Hitoshi-fest: From Particle Physics, Cosmology to Instrumentation

Responding to Hitoshi's Vision #7

Toward New Frontiers in Advanced Cancer Research Employing Cutting-Edge Astronomical X-ray and Gamma-ray Detectors

Tadayuki Takahashi

Joined IPMU in 2018 from ISAS/JAXA

with
Shin'ichiro Takeda, Tadashi Orita, Atsushi Yagishita, Miho Katsuragawa, Izumi Umeda, Hugo Allaire

Hitoshi’s vision #7

https://www.ipmu.jp/sites/default/files/webfm/pdfs/mission/mission_ja/3_b_tokyoj.pdf

Director’s vision (in the IPMU proposal)

2007/Sep/27

数物連携宇宙研究機構

９月２７日

機構長のビジョン、カリフォルニア大学バークレイ校、村山斉

我々は世界で唯一の、純粋数学から理論物理、実験物理、天文学、そして応用数学までにまたがる数物連携の宇宙研究機構を提案する。この機構は、宇宙の基本的原理、宇宙の始まりと終わり、そして宇宙に存在する未知の暗黒物質と暗黒エネルギーに迫る。そのためには、宇宙の統一理論を作り上げる必要がある。これには今までにない新しい数学が必要になり、その新しい数学に基づく物理学の理論が構築される。この理論は、実験で検証される
術的な進歩が新しい実験を可能にし、そこで必
の進歩を促す。こうして螺旋状に進歩していく
味を引き、学生が数学・科学・工学へと進む動
いく。

7. Contribution to Society

7. 社会還元

宇宙を最も基本的なレベルで理解しようとする
ロジーのようには直接応用がうまれるものでは
学生は最先端の基本法則の探求に心を引かれ、特に過去の例を見ると最優秀な若者たちもそのグループに含まれていることが多い。機構の研究者による、宇宙の深い謎を明かす発見は、日本の高校生・大学生の興味を引き、数学や科学を勉強し、次の世代の人材を育成していくことに大きな役割を果たすだろう。この機構に独特なこととしては、数学と物理の間を専門的な職業として行き来し、統計と実験物理の間にも同じことがあると予想される。言うまでもなく、機構で研究する問題は一般の人にも理解し易い問題である。この基礎研究と教育の間の関係は最近では例えば “Rising Above the Gathering Storm” という米 National Research Council からの報告書でも強調されている。

更に、機構の研究で得られた手法やテクノロジーは間接的に社会に役立っていくに違いないと考えている。天文観測や加速器実験からの大規模データを解析する手法は金融市場や生物学のデータ解析に使えるだろう。次世代の実験設備を作るために開発するテクノロジーは、企業による利潤目的だけの研究では長期的すぎて対象にできないものも多い。例えば基礎物理学の実験のために口径２０インチの光電子増倍管を開発し、その技術を応用して特に医学関係の応用では世界の市場の独占に近い位置に上りつめた企業もある。将来のニュートリノ検出器の開発は、原子炉の監視に役立つことも考えられる。また将来の大規模な天文観測に必要なマルチファイバーのテクノロジーは医学に診察、レーザー医療等で役立つ可能性がある。

Technologies

Human resource development.

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<Translation>

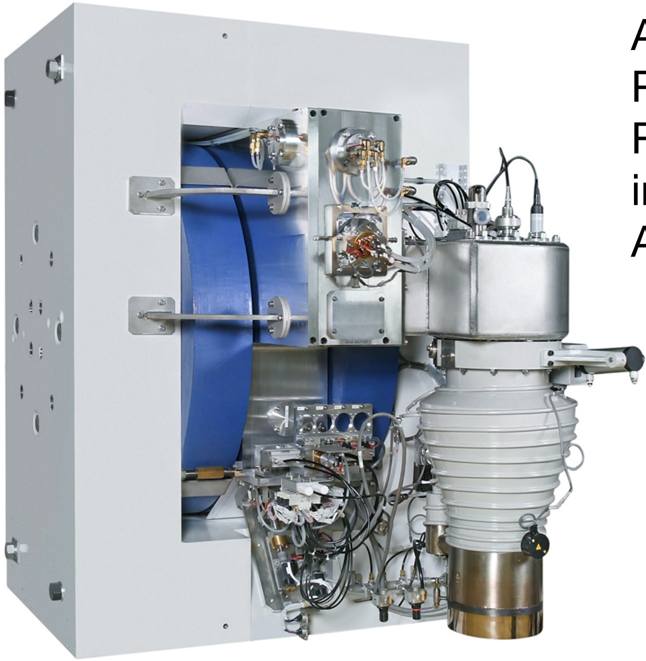
Furthermore, the methods and technologies developed through the institute's research will undoubtedly contribute to society indirectly. Techniques for analyzing large-scale data from astronomical observations and accelerator experiments can also be applied to financial markets and biological data analysis. Technologies developed to create next-generation experimental equipment often cannot be targeted by companies for profit-driven research alone because they require a long-term perspective.

For example, a 20-inch diameter photomultiplier tube was developed for fundamental physics experiments, and a company that applied this technology, particularly in medical applications, has risen to a near-monopoly position in the global market. The development of future neutrino detectors could also contribute to nuclear reactor monitoring. Additionally, multi-fiber technology required for future large-scale astronomical observations has the potential to be useful in medical diagnostics and laser treatments.

Some good examples…

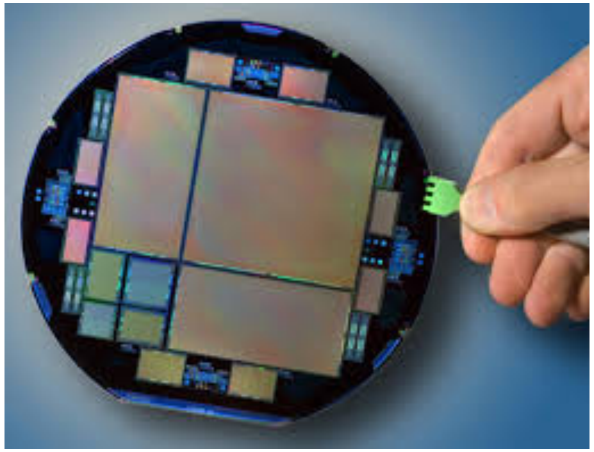
PET (Positron Emission Tomography)
CT (Compute Tomography)

https://www.siemens-healthineers.com/jp/molecular-imaging/pet-ct



Accelerators for Producing Radioisotopes Used in PET and Other Applications

https://www.shi.co.jp/industrial/jp/product/medical/pet-radiopharmacy/cyclotron-hm12.html



LBNL

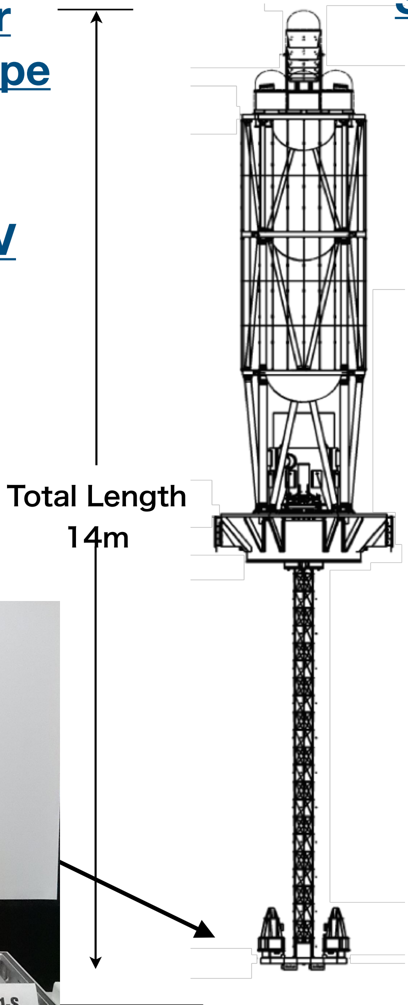
CCD chips
and
CCD Camera

Research aimed at addressing profound scientific questions about the universe has driven the development of cutting-edge detectors with exceptional performance, achieved through an unwavering pursuit of sensitivity and resolution.

Focal Plane Detector
for Hard X-ray Telescope
CdTe ＋ Si DSD

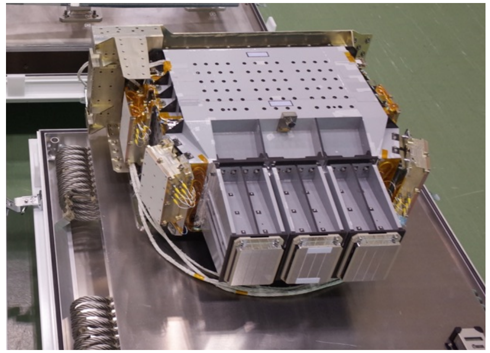
(Double Strip Detector)

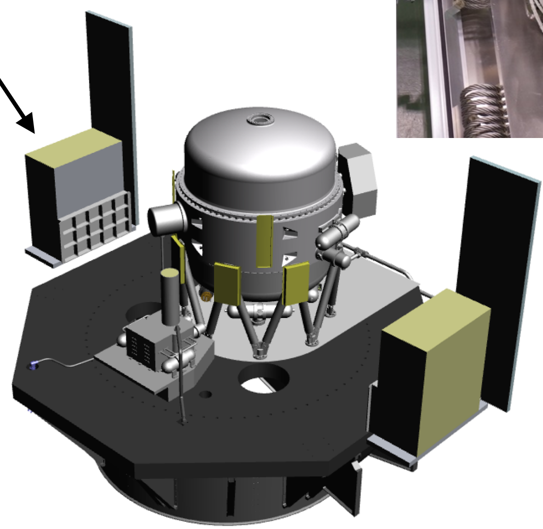
~5-80 keV



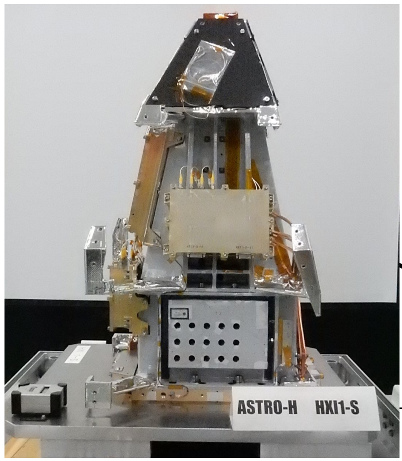
Si/CdTe Semiconductor
Compton Camera
(gamma-ray)

~60-600 keV





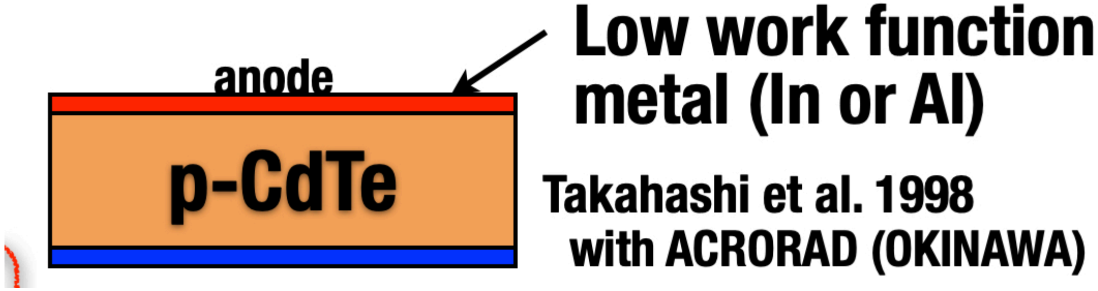
HXI



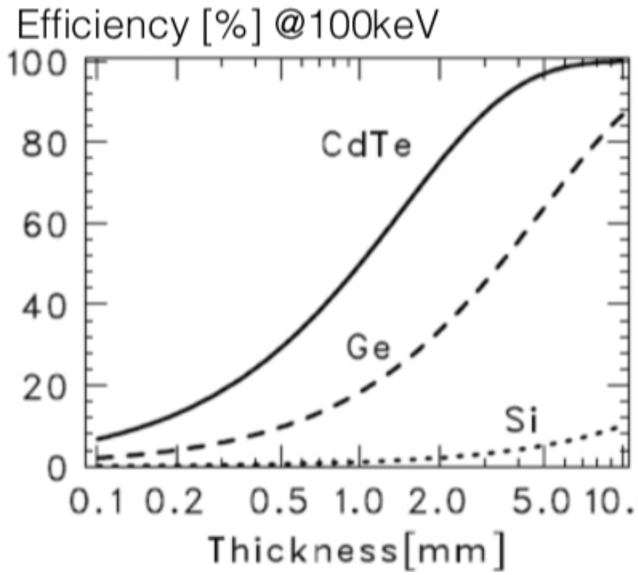
Hitomi (ASTRO-H)
(2016)

Key technology : Gamma-ray semiconductor for imaging

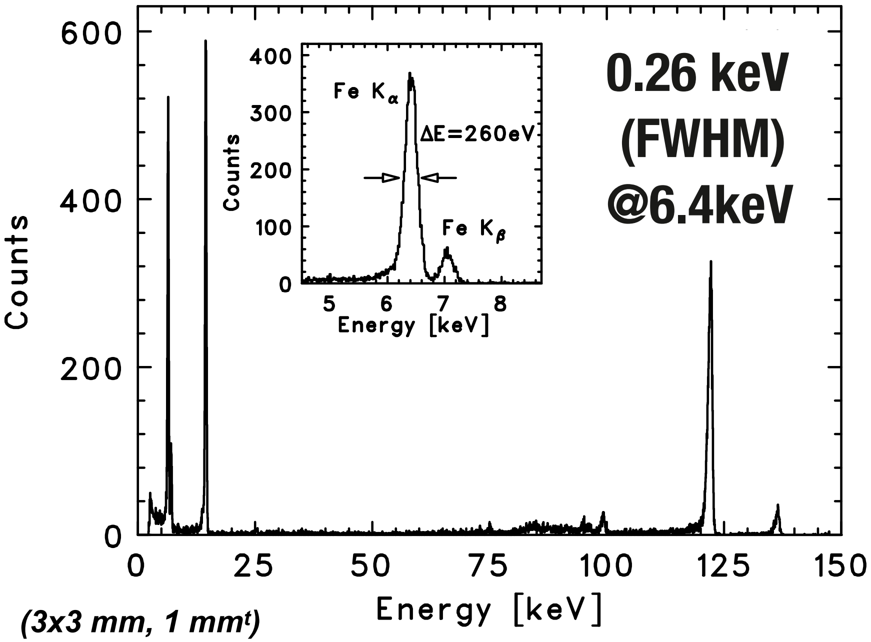
The CdTe diode devices developed by us in the 1990s



Takahashi et al. 1998 with ACRORAD (OKINAWA)

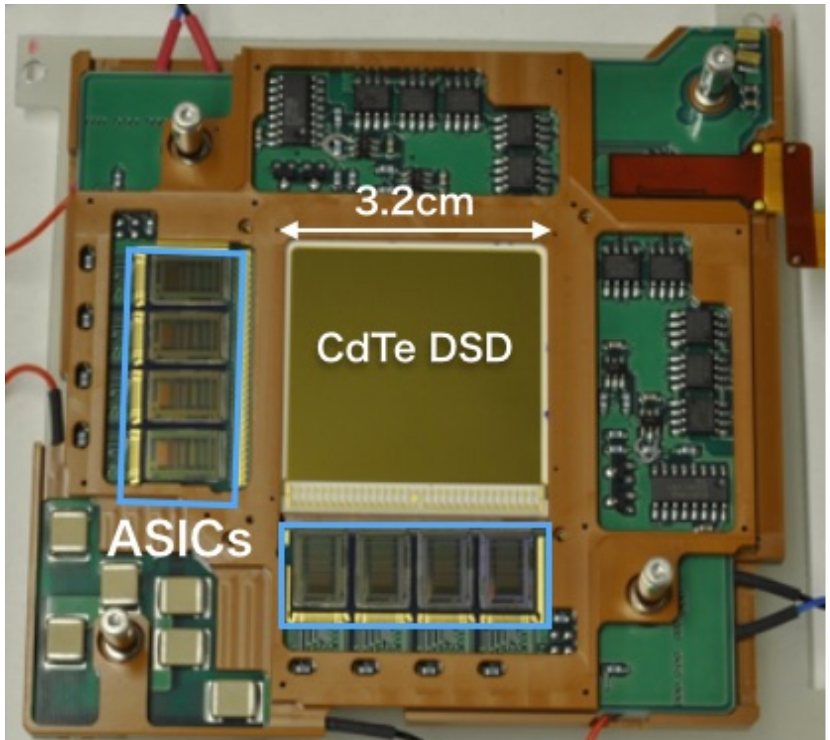


- **Extremely low leakage current**
- **HIgh Energy resolution**
- **Technology for strip and pixel electrode fabrication**



(3x3 mm, 1 mmt)

Takahashi et al. 2005



Toward Hitoshi's vision #7

Hard X-ray and Gamma-ray Imaging Center at Kavli IPMU

Agreement between Kavli IPMU and ISAS/JAXA (2017-2022)

Toward Hitoshi's vision #7

Hard X-ray and Gamma-ray Imaging Center at Kavli IPMU

Agreement between Kavli IPMU and ISAS/JAXA (2017-2022)

I’ve been arguing that the truly destructive innovation happens through basic research that pushes the frontier of knowledge.

Now we have an opportunity to demonstrate this point through the application of gamma-ray astronomy to cancer research.

I’m super excited about this wonderful opportunity for Kavli IPMU to work closely with JAXA and medical researchers,

Overcoming cancer is an urgent issue that humanity must address.

Through our research at IPMU, we have come to realize that the questions we hold are also regarded as frontline challenges by experts in medical research.

1) Is there any way to manage to treat intractable cancer.

2) Why does cancer metastasize, and how does it spread?
Why does it recur even after being surgically removed?
Can't we detect it earlier?

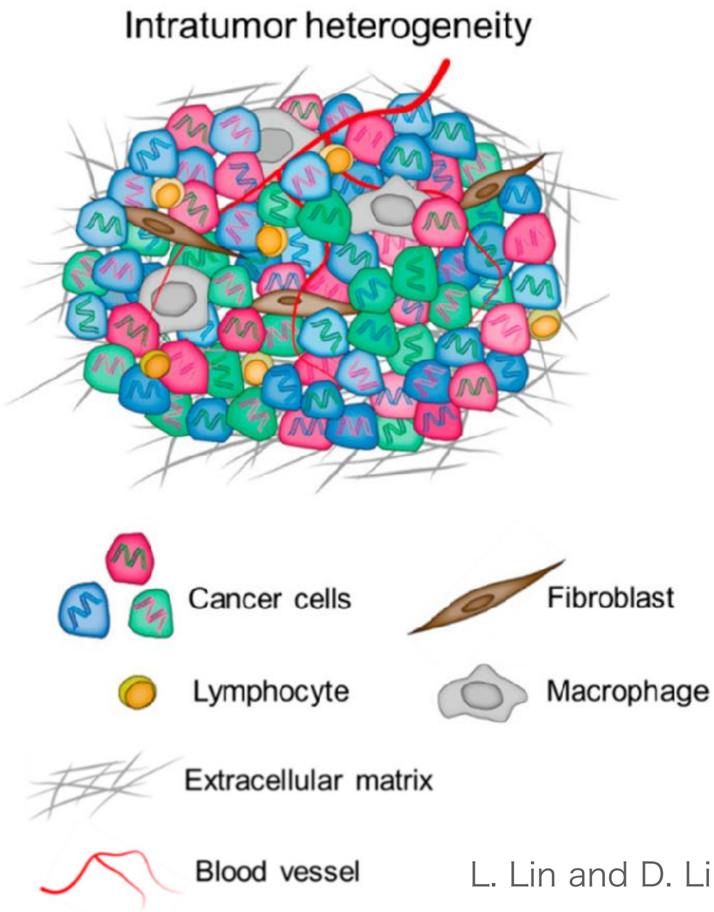
The international journal of science / 20 January 2022

nature

The 'war on cancer' isn't yet won

The US National Cancer Act has fostered great advances in our understanding of the biology that underlies cancer, but challenges remain.

"Today, we know that cancer is not one, but many different diseases."



L. Lin and D. Lin (2019)

"Cancer" is composed of various elements such as cancer cells, fibroblast, lymphocyte and the special microenvironment surrounding the cancer.
→ It is becoming clear that these heterogeneities are deeply related to the malignancy, recurrence, and response to cancer treatment.

Key: simultaneous visualization of multiple radionuclides in vivo with high spacial resolution

Expanding Our Technology into Cancer Research

with

S. Watanabe (JAXA/ISAS)

H. Saya & O. Sampetrean
Keio University,
Department of Medicine

Osaka University
Nuclear Medicine
T. Watabe

National Cancer
Center, H. Fujii

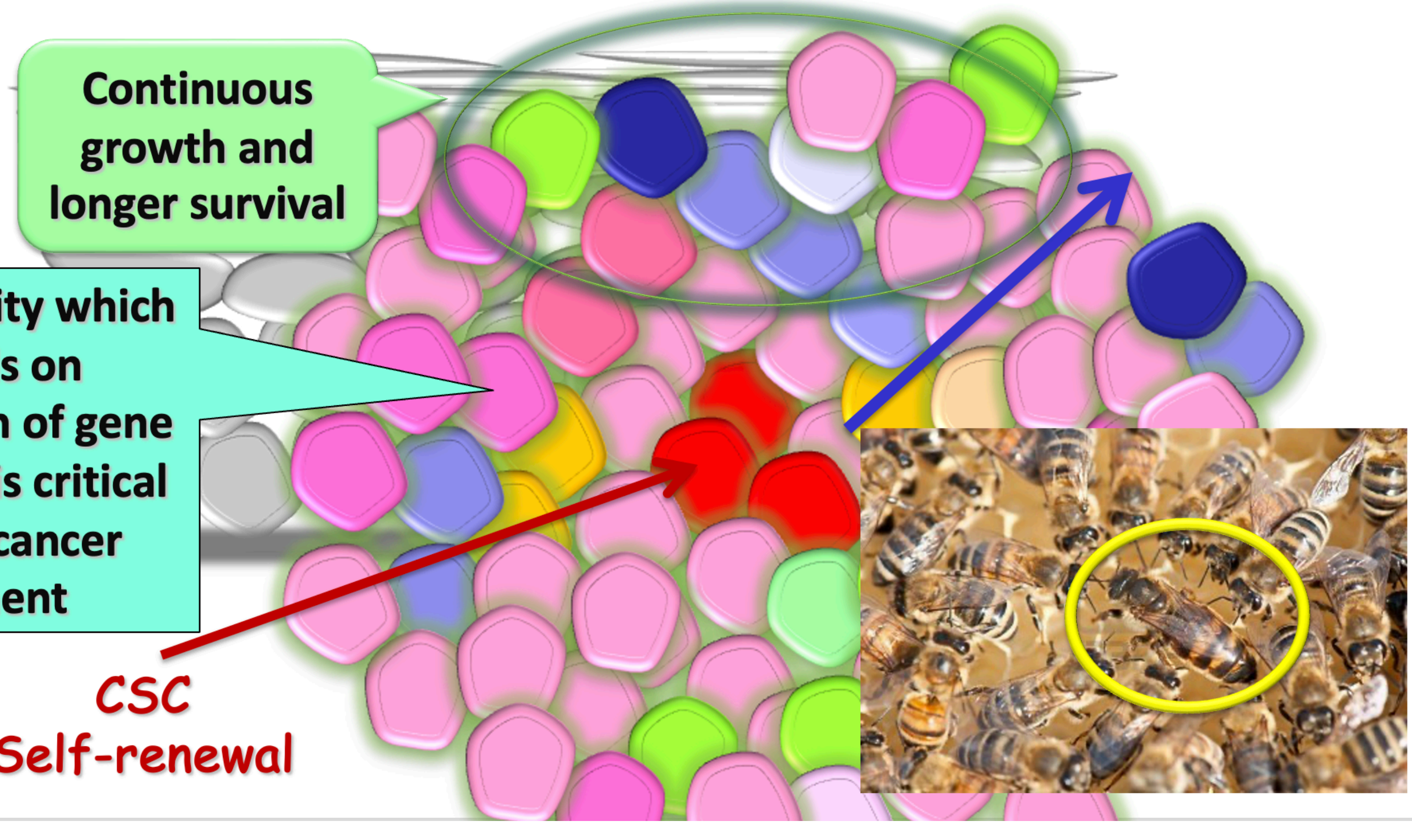
National Cancer
Center, A. Ochiai

with
H. Mizuma (QST)
Y. Kanayama (RIKEN)

IPMU Colloquium (2022)

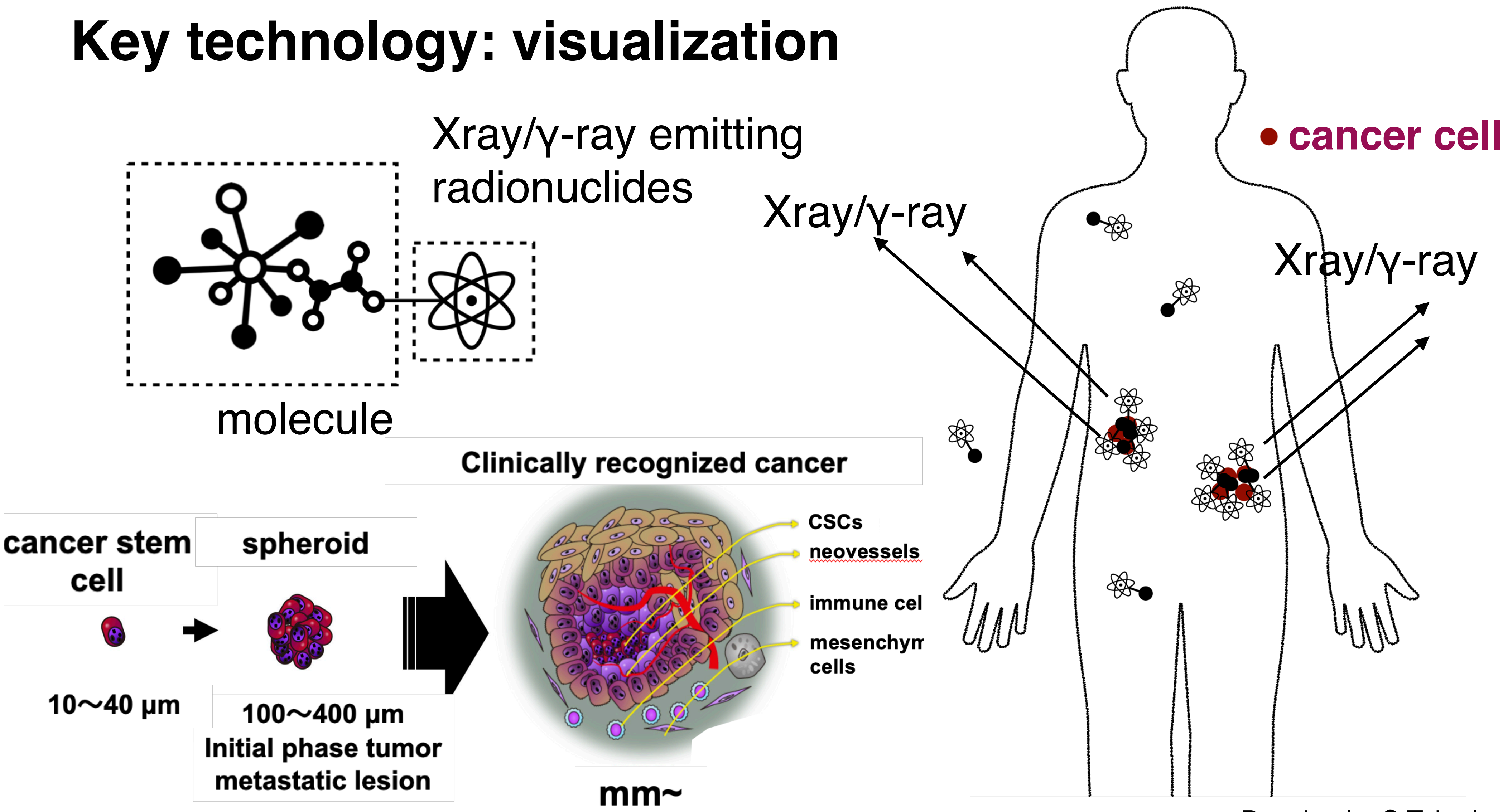
Division of Gene Regulation, Institute for Advanced Medical Research, Keio University School of Medicine

Cancer cells are derived from stem-like cancer cells (cancer stem cells)



Targeting Cancer with Precision

Key technology: visualization



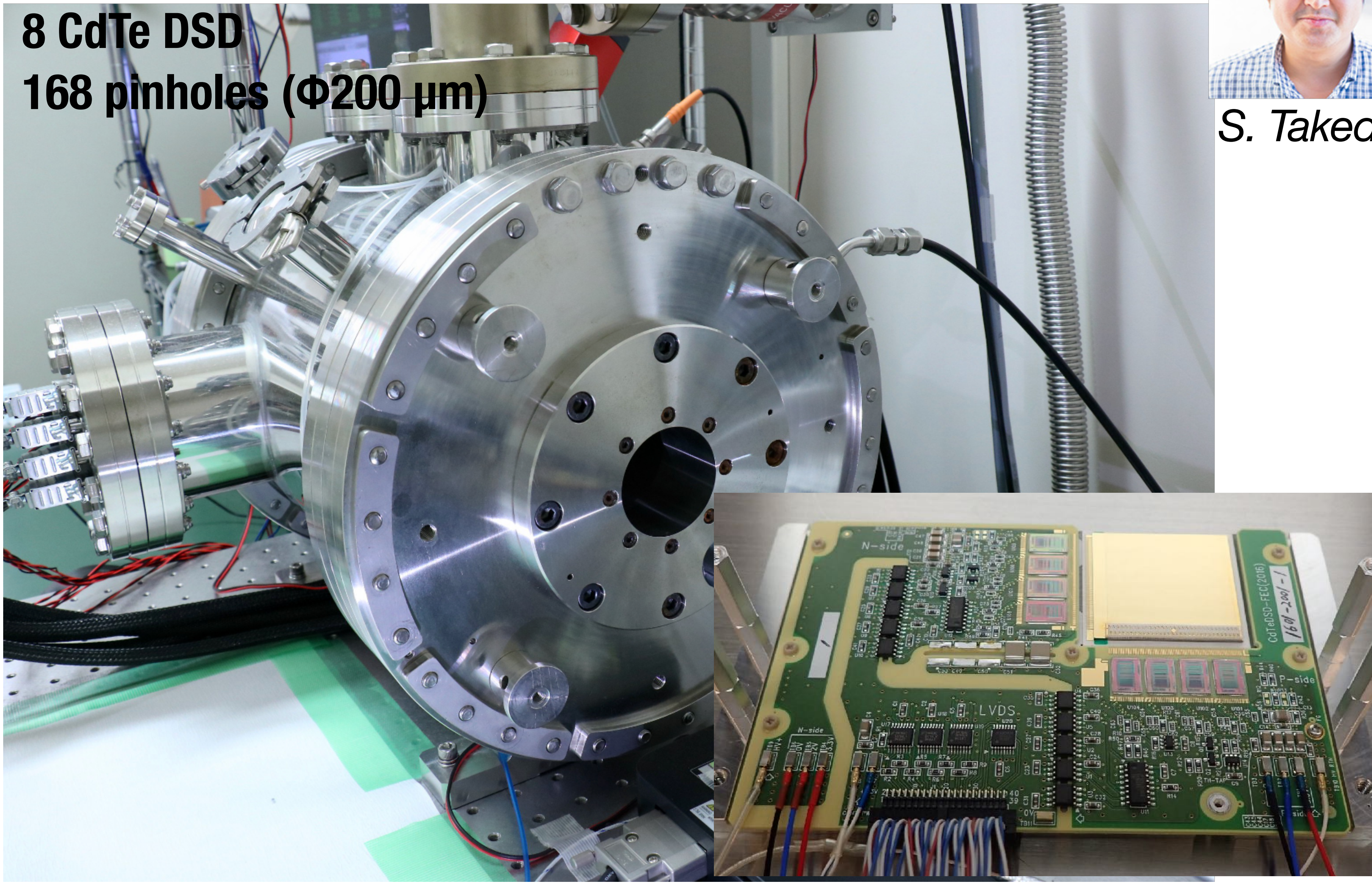
Drawing by S.Takeda

Ultrahigh-Resolution Multi-isotope Tomographic Imager

KAVLI IPMU
東京大学 国際高等研究所 カブリ数物連携宇宙研究機構
KAVLI INSTITUTE FOR THE PHYSICS AND MATHEMATICS OF THE UNIVERSE

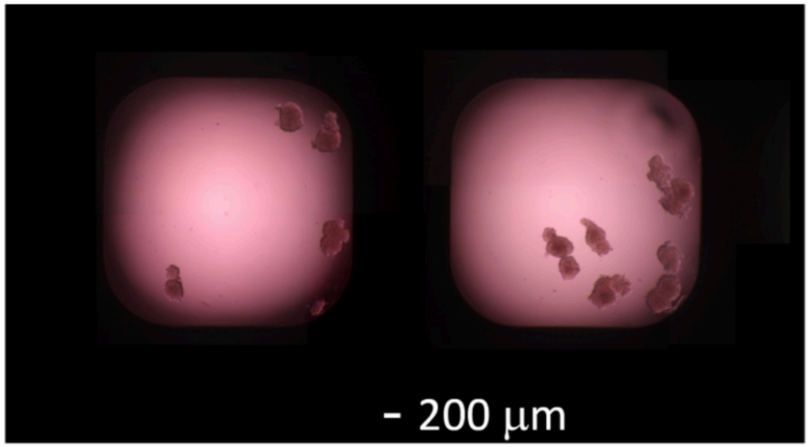
CdTe-DSD SPECT-I:

S. Takeda



Oragonids of NIS (Natrium Iodide Symporter) expressing CSCs which can incorporate 125I

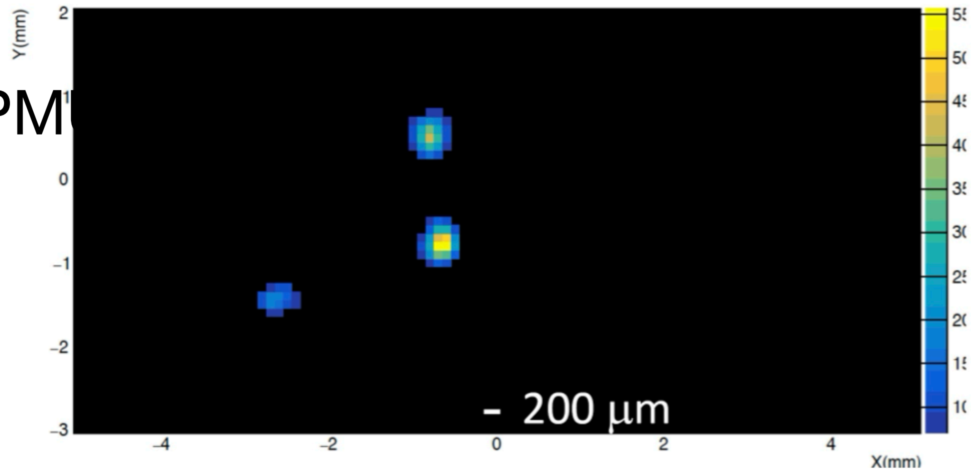
Bright field.



control NIS inhibitor

CdTe-DSD SPECT-I

IPMU



control NIS inhibitor

Toward Detailed Visualization of Metastasis

KAVLI IPMU
東京大学 国際高等研究所 カブリ数物連携宇宙研究機構
KAVLI INSTITUTE FOR THE PHYSICS AND MATHEMATICS OF THE UNIVERSE

Development of Tissue Molecular Imaging Technique Using Multiple Probes at Hundreds of Microns

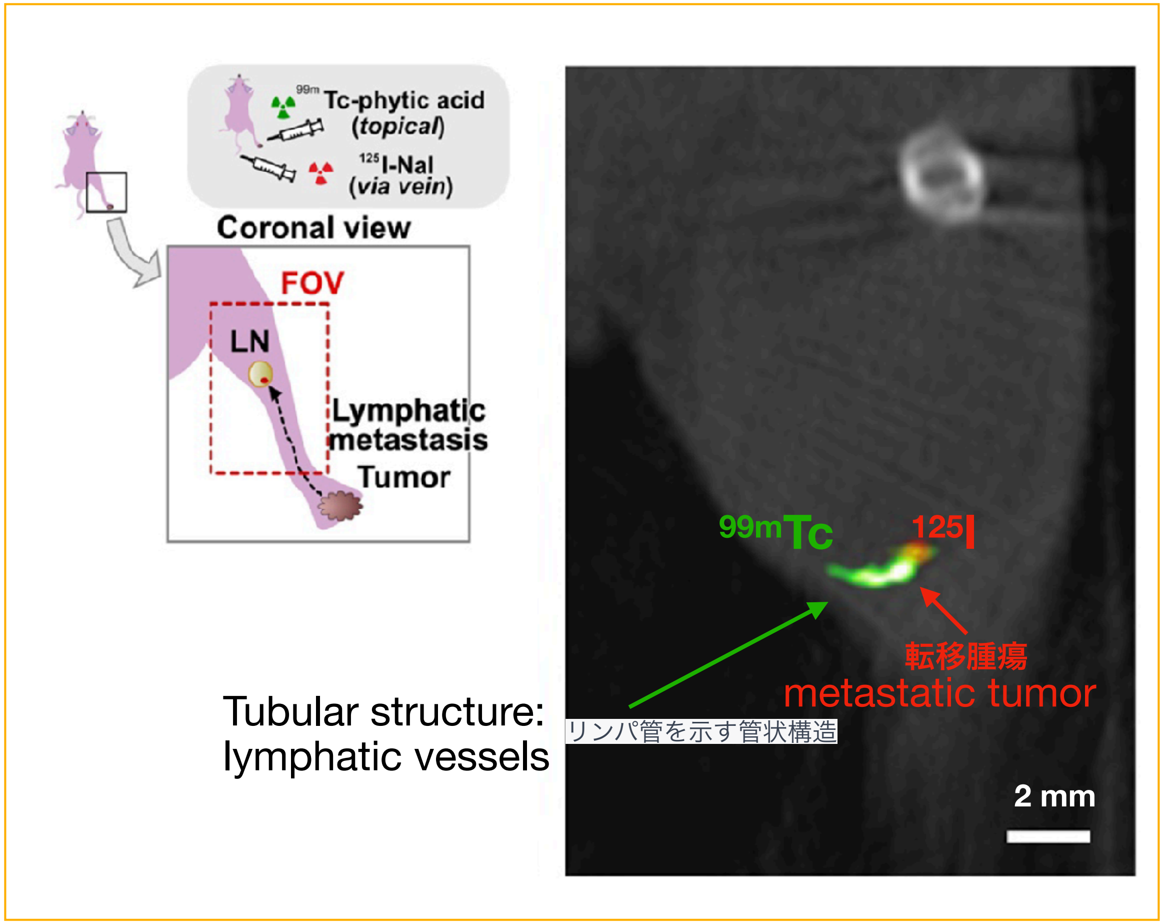
A. Yagishita

IPMU Press release

A. Yagishita, S. Takeda, MK, TT et al. Scientific Reports (2023)

We were able to reveal that cancer in mice, where 4T1-mNIS cancer was implanted in the tip of the foot, has metastasized through the lymphatic vessels to micro-lymph nodes hundreds of micrometers in size. Such precision in imaging is unprecedented

4T1 is a widely used mouse cancer cell line in studies related to breast cancer and metastasis



Toward the Treatment of Hard-to-Treat Cancers

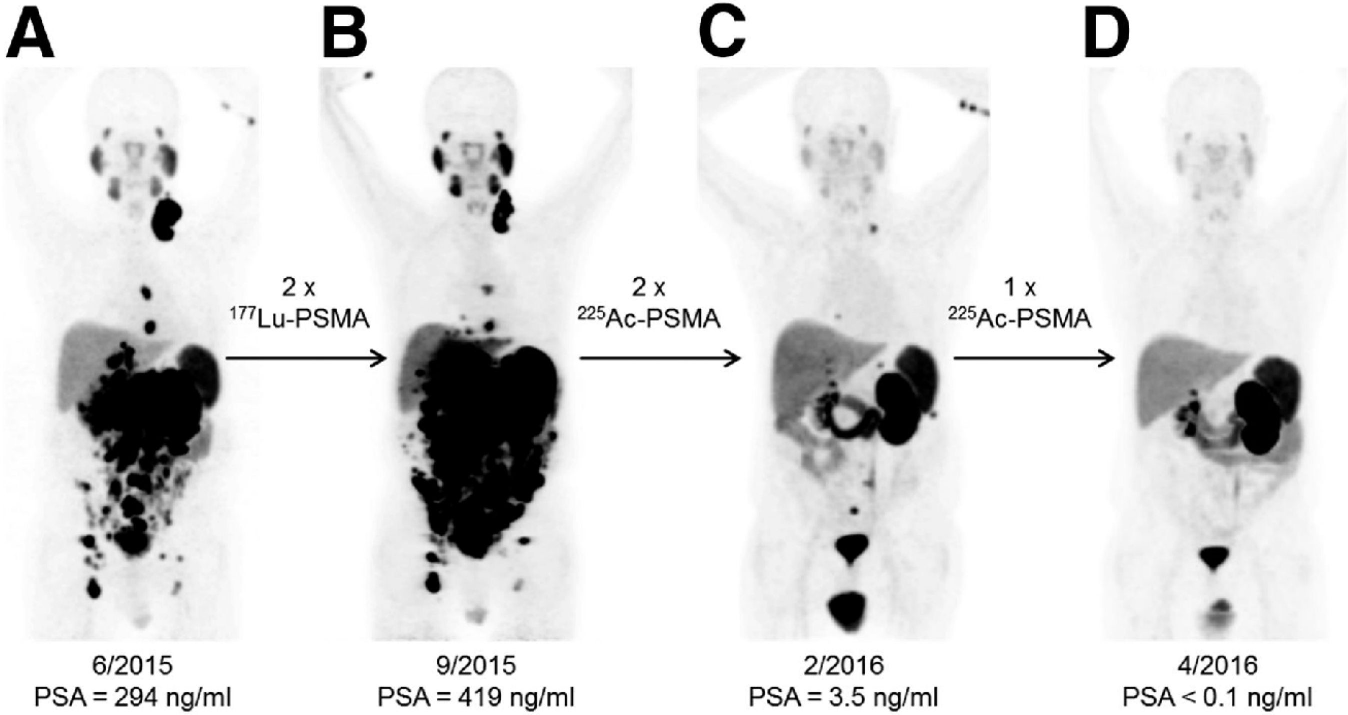
A Glimmer of Hope: Complete cures of advanced-stage cancer with the administration of ^{225}Ac-PSMA617 was reported, recently.

One of the hottest topics in Cancer Research

PET Image with ^{68}Ga

a patient, who had peritoneal carcinomatosis and liver infiltration

腹膜に癌が播種し、肝臓にも浸潤が認められる患者

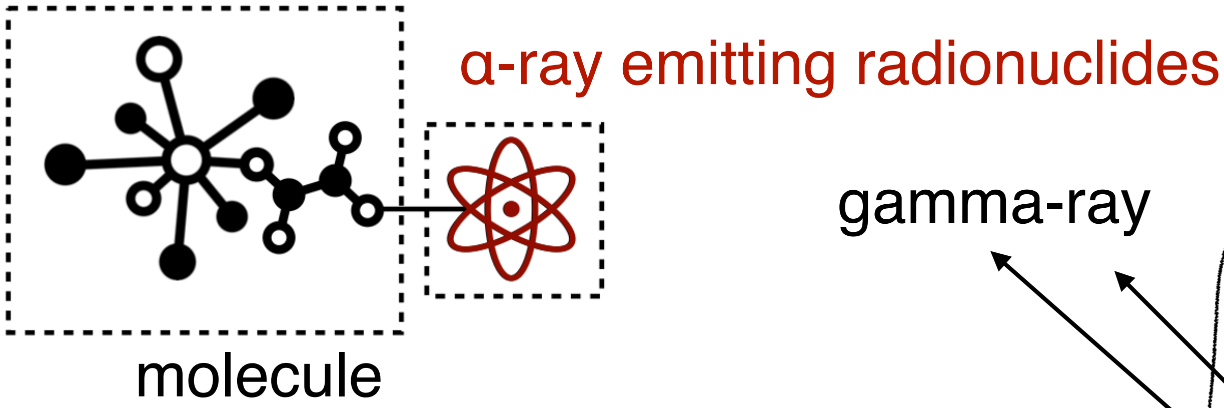


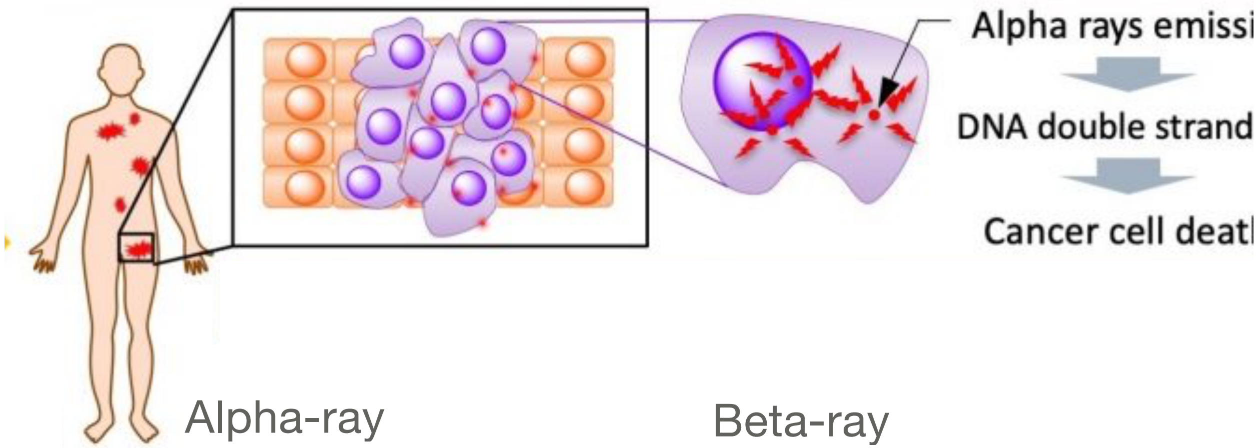
Kratochwil et al. (2016)

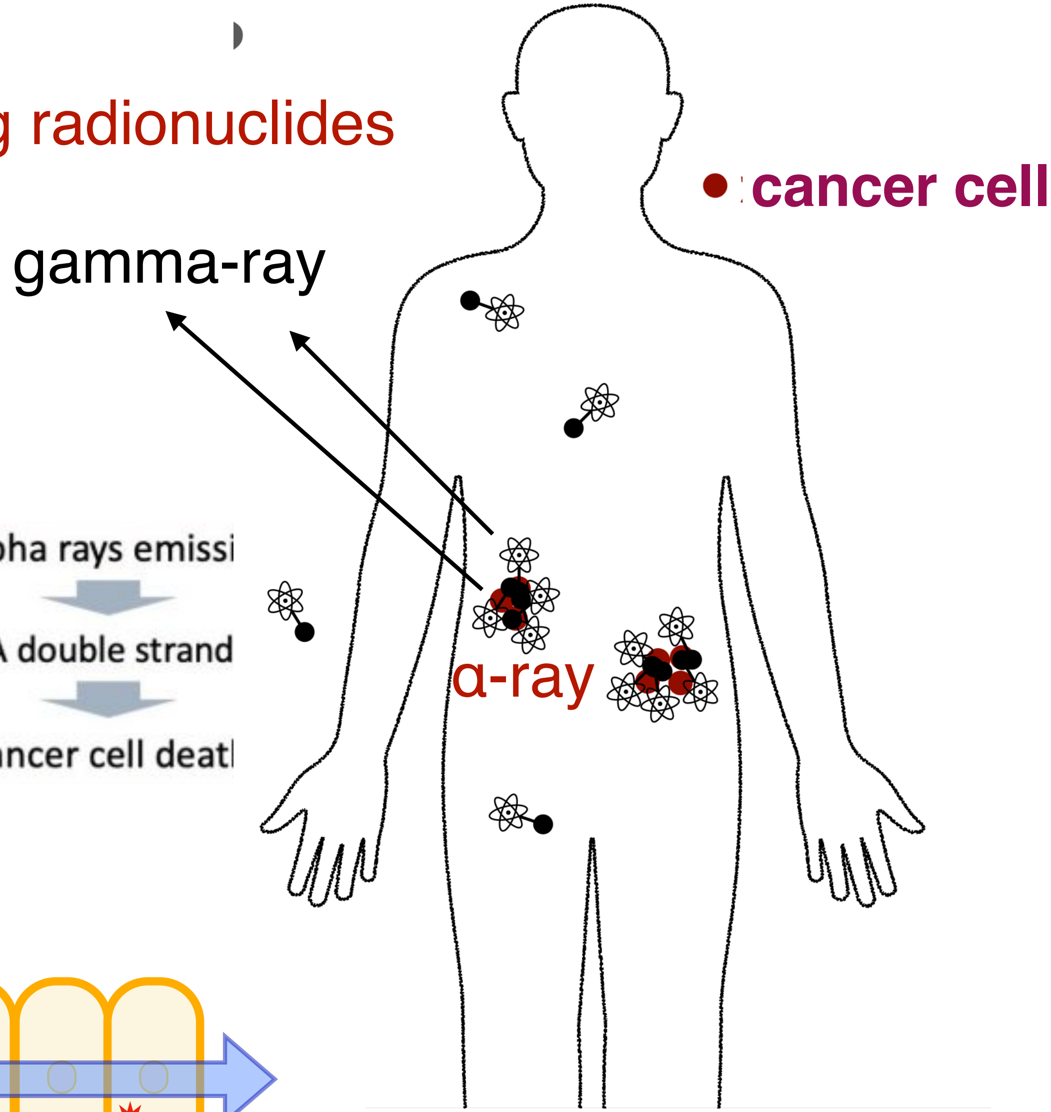
Injection of ^{177}Lu (β-ray) ⟶ Injection of ^{225}Ac(α-ray)

PSMA (Prostate Specific Membrane Antigen), referred to in Japanese as "前立腺特異的膜抗原," is a protein located on the surface of prostate cancer cells. Its expression can increase by tens to hundreds of times in cases of high malignancy or progressive metastasis.

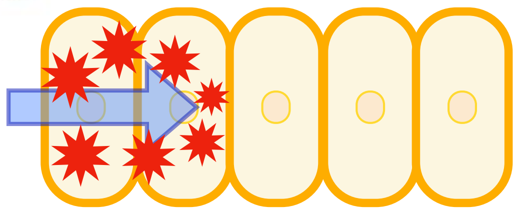
Targeted Alpha-ray Therapy





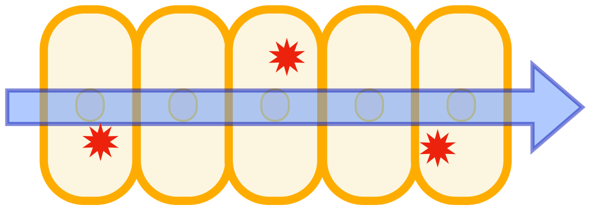


Alpha-ray



Short range & LET = 100 keV/μm

Beta-ray



Long range & LET = 0.8 keV/μm

Drawing by S.Takeda

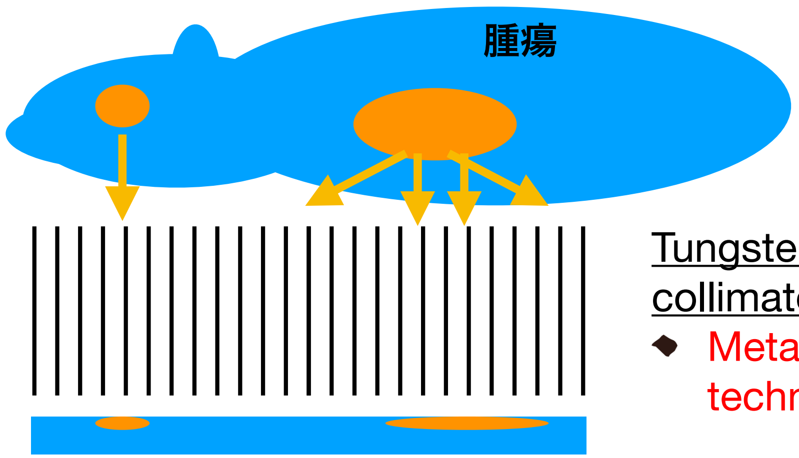
New Treatment Method (Alpha-Particle Radiotherapy)

→Delivering radio-pharmaceuticals labeled with α-ray emitting radionuclides directly to cancer tissues and monitoring their accumulation to assess therapeutic efficacy.

1) An advanced imaging system that accurately maps the distribution of radiopharmaceuticals within the body is crucial for predicting treatment efficacy and potential side effects.
2) To develop alpha-emitting radiopharmaceuticals, initiating studies with small animals is essential.

To effectively image gamma-rays and hard X-rays emitted during alpha decay, <u>a highly sensitive imaging system</u> is essential, which <u>we are confident we can achieve.</u>

Empowering Cancer Drug Development: Advancing Sensor Technologies for Breakthroughs

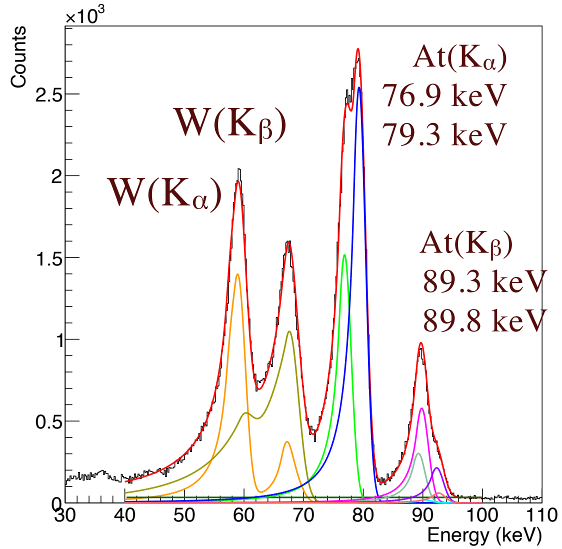


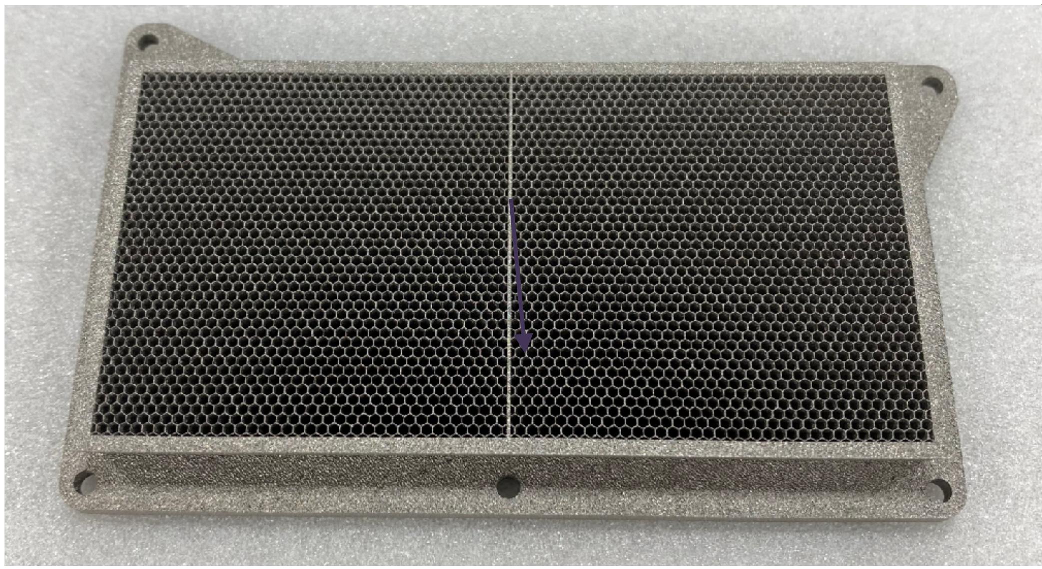
Tungsten parallel-hole collimator

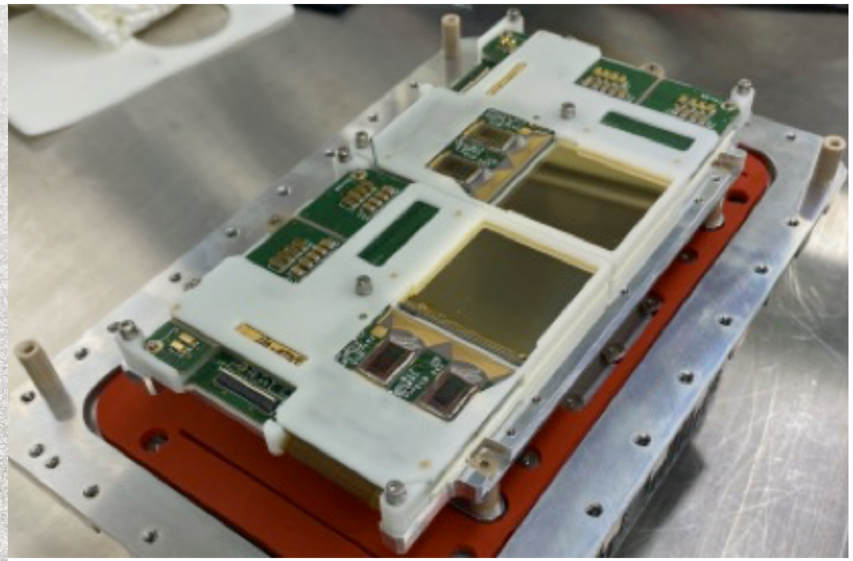
- Metal 3D printing technology

CdTe DSD(CdTe Double Sided Detecter)

^{211}At X-ray Spectrum





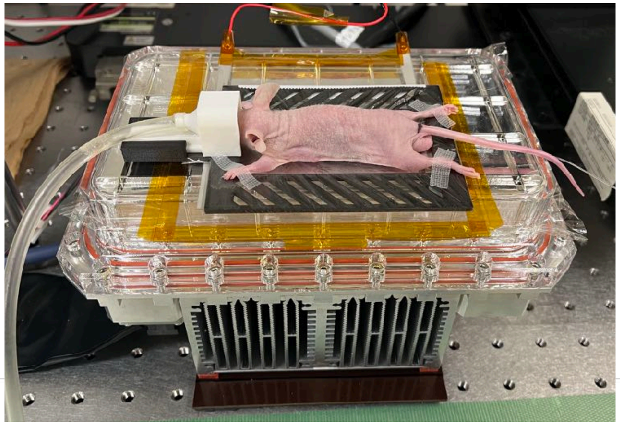


(with Toray Precision)

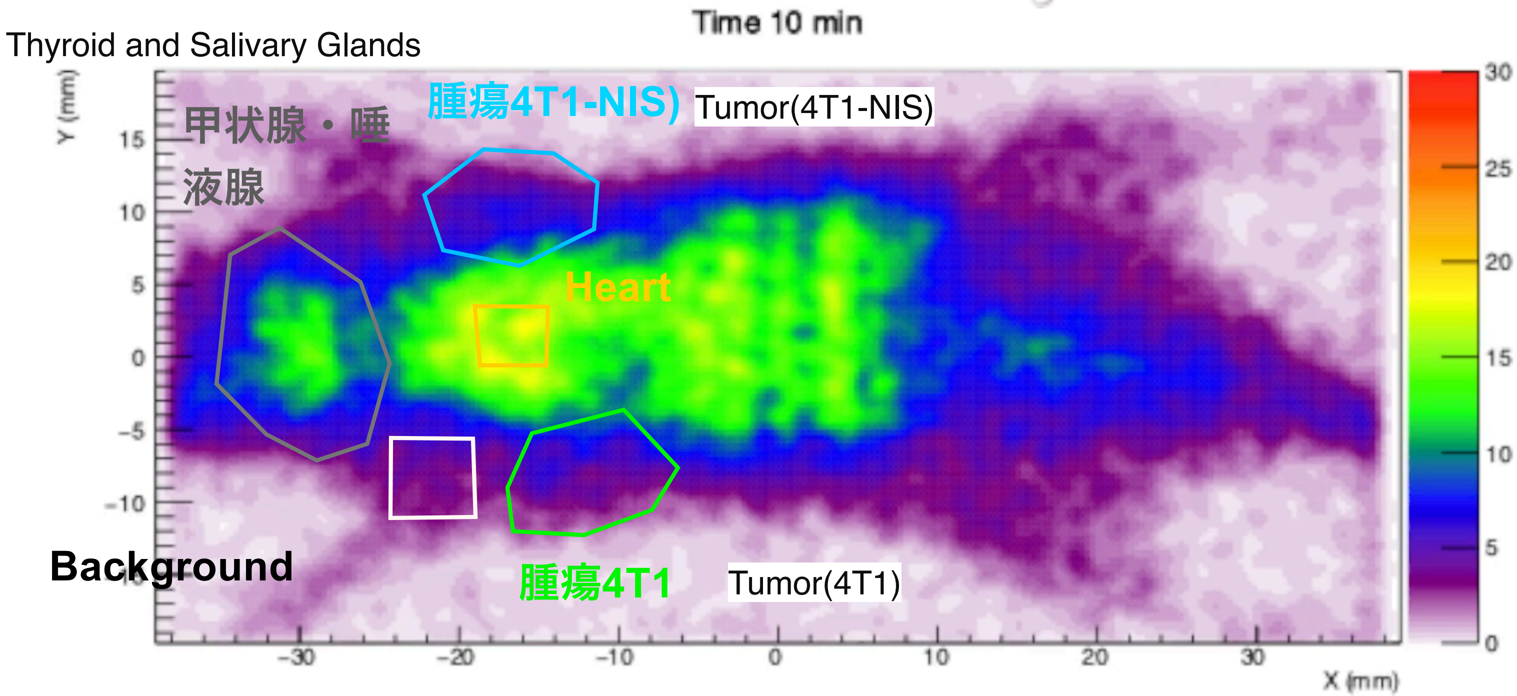
Courtesy iMAGINE-X

Started from a mouse (before human imaging)

Dynamic Imaging of ^{211}At in a mouse



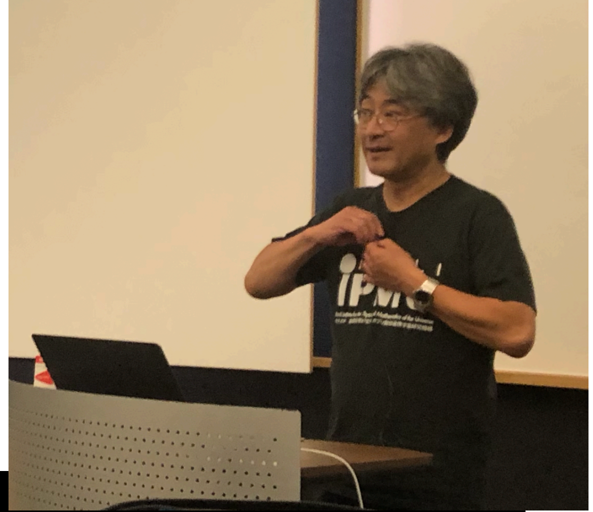
Imaging the Temporal Accumulation of a Radiolabeled Drug in a Tumor-bearing Mouse



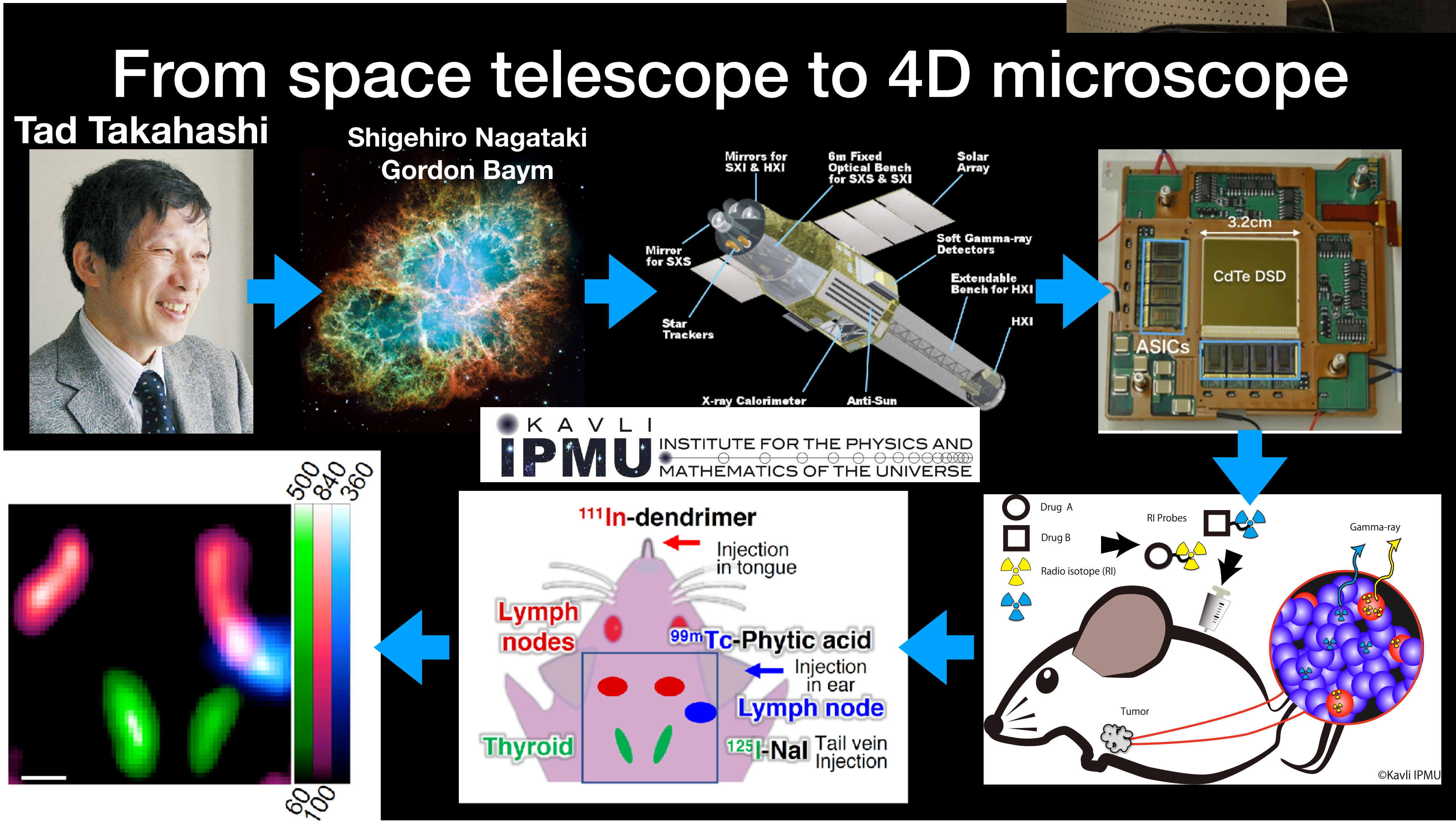
Katsuragawa et al. 2024)

Its excellent performance has been recognized, leading to the joint research with a BIG pharmaceutical company.

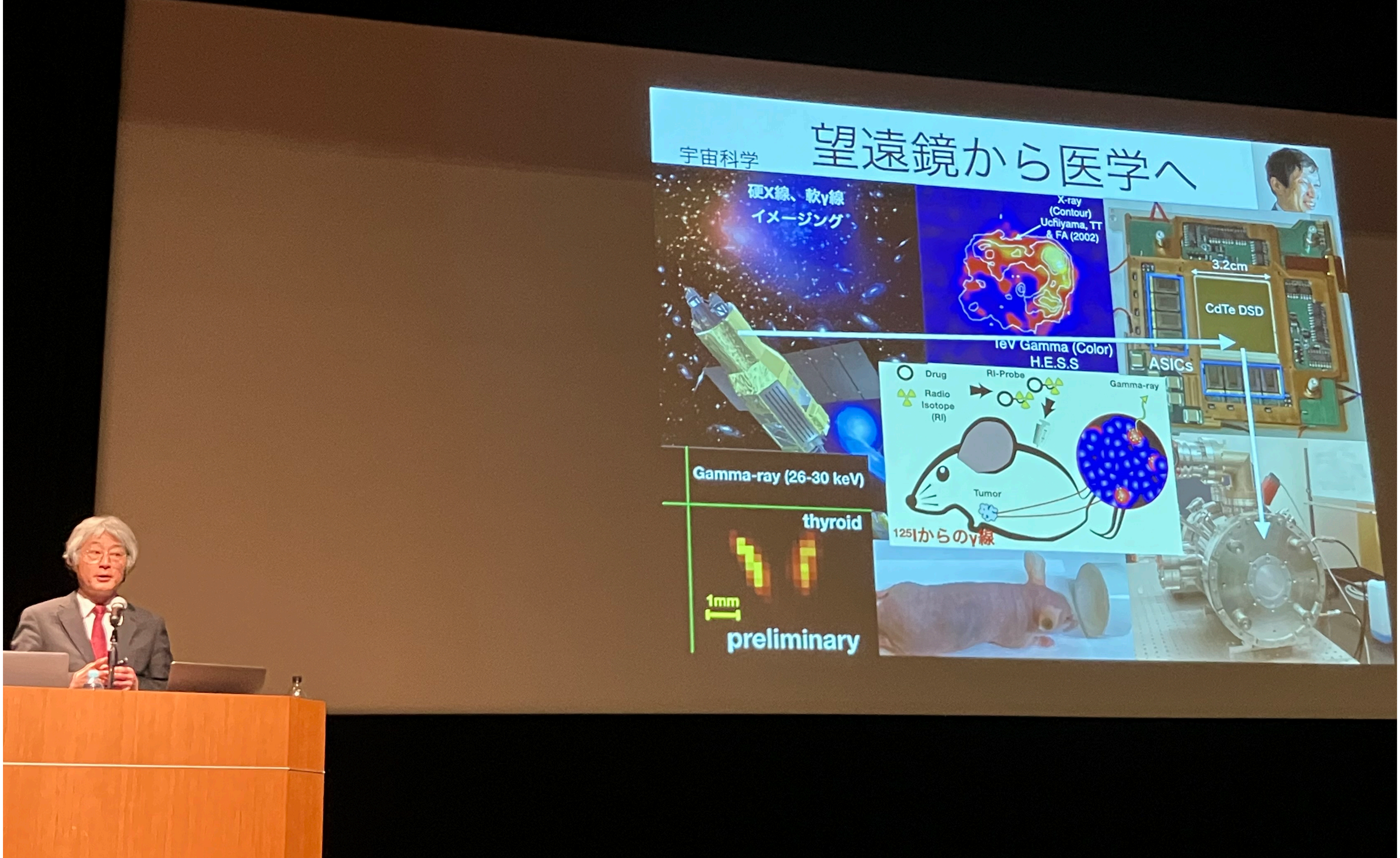
Hitoshi's Constant Support (1)



From his presentation at ISCO-2023



30th Anniversary Ceremony of the Advanced Science Research Center, JAEA
(December 6, 2023)



30th Anniversary Ceremony of the Advanced Science Research Center, JAEA
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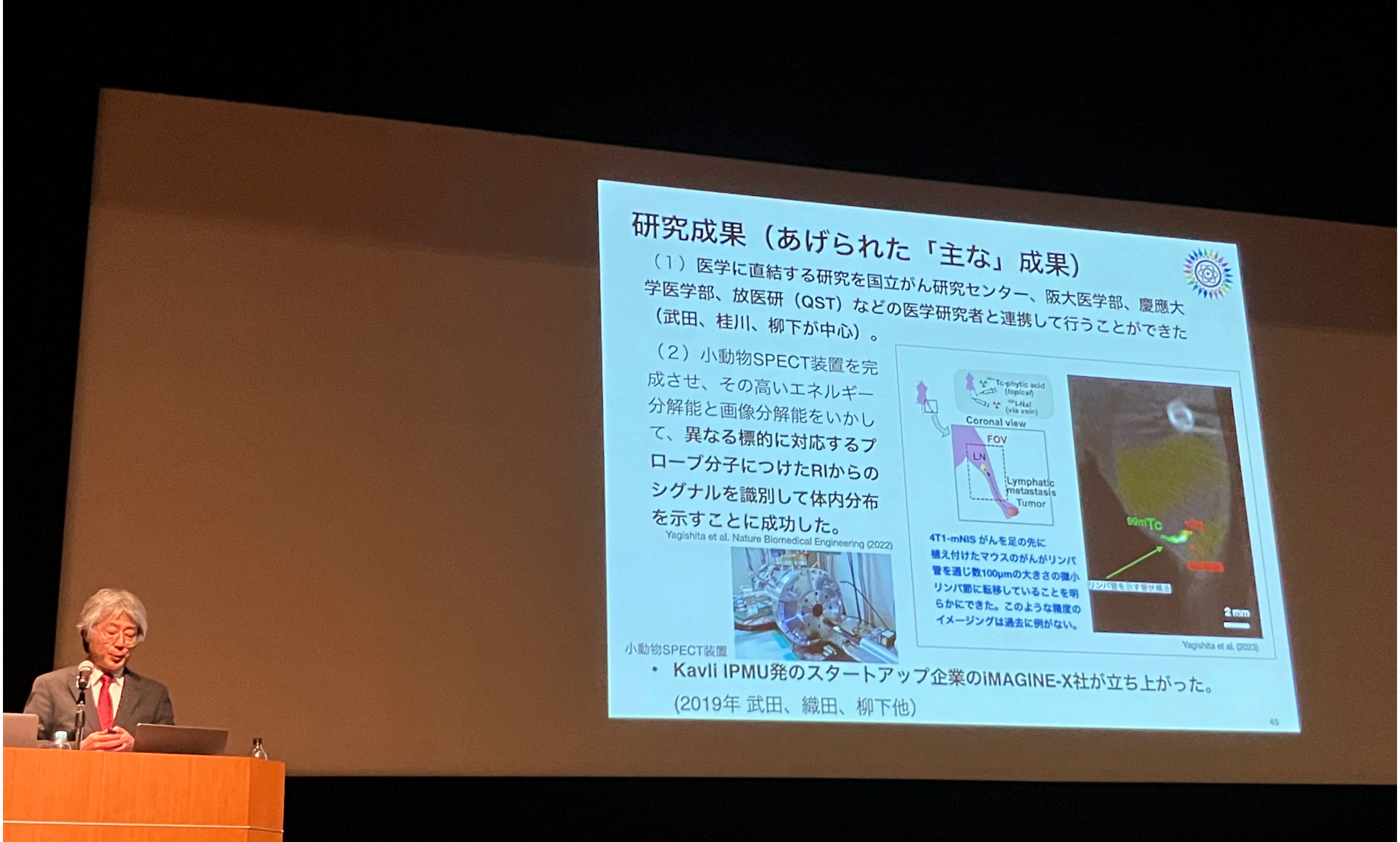


Scientific achievements from IPMU, primarily in the field of physics, have been featured in medical journals.

1. Simultaneous visualization of multiple radionuclides in vivo, A. Yagishita, S. Takeda, M. Katsuragawa, T. Kawamura, H. Matsumura, T. Orita, I.O. Umeda, G. Yabu, P. Caradonna, T. Takahashi, S. Watanabe, Y. Kanayama, H. Mizuma, K. Ohnuki, and H. Fujii, **Nature Biomedical Engineering** (2022, April)
2. New liposome-radionuclide-chelate combination for tumor targeting and rapid healthy tissue clearance, I.O. Umeda. Y. Koike, M.Ogata, E. Kaneko, S. Hamamichi, T. Uehara, K. Moribe, Y. Arano, T. Takahashi, H. Fujii, **Journal of Controlled Release** (2023, August)
3. CdTe-DSD SPECT-I: An Ultrahigh-Resolution Multi-isotope Tomographic Imager for Mice, S. Takeda, T. Orita, A. Yagishita, M. Katsuragawa, G. Yabu, R. Tomaru, F. Moriyama, H. Sugawara, S. Watanabe, H. Mizuma, Y. Kanayama, K. Ohnuki, H. Fujii, L. R. Furenlid, T. Takahashi, I**EEE Transactions on Radiation and Plasma Medical Sciences**(2023, Nov.)
4. Dual-radionuclide in vivo imaging of micro-metastasis and lymph tract with submillimetre resolution, A. Yagishita, S. Takeda, K. Ohnuki, M. Katsuragawa, O. Sampetrean, Hi. Fujii and T. Takahashi, **Scientific Reports** (2023, Nov.)
5. Development and Utility of an Imaging System for Internal Dosimetry of Astatine-211 in Mice.Atsushi Yagishita, M. Katsuragawa, S. Takeda, Y. Shirakami, K. Ooe, A. ToyoshimaT. Takahashi and T Watabe, **Bioengineering,** (2023 Dec.)
6. CdTe XG-Cam: A new high-resolution x-ray and gamma-ray camera for studies of the pharmacokinetics of radiopharmaceuticals in small animals, M. Katsuragawa, A. Yagishita, S. Takeda, T. Minami, K. Ohnuki, H. Fujii, T. Takahashi, **Medical Physics**. (2024 Aug.)

Kavli IPMU Spinoff: Translating Research Achievements into Societal Impact

iMAGINE-X

The primary focus of the startup is the commercialization of **our** technology for space gamma-ray observation, with a particular emphasis on medical applications.

Founding members

Hokuto Inoue
Shin'ichiro Takeda
Tadashi Orita
Atsushi Yagishtia

Technical advisor

Shin Watanabe
Tadayuki Takahashi

Selected Customers

国立がん研究センター

JAXA

高エネルギー加速器研究機構

量子科学技術研究開発機構

理化学研究所

大阪大学

電気通信大学

東京大学

名古屋大学

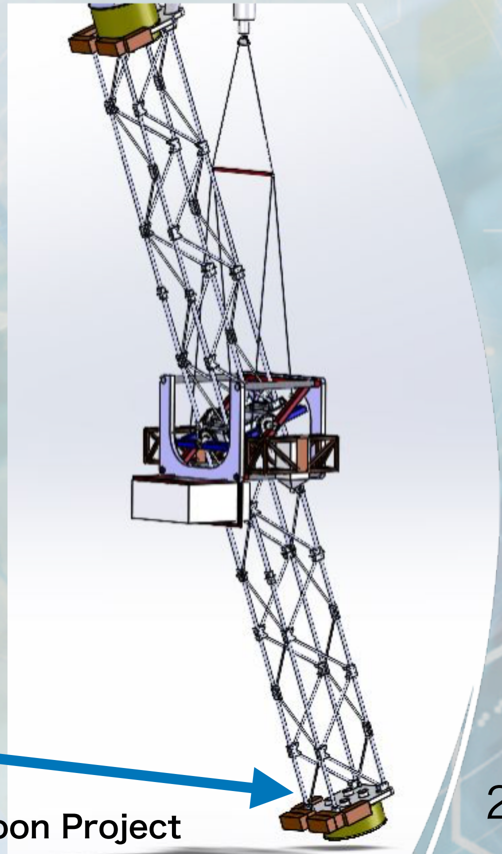
早稲田大学

京都大学

CEA（フランス原子力庁）

アンリツ

NASA



NASA's Super HERO Balloon Project

Another New Connection

NASA's New MeV gamma-ray satellite
(to be launched in 2027)

Particle Theory
x
Experiment

@IPMU

Subgroup	Lead	Co-Leads	Technical Expert(s)
Positrons	Carolyn Kierans (GSFC)	Thomas Siegert (JMU, Germany)	Thomas Siegert (JMU, Germany)
Nucleo-synthesis	Thomas Siegert (JMU, Germany)	Chris Fryer (LANL)	Hiroki Yoneda (JMU, Germany)
GRBs	Eric Burns (LSU)	Steve Boggs (UCSD), Dieter Hartmann (Clemson)	Alyson Joens (UCB) Eliza Neights (GSFC)
Galactic	Julien Malzac (IRAP, France)	Chris Karwin (GSFC)	Chris Karwin (GSFC)
Extragalactic	Marco Ajello (Clemson)	Fabrizio Tavecchio (INAF, Italy)	Jarred Roberts (UCSD)
Dark Matter	Tad Takahashi (IPMU, Japan)	Fabrizio Tavecchio (INAF, Italy), Shigeki Mastumoto (IPMU, Japan), Tom Melia (IPMU, Japan)	Thomas Siegert (JMU, Germany)

To solve Positron Puzzle

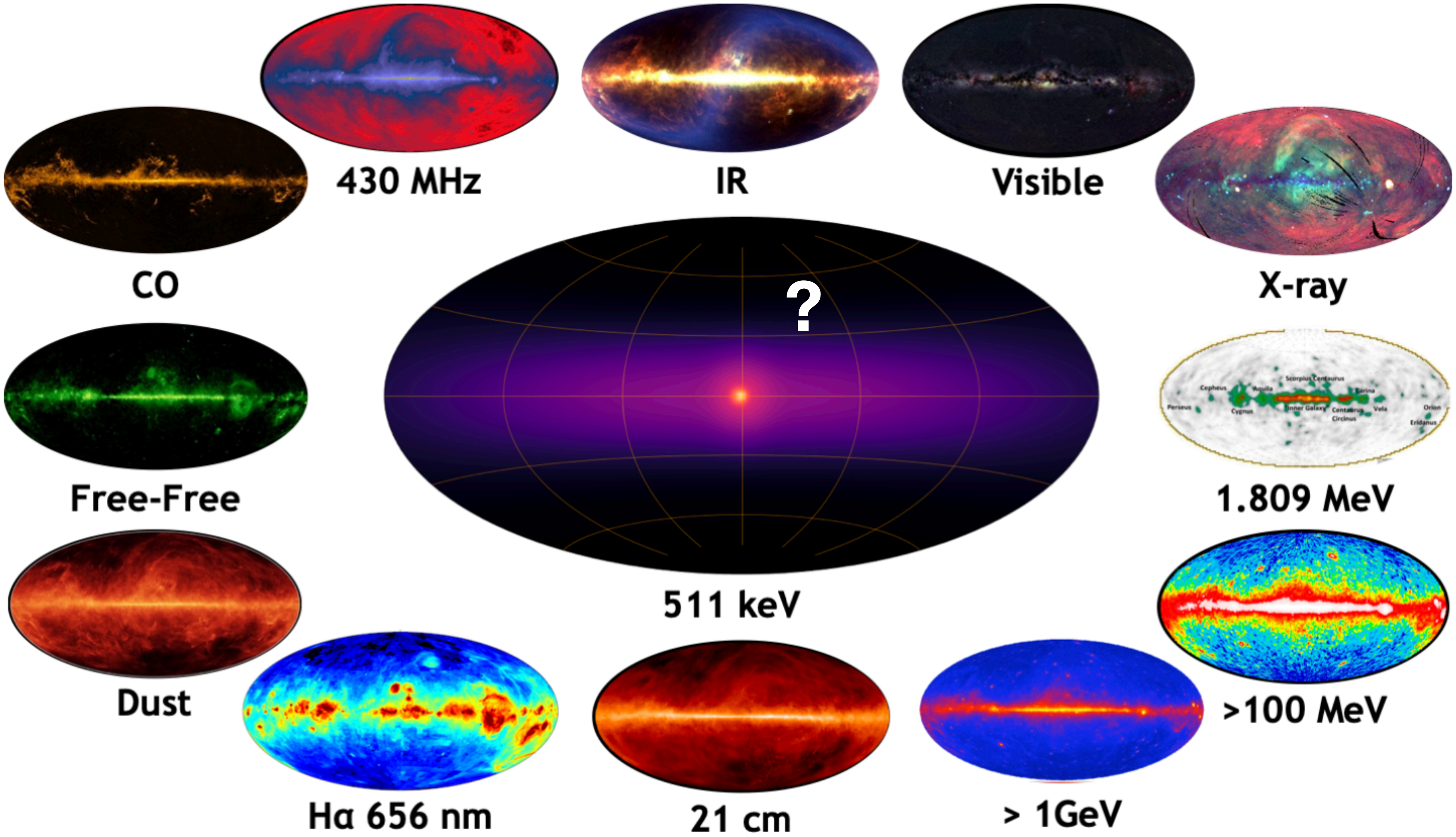


Fig. 1 Full-sky maps at different wavelengths and emission processes compared to a maximum likelihood solution from INTEGRAL/SPI data at 511 keV (Siegert et al, 2016b).

Congratulations on your 60th birthday!

Thanks to Hitoshi's vision and initiative in creating new opportunities, we were able to form an interdisciplinary team. This has opened the path for applying the sensors developed for fundamental science to broader societal contributions.

Thank you very much for everything you have done for us.

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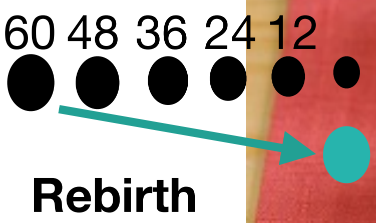
Dragon!



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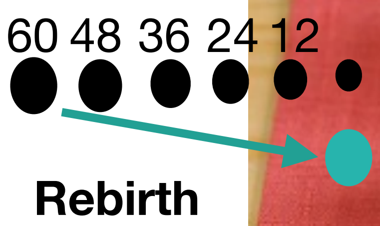
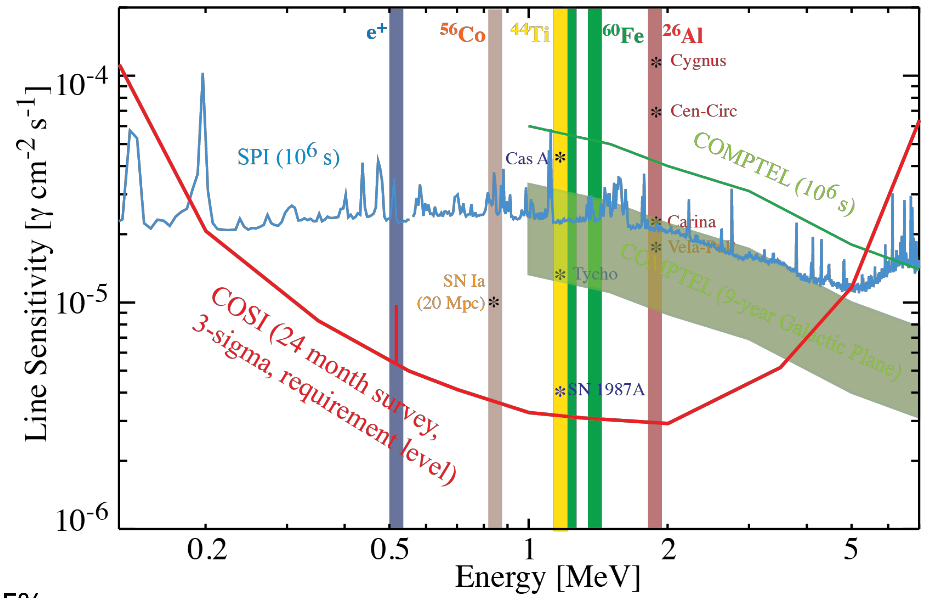


We wish you continued success in all your endeavors.

Measurement requirements for emission line goals

Characteristic	Requirement
Sky Coverage	• >25%-sky instantaneous FOV • 100%-sky each day
Energy Resolution* (FWHM)	• <1.2% @ 0.511 MeV • <0.8% at 1.157 MeV (^{44}Ti)
Narrow Line Sensitivity (2 yr, 3σ, point source)	[photons cm^{-2} s^{-1}] • 1.2x10^{-5} @ 0.511 MeV • 3.0x10^{-6} @ ^{26}Al, ^{60}Fe, and ^{44}Ti
Angular Resolution (FWHM)	• <4.1° @ 0.511 MeV • <2.1° @ 1.8 MeV (^{26}Al)



*Notes on energy resolution:

- For fully reconstructed Compton events (average of 2.5 interactions)
- 1.157 MeV requirement is <0.8% FWHM; capability estimate ~0.4-0.5%