2020 Joint EFOMP/AAPM Symposium

Total Body PET: The Ultimate Molecular Imaging Tool

Overview of Potential Clinical and Research Applications

Terry Jones
University of California, Davis

The New Opportunities Provided by Total Body PET Scanning

Improving "the status quo":

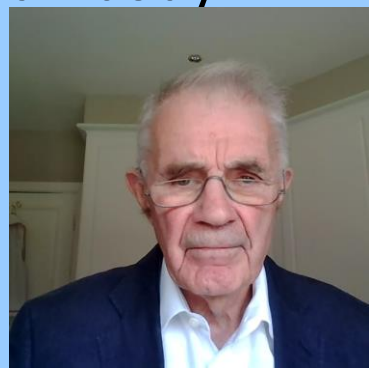
Undertaking current studies better

Realising a "paradigm shift":

Undertaking dynamic tracer studies

of the "Systems Biology"

of the whole human body



Applications of Total Body PET

Cancer

"Systems Biology"

Infection

Heart-Body

Drug Kinetics

Immunotherapy

Drug effects

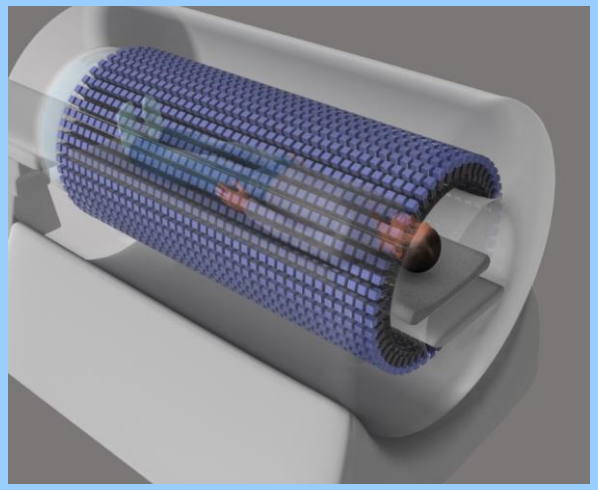
Mental Illness

Lower Radi

Brain-Body

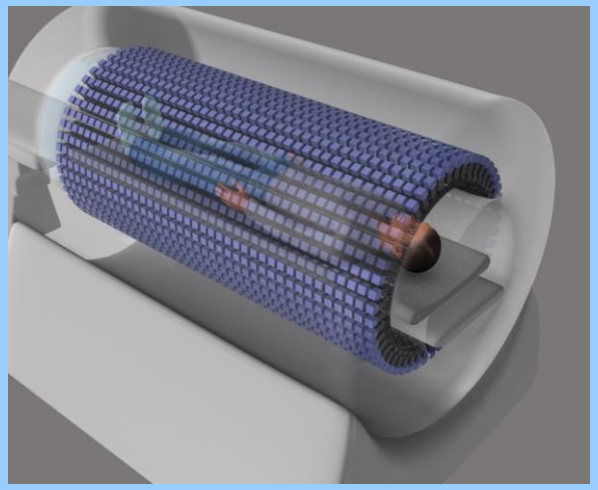
Vision

Clinical Healthcare ⟷ Clinical Research

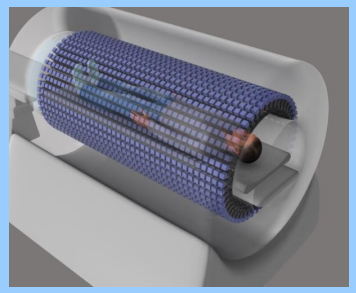


Vision

Clinical Healthcare ⟷ Clinical Research

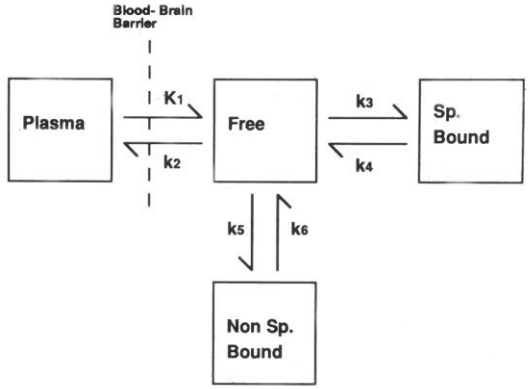


Healthcare
Quality advantages of TB PET



- Significantly improved image quality
- Quantitative imaging (kinetic modelling) verses semi-quantitative-SUV
- Widening the applications of PET-translate from the new research areas developed with TBPET
- Increased range of imaging bio-markers from cor distribution centres-longer shelf life.

Image Kinetics

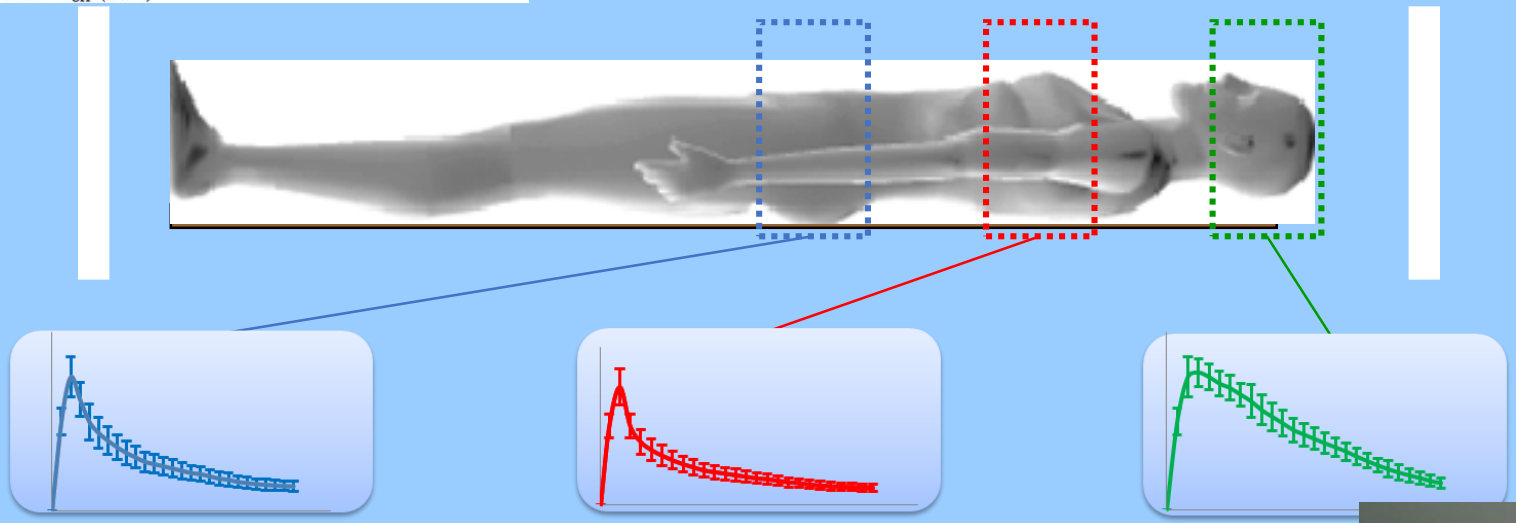


K_1 = flow x extraction (mls min^{-1} ml^{-1}),

k_2 = functional efflux (min^{-1}),

k_3 = combined forward rate constant (K_{ass} x B_{max}) (min^{-1}),

k_4 = dissociation constant = k_{off} (min^{-1})



Regional tissue kinetics & arterial blood input func

with high statistical quality

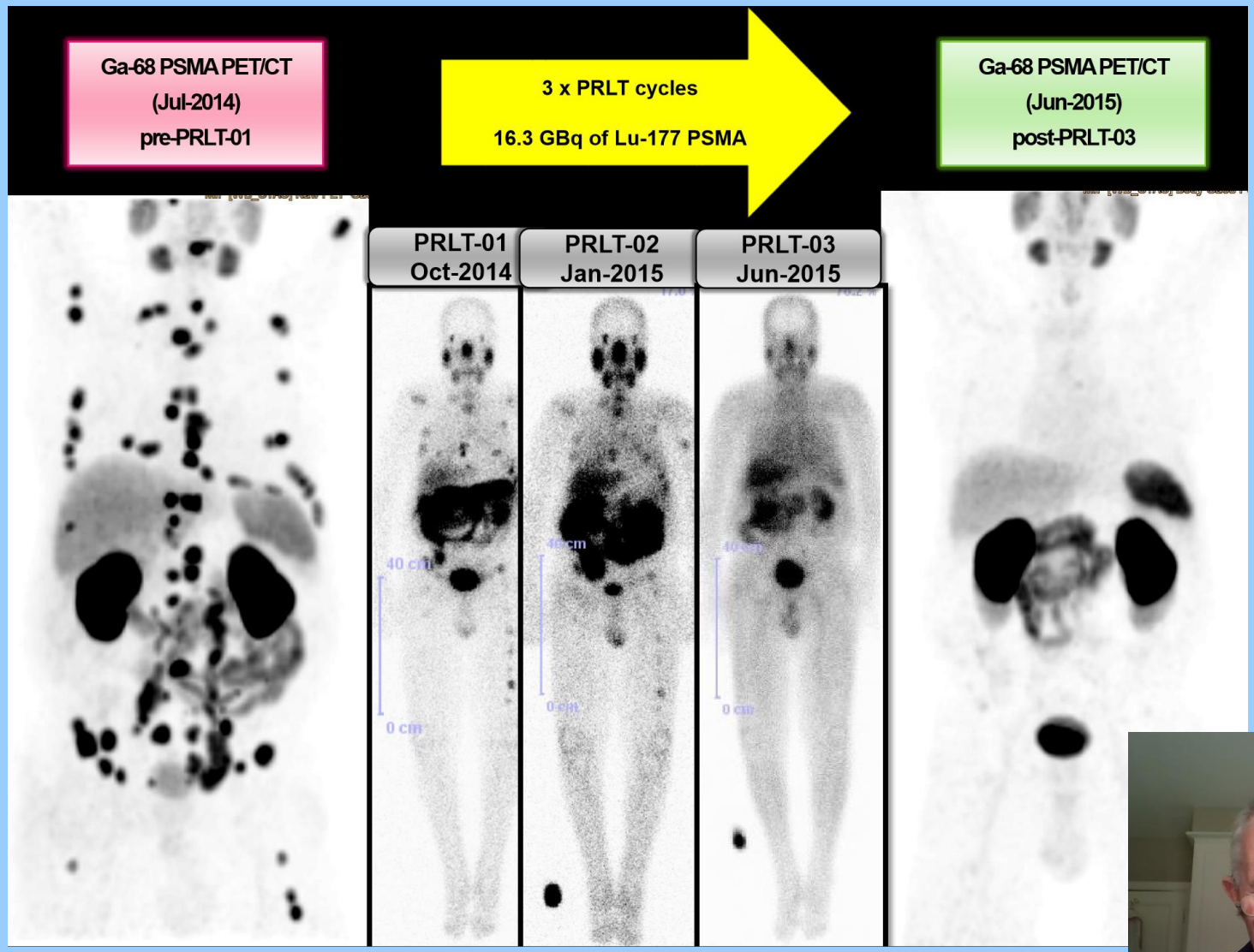
"Effecting the tracer principle for the whole bo

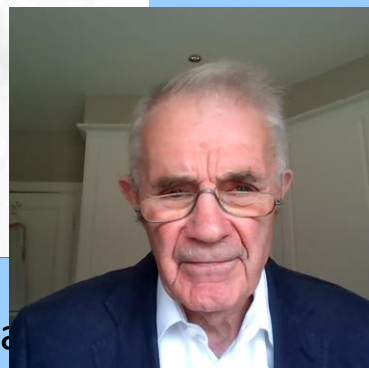
This could promote routine dynamic PET scanning as a quantitative to

for the clinical scientific and healthcare community.

Theranostics

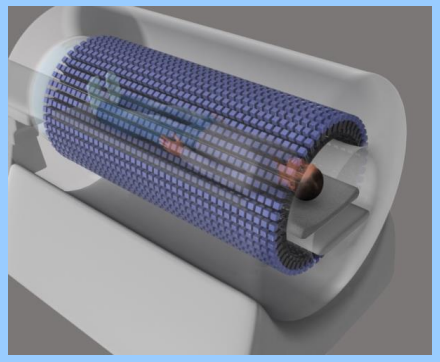
Image guided treatment of metastatic prostate cancer with ^{177}Lu PSMA





Curtesy of Richard Baum Bad Berka

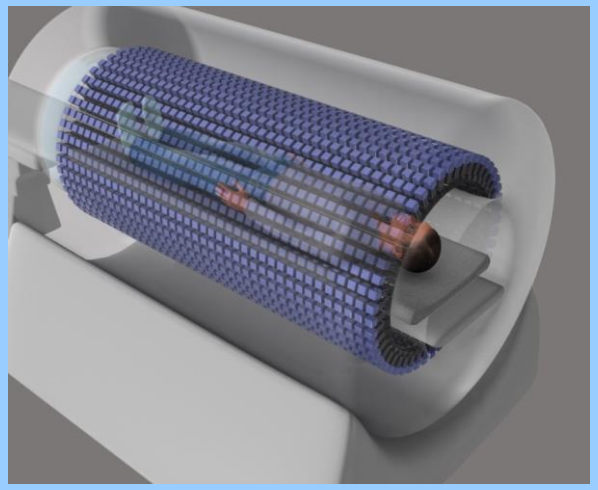
Healthcare <u>Practical/economical</u> advantages of TB PET



- Scan times of minutes: more patient throughput per unit of time
- Scan times of minutes: less movement blurring
- Remove the need for arterial blood sampling
- Could do the clinical load of 3-4 conventional scanners: space and staff saving
- Prescribe scans with lower radiation absorbed dose to patients and staff-opportunities for screening
- Longer shelf life of radio labelled tracers from distribution centres-avo
  in-house GMP production of new tracers
- Patients travelling from molecular-radiotherapy centres for dosimetry

Vision

Clinical Healthcare ⟷ **Clinical Research**



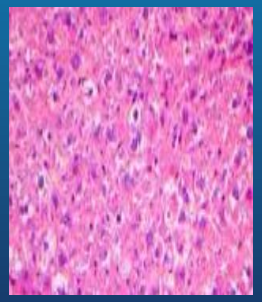
Transformative Clinical Research

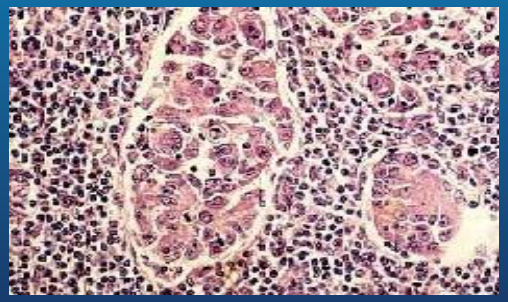
Oncology

Detecting Micro-Metastatic Cancer- The Challenge

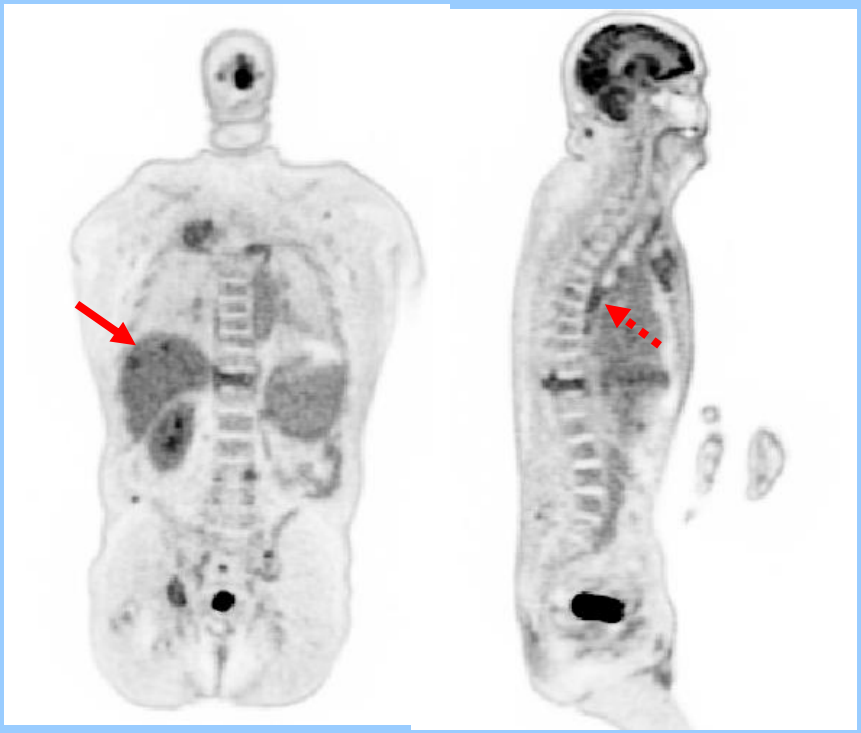
No Mets	**ITC** 1cell-<0.2mm	**Micro Mets 0.2-6mm**	Subclinical 6-9mm	**Clinical >1cm**

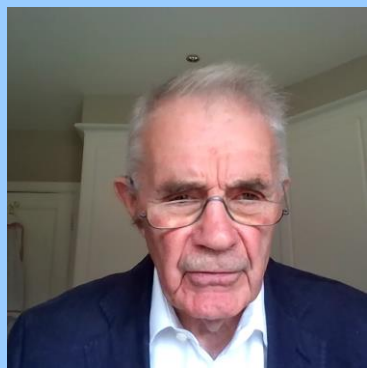
PET Ultra-staging	PET	MRI	CT	USS





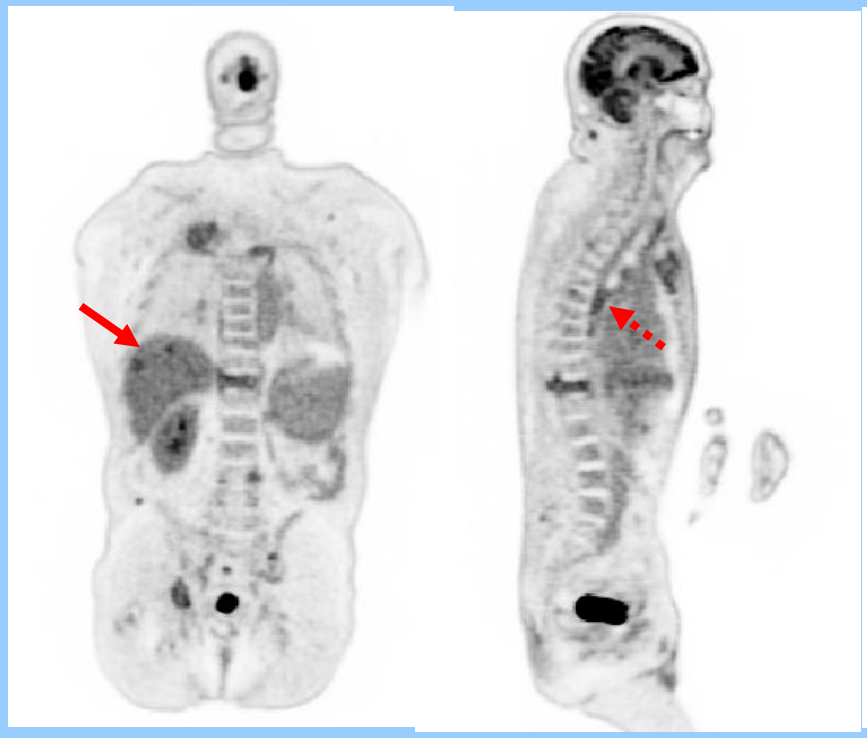
SUV





A Parametric Image of FDG Influx Rate K_i Can Create Higher Lesion Contrast as Compared to Clinical Standard SUV

SUV



K_i

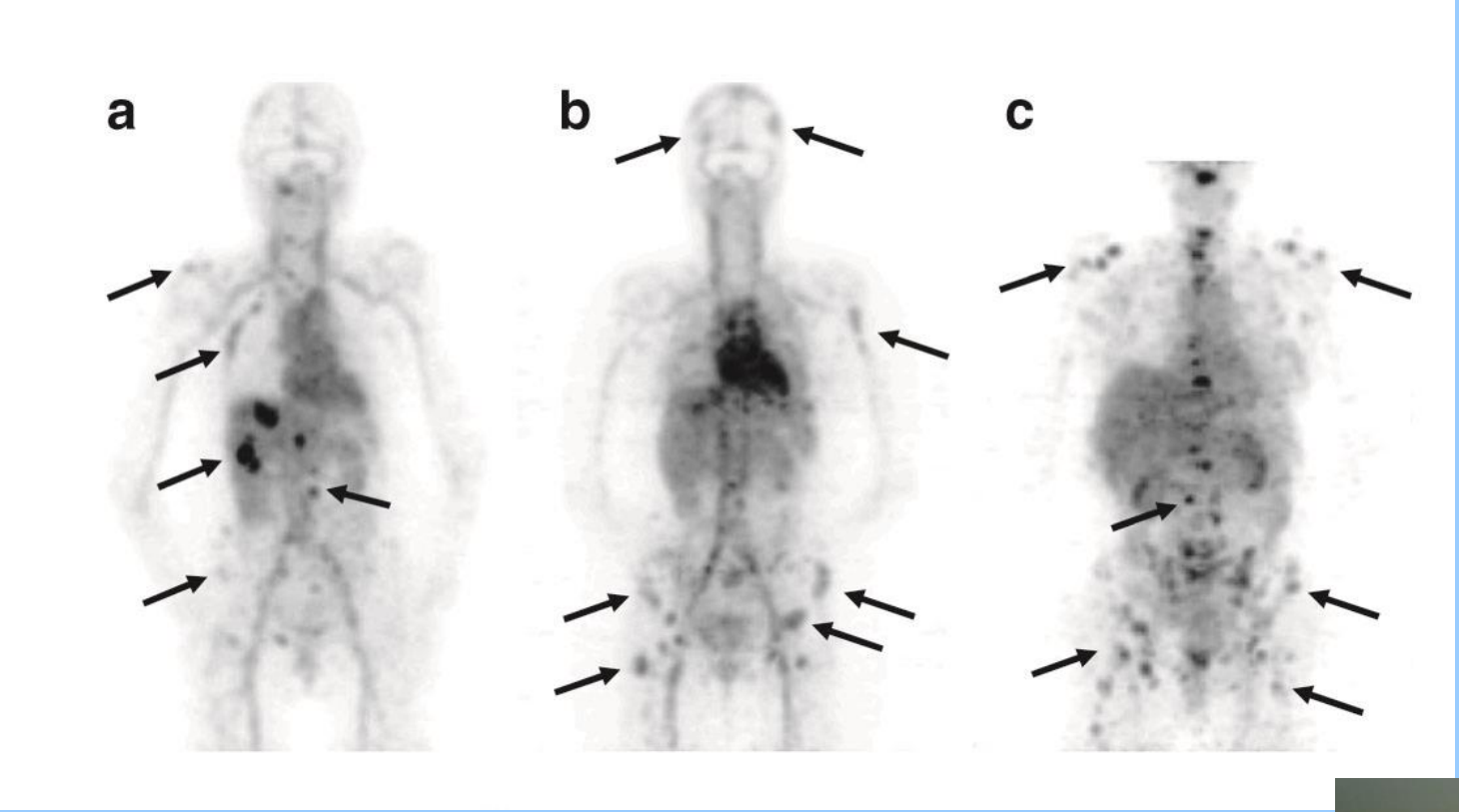
Total-Body Dynamic PET of Metastatic Cancer: First Patient Results
Guobao Wang, Mamta Parikh, Lorenzo Nardo, et al.

SNMMI 2020 Physics, Instrumentation and Data Sciences Summary Se

Transformative
Clinical Research

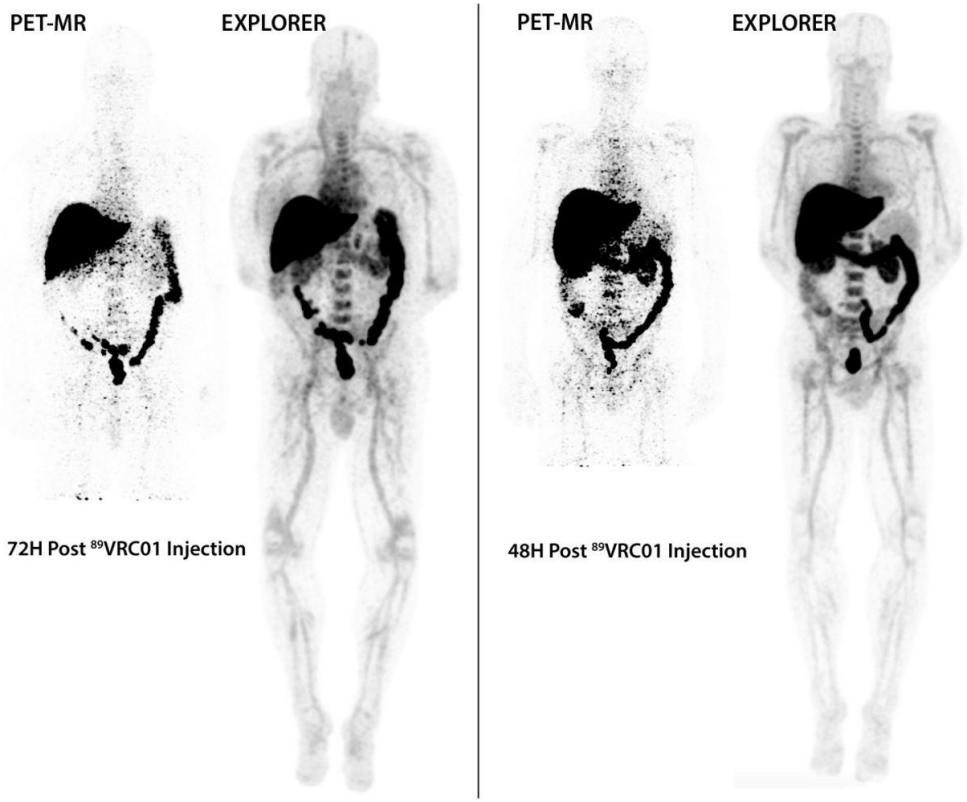
Immune Oncology

Antibody Labelling with ^{89}Zr (78.4 hour half life)



^{89}Zr-trastuzumab uptake **5 days** after the injection.
(**a**) A patient with liver and bone metastases,
and (**b** and **c**) two patients with multiple bone metastases.

Figure 1. ^{89}Zr-VRC01 uptake in HIV patients. Left: ART-suppressed patient (>10 years) 72-76h post injection; Right: Viremic patient 48-52h post injection. Images are maximum intensity projections.



Denis Beckford Vera et al. J Nucl Med 2020;61:545

Antibody–drug conjugates for cancer

Cindy H Chau, Patricia S Steeg, William D Figg

www.thelancet.com **Vol 394 August 31, 2019**

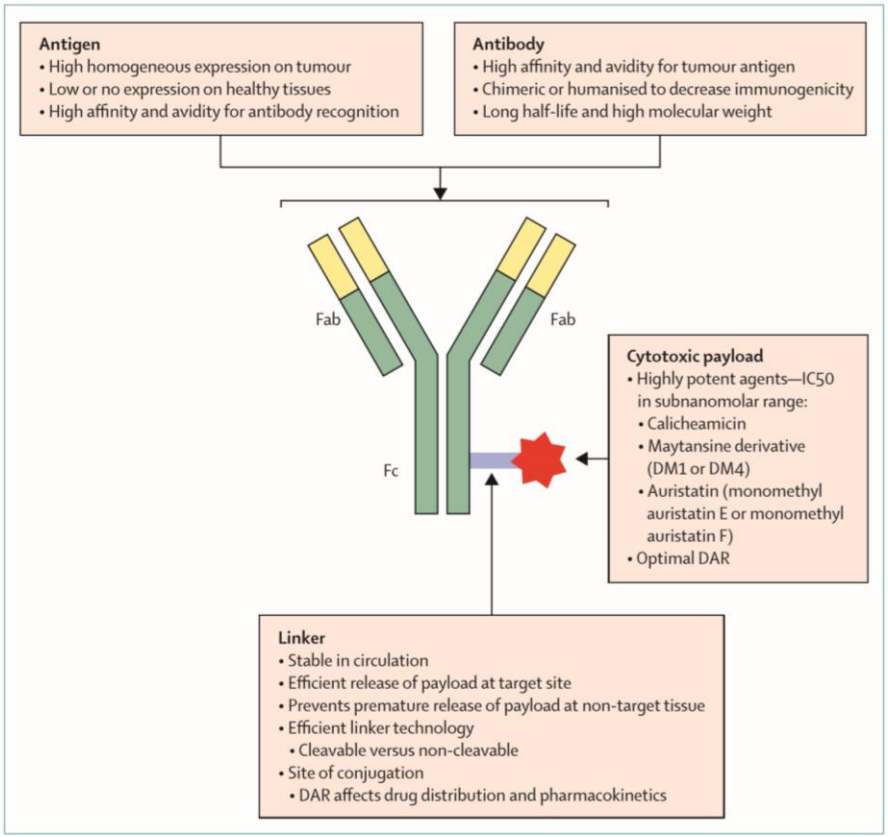
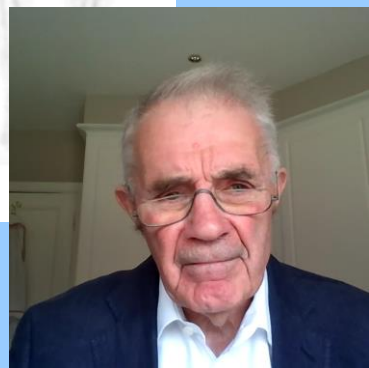
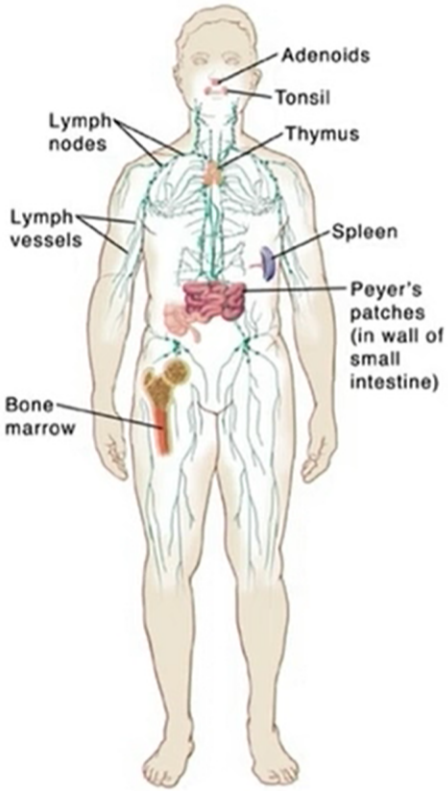


Figure 1: **Structure of an antibody–drug conjugate and properties of the antibody (and target antigen), linker, and cytotoxic payload components**
Fab=antigen-binding fragment. Fc=constant fragment. IC50=half maximal inhibitory concentration. DAR=drug-antibody ratio.



The immune system in health and disease

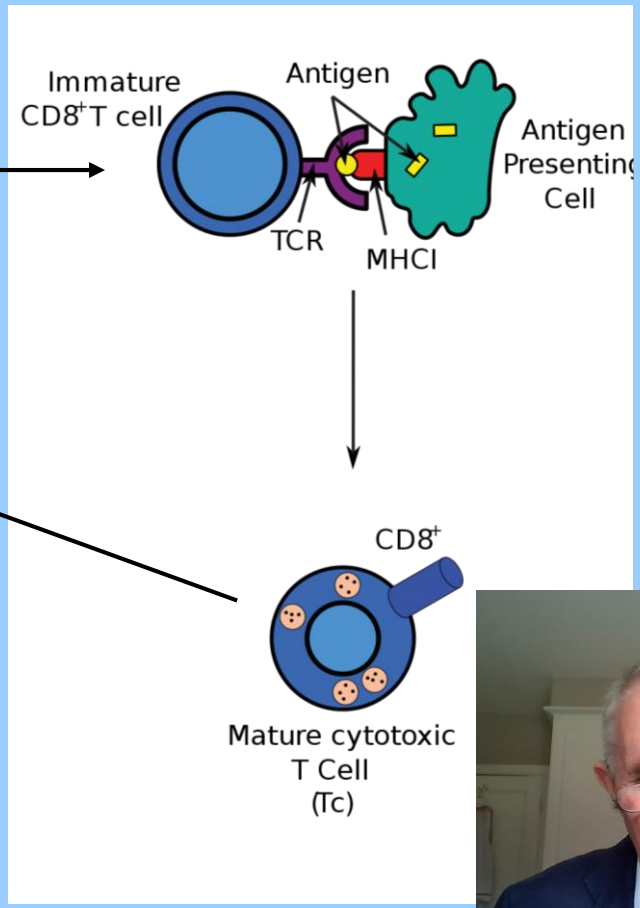


- Central role in development, maintenance/homeostasis, and recognition of self vs. non-self
- Infectious disease, inflammatory processes (autoimmunity, cardiovascular disease, diabetes, neuroinflammation, etc.)
- Oncology: immunosurveillance
  - Ageing
  - Virally-driven malignancies
  - Immunocompromised hosts
  - Immunosuppression in common can

Permission of Anna M

CD8+ T cells (commonly known as **cytotoxic T cells)** are **cells of the immune system** that contribute to the body's adaptive immune response.

These immune cells are characterized by a CD8 protein on their cell surface that allow them to recognize, bind and kill cells infected by intracellular bacteria, intracellular viruses and cancer cells.



The body's immune guided missile

"The Cytotoxic T Cell is the drug"
-Toni Ribas

Clinical Imaging of CD8 T lymphocytes using ^{89}Zr-Df-IAB22M2C

First-in-human imaging with ^{89}Zr-Df-IAB22M2C anti-CD8 minibody in patients with solid malignancies: preliminary pharmacokinetics, biodistribution, and lesion targeting

Neeta Pandit-Taskar et al **J Nucl Med 2020; 61:512-519**

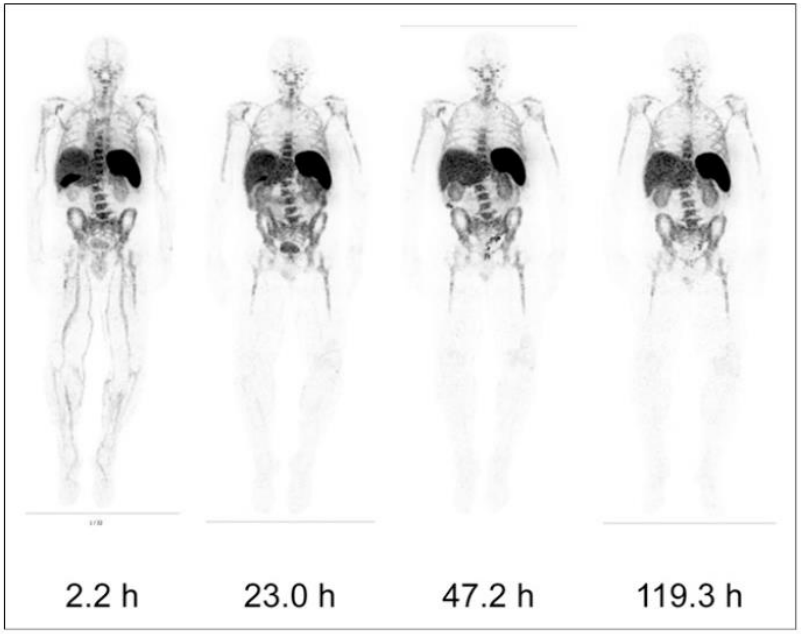


FIGURE 1. Biodistribution: Whole-body images of 1 patient at various times after injection of ^{89}Zr-IAB22M2C (1.5-mg minibody dose). All images show most intense activity within spleen, followed by marrow, liver, and kidneys.

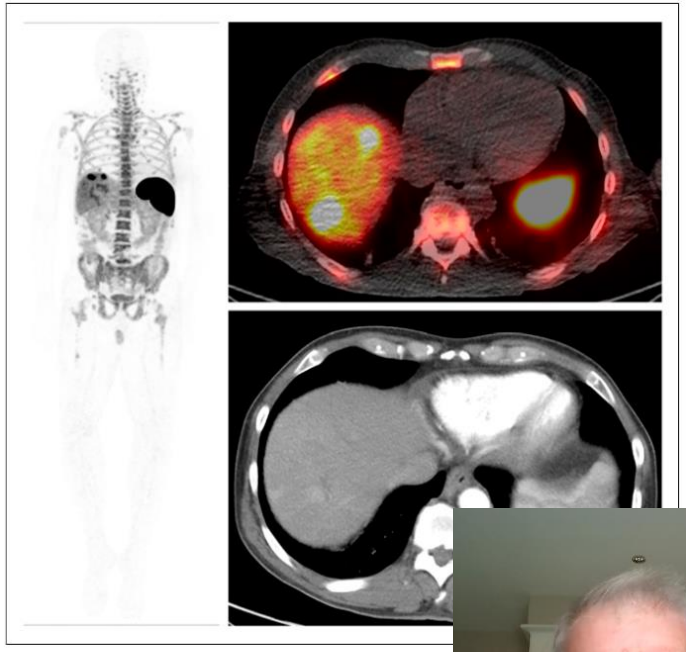
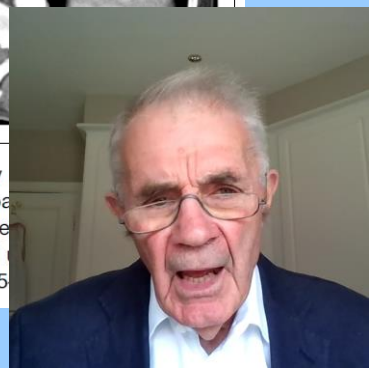
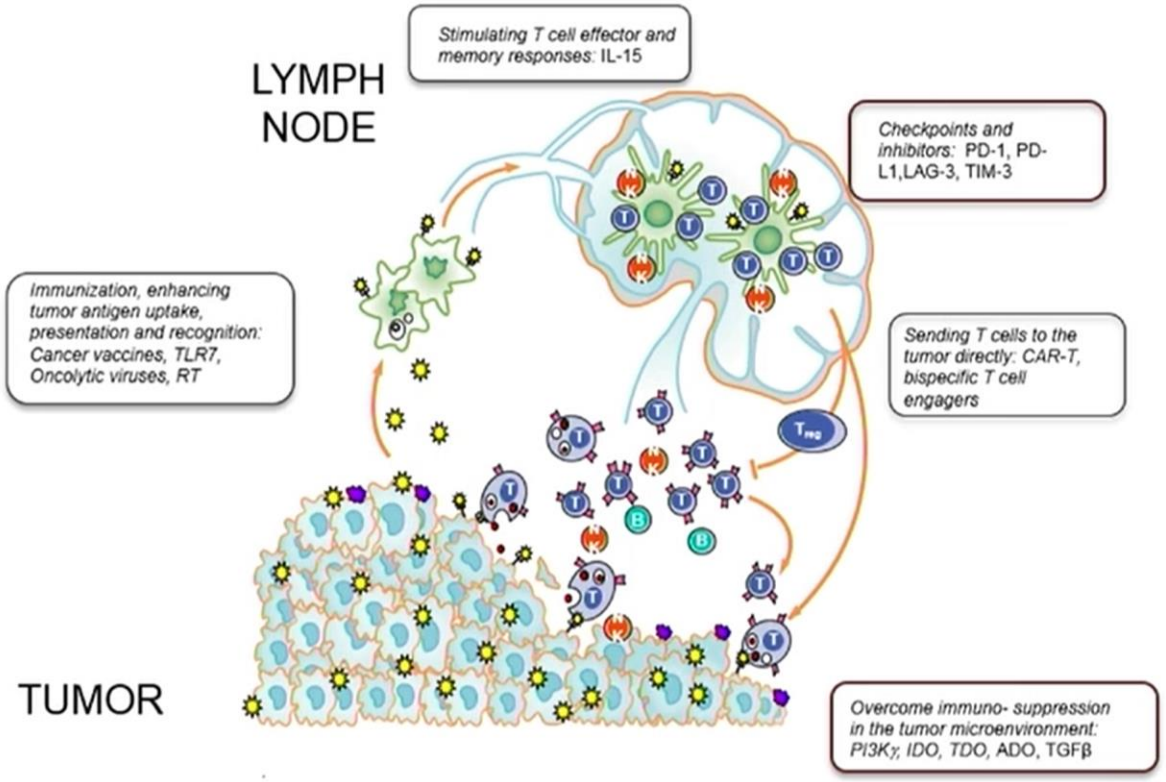


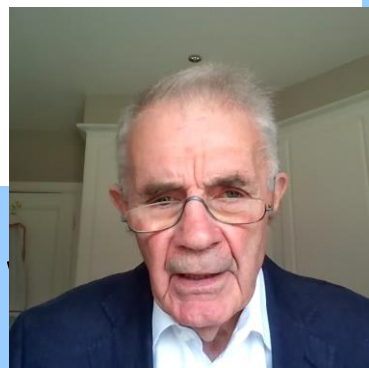
FIGURE 6. Whole-body (maximum-intensity
and ^{89}Zr-IAB22M2C (0.5 mg) images (right) of pa
carcinoma. ^{89}Zr-IAB22M2C–positive lesions are
ses (SUV_{max}, 14.6 and 22.85), and additional
dominal lymph node metastases (SUV_{max}, 5.85



Unlocking the immune system for cancer therapy



Adapted from Mellman, Coukos and Dranoff, Nature 480, 2011



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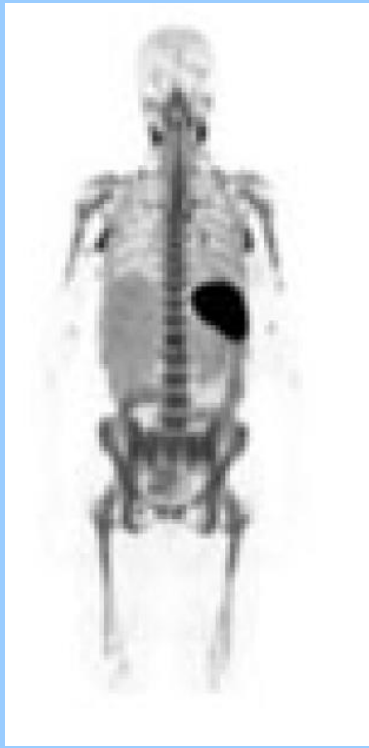
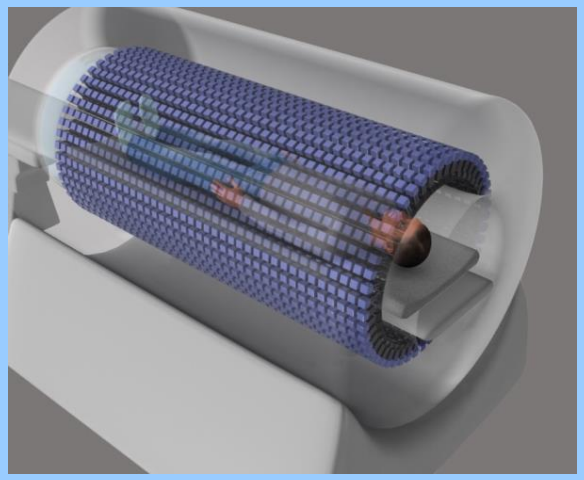


TOTAL BODY PET

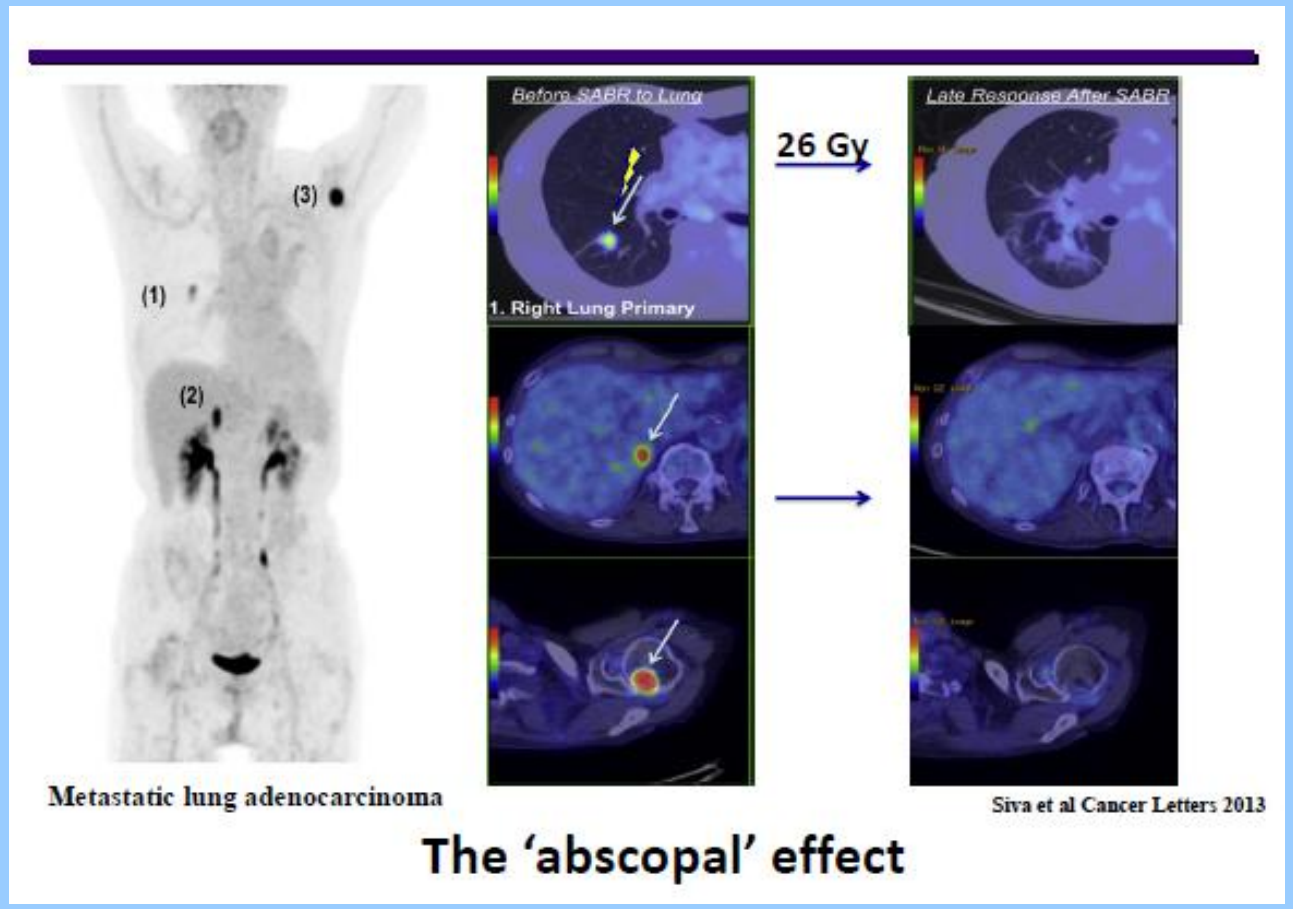


Immune-Therapy of Cancer:

Quantify T Cells activity across the metastases and over day

Abscopal effect of radiotherapy

Radiation and immunotherapy



The Abscopal Effect of Stereotactic Radiotherapy and Immunotherapy: Fool's Gold or El Dorado?

D. Xing [*], S. Siva [*†], G.G. Hanna [*†]

[*] *Division of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia*
[†] *Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia*

Clinical Oncology 31 (2019) 432–443

Conclusions

There is mounting evidence that an immune response-mediated cell kill is one of the key mechanisms of effect in radiotherapy. Radiotherapy, and specifically SABR, in combination with immunotherapy is a promising strategy to enhance the effect of immunotherapy with tolerable side-effects and there is increasing evidence of a synergistic benefit to this combination. A number of clinical studies are now in progress that are examining both the disease setting and the optimal sequence of SABR and immunotherapy combinations.

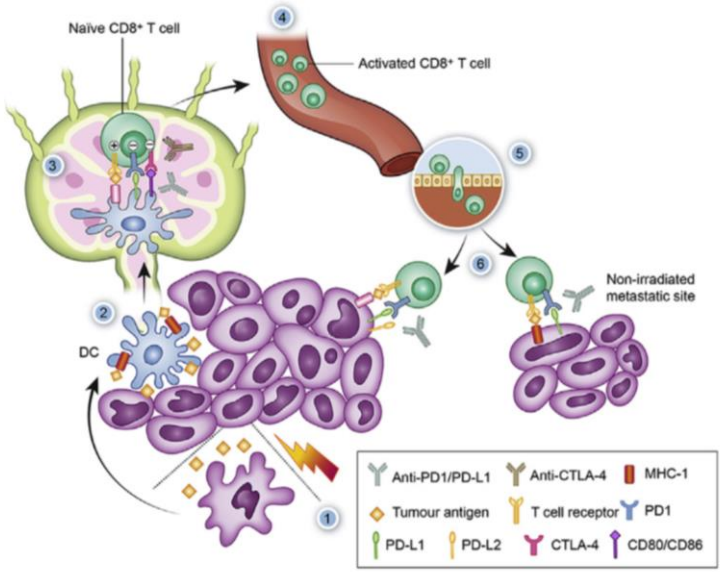
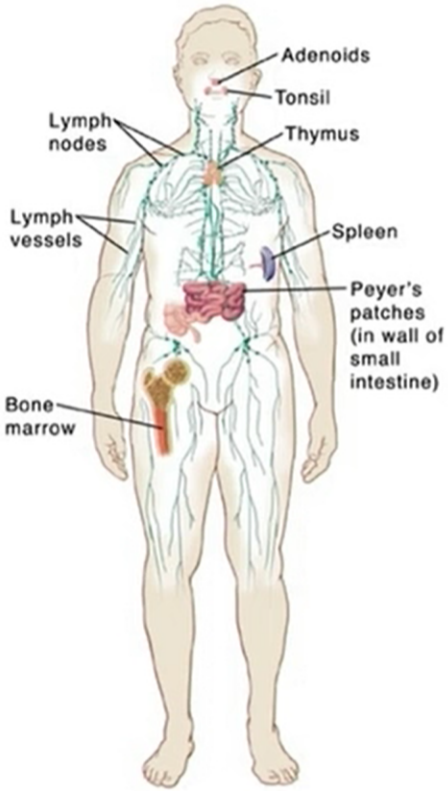


Fig 1. Mechanism of radiation-induced immune response. (1) Tumour cells release tumour antigens after irradiation; (2) tumour antigen can be taken up by dendritic cells (DC, i.e. antigen-presenting cells), which travels to regional lymph nodes; (3) this leads to priming and activation of naive T cells in regional nodes via the interaction of T cell receptors on T cells and major histocompatibility complex class I (MHC-I) on dendritic cells. In parallel to thi
grammed death-ligand 1 (PD-L1) ligands bind to
ceptor and sends an inhibitory signal to the same
their immune response. On the dendritic cells, a
tory signal can occur with CD80/CD86 and CTL
cells. Therapies with monoclonal antibodies a
and anti-CTLA-4 block these inhibitory signals
activated tumour-specific T cells; (5) infiltration o
in both irradiated sites and non-irradiated m
recognition of cancer cells by T cells and killing

The immune system in health and disease



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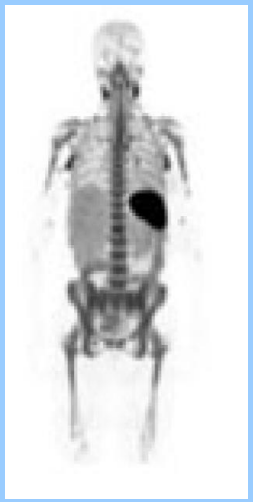
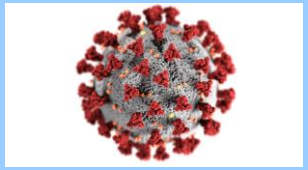
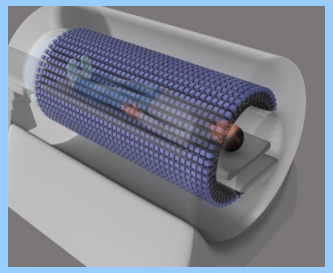






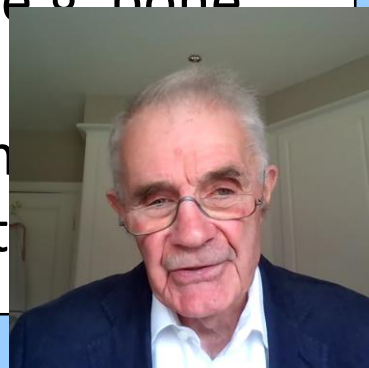
The COVID-19 Viral infection

Clinical Observations

1. In blood, CD8+ T cells have been found to be dis-functionalised and reduced in number
2. Many persons are un-susceptible to COVID-19

Research Questions addressed with Total Body PET:

1. Are CD8+ T Cells reduced due to depleted body stores e.g. bone marrow or are they deposited in other organs?
2. Where are the CD8+ T Cells in patients recovering from
3. Where are the CD8+ T Cells in persons un-susceptible t



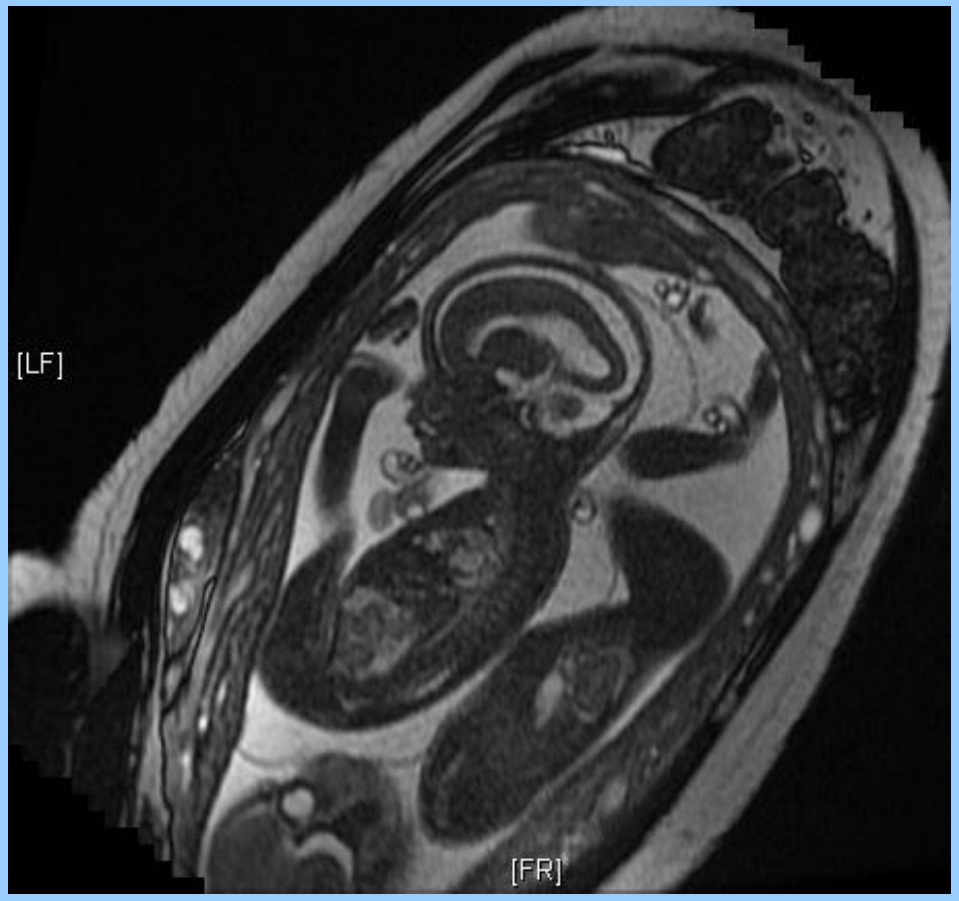
Transformative Clinical Research

Enabling low radiation dose studies

- -Repeat studies
- -Multi-parameter studies
- -Normal subjects
- -Young patients
- -Maternal-Fetal

Equivalent to 0.
65 kg 82 min p.i.

Maternal-Fetal Total Body PET



"Imaging at the beginning of life"

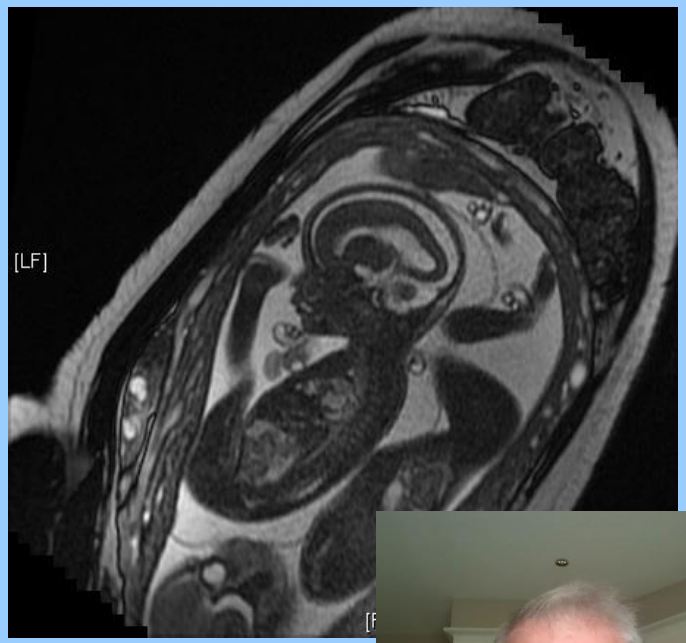
Total-Body PET: Maternal-Fetal Studies

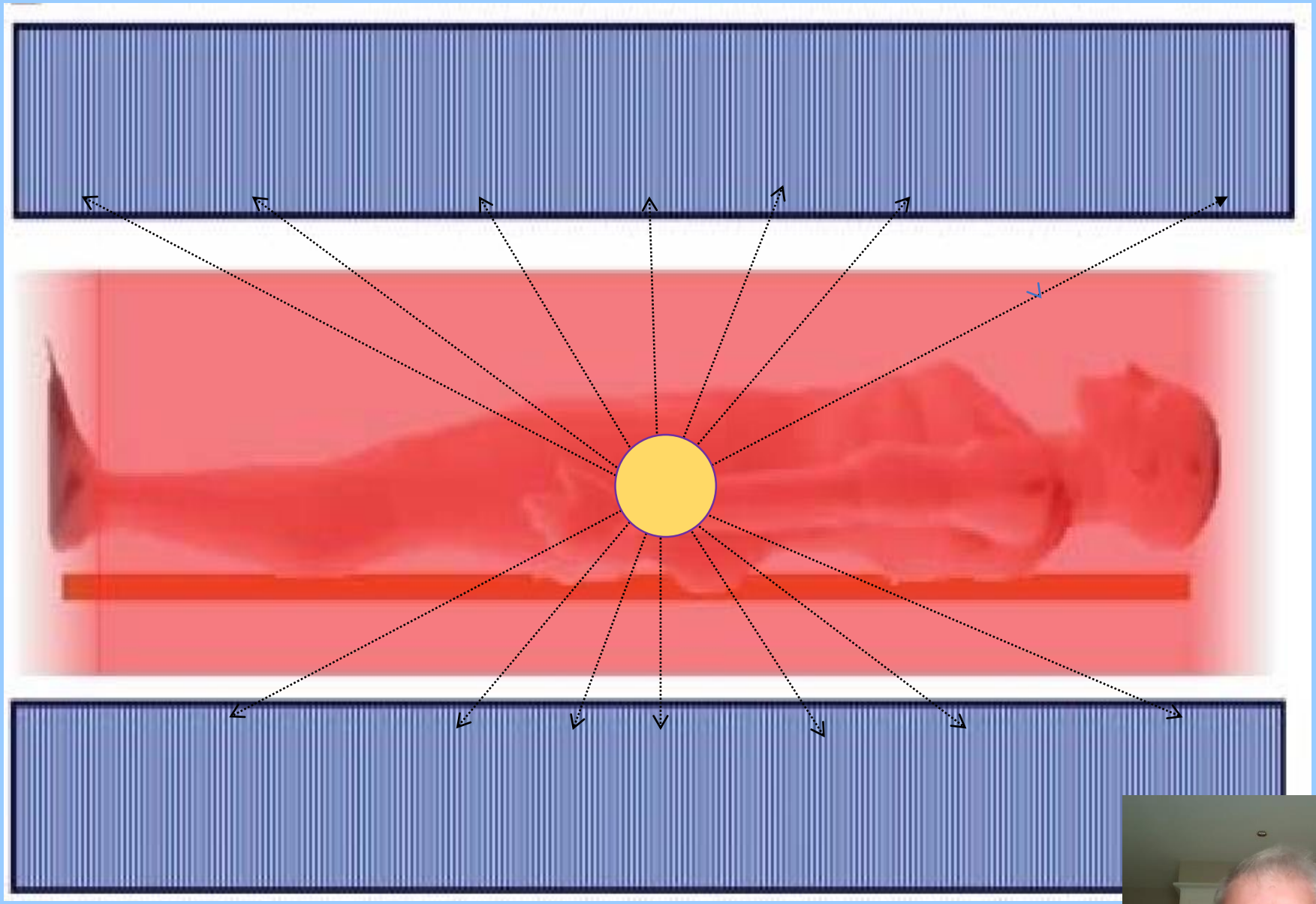
Clinical Challenges

- **Born too soon:**
  - 15M babies born pre-term (<37 weeks) / year
  - 1.1M die because of pre-term complications / year
  - Many surviving pre-term babies have problems as adults (disabled, diabetes, hypertension, heart disease, obesity)
- **Intrauterine Growth Restriction**
  - Raised neonatal mortality and morbidity
  - Diabetes in adulthood
  - Hypertension in adulthood
  - Ischemic heart disease in adulthood
  - Metabolic syndrome (obesity)

Maternal-Fetal Total Body PET Proposed Paradigms

- Placental transport of metabolic substrates
  - Oxygen-$^{15}O_2$
  - Glucose-^{18}FDG
  - Amino Acids-^{11}C,^{18}F
  - Fatty Acids-^{11}C
- Placental system A transporter-^{11}C
- Foetal inflammation-^{11}C
- Foetal infection-^{11}C,^{18}F
- Foetal neuro synapse-^{11}C
- Placenta transport of toxins-^{11}C
- Maternal physiology-$^{15}O_2$





Proposal for low activity whole organ studies:

Recording attenuation corrected counts from a volume of interest ,15cm diame
(2x FWHM 7.5cms) for kinetics and concentrations -avoids noise in reconstr

Transformative Clinical Research

Providing total body kinetics

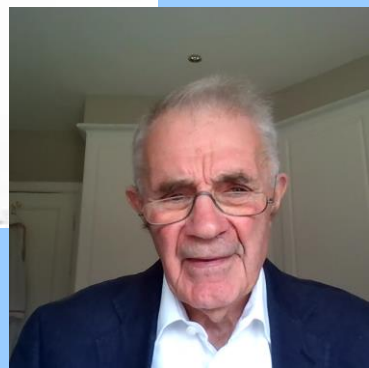
-Total body, kinetic model based, parametric images

-Drug delivery / extended time courses

-Toxicology

-Development of radio-labelled imaging biomarkers

-Studying real-time interactions between the body's organs



Transformative Clinical Research

Studying the body's cardiovascular system

-Distribution of tissue blood flow

-Base-line and challenges (activations)

-Total body distribution of active atheromatous plagues

-Myocardium-Brain inflammation in myocardial disease

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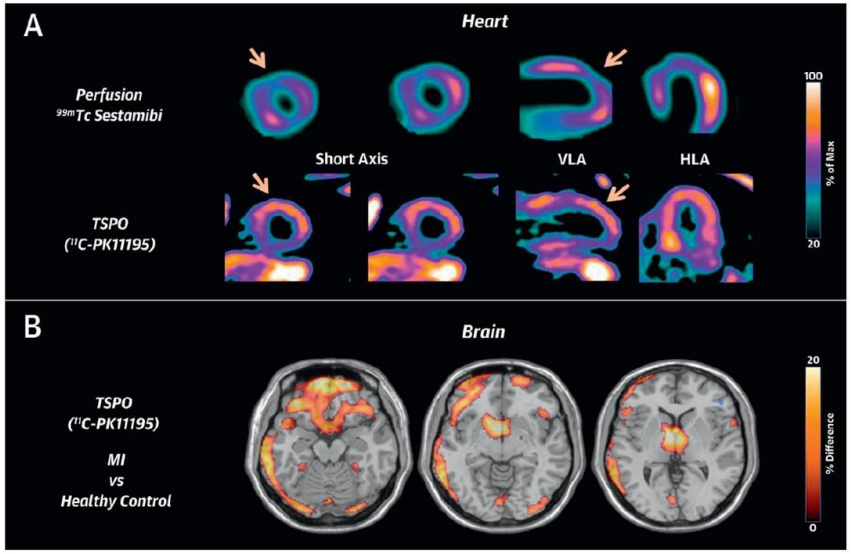
Myocardial Inflammation Predicts Remodeling and Neuroinflammation After Myocardial Infarction

James T. Thackeray, PhD,[a] Henri C. Hupe,[a] Yong Wang, MD,[b] Jens P. Bankstahl, PhD,[a] Georg Berding, MD,[a] Tobias L. Ross, PhD,[a] Johann Bauersachs, MD,[b] Kai C. Wollert, MD,[b] Frank M. Bengel, MD[a]

FIGURE 5 TSPO-Targeted PET Reveals Myocardial Inflammation and Neuroinflammation in Patients After Acute MI



(A) Tomographic images of the heart display elevated TSPO signal in the hypoperfused infarct region in a representative patient **(arrows)**. Images were acquired 4 to 6 days after reperfusion for first acute MI. **(B)** Parametric brain images (statistical parametric mapping) show regional group difference of TSPO signal between infarct patients and healthy volunteers, superimposed to a magnetic resonance imaging template. Elevation of signal is regionally seen in the frontal and temporal cortex. HLA = horizontal long axis; PET = positron emission tomography; VLA = vertical long axis; other abbreviations as in Figure 1.

Transformative Clinical Research

Studying interactive regional pathologies

brain : body

-Anxiety / Depression

-Alzheimer's Disease

-Metabolic syndrome / obesity

-Gut-Brain

-Heart-Brain

-Central-peripheral synapse

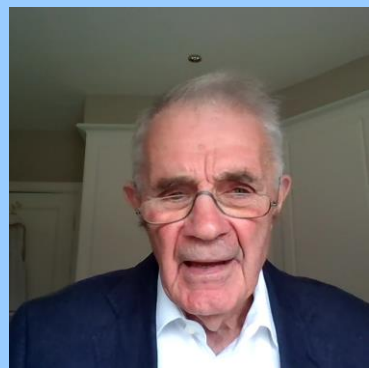
-Neuro regulation of inflammation

The connectome

Parametri

Body and Mind

Current initiatives to integrate mental and physical health-care



Human Brain PET

There are some 70+ validated PET imaging biomarkers for the human brain covering:

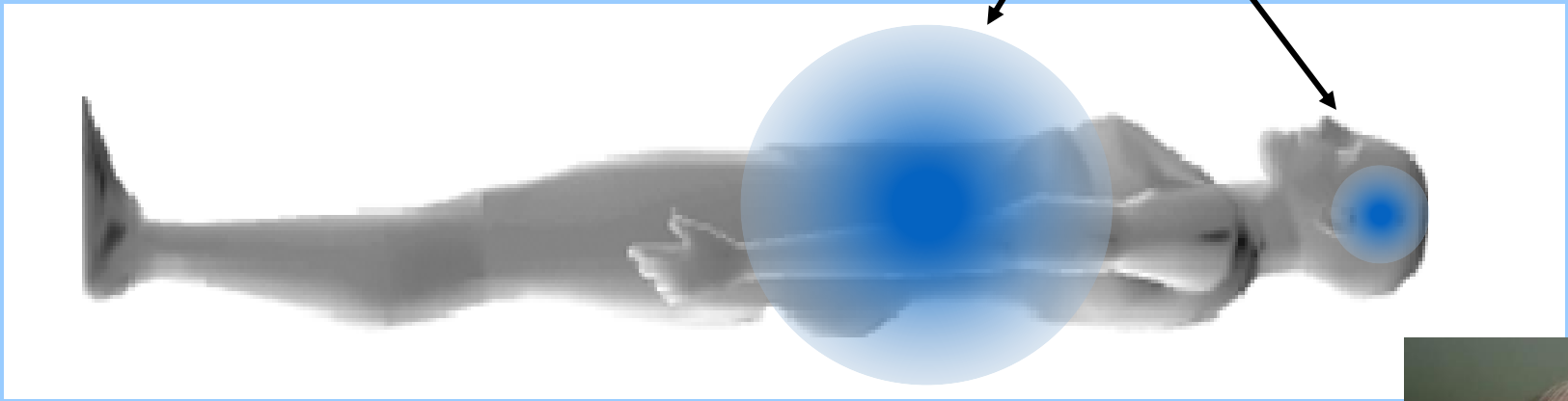
- Perfusion,
- Metabolism,
- Neurotransmitter receptors
- Enzymes
- Aggregated proteins-amyloid/tau
- Activated inflammatory cells

Translate to the Total Body

Note: ½ of the body's
reside outside the br

Total-Body PET: Gut-Brain

Dopamine* & Serotonin*



*PET Imaging ligands exist for Dopamine and Serotonin

Behavioural Brain Research 277 (2015) 32–48

Contents lists available at ScienceDirect

Behavioural Brain Research

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

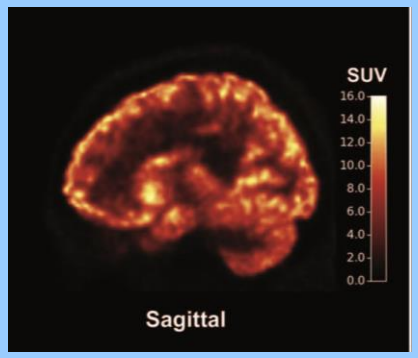
Review

Serotonin, tryptophan metabolism and the brain-gut-microbiome axis

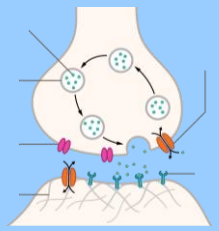
S.M. O'Mahony[a,b,1], G. Clarke[a,c,*,1], Y.E. Borre[a], T.G. Dinan[a,c], J.F. Cryan[a,b]

The brain-gut axis is a bidirectional communication system between the central nervous system and the gastrointestinal tract. Serotonin functions as a key neurotransmitter at both terminals of this network.

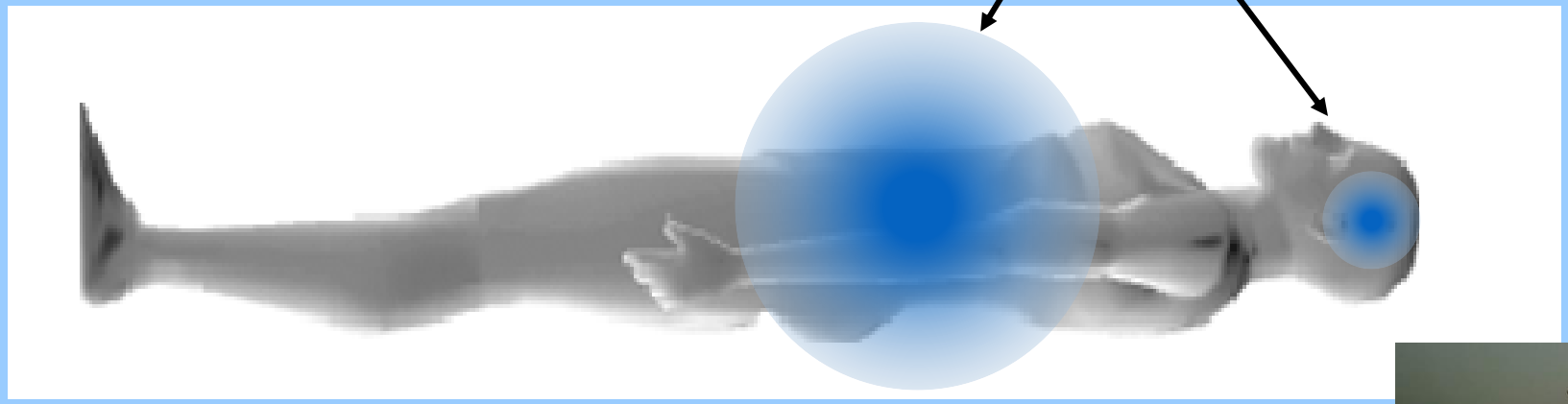
Total-Body PET:
Central [Brain]-Peripheral Synaptic Activity



Synapse Imaging



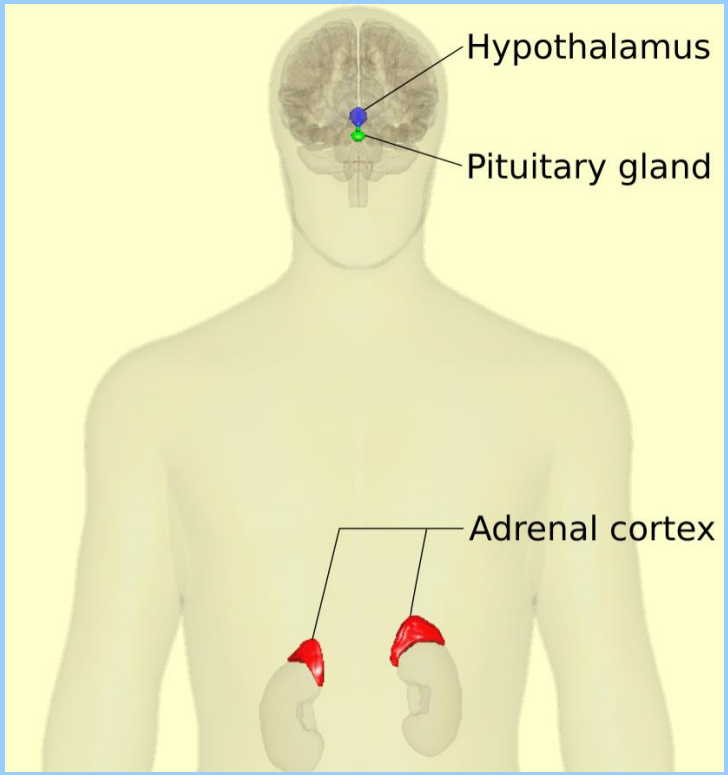
Synaptic Activity*

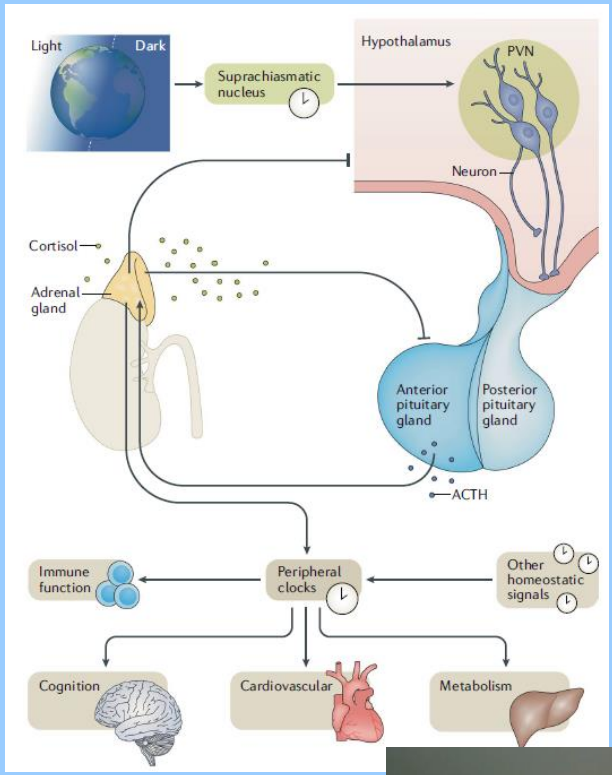


* ^{11}C-UCB-J for Synaptic Vesicle activity

Imaging synaptic density in the living human brain S J. Finnema, N B. N
Eid, Science Translational Medicine.org 20 July 2016 Vol 8 Issue 348 34

Hypothalamus-Pituitary-Adrenal Axis



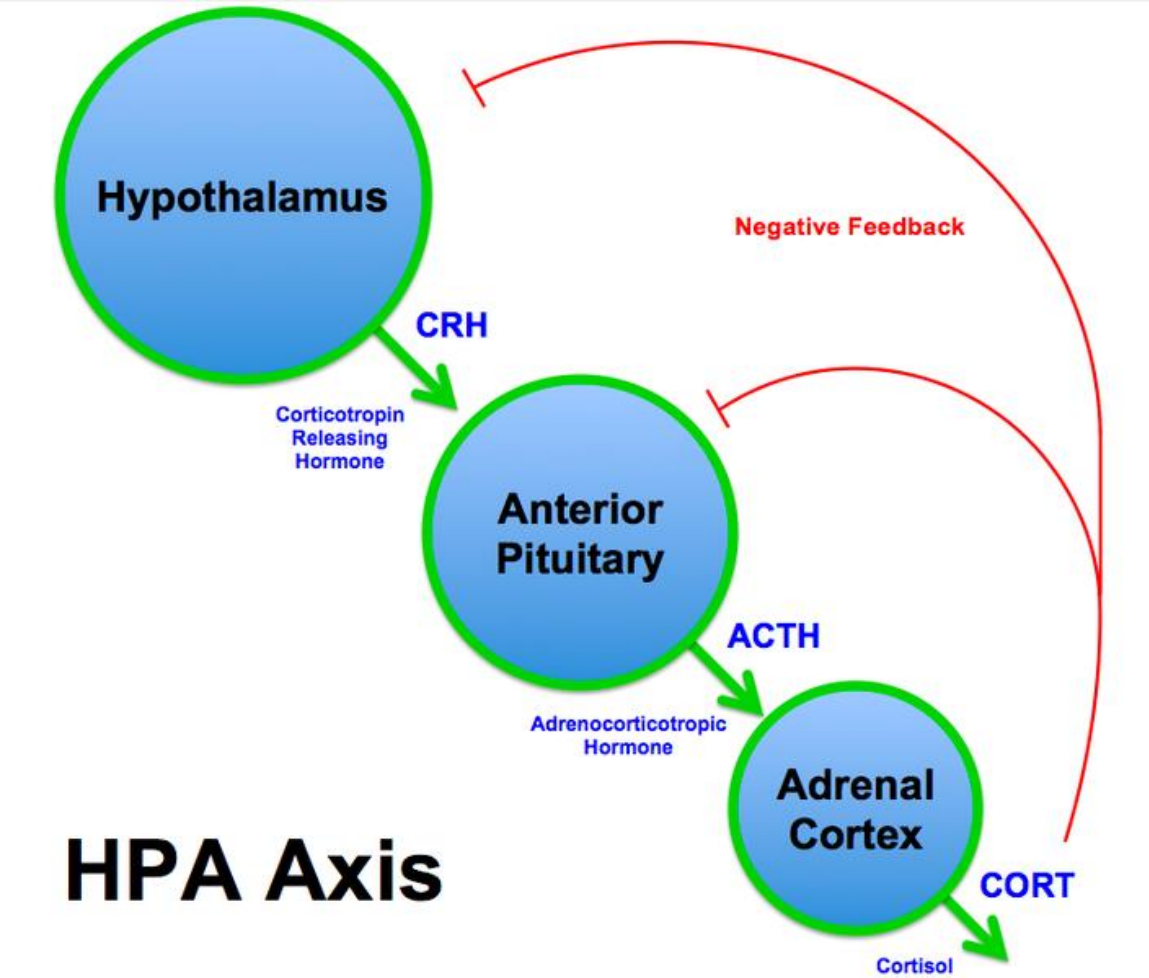


Stress and disease

Major Depressive Disorder, Irritable Bowel Syndrome, Borderline Personality Disorder,

Bipolar Disorder

ADHD



Anxiety Disorder

Insomnia

Alcoholism

Fibromyalgia

Posttraumatic Stress Disorder,

Burnout, Chronic Fatig

Hypothalamus-Anterior Pituitary-Adrenal

$H_2{}^{15}O$ Blood Flow Activation Studies or ^{11}C-precursor –for cortisol synthesis i

Neural regulation of immunity: molecular mechanisms and clinical translation

Valentin A Pavlov[1,2] & Kevin J Tracey[1,2]

156 VOLUME 20 | NUMBER 2 | FEBRUARY 2017 NATURE NEUROSCIENCE

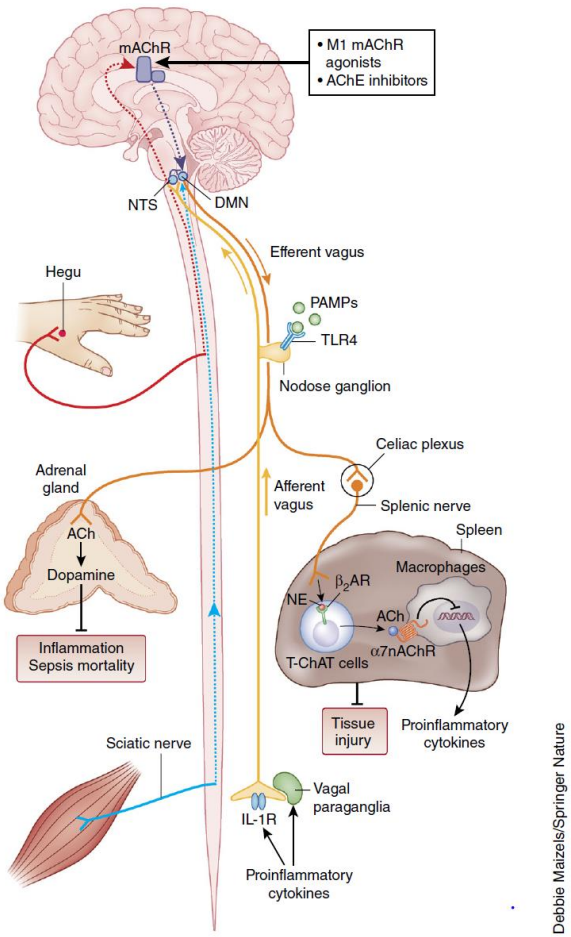


Figure 1 Vagus nerve-mediated reflex circuitry in immunity and inflammation. In the inflammatory reflex, the activity of afferent vagus nerve fibers residing in the nodose ganglion is stimulated by cytokines and PAMPs. The signal is transmitted to the NTS. Reciprocal connections

Neuroscience

Inflammation

"Studies of electrically stimulating the vagus nerv
transmitted through efferent vagus nerve fibers i
of TNF and other proinflammatory cytokines"

Neural regulation of immunity: molecular mechanisms and clinical translation

Valentin A Pavlov[1,2] & Kevin J Tracey[1,2]

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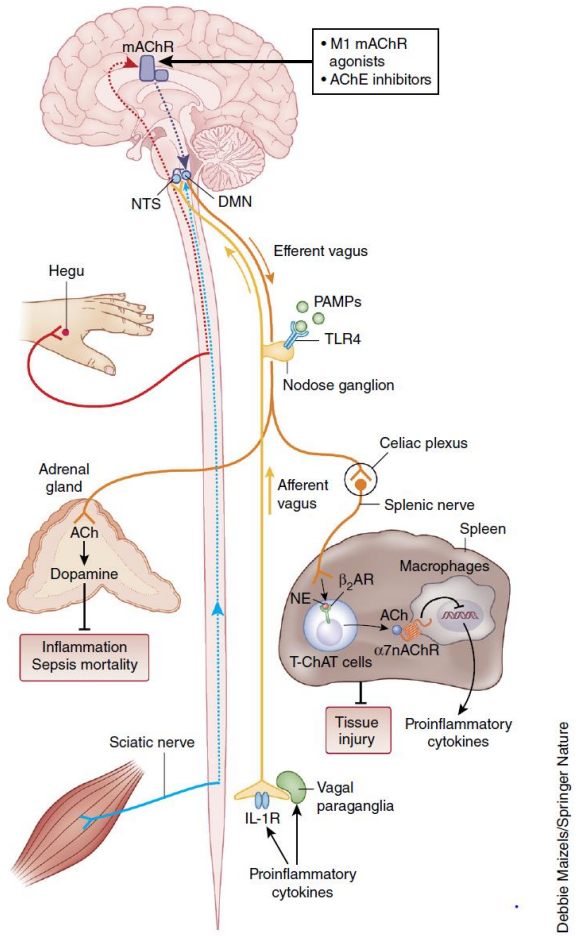
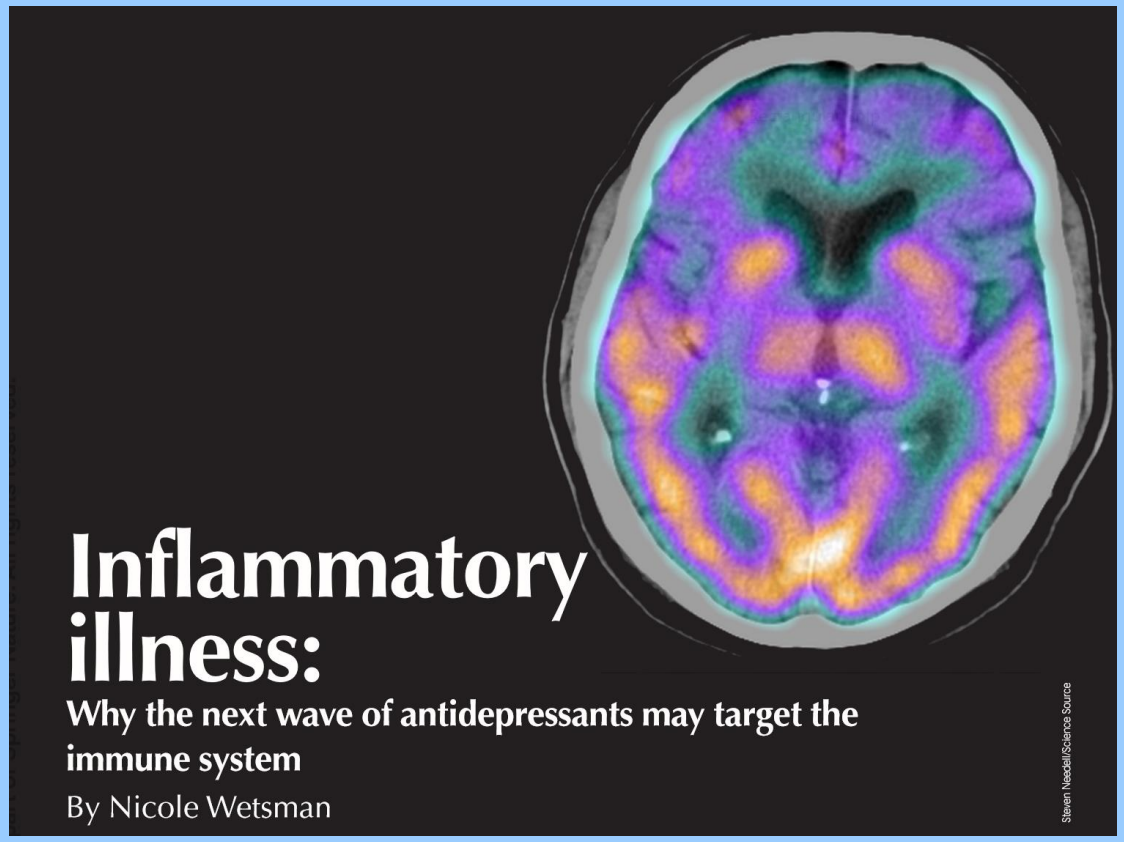


Figure 1 Vagus nerve-mediated reflex circuitry in immunity and inflammation. In the inflammatory reflex, the activity of afferent vagus nerve fibers residing in the nodose ganglion is stimulated by cytokines and PAMPs. The signal is transmitted to the NTS. Reciprocal connections

Neuroscience

Inflammation

Maybe PET image:
Transient perfusion chang
periphery-$H_2{}^{15}O$



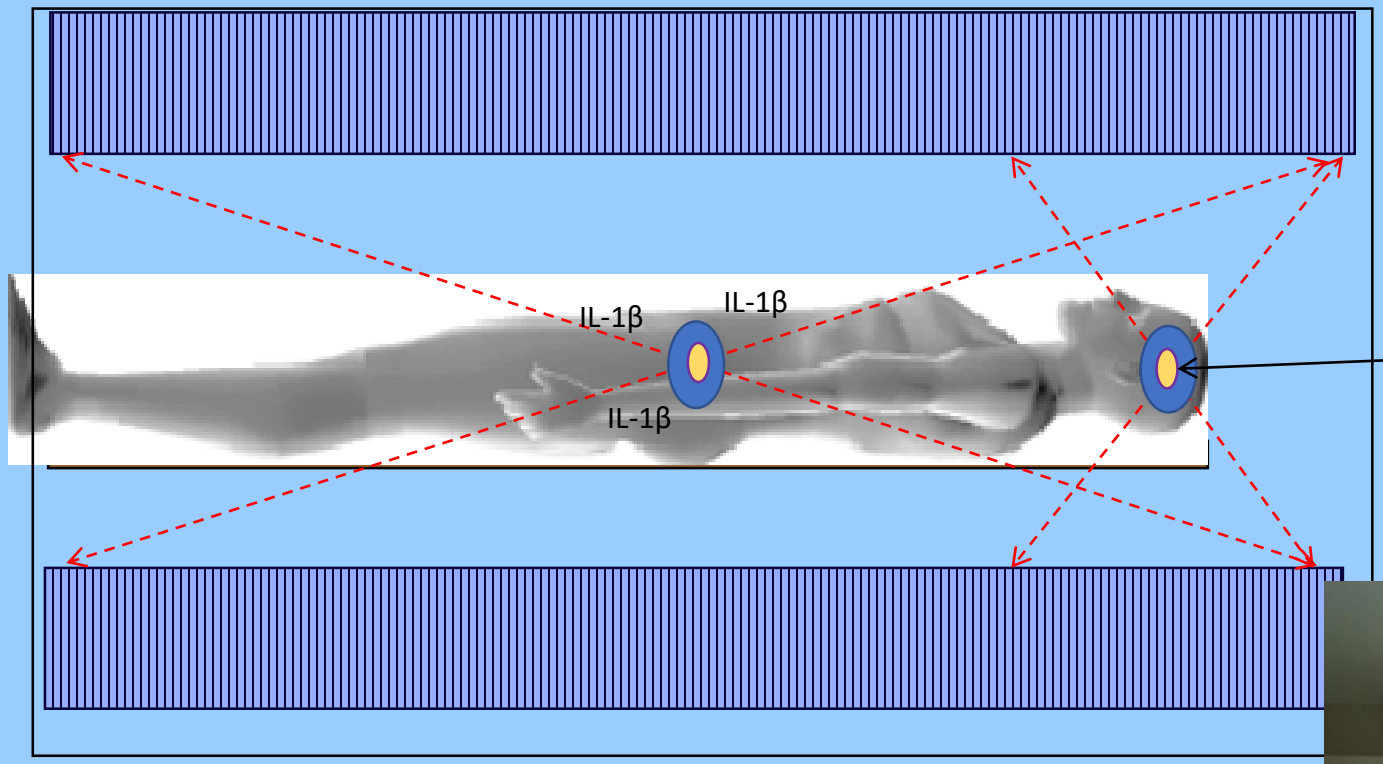
Absolute Measurements of Macrophage Migration Inhibitory Factor and Interleukin-1-β mRNA Levels Accurately Predict Treatment Response in Depressed Patients

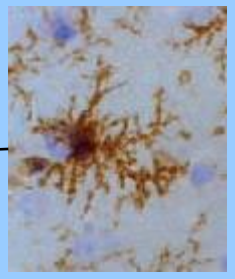
Annamaria Cattaneo, PhD; Clarissa Ferrari, PhD; Rudolf Uher, MD; Luisella Bocchio-Chiavetto, PhD; Marco Andrea Riva, PhD; the MRC ImmunoPsychiatry Consortium, and Carmine M. Pariante, MD, FRCPsych, PhD

International Journal of Neuropsychopharmacology, (2016) 19(10): 1–10

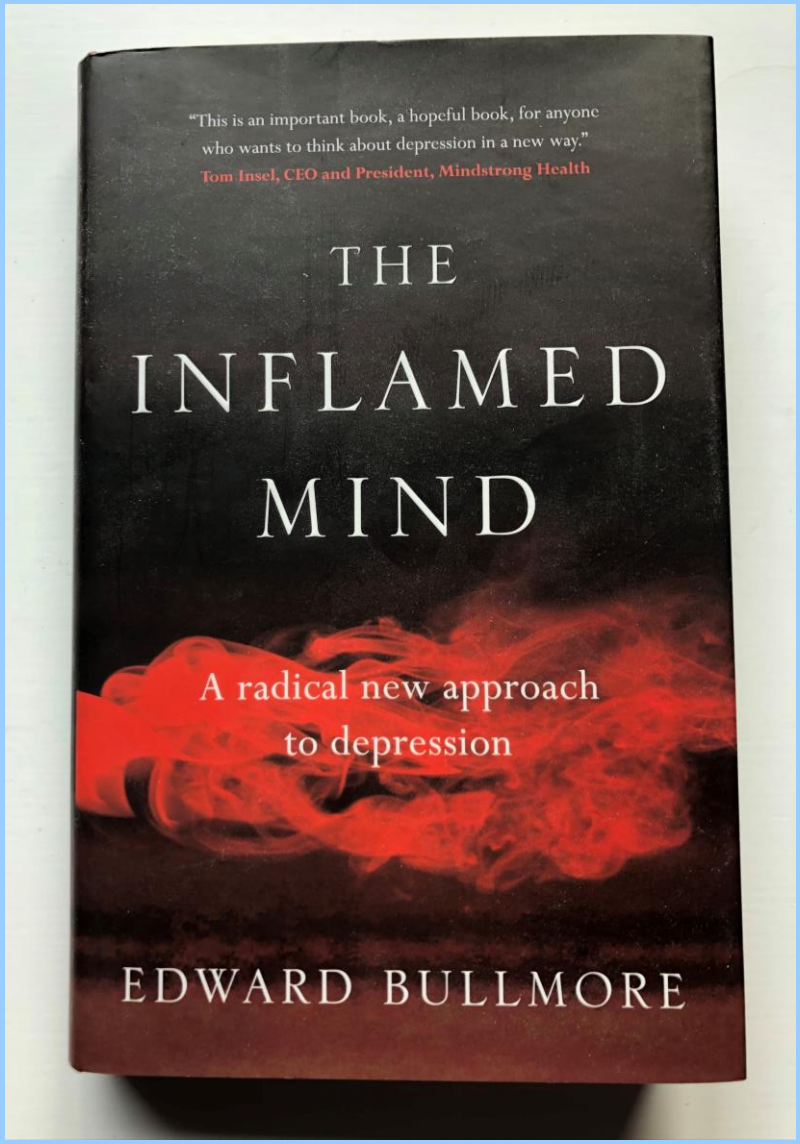
Brain-Body:

Peripheral Inflammation acting on the brain
"Sickness Behaviour "



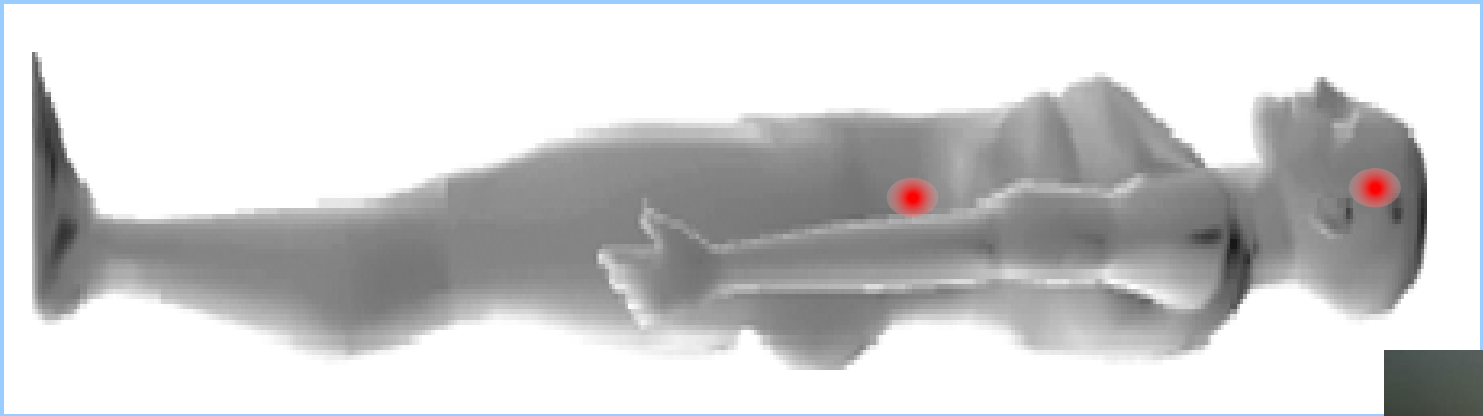


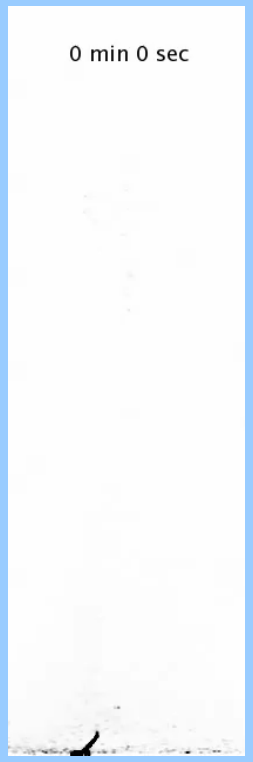
Should we be using a ^{11}C or ^{18}F labelled precursor of I


"This is an important book, a hopeful book, for anyone who wants to think about depression in a new way."
Tom Insel, CEO and President, Mindstrong Health
THE
INFLAMED
MIND
A radical new approach to depression
EDWARD BULLMORE

Translating brain perfusion activation studies to the total body

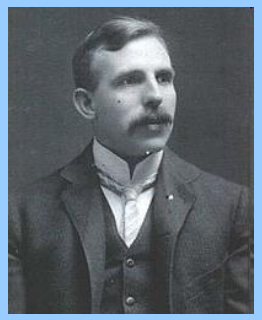
$H_2{}^{15}O$



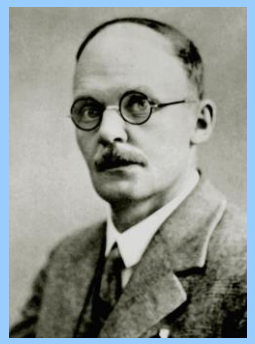


Manchester UK 1911-1913

George Hevesy



Ernest Rutherford



Hans Geiger

The "Tracer principle"

Detect and quantify at single atom level in nonperturbed macroscopic living systems…

A radioactive atom might be used as a "representative" tracer of stable atoms of the same element whenever and where ever it accompanied them in biological systems.

Applications of Total Body PET

Cancer

"Systems Biology"

Infection

Heart-Body

Drug Kinetics

Immunotherapy

Drug effects

Mental Illness

Lower Radi

Brain-Body

Thank you