Radiopharmacy: chemistry and physics applications in breast cancer

Park hotel Villa Quaranta

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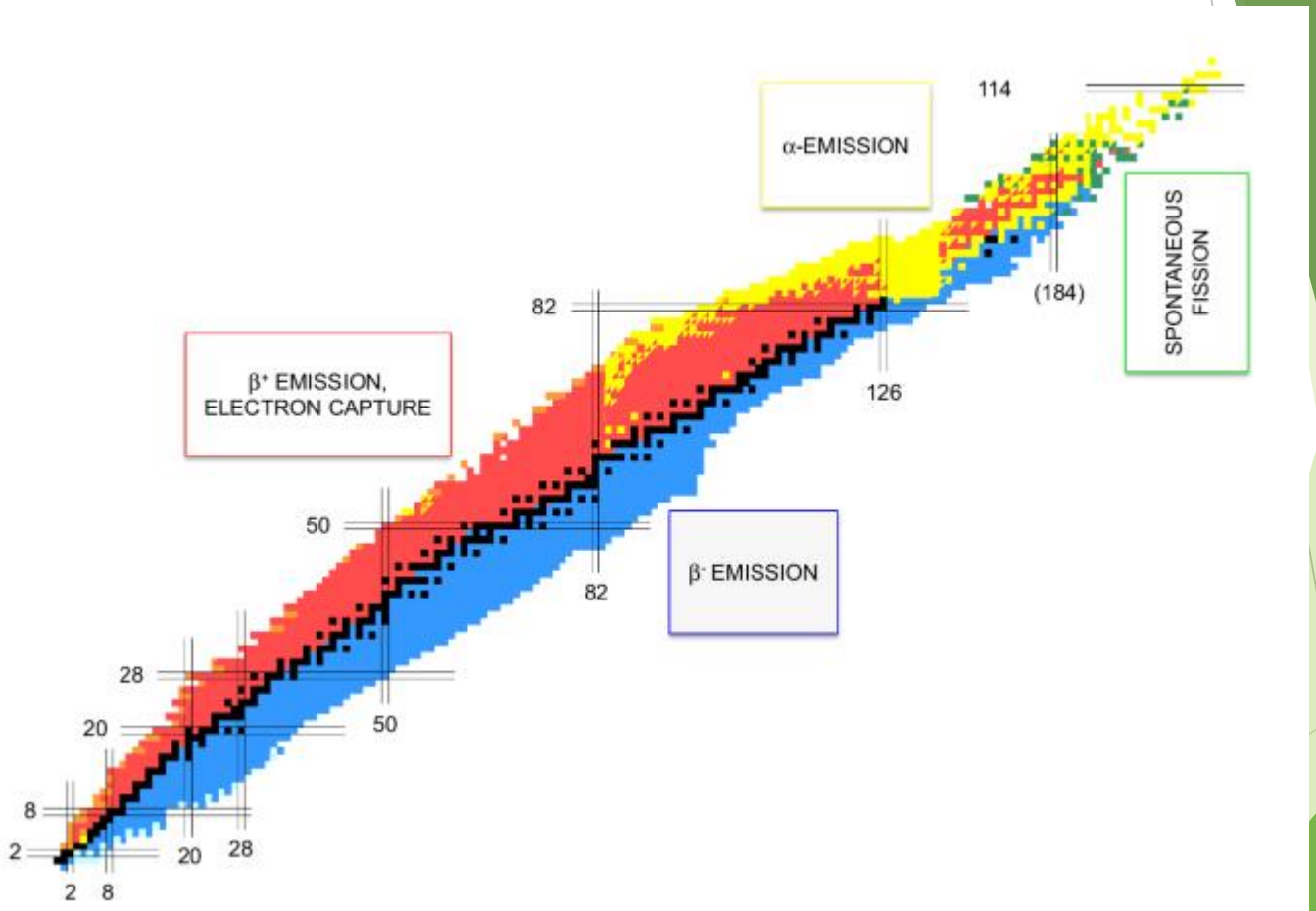
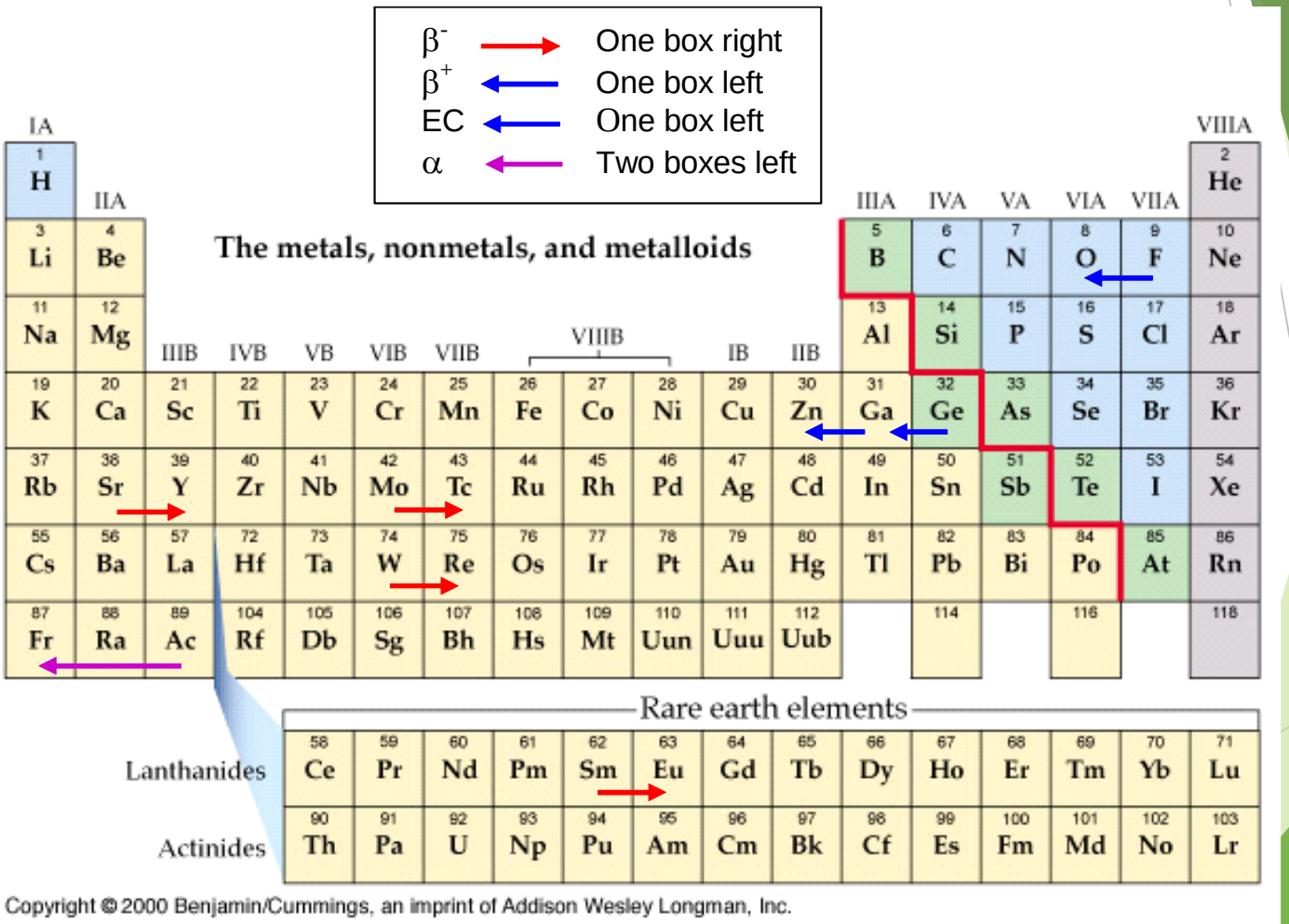
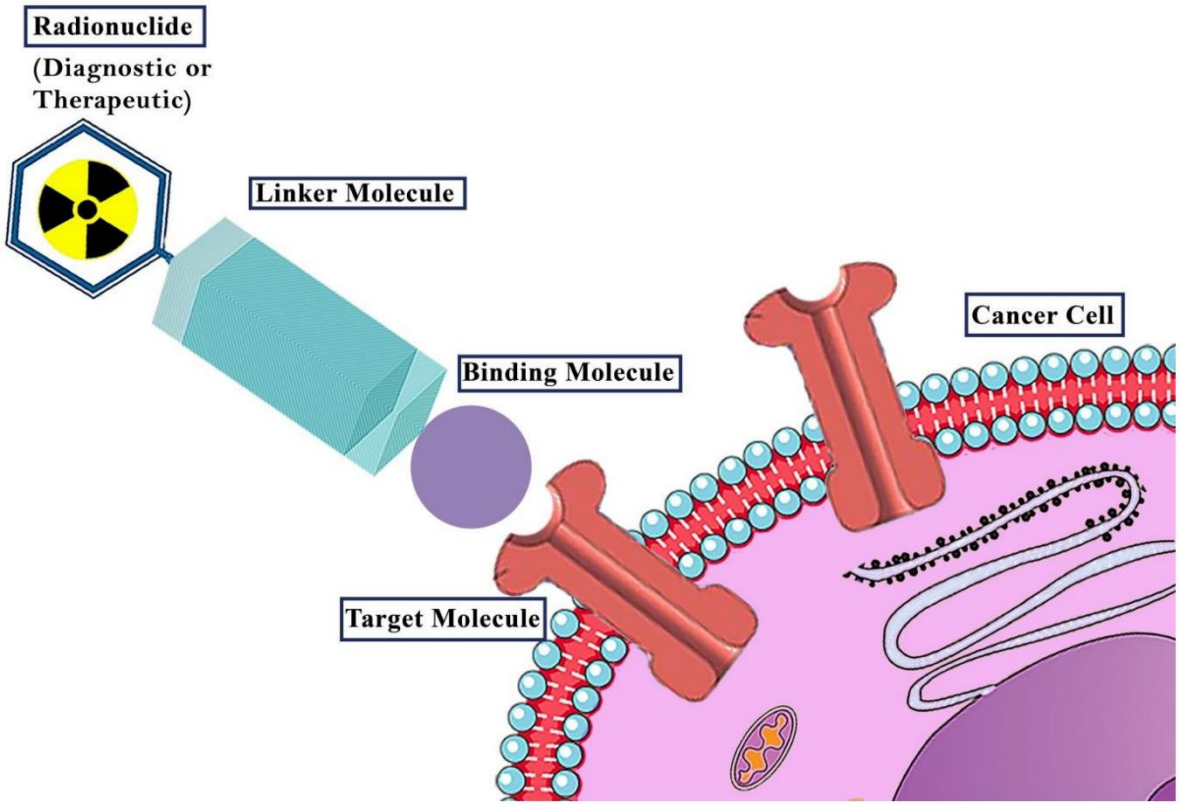
Radionuclide decay



Radionuclide decay



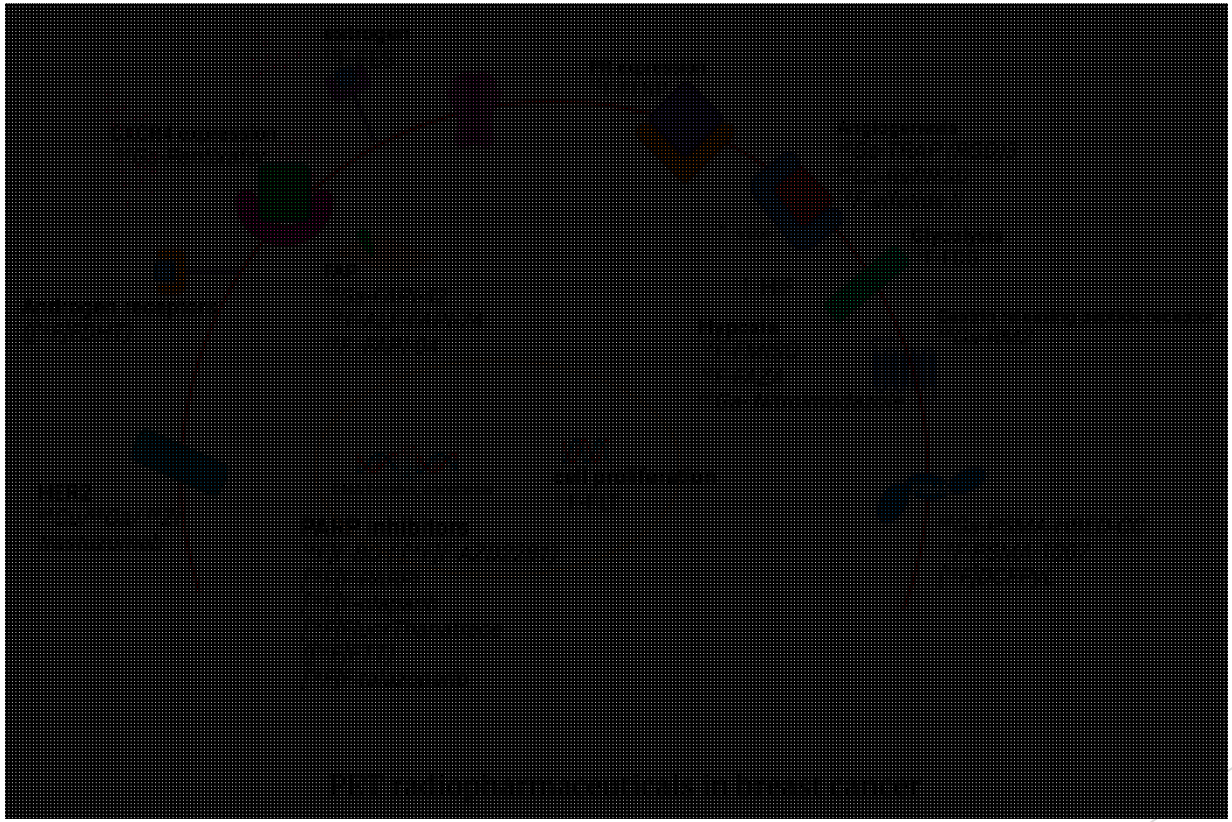
The general concept of theragnostic radiopharmaceuticals



Nuclear Medicine

- Effective and impressive role of nuclear medicine in direct detection of BC initiated first in the early 1990's when technetium-99m-methoxyisobutylisonitrile ([^{99m}Tc]Tc-MIBI) was used for **diagnosis of lesions of dense breasts which were not detectable by mammography**
- A relatively recent huge progress in nuclear medicine is the application of imaging agents for the evaluation of uptake and localisation, biodistribution, the related dose of therapeutic tracer and response to treatment. This remarkable concept is named '**theragnostic**'

PET tracers that target breast cancer and their site of action on the tumor cells



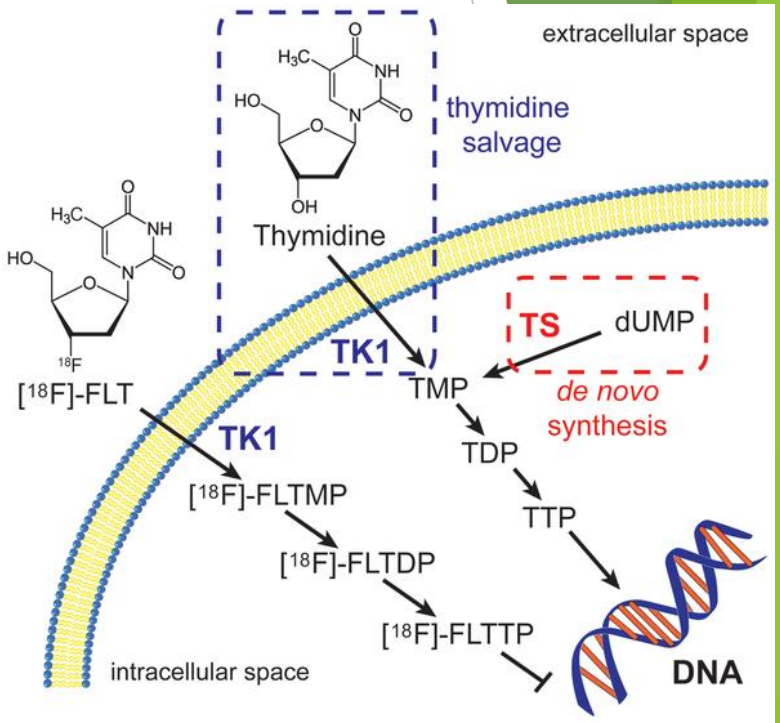
Courtesy: The Role of PET/CT in Breast Cancer Hadebe, Vorster, Diagnostics 2023

PET/TC/MRI
^{18}FDG

- The basic concept used in FDG imaging is that tumor cells consume more glucose than other tissues because of the increased intracellular glycolysis (Warburg effect).
- Despite the chemical and structural differences between FDG and glucose, FDG is processed in human cells identical to glucose. FDG enters the cell via facilitated transport mediated by the glucose transporters known as GLUTs.
- The most common GLUT transporter in humans is GLUT1 which is also most commonly overexpressed in cancers. Further, it has been found that GLUT1 overexpression correlates with tumor development and, thus, a more unfavorable prognosis.

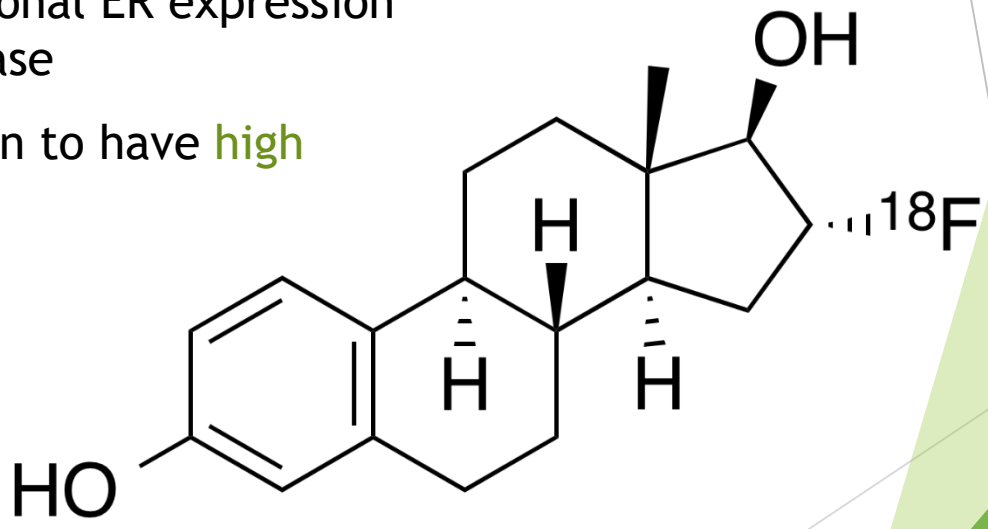
^{18}FLT

- A key factor limiting [^{18}F]-FLT-PET is *de novo* thymidine pathway utilization, although the extent of this limitation is not fully appreciated
- The *de novo* pathway is complementary to thymidine salvage and is fully capable of providing all the thymidine needed for DNA synthesis
- Through the action of the enzyme thymidylate synthase (TS), deoxyuridine monophosphate is converted to thymidine monophosphate, which is subsequently incorporated into DNA
- It is widely assumed that [^{18}F]-FLT PET may underestimate proliferation in *de novo* pathway-dependent tumors



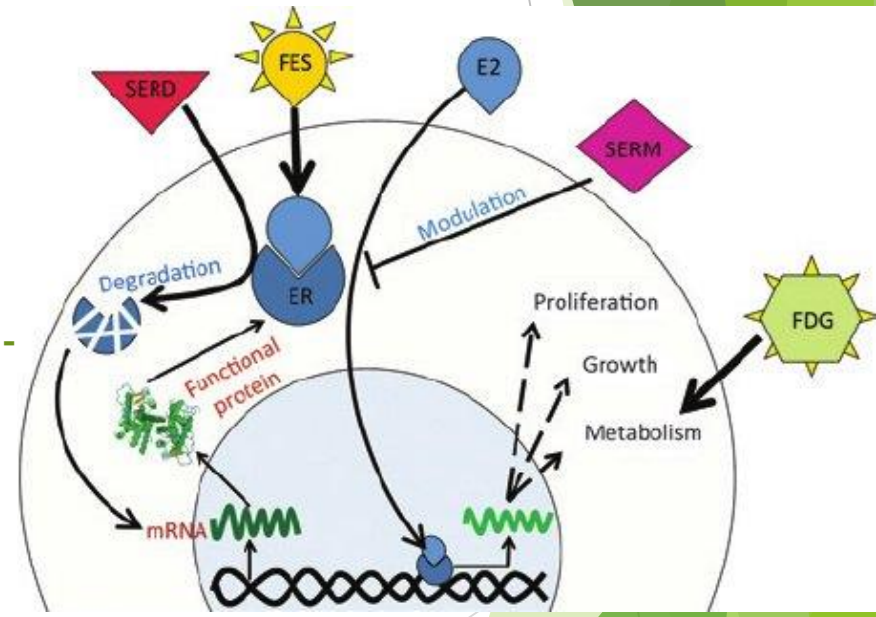
^{18}FES

- There is a growing body of evidence for FES-PET as a non-invasive method for evaluating regional ER expression in metastatic disease
- FES has been shown to have high specificity



^{18}FES

- FES-PET measures regional estrogen binding, allowing identification of cancers likely to respond to targeted endocrine therapy
- Due to the heterogeneous ER expression across sites of disease, FES-PET may even be superior to standard immunohistochemistry

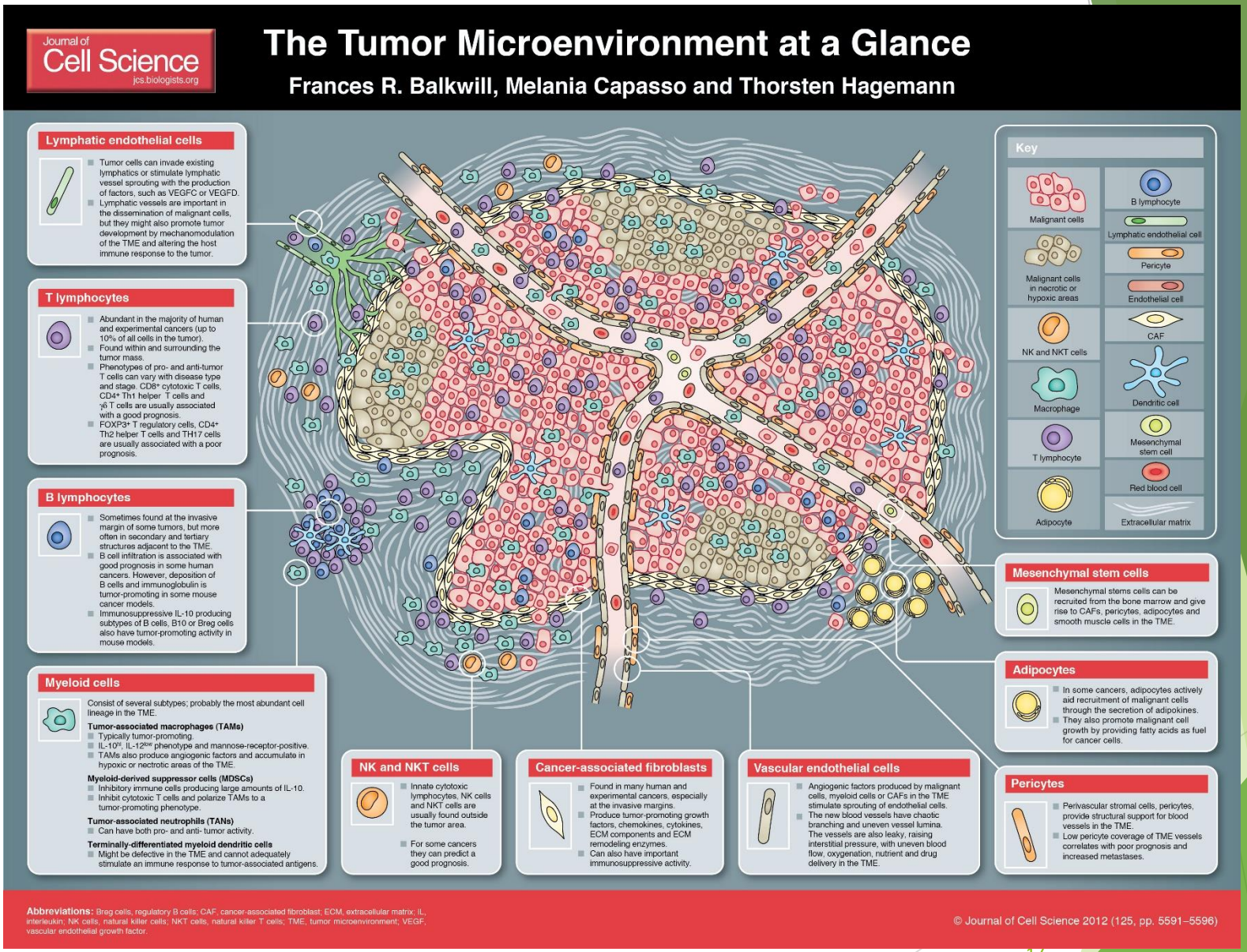


^{89}Zr-Trastuzumab

- Radiolabeled monoclonal anti-HER2 antibodies are among the most studied and most promising probes for molecular imaging of HER2 expression.
- A primary limitation of antibody-based imaging is the relatively large size of antibodies, which results in slow clearance from the blood pool and other compartments, as well as low tumor penetration, resulting in the need for a delay of 4-6 days between tracer injection and imaging to obtain satisfactory tumor-to-blood ratios, and thus requires radionuclides with long half-lives, such as ^{64}Cu or ^{89}Zr.
- One of the promising HER2 PET tracers is the radiolabeled monoclonal antibody ^{89}Z-trastuzumab, with a half-life of 78.4 hours, permitting imaging up to 7 days following injection, to maximize HER2-positive tumor visualization have

^{89}Zr-Trastuzumab

- The combination of HER2 PET imaging to assess the target and other imaging such as FDG-PET/CT to measure early response may by particularly helpful in guiding HER2-targeted therapy
- A nice example is seen in the results of the SEPHIR trial, where the combination of pre-therapy ^{89}Z-trastuzumab-PET and serial FDG-PET/CT provided high positive and negative predictive value for response to HER2-targeted therapy


Journal of Cell Science
jcs.biologists.org
The Tumor Microenvironment at a Glance
Frances R. Balkwill, Melania Capasso and Thorsten Hagemann
Lymphatic endothelial cells
Tumor cells can invade existing lymphatics or stimulate lymphatic vessel sprouting with the production of factors, such as VEGFC or VEGFD.
Lymphatic vessels are important in the dissemination of malignant cells, but they might also promote tumor development by mechanomodulation of the TME and altering the host immune response to the tumor.
T lymphocytes
Abundant in the majority of human and experimental cancers (up to 10% of all cells in the tumor).
Found within and surrounding the tumor mass.
Phenotypes of pro- and anti-tumor T cells can vary with disease type and stage. CD8+ cytotoxic T cells, CD4+ Th1 helper T cells and γδ T cells are usually associated with a good prognosis.
FOXP3+ T regulatory cells, CD4+ Th2 helper T cells and TH17 cells are usually associated with a poor prognosis.
B lymphocytes
Sometimes found at the invasive margin of some tumors, but more often in secondary and tertiary structures adjacent to the TME.
B cell infiltration is associated with good prognosis in some human cancers. However, deposition of B cells and immunoglobulin is tumor-promoting in some mouse cancer models.
Immunosuppressive IL-10 producing subtypes of B cells, B10 or Breg cells also have tumor-promoting activity in mouse models.
Myeloid cells
Consist of several subtypes; probably the most abundant cell lineage in the TME.
Tumor-associated macrophages (TAMs)
Typically tumor-promoting.
IL-10hi, IL-12low phenotype and mannose-receptor-positive.
TAMs also produce angiogenic factors and accumulate in hypoxic or necrotic areas of the TME.
Myeloid-derived suppressor cells (MDSCs)
Inhibitory immune cells producing large amounts of IL-10.
Inhibit cytotoxic T cells and polarize TAMs to a tumor-promoting phenotype.
Tumor-associated neutrophils (TANs)
Can have both pro- and anti- tumor activity.
Terminally-differentiated myeloid dendritic cells
Might be defective in the TME and cannot adequately stimulate an immune response to tumor-associated antigens.
NK and NKT cells
Innate cytotoxic lymphocytes, NK cells and NKT cells are usually found outside the tumor area.
For some cancers they can predict a good prognosis.
Cancer-associated fibroblasts
Found in many human and experimental cancers, especially at the invasive margins.
Produce tumor-promoting growth factors, chemokines, cytokines, ECM components and ECM remodeling enzymes.
Can also have important immunosuppressive activity.
Vascular endothelial cells
Angiogenic factors produced by malignant cells, myeloid cells or CAFs in the TME stimulate sprouting of endothelial cells.
The new blood vessels have chaotic branching and uneven vessel lumina. The vessels are also leaky, raising interstitial pressure, with uneven blood flow, oxygenation, nutrient and drug delivery in the TME.
Pericytes
Perivascular stromal cells, pericytes, provide structural support for blood vessels in the TME.
Low pericyte coverage of TME vessels correlates with poor prognosis and increased metastases.
Mesenchymal stem cells
Mesenchymal stems cells can be recruited from the bone marrow and give rise to CAFs, pericytes, adipocytes and smooth muscle cells in the TME.
Adipocytes
In some cancers, adipocytes actively aid recruitment of malignant cells through the secretion of adipokines.
They also promote malignant cell growth by providing fatty acids as fuel for cancer cells.
Key
Malignant cells
Malignant cells in necrotic or hypoxic areas
NK and NKT cells
Macrophage
T lymphocyte
Adipocyte
B lymphocyte
Lymphatic endothelial cell
Pericyte
Endothelial cell
CAF
Dendritic cell
Mesenchymal stem cell
Red blood cell
Extracellular matrix
Abbreviations: Breg cells, regulatory B cells; CAF, cancer-associated fibroblast; ECM, extracellular matrix; IL, interleukin; NK cells, natural killer cells; NKT cells, natural killer T cells; TME, tumor microenvironment; VEGF, vascular endothelial growth factor.
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^{18}F-FAPi

Stromal remodeling occurs not only in malignancies but also in development, wound healing, chronic inflammation (e.g., arthritis, atherosclerotic plaques, and fibrosis), and certain physiologic processes where FAP is often highly expressed, posing challenges for differentiating benign from malignant, tumor and peritumor chronic inflammation in FAPI imaging

In addition, **some sites with low or moderate FAP expression, such as the** uterus and **breast**, **also showed higher FAPI tracer uptake** in a recent study, and this difference **may be related to the biological age of women**, and large sample studies are needed to confirm this finding

^{18}F-FAPi

- FAPI-specific PET is still controversial in diagnosing **bone metastases and lymph node metastases** in different tumors.
- In another way, **changes in the stroma during tumor development may lead to changes in the expression of FAP,** so whether different aspects of tumor variability may have an impact on FAPI imaging results needs to be further explored.
- FAPIs cannot yet replace the work of FDG, but they can be used as a **complement** to it.

Current productions

- ^{18}FDG
- ^{18}F PSMA-1007
- ^{18}F JK-PSMA-7
- ^{18}F NaF
- ^{18}F FET
- ^{18}F Coline
- ^{18}F DOPA
- ^{124}I NaI
- ^{68}Ga DOTA TOC
- $^{13}NH_3$
- ^{68}Ga NODAGA RGD
- ^{124}I FSH
- ^{124}I Trastuzumab
- ^{89}Zr Trastuzumab
- ^{68}Ga PSMA-11
- ^{18}F[Al]-PSMA-11
- ^{177}Lu DOTATATE
- ^{177}Lu PSMA 617
- ^{225}Ac FAPi 46