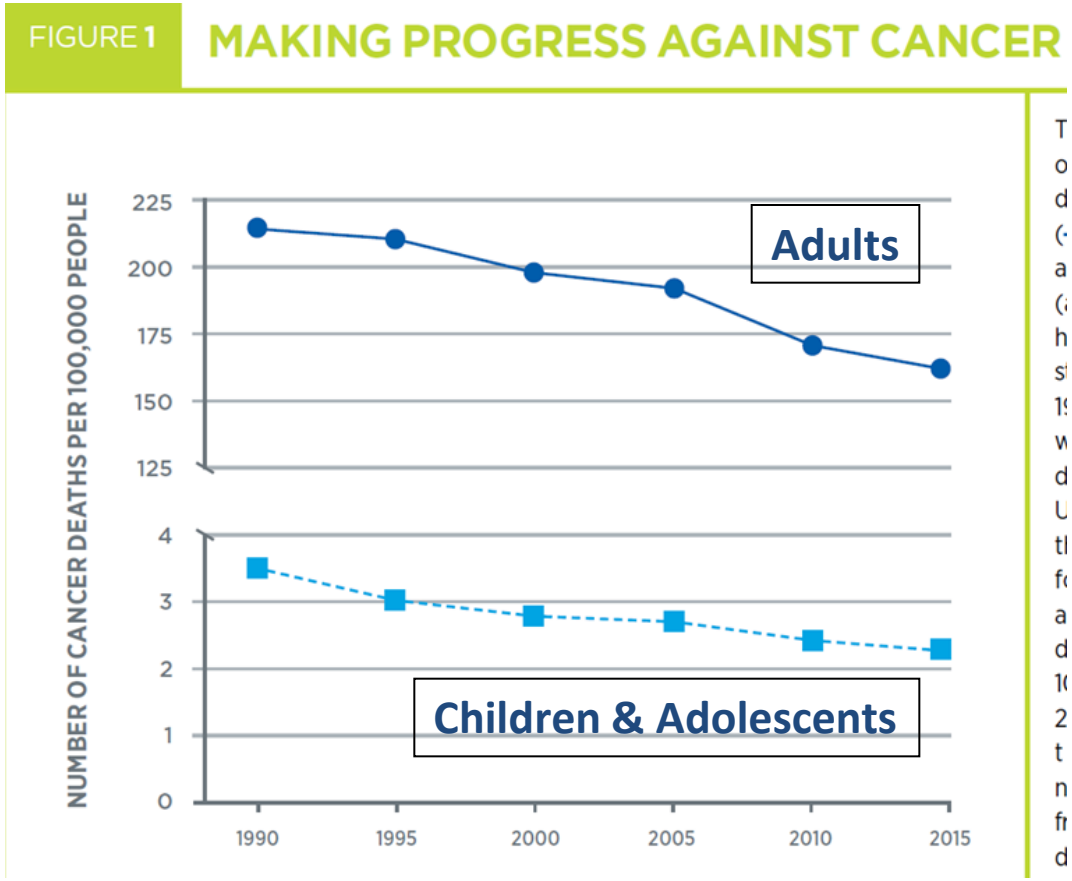
ET LA RECHERCHE?

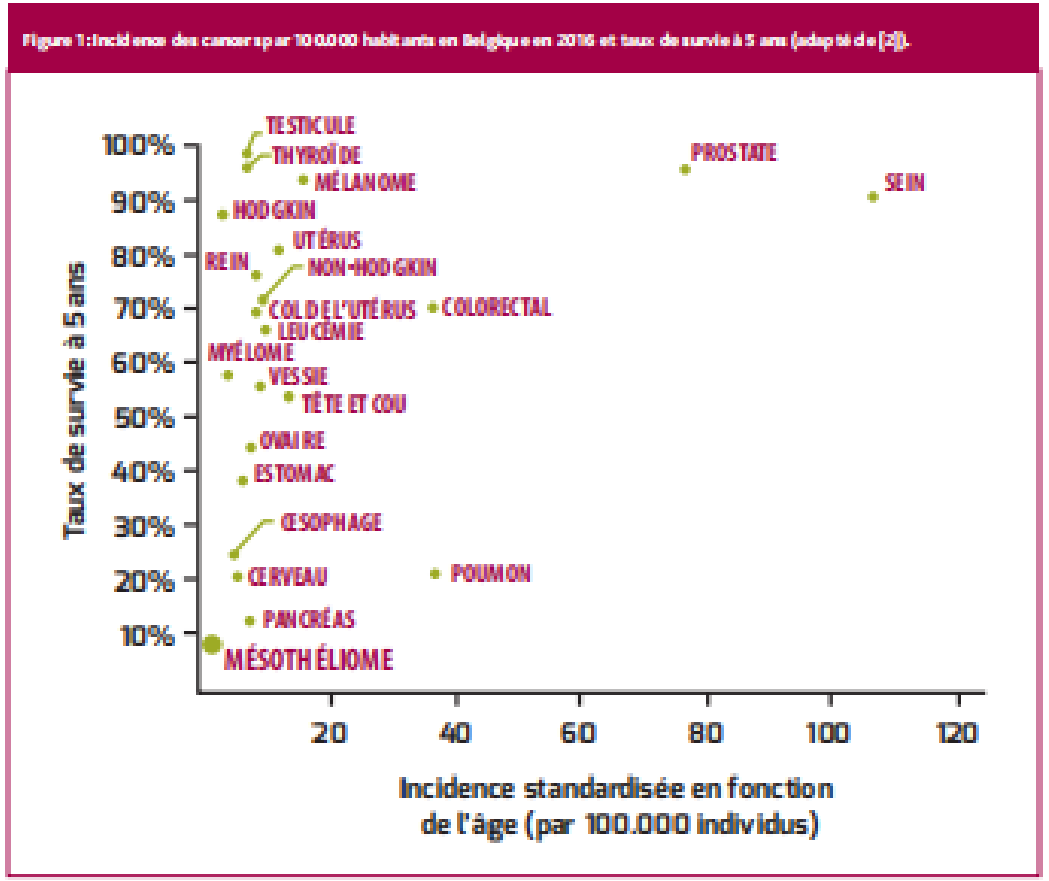
Jacques BONIVER

Au nom des chercheurs de Télévie et de la Fondation Léon Fredericq

Avec des données communiquées par A. Awada, M. Herfs, M.J. Nokin, B. Rogister, C. Sadzot, la Fondation contre le cancer

LES DEFIS





USA

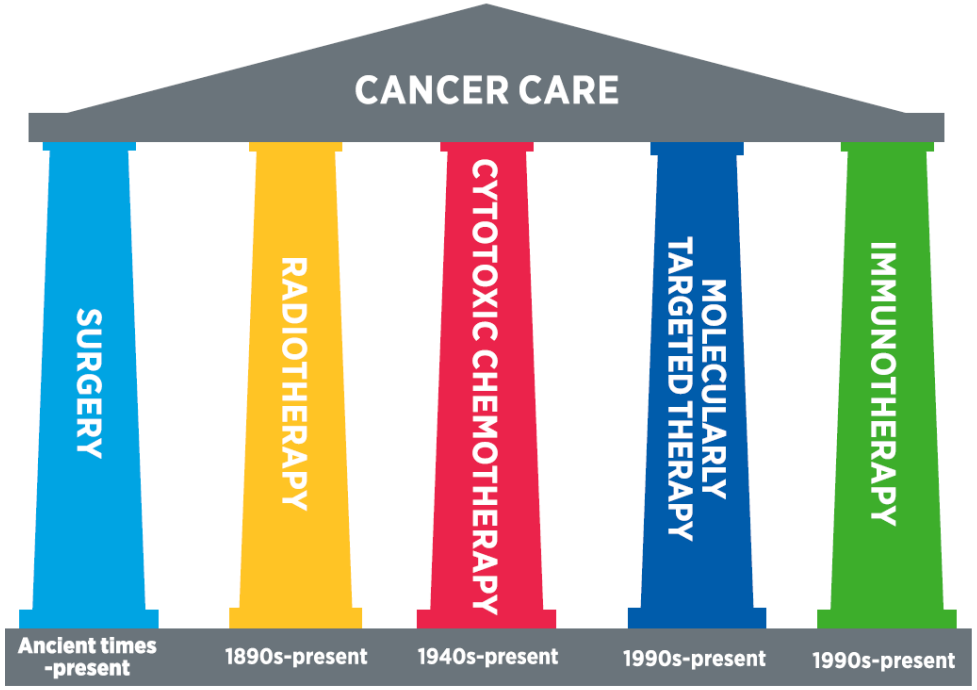
A.AWADA

Cancer patient: from prevention to cure

- Prevention (lifestyle, medicinal)
- Targeted or mass screening
- Diagnosis (conventional or molecular imaging)
- Multidisciplinary therapeutic approach
- Management of acute, subacute and chronic side-effects (all disciplines)
- Management of co-morbidities (all disciplines)
- Psychological support and social reintegration
- Long-term follow-up

A. AWADA

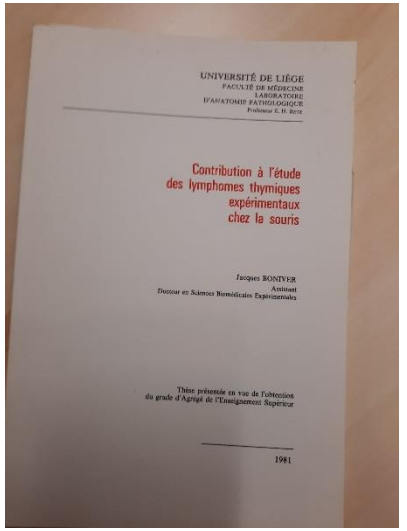
FIGURE 12 THE PILLARS OF CANCER CARE



ET DONC LA RECHERCHE?

THE TARGET CELLS FOR ONCOGENIC TRANSFORMATION

Mon objectif lorsque j'étudiais la pathogénie des lymphomes thymiques induits par irradiation ou par un rétrovirus chez la souris: « what is the target cell? »


UNIVERSITÉ DE LIÈGE
FACULTÉ DE MÉDECINE
LABORATOIRE
D'ANATOMIE PATHOLOGIQUE

Contribution à l'étude
des lymphomes thymiques
expérimentaux
chez la souris

Jacques BONIVER
Assistant
Docteur en Sciences Biomédicales Expérimentales

1981

Cells of origin in cancer

Jane E. Visvader[1,2]

Both solid tumours and leukaemias show considerable histological and functional heterogeneity. It is widely accepted that genetic lesions have a major role in determining tumour phenotype, but evidence is also accumulating that cancers of distinct subtypes within an organ may derive from different 'cells of origin'. These cells acquire the first genetic hit or hits that culminate in the initiation of cancer. The identification of these crucial target cell populations may allow earlier detection of malignancies and better prediction of tumour behaviour, and ultimately may lead to preventive therapies for individuals at high risk of developing cancer.

Nature 2011; 469: 314-322

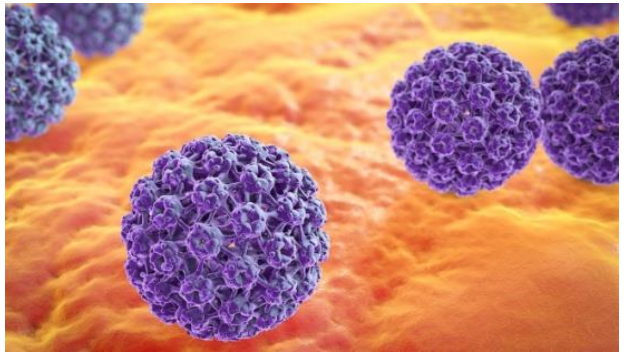
Philippe Delvenne a initié des recherches sur le rôle des HPV dans les cancers de l'utérus avec deux grands axes: le rôle de l'immunité et la caractérisation des cellules cibles.

Laboratoire de Pathologie Expérimentale
Professeur Philippe Delvenne
GIGA-CANCER
Université de Liège, Belgique

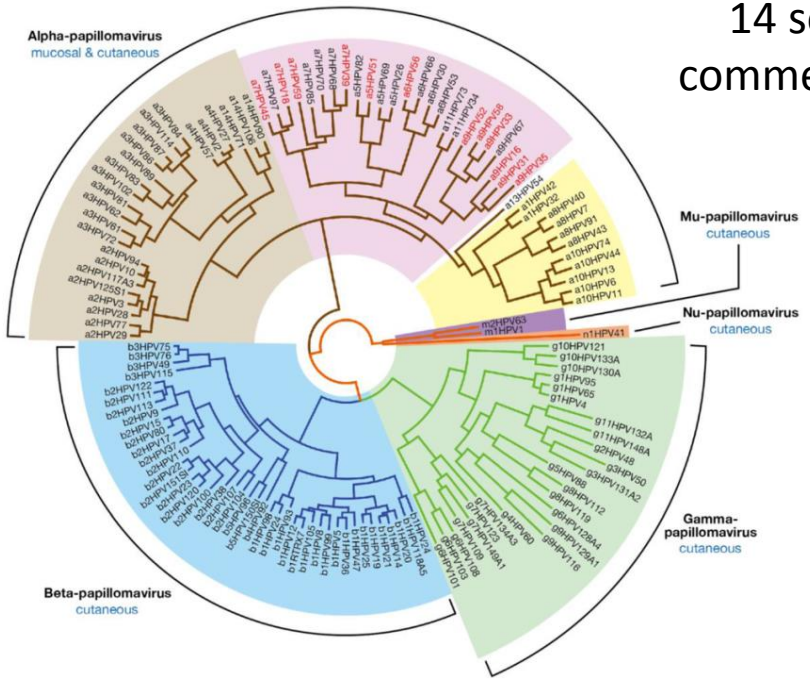
Michael Herfs, PhD
Chercheur Qualifié FNRS

… Et Verviétois d'origine ☺

Les papillomavirus humains (HPV)



>220 génotypes viraux caractérisés



14 sont considérés comme « cancérigène » par l'OMS

Table 1 | **Global estimated number of new cancer cases attributable to HPV in 2012**

Cancer site	New cases (*n*)	Attributable to HPV (*n*)	Attributable fraction (%)*	Attributable by sex (*n*)	
				Men	Women
Cervix uteri	528,000	528,000	100	–	528,000
Anus	40,000	35,000	88	17,000	18,000
Vagina and vulva	49,000	20,000	41	–	20,000
Penis	26,000	13,000	51	13,000	–
Oropharynx	96,000	29,000	31	24,000	6,000
Oral cavity and larynx	358,000	9,000	2.4	7,000	2,000
Total	1,097,000	634,000	58	61,000	574,000

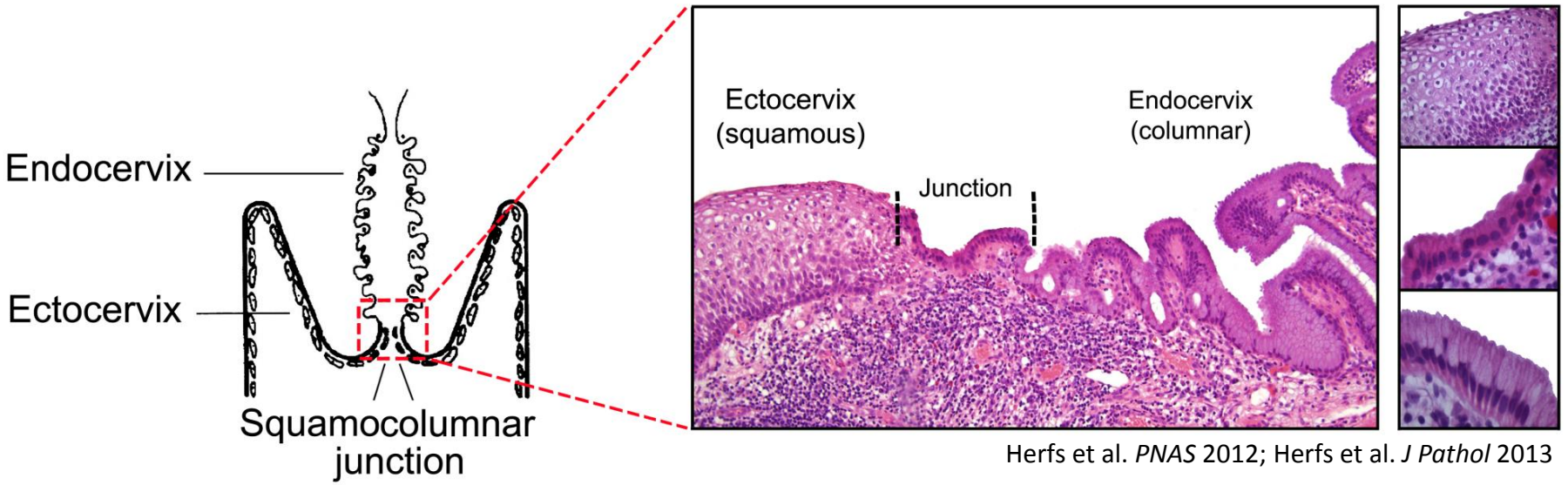
Les infections par HPV sont à l'origine d'environ 5% des cancers diagnostiqués chaque année dans le monde

~80% des cancers HPV-positifs sont diagnostiqués dans le col de l'utérus

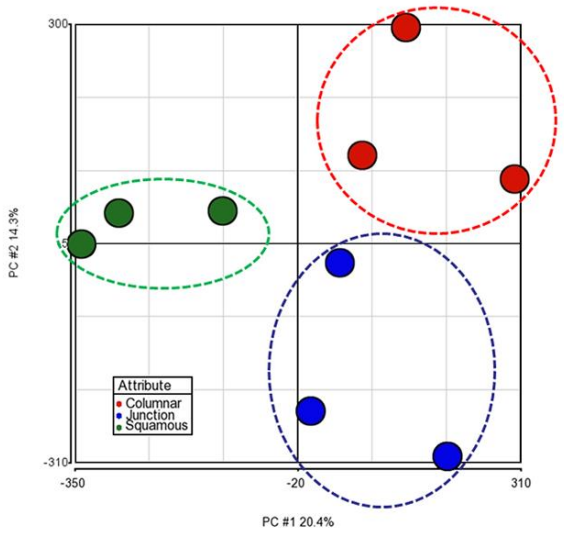
Pourquoi ?

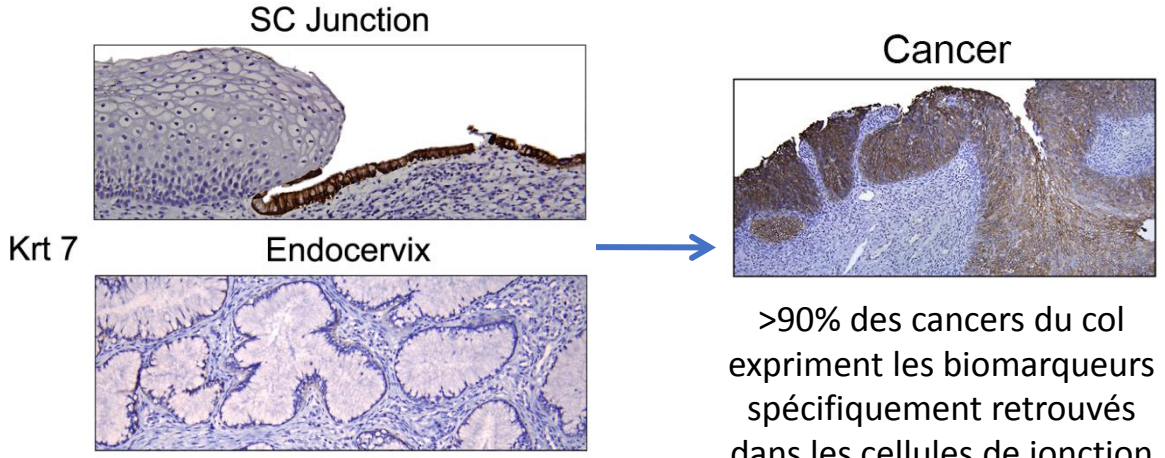
Schiffman et al. *Nat Rev Disease Primers* 2016

Découverte des cellules de jonction (entre la partie interne et externe du col utérin)



Herfs et al. *PNAS* 2012; Herfs et al. *J Pathol* 2013





>90% des cancers du col expriment les biomarqueurs spécifiquement retrouvés dans les cellules de jonction

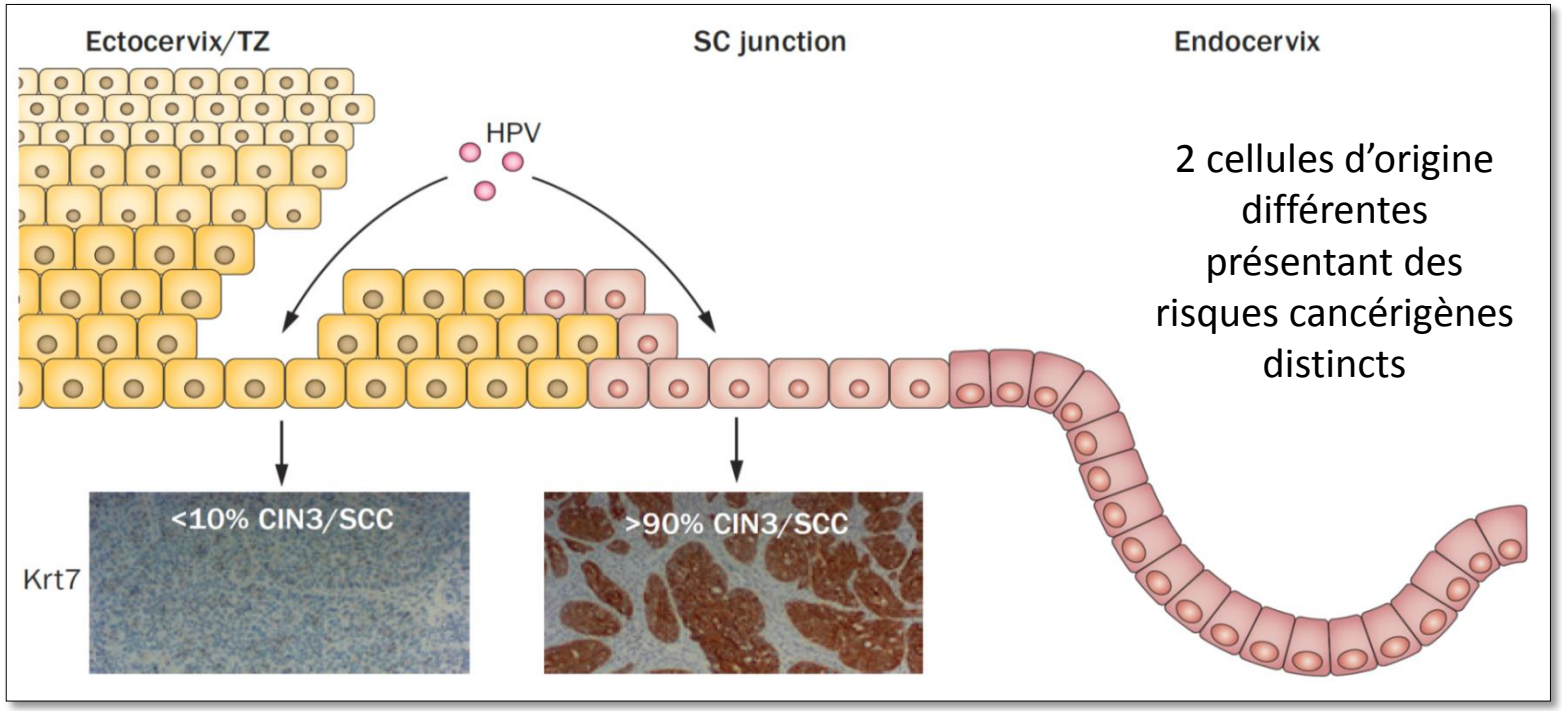
Cellules de jonction = origine de la grande majorité des cancers du col de l'utérus

Implications cliniques de cette découverte

Nouvelle théorie de la cancérisation HPV-dépendante

26 juin 2012

387 citations



→ Les biomarqueurs spécifiques sont couramment utilisés pour mieux « prédire » le risque de développement cancéreux des infections par HPV (médecine personnalisée)

→ Essai clinique analysant l'efficacité « anti-cancéreuse » de la cryoablation prophylactique des cellules de jonction dans les pays ne bénéficiant pas de la vaccination (en cours)

Ces cellules ont un comportement biologique de cellules souches multipotentielles

STEM CELLS

- TOTIPOTENTIAL STEM CELLS: capable to generate a complete embryo (the fecundated egg)
- PLURIPOTENTIAL STEM CELLS: capable to generate cells of different embryonic lineages (the embryonic stem cells and the ipSC)
- MULTIPOTENTIAL STEM CELLS: capable to generate different cell types within a single embryonic lineage (the haematopoïetic stem cells)
- PROGENITOR CELLS: capable to generate cells of a single type (the lymphoid progenitor cells)

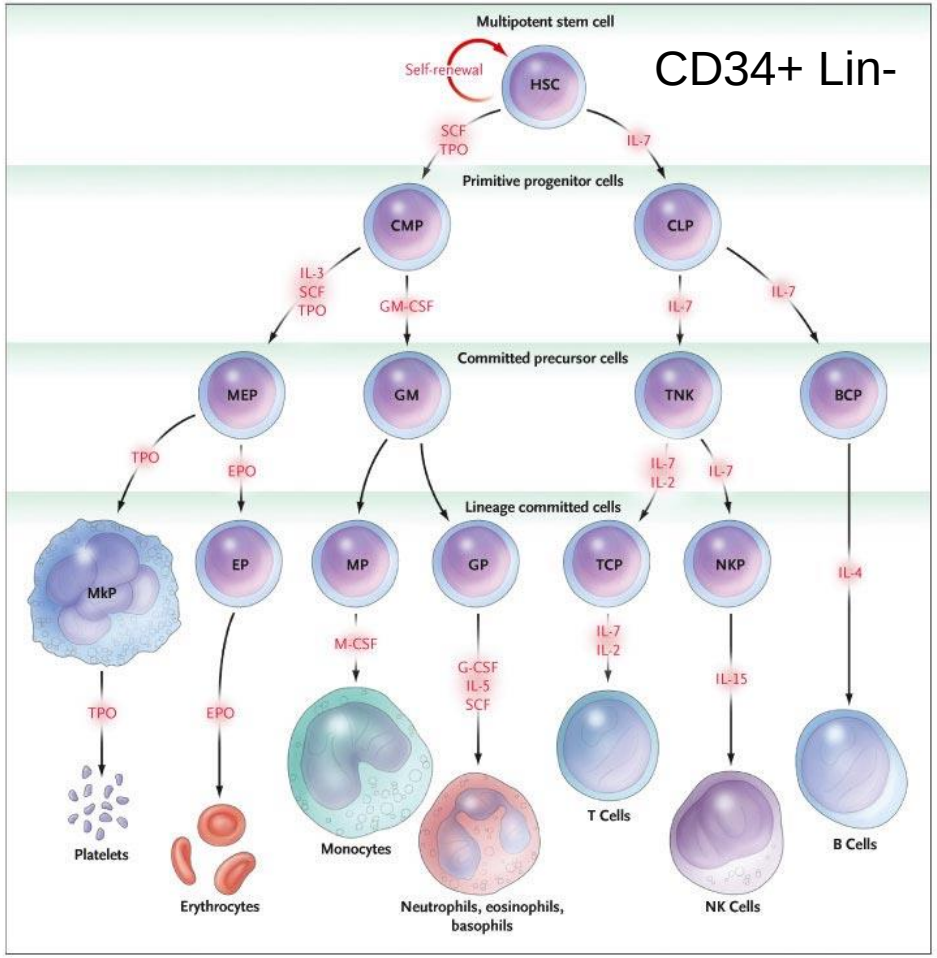
A General Model of Haematopoiesis: the clonal succession model

stem cells

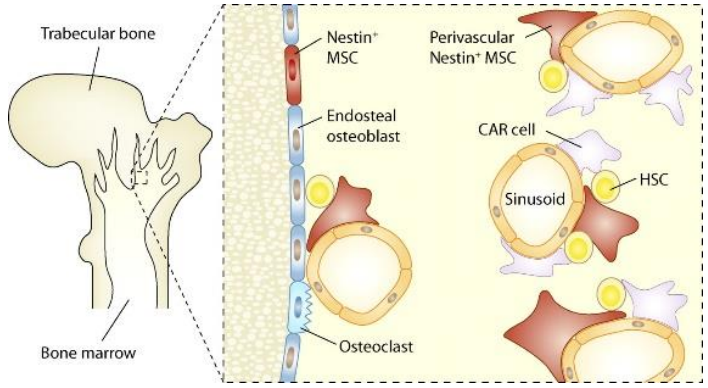
progenitors

differentiated cells

terminally differentiated cells

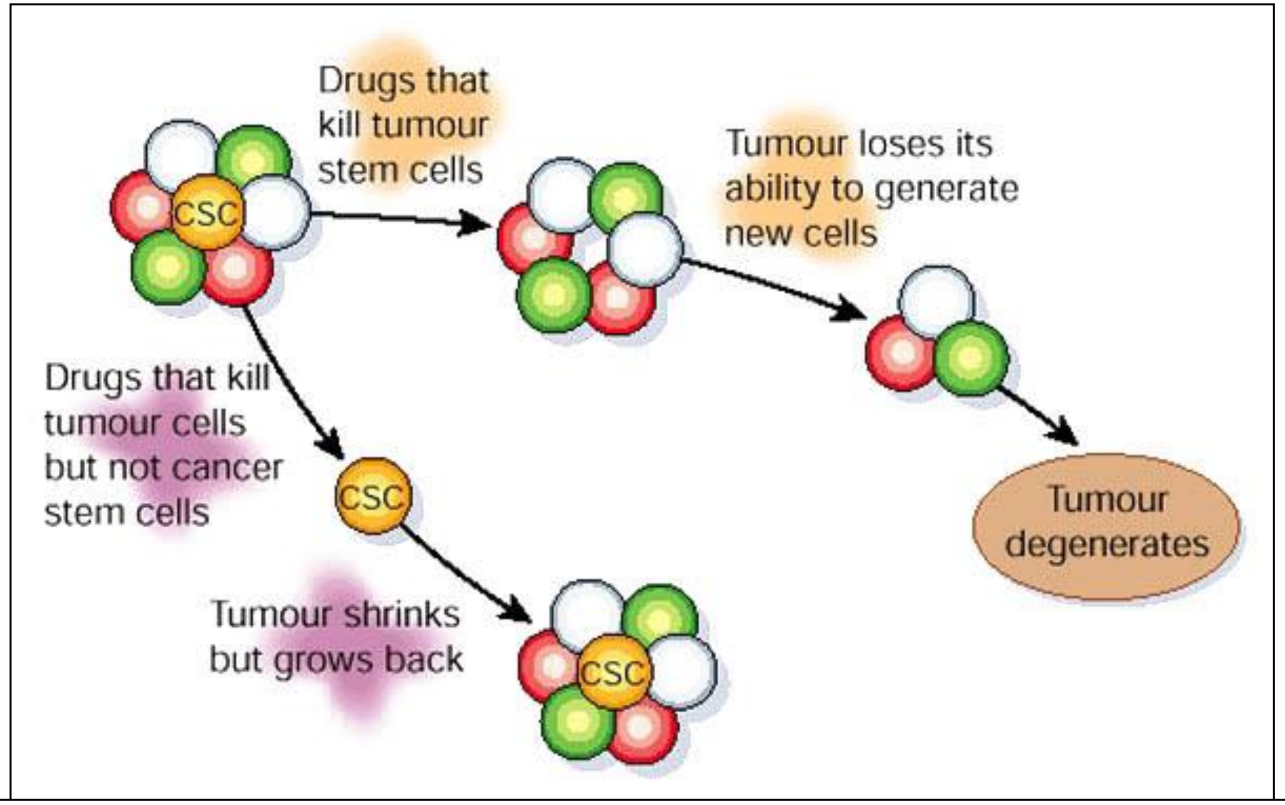


- **Capacity to differentiate in several cell types,**
- **Self renewal ,**
- **Mostly quiescent (G0),**
- **Long term repopulating activity in SCID mice**
- **Interactions with other cells within « niches »,**
- **Specific signaling**
- **Resistance to attacks (hypoxia, radiations, chemicals,..)**



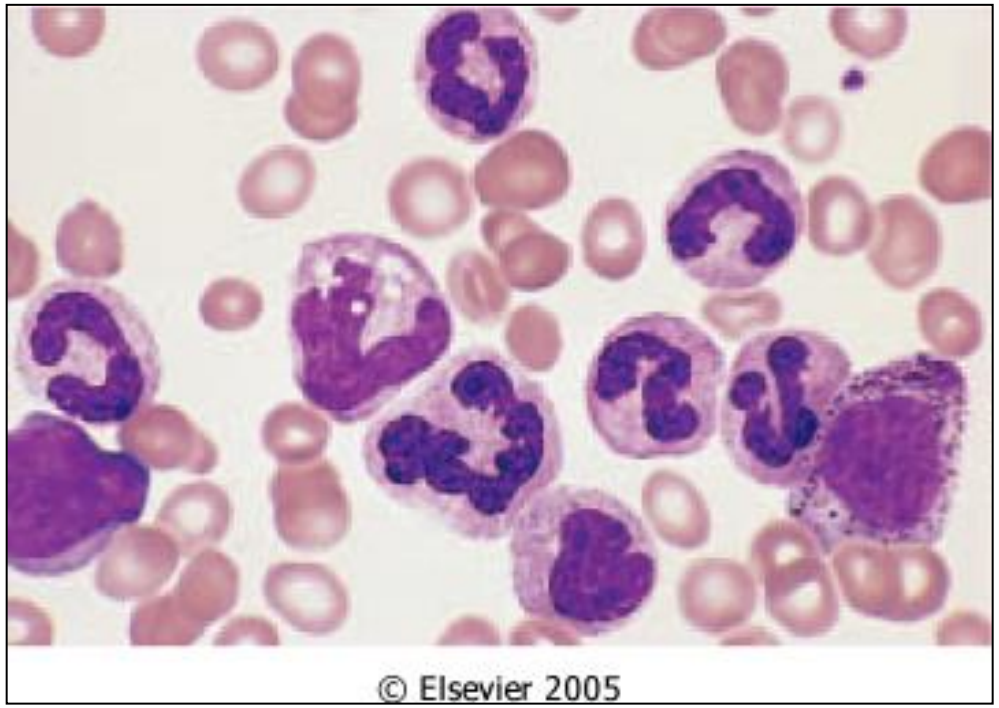
CANCER STEM CELLS AND THERAPY

Are there cancer cells with stem cells properties in a tumor?
What would be the relevance of the existence of cancer stem cells to understand cancer biology and to treat the patients?



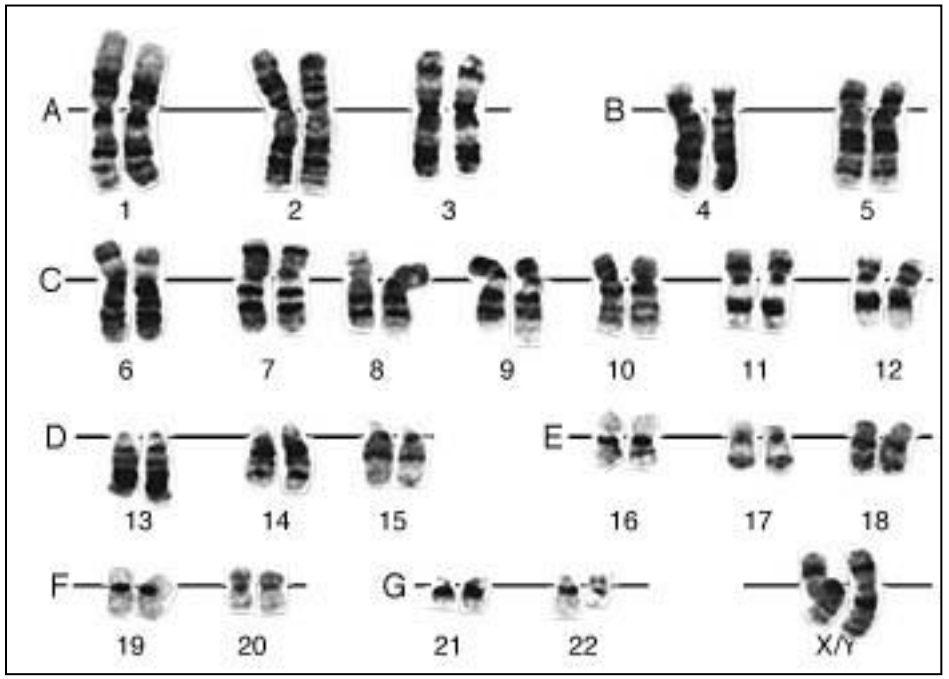
If cancer stem cells are susceptible to therapy, the tumors disappears;
If cancer stem cells are resistant to therapy, even if the bulk of the tumor is sensitive, the tumor shrinks but relapses

The case of Chronic Myelogenous Leukemia



Chronic myelogenous leukemia. Peripheral blood smear shows many mature neutrophils, some metamyelocytes, and a myelocyte. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)

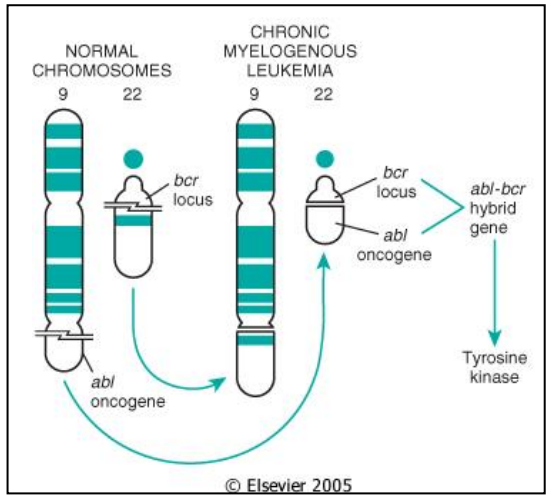
Robbins & Cotran Pathologic Basis of Disease 2005

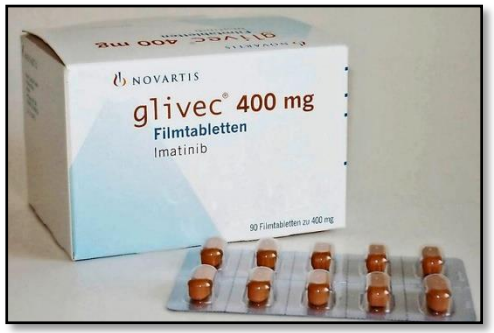


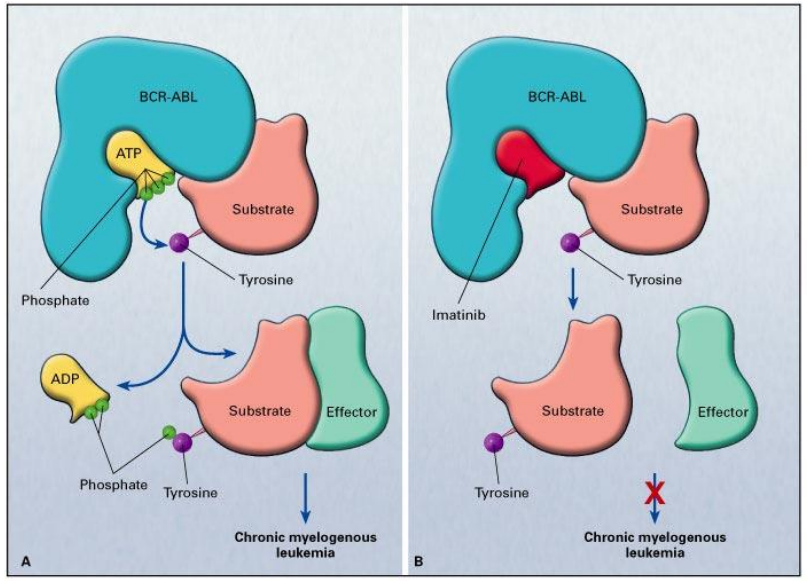
Philadelphia chromosome

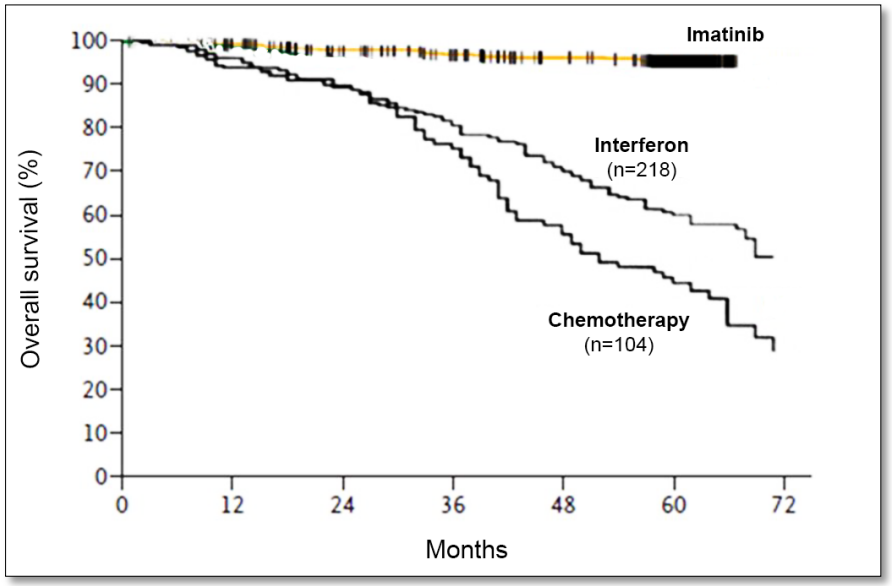
J.D. ROWLEY et al. 1973

Les succès: la leucémie myéloïde chronique





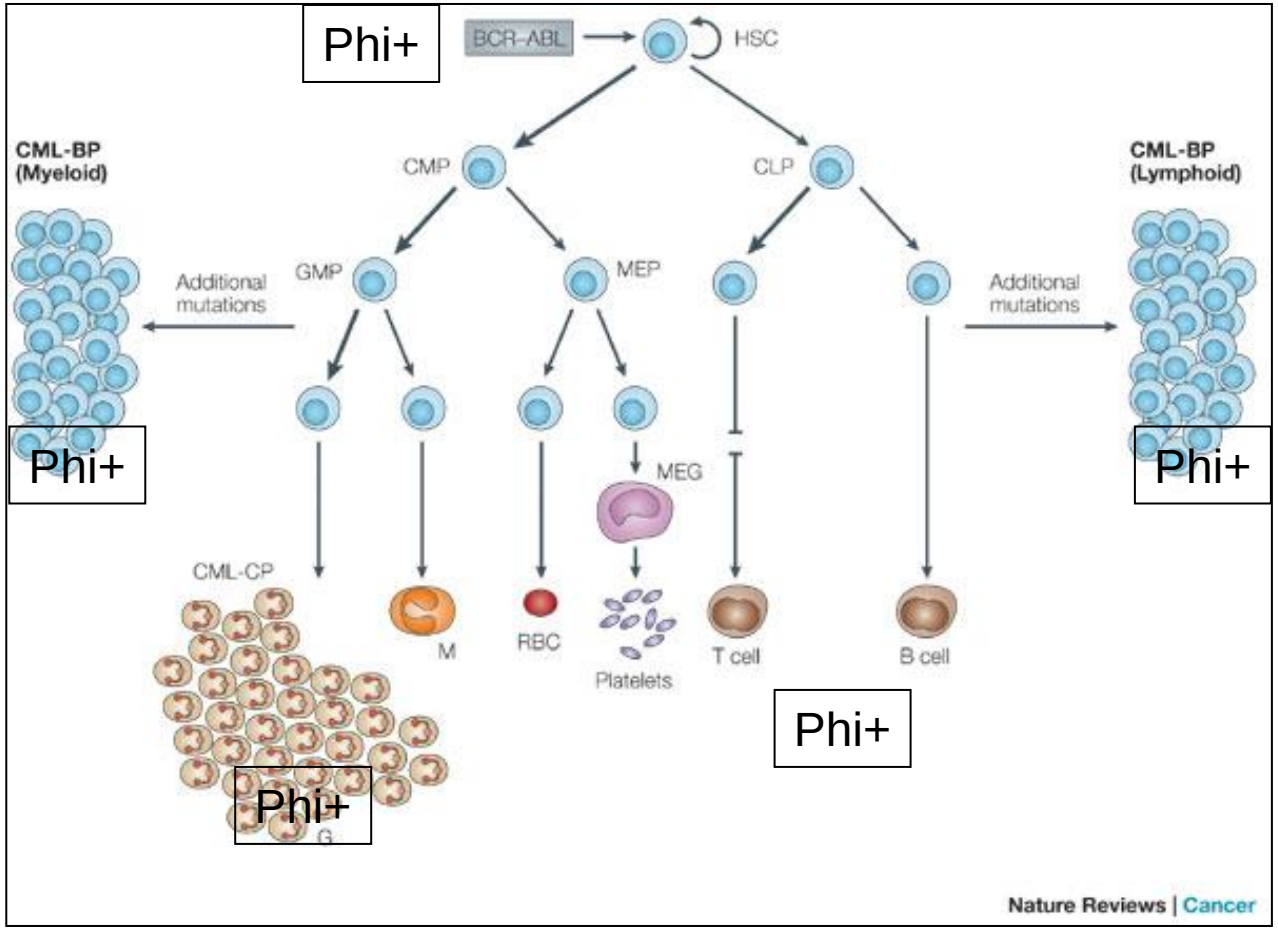


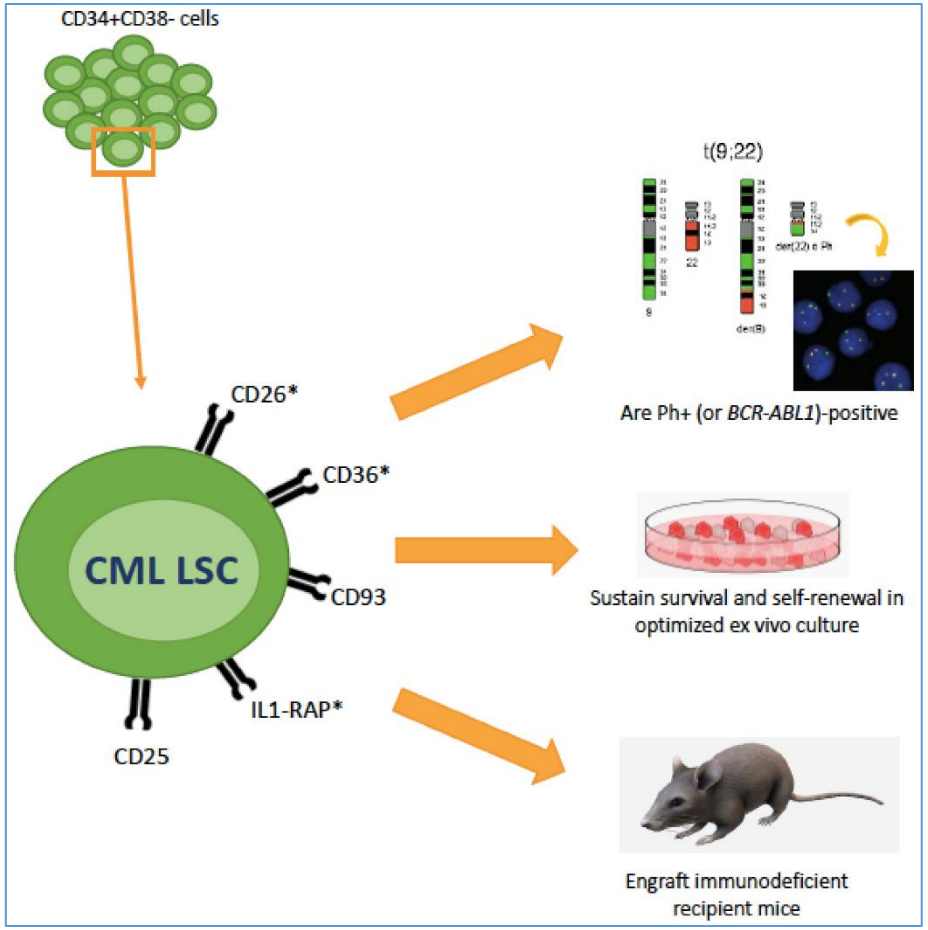


Survie globale: 91%

Drucker et al.
NEJM 2006

LEUKEMIC STEM CELLS





Les « LSC », étant quiescentes, ne sont pas sensibles aux TKI.

Targeting Leukemic Stem Cells in Chronic Myeloid Leukemia: Is It Worth the Effort?
Simona Soverini 1,*, Sara De Santis 1 , Cecilia Monaldi 1 , Samantha Bruno 1 and Manuela Mancini
Int. J. Mol. Sci. **2021**, *22*, 7093

EFFICACITE DES TRAITEMENTS PAR IMATIMIB OU AUTRES TYROSINE KINASE INHIBITEURS

- Espérance de vie quasi égale à celle de la population générale (même âge, pays occidentaux)
- 40 à 60 % des patients atteignent une «deep molecular response »,
  ce qui autorise chez certains patients l'arrêt des traitements par TKI (« treatment free remission »)
- La persistance de cellules porteuses de bcr-abl est souvent due à la persistance de « LCS ».
- Les « LCS », étant quiescentes, ne sont pas sensibles aux TKI.
- Que faire pour éradiquer les « LCS »?

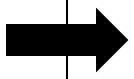
Will We Ever Be Able to Kill CML LSCs?

Targeting Leukemic Stem Cells in Chronic Myeloid Leukemia:
Is It Worth the Effort?
Simona Soverini 1,*, Sara De Santis 1 , Cecilia Monaldi 1 , Samantha Bruno 1 and Manuela Mancini
Int. J. Mol. Sci. **2021**, *22*, 7093

CANCER STEM CELLS

- CANCER STEM CELLS: cancer cells which show similar properties to normal stem cells:

  . phenotype similar to that of normal stem cells,
  - capacity to differentiate into several (cancerous) cell types,
  - self renewal,
  - tumor formation after xenotransplantation in immunodeficient mice
  - quiescence (Go),
  - niches,
  - particular signaling pathways…



the fact that such cells are quiescent with particular signaling pathways might explain that they do not respond to therapies.

Un défi de taille: les glioblastomes

- 600 à 700 nouveaux cas par an en Belgique
- Survie médiane: 15 mois; survie à 2 ans : 10%
- Mortalité: quasi 100%

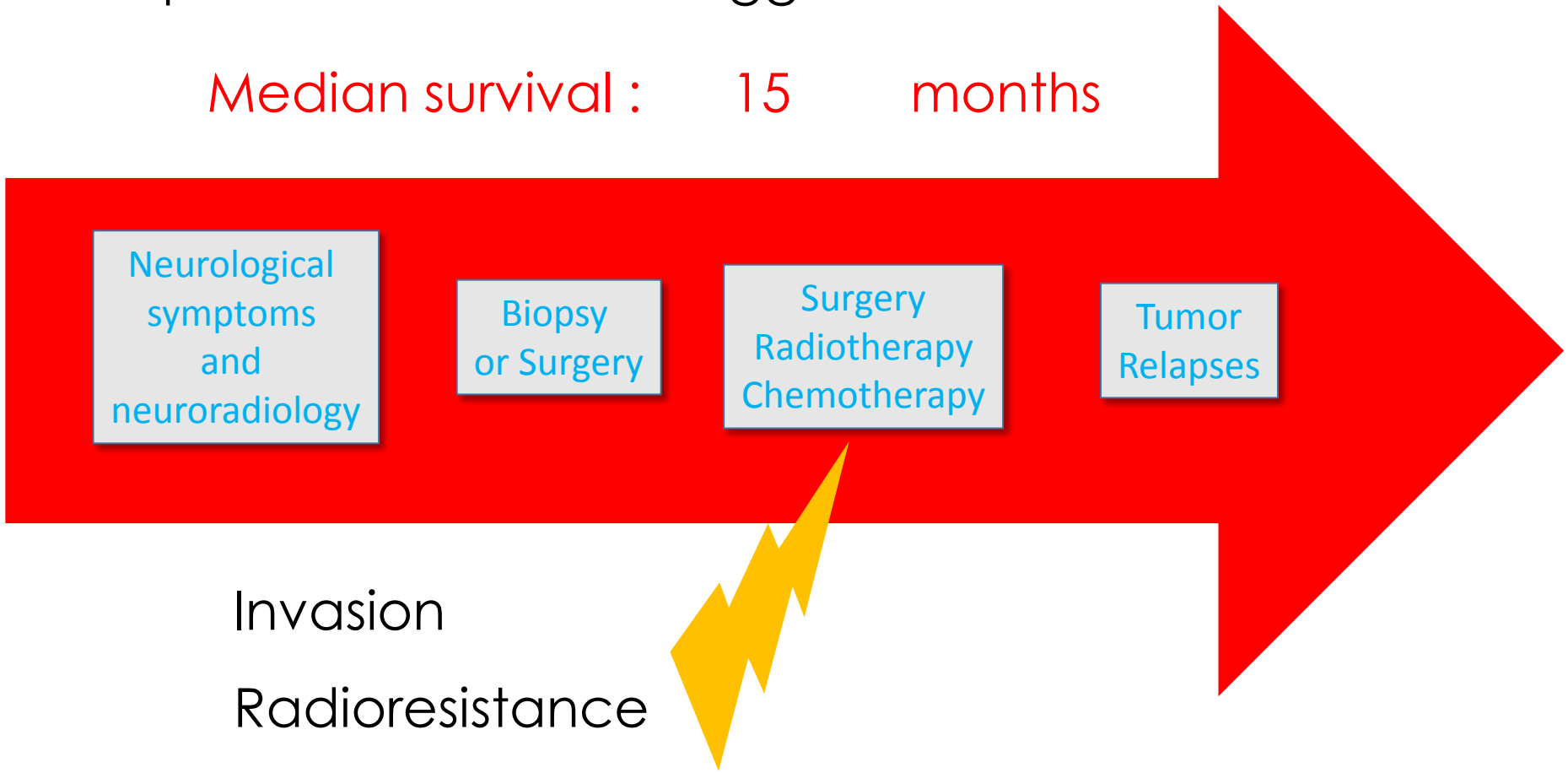
- Traitement : chirurgie extensive + radiothérapie + témozolimide.

- Recherches menées dans le cadre de Télévie : Bernard ROGISTER et al.

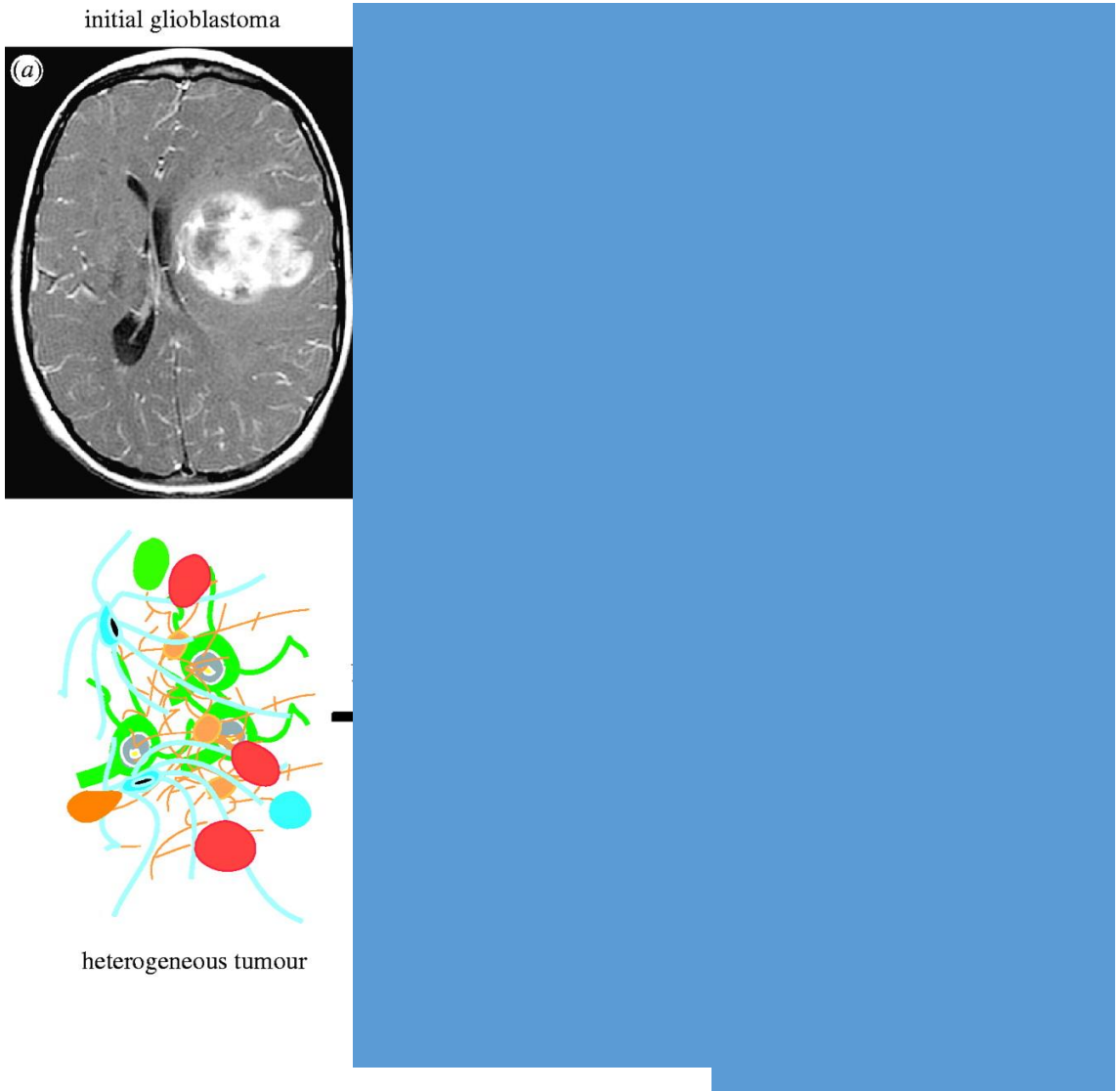
Why studying GBM relapses ?

Most prevalent and most aggressive brain tumor in human

Median survival : 15 months



Recurrence of Glioblastoma

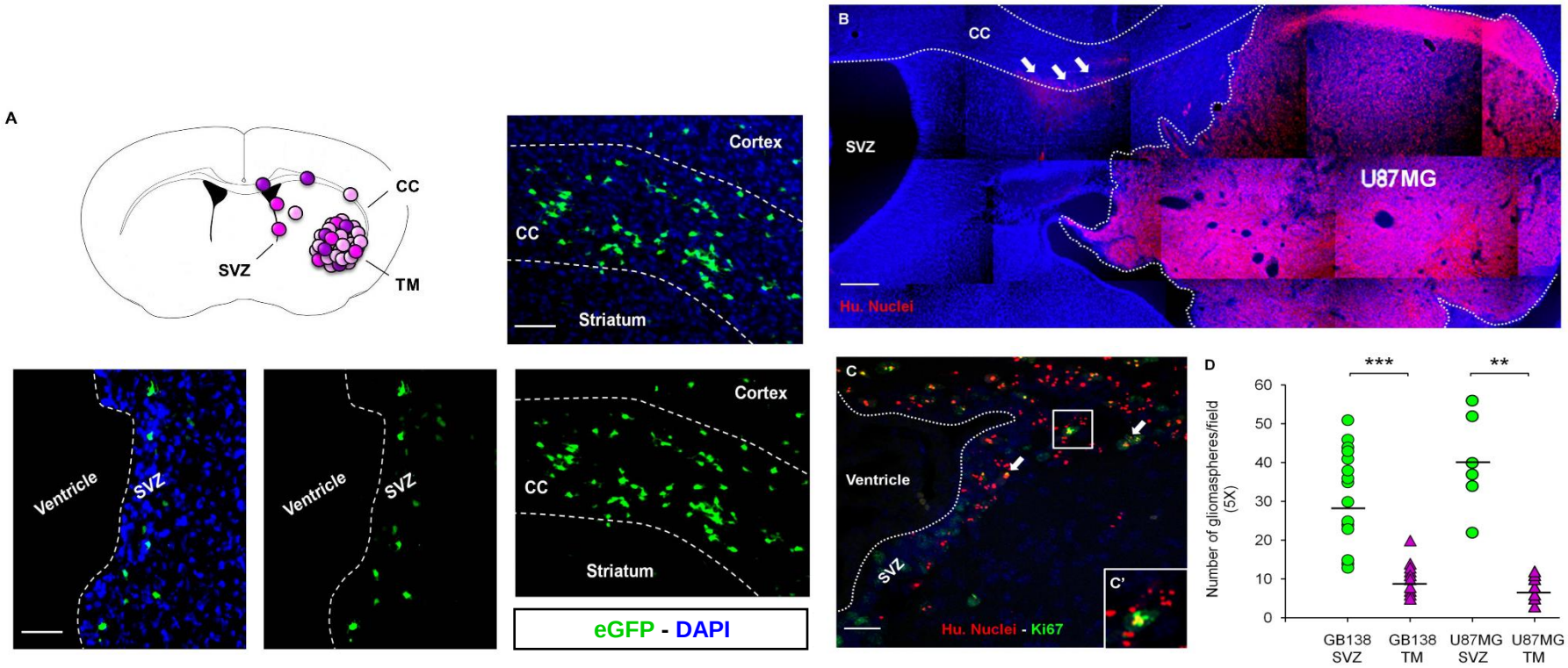


Glioblastoma-Intiating Cells or GICs

- Self-renewal
- Multipotent
- Able to form spheres
- Able to grow a tumor in xenotransplantations
- No specific markers

Phil. Trans. R. Soc. B (2008) 363, 139–152

In vivo model of GBM invasion



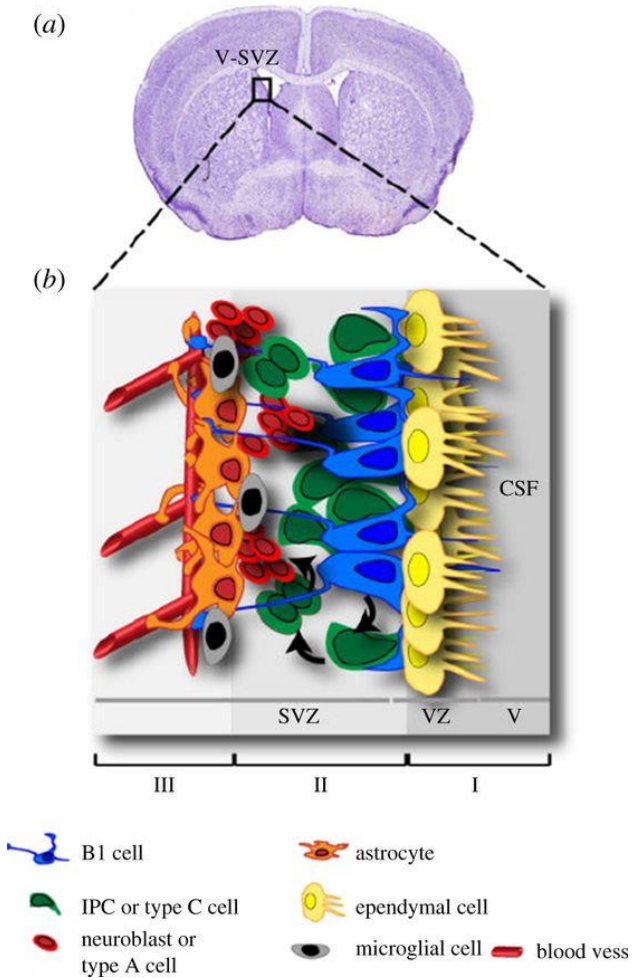
Human GB138 primary cells

Human U87MG cell line

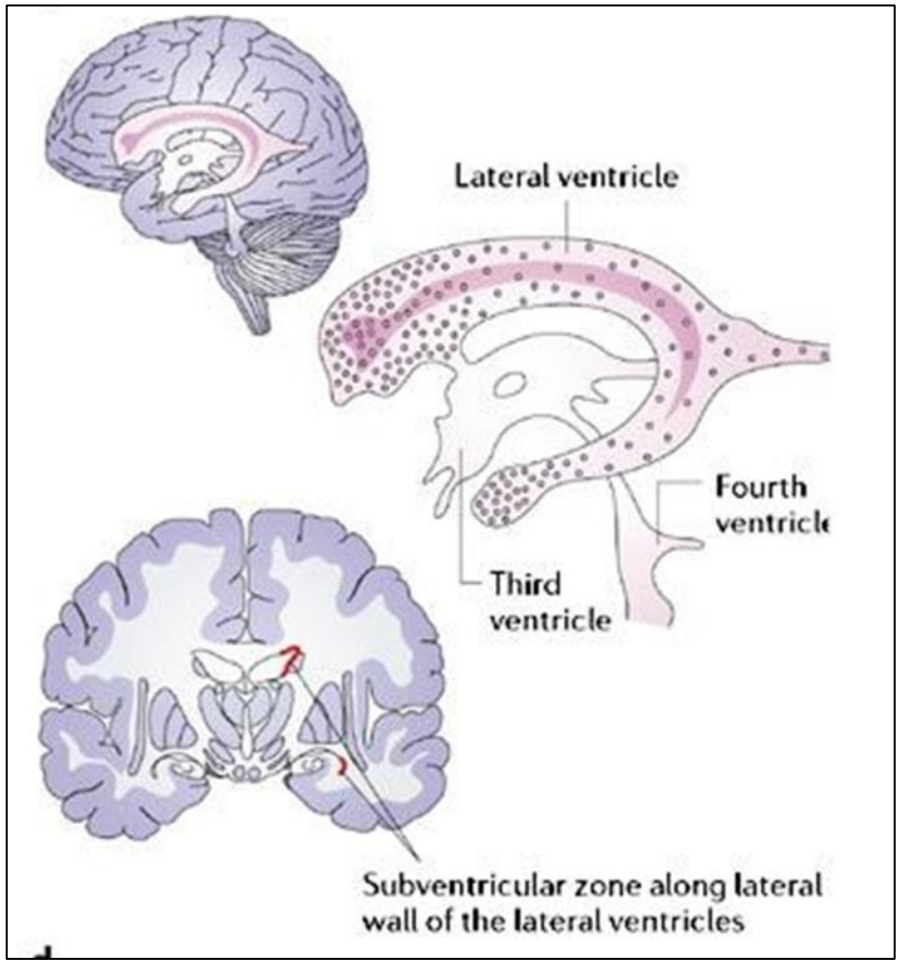
Neuro-Oncology, (2015), 17, 81-94.

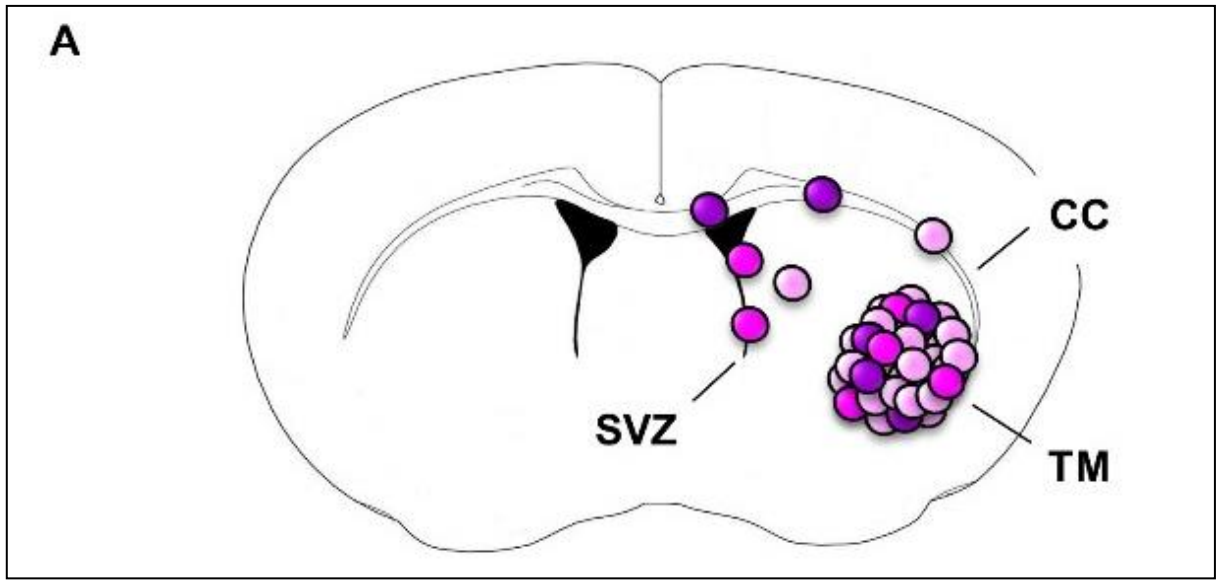
International Journal of Cancer, (2011), 29, 574-585.

GICs and adult Neurogenic Regions?



Phil. Trans. R. Soc. B (2016) 371, In Press.





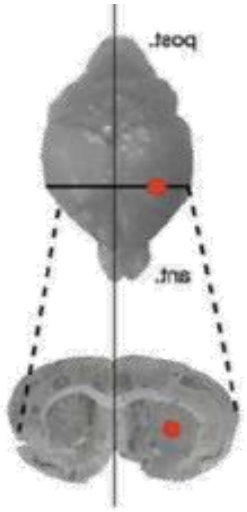
Glioblastoma-Initiating Cells or GICs
= Glioblastoma stem cells

- Self-renewal
- Multipotent
- Able to form spheres
- Able to growth a tumor in xenotransplantations
- 1/ 1000 tumor cells
- No specific differentiation markers
- CXCR4 membrane expression

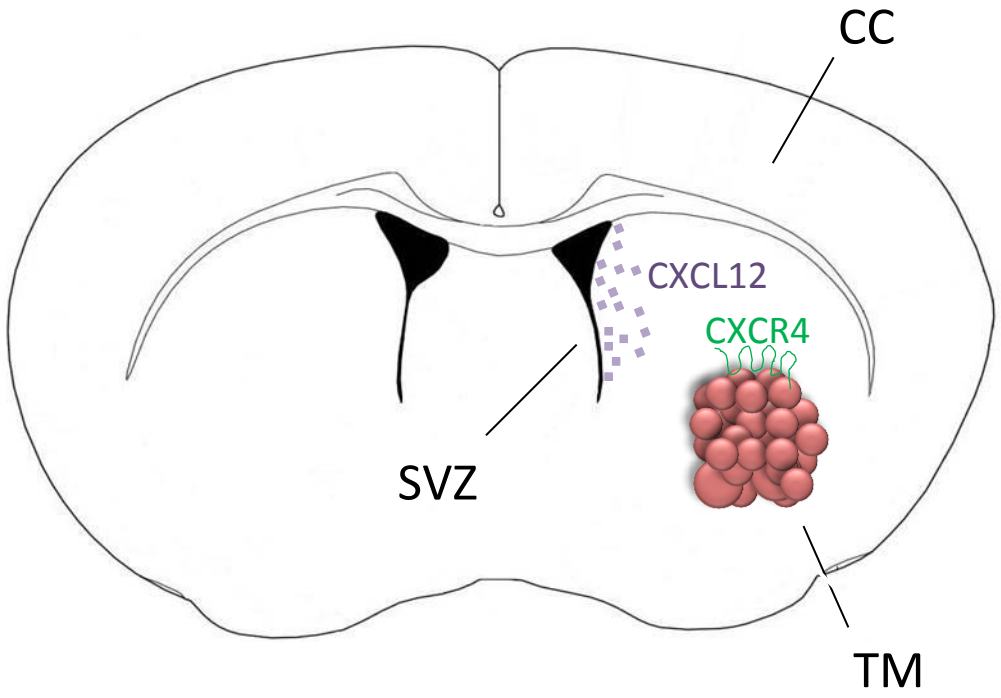
B. ROGISTER et alii

Etude du rôle de la chémokine CXCL12 dans la migration et la la radiorésistance.

Upper View



Coronal Section



Neuro-Oncology

Neuro-Oncology 2014; **0**, 1–13, doi:10.1093/neuonc/nou144

Adult mouse subventricular zones stimulate glioblastoma stem cells specific invasion through CXCL12/CXCR4 signaling

Nicolas Goffart, Jérôme Kroonen, Emmanuel Di Valentin, Matthias Dedobbeleer, Alexandre Denne, Philippe Martinive, and Bernard Rogister

Neuro-Oncology Advance Access published July 1, 2016

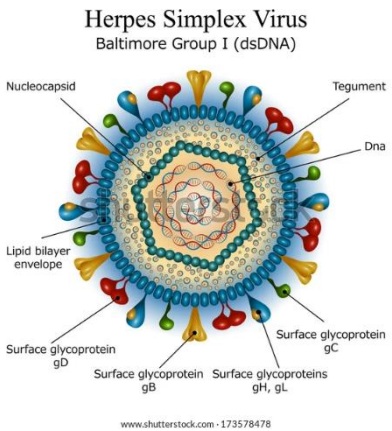
Neuro-Oncology

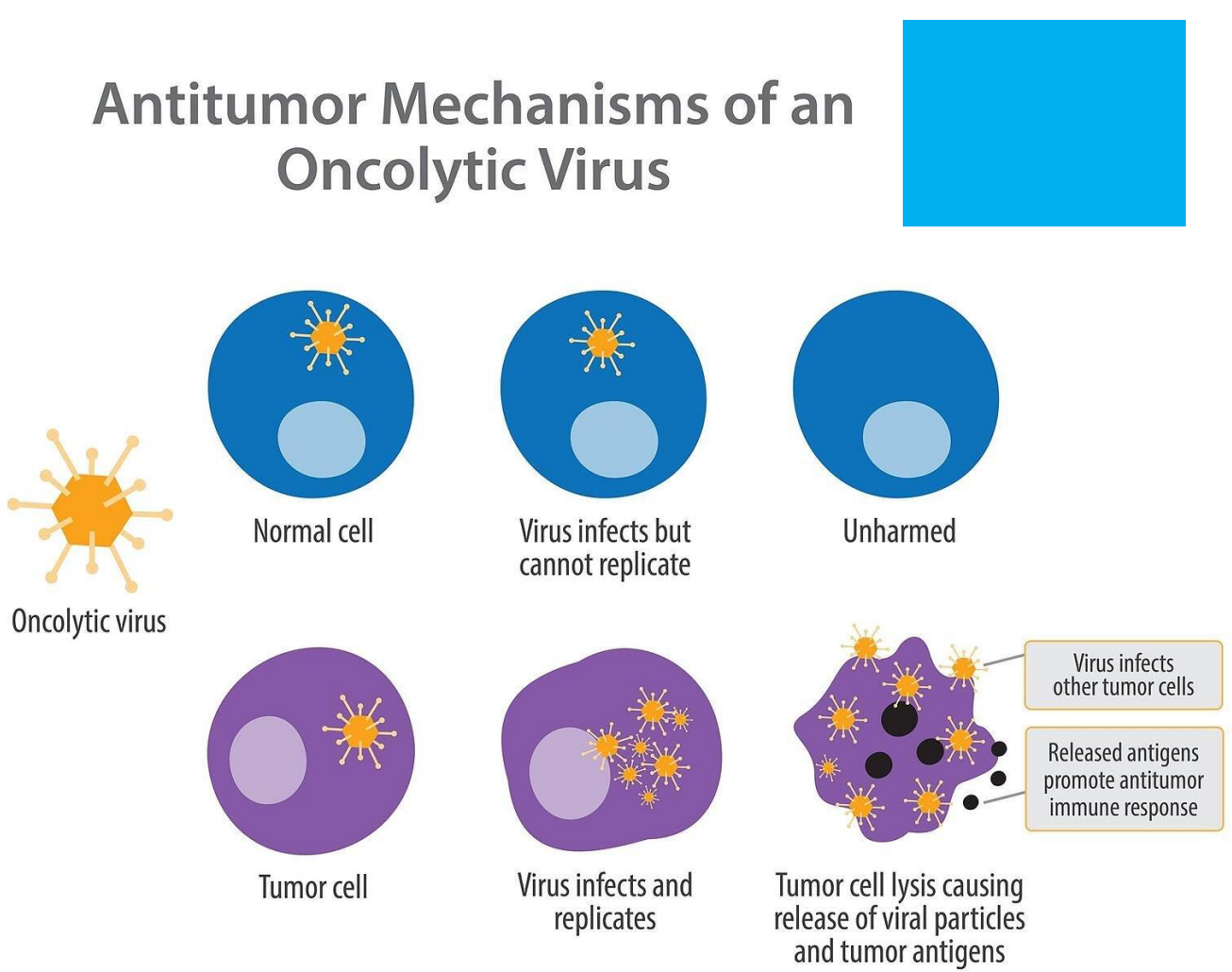
Neuro-Oncology 2016; **0**, 1–11, doi:10.1093/neuonc/now136

CXCL12 mediates glioblastoma resistance to radiotherapy in the subventricular zone

Nicolas Goffart†, Arnaud Lombard†, François Lallemand, Jérôme Kroonen, Jessica Nassen, Emmanuel Di Valentin, Sharon Berendsen, Matthias Dedobbeleer, Estelle Willems, Pierre Robe, Vincent Bours, Didier Martin, Philippe Martinive, Pierre Maquet, and Bernard Rogister

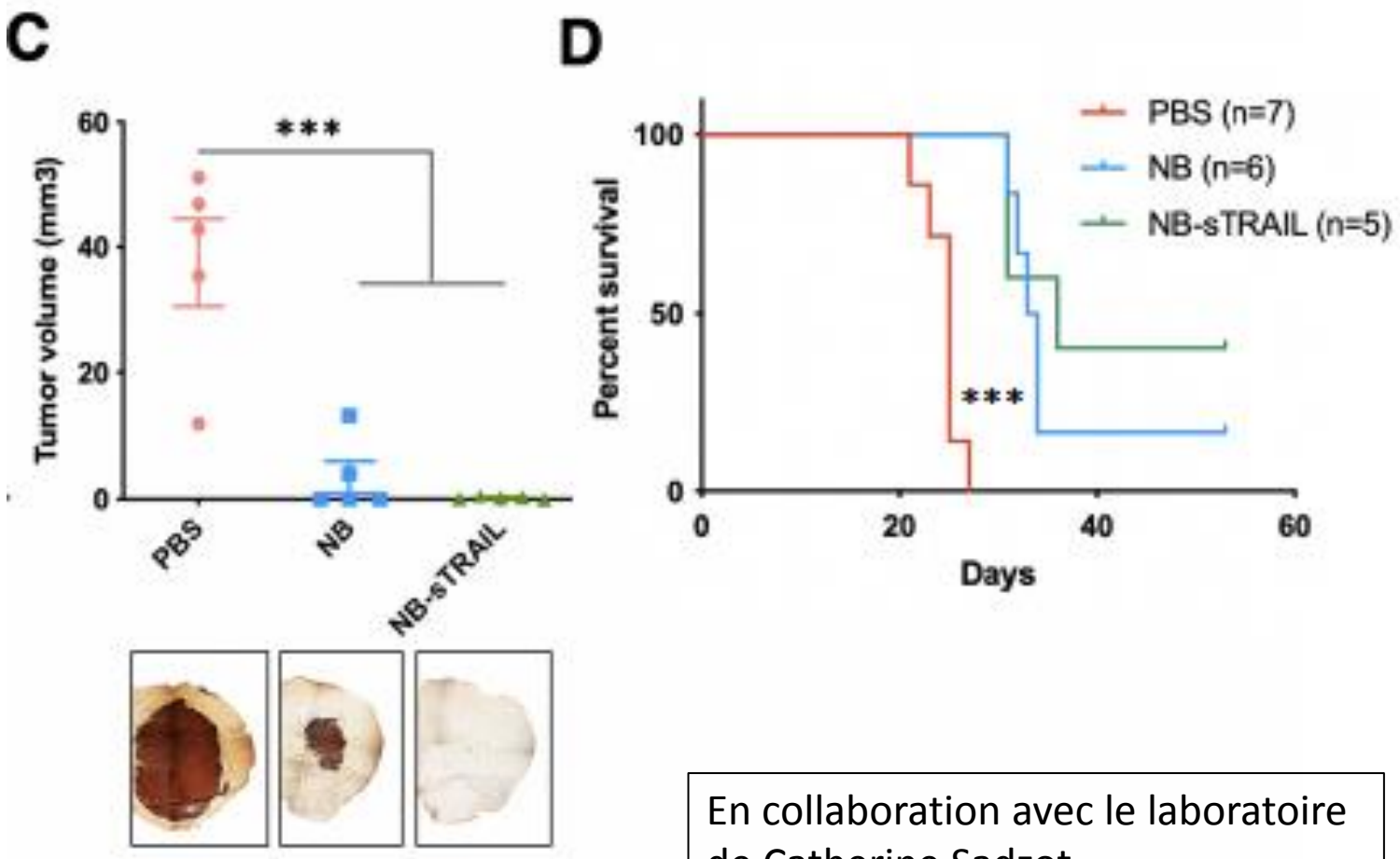
Les virus oncolytiques





Un Herpès virus manipulé pour exprimer à sa surface un nanobody fixant CXCR4.

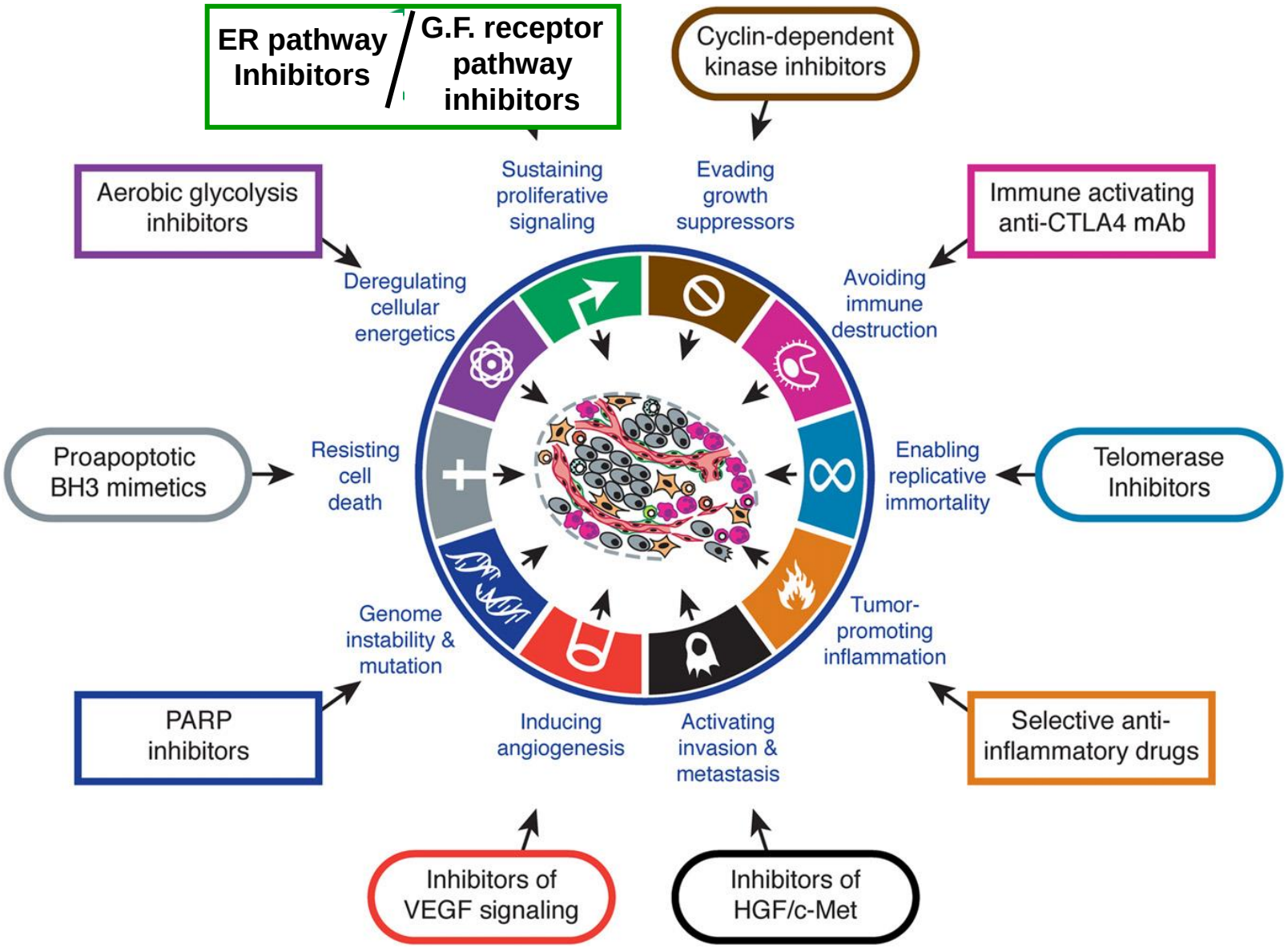
Efficacité in vivo des HSV-NB-CXCR4



En collaboration avec le laboratoire de Catherine Sadzot

THERAPEUTIC TARGETING OF THE HALLMARKS OF CANCER

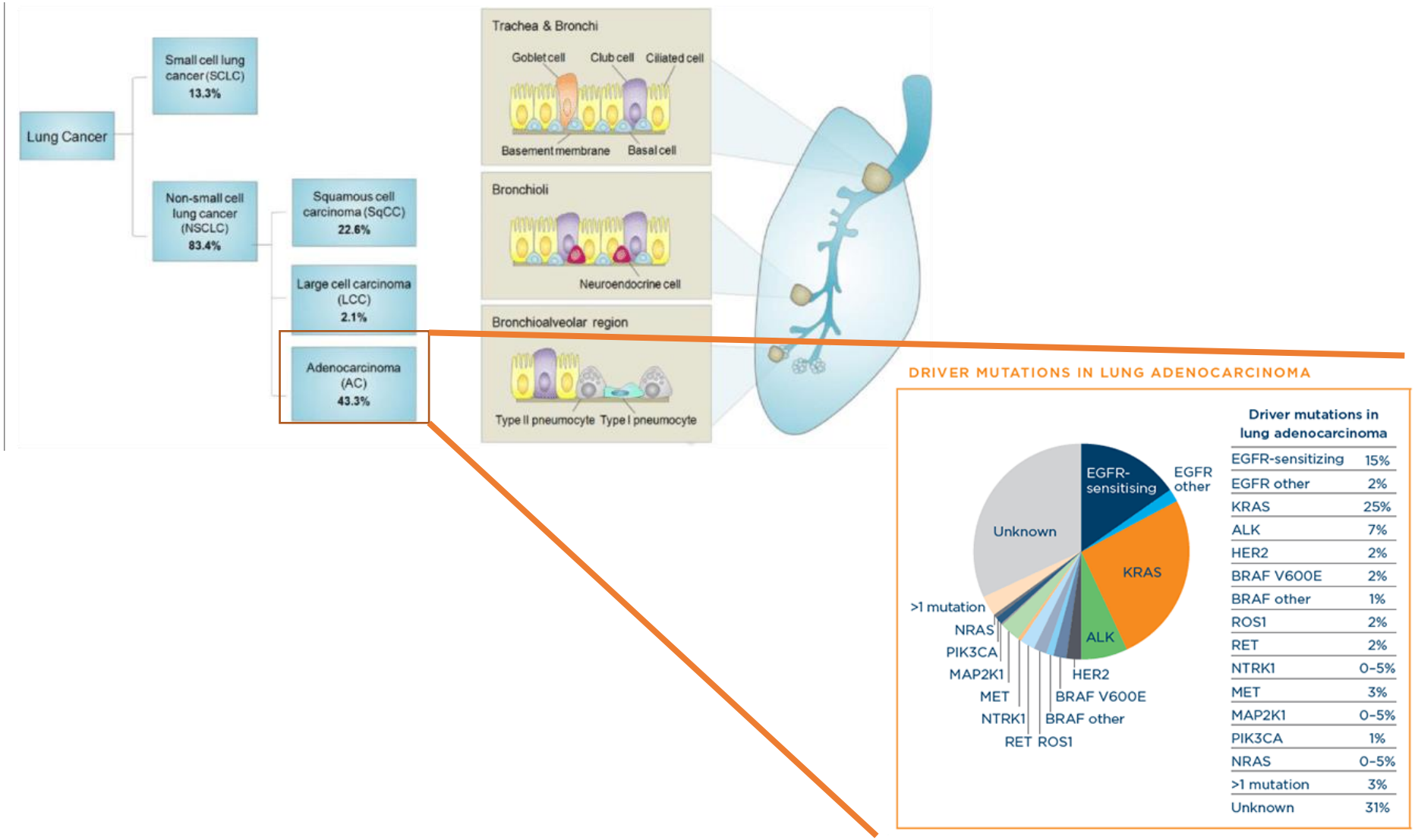
Marie-Julie Nokin, PhD
Laboratoire de Biologie
des Tumeurs et du Développement
GIGA-CANCER, Université de Liège
Professor Didier CATALDO



Hanahan D. and Weinberg R.A., Cell 144, March 4, 2011

A. AWADA

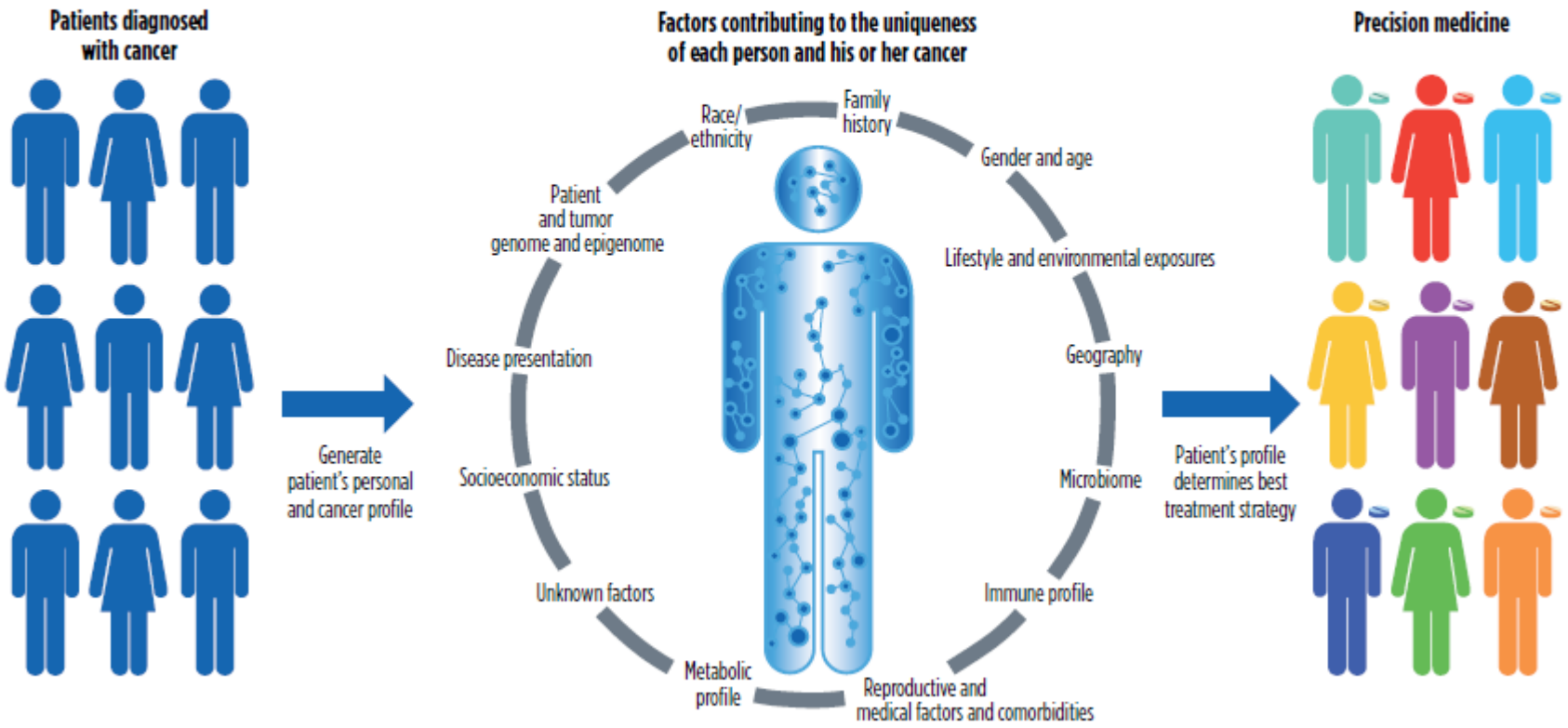
LUNG CANCERS



Sotorasib si RAS$_{G12C}$

Dabrafebib/trametinib

Precision Medicine:
Beyond Tumor Genome and Epigenome



COMMENT ATTEINDRE CETTE MEDECINE DE PRECISION « PERSONNALISEE »?

A. AWADA

Réponse: par la recherche!

- **Les Universités**
- **Le FNRS**
- **Le Télévie (175 projets en cours)**
- **La Fondation contre le cancer**
- **La Fondation Léon Fredericq**
- **L'UE**

LES BUDGETS

- **Oncologie clinique: 4.300 Mios €**
- **Oncologie « hors clinique »: ?**
- **Dépistage (FWB): 1,5 Mio €**
- **Recherche : 134 Mios €**

télévie

televie.be

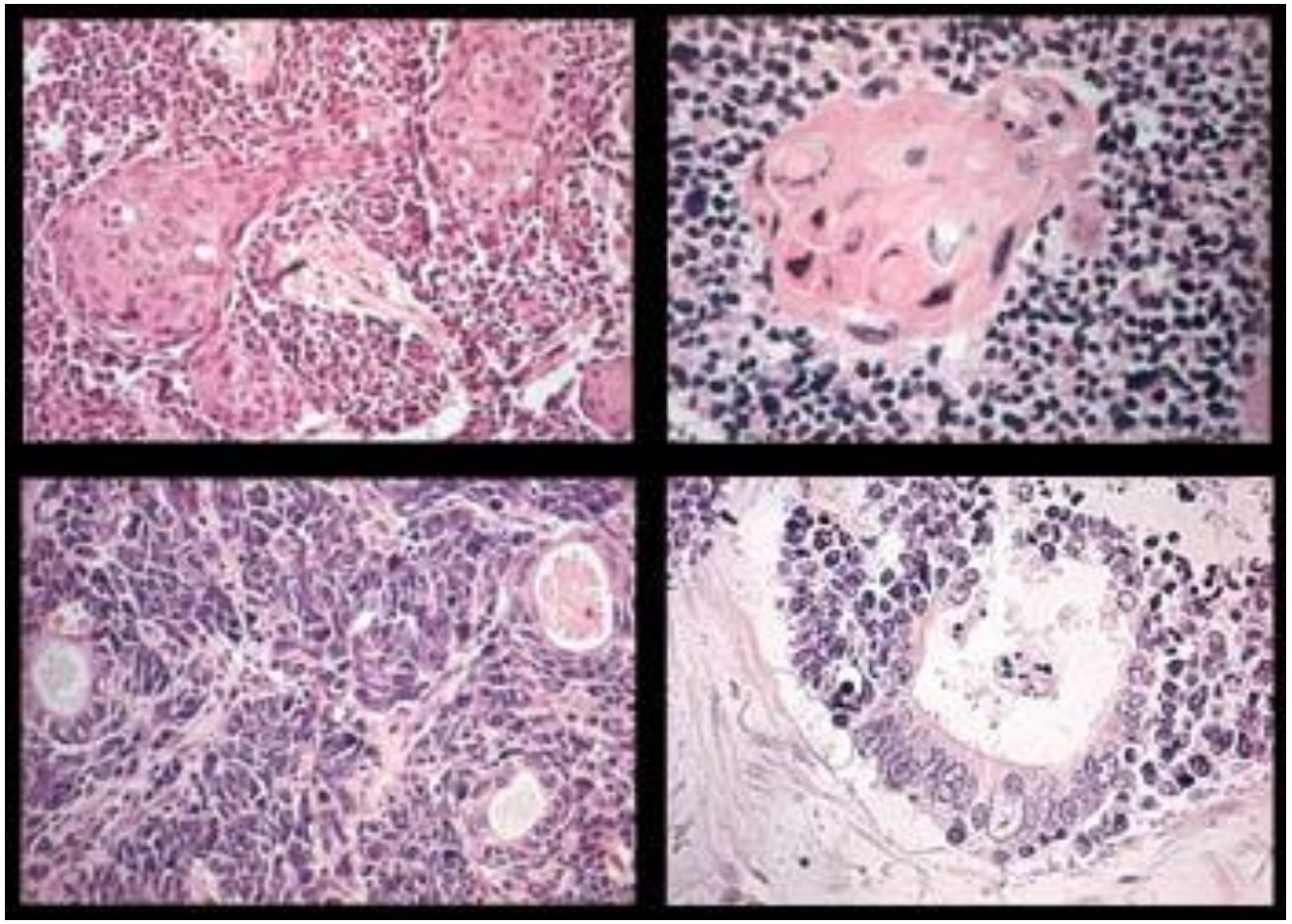
Fondation Léon Fredericq

www.fondationleonfredericq.be

MERCI POUR VOTRE ATTENTION

ET DONC LA RECHERCHE?

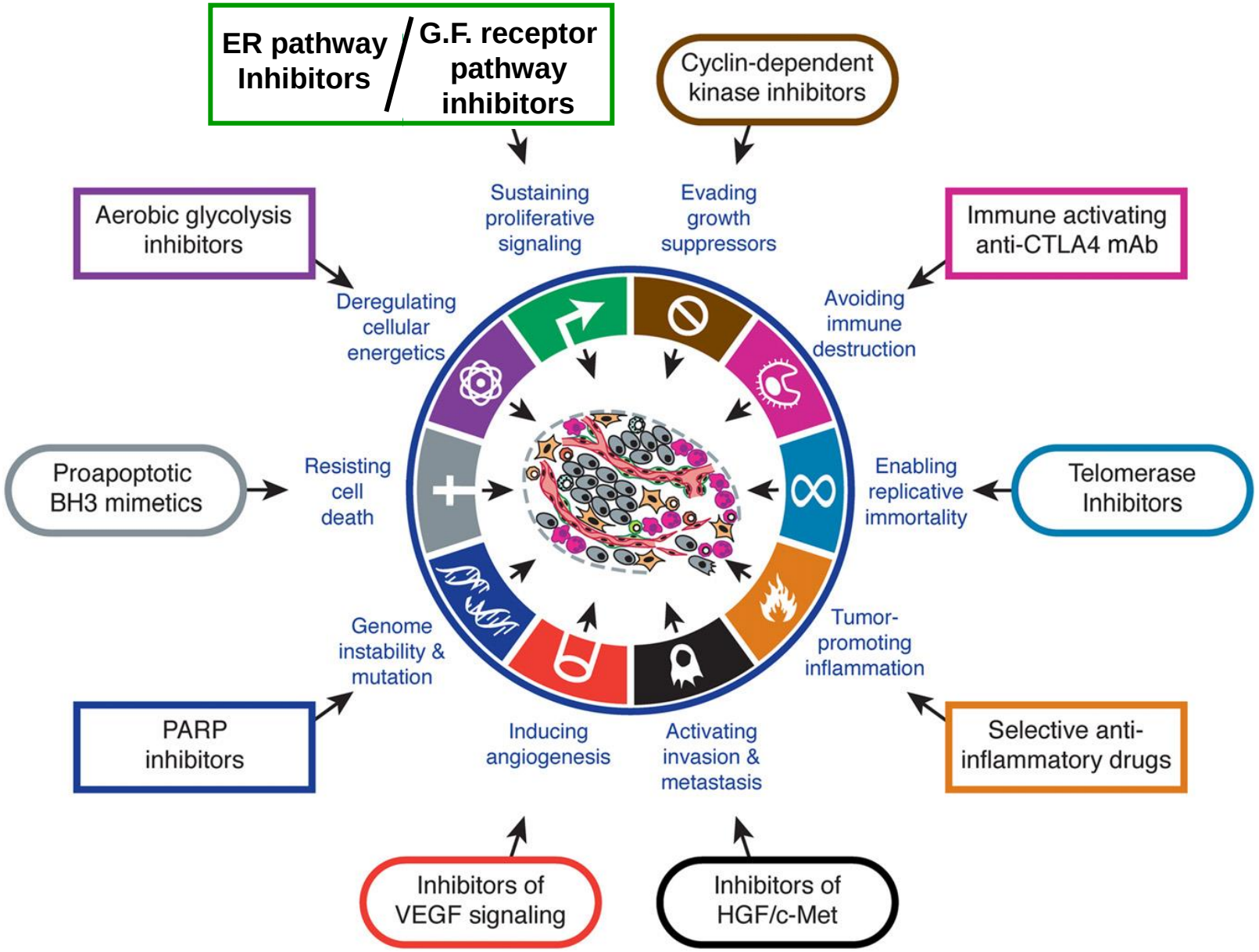
- Recherche fondamentale // Recherche translationnelle // Recherche clinique
- Les défis sont immenses et ce à tous les niveaux de la lutte contre les maladies et en particulier contre les cancers.
- La recherche doit rester libre d'inspiration et ne doit pas être téléguidée.
- Ainsi, on sera sans doute déçu de constater relativement peu d'activités de recherches pour certaines tumeurs.
- On sera sans doute aussi déçu de constater qu'une découverte n'est suivie d'un apport clinique reconnu qu'après de très nombreuses années.
- On constatera aussi parfois un immense « gap » entre ce que l'on sait d'un type de cancer et l'apport de cette connaissance à sa prise en charge.



The patient receives chemotherapy, that results in a complete remission.
However, he relapses a few months later and deseased.
At the post-mortem examination, one finds numerous metastases,
which show either small cell morphology or squamous or glandular differentiation

➡ **<u>Hypothesis:</u> the primary tumor contained cancer stem cells capable to give rise to neuro-endocrine or squamous or glandular tumor cells.**

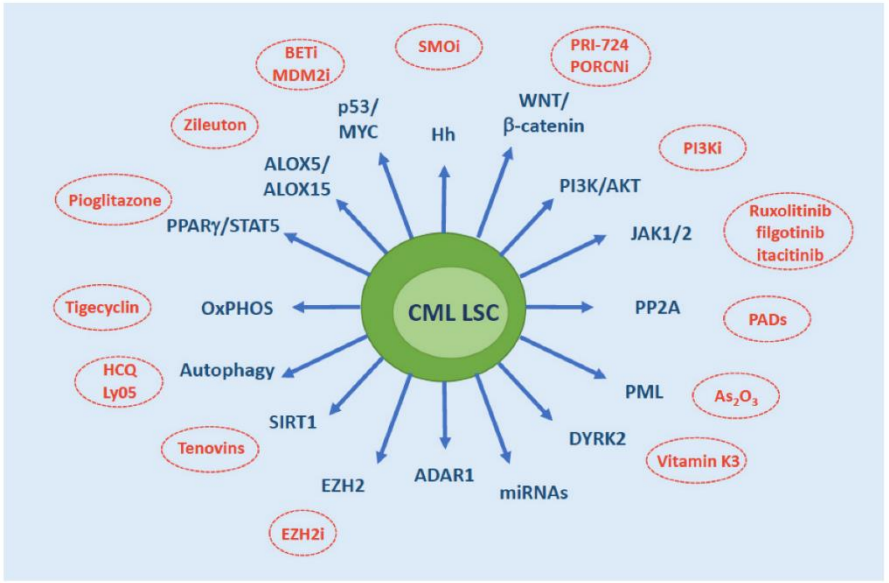
THERAPEUTIC TARGETING OF THE HALLMARKS OF CANCER

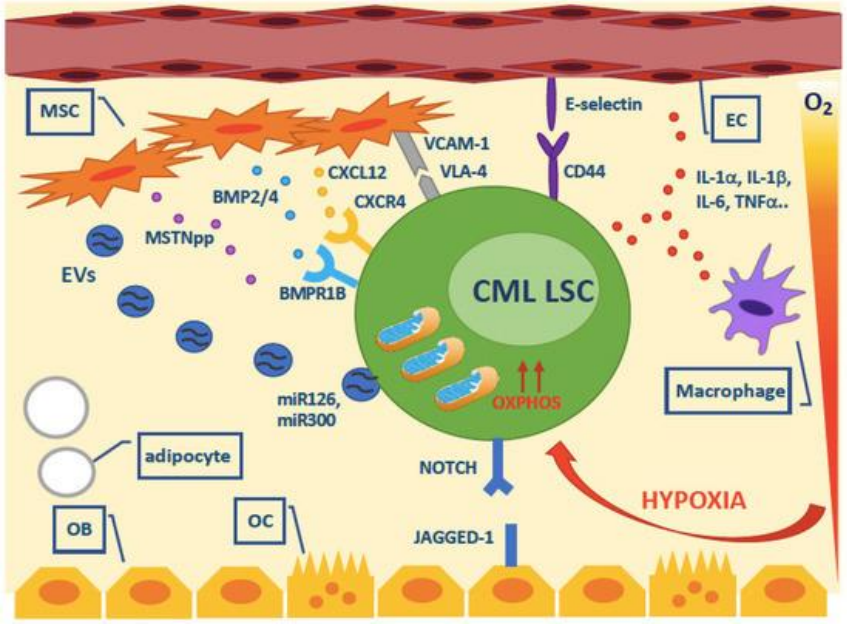


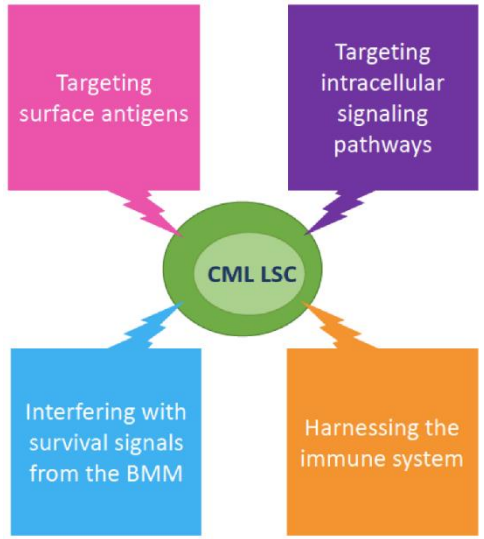
Hanahan D. and Weinberg R.A., Cell 144, March 4, 2011

A. AWADA

Will We Ever Be Able to Kill CML LSCs?







Overview of the therapeutic strategies that have been proposed to eradicate CML LSCs.

Targeting Leukemic Stem Cells in Chronic Myeloid Leukemia:
Is It Worth the Effort?
Simona Soverini 1,*, Sara De Santis 1 , Cecilia Monaldi 1 , Samantha Bruno 1 and Manuela Mancini
Int. J. Mol. Sci. **2021**, *22*, 7093