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Implantable Bio-MEMS for the treatment of Cancer

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ABSTRACT: Treatment of cancer has invoked technological forays that have been vying with each other and which were often supplanted by researchers with fresh and innovative approaches. Notable among these novel approaches is the Micro-Electro-Mechanical System (MEMS) technology, as it has established accomplishments in a variety of industrial areas. We are focusing on the therapeutic applicability of MEMS in biomedical arena, where they are called as Bio-Micro-Electro-Mechanical System (BioMEMS). We are presenting an analysis of the design, principle and performance of various BioMEMS devices and discuss the niche of their efficacy. We are emphasizing on the devices which could be implanted to deliver a single drug or a mixture of drugs in microlitre / nanolitre doses in a controlled timeframe. These BioMEMS are not meant to detect or diagnose but they offer a potential to treat malignancy and prevent the exposure of healthy cells from the severity of chemicals that could harm them.

KEYWORDS: MEMS, BioMEMS, implantable devices, drug delivery, cancer.

I.INTRODUCTION

Cancer is a perilous disease, since it is often terminal. It is estimated that 2.5–3.0 million cancer cases exist in India. About 25% new cases are detected each year and up to 0.4 million patients die each year. Around 70–80 % cases are detected at a late stage when the treatment is very difficult. Early detection of cancer may help in absolute cure of some cancer.

In a human body, the normal cells divide and grow in an arranged manner. But the cancer cells grow out of control, keep growing and crowd out the normal cells. This uncontrolled division and growth of cells within the human body is the hallmark of cancer (carcinoma). Its treatment has frequently been attempted by using chemo- and radio- therapies. The former delivers drug unselectively to the entire body and the later irradiates the cancerous as well as the neighbouring normal cells. Both of these techniques of treatment result in an undesirable damage of the healthy tissues and also necessitate the repetition of doses, causing inconvenience as well as a psychological trauma to the patient. To undo these shortcomings, drug-filled pills that release their contents at a gradual rate were developed. The pill allowed curtailing the frequency of doses and it was considered a tenable alternate mode of drug delivery. But it lacked site-selectivity and dynamic micro-control of the volume of released drug. To resolve this quandary, a multi-disciplinary approach of research was started with an aim to develop safer and effective devices for the controlled delivery of drug at the site of carcinoma.

Among the recently developed devices to treat cancer, the leading ones are the implantable devices, which deliver drugs in miniscule amounts at the site of the tumor. The stipulated drug delivery device ought to be tiny in size, must have bio-compatible casing, should store tiny amount of drug and respond to remote stimuli to release or hold its contents. The combination of such anticipated functionalities logically steer the direction of innovation towards the semiconductor micro-fabrication technology whose propelling emphasis is on similar parameters. The group of such emerging devices developed through the technology used in the fabrication of semiconductor microchips, are called Micro-Electro-Mechanical System (MEMS) [1].

These tiny devices to treat cancer could be constituted through an assembly of few or more component sub-systems such as micropump, microvalve, microactuator, and microneedle. Their configuration could be controlled and actuated to deliver hormones, anti-cancer agents, and vaccines. In biological arena, these devices are called Bio-Micro-Electro-

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Mechanical System (BioMEMS). These devices are sensitive and responsive, allowing accurate control to sense and deliver drug and biomolecules in-vitro and in-vivo. BioMEMS encompass a large variety of electronic devices such as biosensor, and drug delivery system. Rapid advances in medicine call for rapid changes in drug delivery mechanism. Lower side effects, effective drug delivery, low toxicity, ease of use, lowest cost and maintenance, and patient's comforts assume highest priority. In this article, under the heading "Implantable Drug Delivery Devices" we are discussing some of the recently developed devices to treat cancer. Their topical aspects, which are critical for the performance of the implantable devices, are discussed under the heading "Challenges for implementation" and in the Conclusion.

II. LITERATURE SURVEY

Once the size of these BioMEMS is reduced to nanometric dimensions, they begin to match with the size of biological cells and become amenable to be used as tiny probes that can play around with the cellular system [2, 3]. Nano dimensional systems and materials are also being used to deliver drug and gene at the site of tumor to tap their potential in the destruction of the cancer cells [4]. Polymer based therapeutic administration system consists of nano drug carriers such as liposomes, nanoparticles, and dendrimers. The technology can be embodied in various forms such as gels, rods wafers, etc. and its materials could include natural polymers: alginate, chitosan, dextran, etc. to execute the localized and targeted drug delivery for treating cancer [5, 6, 7]. Laser stimulation of nanodimensional dyes and the resultant release of atomic oxygen towards a selective annihilation of cancer cells has also been attempted. Roy et al. have found that its effectiveness can be improved by putting the dye in a porous nanoparticle [8].

Implantable devices are being developed to non-invasively detect the concentrations of metabolite and drugs in the proximity of cancerous tumor. These could improve early detection of metastasis and monitor cancer biomarkers [9].Implantable nanodevices of insulating body having a size smaller than a biopsy needle and carrying magnetic nanoparticles have been tried out. These can continuously track the hormone HCG released by tumor [10].

Attachment of a metallic antenna can send its signal to hand-held detectors and alleviate the MRI to find the concentration of metabolites. It could actuate another device, which gets stimulated to release suitable drugs at the site of treatment on demand. Development of miniaturized implantable devices by using MEMS technology has been reported. These incorporate one or more reservoirs for the drug and microchips to automate the in-vivo delivery of therapeutic agents. These devices are providing an impetus to provide personalized therapy and to top up with the advantages of safety, accuracy and convenience. Multiple reservoirs facilitate the provision of innovative combinations of drugs whose active ingredients need to be protected in hermetically sealed reservoirs [11].

Individual drugs are stored in micro-reservoirs, which are often etched in silicon substrate and covered by gold membrane. The dose of each chemo-therapeutic drug such as BCNU is released by the electrochemical dissolution of the membrane covering its reservoir. The spatial profile of the combination drugs released by the device is found through fluorimetry [12].

III. THE TECHNOLOGICAL ROUTES

Three different approaches have been used to develop systems that could annihilate the cancer cells at their site. These are:

a) Implantable drug delivery devices,
b) Micro-oxygen generator and
c) Bioreactor

In view of their potential applicability, implantable systems have received maximum attention of the researchers. However, let us have a comprehensive look at the three approaches.

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IV. IMPLANTABLE DRUG DELIVERY DEVICES

Various types of implantable drug delivery devices developed for the cancer treatment are discussed. These devices consist of the micromixture for mixing of drugs, microvalve to start and stop the flow of fluid, micropump to control the flow through pressure, microreservior to store the drug, microchannel to transport the drug, batteries, etc. Some components are active and some are passive.

A)MEMS drug delivery device was developed to locally deliver a chemotherapeutic agent BisChloroethylNitrosoUrea (BCNU) in rats [13]. The tumor is artificially created inside the rat's body. MEMS device consists of an array of reservoirs etched into the silicon substrate. When the covering of the reservoir that is gold membrane is activated by electrochemical dissolution, the drug is released. A Pyrex package was developed to improve the BCNU release kinetics and enhance device capacity. Co-formulation of BCNU with polyethylene glycol (PEG) led to complete and rapid release of drug in-vivo. BCNU delivered from the MEMS device showed dose-dependent effect on reducing the tumor growth in the BCNU dosage range of 0.67 to 2mg. BCNU delivered from the activated devices was as effective as equipotent subcutaneous injections of BCNU in inhibiting tumor growth.

B)MEMS based implantable drug delivery system (IDDS) in Fig. 1(a) was proposed to include a subcutaneous reservoir, an in-plane silicon pump and connected circuitry for delivery of therapeutic agents for chemotherapy [14]. The reservoir provides workable solution to small sized pump for implantable drug delivery system. Wireless monitor reservoir level, battery recharging and control the drug flow rate can be done by Telemetry. The flow rate capability of the pump isharmonized with thevenous pressure. The average flow rate is 85 µl / min.

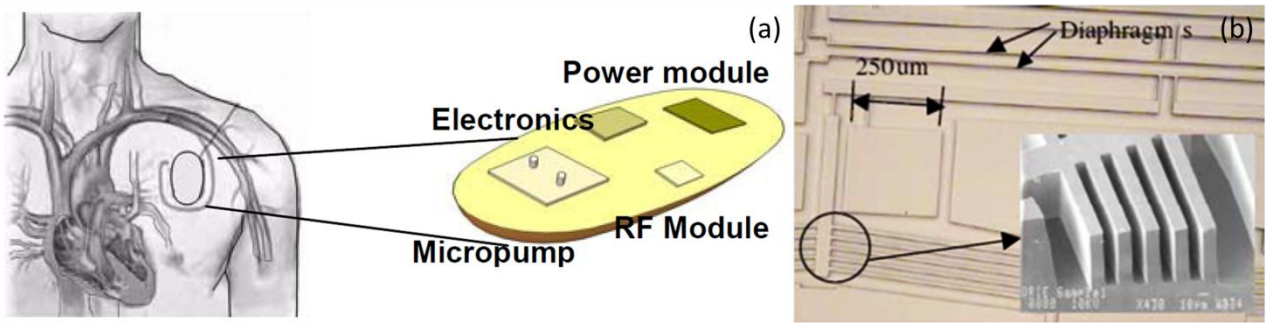

Fig. 1 (a) Catheter; (b) Micropump fabricated on a 100µm Silicon wafer

The micropump is an on-demand active device shown in Fig.1 (b). It can be electrically controlled to deliver exact quantity of therapeutic agents. The requirement to derive the drug from pump to catheter for delivery include: a minimum flow rate of the order of 10 µl/min or more, small size and high reliability. Fabrication of the actuator, diaphragms, reservoir, and I/O fluidic valves is done in a single layer. The micropump is made by using a Deep reactive-ion etching (DRIE- highly anisotropic etch process used to create deep crevices) on machined monolithic structure (Carved or cast from a single piece of material) fabricated on 4 inch, 100µm Silicon-on-insulator (SOI) wafer. The size of the actuator is 12*100*1200µm with a rib angle of 5.7º. The actuation of the pump at 12V causes a deflection of 30µm in the diaphragm which results in the pumping of 3.6~12.6 nl of the drug. The reservoir has smooth contours, contains 5ml of the drug and is easily accessible for refilling. The estimated power consumption for target delivery rate of 10µl/min is in the range of 100-500 mW.

C)Silicon-based implantable drug delivery system (IDDS) was developed for the management of therapeutic peptide leuprolide as a compound in-vivo [15, 16]. As shown in Fig. 2 (a) it contains the drug-filled silicon microchip, control circuitry, telemetry capability, and a battery. It contains multiple drug filled reservoirs. The chip enclosed in titanium case with a battery, control circuitry, and telemetry capability are shown in Fig. 2 (b). The titanium case and the multi-reservoir are sealed so that no air should enter it. They are often fabricated on ceramic substrate and interconnect ions are done using evaporation coated microstructured metallic films.

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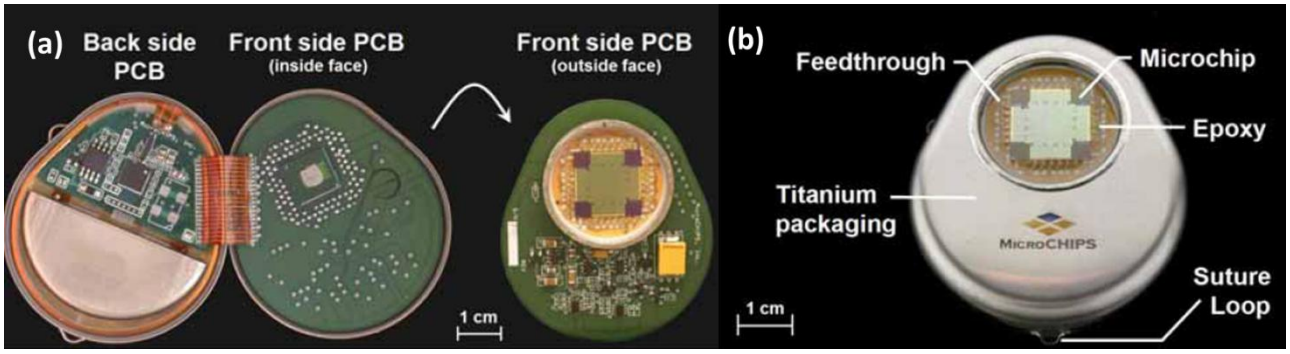

Fig. 2(a) The electronic components on printed circuit boards; (b) The assembled implantable device within the device package

The IDDS shown in Fig. 3(a) & (b) communicates through wireless transmission. The dosing schedule transmitted to this device opens its reservoirs at prescribed times. The drug reservoirs are covered by a thin metal cap. When voltage is applied, the cap gets heated rapidly; it reaches the point of failure and releases the drug. Typically such an activation occurs within 50 microseconds.

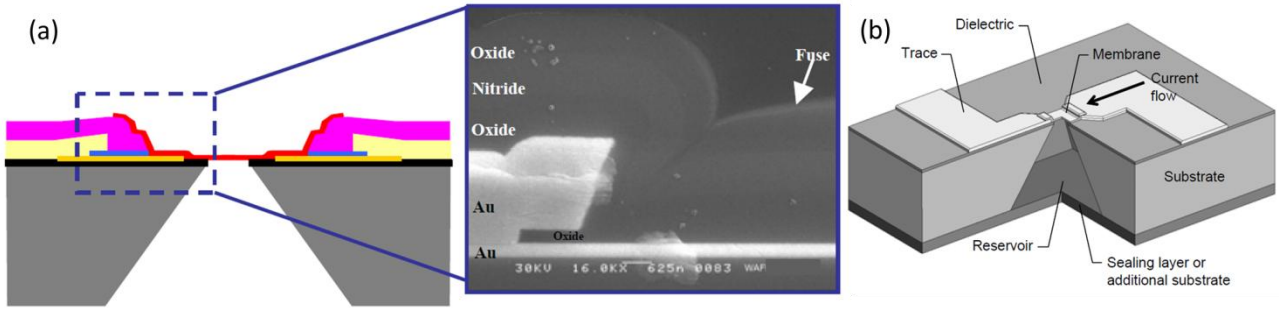

Fig. 3 (a) Detailed cross-section of the metal connection and dielectric step coverage; (b) MEMS Drug delivery Microchip

This controlled drug delivery has been demonstrated in-vitro and in-vivo by using leuprolide for the treatment of endometriosis and prostate cancer. The formulation is prepared by freeze drying leuprolide in a matrix of solid polyethylene glycol (MW 1450 Daltons, mp 42ºC). The formulation (<5% degradation after 6 months at 37ºC) can be processed on the chip at small scale (25 µg/ reservoir), with high accuracy and precision, using commercially available process instrumentation. The inlet ports of the flow cell are connected to a reservoir containing fluid, and the outlet ports are connected to a fraction collector. The volume of the entire system is filled with the fluid during each in-vitro release experiment. After activation, a suitable amount of fluid is pumped through the system in about 90 min.

D)Genseler et al. developed an implantable drug delivery device [17]. Their aim was to reduce the exposure of patients to radiation. For this, the agents in the form of drug i.e., small interfering Ribonucleic acid (siRNA)-gold nanorod complexes (Nanocomplexes) released from the reservoir and delivered to the tumors induced in mice is shown in Fig.4(a). The effect of radiation therapy in combination with the drug actively pumped by electrolysis actuation showed 50% reduction in the size of colon cancer tumor (HT29).

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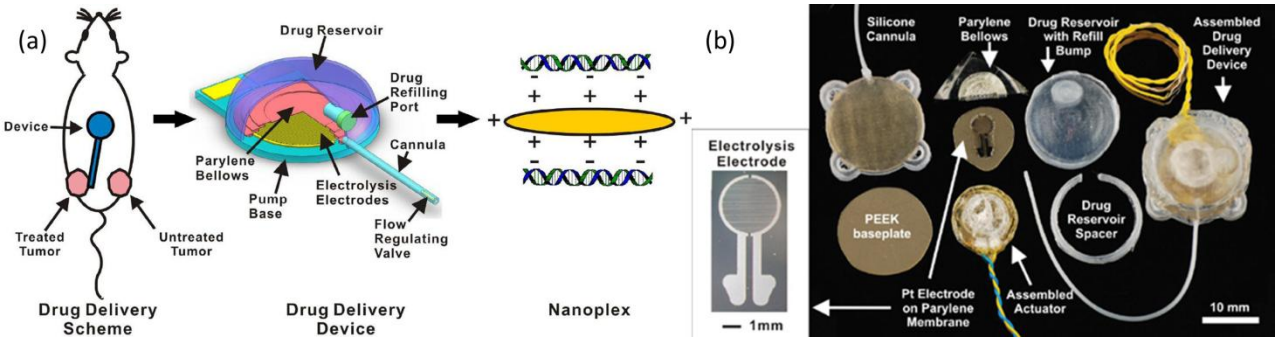

Fig. 4 (a) Left to right:Conceptual depictions of placement of implantable drug pump to deliver nanoplexes to tumors, the drug delivery system and components, and nanoplexer that delivers siRNA; (b) Drug delivery device components for assembly

This device consists of refillable drug reservoir, electrochemical bellows pump and dual regulation valve as shown in Fig. 4(b). Its bellow shaped actuator separates the drug from the electrolyzed fluid and prevents its degradation. The check valves are integrated in the cannula to regulate the drug flow. Its electrolysis based actuation reduces the power consumption as well as heat generation and enhances the driving force. Its flow rate can be controlled by adjusting the applied current. The results are better than those obtained from the diffusion-based delivery and intravenous injections.

E)A magnetically controlled MEMS drug delivery device has been developed for on-demand release of fixed amount of an anti-cancer drug, docetaxel (DTX) [18]. It is shown in Fig. 5(a) & (b). Its drug loaded micro-reservoir has a diameter of 6mm and depth of 550µm. The microreservoir is sealed by 40µm thick elastic magnetic PDMS (polydimethylsiloxane) membrane with a laser-drilled aperture (~100×100µm^2). DTX with low aqueous solubility of approximate 5µg/ml is loaded in the microreservoir .When external magnetic field is applied to the magnetic membrane; it deforms and discharge drug solution from the microreservoir.

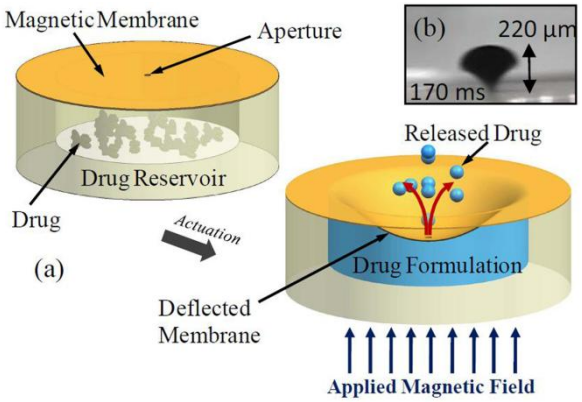

Fig. 5 (a) Principles of operation; (b) Discharge of model dye solution after magnetic actuation

Discharge of the drug solution from this device and the release rates are controlled by an external magnetic field. A constant release rate of 110±17.6 ng per actuation interval has been achieved by using a magnetic actuation of 213mT for 6 intermittent releases over 5 days. Controlled and reproducible release rates of DTX have been achieved for 35 days. It was observed that the cytotoxicity (monitored as cell viability)created by the drug released from the device is not just instantaneous and that DTX maintains these cytotoxicity effects for two months.

F) A microchip for the treatment of brain cancer through chemotherapy [19, 20, 21] has been fabricated by using polymer and it contains multi-reservoir. It provides local and controlled delivery of multiple chemotherapeutic agents with varied dosage. The main drug i.e. 1,3-bis(2-chloroethyl)-1nitrosourea (BCNU) is stable in a narrow thermal window around 37ºC. BCNU has serious side effects in conventional treatment but its localized delivery may decrease or even eliminate some of the negative effects.

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G) Angelica Cobo et al. have developed a micropump, which gets actuated by using electrolysis and is suitable for chronic drug delivery. It has significant advantage has it offers large driving force, low heat generation, low power consumption, and a control of flow rate through applied current after the implantation. It has been developed in two different configurations, viz. a) wired implantable micropump on demand activation [17,22] and b) wireless implantable micropump [23].

V. MICRO-OXYGEN GENERATOR

An implantable micro-oxygen generator (IMOG) shown in Fig. 6(a) & (b), has been developed [24]. It is powered ultrasonically and its operational principle is identical to that of the radar; ultrasonic transceivers send signals to IMOG and receive the echo from it. It is capable of oxygenating the in-situ tumor by using oxygen generated through the electrolysis of water. Local oxygen generation is not affected by increased interstitial pressure or abnormal blood vessels which generally limit the systemic delivery of oxygen to hypoxic regions of solid tumors. Experiment was performed by placing the IMOG inside pancreatic tumor and powered from outside with an ultrasonic transducer. Wireless ultrasonic powering (2.15MHz) was employed to increase the penetration depth and eliminate the directional sensitivity associated with magnetic methods. By using an on-board rectifying circuitry, IMOG converts ultrasonic power to a dc voltage that is then applied to a pair of platinum electrodes, generating oxygen through water electrolysis. The device uses water present in the tissue.

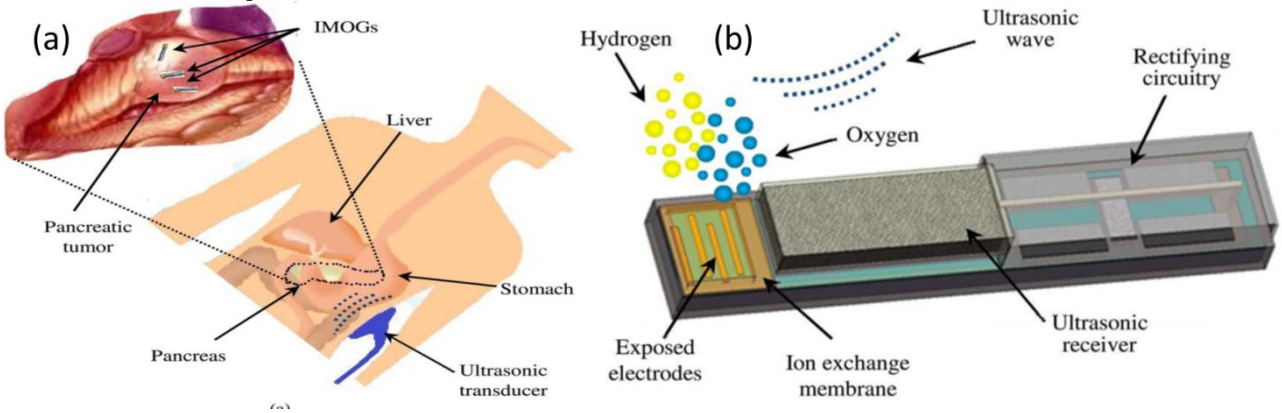

Fig. 6 (a) IMOG implanted in a pancreatic tumor for in situ oxygenation, (b) Detailed schematic of the IMOG showing various components such as ultrasonic receiver, rectifier circuitry, electrodes, and ion exchange membrane

Ultrasonic powering allows a drastic reduction in the total size of the implant by eliminating the need for a large area inductor. IMOG has an overall dimension of 1.2 mm × 1.3 mm × 8mm, small enough to be implanted using a hypodermic (hollow) needle. In-vitro and in-vivo experiments showed that IMOG is capable of generating more than 150μA which, in turn, can create 0.525μL/min of oxygen through electrolytic disassociation. In-vivo experiments in a well-known hypoxic pancreatic tumor model (1 cm^3 in size) was used to verify that IMOG delivered adequate in situ tumor oxygenation in less than 10 min.

VI. BIOREACTOR

Researchers have developed BioMEMS for the Breast Cancer Tissue BioReactor (BCTB) [25]. This is not an implantable device, but used to find best suitable drug for treatment by testing on the patient's tumor externally. It is able to maintain sterile microenvironment, sustain cell growth and organ formation for time duration of three week. It will support the combination of the 3-D culture methodology with control over microenvironmental oxygen and matrix stiffness to execute ex-vivo approximation of the in-vivo tumor microenvironment. Bioreactor also includes sensor to monitor the oxygen states. Tumor tissue is made up of tumor cells and other surrounding cell types in its microenvironment. This diseased tissue normally exists in particular tumor microenvironment such as being less oxygenated and more acidic than healthy tissue. These states intensely impact effectiveness of anti-tumor drug. For disease diagnosis, a tumor is commonly biopsied. If a biopsied portion of the tumor tissue is maintained in

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microenvironment similar to the tumor, it can replicate the same tumor cellular functions ex-vivo.

Such experiments would allow maintaining the in-vivo functionality of a patient's own tumor and these can be used to test the response of anti-tumor drug for that individual patient. Testing of BCTB has been done on mouse models of breast cancer.

VII. CHALLENGES FOR IMPLEMENTATION

Danny Jian Hang Tang, et.al reviewed and discussed the current status of implantable BioMEMS for drug delivery applications [26]. The authors tried to focus on many important factors that impact the performance of implantable BioMEMS devices viz. (i) size of the drug reservoir and its volume, (ii) effective delivery method, (iii) operating time, (iv) controllability of the device and (v) biocompatibility of the device.

A typical microreservoir contains a volume of drug in the range from microliters to a few milliliters. The size of the implantable BioMEMS should be chosen to meet the physiological constraints obligatory to the implantation region. The device should be as small as possible so that it does not harm the tissues rubbing onto the implant. These devices have severely limited volume of their microreservoir and thus they can carry only a tiny volume of the drug. So, one of the following approaches could be used to supplement their payload: (i) external reservoir, (ii) transdermal delivery, (iii) refillable reservoir, and (iv) miniaturization of other device parts, such as the power sources and actuating mechanisms. For implanting the device, minor surgery and local anesthesia are needed. The shape and material of the device often get affected by the time the device is removed.

In order to release the drug contained in their reservoir, a drug delivery device operates using one of the two mechanisms: mechanical or non-mechanical. In both groups of mechanisms, an actuator applies pressure on the drug reservoir and forces it to release the drug from the delivery port. Commonly adopted operating principles of the mechanical actuators are electrostatic, piezoelectric, thermopneumatic or bimetallic actuation. The actuators operating on non-mechanical routes may utilize electroosmotive, electrowetting or evaporation methods [27]. However, non-mechanical mechanisms are highly dependent on the properties of the fluid, that is to be transported and therefore it is a challenge for implementation. Mostly, mechanical mechanisms are preferred, as they provide a general form of fluid manipulation. In actuation method, the flow rate of the drug formulation is controlled when they are pumped out from the device. To increase the drug reservoir volume in the device, the actuation mechanism has to be minimum yet effective. There are three categories for BioMEMS used as drug delivery devices: (i) actuation-less methods, (ii) single chamber actuation methods and (iii) multi-chamber actuation methods.

Implantable device must be able to remain operable for a long period of time to treat the chronic diseases. Due to the small size of these implantable BioMEMS, powering the device for a long time is an issue [28]. However, there are numerous methods, which have been investigated to overcome this issue: (i) the adoption of low power actuation mechanisms and/or (ii) increasing the battery life of the device by enabling the internal batteries to be recharged or by using wireless power. The propagation of drug being released by the BioMEMS can be controlled by electrical signals. In general, there are three ways to control the BioMEMS device: active, passive, and by environmental biological stimulus. The controllability is checked to evaluate the effectively the drug has been delivered, and that is called the response of the device. To increase the response, the control should be increased so that it can regulate the active and passive drug delivery efficiently [29].

The biocompatibility of the implanted BioMEMS devices is an important factor to be considered [30]. Care must be taken since it will be implanted in the body for a long period of time and it will interact with tissues in the body. Following four factors should be considered when designing an implantable BioMEMS device: (i) the impact of the implantable device on the immune response, (ii) minimizing biofouling on the implanted device, (iii) the physical effect of the implant on the surrounding tissues, and (iv) the degree of cell adhesion achieved by the implanted device.

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VIII.CONCLUSION

MEMS based implantable drug delivery devices offer many advantages over conventional drug delivery methods. The implantable BioMEMS devices are emerging as an excellent system in the treatment of chronic diseases such as cancer. We have presented a treatise of several avenues of their ongoing development of relevant BioMEMS and have also discussed the challenges in the adoption of these devices for the treatment of the disease. In every case, these devices must be taken care for the optimization of their design, relative size of their components, especially drug reservoir, operation lifetime, controllability and biocompatibility.

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