بسمه تعالی

جمهوری اسلامی ایران
وزارت بهداشت، درمان و آموزش پزشکی
اداره کل همکاری های بین الملل

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پیوست ..... دارد

جناب آقای دکتر شاهمرادی
سرپرست محترم امور تجهیزات و ملزومات پزشکی
جناب آقای دکتر وطن پور
رئیس محترم دفتر توسعه فناوری سلامت

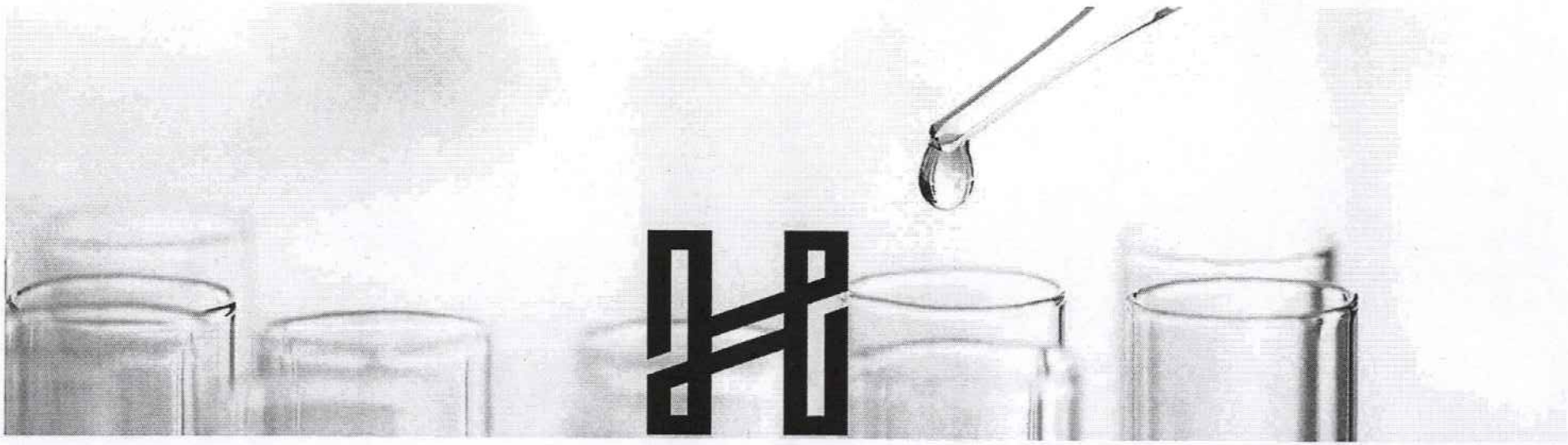
سلام علیکم

با احترام، با عنایت به اعلام آمادگی شرکت ژاپنی Hirotsu Bio Science تولید کننده کیت تشخیص سرطان جهت همکاری با شرکت های علاقمند دانش بنیان و یا مراکز تحقیقاتی پزشکی کشورمان، ضمن ایفاد اطلاعات مربوط به توانمندی های آن شرکت، خواهشمند است دستور فرمایید، نسبت به بررسی مراتب و اعلام نظریه به این حوزه اقدام مقتضی معمول نمایند.

دکتر محسن اسدی لاری
مدیرکل همکاری های بین الملل

نشانی پستی: تهران-شهرک قدس (غرب)،فاز۵ ، خیابان سیمای ایران ، ساختمان ستاد مرکزی وزارت بهداشت ،درمان و آموزش پزشکی،طبقه۱۲
تلفن تماس: ۸۸۳۶۳۷۱۴ نمابر: ۸۸۳۶۳۷۱۵ وب سایت: http://iad.behdasht.gov.ir پست الکترونیک: iad@mohme.gov.ir

HIROTSU BIO SCIENCE
N-NOSE



HIROTSU
BIO SCIENCE

HIROTSU BIO SCIENCE Inc.

What if

a drop of your urine sample allows us

to diagnose your cancer risk

regardless of its type or stage?

HIROTSU
BIO SCIENCE

And what if

that risk assessment could

save your life?

HIROTSU
BIO SCIENCE

Cancer – Present and Future

- Leading cause of death worldwide:
  8.7 million deaths in 2015 - WHO

- In 2030, it is expected to rise to
  13 million

- Global economic impact of premature death and disability from cancer:

  ≒ US$ 900 billion (JPY 100 trillion)

- OECD 2013

Cancer Stages and Mortality

5-year survival rate

	Stomach		Colon	Rectal
	Stage	(%)	Stage	(%)	(%)
Early	**IA**	**93.4**	**0**	**94.8**	**92.9**
	IB	87.0	I	90.6	89.3
	II	68.3	II	83.6	76.4
	IIIA	50.1	IIIa	76.1	64.7
	IIIB	30.8	IIIb	62.1	47.1
Late	**IV**	**16.6**	**IV**	**14.3**	**11.1**

(Japanese Gastric Cancer Association, Japanese Society for Cancer of the Colon and Rectum)

Early Detection

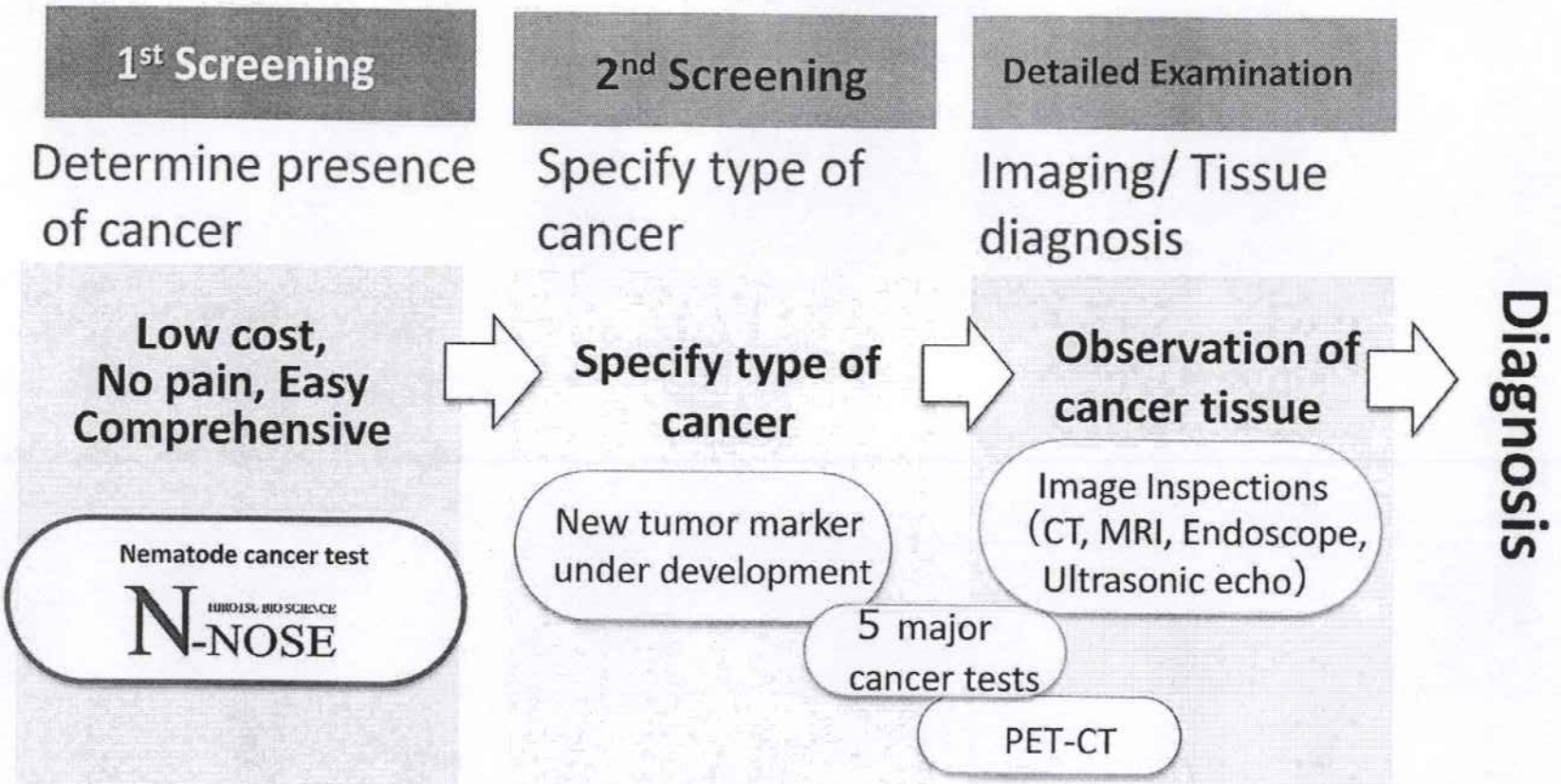
So, we know early detection is the key to stamping out cancer

But the question is of course, *"How?"*

Existing technology cannot offer a solution
Maybe behavioral change is required?

That's where the new concept of "1st Cancer Screening" comes into the picture

Ideal Cancer Screening Process



Ideal 1st screening test was nonexistent until N-NOSE® appears

Tumor marker

What's N-NOSE®?

HIROTSU BIO SCIENCE
N-NOSE

Cancer screening test that can detect presence or absence of cancer from…

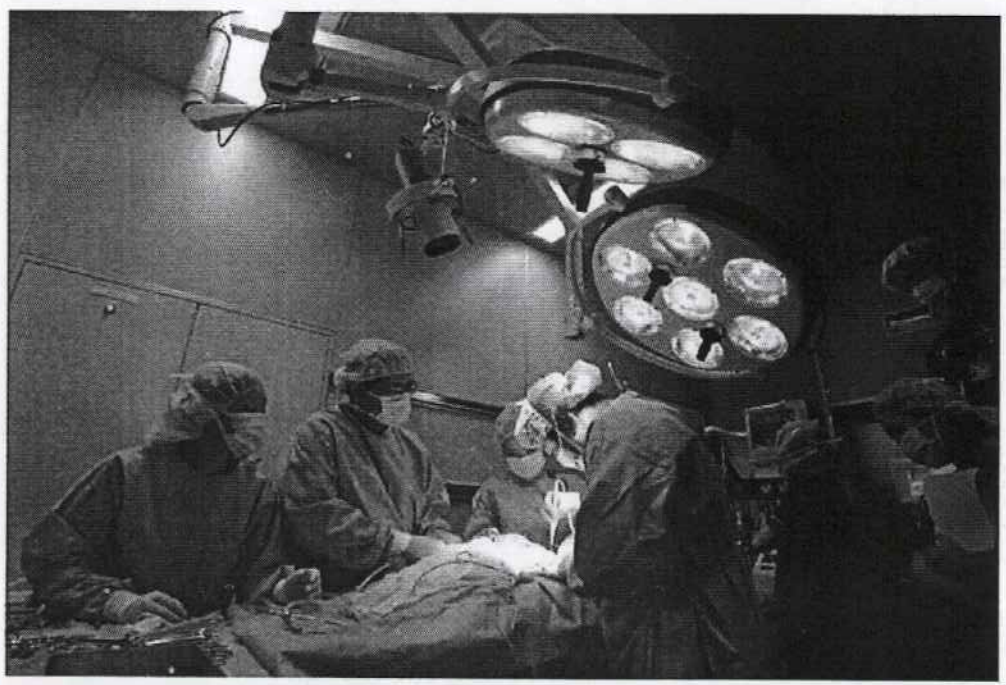
A drop of urine

&

C. elegans

Odor in Cancer

It has been reported that
Cancer patients have specific odorants



For a new cancer test, a new marker is required
→ We focused on "odor"

What's *C. elegans*?

C. elegans (Caenorhabditis elegans)

= A species of Nematode (Roundworm)

- Transparent, about 1 mm in length
- 4 days for alternation of generations
- Hermaphrodites
- Lays 100-300 eggs at a time
- Little individual differences
- Good olfactory system

Easy to
- Keep
- Raise
- Duplicate

at low cost

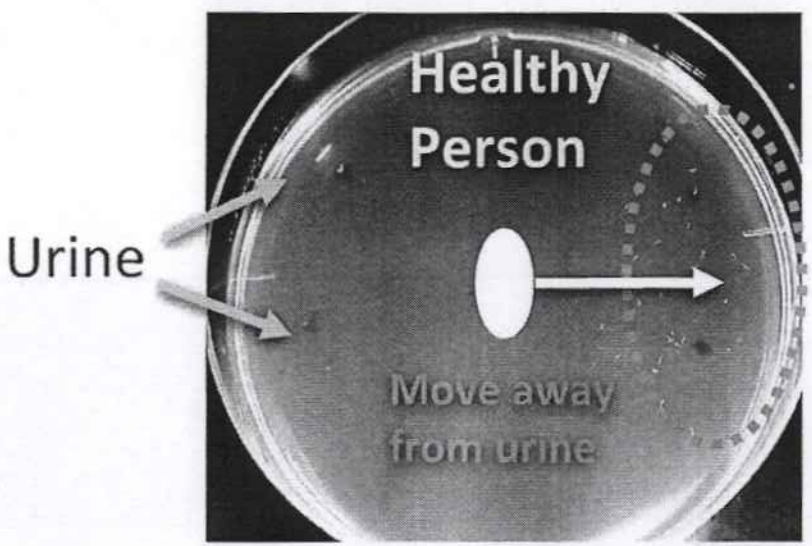
Good Olfactory System

Olfactory receptors bind directory to odors

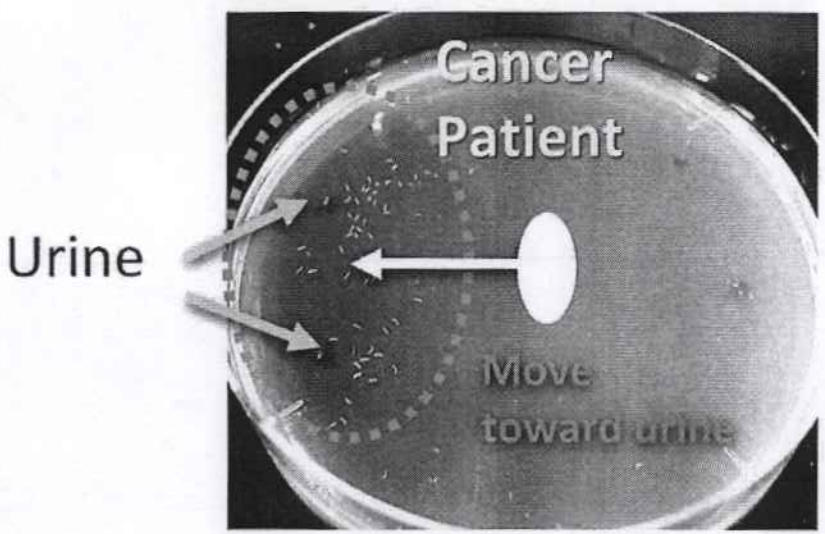
The number of olfactory receptor genes				
Human	Dog	Mouse	*Drosophila*	*C. elegans*
400	800	1,100	60	1,200

Chemotaxis – *C. elegans*

Response to urine from healthy person/ cancer patient



C. elegans move away from the urine of a healthy person



C. elegans move toward the urine of a cancer patient

Why Not Dogs?

- Accuracy depends on the dog's individual differences and conditions

- Keeping dogs is costly

↓

Could be a $2,000 test

Six Prominent Features of N-NOSE

Convenient

The test requires a small amount of urine, just as in a typical health checkup

Inexpensive

Inexpensive since nematodes are inexpensive to breed

Highly accurate

Sensitivity of approximately 85% (as of August 2019)

Early detection is possible

Early detection of cancers as early as Stages 0 and 1 according to clinical studies

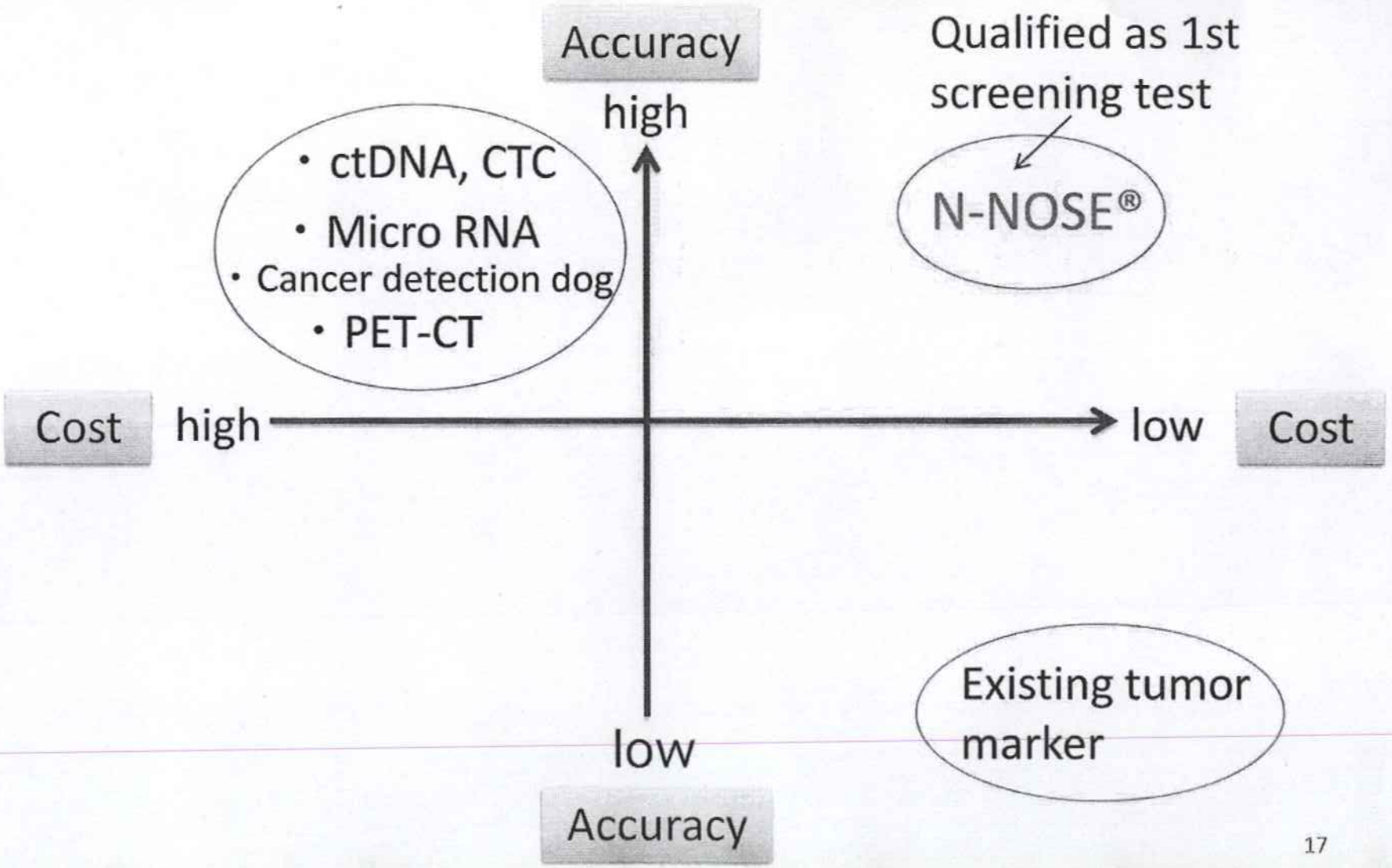
Non-invasive

All what is required is a drop of urine and non-invasive to your body

Detect cancers regardless of locations

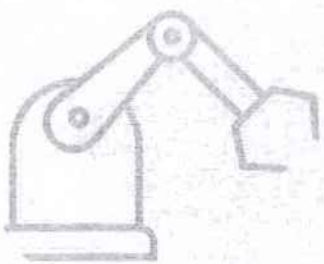
Able to detect cancers regardless of their locations in one test

Essentials for 1st Screening



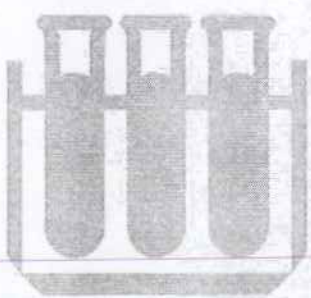
From R&D to Commercial Stage

Indispensable factors for commercialization



★ Automatic analysis machine

(Through-put increase)

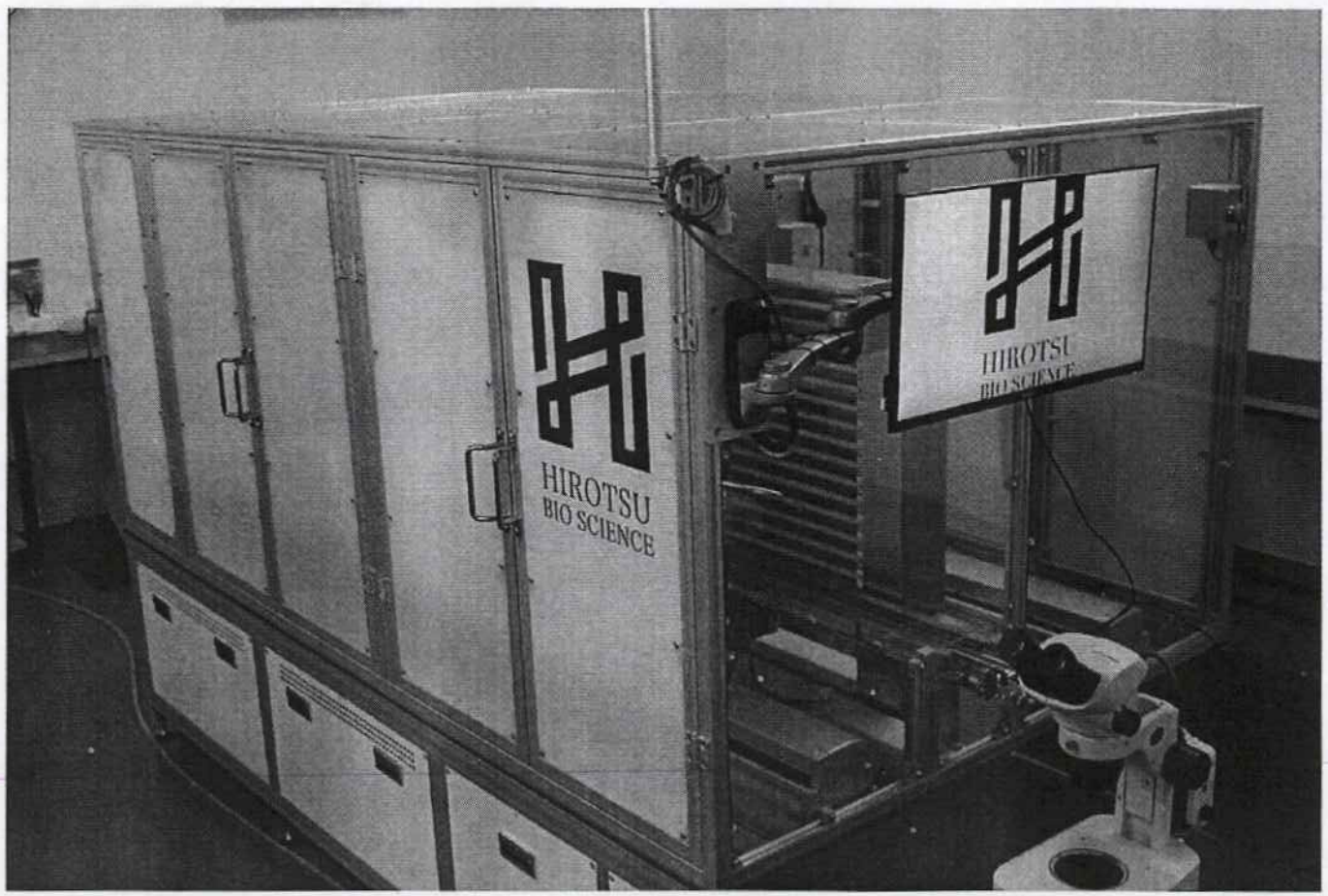


★ Clinical study

(Large scale samples)

Automatic Analysis Machine

Completion of prototype automatic analysis machine



Throughput - Manual vs Automatic

Manual

5 analysis/ day

(per analyst)

Automatic

100 analysis/ day

(per machine)

*Assume 8 hours/ day

In addition, the machine realizes

Temperature control: $\pm 0.1\,^{\circ}C$

Time control: *Second-by-second monitoring*

Basic Study Achievements

Technology based on our knowhow of Nematode Analysis

Science Reprint

Olfactory Plasticity Is Regulated by Pheromonal Signaling in *Caenorhabditis elegans*

Koji Yamada, Takaaki Hirotsu, Masahiro Matsuki, Rebecca A. Butcher, Masahiro Tomioka, Takeshi Ishihara, Jon Clardy, Hirofumi Kunitomo, Yuichi Iino

24 September 2010
Volume 329, pp.1647-1650

ARTICLE

Received 20 Dec 2011 | Accepted 14 Feb 2012 | Published 13 Mar 2012

Odour concentration-dependent olfactory preference change in *C. elegans*

Kazushi Yoshida, Takaaki Hirotsu, Takanobu Tagawa, Shigekazu Oda, Tokumitsu Wakabayashi, Yuichi Iino & Takeshi Ishihara

nature neuroscience

A trophic role for Wnt-Ror kinase signaling during developmental pruning in *Caenorhabditis elegans*

Yu Hayashi, Takaaki Hirotsu, Ryo Iwata, Eriko Koge-Nakadai, Hirofumi Kunitomo, Takeshi Ishihara, Yuichi Iino & Takeo Kubo

OPEN

Temporally-regulated quick activation and inactivation of Ras is important for olfactory behaviour

A role for Ras in inhibiting circular foraging behavior as revealed by a new method for time and cell-specific RNAi

From Basic Study to Clinical Study

N-NOSE® results of Japanese samples

As of December 2019

	Positive / Number of cases	Sensitivity
Cancer patients	**1442 / 1739**	**82.9%**

	Negative / Number of cases	Specificity
Healthy control	**525 / 614**	**85.5%**

＊"Healthy control" includes who visited hospitals for suspected cancer

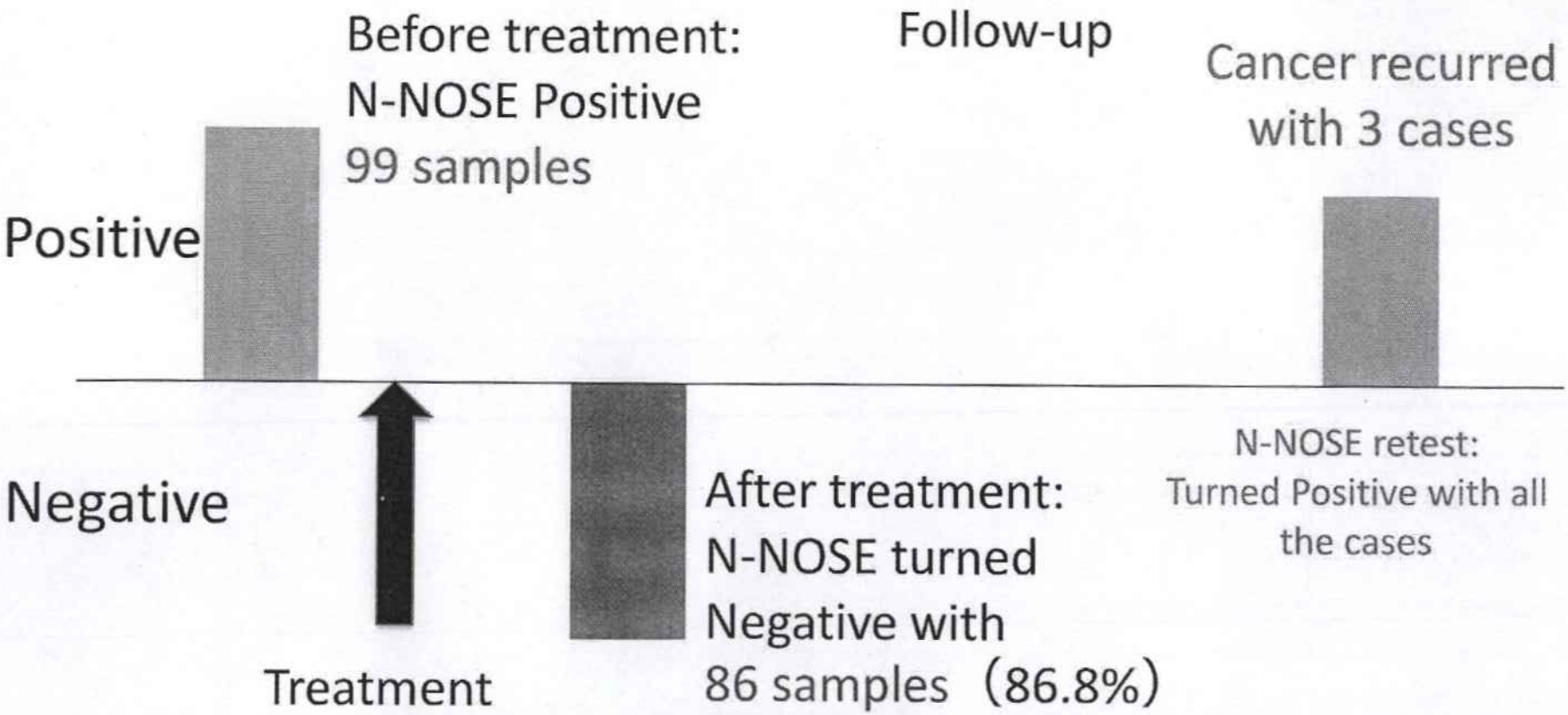
15 Cancer Types

C. elegans respond to 15 cancer types

(As of August 2019)

Stomach	Liver	Prostate
Colorectal	Bile duct	Bladder
Lung	Gall bladder	Breast
Kidney	Ovarian	Esophageal
Pancreatic	Uterine	Oral/Pharyngeal

Detection of Cancer Recurrence



The reaction of *C. elegans* changed

→ ***C. elegans* do react to the odor of cancer**

High Sensitivity – Early Cancer

Sensitivity of N-NOSE® at each stage of cancer
(As of October 2018)

	N-NOSE	CEA	CA19-9
Stage 0-1	87.0%	13.8%	13.8%
Stage 3-4	87.8%	38.3%	52.5%

Patent Status 1

Reference Number	Title of the Invention	Types of Patent Application	National Number/ International Application Number	Office	Filing Date	Applicant	Registration Number
PND14001JP	CANCER DETECTION METHOD USING SENSE OF SMELL OF NEMATODE	National Phase	2015552555	JP	2014/12/10	HIROTSU BIOSCIENCE INC.	6336481
PND14001US		National Phase	15/103,264	US	2014/12/10	HIROTSU BIOSCIENCE INC.	
PND14001EP		National Phase	14870595.7	EP	2014/12/10	HIROTSU BIOSCIENCE INC.	3081935 *Registered in 18 countries
PND14001CN		National Phase	201480075291.9	CN	2014/12/10	HIROTSU BIOSCIENCE INC.	ZL201480075291.9
PND14001KR		National Phase	10-2016-7018261	KR	2014/12/10	HIROTSU BIOSCIENCE INC.	
PND14001SG		National Phase	11201604743Q	SG	2014/12/10	HIROTSU BIOSCIENCE INC.	11201604743Q
PND14001IN		National Phase	201617022947	IN	2014/12/10	HIROTSU BIOSCIENCE INC.	
PND14001MY		National Phase	PI2016001088	MY	2014/12/10	HIROTSU BIOSCIENCE INC.	
PND14001MO		Extensions of Chinese Patents	J/003171	MO	2014/12/10	HIROTSU BIOSCIENCE INC.	J/003171
PND14001HK		Extensions of Chinese Patents	17103012.9	HK	2014/12/10	HIROTSU BIOSCIENCE INC.	HK1229424

Patent Status 2

PNE16001	METHOD FOR EVALUATING TAXIC BEHAVIOR IN RESPONSE TO ODOR SUBSTANCE BASED ON OLFACTORY SENSE IN NEMATODES AND DISH IN EVALUATION METHOD	National Filing	JP2016177664	JP	2016/9/12	HIROTSU BIOSCIENCE INC.	6164622
PNE17001TW		Foreign Application	106130931	TW	2017/9/11	HIROTSU BIOSCIENCE INC.	
PNE17001JP		National Phase	2018538496	JP	2017/9/11	HIROTSU BIOSCIENCE INC.	
PNE17001US		National Phase	16/332164	US	2017/9/11	HIROTSU BIOSCIENCE INC.	
PNE17001AU		National Phase	2017323139	AU	2017/9/11	HIROTSU BIOSCIENCE INC.	
PNM19001	METHOD, SYSTEM AND PROGRAM FOR CHEMOTAXIS ANALYSIS, AND METHOD FOR EVALUATING CANCER RISK	National Filing	in preparation	JP		HIROTSU BIOSCIENCE INC.	
PND17002JP	COMPOUND FOR IMPROVING SENSITIVITY OF OLFACTORY PERCEPTION OF NEMATODE	National Phase	2019510234	JP	2018/3/30	HIROTSU BIOSCIENCE INC.	

Patent Status 3

PND17003JP	DIAGNOSTIC AGENT FOR CANCER CONTAINING NEMATODE MUTANT, AND METHOD FOR ASSESSING MIGRATORY BEHAVIOR USING SAID MUTANT	National Phase	2019510224	JP	2018/3/30	HIROTSU BIOSCIENCE INC.
PND17003AU		National Phase	20182465554	AU	2018/3/30	HIROTSU BIOSCIENCE INC.
PND17003CA		National Phase	3057970	CA	2018/3/30	HIROTSU BIOSCIENCE INC.
PND17004JP	METHOD FOR PREDICTING THERAPEUTIC EFFECT AND/OR RECURRENCE MONITORING IN CANCER PATIENTS	National Phase	2019510235	JP	2018/3/30	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL
PND17004US		National Phase	16/498895	US	2018/3/30	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL
PND17004EP		National Phase		EP	2018/3/30	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL
PND17004AU		National Phase		AU	2018/3/30	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL
PND17004CA		National Phase		CA	2018/3/30	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL
PND17004CN		National Phase		CN	2018/3/30	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL
PND17004KR		National Phase		KR	2018/3/30	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL

Patent Status 4

PND18001PCT	CANCER DETECTION METHOD FOR PETS	PCT International Application	PCT/ JP2019/031912	JP	2019/8/14	HIROTSU BIO SCIENCE INC. OSAKA UNIVERSITY
PNB19002	INFORMATION PROCESSING APPARATUS	National Filing	2019101645	JP	2019/5/30	HIROTSU BIO SCIENCE INC.
PND17005JP	CANCER DETECTION METHOD USING TISSUE SAMPLE	National Phase	2019529724	JP	2018/7/10	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL
PND17005US		National Phase		US	2018/7/10	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL
PND17005EP		National Phase		EP	2018/7/10	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL
PND17005AU		National Phase		AU	2018/7/10	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL
PND17005CN		National Phase		CN	2018/7/10	HIROTSU BIO SCIENCE INC. NANPUH HOSPITAL
PND17006JP	METHOD FOR DETECTING KIDNEY CANCER	National Phase		JP	2018/8/20	HIROTSU BIO SCIENCE INC. KUMAMOTO UNIVERSITY
PND17006US		National Phase		US	2018/8/20	HIROTSU BIO SCIENCE INC. KUMAMOTO UNIVERSITY
PND17006EP		National Phase		EP	2018/8/20	HIROTSU BIO SCIENCE INC. KUMAMOTO UNIVERSITY
PND17006AU		National Phase		AU	2018/8/20	HIROTSU BIO SCIENCE INC. KUMAMOTO UNIVERSITY
PND17006CN		National Phase		CN	2018/8/20	HIROTSU BIO SCIENCE INC. KUMAMOTO UNIVERSITY

Biological Diagnosis

Difference from other cancer test technologies:
Artificial machines or Organisms

When it comes to olfaction,
Organism is more accurate than machine

Nematodes = Low Cost

Totally new concept that realizes high accuracy and low cost at the same time

Society for Biological Diagnosis

President
Dr. Yasuyuki SETO
Director of the University of Tokyo Hospital

Director
Dr. Shinichi TAKAMOTO
San-IKUKAI Hospital
Honorary professor of The University of Tokyo

Director
Dr. Takashi IGARASHI
Director of National Center for Child Health and Development

Director
Dr. Keiko ONO
Professor
The Open University of Japan

Director
Dr. Masazumi ERIGUCHI
Shin-Yamate Hospital

Director
Dr. Kazuyuki CHAYAMA
Professor
Hiroshima University

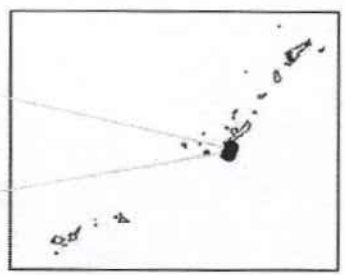
Director
Dr. Shomei RYOZAWA
Professor
Saitama Medical University

Director
Dr. Akira KURITA
Honorary Director of Shikoku Cancer Center

The society was found in August 2018,
to promote diagnosis using organism

Collaborative Studies

With 19 Hospitals and Medical Institutions in Japan



Hills Garden Clinic (Okinawa)

Naha Nishi Clinic (Okinawa)

Engaru Kosei Hospital (Hokkaido)

Ibi Kosei Hospital (Gifu)

Saitama Medical Univ. International Medical Center (Saitama)

JA Onomichi General Hospital (Hiroshima)

Kyoto Prefectural Univ. (Kyoto)

Osaka Univ. (Osaka)

Todachuo General Hospital (Saitama)

Hiroshima Univ. (Hiroshima)

Ageo Central General Hospital (Saitama)

HBS Fukuoka R&D Center

Univ. of Tsukuba Hospital (Ibaraki)

Kurume Univ. (Fukuoka)

Shin-Yamanote Hospital (Tokyo)

JA Inazawa Hospital (Aichi)

HBS Kashiwa R&D Center

Kumamoto Univ. (Kumamoto)

Tokushima Univ. (Tokushima)

HBS Matsuyama R&D Center

Nampu Hospital (Kagoshima)

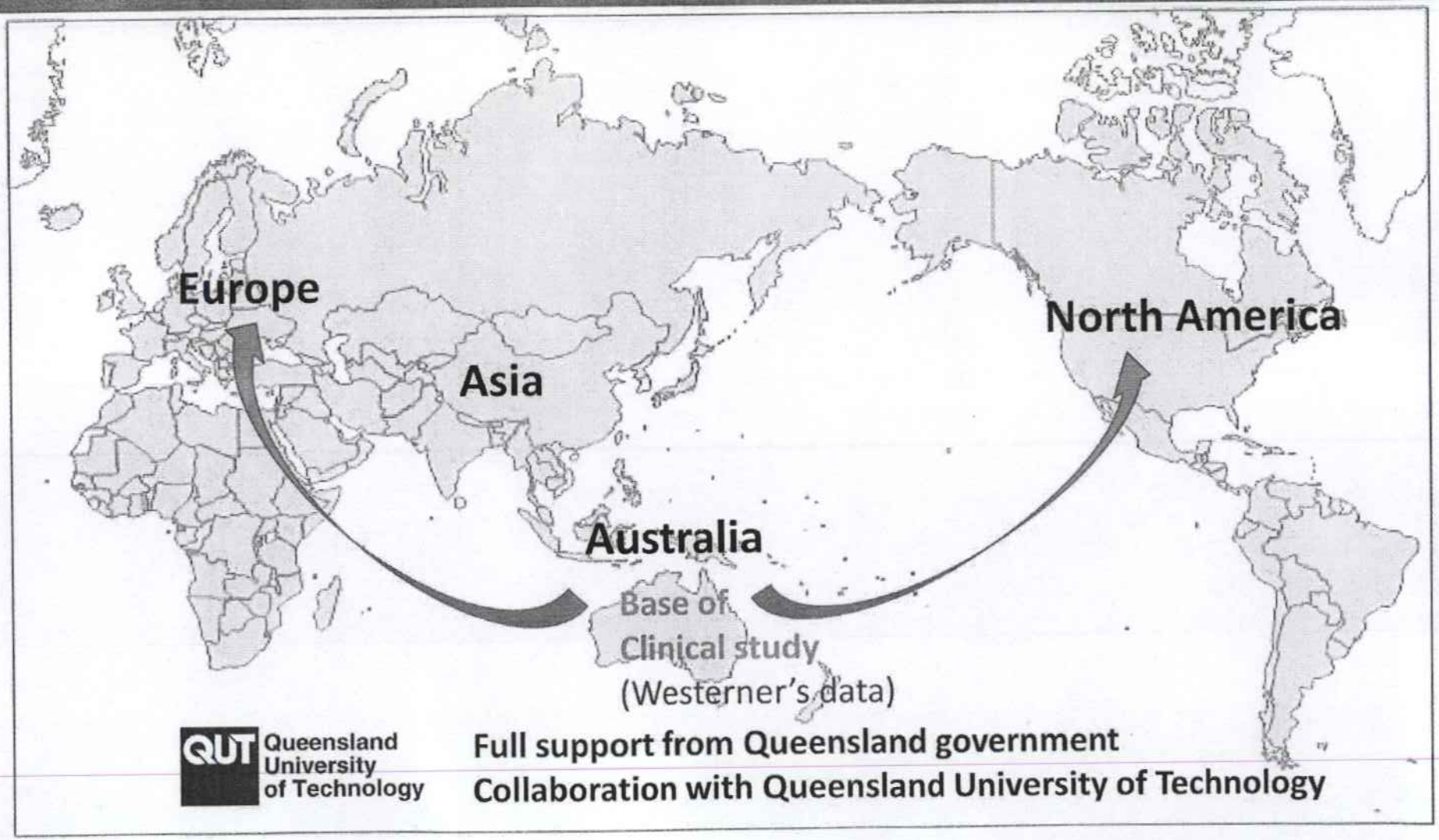
Shikoku Cancer Center (Ehime)

Queensland University of Technology (Australia)

Collaboration in Australia

With Mr. Cameron Dick, Minister of State Development, Queensland
(Aug 21, 2018)

Global Expansion



Queensland University of Technology

Full support from Queensland government

Collaboration with Queensland University of Technology

N-NOSE® Brings a Paradigm Shift

Right now, getting a cancer diagnosis is like
a death sentence for many

When N-NOSE® becomes widely available,
we can have cancers discovered and cured early

Then, the time will come when we feel happy
to get a cancer diagnosis

HIROTSU BIO SCIENCE INC.

Head Office
2F Forum Bldg., 2-24-11 Minamiaoyama Minato-ku, Tokyo,
107-0062, Japan
Tel. +81-3-6277-8902
Fax. +81-3-6277-8905

Capital 2,566,017,000 yen (Including capital reserve)

President & CEO Takaaki Hirotsu

Business Overview
Biological Diagnostics Research:
Research, development, and sale of cancer diagnostic test utilizing *C. elegans* and *C. elegans*olfactory sensors

HIROTSU
BIO SCIENCE