Population Pharmacodynamic Model of the Effects of Recombinant Human Interleukin 21 on Platelets in Humans

M.G. Dodds[1], J.E. Visich[1], I. Nestorov[1], R. Overgaard[2], M.C. Rogge[1]

ZymoGenetics, Inc., U.S.A.[1] • Novo Nordisk A/S, Denmark[2]

Introduction

Interleukin-21 (IL-21) is a novel cytokine with an ability to activate $CD8^+$ killer T-lymphocytes and natural killer (NK) cells, classes of immune cells that can eradicate tumor cells and virally infected cells. Data suggest that both NK and $CD8^+$ T-cells may have a role in controlling tumors. Infiltration of tumors with $CD8^+$ T-cells is a positive prognostic sign in a number of cancers. Furthermore, adoptive transfer of tumor-infiltrating lymphocytes has shown preliminary evidence of therapeutic effect in a number of tumor types, including melanoma. Preclinical studies suggest activation of NK cells and $CD8^+$ T-lymphocytes by administration of recombinant murine IL-21 can result in marked anti-tumor effects in a number of cancer models.

A pharmacodynamic (PD) effect of the drug is the reduction of platelet counts in blood during administration followed by a rapid recovery beyond baseline counts during recovery.

Objective:

- **The aim of this study was to characterize this pharmacodynamic effect of IL-21 using population analysis approach.**

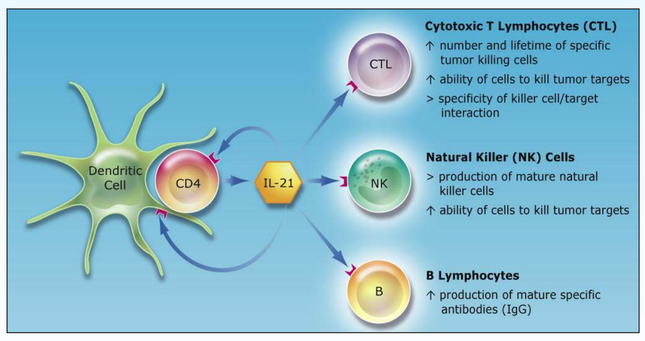


Figure 1. IL-21 elicits pleiotropic immune modulation.

Methods

Phase 1 Study

- This Phase 1 study evaluated the pharmacokinetics and safety of intravenous doses of 3, 10, 30, 50 and 100 µg/kg IL-21 to patients diagnosed with advanced renal cell carcinoma (RCC) or metastatic melanoma (MM) in a cyclic pattern shown in Figure 2.
- IL-21 had not been previously tested in humans.
- 43 subjects treated; 24 MM, 19 RCC; Age (20-80); 35 Male, 8 Female. Table 1 shows the randomization by dose level

	Dose Level (µg/kg)				
	3	10	30	100	50
Dose Escalation	n=3	n=3	n=6	n=2	n=1
MTD Expansion			n=28		

Table 1. Study Design. Dose Escalation: Single arm, open label in sequential cohorts; half-log increments until DLT; de-escalation if MTD reached or exceeded. MTD Expansion: Single arm at the selected dose level established in Dose Escalation.

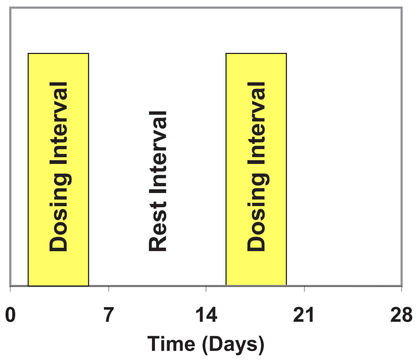


Figure 2. Dosing Regimen. IL-21 was administered intravenously using the following proposed clinical schedule: two courses of five (5) daily doses, separated by a nine (9) day rest period.

Platelet Measurements

- Blood samples were drawn on days 1-8 and day 10 of each cycle.
- Standard CBC panels were performed.
- 722 platelet measurements were available for evaluation.

Model Description

- Platelet data were described by an indirect PD model of enhanced clearance of platelets, *P(t)*, from the blood via a delayed, nonlinear drug effect, *E(t)*.
- Arrival of *de novo* platelets in the blood was assumed to be delayed.
- Megakaryocyte, *M(t)*, synthesis of platelets was assumed to be sensitive to the blood counts of platelets and was described by a sigmoid function parameterized by the time-dependent *P(t)* and baseline blood platelet count, *P0*, platelet half-life, $P_{½}$, and sigmoid coefficient, *PS*.
  - Normal production rate is assumed to meet baseline turnover.
  - Normal production is assumed to be the mid-point of the sigmoid curve.
  - The production rate of *de novo* platelets is assumed to be, at most, twice that of the normal production rate.

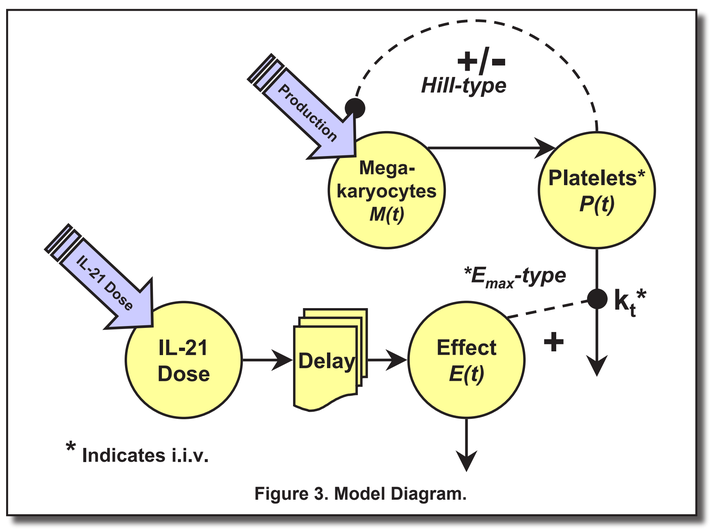


Figure 3. Model Diagram.

$$\frac{d}{dt} P(t) = -k_t \cdot (1 + EP) \cdot P(t) + k_t \cdot M(t)$$

$$EP = \frac{E_{max} \cdot E(t)}{ED_{50} + E(t)}$$

$$P(t = 0) = P0$$

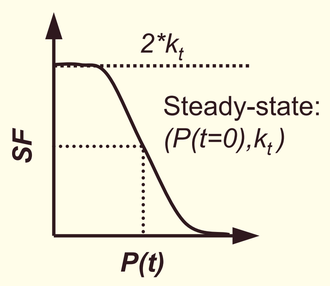
$$\frac{d}{dt} M(t) = -(k_t - SF) \cdot M(t)$$

$$M(t = 0) = P0$$

$$SF = M_{max} \cdot \left(1 - \frac{P(t)^{PS}}{M_{50}^{PS} + P(t)^{PS}}\right)$$

$$M_{max} \equiv 2 \cdot k_t$$

$$M_{50} \equiv P(t = 0)$$



Results

- The analysis of the data was performed using NONMEM V, FOCE with interaction.
- Three random-effects were selected based on the NONMEM objective function values and goodness of fit considerations.
- Diagnostic plots of the fits are given for doses at 3, 10, 50 and 100 µg/kg in figures 4a and 5a and the dose of 30 µg/kg in figures 4b and 5b.
- Parameter estimates are shown in Table 2.

DV versus PRED

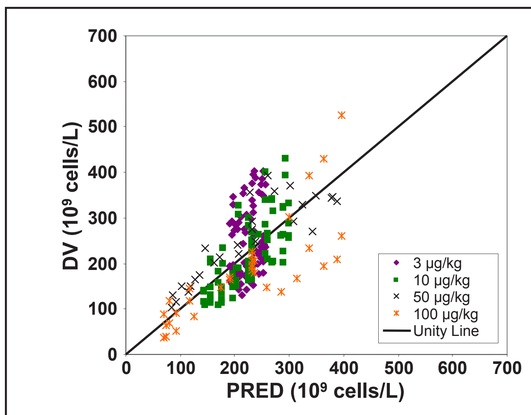


Figure 4a. 3, 10, 50 and 100 µg/kg dose groups

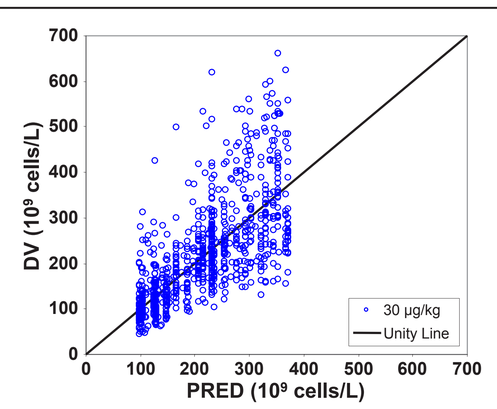


Figure 4b. 30 µg/kg dose group

DV versus IPRED

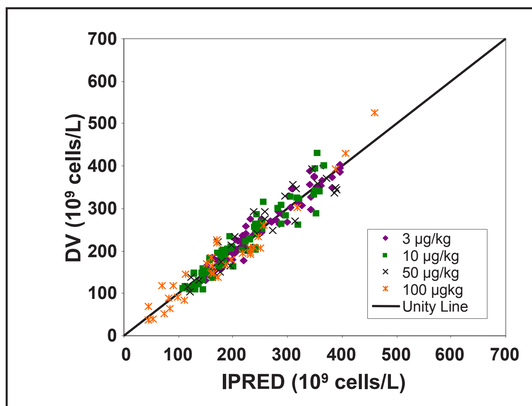


Figure 5a. 3, 10, 50 and 100 µg/kg dose groups

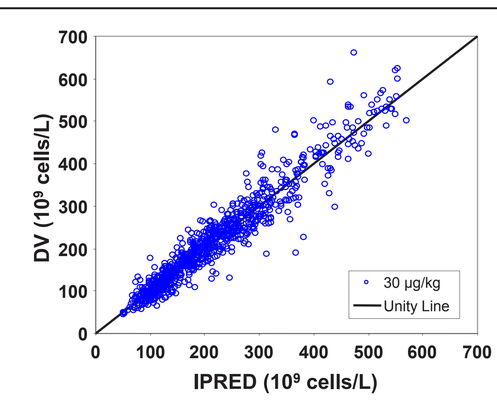


Figure 5b. 30 µg/kg dose group

Predictive Check

- Only Dose Escalation data was used to parameterize the model.
- Estimates from Dose Escalation were used in a Monte Carlo simulation of 30 µg/kg treatment.
- MTD Expansion data was superimposed on the percentiles (10th, 25th, 50th, 75th and 90th) of those simulations and shown in Figure 6.

Results

- During the first recovery period, the model predicted too rapid a recovery
- Overestimated platelet replacement rate

Combined Dose Escalation and MTD Expansion results indicated the transit time for *de novo* platelets was longer than anticipated.

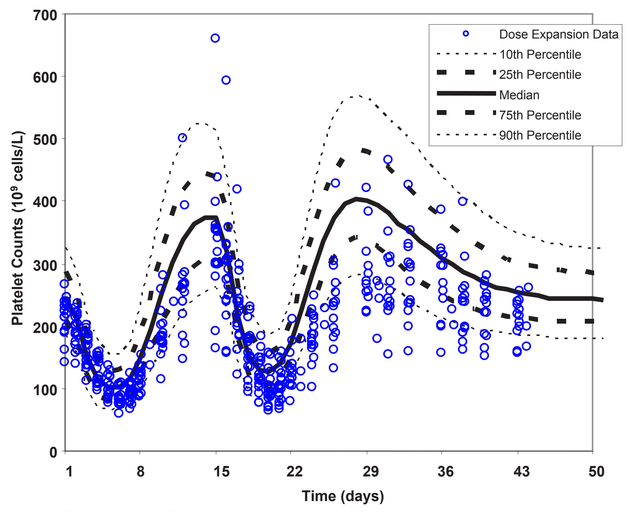


Figure 6. Prediction of dose expansion phase based on dose-escalation phase data estimates.

	Interpretation	Units	Estimate	% RSE
Typical Value (θ)				
$P_{1/2}$	Platelet half-life	Day	3.31	13.4
P_{MET}	MRT of drug effect	Day	2.33	9.44
PS	Hill coefficient; sensitivity of MK to platelet levels		1.71	20.0
P0	Typical platelet baseline	10^9 cells/L	231	4.50
E_{max}	Maximum fold-over baseline platelet elimination		5.49	25.7
ED_{50}	Dose of drug provoking half-maximal platelet elimination	µg/kg	21.9	37.4
Between-Subject Variability (Ω)				
BSV[$P_{1/2}$]	36.1% i.i.v., platelet half-life		0.130	68.3
BSV[*P0*]	28.9% i.i.v., typical platelet baseline		0.0837	24.5
BSV[E_{max}]	34.5% i.i.v., maximum fold-over baseline platelet elimination		0.119	28.0
Residual, Unexplained Variability (∑)				
RUV[Platelet]	14.0% r.u.v. relative to baseline measurements		1050	17.4

Table 2. Combined parameter estimates using Part A and B data.

Conclusions

- **This model described data collected in different patient populations and dose levels.**
- **The interaction of delayed appearance of *de novo* platelets and the regulatory loop model components captured the observed initial decrease in platelets and subsequent rebound.**
- **These results may be useful in designing future studies.**
- **Further refinement of the statistical model, including covariates, is necessary.**

ZYMOGENETICS

1201 Eastlake Avenue East
Seattle, Washington 98102 U.S.A.
(206) 442-6600 • www.zymogenetics.com