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Alternate Dialysis Platforms:

Sorbents

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Sorbents in a Nutshell

- Potential benefits of sorbents — Why?
- Mechanisms for improved solute transport — How?
- Examples of currently available sorbents and sorbents in development — What?

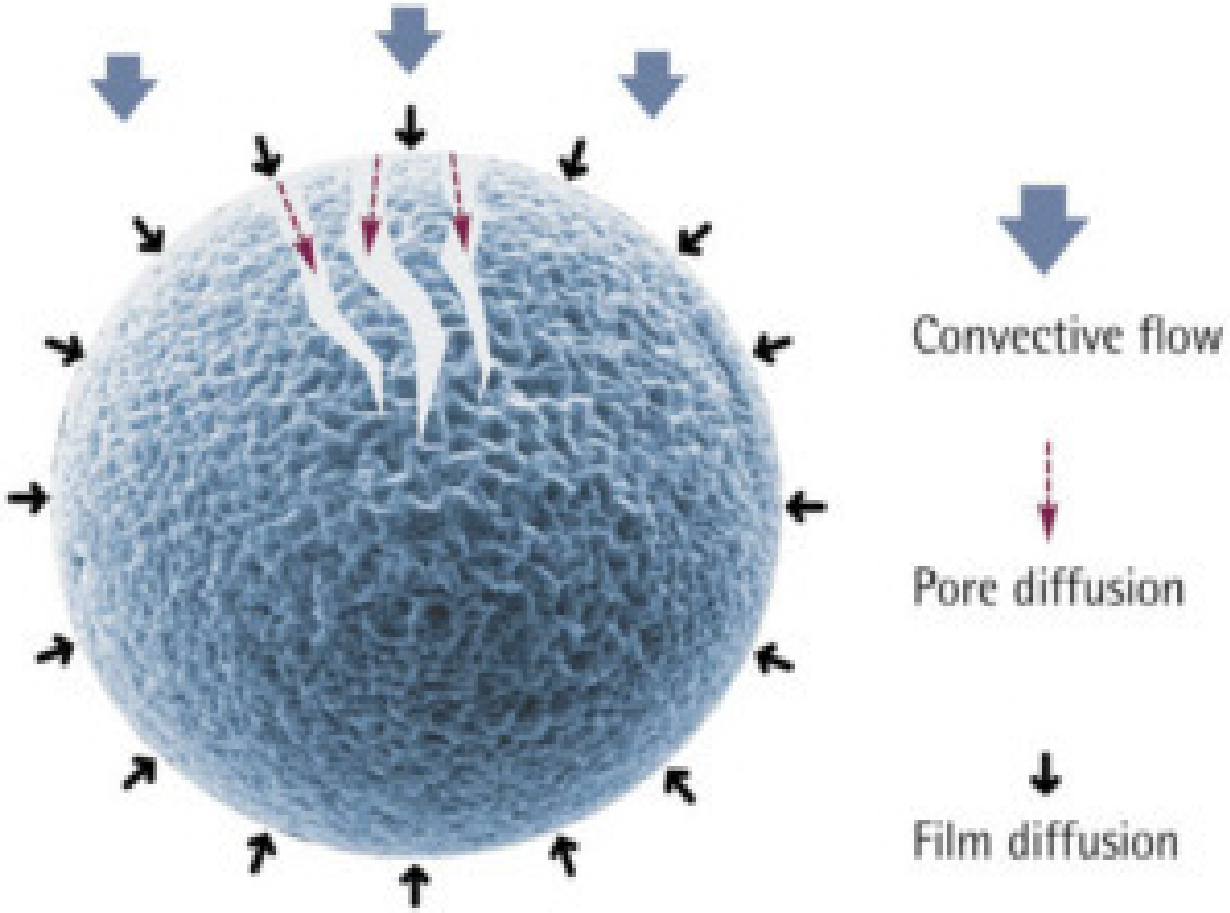
Why sorbents?

- Ability to be used orally
  - for CKD patients not yet on dialyis
- Ability to purify dialysate (reduce water required)
  - e.g. original REDY system and its descendants today
- Ability to target and remove specific toxins or classes of toxins
  - e.g. β2 microglobulin, cytokines (sepsis), viruses
- Ability to overcome transport limitations for hard-to-remove toxins
  - e.g. protein-bound substances

How do sorbents work?

- Adsorption—Adhesion of a Molecule to a Surface
  - Binding occurs as a result of random collisions
  - Generally a reversible, equilibrium process
  - Higher concentration in solution => more solute bound
- High Internal and External Surface Area
  - Typically porous beads offer extremely large internal surface area (e.g. 300-800 m^2/g) for binding.
  - Smaller particles offer better transport due to higher external surface area, but higher pressure drop.
- Mechanism of Binding
  - Van der Waals forces, including hydrogen bonds
  - Electrostatic forces
  - Covalent (not typically used)

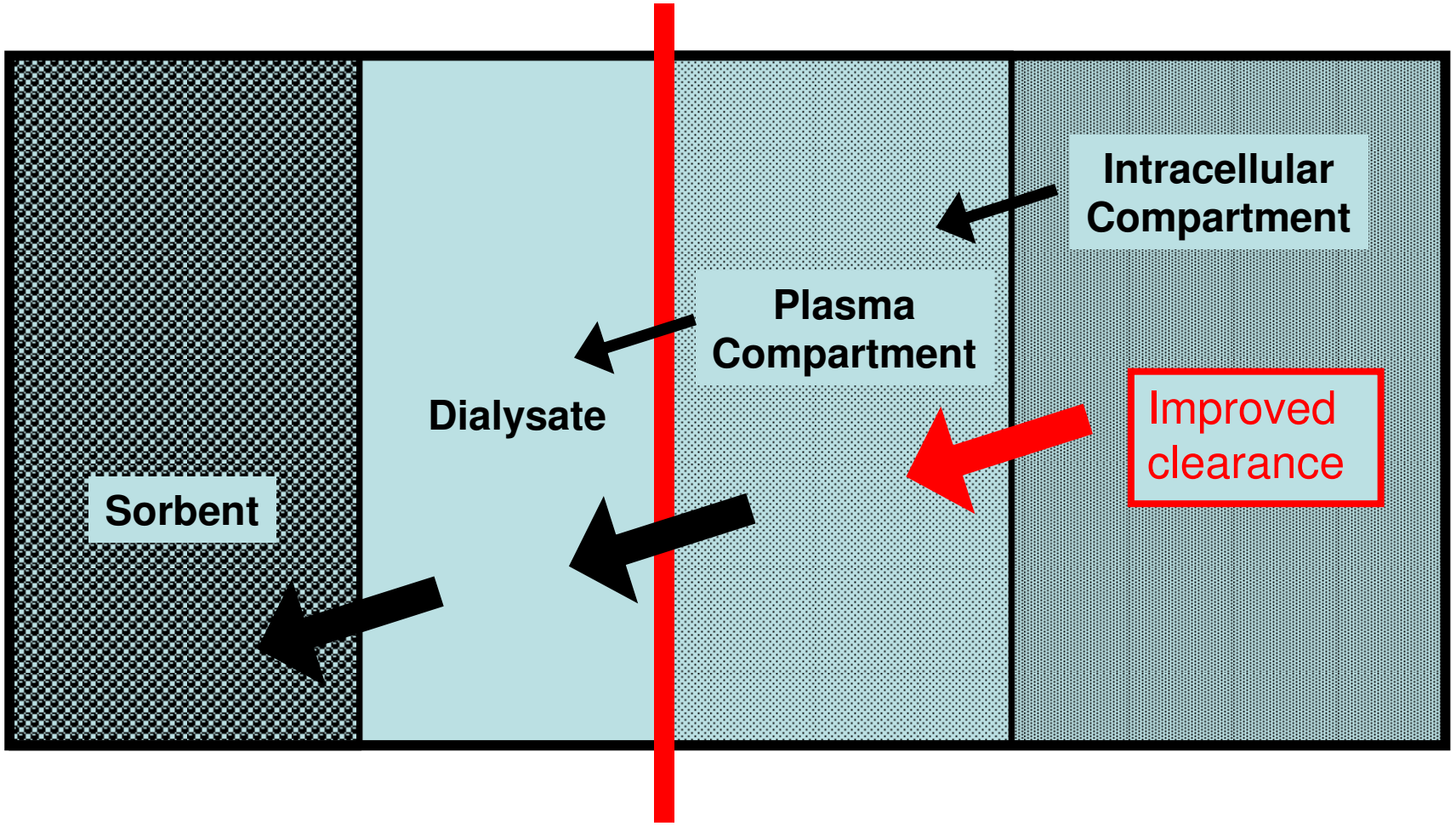
The Evolution of a Sorbent Particle



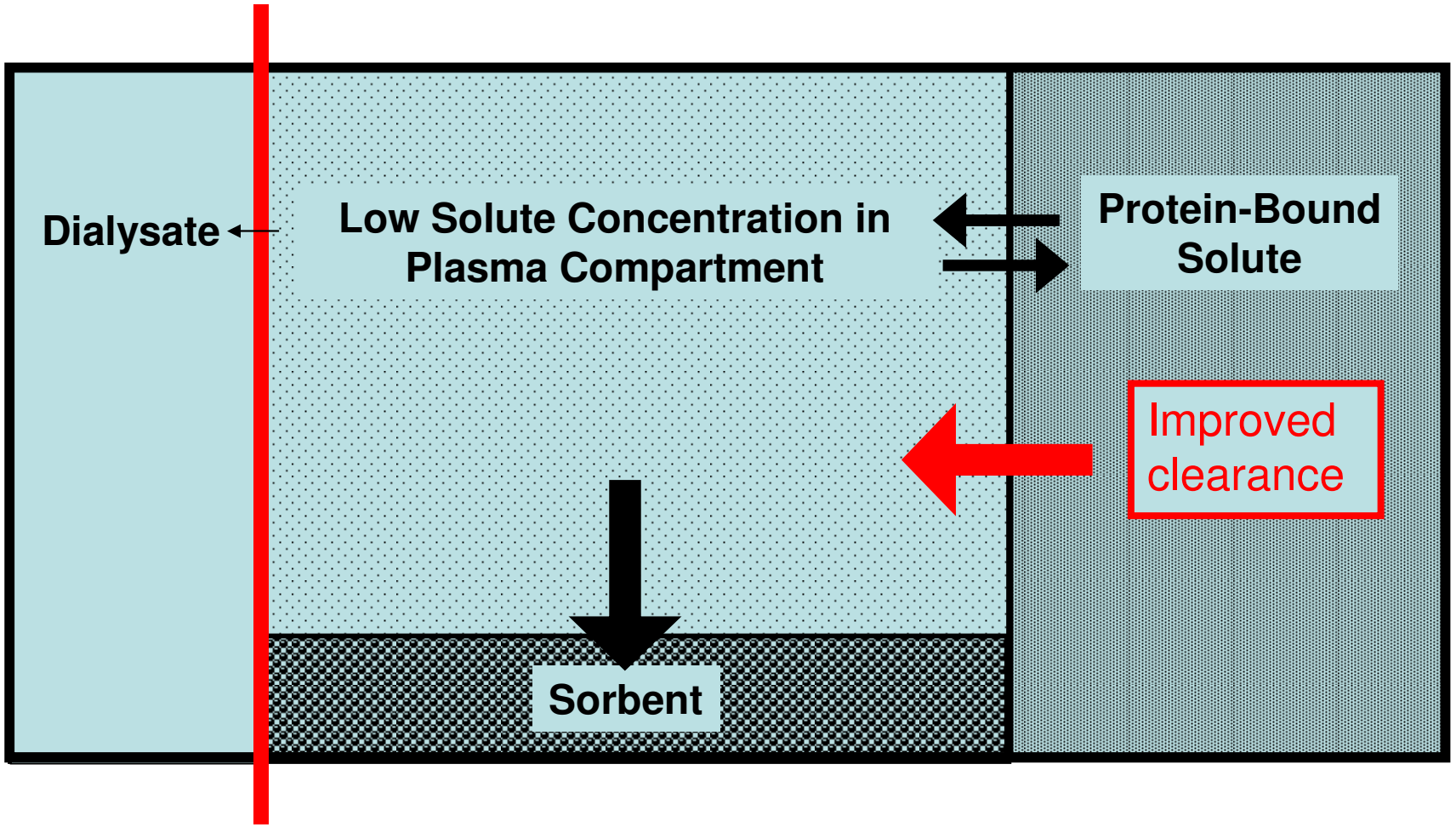
Benefits of Sorbents

- Enhancing removal of one solute while avoiding loss of other solutes
  - A high specificity sorbent preferentially binds one solute.
  - Such sorbents allow removal one solute independent of other similarly-sized molecules, enabling increased removal of large MW toxins.
- Removing unknown solutes
  - A low specificity sorbent (such as activated charcoal) can remove many different solutes.
  - Used in treatment of liver failure and accidental poisoning
  - Also used in sorbent dialysis cartridges that purify tap water
- Removing hard-to-dialyze toxins
  - Solute adsorption drives diffusion into blood compartment, and drives release of protein-bound toxins.
  - A high affinity sorbent is one in which adsorption is thermodynamically favorable compared to desorption, so that bound molecules tend to stick.
  - Such sorbents improve removal from low concentration solutions.

Mechanism for Improved Clearance from Intracellular Compartment



Mechanism for Improved Clearance of Protein-Bound Toxins



Examples of Sorbents in CKD

- Currently available sorbents by mode of use
  - Oral
  - For dialysate regeneration
  - Adsorption from plasma
  - Adsorption from blood
- Sorbents in development
  - For dialysate regeneration
  - Targeting middle molecular size
  - Targeting large molecular size

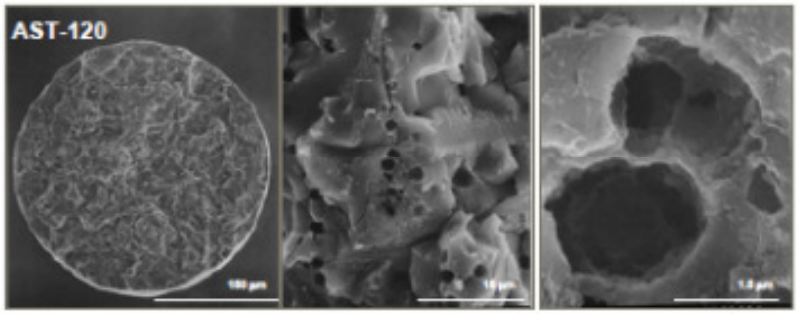
Thanks to Amanda Stennett for assembling the following examples.

Oral sorbent use

- Example: AST-120 (Kureha Corp.)

  Carbon microspheres remove low molecular weight toxins (ammonia, indoles, etc.) but not proteins in the large intestine

- Application: Chronic Kidney Disease Stage 4



Pros:

Engineered to have size specificity not seen in most activated charcoal

Cons:

Can only remove what is available in the intestines

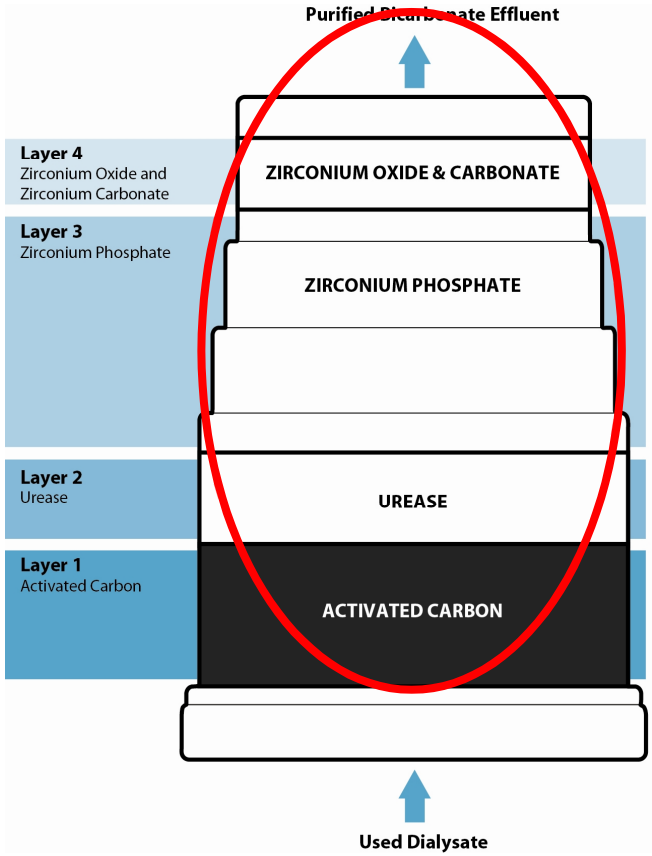
Image: Ocera Therapeutics

For dialysate regeneration

- Example: SORB cartridge (SORB Technology)

  Removes toxins in dialysate (urea, phosphate, etc.) and replaces dialysate components (bicarbonate)

- Application: Stage 5 Chronic Kidney Disease



Pros:

Eliminates need for water purification system

Cons:

Column can saturate and require unplanned end of treatment

Adsorption from plasma

- Example: TheraSorb Ig (Miltenyi Biotec)
  - Selectively removes immunoglobulins using polyclonal sheep anti-human Ig on sepharose support
- Application: Treat humoral rejection of transplant

Ig adsorber

Pros:
Column can be regenerated for multiple treatments

Cons:
Requires plasma separation

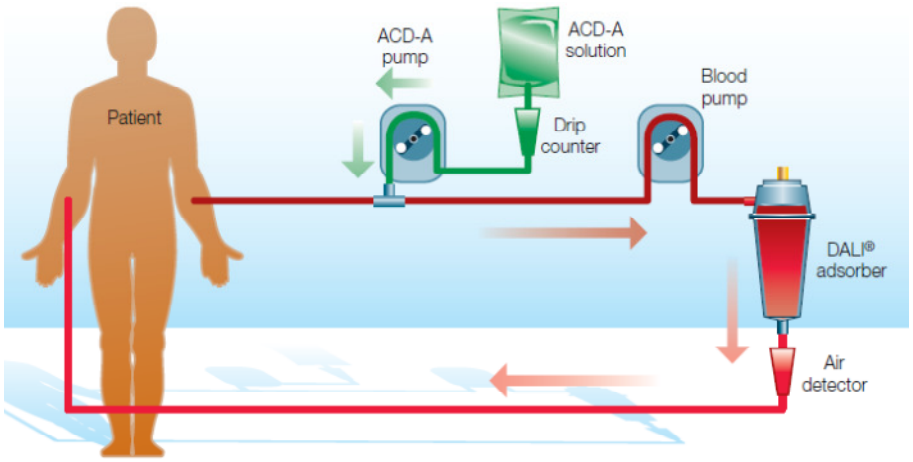
Image: Miltenyi Biotec

Adsorption from blood

- Example: DALI (Fresenius Medical Care)

  Polyacrylate coated polyacrylamide beads remove LDL-cholesterol, lipoprotein A, triglycerides, and some HDL-cholesterol

- Application: Familial hypercholesterolemia



Pros:

Does not require plasma separation
Retains more "good" cholesterol than plasma exchange

Cons:

Possible hypocalcemia due to citrate anticoagulant use

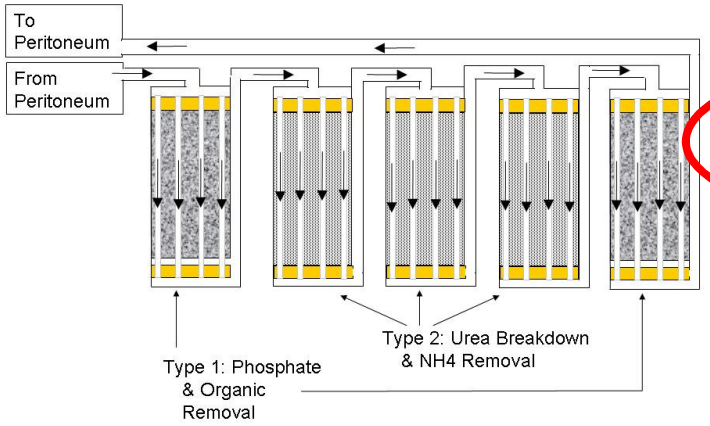
Image: Fresenius Medical Care SE

Sorbents in development
For dialysate regeneration

- Example: WAK (Fresenius Medical Care)

  Combination membrane and sorbents for portable and wearable dialysis

- Application: Stage 5 Chronic Kidney Disease



Recent Innovation

Pros:

Ion-rejecting membrane increases the sorbent capacity by excluding ions competing for ammonia binding sites

Increases patient autonomy

Cons:

Requires patients comfortable with self-care

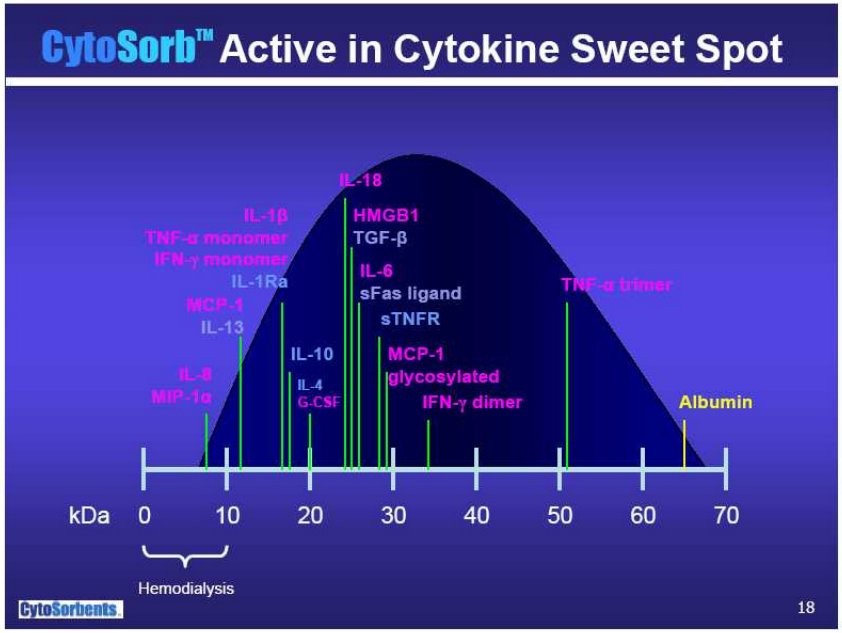
Sorbents in development

Targeting middle molecular size – cytokines

- Example: CytoSorb (CytoSorbents)

  Removes cytokines directly from blood using polymeric beads with size-specific pores

- Application: Adjunctive therapy for sepsis



Pros:

Binds species that are normally retained by dialysis membrane

Cons:

No chemical specificity

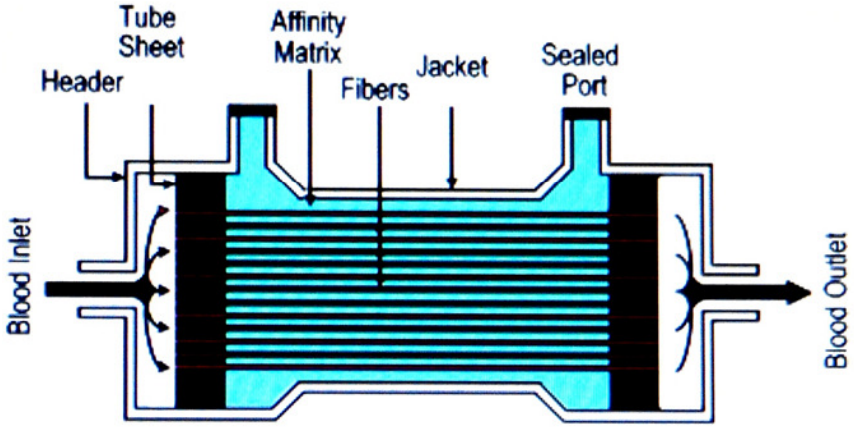
Image: CytoSorbents Investor presentation

Sorbents in development
Targeting large molecular size – Virus

- Example: Hemopurifier (Aethlon Medical)

  Removes pathogens with high mannose content using lectin

- Application: Hepatitis C, HIV



Innovative use of Starling's flow

Pros:

Can remove mutated viruses that are drug/vaccine resistant

Cons:

Can require use in combination with pharmacological agents

Image: Aethlon Medical

Summary

- Use of sorbents in CKD is growing.
- Currently-available sorbents enable removal of a wide spectrum of solutes.
- Sorbents in development provide hope for improving the adequacy of dialysis in the broadest sense of the term.