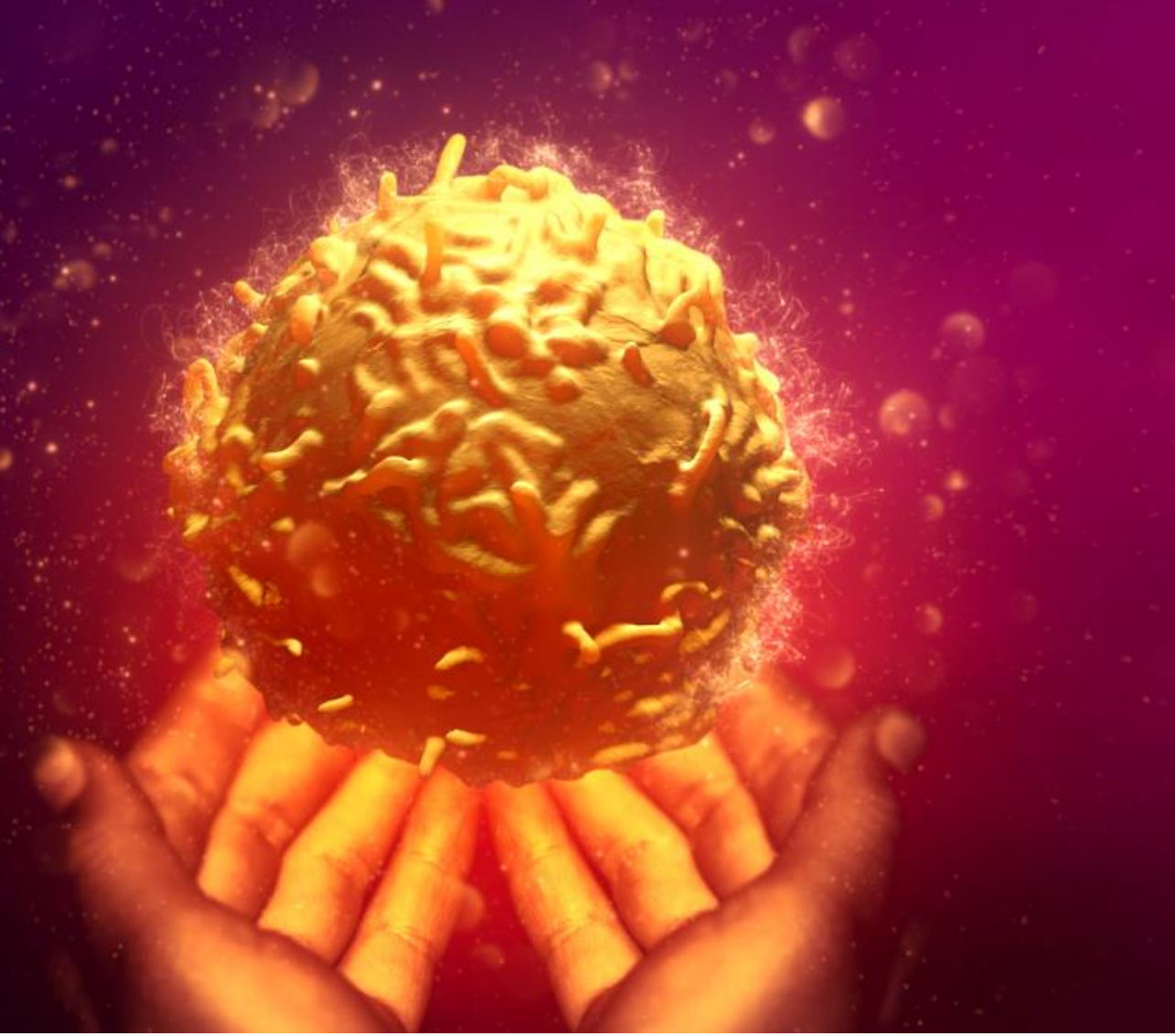
MyD88/CD40 (MC) Enhances Chimeric Antigen Receptor Natural Killer (CAR-NK) Cell Proliferation, Cytokine Release and Anti-Tumor Efficacy Against BCMA^{+} Tumors



Henri Bayle, PhD

ASGCT Annual Meeting

May 2020

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Forward Looking Statement

This presentation contains estimates, projections and other forward-looking statements, concerning, among other things: our research and development activities relating to our GoCAR™ (incorporating “iMC”), GoCAR-T® CaspaCIDe® (“iC9”), and related technologies; our product candidates including BPX-601, BPX-603, OTS GoCAR-NK, and rimiducid; the timing and success of our current and planned clinical trials, including the timing of receipt of data from such clinical trials and the timing of our reports of such data; our plans regarding interactions with the FDA related to the IND submitted for BPX-603; the possible range of applications of our cell therapy programs and potential curative effects and safety in the treatment of diseases, including as compared to other treatment options and competitive therapies; and the success of our collaborations with academic and commercial partners, including with respect to our manufacturing facility. Our estimates, projections and other forward-looking statements are based on our management's current assumptions and expectations of future events and trends, which affect or may affect our business, strategy, operations or financial performance. Although we believe that these estimates, projections and other forward-looking statements are based upon reasonable assumptions, they are subject to numerous known and unknown risks and uncertainties and are made in light of information currently available to us. Many important factors, in addition to the factors described in this presentation, may adversely and materially affect our results as indicated in forward-looking statements. All statements other than statements of historical fact are forward-looking statements.

Estimates, projections and other forward-looking statements speak only as of the date they were made, and, except to the extent required by law, we undertake no obligation to update any forward-looking statement. These statements are also subject to a number of material risks and uncertainties that are described more fully in Bellicum’s filings with the Securities and Exchange Commission, including without limitation our annual report on Form 10-K for the year ended December 31, 2019 and our quarterly report on Form 10-Q for the period ended March 31, 2020.

Building a next generation cell therapy pipeline around the GoCAR platform

GoCAR Platform

Differentiated co-activation domain (MyD88/CD40) and switch technology drive greater proliferation, persistence, power, and performance

BPX-601

- Autologous GoCAR-T targeting PSCA in pancreatic cancer
- Phase 1/2 enrolling
- Data updated ASCO-GI Jan, 2020

BPX-603

- Autologous dual-switch GoCAR-T targeting HER2 in solid tumors
- Update on IND status expected Q3 2020

GoCAR-NK Program

- First off-the-shelf (OTS) GoCAR program BCMA
- Formal preclinical targeting development initiated

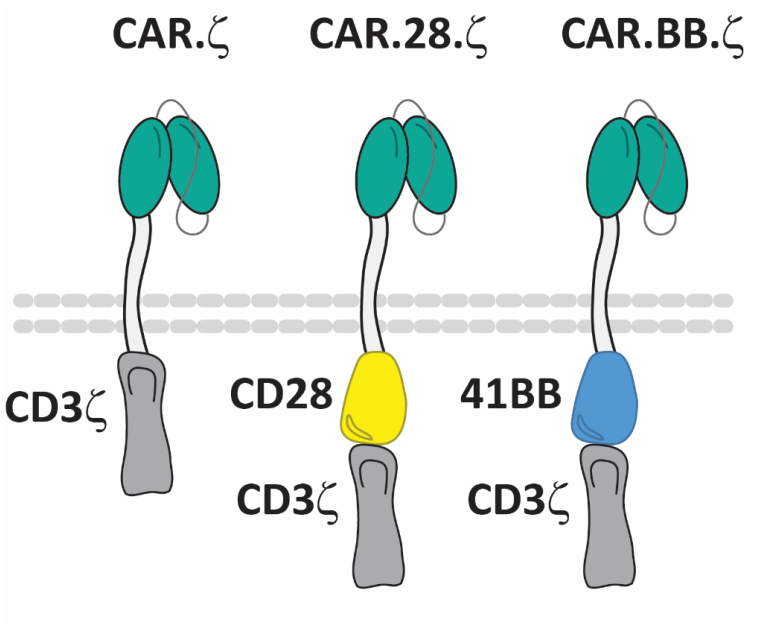
Foster et al., *Mol. Ther., 2017*

Duong et al, *Mol. Ther. Onc., 2018*

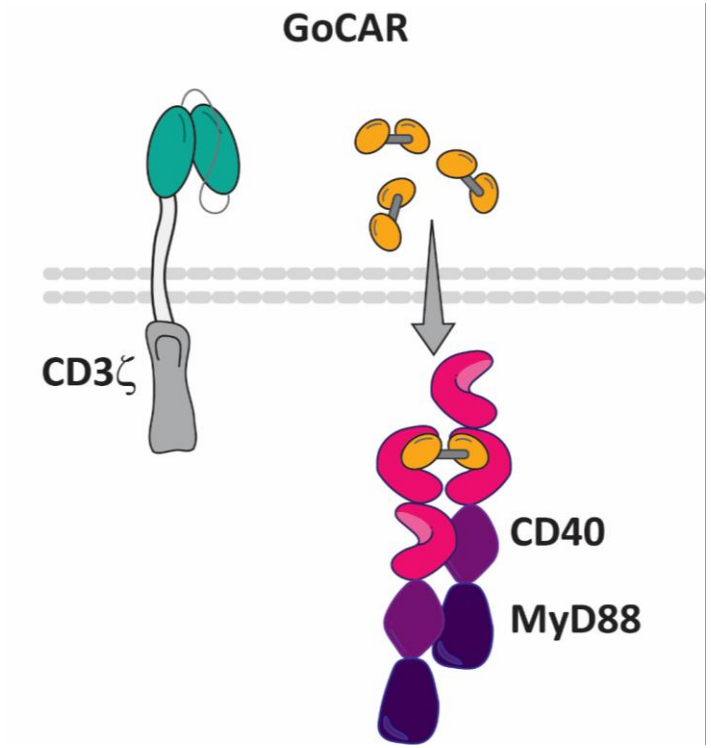
Wang et al., *Blood Advances 2020*

GoCAR: An inducible stimulation platform

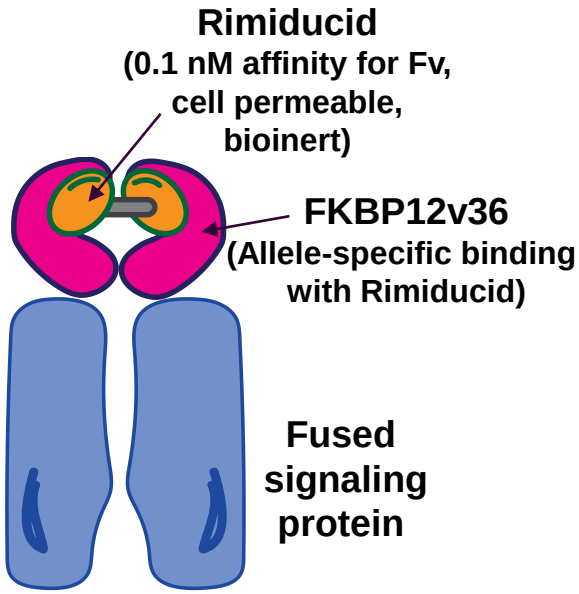
Current Generation CAR Technology



Next Generation GoCAR Technology

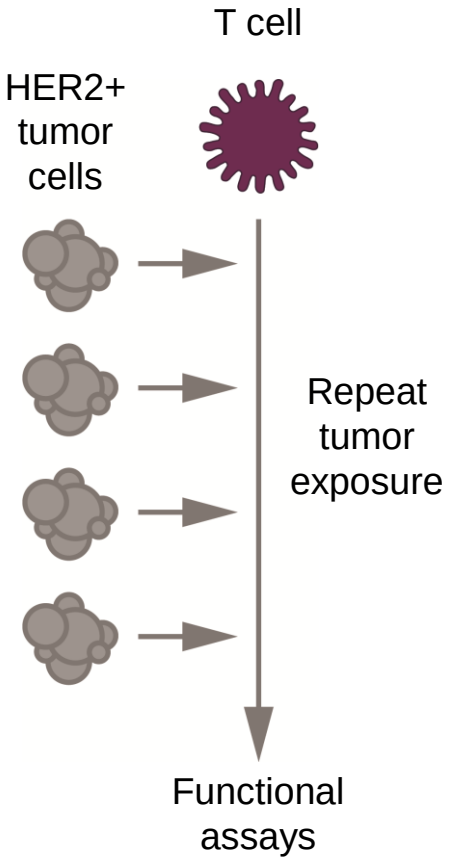


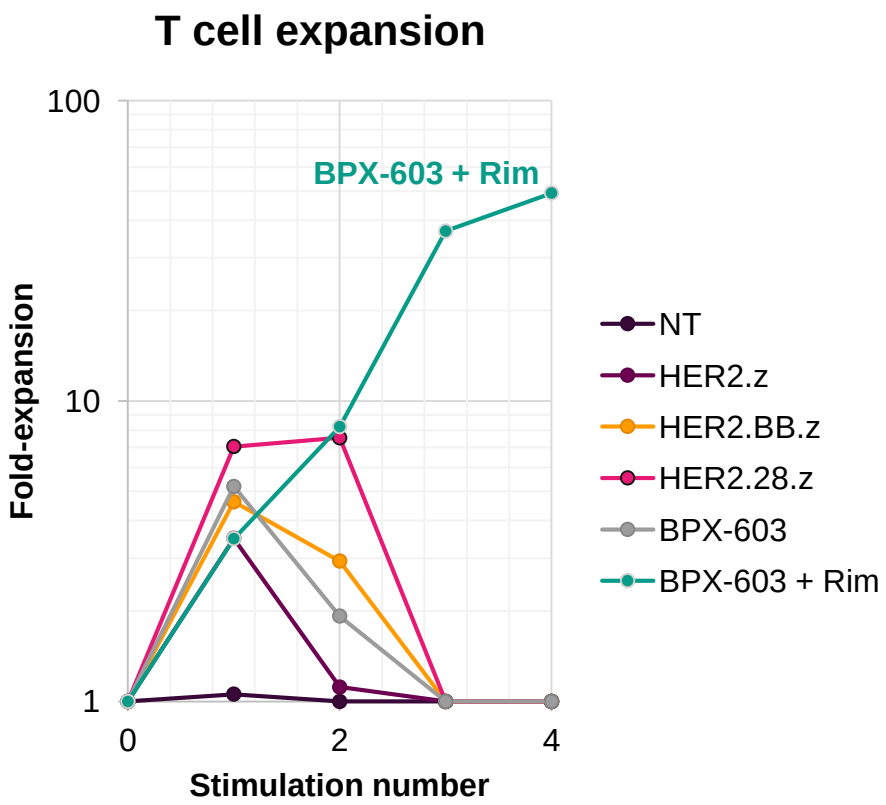
Properties of Rimiducid-FKBP CID

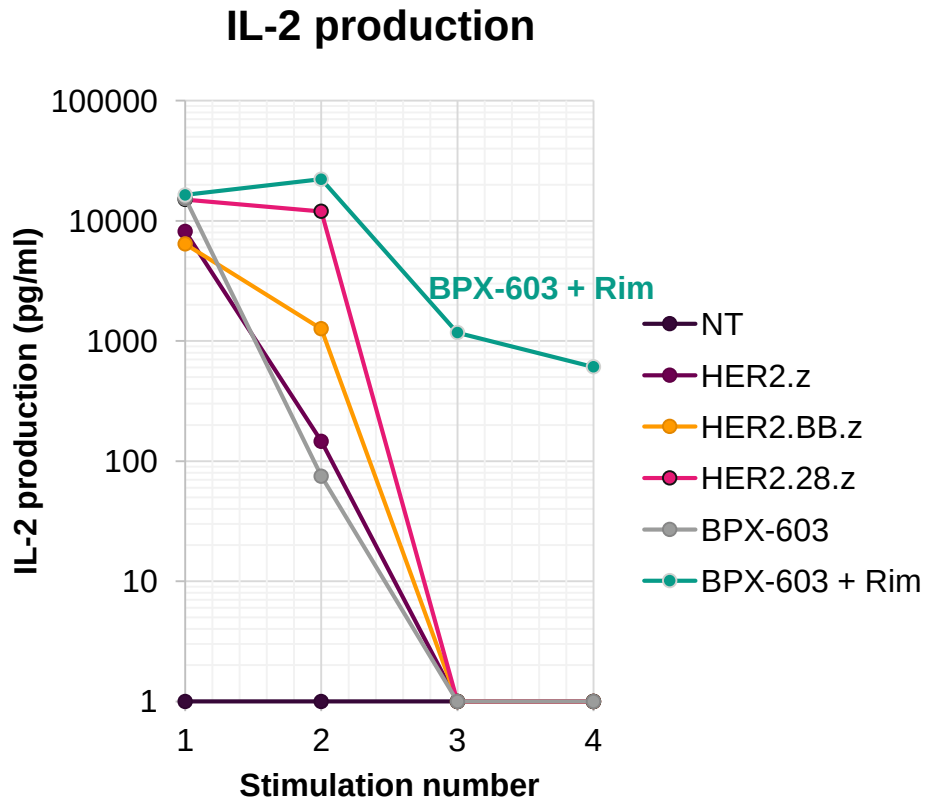


GoCAR Proliferation: Resistance to T Cell Exhaustion

iMC activation limits T cell dysfunction in a repeat tumor stimulation assay

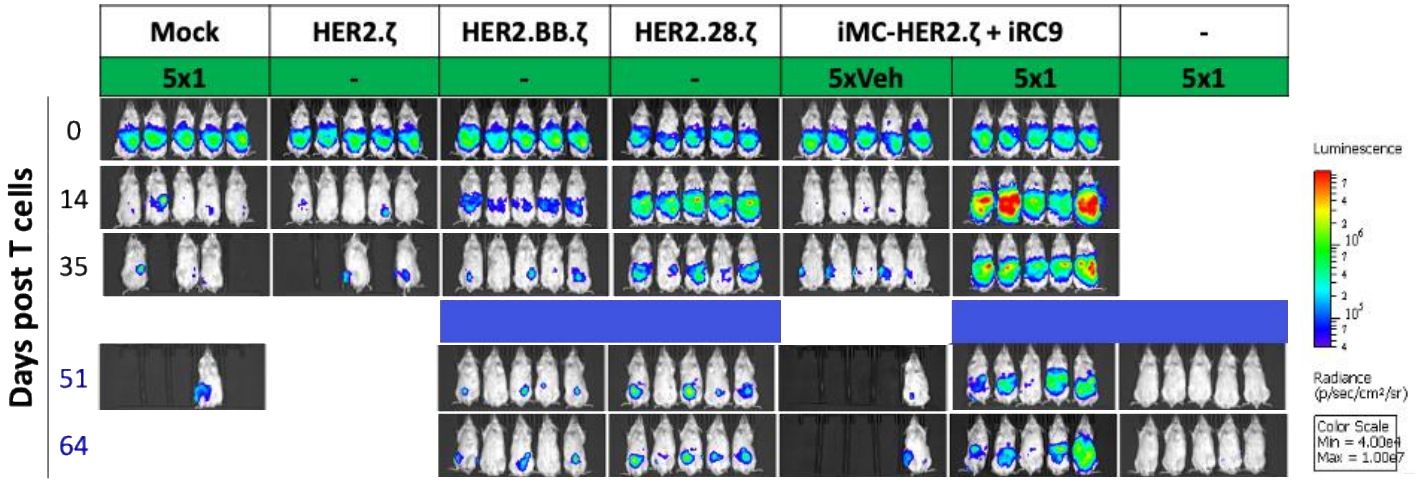


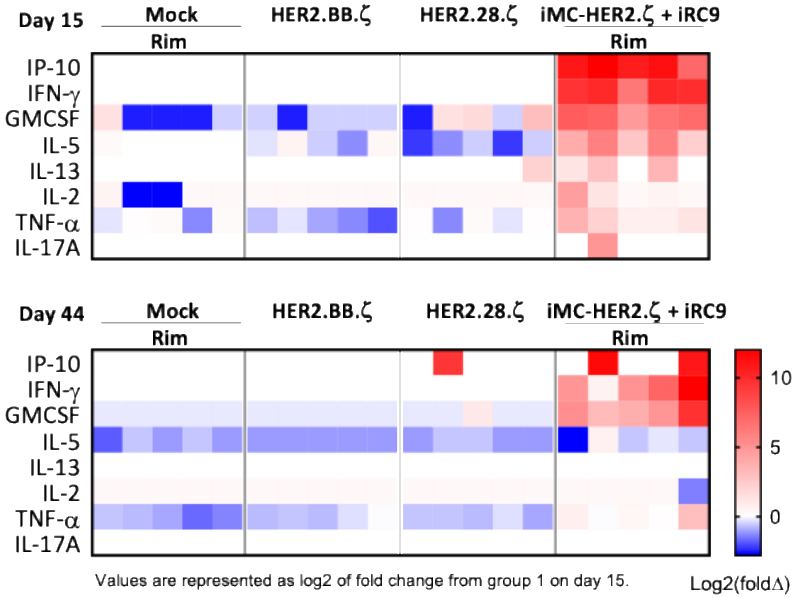




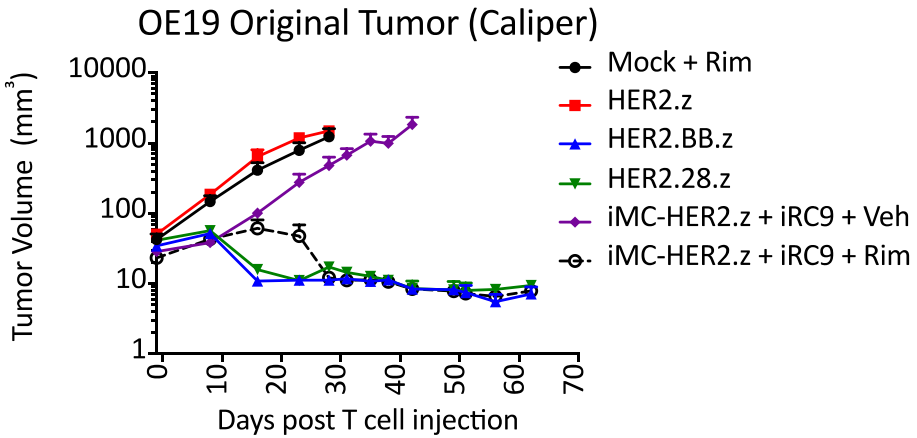
BPX-603 (HER2): Long-term maintenance of efficacy

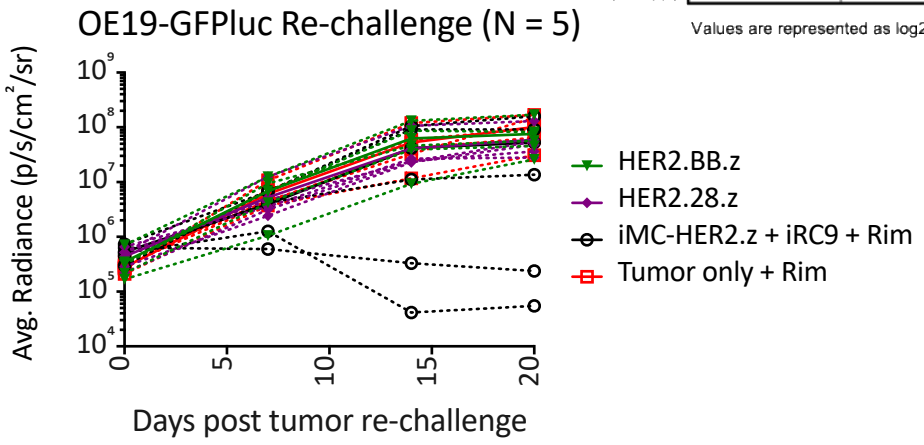
HER2 CAR-T cells





OE19 Tumor





[D0 (5e6 OE19 Re-challenge) = D42 (Days post T cells)]

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iMC enhances the potential of NK and CAR-NK cells as a therapeutic

NK Cells Have Therapeutic Advantages

- **Innate ability to kill tumor cells through multiple mechanisms**
- Good safety profile following adoptive transfer
- Potential off-the-shelf cell therapy given low propensity to cause GvHD

Other NK Cell Features Limit Therapeutic Utility

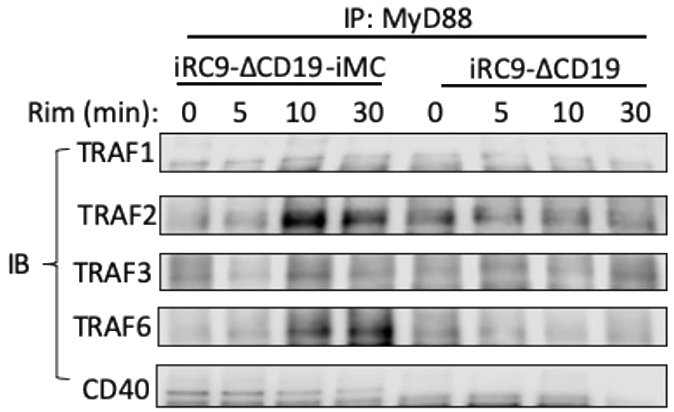
- Unmodified NK cells show limited in vivo expansion and persistence (7-14 days)
- Tumors can develop defense mechanisms to limit NK cell cytotoxicity and cytokine production

Preclinical Data Support GoCAR-NK Advantages

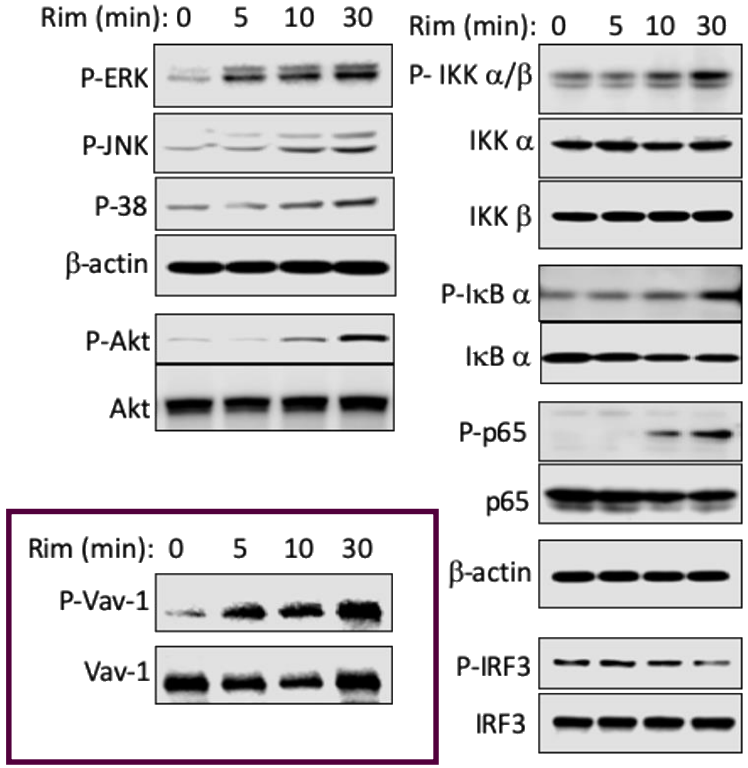
- MC improves proliferation and survival of NK cells
- MC signaling enhances innate cytotoxicity of NK cells
- MC synergizes with IL-15 to further increase anti-tumor potency
- iMC, IL-15 and tumor-specific CAR transgene expression result in superior anti-tumor effects in multiple tumor models

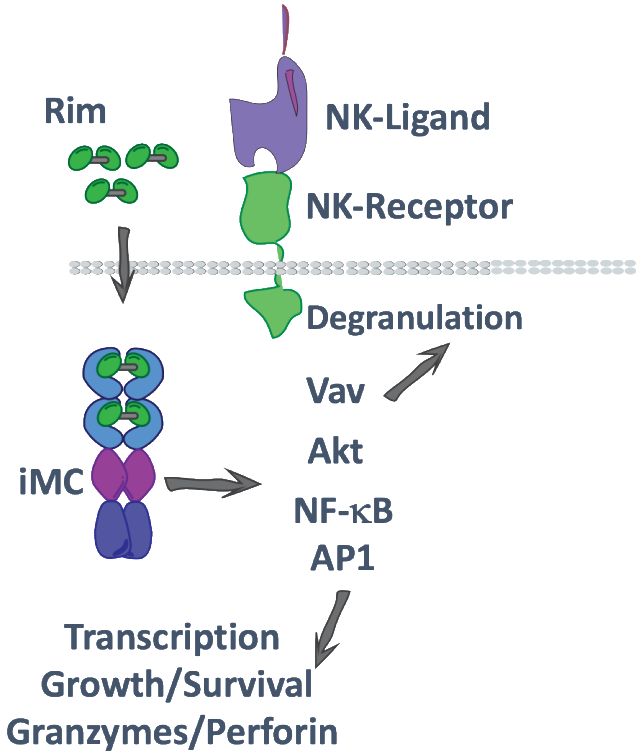
iMC signal transduction in NK cells is similar to T cells

Rim-directed TRAF recruitment



Signal transduction





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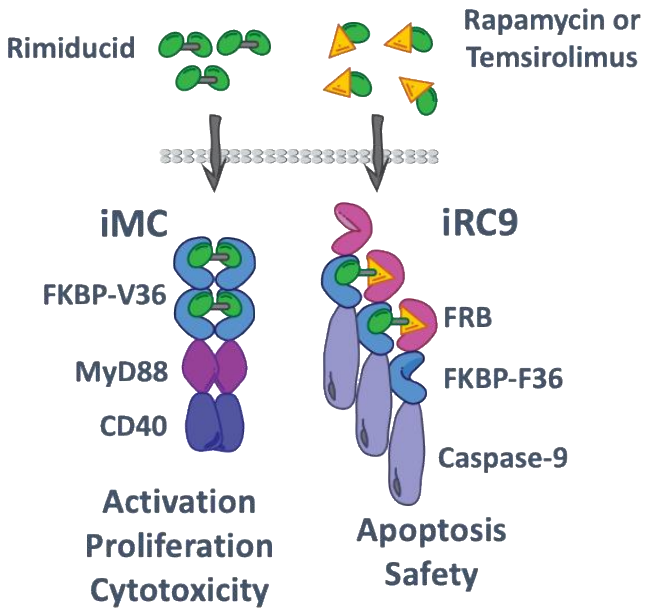
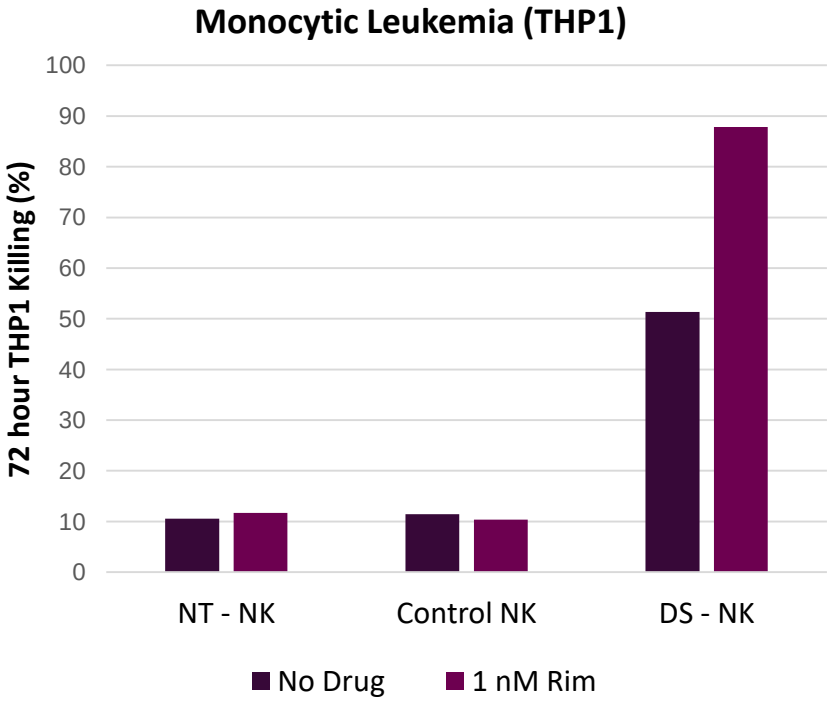
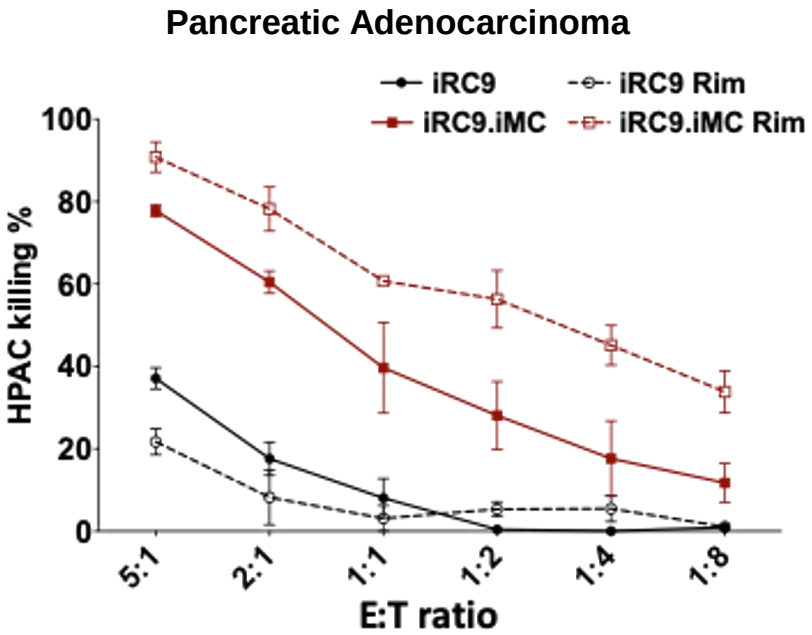
Foster et al, *Mol Ther. 2017;* Wang et al, *Blood Adv. 2020*

iMC Increases Innate Cytotoxicity of NK Cells



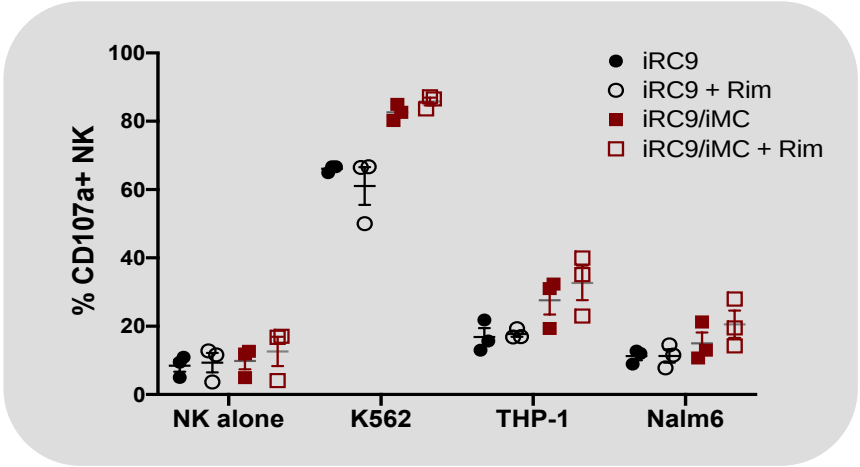




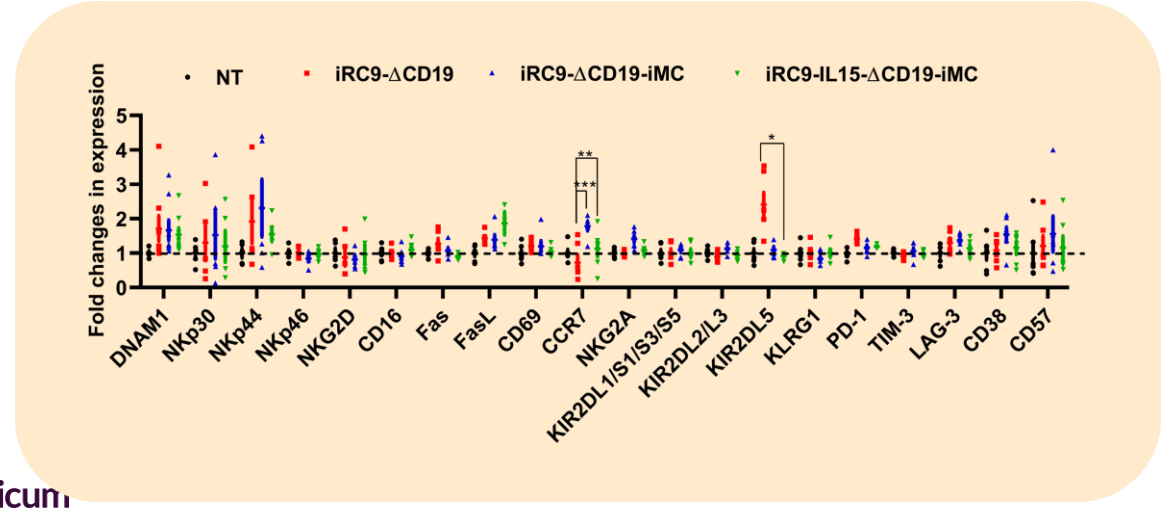
iMC increases the intrinsic killing activity of NK cells

Cytotoxicity is correlated with increased abundance of cytotoxic granules

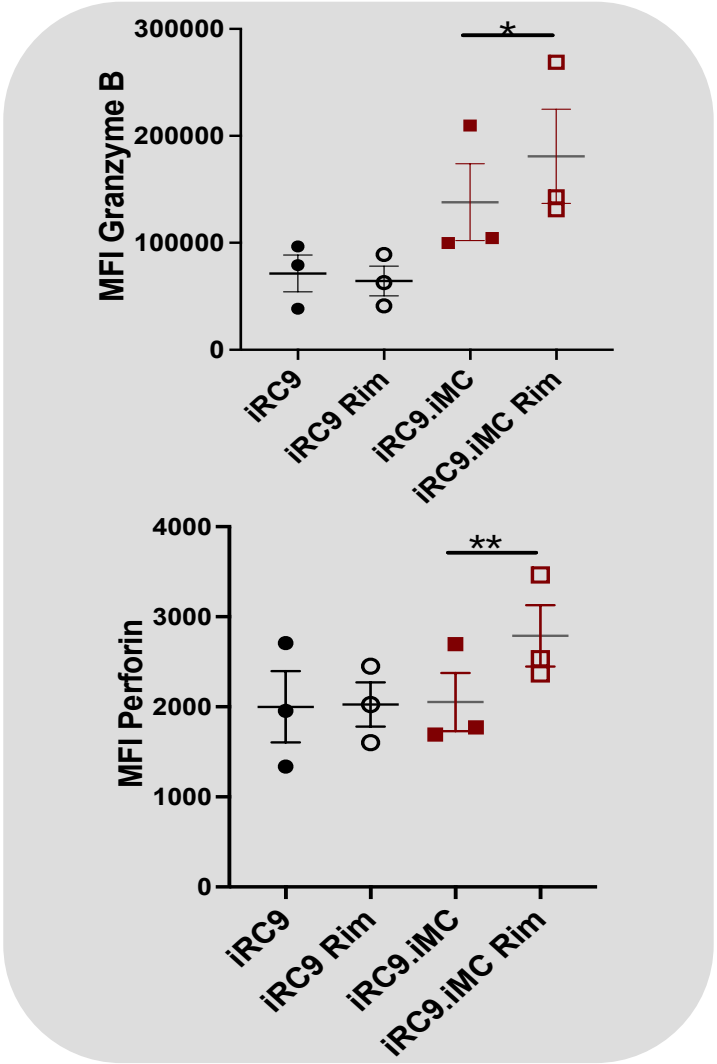
NK cell degranulation



NK-receptor expression

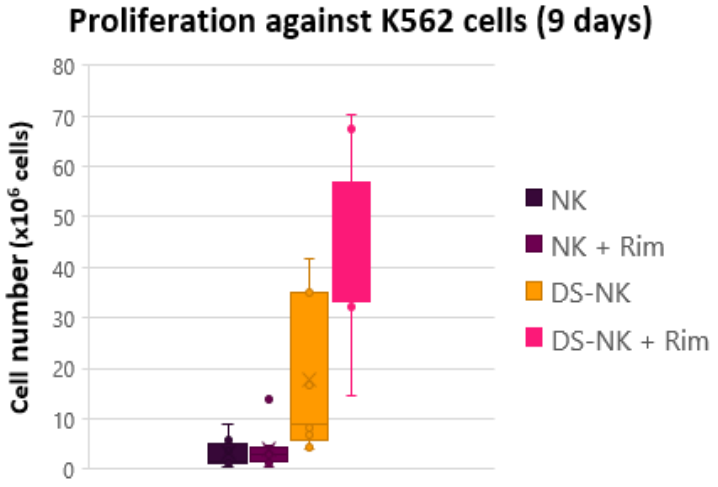


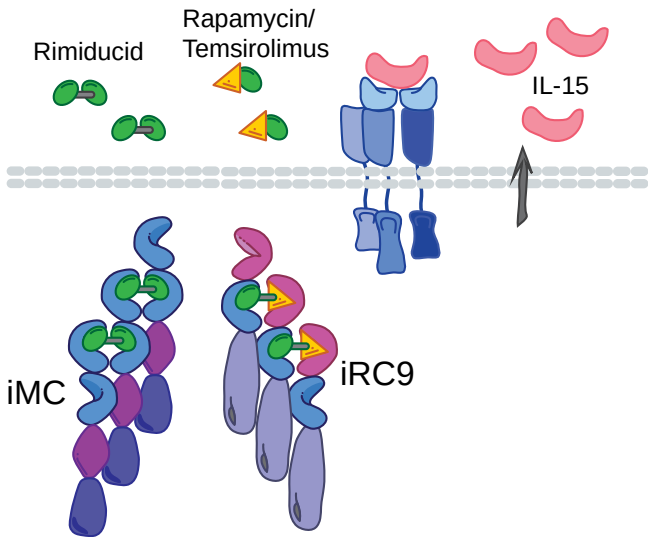
Granule component expression

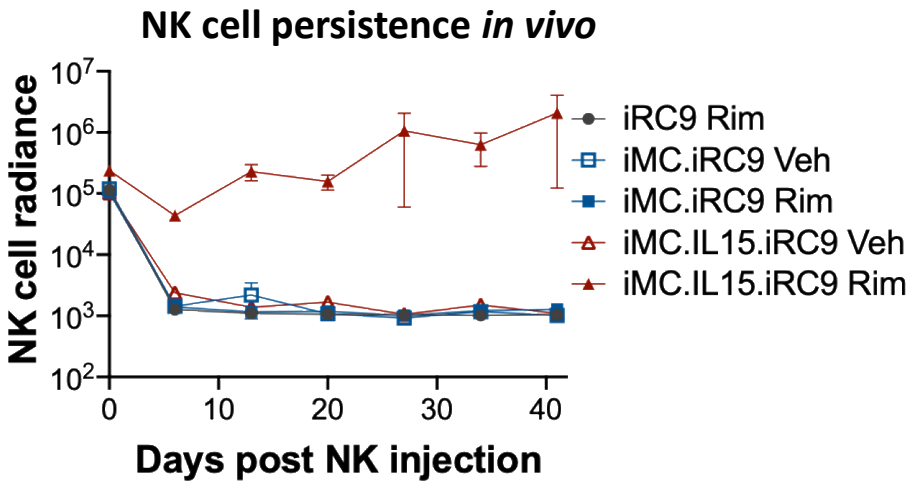


iMC drives NK cell proliferation and persistence

iMC and IL-15 synergize to promote NK cell survival and persistence in vitro and in vivo

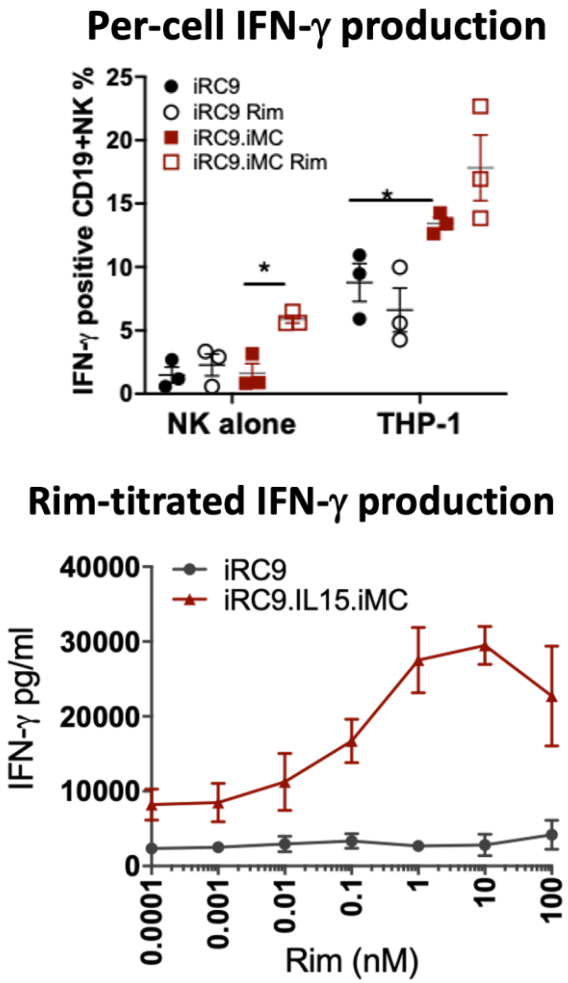


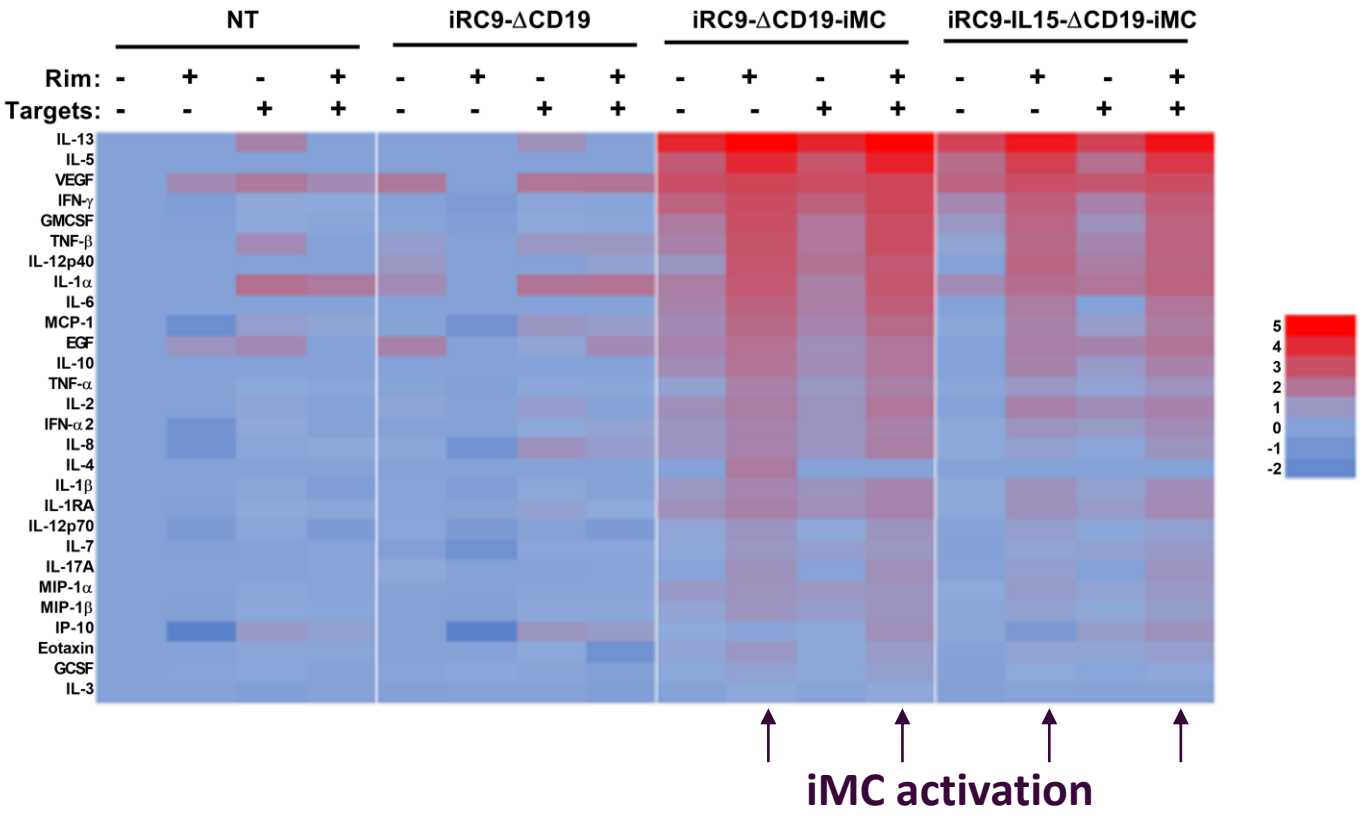




*DS: Dual switch that includes iMC and iRC9 switches;
DS-15: Dual switch and express IL-15

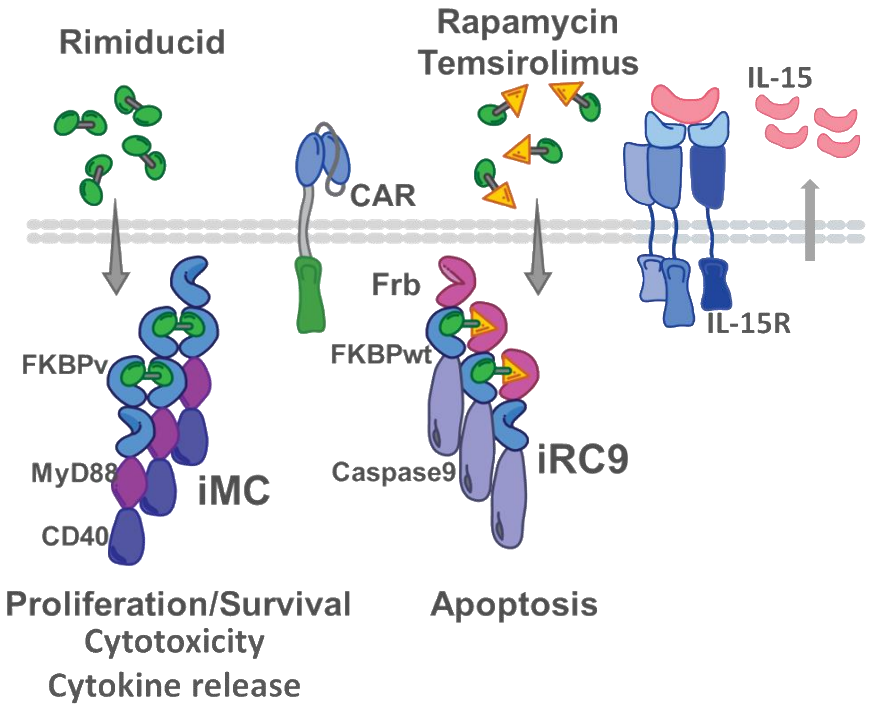
iMC signaling drives pro-inflammatory cytokine production

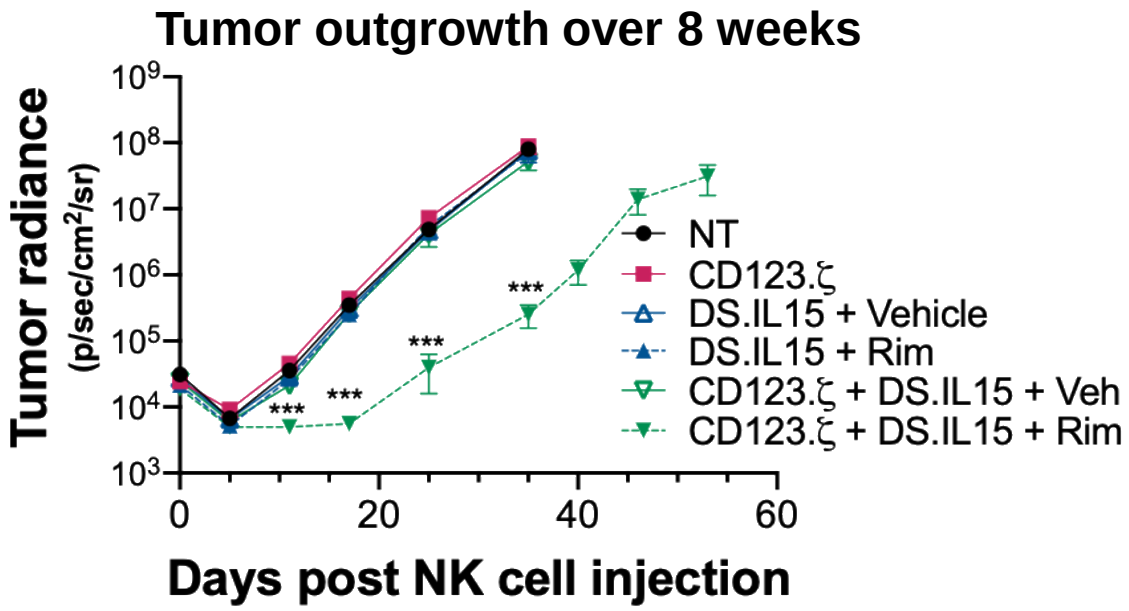




CAR-NK anti-tumor efficacy

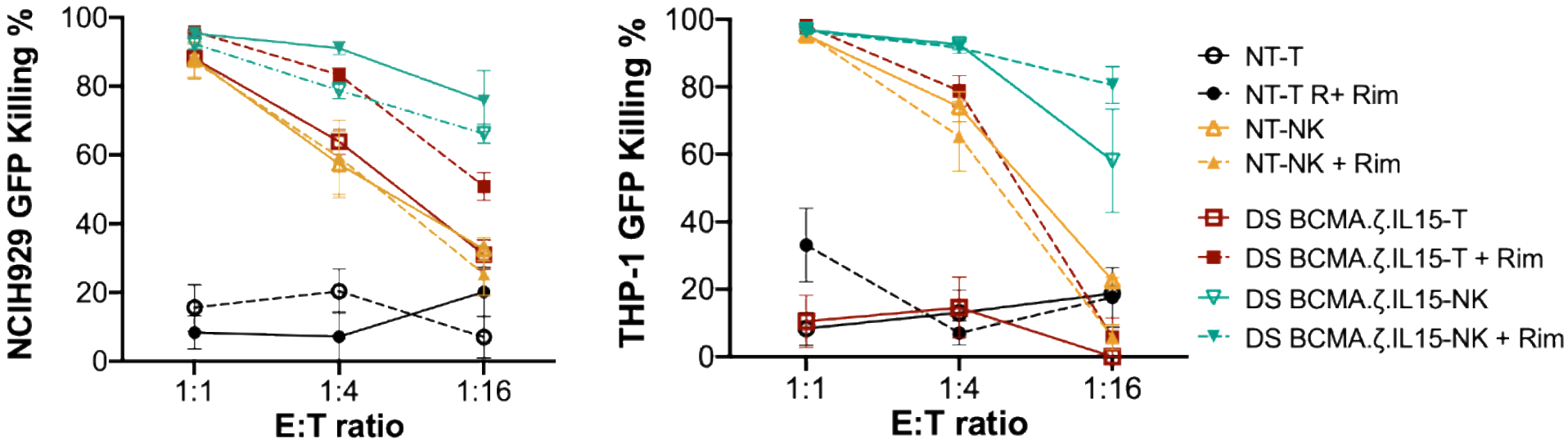
iMC, Rim, IL-15 and a 1st Gen CAR synergize to control leukemia





iMC/IL-15 activity in GoCAR-NK and GoCAR-T cells

Innate killing of NK cells may enhance BCMA CAR-NK cytotoxicity

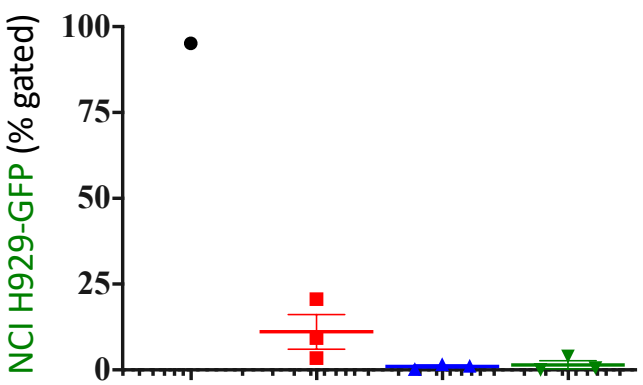


BCMA GoCAR-NK cells maintain long-term potency

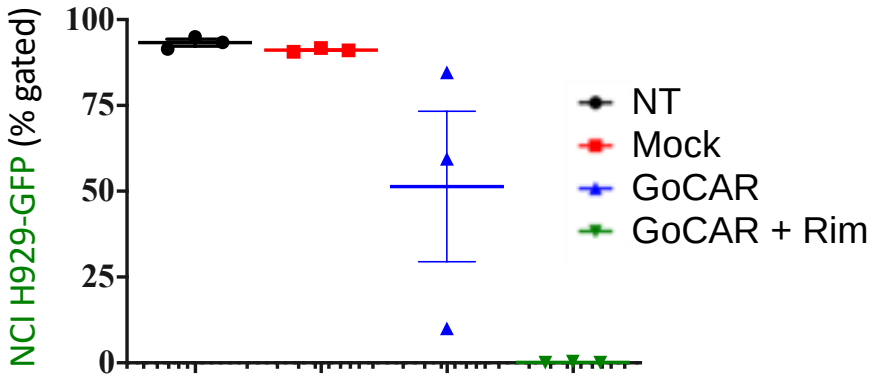
On demand activation of iMC activates cytotoxicity and proliferation after prolonged cell culture

Anti multiple myeloma efficacy

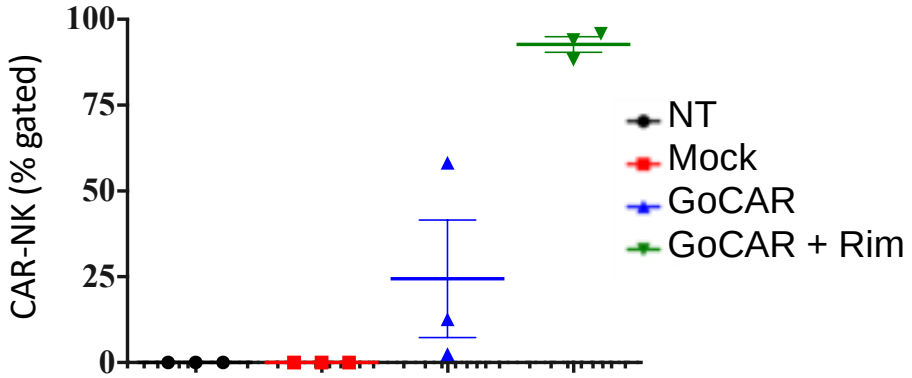
After 7 days in culture



After 34 days in culture



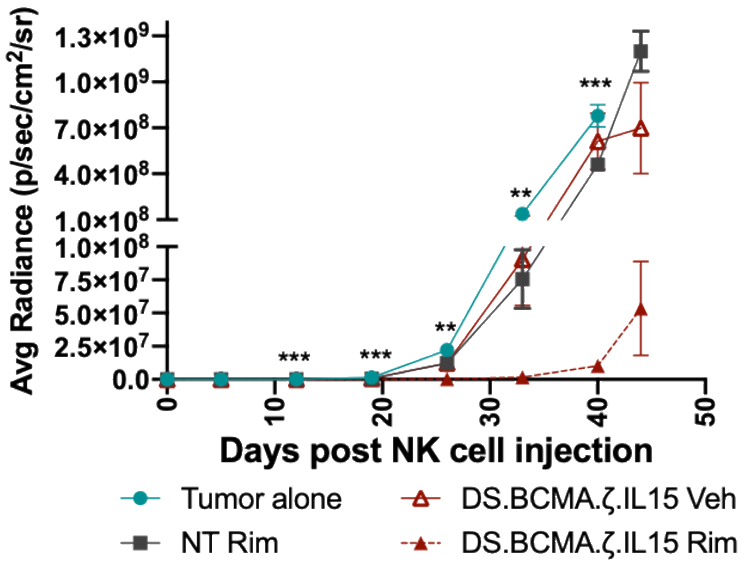
BCMA CAR-NK expansion (34 days IC)



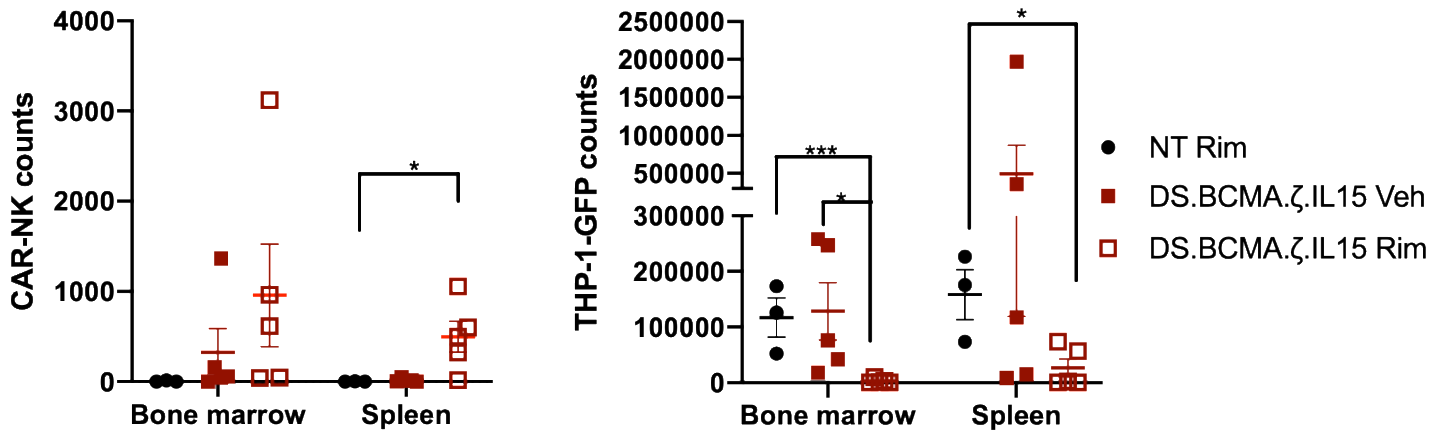
CAR-NK efficacy in anti-BCMA models

Activated iMC enabled BCMA CAR-NK cells control tumor progression in vivo

Tumor outgrowth over 8 weeks



Site-relevant CAR-NK and tumor localizaiton



Summary

- BCMA is a well validated target for autologous CAR-T therapy
  - High response rates observed in pivotal trial (73.4%[1]) with emerging questions about durability (mDoR 10.6mo1)
- GoCAR-NK may improve durability of responses
  - GoCAR enhances NK cell proliferation, persistence and cytotoxicity
  - GoCAR induces proinflammatory cytokine and chemokine production by NK cells with the potential for paracrine effects in the tumor microenvironment
  - GoCAR enhances innate NK cell anti-tumor activity against myeloma cells that may compensate for antigen loss
  - Potential to improve durability using healthy patient donor cells[2,3]
- OTS GoCAR-NK cells expected to have added advantages of shorter time to treatment and lower cost of goods

[1]BMS and Bluebird joint ASH2019 press release, NCT03361748 KarMMa topline data
[2] Graham et al. Cells 2018;
[3] June et al. NEJM 2018

Acknowledgements

Research

- **Xiaomei Wang**
- **MyLinh Duong**
- Daniel Jasinski
- Jan Medina
- Christine Gagliardi
- Eva Morschl
- Mary Brandt
- David Spencer
- **Aaron Foster**

Technical Operations

- **Alan Smith**
- **Joe Senesac**
- Sunandan Saha
- Omar Baez
- Joanna Stanson
- Ren-Li Sun

Clinical/Regulatory

- **Charity Scripture**
- Melissa Aldinger
- Tara Chen
- Aditya Malankar
- Maryam Ansari