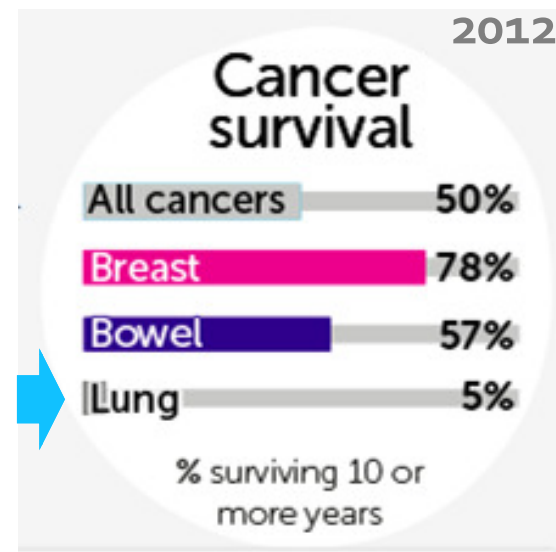
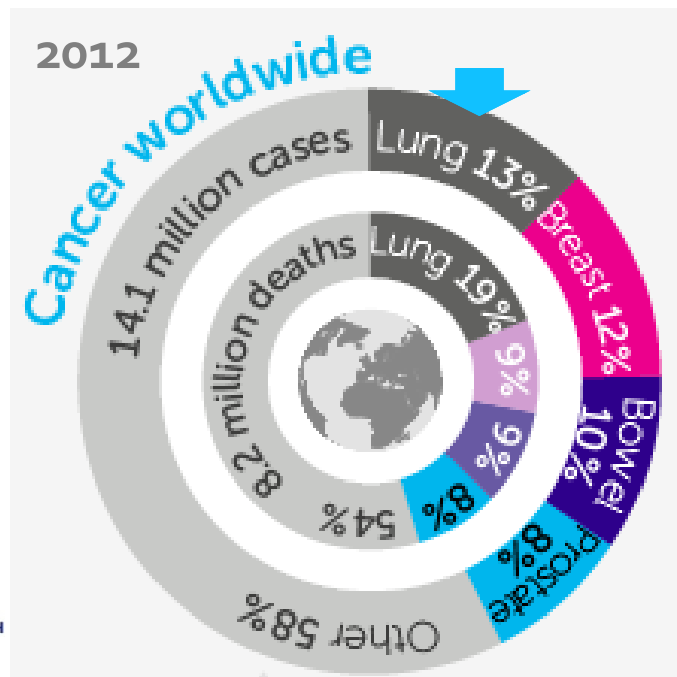


Cancer Stem Cell Markers in Lung Cancers: Proofs of Concepts and Some Reservations

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Hamburg, Germany**

Lung cancer: highest death rate and poorest patient survival



Prepared by:



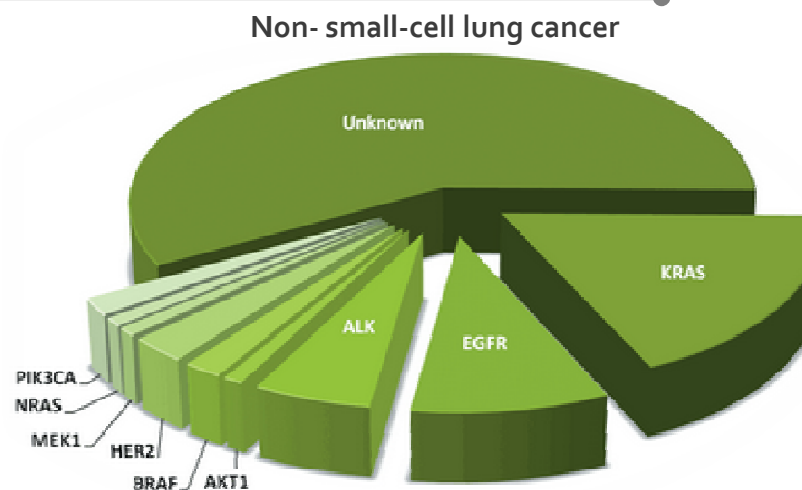
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Current Treatment Modalities in Lung Cancers



Standard therapy

Targeted therapy



ALK- Anaplastic lymphoma kinase
EGFR- Epidermal growth factor receptor
KRAS - Kirsten rat sarcoma viral oncogene

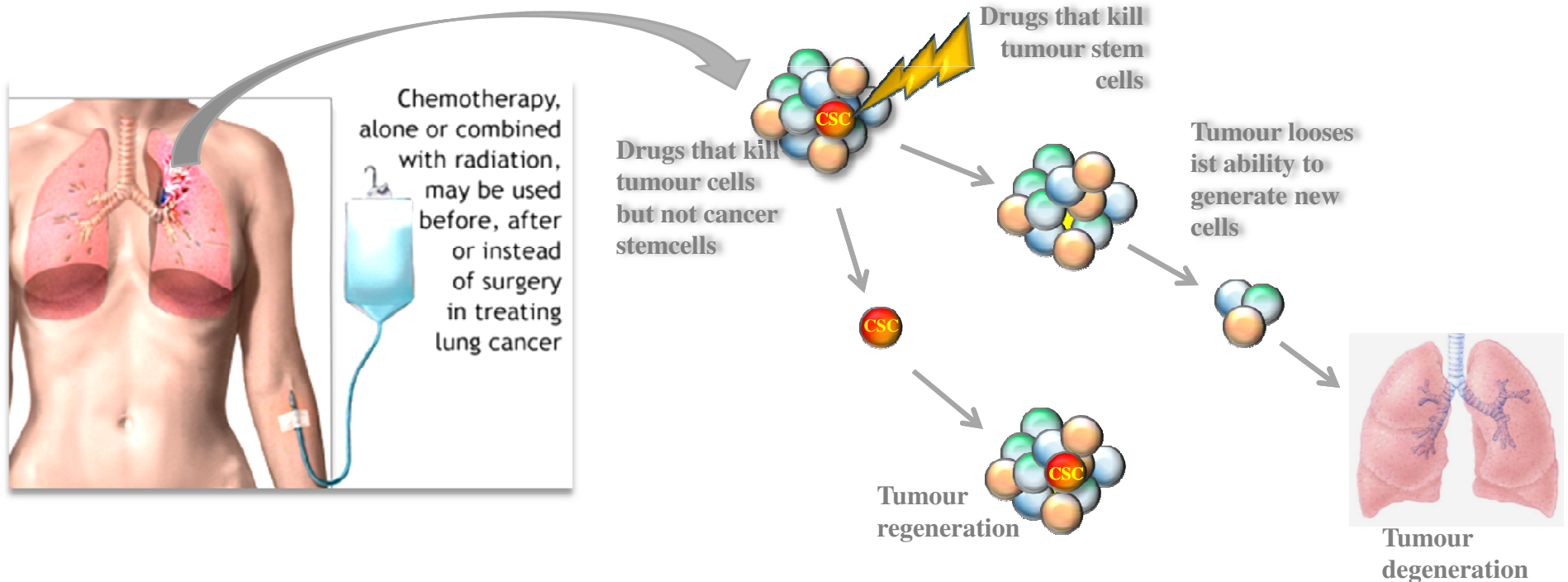
Cancer stem cells within lung tumour are crucial players in cancer therapy

Chemotherapy

- Induces cell death and reduction of tumour bulk
- Drug resistance leads to recurrence or death

Cancer stem cells (CSCs)

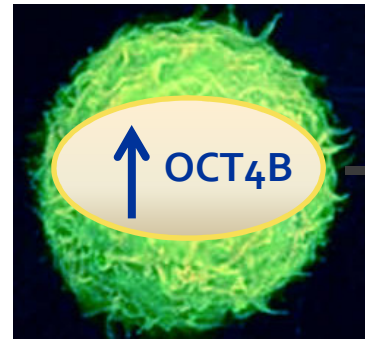
- Self-renewal
- Generate phenotypic heterogeneity
- Tumorigenicity in immunocompromised mice
- **Chemoresistance**



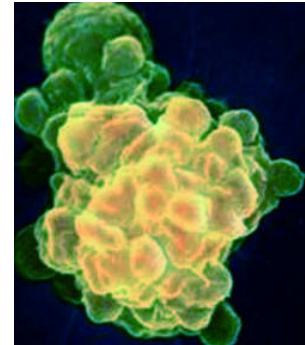
Our goal...

To identify cancer stem cell markers that are involved in the initiation, progress and drug resistance in lung cancers.

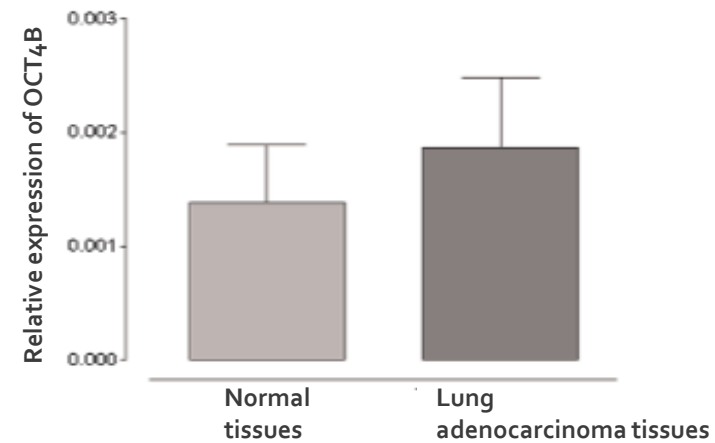
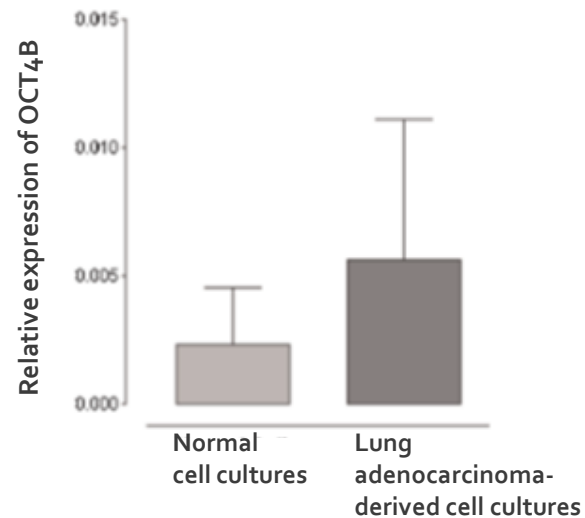
Increased OCT₄B levels in lung tumor tissues



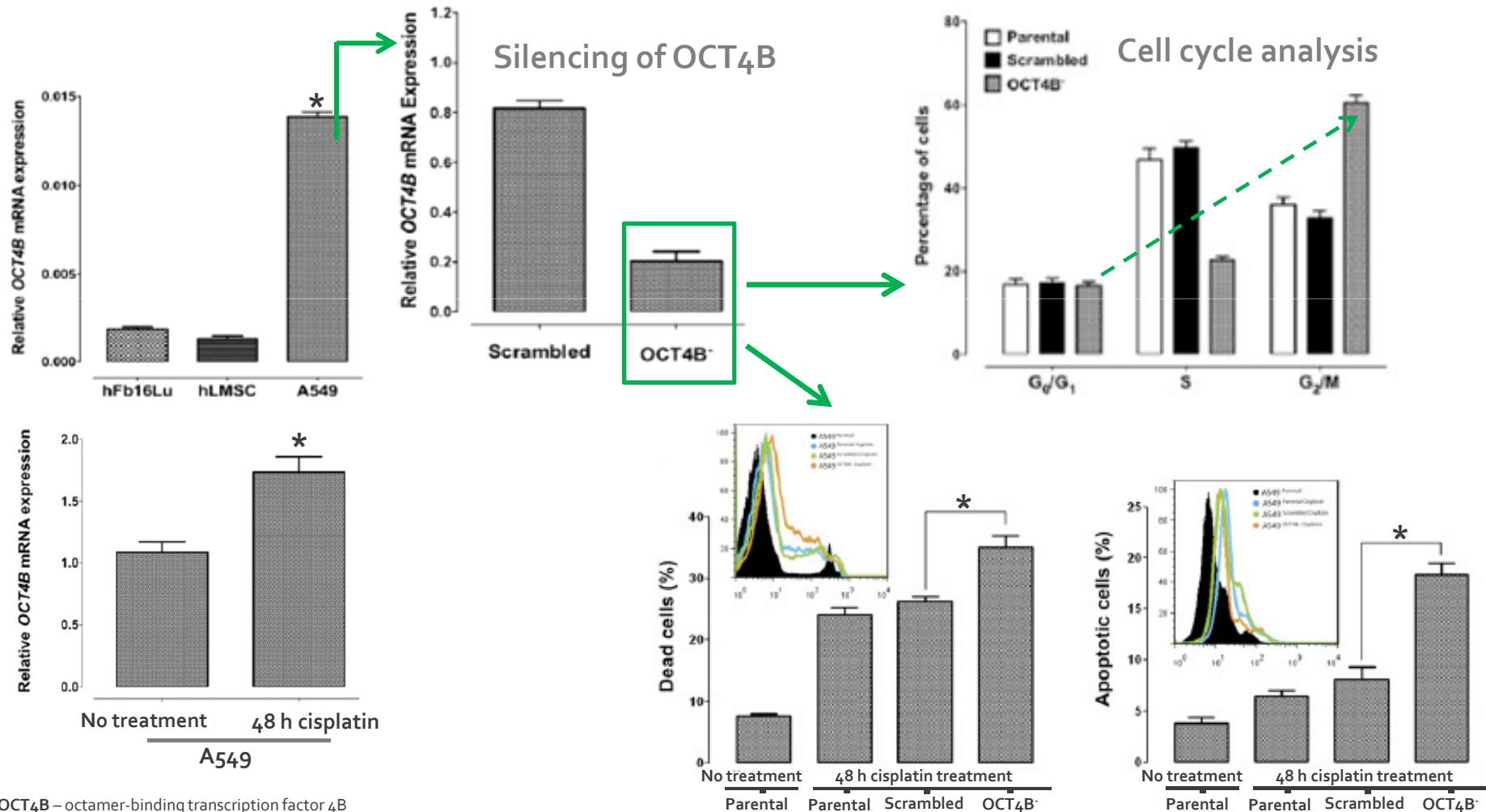
Normal cell



Apoptotic cell

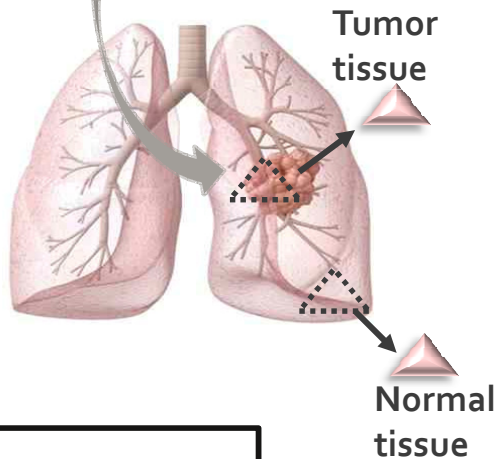


Suppression of OCT4B sensitizes lung adenocarcinoma cells to cisplatin treatment

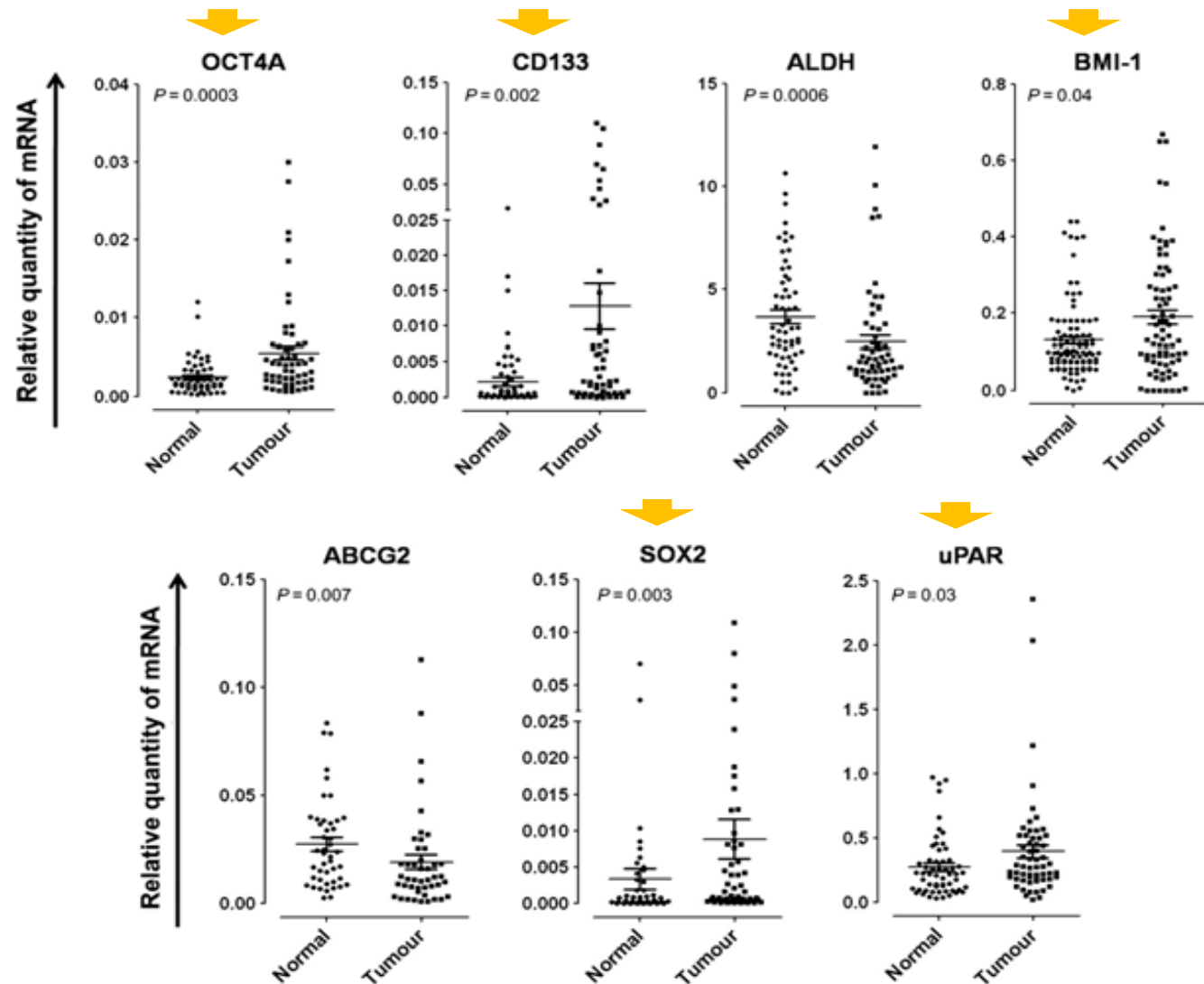


OCT4B – octamer-binding transcription factor 4B
 A549 – lung adenocarcinoma cell line;
 hFb16lu – normal lung fibroblasts;
 hLMSC – human lung mesenchymal stem cells

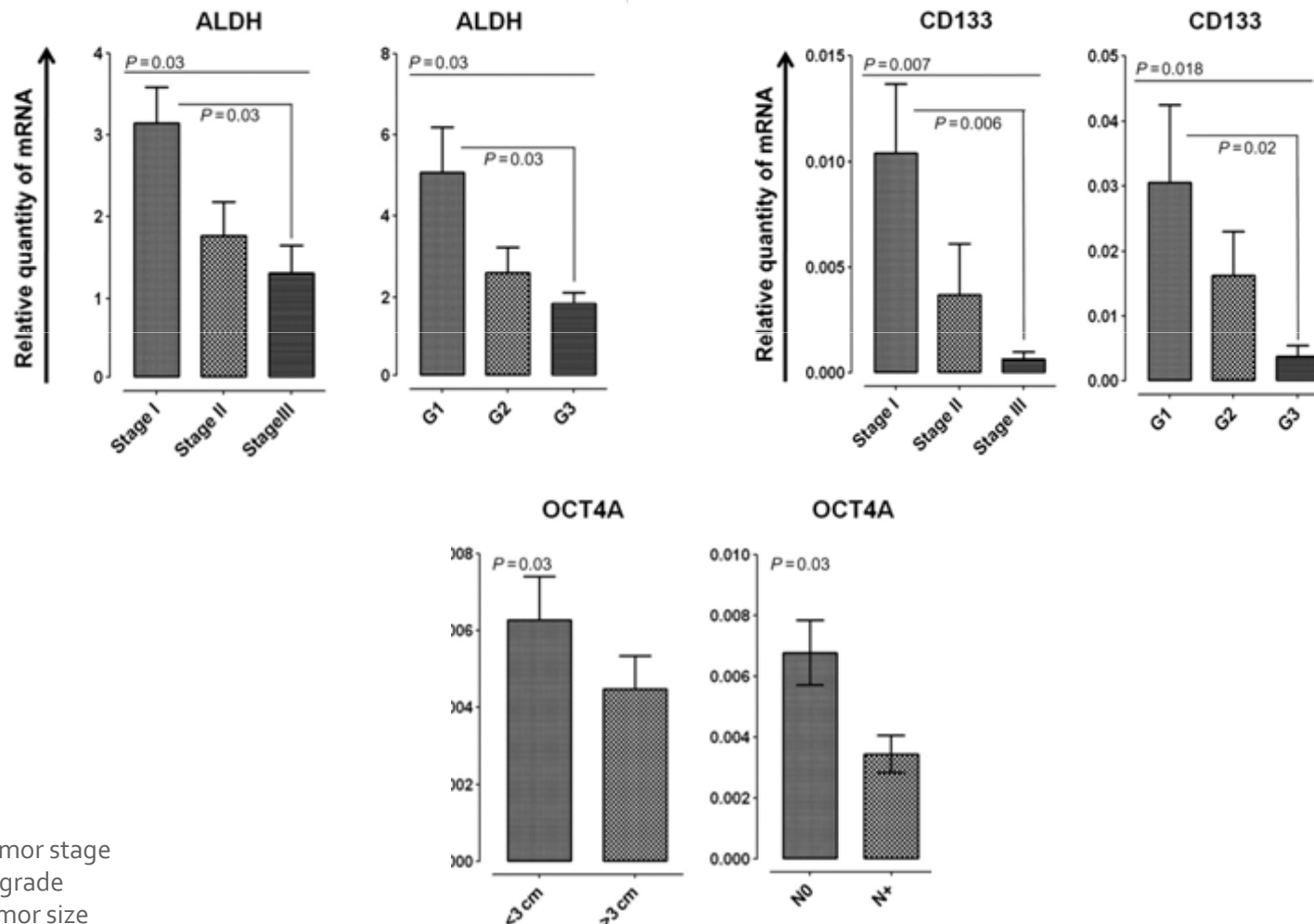
mRNA levels of CSC-associated genes in paired normal and lung adenocarcinoma biopsies



n – 64
 male - 34
 female - 30
 median age – 62

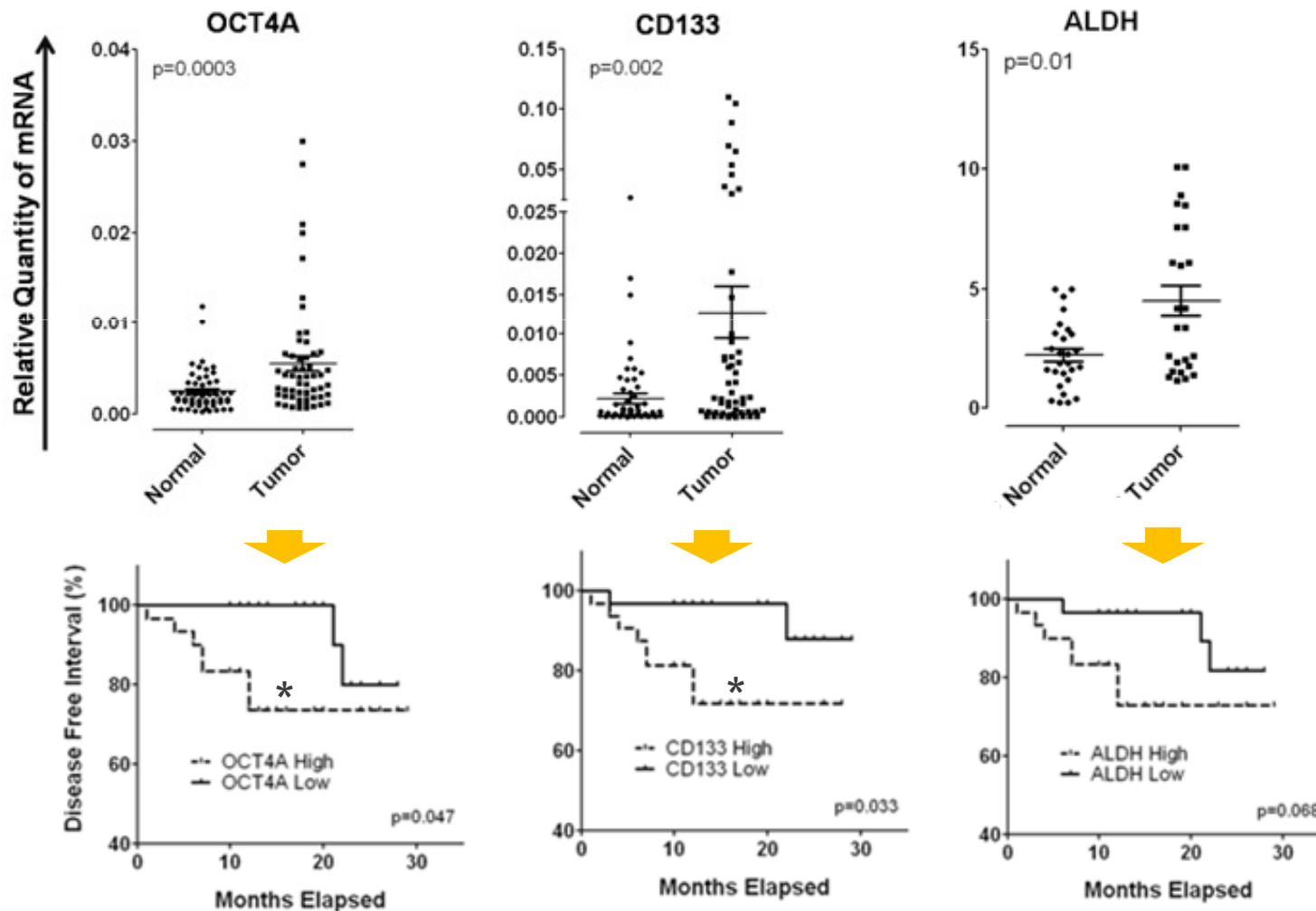


mRNA levels of ALDH, CD133 and OCT4A decreases with increasing tumor stage



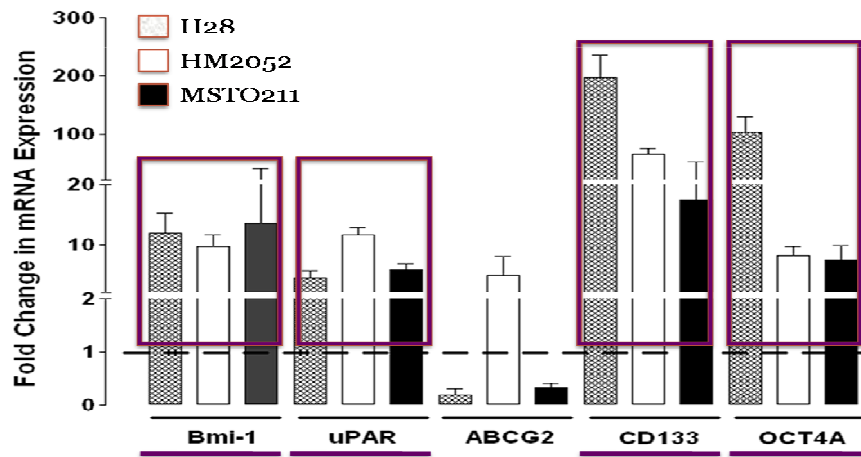
Stage 1-3, tumor stage
 G1 -3, tumor grade
 < / > 3 cm, tumor size
 NO/N+, lymph node metastasis

Increased CSC-associated gene profiles correlate with reduced disease-free intervals in lung adenocarcinoma

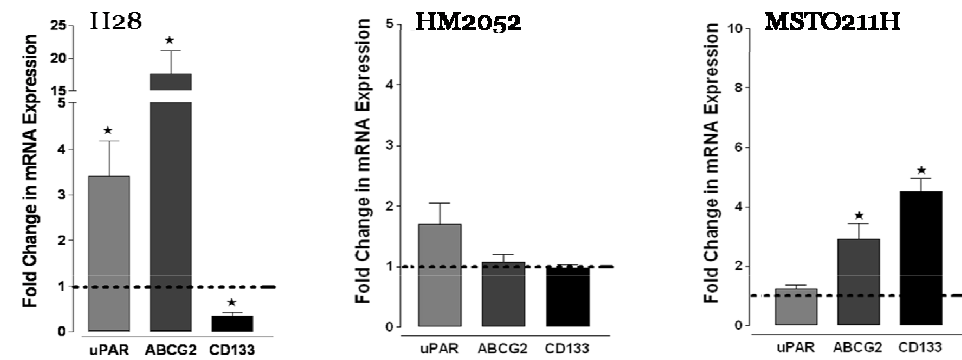


mRNA levels of CSC-associated genes are increased in drug-resistant cells in malignant pleural mesothelioma

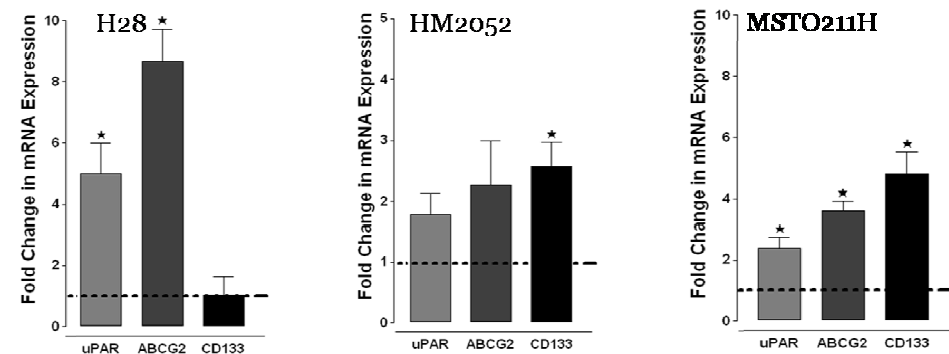
Enhanced expression of CSC markers in MPM cell lines compared to non-malignant mesothelial cells



Increased levels of uPAR, ABCG2 and CD133 in cisplatin-resistant cells



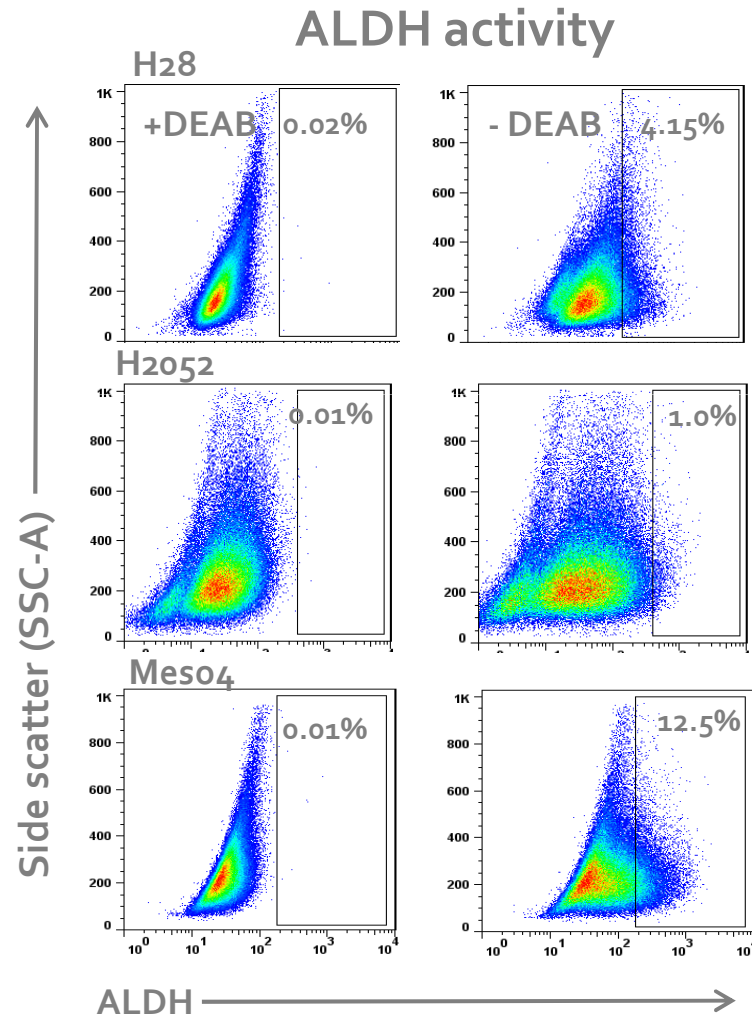
Pemetrexed-resistant cells



H28, H2052, MSTO211H – malignant pleural mesothelioma cell lines
MPM- malignant pleural mesothelioma

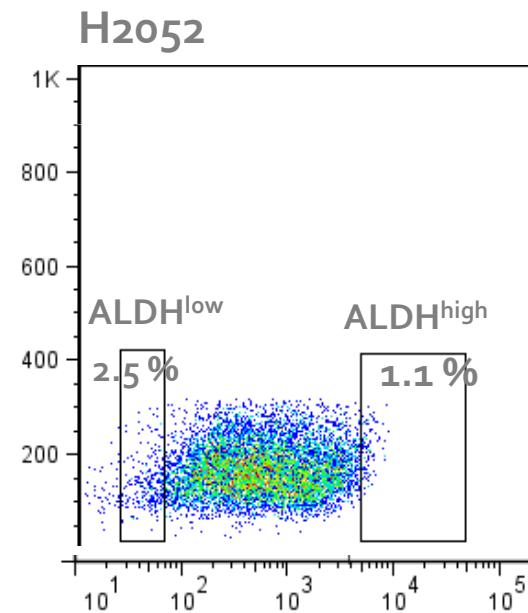
Cortes-Dericks L, et al.
Int J Oncol. 2010 Aug;37(2)

Reliability of ALDH to demarcate a CSC from non-CSC subpopulation in malignant pleural mesothelioma cells



ALDH – Aldehyde dehydrogenase

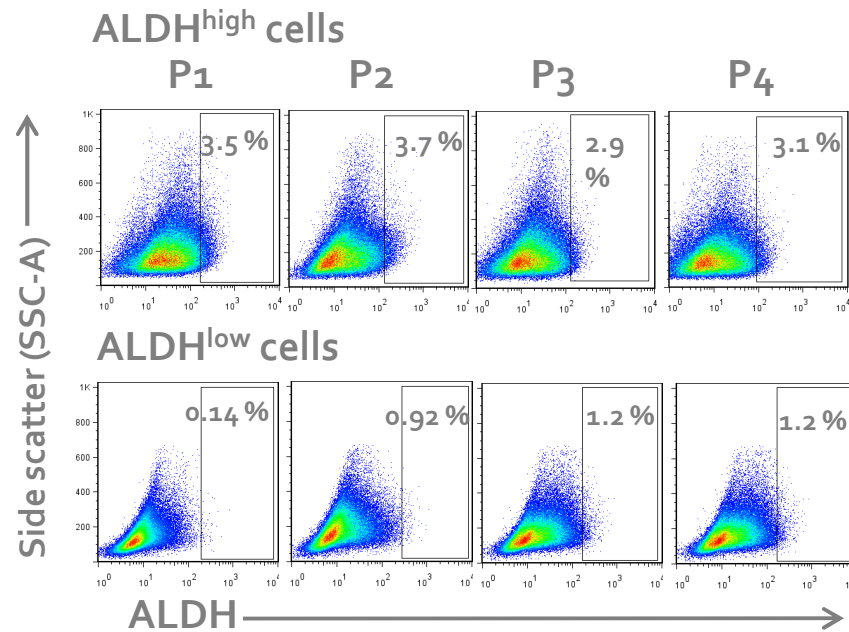
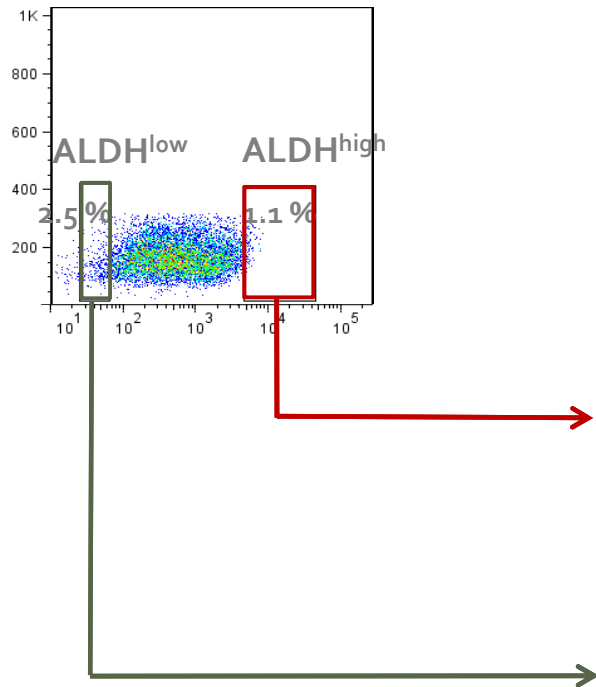
FACS-based ALDH cell sorting



FACS – fluorescence activated cell sorting
H28, H2052, Meso4 – mesothelioma cell lines

Phenotypic generation of ALDH-sorted cells

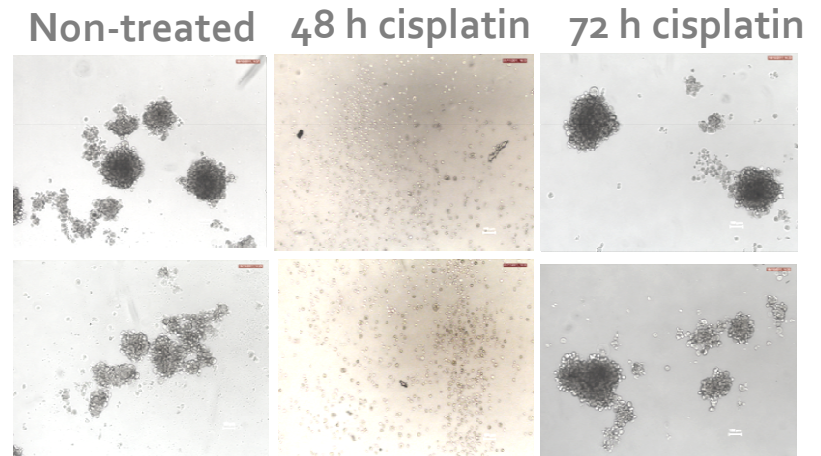
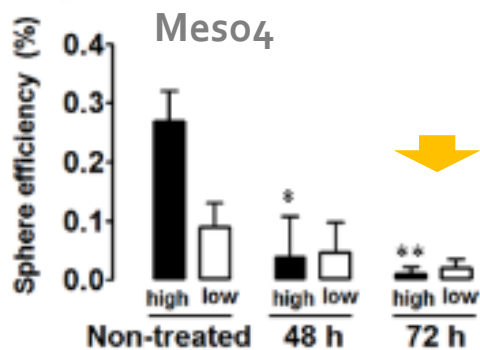
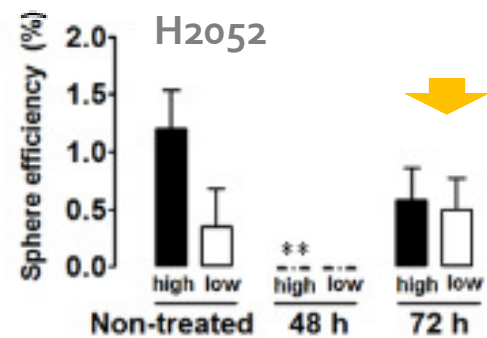
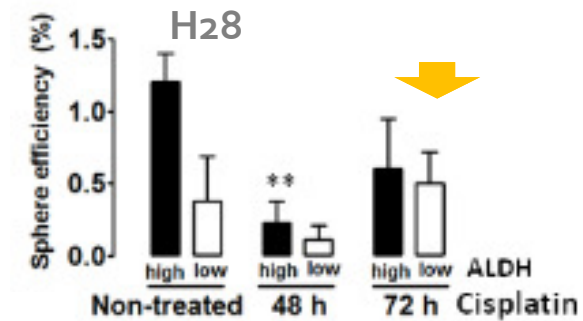
FACS-based sorted H2052



P1 to P4- cell passages

H2052- mesothelioma cell line

Both ALDH^{high} and ALDH^{low} subpopulations contain cisplatin-resistant tumor spheres

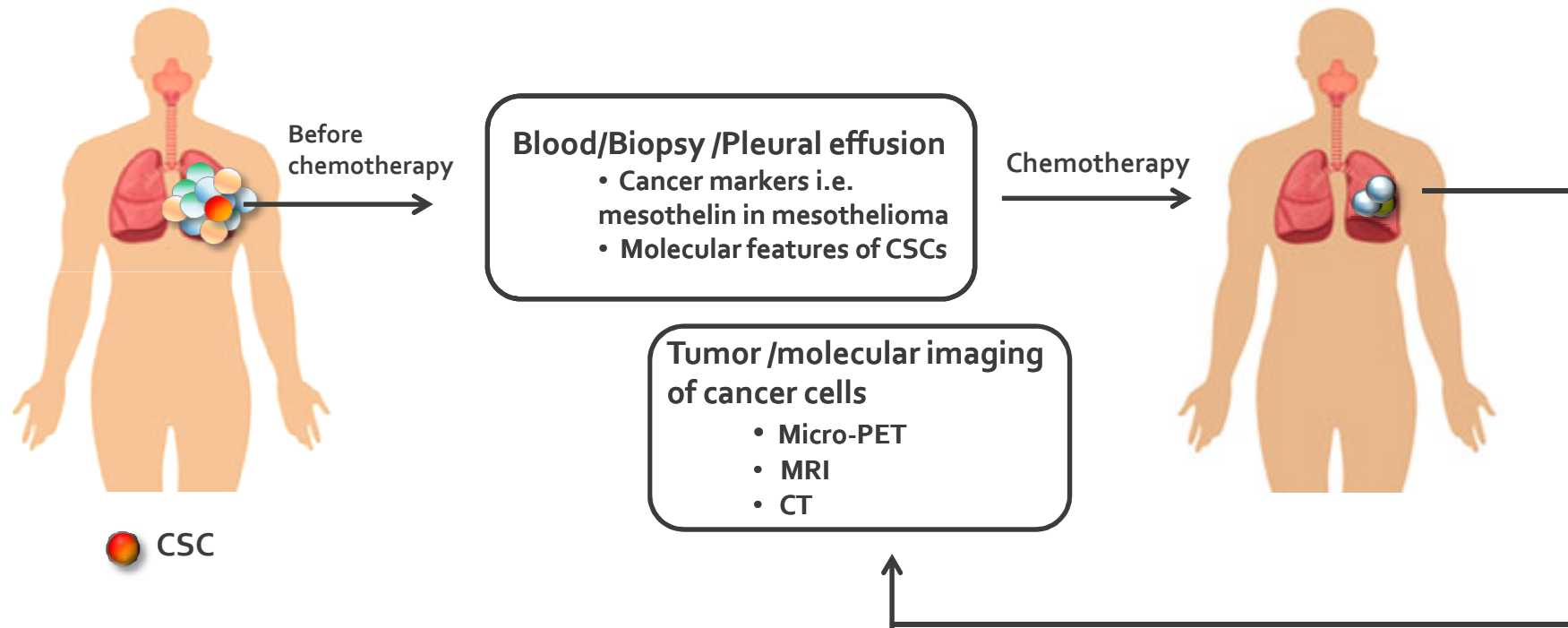


Cisplatin - cisdiamminedichloroplatinum(II)
 Sphere-formation – basic property of putative cancer stem cell population

Conclusions

- Cancer stem cell marker is not universal to any type of cancer.
- Personalized therapy – identification of CSC markers in patient`s clinical specimens before and after therapy may lead to specific targeting of drug-resistant subpopulation.

Tracking patient-specific cancer stem cells



Micro-PET – micro positron emission tomography
MRI – magnetic resonance imaging
CT – computed tomography



Thank you for your attention

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