

Physics for Health in Europe



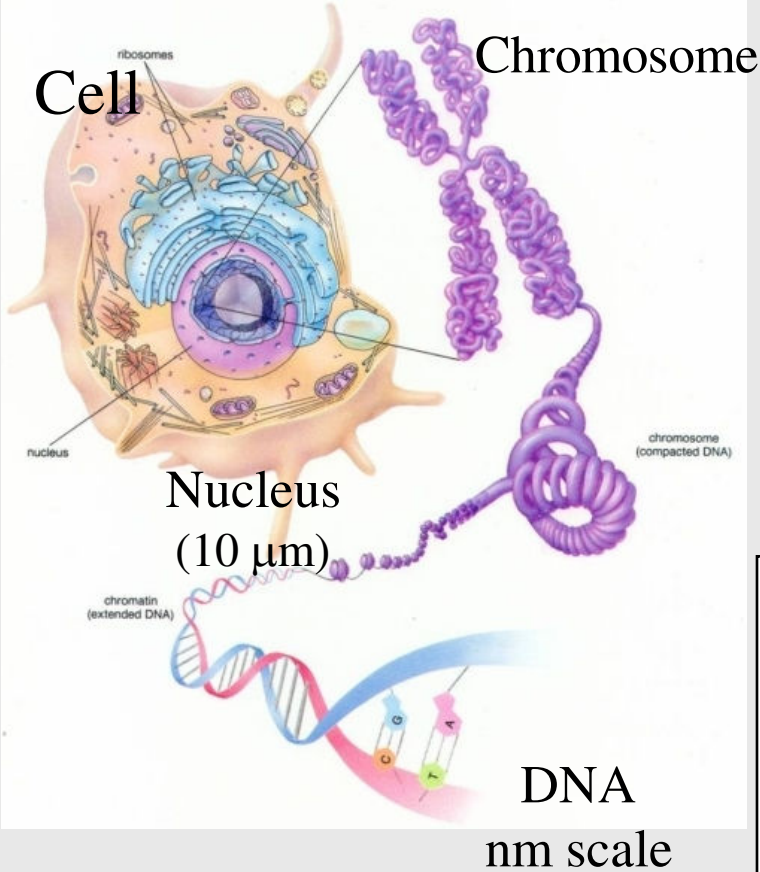
Early events in the formation of genetic damage by heavy ions

G. Taucher-Scholz

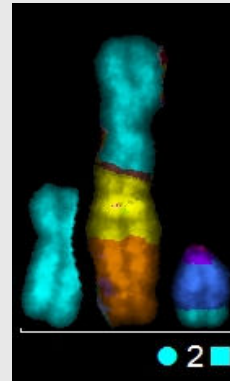
GSI Biophysics
Darmstadt

CERN, Geneva, February 2 - 4, 2010

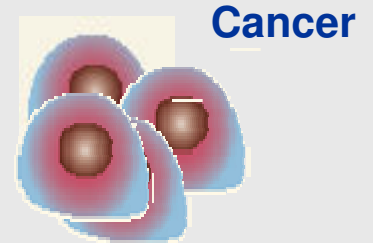
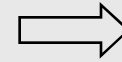
Damage induction after heavy ion irradiation



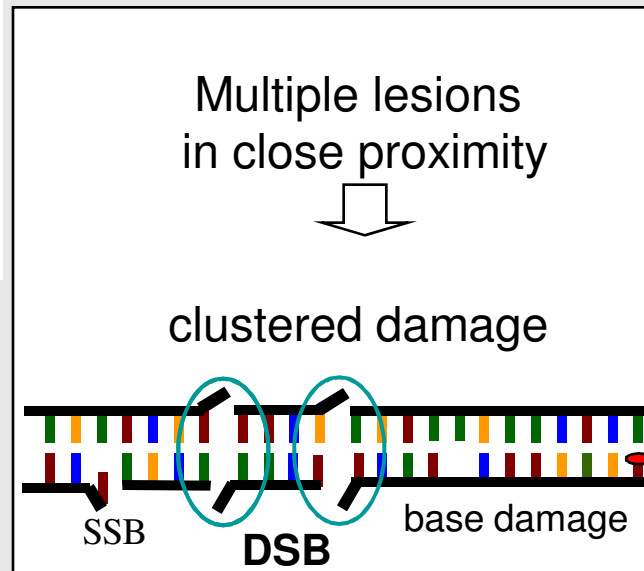
More smaller fragments (AFM)
Psonka-Antonyzk et al. (2009)
Radiat. Res.
⇒ **Impaired DSB repair**



**Mutation
Chromosomal
aberration**

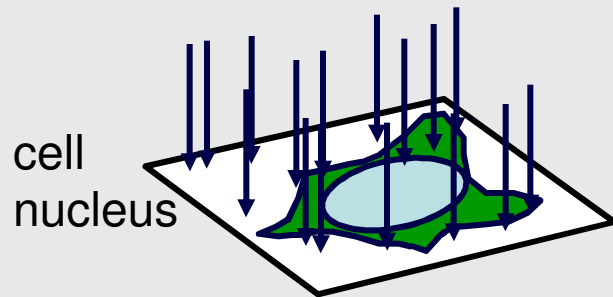


Hartel et al. (2009)
Radiother. Oncol.

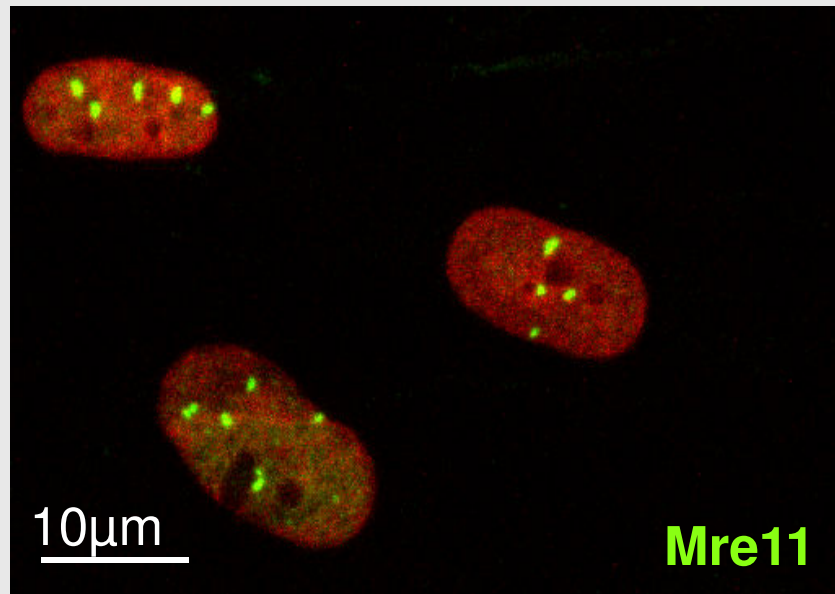


Heavy ions: very localized damage response

Immunostained DNA repair proteins accumulate at damage sites

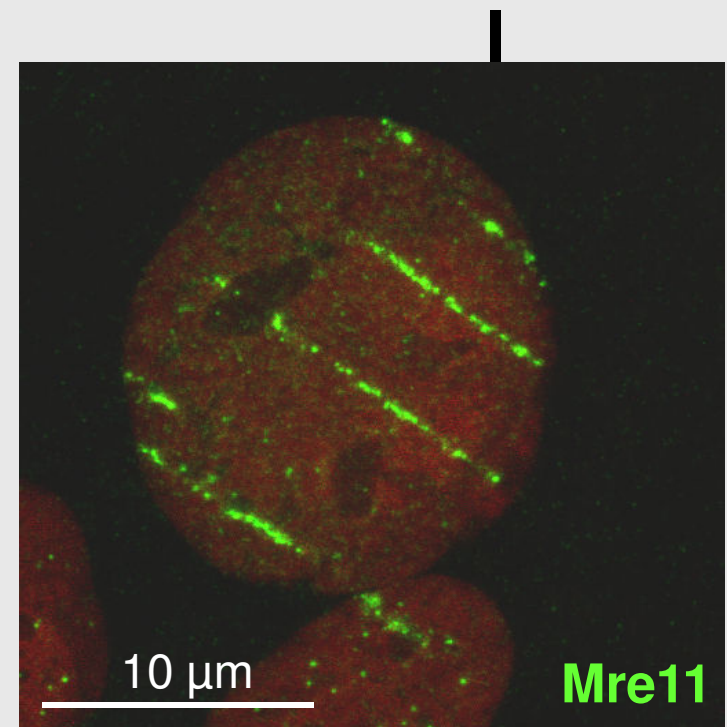


Inhomogenous
microscopic
dose distribution
 μM scale



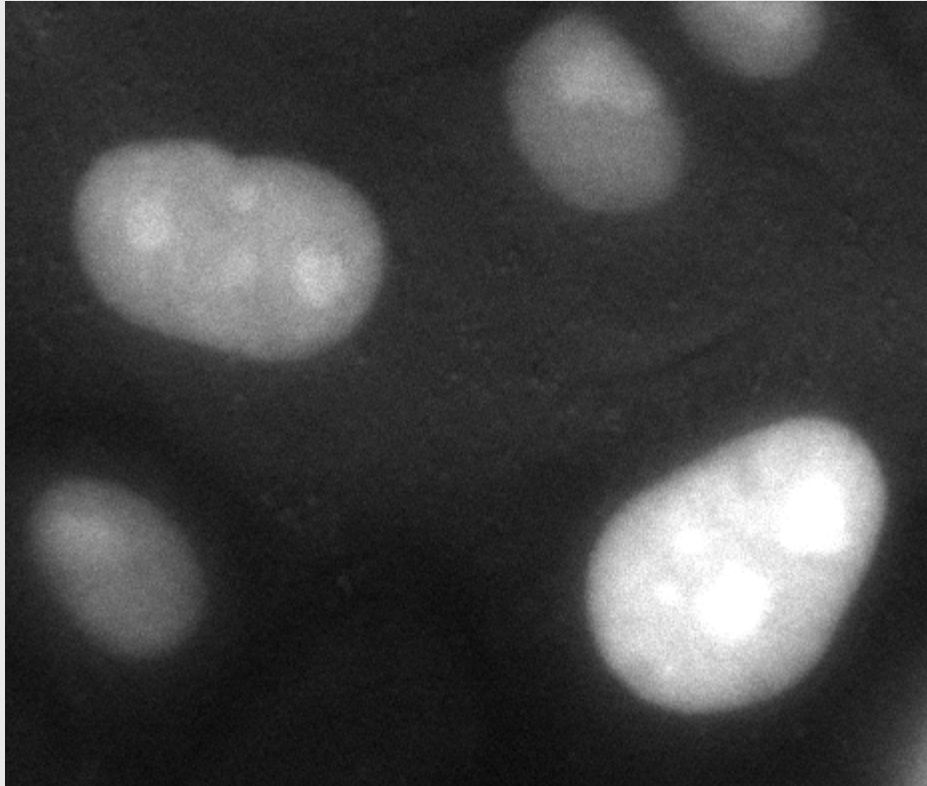
Jakob et al. Radiat. Res. (2000)

Low angle irradiation ($< 5^\circ$)



Jakob et al. Radiat. Res. (2003)

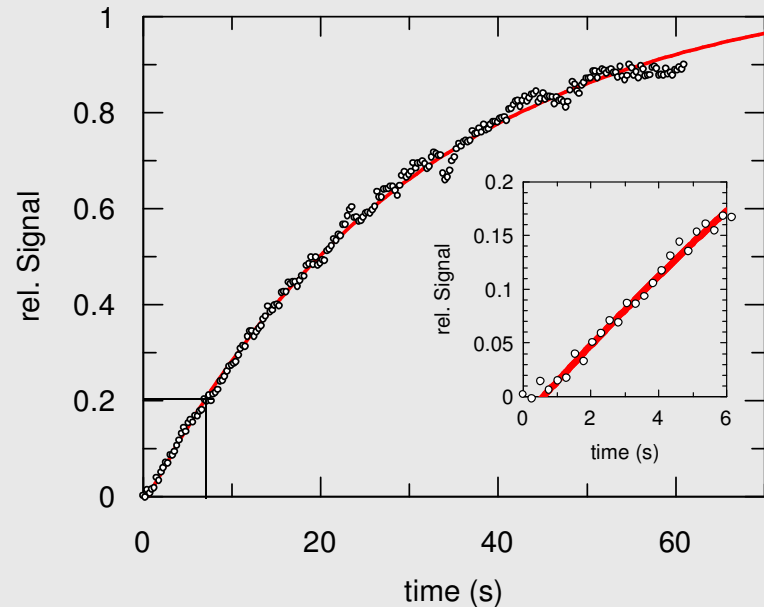
Beamline microscope : repair protein recruitment in living cells



HeLa EGFP-Aprataxin
0 to 1 min after ion irradiation

Live cell online video
microscopy at the beam end

Resolution well below 1 sec

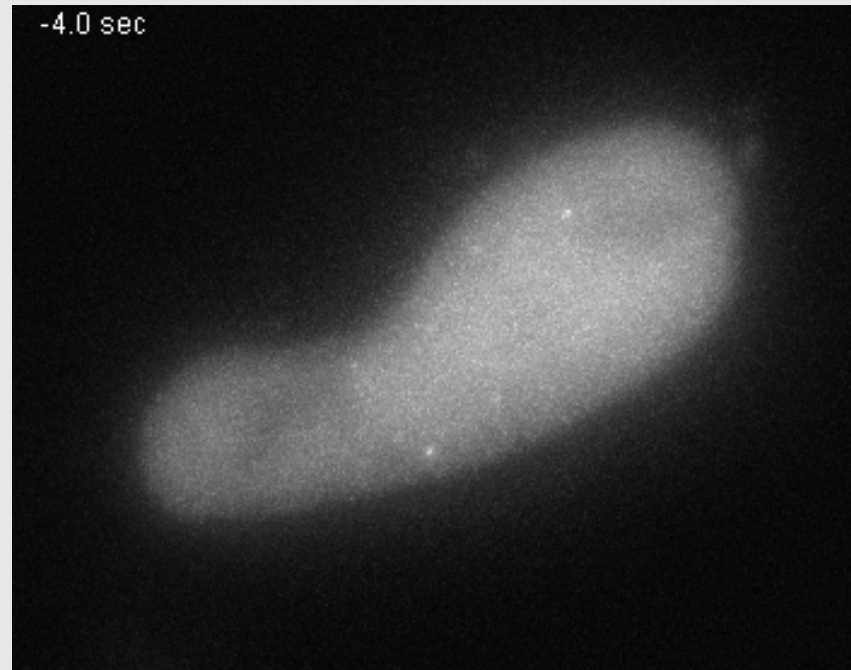


Hierarchy of recruitment
DNA-PKcs < XRCC1 < APTX
NBS1 < 53BP1

Live cell microscopy : High energy beamline

Real time protein recruitment along linear ion tracks

HZE:
1GeV/u Fe

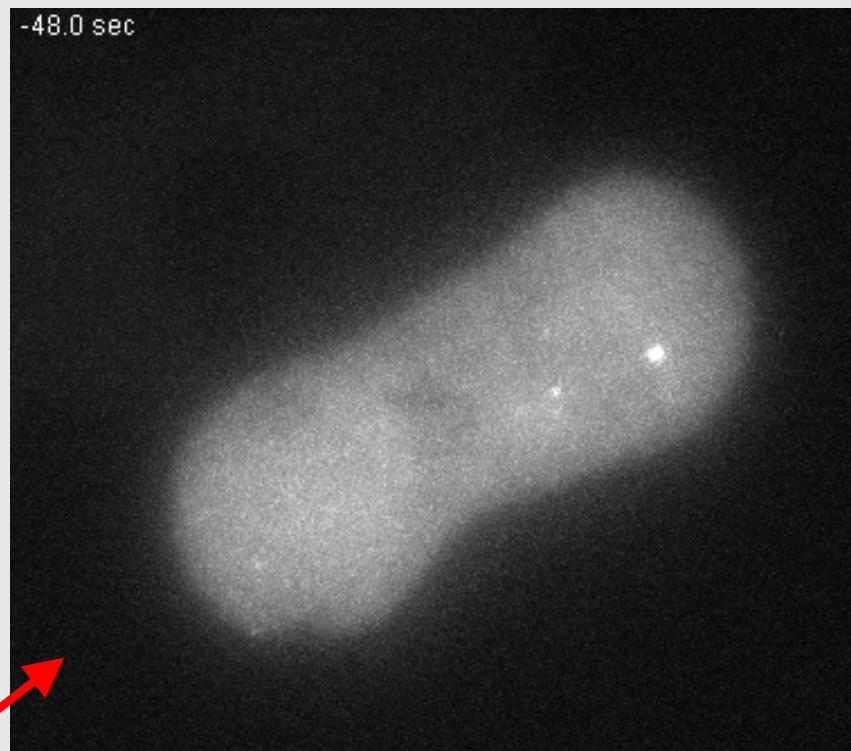


HeLa cells; XRCC1-GFP 7 min time lapse

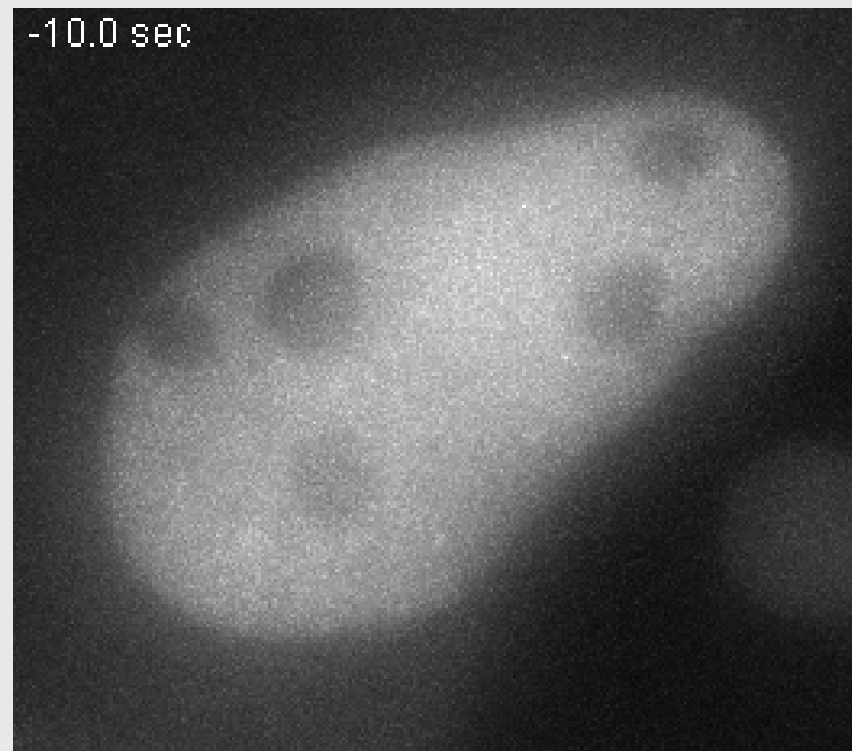
Protein dynamics on linear ion tracks: lesion repair

HZE:

1GeV/u Fe



XRCC1-GFP
SSB repair (10 min)

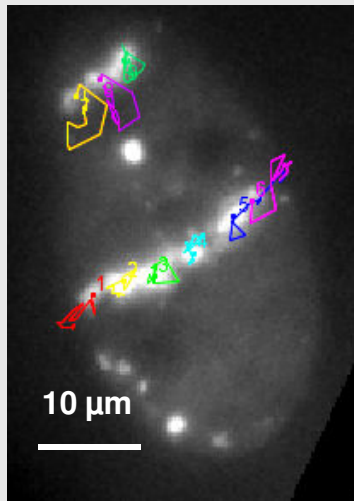


NBS1-GFP
DSB repair (5 min)

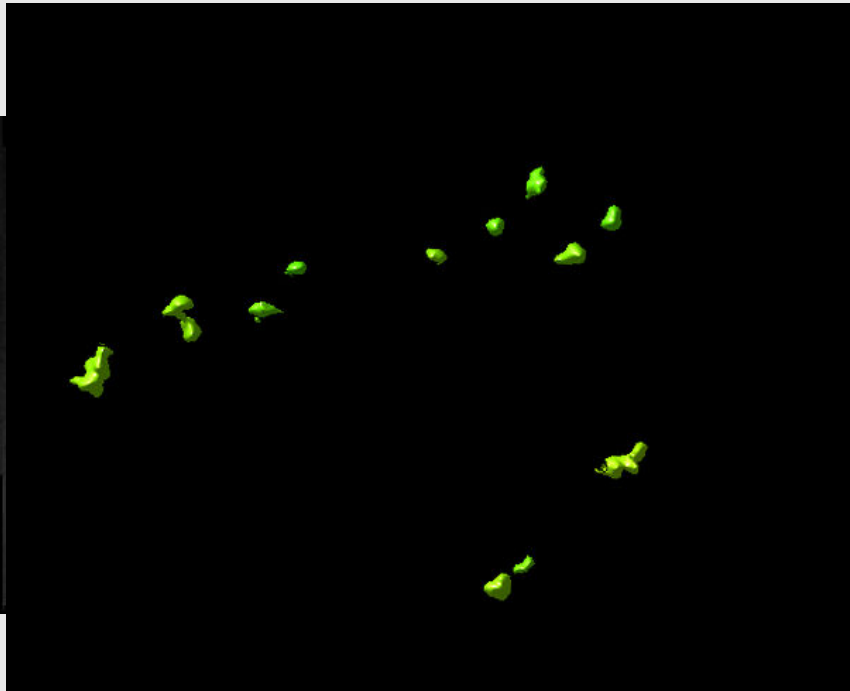
DSBs: motion of damaged chromatin domains

Live cell imaging of DSB marker 53BP1-GFP after low angle ion irradiation in a climate chamber microscope (up to 40h)

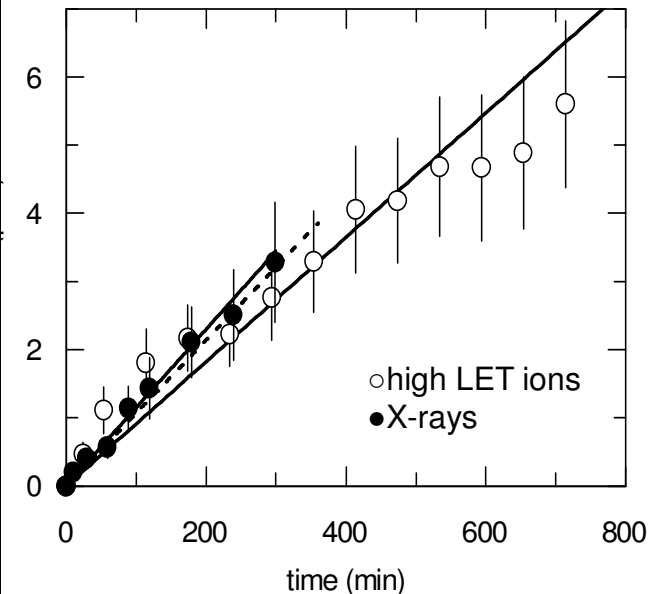
Motional trajectories
foci inside ion tracks



Ni ions, 12h



Mean Square Displacement

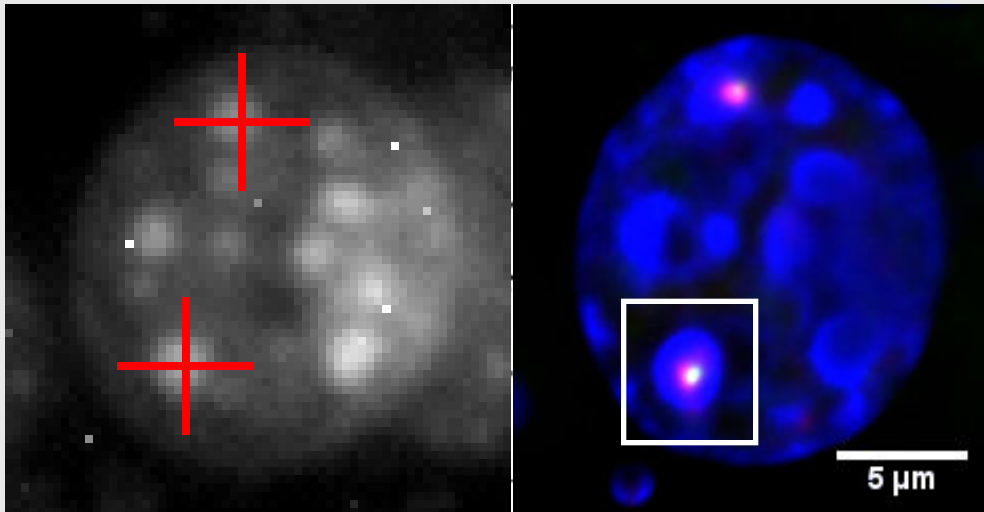


(mean MSD $\sim 0.6 \mu\text{m}^2/\text{h}$)

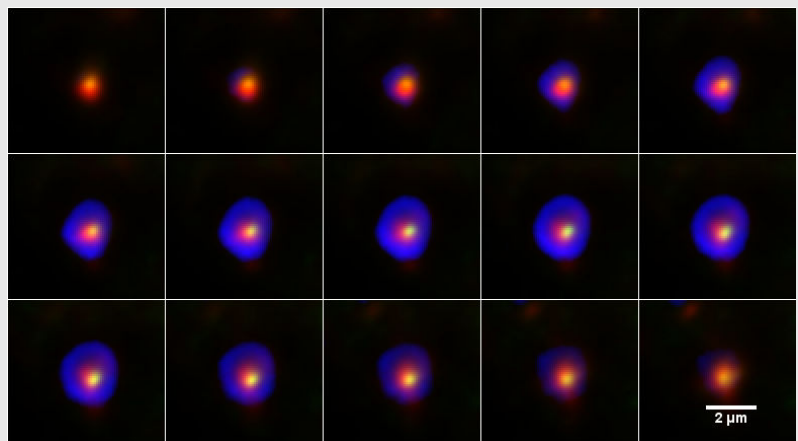
- **Non-directional**
- **independent on radiation type**

Lesion processing:
⇒ **no enhanced DSB mobility**
⇒ **no large scale rearrangements**

GSI microbeam: aimed irradiation of heterochromatin



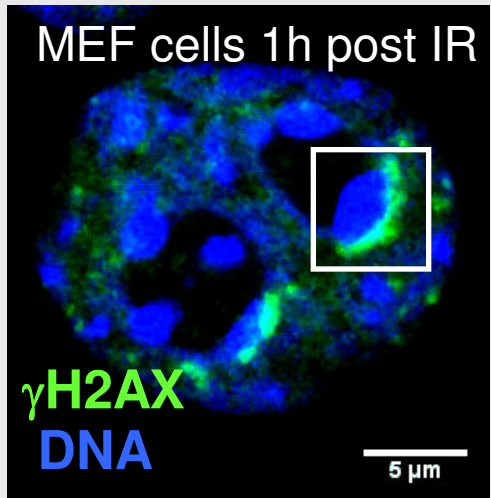
MEF chromocenters targeted with single ions



Individual slices of stack image

IF staining: 7 min post irradiation

TOPRO
XRCC1
γ-H2AX



- Early γ -H2AX within heterochromatin
- Relocation to the periphery

Summary and conclusions

- Molecular basis of heavy ion cellular effects: clustered lesions and extremely localized DNA damage response
- Live cell imaging: Fast and efficient damage response (*repair protein recruitment*) – impaired DSB repair
- DSBs show positional stability independent of radiation type
 - no large scale rearrangements after ion impact
- Similar molecular response to photons and heavy ions – different outcome due to complex lesions

Thank you!

GSI Biophysics

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DNA Damage Research

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Collaborators (selected)

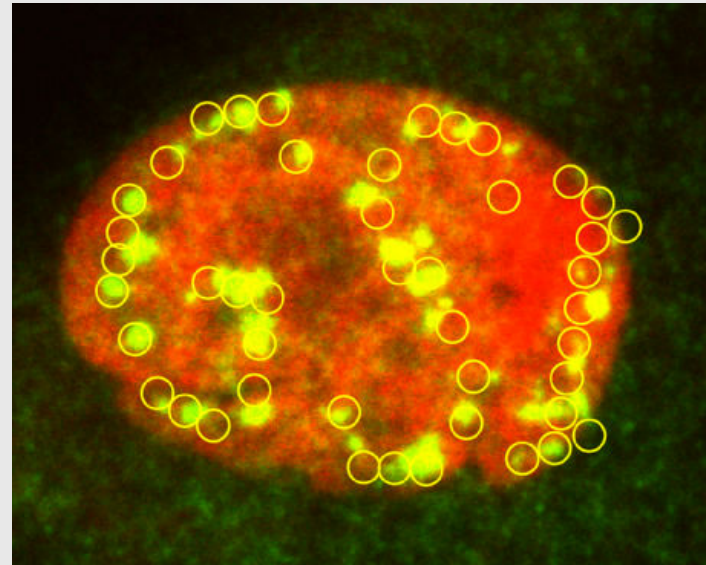
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GSI Heavy Ion Microbeam

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