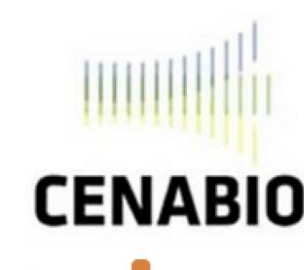




Novos Alvos Moleculares para Radiofármacos Teranósticos

Prof. Sergio A. L. Souza
Faculdade de Medicina - UFRJ



Conflito de interesses

- Prof. Associado Faculdade de Medicina da UFRJ
- Chefe do Departamento de Radiologia / FM / UFRJ
- Prof. do Programa de Pós-Graduação em Medicina (Radiologia)/UFRJ
- Pesquisador do Laboratório de Marcação de Células e Moléculas - HUCFF/UFRJ
- Coordenador do Laboratório microPET/SPECT/CT - Cenabio/UFRJ
- Representante da SBMN no Comitê de Educação Continuada da ALASBIMN
- Diretor adjunto substituto de Ciência e Tecnologia em Inovação e Saúde da FM/UFRJ



O que é Teranóstico?

Terapia + Diagnóstico = Teranóstico

Radionuclídeo

γ
(diagnóstico)

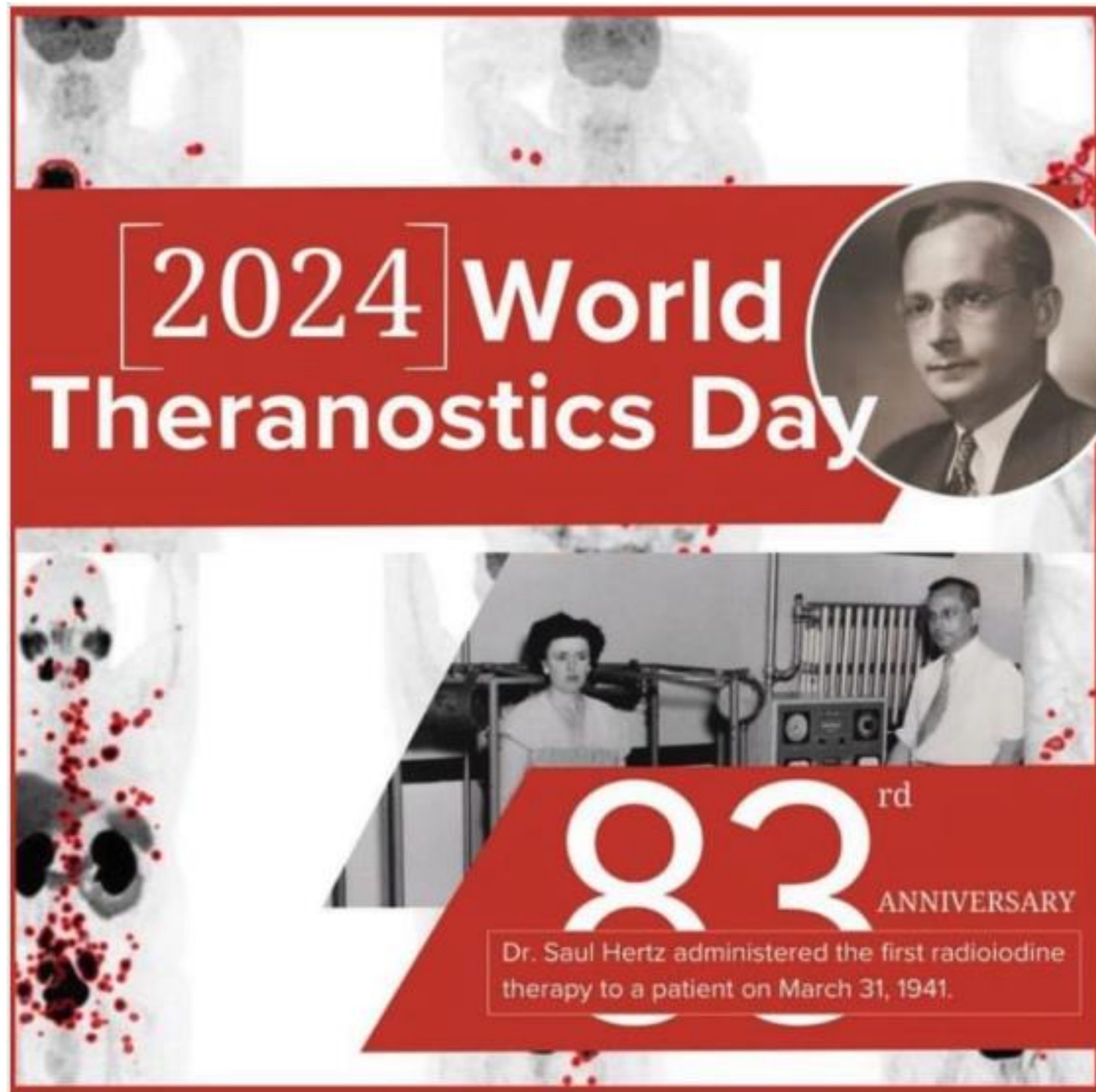
$\beta^- \alpha$
(terapia)

Par de
Radionuclídeos

$\gamma \beta^+$
(diagnóstico)

$\beta^- \alpha$
(terapia)

I-131 – Radionuclídeo Teranóstico Original (1941)



[2024] World Theranostics Day

83rd ANNIVERSARY

Dr. Saul Hertz administered the first radioiodine therapy to a patient on March 31, 1941.

The graphic features a red background with white text and a circular portrait of a man in a suit. It also includes a small image of a woman in a hospital bed and a man standing next to her.

Usado tanto para o diagnóstico, quanto para o tratamento.



RADIO-IODINE HALTS ONE TYPE OF CANCER

Radioactive chemical brings about history-making recovery of patient dying from thyroid tumors

The man shown in the contrasting portraits at right is a Brooklyn shoe salesman named Bernard Brunstein who is destined to become one of the most famous patients in medical history. Brunstein is the first person known to be cured (insofar as a cure can be established by medical tests on a living patient) of metastatic cancer, a form of the disease in which the malignancy spreads through the body from an original tumor. Metastatic cancer has always been 100% fatal. But Brunstein's tumors were destroyed in a simple, almost miraculous way: by the drinking of four doses of radioactive iodine.

When Brunstein was admitted to New York's Montefiore Hospital seven years ago he appeared to be suffering from an overactive thyroid gland rather than from cancer. He had a very fast heart and quivering hands, and he was weak and emaciated. But examination revealed that he had no thyroid gland; it had been removed by surgery 19 years before when it had become cancerous. Apparently some of the cancer cells had sloughed off, however, and had been carried through the circulatory system to other parts of his body: eight cancerous tumors were found growing into the patient's lungs, ribs, femur, spine, pelvis and skull. The tumors, composed of malignant thyroid tissue, were secreting hormones and were otherwise behaving like thyroid glands.

Radio-iodine was given to Brunstein on the theory that his thyroid-like tumors would absorb the drug just as a normal thyroid gland picks up ordinary iodine. If they did, they would be destroyed. For while radio-

iodine is chemically identical with ordinary iodine, it gives off a powerful radiation that can kill any tissue that absorbs it in sufficient concentration. The chemical had never been effectively used as a treatment for cancer, but Brunstein agreed to try it in the hope that it might help. It did. Three months after he drank his first glassful of the tasteless, colorless liquid, his heart began to slow down and he started to put on weight. Geiger counters placed over the tumor sites revealed that there was a heavy concentration of radio-iodine in these areas. After three additional doses the tumors slowly began to diminish in size and eventually disappeared altogether.

Last May a section of Brunstein's skull was removed for a microscopic examination of the site of one of his tumors. Only scar tissue and dead cells remained, and not a single living cancer cell was found (left).

From his experience with Brunstein and subsequent cases Dr. S. M. Seiffin of Montefiore Hospital, an endocrinologist and a pioneer in radiotherapy, has deduced that radio-iodine does not work in many ordinary thyroid cancer cases because most of the chemical is picked up by the thyroid gland itself, and little of it gets to distant tumors. But if the gland is destroyed, the medicine has a better chance of reaching the diseased areas. Of a group of 12 patients treated by Seiffin since 1942, five appear to be recovering and in two others the tumors have stopped growing. Of the five who died, two had their lives prolonged several years, two were near-death when treatment was started, and one died of a different disease.

ATOMIC MEDICINE

Cured of Goitre With One Dose

of Cancer, Goitre and Leukemia

May 11, 1946

RADIOACTIVE IODINE IN THE STUDY OF THYROID PHYSIOLOGY

VII. The Use of Radioactive Iodine Therapy in Hyperthyroidism

SAUL HERTZ, M.D.; ARTHUR ROBERTS, Ph.D.

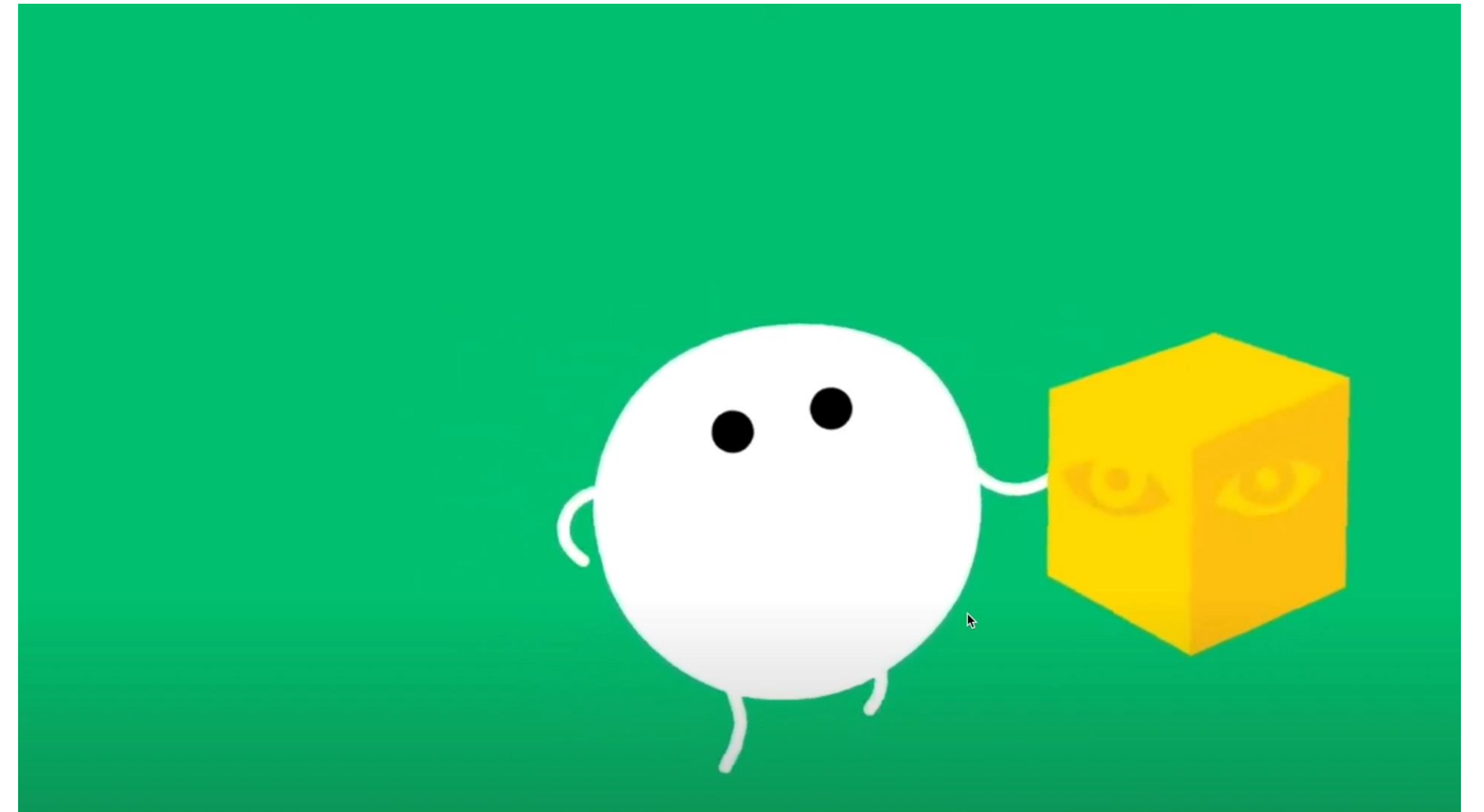
Author Affiliations

JAMA. 1946;131(2):81-86. doi:10.1001/jama.1946.02570190005002

Life Magazine Oct 1949 Edition

Aplicações já bem estabelecidas

- ☢ Câncer de Tireóide
- ☢ Tumores Neuroendócrinos
- ☢ Câncer de Próstata



Novos Alvos Moleculares

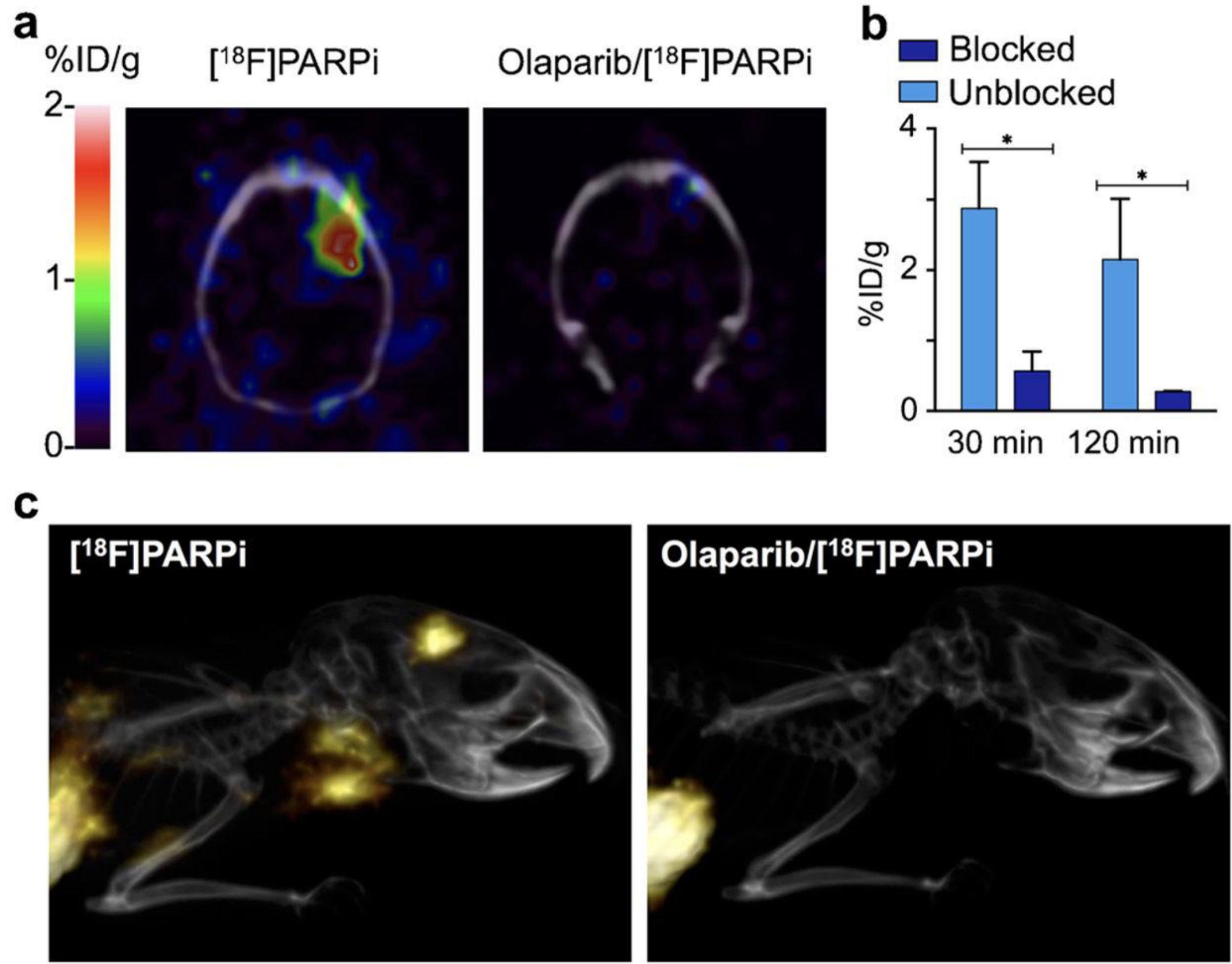
- ⦿ Diferentes doenças expressam diferentes alvos em sua superfície
- ⦿ Esses alvos podem ser de interesse para se acessar a doença de forma mais precisa e precoce
- ⦿ São essas particularidades que nós vamos chamar de alvos moleculares
- ⦿ Era da Medicina de Precisão ou Medicina Personalizada

CENTENAS de alvos moleculares

diferentes

Glioblastoma

- ☢ Tenascina-C
- ☢ EGFR
- ☢ CXCR4
- ☢ SSTR2
- ☢ Caderina-3
- ☢ rNeurokinina-1
- ☢ Integrina alpha-V beta-3
- ☢ Proteína ativadora de fibroblasto (FAP)
- ☢ Poli ADP-ribose polimerase (PARP1)





Laboratório de Marcação de células e moléculas (LMCM/HUCFF/UFRJ)



LMCM
Laboratório de Marcação de Células e Moléculas
Coordenação:
Profª Bianca Gutflen

Convênio

FAPERJ
Fundação Carlos Chagas Filho de Amparo
à Pesquisa do Estado do Rio de Janeiro

PROECHO



Desenvolvimento de novos radiofármacos



Câncer e Coagulação

- Existem alterações no processo de coagulação em pacientes com câncer
- Síndrome de Trousseau - descreve um tromboembolismo venoso em indivíduos com câncer - 10x mais chances de TEV
- GBM - TEV frequente - relacionado à ativação prolongada e exagerada da via do Fator tecidual (TF) na massa tumoral.



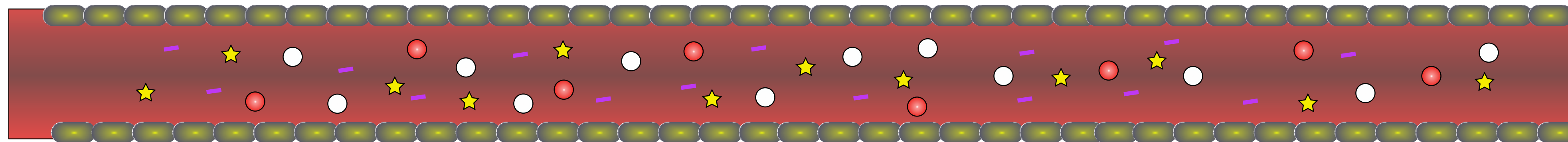
Fator Tecidual (TF)

- O TF é uma glicoproteína transmembrana receptora para os fatores de coagulação VIIa e X.
- Também é conhecido como Tromboplastina, Fator de coagulação III (FIII) ou CD142.
- O TF funciona como um cofator e não é normalmente expresso em células em contato direto com o sangue (tais como células endoteliais e leucócitos), mas apresenta expressão constitutiva em fibroblastos subjacentes ao endotélio vascular.



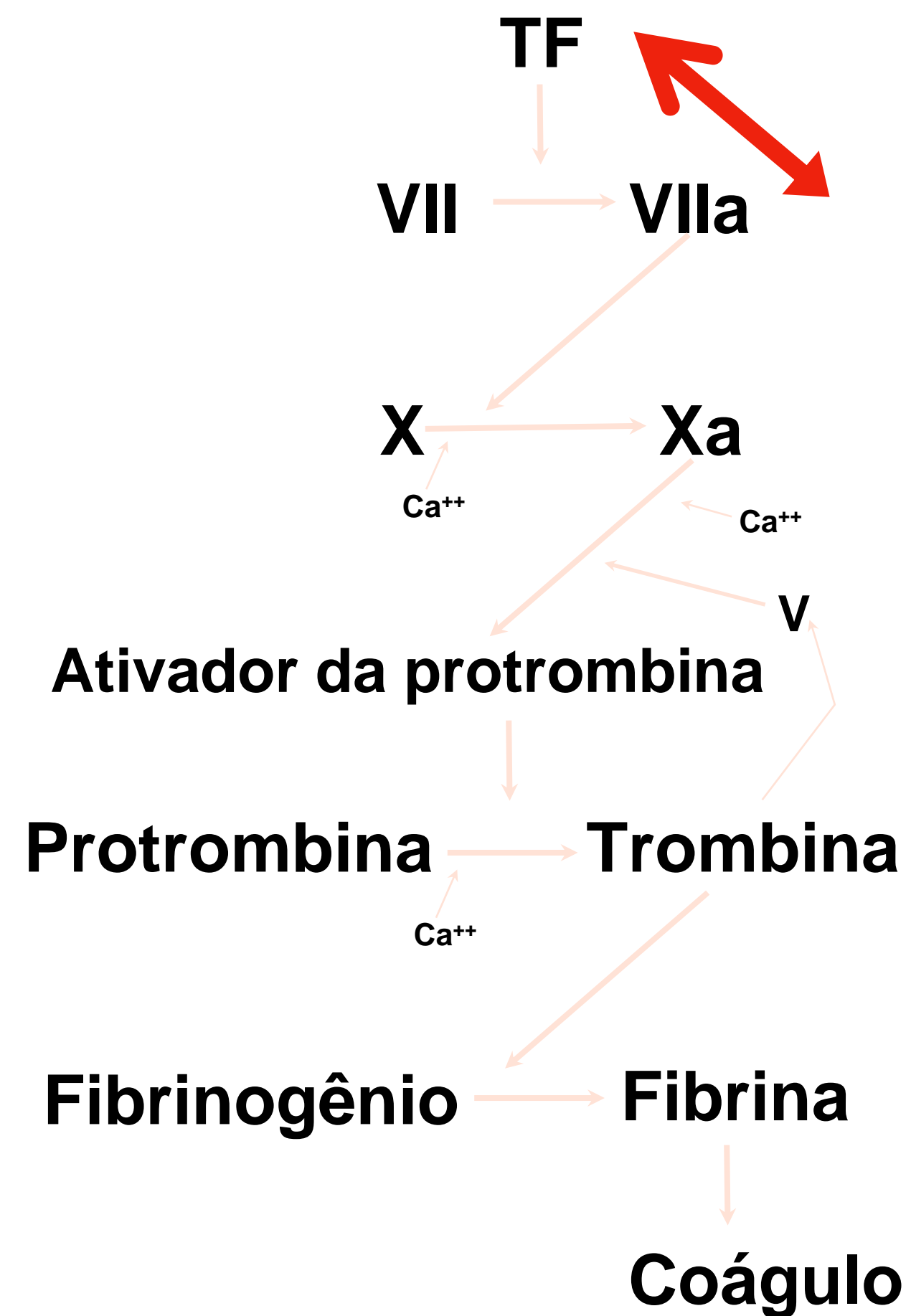
Fator Tecidual (TF)

Em condições normais o endotélio controla a hemostasia, porém uma vez que há dano vascular, é iniciado o processo de coagulação

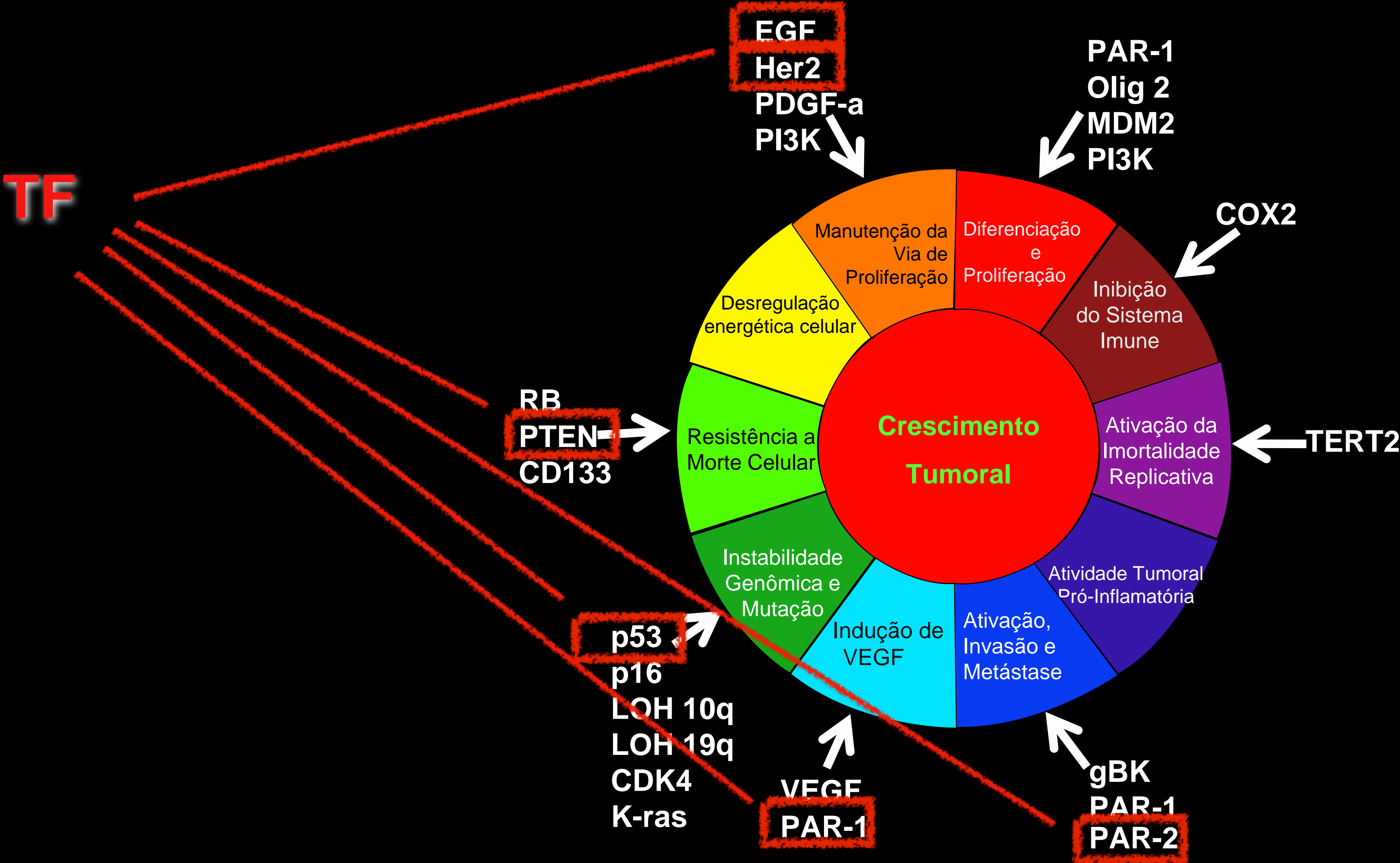


O TF está presente na superfície celular de diferentes tipos celulares, como queratinócitos, células epiteliais do trato respiratório e trato gastrointestinal, cérebro, células musculares cardíacas e glomérulos renais.

Além de estar superexpresso em céls tumorais.




Marcadores Tumorais



Ixolaris

 O Ixolaris é uma proteína não-imunogênica, com meia-vida biológica longa (>24h) e ação anti-coagulante.

 2 Brasileiros - Prof. Robson Monteiro e Prof. Ivo Francischetti descreveram a partir da glândula salivar do carrapato *Ixodes Scapularis* a expressão e caracterização de um novo análogo inibidor da via do fator tecidual (TFPI).

blood

2002 99: 3602-3612
Prepublished online Apr 17, 2002;
doi:10.1182/blood-2001-12-0237

Ixolaris, a novel recombinant tissue factor pathway inhibitor (TFPI) from the salivary gland of the tick, *Ixodes scapularis*: identification of factor X and factor Xa as scaffolds for the inhibition of factor VIIa/tissue factor complex

Ivo M. B. Francischetti, Jesus G. Valenzuela, John F. Andersen, Thomas N. Mather and José M. C. Ribeiro

Thrombosis and
Haemostasis
International Journal for Vascular Biology and Medicine

Antithrombotic properties of Ixolaris, a potent inhibitor of the extrinsic pathway of the coagulation cascade

Rômulo A. Nazareth, Luana S. Tomaz, Susana Ortiz-Costa, Geórgia C. Atella, José M. C. Ribeiro, Ivo M. B. Francischetti, Robson Q. Monteiro

Ixolaris: a Factor Xa heparin-binding exosite inhibitor

Robson Q. MONTEIRO*, Alireza R. REZAIÉ†, José M. C. RIBEIRO‡ and Ivo M. B. FRANCISCHETTI ‡¹

*Instituto de Bioquímica Médica, Programa de Biologia Estrutural, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, 21941-590, Brazil, †Edward A. Doisy Department of Biochemistry and Molecular Biology, St. Louis University School of Medicine, St. Louis, MO 63104, U.S.A., and ‡Section of Medical Entomology, Laboratory of Malaria and Vector Research, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD 20892-8132, U.S.A.

Ixolaris binding to factor X reveals a precursor state of factor Xa heparin-binding exosite

ROBSON Q. MONTEIRO,¹ ALIREZA R. REZAIÉ,² JONG-SUP BAE,² ERIC CALVO,³ JOHN F. ANDERSEN,³ AND IVO M.B. FRANCISCHETTI³

¹Instituto de Bioquímica Médica, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, Rio de Janeiro 21941-590, Brazil

²Edward A. Doisy Department of Biochemistry and Molecular Biology, St. Louis University School of Medicine, St. Louis, Missouri 63104, USA

³Vector Biology Section, Laboratory of Malaria and Vector Research, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892-8132, USA

(RECEIVED May 22, 2007; FINAL REVISION September 28, 2007; ACCEPTED October 3, 2007)



Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres



Full Length Article

^{99m}Tc -ixolaris targets glioblastoma-associated tissue factor: *In vitro* and pre-clinical applications



Thiago Barboza ^a, Tainá Gomes ^{b,c}, Daniella M. Mizurini ^c, Robson Q. Monteiro ^c, Sandra König ^b, Ivo M.B. Francischetti ^{d,1}, Paula V.P. Signoretti ^e, Isalira P. Ramos ^f, Bianca Gutflen ^a, Sergio A.L. Souza ^{a,*}

^a Laboratório de Marcação de Células e Moléculas, Departamento de Radiologia, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil

^b Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil

^c Instituto de Bioquímica Médica Leopoldo de Meis, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil

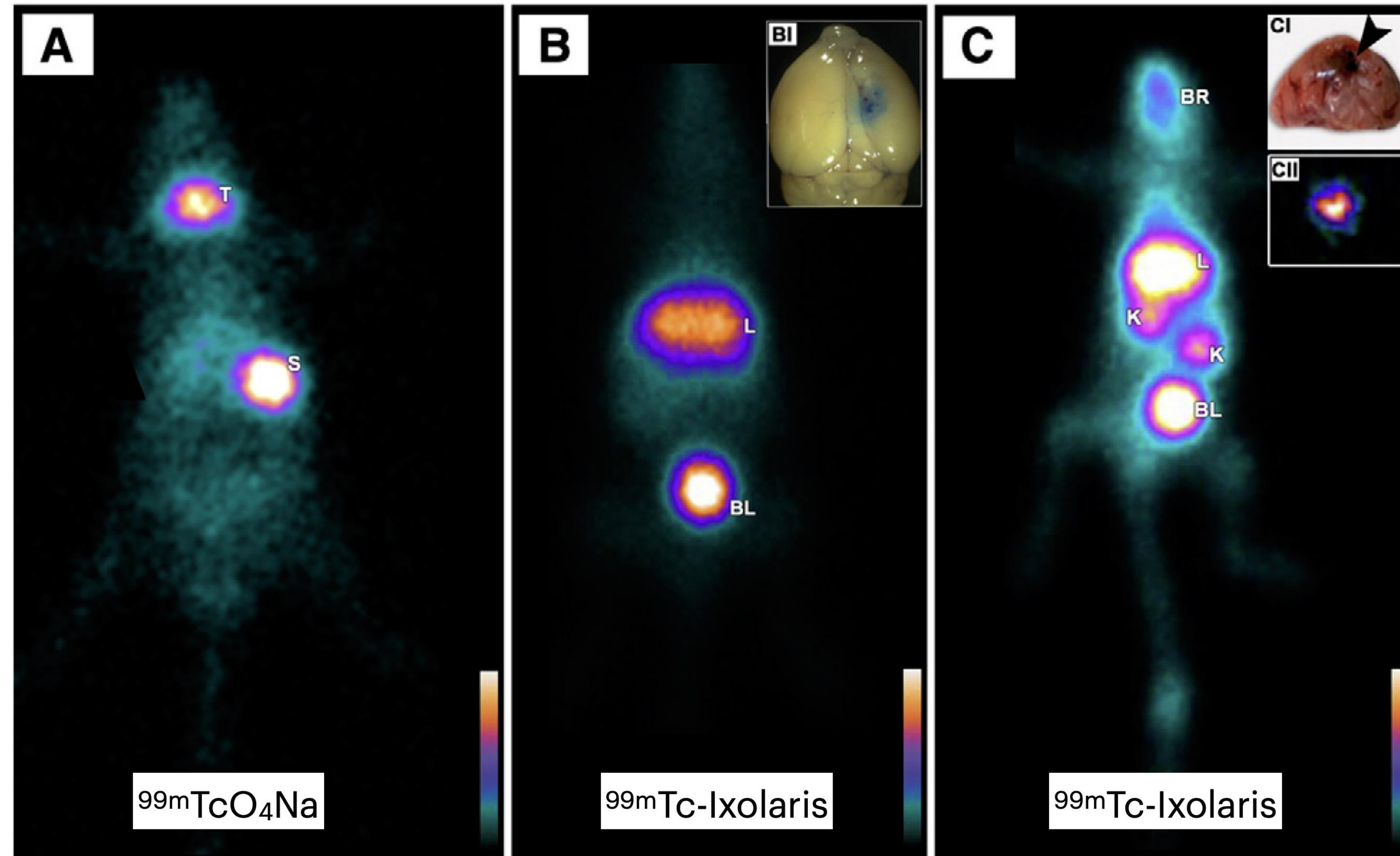
^d Vector Biology Section, Laboratory of Malaria and Vector Research, National Institutes of Health, Bethesda, MD, USA

^e Laboratório de Físico-Química Biológica Aída Hassón Voloch e Laboratório Intermediário de Biomembranas, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil

^f Laboratório de Cardiologia Celular e Molecular, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil



Biodistribuição normal



Thrombosis Research 136 (2015) 432–439



LABORATÓRIO PETSPECTCT
CENABIO/UF RJ

RESEARCH PAPER



Development of ^{131}I -ixolaris as a theranostic agent: metastatic melanoma preclinical studies

Thiago Barboza¹ · Tainá Gomes² · Priscylla da Costa Medeiros¹ · Isalira Peroba Ramos³ · Ivo Francischetti⁴ · Robson Q. Monteiro² · Bianca Gutflen¹ · Sergio Augusto Lopes de Souza^{1,3} 



Objetivos Principais

☢ Comparar a biodistribuição do ^{131}I -Ixolaris e do ^{131}I em camundongos saudáveis e com melanoma metastático

☢ Dividimos o estudo em 3 grupos:

D0 - recebeu o ^{131}I -Ixolaris no mesmo dia da indução do melanoma

D15 - recebeu o ^{131}I -Ixolaris 15 dias após a indução do melanoma

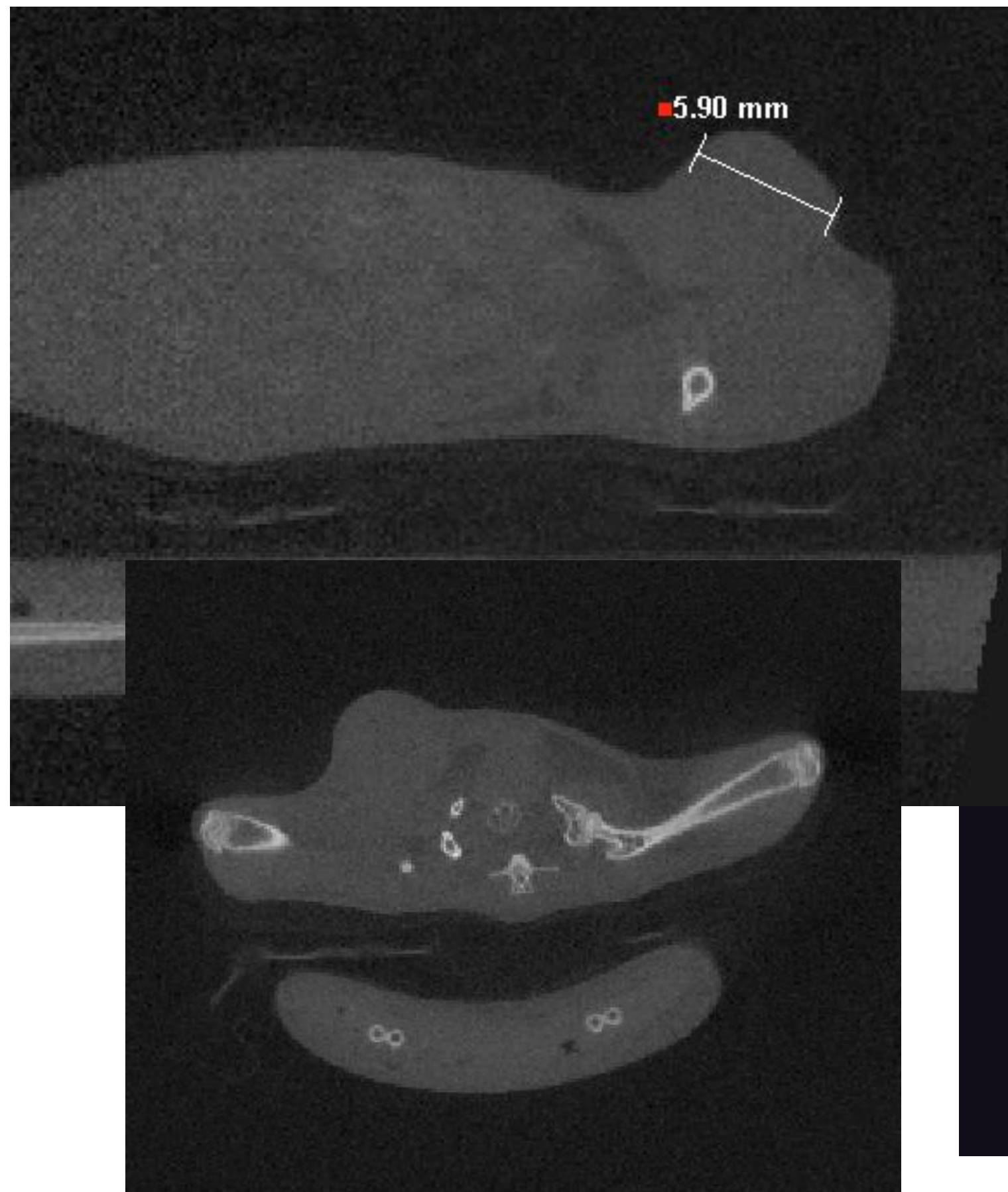
D1/D15 - recebeu um tratamento duplo

☢ Os animais foram sacrificados no D18

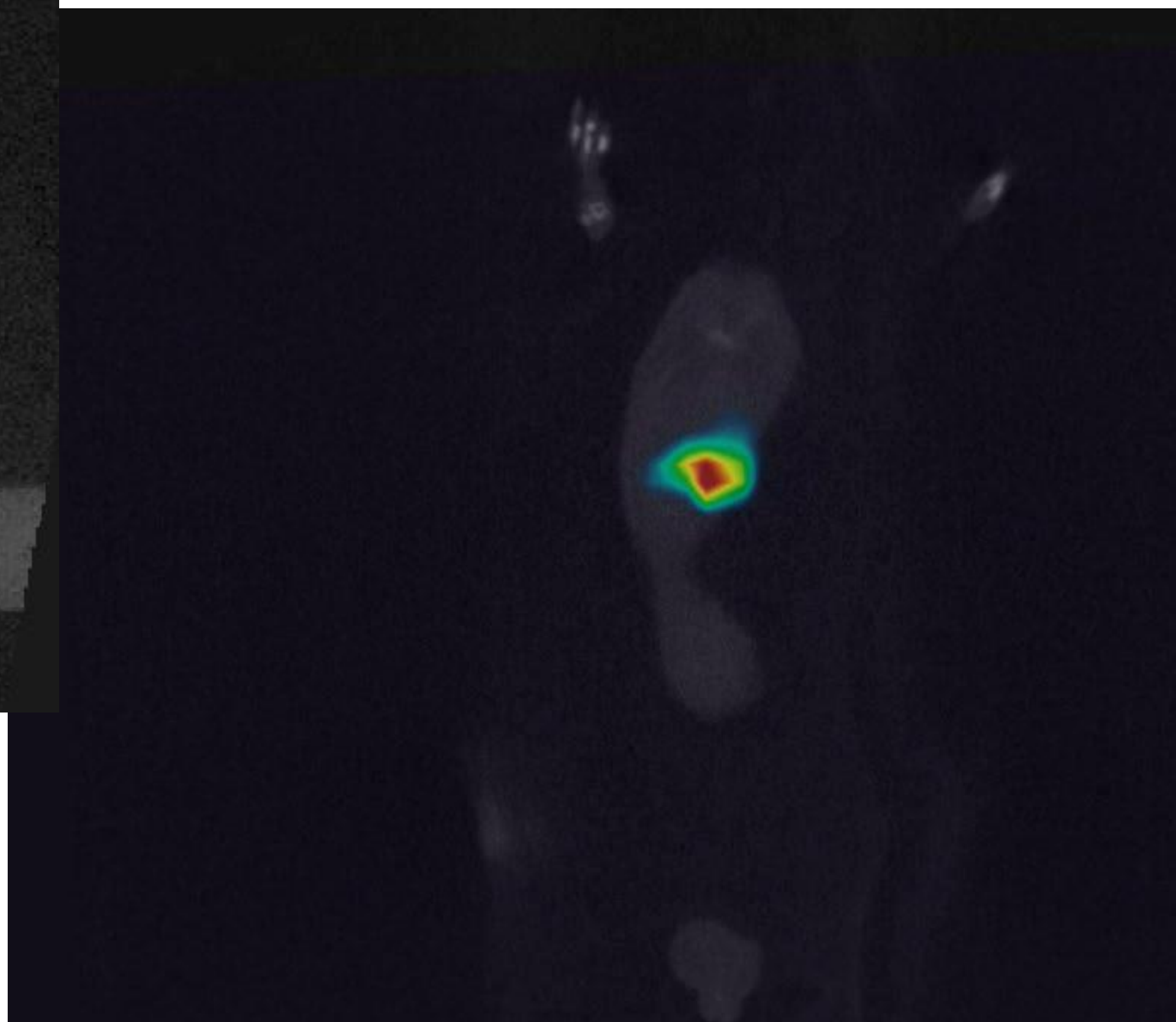
Todos os animais receberam 0,25mCi de ^{131}I -Ixolaris como atividade terapêutica



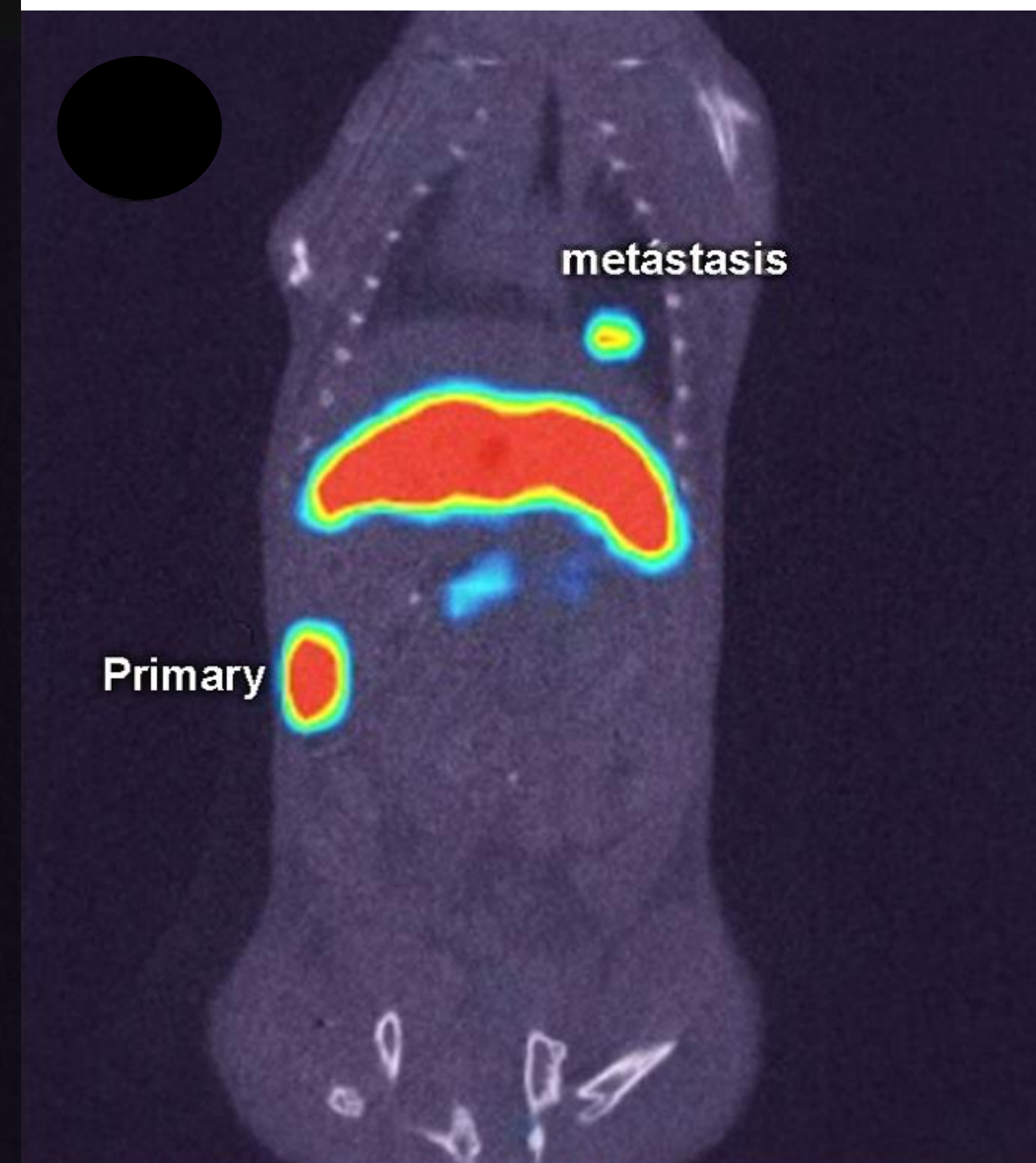
Results



☢ microCT



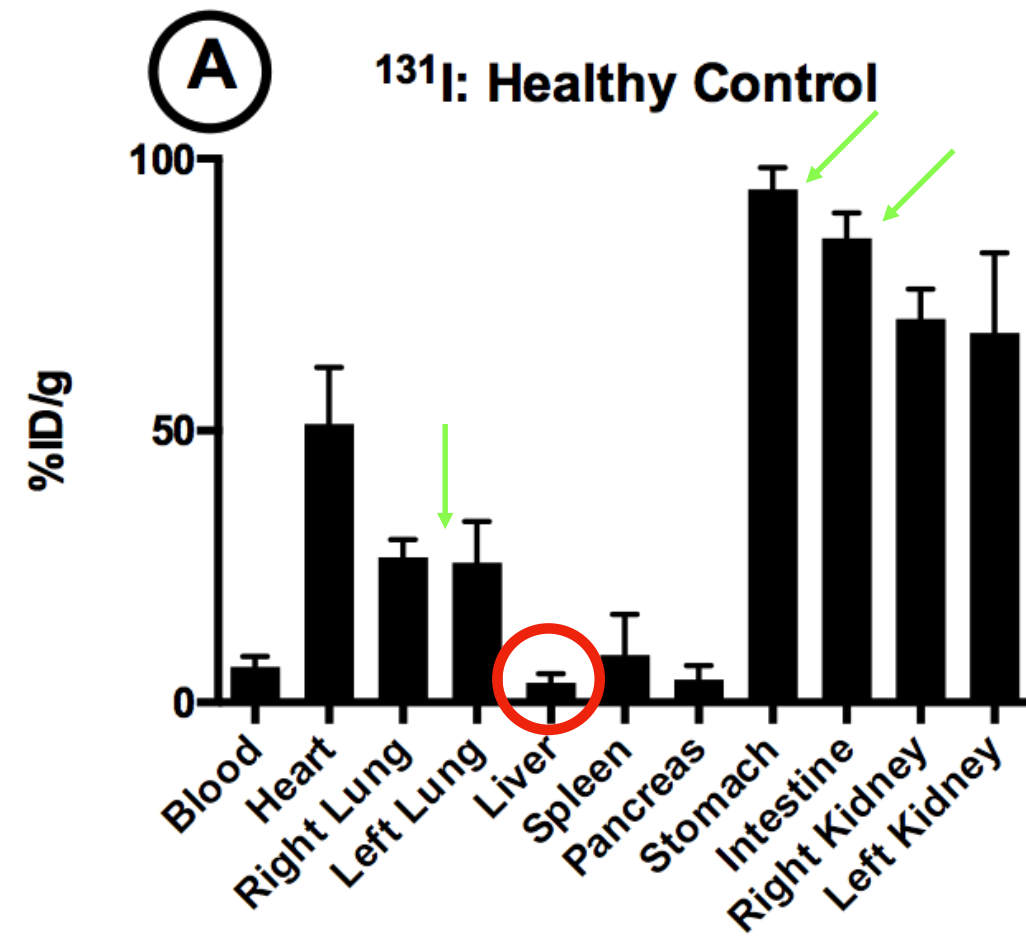
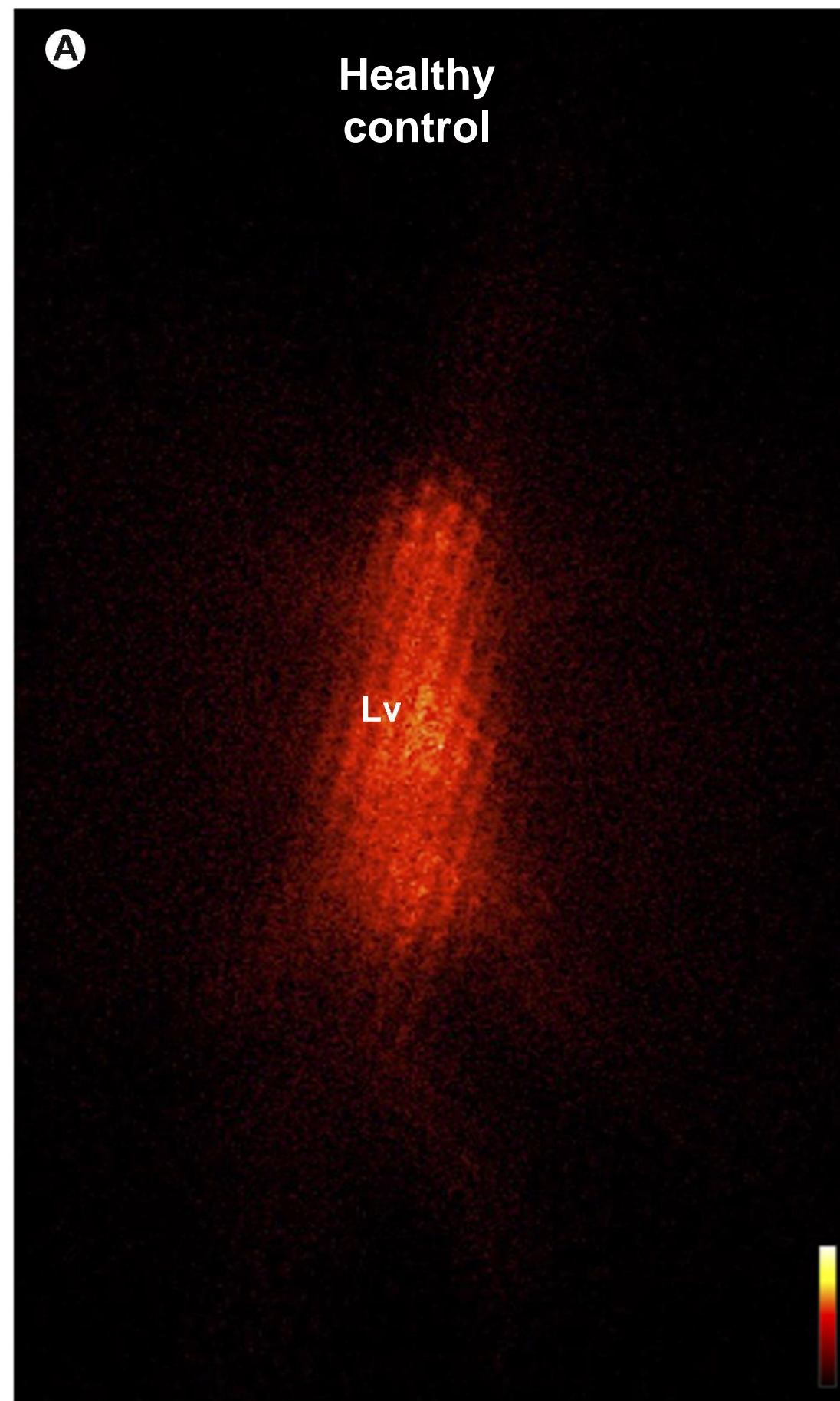
☢ Ixolaris- $^{99\text{m}}\text{Tc}$



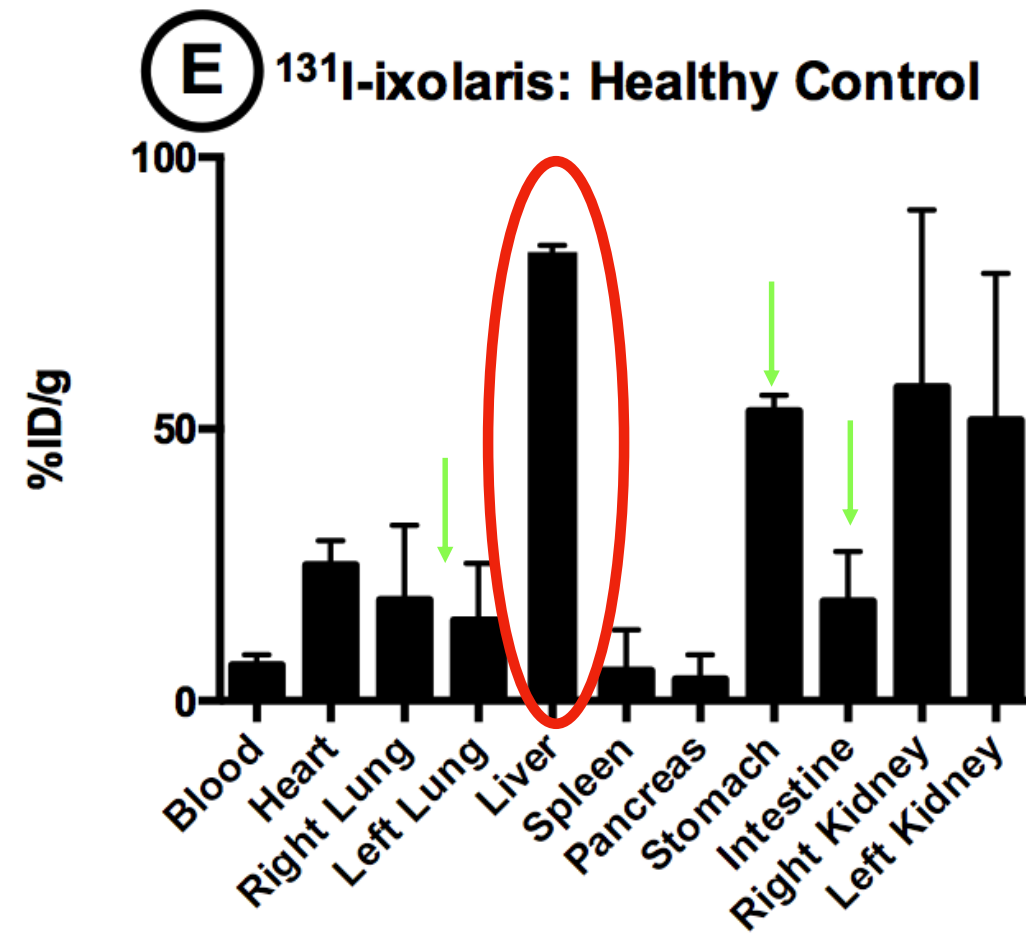
☢ Ixolaris- $^{99\text{m}}\text{Tc}$

Result
 S

¹³¹I-Ixolaris Biodistribution



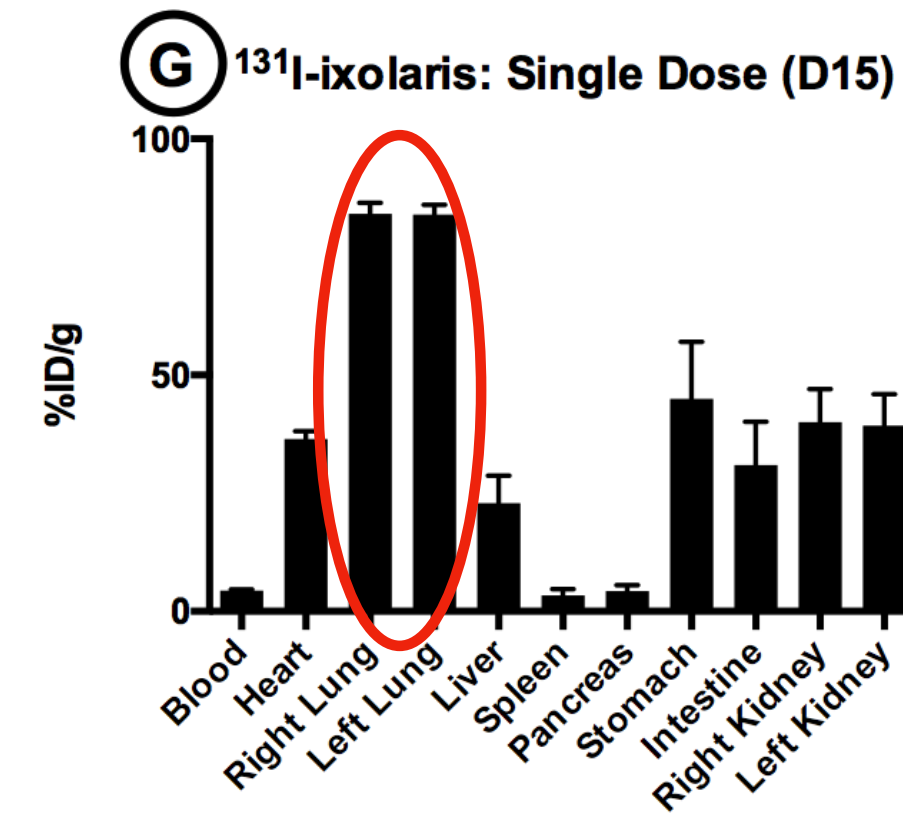
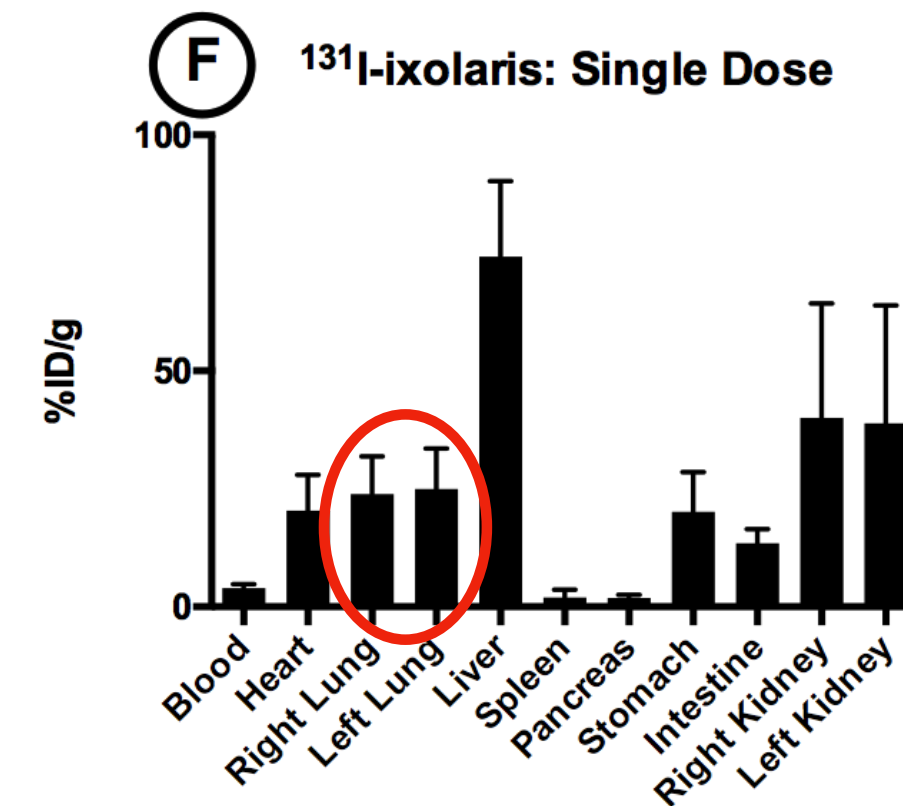
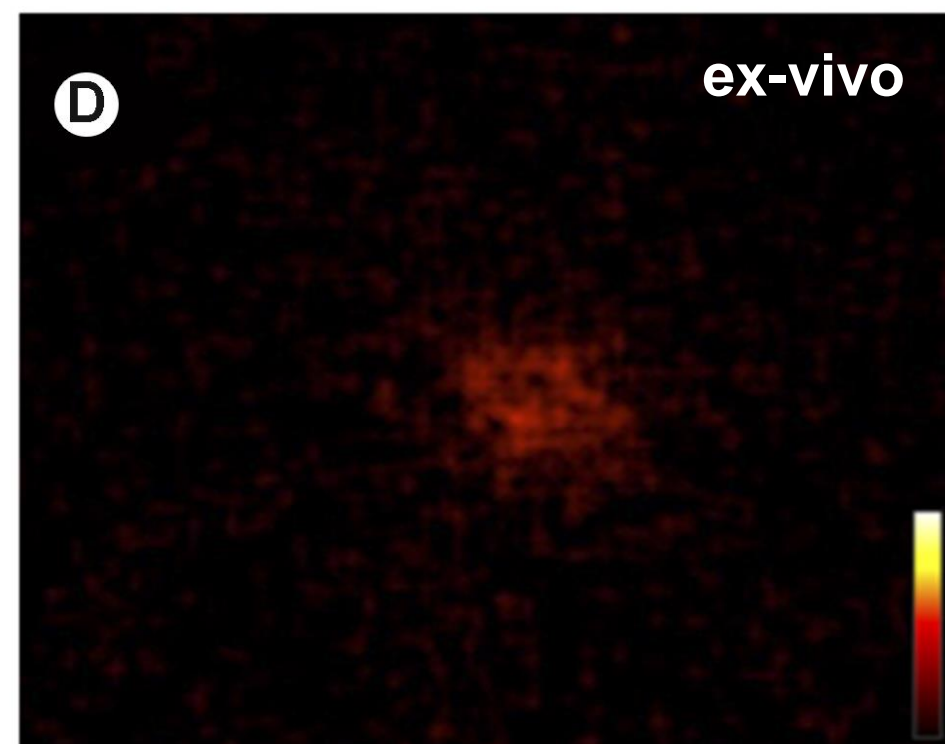
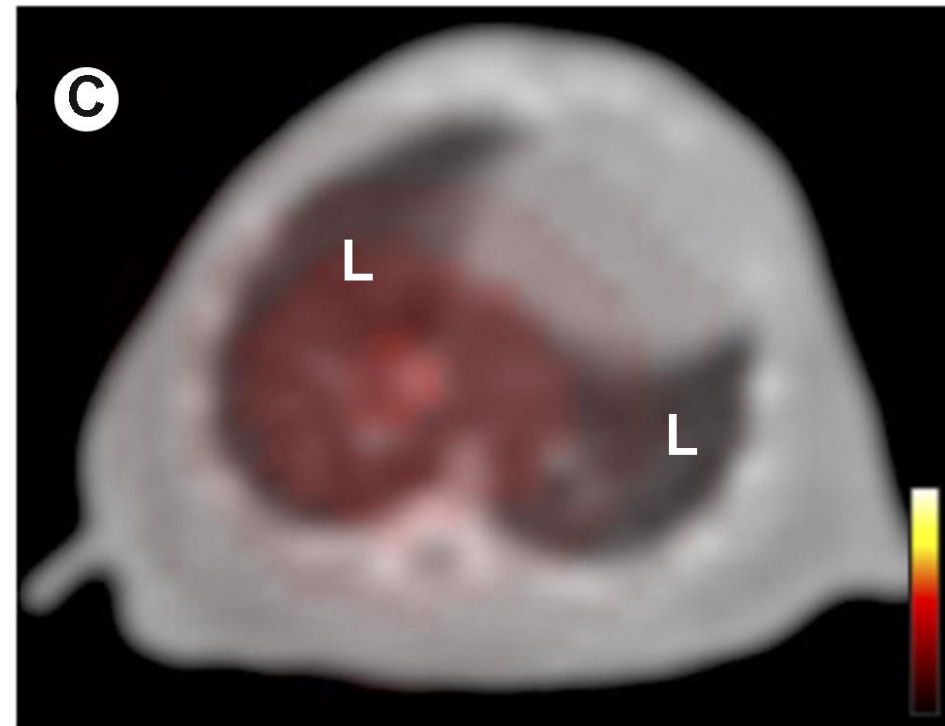
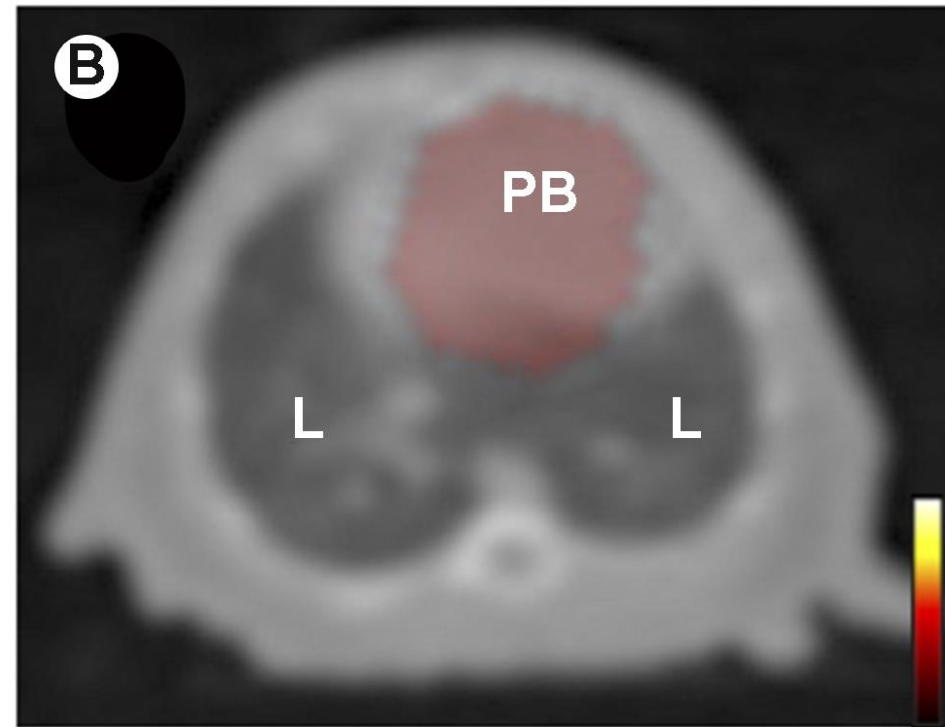
- ↑ Liver
- ↓ Stomach
- ↓ Intestines
- ↓ Lungs



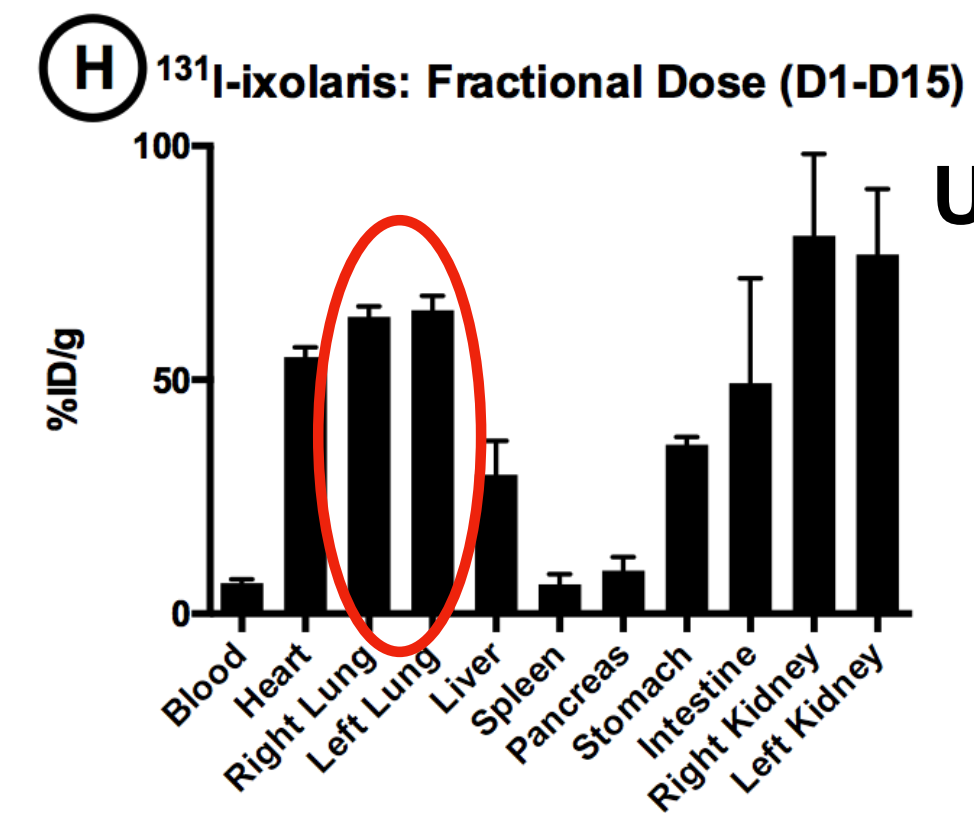
¹³¹I-Ixolaris development as a theranostic agent: metastatic melanoma preclinical studies

Results

¹³¹I-Ixolaris Biodistribution

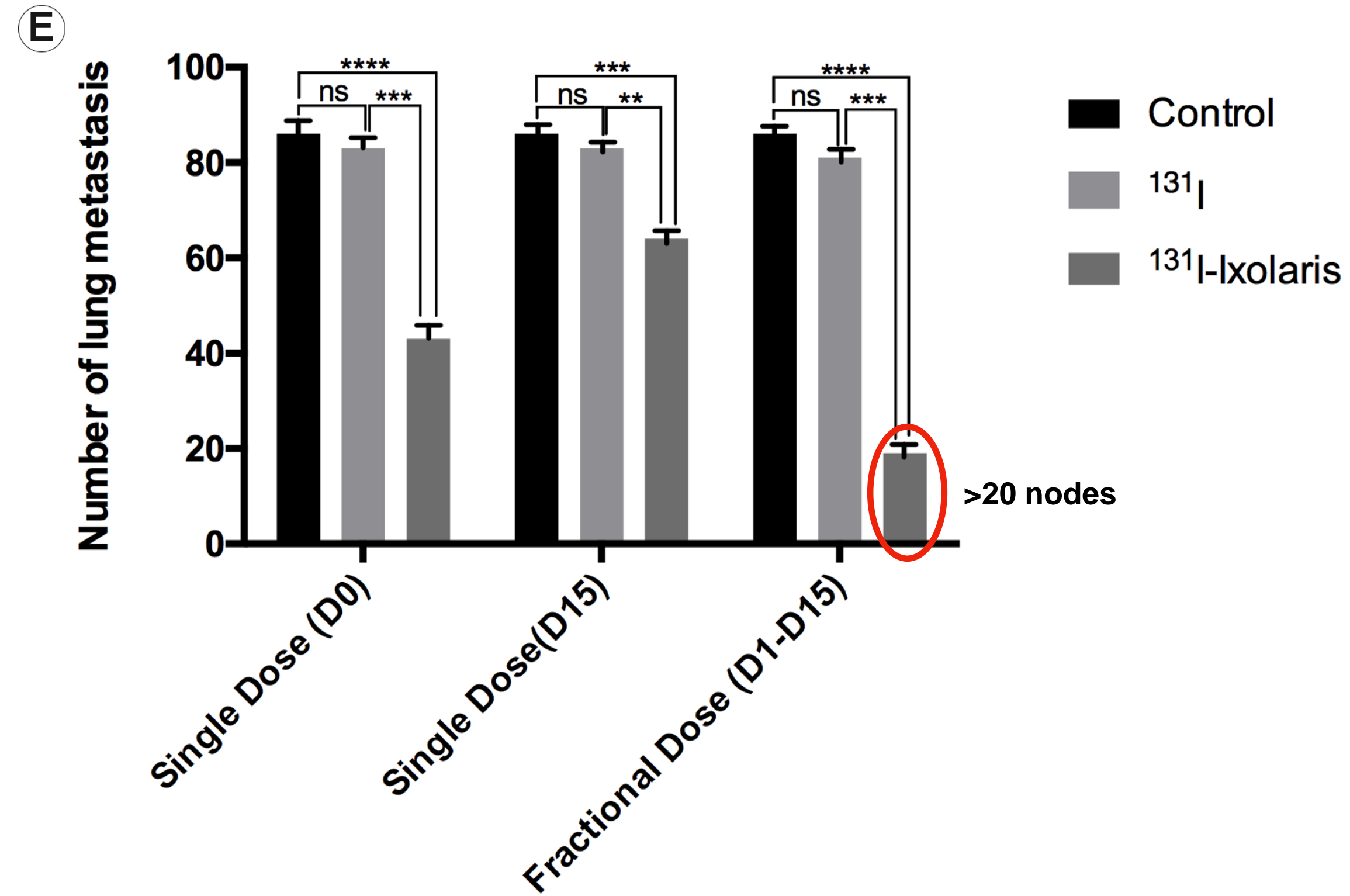
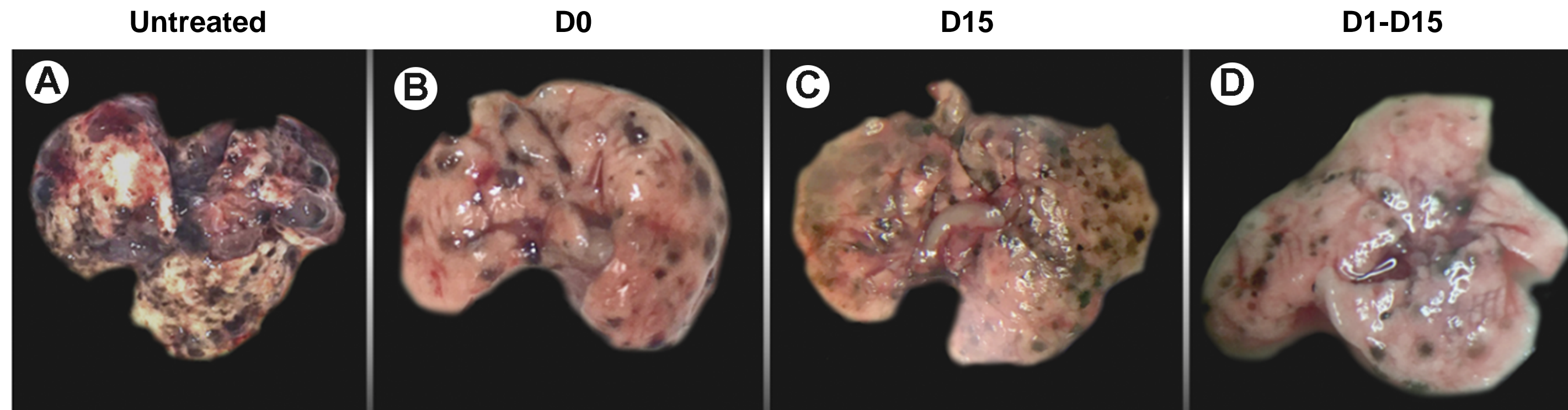


Uptake increase



Uptake increase

Results



Próximos Passos



Público

Pesquisador

CEP

Alterar Meus Dados

Sergio Augusto Lopes de Souza - Pesquisador | V3.8.2

Cadastros

Sua sessão expira em: 39min 31

DETALHAR PROJETO DE PESQUISA

- DADOS DA VERSÃO DO PROJETO DE PESQUISA

Título da Pesquisa: Ixolaris radiomarcado - um agente teranóstico contra o câncer de pele do tipo melanoma

Pesquisador Responsável: Sergio Augusto Lopes de Souza

Área Temática:

Versão: 4

CAAE: 42994821.1.0000.5257

Submetido em: 20/07/2021

Instituição Proponente: UNIVERSIDADE FEDERAL DO RIO DE JANEIRO

Situação da Versão do Projeto: Aprovado

Localização atual da Versão do Projeto: Pesquisador Responsável

Patrocinador Principal: UNIVERSIDADE FEDERAL DO RIO DE JANEIRO



Comprovante de Recepção:  PB_COMPROVANTE_RECEPCAO_1692048





Profa. Bianca Gutfilen



Prof. Thiago Barboza



Dra. Priscylla Medeiros



Prof. Robson Monteiro



Dra. Isalira Peroba



Dra. Tula Celeste

OBRIGADO! THANK YOU! MUCHAS GRACIAS!

sergioalsouza@medicina.ufrj.br

