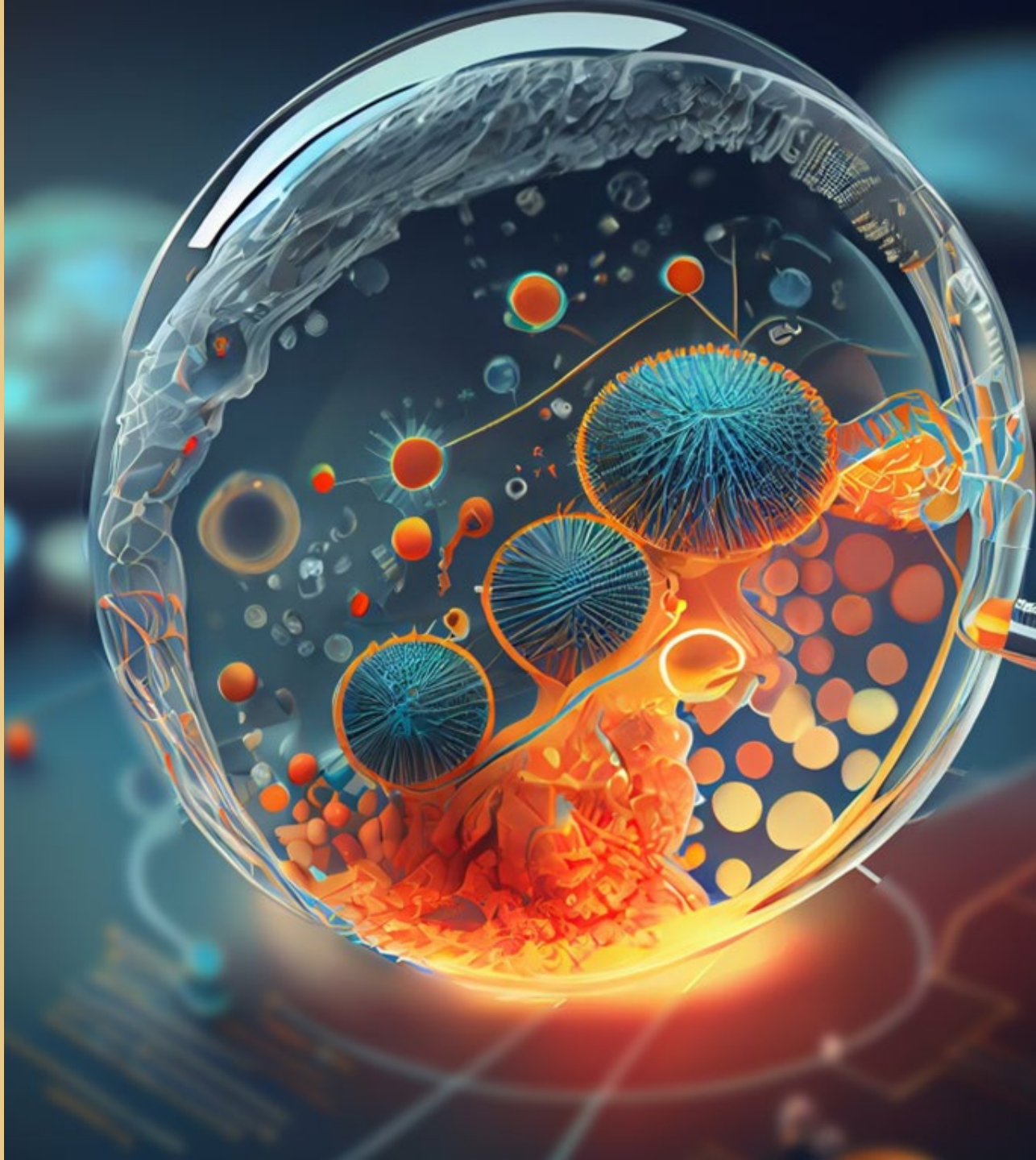
eha Sf(PM)

Targeting apoptosis regulators to enhance natural killer cell-based immunotherapy in aggressive B cell lymphomas

Eva Szegezdi



Conflict of interest

ONK Therapeutics Ltd:

- PhD student of the project is an employee of ONK Therapeutics
- ES has collaborative research projects with ONK Therapeutics on NK cell-based immunotherapies

Contents

01 Relapsed/refractory NHL

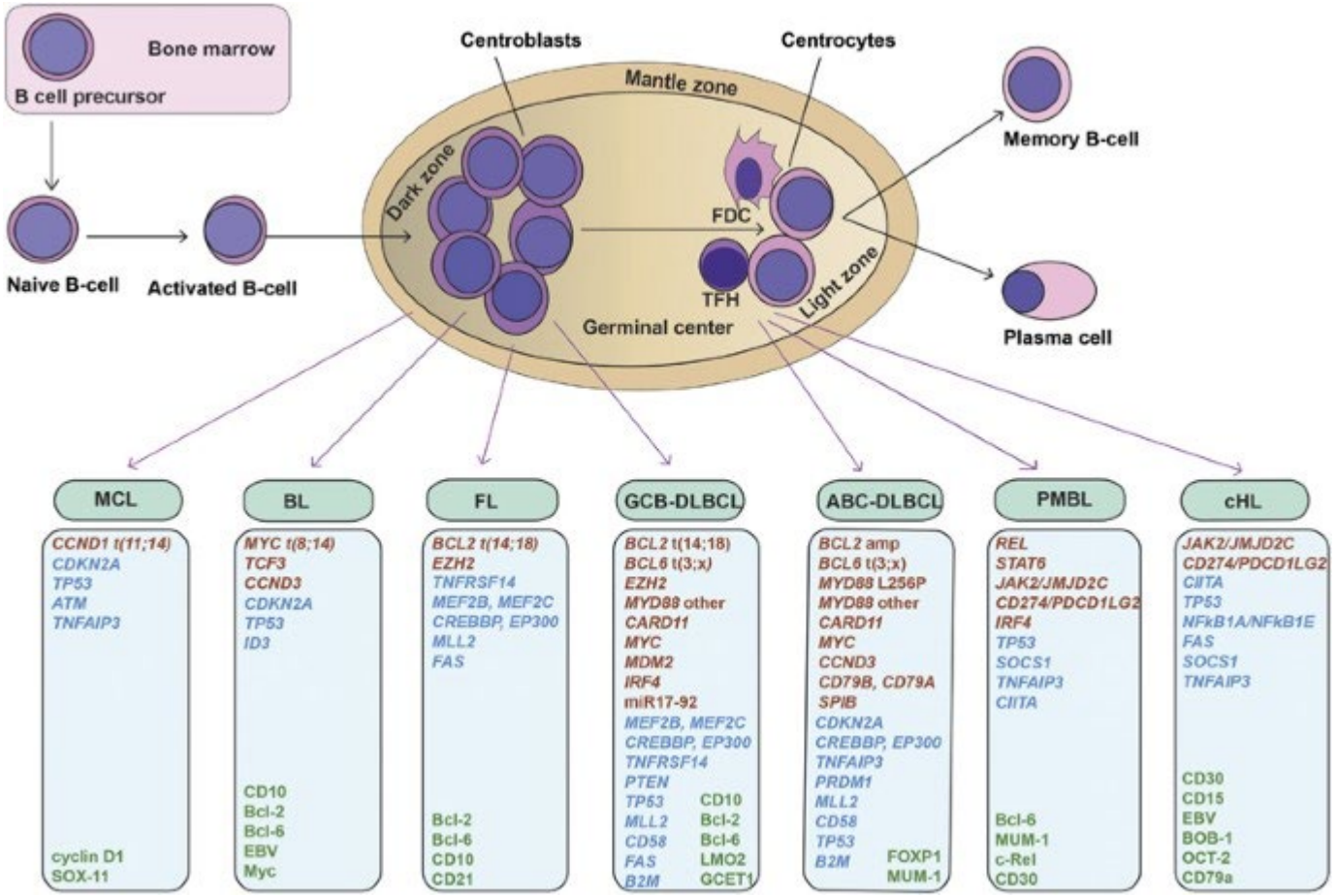
02 T/NK cell therapies for high grade NHL

03 Screen for sensitisers of NK-mediated cytotoxicity

04 Inhibition of cIAPs enhances NK-cytotoxicity

05 TRAIL-NK cells potently kill Smac-mimetic pre-treated NHL cells

Relapsed/Refractory non-Hodgkin lymphoma



Diverse group of diseases

- 60 subtypes
  - Rare cancers
  - 75-80% B cell-derived
- High grade:
  - Diffuse large B-cell lymphoma (DLBCL) (30%)
  - Mantle cell lymphoma (MCL) (3%)—has features of both indolent and aggressive NHL
  - Lymphoblastic lymphoma (2%)
  - Burkitt lymphoma (BL) (2%)

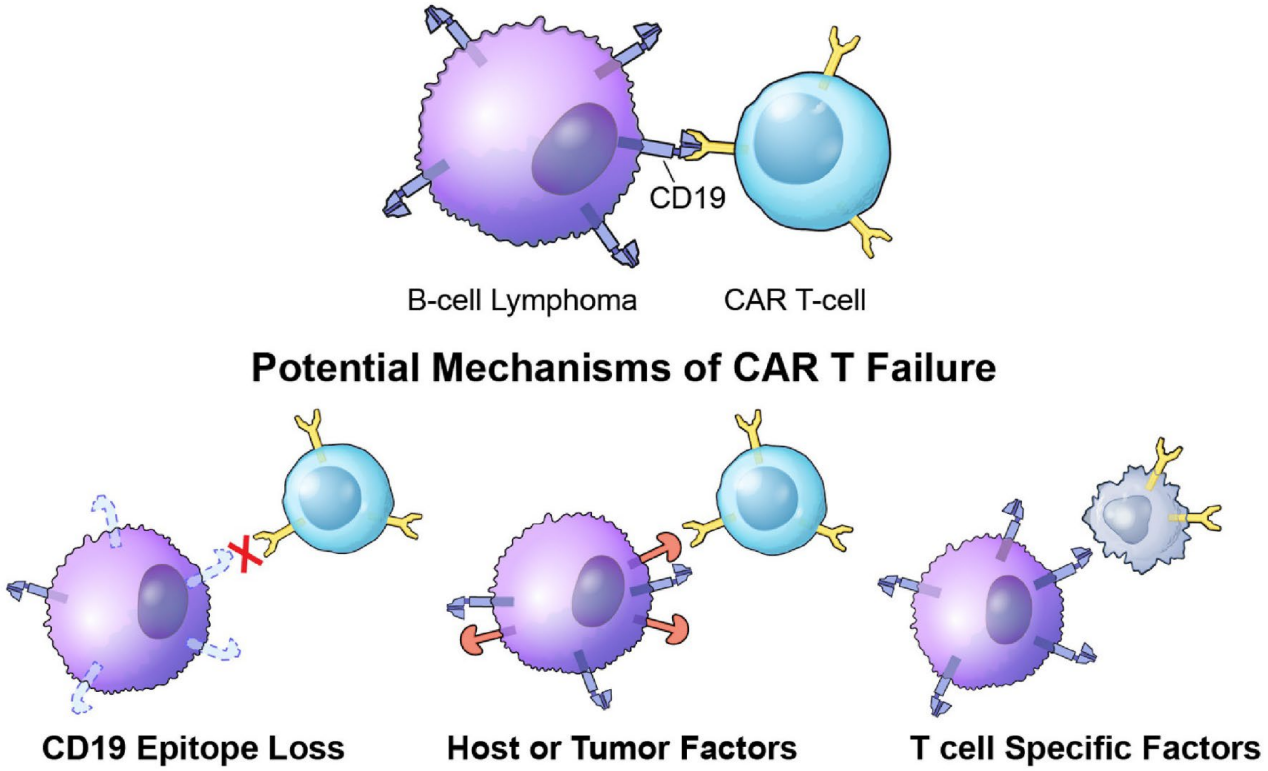
Treatment:

- anti-CD20 antibody + chemotherapy (R-CHOP: rituximab+cyclophosphamide, doxorubicin, vincristine and, prednisone)
- Approx 1/3 of patients refractory/ relapse
- Poor prognosis for R/R-NHL

CAR-T therapy

- Targeting CD19

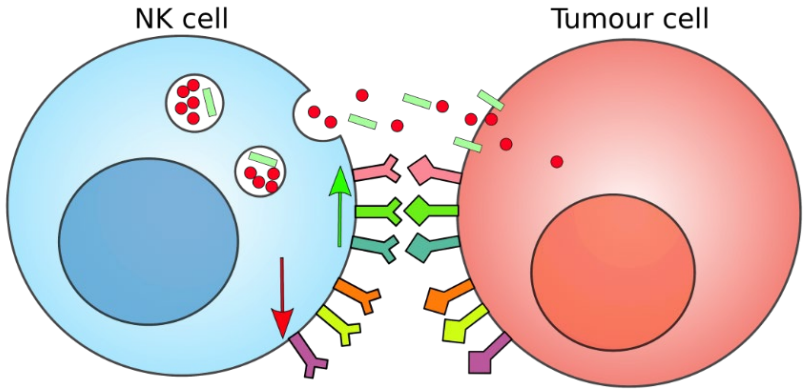
Challenges of CAR-T cell therapy in high grade NHL



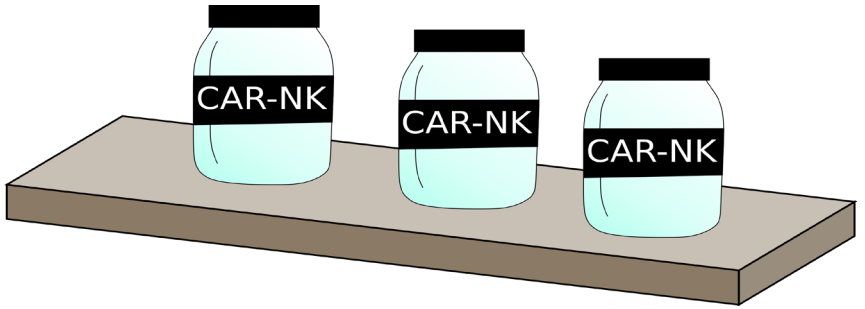
- 50-60% of B-NHL patients relapse after CD19-CAR-T therapy
- Overall survival benefit is moderate

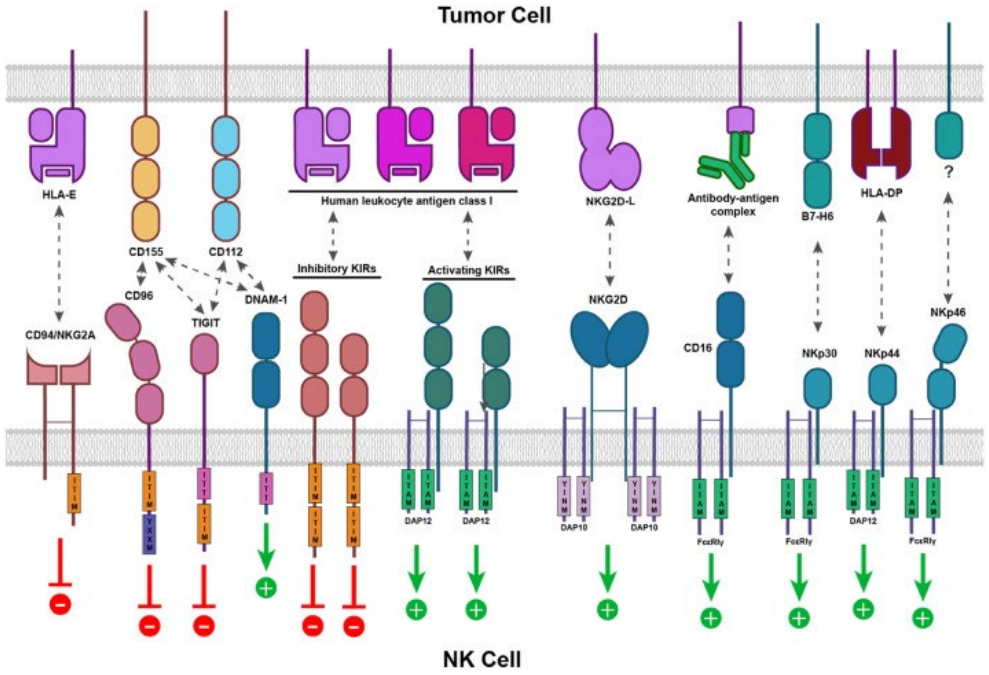
- BELINDA, ZUMA-7, TRANSFORM trials
  - Antigen loss/escape
  - Treatment resistance
  - Limited CAR-T cell persistence

NK cell-based immunotherapy as an alternative



Potential "off the shelf" cell-based therapy





Cells from multiple allogenic source

Low GVHD neurotoxicity, Cytokine release syndrome

Off-the shelf products

High safety

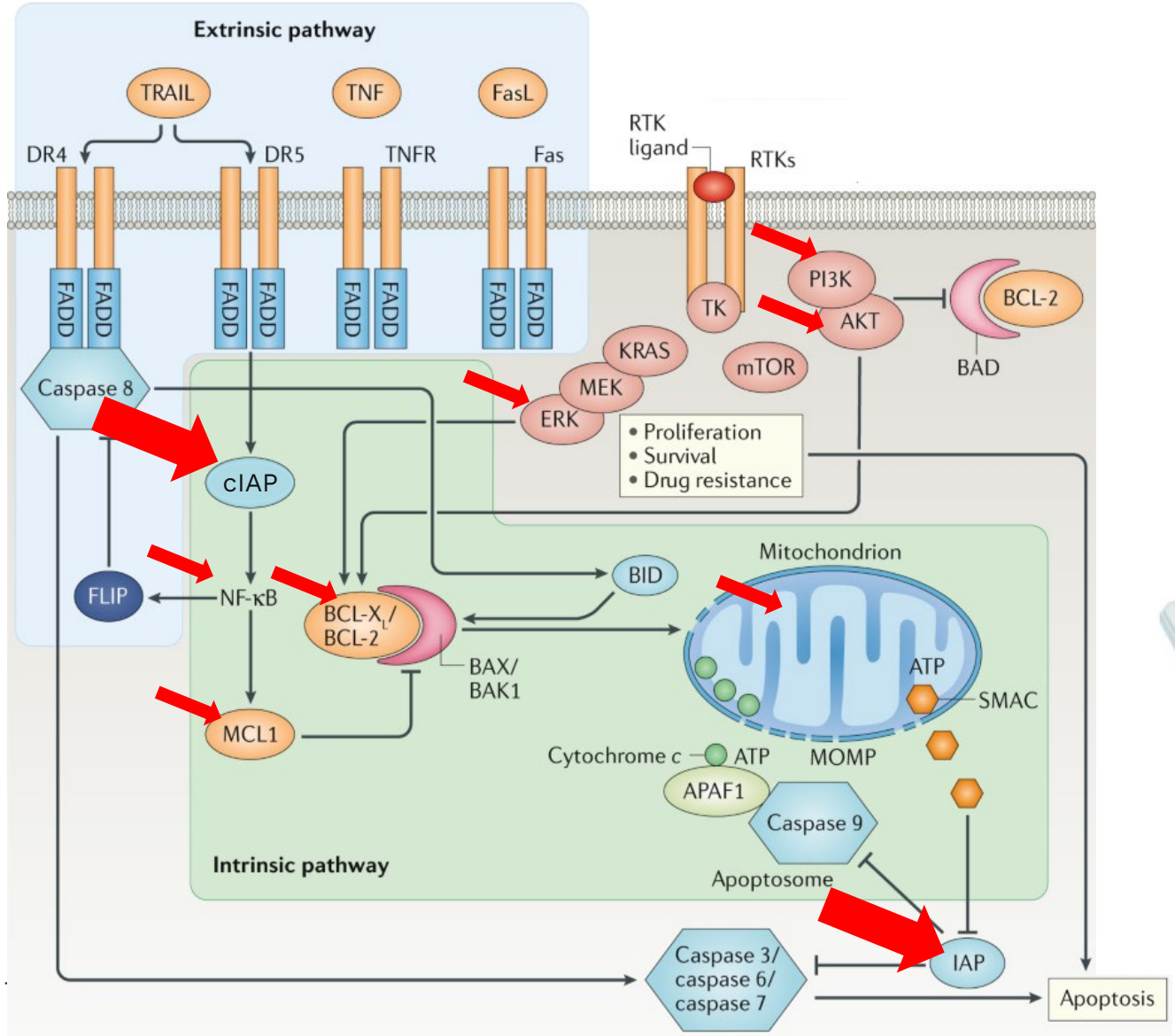
Multiple killing mechanisms

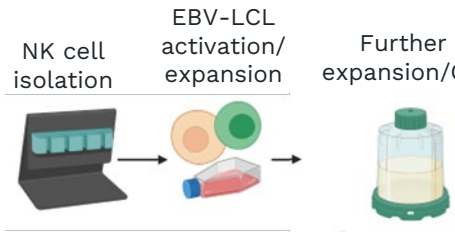
Limited lifespan

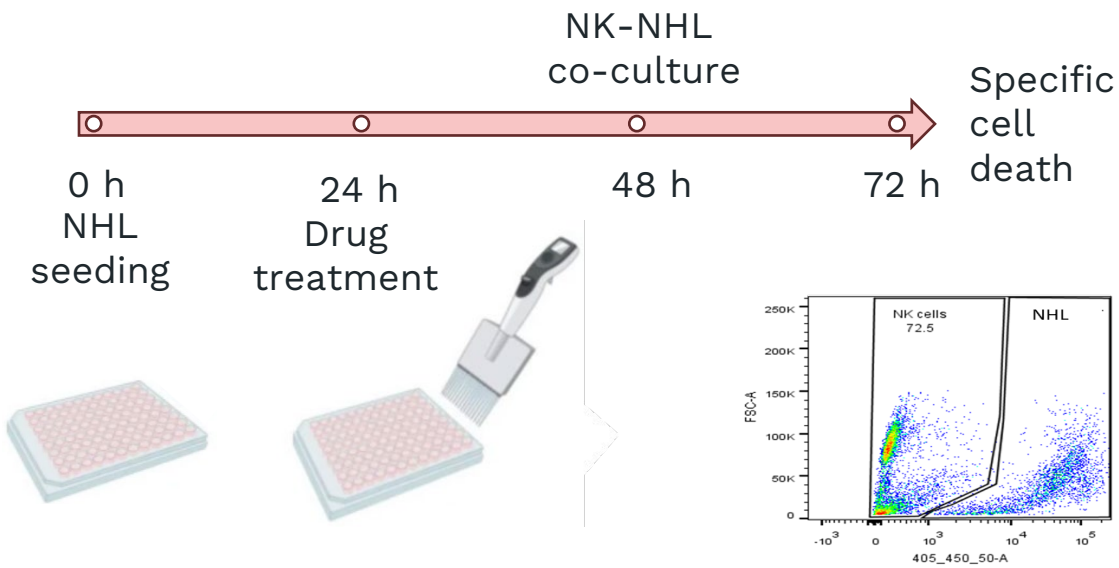
Additional mechanisms to the CAR pathway

Limited on-target off tumour toxicity

Drug screening for NK cytotoxicity sensitisers







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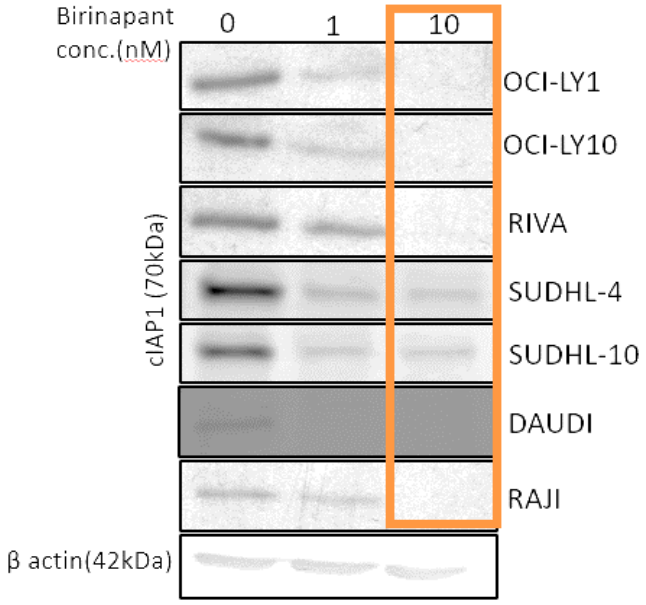
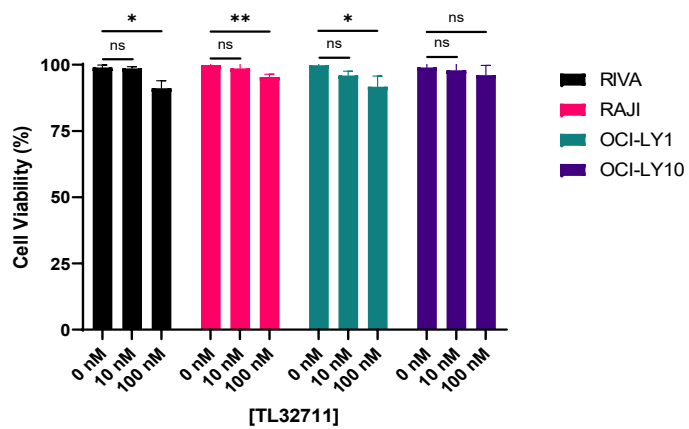
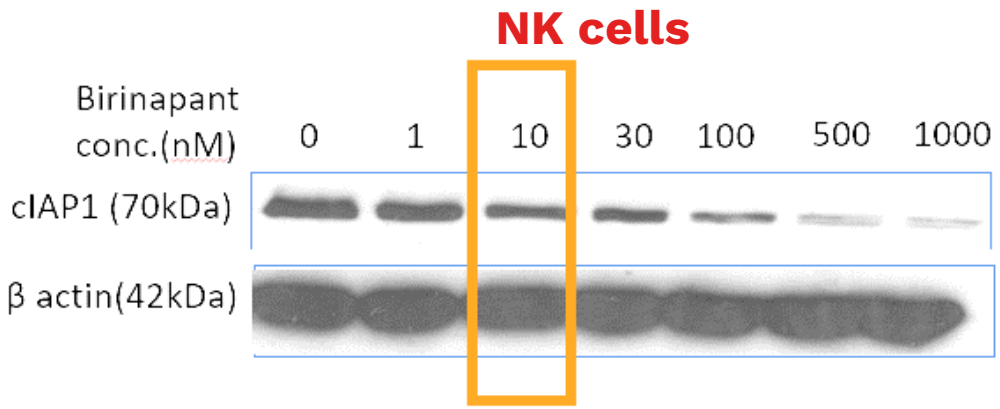
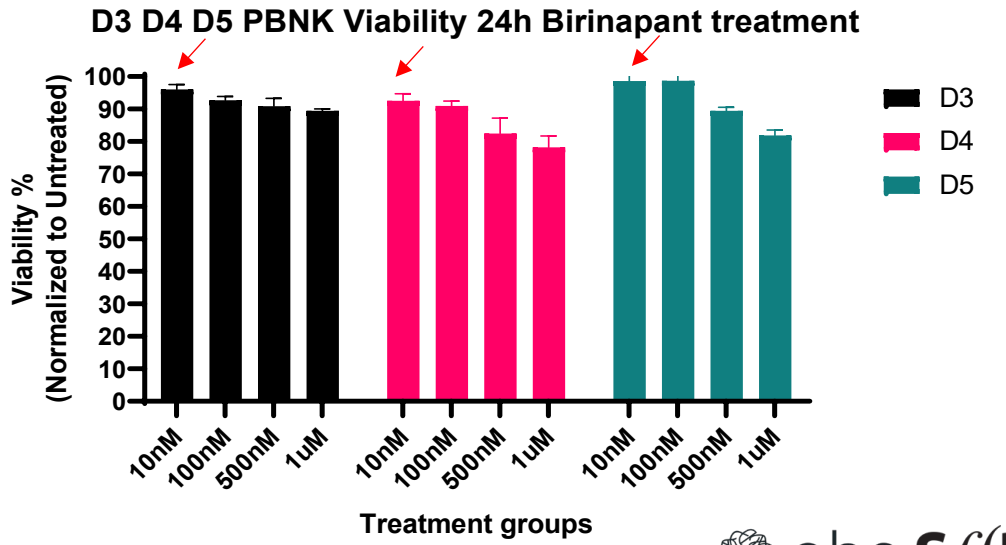
NHL cells, but not NK cells are highly sensitive to cIAP inhibition

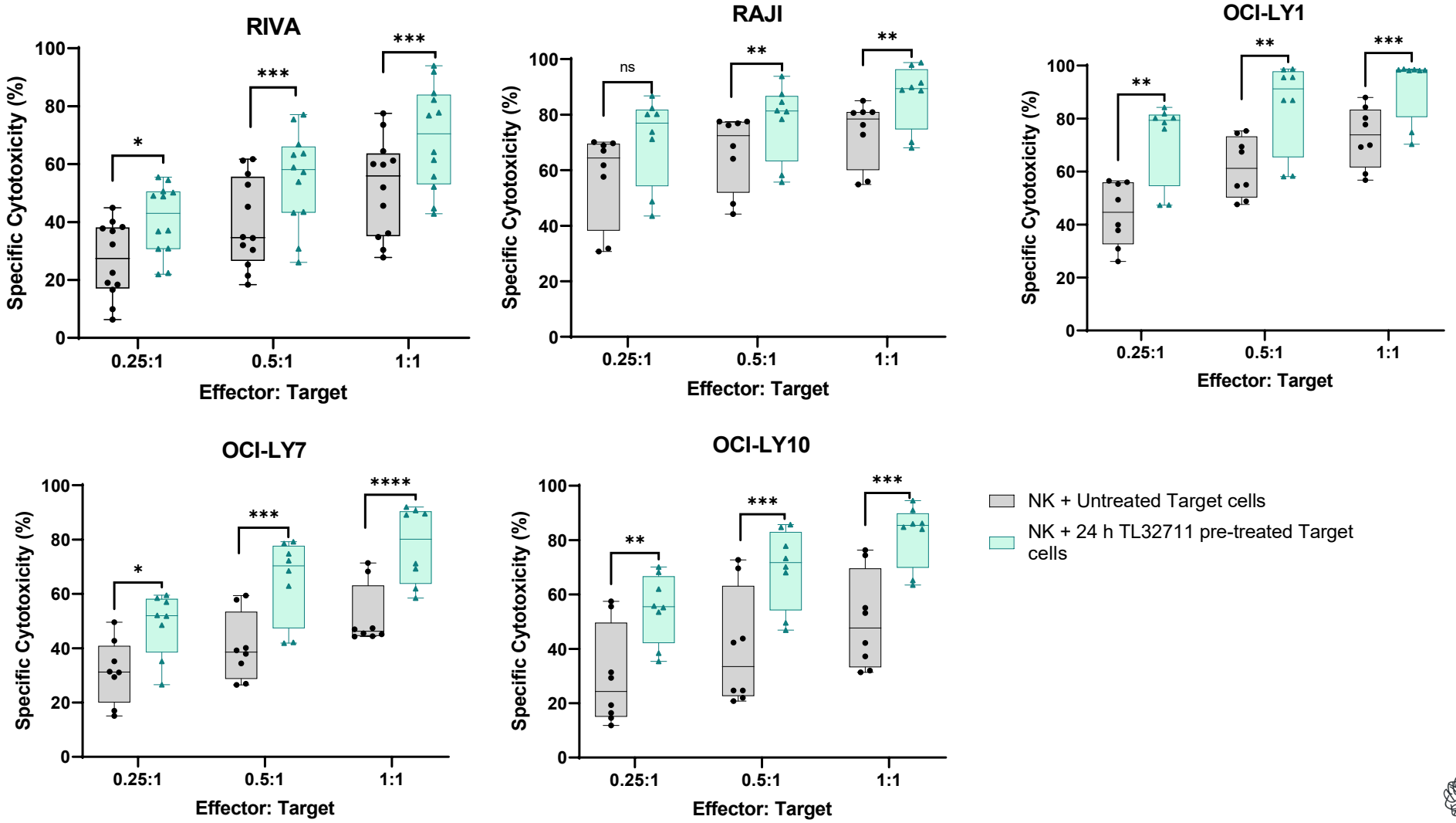




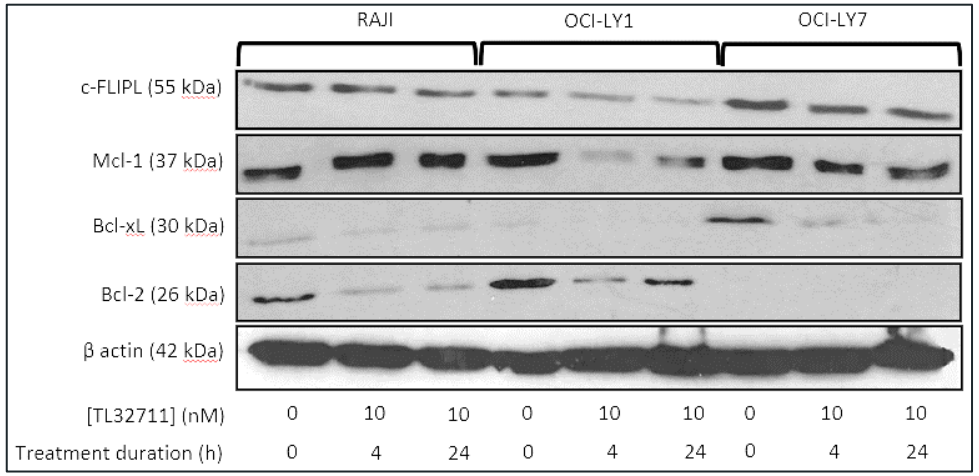


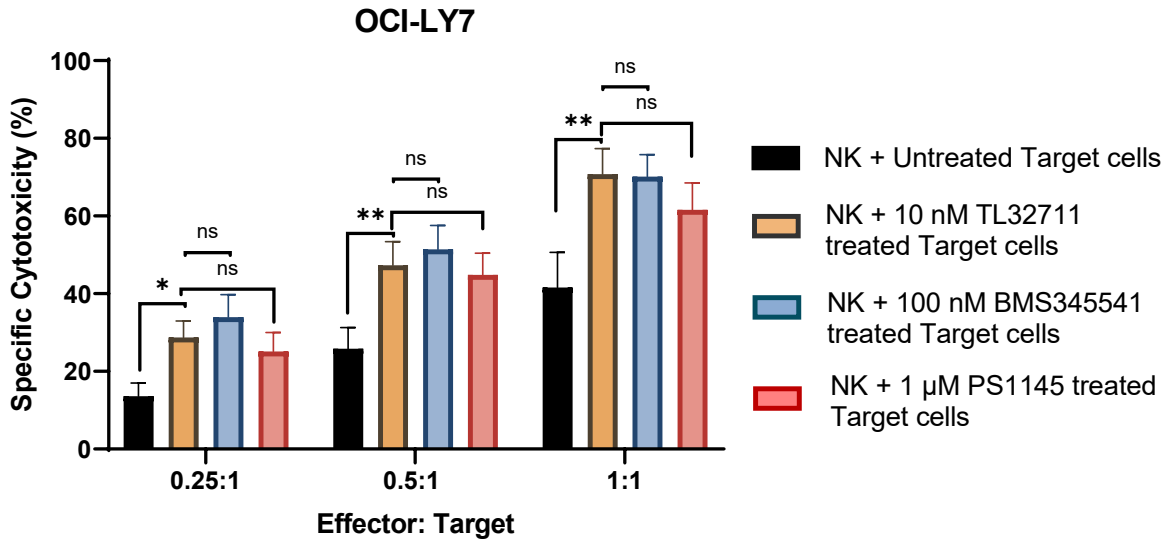


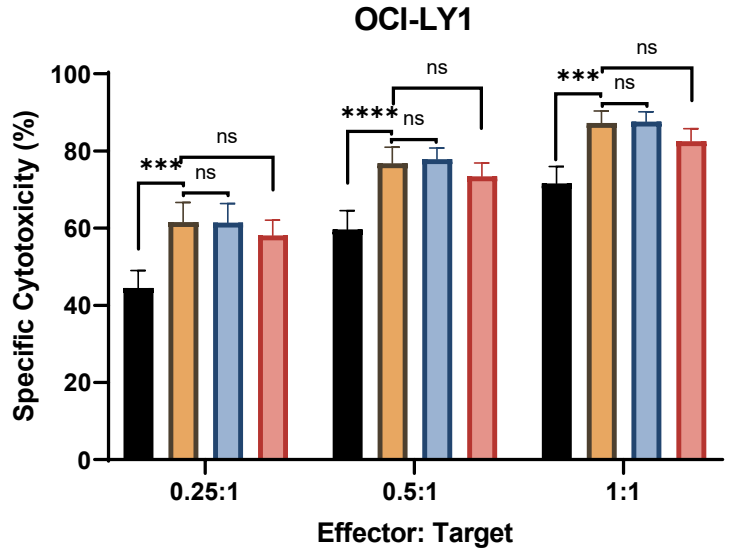
Inhibition of cIAPs sensitise NHL cells towards natural killer cell cytotoxicity



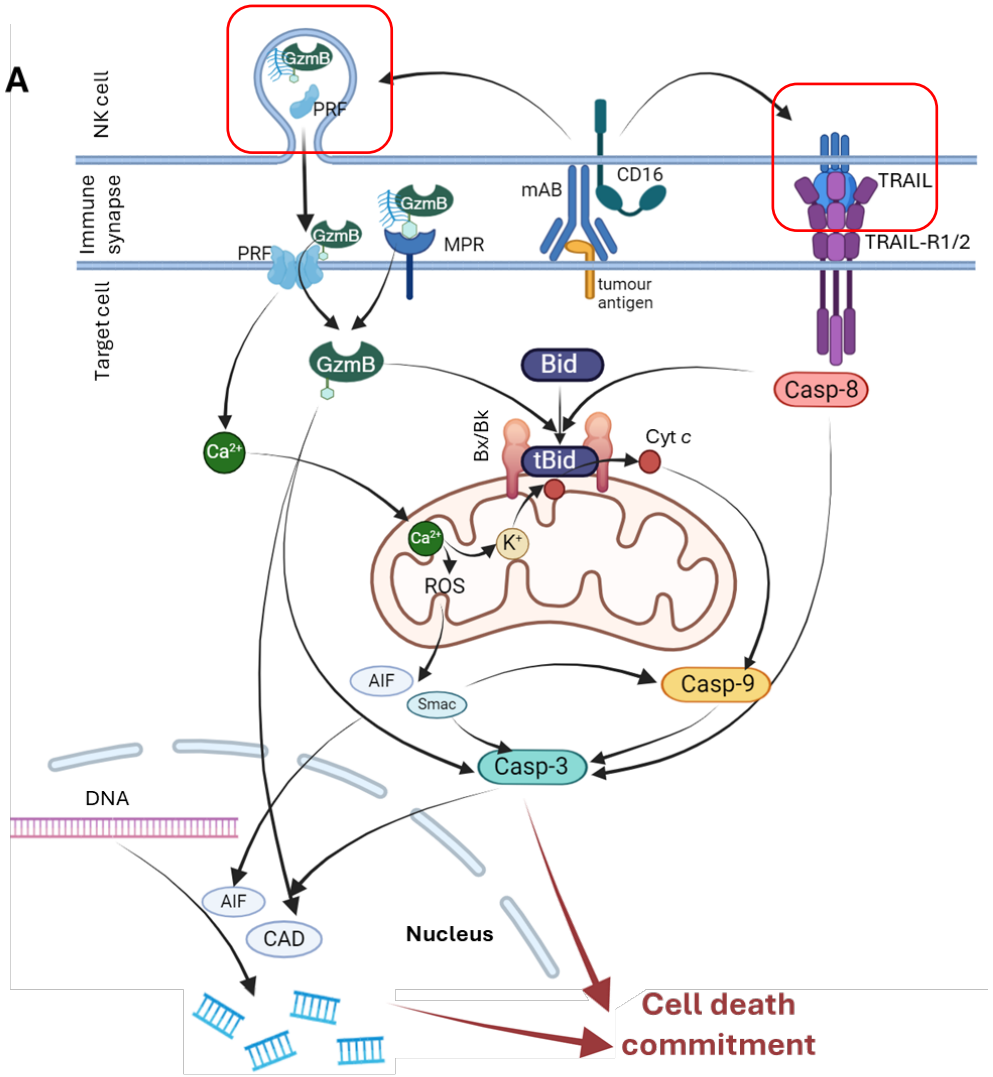
Inhibition of cIAPs lead to downregulation of NF-κB target genes

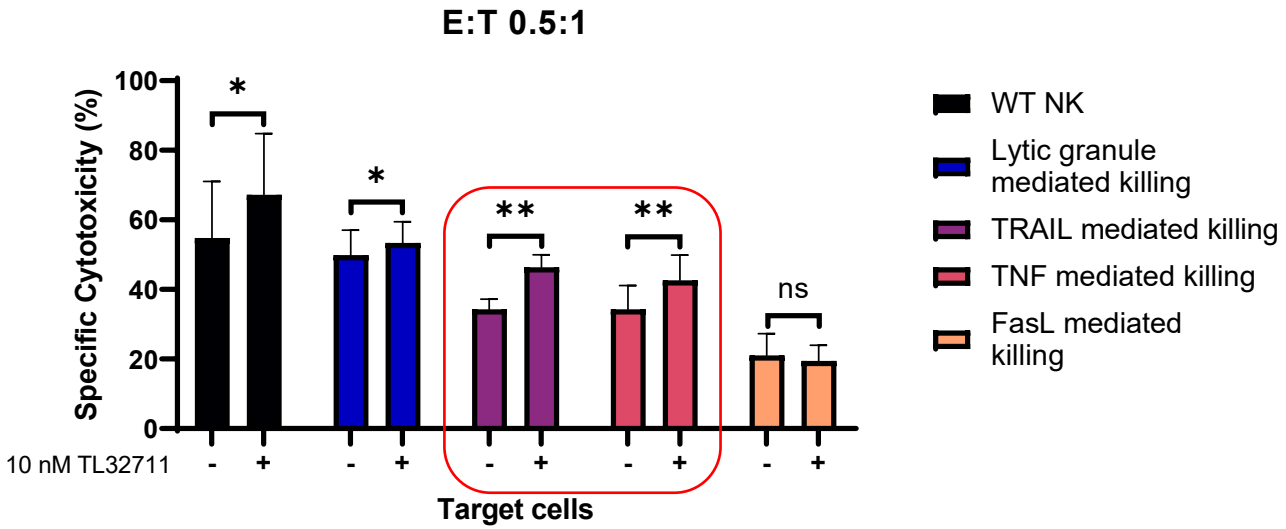




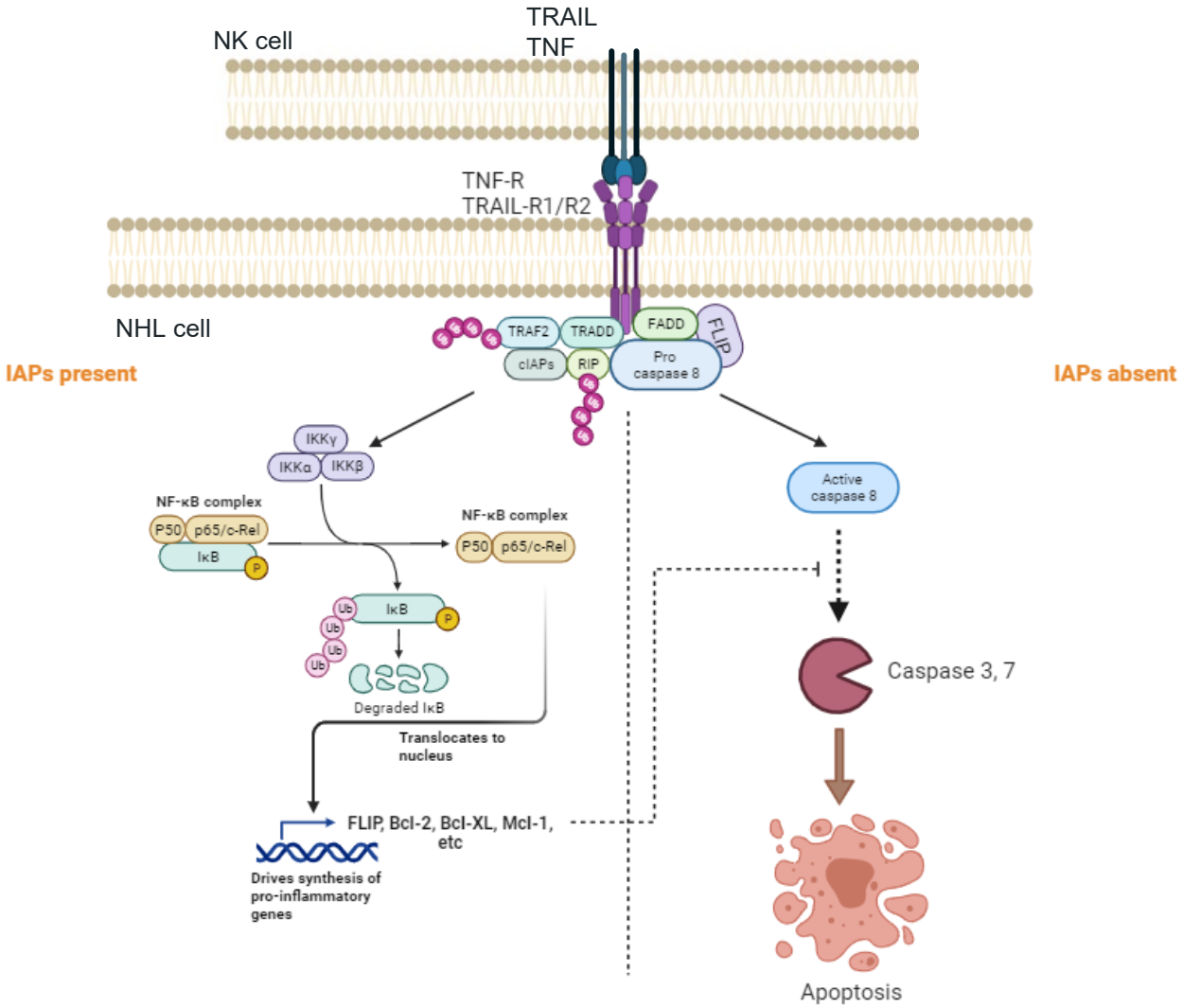


TRAIL plays an important role in the enhanced NK cell cytotoxicity





Conclusions



- Elevated cIAP1/2 (BIRC2/3) expression in NHL drives an anti-apoptotic programme that protects NHL cells from effector immune cell-mediated killing.
- Sublethal dose cIAP1/2 inhibition enhances NHL sensitivity to NK cell-mediated killing via death ligands.
- Ectopic expression of TRAIL further enhances the cytotoxic potential of ex vivo expanded NK cells, potentially by facilitating serial killing activity of NK cells.

Acknowledgements

Ollscoil na Gaillimhe
University of Galway

Eva Szegezdi lab

- *Alessandra Conforte*
- *Margaret Twohig*
- *Javid Sabour Takanlu*
- *Maryam Arif*
- *Micheál Ó Dálaigh*
- *Jacopo Umberto Verga*
- *Wanshan Hu*
- *Leonie Durkan*
- *Rossella Parrotta*
- *Sonia Iranpour*

Ollscoil na Gaillimhe
University of Galway

Prof Michael O'Dwyer

BCNI Biobank

ONK Therapeutics

Helsingin yliopisto
Helsingfors universitet
University of Helsinki

Caroline Heckman lab, Institute of Molecular Medicine (FIMM)

- *Juho Miettinen*
- *Philipp Sergeev*
- *Rhiannon Newman*
- *Minna Suvela*
- *Alun Parsons*
- *Mahesh Tambe*
- *Romika Kumari*
- *Dimitrios Tsallos*
- *Daniela Mendoza*
- *Nemo Ikonen*
- *Ezgi June Olgac*
- *Joseph Daas*

Blood Cancer Network Ireland

Irish Research Council
An Chomhairle um Thaighde in Éirinn

Science Foundation Ireland sfi For what's next

Horizon 2020
Horizon Europe
(2021-2027)

Actions

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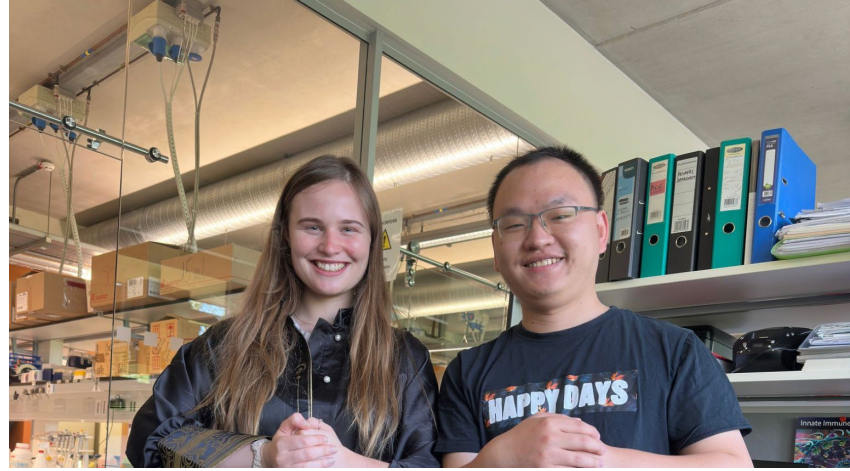
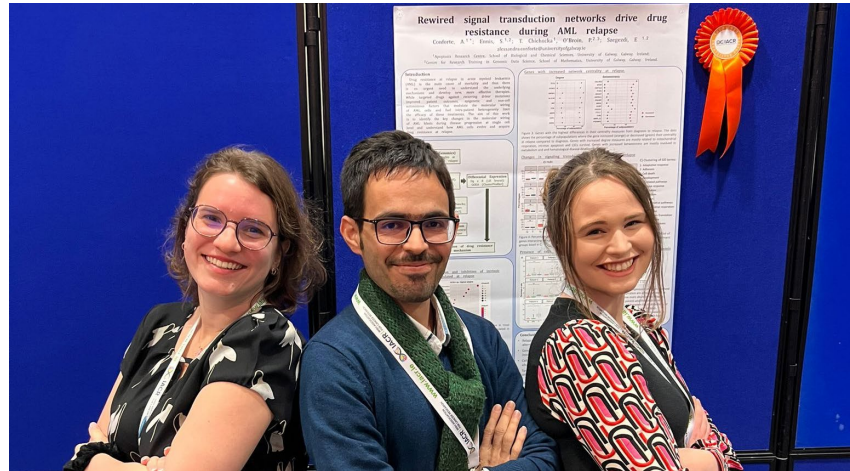
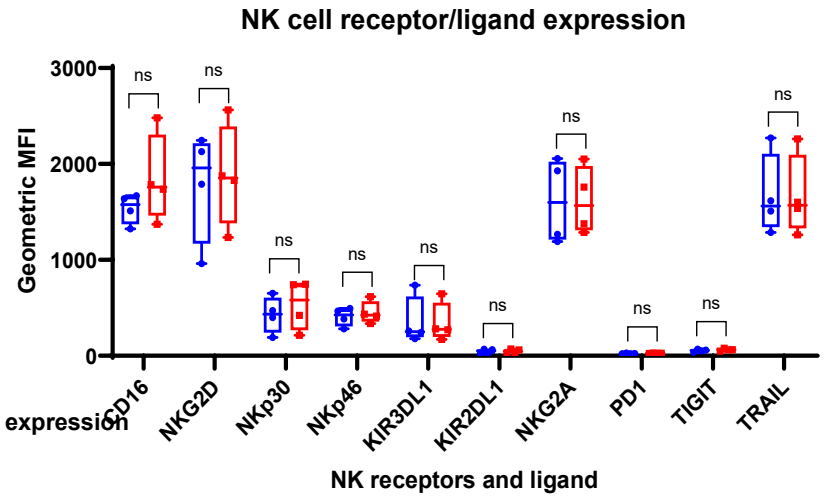
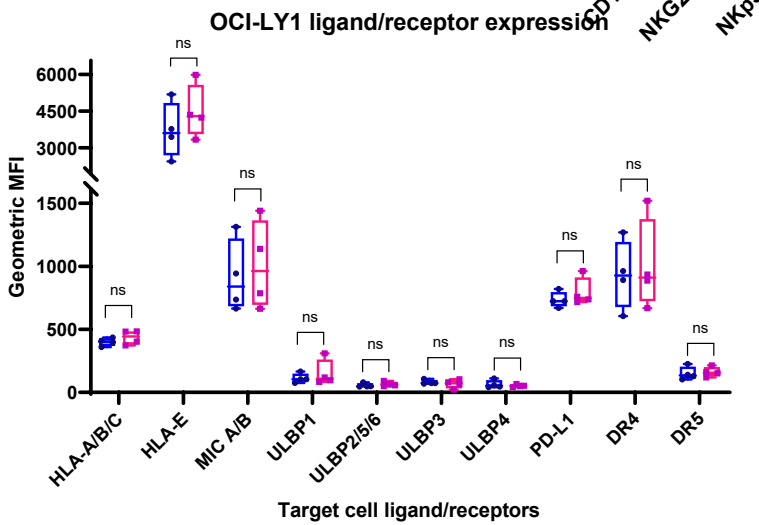
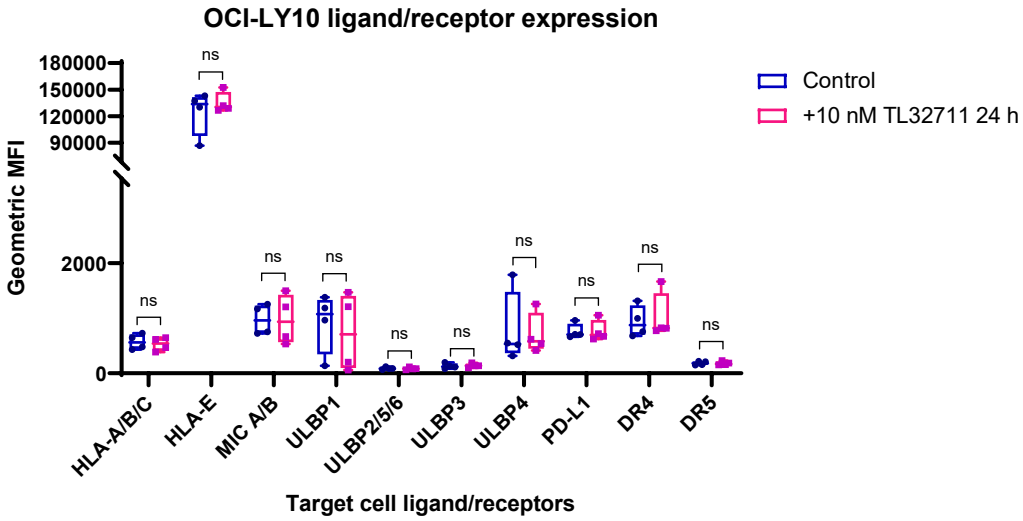

HAPPY DAYS


Rewired signal transduction networks drive drug resistance during AML relapse

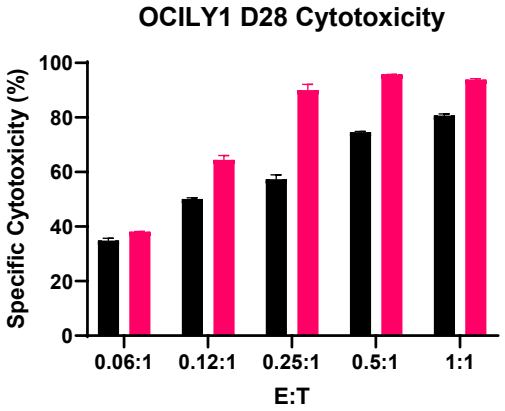
cIAP inhibition does not change NK receptor and ligand expression

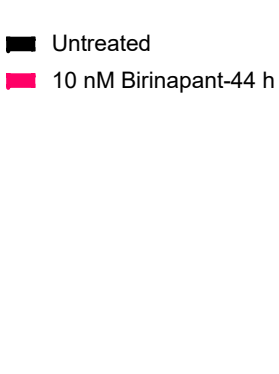


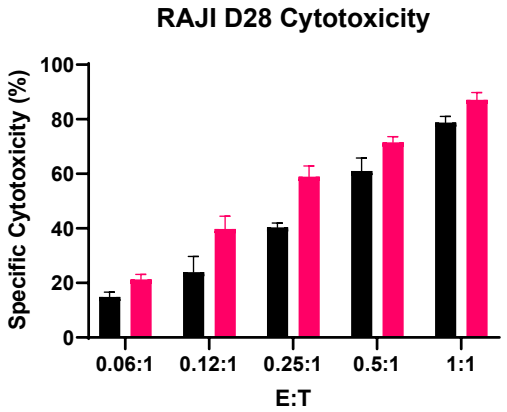


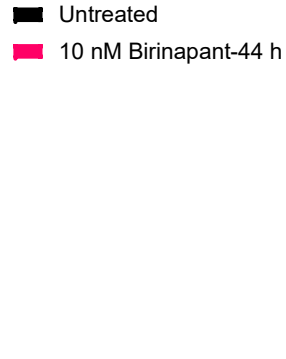


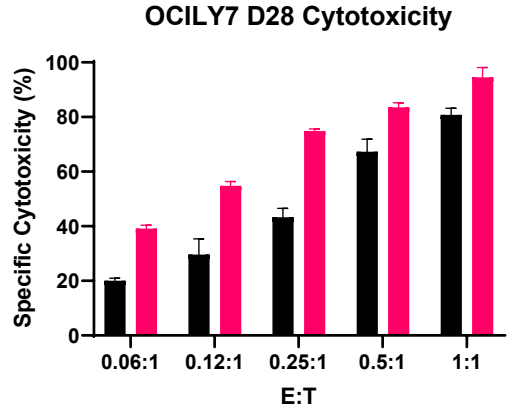
Cytotoxicity of NK cells with target cells pre-treated with 10 nM Birinapant for 24 h and 10 nM birinapant in co-culture

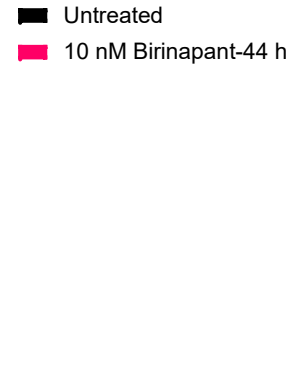


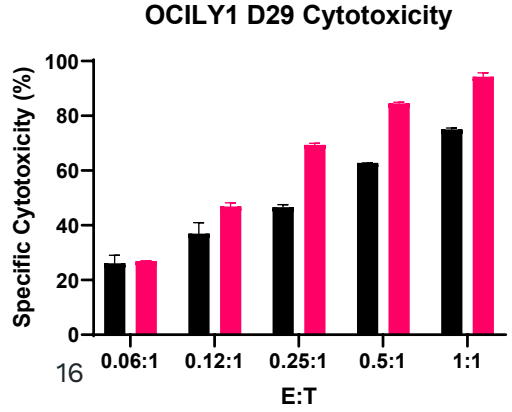


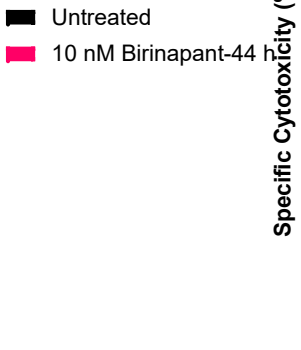


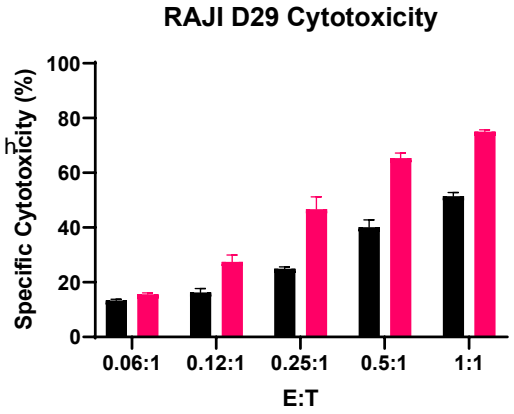


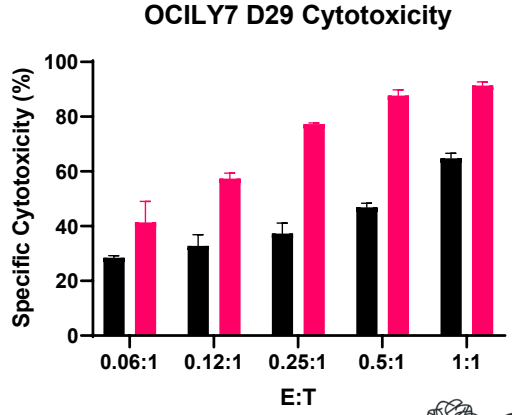




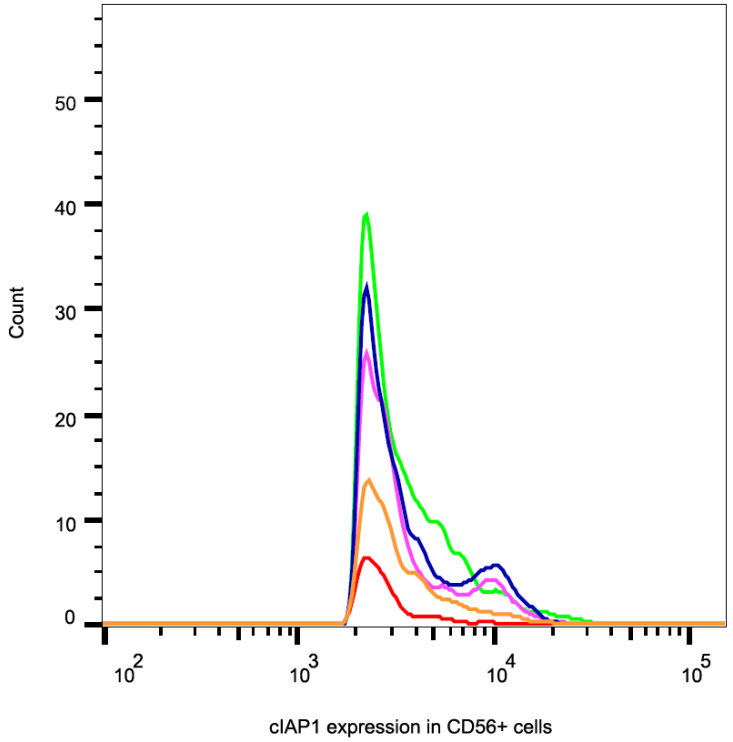


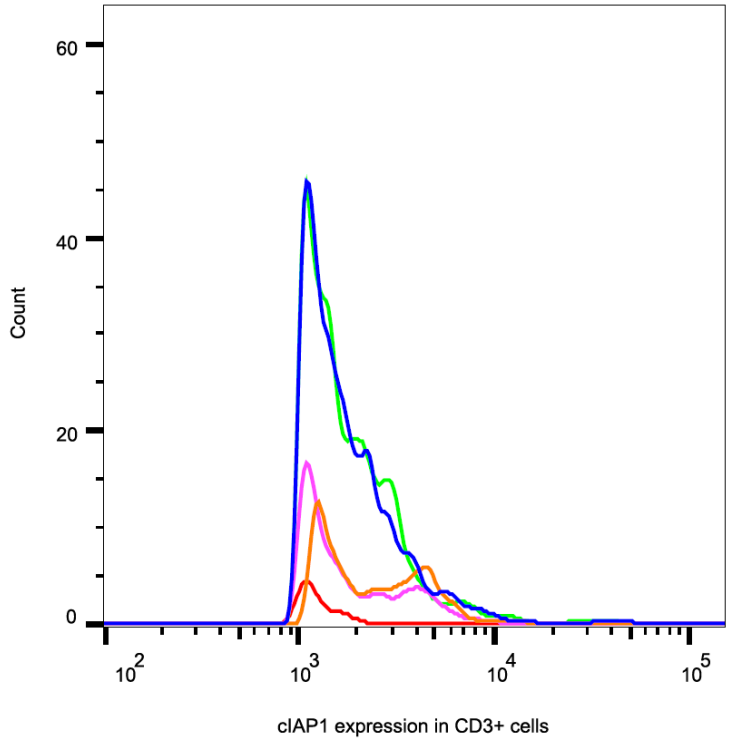


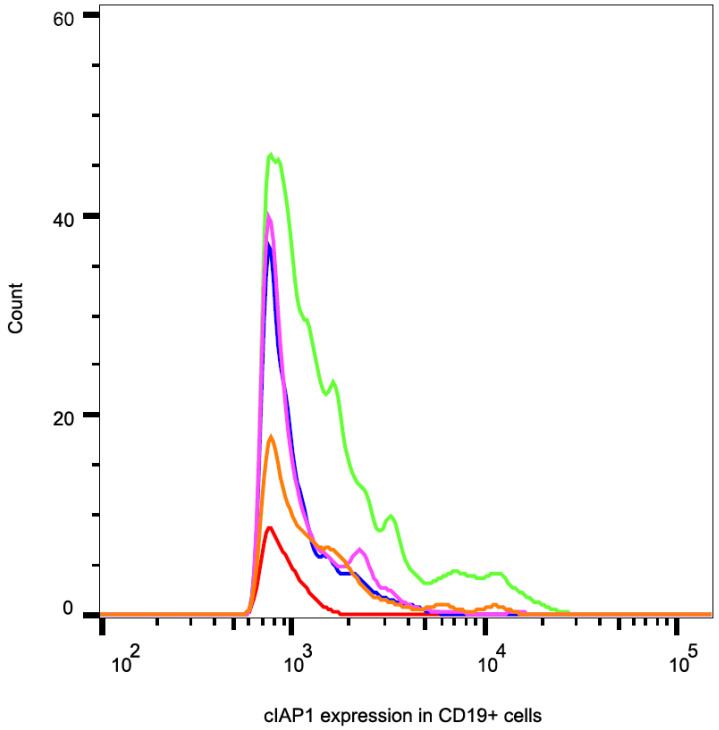




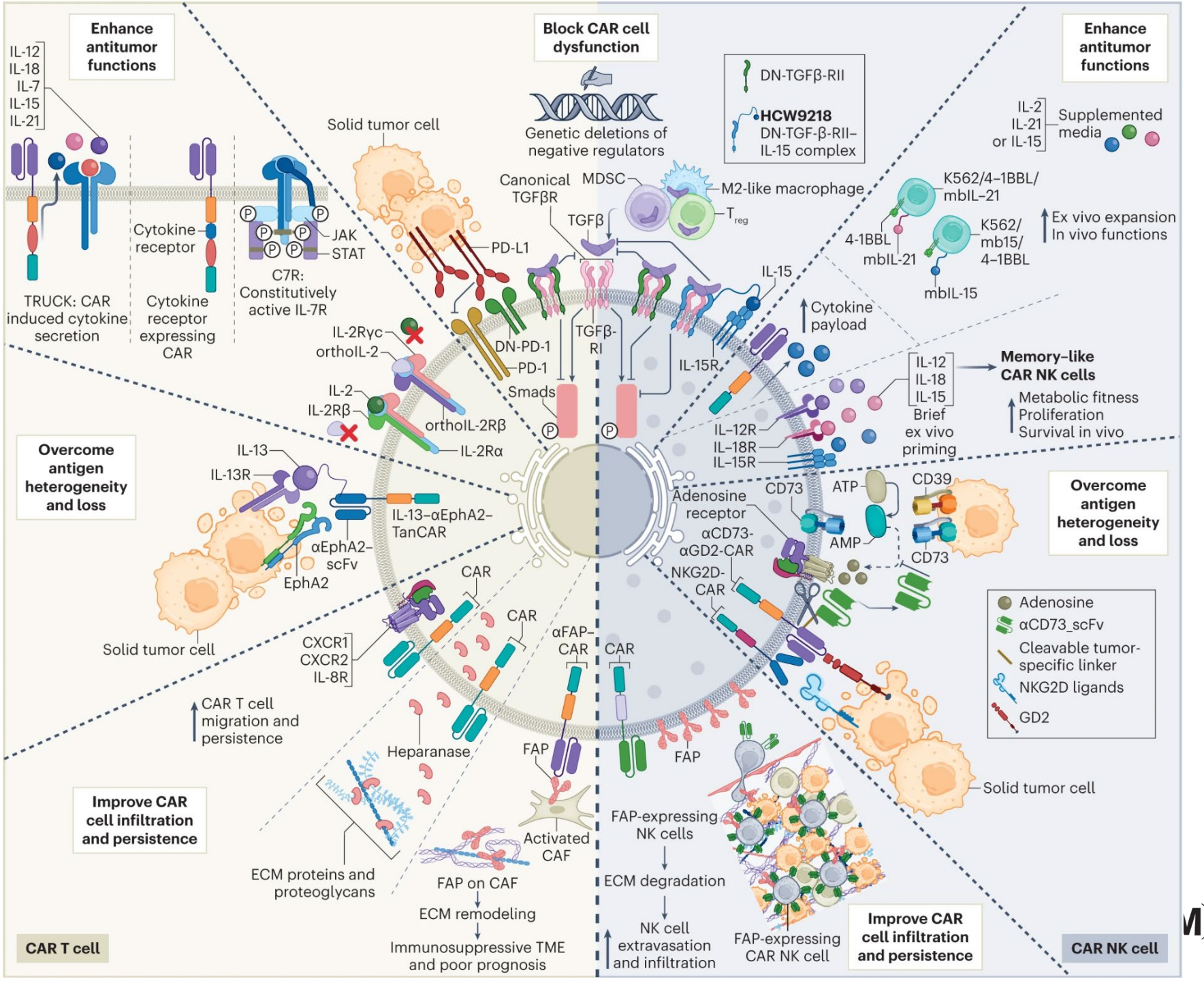
Effect of birinapant treatment on expression of cIAP in primary DLBCL patient sample







- Unstained control
- Untreated DLBCL sample
- DLBCL sample + 10 nM birinapant 24 h
- DLBCL sample + 30 nM birinapant 24 h



 Dagher and Posey, Nat Immunol., 2023