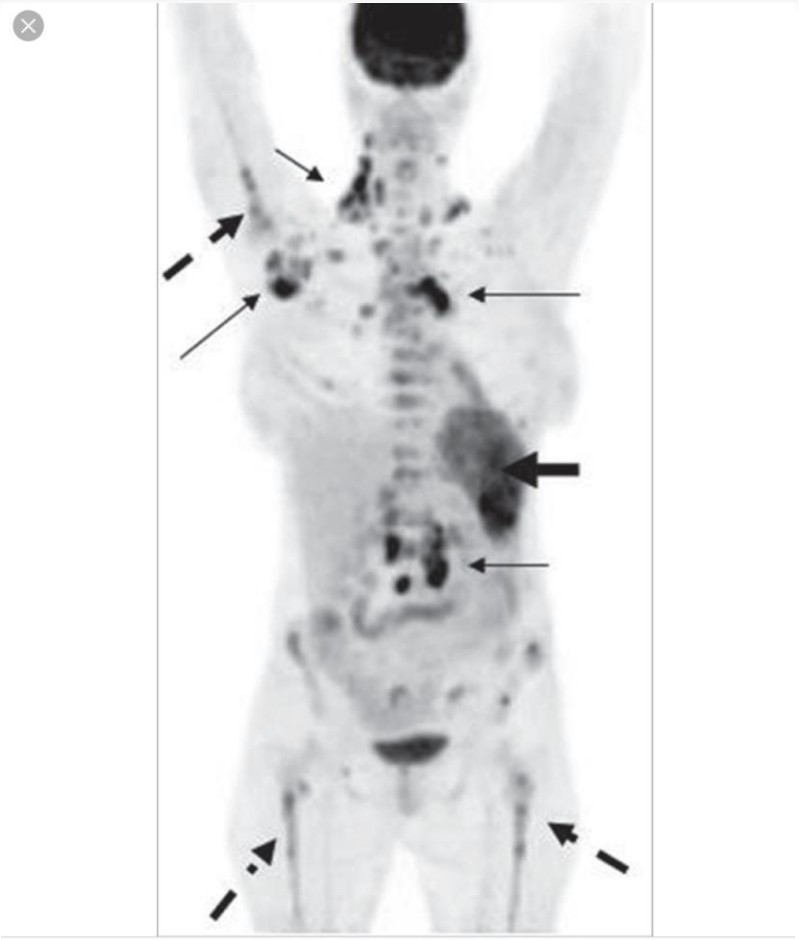
Better Health, Brighter Future

Immuno-oncology problem statement

D. Bottino, Fields Institute 12 Aug 2019

Immuno-oncology problem: background
Non-Hodgkin's Lymphoma (NHL) current paradigm = "cure or else"



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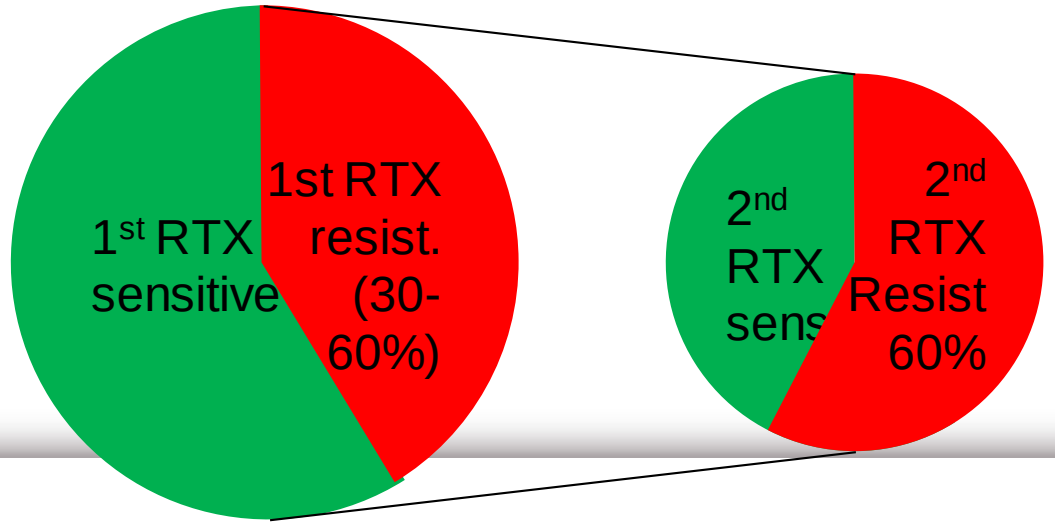
FDG-PET/CT in lymphoma D'souza MM, Jaimini A, Bansal A, Tripathi M, Sharma R, Mondal A, Tripathi RP - Indian J Radiol Imaging

- NHL includes:
  - DLBCL:Diffuse Large B Cell Lymphoma
  - FL: Follicular Lymphoma
  - CD20+
- R-CHOP 1st line therapy
  - R=rituximab (RTX)
  - If cure not achieved, options are limited
- Can we restore RTX sensitivity? In which patients?



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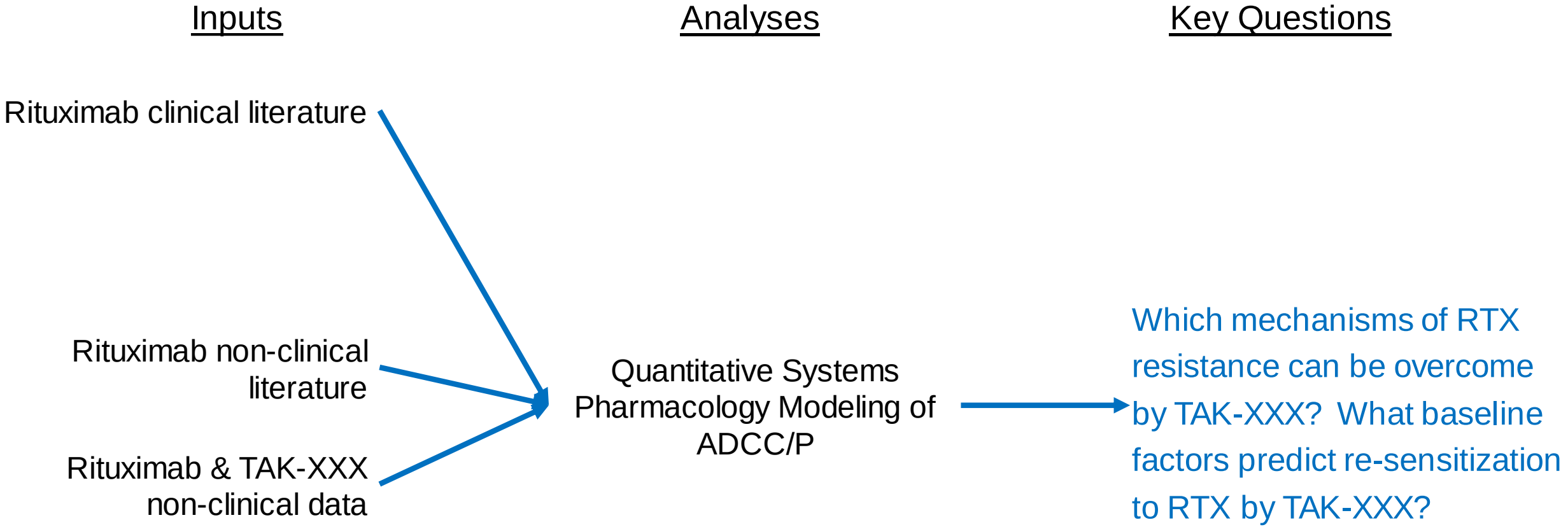
TAK-XXX QS modeling plan

D. Bottino & HB

TAK-XXX Plus Rituximab Proof of Mechanism

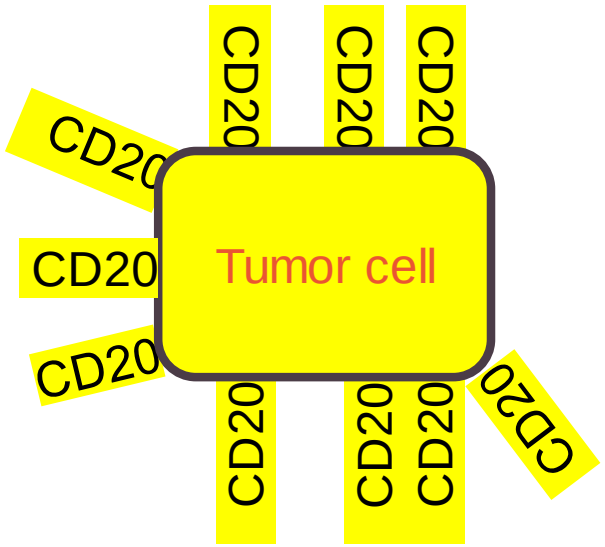
- Therapeutic hypothesis: the combination of TAK-XXX with the IgG1 class antibody Rituximab activates macrophages and NK cells correlates eliciting a robust ADCC and ADCP activity against tumor cells.
- TAK-XXX-YYY clinical trial is designed to generate data supporting the above Proof of Mechanism from a clinical and translational point of view.
- If successful, it will support future developments of TAK-XXX in combination with antibodies in other indications including solid tumors.

Key questions, supporting analyses and required inputs



QSP ADCC/P modeling to predict which mechanisms of resistance (and which patients tumors) TAK-XXX can help overcome

- Some **T**umor cells (most NHL) express CD20



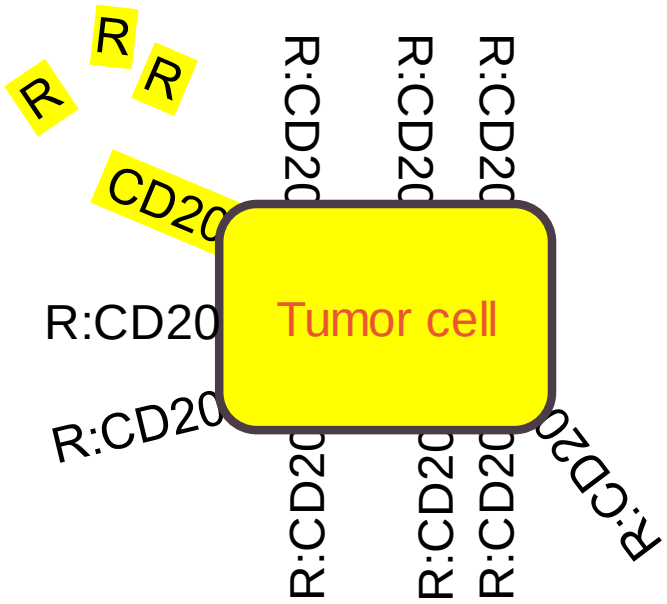
Measured quantity

E:T killing synapse

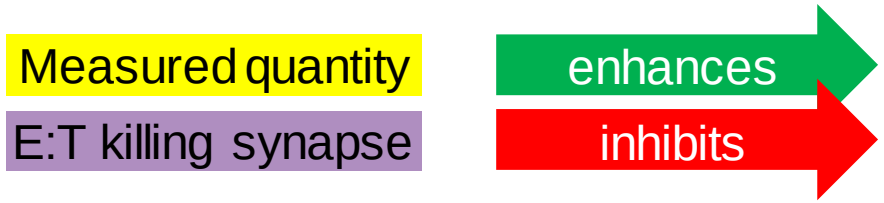
enhances

inhibits

QSP ADCC/P modeling to predict which mechanisms of resistance (and which patients tumors) TAK-XXX can help overcome



- Some **T**umor cells (mostly NHL) express CD20
- **R**ituximab: IgG1 monoclonal antibody (mAb) binds CD20
  - NB: **R**itux has some antitumor effect in vitro absent immune effector cells.



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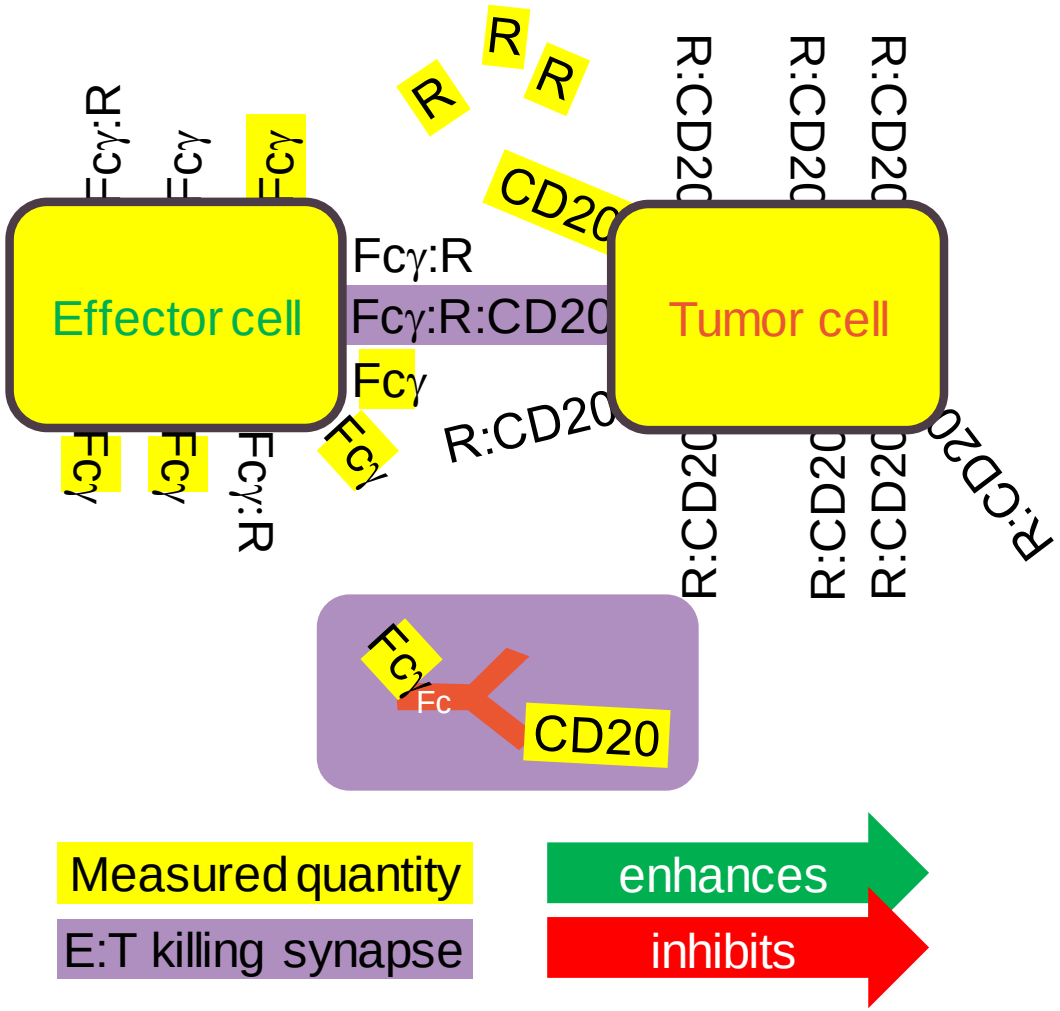

- Some **T**umor cells (most NHLs) express CD20
- **R**ituximab: IgG1 monoclonal antibody (mAb) binds to CD20
  - NB: (**R**itux some effect in vitro w/o immune cells.
  - As an IgG1 mAb, **R**itux has an Fc domain in its heavy chain "tail"
  - CD20+ cells coated ("opsonized") with Ritux can be now "recognized" by immune **E**ffector cells that express **Fc**γRIIIa receptors, which bind to Fc domains of IgG1 mAbs.
- **E**ffector cell types that typically express **Fc**γRIIIa and kill Target cells upon sufficient Fcg:mAb crosslinking:
  - Natural Killer (NK) cells, which perform **A**ntibody **D**ependent **C**ell-Mediated **C**ytotoxicity (by releasing granzymes that perforate Target cell membrane)
  - Macrophages (MΦ), which perform **A**ntibody **D**ependent **C**ell-Mediated **P**hagocytosis (by engulfing the Target cell)

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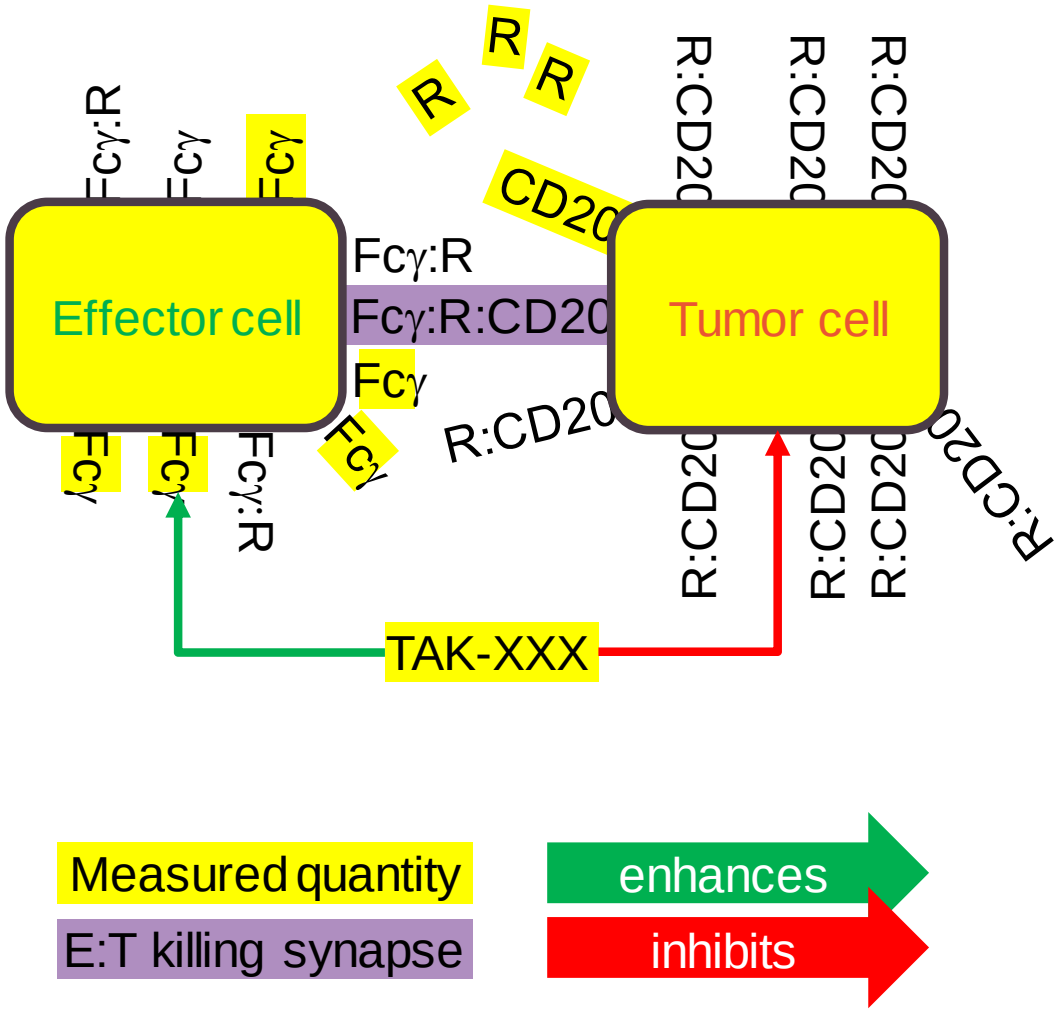

- Some **T**umor cells (most non-Hodgkin lymphomas) express CD20 on their surfaces
- **R**ituximab is an IgG1 monoclonal antibody (mAb) that binds to CD20
  - NB: **R**itux has some antitumor effect in vitro absent immune effector cells.
  - As an IgG1 mAb, **R**itux has an Fc domain in its heavy chain "tail"
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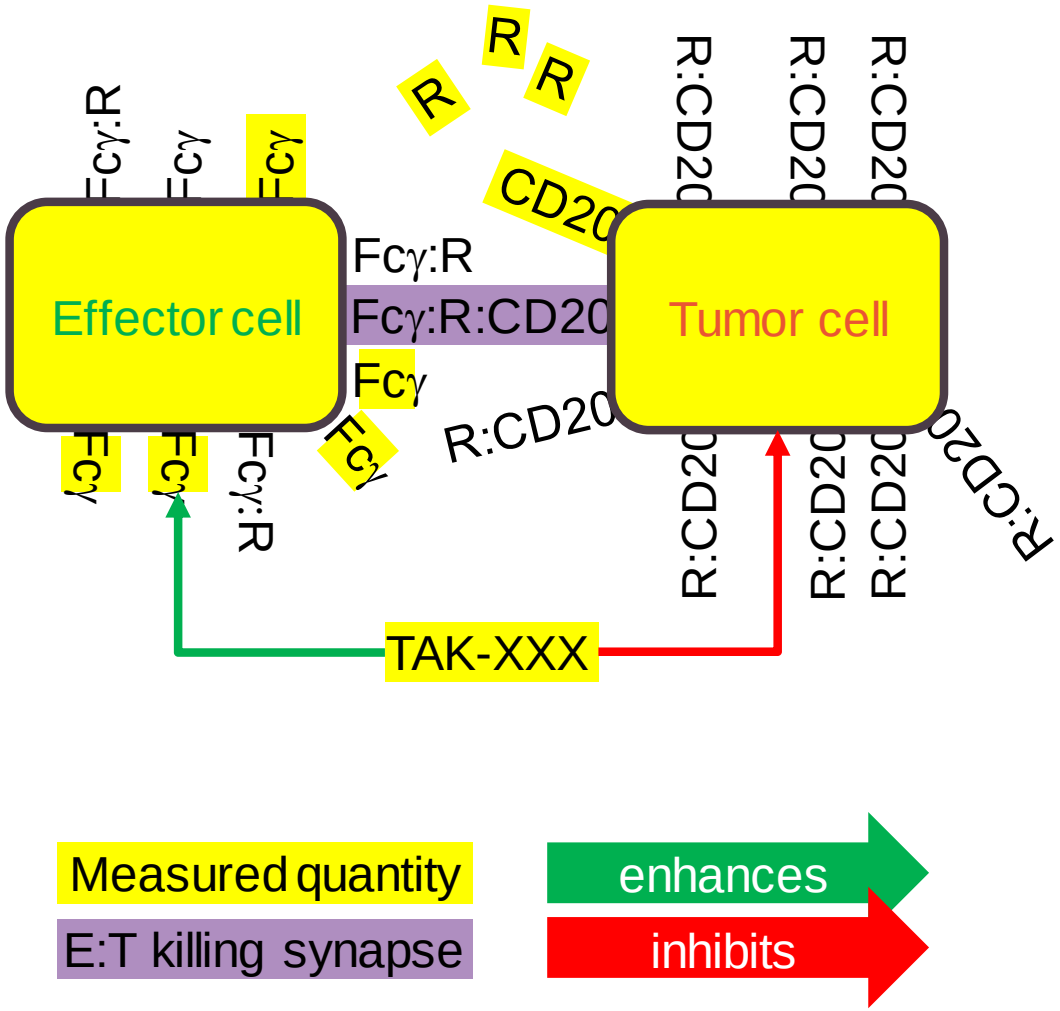
  - Macrophages (MΦ), which perform **A**ntibody **D**ependent **C**ell-Mediated **P**hagocytosis (by engulfing the Target cell)
- In addition to direct antitumor effect, TAK-XXX seems to increase activation (and Fcg expression) of these effector cells.

Your mission, should you choose to accept it…

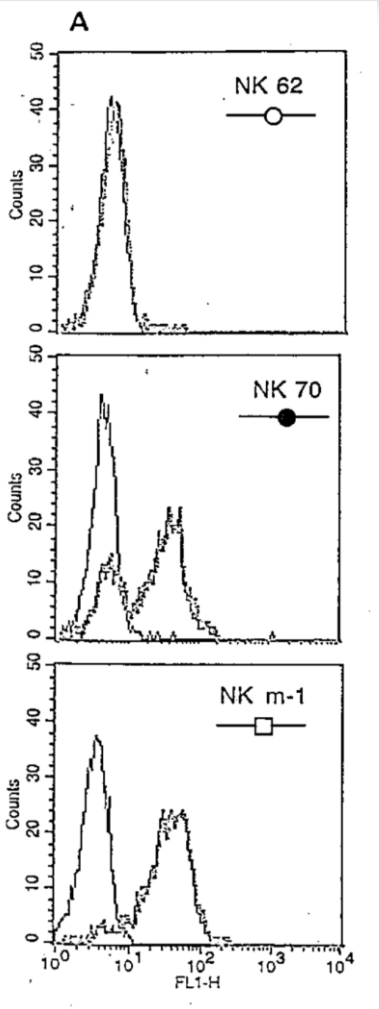


Approach:

1. Build QSP model that can predict degree of Rituximab-dependent effector cell-mediated tumor cell killing as a function of CD20 expression of target cells, FcγRIIIa (CD16) polymorphism status and expression levels on effector cells, effector:target(tumor) (E:T) ratio.
2. Use literature data and parameter estimation to calibrate model parameters. Tune a fudge factor for non-ADCC/P Rituximab MoA's (complement, etc…)
3. Create hypothetical model for direct TAK-XXX effects on NK and MP (and Tumor) cells.
4. Develop virtual patient (VP) CD20 expression and CD16+ cell count / Fcg polymorphism population distributions based on clinical literature in RTX-R/R population
5. Simulate and characterize which VP's respond or don't: prob(response|CD20,CD16,SNP,[R],[XXX])

Time permitting

Sub-questions



CD16/cell

1. Which mechanisms of R resistance could be overcome by increased NK or MP activation and/or increased expression of CD16 by NK and MP cells?
2. For example, in the case of CD20 loss as mechanism of resistance, can increasing NK or MP expression of CD16 overcome partial CD20 loss, and if so, how much CD16 increase is required to overcome a given level of CD20 loss?
3. Some patients have a single-nucleotide polymorphism (SNP) that decreases the affinity of CD16 to the Fc domain of R, potentially diminishing ADCC and therefore R efficacy. What is the relationship of CD16:Fc affinity to ADCC, and to what extent can it be overcome by increasing CD16 expression?
4. How sensitive is ADCC to effector:target (E:T) cell ratio compared to other model parameters?
5. Flow cytometry can be used to estimate the CD16 or CD20 expression levels in tens of thousands of individual effector or tumor cells in each clinical blood or tumor sample. Is this statistical distribution of CD20 levels among tumor cells and CD16 levels among effector (NK & MP) cells in the patient important for predicting ADCC potential, or do frequently used summary measures like median fluorescence intensity (MFI) and percent of cells above a threshold (% positive) suffice (and if so, which one)?

references

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Thank you