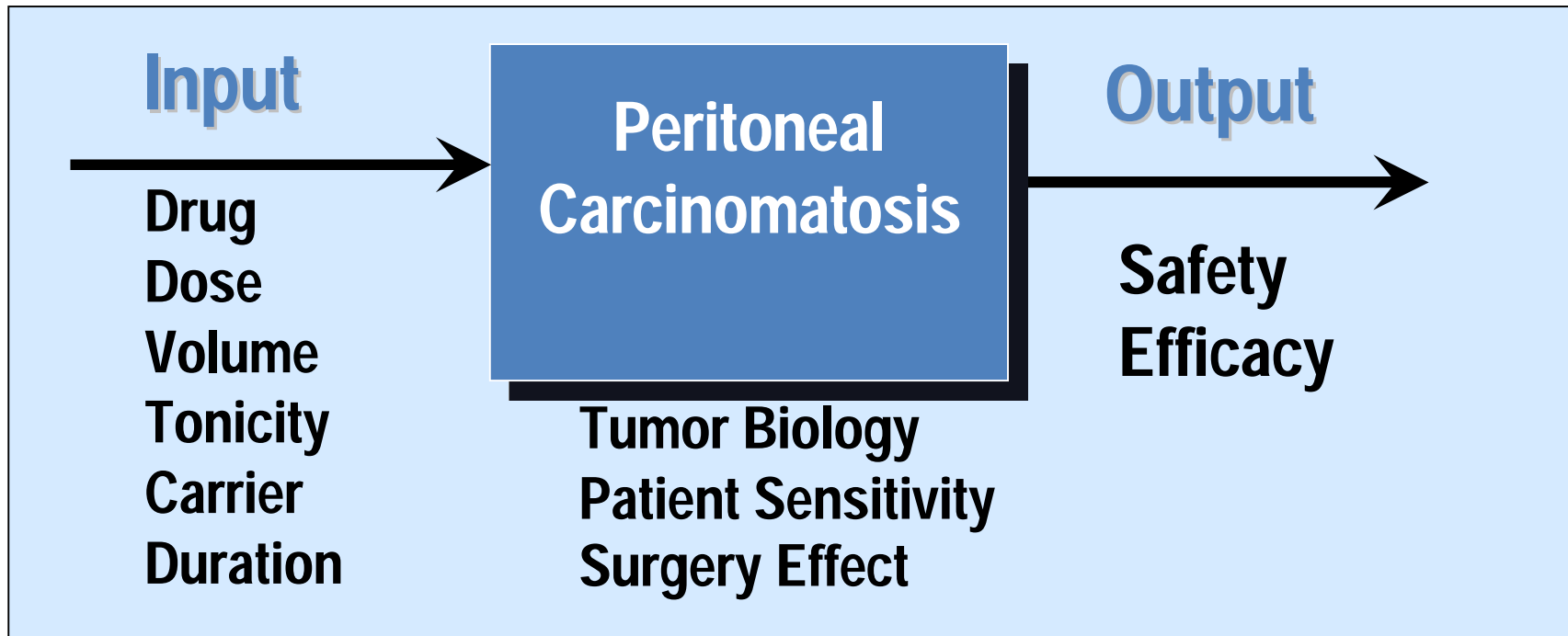


Pharmacological Aspects of Hyperthermic Intraperitoneal Chemotherapy (HIPEC): Pharmacodynamic Considerations

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**III Congreso Nacional SEOQ y V Reunion GECOP
Alicante, 4 de Octubre de 2013**

PKPD knowledge of HIPEC treatments is critical to select dosing regimens that maximize efficacy & minimize toxicity



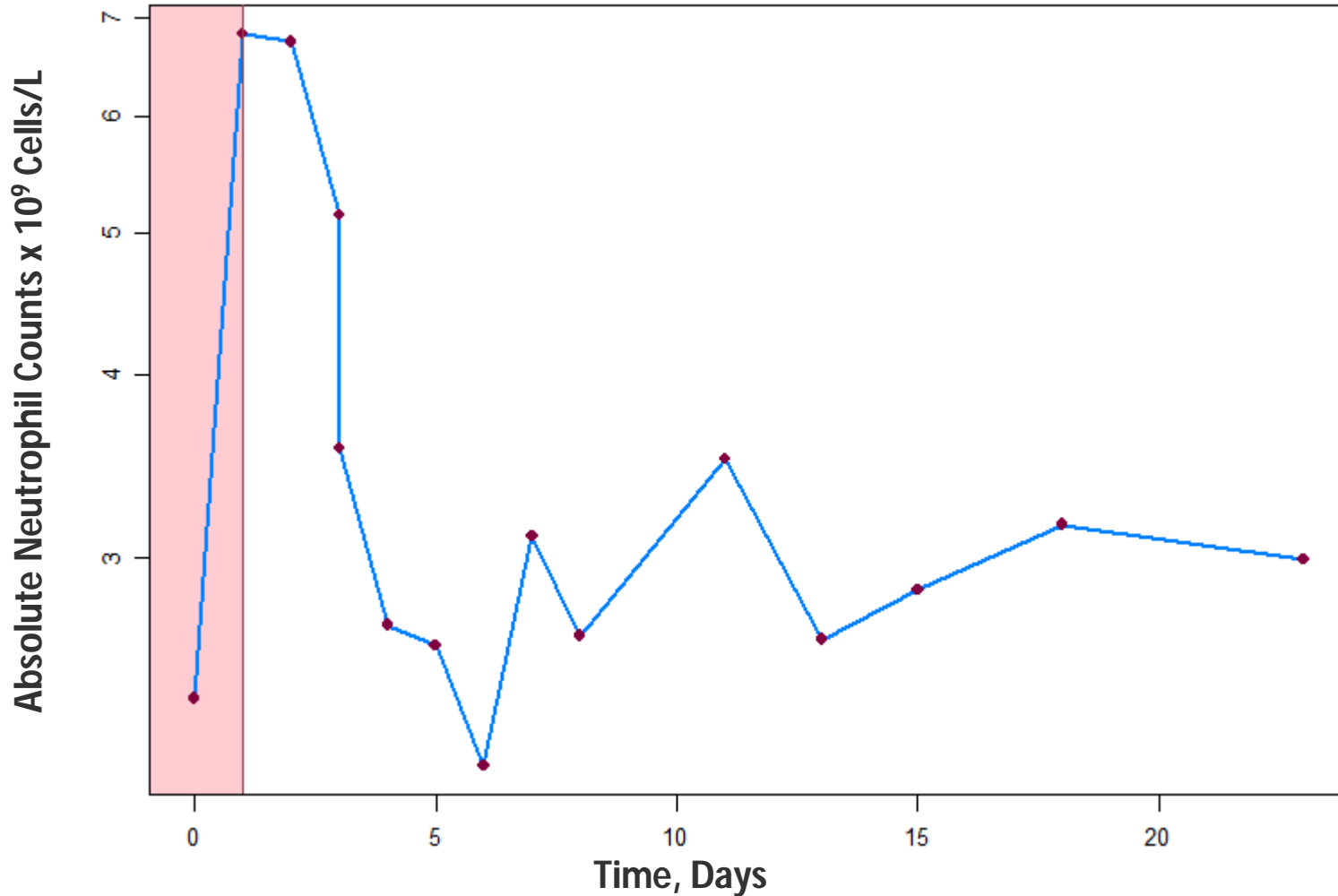
Research Article

Pharmacokinetic and Pharmacodynamic Analysis of Hyperthermic Intraperitoneal Oxaliplatin-Induced Neutropenia in Subjects with Peritoneal Carcinomatosis

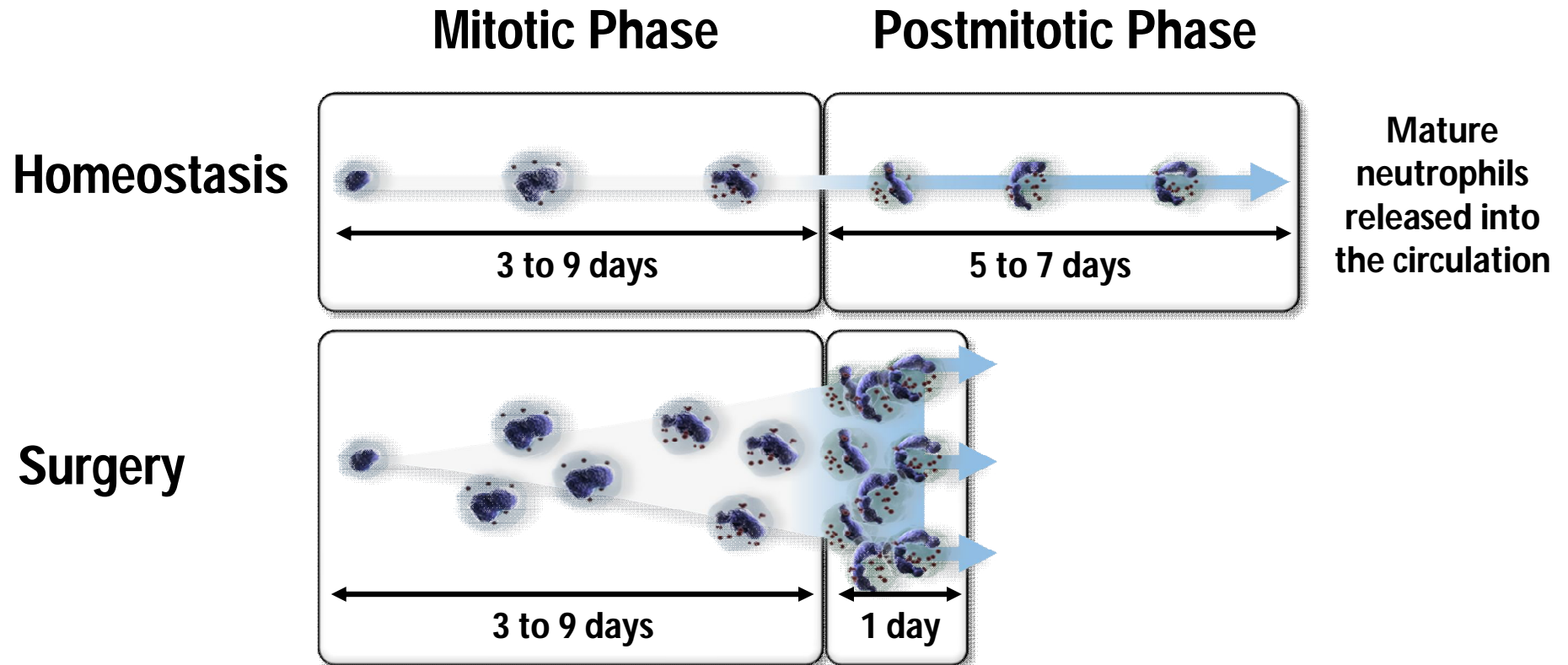
Belén Valenzuela,^{1,4} Ricardo Nalda-Molina,² Pere Bretcha-Boix,¹ Vanesa Escudero-Ortíz,¹ Maria José Duarte,² Vicente Carbonell,³ Manuel Sureda,¹ José Pascual Rebollo,¹ Josep Farré,¹ Antonio Brugarolas,¹ and Juan José Pérez-Ruixo²

- Oxaliplatin maximum tolerated exposure in peritoneum is 240 mg·h/L and exposures >120 mg·h/L require G-CSF support.
- Absolute neutrophil counts after CRS & oxaliplatin potency to induced neutropenia were higher than expected

Time course of ANC following CRS + HIPEC



Surgery effect on granulopoiesis



Study Design

Cohort A

Cytoreductive Surgery
HIPEC Oxaliplatin (Icodextrin 4%)

Cohort B

Cytoreductive Surgery
HIPEC Oxaliplatin (Dextrose 5%)

Cohort C

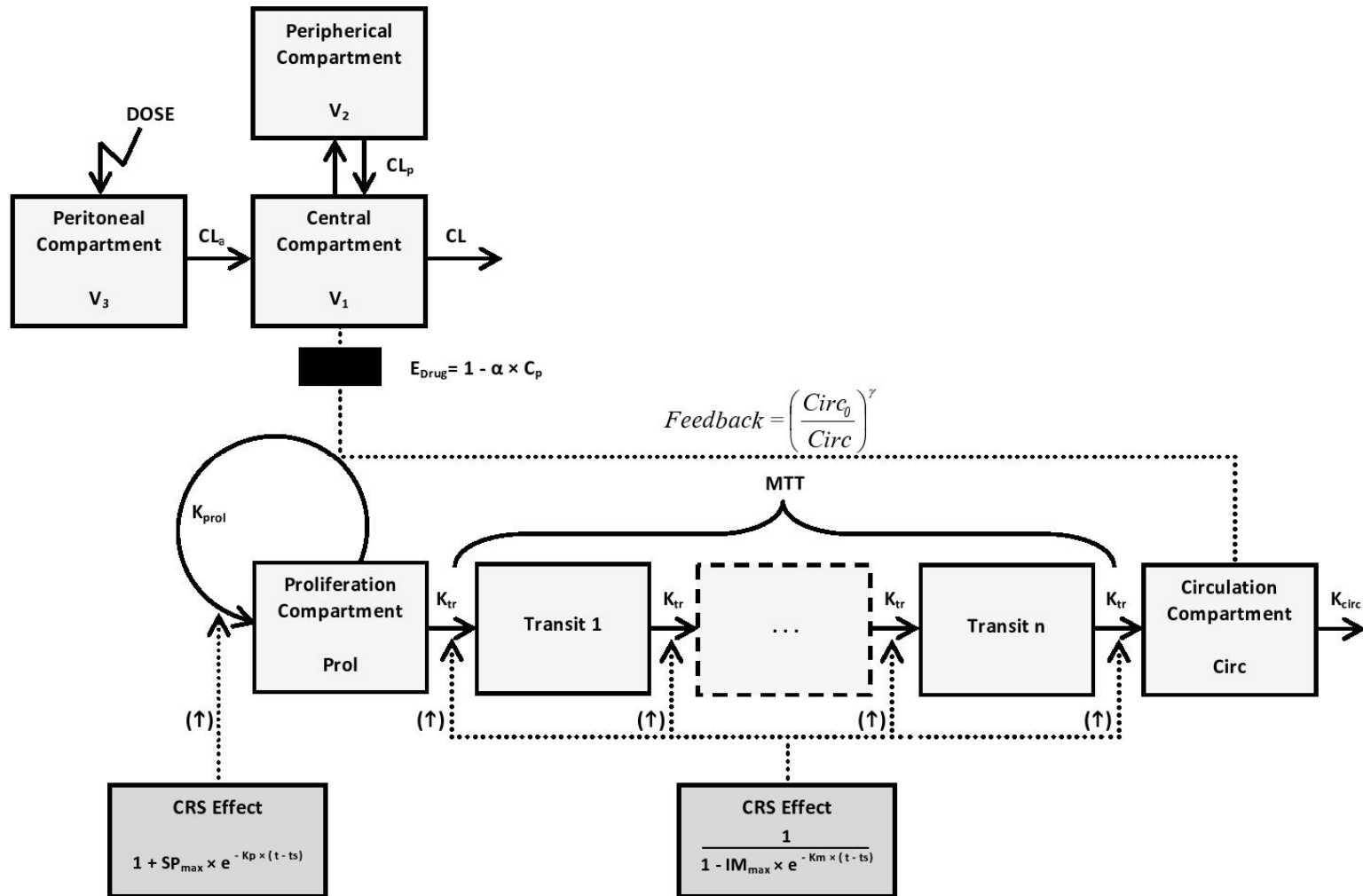
Cytoreductive Surgery

Neutrophil Dynamics in Peritoneal Carcinomatosis Patients Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Oxaliplatin

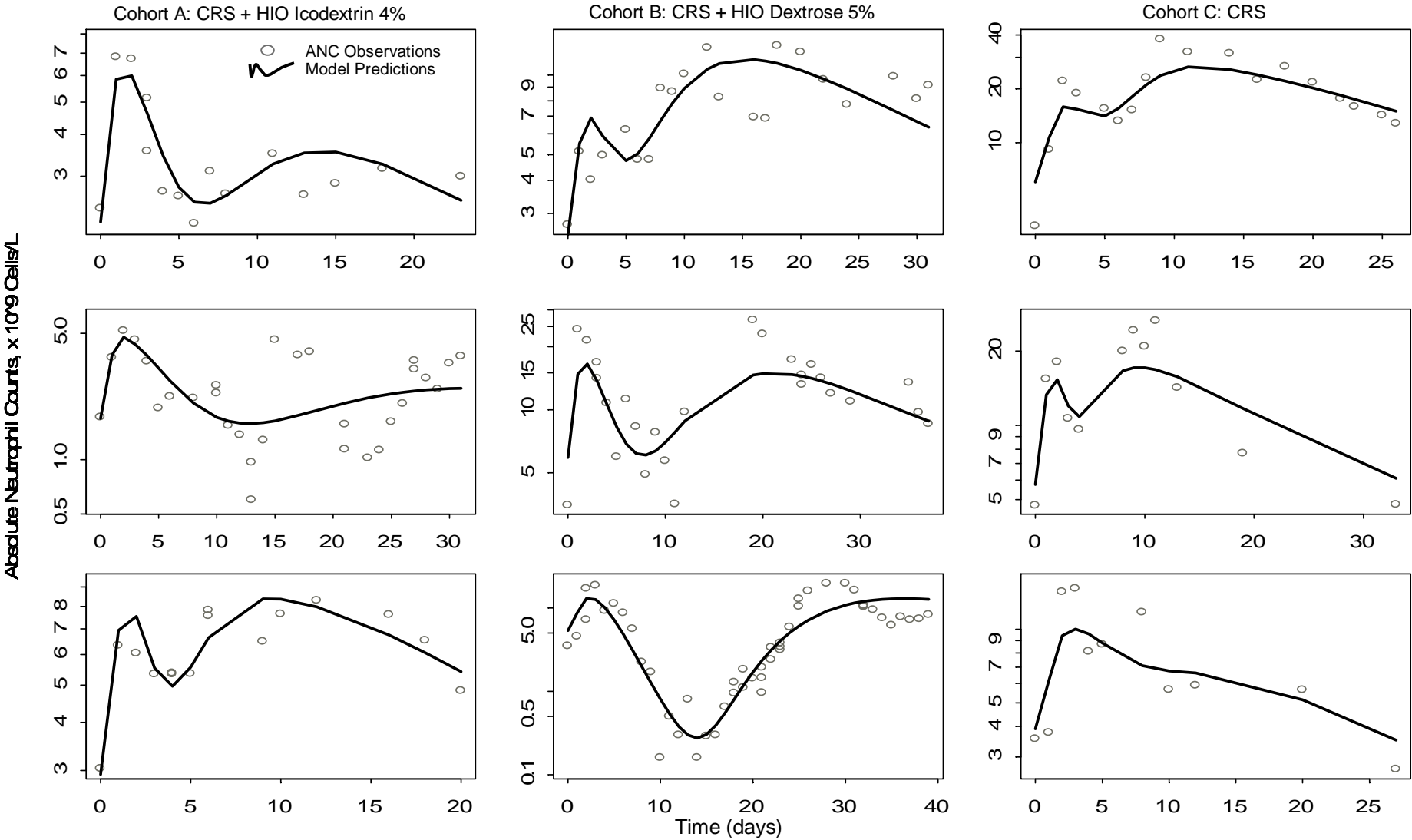
**Carlos Pérez-Ruixo · Belén Valenzuela · José Esteban Peris ·
Pedro Bretcha-Boix · Vanesa Escudero-Ortiz · José Farré-Alegre ·
Juan José Pérez-Ruixo**

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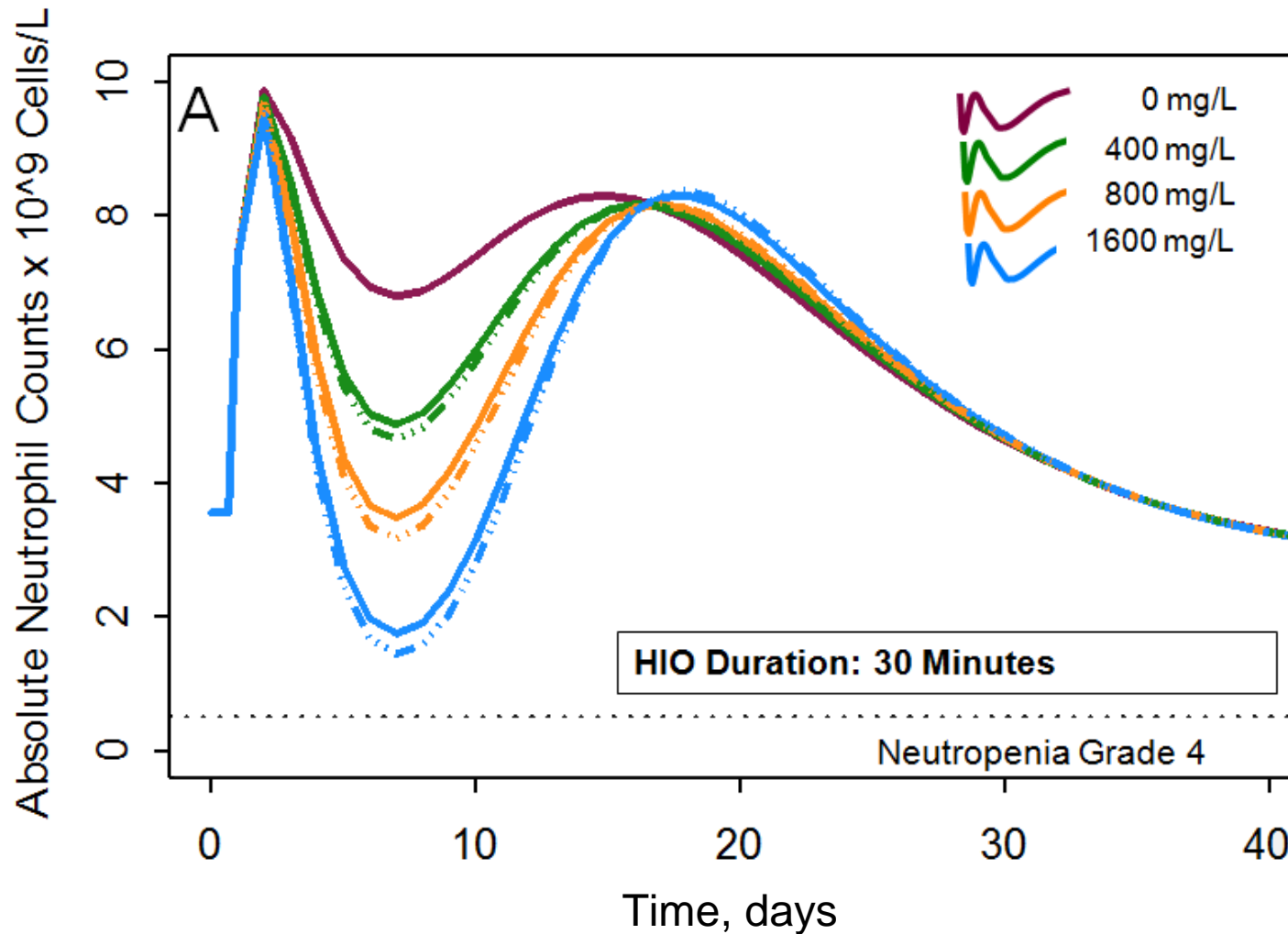
Neutrophil dynamics model for HIPEC



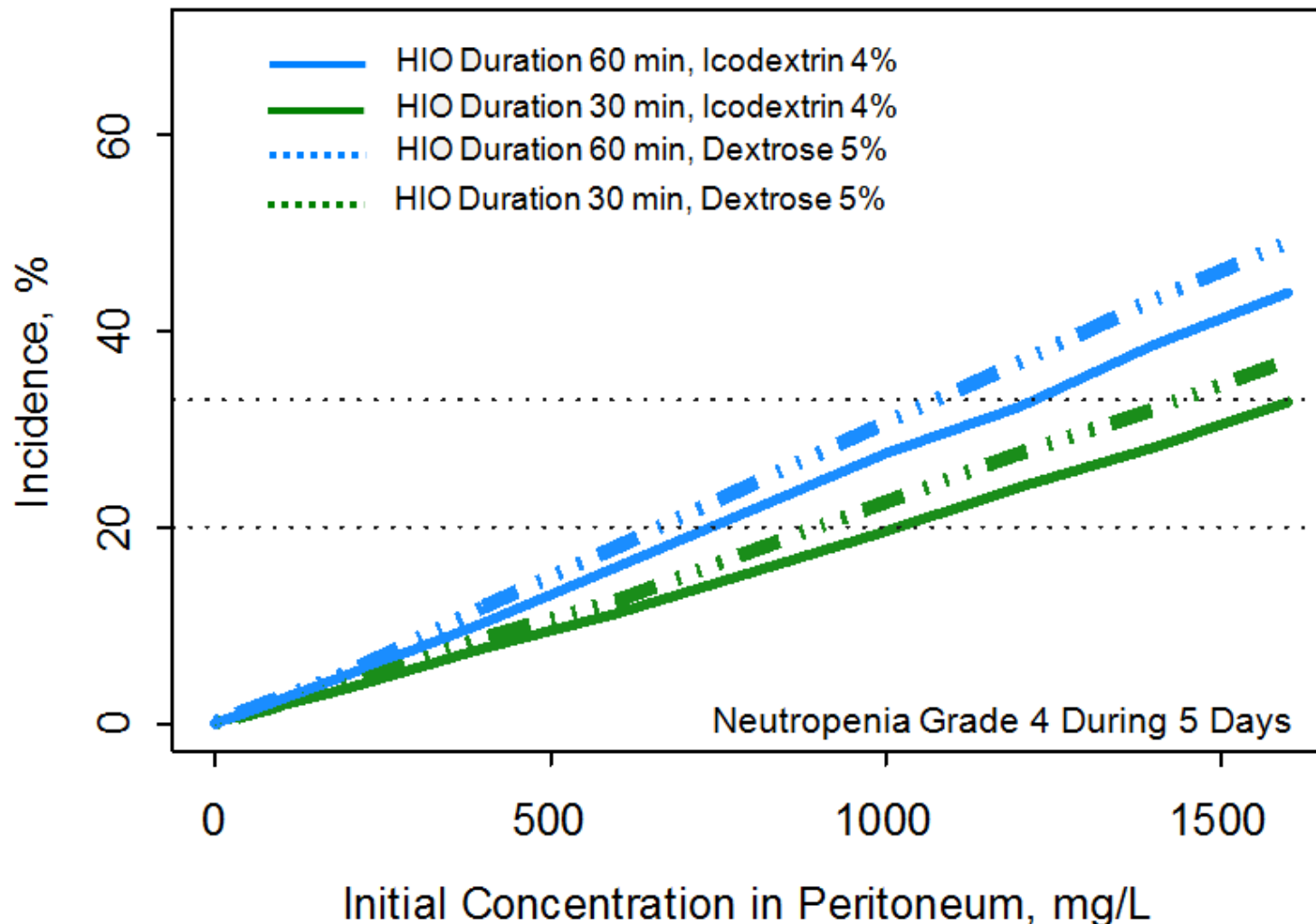
Neutrophil dynamics model predictions



Effect of surgery, oxaliplatin dose and vehicle on the ANC time course



What's the maximum tolerated exposure of oxaliplatin in HIPEC?



Conclusions

- **PKPD knowledge of HIPEC treatments is critical to select dosing regimens that maximize efficacy & minimize toxicity.**
- **Cytoreductive surgery affect the neutrophil dynamics by stimulating the proliferation of precursor cells and reducing the maturation time**
- **Although several Ph1 clinical studies have established the oxaliplatin MTD, our exposure response analysis indicates that higher doses or extended duration might be feasible and should be tested in the context of clinical studies.**