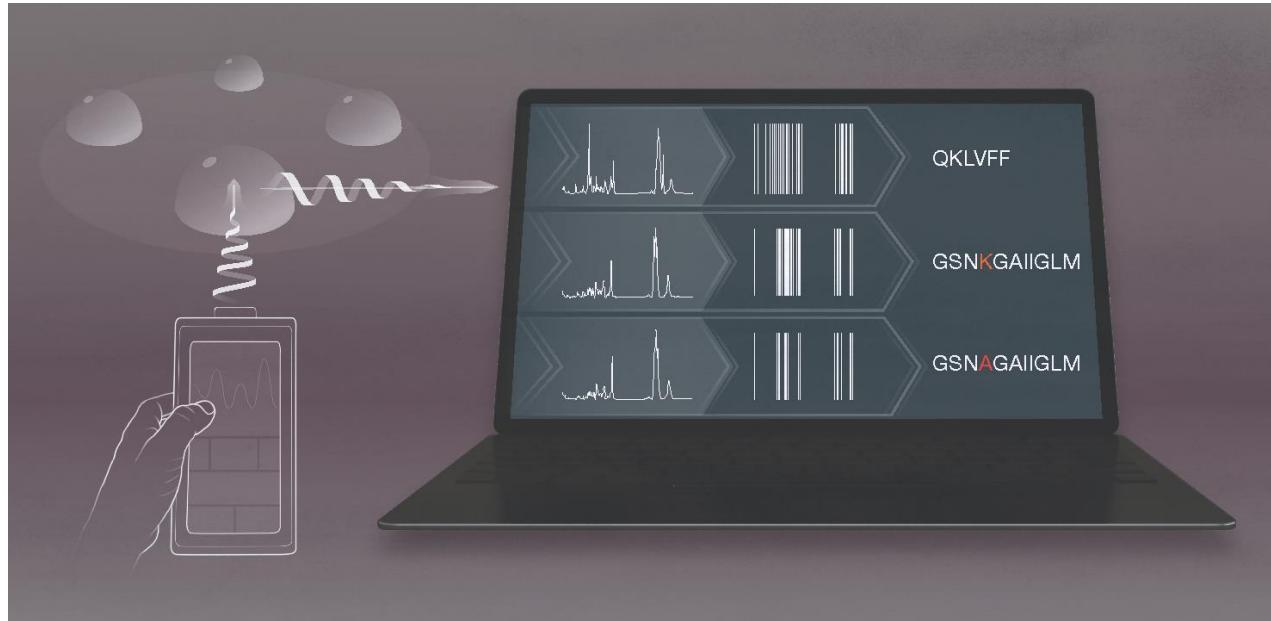


Design and evaluation of hybrid plasmonic nanostructures towards materialization of SERS sensors



PhD candidate : Phuong Hoang

Department : Chemical Engineering

Advisor : Professor Niveen M. Khashab

Date : September 26th, 2019



Overview

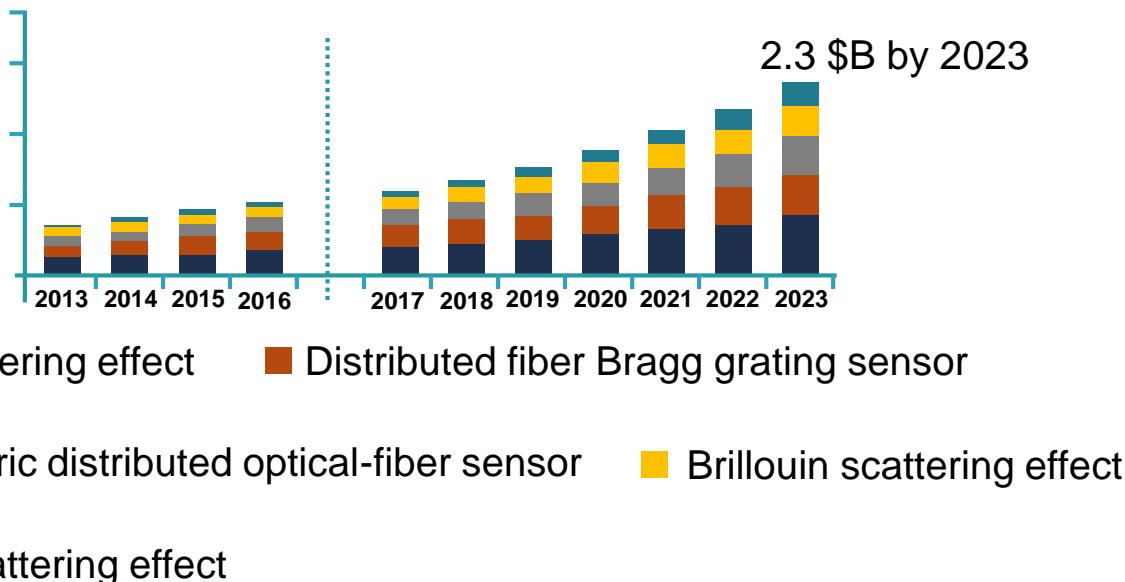
2

- 1. Introduction**
 - Optical sensor
 - Surface enhanced Raman Scattering (SERS) sensor
- 2. Experimental Works**
 - Hybrid materials SERS substrate for detection of structural isomers
 - Chirality-induced SERS nanostructures for detection of stereo isomers
 - Superhydrophobic SERS substrate and signal encoding system for detection of single mutation point in peptide
- 3. Conclusion and future works**

Market value for optical sensors based on scattering process

3

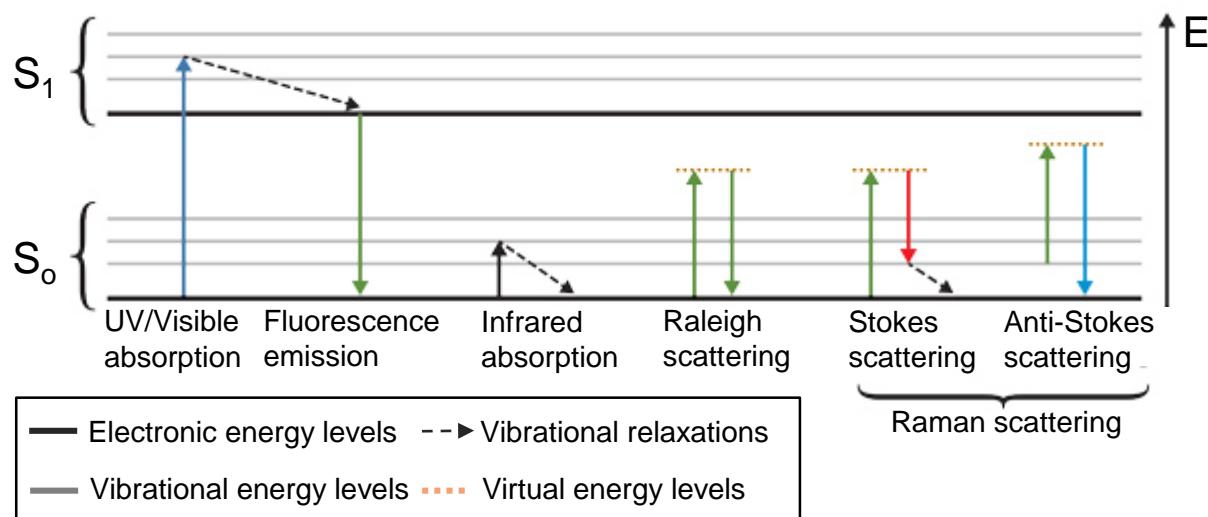
Global distributed fiber optic sensor market by scattering process \$B (2013-2023)



Optical sensors

4

- Sensing mechanisms:
 - Scattering: SERS
 - Absorption: UV-Visible, IR
 - Two photons: Fluorescence
- Advantages:
 - Speed: fast analysis
 - Specificity: chemical structure information
 - Sensitivity: sub ppm (parts per million)

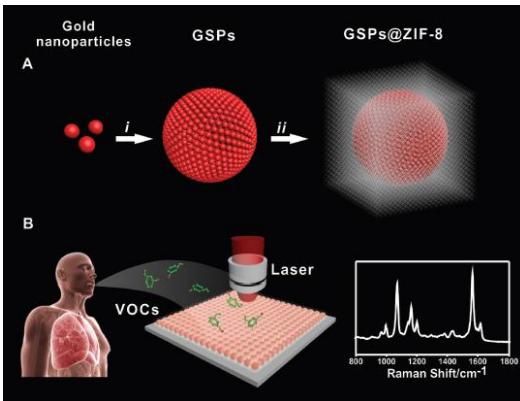


SERS sensors is the most versatile optical sensor

5

- Fingerprint identification
- Minimal sample preparation
- Label-free sensing

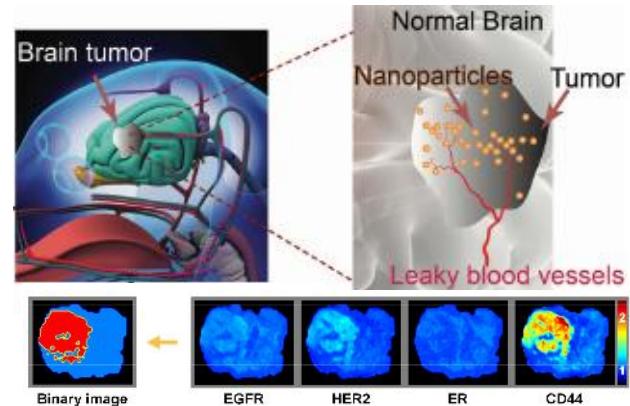
Gas sensor



Pesticides sensor

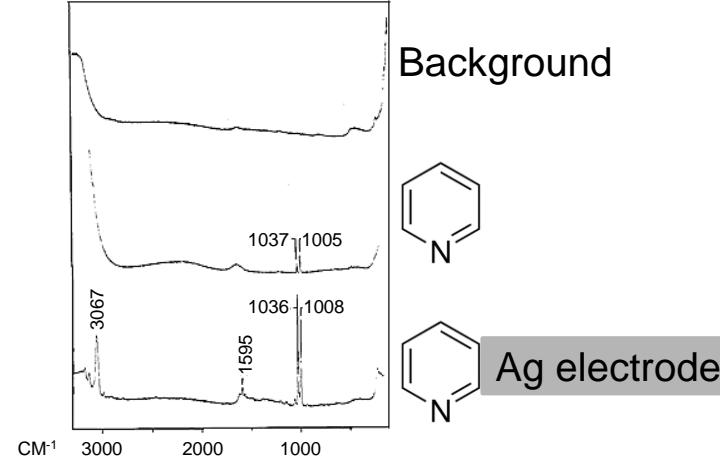
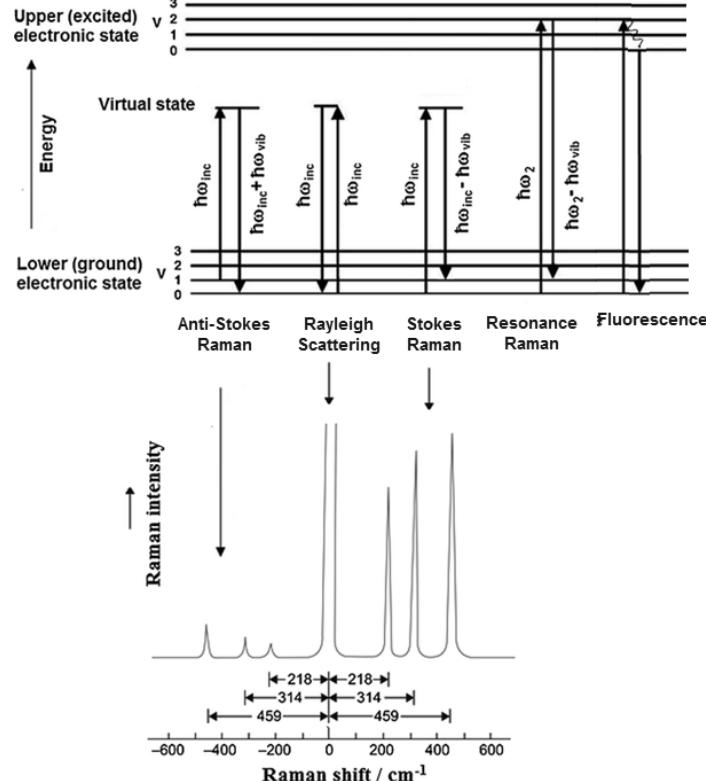


Biosensor



Plasmonic nanostructures: enhance sensitivity of Raman

6



Jeanmaire, D.; Van Duyne, R. J. *J. Electroanal. Chem.* 1977, 84, 1

When a molecule is located in the plasmonic field, signal is enhanced by 10⁶

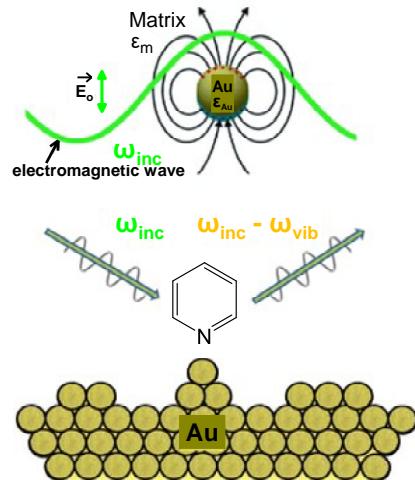
SERS: Sub ppm detection is possible

Mechanism of SERS signal enhancement

7

Electromagnetic enhancement

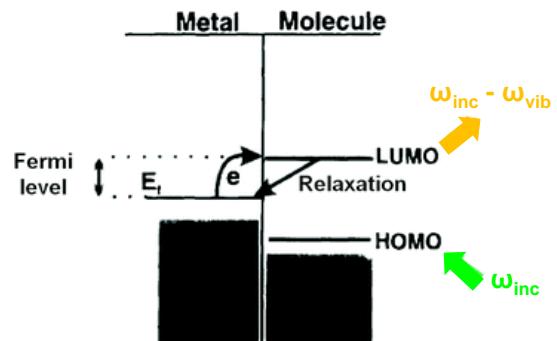
- Local electric field ($\overrightarrow{E}_{local}$) enhanced by excitation of localized surface plasmons
- Enhancement 10^6 - 10^8



Induced dipole moment
in molecule:
 $\vec{p} = \alpha \overrightarrow{E}_{local}$

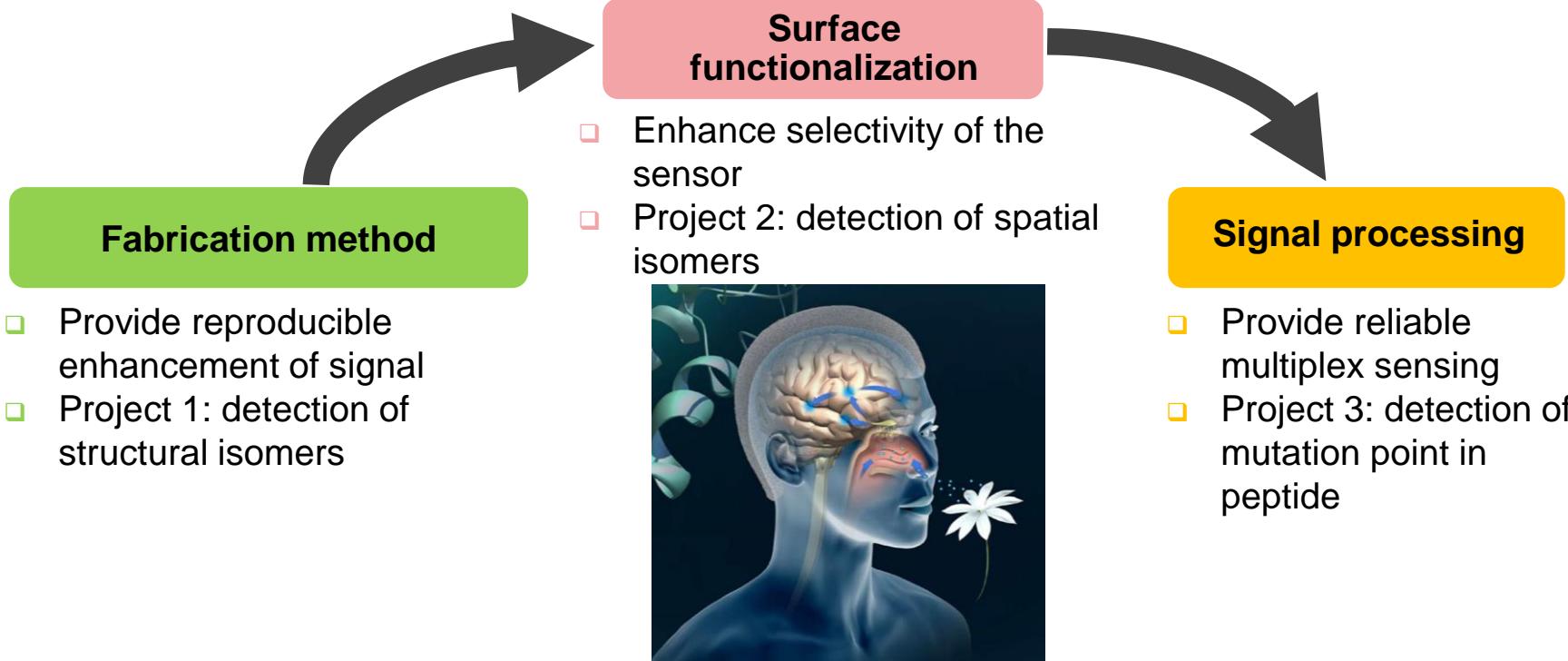
Chemical enhancement

- Molecular polarizability (α) enhanced by charge transfer metal-molecule complex
- Enhancement 10^2 - 10^3



Rationale designs for sensitive and reliable SERS sensors

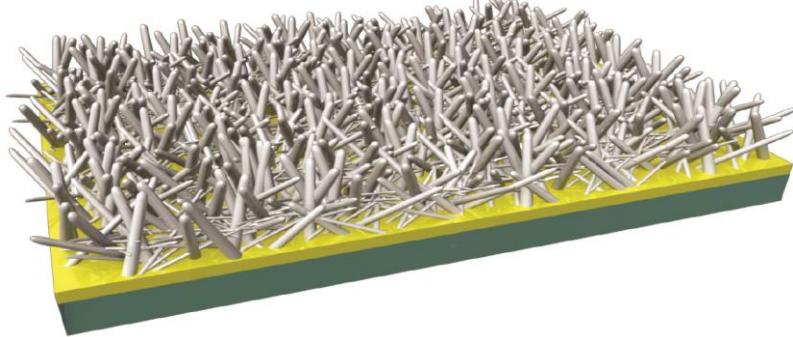
8



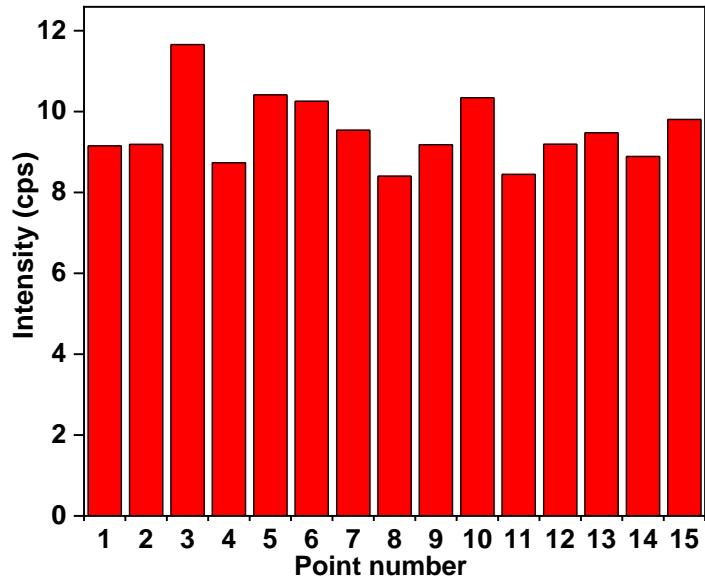
Scope of Project 1: SERS sensor for detection and quantification of petrochemical isomers

9

Control arrangement of plasmonic materials



Reproducible enhancement



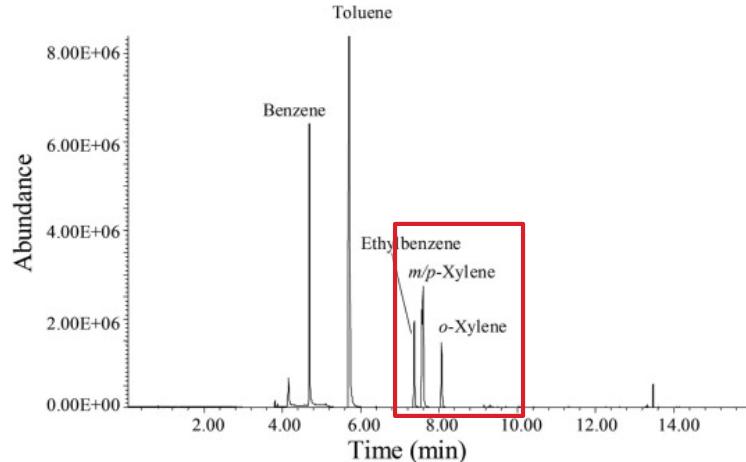
Current limitation in detection method of xylene isomers

10

- Respiratory health problems at 100 ppm; oxidative stress when exposed to 80 ppm concentration

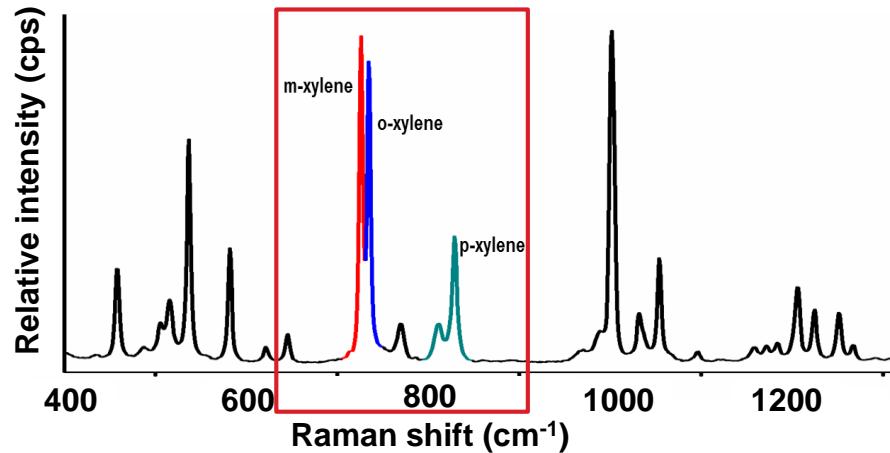
GC-MS:

- High sensitivity
- Intensive sample handling



SERS:

- Lower sensitivity
- Direct sensing, suitable for onsite detection

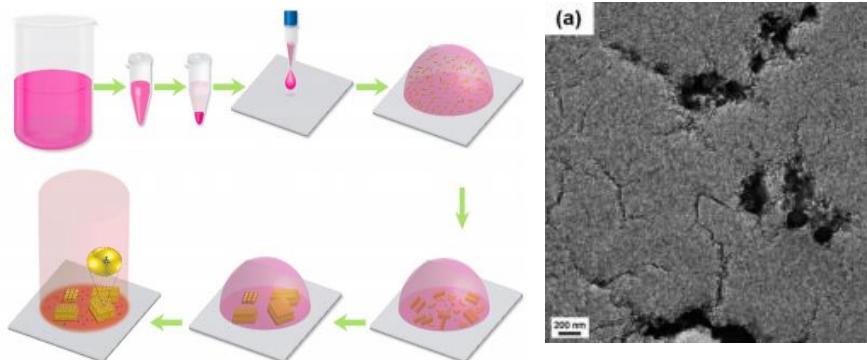


Challenges in SERS sensors designs

11

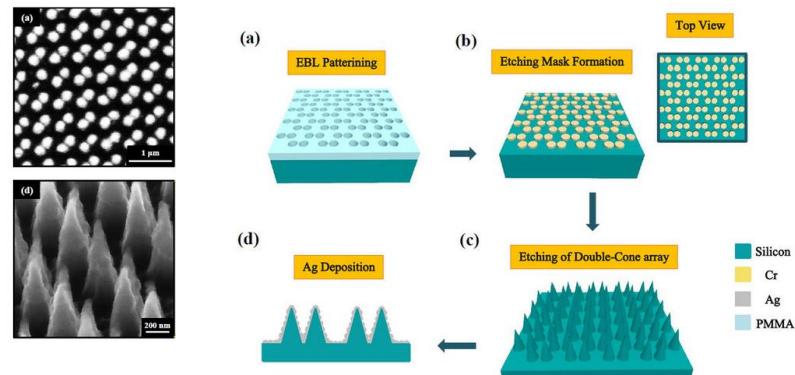
- SERS sensor designs for best output signal:
 - Increased density of “hot-spots”
 - Uniform control of hot-spots

Bottom up



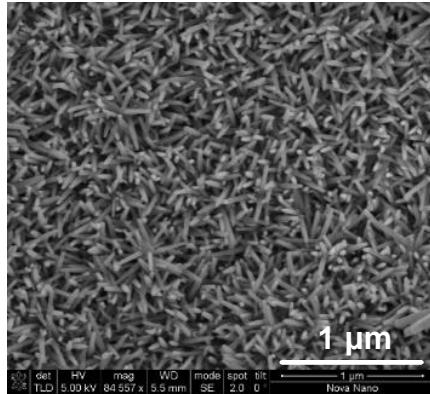
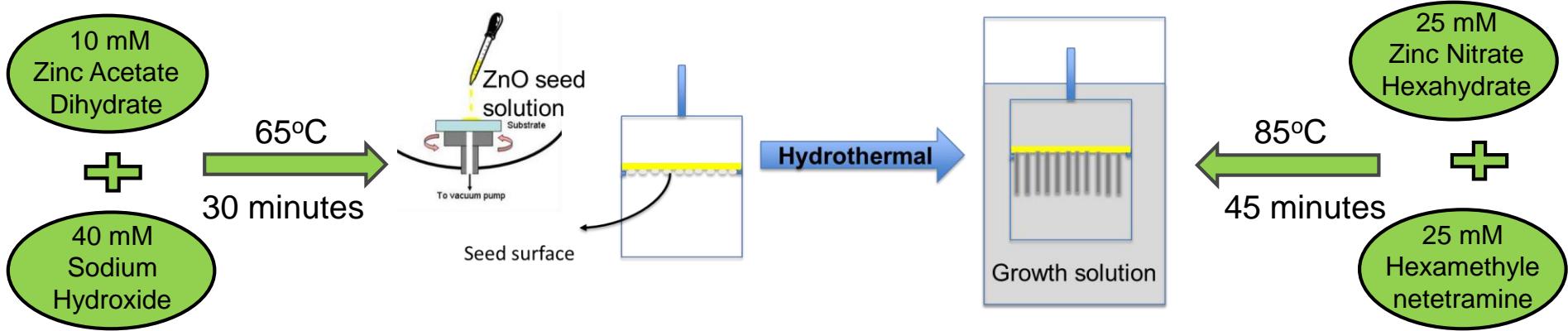
- Requirement of SERS sensors:
 - High through-put manufacture
 - Sensitive and reliable detection

Top down



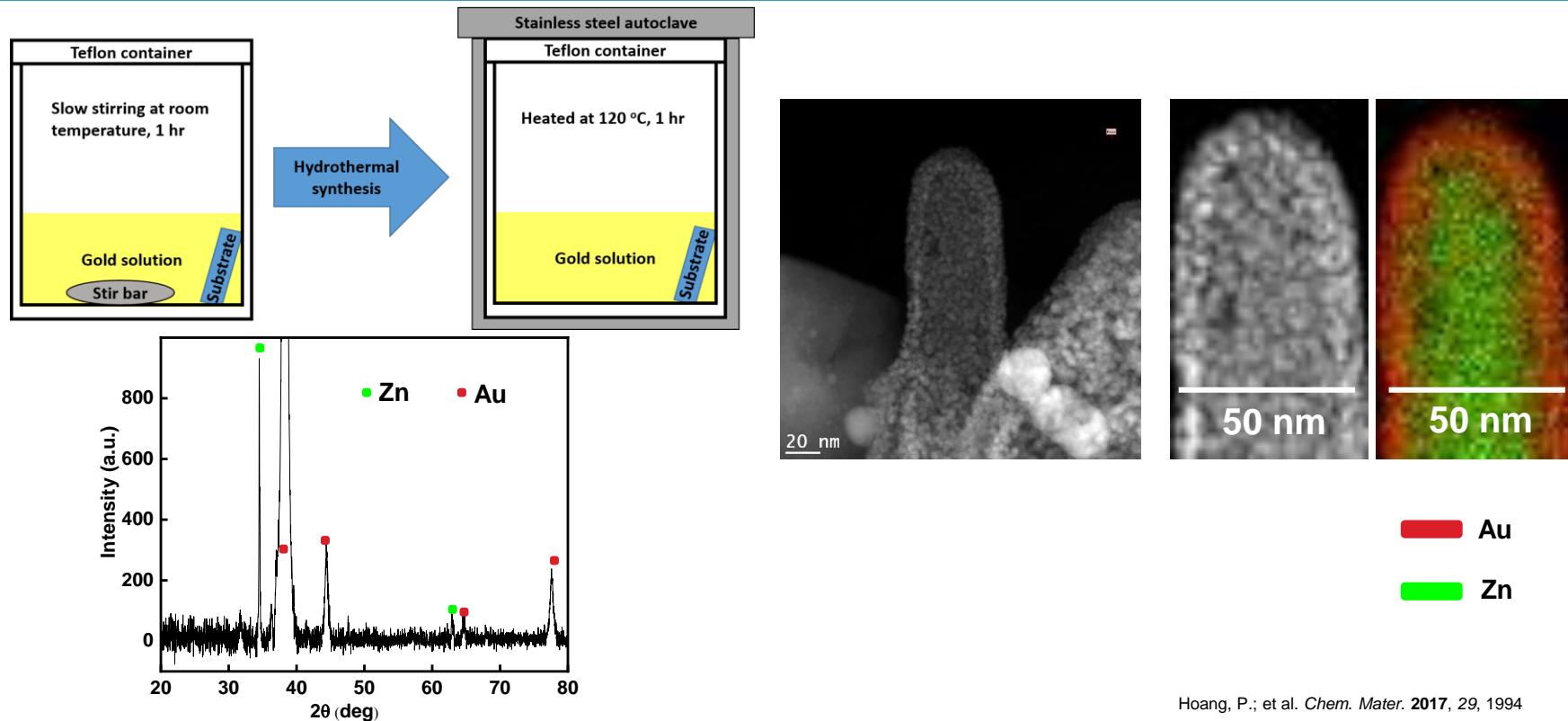
Facile template manufacturing based on Zinc Oxide (ZnO) nanorods

12



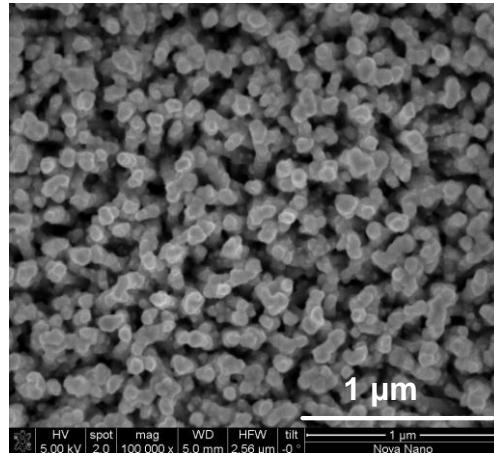
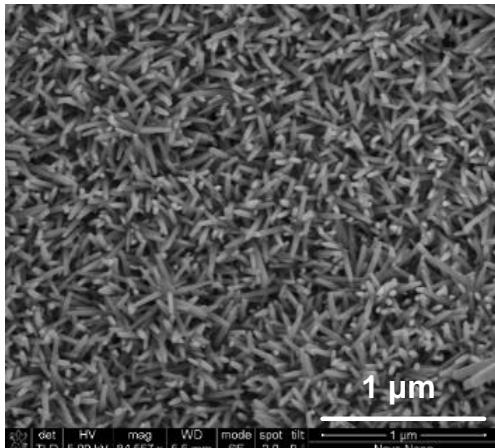
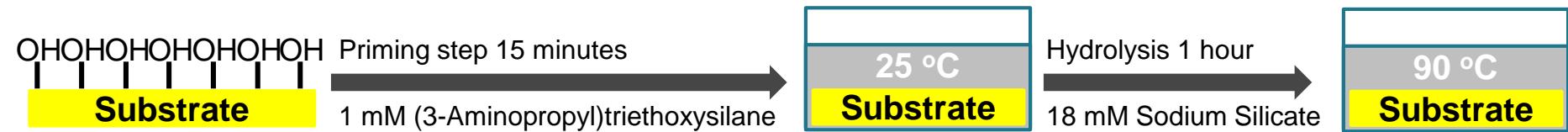
Direct reduction of SERS-active materials on the template

13



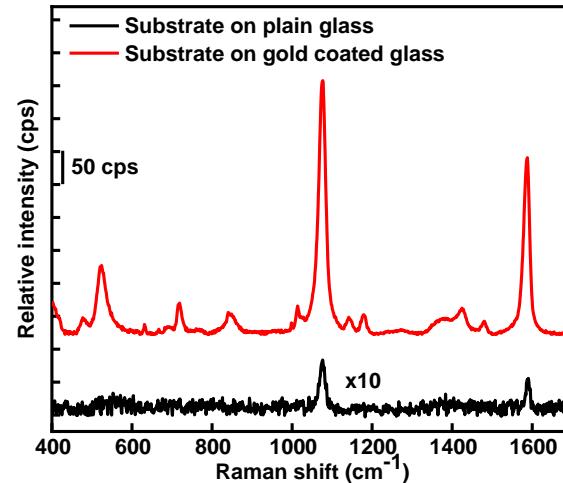
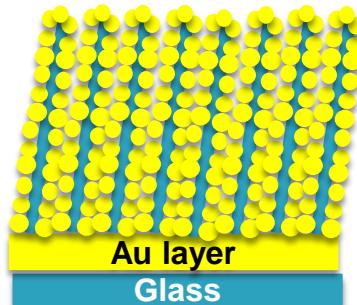
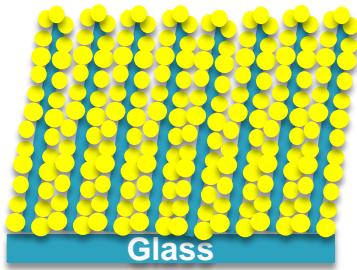
Topological silica coating to improve the stability of SERS sensor

14



Optimization: synergistic LSPR coupling of AuNPs and metallic substrate

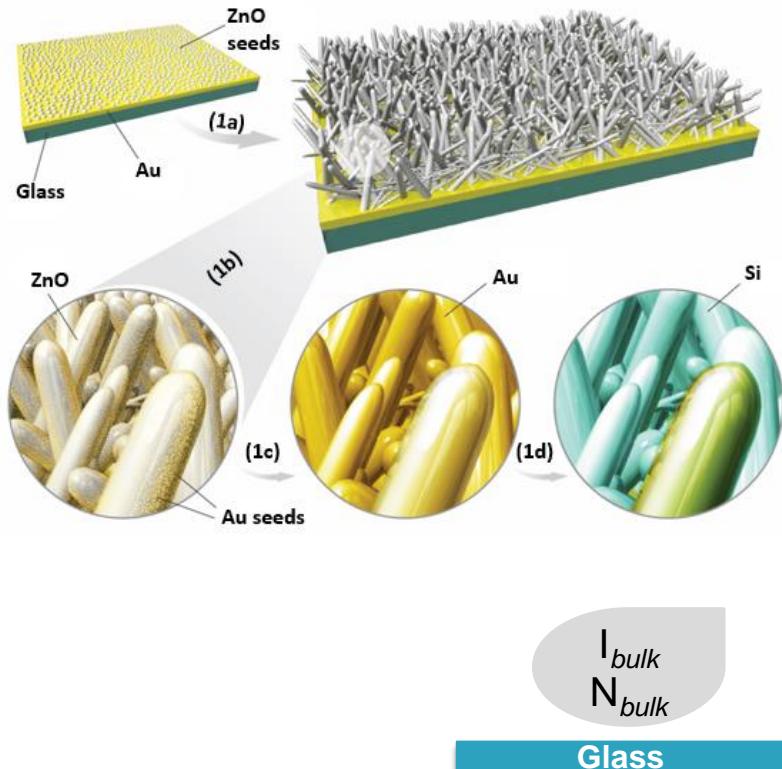
15



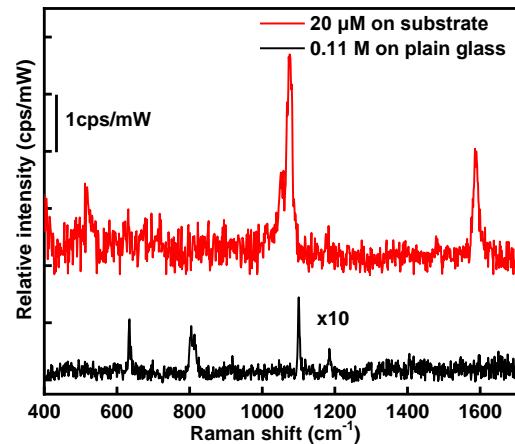
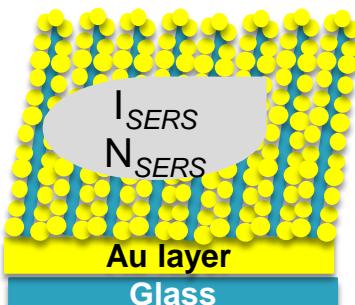
□ Probe: 4-mercaptobenzoic acid (4-MBA)

Performance evaluation

16



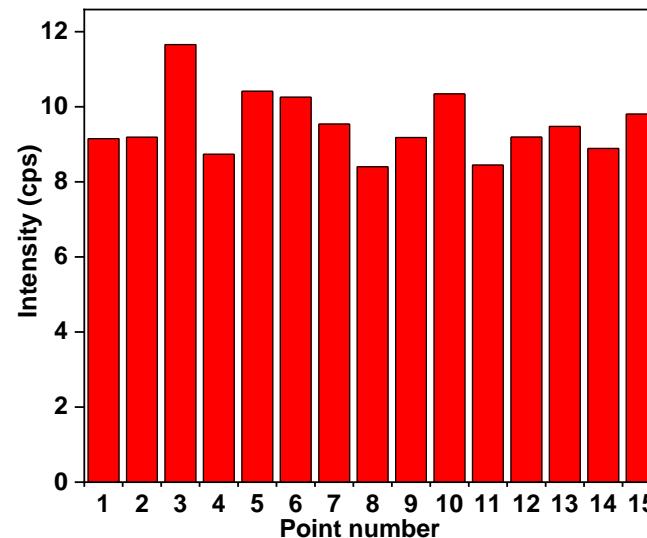
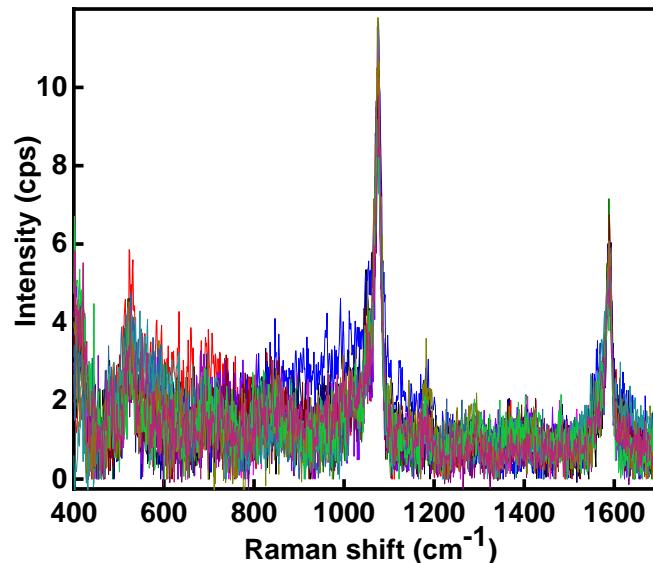
- Enhancement factor (EF) = $\frac{I_{SERS}/N_{SERS}}{I_{bulk}/N_{bulk}}$
 - I_{SERS} , I_{bulk} intensities of the measured peak for SERS and Raman
 - N_{SERS} , N_{bulk} number of probe molecules
- Probe: 4-MBA



Performance evaluation

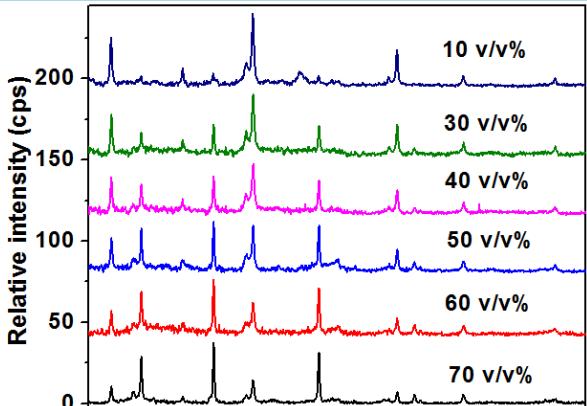
17

- ❑ $EF = 2.4 \times 10^4$
- ❑ Reproducibility of 1 μM of 4-MBA signal at 15 random spots: $\pm 9\%$ deviation

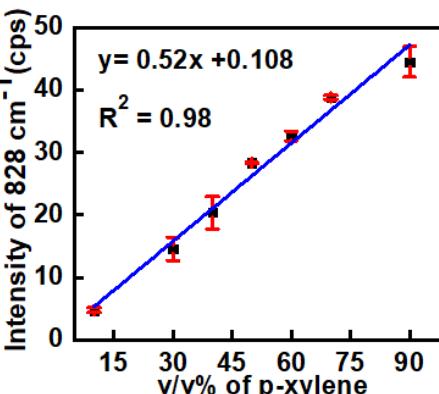
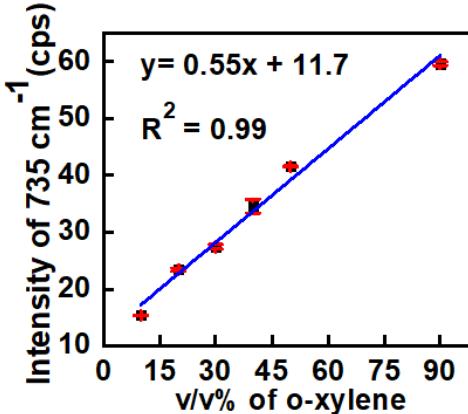
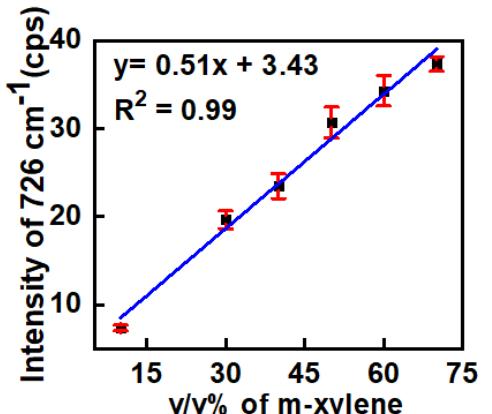
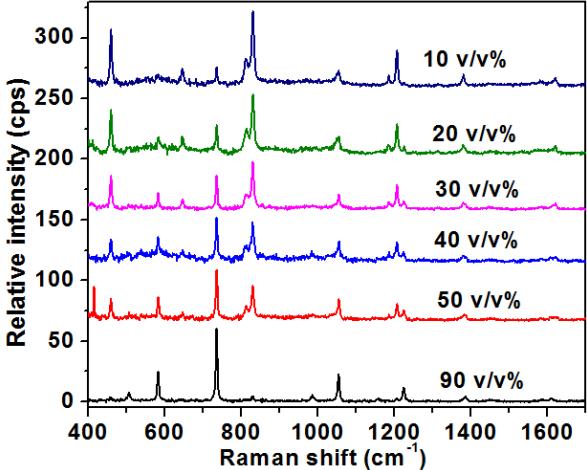


Xylene isomers calibration

m-xylene/p-xylene
v/v%

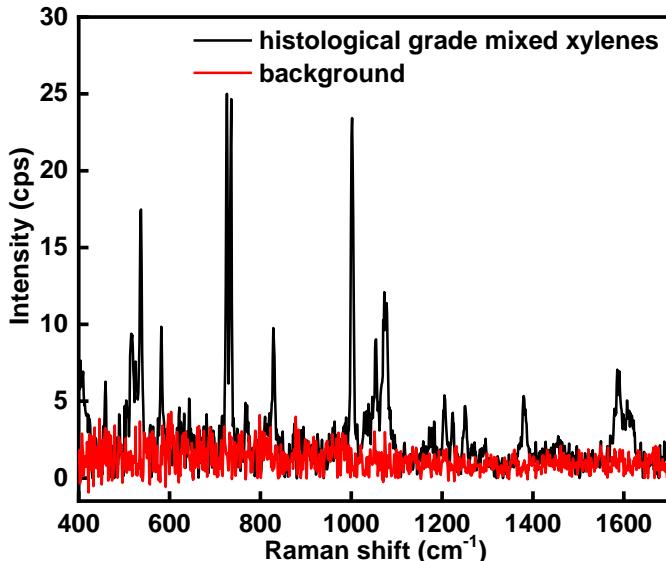


o-xylene/p-xylene
v/v%



Limit of detection (LOD)

19



$$\text{LOD} = \frac{\text{Concentration of analyte}}{\text{Sensor response}} \times \text{Baseline variation}$$

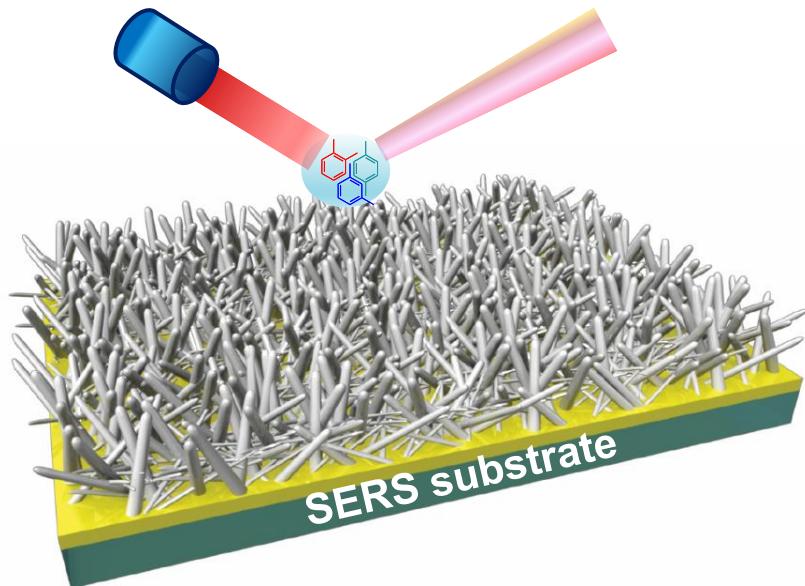
	Calculated from our SERS substrate v/v%	v/v% from manufacture (Product 534056, Batch BCBQ2922V)	% difference
p-xylene	18.44	17.79	3.7
m-xylene	42.42	40.92	3.7
o-xylene	23.61	24.32	2.9

	LOD [ppm]
p-xylene	35
m-xylene	14
o-xylene	14

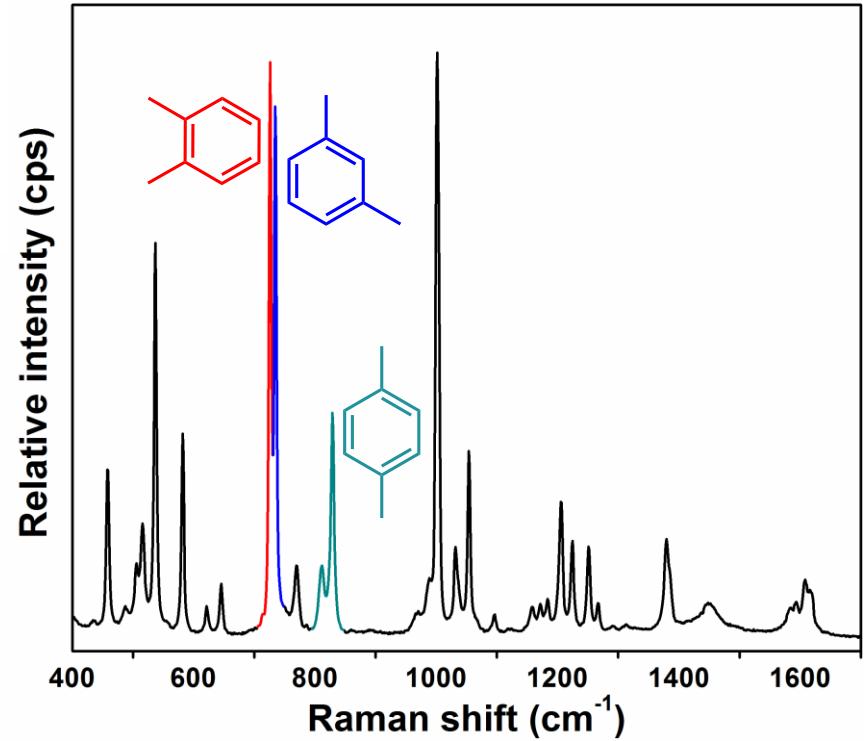
Summary and future directions

20

- Signal enhancement: 2.4×10^4
- Deviation: $\pm 9\%$
- LOD of xylene isomers analysis: 35 ppm

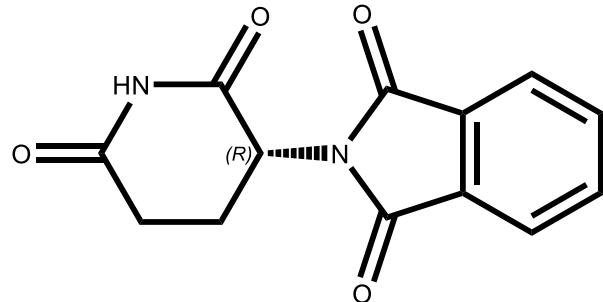


Hoang, P.; et al. *Chem. Mater.* 2017, 29, 1994

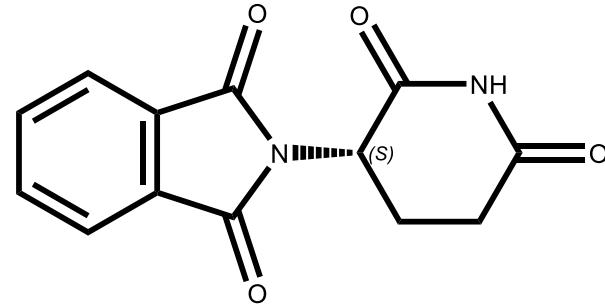


Scope of Project 2: SERS signal to study the selectivity in chiral interactions

Thalidomide



Sedative agent

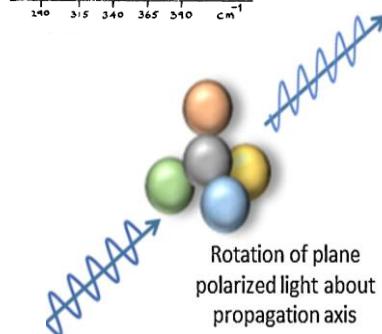
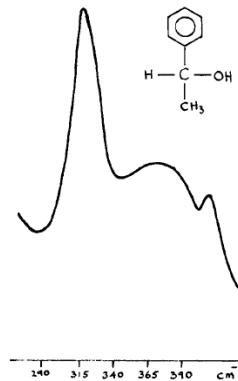


Pharmaceutical impurity:
birth defects

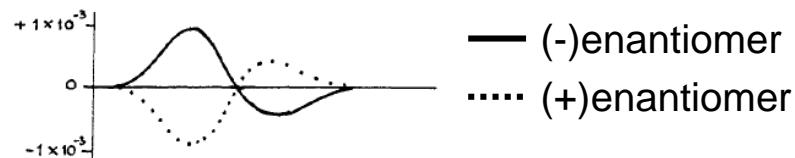
Combining SERS and circular dichroism (CD) light for chirality detection

22

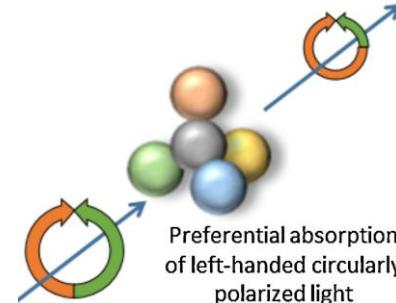
Raman



Raman optical activity (ROA)



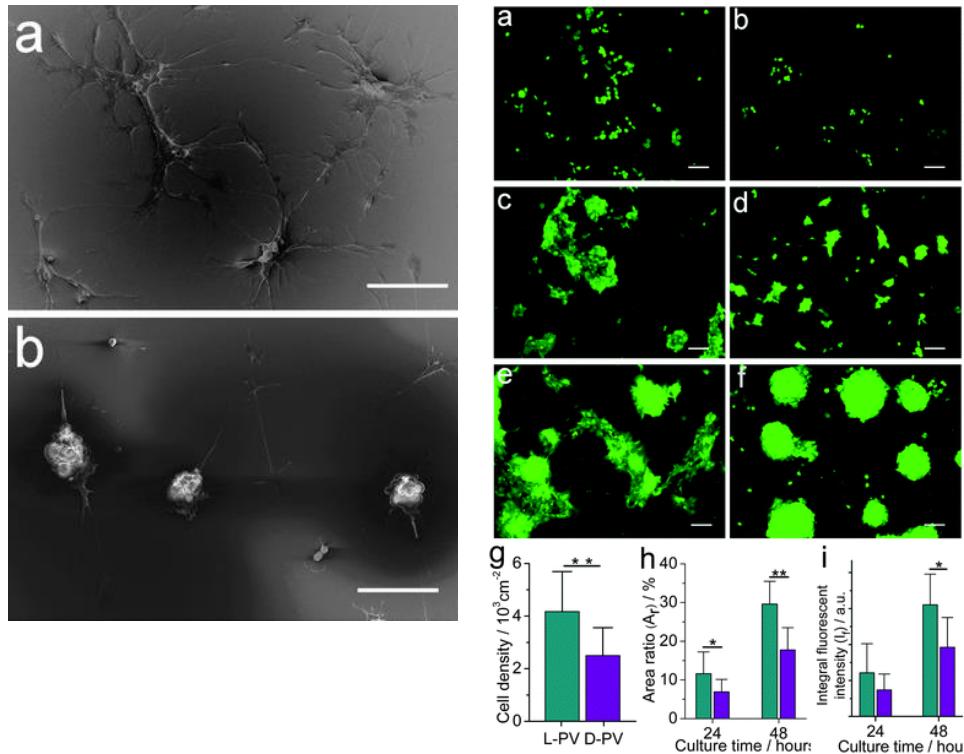
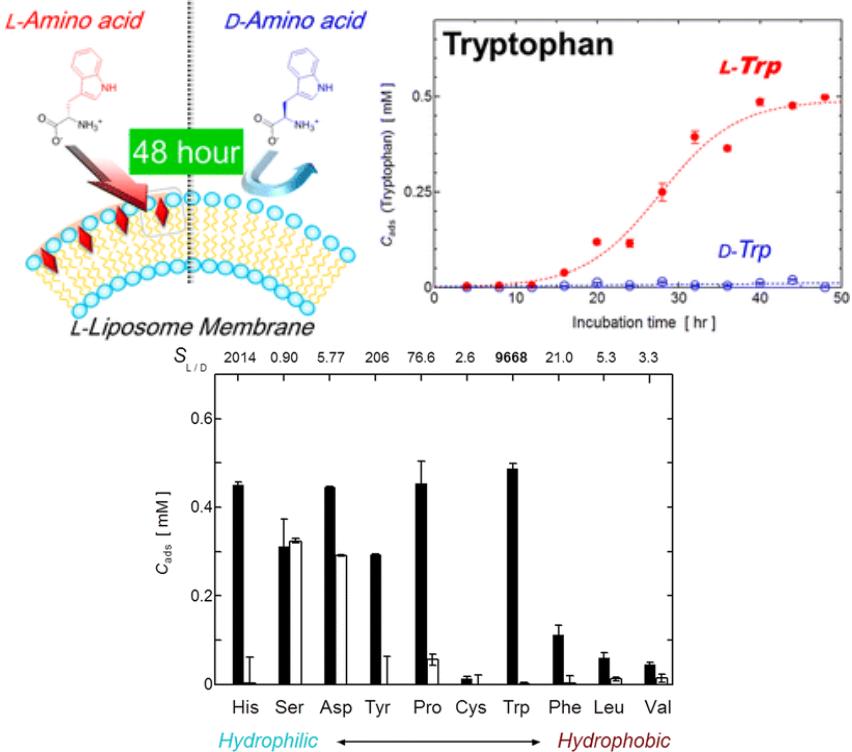
Bradshaw, D. S.; et al. *Chem. Phys. Lett.* 2015, 626, 106



Ben-Moshe, A.; et al. *Nat. Commun.* 2014, 5, 4302

Symmetry selective interactions in biosystem

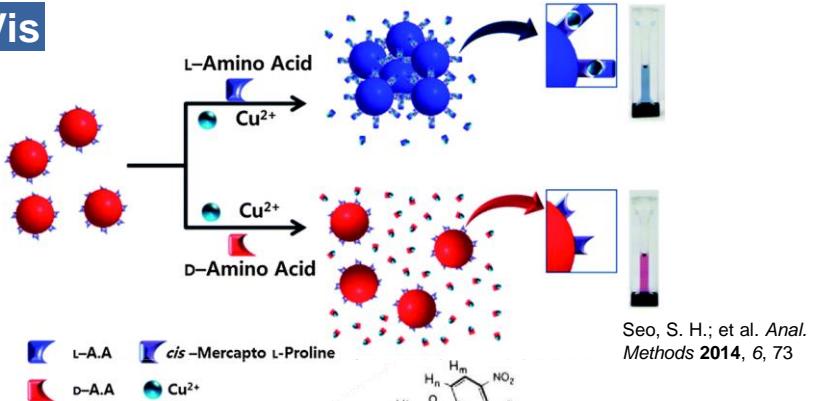
23



Selectivity between chiral molecules

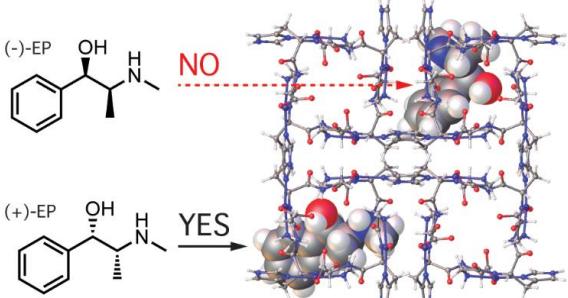
24

UV-Vis



Mechanism

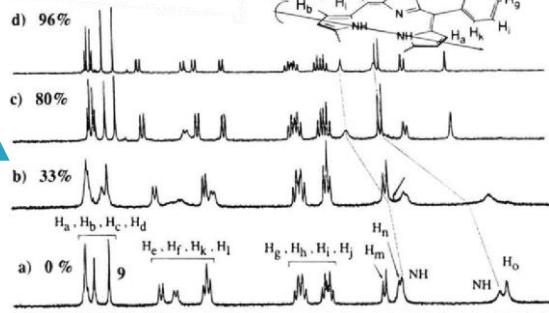
- Hydrogen bonding
- Dipole-dipole
- Steric repulsion



Navarro-Sánchez, J.; et al. *J. Am. Chem. Soc.* 2017, 139, 4294

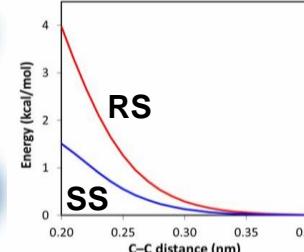
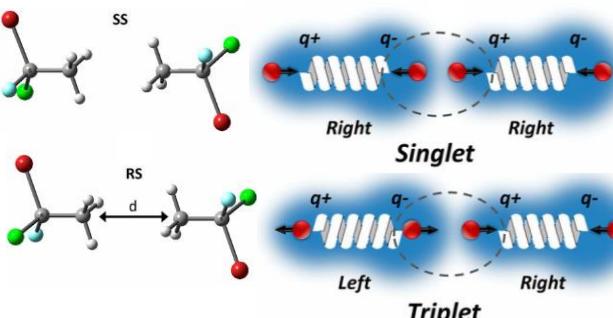
NMR

Concentration L-Val-OMe ↑
% complexation ↑



Kuroda, Y.; et al. *J. Am. Chem. Soc.* 1995, 117, 10950

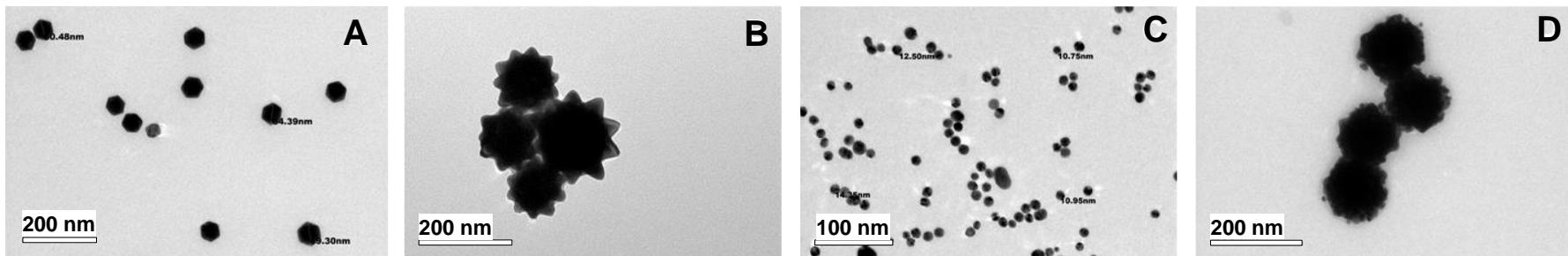
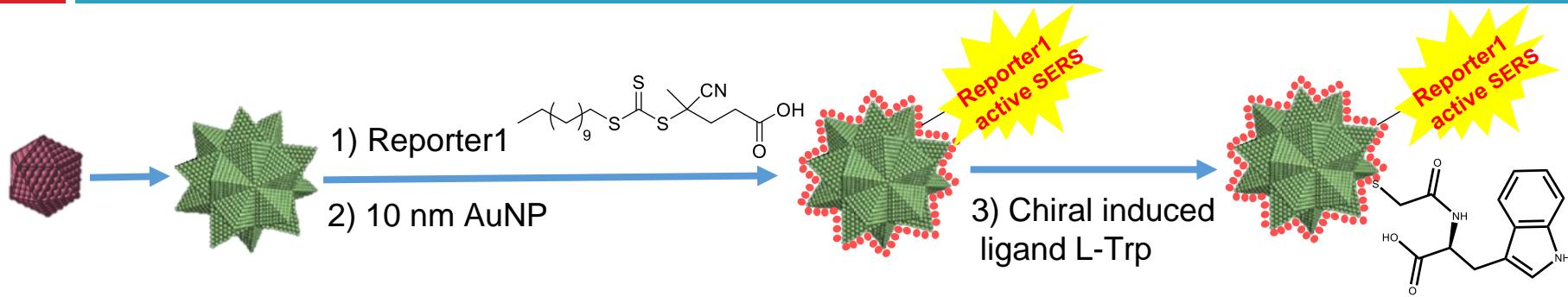
Spin polarization



Kumar, A.; et al. *Proc. Natl. Acad. Sci.* 2017, 114, 2474

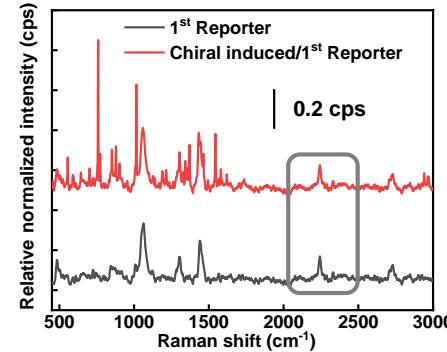
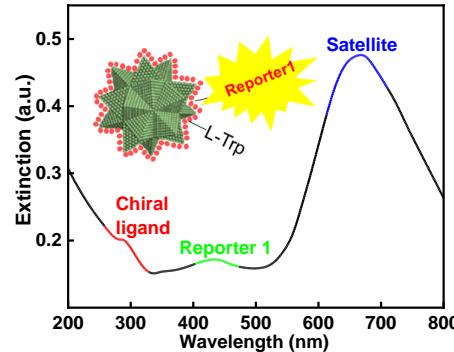
Surface modification of nanostars with first reporter and chiral induced property

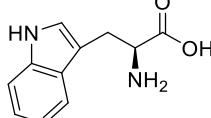
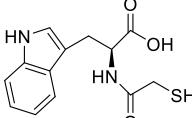
25



Characterization of nanostructure and functionalized ligands

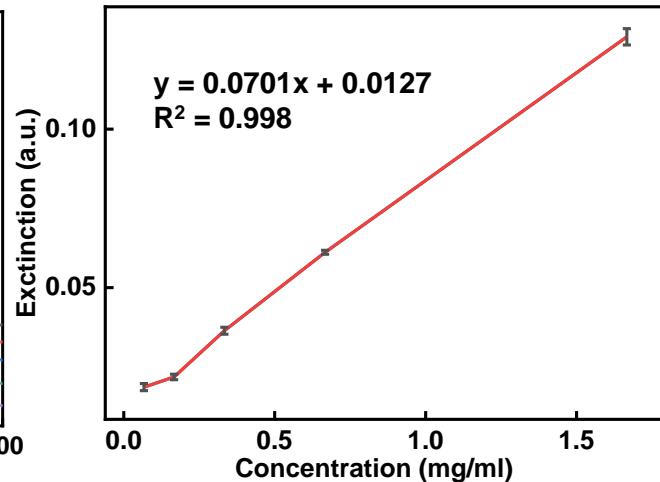
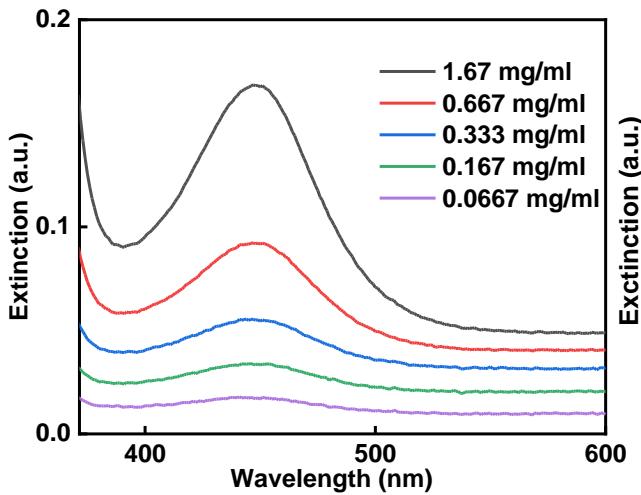
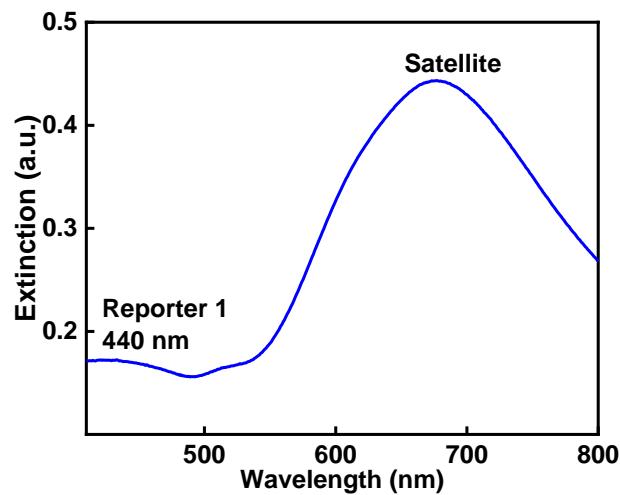
26



Compound	Concentration (mg/ml)	Optical rotation (°)
 L-Trp	9.77	-0.328 ± 0.001
 SH-L-Trp	0.6	+0.022 ± 0.012

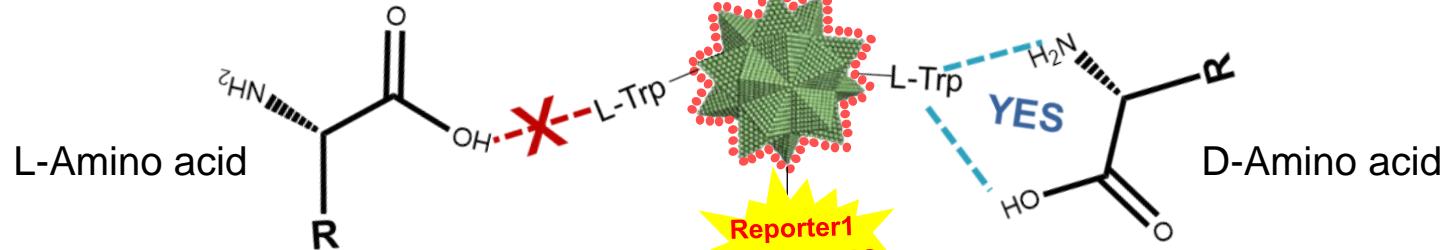
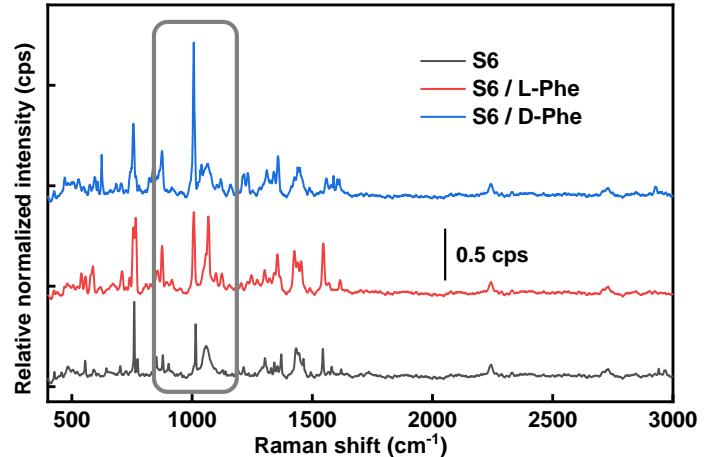
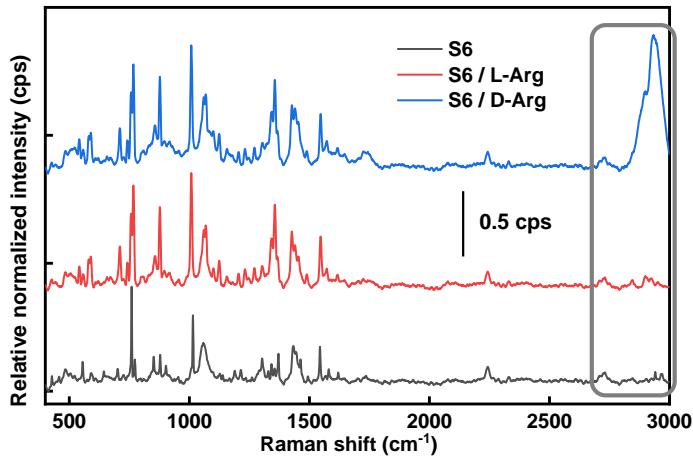
Calibration of SERS active surface area with reporter 1 by UV-Vis absorption

27



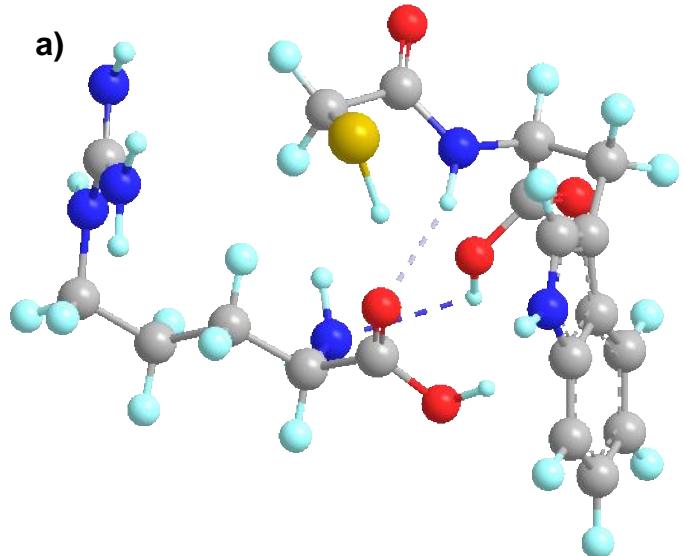
Selective binding of chiral induced structure with D/L-Arg and D/L-Phe

28

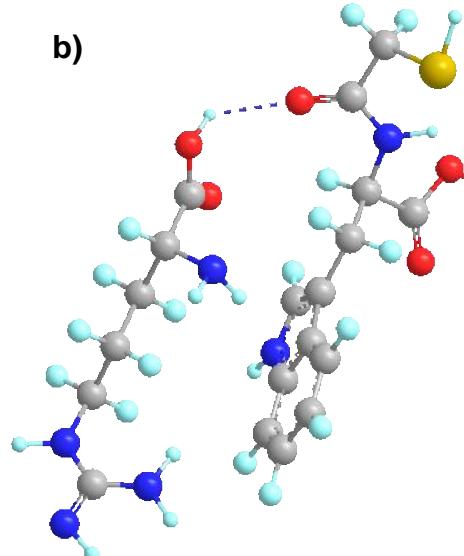


Molecular mechanics version 2 (MM2) study of minimization energy of complex

29



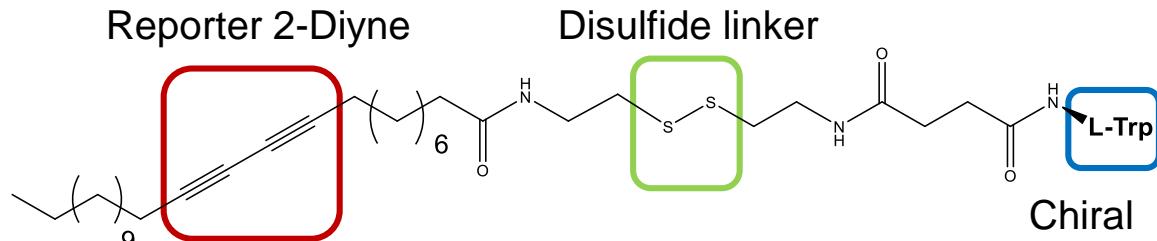
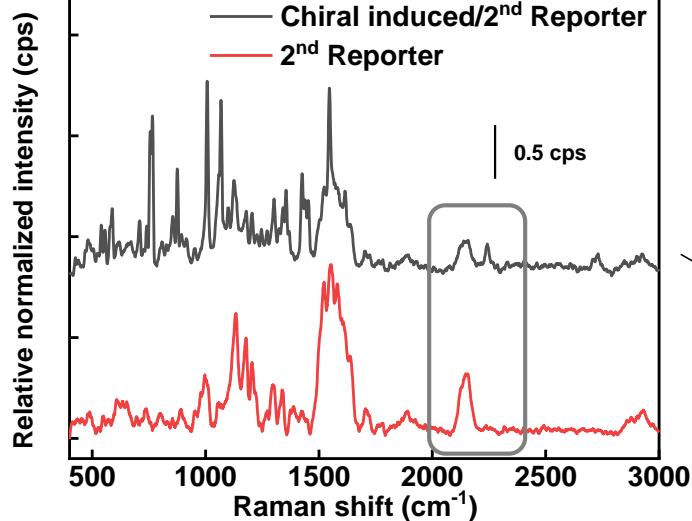
Chiral ligand / D-Arg
-29 kcal/mol



Chiral ligand / L-Arg
-16 kcal/mol

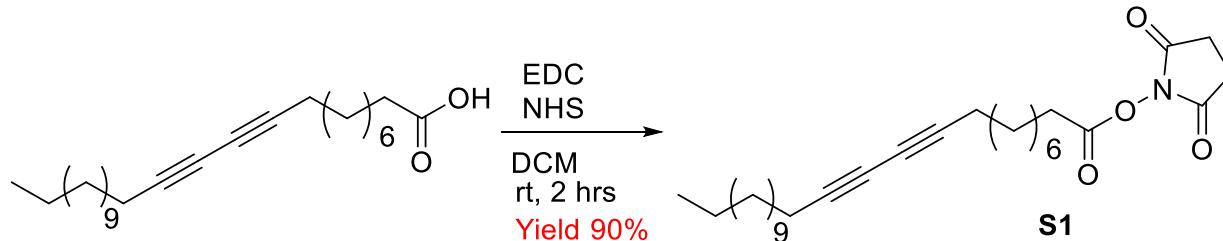
Introduction of stimuli sensitive moiety through –S-S– with chiral induced ligand

30

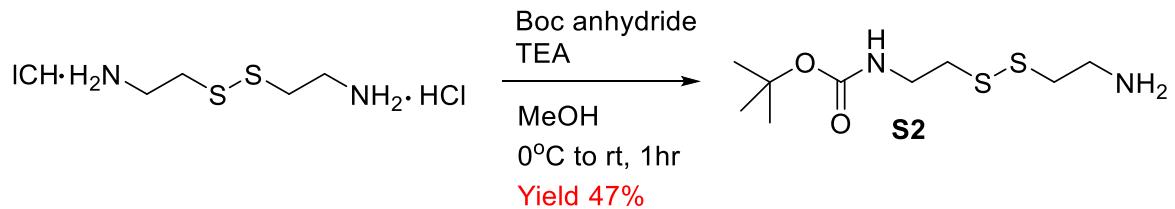


Synthesis of second linker: modification of starting materials

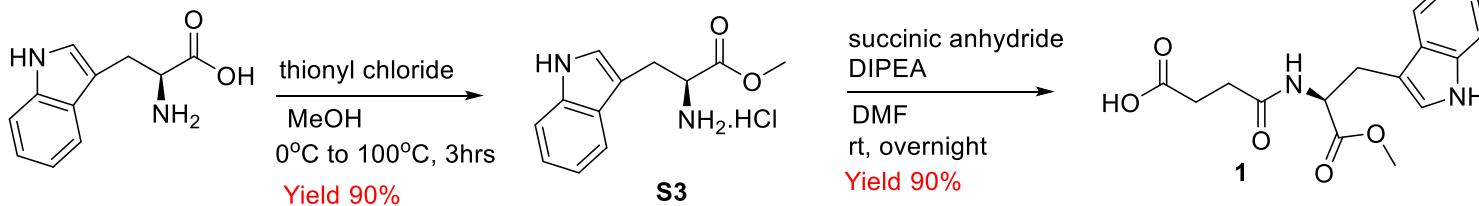
31



Wilson, T.; et.al. *Langmuir* **1994**, 10, 1512



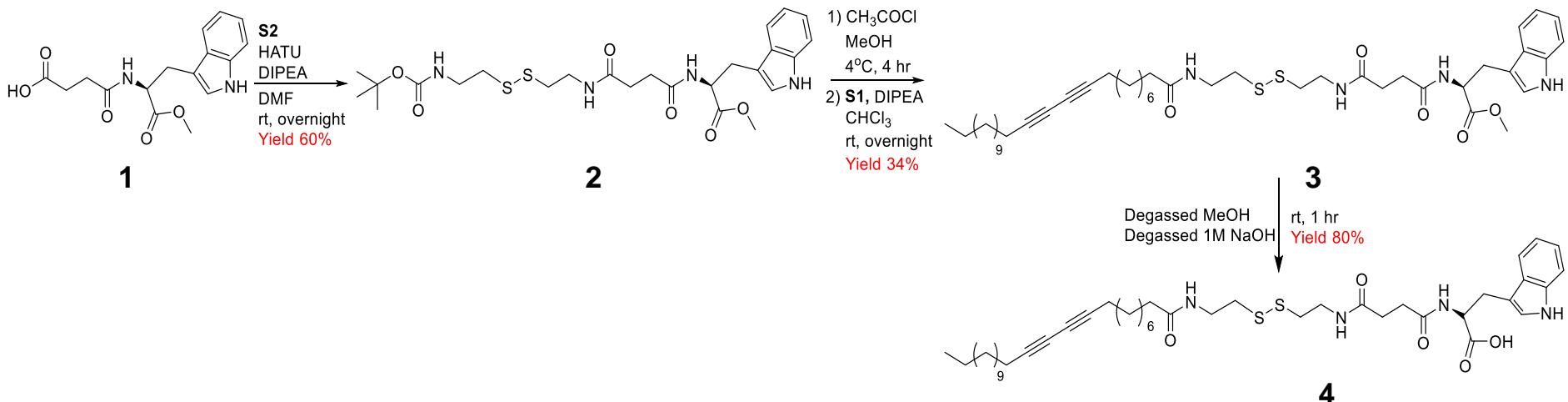
Thielbeer, F.; et.al. *Chem. Sci.* **2013**, 4, 425



Arjomandi, O. K.; et.al. *Eur. J. Med. Chem.* **2016**, 114, 318

Synthesis of second linker: - diyne –S-S–L-Trp

32

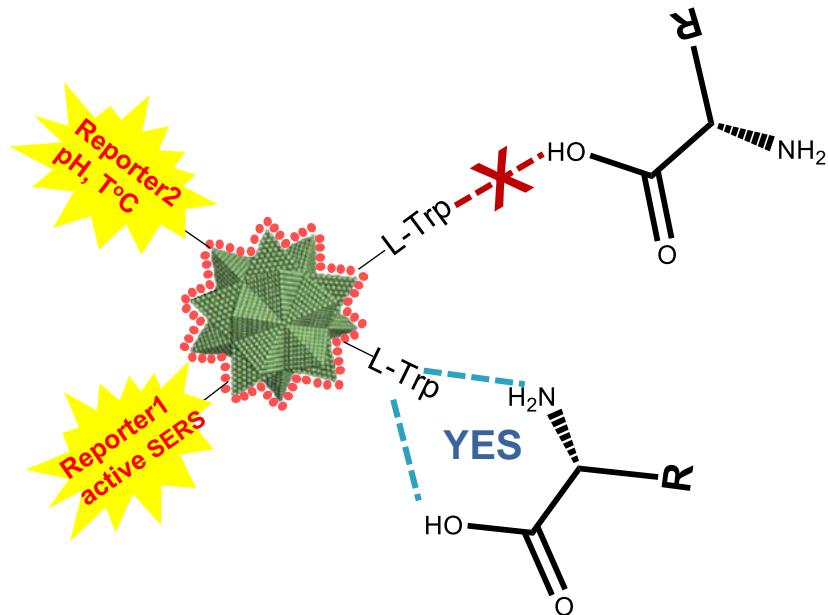


- Compound 2, 3 and 4 are fully characterized with ¹H NMR, ¹³C NMR and mass spectrometry
- CH, CH₂ and CH₃ are assigned based on ¹³C NMR-DEPT 45, 90 and 135

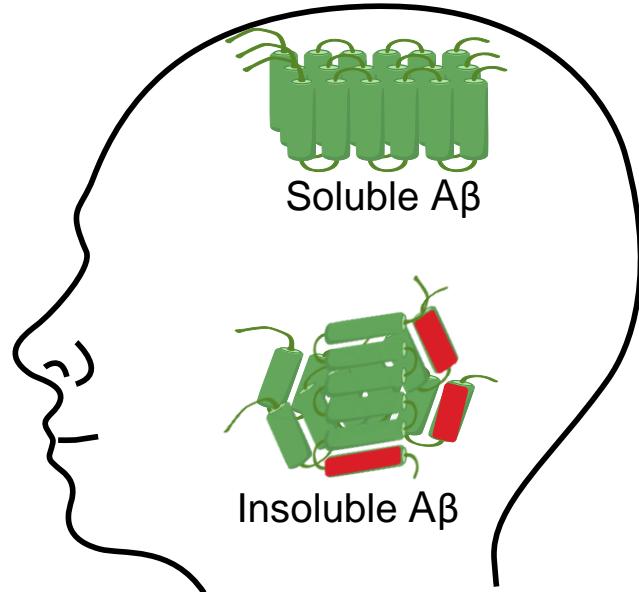
Summary and future directions

33

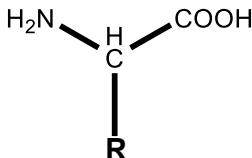
- ❑ Future works: effect of the local environment on stereospecificity
 - ❑ pH and temperature dependent SERS measurements for selective absorption of L/D-Amino acids with chiral induced nanostructure



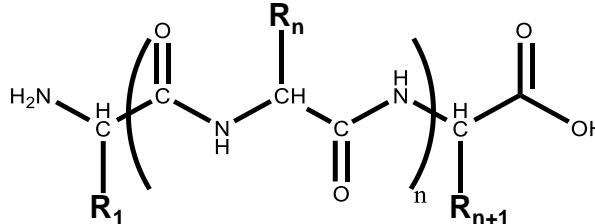
Scope of Project 3: Binary barcodes for single point mutation detection in primary peptide fragments



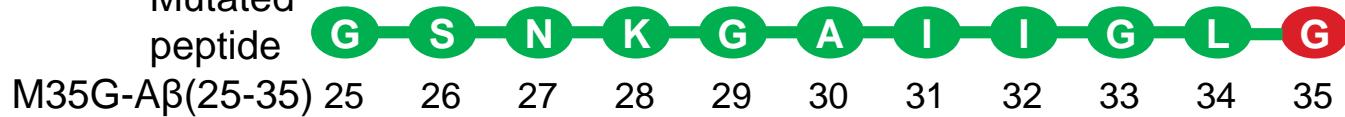
Amino acids (AA)



Peptide
A β (25-35)



Mutated
peptide



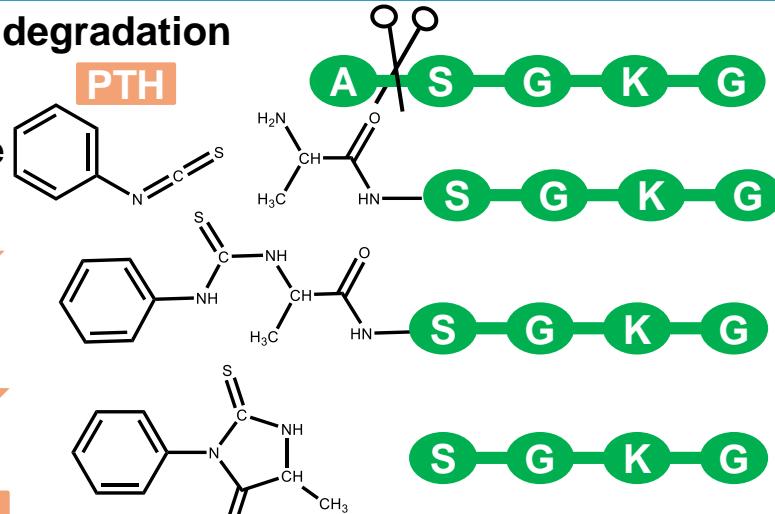
M35G-A β (25-35) 25 26 27 28 29 30 31 32 33 34 35

Established techniques for peptide mutation detection

35

Edman degradation

Phenyl
isothiocyanate

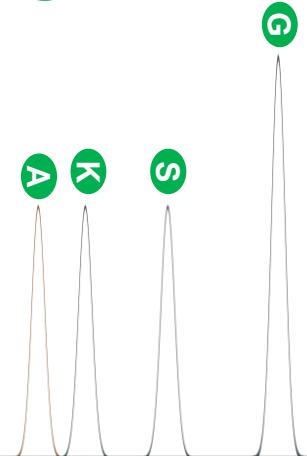


Absorbance at
254 nm

Elution time
(minutes)



Acid hydrolysis

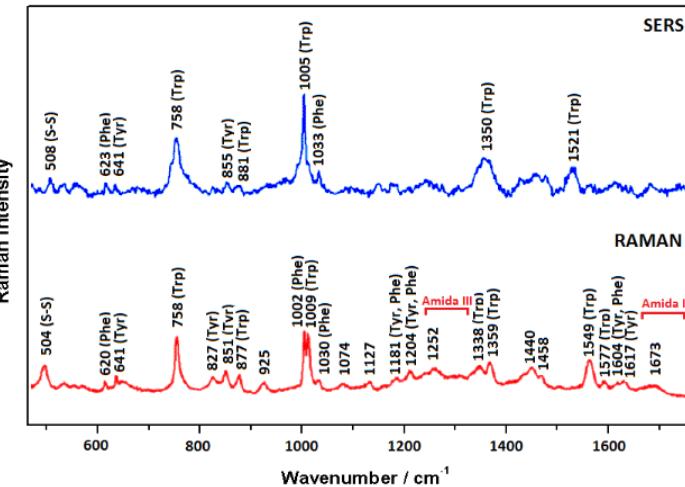


Limitations in detection of amino acids in peptides

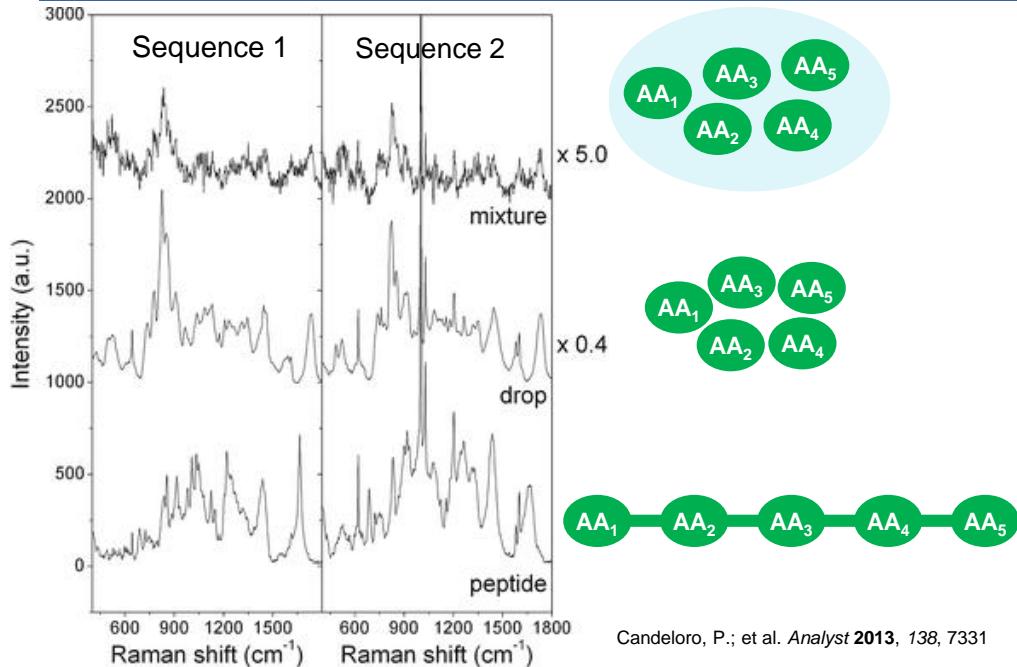
36

Vibrations of aromatic AAs
dominate the spectrum

Phe-Cys-Tyr-Trp-Lys-Val-Cys-Trp



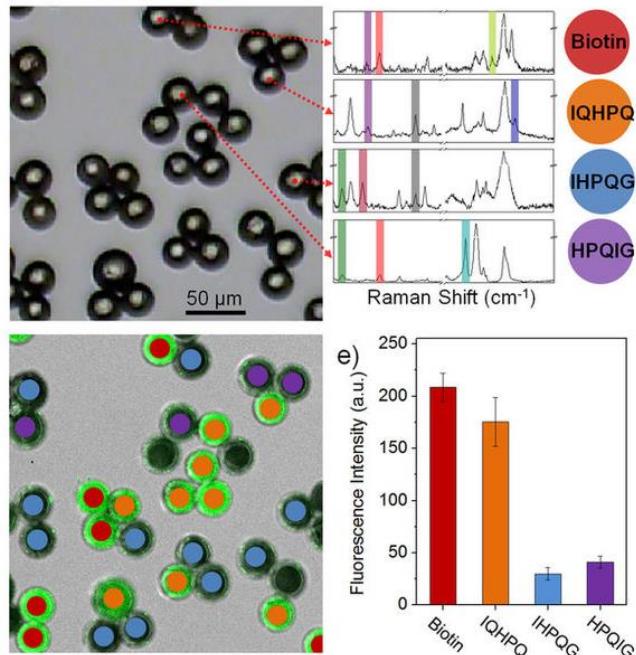
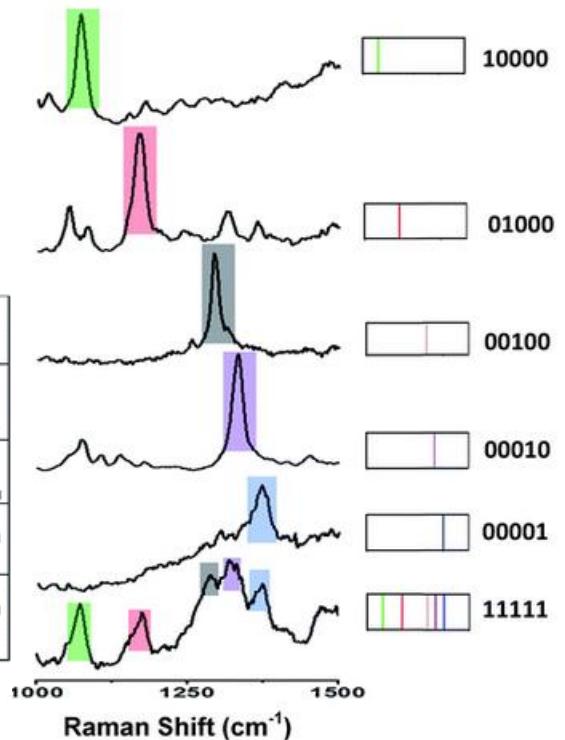
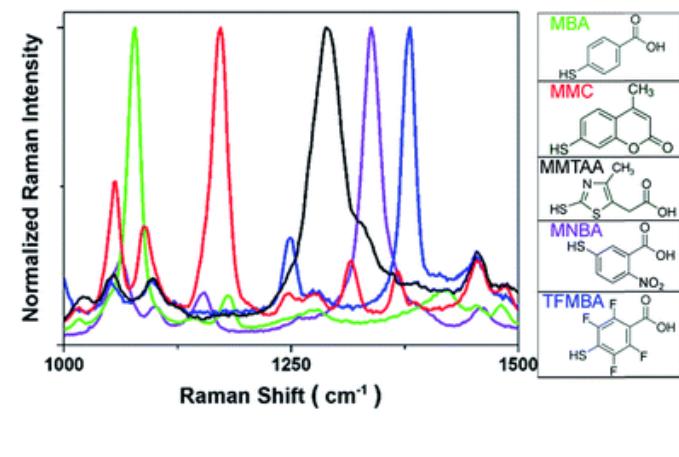
Spectrum of the peptide does not resemble linear combination of spectra of AAs components



Labeling analytes to improve specificity

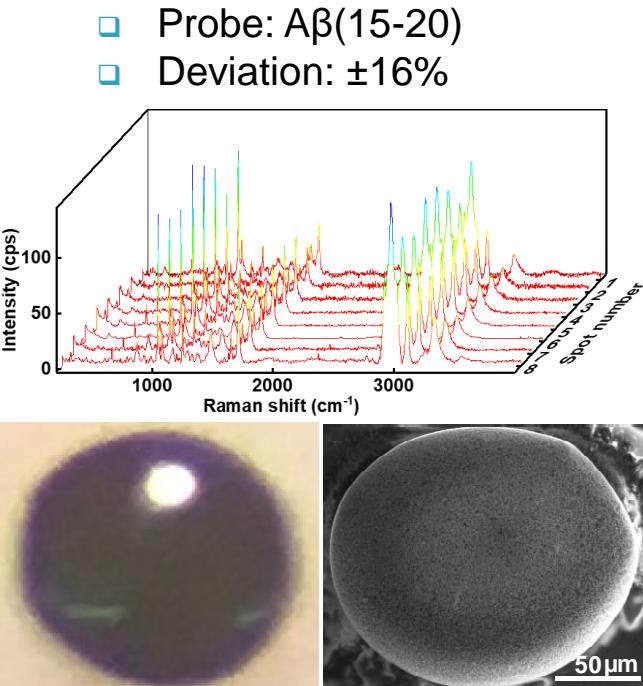
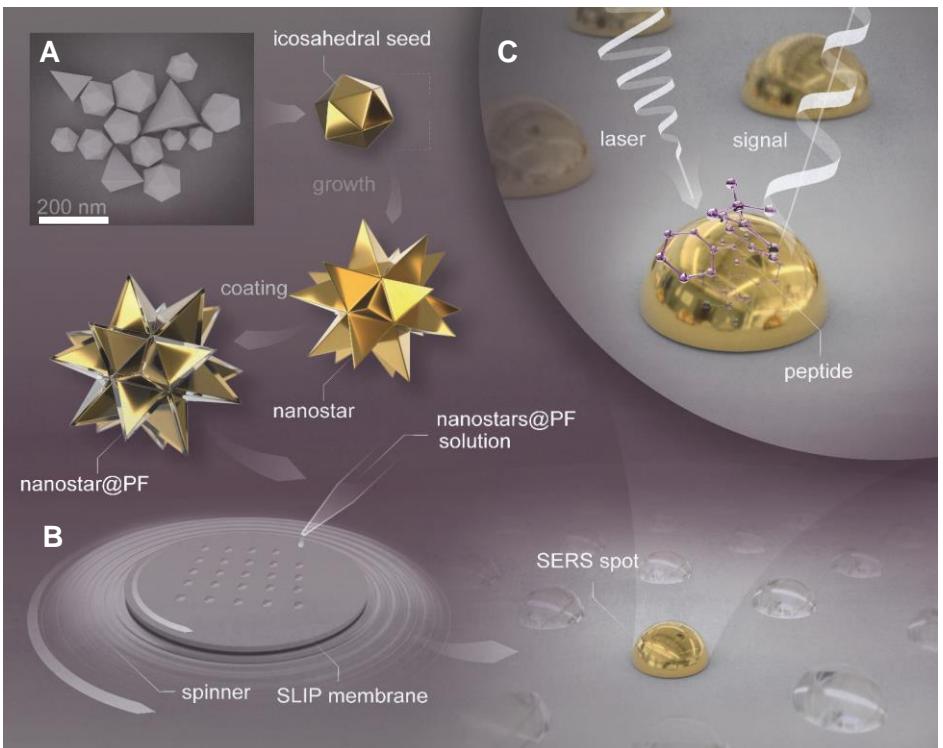
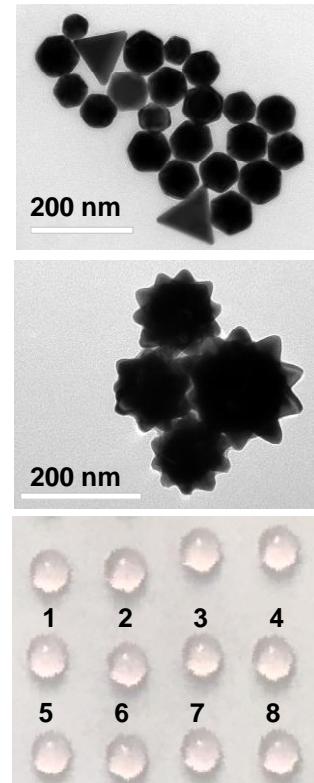
37

- Relatively high sensitivity
- Require synthesis of unique label for each analyte
- Require prior knowledge of chemical compatibility



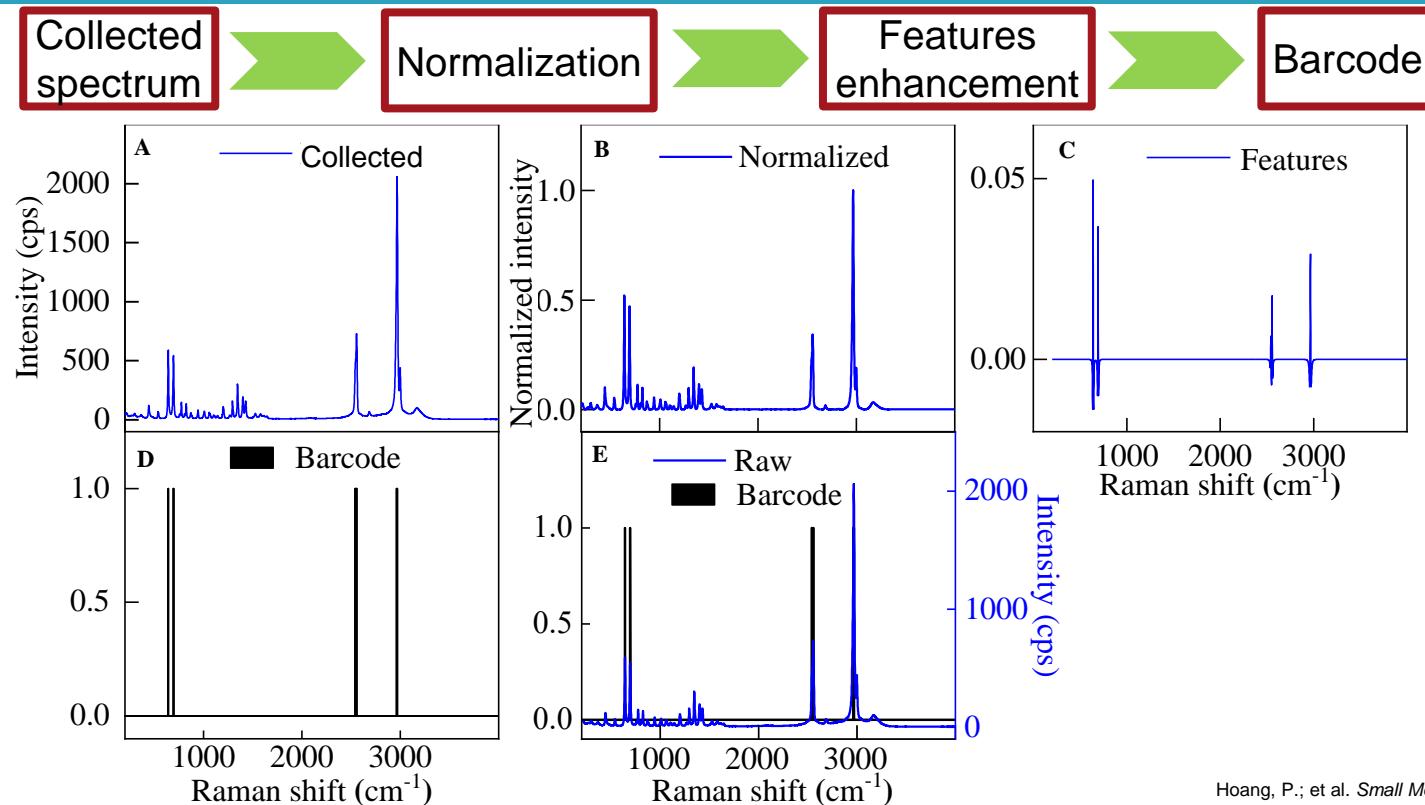
Superhydrophobic SERS substrate to prevent coffee-ring drying defect

38



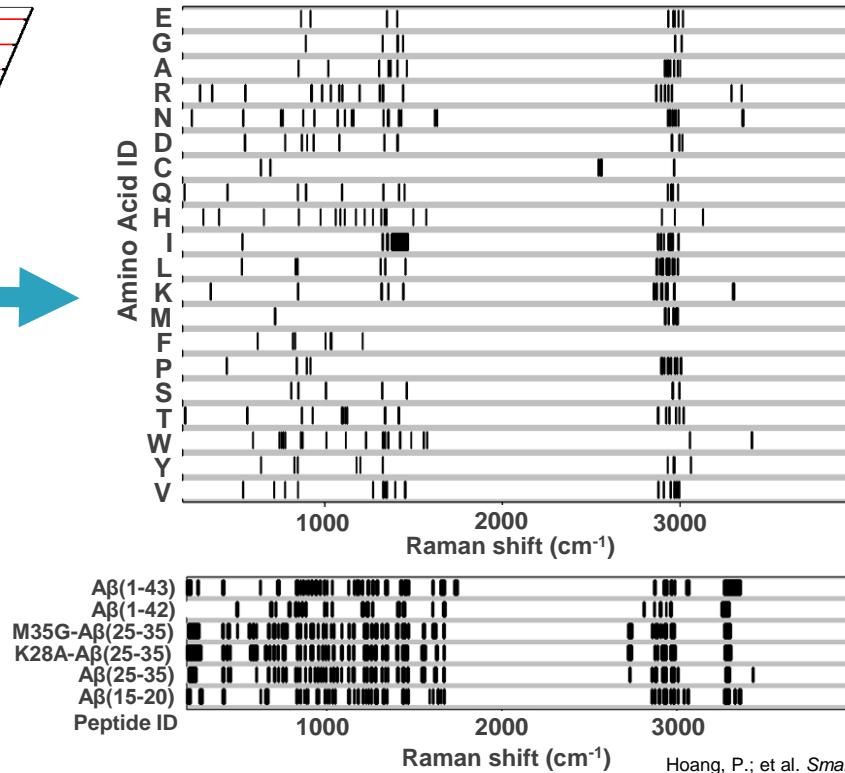
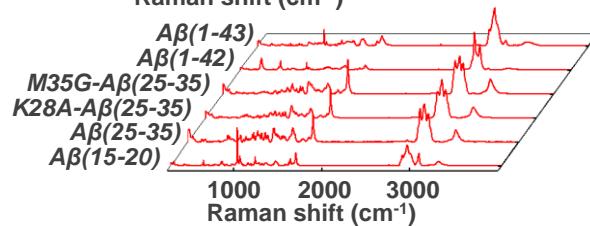
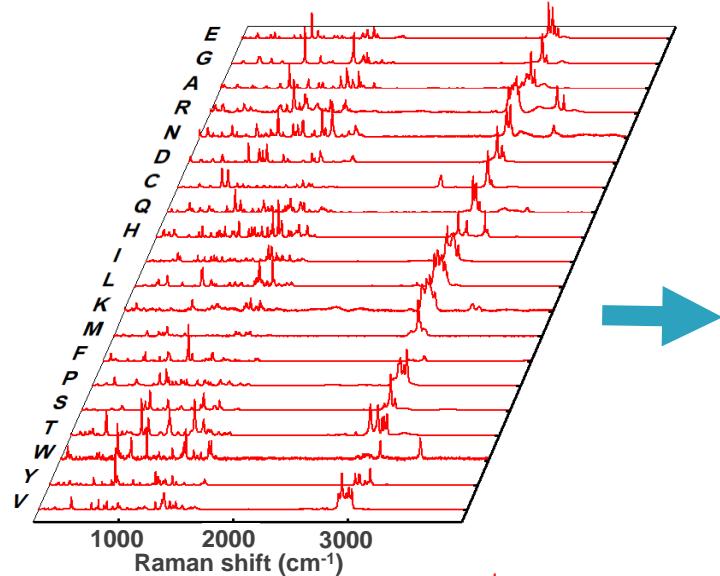
Encoding: conversion of Raman spectrum to optical identification tag (OIT)

39



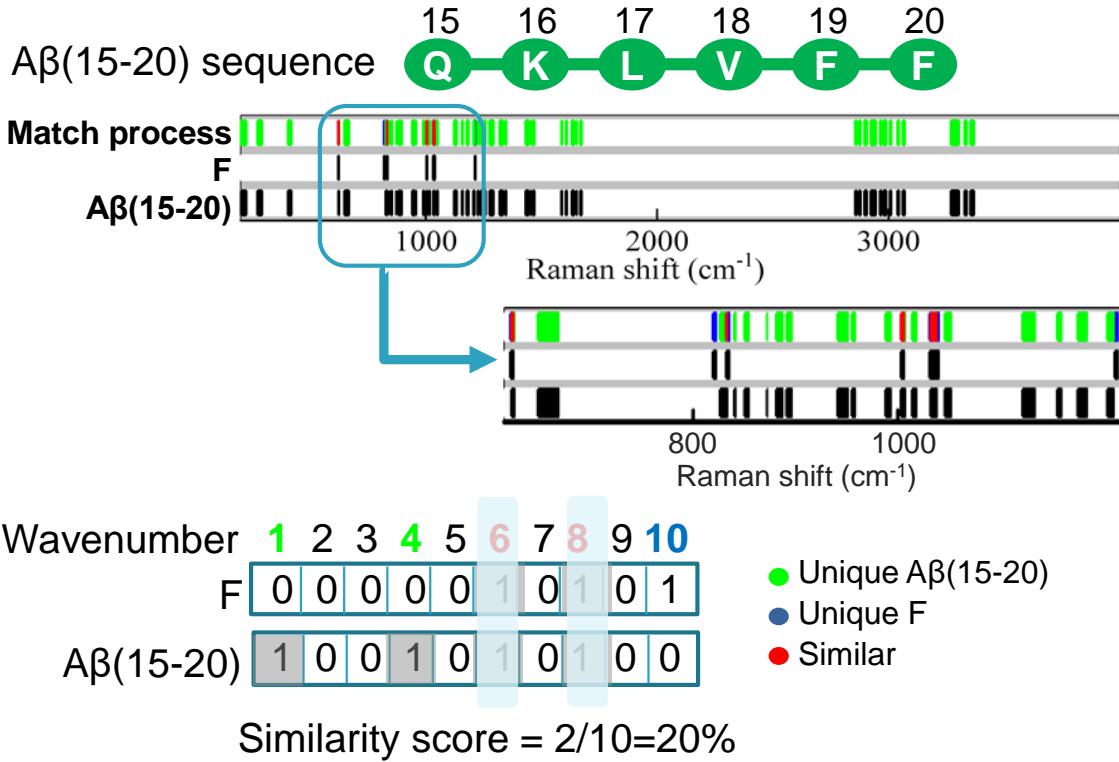
Database of binary barcode OITs contain Raman response of AAs and peptides

40

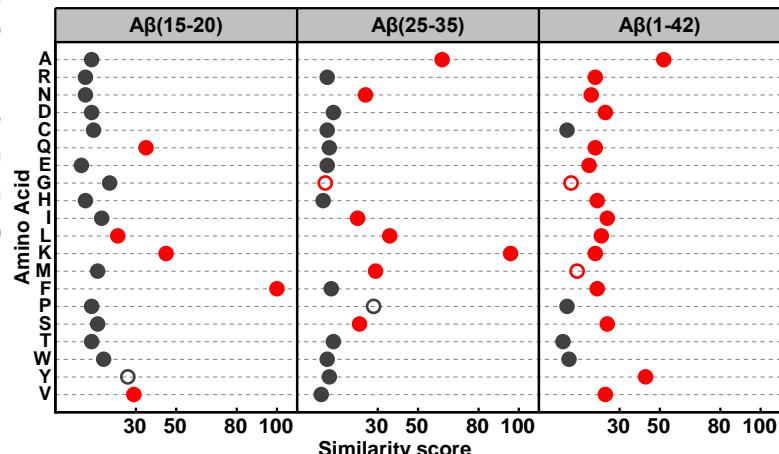


Decoding: OITs screening using Hamming distance

41

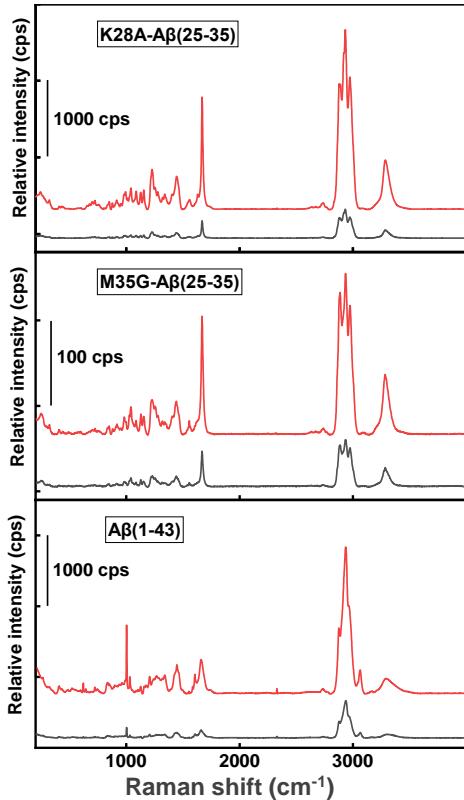


- True positive: AA detected, exist in peptide
- True negative: AA not detected, not exist in peptide
- False positive: AA detected, not exist in peptide
- False negative: AA not detected, exist in peptide



Comparison of SERS and Raman: LOD of mutation point

42



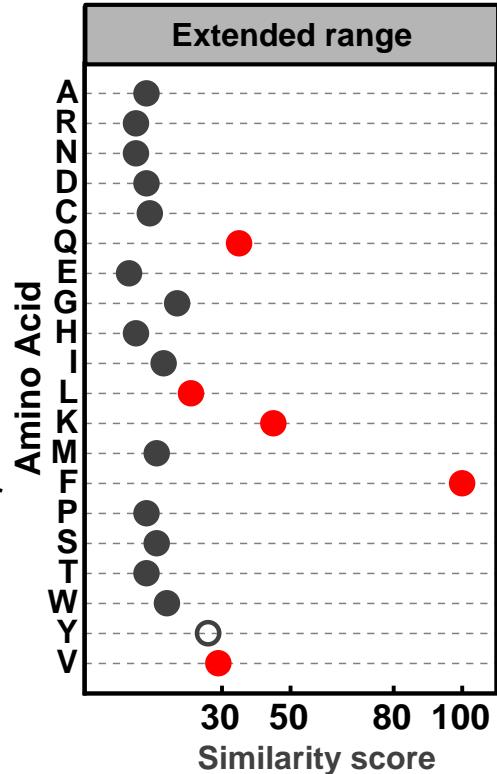
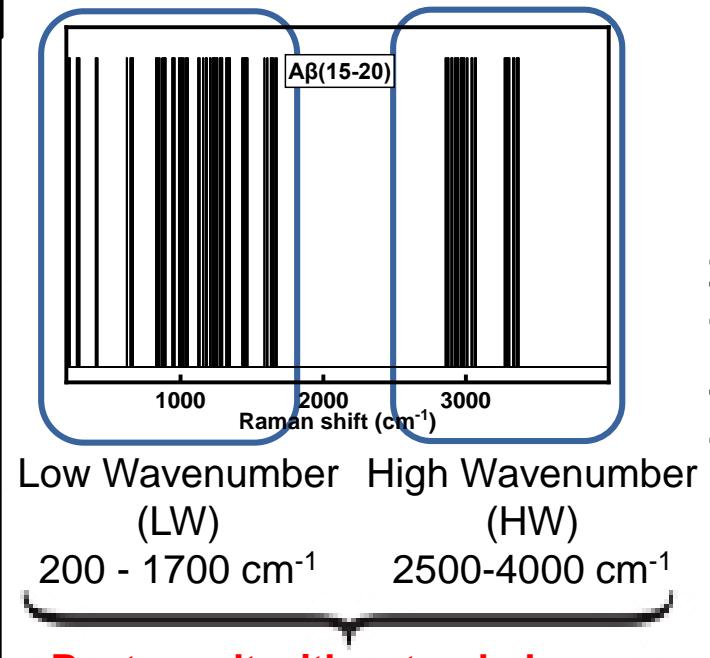
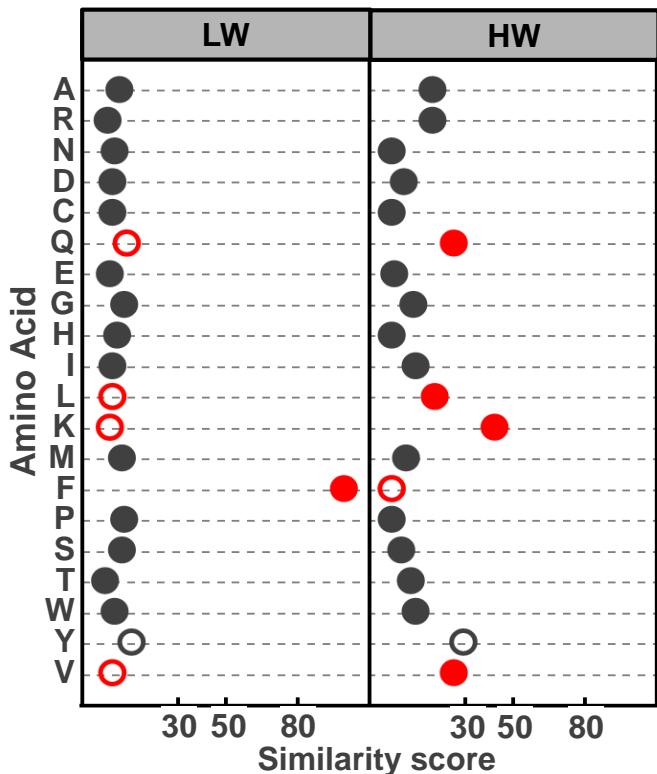
A β Fragment	AA sequence
A β (25-35)	GSNK G AIIGLM
M35G-A β (25-35)	GSNK GAIIGLG
K28A-A β (25-35)	GSN A GAIIGLM
A β (1-42)	DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA
A β (1-43)	DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA T

— SERS
— Raman

Mutated A β	Limit of detection [mol]	
	Raman	SERS
M35G-A β (25-35)	2.09x10 ⁻⁷	2.3x10 ⁻¹²
K28A-A β (25-35)	2 x10 ⁻⁷	1.8x10 ⁻¹²
A β (1-43)	1.08 x10 ⁻⁸	1x10 ⁻⁹

Optimization: screening region in OIT

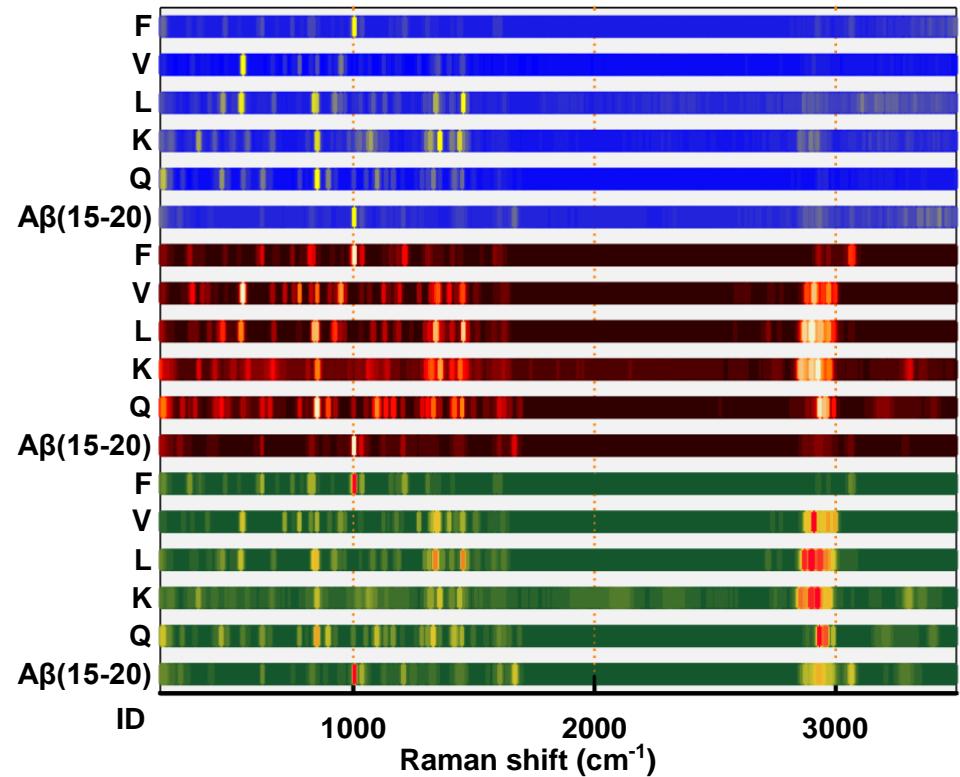
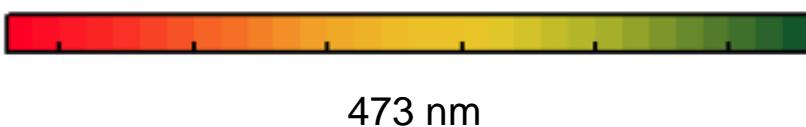
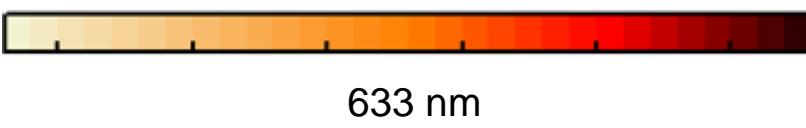
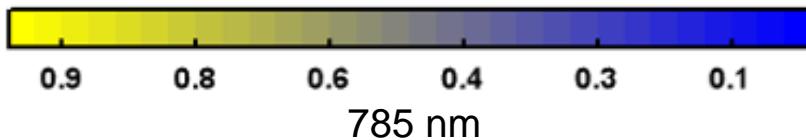
43



Optimization: excitation laser wavelength

44

- Probe A β (15-20) sequence: QKLVFF
- **Best result with 473 nm**



Summary of the optimization process

45

Optimization of the screening range

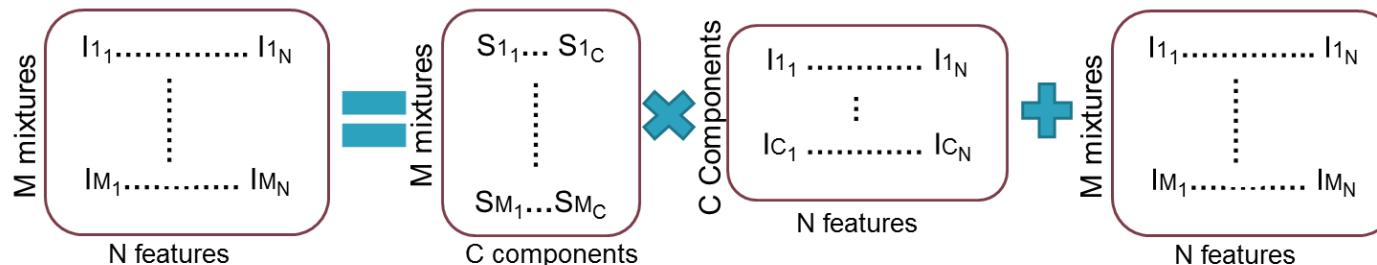
Excitation source [nm]	473 nm		633 nm	785 nm
Scanning range	LW	HW	Extended range 200-4000 cm⁻¹	
True positives	50%	80%	83%	80%
True negatives	78%	93%	100%	93%
False positives	50%	20%	17%	20%
False negatives	22%	7%	0%	6.67% 18.75%
Mathew correlation	0.25	0.69	0.77	0.69 0.27
Sensitivity	50%	80%	83%	80% 50%
Specificity	61%	82%	86%	82% 62%

Optimization of the excitation wavelength

Comparison between OITs screening and MCR-ALS

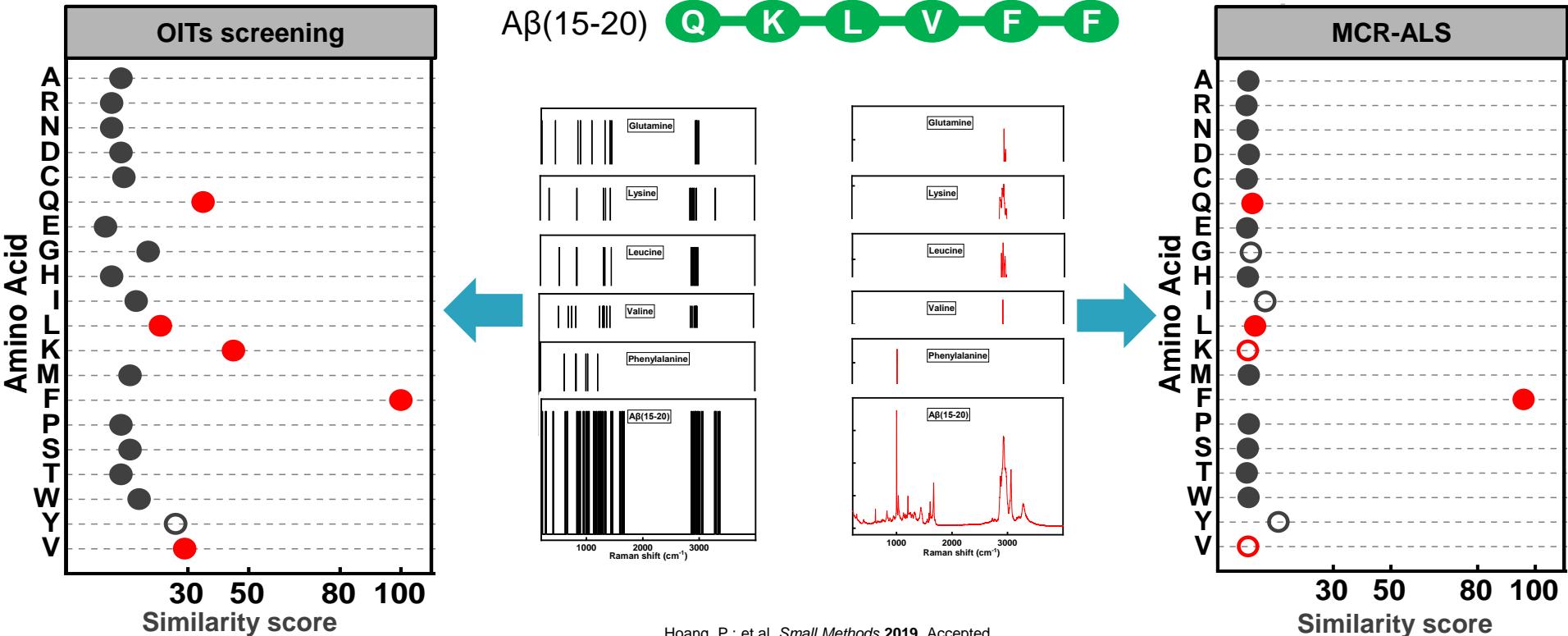
46

- Multivariate Curve Resolution (MCR)
 - Optimized with Alternate Least Squares (ALS) for non-negativity
 - Data matrix $X_{(M \times N)} = T_{(M \times C)} \times P_{(C \times N)} + \text{Residual error}_{(M \times N)}$
 - I_{MN} is mass of mixture M at feature N
 - S_{MC} is contribution of component C in mixture M



Method of comparing components AA spectra and peptide: MCR-ALS at 473 nm

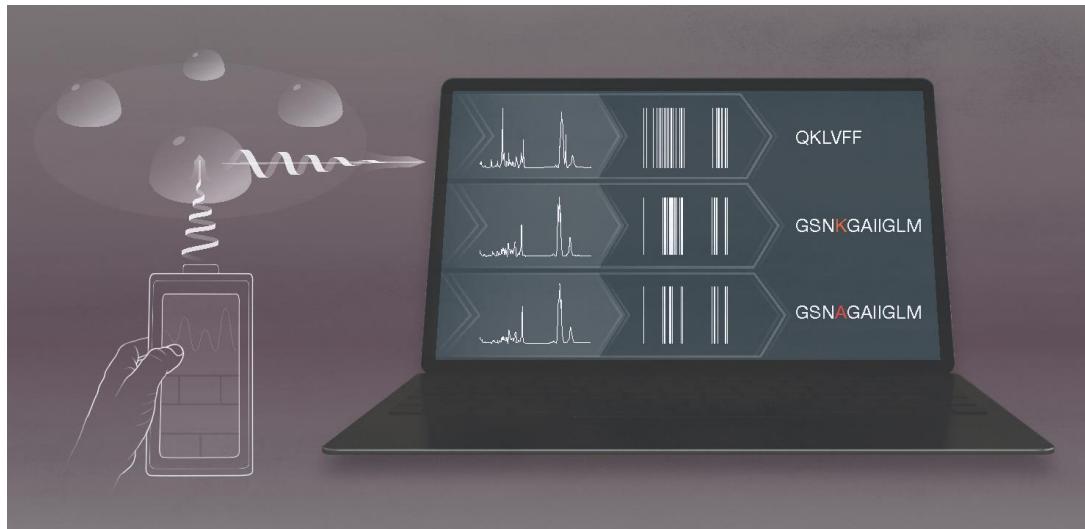
47



Summary and future directions

48

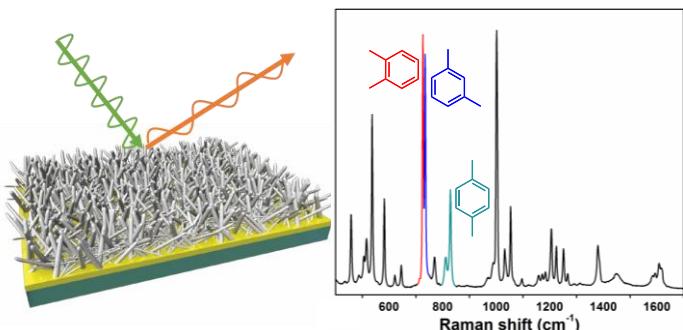
- ❑ Robust signal encoding and component screening method
 - ❑ Optimized at 473 nm for extended screening range (200-4000 cm⁻¹)
- ❑ Point mutation can be detected at sub-nanomol concentration



Conclusion

49

Screening of structural isomers



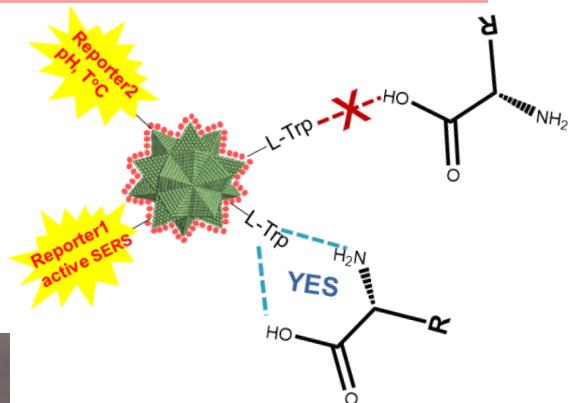
SERS
sensor

Screening of amino acids in peptides



Hoang, P.; Khashab, N. M.
Chem. Mater. 2017, 29, 1994

Screening of stereo isomers



Hoang, P.; Moosa, B.; Carboni, V.;
Khashab, N. M. 2019. In preparation

Publications

50

- ❑ Hoang, P.; Khashab, N. M. *Chem. Mater.* **2017**, 29, 1994
- ❑ Hoang, P., Khashab, N. M. *Small Methods* **2019**. Accepted
- ❑ Hoang, P.; Moosa, B.; Carboni, V.; Khashab, N. M. **2019**. In preparation

- ❑ Chen, Y.; Tao, J.; Hammami, M. A.; Hoang, P.; Khashab, N. M. *Adv. Mater. Interfaces* **2016**, 3, 1500658
- ❑ Rahmani, S.; Chaix, A.; Aggad, D.; Hoang, P.; Moosa, B.; Garcia, M.; Gary-Bobo, M.; Charnay, C.; AlMalik, A.; Durand, J.-O.; Khashab, N. M. *Mol. Syst. Des. Eng.* **2017**, 2, 380
- ❑ Chaix, A.; Mouchaham, G.; Shkurenko, A.; Hoang, P.; Moosa, B.; Bhatt, P. M.; Adil, K.; Salama, K. N.; Eddaoudi, M.; Khashab, N. M. *J. Am. Chem. Soc.* **2018**, 140, 14571

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51

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 - ❑ Prof. Luigi Cavallo
 - ❑ Prof. Emilie Ringe
- ❑ Dr. Basem Moosa, Dr. Valentina Carboni, Dr. Gengwu Zhang, Dr. Yanjun Ding, Laila Khalili Cruz, Ivan Gromicho
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- ❑ Core Labs





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Science and Technology

Smart Hybrid Materials Laboratory
(SHM)

Thank You