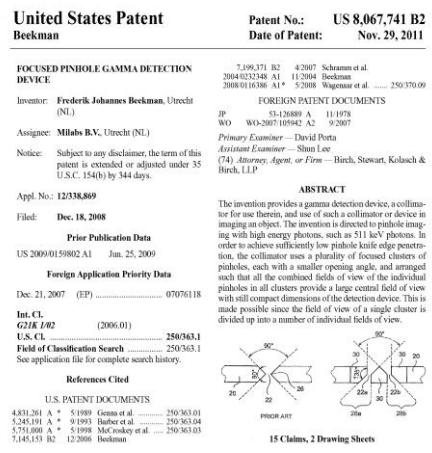
MILabs TODAY

Making Molecular Imaging Clear

10th Anniversary Edition

## Patent Offices Recognize MILabs' PET Innovation



United States Patent
Beekman

Patent No.: US 8,067,741 B2
Date of Patent: Nov. 29, 2011

FOCUSED PINHOLE GAMMA DETECTION DEVICE

Inventor: Frederik Johannes Beekman, Utrecht (NL)

Assignee: Milabs B.V., Utrecht (NL)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 344 days.

Appl. No.: 12/338,869

Filed: Dec. 18, 2008

Prior Publication Data

US 2009/0159802 A1 Jun. 25, 2009

Foreign Application Priority Data

Dec. 21, 2007 (EP) ..... 07076118

Int. Cl.
G21K 1/02 (2006.01)
U.S. Cl. ..... 250/363.1
Field of Classification Search ..... 250/363.1
See application file for complete search history.

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Primary Examiner — David Porta
Assistant Examiner — Shun Lee
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ABSTRACT

The invention provides a gamma detection device, a collimator for use therein, and use of such a collimator or device in imaging an object. The invention is directed to pinhole imaging with high energy photons, such as 511 keV photons. In order to achieve sufficiently low pinhole knife edge penetration, the collimator uses a plurality of focused clusters of pinholes, each with a smaller opening angle, and arranged such that all the combined fields of view of the individual pinholes in all clusters provide a large central field of view with still compact dimensions of the detection device. This is made possible since the field of view of a single cluster is divided up into a number of individual fields of view.

PRIOR ART

15 Claims, 2 Drawing Sheets

**Utrecht, 29 February 2016**

MILabs announced today that after the issue of US patent US8067741 and EU patent EP2073039, the patent offices of the largest countries in Europe have now also granted and published the national patents covering MILabs pioneering work on adaptive PET technology. These patents firmly establish the proprietary nature of MILabs' Stationary Clustered Pinhole (SCP) PET technology.

The inventor, Dr. Freek Beekman and his scientific collaborators at the Technical University of Delft - the Netherlands, commented "This patent application awards over 10 years man years of efforts and field-testing to develop sub-mm adaptive PET technology to a level that outperforms traditional coincidence PET for many preclinical applications."

## New clinical SPECT breakthrough

# MILabs G-SPECT lowers dose, refines resolution and enables dynamic SPECT

Conquering the sensitivity versus resolution trade-off has proved elusive to clinical SPECT developers for twenty years. To succeed, MILabs started therefore from an innovative but proven gyro-free animal SPECT design, then scaled it up for human imaging applications.

The result: a ten-fold improvement in resolution, a more than ten-fold reduction in required tracer dose and powerful dynamic SPECT capabilities.

The reward: recognized as the Innovation of the Year 2015 by the World Molecular Imaging Society.

This PET-like performance of G-SPECT is made possible by the use of a full ring of large stationary detectors. Images are projected at high magnification through many proprietary multi-pinhole collimators.

The outcome is the most powerful clinical SPECT system ever:

- Best resolution, < 3mm, a ten-fold improvement over current systems.
- The only dynamic SPECT - capable system.
- Allows a > 10-fold dose reduction, resulting in cost savings and enabling follow-up scans.
- Adaptable to user-specific studies.
- Fast, saves time and money.
- Reliable and stable: no wear-and-tear from rotating detectors and no instability or calibration problems from detector positioning imprecisions.


## Bestowed with awards

**Worldwide, 2006-2016**

For its game-changing clinical G-SPECT system, MILabs received in 2015 the prestigious Innovation of the Year award from the WMIS.

While this award underscores a ground-breaking innovation in the clinical market, it's just the latest in a long list making MILabs' products the most awarded preclinical imaging systems. Among the awards granted over the last ten years are:

- SNM 2006 Image of the Year
- F&S 2010 Medical Innovation Product Award
- FOM Valorisation Prize 2013
- WMIS 2015 Innovation of the Year award
- JNM 2016 Alavi-Mandell award

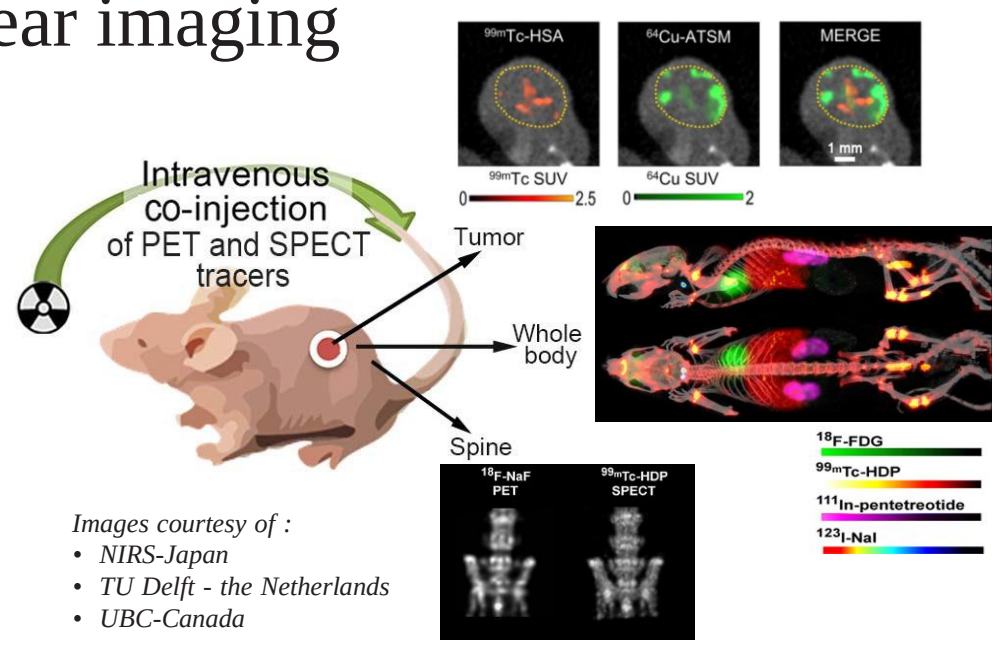
## Concurrent PET/SPECT™:

# Now you can exploit the full potential of preclinical nuclear imaging

When a breakthrough like Concurrent PET/SPECT imaging moves from a research concept to routine use in the preclinical lab, it's easy to get excited about the technology. After all, 0.75mm PET and 0.25mm SPECT resolution is remarkable by any standard.

But the true breakthroughs occur when users are able to start exploring different physiological and molecular functions at the same time, under identical physiological and physical conditions. Now you can perform studies that haven't been done before, no matter what modality used. Here are just a few examples:

- Theranostics: high-energy SPECT with FDG-PET treatment follow-up.
- Comparing immunoPET (e.g. $^{89}$Zr) to immunoSPECT (e.g. $^{111}$In).
- DAT-SPECT and FDG-PET to differentiate typical from atypical parkinsonian syndromes.
- PET/SPECT combined monitoring of treatment response (e.g. $^{111}$In-cetuximab and $^{18}$F-FDG).




*Images courtesy of :*
- *NIRS-Japan*
- *TU Delft - the Netherlands*
- *UBC-Canada*

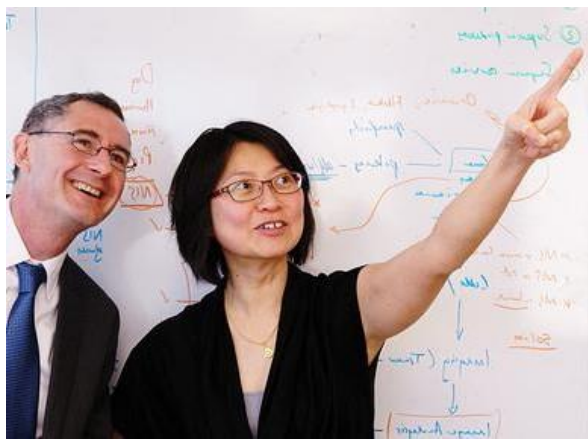
- Bone imaging with $^{99m}$Tc-MDP and $^{18}$F-NaF.
- Switching from preclinical SPECT to a clinical PET tracer.
- αβ plaques imaging: $^{99m}$Tc-HMPAO versus PET ($^{11}$C-PIB, $^{18}$F-amyloid).
- Concurrent perfusion and metabolism imaging to enhance the diagnostic value of cardiac imaging.
- Simultaneous vascularity ($^{99m}$Tc-HSA) and hypoxia ($^{64}$Cu-ATSM) imaging in tumors.
- Single scan comparisons of SPECT vs PET tracers e.g. $^{67}$Ga vs $^{68}$Ga, $^{125}$I/$^{123}$I/$^{131}$I vs $^{124}$I, $^{111}$In vs $^{64}$Cu chelation, etc...
- Elimination of positron range blurring by using analog SPECT rather than PET tracers.

MILabs

## Non-invasive translational reporter gene imaging at Imanis LS and Mayo Clinic

**Rochester - MN, 2015-2016**
Researchers at MayoClinic and Imanis Life Sciences are exploring oncolytic virotherapy as a novel therapeutic approach, using the destructive power of viruses to selectively infect and kill target tumor cells. The NIS reporter gene is used for non- invasive imaging of virus replication.

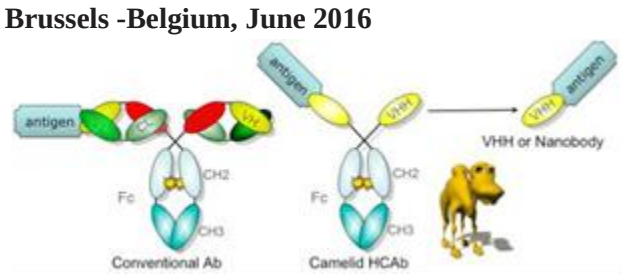
"In order to see the viral spread inside a tumor in a treated animal, we use the U-SPECT/CT system because it provides us with extremely high resolution SPECT images (< 0.25 mm). This enables us to track the expansion of individual infectious centers of a NIS-expressing oncolytic virus in a single tumor nodule of a living animal" explains Dr. Peng.



*Scientific co-founders of Imanis Life Sciences, Kah-Whye Peng, Ph.D. and Stephen J. Russel, M.D., Ph.D., professors at Mayo Clinic*

## Going single-domain: VECTor at ICMI-Brussels

**Brussels -Belgium, June 2016**




*Single-domain antibodies are isolated from camelid animals; the so-called VHH or Nanobody. A Nanobody corresponds to the variable region of a heavy chain of a camelid antibody and has a very small size of around 15 kDa.*

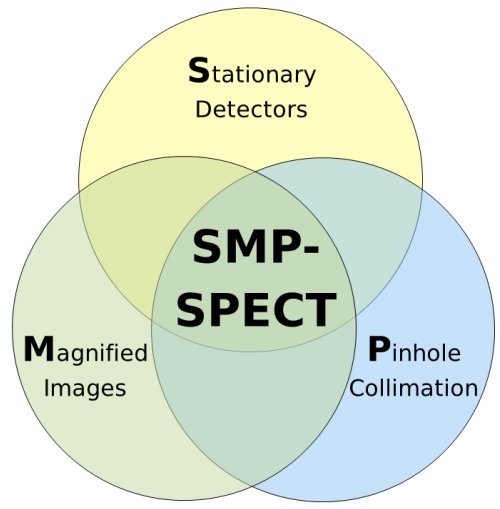
The In-Vivo Cellular and Molecular Imaging (ICMI) center at the Vrije Universiteit Brussel (VUB) leverages recombinant, small antigen- binding fragments that are derived from Camelidae heavy-chain-only antibodies, otherwise called VHH or Nanobodies, for the development of diagnostic imaging agents and radiotherapies.

Since the ICMI studies the flexibility to modify and label these single-domain antibodies with a wide variety of radioisotopes, such as $^{111}$In, $^{99m}$Tc, $^{18}$F, $^{68}$Ga and $^{177}$Lu, their research needs a high throughput, versatile *in vivo* screening system.

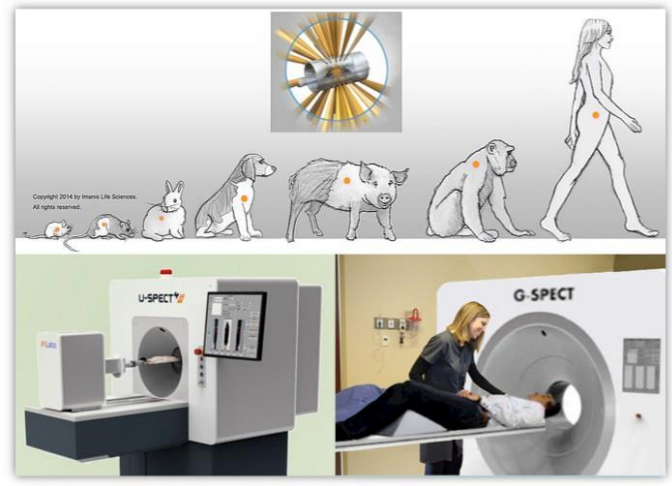
This *in vivo* approach enables ICMI to translate potential candidates quickly into phase 1 and 2 clinical trials. In this respect, the Concurrent PET/ SPECT modality of the MILabs VECtor system is crucial for ICMI's research. According to Dr. Tony Lahoutte, "The ability to image simultaneous SPECT and PET tracers in the same animal at exactly the same time, gives us unique information on certain combinations while providing maximum flexibility. For example if we decide to change from a preclinical SPECT labeled to a PET labeled Nanobody for clinicalphase 1 trails, we can easily compare these tracers one-on-one with the VECTor system".

## The science behind the breakthrough:
# Dynamic HighRez SPECT is finally here

*For diagnostic imaging, the application of dynamic SPECT has eluded many research teams for years. The reason is that all aspects of system design must be optimized to enable dynamic, high-resolution SPECT imaging:*




- Only stationary detectors can be made large enough and positioned with sufficient accuracy to enable high and precise magnification of projected images.
- High magnification is required in order to obtain SPECT images with reconstructed resolutions of < 0.25 mm for mice and < 2.5 mm for humans. For any imaging application, ranging from mice to humans, MILabs' proprietary SPECT technology will deliver image details not available from any other nuclear imaging technology.




*From mouse to humans: one technology, different species, the same outstanding SPECT performance. High resolution, low-dose, dynamic imaging. All capabilities which are typically associated with PET imaging only, are now exclusively available on MILabs' lower cost and simpler-to-use preclinical and clinical U-SPECT and G-SPECT systems.*

- Collimation through a large number of pinholes in combination with high image magnification yields high detection sensitivities, thus enabling for the first time, dynamic SPECT acquisitions with sub-second temporal resolutions. With SMP-SPECT you'll get extra diagnostic data with much lower tracer doses.
- Since SMP-SPECT technology uses gyro-free designs, there is no wear-and-tear from rotating detectors. The result: dramatically improved reliability and high uptime, plus no stability or calibration problems.

## Empowering molecular imaging with a scalable platform:
# MILabs adds fifth modality to its quad-modality upgradeable preclinical imaging platform

**New Concurrent PET/SPECT Modality: Simultaneous PET/SPECT in space and time:**

Although currently not yet accepted as a standard procedure in the molecular imaging community, Concurrent PET/SPECT imaging is opening the way to new PET/SPECT explorations by enabling to study molecular mechanisms and pathways *in vivo* under similar physiological conditions - with image contrasts unsurpassed by any other PET or SPECT system. In addition, perfect spatial and temporal co-registration greatly facilitates the switch from a SPECT-based approach to a PET-based approach if needed for human clinical applications.

**With innovation in every technology, there is more power behind every modality:**

- **SPECT:** best SPECT resolution, unique dynamic SPECT, up to 600 keV at sub-mm resolution.
- **PET:** best PET resolution, highest molecular S/N sensitivity.
- **PET/SPECT:** only PET and SPECT system offering both spatial and temporal registration.
- **Optical Imaging (OI):** bioluminescence, fluorescence and Cherenkov; single-pass OI/X-ray; exclusive OI/PET/CT and OI/SPECT/CT.
- **X-ray CT:** adaptive to your research: fast (< 5 s), high-resolution (< 4 μm), low-dose (< 5 mGy) .

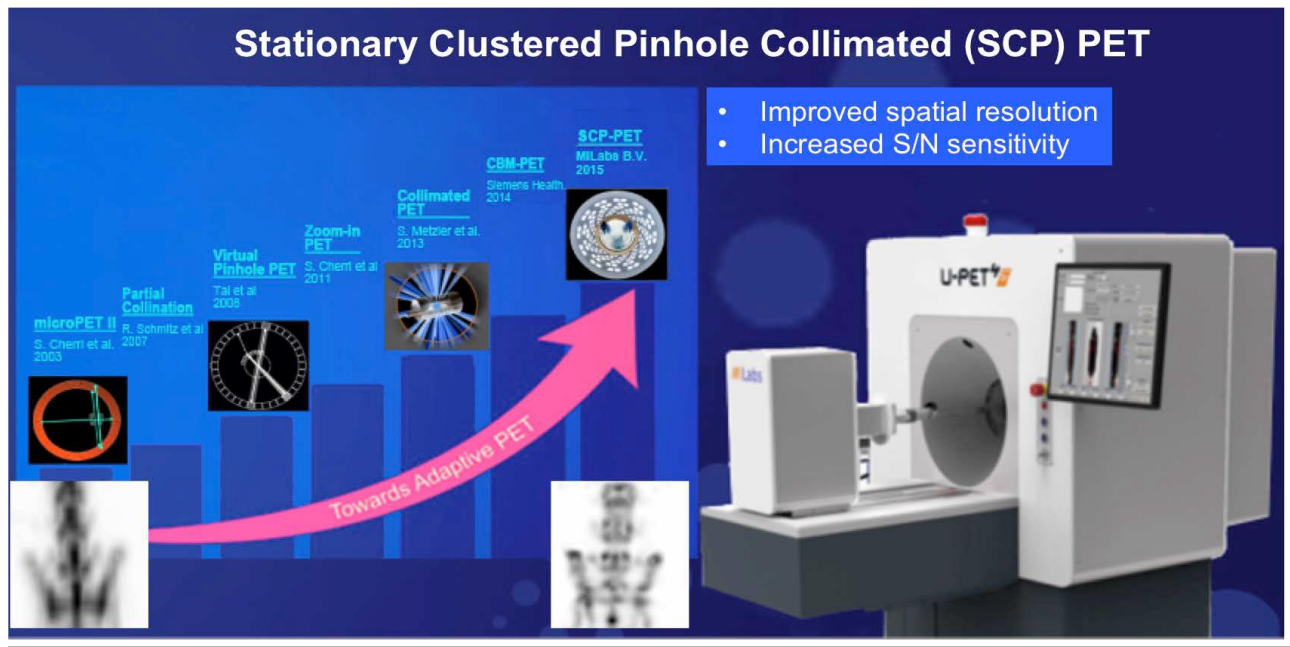

*VECTor PET/SPECT/OI/CT: Fully scalable. A system that can grow with your evolving research needs. Start with X-ray CT, end-up with multiple modalities. Up to five preclinical modalities in one single system - delivering performance far greater than the sum of its parts.*

## Introducing Adaptive PET:

# Towards quantitative PET imaging of organ substructures

**Delft - the Netherlands, 2016**

Through a co-development with TU Delft, MILabs has succeeded in completing the development of Adaptive PET. Over the last decade, many research groups have worked on improving the performance of coincidence PET by using magnified physical collimation rather than coincidence-based electronic collimation. Through the use of a proprietary SCP technology, MILabs Adaptive PET improves spatial resolution to below 0.75 mm and increases S/N sensitivity by eliminating noise from coincidence randoms and scatter. This makes it possible to accurately recover activity in lesions of < 1.0 mm, a requirement for imaging organ substructures in mice.




## MILabs' Concurrent PET/SPECT users worldwide report:

## Doing research that we have not been able to do before

*Prof. Yasuhisa Fujibayashi, PhD, DMedSci, Director Molecular Imaging NIRS, Chiba, Japan*

*Prof. Vesna Sossi, PhD Imaging Director of PET UBC, Vancouver, Canada*

*Prof. Tony Lahoutte, MD, PhD Head of Nuclear Medicine UZ/VUB Brussels, Belgium*


*Prof. Lidian Chen, MD, President of Fujian Univ., Fuzhou, China*

Despite the quite recent introduction of MILabs' Adaptive PET technology, many researchers around the world have already made this enabling *in vivo* imaging technology an integral part of their pre-clinical and translational research work.

From their comments in publications, scientific articles, and at conferences, the overall feeling is that Concurrent PET/SPECT as implemented on the VECTor/CT system, is enabling new diagnostic and treatment approaches.

According to researchers at the Japanese National Institute for Radiological Sciences (NIRS) under direction of Y. Fujibayashi: “We have developed a method to simultaneously visualize vascularity and hypoxia within HT-29 tumors using *in vivo* dual-isotope PET/SPECT imaging. By enabling us to simultaneously observe vascularity and hypoxia with high resolution in tumor microenvironments, we are able to enhance our studies on cancer biology with mouse tumor models, and develop more effective treatment strategies against cancer”.

In a recent publication, the group of Prof. V. Sossi of UBC reports that the VECTor/CT instrument enables simultaneous PET and SPECT at resolutions not previously achievable. “Preclinical PET can be performed at sub-mm spatial resolutions. In situations for which small ROI are imaged, the system provided images with higher resolution and contrast-to-noise ratios as compared with traditional coincidence PET".

Prof. T. Lahoutte of the VUB adds that Concurrent PET/SPECT imaging is very useful for their translational research on Nanobody therapies: "If we decide to change from a preclinical SPECT labeled Nanobody to a PET labeled Nanobody for clinical trials, we can easily compare these tracers one-on-one *in vivo* with the VECTor system".

Prof. Lidian Chen, President of Fujian University concludes:” We are excited to use the simultaneous PET/SPECT capabilities of VECTor/CT. This is a unique advantage for our Traditional Chinese Medicine research. For instance, now we can concurrently study the effect of acupuncture on brain metabolic function (using PET) and injury volume (with SPECT) using models of stroke.

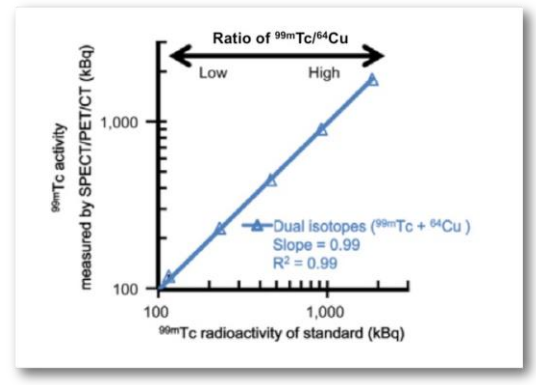
## Multi-institutional validation of Concurrent PET/SPECT

**Chiba - Japan, May 2016**

Researchers of the Japanese National Institute for Radiological Sciences, the Japanese Foundation for Cancer Research, Kyushu University, Kawasaki Medical School, Gifu University of Medical Science, Toho University, the National Cancer Center East and Hokkaido University, have put the VECTor's Concurrent PET/SPECT modality through its paces.

$^{99m}$Tc, $^{18}$F and $^{64}$Cu were used to evaluate spatial resolution, count rate linearity and quantitation capabilities. Simultaneous imaging of co-administered PET and SPECT tracers at different activity ratios were performed to validate the quantitation capabilities of PET and SPECT and compare results to single tracer studies.

Even at high activity ratios, with a 16-fold excess of PET tracer causing down-scatter in the SPECT energy region, excellent quantification results were reported, as illustrated below:



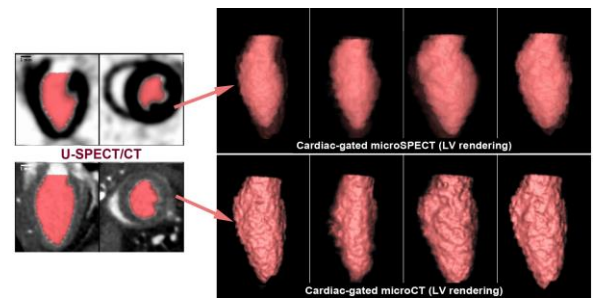

*Concurrent PET/SPECT acquisitions deliver excellent quantitation results, even for SPECT in the presence of high PET activities. Results of this multi-institutional evaluation were reported in the International Journal of Sciences, 2016, Volume 25, No 1, pp 26-39*

## Second MILabs system for Duke, now in Singapore


**Singapore, March 2016**

As a result of the very successful use of the MILabs U-SPECT/CT at the Duke Center for In-Vivo Microscopy in Durham - USA, the Laboratory for Translational and Molecular Imaging (LTMI) at the Duke-NUS Medical School in Singapore has also installed a MILabs VECTor/CT system. “The ability of the system to perform simultaneous PET and SPECT of co-injected tracers combined with fast dynamic acquisitions, are key differentiating features that will enable researchers to expand the scope and breadth of translational imaging applications”, says Dr. Chacko, head of the LMTI.

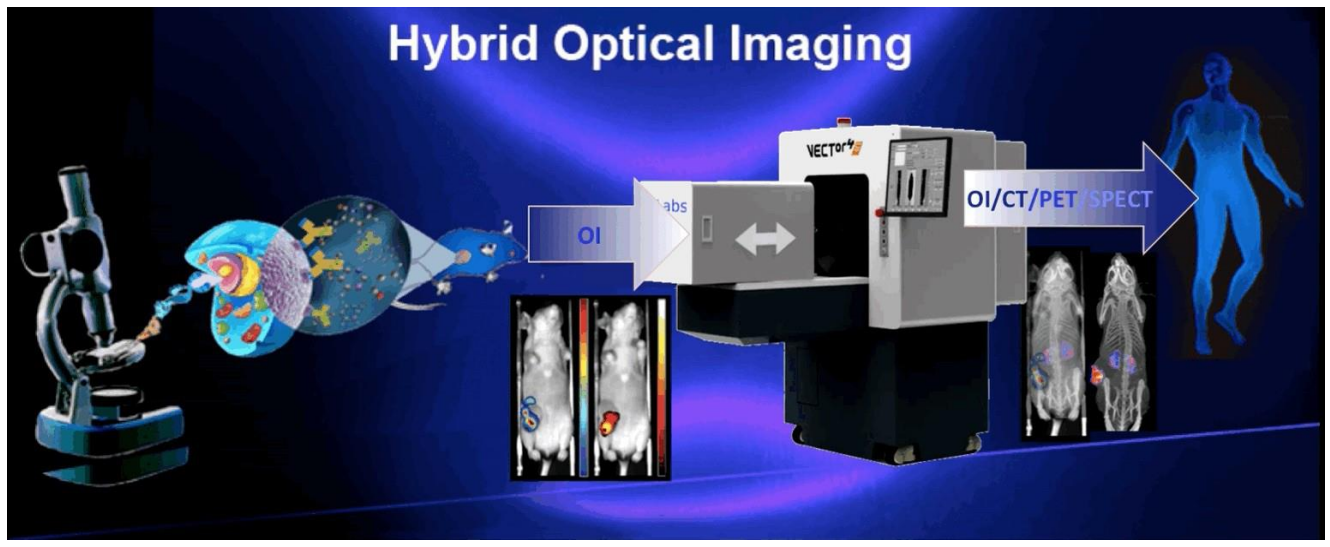
Meanwhile, Prof. Allan Johnson PhD of Duke's Center for In-Vivo Microscopy has compared 4-D microSPECT with microCT to quantitatively assess cardiac function:




*“The favorable comparison shows that high resolution microSPECT should be considered as an alternate imaging modality to microCT. It allows to evaluate function of the mouse heart and provides information about myocardial perfusion” says Prof. Johnson.*

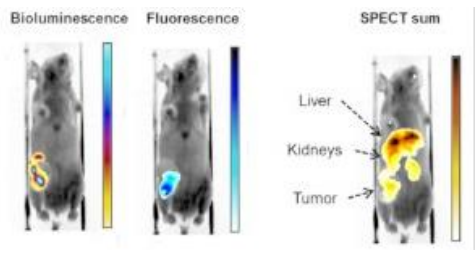
## Introducing Hybrid Optical Imaging

# Taking Optical Imaging into Translational Research



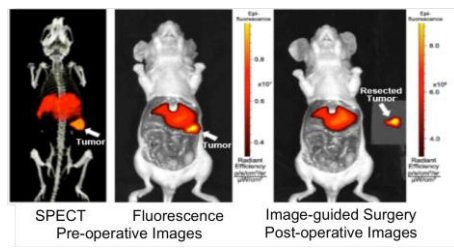

*With MILabs new Optical Imaging module you can expand the application reach of the VECTor/CT imaging platform with bioluminescence, fluorescence and Cherenkov imaging. Now you can take your optical in-vitro and ex-vivo research data and apply dual-modality probes or probe pre-targeting to translate data into in-vivo animal and human studies.*

MILabs' unique VECTor/CT system can combine microCT with the sensitivity of Optical and PET/SPECT in one instrument, thus enabling you to gain greater insights into your disease models while providing the quickest workflow.




*Single-pass Optical, CT and PET/SPECT imaging facilitates translation from in-vitro or ex-vivo to in-vivo applications (M. van Oosterom et al., TU Delft).*

While optical imaging can rely on the vast knowledge accumulated on bioluminescence and fluorescent agents from microscopic imaging, *in vivo* macroscopic imaging of molecular and cellular processes in deep tissue remains a challenge. By incorporating a hybrid optical imaging design on its VECTor platform, MILabs can now provide researchers with complementary imaging modalities such as CT to improve the quality of the data that can be obtained from imaging with bioluminescence and fluorescence probes, and at the same time, use PET/SPECT to facilitate translation to the clinic of their optical probes.




*Example of translation from in-vivo animal into humans using a bi-modal probe for potential image-guided clear cell renal cell carcinoma (ccRCC) applications. By combining a SPECT and fluorescent tracer in a bi-modal SPECT/Fluorescence probe ($^{111}$In- DTPA-G250-IRDye800CW), a powerful complementary imaging system that overcomes the limitations of each individual modality can be developed for improved in-vivo detection and resection of tumors (S. Muselaers et al, UMC St. Radboud)*

## Oxford & Yale acquire MILabs systems

**Oxford & New Haven, June 2016**
The universities of Oxford and Yale are joining the fast growing list of renowned institutions using MILabs molecular imaging systems.

The Oxford Institute for Radiation Oncology is the world's largest and most comprehensive center for research in radiation oncology and biology. The new VECTor/CT system will mainly be used by Dr. Cornelissen to diagnose and treat pancreatic cancer.

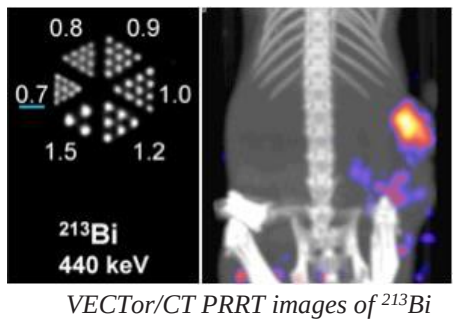
At Yale University, Dr. Sinusas, Director of the Translational Research Imaging Center, will use the cardiac-gated high-resolution SPECT and CT modalities of their new system to develop innovative non-invasive imaging approaches for the assessment of myocardial viability, angiogenesis, and infarction remodeling.


*Sub-mm PET and SPECT imaging with VECTor/CT. Picture courtesy of Univ. of California, San Fransisco (UCSF)*

## MILabs enables high-energy theranostics at Erasmus MC

**Rotterdam - the Netherlands, 2016**
Globally recognized as leading Center of Excellence for Peptide Receptor Radionuclide Therapy (PRRT), Erasmus MC has started to evaluate the promise of $^{213}$Bi for radionuclide therapy. Being a combined alpha, gamma, and X-ray emitter with short half-life (46 min), SPECT imaging of $^{213}$Bi is demanding, since the majority of emitted photons has a much higher energy (440 keV) than common in SPECT. Moreover, dynamic preclinical biodistribution studies with $^{213}$B are challenging due to its short half-life.

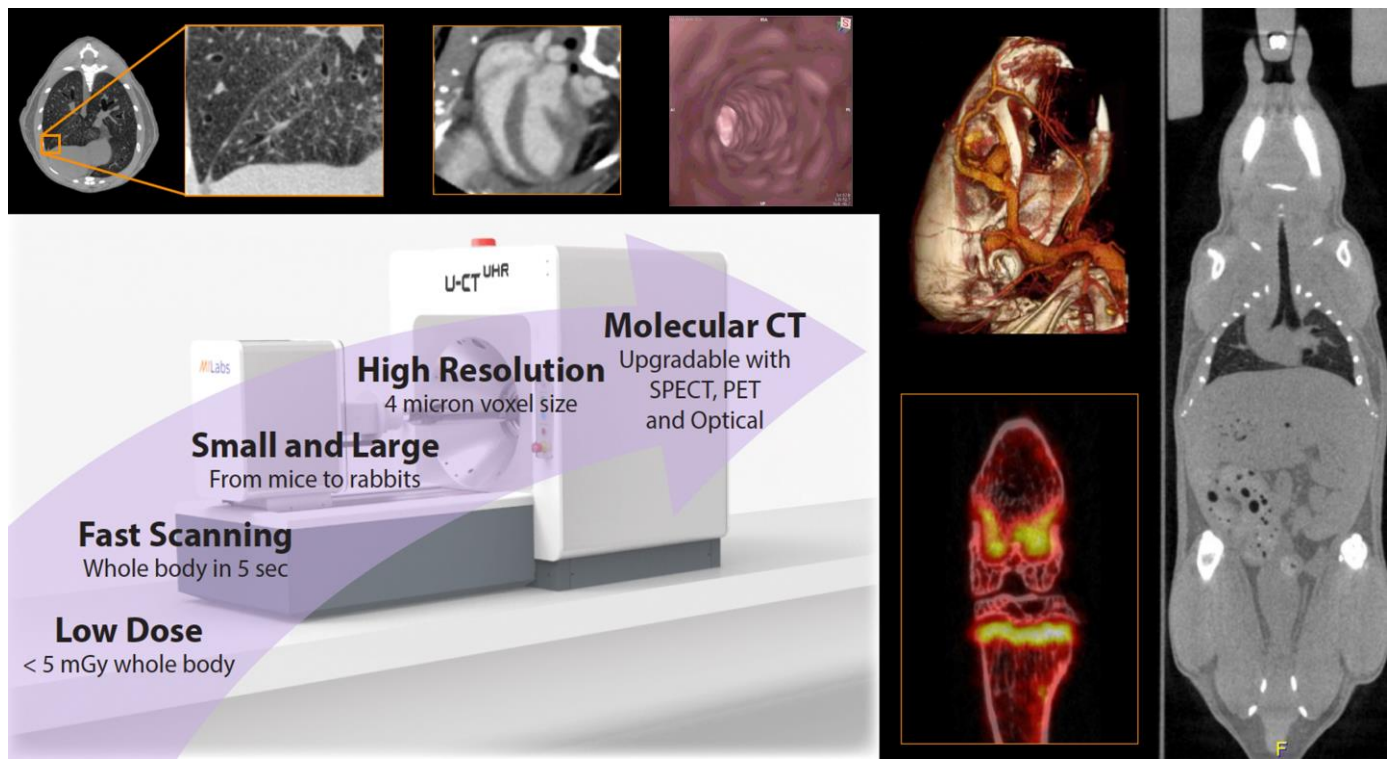
Despite these challenges, the MILabs VECTor is successfully being used at Erasmus MC for imaging $^{213}$Bi and other high energy SPECT isotopes such as $^{131}$I. With its dynamic SPECT capabilities and energy range up to 600 keV, image resolutions down to 0.75 mm are obtained.




*VECTor/CT PRRT images of $^{213}$Bi (J. de Swart et al., JNM, 2016).*

## Finally: Adaptive X-ray CT

# The Most Versatile Preclinical CT system, Ever




*MILabs new Adaptive X-ray CT has been designed for fast, ultra-high-resolution, low-dose imaging of ex-vivo specimens and live animals, from mice to rabbits. It can be used as a stand-alone unit and upgraded at any time to a fully integrated Molecular CT system using nuclear and optical imaging modalities.*

Combining high-speed, low X-ray dose, and high-resolution CT imaging in one instrument, the U-CT system is already powerful as a stand-alone unit.

But there's more: U-CT is also an integral part of MILabs VECTor/CT platform and since U-CT operates on an autonomous rotating gantry, it can be upgraded to Molecular CT without any performance compromises. The end-result is that you can obtain brilliant Molecular Anatomical Images in any configuration.

Designed for fast, ultra-high resolution imaging, the Adaptive X- ray CT system can be used for virtually all preclinical CT imaging as well as certain material analysis applications:

- *Ex-vivo* @ 4 µm voxel resolution.
- Ultra-low dose < 5 mGy whole-body imaging in < 5 seconds for *in-vivo.*
- Respiratory- and cardiac-gating.
- Auto-zoom for focused, whole-body and multi-species imaging.
- Excellent soft-tissue contrast plus dual-energy imaging to selectively enhance soft-tissue detection with contrast agents.
- Vertical specimen positioning option.