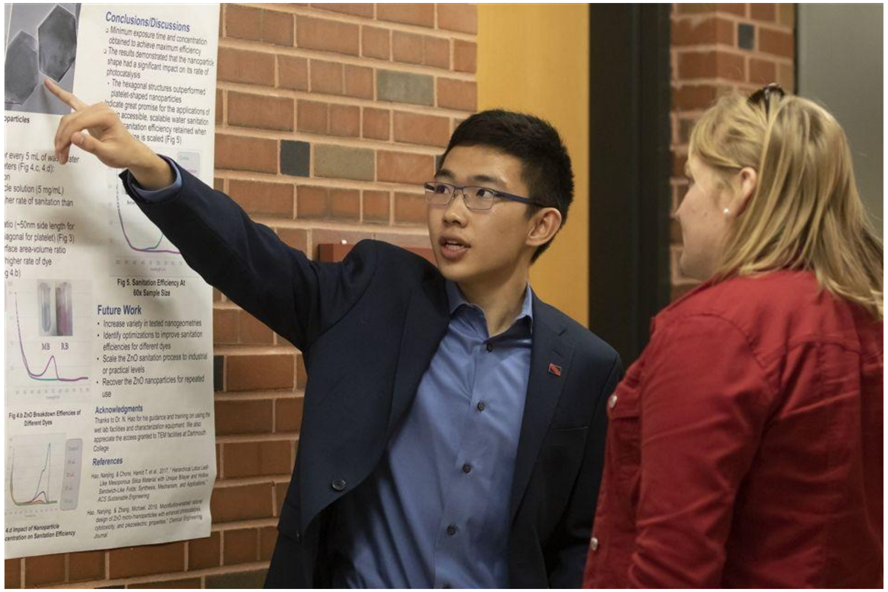
Metal-doped Zinc Oxide Nanochip for Surface-Enhanced Raman Spectroscopic Sensing of Opioids in Liquids

Michael Zhang, The Lawrenceville School
Mercer County Science Fair (MSEF)
March 13, 2021

About Me

I am Michael Zhang, a current senior at the Lawrenceville School. This is my third year participating in the MSEF competition, and I'm very excited to be back to present my work to a panel of distinguished judges.

Achievements



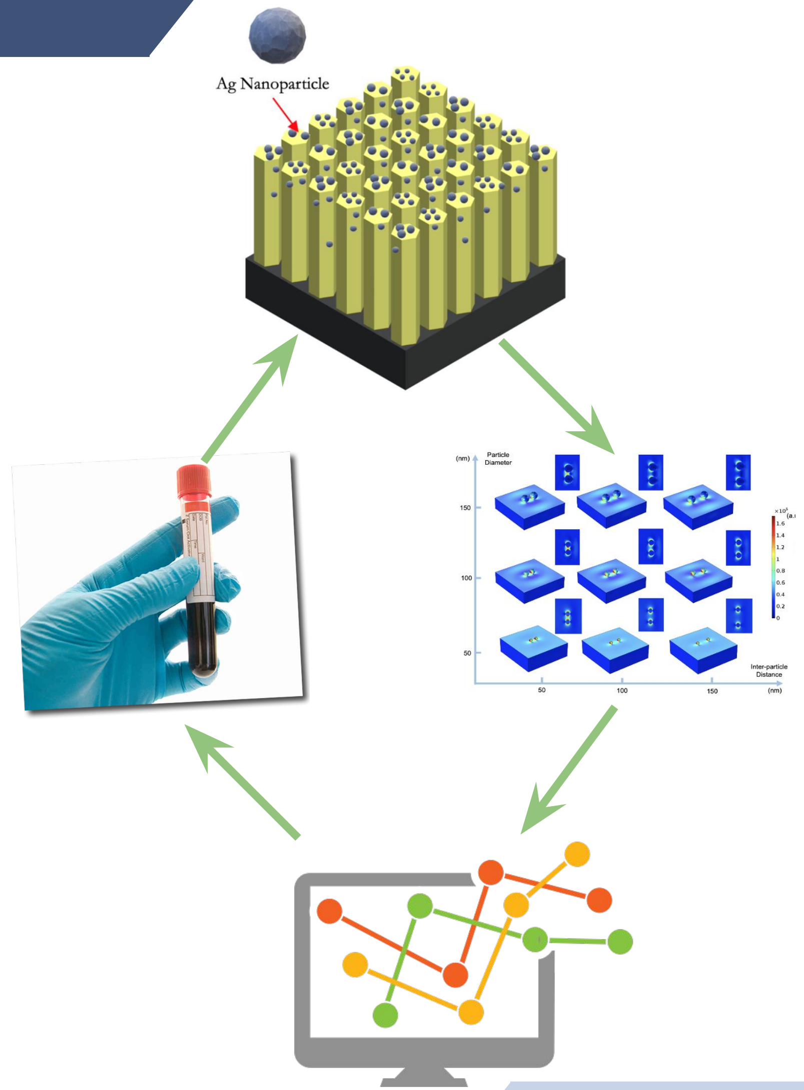
- Regeneron Science Talent Search (STS) 2021 Finalist
- International Science and Engineering Fair (ISEF) 2021 Finalist
- Stockholm Junior Water Prize (2019, 2020)
- MSEF 2020 1st Runner Up (Overall)
- MSEF 2020 1st Place (General Engineering)
- USA Computing Olympiad (USACO) Gold Contestant
- American Invitational Mathematics Examination (AIME) Qualifier
- Lawrenceville Welles Award Recipient
- Executive Editor, *Lawrencium*
- President, Science and Robotics
- Lawrenceville Academic High Honors (every term)

Publications

- "Silver Nanoparticle on Zinc Oxide Array for Label-free Detection of Opioids Through Surface-Enhanced Raman Spectroscopy." ***RSC Advances*.** RA-ART-01-2021-000760.R1 [Accepted] (Co-first author)
- "Label-Free, On-Chip Detection of Opioids Through Surface-Enhanced Raman Spectroscopy." Patent Pending (Reference ID: 094219.00001)
- "Nanomaterials Development: Rational Design, Controllable Synthesis, and On-Chip Applications." ***Biomaterials Science***, 2020, DOI: 10.1039/C9BM01787A. [Link] (Co-first author)
- "Microfluidics-enabled rational design of ZnO micro-/nanoparticles with enhanced photocatalysis, cytotoxicity, and piezoelectric properties." ***Chemical Engineering Journal***, 2019, 378.[Link] (Co-author)

Progress in 2020

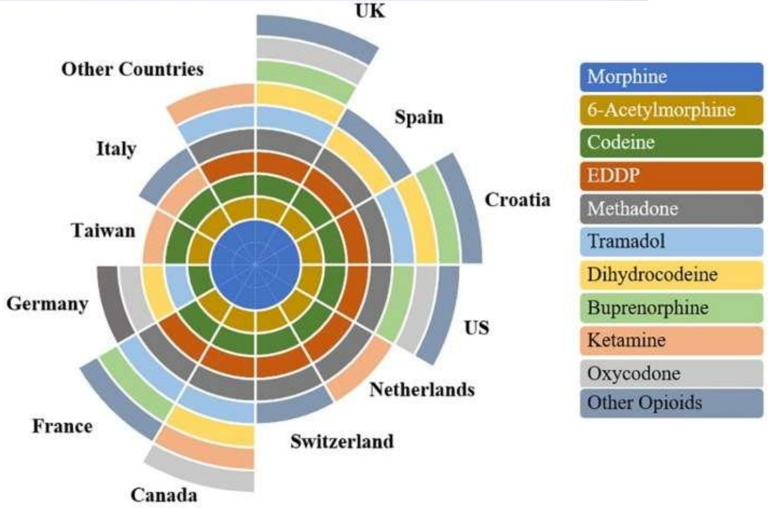
- **Sensor Simulations & Optimizations:** optimized experimental parameters, namely particle size, spacing, and composition
- **Biological Fluids:** demonstrated that my established Ag decorated ZnO nanoarrays retain their detection efficacy in biological mediums
- **New Research Collaborations:** During the pandemic, established collaboration with Dr. Utkan Demirci in Stanford University and successfully continued sensor simulations virtually
- **Research Outcome:**
  - Manuscript accepted in RSC Advances (co-first author)
  - Patent pending (Patent ID: 094219.00001)



Michael Zhang, Congran Jin et. al. Silver Nanoparticle on Zinc Oxide Array for Label-free Detection of Opioids Through Surface-Enhanced Raman Spectroscopy. ***RSC Advances.*** *RA-ART-01-2021-000760.R1*

Introduction

- Opioid abuses and overdoses have been a major American and global issue for decades
- Every recent administration has made it one of their top priorities
- 130 people die every day from just overdosing in the US, with more globally
- Opioid abuse cost the US economy an average of $78.5bn a year and ruin families and communities
- While there are policies to combat and prevent this crisis, little efforts have been made to understand and the extent of this crisis



"The Opioid Crisis: a 21st Century Pain"

— National Institute on Drug Abuse (NIDA)

Current Approaches

- Laboratory-based instruments such as high-resolution mass spectroscopy
    - Large sample processing power, with long processing times
    - Bulky, costly and require infrastructures
- Current portable approaches still face challenges
    - Materials and devices design
    - Bulky and costly lasers
    - Labelling or enhancement materials
    - Detection limited to around **0.1 mg/mL**

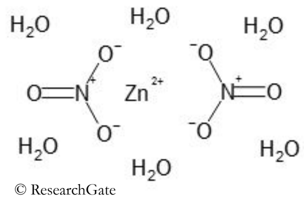
High Resolution Mass Spectrometer © Sciex

Pharmaceutics, 2011, 3(3), 425-439

Materials

- **Oxycodone**: extremely potent and commonly abused opioid, dissolved in methanol to allow for commercial purchase
- **Zinc Oxide (ZnO)**: chosen for its excellent electrochemical and optoelectronic properties, versatile and low-cost manufacturing, and relative eco-friendliness
  - ZnO Nanoparticle Seeding:
    - **Zinc acetate dihydrate**
    - **Sodium hydroxide**
  - ZnO Nanoarray Growth:
    - **Zinc nitrate hexahydrate**
    - **Hexamethylenetetramine** (HMTA)
- **Silver (Ag)**: superior plasmonic performance, coated on ZnO nanoarray to enhance Surface-Enhanced Raman Spectroscopy signal

Zinc Nitrate Hexahydrate
$ZnNO_3*6H_2O$



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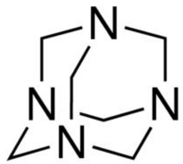
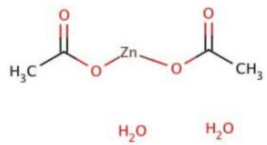
HMTA



Zinc Acetate Dihydrate
$ZnC_4H_6O_4$



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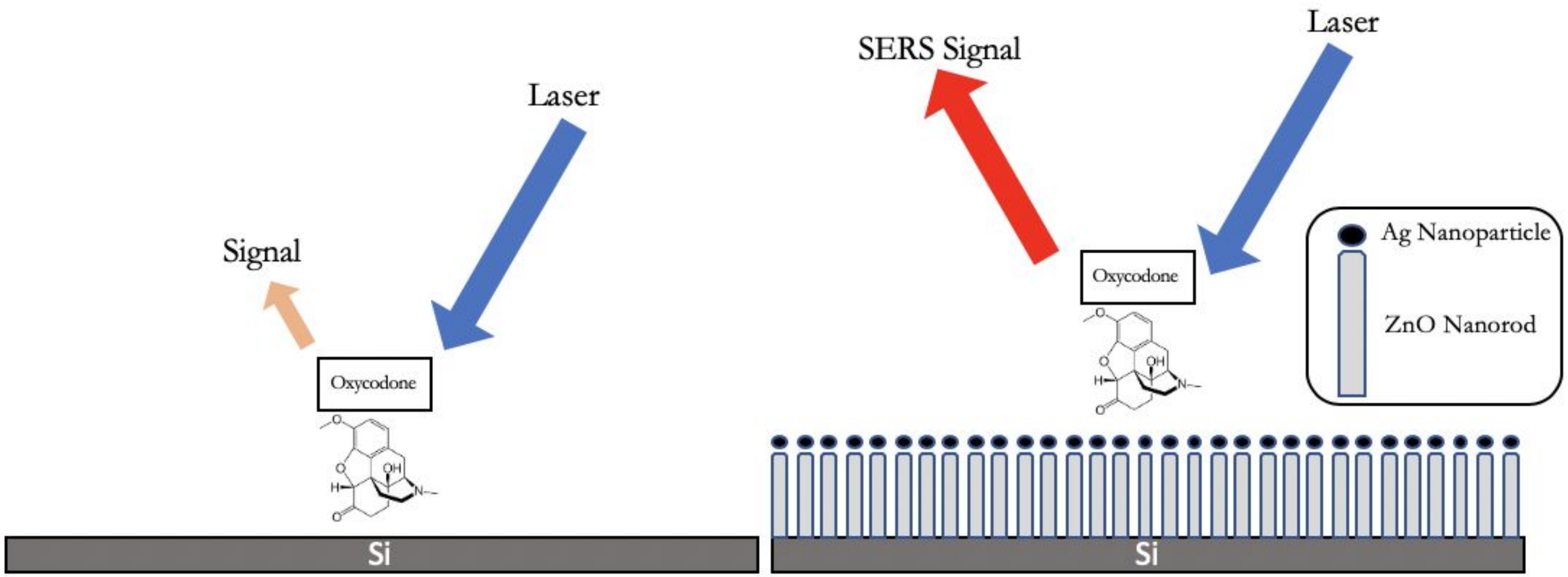
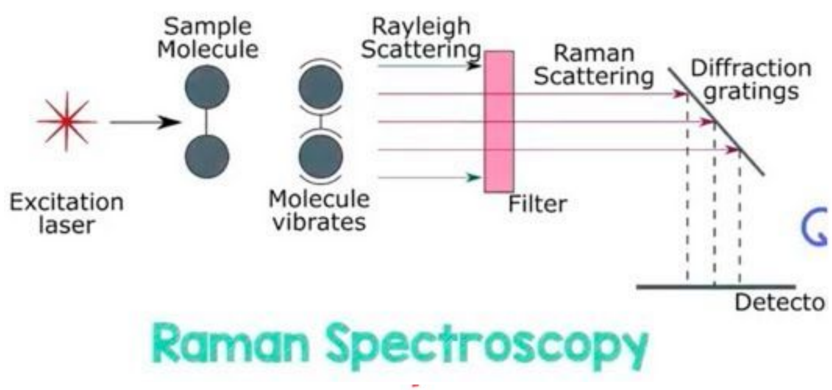
Hypothesis

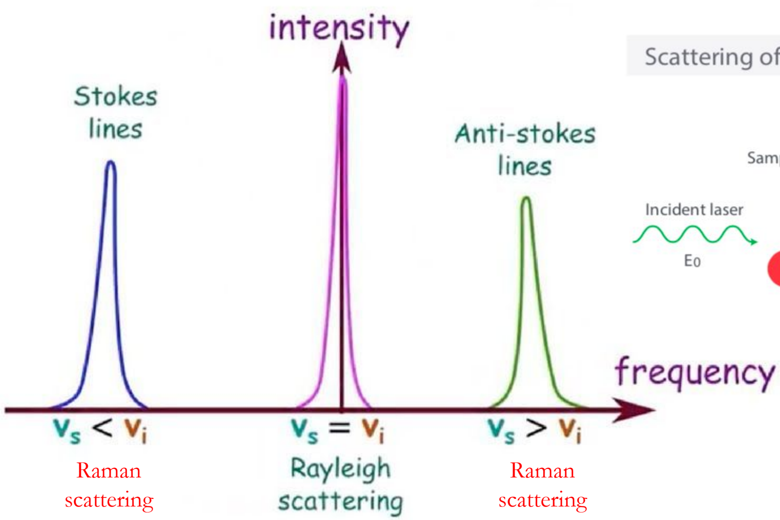
The superior molecular recognition and surface-enhanced optical performance of silver (Ag) nanoparticles on a zinc oxide nanoarray will be maintained in biological detection mediums, and can be optimized by choosing the correct input laser wavelength.

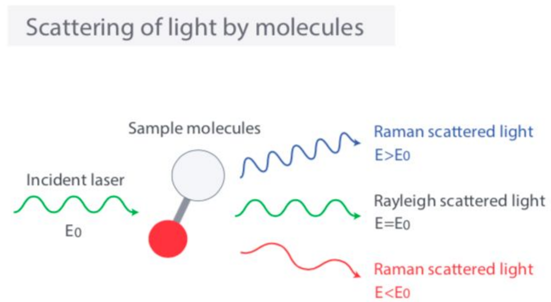


Surface-Enhanced Raman Spectroscopy

- ❑ Raman Spectroscopy creates a molecular "fingerprint"
- ❑ When a molecule is stimulated via laser, its electron and bond configuration scatters the light in a unique way
- ❑ Without enhancement, a molecule's Raman signal is very weak (only ~0.0000001% of scattered waves)
- ❑ By adding plasmonic materials (such as Ag) onto the detection substrate, the Raman signal can be significantly enhanced





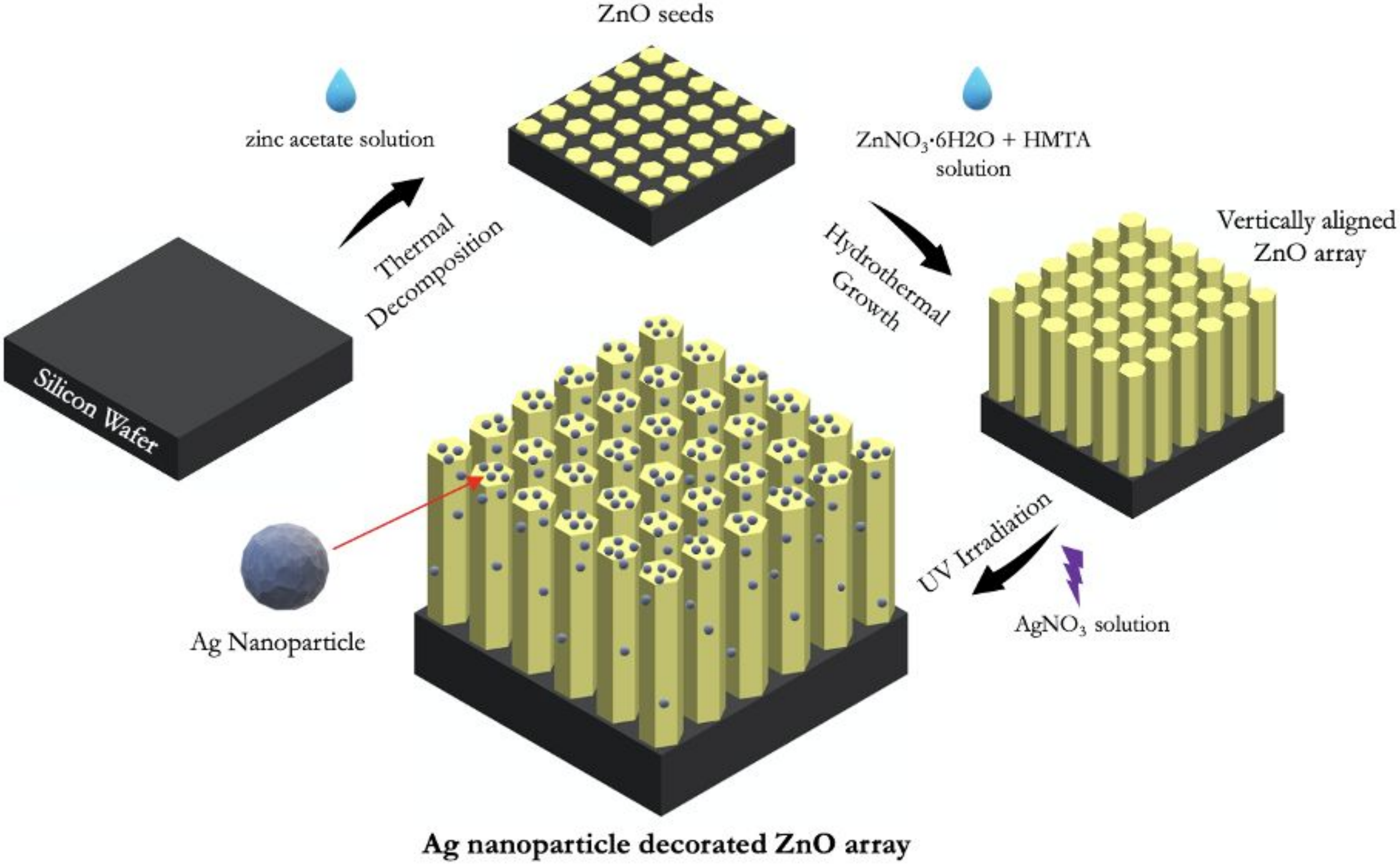


Images From: "Basics and Principle of Raman Spectroscopy," P. Ninjas, 2018

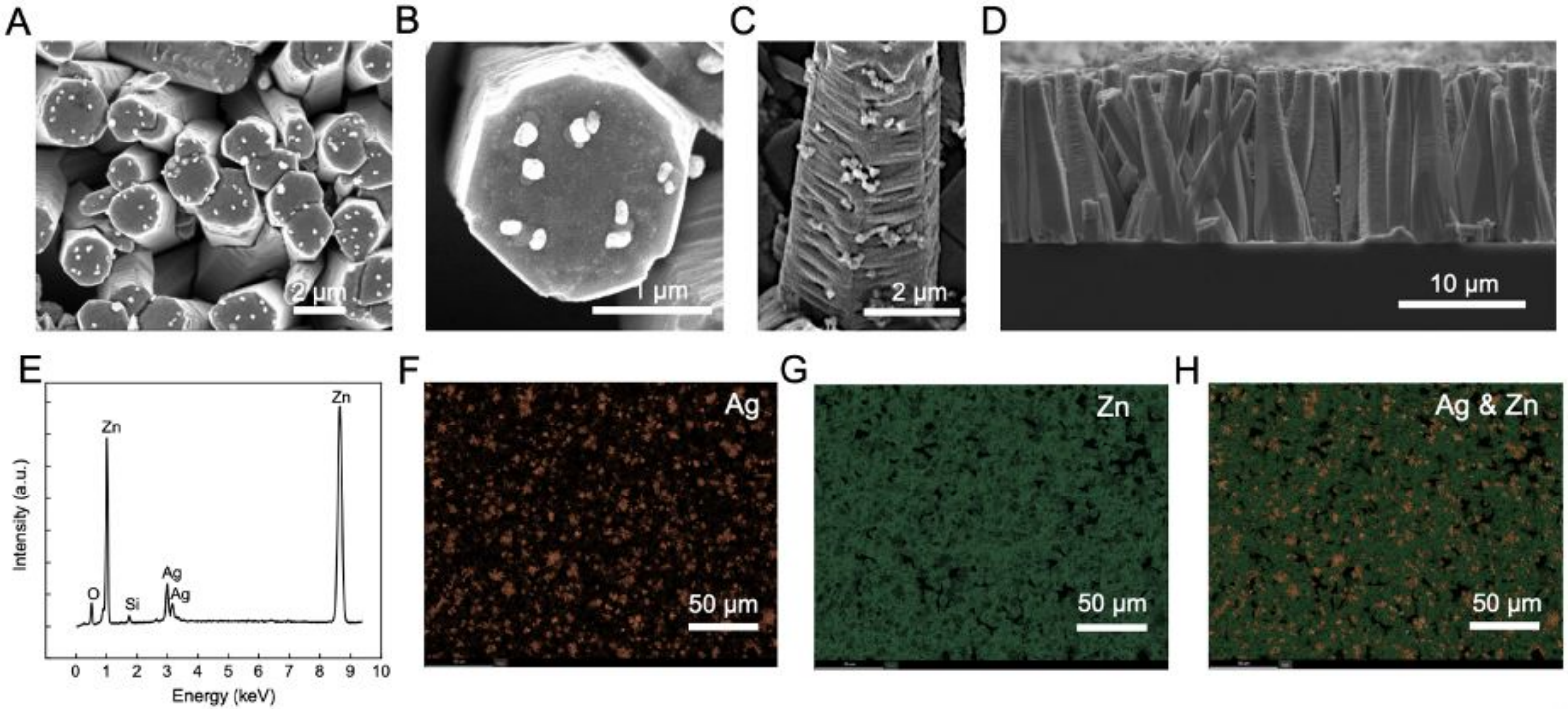
Experimental Procedure

- **Synthesized Silver-Decorated ZnO (Ag@ZnO) Detection Chip**
  - **ZnO nanorod "forest" arrays** through hydrothermal deposition onto a silicon (Si) wafer
  - **Deposited silver (Ag) onto the nanoarray** through the UV photoreduction of an $AgNO_3$ solution with the ZnO substrate immersed
- **Synthesize Blood-Spiked Oxycodone Samples**
  - Add to the raw blood serum that was diluted 100 times with phosphate buffered saline in the serum samples to obtain 900 μg/mL, 90 μg/mL, 9 μg/mL, 900 ng/mL and 90 ng/mL (3x samples per concentration)
  - Use de-identified patient serum samples from Dartmouth-Hitchcock Medical Center
- **Detection of opioids** was achieved through surface-enhanced Raman spectroscopy (SERS), in which the signature peaks of oxycodone (~1400 cm^{-1}, ~1600 cm^{-1}) were identified

Experimental Procedure

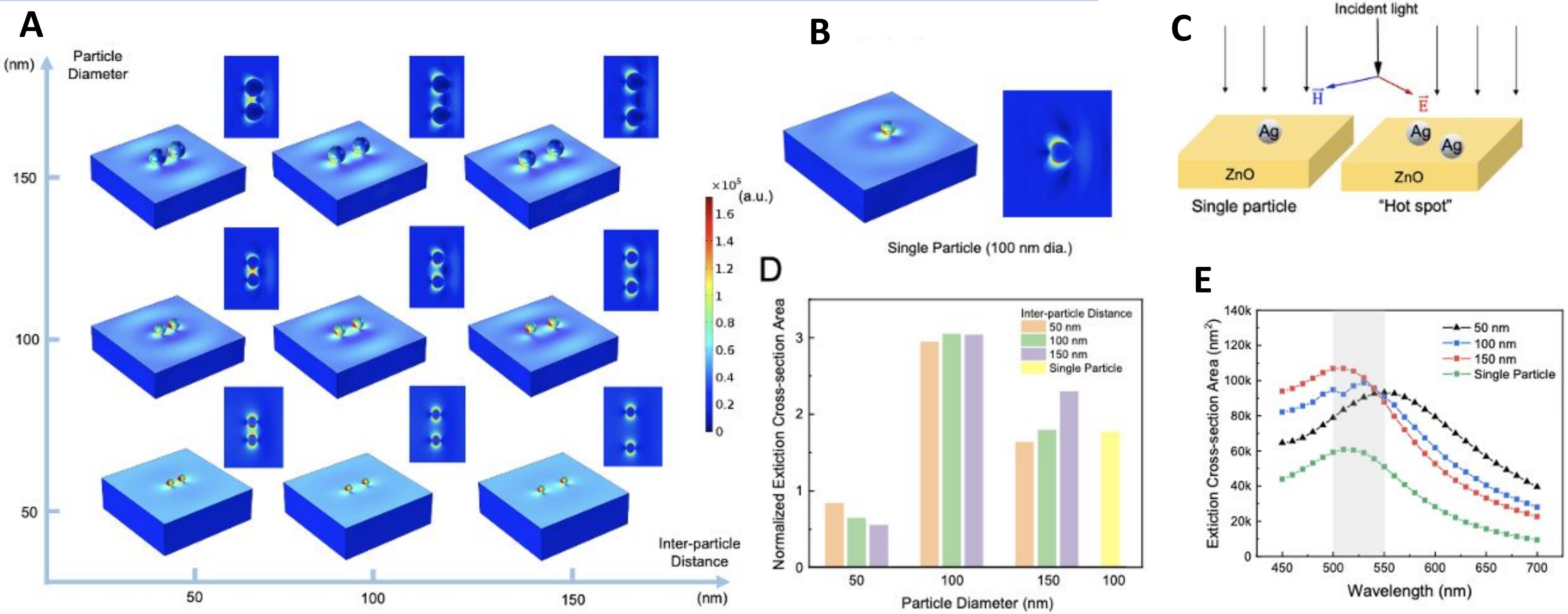


ZnO Nanoarray



- The ZnO nanoarrays were grown at a high density to maximize signal amplification (*Figure A, D*)
- ZnO nanorods were decorated with Ag nanoparticles to maximize light scattering (*Figure A, B, C*)
- ZnO nanorods were grown to a substantial length of ~12 μm to create a substantial optoelectrical effect (*Figure D*)
- Silver nanoparticles are approximately 100-150 nm (*Figure B*)
- EDAX elemental analysis (left) shows the presence and relative distribution of Ag on the ZnO nanoarray (*Figure E-H*)

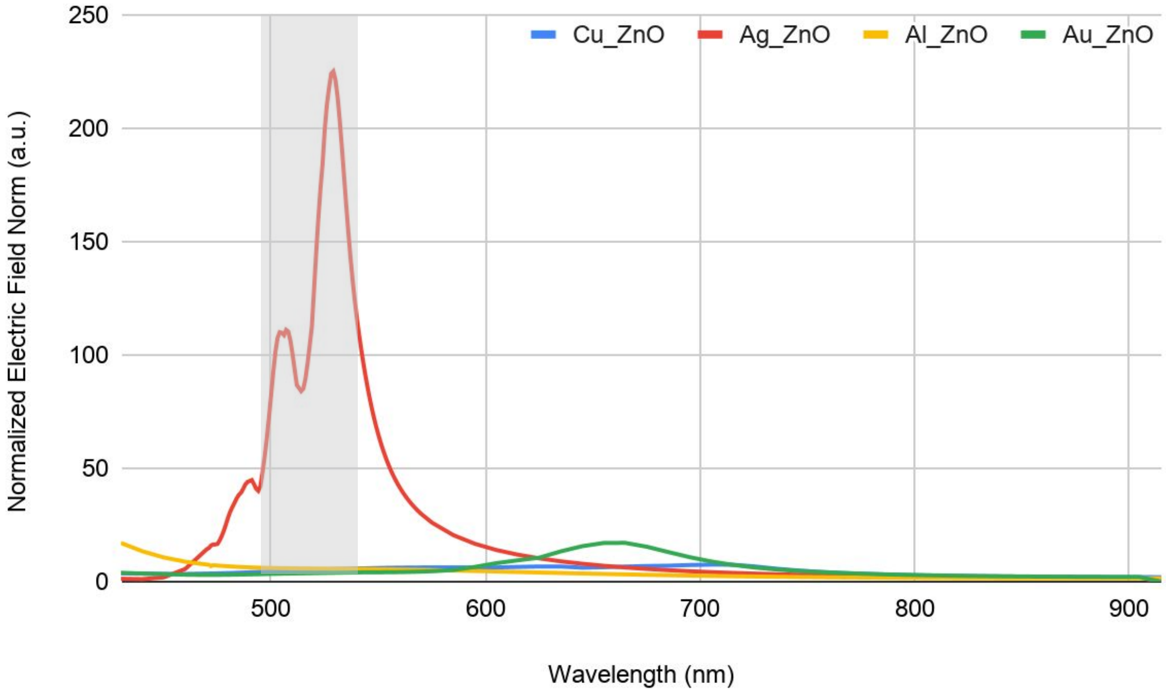
Simulation Results



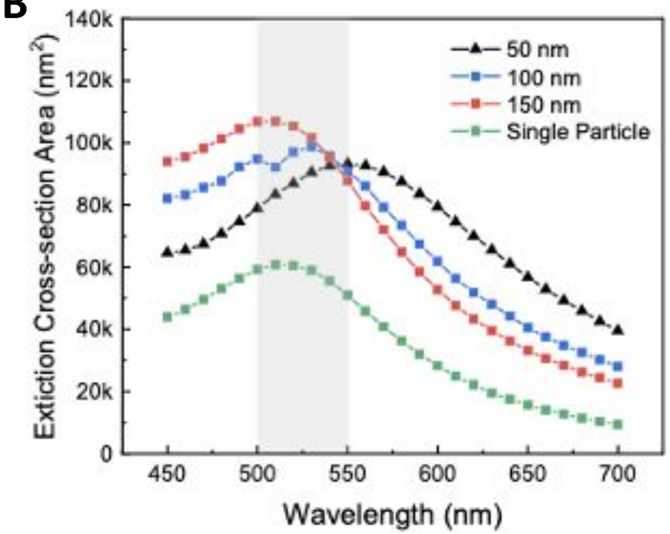
- Simulations varying interparticle distance and particle diameter were performed (COMSOL, *Figure A, B*)
    - Logarithmic color plot indicates local Raman enhancement
- When in close proximity, two silver nanoparticles generate a Raman "hotspot" (indicated with brighter colors) for exponentially increased enhancement (*Figure A, C*)
- Optimal parameters were Ag nanoparticles of ~100 nm with a mean interparticle spacing of 100 nm (*Figure D*)
- Enhancement per molecule of a 100 nm diameter nanoparticle with various spacings, ideal Raman wavelength range is 500-550 nm (*Figure E*)

Simulation Results

A



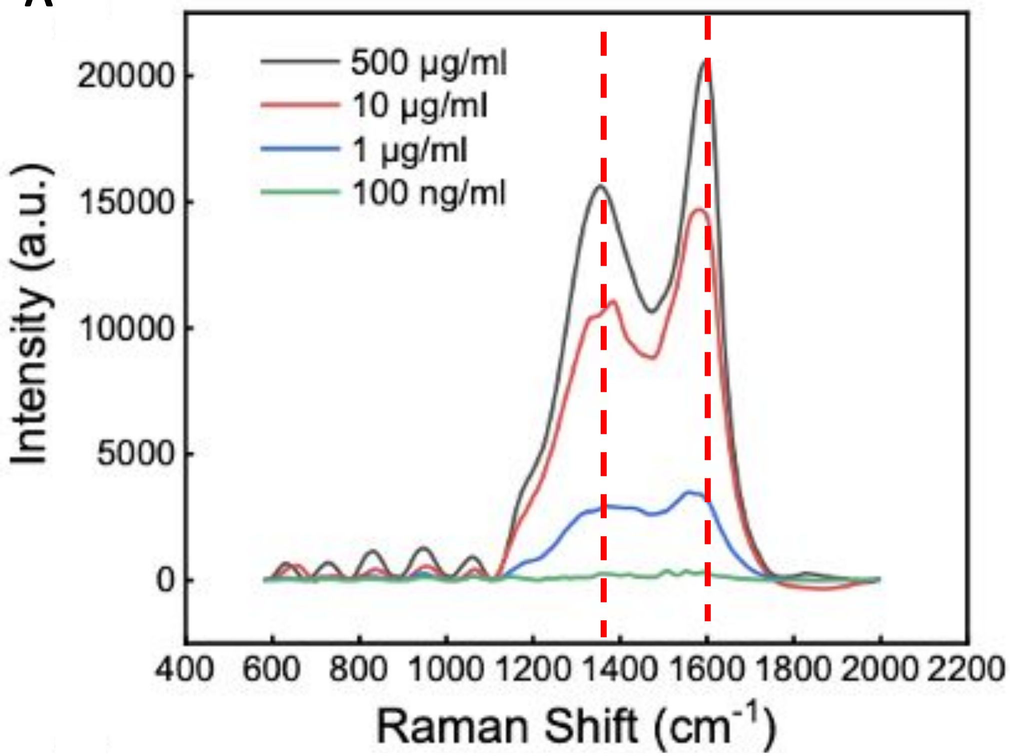
B



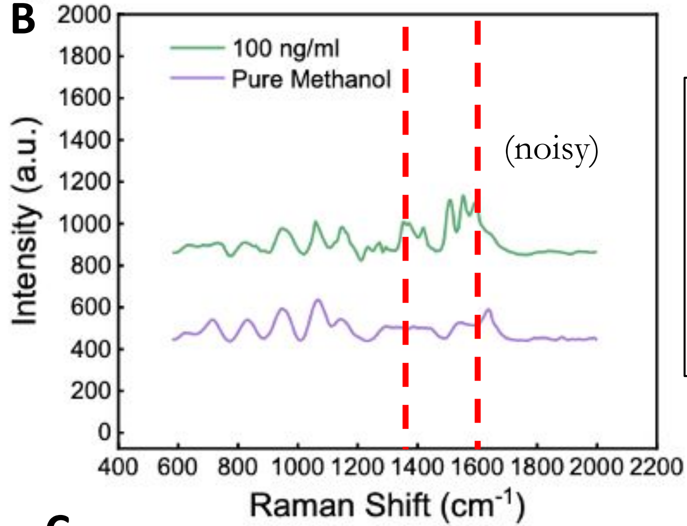
- Simulations varying the composition of nanoparticles were also performed (COMSOL, *Figure A*)
- By an order of magnitude, silver nanoparticles provide far superior enhancement per molecule when compared with copper (Cu), aluminum (Al), and gold (Au)
- As expected, peak enhancement occurs for a Raman wavelength of 500-550 (greyed out in *Figures A, B*)
    - For reference, *Figure B* shows the enhancement fields plot for a 100 nm Ag nanoparticle

Detection in Methanol

A

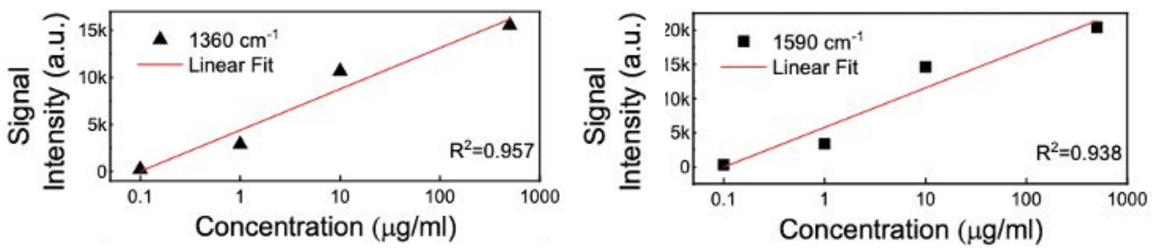


B



Raman signature peaks:
Oxycodone (~1360, ~1600 cm^{-1})
Methanol (~1000, ~1600 cm^{-1})
Silicon (not shown)
Zinc Oxide (~450, ~600 cm^{-1})
Silver (~600, ~1200 cm^{-1})

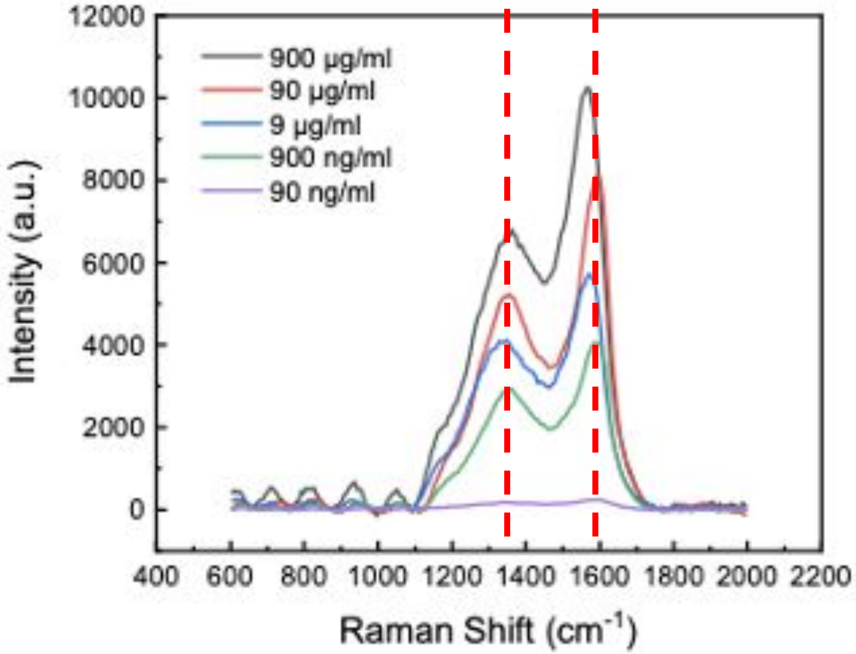
C



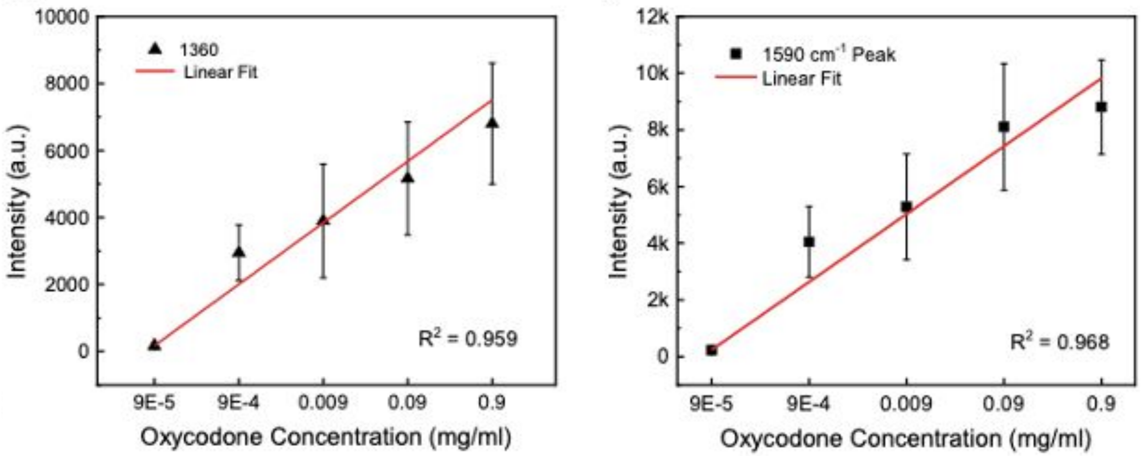
- Oxycodone detectable via it's Raman signature peaks (*Figure A*)
  - Significant peak at detection limit of 0.1 µg/mL, requires signal processing to remove noise (*Figure B*)
- There is a strong linear correlation between the concentration of oxycodone present and intensity of oxycodone Raman peaks (*Figure C*)

Detection in Serum

A



B

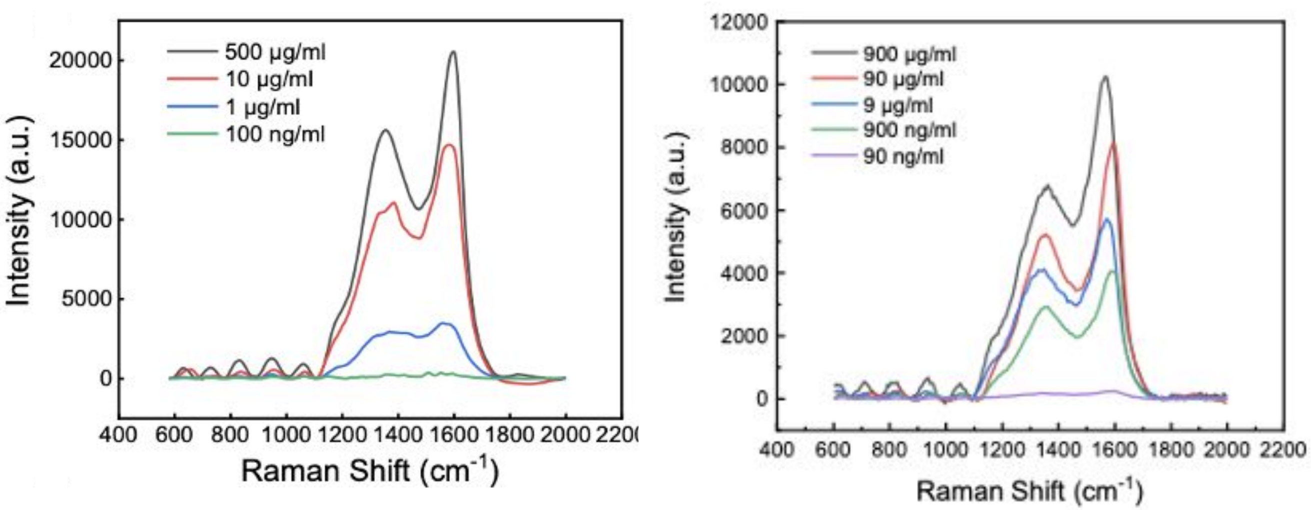


- As with methanol-spiked samples, there exists a strong Raman peak at the signature shifts (1360, 1600 cm^{-1}) (*Figure A*)
- There exists a strong linear relation between the concentration and signal strength, comparable to the one observed in methanol samples (*Figure B*)
- In other words, **the presence of common components found in serum has negligible effects on the enhancement capabilities of the Ag@ZnO chip**

Analysis and Discussion

- Measured Raman peaks have strengths proportional to the concentration of oxycodone **even in biological mediums such as serum**
  - Paves way for not only the detection of oxycodone, but its approximate concentration even in trace amounts
- Peaks appear to dampen at 0.1 µg/mL compared to higher concentration SERS curves
  - However, still significant oxycodone signature peaks at ~1360 cm^{-1} and ~1600 cm^{-1} (compared to baseline)
- **Key Insight:** Experimental layout confirms theoretical predictions
  - Optimal conditions being 100 nm diameter Ag nanoparticles on average 100 nm apart, laser @ 500-550 nm

A. Detection in Methanol **B.** Detection in Blood



Conclusion

- We designed a facile and controllable hydrothermal strategy for the fabrication and Ag decoration of ZnO nanoarrays for the SERS detection of opioids
- Ag decorated ZnO nanoarray significantly enhanced the sensor's detection range to **as low as 0.1 µg/mL, over 1000 times lower than existing method**
  - This was due to the emergence of hybrid properties from the excellent plasmonic performance of Ag and optoelectrical properties of ZnO
- If deployed as a large network, could gather big data necessary to **map out the opioid crisis**
- **Potential Applications**: Can be modified to detect a variety of molecules ranging from heavy metals to COVID-19 particulates.

Acknowledgements

This project was conducted jointly at the Thayer School of Engineering at Dartmouth College, and at the Canary Cancer Institute at Stanford University.

Special thanks to Dr. Utkan Demirci for his guidance, and Amid Mataji for assistance in performing simulations.

Special thanks to Congran Jin and Dr. Nanjing Hao for guidance, to Yuan Nie for training on using the Raman detector and SEM characterization equipment, and to Dr. Yundong Ren for his assistance in performing simulations.

Also we appreciate the access granted to SEM and Raman detector facilities at the Dartmouth College.

Thank You