„History of cancer"

3000-1500 BC, Egyptian papyrus (via Latin, from Greek πάπυρος, papyros)
(George Ebers, Edwin Smith), Pre Columbian mummies and artefacts

500 BC, Hippocrates (melanoma, *melas*, "dark" and *oma* "tumor")
Rebecca V.W. et al. Melanoma Res. 2012, 22(2): 114–122.

460 – 370 BC, Hippocrates:
- Wording: "carcinos" (crab or crayfish, Greek)
- Skin, nose, breast

25 BC – 50 AD, Celsus: "cancer" (crab, Latin)

129-199, Galenus: book on oncology
Distinction between benign (oncos) vs malignant (carcinos) tumour

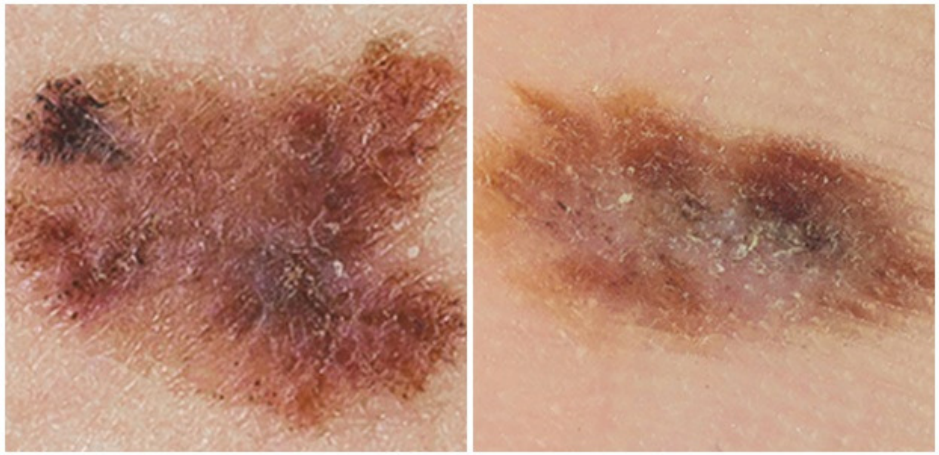
XVII., Adrian Helveticus, surgery
1761, Giovanni Morgagni, Padua: postmortem biopsy
1896, X-ray

Diagnosis of Tumour

- „if it hurts"
- Perception (detected by the five senses)
- Biopsy, histology
- X-ray (chest, mammography, etc.)
- Scintigraphy ("scint," latin scintilla, spark)
- CT
  - SPECT (Single photon emission computed tomography)
    contrast material remains in the blood stream
  - PET (Positron emission tomography)
    tissue absorption of the labelled (contrast) material
- Immundiagnosis – tumormarkers
- DNS chip/DNS array

Melanoma, lymphoma, breast cancer

http://lymphomacancer.co.uk/lymphoma-cancer-types/burkitts-lymphoma-cancer.html



http://daganatok.hu/melanoma/

http://www.naturalnews.com/051601_breast_cancer_Komen_Foundation_industry.html

5-year prevalence (%) vs stages in case of breast cancer

Stadium (phase)	5-year relative prevalence
0	100%
I	98%
IIA	88%
IIB	76%
IIIA	56%
IIIB	49%
IV	16%

Source: American Cancer Society
https://www.cancer.org/research.html

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Biopsy, histology, histopathology

(from Greek *histos*, tissue, *pathos*, suffering and *logos*, study)

a) Atypical structure of the tissue

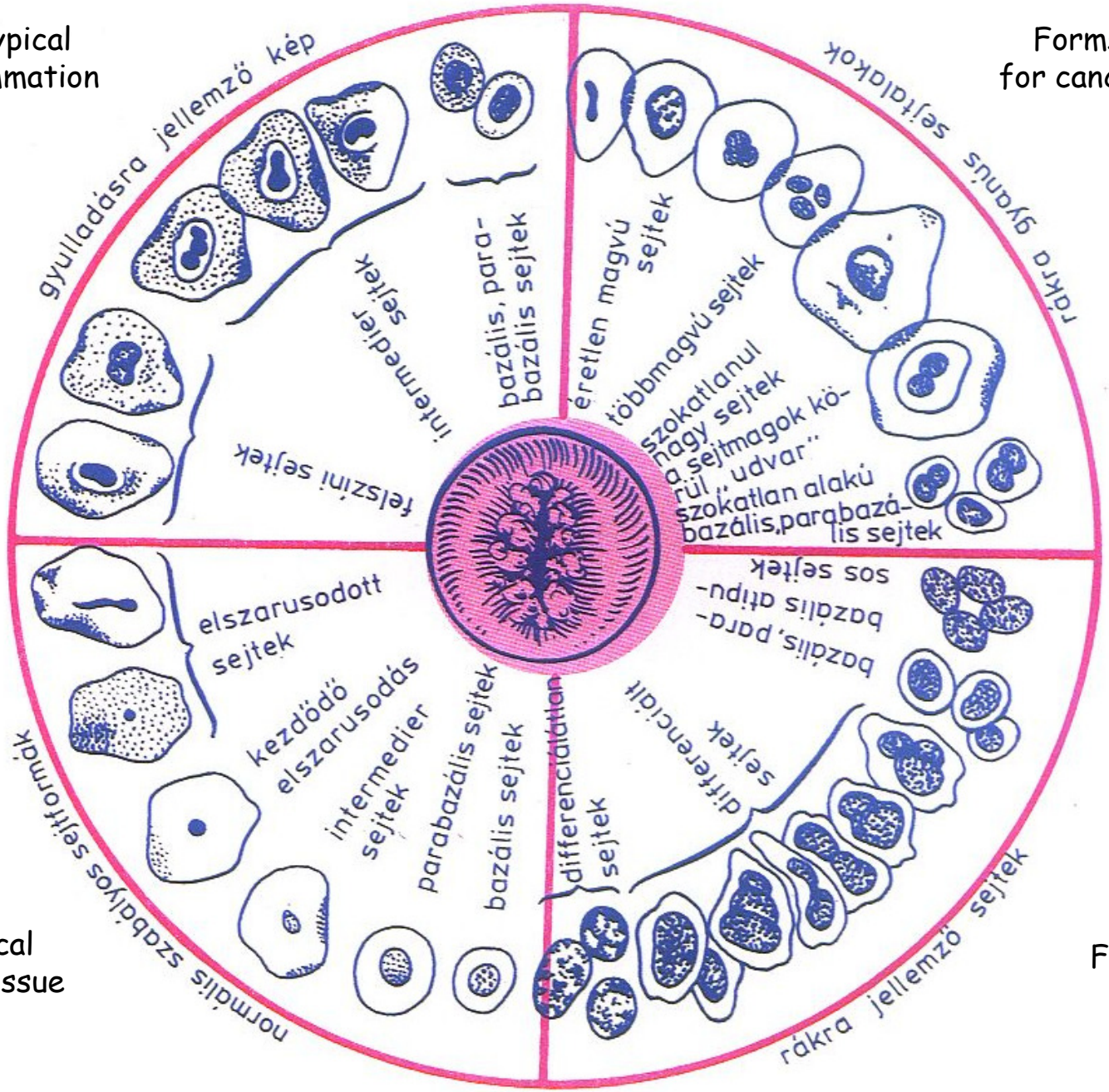
b) Pleomorphism (pleomorphic): Occurring in various distinct forms.
-- In terms of cells, having variation in the size and shape of cells or their nuclei.
-- Different tissue structures within a tumour.

c) High level of cell division.

d) Infiltration: Cancer that has spread beyond the layer of tissue in which it developed and is growing into surrounding, healthy tissues. Also called invasive cancer.

Forms typical
for inflammation

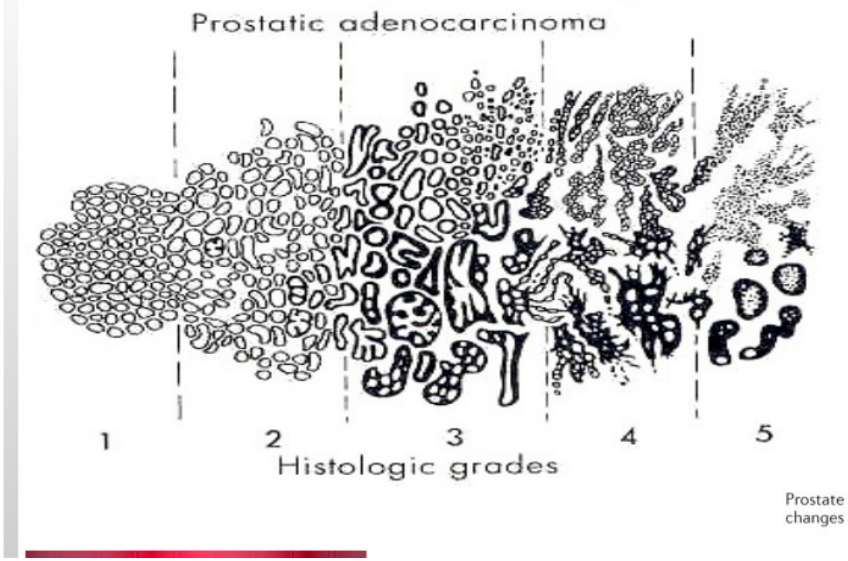
Forms typical
for cancer suspect



Forms typical
for normal tissue

Forms typical
for cancer

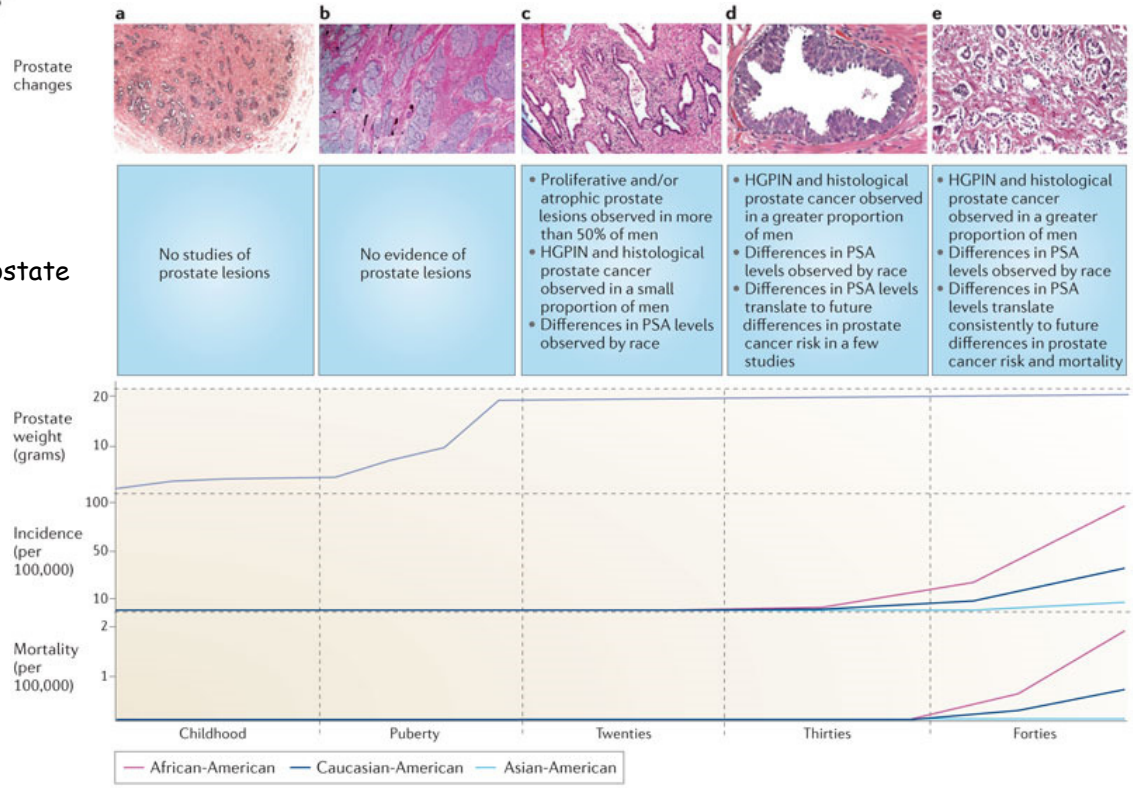
Gleason Grading & Scoring of Prostatic Ca.



https://www.slideshare.net/vmshashi/pathology-of-prostate

Prostate cancer: is it time to expand the research focus to early-life exposures?

S. Sutcliffe & G. A. Colditz
Nature Reviews Cancer 13, 208-518
(March 2013)



http://www.nature.com/nrc/journal/v13/n3/fig_tab/nrc3434_F1.html

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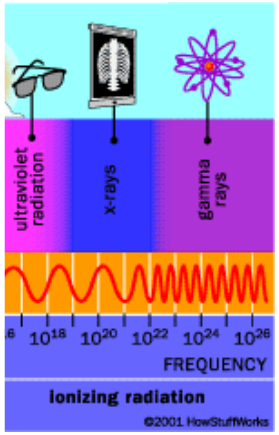


Imaging

1896: W. C. Röntgen: Cathode rays (emitted by the negative electrode, or cathode, in a vacuum tube) for biological and medical imaging (Nobel prize, 1901)

1903: A. H. Becquerel, M. Sklodowska-Curie, P. Curie:
Radioactive decay, also known as nuclear decay or radioactivity, and isotopes in nature (Nobel prize, 1903)

1910-15: Gy. Hevesy György:
Isotopes as biological labels, „reporters" (Nobel prize, 1943)

Using particle accelerator (machine that uses electromagnetic fields to propel charged particles to nearly light speed and to contain them in well-defined beams) for creation of non-natural isotopes.
Based on the idea of L. Szilárd, E. O. Lawrence (Nobel prize, 1939)

1932: C. D. Anderson: Discovery of positron as novel particle (Nobel prize, 1936)

1934: F. Joliot and I. Joliot-Curie: Discovery of the first non-natural isotope emitting positron (Nobel prize, 1935)

1970-74: A. M. Cormack and G. N. Hounsfield: first Computed [Axial] Tomography,
CT computerized axial tomography scan (CAT scan) (Nobel prize, 1979)

1975: M.Ter-Pogossian et al.: the first PET camera, ^{18}F-fluoro-desoxy-glucose

(www.teppet.org)

X-ray

http://www.ibn-tv.com/2011/10/x-ray-not-good-for-lung-cancer-screening/

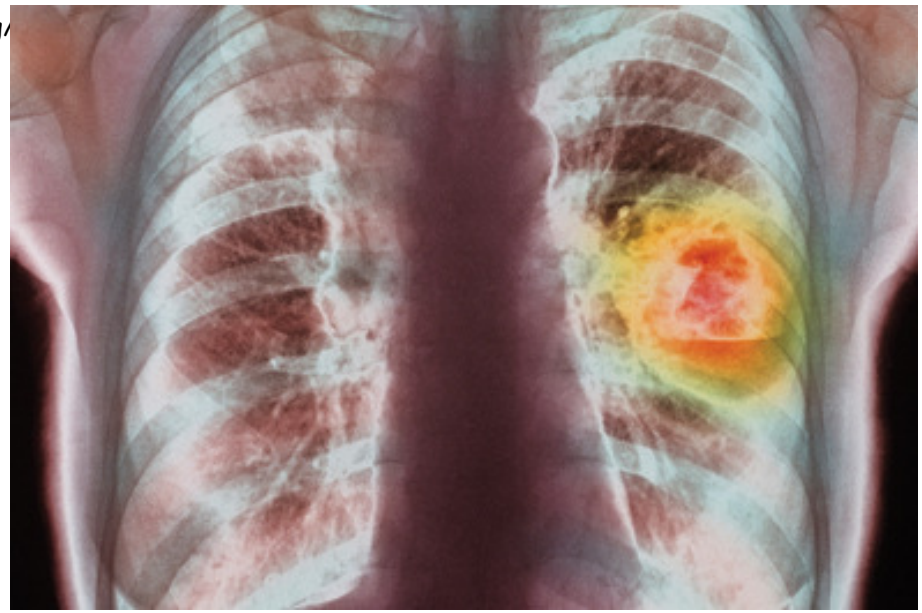
Radiograph

Light/dark, depending on the absorption rates of the various tissues.
Dense materials (e.g. bone): white,
Soft materials (e.g. fat, muscle):
in varying shades of gray.

Originally, X-rays for imaging bones,
Today, improvements:

- better photographic films,
- more accurate focusing systems
- more sensitive detection

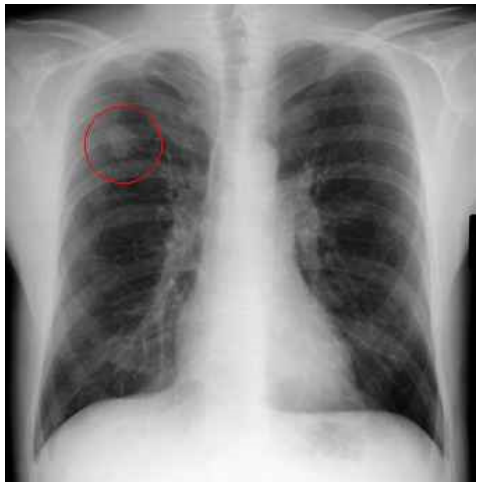
At lower-exposure levels,
fine detail and subtle differences
in tissue density.

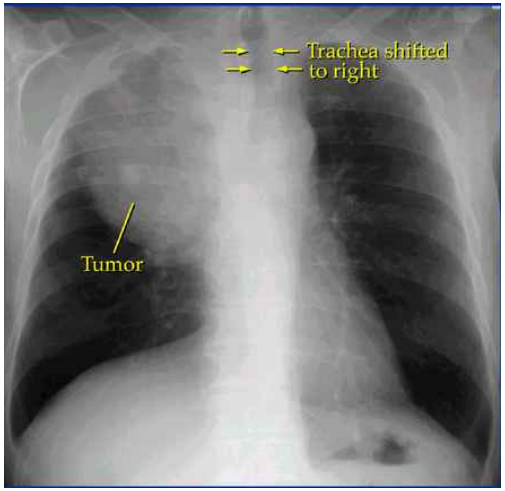


http://www.gponline.com/lung-cancer-missed-gps-unable-access-x-rays/article/1148662

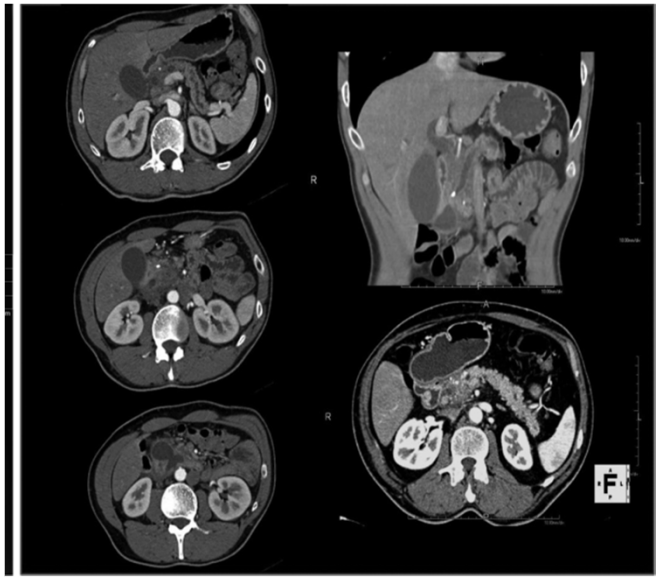
Diagnosis of lung cancer - comparison

Computed tomography (CT): combines multiple X-ray images into a 3D model

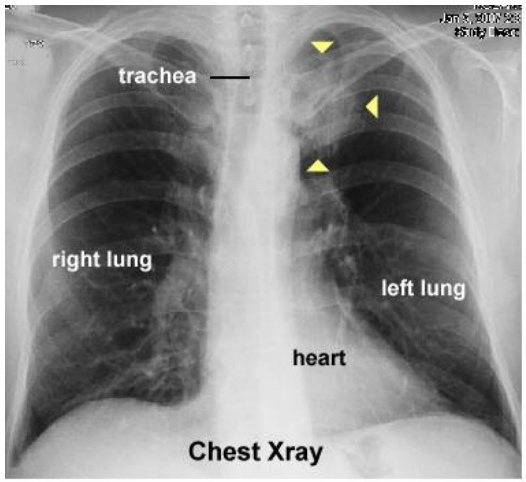


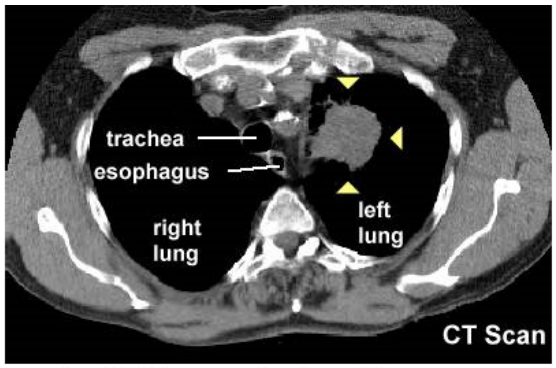


Small (A) and large (B) tumor in the upper right lung



http://emergencymdsc.com/ct-scans/

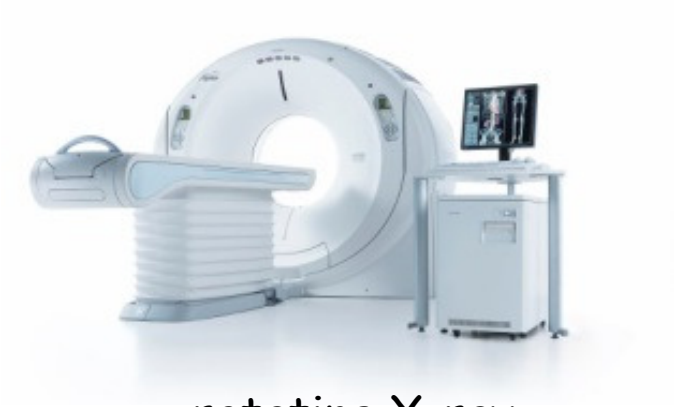




Left Upper Lobe Cancer

note how much more obvious the tumor is on the CT scan compared to chest Xray

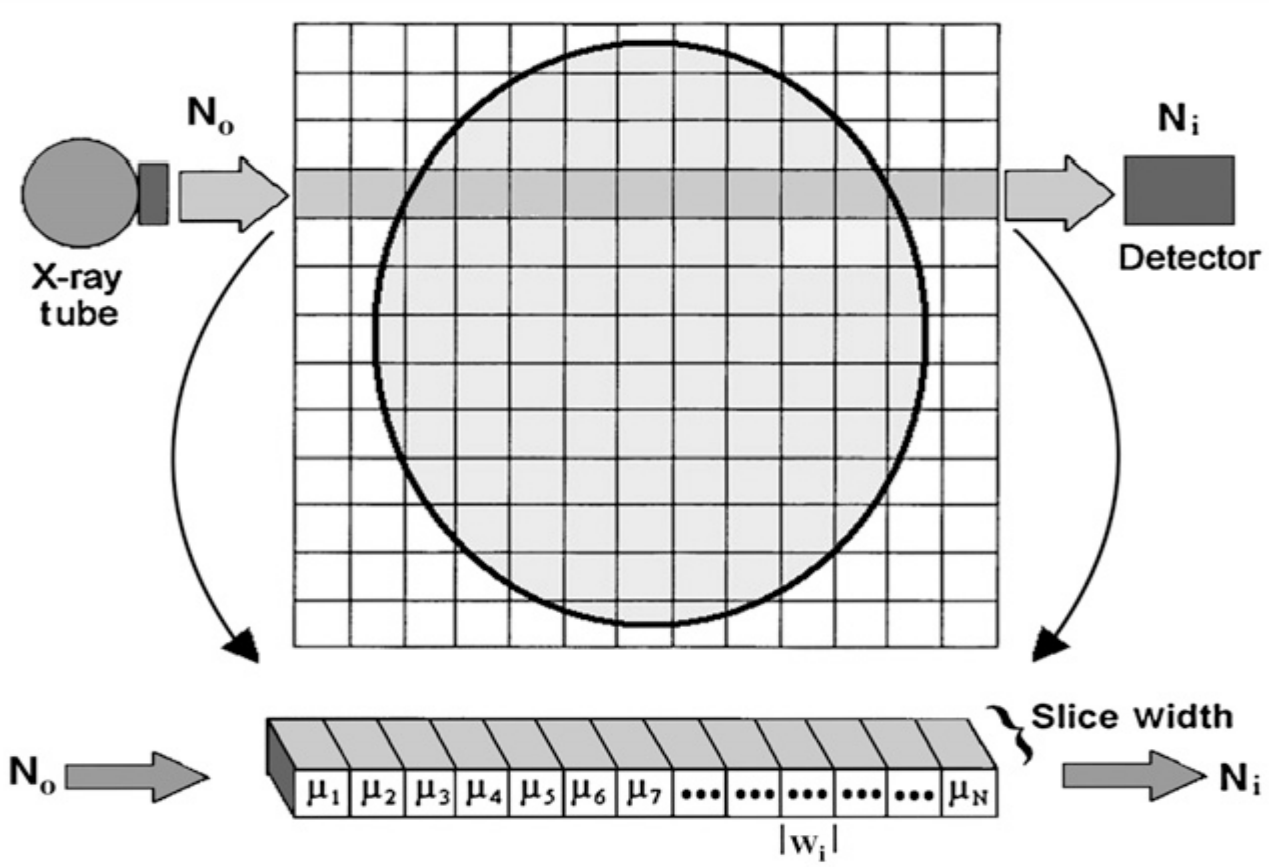
http://www.aboutcancer.com/lung_xrays_abnormal.htm



rotating X-ray

Slices: 1-10 millimeters thick.

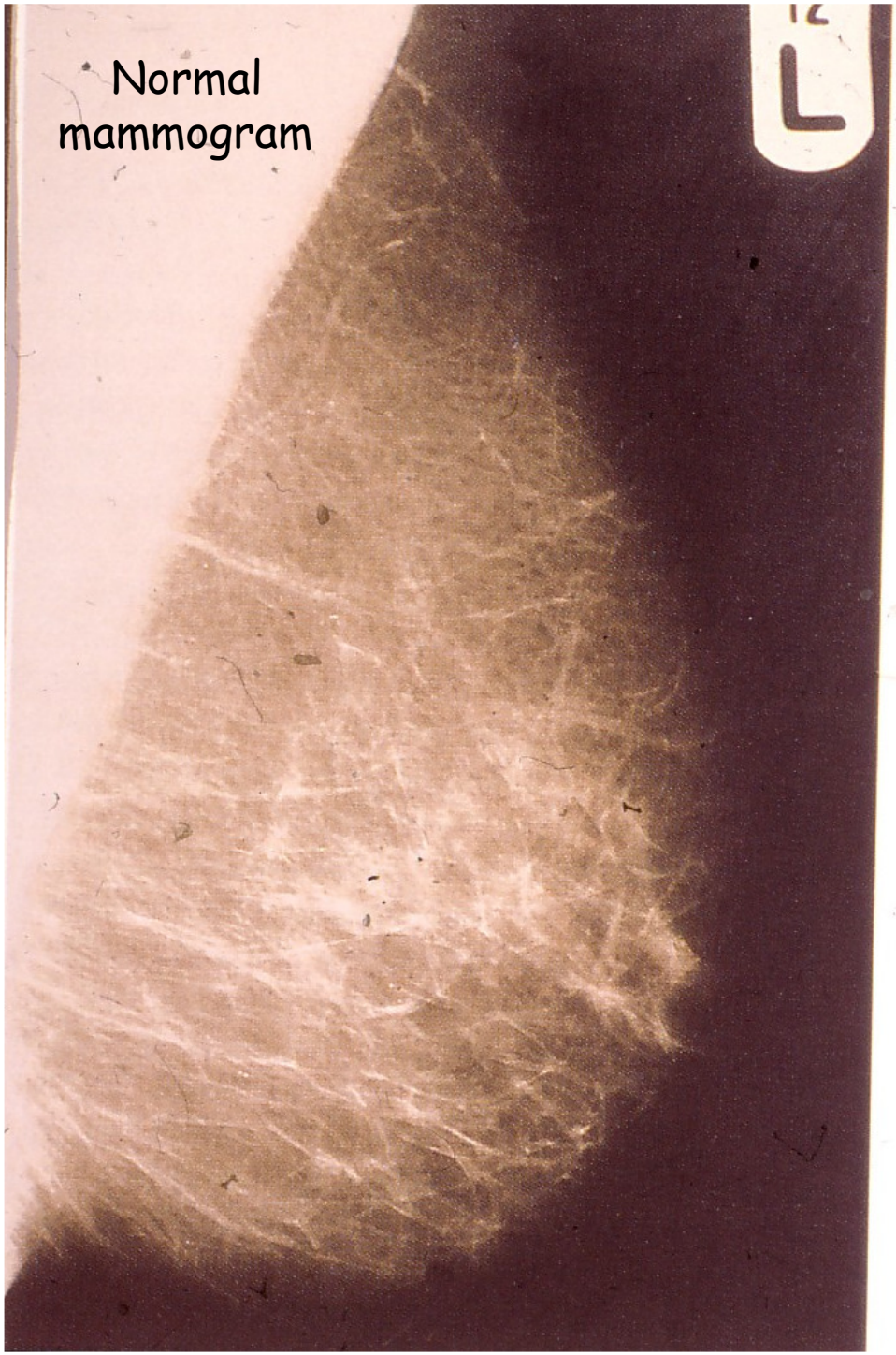
G. N. Hounsfield: The first CT built (1971)
A. M. Cormack: Theoretical background (1963-64)



- Moving X-ray source and detector
- Covering of the whole body
- 1 sec scanning time

The Nobel Prize in Physiology or Medicine 1979

http://www.nobelprize.org



Mammogram showing carcinoma

Oncology in Practice p.4, 3/1994

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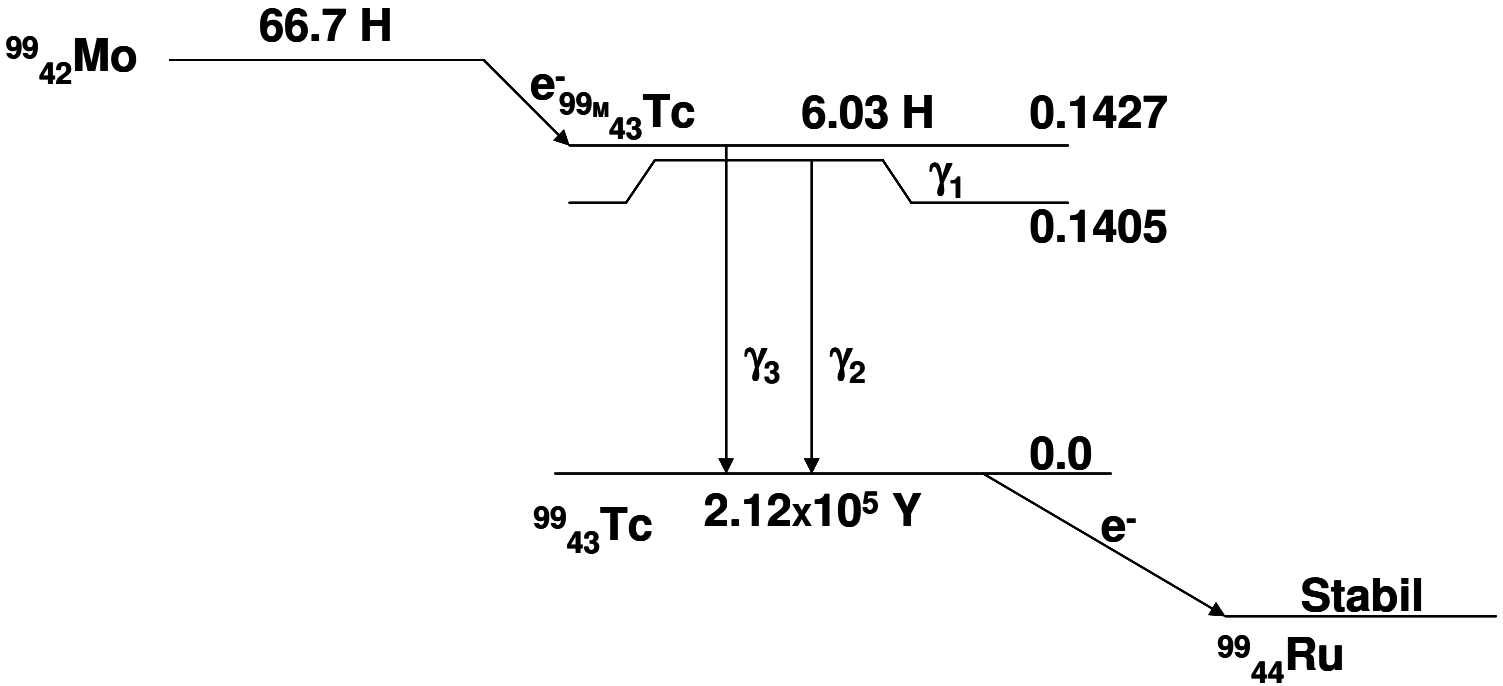
Bone scintigraphy

Phosphorus metabolism disorders are the result of abnormal serum phosphate levels. caused by defects in the intake, excretion and cellular utilization of phosphate.

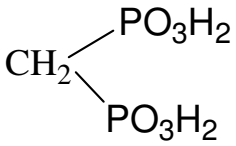
Increased phosphor metabolism in tumouros bone tissues

Increased incorporation of phosphor derivatives.

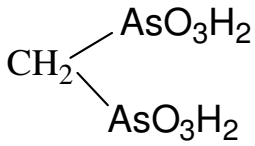
Application of ^{99M}Tc-labelled phosphoric acid.

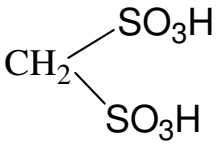


Bone scan (bone scintigraphy) with Tc^{99}-jelzett phosphoric acid derivatives



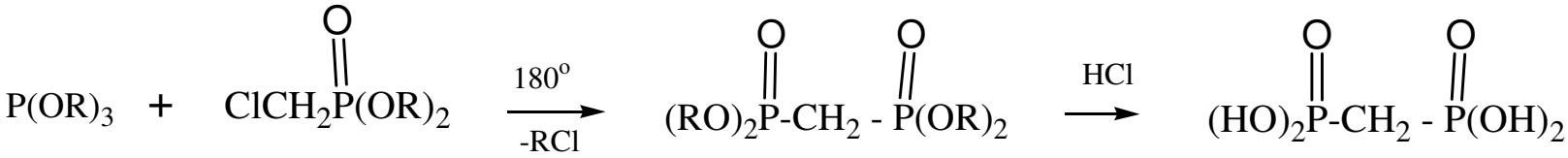
Methane-diphosphonic acid (MDP)
Synthesis: J. Chem. Soc. 1465 (1947)
Application: J. Nucl. Med. 14, 640 (1973)





1980

Michaelis-Arbusov reaction (R = ethyl)



triethylphosphit

chlormethane phosphoris acid
diethyl ester

methane diphosphoric acid
diethyl ester

methane diphosphoric acid

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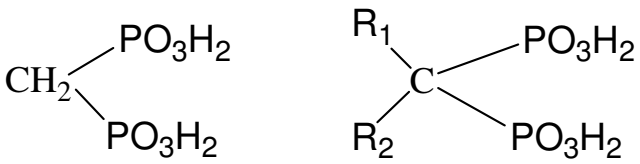
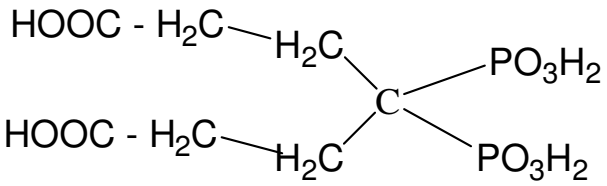
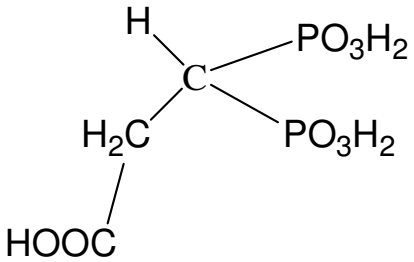
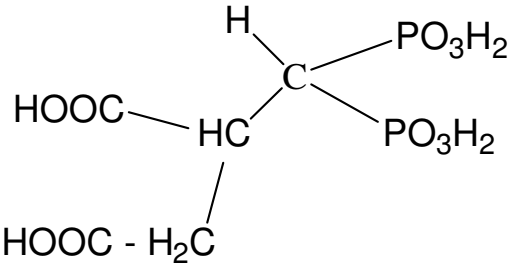


MDP

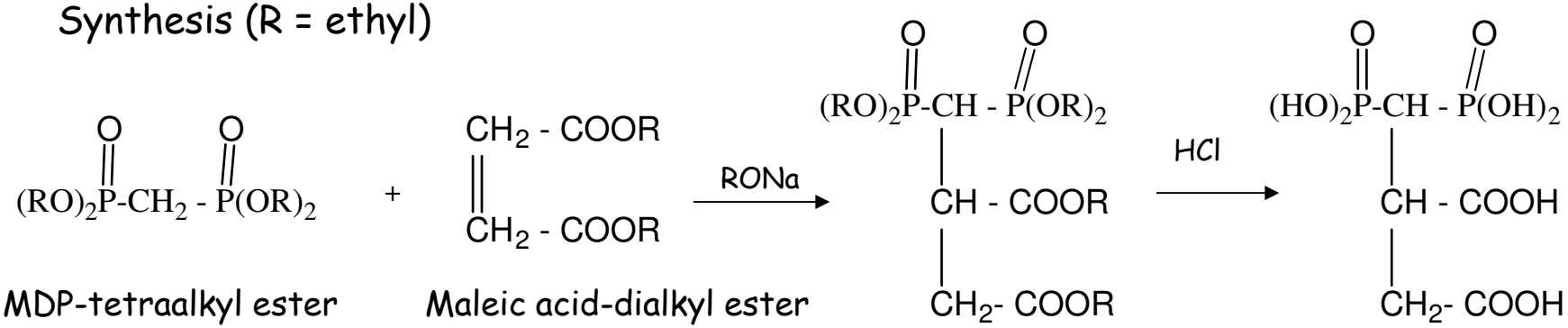






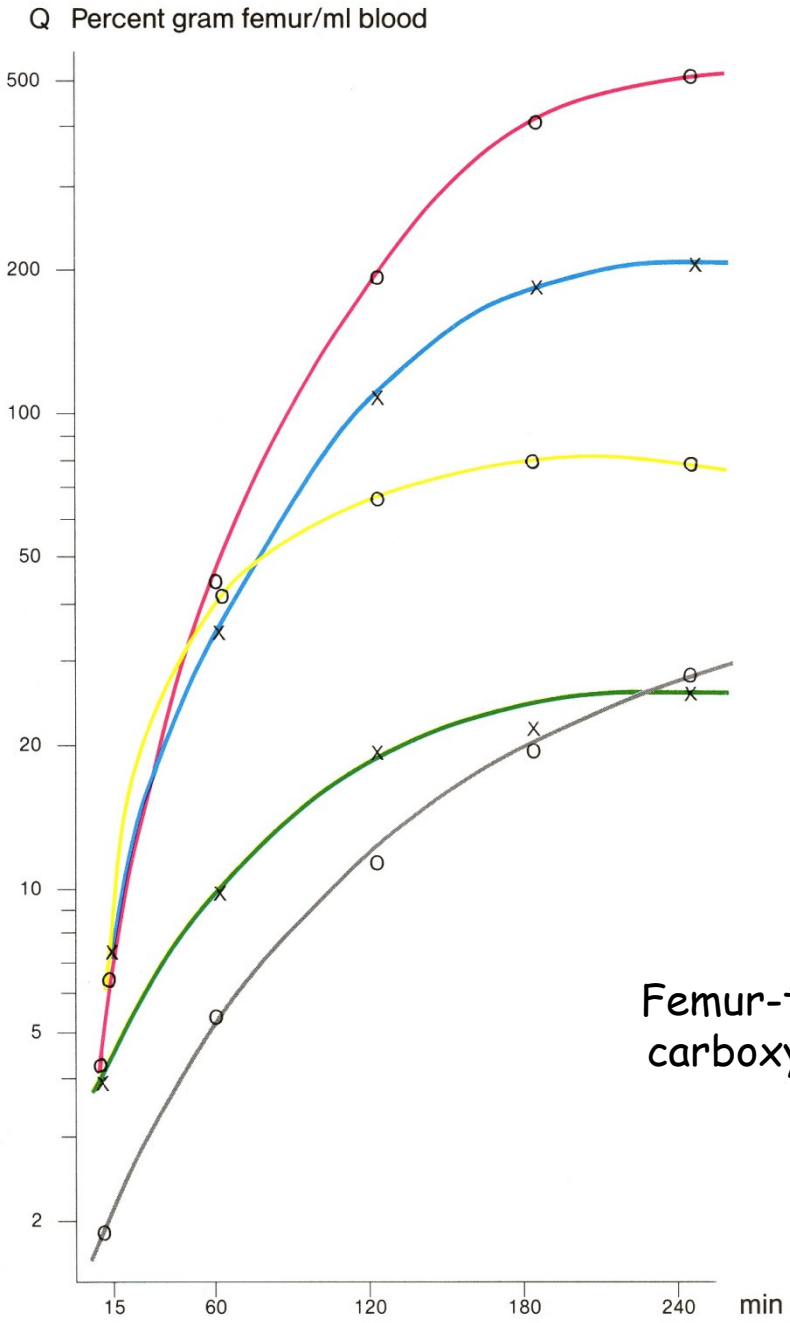
3,3-diphosphono-1,2-propane dicarboxylic acid, DPD

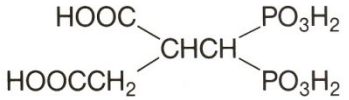
Synthesis (R = ethyl)

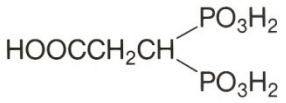


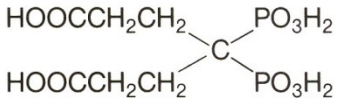
MDP-tetraalkyl ester Maleic acid-dialkyl ester

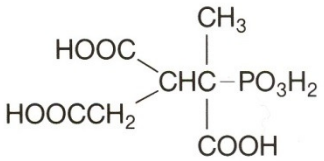
Z.Anorg.Alig.Chem. 457, 219 (1979)

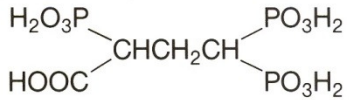






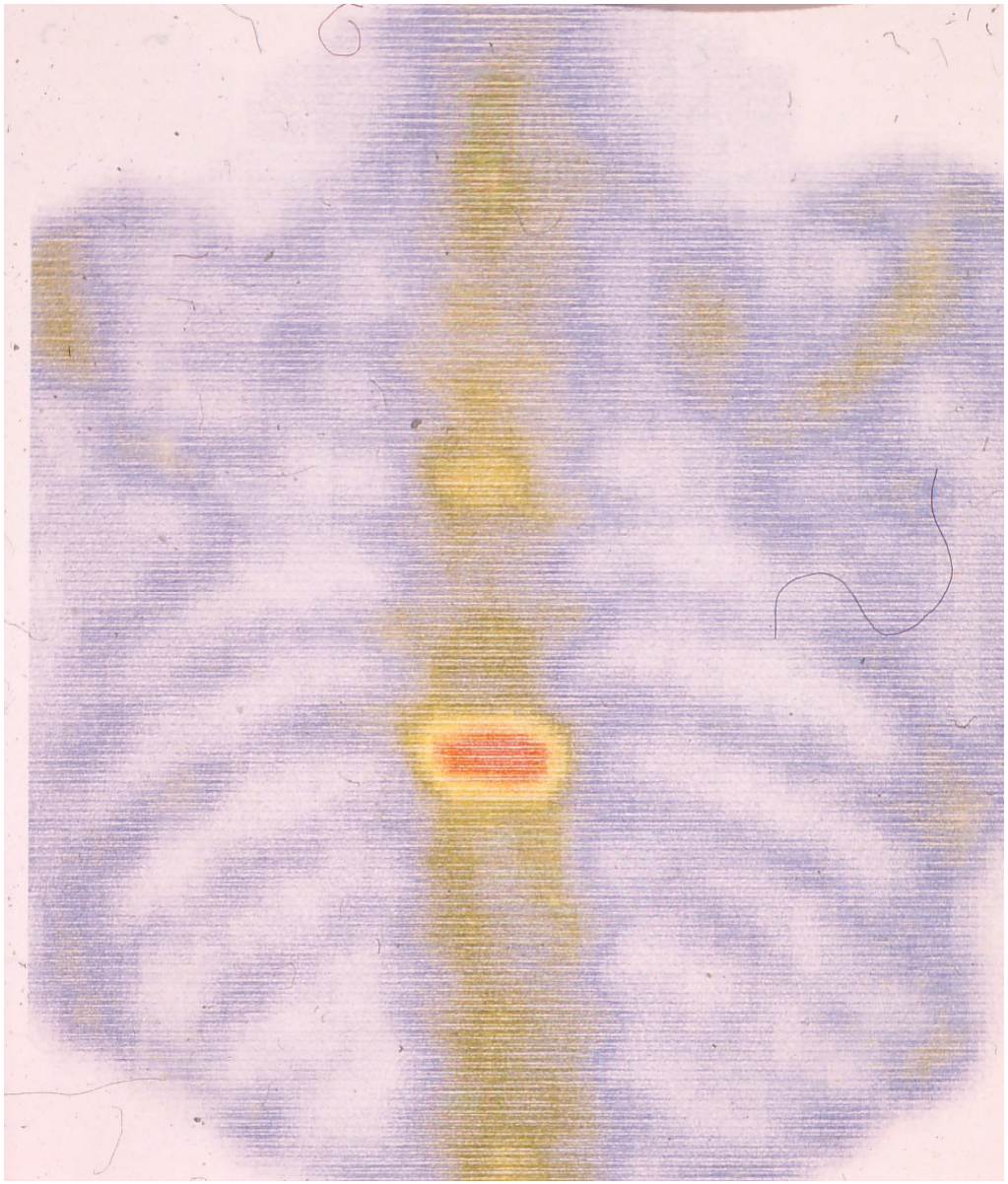




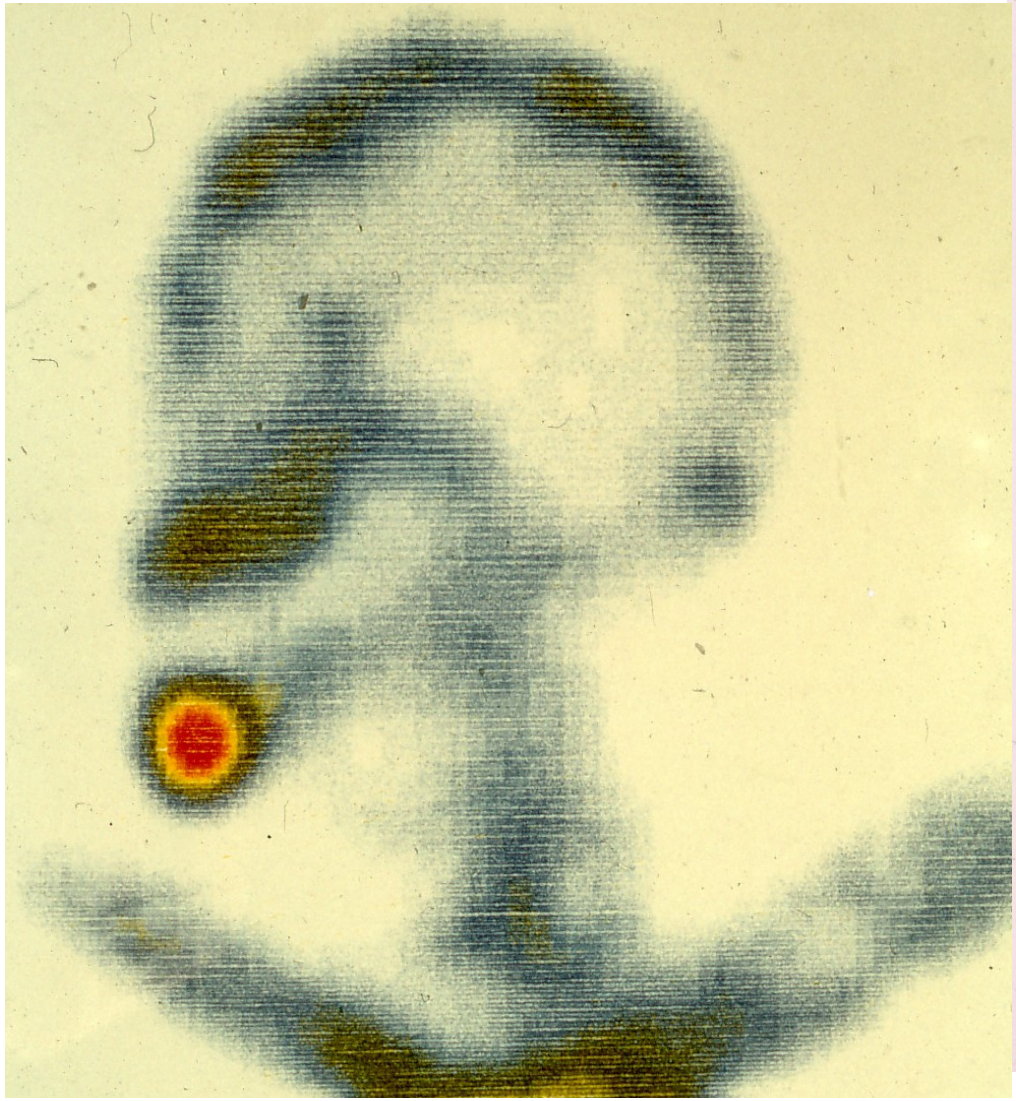


Femur-to-blood uptake ratio (Q) of Tc^{99m} carboxyphosphonates as function of time after i.v. in the rat.

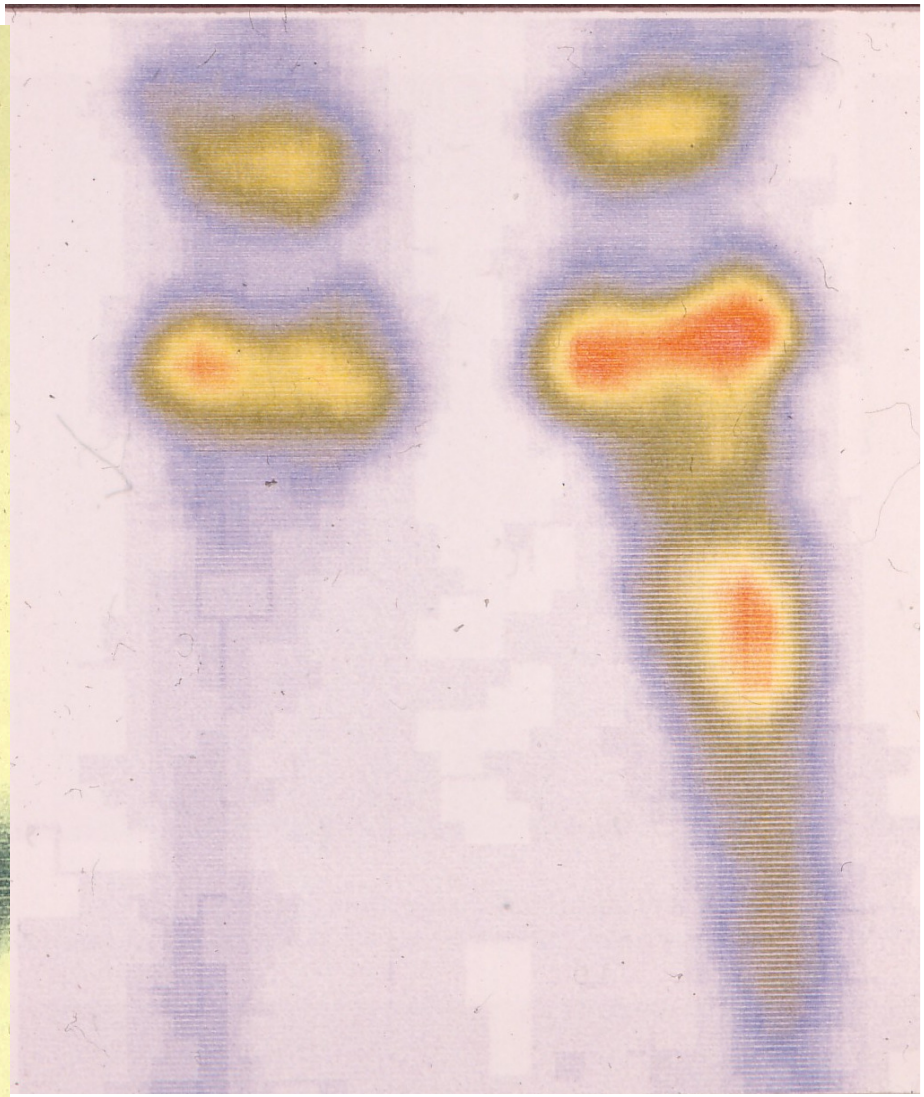
Detection of bone metastasis (breast cancer)



Detection of bone metastasis (carcinoma)



Bone inflammation (periostitis)



Tc99^{m} - 3,3-diphosphono-1,2-propane dicarboxylic acid (DPD)

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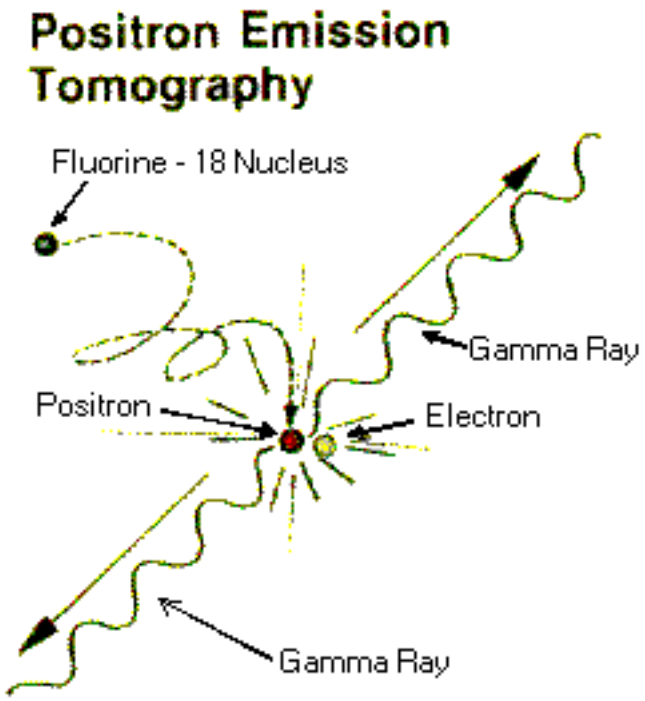
Comparison

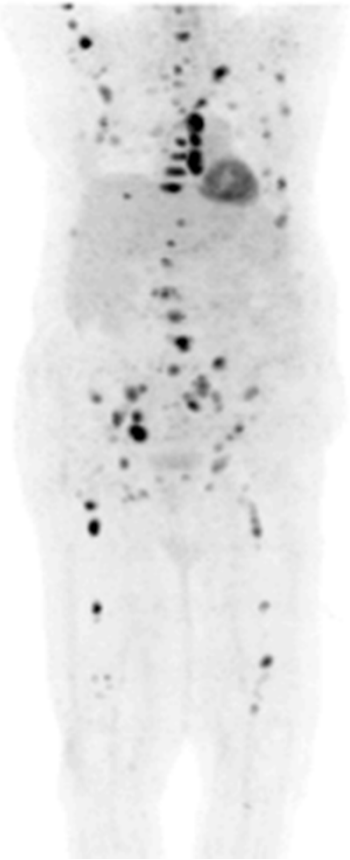
	MRI	CT	SPECT	PET
Principle	Nuclear magnetic resonance	X-ray transmission	photon emission	pozitron emission
Frequent isotopes			Tc	Ga
Target	structure	structure	function	function
Resolution	< 1 mm	1 mm	4-5 mm	2,8 mm
Data collection	20 min	2 min	15 min	20 min
Exposure (mSv)		2-8	6-10	2-10

Gulyás B. Magyar Tudomány, 1999

PET – Positron emission tomography



Photon-pair detection



P(béta$^+$)ET radionuclides commonly used in oncology

Radionuclide		Half-life	Used to measure
$^{15}O_2$	$C^{15}O_2$, H_2O,	2 min	Blood flow
	O_2		Oxygen metabolism
	butanol		
^{13}N	$^{13}NH_3$	10 min	Blood flow
^{11}C	^{11}C-Met, ^{11}C-Tyr	20 min	Amino acid uptake
	^{11}C-glucose		Glucose utilisation
	^{11}C-thymidine		Proliferation
	^{11}C-somatostatin		Somatostatin receptor
^{68}Ga	^{68}Ga-EDTA	68 min	Blood-brain barrier
^{18}F	^{18}F-deoxyglucose (FDG)	110 min	Glucose utilisation
	^{18}F-deoxyuridine		Pyridine uptake
	^{18}F-fluorouracil		Drug uptake
	^{18}F-estradiol		
	18F-DOPA		Estrogen receptors
^{124}I		4 days	Monoclonal antibodies

Wells, P. et al. Clin.Oncol, 1996

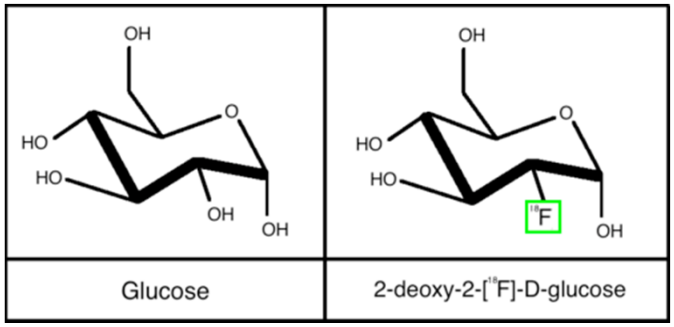
Production and characterization of P(beta$^+$)ET izotopes

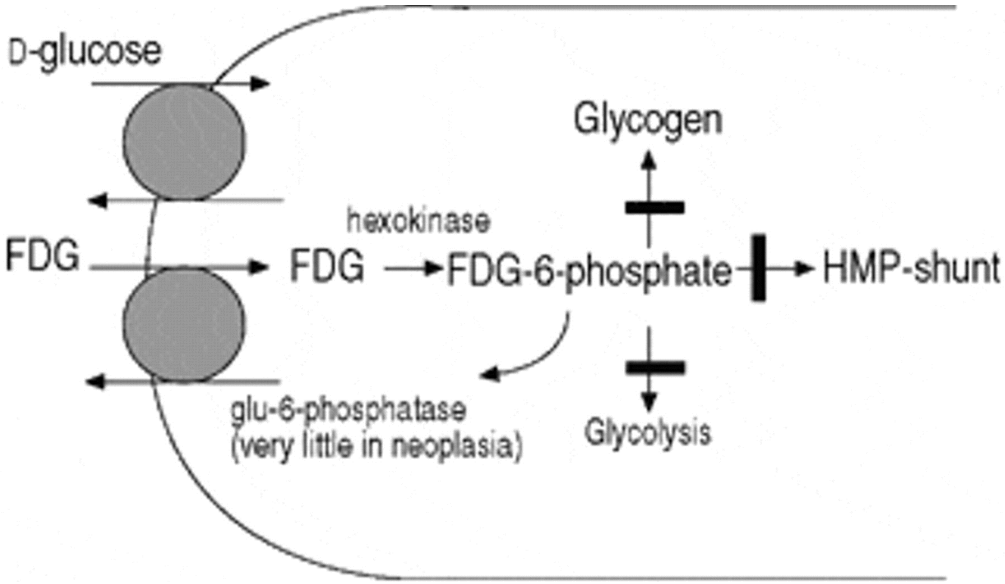
Isotope	Distance	Half-life	Max energy	Reaction
^{15}O	8 mm	2 min	1,74 MeV	14N(d,n) - 15O
^{13}N	5 mm	10 min	1,20 MeV	12C(d,n) – 13N
^{11}C	4 mm	20 min	0,97 MeV	14N(p,a) - 11C
^{18}F	2 mm	110 min	0,64 MeV	18O(p,n) – 18F

Radiolabelled drugs for use in PET

Radiolabelled drugs	Use
^{13}N-cisplatin	kinetic studies
^{13}N or ^{11}C-carmustine	kinetics in normal brain and glioma
(^{11}C-*N*-methyl)temozolomide	*in vivo* mechanism of action
^{11}C-adriamycin	*in vivo* quantify MDR
^{57}Co-bleomycin	tumour and normal tissue kinetics
16-α-(^{18}F)-fluoroestradiol-17-β	measurements of receptor concentration
^{18}F-5-fluorouracil	kinetics, predicting response

Radiolabelled FDG for use in PET





2-Deoxy-2-[^{18}F]fluoroglucose (FDG) $\xrightarrow[\text{hexokinase}]{}$ 2-Deoxy-2-[^{18}F]fluoroglucose-6-phosphate

- a glucose analog,
- taken up by high-glucose-using cells such as brain, kidney, and cancer cells

- phosphorylation prevents the glucose from being released from the cell

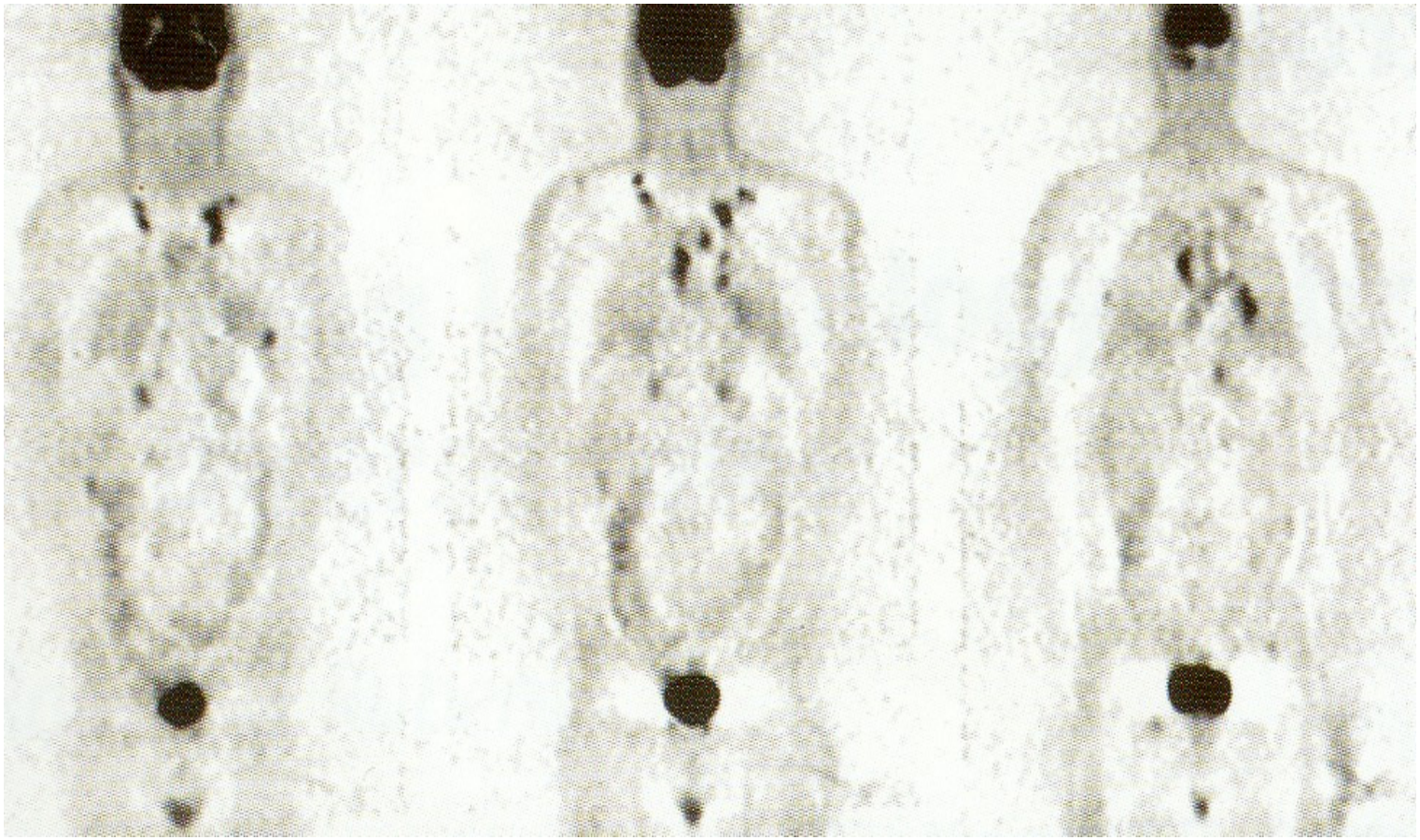
J.F. Vansteenkiste, S.G. Stroobants Eur. Respir J. 2001;17:802-820
Review: Conti PS et al. Nucl.Med.Biol. 23, 717, 1996


TRACERlab


TRACERlab

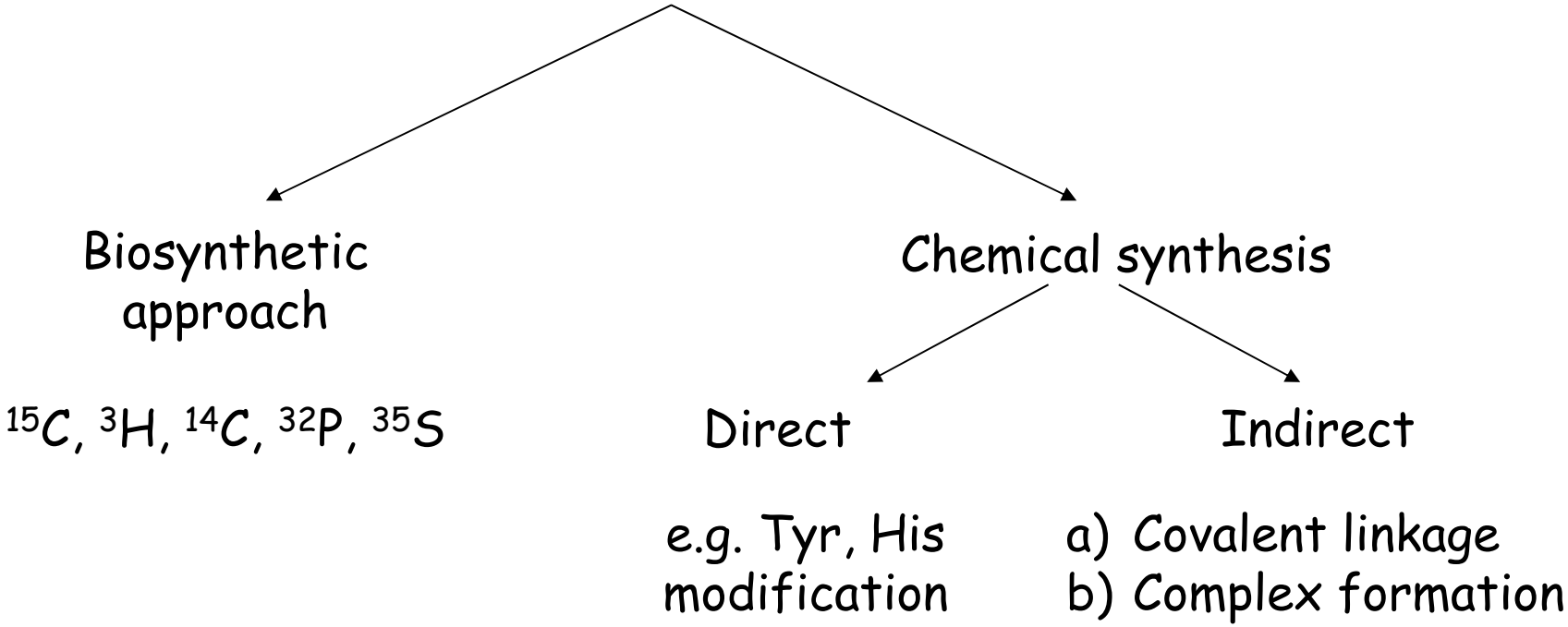
Detection of lung cancer: ^{18}F-deoxyglucose - PET

Lymph node metastasis – brain/bladder (normal)



C.S.Brock et al. Eur.J.Nucl.Med. 24: 691 (1997)

Radioactive isotope conjugates



Considerations

Example: ^{125}I, ^{131}I

(17 iodine, 13 bromine-, 6 chlorine-, 2 fluor isotopes $t_{\frac{1}{2}} > 3$ min)

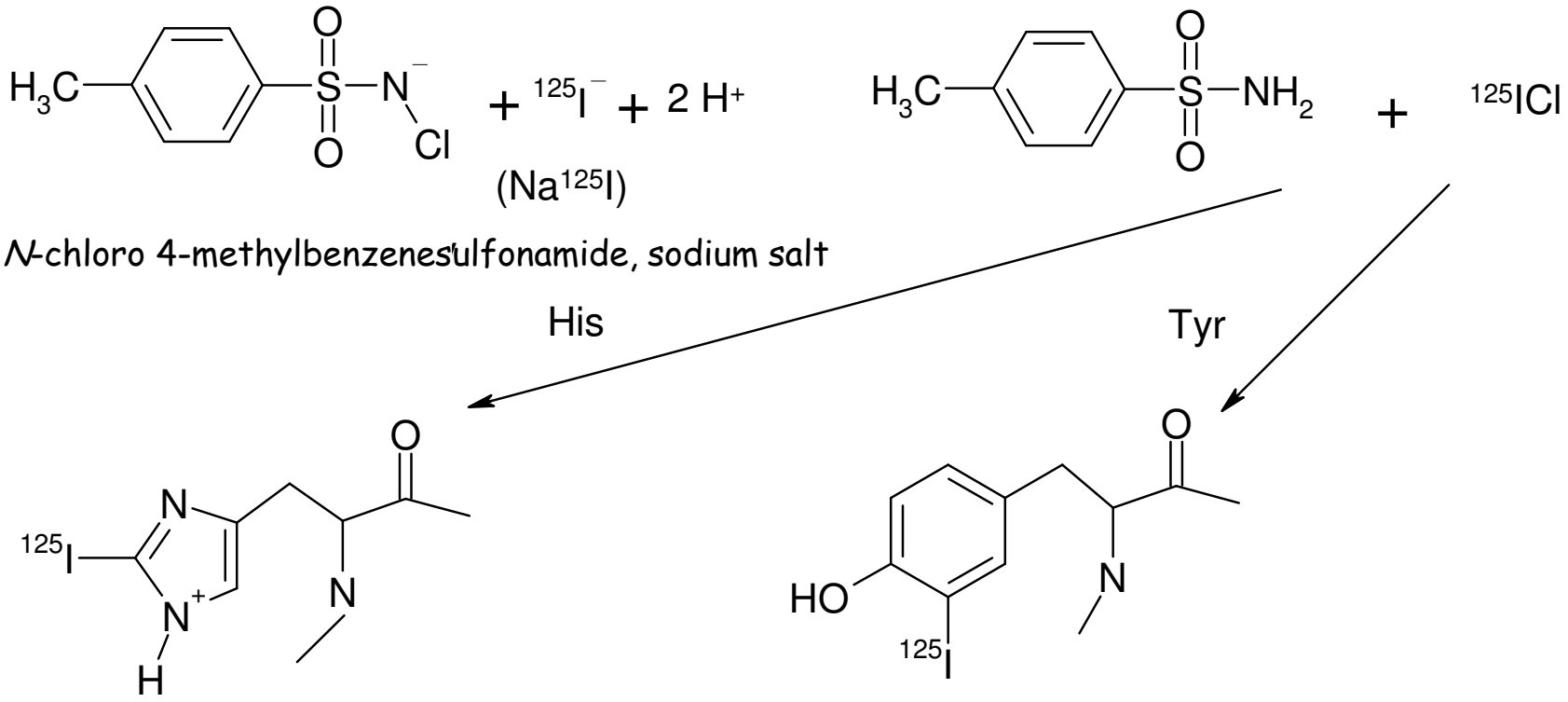
- In vitro
  - Long half-lifetime
  - Low energy emission (photon)
- In vivo „IMAGING"
  - X-ray or γ-emission
  - SPECT, PET
  - γ-camera
  - Relatively high energy, short half life
- In vivo THERAPY
  - No optimal combination (high energy: threat)
  - Low energy, long half-life

Selection of nuclei

Nuclei	Availability	Cost	Half life	Gamma energy (keV)
^{123}I	low	high	13 hr	159
^{131}I	good	low	8 day	364
^{111}In	good	medium	67 hr	173 247
^{67}Ga	good	medium	78 hr	185 300
^{99m}Tc	good	low	6 hr	141

Direct incorporation

Incorporation of iodine isotope into protein
1. Chloramine-T method



N-chloro 4-methylbenzenesulfonamide, sodium salt

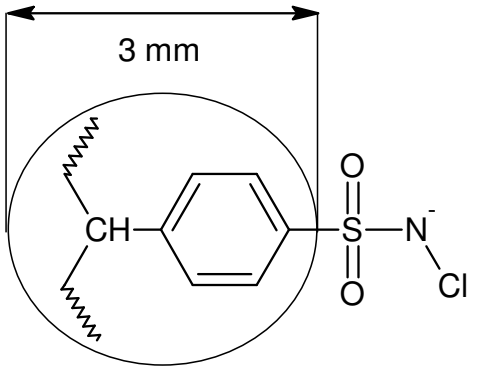
- 30 s – 30 min
- water-soluble
- pH 7 phosphate buffer 0.05 M

Greewood, FC et al. Biochem J 89 114 (1963)
Wilbur, DS Bioconjugate Chem 3 433 (1992)

2. Immobilised Chloramine-T (IODO-BEADS)

U.S. Patent 4448764 és 4436718

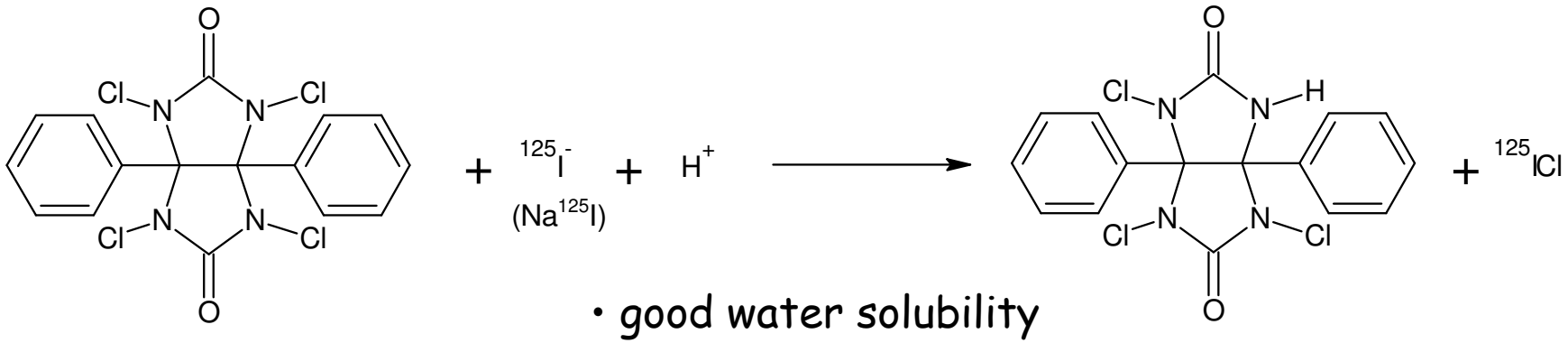
Polystyrene matrix



- 2 – 5 min
- good protein recovery
- mild conditions
- pH 7.2 – 8.4

3. IODO-GEN

Fraker, PJ és Speck, JC BBRC 80 849 (1978)

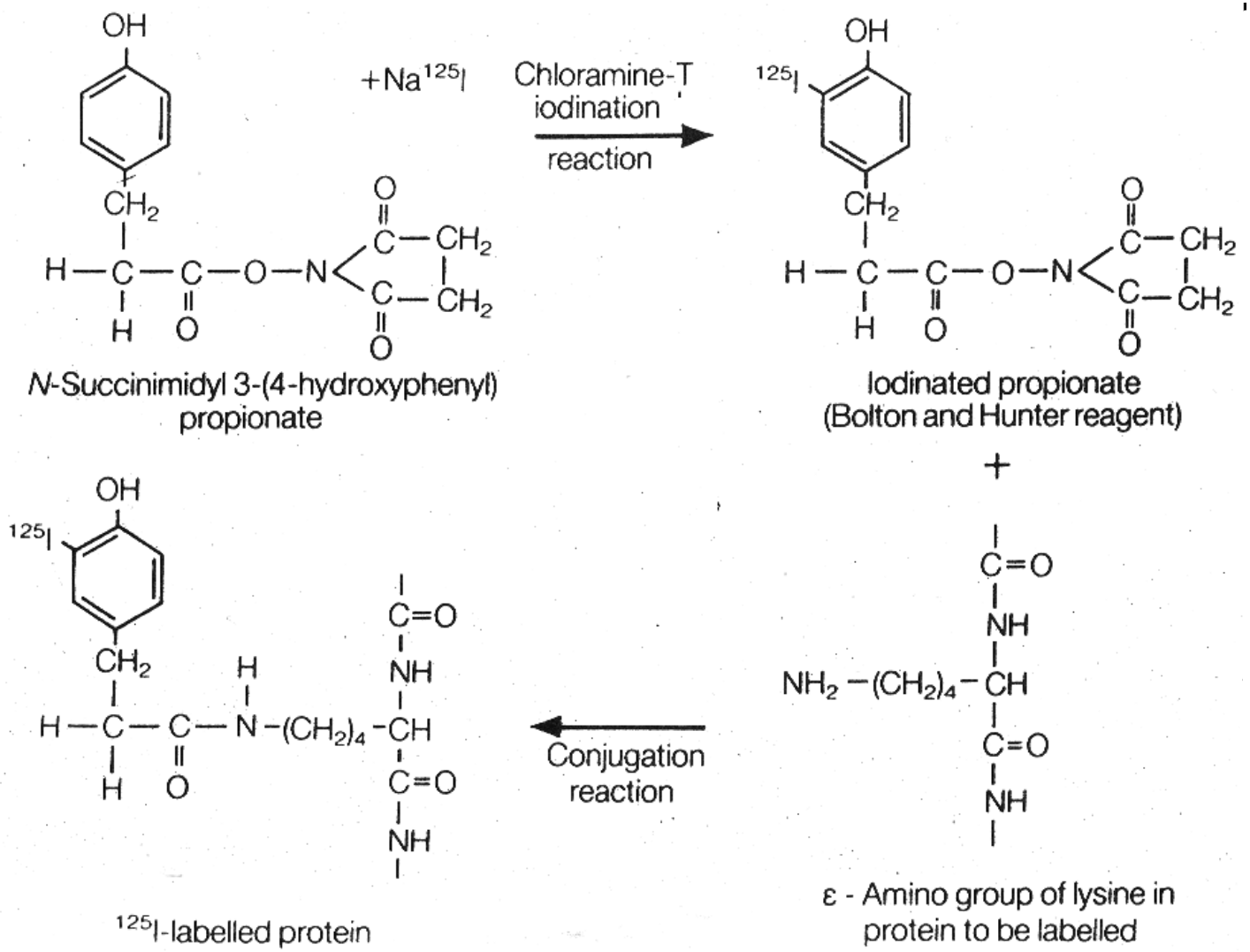


1,3,4,6-Tetrachloro-3a,6a-diphenylglycouril

- good water solubility
- surface adsorption
- quick
- termination by solvent removal

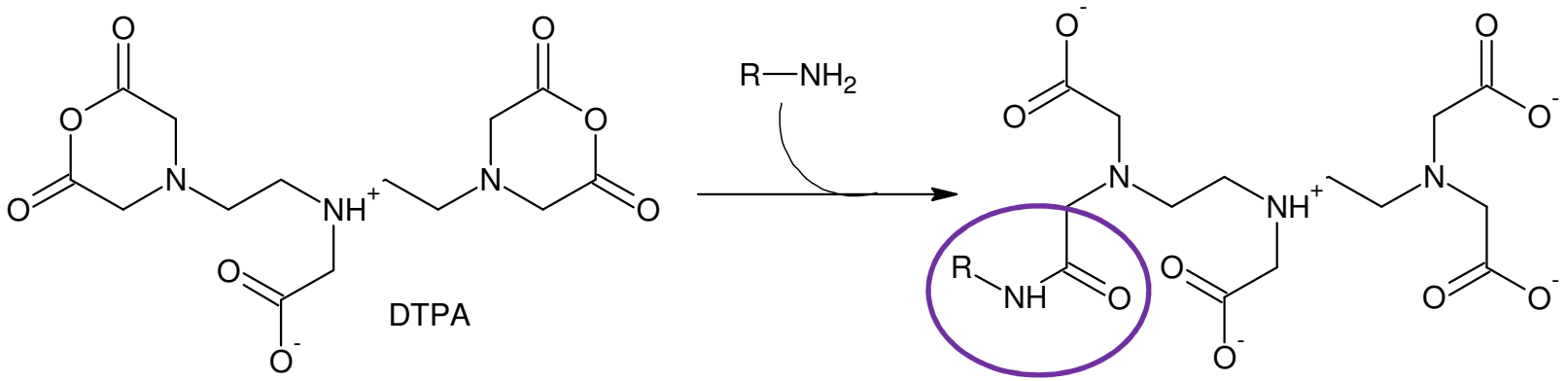
Indirect incorporation

Preparation of conjugates with radiolabel - The Bolton-Hunter reagent

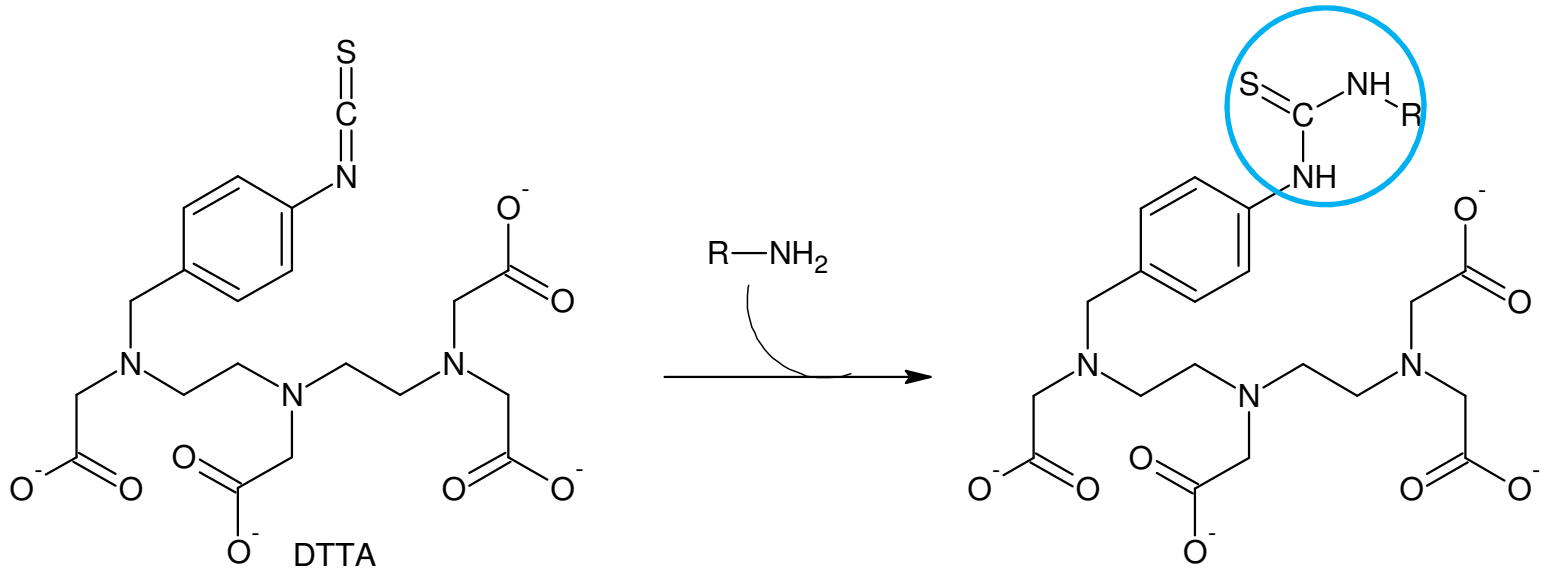


Indirect incorporation by chelators

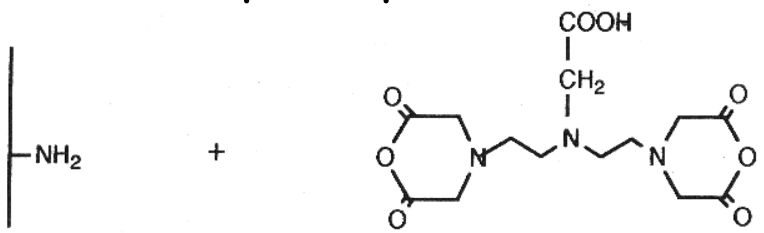
Linear chelators



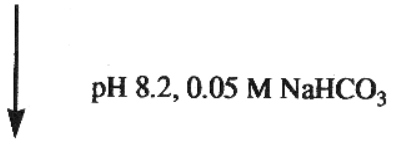
Diethylenetriamine pentaacetic acid (DTPA)

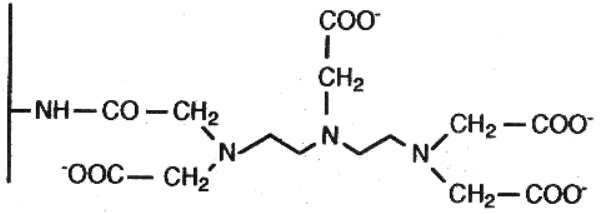


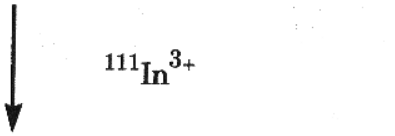
The principle

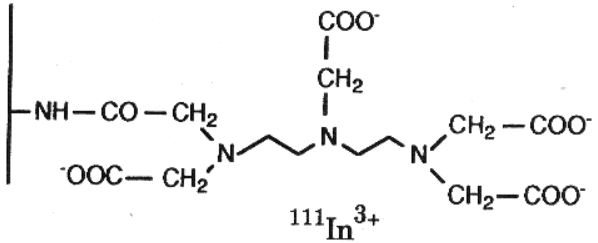


D.J.Hnatowich et al., Science 220,613,1983



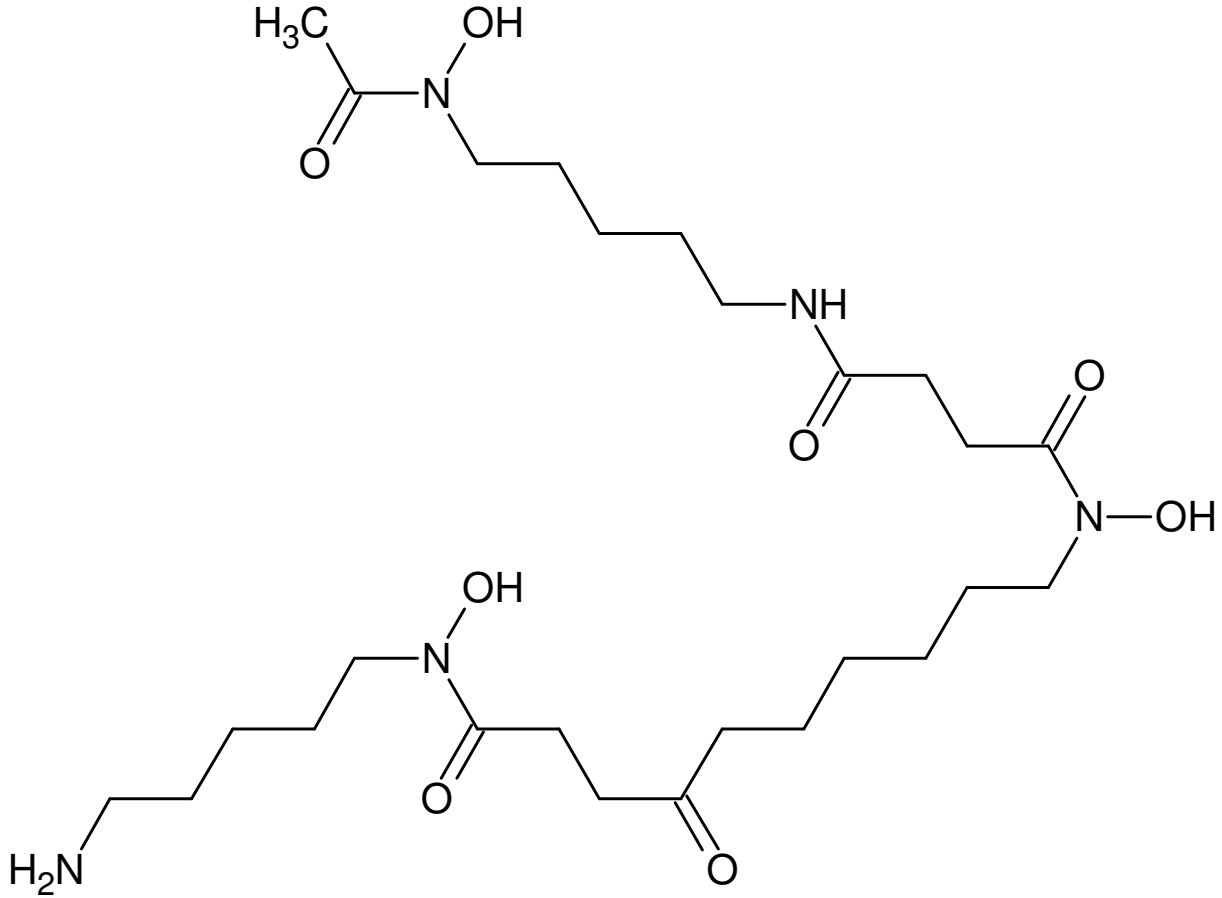






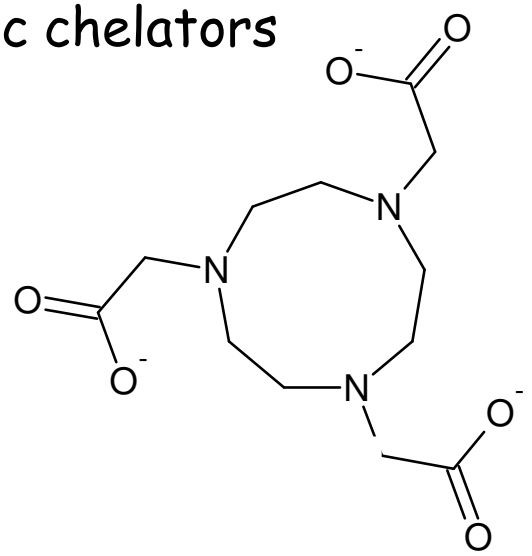
$pK_s = 28.4$

Linear chelators

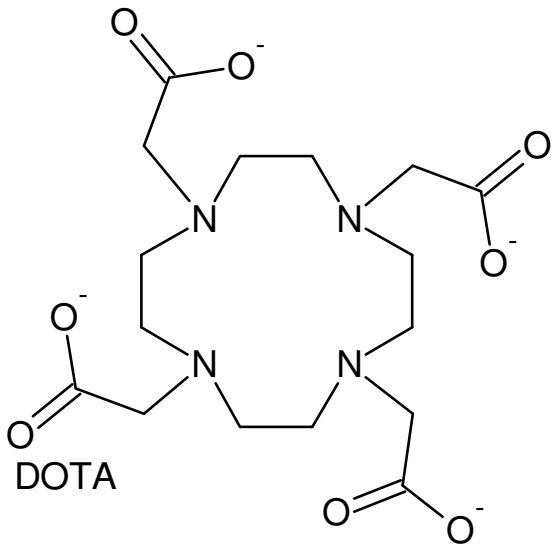


DFA
deferoxamin

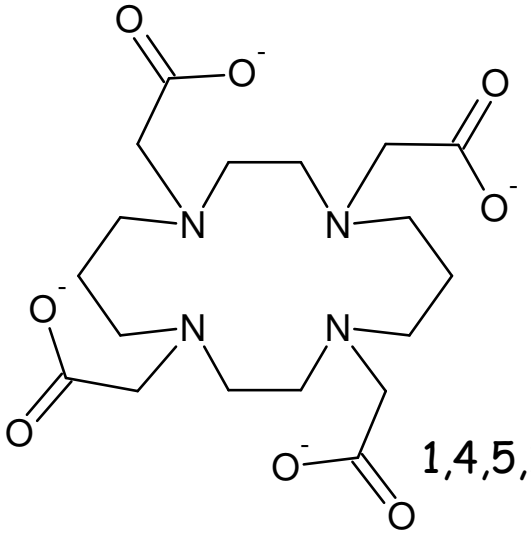
Cyclic chelators



1,4,7-triazacyclononane-1,4,7-triacetic acid



1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid



1,4,5,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid

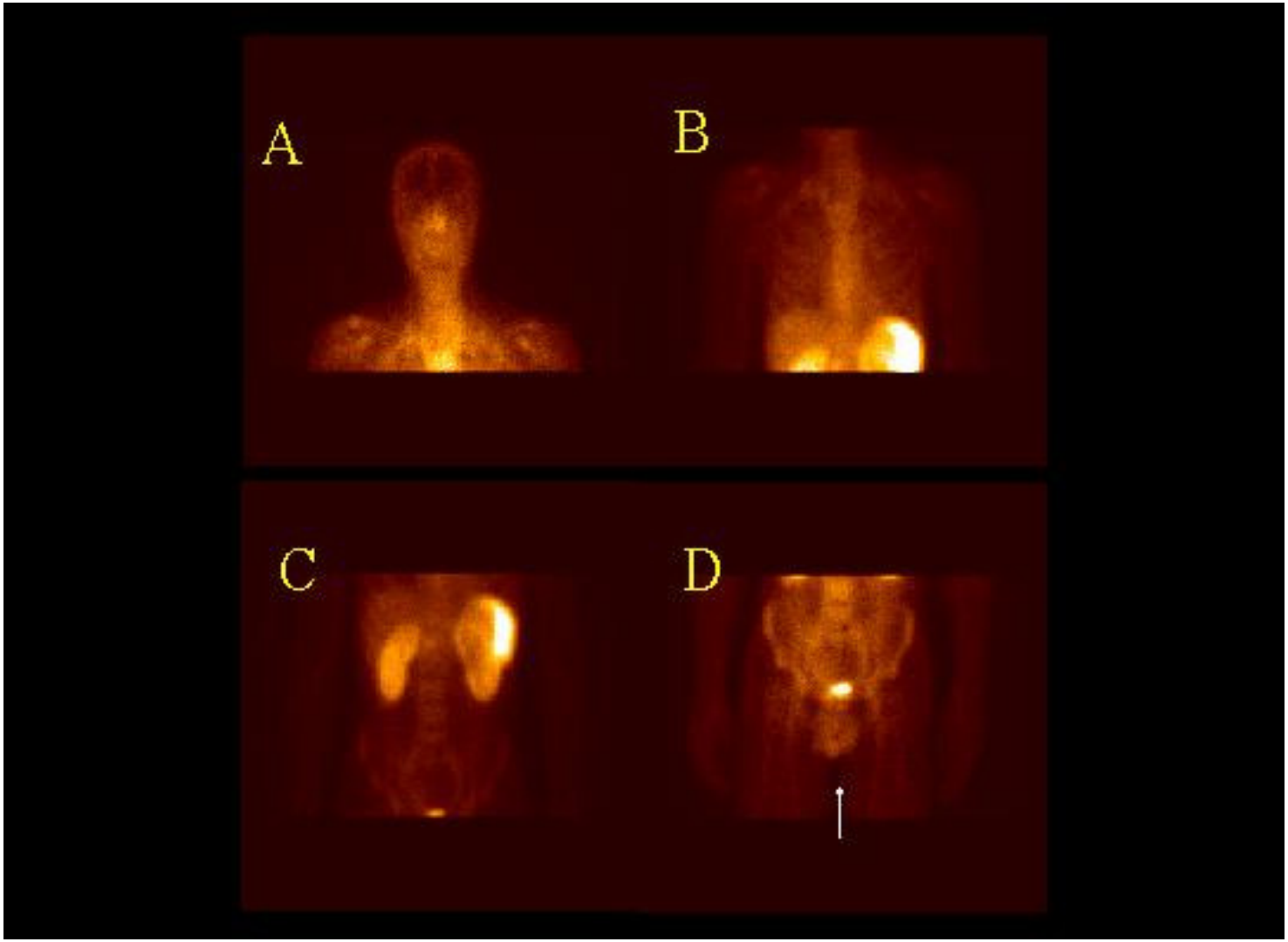
FDA* approved monoclonal antibody conjugates

Abbreviation	Specificity	Type	Indication	Year
Mylotarg	CD33 toxin-linked	humanized	acut myeloid leukemia	2000
Zevalin	CD20 radioligand-linked	mouse	non-Hodgkin lymphoma	2002

*Food and drug administration

Nature Med. 9:129 (2003)

Tc99-radiolabeled mAb against the cellular membrane of the Raji cell component of B cell lymphoma of patients with non-Hodgkin's B-cell lymphoma.



41 year old showing relatively normal distribution of tracer A) Nasopharynx B) Heart C) Liver, Spleen, and Kidney D) Testicles, Bladder and Bone Marrow

Diagnosis of Tumour

- „if it hurts"
- Perception (detected by the five senses)
- Biopsy, histology
- X-ray (chest, mammography, etc.)
- Scintigraphy ("scint," Latin scintilla, spark)
- CT
  - SPECT (Single photon emission computed tomography)
    contrast material remains in the blood stream
  - PET (Positron emission tomography)
    tissue absorption of the labelled (contrast) material
- Immundiagnosis – tumormarkers
- DNS chip/DNS array

Tumour markers

Tumour associated antigens

In healthy tissue as well

Less on normal cells

e.g. Carcinoembryonic antigens (CEA)

Tumour specific antigens

Only in tumour tissue (cells)

Induced by carcinogens (chemical, physical or virus)

In serum

Antigens: CEA (1965), alpha-fetoprotein, CA19-9, CA125, CA15-3 glycoproteins, psotate/-specific antigen (PSA)

Hormones: human chorionic gonadotropin (HCG), insulin, calcitonin, ACTH

Enzymes: Acid phosphatase (ACP), alkaline phosphatase (ALP), catepsin D

Adhesion molecules: ICAM-1, integrin, cadherin

In urine

(bladder cancer) – Mcm5 protein, nuclear matrix protein 22 (NMP22) etc.

Tumormarkers in clinical practice

Bladder	CEA
Breast	CEA, CA 15-3, ferritin
Cervix uteri	CEA
Colon	CEA, CA 19-9, lactate dehydrogenase
Stomach	CEA, CA 19-9, CA 72-4
Leukemia	ferritin, lactate dehydrogenase
Lymphoma	β-2-microglobulin, ferritin, lactate dehydrogenase
Lung (kissejtes)	CEA, bombesin, calcitonin
Ovarium	CA 125, CEA
Thyroid gland	thyreoglobulin, calcitonin
Kidney	erythropoietin, renin
Testis	α-fetoprotein, lactate dehydrogenase

Not suitable for the screening healthy population.
Suitable for monitoring after surgery/treatment to detect relapse.
„Fingerprint"

Mucin glycoproteins

Diagnosis of Tumour

- „if it hurts"
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- X-ray (chest, mammography, etc.)
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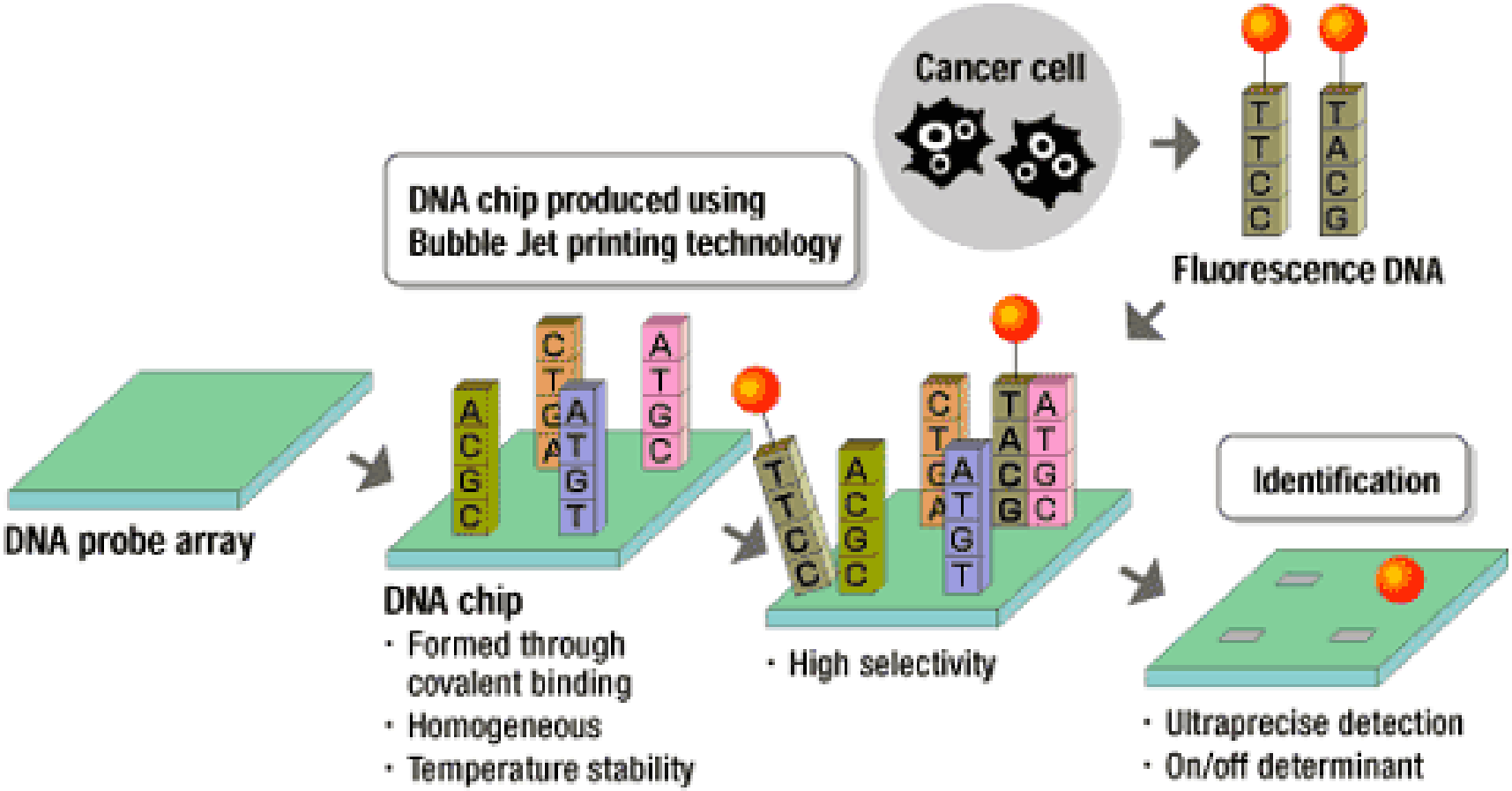
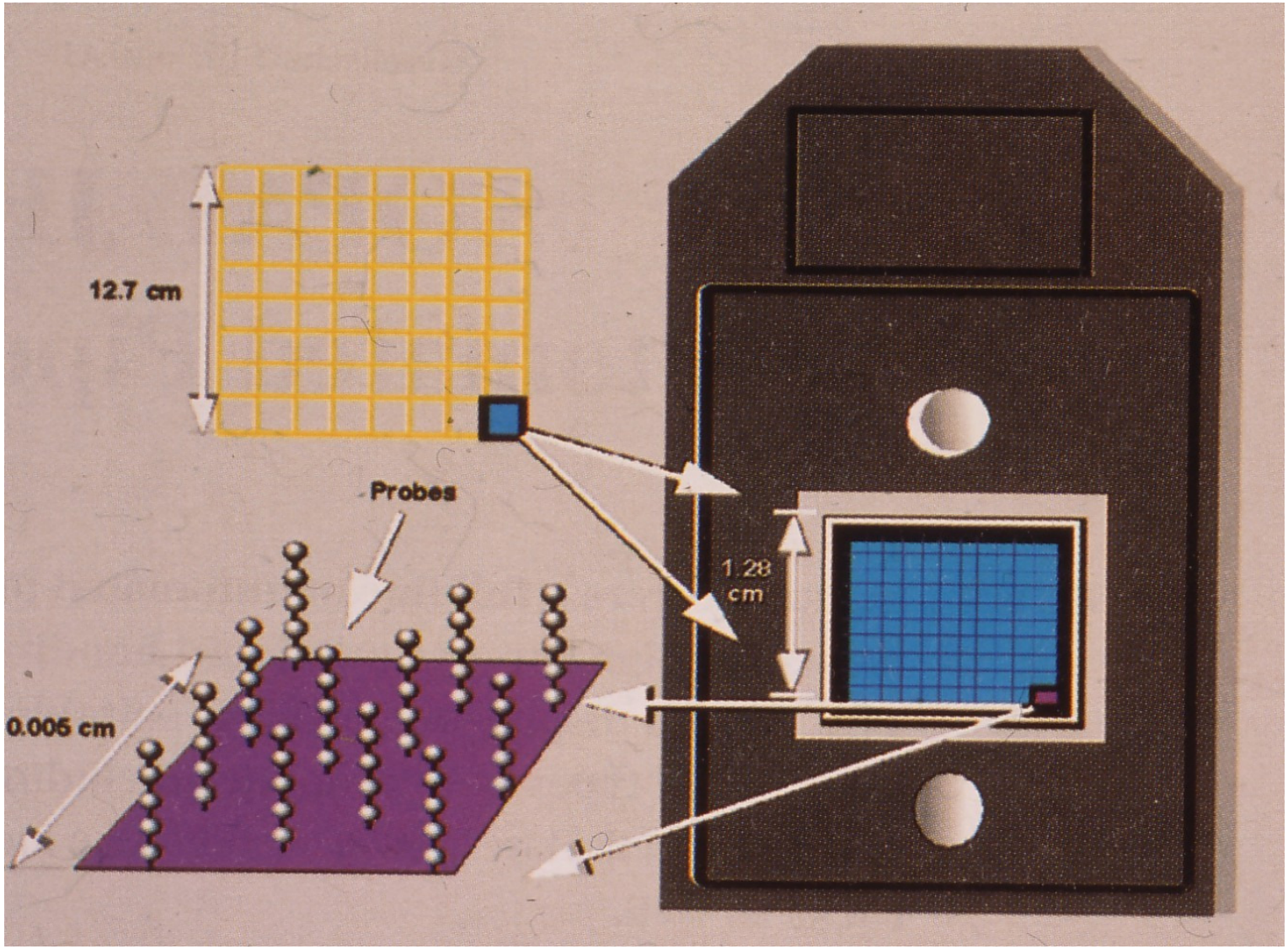
- Immundiagnosis – tumormarkers
- DNA chip/DNA array


Cancer cell
DNA chip produced using
Bubble Jet printing technology
Fluorescence DNA
DNA probe array
DNA chip
· Formed through covalent binding
· Homogeneous
· Temperature stability
· High selectivity
Identification
· Ultraprecise detection
· On/off determinant

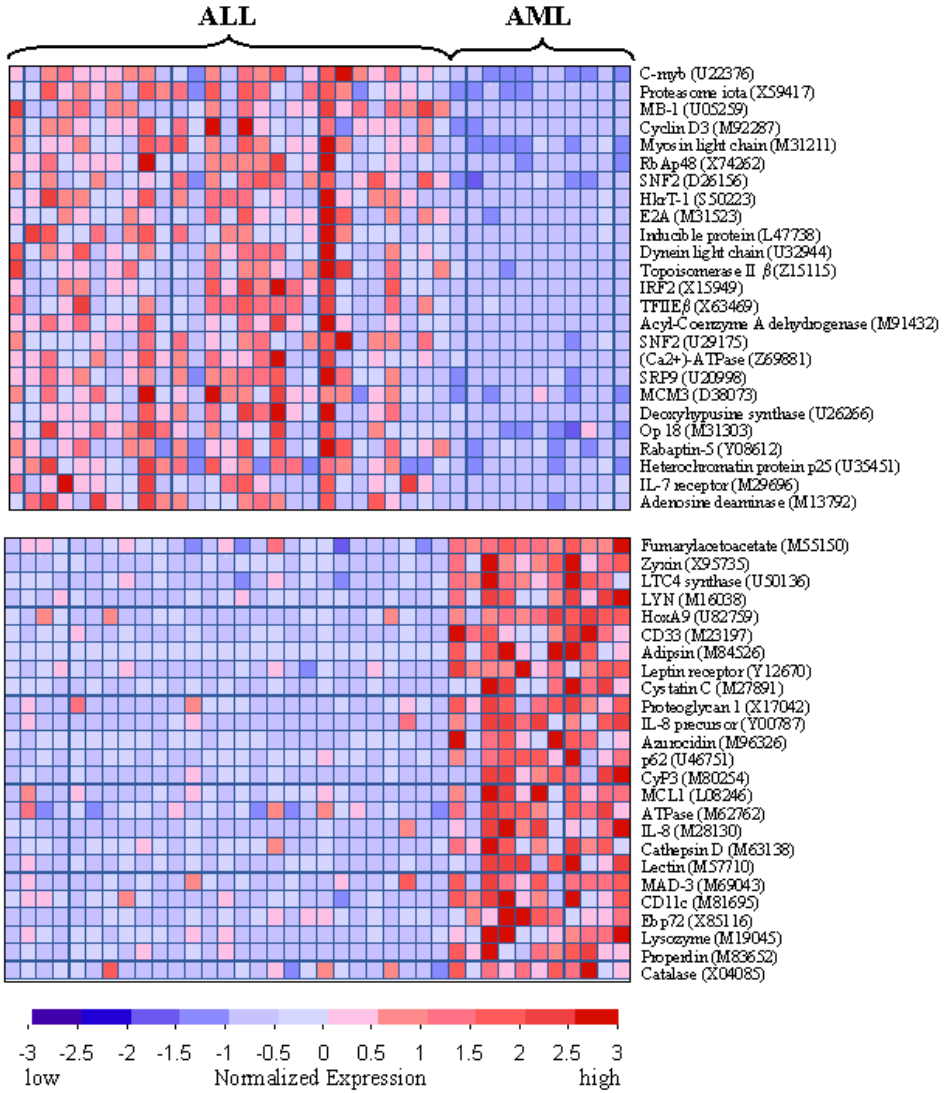
DNA (oligonucleotid) chip



Expression levels of 50 genes most highly correlated with the acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).

Expressed in ALL

Expressed in AML



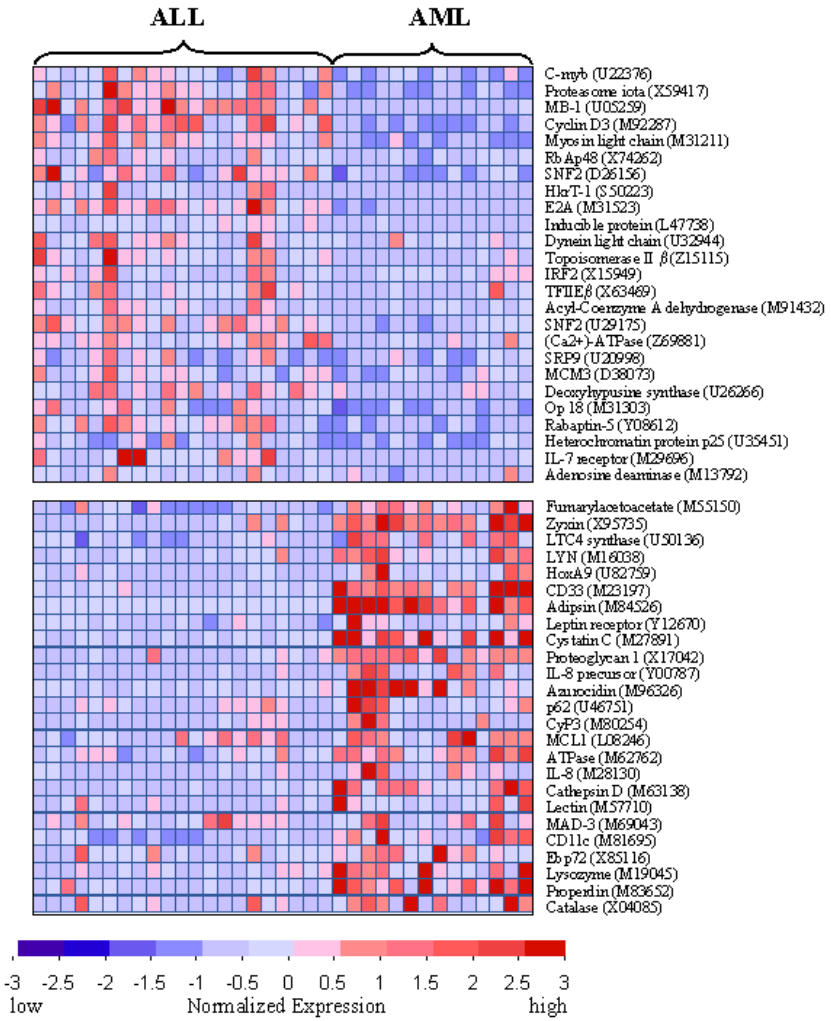
Expression levels greater than the mean: red, below the mean: blue.

TR Golub et al Science 286: 531 (1999)

Expression levels of predictive 50 genes most highly correlated with the ALL-AML in independent dataset.

Independent Set

35 patients



Expressed in ALL

Expressed in AML

Expression levels greater than the mean: red, below the mean: blue.

TR Golub et al Science 286: 531 (1999)