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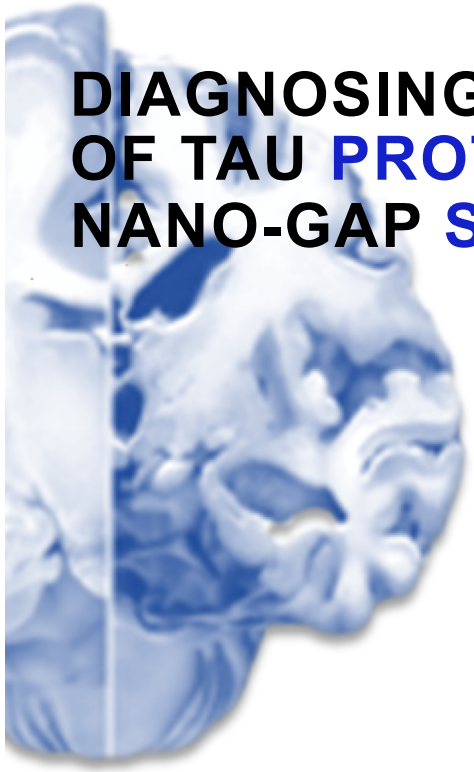

DIAGNOSING ALZHEIMER'S DISEASE THROUGH DETECTION OF TAU PROTEIN IN HUMAN BLOOD USING ULTRASENSITIVE NANO-GAP SENSOR: FROM CSF TO BLOOD

- Nanosensors related to human cognition and brain research

Presenting author: Ph D. Soo Hyun Lee

Center for BioMicrosystems
Brain Science Institute
Korea Institute of Science and Technology

Venue: *Qualcomm Institute, UCSD*

Korea Institute of Science and Technology

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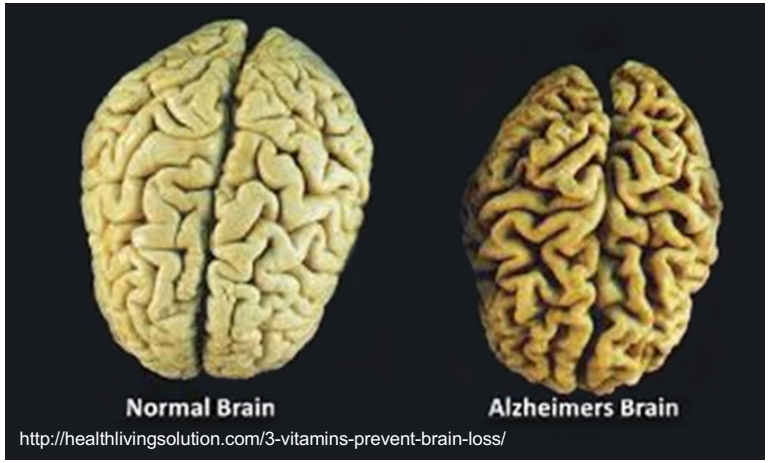
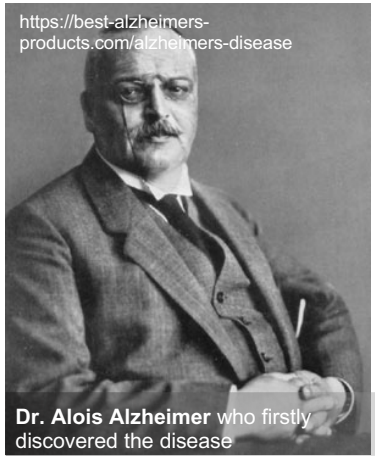
ALZHEIMER'S DISEASES

KIST Brain Science Institute

What is Alzheimer's disease?



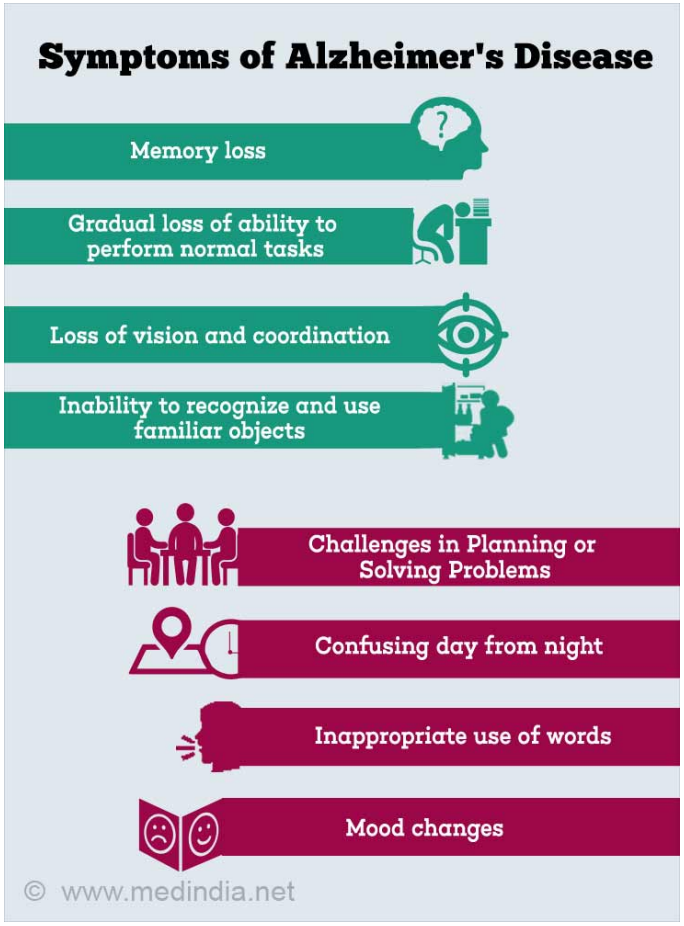
http://healthlivingsolution.com/3-vitamins-prevent-brain-loss/


https://best-alzheimers-products.com/alzheimers-disease

Dr. Alois Alzheimer who firstly discovered the disease


http://www.alzheimersdiseasethebrand.com/curating-and-creating/auguste-deter-and-the-parallel-journey-of-scientific-reason

His first patients, **Auguste Deter**



https://www.weforum.org/agenda/2016/02/could-this-new-alzheimer-s-treatment-restore-memory-function/

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DIAGNOSIS METHODS

Current diagnostic methods

MMSE scoring

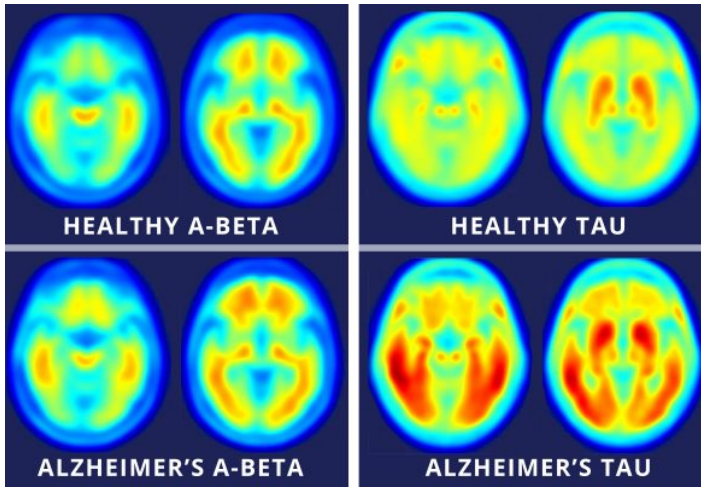
NC 29 (±1.4)

MCI 27 (±1.6)

AD 19 (±4.9)

Zetterberg, H.; Plasma tau levels in Alzheimer's disease. *Alzheimer's research & therapy* **2013,** *5* (2), 9.

Brain Imaging (PET)

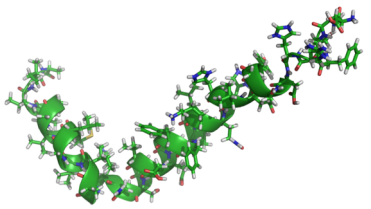


https://medcitynews.com/2016/05/brain-imaging-agent-alzheimer/

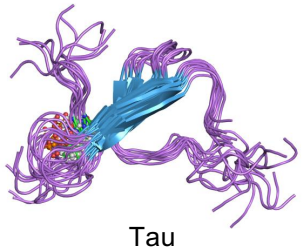
Biomarker quantification in CSF and blood

National Institute On Aging/YouTube

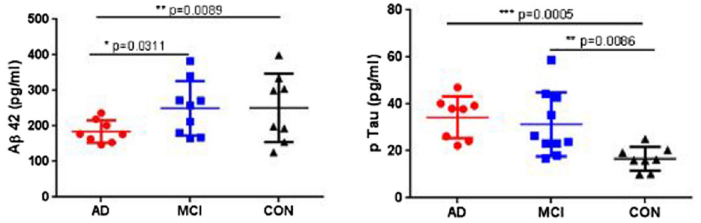
https://www.drugtargetreview.com/



Amyloid beta



Tau



Yang, T et al. *Alzheimer's research & therapy* ***2015***, *7*(1), 14.

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ALZHEIMER'S BIOMARKERS

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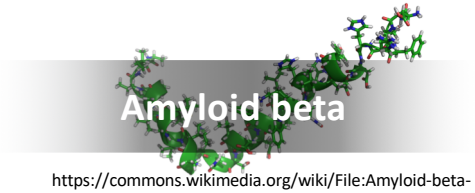
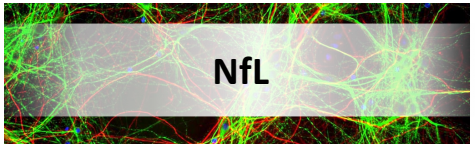
Korea Institute of Science and Technology

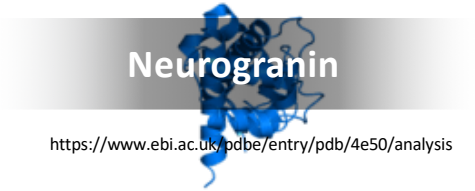


https://commons.wikimedia.org/wiki/File:Amyloid-beta-42_1IYT.png

https://en.wikipedia.org/wiki/Tau_protein#/media/File:PDB_1i8h_EBI.jpg



https://www.labmedica.com/molecular-diagnostics/articles/294777864/neurofilament-light-considered-as-niv-biomarker-for-alzheimers-disease.html



https://www.ebi.ac.uk/pdbe/entry/pdb/4e50/analysis

Sensing platform	Journal/year	Title (corresponding)	Protein form	Limit of detection	Dynamic range	Sensitivity	Specificity
IP-MS	Nature 554, 249-254 2018	High performance plasma amyloid-β biomarkers for Alzheimer's disease (Katsuhiko Yanagisawa)	APP 669-711/Abeta 1-42	2.5Da	~180ng/ml	96.7% (AUC)	81.0% (AUC)
IMR	Journal of Alzheimer's Disease, vol. 61, no. 4, pp. 1323-1332 2018	Assay of plasma phosphorylated tau protein (threonine 181) and total tau protein in early-stage Alzheimer's disease (Shieh-Yueh Yang)	Tau	0.0028 pg/ml	0.001-10000pg/ml	0.793 (ROC)	0.836 (ROC)
Digital ELISA	Alzheimer's Research & Therapy 10:71 2018	Plasma neurofilament light as a potential biomarker of neurodegeneration in Alzheimer's disease (Piotr Lewczuk)	nfl	0.62 pg/ml	unknown	0.84 (ROC)	0.78 (ROC)
ELISA	Alzheimer's & Dimentia 11 1461-1469 2015	C-terminal neurogranin is increased in cerebrospinal fluid but unchanged in plasma in Alzheimer's disease (Eugeen Vanmechelen)	neurogranin	3 pg/ml	3-2000 pg/ml	x	x

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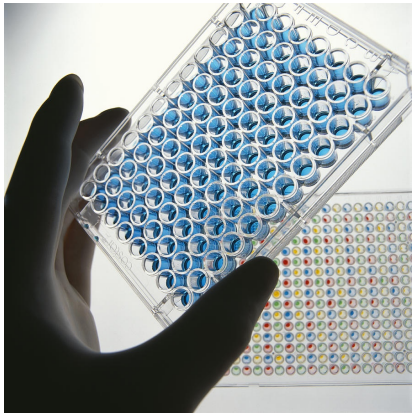
CURRENT DETECTION METHODS USING BIOMARKERS IN BLOOD

Brain Science Institute

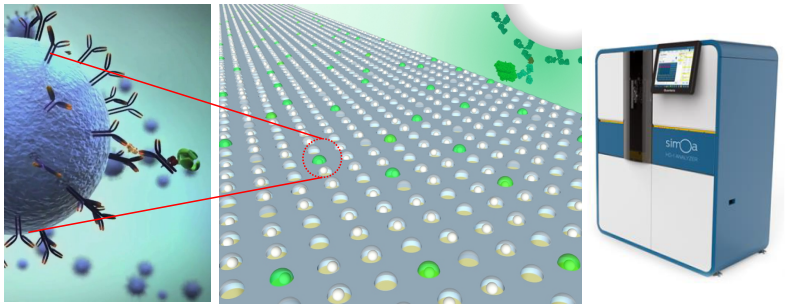
ELISA



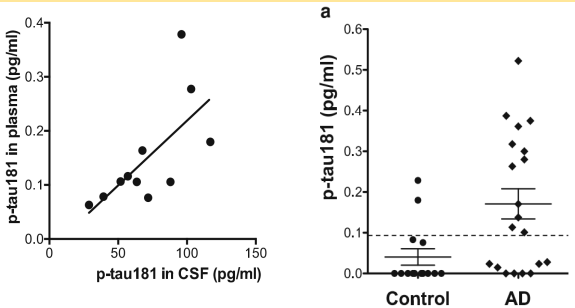
Low sensitivity for detecting Tau in blood (10~1000 pg/ml)

Not enough LOD

Digital ELISA - Quantarix



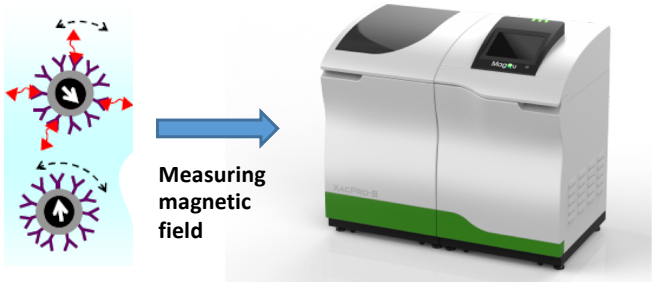
Results : p-Tau181 in Human Blood (Plasma) & CSF



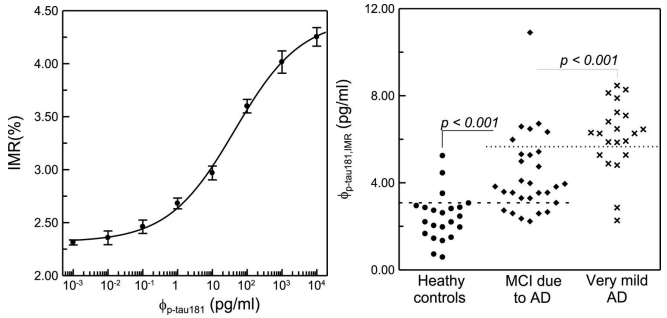
Molecular Neurodegeneration **2017**, *12* (1), 63.

LOD of p-Tau 181 : 0.1 pg/ml

IMR sensor -MagQu



Results: Tau in Human Plasma



LOD of Tau : 0.03 pg/ml

Journal of Alzheimer's Disease ***2018***, *61*(4), 1323-1332.

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WHY WE CHOOSE TAU AND TAU PTM AS A NOVEL BIOMARKER

- **Prognosis monitoring**
- **P tau and O-g Tau**
- **Ratio: P tau/tau *vs.* O-g tau/tau**

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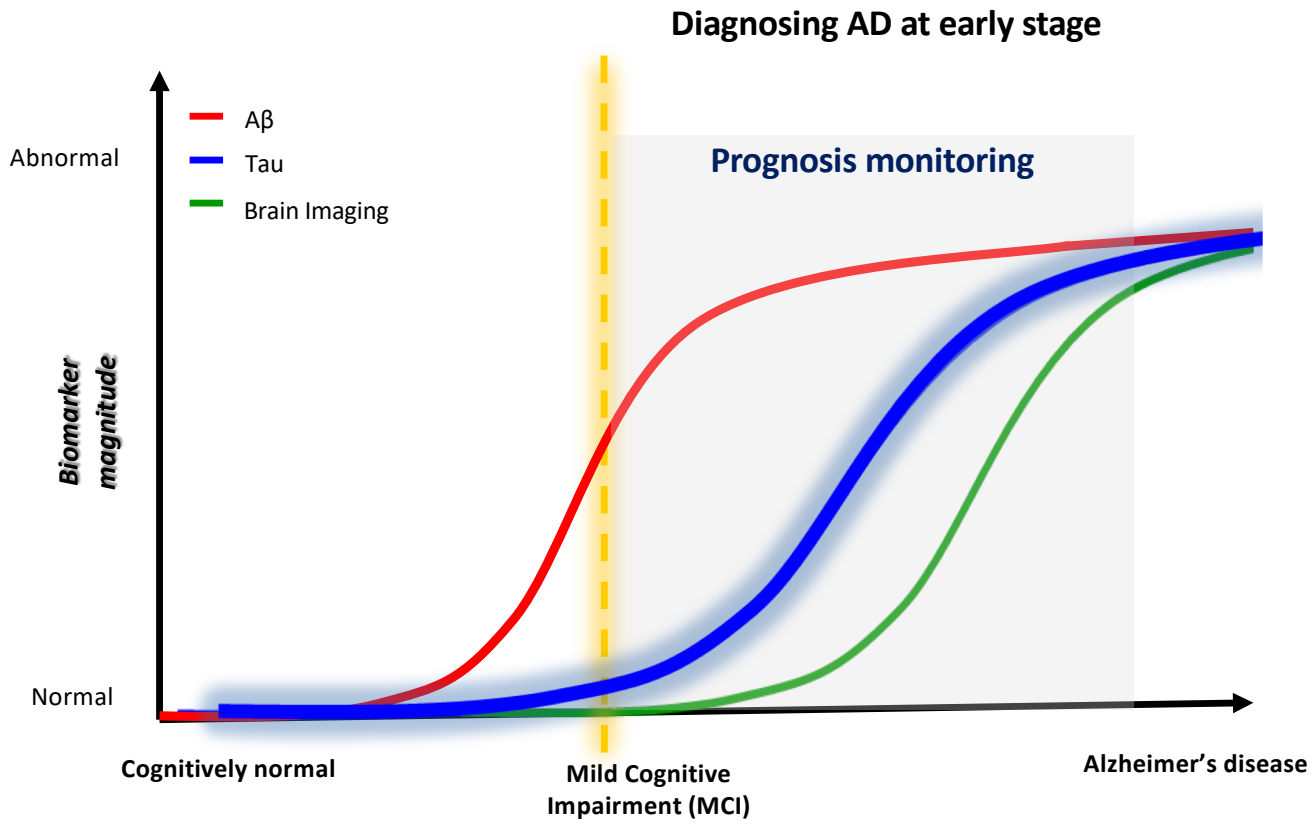
WHY WE CHOOSE TAU AND TAU PTM AS A NOVEL BIOMARKER: PROGNOSIS MONITORING

AD : Alzheimer's diseases



- Brain Imaging (PET) can be diagnosed after the progression of Alzheimer's diseases
- Aβ is unable to prognosis because it is being saturated quickly
- Tau is more suitable for monitoring Alzheimer's disease by detecting concentration of Tau or P Tau continuously

이 그래프의 reference 추가하기

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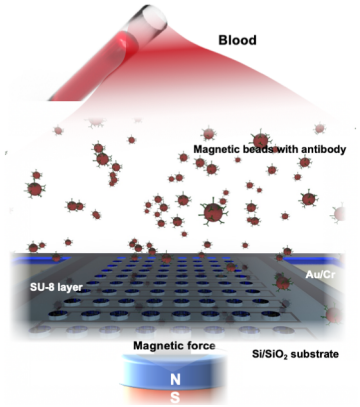
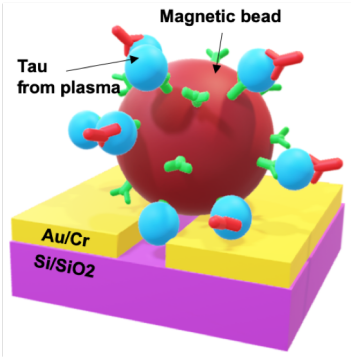
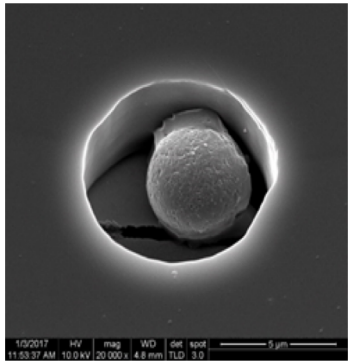
MAGNETIC BEADS BASED NANOGAP SENSOR







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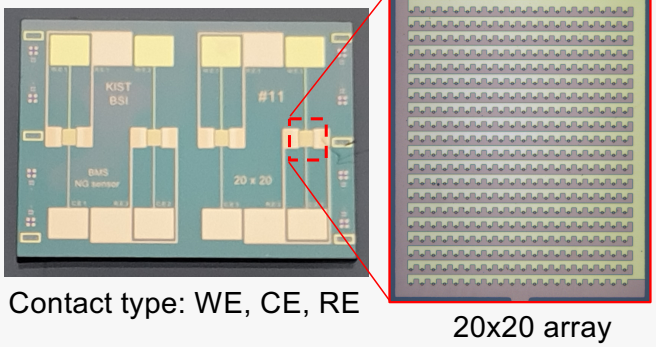
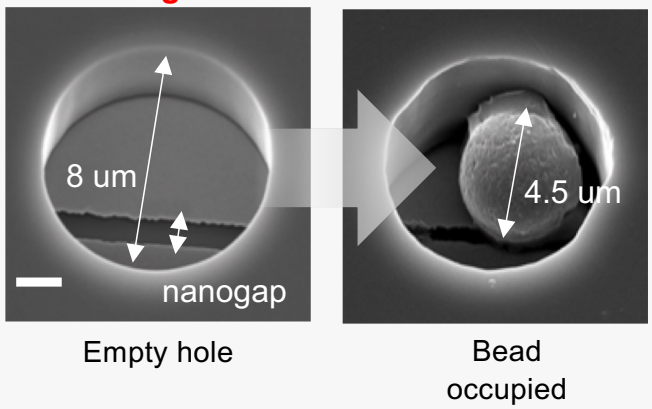
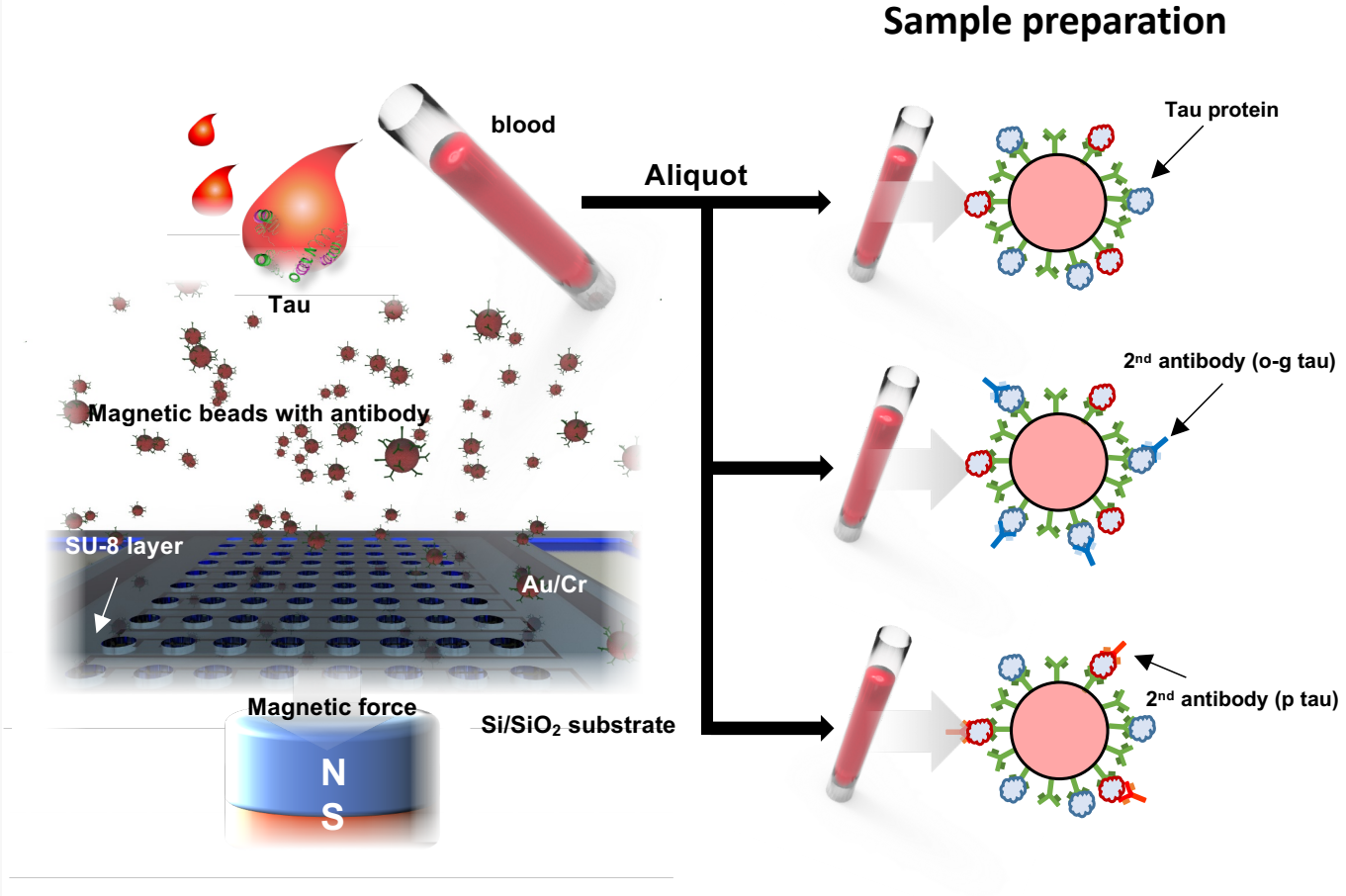
NANOGAP SENSOR PLATFORM
FOR DETECTING TAU, O-G TAU, AND P TAU







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FABRICATION PROCESS OF
MAGNETIC BEAD BASED NANOGAP SENSOR

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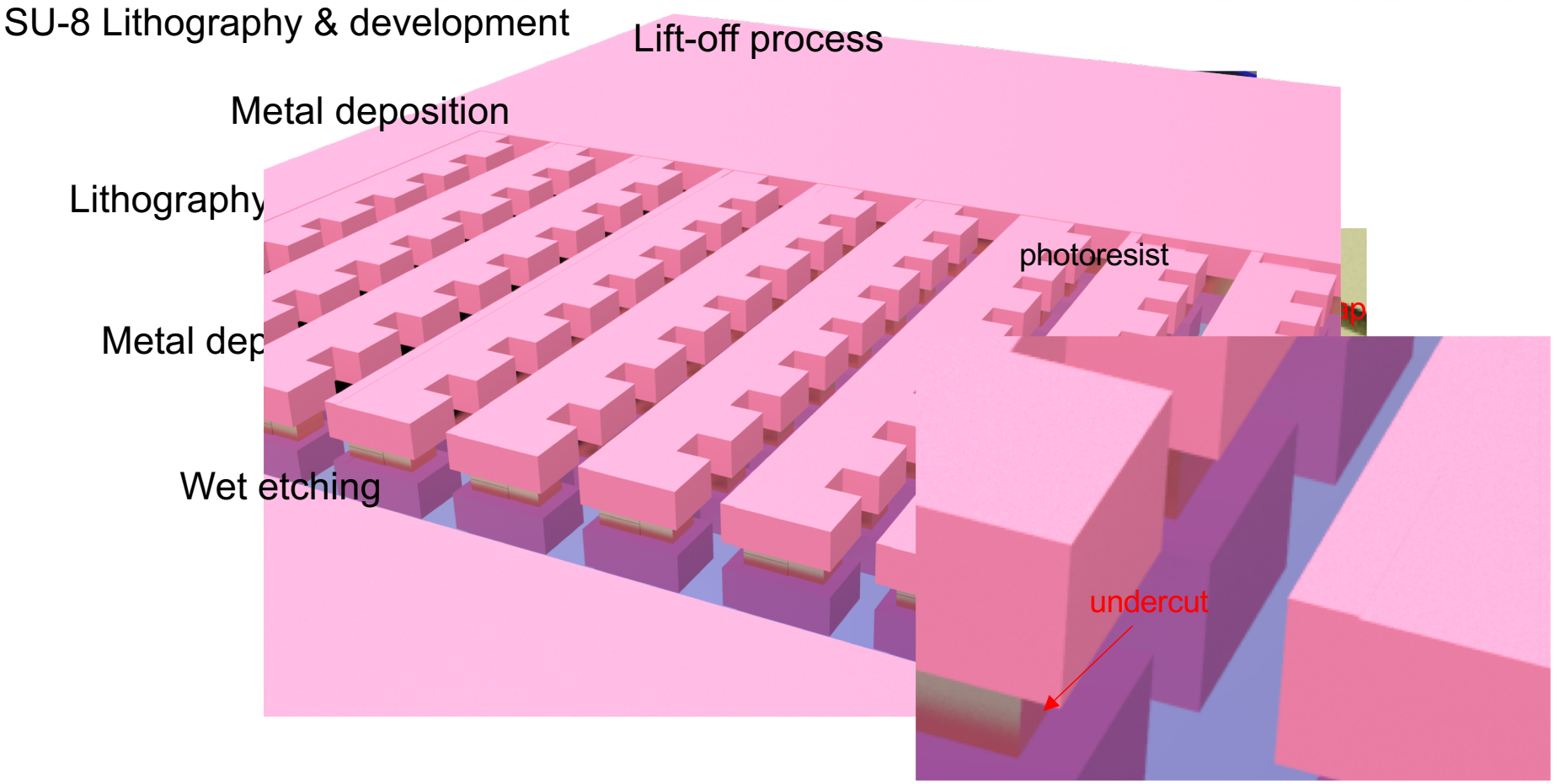
Korea Institute of Science and Technology



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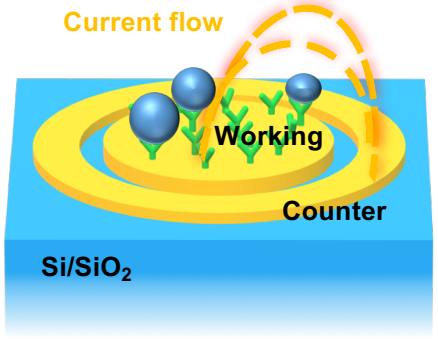
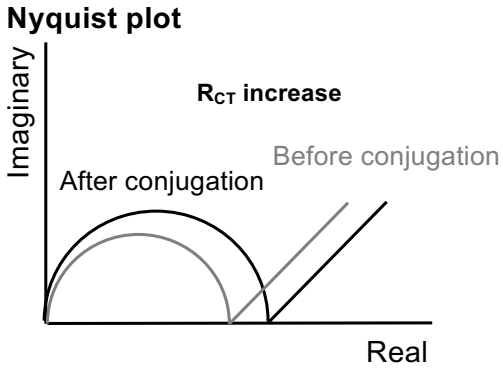
SENSING MECHANISM OF MAGNETIC BEAD BASED NANOGAP SENSOR

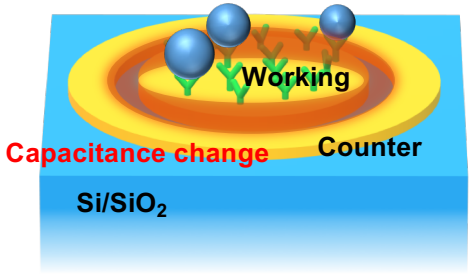
Conventional EC sensor

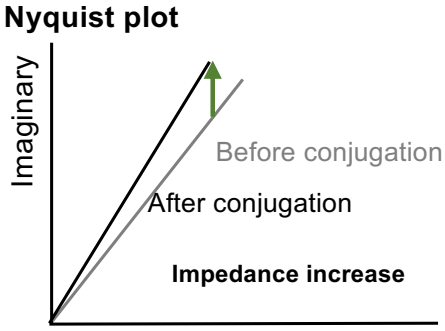




Faradaic type

The interaction of the charged redox species with the charged probe layer can significantly impact R_{ct}

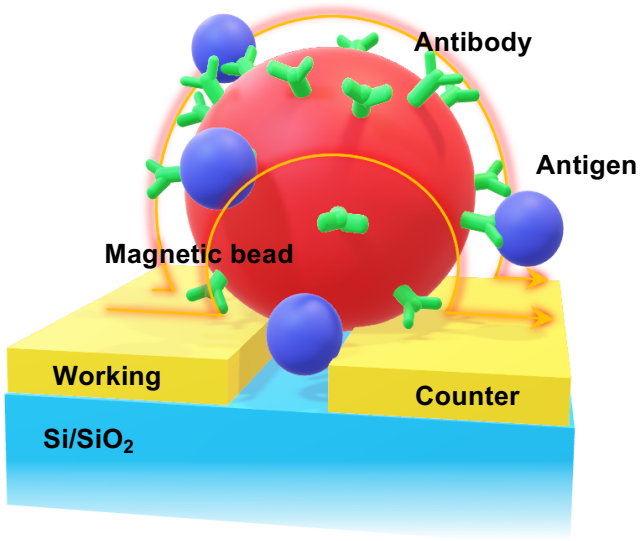




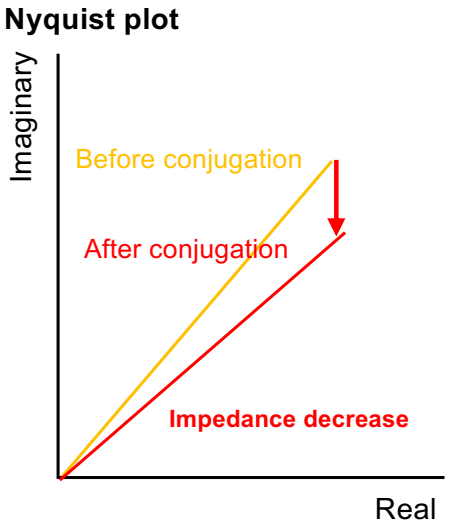
Non-faradaic type

It is common to rationalize changes in C_{surf} as occurring due to displacement of water and ions from the surface upon target binding.

Developed sensor



New concept



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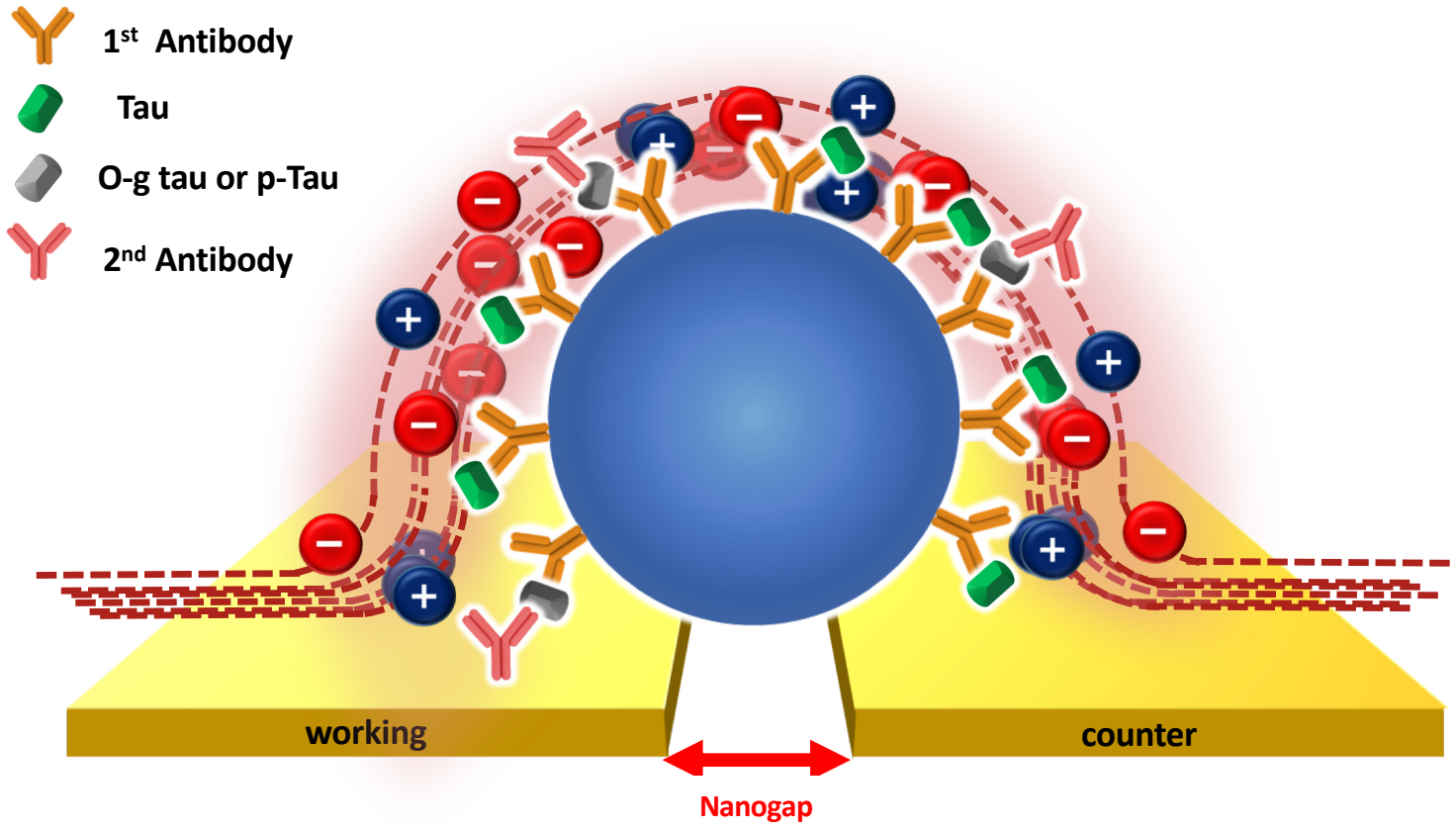
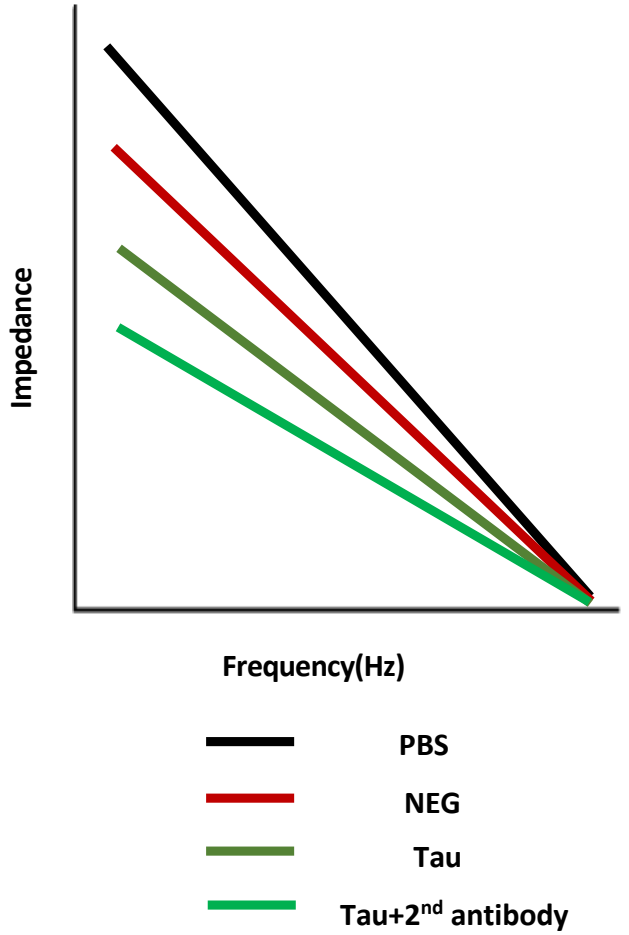
SENSING MECHANISM OF MAGNETIC BEAD BASED NANOGAP SENSOR





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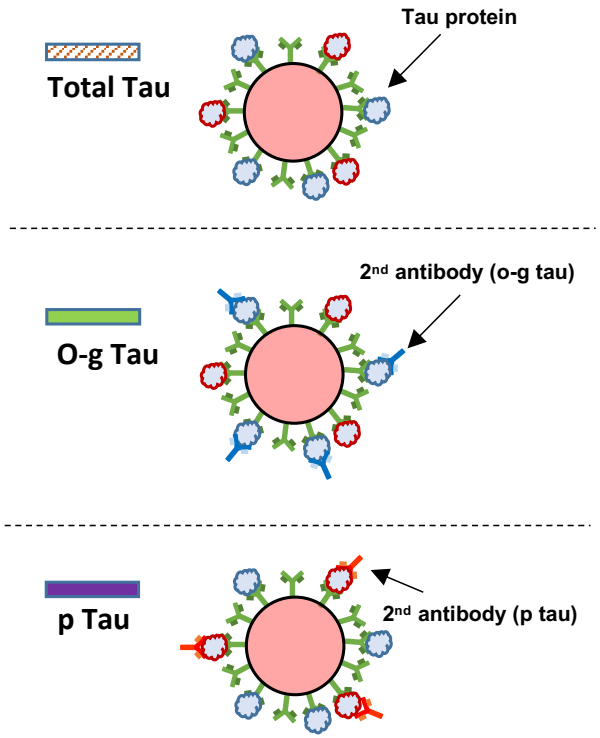
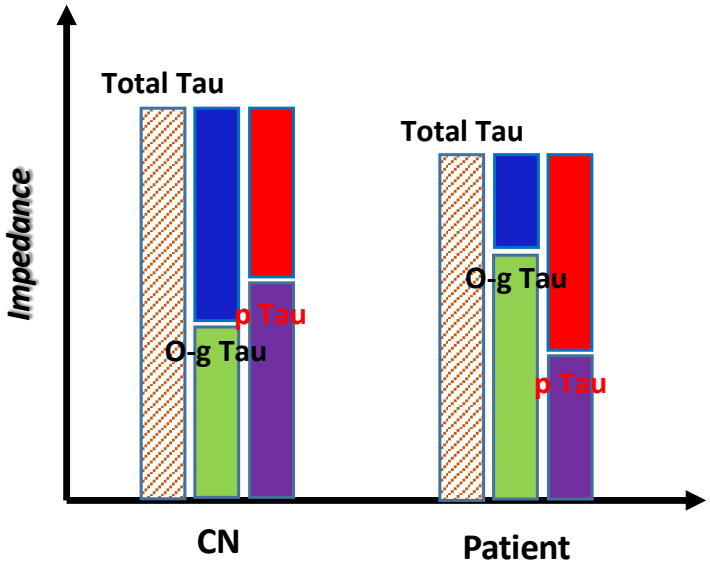
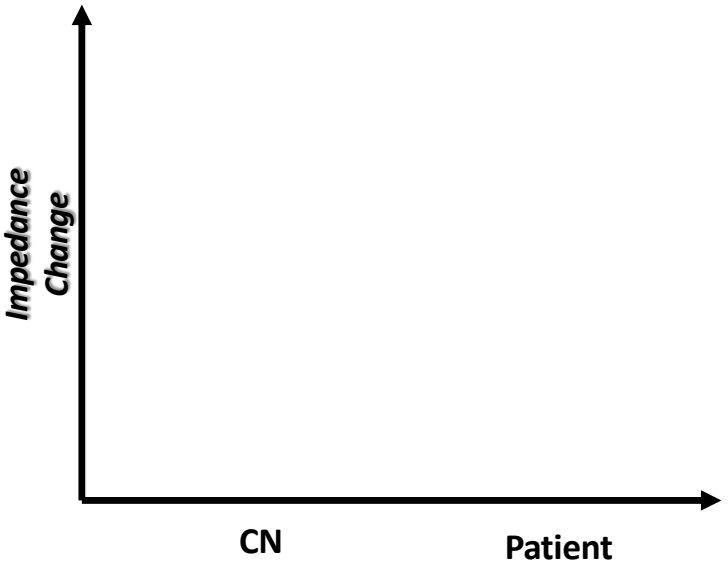
AD DIAGNOSTIC AND PROGNOSIS MONITORING USING TAU PTM
RATIO OF O-G TAU/TAU *AND* P TAU/TAU

❖ AD diagnostic and prognosis monitoring using tau PTM analysis







U.S. patent, "Method for monitoring post-translational modification of protein", 15/696302, notice of allowance
EU patent, "Method for monitoring post-translational modification of protein", 17895180.2, patent pending

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EXPERIMENTAL RESULTS

- **Impedance analysis using Tau recombinant**
- **Limit of Detection and Dynamic Range using cell lysates**
- **The results of AD mouse blood**
- **The results of Human blood**

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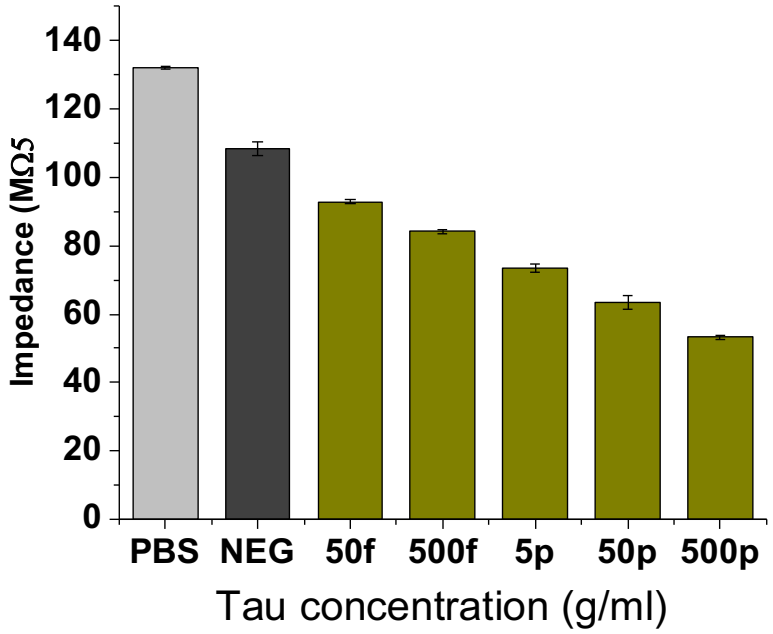
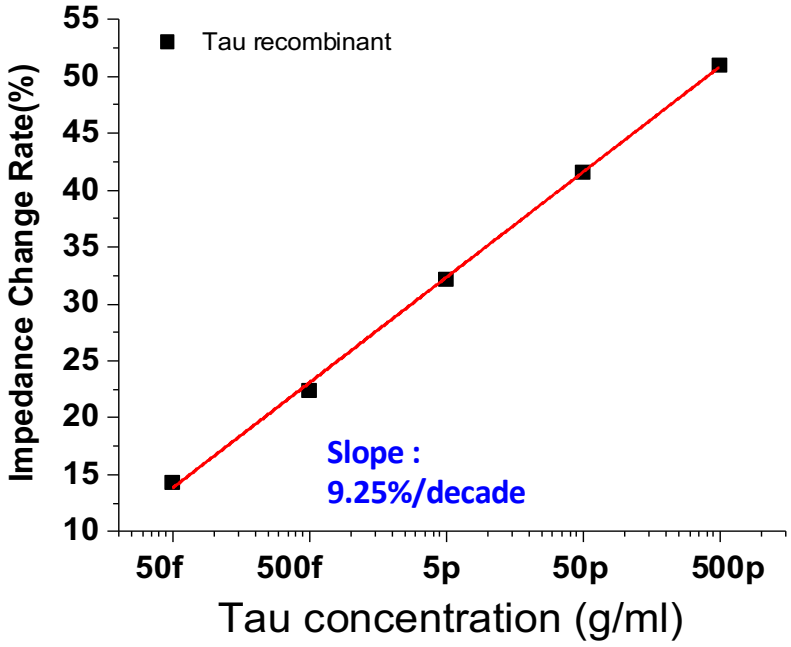
EXPERIMENTAL RESULTS:
LIMIT OF DETECTION AND DYNAMIC RANGE USING TAU RECOMBINANT

❖ **Tau Recombinant measurement (Dynamic Range)**





- **Tau-441 human, recombinant, 2N4R**
- **Concentration of Tau protein range: 50 fg/ml ~ 500 pg/ml**

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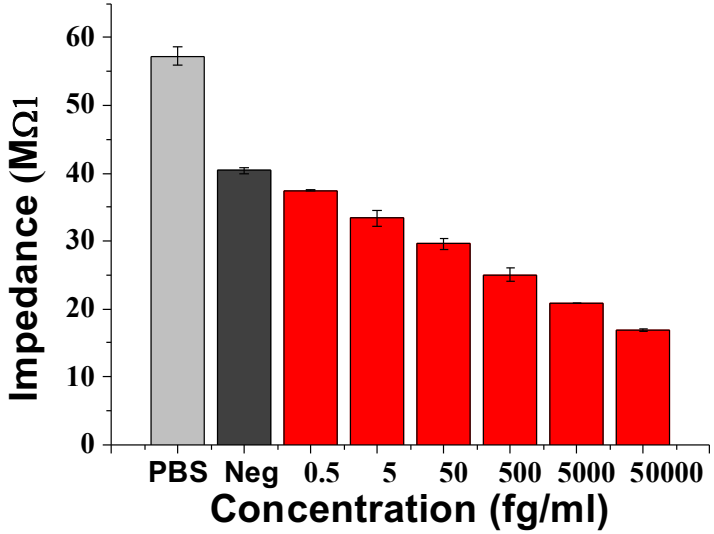
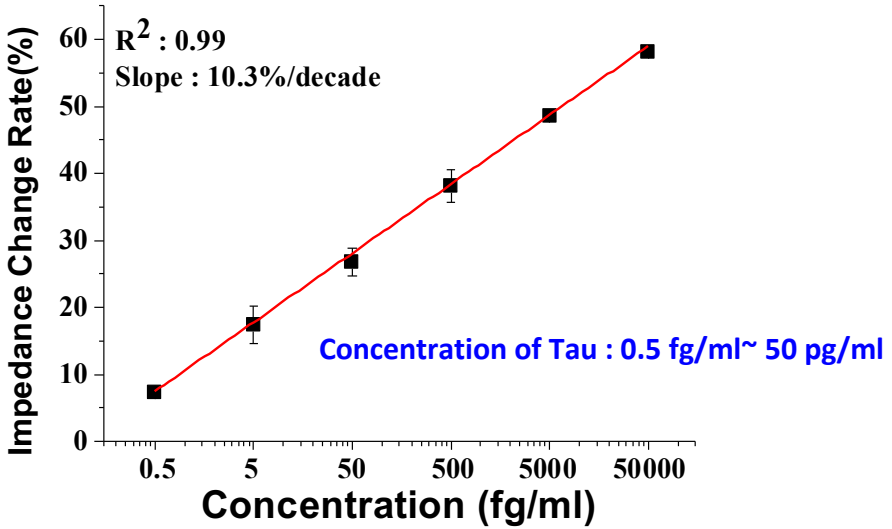
EXPERIMENTAL RESULTS:
LIMIT OF DETECTION AND DYNAMIC RANGE USING CELL LYSATES

- **Impedance is decreased by Tau concentration**





- Ultra-high sensitivity
- Wide Dynamic range

	ELISA	Digital ELISA (quanterix)	Nanogap array sensor
LOD	10 pg/ml	19 fg/ml	0.5 fg/ml
DR	10 pg/ml~ ug/ml	0~360 pg/ml	0.5 fg/ml ~500 pg/ml

LOD : Limit of Detection
DR : Dynamic Range

Lim, S., et al. (2015). "Monitoring of intracellular tau aggregation regulated by OGA/OGT inhibitors ." International journal of molecular sciences **16**(9): 20212-20224.

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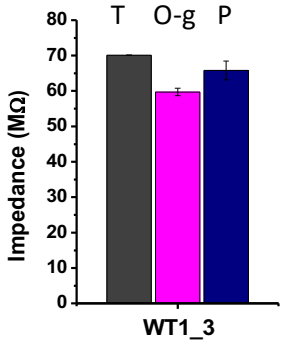
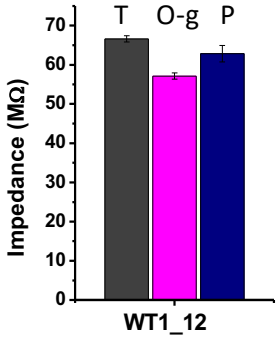
EXPERIMENTAL RESULTS: FROM AD MOUSE BLOOD

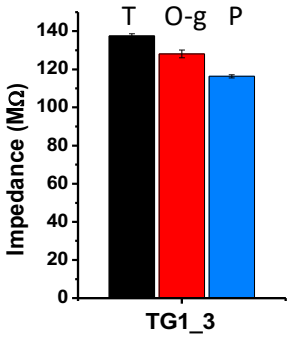
- Tau P301L mouse

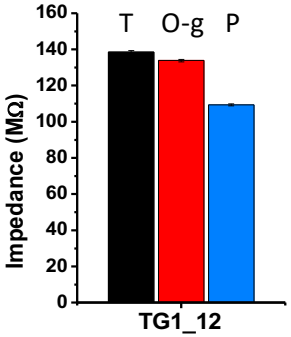
- Wild type mouse 3, 12 month





- Transgenic mouse 3, 12 month





Impedance change rate(%)

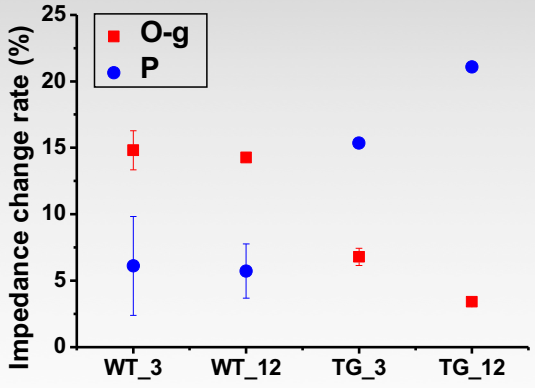
$$= \frac{Z_{Neg} - Z_{T\ tau}}{Z_{Neg}} \times 100\%$$

O-g tau impedance change rate(%)

$$= \frac{Z_{T\ tau} - Z_{O-g\ tau}}{Z_{T\ tau}} \times 100\%$$

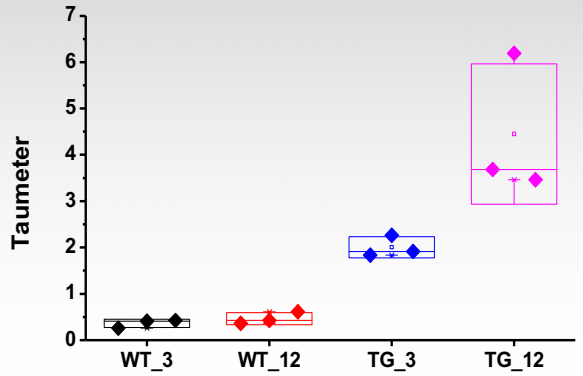
P tau impedance change rate(%)

$$= \frac{Z_{T\ tau} - Z_{P\ tau}}{Z_{T\ tau}} \times 100\%$$



Taumeter

$$= \frac{P\ tau\ impedance\ change\ rate}{O\text{–}g\ tau\ impedance\ change\ rate}$$



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SUMMARY

- ✓ Nanogap sensor platform was successfully developed to measure Tau and Tau PTM in blood for AD's diagnosis and prognosis
- ✓ Tau, O-g tau, and P tau were measured and analyzed using cell lysates (Tau-BiFC), Tau 301pL mouse blood, and human blood.
- ✓ As a novel biomarker to diagnose AD using blood, ***Taumeter*** (P tau/O-g tau) is suggested and measured.
- ✓ Taumeter from mouse and human bloods can improve diagnostic accuracy
- ✓ Taumeter can be a promising biomarker to diagnose and prognose AD

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KIST Brain Science Institute
Korea Institute of Science and Technology

Q & A