Appendix 4

Valorization addendum & patent.
1. VALORIZATION
Novelty and non-obviousness are most important aspects for an idea that may have potential commercial application. Subsequently, non-disclosure is a major factor, as disclosure voids the idea of novelty. Hence, an enthusiastic scientist that shares his novel ideas at a scientific conference may subsequently encounter problems obtaining patent/intellectual property (IP) protection at a later stage. The United States Patent and Trademark Office (USPTO) has clear guidelines on what is novel and non-obvious, and will thoroughly investigate every invention for patentability (1).

The emphasis on valorization is perceived by some to be associated with adverse impact on the research environment, creating "science hypes, premature implementation or translation of research results, loss of public trust in the university research enterprise, research policy conflicts and confusion and damage to the long-term contributions of university research" (2). On the other hand, the individual career and/or financial rewards for spending the better part of one's productive (often frugal!) years in the laboratory can be a welcome addition to the scientific and intellectual prestige.

Recently, there has been some controversy surrounding the patentability of stem cells (3). In line with the decision of unpatentability of natural genes such as in the BRCA1 case (4), naturally occurring stem cells that are isolated from an organism would not be patentable. However, synthetic stem cells would be patentable, under the same law.

Shinya Yamanaka, a former surgeon and the recipient of the 2012 Nobel Prize in Physiology or Medicine is a proponent of stem cell patentability. Since his discovery of iPS cells, he has claimed that "private sector support is indispensable when it comes to translating our research results into effective treatments or drugs and delivering them to the broader population" (5). Despite the existing legal precedents, the discussion on patentability of biological molecules, cells and tissue is far from over.

Some of the work in the present thesis was submitted and approved for a provisional patent application with the help of Columbia University Science and Technology Ventures and the law office of Wai-Kit Chan, in New York (6). This work was mainly based on the development of purification and modification of alginate with the synthetic RGDfK peptide for the generation of biocompatible 3D scaffolds (7-10). However, since the cell type that is used within the alginate matrix could be of paramount importance to the eventual effect on disease parameters (i.e. cardiac function after MI), some of the content in this chapter will be dedicated to the use and modification of specific stem cell populations. As mentioned before, it is currently not possible to patent isolated stem cells, however it is possible to generate artificial cells that are protected by intellectual property laws, as is also illustrated in the proposition #5 of this thesis that quotes Nobel laureate Shinya Yamanaka.

Patents are deemed useful to protect discoveries that are commercially interesting and seem to serve a commercial interest only. Acknowledging that clinically applicable discoveries typically require costly research and testing, it can easily be seen that protection of those discoveries will serve as an incentive to engage in the entire process. The downside of that protection is that initial products will be far more expensive than dictated by their manufacturing costs alone and will therefore be not only available to those (people, nations) who can afford them. This effect is somewhat mitigated by the limited lifetime of a patent. With this perspective, it can be questioned if inventions made with the help of public funding should be patented.

2. SOCIOECONOMIC RELEVANCE
2.1. RELEVANCE OF VALORIZATION FOR BIOMATERIALS IN HF AND IDDM
The growing shortage of organ donors in ageing societies poses a major problem for people with end-stage heart failure, insulin dependent diabetes mellitus, and kidney failure requiring dialysis (mean survival rate from start of dialysis is 3-5 years). Novel approaches need to be explored and cell therapy and tissue engineering potentially add to or constitute these novel approaches. The development of an affordable biocompatible 3D scaffold that could be used off-the-shelf, i.e. ready made without extensive manipulation before implantation, poses an attractive alternative option. A 3D scaffold would also be much less costly, both monetarily and physically, than an organ transplant procedure with all potential complications (surgery, immunosuppression) involved. Of course, an optimal base material needs to be identified and this base material needs to be safe and well tolerated by potential patients. We systematically approached the issues of biocompatibility (i.e. material implantation without cells) and suitability for cell transplantation within an optimal product.

For heart disease, 3D "scaffolds" are clinically used in the form of bioabsorbable vascular 3D PGA tubes, known as stents (11). While not a regenerative medicine approach per se, the materials used for such 3D scaffolds hold promise in other applications such as a (cardiac) muscle regeneration setting. Recently, a scaffold free approach was used in a small clinical trial with cell sheets for cardiomyopathy (12). This approach based on PNlPAAM dissolvable biomaterial seems to be safe, though the actual material in this setting is merely used to facilitate the generation of cell sheets ex vivo and is completely removed before implantation. Instead of a scaffold free approach, a cell free approach developed by the Swiss/Dutch company Xeltis was recently shown for an artificial heart valve, based on a fibrous valvular scaffold, fabricated from a novel supramolecular elastomer,
that enables endogenous cells to enter and produce matrix in vivo (13). The laboratory of Smadar Cohen and her company BioLineRx has developed a soluble alginate scaffold (BL-1040) that was applied in a phase I/II trial and infused in coronary arteries after myocardial infarction (clinical trial identifier NCT00557531).

For IDDM, the biotechnology company ViaCyte has developed a macroencapsulation device (i.e. pouch) that contains ESC derived insulin producing cells (14), which is also used in clinical trials (clinical trial identifier NCT02939118). The device is still in its early development phase but holds promise as a viable approach for the treatment of IDDD.

2.2. RELEVANCE OF VALORIZATION FOR MODIFIED (STEM) CELLS

As with biomaterials, modified (stem) cells that could be used to replace damaged tissues take a long time to test and develop. Bone marrow transplantation (BMT) is such a therapy, but since bone marrow is a natural product, it is not patentable. Whether this is important is another question, since BMT has been a treatment of choice for the treatment of bone marrow malignancies for several decades. Hence non-patentability may even be desirable when it comes to patient’s wellbeing. On the other hand, patents typically expire within 15 years of filing (including R&D time), making the described and protected technology eventually subject to competition by other producers, presumably leading to price reduction.

Exceptions to such rules are known for certain biological drugs as Humira (adalimumab) and Enbrel (etanercept), both TNFα inhibitors against rheumatic diseases. While Humira went to market in 2003 and hence the patent is about to expire, subtle changes in their formulation have stretched its patent life to more than 20 years (15, 16).

A biomaterial may be patentable as a novel device if loaded with specific (stem) cells for a specific application. Newer developments such as CAR-T cells, which have modified chimeric T-cell receptors that may be artificially designed against a specific target (i.e. a specific cancer cell) may be patentable, though there is still debate in courts about this.

A genetic modification technique such as CRISPR/Cas9 which can cut and paste specific genetic sequences in mammalian (stem) cells is another technique that is now planned for use in clinical trial development. The question remains whether one could patent the sequence that is able to modify the DNA, or the resulting modified cell.

3. TARGET GROUPS

3.1. TARGET GROUPS FOR BIOMATERIALS

Sodium alginate has been studied in the clinical setting for HF (17) (clinical trial identifier NCT01226563) and IDDM (18) (clinical trial identifier NCT00940173), as described in Chapter 8 (Section 8, Target Patients) of this thesis. RGD modified alginate such as used in this thesis is further being evaluated in preclinical models, however RGD modified alginate has not yet been tested in clinical trials. Implantation or infusion of such modified alginate may pose some specific hurdles, since modification is done using chemical cross-linkers which could also cause cross-linking of proteins after implantation in vivo, hence there is a need for their sufficient removal from modified scaffolds.

It is not yet clear whether RGD-modified alginate is safe for intracorporal implantation. One approach to overcome this could be to start with the evaluation of RGD-modified alginate in (diabetic) skin wound healing trials; in order to evaluate the pro-angiogenic properties while obviating the need for explantation in case of a foreign body reaction (FBR).

Apart from suitable target patients such as in HF or IDDM, the methods described in the patent application could be relevant to a number of other applications. They include the use of sodium alginate for wound dressing, dentistry and the food industry, which uses sodium alginate as a beer foam stabilizer, as well as a growth substrate for edible muscle fibers (i.e. cultured meat). Biomaterials companies could employ the conditions used in the purification process to purify their biomaterial of choice while significantly reducing the amount of waste generated. The method used for scaffold generation, i.e. freeze gelation, would also be applicable to other biomaterials in order to create highly porous scaffolds designed for varying uses such as sponges or other fluid absorbing materials. In medicine and surgery, alternative implantation sites and disease applications could lead to new approaches in transplantation and regenerative medicine. Hence, off-label use would be possible with a wide range of applications, from wound dressing to food and beverage technologies.

3.2. TARGET GROUPS FOR MODIFIED (STEM) CELLS

In order to replace damaged tissue, modified cells could be employed to enhance their function. For example, mesenchymal stem cells modified with the pro-survival protein AKT could be used in hypoxia driven diseases such as MI. Other cell types could be modified using the same technique, for example cardiac muscle cells. Enhanced survival could lead to enhanced efficacy, however AKT only protects against certain types of cell death, implying that other modifications need to be employed for an optimal product. The optimal combination would need to be determined based on the disease. So, for hypoxic diseases, cells could be rendered less sensitive to hypoxia, while for genetic diseases, the gene of interest would need to be added to the cells to be used in order to replace cells containing loss-of-function gene mutations, for example in sickle-cell anemia.

4. ACTIVITIES/PRODUCTS
Appendix 4 - Valorization addendum & patent.

4.1. ACTIVITIES/PRODUCTS FOR BIOMATERIALS/SODIUM ALGINATE

Alginate is mostly produced in Europe and Asia Pacific (i.e., East Asia, South Asia, Southeast Asia, and Oceania) which therefore have the largest market share in volume. In terms of value however, it is expected that Europe and North America will comprise the most lucrative market in the near future because of high value alginate derivatives.

The market for alginates & derivatives is projected to reach a value of $409.2 million by 2019 growing at a CAGR of 3.8% from 2014 to 2019. Trends such as increasing demand for natural ingredients, clean-label products, and products that boost health and wellness are driving the global alginates & derivatives market. The prevalence of inferior grade alginates extracted from different species of brown algae is one of the major challenges alginate suppliers face. The global wound healing market is estimated at $15 billion annually, and alginates & derivatives market. The prevalence of inferior grade alginates extracted from different species of brown algae is one of the major challenges alginate suppliers face. The global wound healing market is estimated at $15 billion annually, and mostly consists of wound dressings and gauzes (19). Alginate holds about 4% of this market, i.e. $600 million (Figure 1).

4.2. ACTIVITIES/PRODUCTS FOR MODIFIED (STEM) CELLS

In the global stem cells market a sizeable proportion of companies are trying to garner investments from organizations based overseas. This is one of the strategies leveraged by them to grow their market share. Further, they are also establishing partnerships with pharmaceutical organizations to potentially increase revenues, since large pharmaceutical companies have resources that allow them to conduct large scale clinical trials using novel therapeutics. The global market for stem cells is expected to register a CAGR of 13.8% during the period from 2017 to 2025 growing to a value of $271bn by 2025. Depending upon the type of products, the global stem cell market can be divided into adult stem cells, human embryonic stem cells, induced pluripotent stem cells, etc. Of these, the segment of adult stem cells accounts for a leading share in the market. This is related to their ease of controllable expansion, their presumed safety and specific characteristics such as immunomodulation in the case of mesenchymal stem/stromal cells (MSCs) (20). At present, North America dominates the market because of the substantial investments in the field leading to technical progress, wealth, willingness to pay for medical innovations and rising instances of target chronic diseases. As per the TMR report, the market in North America will likely retain its dominant share in the near future to become worth $167bn by 2025.

For HF and IDDM specifically, the clinical stem cell market is limited to experimental research and development phases. While this stimulates economic activity and revenues in the first place, actual reimbursable therapies have to be developed. Most therapeutic stem cell based revenues are made in the bone regeneration field, where approved products are estimated at a value of $600m.

5. INNOVATIONS

5.1. INNOVATIONS FOR BIOMATERIALS/SODIUM ALGINATE

New biomaterials are constantly being developed and optimized for novel clinical applications. Think of coated coronary artery stents with anti-proliferative agents such as rapamycin, to new alloys for hip-or other skeletal replacement/support therapies. For alginate specifically, purification is important, as we have shown in this thesis. Also, alginate modification with biological molecules can be ultimately limitless, as new peptides and/or proteins that can be covalently attached to alginate are continuously being discovered and characterized. Since alginate can be covalently modified using peptides or proteins, it is possible to add specific characteristics to alginate, such as pro-adhesion, pro-survival, or anti-immunogenic. Our patent already describes an improved alginate purification protocol that renders alginate less immunogenic, and the attachment of an adhesion peptide (cyclic RGDfK) that enhances its prosurvival signaling capabilities (6-8, 10).

5.2. INNOVATIONS FOR PRIMARY OR MODIFIED (STEM) CELLS

Similar to novel biomaterials, new (stem) cell types with potential clinical applications continue to be identified and described. The latest clinically applicable cell therapy is probably CAR-T, i.e. T-cells with modified T-cell receptors against specific targets. In this thesis, we also describe the expansion of rare, regulatively CD34+ T-cell types (T_{reg}) (Appendix 3), which have immunosuppressive and transplant tolerance-inducing capacity. Optimization of such expansion methods/protocols that make them suitable for clinical application is another highly important hurdle that needs to be addressed. In our case, we used a genetically modified murine cell-line that stimulates T_{reg}-cells to proliferate. For clinical application, it would be more useful to use a cell-free stimulation system such as modified microbeads. Such systems need to be further optimized for clinical application. We have further described the use of specific cell-surface markers such as CXCR4, the receptor for SDF-1, to redirect CD34+ stem cells to damaged tissues. These receptor modulations may be patented separately for additional indications, as was done by one of the author’s previous principle investigators (21).
Figure 1. Over the 2017 to 2026 period, the compound annual growth rate for the entire wound management market will approach 6%, a respectable rate of growth for an established market, though not quite high enough to encourage investment in the market as a whole. Of course, the total wound market is comprised of a number of very large, slow-growing segments, like traditional adhesive dressings, gauze dressings, and non-adherent dressings, which have annual sales at $3.8 billion, $3.2 billion, and $1.3 billion, respectively (19).

6. PLANNING/REALIZATION

6.1 PLANNING/REALIZATION OF BIOMATERIALS/ SODIUM ALGINATE

In order to bring the sodium alginate technology that was patented in this thesis to market, several steps need to be taken. First, the cost of purification is briefly addressed in chapter 2. We estimate an additional $1500/patient for the production of a purified alginate scaffold for any indication. As a comparison, a drug eluting coronary artery stent can cost around $1500 per patient, depending on a country’s health care and insurance systems. The scaffold price excludes potential cells being prepared to be seeded in or on the scaffold. In addition, alginate has to be prepared in a Good Manufacturing Practice (GMP) environment, which could add to the overall costs, though mass production could significantly lower such expenses. FDA/EMEA would need to be involved, and the design of clinical trials to test a potential product can cost up to US$100m (around $60m for HF or IDDM) (Figure 2) (22). Then there is the chemical modification of sodium alginate and other biomaterials, which would add another level of complexity. Authorities have specific guidelines for purity, immunogenicity and other characteristics for biomaterial trials. While intracoronary infusion of calcium alginate matrix has been studied in congestive heart failure (clinical trial identifier NCT01226563), covalently peptide modified alginate has thus far not been evaluated in clinical trials to our knowledge.

In order to address the use of potentially toxic cross-linkers for the fabrication of RGDfK alginate, it is noted that other cross-linked materials are being evaluated in clinical trials, such as an osteoinductive composite called Smartbone consisting of bovine bone matrix, biodegradable polymers and cell nutrients (clinical trial identifier NCT03462823) for anterior cruciate ligament tears, or the Integra bilayer matrix wound dressing, comprised of a porous matrix of cross-linked bovine collagen and glycosaminoglycan and a semipermeable polysiloxane layer for diabetic foot ulcers (clinical trial identifier NCT03476876).

6.2. PLANNING/REALIZATION OF MODIFIED (STEM) CELLS

Some of the techniques and cells that are described in this thesis are patented by other investigators, for example Mesoblast Ltd. holds patents on human mesenchymal precursor cell (hMPC) technology. Planning and bringing human stem cell therapy to clinic is a multi-decade process, apart from making it profitable. For cell therapy, there are specific guidelines also that need to be followed, both by the FDA and EMEA. The FDA has recently cracked down on “unscrupulous clinics” selling “so-called cures.” The FDA seized materials from one clinic in California, and sent a warning letter to another in Florida (23). The costs involved in culturing and maintaining (stem) cell populations can rise quickly, and efficacy is not always guaranteed (24). In addition, there are challenges lie in the determination of quality and safety. Combining cells with biomaterial scaffolds would create additional challenges. Safety and efficacy testing need to have clearly defined end-points.
Figure 2. Total per-study costs (in $ millions), by clinical trial phase and therapeutic area. As can be observed, Phase 2 costs are lower than Phase 3 costs for all but three therapeutic areas: gastrointestinal, hematology, and immunomodulation. This somewhat counterintuitive relationship is due to a variety of factors, including higher data collection costs, administrative staff costs, and site recruitment costs in Phase 2 than in Phase 3 for these therapeutic areas (22).

7. FINAL WORDS

Some of the procedures described in this thesis are potentially protected by a provisional patent application. However, the EPO ruled against some parts of the patent due to prior art/lack of novelty. When bringing this technology to market, several challenges lie ahead. Valorization may therefore be risky, however the process of setting up a biotechnology start-up firm based on sound science with or even without intellectual property protection is an invaluable addition to any scientist’s experience. As of November 2018, a business plan based on the findings in this thesis is in preparation.

8. REFERENCES

6. S. Yamanaka, Using patents to ensure access to pioneering cell technology. WIPO Magazine 4, (August, 2015).


