Does Nanotechnology Apply to Dialysis?

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Introduction

More than 800,000 patients suffering from end-stage renal disease (ESRD) are today treated with renal replacement therapy (RRT), including renal transplantation [1]. The dialytic forms of RRT include hemodialysis and peritoneal dialysis, with the former being used in a large majority of patients in most countries [2].

Extracorporeal hemodialysis has undergone a series of developments in the last three decades mostly related to improvements in biomaterials and enhancement of the design of the critical disposable devices and machines. In particular, while the initial hemodialysis systems were developed piecemeal by dedicated artisans, who were also engineers and physicians, the most recent devices and machines are highly sophisticated and rely on large production series and standardized manufacturing procedures [3, 4]. This evolution has taken place in conjunction with a significant reduction of hemodialyzer dimensions. An important part of this process has been the significantly better understanding of the physiological effects and consequences of dialysis at a micro-scale level, leading to adequate blood circuit design, smooth and biocompatible blood pathways, standardized thickness and porosity of membranes, and accurate alarm systems and failure controls [5–7].

As a result of this enhanced understanding and technical sophistication, we operate today with hemodialyzers with minimal blood priming required, constant and reproducible performance, and minimal dialytic losses of protein compounds, even in the presence of significantly high sieving coefficients for large molecules [8, 9]. One

may argue that as we continue to increase dialyzer efficiency, we are getting close to the limits imposed by available or potential membranes and by the commonly utilized mass separation processes. For these reasons, a new interest is growing in hyper-selective barrier separation processes made possible by specifically designed synthetic membranes. Similarly, selective solid separation processes based on the use of newly designed adsorbent materials are under evaluation for newer and more efficient blood purification techniques.

The evolution of biomaterials and dialytic techniques has paralleled the evolution of other technologies, including computers and biotechnology [10]. Computers have evolved beyond any expectation, increasing speed, memory, and analytical capabilities, while decreasing in physical size. From the large main frames whose operational time had to be shared among scientists of different institutions, hardware has evolved to highly efficient personal computers, handheld devices, and potent microchips with enormous capacity for data storage and management. Computers have also become key tools in accelerating processes that are occurring in the field of biotechnology, while different biological processes are providing new models for the development of new hardware and software (i.e. DNA-based computers). This process of interaction between biology and electronics/mechanics has been defined 'bionic convergence' and may result in a tremendous impact on medicine. In February 1997, researchers created Dolly, a lamb cloned from the DNA of an adult sheep. What was considered impossible in the past, proved feasible, and demonstrated the growing power of new biotechnologies. Further examples could be repre-

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sented by new DNA-based vaccines, new generations of drugs or newly conceived bioartificial organs. This evolutionary process benefits from a series of recent discoveries and scientific advancements deriving from the merging of new technologies and materials. In this context one of the exciting and emerging fields, with applications in engineering, physics, and biomedicine, is nanotechnology [11–13].

Nanotechnology

Nanotechnology has recently become a buzzword in the popular press: it has been used indiscriminately to describe everything from micro-machines and tiny chemical blobs to the latest shrinking circuits on computer chips. However, according to Eric Drexler, the word ‘nanotechnology’ should only be used to describe atomically precise functional machine systems developed on the scale of the nanometer (one billionth of a meter: 1 nm = 1/1,000,000,000 m) [11]. A vanguard of medical explorers is exploiting the tools of nanotechnology to manipulate molecules either in biological or mechanical systems that may contribute to cell life and death or illness and health. This approach plays on the size scale of biology itself. Theoretically it should be possible to design tiny tools to safely and effectively repair tissues or biomaterials, just as a mechanic works on a car’s engine using tools that are on the same scale as the engine. This might sound like science fiction, but it is reaching the verge of possibility because of the above-mentioned ‘bionic convergence’. The human genome project, diagnostic ‘labs on a chip’, hundreds of molecules sorted and characterized by special procedures, represent just a few examples of this evolving field.

To simplify, nanotechnology is the science of manipulating and building materials on the nanometer scale. Nanomedicine may be defined as the monitoring, repair, construction and control of human biological systems at the molecular level using engineered nano-devices and nano-structures (see appendix for nano-terminology and glossary). Assuming these actions will become feasible, the number of possible applications for medical purposes will be countless [13] (table 1).

The full promise of nanomedicine, however, is unlikely to arrive until after the development of precisely controlled or programmable medical nanomachines and nanorobots. Scaling down mechanical devices was first proposed by Galileo [14]. The possibility of further scaling down to microscopic machines was suggested by the

Table 1. Potential application and pathways for nanomedicine (conditio sine qua non: breakthrough to a ‘universal assembler’)

Early detection of illness accomplished through regular, inexpensive biomonitoring
Accurate diagnosis of genetically defined subtypes of diseases
Biochemically tailored nutraceuticals, antibiotics, immunotherapy
Artificial blood products, skin cartilage and other tissues including possibility for hybrid bioartificial organs
Gene therapy with cellular repair and protein manipulation
Cell-repair machines, healing machines, tissue reconstructors and artificial immuno systems are definitely subject to the assembler-based nanotechnology

Nobel-winning physicist Richard Feynman in 1959 [15] and later was described at length by Eric Drexler in his popular books ‘Engines of Creation’ (1986) [16], ‘Unbounding the Future’ (1991) [17] and finally in his more recent technical book ‘Nanosystems: Molecular Machinery, Manufacturing, and Computation’ (1992) [18]. When such nanomachines are available, the ultimate dream of every healer, medicine man and physician throughout recorded history, to prevent and/or cure disease at the organ/cellular/molecular level, will, at last, become a reality. Programmed nanomachines will be able to execute curative and reconstructive procedures in the human body at the cellular and molecular levels. The dream of scientists already working in this field is even to generate the ‘ultimate nanomachine’ or the micro-machine with capability of self-replication and generation of new machines: this is what the experts call a ‘universal assembler’ and what some believe could someday bring science closer to the very origin of life [19].

Potential of Nanomedicine in Renal Diseases

What is the practical potential for applying nanotechnology to the field of renal disease? How might nanotechnology be used to prevent renal damage, to monitor renal dysfunction, and finally to replace renal function in ESRD patients?

Nanotechnology might contribute to early diagnosis of renal dysfunction with a series of implantable micro-sensors that could detect early biochemical abnormalities or incipient flogistic processes [20–22]. Once ESRD has been reached, these sensors might help to ‘drive’ conservative or substitutive therapies such as hemodialysis. If the possibility to manipulate and repair biological systems and tissues at molecular levels is successfully exploited by

Fig. 1. Cross-sectional microscopic view of a polysulfone membrane (Fresenius Medical Care, Bad Homburg, Germany). The membrane appears constituted of a very thin internal skin layer and an external surrounding membrane. The permeability characteristics are mainly due to the internal skin layer.

nanotechnology, not only repair of the glomerular basement membrane might be possible, but even early removal of immune complexes or dense deposits from the sub-endothelial or sub-epithelial spaces of the glomerular loops may be possible to prevent subsequent pathological lesions from forming. Finally, selective immunotolerance for implanted renal grafts might be created by using circulating nanomachines designed to modulate the immunological response in transplanted patients.

Does Nanotechnology Apply to Dialysis?

Since nanomachines cannot yet be built, it is necessary to credibly establish that such devices are feasible and that molecular manufacturing and manipulation are consistent with known laws of physics and obey sound engineering principles. There are indeed several precursor technologies such as telemicrosurgery, tissue engineering and DNA clonation. The first step in this field was made when a team of scientists at the Almodom Laboratories of IBM (Zurich, Switzerland) used a tunneling scanning microscope to move xenon atoms into patterns on a crystal surface. They were able to arrange individual atoms to build an image of the IBM corporate logo. This was the first public demonstration of precisely manipulated matter at the atomic level.

At this stage of development, if nanotechnology is defined more broadly to include not only assembler-based machine systems, but also any construction of molecular structures sufficiently complex to function as machines or

devices, then prototypes of some initial applications already exist [11–13]. Biosensors based on precisely designed synthetic membranes with ion channels of 1.5 nanometer of diameter or micro-devices for personal status monitoring are in fact under evaluation by the Defense Advanced Research Projects Agency [12]. But how far or close are these applications to dialysis? In the year 2000, a retreat took place with experts in nanotechnology meeting with a group of scientists and physicians involved in dialysis to brainstorm about the potential applications of nanotechnology to dialysis. An interesting discussion originated from the analysis of the unmet clinical needs of today's RRT. New possibilities were identified for application of nanoscience to current devices; precise manipulation of biomaterials and surfaces to make them perfectly hemocompatible; miniaturization of various components and devices to create portable or wearable artificial kidney systems; micro-sensors for continuous monitoring and biofeedback. But while future theoretical applications are being discussed, some initial practical examples of nanotechnology are appearing on the stage. Fresenius Medical Care has recently launched its latest membrane named Helixone® [23]. This is a polysulfone-based high-flux dialysis membrane in which the porosity of the inner layer is finely controlled at the level of nano scale. Polysulfone membranes may have different solute and water permeability depending on their thickness, porosity and structure. In particular, the structure is characterized by an internal thin skin layer (1 μm) surrounded by a sponge-like layer generally asymmetric with a higher density of the polymer in the more internal region (fig. 1). The effec-

Fig. 2. Schematic representation of three different membranes in terms of number of pores, pore size distribution and solute sieving coefficients. Membrane A presents a small average pore size and therefore the sieving capacity is limited for solutes of medium-high molecular weight range. Small solutes are still effectively cleared since the number of pores is sufficiently high. This represents a typical low-flux hemodialysis membrane such as cellulose-based Cuprophane®. Membrane B presents a greater average pore size, although it maintains an adequate number of pores. This describes a typical well-designed high-flux synthetic membrane usable either in hemofiltration, high-flux dialysis or hemodiafiltration. Finally, membrane C represents a typical albumin leaking membrane with a wide distribution of pore sizes but a limited number of pores. This is a good approximation of what is occurring across the human peritoneal mesothelium.

Fig. 3. The structure of the skin layer characterizes the performance of the membrane. Old-fashioned synthetic membranes typically presented variable performances and characteristics. In detail dead end pores or stenotic pores could be present reducing the average area of pores and the performance of the membrane. Recent polysulfone membranes such as the PS600 polysulfone (Fresenius Medical Care, Bad Homburg, Germany) present improved performances and consistent results due to a more homogeneous pore design and an increased average pore size. These membranes however still present a mixture of pore sizes that leads to possible unwanted albumin losses and solute transport limitations. The Helixone® membrane (Fresenius Medical Care), presents a configuration close to the ideal design due to the nanocontrol spinning (NCS) procedure. In particular, pores are smooth and homogeneous in size; the size is concentrated around the desired value with virtually no leak of albumin.

Fig. 4. Schematic representation of the improvements obtained on the Helixone® membrane in terms of number of pores (δ to δ_1), pore size distribution ($\alpha\beta$ to $\alpha_1\beta$) and average pore size (ϵ to ϵ_1). Membrane thickness is adjusted at nanoscale level (1 nm = 0.000000001 m). Increased number of larger pores (β_2 M S = 0.8) results in higher middle molecule removal. Nano controlled maximal size of pores results in limited losses of macromolecules (albumin).

2

3

4

Fig. 5. Effects of nanocontrol spinning on the sieving coefficients of Helixone® compared to the previous polysulfone membrane. While large solutes sieving is improved, the sieving for albumin is maintained or even reduced.

tive permeability of this membrane is given by the internal skin layer and its porosity. The porosity of a membrane (expressed by the number of pores per unit of surface area and the curve of pore size distribution) must be optimized in dialysis in order to achieve the maximal permeability for solutes between 0 and 40,000 D with a minimal or no leak of albumin (MW 48,000 D). In figure 2 we describe three hypothetical membranes characterized by different porosities and consequent sieving characteristics. Membrane A presents an average pore size smaller than the others and therefore the sieving capacity is limited for solutes of medium-high molecular weight range. Small solutes are still effectively cleared since the number of pores is sufficiently high. This represents a typical low-flux hemodialysis membrane such as cellulose-based Cuprophane®. Membrane B, on the other hand, presents a greater average pore size, although it maintains an adequate number of pores. This describes a typical well-designed high-flux synthetic membrane usable either in hemofiltration, high flux dialysis or hemodiafiltration. Finally, membrane C presents a typical albumin leaking membrane with a wide distribution of pore sizes but a limited number of pores. This is a good approximation of what is occurring across the human peritoneal mesothelium.

In figure 3 we schematically report the ideal progression in terms of pore size, diameter and configuration from the old generation of high-flux membranes to the more recently improved polysulfone membranes and finally towards the optimal pore configuration in an ideal high-flux membrane. In detail, while in the old generation of membranes the skin layer presented a series of pores

very different in size and structure leading to fluctuations in performance, the more recent high-flux polysulfone membranes display more homogeneous pore size diameters and a higher number of large pores. In such conditions however the transport of small solutes is still limited by the number of pores per square centimeter and increased average diameter of the pores is accompanied by a certain leak of albumin due to the presence of some pores exceeding the desired cut-off of the membrane. In the ideal membrane on the contrary, the performances are maximized by the increased number of pores and the transport of larger molecules is enhanced thanks to the average increase in pore diameter. At the same time however, the fine control of the pore size and structure allows for a precise range of pore diameters reducing the leak of albumin to negligible values. These results are clearly reported in figures 4 and 5 where the characteristics of the new Helixone® (FMC, Bad Homburg, Germany) membrane are compared to the already optimal characteristics and performance of the PS600® (FMC, Bad Homburg, Germany) polysulfone membrane. The nanocontrol spinning (NCS) procedure applied to the production of the Helixone membrane produces a significant effect on the structure of the skin layer at the nanoscale level. As demonstrated in figure 4 the number of pores is increased, while the spectrum of pore diameters is narrowed and concentrated around the desired values. The effect on solute sieving is depicted in figure 5. While the sieving value for medium sized molecules such as β_2 microglobulin has been increased in comparison to the previous membrane, the sieving for albumin has been reduced with virtually no leak of albumin at all. This finely tuned control of mem-

brane porosity allows one to obtain an almost ideal condition for a dialysis membrane. In practice the nanotechnology (NCS) procedure applied to the Helixone membrane has made possible a refined control of the number, diameter and anatomical characteristics of the pores. By this molecular manufacturing procedure, nanotechnology is applied to dialysis membrane manufacturing leading to improved performances and safety. This approach represents an initial step in the application of nanotechnology to hemodialysis. It also highlights the enormous potential of molecular control in biomaterials design and development at a nanoscale level.

Conclusions

This paper has provided a brief overview of nanotechnology and its present and future applications to the field of RRT. What do we see as the future of nanotechnology and RRT? We will definitely see a progressive miniaturization of current dialysis machines, monitors and devices. We will create increasingly 'intelligent' fibers with immobilized enzymes and diagnostic tools able to provide diagnosis, prescription and delivery of RRT by integrating continuous monitoring, membrane separation processes and metabolism. Intelligent and selective sorbents may be integrated into the fibers to prolong their action and

improve performance. Nanodots responding to specific wavelength beams will be utilized on hollow fibers for diagnostic and molecular detection purposes. If all this can be created at the most precise molecular level, the possibility of hemocompatible and immuno-tolerated implantable devices will be easier and more realistic. The important, but marginal improvements in dialytic technology over the past two decades will likely be overshadowed by this new paradigm in technical development.

How real is the potential of nanotechnology in general and in biomedicine in particular? Just surf the web for a few minutes and see the huge number of companies and institutions investing in this field, and developing training programs and career paths in nanotechnology. Academic as well as business positions are being created at a fantastic speed. Just remember: Leonardo da Vinci clearly envisaged the flying machine much earlier than the Wright brothers took off for the first time. Knowledge and research will help make possible in the near future what today is simply considered impossible. The dream of today will be the reality of tomorrow.

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