Cellular and Molecular Radiobiology Lab (LRCM) activities

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CNAO - IN2P3 WORKSHOP 11/23/2021

LRCM activities

To understand and quantify the biological effects of **innovative radiotherapies by experimental and clinical radiobiology**

✓ **Carbon ion therapy and other ions:**
- **Molecular mechanisms specifically involved in the tumor response**
- Biological data for simulation (PICTURE – E Testa)

✓ Radiosensitizing nanoparticles: AGuIX® and CuPRiX®

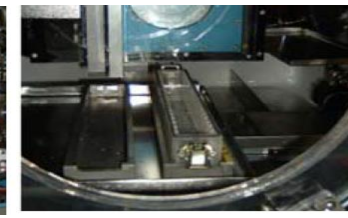
✓ Prediction of tumoral response to radiotherapy (clinics)

Irradiation facilities

Carbon ion Irradiation

GANIL, Caen, France,
(Since 2003, 75 MeV/n)
Coll Y Saintigny and F Chevalier

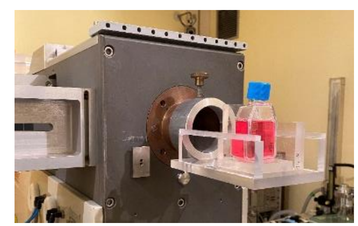
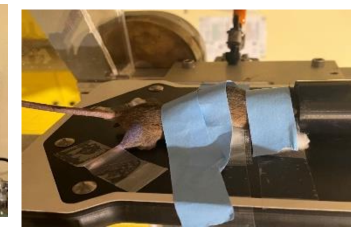

GSI, Darmstadt, Germany
(2004-2012, 9.8 MeV/n)
Coll C Fournier and G Taucher Scholtz

NIRS, Chiba, Japan
(Since 2016, SOBP 290 MeV/n)
Coll T Nakajima

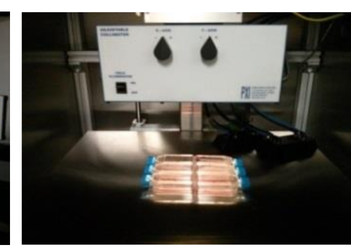

Protons

CAL, Nice, France
(Since 2021, 62.5 MeV/n)
Coll B Cambien

Photons

Lyon-Sud Medical School
Lyon, France, XRAD320, 250 kV

Paradigm of the stealth bomber

to explain the tumor cell response to carbon ions

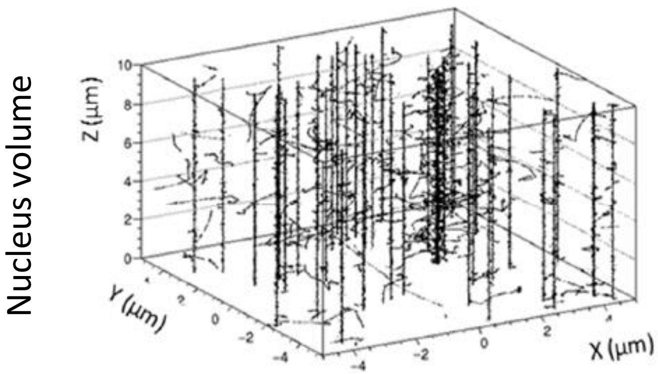
Bomber

Stealth

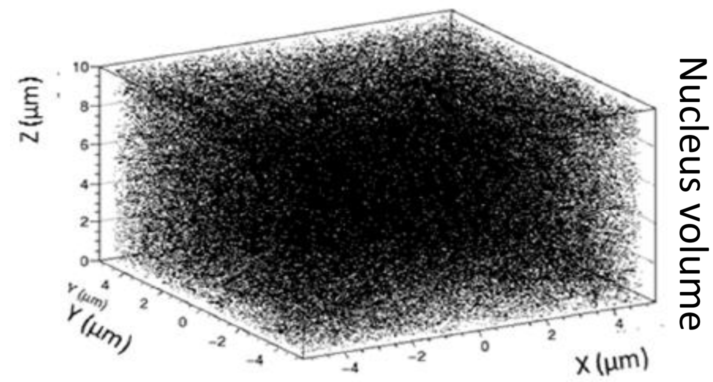
relies on the spatial distribution of Reactive Oxygen Species (ROS) at the nanometric scale

Monte Carlo simulations of OH° radicals (10^{-12} s)

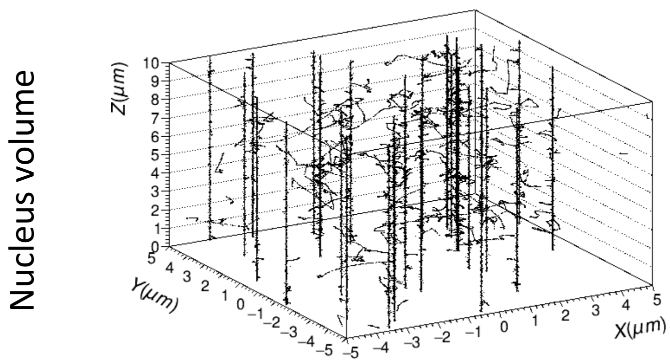
2 Gy C-ions (physical equivalent dose)



2 Gy photons



1 Gy C-ions (biological equivalent dose)



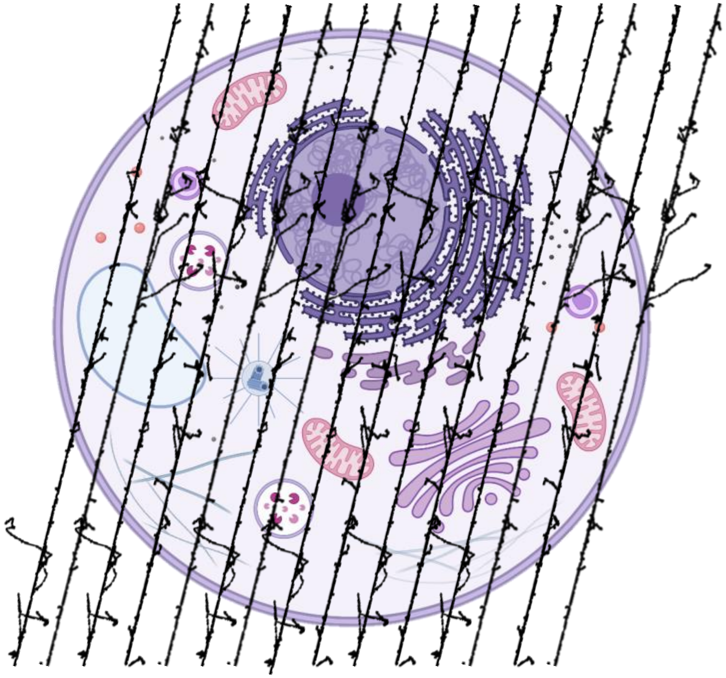
averaged-dose LET of SOBP: 13 keV/µm
(NIRS irradiation)

✓ **Local distribution at the nanometric scale:**
- clusters around tracks (C-ions)
- dense and homogeneous distribution (photons)

➡ **Very different consequences at the cellular level (stealth-bomber)!**

Wozny *et al.* Cancers 2019

The bomber effect

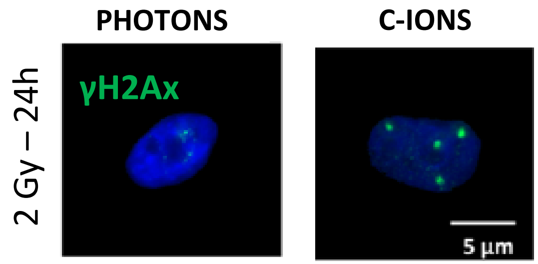


Subcellular biological targets, such as DNA or organelles are on the trajectories of the high-LET particles

The bomber effect

at the DNA level

✓ Complex DNA lesions; clusters of unrepairable DNA lesions (DSBs)



Wozny *et al.*, Scientific Reports, 2020
Wozny *et al.*, Cancers, 2021

✓ Chromosome loss: a specific signature

➡ **Limitation of genomic instability**

Hanot *et al.*, Plos one, 2012

✓ No influence of telomeres' length on cell killing

➡ **Glioblastoma patients with long telomeres can advantageously benefit from a carbontherapy**

Ferrandon *et al.* Mol Neurobiol, 2013

Consequences of the bomber effect

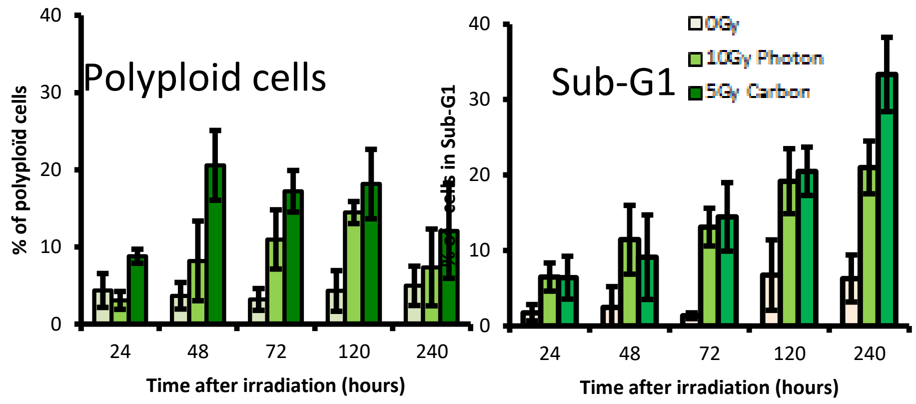
Cell death

✓ **Earlier and more important compared with photons**

✓ **No specific mechanism involved**

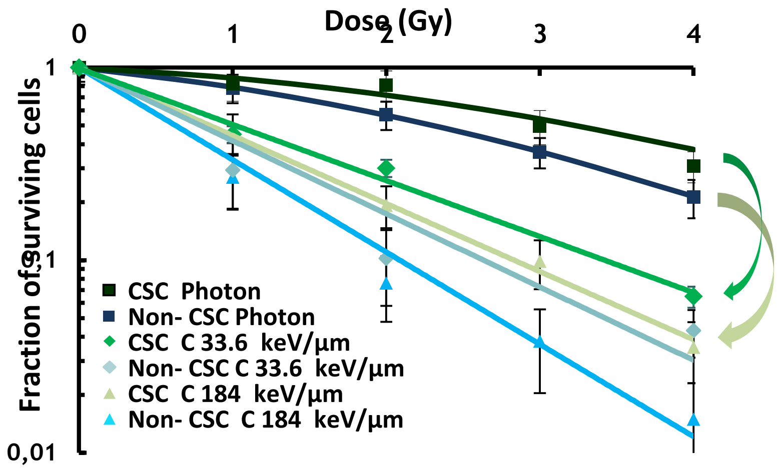
early apoptosis or mitotic death
+ p53-independent ceramide-dependent apoptosis

Maalouf *et al.*, IJROBP 2009
Alphonse *et al.,* BMC Cancer, 2013
Ferrandon *et al.* Cancer Letter, 2015



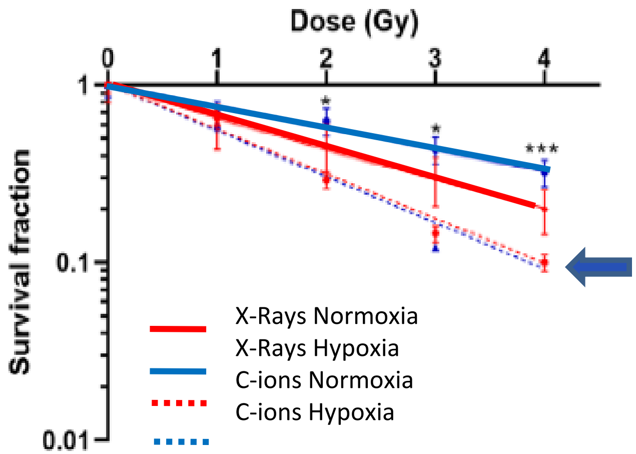
✓ **More efficient on cancer stem cell killing**

Bertrand *et al.,* Stem Cell, 2014
Moncharmont *et al.* Oncotarget, 2016



Consequences of the bomber effect

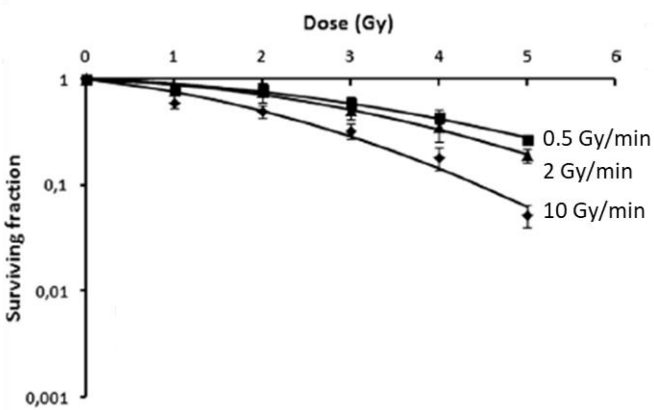
✓ Cell killing is independent of the O_2 concentration

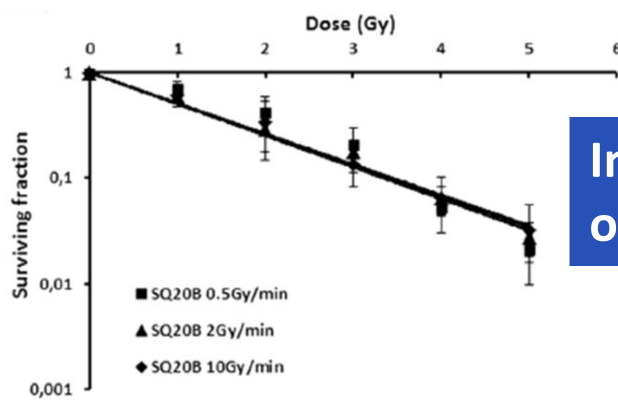


Interest in the treatment of hypoxic tumors

Wozny *et al.*, British Journal of Cancer, 2017
Wozny *et al.* Scientific Reports, 2020

✓ Cell killing is independent of the radiation dose-rate

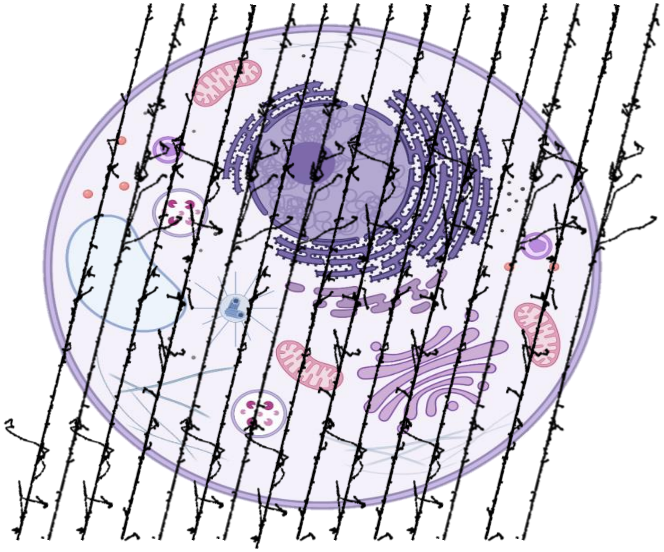




Interest in the planification of treatment

zny *et al.*, Frontiers in Oncology, 2016

The stealth effect



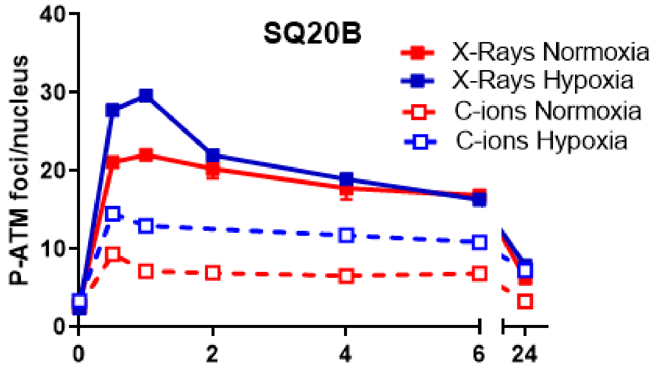
A large proportion of cell volume not hitten by C-ions:

- **thresholds of ROS necessary to trigger survival and defense mechanisms not reached**
- **"cell radars not into alarm"**

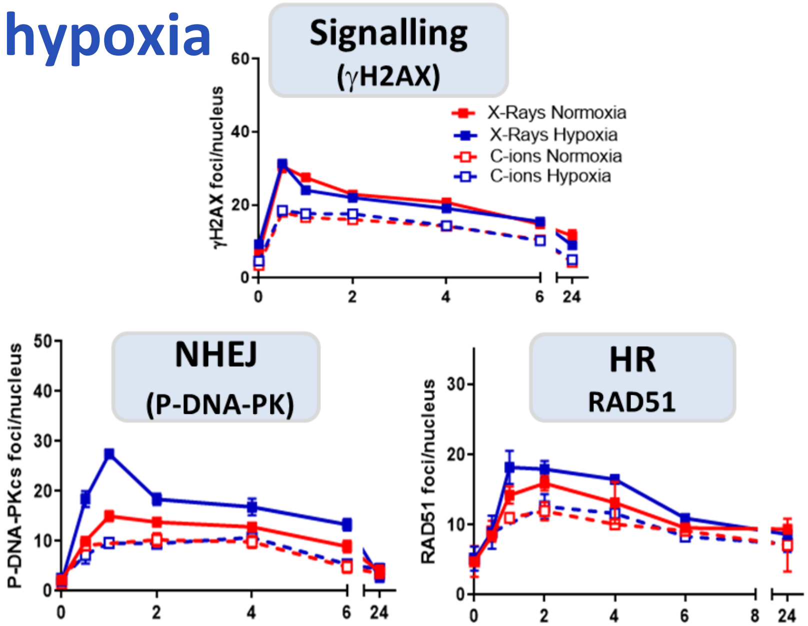
Wozny and Rodriguez-Lafrasse., In prep

The stealth effect

✓ Less DNA Damage detection (ATM nucleoshuttling) under normoxia or hypoxia



✓ Lower DNA damage signalling and repair (NHEJ/HR) under normoxia or hypoxia

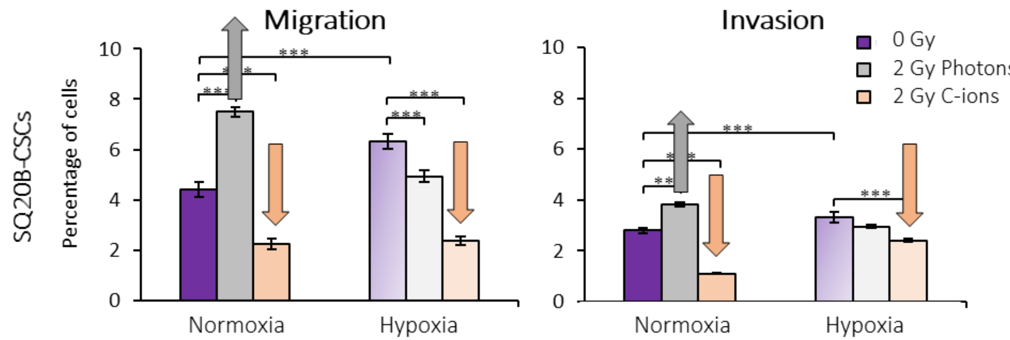


Wozny *et al.*, Scientific Reports, 2020
Wozny et al., Cancers, 2021

The stealth effect

✓ **No HIF1-α stabilisation:** **major transcription factor involved in the response to hypoxia**

✓ **No invasion-migration of CSCs**



✓ **Significant decrease of MMP-2 concentrations**

✓ **Few/no activation of invasion/migration signaling pathways (MEK/p38/JNK ; STAT3 ; Akt/mTOR)**

➡ **Less metastases under normoxia and hypoxia**

Montcharmont *et al.* Oncotarget 2016
Wozny *et al.* Cancers 2019

Summary

Carbon ions better cure radioresistant cancers:

The Bomber effect 

= high RBE and overcoming of radioresistance

- Increased DNA damage
- Independent of the telomere length
- More cell death
- Independent of oxygen concentration and dose rate

The Stealth effect 

= no/less triggering of adverse effects due to the spatial distribution of ROS

- Lower DNA damage detection and repair
- No HIF-1α stabilization
- No invasion/migration
- No/lower activation of cell survival pathways

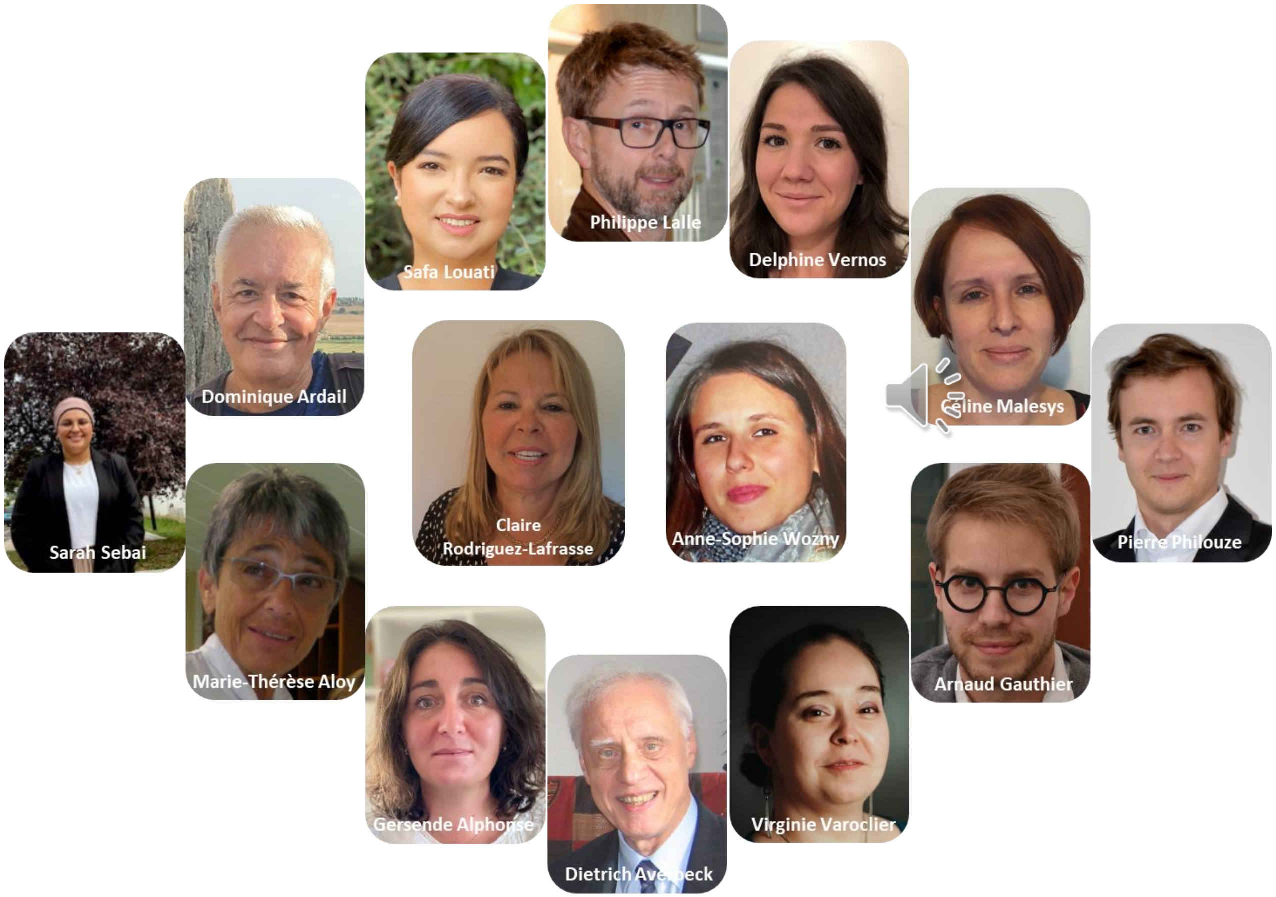
Because of the stealth bomber effect, C-ions will be always superior to the best conventional radiotherapy

Collaboration perspectives

- ✓ **Confirmation of the stealth-bomber effect** of carbon ions on: cell proteostasis, membrane lipids and mitochondrial dynamics
- ✓ **TEL dependence** of the stealth bomber effect (other ions: H^+, He, higher Z …)
- ✓ **Preclinical studies** of **combo carbon ions**/helium/protons/photons with **immuno-therapy**: impact of tumor microenvironment (ongoing experiments with photons and protons)

Acknowledgements

Cellular and Molecular Radiobiology Lab
UMR CNRS 5822



Collaborations

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M.J. Stazia (CDiReC)
C. Tomasetto (IGBMC)
O. Tillement (ILM) …

Thank you for your attention and welcome in Lyon !