cost
EUROPEAN COOPERATION
IN SCIENCE AND TECHNOLOGY

Proposal for a new COST Action:

Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells

StemChem

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The Topic

Cancer arises from accumulation of

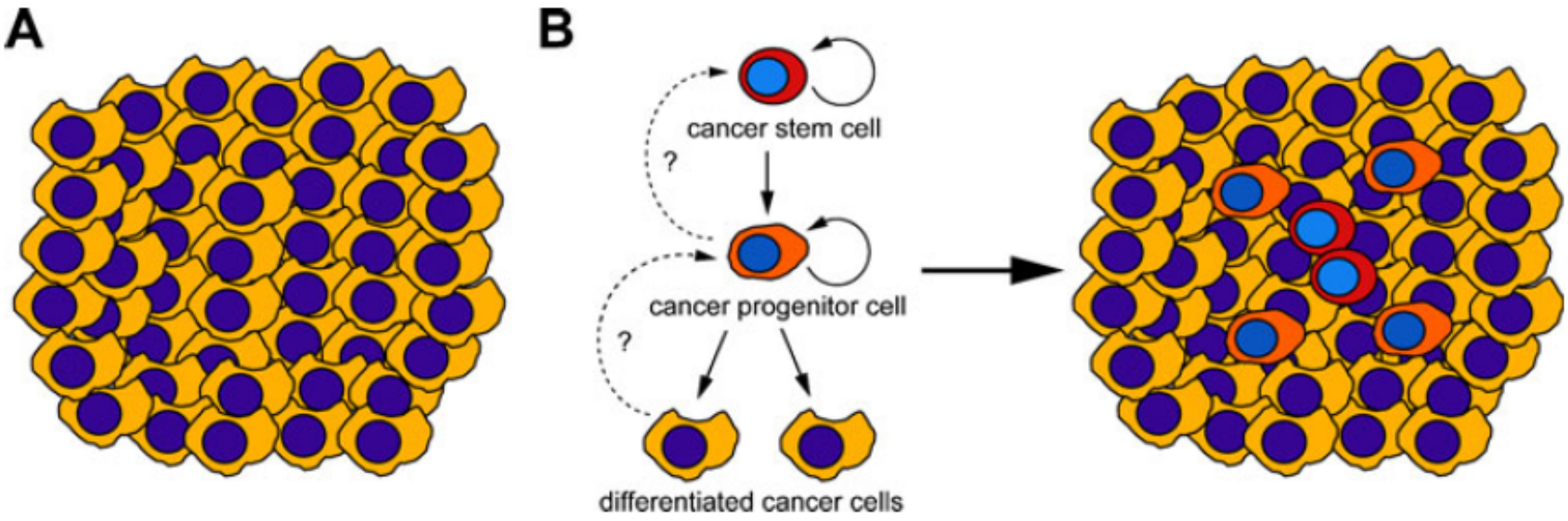
-critical “driver” mutations in cellular oncogenes (e.g. EGFR, Ras)

- tumor suppressors (e.g. p53) that engender uncontrolled growth and the formation of tumours

During malignant progression ……

tumor cell subsets acquire new molecular characteristics that result in

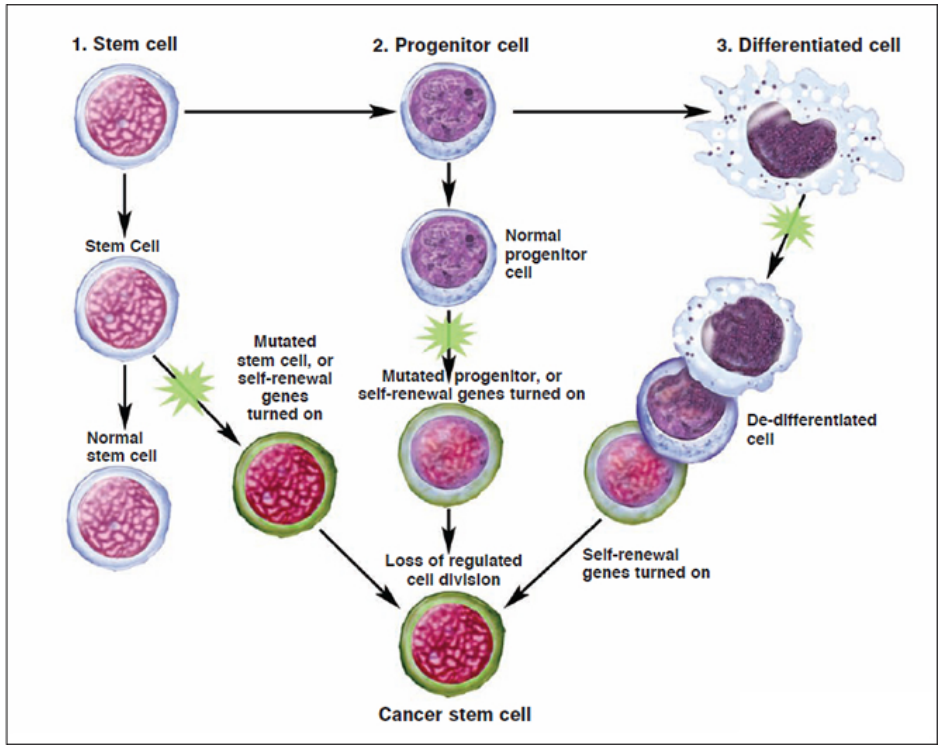
-metastatic ability
-drug resistance



Based on expression of specific markers is possible to isolate from tumors

a subpopulation of cancer cells with enhanced tumor initiating capacity

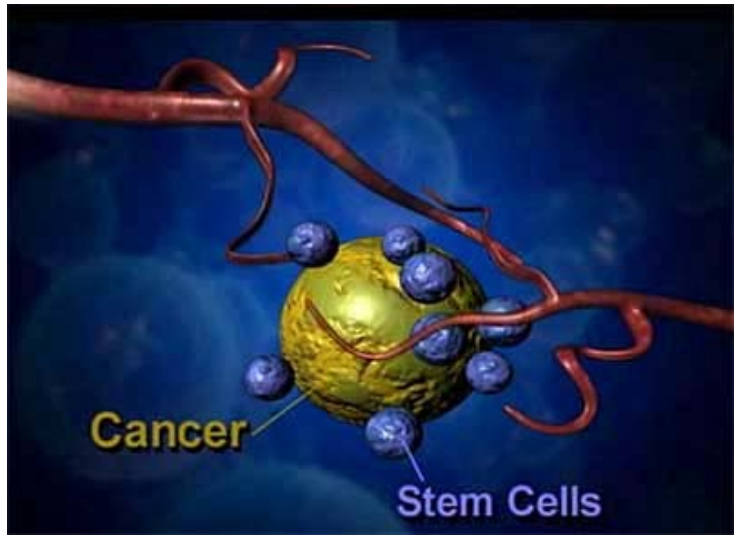
Cancer Stem Cells



Cancer Stem Cells

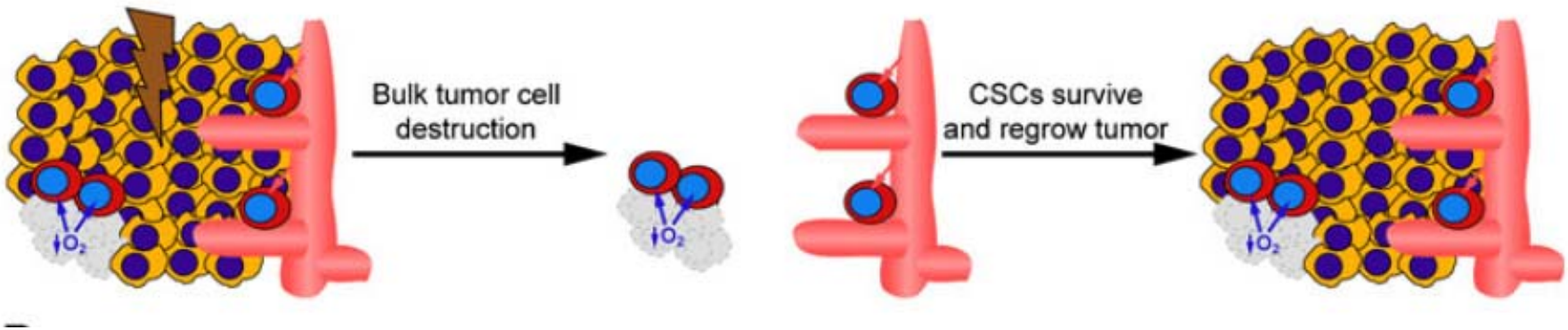
exhibit malignant traits

- Invasiveness
- Survival
- Chemotherapy resistance
- Immune modulation
- Tumor-initiating capacity



Cancer Stem Cells

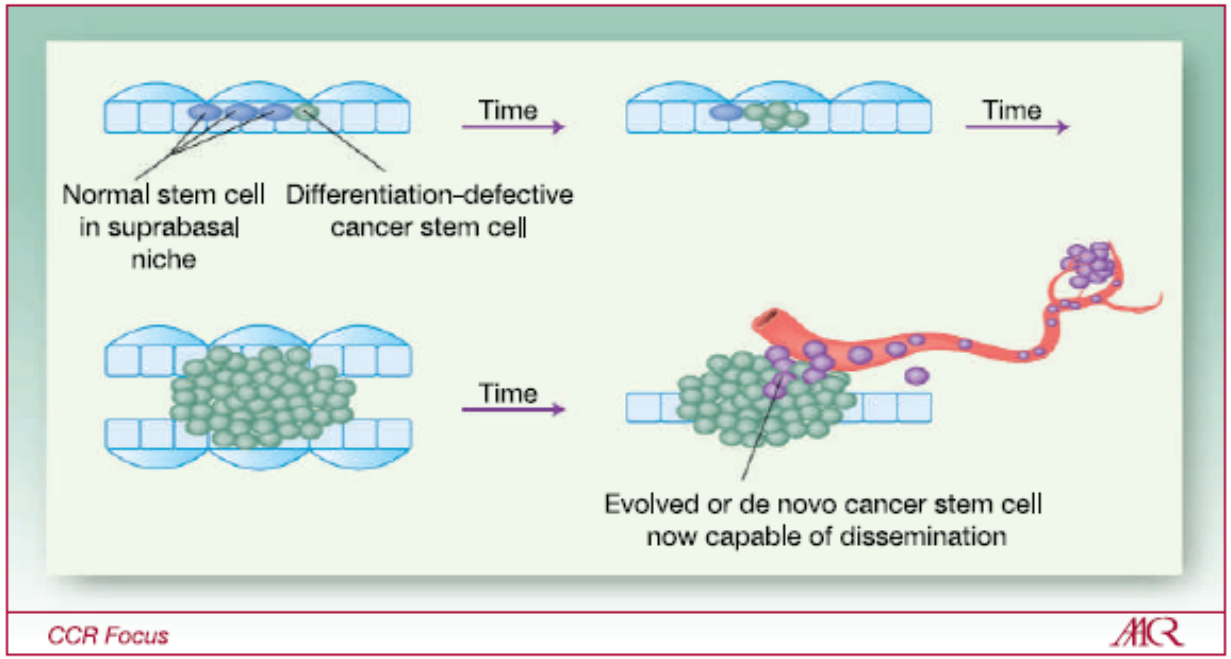
The persistence of CSCs after treatment explains disease recurrence following apparently successful debulking of human solid tumors by surgery, radiation and various forms of hemotherapy.



Cancer Stem Cells

exhibit alterations in

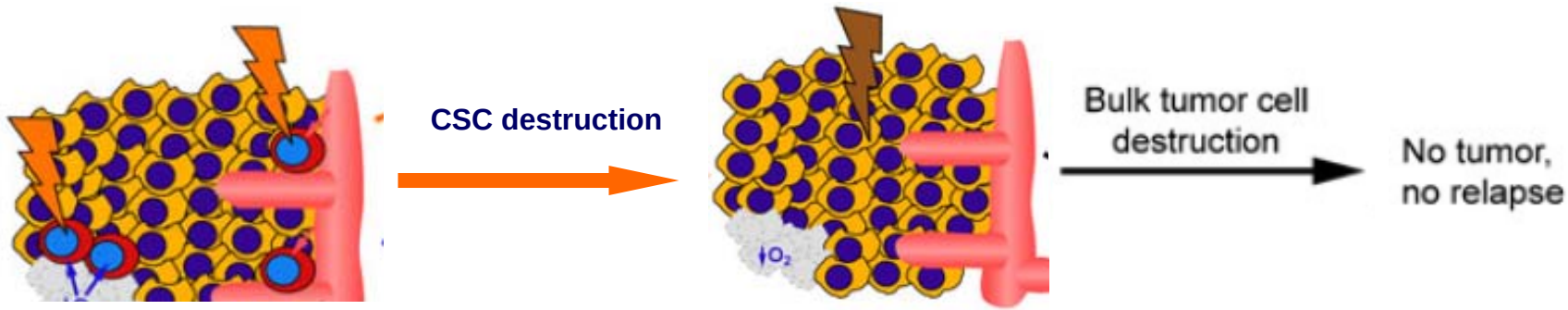
- *signal transduction*
- *morphology*
- *invasiveness*
- *metabolism*
- *cell survival*
- *cell proliferation*



Targeting Cancer Stem Cells

is

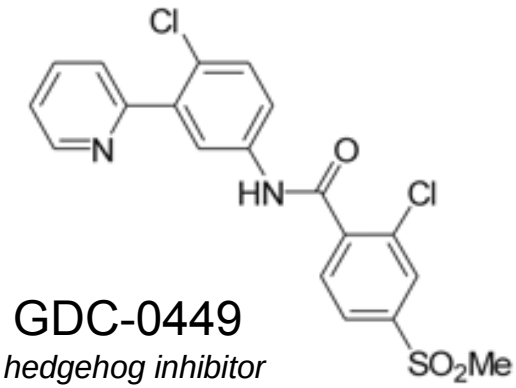
critical to develop successful therapeutics for advanced malignancy



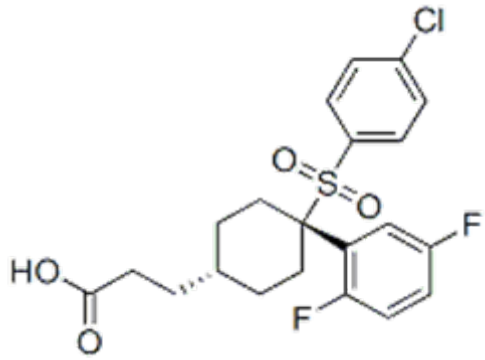
Targeting Cancer Stem Cells

Currently, few anti-cancer stem cell agents are known and new highly active inhibitors are desperately needed.

The first anti-cancer stem cell clinical trials have been launched in the US by Genentech-Roche and Merck



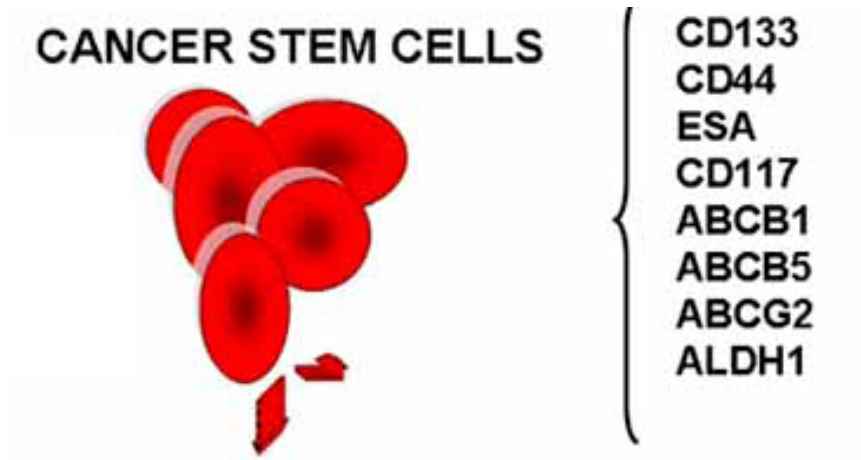
GDC-0449
hedgehog inhibitor



MK-0752
notch inhibitor

Targeting Cancer Stem Cells

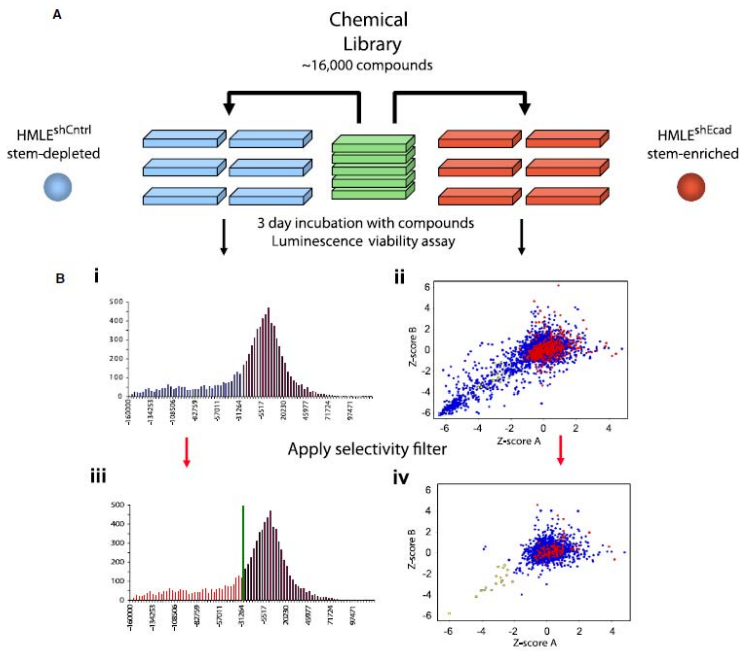
The identification of CSC by the use of specific phenotypic **markers** represents an essential tool for their isolation



Targeting Cancer Stem Cells

The recent advent of CSC *in vitro* model systems…..

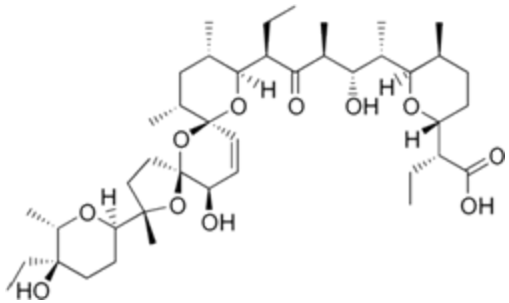
- has spurred interest in screening for CSC targeting small molecules



"…..We describe here an approach to screening for agents with epithelial CSC-specific toxicity…..

One compound, ***salinomycin****, reduces the proportion of CSCs by >100-fold relative to paclitaxel, a commonly used breast cancer chemotherapeutic drug. ….."*

(Cell 2009)



Targeting Cancer Stem Cells

The recent advent of CSC *in vitro* model systems…..

- facilitated a more precise definition of CSC-specific molecular targets

•metabolic enzymes
•cell cycle regulators
•growth factor/receptor
•tyrosine kinase pathways
•cytokine signaling pathways
•actin/intermediate filament cytoskeletal components

Reason of the Action

The incentive for this COST action is that
most EU researchers in this field are currently working independently
with little interdisciplinary activity.

There is a great need for more effective exchange of information,
experience and skills, and to build new collaborative consortia.

Work plan

- Identification of the appropriate **biological targets** to be considered for the creation of small molecule compounds to target CSCs.
- Known types of **inhibitors** will be considered by a biological and chemical point of view.
- Studies of **molecular biology and computational chemistry** will help the design of new compounds
- The **synthesis of quality collections** of compounds will be undertaken with the aim to develop new compounds, new synthetic approaches and convenient preparations.
- New approaches for the **biological evaluation** of the obtained compounds will be studied.

Work plan

Identification of the appropriate biological targets to be considered for the creation of small molecule compounds to target CSCs.

we will discuss the relevance of

tumor mutational status (RAS, PTEN, MYC, telomerase)

metabolic changes (IDH, LDH)

receptor Tk dependent cell signaling (EGF, Axl, PDGF),

known stem cell regulators (Notch, Wnt, Hedgehog)

structural changes

vimentin
ABC transporters,
glycosyltransferase

Work plan

The **Notch pathway** (orange) is activated by binding of transmembrane ligands such as Delta/Deltalike proteins or Jagged to the membrane receptor Notch. This induces cleavage of Notch by γ-secretase, releasing the Notch intracellular domain (NICD), which translocates to the nucleus and activates transcription in complex with cofactors of the CSL family.

Different growth factors (e.g., EGF, FGF, PDGF) can activate receptor tyrosine kinases (RTKs, green) that subsequently promote the activity of phosphatidylinositol-3-kinase (PI3K), Akt and mammalian target of rapamycin (mTOR), among others, leading to enhanced protein translation, cell growth, and proliferation.

Binding of **Hedgehog** (Hh, cyan) ligands to the receptor Patched (PTCH) relieves an inhibition of Smoothened (SMO), triggering a cascade that leads to the translocation of glioma-associated oncogene homologue (Gli) into the nucleus and transcription of target genes.

Work plan

The Wnt pathway (yellow) is initiated by binding of Wnt ligands to a complex of the Frizzled (Fz) and lipoprotein receptor-related protein (LRP) receptors. This sets off a series of signaling steps leading to stabilization of β-catenin, which can proceed to activate gene expression together with the TCF/LEF transcription factors. Endogenous Wnt inhibitors like Dickkopf proteins (DKK) and secreted Frizzled-related proteins (SFRPs) regulate the pathway and could be explored as tools for its pharmacological blockade.

Specific factors in the CSC niches also play critical roles in regulating CSC self-renewal and differentiation. For example, NO produced by endothelial nitric oxide synthase (eNOS, red) can stimulate the production of cyclic guanosine monophosphate (cGMP) and activate protein kinase G (PKG), resulting in enhanced Notch signaling. Low oxygen tension in the hypoxic CSC niche suppresses the activity of prolyl hydroxylase domain-containing proteins (PHDs, blue), leading to stabilization of hypoxia-inducible factors (HIFs) and the transcription of HIF target genes. Notably, the HIF pathway interacts with other pathways, such as Notch, allowing for an intricate oxygen dependent crosstalk between CSC pathways

Organisation: Working Groups

WG-*1*

Biology and Pharmacology

- Identification of the appropriate biological targets
- New approaches for the biological evaluation

WG-*2*

Computational methods and Predictions

- Known types of inhibitors will be considered by a biological and chemical point of view
- Drug design
- Modelling
- Prediction of solubility, biodisponibility

WG-*3*

Synthesis, Medicinal Chemistry, Purification

- Synthesis of quality collection
- Development of new compounds
- New synthetic approaches
- Convenient preparations.