

**12th International Conference on Thalassaemia
and the Haemoglobinopathies**
Antalya, Turkey, May 11-14, 2011

**New advances in blood safety : a regional
experience in France of pathogen inactivation
treatment of labile blood components to
prevent transfusion-transmitted infections**

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Patients and their doctors have always feared medical risks linked to transfusion

Risks of transmission of infectious agents to blood recipients are secondary to contamination of blood donors and of derived labile blood products (red blood cells, platelets, plasma) and of industrially prepared plasma derived drugs.

In a recent past, emerging viruses (HBV, HIV, HCV) have been the cause of human tragedies.

Implementation of preventive measures have reduced the risk of infectious diseases.

These reactive measures do not take into account the occurrence of the next risk and the time to set up a reply.

In France, the introduction of pathogen inactivation of labile blood products has been progressive and is based on technical, microbiological, epidemiological and clinical criteria.

[plasma: 1990-2010 (100%), platelets: 2005 (4/17 regions)]

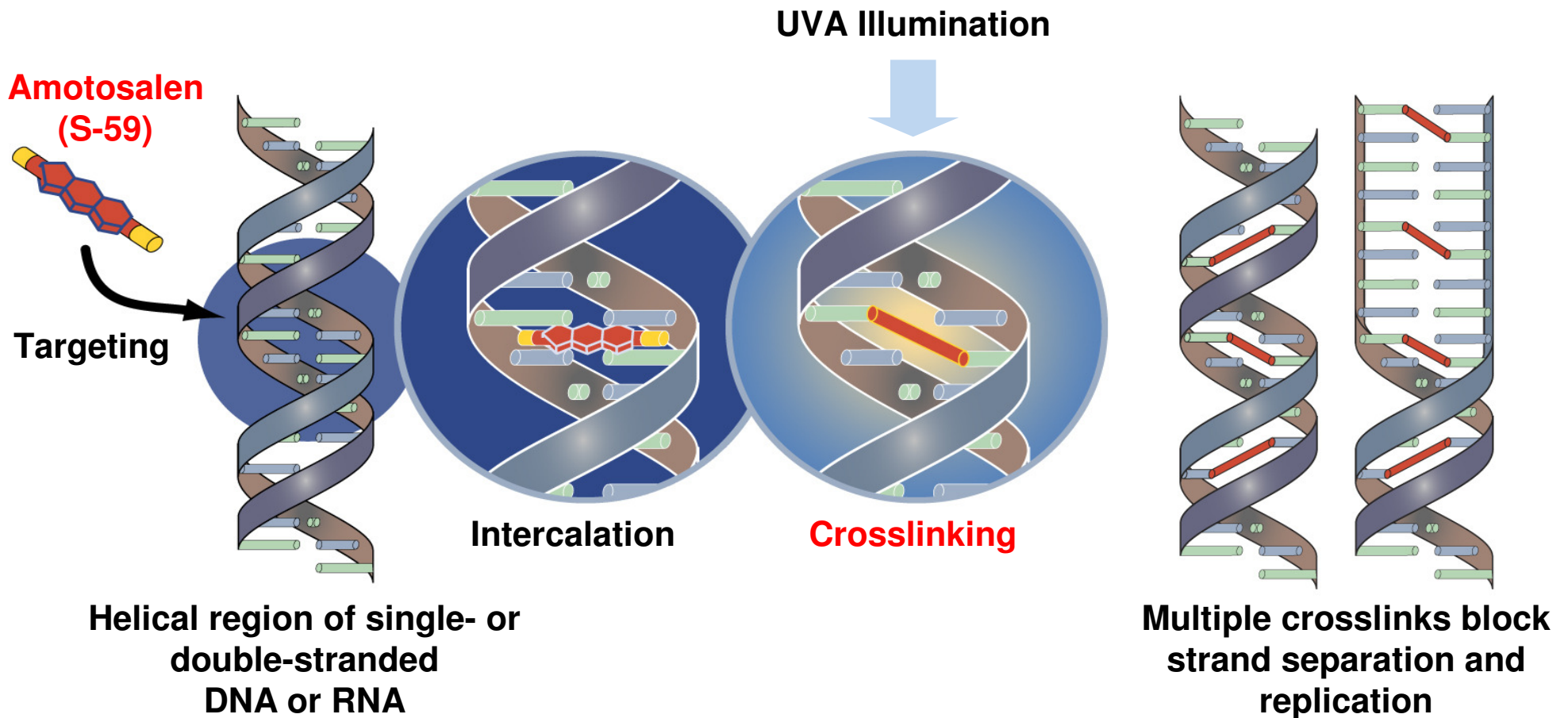
Epidemiological data and pathogen inactivation

1. **Time interval varies** between the recognition of the risk of an infectious disease and implementation of screening in the blood donor : 30 years for hepatitis B, 15 years for hepatitis C, 4 years for HIV and 4 years for WNV.
2. **Following inactivation of plasma derived drugs**, no infection due to these viruses has occurred.
3. **Emerging new pathogens transmitted by transfusion are feared** : WNV, Chikungunya, dengue, XMRV, HHV-8, Q fever, Chagas disease, malaria.
4. **Epidemiological modifications of populations** of donors and recipients secondary to migrations (travel, war, famine) and of climate changes (mosquitos expansion and epidemics).

The **INTERCEPT** blood system

1. Photochemical method using **amotosalen** and **UVA** (320-400 nm)
2. Inactivation of a large spectrum of pathogens : **bacteria, viruses, protozoa, spirochetes and lymphocytes**
3. Platelets (APC or BCPC) resuspended in 35 % plasma and 65 % Intersol
4. Pre-clinical (pharmacokinetics, toxicology) and clinical programs completed (including **euroSPRITE, SPRINT**)
5. CE marking (Class III drug-device combination) in 2002 and marketing approval in 2005 (France, AFSSAPS), 2007 (Germany, PEI), 2009 (Swissmedic)
6. **Approved claims** : transfusion support of patients requiring PC transfusions according to clinical practice guidelines. **INTERCEPT** PC (APC or BCPC) and **INTERCEPT** plasma are not clinically different from untreated PC and PFC
7. Clinical use in Europe : **> 600,000 transfusions**
8. Clinical use in France : EFS-Ile de la Réunion, EFS-Martinique, EFS-Guadeloupe-Guyane and EFS-Alsace (**100 % use**)

Mechanism of action of **amotosalen** for platelets and plasma



INTERCEPT Blood System

A broad spectrum of pathogen inactivation

Enveloped viruses

HIV-1
HIV-2
HBV
DHBV
HCV
BVDV
HTVL-I
HTLV-II
CMV/EBV/HHV-8
WNV
SARS
Vaccinia
Chikungunya
Dengue
Influenza virus (H1N1)
Avian flu virus (H5N1)
XMRV

Non-enveloped viruses

Bluetongue virus, type 11
Simian Adenovirus-15
Feline calicivirus
Parvovirus B19
Human adenovirus 5

Gram-negative bacteria

Klebsiella pneumoniae
Yersinia enterocolitica
Escherichia coli
Pseudomonas aeruginosa
Salmonella choleraesuis
Enterobacter cloacae
Serratia marcescens

Gram-positive bacteria

Staphylococcus epidermidis
Staphylococcus aureus
Streptococcus pyogenes
Listeria monocytogenes
Corynebacterium minutissimum
Bacillus cereus (vegetative)
Lactobacillus sp.
Bifidobacterium adolescentis
Propionibacterium acnes
Clostridium perfringens

Spirochetes

Treponema pallidum
Borrelia burgdorferi

Protozoa

Trypanosoma cruzi
Plasmodium falciparum
Leishmania mexicana
Babesia microti

Residual leukocytes

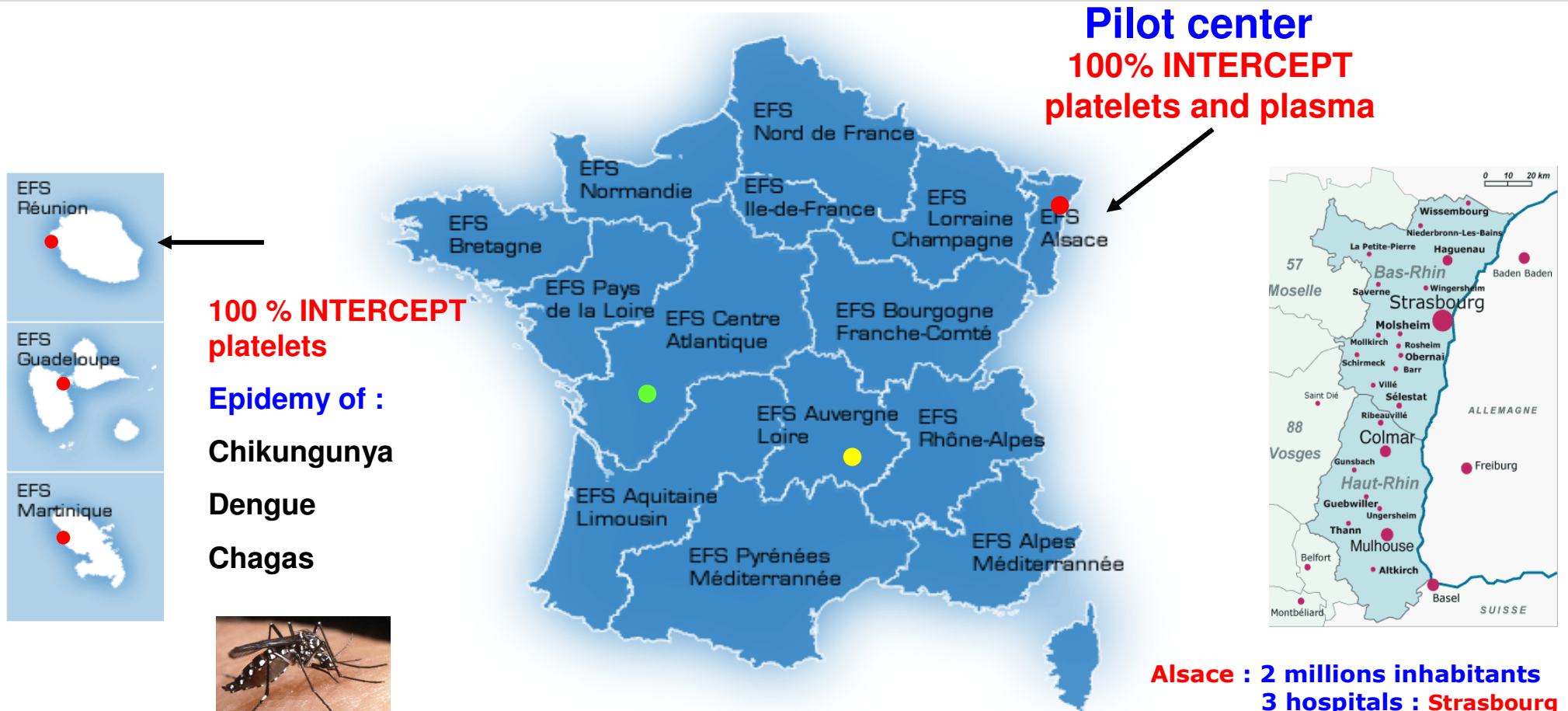
T lymphocytes, cytokines

Bacterial spores resistant

Prions resistant

**In general, 5 to 6 log reduction in infectious assays
In addition replaces gamma irradiation**

Clinical experience with **INTERCEPT** platelets and plasma in France since 2005



- 261,406 platelet doses (France. 2009)
- 370,738 FFP doses (France. 2009)

Platelets and plasma treated with **INTERCEPT** and transfused at EFS-Alsace (2006-2009)

	0-3 years N patients /N units transfused	3-17 years N patients /N units transfused	≥ 17 years N patients /N units transfused
MCPSD-IA	20/33	95/326	7.481/40,104
CPAD-IA	313/1,482	231/3,504	4.282/20,045
PFC-IA	449/1,240	198/1,203	6.618/40,259
Total patients (19.687. 100%)	782/2,755	524/5,033	18,381/100,408
Total units (105.411.100%)	(4.0%/2,6%)	(2,7%/4.6%)	(93,3%/92.8%)

Platelet concentrates (PC) transfused* to **all patients** at EFS-Alsace

	PC (100% plasma)	PC-T-sol (35% plasma)	PC INTERCEPT (35% plasma)
Patients (n)	2,050	1,678	2,069
Age (yrs) (median, min-max)	64 (3 – 97)	63 (<1 – 99)	63 (<1 – 106)
PC transfused (n)	10,629	9,151	13,241
Platelet content per unit	5.2 x 10 ¹¹	4.4 x 10 ¹¹	4.2 x 10 ¹¹
CP mean / patient	5.2	5.5	6.4
PC mean dose plt x10¹¹ / patient	27.1	24.1	26.9
RBCC median / patient	14.4	13.1	13.6
ATR (% / patient)	2.9 %	2 %	1.7 %

Cazenave JP et al. Transfusion 2010; 51: 622-629.

Platelet concentrates (PC) transfused to hematology-oncology patients at EFS-Alsace

	PC (100% plasma)	PC-INTERCEPT (35% plasma)	p
Patients (n)	671	699	
PC unit transfused (n)	5.816	7.675	
Platelet content per unit	5,2 x 10 ¹¹	4,2 x 10 ¹¹	
PC unit transfused x10 ¹¹ /patient	8,7 ± 12,0	11,0 ± 19,9	0,01
Platelet total dose x10 ¹¹ /patient	45,3 ± 62,8	46,1 ± 86,1	0,85
Total RBCC units	15,2 ± 16,5	13,6 ± 18,4	0,10

Cazenave JP et al. Transfusion 2010;51: 622-629.

Transfusion of **INTERCEPT** platelets and surgery during major hereditary thrombopathies

1. Glanzmann thrombasthenia type I with the Gypsy mutation

Patient 1 : 21 year old woman with ovarian cyst resection

- Total dose (D10) : **192.2 x 10¹¹ platelets**
- 3 RBCC + 1 FPC Intercept

Patient 2 : cesarean section in a 22 year old woman

- presence of anti-HLA and anti-HPA1a antibodies
- Total dose (D11) : **186.3 x 10¹¹ platelets**
- no RBCC

Patient 3 : avulsion of 2 molar teeth in a 6 year old boy

- Total dose (D6) : **12 x 10¹¹ platelets**

2. Thrombopenia with absent radius : 2 year old boy

- Born on 23/09/2006 and transfused during his first year in Nancy
- Since 18/05/2007, transfused in Strasbourg : 1 APC Intercept / week, total dose : **91 x 10¹¹ platelets**
- No ATR (24/06/2008)

Hemovigilance Surveillance of Platelet Components Prepared with Pathogen Inactivation Treatment During a Three Year Period

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Significant Reduction of Acute Transfusion Reactions

Table 4: Hemovigilance Data Reported For Transfused Platelet Components (2006 – 2009)

Component	Number PC	Adverse Reactions/10 ⁶ PC	P-Value
CPDA-IA EFS Alsace	16,494	2182	< 0.001
CPD National	385,049	6220	
MCP-IA EFS Alsace	26,312	2166	< 0.001
MCP National	117,795	3179	

- 1 episode of TRALI due to high titer HLA 1 and 2 antibodies in a multiparous apheresis donor.

Frequency of Transfusion Transmitted Bacterial Infections (TTBI) of **conventional platelet concentrates (PC)** and of **INTERCEPT inactivated PC**

Year	Conventional PC			INTERCEPT-PC		
	PC (n)	TTBI	TTBI / 10 ⁴ PC	PC (n)	TTBI	TTBI / 10 ⁴ PC
2006	231,853	4 (0)	0.17	6,420	0	0
2007	232,708	9 (3)	0.39	15,393	0	0
2008	239,349	6 (1)	0.25	15,544	0	0
2009	241,634	9 (0)	0.37	21,767	0	0
2010	253,149	2 (1)	0.08	22,632	0	0
Total	1,198,691	24(5)	0.20	81,766	0	0

AFSSAPS annual hemovigilance reports from 2006 to 2009 (gravity 1-4, imputability 3 and 4)
5 deaths (4 LR-APC / 1 LR-BCPC conventional)

Indications of **INTERCEPT** plasma

- . **INTERCEPT plasma** for support of patients requiring plasma transfusions or exchange, according to clinical practice guidelines. **INTERCEPT Plasma** is transfused according to standards

Clinical studies for each indication

Congenital factor deficiencies

Acquired complex factor deficiencies

Therapeutic plasma exchange : TTP

Regulatory status

- . **CE Mark registration (class III). 2006**

- . **AFSSAPS (France) approval of apheresis plasma. 2006**

Acceptable safety profile

Post-marketing studies

Extend safety profile in special populations

Major improvement of therapeutic plasma availability at EFS-Alsace with **INTERCEPT** plasma

	QUARANTINE	INTERCEPT
Production (1 unit=200mL)	1,500 units / month	1,500 units / month
Plasma in frozen inventory	7,000-8,500 units	6,000-8,000 units
Plasma units available at any time	200-400 units/week (3-4 % of stock)	All units (100 % of stock)
Donors not returning between 4 and 8 months	15 %	N/A
Donor management staff	2 secretaries	No secretary
Male or nulligest female only plasma	Not required	Required and achieved Only males

Number of transfusions or **INTERCEPT plasma (IP)** units per patient by primary diagnosis and incidence of acute transfusion reactions(ATR)

TABLE 3. Number of transfusions and/or components per patient by primary diagnosis and incidence of ATR

Variable	Hematologic disease	Surgery: biopsy or other invasive procedure	Other	Total
Number of patients	748	1048	1436	3232
Number of transfusions	2328	1779	3376	7483
Number of transfusions per patient				
Mean	3.1 ± 5.8	1.7 ± 1.9	2.4 ± 3.0	2.3 ± 3.6
Range	1-68	1-30	1-37	1-68
Number of plasma components per patient				
Mean	6.7 ± 11.3	4.3 ± 5.6	6.6 ± 9.6	5.9 ± 9.1
Range	1-115	1-107	1-130	1-130
Number (%) of transfusions with at least one ATR	4 (0.17)	1 (0.06)	3 (0.09)	8 (0.11)

Hematologic diseases [(748 patients), 2328 IP units, 4 ATR] : congenital coagulation deficiencies (4), acquired coagulopathies (701), immunodeficiencies (20), TTP (20)

Therapeutic Plasma Exchange(TPE) with **INTERCEPT**-treated FFP

	FFP Quarantine period (n=5) (1.9.2006-1.9.2007)		FFP- INTERCEPT period (n=11) (1.9.2007-1.9.2008)	
	Number of plasma exchange/patien	Total plasma infusion volume/pt (L)	Number of plasma exchange/patient	Total plasma infusion volume/pt (L)
Mean	12.2	22.1	16	33.2
SD	11.4	21.7	20.7	44.9
Median	8	14.9	10	17.4
Min	3	7.5	1	1.1
Max	32	60.3	71	153.8
p value			0.71	0.61

TPE for Thrombotic Microangiopathies (TTP and HUS)

Plasma volumes transfused in liver transplantation (0 to day 7)

	FFP Quarantine (2005 et 2007)	Intercept Plasma (2008 et 2010)
Number of patients (n)	215	214
Mean volume transfused /pt (mL)	2271	2277
Median volume transfused /pt (mL)	1302	1887
SD (mL)	3476	2231
Min (mL)	0	0
Max (mL)	29147	13362
p value		0,985

All patients requiring liver transplantation except patients with multiple organ transplantation

Evolution and adverse events in **TPE** and **liver transplantation** with **INTERCEPT** plasma

- Plasma **volumes** exchanged in **TPE** or transfused in **liver transplantation** (within 7 days) are **not different** with **INTERCEPT** plasma or quarantine FFP
- **No serious adverse events declared**
 - TRALI
 - Allergic reactions
- **No relapse** observed in TPE

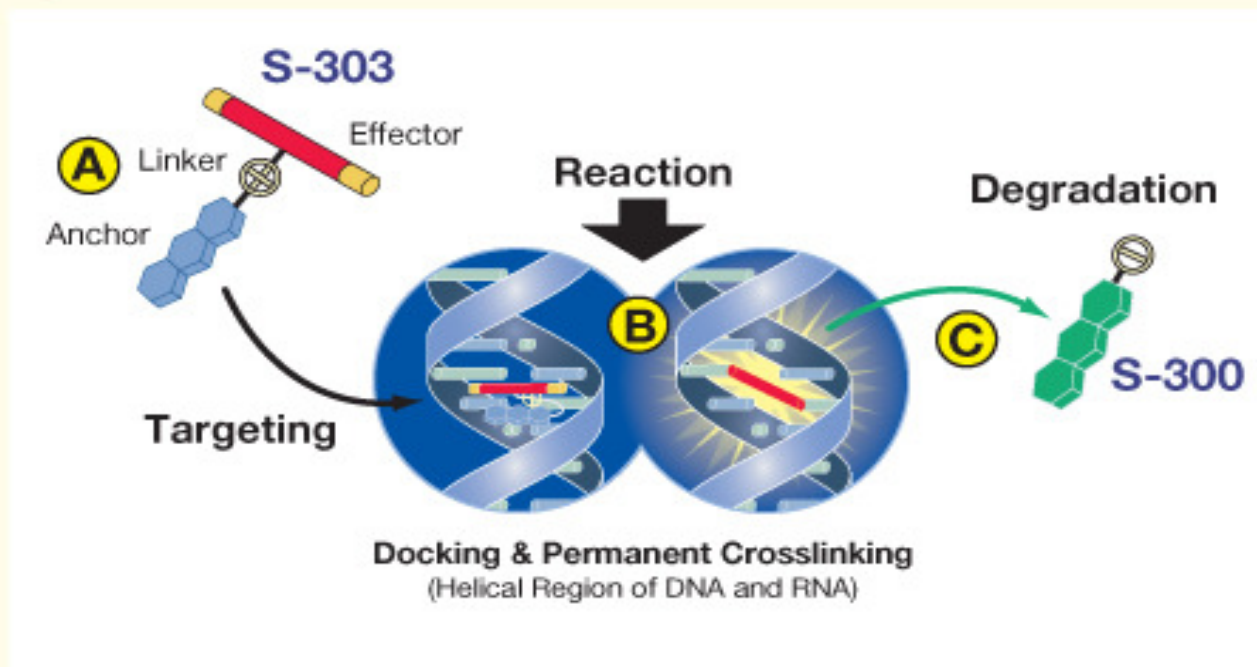
Net cost impact analysis

- Shift from LR- APC to LR- BCPC
- **Save plasma** by the use of **Intersol** from 280 mL (whole blood) to 450 mL (MCS+ mixed apheresis) for transfusion or fractionation
- **Replace gamma irradiation for TA-GvHD**
- **Avoid bacterial detection**
- **Avoid CMV serology for allogeneic transplants**
- **Avoid introduction of new tests, single donor NAT for HBV, WNV**
- **Avoid protozoa tests for Chagas, malaria, leishmania**
- **Have protection against Influenza viruses (H1N1, avian H5N1) and SARS viruses**
- **Reduce donor travel restrictions**
- **Common platform for platelets and plasma**
- **3 therapeutic doses (200mL) in single treatment (replace quarantine)**
- **Reduce platelet wastage (7-day platelets)**

Mechanism of action **INTERCEPT S-303**

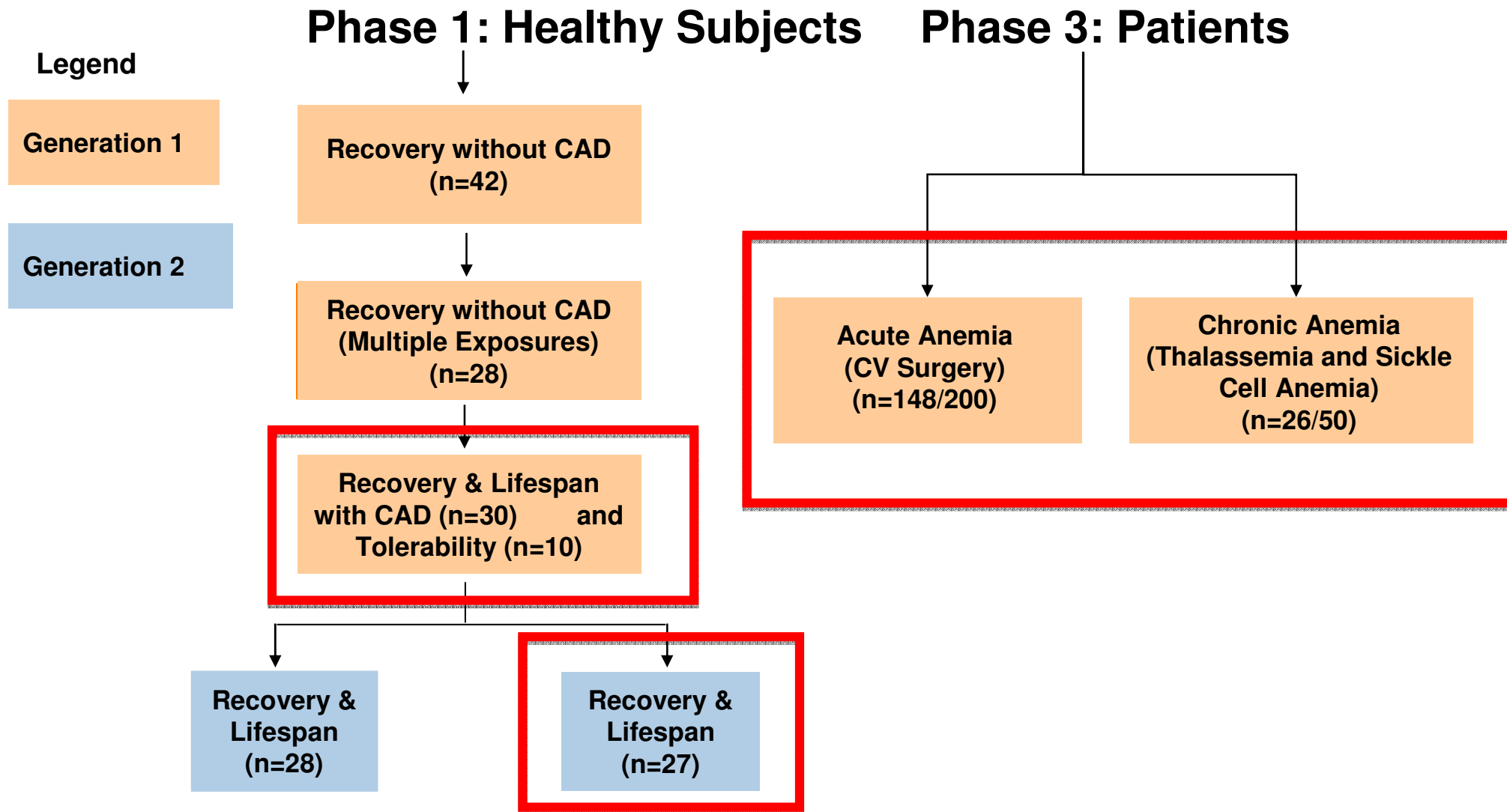
- S-303 is a nucleic acid-targeted alkylator with rapid inactivation kinetics
- S-303 hydrolyzes to an inactive derivative (S-300)
- Glutathione (GSH) is used to quench side reactions

Figure 1: S-303 Treatment Process Mechanism of Action



- Anchor selectively targets nucleic acids
- Effector crosslinks nucleic acids
- Linker temporarily joins anchor and effector
- Cross-linking reaction is faster than linker degradation
- Degradation yields unreactive by-products

INTERCEPT RBC : completed clinical studies



Conclusions

- **INTERCEPT Blood System** for **platelets and plasma** is adapted to the operations of small and large regional blood centers for timely release of products
- Training period is rapid
- Provides consistent doses of platelets and plasma prepared from both whole blood and apheresis collections
- Quality control processes to insure consistent products are achieved
- Implementation **protects from an emerging pathogen**, permits **adequate supplies** of platelets and plasma and avoids **CMV testing** and **gamma irradiation for PC**
- **Final safety in transfusion when plasma, platelets and RBC would be inactivated**



**Thank you for
your attention**