Radiobiology of Auger electron emitters and their potential for radionuclide therapy

Dr Pavel Lobachevsky
Laboratory of Radiation Biology
Joint Institute for Nuclear Research
Dubna, Russian Federation

THE XVI-th INTERNATIONAL SCHOOL-CONFERENCE

"THE ACTUAL PROBLEMS OF MICROWORLD PHYSICS"

Minsk, Belarus, 24 – 31 August, 2025

Radiobiology of Auger Emitters - Topics

1. Auger electron emitters – a special class of radionuclides

(physics of Auger effect and physical properties of Auger emitters)

2. Molecular aspects of Auger decay radiobiology

(DNA damage)

3. Auger emitters potential for radionuclide therapy

(dual targeting strategy)

Radiobiology of Auger Emitters - Topics

1. Auger electron emitters – a special class of radionuclides

    (physics of Auger effect and physical properties of Auger emitters)

2. Molecular aspects of Auger decay radiobiology

    (DNA damage)

3. Auger emitters potential for radionuclide therapy

    (dual targeting strategy)

Physics of Auger effect

Auger emitters – a special class of radionuclides

- each decay event is unique (in contrast to α-, β- and γ-emitters
- nuclear and atomic processes are involved

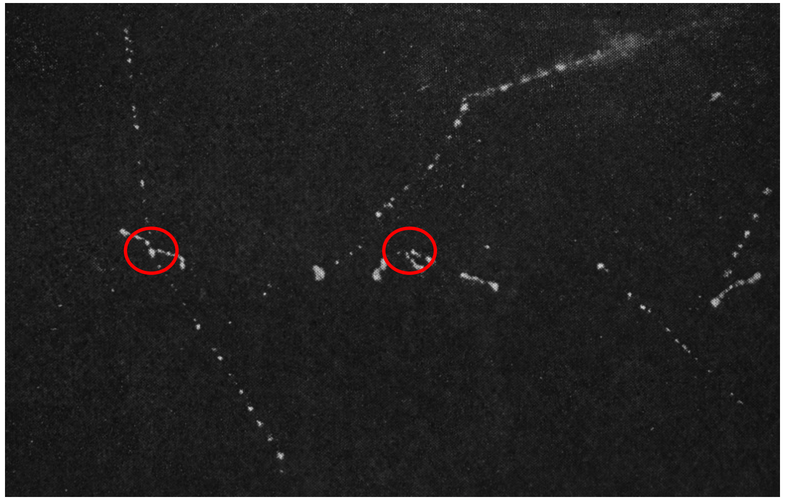
Auger effect – named after Pierre Auger

Physics of Auger effect

Auger emitters – a special class of radionuclides

- **each decay event is unique (in contrast to α-, β- and γ-emitters**
- **nuclear and atomic processes are involved**

Auger effect – named after Pierre Auger



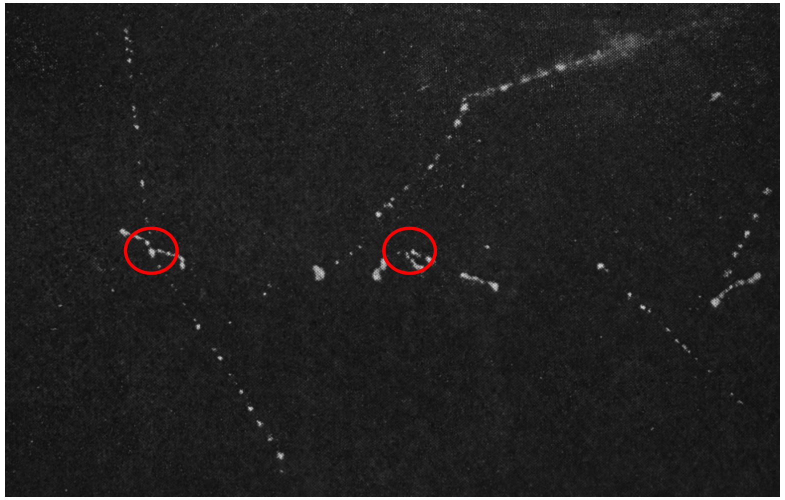
Auger P. *Sur l'effet photoélectrique composé,* 1925.

Physics of Auger effect

Auger emitters – a special class of radionuclides

- **each decay event is unique (in contrast to α-, β- and γ-emitters**
- **nuclear and atomic processes are involved**

Auger effect – named after Pierre Auger



Auger P. *Sur l'effet photoélectrique composé,* 1925.

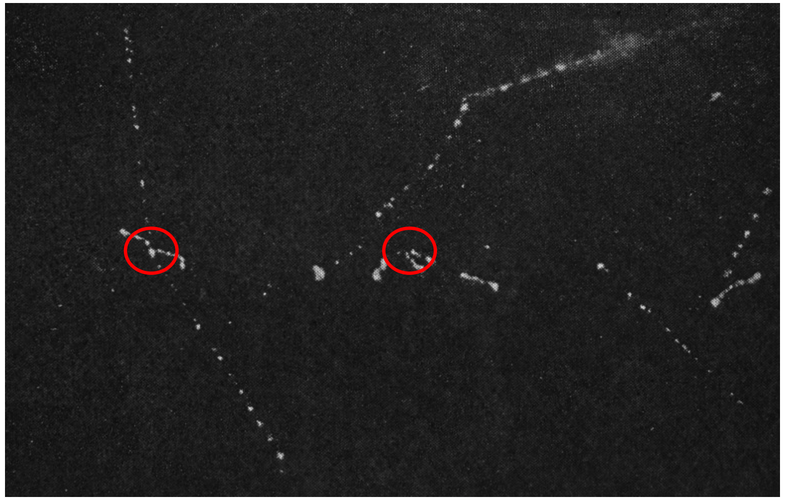
- **Study of photo effect in gaseous phase (Wilson cloud chamber)**
- **Multiple tracks of ionising particles originating from the same point – Auger effect**
- **Pierre Auger interpretation – simultaneous emission of several electrons from ionised atom**

Physics of Auger effect

Auger emitters – a special class of radionuclides

- each decay event is unique (in contrast to α-, β- and γ-emitters
- nuclear and atomic processes are involved

Auger effect – named after Pierre Auger

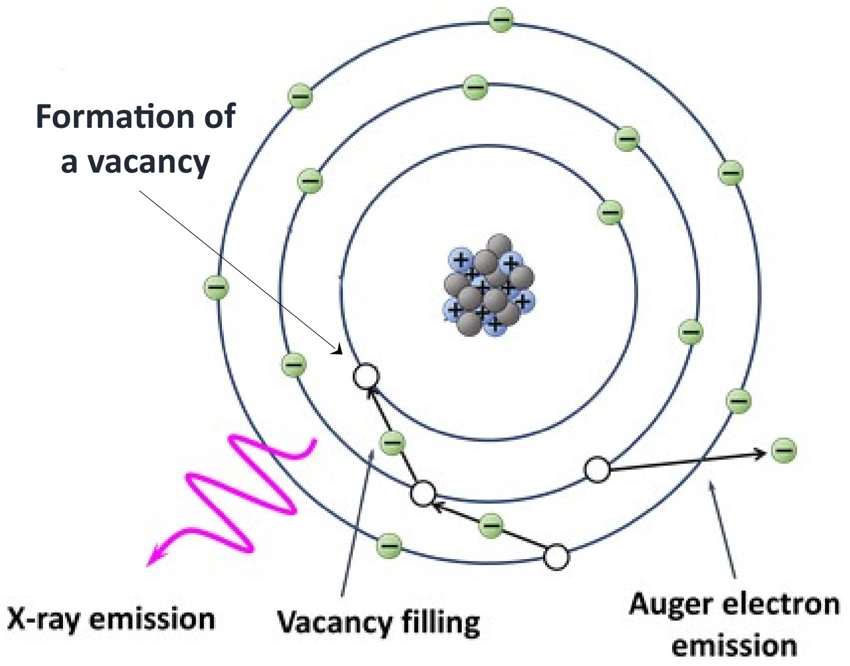


Auger P. *Sur l'effet photoélectrique composé,*1925.

Main feature of Auger effect – emission of multiple electrons (Auger electrons) initiated by a single atomic event

- Study of photo effect in gaseous phase (Wilson cloud chamber)
- Multiple tracks of ionising particles originating from the same point – Auger effect
- Pierre Auger interpretation – simultaneous emission of several electrons from ionised atom

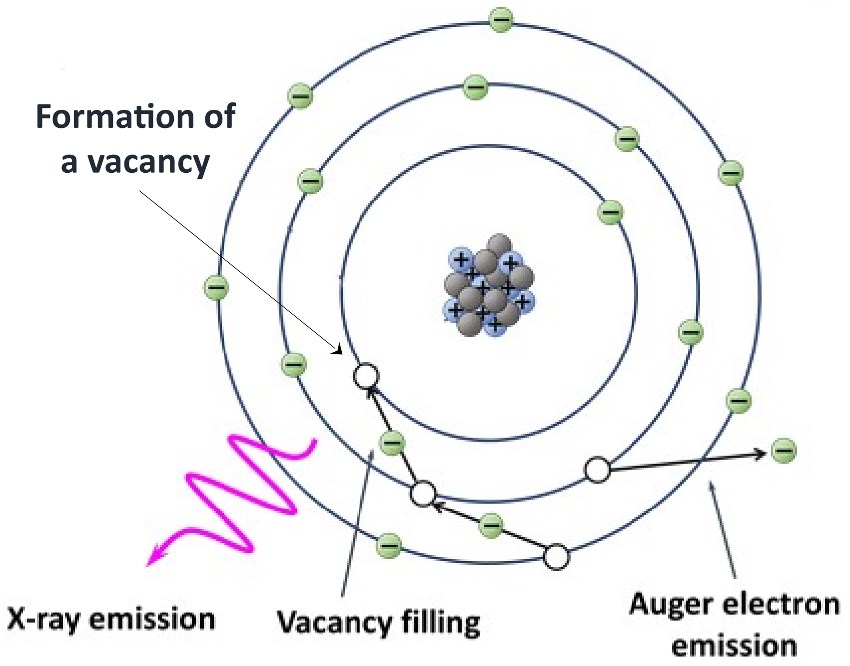
Physics of Auger effect



Auger effect involves:

- Formation of a vacancy in an inner atomic shell
- Filling of this vacancy by another electron; accompanied by
  - formation of a new vacancy, with the transition energy released as:
  - X-ray photon or
  - emission of another electron with formation of one more vacancy
- The process of vacancy filling and electron emission (Auger cascade) continues until
  - all vacancies reach the outer shell (in vacuum) and
  - are filled with electrons from neighbouring atoms (in medium)

Physics of Auger effect



Auger effect involves:

- **Formation of a vacancy in an inner atomic shell**
- **Filling of this vacancy by another electron; accompanied by**
  - **- formation of a new vacancy, with the transition energy released as:**
  - **- X-ray photon or**
  - **- emission of another electron with formation of one more vacancy**
- **The process of vacancy filling and electron emission (Auger cascade) continues until**
  - **- all vacancies reach the outer shell (in vacuum) and**
  - **- are filled with electrons from neighbouring atoms (in medium)**

In summary, Auger effect is:

- **emission from an atom of multiple electrons (Auger electrons) that is**
- **initiated by an inner shell vacancy**

Physics of Auger effect

Inner shell vacancy formation mechanisms:

- photo effect (in Pierre Auger experiments)
- electron capture
- internal conversion

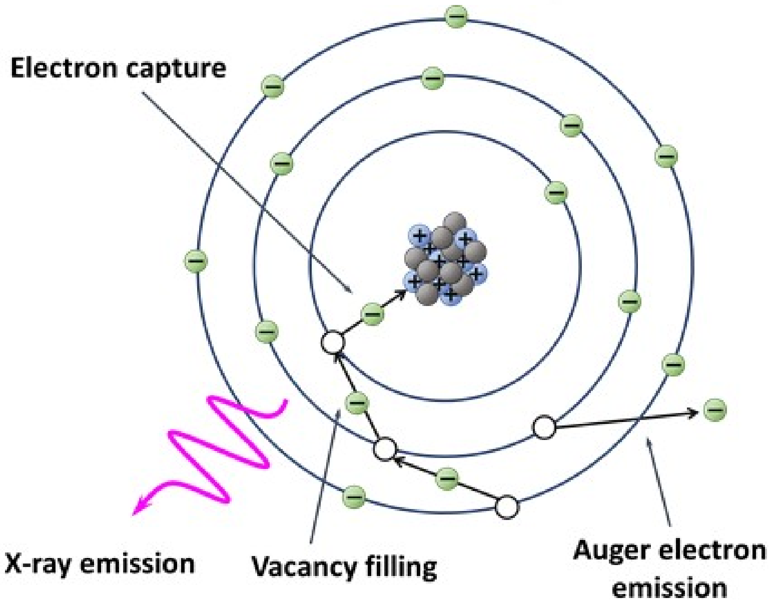
Physics of Auger effect

Inner shell vacancy formation mechanisms:

- photo effect (in Pierre Auger experiments)
- electron capture
- internal conversion

Electron capture (e-capture, K-capture) – a type of radioactive decay (β-decay)

- capture by a nucleus of an electron from inner shell
- reaction $p^+ + e^- \rightarrow n + \nu$ (a type of β-decay)
- the charge of the nucleus decreases by 1, Z -> Z - 1



Physics of Auger effect

Inner shell vacancy formation mechanisms:

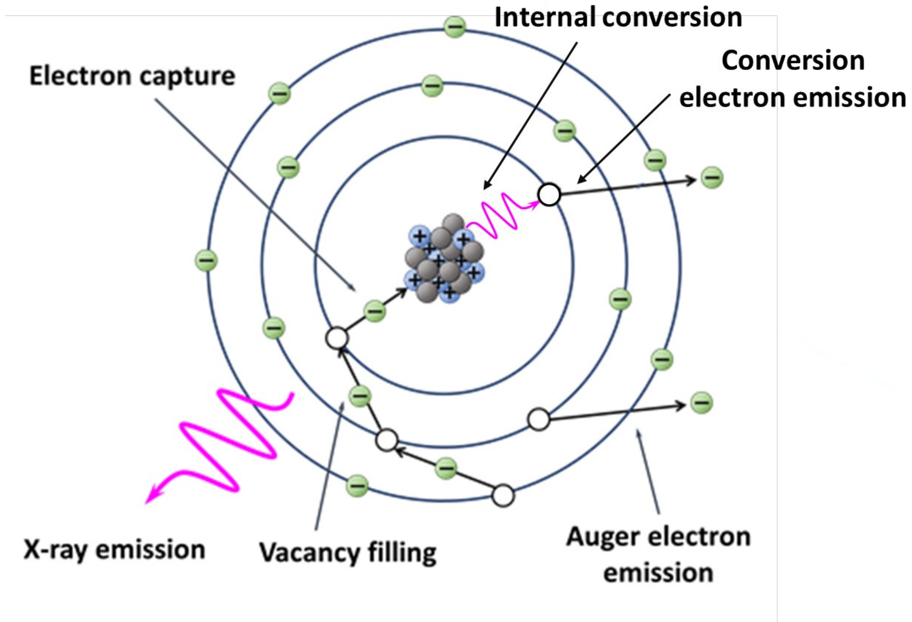
- photo effect (in Pierre Auger experiments)
- electron capture
- internal conversion

Electron capture (e-capture, K-capture) – a type of radioactive decay (β-decay)

- capture by a nucleus of an electron from inner shell
- reaction $p^+ + e^- \to n + \nu$ (a type of β-decay)
- the charge of the nucleus decreases by 1, Z -> Z - 1

Internal conversion – a type of radioactive decay

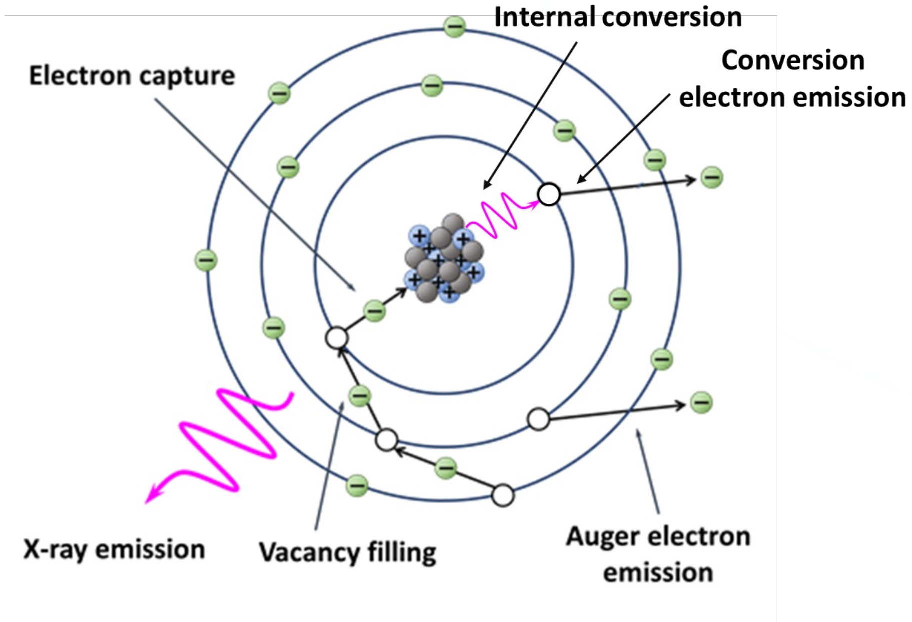
- relaxation of an excited nucleus by transferring energy to the inner shell electron with subsequent emission of this electron



Physics of Auger effect

Inner shell vacancy formation mechanisms:

- photo effect (in Pierre Auger experiments)
- electron capture
- internal conversion



Electron capture (e-capture, K-capture) – a type of radioactive decay (β-decay)

- capture by a nucleus of an electron from inner shell
- reaction $p^+ + e^- \rightarrow n + \nu$ (a type of β-decay)
- the charge of the nucleus decreases by 1, Z -> Z - 1

Internal conversion – a type of radioactive decay

- relaxation of an excited nucleus by transferring energy to the inner shell electron with subsequent emission of this electron

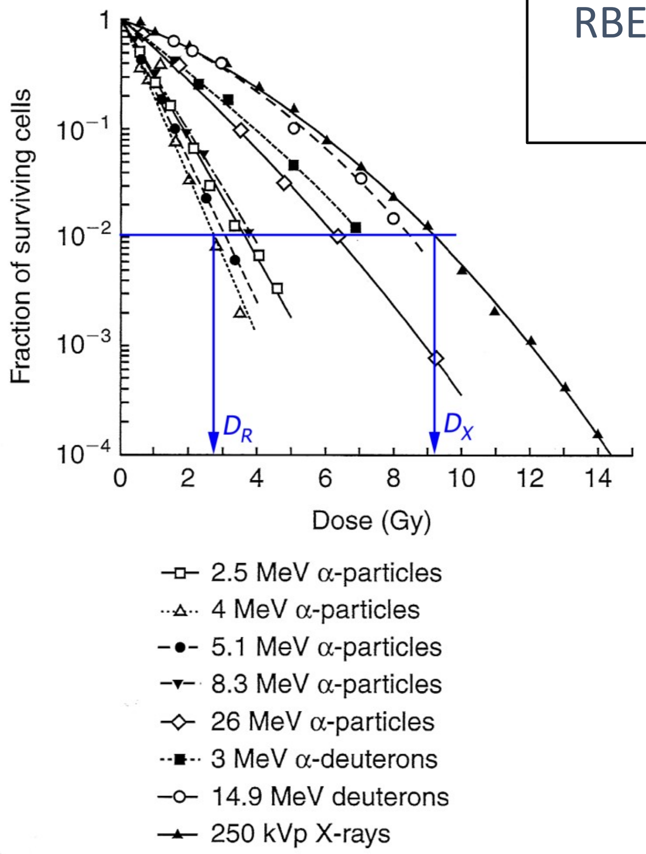
- Photo effect and formation of a vacancy can occur in any atom (non-radioactive) subjected to photon (X-ray) irradiation
- Electron Capture and Internal Conversion – types of radioactive decay –> properties of a range of radionuclides
- These radionuclides – Auger electron emitters or Auger emitters

Radiobiological Properties of Radionuclides for Nuclear Medicine

Properties of radionuclides and their relevance for radionuclide endoradiotherapy

Property/Type	β-emitters	α-emitters	Auger emitters
Energy of ionizing particles	0.1 – 1 MeV	A few MeV	?
LET (Linear Energy Transfer)	Low (≈1 keV/μm)	High (80 -100 keV/μm)	?
Range of ionizing particles/Damage localisation	Order of mm/tissue size	Order of 10 μm /cell size	?
RBE (Relative Biological Effectiveness)	Low (~1)	High (~3)	High
Availability/Production	Relatively simple	Complex	Relatively simple
Conjugation chemistry	Covalent binding/chelating compounds		

Dose – effect curves and biological effectiveness of radiation



Data from Barendsen, 1968

RBE – the ratio of doses of the standard and tested radiation that result in the same level of biological effect

$$RBE = \frac{D_x}{D_R}$$

D_X – dose of the standard radiation (x-rays)

D_R – dose of the tested radiation

For 4 MeV a-particles RBE = 3.2

- What quantitative property of ionising radiation determines its RBE and therefore allows to predict biological response?

- Ionisation density

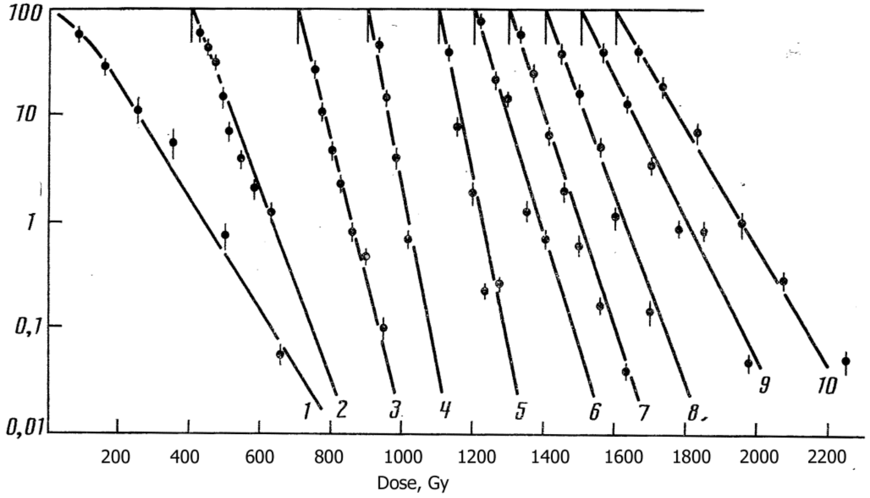
  X-rays – sparsely ionising radiation

  a-particles – densely ionising radiation

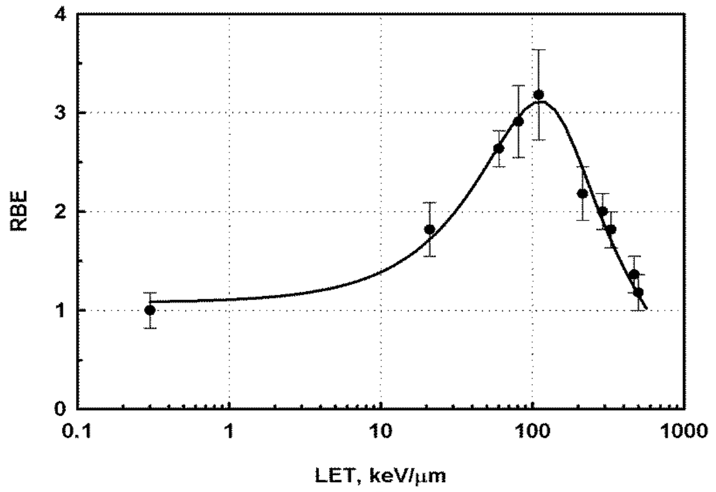
Introduction of LET – Linear Energy Transfer (a measure of ionisation density)

RBE-LET relationship

How Relative Biological Effectiveness depends on LET of radiation?



1 - ^{137}Cs γ-rays, 0.3 keV/μm; 2, 3, 4 - ^{4}He-ions, 21, 60, 81 keV/μm;
5 - α-particles, 110 keV/μm; 6, 7, 8, 9, 10 - ^{12}C-ions, 214, 290, 330, 470, 500 keV/μm.
Saccharomyces cerevisiae strain XS800 (diploid)



Data from P. Lobachevsky et al, 1988<

obtained at U200, LNR JINR

$$RBE = \frac{D_x}{D_R}$$

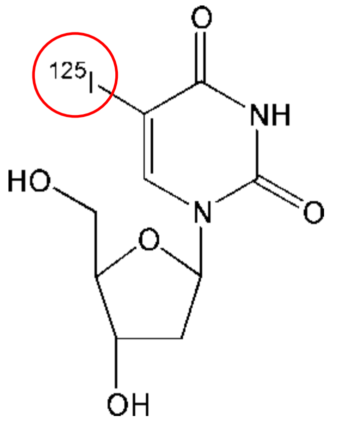
RBE-LET relationship is complex:

- Increasing RBE in the range up to ~ 100 keV/μm
- Maximum at ~ 100 keV/μm
- Fast decrease at LET above ~ 100 keV/μm

Biological consequences of Auger decay - DNA damage

Early radiobiological experiments with ^{125}I

- model – bacteriophage T1 and T4
- end points – survival and induction of single strand and double strand DNA breaks (SSB and DSB)
- radionuclide carrier - [^{125}I] iodo-deoxyuridine (5-^{125}IUdR), thymidine analogue, DNA synthesis precursor
- covalent bond of Auger emitter with DNA

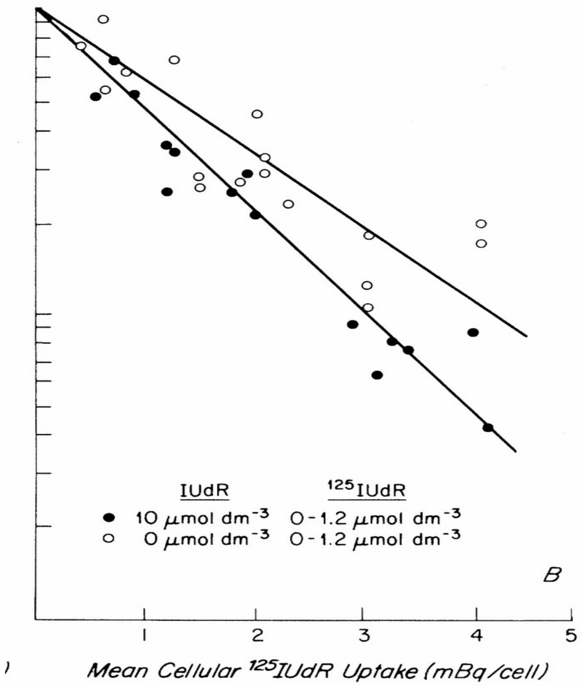


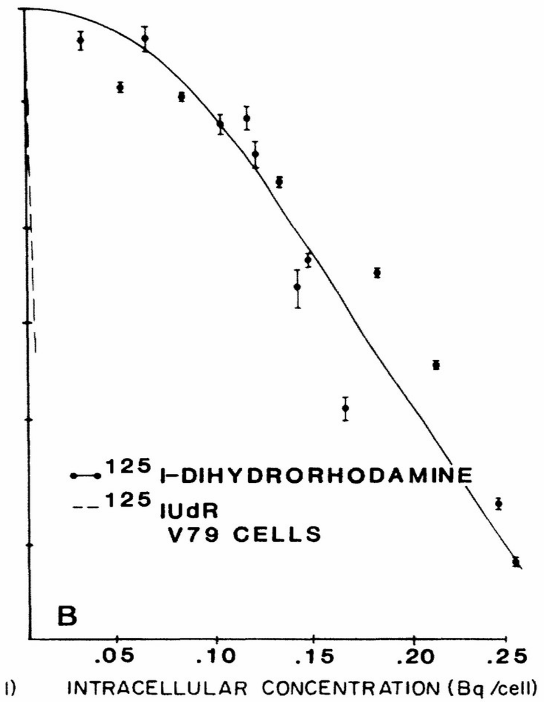
Major conclusion

- decay of ^{125}I, covalently incorporated into DNA results in formation of DNA **DSB with a probability close to 1**
- one DNA DSB induced by ^{125}I-decay is a lethal event for bacteriophage

Schmidt & Hotz, IJRB, 1973
Krisch & Ley, IJRB, 1974
Krisch & Sauri, IJRB, 1975

Radiation biology of Auger decay – cellular effects





Localisation of Auger emitter relative to DNA is of critical importance

Experiments with mammalian cells *(Kassis & Adelstein, Rad Res, 1987)*

Effect of ^{125}I decay: extracellular, in cytoplasm, in cell nucleus

Decay of DNA incorporated ^{125}I ~ 6 fold more efficient that decay of ^{125}I in cytoplasm (based on absorbed dose)

Carrier of ^{125}I	Localisation	D_{37} mBq/cell	D_{37} Gy
Na^{125}I	Extracellular	-	-
[^{125}I]-iodo-dihydrorhodamine (^{125}I-DR)	Cytoplasm	109	4.62
[^{125}I]-iodo-deoxyuridine (5-^{125}IUdR)	Nucleus (DNA)	1.30	0.80

Radiobiological Properties of Radionuclides for Nuclear Medicine

Properties of radionuclides and their relevance for radionuclide endoradiotherapy

Property/Type	β-emitters	α-emitters	Auger emitters
Energy of ionizing particles	0.1 – 1 MeV	A few MeV	?
LET (Linear Energy Transfer)	Low (≈1 keV/μm)	High (80 -100 keV/μm)	?
Range of ionizing particles/Damage localisation	Order of mm/tissue size	Order of 10 μm /cell size	?
RBE (Relative Biological Effectiveness)	Low (~1)	High (~3)	High
Availability/Production	Relatively simple	Complex	Relatively simple
Conjugation chemistry	Covalent binding/chelating compounds		

LET and RBE of Auger electrons – is LET of Auger electrons high?

- It is quite common to attribute high radiobiological efficiency (RBE) of Auger decay to high LET of Auger electrons
- LET of Auger electrons cited as 4 – 26 keV/μm, which is considered as high LET

  Citation: "Both α-particle and Auger electron emitters are considered as high LET radiation qualities; with an LET of 80–100 keV/μm for α-particle emitters and an LET of 4–26 keV/μm for Auger electron emitters."

  Fourie H et al. Estimating the Relative Biological Effectiveness of Auger Electron 123 Emitter I in Human Lymphocytes. Front Phys. 2020;8:567732.

- **Citation points to:**

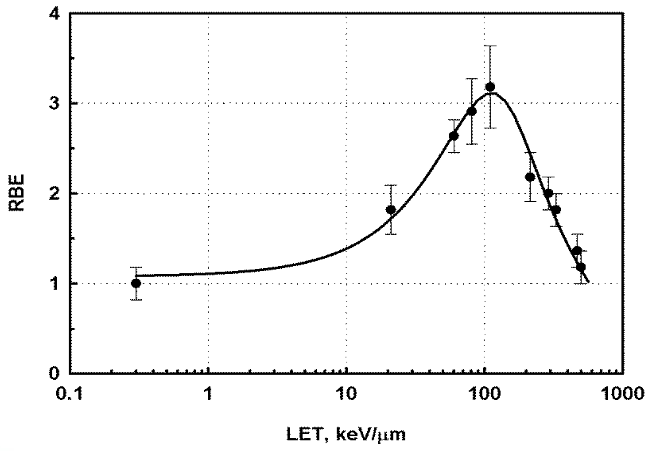
Kassis AI. Molecular and cellular radiobiological effects of Auger emitting radionuclides. Radiat Prot Dosimetry. 2011;143(2–4):241–247

which in turns makes a reference to:

Kassis AI. The Amazing World of Auger Electrons. Int J Radiat Biol. 2004;8(11–12):789–803

which finally refers to:

Cole A. Absorption of 20-eV to 50,000-eV electron beams in air and plastic. Radiat Res. 1969;38:7–33



LET and RBE of Auger electrons – is LET of Auger electrons high?

- It is quite common to attribute high radiobiological efficiency (RBE) of Auger decay to high LET of Auger electrons
- LET of Auger electrons cited as 4 – 26 keV/µm, which is considered as high LET

  Citation: "Both α-particle and Auger electron emitters are considered as high LET radiation qualities; with an LET of 80–100 keV/µm for α-particle emitters and an LET of 4–26 keV/µm for Auger electron emitters."

  Fourie H et al. Estimating the Relative Biological Effectiveness of Auger Electron 123 Emitter I in Human Lymphocytes. Front Phys. 2020;8:567732.

- **Citation points to:**

Kassis AI. Molecular and cellular radiobiological effects of Auger emitting radionuclides. Radiat Prot Dosimetry. 2011;143(2–4):241–247

which in turns makes a reference to:

Kassis AI. The Amazing World of Auger Electrons. Int J Radiat Biol. 2004;8(11–12):789–803

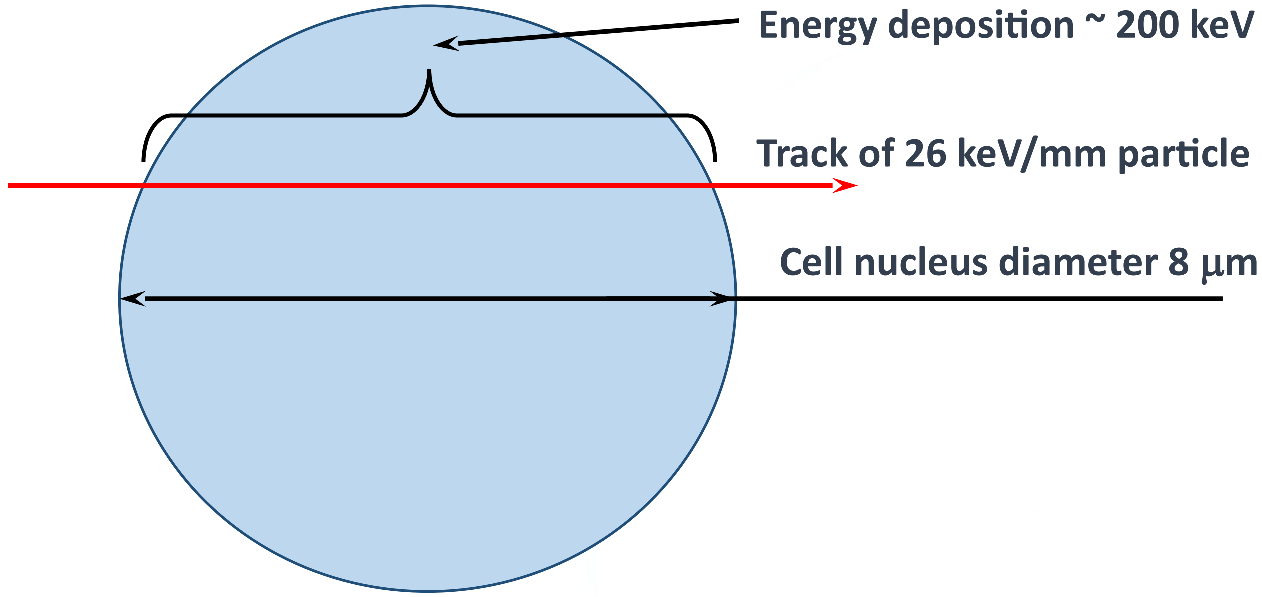
which finally refers to:

Cole A. Absorption of 20-eV to 50,000-eV electron beams in air and plastic. Radiat Res. 1969;38:7–33

Cole A. Radiat Res. 1969;38:7–33

Electron energy, eV	Range, µm(nm)	dE/dx, keV/µm
20	0.00096 (0.96)	11
40	0.0026 (2.6)	14
60	0.0038 (3.8)	26
100	0.0054 (5.4)	26
200	0.0094 (9.4)	23
400	0.019 (19)	17
600	0.032 (32)	14,5

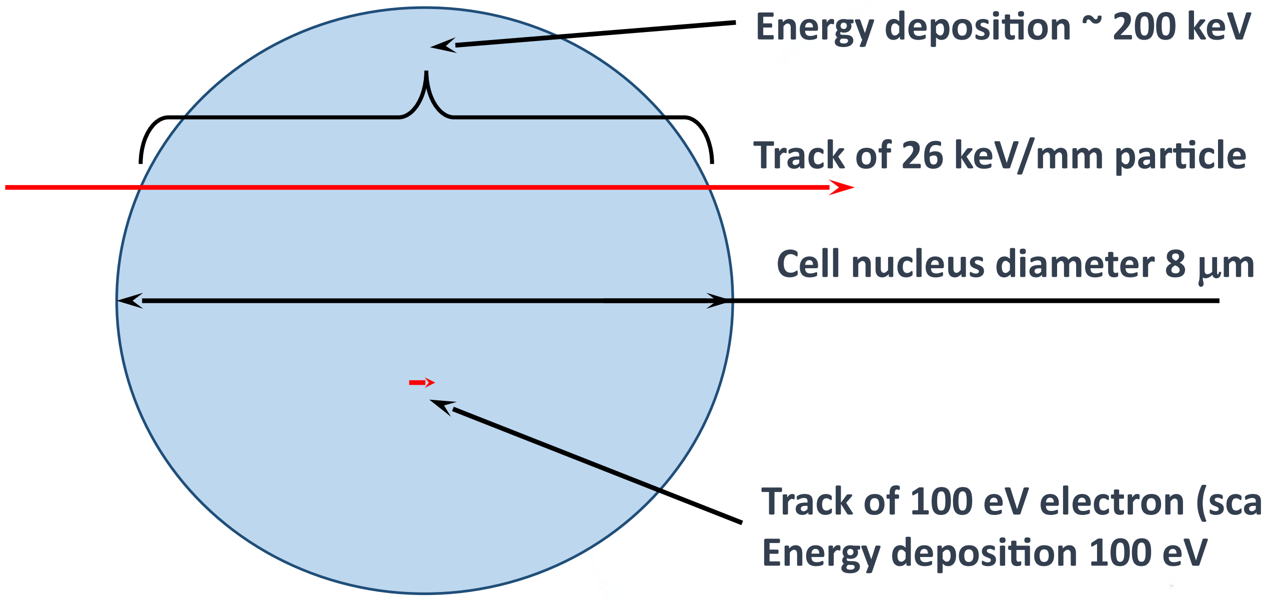
LET and RBE of Auger electrons – is LET of Auger electrons high?



Cole A. Absorption of 20-eV to 50,000-eV electron beams in air and plastic. Radiat Res. 1969;38:7–33

Electron energy, eV	Range, µm(nm)	dE/dx, keV/µm
20	0.00096 (0.96)	11
40	0.0026 (2.6)	14
60	0.0038 (3.8)	26
100	0.0054 (5.4)	26
200	0.0094 (9.4)	23
400	0.019 (19)	17
600	0.032 (32)	14,5

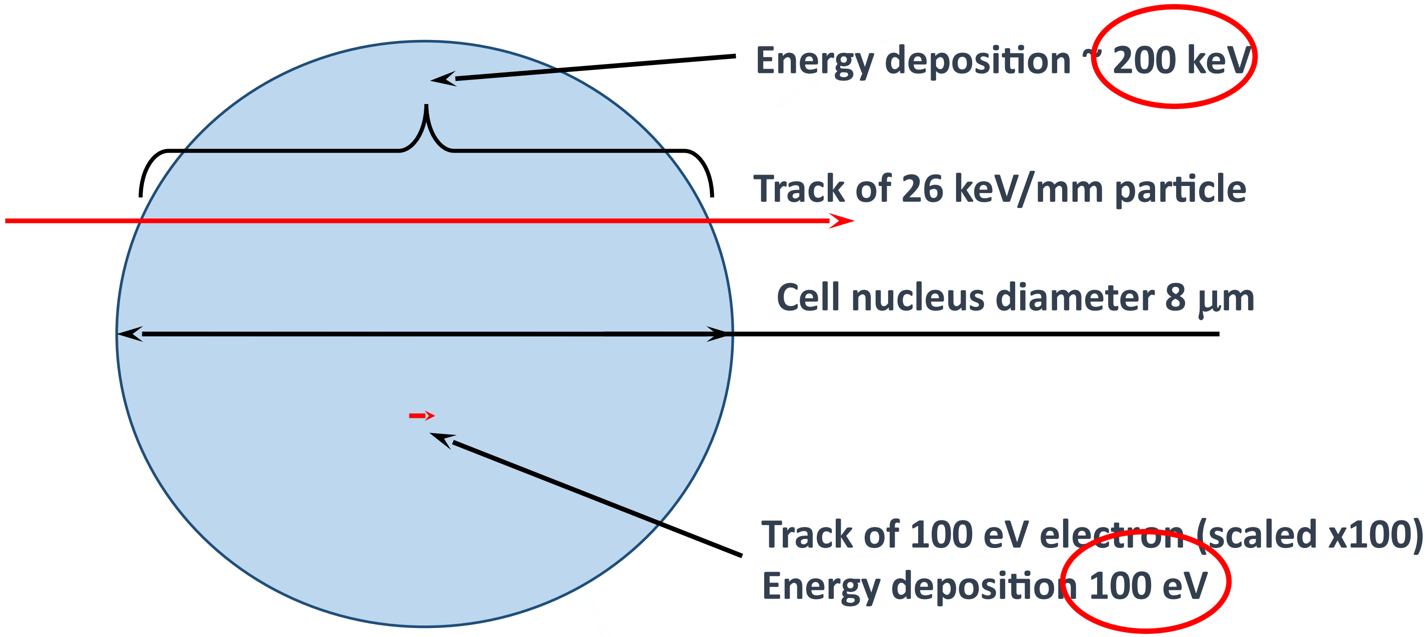
LET and RBE of Auger electrons – is LET of Auger electrons high?

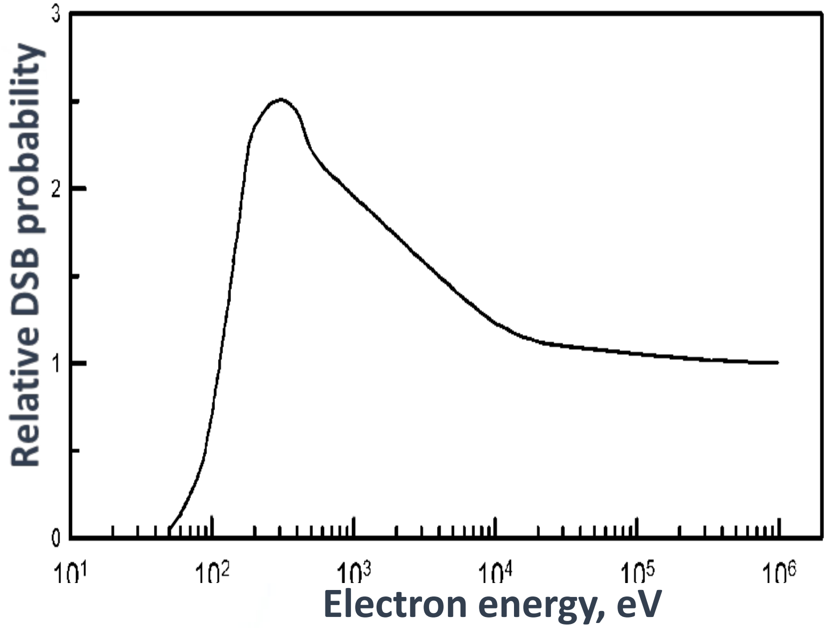


Cole A. Absorption of 20-eV to 50,000-eV electron beams in air and plastic. Radiat Res. 1969;38:7–33

Electron energy, eV	Range, μm(nm)	dE/dx, keV/μm
20	0.00096 (0.96)	11
40	0.0026 (2.6)	14
60	0.0038 (3.8)	26
100	0.0054 (5.4)	26
200	0.0094 (9.4)	23
400	0.019 (19)	17
600	0.032 (32)	14,5

LET and RBE of Auger electrons – is LET of Auger electrons high?





Michalik & Frankenberg, 1994

- Are these two events biologically equivalent? - No
- The concept of LET is not applicable to Auger electrons (in radiobiological context)
- LET is a macroscopic (statistical average) value
- Microscopic energy deposition analysis is required
- High local energy deposition – result of simultaneous emission of multiple electrons

Auger emitters – biologically relevant properties

Important physical properties of Auger emitters for radiation biology:

- **the energy and range of Auger electrons**

- **the number of electrons emitted per decay**

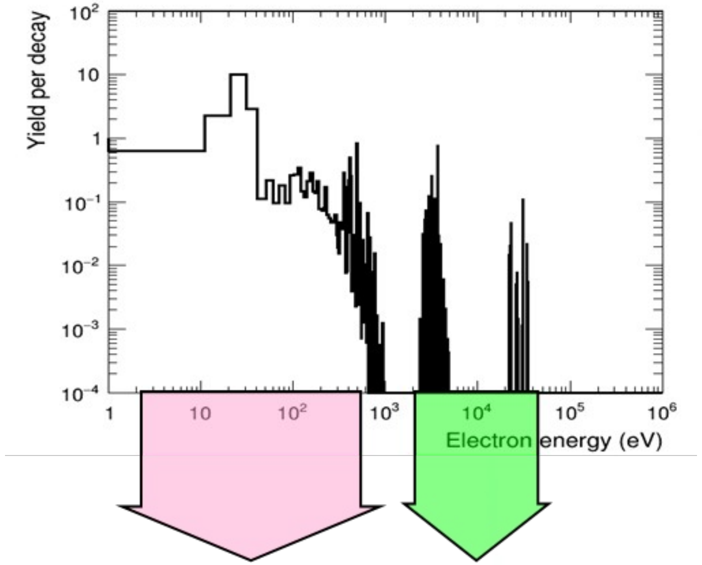
Auger emitters – biologically relevant properties

Important physical properties of Auger emitters for radiation biology:

- the energy and range of Auger electrons

- the number of electrons emitted per decay

Auger emitters – energy and range of Auger electrons (^{125}I)

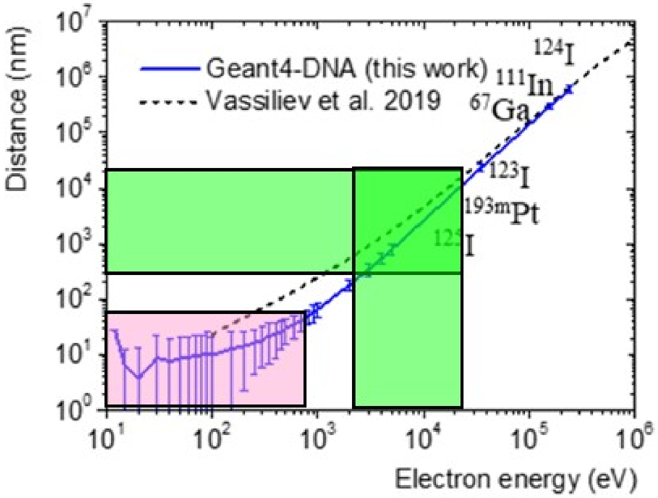


0.02 - 0.9 keV

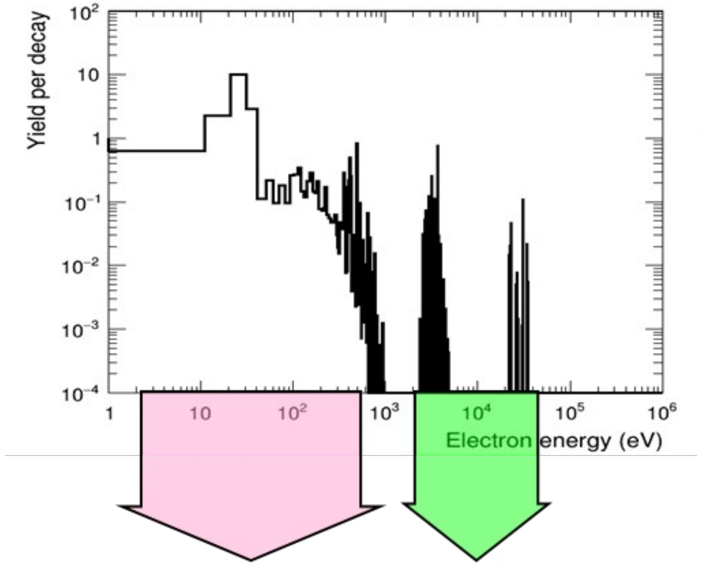
1 – 50 nm

2.5 - 35 keV

0.2 - 20 µm



Auger emitters – energy and range of Auger electrons (^{125}I)

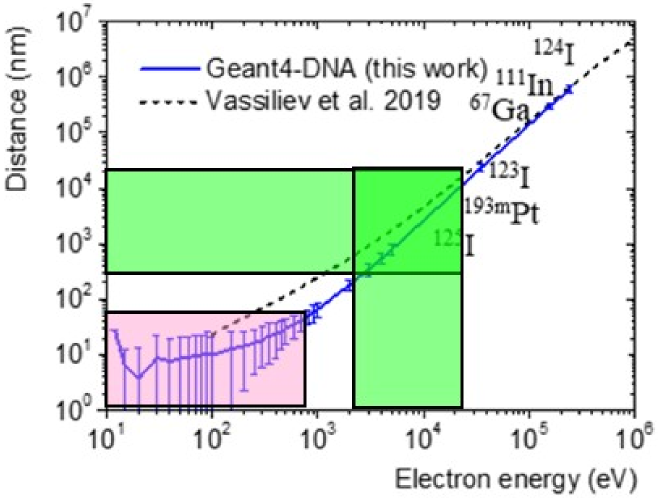


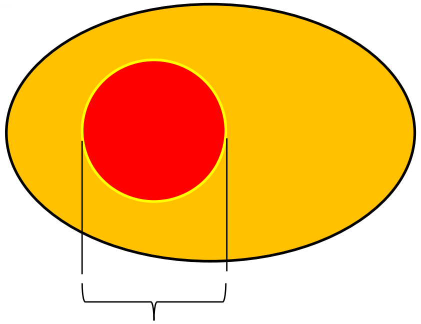
0.02 - 0.9 keV

1 – 50 nm

2.5 - 35 keV

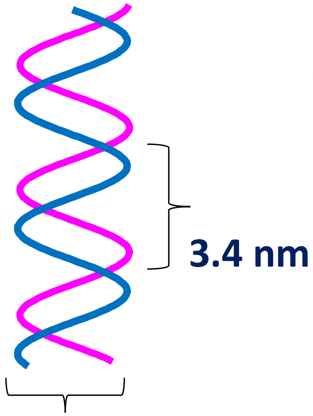
0.2 - 20 μm





Cell nucleus

diameter 4 – 8 μm

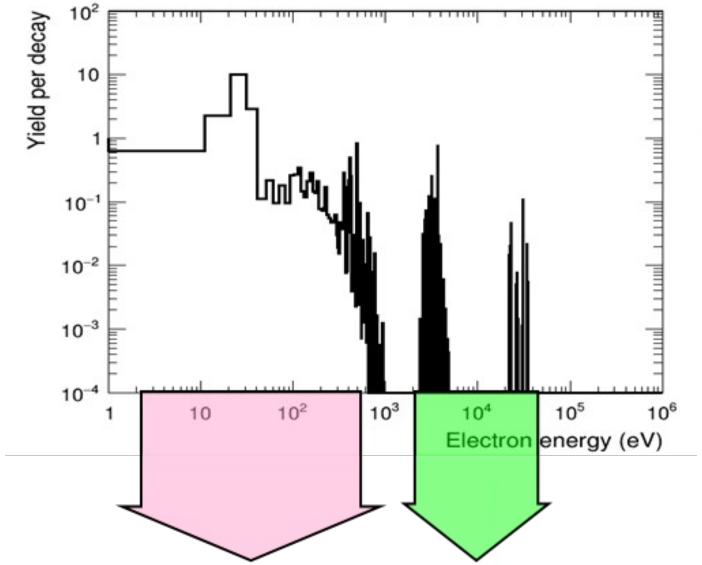


2 nm – DNA double helix diameter

Range of Auger electrons:

- for energies < 1 keV – up to 50 nm, dimensions of DNA molecule (2 nm – DNA double helix diameter, 0.3 nm – inter-base distance)
- for energies < 30 keV – up to 20 μm, nucleus size (8 μm – nucleus diameter in mammalian cells)

Auger emitters – energy and range of Auger electrons (^{125}I)

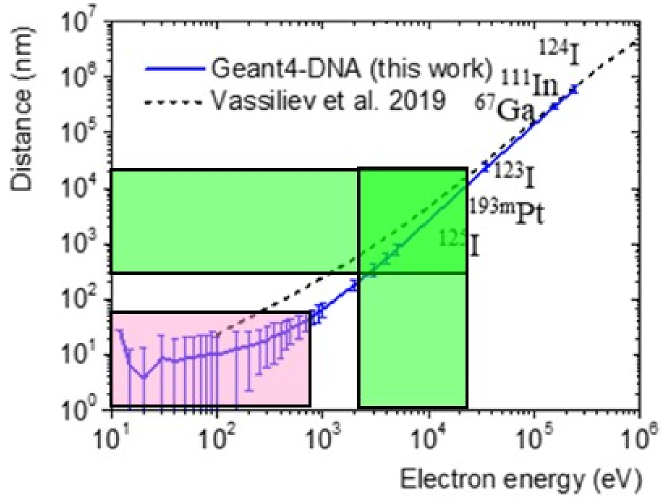


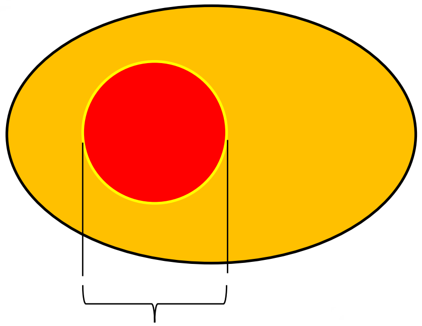
0.02 - 0.9 keV

1 – 50 nm

2.5 - 35 keV

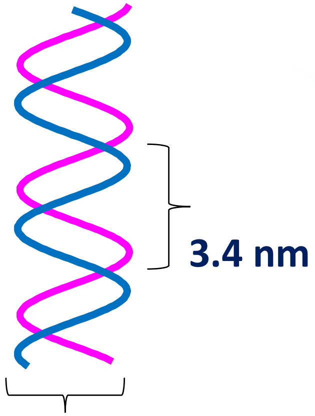
0.2 - 20 μm





Cell nucleus

diameter 4 – 8 μm



2 nm – DNA double helix diameter

Range of Auger electrons:

- for energies < 1 keV – up to 50 nm, dimensions of DNA molecule (2 nm – DNA double helix diameter, 0.3 nm – inter-base distance)
- for energies < 30 keV – up to 20 μm, nucleus size (8 μm – nucleus diameter in mammalian cells)

Number of Auger electrons by ^{125}I decay – 25 on average

Critical consequences of Auger decay for radiation biology:

- the range of Auger electrons is comparable to the size of cell nucleus
- high local deposition of absorbed energy from multiple electrons (within the size of DNA and cell nucleus)

Auger emitters – biologically relevant properties

Important physical properties of Auger emitters for radiation biology:

- the energy and range of Auger electrons

- **the number of electrons emitted per decay**

Auger emitters – biologically relevant properties

Nuclide	Total Decay Energy keV	Half-Life Time	Auger electrons	Conversion electron	X-Rays	γ-Rays
			Yield/Decay (Energy, keV)	Yield/Decay (Energy, keV)	Yield/Decay (Energy, keV)	Yield/Decay (Energy, keV)
^{67}Ga	201.6	3.26 d	4.7 (6.26)	0.32 (28.1)	0.57 (4.9)	0.88 (162.3)
^{111}In	419.2	2.80 d	14.7 (6.75)	0.16 (26.0)	0.89 (20.0)	1.84 (366.5)
^{99m}Tc	142.6	6.01 h	4.0 (0.90)	1.1 (15.4)	0.079 (1.37)	0.89 (125.0)
^{123}I	200.4	13.2 h	14.9 (7.4)	0.15 (20.2)	0.93 (24.1)	0.87 (148.6)
^{124}I*		4.18 d	8.4 (4.74)	0.0035 ()	0.65 (17.1)	0.92 (863)
^{125}I	61.4	60.4 d	24.9 (12.2)	0.94 (7.2)	1.53 (39.7)	0.065 (2.3)

Howell RW, *Medical Physics*, 1992
Pomplun E, 1992
Humm JL, 1994
Lee BQ, IJRB, 2015

* Positron emission yield 0.23

Radiobiology of Auger Emitters - Topics

1. Auger electron emitters – a special class of radionuclides

(physics of Auger effect and physical properties of Auger emitters)

2. Molecular aspects of Auger decay radiobiology

(DNA damage)

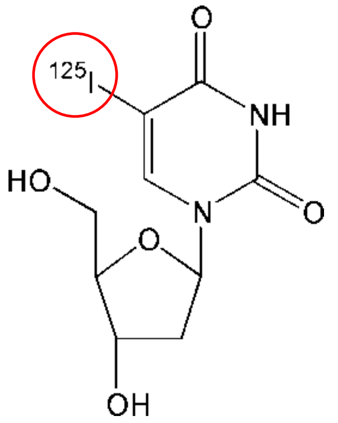
3. Auger emitters potential for radionuclide therapy

(dual targeting strategy)

Biological consequences of Auger decay - DNA damage

Early radiobiological experiments with ^{125}I

- model – bacteriophage T1 and T4
- end points – survival and induction of single strand and double strand DNA breaks (SSB and DSB)
- radionuclide carrier - [^{125}I] iodo-deoxyuridine (5-^{125}IUdR), thymidine analogue, DNA synthesis precursor
- covalent bond of Auger emitter with DNA



Major conclusion

- decay of ^{125}I, covalently incorporated into DNA results in formation of DNA **DSB with a probability close to 1**
- one DNA DSB induced by ^{125}I-decay is a lethal event for bacteriophage

Schmidt & Hotz, *IJRB*, 1973
Krisch & Ley, *IJRB*, 1974
Krisch & Sauri, IJRB, 1975

Biological consequences of Auger decay - DNA damage

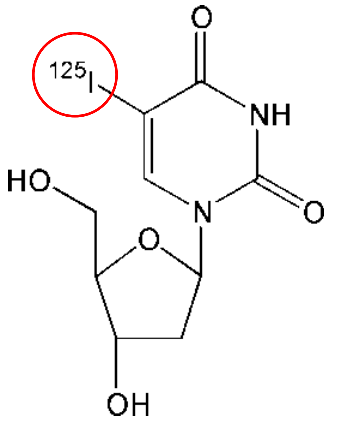
^{125}I: One decay event – one DNA DSB – 100% efficiency of DNA damage

Mechanisms?

1. Auger electrons emission (obvious and traditional)

2. Non-traditional mechanism: (not obvious and alternative)

   Molecule fragmentation as a result of coulombic explosion of multiply charged (+7-20) daughter atom ^{125}Te

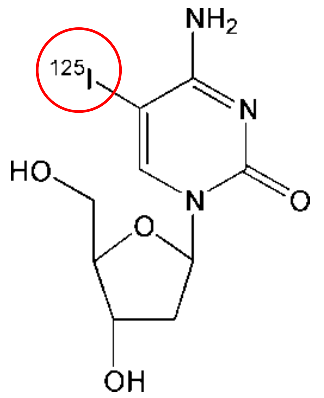


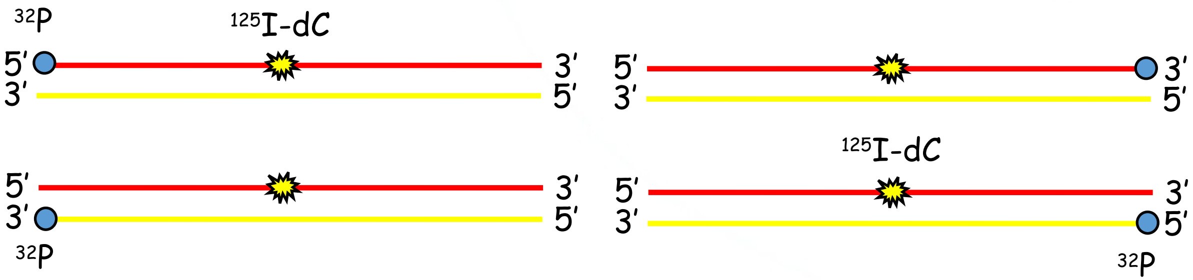
Auger decay DNA damage – mapping DNA breaks

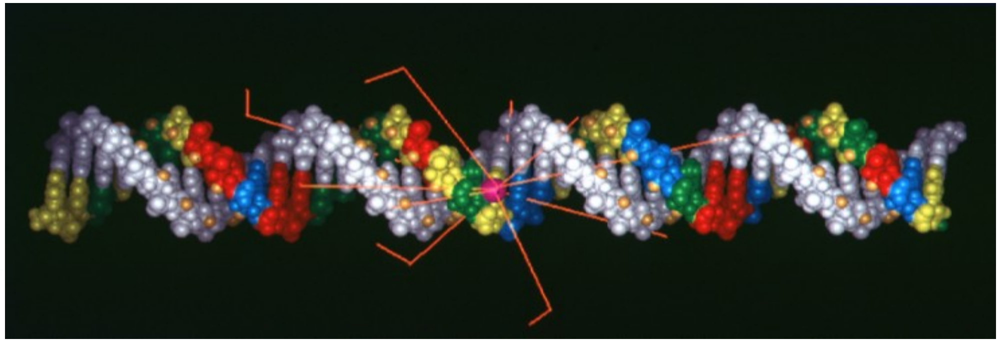
Experiments with synthetic oligodeoxynucleotides

(Lobachevsky & Martin, Rad Res, 2000)

- **model – 41 bp oligodeoxynucleotide incorporating single ^{125}I and complementary 41 bp fragment**
- **end point – induction of DNA SSB +/- DMSO - dimethylsolphoxide**
- **method – sequencing gel electrophoresis (^{32}P-label for detection)**
- **radionuclide carrier – [^{125}I]-iodo-deoxycytidine (5-^{125}IdC), incorporated in one DNA strand**



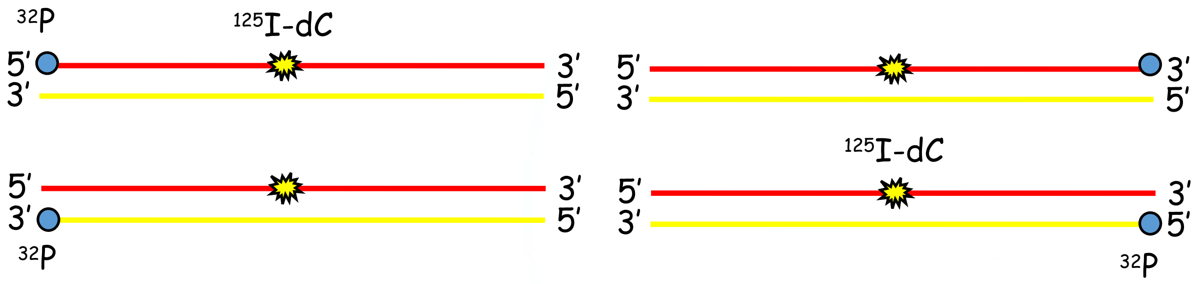




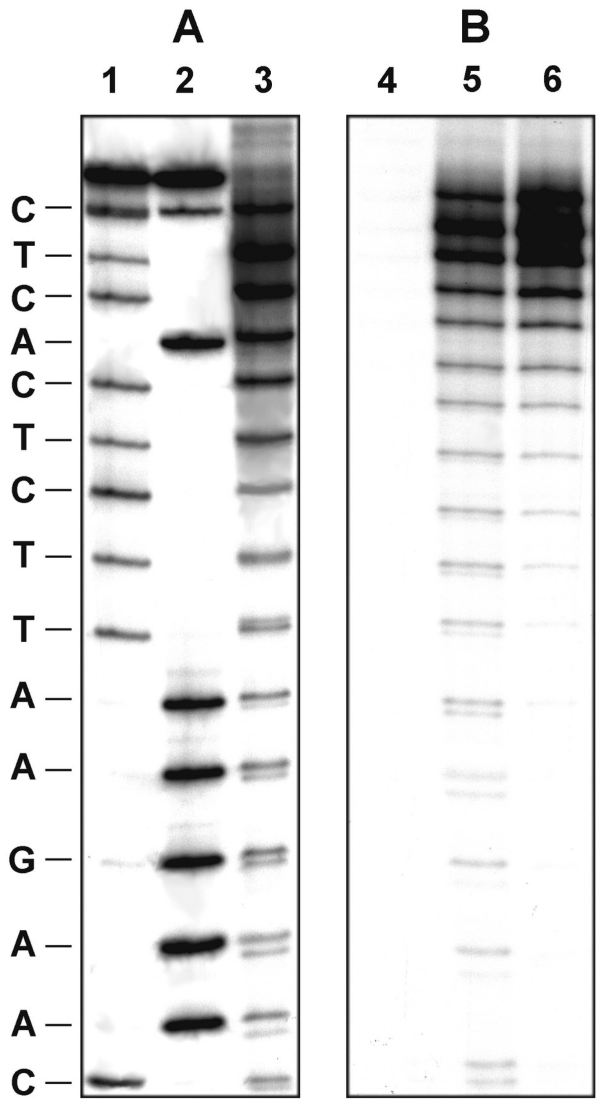
Auger decay DNA damage – mapping DNA breaks

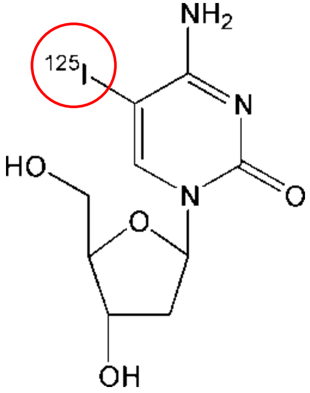
Experiments with synthetic oligodeoxynucleotides

Detection of DNA fragments



Decay induced fragments of various length

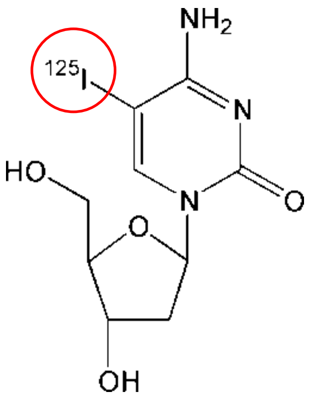


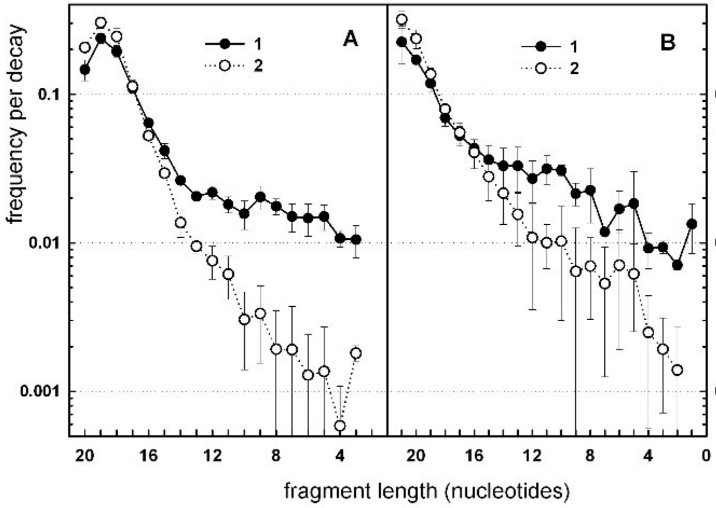


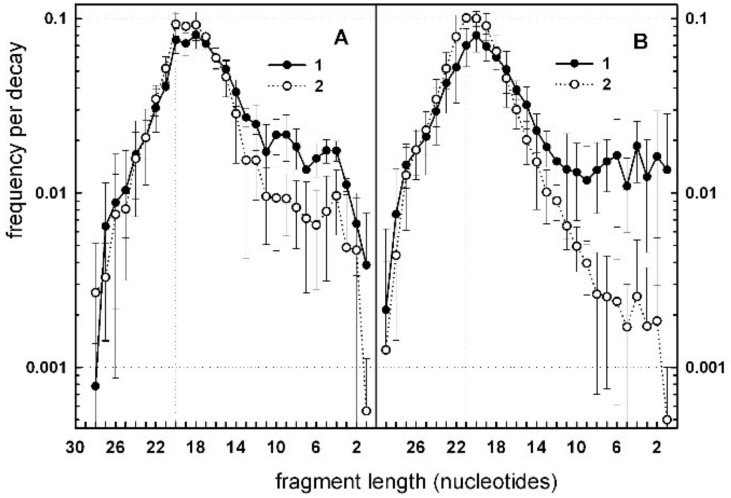
Auger decay DNA damage – mapping DNA breaks

Experiments with synthetic oligodeoxynucleotides

Fragment size distributions

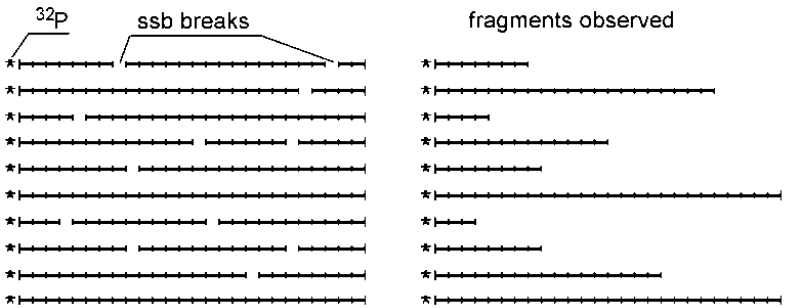






$$f_i = p_i(1 - p_{i-1})\ldots(1 - p_0)$$

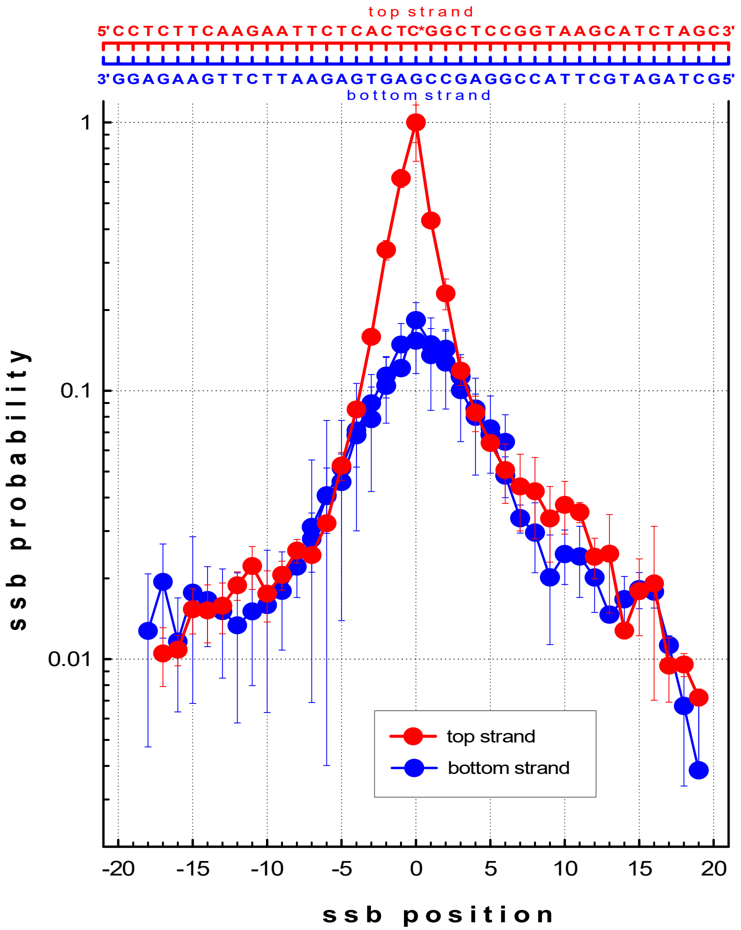
$$p_i = \frac{1}{1 - \sum_{j}^{i-1} f_i}$$



f_i – fragment detection frequency

p_i – probability of SSB

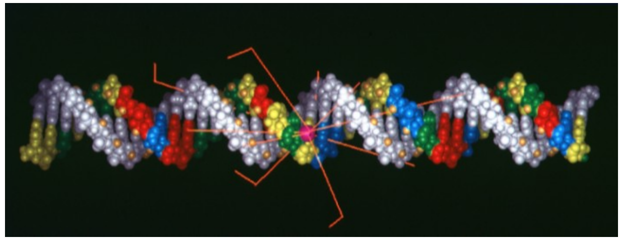
Auger decay DNA damage – mapping DNA breaks

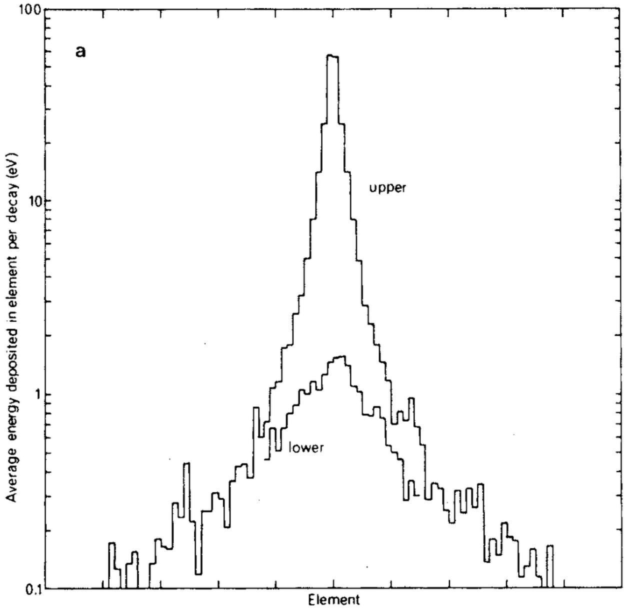


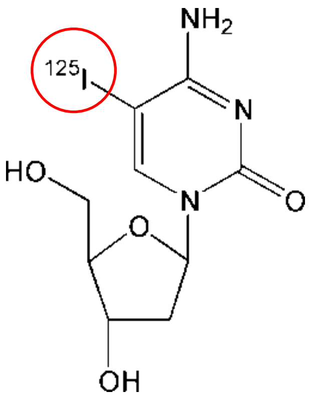
DNA SSB per ^{125}I decay probability map

Experiments with synthetic oligodeoxynucleotides

SSB probabilities







Energy deposition in DNA elements per ^{125}I decay

Humm & Charlton, 1988

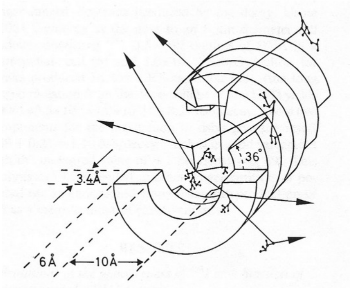
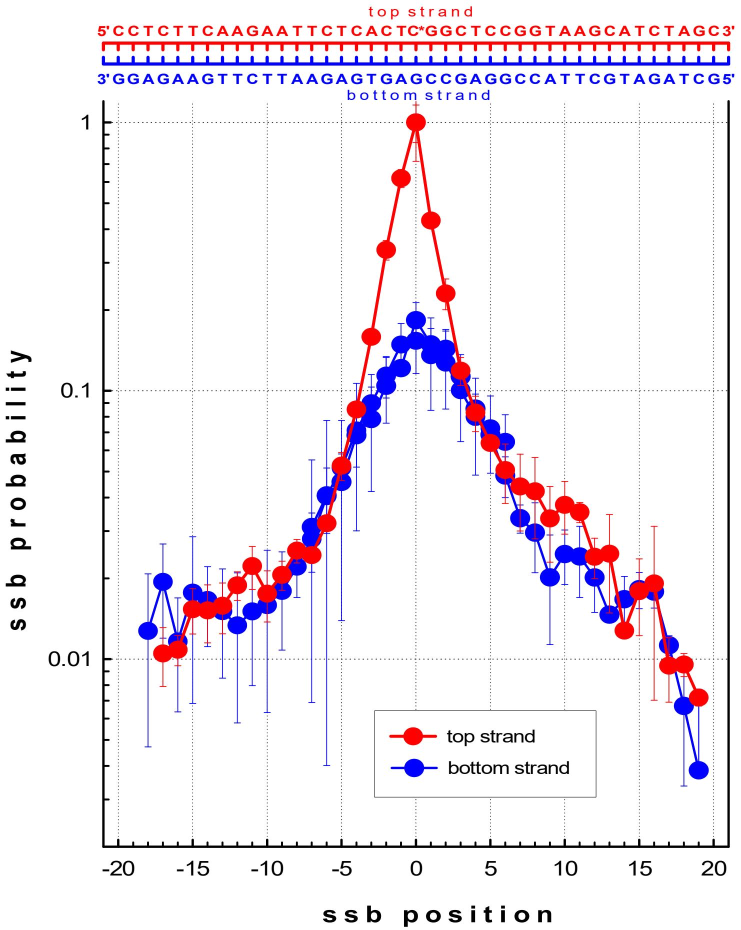


Fig. 1. Schematic diagram of an Auger source decaying in the DNA. The DNA model is described in the text. Each decay produces a set of individual electron tracks producing energy depositions at random through the DNA.

Auger decay DNA damage – mapping DNA breaks



DNA SSB per ^{125}I decay probability map

Experiments with synthetic oligodeoxynucleotides

- Majority of breaks within +/- 5 bp
- Probability if DSB – 0.8
- On average 3.67 breaks in top strand and 1.53 breaks in complementary strand
- Formation of clustered damage – DNA DSB of high complexity – high radiobiological efficiency of ^{125}I-decay

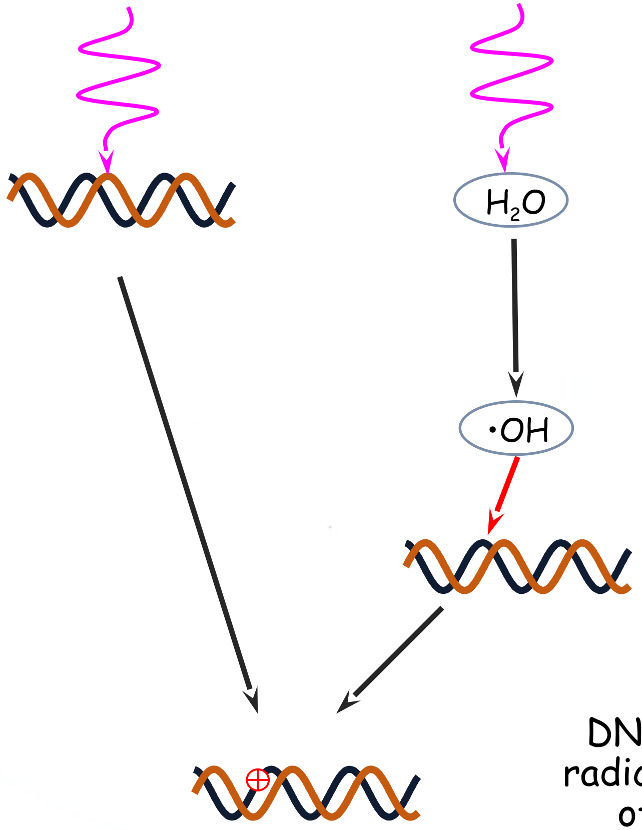
Direct and indirect mechanism or radiation action

Direct mechanism

Direct interaction of ionising particle with DNA molecule

Ionisation of atoms in DNA molecule and formation of radicals

$$DNA \xrightarrow{\text{radiation}} DNA^{\cdot +} + e^{-}$$



Indirect mechanism

Ionisation of water molecules

Formation of •OH radicals (2.7/100 eV)

$$H_2O \xrightarrow{\text{radiation}} H_2O^{\cdot +} + e^{-}$$

$$H_2O \xrightarrow{\text{radiation}} H_2O^{*}$$

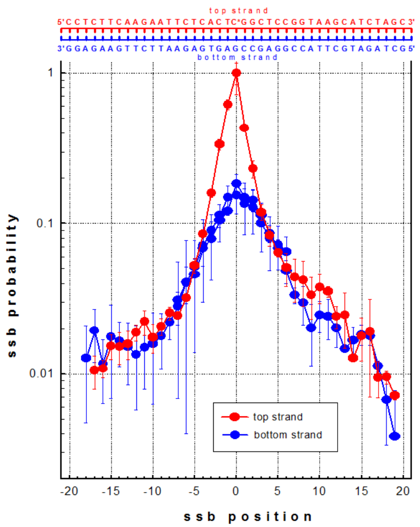
$$H_2O^{\cdot +} + H_2O \rightarrow H_3O^{+} + {}^{\cdot}OH$$

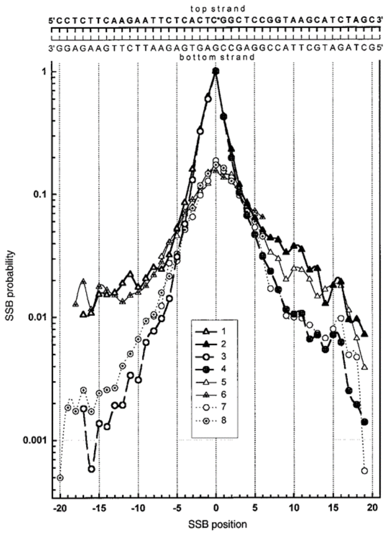
$$H_2O^{*} \rightarrow H^{\cdot} + {}^{\cdot}OH$$

DNA attack by •OH radicals and formation of DNA radicals

Indirect mechanism can be blocked by addition of radical scavengers, such as DMSO - dimethylsulphoxide

Auger decay – contribution of three DNA damage mechanisms





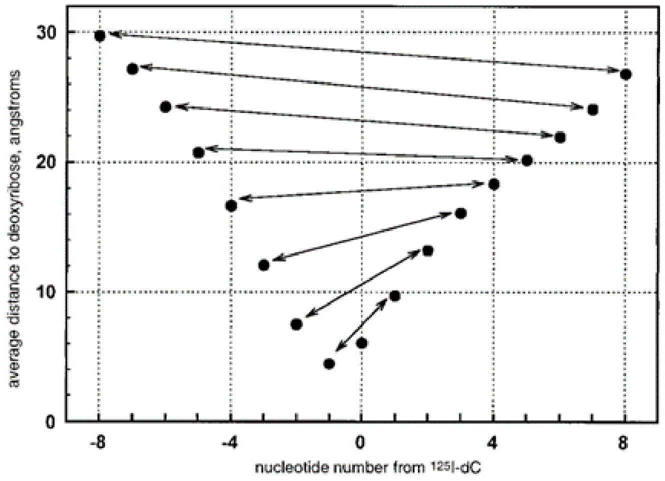


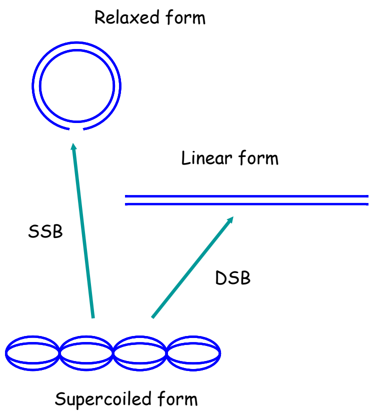
FIG. 1. Average distance from an ^{125}I atom to carbons of the deoxyribosyl moiety in the top strand. Negative nucleotide numbers correspond to the 5′ direction, positive ones to the 3′ direction. Corresponding nucleotides are indicated by arrows.

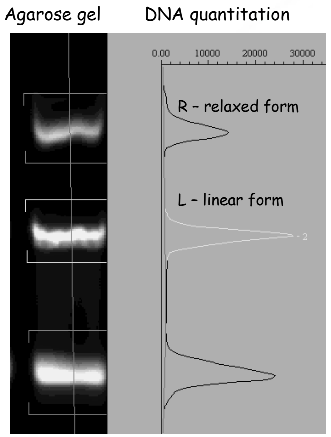
Contribution of three mechanisms:

- Non-radiation mechanism - neutralisation of charged ^{125}Te atom
- Radiation direct mechanism – direct energy deposition in DNA from Auger electrons
- Radiation indirect – (hydroxyl) radical attack of DNA

Component/DNA strand	Non-radiation (charge neutralisation)	Radiation direct	Radiation indirect (DMSO scavengeable)
^{125}I-incorporating (top)	2.37 (55%)	1.24 (29%)	0.68 (16%)
Complementary (bottom)	0.65 (35%)	0.75 (41%)	0.43 (24%)
DNA duplex	3.02 (49%)	1.99 (33%)	1.11 (18%)

DNA damage – Auger decay in DNA ligand





$$N_{dsb} = \frac{L}{1-L}$$

$$N_{ssb} = \ln\left(\frac{1-L}{S}\right)$$

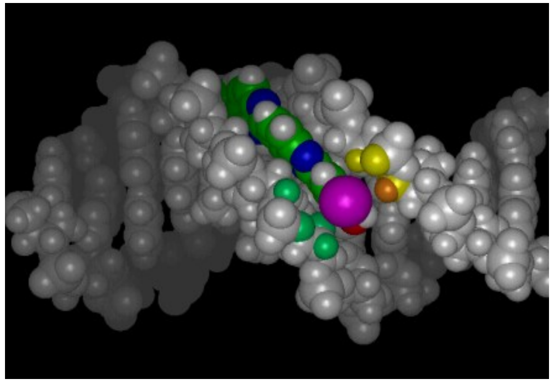
$$S = \frac{e^{-N_{ssb}}}{1+N_{dsb}}$$

$$R = \frac{1-e^{-N_{ssb}}}{1+N_{dsb}}$$

$$L = \frac{N_{dsb}}{1+N_{dsb}}$$

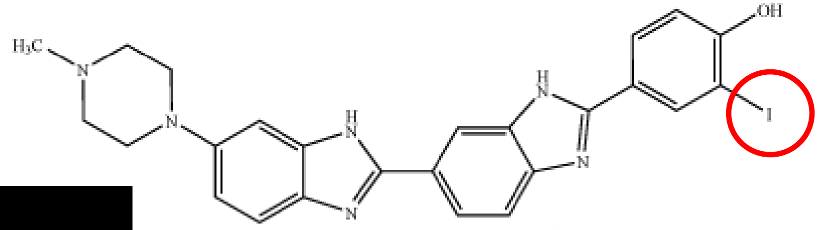
Quantitation of SSB and DSB yield from the fractions of relaxed and linear form in plasmid DNA model

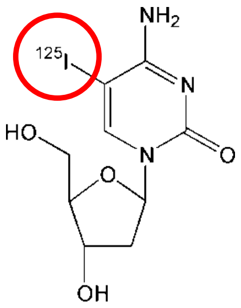
pBR322 – 4361 bp

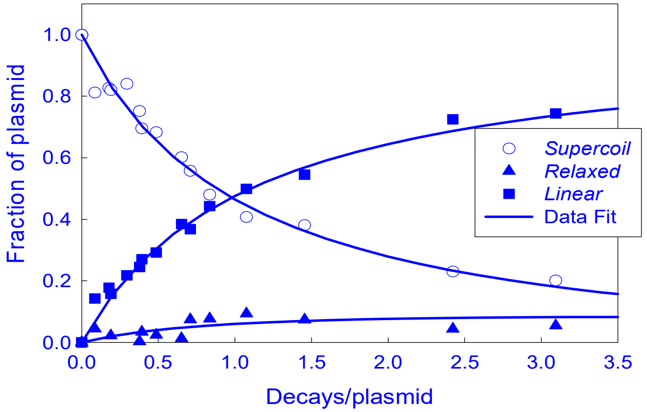


DNA minor groove binding ligand

^{125}I – iodoHoechst 33258



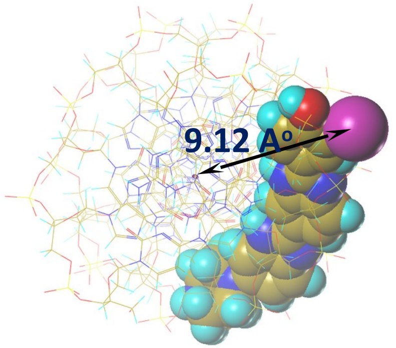


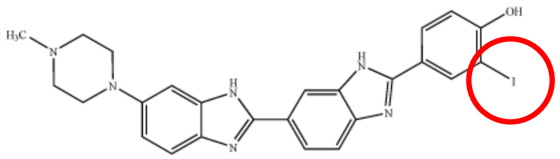


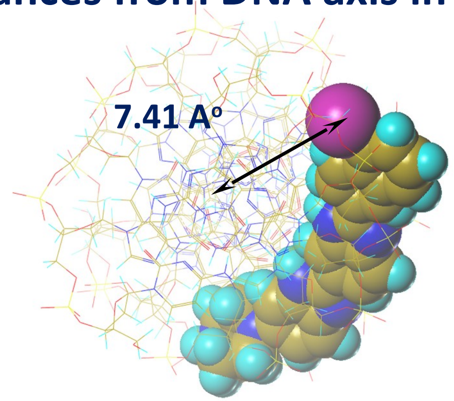
DSB probability – 0.8-0.9 per decay per molecule

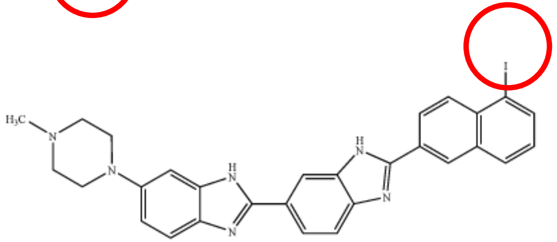
Auger decay in DNA ligand – the role of distance

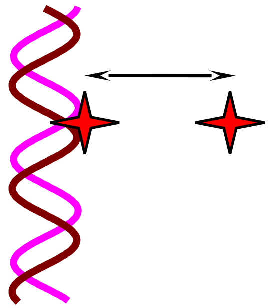
A series of DNA minor groove ligands that position ^{125}I at various distances from DNA axis in plasmid DNA model









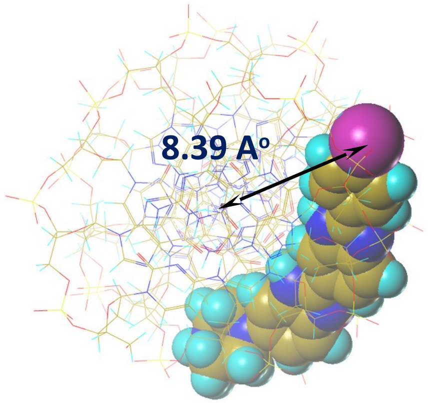


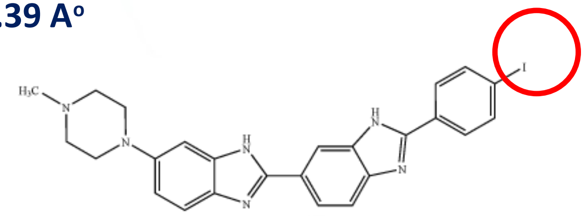
Iodo-Hoechst 33258, R = 9.12 A°

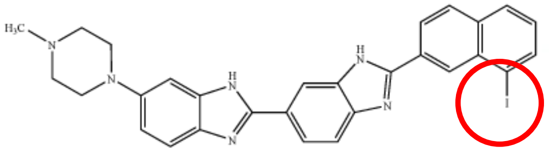
Bi-Benzimidazole-5-Iodo-Naphthyl, R = 7.41 A°

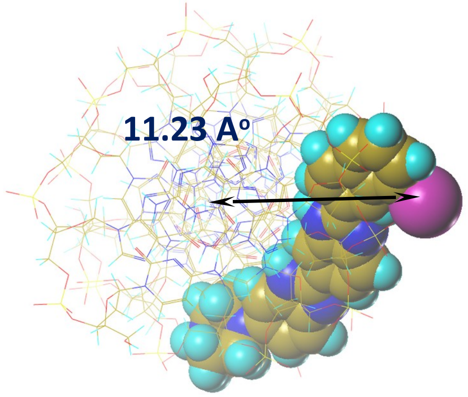
Para-Iodo-Hoechst, R = 8.39 A°

Bi-Benzimidazole-8-Iodo-Naphthyl, R = 11.23 A°





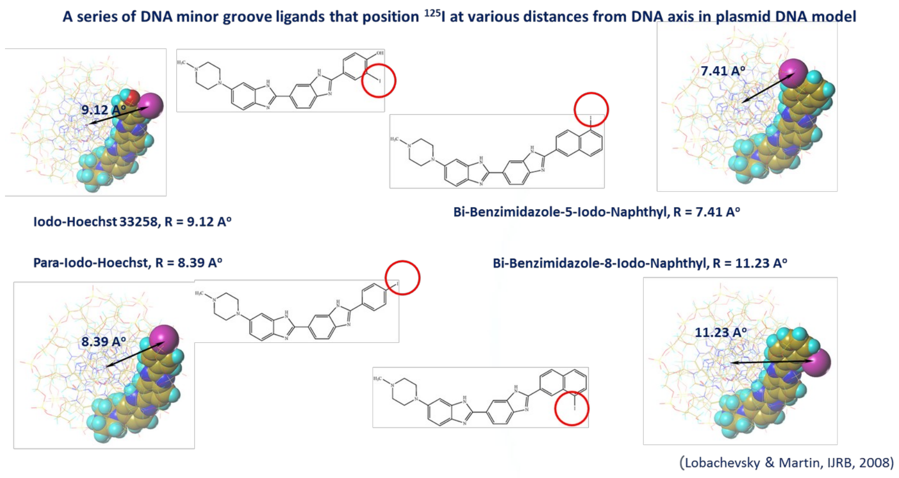


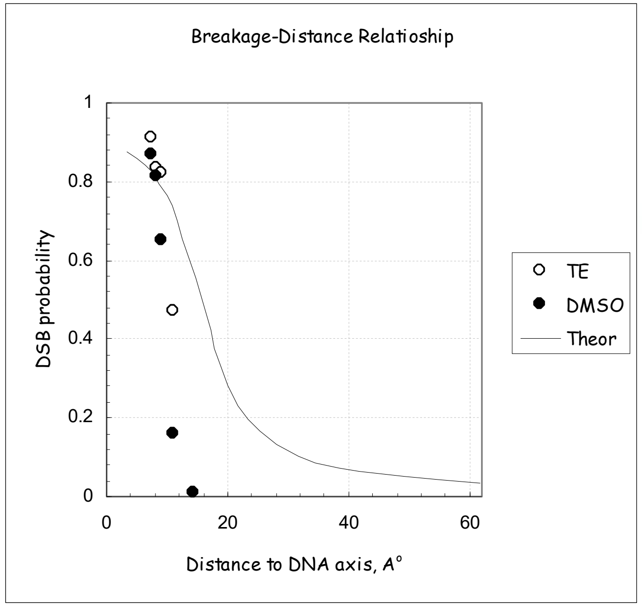


(Lobachevsky & Martin, IJRB, 2008)

Auger decay in DNA ligand – the role of distance

A series of DNA minor groove ligands that position ^{125}I at various distances from DNA axis in plasmid DNA model





(Lobachevsky & Martin, IJRB, 2008)

Ligand	Distance from ^{125}I to DNA axis	DSB (TE)	DSB (DMSO)
BB5IN	7.41	0.91	0.87
PIH	8.39	0.84	0.81
IH33258	9.12	0.82	0.65
BB8IN	11.22	0.47	0.157

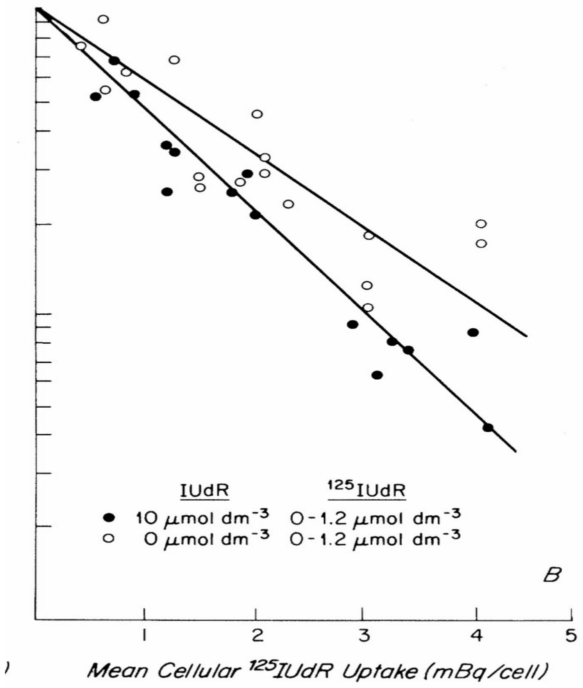
- **Decrease of DNA DSB probability with increasing distance to DNA axis**
- **Distance – critical parameter**
- **Discrepancy with Monte Carlo result – non-radiation component**

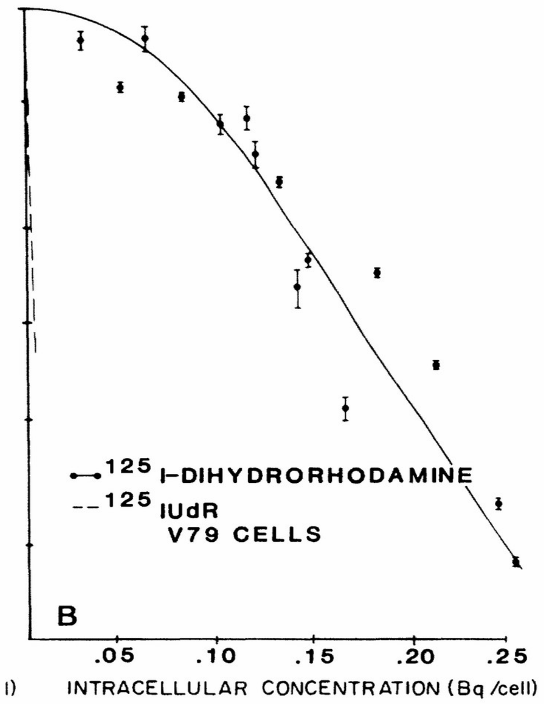
Auger decay in DNA ligand – iodine isotopes ^{123}I, ^{124}I, ^{125}I

	Buffer	^{125}I	^{123}I	^{124}I
Auger electrons (Energy, keV)		24.9 (12.2)	14.9 (7.4)	8.4 (4.74)
DSB (linearisation) /decay	TE	0.82	0.62	0.54
	TE+DMSO	0.65	0.54	0.43
SSB (relaxation) /decay	TE	0.09	0.30	0.40
	TE+DMSO	0.15	0.36	0.41

Decay of "weaker" Auger emitters ^{123}I and ^{124}I is efficient in induction of DNA breaks

Radiation biology of Auger decay – cellular effects





Localisation of Auger emitter relative to DNA is of critical importance

Experiments with mammalian cells *(Kassis & Adelstein, Rad Res, 1987)*

Effect of ^{125}I decay: extracellular, in cytoplasm, in cell nucleus

Decay of DNA incorporated ^{125}I ~ 6 fold more efficient that decay of ^{125}I in cytoplasm (based on absorbed dose)

Carrier of ^{125}I	Localisation	D_{37} mBq/cell	D_{37} Gy
$Na^{125}I$	Extracellular	-	-
[^{125}I]-iodo-dihydrorhodamine (^{125}I-DR)	Cytoplasm	109	4.62
[^{125}I]-iodo-deoxyuridine (5-^{125}IUdR)	Nucleus (DNA)	1.30	0.80

Radiobiology of Auger Emitters - Topics

1. Auger electron emitters – a special class of radionuclides

    (physics of Auger effect and physical properties of Auger emitters)

2. Molecular aspects of Auger decay radiobiology

    (DNA damage)

3. **Auger emitters potential for radionuclide therapy**

    (dual targeting strategy)

Auger emitters potential for radionuclide therapy

Properties/Advantages of Auger emitters (iodine-125):

- Highly localised energy deposition
- Efficient induction of DNA damage (complex DSB) by DNA associated decay -> High cytotoxicity of DNA associated radionuclide
- Strong dependence on decay-DNA distance
- Strong dependence of radiotoxicity on decay localisation (DNA or cytoplasm) presents a potential for selective action on certain cells or cell types without damage to neighbouring cells
- Theranostic opportunities – accompanying gamma (SPECT) or positron (PET) emission

Requirements:

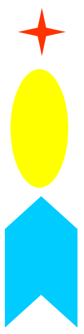
- - Localisation of Auger decay in close vicinity to cellular DNA
- - Selective delivery of Auger emitters to cells of malignant tumours

Auger emitters potential for radionuclide therapy

Approach – Dual targeting strategy

Three-component conjugate – a key element of the strategy

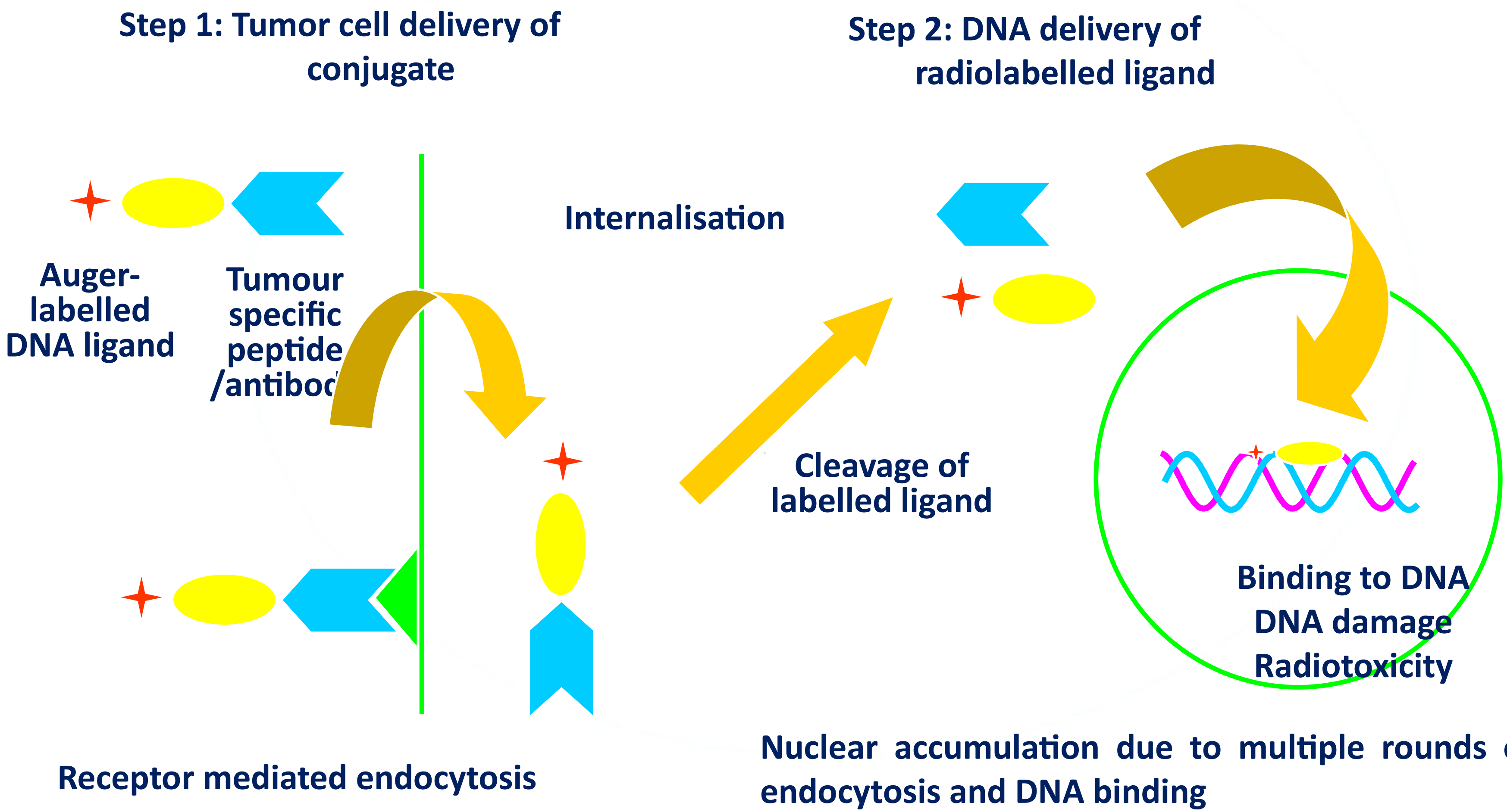
(module transporter)



- Auger electron emitter (^{123}I, ^{124}I, ^{125}I, ^{111}In, ^{99m}Tc)
- DNA ligand
- Peptide/protein/antibody highly specific to tumour cell receptors
(octreotide, transferrin, EGF receptor antibody etc)

Auger emitters potential for radionuclide therapy

Dual targeting strategy



Nuclear accumulation due to multiple rounds of endocytosis and DNA binding

Auger emitters potential for radionuclide therapy

Dual targeting strategy – Octreotide model

Model – Octreotide (octreotate):

- Octreotide - peptide (8 amino acids) – analogue of somatostatin (growth hormone inhibiting hormone) (14 or 28 amino acids)
- somatostatin receptors (SSTR) are over expressed in many tumours (gastrointestinal, prostate, mammary gland, neuroendocrine)
- radiolabelled Octreotide is used in nuclear medicine

International Journal of Radiation Biology, December 2012; 88(12): 1009–1018

ISSN 0955-3002 print / ISSN 1362-3095 online
DOI: 10.3109/09553002.2012.666375

informa healthcare

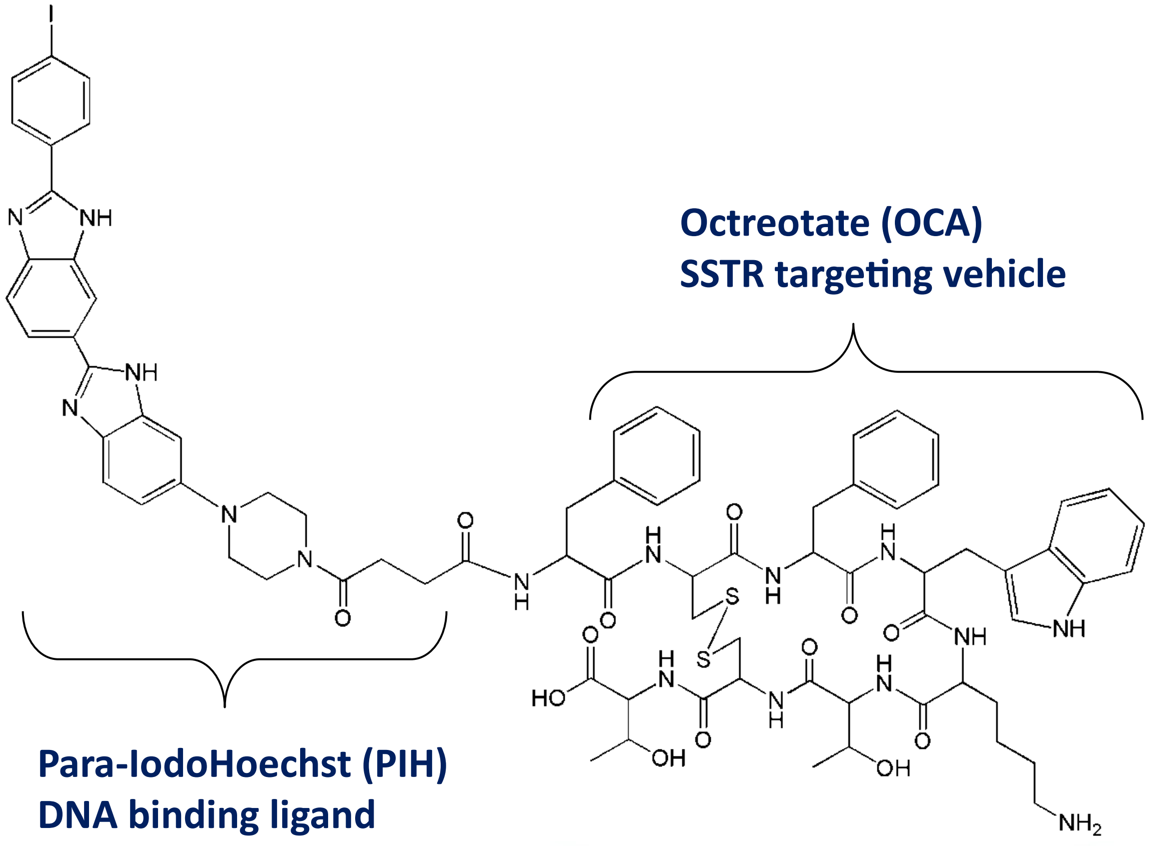
Tumour targeting of Auger emitters using DNA ligands conjugated to octreotate

Pavel Lobachevsky[1], Jai Smith[1], Delphine Denoyer[1], Colin Skene[2], Jonathan White[2], Bernard L. Flynn[3], Daniel J. Kerr[3], Rodney J. Hicks[1] & Roger F. Martin[1]

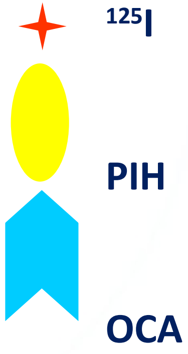
Auger emitters potential for radionuclide therapy

Dual targeting strategy – Octreotide model

Octreotate (OCA)
SSTR targeting vehicle



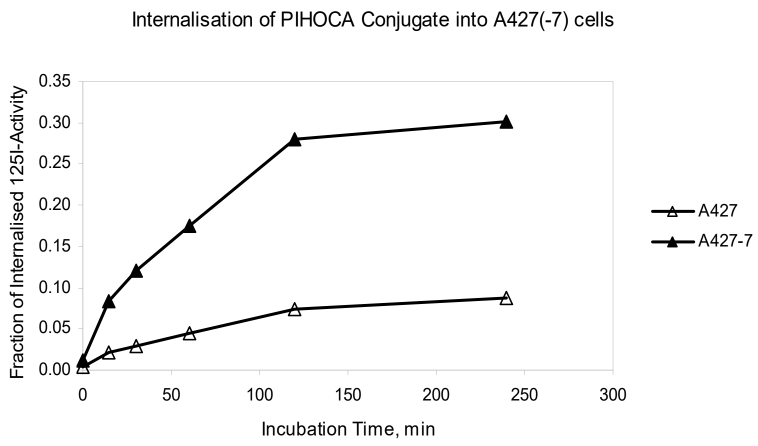
Para-IodoHoechst (PIH)
DNA binding ligand

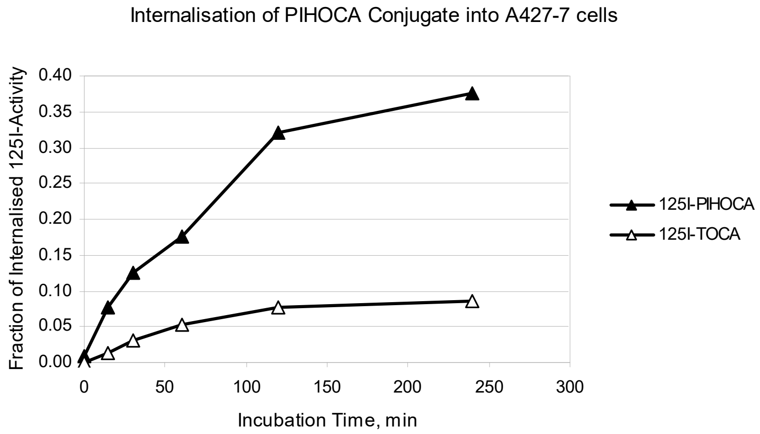


Three component conjugate (^{125}I-PIH-OCA)

Auger emitters potential for radionuclide therapy

Dual targeting strategy – Octreotide model, *in vitro* experiments



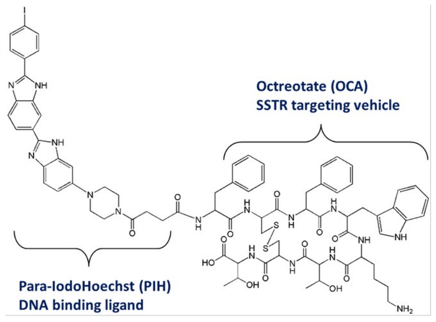


Accumulation of Auger emitter ^{125}I in cells

Open symbols – A427 (parent line)

Black symbols – A427-7 (SSTR2 expressing)

Accumulation is mediated by SSTR2 receptors



Three component conjugate (^{125}I-PIH-OCA)

Open symbols– directly labelled ^{125}I-TOCA w/o DNA ligand

Black symbols – conjugate (^{125}I-PIH-OCA)

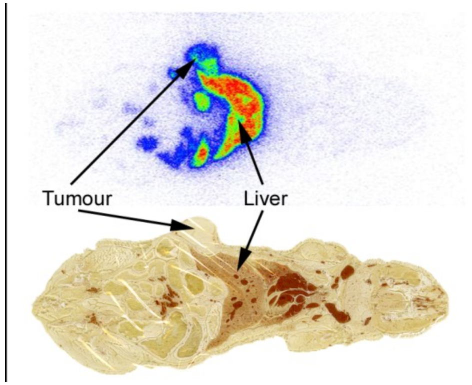
Accumulation is mediated by DNA binding of ^{125}I-PIH

Cell culture – A427 (human non-small cell lung carcinoma) and clone

A427-7 stably transfected with somatostatin receptor (SSTR2) gene

Auger emitters potential for radionuclide therapy

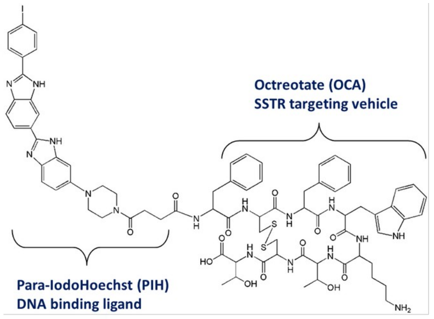
Dual targeting strategy – Octreotide model, *in vivo* experiments



^{125}I -PIH-OCA

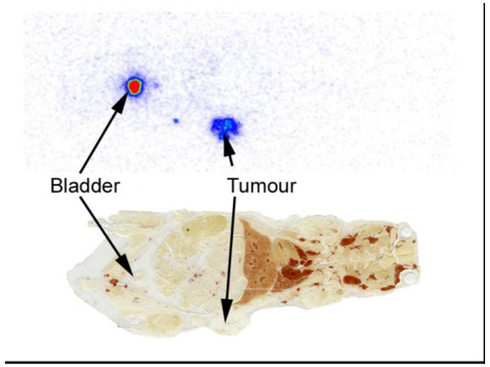
Biodistribution of Auger emitter in mouse tissues

24 hr after injection



Three component conjugate (^{125}I-PIH-OCA)

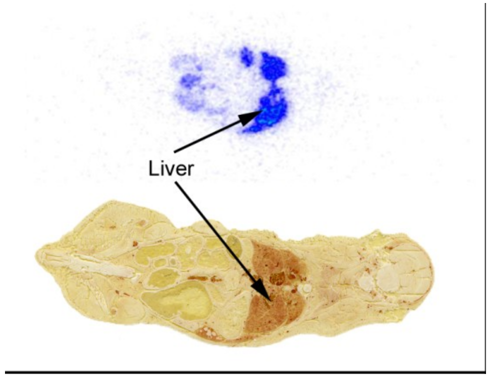
Accumulation of Auger emitter in tumour following injection of both ^{125}I -PIH-OCA and ^{125}I-TOCA



^{125}I-TOCA

Accumulation of Auger emitter in liver following injection of ^{125}I -PIH-OCA and ^{125}I -PIH

There is targeted delivery of Auger emitter, however:



^{125}I-PIH

Premature cleavage of DNA ligand and its accumulation in liver

Auger emitters potential for radionuclide therapy

Dual targeting strategy – Octreotide model

Experimental studies demonstrate the feasibility of targeted delivery of Auger emitters to nucleus and DNA of tumour cells

Radiobiology of Auger electron emitters

and their potential for radionuclide therapy

Thank you for your attention!