"Molecular Imaging in Rheumatology Novel PET-tracers in RA"

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Rheumatoid Arthritis (RA)

- **RA is one of the most common rheumatic diseases, affecting approximately 0.5–1.0% of the population.**

  (The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1316–22.)

- **RA is characterized by autoantibody production and chronic synovial inflammation, often resulting in structural joint damage.**

Novel PET-tracers for imaging of rheumatoid arthritis (R.A.)

- ✓ Over the past two decades, treatment of RA has significantly improved with the introduction of biological disease-modifying anti-rheumatic drugs (DMARDs).

- ✓ Currently, (early) assessment of RA disease activity and response to therapy mainly consists of physical examination and laboratory analyses.

Novel PET-tracers for imaging of rheumatoid arthritis (R.A.)

- Local evaluation of inflammatory changes in soft-tissue have been obtained by anatomical imaging modalities such as magnetic resonance imaging (MRI) and musculoskeletal ultrasound (MSUS), both enabling a highly sensitive detection of synovitis.

- However, these techniques do not allow visualization of immunopathological features of the individual RA patient, which could be used to diagnose the disease in an early stage and guide selection of targeted therapy and monitor treatment efficacy based on these specific features.

Novel PET-tracers for imaging of rheumatoid arthritis (R.A.)

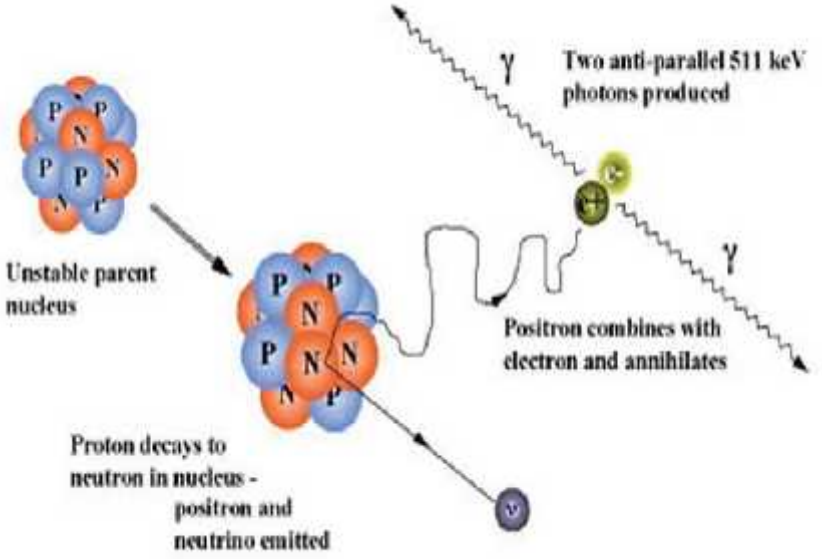
- ✓ The classical method to determine the immuno-pathological features and treatment re… the site of inflammation is histopathol… …ies, which can be obt… arth…

PET-imaging

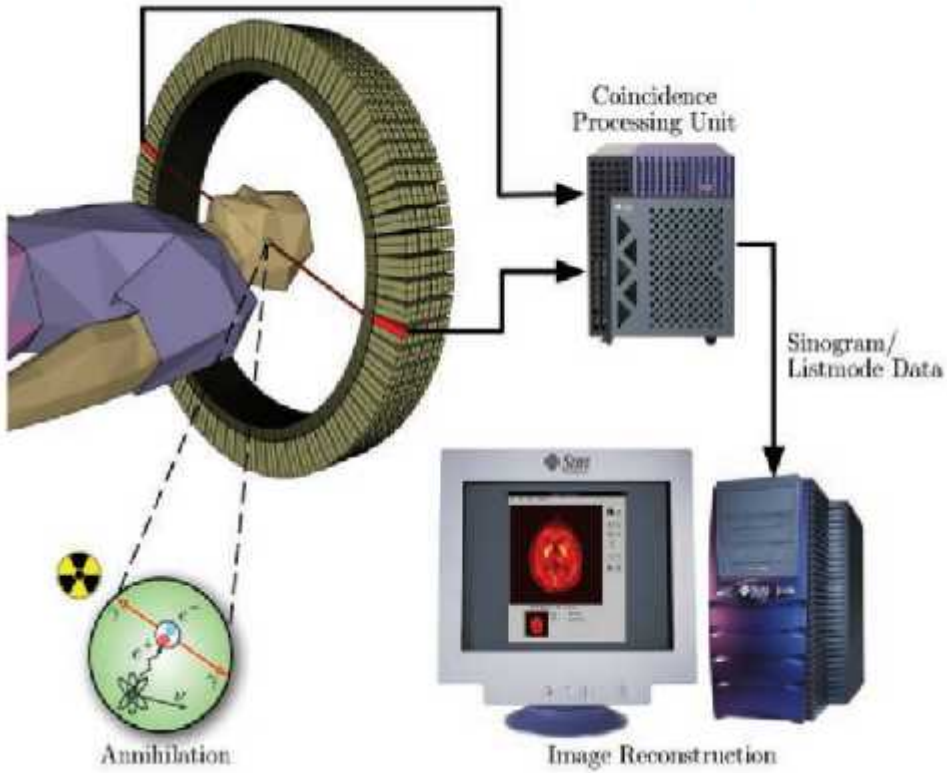
- ✓ Need has a… …ely visualize molecular markers in inflammation and accurately track changes in multiple joints simultaneously.

PET-imaging principles

Annihilation phenomenon

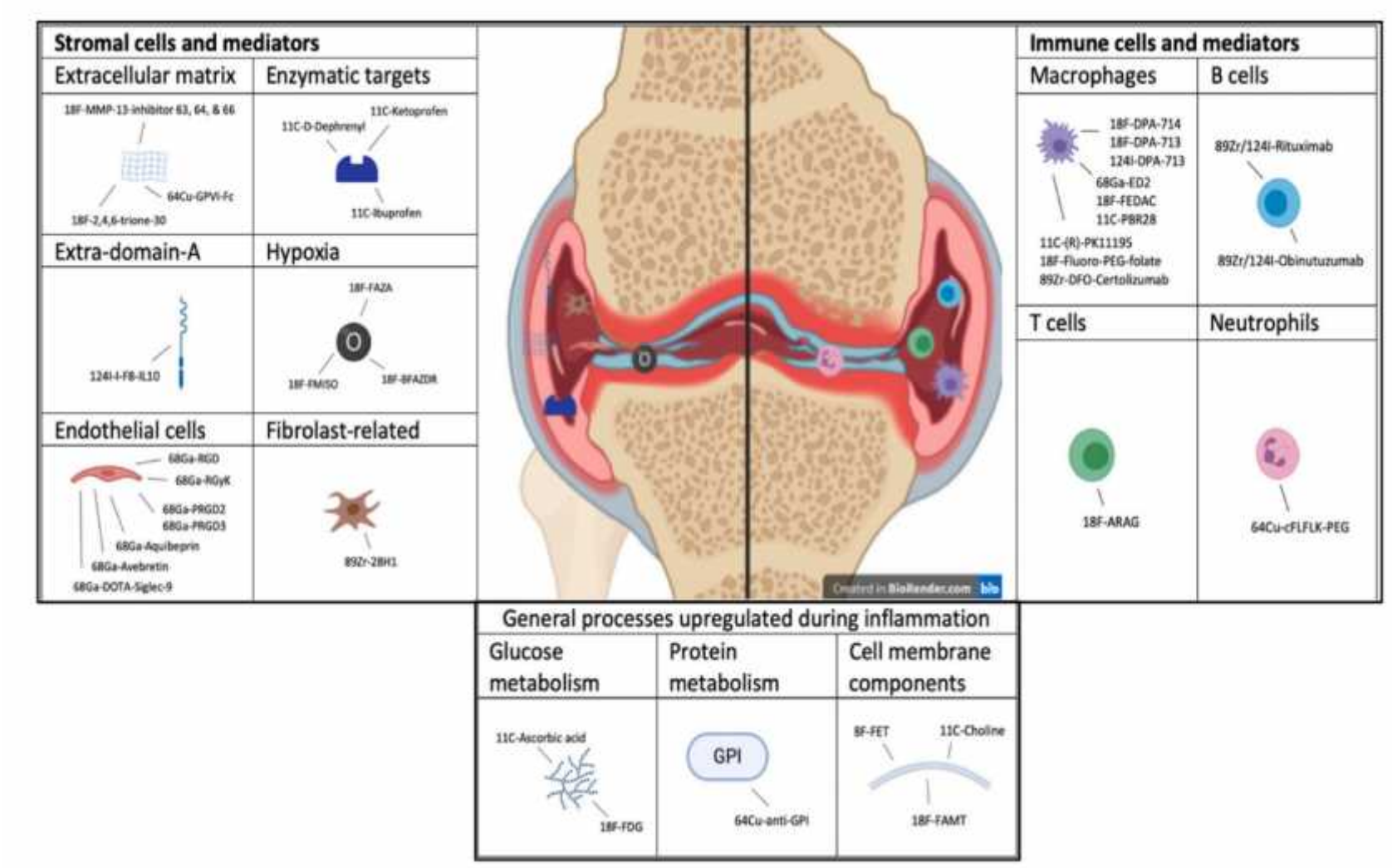


3D-Whole body Bio-distribution



Novel PET-tracers for imaging of rheumatoid arthritis (R.A.)

Schematic representation of the inflamed RA knee joint



J.M.A. van der Krogt et al., Autoimmunity Reviews 2021

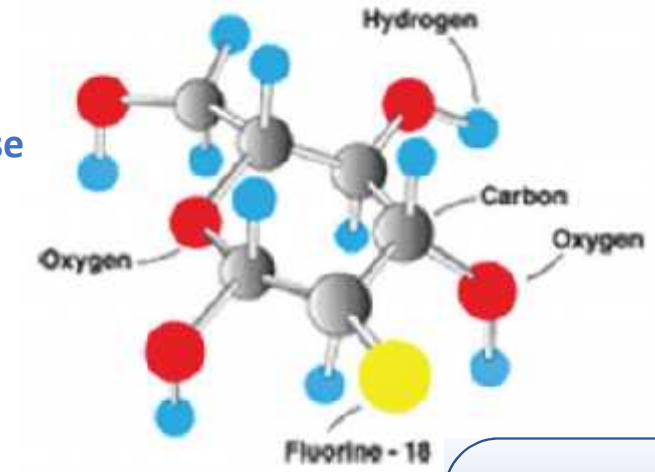
PET-tracers in RA

Molecular Target

Glucose metabolism.

Glucose metabolism is upregulated in inflammatory processes

(18F) Fluorodeoxyglucose

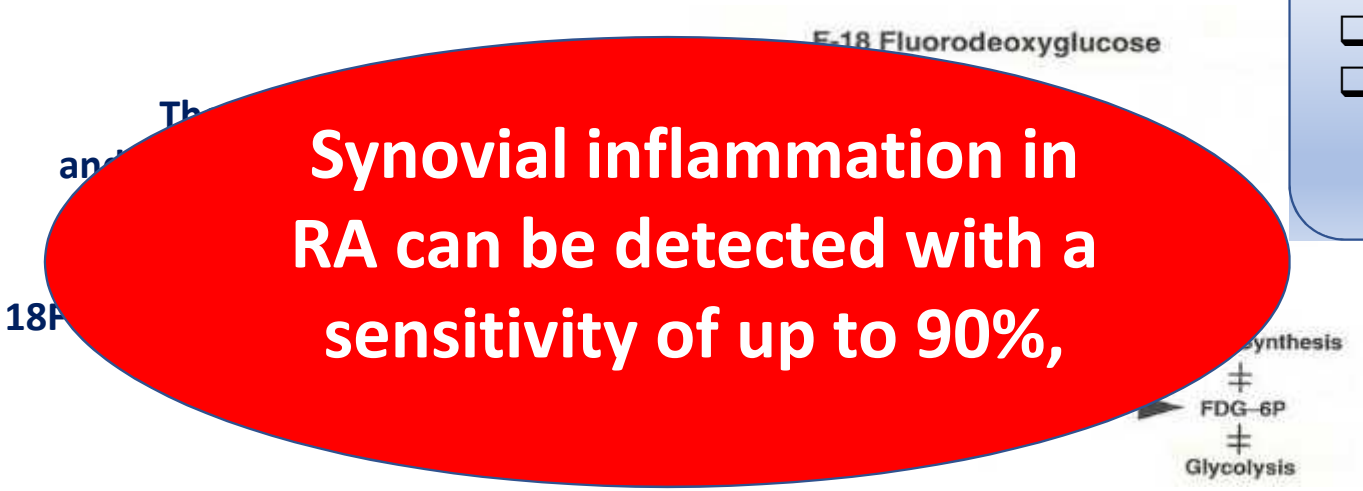


Cells with glycolytic activity.

- ❑ Macrophages
- ❑ Granulocytes

in an inflammatory setting such as RA

Synovial inflammation in RA can be detected with a sensitivity of up to 90%,



PET-tracers in RA

18F-FDG

Prognostic Value

- Prospective study included 15 patients (12 women, 3 men) with active RA refractory to anti-TNFα treatments.
- 18F- FDG PET/CT at baseline and 16 weeks after treatment with rituximab.

- Strong correlation of the 3 PET-parameters with US, CRP and Disease Activity Scores (DAS28) at baseline at week 16.

- Number of PET-positive joints (visual evaluation)
- Sum of all SUVs (cumulative SUV).
- Composite index taking into account both parameters.

CI = cumulative SUV x (number of PET positive joints/total number of joints evaluated).

Prognostic Value

The metabolic response PET/CT joint analysis predicted the outcome of Rituximab treatment with
high NPV of 91%,
91% specificity,
86% accuracy.

FOSSE et al. European Journal of Hybrid Imaging (2018)

PET-tracers in RA

18F-FDG

- ✓ **18F-FDG as a tool for diagnostic, monitoring and prognostic purposes in RA.**
- ✓ **Nevertheless, a drawback is the lack of specificity of 18F-FDG PET for differentiation between RA and other joint diseases such as osteoarthritis.**
- ✓ **This has stimulated the search for more specific tracers to image RA.**

FOSSE et al. European Journal of Hybrid Imaging (2018)

Novel PET-tracers in RA

Molecular Target

T-lymphocytes.

- (T cells) play an important role in the initiation and development of RA.
- Activation of T cells can be mediated through the recognition of antigens, which can be presented by antigen-presenting cells such as B-cells, macrophages, & dendritic cells.
- T-cells can become autoreactive and induce pro-inflammatory responses which can lead to inflammation and ultimately the destruction of healthy tissue.

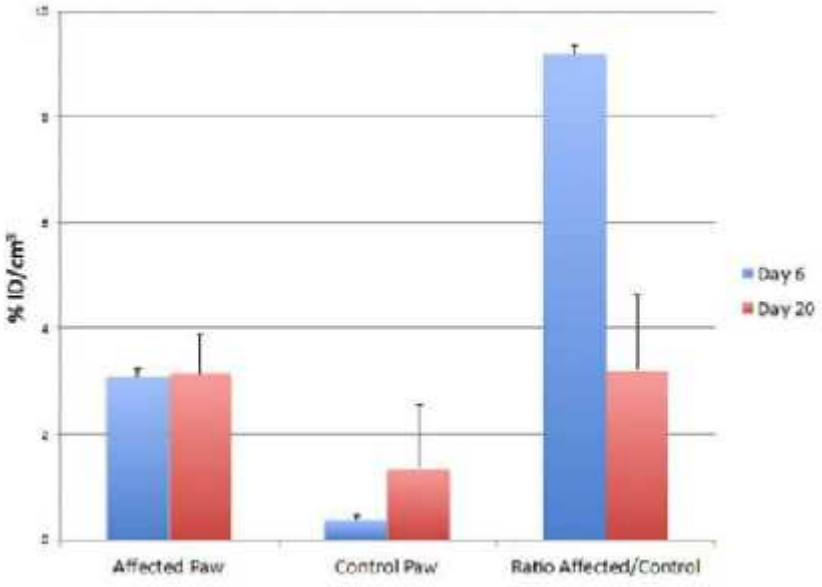
PET imaging of T-cell activity can be done by targeting deoxycytidine kinase (dCK), which has been associated with the homeostatic proliferation and survival of peripheral T cells.

Fluorine-18-labeled 9-b-Darabinofuranosylguanine ([18F]F-AraG)

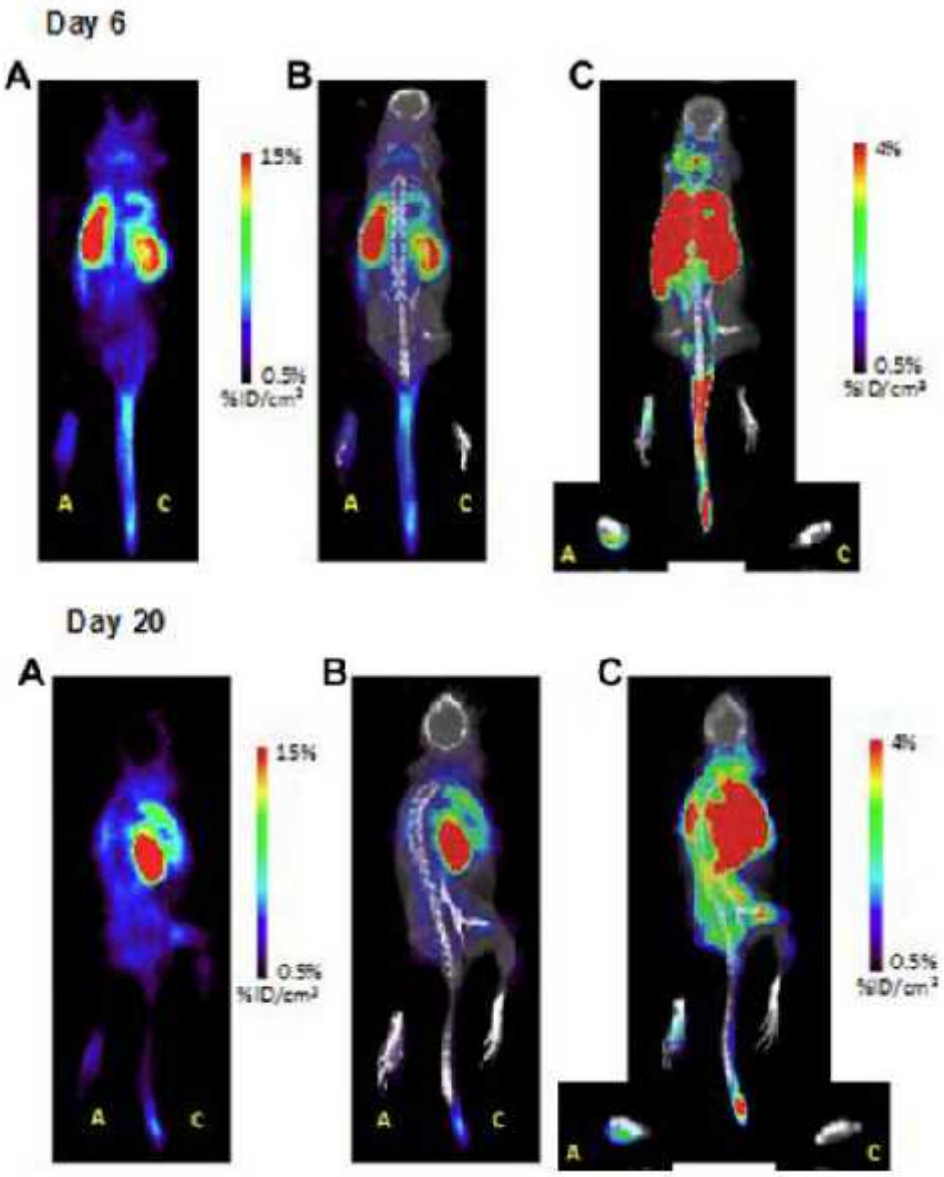
- ✓ **Positron-emitting guanosine analog that can be phosphorylated**
- ✓ **Phosphorylated [18F]F-AraG accumulates in activated T cells, allowing imaging with PET.**

Novel PET-tracers in RA

Fluorine-18-labeled 9-b-Darabinofuranosylguanine ([18F]F-AraG)



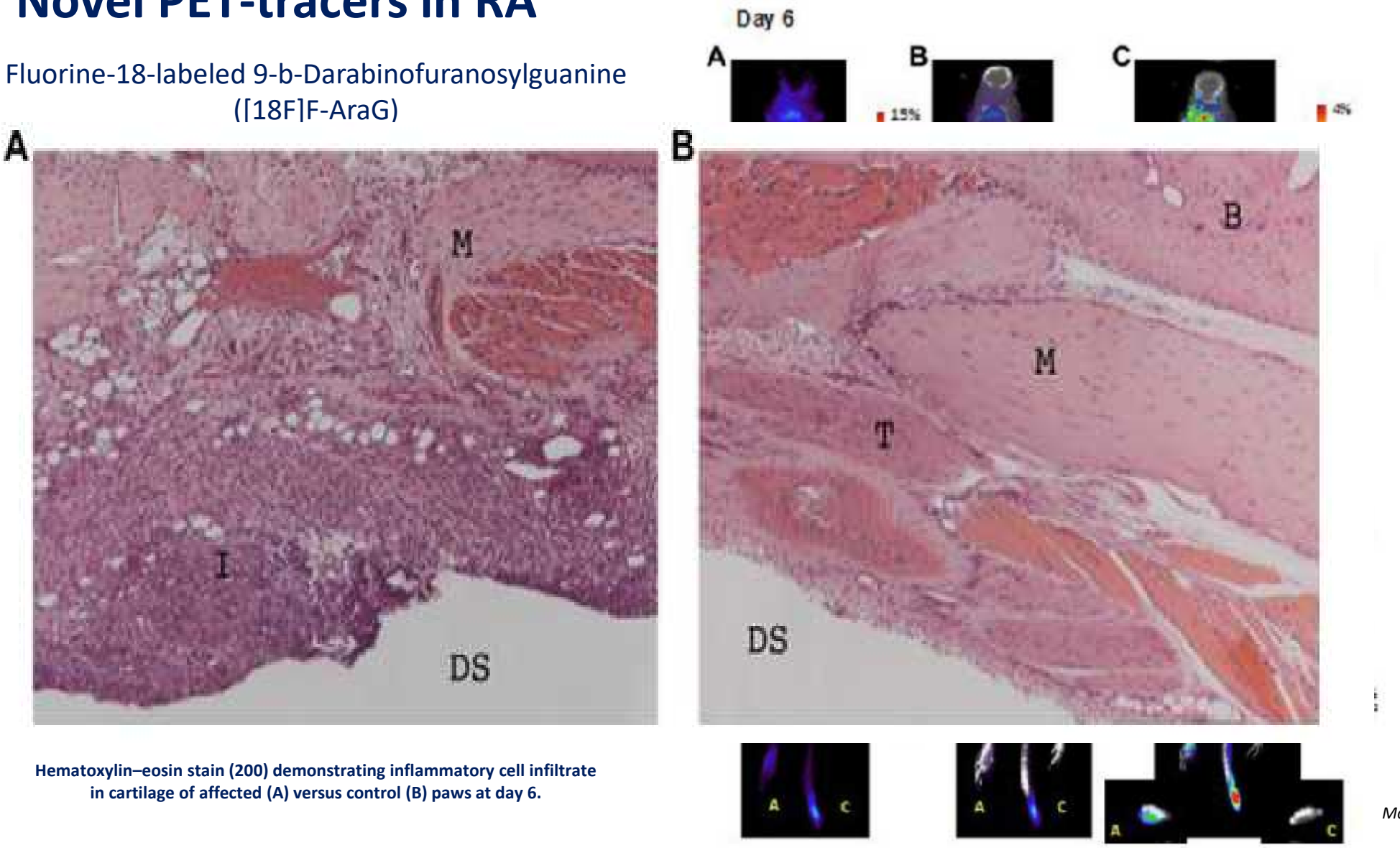
- Differential uptake of [18F]F-AraG was demonstrated on imaging of the affected joint when compared to control at both acute and chronic time points.
- Corresponding changes in markers of T-cell activation observed on flow cytometry.



Franc BL et al, Molecular Imaging 2017

Novel PET-tracers in RA

Fluorine-18-labeled 9-b-Darabinofuranosylguanine
([18F]F-AraG)



Hematoxylin–eosin stain (200) demonstrating inflammatory cell infiltrate in cartilage of affected (A) versus control (B) paws at day 6.

Franc BL et al,
Molecular Imaging 2017

Novel PET-tracers in RA

Molecular Target

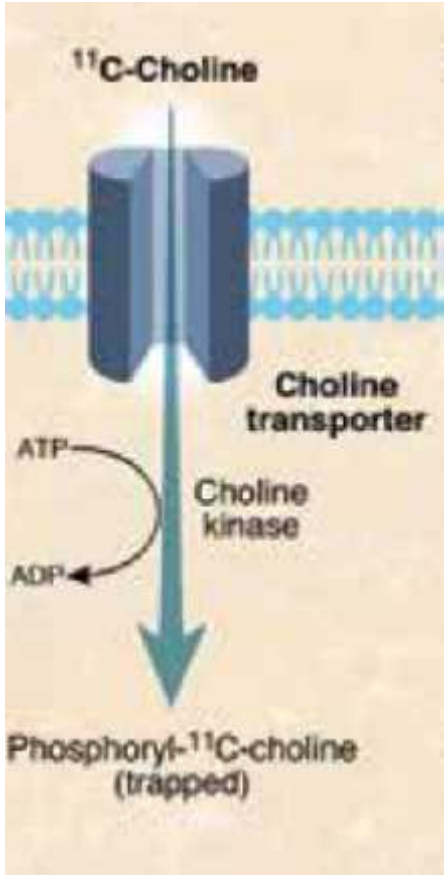
↓

Cell membrane components

Choline

- ✓ Substrate used in the production of phospholipids, an integral part of the cell membranes.
- ✓ Inflamed synovium of RA patients → Cell membranes synthesis is increased

Uptake Mechanism

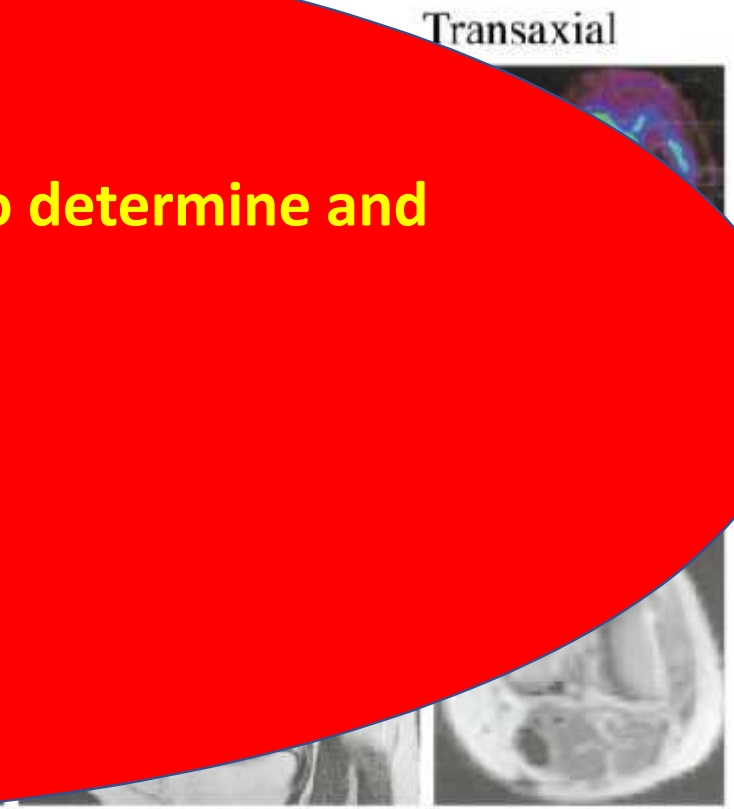


Novel PET-tracers in RA

^{11}C-Choline

Comparative study with ^{18}F-FDG

- 10 patients with RA and cli
  inflammatio



- ❑Potential of ^{11}C-choline as a tracer to determine and monitor inflammation in RA
- ❑Further examination is needed.

Roivainen et al, Arthritis Rheum.

Novel PET-tracers in RA

Molecular Target

Membrane of macrophage mitochondria

Mitochondria support the initiation of RA disease activity.

- ✓ Mitochondria are key to the production of ATP that is needed during RA disease activity due to an increase in metabolic activity of macrophages.
- ✓ Mitochondria are involved in the production of reactive oxygen species (ROS), which set the threshold for T cell activation and are thereby involved in the regulation of chronic autoimmune inflammation.

Different structures within the mitochondrial membrane have been highlighted as excellent PET targets for RA.

4 TSPO PET tracers
(over the past decade)

First generation
11C-(R)-PK11195
11C-PBR28

Second Generation
18F-DPA-714
11C-DPA-713

n
s

Novel PET-tracers in RA

✓ 2nd generation TSPO PET tracers generally a lower background uptake is found.

✓ 2nd generation TSPO macrophage PET provides new opportunities for both early diagnosis and therapy monitoring of RA.

Bruijnen STG et al, Plos one, 2019

Novel PET-tracers in RA

Molecular Target

Folate receptor (FR)

Plasma anchored transmembrane carrier protein, highly expressed on the surface of activated macrophages in RA patients

[18F]fluoro-PEG-folate
(polyethylene glycol folate)
has been proposed as a novel candidate folate-based PET tracer

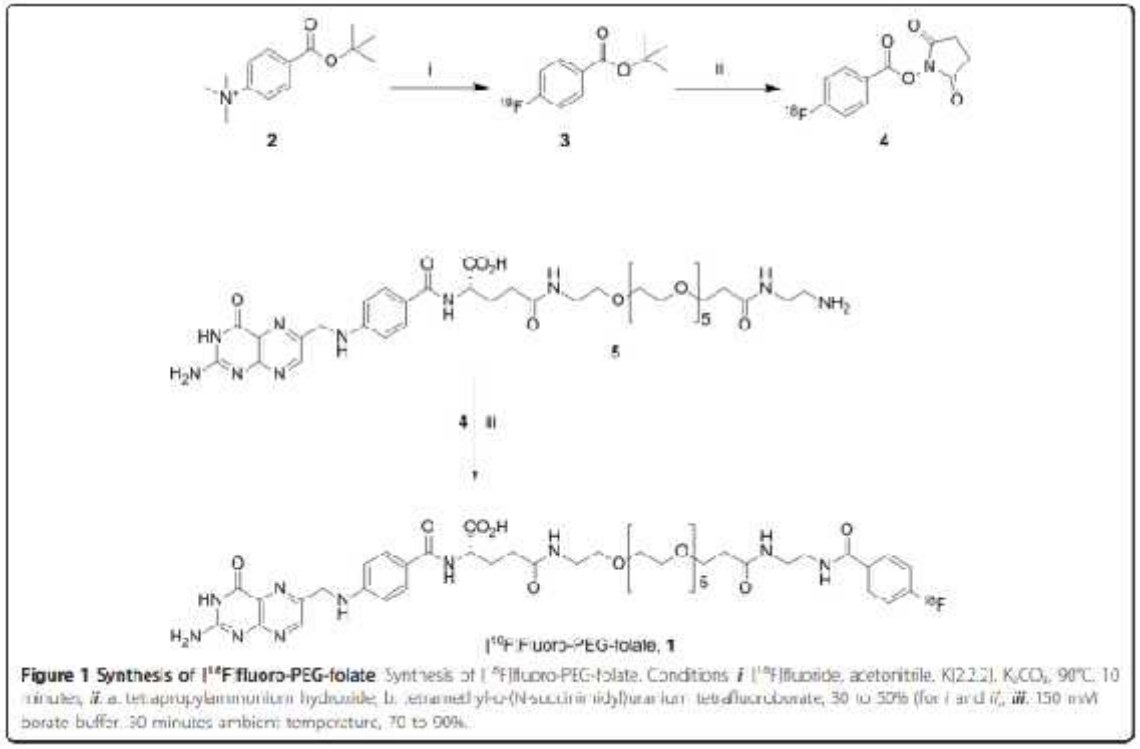


Figure 1 Synthesis of [^{18}F]fluoro-PEG-folate Synthesis of [^{18}F]fluoro-PEG-folate. Conditions *i* [^{18}F]fluoride, acetonitrile, K[2.2.2], K_2CO_3, 90°C, 10 minutes, *ii*. a. tetrapropylammonium hydroxide; b. tetramethyl-*N*-succinimidyluranium tetrafluoroborate, 30 to 50% (for *i* and *ii*), *iii*. 150 mM borate buffer, 30 minutes ambient temperature, 70 to 90%.

Novel PET-tracers in RA

First in man study of [18F] fuoro-PEG-folate PET

- ✓ **Biodistribution demonstrated fast clearance of [18F]fuoro-PEG-folate from heart and blood vessels and no dose limiting uptake in organs.**
- ✓ **[18F]fuoro-PEG-folate showed uptake in arthritic joints with significantly lower background and hence significantly higher target-to-background ratios.**
- ✓ **Dynamic scanning demonstrated fast tracer uptake in affected joints, reaching a plateau after 60 mins, coexisting with a rapid blood clearance.**
- ✓ **This first in man study demonstrates the potential of [18F]fuoro-PEG-folate to image arthritis activity in RA with favorable imaging characteristics of rapid clearance and low background uptake, that allow for detection of infammatory activity in the whole body.**

Verwweij NJF et al., Sci Rep. 2020

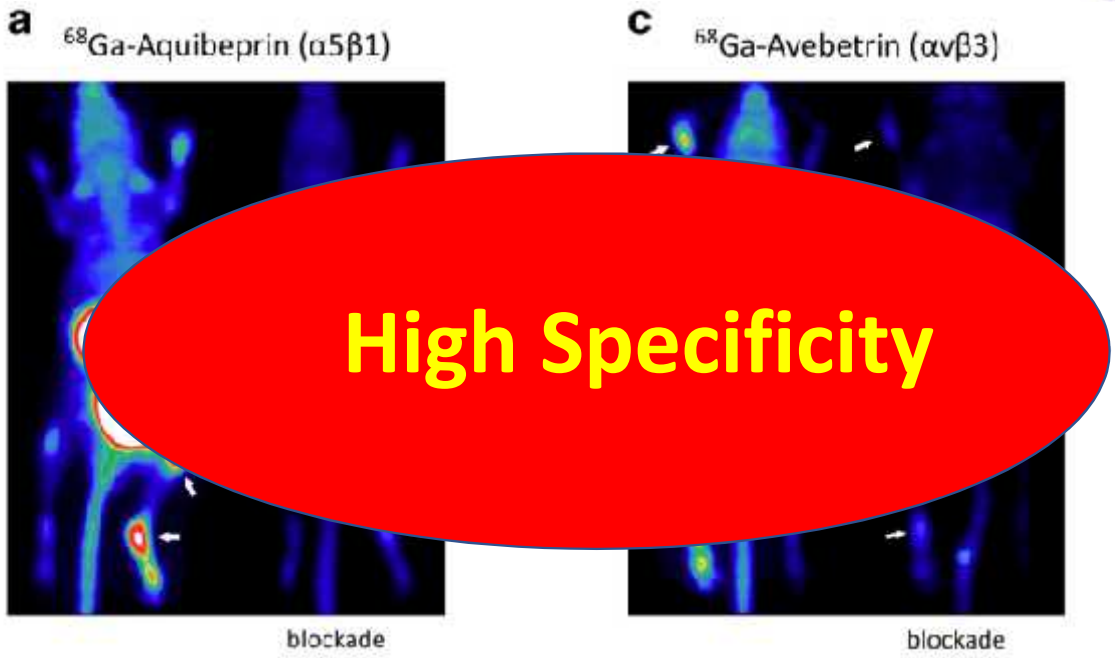
Novel PET-tracers in RA

Molecular Target

Alpha-5 beta-1 (α5β1) integrin

- ✓ Transmembrane receptor recently found in proliferating synovial tissue.
- ✓ Increased expression in arthritic joints, specifically in endothelial cells and to a lesser extent in macrophages.

PET imaging of integrin subtypes αvβ3 and α5β1



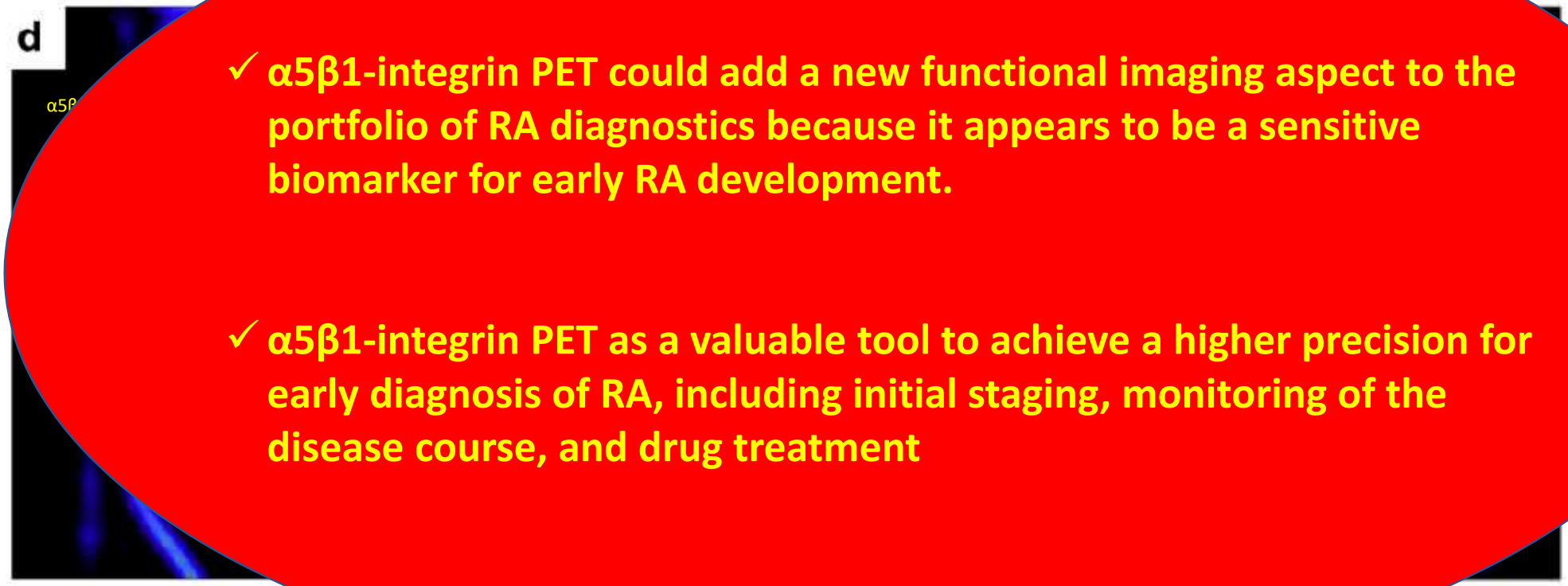
Saturation of the receptor binding capacity by means of co-injection of a large dose of unlabeled compound (blockade) resulted in a virtually complete reduction of the uptake in arthritic joints for both tracers.

Notni et al, EJNMMI 2019

Novel PET-tracers in RA

PET i… …α5β1

non-a…



Both tracers show a low uptake … …e signal for 68Ga-… …Ga-Avebetrin

- ✓ **α5β1-integrin PET could add a new functional imaging aspect to the portfolio of RA diagnostics because it appears to be a sensitive biomarker for early RA development.**
- ✓ **α5β1-integrin PET as a valuable tool to achieve a higher precision for early diagnosis of RA, including initial staging, monitoring of the disease course, and drug treatment**

Notni et al, EJNMMI 2019

Novel PET-tracers in RA

Molecular Target

Tumor necrosis factor alpha (TNF-α)

A cytokine mainly produced by macrophages in the inflamed synovial tissue of RA patients, making this target suitable for immune cell-specific targeting in RA diagnosis and disease activity monitoring.

✓ Some RA patients experience a rapid clinical response to TNFα inhibitors such as certolizumab pegol (CZP).

- ❑ CZP was modified with p-isothiocyanatobenzyl- deferoxamine (DFO) and radiolabeled with Zr-89.
- ❑ Immuno-PET imaging of TNFα in transgenic human TNFα-expressing mice.

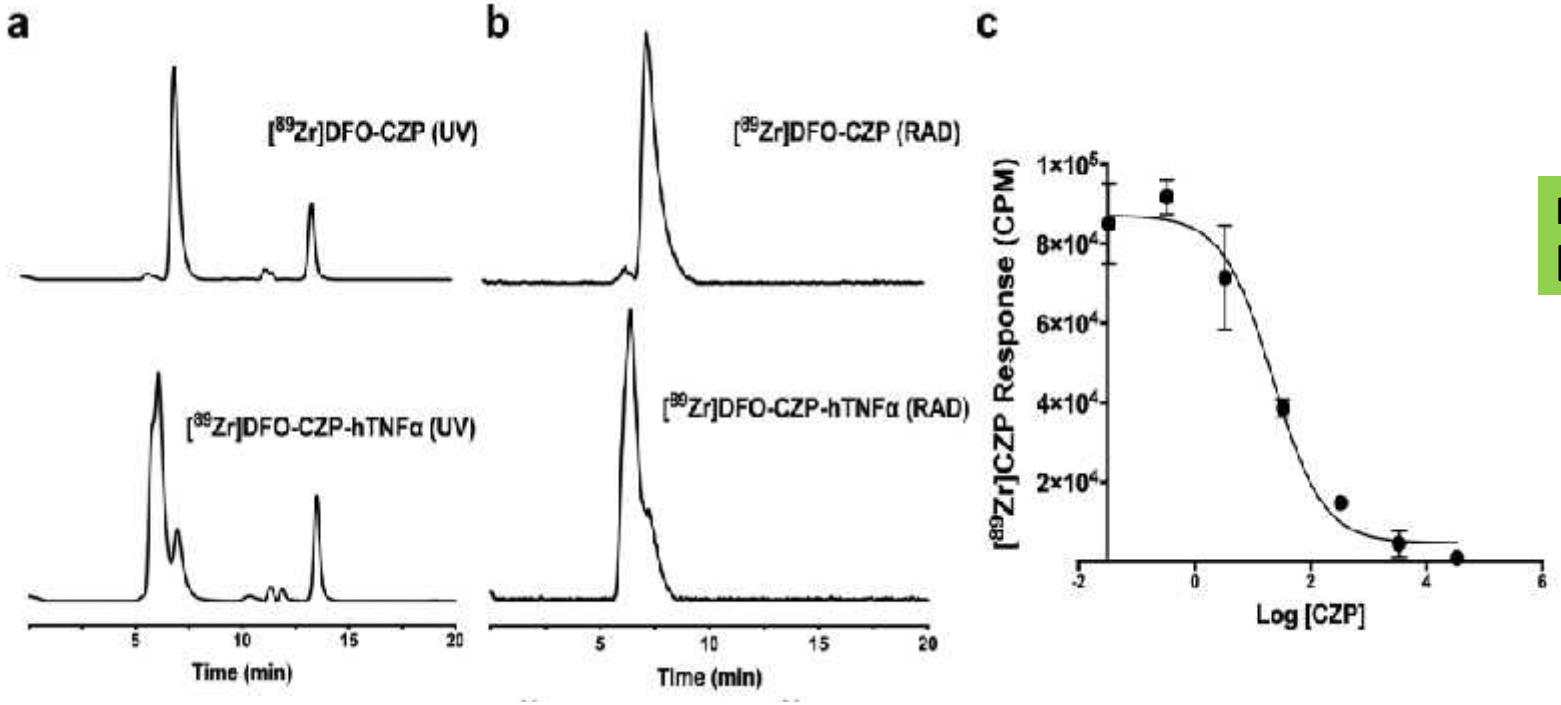
Beckford-Vera D et al., Molecular Imag. & Biol. 2022

Novel PET-tracers in RA

PET/CT Imaging of Human TNFα

[89Zr]Certolizumab Pegol

HPLC chromatograms



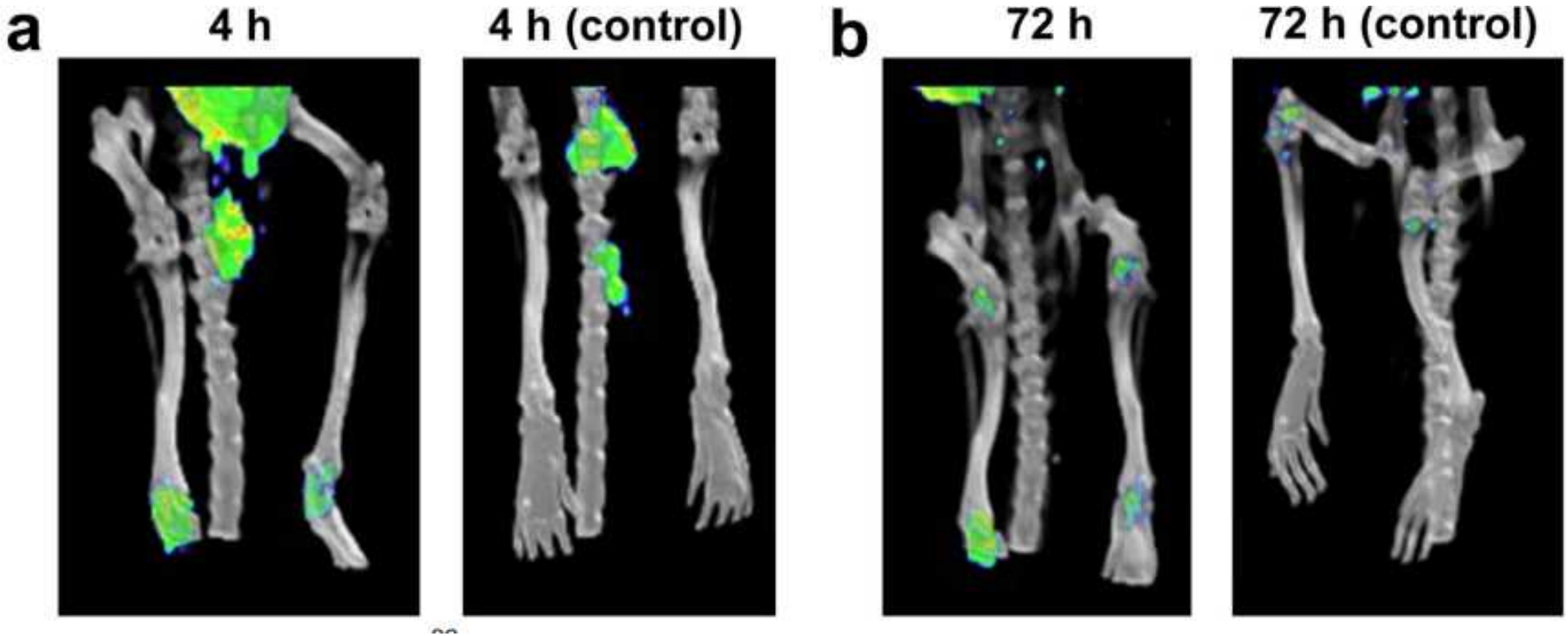
Radiochemical purity of [89Zr]DFO-CZP > 97 %.

Beckford-Vera D et al., Molecular Imag. & Biol. 2022

Novel PET-tracers in RA

PET/CT Imaging of Human TNFα

[89Zr]Certolizumab Pegol



Beckford-Vera D et al., Molecular Imag. & Biol. 2022

Novel PET-tracers in RA

PET/CT Imaging of Human TNFα

[89Zr]Certolizumab Pegol

- ✓ **Increasing uptake of the tracer in forepaw and hind paw joints with disease progression.**
- ✓ **No uptake was observed in the model previously administered with an excess amount of unmodified CZP and in normal control mice.**
- ✓ **In vivo increased specific uptake of [89Zr]DFO-CZP.**
- ✓ **Feasibility of immuno-PET imaging of human TNFα with [89Zr]DFO-CZP has been demonstrated in a preclinical model of RA.**

Novel PET-tracers in RA

Conclusions (I)

- ✓ Besides the widely clinically available FDG, a spectrum of specific tracers for the detection and (therapy) monitoring of disease activity in RA are upcoming.

- ✓ The number of RA-related targets that can be visualized by PET is still growing, promoted by the increased biological knowledge of discriminating markers to visualize (subsets of) immune cells or other relevant targets in RA.

- ✓ Most tracers have only been evaluated in small patient cohorts or have only been tested pre-clinically.

Novel PET-tracers in RA

Conclusions (I)

- ✓ Practically, not all described PET tracers will end up in clinical practice for RA.
- ✓ Future studies are needed to further select those PET tracers that will contribute best to clinical needs.
- ✓ This will depend on the immunological knowledge that becomes further available, but also on physical properties of the tracers.
- ✓ Specificity, pharmacokinetics and dynamics of the tracers play an important role in the ability to reliably visualize and quantify the tracer binding in the inflamed synovial tissue.

Novel PET-tracers in RA

Future Prospects

- ✓PET holds promise for early diagnosis of RA, detecting arthritis activity in individuals at risk, even before development of clinical symptoms.

- ✓PET will facilitate monitoring of disease activity to determine treatment efficacy in an early stage of treatment.

- ✓This has important clinical consequences, since early assessment of treatment failure can be followed by a timely switch of therapy which will significantly reduce costs and improve treatment outcome by reduction of pain and joint damage and increase in societal participation.

Novel PET-tracers in RA

Future Prospects

- ✓PET facilitates stratification of RA patients based on the cellular composition within the inflamed joint, and apply individualized therapy. For this purpose 2 to 3 PET tracers with different targets may have to be used.

- ✓This may only be feasible if there is no binding competition between the tracers, radiation burden can be kept to an acceptable limit and a patient friendly scan protocol can be developed.

Novel PET-tracers in RA

Future Prospects

Introduction of the Total Body PET scanner

(a) R

(a)

PET will make major contribution to development of personalized medicine in Rheumtology

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Thank you!

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