8th January 2022

NLP Seminar

WINN AUNG
Department of Molecular Imaging and Theranostics
Institute for Quantum Medical Sciences
National Institutes for Quantum Science and Technology
Chiba, Japan

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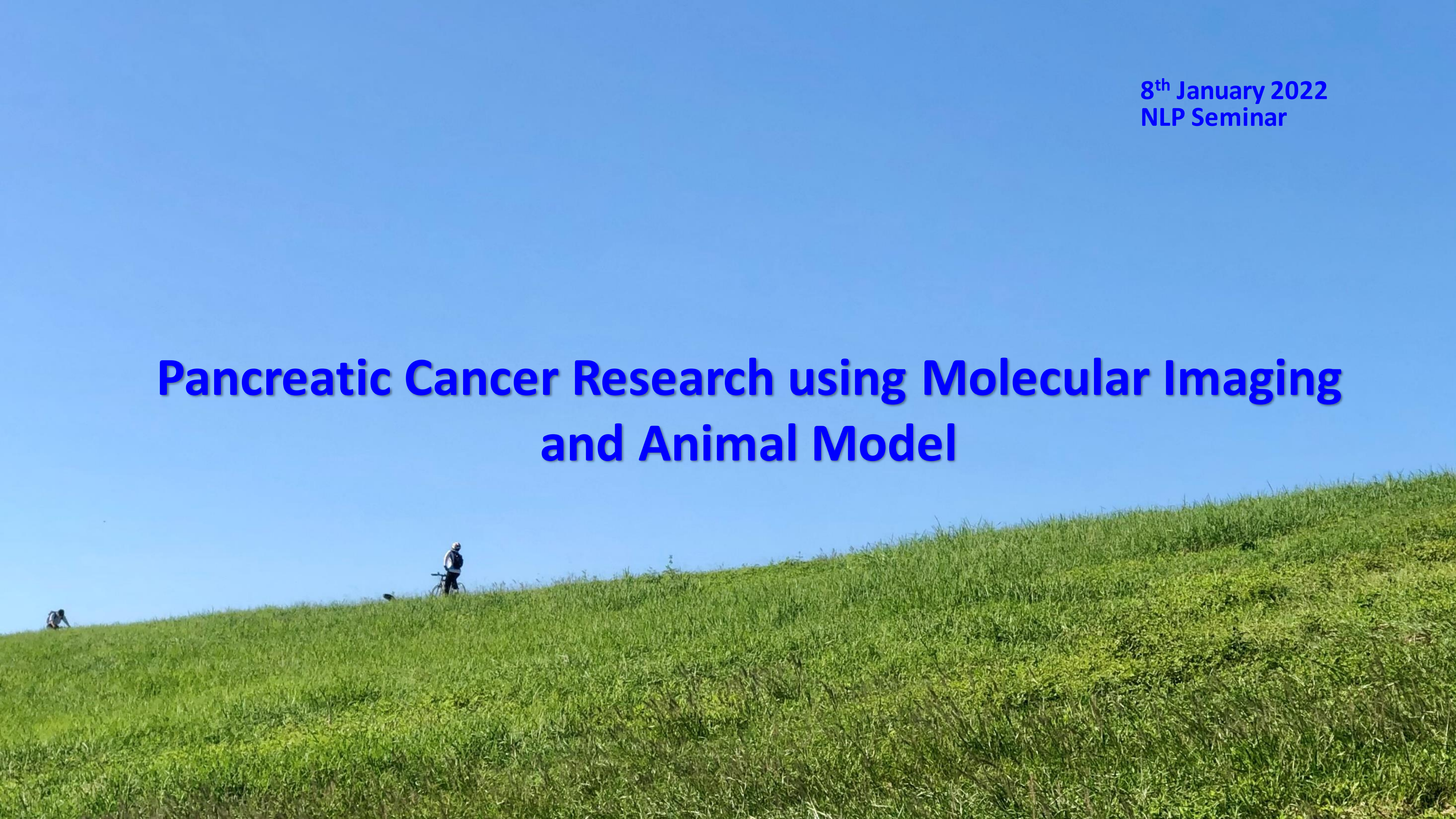
Pancreatic Cancer Research using Molecular Imaging and Animal Model



Looking Back to the Past

1963: Born in Minhla, MYN
1978: Passed Matriculation

1982-1987: IM(1), Yangon, MYN
M.B.,B.S.
1988-1992: General practitioner

1992: Leave from Myanmar
1992-1994: Japanese Language School, Tokyo, JPN
1994-1997: IT and Accounting School, Tokyo, JPN

1998-2002: Tokyo Medical and Dental University in Tokyo, JPN
Ph.D. in Medical Science (Radiology)

2002-2003: Postdoc at NIRS, Chiba, JPN
2003-2006: Research Fellow at NIRS in Chiba, JPN
2006-2011: Researcher at Molecular Imaging Center, NIR, Chiba, JPN
2011-2017: Senior Researcher at Molecular Imaging Center, NIR, Chiba, JPN
2017-present: Senior Researcher, QST, Chiba, JPN

what I enjoy doing in my free time

Reading and writing poetry

Organizations of National Institute for QuantumScience and Technology (QST)

NIRS + JAEA → QST →

- National Institutes for Quantum and Radiological Science and Technology
  - Quantum Life and Medical Science Directorate
    - Dept. of Research Planning and Promotion
    - Dept. of Administrative Services
    - Dept. of Engineering and Safety
    - Human Resources Development Center
    - Quality Assurance and Audit Office
    - Laboratory Animal and Genome Sciences Section
    - Institute for Quantum Medical Science
      - Dept. of Charged Particle Therapy Research
      - Dept. of Molecular Imaging and Theranostics
      - Dept. of Functional Brain Imaging
      - Dept. of Accelerator and Medical Physics
      - Dept. of Advanced Nuclear Medicine Sciences
    - National Institute of Radiological Sciences
      - Dept. of Radiation Emergency Medicine
      - Dept. of Radiation Emergency Management
      - Dept. of Radiation Measurement and Dose Assesment
      - Dept. of Radioecology and Fukushima Project
      - Dept. of Radiation Effects Research
      - Dept. of Radiation Regulatory Science Research
    - QST Hospital
      - Dept. of Hospital Management
      - Dept. of Radiation Medicine
      - Dept. of Medical Technology
      - Dept. of Nursing
    - Institute for Quantum Life Science
  - Quantum Beam Science Research Directorate
  - Fusion Energy Directorate

Research Group

- Experimental Nuclear Medicine Group
- Applied MRI Research Group
- Diagnostic and Therapeutic Nuclear Medicine Group
- Functional and Molecular Imaging Group

Focus of ENM Group

◆ What is the focus of group?

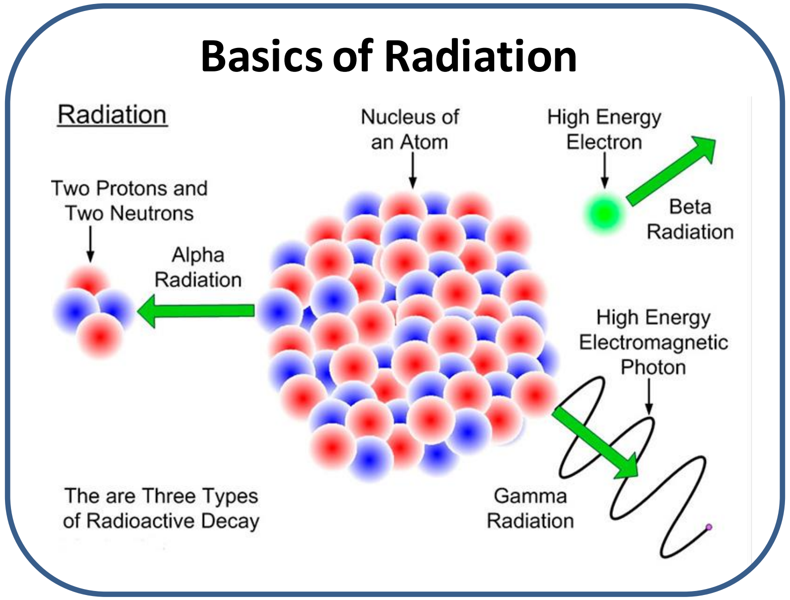
- To develop new multifunctional agents, especially radionuclide agents, for cancer imaging and therapy
  (Assess these agents at pre-clinical level)

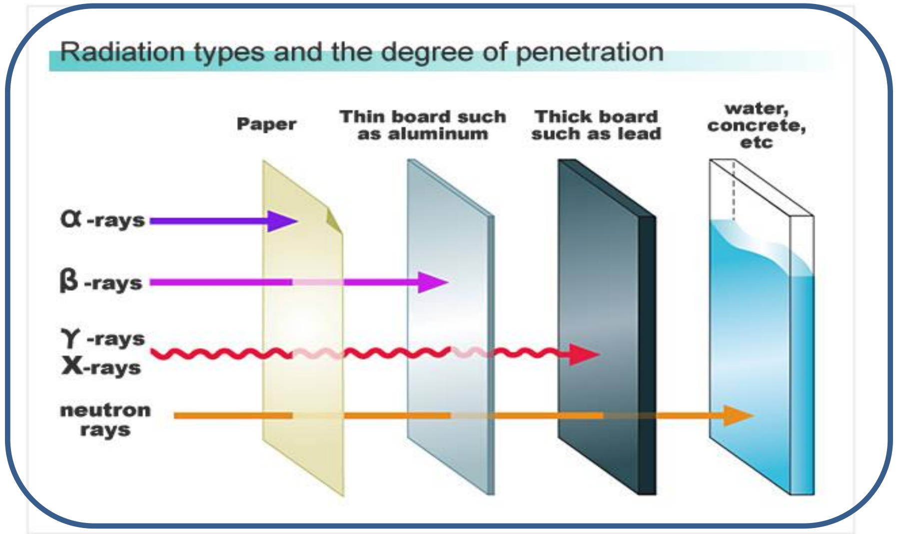
Cancer imaging

- To develop a new molecular imaging agent → candidate probes are labeled with suitable radionuclides (that emits γ-rays or positrons) to enable imaging
  - Candidate probes → such as antibody/peptide/small molecule
  - Radionuclide that emits γ-rays → such as ^{111}In (SPECT)
  - Radionuclide that emits positrons, β^+ → such as ^{18}F, ^{64}Cu ^{89}Zr (PET)

Cancer therapy

- To develop the targeted radionuclide therapy (TRT)→ candidate probes are labeled with cytotoxic radionuclides (α- and β-ray emitters) and evaluated for their therapeutic efficacy
  - Candidate probes → such as antibody/peptide/small molecule
  - Radionuclide that emits β^--ray →such as ^{90}Y, ^{64}cu, ^{67}cu, ^{131}I
  - Radionuclide that emits α-particles → Such as ^{211}At,^{225}Ac, ^{213}Bi, ^{224}Ra





Outline of today's talk

- **Introduction of Pancreatic Cancer**

- **Animal model for preclinical research**

- **Introduction of Molecular Imaging**

- **Some results of our researches**

  - Micro-Positron Emission Tomography/Contrast-Enhanced Computed Tomography imaging of orthotopic pancreatic tumor-bearing mice using the $\alpha_v\beta_3$ integrin tracer ^{64}Cu-labeled cyclam-RAFT-c(-RGDfK-)$_4$. *Mol Imag; 12(6): 376-387 (2013).* (Aung W et.al)
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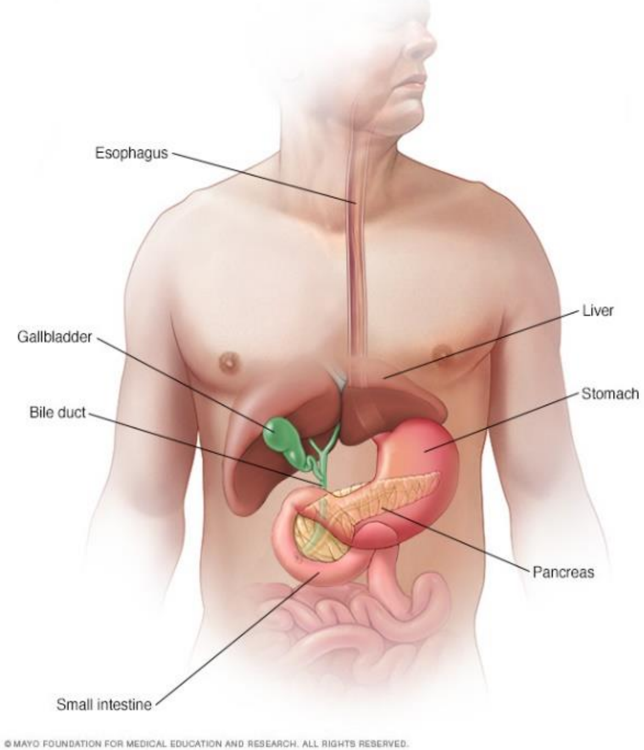
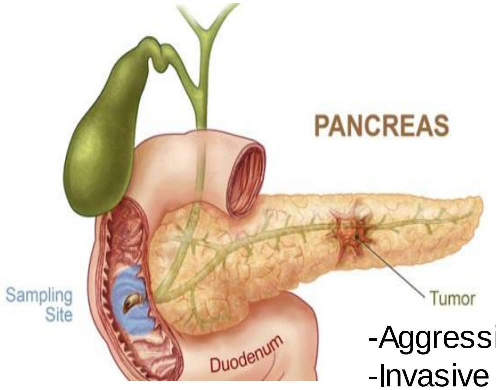
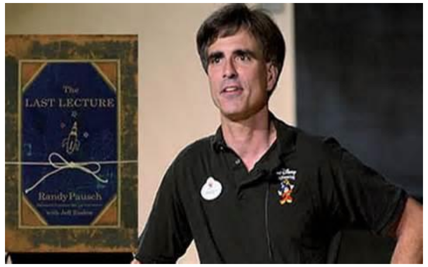
  - Anticancer effect of dihydroartemisinin (DHA) in a pancreatic tumor model evaluated by conventional methods and optical imaging. *Anticancer Res; 31(5):1549-1558 (2011).* (Aung W et.al)

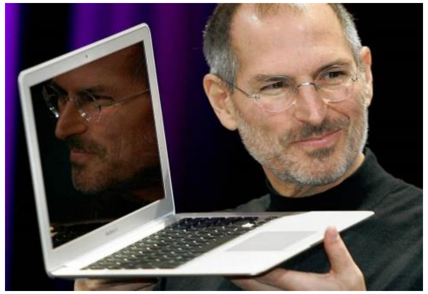
Introduction of Pancreatic Cancer





-Aggressive
-Invasive
-Metaststic





Pancreatic Cancer, Why?

Peoples who fought a battle with pancreatic cancer and passed away

Too many……

My brother's friend
Randy Pausch, The speaker of "Last Lecture"
Steve Jobs, Apple CEO
Ralph Steinman, Nobel prize winner
Patrick Swayze, Actor
Hiyoshi Mimi, Singer and actress
………………
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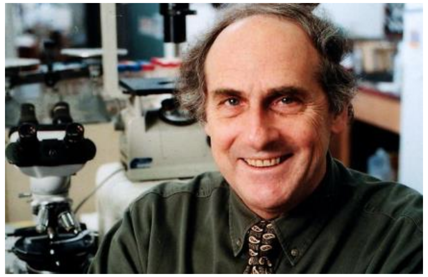
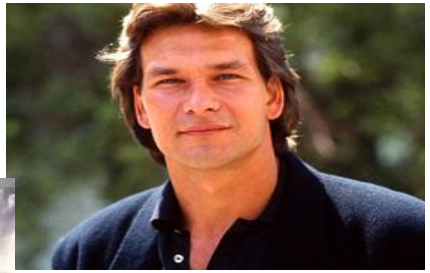
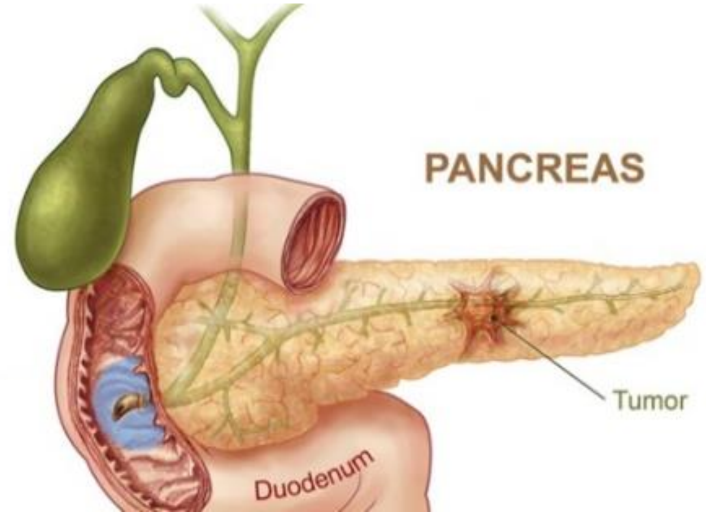




Introduction of Pancreatic Cancer

Pancreatic Cancer by the numbers



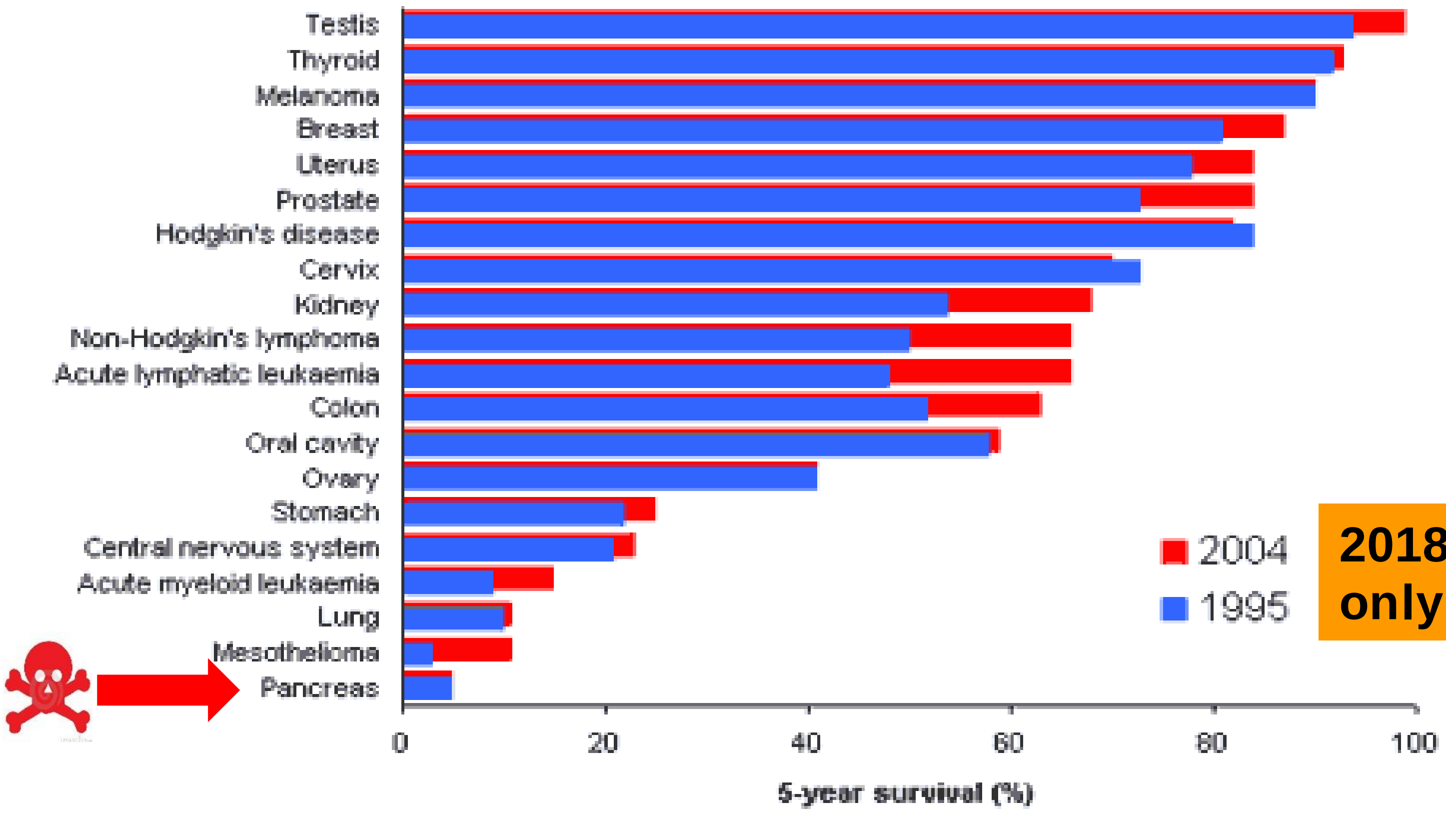
-Aggressive
-Invasive
-Metaststic

- ♦ Pancreatic cancer kills **117** people every day.
- ♦ Highest mortality rate, **91%** of patients die.
- ♦ **71%** of patient die within first year of diagnosis.
- ♦ **85%** of patient have metastasis by time of diagnosis.
- ♦ Five-years survival rate is **9%**.
- ♦ In 2018, **4th** leading cause of cancer-related deaths.
- ♦ By 2030, **2nd** leading cause of cancer-related deaths.
- ♦ Survival rate has not much improved in **40 yrs**.

https://www.suzannewrightfoundation.org/harpa/

Introduction of Pancreatic Cancer

Five-years survival rate of Pancreatic Cancer comparing with other Cancers

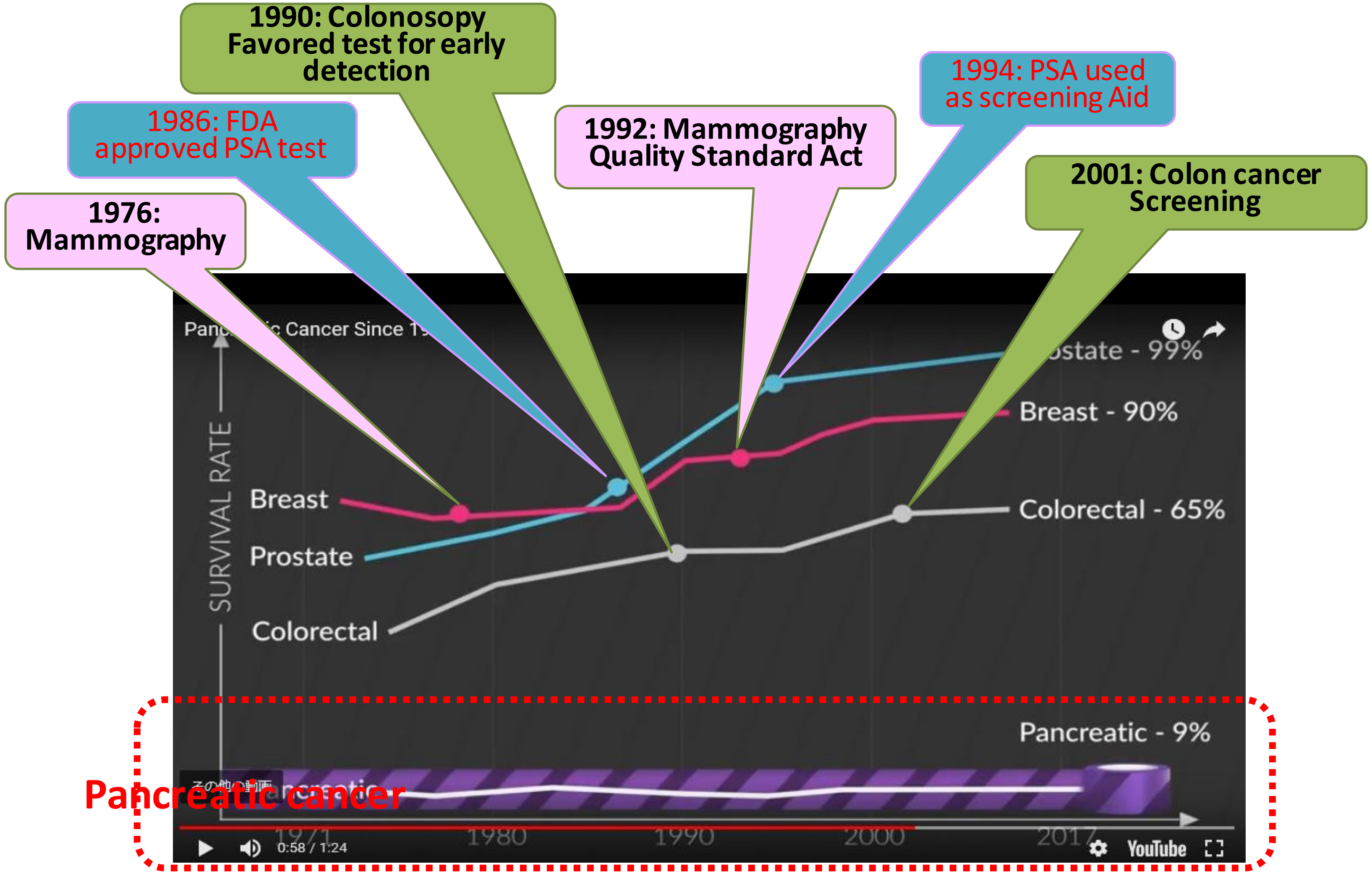


2018→ Remained only 9%

http://www.cancervic.org.au/

Introduction of Pancreatic Cancer

Five-years survival rate of Pancreatic Cancer comparing with other Cancers



No remarkable change in 40 years

https://www.suzannewrightfoundation.org/harpa/

Introduction of Pancreatic Cancer

Most common molecular alterations in pancreatic cancer

Target frequency of mutation or overexpression in pancreatic cancer (%)

1.Growth /survival factor & receptor

- Epidermal growth factor receptor (EGFR) (25-65%)
- Vascular endothelial growth factor recptor(VEGFR) (up to 90%)
- Hepatocyte growth factor receptor (HGFR) (78%)
- Insulin-like growth factor-I receptor (IGF-1R) (64%)
- Cholecystokinin-B and gastrin receptor (CCK/Gastrin R) (74-95%)
- Integrin receptor (58%)

2. Oncogene

- KRAS (74-100%)
- Her2/Her3 (16-65%)
- Akt2 (10-72%)
- Notch 1 (50-90%)
- Notch 3 (70%)
- COX-2 (Cyclo-oxygenase) (67-90%)
- p16 (27-96%)

3. Tumor suppresor gene

- p53 (43-76%)
- SMAD4 (50%)
- SHH (Sonic hedgehog) (70%)

4. Matrix proteases

- MMP (?)

5. Protein Kinase

- mTOR (?)

6. Others Glycoprotein

- CA-19-9
- Mucins
- Mesothelin (86%)

Deranged molecules/genes and aberrant molecular pathways involved in the pathogenesis of pancreatic cancer are attracting diagnostic or therapeutic focus.

Strimpakos AS, et.al Gut Liver. 2010 December; 4(4): 433–449

Han HW et.al. *Nat Rev Gastroenterol Hepatol. 2009*

Introduction of Pancreatic Cancer

Several steps involved in medical research

Discovery

- Active principles
- Targets
- Drug candidates

(Bioassay, Screening)

2-5 yrs

Pre-clinical Research

- Safety and efficacy studies using cells and animal models

1-5 yrs

Clinical Research

- Safety and efficacy studies in participants

- Phase 1 → <100
- Phase 2 → <1000
- Phase 3 → >1000

6-10 yrs

Approval

- After review

1-2yrs

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- **Animal model for preclinical research**

- **Introduction of Molecular Imaging**

- **Some results of our researches**
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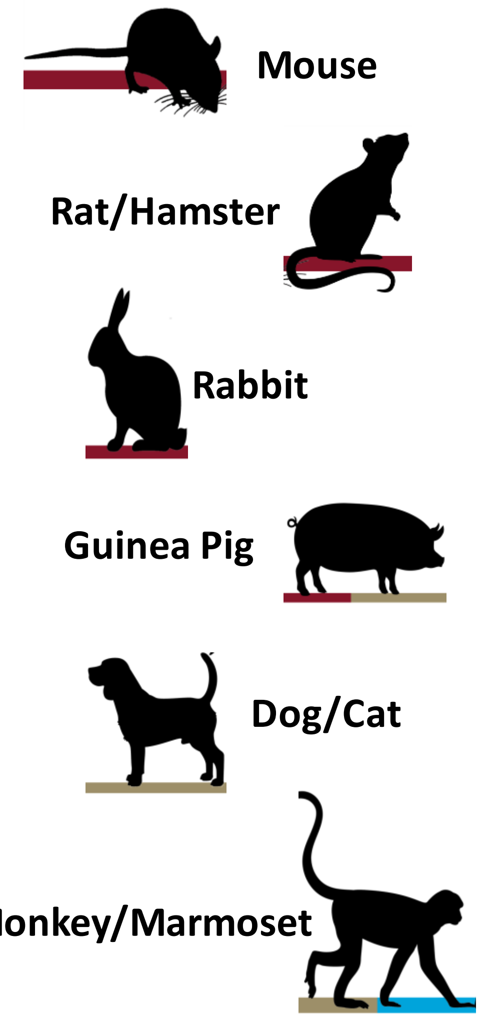
Animal models for preclinical Cancer research

Animals used in cancer research



Mice have been employed as models of cancer for over a century.

◆ Types of mouse model

1. Genetically engineered mouse model
2. Human xenograft mouse model
   - 2-1. Heterotopic transplantation (Subcutaneous)
   - 2-2. Orthotopic transplantation

◆ **Orthotopic pancreatic tumor** more closely mimics the natural biological behavior and characteristics of human pancreatic cancer because it could grow in its native microenviroment and reliably replicate the certain considerable characters of the human malignancy, such as local invasion and metastasis.

◆ A variety of techniques to generate orthotopic pancreatic cancer model

1. Direct injection of tumor cells into the pancreas
   - 1.1. with matrigel
   - 1.2. without matrigel
2. Surgical transplantation of small tumor fragments
   - 2.1. derived from subcutaneous tumors in donor animals
   - 2.2. directly from patient specimens

Animal models for preclinical Cancer research

Advantages & Disadvantages of orthotopic model

◆ Advantages

- Relevant site for tumor-host interactions
- The emergence of disease-relevant metastases and loco-regional growth
- The ability to study tumor site-specific dependence of therapy

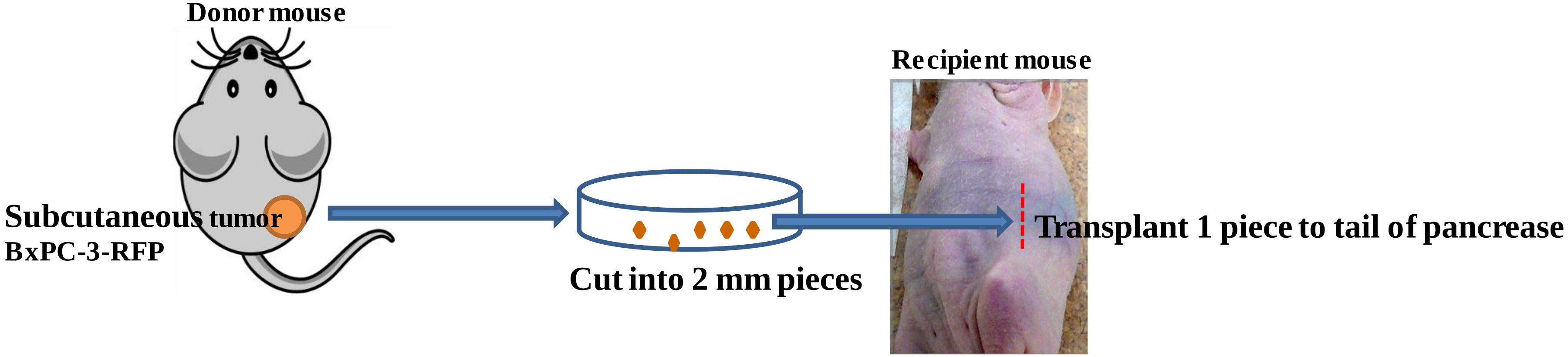
◆ Disadvantages

- Consuming the time and labor
- Demanding skillful work
- High cost
- Requiring longer healing and recovery time
- Limited throughput because of imaging methods are necessary to monitor the tumor

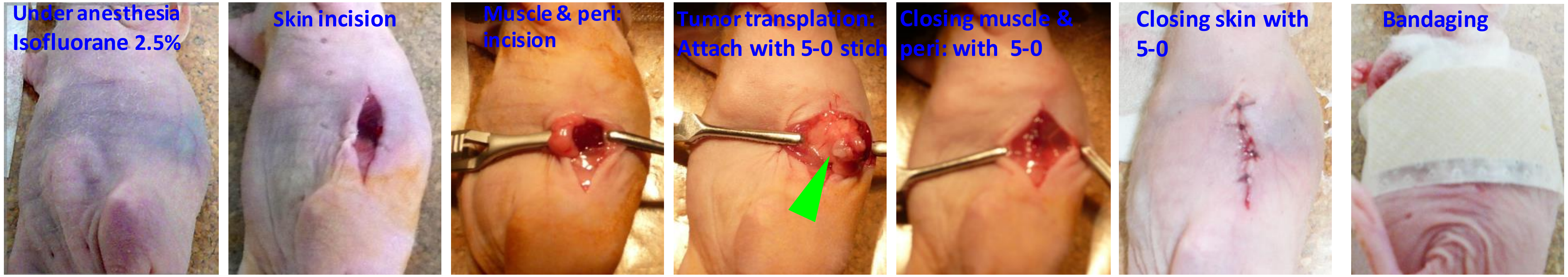
Nonetheless, orthotopic tumor models are emerging as the preference for cancer research due to the increased clinical relevance.

Animal models for preclinical Cancer research

Establishment of clinically relevant orthotopic pancreatic cancer model



Surgical Orthotopic Implantation (SOI) procedure



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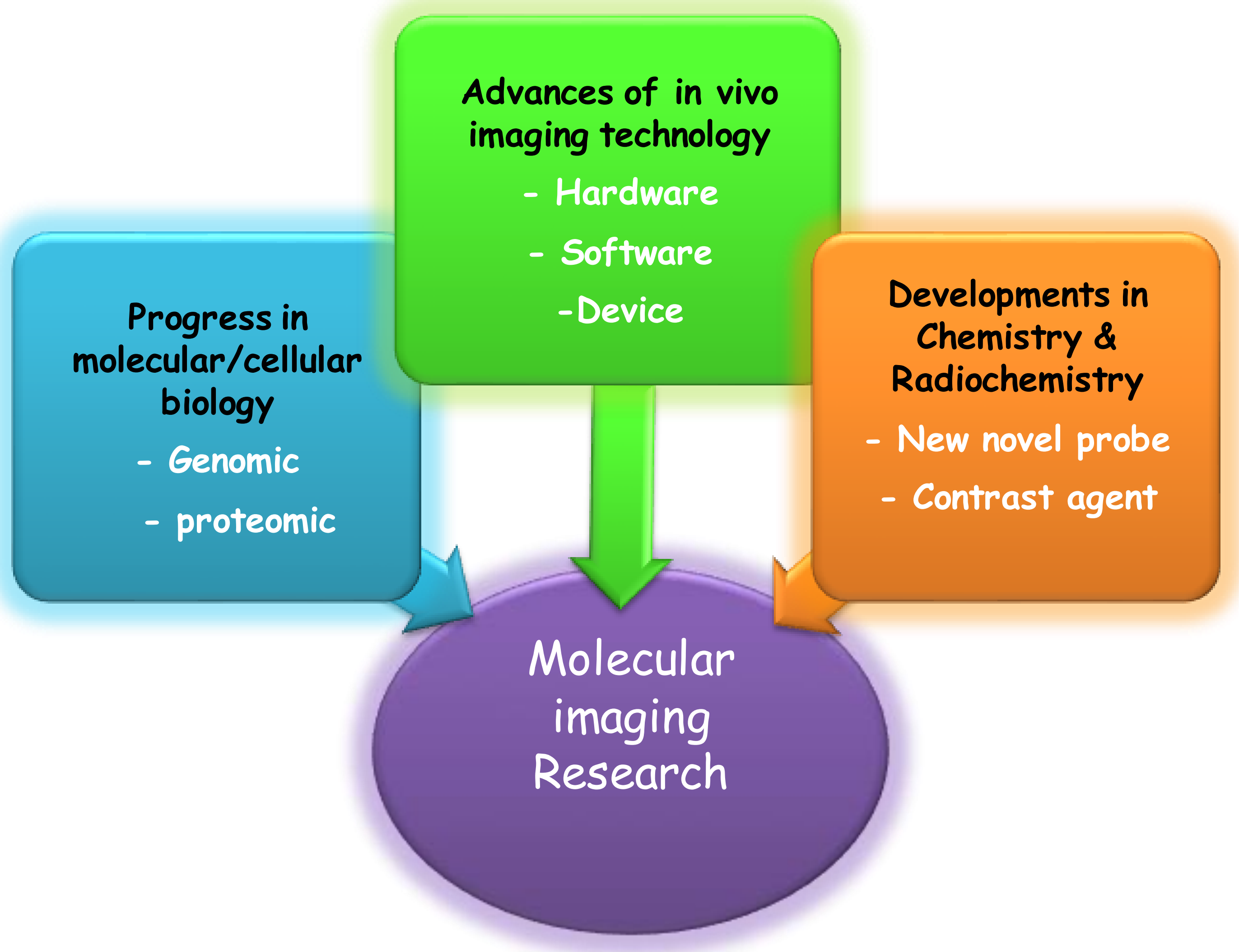
Introduction of Molecular Imaging

Pillars of Molecular Imaging



Introduction of Molecular Imaging

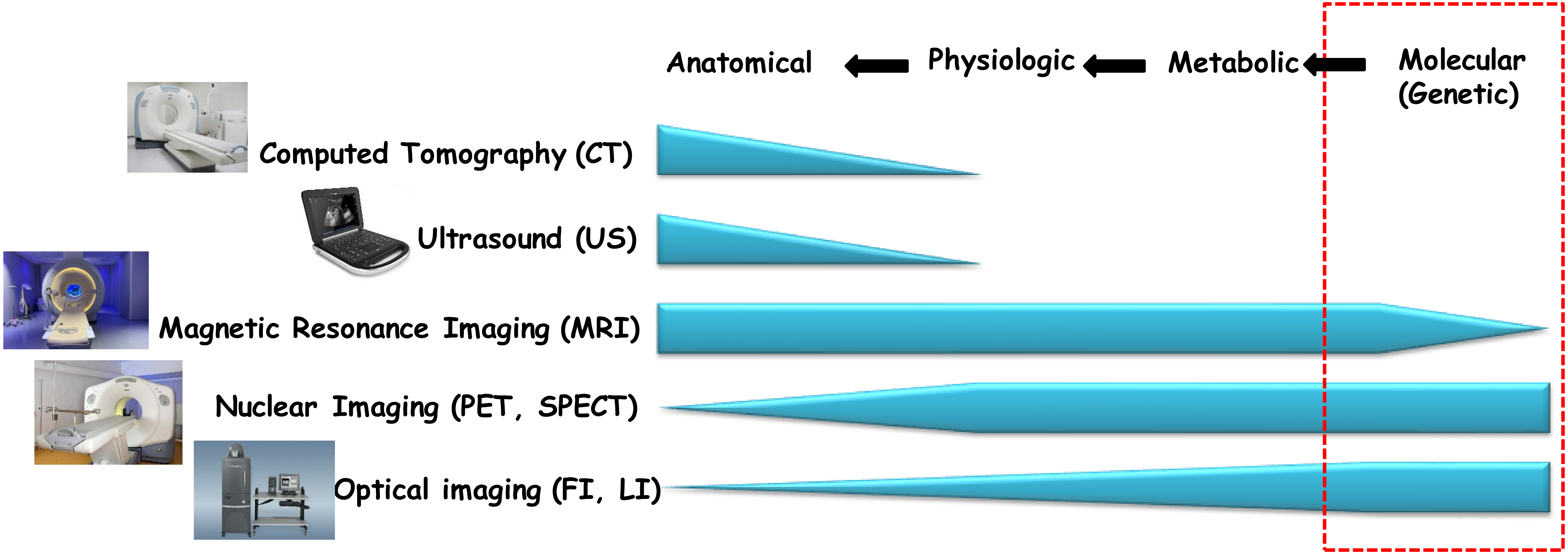
What is the Molecular Imaging?

- **Molecular Imaging (MI) is a growing biomedical research discipline that enables the visualization, characterization, and quantification of biologic processes taking place at the cellular and subcellular levels within intact living subjects, including patients. (Ref: Molecular Imaging Program at Stanford (MIPS))**

- Molecular imaging originated from the field of radiology from a need to better understand fundamental molecular processes inside organisms in a noninvasive manner. Molecular imaging is a field of medical imaging that focuses on imaging molecules of medical interest within living patients. (Ref: Advances in Molecular Imaging, Book)

Introduction of Molecular Imaging

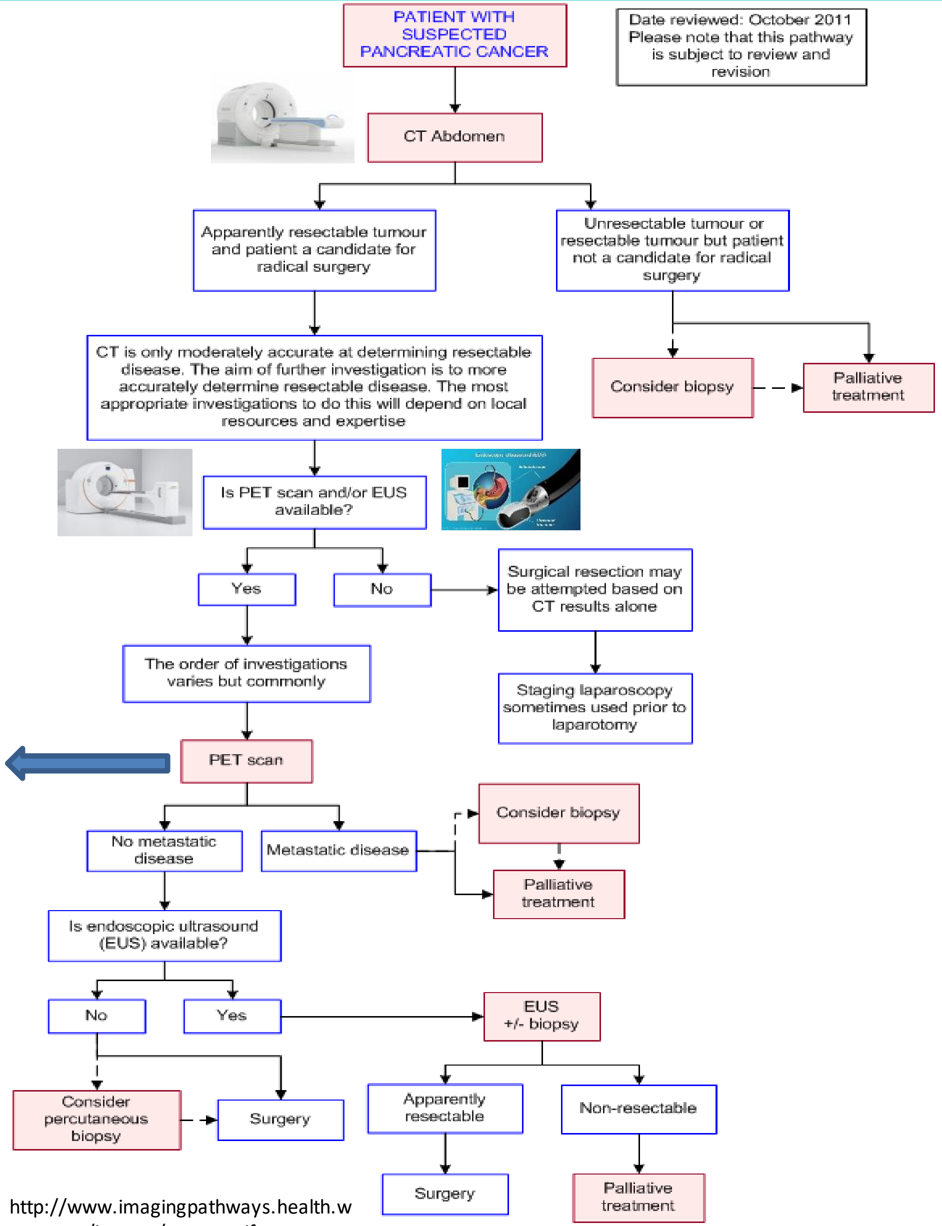
Current imaging modality and molecular imaging



(PET) Positron Emission Tomography
(SPECT) Single Photon Emission Computed Tomography
(FI) Fluorescence Imaging
(LI) Luminescence Imaging

Weissleder R. et al. Radiology 2001

Current trend for diagnosis and treatment of pancreatic cancer

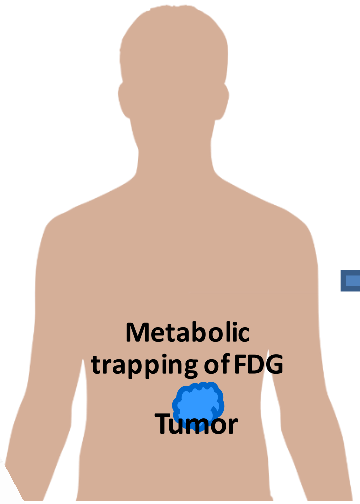


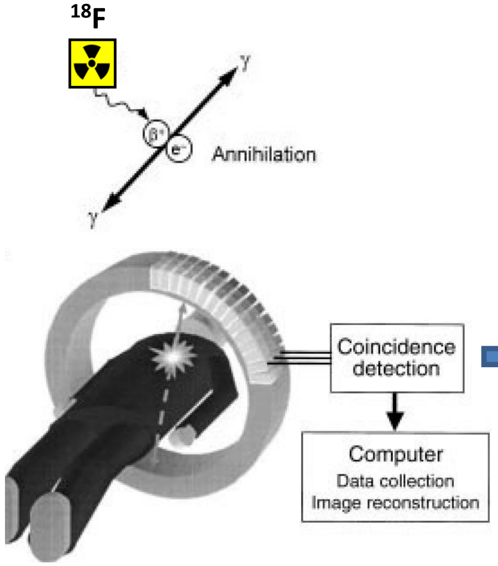
http://www.imagingpathways.health.wa.gov.au/images/pan_ca.gif

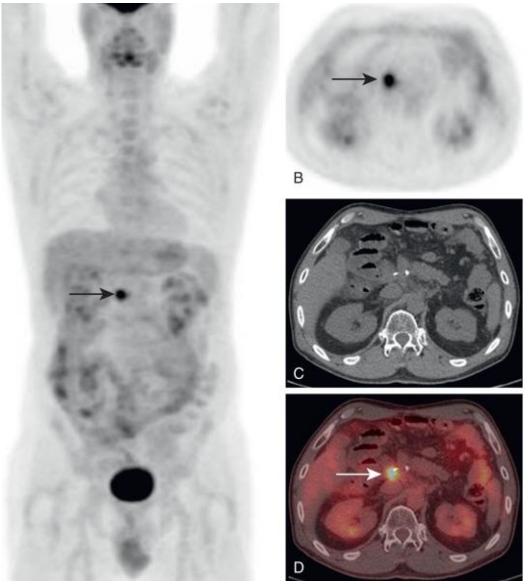
Pitfalls of FDG-PET

- False (+) due to pancreatitis
- False (-) due to hyperglycemia
- Small lesion

FDG-PET imaging of pancreatic cancer





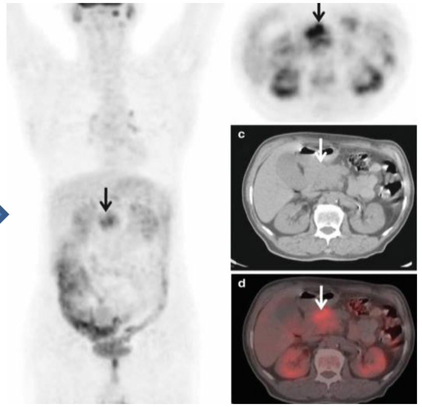


https://radiologykey.com/

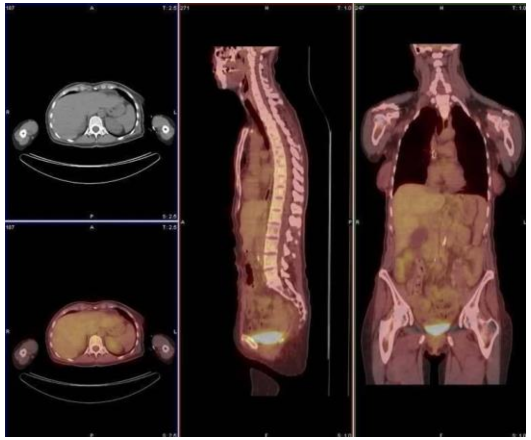
But,

Pitfalls of FDG-PET

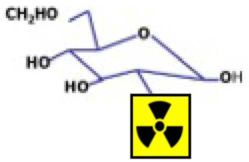
False (+) due to pancreatitis



False (-) due to hyperglycemia

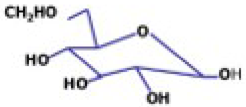


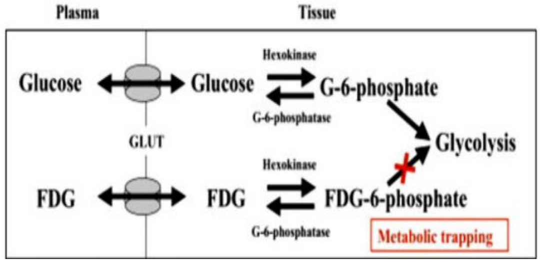
FDG



^{18}F

Glucose





FDG

- Most widely used PET tracer
- Related to glucose metabolism
- Taken up most tumors

Published radionuclide-based imaging studies for pancreatic cancer

1. Metabolism

- ^{18}F-FDG → tumor glucose uptake
- ^{18}F-FEC (fluoroethylcholine) → incorporate into cells through phosphoryl choline synthesis
- ^{11}C-Acetate → incorporate into cell citric acid cycle

2. Peptides that bind to the target molecule

- ^{18}F-FBA-A20FMDV2, ^{64}Cu/^{18}F-Cystine knot peptides (bind to $\alpha_v\beta_6$ integrin)
- ^{18}F/^{111}In-RGD (bind to $\alpha_v\beta_3$ integrin)
- ^{64}Cu/^{111}In-WT4351(designed to bind to the IGF1R and to internalize and hybridize with *KRAS* mRNA)

3. Antibodies that bind to bind to the target antigen

- ^{89}Zr-Bevacizumab (VEGF monoclonal antibody)

4. Ligands that bind to the receptor

- ^{123}I-VEGF$_{165}$ (bind to VEGFR)
- ^{18}F-Sigma 2 ligand (bind to Sigma R)
- ^{99m}Tc-Demogastrin (bind to Cholecystokinin-B, gastrin R)

5. Proliferation

- ^{18}F-FLT (trapped inside the cell after phosphorylation by TK1)

6. Protein synthesis, transport

- ^{11}C-Methionine→ Malignant transformation increases the use of amino acids
- ^{123}I-AIPA (Amino-iodophenylalanine), ^{123}I-IPA (Iodophenylalanine)

7. Other

- ^{68}Ga-Cloride
- ^{68}Ga-DOTA
- ^{11}C-Glycylsarcosine (targeted to H^+/Peptide transporter)
- ^{18}F-FEDL(Fluoroethyl-Deoxylactose) → binding to lactose binding protein in peritumoral pancreatic acinar cells

Outline of today's talk

◆ **Introduction of Pancreatic Cancer**

◆ **Animal model for preclinical research**

◆ **Introduction of Molecular Imaging**

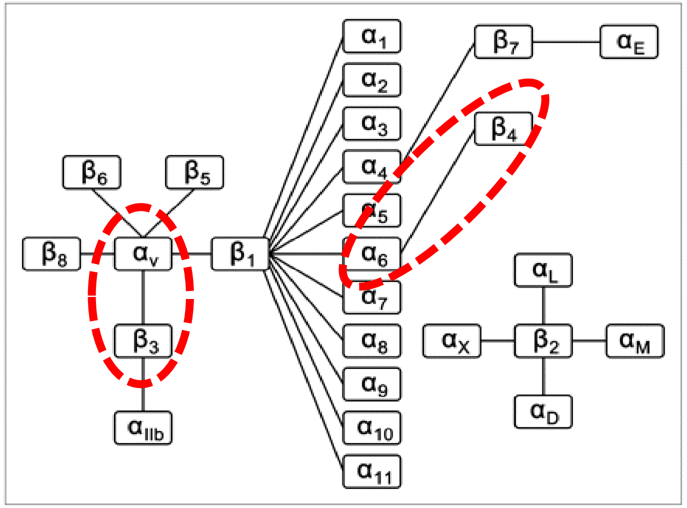
◆ **Some results of our researches (New strategies for diagnosis and treatment of pancreatic cancer)**

- Micro-Positron Emission Tomography/Contrast-Enhanced Computed Tomography imaging of orthotopic pancreatic tumor-bearing mice using the **$\alpha_v\beta_3$ integrin** tracer **^{64}Cu-labeled cyclam-RAFT-c(-RGDfK-)$_4$**. *Mol Imag; 12(6): 376-387 (2013).* (Aung W et.al) ← **Peptide**
- Immunotargeting of **integrin $\alpha_6\beta_4$** for single-photon emission computed tomography and near-infrared fluorescence imaging in a pancreatic cancer model. *Mol Imag; 15: (2016).* (Aung W et.al) ← **Antibody**
- Radioimmunotherapy of pancreatic cancer xenografts in nude mice using ^{90}Y-labeled anti-$\alpha_6\beta_4$ integrin antibody. *Oncotarget; 7: (2016).* (Aung W et.al) ← **Antibody**
- Anticancer effect of dihydroartemisinin (DHA) in a pancreatic tumor model evaluated by conventional methods and optical imaging. *Anticancer Res; 31(5):1549-1558 (2011).* (Aung W et.al) ← **Drug**

Our studies targeting some of Integrin molecules

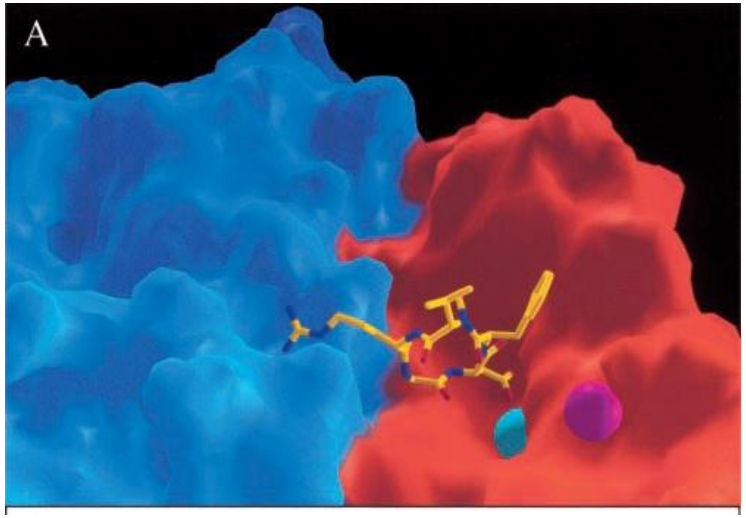
Integrins

- A family of **adhesion molecules** consisting of two noncovalently bound transmembrane subunits α and β.
- In mammals, **18α and 8β subunits** assemble into 24 different receptors.
- Integrins signaling plays a key role in tumor angiogenesis and tumor progression, invasion and metastasis.
- **Integrins expressed on carcinoma cells** and activated endothelial cells.
- $\alpha_v\beta_3$ is most extensively studied and excellent maker for tumor angiogenesis and metastasis imaging.
- **$\alpha_v\beta_3$ bind to Arg-Gly-Asp (RGD)** containing components of the interstitial matrix, such as vitronectin, fibronectin and thrombospondin.
- Arg-Gly-Asp (RGD) can be expected to use as Tumor Targeting Conjugates



Integrin family, composed of **24 heterodimers**

J Nucl Med: 2008 Jun;49 Suppl 2:113S-28S.



α v β3 RGD-peptide

Xiong, J. P. et al. *Science 2002, 296,151-155.*

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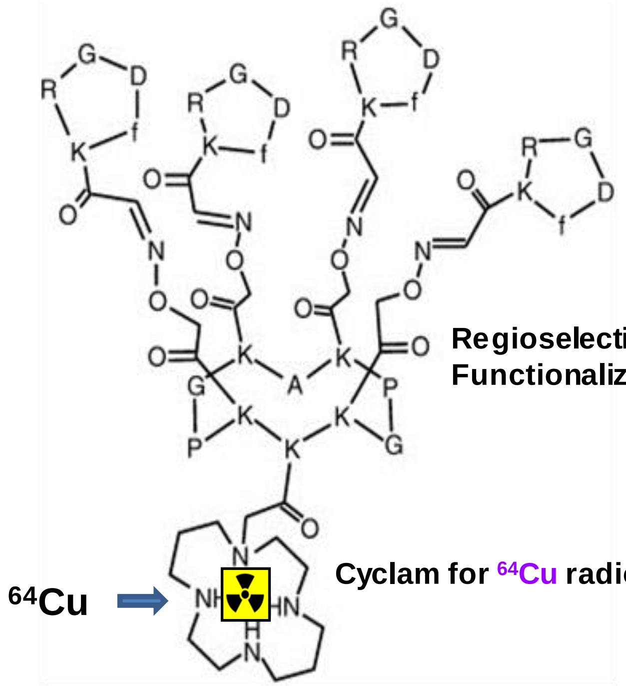
Integrin ($\alpha_v\beta_3$) targeted ^{64}Cu-RAFT-RGD-PET imaging

Objective

Preclinical study of potential applicabilty of ^{64}Cu-RAFT-RGD, a PET probe, for $\alpha_v\beta_3$ Integrin expressing orthotopic pancreatic tumor imaging

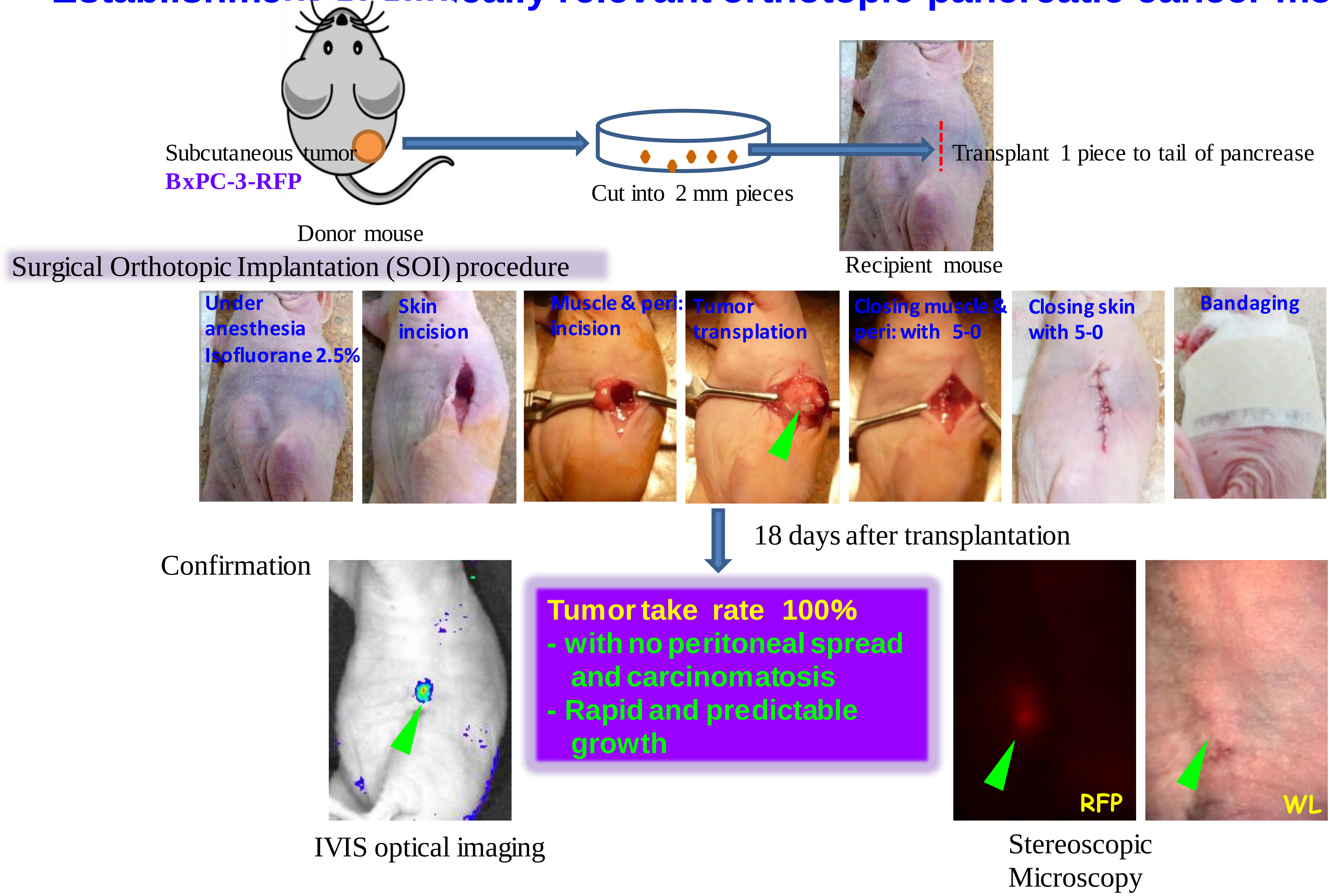


(RAFT-RGD was Provided from University of Joseph Fourier, France)

Chemical structure of cyclam-RAFT-c(-RGDfK-)$_4$.
Jin ZH et.al Nucl Med Biol 2011; 38(4):529-40

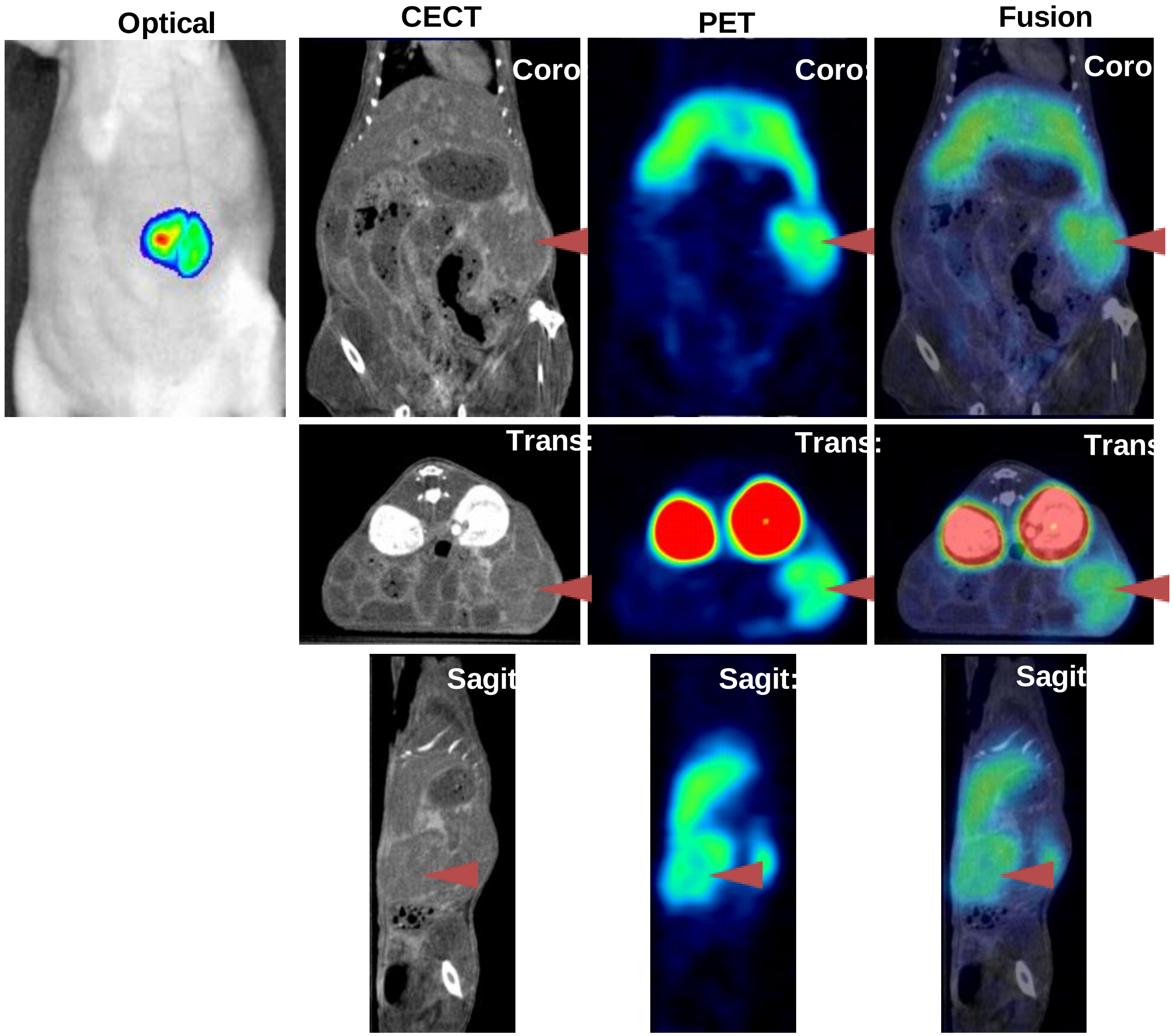
New strategies for diagnosis of pancreatic cancer

Establishment of clinically relevant orthotopic pancreatic cancer model



New strategies for diagnosis of pancreatic cancer

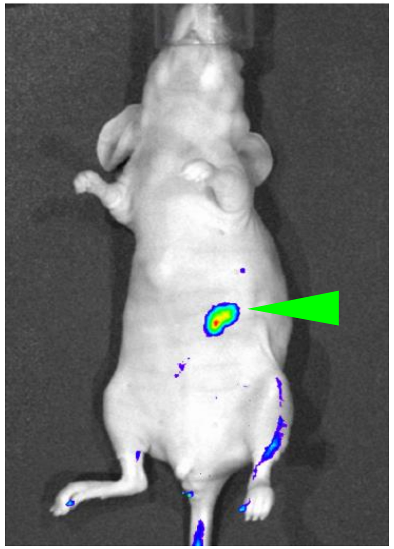
^{64}Cu-RAFT-RGD PET co-registered with CECT images of orthotopic pancreatic tumor



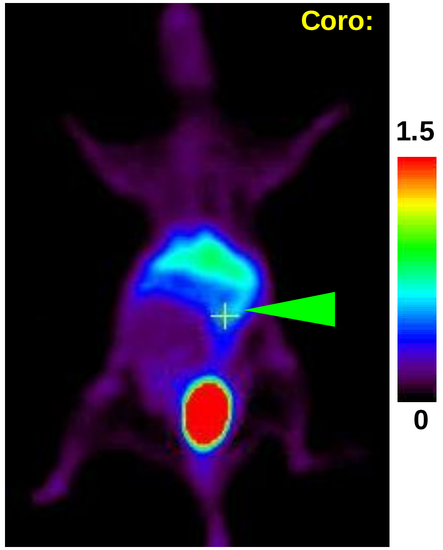
New strategies for diagnosis of pancreatic cancer

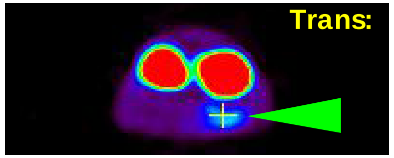
Optical Imaging, ^{64}Cu-RAFT-RGD PET imaging and *ex vivo* Gross inspection

In Vivo Optical



PET





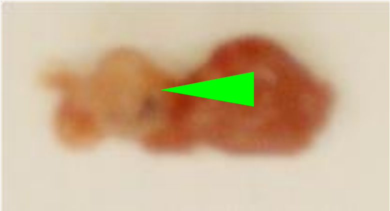
BxPC3-RFP tumor SUV = 0.43

^{64}Cu-Cyclam-RAFT-c-(-RGDfK-)$_4$ PET

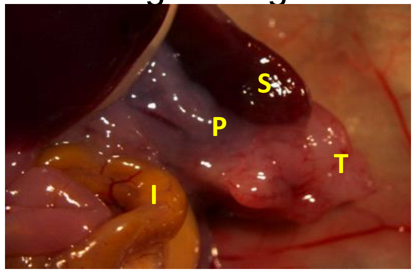
(2 hr, Static 30min a/t 0.200 mCi)

Gross

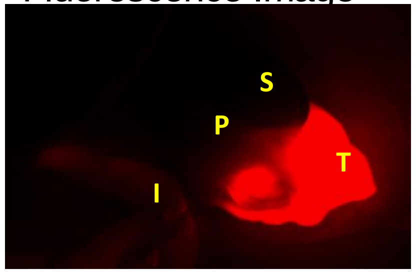
Gross specimen



White light Image



Fluorescence Image

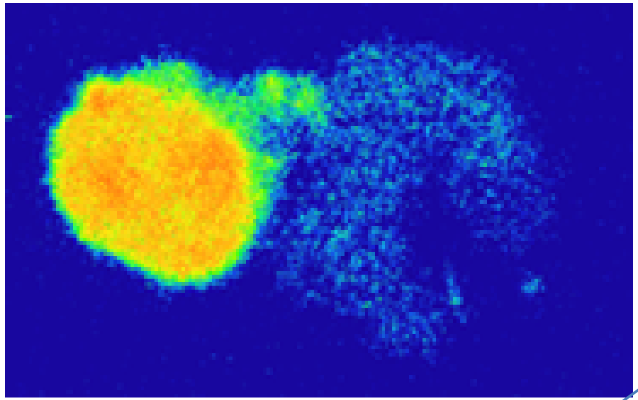


T = Tumor, P = Pancreas,
S =Spleen, I = Intestine

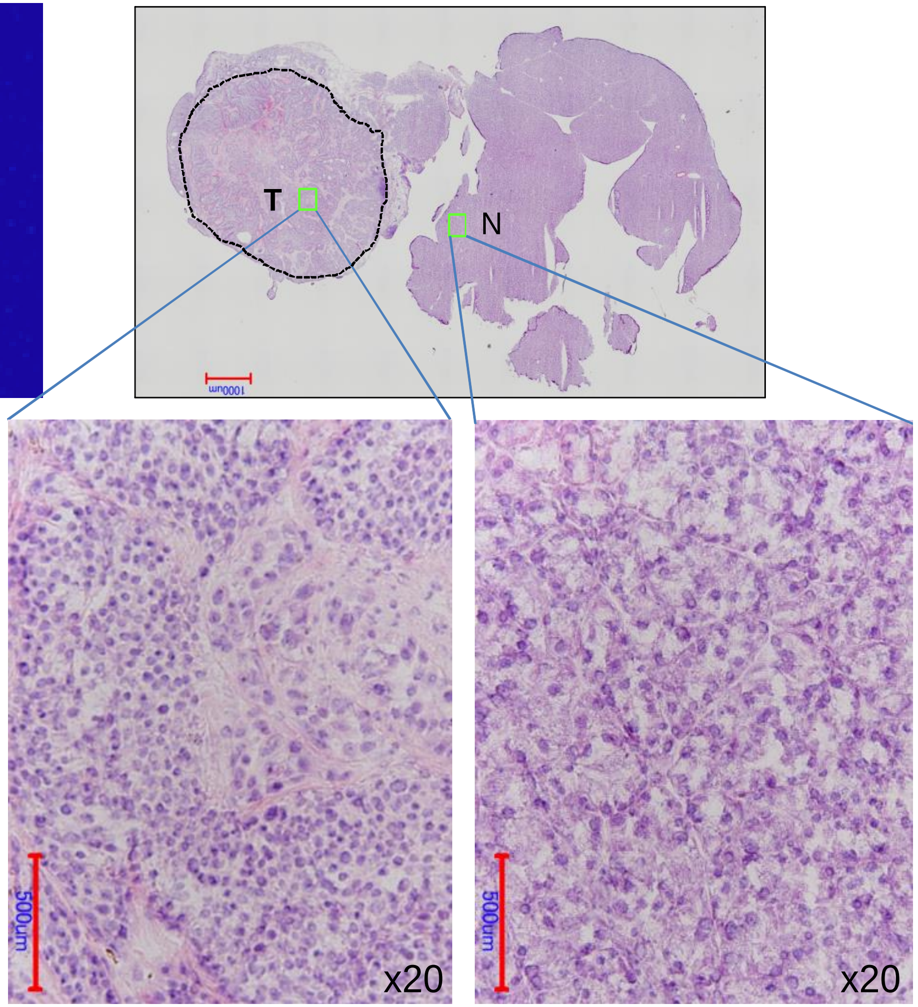
New strategies for diagnosis of pancreatic cancer

Ex vivo Autoradiography and H&E staining of tumor frozen sections after imaging

Autoradiography



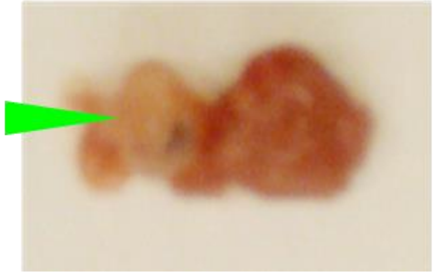
Histological examination



Tumor

Normal Pancreas

Excised tumor and normal Pan:

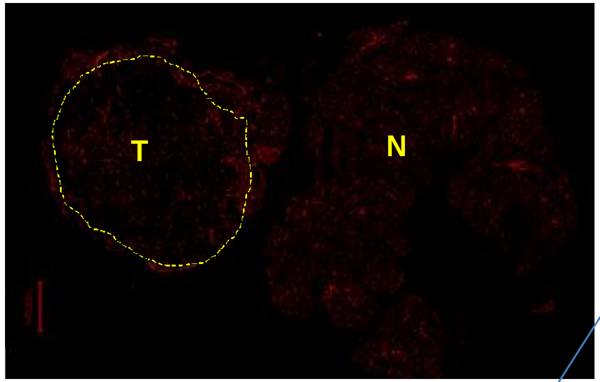


Neoplastic cells with pleomorphic nuclei, prominent nucleoli and some regions of desmoplasia

New strategies for diagnosis of pancreatic cancer

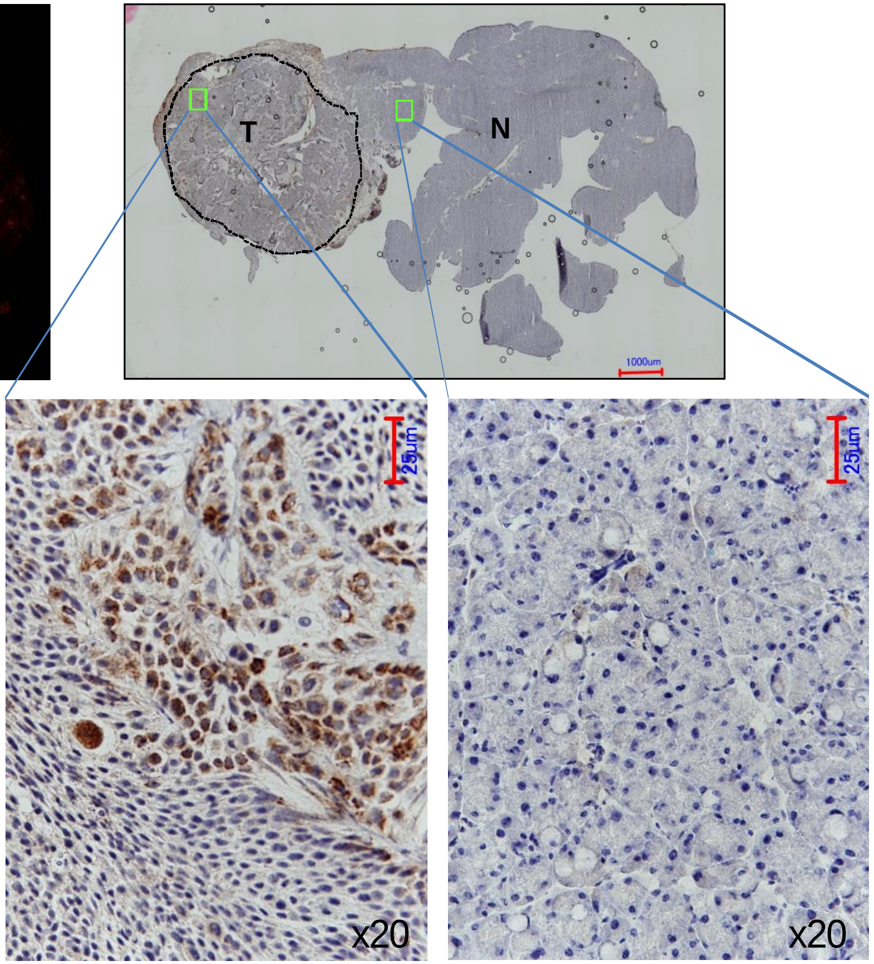
Immunofluorescence and Immunohistochemical staining of tumor frozen section

IF exam: with CD 31



Unabundant vascularity in tumor area

IHC exam: with $\alpha_v\beta_3$



Tumor

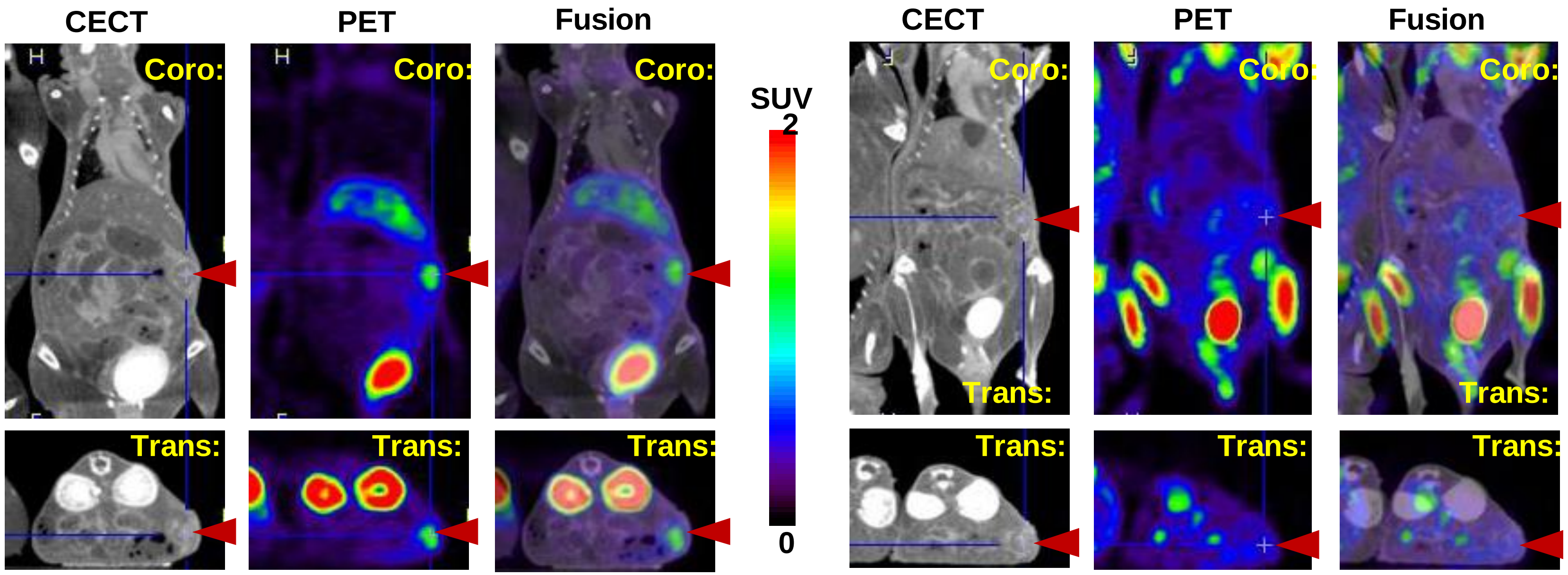
Normal Pancreas

Enhanced expression of $\alpha_v\beta_3$ in tumor area

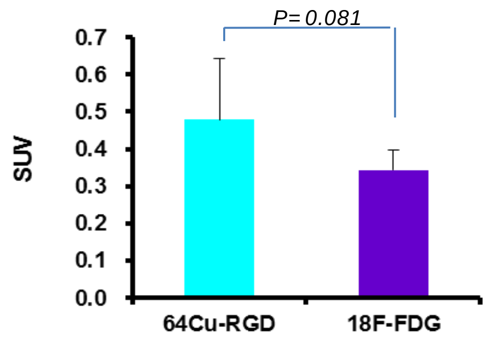
New strategies for diagnosis of pancreatic cancer

Comparison of ^{64}Cu-RAFT-RGD and ^{18}F-FDG uptake (SUV) in orthotopic pancreatic tumor

^{64}Cu-RAFT-RGD ^{18}F-FDG



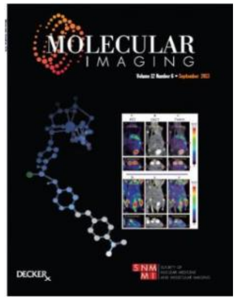
Standardized Uptake Value (SUV)



^{64}Cu-RAFTRGD (n = 6), ^{18}F-FDG (n = 8)

Conclusion

Our results indicate that ^{64}Cu-RAFT-RGD might be a potentially applicable candidate for the diagnosis of pancreatic cancer expressing $\alpha_v\beta_3$.



Aung W, Jin ZH et al. Mol Imag 2013

Outline of today's talk

◆ **Introduction of Pancreatic Cancer**

◆ **Animal model for preclinical research**

◆ **Introduction of Molecular Imaging**

◆ **Some results of our researches (New strategies for diagnosis and treatment of pancreatic cancer)**

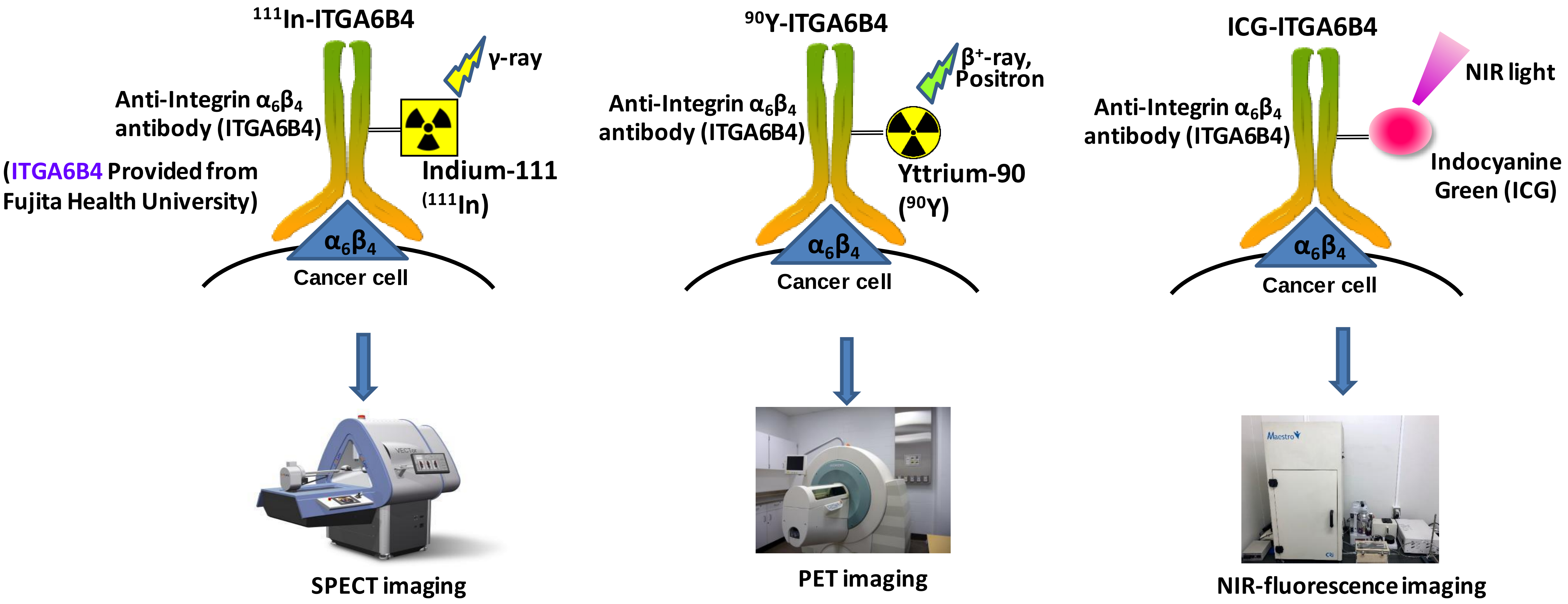
- Micro-Positron Emission Tomography/Contrast-Enhanced Computed Tomography imaging of orthotopic pancreatic tumor-bearing mice using the **$\alpha_v\beta_3$ integrin** tracer **^{64}Cu-labeled cyclam-RAFT-c(-RGDfK-)$_4$**. *Mol Imag; 12(6): 376-387 (2013).* (Aung W et.al) ← **Peptide**
- Immunotargeting of **integrin $\alpha_6\beta_4$** for single-photon emission computed tomography and near-infrared fluorescence imaging in a pancreatic cancer model. *Mol Imag; 15: (2016).* (Aung W et.al) ← **Antibody**
- Radioimmunotherapy of pancreatic cancer xenografts in nude mice using ^{90}Y-labeled anti-$\alpha_6\beta_4$ integrin antibody. *Oncotarget; 7: (2016).* (Aung W et.al) ← **Antibody**
- Anticancer effect of dihydroartemisinin (DHA) in a pancreatic tumor model evaluated by conventional methods and optical imaging. *Anticancer Res; 31(5):1549-1558 (2011).* (Aung W et.al) ← **Drug**

New strategies for diagnosis of pancreatic cancer

Immunotargeting of Integrin ($\alpha_6\beta_4$) with SPECT, PET and NIR-fluorescence imaging

Objective

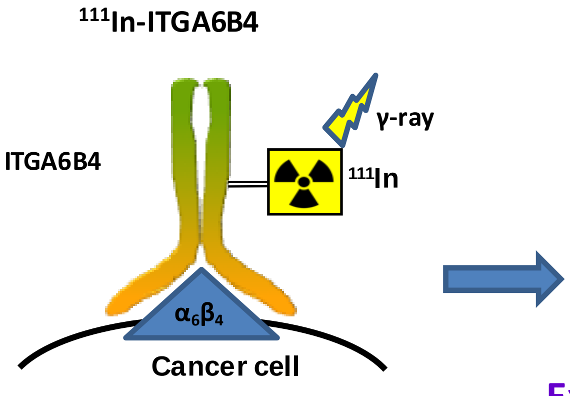
Immunotargeting of integrin $\alpha_6\beta_4$ for single-photon emission computed tomography, PET and near-infrared fluorescence imaging in a pancreatic cancer model

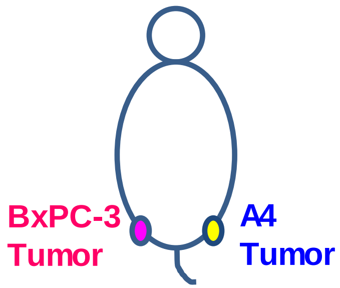


New strategies for diagnosis of pancreatic cancer

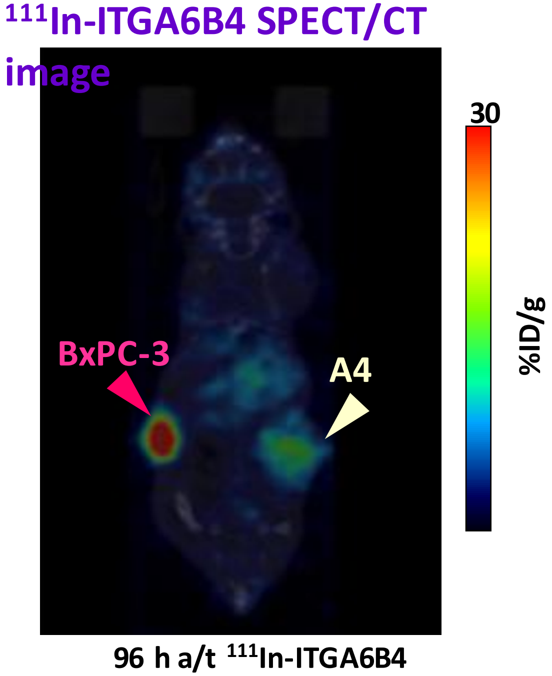
Immunotargeting of Integrin ($\alpha_6\beta_4$) with ^{111}In-ITGA6B4-SPECT imaging

◆ *In vivo* visualization of tumor by SPECT/CT imaging with ^{111}In-ITGA6B4

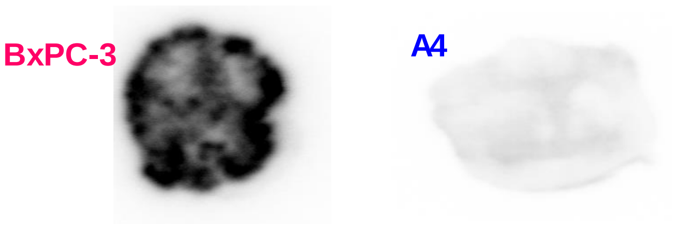




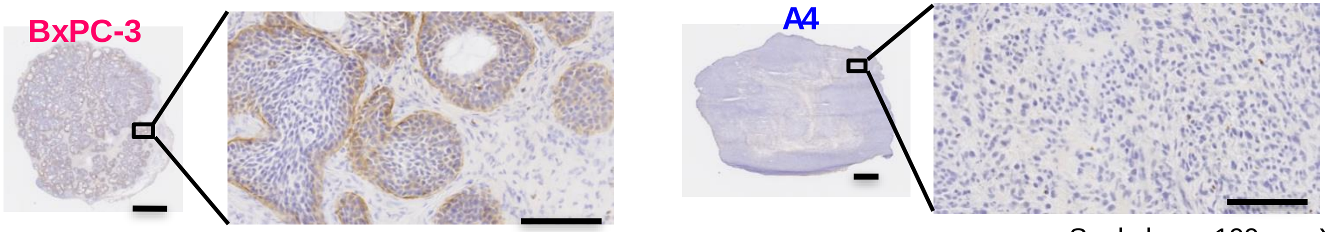
Expression of $\alpha_6\beta_4$ in cell line (Confirmed with WB)



Ex vivo Autoradiography



IHC with ITGA6B4



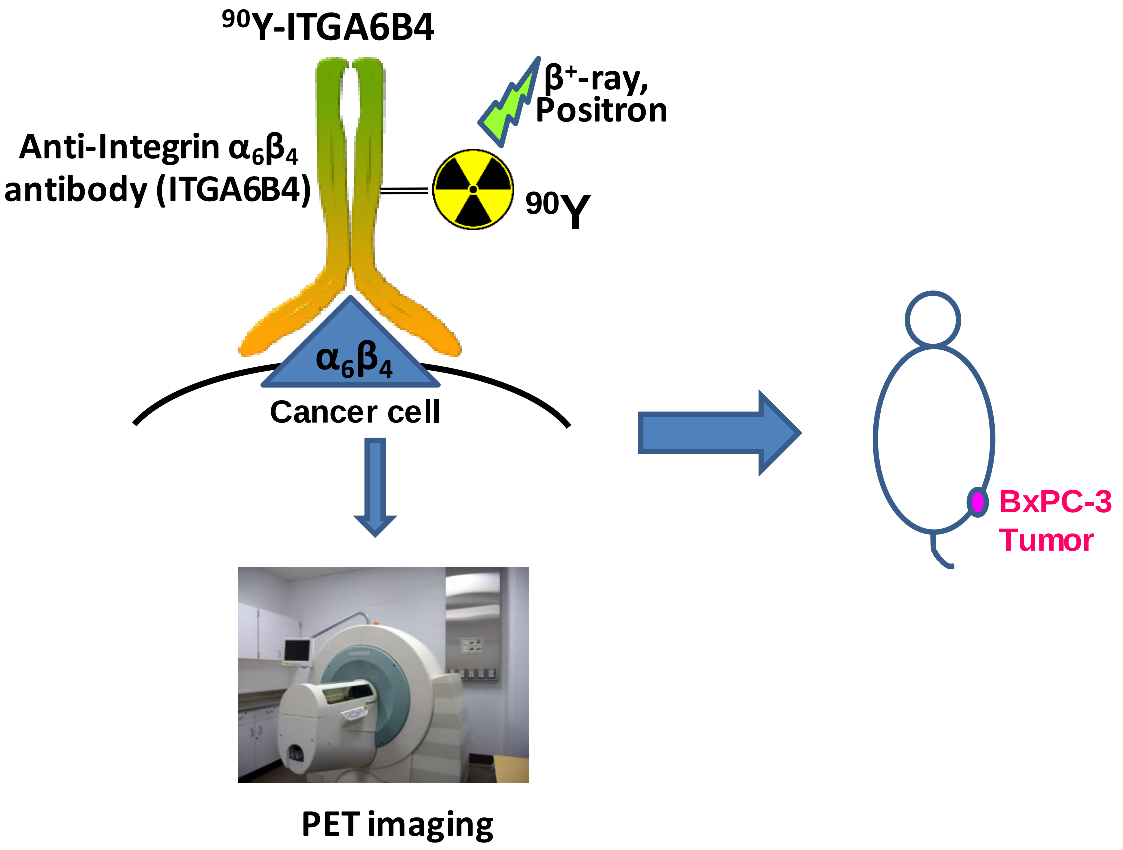
Scale bar = 100 μm, X20

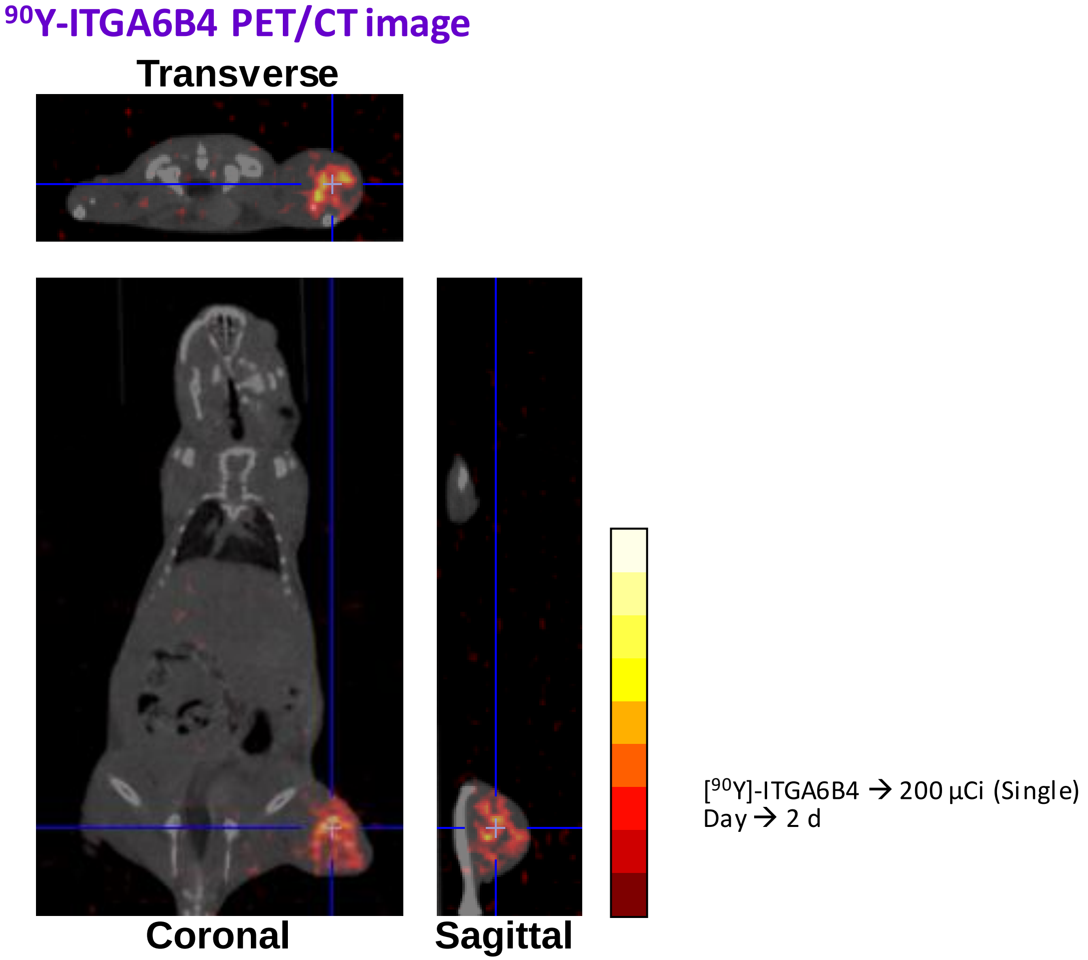
Aung W et al. Mol Imag 2016

New strategies for diagnosis of pancreatic cancer

Immunotargeting of Integrin ($\alpha_6\beta_4$) with ^{90}Y-ITGA6B4-PET

- Visualization of ^{90}Y-ITGA6B4 uptake in tumor with PET/CT



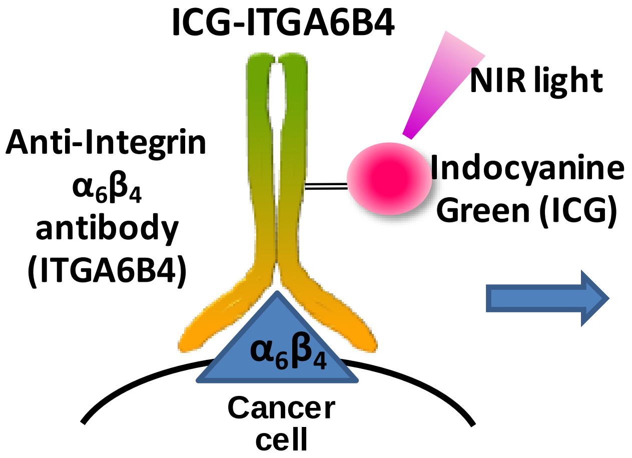


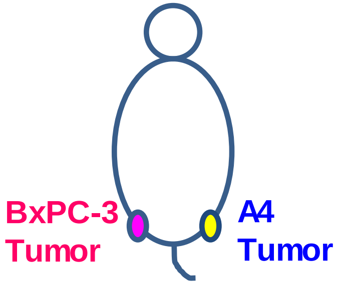
Aung W et al. Oncotarget 2016

New strategies for diagnosis of pancreatic cancer

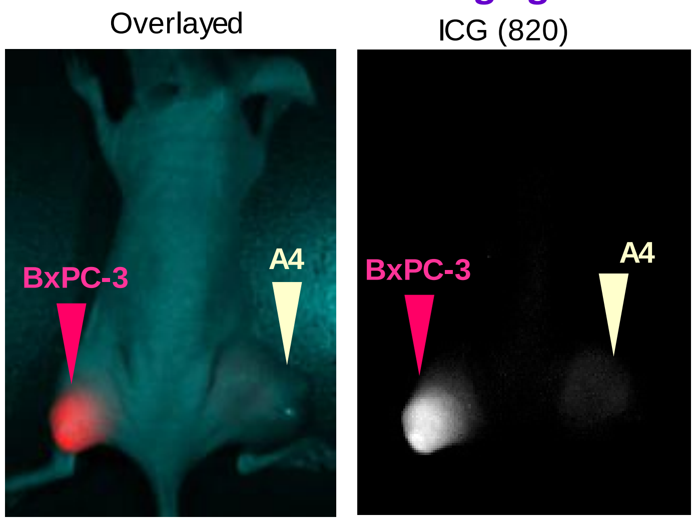
Immunotargeting of Integrin ($\alpha_6\beta_4$) with ICG-ITGA6B4 imaging

◆ *In vivo* visualization of tumor by NIR-fluorescence imaging with ICG-ITGA6B4



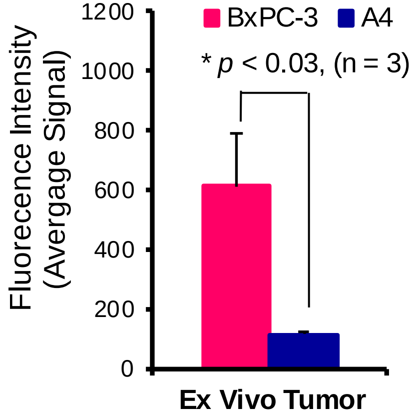


ICG-ITGA6B4 NIR imaging

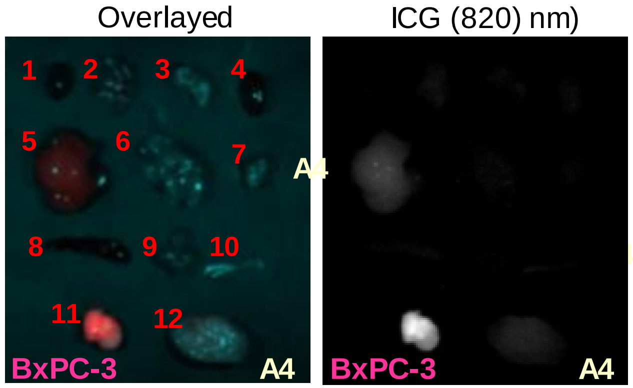


96 h a/t ICG-ITGA6B4

Fluorescence Signal



Ex vivo tumors and tissues



1 = Heart
2 = Lung
3 = Stomach
4 = Kidney
5 = Liver
6 = Small intestine
7 = Pancreas
8 = Spleen
9 = Muscle
10 = Bone
11 = BxPC3 tumor
12 = A4 tumor

Conclusion

Our results validated the specific binding of three probes to $\alpha_6\beta_4$. Therefore, $\alpha_6\beta_4$ is a desirable target for the diagnosis of pancreatic cancer and that it could be detected by radionuclide imaging and NIR imaging using a radiolabeled or ICG-labeled $\alpha_6\beta_4$ antibody.

Aung W, et al. Mol Imag 2016

Current trend for diagnosis and treatment of pancreatic cancer

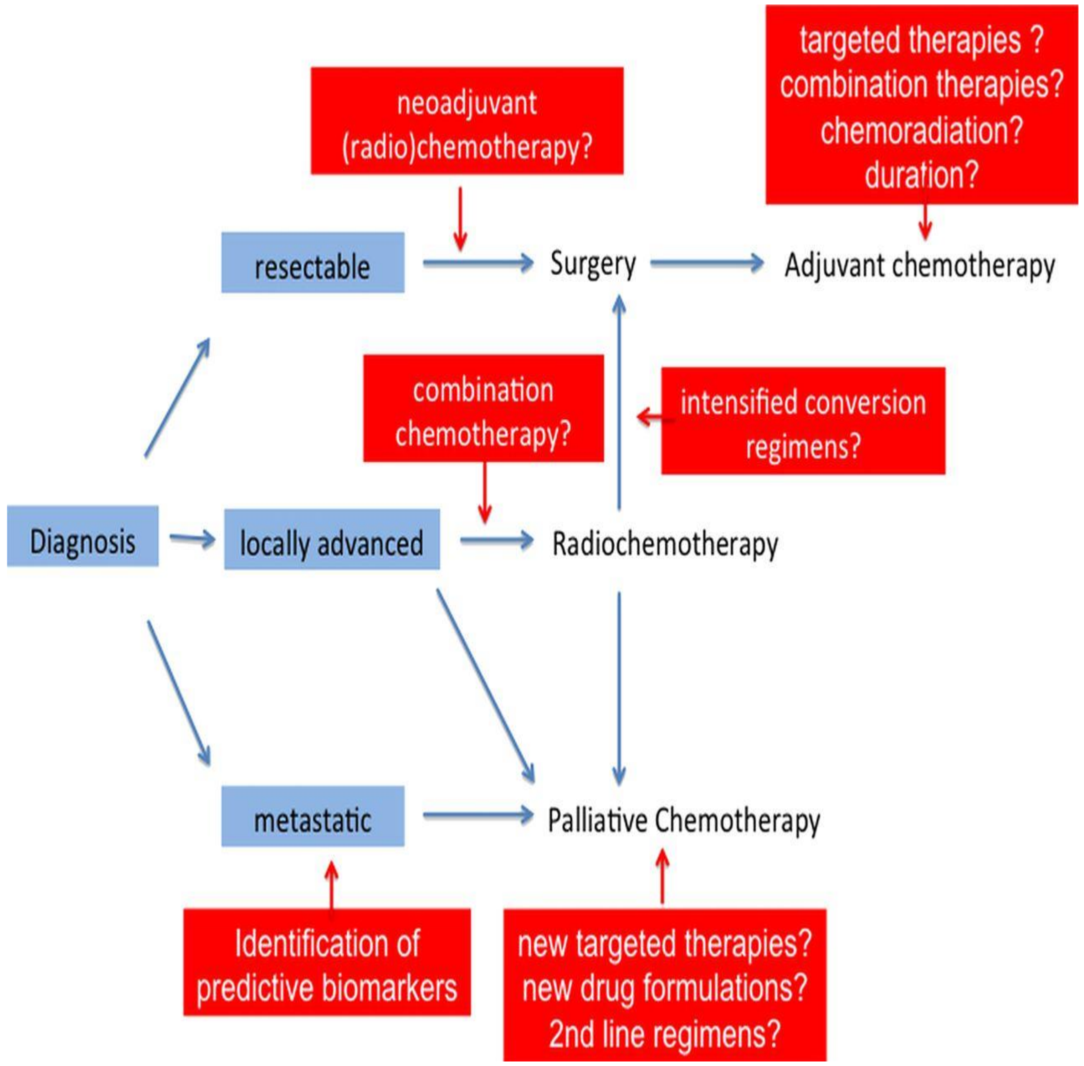
Current trend for pancreatic cancer treatment and outcomes

◆ Current treatment

- Surgery (10~15%)
- Chemotherapy
    - Gemcitabine or Fluorouracil
    - FOLFIRINOX chemotherapy regimen (Folinic acid, Leucovorin Fluorouracil, Irinotecan, Oxaliplatin)
    - Albumin-bound Paclitaxel (Abraxane®)
- Adjuvant radiotherapy/ Neoadjuvant therapy
- Palliative care

◆ Outcomes

- Not yet obtained satisfactory success
  (No early detection test, No curative treatments)
- Poor prognosis
  (No change in 40 years)



New strategies treatment of pancreatic cancer

- **Immunotherapy**
  - Immune checkpoint blockade agents (Anti-PD-1, Anti-PD-L1, Anti-CTLA-4)
  - Antitumor Vaccines

- **Antibody-drug conjugate (ADC)**

- **Radioimmunotherapy (RIT)**
  - IT represents a selective internal radiation therapy, that is, the use of cytotoxic radionuclides (eg: Y-90, Lu-177, Cu-64, At-211) conjugated to tumor-directed antibodies.

- **Molecular-targeted Therapy**
  - Anti-angiogenesis drug, tyrosine kinase inhihitors

- **Tumour-targeted oncolytic viral Therapy (TOVs)**
  - ONYX-015

- **High-intensity focused ultrasound (HIFU)**

- **Photoimmunotherapy (PIT)/Photodynamic therapy (PDT)**
  - Advanced alternative molecular-targeted cancer therapy committed by tumor targeted antibody labeled with photosensitizing fluorophore which is activated and cytotoxic upon irradiation with NIR light.

Outline of today's talk

- **Introduction of Pancreatic Cancer**

- **Animal model for preclinical research**

- **Introduction of Molecular Imaging**

- **Some results of our researches (New strategies for diagnosis and treatment of pancreatic cancer)**
  - Micro-Positron Emission Tomography/Contrast-Enhanced Computed Tomography imaging of orthotopic pancreatic tumor-bearing mice using the **$\alpha_v\beta_3$ integrin** tracer **^{64}Cu-labeled cyclam-RAFT-c(-RGDfK-)$_4$**. *Mol Imag; 12(6): 376-387 (2013).* (Aung W et.al) ← **Peptide**
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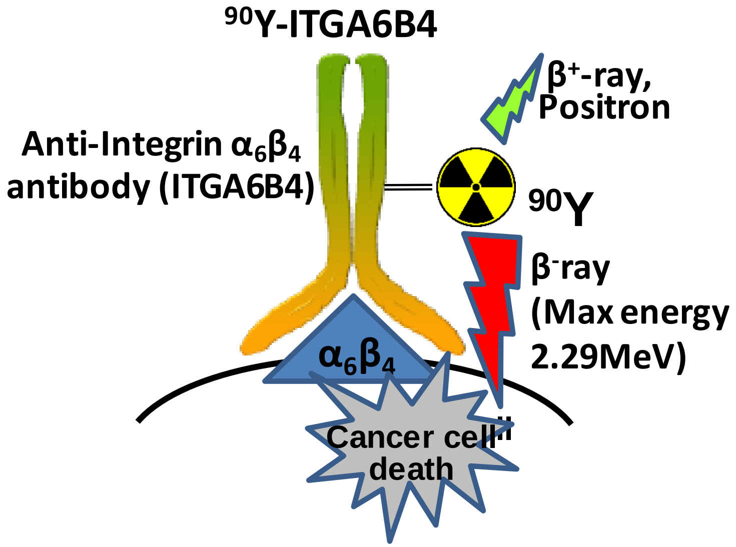
New strategies treatment of pancreatic cancer

Radioimmunotherapy (RIT) using ^{90}Y-labeled anti-$\alpha_6\beta_4$ integrin antibody

Objective

To assess the radioimmunotherapeutic effet of ^{90}Y-ITGA6B4 in a pancreatic cancer model



Study Design

◆ **Preparation of probe**

1. Radiolabeling (Yittrium-90, HL 2.7 d, Max energy of β emission 2.29 MeV, effective path length 5.3 mm) of Antibody

◆ **Subjects (tumor bearing nude mice)**

Five groups of mice bearing subcutaneous pancreatic tumor (BxPC-3) receiving

1. ^{90}Y-ITGA6B4 (20 μg, 3.7 MBq) x 1 times inj: (HS)
2. ^{90}Y-ITGA6B4 (20 μg, 3.7 MBq) x 2 times inj: (HD)
3. Cold ITGA6B4 x (20 μg) 1 times inj: (CS)
4. Cold ITGA6B4 x (20 μg) 2 times inj: (CD)
5. Untreated Control (no injection) (C)

◆ **To examine the treatment efficacy**

1. Tumor volume measurement (Every 3-4 days)
2. Immunohistochemical examination of tumor (2 days after ^{90}Y-ITGA6B4 injection)

◆ **To examine the treatment toxicity**

1. Body weight change
2. Blood tests

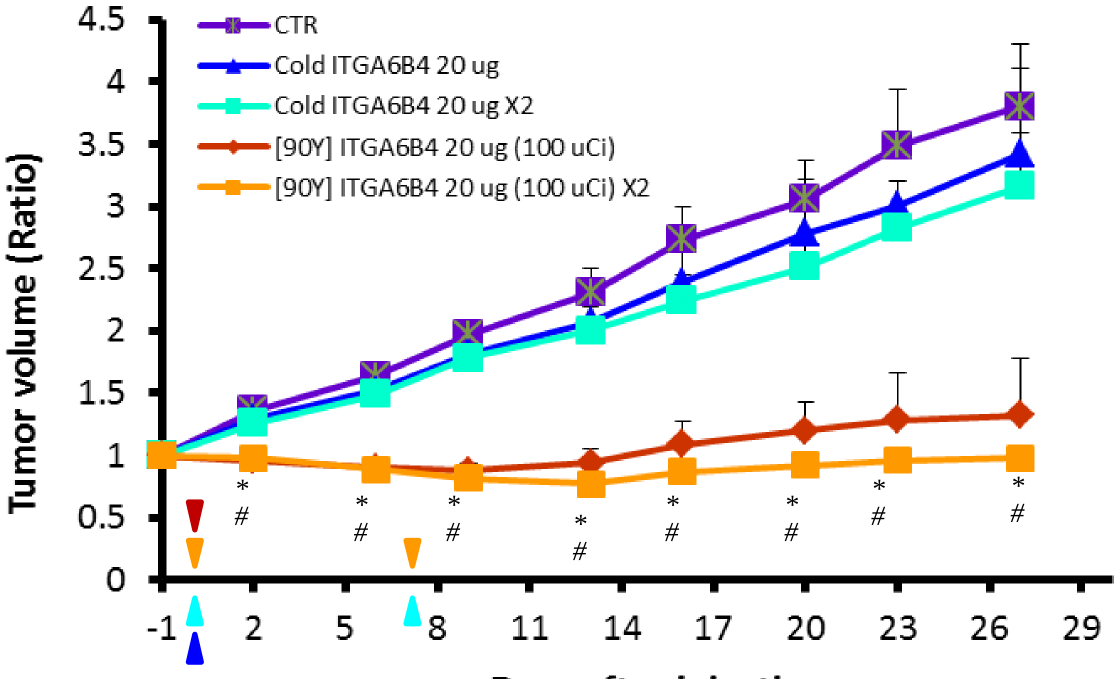
1. Biochemical tests (Liver function)
2. Biochemical tests (Renal function)

RIT using ^{90}Y-labeled anti-$\alpha_6\beta_4$ integrin antibody

Evaluation of treatment efficacy

Tumor volume change

-Monitored by caliper measurements (V(mm³)=length (mm) × (width [mm])²/2)
-Relative tumor volume was calculated as the volume at the indicated day divided by the volume at the 1 day before of treatment.



(n= 6~7)

* $p < 0.04$ 100 µCi injection group *vs.* Other groups (Control, Cold ITGA6B4, Cold ITGA6B4 x2) at each time point (n= 6~7)
\# $p < 0.04$ 100 µCi injection x2 group *vs.* Other groups (Control, Cold ITGA6B4, Cold ITGA6B4 x2) at each time point (n= 6~7)

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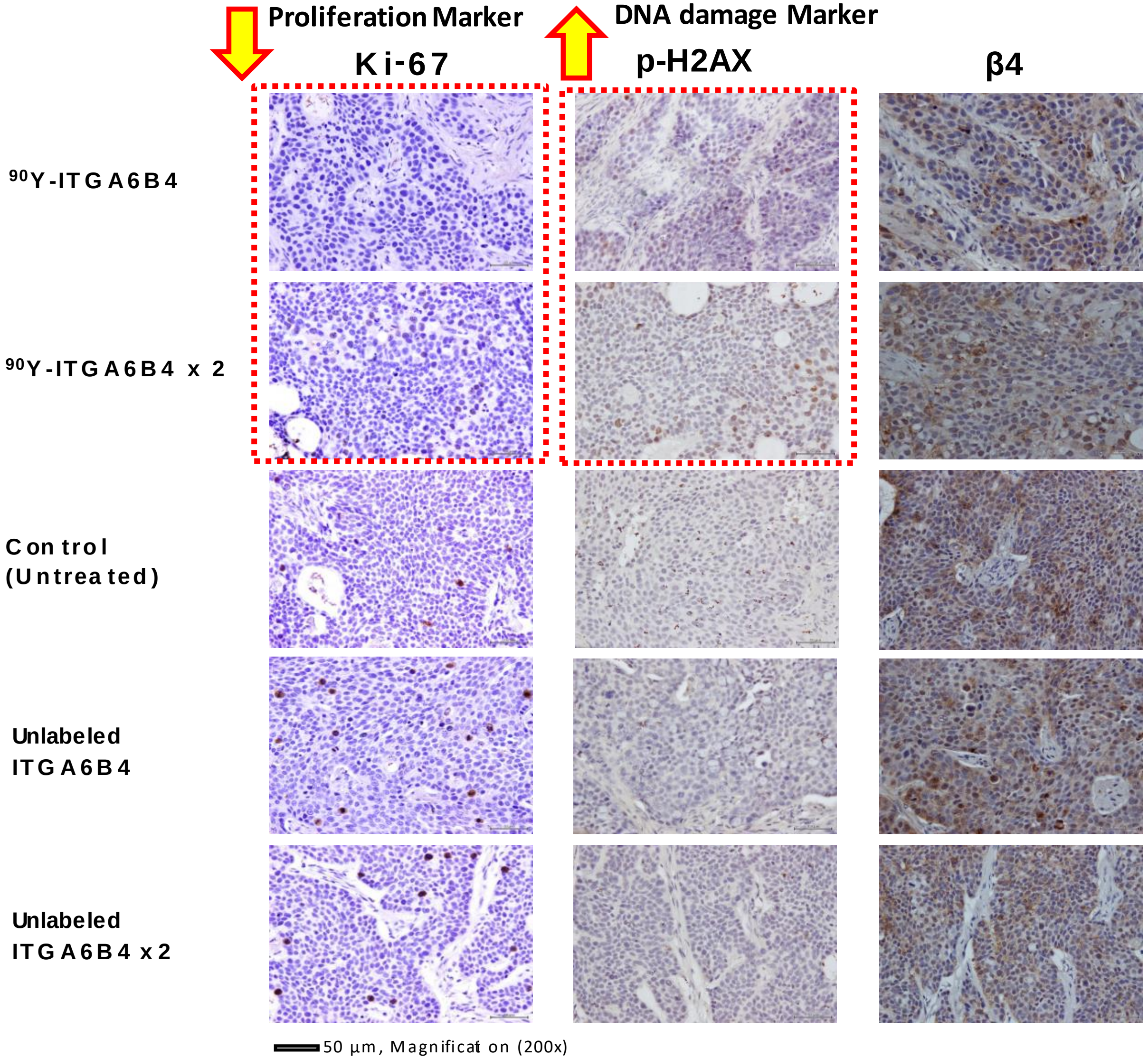
RIT using ^{90}Y-labeled anti-$\alpha_6\beta_4$ integrin antibody

Evaluation of treatment efficacy

Comparison of immunohistochemical examination (Ki-67, p-H2AX)



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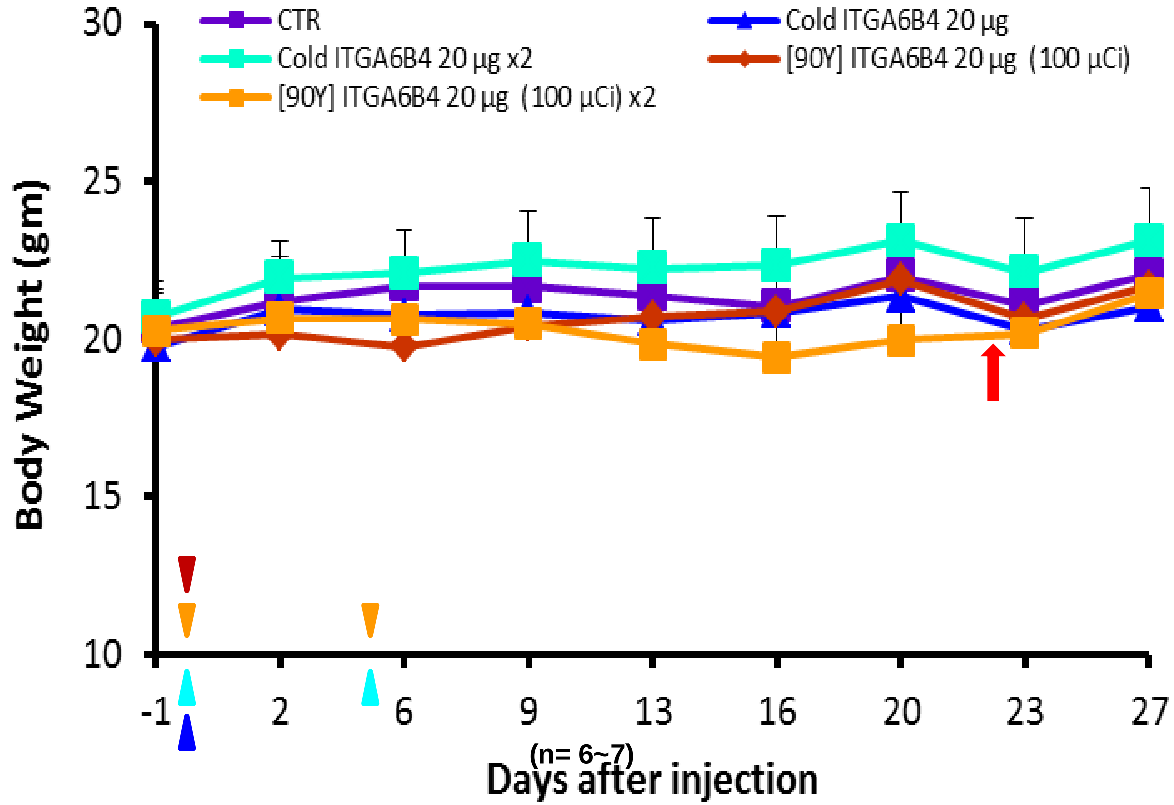
RIT using ^{90}Y-labeled anti-$\alpha_6\beta_4$ integrin antibody

Examination of treatment toxicity

Body weight change



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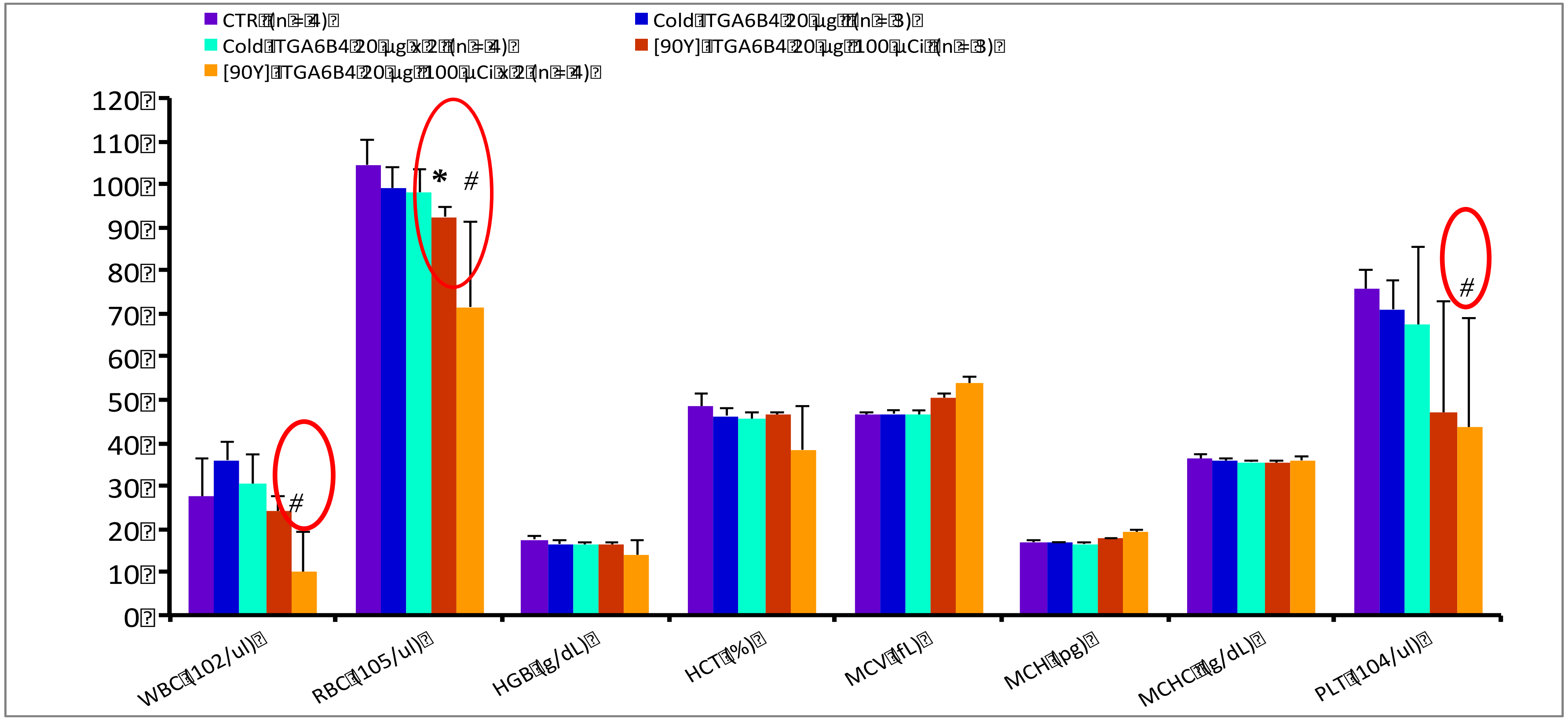
RIT using ^{90}Y-labeled anti-$\alpha_6\beta_4$ integrin antibody

Examination of treatment toxicity

Blood tests for hematological parameters



47~92	70.9~87.0	13.5~17.1	40.4~49.6	52.4~61.2	17.8~20.2	32.0~35.2	59.7~149

* $p < 0.05$ 100 µCi injection group *vs.* Control group
\# $p < 0.05$ 100 µCi injection x 2 group *vs.* Control group

(Myelosuppression → leucopenia, thrombocytopenia, anemia)

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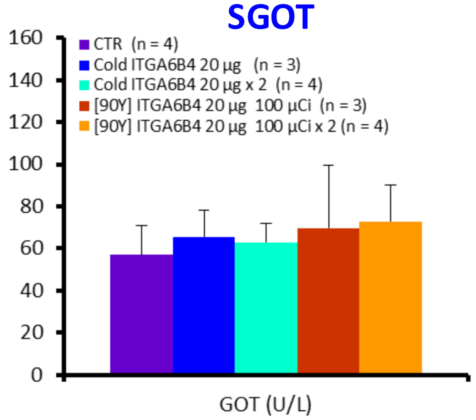
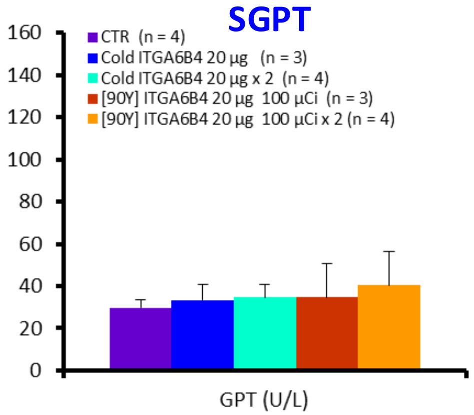
RIT using ^{90}Y-labeled anti-$\alpha_6\beta_4$ integrin antibody

Examination of treatment toxicity

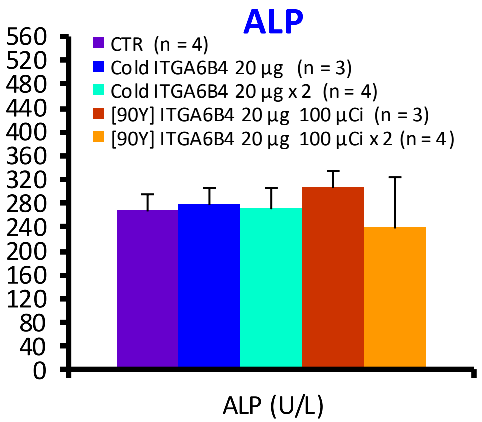
Biochemical tests (Liver Function)



8~38

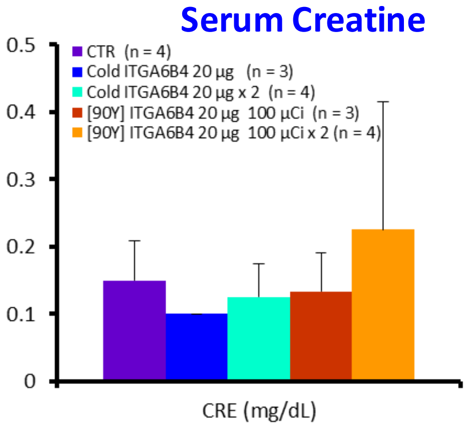


4~44

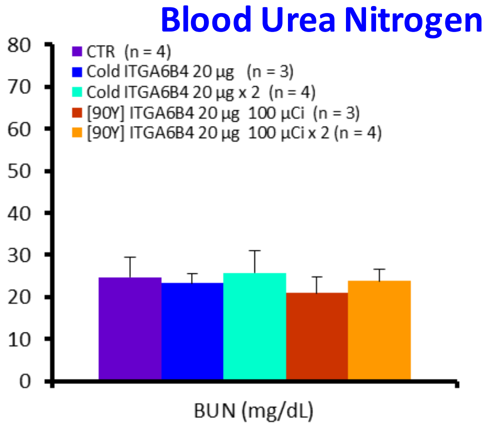


104~338

Biochemical tests (Renal Function)



M- 0.6~1.1; F- 0.4~0.8



8~23

No significant differences → Between 100 μCi injection group *vs.* Other groups (Control, Cold ITGA6B4, Cold ITGA6B4 x2)
No significant differences → Between 100 μCi injection group x2 group *vs.* Other groups (Control, Cold ITGA6B4, Cold ITGA6B4 x2)

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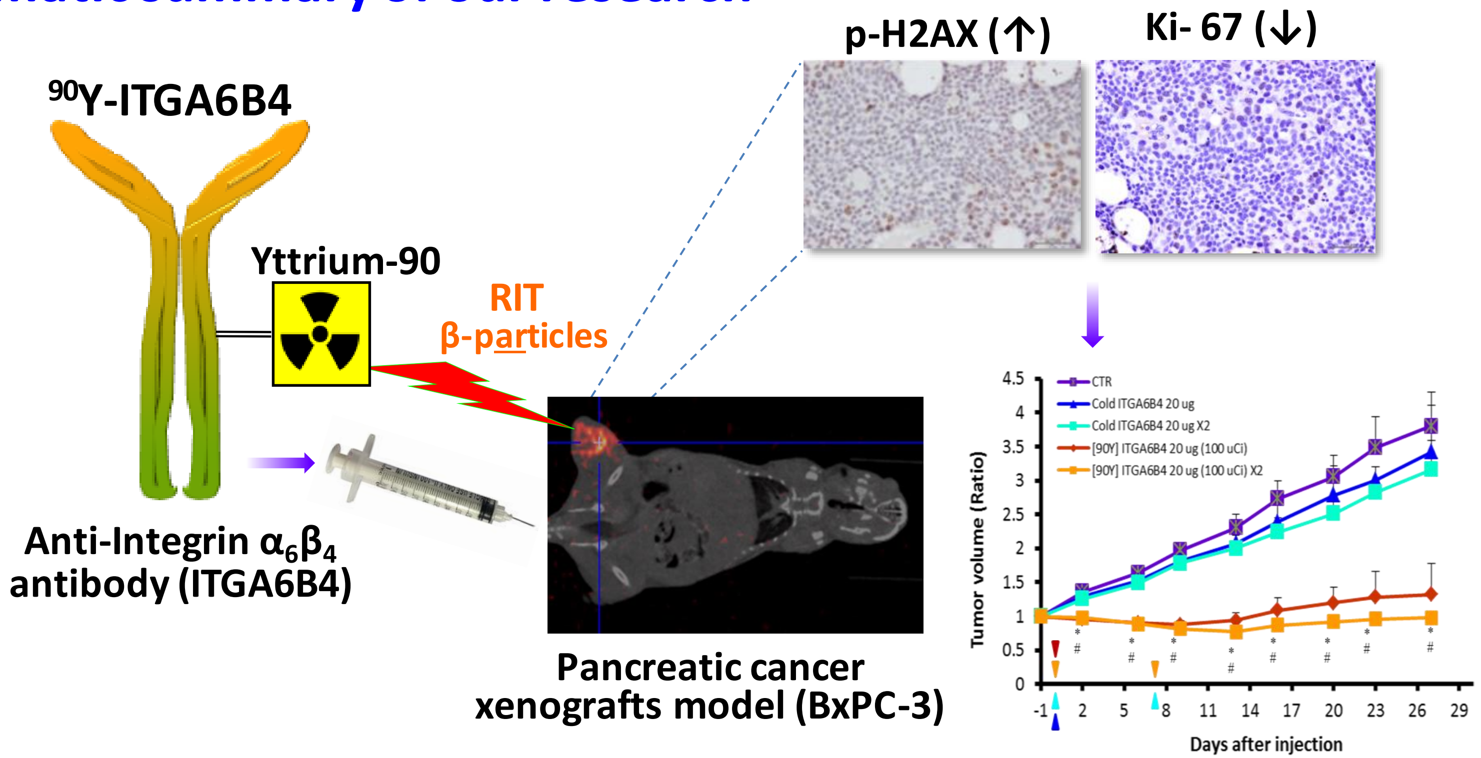
RIT using ^{90}Y-labeled anti-$\alpha_6\beta_4$ integrin antibody

Schematic summary of our research



Conclusion

Our results suggest that Yttrium-90-labeled ITGA6B4 is a promising radioimmunotherapeutic agent against $\alpha_6\beta_4$ overexpressing tumors.

Aung W et al. Oncotarget 2016

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- **Animal model for preclinical research**

- **Introduction of Molecular Imaging**

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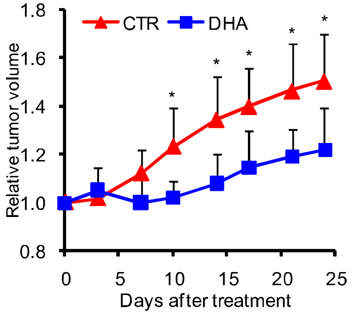
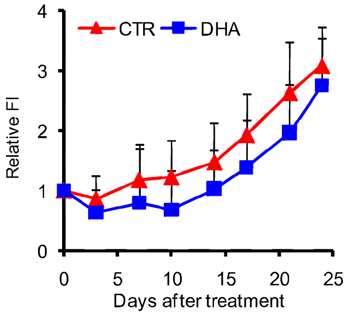
New strategies treatment of pancreatic cancer

Objective

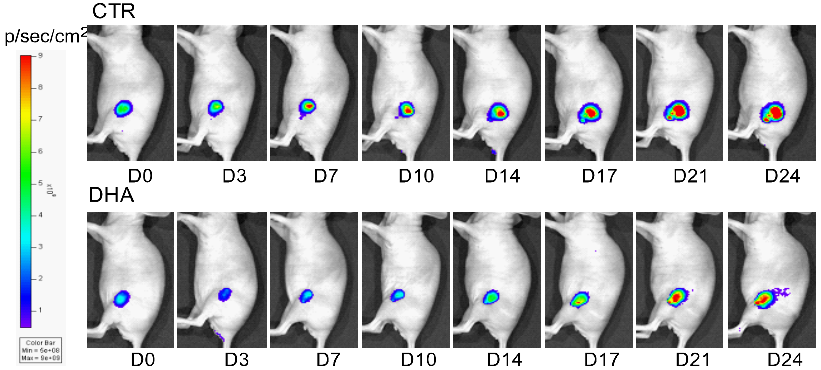
To evaluate the anticancer effect of dihydroartemisinin (DHA) in a pancreatic tumor model by the conventional methods and optical imaging

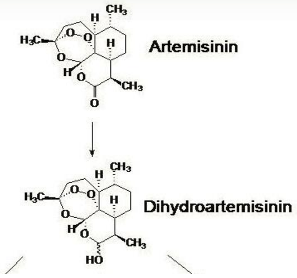
Effect of DHA on tumor growth (BxPC-3-RFP)



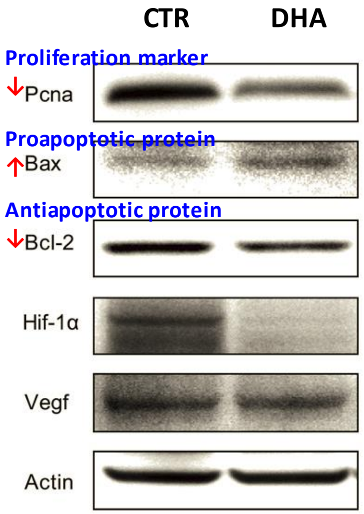


Representative images for temporal analysis of a tumor

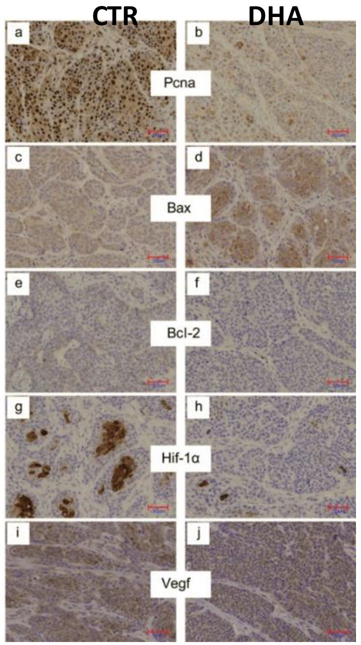




Western blot



IHC



Conclusion

Our findings substantiate that DHA is a potential anticancer therapeutic for pancreatic cancer.

Aung W et al. Anticancer Res; 2011

Take-home messages

◆ Molecular imaging and Animal Model can be applied to many aspects of Cancer Research:

- Diagnosis → Early detection/screening
- Therapy → Monitoring of therapeutic drug delivery/effect of treatment/Follow-up of treatment and Treatment selection

◆ It is expected that molecular imaging with various imaging modalities will be integrated into more frequent clinical use in future.

◆ **Although the rate of successful translation from animal models to human diseases is modest, further advances in technology and knowledges in various research fields such as molecular biology, radiochemistry, photochemistry, robotics, computers, and nanomaterials will accelerate the application.**

NLP Seminar

Thank you for your attention！