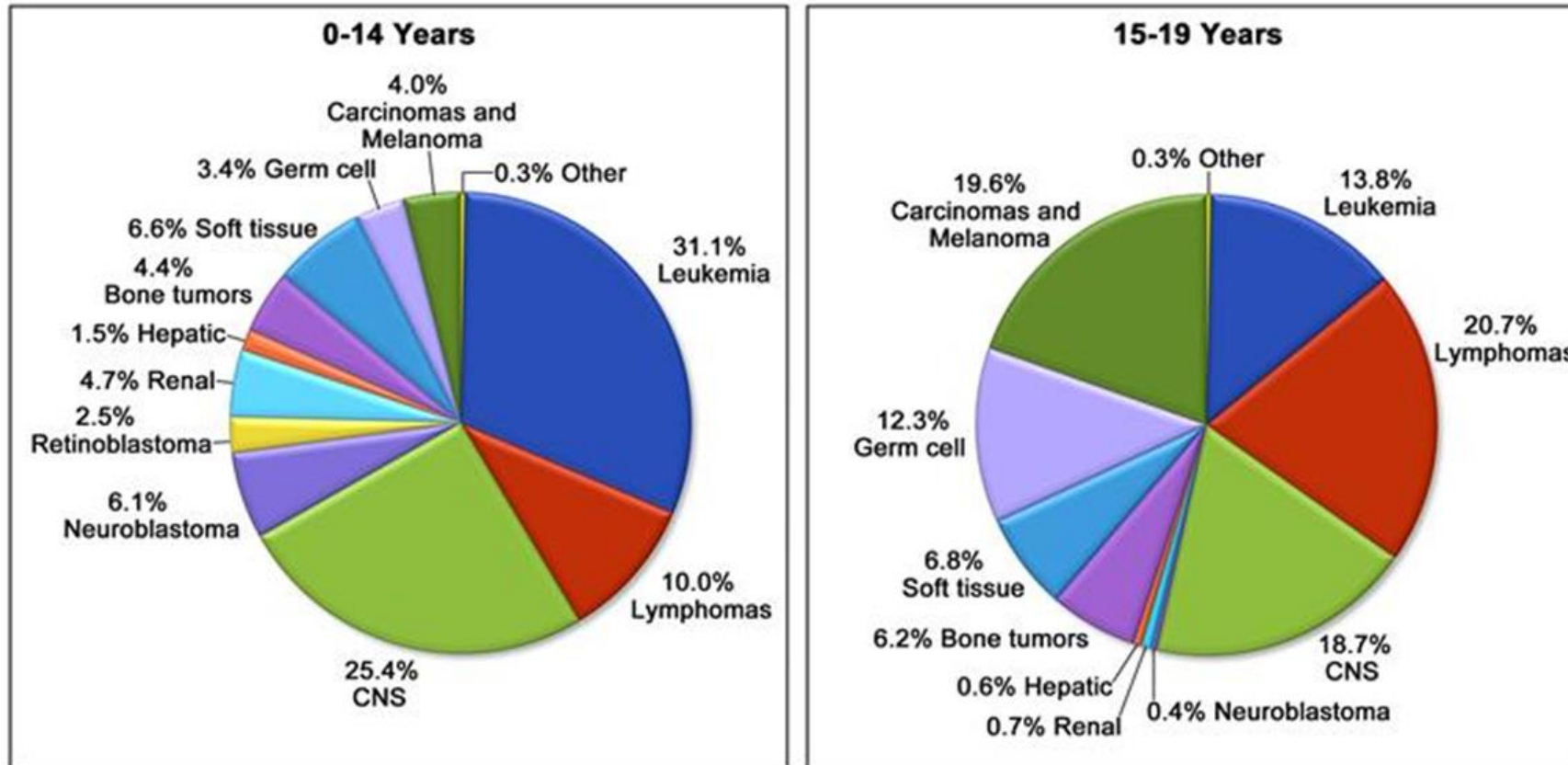


# Perspectives thérapeutiques en oncologie pédiatrique

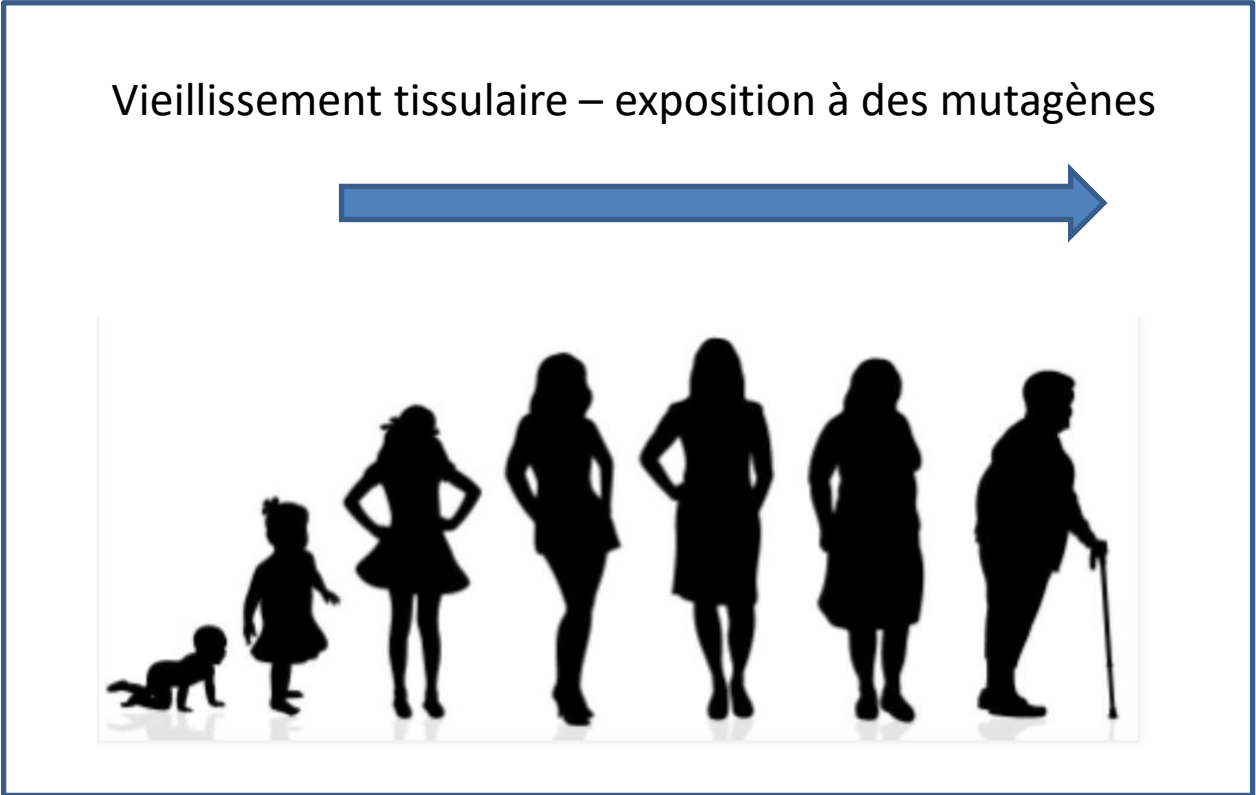
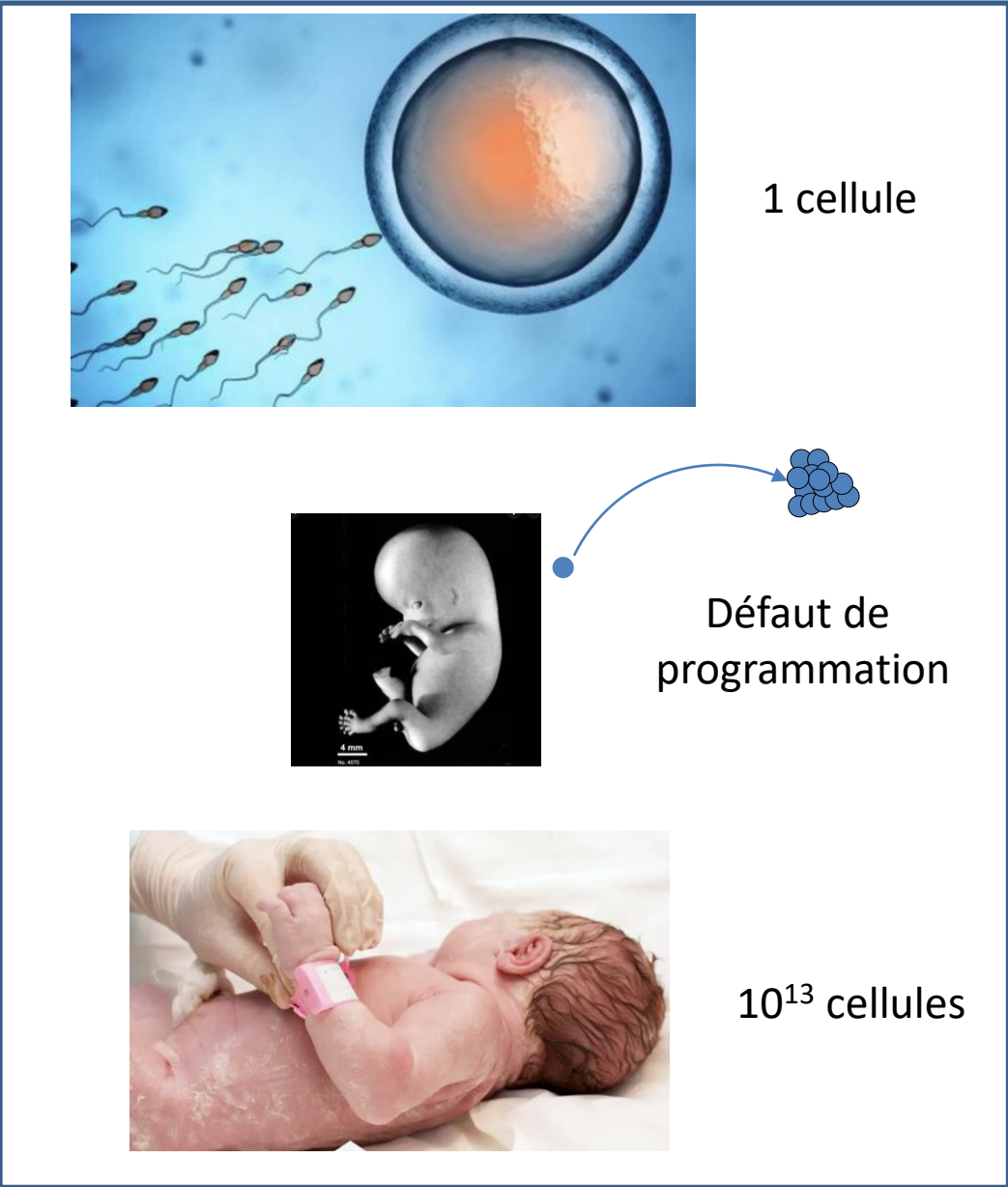
Olivier Delattre  
Inserm/Institut Curie

# Les types de cancers chez l'enfant et l'AJA

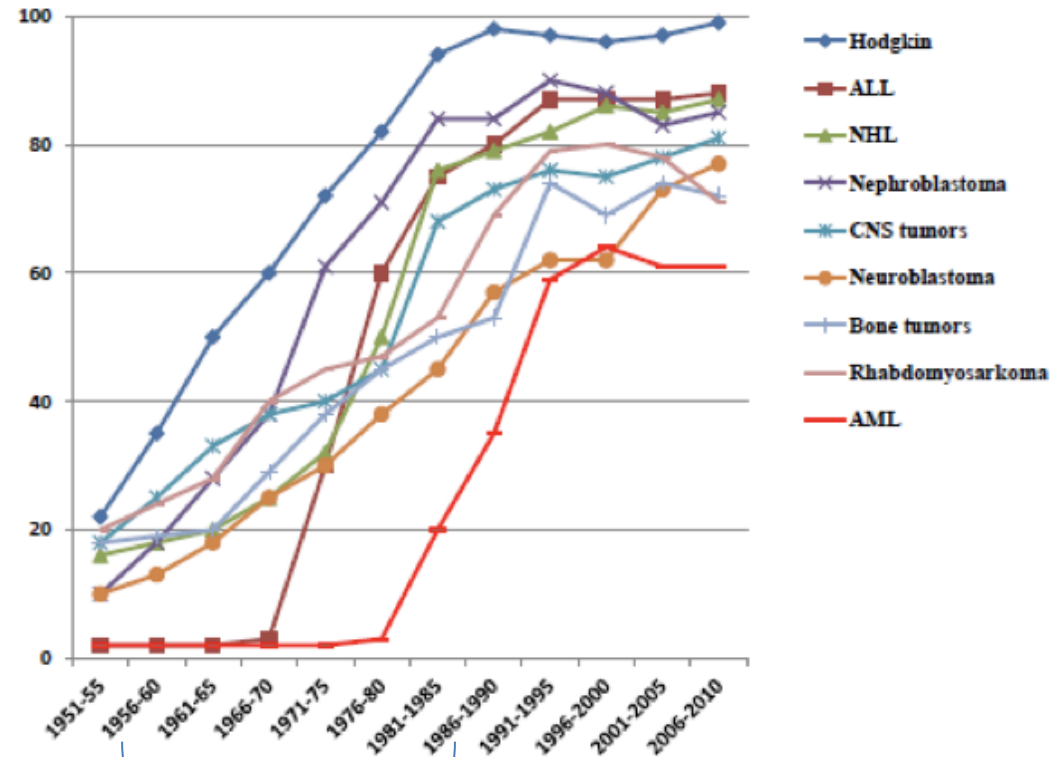
**Age-Adjusted and Age-Specific Cancer Incidence Rates for Patients 0-19 Years of Age (SEER 2005-2009)**



# Les cancers de l'enfant/AJA sont fondamentalement différents de ceux de l'adulte



# Survie à 5 ans des cancers de l'enfant



5-year survival in pediatric oncology in Sweden 1951-2010

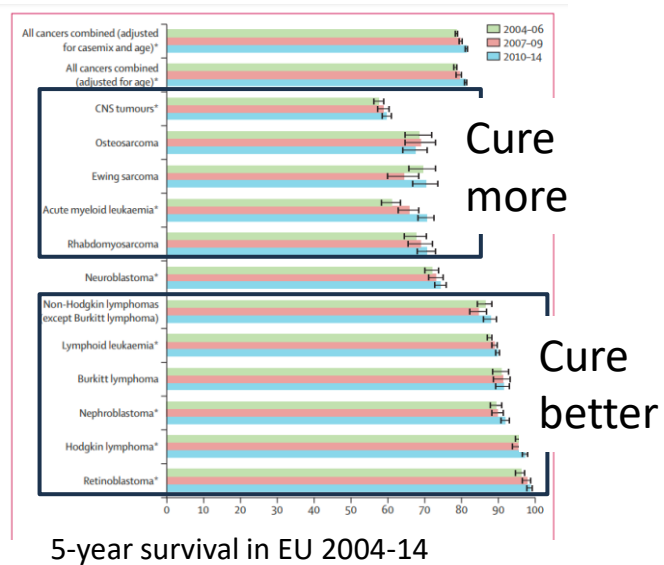
Essais cliniques recherchant la meilleure combinaison de chimiothérapie, chirurgie, radiothérapie  
Et progrès majeurs des techniques chirurgicales, de radiothérapie et des soins de support



Recherche fondamentale.  
Applications émergentes en thérapie

# Nombreuses séquelles à long terme

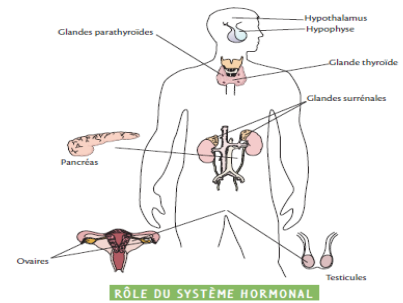
Overall, 81% survival



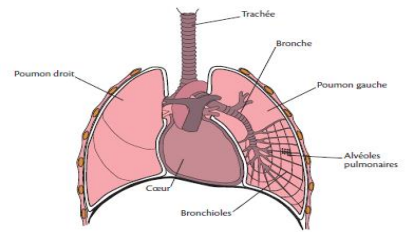
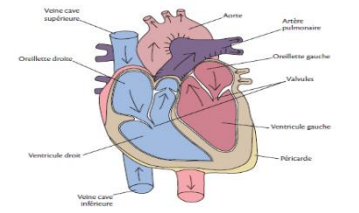
Botta et al, Lancet Oncol 2022

Cure more

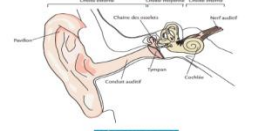
Cure better



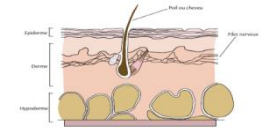
RÔLE DU SYSTÈME HORMONAL



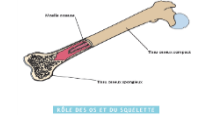
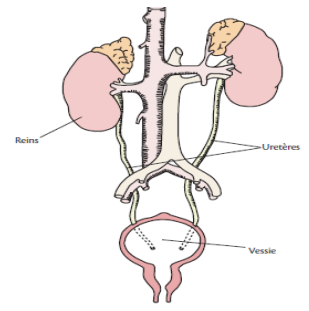
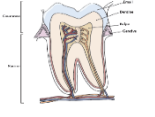
## LE DÉPISTAGE DES TUMEURS BÉNIGNES ET D'AUTRES CANCERS



RÔLE DE L'OREILLE

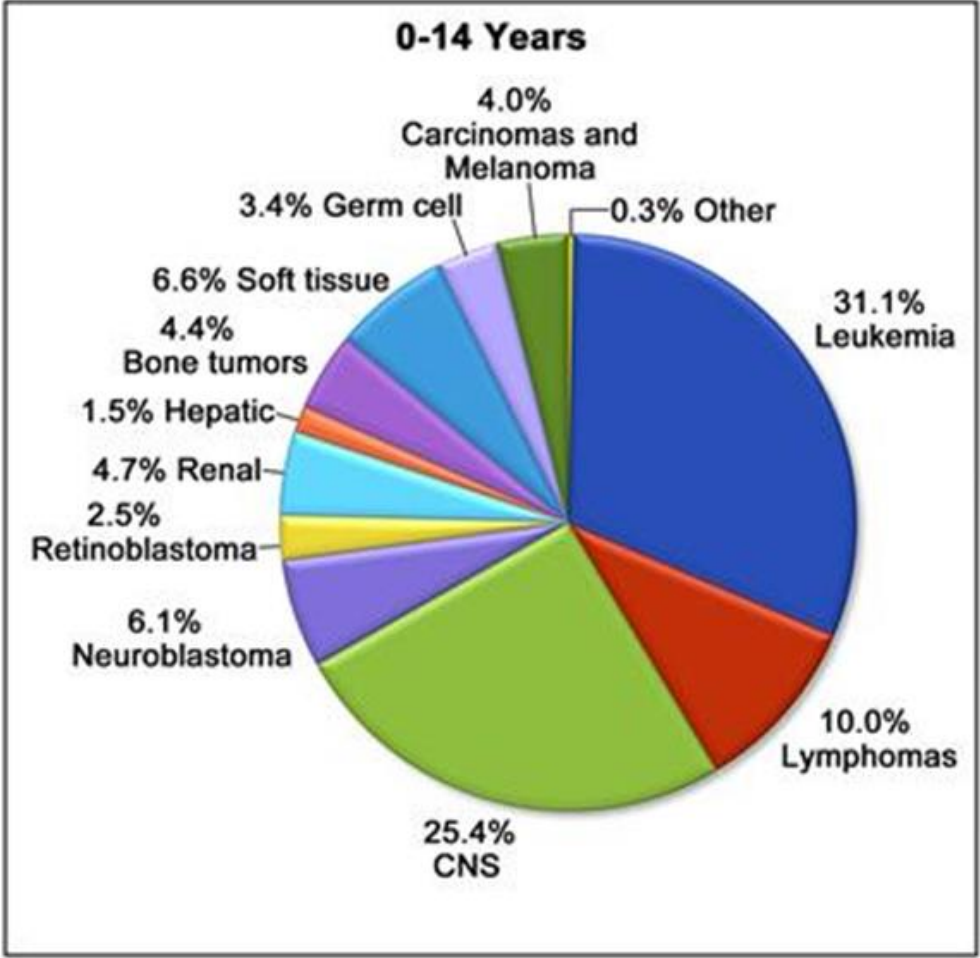


RÔLE DE LA PEAU

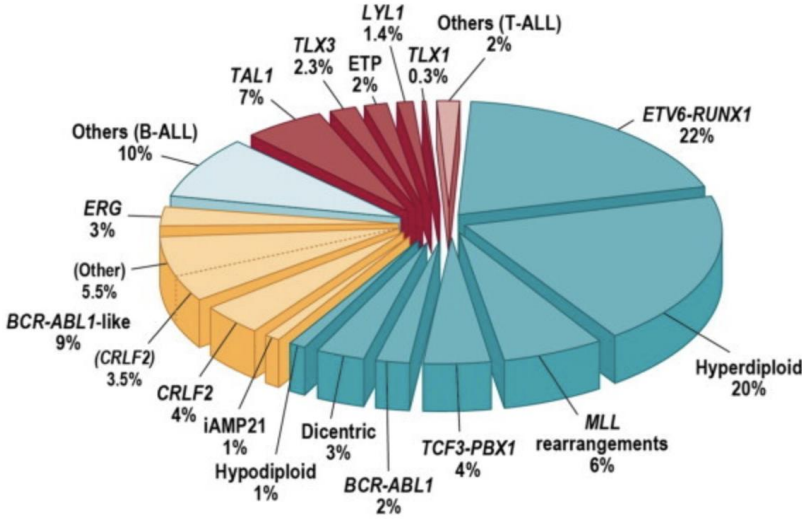


RÔLE DE LA SQUELETTE

# Complexification considérable de la classification au cours des dernières années

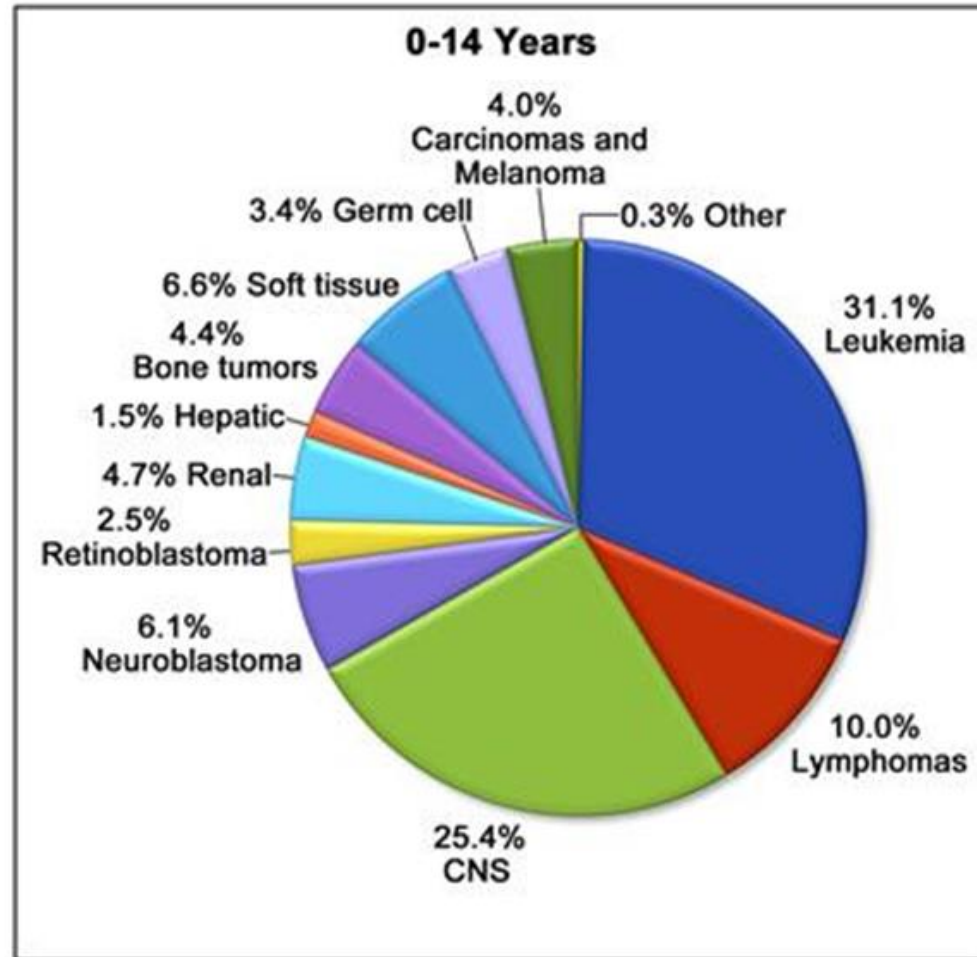


## Exemple des Leucémies Aigues Lymphoblastiques

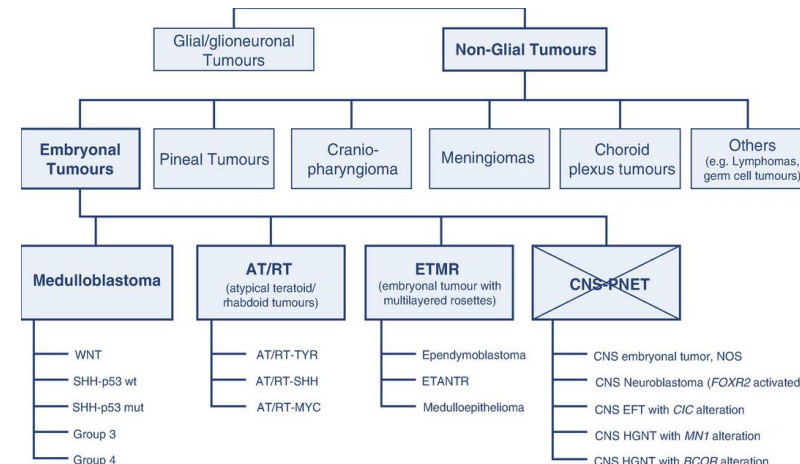
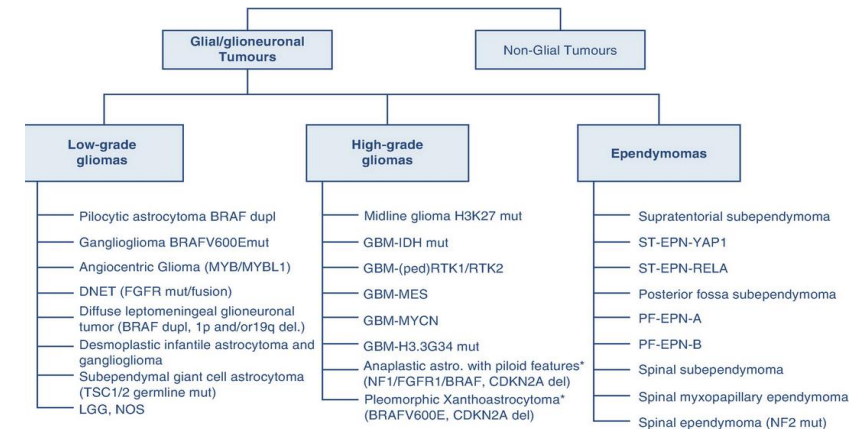


Mullighan, Seminars in Hematology, 2013

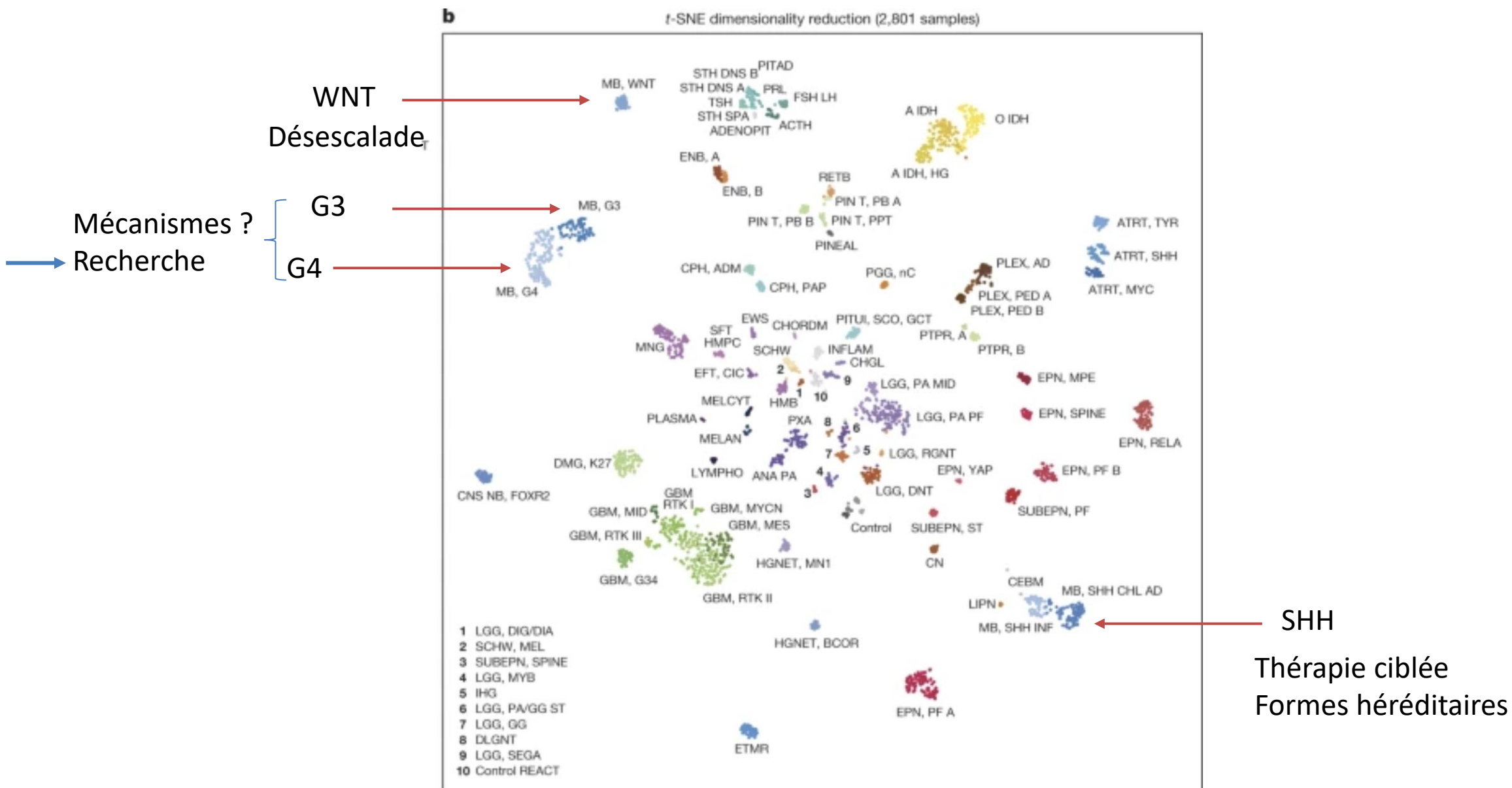
# Complexification considérable au cours des dernières années



## Exemple des tumeurs cérébrales

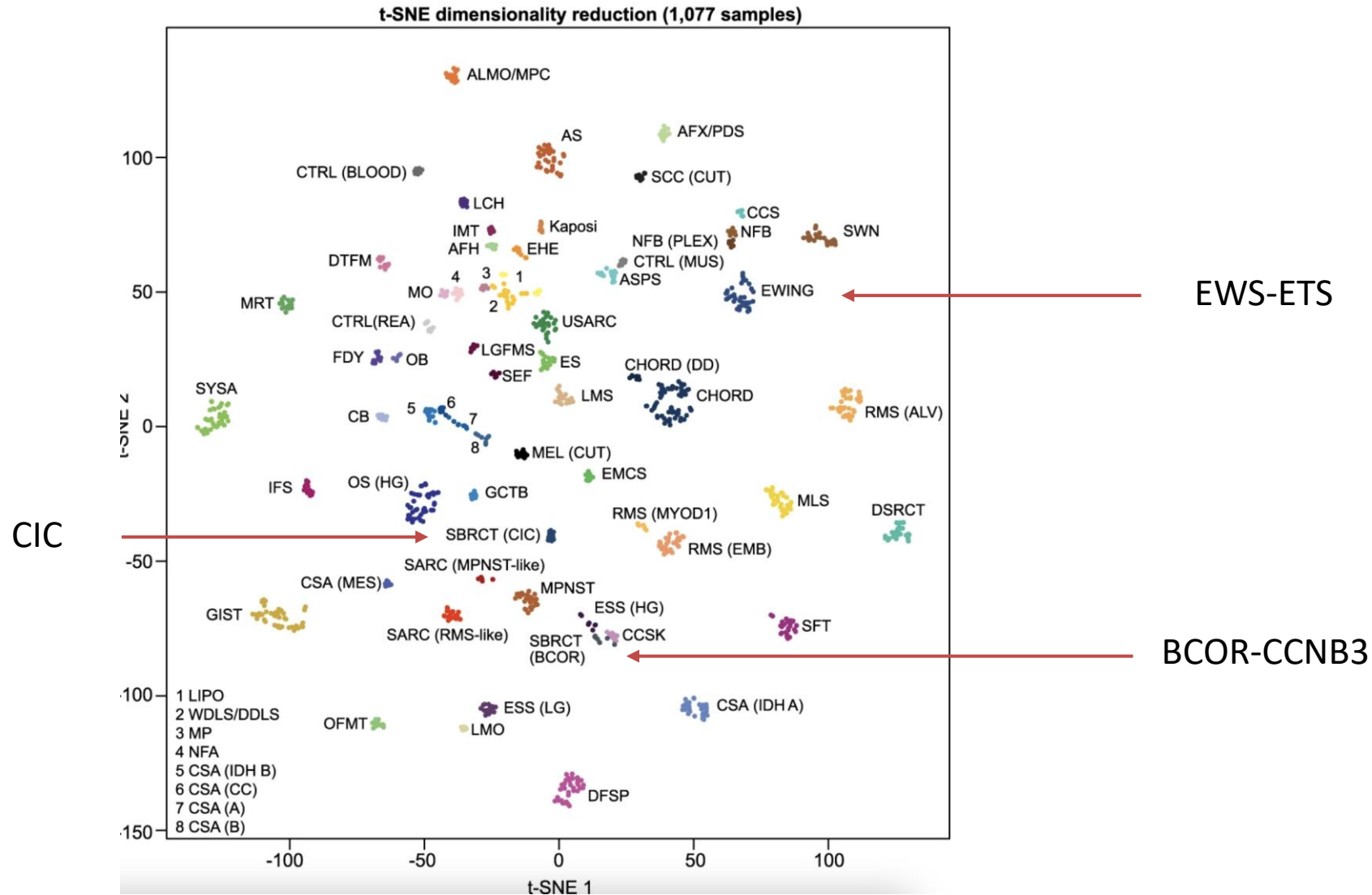


# Les différents médulloblastomes: des implications cliniques majeures

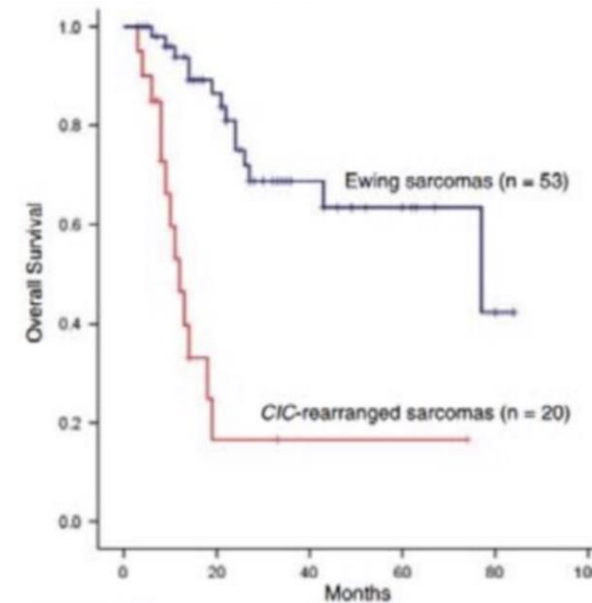
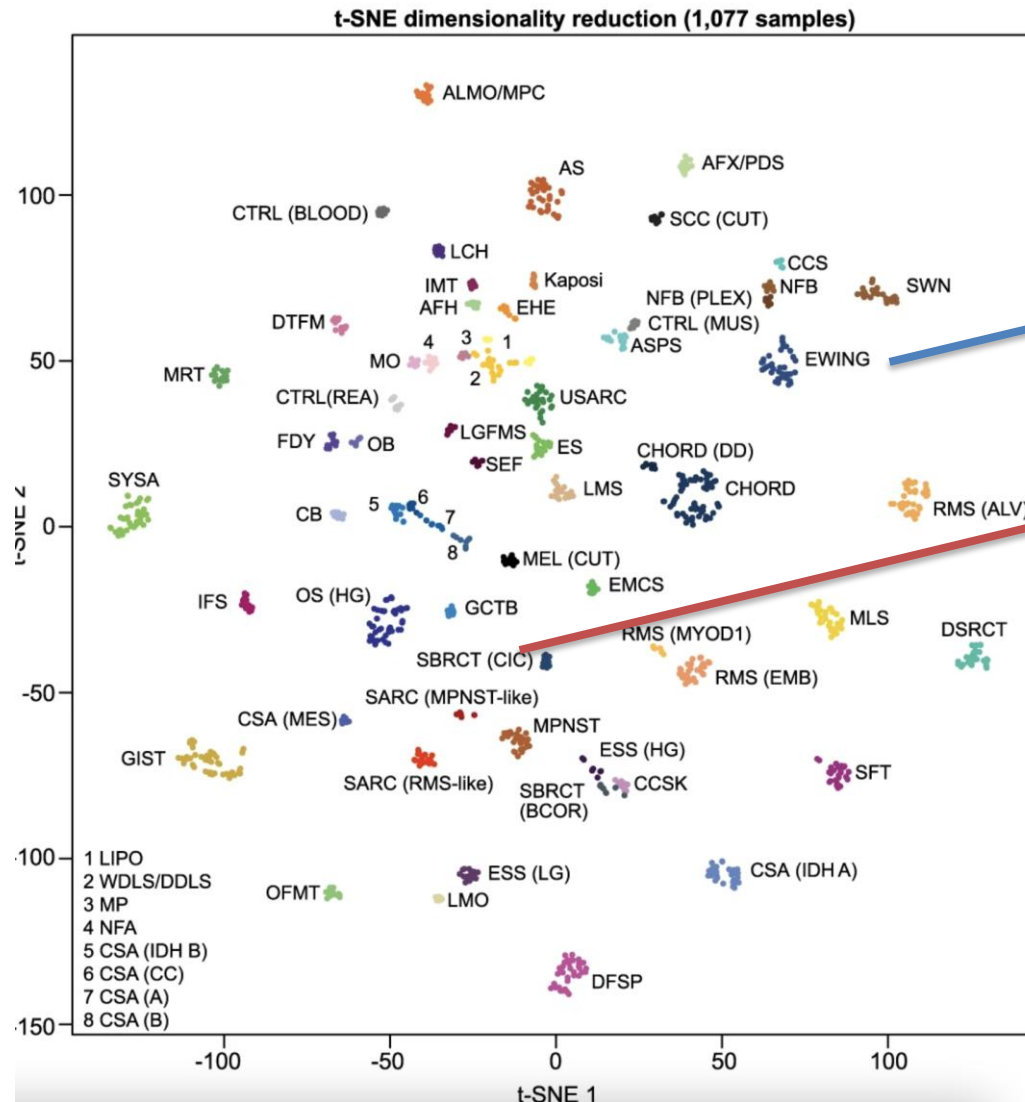




# Exemple des sarcomes Ewing et Ewing-like



# Exemple des sarcomes Ewing et Ewing-like



Inefficacité du traitement des CIC  
par les protocoles Ewing

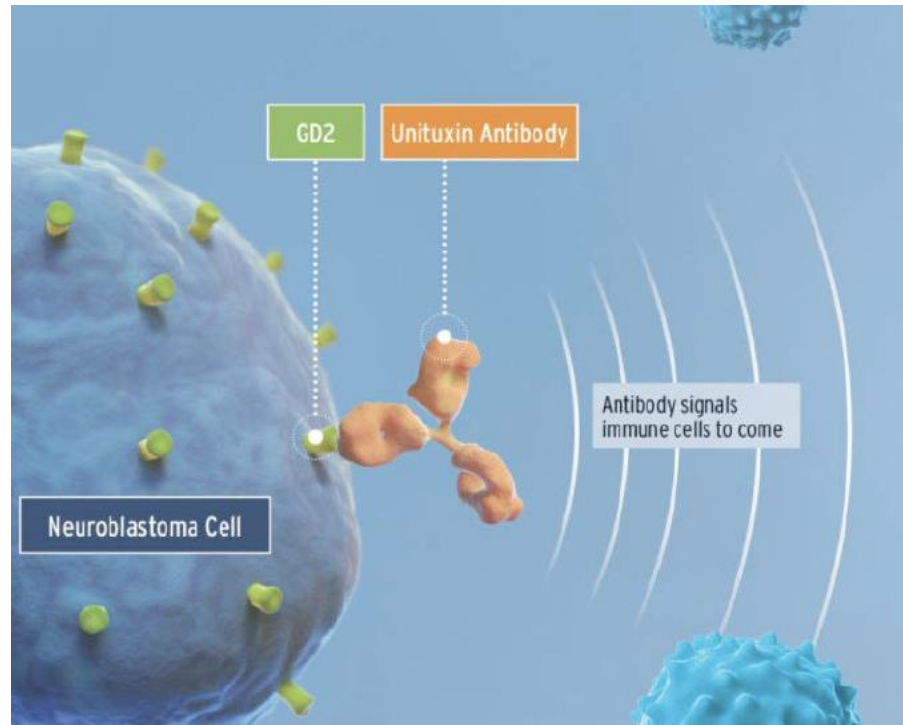
# Des raisons d'être optimistes

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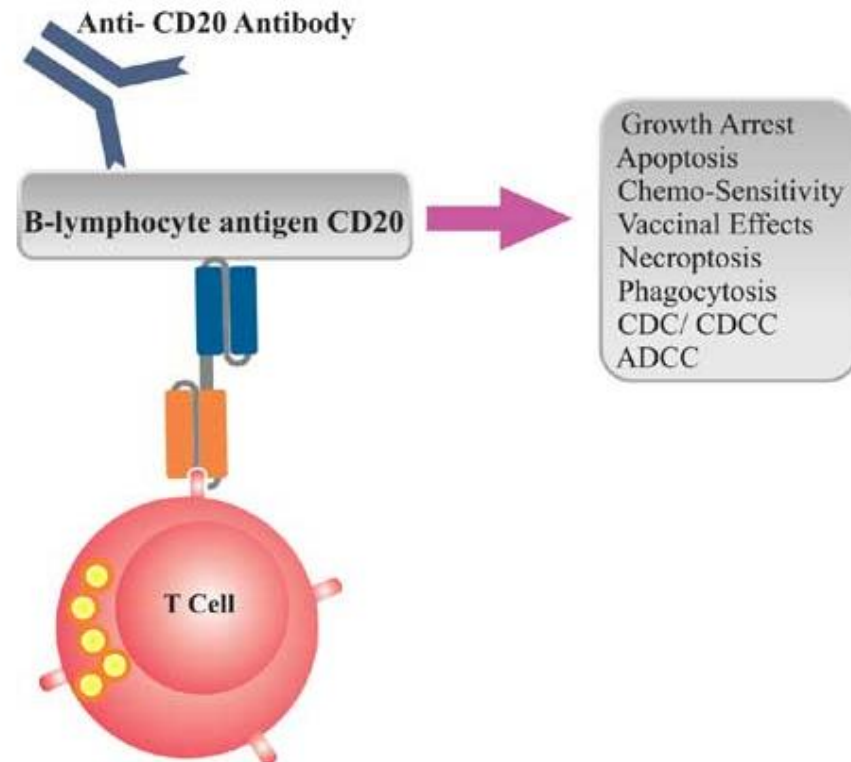
- Les success stories (CAR-T CD19, NTRK...)
- Progrès considérables de la connaissance des mécanismes de développement de ces tumeurs. Applications thérapeutiques émergentes (progrès de la chimie, de l'immuno...)
- L'évolution de l'environnement réglementaire (Plans d'Investigation Pédiatrique)
- Caractérisation moléculaire en clinique (FMG en relai des plateformes de génétique de l'Inca)
- Un investissement financier majeur à l'international dans ce domaine (moonshot, PMC, KiTZ-Heidelberg, Cancer Research-UK Grand Challenge...)

# Quelques success stories: les anticorps monoclonaux

Anti GD2 in neuroblastoma



Anti CD20 in B cell malignancies



# Les inhibiteurs de TRK

1998

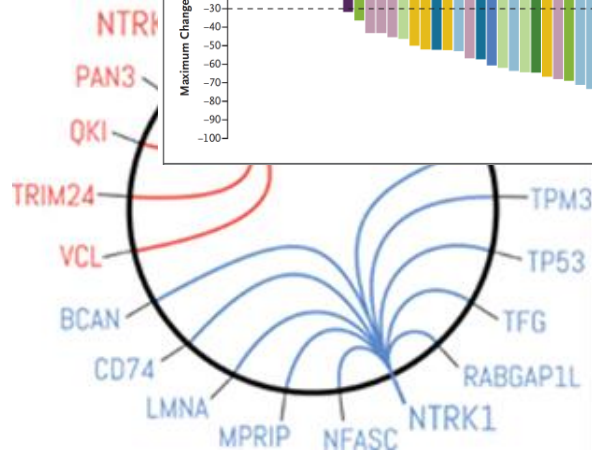
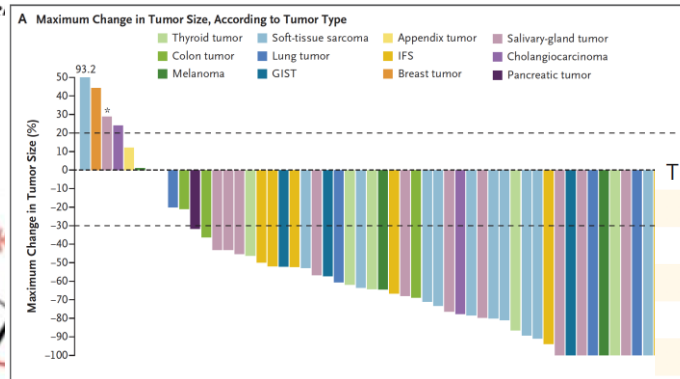


Letter | Published: 01 February 1998

## A novel ETV6-NTRK3 gene fusion in congenital fibrosarcoma

Stevan R. Knezevich, Deborah E. McFadden, Wen Tao, Jerian F. Lim & Poul H.B. Sorensen

Nature Genetics 18, 184–187 (1998) | Download Citation | 775 Accesses | 436 Citations | 9 Altmetric | Metrics



20yrs



2018

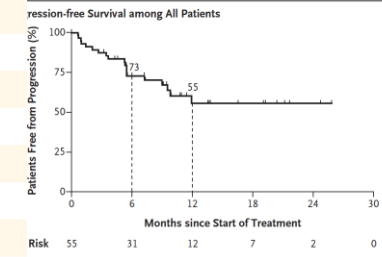
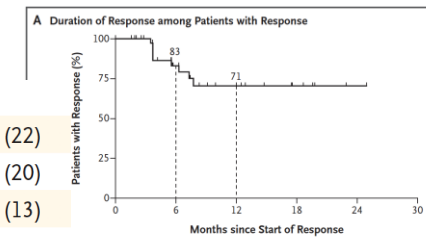
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children

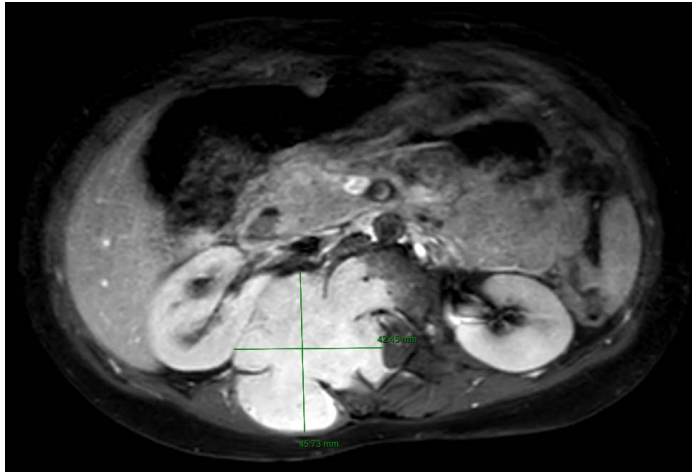
A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

| Tumor type                | no. (%) |
|---------------------------|---------|
| Salivary-gland tumor      | 12 (22) |
| Other soft-tissue sarcoma | 11 (20) |
| Infantile fibrosarcoma    | 7 (13)  |
| Thyroid tumor             | 5 (9)   |
| Colon tumor               | 4 (7)   |
| Lung tumor                | 4 (7)   |
| Melanoma                  | 4 (7)   |
| GIST                      | 3 (5)   |
| Cholangiocarcinoma        | 2 (4)   |
| Appendix tumor            | 1 (2)   |
| Breast tumor              | 1 (2)   |
| Pancreatic tumor          | 1 (2)   |



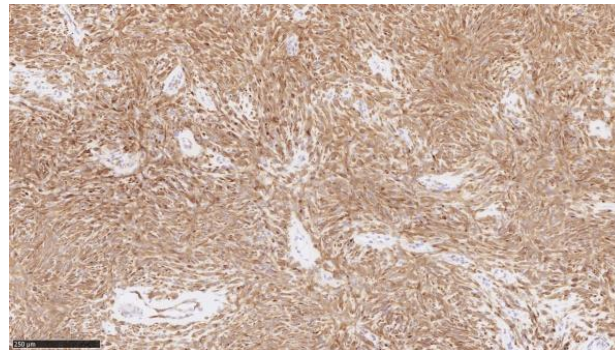
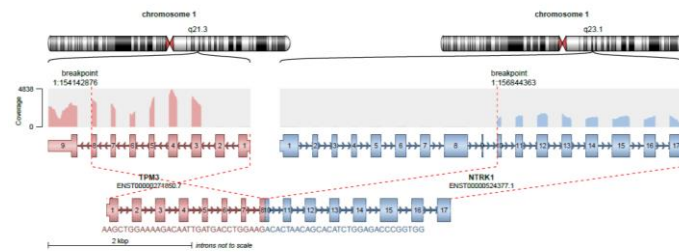
# La success story des inhibiteurs de TRK

Fillette de 4ans

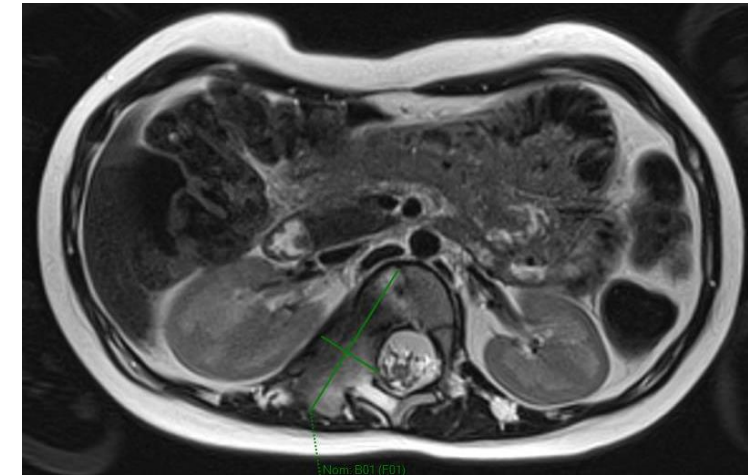


Discussion pluri disciplinaire  
Chirurgie très complexe  
Chimiothérapie laquelle?  
Irradiation mais risque ++ de séquelles

RNAseq  
Fusion **TPM3-NTRK1**

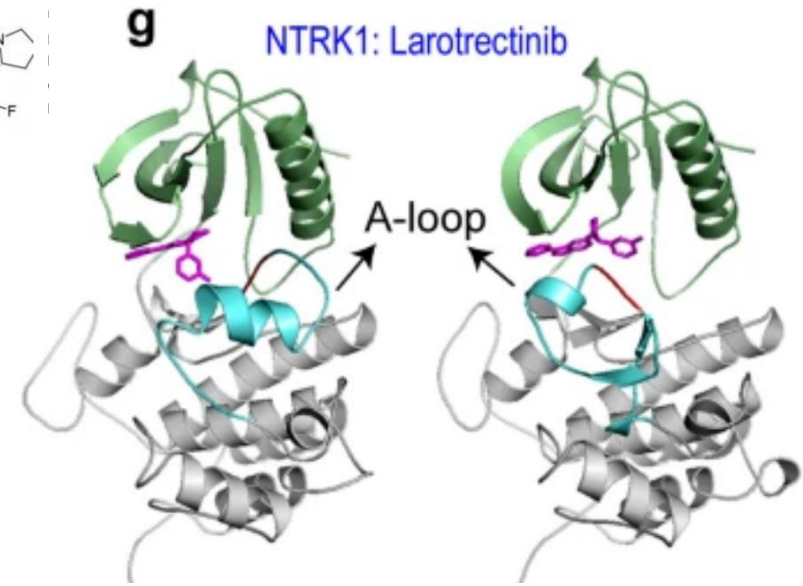
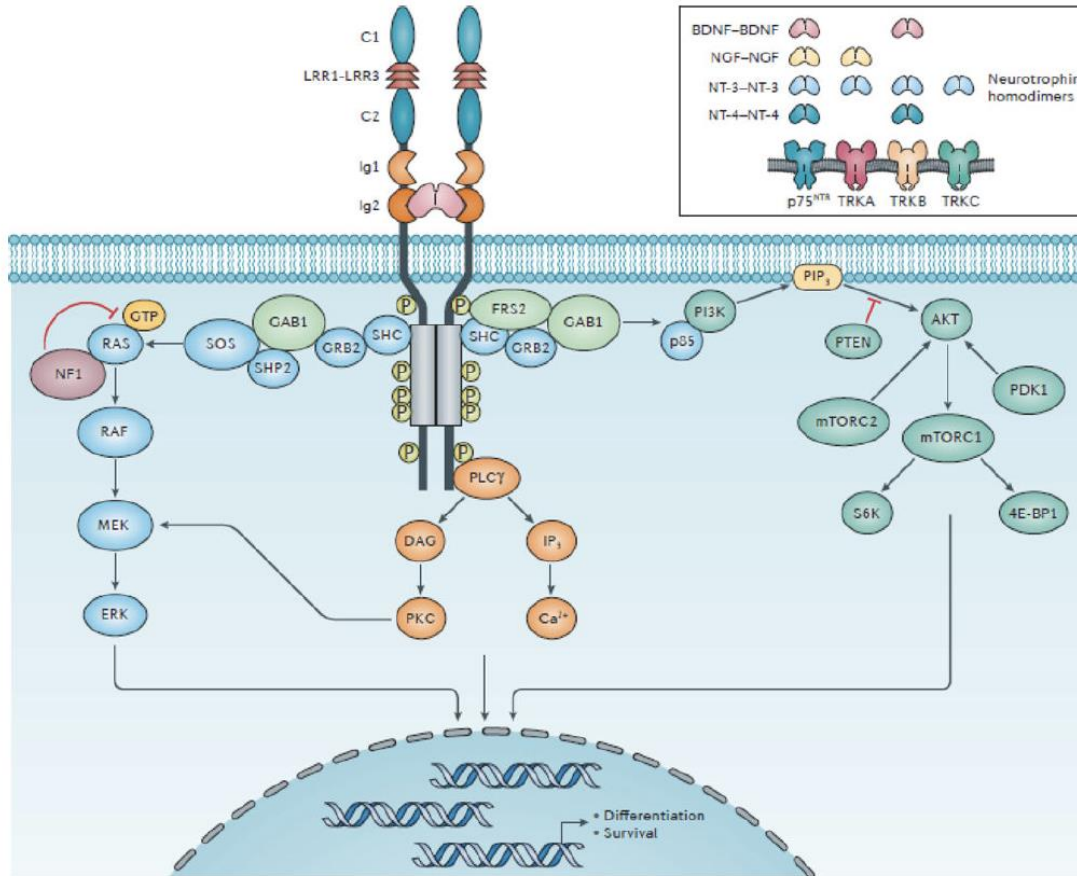
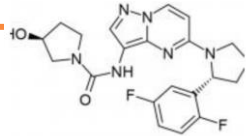


larotrectinib

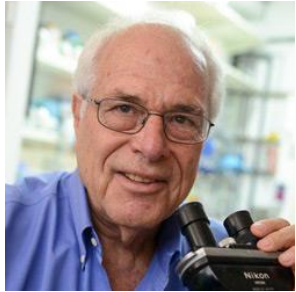


Après 1 mois

# Mecanisme d'action



# La success story du ciblage du CD19 par les CAR-T cells



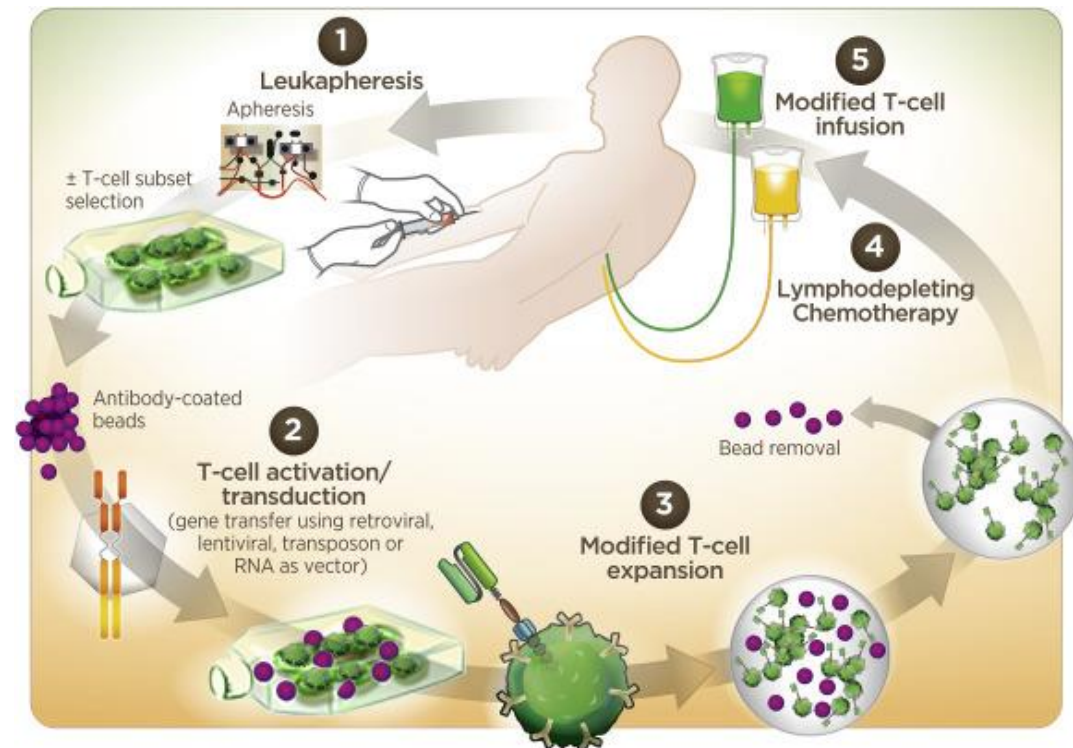
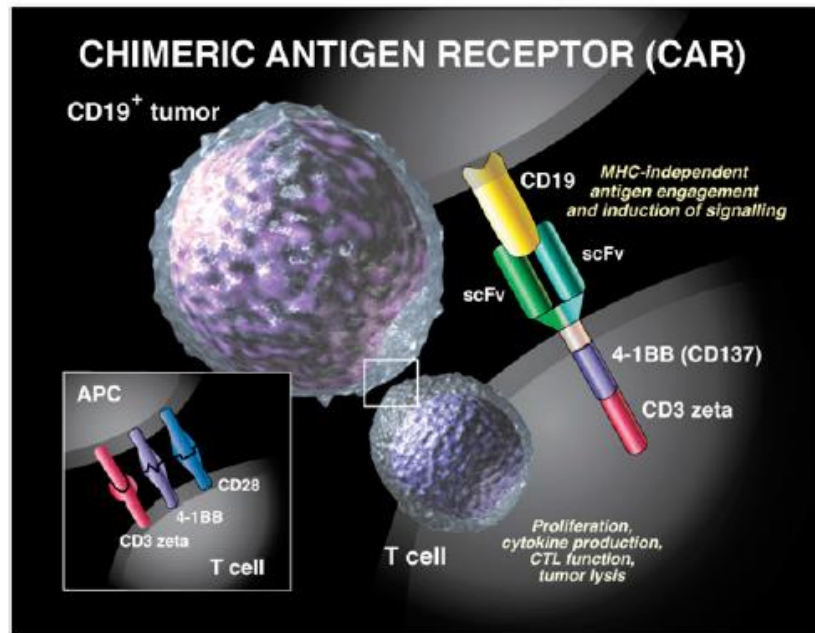
Zelig Eshhar

Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity  
Gross G, Waks T, Eshhar Z.  
**Proc Natl Acad Sci USA 1989** Dec;86(24):10024-8.

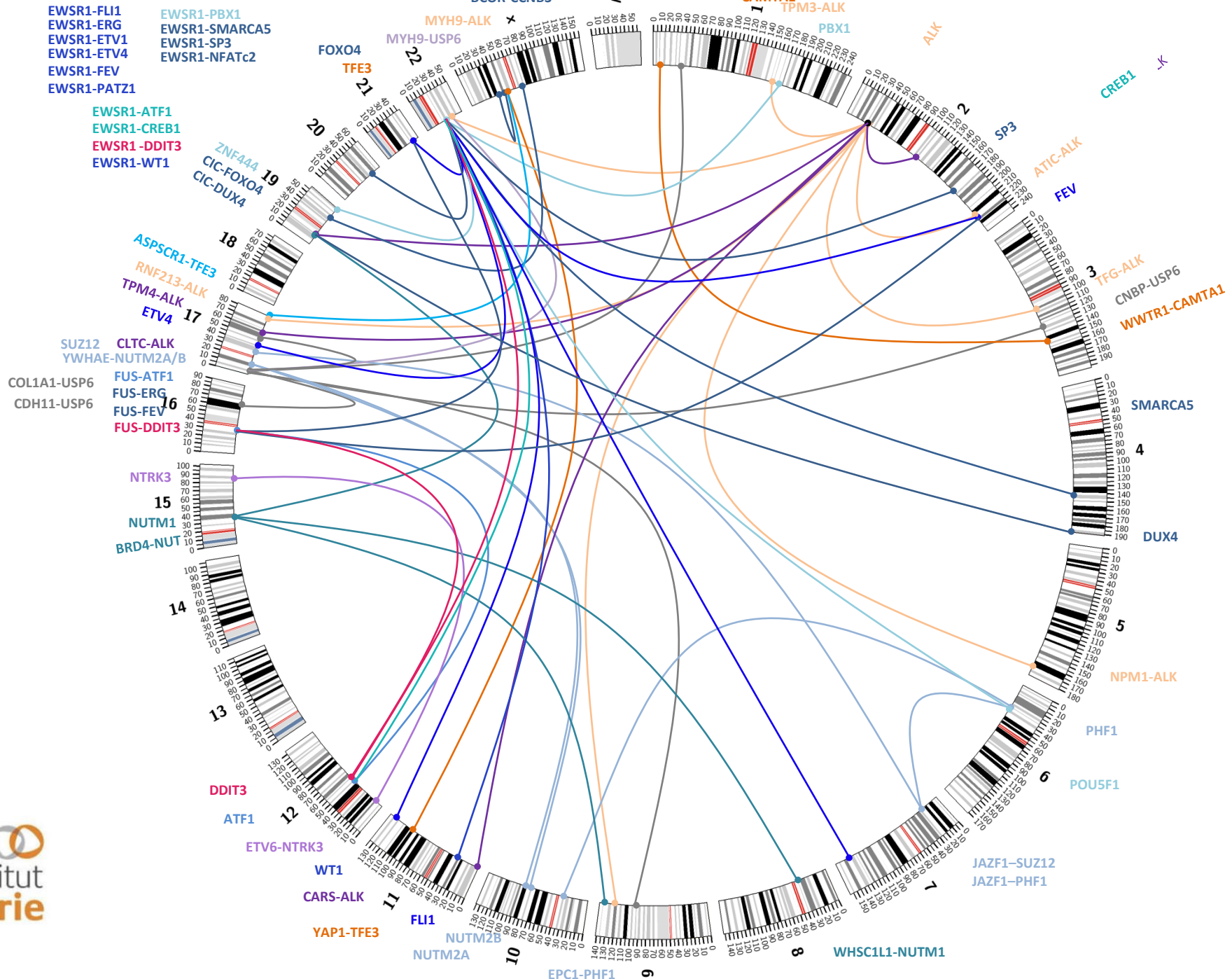


Steve Grupp

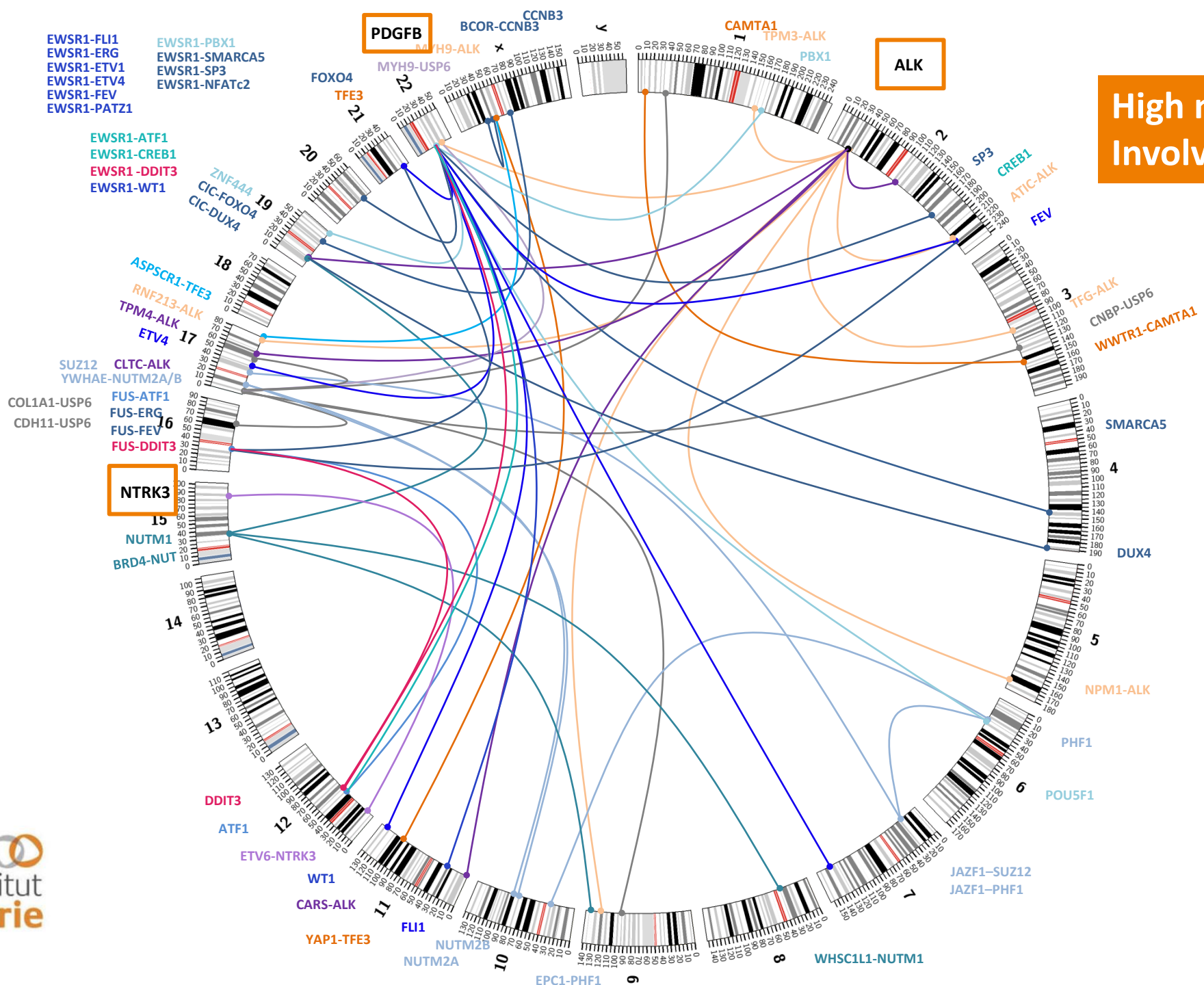
Chimeric antigen receptor-modified T cells for acute lymphoid leukemia.  
Grupp SA, ..., June CH.  
**N Engl J Med 2013** Apr 18;368(16):1509-1518.







High number of gene fusions  
Involving transcription factors

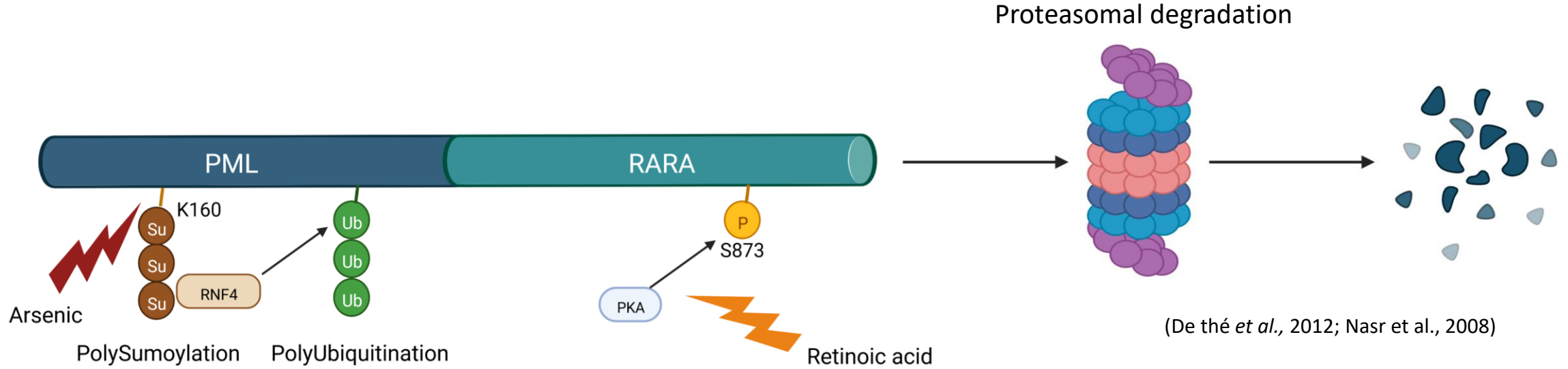




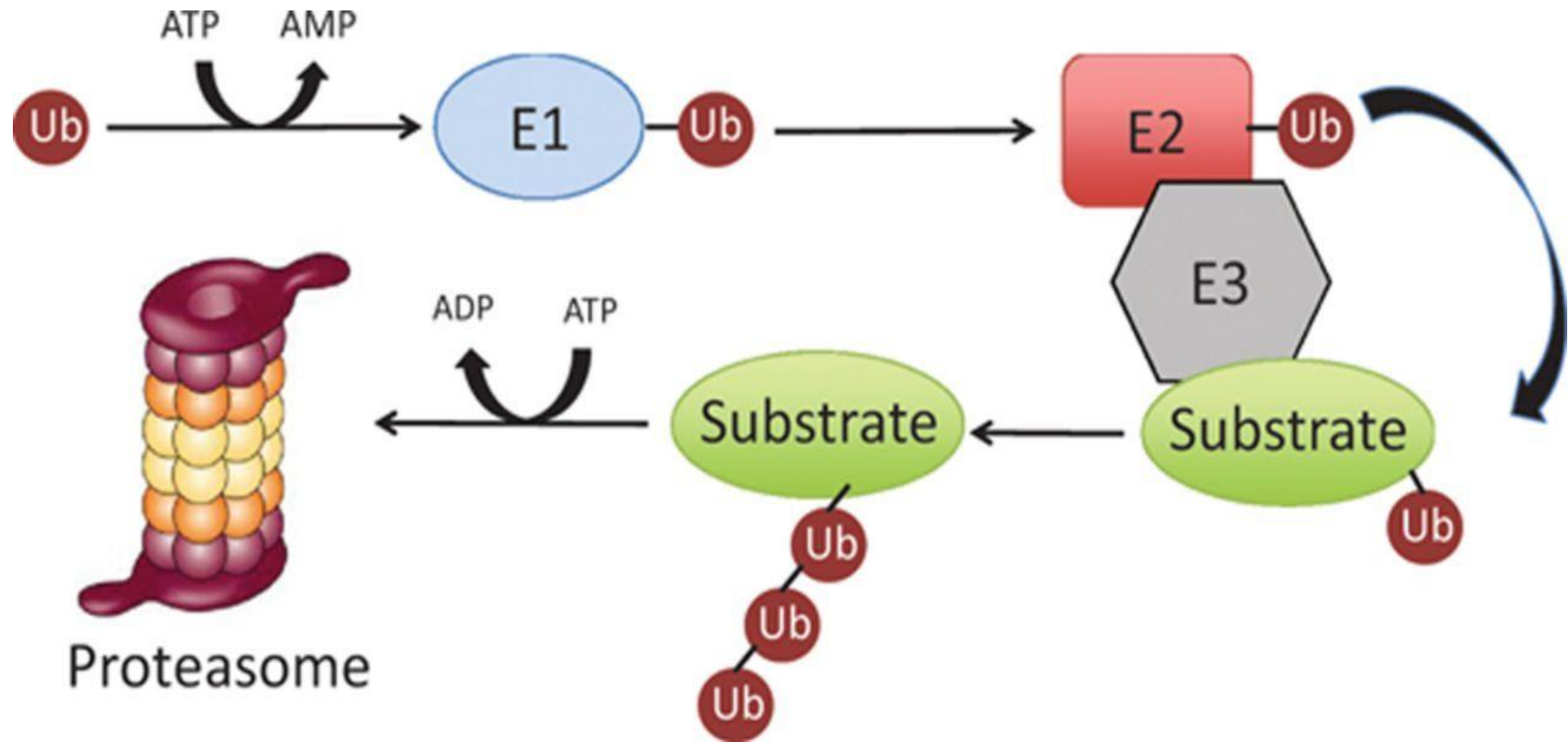
Et si on pouvait dégrader  
les protéines oncogènes,  
“driver” du processus  
tumoral !!

# La success story des leucémies à promyélocytes

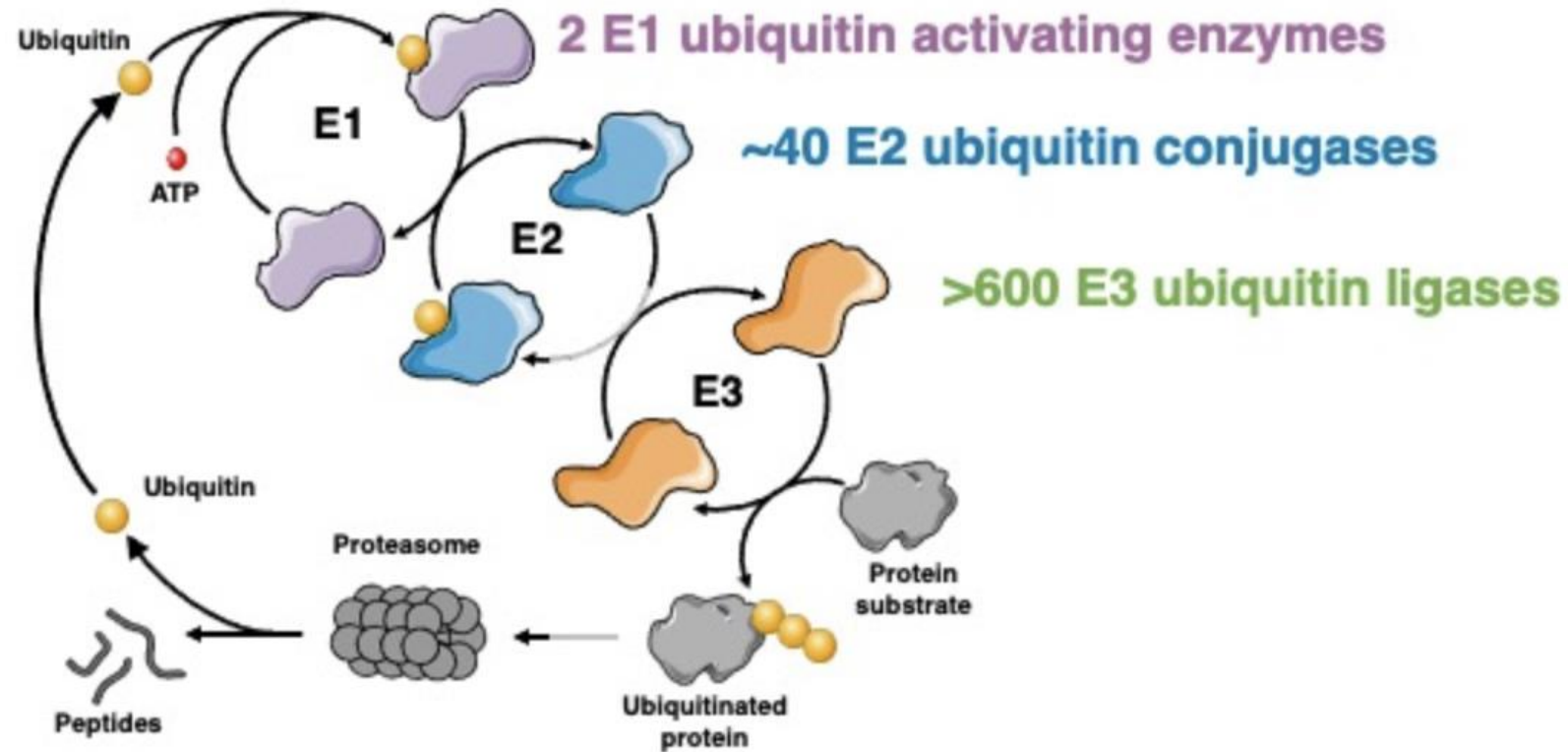
- Arsenic and Retinoic Acid : Proteasomal degradation of PML-RARA
  - **Arsenic**: Degradation through **sumoylation**
  - **Retinoic Acid**: Degradation through **phosphorylation**



# Le système Ubiquitin-Proteasome

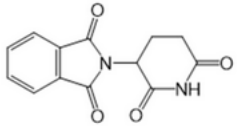


# Le système Ubiquitin-Proteasome

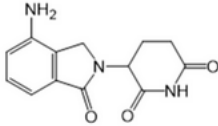


# L'effet tératogène du thalidomide

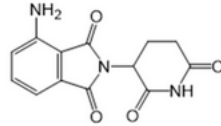
(A) Thalidomide



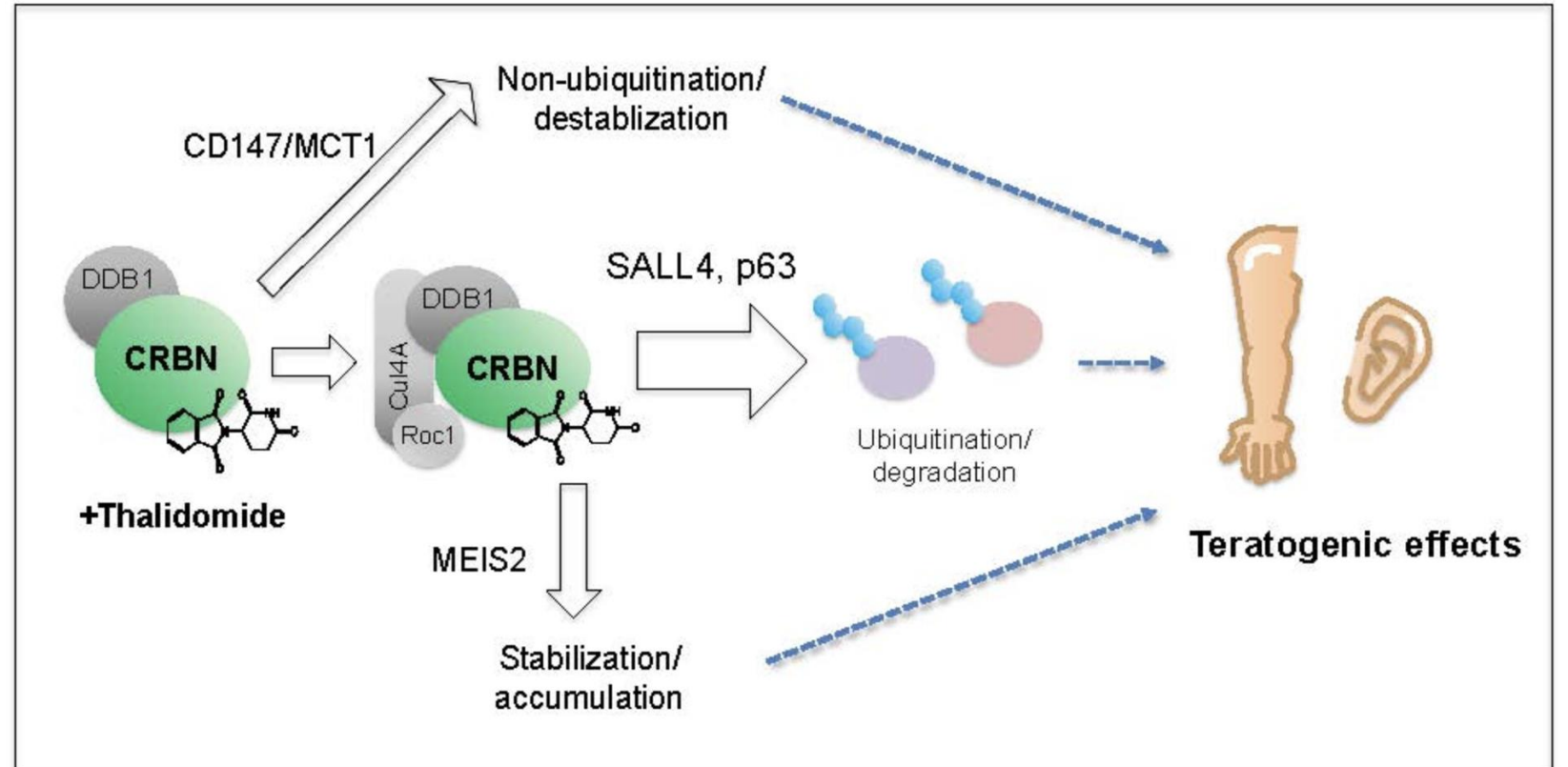
(B) Lenalidomide



(C) Pomalidomide

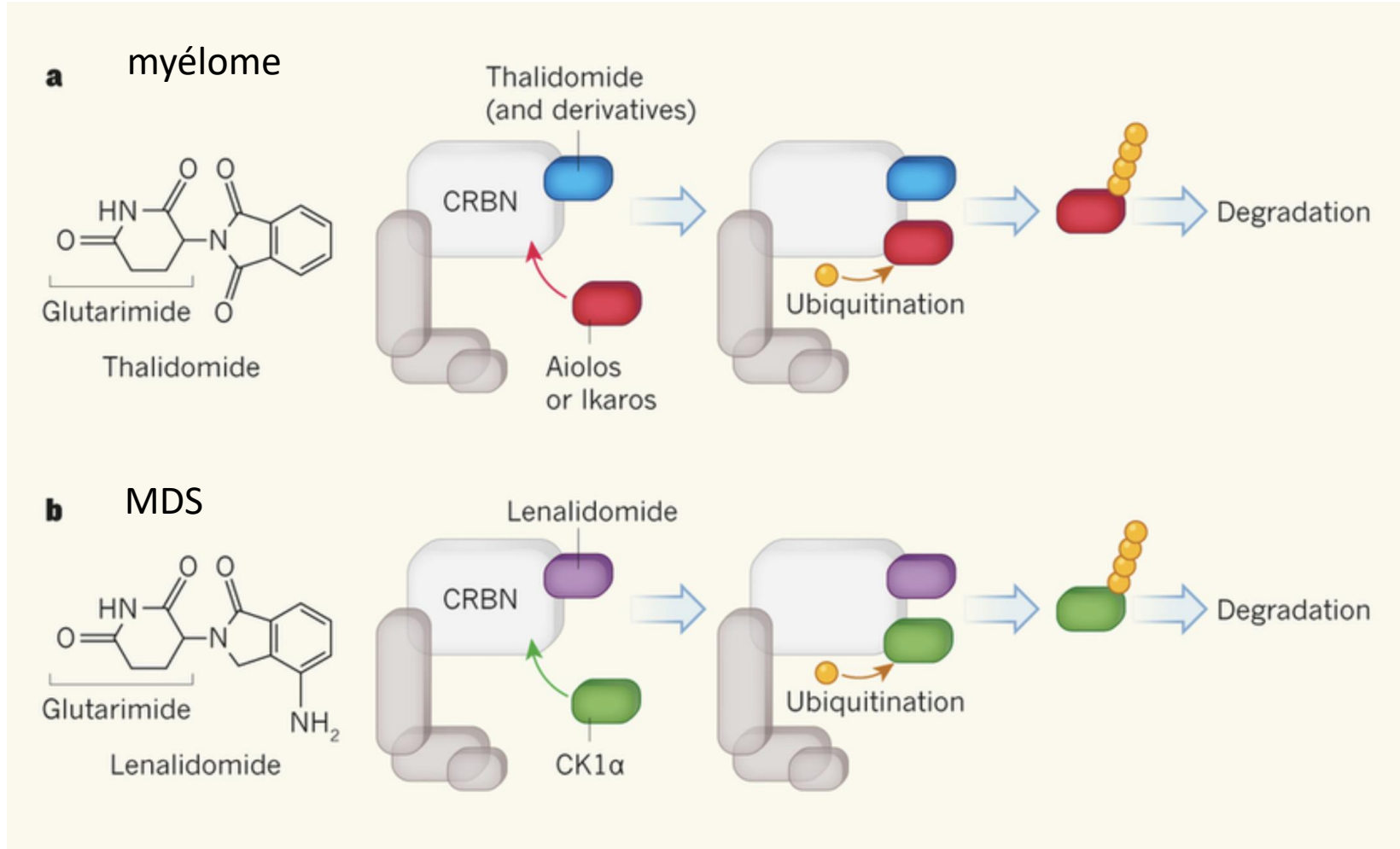


CRBN est une E3-ligase



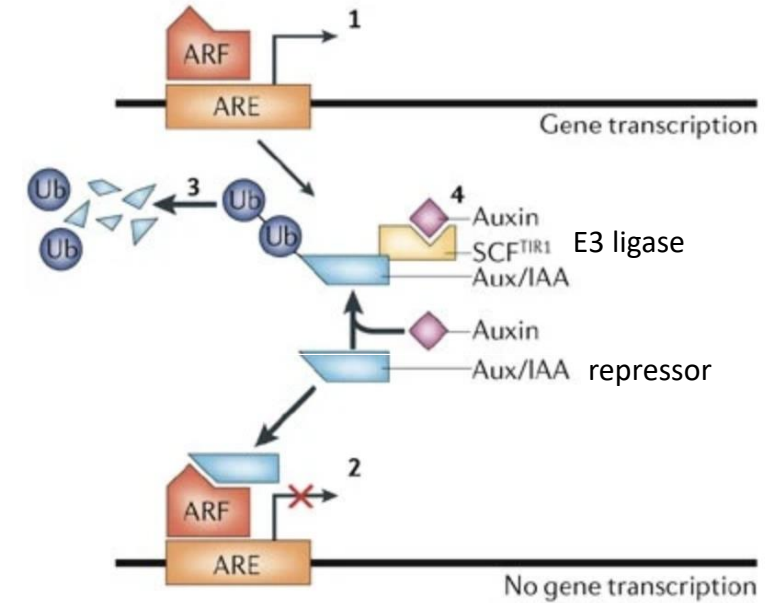
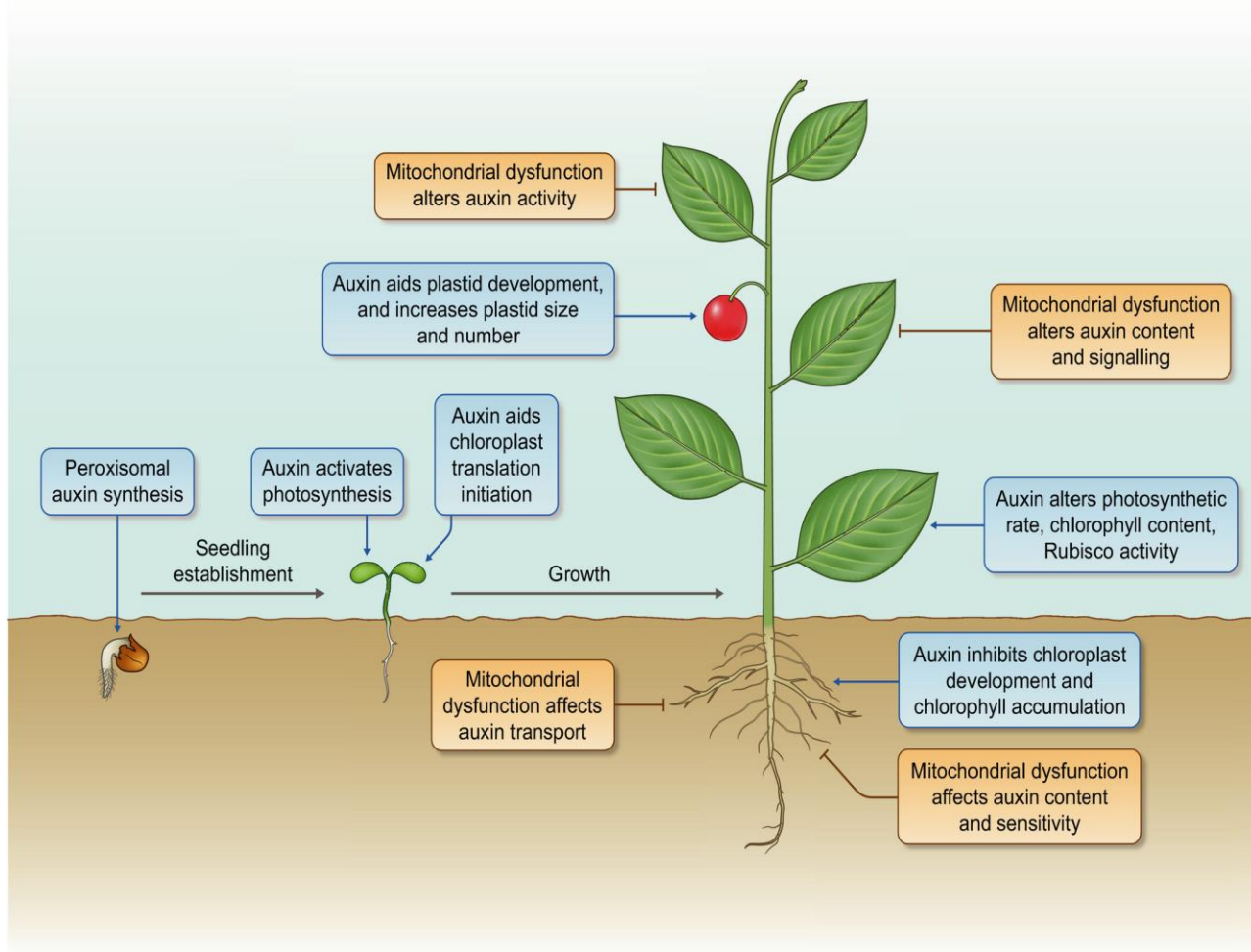
Concept de "molecular glue"

# Thalidomide et dérivés dans les hémopathies malignes





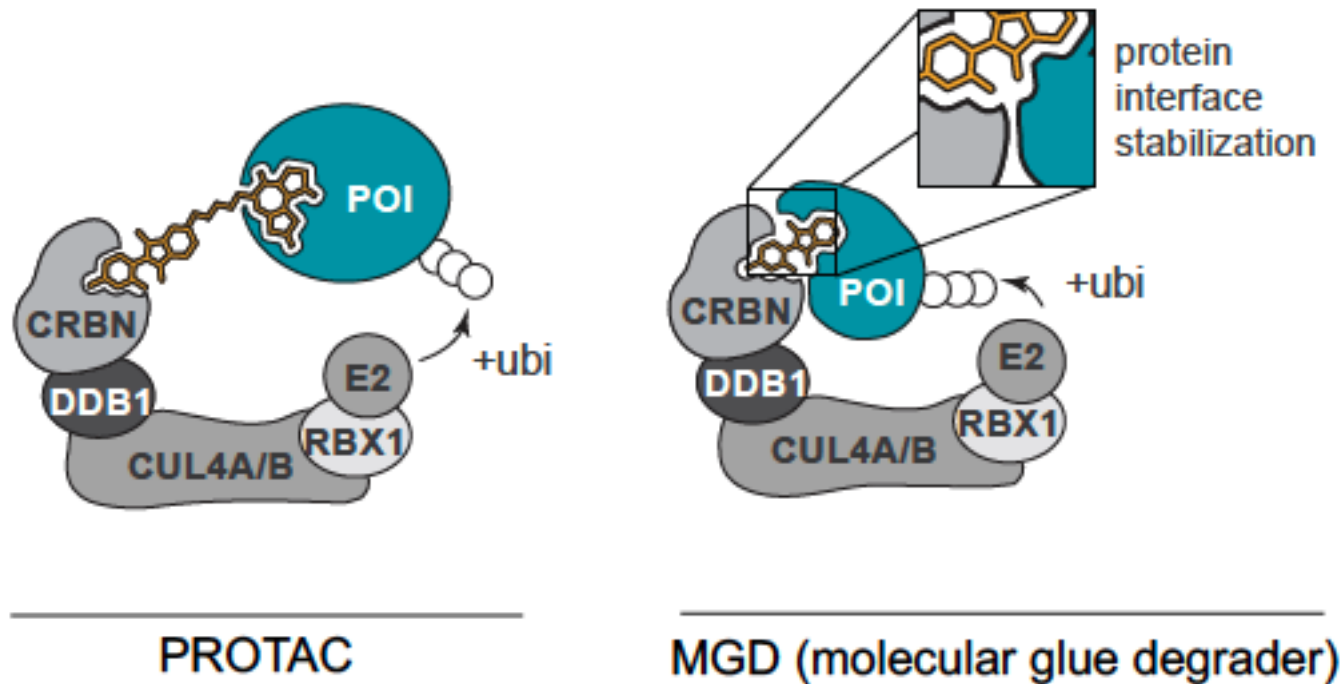
# la phytohormone auxine, le concept de “molecular glues”



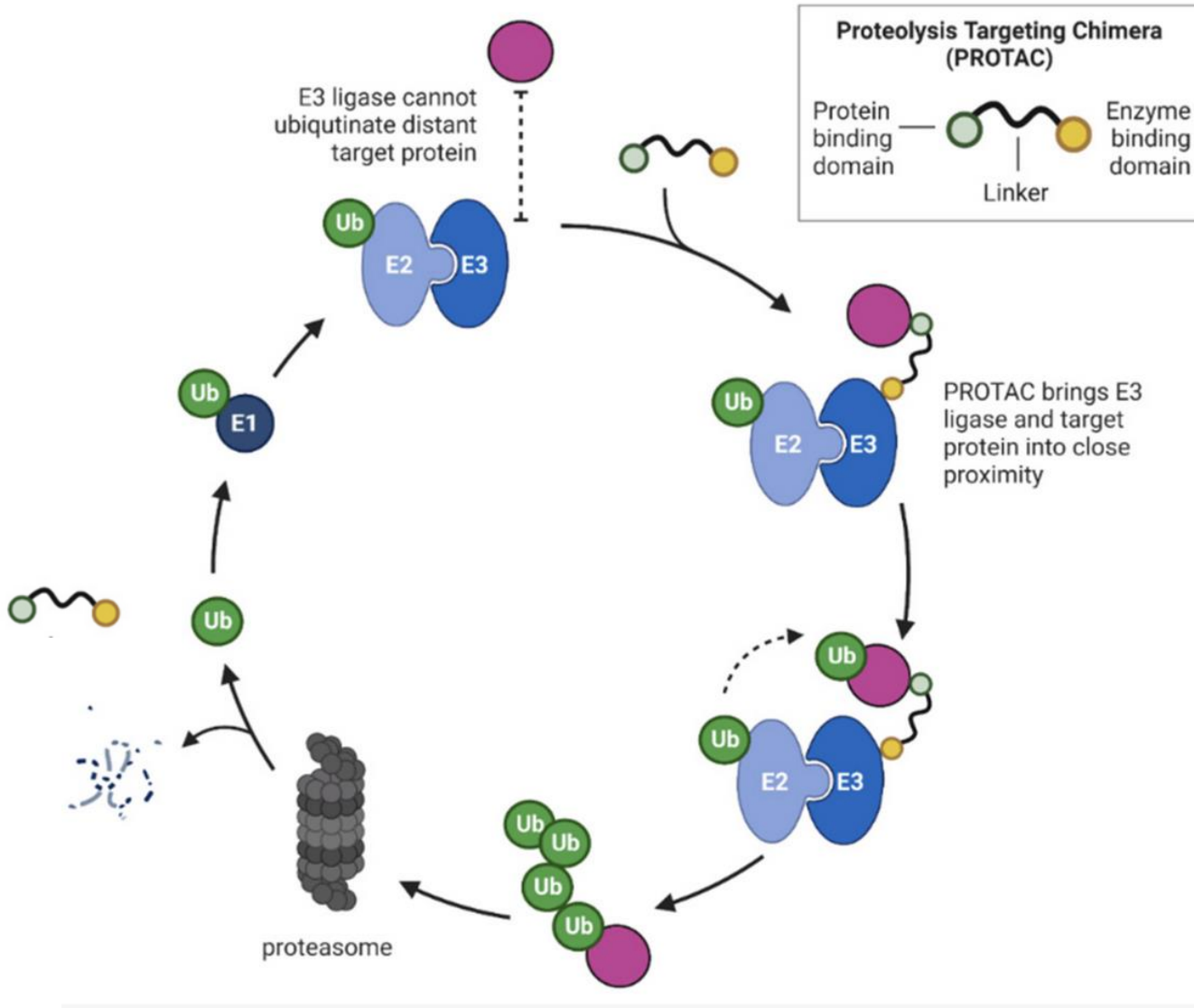
Les exemples précédents montrent le potentiel  
d'une dégradation protéique ciblée (TPD: Targeted Protein Degradation)

---

concepts de "molecular glue" et de PROTAC (PROteolysis-TArgeting Chimeras)



# Le principe des PROTAC



Induire une interaction entre une protéine d'intérêt et une E3-ligase pour induire sa dégradation

Table 1 | **Heterobifunctional PROTAC targeted protein degraders in clinical development**

| Company                | Degrader | Target             | Indications                                  | E3 ligase   | ROA         | Highest phase | Clinical trial no. (if applicable) |
|------------------------|----------|--------------------|--|-------------|-------------|---------------|------------------------------------|
| Arvinas                | ARV-110  | AR                 | Prostate cancer                              | CRBN        | Oral        | Phase II      | NCT03888612                        |
| Arvinas/Pfizer         | ARV-471  | ER                 | Breast cancer                                | CRBN        | Oral        | Phase II      | NCT04072952                        |
| Accutar Biotech        | AC682    | ER                 | Breast cancer                                | CRBN        | Oral        | Phase I       | NCT05080842                        |
| Arvinas                | ARV-766  | AR                 | Prostate cancer                              | Undisclosed | Oral        | Phase I       | NCT05067140                        |
| Bristol Myers Squibb   | CC-94676 | AR                 | Prostate cancer                              | CRBN        | Oral        | Phase I       | NCT04428788                        |
| Dialectic Therapeutics | DT2216   | BCL-x <sub>L</sub> | Liquid and solid tumours                     | VHL         | I.v.        | Phase I       | NCT04886622                        |
| Foghorn Therapeutics   | FHD-609  | BRD9               | Synovial sarcoma                             | Undisclosed | I.v.        | Phase I       | NCT04965753                        |
| Kymera/Sanofi          | KT-474   | IRAK4              | Autoimmune diseases (e.g., AD, HS, RA)       | Undisclosed | Oral        | Phase I       | NCT04772885                        |
| Kymera                 | KT-413   | IRAK4              | Diffuse large B cell lymphoma (MYD88-mutant) | CRBN        | I.v.        | Phase I       |                                    |
| Kymera                 | KT-333   | STAT3              | Liquid and solid tumours                     | Undisclosed | Undisclosed | Phase I       |                                    |
| Nurix Therapeutics     | NX-2127  | BTK                | B cell malignancies                          | CRBN        | Oral        | Phase I       | NCT04830137                        |
| Nurix Therapeutics     | NX-5948  | BTK                | B cell malignancies and autoimmune diseases  | CRBN        | Oral        | Phase I       | NCT05131022                        |
| C4 Therapeutics        | CFT8634  | BRD9               | Synovial sarcoma                             | CRBN        | Oral        | IND-e         |                                    |
| C4 Therapeutics        | CFT8919  | EGFR-L858R         | Non-small-cell lung cancer                   | CRBN        | Oral        | IND-e         |                                    |
| Cullgen                | CG001419 | TRK                | Cancer and other indications                 | CRBN        | Oral        | IND-e         |                                    |

# Applications en oncologie pédiatrique

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Dégradation de protéines oncogènes bien caractérisée:

Tumeurs solides MYCN, EWSR1-FLI1, PAX3/7-FOXO1, EWSR1-WT1, ALK...

Protéines de fusion des leucémies, lymphomes

Dégradation des partenaires indispensables à l'action des protéines oncogènes

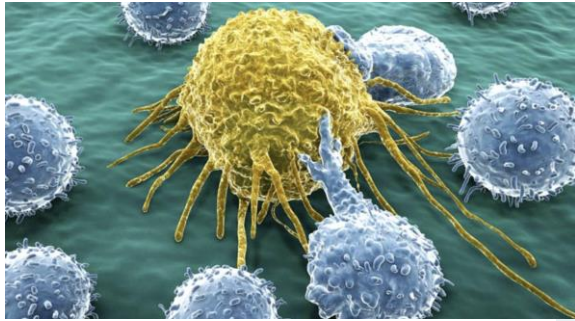
Complexe SWI/SNF, histone acétyl transférase...

Ligands de E3 ligases bien connus pour VHL (HIF1 $\alpha$  mimétiques) et CRBN (dérivés du thalidomide)

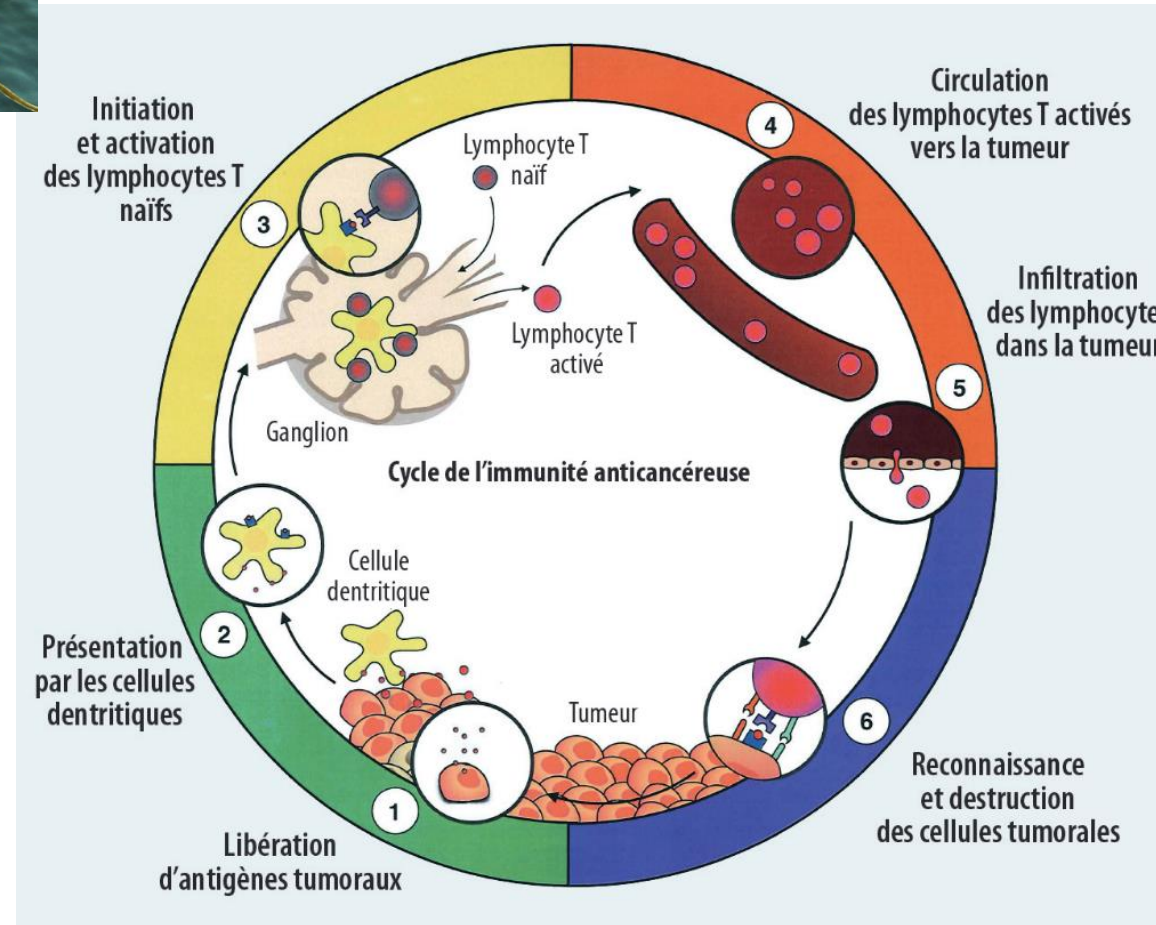
Ligands des protéines d'intérêt:

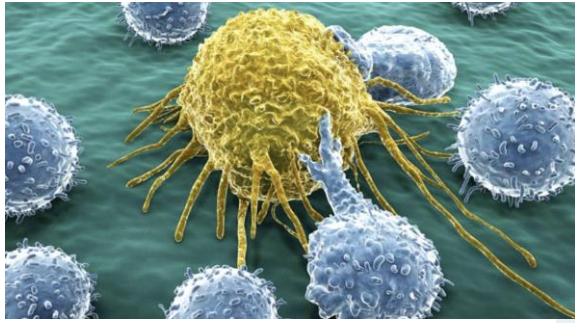
ligands connus (hormones, inhibiteurs, ...)

criblage en cours pour de nombreuses protéines (DNA-encoded chemical libraries)

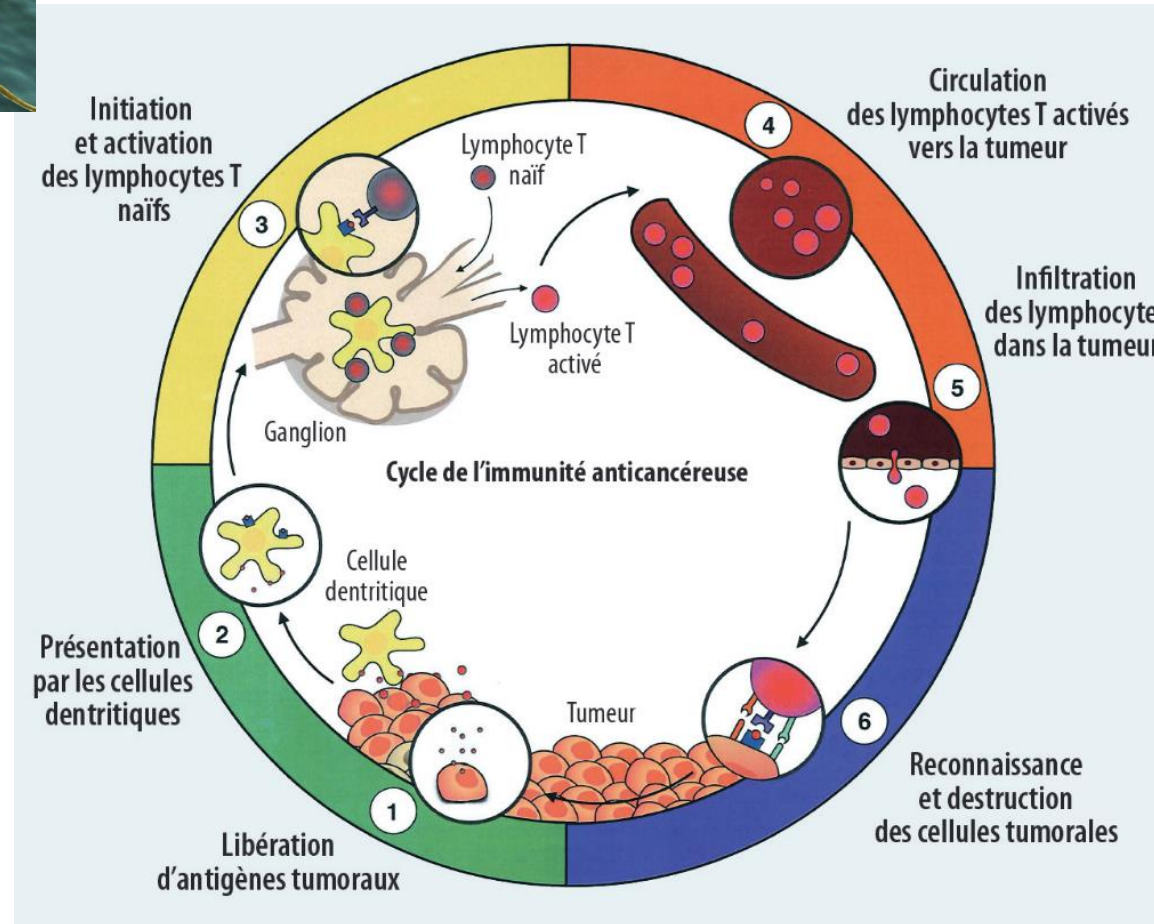


# La réponse immunitaire anti tumorale



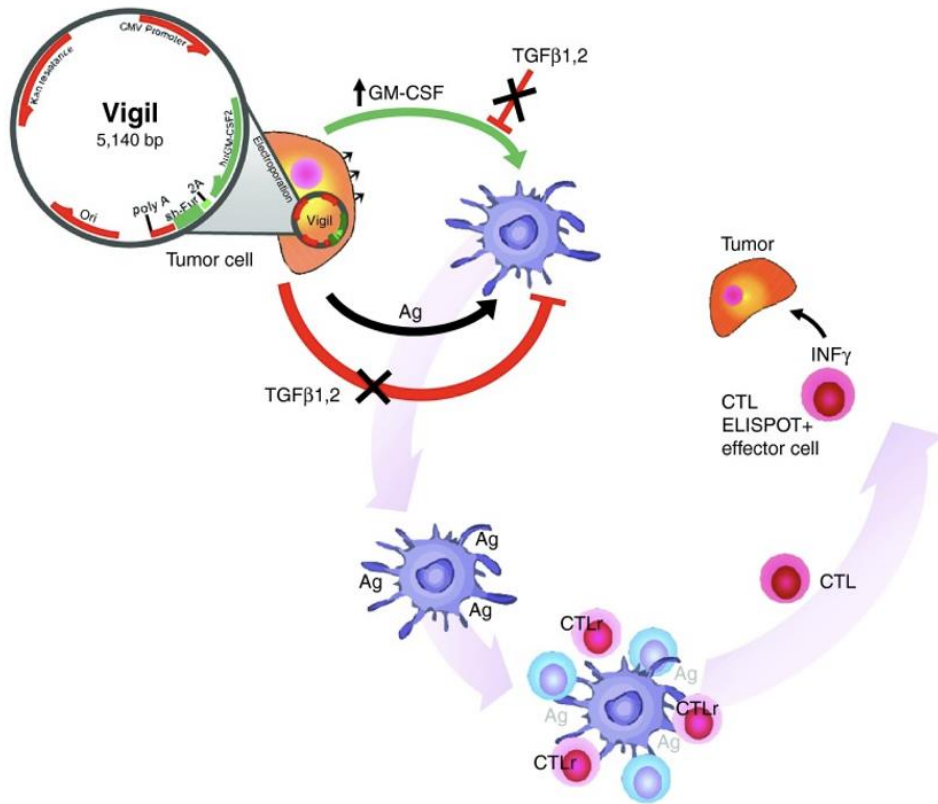
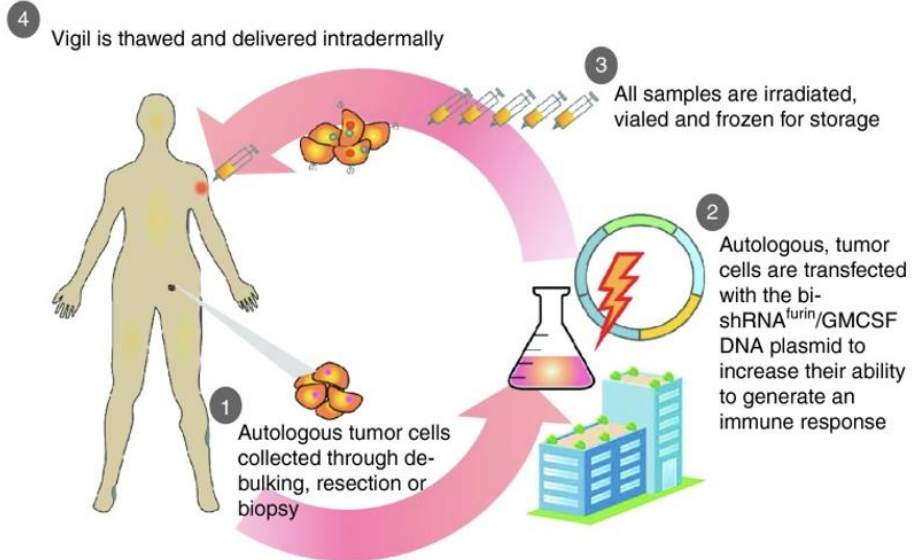


# Quelques stratégies d'immunothérapie

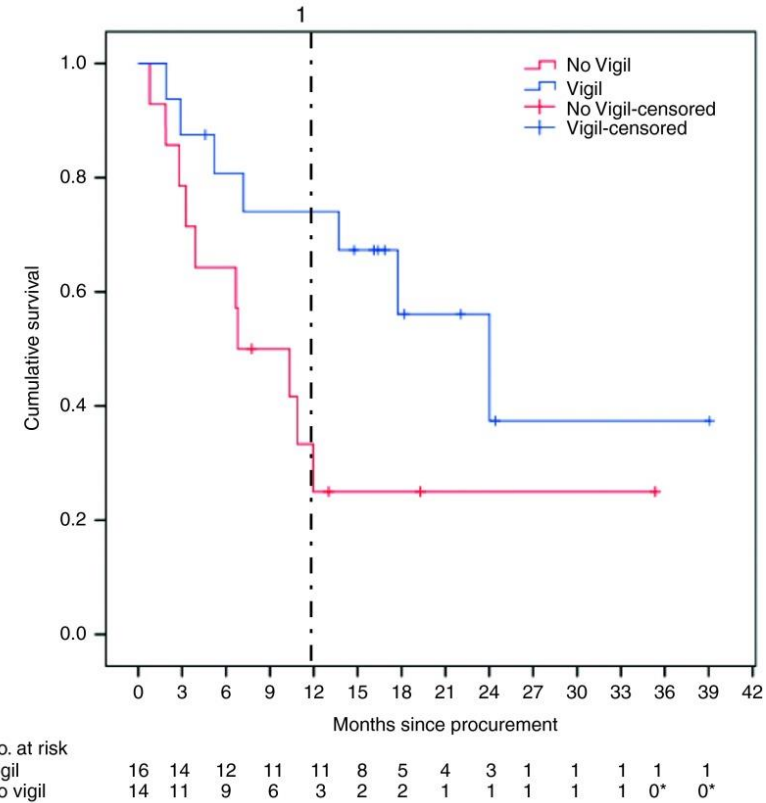


Vaccination sur néoantigènes mutationnels rares en oncologie pédiatrique

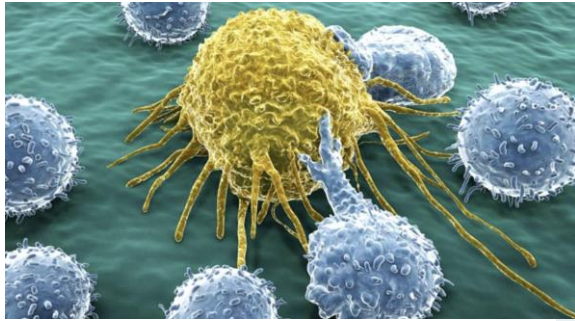
Vaccination  
Pour "forcer"  
La reconnaissance des Ag tumoraux

**a****b**

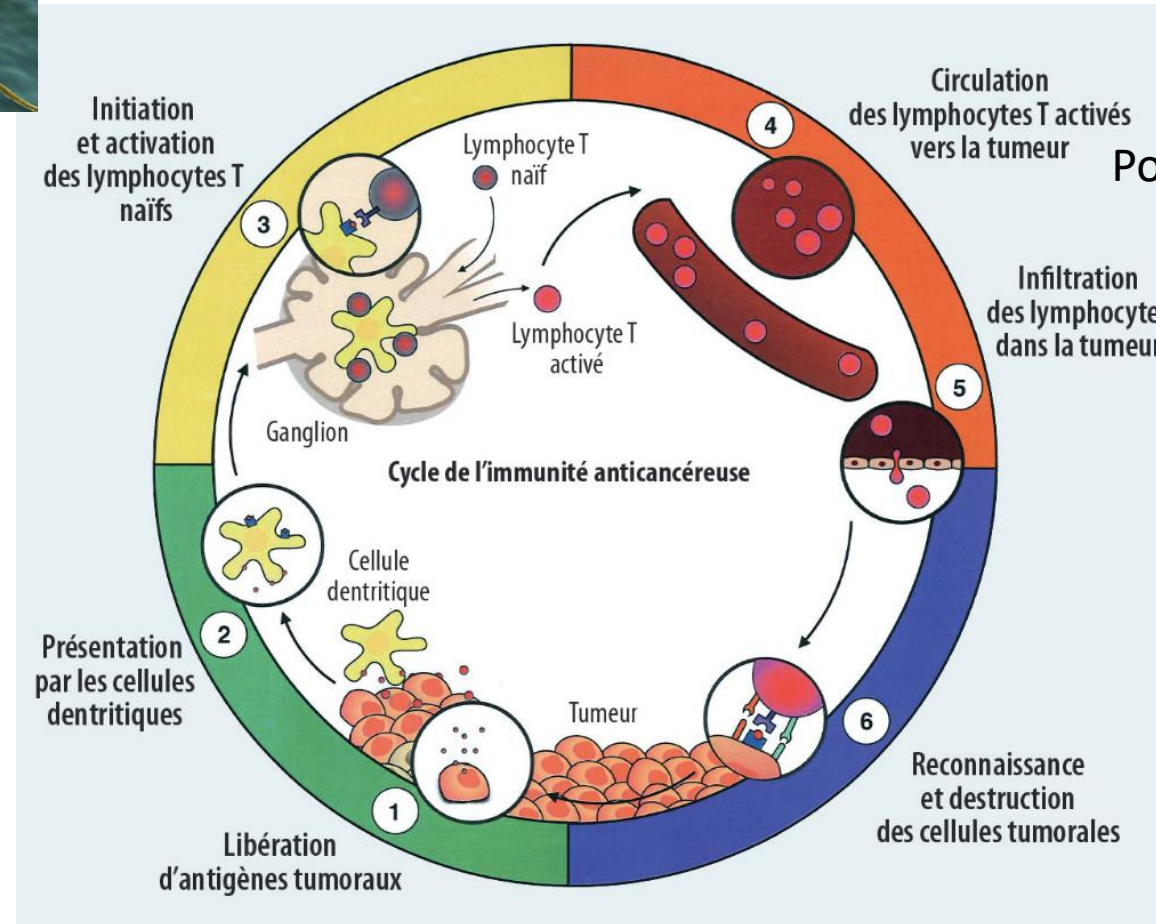
Vigil (a vaccine using autologous tumor cells modified to stimulate antigen presentation) shows efficacy in Ewing sarcoma patients





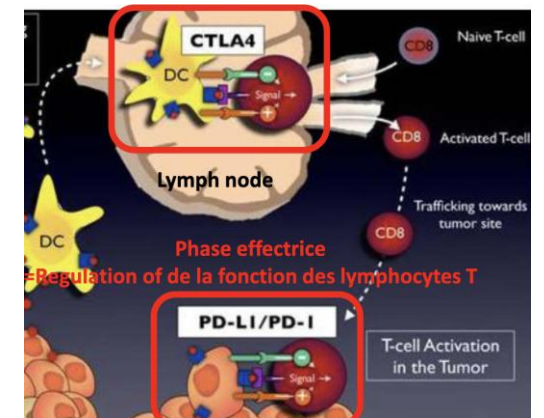


# Quelques stratégies d'immunothérapie

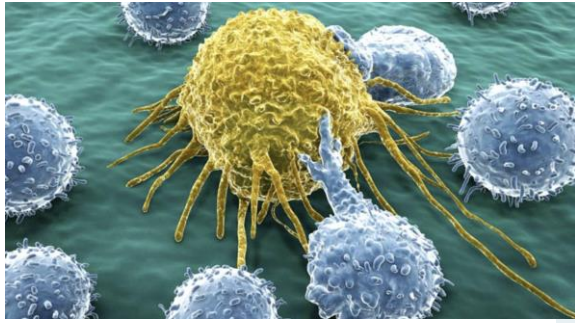


## Immune checkpoint Inhibitors

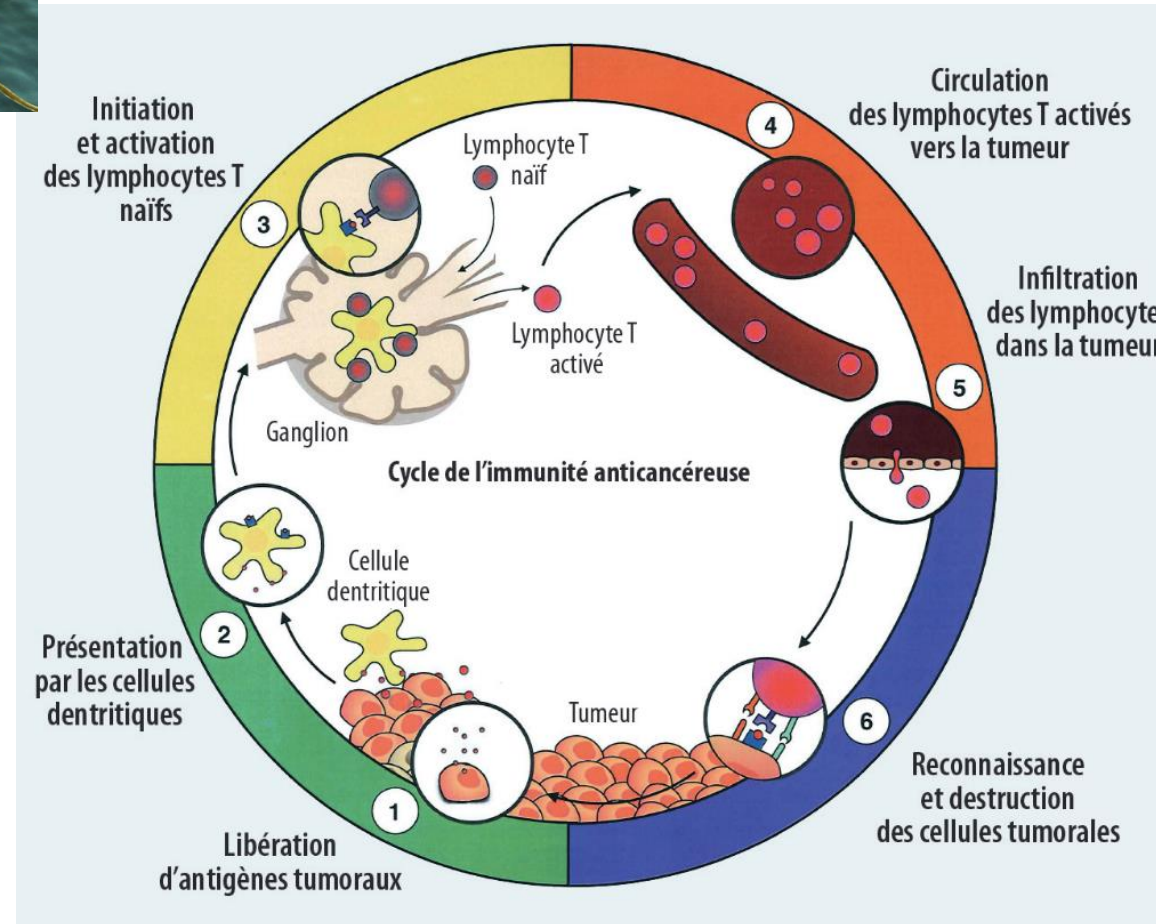
Pour réactiver le système immunitaire



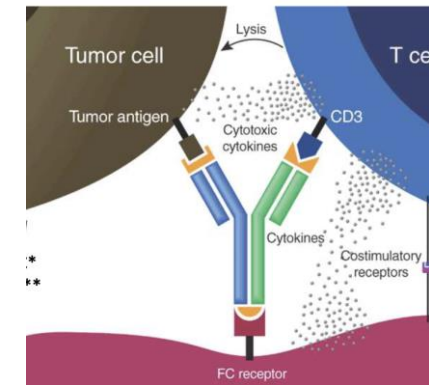
Peu d'efficacité dans les cancers pédiatriques (MDH, CMMRD, SMARCB1)



# Quelques stratégies d'immunothérapie

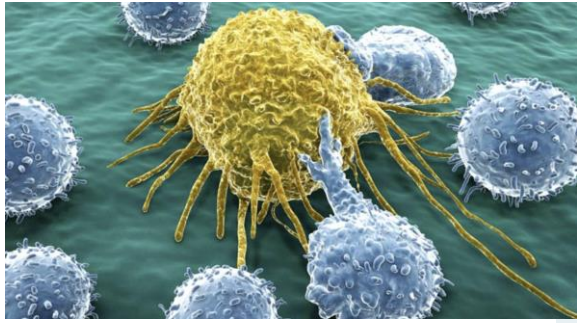


## Bispecific T-cell engager

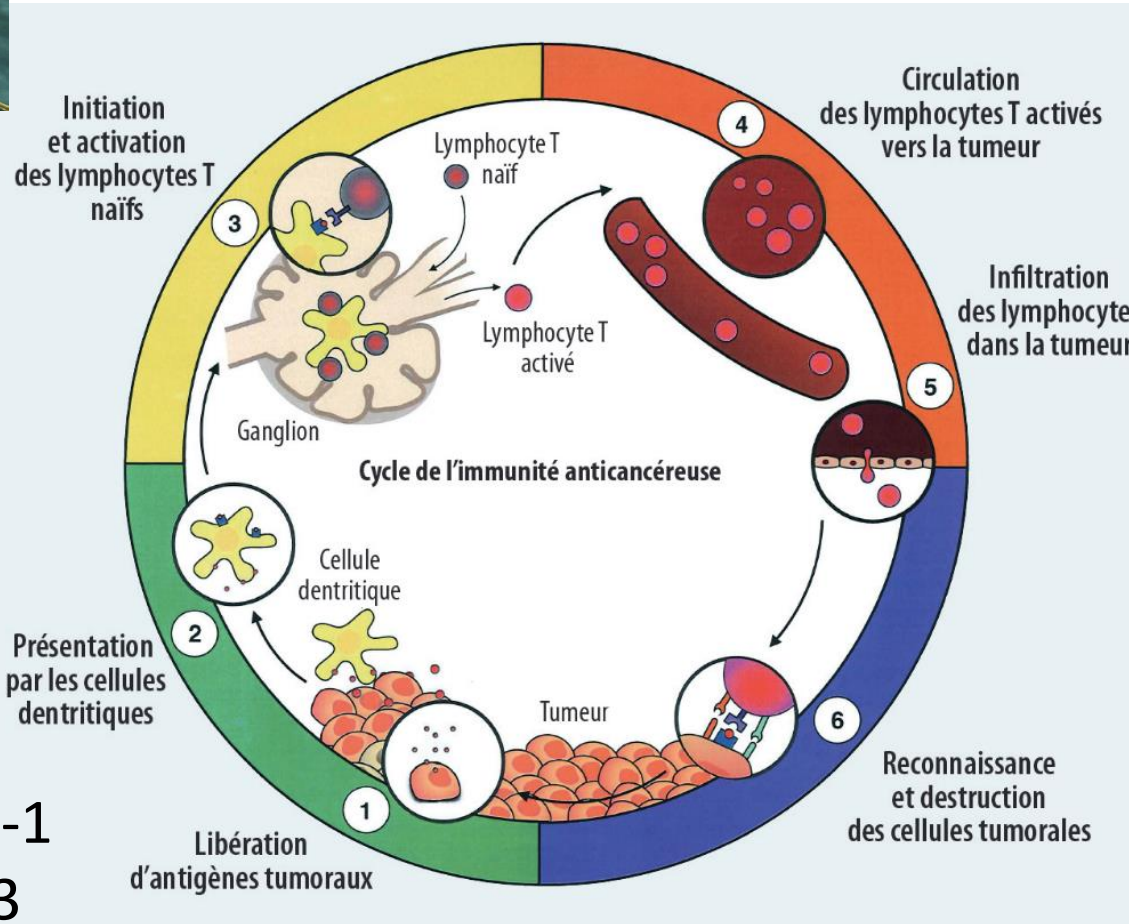


3F8-bispecific (GD2-CD3) antibody in Nb, OS...

NCT03860207

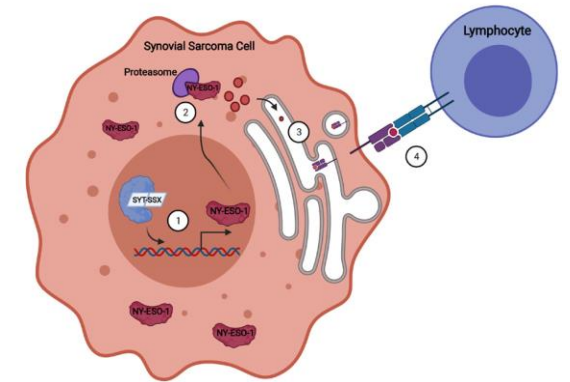


# Quelques stratégies d'immunothérapie



NY-ESO-1  
MAGE-3

## TCR T-Cells



Nombreux essais cliniques  
Dans synoviosarcome

ORIGINAL ARTICLE

# GD2-CART01 for Relapsed or Refractory High-Risk Neuroblastoma

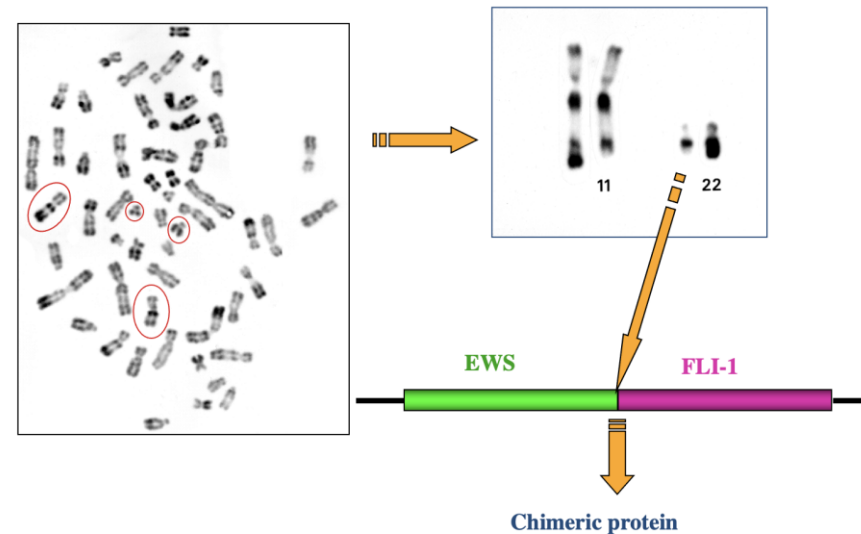
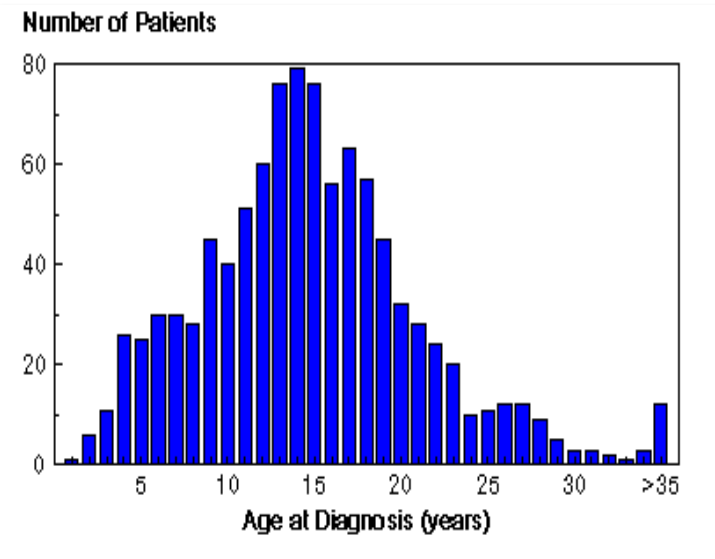
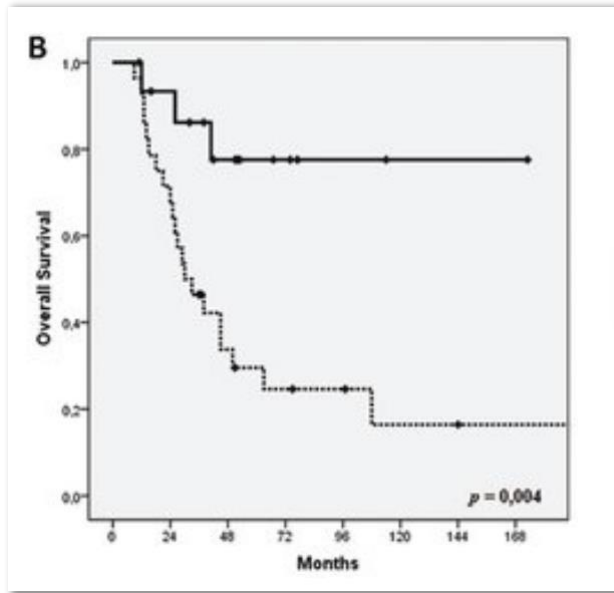
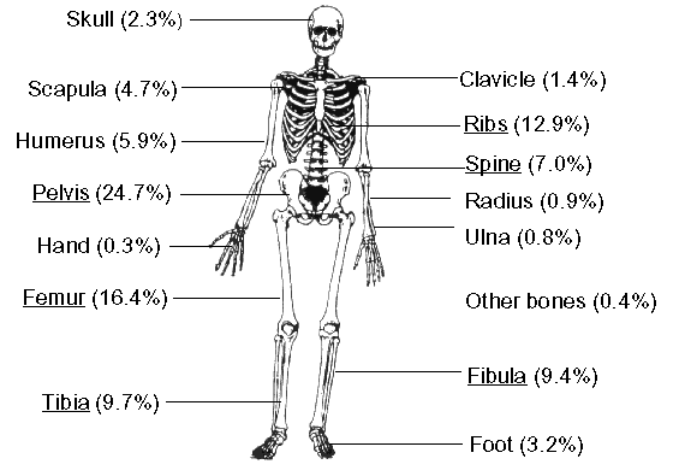
F. Del Bufalo, B. De Angelis, I. Caruana, G. Del Baldo, M.A. De Ioris, A. Serra, A. Mastronuzzi, M.G. Cefalo, D. Pagliara, M. Amicucci, G. Li Pira, G. Leone, V. Bertaina, M. Sinibaldi, S. Di Cecca, M. Guercio, Z. Abbaszadeh, L. Iaffaldano, M. Gunetti, S. Iacovelli, R. Bugianesi, S. Macchia, M. Algeri, P. Merli, F. Galaverna, R. Abbas, M.C. Garganese, M.F. Villani, G.S. Colafati, F. Bonetti, M. Rabusin, K. Perruccio, V. Folsi, C. Quintarelli, and F. Locatelli, for the Precision Medicine Team—IRCCS Ospedale Pediatrico Bambino Gesù\*

# CAR-T en essais cliniques en oncopédiatrie

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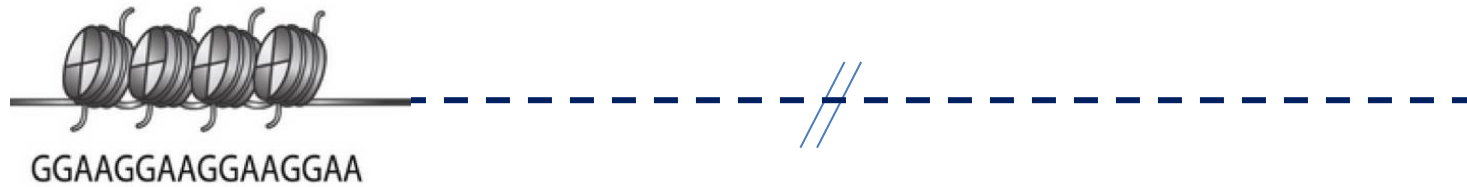
|            |                                       |
|------------|---------------------------------------|
| GD2        | Neuroblastome<br>Tumeurs cérébrales   |
| HER2       | Tumeurs cérébrales                    |
| B7-H3      | Tumeurs cérébrales<br>Tumeurs solides |
| EGFR       | Tumeurs cérébrales                    |
| CD171      | Neuroblastome                         |
| CD22       | B-cell malignancies                   |
| Glypican-3 | Tumeurs solides                       |
| CD7        | T-ALL                                 |
| CD19       | T-ALL                                 |
| CD30       | MDH                                   |
| CD123      | Tumeurs solides                       |

# Ewing sarcoma

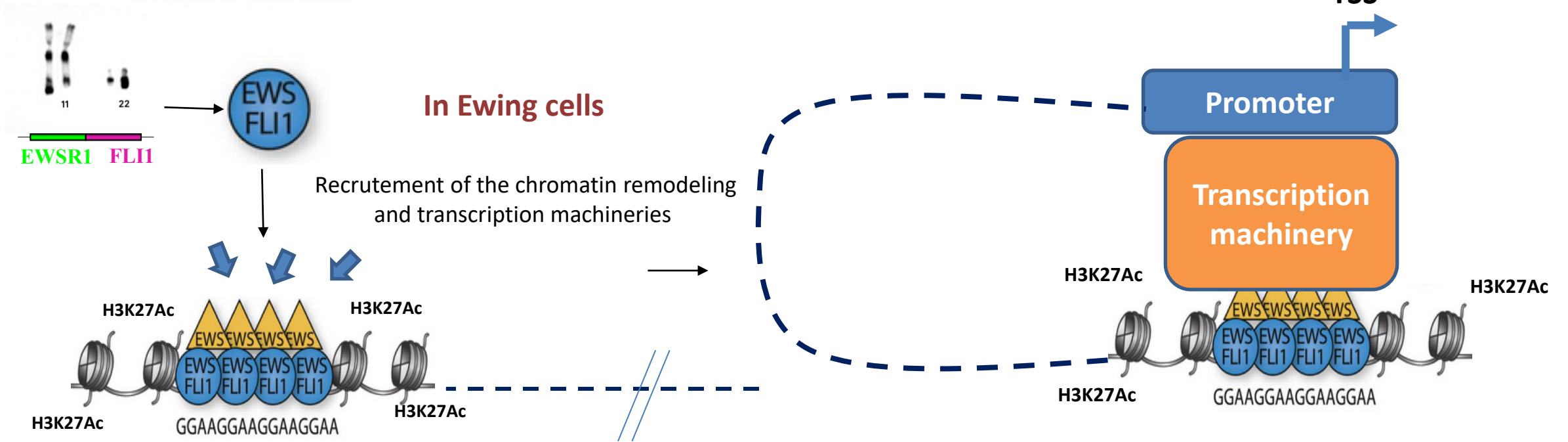


# EWSR1-FLI1 creates neo enhancers at GGAA repeats

In the cell of origin



In Ewing cells



neo enhancers

Complete cell reprogramming

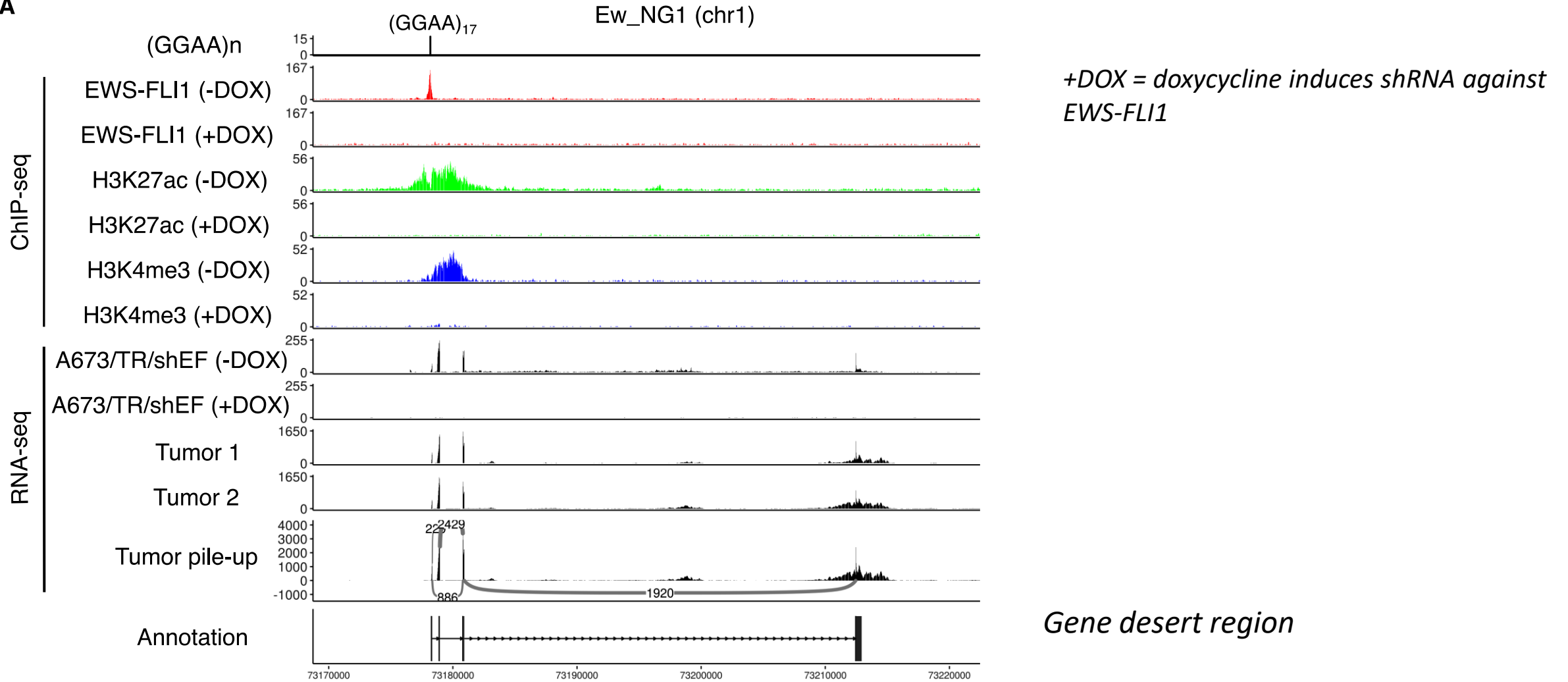
Chong et al, Science, 2018  
Boulay et al, Cell, 2017

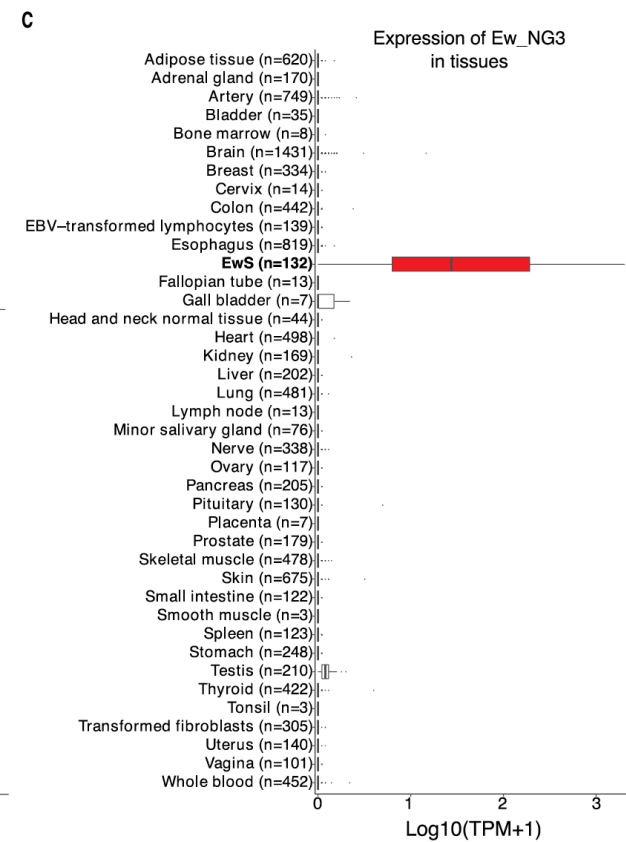
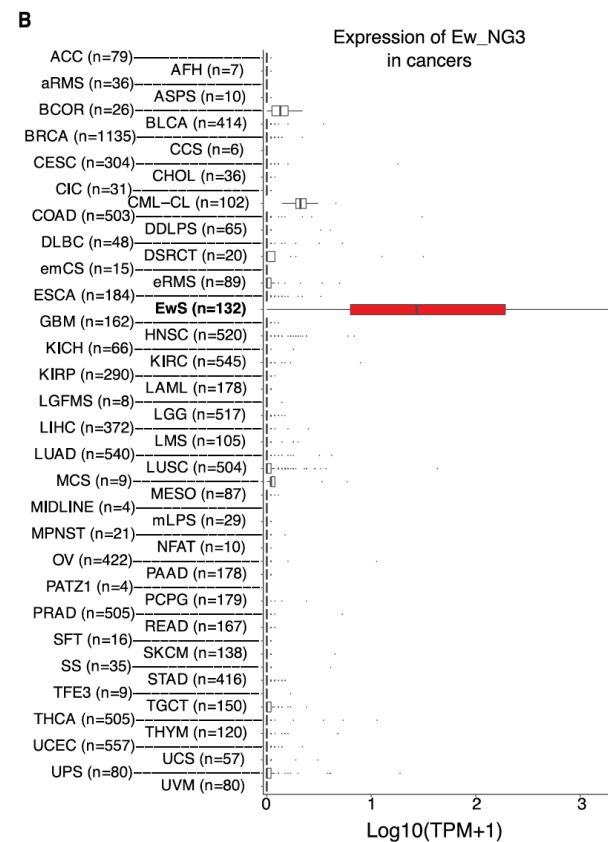
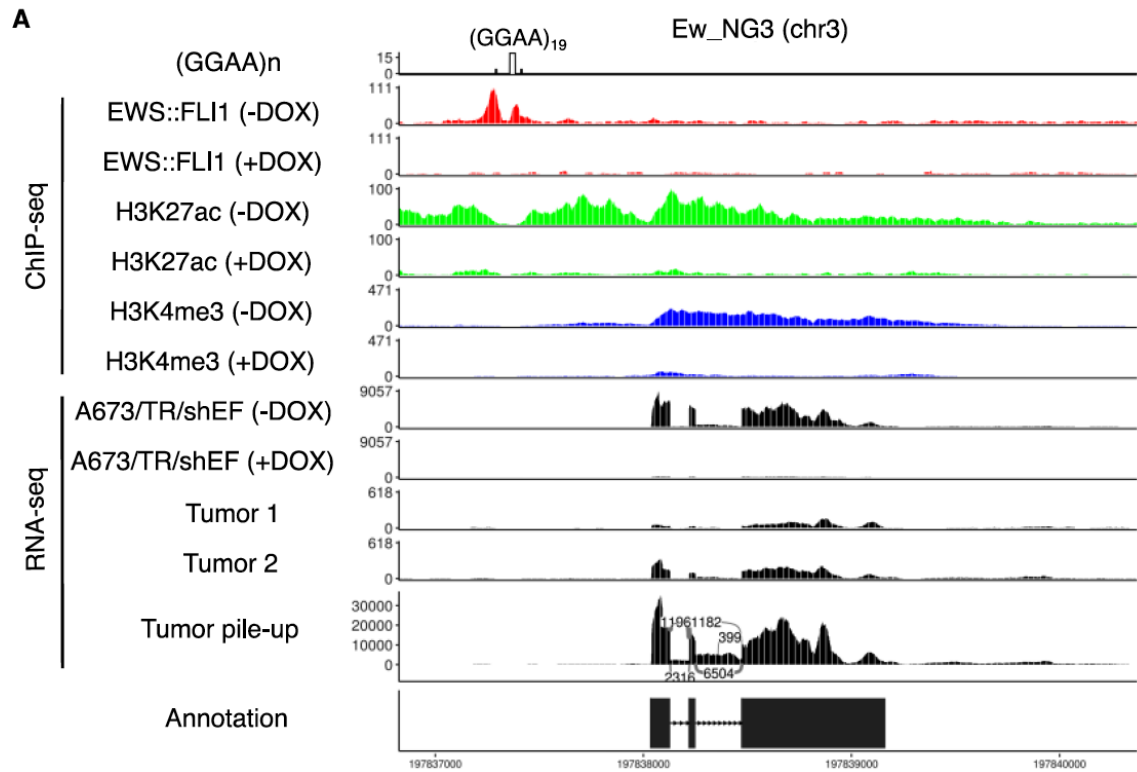




# Identification of new genes in Ewing sarcoma in gene desert regions

A

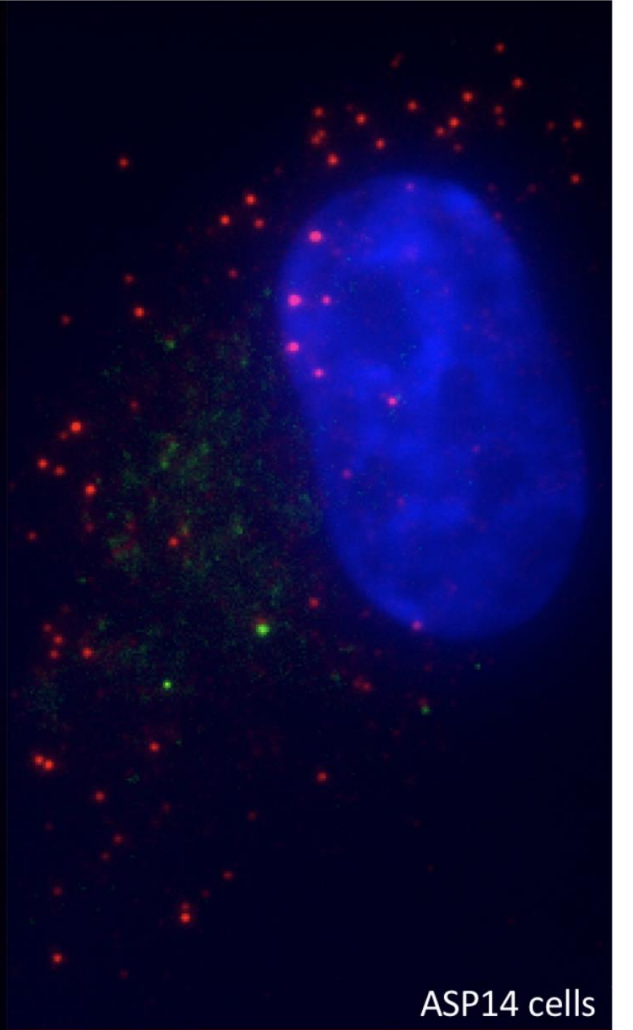
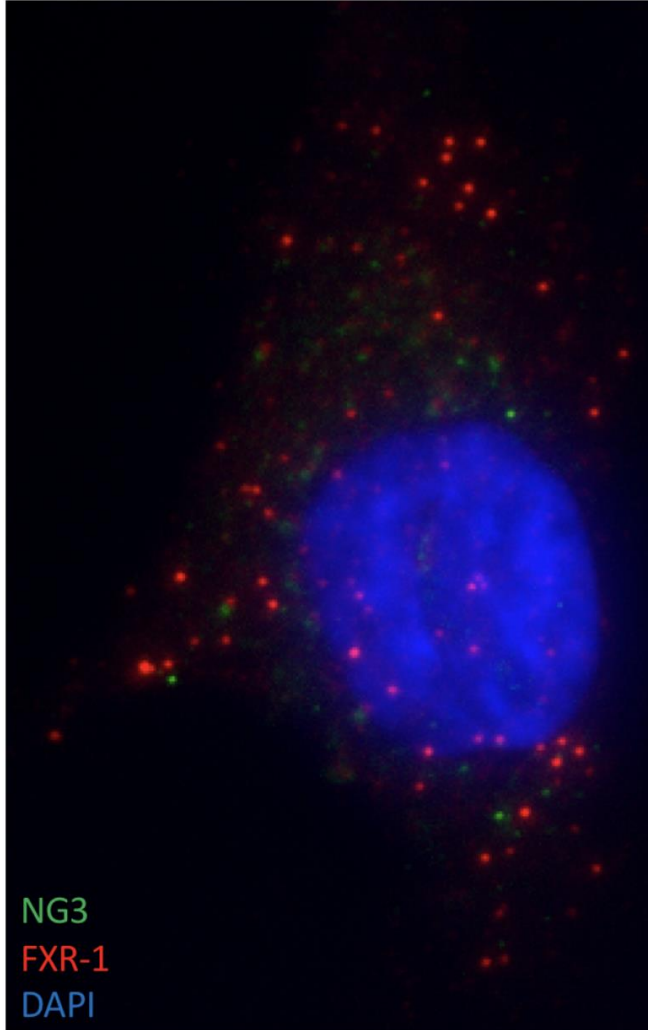
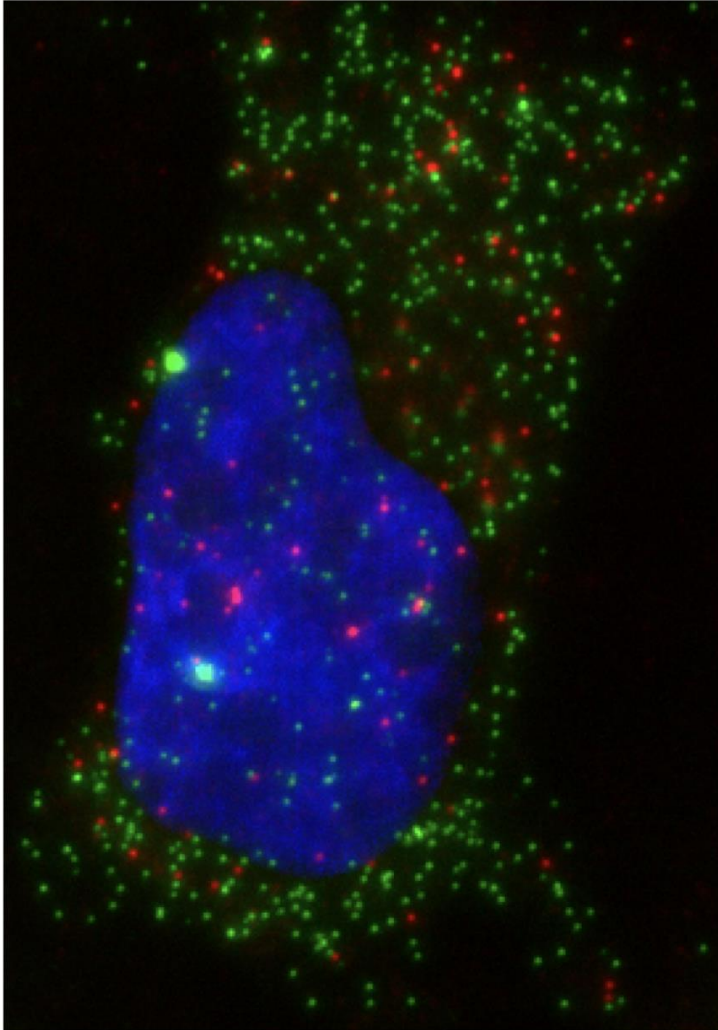




-DOX

+DOX

RNA  
FISH

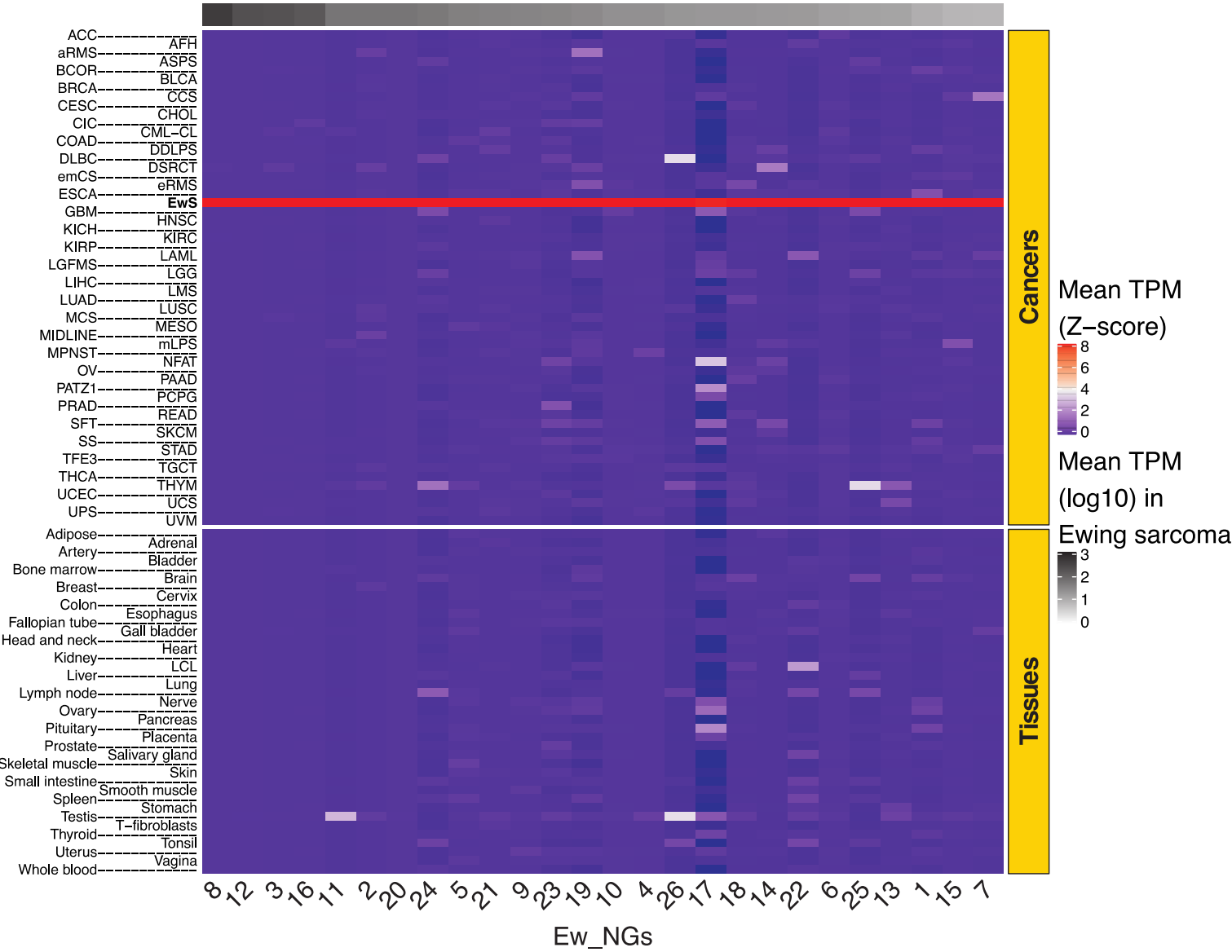


NG3  
FXR-1  
DAPI

ASP14 cells

Kyra Bergman & antoine Coulon

# 25 neogenes (Ew\_NG) found in Ewing sarcoma from short-read RNA-seq

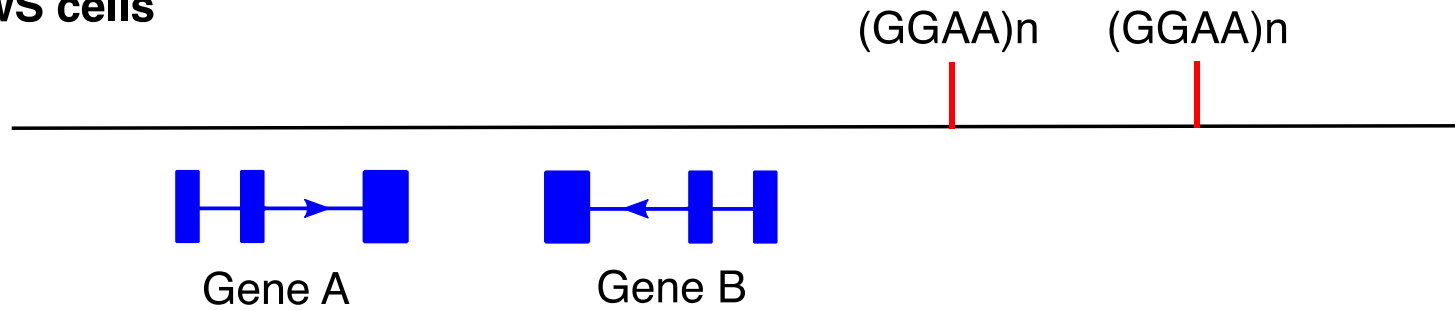


Neotranscripts are **broadly and specifically expressed** in Ewing sarcoma

# Proposed mechanism for EWS-FLI1-driven neogenes (Ew\_NGs)

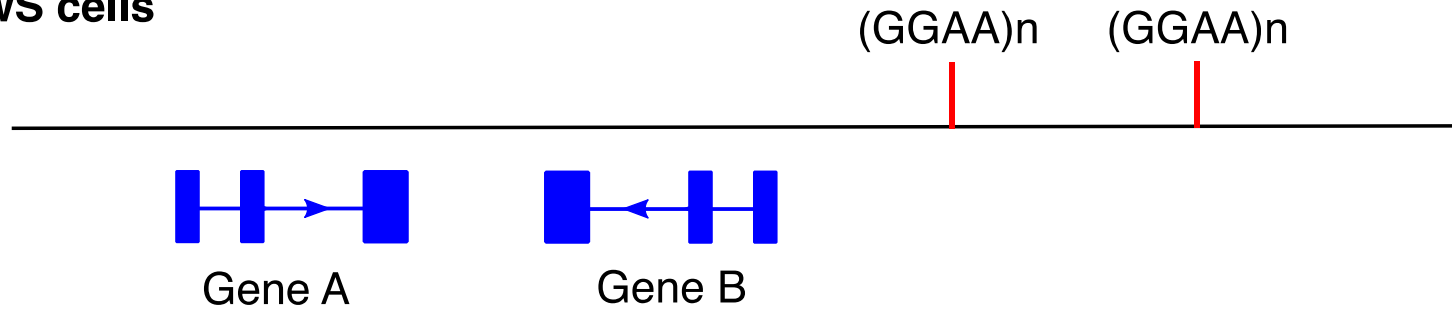
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Non-EwS cells

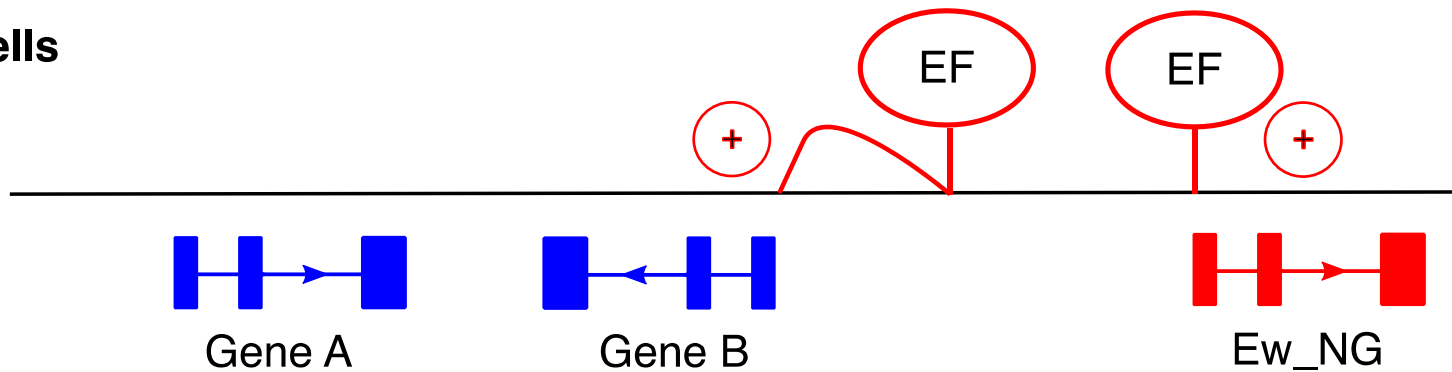


# Proposed mechanism for EWS-FLI1-driven neogenes (Ew\_NGs)

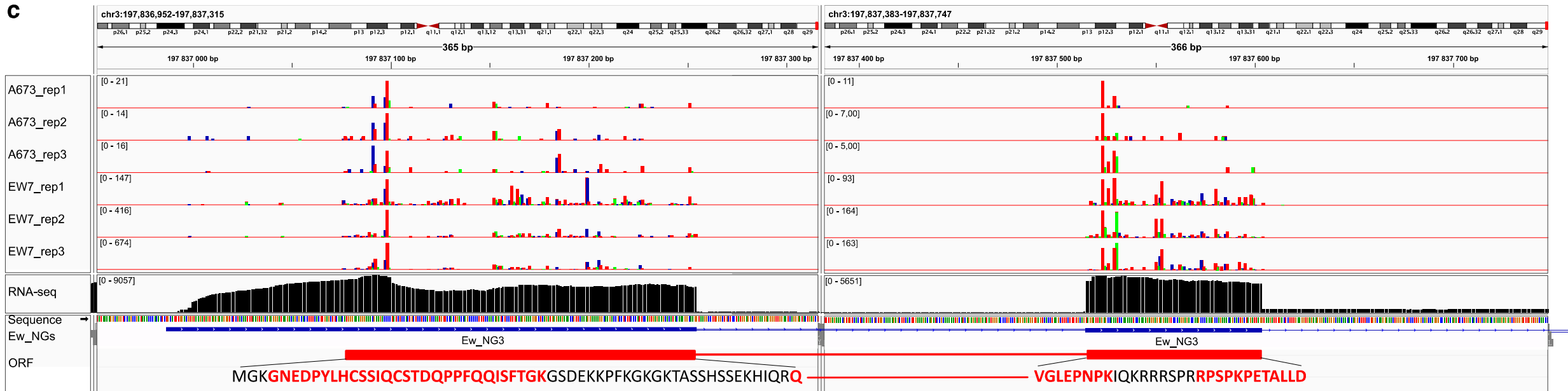
Non-EwS cells



EwS cells



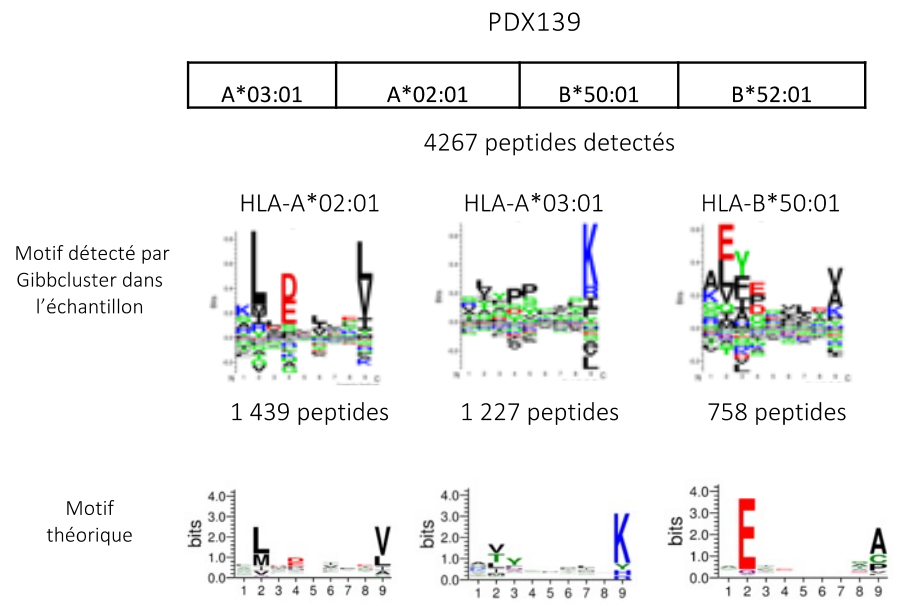
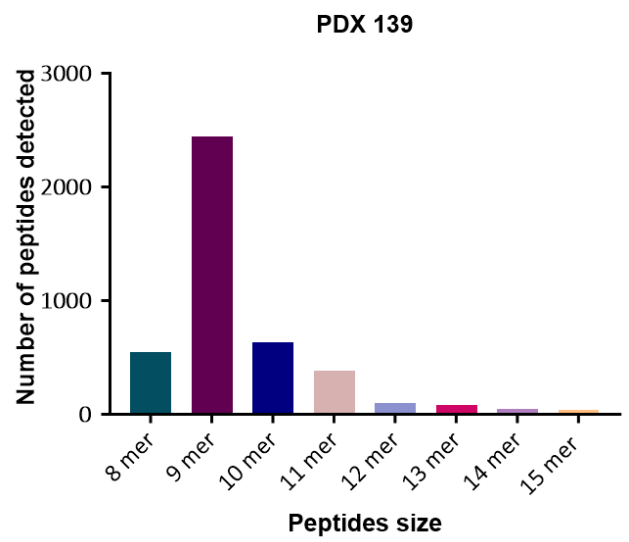
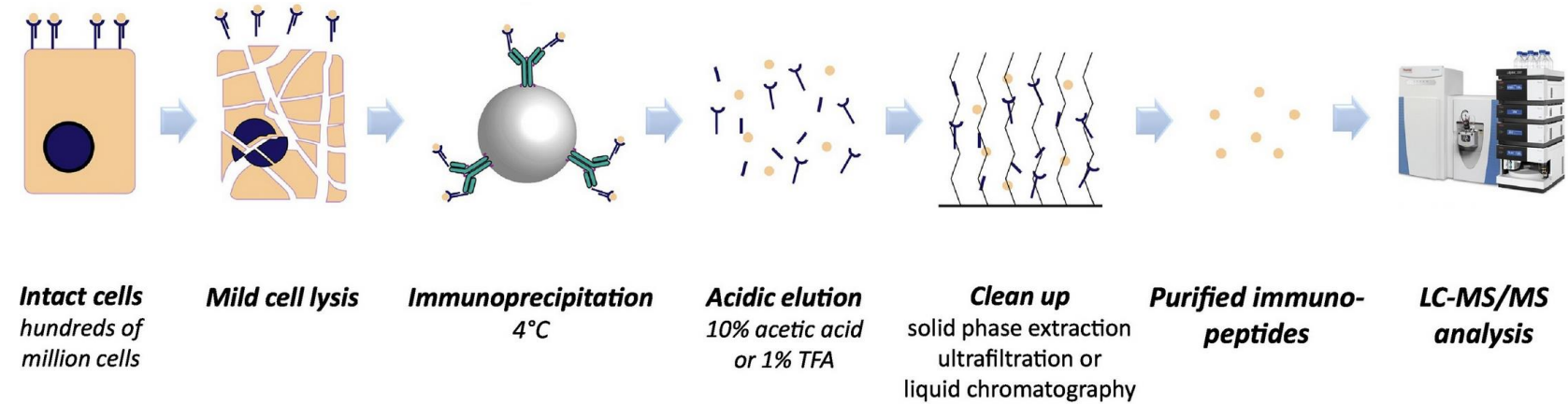
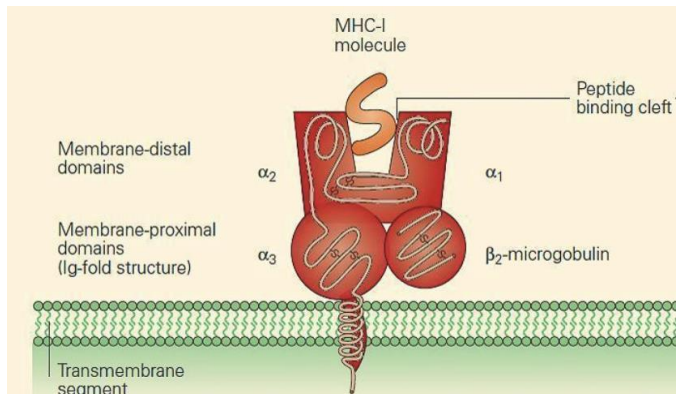
# Ces néogènes sont-ils traduits en protéines?



3 peptides identified independently in **mass spectrometry** of Ewing sarcoma cell lines

Céline Collin & Floriane Petit

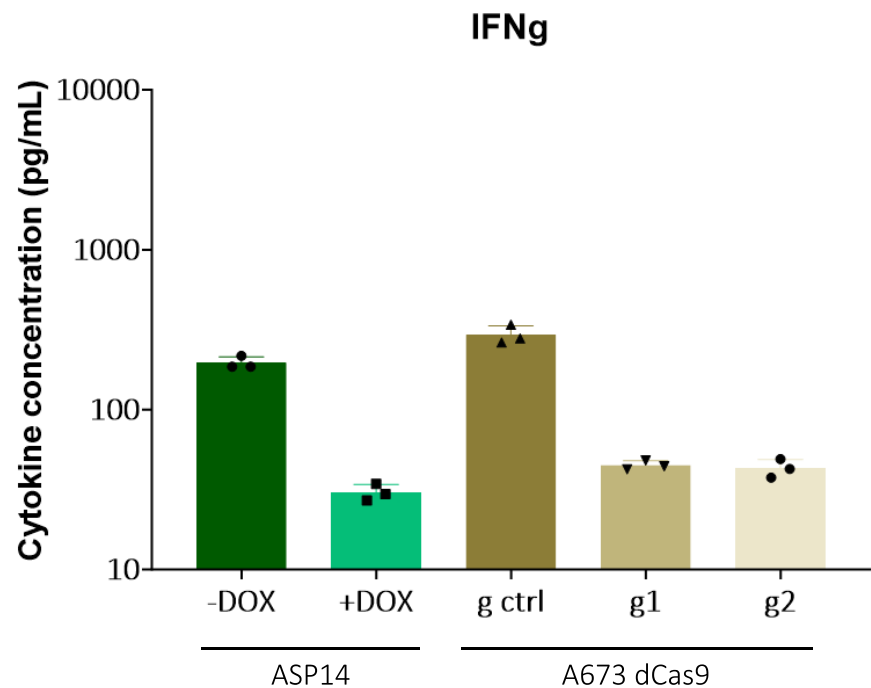
# Des néopeptides correspondants à ces protéines sont-ils associés au MHC-I ?



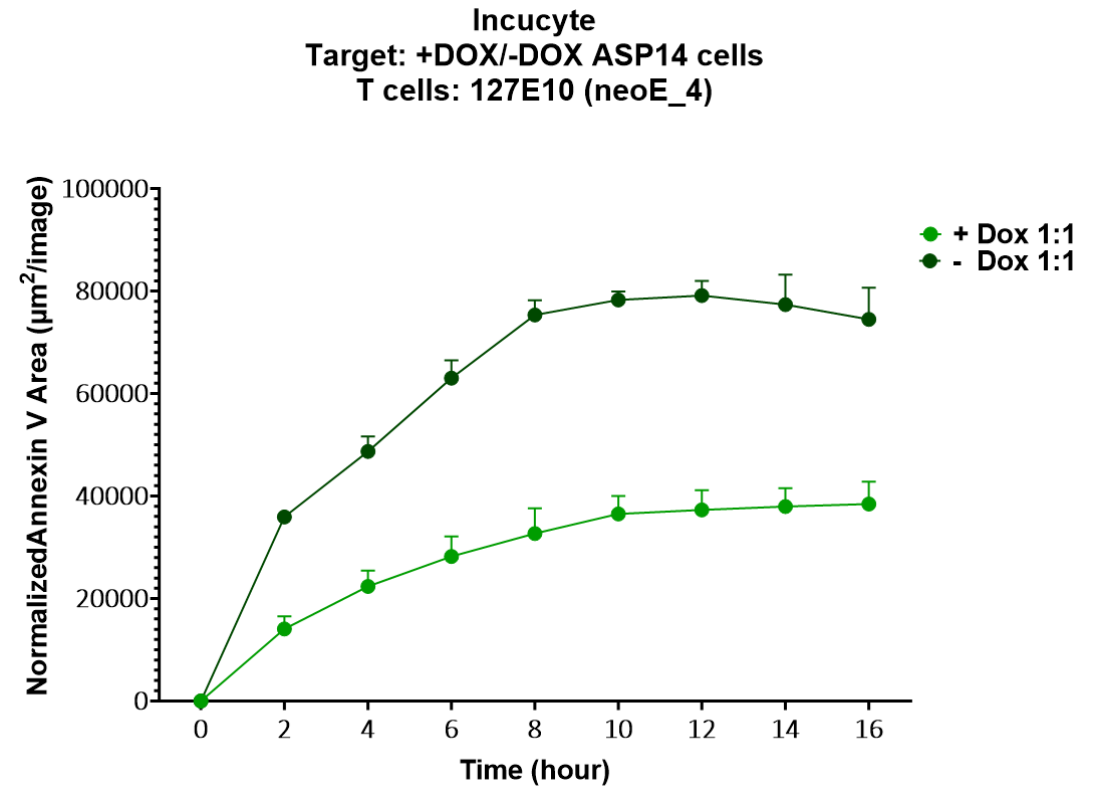


# Identification de CD8 T-cells capables de reconnaître ces peptides (HLA-A2)

Activées en présence de cellules d'Ewing HLA-A2



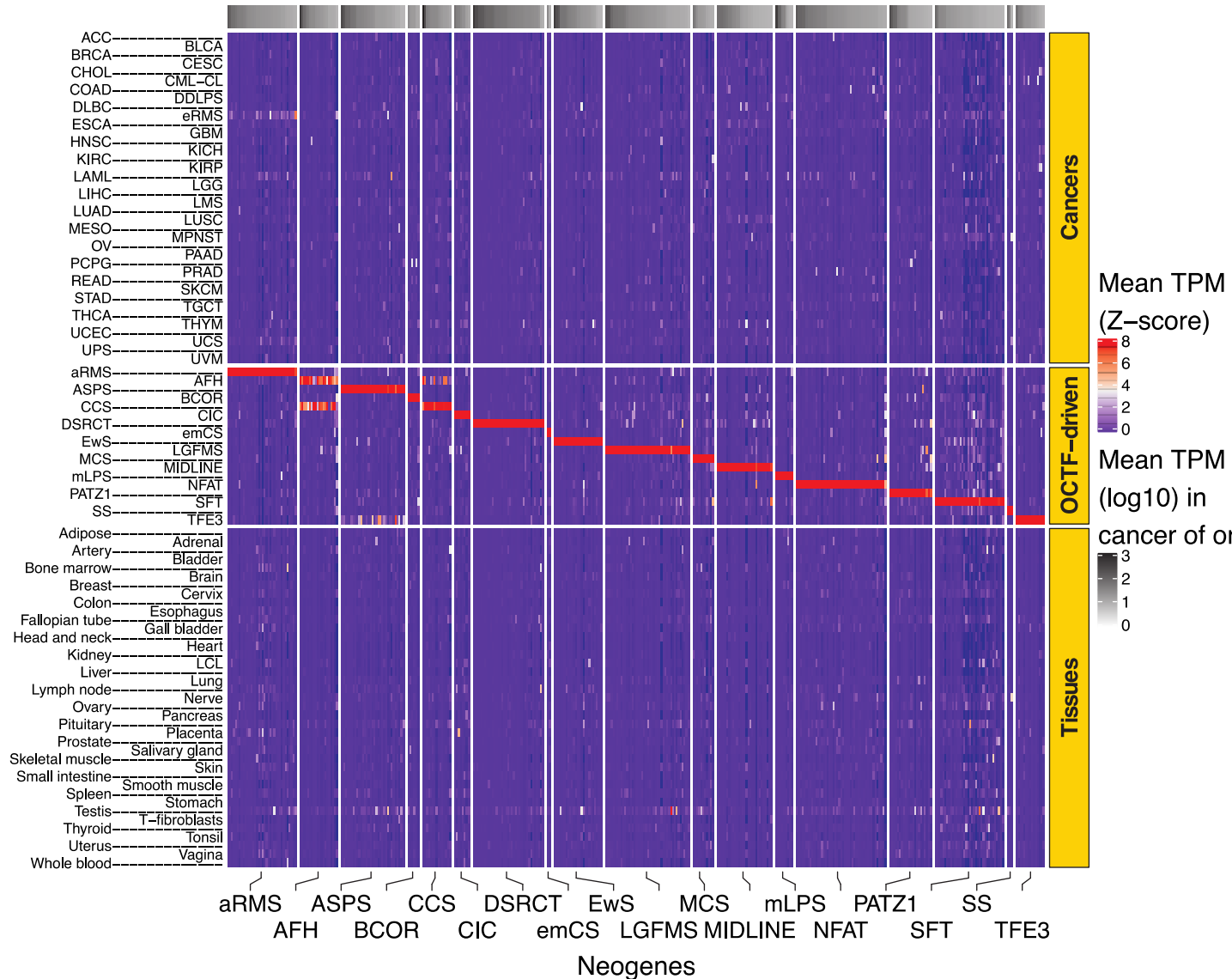
Capables de tuer des cellules d'Ewing



| <b>Cancer type</b>                     | <b>Abbreviation</b> | <b>OCTF</b>      |
|--|---------------------|------------------|
| Angiomatoid fibrous histiocytoma       | AFH                 | EWSR1-ATF1/CREB1 |
| Alveolar rhabdomyosarcoma              | aRMS                | PAX3/PAX7-FOXO1  |
| Alveolar soft part sarcoma             | ASPS                | ASPSCR1-TFE3     |
| BCOR-rearranged sarcoma                | BCOR                | BCOR-CCNB3       |
| Clear cell sarcoma                     | CCS                 | EWSR1-ATF1/CREB1 |
| CIC-fused sarcoma                      | CIC                 | CIC-DUX4/NUTM1   |
| Desmoplastic small round cell tumor    | DSRCT               | EWSR1-WT1        |
| Extraskeletal myxoid chondrosarcoma    | emCS                | EWSR1-NR4A3      |
| Ewing sarcoma                          | EwS                 | EWSR1-FLI1/ERG   |
| Low-grade fibromyxoid sarcoma          | LGFMS               | FUS-CREB3L2      |
| Mesenchymal chondrosarcoma             | MCS                 | HEY-NCOA2        |
| Midline carcinoma                      | MIDLINE             | BRD-NUT          |
| Myxoid liposarcoma                     | mLPS                | FUS-DDIT3        |
| EWSR1-NFATC2 sarcoma                   | NFAT                | EWSR1-NFATC2     |
| EWSR1-PATZ1 sarcoma                    | PATZ1               | EWSR1-PATZ1      |
| Solitary fibrous tumor                 | SFT                 | NAB2-STAT6       |
| Synovial sarcoma                       | SS                  | SS18-SSX1/SSX2   |
| TFE3-translocated renal cell carcinoma | TFE3                | ASPSCR1-TFE3     |



# 398 neogenes (encoding 807 neotranscripts) are found in 18 OCTF-driven cancers



Angiofibromatoid histiocytoma and Clear cell Sarcoma are **driven by similar fusion genes [EWSR1/FUS-CREB family members (ATF1, CREB1, CREM)]** and express **common neotranscripts**



# Fort intérêt potentiel de ces néogènes pour l'immunothérapie

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**Si les peptides correspondants sont présentés par le complexe MHC ils constitueraient des antigènes présentant les caractéristiques suivantes:**

- Une forte spécificité tumorale car non-exprimés dans les tissus normaux
- Ils sont publics, cad exprimés dans toutes les tumeurs du même type (≠ mutations)
- Exprimés de façon clonale dans les cellules tumorales
- Directement liés au processus oncogène

**Excellents candidats pour des approches de vaccination, BiTE ou TCR-T cells**

## INSERM-CURIE U830

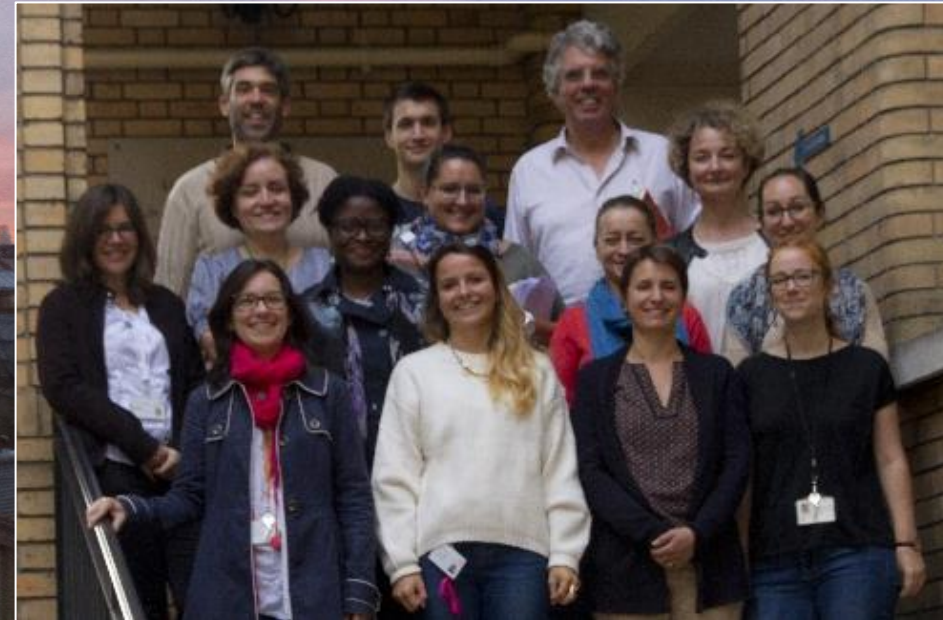
**Sakina Zaidi**  
**Karine Laud**  
**Sandrine Grossetête-Lalami**  
**Nadège Gruel**  
**Jill Pilet**  
**Olivier Saulnier**  
**Julien Vibert**  
**Florine Petit**  
**Céline Collin**



**Josh Waterfall's group**  
**Ana Lalanne & Olivier Lantz**

**Sequencing platform**  
Sylvain Baulande,  
Virginie Bernard  
Virginie Raynal  
Mylene Bohec

**Bioinformatics, U 900**  
Andrei Zinovyev  
Aziz Fouché-Asnoun  
Nicolas Servant  
Emmanuel barillot



**Pathologists and clinicians**  
**Patients and their families**

