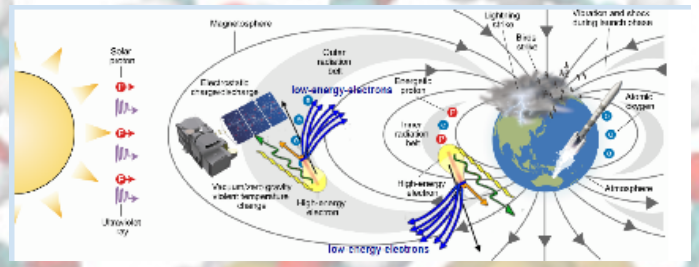
Roma
15/11/2022

LEE2022



Low energy electrons and biomolecules

P. Bolognesi, J. Chiarinelli, L. Carlini, M.C. Castrovilli, A.R. Casavola and L. Avaldi

CNR-ISM, Area della Ricerca di Roma 1, Monterotondo Scalo (Roma), Italia

CNR - ISM
Istituto di Struttura
della Materia

Consiglio Nazionale delle Ricerche

Menù of the day

1. *'RADIATION IS EVERYWHERE'*

✓ We are constantly exposed to radiation, of different nature and energy…
this is a matter of fact !

✓ We all know radiation is harmful

✓ …but for the same reason, radiation can also be a useful tool for medical treatment

2. RADIATION AND BIOMOLECULECUR SYSTEMS

✓ Direct and indirect damage: what happens at the microscopic level ?

✓ Let's focus on secondary damage, and in particular the role of (low energy) electrons

3. WHY ARE LOW ENERGY ELECTRONS SO DANGEROUS ?

✓ They are the most numerous particles …

✓ and can dissociate nucleobases even below IP

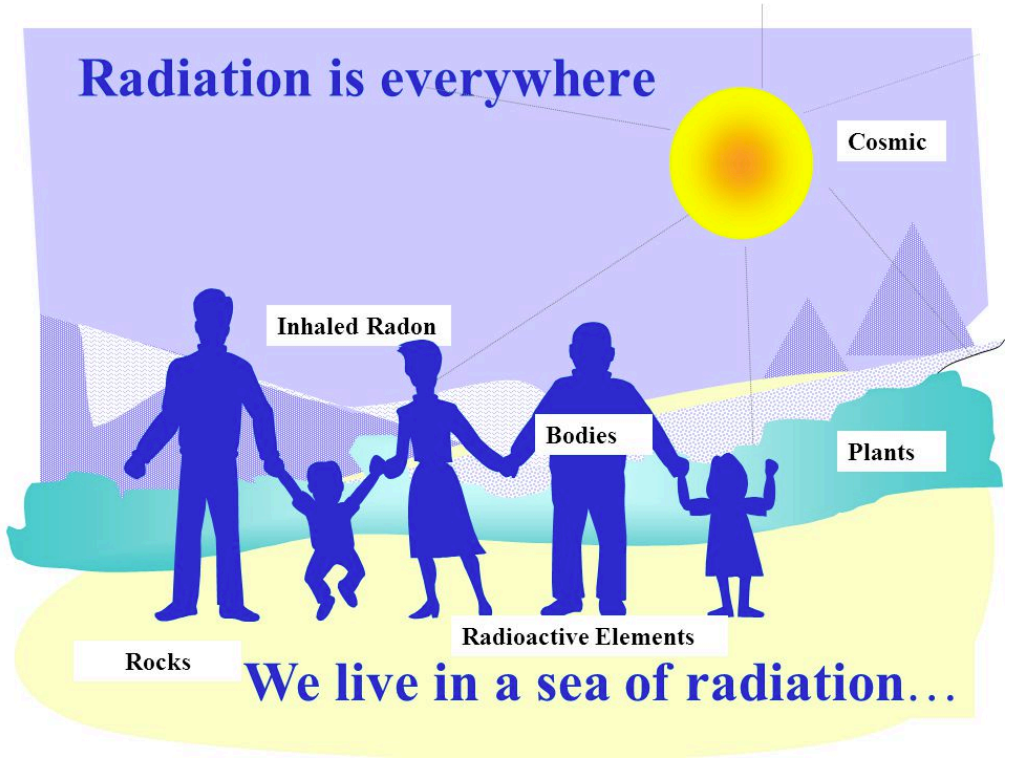
4. HOW CAN WE HAVE THEN 'FIGTH FOR US', INSTEAD OF 'AGAINST US'

✓ Radiosensitisers in radiotheraphy.

'Radiation is everywhere'

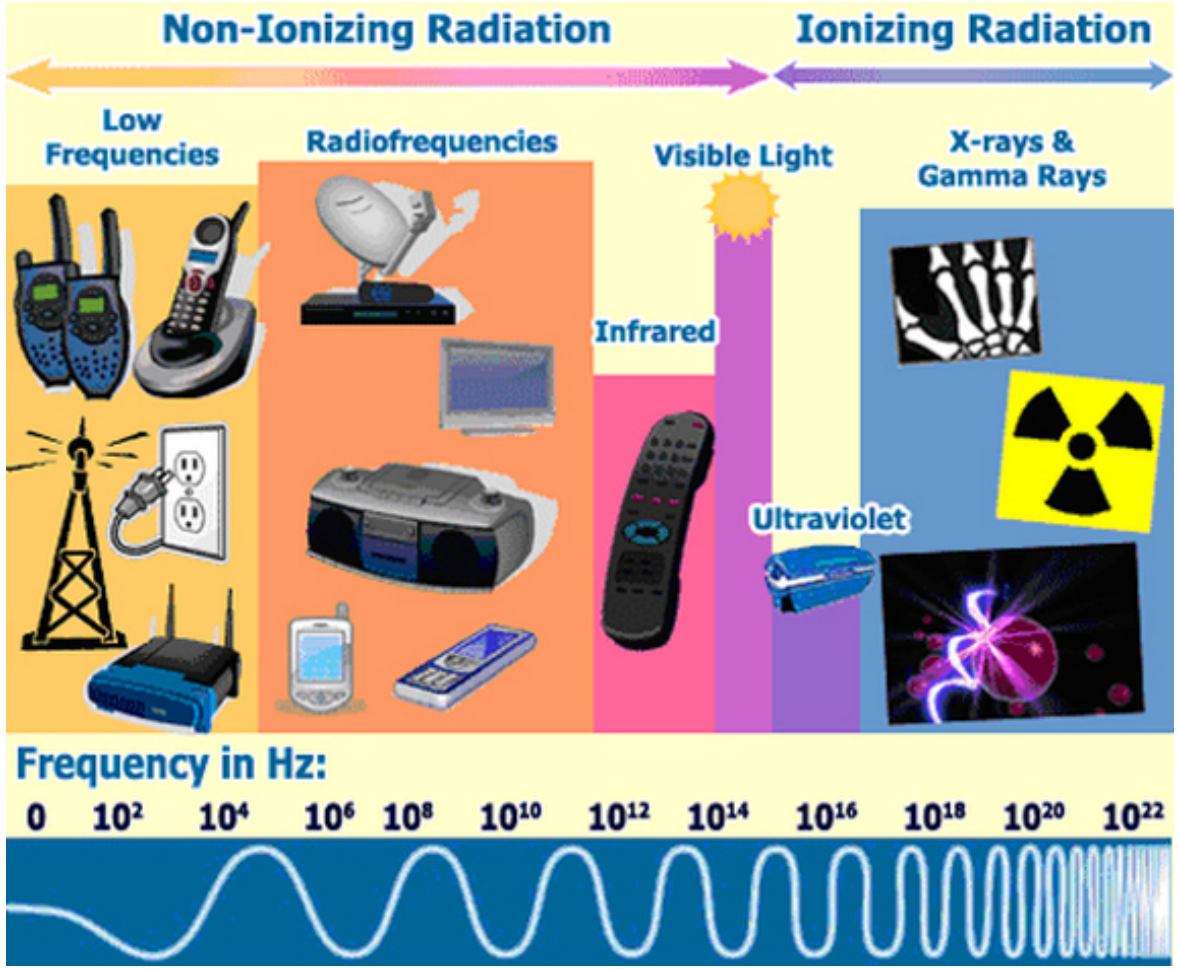
Our body is CONSTANTLY crossed by radiation, of natural and of anthropic origin.

Natural sources

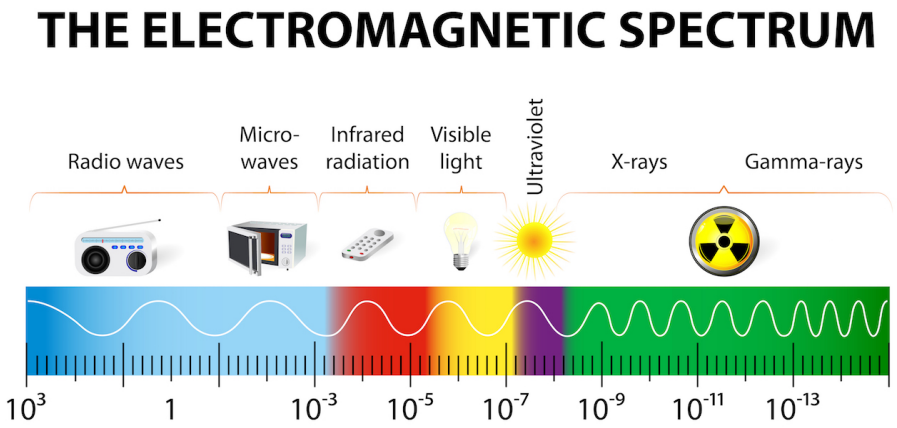


COSMIC RAYS, for example: (89%) protons; (10%) He^{+}; (1%) heavier nuclei, all the way up to uranium.
When they arrive at Earth, they collide with the nuclei of atoms in the upper atmosphere, creating more particles…

Anthropic sources

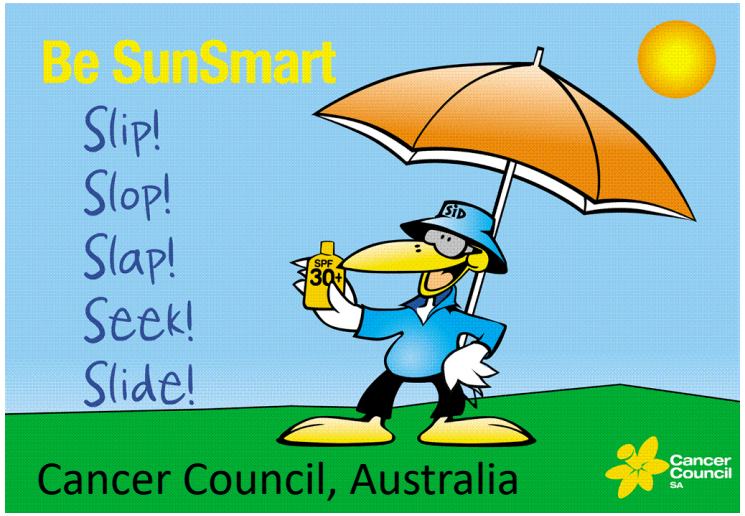


But this is not necessarily a bad news

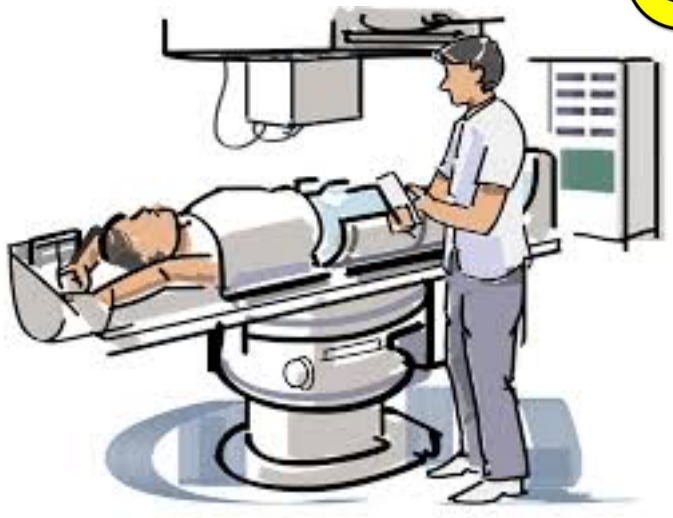


Radiotherapy begins with high energy:
photons : variable between 60 KeV to 25 MeV
electrons : 4–20 MeV
protons : 230 to 250 MeV
multiply charged ions : 100-450 MeV/u

BIOLOGICAL DAMAGE



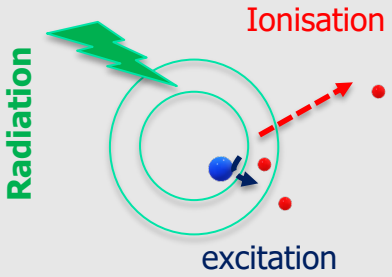
RADIOTHERAPY

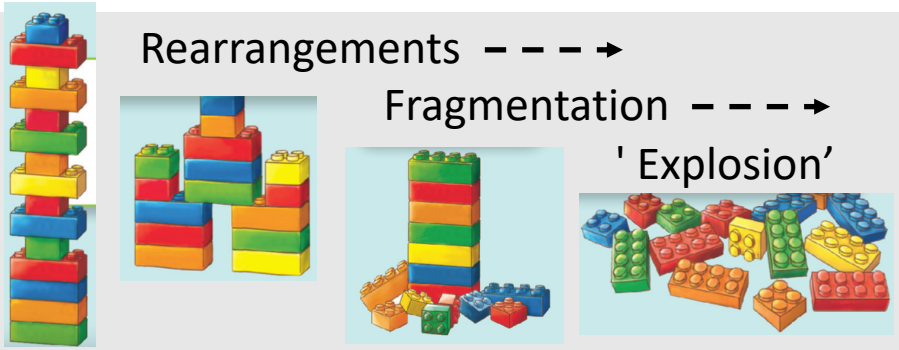


TWO SIDES OF THE SAME COIN, KNOWLEDGE AND UNDERSTANDING MAKE THE DIFFERENCE

What happens at the microscopic level ?

Physical Stage	Chemical Stage	Biological Stage
Energy transfer from radiation to specific target atoms/ molecules: - Ionization/photoelectron release - electronic excitations - molecular de-excitation and electron decay Electron dynamics is ultra fast, and drives the next stage, with nuclear rearrangement.	**Molecular rearrangement** and chemical reactions: - molecular vibration electronic decay molecular dissociation Formations of radicals, chemical reactions and formation of new structures	Biological and biochemical effects: - damage at cellular level - mutagenesis - cell death biological dysfunctions on organs and tissues ...
10^{-18} - 10^{-16} seconds	10^{-16} - 10^{-3} seconds	Seconds - years

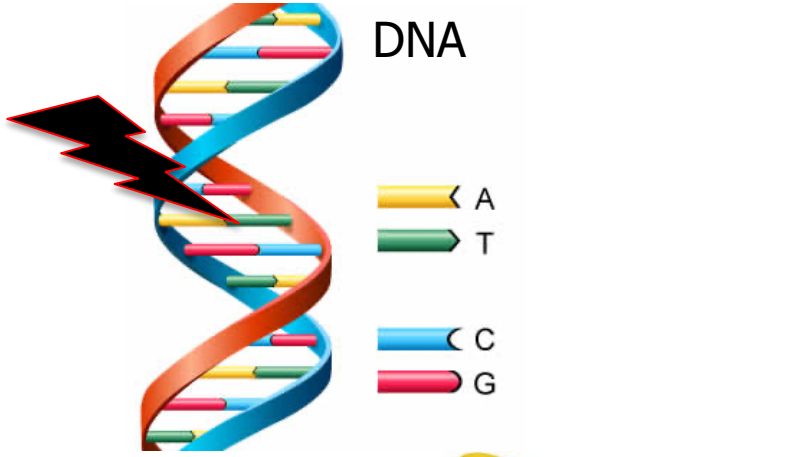




Direct and indirect radiation damage… it is a matter of statistics

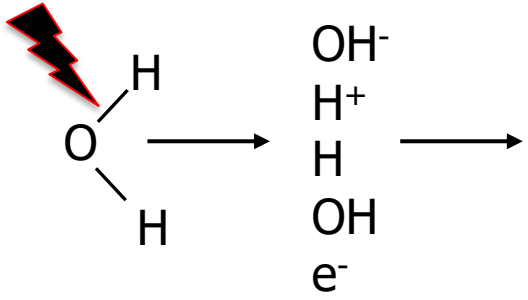
DIRECT DAMAGE
Radiation directly interacts with DNA, producing a lesion

But the **genetic material represents < 0,001 %** of a human body, which is instead made by 70% of water, 10% of carbon, nitrogen, calcium …



in any case…

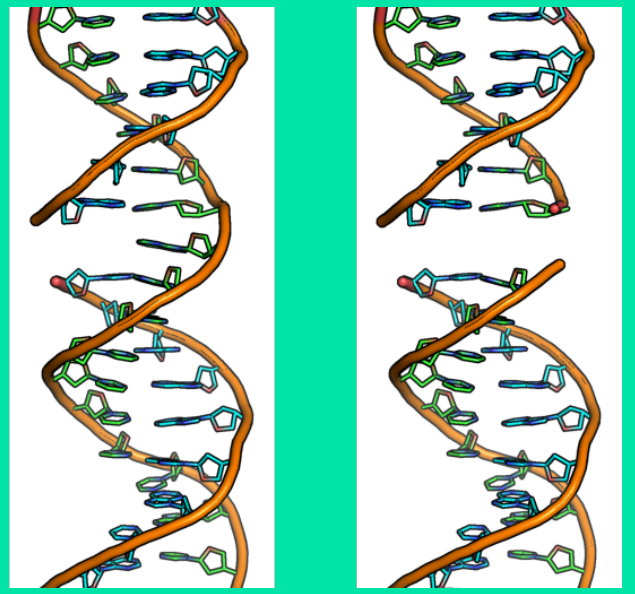
INDIRECT DAMAGE
It is therefore natural to assume that the primary incident radiation beam mostly interacts with water and other material surrounding DNA



which release ions, radicals, neutral species … and **electrons** !

Single strand break
SSB

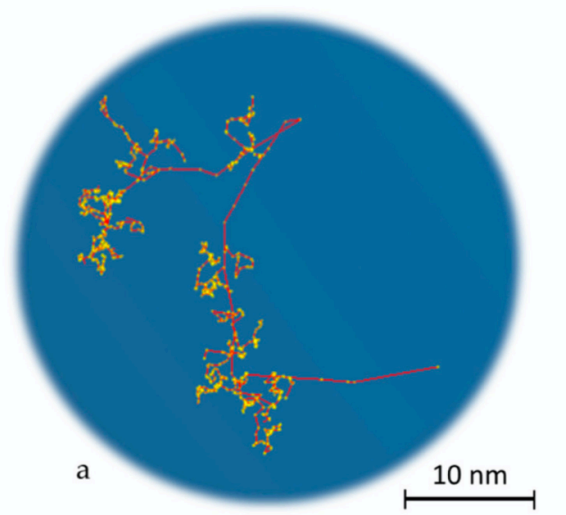
DSB
Double strand break



Can be reparable or not, give rise to mutagenesis and/or cellular death

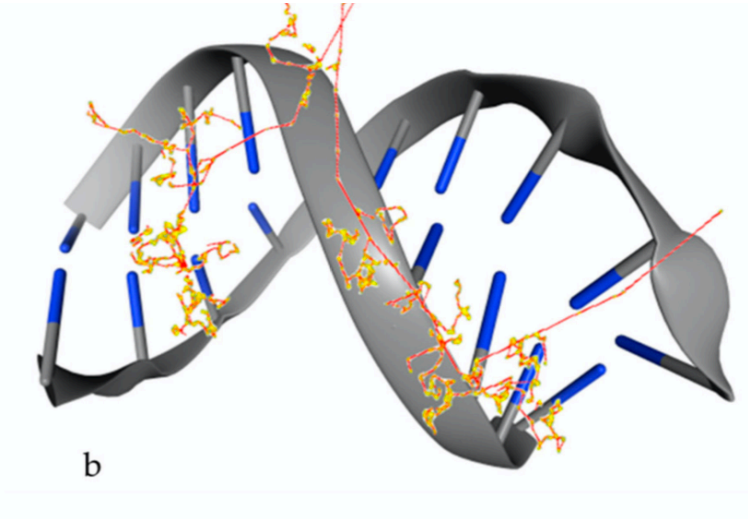
A botton-up approach to quantify biological radiation damage

To understand radiosensitivity of biological systems, we must investigate the nanoscale dynamics of these radiation energy interactions and deposition processes.



Track structure of an electron (10 KeV) in water as simulated in Geant4-DNA.
Cancers **2020**, *12*, 799

These complex processes can be simulated in **event-by-event MC simulations** that propagate from primary collision/absorption to secondary events and eventually hit DNA
→ evaluation of the 'damage'



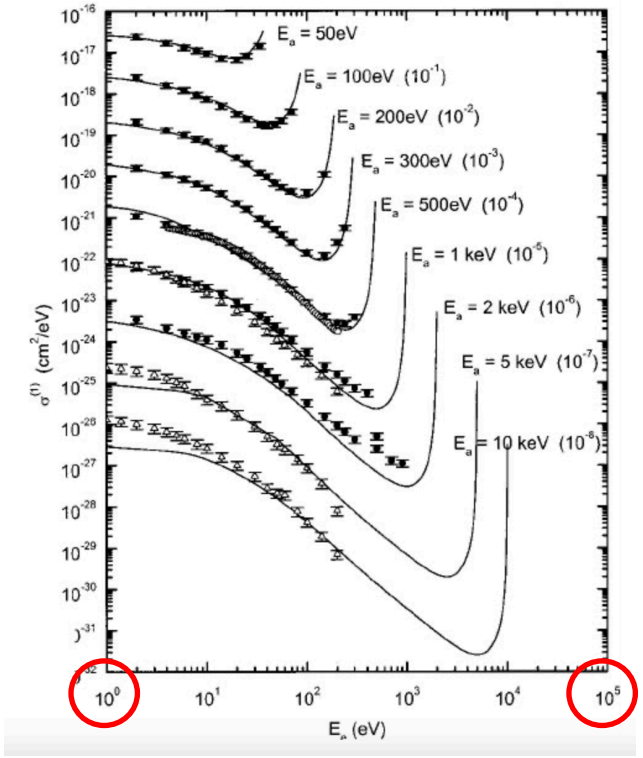
Energy deposition in water is transformed to single or double strand breaks.

HOWEVER… they require an **enormous** data base of information on total and differential cross sections for **each** possible process/radiation.

MD simulations need cross sections, just a glimpse on water case

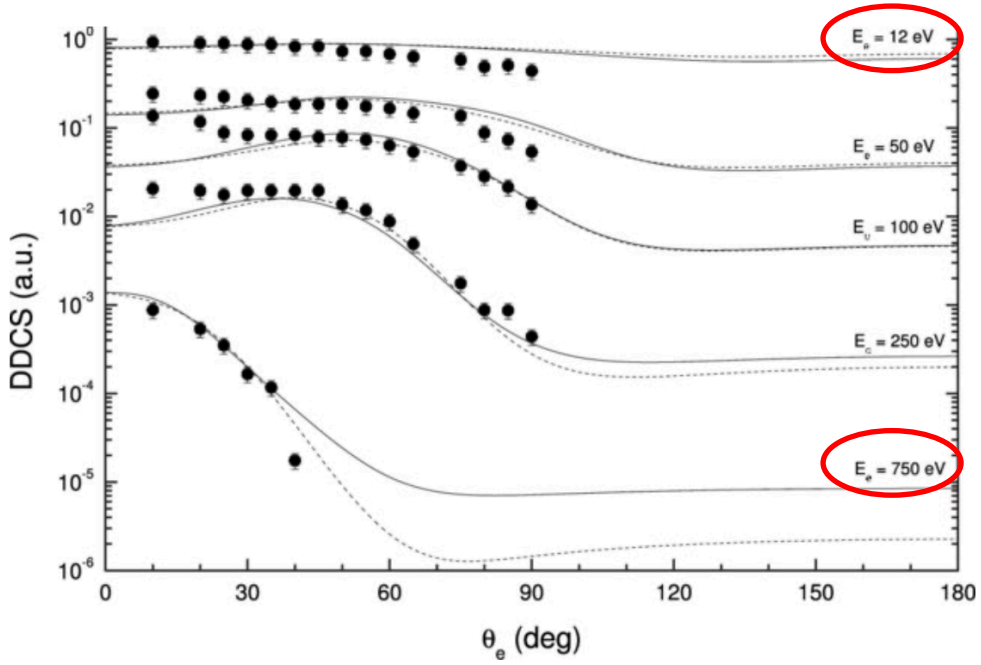
Cross section calculation/measurements require fundamental knowledge

Total ionization cross sections, Th vs Expt



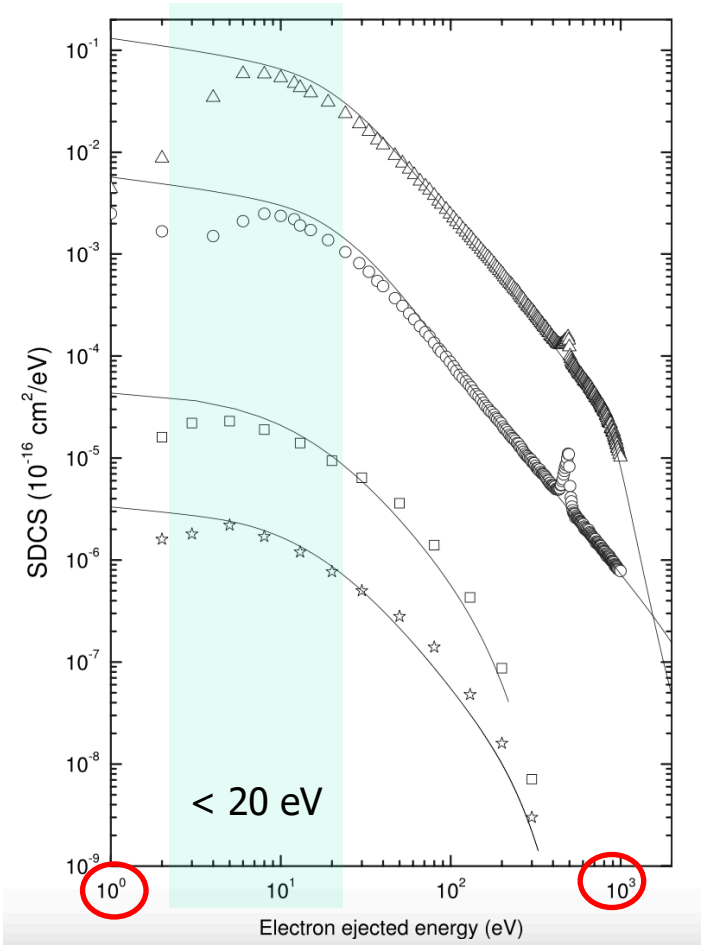
J. Chem. Phys. **117**, 197 (2002)

Doubly differential cross sections for single ionization 0.3 MeV protons



Phys.Rev. A 75, 022720 (2007)

A huge task !

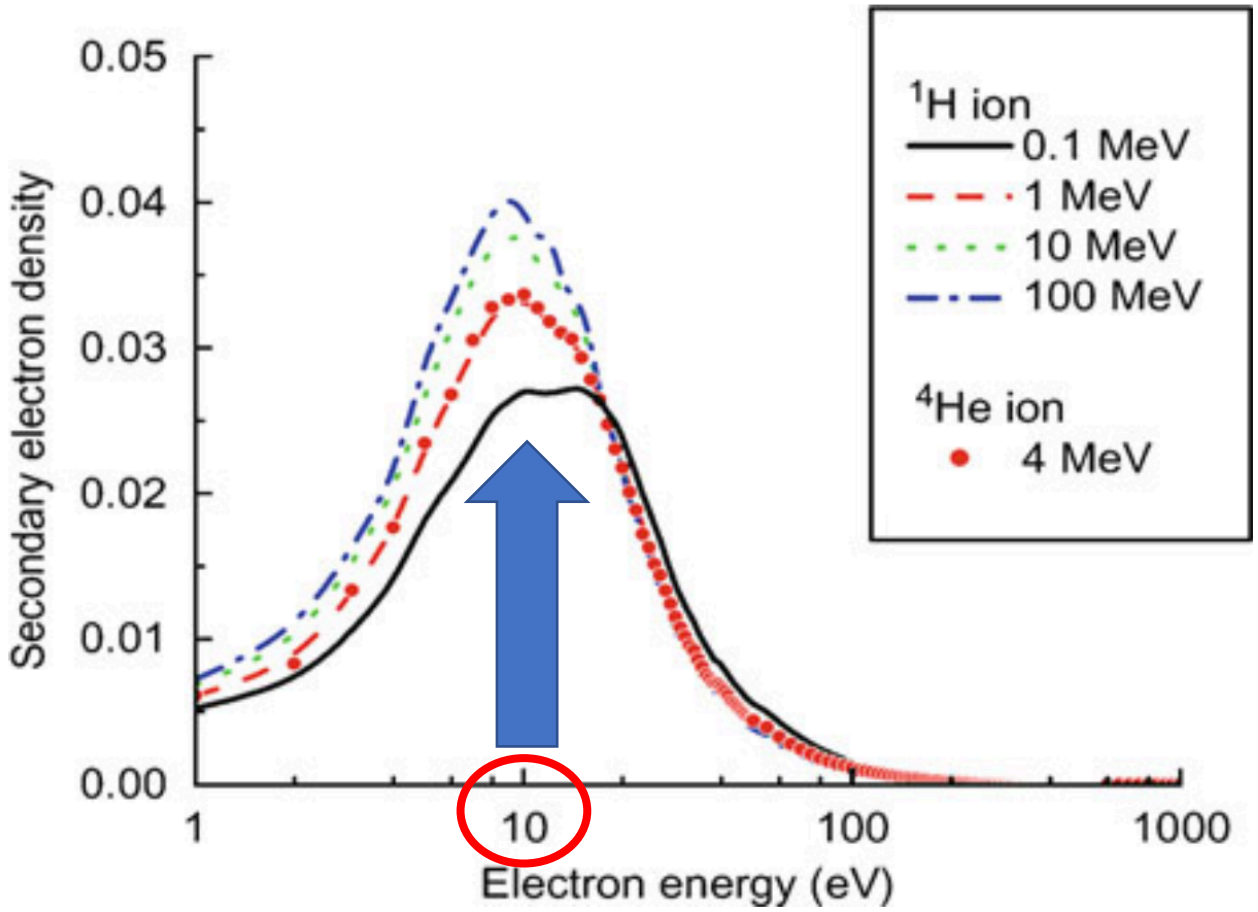


Ejection of electrons by protons (0.5 -1.5 MeV)

Why secondary electrons, and why LEE in particular ?

In particular, the mechanisms of action of LEE with biomolecules must be known, from gas to condensed phase and ultimately biological tissue and cells.

Majority of the reactive species, which initiate further chemical reactions, are created by secondary electrons



Rad. Phys. Chem. 76, 1244 (2007)

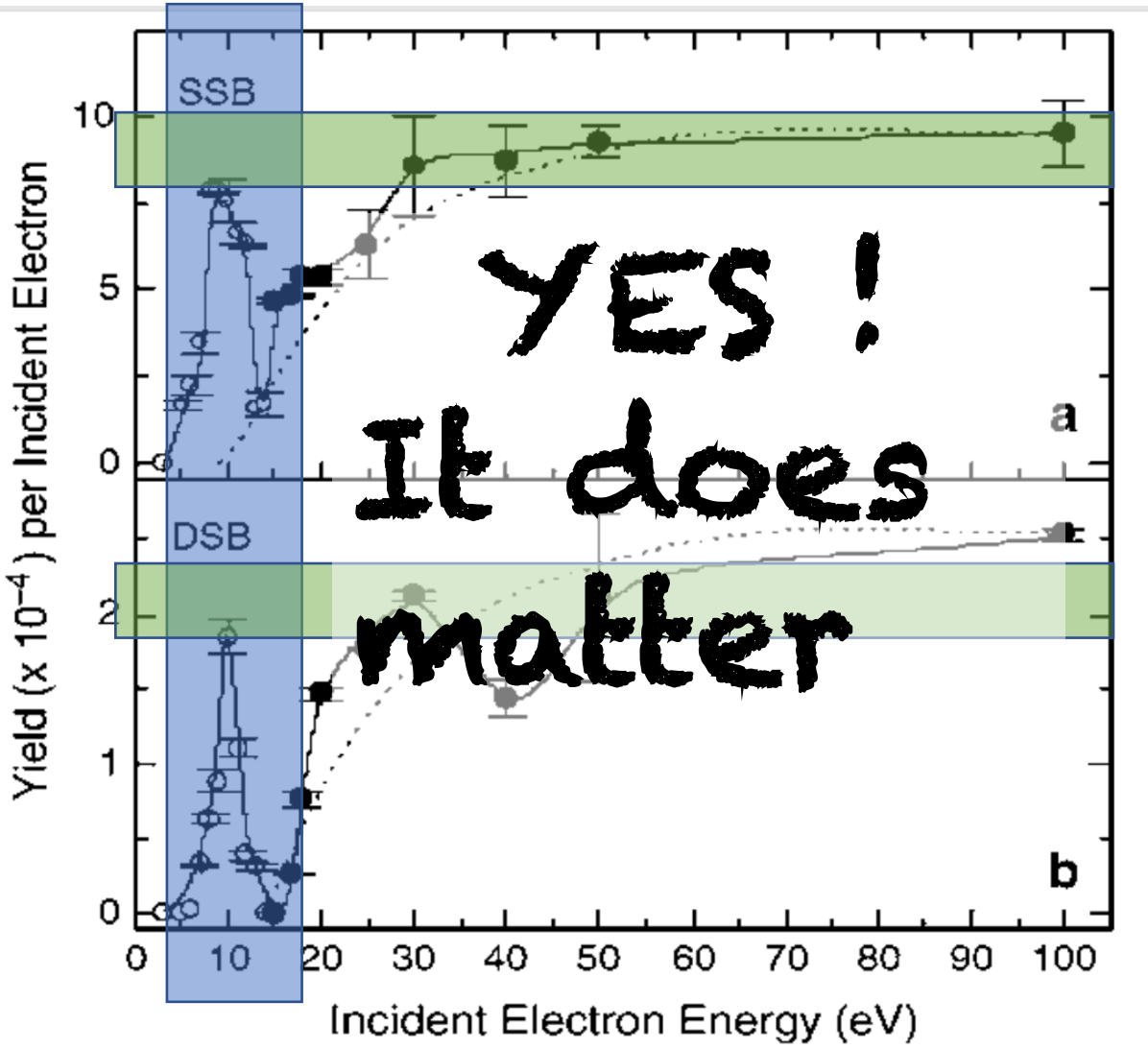
Does it matter to have all these LEE ?

SUMMARY SO FAR

- ✓ High energy radiations produce large amount of secondary electrons (among other species)
- ✓ Secondary electrons trigger further damage within ps time and nm distance from primary source,
- ✓ electron energy distribution thermalizes and peaks around 10 eV

What about these LEE, 0-30 eV ??
SHOULD WE WORRY ABOUT THEM ?

- Electrons of 10 eV induce SSB and DSB in DNA
- with a probability similar to that of 100 eV electrons, which is where electrons have the highest cross section to damage molecules .



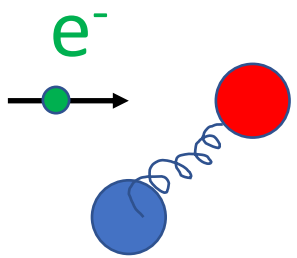
3 MARCH 2000 VOL 287 SCIENCE

J. Am. Chem. Soc. 125, 4467 (2003)

How do LEE dissociate DNA and plasmide below IP ?

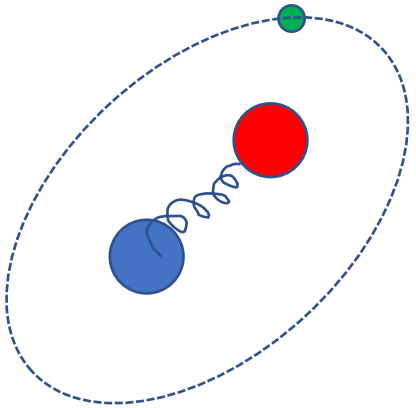
Now we know the answer is YES, LEE can be **BIG PROBLEM**, perhaps the major cause of radiation damage, in biomolecular systems according to some authors. But HOW ?!

Dissociative Electron Attachment (DEA)

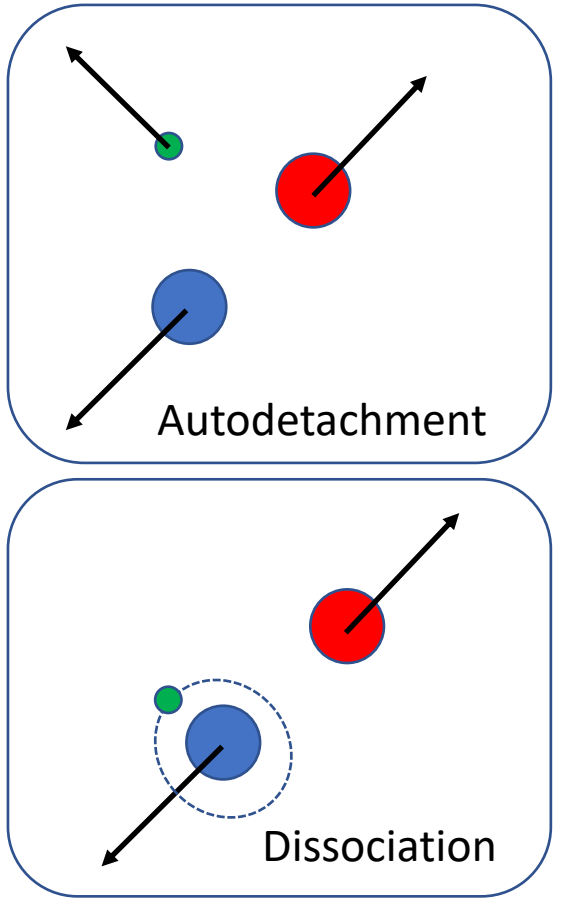


Collision

Transient negative ion by resonant capture



Dissociation

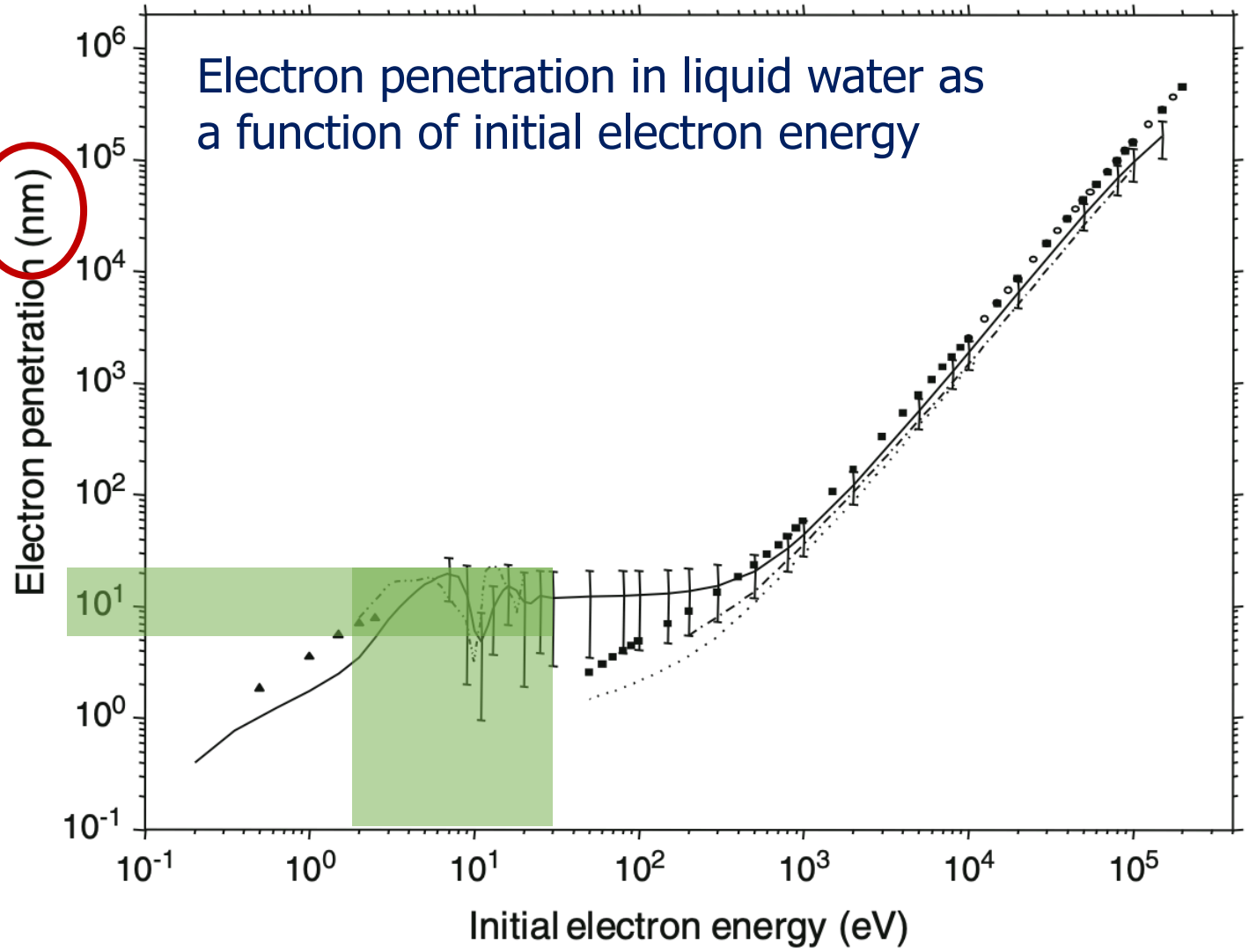


A ‘simple’ but effective break-up mechanism

LEE can produce a ‘localised’ damage

Electrons of energy 1–30 eV have a very short penetration range. So

- ✓ **damage they produce can be confined** within a range of a few biomolecules near the their source
- ✓ they can easily produce **clustered damage** in large biomolecule; i.e. a type of lesions which is difficult to repair.



Gustavo Garcıa Gomez-Tejedor Martina Christina Fuss Editors Radiation Damage in Biomolecular Systems, Springer (2012), Chapter 1

Summarising, it all sounds very bad. But...

- ✓ can relocate the distribution of radiation energy within nanoscopic volumes, around irradiation site

- ✓ Increasing their number near DNA of tumour cells we can enhance the radiation effects, and make radio/photo theraphy more effective

Electrons of 1–30 eV

- ✓ are created in much larger numbers than those of higher energies
- ✓ have considerable efficiency to break DNA
- ✓ produce multiply clustered damage on the same sites
- ✓ have the shortest possible range in biological tissue, so…

Let's make LEE help for us against tumour cells

Stage 1.
Fundamental knowledge

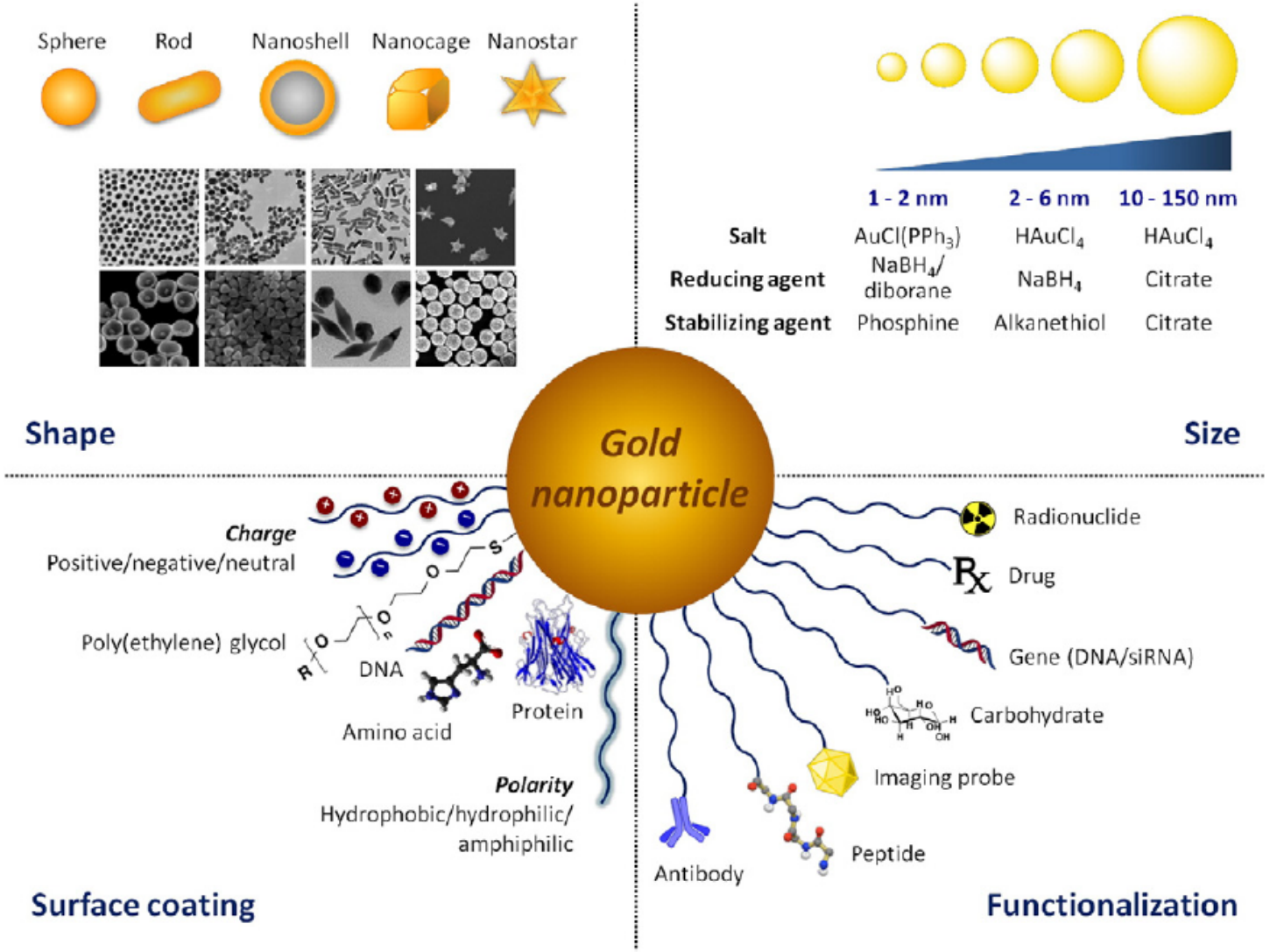
Stage 2.
Targeted Application

Now we **understand** the process that cause the damage and we can **design radiosensitisers** that exploit the harmful effect of LEE specifically against tumour cells, i.e. make radiotherapy more effective against 'sensitised' tumour cells, reducing the overall dose needed to achieve therapy and therefore side effects for patients.

The next task is then design specific **RADIOSENSITISERS**

Of course, this opens an entire new field

LEE and radiosensitisers in nanoparticle (NP): why NP



Just the word NP opens a huge field, and our application on secondary electrons, in particular LEE emission, only scratches the surface on a very specific application.

(Metal) NP are very versatile

For example, can be bound to specific ligands that serve as a **vehicle to deliver NPs to cancer cells**, cross membranes and approach the nucleus.

S. Her et al. / Advanced Drug Delivery Reviews 109 (2017) 84

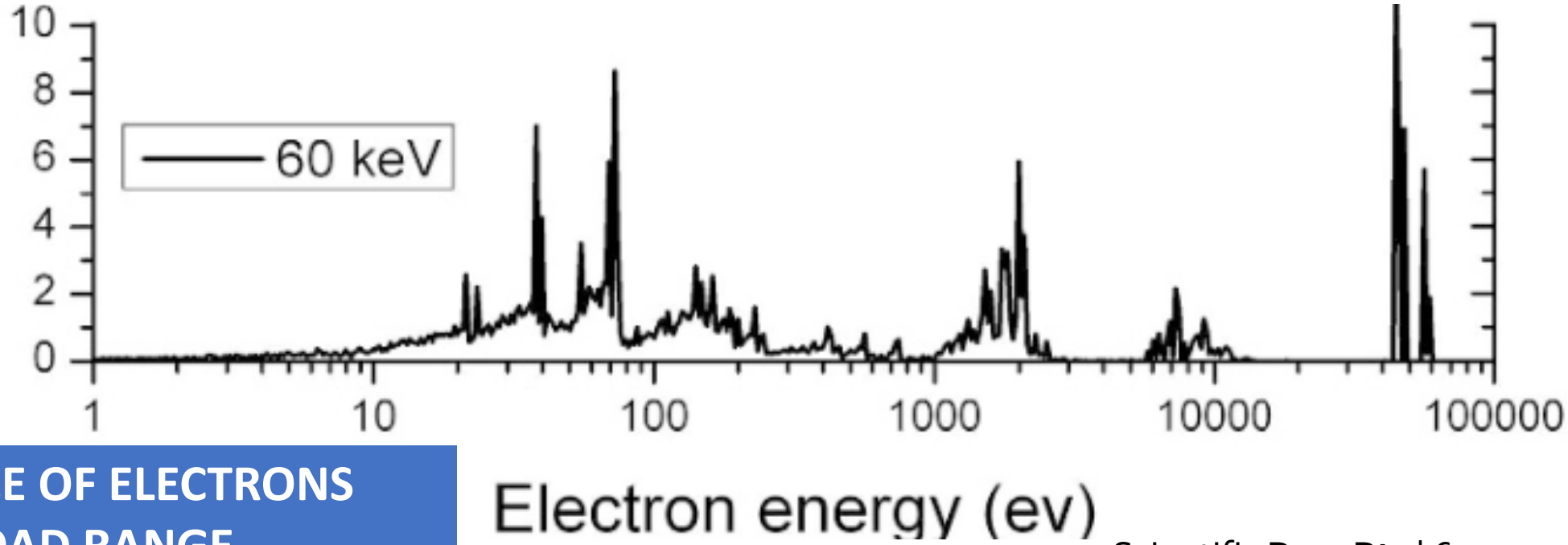
Where it all comes together: radiosensitisations, NP, LEE

- ✓ (Metal) NP have long been considered promising sensitisers
- ✓ Metals increase the absorption of ionizing radiation and absorb higher energy compared to organic

  BE of Au(1s) is about 80.7 keV

  i.e. store high energy close to target, and
- ✓ release it in an avalanche of secondary electrons that shortly thermalize into LEE

Emission of secondary electrons From 2nm GNP

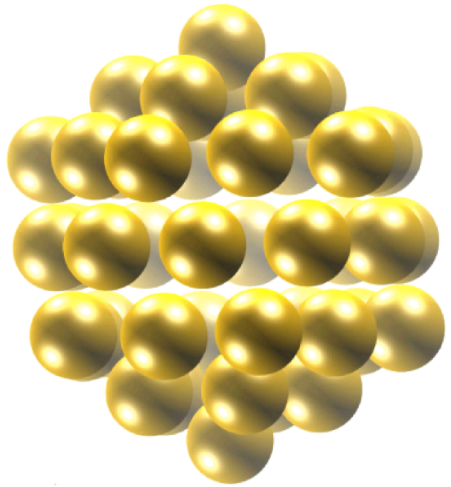


A GREAT SOURCE OF ELECTRONS OVER A BROAD RANGE…

Scientific **RepoRts** | 6:19442

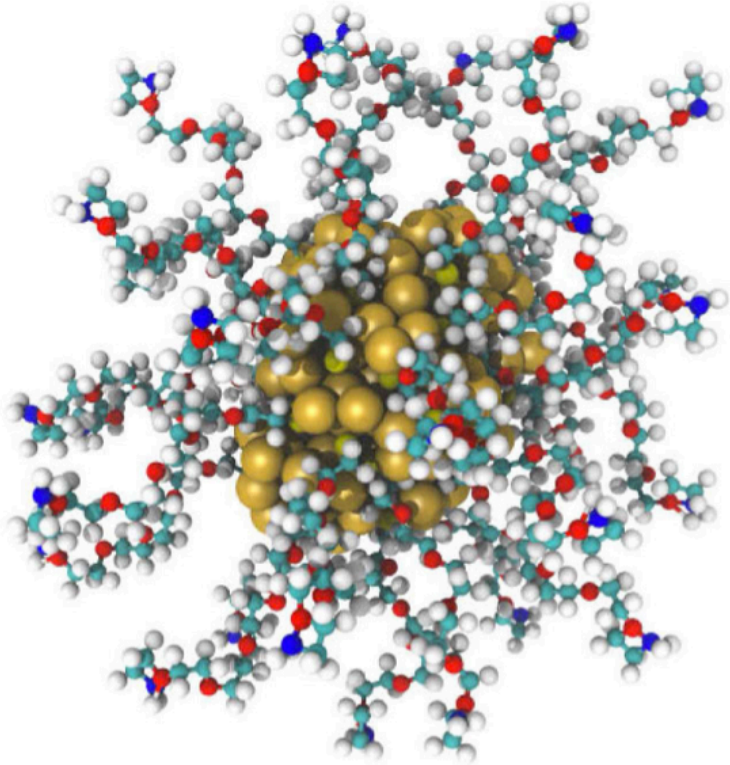
Radiosensitisations, NP, LEE

This broad energy distribution and high initial emission energies are very 'helpful' to overtake the 'barrier' due to long/thick coating layers of functionalised NP, compared to 'naked' NP



J. Phys. Chem. C 2015, 119, 11000−11013

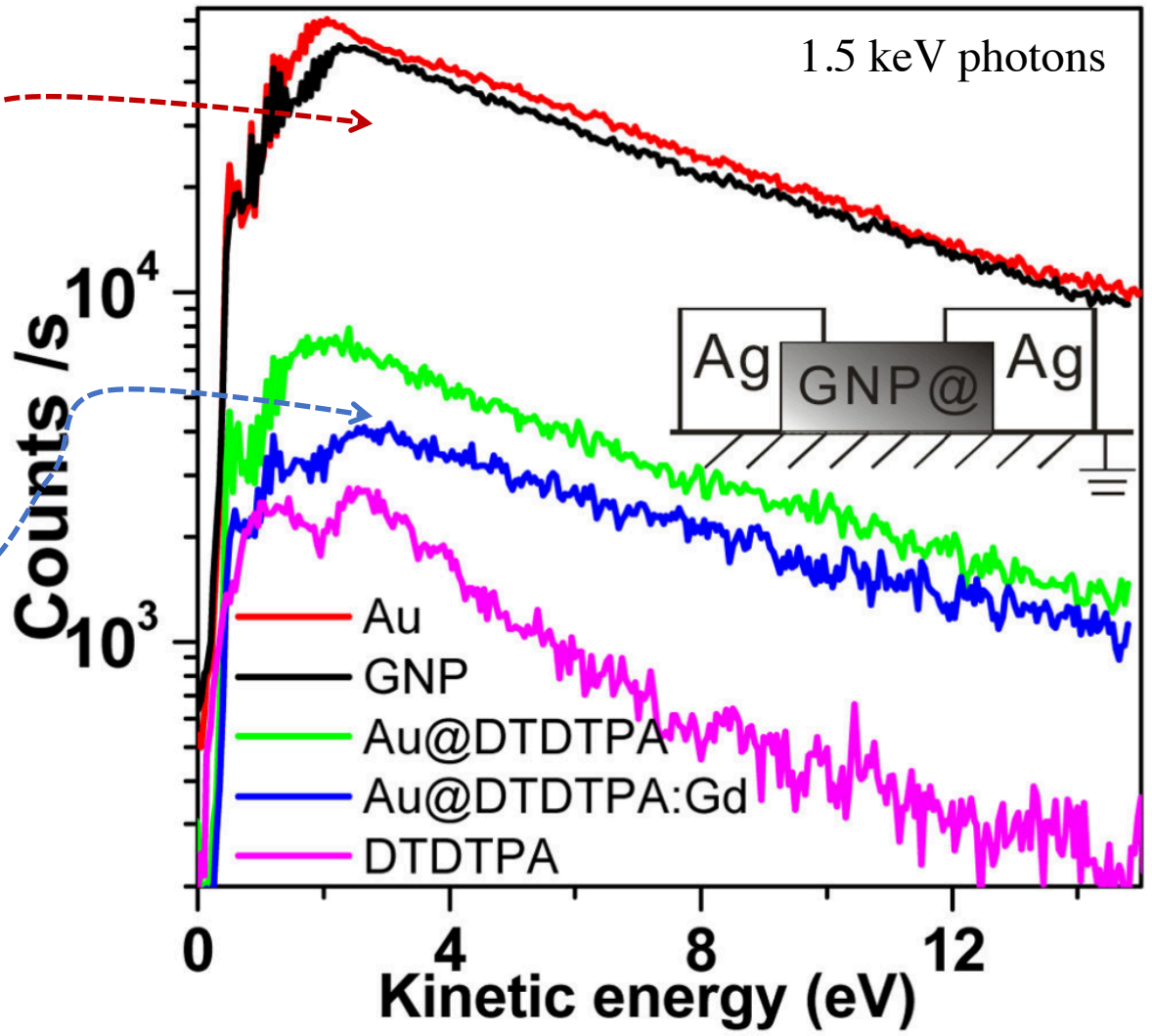
In fact, the amount of DNA damage appears to be related to the thickness of the linker.



European Physical Journal D 72, 116 (2018)

Demonstration of the attenuation due to coating on the NP

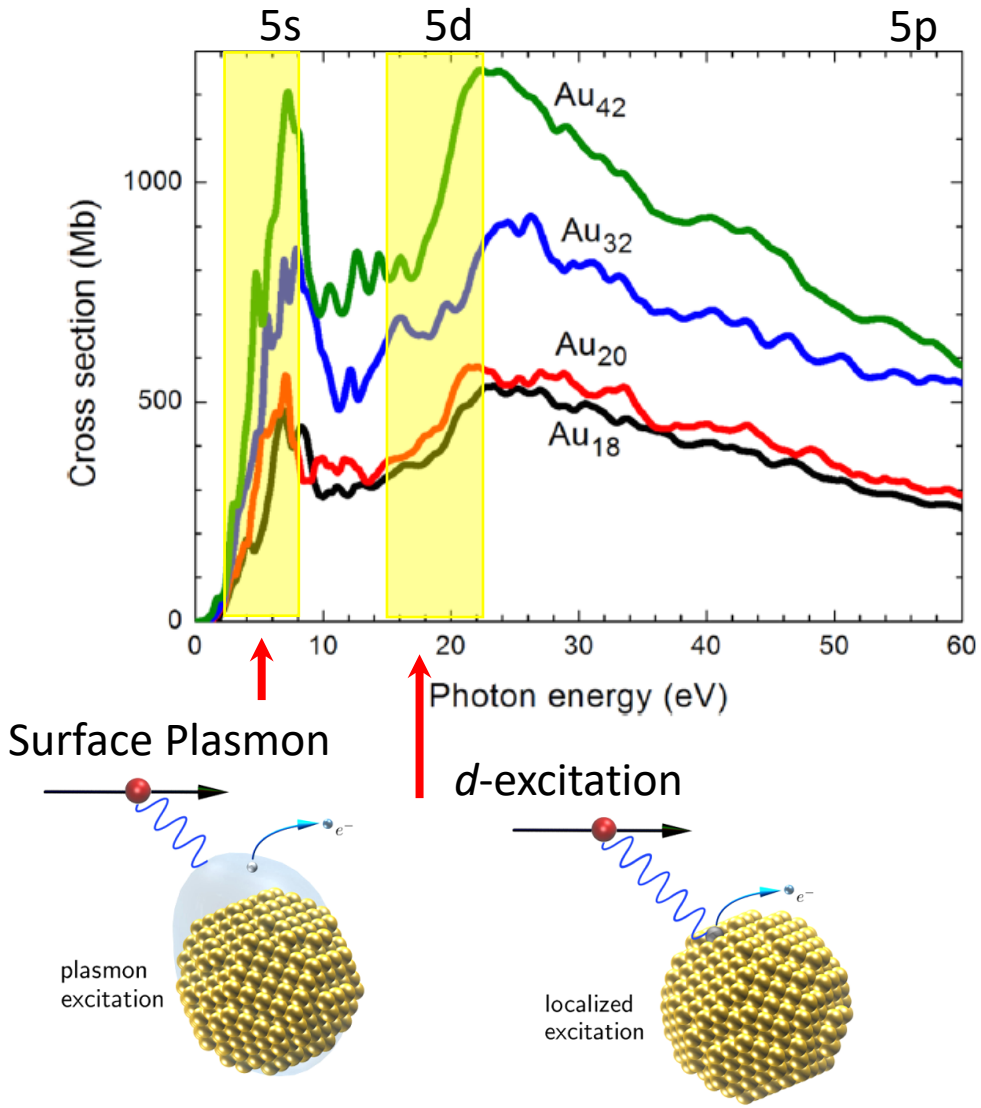
Intensity distribution of **0–15 eV** secondary electrons emitted from
- a gold surface
- GNP films without the linker: intensity of SE is almost the same as that of pure gold substrate
- GNP films with linkers: the intensity of SE are about one order of magnitude smaller than that of pure GNP.



Mechanisms that involve 'low energy transfer' to metal NP

SUMMARISING SO FAR:

- ✓ NP are efficient tools to specifically target tumours cell, perhaps even penetrate near DNA,
- ✓ absorb and localise high energy which
- ✓ is then 'converted' into electron emission (and/or temperature)



Collective plasmon excitation & atomic giant resonances

- ✓ Activated by low energy electrons (0-30 eV … and we have many)
- ✓ Very high absorption cross sections
- ✓ Emission of secondary electrons

Verkhovtsev et al, JPC C 2015, 119, 11000
Verkhovtsev et al, PRL 2015, 114, 063401

Low Energy Electrons in radiobiology: '*a bless or a curse*' ?

" Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more, so that we may fear less."

(Marie Curie)

Thanks

CNR - ISM
Istituto di Struttura
della Materia