Cancer Stem Cells: implications in chemoresistance and perspectives in lung cancer therapy

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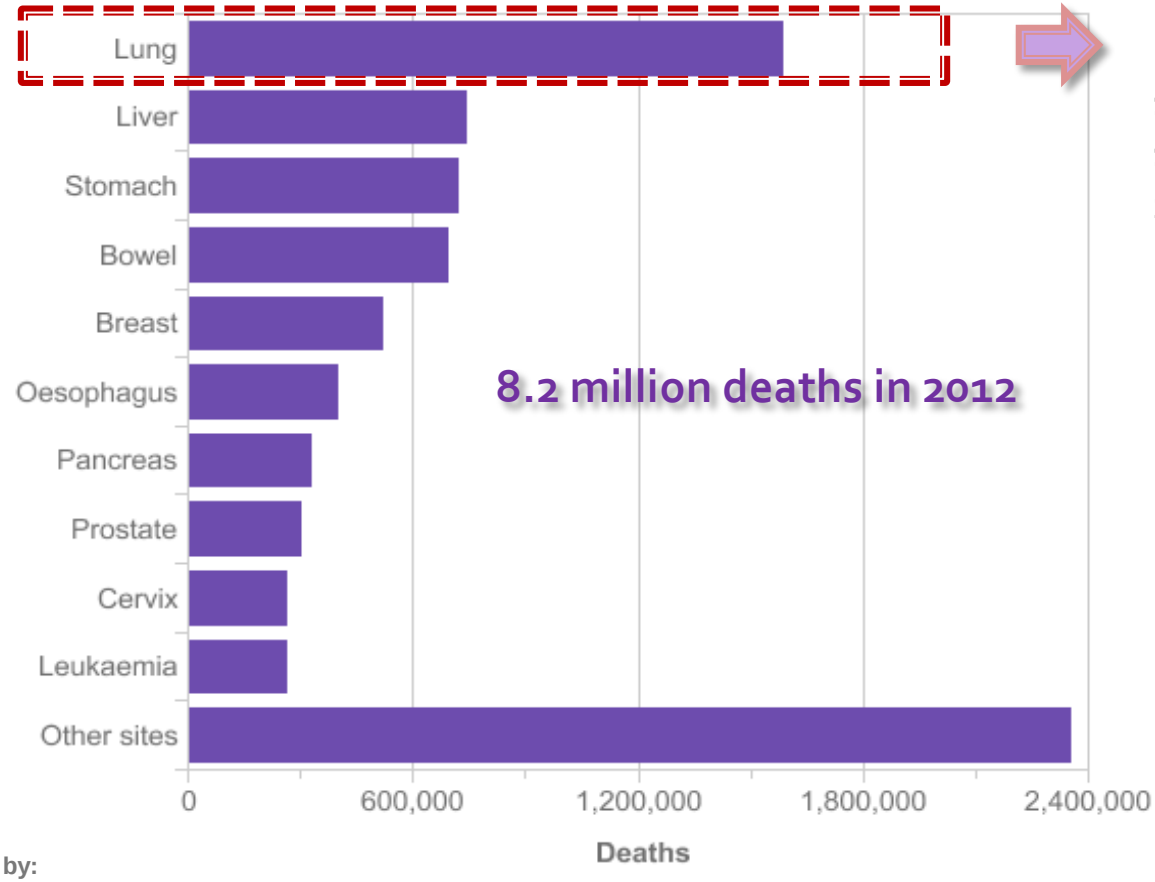
10 Most Common Causes of Cancer Deaths: 2012 Estimates Worldwide

Total Number of Deaths from Cancer per Year, Worldwide



Lung cancer
1.59 million deaths
1.8 million new cases in 2012.

Prepared by:
CANCER RESEARCH UK

World Health Organization
http://www.who.int/en/

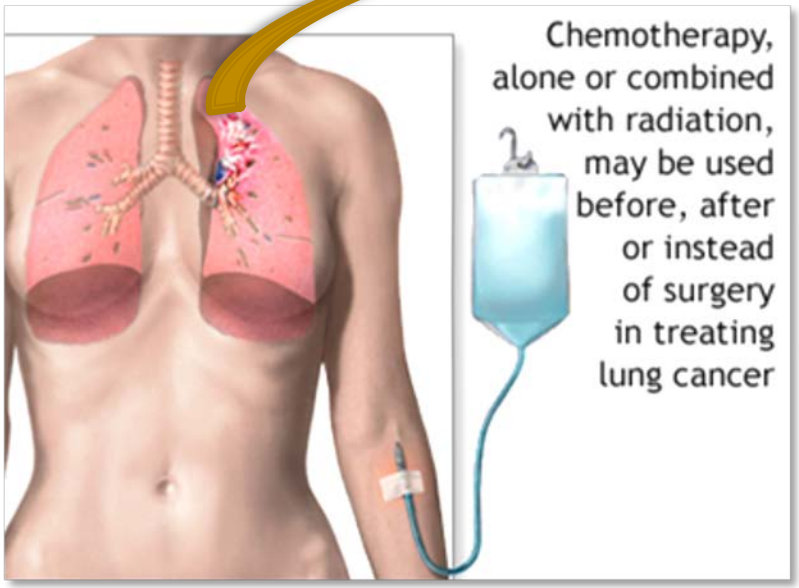
Cancer stem cells in lung tumour are crucial players in chemoresistance

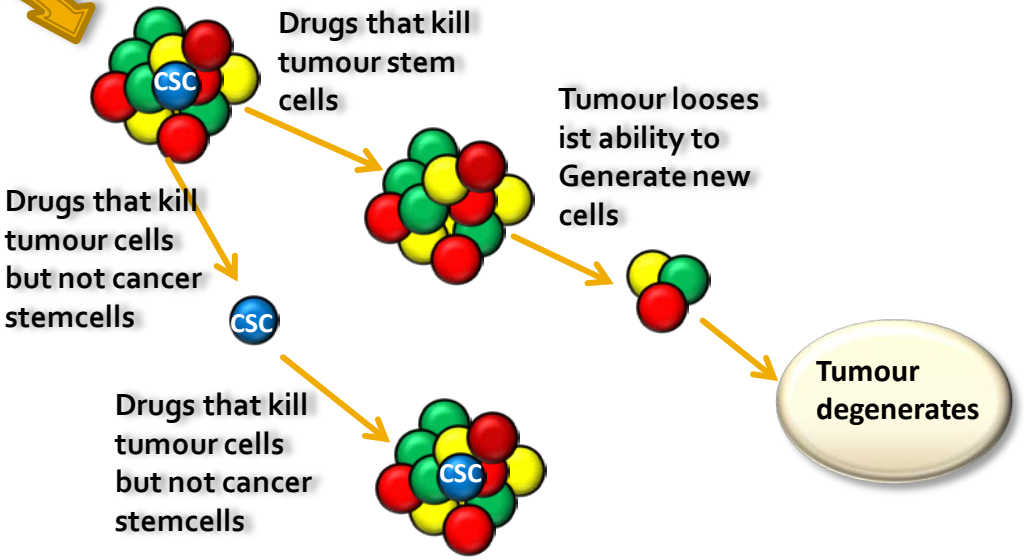
Chemotherapy

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

Cancer stem cells (CSCs)

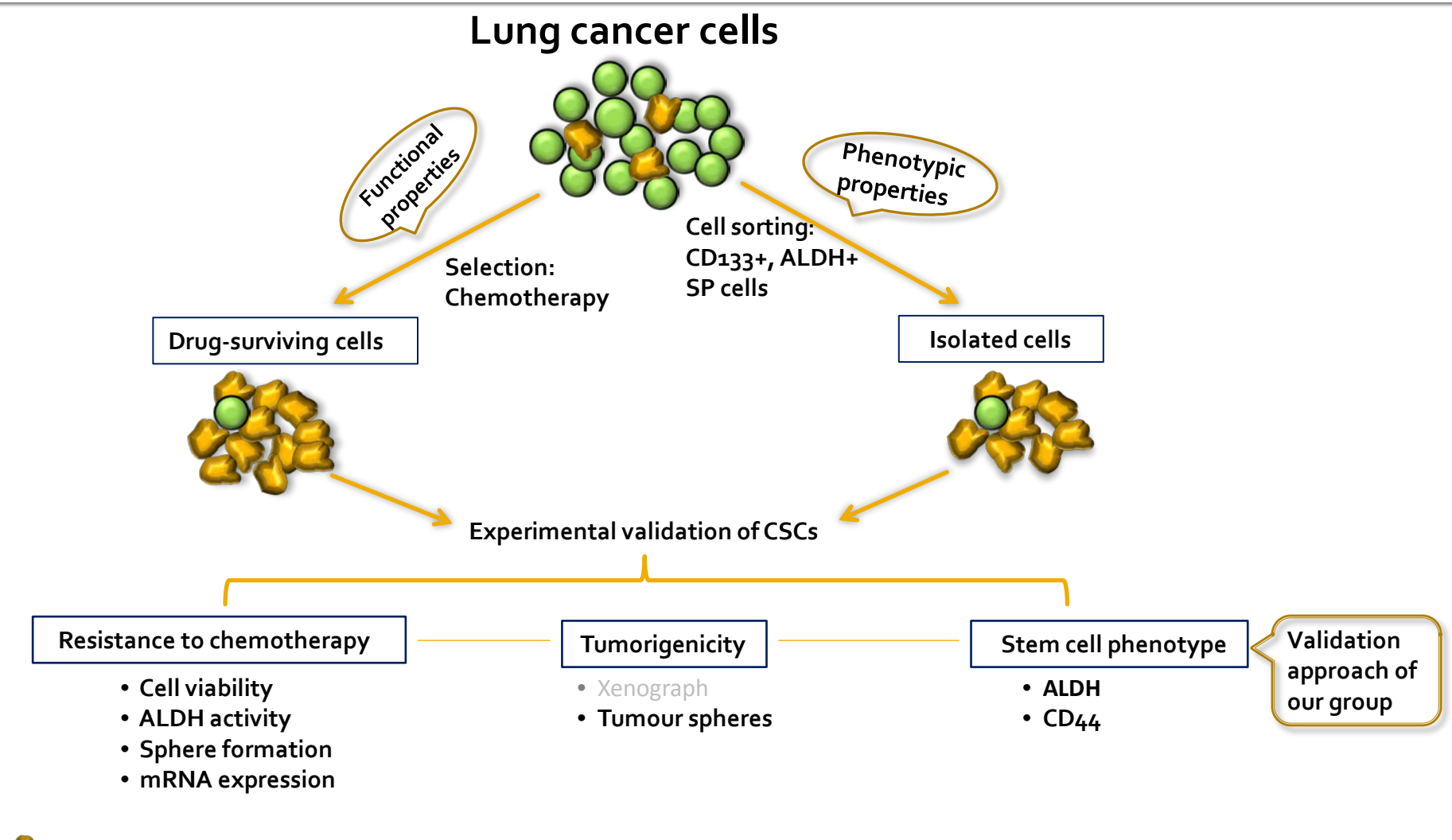
- Self-renewal
- Generate phenotypic heterogeneity
- Tumorigenicity in immunocompromised mice
- **Chemoresistance**





Reya T, et. al.,Nature 414, 105-111(2001)

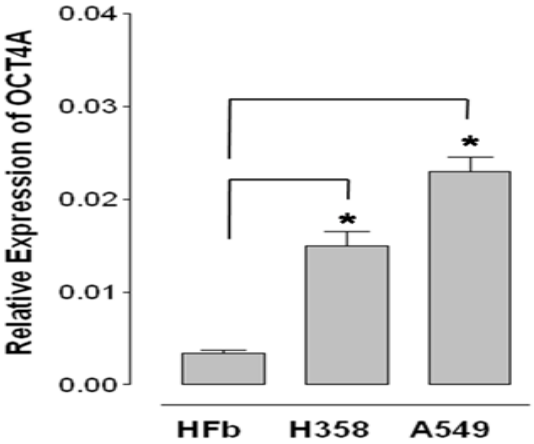
In vitro validation of lung cancer stem cells

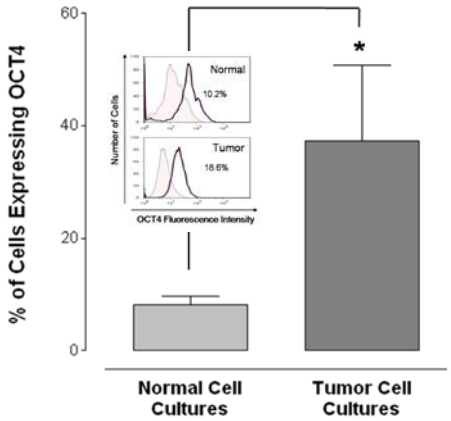


Adapted from: J Oncol. 2011;
Rivera C et al.

Atypical expression and distribution of OCT4A in human lung adenocarcinoma

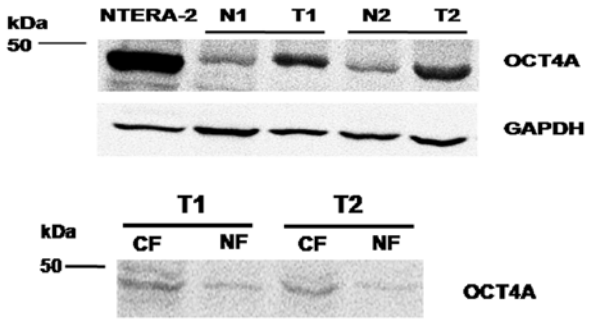
Flow cytometry-based analysis of OCT4A





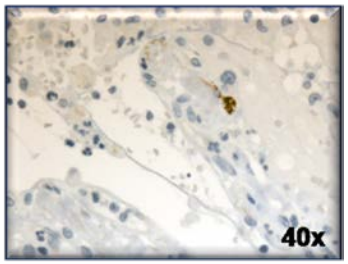
H358, A549 – lung adenocarcinoma cell line
HFb – normal lung fibroblast cell line

Western blot analysis of OCT4A expression and intracellular distribution

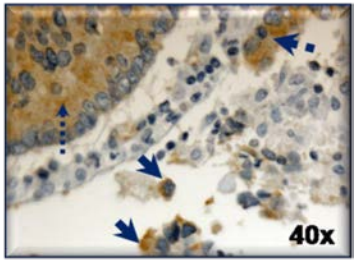


CF- cytosolic fraction
NF- nuclear fraction

High expression of OCT4A (pointed by arrrows) in tumour tissue

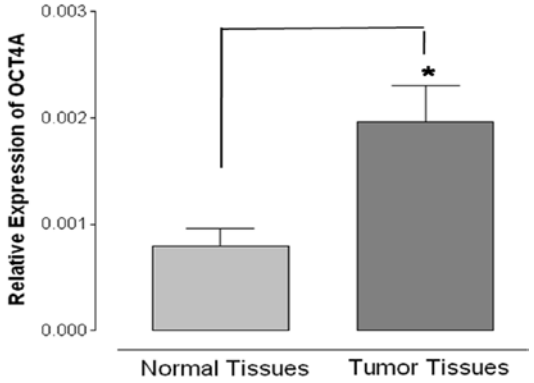


Normal lung biopsy



Tumour lung biopsy

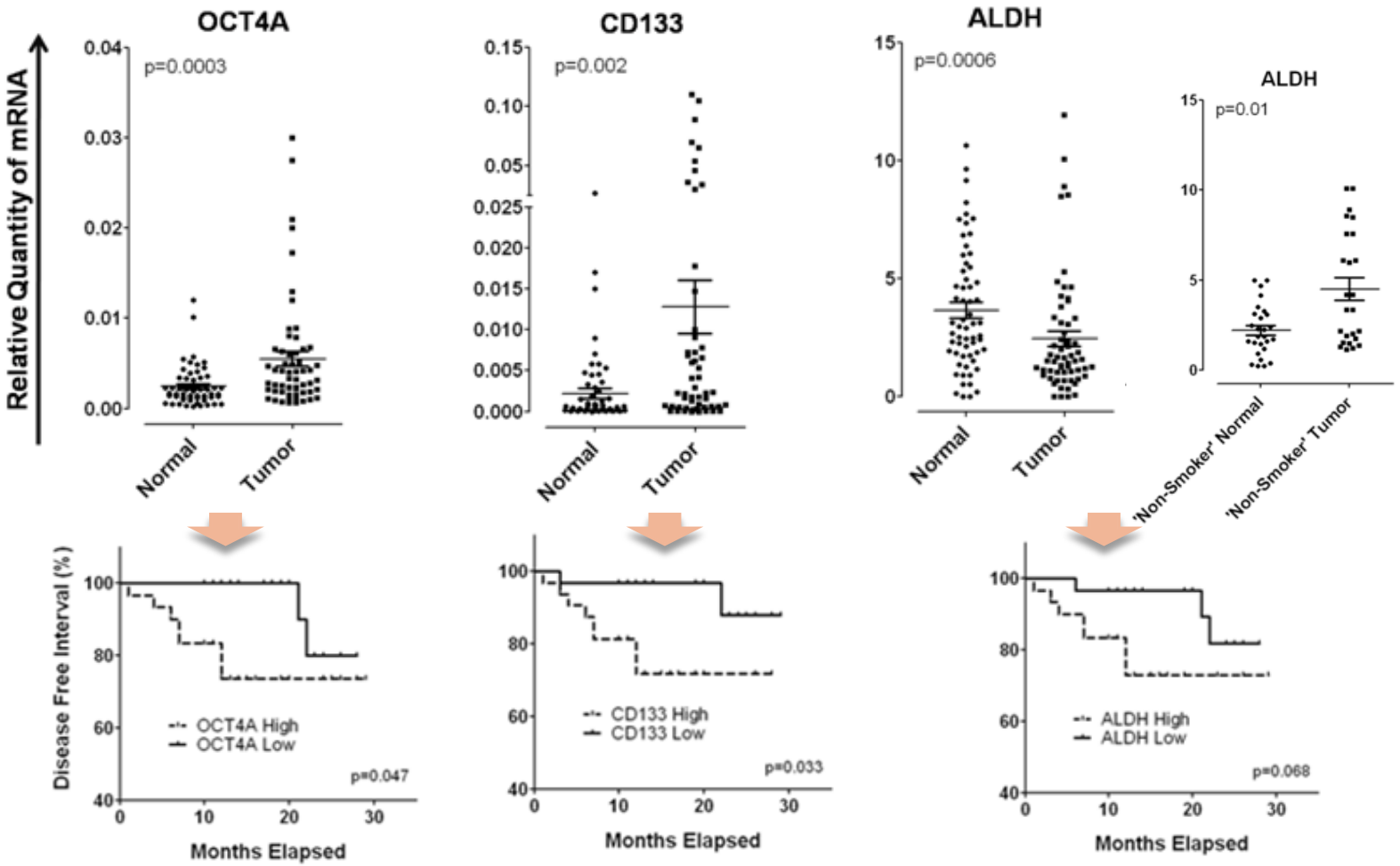
mRNA levels of OCT4A



Karoubi G, Cortes-Dericks L et al.
J Surg Oncol.2010 Nov 1;102(6):689-98.

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

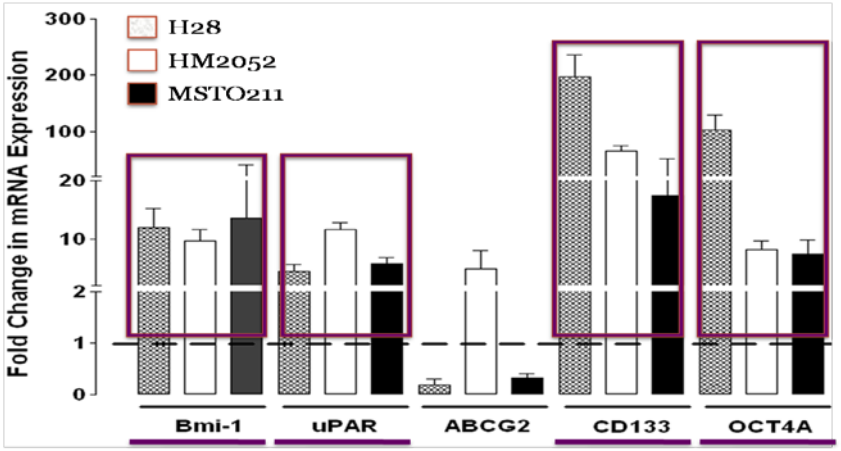
Gene expression in normal and corresponding tumour lung tissues



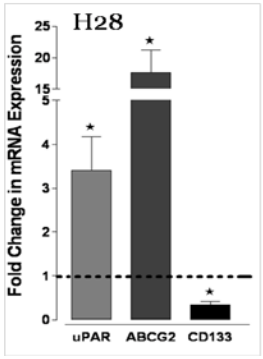
Cortes-Dericks et al.
Eur J Cardiothorac Surg. 2012 Jun;41

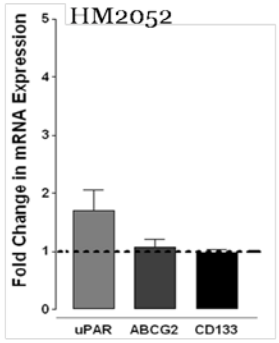
Increased mRNA levels of putative CSC genes shows involvement in drug tolerance to cisplatin and pemetrexed

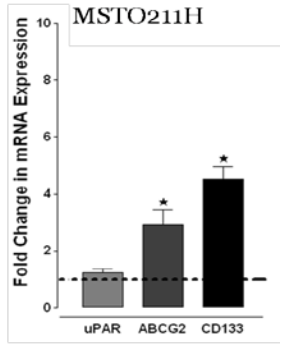
Enhanced expression of CSC markers in MPM cell lines compared to non-malignant mesothelial cells



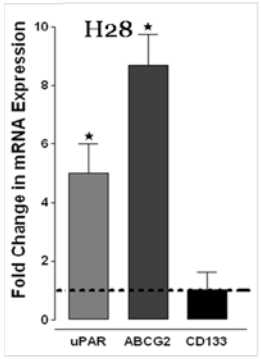
Upregulation of uPAR, ABCG2 and CD133 after cisplatin treatment

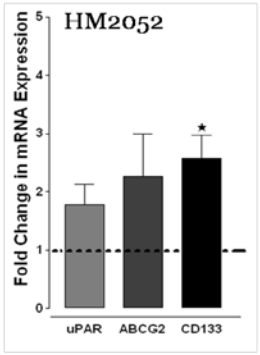


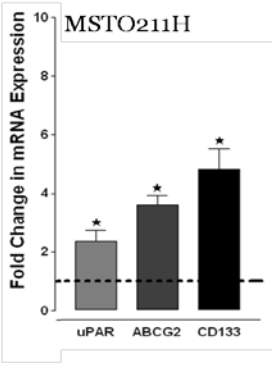




Upregulation of uPAR, ABCG2 and CD133 after pemetrexed treatment



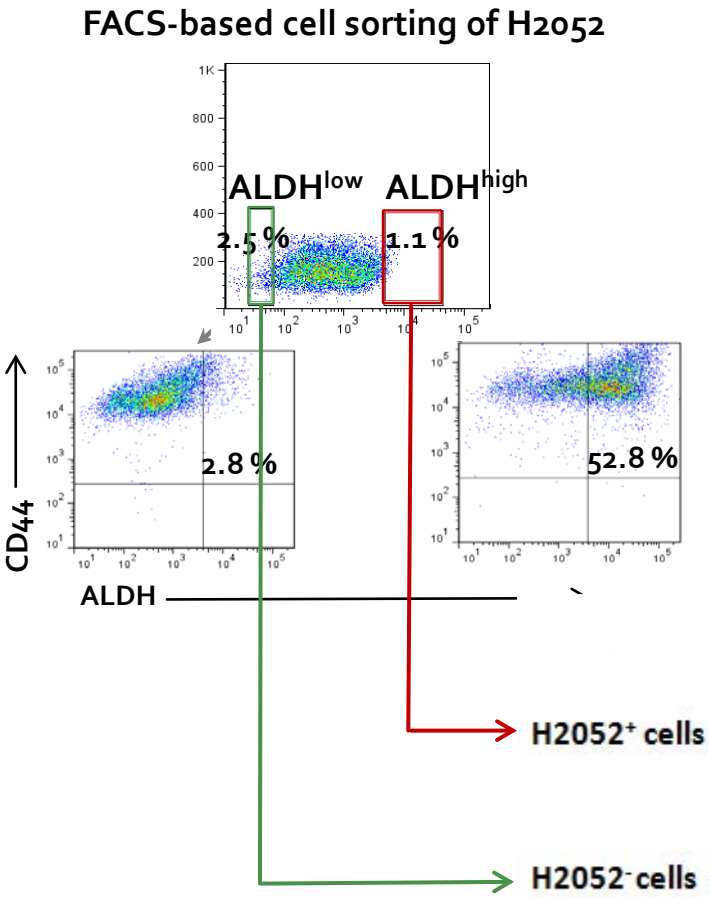


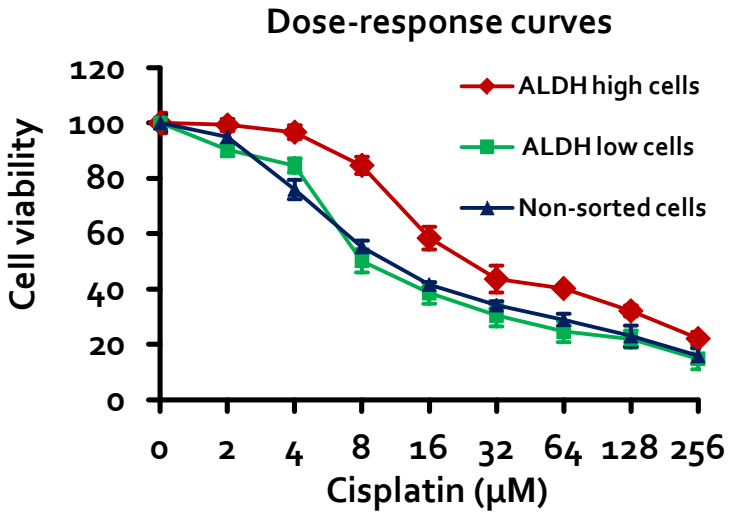


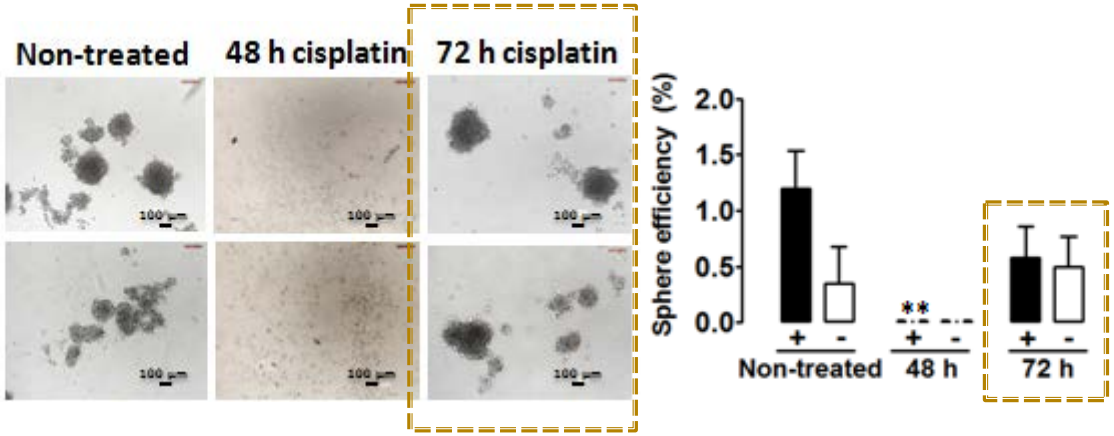
H28, H2052 – malignant pleural mesothelioma cell lines;
MSTO211H – non-malignant cells;
MPM- malignant pleural mesothelioma

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

Aldehyde dehydrogenase (ALDH) and sphere formation assay to assess chemoresistance of putative cancer stem cells in malignant pleural mesothelioma cell line







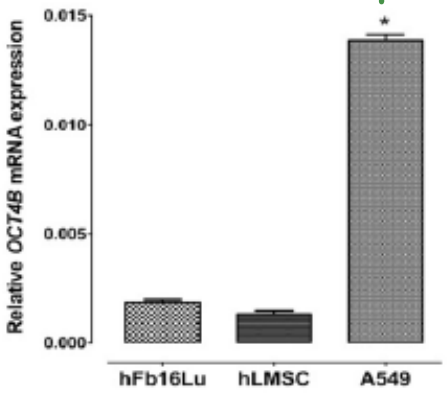
H2052- mesothelioma cell line

Sphere formation of non-cisplatin and cisplatin-treated cells

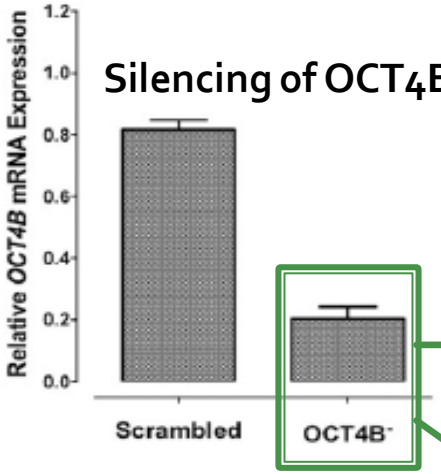
Cortes-Dericks L et al. BMC Cancer. 2014, 14:304

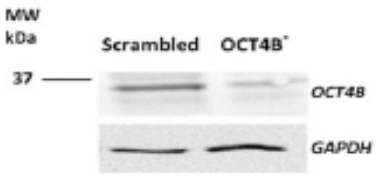
Suppression of OCT4B sensitizes lung adenocarcinoma cells to cisplatin treatment

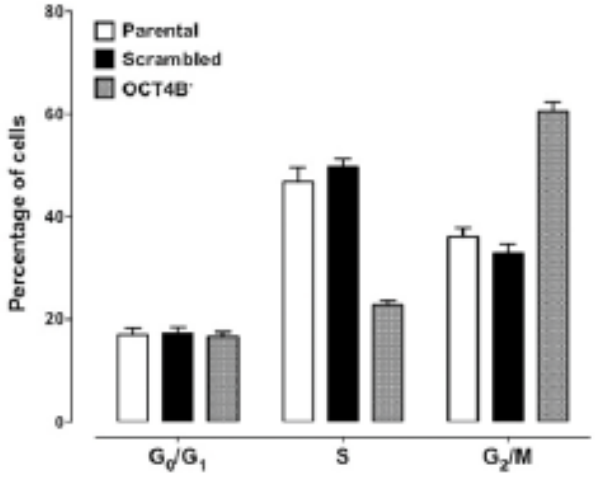
Increased expression of OCT4B in A549 cells compared to non-cancer cell lines

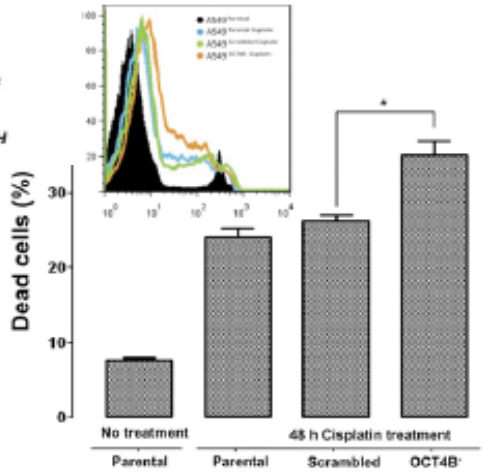


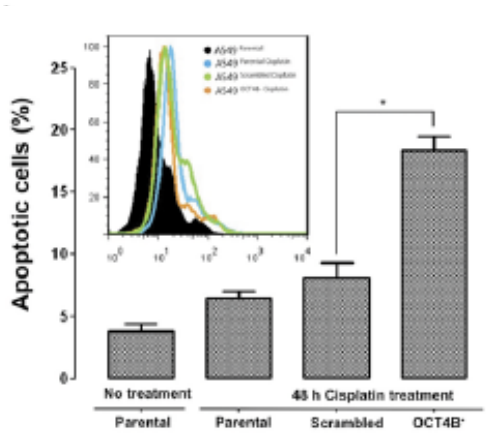
Silencing of OCT4B







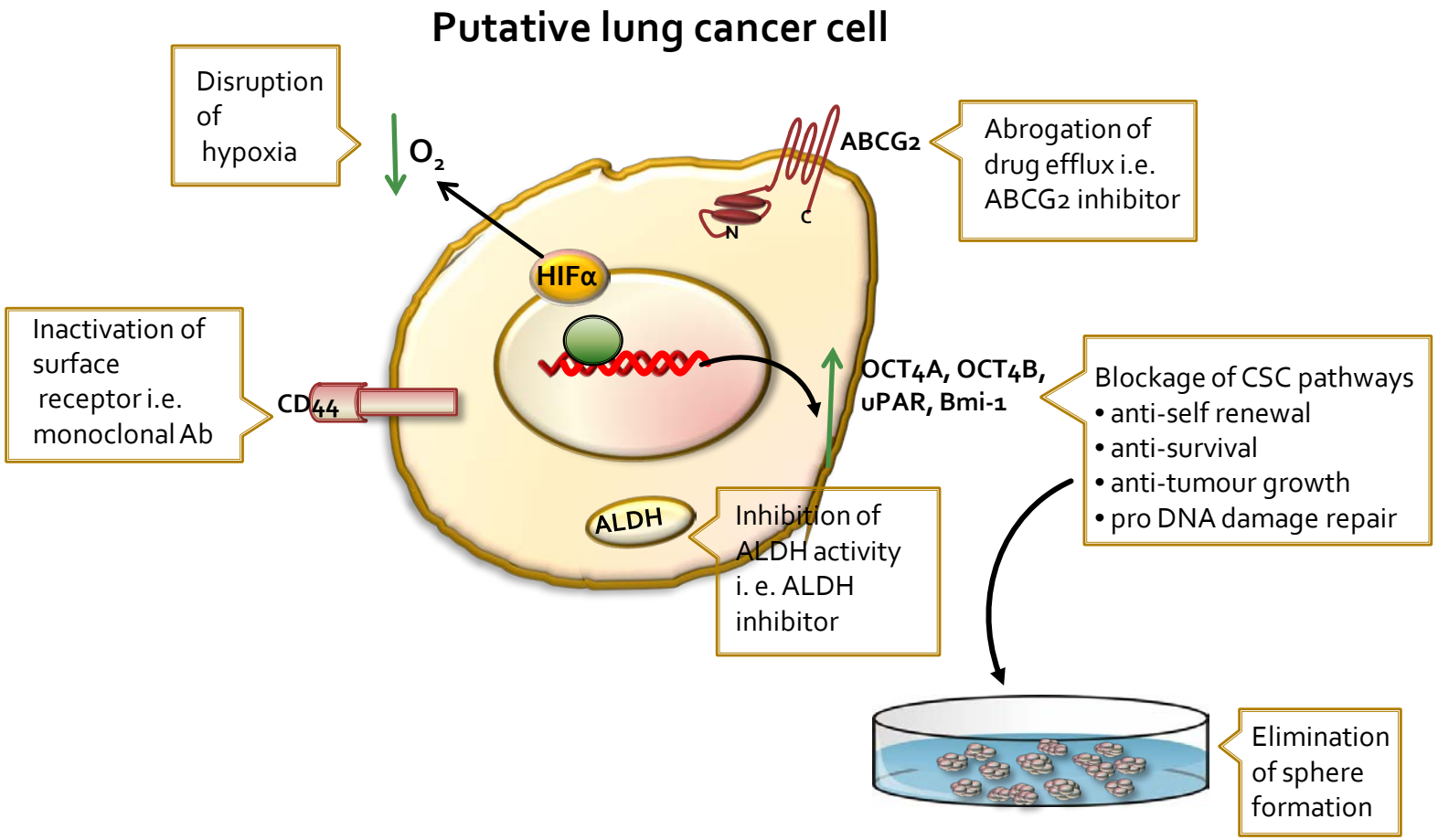




OCT4B – octamer-binding transcription factor 4B
A549 – lung adenocarcinoma cell line;
hFb16lu – normal lung fibroblasts;
hLMSC – human lung mesenchymal stem cells

Cortes-Dericks L et al.
Anticancer Res. 2013 Dec;33(12)

Potential tools to target cancer stem cells in lung cancer



Conclusions and future directions

- Lung cancers show adherance to cancer stem cell theory – but show functional differences that affect response to therapy and prognosis.

- Cancer stem cell markers have proven useful in identifying roles in lung carcinogenesis and chemoresistance - but may change dramatically as a result of assay conditions.

- Heterogeneity in lung cancers warrants that cancer stem cells should be confirmed in functional assays in each patient.