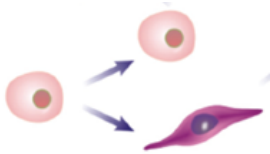
Comenius University, Faculty of Natural Sciences,
Department of Organic Chemistry, Bratislava, Slovakia

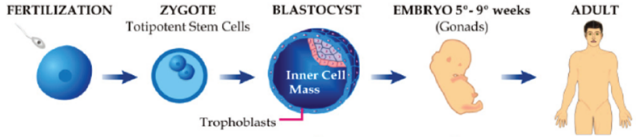
Stem Cells in Medicinal Chemistry



Andrej Boháč

Stem Cells - Definition

All adult cells derive from single egg cell after fertilisation to form multicellular organisms (100 x 10E12) possessing different organs and tissues (200) with different look, properties and functions (brain, skin, gut, liver, lung, muscle, bone, cartilage...etc). **The cells** in adult body **became specialised** (**differentiated**) albeit cells have DNA information about the whole body despite **they differ**. **Some** exception represent stem cells a **small population of cells** present **in each tissue** of the adult body that are not fully specialised.



Stem cells (SCs):
have been **uncovered in 60-ties** (e.g. *Nature* 1963 197 452–4. University of Toronto)
they have **potential to regenerate tissue** over a lifetime (e.g. injury)
they are **highly plastic biological cells** that can form different specialised cells (organs)
they can be isolated a defined by distinctive set of **cell surface markers**
stem cell **function is regulated** in a **feed back mechanism** (activating and deactivating factors)

Mammalian SCs:

- **embryonic stem cells** (inner cell mass of blastocysts) **can differentiate into all** the specialized **cells** (pluripotency)
- **adult stem cells** act as a **repair system for the body**, **replenishing adult tissues**

Stem Cells – Basic Information

Integrity of **adult tissues** is maintained by the **continuous replacement of cells** that regularly differentiate and die. In most adult tissues are **pools of stem cells** able:
a/ **multiply and differentiate** into specialised tissue of origin
b/ maintain a **reserve of undifferentiated cells**. **Adult progenitor cells** are tissues-specific **somatic stem cells**
(e.g. regeneration capacity of liver – rat 2/3 hepatectomy, regeneration within 5-7 days)

STEM CELLS differ from other cells:
a/ they are **undifferentiated** (**unspecialised**)
b/ able to **multiply** for long period **while remaining undifferentiated**,
(small number of SC can create a large population of similar cells)
c/ the are **capable of differentiating** into specialised cells of a particular tissue

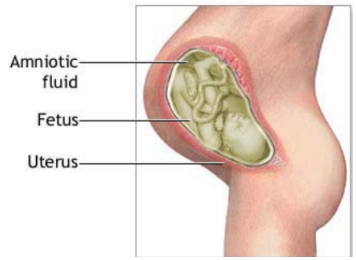
Sources of SC:

- bone marrow
- adipose tissue (lipid cells)
- blood, umbilical cord, amniotic fluid ... etc.

Medical therapies e.g.: **bone marrow transplantation (leukemia)**, other aplications possible in regenerative medicine

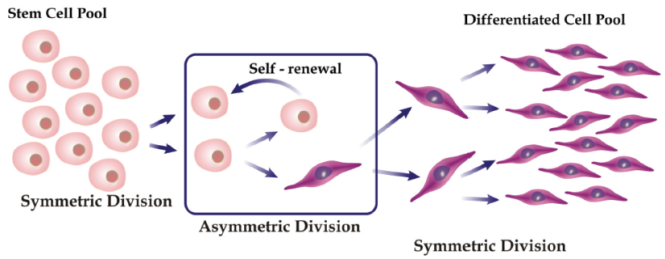
Somatic Stem Cells

Stem cells are also found **in amniotic fluid** (the nourishing and protecting liquid of a pregnant woman). These stem cells **are very active**, expand extensively without feeders and are **not tumorigenic**. Amniotic stem cells **are multipotent** and **can differentiate in cells of adipogenic, osteogenic, myogenic, endothelial, hepatic and also neuronal lines**. **Use of stem cells from amniotic fluid overcomes the ethical objections** to using human embryos as a source of cells. It is possible to collect amniotic stem cells, the first US Amniotic stem cells bank was opened in 2009.



Stem Cells – Self-renewal

STEM CELLS are **only cells with self-renewal capacity that is their fundamental characteristic**. Stem cell **can** be induced to **undergo symmetric division:** providing two daughter cells having the same stem cell potential (e.g. embryonic development or tissue injury), **or asymmetric division:** one remains undifferentiated (**maintaining SC population**) while the daughter cell differentiate into special cell to generate new tissue mass.

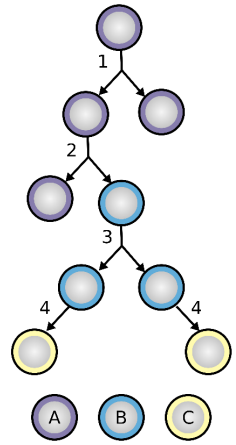


Stem Cells population is maintained!

Stem cell **division and differentiation**.

1: **symmetric stem cell division**
2: **asymmetric stem cell division**
3: **progenitor division**
4: **terminal differentiation**

2: **Asymmetric stem cell division** produces **one stem cell and a progenitor cell with limited self-renewal potential**. **Stem cells can replicate indefinitely, whereas progenitor cells can divide only a limited number of times and is pushed to differentiate into its "target" cell Progenitors** can go through **several rounds of cell division before terminally differentiating into a mature cell.**



A: **stem** cell; B: **progenitor** cell; C: **differentiated** cell

Stem Cells – Potency (Plasticity)

Stem Cells Potency (Plasticity) specifies **the potential of stem cells to differentiate** into different cell types

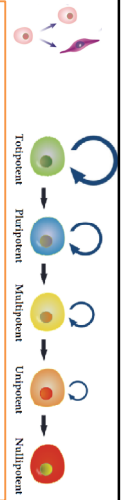
•Cells derived from a single egg cell after fertilisation are **TOTIPOTENT Stem Cells**. They **can differentiate to construct a complete, viable organism**. These cells are **produced from the fusion of an egg and sperm cell**. Cells produced by the first few divisions of the fertilized egg are also totipoten.

•**Four days after** totipotent stem cells divide to form initial cells. After this point they lose their high proliferative potential and **specialise to PLURIPOTENT SC**. They can differentiate into nearly all cells (e.g. excluding a placenta). They can develop into **each of the more than 200 cell types of the adult body**.

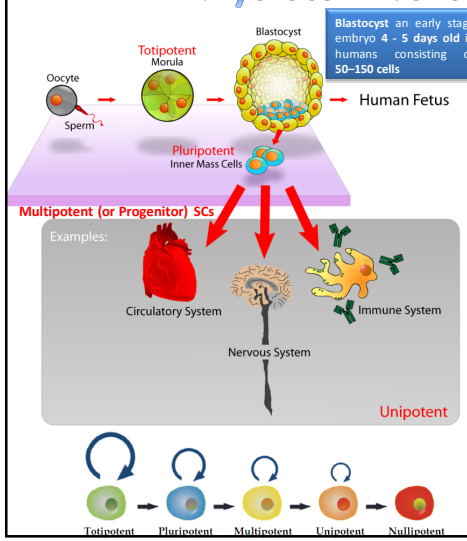
•**Then** pluripotent SC divide and **mature into more specialized stem cells PROGENITOR Cells** called also **MULTIPOTENT SC**. They can generate specific cell groups of **closely related family** e.g. form **ectoderm** (skin, brain, mammary glands) or **mesoderm** (muscle, bone, adipose tissue, cartilage, blood cells, vessels, bone marrow) or **endoderm** (gut, liver, lung).

•Multipotent SC then specialised to **UNIPOTENT SC**. They can produce **only one cell lineage, their own** (e.g., nerve stem cells), but **have the property of self-renewal**, which **distinguishes them from non-stem cells**. Unipotent SC act as cell **reservoirs for different tissues**.

•Unipotent SC originate the **NULLIPOTENT** cells that are **terminally differentiated and lost their self-renewal capabilities**.



Embryo Stem Cells – Potency



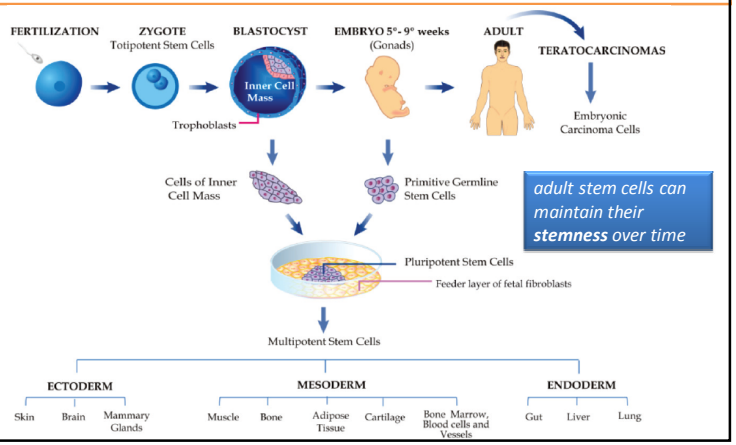
Totipotent SCs, origin from an earlier stage of the embryo development, they are **able to become all tissues in the body**.

Pluripotent SCs, embryonic stem cells from inner cell mass of blastocyst. can develop **more than 200 cell types of the adult body**

Multipotent (or Progenitor) SCs. can generate **closely related family** cells e.g. circulatory system, or nervous system...etc.

Unipotent SCs can produce **only one cell type, their own**, but still **have the property of self-renewal**

The **totipotent SC zygote** is **formed after egg fertilisation** of an ovule by a spermatozoid and **undergoes several mitotic divisions to form blastocyst**, which is divided into extraembryonic (trophoblasts) - cover and embryonic components (inner cell mass, **embryonic stem cells**), **from which all tissues of adult organism originate consits from pluripotent stem cells that can be differentiated into cells of every lineage in human body**. **Stem cells restricted to one lineage** (ectoderm, mesoderm or endoderm) are **called multipotent stem cells**



Embryonic Stem Cells Behaviour

ESC characterisation: a **human embryonic stem cells** are defined by the **expression of several transcription factors** and **cell surface proteins**. The transcription factors **Oct-4**, **Nanog** and **Sox2** form the core regulatory network **that ensures the suppression of genes that lead to differentiation** and the **maintenance of pluripotency**. The **cell surface antigens** most commonly used **to identify hESC** are the **glycolipids** **stage specific embryonic antigen**.

ESC exploitation: because of **embryonic stem cells abilities of unlimited expansion and pluripotency**, they remain a theoretically **potential source for regenerative medicine and tissue replacement after injury or disease**. Many nations currently have **moratoria on ES cell research**.

ECS properties: Embryonic stem cells **will rapidly differentiate without optimal *in vitro* culture conditions** or genetic manipulation. **Pluripotent embryonic stem cells**, **require specific signals for correct differentiation**, if injected directly into another body, ES cells will differentiate into many different types of cells, causing a **tumor teratoma**.

Human embryonic stem cells (hES) are possible **grown** on a feeder layer of mouse embryonic fibroblasts and **require the presence of** basic fibroblast growth factor (**bFGF or FGF-2**).

SOMATIC Stem Cells & Medical Uses

Somatic (from Greek "of the body") stem cells can be found in children, as well as adults.

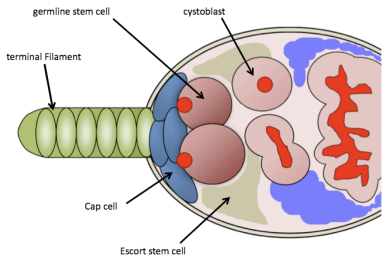
Adult Stem Cells:
Pluripotent adult stem cells are rare but can be found in a number of tissues including **umbilical cord blood**, **dental pulp** (8-10 y/o, can be in future a source for personal banking)

Most adult stem cells are multipotent **(lineage-restricted)** and are generally referred to by their tissue origin (mesenchymal stem cell, adipose-derived stem cell, endothelial stem cell, dental pulp stem cell, etc.).

Stem Cell Niche

Stem cell niche represents **microenvironment in which stem cells are found**, **which interacts with stem cells to regulate stem cell behaviour, various niche factors act on stem cells to alter gene expression**, and **induce their proliferation** or **differentiation** for the development of the foetus. The interplay between stem cells and their niche creates the **dynamic system necessary for sustaining tissues in adults.**

Germ Stem Cells Niche in Drosophila ovaries **consists of** necessary **somatic cells-terminal filament cells, cap cells, escort cells, and other stem cells**. Niche holds on average **2-3 GSCs**, which are directly **attached to somatic cap cells and escort stem cells.**



Two daughter cells in SC Niche:
a/ **one stays** in stem cell niche **retains its self-renewal properties**, receives inhibitory differentiation factors
b/ **the second leaves the niche to proliferate, differentiate** (progeny cell) along a determinate lineage, can receive **differentiation signals** that can force it to become a functional mature cell

Adult Stem Cell - Niches

STEM CELL NICHE define the location of SCs, special microenvironment **where stem cells reside**, **structure and function depending on tissue type**, functions as a physical **anchor for stem cells by generating factors that control SC proliferation and fate**. **Niches are specific for each SC type**, they have also common features .

Inside the niche are **often SCc in the quiescent state**. Niches for quiescent SC are **located in hypoxic tissue regions** (poor in vasculature). E.g. in bone marrow quiescent HSCs are **maintained in osteoblastic niche (hypoxic niche). INTERGRINES** (type of collagen I-V), **CADHERINES**, **BETA-CATENINE** play important role in **SCs microenvironment interactions.**

Hematopoietic stem cell niche (**in the bone marrow is formed by cells:** *subendosteal osteoblasts, sinusoidal endothelial cells and bone marrow stromal cells which includes a mix of fibroblastoid, monocytic and adipocytic cells.*)

Hair follicle stem cell niche (*to host the skin stem cells*)

Cardiovascular stem cell niche (*can be found within the right ventricular free wall, atria of the heart*)

Intestinal stem cell niche etc...

Stem Cells - Niche

Within the human body, **stem cell niches maintain adult stem cells in a quiescent state**, but **after tissue injury**, the surrounding micro-environment actively **signals to stem cells** to either **promote self renewal or differentiation to form new tissues**. Several **factors** are important **to regulate stem cell** characteristics within the niche: **cell-cell interactions between stem cells**, as well as **interactions between stem cells and neighbouring differentiated cells**, interactions between **stem cells and adhesion molecules**, **extracellular matrix components**, the **oxygen tension, growth factors, cytokines**, and physiochemical nature of the environment including the **pH, ionic strength** (e.g. **Ca2+ concentration**) and **metabolites**, like **ATP**, are **also important**. Stem cells remain undifferentiated due to environmental cues in their particular niche. **Stem cells differentiate when they leave that niche or no longer receive those signals.**

Scientists are trying to replicate the *in vivo* niche conditions in vitro. This is because **for regenerative therapies**, cell proliferation and differentiation in flasks. **Human embryonic stem cells** are **often grown in fibroblastic growth factor-2 containing fetal bovine serum** supplemented media. **Adult stem cells remain in an undifferentiated state throughout adult life.** However, when they are **cultured in vitro, they often undergo an 'aging' process** in which their morphology is changed and their **proliferative capacity is decreased**.

Germ Stem Cell - Niche

Molecular Mechanisms of GSC maintenance and activity

Local signals
The Bone Morphogenetic Protein (**BMP**) ligands Decapentaplegic (**Dpp**) and Glass-bottom-boat (**Gbb**) ligand are directly signalled to the GSCs, and **are essential for GSC maintenance and self-renewal**. **BMP signalling** in the niche functions to directly **repress expression** of *Bag-of-marbles* (***Bam***) in GSCs, which is **up-regulated in developing cystoblast cells**. **Loss of function of *dpp*** in the niche results in de-repression of Bam in GSCs, **resulting in rapid differentiation of the GSCs.** Along with BMP signalling, **cap cells also signal other molecules** to GSCs: Yb and Piwi.

Physical attachment
The GSCs are physically **attached to the cap cells** by Drosophila **E-cadherin** (DE-cadherin) adherents junctions and **if this physical attachment is lost GSCs will differentiate and lose their identity as a stem cell**.

Systemic signals regulating GSCs
Both **diet and insulin-like signalling directly control GSC proliferation** in *Drosophila melanogaster*. **Increasing** levels of **insulin-like peptide** (**DILP**) through diet results in **increased GSC proliferation**. **DILPs regulate also cap cell quantities** and regulate the physical attachment of GSCs to cap cells.

Germ Stem Cell - Niche

Molecular Mechanisms of GSC maintenance and activity:

Renewal mechanisms
There are **two mechanisms for stem cell renewal**: **symmetrical GSC division** or **de-differentiation of cystoblasts**. If GSCs are ablated to create an **empty niche and the cap cells are still present** and sending maintenance signals, **differentiated cystoblasts can be recruited to the niche and de-differentiate into functional GSCs**.

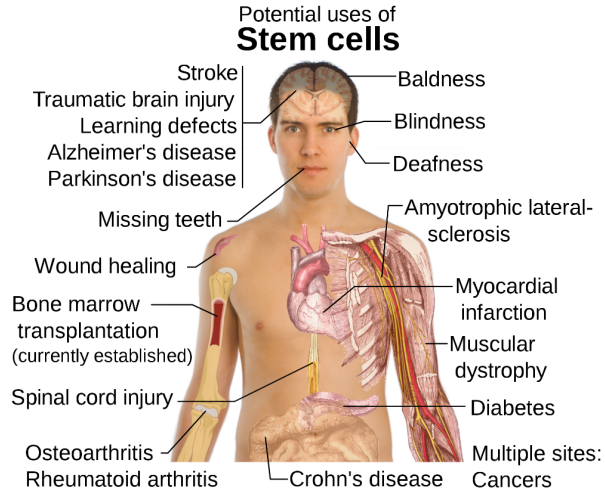
Stem cell aging
As the *Drosophila* female ages, the **stem cell niche undergoes age-dependent loss of GSC presence and activity**. These losses are thought **by degradation of the important signalling factors** (e.g. Dpp, Gbb and Shg signalling) from the niche **that maintains GSCs and their activity**. Progressive **decline in GSC activity** contributes to the observed **reduction in fecundity** at old age, **there is age-dependent reduction of adhesion of GSCs to the cap cells** and there is **accumulation of Reactive Oxygen species (ROS) resulting in cellular damage** which contributes to GSC aging. There is an observed **reduction in the number of cap cells and the physical attachment of GSCs to cap cells** through aging.

Stem Cells Exploitation

Medical Exploitation:

Adult stem cell treatments **have been successfully used for many years to treat leukemia through bone marrow transplants**. The **use of adult stem cells in research and therapy is not as controversial as** the use of **embryonic stem cells**, because the **production** of adult stem cells **does not require the destruction of an embryo**. By autograft, the risk of rejection does not exist. An **extremely rich source for adult mesenchymal stem cells is** the **developing tooth in children**.

Stem Cells - Medical Uses



Induced Pluripotent Stem Cells

Researchers could directly convert mouse fibroblasts (skin cells) into fully functional neurons. This "induced neurons" (iN) cell inspires the researchers to induce other cell types **implies that all cells have potential to be totipotent:** with the proper tools, all cells may form all kinds of tissue.

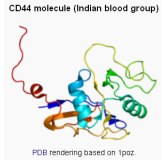
Induced Pluripotent Stem Cells are not adult stem cells, but **rather adult cells** (e.g. **epithelial cells**) **reprogrammed to give rise to pluripotent capabilities**. Using **genetic** reprogramming **with protein transcription factors**, **pluripotent stem cells equivalent to embryonic stem cells have been derived from human adult skin tissue**. Researchers used the **transcription factors Oct3/4, Sox2, c-Myc, and Klf4** in their experiments on cells from human faces. Others used a different set of factors, Oct4, Sox2, **Nanog** and **Lin28** and carried out their experiments using cells from human foreskin.

Stem Cells Treatments

Stem cell therapy has the **potential to dramatically change the treatment of human disease**. A number of adult stem cell therapies already exist, particularly **bone marrow transplants that are used to treat leukaemia**. In the future to treat a wider variety of diseases including **cancer, Parkinson's disease, spinal cord injuries, Amyotrophic lateral sclerosis, multiple sclerosis**, and **muscle damage** etc.
One concern of treatment is the risk that transplanted stem cells could form tumors and become cancerous if cell division continues uncontrollably.
The recent development of **Induced pluripotent stem cell (iPS cells)** has been called a bypass of laws limiting the destruction of human embryos, but it is still not completely clear whether hiPS cells are equivalent to hES cells.

Cancer Stem Cells

CANCER STEM CELLS (CSCs): tumour contains only a **very small subpopulation of cancer stem cells (one CSC in a million tumour cells)** similar with properties to normal SCs. **Transplantation of tumour cells** (expressed certain cell surface markers associated with normal SCc (e.g. the cell surface glycoprotein CD44 involved in cell–cell interactions, cell adhesion...) proved their **malignant potential**, ability to give rise to new tumours when xenografted in immunodeficient mice while other kind of isolated tutor cell could not.

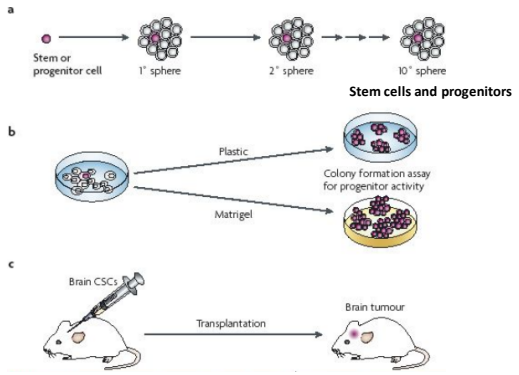


CSCs PROPERTIES:
- **indefinite proliferation and self-renewal** capacity
- form **differentiated cells**
- resistant to **apoptosis** and **drugs (chemotherapy)** (due to active telomerase expression and elevated membrane transport activity)
- induce **angiogenesis**
- **migrate and propagate**

Cancers stem cells (CSCs) **drive the disease**. **CSCs biological properties are often very different than the major tumour cell population. Conventional treatments are often not effective to kill them**. **Recent findings suggest that recurrent tumours are derived from cancer stem cells (CSCs) that function as the "root" of the tumour.**

CSCs have been identified in leukaemia and several solid tumours of the: brain, breast, colon, ovary, pancreas, prostate, melanoma, multiple myeloma.

tumorsphere formation, a characteristic ability of cancer stem cells

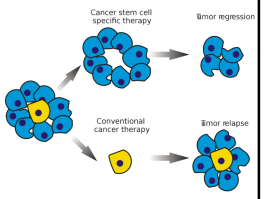


a/ The non-adherent sphere assay predicts that a **cancer stem cell (CSC) can be serially passaged for many cycles and** that **it generates a tumour sphere** resembling the primary sphere in each case. b/ Tumour cells may be passaged directly on plastic or embedded in Matrigel, a substitute for the basement membrane. Each colony-forming assay represents a read-out for progenitor cell activity. **Stem cells and progenitors cannot be distinguished in these assays**.
c/ The gold-standard for **evaluating the presence of CSCs is orthotopic transplantation of sorted human subpopulations** into an immunocompromised mouse.

Cancer Stem Cells

Cancer stem cells (CSCs) are cancer cells (**found within tumors** or hematological cancers) that possess **the ability to give rise to all cell types found in a particular cancer sample. CSCs are** therefore **tumorigenic** (tumour-forming) in contrast to other non-tumorigenic cancer cells. **CSCs may generate tumors through** the stem cell processes of **self-renewal and differentiation into multiple cell types**. Such cells are proposed to **persist in tumours as a distinct population and cause relapse and metastasis** by giving rise to new tumours. Therefore, **development of specific therapies targeted at CSCs holds hope for improvement of survival** and quality of life **of cancer patients**.

The theory suggests that **conventional chemotherapies kill differentiated or differentiating cells**, **which form the bulk of the tumour** but are unable to generate new cells. **The more dangerous population of CSCs,** which is tumorigenic, **could remain untouched and cause a relapse of the disease.**



Stem cell specific and conventional cancer therapies

Cancer Stem Cells Evidence

The first conclusive evidence for CSCs was published in 1997 a subpopulation of leukaemic cells that express a specific surface marker CD34, but lacks the CD38 marker. In cancer research experiments, **tumor cells are sometimes injected into an experimental animal**. Efficient tumor formation **requires thousands or tens of thousands (1 000 – 100 000) of cells to be introduced** (i.e. the tumor cells lose their viability during transfer, or the critical importance of the microenvironment) but **only a small fraction of the injected cells, the CSCs, have the potential to generate a tumor** (e.g. In human acute myeloid leukemia **1 in 10,000**).

Further evidence: **tumors** are very heterogeneous and **contain multiple cell types** native to the host organ, **heterogeneity is commonly retained by tumor metastases**. This implies that **the cell that produced them had the capacity to generate multiple cell types (possesses multidifferentiative potential, a classical hallmark of stem cells).**

http://www.uniprot.org/docs/cdlist.txt

Cancer Stem Cells Importance

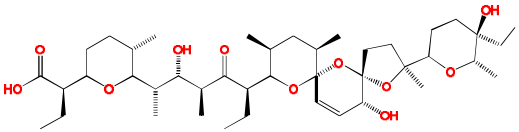
Normal somatic stem cells are naturally **resistant to chemotherapeutic agents**- they have various pumps (such as MDR) that pump out drugs, DNA repair proteins and they also have a **slow rate of cell turnover** (chemotherapeutic agents naturally target rapidly replicating cells). **CSCs that have mutated** from normal stem cells **may also express proteins that would increase their resistance** towards chemotherapeutic agents. These **surviving CSCs then repopulate the tumor, causing relapse. By selectively targeting CSCs**, it would be possible to **treat** patients with **aggressive tumors**, as well as **preventing the tumor from metastasizing**. As **the tumor size increases**, **it becomes** more and more **difficult to remove the tumor without resistance** and **reappear**. Some treatments with chemotherapy, such as paclitaxel in ovarian cancer (discovered in late stages) **induce chemoresistance in 55-75% and relapse <2 years**. It potentially does this by destroying only the cancer cells susceptible to the drug and **allowing the cells which are unaffected by paclitaxel to regrow.**

If current treatments of cancer do not properly destroy enough CSCs, the tumor will reappear. If it is possible to **eliminate the cancer stem cell**, then a potential **cure may be achieved if there are no more CSCs to repopulate a cancer**.

Understanding the mechanisms by which **pluripotency, self-renewal, and subsequent differentiation are controlled in embryonic stem cells is crucial to utilizing them therapeutically.**

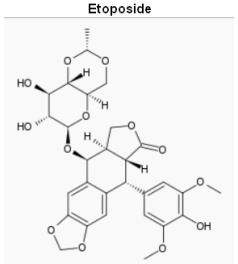
Cancer Stem Cells - Treatment

In **2009** study screened 16,000 different chemical compounds found that only a small subset, including **salinomycin and etoposide**, **targeted cancer stem cells responsible for metastasis and relapse**. **Salinomycin** (from mould *Streptomyces albus*) **selectively reduces** the proportion of **breast CSCs in mice** by more than **100-fold relative to Paclitaxel**.
The **mechanism remains unknown**, it is thought to be due to its action as a **potassium ionophore**. Studies performed **in 2011** showed that **salinomycin could also induce apoptosis of human cancer cells.**



Salinomycin

Etoposide



Cancer Stem Cells

The **design of new drugs for the treatment of CSCs** will likely **require an understanding of the cellular mechanisms that regulate cancer stem cells**.

Bmi-1 **oncogenic protein specifically regulate hematopoietic stem cells (HSCs)**, it is necessary for their efficient **self-renewing** of **HSCs** as well as **neural stem cells**. Seems to play an important role in several types of cancer, such as bladder, skin, prostate, breast, ovarian, colorectal as well as haematological malignancies. (PDB: 2ckI)

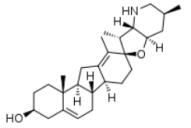
Notch The **Notch pathway** is a highly conserved **cell signalling system control of stem cell proliferation** for several cell types (**hematopoietic, neural** and **mammary stem cells)**. Components of the Notch pathway have been proposed to act as **oncogenes**. **Four different notch receptors** (**NOTCH1-NOTCH4**). The notch receptor is a **single-pass transmembrane receptor and promotes proliferative signalling** during neurogenesis and its activity is inhibited by Numb to promote neural differentiation. **Notch pathway** maintaining SCs **in an undifferentiated state**

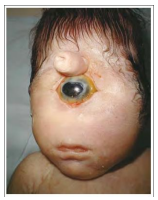
Sonic hedgehog and Wnt developmental **pathways** are also strongly implicated **as stem cell regulators** Both Sonic hedgehog (SHH) and Wnt pathways are commonly **hyperactivated in tumors** and are required **to sustain tumour growth**. Sonic hedgehog blockers are available, such as **cyclopamine**, **DMAPT.** A clinical **trial of DMAPT** started in England.

Finally, the **enzyme telomerase may qualify as a study subject in CSC physiology**. **GRN163L (Imetelstat)** was recently **started in trials to target myeloma stem cells**.

Cyclopamine was named for one-eyed lambs which were born to sheep which grazed on wild corn lily. Eleven-year investigation led to the identification of **cyclopamine as the cause of the birth defect**. Cyclopamine is a naturally occurring steroidal alkaloid. It is a teratogen isolated from the corn lily (*Veratrum californicum*) that **causes usually fatal birth defects**. It can prevent the fetal brain from dividing into two lobes and **cause the development of a single eye** (cyclopia).

Cyclopamine

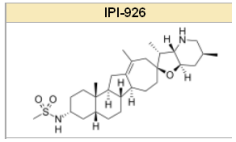




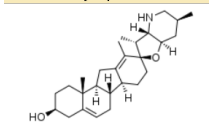
Cyclopamine acts as a primary **inhibitor of the hedgehog signal-transduction pathway** (Hh) **in cells** by **influencing** the balance between the active and inactive forms of the **smoothened** protein. This pathway is used **by cells to help them react to external chemical signals**. The pathway carries out **important functions in embryonic development** and when it goes awry, deformities can occur. However, errant **activation of the pathway can also trigger cancer in adult humans**, leading to basal cell carcinoma, medulloblastoma, rhabdomyosarcoma, and prostate, pancreatic and breast cancers. Cyclopamine is useful in studying the role of Hh in normal development, and as a potential treatment for certain cancers in which Hh is overexpressed.

Cyclopamine and its **derivative** IPI-926 is in clinical trials for the treatment of various types of cancer that result from excessive Hh activity.

IPI-926



Cyclopamine

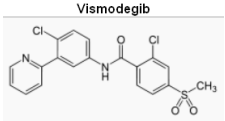


IPI-926 is a semi-synthetic **cyclopamine derivative** that is currently undergoing clinical trials for the treatment of various types of cancer. IPI-926 inhibits the **G protein-coupled receptor smoothened**, **a key component** of the **hedgehog signaling pathway**. **IPI-926** is a member of a new class of anti-cancer compounds known as **Hedgehog Inhibitors (Hhi) (or an agonist of Smo).**

IPI-926 is targeting cancer stem cells. There are currently no drugs in the Hhi class FDA approved, however IPI-926 and GDC-0449 are the 2 leading compounds in the class. **IPI-926, GDC-0449,** and **LDE-225** are the only compounds that **have generic names** passed by the United States Adopted Name (USAN) council (**Infinity** IPI-926/**saridegib**, **Genentech** GDC-0449/**vismodegib**, and **Novartis** LDE-225/**erismodegib**). Although **saridegib** is further along in **pancreatic cancer** (one of the hardest to treat and deadliest cancers) **and chondrosarcoma**, **GDC-0449** for the treatment of adults with **advanced basal cell carcinoma (BCC)** when surgery is no longer an option it appears that Roche/Genentech may be **the first Hhi** to market with GDC-0449.

Other Hhi-class compounds: Exelixis/Bristol-Myers Squibb's **BMS-833923 (XL139)**, Millennium Pharmaceuticals's **TAK-441**, Pfizer's **PF-04449913**.

Vismodegib



Vismodegib (trade name **Erivedge**) is a drug for the treatment of basal-cell carcinoma (BCC). The approval of vismodegib on January 30th, 2012, represents the first Hedgehog signaling pathway targeting agent to gain FDA approval.[1] The drug is also undergoing clinical trials for metastatic colorectal cancer, small-cell lung cancer, advanced stomach cancer, pancreatic cancer, medulloblastoma and chondrosarcoma as of June 2011.[2]

[edit] Indication

Vismodegib is indicated for patients with BCC, which has metastasized to other parts of the body, relapsed after surgery, or cannot be treated with surgery or radiation.[3]

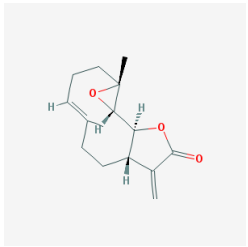
[edit] Mechanism of action

The substance acts as a cyclopamine-competitive antagonist of the smoothened receptor (SMO) which is part of the hedgehog signaling pathway.[2] SMO inhibition causes the transcription factors GLI1 and GLI2 to remain inactive, which prevents the expression of tumor mediating genes within the hedgehog pathway.[4] This pathway is pathogenetically relevant in more than 90% of basal-cell carcinomas.[5]

[edit] See also

- Cyclopamine, a naturally occurring SMO antagonist

DMAPT/parthenolide



Dimethylaminoparthenolide (*DMAPT*) is a water soluble *parthenolide* analog with preclinical activity in hematologic malignancies

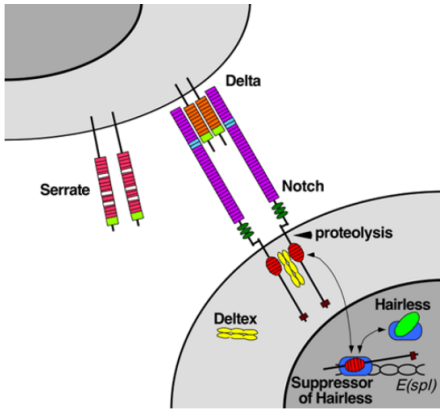
GRN163L (Imetelstat)

the **enzyme telomerase GRN163L (Imetelstat)** was recently **started in trials to target myeloma stem cells**.

Hedgehog signaling pathway

http://en.wikipedia.org/wiki/Hedgehog_signaling_pathway

Notch signalling pathway

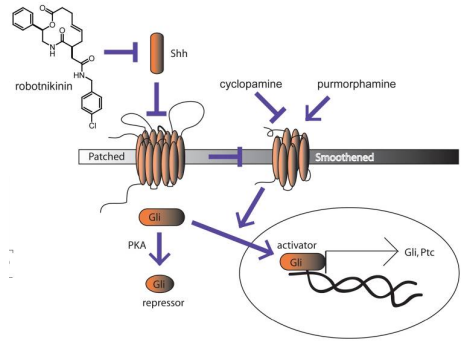


The **Notch receptor sits the cell membrane**, with part of it inside and part outside. **Ligand proteins binding to the extracellular domain induce proteolytic cleavage and release of the intracellular domain**, which **enters the cell nucleus to modify gene expression**.

Sonic hedgehod

Sonic hedgehog homolog (SHH) is the **ligand** of the hedgehog signalling pathway. **It controls cell division of adult stem cells** and has been implicated in development of some cancers. (PDB: 1vhh)

Robotnikinin, a small molecule that **binds the extracellular Sonic hedgehog (Shh) protein** and **blocks Shh signaling** in cell lines

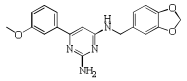


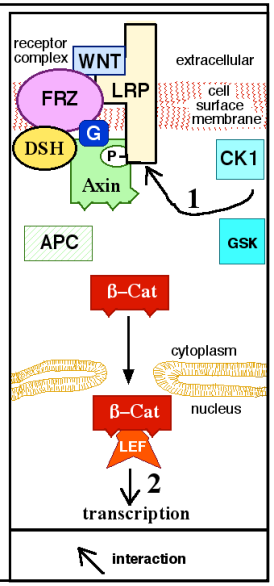
Wnt signalling pathway

The **Wnt** (WINGLESS related protein) a **signalling proteins can act as Stem Cell Growth Factors**, promoting the **maintenance, proliferation and differentiation of SCs**. (**Wnt) pathway** is important for SC **self-renewal**. AXIN is inhibitor of Wnt pathway, inhibits SC proliferation. (**BMP**) **bone morphogenic protein signalling pathway** suppresses Wnt pathway

Axin, GSK and APC form a "destruction complex," and β-Cat is destroyed but **in a case Wnt activates the receptor**. Axin is removed from the "destruction complex." **β-Cat moves into the nucleus**, binds to a transcription factor **TCF3** on DNA, **repressing** nanog, a gene required for **stem cell pluripotency and self-renewal.**

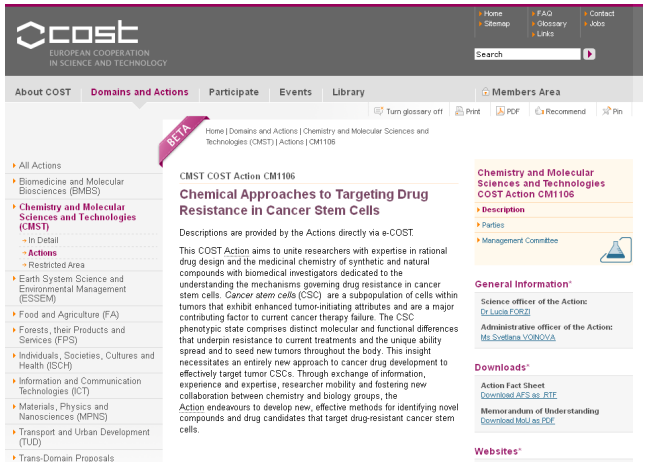
2-amino-4-[3,4-(methylenedioxy)benzyl-amino]-6-(3-methoxyphenyl)**pyrimidine is an agonist of Wnt signaling**





COST Action CM1106 – 2012-2015

Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells



COST Action CM1106 – 2012-2015

Cancer stem cells (CSC) are a **subpopulation of cells within tumours** that **exhibit enhanced tumour-initiating invasiveness, survival, chemotherapy resistance, immune modulation, self-renewal and drug resistance characteristics** and **are a major contributing factor** following standard-of-care radiation and chemotherapeutic treatment **failure**. They have **unique ability spread and to seed new tumors** throughout the body. This insight necessitates an entirely **new approach to cancer drug** development to **effectively target tumour CSCs**. Action endeavours to develop new, effective methods for **identifying novel compounds** and drug candidates **that target drug-resistant cancer stem cells.**
and **tumour-initiating capacity**

Currently, only **few anti-cancer stem cell agents are known**. **CSC *in vitro* model** systems allowed screening for CSC targeting small molecules (Gupta *et al., Cell*, 2009, 4:645-59);

There are **identified some of CSC-specific molecular targets**, including metabolic enzymes, cell cycle regulators, growth factor/receptor tyrosine kinase and cytokine signalling pathways, and actin/intermediate filament cytoskeletal components (Thompsen *et al., Clin Exp Metastasis*, 2011, (2):137-55).

The **first anti-cancer stem cell clinical trials** have **recently been launched in the US** by **Genentech-Roche** (GDC-0449, **hedgehog inhibitor**) and **Merck** (**MK-0752 , notch inhibitor**)

Within the COST Action the relevance of tumour **mutational status targets** (**RAS protein, Phosphatase and tensin homolog PTEN, MYC regulator gen, telomerase**), **metabolic changes targets** (Isocitrate Dehydrogenase **IDH,** Lactate Dehydrogenase **LDH**), **receptor trysonine kinase dependent cell signalling** (**EGF, Axl gene,** platelet-derived growth factor **PDGF**), known **stem cell regulators** (**Notch, Hedgehog**) and **structural changes targets** (**vimentin, ABC transporters, glycosyltransferase**) **that collectively govern self renewal, drug resistance and metastasis will be studied**

Thank you for your attention

CSCs - links

Cancer Stem Cell **Project** - http://www.cancerstemcells.ca/project/index.html
Canada Identification of Genetic Pathways that Regulate CSCs 2006-8
Cancer Stem Cells **Consortium** - http://cancerstemcellnews.blogspot.com/
Cancer Stem Cell News
http://www.cancerstemcellconsortium.ca/

Cancer Stem Cells **Research Program** - http://cancer.stanford.edu/research/stemcell/

Cancer Stem Cell (CSC) Marker
http://www.sinobiological.com/Cancer-Stem-Cell-a-912.html

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Literature:

Identification of Selective Inhibitors of Cancer Stem Cells by High-Throughput Screening - P. B. Gupta, R. Weinberg, E. S. Lander - *Cell* **2009**, *134,* 645 – 659.

Cyclopamine and Hedgehog Signaling: Chemistry,Biology, Medical Perspectives - A. Gianni*set al* - *Angew. Chem. Int. Ed.* **2010**, *49,* 3418–3427.

Chemical Control of Stem Cell Fate and Developmental Potential - C. A. Lyssiotis, P. G. Shultz

CSCs – more info

TGF-beta (transformation growth factor beta) + family members (**BMPs, nodal, activins**) maintenance and differentiation of various adult tissue specific SCs