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Internship Report
Massachusetts Institute of Technology
David H. Koch Institute for Integrative Cancer Research
Laboratory of Prof. Michael J. Cima
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Abstract

My internship at the Massachusetts Institute of Technology (MIT) in Cambridge/USA was mainly funded by a generous grant from the Austrian Marshall Plan Foundation/ Vienna. The grant was a central requirement for acceptance at the David Koch Institute at MIT for a three-month internship in the field of biomedical engineering at Professors Michael J. Cima's laboratory and I was allowed to work there from the 1st of July to the 30th of September 2011. My supervisor was Miss "Maple" Hongye Ye, a young and dedicated scientist from Singapore. Her research work concerns the field of drug delivery. One of her projects deals with the development of a small device for implantations into the intraperitoneal cavity for ovarian cancer therapy. Another one of her projects revolves around designing a pretzel shaped device, which is intravesical and is instilled into the bladder. It is designed to remain there for a pre-determined period of time delivering the determined dose of the drug throughout. This method is applied to conditions such as overactive bladder, interstitial cystitis/ painful bladder syndrome and bladder cancer.

During my internship my task was to help Miss Ye conduct these projects. I helped with the optimization of the devices in terms of drug delivery rate and surface functionalization, the implantations and instillations of the devices and the taking of controlling images of the tumor size status. I also undertook a mini project in which I was responsible for degradation of a particular material and testing the properties for material optimization and surface functionalization. This was a project, which was set for one month but will be continuing in the coming months.

For a big part of my stay I had to take obligatory laboratory orientations and safety instructions of the Bio safety Level 1 (BL1) and Bio safety Level 2 (BL2) area. For the treatment of animals, I had to attend mandatory courses where I learnt aspects that can compromise pathologies and where I also learnt how to handle animals properly. I was introduced to the animal facilities and containment areas. I also got special training for animal survival surgery, which allowed me to help Miss Ye with her implantations and surgeries.

Introduction

The Massachusetts Institute of Technology (MIT) is a private research university located in Cambridge, Massachusetts, near to Boston and the university celebrates its 150th anniversary this year. MIT has five schools and one college, containing a total of 32 academic departments, with a strong emphasis on scientific and technological research.

MIT enrolled over 4 000 undergraduates and more than 6 000 graduate students for 2010–2011.¹ This outstanding university has produced 77 Nobel Laureates as well as numerous recipients of the highest national and international scientific awards.² A strong entrepreneurial culture and generous financial resources are evident everywhere and differ from the more modest financial budgets of our universities in Austria. These might be some reasons why MIT is consistently ranked among the best 5 universities of the world. The US News and World Report, the Ranking-Platform der Schweizer Universitäten³ the ARWU – Shanghai Ranking and the QS World University Rankings⁴ confirm the top position of MIT, which is mostly in first, second, or third place in the list depending on the criteria applied. The undergraduate engineering and doctoral programs are in the leading position, and the undergraduate business program is No. 2.⁵

The Koch Institute for Integrative Cancer Research was launched in 2007 and is a disease-focused research institution fighting against cancer. One of the key strengths of this department is its interdisciplinary approach, which gives its research insights from a broad range of different subjects.

It includes 40 laboratories in five main groups with focus on the following areas of research:

- developing nanotechnology-based cancer therapeutics,
- creating novel devices for cancer detection and monitoring,
- exploring the molecular and cellular basis of metastasis,
- advancing personalized medicine through analysis of cancer pathways and drug resistance and
- engineering the immune system to fight cancer.

In each of them there are cross-disciplinary teams of faculty members and a close relationship with hospitals and industry are maintained.⁶

The Koch Institute brings together scientists from related fields such as medical science, chemistry, engineering, materials and computer science. The majority of the Koch Institute's workforce are international postgraduate students, PhD-students and researchers in post-

doctoral positions. MIT has an Undergraduate Research Partnership Program and supports research partnership between MIT undergraduate students and its faculty.

The Laboratory of Professor Michael J. Cima develops materials and engineered systems focused on diagnostics and treatments for cancer, metabolic diseases and urological disorders.

Dr Michael J. Cima is a professor of Materials Science and Engineering at MIT. He got elected as a full professor at MIT in 1995. He now holds the David H. Koch Chair of Engineering at MIT and is author and co-author of over 200 peer reviewed scientific publications, holds 37 US patents and is a recognized expert in the field of materials processing. He was appointed faculty director of the Lemelson-MIT Program in 2009, which is a program designed to inspire young people to be inventive across the United States.⁷

Professor Cima's lab is creating tiny nanosensors that are chemically sensitive to different molecules. These sensors can hopefully be used to help determine proper dosage for chemotherapy. In order to create these tiny devices Professor Cima brought together scientists from different disciplines such as chemical engineers, electrical engineers or engineers of material sciences as well as medical doctors. Many of the scientists are engaged in doctoral or postdoctoral research. The interdisciplinary lab is highly multicultural. Most of the scientists come from Asia and the United States. Asian countries like Singapore, China, Pakistan, Philippines, Iran, Russia or Indonesia are represented by numerous members of the staff. Other students come from Columbia and Cyprus. Only two of the 15 students were born and raised in the United States. But all of the PhD's and Post-Docs have already attended undergraduate schools in the United States. Most of these students studied material science, mechanical engineering, biomedical engineering or electrical engineering.

Professor Cima himself is a chemical engineer. For a long time he focused upon material optimization and at that time he was mostly working with ceramics. Five years ago he changed to biomedical engineering, and he has since enjoyed a lot of success in this field.

One important research field of the Cima laboratory is advancing the field of implantable miniature devices for cancer monitoring and detection and creating novel drug delivery systems based on treatments that were in clinical use by 2003.

1. Different Drug Delivery Devices

An article by Moses, Brem and Langer in the online journal Cell discussed a number of drug delivery systems such as controlled delivery of cancer therapeutics, local chemotherapy, polymer drug conjugates, liposomal systems and transdermal drug delivery patches that were in broad clinical use in 2003.⁸ The results of their investigation into novel drug delivery systems aiming at cancer therapeutics show that they have several advantages compared to older chemotherapeutic methods. They show that the common method of intravenous administration of anticancer drugs will penetrate most tissues with no specificity in relation to the actual tumor. The controlled local delivery, however, reduces side effects and aids pain management of cancer progression and chemotherapy. It is possible that even cancer prevention may be possible. Table 1 offers examples of drug delivery systems approved and in clinical use. (⁸ p.339))

| Delivery name | Drug | Type of system | Cancer treatment |
|------------------------|----------------|--------------------------------|--|
| Zoladex | LHRH analog | Injectable polymer rod | Advanced prostate cancer |
| Lypron depot | LHRH analog | Injectable polymer microsphere | Advanced prostate cancer |
| Decapeptyl | LHRH analog | Injectable polymere Microphere | Advanced prostate cancer |
| Gliadel | BCNU | Implantable wafer | Malignant gliomas |
| Doxil | Doxorubicin | Liposome | Ovarian cancer, AIDS-related Kaposi's sarcoma |
| AmBisome | Amphotericin | Liposome | Fungal Infections for patients undergoing chemotherapy |
| Daunoxome | Daunorubicin | Liposome | AIDS-related Kaposi's |
| Zinostatin (stimalmer) | SMANCS | Polymer drug | Hepatocellular carcinoma |
| Oncaspar | L-Asparaginase | PEGylated drug | Acute lymphoblastic |

| | | | |
|-------------|----------------------|------------------------------------|---|
| | | | leukemia |
| PEG instron | α -Interferon | PEGylated drug | Various cancers |
| Neulasta | G-CSF | PEGylated drug | Prevention of neutropenia associated with cancer chemotherapy |
| Durogesic | Fentanyl | Transdermal patch | Pain management |
| Habitrol | Nicotine | Transdermal patch | Smoking cessation – cancer prevention |
| Nicotrol | Nicotine | Transdermal patch | Smoking cessation – cancer prevention |
| Nicoderm | Nicotine | Transdermal patch | Smoking cessation – cancer prevention |
| Prostep | Nicotine | Transdermal patch | Smoking cessation – cancer prevention |
| Depocyt | Cytosine arabinocide | Lipid depot in cerebrospinal fluid | Carcinomatous meningitis |

1.1. Controlled Delivery of Novel Cancer Therapeutics

Historically, one central research problem faced by scientists conducting cancer research is the fact that large molecules, mostly consisting of peptides and polypeptides, aren't able to diffuse through the materials of drug delivery systems. This has led to research that finally discovered that it was possible to physically embed the molecules in polymers. They provide a network of interconnecting pores whose size can be regulated and the drug can diffuse with the adequate rate and duration of drug release depending on the material composition. The materials used for the devices changed from non-degradable polymers like ethylene-vinyl acetate copolymer to degradable polymers like lactic-glycolic acid copolymers, which made the releasing of leuprolide acetate for the treatment of advanced prostate cancer possible. The concept of embedded molecules diffusing through the pores and material degradation has led to the first injectable delivery systems, which have been successfully used by hundreds of thousands of patients. The lifetime of drugs can be extended by the chemical binding of drugs to water-soluble polymers (⁸ p. 337).

1.2. Local Chemotherapy

Local chemotherapy has the advantage of targeting the cancer directly, which reduces systemic burdens and other harmful side effects. The toxicity of cancer drug is very high but now the drug concentration can be reduced because the drug can be delivered directly to the tumor and is therefore more effective. Polyanhydrides in the shape of wafers are placed at the surface of the brain after the removal of a brain tumor to locally deliver chemotherapeutic drugs like BCNU in order to remove any remaining tumor tissues. See Figure 1 (⁸ p.338).

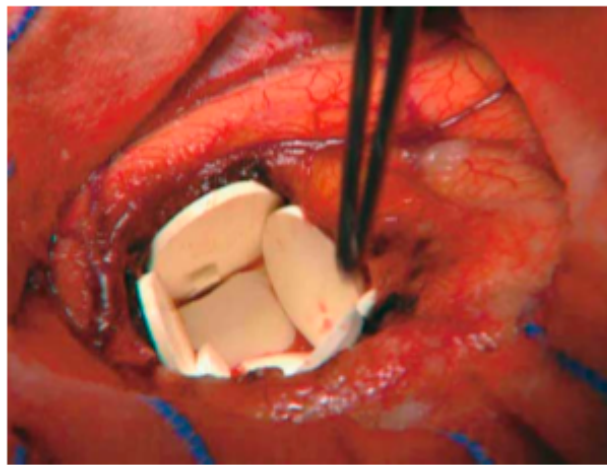


Figure 1: Polymer implants impregnated with BCNU are shown lining a Human brain tumor resection cavity where the loaded drug will gradually be released as polymer wafers dissolve (⁸ p.338)

Since the drug is released locally and in a short amount of time (within 3 weeks) the survival rate is 5 times higher (31%) than with traditional treatment methods. This approach was approved in 1996 by the U.S. Food and Drug Administration for patients with recurrent glioblastoma.

1.3. Targeted Delivery and Altering Pharmacokinetics

One method is to combine small molecular drugs used for chemotherapy to polymers, which have the effect of altering the biodistribution of the drug following intravenous administration. Normally the drug quickly passes through cell membranes and distributes

throughout the body's system with no selectivity towards the tumor. The polymer drug, however, can last longer in the bloodstream than the pure drug because of designed linkages, which are necessary as the drug can only gain access into the cell through endocytosis.

Another method is to encapsulate the drug into liposomes, which then in the bloodstream effuse through diffusion through the liposomes or degradation of the liposomes. The big advantages of the encapsulation of the drug into liposomes are lower cardiac toxicity and high drug carrying capacity (⁸ p.338).

1.4. Transdermal Delivery

Polymers in the shape of patches let the drug diffuse through the material and the skin layer into the body's system. Especially in the field of smoking prevention the transdermal patch has achieved some great results. Four times as many people quit smoking when using the patches compared to people getting a placebo treatment. These patches combined with opioids are used as analgetics which can work for up to three years.

1.5. Targeting the Tumor Vasculature

Cancer therapies that focus on suppression of the vasculature represent an important opportunity for drug delivery. Proteins like endostatin, angiostatin and troponin that are different endogenous inhibitors require different drug delivery approaches than smaller, synthetic drug preparations. For example endostatin was very successfully applied in the case of pancreatic cancer compared to bolus administration and this led to the use of osmotic pumps. The vasculature of tumors with their increased permeability has been exploited to deliver tumor suppressing drugs. Due to the toxicity of many drugs they might be ineffective when administered at high doses systematically but effective when sustained-release polymers delivery is applied.

The vasculature of tumors has an increased permeability which supports the delivery of tumor suppressing drugs. The goal is concentrating the drug in the tumor vessel by manipulation of the physiochemical properties of liposomes (⁸ p.340).

2. The Cima Laboratory

Over the last few years research has focused upon new therapies for cancer with improved chemotherapeutic agents. The development of improved methods of drug delivery for chemotherapeutic agents are an essential part of the fight against a broad spectrum of different cancers.

2.1. The Next Generation of Drug-Delivery Microdevices⁹

The field of drug delivery devices has gone further into the field of nano and micro devices in order to be able to release drugs more accurately and precisely. The surgically invasion can be kept to a minimum reducing potential infections and pain. These devices are intended to be applied in cases of acute and chronic illness. The generation of drug delivery devices can be divided into two groups: passive and active micro devices.

2.1.1. Passive Devices

Passive devices consist of a membrane (poly(lactide)-co-glycolide) covering the holes of a single or multi-reservoir made of PLLA (poly(L-lactic acid)). The membrane is gradually degrading because of the reaction between the material and the body's environment. The slow release of the drug through the membrane takes place when water enters the polymer, swells and then hydrolysis occurs. The drug release ends before the polymer totally reacts with the body's environment but is limited for long term treatments where the dose doesn't have to be controlled and feedback is not necessary. The reservoir based microdevices also have a problem with high dose-compounds capabilities, since the space for the chemotherapeutic drug is limited. On the other hand it has quite big dimensions. The production of the device takes a long time and is sensitive to human mistakes during construction.

Another type of passive device is the polymer wafer device which releases the chemotherapeutic drug carmustine (BCNU), which applied in the case of brain tumors. The dimensions of this passive drug delivery device are also quite big but the drug concentration is limited as in the case of the reservoir-based device.

A new device made of liquid crystal polymer and PLLA via the injection molding process seems to be the answer to the problems concerning the big dimensions of the device and the payload, shown in Figure 2. Liquid crystals are not biodegradable but biocompatible, so that the material shouldn't affect the body's system. In this device the hole in the cap (150-180 μm) is sealed with a membrane of poly(lactide)-co-glycolide. The release rate is controlled by the size of the hole and the molecular weight of the membrane. The inner volume of the device now measures 15 μl , which is bigger than the reservoir-based device made out of PLLA and the polymer wafer. Since the size now is around 3 mm this device is a good option for intracranial procedures. The future hope for this approach is to be able to release more than one chemotherapeutic drug simultaneously from more than one reservoir. This could help the efficacy of the cancer treatment. (9 p.2f)

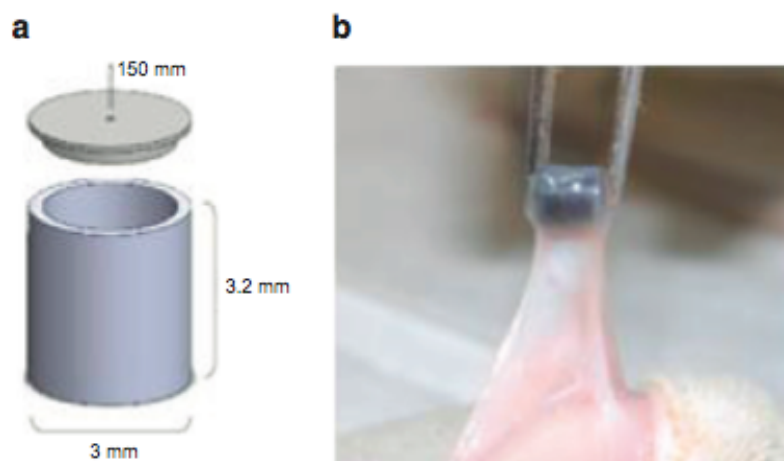


Figure 2: Passive-delivery devices. (a) Schematic of the liquid polymer-based passive drug-delivery device. (b) Actual device implanted in a rat. (9 p.2)

The glioblastoma multiforme (GBM) is a very aggressive cancer with a dark prognosis. Applying agents capable of crossing the blood-brain barrier has shown modest increases in patient survival, but only in combination with unsatisfactory systemic, dose-limiting toxicity. The next steps for improvement should focus upon the delivery of effective chemotherapeutic drugs directly to the brain tumor site. An interaction between the BCNU delivered by biodegradable polyanhydride wafers and the systemic alkylating agent temozolomide is able to deliver high effective doses whilst decreasing the systemic toxicity. Some in vitro trials of the drug release rate showed that releasing the BCNU and temozolomide drugs in

combination directly at the brain tumor site was capable of prolonging animal survival and might be a new form for treatment for intracranial tumors.

This new device shows single or multiple orifices and is demonstrated in Figure 3.¹⁰

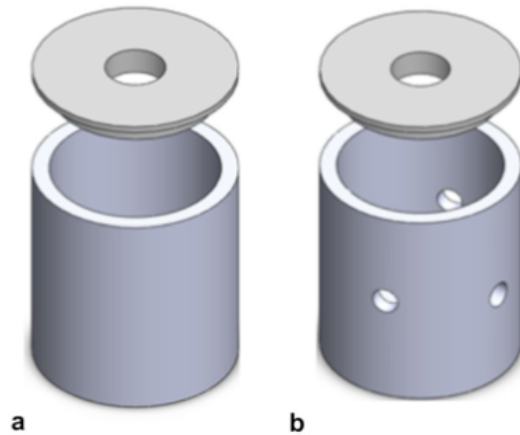


Figure 3: Microcapsule device design. a) Single-orifice device. b) Multiple-orifice device (¹⁰ p.2534).

2.1.2. Active Devices

Active delivery devices are based on microelectromechanical systems (MEMS) technology to release the drug from single or multiple reservoirs.¹¹ This is a kind of controlled drug release which starts with the electrochemical dissolution of a gold or polymeric membrane which lets the drug effuse. This new systems can deliver specific drugs and determine the required dose for the treatment. The drug release mechanism for active devices controls the dose of the chemotherapeutics and the type of delivery, which can be continuous or pulsatile and utilizes diffusion and/ or osmotic pressure mechanisms. The challenge is to miniaturize the supporting for powering the MEMS and to fit it into micro devices and to make it biocompatible and implantable.

The next steps for improvement of active delivery devices are to increase the capacity of the payload and to secure the reliability of drug release. With Pyrex reservoirs the payload could be increased while the size of the device could be reduced. Through the new Pyrex packages the profile of multiple substances could be controlled precisely. It has been shown to be as effective as subcutaneous injections of BCNU in inhibiting tumor growth (⁹ p.1)

The new generation of active devices melts the gold membrane down via an electrical pulse producing localized heating. This renewal was important because the electrochemical

dissolution of the gold or polymeric membrane was dependent on environmental conditions and therefore not 100% reliable. The device is shown in Figure 4.

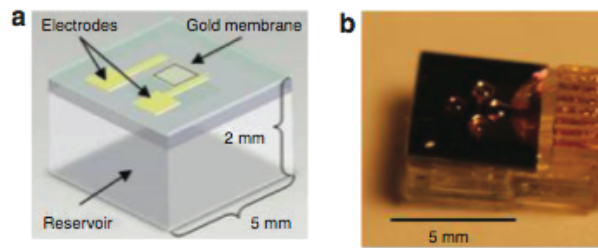


Figure 4: Active-delivery devices for slow, controlled delivery.
 (a) Schematic device. (b) Actual silicon-based active device. (9 p.3)

A specific implantable rapid-drug-delivery device (IRD³) has been designed for immediate treatment of hemorrhagic shock and as a preventive subcutaneous implant for high-risk patients e.g. soldiers on the battlefield. The device consists of a reservoir, a thermal activator and a sealing membrane using MEMS technology. A triggering algorithm considers blood pressure and heart rate values from standard electrocardiogram (9 p.3).

Ongoing research has shown that freeze-drying the chemotherapeutic drug increased the shelf life and advanced the drug stability also in harsh environmental conditions. In Figure 5 these rapid reconstitution packages are shown. This device is composed from two attaching reservoirs. One is the IRD³ filled with a mixing solution and another reservoir separated through a silicone chip with sealed silicone nitride membrane where the lyophilized atropine is based. The device is capped with another membrane chip (9 p.3f).

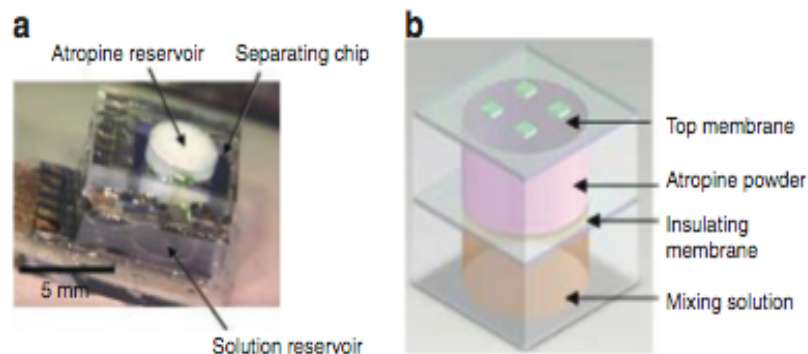


Figure 5: Active-delivery devices for rapid, controlled reconstitution and delivery.
 (a) Photograph of a reconstitution device containing water and lyophilized drug.
 (b) Modular schematic of reconstitution device. (9 p.4)

2.2. An Intravesical Device for Sustained Delivery¹²

There are already some common treatment methods like oral medication, transdermal patches, and intravesical instillation of therapeutic drugs to help several conditions concerning the bladder. Overactive bladder (OAB), interstitial cystitis/painful bladder syndrome (IC/PBS) and bladder cancer are known and widespread illnesses in the US. The symptoms of the IC/PBS are mostly chronic and affects more than 1 million people in the US and symptoms predominantly revolve around urinary urgency. OAB affects around 33 million men and women.

The instillation of the device through the urethra into the bladder has numerous advantages such as local drug release, which lowers the systemic burden and also lowers drug concentration. It also avoids invasive treatment, which decreases the inflammation risk of the incision and reduces the recuperation time of the living corpus and other side effects compared to oral medications. This intravesical instillation is a good alternative for those who are immune to oral medication because of systemic side effects.

At the instillation of therapeutic drugs a certain amount of the drug solution is instilled through a urethral catheter. The drug is kept for around 2 hours inside the bladder until it is voided, when the majority of the drug is destroyed. The drug exposure time is short because of the limited remaining time of the drug in the bladder. Since the exposure time is as important as the drug concentration it would be necessary to re-instill the therapeutic drugs again but this will also increase the possibility of infections.

Extension of drug maintenance in the bladder and preservation of effective drug concentration are the main targets of a new intravesical drug delivery design.

A new device of lidocain which is intravesically instilled into the bladder three times a week for 2 weeks shows immediate and lasting relief of pain, urgency and frequency of IC/PBS patients. To intravesical instill daily for 5 days also leads to sustained symptom relief even after the end of treatment.

The intravesical lidocain delivery device can be deployed into the bladder through a cystoscope and voided afterwards. This means that this invasion is possible without surgery. The cystoscope procedure is schematically shown in Figure 6.

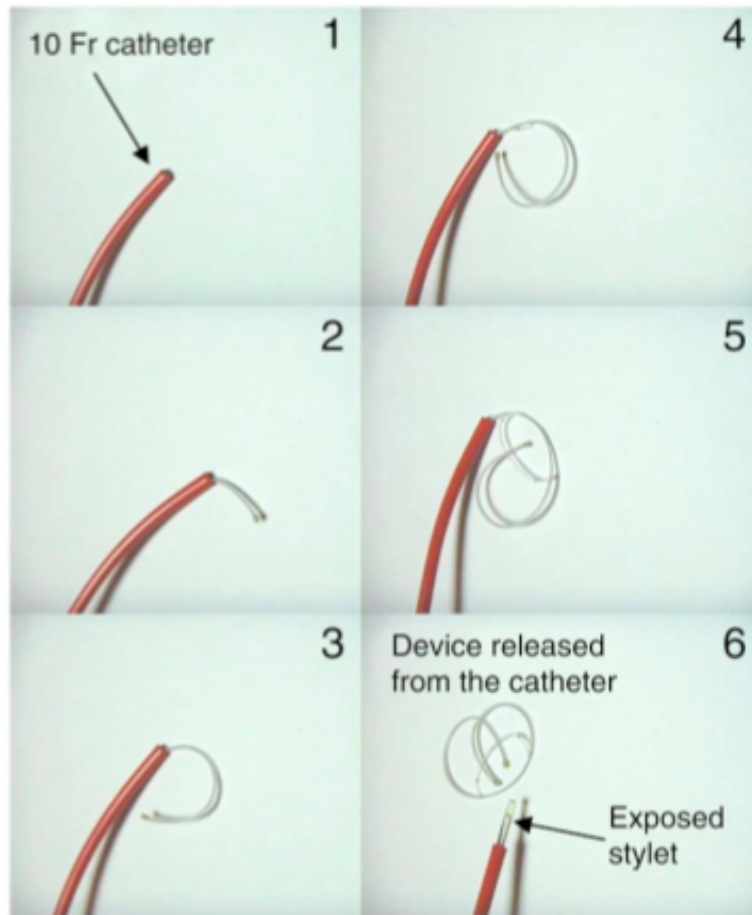


Figure 6: The sequence of deployment of the device by the catheter–stylet system. (¹² p.136)

The device consists of a reservoir unit, which contains the drug and is made of a water permeable silicone tube with an orifice used as an osmotic pump and a retention frame, which is necessary to keep the shape, while trying to avoid irritation and not being voided. Shown in Figure 7.

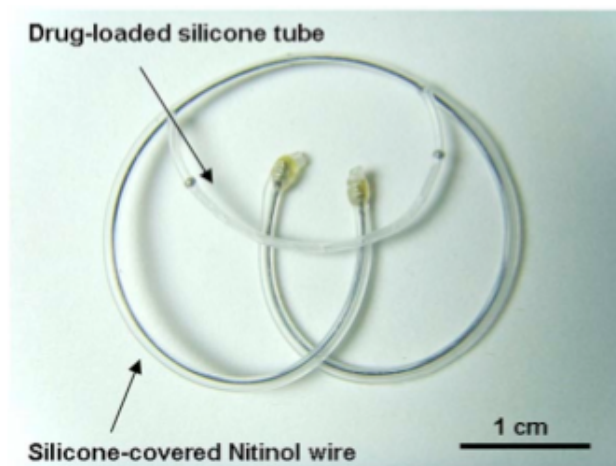


Figure 7: A fabricated device consisting of a drug reservoir/orifice unit and a Nitinol retention frame (¹² p.134).

The device was instilled into an in-vivo rabbit model, where it was kept for more than 3 days. The lidocain concentration in the bladder tissue was higher than 0.1 $\mu\text{g/g}$ during the period. This device has the potential to effectively treat bladder conditions such as IC/PBS with the possibility to extend the drug exposure time and increase the drug concentration. This device in combination with other therapeutics is a promising approach for treatment of various types of bladder disorder such as OAB and superficial cancer.

2.3. Hongye Ye's Research Projects

I helped Miss Hongye Ye, whose research is aimed at the development of two different drug delivery devices. One is an intraperitoneal drug delivery device which is tested in mice and the second one is a device which is intravesical and is instilled into the bladder of rabbits.

2.3.1. Intraperitoneal Implantable Drug Delivery Devices for Ovarian Cancer

This project was focused on reaching the right drug release rate of the device. We tried to find an adequate shape and design for the device to be able to release the drug at a particular rate. This method is closely related to another similar treatment method, which is already known as being successful. The device is still in the development phase and a new test setup of in-vivo trials is going to be started.

2.3.2. Intravesical Instillation of Drug Delivery Devices for Bladder Disorders and Bladder Cancer

The second research project concerns the development of a device to be instilled into the bladder, which is biodegradable over time. The difficulty in this project is to maintain the device in the bladder for the appropriate time in order to be able to release the drug for the exact period. A very important aspect of the research is to find the material composition to produce the device with the relevant material properties.

2.4. My Assignments

Professor Cima introduced me to the biomedical projects he is working on at the moment. I was very interested to learn about Professor Cima's projects and I feel that his insights filled a gap in my own studies thus far. I am now thinking of changing the direction of my studies towards biomedical engineering, since I was allowed to help Miss Hongye Ye with her drug delivery devices projects and was able to see the interaction between biology and engineering science.

2.4.1 My Work-Experience Traineeship under the Supervision of Hongye Ye

Most of the time I helped Miss Hongye Ye with her projects. I shadowed her and helped her in the fields I was allowed to assist. Since I was an undergraduate student my duties and responsibilities were restricted.

At the very beginning Miss Hongye introduced me to her two different projects. I was shown the devices and the drugs used.

The first project revolves around treating ovarian cancer with an implantable device placed in the intraperitoneal cavity. The major advantage of the device is that it will deliver the drugs locally to ovarian tumors. I was introduced to the development of the device used for this project and to the problems associated with this device. I learned to produce the device and was encouraged to think about solutions and/or improvements myself. With my background in materials science, which in Austria focuses heavily upon metals. I took this opportunity and improved my knowledge of plastics. I started with reading papers about the project, the materials, successful treatment methods and the machines used to be able to follow the project closely and to come up with some useful ideas.

The second project deals with an intravesical instillation of a device into the bladder. The underlying philosophy of this device is that it can get into the body and back out without the need for an operation, which will decrease the possibility of infections enormously.

These are medium and long term projects and the data has not been published yet. As a consequence, I am not allowed to publish any findings made during my stay.

2.4.2. Tensile Testing

When Miss Hongye Ye went on her vacation I got a little project of my own which was dealing with in-vitro trials. The devices we used were instilled intravesically into a rabbit to test the properties and reactions in living animals. This will help make predictions about the material reacting in the body system (in-vivo). This project is likely to have very strong potential.

A pretzel shaped device made of a certain material was intravesically instilled into the rabbits bladders to work on overactive bladder, interstitial cystitis/painful bladder syndrome and bladder cancer. Since the material used is biodegradable, the device can get out of the bladder again in a non-surgical fashion (¹² p.133).

The actual rabbit device is pretzel-shaped. So the first idea was to measure the force, needed to straighten out the device, assuming that the device is straight when it is able to go through the urethra. It is also important to consider how strong the urethra is to be able to straighten the device out. So, we are now trying to measure the point at which the material degraded enough to be voided out.

The devices are kept in Petri dishes filled with synthetic urine in the incubator. Twice a week the synthetic urine is changed. We took 2 time points of the tensile modulus per week with the Instron Machine. For some visual background of the change in the stiffness of the device we are also taking a picture of each sample twice a week.

To be able to explain the voiding out of the devices with a material property using a standardized tensile test to make it internationally representative is important. Since we have results of earlier in vivo trials and are trying to reach the retention of one month of the device in the bladder we only could take one of the materials for further devices.

We used 5 different types of materials. Materials made from the same original material and under the same conditions already have a significant difference of properties.

The clamps of the Instron are laminated. This is necessary so that there is no slippage in between the runs per sample. The distance between the two clamps depends on the length of the device.

Since we are confirming our study to the field of linear elasticity, we can use straight devices instead of dog bone shaped samples.¹³

Areas of possible error in this test setup could be the surface roughness of the device, which is very important in terms of tensile testing. Another thing to notice is that the devices cool down after some time when out of the incubator. When they are actually going to be tested, they will need to be at room temperature. The distance between the two clamps has a big influence upon the modulus as well. Since the starting materials already show differences in terms of their properties, the tensile modulus is also affected by it.

2.4.3. Necessary Training

Before being allowed to work in the laboratory it is mandatory to attend training, instructions, orientations and it is also a requirement to sit online and classroom courses. MIT has strict regulations about safety and ethics for working in the laboratory and for working with animals.

Laboratory Specific Chemical Hygiene Training: The safety representative, Lennard Regione, of the Cima Laboratory, led this training course. He gave me a laboratory orientation and explained safety rules and disposal plans within the lab.

Emergency Preparedness Plan: I had to memorize a map to be able to find the closest exit in case of emergency.

Hazardous Waste Management: This was an online course to learn safety regulations of storing disposal and other disposal rules and signs.

Chemical Hygiene Training: This training explained the right way to work with potentially hazardous materials and how to use PPE (Personal Protective Equipment).

General Bio-safety for Researchers: In this lesson we were taught how to use the PPE, work in a safe way and to reduce potential jeopardy.

Blood born Pathogen: In this course we learned to which pathogens we are potentially exposed.

Mice/Rabbits Handling Online Test: This online test asked questions about adequate recuperation time of recently shipped animals, general responsibility for animals or after surgery surveillance.

Building Orientation: The animal facilities were introduced. The facility managers showed us where to find surgery equipment, syringes, cards, cubicles, food, water, heating pads, light and oxygen tanks.

Mice/Rabbits Handling Training: This training started with a speech about ethics and respect concerning animal experimentation. Furthermore we learned how to handle mice and rabbits and how to give intraperitoneal injections to mice. The right handling technique and treatment of these two animals was also taught.

Survival surgery/Wet Lab: In this lab students get trained how to perform sterilization on mice, how to cut the muscle and the skin layer with a scalpel. We were also taught how to suture the muscle layer and how to clip the skin layer.

Handling Hazardous Materials Training: Students were showed in which facilities they are allowed to work with a certain potentially hazardous material and how to label everything correctly.

Xenograph Machine: I was taught how to give intraperitoneal injections with Luciferin (fluorescent substance) in order to take images with the Xenograph so that the tumors of the mice will become visible on the computer.

HPLC-High Pressure Liquid Chromatography: This is a machine, which is able to disperse a mixture of liquid compounds into its substances so that it is possible to state its elements.

Human Cell Line Culture Development: Miss Hongye Ye showed me how to grow human cell lines in Petri dishes. I learned about the time span they need to grow, the amount of cells needed and the requirements to be allowed to produce them.

Instron: This is a tensile testing machine to get different material properties.

Value of my Internship

This internship has dramatically improved my understanding of the field of biomedical engineering. I got to experience first-hand what it means to work at a world-famous university laboratory with ambitious and highly motivated scientists accompanied by appropriate resources and an outstanding infrastructure.

I gained skills for conducting technical treatments of cancer research. I had access to all the animal facilities and was allowed to work on research for future cancer treatments. I got the opportunity to study in a completely different field. My major subject at University of Leoben/Montanuniversität is focused on metals and I found that biomedical engineering is a great interaction between two totally different and complex fields of science. I saw the possibilities of using different kinds of materials in the field of applied research. I also learned about focusing on different material properties throughout my stay at MIT.

I learned project management and the aspects that one must consider before starting a project. I was taught how to design a device for a certain project and think about how this device would react at in-vivo trials. I had to read papers, research proposals and reports from former researchers about the project, learn about the materials, the machines used and some already known treatment methods to be able to follow the project and to participate in discussions about how to improve the device and/or the treatment method.

My experience at MIT also introduced me to the field of animal experimentation. I was handling animals and machines myself and I began to appreciate the complexity of designing

devices for use in animals. I am very grateful to MIT for giving me the opportunity to witness first-hand how a world-class laboratory operates and I am particularly grateful for the level of trust I was shown by members of staff and students at MIT. The ability to partake in these projects as well the practical experience that I gained have added to my studies and knowledge enormously.

Refereces

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