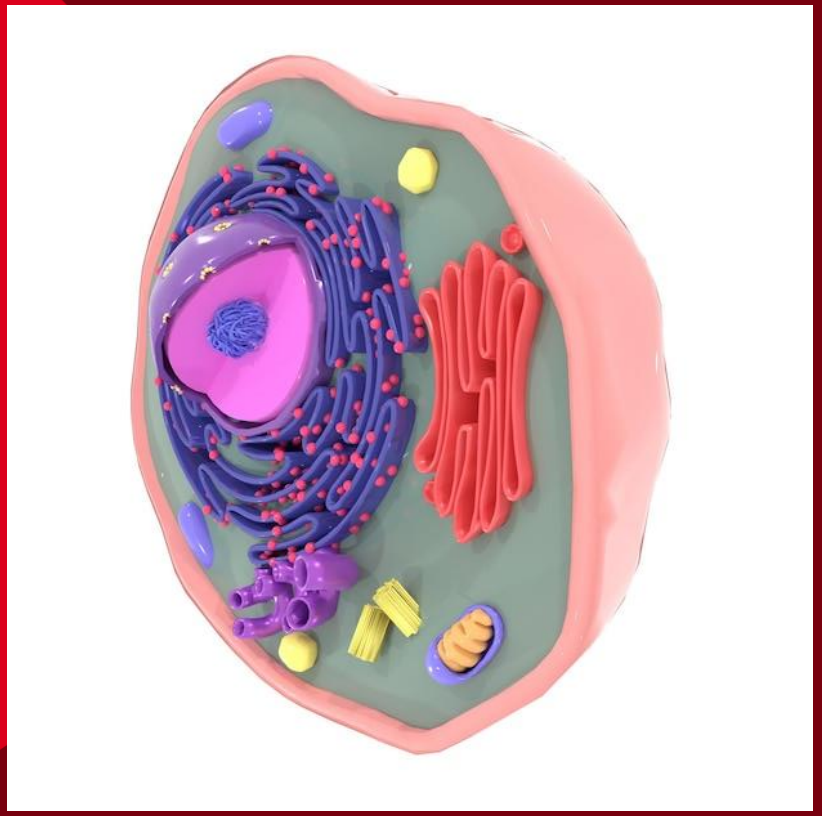
Kræftcellers Reparationssystem

Jesper Nylandsted

Danish Cancer Institute

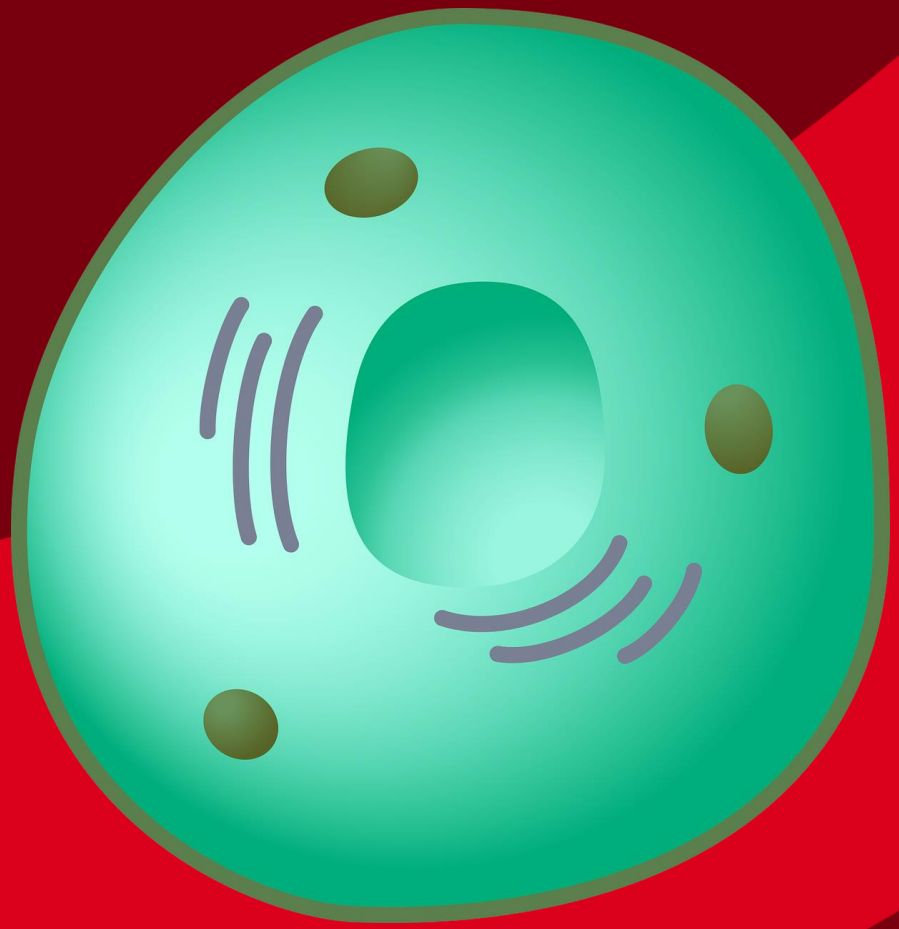


Kræftens Bekæmpelse, Center for Kræftforskning

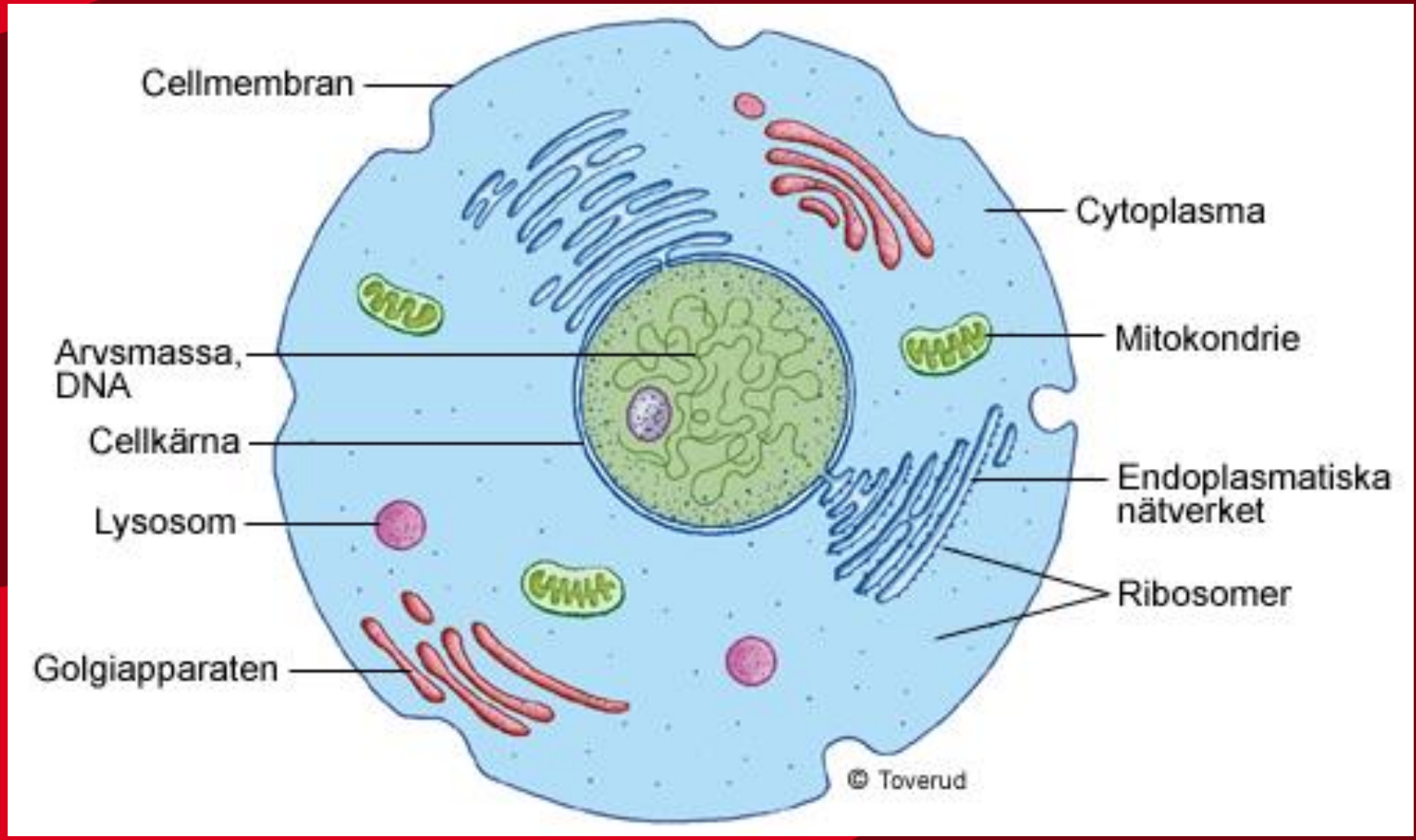
The Danish Cancer Institute is Denmark's largest NGO and dedicates more than 60% of the budget to research, with the remainder shared between information and patient support initiatives.

The research at the Danish Cancer Society Research Center is organized in 25 research groups and four core facilities. The institute is an international and multidisciplinary research environment with more than 300 researchers from 25 countries and an annual research production of around 300 peer-reviewed publications.

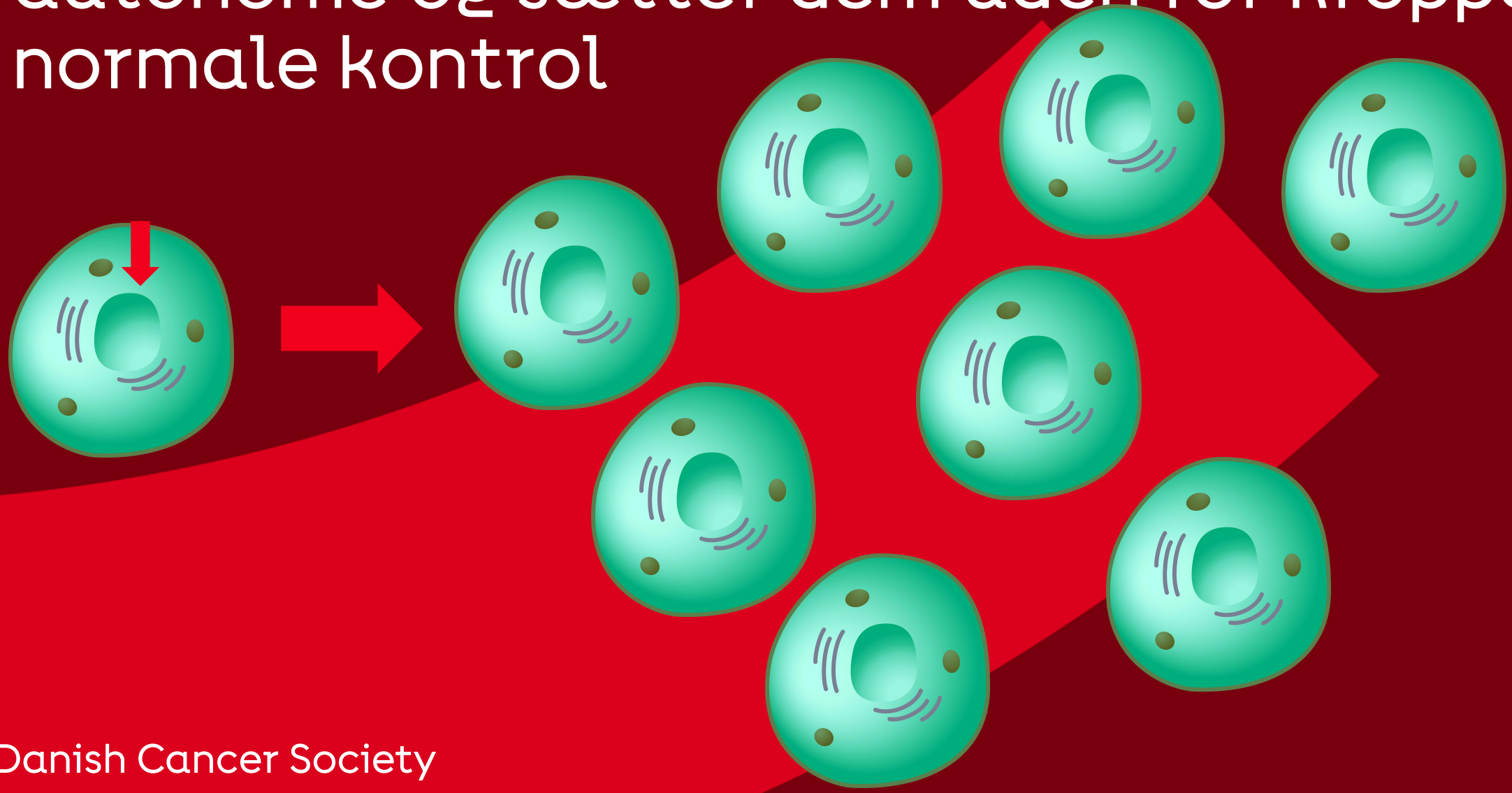
Et lynkursus I cellebiologi



Danish Cancer Society

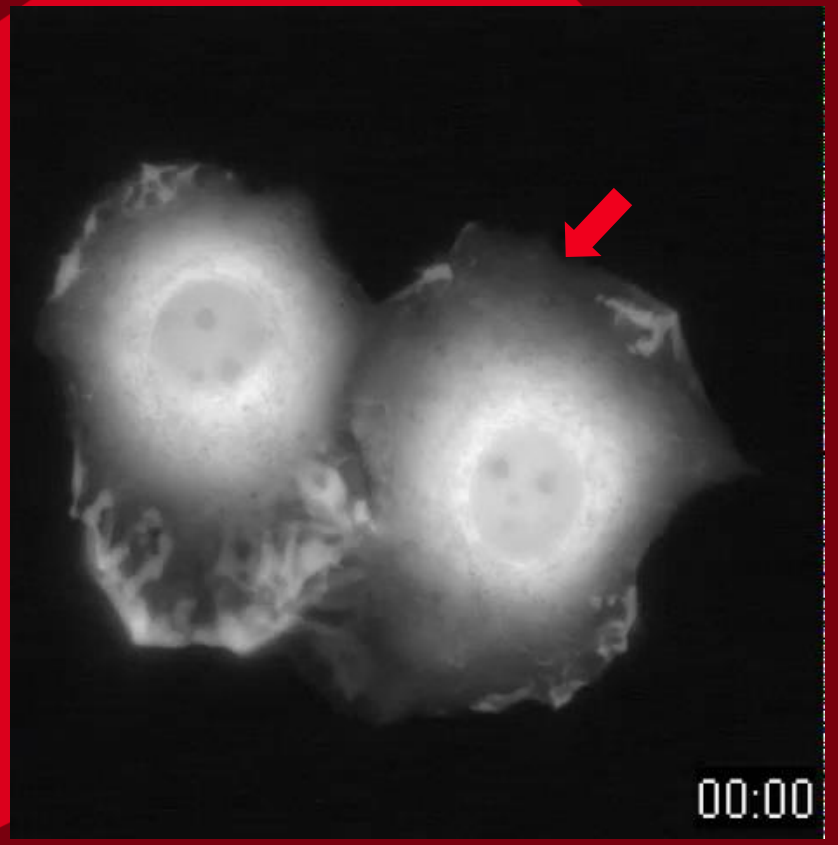

Cellmembran
Cytoplasma
Arvsmassa, DNA
Mitokondrie
Cellkärna
Endoplasmatiska nätverket
Lysosom
Ribosomer
Golgiapparaten
© Toverud

Kræftceller har mutationer, som gør dem autonome og sætter dem uden for kroppens normale kontrol



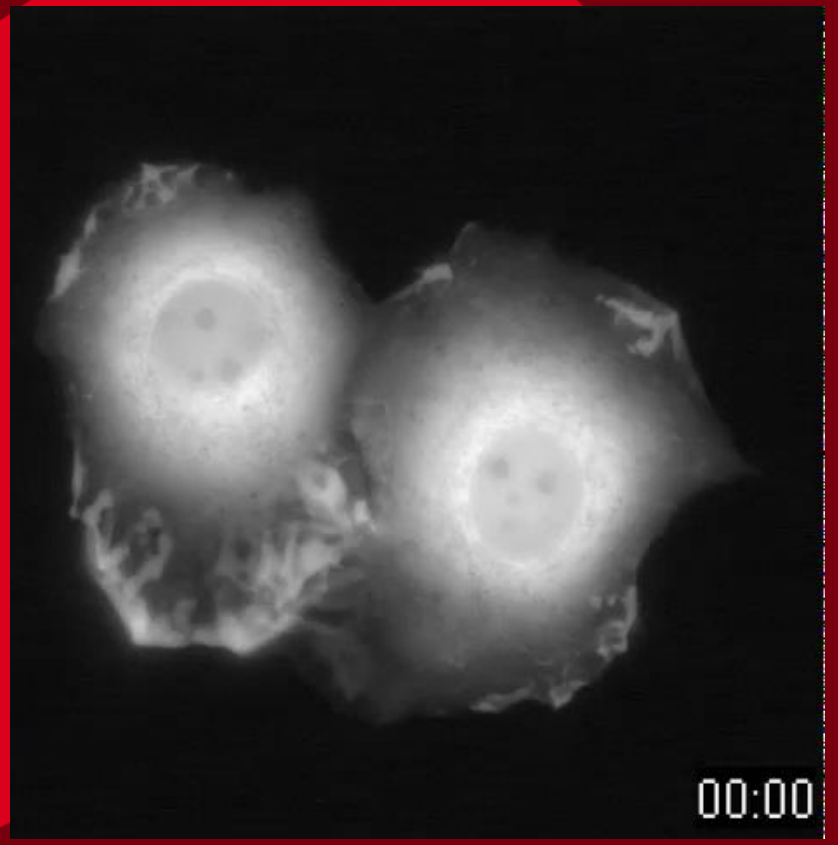
Danish Cancer Society

Lapning af huller i cellers omgivende membran – et spørgsmål om liv eller død



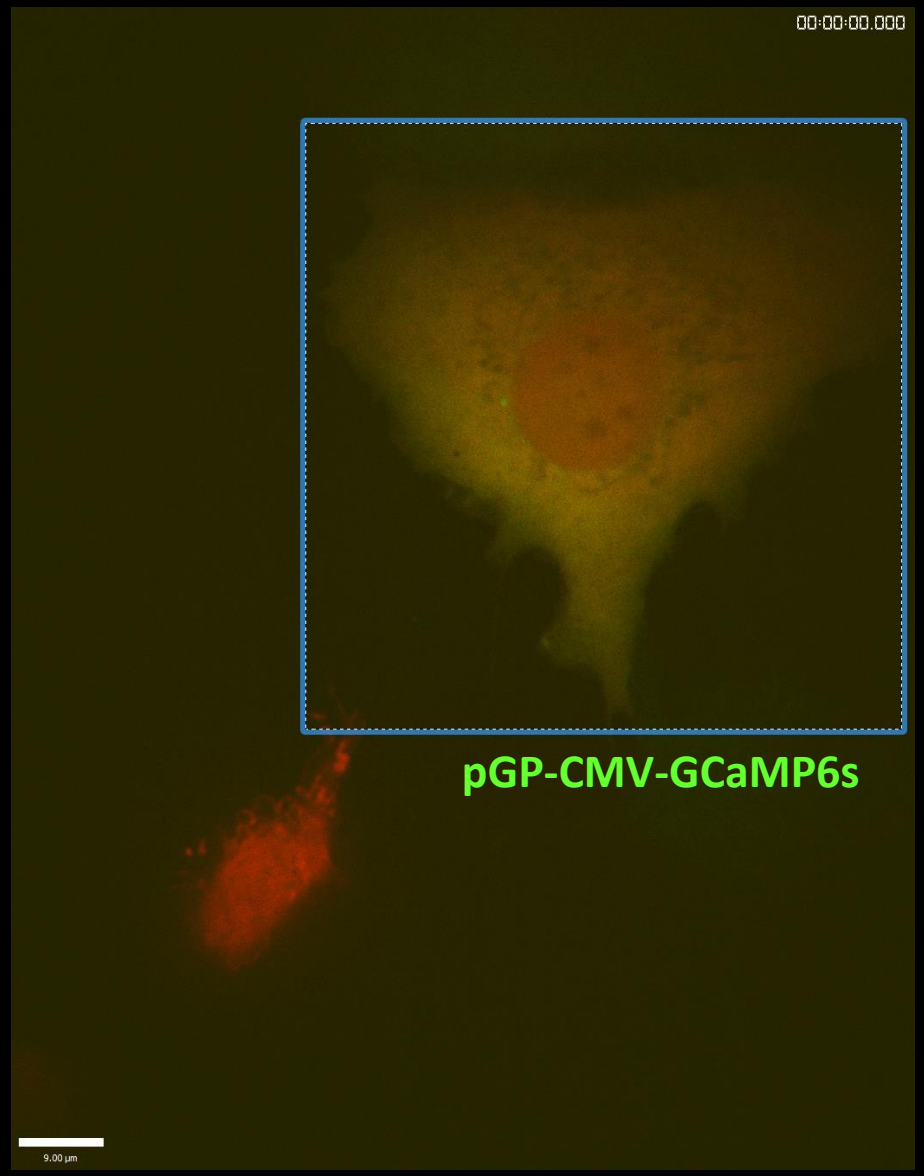
Danish Cancer Society

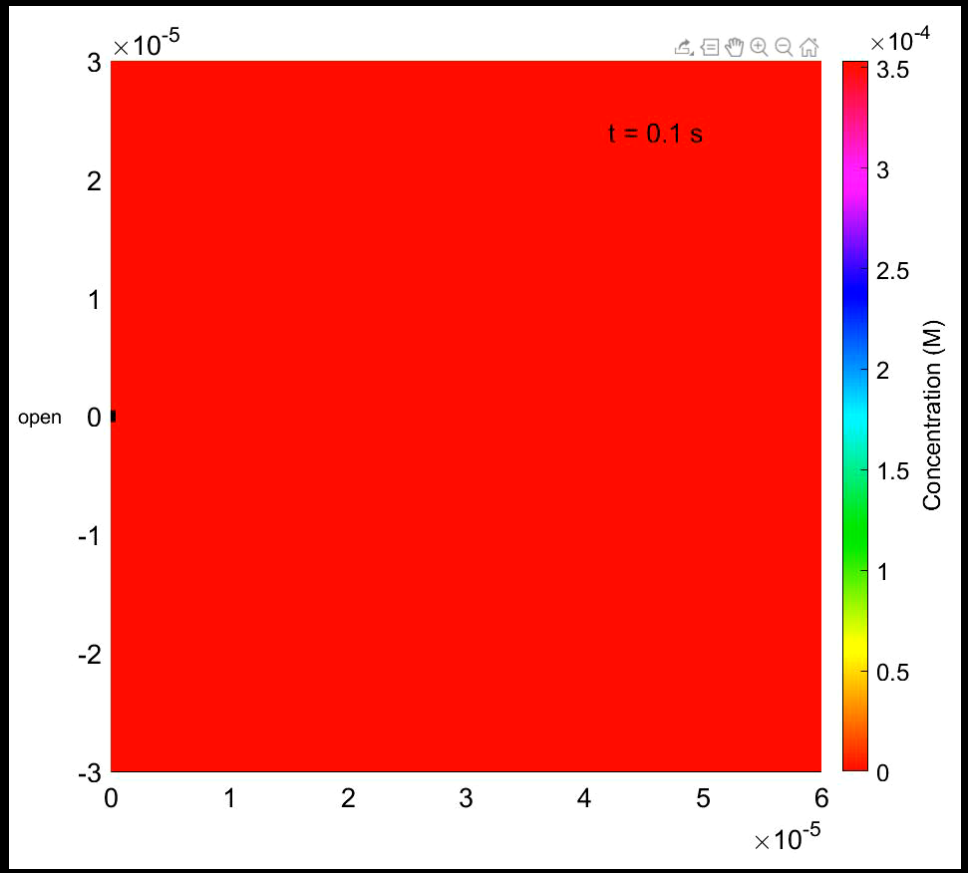
Celler kan lappe huller og reparere sig selv



Danish Cancer Society

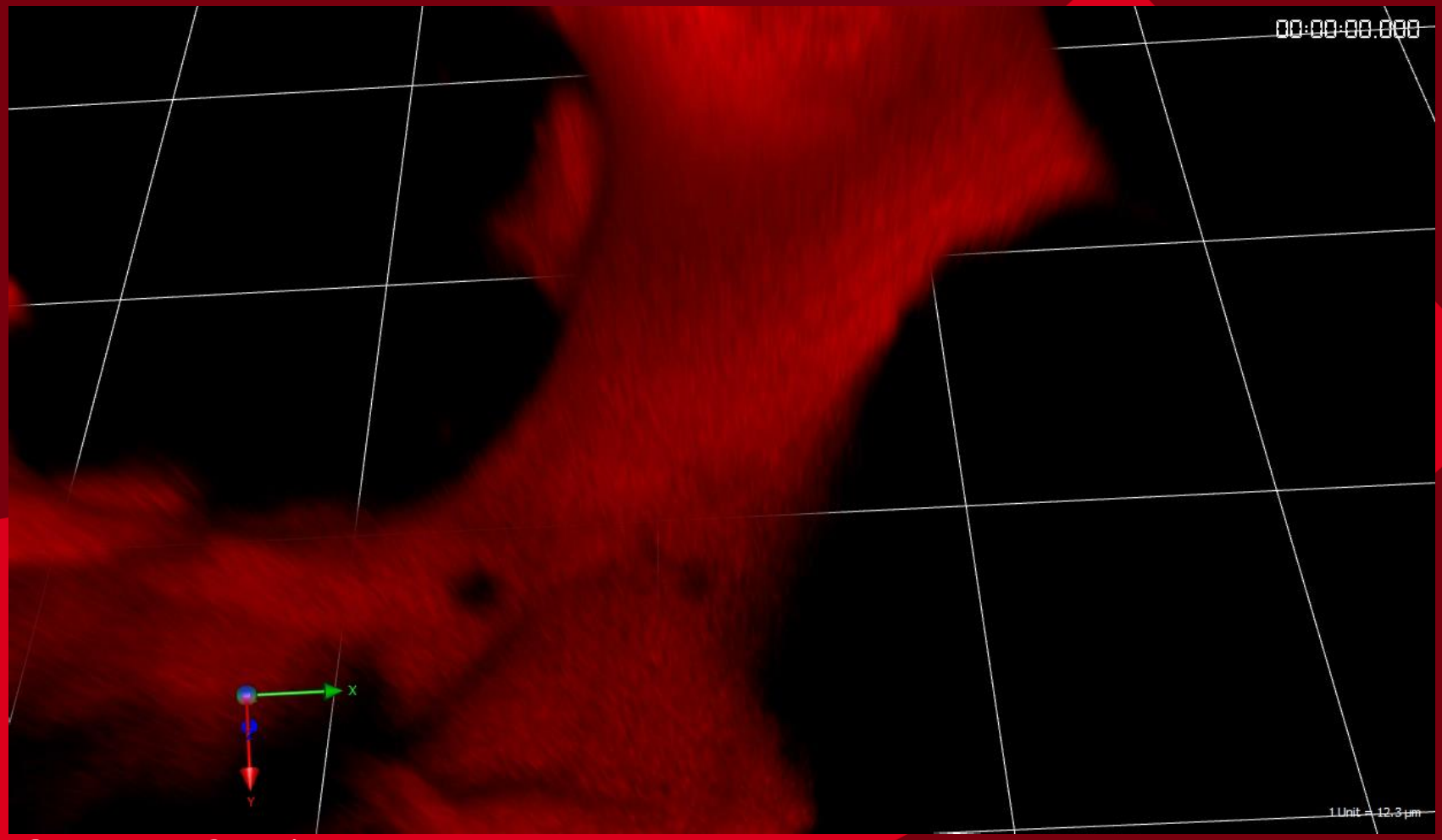
Calcium strømmer igennem hullet og igangsætter cellens reparationsværktøj





Cellereparation under metastasering

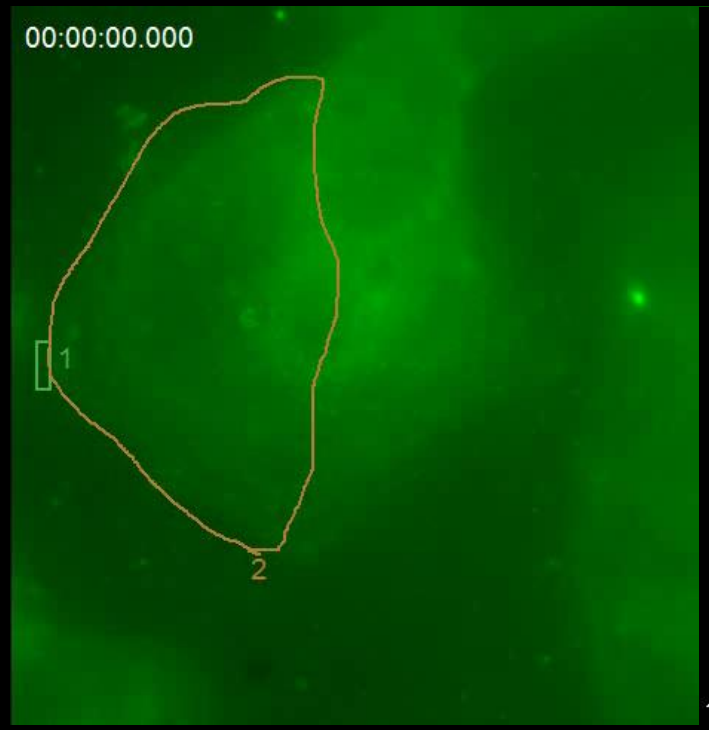
Huller I celler bliver repareret lynhurtigt



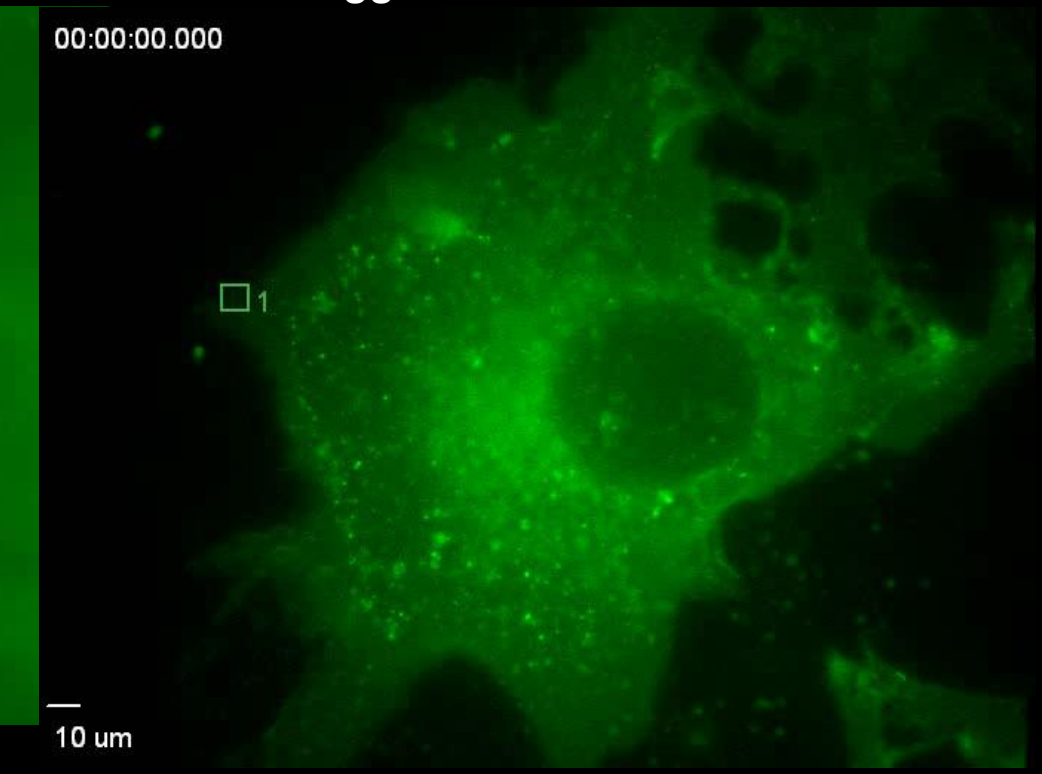
Danish Cancer Society

Kræftceller har effektive reparationsværktøjer

Kontrol celle



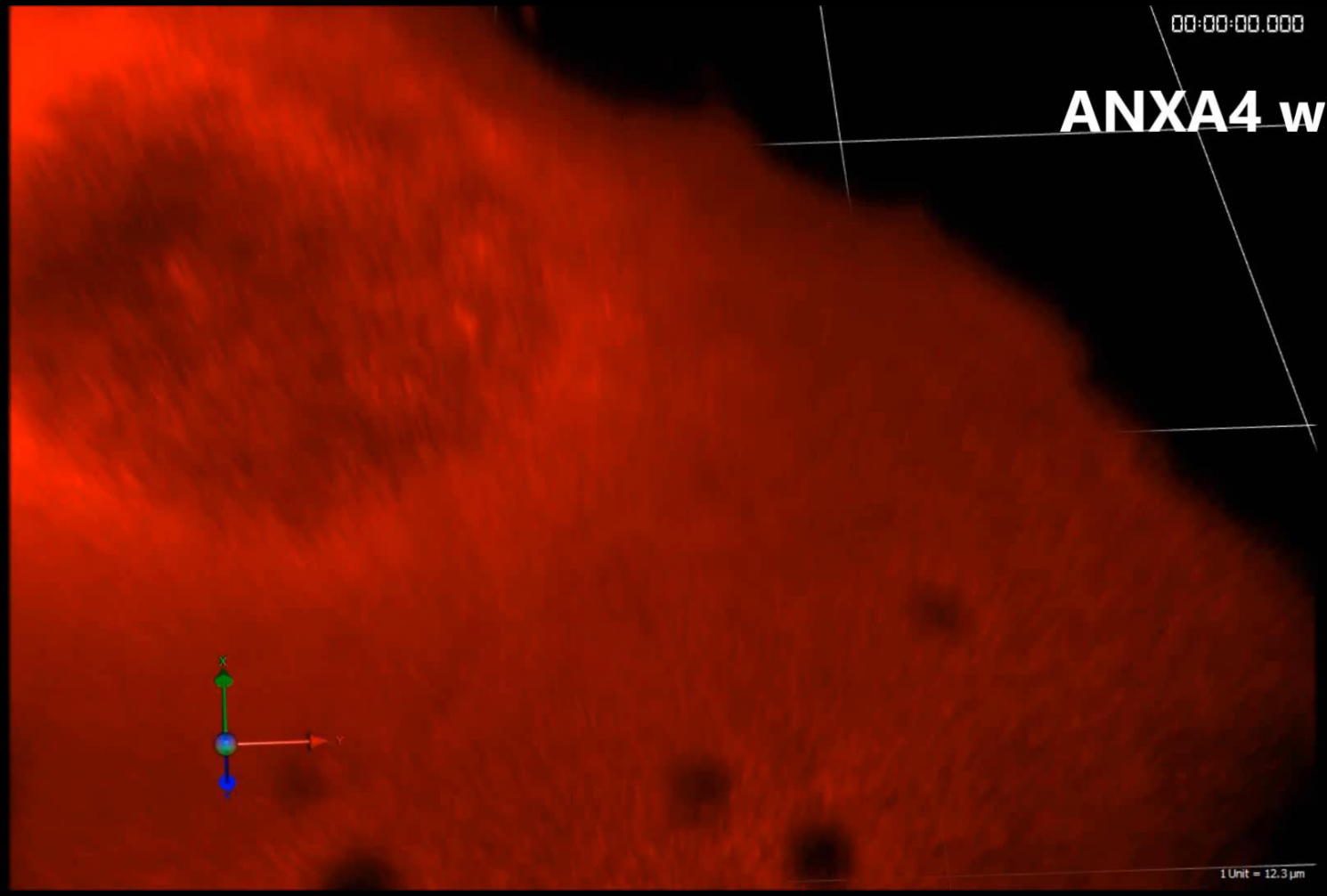
Aggressiv kræftcelle

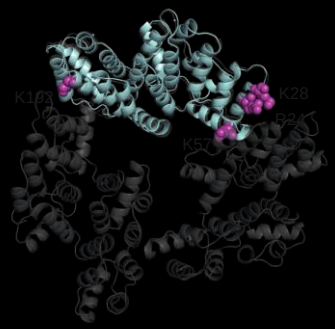


Impermeant FM1-43 dye

Jaiswal et al., Nature Commun, 2014

Annexin proteiner bøjer og limer huller sammen

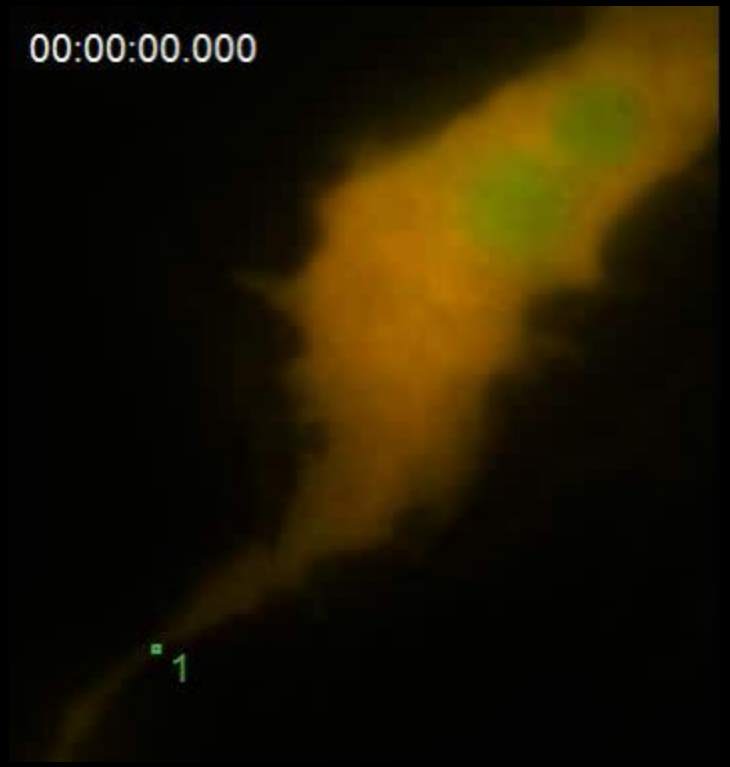




Annexin A4

Boye et al. Nature Commun. 2017

Kræftceller kan afskære dele af deres beskadigede membran

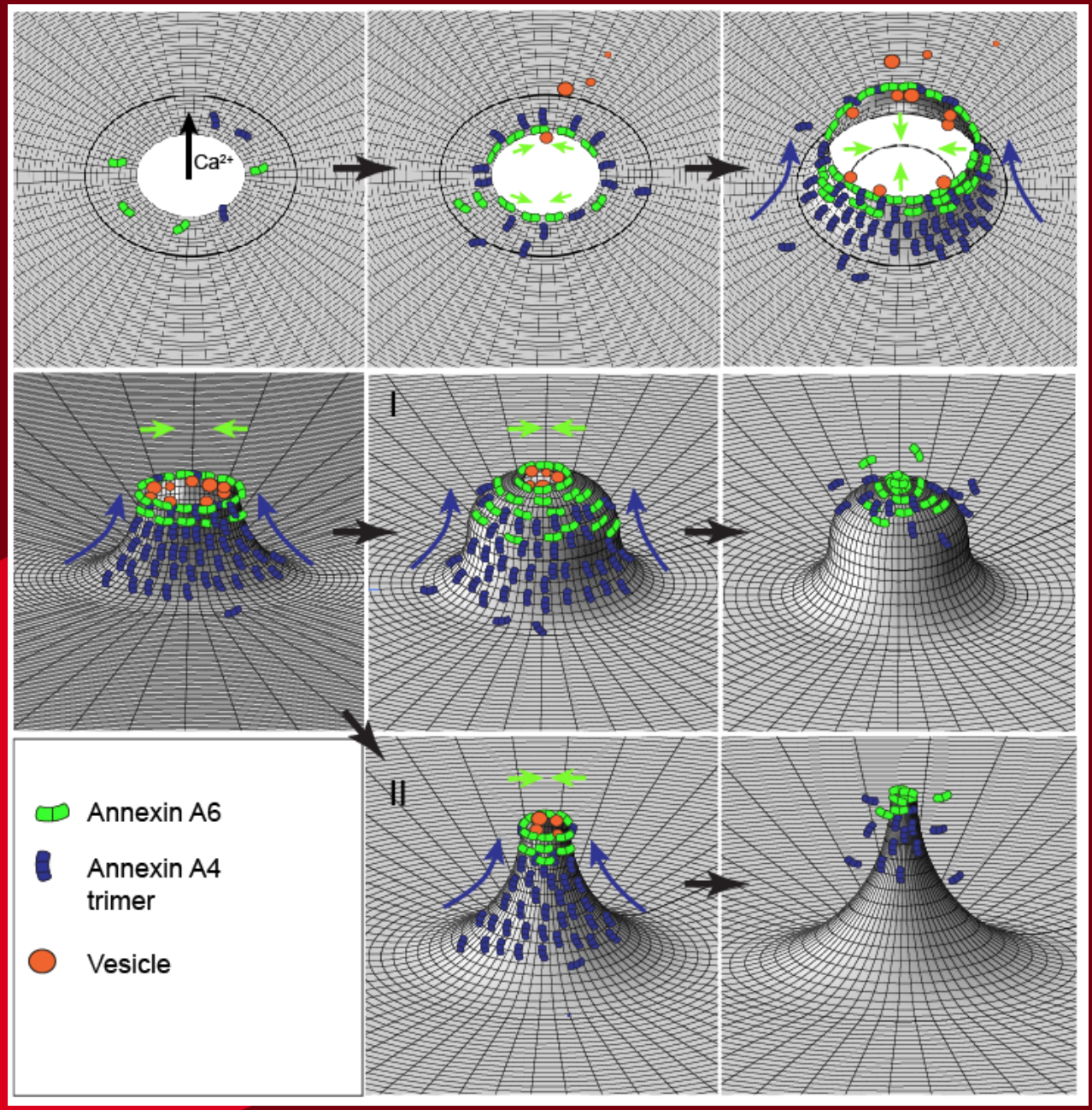


S100A11-RFP
Annexin A1-GFP

Minus Calcium

Jaiswal et al., Nature Commun, 2014

Reparation med Annexin proteiner

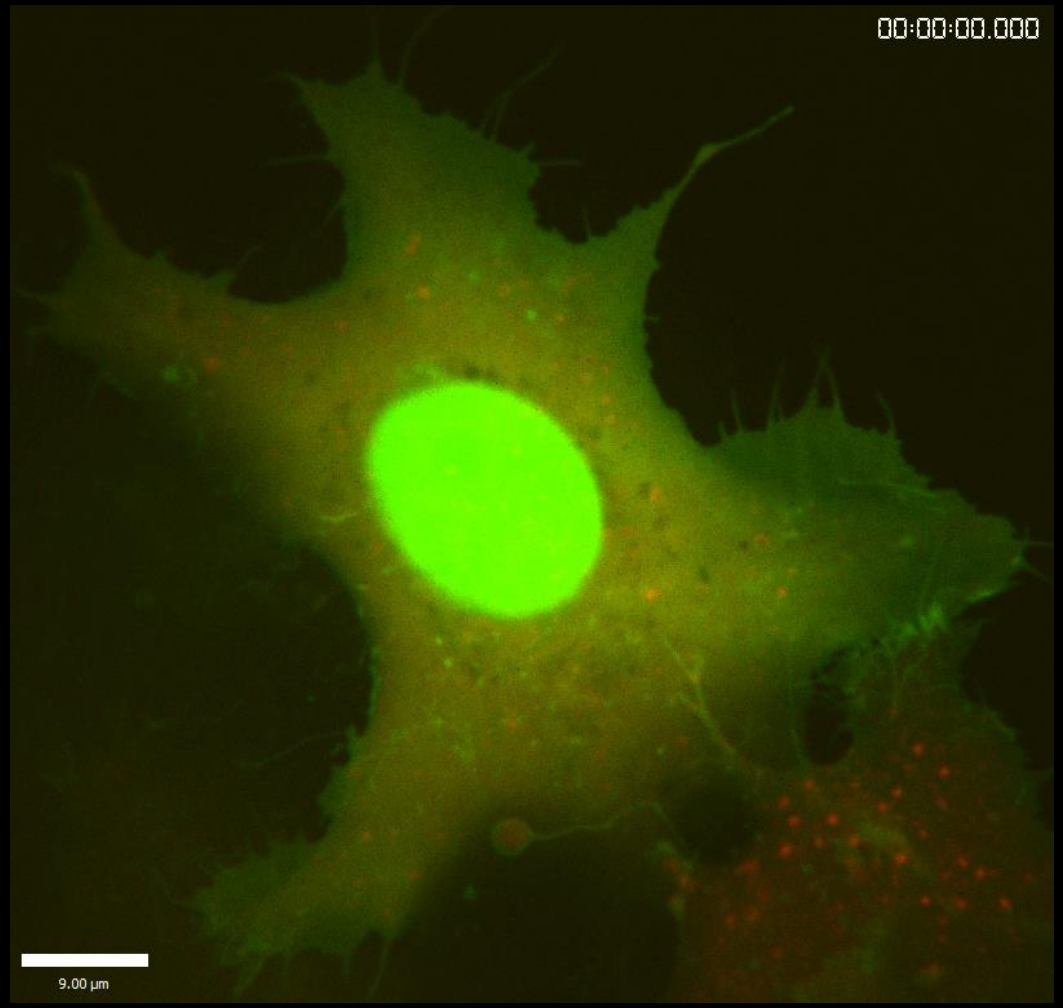


Danish Cancer Society

Kræftceller fjerner deres ødelagte membran ved at spise den (makropinocytose)

Rab5b-RFP
(early endosomes)

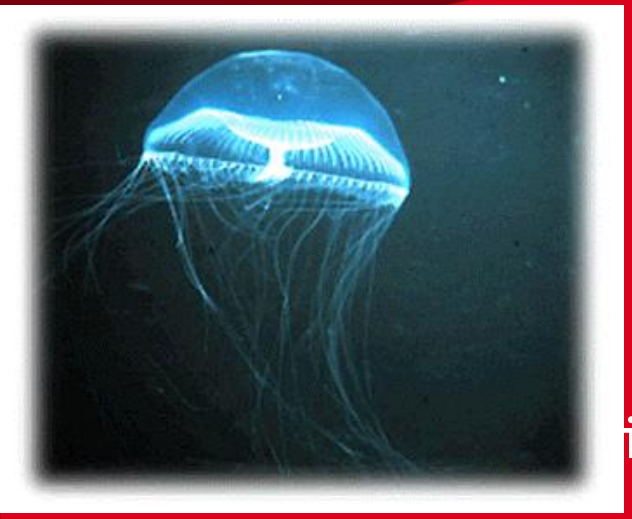
Rab35-GFP
Phagocytosis marker

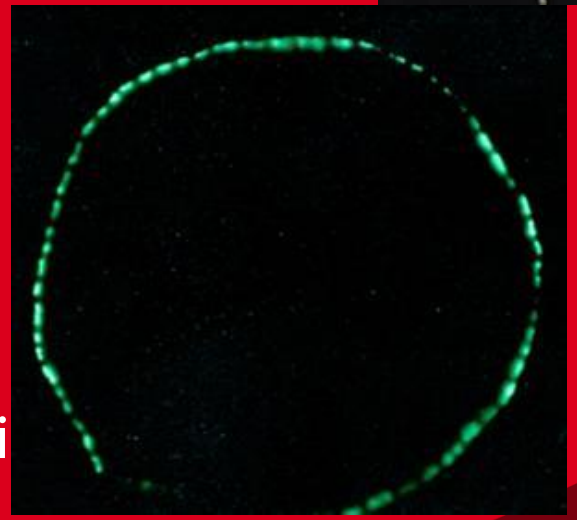


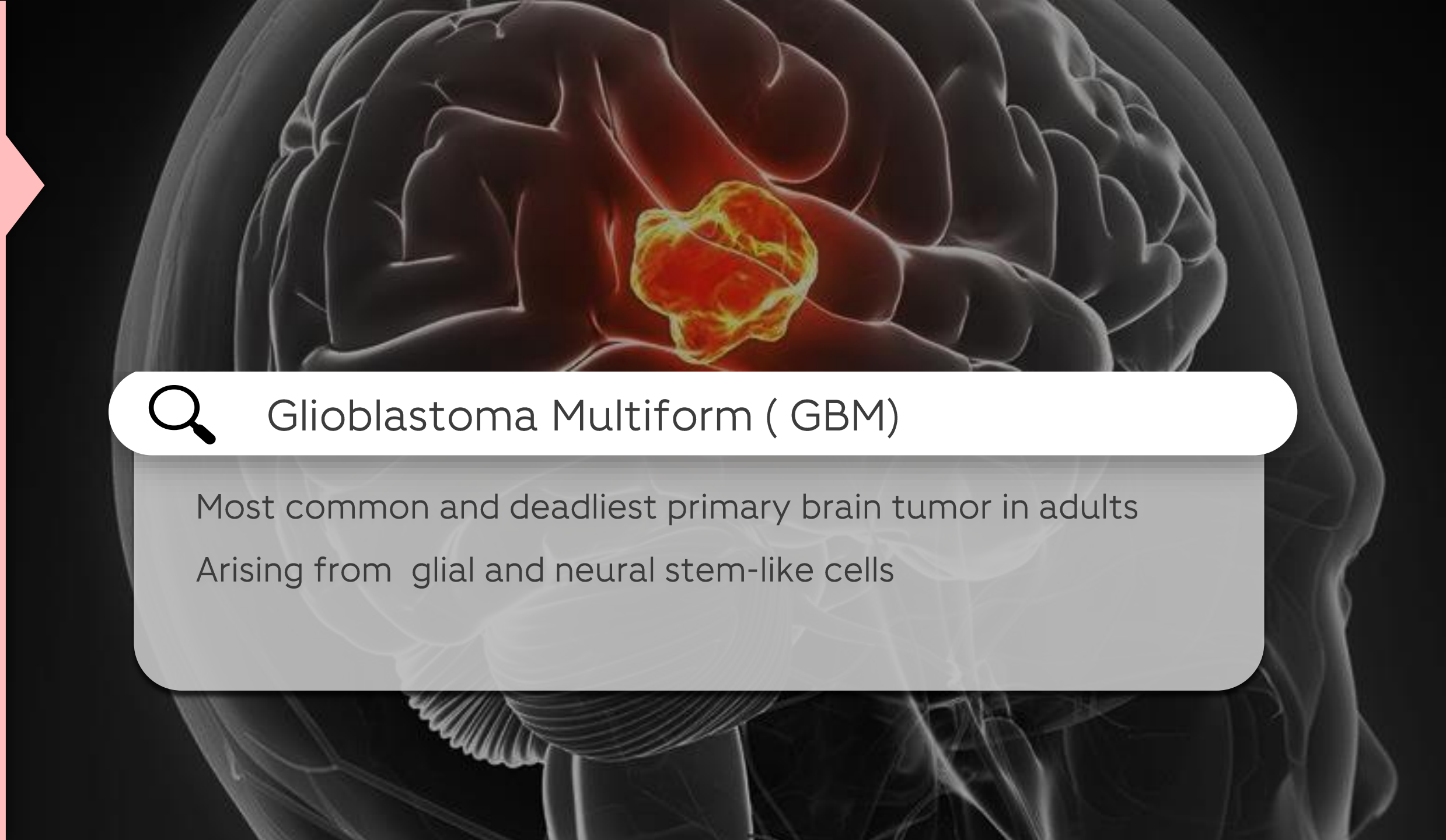
Sønder et al.,
Science Advances, 2021

Grønt flurescerende protein GFP

GFP isoleret fra en gople, Aequorea Victoria







Glioblastoma Multiform (GBM)

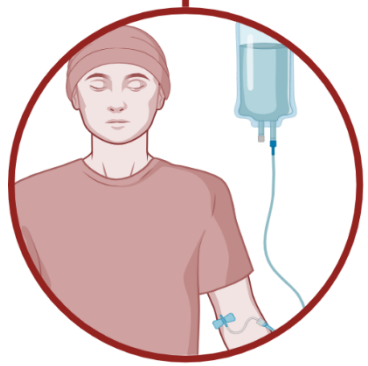
Most common and deadliest primary brain tumor in adults

Arising from glial and neural stem-like cells

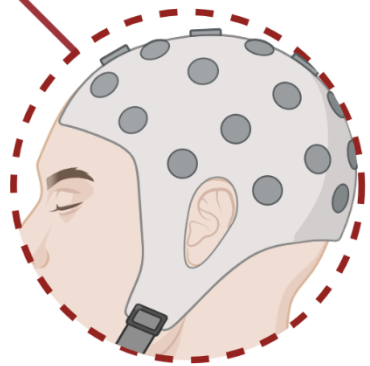
Glioblastoma Treatment Options

Surgery

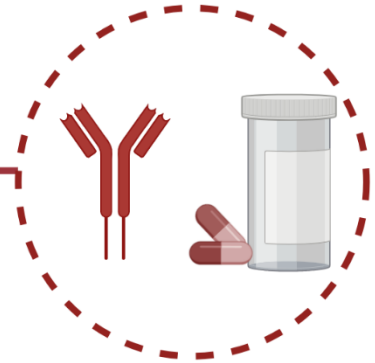
Radiation



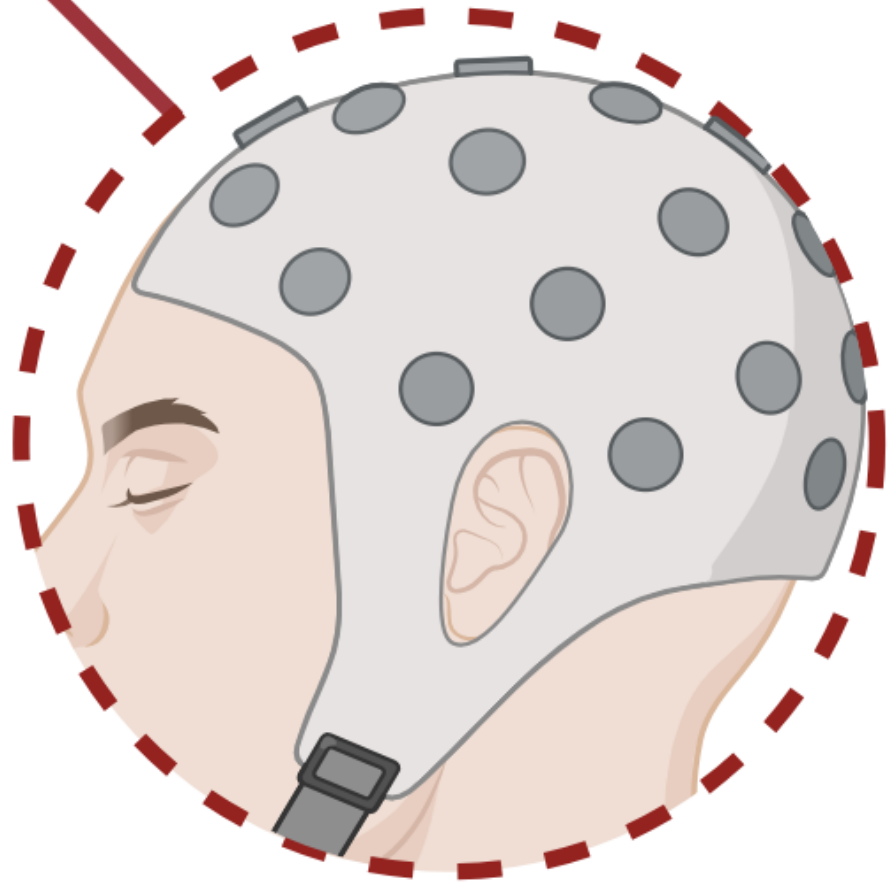
Chemotherapy (temozolomide)



Tumor treating fields (TTF)



Immunotherapy and targeted therapy



Tumor treating fields (TTF)

Tumor treating fields (TTFields)

Alternating electric fields

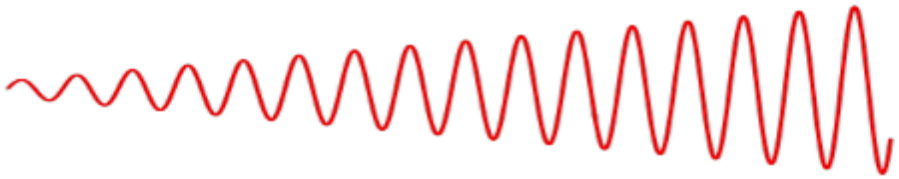
Arrays of electrodes connected to a transducer

Placed on the shaved head

Increased median OS by 4.9 months

Alternating electric fields

Intensity (V/cm)

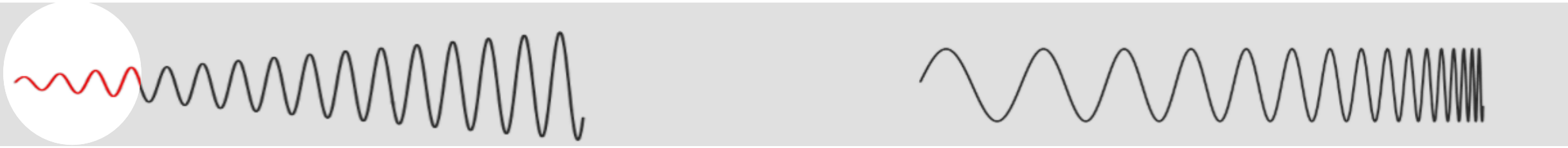


Frequency (kHz)

Alternating electric fields

Intensity (V/cm)

Frequency (kHz)

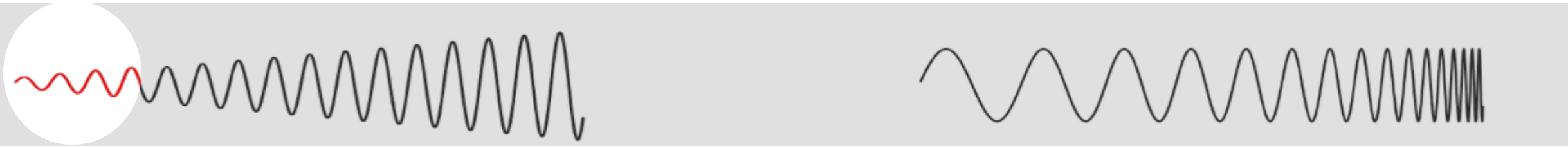


low-intensity
(1–3 V/cm)

Alternating electric fields

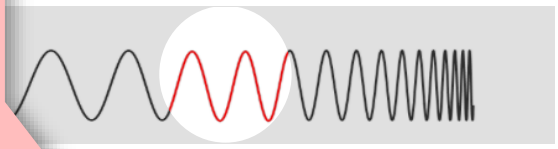
Intensity (V/cm)

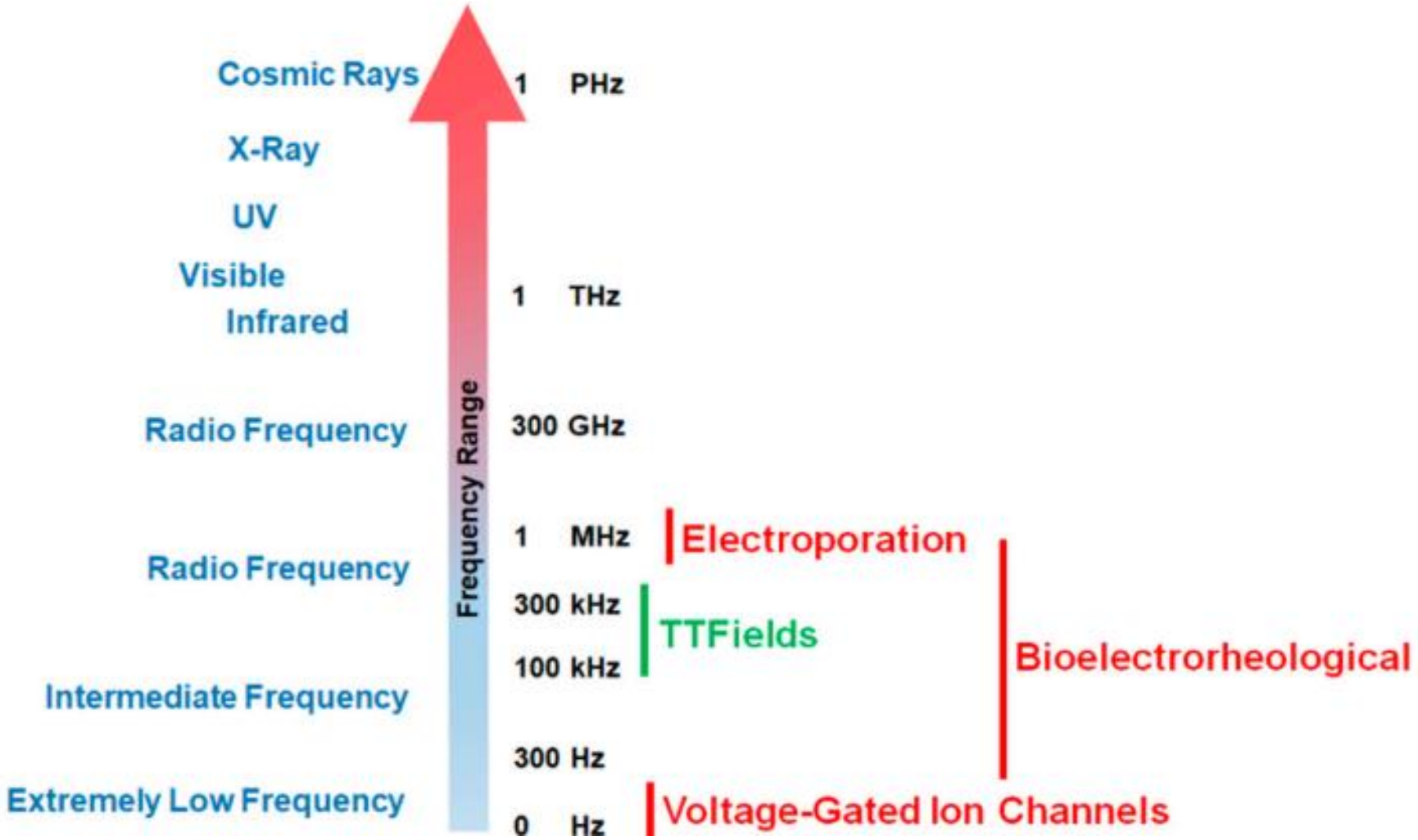
Frequency (kHz)



low-intensity
(1–3 V/cm)

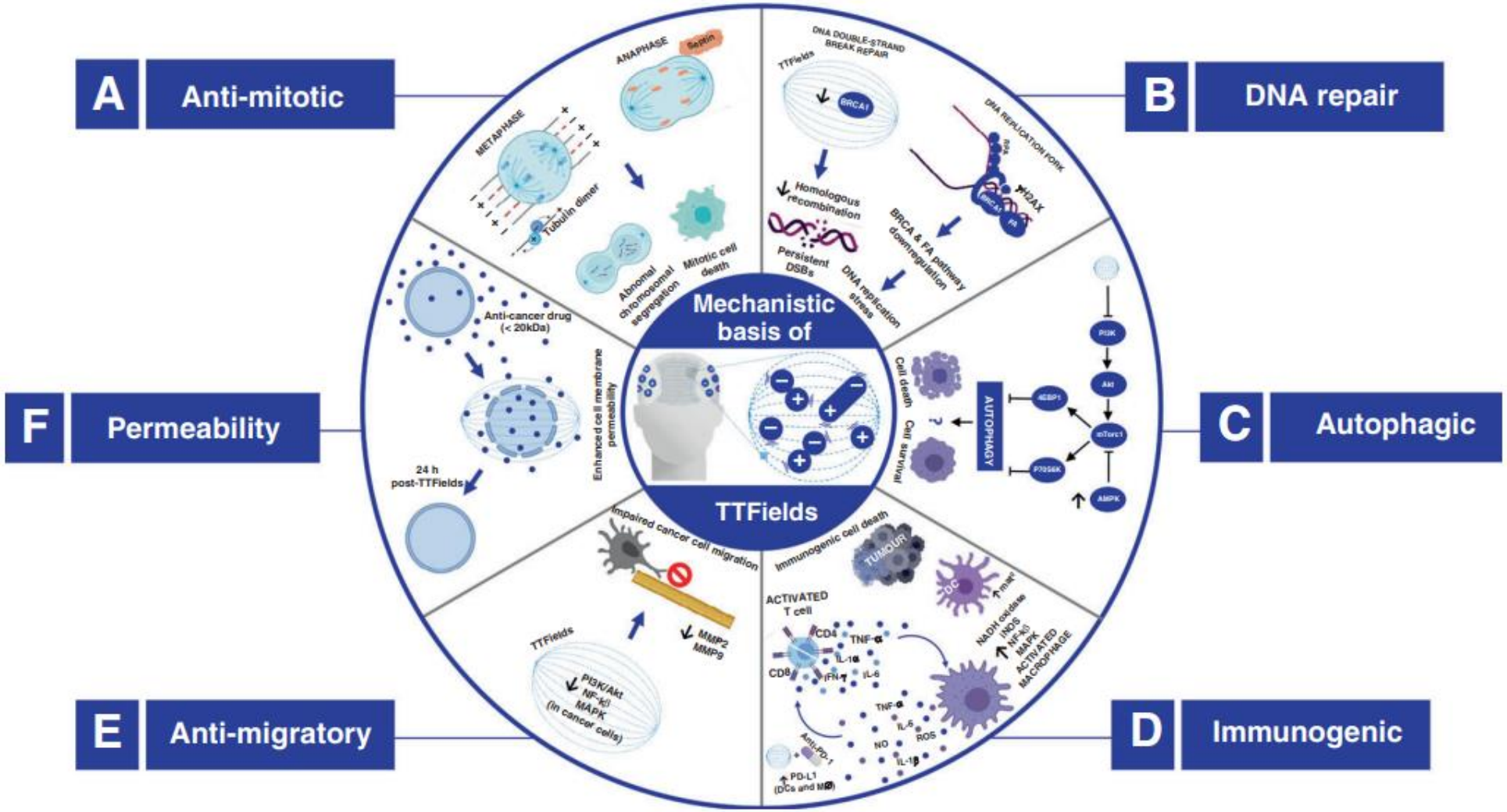
Frequency (kHz)





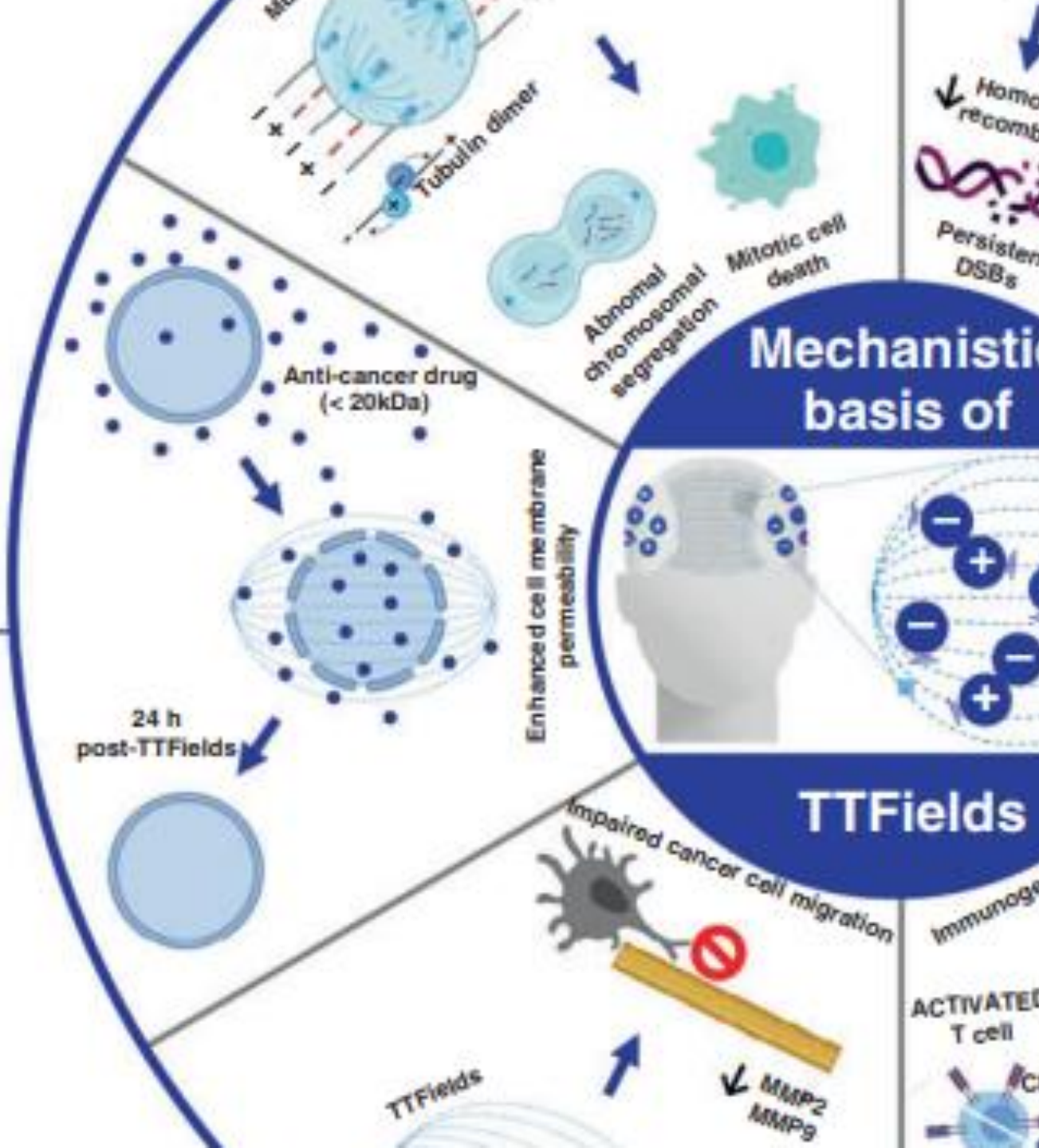
What are the mechanisms of TTFields?

Effects of TTFields



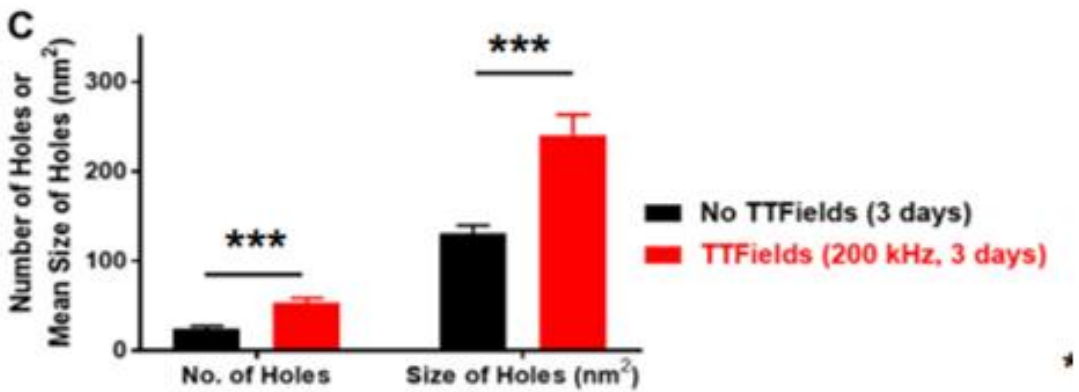
F

Permeability

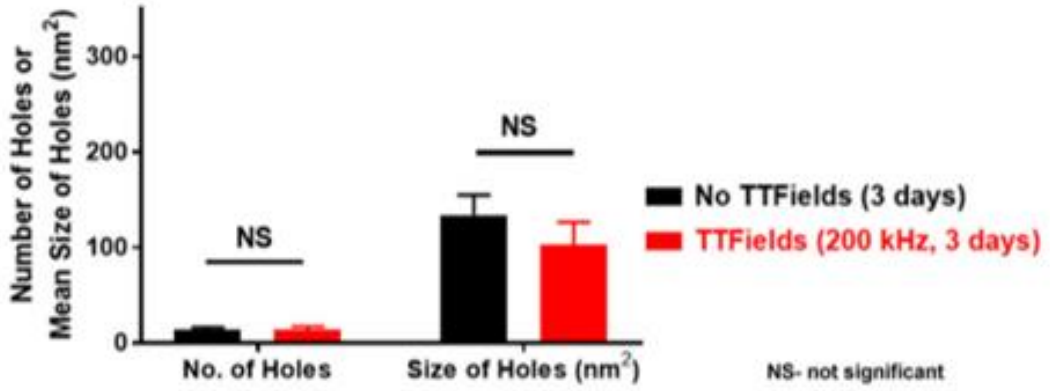


Plasma membrane holes in GBM cells upon exposure to TTFields.

Glioblastoma cells

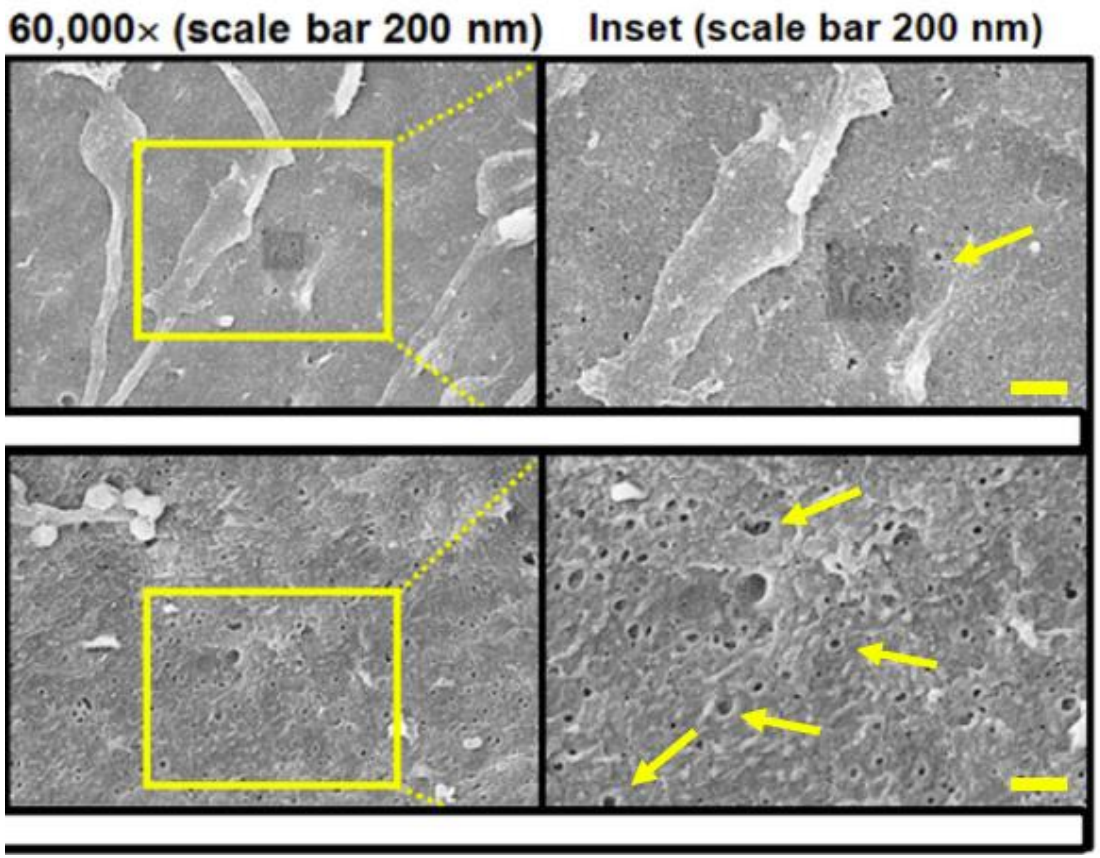


Dermal fibroblast

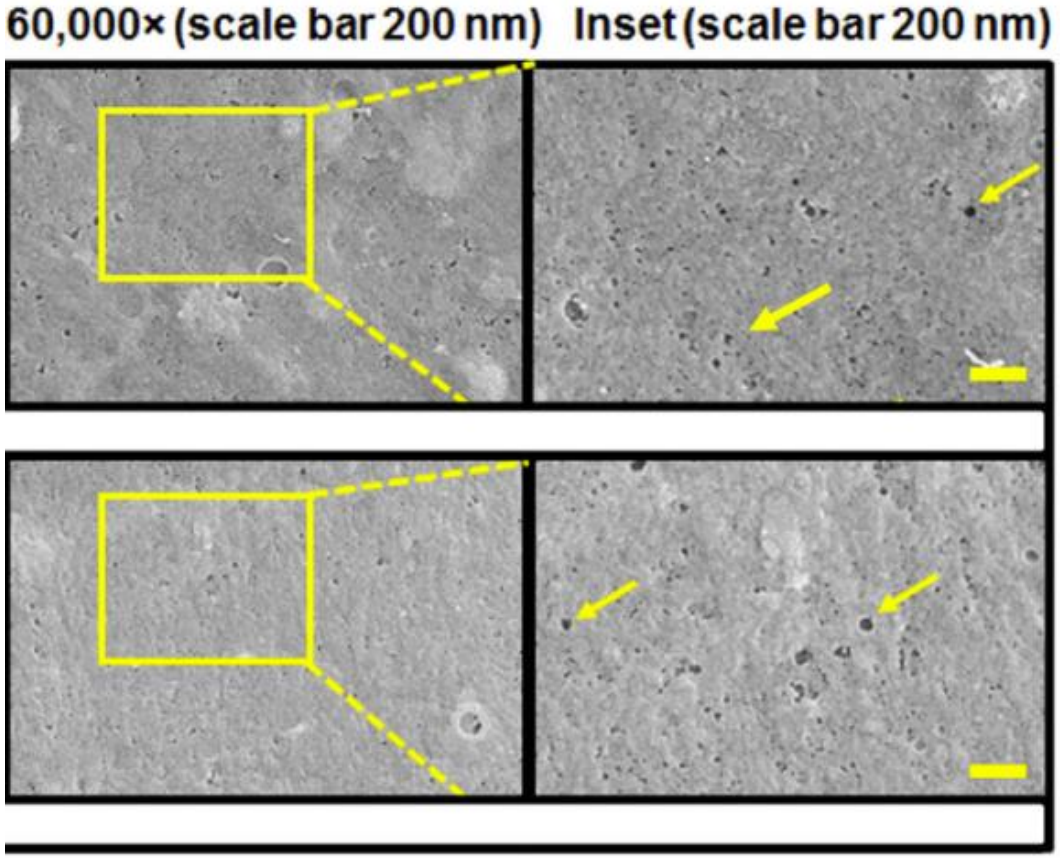


Chang et al, 2018

Glioblastoma cells



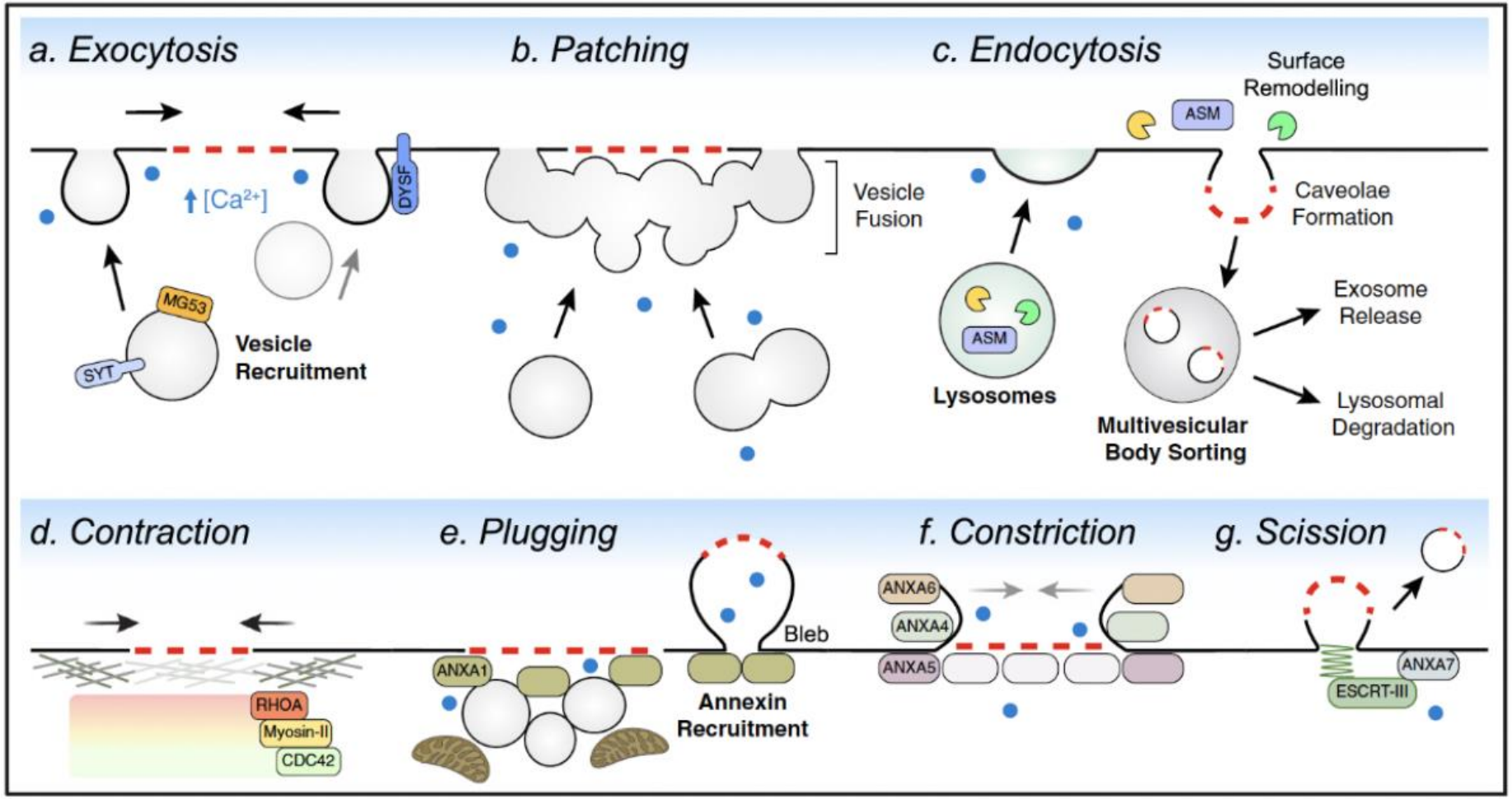
Dermal fibroblast

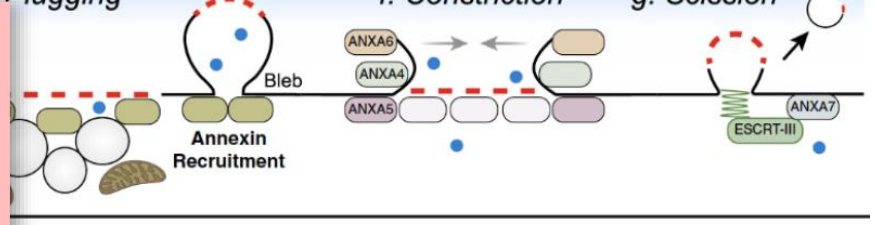


Chang et al, 2018

Why is this interessting for us ?

Membrane Repair Mechanisms





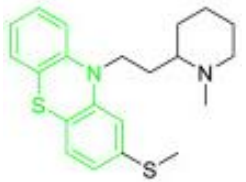
JBC | JOURNAL OF BIOLOGICAL CHEMISTRY

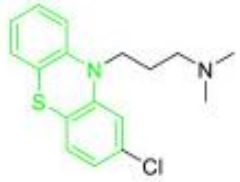
Volume 297, Issue 2, August 2021, 101012

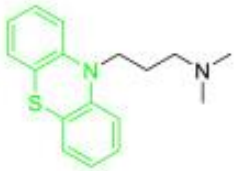
Research Article

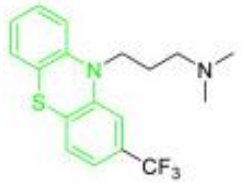
Phenothiazines alter plasma membrane properties and sensitize cancer cells to injury by inhibiting annexin-mediated repair

Anne Sofie Busk Heitmann [1], Ali Asghar Hakami Zanjani [2], Martin Berg Klenow [2], Anna Mularski [2], Stine Lauritzen Sønder [1], Frederik Wendelboe Lund [2], Theresa Louise Boye [1], Catarina Dias [1], Poul Martin Bendix [3], Adam Cohen Simonsen [2], Himanshu Khandelia [2], Jesper Nylandsted [1 4]

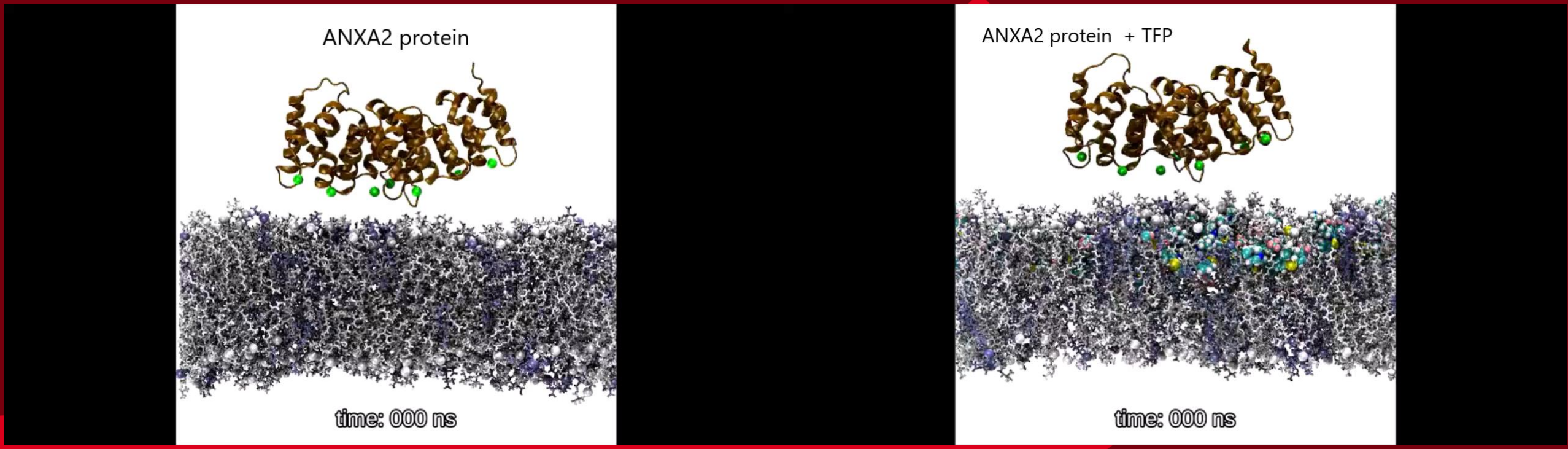








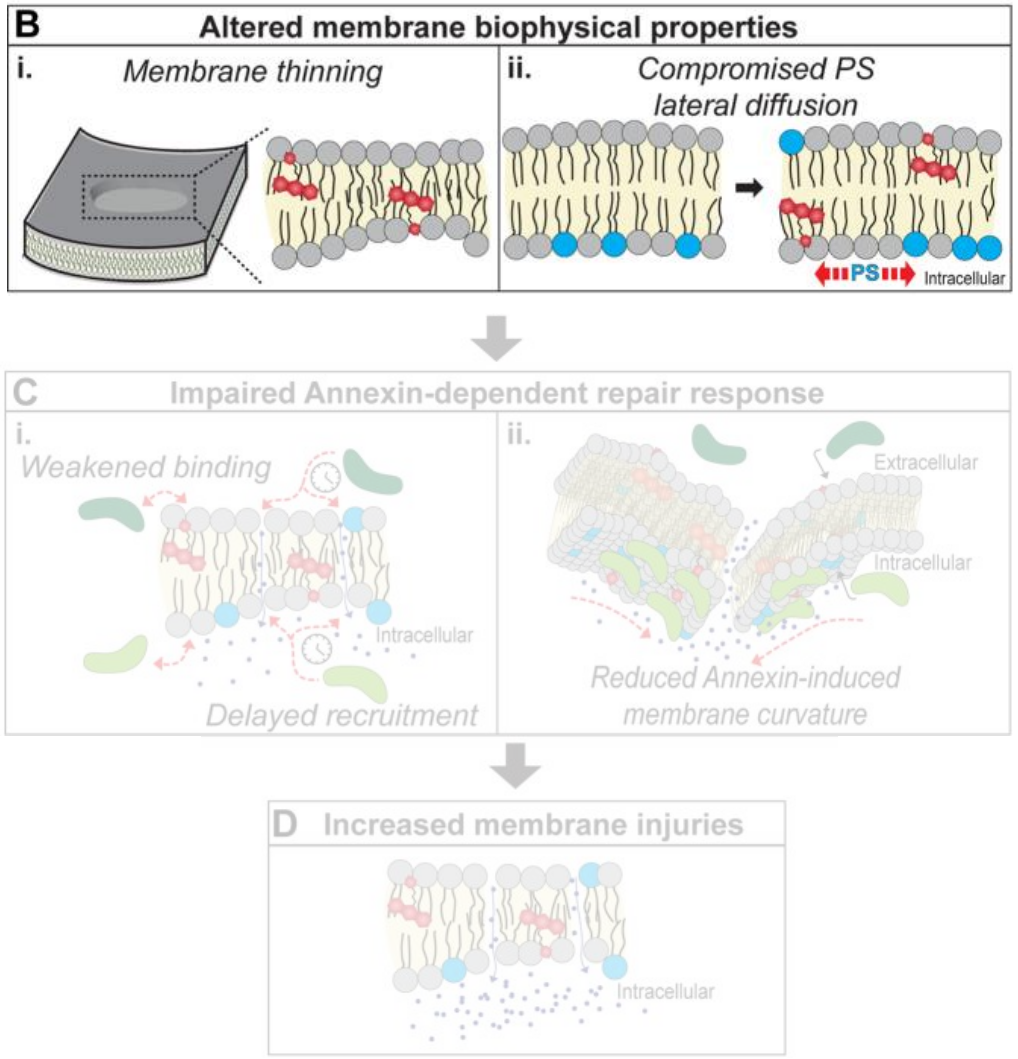
Phenothiaziner kan muligvis bruges til at ramme kræftcellers reparation ved at hæmme Annexiner

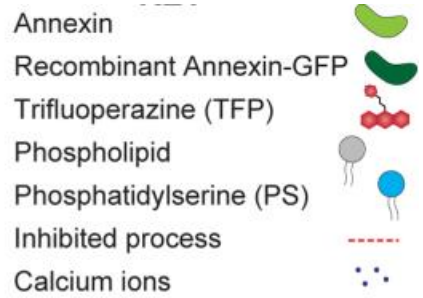


Heitmann et al., J Biol Chem, **2021**

Trifluoperazine

Effects of TFP on the membranes of cancer cells





Trifluoperazine

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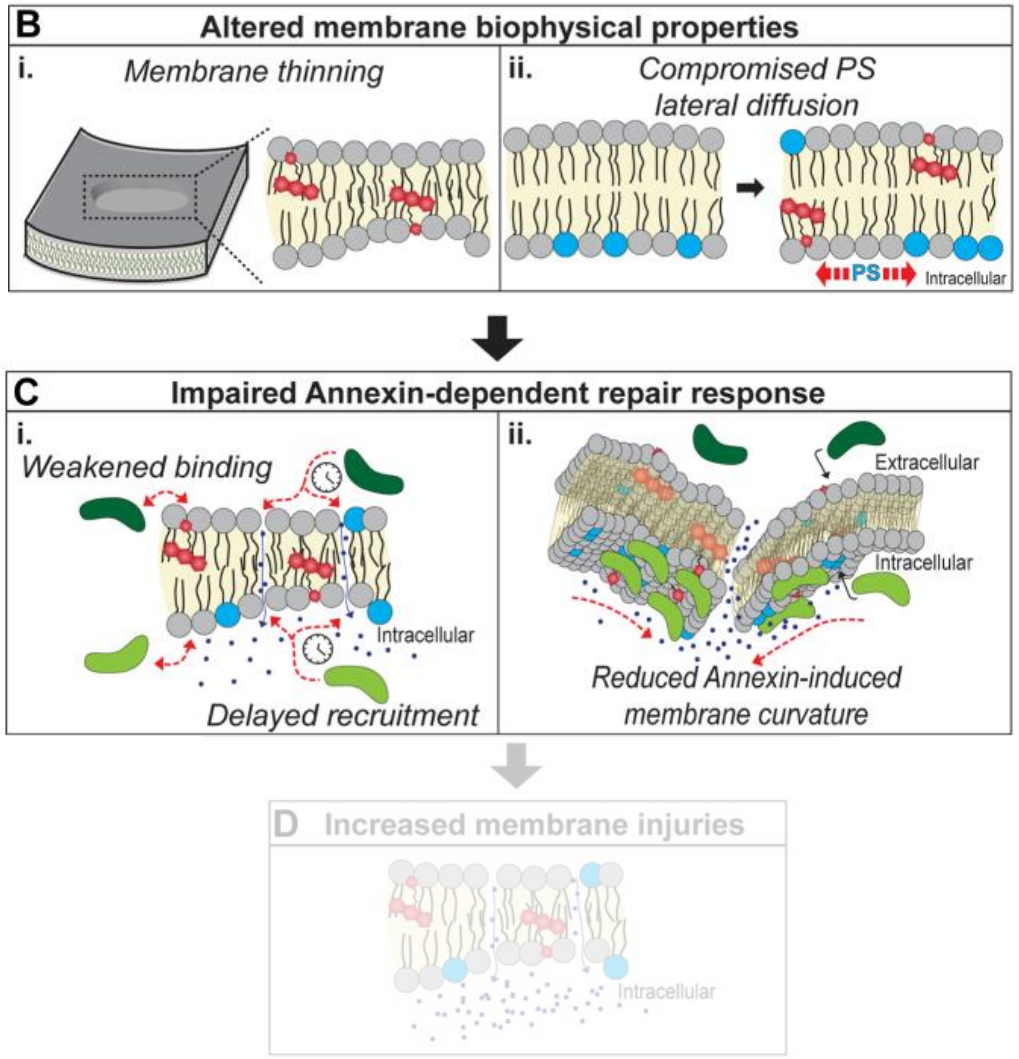
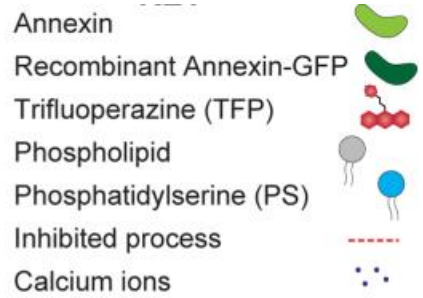
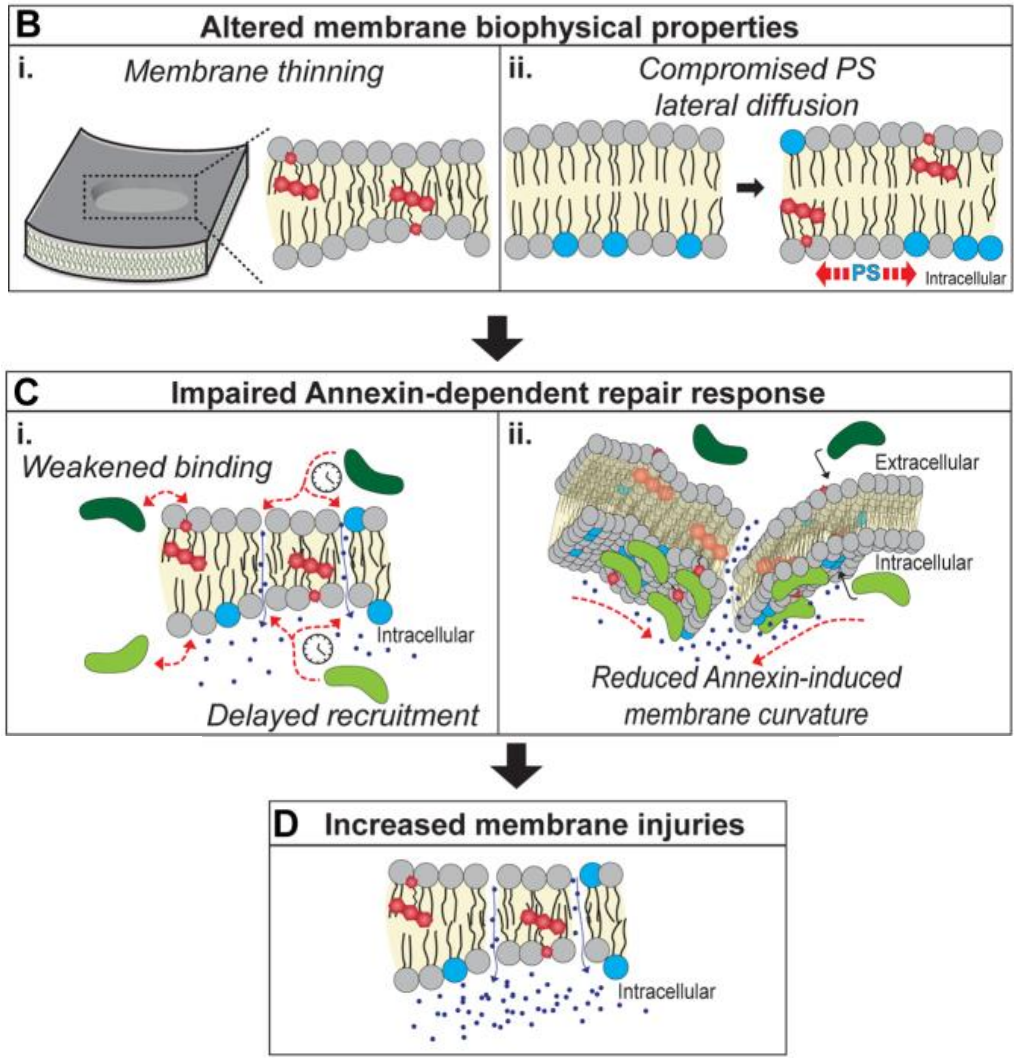
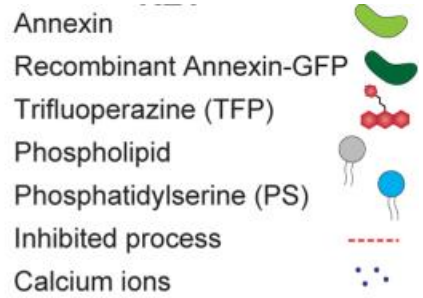




Trifluoperazine

Effects of TFP on the membranes of cancer cells





Methods

TTFields applications

→ inovitro

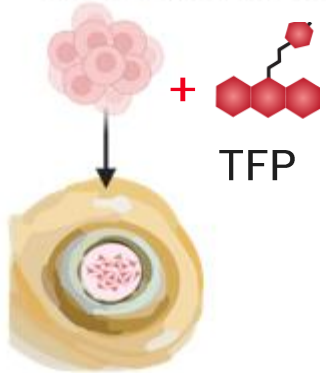
→ inovitro-live

→ inovivo

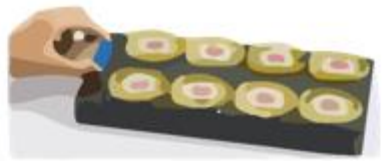
Methods

TTFields in vitro Application

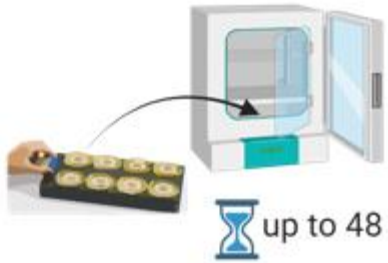
1 Cell seeding on cover slips in ceramic dishes



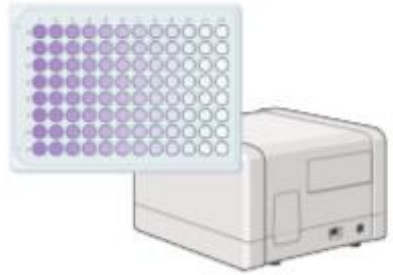
2 Attaching the baseplate to the TTFields generator



3 Incubation +/- TFP



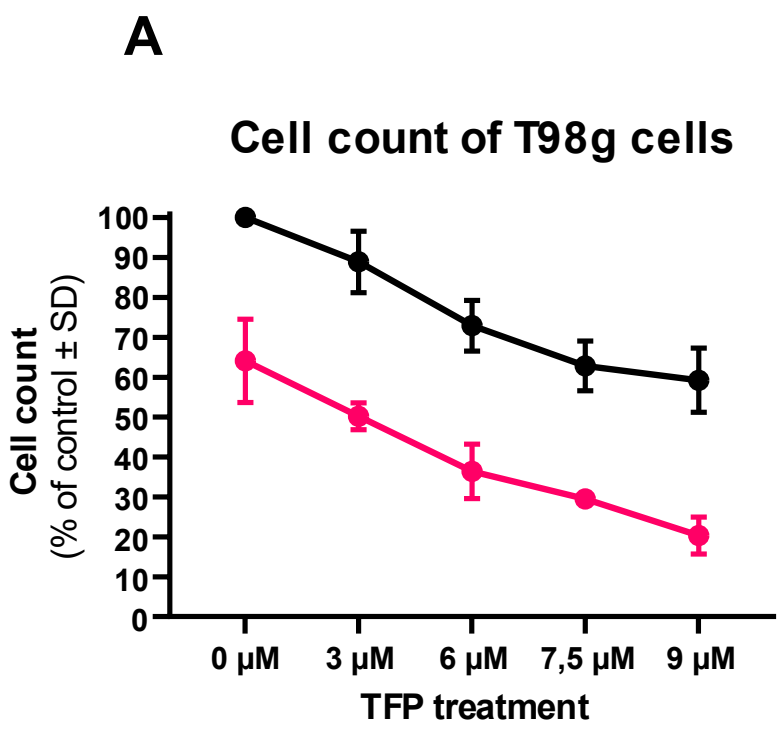
4 Cell death measurement

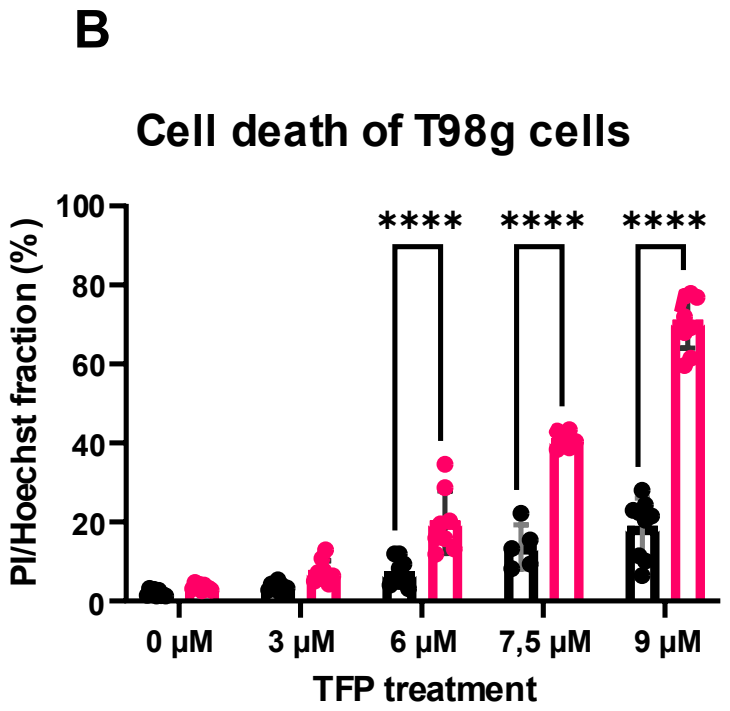


Preliminary Results

How Does the Co-Treatment of TTFields and TFP Influence Cell Growth and Cell Death?

How Does the Co-Treatment of TTFields and TFP Influence Cell Growth and Cell Death?





no TTFields

TTFields

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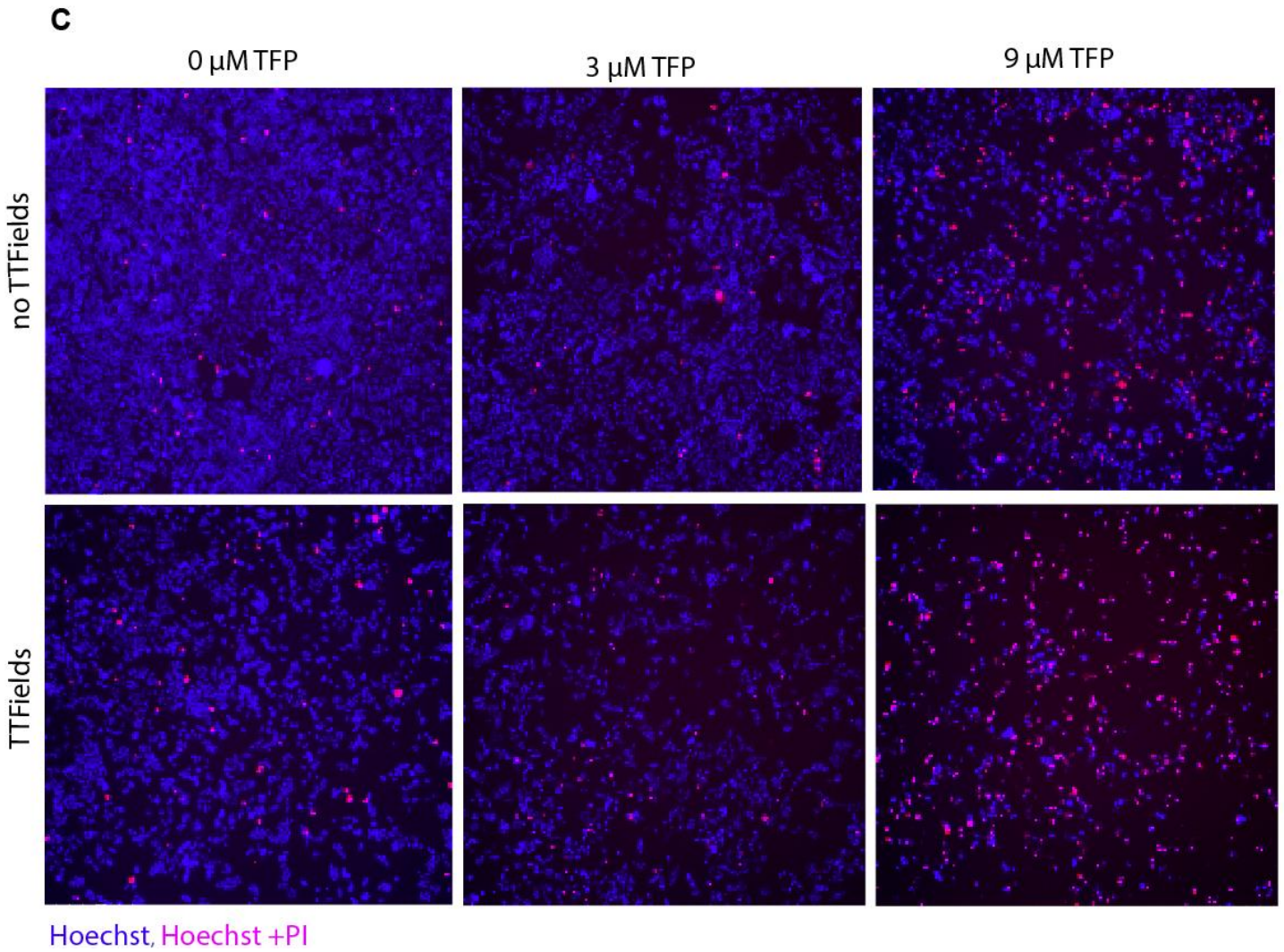
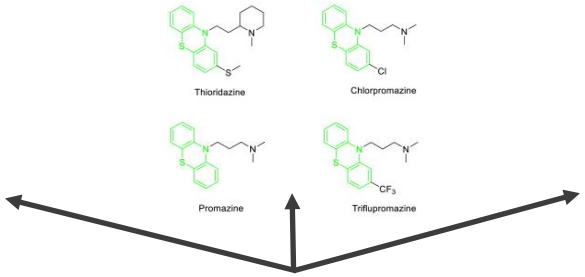
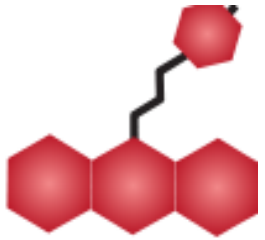


Perspectives

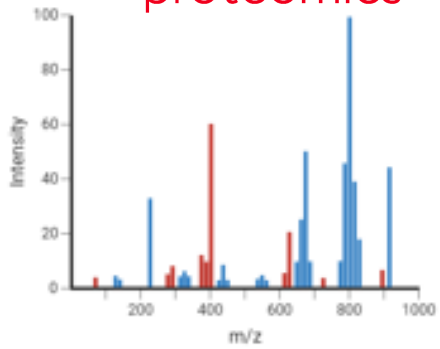
TTFields in vivo

Other derivatives of phenothiazines

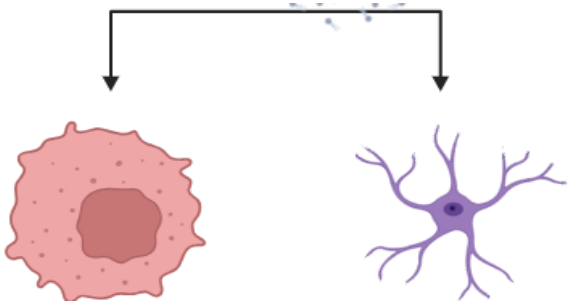




Lipidomics and proteomics



Confirm the effect of TFP



Other GBM cell

Primary glia cells

Application of TTFields

Other GBM cell

Primary glia cells