Phenotypic Plasticity in Neuroblastoma: Implications for Evolutionary and Targeted Therapy

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Introduction

Neuroblastoma (NB) is a paediatric cancer, affecting children under the age of 5 years old, accounting for 15% of all paediatric cancer deaths [1,3].

Problem: NB contains 3 cell types: noradrenergic-like cells (ADRN), mesenchymal-like cells (MES) and an intermediate cell type (I-type). These cells show resistance to different treatments, and are able to interconvert to escape treatment[2,4].

Research Aim: To understand and exploit the interconversion dynamics in the context of NB treatment with targeted therapies.

Model Structure

System of ODEs for each cell population and drug

N = ADRN , I = I-type, S = MES , D = Drug, T = Total population

$$P = N + S + I \tag{1}$$

$$\frac{dN}{dt} = k_1^N N\left(1 - \frac{P}{1}\right) - k_2^N ND + k_3^{(S,N)} S + k_3^{(I,N)} I - k_3^{(N,S)} N - k_3^{(N,I)} N \tag{2}$$

$$\frac{dS}{dt} = k_1^S S\left(1 - \frac{P}{1}\right) - k_2^S SD + k_3^{(N,S)} N + k_3^{(I,S)} I - k_3^{(S,N)} S - k_3^{(S,I)} S \tag{3}$$

$$\frac{dI}{dt} = k_1^I I\left(1 - \frac{P}{1}\right) - k_2^I ID + k_3^{(S,I)} S + k_3^{(N,I)} N - k_3^{(I,S)} I - k_3^{(I,N)} I \tag{4}$$

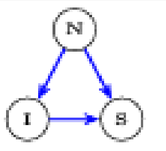
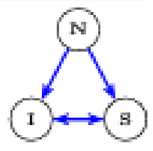
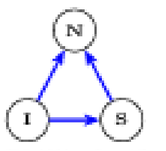
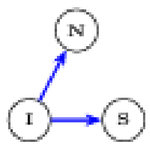
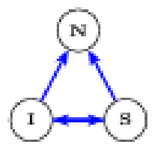
$$J = \begin{pmatrix} k_1^N\left(1 - \frac{N+S+I}{K}\right) & k_3^{IN} - \frac{k_1^N N}{K} & k_3^{SN} - \frac{k_1^N N}{K} \\ -\frac{k_1^N N}{K} - k_2^N D - k_3^{NI} - k_3^{NS} & & \\ k_3^{NI} - \frac{k_1^I I}{K} & k_1^I\left(1 - \frac{N+S+I}{K}\right) & k_3^{SI} - \frac{k_1^I I}{K} \\ & -\frac{k_1^I I}{K} - k_2^I D - k_3^{IN} - k_3^{IS} & \\ k_3^{NS} - \frac{k_1^S S}{K} & k_3^{IS} - \frac{k_1^S S}{K} & k_1^S\left(1 - \frac{N+S+I}{K}\right) \\ & & -\frac{k_1^S S}{K} - k_2^S D - k_3^{SI} - k_3^{SN} \end{pmatrix} \tag{5}$$

k1 = growth rate. k2 = drug dependant death rate. k3 = Interconversion between the cell types

64 Interconversion Patterns

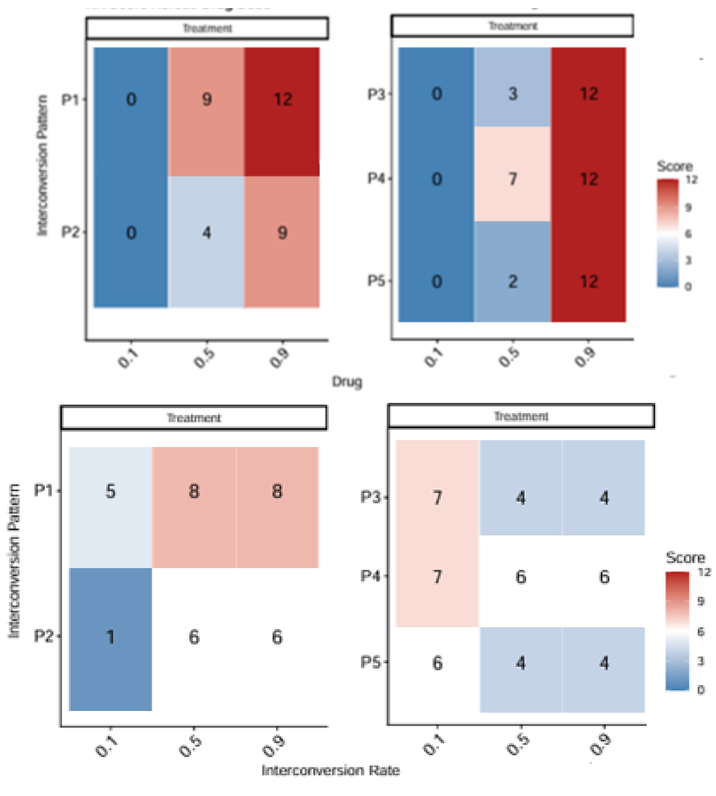
In Silico Drug Trial

- P1, P3 & P4 are supported by existing biological literature as natural transitions.

Target Cell	Pattern
N-suppressing	 P1:<N> |I> |S|
	 P2:<N> |I><S|
S-suppressing	 P3:|N| <I> |S>
	 P4:|N| <I> |S|
	 P5:|N| <I><S>

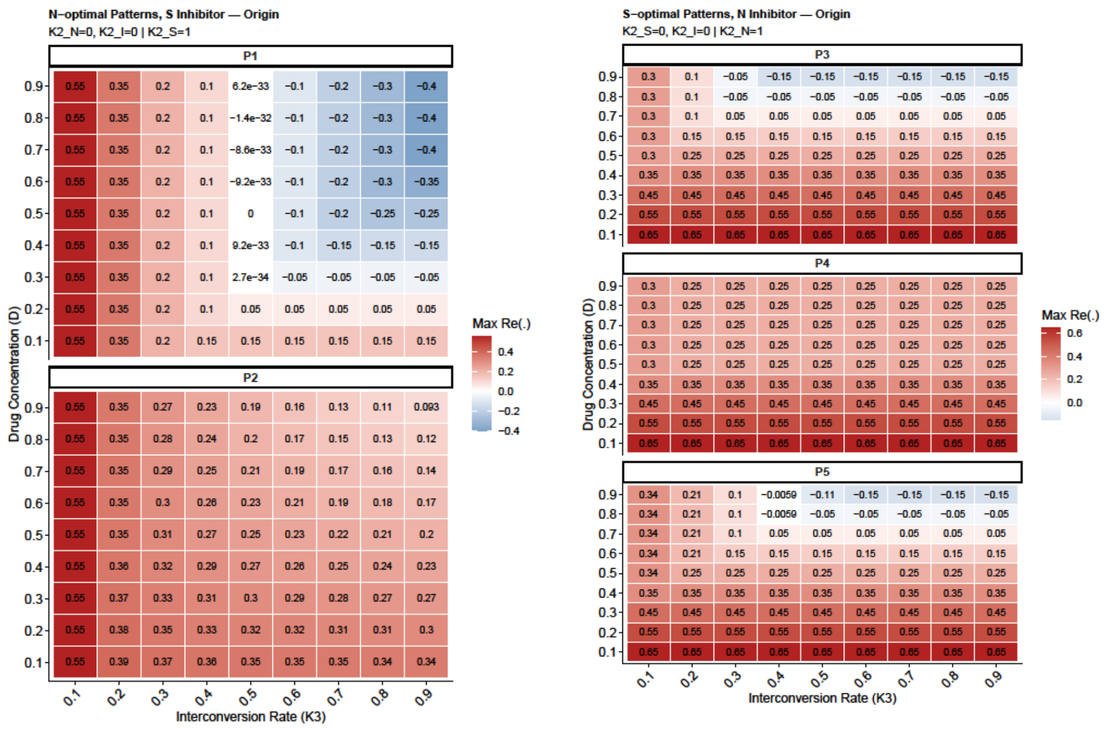
Sensitivity

- P1 was most effective at medium-to-high S inhibitor doses.
- P3-P5 were most effective at low interconversion rate.



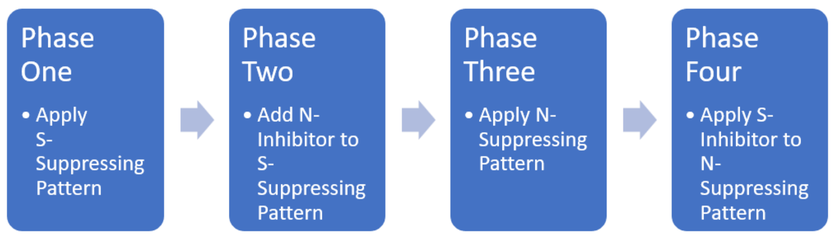
Stability

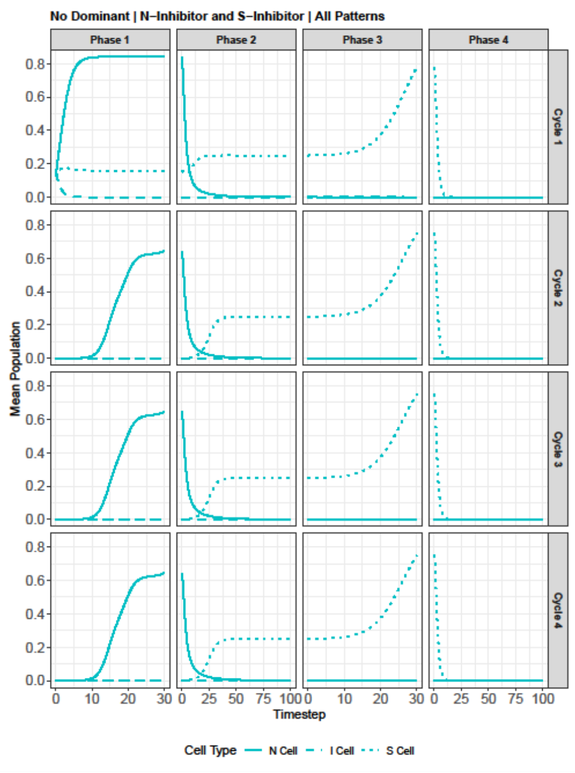
- P1 had the most stable combinations of interconversion rates and drug doses.



Validity

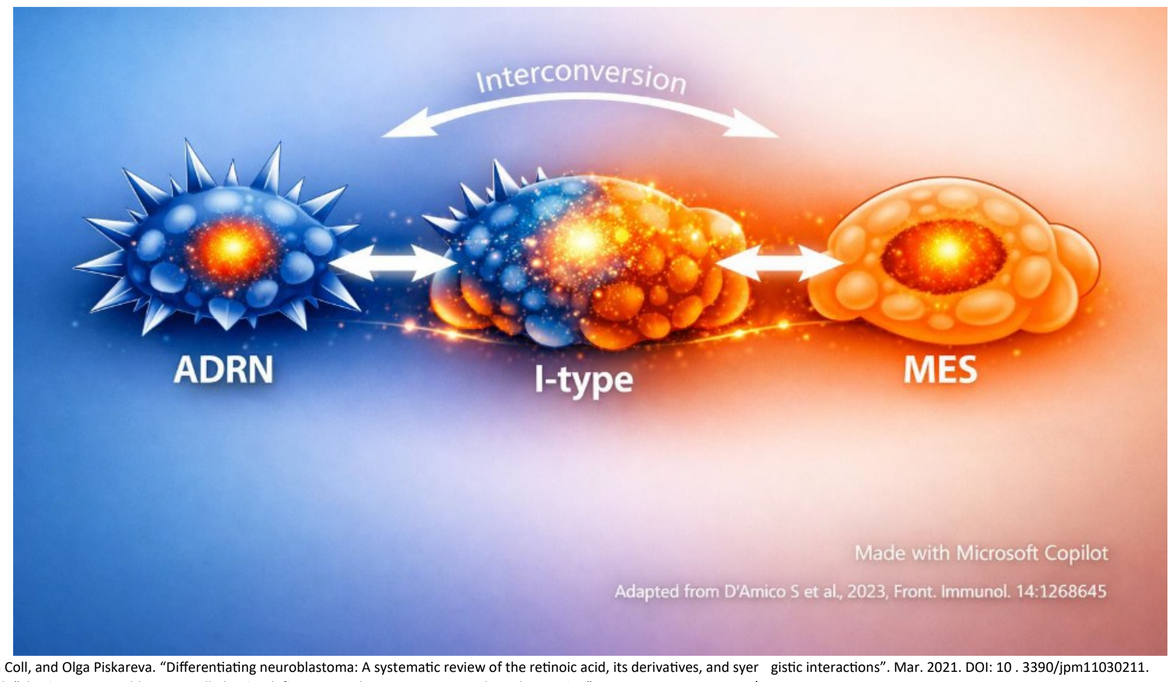
- Different treatment schedules worked as expected.





Conclusions

- Of 64 possible interconversion patterns, only 5 meaningfully suppress a target cell population. P1, P2 (N-suppressing) and P3, P4, P5 (S-suppressing).
- P1 + S-inhibitor + high interconversion rate and P3 + N-inhibitor + low interconversion rates were the best combinations. P1 is best for maintenance therapy.
- Next step will incorporate resistance mutation.



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[2]Margot Gautier et al. "Plasticity in neuroblastoma cell identity defines a noradrenergic-to-mesenchymal transition". June 2021. DOI: 10.3390/cancers13122904.
[3]Roshna Lawrence Gomez et al. "Tumoral heterogeneity in neuroblastoma". Nov. 2022. DOI:10.1016 j.bbcan.2022.188805.
[4]Maged Zeineldin, Anand G. Patel, and Michael A. Dyer. "Neuroblastoma: When differentiation goes awry". Sept. 2022. DOI:0.1016/.neuron.2022.07.012.