Table 3
Extent of TSE agent removal during nanofiltration of plasma-derived coagulation factor concentrates. Adapted from Refs. [43,62]

| Starting plasma fraction | Nanofilter | End-product | Agent | Spike | Assays | Reduction factor |
|---|---|---|---|---|---|---|
| *DEAE-Toyopearl 650M eluate* | Planova 35N | vWF | 263K | MF | WB | ≥ *3.1* [61] |
| *DEAE-Toyopearl 650M eluate* | Planova 35N + 15N | FVIII | 263K | MF | Bioassay | ≥ 3.3 [61] |
| *SD + DEAE-Toyopearl 650M eluate* | Planova 35N + 15N | FVIII | 263K | MF | WB | ≥ *5.1* [61] |
| *Monoclonal antibody chromatography eluate* | Planova 75N + 35N + 35 + 15N | FVIII | 263K | BH + SD | Bioassay | *4* + *0.3* + *1.3* + ≥ *0.5* [62] |
| *Monoclonal antibody chromatography eluate* | Planova 75N + 35N + 35N + 15N | FVIII | 263K | PrPsc + SD | Bioassay | *3.1* + *0* + *0.8* + ≥ *2* [62] |
| *Ion-exchange chromatography + heparin-Sepharose eluate* | Planova 15N | FIX | 263K | MF | Bioassay | *4.8* [61] |
| *Ion-exchange chromatography + heparin-Sepharose eluate* | Planova 15N | FIX | BSE 6PB1 | BH + sonication | Bioassay | *5.3* [42] |

MF: microsomal fraction; BH: brain homogeneate; WB: Western-blot; SD: solvent-detergent.

tate [39]. Using blood from scrapie-infected hamsters, and in spiking studies where scrapie 263K $PrP^{sc}$ was added to human plasma, 20% and 10% of the infectivity partitioned in the cryoprecipitate, respectively [35,54]. By contrast, when human plasma was spiked with scrapie 263K brain homogeneate (BH), 90% of $PrP^{sc}$ was found in the cryoprecipitate. These contradictory results may highlight the influence of the nature of the experimental model used, in particular the physicochemical nature of the spike [34], or of the variations in the down-scaling of the cryoprecipitation procedure, or they actually illustrate the fact that cryoprecipitation does not ensure robust partitioning of TSE infectivity.

*3.3.2.2. Ethanol precipitation.* The capacity of precipitation steps to remove prions efficiently has first been shown by partitioning of endogenous infectivity using a rodent model. It is particularly well documented for the ethanol fractionation process isolating albumin and immunoglobulins. In the albumin fractionation procedure using either the Cohn-Oncley or the Kistler and Nitchman processes, major and consistent reduction factors (typically 3–5 logs) of TSE agent have been found by various groups, most specifically during the precipitation of fraction II + III, fraction III, and fraction IV, or their equivalents using slightly modified fractionation conditions [35,42] (Table 4). Similar experiments revealed 3–5 logs removal during the precipitation III or I+III used in the IgG process [35,42]. These data suggest that, in spite of variations in the conditions (such as ethanol concentration and pH) used, reproducible clearance of $PrP^{TSE}$ takes place. Removal is achieved when the precipitate is separated. It has been speculated that prion removal in precipitates is possibly due to aggregation and is dependent upon pH and presence of alcohol [35,55]. Other precipitation steps, using caprylic acid during immunoglobulins production [56] or polyethylene glycol also contribute to prion removal [42].

*3.3.2.3. Depth filtration.* Depth filters are made of a combination of a matrix (generally based on cellulose), filter aids (diatomeous earth, resins, or other adsorbents), and a drainage system. They are used to clarify crude protein solutions and

Table 4
Extent of TSE agent removal during the ethanol plasma fractionation process in the manufacture of albumin and immunoglobulin G. Adapted from Refs. [41,43,62]

| Step | Fraction evaluated | Agent | Spike | Assays | Reduction factor ($log_{10}$) |
|---|---|---|---|---|---|
| *Precipitation of fraction I* | Supernatant | 263K | BH | WB | 1.1 [41,43] |
| *Precipitation of I + II + III* | – | 263K | MF | WB | 1.3 [34] |
| *Precipitation of I + II + III* | – | 263K | MF | WB | ≥ 2.8[a] [42] |
| *Precipitation of fraction II + III* | – | 263K | BH | WB | ≥ 4.7 [41,43] |
| – | – | 263K | BH | Bioassay | 6.0 [41] |
| – | – | Sc237 | BH/MF/CLD/PrPSc | CDI | 3.6/3.1/3.1/4.0 [34] |
| – | – | 263K | BH | WB | ≥ 4.2/ ≥ 4.1 [41,43] |
| – | – | 263K | BH | Bioassay | 3.7/4.6 [41] |
| *Precipitation of fraction I + III*[b] | – | 263K | MF | WB | ≥ 3.5[a] [42] |
| *Precipitation of fraction IV*[c] | – | 263K | MF | WB | ≥ 3.0 [35] |
| – | – | Sc237 | BH/MF/CLD/PrPSc | CDI | 3.2/3.4/3.2/2.2 [34] |
| – | – | 263K | MF | WB | ≥ 3.7 [35] |
| – | – | 263K | MF | WB | ≥ 4.3[a] [42] |
| – | – | 263K | BH | WB | ≥ 4.3 [41,43] |
| – | – | 263K | BH | Bioassay | 5.3 [41] |

BH: brain homogeneate; MF: microsomal fraction; CLD: caveolae-like domain; WB: Western-blot; CDI: conformation-dependent immunoassay.
[a] Evaluated together with filter aids to remove precipitates.
[b] Precipitate discarded during the manufacture of IgG.
[c] Precipitate discarded during the manufacture of albumin.

Table 5
Extent of TSE agent removal during depth filtration of albumin and immunoglobulin G fractions. Adapted from Refs. [41,43,62]

| Fraction | Filter | Agent | Spike | Assays | Reduction factor ($log_{10}$) |
|---|---|---|---|---|---|
| *Supernatant I* | Seitz Supra P80 | Sc237 | BH/MF | CDI | –0.1/0.1 [34] |
| *Supernatant III* | Millipore AP20 | BSE 301V | MF | Bioassay | 2.4 [37] |
| – | Seitz KS80P | BSE 301V | MF | Bioassay | ≥ 3.1 [37] |
| – | Cuno Zetaplus | 263K | BH | WB | ≥ 3.3 [55] |
| *Supernatant IV* | Seitz Supra P80 | Sc237 | CLD/PrPsc | CDI | ≥ 0.9/ ≥ 2.4 [34] |
| – | Seitz AKS5 (carbon) | 263K | MF | WB | 2.7 [42] |
| *Fraction V (albumin)* | Cuno Delipid-I | 263K | MF | WB | 2.3 [35] |
| – | Seitz KS80P | 263K | MF | WB | ≥ 4.9 [35] |
| *Fraction II (IgG)* | Seitz K200P | 263K | MF | WB | ≥ 2.8 [35] |
| – | $Ca_3PO_4$ + filter aid + Cuno | 263K | MF | Bioassay | 2.5 [42] |
| – | Cuno | 263K | BH | Bioassay | ≥ 4.9 [57] |

BH: brain homogeneate; MF: microsomal fraction; CLD: caveolae-like domains; CDI: conformation-dependent immunoassay; WB: Western-blot.

Table 6
Extent of TSE agent removal during nanofiltration of plasma-derived albumin, and IgG. Adapted from Refs. [43,62]

| End-product | Nanofilter | Agent | Spike | Assays | Reduction factor |
|---|---|---|---|---|---|
| Albumin[a] | Planova 35N | CJD | BH | Bioassay | ≥ 5.9 [53] |
| Albumin[a] | Planova 35N | ME7 | BH | Bioassay | 4.93 [36] |
| Albumin + detergent[a] | Planova 35N | ME7 | BH | Bioassay | 1.61 [36] |
| Albumin[a] | Planova 15N | ME7 | BH | Bioassay | ≥ 5.87 [36] |
| Albumin + detergent[a] | Planova 15N | ME7 | BH | Bioassay | ≥ 4.21 [36] |
| RhO (D) IgG | VIRESOLVE 180 | 263K | Detergent treated, sonicated and filtered BH | WB | ≥ 2.5 [63] |
| IgG | DV50 | 263K | BH | Bioassay | 4.4 [64] |
| IgG | Planova 75N + 35N | 263K | MF | Bioassay | 3.2 [61] |

BH: brain homogeneate; MF: microsomal fraction; WB: Western-blot.
[a] Nanofiltration is not used during production of albumin preparations; a detergent was added for experimental purposes only.

remove precipitates. As such they are an important adjunct to the ethanol precipitation process. Principle of action encompasses both removal of particulates larger than the pore-size by size-exclusion, and of smaller elements by adsorption. During immunoglobulin manufacture, the supernatant of Fraction III (Supernatant III) and the re-dissolved Fraction II precipitate, and during production of albumin, the Supernatant IV and the re-dissolved Fraction V, generally undergo depth filtration steps. Experimental spiking experiments (Table 5) have shown that several types and grades of depth filters can remove prions [35,37,42]. Depending upon the type of depth filter or the physico-chemical parameters of the suspension, $PrP^{TSE}$ removal may be due to an aggregation in the presence of alcohol [55] or to hydrophobic adsorption on the filter aids [42]. The impact of protein composition and content remains to be investigated and understood to demonstrate and guarantee the robustness of this non-specific removal.

*3.3.2.4. Nanofiltration.* Table 6 shows experimental data on the removal of TSE agents during nanofiltration of albumin and IgG. As for coagulation factors, high reduction factors have been found. Prion partitioning is presumed to result from a size-exclusion mechanism.

### *3.4. Cleaning and sanitization*

Most equipment, including stainless steel reactors, chromatographic gels and columns, ultrafilters are re-used and, therefore, must undergo steam (SIP) or chemical (CIP) sanitizing procedures between production batches. These processes should be validated to ensure proper bacterial, pyrogenic, viral, and protein decontaminations. Experience gained with the sterilization of surgical instruments has shown that autoclaving at 134 °C for 18 min or 121 °C for 30 min reduced the transmission of prion infectivity by a factor > 5 $log_{10}$ [57, 58] but autoclaving without immersion is less effective (4–4.5 log reduction) [58]. Standard chemical decontamination methods (NaOH 1 N, NaOCl 20,000 ppm) and hydrogen peroxide alone achieved a reduction of > 6.5 and 4.5 $log_{10}$, respectively [58]. By experiments involving a hamster scrapie strain 263K BH model, it was shown that 0.1 M NaOH for 15 min, in the absence of detergent, at 4 and 18 °C caused a reduction of 3.5 and 4.0 $log_{10}$ of the prion protein, respectively. In the presence of sarkosyl, a 60-min incubation in NaOH further enhanced PrPRES reduction to > or = 4.5 $log_{10}$, with no residual infectivity. Therefore 0.1 N NaOH could also effectively inactivate prions, and its efficacy can be enhanced by the addition of sarkosyl [59]. A separate study shows that 0.1 M NaOH at 60 °C for 2 min and 0.25 M NaOH at 30 °C for 60 min inactivate 3.96 and 3.93 $log_{10}$ of mouse-adapted scrapie strain ME7, respectively, and 0.5 M NaOH at 30 °C for 60 or 75 min inactivates ≥ 4.23 and 4.15 $log_{10}$ [60].

## 4. Conclusion

There is so far no evidence of transmission of prions by plasma derivatives. The prevalence of the disease in the population is considered to be very low, although possibly not quite as low as initially considered [5,6]. Based on experimental models, it is believed that the infectivity in the plasma does

not exceed a few infectious doses per ml. By lack of knowledge of the nature of the agent associated to the infectivity in plasma, and in the absence of validated screening tests, alternative precautionary measures have been introduced to prevent the possibility of transmission of vCJD by plasma derivatives. Epidemiological surveillance of the population is in place in countries where BSE and vCJD cases have been identified. In some countries, blood donation deferral criteria include travel or residence of donors in BSE countries, and history of previous transfusion or tissue transplantation. Based on filtration experiments of blood collected from scrapie-infected hamsters, leucoreduction decreases by about 50% the prion infectivity in plasma [22,27]. Extent of removal of TSE agents during the plasma fractionation process appears to be substantial. Data from various laboratories and using different experimental models show several logs removal of TSE infectivity during the fractionation process. The most effective, but non-specific, removal steps are ethanol precipitation, depth filtration, and ion-exchange chromatography. Nanofiltration was also demonstrated to remove several logs of TSE infectivity, possibly based on a specific prion removal mechanism by size-exclusion. Uncertainty on the validity of these experimental studies remains, and additional studies are needed, since the biochemical features of the infective agent in blood and plasma is not known, nor the extent to which it may be present in blood donations. Research should continue, aiming at identifying the features of TSE agents in human plasma and at ensuring the robustness of prion removal steps and sanitizing procedures during plasma product manufacture.

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別紙様式第２－１

# 医薬品　研究報告　調査報告書

| 識別番号・報告回数 | | | 報告日 | 第一報入手日<br>平成19年5月7日 | 新医薬品等の区分<br>該当なし | 機構処理欄 |
|---|---|---|---|---|---|---|
| 一般的名称 | テクネチウム大凝集人血清アルブミン（99mTc） | | 研究報告の公表状況 | ProMED-mail／20070423.1325(2007年4月23日)<br>1:Herald Sun online、2: Mailman School of Public Health, Columbia University, press release | 公表国<br>オーストラリア | |
| 販売名（企業名） | テクネMAAキット（富士フイルムＲＩファーマ株式会社） | | | | | |

| 研究報告の概要 | 使用上の注意記載状況・その他参考事項等 |
|---|---|
| オーストラリア（ヴィクトリア）において、一人のドナーから臓器提供を受けた３人（腎臓を移植された63歳女性、肝臓を移植された64歳の男性、腎臓を移植された３例目）の死因について、コロンビア大学とメルボルンの科学者らによって新たなウイルス（リンパ球性脈絡髄炎ウイルスに関連するアレナウイルス科）が発見された。しかしこのウイルスが単に付着しているだけか、組織拒絶と死の原因となるかどうかは未解決である。 | 特になし |

| 報告企業の意見 | 今後の対応 |
|---|---|
| 臓器移植後死亡した３例の死因についての研究報告であり、これまで知られていない新ウイルス（リンパ球性脈絡髄炎ウイルスに関連するアレナウイルス科）が発見され、同科には出血熱性のラッサウイルスやマチュポウイルス等あることより、重大な感染症である可能性が考えられる。<br>本報告は、新たに判明した感染症に関するものであり、かつ、重大な感染症に関するものと判断する。 | 本報告はヒト血液を原料とする血漿分画製剤等とは直接関連するものではなく、現時点で特に当該生物由来製品に関し、措置等を行う必要はないと判断する。しかしこのウイルスが単に臓器に付着しているだけか、組織拒絶と死の原因となるかどうかは未解決であると報告されているため、今後も情報収集が必要であると考える。 |

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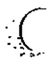

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**Subject** PRO/AH/EDR> Arenavirus, organ transplants - Australia (VIC)

ARENAVIRUS, ORGAN TRANSPLANTS - AUSTRALIA (VICTORIA)
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[1]
Date: Sun 22 Apr 2007
Source: Herald Sun online [edited]
<http://www.news.com.au/sundayheraldsun/story/0,,21598166-2862,00.html

Australia: Novel virus responsible for deaths of organ donation recipi
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A virus unknown to medical science was behind the deaths of 3 Victorians who received organs from the one donor. The unnamed bug has been linked to Ebola virus, [a virus] responsible for the deaths of thousands in central Africa since the 1970s. [This is an incorrect statement. The organ transplant-associated virus is not related to Ebola virus; see part [2] below. - Mod.CP]. After baffling local scientists, experts from New York's Columbia University were called in to help solve the mystery of the multiple transplant deaths being investigated by the coroner.

Initial investigations and tests had been unable to determine any common link between the donor and the 3 recipients. The presence of the virus in the recipients is thought to be a world first. One of the New York team said: "The discovery of this virus is of national and international significance."

The Sunday Herald Sun revealed the deaths in February 2007. A 63-year-old woman died after receiving a kidney transplant at Austin Hospital. A 64-year-old man died after receiving a liver transplant there. The 3rd victim received a kidney at Royal Melbourne Hospital.

The male donor whose organs carried the suspected killer bug had died in Dandenong Hospital of a brain hemorrhage in December 2006 after returning from overseas; it is believed most of his trip was spent in Europe.

The virus is part of the rodent-borne arenavirus family and can cause "old-world" diseases such as Yellow Fever, Ebola and Lymphocytic choriomeningitis. [This statement is incorrect: yellow fever is caused by a flavivirus and Ebola hemorrhagic fever is caused by a filovirus; only lymphocytic choriomeningitis (LCM) is caused by an old-world arenavirus. - Mod.CP]. Victoria's acting Chief Health Officer, Dr John Carnie, confirmed the virus [LCM virus?] had been detected in multiple samples from all 3 transplant patients. But there was no evidence the virus represented a public health risk, he said.

Health authorities are examining whether future donated organs can be screened for [LCM?] virus. A spokesman for the Victoria Coroner's office said families of the victims were told yesterday [21 Apr 2007]. There would be a formal inquest.

Experts from Columbia's Greene Infectious Diseases Laboratory helped

solve the mystery. Initial investigations and tests were unable to determine any common link between the donor and the 3 recipients. Dr Carnie said the risk to the public was minimal because "these viruses [?] affect immunocompromised people, and it is rarely fatal in those with normal immune systems. We have not had any indication of any unexplained illnesses among families of the donor or recipients," he said. "This would be the case if it was transmissible person to person. Our supposition is it was transmitted by organ transplantation."

Cutting edge techniques were used for the 1st time by the Greene lab -- in collaboration with Victorian Infectious Diseases Reference Laboratory -- to gene sequence the virus. "Our gene technology enables unbiased sequencing of all agents present," Columbia's Prof. Ian Lipkin said. "We found a handful (of combinations) that were related to Lassa virus or LCM virus [both old world arenaviruses - Mod.CP]. Using these clues we can confidently say this is a new virus, present in the original organs and so different than anything seen before."

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Communicated by:
ProMED-mail Rapporteur Brent Barrett

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[2]
Date: Sat 21 Apr 2007
Source: Mailman School of Public Health, Columbia University, press release [edited]
<http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/stor

Scientists Discover New Virus Responsible for Deaths of 3 Transplant Recipients From Single Donor in Victoria, Australia
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Knowledge of genetic sequence of virus will enable improvements in screening to enhance transplantation safety. Scientists in the Greene Infectious Disease Laboratory of Columbia University Mailman School of Public Health and colleagues in the Victoria Infectious Diseases Reference Laboratory in Melbourne, Australia and 454 Life Sciences have discovered a new virus that was responsible for the deaths of 3 transplant recipients who received organs from a single donor in Victoria, Australia.

The previously unknown virus, which is related to lymphocytic choriomeningitis virus (LCMV), was found using rapid sequencing technology established by 454 Life Sciences and bioinformatics algorithms developed in the Greene Laboratory with support from the National Institute of Allergy and Infectious Diseases. Known strains of LCMV have been implicated in a small number of cases of disease transmission by organ transplantation [see references below], however, the newly discovered virus is sufficiently different that it could not be detected using existing screening methods.

Over 30 000 organ transplants are performed in the U.S. each year. Knowledge of the genetic sequence of this virus will enable improvements in screening that will enhance the safety of transplantation.

Ian Lipkin, MD, director of the Greene Laboratory and Principal Investigator of the Northeast Biodefense Center, emphasized the importance of academic, public health, and industrial partnership in this work. "This was a team effort. Drs. Mike Catton and Julian Druce at the Victorian Infectious Disease Reference Laboratory reached out to us after a comprehensive state-of-the-art investigation failed to turn up leads," stated Dr. Lipkin. "We succeeded in identifying the virus responsible for the deaths by building on their work and utilizing new tools for pathogen surveillance and discovery developed in the Greene Laboratory and 454 Life Sciences."

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Communicated by: ProMED-mail <promed@promedmail.org>

[Lymphocytic choriomeningitis virtu (LCMV) is the type species of the genus _Arenavirus_ of the _Areanviridae_ family of bipartitie genome

RNA viruses. The reservoir hosts of almost all arenaviruses are rodents. LCMV is found in wild and laboratory mice, and other related "old world" arenaviruses are found in African species of rodents. Human LCMV infection may occur in rural and urban areas with high densities of rodents. Laboratory-acquired infections occur sporadically, and, previously, there have been a small number of cases of LCMV transmission by organ transplantation as mentioned by Professor Lipkin above. The virus detected by Professor Lipkin's group appears to be an LCMV-like agent but distinct from previously isolated strains of LCMV. It is unresolved, however, whether these organ-transplanted viruses are merely passengers or are responsible also for tissue-rejection illness and death. - Mod.CP]

[see also:
2005
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LCMV, transplant recipients, fatal - USA (02) 20050526.1459
LCMV, transplant recipients, fatal - USA 20050524.1426
1995
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LCMV & birth defects - USA 19951119.1095]
.......................mpp/cp/msp/lm

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# 医薬品 研究報告 調査報告書

| 識別番号・報告回数 | | | 報告日 | 第一報入手日 | 新医薬品等の区分 | 機構処理欄 |
|---|---|---|---|---|---|---|
| | | | | 2007. 4. 19 | 該当なし | |
| 一般的名称 | 人赤血球濃厚液 | | 研究報告の公表状況 | AbuBakar S, Sam IC, Wong PF, MatRahim N, Hooi PS, Roslan N. Emerg Infect Dis. 2007 Jan;13(1):147-9. | 公表国 | |
| 販売名（企業名） | 赤血球M・A・P「日赤」（日本赤十字社）<br>照射赤血球M・A・P「日赤」（日本赤十字社）<br>赤血球濃厚液-LR「日赤」（日本赤十字社）<br>照射赤血球濃厚液-LR「日赤」（日本赤十字社） | | | | マレーシア | |

| 研究報告の概要 | 使用上の注意記載状況・その他参考事項等 |
|---|---|
| ○マレーシアにおけるチクングニヤウイルス感染の再興<br>最近マレーシアでは、7年間検出されていなかったチクングニヤウイルス感染が再興した。分離ウイルスのゲノム配列は、1998年のアウトブレイク時のMalaysian 分離ウイルスの配列との相同性が高かった。この感染の再興は、他のインド洋諸国における流行には関与しないが、マレーシア特有のチクングニヤが流行する可能性が浮上している。 | 赤血球M・A・P「日赤」<br>照射赤血球M・A・P「日赤」<br>赤血球濃厚液-LR「日赤」<br>照射赤血球濃厚液-LR「日赤」<br><br>血液を介するウイルス、細菌、原虫等の感染<br>vCJD等の伝播のリスク |

| 報告企業の意見 | 今後の対応 |
|---|---|
| マレーシアで7年間検出されていなかったチクングニヤウイルス感染が再興し、ウイルスのゲノム配列は他のインド洋諸国における流行株とは異なっていたとの報告である。 | 日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国後4週間は献血不適としている。国内でチクングニヤ感染が確認されたため、渡航歴確認の徹底を図っている。また、チクングニヤ熱の既往歴がある場合、治癒後6ヵ月間は献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。 |