MORF2

- **FUTURE DIRECTION AND CONCLUSIONS**

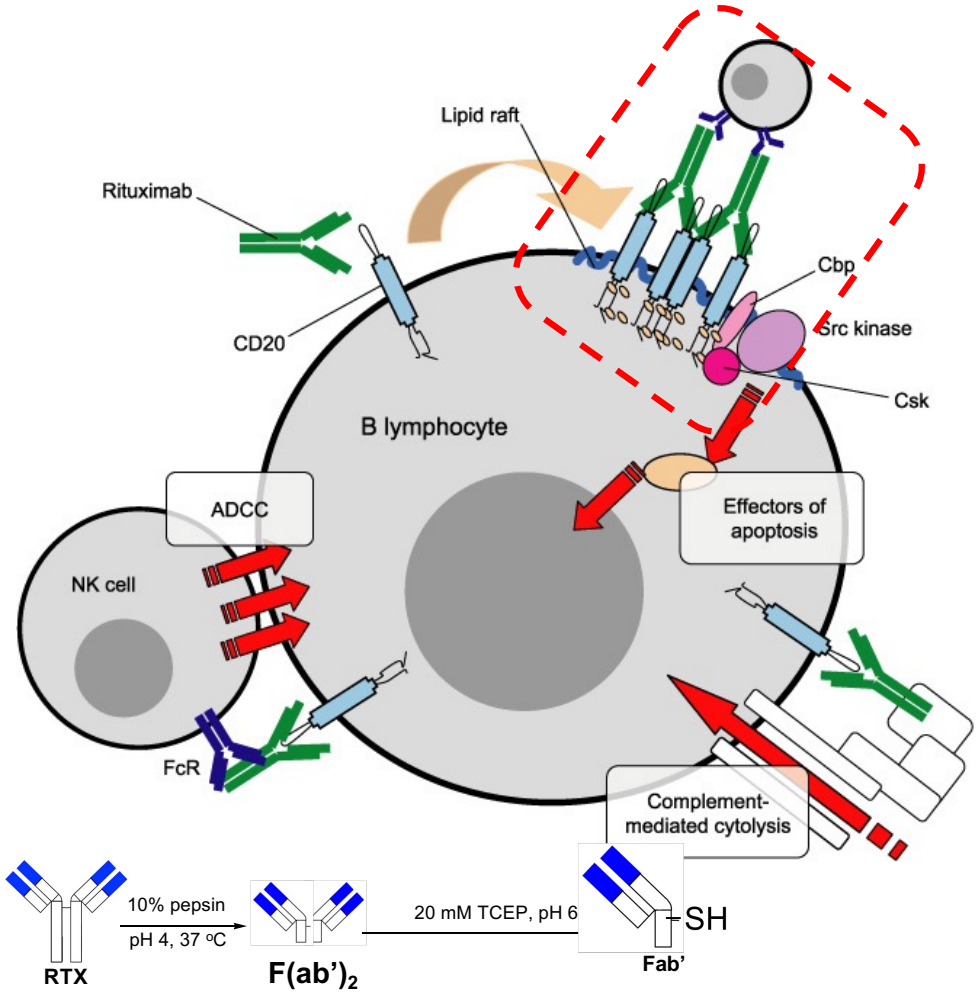
DFMT, *an innovative paradigm for treatment of B cell malignancies*, was generated by **applying biomaterials design attitudes to the design of nanomedicines**

a. Self-assembly of graft copolymers into hydrogels **b. Receptor crosslinking**



Biorecognition - A Key to Drug-free Macromolecular Therapeutics

Rituximab: mAb that has Revolutionized Treatment of Lymphoma

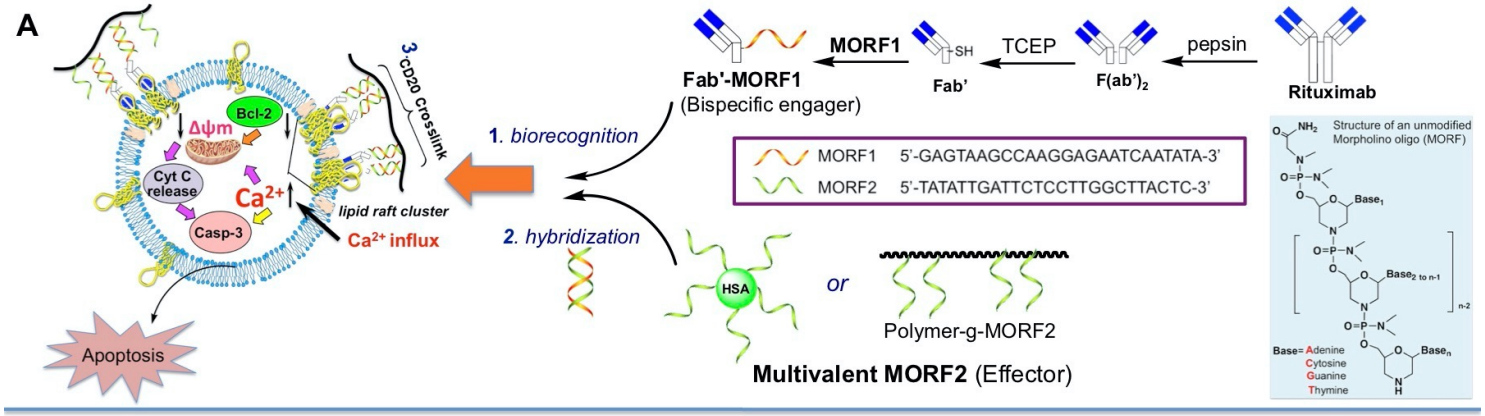


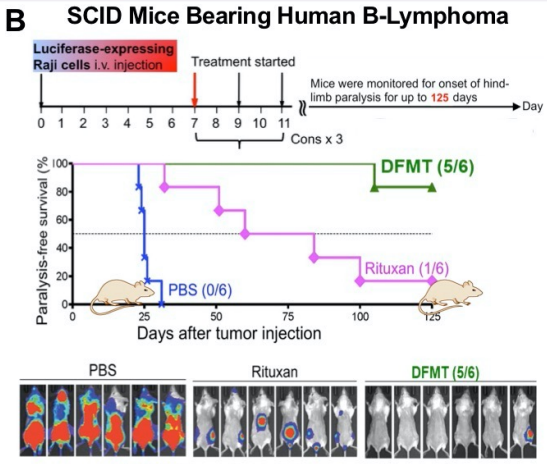
mouse/human chimeric mAb targeting CD20

Fc fragment ~ side effect
~ resistance

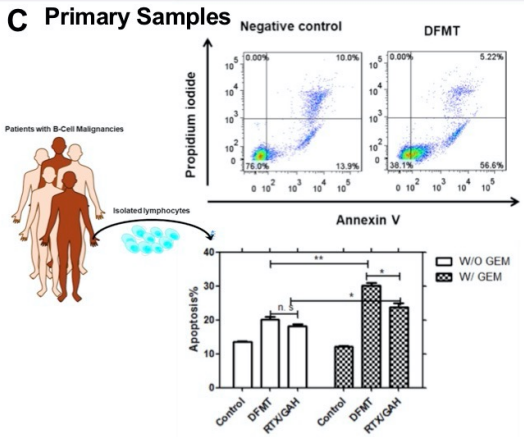
stke.sciencemag.org

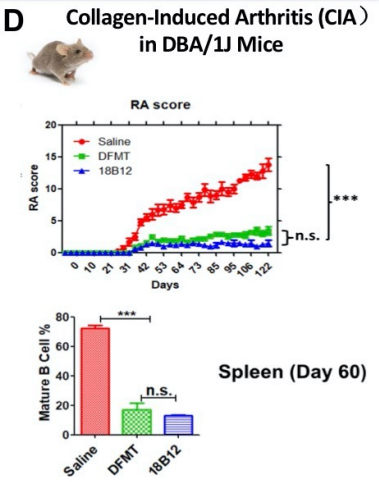
STATE-OF-THE-ART OF DRUG-FREE MACROMOLECULAR THERAPEUTICS (DFMT)





IVIS imaging taken on Day 25.





T.W. Chu et al., ACS Nano 8, 719 (2014)
T.W. Chu et al., Theranostics 5, 834 (2015)
J. Wang et al., Nanomedicine 16,217 (2019)
J. Wang et al., Macromol. Biosci. 1900445 (2020)

High-risk mutations such as 17p13 and 11q22 deletions, usually considered as poor prognostic factors in CLL, did not hamper the therapeutic efficacy of DFMT treatment.

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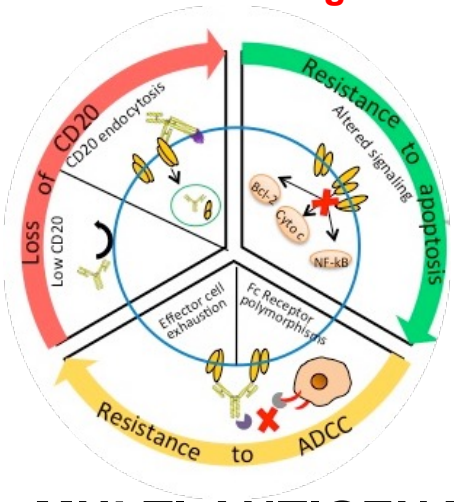
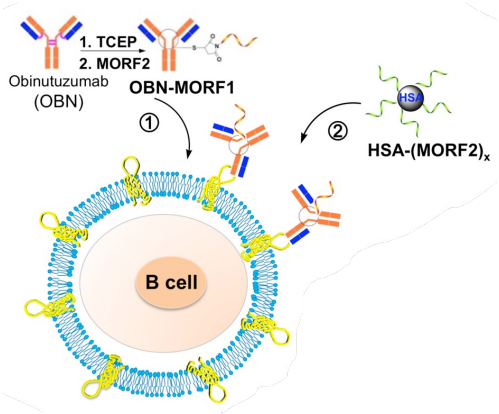
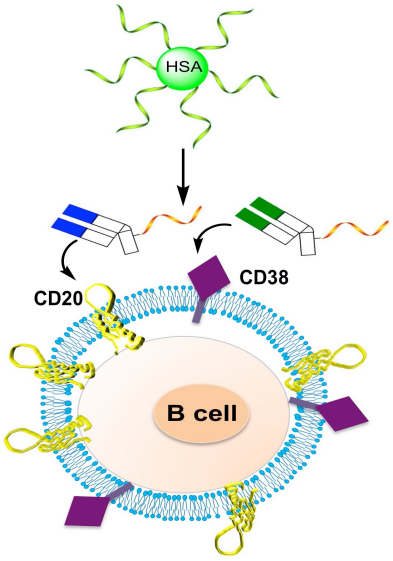




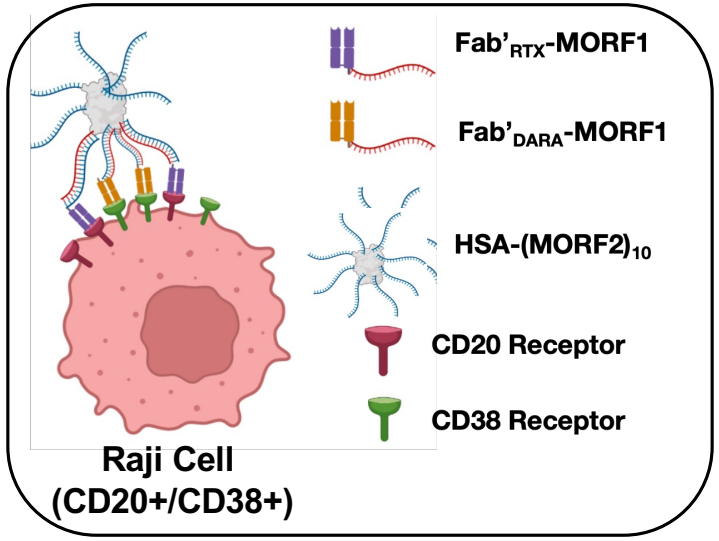


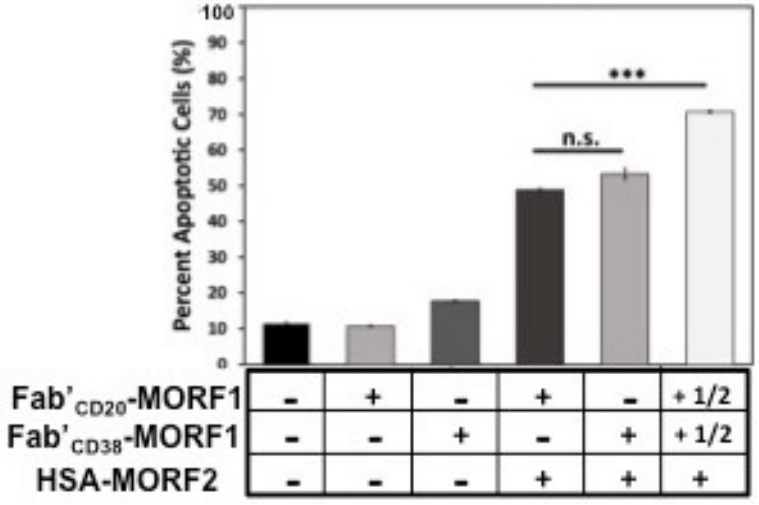
- **MULTI-ANTIGEN T CELL HYBRIDIZERS (MATCH)**

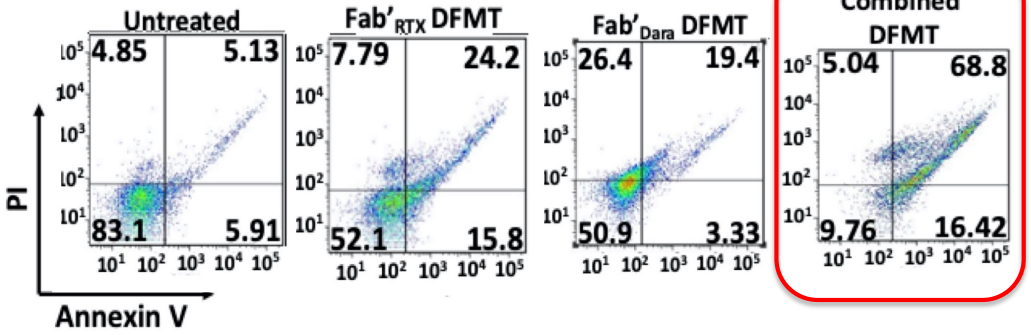
  Fab'$_{B\ cell}$-MORF1 +Fab'$_{T\ cell}$-MORF2

- **FUTURE DIRECTION AND CONCLUSIONS**

DUAL RECEPTOR CROSSLINKING IS MORE EFFICIENT





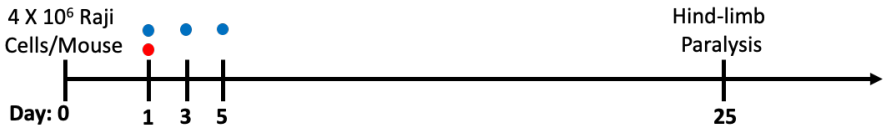


Half concentration of each treatment combined induced higher apoptosis levels than full concentration of each treatment individually.

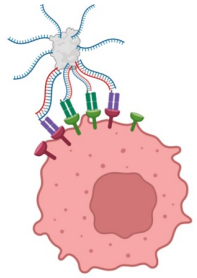
M.T. Gambles et al., J. Controlled Release 350, 584 (2022)

HIGH EFFICACY OF DUAL-TARGET CROSSLINKING IN HUMAN XENOGRAFT MOUSE MODEL OF DISSEMINATED LYMPHOMA

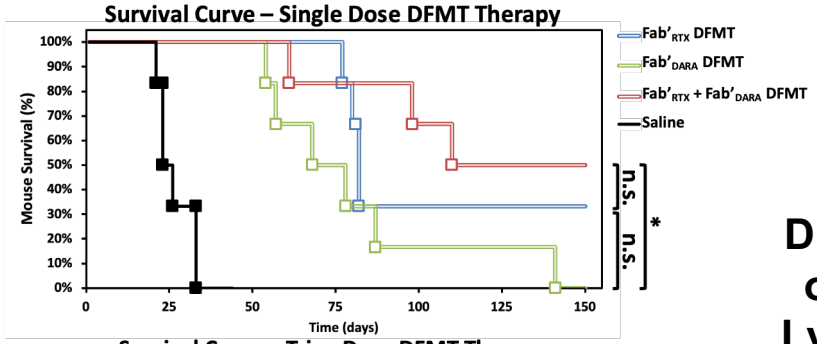
F C.B-17 SCID

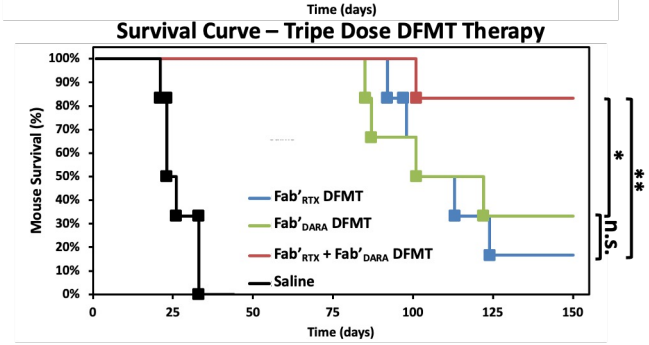


α-CD38	α-CD20	α-CD38 + α-CD20
Fab'$_{DARA}$ DFMT	Fab'$_{RTX}$ DFMT	Fab'$_{DARA}$ + Fab'$_{RTX}$ DFMT
Single Dose Triple Dose	Single Dose Triple Dose	Single Dose Triple Dose



HSA-(MORF2)$_{10}$





Dual-Target DFMT on CD20$^+$/CD38$^+$ Lymphoma Mouse Model

M.T. Gambles et al., J. Controlled Release 350, 584-599 (2022)

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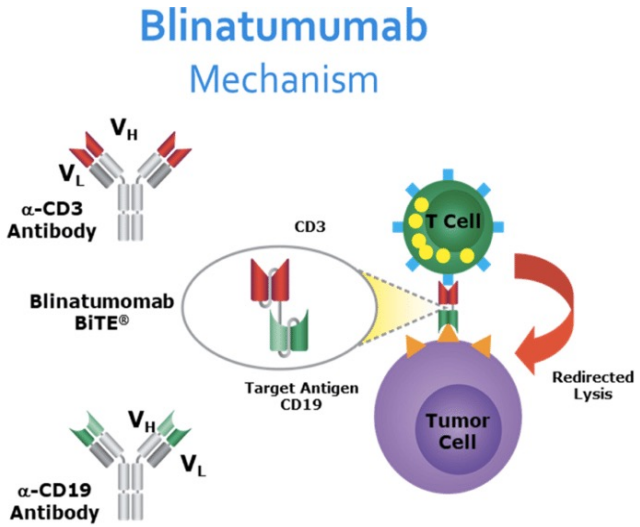
- **FUTURE DIRECTION AND CONCLUSIONS**

T Cells, Cancer Cells, and BiTEs

Bispecific T-cell engager antibody

Designed to direct cytotoxic T cells to CD19 expressing cancer cells

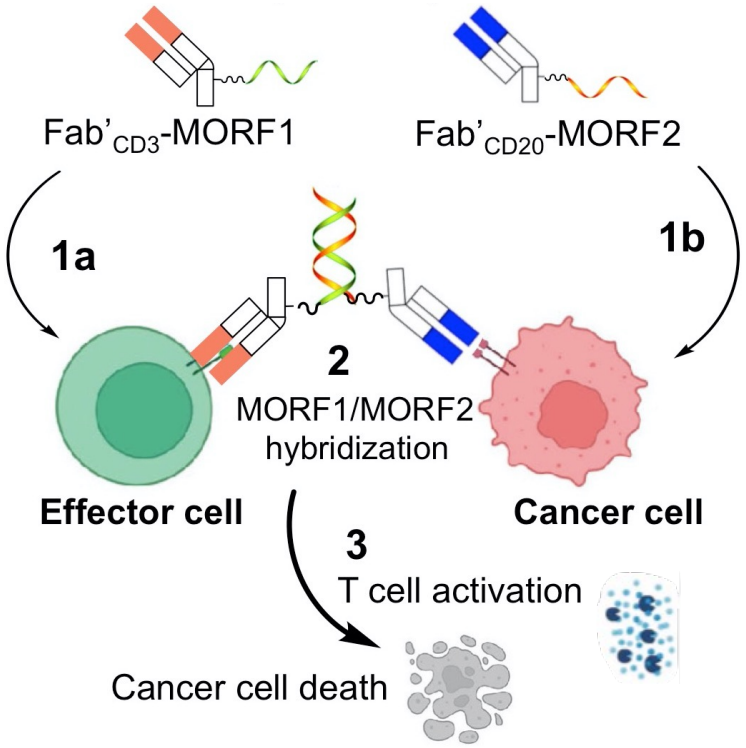


Teclistamab

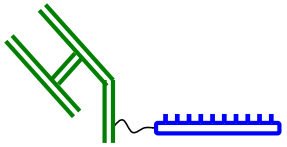
Designed to direct cytotoxic T cells to BCMA* expressing cancer cells

** B cell maturation antigen*

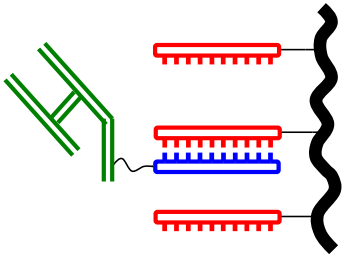
M. Sanford, Drugs 75, 321 (2015)

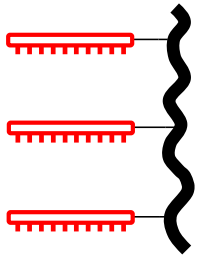


From DFMT to MATCH



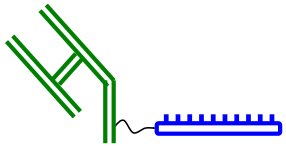
Fab'-MORF1



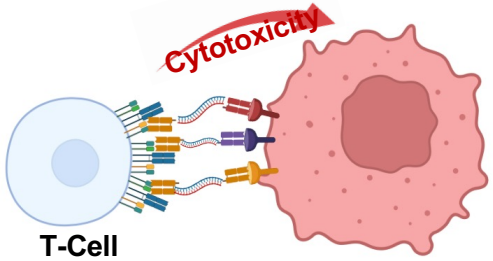


P-(MORF2)$_x$

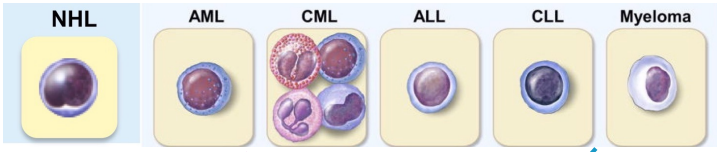
MULTI-ANTIGEN T CELL HYBRIDIZERS (MATCH)

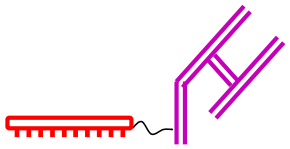


Fab'$_{CD3}$-MORF2

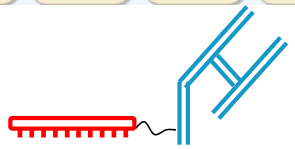


Hematological malignancies and surface markers

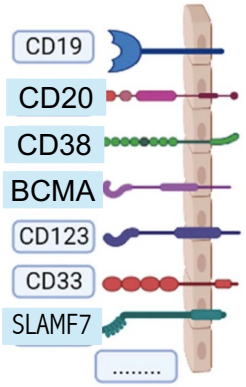


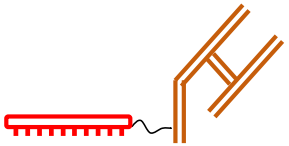


Fab'$_{CD20}$-MORF1

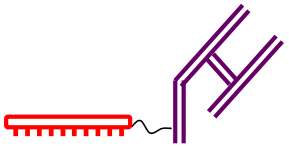


Fab'$_{BCMA}$-MORF1



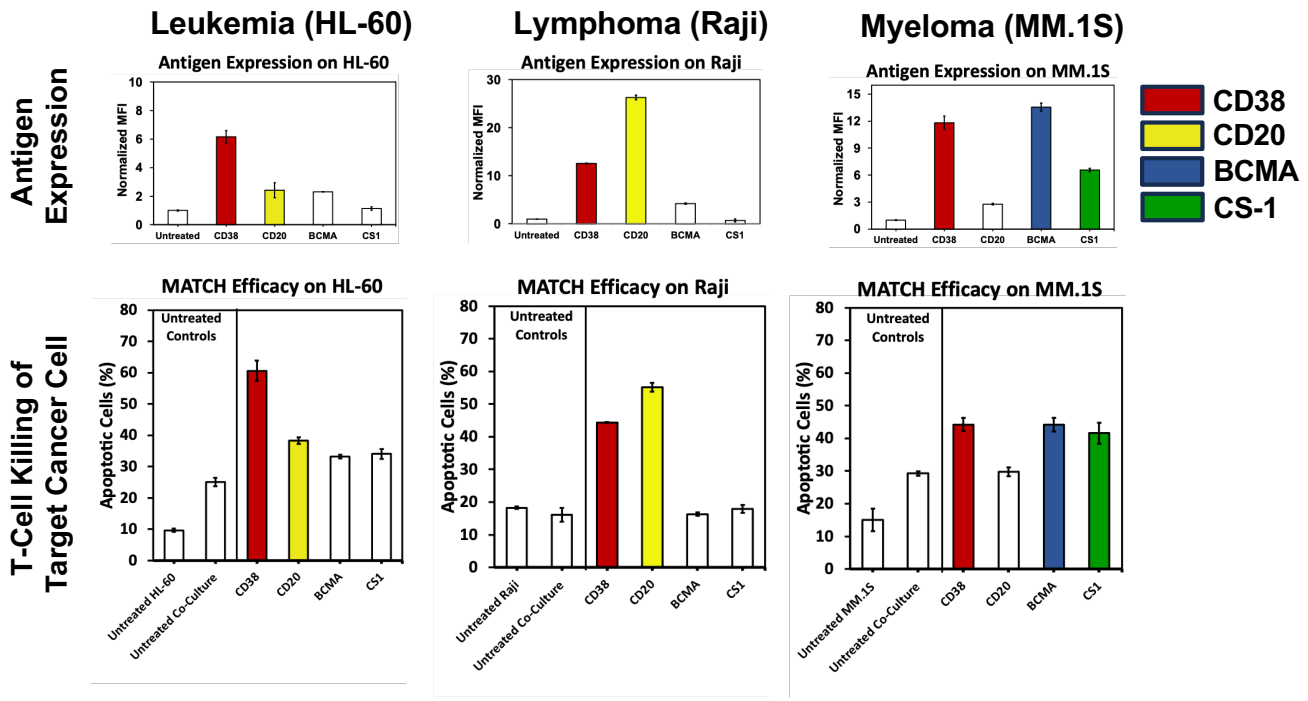


Fab'$_{CD38}$-MORF1



Fab'$_{SLAMF7}$-MORF1

MATCH Induces Antigen-Specific T-Cell Activation on B-Cell Cancers

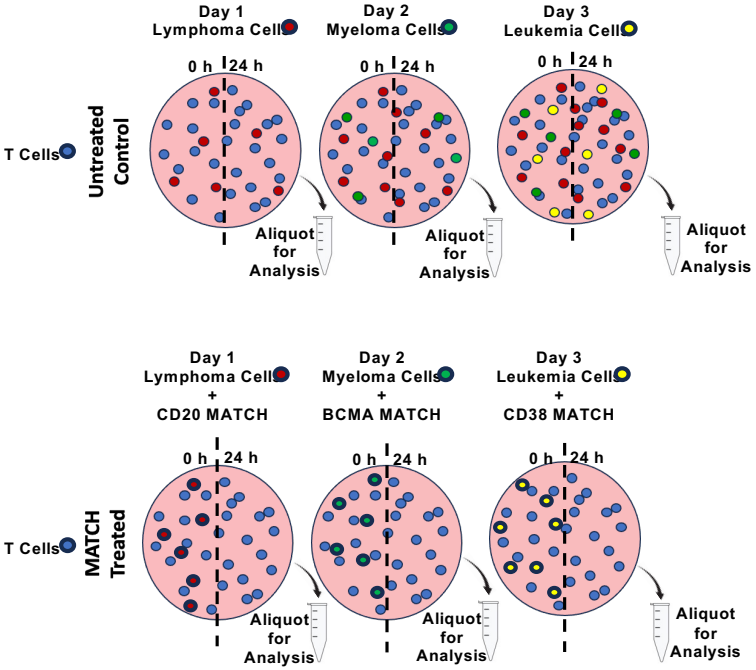


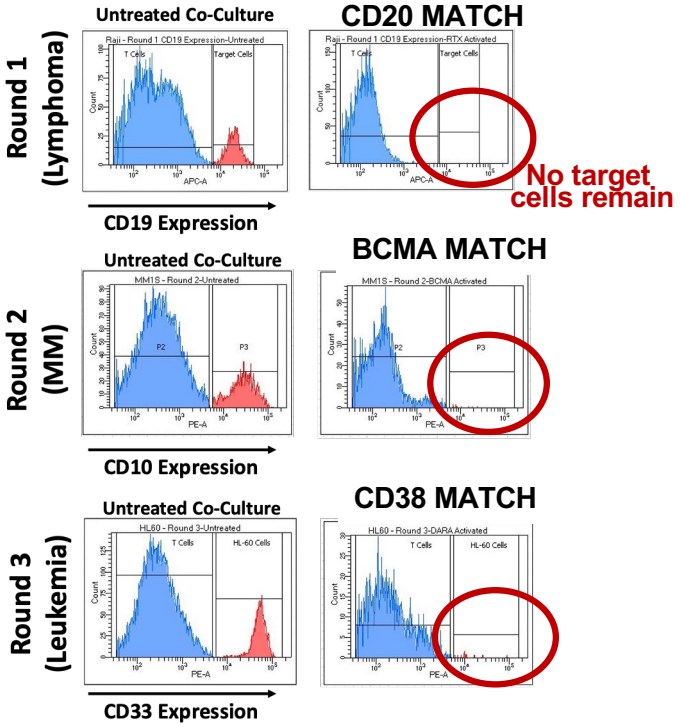
T-cell activation and cytotoxicity is achievable on an antigen-specific basis against three different B-cell cancers: leukemia, lymphoma, and multiple myeloma.

Unpublished

Challenging T-Cells with Three Different B-Cell Cancers

The same cohort of T-cells killed three different malignancies, consecutively





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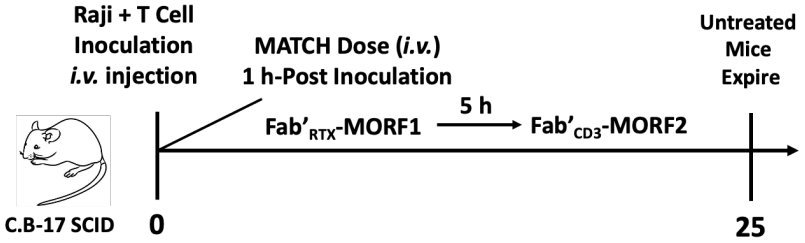
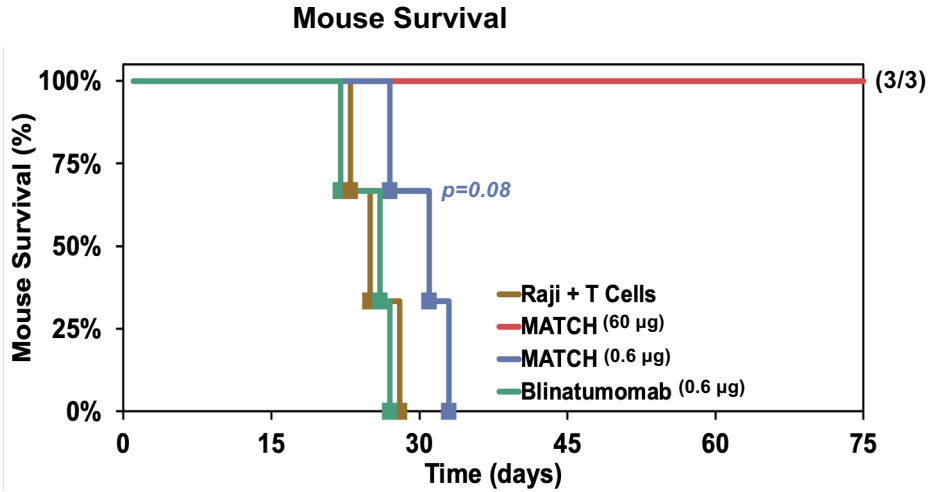
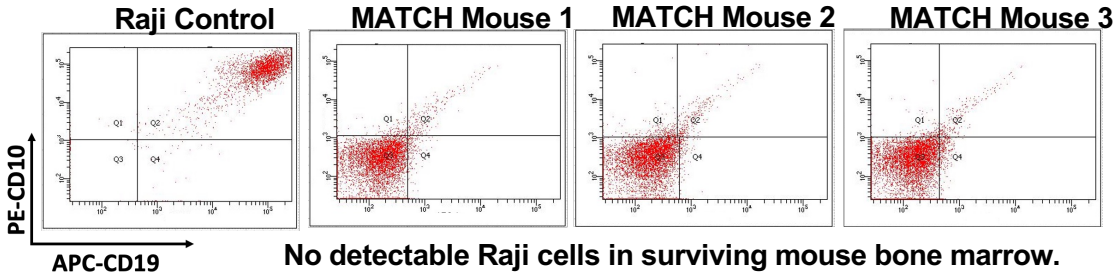
CD20-Directed MATCH Efficacy *In Vivo* – Pilot Efficacy Study



A single dose of CD20-directed MATCH cured 3/3 mice





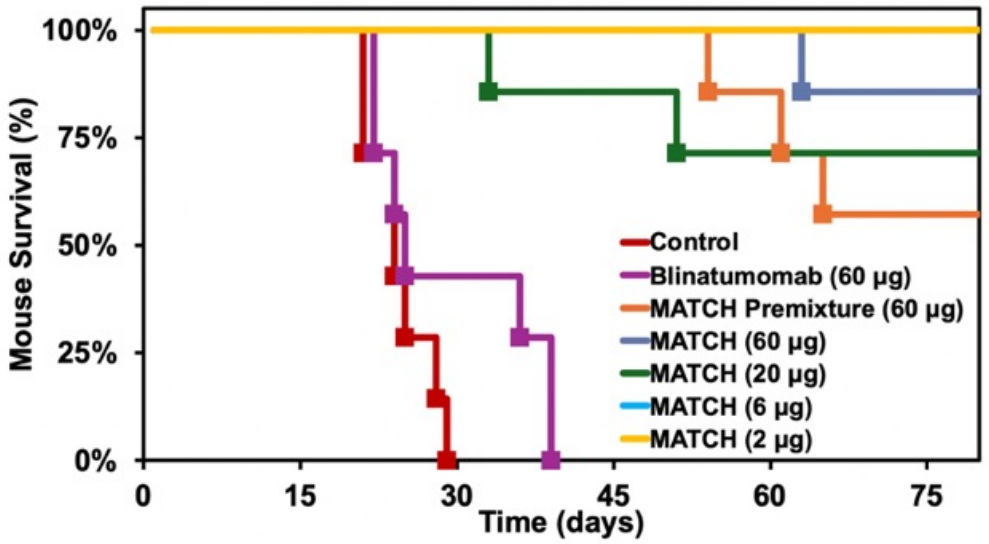
No detectable Raji cells in surviving mouse bone marrow.

Unpublished

MATCH: In vivo evaluation of optimal T cell engager dose

Comparison of Blinatumomab with MATCH: Fab'$_{RTX}$-MORF1 + Fab'$_{CD3}$-MORF2

Hypothesis: A lower dose of the T cell engager (lower than 1-to-1 MORF1/MORF2) will be more efficacious.

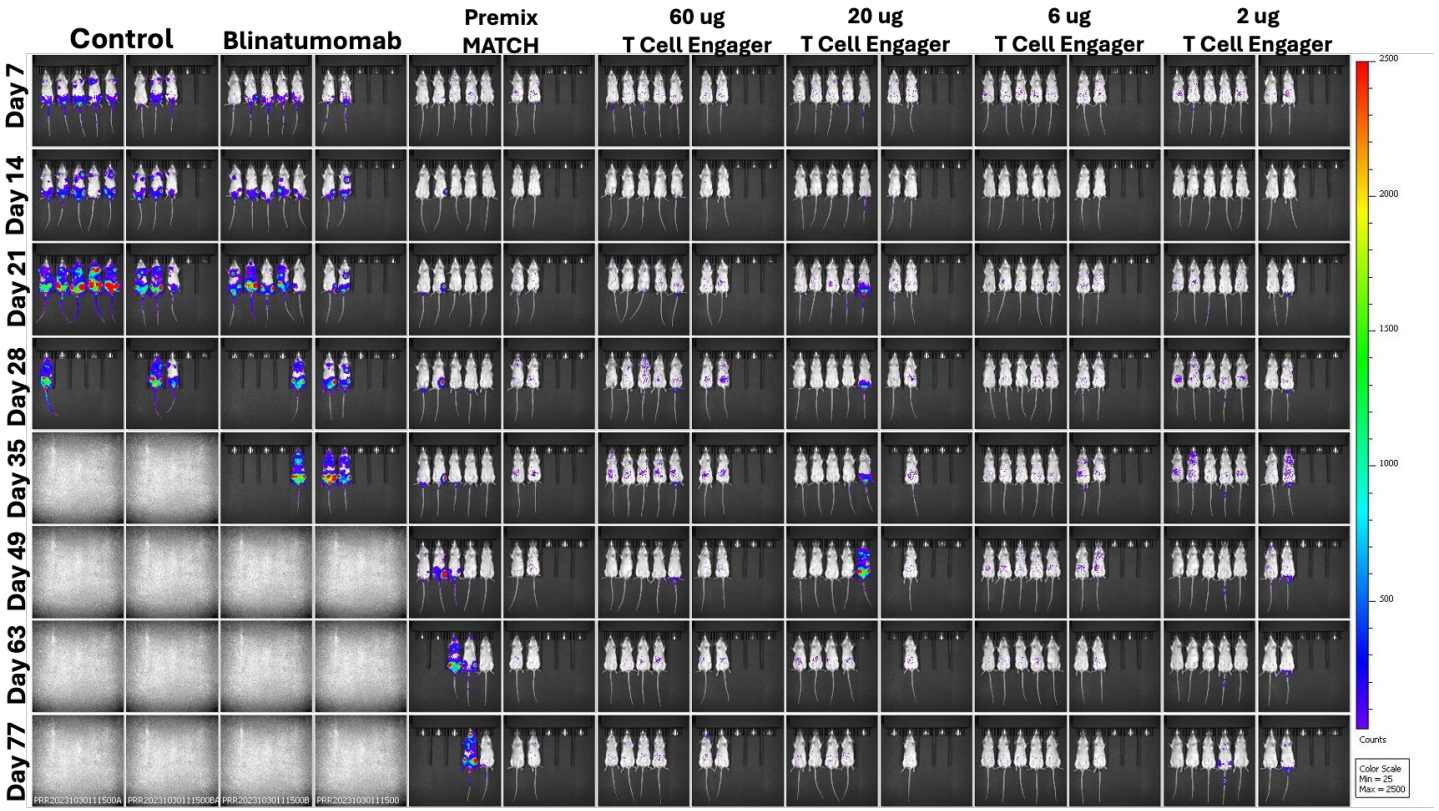


C.B-17 SCID mice, Raji-Luc cells, consecutive administration: 1 nmol Fab'$_{RTX}$-MORF1 + 5 h later 1 nmol Fab'$_{CD3}$-MORF2

Groups of mice were given different concentrations of T-cell engager (Fab'$_{CD3}$-MORF2). CD20-directed MATCH was also compared to blinatumomab administered as a single, 60 µg bolus *i.v.* injection.

Unpublished

Fab'$_{CD3}$-MORF2 Dose Optimization *In Vivo*



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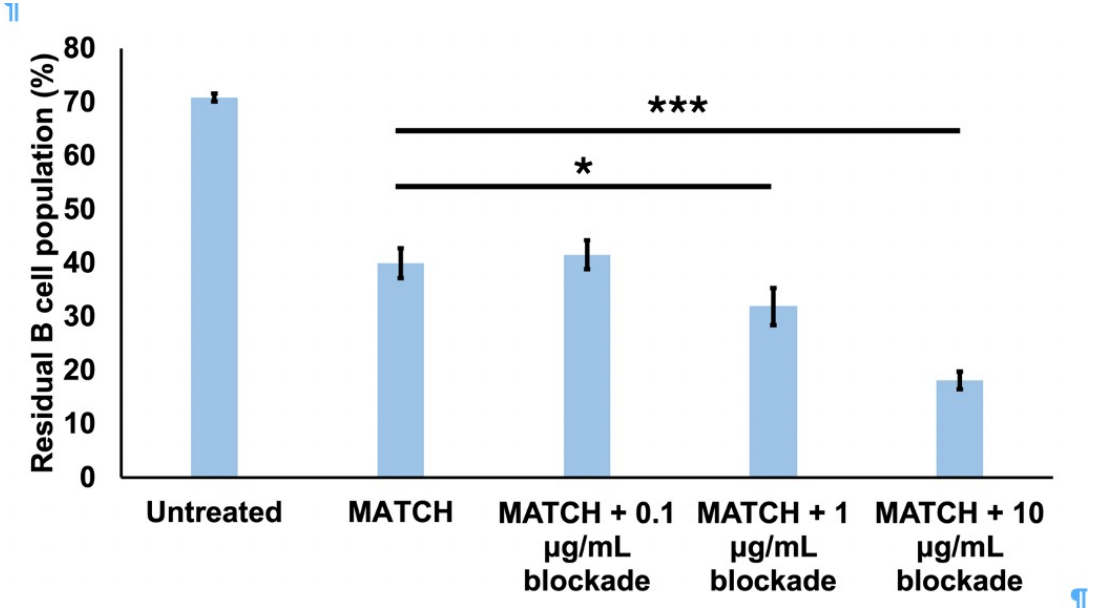
B CELL RESIDUAL POPULATIONS FOLLOWING SIMULTANEOUS MATCH TREATMENT AND IL-10 BLOCKADE

T cell exhaustion is a dysfunctional state wherein T cells demonstrate reduced cytotoxic capacity, is a significant hurdle for T cell-mediated cancer clearance. Surface markers of T cell exhaustion include PD-1, TIM3, LAG3, TIGIT, CTLA-4. Reduction of exhaustion: blockade of PD-1, TIM3, IL-10.



IL-10 blockade attenuates exhaustion and improves rates of B cell ablation.

Co-culture (48 h) in 24-well plate seeded with 50,000 T cells and 150,000 B cells per well in 800 µL RPMI medium. Samples were treated with 50 nM Fab'$_{RTX}$-MORF1 and 50 nM Fab'$_{CD3}$-MORF2. Experimental groups were treated with 0.1, 1.0, or 10 µg/mL of αIL-10 monoclonal Ab.

Unpublished

Conclusions and Future Directions

- Drug-free macromolecular therapeutics (DFMT) represent a promising avenue for developing highly specific, effective and safer treatments.
- MATCH involves the creation of a cancer B cell targeting mini-library based on the antigen profile on target cells that dimerize with T cell engaging conjugate.
- Further research will focus on optimization of MATCH multi-target therapeutic approaches for the treatment of lymphomas, multiple myelomas, and leukemias.
- Development of Personalized Medicine based on individual patient disease profiles.

THANKS TO ALL MY COWORKERS AND COLLABORATORS

CURRENT JK LAB MEMBERS

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Isaac Kendell, MS Student
Lara Schlickmann, UG Student
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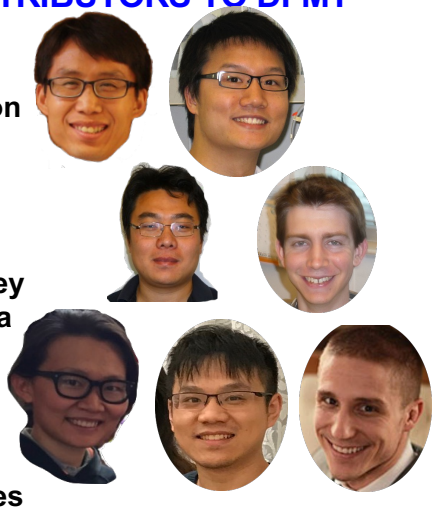
Dr. Rui Zhang
Dr. Jiawei Wang
Dr. Chris Radford
Dr. Lian Li
Dr. Tommy Gambles



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