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Microdevice Development and Artificial Organs

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Over the past several decades, there has been an explosion in the development of microfabricated medical sensors and actuators. From the earliest development of silicon based MicroElectroMechanical Systems or MEMS devices there has been an interest in developing MEMS technology to support the medical field (biomedical MEMS or BioMEMS) (1, 2). Many of these technologies have positively impacted the medical field in general and the Artificial Organs field in particular. These technologies have brought medical sensors into the clinic, operating rooms or even as implantable technologies (Figure 1). As the BioMEMS field has matured, devices are increasing being developed as an active interface between the artificial microdevice and patients. Microfabricated medical transducers have evolved from solid state physical transducers such as force, pressure and flow sensors for measuring respiration, blood pressure and flow rates, into microfabricated multielectrode intracortical stimulating and recording arrays (neural probes) (3, 4), neural prostheses (5, 6), and polymer based microfluidic devices (7, 8) to perform highly sensitive point of care diagnostic assays (9) or supporting microscale cell cultures or Organ on a Chip platforms (10, 11). At this time we are also beginning to see widespread commercialization of many of these diagnostic technologies (12). Such sensors are also part of the trend of creating sensorized or ‘smart’ products and creating the so-called ‘internet of things’ for wearable diagnostics or personalized healthcare monitors (9).

Early medical MEMS transducers were developed in the form of solid state physical sensors to measure pressure, flow, and strain (force). Such physical sensors are a mature technology which have been instrumental in enabling low cost or autonomous monitoring of patients, providing diagnostic information to clinicians, or allowing feedback control of medical equipment. These types of devices have been utilized to measure or monitor physiological parameters of a patient; such as blood pressure (13) and flow rates, spirometers, and respiration rate monitors. They can also be used to monitor patient activity outside the clinic such as force sensors or accelerometers embedded in sports equipment and helmets to assess concussion or injuries, or pressure sensors and accelerometers embedded in footwear to assess gait, balance and foot ulcer risk. Such sensors have also been incorporated into

numerous medical and surgical devices and instrumentation along with controllers to regulate equipment function. These include: incorporation of pressure and flow sensors into implantable blood pumps and extracorporeal circulatory support to monitor or adjust pressure and flow rate outputs, incorporating force sensors within surgical tools or robotic surgical platforms to provide force feedback information to surgeons (1, 2).

A second impact of BioMEMS technology has been the development of microfabricated neural prostheses which can act as either sensors (multielectrode recording arrays) or actuators (neural stimulators) (3–6). Microfabricated silicon and polymer intracortical probes are being increasingly investigated as part of Brain Computer Interfaces (BCIs) where motor intent of a paraplegic or quadriplegic patient can be recorded, decoded and these signals can be used to drive a robotic prosthesis. Deep Brain Stimulation (DBS) of implanted probes is also used to treat motor (Parkinson's disease) or behavioral (Depression, Obsessive Compulsive Disorder, Tourette Syndrome) disorders. Although commercial deep brain stimulation are microwire arrays, silicon neuroprobes are also being investigated for neural stimulation. One of the challenges to microfabricated neural probe development has been the ability to achieve consistent long-term neural recordings which has prevented the widespread clinical use of intracortical probe technology in humans. One of the prominent causes for recording failure is the development of a glial scar layer around implanted probes which isolates the implant from adjacent neural cells and increases the electrode impedance to neural signal acquisition of local field potential diminishing probe recording quality over time. An active area of research is to improve the electrode-cell interface and limit the degree of gliosis around probes by incorporating or coating them with anti-inflammatory drugs or neural cell adhesion molecules, decreasing electrode impedance using conductive materials such as conductive polymers, or to manipulate device size and material to create more flexible neural probes. Several studies have shown that flexible polymer based probes provide a better mechanical match of the device compliance with that of adjacent neural tissues which attenuates chronic tissue responses. In addition to cortical probes, progress in fabricating cochlear and retinal neuroprostheses use direct electrical stimulation to restore hearing and vision in patients. A cochlear implant transmits signals from a sound recording array directly into the cochlear nerve bypassing hair cell movements in the cochlea which can be damaged in sensorineural hearing loss (5). A retinal implant can treat patients who have loss of photoreceptors by decoding pixels recorded from an external camera (usually embedded in a special pair of glasses) and using an electrode array to directly stimulate the retinal ganglion cells thereby bypassing the damaged layers of the retina (6). These types of neuroprostheses have been critical towards restoring independence in paralyzed patients, as well as hearing and sight. The promise of using microfabricated electrode arrays is to improve the recording potential of motor intent, allow precise stimulation of specific brain regions enabling more targeted stimulation of deep brain structures or to improve resolution of restorative implants treating hearing and vision loss.

A third impact of microdevices has been the development of microfluidic diagnostics which can aid clinical activity by providing point of care analysis of clinical samples. Amongst the microfluidic systems which are in development or have been commercialized (12) a large number of these systems are being developed as portable blood separation and analysis platforms. Point of care blood analyses range from portable blood chemistry analyzers

which can be analyzed at a patient bedside usually from a finger prick drop of blood to the development of portable flow cytometry systems (14) with the hope of performing complete blood count (CBC) analyses at the point of care (15). Another promising application of microfluidic blood analysis platforms is the potential to create automated blood sampling and diagnostic tools which may be used for high frequency blood analysis (16, 17). Such tools may be especially useful for analyzing blood during extracorporeal circulation including cardiopulmonary bypass, extracorporeal life support (ECLS) and hemodialysis to monitor blood health, blood biomarkers and immune activation to provide clinicians information about a patient's blood health during circulation. Of particular interest is the development of microimmunoassays (18, 19) which can detect multiple biomarkers in parallel. When implemented as a continuous flow diagnostic, such devices may be used to measure plasma biomarker concentrations at high sampling frequencies within a microfluidic analytical system during extracorporeal procedures (16, 17) which would allow the clinical team to determine any significant changes in blood health as soon as they occur in order to anticipate complications in patients and allow earlier intervention and treatment adjustments.

Micro and nanotechnologies are also being developed as components within Artificial Organs, especially in extracorporeal circulation devices. The development of microfabricated hemodialysis membranes (20) have well defined pore sizes with extremely narrow size distributions and well defined molecular weight cutoffs (MWCO) and the potential of portable hemodialysis systems (21, 22) could have a major impact on the quality of life of dialysis patients by allowing portable, continuous blood hemodialysis to reduce waste accumulation in the bloodstream and decreasing the time spent undergoing hemodialysis treatment at a dialysis clinic.

Finally, Organ on a Chip platforms may be used either as artificial organs as themselves, or as platforms for studying physiology or disease progression (10, 11). Organ on a Chip platforms are usually developed as artificial polymeric microfluidic structures which support organ specific cell culture and are often designed to promote organ specific cell organization or physiological environment. A number of microscale organoids have been realized including: cardiac microtissues (heart on a chip), lung alveolar epithelial cells with pneumatically actuated respiration simulation (lung on a chip), organized renal proximal tubular epithelial cell cultures to create simulated nephrons (kidney on a chip), organotypic brain slice cultures (brain on a chip), multi-compartment neural cultures with communicative microchannels (neurocircuitry on a chip) (23, 24), hepatocyte cultures to monitor drug metabolism (liver on a chip), and platforms for supporting endothelial cell organization and vascularization (blood vessel on a chip). Such systems are notable for their ability to promote multicellular organoid organization and mimic natural physiological processes. These systems are most often used to study disease progression or drug interactions but several also enable the study of mechanotransduction pathways; especially in lung on a chip and blood vessel on a chip type devices.

The development of microtechnologies and microfluidic platforms have had a major and continuing impact on the advancement of Artificial Organs. Physical sensors, neural implants, clinical diagnostics, and microcellular engineering platforms augment and

complement the development of many types of artificial organs either as a part of the artificial organ itself or providing diagnostics during development and testing of these systems. However, despite these impacts, many of these technologies face particular challenges towards obtaining FDA approval and widespread implementation including: ensuring biocompatibility and long term performance of implanted and blood contacting devices and microfabricated components as well as addressing the significantly higher manufacturing and development costs of microdevices compared to other manufacturing methods which create barriers to market introduction. In order to have the greatest impact such biomedical microdevices should be developed in close consultation between engineers, clinicians and basic science disciplines so that the need for and effect of novel diagnostics may be understood in the context of up-to-date best clinical practices. In this way translational advances may be made by the combined and coordinated expertise of researchers optimally combining their respective expertise to develop next generation diagnostics which are best suited to clinical needs. These medical microdevices are beginning to be introduced into medical practice and will continue to have a positive impact on patients' treatment and quality of life.

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Biography

Jeffrey D. Zahn is a professor of Biomedical Engineering at Rutgers University and serves on the editorial board of *Artificial Organs*. He was awarded a doctorate in Bioengineering from the Joint Graduate Group in Bioengineering from the University of California at San Francisco and Berkeley. Dr. Zahn's research focuses around the development of microfabricated devices for point of care clinical diagnostics and health management. Dr. Zahn's current research areas include: blood handling and analysis microdevices, a 'smart' single cell electroporation and cell transformation microdevice, neural cell culture platforms, multielectrode arrays and flexible cortical neural probes.

Figure 1.

A montage of several devices fabricated by Dr. Zahn and research colleagues (A) Continuous plasma sample collection sampled from an animal model of pediatric ECLS at the PSUHMC animal farm using the device reported in (16). (B) Dr. Zahn and colleagues in the surgical suite during collection. (C) A microfluidic magnetic immunocytometry processing platform (18) (D) A polymer intracortical recording probe with 16 independent recording electrodes. (E) Compartmentalized neural cultures to create mini-neurocircuits (23)