APP N03-3

Annotated Bibliography-Nano

Engr 1282

Spring 2020

AJ Senthilkumar

M. Parke 12:40

02.14.20

Exploratory Design in Medical Nanotechnology: A Mechanical Artificial Red Cell

Frcitas, Robert A. “Exploratory Design in Medical Nanotechnology: A Mechanical Artificial Red Cell.” *Artificial Cells, Blood Substitutes, and Biotechnology*, vol. 26, no. 4, 1998, pp. 411–430., doi:10.3109/10731199809117682.

This article describes the design for an artificial red blood cell. This blood cell will deliver more oxygen throughout the body and will also manage carbonic acidity. It is powered by glucose and also has many technologies to communicate information about pressure and reactions throughout the body back to the physician. This device allows for a more comprehensive understanding of the body as well as a heightened functioning of the bloodstream. The device is made of a very strong material that also allows for proper amounts of pressure throughout the bloodstream. There is also a detailed description of the motor that allows for the correct flow of Carbon Dioxide. This device is detailed and has accounted for many precautions with the use of the device. The intended administration of the device is via injection. The only limitations of the device is that the field is not advanced enough to create the device. The design of the artificial respirocyte is detailed and explains the purpose of each decision with the device. The advantages of this device is that it is very effective in improving blood flow through the device but it is so advanced that there is not enough available in the field to construct the device. Future research on this topic relates to the construction of the product. This article was written in 1998 so many developments have been made to the industry since then.

Nanotechnology and nanomaterial-based no-wash electrochemical biosensors: from design to application

Zhang, Yong, and Xiaoyuan Chen. “Nanotechnology and Nanomaterial-Based No-Wash Electrochemical Biosensors: from Design to Application.” *Nanoscale*, vol. 11, no. 41, 2019, pp. 19105–19118., doi:10.1039/c9nr05696c.

The subject of this article is how no-wash ECBs are improved by various nanomaterials and why they are better than assays. The no-wash sensor is used to detect various things and is better than what is currently on the market because it reduces the time it takes to detect and utilizes a simpler procedure. This can revolutionize the way that signals are detected and diagnosed and further many fields. It is especially useful in diagnosis, food analysis, and environmental analysis. In a specific example, it has been used to identify Cotinine, a substance that metabolizes nicotine. This has been used to analyze smoke exposure and tobacco use. It is advantageous because they significantly reduce the time of detection and also can be used on a smaller scale. There are some disadvantages to this product, the main one being that they cannot resist environmental shifts in signals. There are many differences in the human body and the

no-wash ECB cannot resist them completely, thus this can pose some issues in the accuracy of the product. Future research was summarized in three bullets; one, more advanced nanomaterials need to be used to amplify the signal to noise ratio so that it is more suitable in physiological settings. Two, more research needs to be done so that the no-wash ECB can be used on a more widespread scale. The authors say that there are no conflicts of interest.

Micro- and nanotechnology for viral detection

Cheng, Xuanhong, et al. "Micro- and Nanotechnology for Viral Detection." ***Analytical and Bioanalytical Chemistry*****, vol. 393, no. 2, Apr. 2008, pp. 487–501., doi:10.1007/s00216-008-2514-x.**

This article focuses on the importance of viral detection. Viruses can be difficult to detect because they are so large and complex. The general approach to detecting these viruses are as follows: seek a response from the host to the virus, detect a viruses' "fingerprint", and detecting the viral particles. These three approaches have been enhanced with nanotechnology. IFA and EIA are used to flag responses and signal them when a virus enters. Thus, the virus can be detected by the signal. There are many optical approaches each with their own benefits. They use enzymes as the detection agents. Additionally, there are lab-on-a-chip solutions. There have been genetic analysis microchips used to detect pathogens. These devices are small enough to go through the bloodstream but can accurately identify foreign bodies. These solutions are generally expensive, which is why the new developments are advantageous. Thermal plastic chips that have been impregnated with silica particles are financially advantageous and can diagnose on a larger scale. Further research must be done in development and accessibility of the products.

Dynamics Analysis and Motion Planning for Automated Cell Transportation With Optical Tweezers

Wu, Yanhua, et al. "Dynamics Analysis and Motion Planning for Automated Cell Transportation With Optical Tweezers." ***IEEE/ASME Transactions on Mechatronics*****, vol. 18, no. 2, 2013, pp. 706–713., doi:10.1109/tmech.2011.2181856.**

The subject of this article is the use of optical tweezers in the aid of cell transport. The optical tweezers can move nanosized particles automatically without contact. This device is used in many applications and can be adjusted for many different purposes. Transporting these cells is important to develop solutions to many medical issues. Unlike pipettes and other alternatives, optical tweezers can place a cell at a specified location which makes it convenient for further work. This plan relies on manipulations of velocity in order to project the cells through the path.

There is also path planning involved using a laser pointer which allows for more direct movement. Future research should involve a more automated approach to allow for path planning. This method is very convenient but it is meticulous and time-consuming, which is why an automated path planner would make this option more favorable.

The emerging field of RNA nanotechnology

Guo, Peixuan. "The Emerging Field of RNA Nanotechnology." *RNA Nanotechnology and Therapeutics*, 2013, pp. 3–22., doi:10.1201/b15152-3.

RNA is an important tool in DNA replication because RNA can be used to manipulate various parts to get the desired results. RNA is made up of blocks that can be programmed to perform certain tasks in the body. RNA manipulation is compared to the stretching and folding of DNA particles. Many of these methods rely upon the structure of DNA. The applications of RNA are used for structural purposes in tools like dimers and trimers. Many of the applications are for diagnosis. RNA can be used to create signals to detect certain pathogens and therefore diagnose diseases. The current problem with these technologies is that they are difficult to reproduce on a large scale, with RNA, they are easily replicable and able to be manufactured on a large scale with minimal errors. As an aside, the FDA classifies RNA as a chemical entity instead of a biological one which would allow for easier approval from the FDA. The primary challenge is predicting RNA folding, it is generally unstable in the human body which makes it difficult to predict its patterns. It is also very expensive.

Annotated Bibliography Nanotechnology

Engineering 1282.02H

Spring 2020

Jess Timog, Seat 12

C. Wallwey GTA MWF 12:40PM

Date of Submission: 2/14/2020

1. **Baig, Mirza Muhammad Faran Ashraf, et al. "Synthetic NRG-1 functionalized DNA nanospindels toward HER2/neu targets for *in vitro* anti-cancer activity assessment toward breast cancer MCF-7 cells." *Journal of Pharmaceutical and Biomedical Analysis* 182 (2020).**

   The delivery of an anti-tumor drug, Daunorubicin (DR), was done by the experimentation of nanospindels. This study was accomplished by designing and programming the size, shape, and topology of the nanospindels (DNA-NS). DNA-NS was preferable for transporting this drug due to its ability to act as a macromolecule when bind with DR with the characteristics of being rigid, stable, and having a monocrystalline structure. The drug was able to bind to the nano-architects because of the drug's intrinsic DNA binding ability. Once they were bound together, DNA-NS interacts with the cell's surface receptors and is internalized by the breast cells. The DNA-NS is digests by lysosomes, releasing DR, and causing apoptosis to only the cancerous cells.

   The results of this study showed that the delivery system was successful. The nanospindels improves on the accuracy and efficiency of the delivery of anti-tumor drugs. Rather than the patient having exposure to DR in unwanted sits and causing cytotoxicity to normal cells, the study allows a new method of precise targeting of cancerous cells. The advantage to this technology is that it has enhanced apoptosis to targeted cells, as compared to the drug being delivered without the nanospindels in the study where the results showed a greater chance of paxillin medicated exocytosis. However, the nanospindels showed reduced viability to surrounding cells and must have further research on the accuracy in the technology in delivering the anti-tumor drugs. As stated in the study, there is no presence of competing interest or institutions. Grants and accommodations that were given to achieve this study was the State Key Laboratory of Analytical Chemistry of Life Science and National Key R&D Program of China.

2. **Nadappuram, Binoy Paulose, et al. "Nanoscale tweezers for single-cell biopsies." *Nature Nanotechnology* 14.1 (2019) : 80-88.**

   The extraction and study of single cells was carried out through the experimentation of nanoscale tweezers. This study was accomplished creating double barreled quartz capillaries with nanoelectrodes at the tip. A steady-state current was used in each of the nanoelectrodes and applied by AC signal to the nanoelectrodes through copper wires. Dielectrophoresis (DEP) is used to trap the targeted molecules or organelles between the nanoelectrodes with a distance of 10-20 nanometers and creating a high electric field gradient. The user is able to control the XYZ positioning of the nanopipette and the duration and strength of voltage that is delivered. The problem with technology before was that single cells could not be studied in action due to its loss of interconnection and resulting lysis when extraction was to occur. This device tested its ability to extract DNA directly from the nucleus of human osteosarcoma and human pulmonary artery endothelial cells, while keeping their viability intact.

   The results of the experiment showed that the tweezers were successful. The trapping efficiency increased as the applied voltage increased, however this resulted in unwanted

heating and bubbling with the cell. Trapping within a solution that contained DNA of various sizes and fluorescently labelled. The functional integrity of the DNA extraction was checked by a quantitative polymerase chain reaction (qPCR) and showed that it was successful in that extracting only rDNA and minimal amount of cytoplasm and media. Trapping within a cell, a similar florescent indicator was used to identify mRNA from cytoplasm and mitochondrion from a neuron. Before, during, and after, the variation of florescence presence was monitored, graphed, and pictured to show the success of the extraction of its presence and then lack thereof. The cell was able to be biopsied twice with the tweezers and it was still viable due to its precision.

The disadvantage of this technology is how the most efficient method of extraction also effects the surrounding area due to heat. The problem of radiating heat from the AC current has to be addressed before it can be further applied into the field. A conflict of interest that could be found is the IC Research Fellowship funding and that the group must have viable results in order to justify its research and use of money. The advantage with the nanoscale tweezers is that is cheap to manufacture, user-friendly, and can be modified to extract other biopsies.

3. Perton, Francis, et al. "Wrapped stellate silica nanocomposites as biocompatible luminescent nanoplatforms assessed *in vivo*." *Journal of Colloid and Interface Science* 542 (2019) : 469-482.

   This study was done to address the problem of limited photostability and broad emission spectra that caused florescence overlapping which could be solved using quantum dots (QD), however QDs release toxins. There was a need for a new encapsulation of QD that would be simplified with a high yield of synthesis for medical use, control of the nanocomposite structure and homogenous dispersion of composite particles and pore size. The study used stellate mesoporous silica (STMS) that would hold QD with high efficiency in delivery. It was judged based on its structure, colloidal stability, the change in its surface, and the florescence imagery. Two types of wrapping, small pore silica (SPS) and tight polymer capping, were tested to determine which pore size would be most stable in containing QD.

   The results showed that the SPS was the most secure wrapping of QD in that it had the facility that was highly controllable and functional in stopping the release of the toxins. The advantages to this technology are that it prolonged the shelf life and storage time for the drug since it contained the drug's release of toxins and has a high colloidal stability in a broad range in pH levels. The disadvantage is that it is only known that it keeps in the toxins of QD, other drugs were not tested with this coating. Further testing would be to see if there were more functionalities to silica nanoplatforms which can combine with luminescence and to test the coating in mice since it was done on zebrafish in this study. The article states that there are no conflicts of interest toward this study and was granted money from the European Regional Development Fund and Institut National du Cancer.

4. Polyakova, V. V., et al. “Combined scanning probe nanolithography and liquid etching techniques for profiled nanostructures formation.” *Journal of Physics: Conference Series* 1410.1 (2019) : 99-105.

   This study was carried out in order to discover more in local anodic oxidation (LAO), liquid etching, and the effect of voltage amplitude to nanostructures. This study was accomplished by inserting an AFM probe into oxide nanostructures and increasing the amplitude of the voltage. A mask of liquid etching was used to study the profile of the silicon that was probed. The profilogram that was produced from the probing showed that as the impulses of applied voltage increased, the height and diameter of the oxide nanostructures would increase, and the depth and diameter of the profiled nanostructures on the silicon surface.

   The research was done due to the need for more resolution and accuracy in technology, especially since nanoelectronics are shrinking, thus the accuracy of memristors and lithography needs to improve. The advantage to this method is that it validates the need for more research in this field in order to compete with the technology decreasing in size. The disadvantage to this study is that the results were inconclusive and simply claiming that more research was needed to be done. Further research that was proposed by the study was how the effect of high levels of voltage on nanostructures. This research was funded by the Grant of the President of the Russian Federation.

5. Zhang, Jiaqi, Zhu, Qi, & Xing, Zipeng. “Preparation of new materials by ethylene glycol modification and $Al(OH)_3$ removing NZVI to remove sulfides in water.” *Journal of Hazardous Materials* 390 (2020).

   This study used nanoscale zero-valent iron (NZVI) due to its high surface area, standard redox potential, high allowance of reactivity with contaminants, specific affinity to contaminants in aqueous solutions, in order to remove sulfides in water. The problem being addressed by this study is that water contaminated by the smallest amount of sulfide cannot be used in municipalities and industry due to its odor. Other methods were used but none could completely remove the presence of sulfide and the pH levels would restrict the product that could be used in removal.

   Four study groups were used to test the efficiency of various variables for removing sulfide. Ethylene glycol (EG) was used since it prevented the oxidation of NZVI during preparation and drying when coming into contact with air and $Al(OH)_3$ was used since it had suspension stability and was positively charged and can remove negatively charged particles through electrostatic adsorption. Sulfide was removed by $Al(OH)_3$ attracting it toward the NZVI and the $Al(OH)_3$ and EG coated NZVI adorbs it through its hydroxide and oxide shell. The four study groups were NZVI coated in both EG and $Al(OH)_3$, NZVI coated in only EG or $Al(OH)_3$, and NZVI by itself. When placed into an aqueous solution containing sulfide, NZVI coated in both substances was 99.3% efficient in collecting and removing sulfide.

The advantage to this study is that the coatings were cheap and environmentally safe and can be used to remove sulfide in waterways. The disadvantages are that water corrosion prevents NZVI from being long lasting and EG cannot work under aerobic conditions. For further testing, the study recommended to reduce the presence of iron oxide production by having a tighter coating of EG and $Al(OH)_3$. The author declared that there was no conflict of interest for the research and it was funded by Heilongjiang provincial institutions of higher learning basic research funds basic research projects.

Annotated Nanotechnology Bibliography

Engineering 1282.02H

Spring 2020

Sean Sullivan

C. Wallwey 10/02/19 12:40PM

Date of Submission: 2/14/20

Article I: Nanotechnology in the arena of cancer immunotherapy

Citation:

> Asadujjaman, M., Cho, K.H., Jang, D. et al. "Nanotechnology in the Arena of Cancer Immunotherapy." SpringerLink, Springer Nature Switzerland, 19 Jan. 2020, link.springer.com/article/10.1007%2Fs12272-020-01207-4.

Article Summary:

This article details new innovative methods for using nanotechnology to aid immunotherapy in cancer treatment. Traditionally, immunotherapy was never seen as a viable addition to cancer treatment as it was too difficult to exact on cancerous material. Cancerous tumors contain an extremely immunosuppressive environment, making any type of immune response difficult in a cancerous region. However, thanks to numerous new technological developments, nanotechnology is now becoming a method for which immunotherapy can be successfully used in cancer treatment.

New technologies focus mainly on creating "tumor vaccines", molecules injected into a tumor that attach onto cells and elicit an immune response. Using micelles (small lipid layers formed to suspend chemicals inside), nanotechnology scientists can inject antigens that attach themselves to the cancerous cells and alert the immune system of their presence.

Other technologies such as nucleic acids are being considered for cancer treatment as well, since their toxic properties make them ideal candidates to directly induce cell lysis (death). These nucleic acids are relatively unstable, and are highly difficult to control, so more research must be conducted into their safe delivery before they can be used *in vivo*.

Article II: Nanotechnology applied to overcome tumor drug resistance

Citation:

> Gao, Z., Zhang, L., Sun, Y. "Nanotechnology applied to overcome tumor drug resistance." Elsevier B.V., PubMed, US National Library of Medicine National Institutes of Health, 12 June 2012, https://www.ncbi.nlm.nih.gov/pubmed/22698943.

Article Summary:

In this article, new emerging forms of nanotechnology are explored as possible venues to combat cancer cell drug resistance. It first emphasizes multidrug resistance as a primary issue in cancer treatment, since cancerous cells can develop resistance to the toxicity induced by chemotherapy as well as the accompanying oral drugs used in most treatments. The article mentions "ATP-binding cassette" transporters as the cause of the pseudo-immunity, as they initiate an efficient process of pumping drug material out of the cytoplasm as soon as it enters. However, other processes protect these canerous cells too, such as increased DNA repair activity and cell detoxification. To create more effective therapies for cancer treatment, the authors suggest that technologies are developed to attack several of these immunity vectors instead of just one. Nanotechnology, they suggest, is a key factor in the development of these new therapies.

The authors mention that nanoparticles can be designed to hold toxic chemicals inside them, waiting to deliver the drugs to only the infected cells. Their first specification of these nanoparticles is that they are between 10 and 100nm, as smaller particles would get flushed out by the liver and kidneys, and larger particles could not enter their target cells. These drugs can trigger "stealth endocytosis", a method of entering a cell that avoids alerting the cell membrane to the true contents of the invading object. They propose a glycol-based polypeptide body that holds toxic, highly-reactive substances to release upon entry to the cell.

Finally, the authors propose targeted heat as an entirely new cancer treatment vector. Using carbon nanotubes, researchers demonstrated the ability to inject substances into cancerous cells that absorbed the surrounding IR radiation and caused cell death through hyperthermia.

Article III: Scale-effects on oscillation characteristics of externally driven micropump

Citation:

Kanda, K., et al. “Scale-Effects on Oscillation Characteristics of Externally Driven Micropump.” 2007 Digest of Papers Microprocesses and Nanotechnology, Microprocesses and Nanotechnology, 2007 Digest of Papers, Nov. 2007, pp. 342–343. EBSCOhost, doi:10.1109/IMNC.2007.4456244.20-01207-4.

Article Summary:

This article details the application of actuators inside microchannels and LOC (lab on chips). The authors discuss the results from scaling down cantilever actuators, and any issues associated with their use.

The authors used a piezoelectric cantilever assumed to be “oscillating a microchannel wall” to signify a micropump. Once scaled down, the researchers determined that decreasing resonant frequencies led to negative influence on the channel actuation. Interestingly, they found no change of interference in the presence or absence of water in such channel. When testing the same circumstances with a thin film actuator, they found no interference and no negative effect on channel actuation. Conversely, they discovered a substantial change in the actuation frequency of the thin film channel with added water, leading them to conclude that water mass is only negligible in the cantilever actuator. For applications in nanotechnology, the optimal actuator will therefore largely depend on the qualities of the solution present and the type of actuation desired.

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Article IV: Label-free biomarker detection from whole blood

Citation:

Stern, E., Vacic, A., Rajan, N. et al. Label-free biomarker detection from whole blood. Nature Nanotech 5, 138–142 (2010). https://doi.org/10.1038/nnano.2009.353

Article Summary:

This article discusses a new concept for improved detection of biomarkers on a microchip. Previously, issues such as biofouling and nonspecific binding made it very difficult to accurately detect biomarkers from liquids such as human blood. With this new innovation, the authors say they can effectively isolate the biomarker detector the incoming blood and can instead pre-concentrate the biomarkers and "wash" the solution.

At the time of publication, label-free nanosensors were the most promising technolgoies for detecting biomarkers in liquids like blood. However, these sensors require purified buffers to take their measurements, making them impractical for most uses. The researchers' breakthrough, therefore, was to improve the environment around the sensor to increase its commercial viability. They created a microfluidic purification chip designed to capture biomarkers from solutions, wash the input channel, and release the antigens into a pure buffer suitable for biomarker detection.

The researchers describe their chip's detection process as follows. First, blood flows through the chip, and specific antibodies attached to the walls bind to biomarkers in the blood and hold them in place. Next, "wash and sensing buffers" are sent through the device. After washing, the solution is treated with UV light (to release the antibodies and attached biomarkers). After completion of this process, the nanosensor can easily detect the target biomarkers from the purified buffer.

The researchers' method of cleansing the input liquid into a pure buffer with target antibodies shows immense promise in the context of increasing availability of biomarker detection chips. Since this method increases the ease of detection, nanosensors can be configured to detect very minute changes in DNA, or very obscure biomarkers, allowing for a greater range of testing accuracy and reliability. Since many diseases can manifest in small cellular DNA changes, this proof-of-concept opens up many new opportunities to detect diseases that previously could not be studied without extensive resources.

Article V: Nano/Microfluidics for diagnosis of infectious diseases in developing countries.

Citation:

> Lee, Won Gu, et al. "Nano/Microfluidics for Diagnosis of Infectious Diseases in Developing Countries." ScienceDirect, Elsevier, PubMed, US National Library of Medicine National Institutes of Health, 30 Nov. 2009, https://www.ncbi.nlm.nih.gov/pubmed/19954755.

Article Summary:

In this article, new methods of using nanotechnology and microfluidics for disease detection in emerging countries are discussed. First, the authors define nanofluidics as the field of study in fluid flow in and around nanoscale object. Nanotechnology is the process by which this can be made possible. The authors first postulate that new technologies must be disposable, cost-effective, and portable, if they are to be widely used. They state that manufacturing microfabricated labs-on-a-chip can be done easily is used with common, mass-production capable materials like simple plastics.

Aside from their manufacturing, chips often have issues shrinking detection devices onto a microchip, the authors state. They say that a new technology called "mobile-based clinical microscopy" shows promise, as it essentially turns smartphone cameras into the detection devices for various diseases. Using bright field and fluorescence imaging, these devices were successfully used to detect tuberculosis and malaria. The authors say this method shows great promise in the field of nanotechnology as it allows LOC devices to become even smaller with their imaging processes taking place on external devices.

The researchers also detail new detection methods in their article, referencing specific innovations in cytometry to detect HIV in infected patients. They describe a microfabricated device that uses a channel with a 100μm inlet and 500μm outlet, to prioritize flow. They also say the channel was designed to be as simple as possible, since complex channel geometry decreased effectiveness of testing.

Finally, the authors mention issues regarding their meta-study of new nanotechnology and microfluidics findings. They say that diseases like HIV must be detected carefully, as current technologies require 400 copies of HIV per mL of whole blood. With other diseases like malaria, specific number of copies is less important, but creating dynamic testing environments where the disease can incubate and spread will be most useful.

APP N03-3

Engineering 1282H

Spring 2020

Zachary Niswonger

Parke 12:40 PM

Date of Submission: 2/13/20

Gao, N., Wang, W., Yang, E. H., "An Experimental Study on Ferromagnetic Nickel Nanowires Functionalized with Antibodies for Cell Separation." ***Nanotechnology*** **12.21 (2010): 1-9**

Previously, one main method for cell separation was coating iron oxide beads with antibodies specifically for the antigens of the cells to be separated, allowing the cells to bind to the beads via these interactions, then using a magnetic field to pull them out. However, this method is inefficient, leading the researchers to create a more efficient method, which they determined to be using nickel nanowires which had a much higher surface area to volume ratio. However, despite using materials more efficiently, these nanowires appeared to have a more toxic effect on the cells they were separating.

First, 25 micrometer nickel nanowires were constructed using templates, and then the antibodies were attached using a process of various rinses, incubations, and suspensions. Then, iron oxide beads were prepared similarly as a control group. The beads and nanowires were then stained red in order to observe the immobilization of the antibodies on the wires and beads. Next, the cell mixture to be separated was prepared, with MS1 cells to be separated. Then, multiple tests were prepared. A cell viability test was conducted by seeding MS1 cells into well plates and adding nickel nanowires, which were added to the wells and allowed to culture in order to determine the nanowire effect on cell growth. Next, cells were similarly seeded in well-plates, nanowires were added, and the wells were prepared for observation, in order to image the cells and nanowires. Finally, the cells and nanowires were added to a centrifuge tube and incubated, then placed under a magnetic field.

Firstly, the results showed that the beads and nanowires had similar antibody immobilization due to the brightness of the red fluorescent staining, however the nanowires have a much larger surface area to volume ratio making them more efficient. The test on cell growth showed similar results for the beads and wires and showed that cells were mostly still viable after contact with the nanowire and beads, however the toxicity of the nanowires raised as the ratio of wires to cells rose. The data also showed that cells separated by a large number of nickel nanowires were much more negatively affected by toxicity than those separated by few, which had almost no impact via toxicity. The nanowires were also shown to cause a greater decrease in cell growth than the beads for times greater than 1 day. Nanowires were also shown to be internalized by the cells much less frequently when they had actually been functionalized, but still a high amount were internalized. Then, the optimal concentration of nanowires for separation was determined by mixing cells with different nanowire concentrations. Finally, the nanowires were compared to the beads with the same concentration at different cell concentrations and the nanowires outperformed the beads at low cell concentration and performed similarly at high cell concentration.

Further studies on nickel nanowires as well as on nanowires of other material should be conducted in order to optimize cell separation. The authors made no acknowledgements to any funding sources.

He, Fengjiao, and Suqin Liu. "Detection of P. Aeruginosa Using Nano-Structured Electrode-Separated Piezoelectric DNA Biosensor." Talanta, vol. 62, no. 2, Feb. 2004, pp. 271–277.

This paper described the use of a quartz piezoelectric sensor that was used to detect P. aeruginosa. This was done by first extracting a source DNA from a sample of P. aeruginosa. This extracted DNA was then incubated and stored in a variety of different mediums for testing. The quartz piezoelectric sensor itself was constructed using silver coat electrodes, a transistor-transistor logic circuit for measuring, and a PC computer was used as a frequency counter. Next, membranes were synthesized using a sol-gel method and magnetic stirring machine. The experiment itself was conducted by coating the quartz crystal in the previously prepared membrane, then injecting single strand DNA into a detection cell followed by the P. aeruginosa DNA, then UV, IR, and SEM imaging were used to detect the presence of P. aeruginosa in the sample cell. Firstly, the UV light was used to determine whether or not the sample DNA had been contaminated in the preparation process, then the IR and SEM imaging were used to see the reaction product of the membrane and the membrane itself respectively. Other testing was also done which showed that the membrane was unstable in acidic solution while still stable in neutral and alkaline solutions, which meant that after testing acidic solutions could be used to recover the quartz crystal. Using the hybridization amount of the DNA with ss-DNA, the concentration of P. aeruginosa could be detected, and showed a linear relationship between frequency and mass of DNA.

This method of detection has various advantages over previous methods, as it could easily detect the presence of P. aeruginosa and roughly estimate the concentration, while previous methods were time consuming, had poor accuracy, and low detection limit. These previous methods included incubation and biochemistry reaction methods which identified the P. aeruginosa based on pigment and color but this did not suit some types of the bacteria. The Gram-stained method which also could not differentiate between cell types. This new method improved on all of these issues while also having the added advantage of the quartz crystal being entirely reusable. However, this method still requires a decent amount of preparation time, and only gives a very rough estimate of the bacteria concentration. It is suggested that this method be used in further research in the areas of environmental toxicants and bacteria, and it is also stated that this method can be further refined and improved to improve results.

This project was supported by the National Science Foundation of China, and shows no discernable conflicts of interest.

Kaja, S., et al. "Detection of Novel Biomarkers for Ovarian Cancer with an Optical Nanotechnology Detection System Enabling Label-Free Diagnostics." *Journal of Biomedical Optics* 17.8 (2012): 1-9

Current methods of diagnosing ovarian carcinoma need to be improved upon, as the current 5 year survival rate is only 50% due to the often late-stage diagnosis of the disease. Also, current technologies for biomarker diagnostics are costly and not time efficient. Typically,

biomarkers would be tested for using the ELISA test but there are currently no established biomarkers, therefore no validated tests. Because of this, these researches investigated a panel of six possible biomarkers utilizing an optical biosensor based on guided-mode resonance.

To conduct the experiment, first five different cell lines were used as models for ovarian carcinoma and cultured according to supplier recommendation. Then, the protein antibodies were obtained which would be used to detect the presence of the biomarkers. Then, the control data was gathered using the established method of immunoblotting, which involved separating the proteins from solution using electric signals and determining the concentration of protein. These concentrations were then plotted and a standard curve was generated. The guided-mode resonance, or GMR, detection worked by shining a light on the sample with a sensor which reflects a different wavelength at a different angle. This, with the use of an optical spectrum analyzer, could detect the presence of the proteins by following the shift in wavelength caused by the reaction of the antibodies with the proteins. The sensor itself is coated with silane which bonds the antibody to the surface of the sensor in order to enhance detection. The results showed that using the GMR method yielded similar results to the control group, showing the GMR method is effective in detecting proteins. They also tested for other biomarkers known to be present, but in too small of quantities to typically be discovered, however the GMR method was able to detect them, showing it had better sensitivity than previous methods. They then identified three specific biomarkers that were indicated to be more consistent according to the data, which were fibronectin, apolipoprotein A1, and TIMP3.

The authors suggested that future research be done on the accuracy of biomarker testing in ovarian carcinoma. This study was funded by an NIH grant as well as multiple other companies, none of which present conflicts of interest.

Lee, W.G., Kim, Y, Chung, B.G., Demirci, U,. Khademhosseini. “Nano/Microfluidics for Diagnosis of Infectious Diseases in Developing Countries.” *Advanced Drug Delivery Reviews* 62 (2010): 449-457

This journal article summarizes multiple new innovations in disease diagnosis by nanotechnology and microfluidics. These nanotechnology innovations address many of the weaknesses of conventional methods, as they allow for real time disease monitoring, are more affordable, need less equipment, and are easier to use and deliver to needy areas. However, nanotechnology still has its weaknesses, especially in diseases prevalent in developing areas such as HIV, malaria, and tuberculosis. These difficulties include being unable to detect the presence of disease sufficiently, difficulty optimizing methods, cost, and a lack of medical standards when it comes to nanotechnology.

The first innovation discusses is on chip detection and imaging, such as optical microscopy which has improved after the emergence of optofluidic technologies which utilize absorbance, fluorescence, chemiluminescence, and others. However, these can be expensive and difficult to maintain. Next, it addressed on-chip flow cytometry, which is the rapid counting of cells. The combination of miniaturized flow channels and digital camera technology has led to

the development of effective cytometry on chips. Lensless imaging techniques have also been developed for this use. An important concept from these innovations is the manipulation of flow channel geometry, as widening the channel at the point of observation slows the fluid at that point to allow more effective counting. On-chip immunoassay has also had recent developments leading to a great increase in speed and decrease in sample size compared to conventional methods. For example, an on-chip immunoassay to measure the concentration of molecules within channels has been developed as well as a dry cantilever assay which can also be useful for these nanochips. Finally, nanosensors using surface plasmon resonance and atomic force microscopy have been developed that when combined with imaging technology can rapidly detect diseases. Another example is the use of a silicon chip with a microarray of antibodies and an atomic force microscopy-based detector to detect viruses by detecting particles that interacted with the AFM tip.

The article suggests the continued development of previous nanotechnology chips that have been effective but not good enough, as well as continuing to find ways to minimize cost and complexity. This article was supported by NIH grants as well as partially by a Korea Research Foundation Grant, which indicates no conflicts of interest.

Verdoodt, N., Basso, C.R., Rossi, B.F., Pedrosa, V.A. "Development of a rapid and sensitive immunosensor for the detection of bacteria." ***Food Chemistry*** **221.1 (2017): 1792-1796.**

One popular previous method of bacteria detection is polymerase chain reaction and other sequencing approaches; however these have very high costs and involve complex genome amplification. Microbiological methods are the current best technique but require several days to be completed. This journal details the use of a new detection method, gold nanoparticles. This method is low in cost, relatively simple, and is much quicker. This method requires only a portable UV-visible spectrophotometer, however many of the reactions that indicate detection can be seen with the naked eye. The major downside of this method is its inability to detect Gram-negative bacteria, which previous methods have been able to detect.

This experiment specifically aimed to detect two bacterial special, staphylococcus aureus and lactobacillus using AuNP, or gold nanoparticles. First, UV-Vis spectrometry and electron microscope equipment were used to monitor the preparation of the nanoparticles and obtain the spectra of the particles. Next, the bacteria samples were cultured and incubated, then the cells were counted. Samples of sugarcane were also gathered, blended, and plated out to be incubated for 4 days, with the bacteria then being counted. Finally, 200 microliters of colloidal AuNP solution was prepared by first preparing a solution of $HAuCl_4$ and sodium citrate trihydrate, which was then added to the solution of AuNPs, and finally 0.1 M NHS and 0.4 M EDC were added to finish the suspension. This colloidal solution was then used to detect bacteria in the samples as the AuNPs change color upon recognition of Gram-positive bacteria, which means that the spectra of a sample containing bacteria will shift in comparison to the spectra of just AuNPs. The results of all the testing strongly supported this, as well as the different bacteria

causing different shifts in wavelength of the spectra. Overall, this showed that AuNPs were able to accurately detect bacteria with excellent discrimination between different species.

Further application of this process in the field of food pathogens is suggested, however it could also be useful in other fields. This research project received a grant from FAPESP and also gave thanks to CNPq and CAPES.