



ProMetic



American Red Cross

## PATHOGEN REMOVAL AND DIAGNOSTIC TECHNOLOGIES INC.

### BACKGROUND

The American Red Cross (ARC) and ProMetic Life Sciences Inc. (PLI) established a joint-venture company, Pathogen Removal and Diagnostic Technologies Inc. (PRDT), in April 2002 to develop and commercialize products to diagnose and reduce pathogens in blood, blood derivatives, biopharmaceuticals and other biological products.

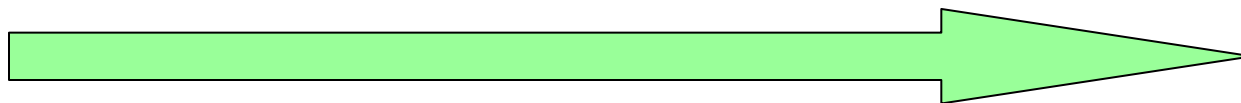
PRDT formed a strategic alliance with MacoPharma in 2004. The alliance's initial product focuses on reduction of Transmissible Spongiform Encephalopathy (TSE) such as vCJD, from blood and blood products. The first product will be a stand-alone sterile docking prion reduction filter. Subsequent products will focus on removal of other pathogens such as viruses from blood and blood products.

### STRATEGY

PRDT's strategy is to provide cost effective, simple-to-use removal solutions to address safety concerns of pathogen contamination in biological products. PRDT will commercialize products alone and in partnership with major companies in the fields of blood processing, plasma fractionation, and biopharmaceuticals. The products are developed to be compatible with blood banking and manufacturing practices, avoiding the introduction of chemically reactive molecules.

PRDT has adopted the following strategy for development and commercialization of its first products;

Combinatorial & rational chemistry	Screening expertise, reagents	Prion expertise, reagents, facilities & collaborators	Affinity support: technical expertise, manufacturing facility, regulatory support	Customers & implementation
PROMETIC, PRDT	PRDT	ARC, PRDT	MACOPHARMA PROMETIC (PRDT)	MACOPHARMA PROMETIC



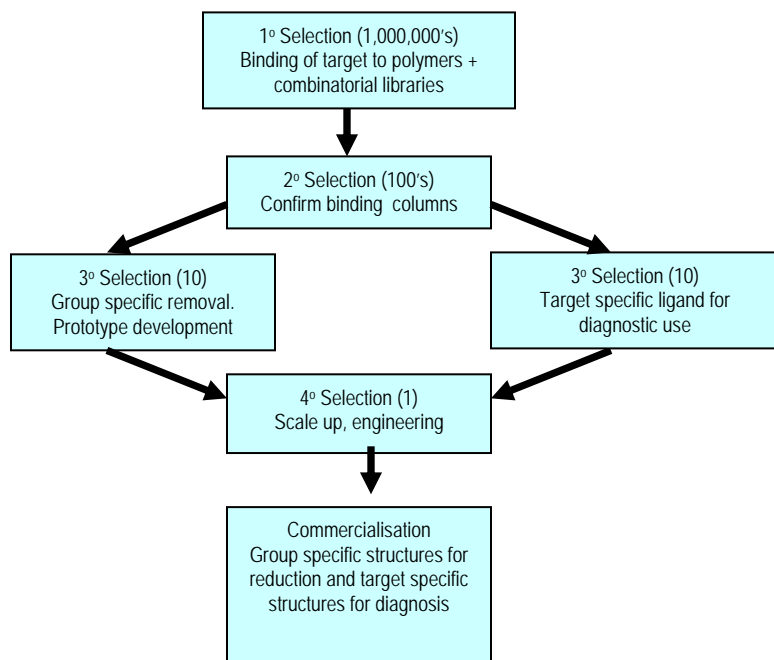
Research to proof-of-principle

Development

Commercialization

## TECHNICAL APPROACH

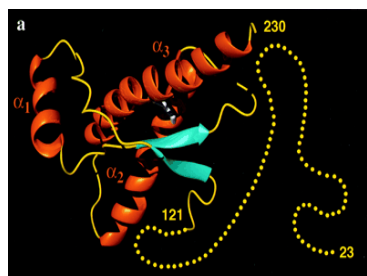
Affinity is the most specific interaction used in separation sciences today. Affinity interactions selectively adsorb and concentrate targeted proteins and pathogens on immobilized supports. PRDT focuses on



PRDT Technical approach one product resulting from screening of millions of initial ligands

combinatorial chemical libraries synthesized on beads (each bead has a unique chemical) to identify structures with the required specificity (ligands). Millions of different structures are evaluated using proprietary 1° selection techniques and only those few with the desired qualities are taken into development where they are immobilised onto inert supports (2° selection) (figure 1). Group specific structures that bind to a wide range of pathogens (e.g., human and animal TSE's and classes of virus) are useful for removal while structures that bind specifically to infectious human prion protein or individual viruses are useful for diagnostics (3° selection). Structure activity relationships are performed on one lead (4° selection) and the mode of interaction defined for optimization of the chemical structure and the inert support.

## ABOUT TSE (ALSO CALLED PRION DISEASE)



TSEs, or Transmissible Spongiform Encephalo-pathies, are fatal brain diseases that include *Creutzfeldt-Jakob Disease* (variant and sporadic CJD) in humans, scrapie in sheep and BSE or “mad cow disease” in cattle. The magnitude of exposure to the neurodegenerative disorder, variant Creutzfeldt-Jakob disease (vCJD), remains unknown. Over 150 people have contracted vCJD, the human form of “mad cow disease”, largely in the United Kingdom, following the outbreak of Bovine Spongiform Encephalopathy (BSE) in the mid 1980s. Recent cases of BSE in North America and Japan and two cases of vCJD in the UK linked to blood transfusion have heightened concerns over transmission of the disease.

Abnormal prion proteins (PrP<sup>sc</sup>) are thought to be essential and may be sufficient to transmit the disease. Normal prion protein (PrP<sup>c</sup>) is found throughout the body and during infections is thought to change shape and accumulate in large deposits in the brain and nervous system. The resulting damage causes sponge-like holes to appear in the brain causing a fatal degenerative central nervous system disorder.

Until recently, vCJD was thought to be associated with individuals with a specific genetic make up (MM at codon 129 of the prion protein gene). This limited the potential of the disease to approximately 42% of the population. Of particular concern is a case of vCJD in 2004 where a recipient of a blood transfusion contracted vCJD. This individual was of a genotype previously thought to be resistant to the disease (MV at codon 129 of the prion protein gene). This means that at least 89% of the population may be susceptible to vCJD.

Further evidence which has served to heighten fears was the publication of a study in 2004 where scientists examined appendix and tonsil samples of over 12,000 people who had undergone routine surgery. Three (3) cases of vCJD were found, indicating that at least 3,800 people in Britain may be incubating the disease without knowing it.

There are currently several ways of preventing potential infections of vCJD through blood transfusion:

- **Deferral** – removal of individuals from specific high risk groups, e.g., anyone who has received a blood transfusion since 1980, from the blood donating pool;
- **Sourcing** – this has been implemented for plasma protein products with UK sourcing U.S. plasma; however, it is not possible for blood donations;
- **Testing** – no available test is sensitive enough to detect prion protein associated with vCJD;
- **Removal** – universal leukodepletion (removal of white cells) was initiated in UK in the late 1990s. However, this only removes approximately 40% of infectivity, as demonstrated by one of PRDT's co-founders, Dr. R. Rohwer (Lancet 2004).

PRDT and MacoPharma firmly believe that removal is the most rigorous approach to reducing potential risk of contamination of the blood supply by vCJD. To that end, the two companies have developed a filter with a selective compound or ligand which, when chemically bound to an inert support, can bind and therefore remove abnormal prion protein and infectivity.

There is an active project running between PRDT, MacoPharma and the Transfusion Services of UK and Ireland to evaluate this technology.

#### THE PRION REDUCTION FILTER TECHNOLOGY



PRDT has completed evaluation of millions of different chemical structures and has identified a lead compound that will specifically adsorb a variety of different prion proteins (e.g., human infectious prion, vCJD, hamster and mouse prion) from biological solutions without affecting other constituents of, for example, blood. Structure optimisation is complete and involved studying the removal of infectious prion from infected red blood cell concentrate by passing it over a device which contained the immobilised ligand. The blood cell preparation was subsequently re-introduced to non-infected animals to establish removal of infectivity. PRDT has demonstrated removal of PrP<sup>Sc</sup> from spiked rbcc to the limit of detection by Western Blot and a 4 log<sub>10</sub> or **99.99%** reduction in infectivity in the in-vivo model. A further study was conducted to evaluate the utility of the device in removal of infectious

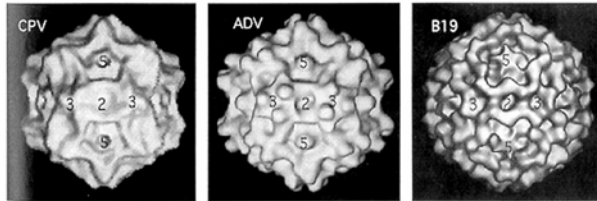
prion and associated infectivity from infected blood, i.e., endogenous or blood borne infectivity. In this model hamsters were infected with TSE and their blood taken, pooled and passed over the affinity matrix. Uninfected animals were subsequently inoculated with untreated blood and blood that had been treated with the PRDT affinity resin. There were no infections detected in the PRDT treated product demonstrating that the resin had removed infectivity to the limit of detection of the bioassay. This equates to an infectivity level of <0.2 ID/ml or a reduction in infectivity of > 1.2log<sub>10</sub>.

The prion reduction filter, P-Capt™ achieved European Regulatory approval in September 2006 (CE mark) and is under evaluation by UK and Irish Blood Services.

The first product is aimed at removal of prion protein from red blood cell concentrate; however, PRDT has already demonstrated the utility of its device (in-vitro) for removal of PrP<sup>Sc</sup> by the filter in the presence of whole blood and plasma. Development efforts are now focused on process optimisation and scale up of the ligand immobilised to inert resin, incorporation of the resin into a non-woven membrane and manufacture of the final filter device.

## VIRUSES

PRDT is currently investigating ligands capable of binding and removing viruses from blood donations without the need for introduction of harsh chemical treatment. The ligand technology targets canyons or hydrophobic pockets in viruses. While the topography of viruses is very different even within the same family, canyons are a common basic structure in all viruses, with multiple copies for each virus. They are required for infectivity and there is no competition for binding with antibodies. Utilising this approach



Differences in surface topography of Canine Parvovirus (CPV), Aleutian Mink Disease Parvovirus (ADV) and Parvovirus B19 (B19)

PRDT is investigating ligands which bind different viruses from the same family and from different families. PRDT is evaluating millions of different chemical structures and has identified a number of lead compounds that will specifically adsorb a variety of different non-enveloped and enveloped viruses such as B19 (human parvovirus), PPV, BVD model virus for Hepatitis C & West Nile Viruses)

from solutions such as buffer, fibrinogen and IVIG. Utilising validated TCID<sub>50</sub> and PCR assays, PRDT has demonstrated that the immobilised ligands can reduce viruses by 4 logs from contaminated protein solutions. It is thought that this approach may also be a powerful tool for rapid screening and elimination of new viruses from the blood supply. Implementation of PRDT technology for virus removal will aim to reduce selected viruses in any given red blood cell concentrate unit by more than 6 logs. It is anticipated that this will reduce the risk of viral infection through whole-blood donations to a minimum level.

## RISK OF VIRAL INFECTION FROM BLOOD DONATIONS

The likelihood of virus transmission through transfusion is summarised below (U.S. only) for a number of key viruses. In developed countries, the risk of viral infection transmission through transfusion has exhibited a downward trend over recent years.

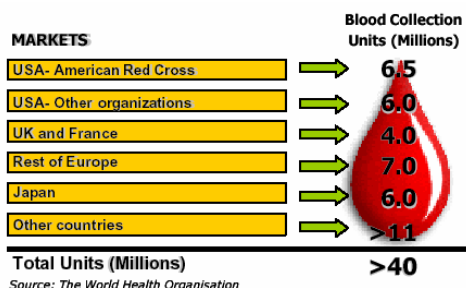
In the U.S., the risk of transmission of certain viruses expressed as risk – rate of infectious donations collected during window period (time between infection and detectability by screening tests, representing the greatest threat to blood safety) – was assessed during the period 2000-2001 (from Dodd et al, Transfusion August 2002).

- HBV (corrected) - Risk 1:205,000
- HCV (+ NAT) - Risk 1:1,935,000
- HIV (+ NAT) - Risk 1:2,135,000

In addition to the above viruses, more recent problems, e.g., West Nile Virus (WNV) have resulted in a risk of 1:36,000 in 2002. The introduction of NAT testing in July 2003 interdicted approximately 163 viremic donations.

Risk of transmission of viral infection in resource restricted countries is significantly higher due to lack of infrastructure, lack of NAT screening and insensitivity of assays used. WHO estimates at least 13 million of 75 million units collected in the world each year are not completely tested using basic serologic assays, including up to 45% of blood donations in developing countries.

## POTENTIAL MARKET



Worldwide, over 40 million units of blood are collected and processed annually. By far, the most widely transfused blood component is red blood cell concentrate (rbcc), which is the component targeted by PRDT's first product. Filters to treat whole blood, platelets and plasma will follow. This technology will be launched initially in Europe, followed by other territories.

Following the introduction of the prion reduction device, the filter may be engineered to allow reduction of additional pathogens such as viruses within the same system. This will provide a cost-effective way to help reduce the risk of transmission of other diseases through transfusion.

Therefore, the market opportunity for the first product offering is substantial.

#### **MORE ABOUT PATHOGEN REMOVAL AND DIAGNOSTIC TECHNOLOGIES INC. (PRDT)**

PRDT is a joint venture company established in April 2002 by the Red Cross and ProMetic. PRDT allows for a reciprocal exchange of technology and a knowledge base developed between the Red Cross and ProMetic. PRDT's main goal is to develop products and devices to remove and detect different pathogens from biological sources. This research augments work that ProMetic, the Red Cross and PRDT's scientific founders have been conducting independently for many years. PRDT's initial focus is a filter designed for the removal of abnormal prion proteins from blood and blood components.

#### **MORE ABOUT THE AMERICAN RED CROSS**

The American National Red Cross is where people mobilize to help their neighbors—across the street, across the country, and across the world—in emergencies. Each year, in communities large and small, victims of some 70,000 disasters turn to neighbors familiar and new—the nearly one million volunteers and 35,000 employees of the Red Cross. Through almost 900 locally supported chapters, more than 15 million people gain the skills they need to prepare for and respond to emergencies in their homes, communities and world. Some four million people give blood—the gift of life—through the Red Cross, making it the largest supplier of blood and blood products in the United States. And the Red Cross helps thousands of U.S. service members separated from their families by military duty stay connected. As part of the International Red Cross and Red Crescent Movement, a global network of 181 national societies, the Red Cross helps restore hope and dignity to the world's most vulnerable people. An average of 91 cents of every dollar the Red Cross spends is invested in humanitarian services and programs. The Red Cross is not a government agency; it relies on donations of time, money, and blood to do its work. Marsha J. Evans is the President and CEO of The American National Red Cross.

#### **MORE ABOUT MACOPHARMA**

MacoPharma is an innovator in global healthcare with expertise in the fields of transfusion and infusion. It has become the largest supplier of in-line leukoreduction filtration sets in Europe and is expanding its efforts into the cellular therapy field by developing products for cell expansion, in addition to cell/organ processing and freezing. Headquartered in the Lille metropolitan area (France), MacoPharma has three manufacturing facilities in Europe and their products are sold into more than 55 countries worldwide. One of MacoPharma's aims is to provide a comprehensive range for the pathogen reduction of infectious agents in plasma, platelets and red cells. This is aligned with the MacoPharma's product development strategy of the continuous quest, through partnerships, for improved safety, efficacy, and quality of transfusion, infusion and cellular therapy. [www.macopharma.com](http://www.macopharma.com)

#### **MORE ABOUT PROMETIC LIFE SCIENCES INC.**

ProMetic Life Sciences Inc. (TSX: PLI) [www.prometic.com](http://www.prometic.com) is a biopharmaceutical company specialized in the research, development, manufacture and marketing of a variety of commercial applications derived from its proprietary enabling technology, Mimetic Ligand™ which is used in large-scale purification of biologics and the elimination of pathogens. ProMetic is also active in therapeutic drug development with the mission to bring to market effective, innovative, lower cost, less toxic products for the treatment of inflammation and cancer. The Company's Mimetic Ligand™ technology is also leveraged into its drug discovery platform aiming at replacing complex, expensive proteins with synthetic “drug-like” protein mimetics. Headquartered in Montréal (Canada), ProMetic has R&D and manufacturing facilities in the UK and business development activities in the US, Europe, Asia and MENA countries (Middle East and North Africa).