BioHadron

Specificities of the tumor molecular response to carbon ions

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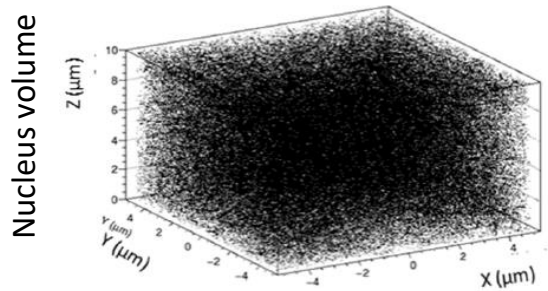
Paradigm of the stealth bomber

Relies on the local distribution of Reactive Oxygen Species (ROS) at the nanometric scale

Monte-Carlo simulation of **OH°** at 10^{-12}s:

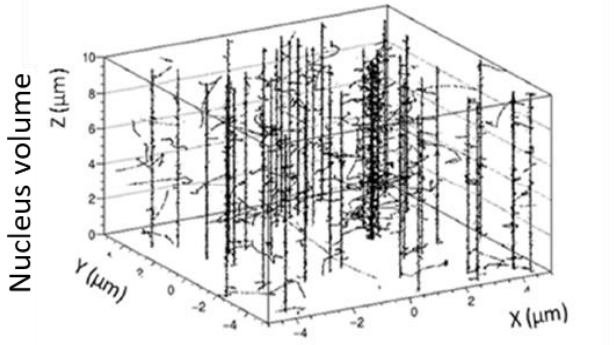
2 Gy photons



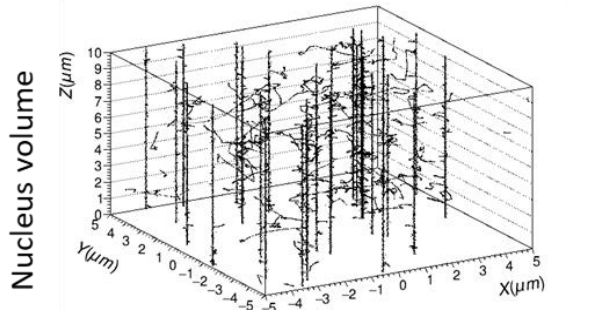
simulations C. Monini & M Beuve

uniform distribution

2 Gy C-ions (physical equiv. dose)



1 Gy C-ions (biological equiv. dose)



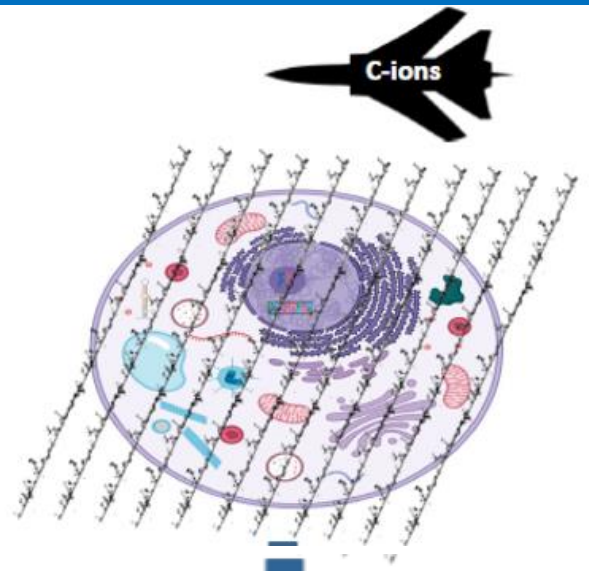
mixed radiation field reproducing the NIRS irradiation (dose-averaged LET) ~13 keV/m)

Wozny *et al.* Cancers 2019

concentrated along the tracks

Very different consequences at the subcellular and molecular levels!

Paradigm of the stealth bomber



Subcellar targets on the trajectory of C-ions tracks

ROS-induced complex damage at the DNA and molecular levels

Bomber effect

Very low production of ROS out of the C-ion tracks

Absence of triggering of cellular alarms and defense mechanisms outside areas hit by ROS

Stealth effect

Our experimental data supporting both effects?

Wozny & Rodriguez-Lafrasse, BJC 2023

Paradigm of the stealth bomber

The Bomber effect

DNA
- Increased clustered DNA damage
- More complex chromosomal aberrations
- Non-transmission of chromosomal lesions to progeny
- Killing independent of the telomere length

- Enhanced mitochondrial dysfunction
- More cell death (cancer stem cells)

- Low dependence on the oxygen concentration
- Low dependence on the dose-rate

- **Abnormal proteostasis**

Maalouf *et al.* 2009, IJROBP
Hanot *et al.* 2012 Plos One
Alphonse *et al.* 2013 BMC cancer
Ferrandon *et al.* 2013 Mol Neurobiol
Bertrand *et al.* 2014 Stem Cell Rep

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Wozny *et al.* 2016 Frontiers in Oncology
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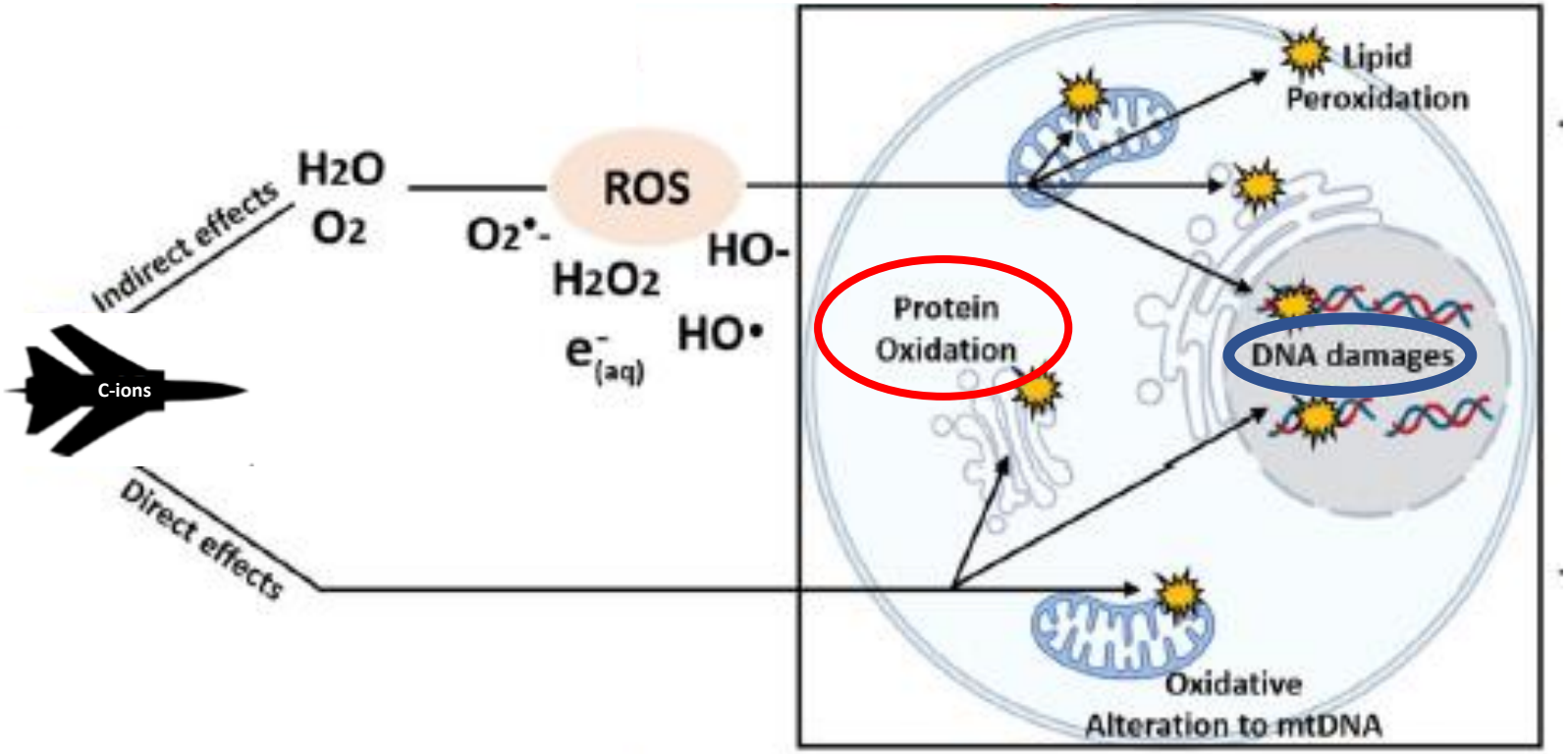
Wozny *et al.* 2020 Scientific Reports
Wozny *et al.* 2021 Cancers
Louati *et al*. in preparation
Wozny *et al.* in preparation

Wozny AS, Rodriguez-Lafrasse C. The 'stealth-bomber' paradigm for deciphering the tumour response to carbon-ion irradiation.
Br J Cancer. 2023 Apr;128(8):1429-1438. doi: 10.1038/s41416-022-02117-6.

The bomber effect

Consequences of the bomber effect: abnormal proteostasis ?



Adapted from Kacem, IJROBP 2022

➡ **Protein oxidation = alteration of cellular functions and metabolism**

Averbeck & Rodriguez-Lafrasse, IJMS 2022

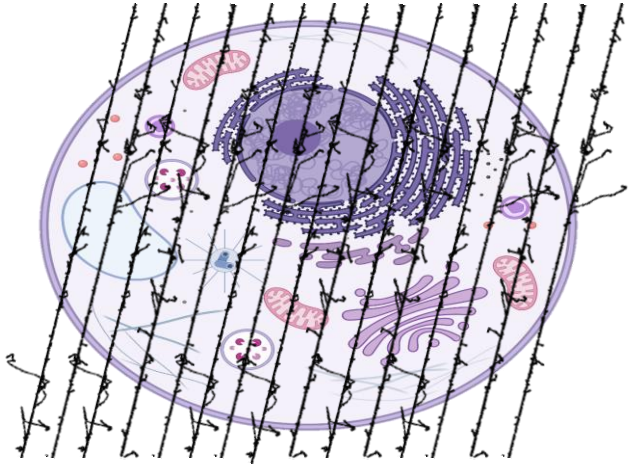
The bomber effect

Consequences of the bomber effect: abnormal proteostasis

Kinetic studies of radiation-induced oxidized proteins

Non published data

The stealth effect



A large proportion of cell volume at the nanometric scale not hit by C-ions: thresholds of ROS necessary to trigger survival and defense mechanisms not reached

C-ions cross cell radars and lines of defense without being spotted

Wozny & Rodriguez-Lafrasse, BJC 2023

Paradigm of the stealth bomber

The Bomber effect

- Increased clustered DNA damage
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- Killing independent of the telomere length
- Enhanced mitochondrial dysfunction
- More cell death (cancer stem cells)
- Low dependence on the oxygen concentration
- Low dependence on the dose-rate
- Abnormal proteostasis

The Stealth effect

- Lower DNA damage detection and repair
- No HIF-1α stabilisation
- No/lower invasion & migration
- No/lower activation of cell survival pathways (cancer stem cells)
- **No stress granules formation**

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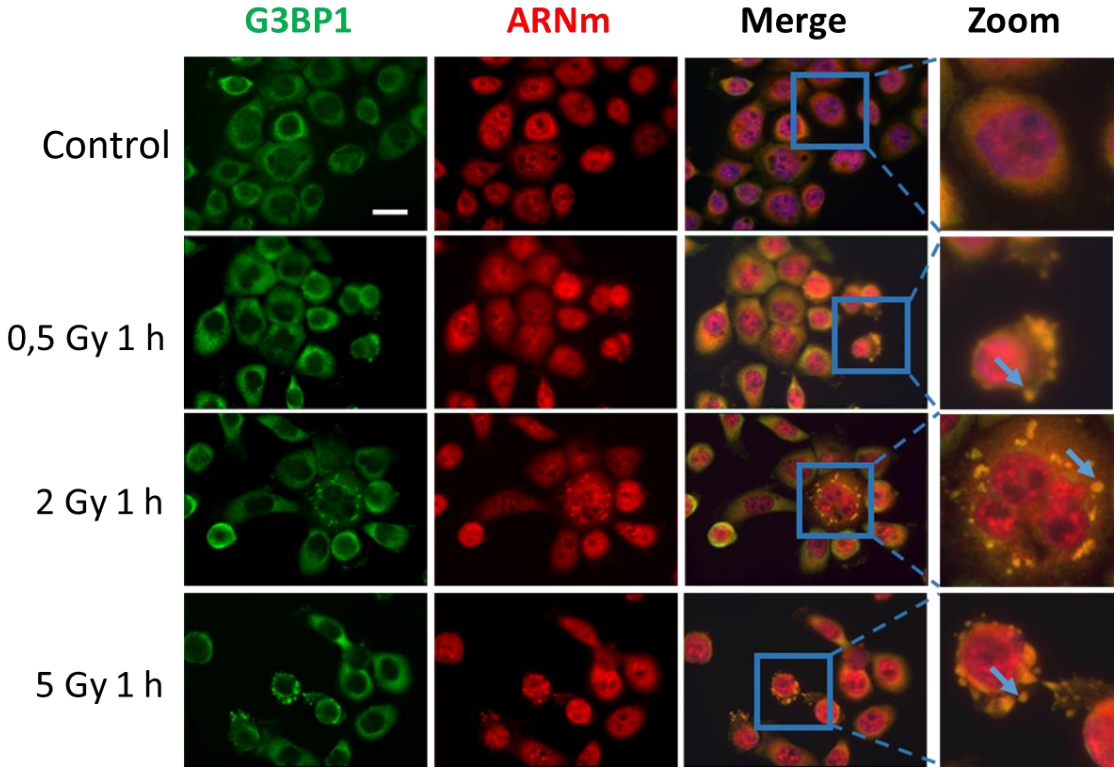
The stealth effect

Consequences of the stealth effect: stress granule formation ?

- non-membrane cytoplasmic aggregates
- dynamically store mRNAs in response to different (oxidative) stress
- regulate gene expression by delaying the translation of specific transcripts



Carbon ions : Non published data

Formation of SG in **radiosensitive** cells from 30’ to 2h after **photon irradiation** depending on **ROS**

Laouti et al., IJROBP 2023

Specificities of the tumor molecular response to carbon ions

Efficacy of the combination of carbon ion, protons, and photons with Immunotherapy?

Non published data

Project at CNAO

Mathilde TISSOT (PhD student 11/2023 – 10/2026)

Anne-Sophie Wozny (Assistant Professor)

Gersende Alphonse (Research Engineer)

Scientific project with CNAO

1. Beam characterization and biological data for NanOx model

- ✓ Cell survival curves at **different positions in the SOBP** (Carbon ions, Helium)
- ✓ **RBE determination** for different endpoints in HNSCC, glioblastoma and CHO cultured cells and spheroids

Scientific project with CNAO

2. Specificities of the tumor molecular response to carbon ions

- ***In cellulo experiments***

Investigating the abnormal proteostasis to support the bomber effect:

✓ Characterization (identification) of the oxidized proteins (Coll. B. Cambien (TIRO), Nice)
- at different TEL
- at different doses
- with C-ions and Helium

✓ Determination of the fate of oxidized proteins

Investigating the non-activation of survival pathways to support the stealth effect:

✓ MAPK and NF-KB pathways

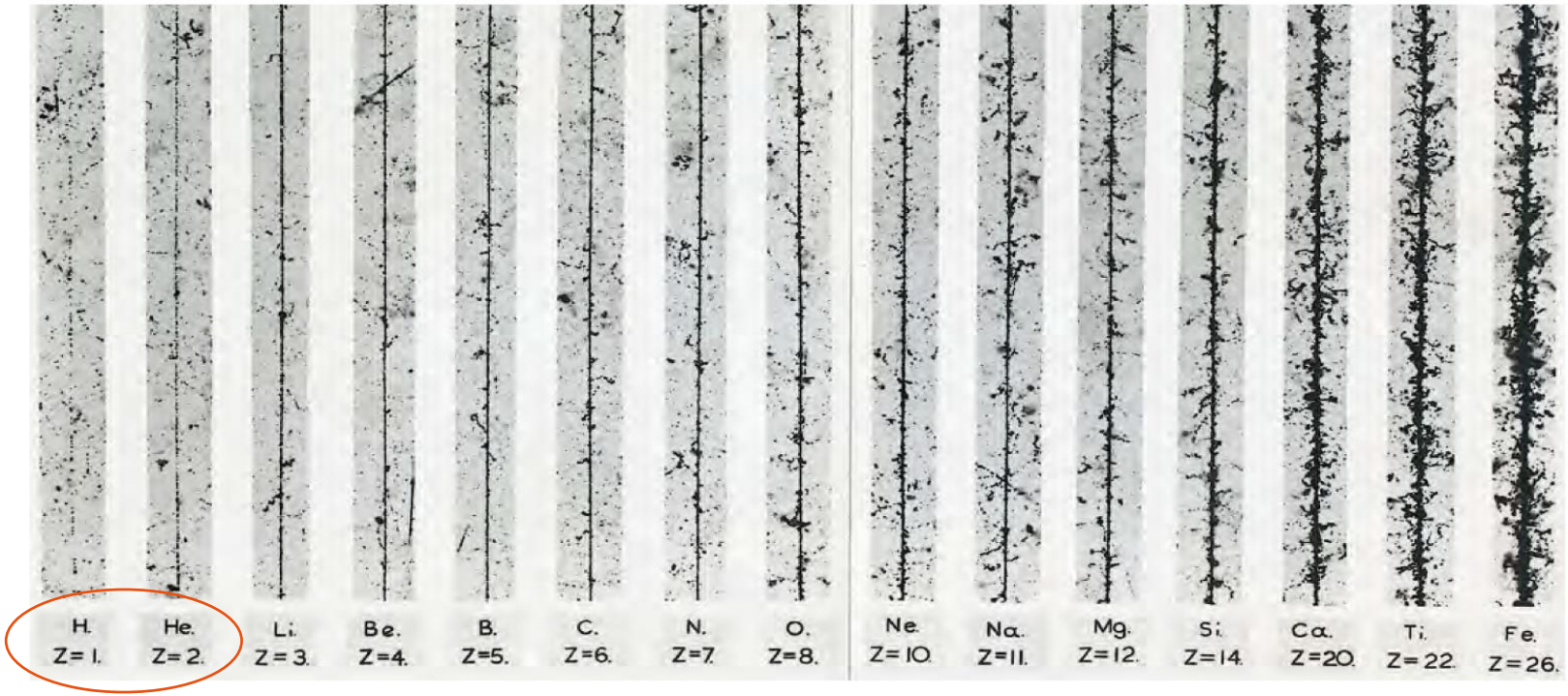
Scientific project with CNAO

2. Specificities of the tumor molecular response to carbon ions

- ***In cellulo experiments***

Investigating the Stealth bomber paradigm in response to other ions:

- ✓ Protons, Helium ?
- ✓ LET-dependent effect?



Scientific project with CNAO

- ***In ovo experiments***

  Alternative to mammalian tumor models, no ethical committee, easy to manipulate

Scientific project with CNAO

- ***In vivo experiments*** (if possible, ethical committee)

  ✓ Confirmation of results and continuation of experiments **in mice with HNSCC tumors,** treated with **carbon ions or helium combined** or not with **immunotherapy**

  ✓ **MITI Project (coll IRSN) : Understanding** the **influence of tumor cell irradiation** with different types of beams (photons, protons, carbon ions) **on endothelial cell phenotype and the immune system**

THANK YOU FOR YOUR ATTENTION !

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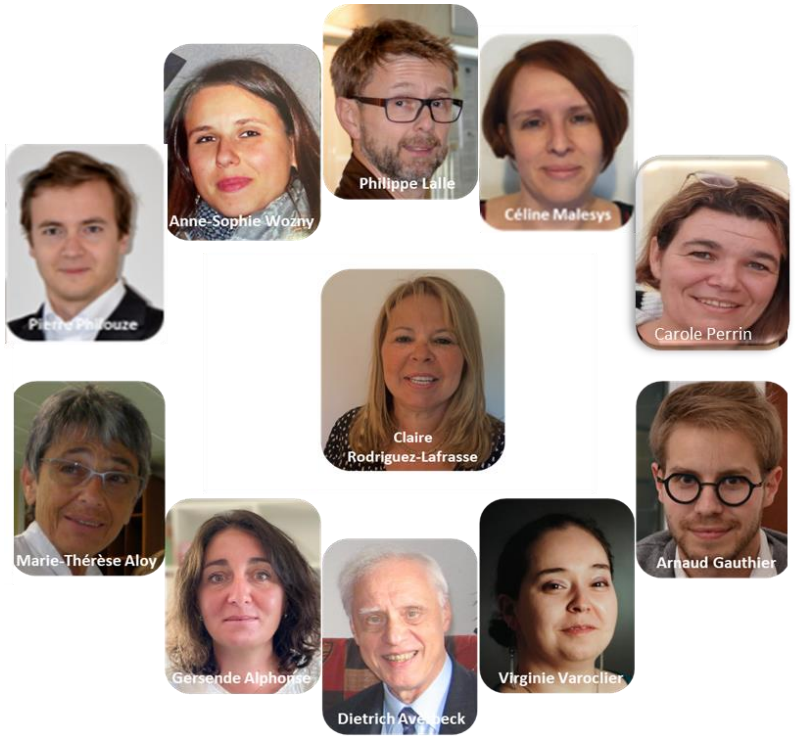

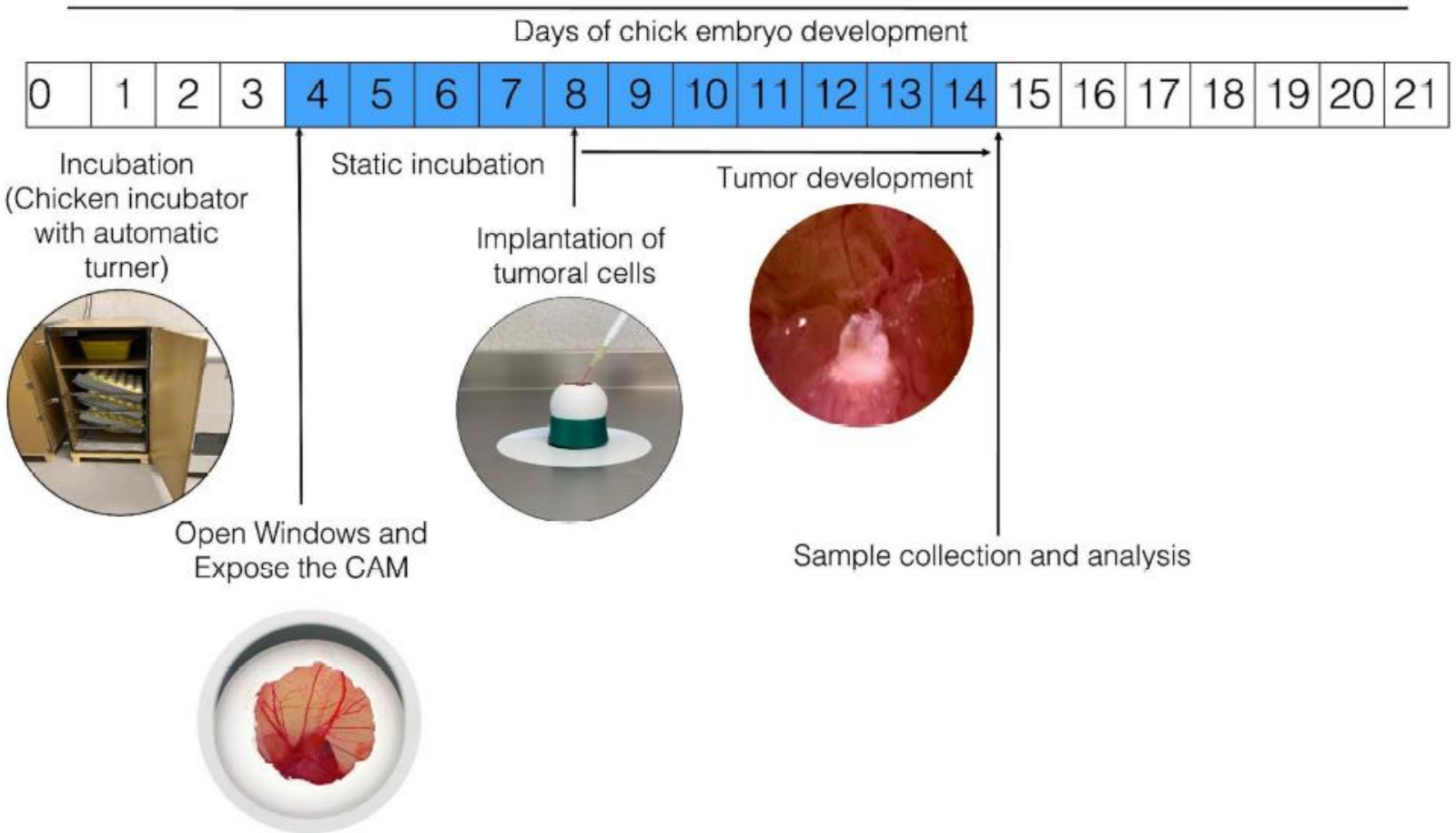

Patiño-Morales, IJMS 2023