ASP Seminar

Monte Carlo Simulations in Radiotherapy: Enhancing Treatment with Radioprotectors and FLASH-RT

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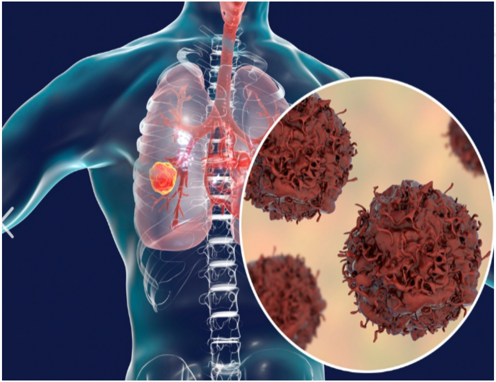
Outline

- Cancer



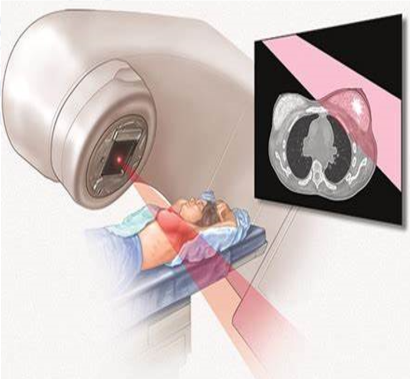
- Cancer incidence was $\sim$ 19 *million* new cases in 2020, accounting for nearly 10 million deaths
- With projections indicating an increase to $\sim$ 28 *million* by 2040

Background and Motivation

Short description of the project

- Radiation therapy (RT)

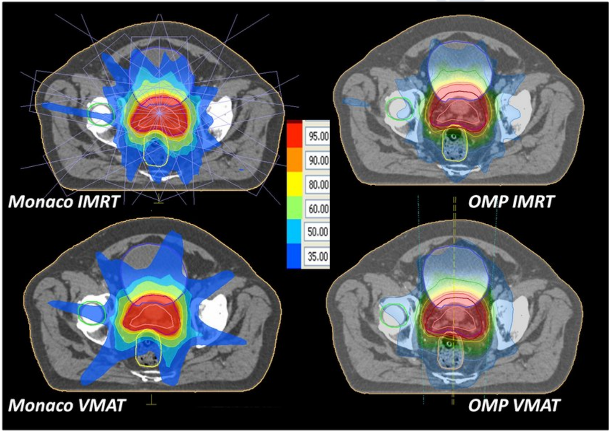
- **50% of cancer patients receive radiation therapy during their course of illness**
- **It contributes towards 40% of curative treatment of cancer**



External radiation beam therapy

Background and Motivation
Short description of the project

- Radiation therapy goal



External beam photon

Background and Motivation

Short description of the project

- Radiotherapy techniques

Technological progress of RT techniques

Heavy particles: protons and carbon ions

Conventional RT has undergone a major expansion

- 3-D technique
- Intensity-Modulated
- Volumetric Modulated Arc
- Stereotactic Irradiation
- Image-Guided Radiotherapy

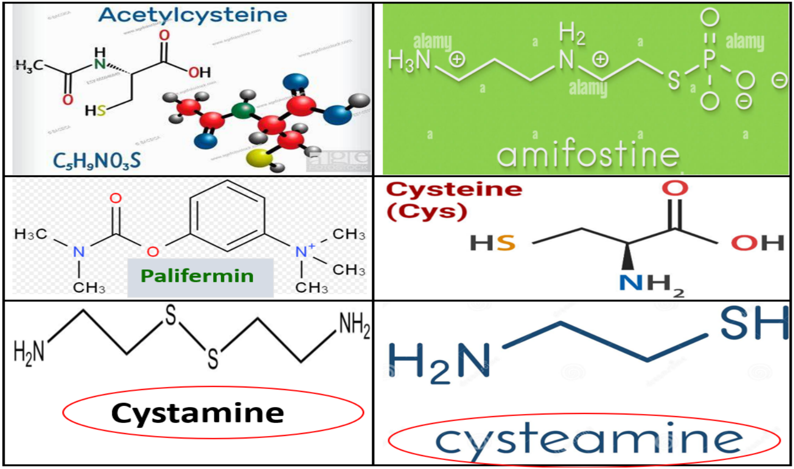
Background and Motivation

Short description of the project

Clinical management of cancer

Rising incidence of the disease

- Radioprotectors

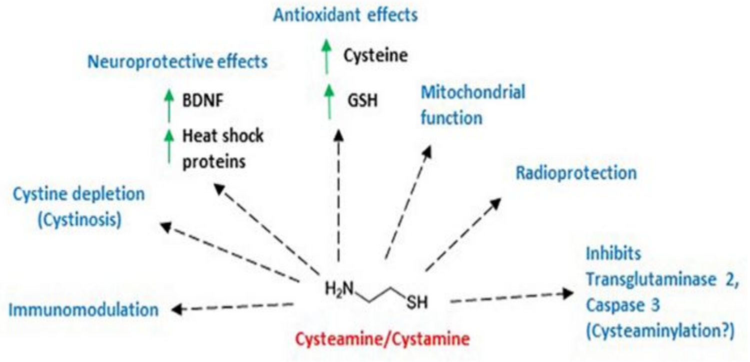


Chemical structure of radioprotectors

Background and Motivation

Short description of the project

In addition to their radioprotective role, Cystamine/Cysteamine hold many clinical properties

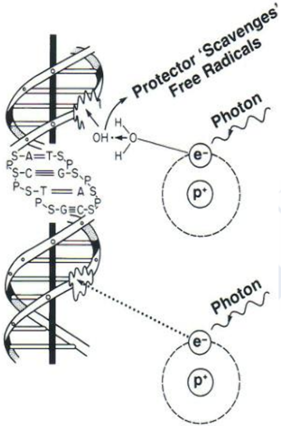


Clinical properties of Cysteamine & Cystamine (Bindu et al., 2021)

Background and Motivation

Short description of the project

- Radioprotectors Mechanism of action



Radioprotectors Mechanism of action

- **How do they work?**

- Radioprotectors exert their effects by scavenging free radicals, thereby reducing damages they may cause to DNA, and other cellular components

Background and Motivation

Short description of the project

- Previous works - Protective agents - Conventional-RT

Healy, J. B. (1960). A trial of cystamine in radiation sickness. *The British Journal of Radiology, 33(392)*, 512-514.

Wasserman, T. H., Brizel, D. M. (2001). The role of amifostine as a radioprotector. *Oncology (Williston Park, NY), 15(10), 1349-54.*

Ambroż, H. B., Kornacka, E. M., & Przybytniak, G. K.(2004) Influence of cysteamine on the protection and repair of radiation-induced damage to DNA. *Radiation Physics and Chemistry, vol. 70, no 6, p. 677-686.*

Adnan, M., Rasul, A., Shah, M. A., Hussain, G., Asrar, M., Riaz, A., ... Hussain, S. M. (2022). Radioprotective role of natural polyphenols: From sources to mechanisms. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 22(1)*, 30-39.

Background and Motivation

Short description of the project

- Previous works - Protective agents - Conventional-RT

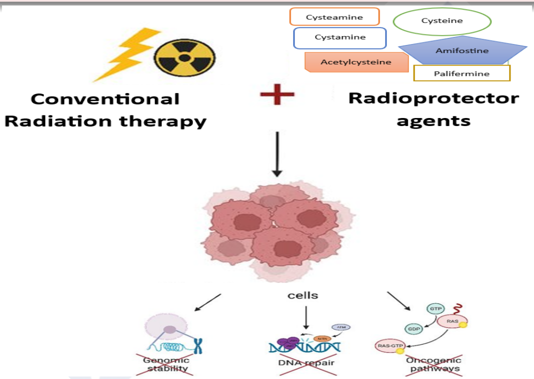
- These studies have clearly demonstrated that radioprotectors such as amifostine, cystamine, and cysteamine possess radioprotective properties, characterized by their ability to scavenge free radicals

- Why are they nowadays not frequently used in clinical settings ?

Background and Motivation

Short description of the project

- Protective agents - Conventional-RT



- Conventional RT is limited by the toxicity and adverse effects of ionizing radiation on healthy tissues
- Complexity of targeted administration of radioprotectors

Background and Motivation

Short description of the project

FLASH radiotherapy

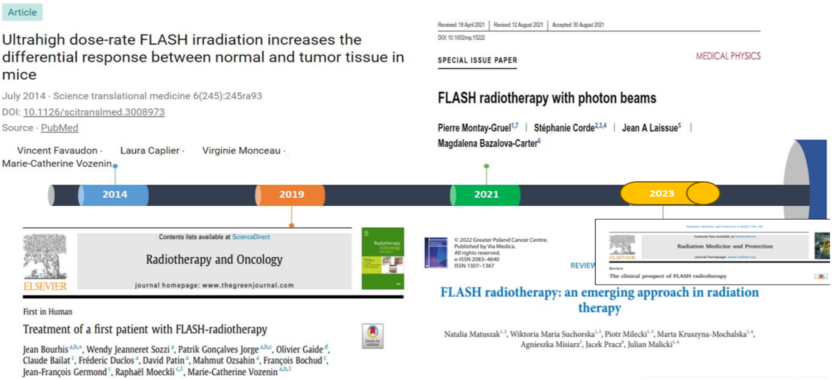
- The advent of FLASH-RT has revolutionized the field of radiotherapy

- FLASH-RT is a RT technique that delivers radiation doses at ultra-high doses, typically exceeding 40 Gy/s
- This approach minimizes damage to healthy tissue while destroying effectively tumor cells
- FLASH radiotherapy is delivered in a single dose, unlike conventional RT, which is administered in multiple fractions

Background and Motivation

Short description of the project

- Previous works - FLASH radiotherapy

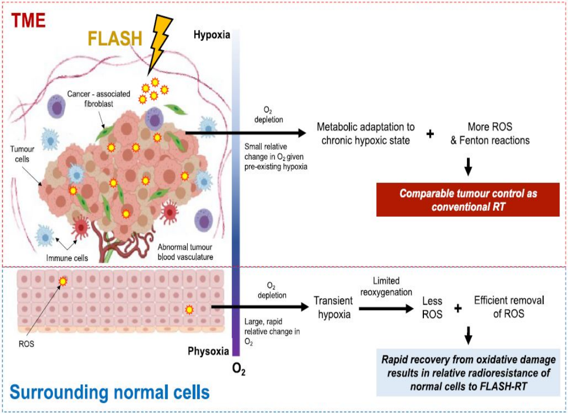


Following this initial trial, several research works are continuing to improve cancer treatment by FLASH radiotherapy

Background and Motivation

Short description of the project

- Biological mechanism of FLASH-RT



FLASH-RT & Conventional-RT (Binwei et al., 2021)

FLASH-RT hypothesis:

- Oxygen depletion
  - FLASH-RT induces a rapid depletion of oxygen, which minimizes reactive oxygen species (ROS) and free radical production, reducing normal tissue damage

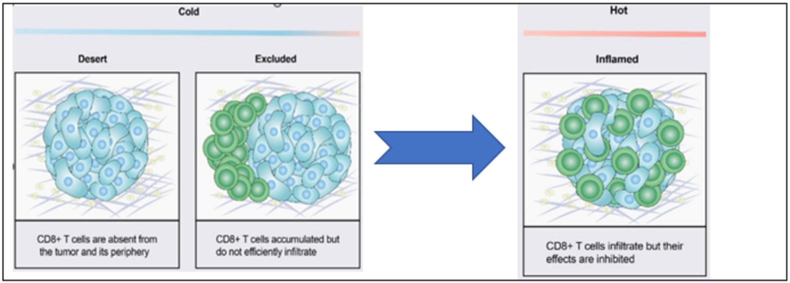
Background and Motivation

Short description of the project

- Biological mechanism of FLASH-RT

FLASH-RT hypothesis:

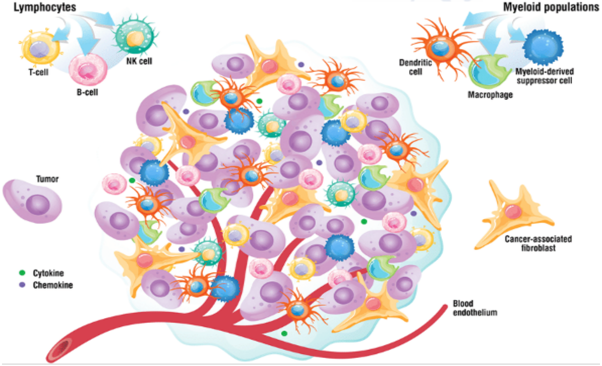
- Mitochondrial Protection and Immune Response
  - FLASH-RT protects healthy mitochondrial cells
  - FLASH-RT can promote the transformation of "cold tumors" into " hot tumors "



  - FLASH-RT can enhance immune response against tumors
  - FLASH-RT can generate an abscopal response

Tumor microenvironment (TME)

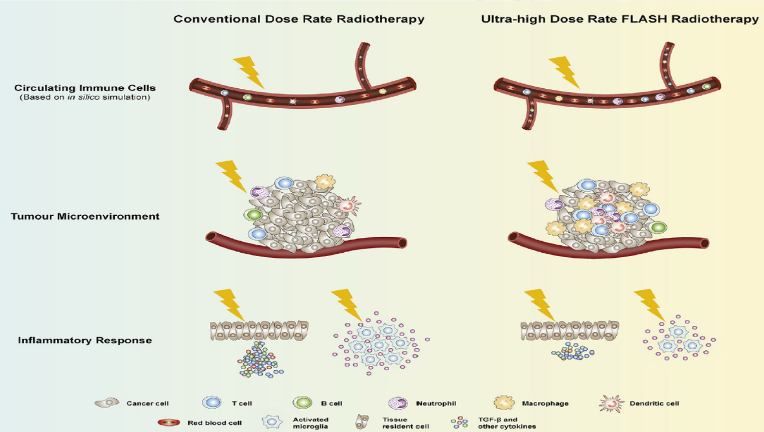
The TME is a complex network of extracellular, composed of cancer-associated fibroblasts, various immune cells, and non-cellular components



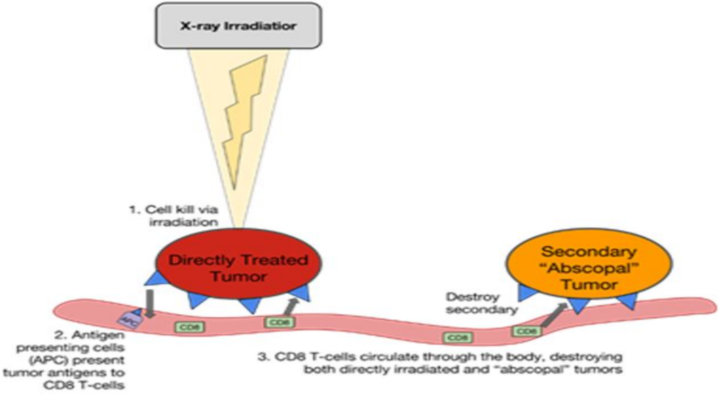
- Understanding the impact of radiotherapy on the immune microenvironment is crucial for enhancing the effectiveness of radiotherapy as a cancer treatment

CONV-RT vs FLASH RT

Radiotherapy can induce upregulation of immunostimulatory cells (CD8+ T cells, NK cells) and immunosuppressive cells (Tregs, MDSCs, M2 macrophages)



- Abscopal effect
- The abscopal response is when radiation therapy on one tumor not only affects that tumor but also helps the immune system attack other tumors in the body that weren't directly treated



Abscopal effect

Background and Motivation

Short description of the project

FLASH-RT induces:

- Activation of immune cells
- Reduction in the production of reactive oxygen species (ROS) and free radicals

- Although FLASH-RT seems to improve the cancer treatment therapeutic ratio, it does not provide total protection of surrounding healthy tissue

- It is therefore expected that the combination of a radioprotective agent with FLASH-RT could further improve the therapeutic ratio in cancer treatment

Background and Motivation

Short description of the project

- Nuclear power plant accident - nuclear weapons deployment

Fukushima-Daiichi-Nuclear-Plant

Nuclear weapons deployment

Background and Motivation

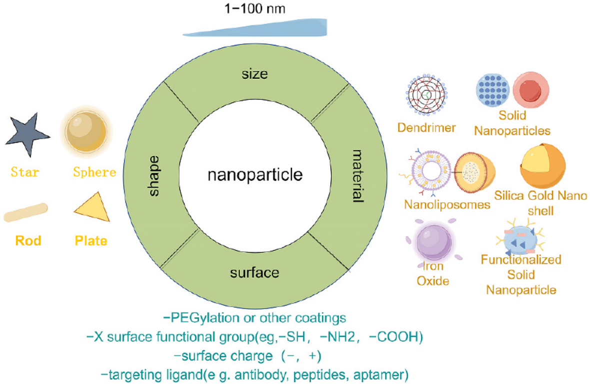
Short description of the project

- Nuclear terrorism and for the protection of astronauts

Nuclear/radiological terrorism

Astronauts/cosmonauts

- **Controlled Release and Targeting**: Nanoparticles can be designed to deliver cystamine or cysteamine in a targeted and controlled manner, precisely reaching damaged tissues or areas that need protection



- **Increased Stability and Bioavailability**: By encapsulating cystamine or cysteamine in nanoparticles, their stability and bioavailability in the body can be improved

Limits and Problems

- No studies have explored the synergy between FLASH-RT and radioprotectors such as cystamine and cysteamine
- No study has been conducted to compare the radioprotective capacity of cysteamine with that of cystamine under various LETs and High Dose Rates irradiation conditions
- Lack of data to better understand the mechanisms underlying the FLAH radiotherapy
- Protection of population from unintentional exposure at Ultra-High Dose Rate

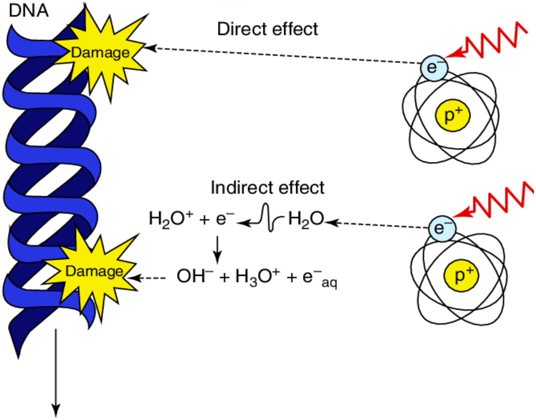
Objective

- The aim of this research is to elucidate the mechanisms underlying the efficacy of cystamine and cysteamine as radioprotectors in the context of FLASH radiotherapy and hadrontherapy from a radiochemical perspective using Monte Carlo simulation

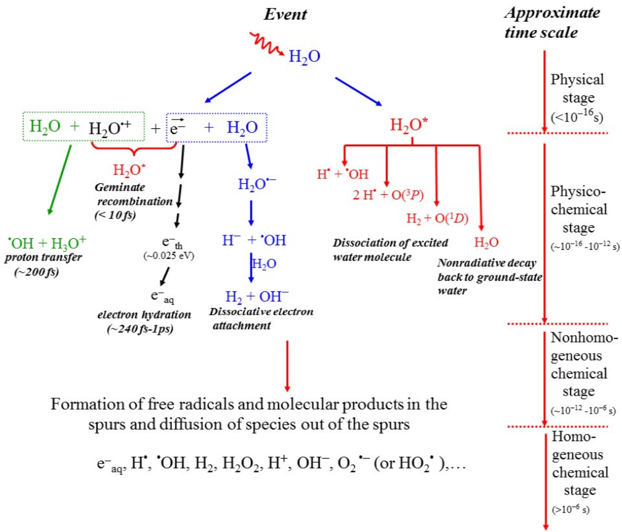
Background and Motivation

Ionizing radiation - Radiolysis of water - DNA damage

Ionizing-radiation-induces-direct-DNA-damage-and-indirect-damage-through-the-radiolysis

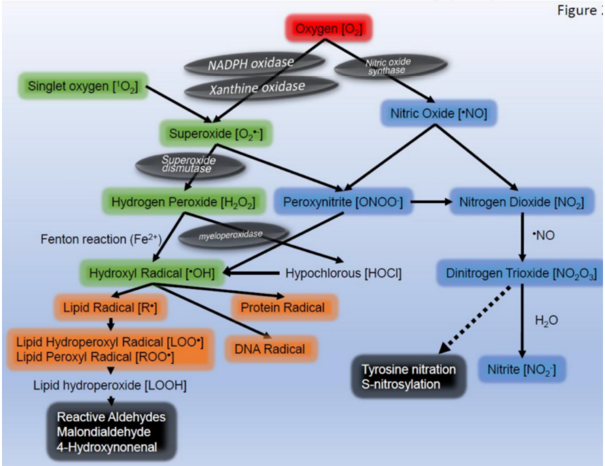


Side effects following cancer treatment with radiotherapy are mostly caused by the indirect effects of radiation through the formation of free radicals


Event
H2O
Approximate time scale
H2O + H2O•+
+ e⁻ + H2O
H2O*
H2O*
Geminate recombination (< 10 fs)
H2O•−
H• + •OH
2 H• + O(3P)
H2 + O(1D)
H2O
•OH + H3O+
proton transfer (~200 fs)
e⁻th (~0.025 eV)
H⁻ + •OH
H2O
H2 + OH⁻
Dissociative electron attachment
e⁻aq
electron hydration (~240 fs-1ps)
Dissociation of excited water molecule
Nonradiative decay back to ground-state water
Physical stage (<10⁻¹⁶ s)
Physico-chemical stage (~10⁻¹⁶ -10⁻¹² s)
Nonhomo-geneous chemical stage (~10⁻¹² -10⁻⁶ s)
Homo-geneous chemical stage (>10⁻⁶ s)
Formation of free radicals and molecular products in the spurs and diffusion of species out of the spurs
e⁻aq, H•, •OH, H2, H2O2, H+, OH⁻, O2•− (or HO2•),…

Reaction pathway of reactive oxygen species and free radicals

- In the living body, free radicals exist as ROS, lipid, protein, and DNA radicals



- The amount of free radicals is determined in terms of radiolytic yields

Radiolytic yields

$$G(X) = \frac{\text{Number of species formed or disappeared}}{\text{100 eV absorbed}}$$

It is expressed in molecules/100 eV

1 molecule/l00 eV $= 1.036x10^{-7} mol/J$

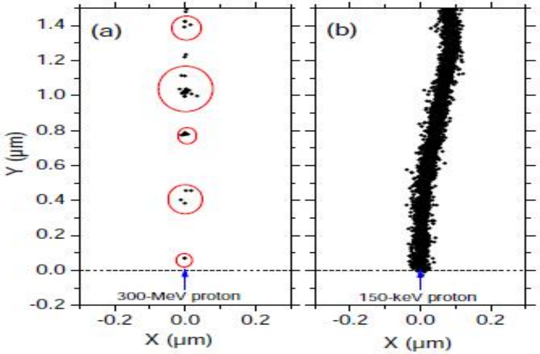
Influence of parameters

Radiolytic yields change as a function of several parameters such as

- Time
- pH
- Type of ionizing particle
- Linear Energy Transfer (LET)
- Dose Rate
- Solute concentration

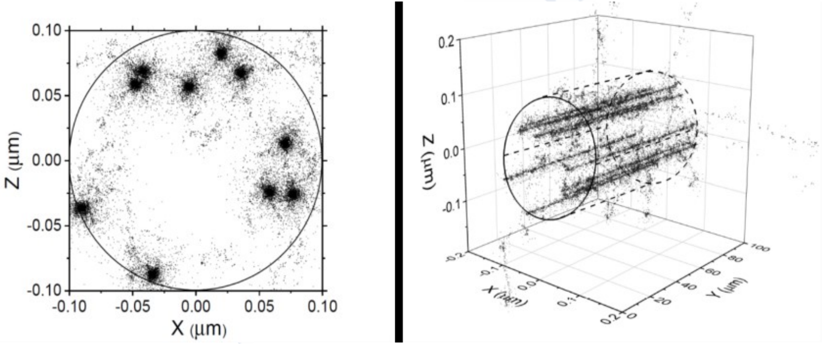
Influence of LET

The radiolytic yield of the formed species are dependent on the spatial distribution of the energy deposited in the studied medium



Low LET & High LET (KANIKE et al., 2015)

Influence of Dose Rate



Left panel: Illustration of our simulation model in the case of ten 300 MeV incident protons ($LET \sim 0.3 keV/\mu m$), which randomly and simultaneously impact the XZ plane perpendicularly on the surface of the solution within a circle of radius $R_o = 0.1\mu m$. Right panel: 3D representation of the N = 10 proton tracks traversing through the solution calculated at $\sim 1ps$ from our Monte Carlo code. All protons travel along the Y-axis over the whole track length chosen for the calculations.

Influence of solute concentration

When chemical scavengers are present in a solution, they are able to capture the radical species resulting from the radiolysis of water

$$R + S \xrightarrow{k_{rs}} P$$

The efficiency with which the solute S reacts with the radical R is characterized by the scavenging power of S expressed in s^{-1} and defined as:

$$\text{Scavenging power} = k_{rs} \times [\text{S}]$$

Materials and methods

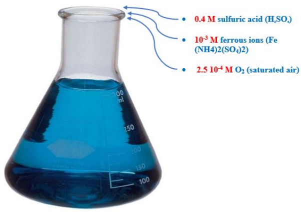
Study Model

- This quantitative study was conducted using the Fricke dosimeter as a model through Monte Carlo simulations

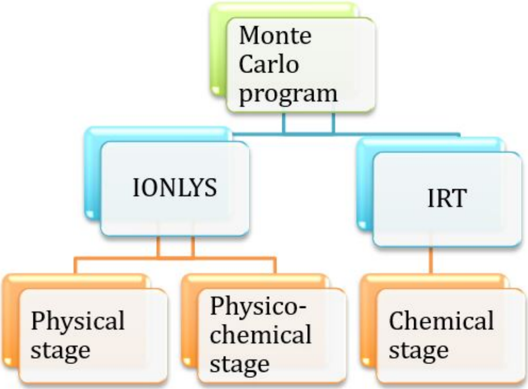
- What is the Fricke dosimeter ?

- The Fricke dosimeter is a dosimetry method that uses a ferrous sulfate solution to measure the absorbed radiation dose, mainly in the context of radiotherapy
- The Fricke dosimeter is quite sensitive and can measure relatively low radiation doses, which makes it useful in medical applications

- The standard Fricke dosimeter is composed of:



Structure of our program



- Free radicals in the Fricke dosimeter are quantified by the oxidation of Fe^{2+} to Fe^{3+}

Chemical Reactions

- Main reactions for ferric ion production in Fricke solution

R.(1)	$Fe^{2+} + {}^{\bullet}OH \rightarrow Fe^{3+} + OH^{-}$	$k = 3.4 \times 10^{8}$
R.(2)	$e^{-}_{aq} + H_3O^{+} \leftrightarrow H^{\bullet} + H_2O$	$k = 2.3. \times 10^{10}$
R.(3)	$H^{\bullet} + O_2 \rightarrow HO_2{}^{\bullet}$	$k = 2.1 \times 10^{10}$
R.(4)	$Fe^{2+} + HO_2{}^{\bullet} \rightarrow Fe^{3+} + HO_2{}^{-}$	$k = 7.9 \times 10^{5}$
R.(5)	$HO_{2}- + H_3O^{+} \rightarrow H_2O_2 + H_2O$	$k = 5.0 \times 10^{10}$
R.(6)	$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^{-}$	$k = 52$
R.(7)	$Fe^{2+} + H^{\bullet} \rightarrow Fe^{3+} + H_2$	$k = 1.3 \times 10^{7}$

- These reactions are function of the rate constant, noted k, expressed in $M^{-1}s^{-1}$

Materials and methods

Fricke Dosimeter - Chemical reactions - Radiolytic yields

- $G(\mathrm{Fe}^{3+}) = \sum g_i$,

  where g_i represents the produced radical or molecular species

- The $G(\mathrm{Fe}^{3+})$ value in aerated environments (analogous to healthy tissue) is:

$$G(\mathrm{Fe}^{3+}) = 15.5\ molecule/100eV \quad (1)$$

- In extreme hypoxic environments (analogous to tumors), the $G(\mathrm{Fe}^{3+})$ value is:

$$G(\mathrm{Fe}^{3+}) = 8.1\ molecule/100eV \quad (2)$$

The radioprotective properties of radioprotectors are evaluated by the decrease of $G(\mathrm{Fe}^{3+})$

Chemical Reactions - Fricke solution - Radioprotectors

Cystamine (RSSR)

		$(M^{-1}s^{-1})$
E.(1)	$RSSR + e^-_{aq} \rightarrow (RSSR)^{\bullet -}$	$k = 4.1 \times 10^{10}$
E.(2)	$RSSR + H^\bullet \rightarrow RS^\bullet + RSH$	$k = 8 \times 10^9$
E.(3)	$RSSR + {}^\bullet OH\ (+ H^+) \rightarrow (RSSR)^{\bullet +}) + H_2O$	$k = 1.7 \times 10^{10}$
E.(4)	$Fe^{2+} + RS^\bullet \rightarrow Fe^{3+} + RS^-$	$k = 2.5 \times 10^8$
E.(5)	$Fe^{2+} + RSSR^{\bullet +} \rightarrow Fe^{3+} + RSSR$	$k = 2 \times 10^6$

Cysteamine (RSH)

E.(1)	$RSH + e^-_{aq}(+H^+) \rightarrow R^\bullet + H_2S$	$k = 3 \times 10^{10}$
E.(2)	$RSH + H^\bullet \rightarrow RS^\bullet + H_2$	$k = 1.8 \times 10^9$
E.(3)	$RSH + {}^\bullet OH \rightarrow RS^\bullet + H_2O$	$k = 1.7 \times 10^{10}$
E.(4)	$Fe^{2+} + RS^\bullet(+H^+) \rightarrow Fe^{3+} + RSH$	$k = 2.5 \times 10^8$

- Rate constant
- Diffusion constant
- Radioprotectors concentration

Results and discussions

1^{st} Publication

molecules

MDPI

Article

Effect of Linear Energy Transfer on Cystamine's Radioprotective Activity: A Study Using the Fricke Dosimeter with 6–500 MeV per Nucleon Carbon Ions—Implication for Carbon Ion Hadrontherapy

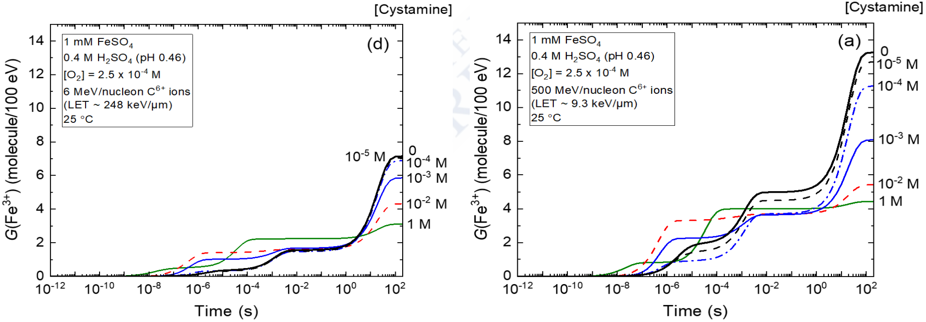
Samafou Penabeï, Esteban Sepulveda, Abdullah Muhammad Zakaria, Jintana Meesungnoen and Jean-Paul Jay-Gerin *

Results and discussions - 1st Publication

$G(Fe^{3+})$ in Fricke Solutions and in the presence of Cystamine (dimer) Subjected to extreme energies 6–500 MeV per Nucleon Carbon Ion Irradiation

(Fig.1-a) $G(Fe^{3+})$ in presence of Cystamine subjected 6 MeV/Nucleon Carbon Ion

(Fig.1- b) $G(Fe^{3+})$ in presence of Cystamine Subjected 500 MeV/Nucleon Carbon Ion

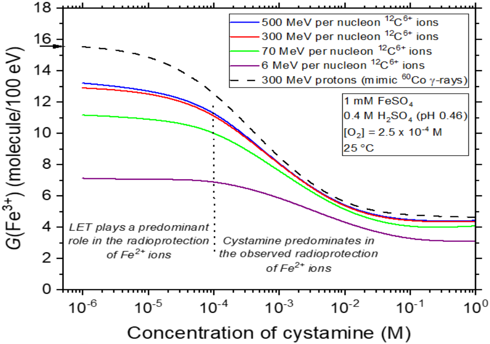


Time evolution of $G(Fe^{3+})$

- $G(Fe^{3+})$ decrease as cystamine concentration increases, regardless the source of irradiation (low or high LET)
- However, cystamine is much more effective against low-LET (9.3 keV/μm)irradiations

Dependence of the $G(Fe^{3+})$ as a function of cystamine concentration, ranging from 10^{-6} to 1 M, in Fricke solutions, subjected to 6 - 500 MeV/Nucleon Carbon Ion

(Fig.2) Dependence of the $G(Fe^{3+})$ as a function of cystamine concentration - 10^{-6} to 1 M



Time evolution of $G(Fe^{3+})$

- Figure 3 indicates that the decrease in $G(Fe^{3+})$ can be attributed to two radioprotective effects: LET itself and due to the presence of cystamine
- As the LET increases, the efficiency of cystamine declines gradually

Results and discussions

2^{nd} Publication

antioxidants

MDPI

Communication

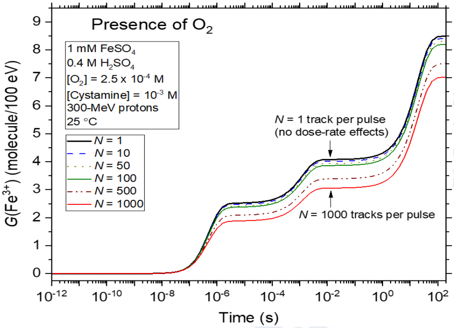
Assessment of Cystamine's Radioprotective/Antioxidant Ability under High-Dose-Rate Irradiation: A Monte Carlo Multi-Track Chemistry Simulation Study

Samafou Penabeï, Jintana Meesungnoen and Jean-Paul Jay-Gerin *

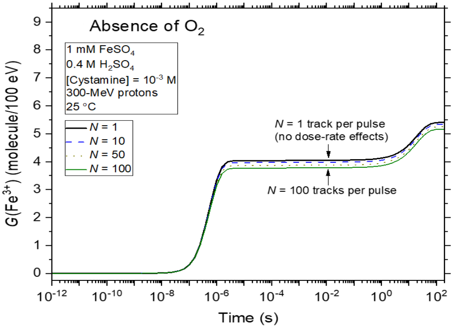
Results and discussions - 2^{nd} Publication

Effect of dose rate on $G(Fe^{3+})$ in aerated and dearerated Fricke solutions, with added cystamine at $10^{-3}M$, subjected to 300 MeV proton irradiation

(Fig. 1-a) Presence of O_2 with cysta $10^{-3}M$



(Fig. 1-b) Absence of O_2 with cysta $10^{-3}M$



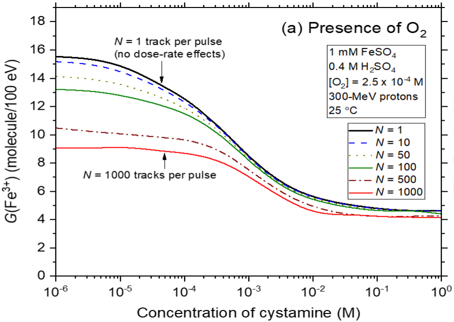
Time evolution of $G(Fe^{3+})$

- $G(Fe^{3+})$ decreases in the presence of cystamine under both aerated and deaerated conditions, and this decrease becomes more pronounced with increasing dose rate.
- For example, for $N = 100$, in aerated solution, $G(Fe^{3+})$ decreases from 15.5 to 8 (i.e., a decrease of about 7.5 G-units).
- In the absence of oxygen, this decrease in $G(Fe^{3+})$ is attenuated as the dose rate increases, with $G(Fe^{3+})$ decreasing from 8.1 to 5.2 (i.e., a reduction of 2.9 G-units)

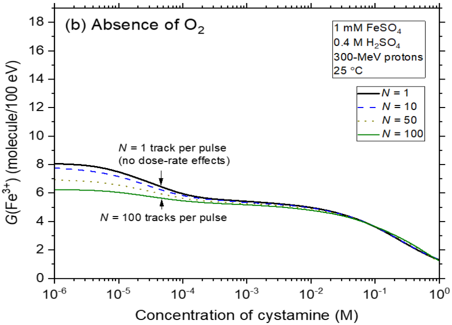
Results and discussions - 2^{nd} Publication

Dependence of the $G(Fe^{3+})$ as a function of cystamine concentration, ranging from 10^{-6} to 1 M, in aerated and deaerated Fricke solutions, under different dose rates

(Fig. 2-a) Presence of O_2 with cystamine



(Fig. 2-b) Absence of O_2 with cystamine



Time evolution of $G(Fe^{3+})$

- As N increases, $G(Fe^{3+})$ in aerated and de-aerated solutions gradually decreases at low cystamine concentrations
- In aerated environment, at concentrations between $10^{-4}M$ and $10^{-2}M$, $G(Fe^{3+})$ decreases sharply with increasing cystamine concentration and stabilizes after $10^{-2}M$
- In deaerated environment, $G(Fe^{3+})$ decreases gradually at concentrations between $10^{-4}M$ and $10^{-2}M$ and decreases sharply after $10^{-2}M$

International Journal of *Molecular Sciences*

MDPI

Article

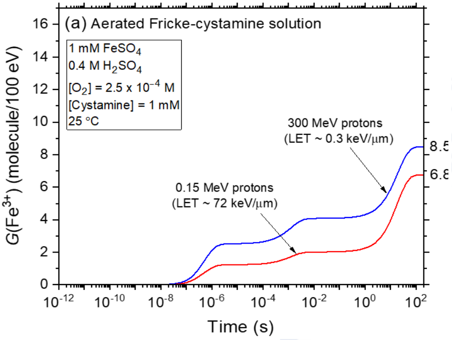
Comparative Analysis of Cystamine and Cysteamine as Radioprotectors and Antioxidants: Insights from Monte Carlo Chemical Modeling under High Linear Energy Transfer Radiation and High Dose Rates

Samafou Penabeï, Jintana Meesungnoen and Jean-Paul Jay-Gerin *

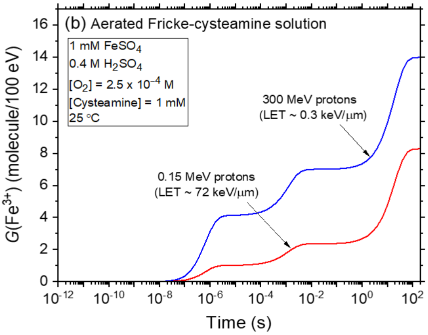
Results and discussions - 3^{rd} Article

$G(Fe^{3+})$ in aerated Fricke solutions, with added cystamine and cysteamine at $1mM$, subjected to proton irradiation for extreme energies - 0.15 MeV and 300 MeV

(Fig. 1-a) Presence of O_2 with Cystamine



(Fig. 1-b) Presence of O_2 with cysteamine



Time evolution of $G(Fe^{3+})$

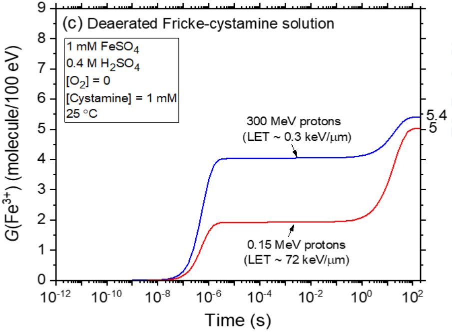
- In the presence of cystamine, $G(\mathrm{Fe}^{3+})$ is less sensitive to LET (ranging from approximately 0.3 to 72 keV$/\mu$m), decreasing from about 8.5 to 6.8 molecules/100 eV, corresponding to a reduction of 1.7 G units.
- With cysteamine, the decrease is more pronounced, from 14 to 8.3 molecules per 100 eV (a 5.7 G-unit drop)

Results and discussions - 3^{rd} Article

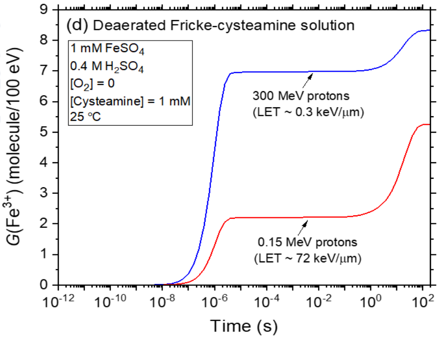
$G(Fe^{3+})$ in deaerated Fricke solutions, with added cystamine and cysteamine at $1mM$, subjected to proton irradiation for extreme energies - 0.15 MeV and 300 MeV

- A similar observation is made under oxygen-free conditions

(Fig. 1-c) Absence of O_2 with Cystamine



(Fig. 1-d) Absence of O_2 with cysteamine



Time evolution of $G(Fe^{3+})$

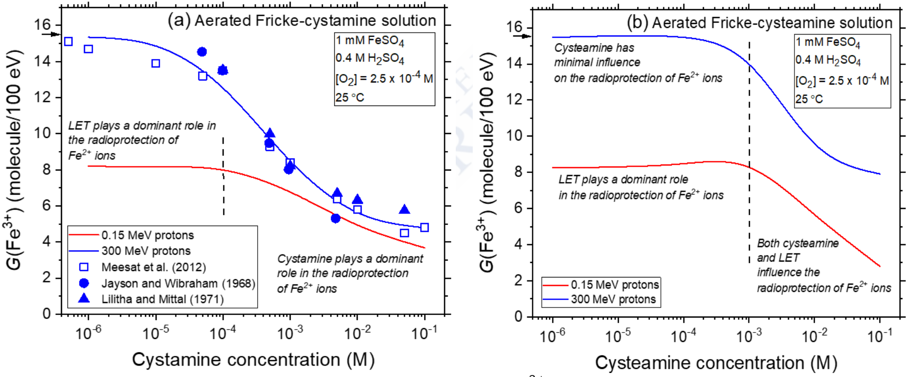
- LET is less effective in reducing $G(Fe^{3+})$ when cystamine is used as opposed to cysteamine

Results and discussions - 3^{rd} Article

Dependence of the $G(Fe^{3+})$ as a function of cystamine/cysteamine concentration, ranging from 10^{-6} to 0.1 M, in aerated Fricke solutions

(Fig. 2-a) Presence of O_2 with cystamine

(Fig. 2-b) Presence of O_2 with cysteamine



Time evolution of $G(Fe^{3+})$

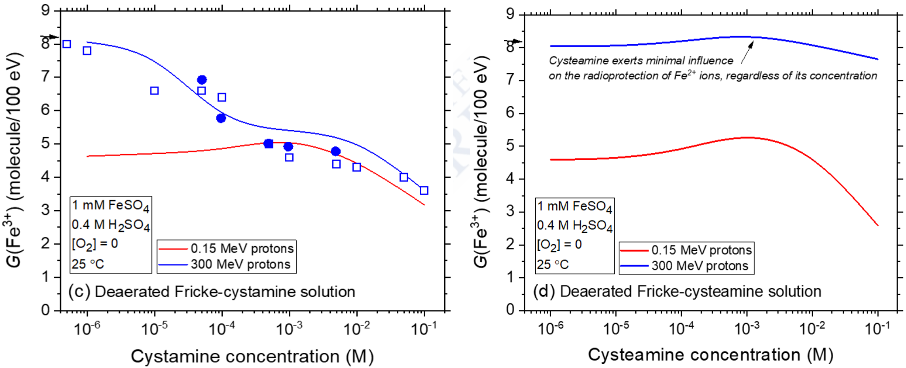
- In an aerated environment, and with the addition of either cystamine or cysteamine, $G(Fe^{3+})$ decreases, regardless of energy

Results and discussions - 3^{rd} Article

Dependence of the $G(Fe^{3+})$ as a function of cystamine/cysteamine concentration, ranging from 10^{-6} to 0.1 M, in deaerated Fricke solutions

(Fig. 2-c) Absence of O_2 with cystamine

(Fig. 2-d) Absence of O_2 with cysteamine



Time evolution of $G(Fe^{3+})$

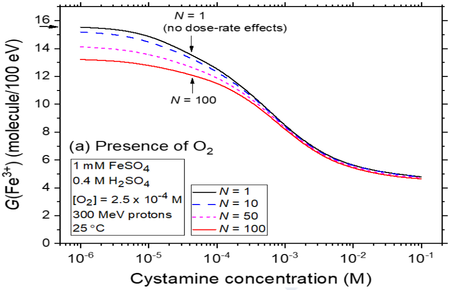
- The same observation in aerated conditions is made in deaerated conditions with cystamine.
- However, with cysteamine, $G(Fe^{3+})$ remains unchanged at high energies but decreases at low energies

Results and discussions - 3^{rd} Article

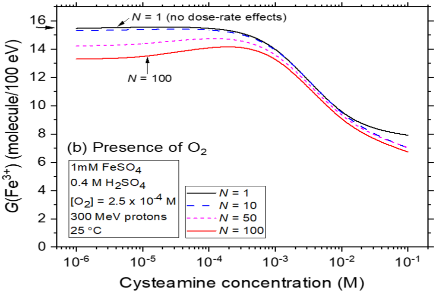
Dependence of the $G(Fe^{3+})$ as a function of cystamine/cysteamine concentration, ranging from 10^{-6} to 0.1 M, in aerated Fricke solutions, under different dose rates

- In an aerated environment with cystamine or cysteamine, $G(Fe^{3+})$ decreases with increasing radioprotector concentration and dose rate, indicating their ability to scavenge free radicals

(Fig. 3-a) Aerated and with added Cystamine: 10^{-6} to 0.1



(Fig. 3-b) Aerated and with added Cysteamine: 10^{-6} to 0.1



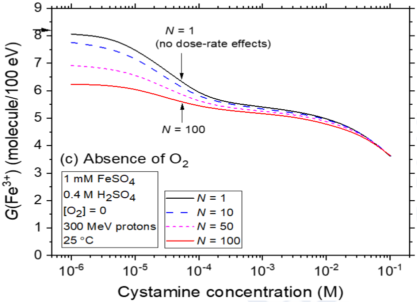
Time evolution of $G(Fe^{3+})$

- Cystamine is more effective at concentrations between 10^{-4} and 10^{-2} M, as indicated by the significant decrease in $G(Fe^{3+})$
- Cysteamine is more effective at concentrations between 10^{-3} and 0.1 M, as indicated by a significant reduction in $G(Fe^{3+})$ within this range

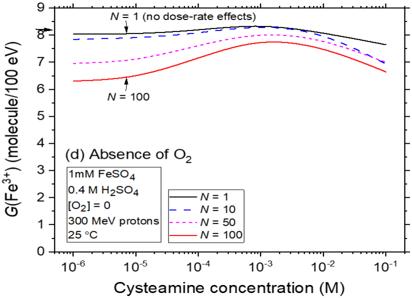
Results and discussions - 3^{rd} Article

Dependence of the $G(Fe^{3+})$ as a function of cystamine/cysteamine concentration, ranging from 10^{-6} to 0.1 M, in de-aerated Fricke solutions, under different dose rates

(Fig. 3-c) Deaerated - cystamine: 10^{-6} - 0.1 M



(Fig. 3-d) Deaerated - cysteamine: 10^{-6} - 0.1 M



Time evolution of $G(Fe^{3+})$

- In a deaerated environment, in the presence of cystamine, the same remark as in an aerated environment is observed: $G(Fe^{3+})$ decreases as a function of the added radioprotector concentration
- However, in the presence of cysteamine, $G(Fe^{3+})$ does not decrease as a function of the added radioprotector concentration
- In the range $10^{-3}M$ to $10^{-2}M$, cysteamine reaches its maximum unprotective capacity in a deaerated environment ("tumor-like"), which is beneficial for the treatment of cancer by radiotherapy

Conclusions and perspectives

Conclusion

- Objectives
- Achievements

- Cystamine offers protection to (healthy tissue) like and (tumors) like environments, although its capacity in a deaerated environment is lower than in an aerated environment
- Cysteamine provides protection to (healthy tissues) like environments but not to tumors like environments (tumors), especially at the concentration of approximately 10^{-3} - 10^{-2} M
- The radioprotective capacity of cystamine and Cysteamine decrease with increasing radiation LET
- Cysteamine offer better tissue protection under high dose rates irradiation "FLASH-RT" in comparison to CONV-RT without compromising the treatment compared to cystamine

Conclusion and perspectives

Perspectives

- Predictive Modeling with AI: Use machine learning algorithms to predict the radioprotective effectiveness of radioprotectors under various FLASH RT parameters
- Optimization of Simulation Parameters: Apply AI to identify optimal Monte Carlo simulation conditions, thus accelerating the search for effective radioprotective scenarios
- Development of an Integrated AI Model: Create an AI model capable of combining simulation and biological data to anticipate the effects of radioprotectors under real conditions and minimize toxicity

THANK YOU FOR YOUR KIND ATTENTION