A Challenge of More Active Removal of Large-Middle Molecules -- A New Member of the Super High-Flux Polyether Sulfone (PES) Membrane Dialyzer

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Akihiro C. Yamashita, Ph.D.

Professor & Pro-Vice-Chancellor
Department of Chemical Science and Technology
Faculty of Bioscience and Applied Chemistry
Hosei University, Tokyo, Japan

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38th Annual ISBP Congress 2023

COI Disclosure

Akihiro C. Yamashita, Ph.D.

Consultant: Nikkiso Co., Tokyo, Japan, Japan Hemotech Co., Yokohama, Japan, Asahi-Kasei Medical Co., Tokyo, Japan.

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Other: This presentation is supported by Nipro Co., Osaka, Japan.

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1. *Introduction*
2. Current dialysis situations in Japan
3. What is the target solute to be removed?
4. Current Dialysis Membrane
5. A New Member of Nipro's PES dialyzer
6. Conclusions

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Clinical Evaluation of Protein Permeating Hemofilter and Analysis of Middle Molecules in Ultrafiltrate

Saito, A., Chung, T. G., Kanazawa, I., Oda, O. and Ohta, K.
The Bio-dynamics Research Institute, Nagoya, Japan.

Hemodiafiltration repeating a period without filtering protein and one filtering considerable albumin, transferrin, etc. per treatment, switched for 2-3 mos have been performed in 3 patients with numerous complications. Changes in clinical conditions have been observed and the ultrafiltrate obtained from the hemofilters was analyzed. The Rhone-Peulenc RP-6 and the Toray B1L were used as a non-albumin filtering hemofilter and the Cordis Dow Duo-flux , as an albumin filtering hemofilter. Several effects were seen at Duo-flux treatment period. *Elevation of hematocrit was striking*, ectopic calcification unable to be treated at RP-6 and B1L treatment period disappeared in 2 patients and *pruritus and irritation were eliminated in the 2 patients*. Although *5-8g of protein was lost with Duo-flux*, there was *no reduction in serum total protein and transferrin*. Nine kinds of protein with molecular weight smaller than transferrin (8,000 dalton) were detected in the ultrafiltrate obtained at Duo-flux treatment period. Although a striking increase of removal was seen at fraction a which is of the highest molecular weight out of middle molecular fractions, there was no difference in the removal of middle molecular fractions smaller than this. Key words: Protein permeating hemofilter, anemia, middle molecules, hemofiltration.

JINKO-ZOKI (*Jpn J Artif Organs*), 10(6), 907-911, *1981*.

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- We started using "MCO" like membranes since 1981 in Japan.
- Most treatments including both HD and HDF have been performed with this kind of membrane.

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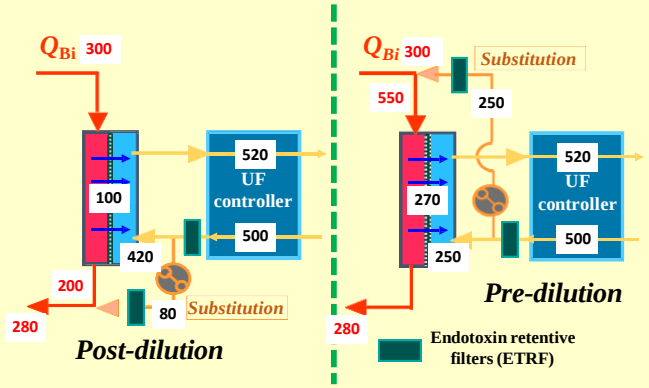

Fig.1 On-line hemodiafiltration (HDF)

Rindi P, *et al.*: Trans ASAIO, 34, 765,1988.

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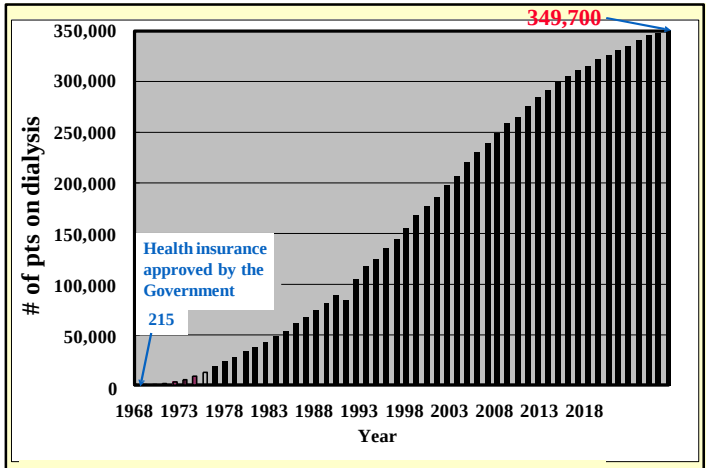

Fig.2 Number of dialysis patients in Japan (JSDT, 2022)
2,914 pts/million population

JSDT Statistics as of 12/31/21

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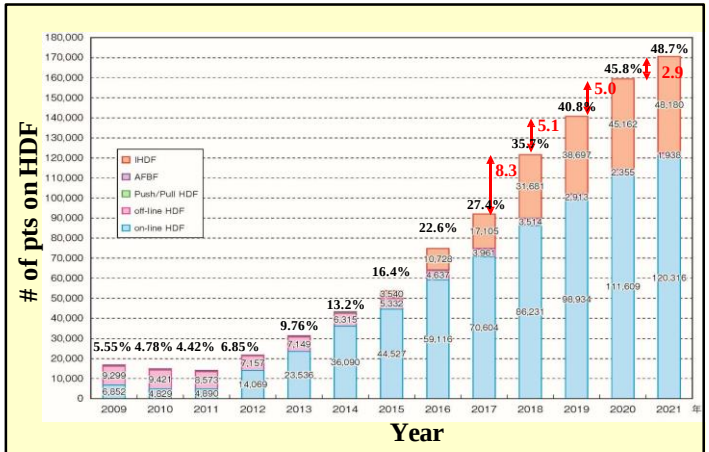

Fig.3 Number of dialysis patients in Japan (JSDT, 2022)
2,914 pts/million population

JSDT Statistics as of 12/31/21

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Table 1 Dialyzer categories in Japanese reimbursement system until March 31, 2016

HEMO study	Class	Clearance for b_2-MG [mL/min]	Reimbursement
Low-flux	I	Very low-flux < 10	Low
High-flux	II	Low-flux >=10 ~ < 30	
	III	Mid/High-flux >=30 ~ < 50	
	IV	>=50 ~ < 70	
	V	Super high-flux >= 70	High

1) Exp. Cond.: Q_B = 200 mL/min, Q_D = 500 mL/min, Q_F = 10 mL/min/m².
2) A_0 = 1.5 m²
3) *If* A_0 is NOT1.5 m², use of the closest model is recommended. Clearance for b_2-MG under A_0 = 1.5 m² may be estimated by using the performance evaluation equations with K_oA as a constant.

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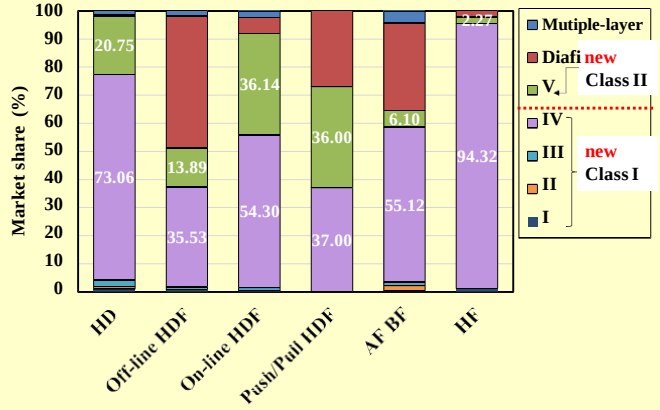

Fig.4 Market share of various kind of dialyzers

JSDT Statistics as of 12/31/10

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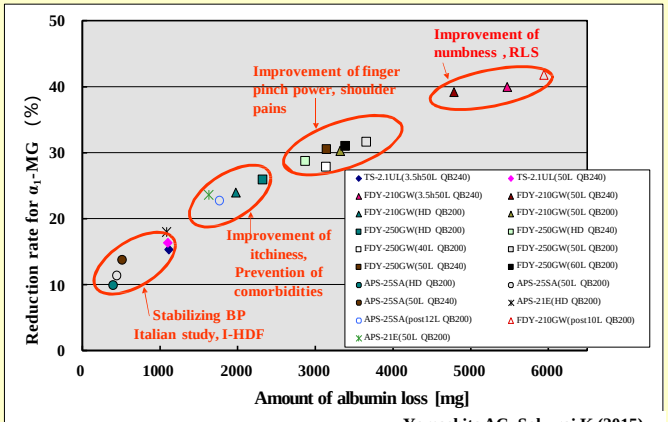

Fig.5 Relationship between the reduction rate for α_1-MG and amount of albumin loss

Yamashita AC, Sakurai K (2015). Updates in Hemodialysis, ISBN: 978-953-51-2162-6, InTech,

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α_1-microglobulin（α_1-MG）

Is α_1-MG a toxic substance to be removed?

A model has been proposed in which A1M is described as a circulating "waste bin" which continuously removes free radicals and oxidizing agents, particularly heme, from the tissues.

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Since α_1-MG is a very strong anti-oxidant, it should be removed from the patients on dialysis to accelerate the turn-over.

Experiment @performed by Prof. Tomo (Oita Univ., Japan)

Exp. 1, 2, 3, 4

2mM $FeSO_4$+2 mM DATAPAC（100μL）+ 20 mM H_2O_2（100μL）

Exp. 5, 6, 7, 8

2mM $FeSO_4$+2 mM DATAPAC（100μL）+ 20 mM H_2O_2（100μL）+ recombinant α_1MG（60μg）（Nipro Co.）

Exp. 9, 10, 11,12

2mM $FeSO_4$+2 mM DATAPAC（100μL）+ 20 mM H_2O_2（100μL）+ recombinant ALB（123 μg）（SIGMA）

The same moles of α1MG and ALB were used. Chemiluminescence was measured by Promega after addition of luminol and T-buooh.

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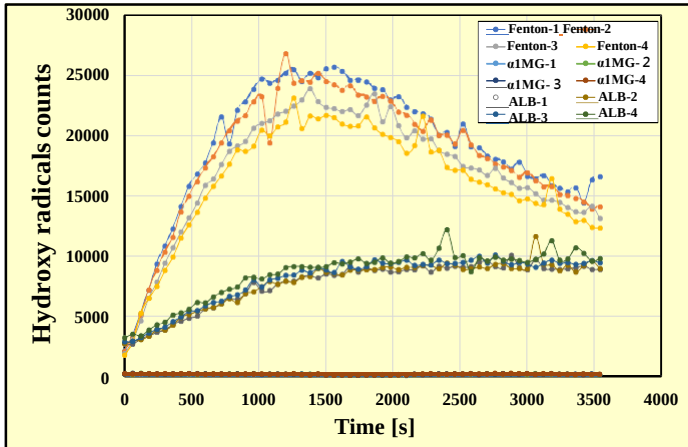

Fig.6 Chemiluminescence curve (Fenton reaction, Fenton reaction+α_1MG, Fenton reaction + ALB, courtesy of Dr. Tomo)

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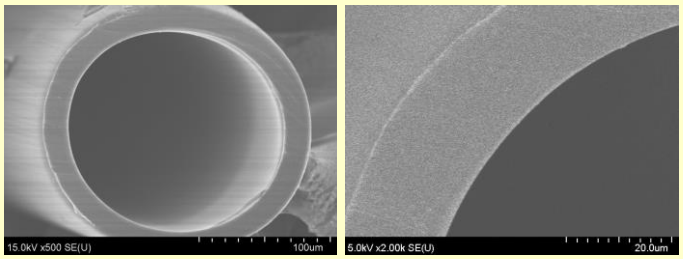

Magnification = 500 Magnification = 2,000

Fig.7 Cross-section of EVAL dialysis membrane (Asahi-Kasei Co., FE-SEM)

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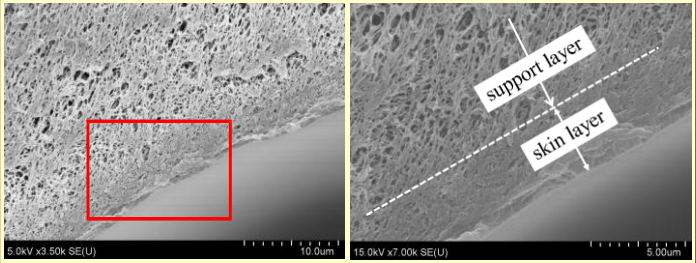

Magnification = 3,500 Magnification = 7,000

Fig.8 Cross-section of the polysulfone dialysis membrane (Asahi-Kasei, Co., FE-SEM)

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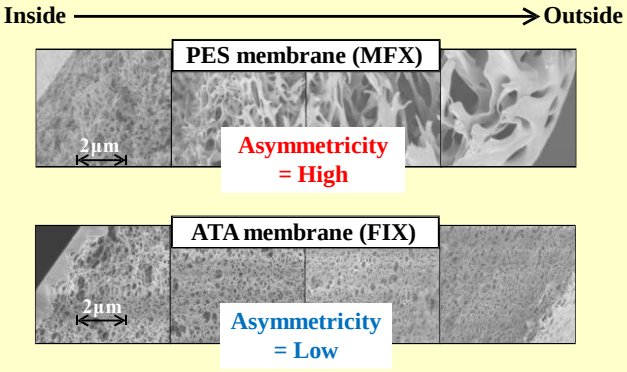

Fig.9 Comparison of asymmetricity of PES and ATAmembrane

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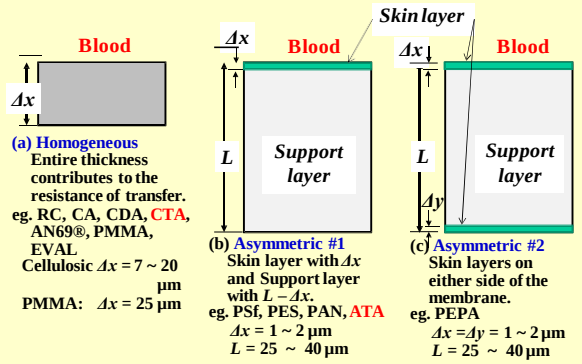

(a) Homogeneous
Entire thickness contributes to the resistance of transfer.
eg. RC, CA, CDA, CTA, AN69®, PMMA, EVAL
Cellulosic Δx = 7 ~ 20 μm
PMMA: Δx = 25 μm

(b) Asymmetric #1
Skin layer with Δx and Support layer with $L - \Delta x$.
eg. PSf, PES, PAN, ATA
Δx = 1 ~ 2 μm
L = 25 ~ 40 μm

(c) Asymmetric #2
Skin layers on either side of the membrane.
eg. PEPA
$\Delta x = \Delta y$ = 1 ~ 2 μm
L = 25 ~ 40 μm

Fig.10 Physical structures of dialysis membrane

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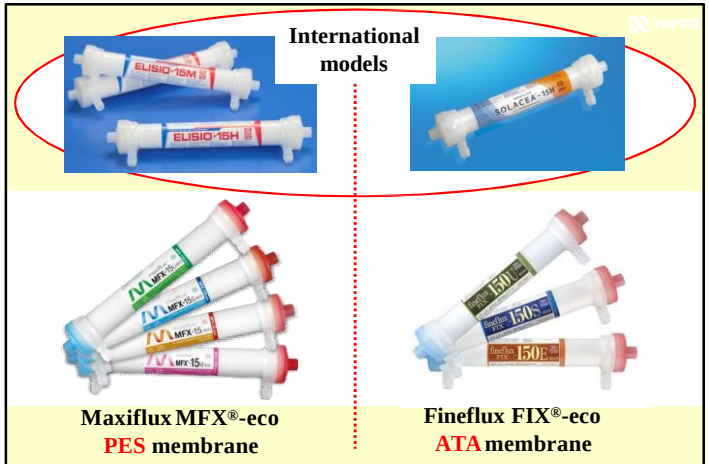

Maxiflux MFX®-eco PES membrane

Fineflux FIX®-eco ATA membrane

Fig.11 Dialyzers/diafilter from Nipro Co., Japan

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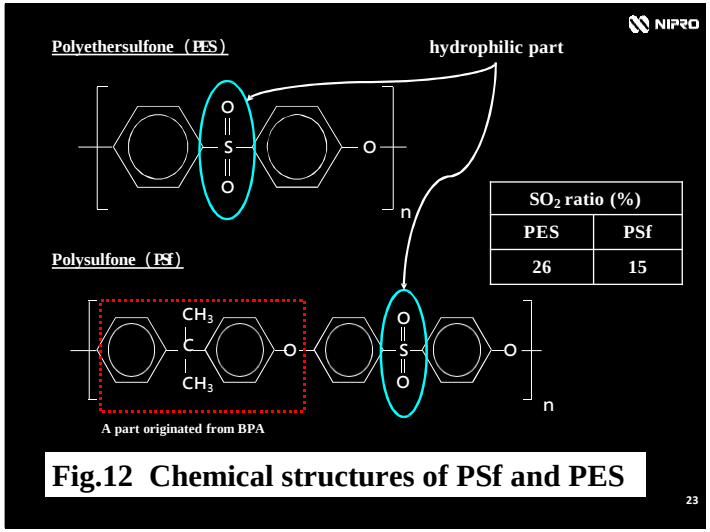

SO_2 ratio (%)	
PES	PSf
26	15

Fig.12 Chemical structures of PSf and PES

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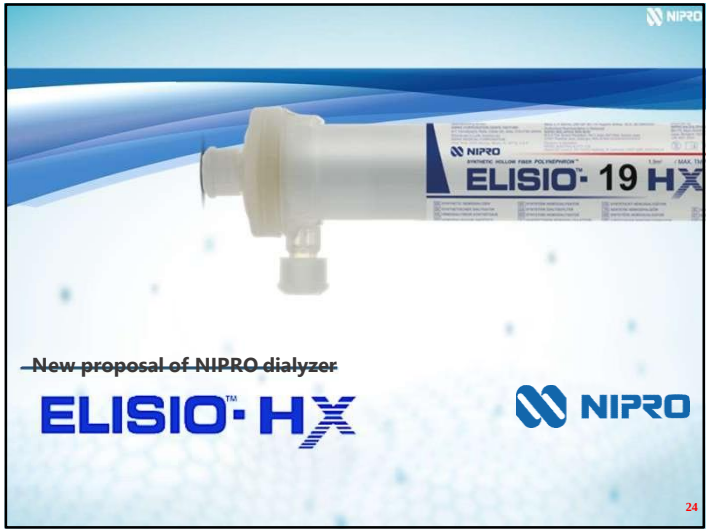

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ELISIO Product Range

Removal Performance

High Flux	ELISIO-H
*Mild-High Flux	ELISIO-K
Middle Flux	ELISIO-M
Low Flux	ELISIO-L

※Mild High-Flux means high flux dialyzer which will show smaller amount of albumin losses compared to ELISIO-H.

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Super High Flux NEW ELISIO-HX

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Why is the survival rate of Japan better ?

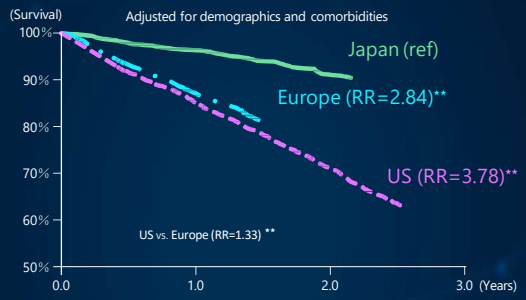

Fig.13 Survival among HD patients in Japan, Europe and the United States

Source: Edited and created by NIPRO based on Robinson, BM and Port, FK. CJASN 4: S12-S17, 2009

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Why the survival rate of Japan is better ?

in Japan's case

- Percentage of AVF shunt is high
- Patients can follow the schedule of dialysis
- Much more treatment time by doctors
- ?

And more factors are correlated with this results・・・

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Difference of dialyzer between EU,US and Japan

Parameter		Low-flux	Mid-flux	High-flux
UF	mL/mmHg/h	<20	20-30	30-50
Urea	Kd(mL/min)	<180	180-200	200-220
	KoA(mL/min)	<500	500-600	600-700
	eKt/V	<1.2	1.2-1.4	1.4-1.6
β2MG	Kd(mL/min)	**<20**	**20-40**	**40-60**
	KoA(mL/min)	<30	30-50	50-100
Albumin leakage	g/session	0	0	<2

Classification in Japan-2013		Ⅰ	Ⅱ	Ⅲ	Ⅳ	Ⅴ
β2MG clearance	mL/min	<10	10-30	30-50	50-70	≧70

※QB=200mL/min, membrane surface area1.5m²

Source: Masanori Abe 「The 63rd Annual Meeting of the Japanese Society for Dialysis Therapy」

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Difference of dialyzer between EU,US and Japan

There are no Super High-Flux (Ⅳ or Ⅴ) class dialyzers in EU, US and countries other than Japan

Super-high-flux	
Ⅳ	Ⅴ
50-70	≧70

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Sales percentage of NIPRO dialyzer

No.1 in Japan market

Ⅴ Class	67%
Ⅳ Class	32%
Ⅲ Class	0%
Ⅱ Class	1%
Ⅰ Class	

Removal Performance

No.2 in International market

Super High Flux	Not launched yet	
High Flux	ELISIO-H	30%
Mild-High Flux	ELISIO-K	2%
Middle Flux	ELISIO-M	7%
Low Flux	ELISIO-L	11%

※Mild High-Flux means high flux dialyzer which will show smaller amount of albumin losses compared to ELISIO-H

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Sales percentage of NIPRO dialyzer

No.1 in Japan market

Ⅴ Class	67%
Ⅳ Class	32%

99%

No.2 in International market

Super High Flux	Not launched yet	
High Flux	ELISIO-H	30%

NIPRO has a long experience with High-Flux and Super High-Flux (ELISIO) in Japan's market as one of the market leader

※Mild High-Flux means high flux dialyzer which will show smaller amount of albumin losses compared to ELISIO-H

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β2MG is reported as one of the risk factors of dialysis amyloidosis and mortality rate also increases in proportion to pre-β2MG concentration.

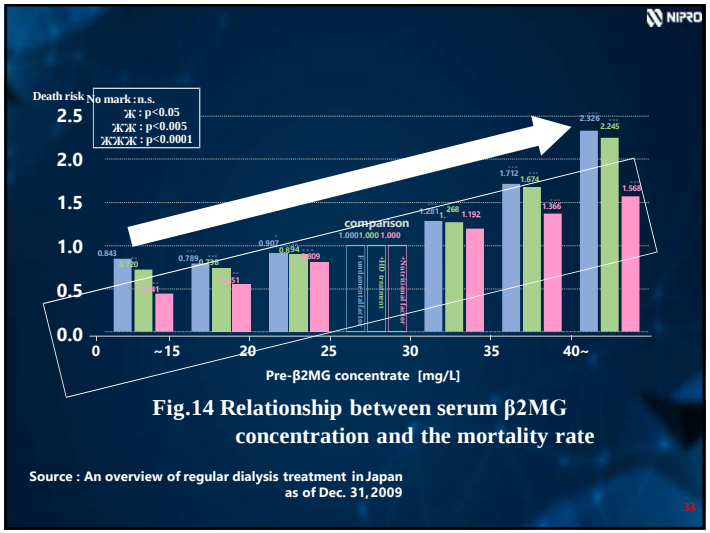

Fig.14 Relationship between serum β2MG concentration and the mortality rate

Source : An overview of regular dialysis treatment in Japan as of Dec. 31, 2009

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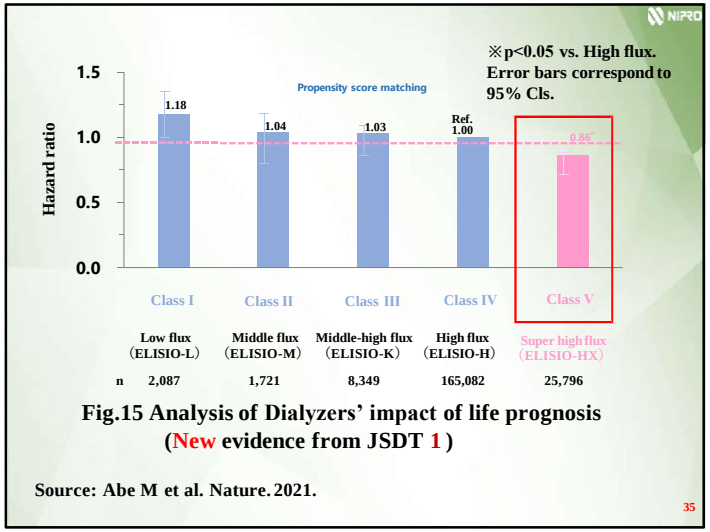

Fig.15 Analysis of Dialyzers' impact of life prognosis (New evidence from JSDT 1)

Source: Abe M et al. Nature. 2021.

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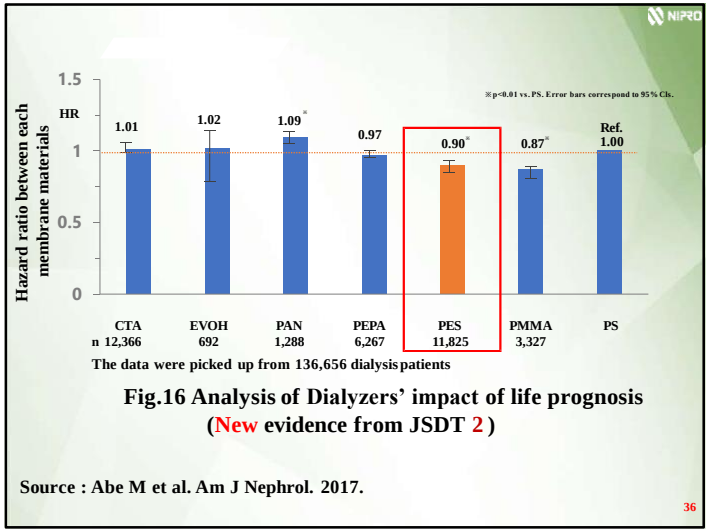

Fig.16 Analysis of Dialyzers' impact of life prognosis (New evidence from JSDT 2)

Source : Abe M et al. Am J Nephrol. 2017.

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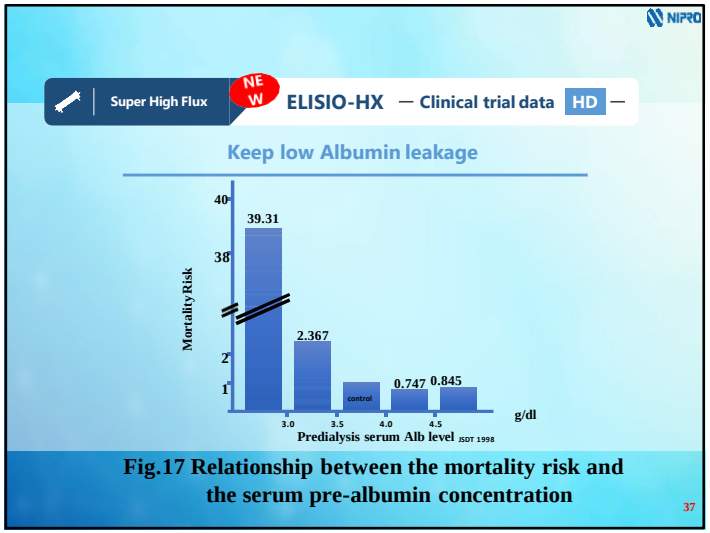

Fig.17 Relationship between the mortality risk and the serum pre-albumin concentration

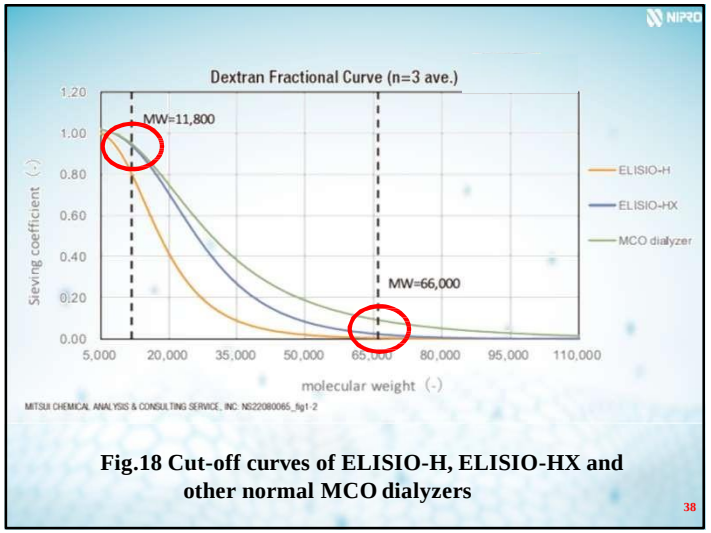

Fig.18 Cut-off curves of ELISIO-H, ELISIO-HX and other normal MCO dialyzers

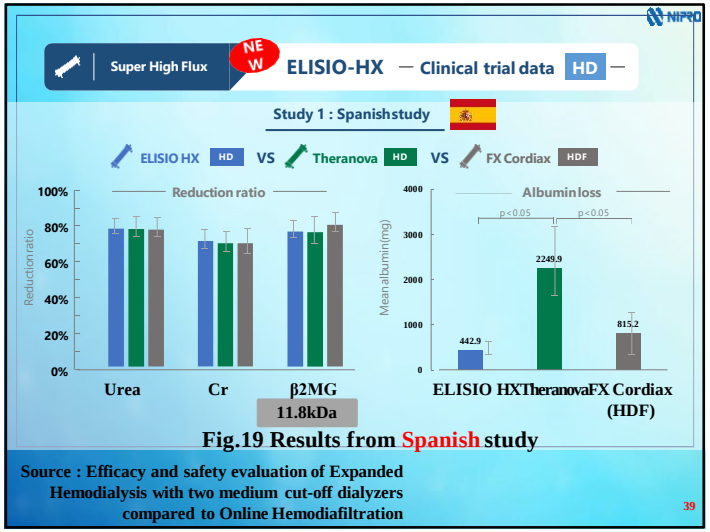

Fig.19 Results from Spanish study

Source : Efficacy and safety evaluation of Expanded Hemodialysis with two medium cut-off dialyzers compared to Online Hemodiafiltration

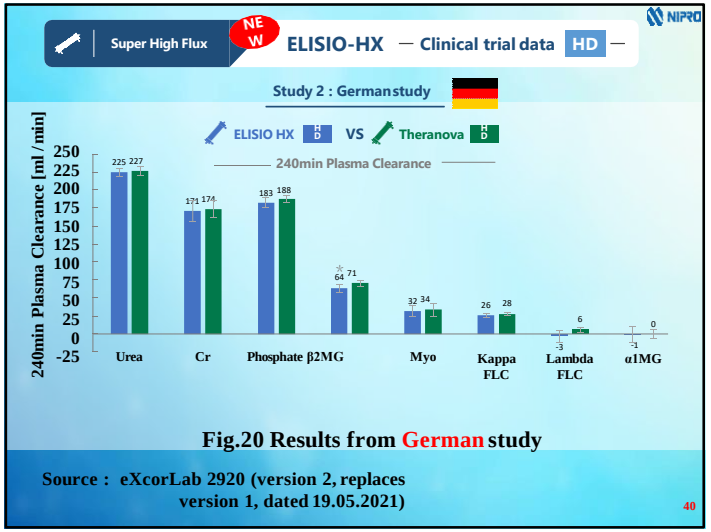

Fig.20 Results from German study

Source : eXcorLab 2920 (version 2, replaces version 1, dated 19.05.2021)

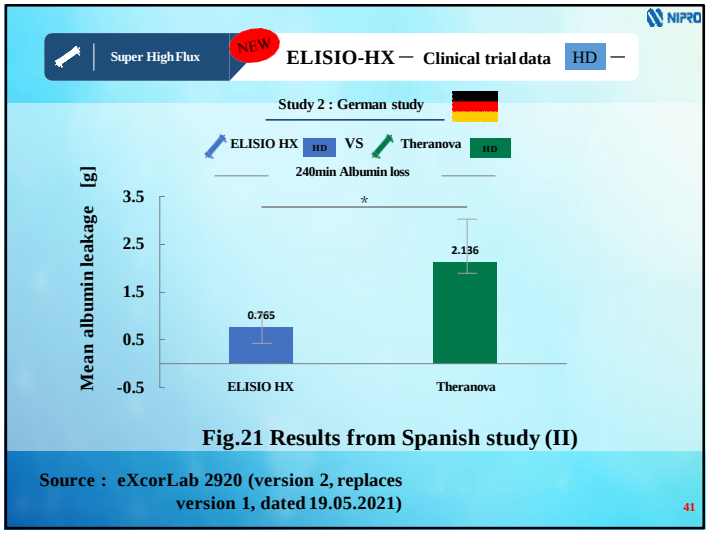

Fig.21 Results from Spanish study (II)

Source : eXcorLab 2920 (version 2, replaces version 1, dated 19.05.2021)

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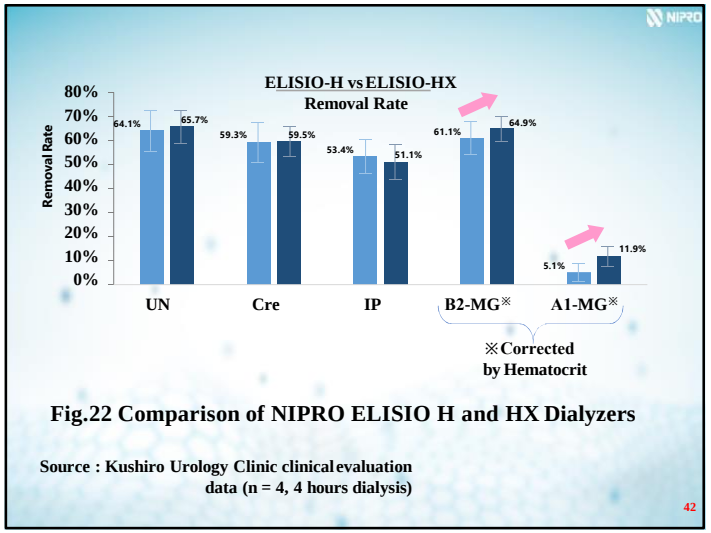

Fig.22 Comparison of NIPRO ELISIO H and HX Dialyzers

Source : Kushiro Urology Clinic clinical evaluation data (n = 4, 4 hours dialysis)

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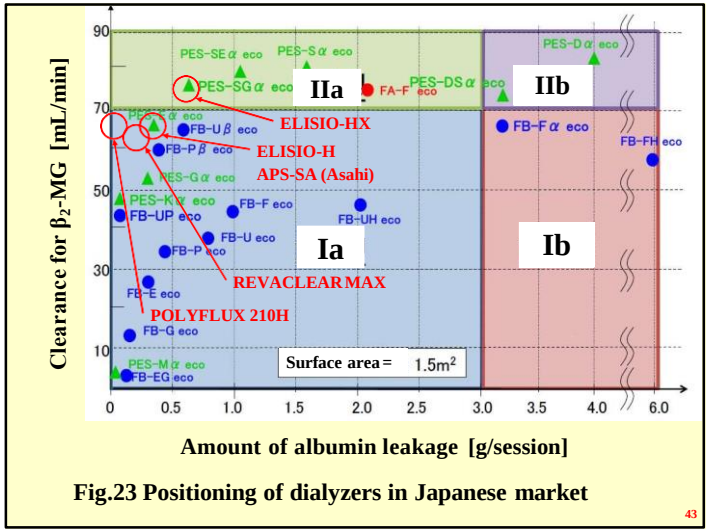

Fig.23 Positioning of dialyzers in Japanese market

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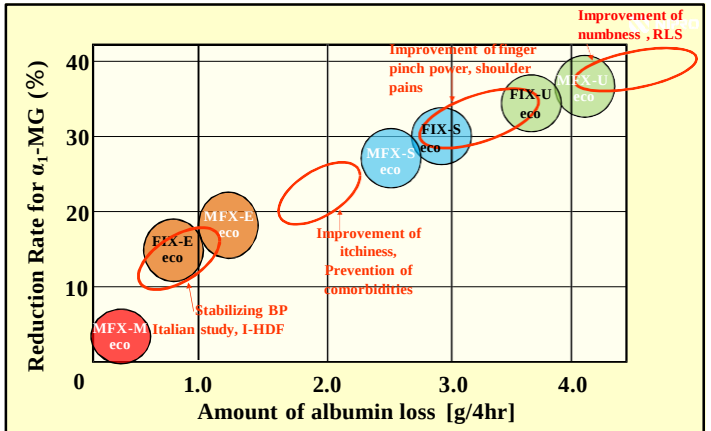

Fig.24 Target removal of pre-dilution on-line HDF with replacement of 36 L (based on *in vitro* experience)

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Conclusions

1. Current trend of Japanese treatment is on-line pre-dilution HDF, expecting even better clinical outcomes.
2. Removing α_1-MG is important not because it is toxic but because it should be renewed.
3. A new high-end ELISIO family member, HX, is available (for HD only) that is expected a little higher removal of medium- and large- middle molecules with a limited albumin leakage.

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CHAPTER 1
DIALYSIS DOSE (SMALL SOLUTES) AND DIALYSIS TIME

Statements

1. Dialysis dose is expressed by the single-pool *Kt/V* for urea (*spKt/V*). (1B)
2. Measurement of the dialysis dose is done at least once a month.
3. Recommended delivered dialysis dose by *spKt/V* is the following:
   i. The minimal adequate dose is 1.2. (1B)
   ii. The target dose is 1.4 or higher. (2B)
4. The recommended minimal dialysis time is 4 h or longer. (1B)

*These recommendations are for patients with maintenance HD three times per week for less than 6 h.

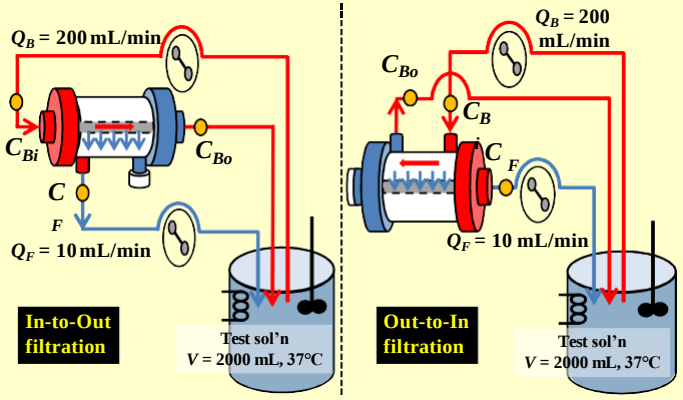

Fig.11 Forward (In-to-Out) and backward (Out-to-In) ultrafiltration experiments

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A semi-quantitative index for asymmetricity of the membrane from ultrafiltration experiments

***Index for Asymmetricity* (*IA*)**

$$IA = \frac{s.c.\ in\ Out-to-In\ filtraation}{s.c.\ in\ In-to-Out\ filtraation}$$

***s.c.*: *Sieving coefficient* [-]**

1) Yamashita AC, Masaki H, Kobayashi E, Sukegawa T: *Hemodial Int* 2015, 19, S20-S25
2) Yamashita AC, Kakee T, Ono T, Motegi J, Yamaguchi S, Sunohara T: *Membranes* 2022, 12, 624

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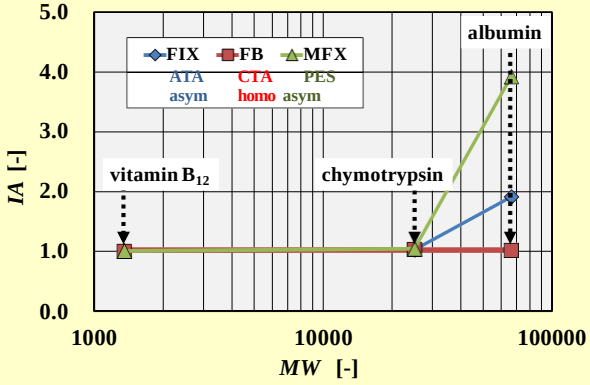

Fig.12 Molecular weight spectrum of *IA*

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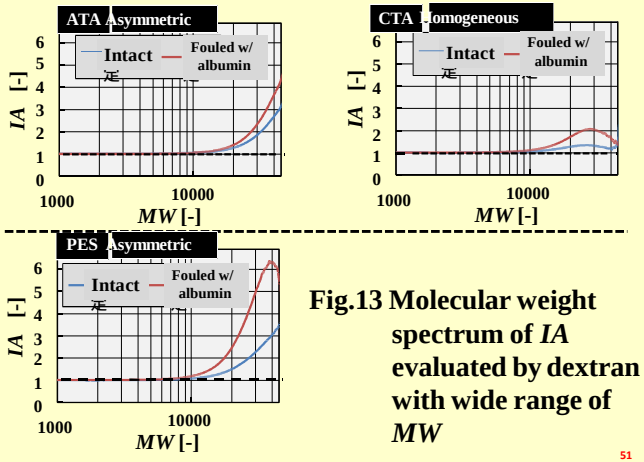

Fig.13 Molecular weight spectrum of *IA* evaluated by dextran with wide range of *MW*

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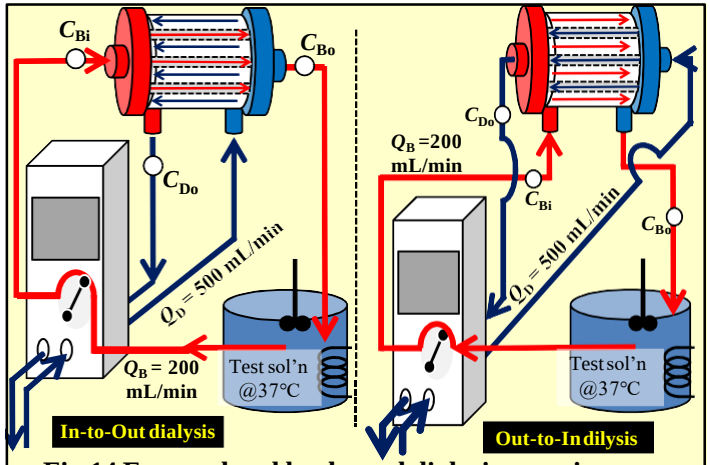

Fig.14 Forward and backward dialysis experiments to investigate the membrane structure

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ATA has anti-fouling feature due to a better smoothness of the inner surface.

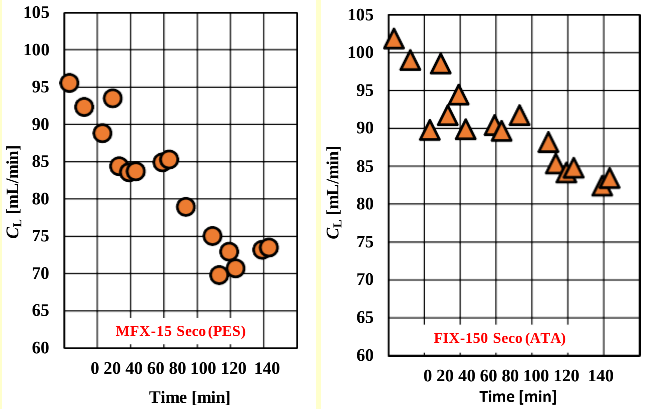

Fig.19 Time dependent profile of C_L for inulin Q_F = 0 mL/min

Wada M, Kiguchi T, Yamashita AC: *J Artif Organs*, 2020.

53

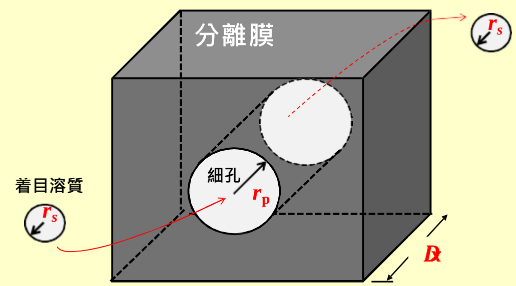

図3．細孔理論（Pore Theory）

細孔半径r_p [m]、分離に寄与する膜厚みDx[m]の分離膜を半径 r_s [m]の溶質が透過する。

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細孔理論で使用される数式

$$k_M = D_w \times f(q) \times S_D \times \left(\frac{A_k}{\tau \times \Delta x}\right)$$ 溶質透過係数

$$L_p = \left(\frac{r_p^2}{8\mu}\right) \times \left(\frac{A_k}{\tau \times \Delta x}\right)$$ 濾過係数

$$q = \frac{r_s}{r_p}$$

$$\sigma = 1 - g(q) \times S_F$$ スタベルマンの反射係数

$$S_D = (1-q)^2$$

$$S_F = 2(1-q)^2 - (1-q)^4$$

$$f(q) = \frac{1 - 2.1050q + 2.0865q^3 - 1.7068q^5 + 0.72603q^6}{1 - 0.75857q^5}$$

$$g(q) = \frac{1 - (2/3)q^2 - 0.20217q^5}{1 - 0.75857q^5}$$

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細孔理論から透水性の向上を考える

$$L_p = \left(\frac{r_p^2}{8\mu}\right) \times \left(\frac{A_k}{\tau \times \Delta x}\right)$$

表2．膜の透水性能を支配する因子

リスク大

#	名 称	記号	単位	透水性の向上のために	影響度	調節可能性
1	表面開孔率	A_k	[-]	大	中	中
2	細孔半径	r_p	[m]	大	大	大
3	（分離に寄与する）膜厚み	Dx	[m]	小	中	中
4	溶媒の粘度	m	[kg/(m s)]	小	中	ー
5	曲路率 (迷宮度）	t	[-]	小	中	ー

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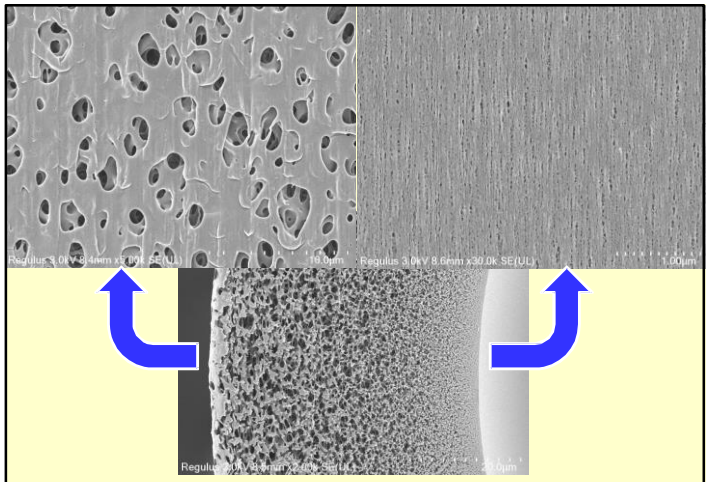

図4. 欧州で生産されたPES膜のFE-SEM像

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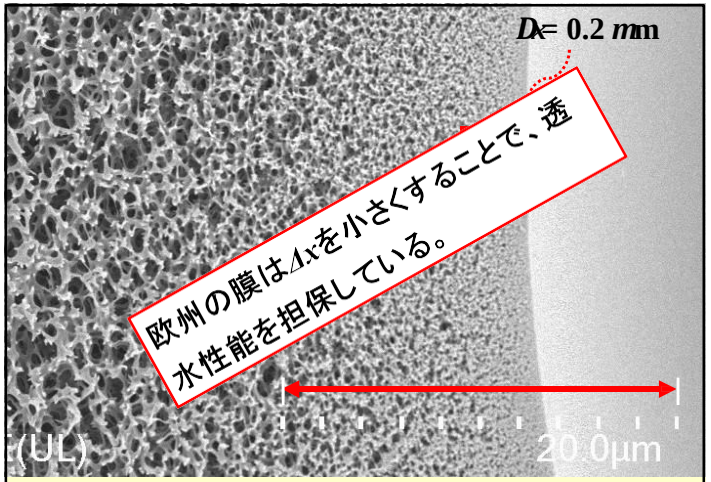

図5. 欧州で生産されたPES膜の断面構造の詳細（II）

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細孔理論から溶質透過係数を考える

$$k_M = D_w \times f(q) \times S \times \left(\frac{A_k}{\tau \times \Delta x}\right)$$

$f(q)$ ≈ 1

$$f(q) = \frac{1 - 2.1050q + 2.0865q^3 - 1.7068q^5 + 0.72603q^6}{1 - 0.75857q^5} \approx 1$$

$S_D = (1 - q^2) \approx 1$

$q = \frac{r_s}{r_p} \approx 0$

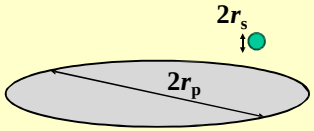

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図6. 細孔半径r_pと溶質半径r_sの関係

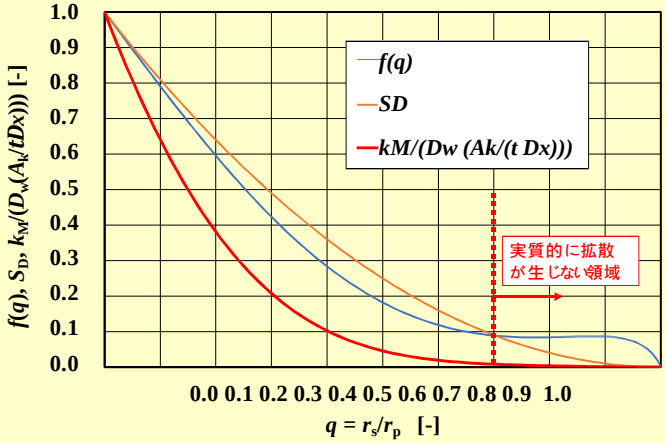

図7. qと溶質透過係数との関係

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細孔理論からStarvermanの反射係数を考える

$$\sigma = 1 - g(q) \times S_F$$

≈ 0

$$g(q) = \frac{1 - \frac{2}{3}q^2 - 0.20217q^5}{1 - 0.75857q^5} \approx 1$$

$$S_F = 2\{1 - q^2\} - 1\{1 - q^4\} \approx 1$$

$$q = \frac{r_s}{r_p} \approx 0$$

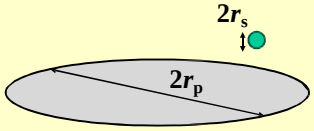

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図6. 細孔半径r_pと溶質半径r_sの関係

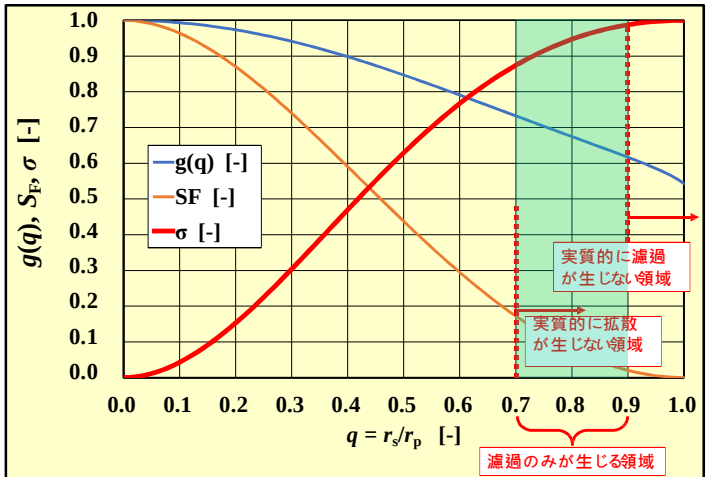

図8. qとStavermanの反射係数との関係

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$$0.7 < \frac{r_s}{r_p} < 0.9$$

アルブミンではr_s = 35.5 Å

1) r_p < 39.4 Å であれば、アルブミンの漏出はない。

2) $r_p > \frac{35.5}{0.9} = 39.4$ Å であれば、アルブミンは濾過で透過する可能性がある。

3) $r_p > \frac{35.5}{0.7} = 50.7$ Å であれば、アルブミンは濾過に加えて、拡散でも透過する可能性がある。

血液浄化膜の製造は、10 Å = 1 nmの精度が要求される、ナノテクノロジーである。

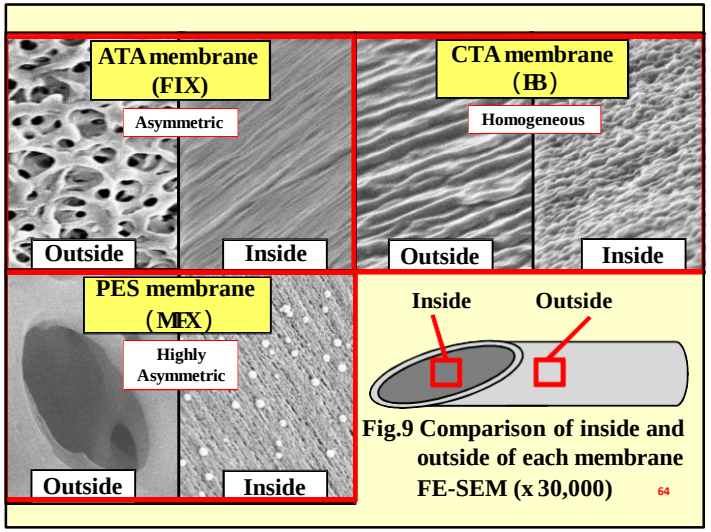

Fig.9 Comparison of inside and outside of each membrane FE-SEM (x 30,000)

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Question) Can we know the degree of asymmetricity of the membrane?

In on-line pre-dilution HDF,
- normally net Q_{Di} is greatly reduced due to substitution,

then the diffusive clearance should be significantly reduced.

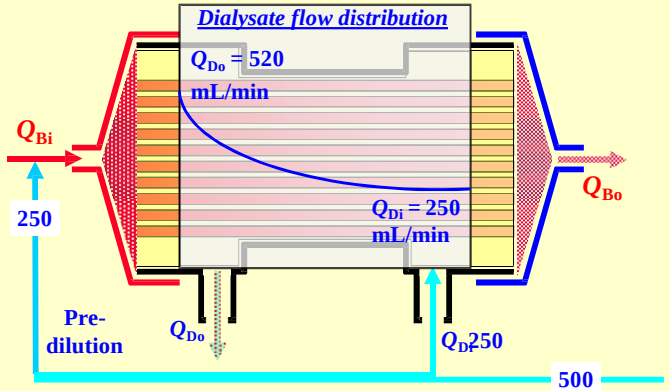

Fig.5 On-line pre-dilution hemodiafiltration (HDF)

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In on-line pre-dilution HDF, relatively smaller amount of ultrafiltration may decrease clearance.

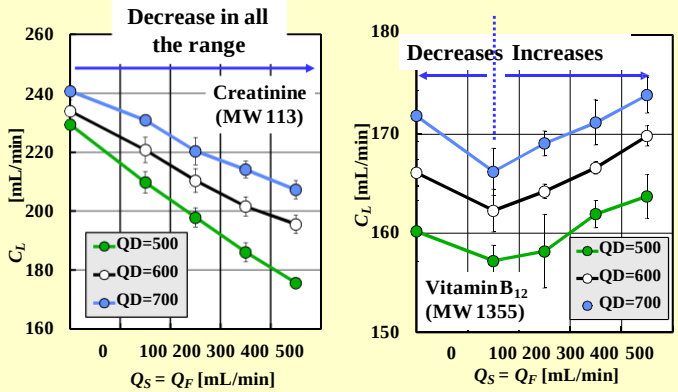

Fig.6 Relationship between clearance and $Q_S = Q_F$ in on-line pre-dilution HDF
Q_B = 250 mL/min, FDY-180GW

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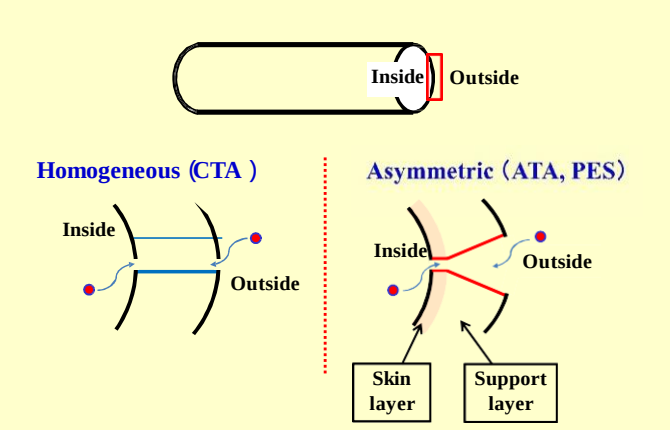

Fig.10 Membrane structure and mass transfer

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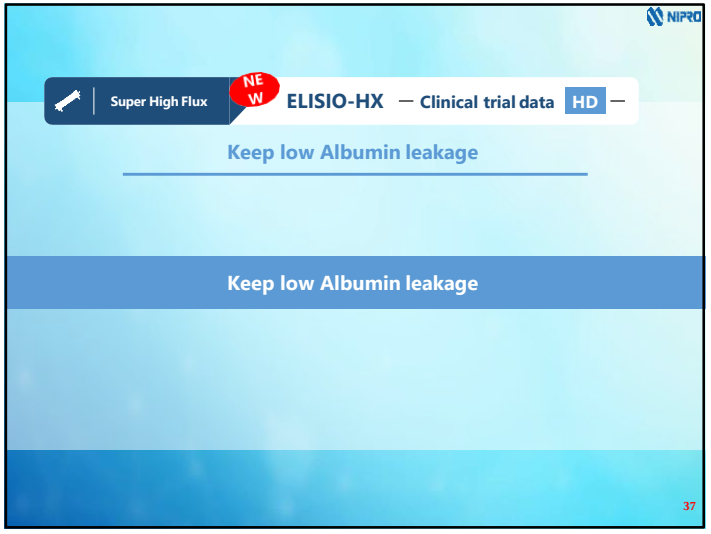

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