(BIO)ARTIFICIAL ORGANS TO MIMIC OR REPLACE PATIENT FAILING ORGANS

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IN AUGURAL LECTURE
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UNIVERSITY OF TWENTE.
Inaugural lecture given to mark the assumption of the position as Professor of (Bio)artificial organs at the Faculty of Science and Technology at the University of Twente on Thursday 8th June by

PROF. DR. DIMITRIOS STAMATIALIS
Dear Mr Rector, Mr Dean of our faculty
Dear family and friends, colleagues, Ladies and Gentlemen

I would like to welcome you all to my inaugural lecture on: “(Bio)artificial organs to mimic or replace patient failing organs”. I have intentionally underlined the words “(Bio)artificial organs” and “Patient”, since these would be the most important keywords of this inaugural lecture.

1. PATIENT: THE MAIN FOCUS

The best way to start would be focussing on a patient, a rather specific patient:

- Male - 76 years old
- He suffers from diabetes type 2, for almost 20 years
- He follows a strict diet, take lots of medication and insulin injections

Despite all these efforts, the glucose levels in his blood are not well regulated. He often suffers from events of hypoglycemia (less often of hyperglycemia) and throughout the years he had several other complications. He has cardiovascular problems - actually suffered a heart attack and a stroke a few years ago - has limited kidney function and serious vision problems. Unfortunately, the last 2 years he is almost immobile at home.

The question to all, bioengineers, chemists, pharmacists, medical doctors... in the academia and in the industry... the question to the health system, in general, is very direct:

“Can we help this complex patient which actually is not an exceptional case?”

In fact, with the ageing of the population and the particular life style, especially in the western world, in the next years we expect having more “complex patients”. The facts concerning, for example, diabetes, renal replacement therapies and chronic obstructive pulmonary disease (COPD mainly caused by smoking) are clear:

Diabetes
According to the World Health Organization (WHO), the number of patients with diabetes type 2 raised from 108 million in 1980 to 422 million in 2014 [1]. Diabetes type 2 is the major cause of blindness, kidney failure, heart attacks, strokes and lower limb amputation. In 2012, 1.5 million deaths were directly caused by diabetes whereas 2.2 million deaths were attributable to high blood glucose. Prevention or even delay of the onset of diabetes type 2 can be achieved when people follow a healthy diet, have regular physical activity and maintain a normal body weight, without smoking. Unless we follow these, WHO projects that diabetes will be the 7th leading cause of death in 2030.

In contrast to diabetes type 2 which could be considered as a “life style disease”, diabetes type 1 is an autoimmune disorder characterized by destruction of insulin-producing $\beta$-cells within the islets of Langerhans, resulting in absolute insulin deficiency. Currently, type 1 diabetes accounts for 5-10% of the total cases of diabetes worldwide, occurring mainly in children and young adults [2]. In the Netherlands, there are more than 100,000 patients (source Diabetes Fonds). Although insulin therapy can be effective in regulating the blood glucose levels there, it still lacks the precise glycemic control that the normal physiological system has. Therefore, it often results in hypoglycemic events, while in the long term micro/macrovascular complications affect many patients [3].

Renal therapies
In the Netherlands, almost 13,000 patients need renal replacement therapy, among those, 6,500 patients need kidney dialysis. In Europe and worldwide the dialysis patients are approximately 350,000 and 3 million, respectively. Although the number of these patients is not high in comparison to diabetes or other diseases, the dialysis therapy is very expensive, for example in the Netherlands it costs approximately € 90,000 per patient per year. Besides, the mortality of the patients is high. As is illustrated in Figure 1, the expected remaining lifetime for patients on dialysis is much lower than for the general population and it is strongly reduced when compared with that of transplant recipients [4].
Chronic obstructive pulmonary disease (COPD)

The COPD is a progressive life-threatening lung disease that causes breathlessness and predisposes to exacerbations and serious illness. Its primary cause is smoking (either active or second-hand smoke) and to other risk factors, such as, air pollution, occupational dusts and fumes. Globally, 3 million deaths in 2015 (5% of all deaths, 90% of deaths in low and middle income countries) can be attributed to COPD.

COPD is likely to increase in coming years due to higher smoking prevalence and aging populations in many countries. It is not curable, but treatment can relieve symptoms, improve quality of life and reduce the risk of death [5].

Figure 1. Expected remaining lifetimes of dialysis and renal transplant patients in 2010 and 2011 compared with the 2005 general population statistics. Taken from [4], open access article.
2. THE NEED AND THE SOLUTION – (BIO)ARTIFICIAL ORGANS

The very good option for lots of the complex patients would be organ transplantation. However, there is significant shortage of donor organs. For example, in the Netherlands, the waiting list for kidney transplantation is approximately 4 years, whereas the graft survival is between 10-20 years and not everyone is eligible. The pancreas facts are quite similar, there the issue is most critical since the donor has to be a diseased person.

It is obvious that there is urgent need for bioengineering organs to assist, mimic or replace failing patient organs. The chair of “(Bio)artificial organs” has the ambition to take-on the challenge and help these patients by contributing to the development of:

**Artificial organs:** based on new biomaterials and designs, to assist or mimic a patient organ. Typical examples here are:
(i) new generation of artificial kidney devices for better and more continuous patient treatment – including portable kidney devices
(ii) new artificial liver devices for blood detoxification using novel sorbents.

**Bioartificial organs:** combining biomaterials and biological cells to fully replace failing patient organs. Typical examples here are:
(i) bioartificial kidney devices, combining biomaterials and kidney epithelial cells for improved blood detoxification
(ii) bioartificial pancreas devices, with encapsulated pancreatic cells for treatment of diabetes
(iii) bioartificial lungs for studying effect of smoke and the lung regeneration.

In this field of research, the challenges (scientific and technological) are big. There is need for new biomaterials, need for better understanding of the biomaterial tissue interaction, need for achieving better immune protection. The organ complexity increases from artificial to bioartificial, and the regulatory demands increase from extracorporeal (placed outside the body) to implantable (placed inside the body) organs.
To stimulate this research, the European Society of Artificial organs (ESAO) established in 2016 a new working group on “Bioartificial organs” which I am currently honoured to chair. The group includes experts from various disciplines and focuses on organizing meetings, training events, and outreach activities (http://www.esao.org/working-groups/bioartificial-organs/).

In the next sections, some of the strategies to develop (bio) artificial organs are discussed. In every case, I start with the small introduction about the organ which needs to be assisted or replaced.

2.1. (BIO)ARTIFICIAL KIDNEY FOR TREATMENT OF CHRONIC KIDNEY DISEASE

The kidneys
In general, people have two kidneys and which are located in the abdominal cavity and are approximately 11 cm long and about 160 grams each [6]. The kidneys regulate [7]:
- Body fluid osmolarity and volume
- Electrolyte and Acid-base balance
- Excretion of metabolic products and foreign substances
- Production and secretion of hormones

Each kidney contains approximately 1,2 million nephrons which are the functional units for blood cleansing and forming urine. Renal failure results in accumulation of waste products and excess fluids in the body. The yearly growth of dialysis patients is 7–8%.

Renal failure - Extracorporeal blood purification
For patients with End Stage Renal Disease (ESRD), where the kidney function is less than 10%, the best solution is kidney transplantation. However, since the mean time on the transplant waiting list is 4 years and not all patients are eligible for transplantation, most ESRD patients rely on blood purification via an artificial kidney. During this dialysis treatment, blood is cleansed, mostly at a specific dialysis unit in the hospital, thrice weekly for about 4 hours per session [6] (Figure 2). In fact there, blood is taken out of the body and passes through a special hollow fiber membrane device that removes waste and extra fluids (Figure 3). The clean blood is then returned to the patient. The process is controlled by a dialysis machine which is equipped with a blood pump and monitoring systems to ensure safety. The machine can also administer drugs, for example heparin to avoid blood clotting during treatment.
The membrane (Figure 3) contains pores that allow small molecules such as water, urea, creatinine, and glucose to pass through whereas the blood cells and most plasma proteins, including albumin, are retained.

The molecules after passing through the membrane pores due to diffusion and/or convection are washed away via the dialysate solution. The latter is an electrolyte solution similar to the normal body fluid (purified water, sodium, potassium, calcium, magnesium, chloride). For each treatment, more than 120 litres of water are consumed, mostly for the dialysate solution.
Despite the great success of the treatment in keeping the patients alive, it is still incomplete. It mainly removes small, non-protein bound substances, leaving toxic larger middle-sized molecules and protein-bound uremic toxins untouched [8]. Furthermore, the inadequate volume and blood pressure control, due to the intermittent character of the therapy (thrice a week) contributes to high mortality of patients. Continuous treatment or increased frequency and duration could potentially contribute to gradual removal of excess fluids and improve clearance of uremic waste, potassium and phosphate.

**Innovations for better treatment**

Recently, we have developed new artificial kidney devices which can achieve better treatment. There, we apply a double layer mixed matrix membrane (MMM) [9-11]. The membrane combines the benefits of diffusion and convection, provided by the membrane structure, and adsorption, achieved by activated carbon particles dispersed through the membrane. To avoid blood-sorbent contact, the blood side of the MMM consists of a particle-free polymeric layer, see Figure 4a. So far, we have produced two generations, MMM 1.0 with large pores, MMM 2.0 with small pores. Both have superior performance for removing of protein bound toxins, in vitro, in comparison to membranes currently used in the clinic (Figure 4b, 4c). In the next period, we will perform in vivo studies within a new collaborative program between our research institute, MIRA, and the Utrecht University Medical Center.

In the kidney, complete solute removal is achieved by combining the removal of small solutes through glomerular filtration with the removal of the larger ones and protein bound solutes by the proximal tubule, see Figure 5a. Since the current dialysis only mimics the glomerular function, for achieving complete solute treatment one needs to combine dialysis with a Bioartificial kidney (BAK) which would mimic the proximal tubule function. The BAK can be realized through the creation of ‘living membranes’ by coupling artificial membranes with functional kidney cells [12], see Figure 5b.
Figure 4. (a) Concept of a dual layer MMM combining diffusion and adsorption in one step. Taken from [9] with permission from Elsevier. (b) Scanning electron microscopy image of the cross section of a MMM. (c) Removal of protein-bound toxins, indoxyl sulfate (IS) and p-cresyl sulfate (pCS) by the MMM in comparison to literature studies. Ultrafiltration coefficient (UC) represents the type of membrane used in the studies. Low (high) UC represents membranes with low (high) permeability of water and toxins. Taken from [11], open access article.
In the last few years, together with my close collaborator, Prof. Roos Masereeuw, from the University of Utrecht, we have been working very hard towards the development of a BAK device. Specifically, we have focused on the availability of kidney cells capable of removal uremic retention solutes and the development of an up-scaled living membrane consisting of tight cellular monolayer with very good functionality, Figure 5b. In the near future, the up-scaled BAK will be tested for safety in animals and towards short and long term efficiency of uremic solute removal under uremic conditions.
In the last few years, I have been honoured to obtain funding from the Nierstichting which actually aims to develop a portable dialysis device, see Figure 6. In the future, both the MMM and BAK devices could be included in new generations of this portable device.

Figure 6. Artist impression of the prototype portable artificial kidney device under development. Photo reproduced with the permission of the Nierstichting.

2.2. (BIO)ARTIFICIAL PANCREAS FOR TREATMENT OF DIABETES

In the pancreas, the beta cells located in pancreatic areas called the islets of Langerhans are responsible for the regulation of normal blood glucose levels. This regulation occurs via a rather sophisticated mechanism which involves the production of insulin and amylin to decrease, and of glucagon to increase, the glucose levels in the blood [6] (Figure 7a).

In patients with diabetes the blood glucose levels are inadequately maintained due to the lack of insulin, therefore the patients need to follow a strict diet in combination with insulin administration, either by multiple daily injections or through an “artificial pancreas”, a device which combines glucose monitoring with subcutaneous insulin infusion [13]. However, this system still has several limitations mainly related to delayed glucose sensing and insulin absorption into the blood stream. In addition, pancreas transplantation involves a complicated abdominal surgery [14] and the treatment is accompanied with long-term immunosuppressive therapy to avoid rejection of the donor tissue.
Due to shortage of donors, a whole pancreas transplantation is restricted to certain group of patients, often when kidney replacement is necessary, too [14, 15]. For Type 1 Diabetes patients, clinical islet transplantation has lower risk compared to total pancreas transplantation. There, after isolation of islets from a donor pancreas, they are transplanted in the patient liver via infusion in the portal vein. After this, the islets will embolize in the microvasculature of the liver and perform their endocrine function.

In our recent research project, funded by the Juvenile Diabetes Research Foundation (JDRF), together with my collaborator dr. van Apeldoorn, we have developed a bioartificial encapsulation pancreas device based on microwell membranes, see Figure 7b. Pancreatic islets of Langerhans are seeded in microwells to avoid aggregation, whereas the membrane
Porosity is tailored to achieve islet shielding from the host immune system. The encapsulated islets maintain their glucose responsiveness, in vitro, comparable to non-encapsulated cells. For future clinical implementation, we would need to develop a larger diameter devices able to encapsulate higher number of islets. Here, as in all organs, the development has to go through an important trajectory which includes testing first in vitro and later in vivo, before entering clinical studies with humans.
3. THE FUTURE IS EXCITING

The future is certainly exciting. The strategy of the (bio)artificial organs chair fits perfectly to:

- Strategic vision of the University of Twente: “High Tech - Human Touch”
- European Union programs about “Healthy aging”; “Health” and others
- Top sector “Life science and health” of the Dutch government
- Vision of Dutch government (“scientific vision 2025”)

Besides, to perform such multidisciplinary research, one needs very good collaborations, nationally and internationally, as well as, securing appropriate funding.
Throughout the years, I have been working with several top scientists in the Netherlands and abroad (Table 1 lists current collaborators and the topics / organs). Furthermore, I have been involved in several international activities including:
- Board member of the European Society of Artificial Organs (ESAO)
- Chairman of the working group: “Bioartificial organs” of ESAO.
- Editor of the “International journal of artificial organs”, official journal of ESAO
- Member of the EuTox group, ESAO working group coordinates European research on uremic toxins (members only by invitation).
- Member of: American Society of artificial organs (ASAIO), ESAO, European Membrane Society (EMS), European Society of Biomaterials (ESB), European Tissue Engineering society (ETES), European association for the study of diabetes (EASD).

All these collaborations and activities are extremely important for achieving breakthroughs in the field. The need for good interaction between scientists of various disciplines (as I describe in the section about education, even integration of disciplines is required) is very important to develop these complex organs and treat the complex patients.
Obviously, pursuit of funding for this research is very important, especially since this type of research is quite expensive. Financial support from the Dutch government (NWO, STW, Health Holland, ZonMW), the EU, as well as, patient organizations (Longfonds, Nierstichting, Diabetes fonds JDRF, European Society for the Study of Diabetes) would be critical for success. Lastly, the support of the private sector, especially of the large (pharmaceutical and other) companies would be crucial here. Some of them are quite conservative and are often focusing on short term profits rather than supporting long term innovation projects. Reaching out to them and making known our ideas will continue to be one of the most important tasks of my position.

Table 1. Current collaborations of the chair of (bio)artificial organs.

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<tr>
<th>University of Twente</th>
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<tbody>
<tr>
<td>Biomaterials science and technology</td>
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<td>Developmental Bioengineering</td>
<td>(Prof. Karperien, pancreas)</td>
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<td>Advanced Stem Cell Technologies</td>
<td>(Prof. Passier – Heart)</td>
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<td>BIOS</td>
<td>(Prof. van der Berg)</td>
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<td>Health Technology and Services Research</td>
<td>(Prof. Ijzerman, economics of organ research)</td>
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<td>Utrecht Univ.</td>
<td>(Prof. Masereeuw – bioartificial kidney)</td>
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<tr>
<td>Maastricht Univ.</td>
<td>(Prof. de Boer – Topochip, kidney, bone)</td>
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<td>(Prof Verhaar, Dr. Gerritsen – artificial kidney)</td>
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<tr>
<td>UMC Maastricht</td>
<td>(Prof. Kooman – artificial kidney)</td>
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<tr>
<td>Radboud UMC</td>
<td>(Dr. van der Vlag – kidney, Prof. Hoenderop, Gut)</td>
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<tr>
<td>UMC Leiden</td>
<td>(Prof. Hiemstra – lung, Prof. Koning – pancreas)</td>
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<tr>
<td>UMC Groningen</td>
<td>(Prof. de Vos – diabetes)</td>
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<tr>
<td>UMC Gent</td>
<td>(Prof. Vanholder – artificial kidney)</td>
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4. EDUCATION

The need for a new engineer and integration of disciplines
Throughout the years in the University of Twente, I have been involved in education with great passion. The close contact to the young enthusiastic students and the ambition to shape “a little bit” their future career has been always very stimulating to me. This was actually one of my drivers for pursuing a career in academia.

One of the things that puzzled me, since early on, is that engineering studies are often considered less challenging than the traditional studies. Some think that if a student is not good enough for studying physics, chemistry or biology, he / she probably can be good enough for studying, for example, biomedical engineering. However, in Greece where I come from, the engineering studies actually attract the best students. There, the students need to pass national exams to enter the University and in fact most engineering studies (chemical, biological, biomedical, electrical, computer engineering) have higher thresholds to reach, in comparison to “monodisciplinary” studies.

In the last years while coordinating research in the biomedical applications, I have also observed that in spite of the huge potential of biomaterials science, cell biology and medicine for achieving human health, there is a lack of communication between these disciplines.

I believe that it is an urgent need for integration of knowledge and interdisciplinary, multidisciplinary collaborations between biomaterial scientists, bioengineers, biologists, medical doctors and other clinicians to overcome the current barriers and to face the future scientific and technological challenges. There is no question in my mind that in order to make important breakthroughs in the field of (bio)artificial organs, we need to achieve an integration of disciplines. This can be achieved but educating and training very good engineers and establish very good collaborations.
Education vision
The University of Twente has very strong and well established undergraduate studies in Biomedical Engineering and Technical medicine, the latter has been evaluated as “Top study” in 2016. It is my ambition to continue contributing to the education programs of both studies and when possible, to the education program of the Twente Graduate School (TGS). The role of the latter is very important for the education of young researchers (mostly PhD students) and for making them capable of addressing highly multidisciplinary projects. Understandably, these researchers would not become experts in all the disciplines involved. But at the end of their training, they would have further developed their initial background as well as acquired complementary basic, but sufficient knowledge, on the other disciplines involved in the research. The immediate benefit for the researchers will be the development of their respective chosen discipline complemented by the acquisition of additional scientific skills which will reinforce their capacity to progress in the field. The longer-term benefits for them will be the building of their capacity to work across disciplines and clinical and industrial institutions.
In the period 2012-2016, as a coordinator of the European Training project BIOART (http://www.bioart-fp7.eu) I have been involved in the development of an interdisciplinary training program and the results were very rewarding. Students of different backgrounds and from different nationalities were trained via research and learned a lot while producing very good science (and also having good fun, Figure 9).

Figure 9. Photo of the participants to the BIOART summer school organised in June 2015 at the University of Twente.
5. THE UNIVERSITY –
THE ACADEMIC WORK

Perhaps most of the people here at my inaugural lecture are not aware
that the new academician, certainly a full professor, is expected to be,
simultaneously, a great scientist, an inspiring educator and even a greater
manager (of people, of finances, etc). Besides, every research chair more
or less works as a business unit, with income and expenses.
The professor, “the superman”, quite often alone (due to financial
constraints) has to work harder and longer hours to obtain yet more
funding, to teach more hours and to larger classes, to establish national
and international collaborations, to publish more, preferably to high end
scientific journals. In his spare time, he should develop new products,
obtain patents and establish companies.
I strongly believe that this model is unsustainable. The University should be
a creative environment where knowledge and excellence is pursued. The
academics need to obtain “space” (time, freedom) to pursue this within
a supporting organization which works with them, supports them, and
encourages them.
6. FAMOUS LAST WORDS

I would like to thank the pro-dean health Prof. Maarten IJzerman, the dean Prof. Hans Hilgenkamp of our faculty, TNW, and the director of our institute MIRA, Prof. Albert van der Berg, for their continuous support.

I would like to thank, Prof. Matthias Wessling, who actually hired me as a young assistant professor in 2002 and gave me the opportunity to develop during my tenure at the Membrane Science and Technology group.

Many thanks to Prof. Dirk Grijpma and the whole Biomaterials Science and Technology group which has been my “home” for the last 7 years.
Dear Dirk, I appreciate very much your continuous efforts to create a fantastic and stimulating environment to work in. I also liked that you gave me the absolute freedom to pursue my dreams.

I have been working in academia since 1989, All these years, I had several important collaborations and I met and worked with lots of people around the world. I, however, had only two mentors, Dr. John Petropoulos and Dr. Meropi Sanopoulou, my PhD advisors at the Demokritos National research center in Greece in the period 1990 - 1995.
Dear John, dear Meropi, I learned almost everything from you; how to perform very good research; how to present my work and write papers.
I also learned about setting goals and making clear plans to reach them... with hard work (and a bit of luck).

I would like to thank my parents, Fotios and Maria Stamatialis and my sister Kyriaki Delimbasis for their love and support.
My parents devoted their lives to us, myself and my sister; to guide us through life, making sure we got great education, despite the financial constraints. Both my parents were actually very good students, but they had to stop school early on to work and support their families.
As my father told me recently, I am the only Stamatialis (till today) who finished University, who got a PhD, who pursued an academic career, who became, today, a Professor.
It is really unfortunate that both my parents due to their poor health (patient F, is actually my father) could not join my inauguration. I love you all very much. ΣΑΣ ΑΓΑΠΟ ΠΑΡΑ ΠΟΛΥ!

My grandmother, Kaliopi, was an important factor shaping up my character and my career. She fought in two wars, she was strong, opinionated, politically active till she passed away a few years ago. She was a fantastic person to be around. She taught me how to fight, never give up and always try to become better. My granny, γιαγια, was always present to the important events of my life. I am sure she would have liked to be here today... I am sure she is watching from up there now! ΣΕ ΑΓΑΠΟ ΠΑΡΑ ΠΟΛΥ ΓΙΑΓΙΑ!

I would like to thank from the bottom of my heart, my wife Ellie - the love of my life - and my fantastic boys – Daniel and Thomas – for their love and support. Ellie has been an important pillar of our family. She is strong and funny, ... lovely woman and a great mother for our boys. Having our two boys, Daniel and Thomas, quite late in our lives was first a challenge and then a blessing. They are smart, creative, opinionated (I expect more Dr. in the family) funny, lovely to be around. I love you all very much.

Finally, I would like to thank all my undergraduate students and PhD students (past and current) who keep me alert every day, and of course… I would like to thank all of you who attended my inaugural lecture today and shared this special moment with me and my family.

Mr. Rector! Ik heb gezegd!

Enschede June 8, 2017
LITERATURE


