Βιοανόργανη Χημεία

Ραδιοφάρμακα

ΔΔΜΠΣ «ΑΝΟΡΓΑΝΗ ΒΙΟΛΟΓΙΚΗ ΧΗΜΕΙΑ»

Κων/νος Μήλιος
Αναπλ.Καθ. Ανόργανης Χημείας,
Τμήμα Χημείας, Παν/μιο Κρήτης

…literature…

1) Chris Jones, John Thornback, *Medicinal Applications of Coordination Chemistry*, RSC Publishing, Cambridge, 2007.

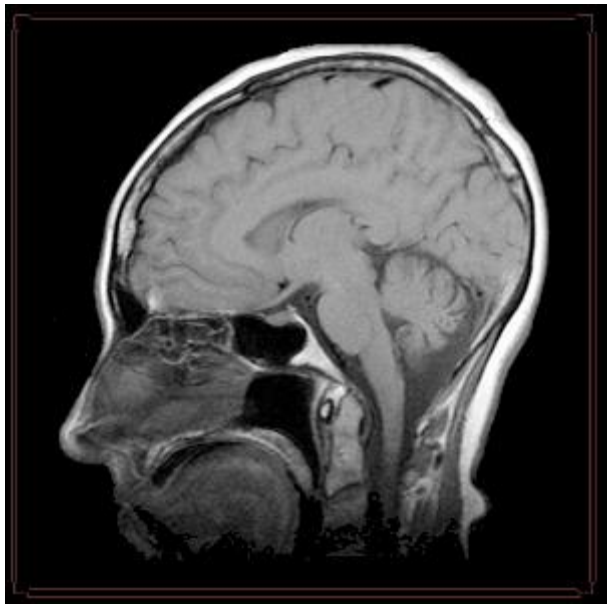
2) *Uses of Inorganic Chemistry in Medicine*. Ed: Nicholas P. Farell, RSC Publishing, Cambridge, 1999.

3) Thomas Nogrady, Donald F. Weaver, *Medicinal Chemistry: A Molecular and Biochemical Approach*, Oxford University Press, New York 2005.

Metal Ions In Medicine

Diagnosis

Magnetic Resonance Imaging (MRI)



Treatment

Metal-based drugs

Anti-cancer drugs
Anti-inflammatory drugs
Anti-virus drugs
Alzheimer's drugs
Lanthanide-based drugs
Li-based drugs
V-based insulin regulators
Radiopharmacology

Metal-Based Drugs

$CuSO_4 \cdot 5H_2O$: Ancient Egypt as potion, sterilizing effect
Au: Arabia and China (2500 BC)
Hg: Europe (15^{th} century) to treat syphilis

1890s: Koch's observation for bactericidal action of Au compounds
1909: Erlich used As(III) cmps. to treat syphilis
1921: Bi(III) cmps to treat syphilis
1930s: Au drugs against rheumatoid arthritis

1953: Korngold and Pressman showed that radioactive iodine can target tumours in rats
1964: *MSU*, Barnett Rosenberg found that Pt(II) inhibits cell division…1974 *cis*-$[Pt(NH_3)_2Cl_2]$ approved by FDA for testicular and ovarian cancer.

"magic bullet" P. Erlich: a dye carrying a toxic heavy metal which would target disease causing agents, while leaving healthy cells unharmed…in 2002 FDA approved a radioactive Y compd. for radioimmunotherapy.

Today…

Gold drugs to treat rheumatoid arthritis…
Lithium for depression…
Platinum to treat certain cancer types…
Bismuth for stomach ulcers…
Vanadium for diabetes…
Iron for anaemia…
Iron to control blood pressure…
Cobalt in Vitamin B_{12} to treat pernicious anaemia…
Radioactive metals for cancer…

Metallopharmaceuticals…

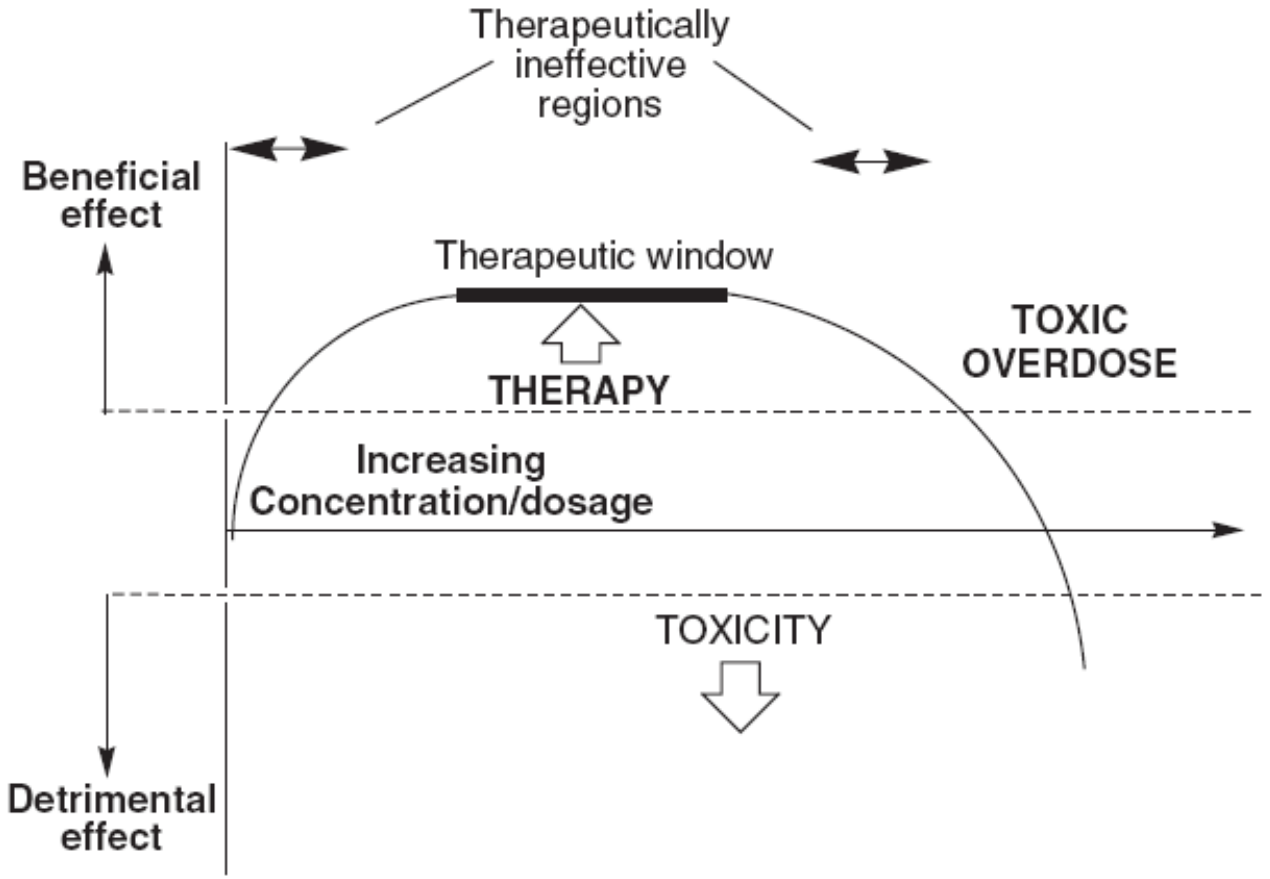
Metals are in general toxic and unstable…in the old days treatment with metals was as dangerous as the disease!!!

1) **Maximum effect with minimum dose and minimal toxic side-effects**.

Therapeutic Index= LD_{50}/ED_{50} Small or big????anything "strange"??

Increasing the dose of the drug does not mean increasing its beneficial effect! We have to consider the "*therapeutic window*"

…e.g. carrots and Vitamin A



The effect of increasing pharmaceutical dosage, or concentration in vivo, on benefit to the patient. Initially the beneficial effect increases with increasing concentration but at high doses, toxic effects predominate. Dosage regimes need to be adjusted to keep concentrations within the therapeutic window

Clinical Trials…tough one!

Phase I: Small group of **healthy** people take the drug to test its absorption, biodistribution, pharmokinetics, accumulation, side-effects and dosage. (Volunteers!!!)

Phase II: Small group of **patients** receive the drug to test its activity. Optimum dosage and adverse reactions are assessed.

Phase III: Large groups of **patients** are evaluated. Double trials, blinds, placebo.

Phase IV: **Patients** are still monitored…approval follows…fine-tuning of procedures

cis-platin took **14 years** to hit the shelves since it was first discovered in 1964.

Radiopharmaceuticals…

Targeted Radiotherapy: combating cancer

Radiolabeled molecules:

For delivery of therapeutic doses of ionisation to *specific* disease sites.

Radiopharmaceuticals, drugs containing a radionuclide: used routinely in nuclear medicine departments for the diagnosis of disease and are **under investigation** for use in the treatment of disease

Ατομικός αριθμός (Z) = # πρωτονίων του πυρήνα

Μαζικός αριθμός (A) = # πρωτονίων + # νετρονίων

= ***Ατομικός αριθμός*** (Z) + # νετρονίων

Μαζικός αριθμός → $^{A}_{Z}X$ ← Σύμβολο στοιχείου

Ατομικός αριθμός →

	πρωτόνιο	νετρόνιο	ηλεκτρόνιο	ποσιτρόνιο	α σωματίδιο
	$^{1}_{1}p$ or $^{1}_{1}H$	$^{1}_{0}n$	$^{0}_{-1}e$ or $^{0}_{-1}\beta$	$^{0}_{+1}e$ or $^{0}_{+1}\beta$	$^{4}_{2}He$ or $^{4}_{2}\alpha$
A	1	1	0	0	4
Z	1	0	-1	+1	2

Τύποι Ακτινοβολίας

- (α) – πυρήνες ^{4}He $\quad {}^{4}_{2}He$
- (β) – το ηλεκτρόνιο $\quad {}^{0}_{-1}e$
- (γ) – καθαρή ενέργεια $\quad {}^{0}_{0}\gamma$

Πυρηνικές αντιδράσεις

1. Διατήρηση μαζικού αριθμού (A)

πρωτονίων και νετρονίων των προιόντων = # πρωτονίων και νετρονίων των αντιδρώντων.

$$^{235}_{92}U + ^{1}_{0}n \longrightarrow ^{138}_{55}Cs + ^{96}_{37}Rb + 2\,^{1}_{0}n$$

235 + 1 = 138 + 96 + 2x1

2. Διατήρηση ατομικού αριθμού (Z) ή πυρηνικού φορτίου

πυρηνικών φορτίων των προιόντων = # πυρηνικών φορτίων των αντιδρώντων.

$$^{235}_{92}U + ^{1}_{0}n \longrightarrow ^{138}_{55}Cs + ^{96}_{37}Rb + 2\,^{1}_{0}n$$

92 + 0 = 55 + 37 + 2x0

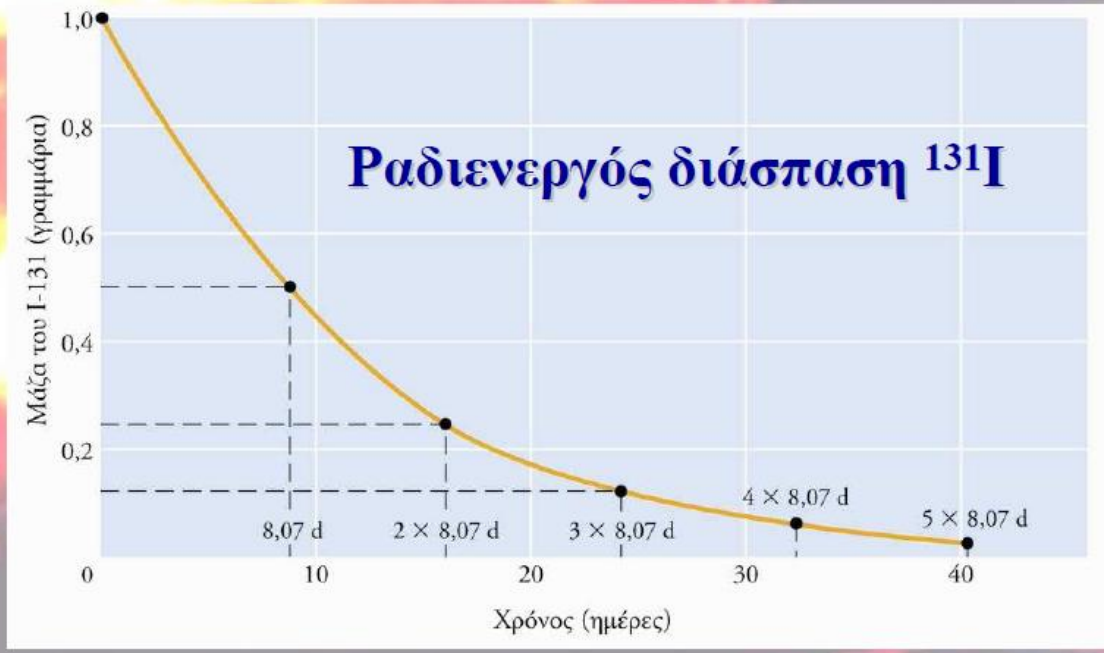
Τύποι ραδιενεργού διάσπασης

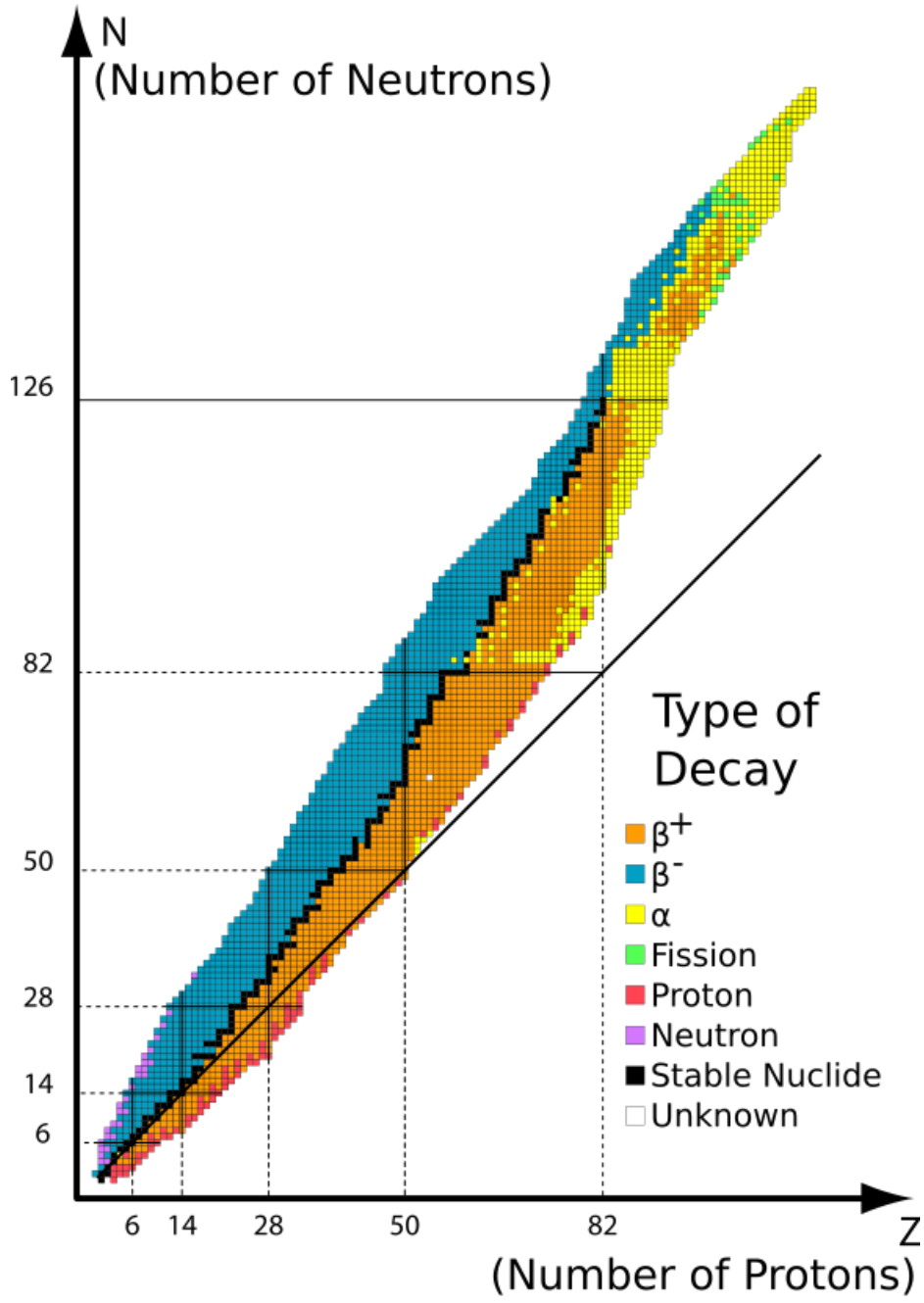
Τύποι διάσπασης	Ακτινοβολία	Ισοδύναμη διαδικασία	Απορρέουσα μεταβολή του πυρήνα		Συνήθης κατάσταση πυρήνα
			Ατομικός αριθμός	Μαζικός αριθμός	
Εκπομπή άλφα (α)	${}_{2}^{4}\mathrm{He}$	—	−2	−4	$Z > 83$
Εκπομπή βήτα (β)	${}_{-1}^{0}\mathrm{e}$	${}_{0}^{1}\mathrm{n} \longrightarrow {}_{1}^{1}\mathrm{p} + {}_{-1}^{0}\mathrm{e}$	+1	0	N/Z πολύ μεγάλο
Εκπομπή ποζιτρονίου (β^+)	${}_{1}^{0}\mathrm{e}$	${}_{1}^{1}\mathrm{p} \longrightarrow {}_{0}^{1}\mathrm{n} + {}_{1}^{0}\mathrm{e}$	−1	0	N/Z πολύ μικρό
Σύλληψη ηλεκτρονίου (EC)	ακτίνες X	${}_{1}^{1}\mathrm{p} + {}_{-1}^{0}\mathrm{e} \longrightarrow {}_{0}^{1}\mathrm{n}$	−1	0	N/Z πολύ μικρό
Εκπομπή γάμμα (γ)	${}_{0}^{0}\gamma$	—	0	0	Διεγερμένη

- Όλα τα ισότοπα των στοιχείων με ατομικούς αριθμούς > 83 είναι ραδιενεργά

Χρόνος ημιζωής

- **Χρόνος ημιζωής** είναι ο χρόνος που απαιτείται για να διασπαστούν οι μισοί πυρήνες σε ένα δείγμα.
- Η ταχύτητα της διάσπασης εξαρτάται μόνο από τη συγκέντρωση του ραδιενεργού δείγματος.




N
(Number of Neutrons)
126
82
50
28
14
6
6
14
28
50
82
Z
(Number of Protons)
Type of Decay
β+
β-
α
Fission
Proton
Neutron
Stable Nuclide
Unknown

Isotope	Half-life (yr)	Rel. Abundance
Holmium-166m	1,200	none
Berkelium-247	1,380	none
Radium-226	1,600	trace
Molybdenum-93	4,000	none
Holmium-153	4,570	none
Curium-246	4,730	none
Carbon-14	5,730	trace
Plutonium-240	6,563	none
Thorium-229	7,340	none
Americium-243	7,370	none
Curium-245	8,500	none
Curium-250	9,000	none
Tin-126	10,000	none
Niobium-94	20,300	none
Plutonium-239	24,110	none
Protactinium-231	32,760	trace
Lead-202	52,500	none
Lanthanum-137	60,000	none
Thorium-230	75,380	none
Nickel-59	76,000	none
Thorium-230	77,000	trace
Calcium-41	103,000	none
Neptunium-236	154,000	none
Uranium-233	159,200	none
Rhenium-186m	200,000	none
Technetium-99	211,000	none
Krypton-81	229,000	none
Uranium-234	245,500	trace
Chlorine-36	301,000	none
Curium-248	340,000	none
Bismuth-208	368,000	none
Plutonium-242	373,300	none
Aluminum-26	717,000	none
Selenium-79	1,130,000	none
Iron-60	1,500,000	none
Beryllium-10	1,510,000	none
Zircon-93	1,530,000	none
Curium-247	1,560,000	none
Gadolinium-150	1,790,000	none
Neptunium-237	2,144,000	none
Cesium-135	2,300,000	none
Technetium-97	2,600,000	none
Dysprosium-154	3,000,000	none
Bismuth-210m	3,040,000	none
Manganese-53	3,740,000	none
Technetium-98	4,200,000	none
Palladium-107	6,500,000	none
Hafnium-182	9,000,000	none
Lead-205	15,300,000	none
Curium-247	15,600,000	none
Iodine-129	17,000,000	trace
Uranium-236	23,420,000	none
Niobium-92	34,700,000	none
Plutonium-244	80,800,000	none
Samarium-146	103,000,000	none
Uranium-236	234,200,000	none
Uranium-235	703,800,000	rare
Potassium-40	1,280,000,000	rare
Uranium-238	4,468,000,000	common

Rubidium-87	4,750,000,000	common
Thorium-232	14,100,000,000	common
Lutetium-176	37,800,000,000	rare
Rhenium-187	43,500,000,000	common
Lanthanum-138	105,000,000,000	rare
Samarium-147	106,000,000,000	common
Platinum-190	650,000,000,000	rare
Tellurium-123	>1 x 10^13	rare
Osmium-184	>5.6 x 10^13	rare
Gadolinium-152	1.08 x 10^14	rare
Tantalum-180m	>1.2 x 10^15	rare
Xenon-124	>1.6 x 10^14	rare
Indium-115	4.41 x 10^14	common
Zinc-70	>5 x 10^14	rare
Hafnium-174	2.0 x 10^15	rare
Osmium-186	2.0 x 10^15	common
Samarium-149	>2 x 10^15	common
Neodymium-144	2.29 x 10^15	common
Samarium-148	7 x 10^15	common
Cadmium-113	7.7 x 10^15	common
Cerium-142	>5 x 10^16	common
Tungsten-183	>1.1 x 10^17	common
Vanadium-50	1.4 x 10^17	rare
Lead-204	1.4 x 10^17	common
Chromium-50	>1.8 x 10^17	common
Tungsten-184	>3 x 10^17	common
Calcium-48	>6.3 x 10^18	common
Molybdenum-100	1.0 x 10^19	common
Neodynium-150	>1.1 x 10^19	common
Zircon-96	>3.8 x 10^19	common
Selenium-82	1.1 x 10^20	common

Tellurium-130	7.9 x 10^20	common
Xenon-136	>2.4 x 10^21	common
Tellurium-128	2.2 x 10^24	common

Radiopharmaceuticals can be divided into two primary classes:

(1)those whose biological distribution is determined strictly by blood flow, and

(2) those whose ultimate distribution is determined by specific biochemical or receptor binding interactions

Obviously, the latter class is initially distributed by blood flow, but their tissue uptake and retention rely on specific interactions of the radiopharmaceutical in a biochemical process, such as enzymatic reduction, or specific receptor binding, as is observed in antibody-antigen interaction

The term "pharmaceutical" generally connotes organic, medicinal, or natural products chemistry. The majority of therapeutic drugs are organic or bioorganic molecules. This is not surprising considering the composition of biological systems and the involvement of organic compounds in these systems…but things are changing…RAPIDLY…

The most efficacious radiopharmaceuticals, diagnostic and therapeutic, would most likely be organic molecules if it were not for the fact that the **radionuclide is an essential element of the radiopharmaceutical**. The substitution of a radioisotope of carbon for a nonradioactive carbon atom in an organic or bioorganic molecule would probably be ideal. However, **the radionuclides with physical (or nuclear) properties suitable for use in either a diagnostic or therapeutic radiopharmaceutical are predominantly metals**

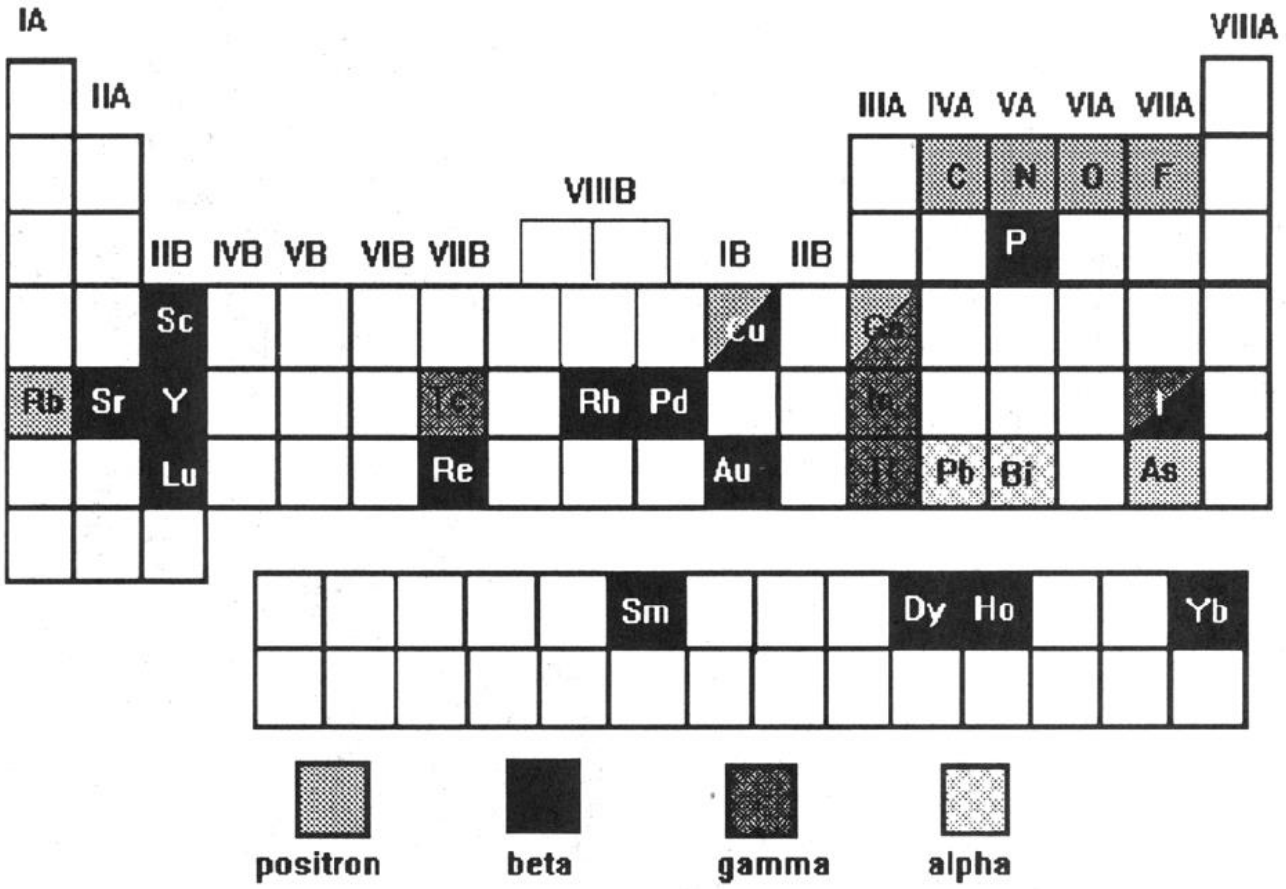
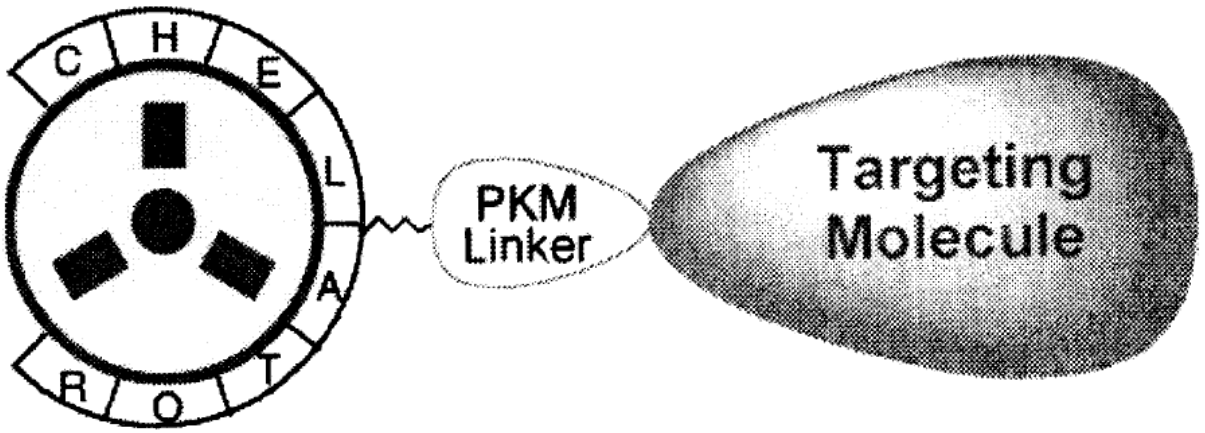


Figure 1. The radiopharmaceutical chemist's periodic table showing the most medically useful radionuclides. Split patterns indicate more than one type of radioisotope (e.g., iodine has both gamma- and beta-emitting radioisotopes).

Metals offer many opportunities for designing radiopharmaceuticals by modifying **the environment around the metal and allowing specific in vivo targeting to be incorporated into the molecule**. The radiopharmaceutical may be designed to be **(1) metal essential,** whereby the biological distribution is determined by the properties of the coordination compound, or **(2) metal tagged**, in which case the properties of a carrier molecule, such as an antibody, determine the biological distribution, and the metal or metal complex is simply along for the ride…



The biological system consists of circulating blood at a **pH of ca. 7.4** and a **temperature of ca. 37 ^{O}C** and contains **various proteins**, **enzymes**, **cells**, and so on. In addition, **compounds in the blood** (e.g., transferrin) could potentially challenge the integrity of the complex of interest. The stability that is important for a radiopharmaceutical is **kinetic stability**. **The radiopharmaceutical must be stable sufficiently long to reach its destination, and in some cases it must remain intact during its lifetime in the body.**

- **Therapeutic radiopharmaceuticals** should deliver localised cytotoxic doses of ionising radiation. The radionuclides used emit **β^- particles** (electrons) or **α particles** (helium-4 nuclei, $^{4}_{2}He^{2+}$). A major aim is often to treat secondary or metastatic cancer sites.

- Most radiotherapeutic nuclides used in the clinic are **β^- emitters**. Examples are (half-lives in brackets):

^{32}P (14.3 d), ^{47}Sc (3.4 d), ^{64}Cu (0.5 d), ^{67}Cu (2.6 d)

^{89}Sr (50.5 d), ^{90}Y (2.7 d), ^{105}Rh (1.5 h), ^{111}Ag (7.5 h)

^{117m}Sn (13.6 h), ^{131}I (8.0 h), ^{149}Pm (2.2 h), ^{153}Sm (1.9 h)

^{166}Ho (1.1 h), ^{177}Lu (6.7 h), ^{186}Re (3.8 h), ^{188}Re (0.7 h)

Three main ways of radiation delivery are currently used:

External irradiation

Implantable “seeds”

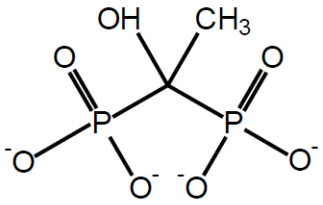
Systemic administration

History

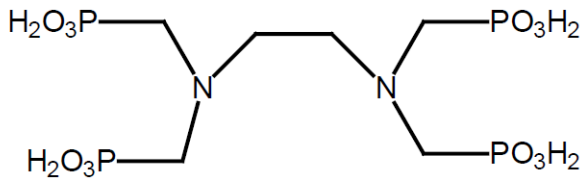
Radiotherapy has been around for over four decades.

Radioiodine (^{131}I) has been used in the treatment of thyroid disorders and strontium chloride (^{89}Sr) and sodium phosphate for the relief of pain associated with bone metastases.

- Since 1942, radiopharmaceuticals have been used to relieve pain from **skeletal metastases**. A major constituent of bone is the mineral hydroxyapatite. This can be targeted with ^{32}P-orthophosphate, ^{89}Sr-strontium chloride (similar chemistry of Ca^{II} and Sr^{II}) and with phosphonate complexes of radionuclides such as ^{153}Sm and ^{186}Re. Typical phosphonate ligands are shown, hydroxyethylidene-1,1-diphosphonic acid (**HEDP**) and ethylenediaminetetramethylenephosphonate (**EDTMP**) are shown in **Chart 3.1**



HEDP



EDTMP

Chart 3.1 The phosphonate ligands hydroxyethylidene-1,1-diphosphonic acid (HEDP) and ethylenediaminetetramethylenephosphonate (EDTMP) which are used in radiopharmaceuticals of ^{153}Sm and ^{186}Re.

- Radiation from radionuclides emitting **α-particles** extends only a few cell diameters (40 – 100 μm). These high-energy helium nuclei are highly cytotoxic and effective in the treatment of tumors with small diameters whilst causing little damage to normal tissues. Most attention has focussed on the α-emitters

^{211}**At** ($t_{1/2}$ 7.2 h), and ^{212}**Bi** ($t_{1/2}$ 1 h)

Radionuclides which emit a-particles are of potential interest in situations where very short range (0.1 mm) cytotoxic effects are sought. As an example irradiation of cancerous bone surfaces to control pain while not irradiating the blood forming bone marrow could be of interest.

Although accumulation of ^{211}At-labelled antibodies in tumors has been found, ^{211}At levels in normal tissue were a cause for concern suggesting that intravenous administration of ^{211}At agents may be problematic. Direct injection into tumors may offer a more viable approach.

Although there has been some research interest in the therapeutic use of a-emitters, this is a very challenging technology and obtaining regulatory approval for clinical use may not be easy.

- These radiocompounds localise in the area for treatment but cannot be used to treat conditions elsewhere in the body.

- Site specific localisation is required and would allow widely disseminated diseases to be treated.

How can we achieve this localisation?

Antibodies are a biological answer to providing specific binding to cellular targets.

Although some success has been met with solely antibody based therapy coupling of the targeting group with a radiometal could allow more efficient cell kill.

Recent advances in biology, biochemistry and chemistry mean that a lot more is known about cell surface receptors:

radionuclides could be targeted by binding to other molecules such as short peptides.

Choice of radioisotope

Properties of a radionuclide:

- nuclear emission properties
- half life
- decay characteristics
- cost
- availability

Particle emitting radionuclides (e.g. α- or β-particles) are effective for delivering localised cytotoxic doses of ionizing radiation.

The half life($t_{1/2}$)should be matched with the biolocalisation and clearance of the drug.

Radioisotopes often emit more than one type of radiation. High levels of gamma radiation can be harmful to the patient. Low levels could be utilised in simultaneous imaging (*c.f.* technetium imaging).

Yttrium-90 is a β-particle emitter has no gamma emission and has $t_{1/2}$ of 2.7 days and a max E_{β} of 2.27MeV.

Along with ^{186}Re and ^{67}Cu the yttrium isotope was identified as a lead β-emitting isotope for therapeutic use against small metastatic tumours.

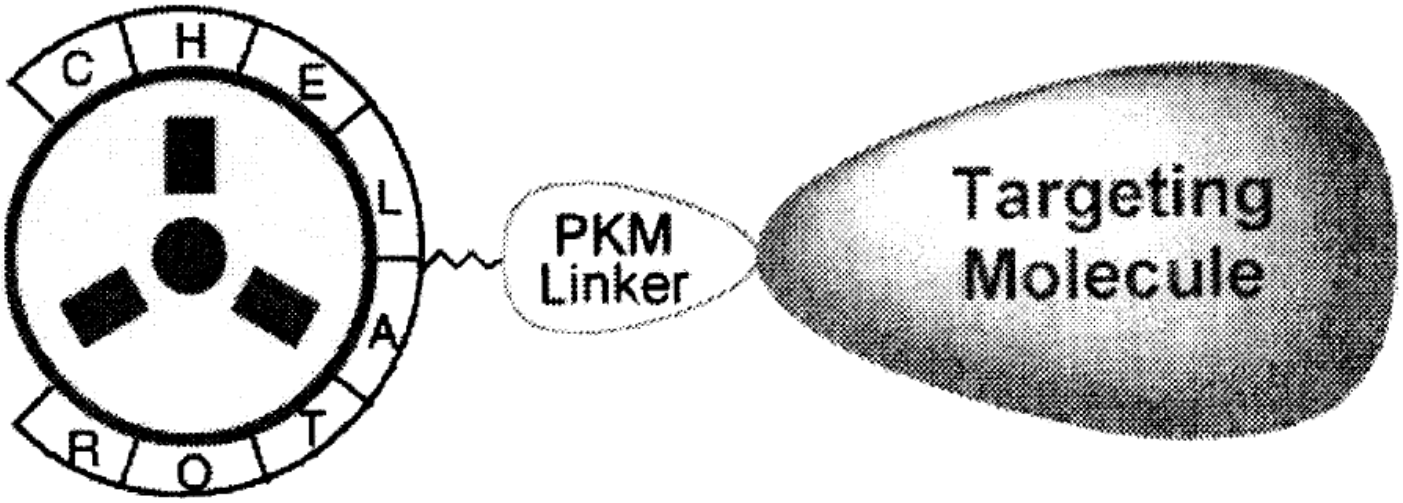
α-emitters would be useful against single cell targets e.g. blood borne maligancies.

Antibodies

What type of antibodies should be used?

Human antibodies can be retained for too long especially in the spleen.

This could result in a high radiation dose to other tissues.


CHELATOR
PKM
Linker
Targeting
Molecule

Newly licensed drug

Murine (mouse/rat) antibodies have been used in all clinical studies so far.

Zevalin- licensed (US) on 20th Feb 2002 to IDEC pharmaceuticals.

(www.zevalin.com)

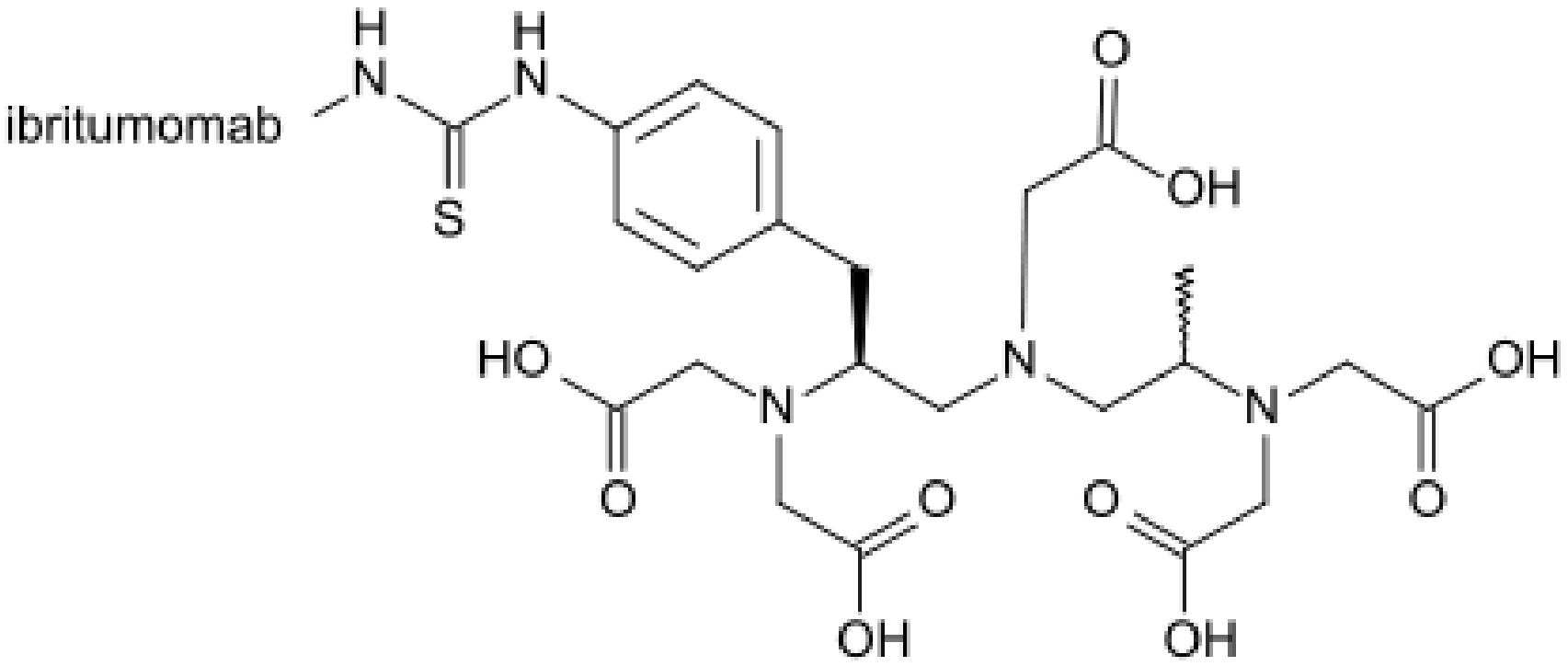
Zevalin

A licensing deal has been signed with Schering AG for the european market.

Utilised to combat B-cell non-hodgkins lymphoma. Anti- CD20 antibody utilised for targeting.

Finished phase III clinical trials and licensed in UK in 2004.

[The chelating ligand used to coordinate the metal is a DTPA based chelate (*c.f.* gadolinium compounds for MRI)]



...along with ^{90}Y or ^{111}In

- Dr Thomas Witzig, from the Mayo Clinic in Rochester, Minnesota, who helped conduct the study, said: "Unlike chemotherapy, which goes through the whole body, Zevalin carries the radiation payload directly to the tumour.

- "The drug radiates only about a five millimetre area around the tumour."
- He said because the drug was so much easier on the body than standard chemotherapy, the treatment could be given on an outpatient basis.
- Dr Witzig added: "There's no hair loss or prolonged fatigue, nausea or vomiting. The most significant side effect is a temporary decrease in blood count."

Peptide conjugated radionuclides

Internalised in the cell rather than bound to membrane receptors.

Theoretically could also be used for weaker emitters (e.g. alpha particles).

Again the majority of clinical trials are proceeding with yttrium chelates.

Table 4 *Examples of β-emitting radionuclides of potential interest for therapy applications*

Radionuclide	*Source*	*$T_{1/2}$ (days)*	*γ energy (keV)*	*γ yield (%)*	*β energy (MeV)*	*β yield (%)*	*Average β energy (MeV)*	*Average range (mm)*	*Maximum range (mm)*
^{47}Sc	Cyclotron	3.4	159	68	0.6	40			
^{64}Cu	Cyclotron	0.5	511	38	0.57	40			
^{67}Cu	Cyclotron	2.6	184	48	0.57	20			
			92	23					
^{89}Sr	Reactor	50.5			1.46	99	0.58	2.4	6.7
^{90}Y	^{90}Sr decay	2.7			2.27	100			
^{105}Rh	Reactor	1.5	319	19	0.25	20			
			306	5	0.57	75			
^{111}Ag	Cyclotron	7.5	342	6	1.05	93			
^{117m}Sn	Reactor	13.6	159	86	0.13	Conversion		0.22	0.29
					0.15	electrons		0.29	
^{149}Pm	Reactor	2.2	286	3	1.07	89			
^{153}Sm	Reactor	1.9	103	29	0.68	32	0.22	0.55	3.4
					0.7	48			
					0.81	20			
^{166}Ho	Reactor	1.1	810	6	1.76	47	0.67	3.3	8.6
					1.84	52			
^{177}Lu	Reactor	6.7	113	6	0.5	86	0.14	0.35	
			208	11					
^{186}Re	Reactor	3.8	137	9	1.08	71	0.33	1.05	4.7
^{188}Re	^{188}W/^{188}Re generator	0.71	155	10	2.12	100	0.64	3.8	11

a range of half lives and β-particle energies which affect the range of the radiation in tissue

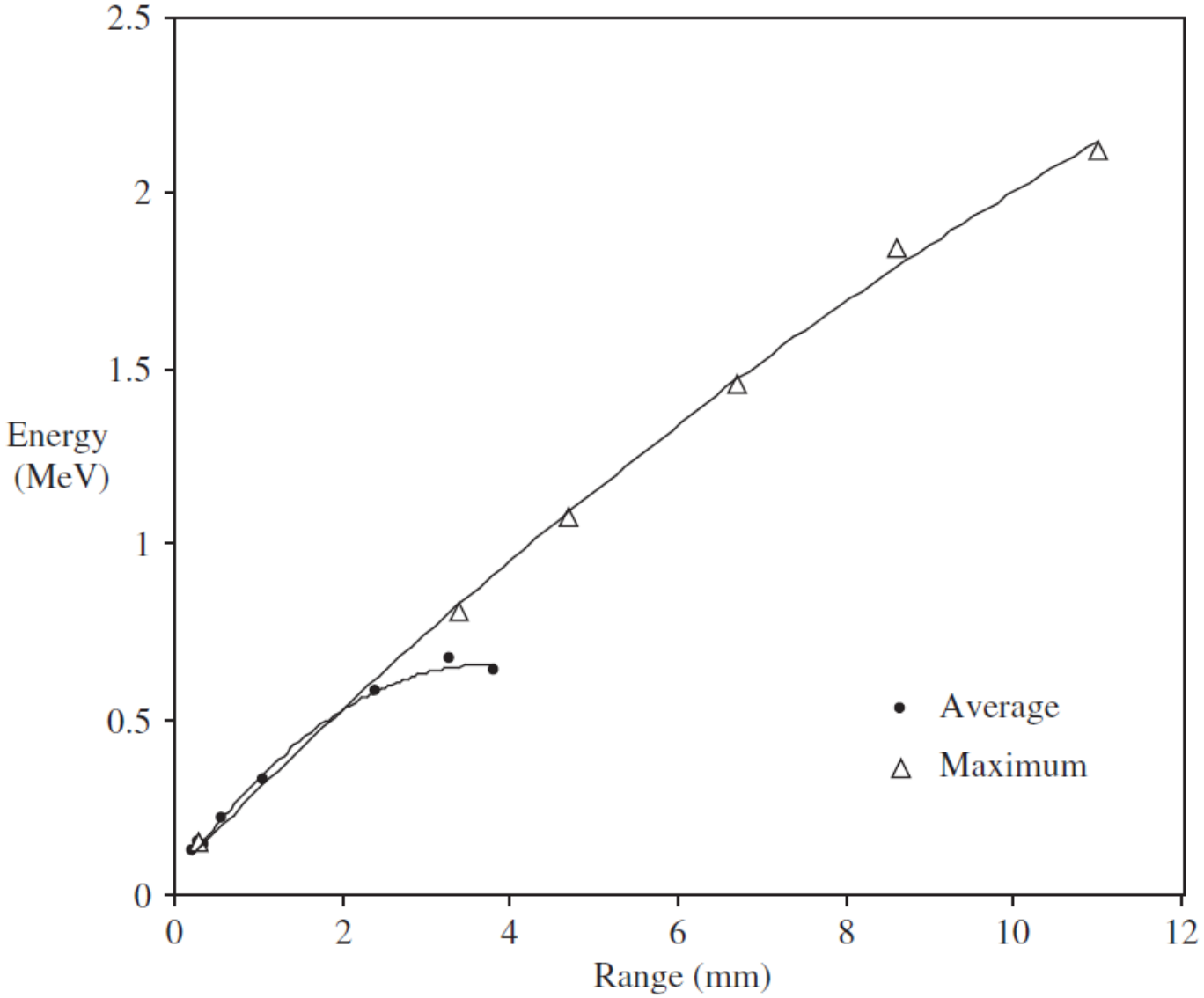


Figure 19 *A plot of range against energy for β-particles from some radionuclides used in therapy*
(Data taken from Table 4).

Each year in the USA alone the combined total number of cases of breast and prostate cancer exceeds 350,000 and, of these, up to about 80%will develop bone metastases. These bone lesions are difficult to manage and a major cause of pain associated with cancer !!!

Since bone contains phosphate as a major component, the non-metallic β-emitter ^{32}P, in the form of ^{32}P-phosphate, has been evaluated as a means of alleviating this pain. However, the 1.71 MeV energy of the β-particles emitted by ^{32}P makes them sufficiently penetrating to give unacceptably high doses to the blood forming bone marrow. The other major component of bone is Ca and the chemically related element Sr has a radionuclide, ^{89}Sr, with a β- emission energy of 1.46 MeV which is less penetrating. Like its smaller ionic radius counterpart, the Sr^{2+} ion has a high affinity for newly forming bone, as found in metastases, and is deposited at or near the bone surface...

It is thought that $^{89}Sr^{2+}$ is taken up in the hydroxyapatite matrix of bone through similar mechanisms to Ca^{2+} uptake, and through exchange with Ca^{2+} already present

The ^{89}Sr is manufactured as the chloride salt (which is soluble), and when dissolved in normal saline can be injected intravenously. Typically, cancer patients will be treated with a dose of 150 MBq. The patient needs to take precautions following this because their urine becomes contaminated with radioactivity, so they need to sit to urinate and double flush the toilet.

The beta particles travel about 3.5 mm in bone (energy 0.583 MeV) and 6.5 mm in tissue, so there is no requirement to isolate patients who have been treated except to say they should not have any one (especially young children) sitting in their laps for 10–40 days.

The variation in time results from the variable clearing time for ^{89}Sr which depends on renal function and the number of bony metastases. With a lot of bony metastases, the entire ^{89}Sr dose can be taken up into bone and so the radioactivity is retained to decay over a 50.5 day half-life. It takes about 10 half-lives or about 500 days for 99.9% of the radioactive strontium to decay. However, where there are few bony metastases, the large proportion of ^{89}Sr not taken up by the bone will be filtered by the kidney, so that the effective half-life (a combination of the physical and biological half-life) will be much shorter.