Mathematical Modelling of CD19⁺ B Cell Reconstitution in Children After Insult to the Immune System

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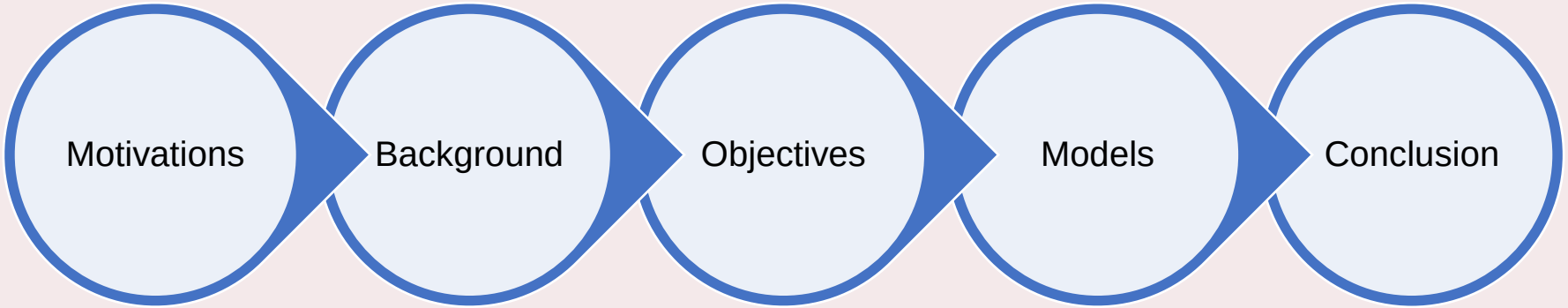
Overview



Overview

Motivations

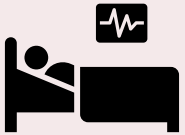
Previous immune reconstitution studies following haematopoietic stem cell transplantation **(HSCT)**

- T cells
- Adults
- Survival analysis

Unmet Need

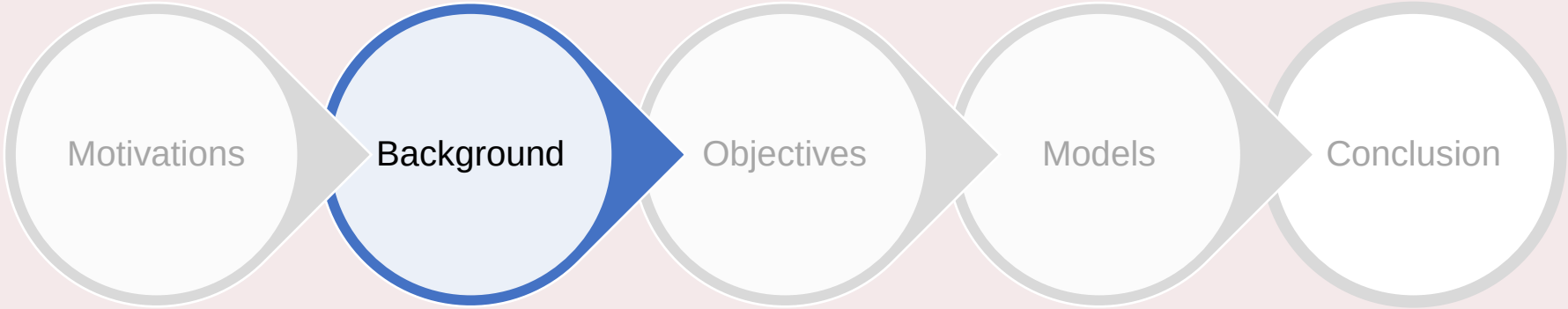
- B cells
- Children
- Pharmacometrics

Clinical Impact



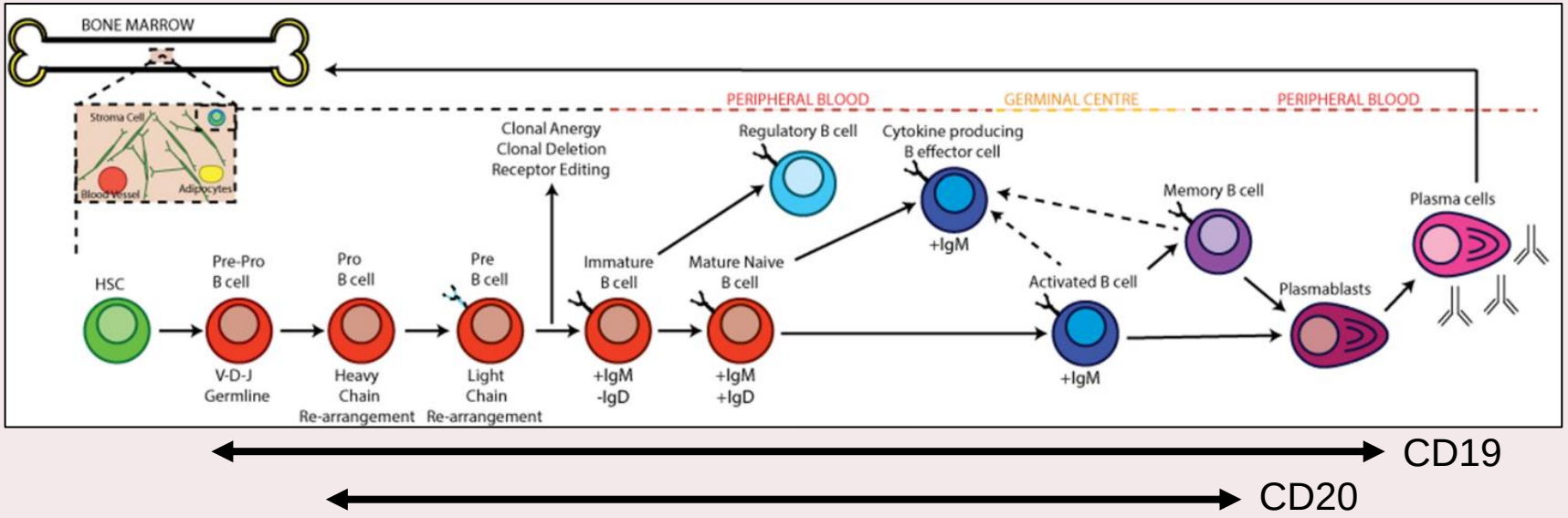
- Key factors associated with B cell recovery
- Treatment decisions
- Predict B cell recovery trajectories

Overview



Background

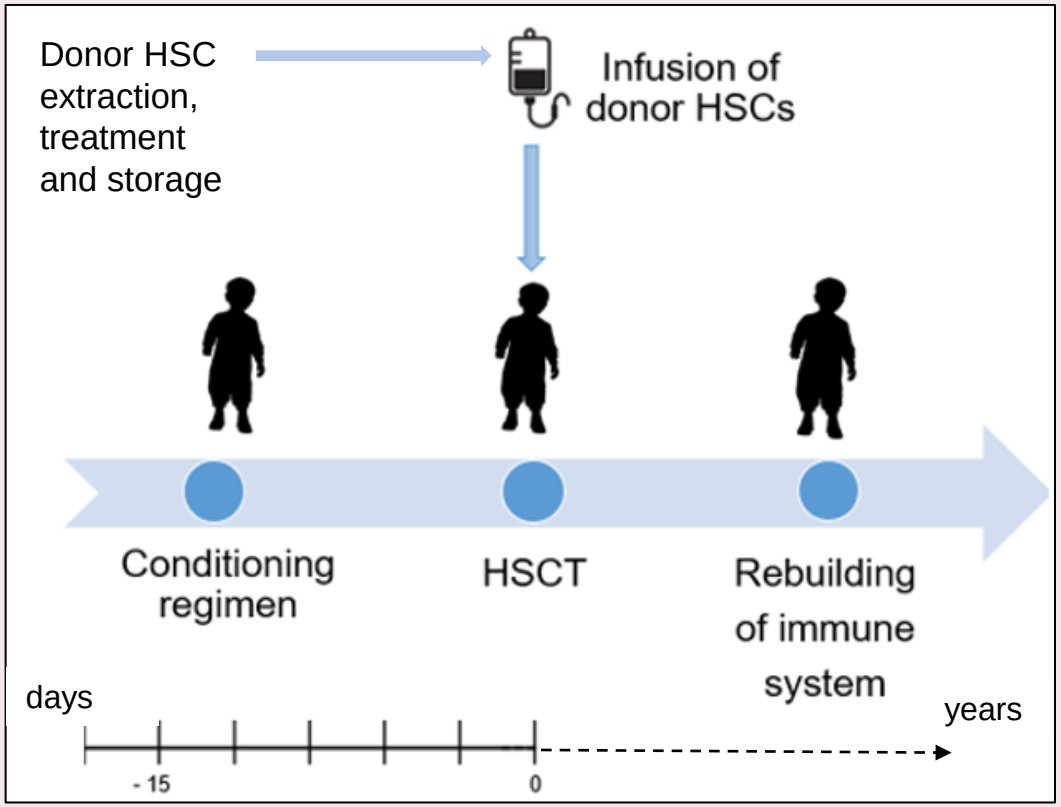
B cells: key function in adaptive immunity as antibody-producing and antigen-presenting cells



Wilkinson and Rosser (2019) Front. Immunol [1]

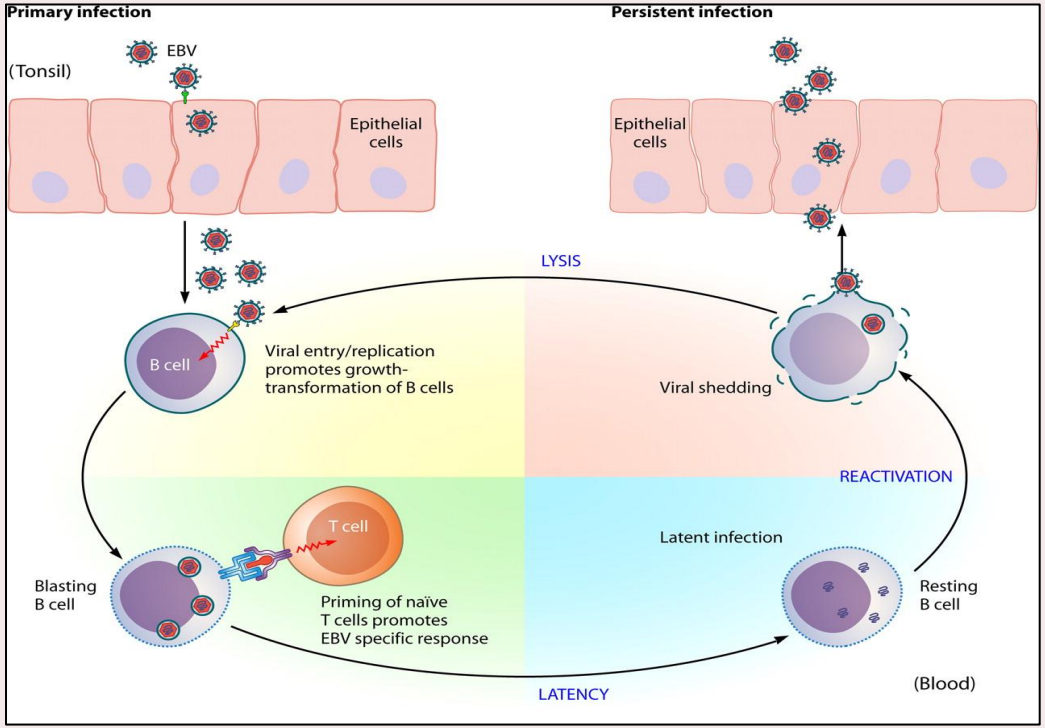
Background

HSCT : Procedure to replace damaged HSCs with healthy HSCs



Background

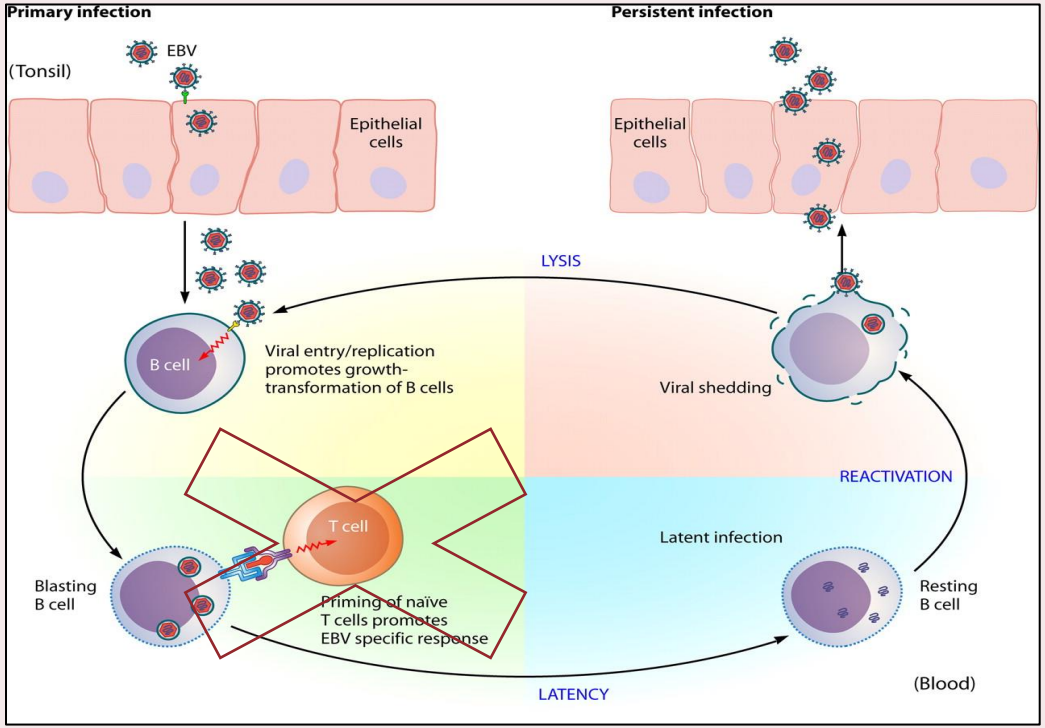
Epstein-Barr Virus (EBV): Commonly reactivated post-HSCT due to reduced EBV-specific cytotoxic T cells



Odumade et al (2011) Clin Microbiol Rev [2]

Background

EBV: EBV reactivation is the leading cause of post-transplant lymphoproliferative disease (EBV-PTLD)

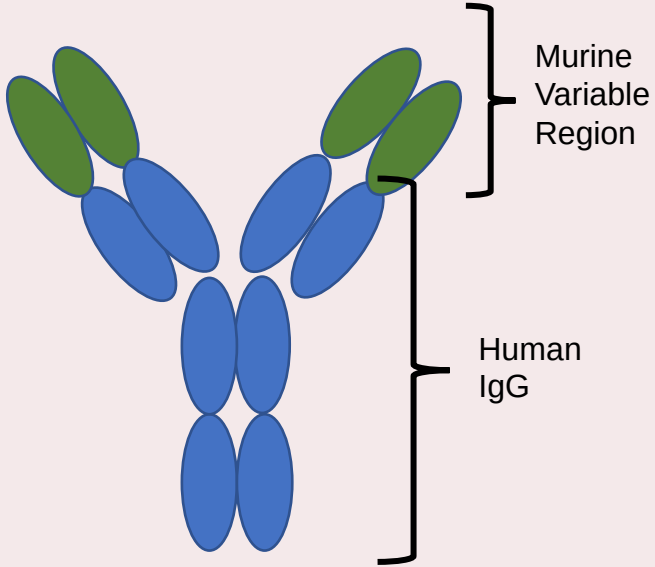


Odumade et al (2011) Clin Microbiol Rev [2]

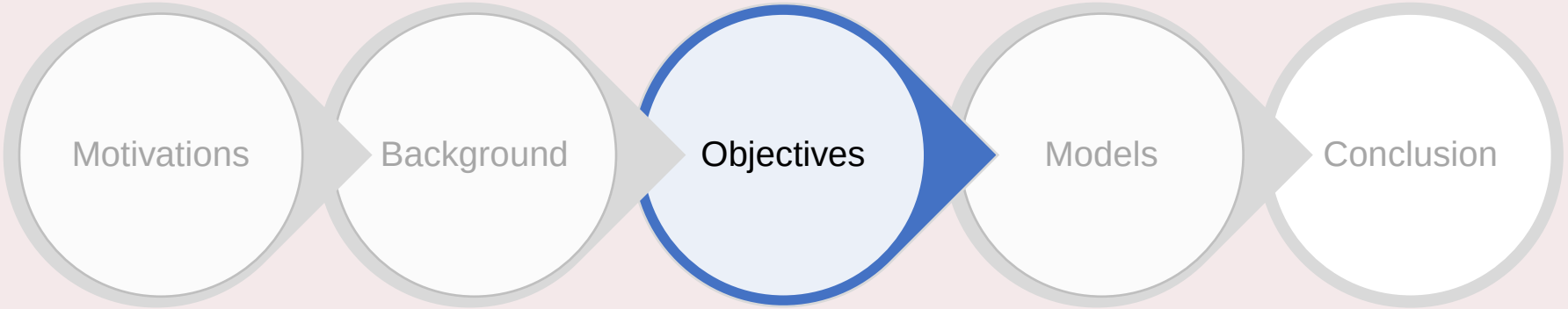
Background

Rituximab: Prescribed off-label for children with EBV post-HSCT

- Chimeric monoclonal antibody targeting $CD20^{+}$ on B cells
- Limited licensure in children
  - Rare vascular disorders
  - Previously untreated B lymphoma
- Reported half-life
  - Adults
    - 17.4 days *(Gibiansky et al (2021) CPT:PSP [3])*
    - 19.7 days *(Ng et al (2005) J Clin Pharmacol [4])*
  - Children
    - 26-29 days *(Barth et al (2013) BJH [5])*
    - 19.3 days *(Pan et al (2019) BJCP [6])*



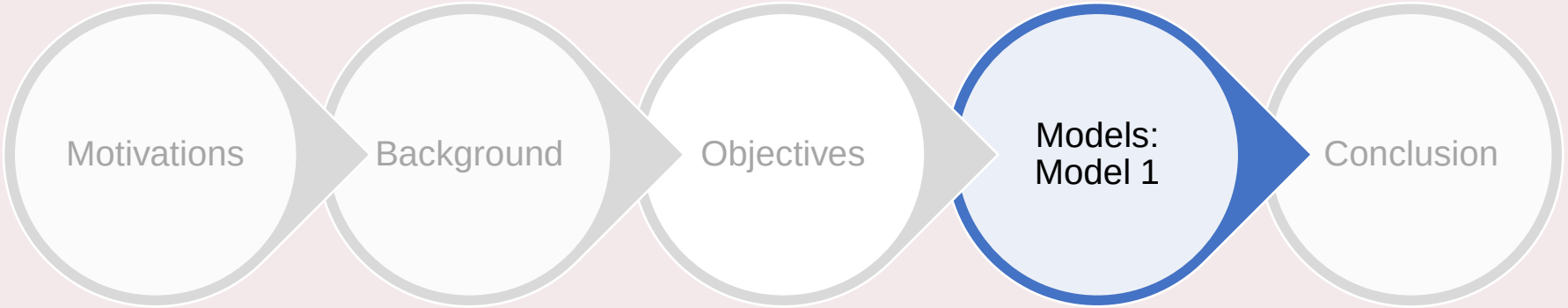
Overview



Objectives

1. Quantify $CD19^+$ B cell reconstitution in children post-HSCT, scaling for age-related effects and estimating time delay to B cell production
2. Identify the pharmacodynamics (PD) of rituximab in children with EBV post-HSCT
3. Quantify viral dynamics of EBV reactivation post-HSCT

Overview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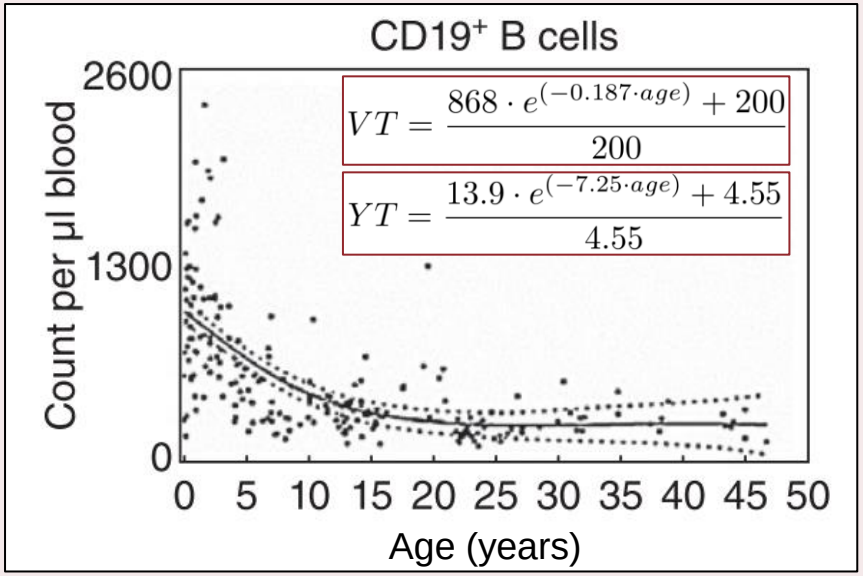
CD19⁺ B cell reconstitution in children post-HSCT

a) Scale for age-related effects

Developed B cell maturation function using non-linear least squares (VT: B cells, YT: Ki67)



Morbach et al (2010), Clin & Exp Immuno.[7]

b) Estimate time delay between HSCT and CD19⁺ B cell production

Tested two functions

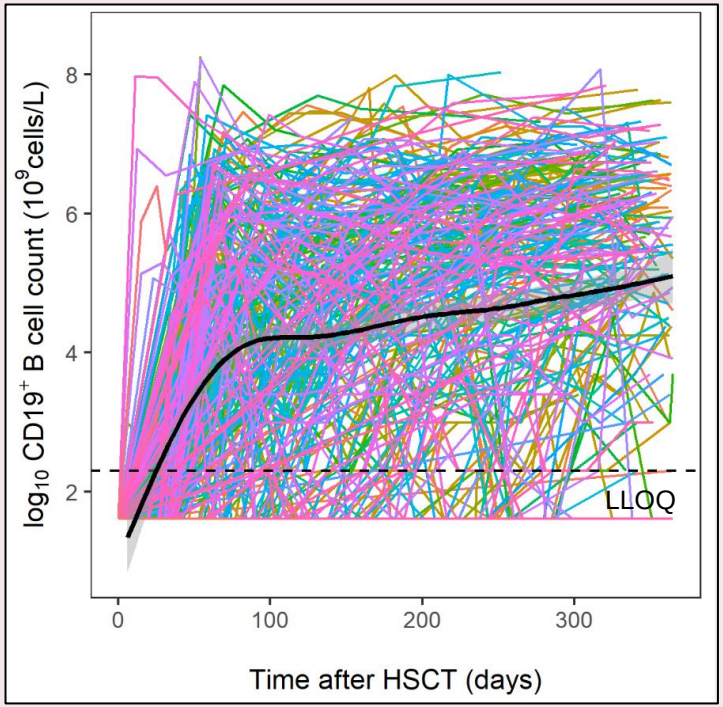
Equation	Parameters	Description
$y = \frac{1 - exp^{(\frac{-2t}{\lambda_h})}}{1 + exp(\lambda_r(1 - \frac{t}{\lambda_h}))}$	λ_h (days)	Time to recovery of bone marrow output of CD19⁺ B cells
	λ_r	Rate of recovery in bone marrow output of CD19⁺ B cells
$y = \frac{t^{Hill}}{t^{Hill} + T50^{Hill}}$	T50 (days)	Time to half-maximal bone marrow output of CD19⁺ B cells
	Hill co-efficient	Steepness of slope of CD19⁺ B cell recovery

Hoare et al (2017), Clin. Pharmacol. Ther [8]

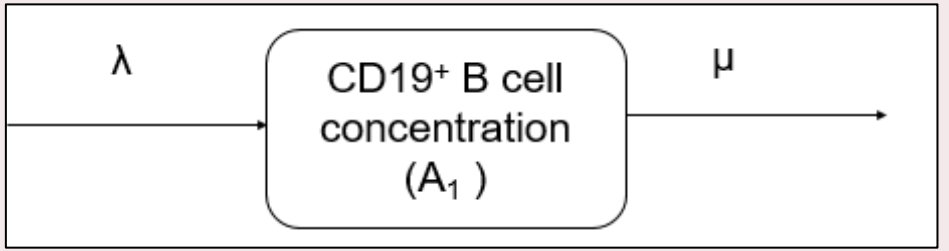
CD19⁺ B cell reconstitution in children post-HSCT

Data and Model

4115 CD19⁺ B cell counts from 359 children



Schematic and ODE



$$\frac{dA_1}{dt} = \lambda \cdot \left(\frac{T^\gamma}{T^\gamma + T50^\gamma} \right) - \mu(A_1)$$

$$\lambda = \lambda_{adult} \cdot VT \cdot YT$$

$$\mu = \mu_{adult} \cdot YT$$

CD19⁺ B cell reconstitution in children post-HSCT

Results

Description	Parameter/ Covariate (units)	Estimate/Effect size (% RSE)	% BSV (% RSE)	Bootstrap 95% CI	Bootstrap median
Number of CD19⁺ B cells at steady state	*Setpoint ($x10^6$ cells/L)	*112	-	-	-
CD19⁺ B cell production rate constant	λ ($x\ 10^6$ cells/day)	1.68 (2.45)	115.76 (0.0011)	1.36 – 2.05	1.68
CD19⁺ B cell death rate constant	μ (cells/day)	0.015 (3.00)	113.58 (0.0061)	0.013 – 0.018	0.015
Steepness of slope of CD19⁺ B cell recovery	Hill	4.17 (0.49)	-	4.05 – 4.29	4.17
Time to half-maximal output of CD19⁺ B cells from bone marrow	T50 (days)	58.9 (1.07)	137.48 (0.0033)	44.0 – 64.0	58.3
Effect of MAC on T50	T50_MAC	0.166 (10.12)	-	0.039 – 0.322	0.166
Effect of PID on T50	T50_PID	-0.551 (0.16)	-	-0.595 – to -0.457	-0.551
Effect of matched donor on T50	T50_Donor	-0.00998 (25.75)	-	-0.116 – 0.0786	0.00710

Higher than reported in adults (Macallan et al (2005) Blood [9])

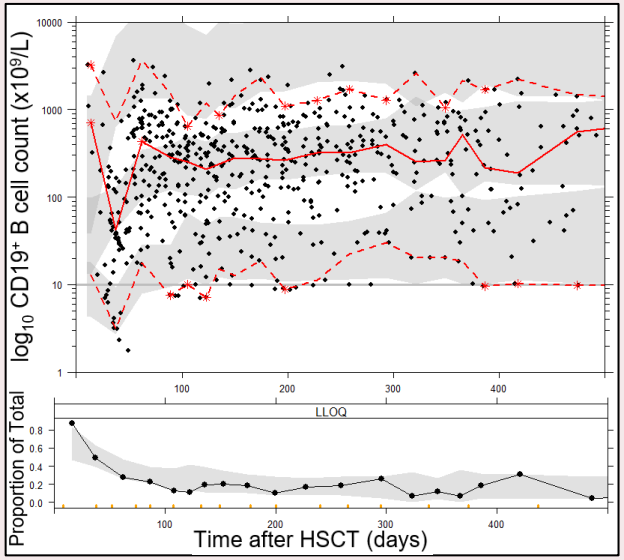
Aligns with experimental data (Marie-Cardine et al (2008), Clin. Imm. Ther [10])

- *Denotes derived parameter (λ/μ).
- Initial condition of B cell compartment set to 5 x 10^6 cells/mL.
- Linearly parameterised covariate effects, i.e. multiplication of typical parameter value by (1 + effect size).

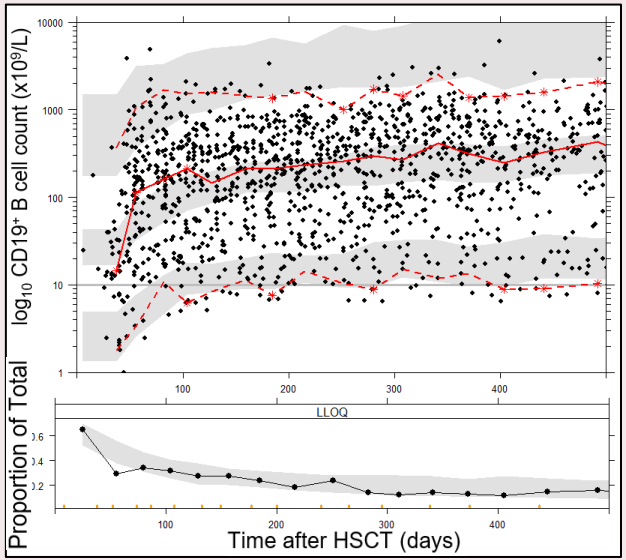
CD19⁺ B cell reconstitution in children post-HSCT

Model Evaluation by age group

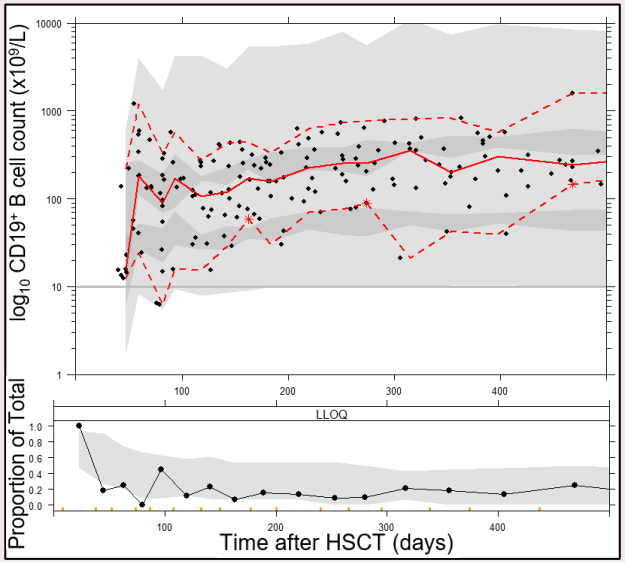
(A) Infants (< 2 years)



(B) Children (≥ 2 years and < 12 years)



(C) Adolescents (≥ 12 years)

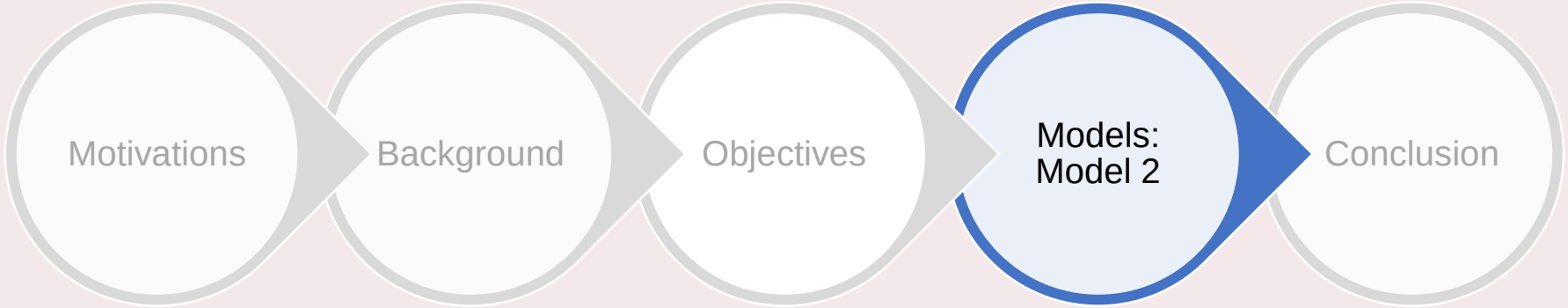


Black dots are observed data, solid red line is observed median, dotted red line is observed 2.5th, 50th and 97.5th percentiles and grey shaded area is 95% prediction intervals for 2.5th, 50th and 97.5th percentiles.

Summary of Model 1

1. Built PD model to quantify $CD19^+$ B cell reconstitution in children post-HSCT
2. Developed B cell maturation function based on $CD19^+$ B cell count and Ki67 for *a priori* scaling of age-related effects
3. Incorporated Hill-type equation to estimate time delay between HSCT and $CD19^+$ B cell production by the bone marrow

Overview


Motivations
Background
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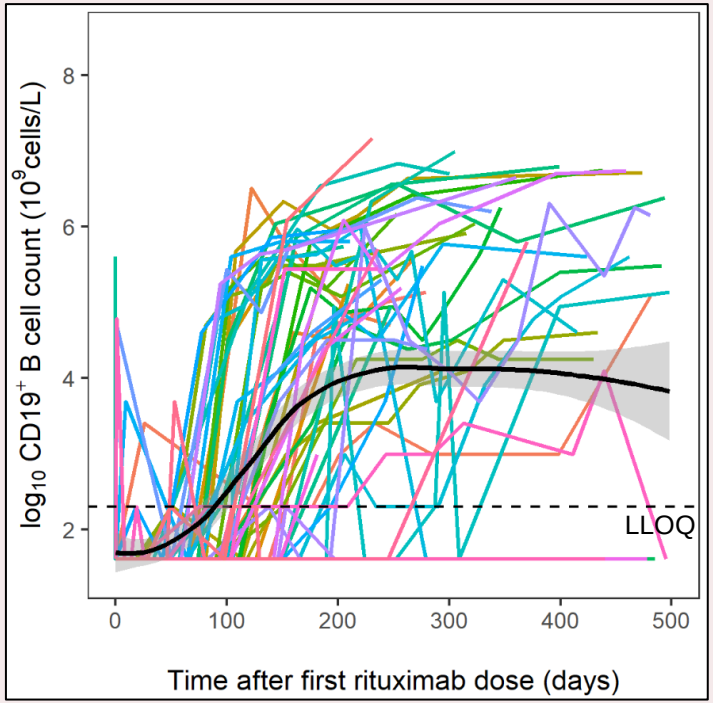
Models:
Model 2
Conclusion

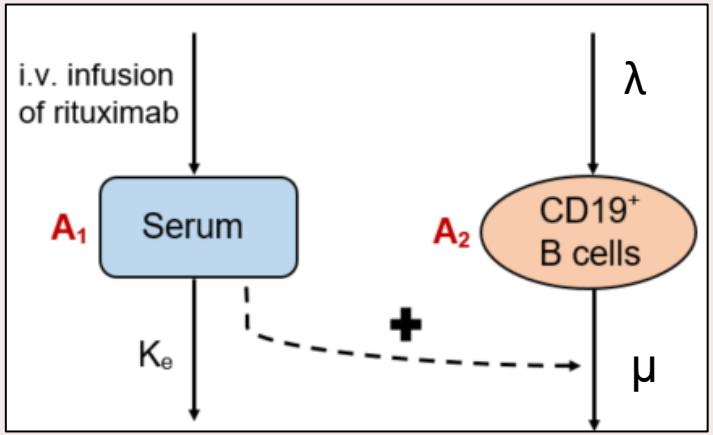
Rituximab PD in children with EBV post-HSCT

Data and Model

619 CD19⁺ B cell counts from 55 children



Schematic and ODE



$$\frac{dA_1}{dt} = -k_e \cdot A_1$$

$$\frac{dA_2}{dt} = \lambda \cdot \left(\frac{T^\gamma}{T^\gamma + T50^\gamma}\right) - \mu \cdot \left(1 + \frac{E_{max} \cdot A_1}{ED_{50} + A_1}\right) \cdot A_2$$

Rituximab PD in children with EBV post-HSCT

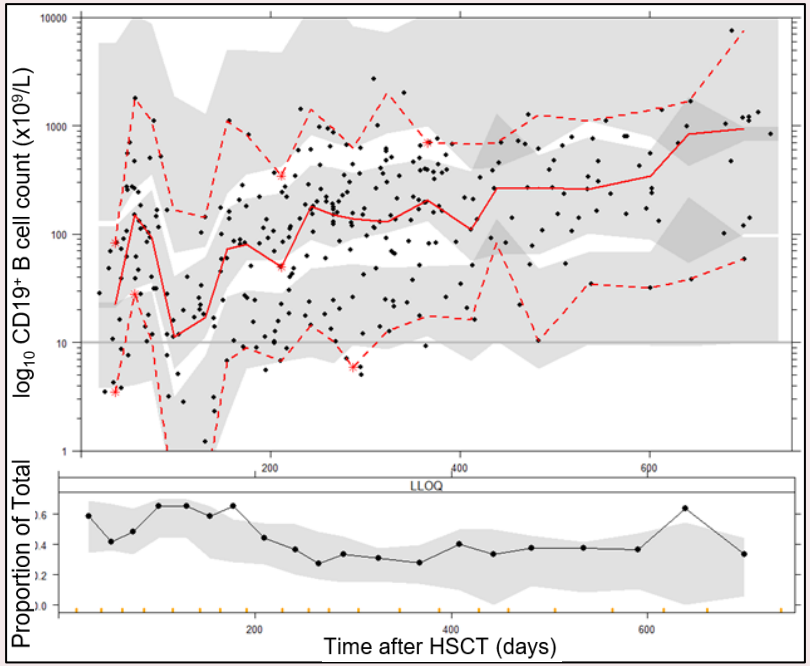
Results and Model Evaluation

Description	Parameter/ Covariate (units)	Estimate/Effect size
Number of CD19⁺ B cells at steady state	*Setpoint (x10⁶ cells/L)	*79.5
CD19⁺ B cell production rate constant	λ (x 10⁶ cells/day)	1.4
CD19⁺ B cell death rate constant	μ (cells/day)	0.017
Steepness of slope of CD19⁺ B cell recovery	Hill	3.18
Time to half-maximal output of CD19⁺ B cells from bone marrow	T50 (days)	44.8
Rituximab elimination rate constant	K_e (/day)	0.109
Maximum killing effect of rituximab on CD19⁺ B cells	E_{max}	84.4
Rituximab dose producing 50% of maximum killing effect	ED50 (mg)	0.921
Effect of MAC on T50	T50_MAC	0.954
Effect of PID on T50	T50_PID	-0.474
Effect of matched donor on T50	T50_Donor	-0.465

Estimated half-life (children):

-26±3 days
-19.3 days (11.1–73.7)
-6.35 days Current study

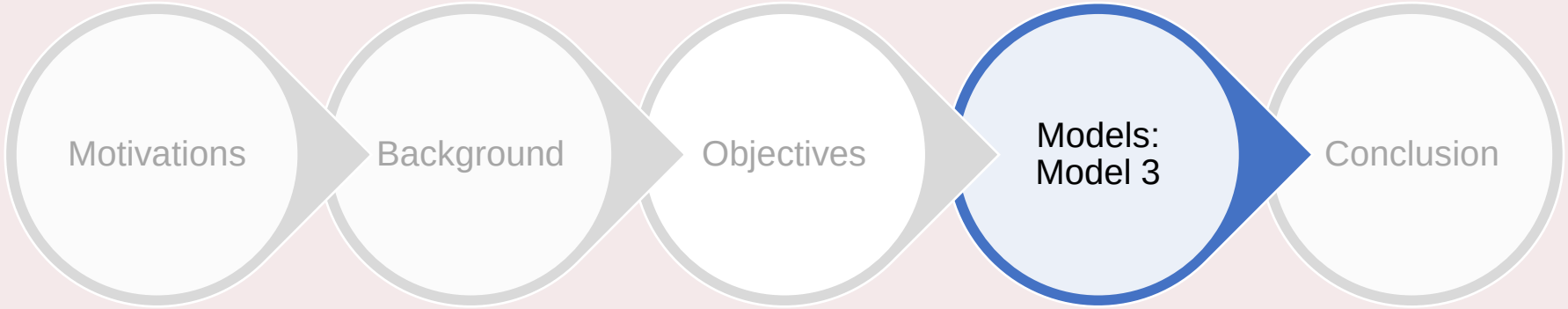
Higher in non-rituximab patients



Summary of Model 2

1. Built K-PD model to quantify rituximab PD in children with EBV post-HSCT
2. Incorporated rituximab drug effect using E_{max} model
3. Estimated elimination half-life of 6.35 days for rituximab

Overview


Motivations
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Model 3
Conclusion

Dynamics of EBV reactivation post-HSCT

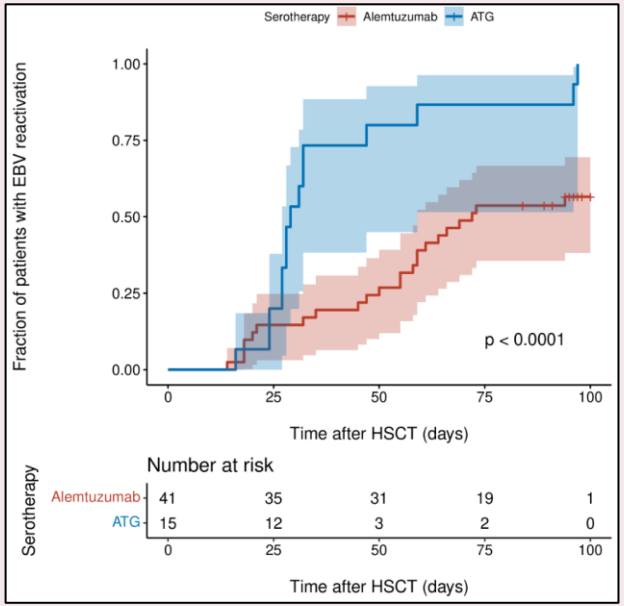
Cox proportional hazards (PH): Cox-PH model for EBV reactivation in first 100 days post-HSCT in 56 children

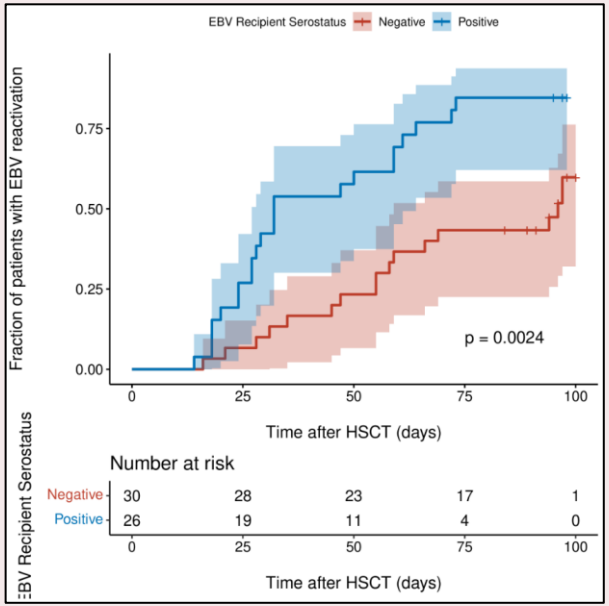
Covariates tested:

HSCT
- Donor type
- HSC source
- Cond'g regimen type

Patient
- PID diagnosis
- Age
- Donor/Recipient EBV serostatus

Immune cells + drug admin.
- $AUC_{0\text{-}100}$ for ALC/ $CD19^+$ B/ $CD4^+$ T/$CD8^+$ T cells
- No. of Rituximab Doses
- Pre-HSCT Alemtuzumab or Anti-thymocyte globulin (ATG)

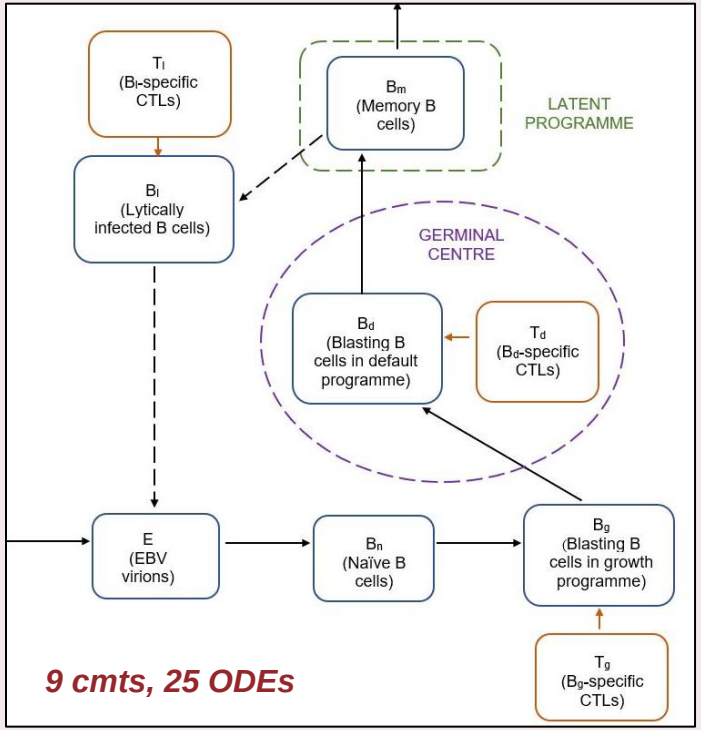


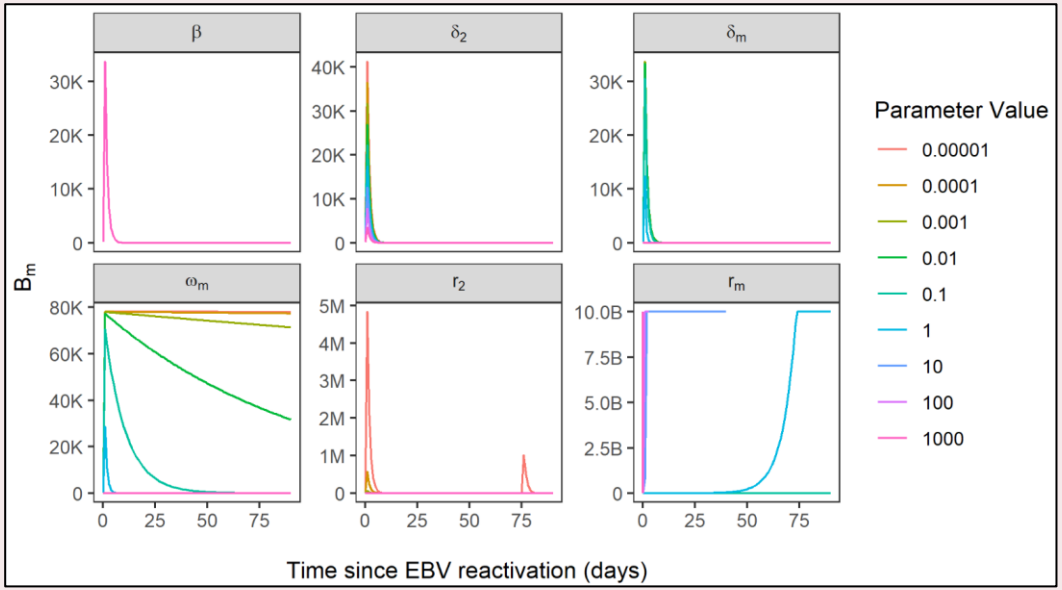


Kania et al (2022) Front Immunol [11]

Dynamics of EBV reactivation post-HSCT

Sensitivity analysis: Previously reported mechanistic mathematical model of EBV kinetics





β, NK effect on EBV inf'n; δ_2, CTL killing rate of infected B cells; δ_m, death rate of inf'd memory B cells; ω_m, memory B cell reactivation rate; r_2, CTL activation rate against infected B cells; r_m, memory B cell prolif'n rate

Akinwumi (2018) University of Alberta [12]

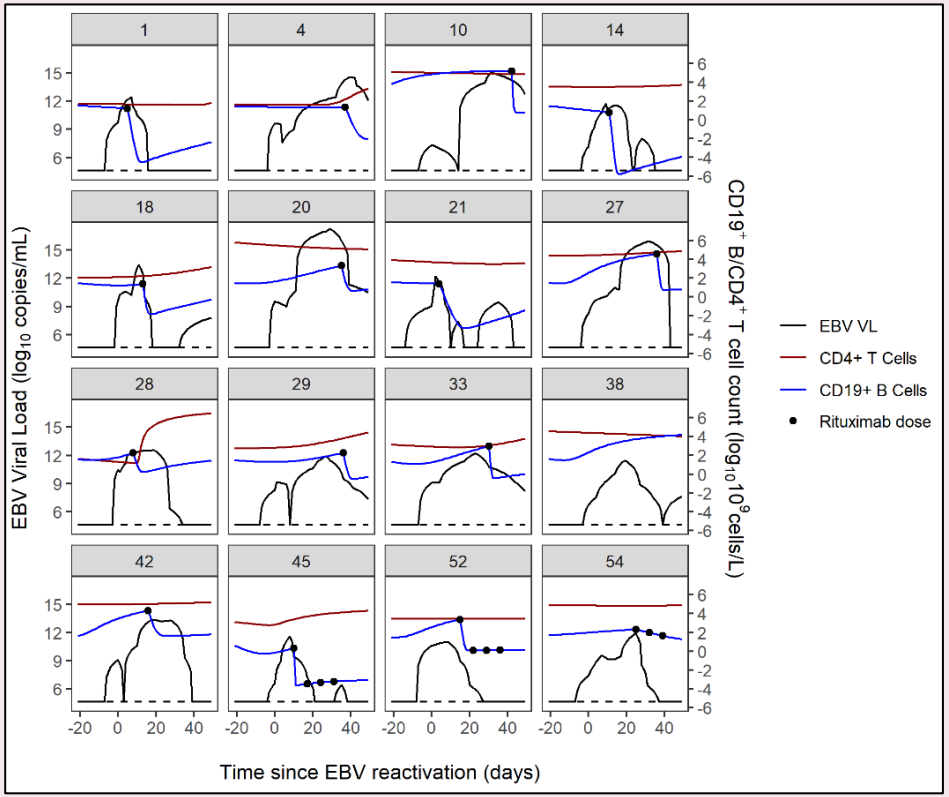
Kania et al (2022) Front Immunol [11]

Dynamics of EBV reactivation post-HSCT

Pharmacometric approach

Rituximab PD model + knowledge from sensitivity analysis of previously reported model

Pharmacometric model of EBV reactivation dynamics post-HSCT



Kania et al (2022) Front Immunol [11]

Dynamics of EBV reactivation post-HSCT

ODEs and Individuals Fits

$$\frac{dA_1}{dt} = -k_e \cdot A_1$$

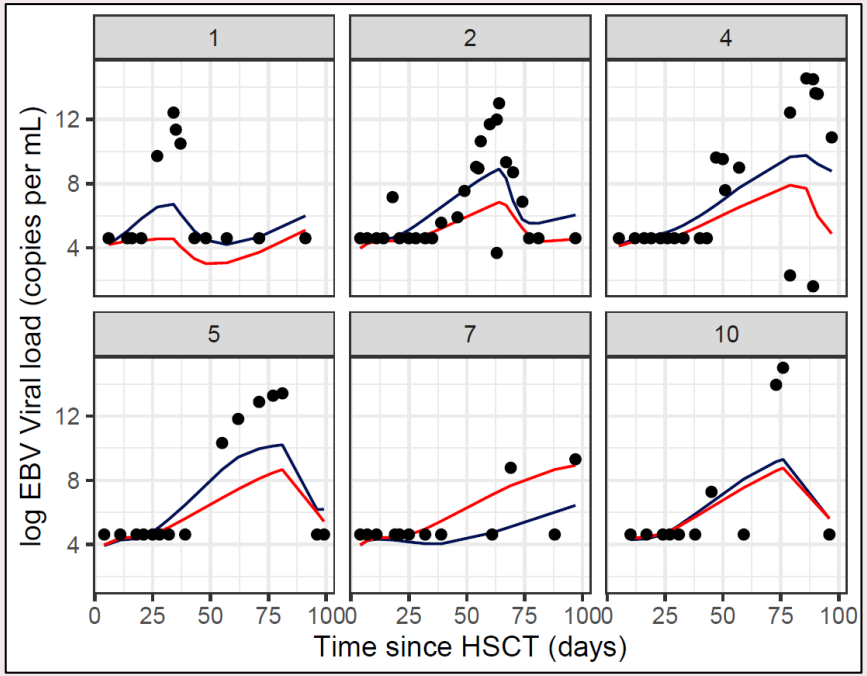
$$\frac{dA_2}{dt} = \lambda \cdot \left(\frac{T^\gamma}{T^\gamma + T50^\gamma}\right) - \mu \cdot \left(1 + \frac{E_{max} \cdot A_1}{ED_{50} + A_1}\right) \cdot A_2$$

$$\frac{dA_3}{dt} = K \cdot A_2 \cdot -\delta \cdot \left(1 + \frac{E_{max} \cdot A_1}{ED_{50} + A_1}\right) \cdot A_3 - Q \cdot A_3 \cdot A_5$$

$$\frac{dA_4}{dt} = N \cdot \delta \cdot A_3 - C \cdot A_4$$

$$\frac{dA_5}{dt} = R \cdot A_3 - D \cdot A_5$$

K, Production rate of infected B cells; δ, Death rate of infected B cells; Q, CTL killing rate of infected B cells; N, viral burst size; C, viral clearance rate; R, Proliferation rate of EBV-specific CTLs ; D, CTL death rate

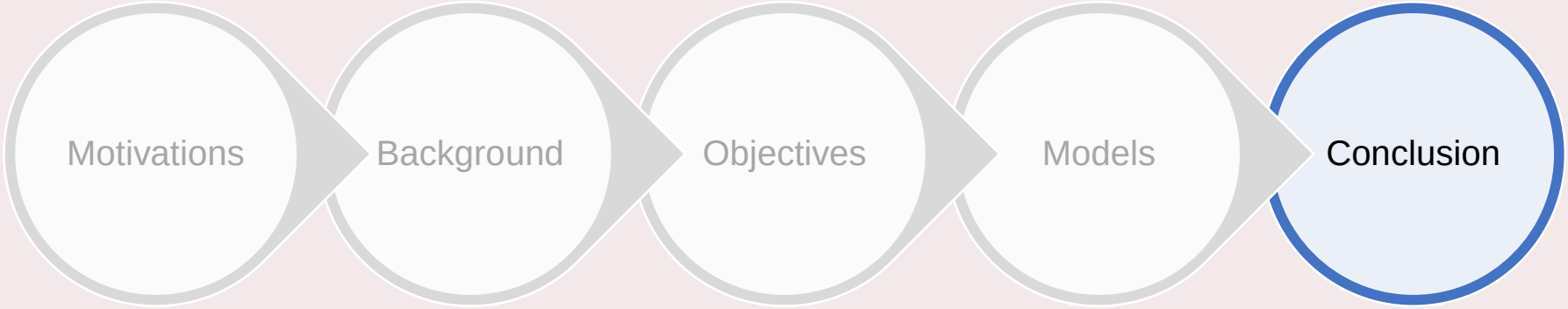


Wang et al (2013) J. Math. Biol[13]

Summary of Model 3

1. Pre-HSCT ATG and recipient EBV seropositivity are significant risk factors for EBV reactivation in first 100 days post-HSCT in Cox-PH model
2. Parameters related to memory B cells and CTLs drive EBV viral load according to sensitivity analysis
3. Developing pharmacometric model to quantify dynamics of EBV reactivation post-HSCT

Overview



Conclusion

Unmet Need

?

- B cells
- Children
- Pharmacometrics

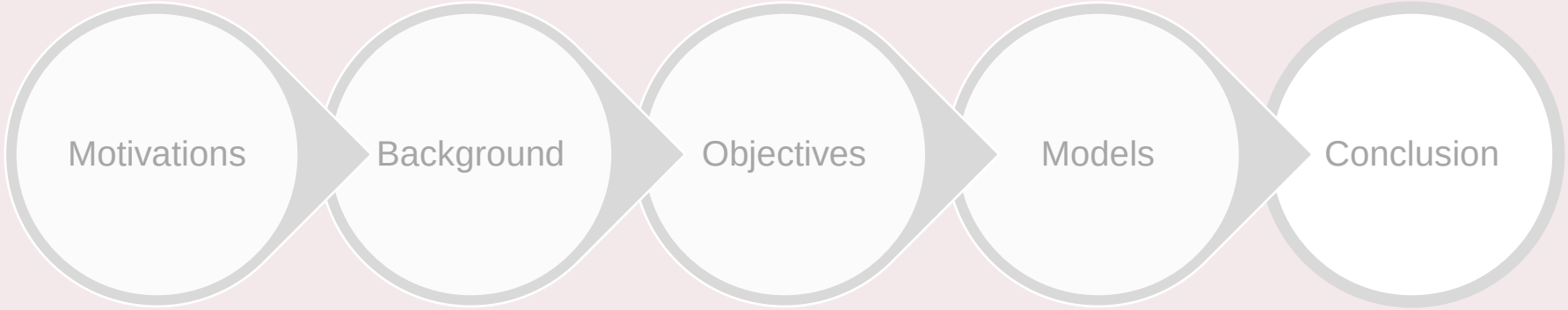
Our Work

- Built pharmacometric models with age scaling for:
  - $CD19^+$ B cell reconstitution in children post-HSCT
  - Rituximab PD in children with EBV post-HSCT
  - EBV reactivation in children post-HSCT
- Future work on bioequivalence in rituximab biosimilars

Clinical Impact

- PID diagnosis, MAC and matched donor affect B cell recovery
- Inform rituximab dosing
- Models can predict patients' B cell recovery trajectories

Overview



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