Postoperative Monitoring of Tumor Formation

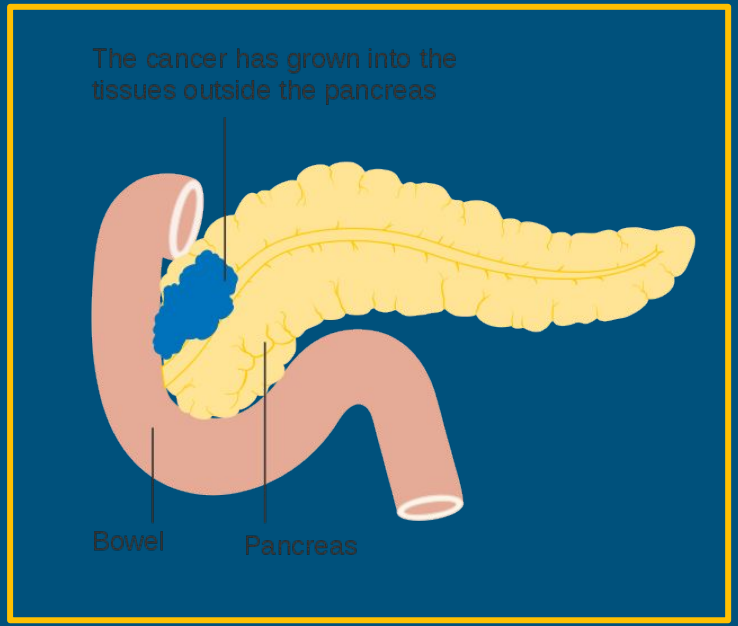
Enrico, Terry, Raymond, Cole, Lewis

Background

-Causes: Not clear, but smoking and family history have an influence. Risk factors can also be diabetes, drinking, obesity, age, etc.

-Most pancreatic cancer begins in the cells that line the ducts of the pancreas. Less often, cancer can form in the hormone-producing cells or the neuroendocrine cells of the pancreas (Mayo Clinic).

-Cancer biomarkers: They help make a diagnosis of cancer and can vary based on tumor location and target cell.

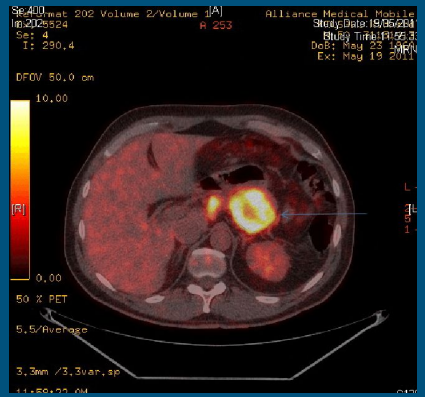


Stage III

Current Techniques

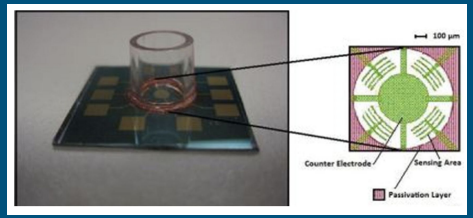
Common methods

- CT scans: images of abdomen, useful to detect spread of pancreatic cancer and monitor patients after treatment.
- PET scan: radioactive sugar that collects in cancer cells. Supports CT scan imaging.
- MRI: detailed organ pictures.
- Endoscopic Retrograde cholangiopancreatography: uses dye to see blockages in bile and pancreatic ducts.
- CA 19-9 Blood Test: Keep track of disease progression.



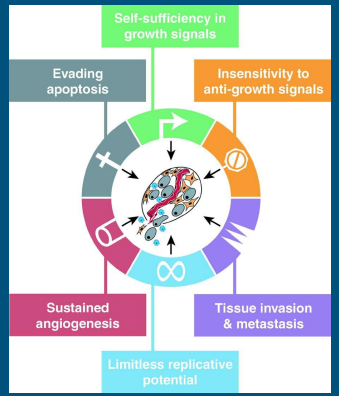
Nanotechnology

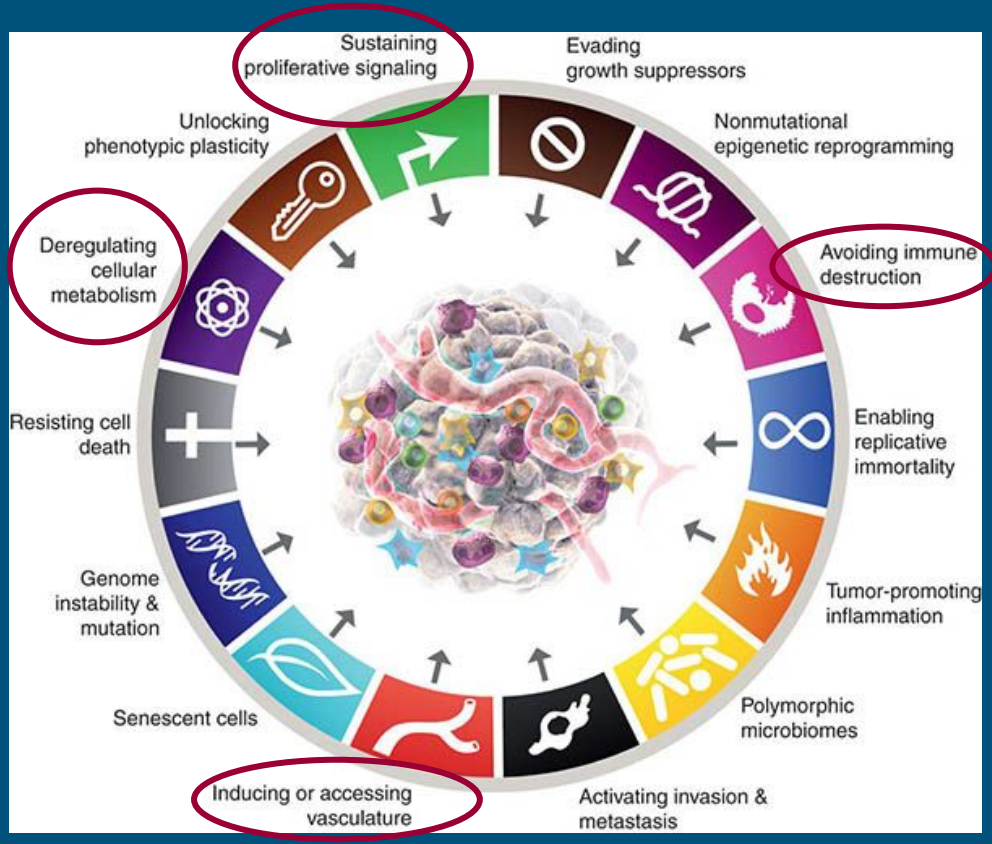
- Peptide, molecular, and metal-based activatable probes that increase imaging resolution.
- Bio-impedance-based sensors.
- FET sensors to detect volatile organic compounds.
- Surface acoustic wave based sensor to measure cell stiffness and adhesion.



The Hallmarks of Cancer

Though cancer is presented with a large level of heterogeneity, there are a few factors that remain constant known as **The Hallmarks of Cancer**





Theory

pH

- Cancer induces ***angiogenesis***, the formation of new blood vessels to supply oxygen and nutrients to growing tumors
- This results in poorly organized vasculature, causing hypoxia
- Cancer cells then undergo aerobic glycolysis, resulting in a metabolic switch that produces more lactate known as the **Warburg Effect**
- Overproduction of lactate paired with accumulation of acidic metabolic leads to a lower pH

Glucose Uptake

- In order to sustain its unregulated growth, cancer cells require a lot of energy to avoid destruction and allow replication
- They support this in part through increasing glucose uptake to serve as an energy source
- This results in lower glucose levels in the fluid surrounding tumors

Idea: *By monitoring by for physiological changes that are highly associated with pancreatic cancer, a device implanted near the site of tumor removal allowing for early detection and subsequent treatment of cancer recurrence can be developed*

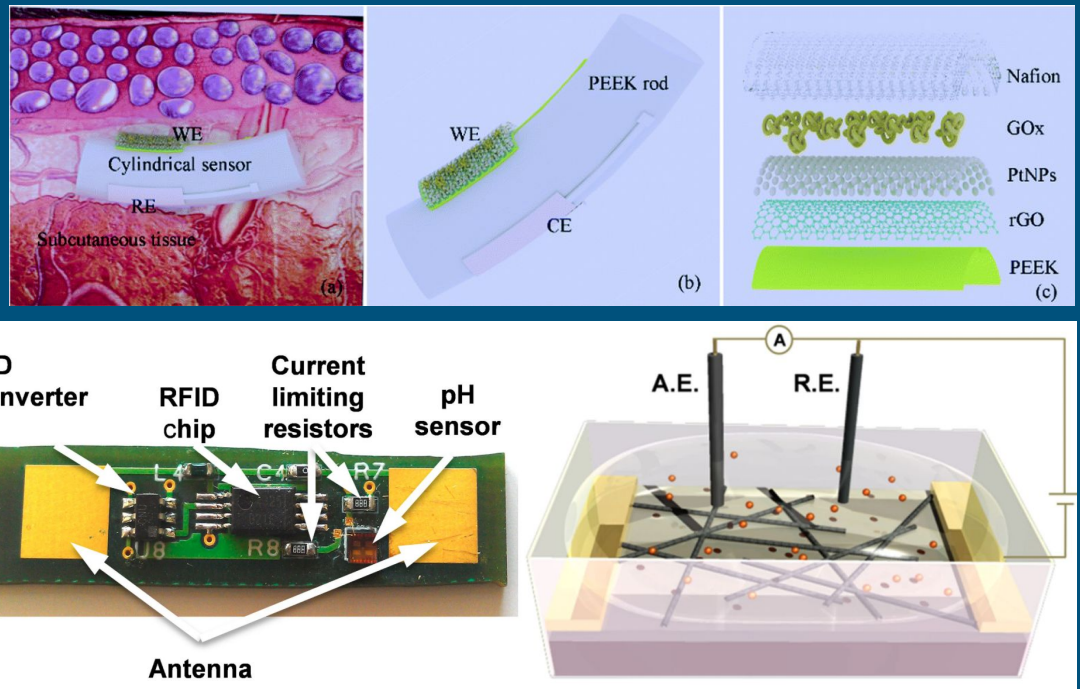
Proposed Biosensor Combination

Glucose monitoring

- Polyetheretherketone (PEEK) cylindrical flexible enzyme-electrode sensor
- 3D nanostructure consisting of graphene and platinum nanoparticles

pH monitoring

- Chemiresistor based on carbon nanotubes



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Gou, P., Kraut, N., Feigel, I. *et al.* Carbon Nanotube Chemiresistor for Wireless pH Sensing. *Sci Rep* 4, 4468 (2014). https://doi.org/10.1038/srep04468

Sensor Functionality

pH Sensor

- Surface of **ox-SWNTs** interact with ions in solution => changes in **conductivity** related to pH
- **Conductive polymer** PAA enhances the sensor's sensitivity and stability
- Radio Frequency Identification (RFID) tag allows for **wireless monitoring**
- Accurate detection of pH for 120 days

Glucose Level Sensor

- Glucose oxidase (GOx) is an **enzyme** that reacts with glucose => **electrical signal** proportional to concentration
- Nanoparticles enhance **sensitivity**
- Cylinder = more **surface area** for given volume, increasing sensitivity
- Detect the glucose concentration ranging from 0 to 570 mg/dL

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Materials

pH Detector

- Single-walled carbon nanotube (SWNT)
- 1-aminoantracene (AA)
- Anhydrous acetonitrile (MeCN)
- Tetrabutylammonium perchlorate (TBAP)
- H_2SO_4
- HNO_3
- Gold Electrodes
- N,N-dimethylformamide (DMF)
- Platinum wire
- Ag/AgCl quasi-reference electrode

Glucose Level Detector

- Polyetheretherketone (**PEEK**): 1 mm x 5 mm
- 3-Aminopropyl) trimethoxysilane (APTES)
- 3-mercaptopropyl trimethoxysilane (MPTMS)
- Glucose oxidase (GOx)
- Silver ink
- Graphene ink
- **Nafion** solution
- Platinum nanoparticle (**PtNP**) ink

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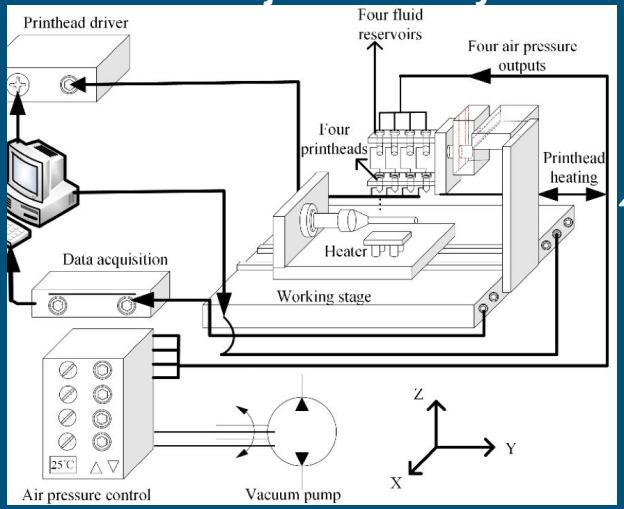
Fabrication - Glucose Sensor

3D print PEEK tube

Treat with O_2 plasma

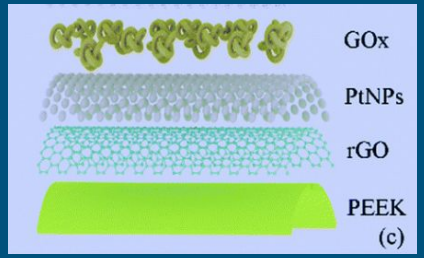
Treat in APTES, MPTMS mixture

Rotated Inkjet Printer System



- Working Electrode (WE) - Gold ink, graphene ink, and PtNP ink
- Silver ink was utilized for the Counter Electrode and Reference Electrode

Working Electrode Layers



Anneal Each Layer After Print

- 50 mM FeCl3 solution (CE, RE)
- 10 µL Nafion solution (WE)

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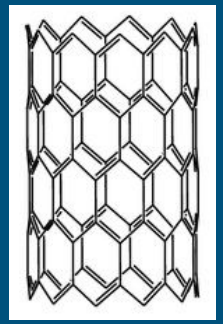
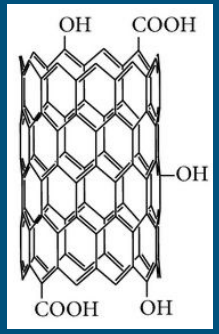
Fabrication - pH Sensor

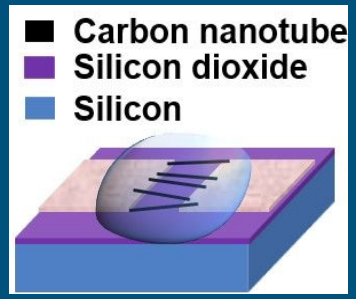


Single-walled Carbon Nanotubes (SWNTs)

H2SO4/HNO3 sonicate

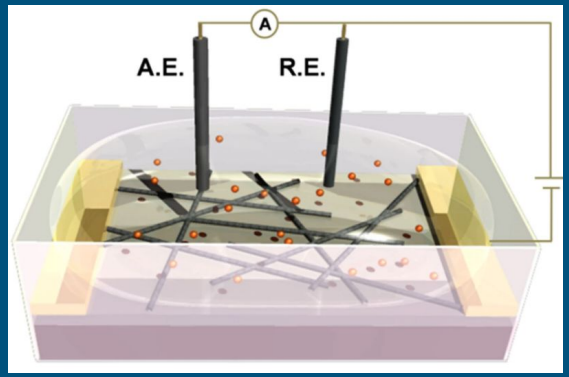


oxidized SWNTs (ox-SWNTs)



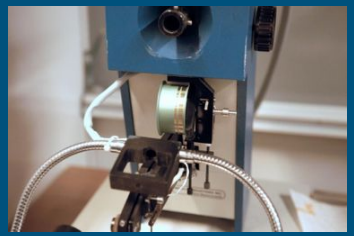
Li, W., Hennrich, F., Flavel, B.S. *et al.*

- **Deposit** suspensions of ox-SWNTs on Si chips via **dielectrophoresis** for FET experiments



- **Electropolymerize** (EP) the conductive polymer, PAA, on the ox-SWNT network by cyclic voltammetry in an electrolyte solution containing AA

wire bonding



Steven S. Saliterman

Oxidation
Photolithography
Plasma etching
Resist stripping

Silicon wafer

Steven S. Saliterman

Kamil, A., Hussein, F., Halbus, A., & Bahnemann, D. (2014). Preparation, Characterization, and Photocatalytic Applications of MWCNTs/TiO2 Composite. *International Journal of Photoenergy*, *2014*, 8 pages. https://doi.org/10.1155/2014/475713

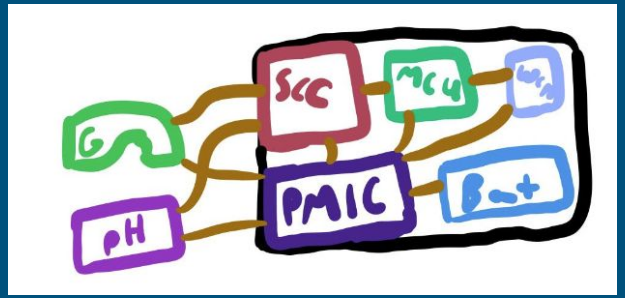
Fabrication- Integration

Components:

- Signal Conditioning Circuitry
  - Amplifiers, filters, analog to digital converter
- Microcontroller
  - Data Processing
- Power Management Integrated Circuit
  - Interface between battery and sensors
- Wireless Communication Module
- Gold Wire
- Battery

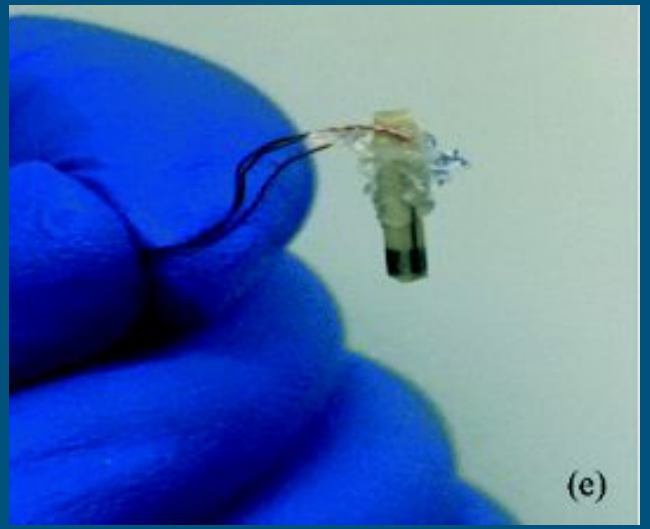
Assembly:

- Attach all components onto a silicon chip using a biocompatible adhesive such as medical grade epoxy
- Connect sensors to circuitry using gold wiring
- Encapsulate components with PDMS



Device Performance Testing

- Filtration and removal of only the analyte from the interstitial fluid in sufficient concentrations for detection to determine selectivity and sensitivity
- The nature of the device places less emphasis on response time, instead reproducibility and stability are vital to device performance
- Animal model to compare external recordings to internal recordings of the device



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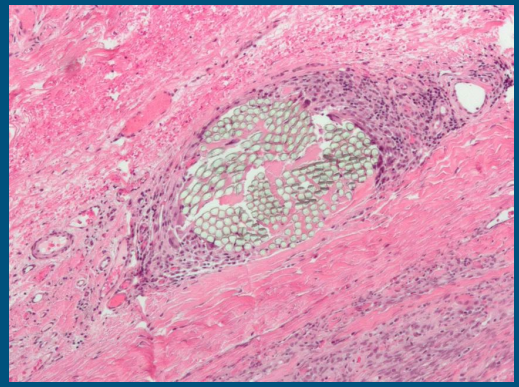
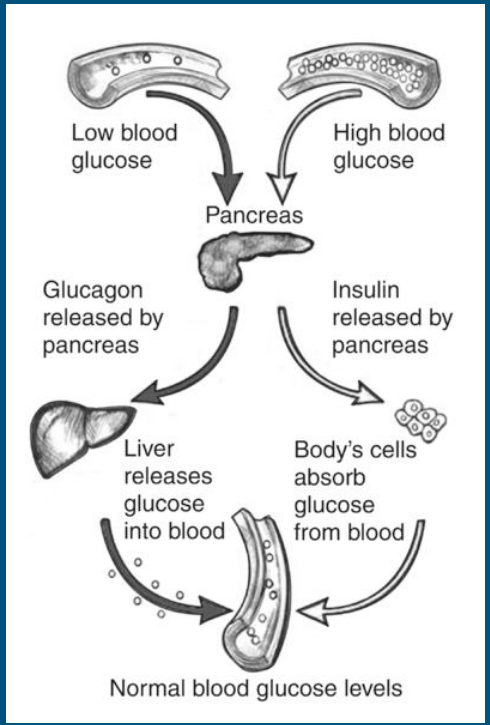
Biocompatibility Testing Methods

- At 7 days analyze for aggressive macrophages
- At 14 days confirm no enlargement of foreign body giant cells or nuclei consolidation
- These signs lead to biofouling of the device, preventing proper use
- If these biocompatibility problems arise, surface modification needs to be conducted to prevent non-specific protein absorption.



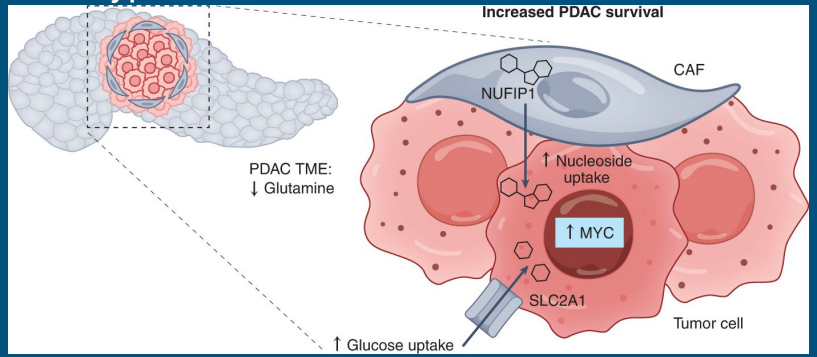
Potential Limitations

- Ignoring other relevant biomarkers
  - Only measures glucose and pH
  - Carbohydrate antigen (CA) & Carcinoembryonic antigen (CEA)
- Sensitivity of device
  - Any inflammation from the device would likely affect pH and glucose readings
  - Glucose levels vary throughout the day
  - Data analysis varies by subject
    - Difference in biological responses to the device
    - Difference in thresholds causing Type 1 and Type 2 errors



Future Innovations and Directions

- Measuring and analyzing previously mentioned biomarkers
  - Carbohydrate antigen (CA) & Carcinoembryonic antigen (CEA)
- Supplying power for longevity
  - Ensuring sustained device operation
- Expand into specific types of cancers
  - Increase specificity of biomarkers for certain cancer type
  - Use unique markers like PDAC (85% of cases)



Questions?

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