Tempo

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Inaugurele rede

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Tempo: Timing and Metamorphosis in Biofabrication

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Geachte Rector, Geachte leden van de Raad van Bestuur en van de Raad van Toezicht,

Dear colleagues and friends,

Time and Metamorphosis. Nature is plenty of processes where changes in time and space dictate functionality.

Although metamorphosis has been well known in literature by the celebre novel of Kafka as a dreadful event transforming a man into a worm, it is in the concept of nature transforming matter into a new form of life that I like to talk to you about time and metamorphosis today. One of the simplest examples of metamorphosis is the physical state change of water into ice, where in fact completely new properties are acquired by the same chemical compound. We are surrounded by metamorphic events. Think of a worm fabricating for itself a womb to become a butterfly, or our own life where we continuously go through phases, changes, and adaptations of our own self thanks to the experience we make and the environment we are surrounded. When looking at bigger time scales, our universe is again full of metamorphic examples. Let us consider supernovas; the energy produced from their explosion results in the production of elements that are what we have in nature today (including us). Or take a black-hole. Normally known as an event of death, in fact more and more studies indicate that through its gravitational forces, gases and matters are forced together to

implode. Today this implosion is hypothesized to form new stars and galaxies.

Time and Metamorphosis are intimately connected, not only in nature, but in many other disciplines. In art, metamorphosis has been central to a genial Dutch Artist, Maurits Escher, who was also one of the first examples of true internationality. Escher wisely fused metamorphosis with mathematics. With his engravings, Escher was also an inspirer of many other mathematicians, physicists, and crystallographers, among other scientists. Metamorphosis II is one such fine example where geometry and mathematical repetitions fuse together to generate different forms of lives, which again fuse with real life memories of his past time in Italy.

Although mostly allegorical, the work of Jeroen van Aken, commonly known as Hyeronymus Bosch, is somewhat metamorphic and yet timeless. Bosch had to bring in a lot of creativity to impart to the symbols in his painting their meaning. This was also possible thanks to the lack of schemes that he had to follow at that time. The garden of earthly delights is the climax of Bosch symbolism, almost hallucinogenic, where metamorphosis appears since the very beginning as the painting opens up from its close version representing the creation of the world to show the tryptic that depicts different phases of life. As we move from left to right in this tryptic. It is so that joyful elements of our life such as the heart and the light of a lantern are transformed to a terrible instrument of torture and a piece of furniture, as examples of the danger we may incur when falling into temptation.

Bosch was an inspirer of many artists after him: the Dutch Peter Breugel the Elder, as well as the Italian Giuseppe Arcimboldo with his

fantastic portraits where vegetables and men merge together. But it is the most eclectic Italian artist of those times, Leonardo da Vinci, who also worked a lot with changes in time and space. Both artist and scientist, the most arduous attempt to aim for metamorphosis is said to be present in his masterpiece “Monnalisa”, where rumours conjecture that Leonardo made a transfiguration of himself. Whereas, it is more common to learn about his attempts to approach the topic of metamorphosis in his studies of human anatomy with the famous Vitruvian man drawing, which then led to invent probably the very first form of “flight”.

Time and Metamorphosis are also central to men’s development as a human being. In this centrality, history plays an important role, as we develop through our experiences and make treasure of such experiences evolving into a new person. Remembering our past to influence our future is a very old tradition that dates back since the Romans who brought this concept to the extreme by deifying the spirits of their ancestors (Lares). Romans would often ask advice to their ancestors, in real life identified through little statues that were located in a sacred place in their homes, for their future actions. Lares, ancestors as called in Latin, would protect Romans in family business, in public activities, as well as during their travels.

So is for the collectivity of an organization. MERLN is a relatively new institute here at Maastricht University, which has deep roots in our past history. Looking at the roots of MERLN, therefore, I would like to bring you into a time ship journey back to the eighties. At that time, I was a kid romantically in love with astrophysics. I wanted to be an Astronaut. I realized soon enough that it would be too dreamy. I diverged into

medicine to become a physician, a cardiac surgeon like one of my closest uncles, and landed back on earth with biomedical engineering.

In the eighties, the roots of this group of scientists that today form MERLN were seeded in Leiden with one of the first group of Biomaterials formed in Europe from Klaas de Groot, Clemens van Blitterswijk, and Joost de Wijn. Clemens, Klaas, and Joost represent probably one of the very first examples in the world of the added value of interdisciplinary collaboration where a biologist, a material scientist, and a chemist join forces. Their synergy resulted in landmark developments: a first implant for middle-ear bone ossicle regeneration today replenished by scaffold-based and a scaffold-free biofabrication approaches, plasma coating technology today used in an uncountable amount of medical implants, and a new biodegradable material family facing again today a sort of renaissance.

Back to the future, I would like to offer my personal vision on what is needed to make the ultimate goal of biofabrication in regenerative medicine, which is the printing of organs, happening. If we really want to be successful in printing an organ and translate it to the clinics in 30 years from now, which would be a tremendous accomplishment from the scientific community as it would obviously decrease the organ transplantation waiting lists and the associated healthcare costs, we need to deepen our understanding of morphogenetic biological processes for a targeted organ. Some of us tend to believe that we would need to build a sort of cellular atlas. Whether this is really needed or a good understanding of human developmental biology would suffice is early to say. Such maturation of our biological understanding of the human body will have to be accompanied also by new technologies enabling higher degree of biomimicry. This hard-core

advance may also bring with it an ethical dilemma: will we be moving ultimately to even better than what nature does? Where is the limit? Will we be able to ultimately print a human being? What is the connection with religion? Even when this would be technologically possible one day, are we really going to do it? What about printing our soul? I feel too small to answer these questions alone, but certainly the community will have to think about these dilemmas. Concerted efforts from the community are also needed. The biofabrication community is one of the youngest, and in this respect synergies with other scientific communities like the European Society of Biomaterials or the Tissue Engineering and Regenerative Medicine International Society communities will be beneficial to seek for collaborations. We should work together in a cohesive manner to achieve this major milestone that is organ printing, respecting each other expertise, respecting each other initiatives, and building upon these for an achievement that will certainly live longer than our own egos and any possible scientific paper we may be able to write of it.

From Leiden to Bilthoven, this trio of formidable scientists founded one of the first Tissue Engineering companies worldwide, the largest in Europe, Isotis. Pamela and Jan became part of the team: Jan as a group leader building molecular biology expertise and Pamela focusing on her Ph.D. studies to understand the phenomena at the base of osteoinductive inorganic biomaterials. I joined such a stimulating environment as Ph. D. student in 2003 under the supervision of Clemens and Joost. This was not only the place where a number of today's MERLN group leaders were formed, but also where leaders of the Biofabrication community such as Jos Malda and Tim Woodfield obtained their Ph.D. As a Ph.D. student I could witness the creation of

several spin-off companies, some of which like Progentix and CellCotec became a solid reality, a unique experience for a young scientist which left an imprint for the years to come.

A bit less in the future. In the next 10-15 years, biofabrication technologies will create 3D *in vitro* models that can be used to study those morphogenetic processes so direly needed to be understood for organ printing. Not only, these models could also be used, and in fact are already used, as platforms for drug and other therapy screening. We are not flat. We should move away from 2D cultures, yet it is so difficult to do so. So, if it is true that these 3D *in vitro* models can help us understanding how tissues and organs grow and develop in time, if it is true that we are incredibly complex forms of life, we should also dare to start abandoning conventional and conservative approaches such as 2D cultures and move more and more towards 3D culture systems. Systems that we and others have already developed and started to use. Own examples consist of scaffolds used to study stem cell biology and biofabricated platform for neural biology. A collegial example that our lab contributed to revive consists in creating a human-on-a-bioreactor against the so popular today concept of human-on-chip, which should be able to capture the same functionalities of the latter without oversimplifying the complexity of our organism.

From Bilthoven to Enschede, where Joost and Klaas enjoy a well-deserved retirement. I learned a lot from Joost and Klaas. Science is passion, where you can combine past and new knowledge with fun. Science is rigorous and not a game. Yet, when combined with fun in doing it, you can really leave a significant contribution with your work to the society. A scientist can be kind and firm at the same time. When combined, kindness and firmness are the strongest virtue of a

professional. In Enschede the group is enriched by Roman and his expertise in microfabrication, which was fundamental to shape a new paradigm shift in biomaterials where screening platforms are central. His contribution helped forging new spin-off companies such as Materiomics and Screvo.

A further bit less into the future. In the next 5-10 years, to create 3D models that can be good approximation of *in vivo* scenarios, dynamic biomaterial platforms are needed. Here, I hope that the collaboration with Roman Truckenmueller on the technological side and with Matt Baker on the chemistry side will enable us to reach an exquisite control between synthetic and natural systems, where ultimately a library of smart biomaterials able to control a specific cellular function can be created and with a combinatorial approach we will be able to mimic all the functions that cells naturally perform. In doing so, we will also need to control that bioactivity is in balance with homeostasis, that is in maintaining our engineered biological system in equilibrium.

From Enschede to Maastricht. A logical move, where MU is at the center of an ecosystem bridging clinics and valorization together with MUMC+ and Brightlands. The essence of such an ecosystem is collaboration. MERLN was created also in this spirit, to merge our past collaboration network with new local and international parties.

Tomorrow Science is shaped by the science of today. The model of public-private partnerships has been a very successful one in the past few years, especially in the Netherlands. There will be still the need for public-private partnerships that are sustainable, where each party knows its role as in a clock mechanism and as a whole we can change tomorrow's healthcare. This is what made the additive manufacturing

biomedical program at Brightlands Materials Center possible, where together with other public and private partners we aim at understanding better the processes at the base of different additive manufacturing technologies and by doing so we will also be able to synthesize new bioactive materials for applications spanning from skeletal to heart and soft organ tissues. Similarly, at a European level the creation of a public-private partnership was essential in the success of FAST, where we want to develop new printing technologies for bone regeneration. And yet, we should not forget fundamental science, without which there will be no oil to the engine of public-private partnerships.

How can I engineer a biomaterial system that enables the regeneration of self-sustaining tissues? The answer lies in two key elements: 1) engineering materials that mimic the delivery in **space and time** of **biological and physical** signals to cells as it happens in our body at 2) **different scales**. Now, imagine for a second a situation where you have been in the right place at the wrong time or in the wrong place at the wrong time… You will agree with me that arriving at the airport when the flight just departed or receiving a parking ticket for parking your car in a no parking zone are good examples of these scenarios. Likewise, in our body signals need to be delivered at the correct space and time to be effectively received by the cells. If this doesn't occur, unhealthy phenomena can happen such as a healed bone that results in a non-functional limb or a cyst, which is a mass of cells in the wrong place and developing in a wrong time scale in our body.

As we run after the history of MERLN and my personal vision of the future of biofabrication for regenerative medicine, I allowed myself to make an experiment with you all, where I moved now back and forth in

time from past to future in reverse order. Summarizing the future of biofabrication, whereas we are able today to create small-scale tissues for regenerative medicine, drug discovery and toxicity testing, we should be able to translate to the clinics simple tissues for more complex implants in 4-5 years from now, to move to lobs or functional units of organs in 10-15 years from now, and to full organs in 20-30 year from now.

This is what I strive for my group to work on. Combining materials science, technology, and organ regeneration, we want to move away from the conventional dogma that all tissues are homogenous and replicate the actual heterogeneity and anisotropy of biological systems, considering them from a true biological system perspective, towards integrating the neurovascular tree with the immune system response and the lymphatic system. All elements that will improve 3D *in vitro* models, which will then contribute to reach the final goal of organ printing.

I would like to introduce **my group within MERLN.** As I often refer to them recently, inspired by a cover of Nature which recognized for the first time so clearly the need for interdisciplinarity, a group of superheroes. To them I say: play hard. Always keep listening to the kid in you, as Giovanni Pascoli, an Italian poet of the late 19th century used to say. Balance Eureka moments, with dreaming nature and critical view on data. Do not be overcome by the intrinsic scepticism of a scientist, otherwise you may run the risk to become too objective and lose the capacity of making new hypothesis and discoveries. Like Poincare' who solved one of his famous mathematical conjectures in a daydream moment; or Watson who discovered the DNA structure after formulating hypothesis of symmetry that seemed originally illogical. Or

again Paul Klee, who used to get inspiration from microscopy slides for his paintings. Intuitions are the essence of science. Like Archimedes who discovered the famous principle of buoyance bodies only after immerging himself into a bath. In pursuing your next discovery, do not be afraid to fail! Failed experiments are also quite revealing. Like Faraday, who was originally put off from Davy (his supervisor) to work on glass properties. He failed in his assignment, but kept a piece of glass, which became essential when he found the connection between electromagnetic fields and light waves. Light moving in air is not affected by magnets. Nor in liquids. Nor in gases, nor in many solids. Through glass it is. This observation led Faraday thereafter to formulate the existence of the interplay between relativity and electromagnetism, and the unity of electricity, magnetism, and light. To you, I ask to dream big, get things done, and have fun while doing science.

Today MERLN. I wish for MERLN that we keep pushing boundaries. Remember the past, to change the future. Like Janus the gate keepers of Romans, we should strive to be the gate keepers of science in regenerative medicine. Janus is also a symbol for a new beginning. Jan, I wish we discover together new biological pathways through screening platforms. Pamela, I wish we find new material properties by structuring inorganic and organic matters together. Roman, I wish we can build many more bottom-up approaches for regenerative medicine applications together. In doing so, I hope to find more and more collaborative ground with MERLN young faculty, to whom I take the freedom to give an advice based on my own sometimes restless past experience: balance ambitions with wisdom to know to wait the right time. In Italian we say “when you are young you like to grow up to feel

more freedom. Then you grow up, to find out that you will not have as much freedom as when you were young".

If Maastricht University (MU) is central for the ecosystem in the region formed together with MUMC+, other academic hospitals in the country, and the Brightlands campus, MU could also be considered as gatekeeper, as a Janus, of those collaborations needed to bring new therapies to the clinics through the market. Here I have found plenty of energetic collaborators. Together with them, I am sure that we will make new exciting clinical applications, but it is somebody from outside Maastricht University that I first would like to acknowledge: Joris Rotmans from Leiden University Medical Centrum. There are plenty of collaborators that a scientist finds along his path. Most of them come and go. A handful come and stay. Joris certainly belongs to the handful ones. Dear Joris, I wish we can keep working at the unison as we have been doing in the past 5 years. You made me re-discovering the power of our body response to biomaterials and with that, I hope that together we will be able to improve the life of dialytic patients first and who knows what does the future reserves more. At Maastricht University, I would like to acknowledge the collaboration with Pieter Emans and Chris Arts at the orthopaedic department, with whom we hope to bring scaffolds for osteochondral regeneration to the patients, Peter Kessler at the cranio-maxillofacial department, with whom we will work on 3D printing solutions for complex bone defects, Sandro Gelsomino at the cardiothoracic surgery department with whom we will explore treatments for infarcted patients, Jeroen Kooman at the general medicine department with whom we will move the first steps in the realm of organ bioprinting, Steven Olde Damink at the general medicine department with whom we are thinking of several solutions in

the gastroenterology system, and Rene van der Hulst at the plastic surgery department with whom we would like to explore solutions for breast regeneration after cancer resection.

Finally, I would like to thank Maastricht University for the continuous support and ask for a small thing. Simplify! Simplify procedures, simplify processes, and simplify implementation. MERLN is a continuously increasing community of highly ambitious scientists that come from the most disparate parts of the world. To make our contribution to science, we have left home, made of Maastricht our new home, yet without forgetting our families, friends, and traditions. We carry a load of motivation to have taken such a decision in our lives. It would be a tremendous shot of energy for us when the organization can steer this power into more efficient science. It will be a terrific shot of energy from us back to the organization to contribute to its growth.

Ik heb gezegd.

Prof. Dr. Ir. Lorenzo Moroni

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