WAKE FOREST
UNIVERSITY
SCHOOL *of* MEDICINE
THE BOWMAN GRAY CAMPUS

Department of Pathology

September 6, 2005

Yves Brun, Systems Biology/Microbiology Faculty Search,
Department of Biology, Indiana University,
Jordan Hall 142, 1001 E 3rd Street,
Bloomington, IN 47405-7005

Dear Dr. Brun,

I would like to apply for the open position in your institution (FACULTY POSITIONS, SYSTEMS BIOLOGY/MICROBIOLOGY). I am sending a set of my credentials to you and representatives of the respective institutions. The paramount experience that has influenced my decision to apply for this position, however, was several years of Biomedical research positions (Postdoctoral, Senior Research Fellow, and Scientist) following my MS.c. and Ph.D. from University of Waterloo. Currently I am conducting research in the area of cancer biology at Wake Forest University Baptist Medical Center. I have also initiated to use nanotechnology as our center stage to develop nanoscale devices that can deliver cancer prevention agents and also create biofouling-indifferent sensors that can detect cancer-associated biomarkers. Concomitant with my current study I have a collaborative research with different institutions (JPL, NASA; Department of Physics (WFU) and MEM Engineering section of the University of Maryland), to develop different components for this project. I am very independent investigator and on the side of academic career I am very entrepreneur and creative. I am looking forward to find a suitable position in a reputable institution and continue my studies. From point of material science I have been working with JPL, NASA and University of Wellesley, Auckland, New Zealand. I have a chance to receive fund from different funding agencies including Congressionally Directed Medical Research Programs (CDMRP).

As my enclosed curriculum vita indicates, I received my Ph.D., with a major in molecular biology/toxicology from University of Waterloo in 2000. Prior to that, I obtained a MS.c. in microbial biotechnology (UFW) and a BS.c. in biological sciences. I also had biomedical and molecular biology training and work experience at Children Hospital Medical Center, LSU Health Science Center in different research projects. My expertise extends to experience in industrial, medical research activities, teaching as well as providing problem solution & training programs.

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I have acquired the high degree of expertise in analytical and communication skills. Moreover, my familiarity with state-of-the-art computer assisted researching biotechnology expanded my skills. I have had a chance to involve in different research projects and acquainted with many laboratories. These work experiences have enhanced my appreciation for the research I am pursuing. As you will note I supplemented my formal academic training with seminars and presentations in various institutions.

Details of my background and contributions are documented in my enclosed CV. I am Canadian citizen and established my higher education in Canada. Please feel free to contact me at 336-716-3975 or by e-mail at amallaki@wfubmc.edu. Thank you for taking the time to review my CV, and I look forward to receive your response.

Kind Regards,

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Title/Referral Page
No Page Limit

a. Proposal title (up to 160 characters)

Use of Bi-layer Polypyrrole Actuating Valve for Auto-responsive Drug (Anti-Cancer) Delivery System

b. Proposal log number

BC050165

c. PI's full name (first, middle initial, last)

DR. ALI MALLAKIN

d. PI's institution

WAKE FOREST UNIVERSITY BAPTIST MEDICAL CENTER

e. Award mechanism

CLINICAL TRANSLATIONAL RESEARCH AWARD (CTR)

f. Keyword descriptive technical terms

Bi-layer Polymeric Valve, Polypyrrole, Breast Tumor, Anti-Cancer Drugs, Delivery System

g. Conflicts of interest: Include the following information (no page limit)

Name	Institutional Affiliation(s)	Role(s) on Proposed Project or Perceived Conflicts of Interest

Pre-proposal Translatability Statement: The clinical trial is a necessary segment of research in the medical technology and/or drug development processes that tests the product or device to determine such factors as safety, efficacy, and adverse reactions in a human population. It has been reported that patients with advanced cancer who used an implantable drug-delivery device to control their pain had better pain relief, fewer toxic side effects, and better survival than patients who received intensive medical pain management. When the oral medication can not relieve the pain or causes uncomfortable side effects that impact the quality of life, suitable drug delivery system may be a promising alternative to be selected. Clinical studies have shown that improved pain relief (in our study: application of anti-cancer drug such as "letrozole", which indicates it can prevent breast cancer) is possible with a programmable well selected drug delivery system. Doctors have been using letrozole to treat breast cancer after it spreads.

A drug delivery system is a clinically proven pain management therapy that delivers pain medication directly to the area (e.g spine). Delivery of pain medication to the spinal fluid blocks pain signals that travel to the brain. This mode of delivery can provide significant pain control with a small fraction of the dose that would be required with oral medications. The current drug delivery systems consist of a small device, sometimes called a pain-control pump, surgically placed under the skin of the abdomen, and a soft tube carries the medication to the designated area (e.g.intrathecal). The medication dosage can also be determined by a physician through a portable computer and suitable software. In our study following a successful in-vitro drug delivery test, in order to translate the in-vitro study of the bi-layer polypyrrole actuating valve to clinical trail, first initial in-vivo study will be performed on animal models. Upon acceptable results from this study the model will be implemented to one year clinical trial. For this purpose the trial that involves $\simeq$ 100 patients can be designed. They will be assigned to two groups. One group will receive anti-cancer drug, or comprehensive medical management for their pain. A team of health care professionals who know the most effective anti-cancer drug or pain medication for each patient start the least toxic dose and move up to medications with more side effects until the pain is relieved. The second group will receive the anti-cancer drug or CMM via the drug delivery device. The drug delivery system delivers anti-tumor or "narcotic" pain medications (e.g. morphine) to the location (e.g. spinal fluid or tumor cells). In this case much smaller doses is required compared when the same drugs are taken by mouth or injected. Our device will be designed in a form of "auto-responsive drug delivery system", in which a sensor measures a specific marker (e.g specific tumor marker) and releases medication that the patient requires at any given moment. In case of pain the trial participants rate their pain as well as the side effects of their pain medication (constipation, fatigue...etc) on scales from 0 (least) to 10 (worst). In case of anti-cancer drug, the professionals determine the effect of drugs on tumor cells by use of clinical procedures. Survival rate will be also determined. The better survival among users of the auto-responsive drug delivery device can be expected, which may be explained by the fact that they experienced a larger reduction in toxic side effects. The percent of patients that their pain and/or tumor could not be treated by the conventional drug delivery methods will be also determined. This is a well-designed study that shows a real benefit from the use of a drug delivery system for control of cancer (or pain).

Pre-proposal Body:

A wide range of materials has been investigated for use within the human body. One class of useful devices that can be created with "biocompatible materials" is the micro-fabricated drug delivery devices. The conductive polymer polypyrrole (PPy) is a suitable material for the development of biocompatible actuators. Conducting polymers (e.g. EAP, PPy), undergo volume changes upon electrochemical actuation. The electrical actuation of these materials is based on the fact that their oxidized state has different electric charge than that of their reduced state.

Controlled drug release involves the combination of a polymer with the active agent in such a way that the agent can be delivered in a designed manner. These devices are designed to control the release of active agents that will create desired effects within the body or target organ. Recent works by different investigators have shown that micro particles functionalized with specific binding moieties can bind to target areas to accomplish site-specific delivery. Implantable and/or self-responsive drug delivery devices with sensors, telemetry, valves, and drug storage reservoirs will provide patients with an alternative method of medication. There is still a need to develop a "responsive drug delivery system", in which a sensor measures a marker in patient's body and releases medication that the patient requires at any given moment. In this way, it is possible to control the drug concentration in the patient's body and enhance the drug efficiency. In order to achieve a responsive drug delivery system, a reliable release device (e.g., a valve) needs to be developed. The requirements for such a release method are biocompatibility, low energy consumption, and minimal or no leakage. We plan to develop an auto-responsive drug delivery device that incorporated a biosensor capable of sensing and actuating the release drugs in response to a patient's therapeutic needs.

Drug reservoirs covered by polymeric valves which can be opened and closed reversibly by applying a small voltage has already been developed. The valves are designed as a bi-layer structure, one layer of which is a thin metal film (gold), functioning as a structural layer and a working electrode, and the other is an electrochemically deposited polypyrrole (PPy) film. The latter can shrink depending on applied voltages. The actuation mechanism of the polypyrrole film is based on ion flux in and out of the polymer upon oxidizing and reducing the film (Dr.E.Smela, University of Maryland). The volume change of the polypyrrole film forces the bi-layer to bend, resulting in the opening and closing of the valve. In practice this valve can work as an "artificial muscle." This type of actuator only operates in electrolytic solutions, such as body fluids. Fortunately, it has been demonstrated that Polypyrrole is biocompatible and unlikely to cause side effects in body. To reduce the power consumption needed for actuation of the valve and control the amount of drug released from the chamber, the size of the valve can be adjusted to micrometer. Using MEMS processes, the distance between the two electrodes can be further decreased so that lower voltages can be applied to actuate the valves. The voltage required for the actuation can be low as 1 V and the current lower than 1 mA for an actuator with an area of 4×10^{-2} mm. By cycling the voltage between negative and positive values, the bi-layer valves can be opened and closed repeatedly.

Experimental Design and Methodology:

Design and production of bilayer valves will perform through collaboration with Dr. E. Smela, University of Maryland. In brief, silicon wafer covered with a SiO_2 film (~150nm) insulator can be used as the substrate of the drug delivery device. Initially the RCA1 (DI water: NH_4OH (27%): H_2O_2 = 5:1:1 by volume ratio) wafer cleaning process will be used to clean the wafer. After the wafer cleaning process, Cr/Au (5nm/30nm) metal layers will be deposited on the top of the wafer surface. Photoresist (Shipley 1827) will be applied to pattern the metal layer on the SiO_2. A dilute polyimide, that can be used as a differential adhesion layer to seal the vial, will be coated on the substrate, after which the same photoresist will be used to pattern the polyimide thin layer. A second, thicker Au layer (~300nm) will be deposit on the polyimide and original Au layer, and the same photoresist applies to pattern the Au layer. Next, the back side of the wafer engraves to act as the drug reservoir. Photoresist (AZ 4620) which can form thicker layers will be used to pattern the back side of the wafer and the wafer will be imprinted using deep reactive ion etching (DRIE).

To test this drug delivery device a PDMS chip with a small chamber to store the drug fill with fluorescent dye. Finally, epoxy glue used to seal the PDMS chip against the vials.

Electrochemical Function:

A potentiostat (Gamry Instrument PC4/750) controlled by related software can be used for the electropolymerization of pyrole and to actuate the drug release valve. Experiments have been already executed in a single compartment glass cell.

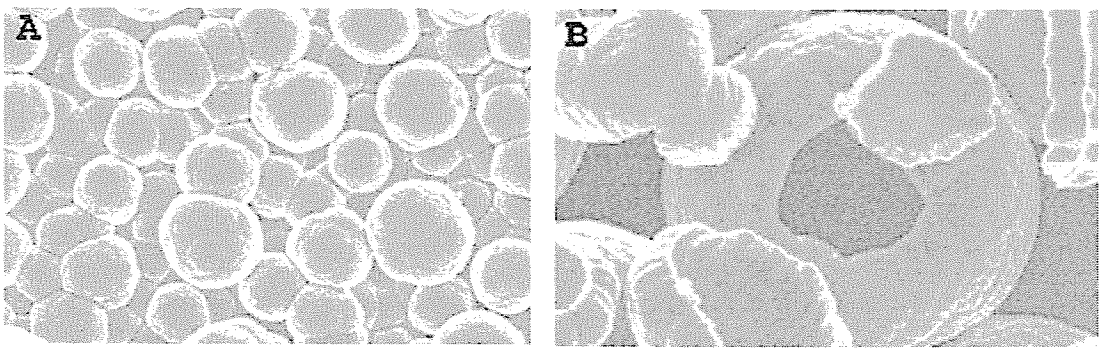

Figure 1. A) Scanning Electron Microscope (SEM) picture of uniform PPy film, B) Picture of non-uniform PPy film shows how the actuating valve functions.

In an experiment that has been conducted previously by the M. Madou and S. Daunert group, when the device was immersed into the buffer and the flap was opened by the application of a potential (1Volt), fluorescent dye was released and observed by eye. Although some valves were not functional, functional valves showed no observable dye leakage before actuation. Upon closing the functional valves, no dye leakage was observed. A prototype of a the drug delivery device has demonstrated that a Au/PPy(DBS) bilayer as a valve can be opened and closed in a short time (~20s). This preliminary test demonstrated the possibility for achieving efficient drug release by bending the bilayer from the substrate simply by applying a small potential.

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Biographical Sketch of Investigators:

I. Elizabeth Smela., PhD., She is associate professor of Mechanical Engineering at the Department of Mechanical Engineering, University of Maryland. She has interest on microfabricating conjugated polymer-based devices on silicon, including actuators, light emitting diodes (LEDs), and sensors. Also her other interests are combining organic materials, especially conjugated polymers, with silicon microfabrication techniques to make new devices; microactuators and microfabricated light emitting diodes (LEDs) and sensors; the combination of living cells with sensors and microfabricated systems; fiber optic sensors, surface modification and self-assembled monolayers, characterization of conjugated polymer materials and their behavior; development of functional materials with tailored morphologies.

II. Edward A. Levine, M.D., E. Levine is a professor in the Section of Surgical Oncology at Wake Forest University School of Medicine. He initiated the sentinel node mapping program for breast cancer at Wake Forest University Baptist Medical Center. His program is one of a programs approved in North America for participation in the mapping trial. The primary goals of his study is to determine a) control of the spread of breast cancer is equivalent between the two procedures, b) the overall survival and number of years without recurrence are comparable, and c) the side effects associated with sentinel node removal (lymphedema or swelling caused by excess fluid buildup, a persistent burning sensation, infection and limitation of shoulder movement) are less severe than those from conventional axillary dissection. The results of his study will provide essential information about survival, cancer control, and surgical side effects so doctors can make informed decisions about treatment.

III. Ali Mallakin, PhD., He is NIH research scientist/visiting faculty working in the area of cancer biology at Wake Forest University Baptist Medical Center. He gained his M.Sc. and Ph.D. in Microbial Biotechnology and Molecular Toxicology respectively at University Waterloo, ON, Canada, followed by training in signal transduction, virology, ophthalmology, genetic (application of micro-array technology) in the United States. He has more than ten years industrial/laboratory research experience. Currently he works on the aberrant expression, deletion and mutation of *h*DMP1 in human lung and breast cancer. He would like to provide new evidence that suggest the importance of the *h*DMP1 transcription factor in Ras-ARF signaling. He also apply gene micro-array to extent his observation of the complicated process of lung and breast carcinogenesis and pattern of gene expression. Recently he has been involved with the application of nanothechnology in cancer biology. His research interest also involves chemical engineering, biochemistry and computation microscopy, which gained through collaborative work. He has been collaborating with different agencies such as JPL, NASA on different projects.

IV. Kazushi Inoue, MD., PhD. He is assistant professor of pathology and cancer biology at Wake Forest Universiy Baptist Medical Center. He is an MD/PhD trained in Japan followed by training, first for 6 years at Osaka University on Leukemia, and for another 6 years in United States. He currently works on understanding the mechanisms of

regulation of the Dmp1-Arf-p53 signaling. INK4a/ARF located on human chromosome 9p21 is disrupted in nearly 40% of human cancers, at a frequency estimated to be close to that of the p53 locus. This locus encodes two distinct tumor suppressor proteins: $p16^{INK4a}$, which specifically binds to CDK4 to inhibit Rb phosphorylation by CDKs; and $p14^{ARF}$ ($p19^{Arf}$ in mice), which binds and negatively regulates MDM2, thereby stabilizing and activating p53. $p19^{Arf}$ is induced by potentially oncogenic signals stemming from overexpression of oncogenes such as c-Myc, E1A, E2F-1, and activated Ras.

V. Martin Guthold. PhD., He is assistant professor at the Department of Physics, Wake Forest University. His general research interests are in the areas of Biophysics, Molecular Biology and nanotechnology. He is using the nanoManipulator - a modified scanning force microscope - to mechanically manipulate biological macromolecules (DNA, fibrin, pili fibers) to measure their physical and mechanical properties. These properties will be related to the physiological function of the biomolecules. In particular, he is working on the nanoManipulator (the nanoManipulator is a modified Scanning Force Microscope with which the sample can be not only imaged but also manipulated in a controlled matter).

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