ISCO2023

New treatment strategies for intractable cancers brought about by the fusion of different fields of science

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Fujita Health University, Aichi, Japan

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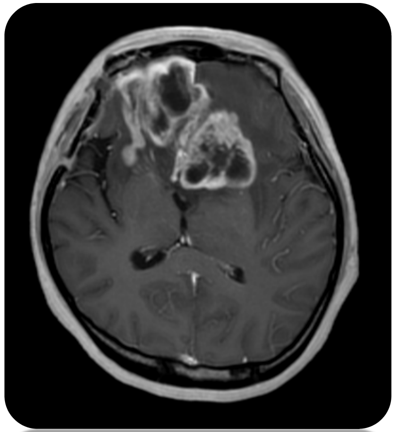
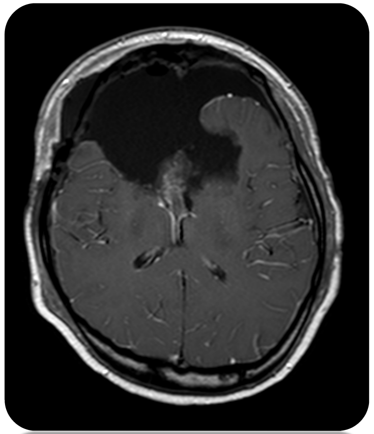
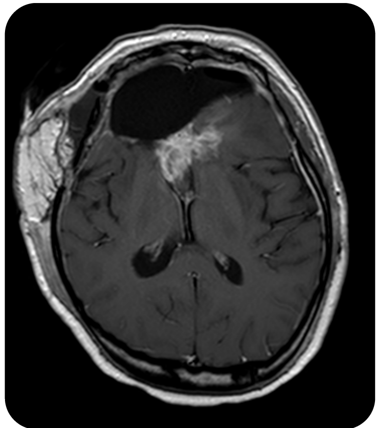
Malignant brain cancer : Glioblastoma



surgery



Radiation therapy
Chemotherapy



Resistance and Recurrence

Cancer

A phenomenon in which normal cells change due to gene mutations, break the rules, proliferate abnormally, and survive for a long time.

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Cancer cells invade surrounding organs or metastasize to distant organs, resulting in impairment of their functions.

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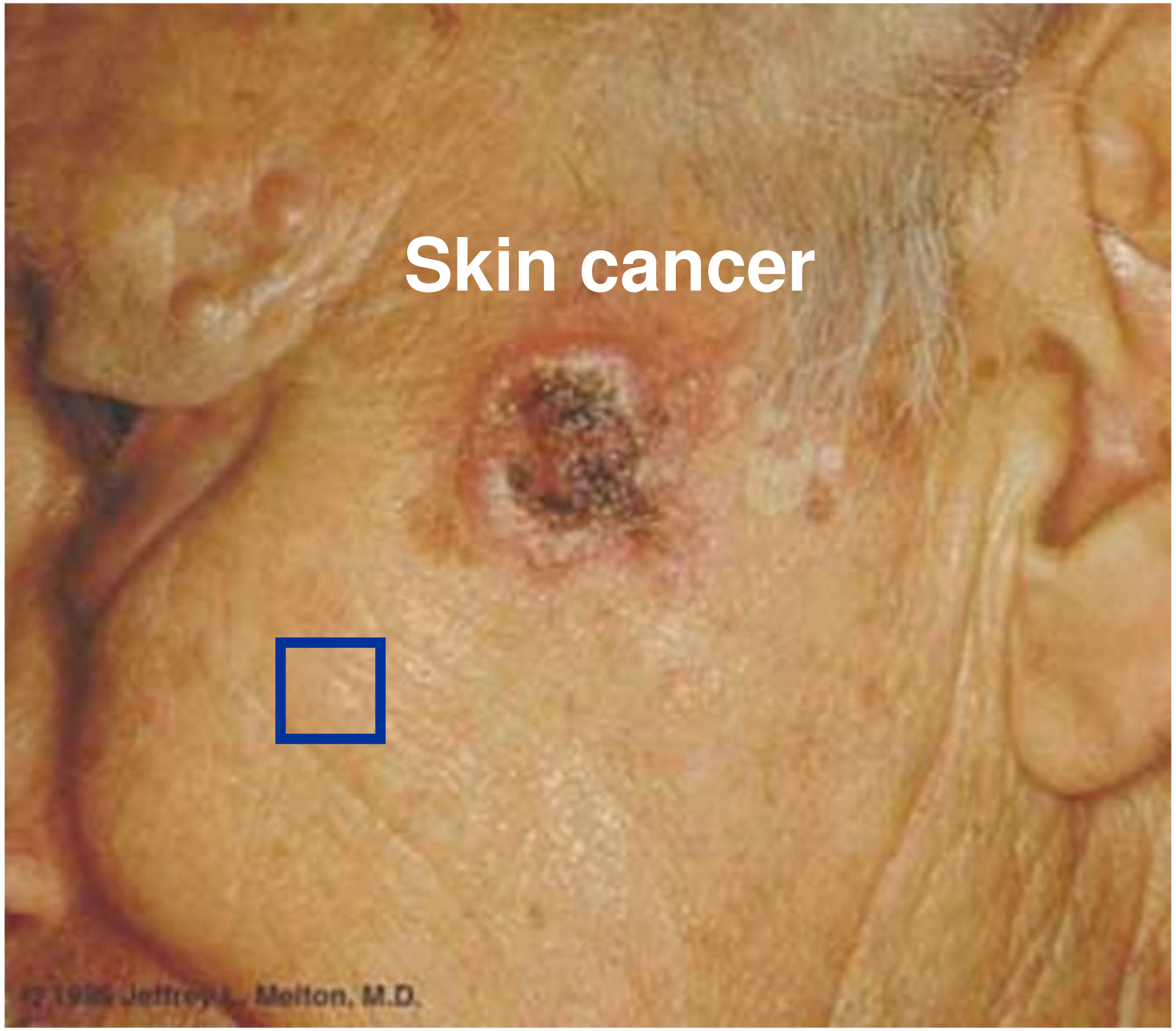
Without treatment, various organ disorders eventually occur, leading to death.

How does cancer arise?

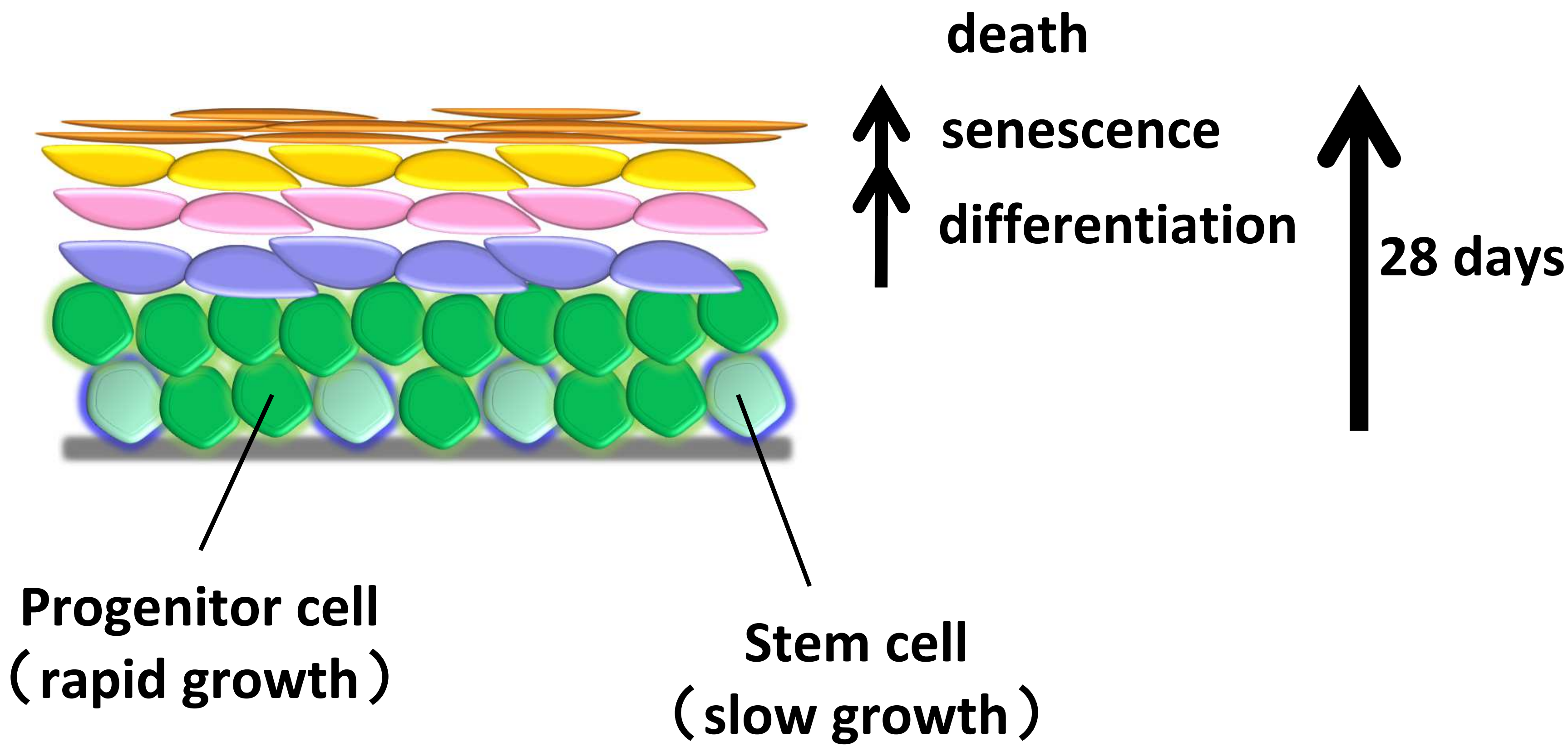


Normal skin structure

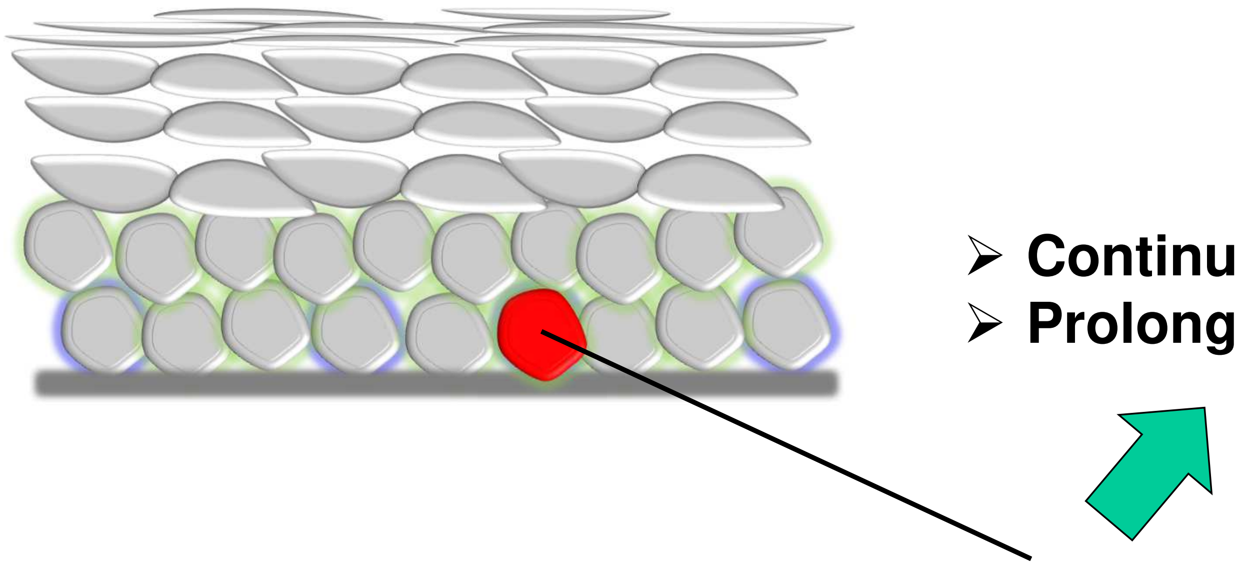
http://www.kumc.edu/instruction/medicine/anatomy/histoweb/skin/skin.htm

Normal tissue organization

Regulated cell proliferation, rapid turnover



Cancer cells are derived from stem-like cancer cells (cancer stem cells)



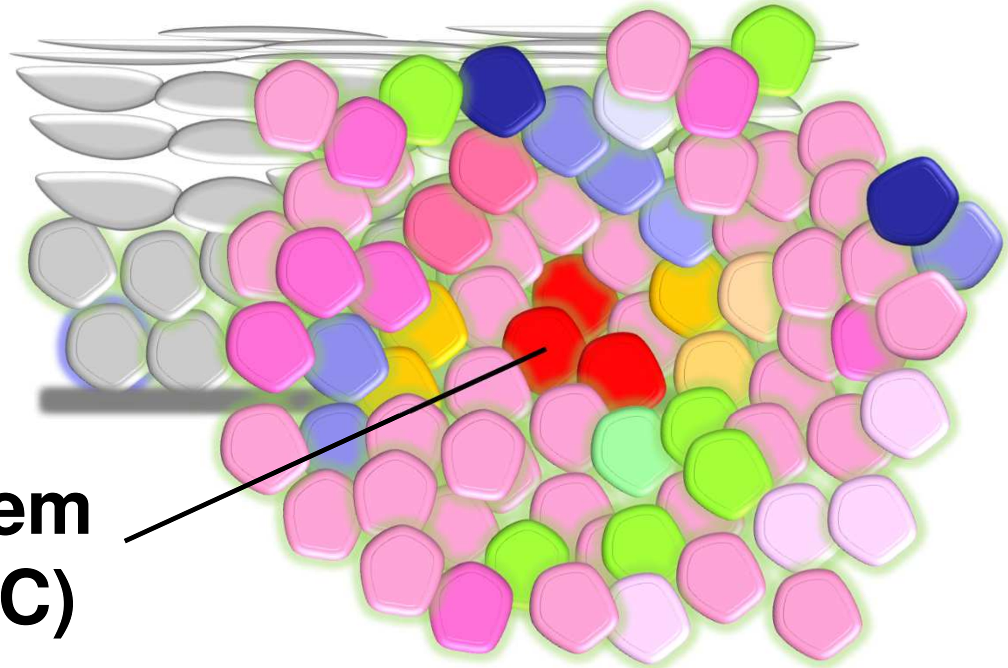
- Continuous growth
- Prolonged survival

Critical mutation(s) in
a stem cell or a progenitor cell

Cancer cells are derived from stem-like cancer cells (cancer stem cells)

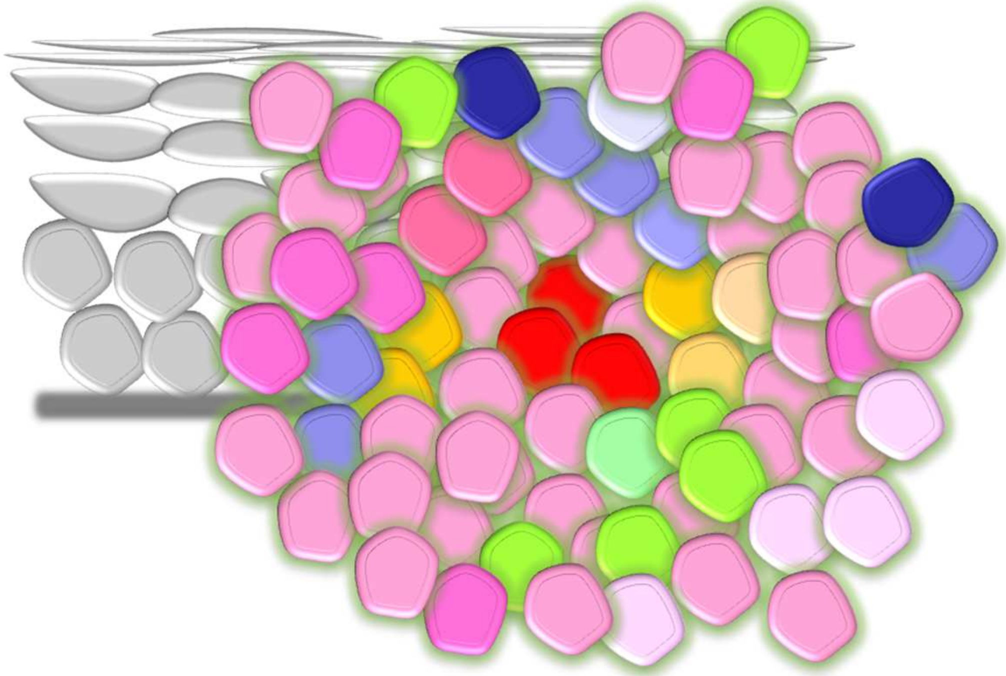
Character of cell is determined by which genes are expressed

The combination of 23,000 gene expressions determines the nature of each cell



Cancer stem cells (CSC)

Cancer cells are derived from stem-like cancer cells (cancer stem cells)



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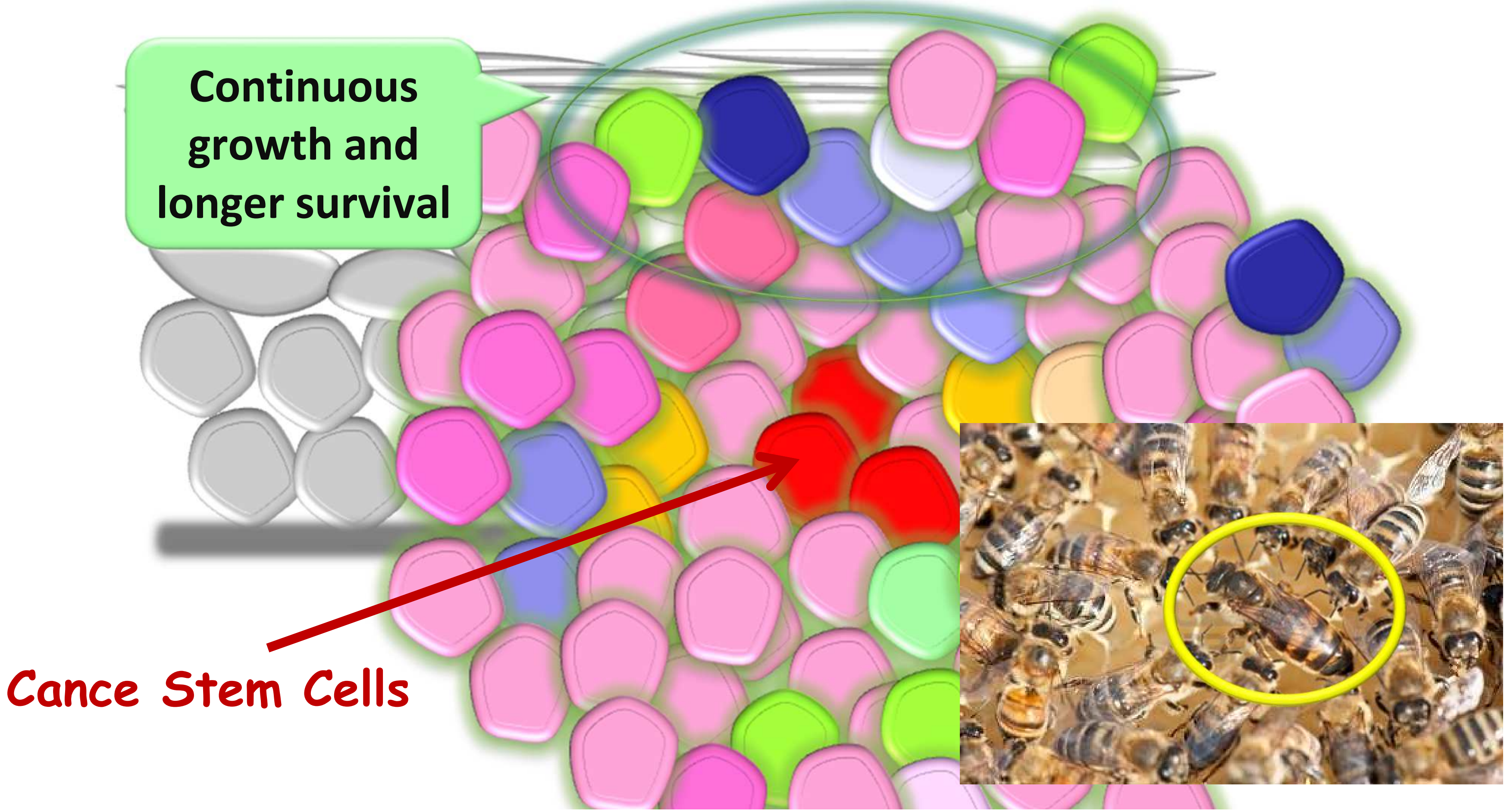


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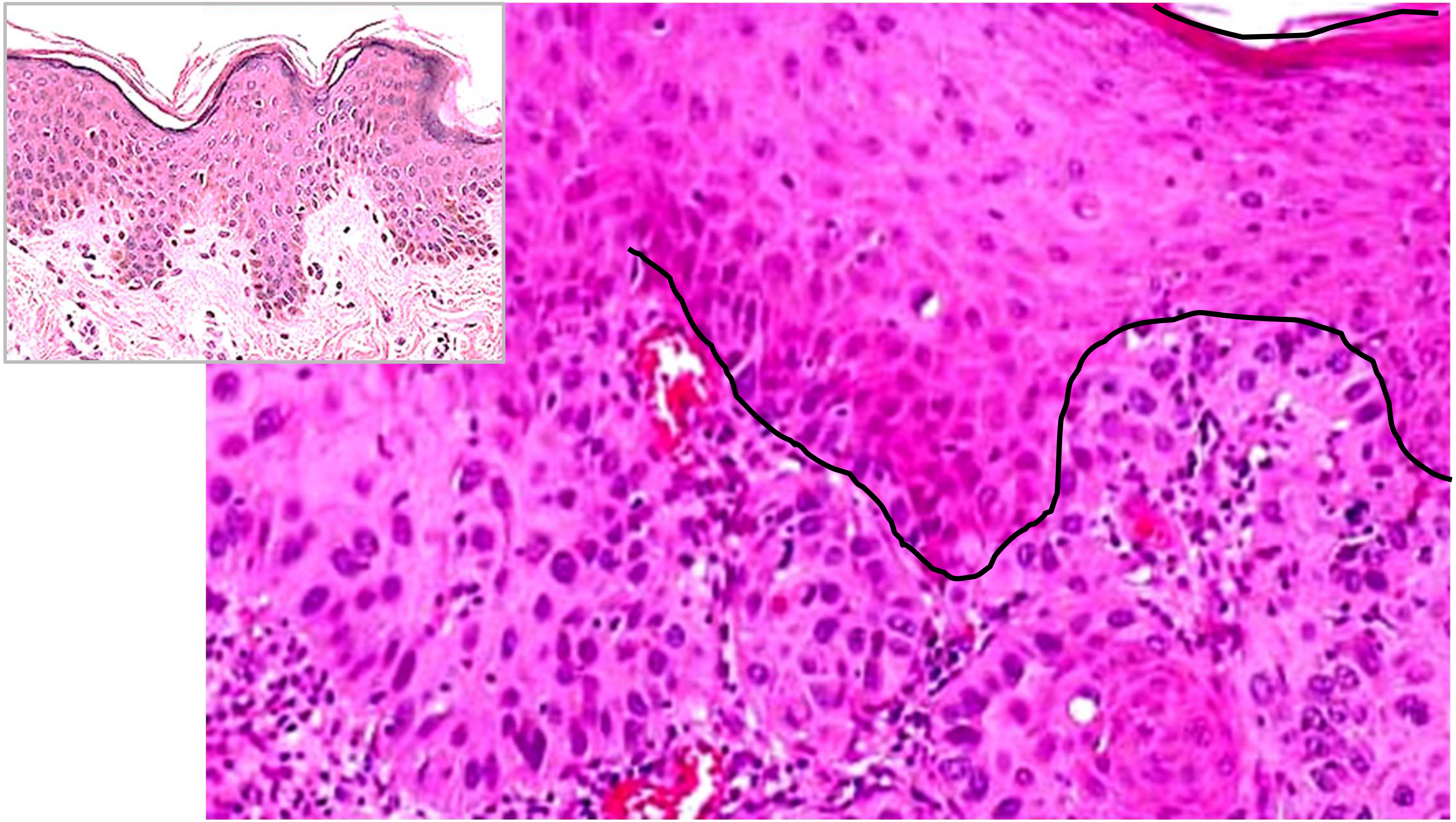
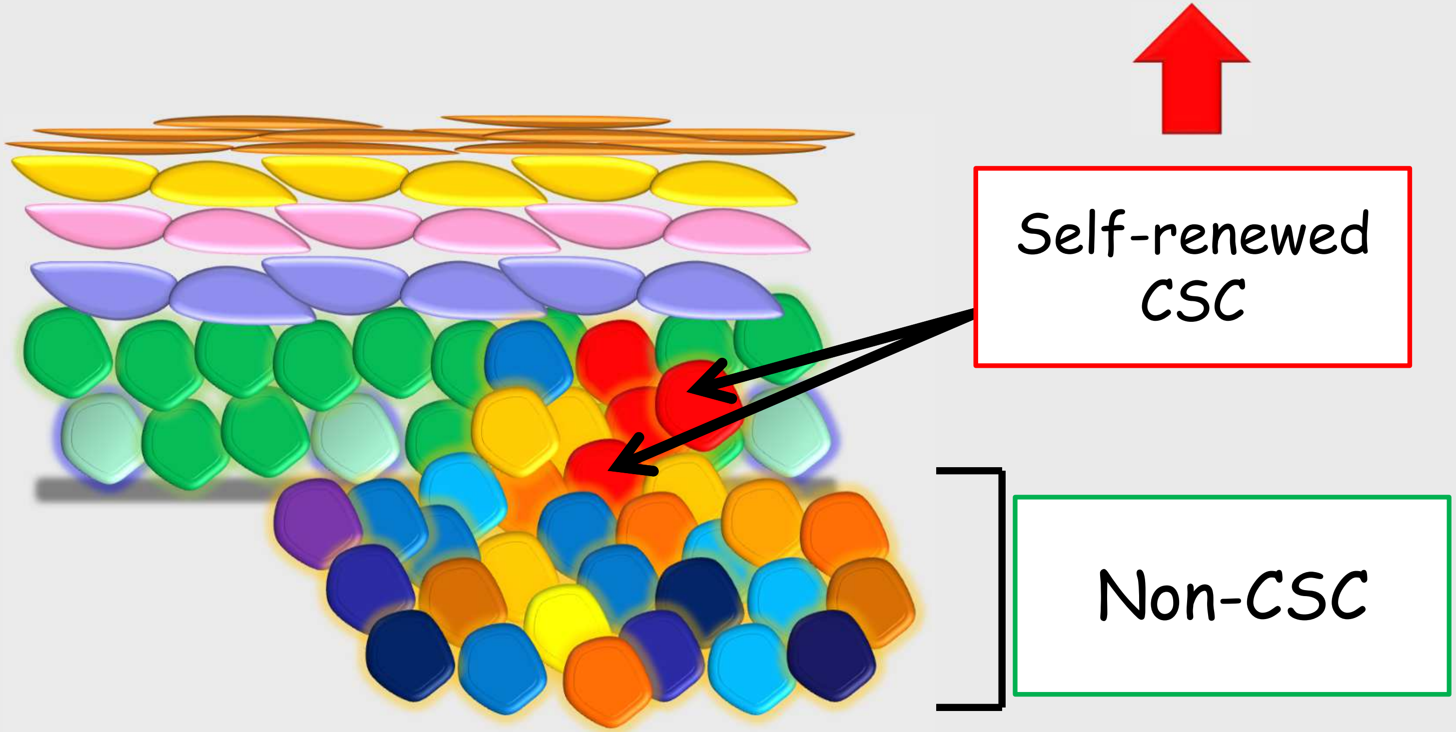
Structure of skin cancer



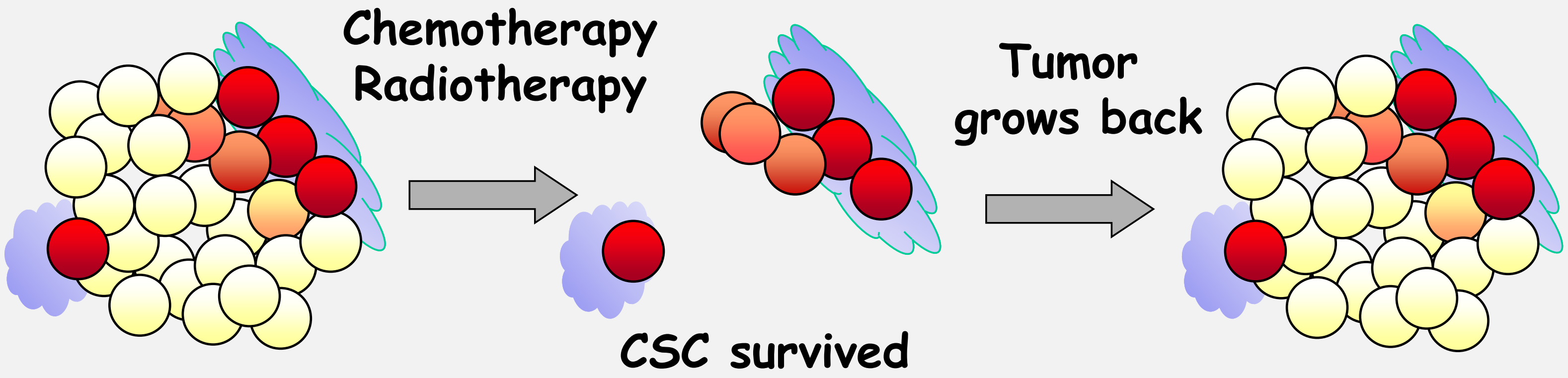
Cancer stem cells (CSCs)

CSC is resistant to conventional therapies

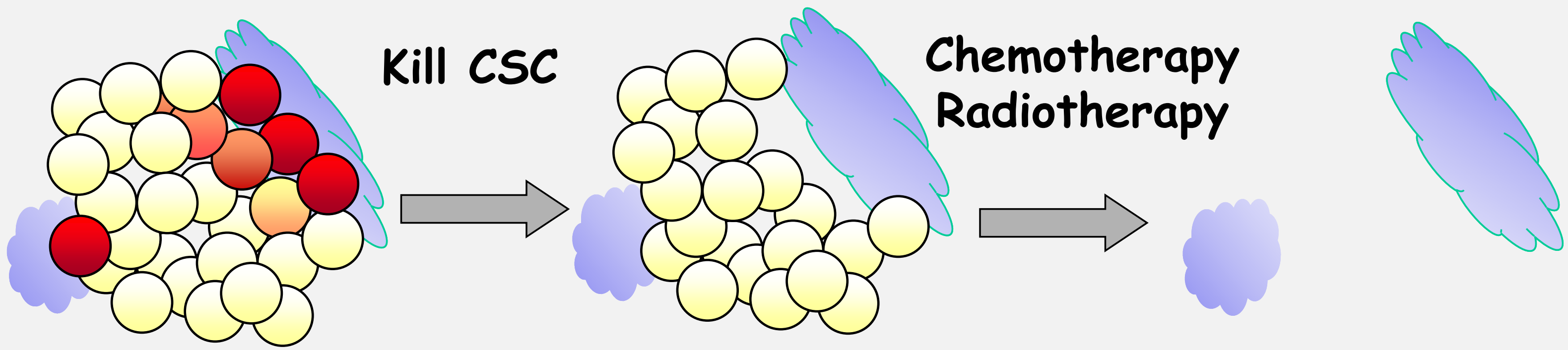


Therapeutic predictions of cancer stem cell model

Conventional cancer therapy



Anti-cancer stem cell therapy



What do we need for cancer eradication?

Targets

(cell, gene, protein mRNA, signal etc)

↔

Modalities

(small molecule, nucleic acid, antibody, peptide etc)

- **Novel therapeutic strategies for elimination of cancer stem cells**
- Detection of cancer stem cells in whole body
- Monitoring the cancer stem cells in patients treated by various therapeutic interventions

Therapeutic resistant mechanisms of cancer stem cells

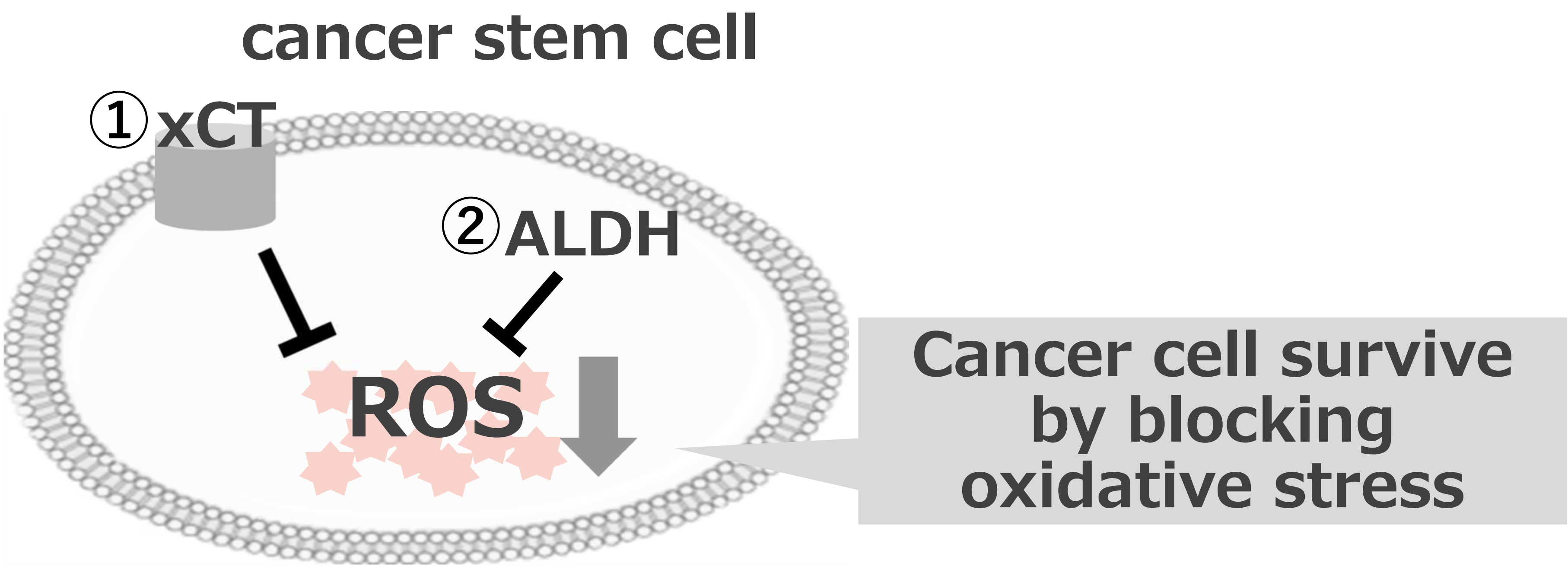
- Resistant cells require **high energy production** (high ATP production) for survival and growth.
- High-energy-producing cells produce large amounts of **reactive oxygen species (ROS).**
- Resistant cells have **anti-oxidant system** for survival.

Blocking the anti-oxidant system may induce cell death in the resistant cells

Ishimoto et al., *Cancer Cell* 2011 Yae et al. *Nat Commun*, 2012

Drugs Induce Ferroptosis in Cancer Stem Cells

Two primary targets:
xCT and **ALDH** both collaborate to block oxidative stress



Okazaki et al., *Oncotarget* 2019
Otsuki et al., *Cancer Sci* 2020

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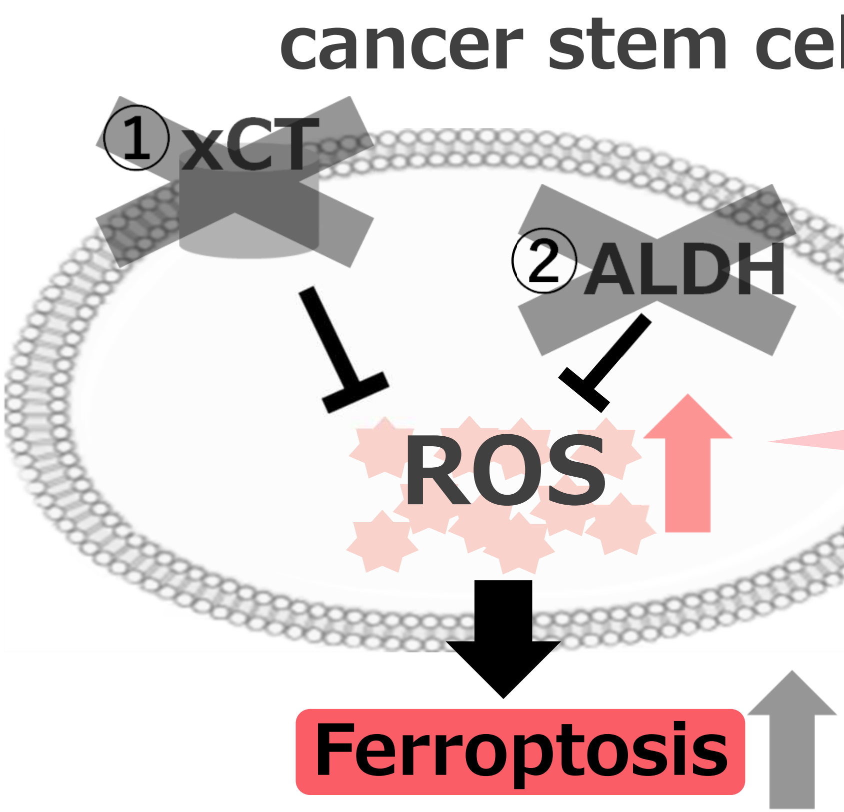

Inhibition of xCT+ALDH induces Ferroptosis

Okazaki et al., *Oncotarget* 2019
Otsuki et al., *Cancer Sci* 2020

Drugs Induce Ferroptosis in Cancer Stem Cells

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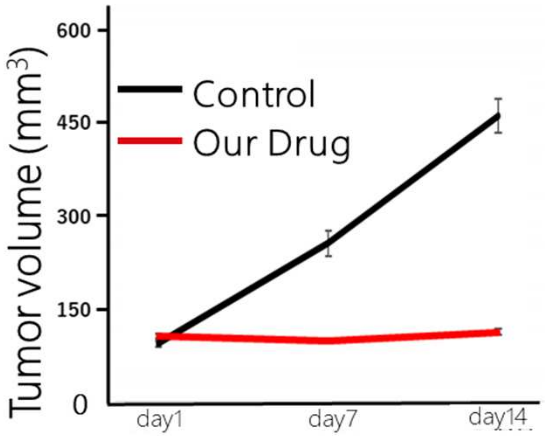
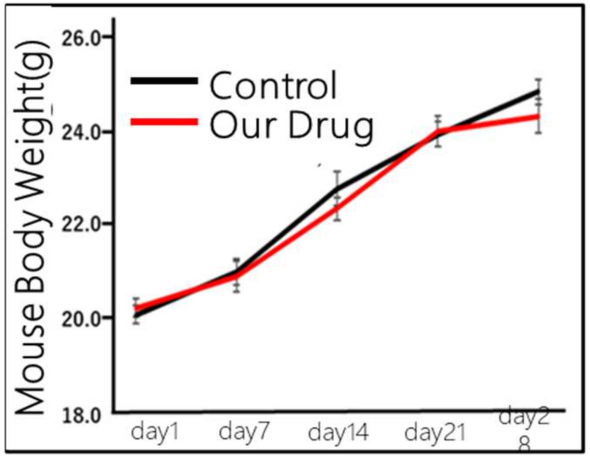
In vivo Mouse Model (HCT116 colon cancer cell line)





➡ Phase I clinical trial in 2024

Otsuki et al., *Cancer Sci* 2020

What do we need for cancer eradication?

Targets

(cell, gene, protein mRNA, signal etc)

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- Novel therapeutic strategies for elimination of cancer stem cells
- **Detection of cancer stem cells in whole body**
- **Monitoring the cancer stem cells in patients treated by various therapeutic interventions**

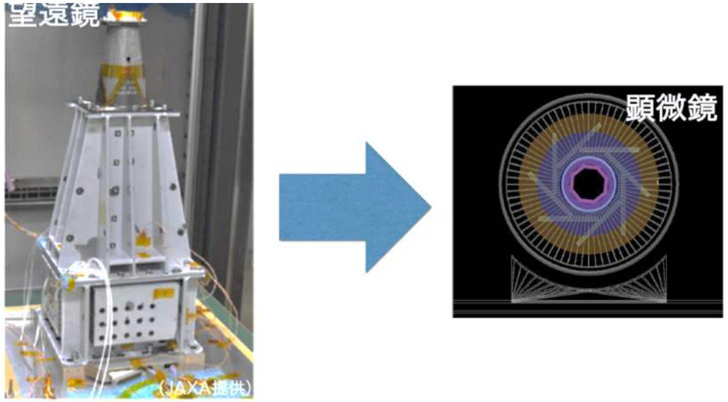
OIST Mini Symposium "New Medical Imaging and Advanced Cancer Therapy (BNCT) Instrumentation" **May 14-16, 2015**

Organizer: Hirotaka Sugawara, Advanced Medical Instrumentation Unit, OIST

Kavli IPMU-JAXA-Keio collaboration project

Whole body imaging of cancer stem cells and therapeutic resistant cells by applying the technologies of particle physics and space science

Technologies for space telescope are applied to microscope

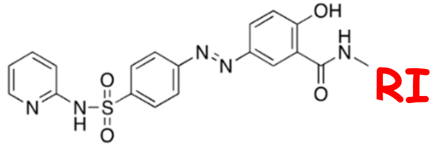


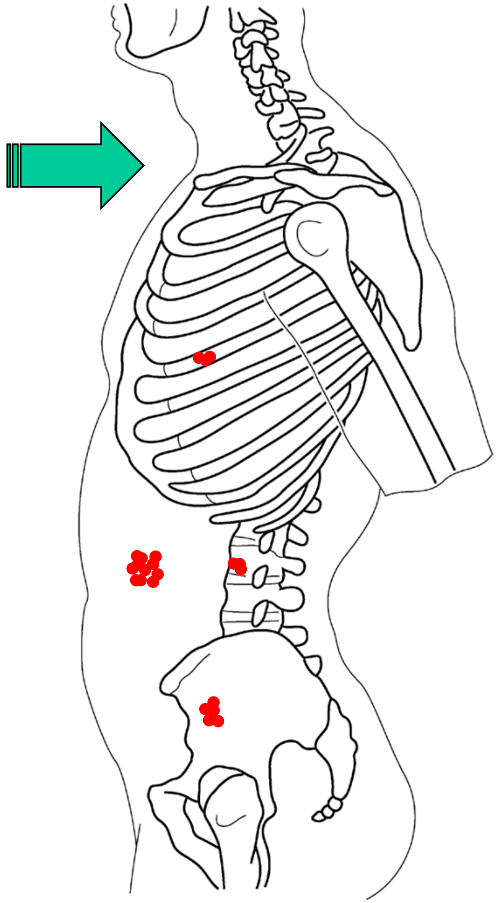
March 26, 2018

Application of the most advanced space exploration sensors to medicine

Space exploration sensors may allow the detection of RI-labeled compounds incorporated in cancer stem cells.

xCT inhibitor





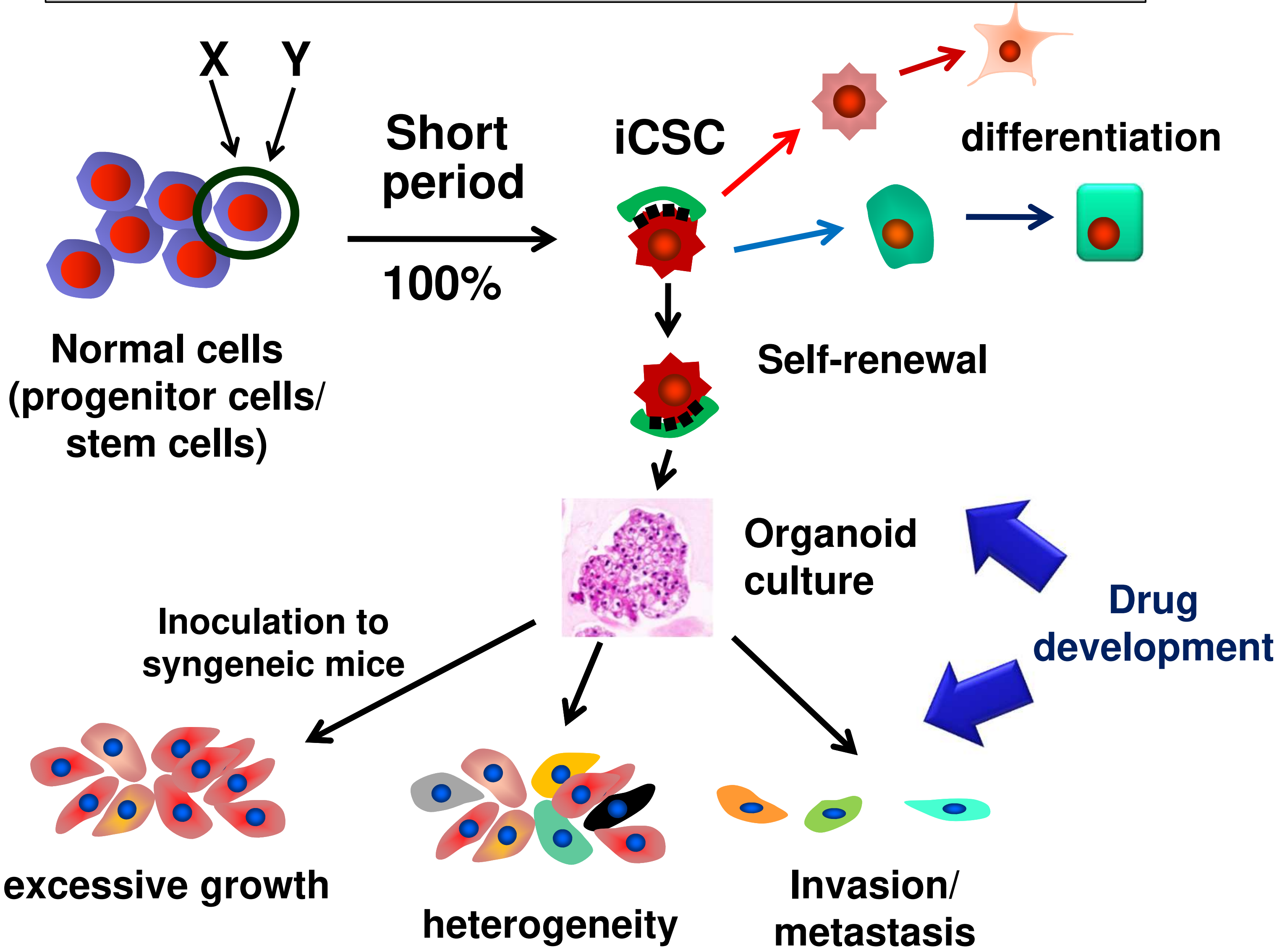
Theranostics = Therpeutic +Diagnostic

(Alphatherapy, BNCT etc.)

^{225}Ac ^{211}At

Animal models which pathologically and clinically recapitulate human cancers

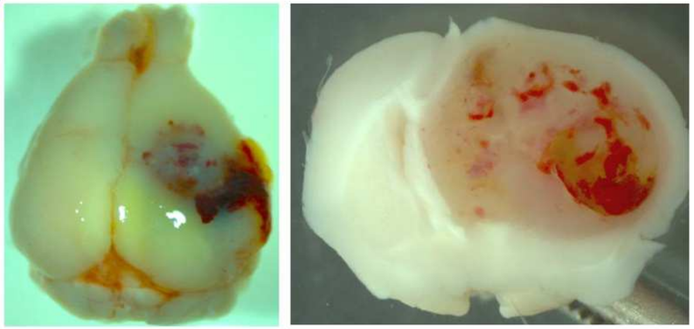
Induced cancer stem cell : iCSC



Mouse cancer models established by using iCSC

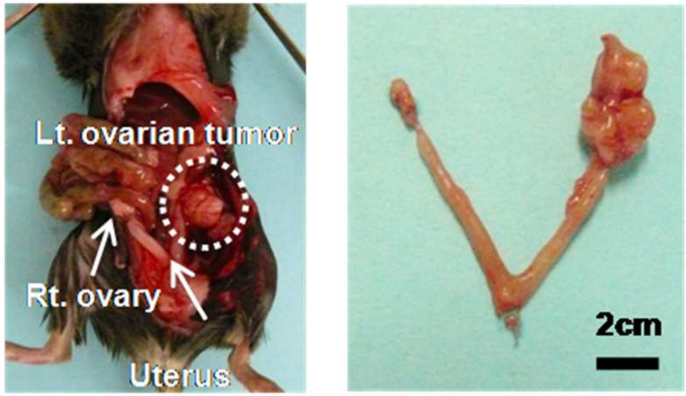
tumor	cells-of-origin	transgenes	pathology	references
lymphoma	HSCs/progenitors	• N-myc • c-myc	• Pre-B LBL • Mature B-cell lymphoma	Oncogene (2011) Blood (2017) Cancer Res (2020)
osteosarcoma	INK4a/Arf KO BMSCs	• c-myc	• Osteosarcoma	JEM (2009) Oncogene (2010) Cancer Res (2019)
brain tumors	INK4a/Arf KO neural stem cells	• RasV12 • c-myc	• Glioblastoma • PNET	Neoplasia (2011) Stem Cells (2013) Neuro-Oncol (2014) Neuro-Oncol (2017) Nat Cell Biol (2019) Commun Biol (2020) JCI (2021)
breast cancer	INK4a/Arf KO mammary stem cells	• RasV12	• Basal type	Oncogene (2013)
ovarian cancer	Normal ovarian Premature epithelial cells	• p53siRNA +RasV12 +c-myc	• Serous adenocarcinoma	Carcinogenesis (2011)
lung cancer	INK4a/Arf KO EpCAM-positive lung cells	• KRasV12 • ELM4-ALK	• Adenocarcinoma • Adenocarcinoma	Cancers (2021)
cholangio-carcinoma	INK4a/Arf KO EpCAM-positive bile duct cells	• KRasV12	• Adenocarcinoma	Cancer Sci (2021)

iCSC-based mouse tumor models



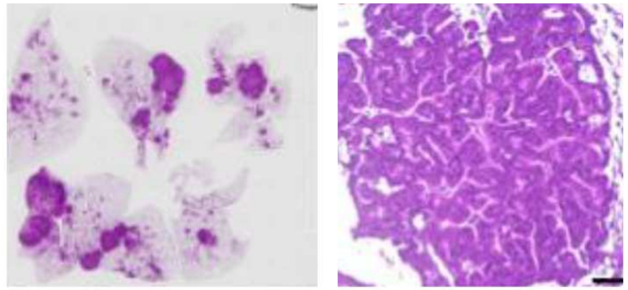
Glioblastoma multiforme

Sampetrean *et al., Neoplasia* (2011)



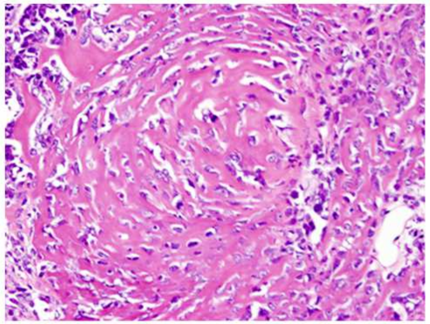
Ovarian serous adenocarcinoma

Motohara *et al., Carcinogenesis* (2011)



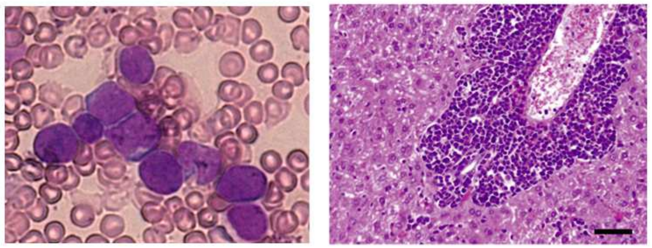
Lung adenocarcinoma

Semba et al., Cancers (2021)



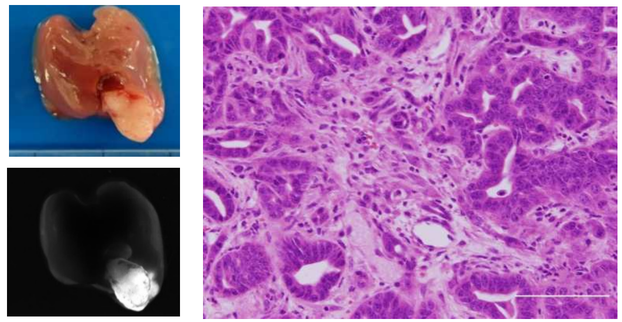
Osteosarcoma

Shimizu *et al., Oncogene* (2010)



Pre-B lymphoblastic leukemia

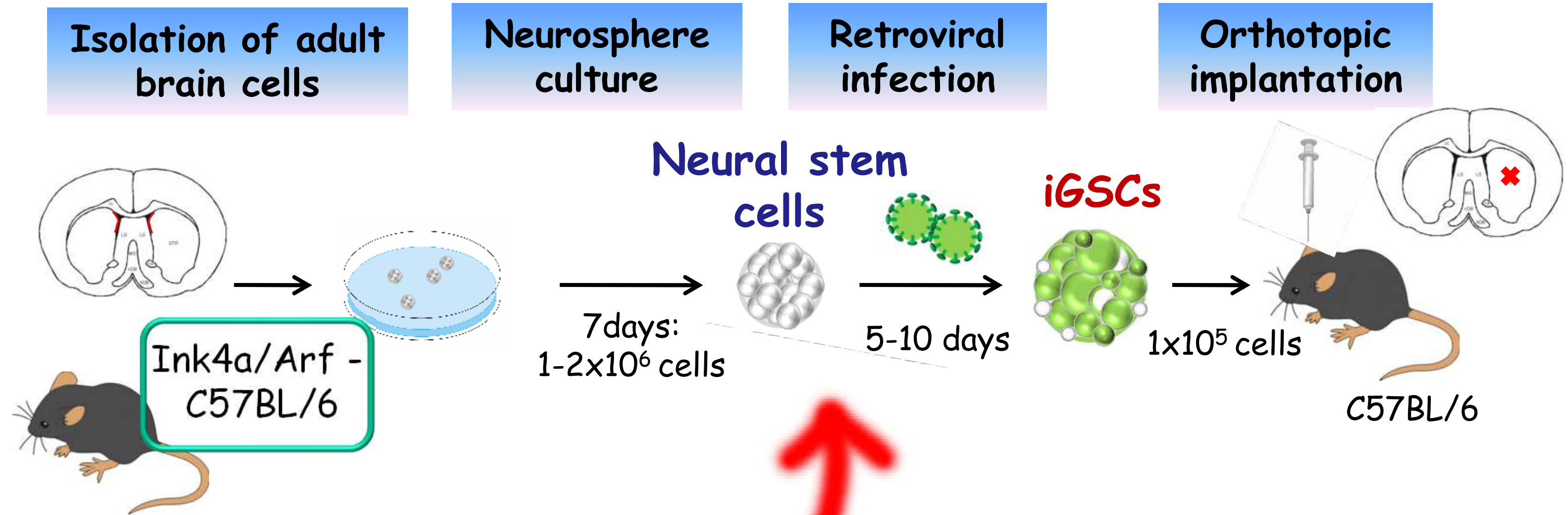
Sugihara *et al., Oncogene* (2011)



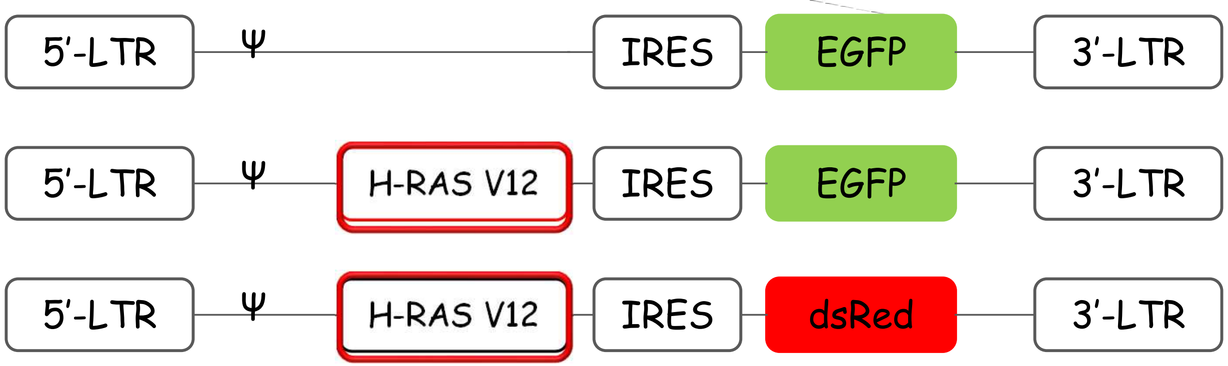
Cholangiocarcinoma

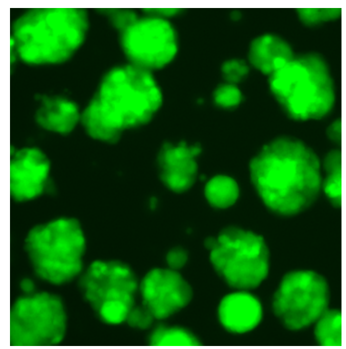
Kasuga et al., Cancer Sci (2021)

Genetically engineered glioma model



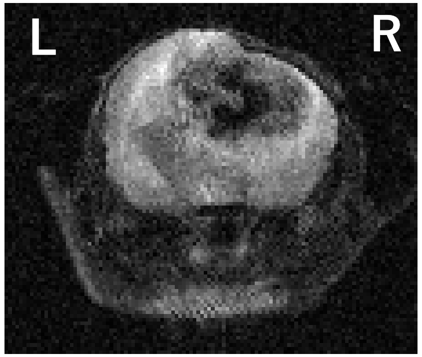
Retroviral constructs





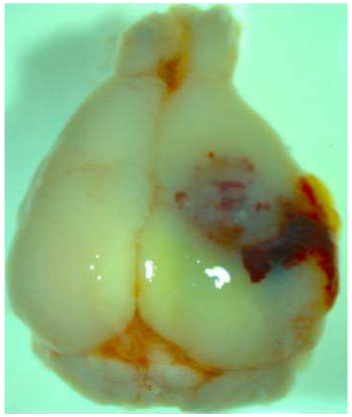
Sampetrean et.al., *Neoplasia* 2011

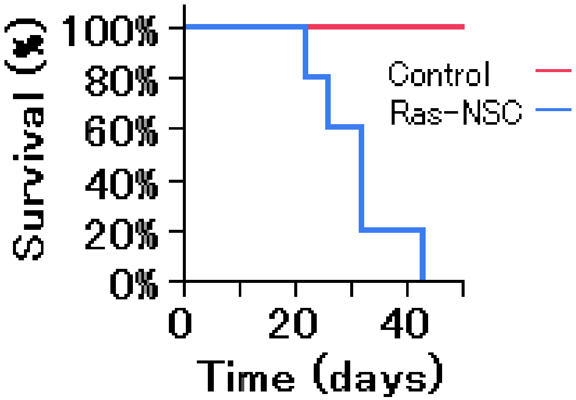
Glioma stem cell (GSC)-based brain tumor model

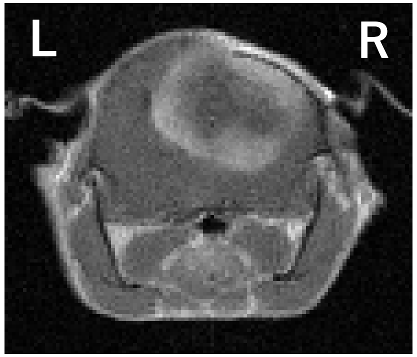


T2WI

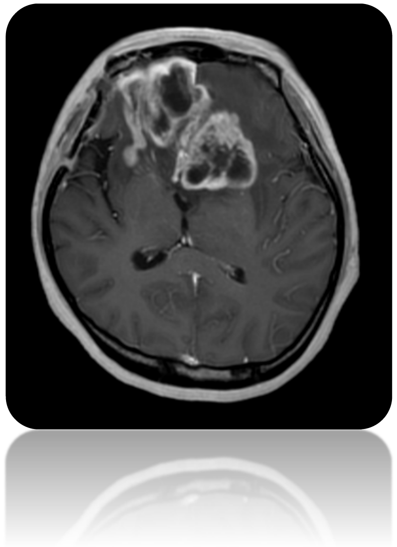
Human glioblastoma







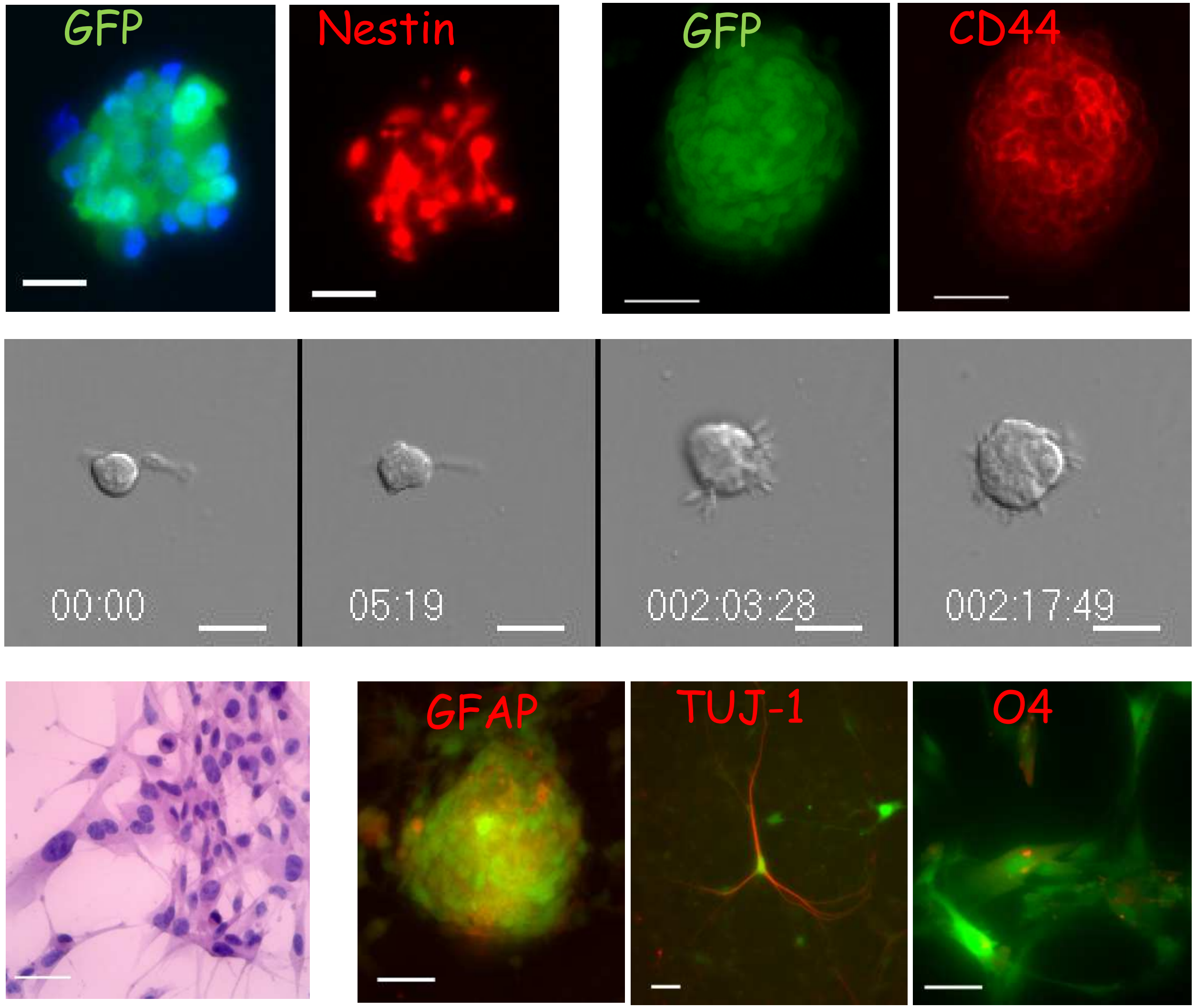
T1WIGd



100% penetrance, 5-week median survival

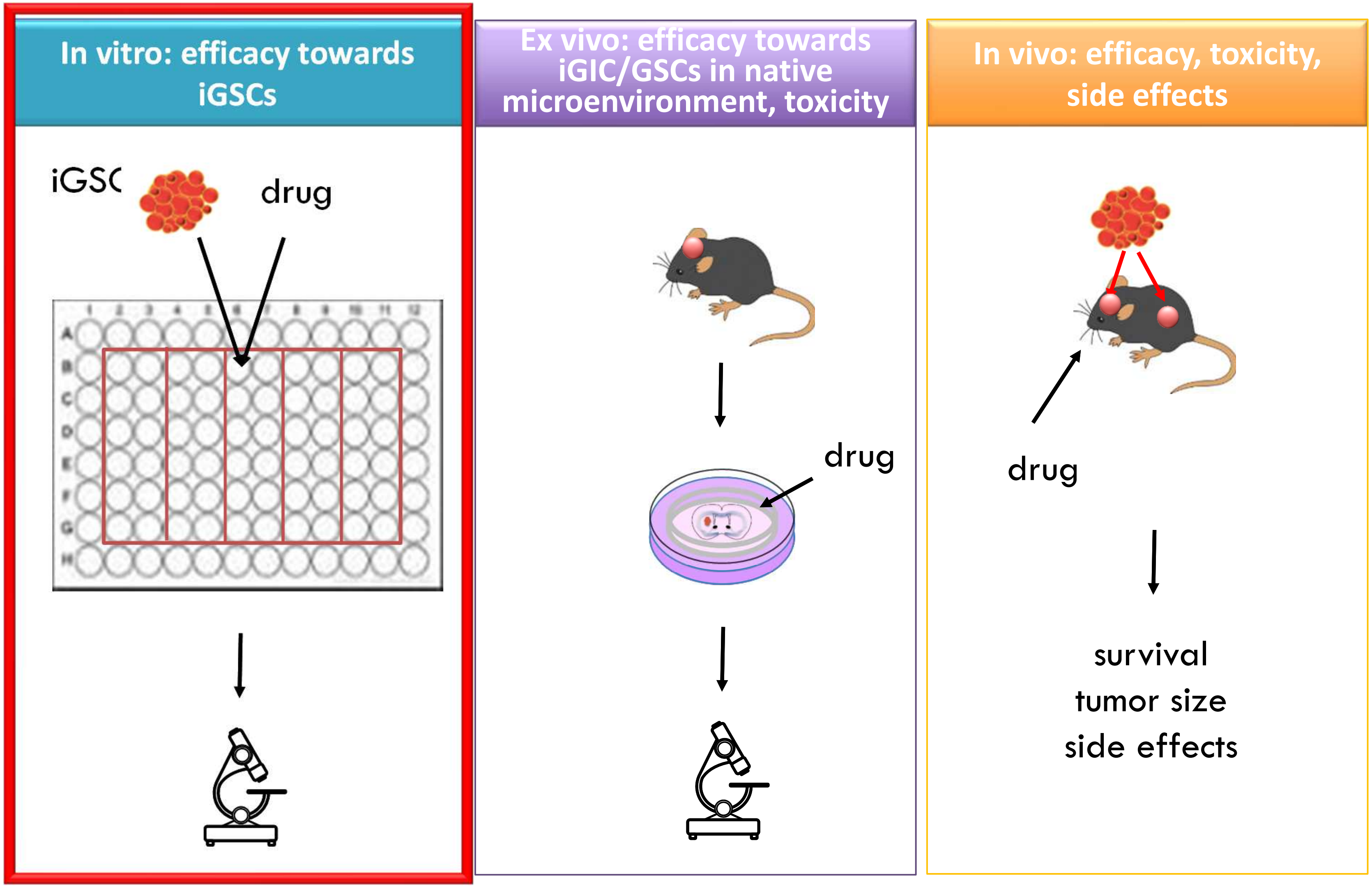
Sampetrean et.al., Neoplasia 2011

Self-renewal and differentiation abilities of GSCs

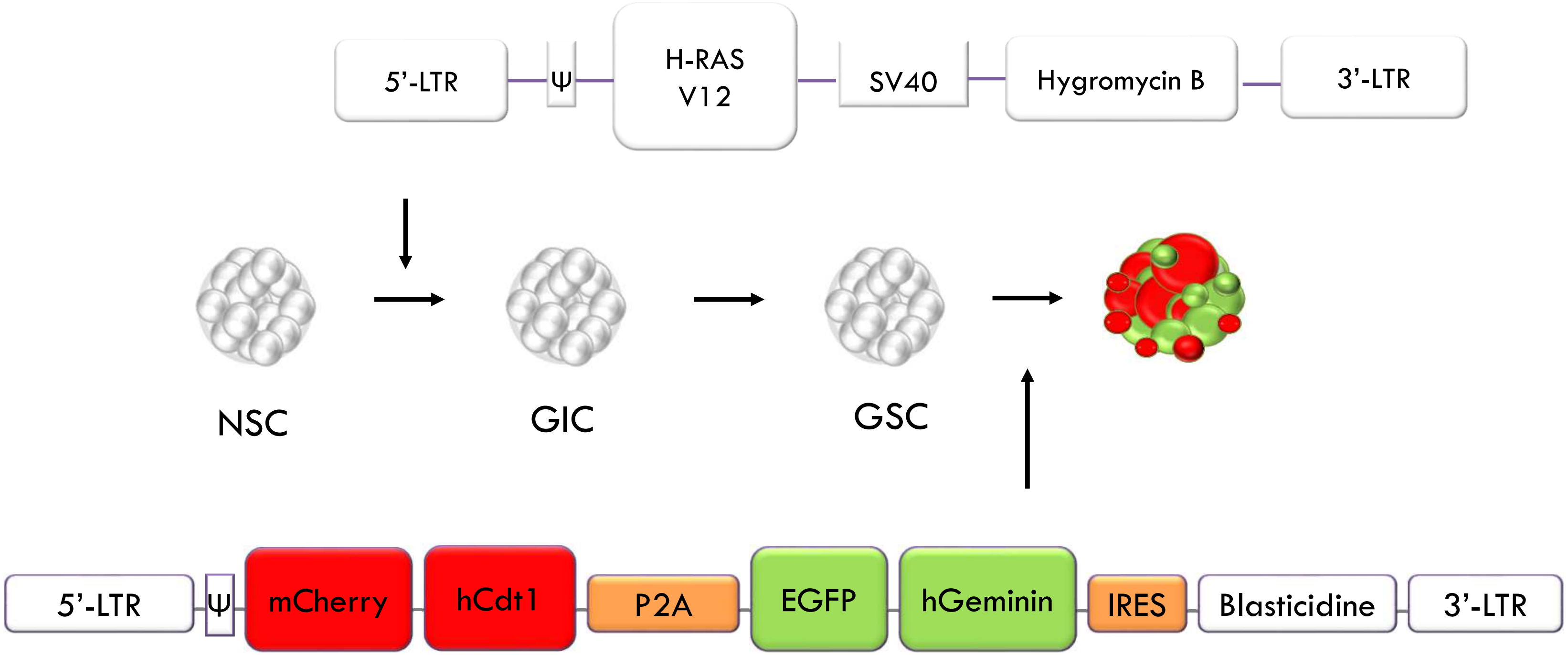


Sampetrean et.al., Neoplasia 2011

In vitro/ex vivo/in vivo evaluation



Cell cycle visualization

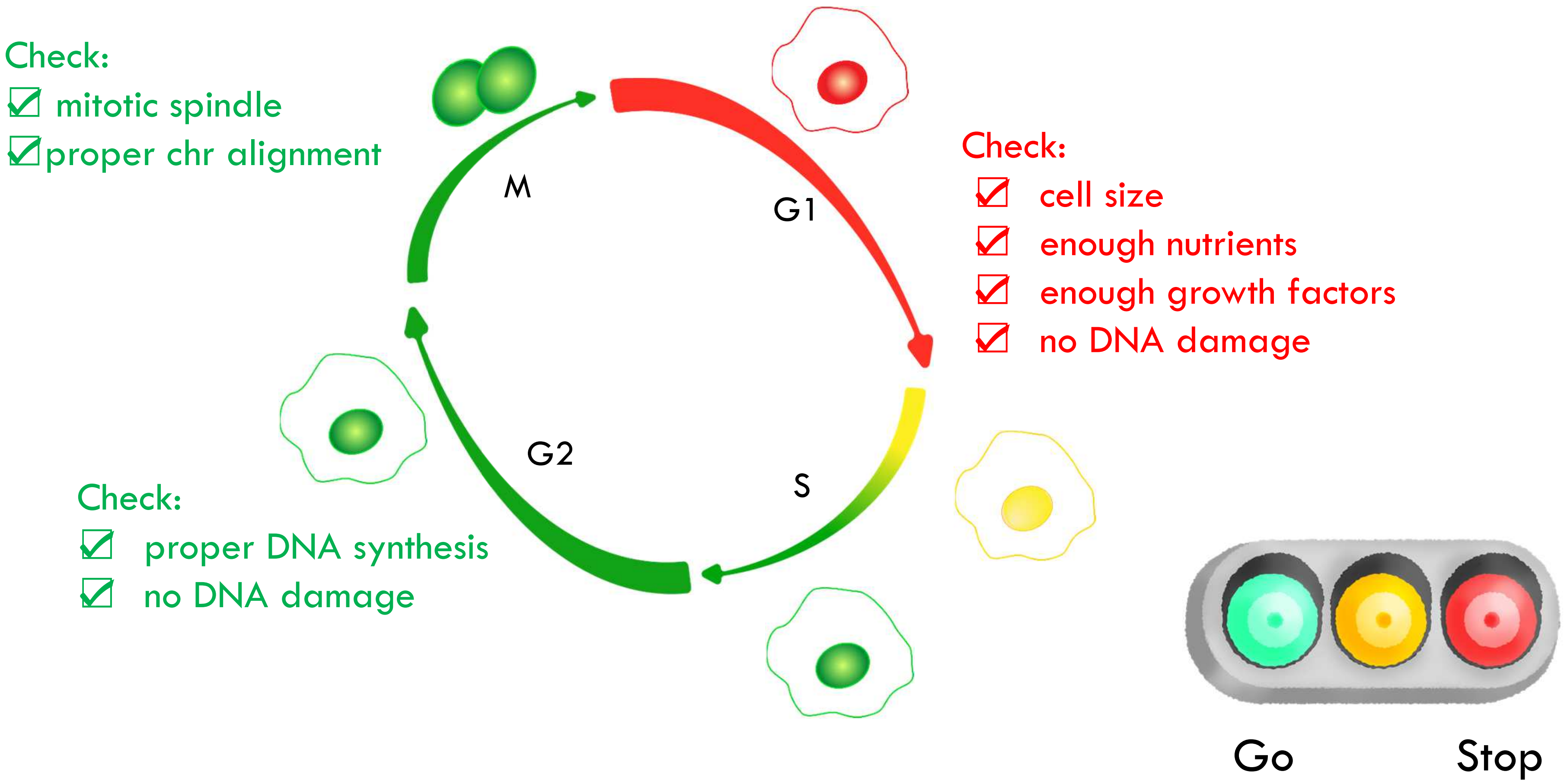


"FUCCI": fluorescent ubiquitination-based cell cycle indicator

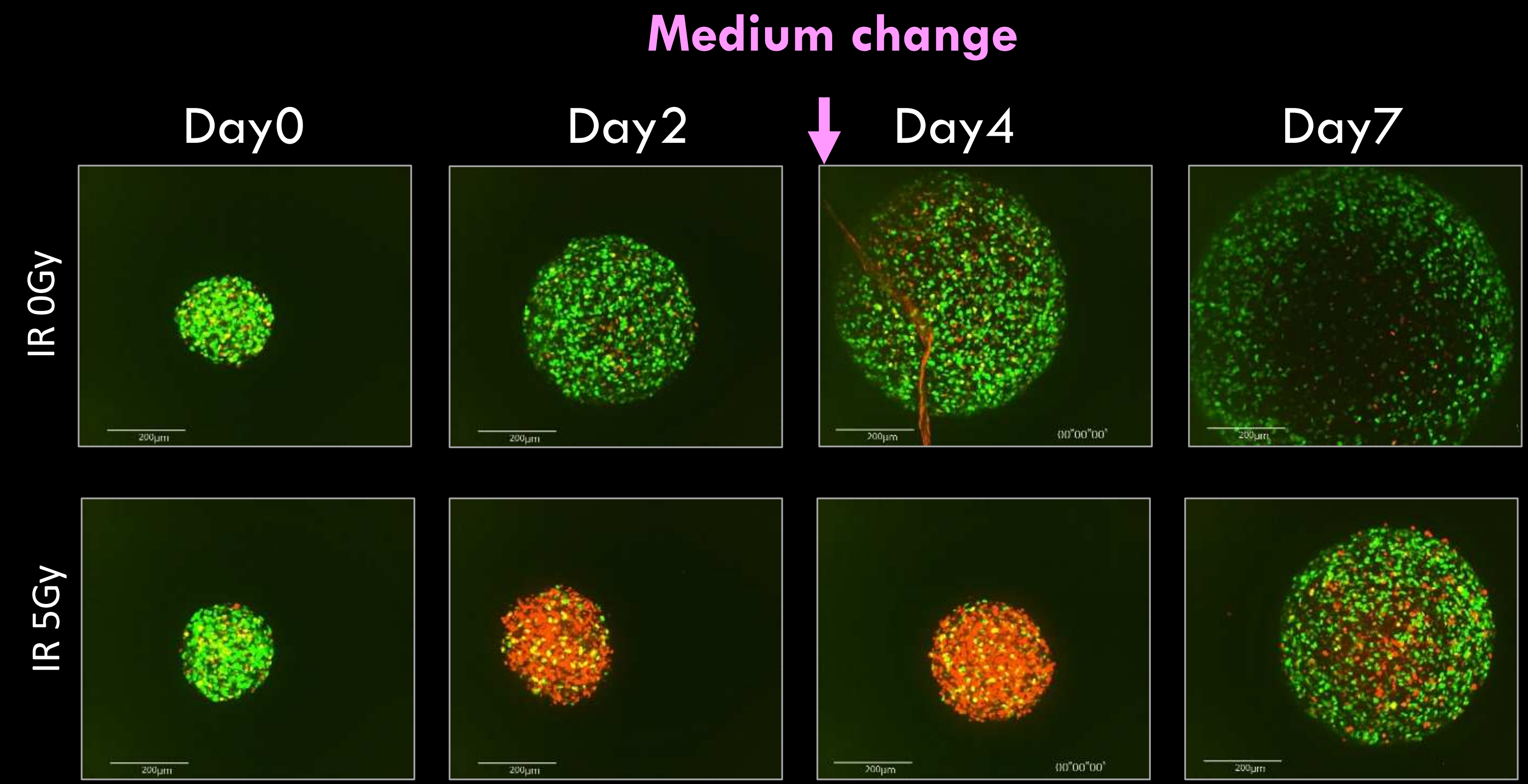
A genetic marker for visualization of cell cycle

Sakaue-Sawano, Cell, 2008
RL Mort, Cell Cycle , 2014

Cell cycle visualization

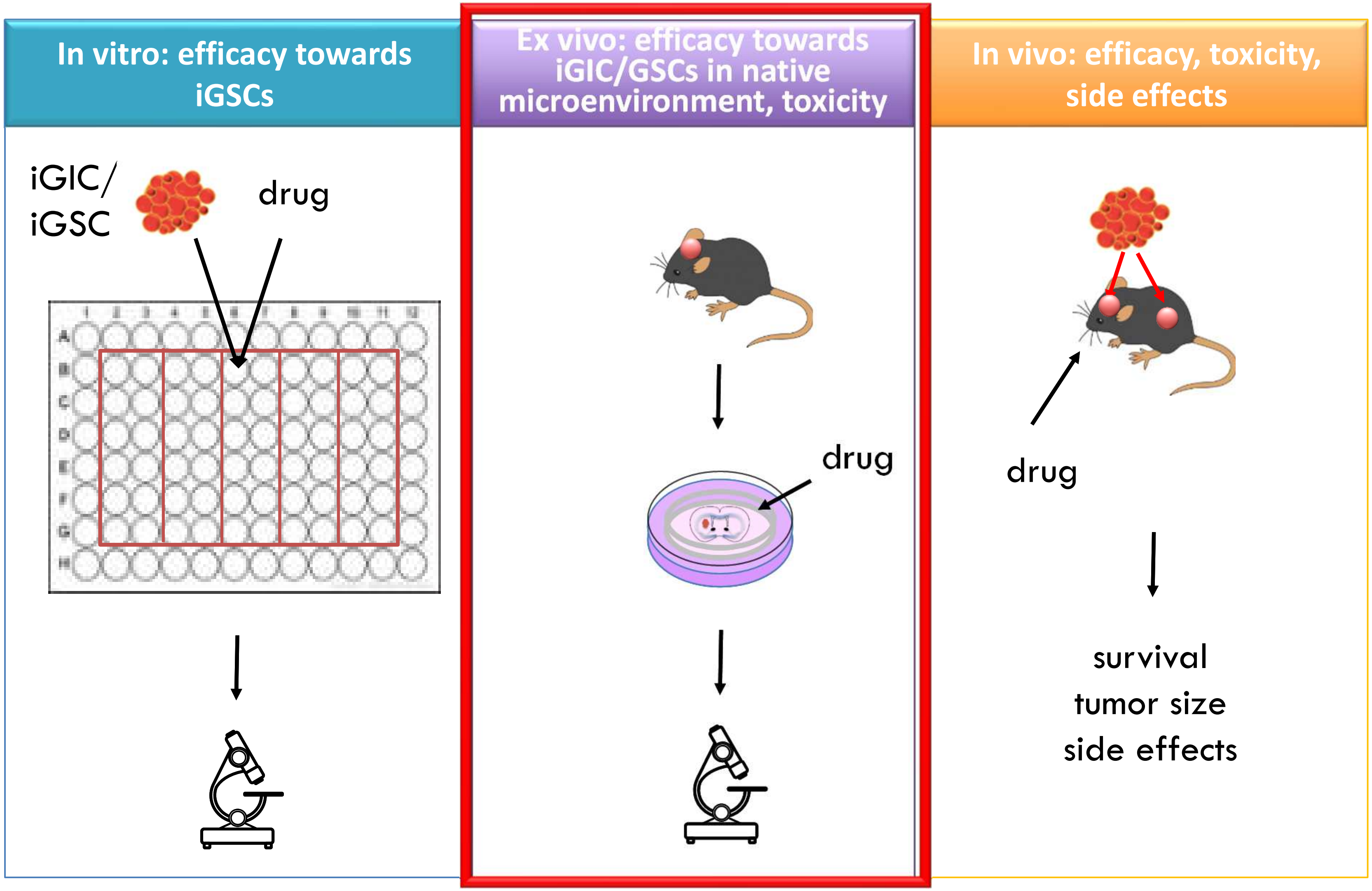


Radiation-induced changes in the cell cycle
- GSCs -

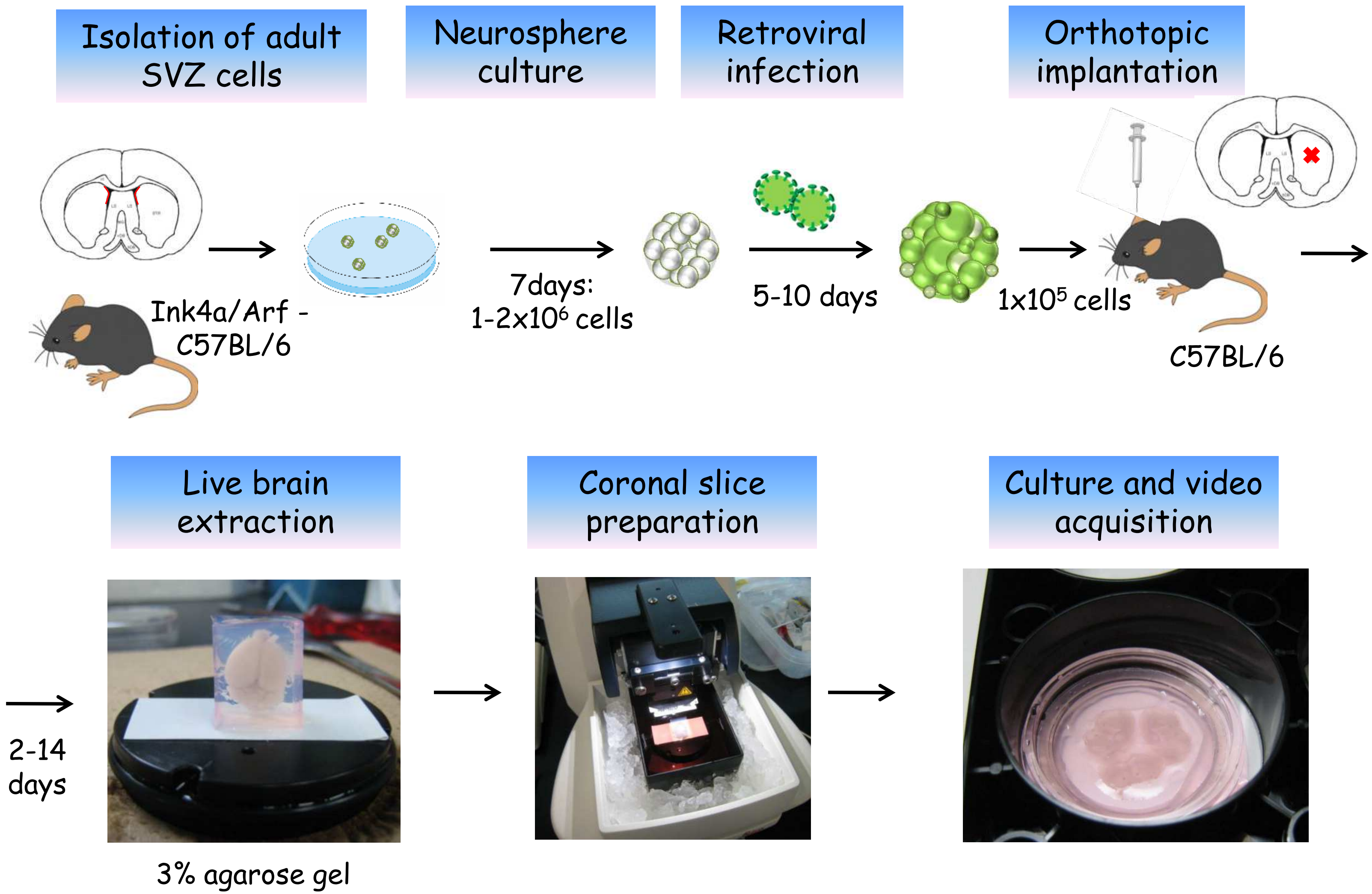


Regrowth after 5Gy seen after day 4, in a nutrient/oxygen-dependent manner.

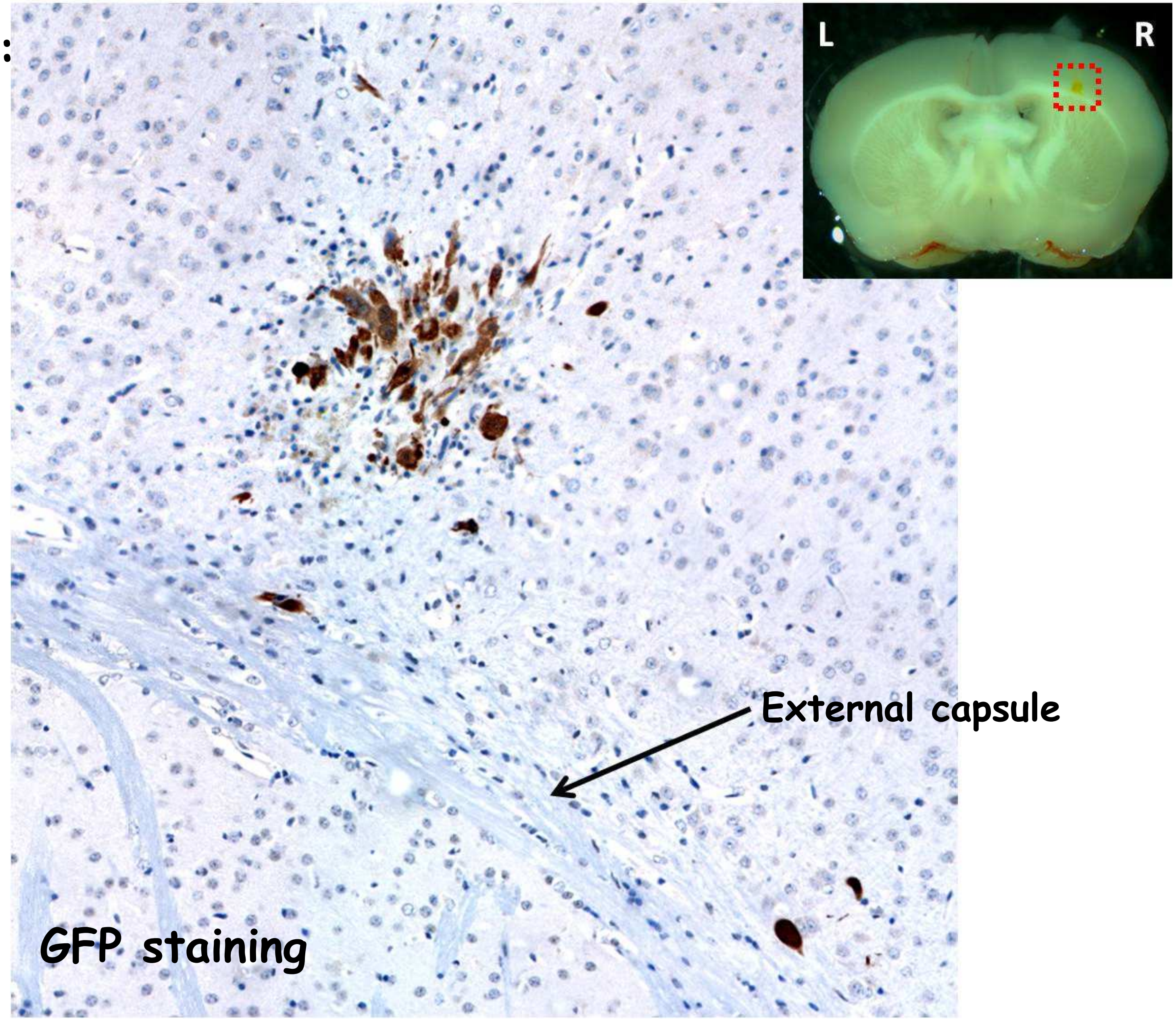
In vitro/ex vivo/in vivo evaluation



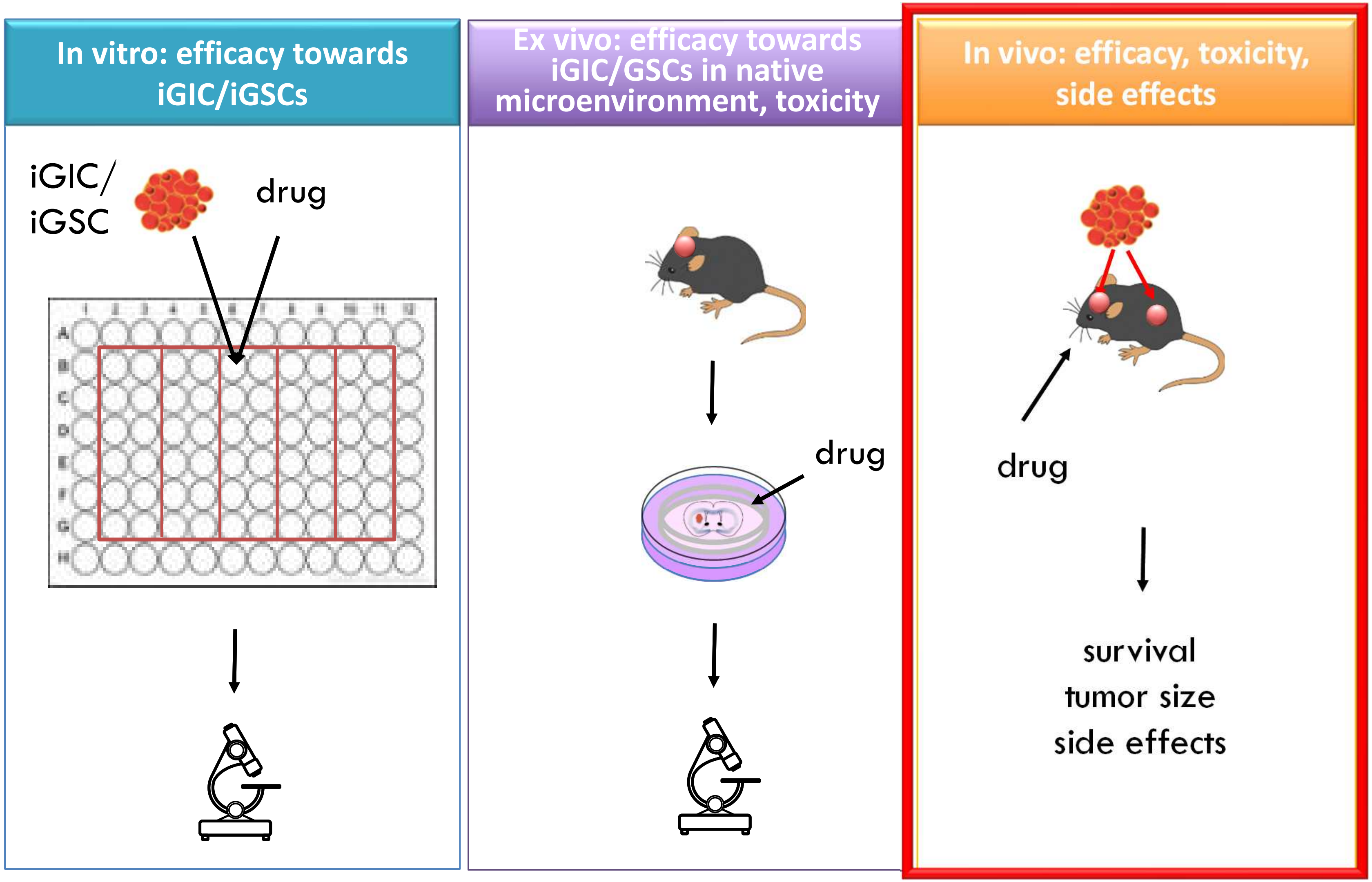
Brain slice culture for visualizing iCSC in brain



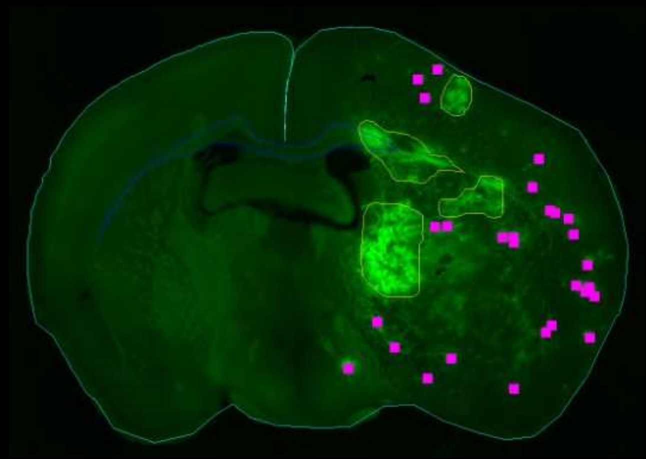
Week 1:



In vitro/ex vivo/in vivo evaluation



High invasion ability of glioma iCSC



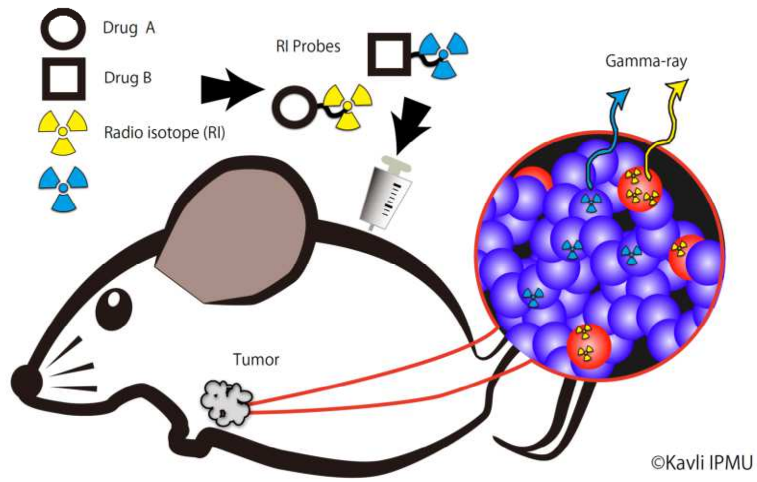
However, there is no way to detect a specific cancer cell population from outside the body without invasive procedures.

PET can detect approximately 1cm tumor which contains 10^9 cells.

Activities at Kavli IPMU

Interdisciplinary approach of applying cutting-edge technologies at the frontier of cancer research

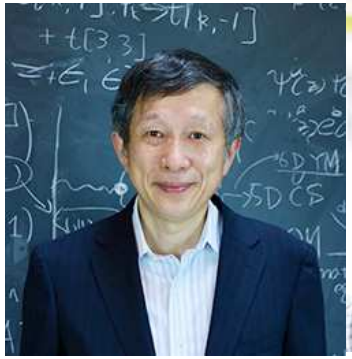
- Development of advanced gamma-ray imagers for Imaging of intratumoral heterogeneity with ultra-high spatial resolution (~100 μm)
- Studies of image-reconstruction algorithm (3D, Inverse Problem, Statistical Analysis of Big Data, Deep Learning)



Activities include studies of RI-labeled Molecules and Drug Delivery System

- Designing and structural formula of chemical compounds for use in biological experiments
- Synthesizing radioisotope-labeled drugs
- Biological analyses using cells and small animals with Keio U., National Cancer C.

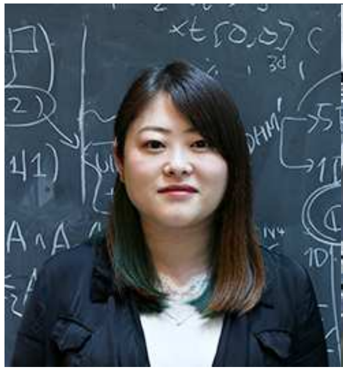
Team Takahashi in Kavli IPMU



Takahashi

Takeda

Yagishita



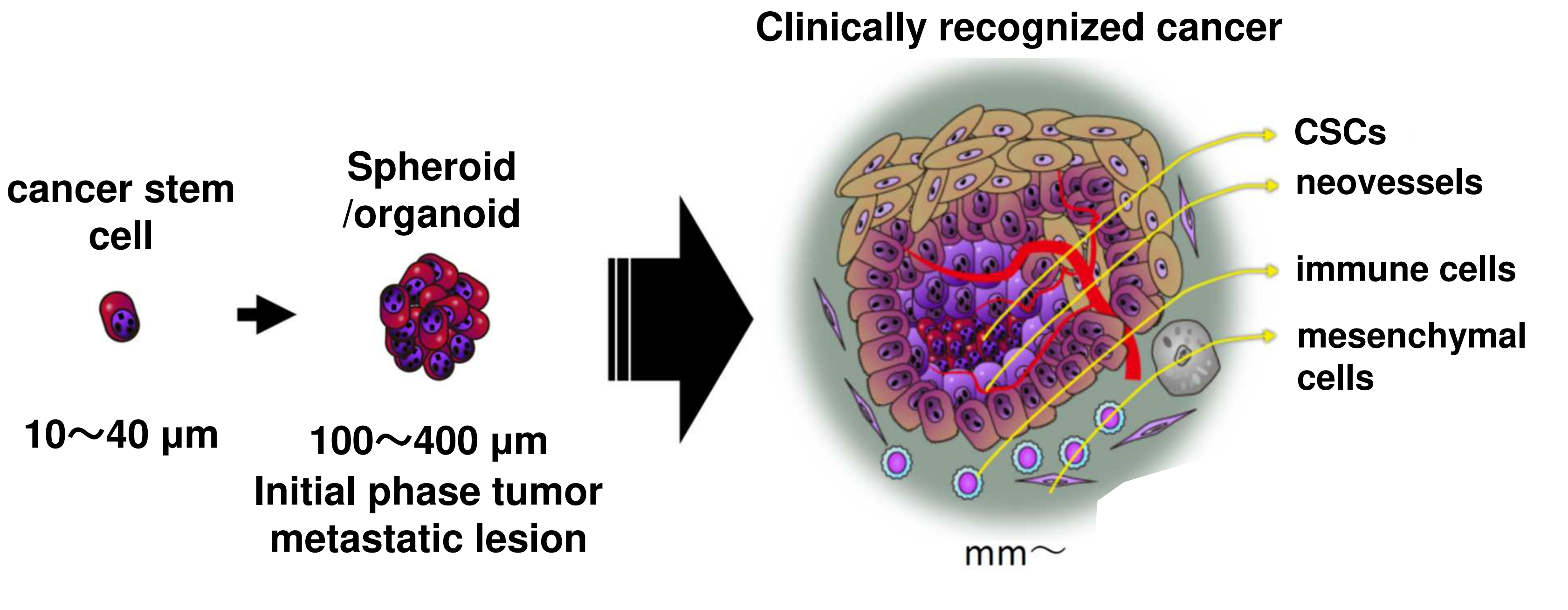
Katsuragawa

Orita

Umeda

Sampetrean

Imaging of cancer stem cells

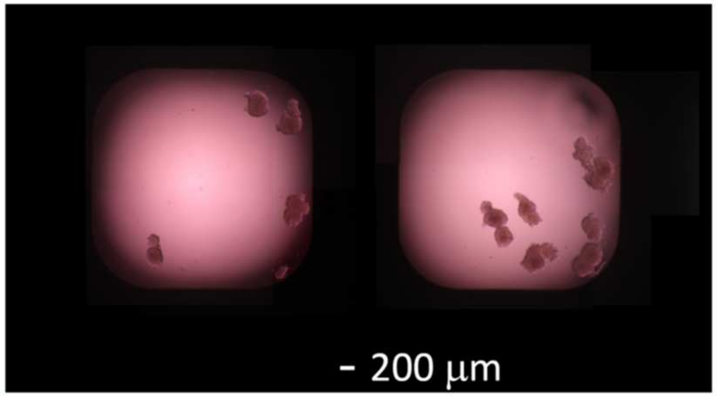


Separation of cancer stem cells from other cells requires high spatial resolution and multi-probe detection

SPECT imaging of cancer stem cell organoid

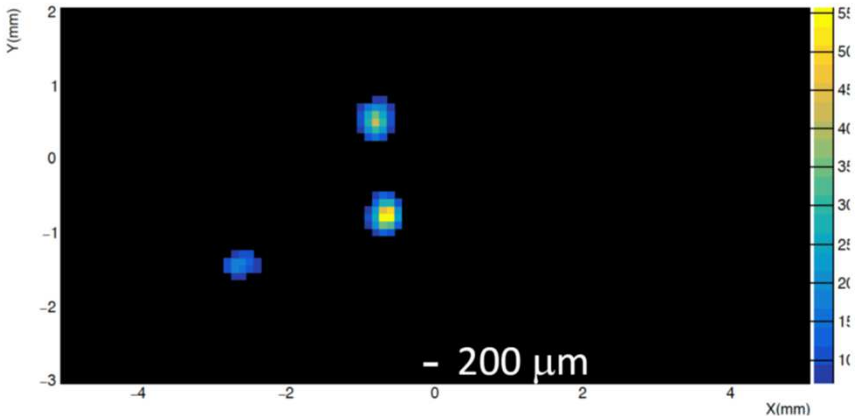
Organoids of NIS (natrium iodide symporter) expressing CSCs which can incorporate ^{125}I

Bright field.



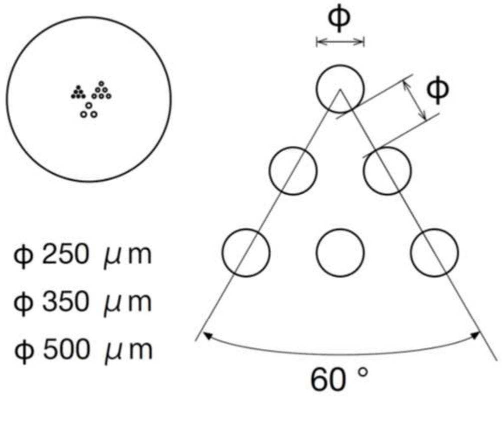
control NIS inhibitor

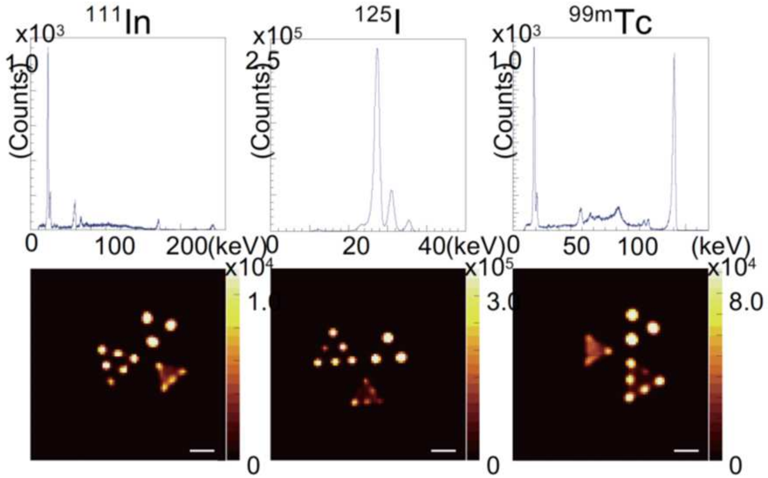
SPECT



control NIS inhibitor

multi-nuclide in vivo imaging



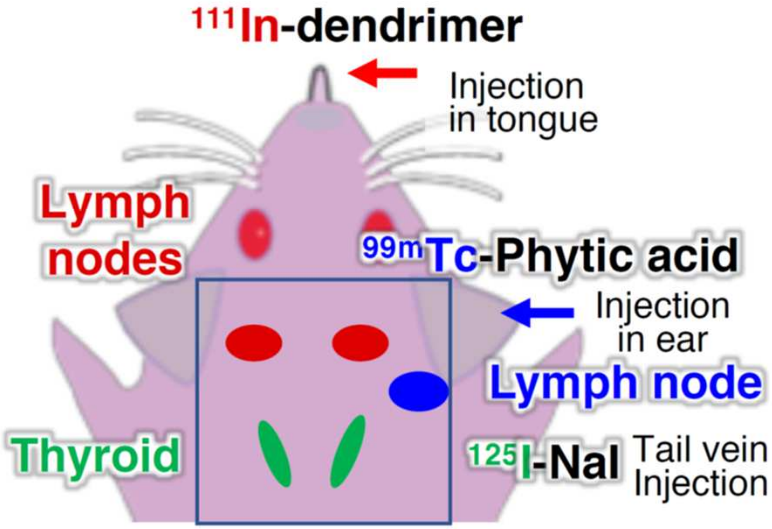


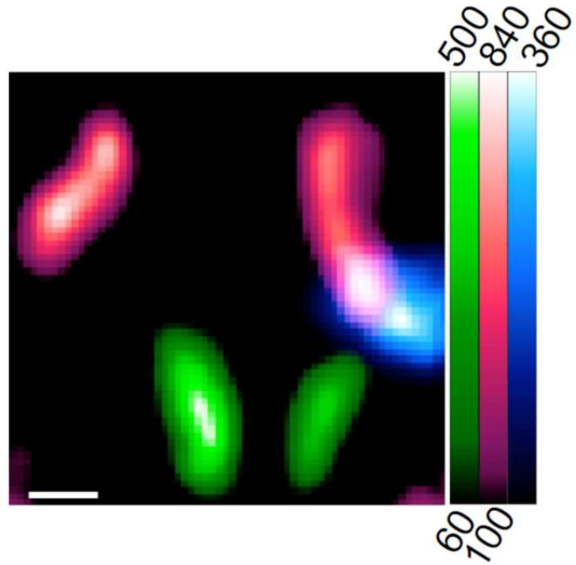
Spatial resolution

^{111}In (20-25 keV): ～250 μm

^{125}I (25-29 keV): ～250 μm

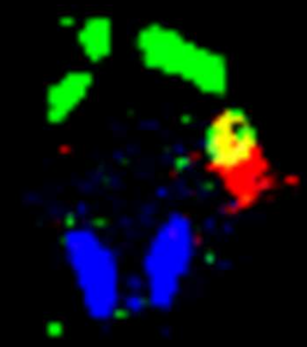
^{99m}Tc (135-143 keV): ～350 μm

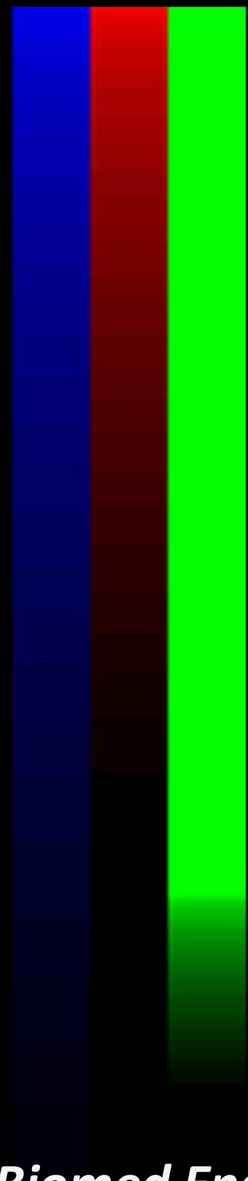




Yagishita, Takeda et al., *Nat Biomed Eng* 2022

multi-nuclide in vivo imaging





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Conclusions

- **Collaborative research to detect heterogeneous cell groups in tumor tissue with 3D and multi-probe using state-of-the-art space observation sensor technology has started.**
- **We intend to build a system that can detect cancer cells with different properties in the living body at the single cell level and rapidly evaluate the therapeutic effect.**
- **We intend to developed a new THERANOSTICS by loading RI into the specific probe.**