

Symposium 2022 for Moonshot Goal 7  
"To Age to 100 without Health Concerns "

# Microinflammation Controlling by Quantum Technology and Neural Pathways!



HOKKAIDO  
UNIVERSITY



Institute for Genetic Medicine  
HOKKAIDO UNIVERSITY

Hokkaido University  
Institute for Genetic Medicine  
**MURAKAMI Masaaki**

# Transforming our world: 2040

By 2040,  
We will realize a society  
with a long and healthy life expectancy  
by developing **automated medicine at the time of  
presymptomatic period** including quantum and  
neuromodulation technologies  
to control the onset of diseases

# Microinflammation Control Project: The Future

Curing majority of diseases and disorders by quantum and neuromodulation technologies

**G3 Neuromodulation**  
Gateway Reflex and VNS

Next-gen MRI, PET

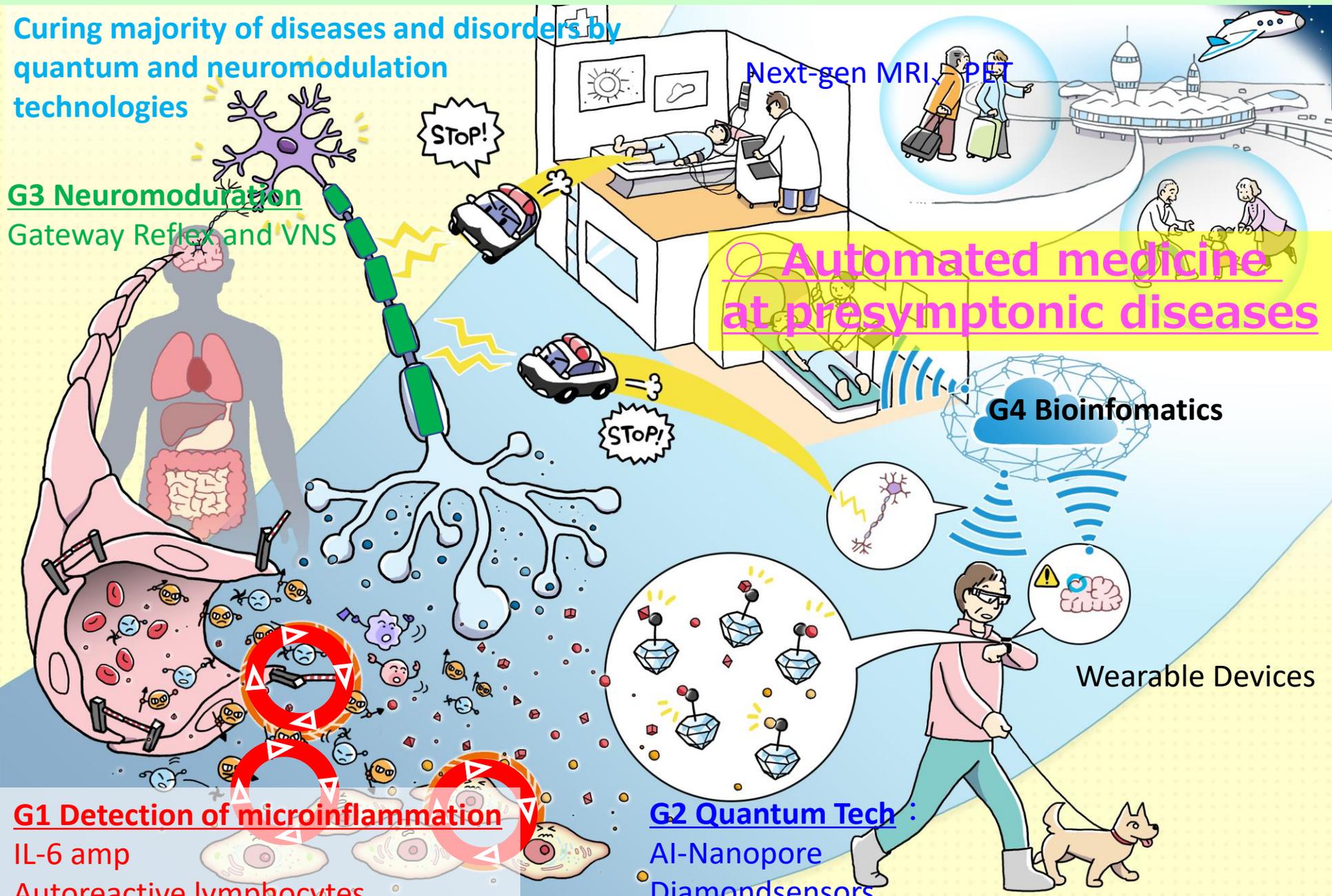
**Automated medicine at presymptomatic diseases**

**G4 Bioinformatics**

Wearable Devices

**G1 Detection of microinflammation**  
IL-6 amp  
Autoreactive lymphocytes

**G2 Quantum Tech :**  
AI-Nanopore  
Diamondsensors



# Future plan

9 産業と技術革新の  
基盤をつくろう



- **Social implementation: Creation of an innovative medical industry**  
Ultrasensitive quantum technology and neuromodulation technology  
for detection and removal of microinflammation

2023-25 年



**Clinical  
research**

2028 年



**Preemptive  
medicine**

2030 年



**Preventing disease  
in daily life**

2040 年



**Healthy longevity**

3 GOOD HEALTH  
AND WELL-BEING



- **Cure pre-disease by controlling micro-inflammation**  
A healthy and long-living society  
where people can enjoy life without health concerns until they are 100 years old

# Members integrated medicine, engineering, and information

Project manager: MURAKAMI Masaaki (Hokkaido Univ.)

① Understanding of the nature of pre-disease

- (1) Completion of an analysis platform for basic immune cell and genetic information (Hokkaido Univ.),**
- (2) Discovery of novel marker factors of inflammation**
- (3) Discovery that novel neural circuits are associated with inflammation**

② Quantum power for finding the onset of pre-disease

- (1) Completion of microinflammation detection platform with diamond sensor (Hokkaido Univ.),**
- (2) Novel imaging methods for microinflammation and neural circuits (Hokkaido Univ.),**
- (3) Novel methods for isolation and detection of factors that mark inflammation**
- (4) A novel method of gene transfer to cells**

③ Neuromodulation technology for regulating the onset of pre-disease

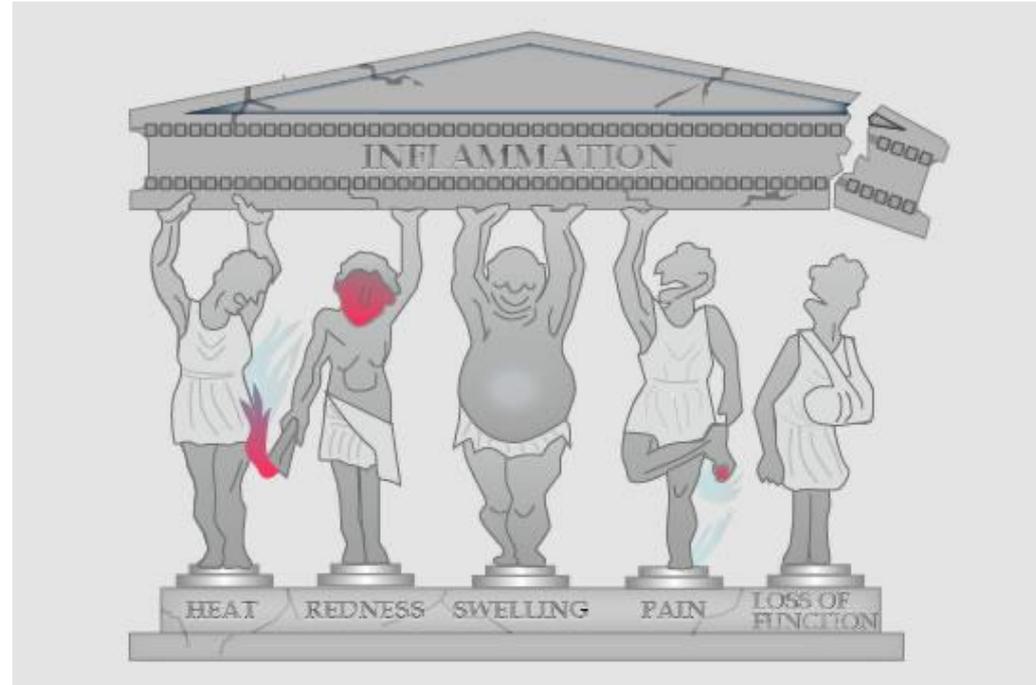
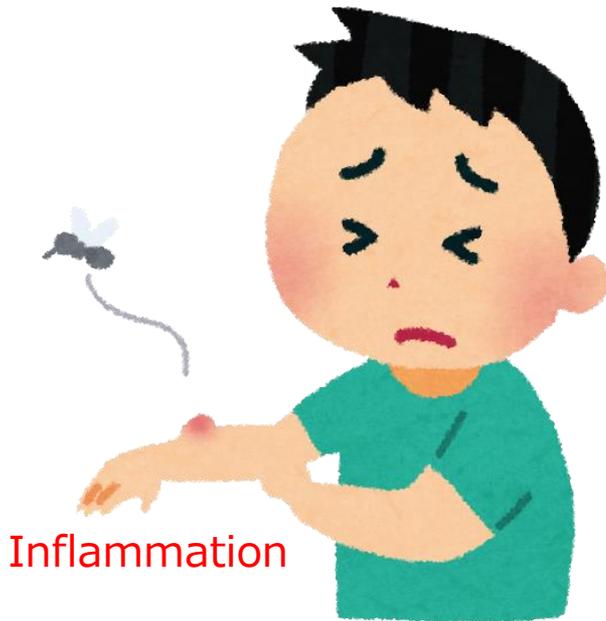
- (1) Clinical studies of neuromodulation have begun.**
- (2) Novel neurostimulation methods using ultrasound-gene transfer is under development.**

④ Big data analysis with AI and device development

- (1) Novel Inflammation Analysis and Detection Methods Using Information Science Under Development**

# Inflammation ?

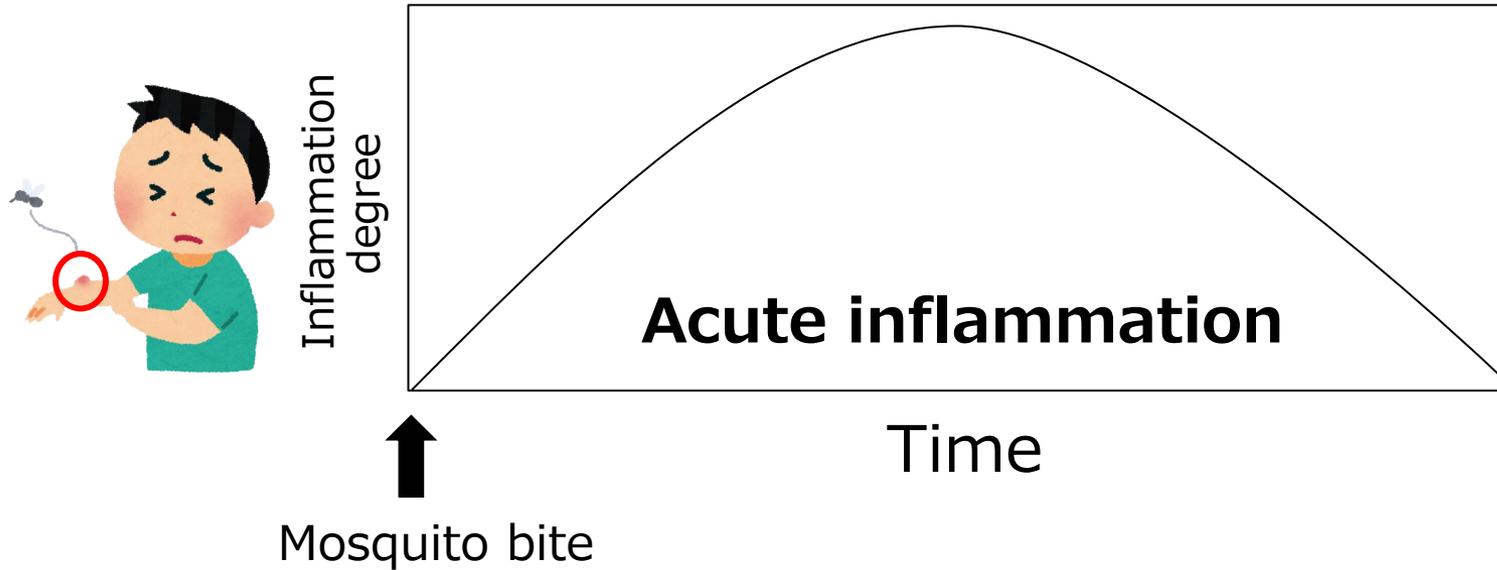
Heat, Redness, Swelling, Pain, Loss of function



<https://www.jst.go.jp/crest/inflam/en/illust/index.html>

Inflammation is associated with various diseases and disorders.

# What is happened in the inflammation lesion ?

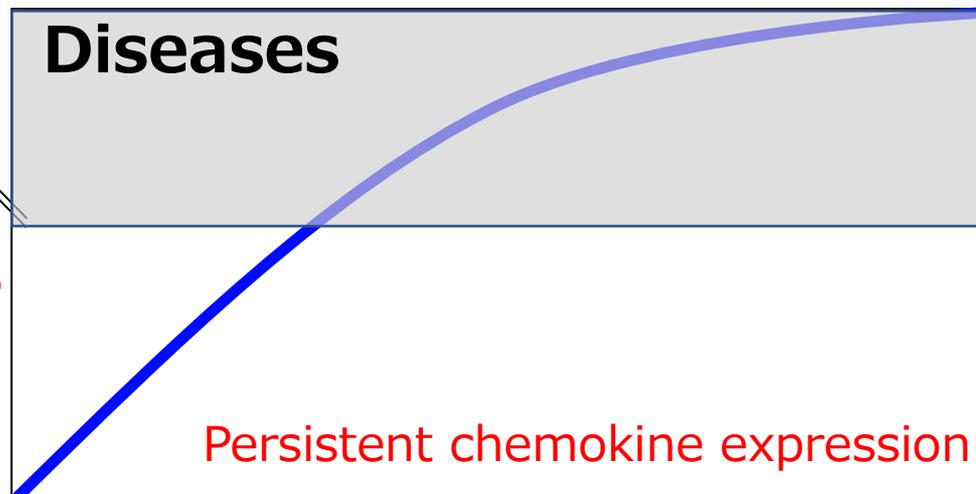


1. Heat, Redness, Swelling, Pain, Loss of function
2. Dysregulation of tissue homeostasis
3. Accumulation of Immune cells from the blood
4. Chemokines, Cytokines, Growth factors

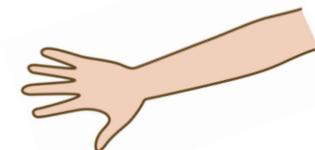
# Chemokines accumulate immune cells



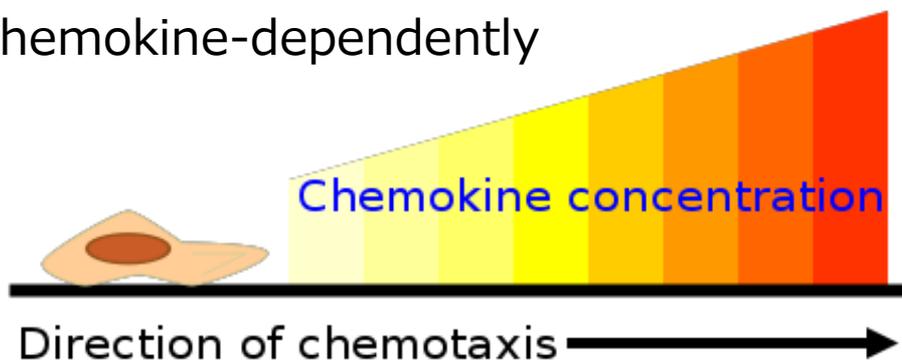
Chemokine expression



Acute inflammation



Accumulation of immune cells chemokine-dependently



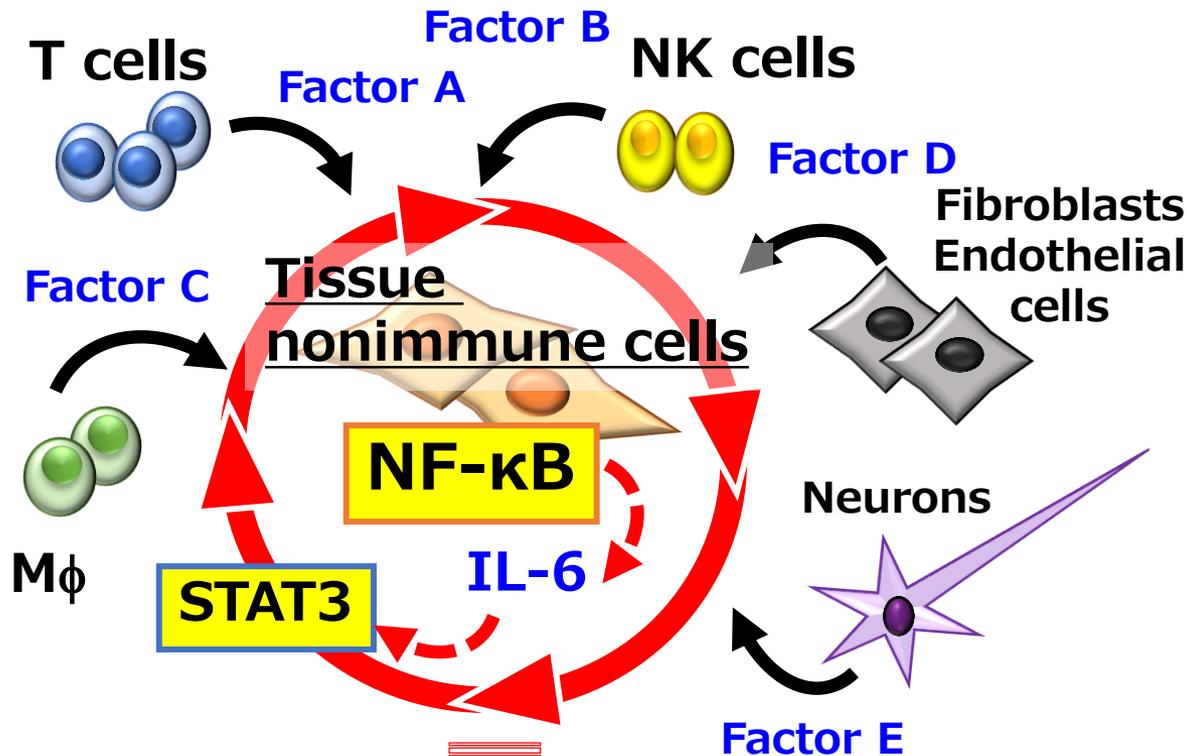
Chemokine concentration

Direction of chemotaxis

Chronic inflammation



# IL-6 amplifier, a mechanism of chemokine inducer

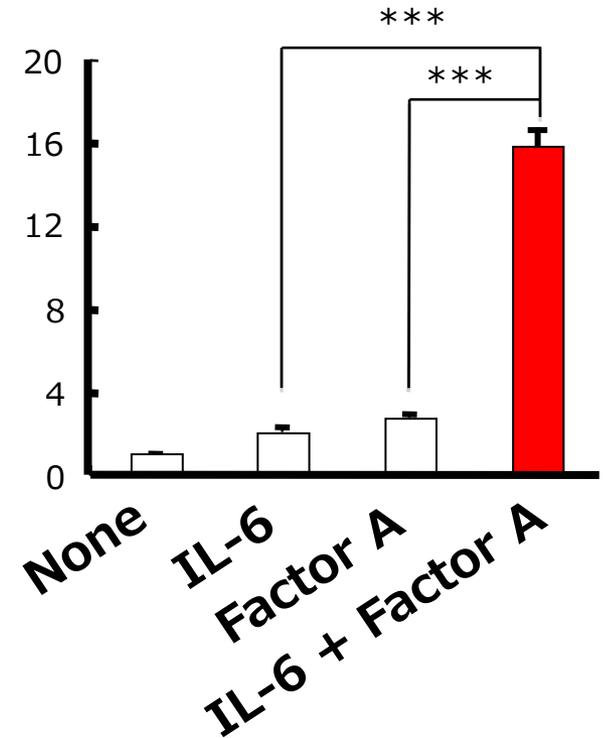


**Chemokines etc**

Accumulation of immune cells  
Growth of surrounding cells  
Loss of tissue functions

**Chronic inflammation = diseases**

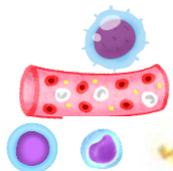
**Chemokine expression**



○ Microinflammation induces chronic inflammation

# Gateway reflex, which is a neural circuit regulating blood vessels

Inflammation



Gravity



Pain



Electric Stim



Light



Stress

## Environmental Stimulus

*Arima et al., 2012*

Neurotransmitters

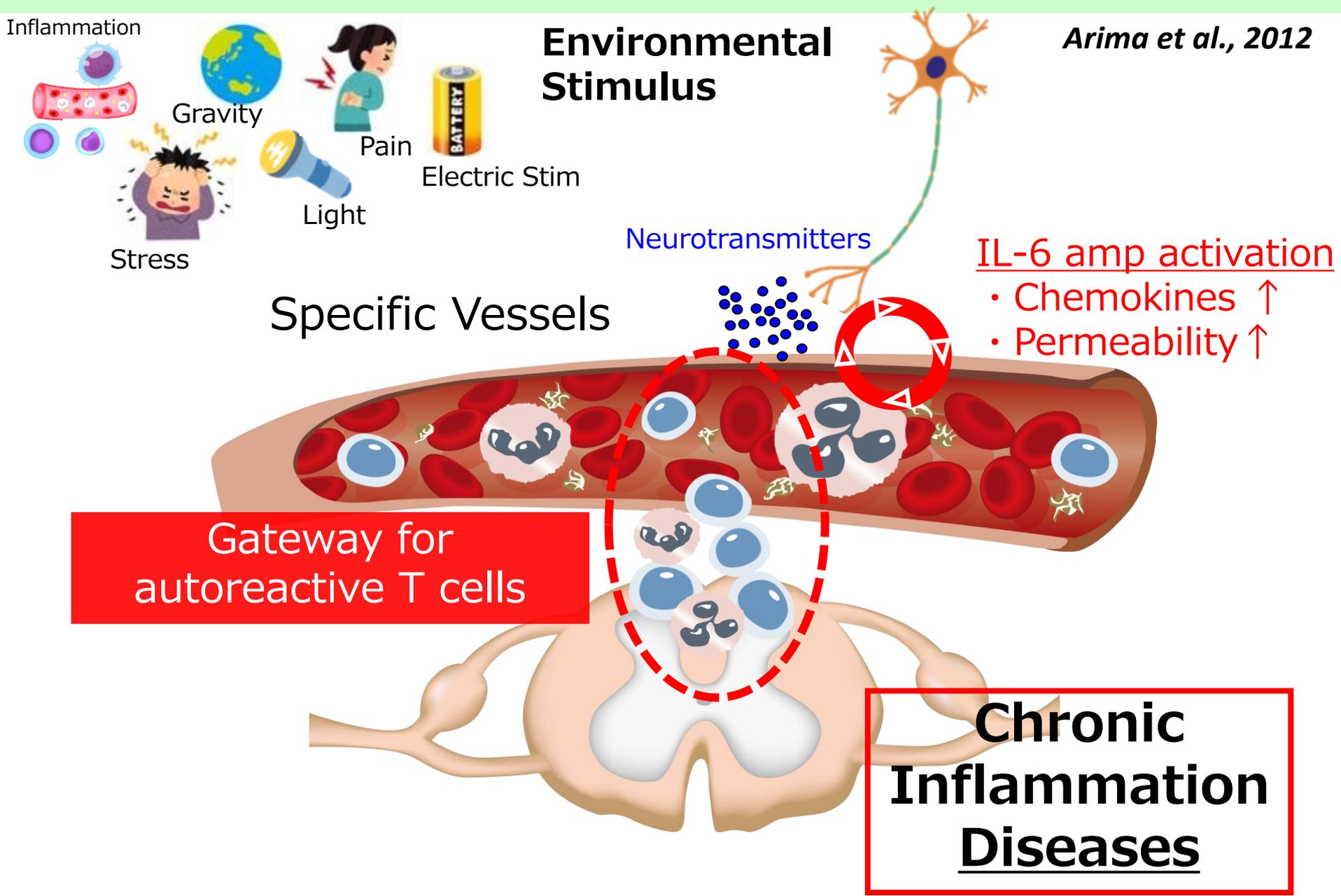
## Specific Vessels

IL-6 amp activation

- Chemokines  $\uparrow$
- Permeability  $\uparrow$

Gateway for autoreactive T cells

**Chronic Inflammation Diseases**



# Project brief

## Chronic inflammation is directly linked to major diseases

- Dementia such as Alzheimer's disease
- Immune diseases such as rheumatoid arthritis and multiple sclerosis
- Cerebrovascular and cardiovascular diseases caused by atherosclerosis



## **[Our solution for curing chronic diseases]**

Understanding the state of "pre-disease"  
by analyzing the gateway reflex and IL-6 amplifier

Development of innovative quantum and neuronal technologies  
to detect and control tissue-specific microinflammation



**Realization of a healthy and long-living society**

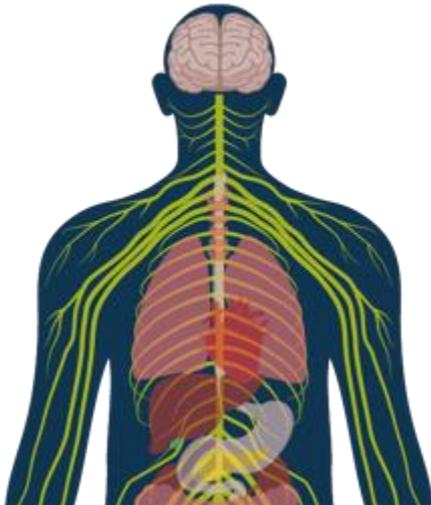
# Breakthroughs to be achieved in this project

1. Quantum Technology  
for **detecting the onset of pre-disease**

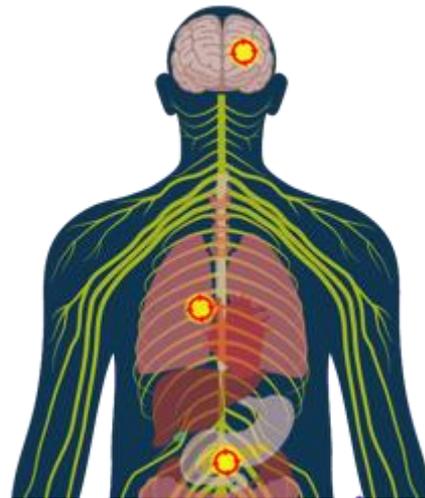
2. Neuromodulation Technology  
for **removing the onset of pre-disease**



Normal state

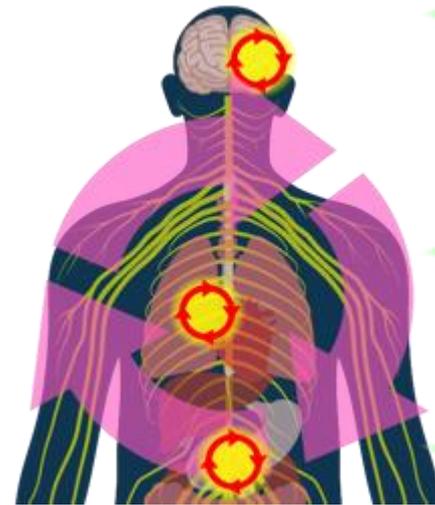


pre-disease



Microinflammation  
= onset of disease

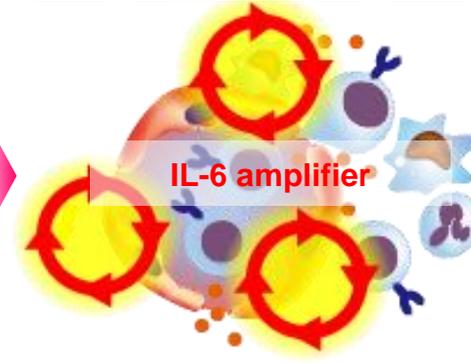
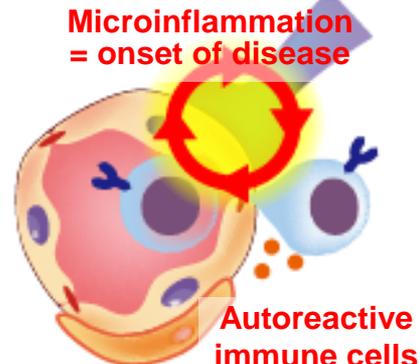
Chronic inflammation



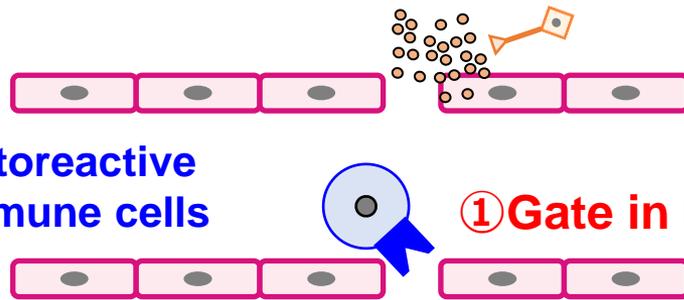
CNS disease

Circulatory disorder

Immune disease



# Detection of Inflammation by IL-6 Amp and immune cells



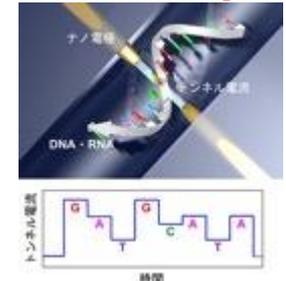
We have proven:

- (1) Each organ and disease has cells that are easily started IL-6 amplification
- (2) Autoreactive lymphocytes

**Specific factors via their activation**

- Quantum technologies:

**Diamond nanosensor and Nanopore**



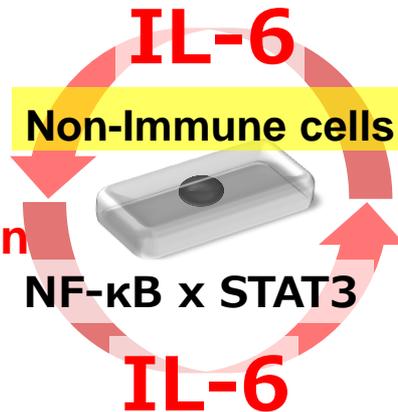
- Quantum Imaging

**Next Gen. PET • MRI**



**Technologies for detecting The onset of disease**

**② Mechanism of microinflammation to chronic inflammation**



Autoimmune disease, Metabolic syndrome, Neurodegenerative disease, Psychiatric disorders, Atopic dermatitis, Allergies, Infection disease, Graft rejection, Rheumatoid arthritis, Multiple sclerosis, Pneumonia, Nephritis, Dermatitis, Cancer, Keloid, Osteoarthritis, etc.

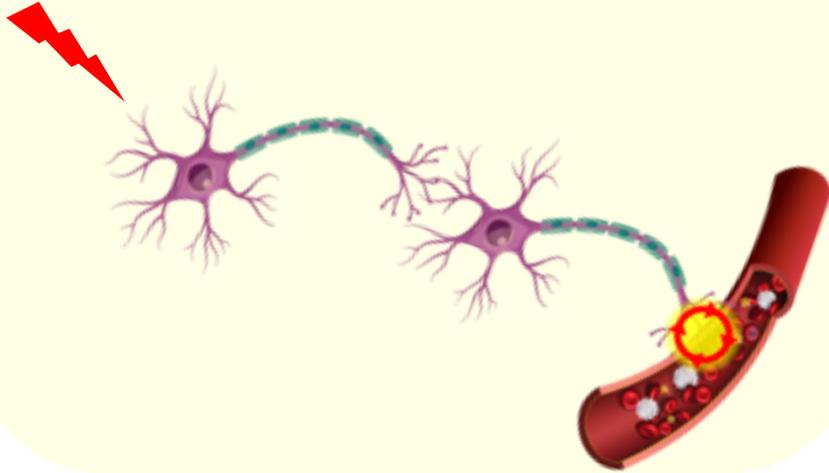
**Technologies for removing the onset of pre-disease: Utilization of the neuronal network**

# Novel Neuromodulation Technology

## ● Gateway Reflex

Discovered in Japan

- Mechanism of neuronal activation-mediated immune cell gateways

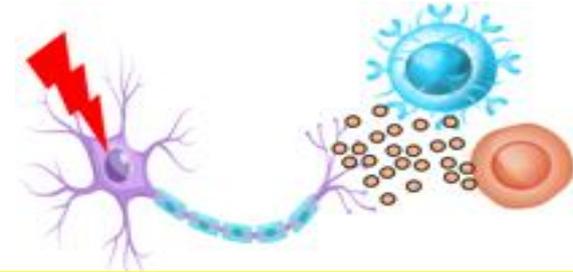


By the neuronal power, we prevent the formation of blood vessel gate and the entry of autoreactive immune cells.

## ● Inflammation Reflex

Discovered in USA Dr. K. J. Tracey

- Vagus nerve-mediated inflammation suppression



- Collaboration with Epilepsy Center in Hokkaido Univ.



# Two Breakthrough Innovations

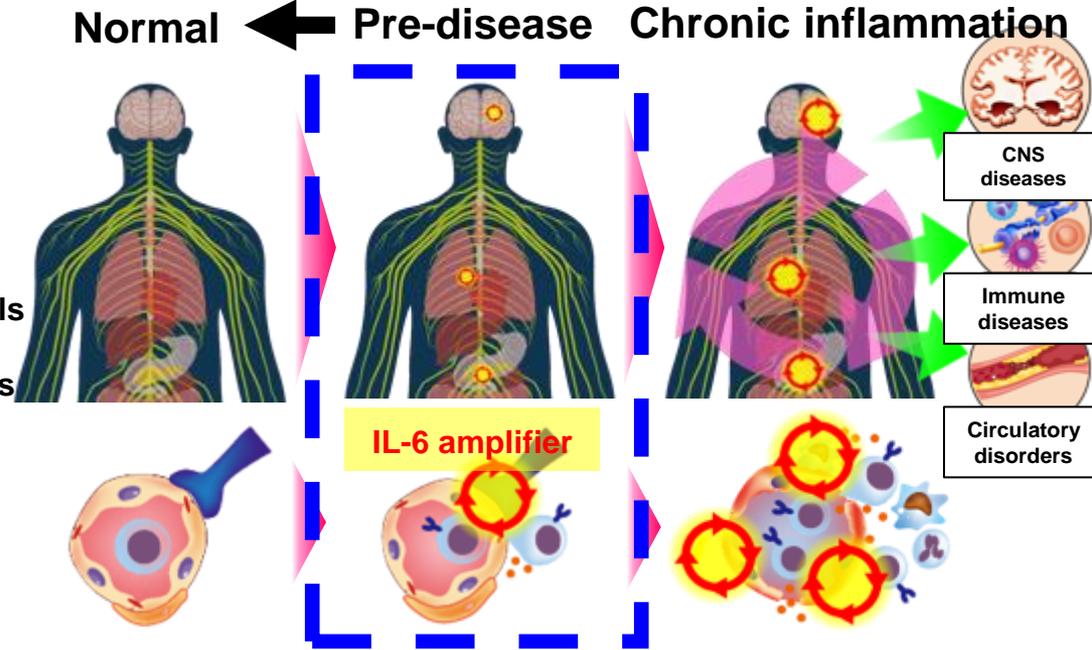
● Development of two technologies to restore "pre-disease" to "normal" in the very early stage of chronic inflammation

## 1. Technology to define pre-disease : Quantum technologies

- (i) Comprehensive analysis of autoreactive T cells
- (ii) Identification of IL-6 amplifier markers using nanodiamonds, nanobodies, and microfluidics
- (iii) Super-sensitive quantum imaging

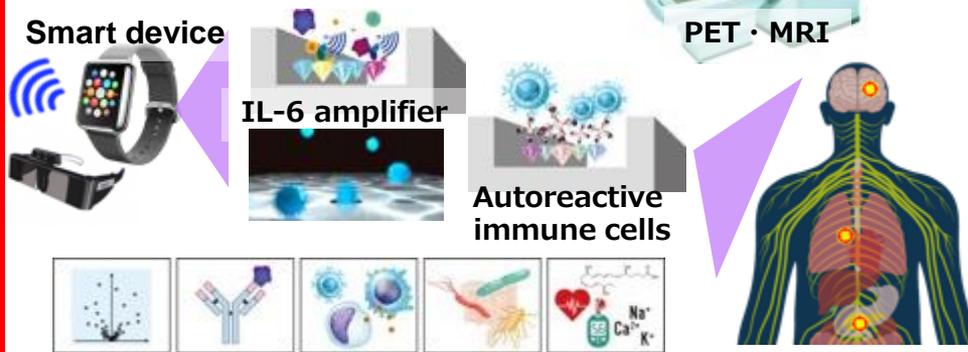
## 2. Technology to regulate pre-disease : Neuromodulation technologies

- (i) Two neuromodulation technologies specific to Gateway Reflexes
- (ii) Inhibition of autoreactive T cells and tissue-specific IL-6 amplifier



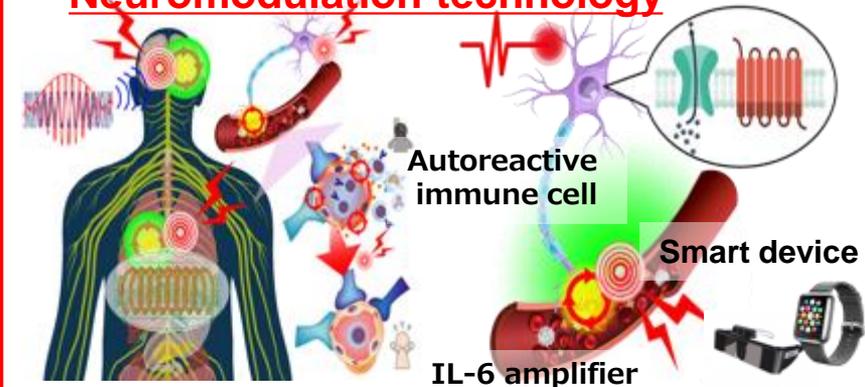
## 1. Define pre-disease

Cutting-edge quantum technology



## 2. Regulate pre-disease

Neuromodulation technology



# Annual planning

2021

2022

2023

2024

2025

2040

**G2 Quantum technology** for ultra-early detection of microinflammation

Diamond nanosensor, Nanopore AI, etc. Sensitization and Optimization

**Define  
Pre-disease**

**G1 Identifivation of factors** to detect microinflammation

**G3 Neuromodulation technology** to control microinflammation

Non-invasive treatment in patients

Cohort studies in healthy subjects

**Regulate  
Pre-disease**

**G4 Information Science:** Big data analysis and device development

# Project progress in 2022

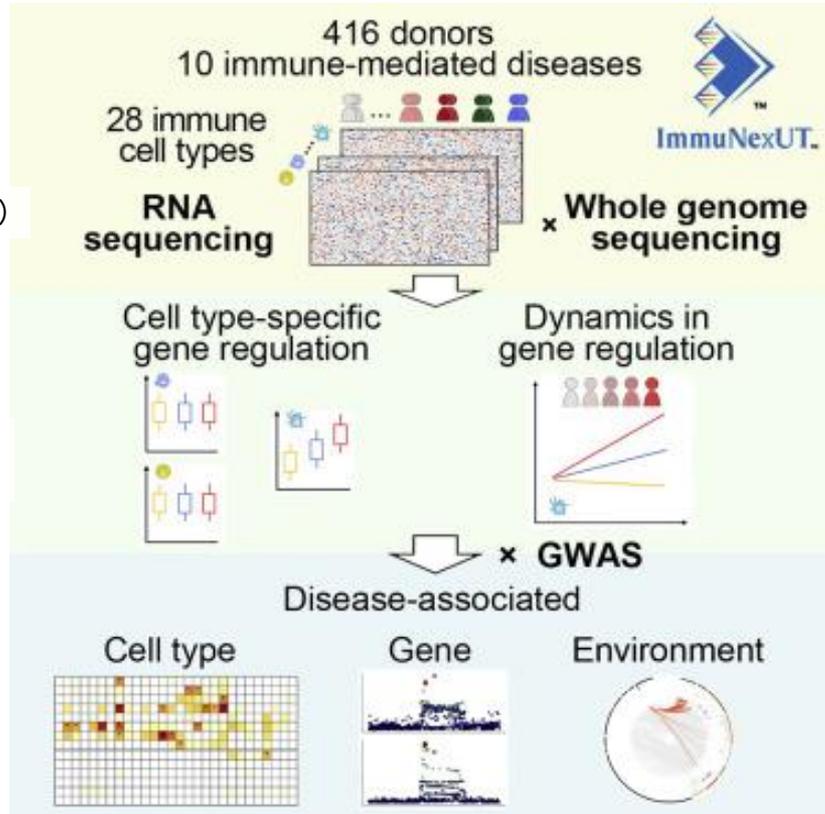
## G1 Identification of IL-6 amp factors and gateway reflex mechanisms



Fujio(U. Tokyo)



Murakami  
(Hokkaido U)



Completion of **the immune cell analysis platform** that enables analysis from the cellular to the genetic level  
Cell, 2021 (IF = 38.6)

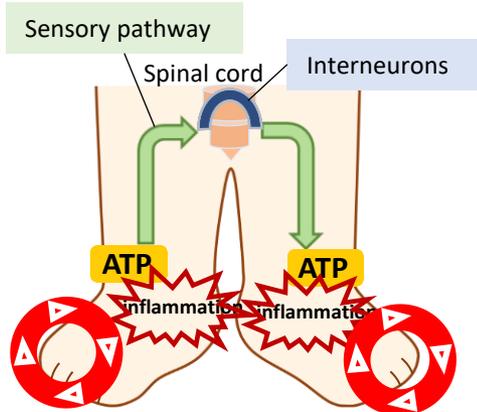
• Same platforms for humans and laboratory animals are also in place at Hokkaido University.

**Establishment of Immune Cell and Gene Information Analysis Platform in the University of Tokyo and Hokkaido University.**



# Project progress in 2022

## G1 Identification of IL-6 amp factors and gateway reflex mechanisms



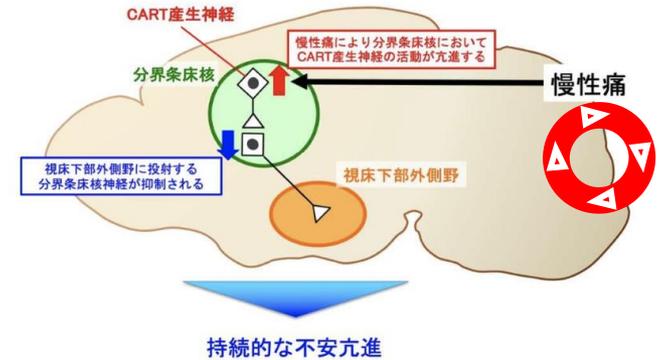
Murakami  
(Hokkaido U)



Atsumi  
(Hokkaido U)



Minami  
(Hokkaido U)

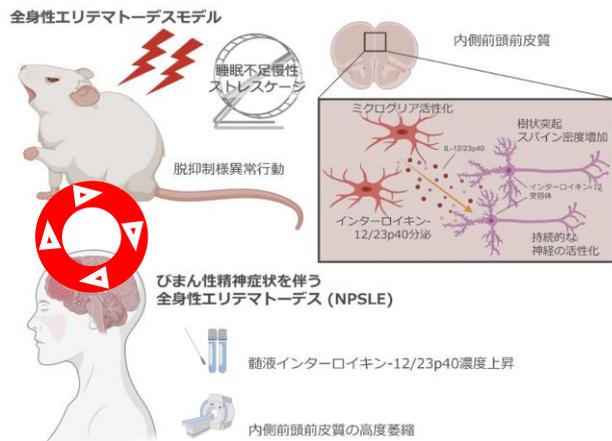


### Specific neuronal circuit induces inflammation in remote tissues

J Exp Med, 2022 (IF = 14.3)

### Discovery of Neural Circuit for Chronic Pain-mediated Anxiety

Science Advances, 2022 (IF = 14.1)



### Discovery of Novel Neuronal Circuits Linked to Inflammation

• Three novel neuronal circuits are associated with inflammation. Artificial manipulation of these circuits could suppress the inflammatory disease.

### Chronic stress-mediated exacerbation of autoimmune disease via abnormal activation of specific neural circuits

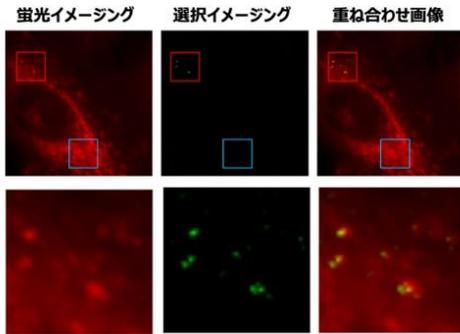
Ann Rheum Dis 2022 (IF = 28.0)

# Project progress in 2022

**G2 Quantum technology** for ultra-early detection of microinflammation



Igarashi  
(QST)



**Sensitivity of diamond sensor was increased  
100 times more**

ACS Nano, 2021 (IF = 15.9)

**Nanodiamond-Platform for Microinflammation  
was Progressed.**

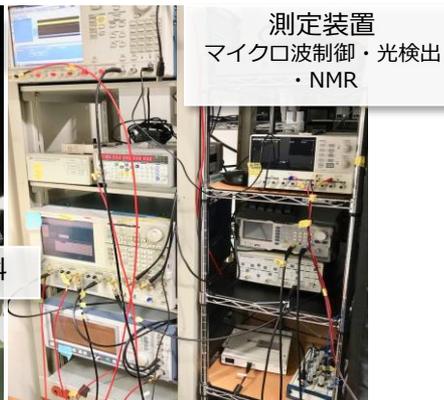
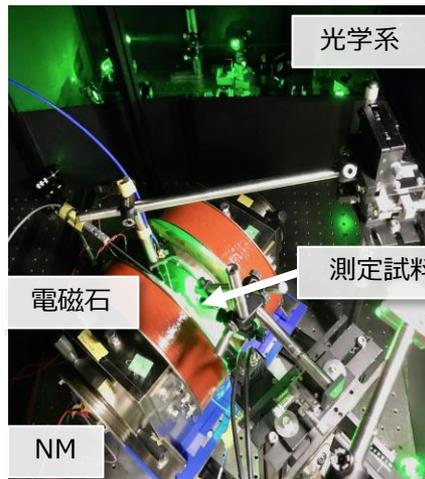
**Improvement of the sensitivity of diamond sensor.  
Development of multiple high-performance  
microscopes fo diamond-detection.**



Murakami  
(Hokkaido U)



Igarashi  
(QST)



量子NMR装置は**世界で4台目**  
(2台はHarvard大, 1台は京大)

Installation of special  
microscope for diamond  
sensor detection was  
completed at Hokkaido  
University.

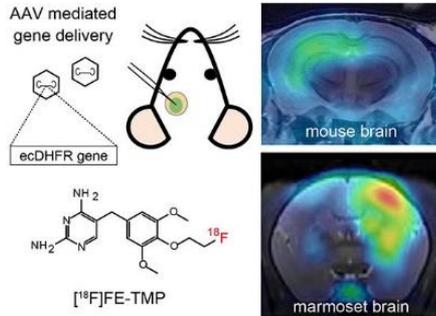
Installation of special  
microscope for diamond  
sensor detection started  
at QST.

# Project progress in 2022

**G2 Quantum technology** for ultra-early detection of microinflammation



Higurashi(QST)



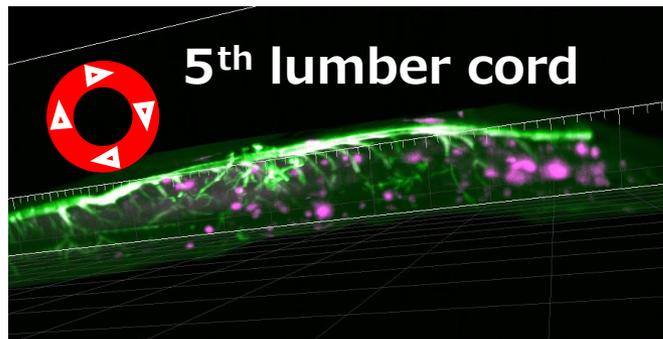
**Novel Imaging Method for Microinflammation and Neuronal Circuits. Two novel methods to find microinflammation and its associated neural circuits were developed.**

## Novel Imaging Method of Neural Circuits by PET Reporter

EMBO Journal, 2021 (IF = 9.9)

## Development of a novel microinflammation detection method using tissue clearing and a light sheet microscopy.

Manuscript under preparation



Tainaka  
(Niigata U)



Murakami  
(Hokkaido U)

# Project progress in 2022

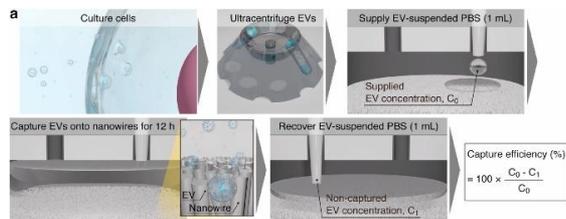
**G2 Quantum technology** for ultra-early detection of microinflammation



Yasuda  
(Nagoya U)

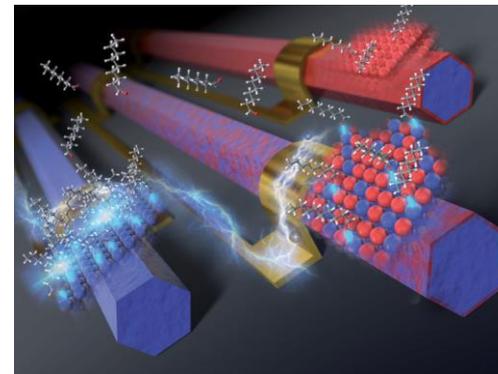


Yanagida  
(U of Tokyo)



**Development of a new method for isolation of inflammatory extracellular vesicles**

Biosens Bioelectron, 2021  
(IF = 10.3)



**New PEG-Carbon sensors for Metabolites Monitoring**

ACS Sens, 2021 (IF = 9.5)

**Novel methods for the isolation and detection of factors that are related to inflammation.**

**Development of a novel method for isolation and detection of extracellular vesicles, which were related to inflammation.**

**Novel sensor to detect metabolic changes during inflammation was developed.**

# Project progress in 2022

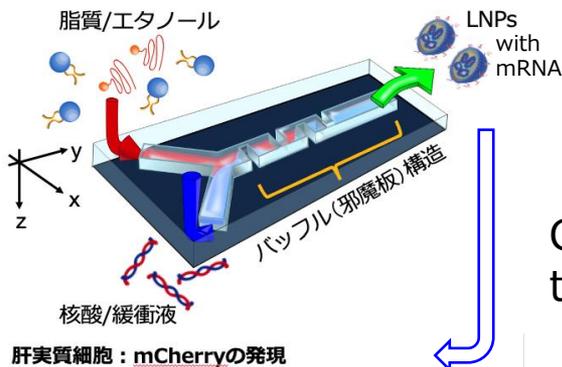
**G2 Quantum technology** for ultra-early detection of microinflammation

## Novel gene transfer technology with artificial extracellular vesicles

J Control Release, 2022 (IF = 9.8)



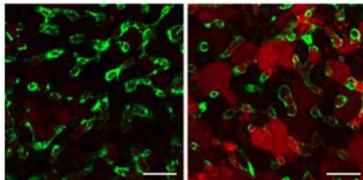
渡慶次(北大)



Artificial Extracellular Vesicles

Gene transfer to  
the Artificial Extracellular Vesicles

肝実質細胞 : mCherryの発現



左 : MC3  
右 : CL4H6

**Development of a novel method of gene transfer into cells by using artificial extracellular vesicles**  
**The method can suppress activation of neurons, which are important for the gateway reflexes.**

# Project progress in 2022

**G3 Neuromodulation technology** to control microinflammation

## Clinical study of non-invasive VNS therapy begins



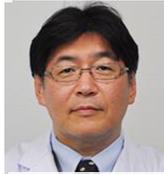
Murakami  
(Hokkaido U)



Shiraishi  
(Hokkaido U)



Atsumi  
(Hokkaido U)



Iwasaki  
(Hokkaido U)

## New neuromodulation method using ultrasound genetics



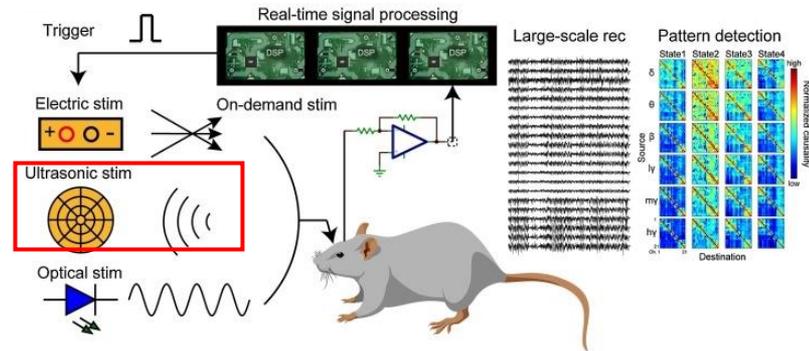
Murakami  
(Hokkaido U)



Takeuchi  
(Hokkaido U)



Higuchi  
(QST)



Clinical studies of neuromodulation begin and novel ultrasound-based nerve stimulation method was developed.

1. Clinical studies of noninvasive neuromodulation in epilepsy have begun.
2. Neuromodulation technology using ultrasound genetics is under development.

# Project progress in 2022

## G4 Information Science: Big data analysis and device development

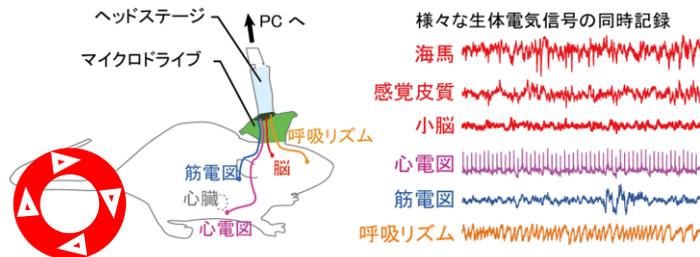
Developing new methods of measuring and analyzing physiological information from pre-disease to disease onset.



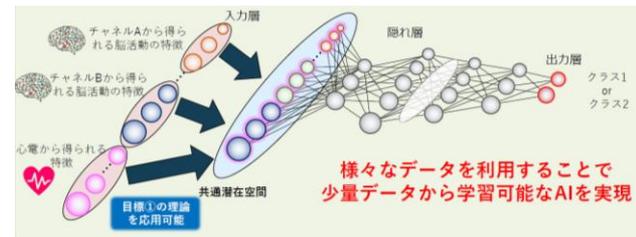
Sasaki  
(Tohoku U)



Haseyama  
(Hokkaido U)

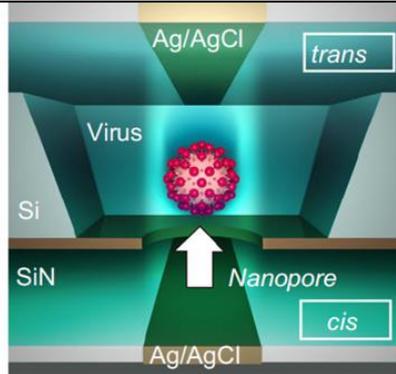


Animal models of MS and RA



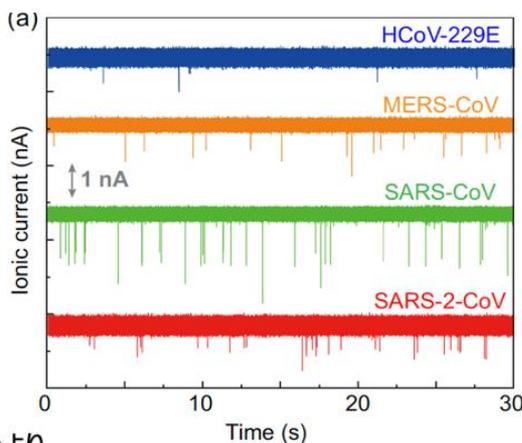
## AI-Nanopore Successfully Detects New Coronavirus Nat Commun, 2021 (IF = 14.9)

Virus passing through AI nanopores



Taniguchi et al., Nat Communより

Analysis of existing coronavirus species



Taniguchi  
(Osaka U)



Washio  
(Osaka U)



Murakami  
(Hokkaido U)

• Variant detection by AI-nanopore (paper in preparation)

Inflammation analysis and detection methods are under development

# Microinflammation Control Project: The Future

Curing majority of diseases and disorders by quantum and neuromodulation technologies

**G3 Neuromodulation**  
Gateway Reflex and VNS

Next-gen MRI, PET

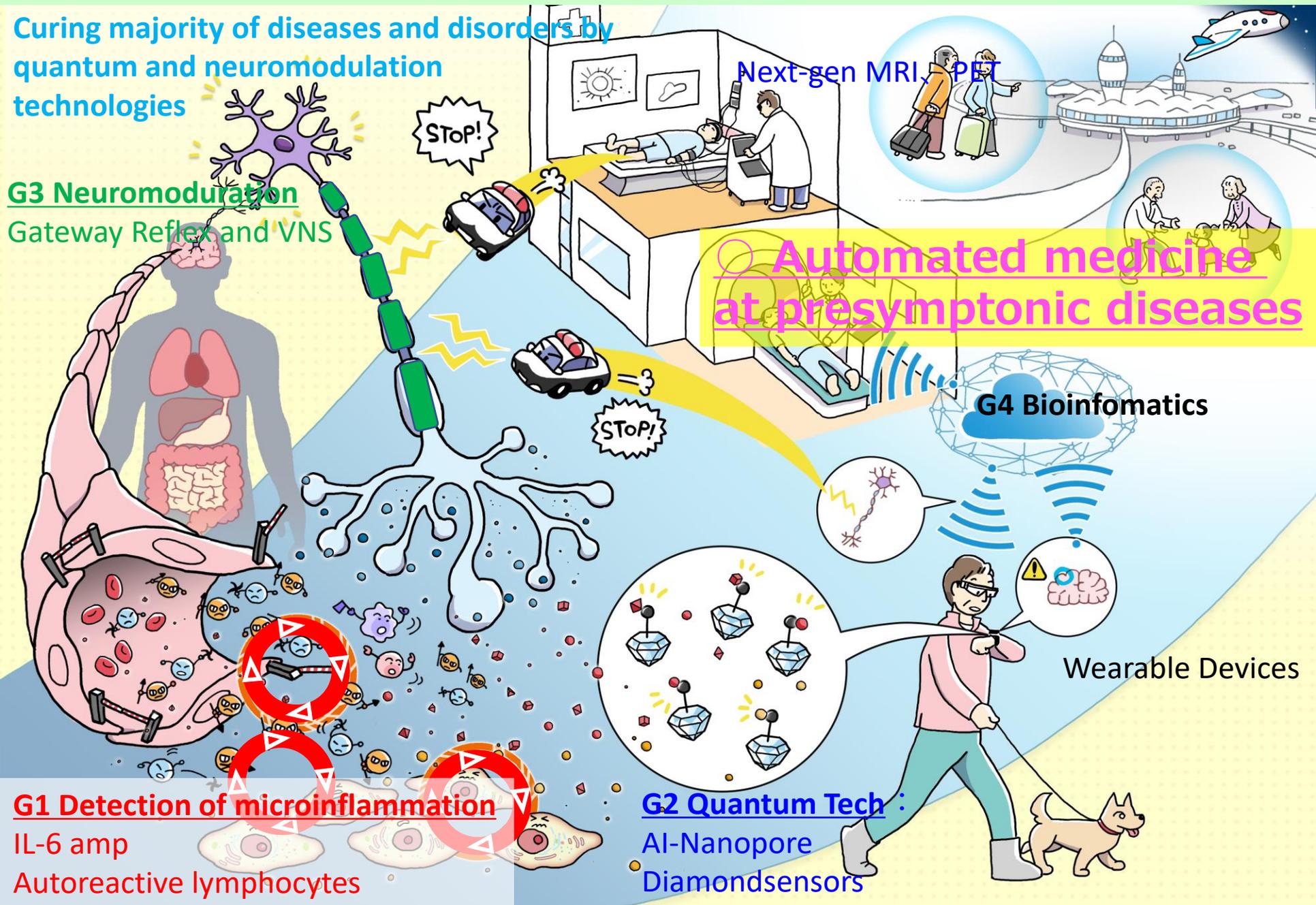
**Automated medicine at presymptomatic diseases**

**G4 Bioinformatics**

Wearable Devices

**G1 Detection of microinflammation**  
IL-6 amp  
Autoreactive lymphocytes

**G2 Quantum Tech :**  
AI-Nanopore  
Diamondsensors



# Transforming Our World: 2040

We establish technologies for detection and remove the onset of pre-disease, which make free from major diseases automatically.

We ensure good health and promote well-being for all ages in 2040.