

Cerus Corporation
2550 Stanwell Drive, Concord, CA 94520 USA
www.cerus.com
1.925.288.6000

Adonis Stassinopoulos, Ph.D.
Vice President Global Scientific Affairs
T: 925-288-6024



**Replacement of Gamma Irradiation by Amotosalen Treatment
Cumulative Clinical Data of Routine Use**

A Stassinopoulos, L Corash

Cerus Corporation, Concord, CA, USA

**Presented at the 29th Annual Conference
of the British Blood Transfusion Society (BBTS)
Glasgow, Scotland • September 7th - 10th, 2011**

Replacement of Gamma Irradiation by Amotosalen Treatment Cumulative Clinical Data of Routine Use



A Stassinopoulos, L Corash
Cerus Corporation, Concord, CA, USA



Background

The INTERCEPT Blood System™ (IBS) for platelets received CE Mark registration as a Class III Medical Device in 2002 for pathogen inactivation treatment of platelet components (Figure 1). IBS is in routine use in a number of countries in Europe, CIS and the Middle East. Prior to CE registration of INTERCEPT™, gamma irradiation was the standard method used to prevent transfusion-associated graft versus host disease (TA-GVHD). CE Mark approval for replacing gamma irradiation for prevention of TA-GVHD was received for the IBS in 2008. Additionally, the Paul Ehrlich Institute (PEI) of Germany, the Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps) of France, and the SwissMedic of Switzerland separately also approved the use of INTERCEPT in place of gamma

irradiation for prevention of TA-GVHD for all patient populations at risk.

These approvals were supported by *in vitro* and *in vivo* studies including a clonal T cell proliferation assay by limiting dilution analysis demonstrating robust inactivation of T cells by INTERCEPT treatment to the same level as gamma irradiation, but with a 3000-fold efficacy margin (Figure 2). Additional complementary assays demonstrated high levels of genomic DNA modification (1 adduct/83 base pairs) (Figure 3), complete inhibition of cytokine synthesis, and elimination of early activation antigen presentation (Figure 4). *In vivo* animal studies confirmed that INTERCEPT inactivated T-cells could not initiate TA-GVHD in immuno-compromised recipients.

Aims

To evaluate the efficacy of INTERCEPT in T-cell inactivation for prevention of TA-GVHD in clinical use.

Methods

We analyzed 8 years of cumulative experience obtained from clinical trial and routine use of INTERCEPT treated platelet components, without gamma irradiation, transfused in a broad patient population. Data were obtained from clinical trial databases and hemovigilance (HV) studies. The populations studied were enriched for immune-compromised hematology-oncology patients and hematopoietic stem cell transplantation (HSCT) recipients at risk for TA-GVHD.

Figure 1: The INTERCEPT Blood System for Platelets

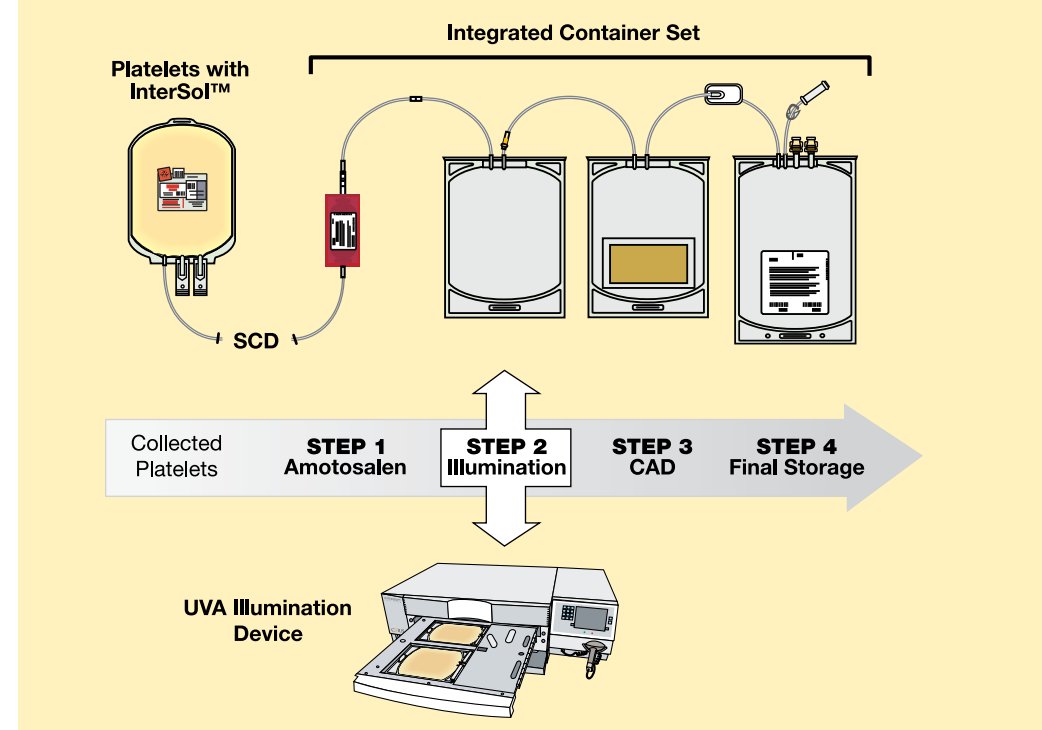


Figure 3: INTERCEPT Mechanism of Action

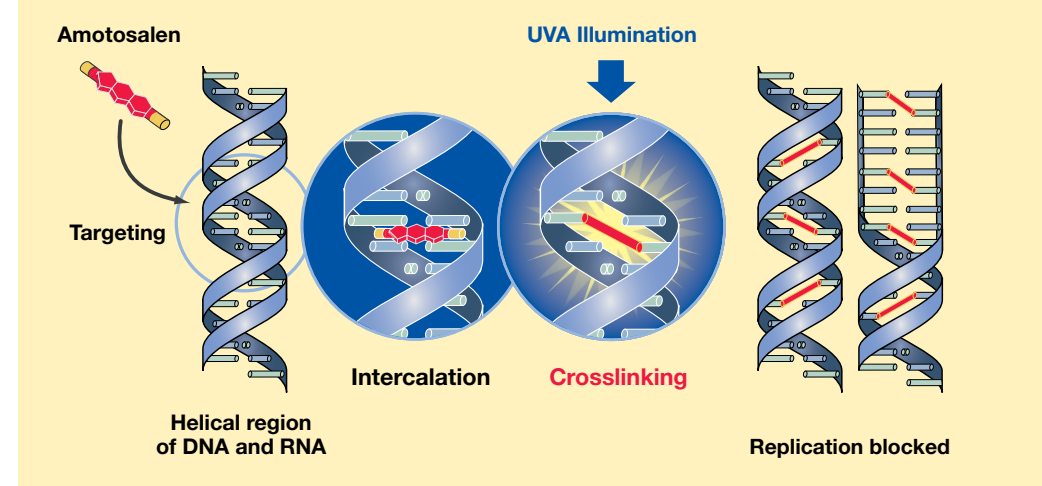


Figure 2: INTERCEPT PI Treatment Inactivates T Leukocytes with an Increased Efficacy Margin vs. Gamma Irradiation

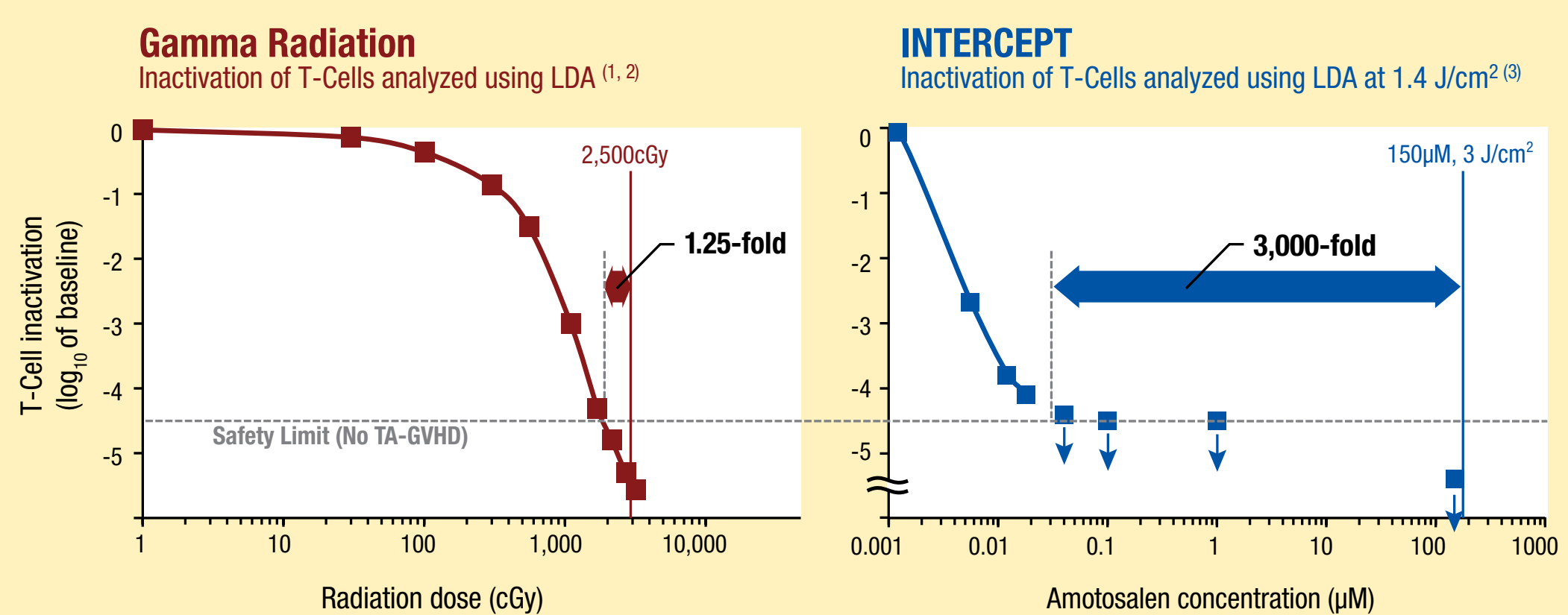
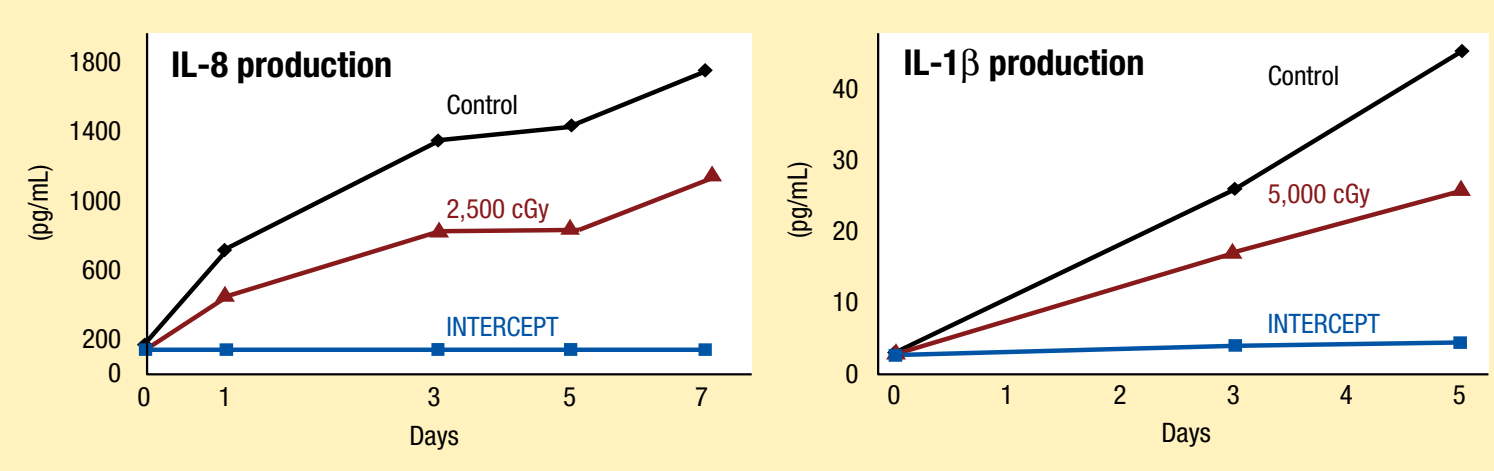


Figure 4: INTERCEPT Treatment of Platelet Concentrates Results in Complete Inhibition of Cytokine Synthesis during Platelet Concentrate Storage, while Gamma Irradiation Causes Partial Inhibition



Results

The cumulative frequency table of TA-GVHD for patients transfused with INTERCEPT platelet components in place of gamma irradiation includes hematology-oncology, HSCT recipients, and pediatric patients from 24 centers in 12 European countries (Table 1). A significant number of HSCT patients were evaluated and no cases of TA-GVHD were reported. In addition to the Phase III and HV studies, blood centers have purchased

INTERCEPT kits representing production of more than 800,000 platelet components to date. Most blood centers using INTERCEPT have discontinued gamma irradiation and rely on the inactivation process to provide protection against TA-GVHD. No cases of TA-GVHD have been reported by these centers in association with transfusion of INTERCEPT platelet components. The data presented in this report indicate that a

robust pathogen inactivation methodology can replace gamma irradiation of blood components for T-Cell inactivation. As reported recently⁽⁵⁾, in addition to the prevention of microbial transmission, eliminating gamma irradiation should be considered an important advantage of PI when the risks and benefits are assessed (Table 2).

Table 1: Summary of TA-GVHD Incidence in Patients Receiving Non-Gamma Irradiated INTERCEPT Platelet Components in Clinical Trials and Hemovigilance (HV) Studies

Study	Number of Transfusions	% Non-gamma irradiated platelets	Total Number of Patients	Hem-Onc Patients	HSCT Patients	Incidence of TA-GVHD
Phase III Trials ^d	529	100%	87	82	28	0
HV1 ^e	5,106	97.3% ^a	651	378	47	0
HV2 ^f	7,437	98.9% ^b	1,400	748	121	0
HV3 ^c	6,991	95% ^c	2,062	974	310	0
Mt. Godinne ^g	3,645	100%	186	186	186	0
Pediatric ^h	500	100%	83	48	10	0
Basel ⁱ	551	100%	46	38	15	0
Lübeck ^j	560	100%	52	52	17	0
Strasbourg ^k	55,104	100%	~8,000	~4,400	not available	0

a. Prior to CE Mark gamma replacement approval 139 of the 5,106 products (2.7%) performed in Trondheim, Norway were gamma irradiated; b. Prior to Afssaps' approval, a small number of products (82 of 7,437, or 1.1%) performed in France were gamma irradiated; c. Database closed; d. van Rhenen et al. *Blood* 2003;101: 2426-33. Janetzko et al. *Transfusion* 2005;45: 1443-52; e. Osselaer JC et al. *Transfusion* 2008;48: 1061-71; f. Osselaer JC et al. *Vox Sang* 2008;94: 315-23; g. Osselaer JC et al. *Vox Sang* 2010;99:428; h. Van haute I, et al. *Vox Sang* 2006;91: 177; i. Stebler C, et al. *Vox Sang* 2007;93: 172; j. Schlenke P, et al. *Vox Sang* 2007;93: 171; k. JP Cazenave. *Bull Acad Natle Med*. 2010.

Table 2: Summary of Disadvantages and Risks Associated with Use of Gamma Irradiation

Issue	Effect
Damages blood products	• Decreased 1-hour Post-Tx increments and increased probability for development of platelet refractoriness ⁽⁶⁾ • Damage of RBC causes increased hemolysis and potassium leakage ⁽⁷⁾
Generates double inventory leading to transfusion errors	• Mistakes in transfusion of non-irradiated components to immune-compromised individuals ⁽⁸⁾
Needs to be regulated tightly in order to be effective	• Failure of gamma irradiation to prevent TA GVHD ^(9, 10)
Can cause priming of leukocytes	• Physiological effects in blood product recipients ⁽¹¹⁾
Can cause viral reactivations	• Infections in product recipients ⁽¹²⁾
Cesium (Cs) Irradiators are expensive to purchase and maintain ⁽¹³⁾ , challenging to calibrate ⁽¹⁴⁾	• Additional Costs • Additional personnel hours
Cs Irradiators (Cs) are a security threat ⁽¹⁵⁾	• Inconvenient control processes required leading to indirect cost and expenses

Conclusions

Cumulatively, the clinical and routine experience supports use of INTERCEPT treatment in place of gamma irradiation to prevent TA-GVHD in at-risk patients.

References

- Pelszynski MM, et al. *Blood* 1994;83:1683-9.
- Luban, NL et al. *Transfusion* 2000; 40: 348.
- Grass JA et al. *Blood* 1998;91:2180.
- Hei D, et al. *Transfusion* 1999;39:239-48.
- Mintz PD. *Transfusion* 2011;51:1369-76.
- Slichter SJ *Hematol Oncol Clin N Am* 21 2007 697-729.
- Mintz P, Anderson G. *Ann Clin Lab Sci* 1993; 23:216-20.
- King KE, et al. *Transfusion* 2011;51:916-20.
- Drobyski W, et al. *Blood* 1989;74:2285-94.
- Lowenthal RM et al. *Transfusion* 1993;524.
- Chin-Yee I, et al. *TransfusMed* 1998;8:49-56.
- Ferrieu C, et al. *Radiat Res* 2003;159:268-73.
- AABB. Nuclear regulatory commission public meeting on cesium chloride uses, including blood irradiators. 2008. <http://www.aabb.org/events/government/public/Pages/nrcmeeting092908.aspx>
- Carson TH, editor. *Standards for blood banks and transfusion services*. 27th ed. Bethesda (MD): AABB; 2011.
- Wiggins JT. *International radioactive source security efforts*. 2010. <http://www.nrc.gov/irsrcmeeting092908.aspx>

Presented at the 29th Annual Conference of the British Blood Transfusion Society (BBTS)
Glasgow, Scotland • September 7th - 10th, 2011