

# pharma point

No. 1 · July 2004

Newsletter of the Swiss Society for Pharmaceutical Sciences (SSPhS)

## Topic of the first edition: The potential of pharmaceutical biotechnology

### Preface

In 2002 the project team "Future of the SSPhS" was created for reviewing the work of the SSPhS, for investigating a potentially new orientation and to evaluate if a merger with related societies could be feasible. The latter had been suggested by a SSPhS member, also being member of the GSIA (Swiss Society of Industrial Pharmacists). The subsequent negotiations with the GSIA were not fruitful, hence the extraordinary member assembly on 1. 4. 2004 decided to follow the concept of the above referred project team, i.e. focussing the activities of the SSPhS on the following:

#### ● General PR activities

#### ● Activities within the EUFEPS

The SSPhS, as a national society, is linked to all other scientific pharmaceutical societies via the EUFEPS (European Federation of Pharmaceutical Scientists).

On June 12-17 2005 the EUFEPS will organize a "pharmaceutical science fair" at Nice.

(see: <http://www.pharmscifair.org/images/pharmscifair.pdf>)  
The SSPhS will be present with an information booth. A participation in the lecture program is also foreseen. Suggestions for the concept of the booth can be addressed to Dr. Gabriele Betz (Gabriele.Betz@unibas.ch)

#### ● Awards

The **Reichstein Medal** awarded to people according to their merits about pharmaceutical sciences, is meanwhile also granted to successful industrialists for supporting young scientists and to people having supported the practical exploitation of pharmaceutical sciences. Hence it is foreseen to award the Reichstein Medal 2005 to Jean-Pierre Lorent, the first director of the Swiss Toxicological Information Centre, during the forthcoming "Pharma Day 05" at the Pharmacentre Basel-Zürich on 10-11. 03. 2005, for his merits in establishing the Information Center.

**PhD student award:** This price is a indivisible financial award of SFR 1000.– per year for the best poster or oral presentation during a relevant university event and also includes a free SSPhS membership for 2 years. The price is awarded on suggestion of the competent academic institution in Geneva/ Lausanne or Basel/Zürich, being reviewed by a SSPhS jury.

#### ● Other activities

Further foreseen is the creation of a **SSPhS Scientific Advisory Board** consisting of SGPhW members having been awarded as "**Fellows of the SSPhS**". This body is supposed to function as a Swiss Academy of Pharmaceutical Sciences. Relevant membership proposals for fellows are to be addressed to the president.

#### ● Improved presence of the SSPhS

● **Web:** The website [www.sgphw.ch](http://www.sgphw.ch) was created and maintained by Michael Flück, who unfortunately can no longer follow this up. I take this opportunity to sincerely thank him for all his past efforts. Klaus Eichler from our collective member Glatt will continue his work. The homepage contains:

● **on-line application forms for individual and collective membership.** For a successful future of the SSPhS it is **essential** to enlarge the number of members considerably.

● information on the Reichstein Medal winners

● an extensive link section

The website is recognized by the relevant search engines. Relevant links will be established with quite a number of related web sites.

Further links can be proposed to the webmaster ([klaus.eichler@glatt.de](mailto:klaus.eichler@glatt.de))

#### And last, not least:

● The newsletter **pharmapoint**, which will focus on topics of general interest, will be send to all SSPhS members (for further distribution by the collective members) in e-format at least twice a year.

We sincerely welcome as new collective member the **Swiss Society for Radiopharmacy / Radiopharmaceutical Chemistry**.

We are pleased to herewith present our first edition of the **pharmapoint**. The editing committee will be happy to receive your further suggestions and creatively critical comments.

Basel, July 2004

Prof. Dr. Hans Leuenberger  
President of the SSPhS

# PHARMACEUTICAL BIOTECHNOLOGY

## The Way Foreword for New Product Introduction

How will the pharmaceutical industry, over the coming decade, introduce new products? In-house development of new drugs costs on the order of Euro 500 M, with pipelines typically on the order of seven years. Acquisition of medically oriented start-ups with a new product out of the pipeline, reduces these expenses, generally fivefold, though there remains significant marketing costs in launching a new biologic, typically in several countries concomitantly. One option may be to look outside the typical value chain of Pharma sector. Figure 1 demonstrates, using the example of water soluble materials such as alginate, extracted from sea-weed and used in a variety of pharmaceutical, food, and medical, applications, how the cost varies with purity.

The pharmaceutical industry could reasonably anticipate paying on the order of Euro 1-10k per kilogram for alginates, used as, for example, controlled drug delivery vehicles. However, in the food sector, alginates which have been purified to near-FDA standards are available, many through start-ups with unique intellectual property and values on the order of Euro 10 M. Similarly, medical grade materials, which are an order of magnitude more expensive than those typically used in Pharma, also present opportunities since their processes only require scale-up to be optimized for larger applications. One could make the case that such up- and down-stream possibilities are less expensive for the pharmaceutical industry than either in-house development or acquisition of similar, though smaller, firms.

In the food sector, hundreds of materials are available at costs in the 10-100 Euro per kilogram range. Moving these processes into GMP facilities, and improving purification methods, at scale, is one option for drug delivery. Another is in medically proven biomaterials. Given that the material cost of a transplantation is limited to 3% of the total billing though insurance companies, the specialized FDA approved, transplant proven, materials, can be scaled-up. A lower number of materials are available, however, the problems

are limited to process science, which the sector already masters, though generally through out-sourced contract, typically with formulators or dryers (e.g. tableting). It is these opportunities which we see as the future of pharmaceutical biotechnology. One that avoids Euro 500 M development costs for drugs, and Euro 100 M acquisition fees, and involves biotech startups, or the licensing of their patented products, or processes. While this may not reduce, significantly, the time in the

regulatory pipeline, pharmaceutical biotechnology will have a lower cost than pure Pharma. Furthermore, Biotech still has access to venture capital funding, and has modest valuations, which reflect the decreases in the high-tech stock markets over the last few years. Pharma, with its recent mega-fusions, remains highly valued. Drug related revenues from IP licensing are also lucrative, as one Swiss multinational has shown. The present issue of PharmaPoint discusses pharmaceutical

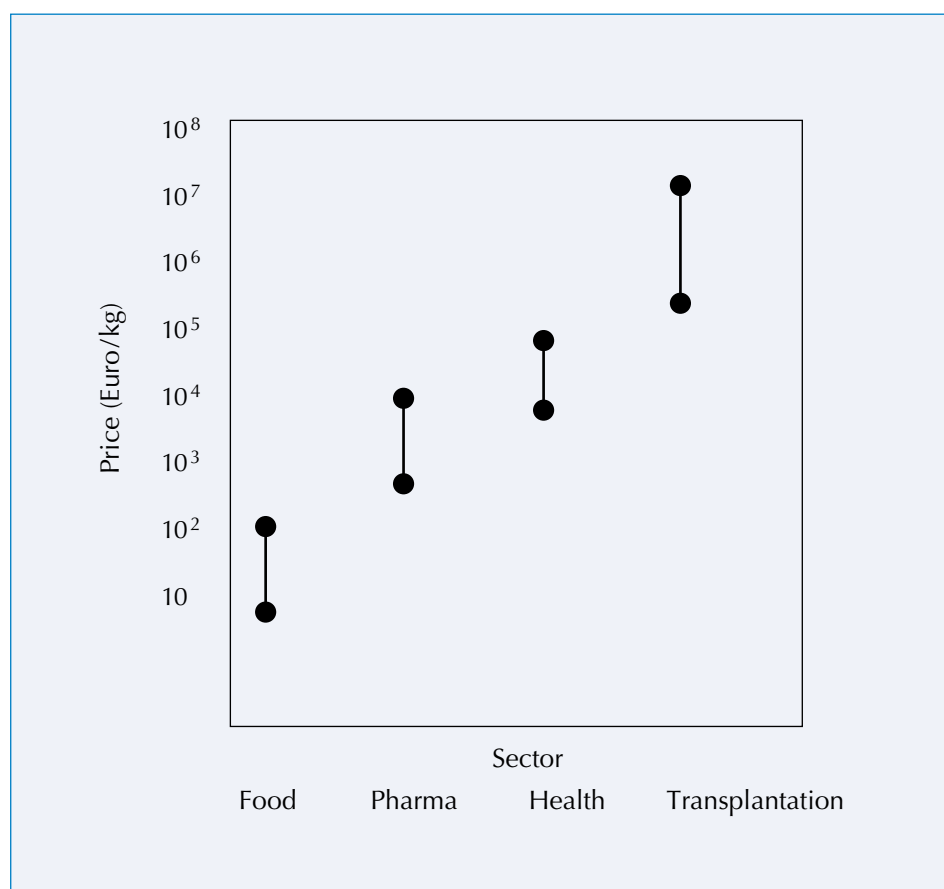


Figure 1. Increase in the price of materials as a function of purity. Pharma, medicine and transplantation require FDA approved materials, with the latter adding a very high value for clinically proven batches, as is also the case in enzymes.



David Hunkeler is a former professor of chemical engineering, materials science and technology management at Vanderbilt University (Nashville, USA) and the ETH-Lausanne (Switzerland). He was elected Young Entrepreneur of the Year in 1999 in Switzerland.

biotechnology from a product perspective. Two forms of Pharma-grade alginates are discussed. Michael Dornish presents FMC's highly purified grade of biomaterials while Berit Strand discusses the enzymatic modification of ideal biomaterials. These, and similar, immunoprotection barriers are discussed by

David Humes in his presentation of the bioartificial liver. Finally, Cytion provides an excellent example of miniaturization in analytics, aimed at increasing the speed and reducing the cost in cell characterization. Pharmaceutical biotechnology, while emerging, may not be all-new. Still, with the relative

valuations in the market now, and the reduced number of drugs in the FDA pipeline over the past two years (new registrations have decreased from 90 to 60 to 30 per annum), the timing has never been better for Pharma to move towards biotechnology, and medicine.

## Ultrapure alginate for tissue engineered medical products

Michael Dornish

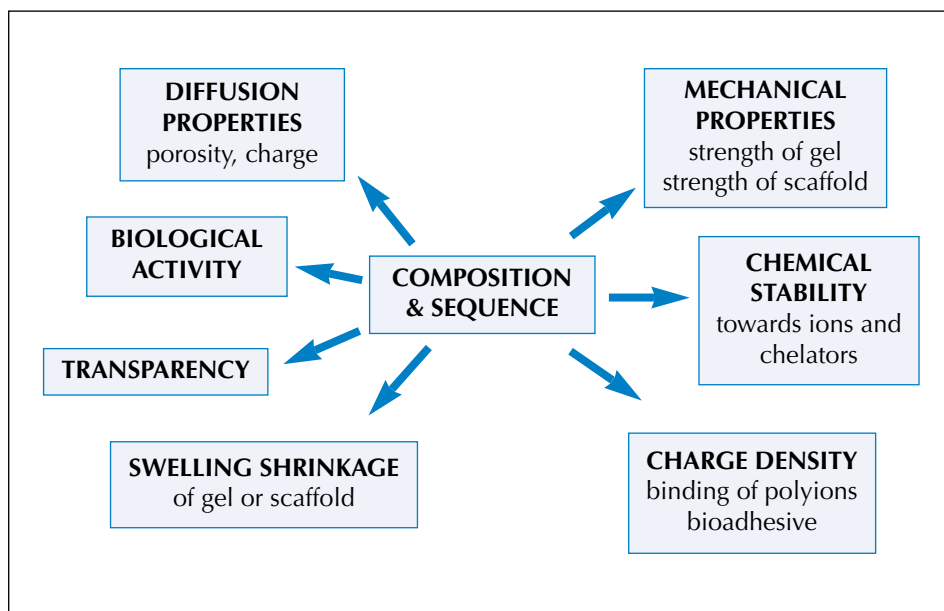
NovaMarix / FMC BioPolymer AS, Gaustadalleen 21, N - 0349 Oslo, Norway  
Email: michael\_dornish@fmc.com; novamatrix\_info@fmc.com

In the emerging area as of tissue engineering and directed drug delivery there is a need for excipients and structural materials that possess specific functionality. Scaffolds and matrices for tissue regeneration must possess enable or induce cell growth while, at the same time, remaining inert (biocompatible) and either permanent or biodegradable. Alginate has shown interesting potential for use as a scaffold material in tissue engineered medical products, as a drug-containing material for depot delivery, and as an encapsulating matrix for the immobilization of living cells. The uniqueness of alginate as an immobilizing agent rests in its ability to form instantaneous gels with most di- and multivalent cations, with the exception of  $Mg^{2+}$ . Alginate can be made into homogeneous or the more stable heterogeneous beads, as well as nano- and microcapsules.

The functionality of alginate is related to the chemical and structural composition of the polymer. However, in order to ensure that the functionality is appropriate for a given application, alginate must be fully characterized. Composition and sequential structure together with molecular weight and molecular conformation are the key characteristics of alginate in determining its properties and functionality. The composition and sequential structure of alginate can be determined by high-resolution NMR. Molecular weight can be determined by size-exclusion chromatography combined with light scattering detection. As shown here, changes in biopolymer

composition and sequence can influence a wide range of functionalities. For pharmaceutical and biomedical applications of alginate to be successful, regulatory issues must also be addressed. There are three main areas in this respect which must be dealt with: (1) characterization and functionality, (2) product reproducibility and manufactu-

re, and (3) toxicology and long-term safety. Ultrapure alginates, made in accordance with cGMP and ISO 9000 quality guidelines and documented in a Drug Master File, have been successfully utilized for applications inside the human body. PRONOVA™ sterile and non-sterile ultrapure alginate products meet such requirements.



Michael Dornish, Ph.D. VP Research & Development, FMC Biopolymer AS, Oslo, Norway. Main tasks are initiating and coordinating R&D projects in the fields of tissue engineering, cell encapsulation and drug delivery using ultrapure biopolymers. Participation in international organizations developing standards for biomaterials in tissue-engineered medical products, such as the ASTM. Conducts safety and toxicology studies of biopolymers as well as preparing regulatory filings.

# Microcapsules made from Structural Engineered Alginate

Berit L. Strand, Yrr A. Mørch and Gudmund Skjåk-Bræk

Department of Biotechnology, Norwegian University of Science and Technology, Trondheim, Norway.

Immunoprotective barriers may allow transplantation of cells and tissue without the need for immunosuppression. Living cells are encapsulated in a semipermeable membrane that allows nutrients, oxygen and cell products to pass whereas the host immune system is kept on the outside (Figure 1a).

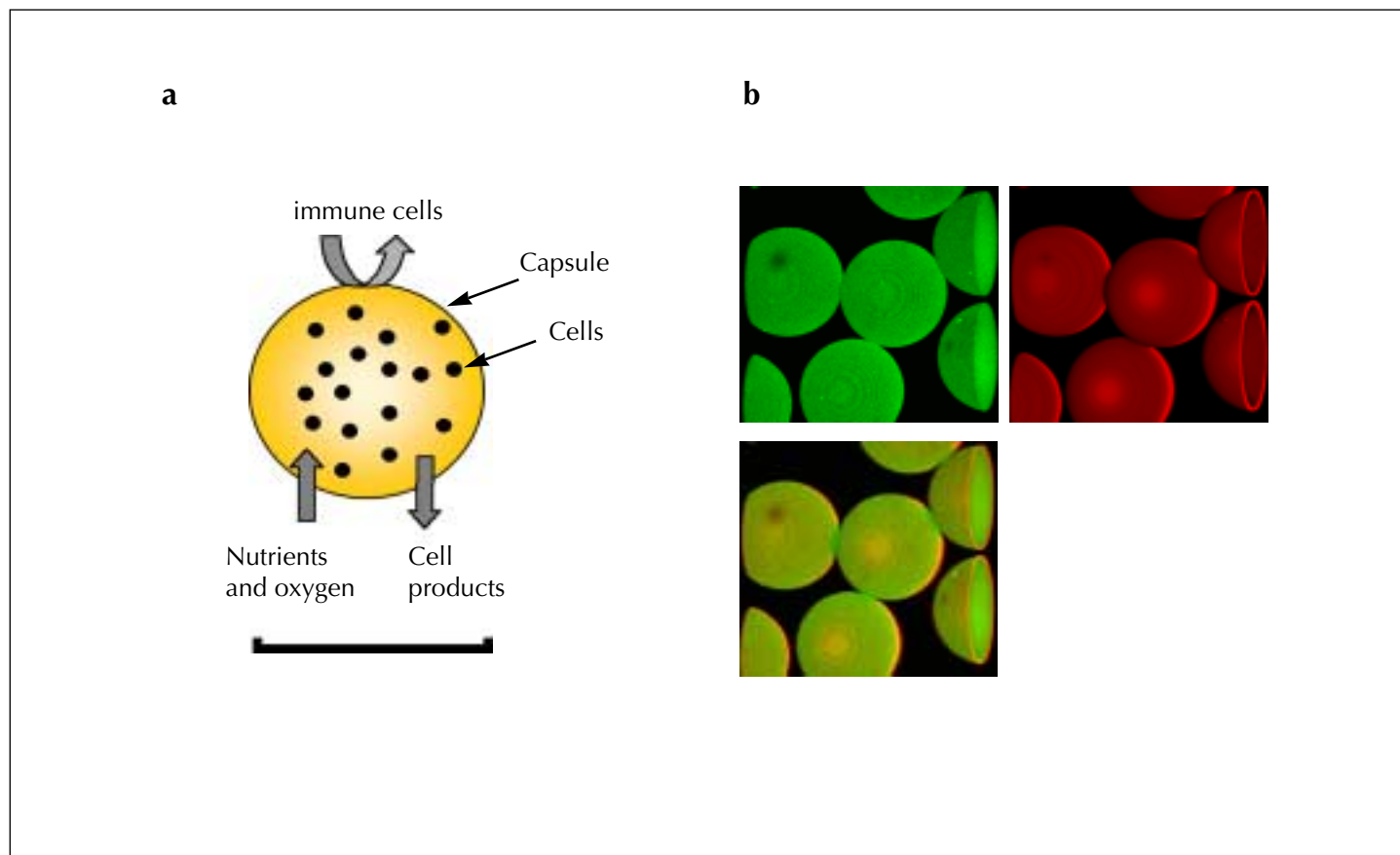


Figure 1. (a) Immunoisolation of transplanted cells by microencapsulation. (Scalebar 100-1000  $\mu\text{m}$ ) (b) Alginate-poly-L-lysine(PLL)-alginate microcapsules visualized in a confocal microscope: The upper left micrograph shows the alginate (green fluorescent label), the upper right the PLL (red fluorescent label) and the lower left alginate and PLL overlaid (Adapted from *Biotechnology and Bioengineering* 2003).

The potential for encapsulation in cell therapy is enormous as the products released from the microcapsules may be all kinds of biologically active materials secreted from cells. Alginate is the far most used polymer for cell encapsulation as it allows encapsulation under physiological conditions. Divalent ions cross-link the alginate in a gel core that entraps the cells and a polycation/polyanion layer is finally added (Figure 1b). The stability, permeability and biocompatibility of the capsules are determined by the type and exposure of divalent ions and polycations, as well as the alginate composition. We are now able to tailor alginate composition by enzymatic modification.

By introducing more flexible segments in the alginate chain, we can make microcapsules that are smaller, more stable and less permeable than earlier. This allows reducing or omitting the toxic polycation coating while still

obtaining a stable capsule with reduced permeability. In addition, the novel alginates bind better as a coating to the alginate-PLL core and by this also increases the capsule biocompatibility.

Berit L. Strand, PhD, is currently a post.doc. at Department of Biotechnology at NTNU in Trondheim, Norway.

The main focus of her PhD and present work is encapsulation in alginate for cell transplantation and the development of new and tailored alginates that are particularly suitable for cell encapsulation. In 2003 she was awarded the price as the young scientist of the year (The Norwegian Society of Chartered Engineers).



# Clinical Trial of a Bioartificial Kidney

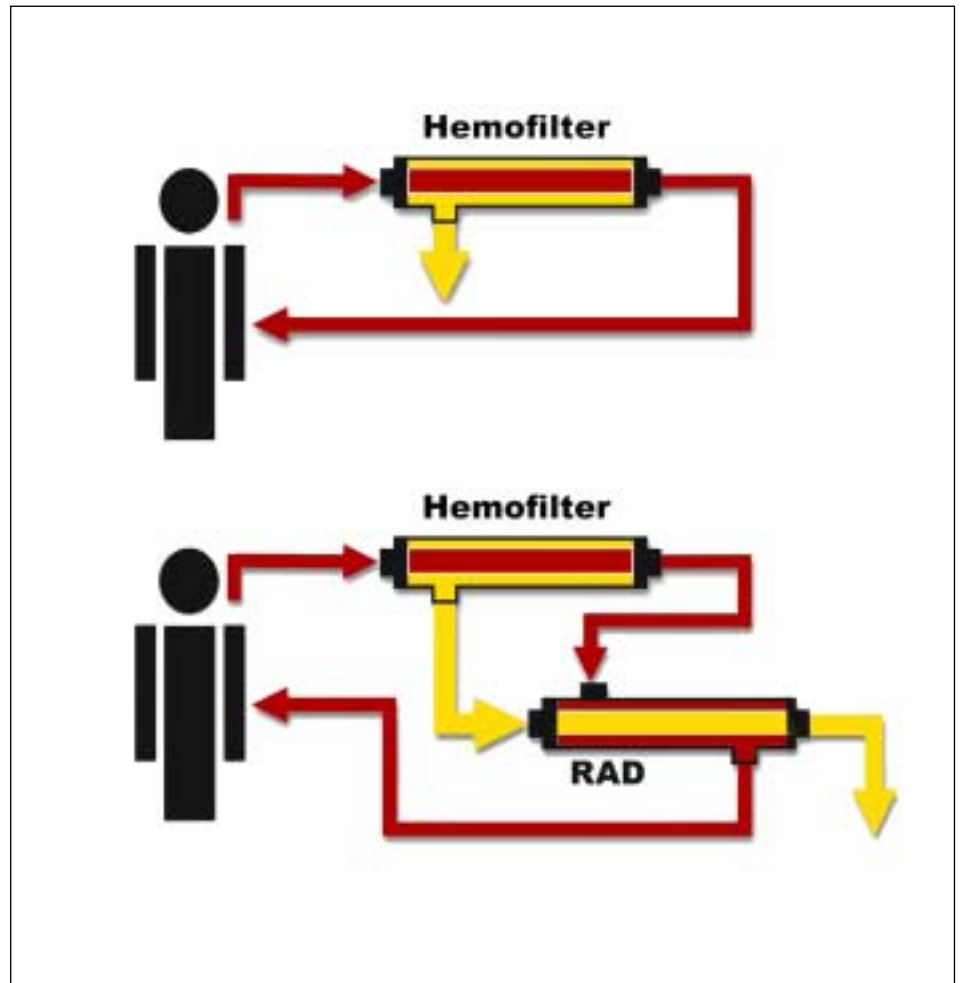
Daniel S. Cutler  
Humes Laboratory Spokesman

Phase I safety trials have concluded and Phase II clinical trial is now being designed to investigate the efficacy of a renal assist device (RAD) as an adjunctive therapy in the treatment of acute renal failure (ARF). Containing living human kidney cells, the device has also been termed a "bioartificial kidney". (It is not currently being investigated for treatment of chronic renal failure and is not an option for patients on dialysis.)

Acute renal failure is a sudden loss of kidney function. It can be brought on by an injury to the cells of the renal proximal tubule (RPT), resulting in a condition called acute tubular necrosis (ATN) -- the clinical diagnosis of patients in this study. Injury to the RPT cells may be caused by exposure to nephrotoxins such as aminoglycoside antibiotics, or by hypoxia, due to blood flow interruption, as sometimes happens in the course of coronary bypass and other surgeries.

Unlike end stage renal failure, the kidney in ARF may heal itself, if the patient can be supported throughout the episode. Unfortunately, the temporary loss of kidney function can send the patient into a downward spiral of worsening conditions, resulting in death. Patients in ARF are susceptible to developing systemic inflammatory response syndrome (SIRS). Most commonly secondary to bacterial sepsis, the condition results in cardiovascular collapse, leading to ischemia, multiorgan failure and death.

The single factor most responsible for death – development of infection culminating in septic shock – is due to an impairment of host defenses. The renal assist device (RAD) was conceived in the belief that living cells can improve patients' infection-fighting capability lost in ARF, staving off infection and breaking the downward spiral. In an important pre-clinical study (Nature Biotechnology 1999, 17:451-455) the RPT cells in the RAD were shown to replace key metabolic and endocrinologic kidney functions important in host defense. Early data from the safety trial suggests the living



cells in the RAD performed similarly in the human study. Whether this actually translates to clinical benefit in humans is under investigation.

In the deadly SIRS phenomenon, the usually helpful inflammatory response goes out of control, threatening to bring about life-endangering loss of blood perfusion to the vital organs. RPT cells are increasingly understood to have a role in regulating the inflammatory response, through their mediation of cytokines, small messenger molecules that promote or suppress inflammation. The cells may, therefore, prove to be of further benefit in controlling the maladaptive inflammation of SIRS. In an animal model a RAD was shown to ameliorate the effects of endotoxic shock (J Am Soc Nephrol 1999, 10:199A). Again, whether this translates to human clinical benefit is being determined.

Currently, patients in acute renal failure are supported by hemofiltration or dialysis therapy, the goal of which is to maintain fluid and electrolyte balance and improve nutritional status. Though life-saving for many, these established therapies too often prove inadequate for the majority of patients, despite their success at managing uremia. Developers of RAD therapy postulate the shortcoming is due to the fact that current therapy replaces only the filtrative function of the kidney, but none of the metabolic and hormonal functions that reside in the RPT cells.

Like the natural organ it is designed to emulate, the RAD functions in two steps. Just as the nephron, the kidney's functional unit, is comprised of a filtering glomerulus followed by a metabolically active renal tubule, RAD therapy consists of hemofiltration followed in series by a unit containing living renal

proximal tubule cells. The treatment is an extracorporeal blood perfusion circuit applied in the ICU. The cell-filled RAD cartridge is on an ancillary circuit that shunts off the traditional CVVH circuit. Grossly, the cartridge appears as an off-the-shelf hemofilter. Unseen by the naked eye are the living cells that distinguish this technology.



*Dr. med. H. David Humes controls the kidney function supporting instrument (RAD) at the bedside of a patient, during the 1. phase of the clinical study at the University of Michigan.*

The cells originate from human kidneys donated for transplant that are later discovered to be unsuitable for use, due to anatomic anomalies or other reasons. Progenitor RPT cells are harvested from the organs, expanded, and seeded into the hollow fiber membranes of a standard hemofilter. The cells are then grown along the inner surface of the fibers. This arrangement is designed to duplicate the architecture of the natural renal tubule. Encapsulated within the hollow fibers, the RPT cells are protected from the patient's immune system while, at the same time, the porous walls of the fibers allow them to carry on physiologic exchange with the environment.

Blood diverted from the patient is processed through the hemofilter, as is commonly done. But rather than being discarded, the ultrafiltrate produced is then shunted to the RAD, pumped through the lumens of its hollow fibers where it comes into contact with the living RPT cells. Meanwhile, the blood that exits the hemofilter is delivered into the RAD cartridge where it percolates around and between the hollow fibers. The blood then rejoins the hemofiltration circuit for return to the patient's body.

The RAD is an example of tissue engineering, the burgeoning technolo-

gy of designing for manufacture living tissue. Early advances in biotechnology concentrated on producing a single protein targeting a precise shortcoming (i.e. insulin). Proponents of the tissue engineering approach hope to address more complex, multivariate problems, using living tissue's naturally evolved mechanisms to therapeutically respond to clinical challenges. The RPT cells in the RAD, for example, are being studied to determine whether they can custom produce for each patient an individualized optimal balance of inflammation-controlling cytokines. The investigation underway will ultimately determine whether the postulated replacement of this ability and other RPT cell functions lost in ARF can translate into clinical benefits to change the current natural history of this disease process.

Based on the research of David Humes, MD, the physician-sponsored Phase I trials were carried out at the University of Michigan and the Cleveland Clinic Foundation under the Investigational New Drug Application (IND) allowed by the Food and Drug Administration, and with support from Nephros Therapeutics, a biotechnology company licensed by the University of Michigan to develop Humes' basic research findings into useful products.

H. David Humes, M.D.  
Professor of Internal Medicine

#### Biosketch

Dr. Humes graduated from medical school in 1973 at the University of California, San Francisco, where he stayed to complete his internship and residency training in 1975. In 1977, he joined the faculty at Harvard Medical School as an Instructor and departed in 1979 as an Assistant Professor of Medicine. The University of Michigan recruited Dr. Humes as an Assistant Professor of Internal Medicine in 1979 becoming a full Professor in 1986. In 1996, Dr. Humes was appointed the John G. Searle Professor and Chair of the Department of Internal Medicine at the University of Michigan, a position he held until 2000. He has published approximately 150 scientific papers, edited five textbooks, is currently Editor-in-Chief of *Kelley's Textbook of Internal Medicine*, and has 22 patents. He has been awarded a number of highly acclaimed awards in Nephrology, including The President's Award from the National Kidney Foundation and the A.N. Richards Distinguished Achievement Award in Nephrology. He was a founder, director, and CEO of Academic Network for Clinical Research, Inc., a clinical trials site management organization comprising a consortium of academic medical centers. Most notably, he is the scientific founder, director, and chief science officer of Nephros Therapeutics, Inc., a biotechnology company directed to bioartificial organs and drug-delivery devices.

Dan Cutler is a certified medical illustrator and writer. He has been explaining this technology visually and verbally since its inception and now functions as spokesperson for the Humes lab.

#### Impressum

Editing Committee:  
Dr. Ewart Cole  
*Capsugel Arlesheim*  
Klaus Eichler  
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Guest editor for the special topic of this edition:

Dr. David Hunkeler  
*Aqua+Tech, La Plaine*

Layout:  
Schmidhauser Mediengestaltung  
[www.schmidhauser.de](http://www.schmidhauser.de)

Contact:  
Dr. Claudia Reinke, MedSciences  
Schützenmattstrasse 1  
4051 Basel

Internet: [www.sgphw.ch](http://www.sgphw.ch)

