

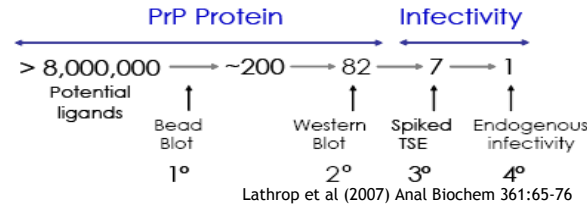
## 1. Introduction

Transmissible spongiform encephalopathies (TSEs), also known as prion diseases, can be transmitted by blood and blood components. Blood leucoreduction provides only a partial protection against TSE transmission as only about 50% of endogenous blood infectivity remains in the leucoreduced blood.

Pathogen Removal and Diagnostic Technologies Inc. (PRDT), a joint venture between ProMetic and the American Red Cross, identified ligands with strong and selective binding to the TSE causative agent. A panel of resins was selected from among the best prion binders and several were shown to reduce brain-derived scrapie infectivity by 3-4 log<sub>10</sub> from Red Blood Cell Concentrate (RBC). One selected for endogenous challenge captured all detectable endogenous infectivity from leucoreduced scrapie-infected whole blood from hamsters as measured by bioassay. This resin was incorporated into a filter developed by MacoPharma as a prion capture device termed P-Capt™, which is CE-marked, and available for commercialization.

## 2. Ligand Selection

### Process Schematics for Ligand Selection



- Peptide ligands
  - 1-6 amino acid residues investigated
  - Solid-phase libraries
  - Millions of possible sequences
- Polymers
  - Commercially available
  - Mimetic ligands
  - Triazine-based ligands

### Infectivity Reduction Studies

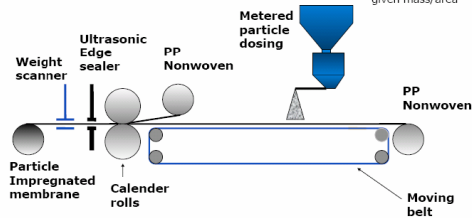
- More than 3 log<sub>10</sub> removal of hamster-adapted 263K scrapie brain infectivity spiked in leucoreduced human red blood cells at a concentration 2,000,000-fold higher than expected in RBC (Gregori et al. (2006) Transfusion 46:1152-1161)
- Removal of all detectable endogenous infectivity from hamster blood (Gregori et al. (2006) Lancet 368:2226-2230)

**All detectable endogenous infectivity was removed from challenge by the selected ligand**

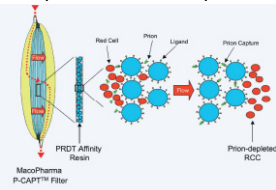
## 3. Device Development

Particle-impregnated membrane (PIM) is produced as below, resulting in a layer of resin between two sheets of nonwoven membrane

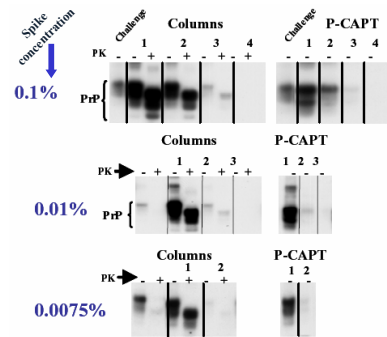
Controlled to obtain given mass/area



- Multiple layers of PIM are stacked and fused together and encased, forming the final device
- Resin is immobilized between the membrane layers, while RBC pass unimpeded
- As RBC pass through the multiple layers, prions are removed by adsorption to the resin particles

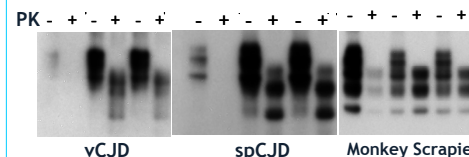


## 4. Binding of PrP to P-Capt™



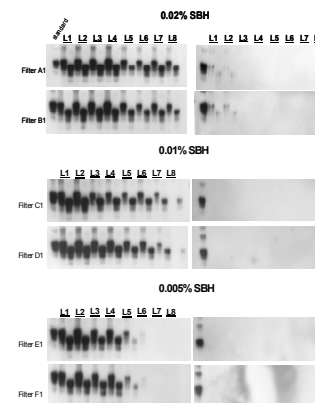
- Signal shows material bound to columns or devices in series
- Device has a behavior similar to packed columns at the different spike concentrations tested

**Packed columns and device bind PrP similarly**



**Resin binds different TSE agents efficiently**

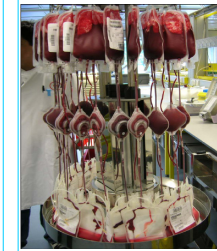
## 5. Binding of PrP to P-Capt™ Layers



- Each layer works as a discreet component, maximizing removal
- At a spike concentration of 0.005%, device removed 10<sup>7</sup> ID<sub>50</sub>, 4 to 5 orders of magnitude greater infectivity than expected in a unit of leucoreduced RBC

**Device has excess layers and excess binding capacity**

## 6. Hemocompatibility



- Hemocompatibility of resin showed no negative effects
  - No hemolysis
  - No platelet activation
  - No complement activation
  - No Factor VII activation
  - RBC yields are within the acceptable limits

## 7. P-Capt™ Device



- CE-marked
- Manufactured and marketed by MacoPharma SA
- No impact on red blood cells or activation of coagulation factors, platelets or complement
- No adverse effects detected in human safety trials

- Efficacy of removal
  - >3 log<sub>10</sub> reduction of exogenous brain spike infectivity in RBC containing 2,000,000 times the level of infectivity expected in RBC
  - Removal of all detectable endogenous infectivity from whole blood