REMI GROUP

Blood Bank Chronicles

The Transfusion Medicine Update

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Index

'Pathogen Inactivation – Ray of Hope to Reality'

Editorial

New Promising Roads to Safe Blood

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Transfusion transmitted infections (TTI) are great concern for safety to patients. Since starting of blood transfusion scientifically in the early 1940s, various transfusion associated problems have come to the forefront of scientific community. TTI transmission was first observed in the process of blood transfusion in late 1940s. Till early seventies, blood bank personnel were only concentrating with few blood borne infections like syphilis and serum hepatitis by 'Australia antigens'. However, the scientific community has proved that multiple agents are responsible for TTI. Some of them are known and many are unknown. Battery of tests is done on collected units to make the unit safe for transfusion. However, TTI testing does not give absolute safety. Moreover, emerging pathogens have shown their virulent nature in transmitting diseases through blood transfusion like West Nile virus in USA; Chikungunya and Dengue virus in the Indian Ocean area. Though, Transfusion Medicine has achieved much improvement in providing safety to blood products, 'zero risk' in transfusion seems to be a distant goal.

To make transfusion therapy safe, the novel idea of pathogen inactivation was developed. This technology is unique and if any of these existing TTI testing techniques fail to detect any traces of pathogen, it kills/ inactivates pathogen in the blood/ component units. Though this concept gives us blood components near to 'zero risk' (in TTI), there is a ethical and technical concerns about adding additional materials/ chemical and infusing to a patient. However, it has been proved that all existing (& approved) technologies are very effective without any side effects to human beings. As this is a new technology and price is a barrier, we should do whatever best we can do to make the transfusion therapy safe from transmission of TTI.

In this special issue of News Letter, 'pathogen inactivation' has been taken as a

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Best Practices

Pathogen Inactivation - Challenges Ahead & Current Scenario

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Transfusion of labile blood components can be lifesaving but also comes with potential risks. Significant progress has been made to reduce the risk of transmission of viruses and bacteria via the blood products. The risk of transfusion-transmitted infections (TTI) today is lower than ever due to the improvements in blood collection and refinement of tests. Still the transfusion medicine community is currently embracing a paradigm shift leading to a more pro-active approach to blood safety, namely pathogen inactivation, in order to satisfy the need for safer blood products. This pro-active approach has the advantage that even newly emerging and yet unknown pathogens may be inactivated and there is no need to wait until new specific tests are developed.

It is well established, that there are several limitations of the reactive approach (bacterial detection, NAT, antibody testing) for preventing TTI. Current technologies can only be applied to some known pathogens. Even though, serological and nucleic acid testing (NAT) reduces the risk of the TTI such as HBC, HCV and HIV, they have not completely eliminated the risk.[1] A potential risk for transmission also exists for pathogens currently not tested for, such as West Nile Virus, Dengue and Chikungunya viruses (WNV, DENV and CHIKV). These pathogens are of major international public health concerns with extensive geographical spread that has expanded from tropical regions to some temperate places such as Italy, France, Nepal and China.[2-5]

Besides re-emerging pathogens, bacterial contamination, especially of platelet concentrates (PC) due to their storage at ambient temperature, is recognized as the most common cause of TTI.[6] Several studies demonstrated that platelets contaminated with bacteria continue to be transfused even though bacterial detection methods have been implemented.[7] Approximately 1 in 1,500 PC is contaminated with bacteria after early screening.[8] Bacteria may be present in asymptomatic donors or enter the blood at very low levels during collection, which makes them difficult to detect with early sampling, but which may still grow to life-threatening levels during RT storage. As the platelets are frequently given to patients with impaired immune systems, the patients are more susceptible to bacterial infections. On average a hematology-oncology patient receives 6 PC per treatment cycle. Thus, the risk to be transfused with a contaminated product could be as high as 1:250.[7] PC stored for 4 or 5 days are responsible for the majority of septic cases. This finding, among others, led to the reduction of the shelf life for PC from 5 to 4 days in Germany, except for inactivated PC which can be stored for up to 5 days. Hence, bacterial contamination might become the driving force leading to broad implementation of pathogen inactivation (PI) technologies. In contrast to bacterial detection, effective pathogen inactivation of platelet products could greatly diminish the risk that low levels of bacteria could multiply in a platelet component during storage.

Considerable progress has been made since the beginning of the 90's in the development of different technologies to reduce the risk of infection from single-donor or from pooled blood components. The robustness of the different PI technologies and their effect on blood components differ significantly. The current technologies apply light of different wavelength with or without chemical compounds to target the genome of pathogens and leukocytes. The exact mechanism of action of the PI technology and its specificity determine the impact on the blood component and thus the safety and efficacy in patients.

Any method applying a photoreactive compound, independent of the compound being 'natural' or synthetic and UV light will lead to the generation of photoproducts. For any technology with a mechanism of action involving direct interaction with DNA or RNA, it is critical to establish the safety profile. Toxicological evaluation of the INTERCEPT technology has been addressed through pre-clinical and clinical programs using in vitro and in vivo tests within ICH guidelines, demonstrating high safety margins.[9]

The INTERCEPT technology for plasma and platelets uses amotosalen, a synthetic psoralen (S-59-HCl) as active compound and ultraviolet-A (UVA) light. Amotosalen intercalates in single or double strand DNA and RNA of pathogens or leukocytes. Upon activation by UVA light, amotosalen forms covalent bonds cross-linking nucleic acids, thereby preventing strand separation and replication. Recent functional and proteomic analyses have shown that the treatment has minimal effects on platelets.[10] The technology does not require characterization of the pathogen to be effective, therefore even yet unknown pathogens may be inactivated. INTERCEPT has shown its applicability in routine use during ongoing epidemics of Chikungunya.[5]

The ideal PI technology should be effective not only against a wide range of pathogens with the high levels of inactivation but also have minimal side-effects and minimal impact on the product quality. In addition it should be simple to implement in current blood bank processes and be economically favorable.

The INTERCEPT Blood System for pathogen inactivation of plasma and platelets is the most extensively characterized of the currently available technologies, with a comprehensive pre-clinical and clinical development programme.[11-12] A total of 16 clinical studies have been performed for platelets and plasma pre-approval, in addition to post-marketing experience and hemovigilance studies. The INTERCEPT Blood System for platelets and plasma has delivered

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Transfusion Medicine Chronicles

1971 : The practice of testing donated blood for hepatitis B begins

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safe and effective blood components in routine blood center operations for over ten years and kits have been sold to produce over 2 million transfusable units in over 100 blood centers in 20 countries throughout Europe, the Middle East and Asia.

Clearly, regulatory agencies have a major responsibility in the evaluation of new technologies. The INTERCEPT Blood System is CE Mark as a Class III medical device, which is subject to stringent conformity assessment to demonstrate efficacy and safety. The INTERCEPT Blood System for platelets received CE mark in 2002 and for plasma in 2006. Subsequent to CE Mark registration, platelets and plasma components treated with the INTERCEPT Blood System received additional marketing authorization approval from the local authorities, the first centers started to use the technology in Germany and it is in routine use in several centers in Austria, France and Switzerland. Approval from the US regulatory agency (FDA) is currently being pursued through the Premarket Approval Application (PMA) pathway.

In addition to the clinical development program, multi-national active hemovigilance (HV) programs have demonstrated the safety of the INTERCEPT treated products.[13-14] No other pathogen inactivation technology has established a comparable voluntary active HV program. Experience data with INTERCEPT treated PC and plasma continue to be reported through the national HV programs of France and Switzerland.

In 2009, after a child died from a Klebsiella contaminated PC transfusion, the Swiss Red Cross (SRC) decided to implement the INTERCEPT Blood System for pathogen inactivation which was approved by the Swiss regulatory authorities. In addition, lower rates of acute transfusion reactions were reported in Switzerland.[15] Most importantly, the national data from Switzerland and France show a favorable outcome concerning transfusion transmitted bacterial infections (TTBI) when comparing the INTERCEPT PC with conventional PC (Table).

Comparison of Transfusion Transmitted Infections (TTI) after PC Transfusions

Year	Conventional-PC		INTERCEPT-PC	
	PC(n)	TTI *(Fatalities)*	PC(n)	TTI *(Fatalities)*
France*		* AFSSAPS annual hemovigilance reports from 2006-2011 and interim data for 2012		
2006	231 853	4 (0)	6 420	0
2007	232 708	9 (2)	15 393	0
2008	239 349	6 (1)	15 544	0
2009	241 634	9 (0)	21 767	0
2010	253 149	2 (1)	21 897	0
2011	267 785	3 (1)	23 179	0
2012	275 834	8 (2)	24 849	0
Switzerland**		** Swissmedic Haemovigilance Annual Reports 2010-2012		
2010	29 990	1 (0)	0	0
2011	6 600	0	26 500	0
2012	0	0	34 265	0
Total *(*+**)*	1 778 812	42 (7)	189 814	0

The implementation of INTERCEPT reduced the need for introduction of new, additional pathogen testing. Several centers utilizing INTERCEPT have replaced CMV serology testing and leukoreduction for prevention of transfusion-transmitted CMV infection. In addition INTERCEPT may be used as an alternative to gamma-irradiation to prevent GVHD for all patient groups. INTERCEPT treatment of platelets also allows for the storage for up to 7 days (here regional regulations apply), which offers the potential to improve availability of platelet components for transfusion and improve the supply of platelet components through reduced wastage. INTERCEPT has been shown to reduce the incidence of bacterial infection in blood component recipients which provides both a patient benefit and also decreased medical costs associated with treating any infection.[12]

At present the INTERCEPT technology for red blood cells is in clinical development. Two phase III studies are in progress for support of acute (cardio-surgery) and chronic anemia (Thalassemia). Upon successful outcomes for the phase III studies and regulatory approval, the INTERCEPT technology will be available for all 3 labile blood components.[16] In addition whole blood treatment is under development in collaboration with the Swiss Red Cross with a target of providing safer blood in developing countries.

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1972 : Apheresis - The process of separating out only one type of blood cell from donated blood

Pathogen Inactivation and Blood Safety in Developing Countries

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Blood Safety in Developing Countries:

The safety of blood and its components continues to be a global problem. Using human blood, especially in developing countries where blood-borne pathogens are endemic, poses significant safety concerns. Implementation of safety measures, such as donor selection, staff training and the practice of closed system processing, is highly desirable. The execution of careful screening of blood for the presence of pathogens would significantly reduce the risk of TTIs in developing countries, as is the case in the developed countries. More than two-thirds of the world does not have access to safe blood.[1] Each year unsafe blood transfusions in developing countries result in eight to 16 million hepatitis B virus (HBV) infections, 2.3–4.7 million hepatitis C virus (HCV) infections and 80,000–160,000 HIV infections.[2]

Newer threats to Blood Safety:

Enhanced safety is called for, not only for recognized agents (especially bacteria, which cause most current transfusion-transmissible infections [TTIs] and have only recently been addressed) but also for potential future "emerging" TTIs. These possibilities are not merely theoretical. TTIs of HIV-1, HIV-2, hepatitis B virus vaccine escape mutants, human herpes virus 8, West Nile fever virus, and variant Creutzfeld-Jakob disease amply demonstrate the continual emergence of such threats. For recognized agents, the possibilities of test errors, misreporting, process-control failures, and false-negative results (although rare with modern automation) still remain.

A growing number of viral, bacterial and protozoa pathogens have been identified as potentially transmissible via blood transfusion. New pathogens are regularly identified,[3] eg. the West Nile virus (WNV) in the US and, more recently, the Chikungunya virus in the Indian Ocean area.[4] Among the arboviral infections that have been on the radar for increased activity in the last decade are: WNV, Dengue viruses (DENV) and Chikungunya virus (CHIKV). In addition, other arboviral infections such as Yellow Fever, Saint Louis encephalitis, Tick-borne encephalitis, Rift Valley fever, Japanese encephalitis, Powassan encephalitis, Murray Valley encephalitis and Zika fever have been reported as emerging or re-emerging in various areas around the globe.[5] Alertness and surveillance are required to allow implementation of measures to mitigate risk of transmission to blood recipients including blood screening tests when available and appropriate.

Bacterial contamination, particularly of platelet concentrates, and protozoa transmitted by blood components still represent sizeable risks in developed countries. Platelet concentrates are stored at room temperature and are thus more susceptible to bacterial growth. Mortality and morbidity associated with blood transfusions that have been contaminated by pathogens, especially in developing countries, have been well established. HCV and Malaria are also a major transfusion transmitted infection (TTI) and occurs especially in developing countries due to serious constraints of technical and scientific advancements and concerned resources.[6,7]

Approach towards Blood Safety:

There are three main approaches used to identify and prevent the use of contaminated blood collected for the purpose of transfusion:

The safety of blood supplies has been significantly improved in some countries by the selection of non-remunerated voluntary donors who are at low risk of TTI's.[8] Testing procedures for TTI's have the greatest challenge of detecting infections during Window Period. The challenge of pathogen inactivation in blood is to reduce the level of pathogen infectivity without significantly compromising the key essential cellular or protein components or introducing some new toxicity, carcinogenicity or teratogenicity.[9]

Pathogen Inactivation Techniques:

Solvent detergent (SD) treatment has been successfully applied with pooled plasma during the last 20 years. The solvent detergent destroys 'enveloped' viruses including HIV-1, HIV-2, HCV, HBV and HTLV-I/II. It does not destroy 'non-enveloped' viruses such as parvovirus and the hepatitis A virus. Other inactivation procedures, such as pasteurisation and dry-heat application, are effective in inactivating 'enveloped' and 'non-enveloped' viruses (e.g. HAV and the B19 virus).[9] These procedures are used for isolated blood proteins, such as albumin or clotting factors.

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Transfusion Medicine Chronicles

1980 : The practice of testing donated blood for HIV begins.

Facts Compendium

Pathogen Inactivation - A Comparative Analysis*

System Name	Mirasol	Intercept	Theraflex
Company	TerumoBCT	Cerus Cooperation	Maco Pharma
Photosensitizer	Riboflavin (50µM)	Amotosalen (150µM)	Methylene blue
UV Type	UVA + UVB (280 – 400 nm; max at 313 nm)	UVA (320 – 400 nm)	UVC (254 nm)
Energy	6.24 J/ml for 10 min	3 J/cm2 for 3 min	0.2 J/cm2 for < 1min
Mechanism	Oxidization of guanosine bases causing single strands breaks	Covalent crosslinking between nucleic acids	Cyclobutane pyrimidine dimers causing blockage of nucleic acid transcripts
Platelet Storage medium	Plasma, SSP+	Intersol and SSP+	SSP+

*Reference : http://novascotia.ca/dhw/nspbcp/docs/Pathogen_Inactivation.pdf

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theme to stimulate its readers to this new subject. As I always say, we are technologically about 7-8 years behind the Western world. This state of the art technology is on our doorstep to explore a new horizon in TTI prevention. The best part of pathogen activation technique is that it acts on liquid blood and components and can be transfused immediately. There are techniques available to inactivate pathogen in red cells, platelets and plasma. There are limited numbers of manufacturers who have developed different products for this purpose. Review of literature has shown that all commercially available products are effective with some strength and weakness in each system.

Now, a new technology is in front of us and it depends on how and when we adopt this to our routine system. I still remember that I was not in favour of doing NAT test in India due to cost in 2002. However, situation has changed in last 12 years. Few factors like fear for legal implications, demand from clinicians/ patients, affordability, better awareness and competitiveness have forced us adopt routine NAT testing in many blood banks. I foresee the same repetition for this technology. Price may be a barrier. However, as a scientific worker and dealing with lifesaving products, we cannot ignore the value addition and safety added by this technology in treating patients.

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Most other inactivation approaches use chemicals that target the nucleic acids of pathogens.[9] The blood products that the chemicals are added to are then subjected to ultraviolet (UV) radiation. It causes the compounds to link to the pathogen's nucleic acids, preventing their replication. Methylene blue-light treatment of single-donor plasma units has a similarly long track record to pooled SD-treated plasma. The development of safe, inexpensive and easy-to-implement approaches to inactivate or remove a broad spectrum of pathogens is highly desirable. One such approach may be the use of devices that filter out and/or deactivate the pathogens in whole blood or blood products during their passage through the device.

In many developing areas of the world, where infections are rampant and blood transfusions are highly risky, cheap, one-time-usage, disposable and wide-spectrum pathogen removal/inactivation systems are desirable. In principle, an all-embracing, pan-effective microbe-inactivation procedure offers a potential solution to blood safety concerns. If such a system can take care of leukocytes in the blood, the need for leukodepletion and gamma irradiation also can be curtailed. The potential value of effective pathogen-inactivation systems for developing countries should not be forgotten once such systems are fully developed.

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1999 : The use of nucleic acid amplification testing for active viruses in donated blood begins.

Pathogen Inactivation: Pathophysiology

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Pathogen Inactivation (PI) is a proactive technology for enhanced blood safety wherein chemical compounds added to render blood residual or undetected pathogens to noninfectious or lead to reductions in infectivity of a variety of transfusion transmitted infections (TTI), including viruses, bacteria, and protozoa.

Nucleic acid testing has markedly reduced but not completely eliminated the risk of known TTI. The concern remains about the tests with limited sensitivity (e.g. for detection of bacterial contamination) and 'emerging' pathogens, for which accurate tests have not been developed, which still pose continued threats to blood recipients.[1]

The PI technology for plasma was described more than two decades ago followed by PI for platelets and now for red cells/whole blood have been developed more recently. None of the routinely available blood components (red cells, platelets and plasma) require nucleic acid replication for successful in vivo effect; thus PI approach should not interfere with the effectiveness of the blood component.

The first commercialized pathogen inactivation technique applied to blood components was solvent detergent treatment of pooled plasma, which involves disruption of viral lipid envelopes by the solvent-detergent combination and requires removal of these chemicals after processing. It is only effective against lipid-enveloped viruses, disrupts cells hence is not applicable to cellular blood components.[2] Methods used in the plasma fractionation industry have also been applied to plasma, such as Nano-filtration and Pasteurization but these have not been implemented to full-scale clinical use. Recent developments in PI for plasma and platelets have relied more on the use of combinations of visible or ultraviolet (UV) light and photosensitizers to modify nucleic acids. The rationale for targeting nucleic acids is that pathogens require nucleic acid function that is unnecessary for the therapeutic efficacy of platelets, plasma, and red blood cells. There should be at least 4-6 log reduction for sufficient pathogen reduction.

The INTERCEPT (IBS, Cerus Corporation, USA) technology for plasma and platelets uses a synthetic psoralen, amotosalen, which after binding nucleic acids and only upon activation by UV-A light cross-links nucleic acids in an oxygen-independent manner (photo-chemical reaction).[3] Amotosalen works by intercalating into the helical regions of DNA or RNA, where it forms fixed cross-links on exposure to UV light of wavelengths of 320 to 400 nm. The cross-links are so extensive that they prevent separation of the strands of nucleic acids, which, in turn, prevents nucleic acid replication.[6]

Alternative photo-inactivation technologies for platelet and plasma (Mirasol "riboflavin plus UV", TerumoBCT, USA)[4] or plasma (methylene blue plus visible light, Macopharma, France) PI depend on the generation of reactive oxygen species for their action.[5] The mechanism of riboflavin based technology is by damage to nucleic acids when exposed to 265 to 370 nm of UV light, as photolysis of the compound induces guanine oxidation, resulting in single-strand breaks.[7] Some of the important PI technologies for various blood components which are licensed or under clinical trials in Europe / USA are outlined in **Table 1**.

Table 1 - PI methods for various blood components

Blood Component	Method
Plasma	• Solvent-Detergent • Methyelene blue+visible light • Amotosalen+UV • Riboflavin+UV
Platelets	• Amotosalen+UV • Riboflavin+UV
Red Blood Cells / Whole Blood	• S-303 FRALE • Riboflavin+UV

Generally, PI is effective against lipid-enveloped viruses, parasites and bacteria, but less so for nonlipid-enveloped viruses and bacterial spores.[8] Of note, hepatitis A virus (HAV) is not susceptible to inactivation by INTERCEPT[9] whereas, Mirasol PI technology has been found to be effective for HAV.[10] These PI methods which target nucleic acids are not effective against prions, which is one of the limitations of these technologies.

Apart from enhancing blood safety in terms of pathogen reduction or inactivation, an additional benefit from the PI technology is the potential to eliminate the risk of transfusion-transmitted graft-vs-host disease as white blood cells are inactivated thus it can replace the need for gamma-irradiation of cellular blood components. Moreover, it can also prevent febrile nonhemolytic transfusion reactions besides being seriously considered as an alternative to CMV safe blood.

These PI technologies are otherwise safe as regard to tolerability, toxicity and mutagenicity. However, in vitro and in vivo data show that most pathogen-inactivated blood products are slightly compromised compared with untreated products. It has been observed that most PI methods result in loss of some cellular viability and plasma procoagulant activity. Methyl Blue treatment appears to reduce the activity of most procoagulant proteins 10–15%, and fibrinogen and factor VIII 25–35%.[8]

Out of all blood components, red cell units pose a challenge for photoinactivation techniques because of hemoglobin's absorption spectrum, higher viscosity and long

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Transfusion Medicine Chronicles

2005 : The FDA approves the first West Nile virus blood test to screen blood donors.

Upcoming Events

33rd International Congress of ISBT
May 31 – June 5, 2014, Gangnam-gu, Seoul, South Korea, www.isbtweb.org

12th Annual Meeting of International Society of Stem Cell Research (ISSCR)
Jun 18 – 21, 2014, Vancouver, Canada
www.isscr.org

Xth Annual AATM Conference
Sep 18 – 19, 2014, Kathmandu, Nepal
www.saatm.org

TRANSCON 2014 - 39th Annual national conference of SBTI
Oct 15 - 19 2014, Ludhiana, Punjab
www.isbti.org

AABB Annual Meeting
Oct 25 – 28, 2014, Philadelphia, www.aabb.org

3rd Annual Conference of Indian Society of Transfusion Medicine
Nov 14-16, 2014, Ahmedabad, India, transmedcon14@yahoo.com

Blood Bank Chronicles Important Links

PI method - Intercept	www.interceptbloodsystem.com
PI method - Mirasol	www.terumobct.com
PI method -Theraflex	www.macopharma.com

Quiz

Q. Select the Pathogen Inactivation Method used for Platelets?

a) Amotosalen+UV
b) Riboflavin+UV
c) S-303 FRALE
d) Both a & b

To enroll yourself for the lucky draw, Send us the Mail to us on supportggn@remilabworld.com

you have to type the following

1. Mention the subject = Lucky Draw Registration
2. Type the correct option in the mail
3. Mention your mobile no., Blood Bank Name & Contact details

Send the Answer for the question to us to win lucky draw (5 Nos) : - *Last date of enrollment : 31st May 14*

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storage time. Cerus' PI technique uses a chemical, S-303, activated on the pH change when encountering the blood component which has recently been modified to minimize adverse events. The technology has also shown promise for application to whole blood.[11] Similarly whole blood PI technology being developed by TerumoBCT would be a breakthrough technology which might change the way we look at PI methods for blood products. Preliminary results suggest good retention of blood cell functionality so that PI of all blood products using the same system may be acceptable for broad implementation in the near future.

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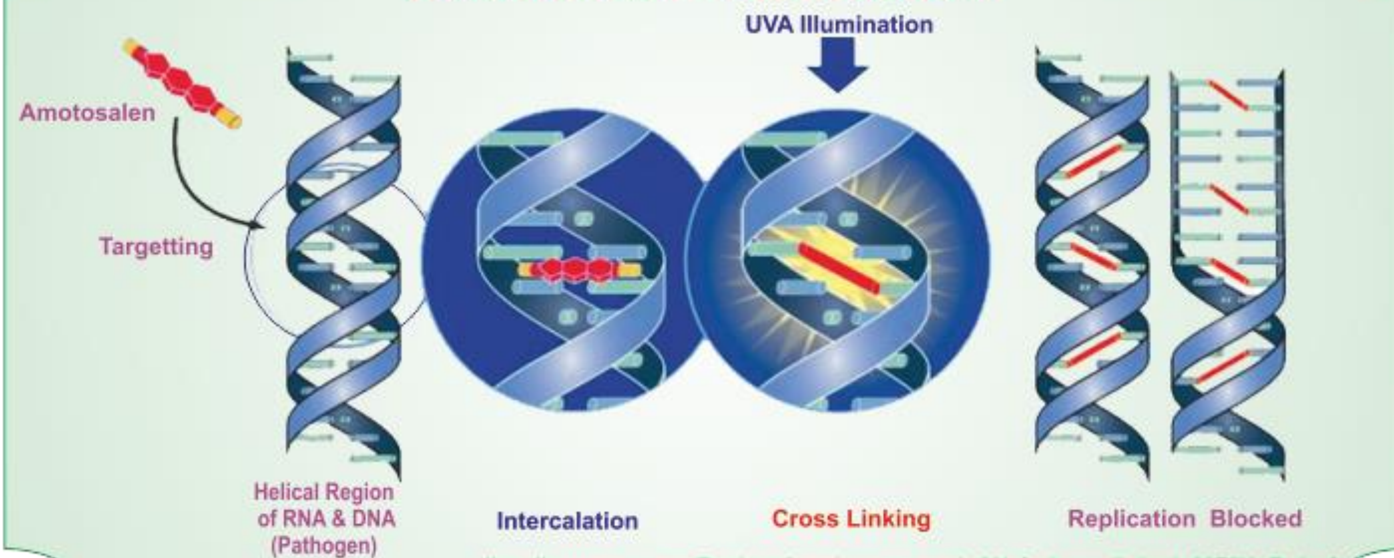
1969 : Scott Murphy and Frank Gardner develop a method for storing platelets at room temperature.

Blood Bank Chronicles Gallery

Pathogen Inactivation - Mode of Action*



*http://www.cerus.com/Products/how-intercept-works2/default.aspx#sthash.66Z5KwFt.dpuf

Humor

Last Quiz Winners

Dear Customer,

We are happy to announce that lucky draw winners of last issue quiz are as follows: -

1. Dr. Preet Valecha, Navjivan Blood Bank, Mumbai
2. Ms. Mansi Sawant, S R Mehta, Mumbai
3. Dr. Anil Kumar Gupta, ESI Blood bank, New Delhi
4. Dr. Anand Khiste, IRCS, Sholapur

Congratulations to All the Winners!!!
Your gift will reach to you in next 30 days.

Disclaimer
Blood Bank Chronicles is aimed purely for the educational purpose & providing a knowledge platform to the medical community. [illegible]