

New biomaterials derived from poly(lactic acids) : novel approaches to combine biodegradation, x-ray contrast and controlled local drug release

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Valorization

Social and Economic Relevance of the Results

The radiopaque polymeric blends, derived from poly(lactic acid) (PLA) and described in **Chapters 2** and **3** of this thesis, are innovative and new materials. They were not described in the scientific or patent literature hitherto. The key hypothesis behind this research- and development work was that these blended materials would uniquely combine: (i) controlled bio-degradation; (ii) sufficient strength; (iii) radiopacity. It was anticipated that this combination of physical properties could provide the basis for the development of a new type of biodegradable endovascular stents. These, in turn, could potentially be developed further to become the next generation of the well-known biodegradable vascular stents.

The results, as described in **Chapters 2** and **3**, were in line with our hypothesis. The blends derived from poly(L-lactic acid) (Chapter 3) appeared suitable for the construction of endovascular stents. Most importantly, the feature of X-ray visibility will contribute to the safety and accuracy of endovascular stenting. Cardiologists are used to radiopaque stents (metallic stents can be monitored real time through X-ray fluoroscopy during the procedure). However, when using biodegradable stents, it is not possible to clearly visualize the stent: merely two metallic “contrast points” can be seen.

Although there is still a long way to go, the results of the thesis may provide the basis for this new generation of biodegradable stents. On the one hand it is well imaginable that this can lead to new innovative products and new industrial activity. On the other hand, the new biodegradable radiopaque stents have the potency of leading to improved clinical results, because stent placement can be monitored better than in case of classical biodegradable stents, and because the degradation can – in principle - be monitored non-invasively during a post-procedural X-ray investigation.

Chapters 4 and **5** describe, for the first time, microspheres composed of poly(D,L-lactic acid) (PDLLA), which are suitable for transarterial embolization therapy. The microspheres had an additional feature: they contain one or two drugs, and these drugs are released *in situ* in a concerted fashion controlled by structure of the microspheres and the breakdown of the polymer matrix. The drugs that

were studied were cisplatin (a well-known cytostatic drug) and sorafenib tosylate (a relatively new drug that inhibits angiogenesis).

It is clear that transarterial embolization will gain importance in oncology in the near future. Minimally invasive therapies will compete more and more with “classical” surgery. The research leading to **Chapters 4** and **5** was conducted on the basis of the hypothesis that drug-releasing embolic particles would be mandatory in order to enhance the efficacy of embolization therapies in oncology. Chapters 4 and 5 describe the manufacture of biodegradable embolic microspheres (consisting of PDLA as the polymer matrix), with either cisplatin or sorafenib tosylate embedded in them. In addition, PDLA microspheres containing both cisplatin and sorafenib tosylate were developed. Although there is still a long way to go, it is clear that these particles can be developed further into new and innovative medical device/drug combination products for cancer therapy. This concept may lay the basis for new economic activities and new job opportunities. It is widely agreed that in the near future numerous patients will benefit from the development of minimally invasive treatment modalities. This is particularly true for patients suffering from hepatocellular carcinoma, since transarterial chemoembolization is the most commonly offered therapy for these patients [1]. It must be noted that this is an emerging field of research and development. Globally, at least 20 research groups work on the development of embolization particles that release drugs *in situ*. However, the combination of cisplatin and sorafenib tosylate in one microsphere, as reported in this thesis, is unique, and can be potentially translated into new business and improved therapies.

Target Groups

The groups that may interest in or can benefit from the valorization of the results of this thesis include companies, patients and the healthcare system as a whole.

Companies

Companies in biomedical field could be interested in valorization of our results, since the impetus of the thesis directly comes from the limitations of some commercial products and thus have a high promise to be translated into medical products/devices. Research in **Chapters 2** and **3** provides a novel solution to the translucency issues of PLA-based stents currently available in the market, e.g.

ABSORB BVS (Abbott Vascular, Santa Clara, CA, USA) and DESolve (Elixir Medical, CA, USA). **Chapters 4 and 5** focus on biodegradable drug-loaded PDLLA microspheres. The impetus of these two chapters comes from: (i) concerns over non-degradable embolic microspheres for transarterial embolization, such as DC Bead® (Biocompatibles, Farnham, UK); (ii) local delivery of drug combinations (i.e. cisplatin and sorafenib tosylate). Valorization of these results may lead to new competitive products and economic benefits.

Patients

A great number of people nowadays suffer from coronary artery disease (CAD) and hepatocellular carcinoma. CAD is narrowing or blockage of coronary arteries preventing adequate blood supply to the heart, which can lead to angina, arrhythmia, heart failure and heart attack. CAD is one of the leading causes of death worldwide over the last decade. In 2013, CAD became the top cause of death, responsible for 16.8% (8.14 million) of all deaths worldwide [2]. In the light of these numbers, it can easily be appreciated that treatment of CAD is high on the agenda. Coronary angioplasty with a stent is one of the most commonly used interventional procedures to treat CAD. Hepatocellular carcinoma is the sixth most frequent cancer and the third top cause of cancer-related death globally [3]. Transarterial chemoembolization is the standard care of patients with hepatocellular carcinoma, in particular those at the intermediate stage [4]. The incidence and mortality rates of hepatocellular carcinoma have been reported to increase, primarily resulting from the rise in hepatitis C virus infections [5-6]. Valorization of our results may lead to new medical devices (radiopaque biodegradable stents and biodegradable microspheres for transarterial chemoembolization), which could be transformed into better therapeutic performance and finally benefit patients.

Healthcare System

Minimally invasive procedures such as stenting and transarterial chemoembolization are generally cheaper and faster than the corresponding surgical counterpart procedures (bypass surgery and surgical tumor resection). The choice between minimally invasive therapy or surgical intervention primarily depends on the patients' conditions. For patients with complex CAD (e.g. 3-vessel or left main coronary artery disease), bypass surgery is cost-effective. For patients

with less complex CAD (e.g. low SYNTAX scores for 3-vessel disease), coronary angioplasty with a stent is found to be attractive [7-8]. Transarterial chemoembolization is the recommended procedure to treat hepatocellular carcinoma for patients not amenable to curative therapies, i.e. tumor resection, ablation and liver transplantation [9]. Our results and the possible valorization of our results might contribute to the evolution of the safety and efficacy of these two minimally invasive procedures. More patients with CAD or hepatocellular carcinoma could become candidates to these less costly treatments with the advance in therapeutic technologies, which will benefit the whole healthcare system.

Products and Innovation

Valorization of the results of this thesis will lead to new innovative products, which are medical device/drug combinations. These are: biodegradable radiopaque endovascular stents, or biodegradable drug-releasing embolic microspheres.

The results of the thesis and the foreseen products are certainly innovative. With respect to the results of **Chapters 2 and 3**, this is clear from the fact that the blend materials introduce a new feature that is not encountered in any of the existing biodegradable PLA-based stents. This feature is X-ray visibility. Presently ABSORB BVS and DESolve are the only two CE mark approved PLA-based bioresorbable drug-eluting coronary stents available in the market. One important difference between these two stents and metal stents is that the struts of these PLA-based stents are translucent. As a result, two metal markers are incorporated at both ends of ABSORB BVS and DESolve. These metal markers allow interventionalists to navigate the stent, i.e. monitor the location of the stent by X-ray imaging and deploy the stents precisely. However, it is impossible to monitor expansion of the stent or detect fracture of the stent with these markers. Whole stent X-ray visibility may improve safety and accuracy of stent implantation.

The results as described in **Chapters 4 and 5** are innovative as well. The microspheres loaded with cisplatin and sorafenib tosylate reported here have not been described previously. Furthermore, the combination of cisplatin and sorafenib tosylate, showing high therapeutic efficacy in our *in vivo* experiments, could be considered as an example of “inventive step”. DC Bead® is the most widely used drug-eluting microsphere product in transarterial chemoembolization. Compared with DC Bead® composed of non-degradable poly(vinyl alcohol), one important feature of the foreseen product based on our results would be the

degradability. This feature could avoid the risk of late foreign-body reactions to non-degradable microspheres. In addition, the drug loading and releasing of DC Bead® depend on the binding between the drug and the poly(vinyl alcohol) matrix; drugs that lack binding will be released uncontrollably [10]. For the PDLLA microspheres we presented, drugs are physically incorporated inside the polymer matrix, i.e. the drug loading or release kinetics is not related to the binding between the drug and the polymer matrix. This indicates that more options of drug or drug combinations could be loaded to these PDLLA microspheres as compared to DC Bead®. Moreover, drug release of these PDLLA microspheres is determined by structure, as well as the degradation process of the microspheres, which could provide a fine-tuning of the drug release kinetics.

Market, Schedule and Implementation

The foreseen radiopaque PLA-based bioresorbable stents present a promising innovation with a large potential market. According to a report on coronary stents from Globaldata, the global stents market for CAD was \$4.89 billion in 2013 and is expected to increase to \$5.62 billion by 2020 [11]. The market growth is attributed to the rising prevalence of CAD due to aging of the population as well as to the epidemic of obesity and diabetes [12]. The stents currently used in clinic include bare metal stents, drug-eluting stents (DES) and bioresorbable stents. Lots of efforts have been devoted to the design of DES to improve their efficacy and safety over the last decade. DES have become the first choice in coronary angioplasty to treat CAD. In 2010, DES held 55% - 60% of the global coronary stents market and the share is expected to increase considering the high-adoption rate of DES [13]. In contrast to DES, the market of bioresorbable stents is still in its infancy. The small market share of bioresorbable stents is directly associated with their availability in the market. Abbott Vascular is the leader in the bioresorbable stent market. Their product, ABSORB BVS, leads the market and is authorized for sale in Europe, parts of Asia Pacific and Latin America. ABSORB BVS is still not approved for sale in some countries that hold large stent market, e.g. the USA, Japan and China. In the USA, ABSORB BVS is a device still under investigation and will probably be the first bioresorbable stent approved in the near future. Meanwhile, in countries where bioresorbable stents are approved for sale, these stents still have not received as high acceptance as DES in clinical practice. The reason for this is the limited knowledge regarding the very long-term results for bioresorbable stents as compared to DES. Several clinical trials and registries

currently running for further evaluating the safety and efficacy of bioresorbable stents [14] will help to achieve high-adoption of bioresorbable stents in the future.

Unlike biodegradable stents, we must admit that the foreseen embolic biodegradable drug-eluting microspheres do not have a really large market, which is also the case for the commercial drug-eluting beads, e.g. DC Bead®. The reason for this is the limited number of patients suitable for transarterial embolization. Although hepatocellular carcinoma is the sixth most frequent cancer worldwide, only less than 15% of the patients are ideal candidates for transarterial embolization [15].

The pathways to commercialization and clinical use of any of the foreseen products as described above will typically last several years at least or even decades. This is especially true since the anticipated products are medical device/drug combinations, which implies that there will be numerous strict regulatory requirements to be met on the route to CE certification. The most straightforward way to accomplish the development of such products is to establish one or more high-tech companies with a specific mission to translate the current findings into one or more products. Financing of such an endeavor will be critical and risky, since this is a highly competitive research & development area. In addition, there are already products that dominate the market, such as ABSORB BVS and DC Bead®. Nevertheless, there are huge potential benefits, since the foreseen products, emerging from this thesis research could provide ample opportunities for new business and improved therapeutic techniques.

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