



Modeling Cell-Cell Interactions in T-Cell Dependent Cytotoxicity (TDCC)-Based Cancer Therapeutics

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IMA Bootcamp Kickoff

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Better Health, Brighter Future



A little about me



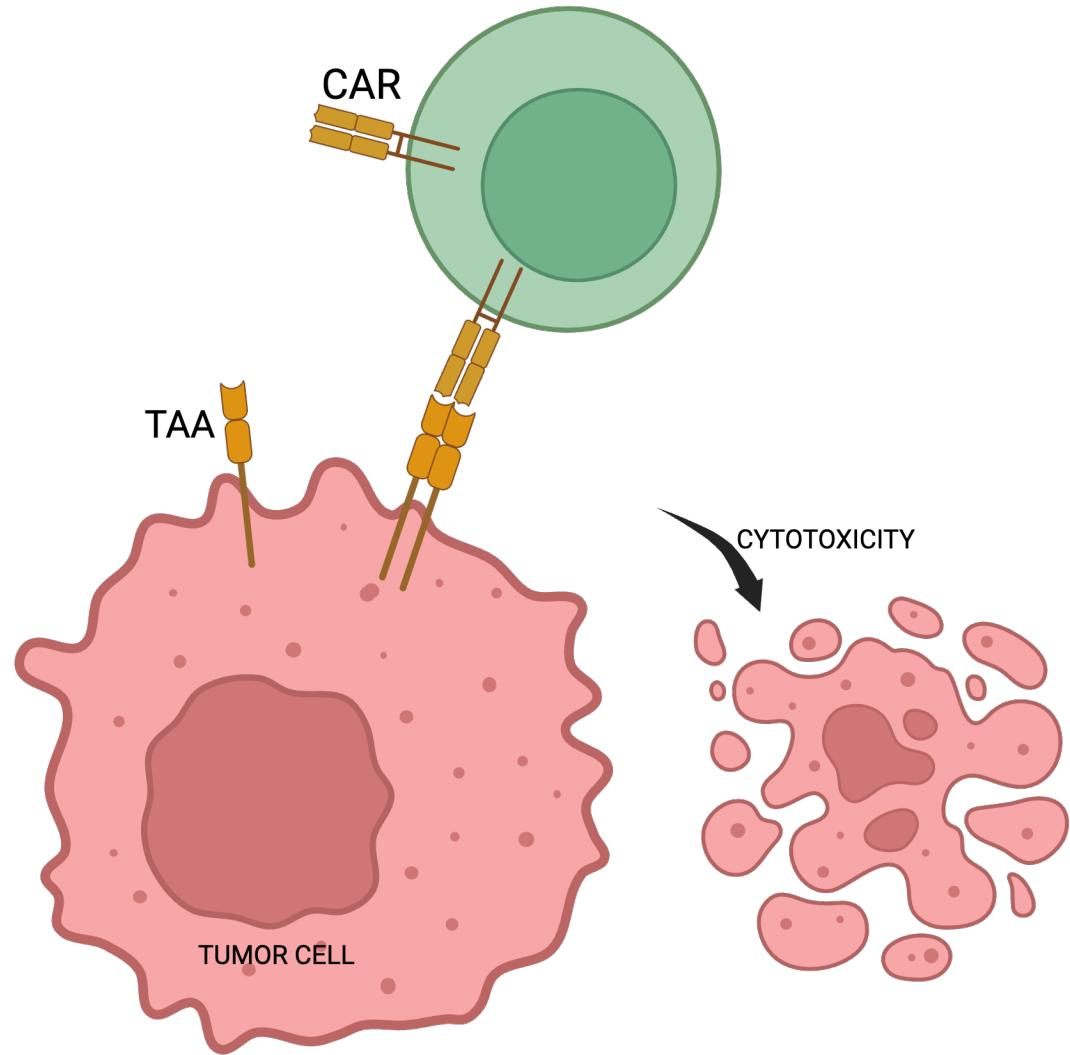
- Education:
 - Hamilton College (BA-Math)
 - Tulane University (PhD, App Math)
 - U of Utah (instructorship)
 - UC Berkeley (NIH postdoc)
- Work:
 - Physiome Sciences
 - Bioanalytics Group LLC
 - Novartis Pharma (ONC)
 - Roche Pharma (ONC)
 - Takeda Pharma (ONC)
- Hobbies:
 - Karate
 - Aikido
 - Yoga
 - Woodworking
- Fam
 - Wife, 2 kids, 2 cats, 1 dog



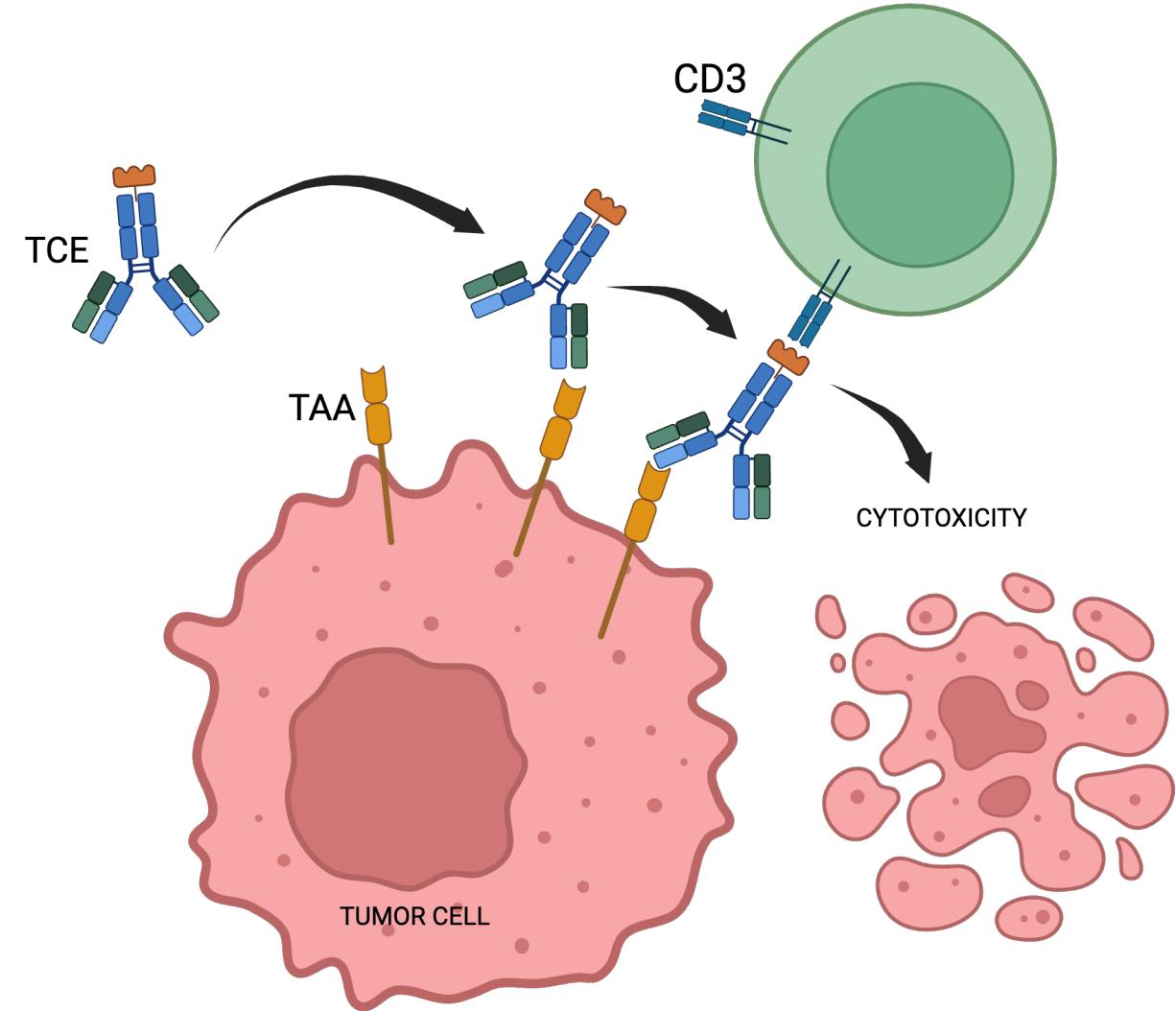
Cancer research has recently focused on exploiting effector T cell capabilities to detect and kill cancer cells expressing a tumor-associated antigen (TAA)



Chimeric Antigen Receptor (CAR) T cell



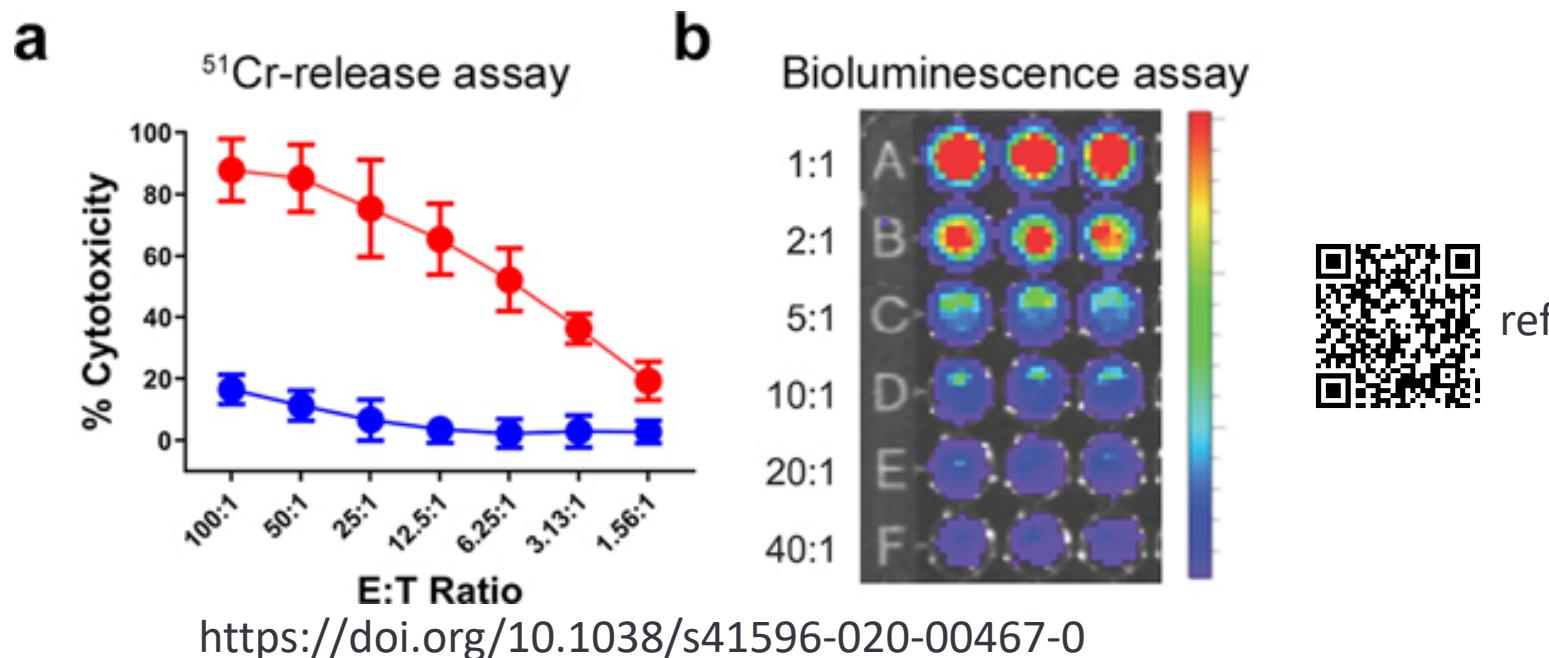
T-Cell Engager (TCE)



Discovery & optimization of CAR & TCE therapies rely heavily on in vitro assays measuring target cell killing as a function of Effector:Target cell ratio (E:T)

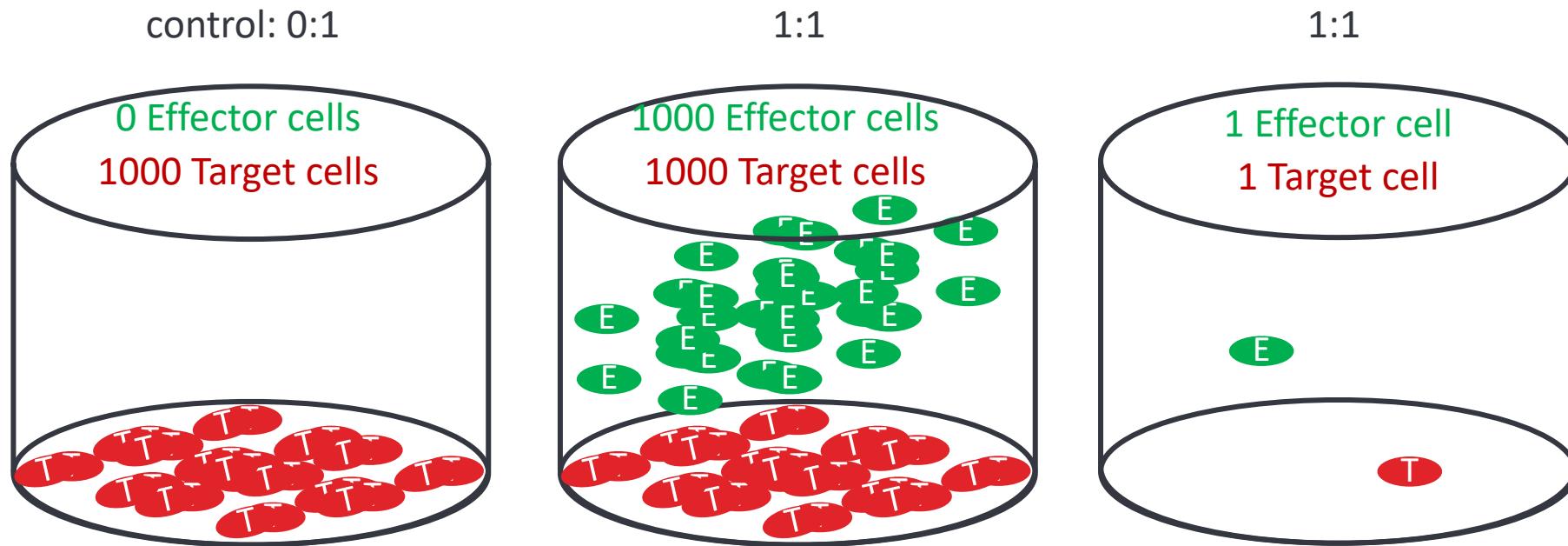


- Most in vitro assays are run at super-physiologic E:T ratios to maximize S/N
- In vivo and clinical tumors have much lower E:T ratios (~1:100 in nature, likely higher for cell therapies)
- Modeling needed to “extrapolate down” to physiologic E:T ratios



- But is E:T ratio even the correct independent variable? Is killing invariant under fixed E:T ratio?

Thought experiment: 2 wells with E:T = 1:1



- Incubate for $t_f = 24$ hours & compare the number of Target cells at 24h to the control well: $F \equiv \frac{T(t_f; E_0, T_0)}{T(t_f; 0, T_0)}$
- On one hand, they might have the same expected F ... albeit with very different variances
- On the other hand, interactions are more likely in the well with 1000 Effector and Target cells ...
- Spatial considerations: typically, not a well-mixed system: Target cells are plated first, and effector cells added

Boot Camp Project Team (BCPT)

Goal: (ODE) model relationship between effector and target cell densities and cytotoxicity

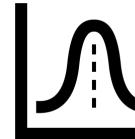


- Some approaches to consider:

- Agent based modeling (to develop intuition, ‘quick win’)



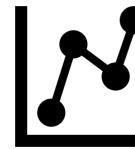
- Stochastic PDE's (distribution of F across replicate wells as a function of time & N & E:T)



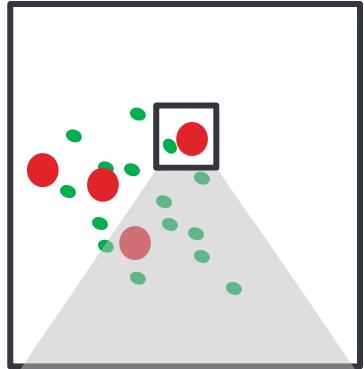
- Homogenization + Ordinary Differential Equations



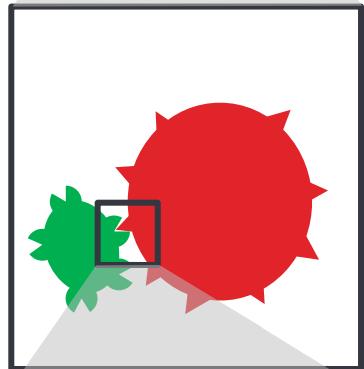
- Analyze and fit models to in vitro data (if available)



Let's stick to cell therapy, and assume constant $\text{Pr}(\text{kill} \mid \text{collision})$



$$\text{Pr}(\text{collision} \mid E, T)$$



$$\text{Pr}(\text{synapse} \mid \text{collision}; C_E, A_T, k_D)$$



$$\text{Pr}(\text{kill} \mid \text{synapse}; \Phi_E, \Phi_T)$$

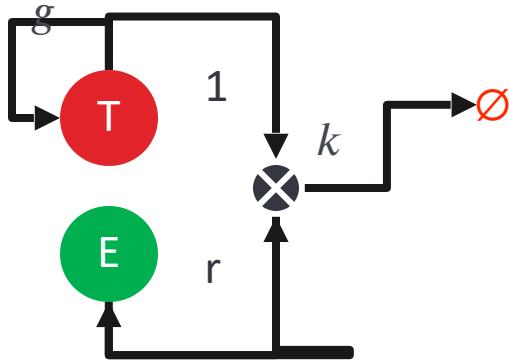


- $E(t)$ = # of Effector Cells per unit volume (or well bottom area)
- $T(t)$ = # of Target Cells per unit volume (or well bottom area)

- C_E = # of CARs per Effector cell
- A_T = # of Antigens per Tumor cell
- k_D = dissociation const for CAR:TAA

- Φ_E = other Effector cell Properties (donor or NCR numbers per cell)
- Φ_T = other Target cell Properties (cell line or Stress Ligand #s per cell)

Some frequently used TDCC ODE models



Pred-prey or ‘cellular mass action’:

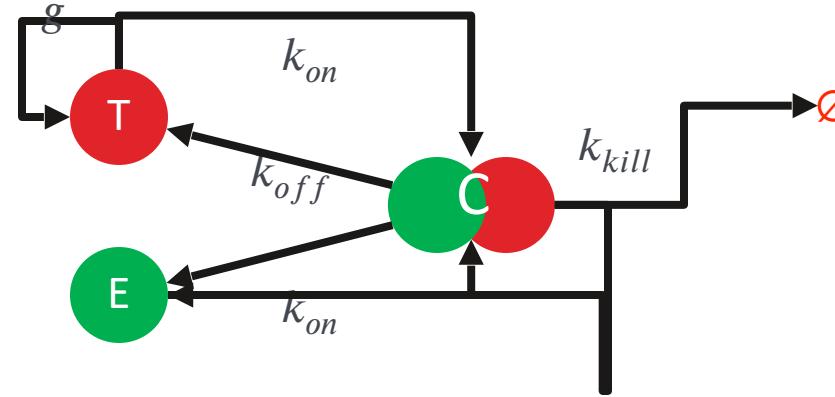
$$\frac{dT}{dt} = gT - kE^rT, \text{ where } r > 0 \text{ is a cellular “stoichiometry” constant (often } r=1\text{)}$$

Let’s assume $E \equiv E_0$

Then the ODE is separable, and we get

$$F \equiv \frac{T(t_f; E_0)}{T(t_f; 0)} = \frac{T_0 e^{(g-E_0)t_f}}{T_0 e^{gt_f}} = e^{-E_0 t_f}$$

This only depends on E_0 , not T_0



Cellular ‘enzymatic reaction’ where E is the ‘enzyme’ and T is the ‘substrate’:

$$\begin{aligned}\frac{dT}{dt} &= gT - k_{on}E \cdot T + k_{off}C \\ \frac{dE}{dt} &= -k_{on}E \cdot T + k_{off}C + k_{kill}C \\ \frac{dC}{dt} &= k_{on}E \cdot T - k_{off}C - k_{kill}C\end{aligned}$$



initial exercise: can we find expression for F at a given time t_f ? at steady state?

conservation... what if E’s proliferate too?



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