COMBOREIN : en route vers une médecine personnalisée dans le carcinome rénal à cellules claires

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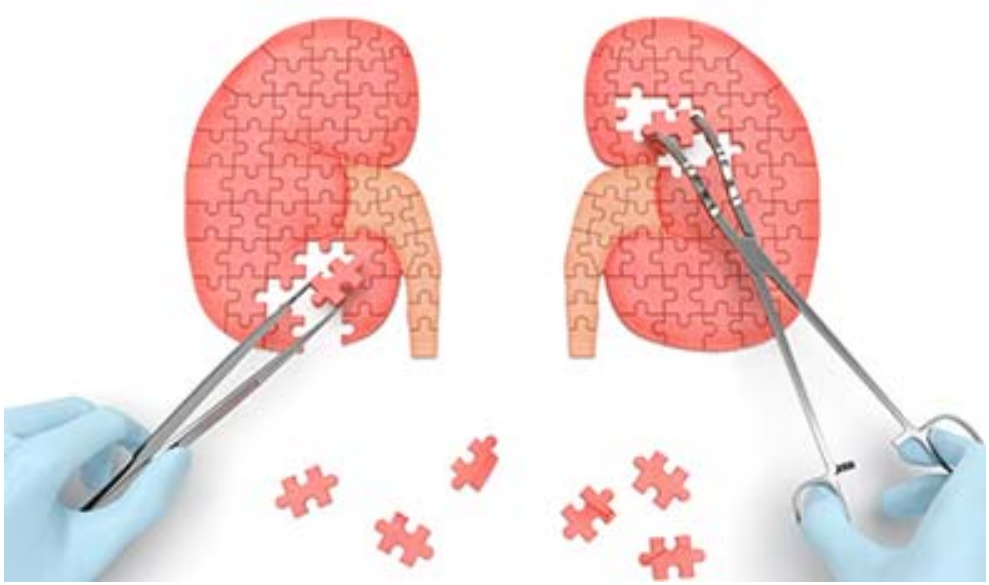
The Kidney cancer

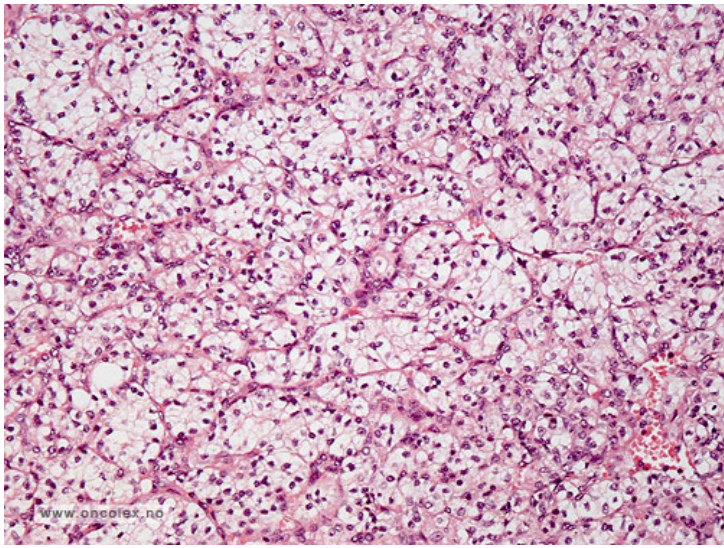


Renal Cell Carcinoma Epidemiology

- 3% of all cancers
- 2.6 % of death by cancer
- 30% Metastatic at the time of diagnosis
- Prognosis : 5-Year survival rate
    - Local tumor <4cm -95%
    - Metastatic-5%
- Risk factor :
    - Severe renal dysfunction – Dialysis
    - Hypertension
    - Obesity
    - Tobacco

Histology

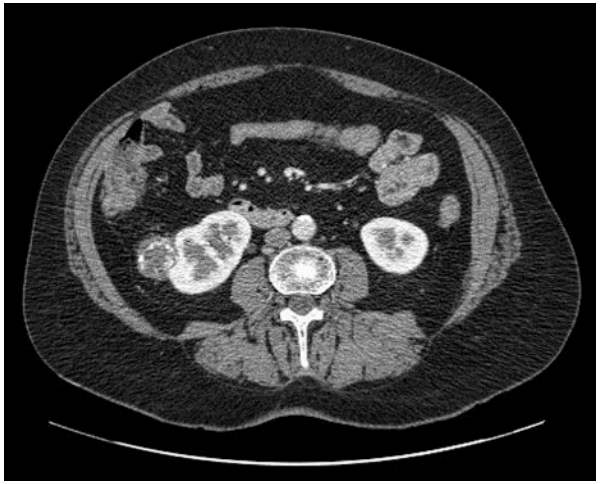
- Benign Tumor :
  - Oncocytoma
  - Angiomyolipoma
- Malignant tumor
  - Renal cell carcinoma
    - Clear cell carcinoma (90%)
    - Papillary renal cell carcinoma
    - Chromophobe renal carcinoma
  - Other types (<7%)
- Secondary tumor (Lymphoma,…)



HE coloration-Clear cell carninoma

Cystic ≠ Solid ≠ Malignant

Diagnosis

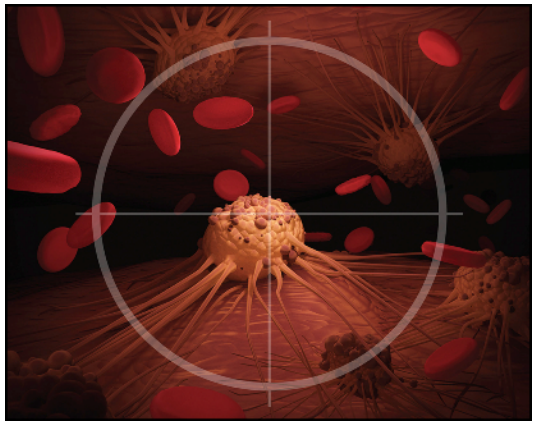


- Clinical signs :
  - Hematuria
  - Flanc pain or masses
  - Asthenia
  - Fever
- Asymptomatic in more than 50% of case
- Mostly accidental discovery
- Scannographic or Ultra-sond exams confirm the diagnosis
- No Biomarker available

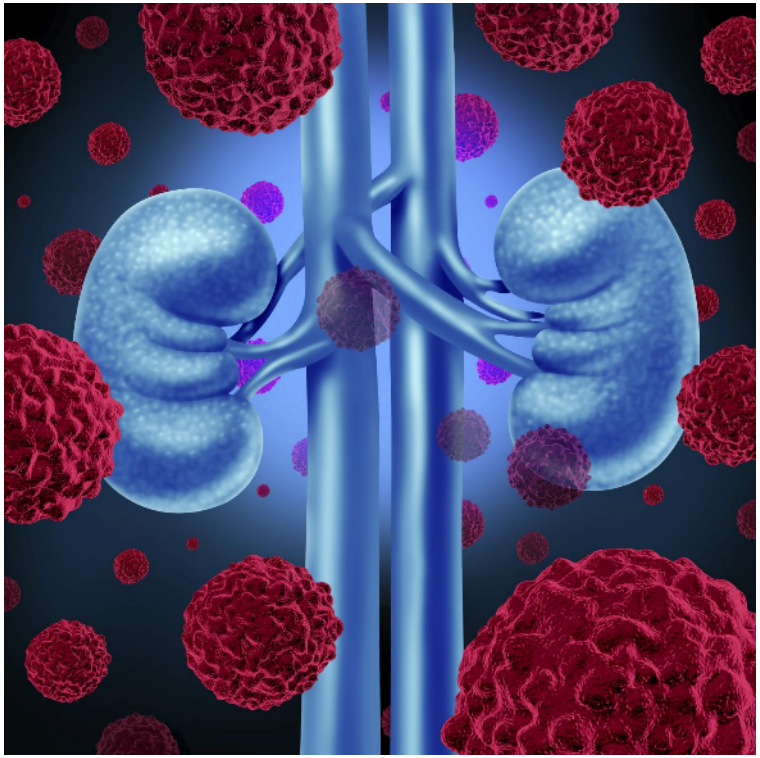
Treatments

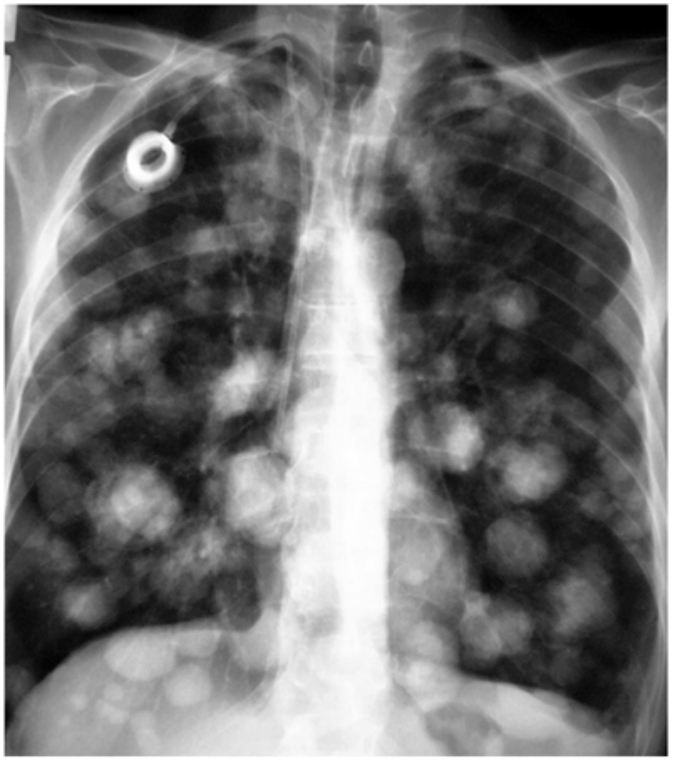
- Localized disease
  - Partial nephrectomy
- Locally advenced
  - Total nephrectomy
  - +/- Lymph node dissection

- Metastatic Disease
  - Site : Lung, Bone, Liver Lynmph node
  - No effect of conventional therapy
  - Targeted therapy
  - Immunotherapy



Metastatic disease



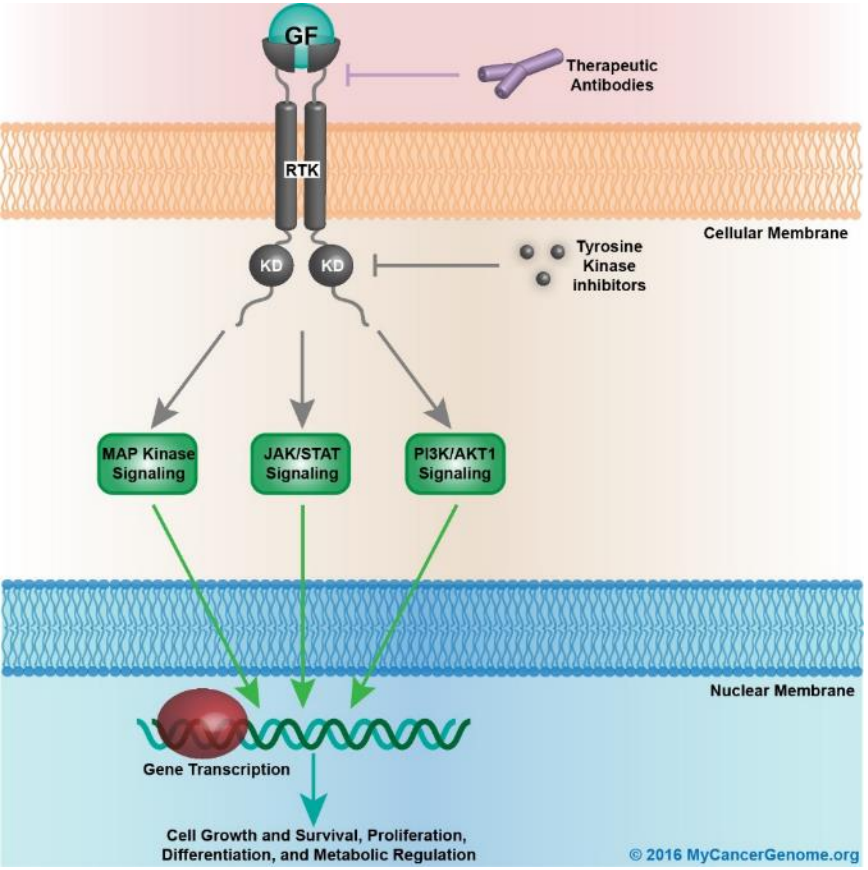


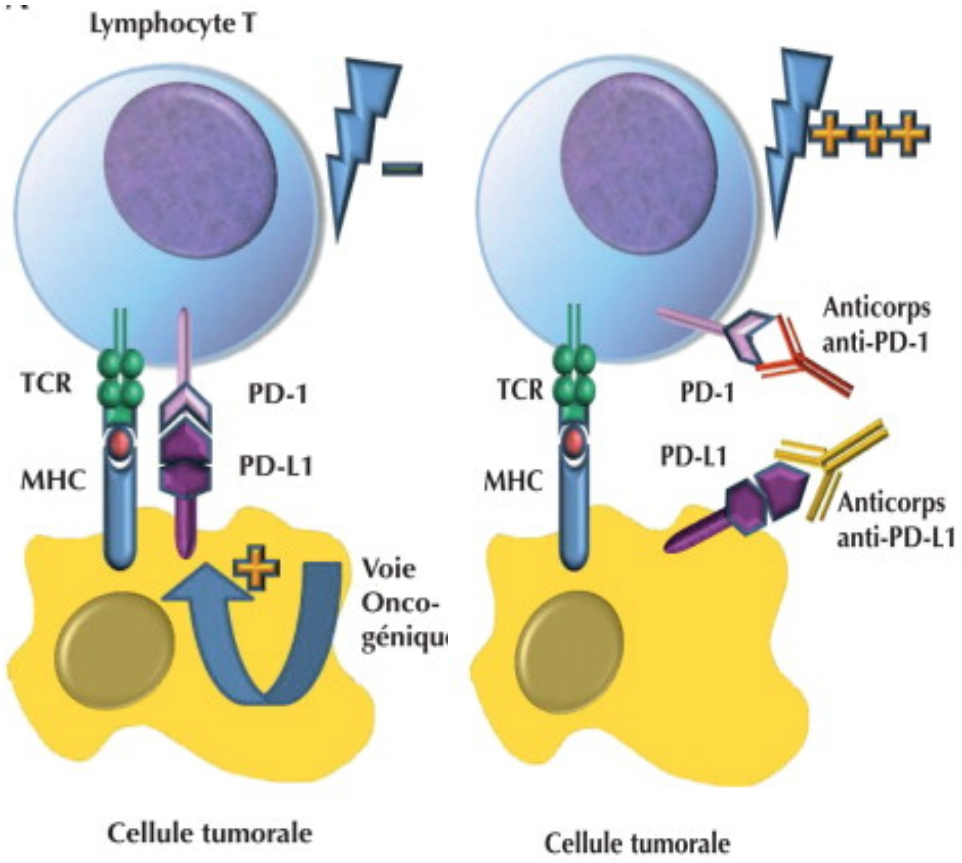
Treatments

- Resistant to conventional therapies (chemotherapy or radiotherapy)

- Targeted therapies (TKI : Sunitinib, Pazopanib, Temsilorimus)
    - short term response
    - relapse and metastasis
- Immunotherapy (Anti PD-1, Anti-PD-L1, Anti-CLA4)

Targeted Therapy Vs Immunotherapy





Targeted Therapies Vs Immunotherapy

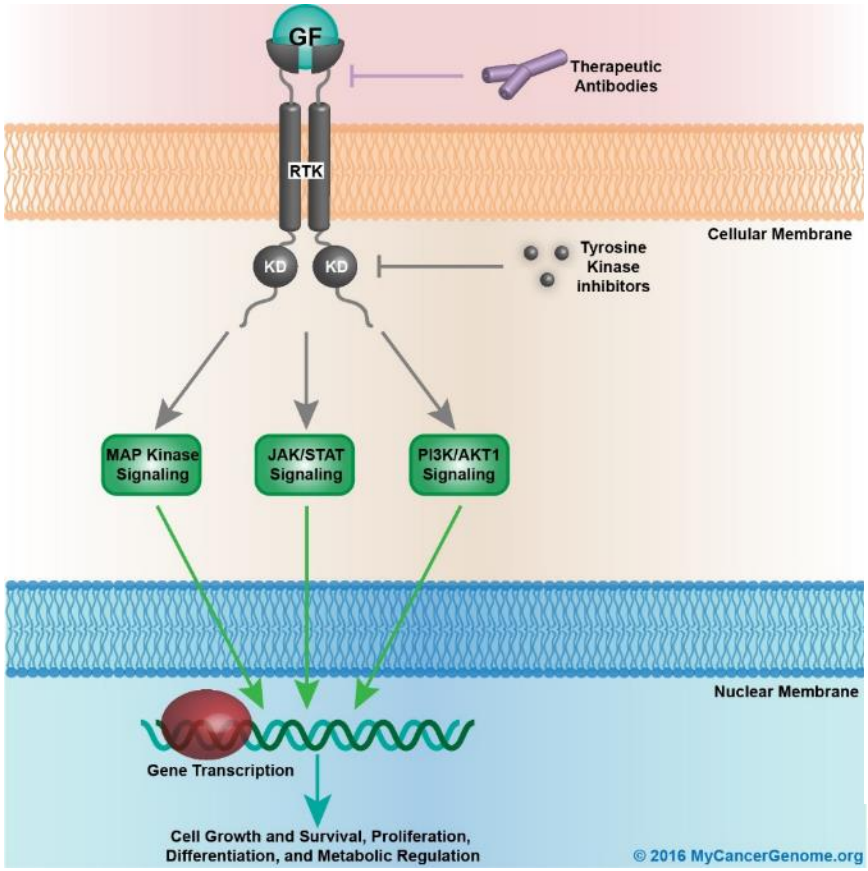


Figure 3A. Immunotherapy agents such as nivolumab and pembrolizumab stick to PD-1 so it can't interact with PD-L1.

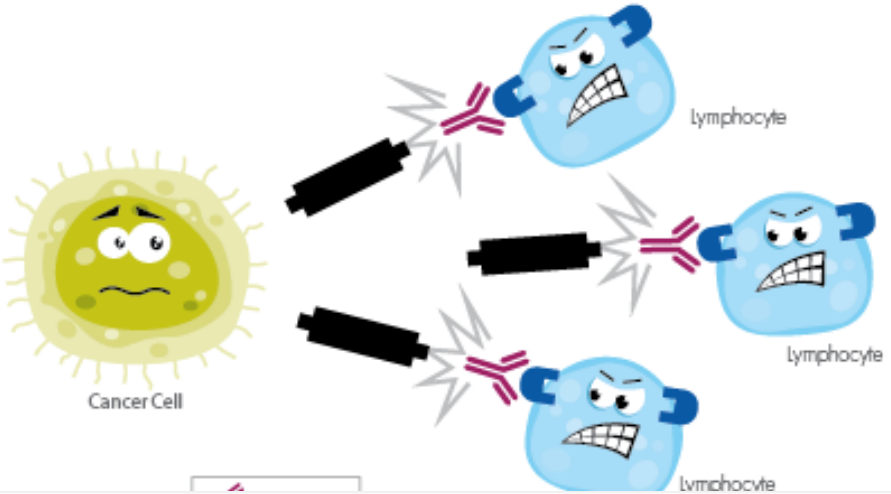
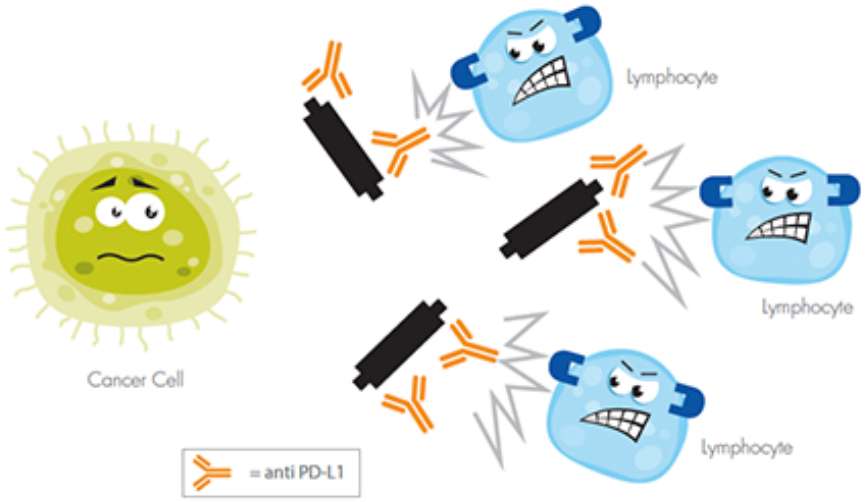
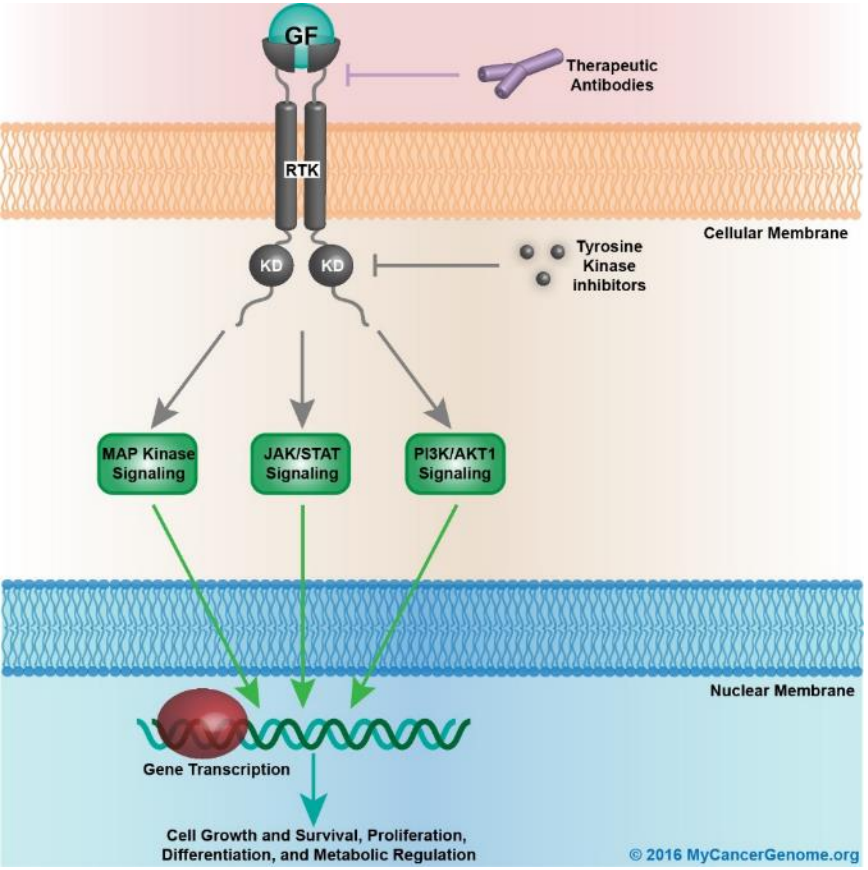
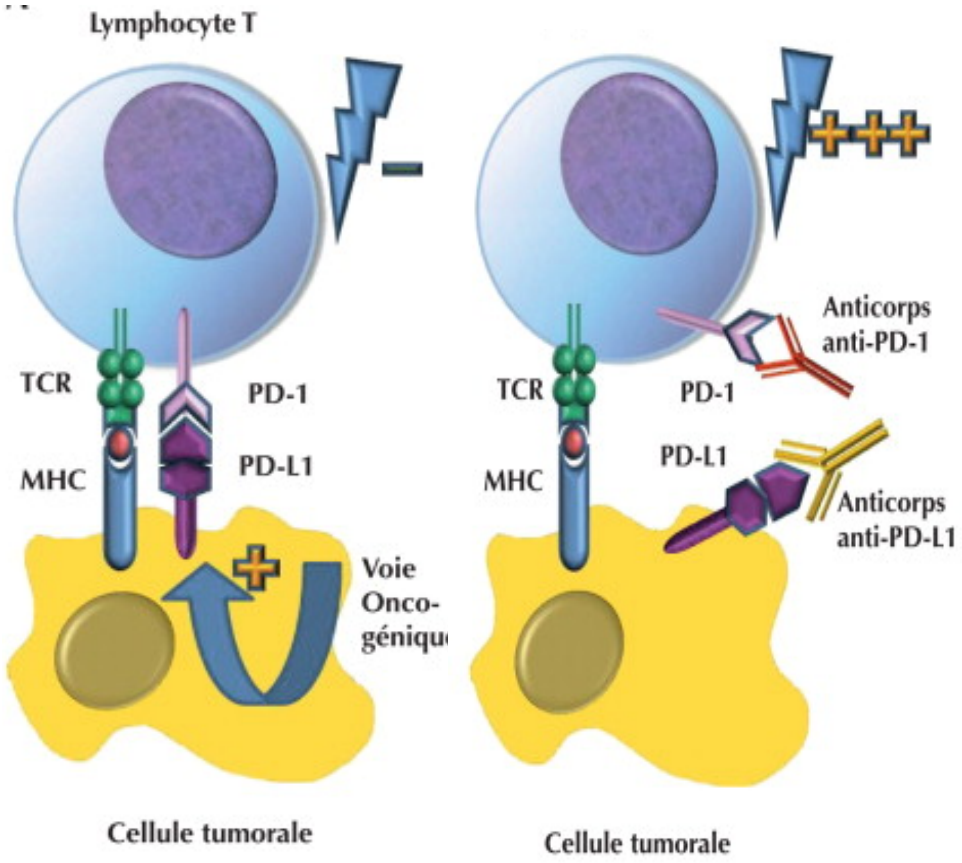


Figure 3B. Atezolizumab and other immunotherapies in development that bind to PD-L1 and inhibit PD-1 from binding to PD-L1.

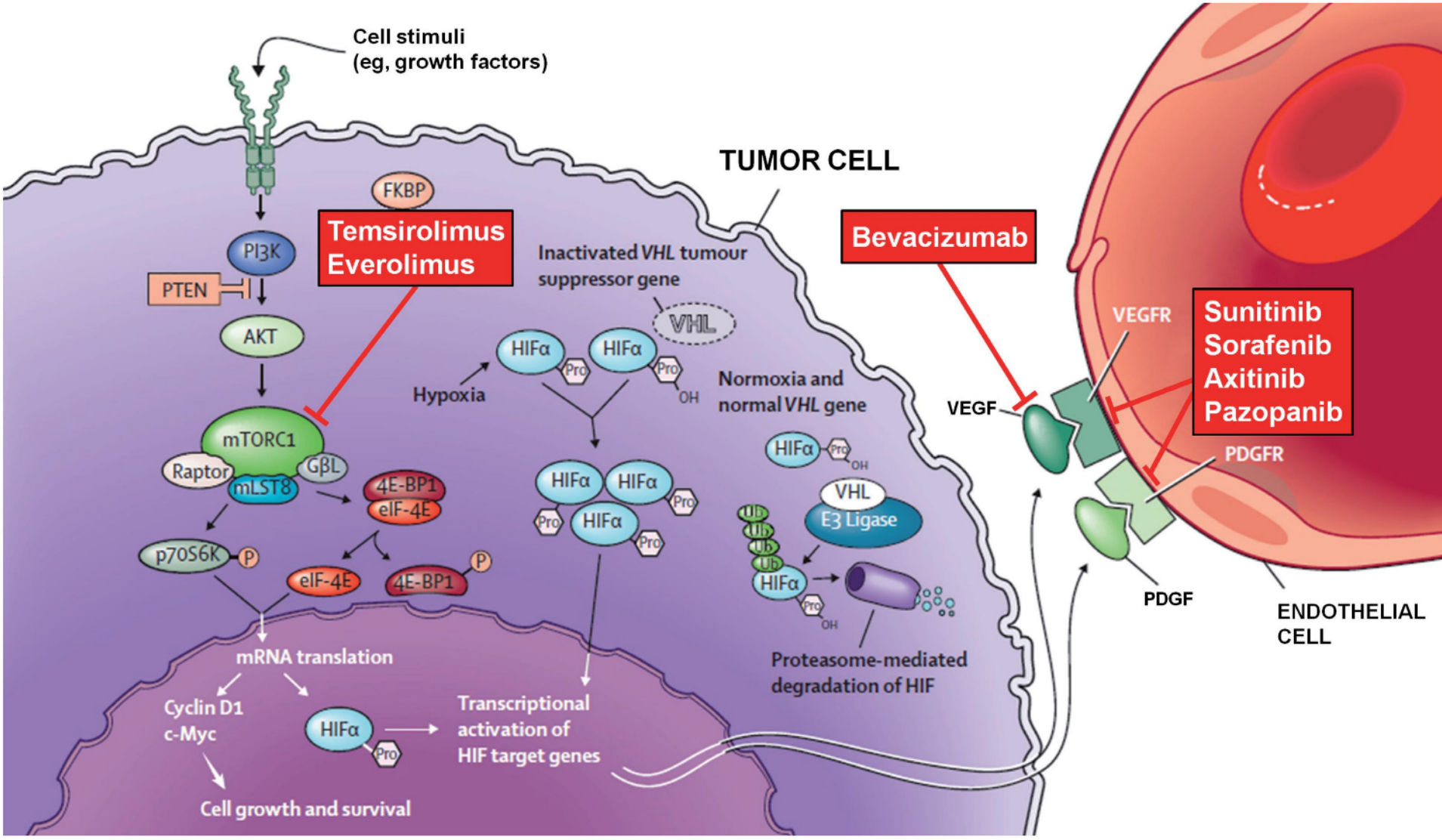


Targeted Therapy Vs Immunotherapy





Different Pathways



CCAFU French GUIDELINES 2016-2018

Tableau 7. La classification de Heng.

Classification de HENG	
Index de Karnofsky (performance status)	Inférieur à 80 %
Intervalle libre entre le diagnostic et le traitement systémique	Inférieur à 1 an
Hémoglobinémie	Inférieure à la normale
Calcémie corrigée	Supérieure à la normale
Thrombocytémie	Supérieure à la normale
Neutrophilie	Supérieure à la normale

0 facteur : bon pronostic
1 ou 2 facteurs : pronostic intermédiaire
3 facteurs ou plus : mauvais pronostic

Sous type histologique et ligne thérapeutique	Classification pronostique	Standard	Option
Carcinome à cellules claires Première ligne	Bon ou intermédiaire	Sunitinib Bevacizumab + IFN Pazopanib	IL2 haute dose Sorafenib Bevacizumab + faible dose IFN
	Mauvais	Temsirolimus	Sunitinib Sorafenib Pazopanib
Carcinome à cellules claires Deuxième ligne	Post cytokines	Axitinib Sorafenib Pazopanib	Sunitinib
	Post-TKI anti-VEGFRs	Nivolumab* Cabozantinib**	Axitinib Everolimus Sorafenib

- Do not offer cytoreductive nephrectomy in poor-risk patients
- Cytoreductive nephrectomy can be offered to favourable- and intermediate-risk patients with metastatic RCC
- Perform immediate cytoreductive nephrectomy and metastasectomy in patients with oligometastases when complete resection can be achieved

What's New?

The NEW ENGLAND JOURNAL of MEDICINE

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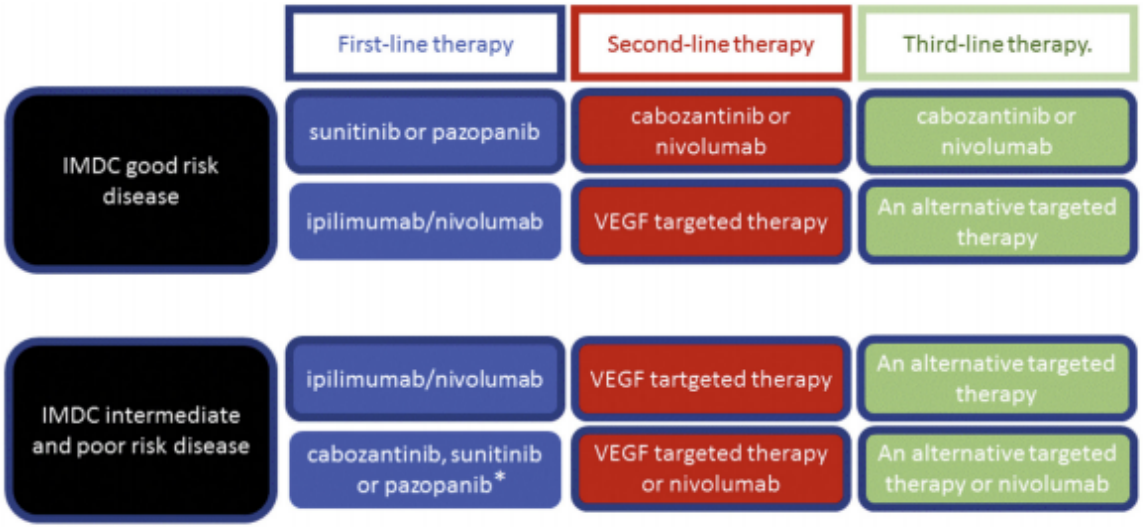
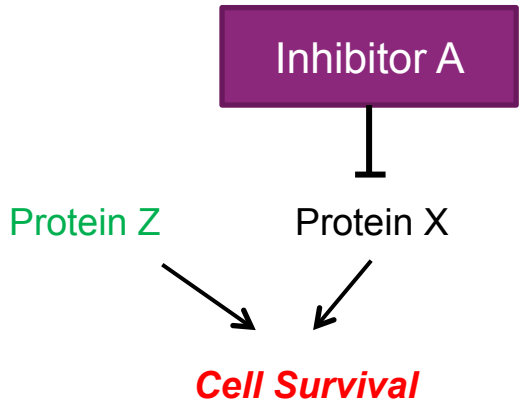
Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*

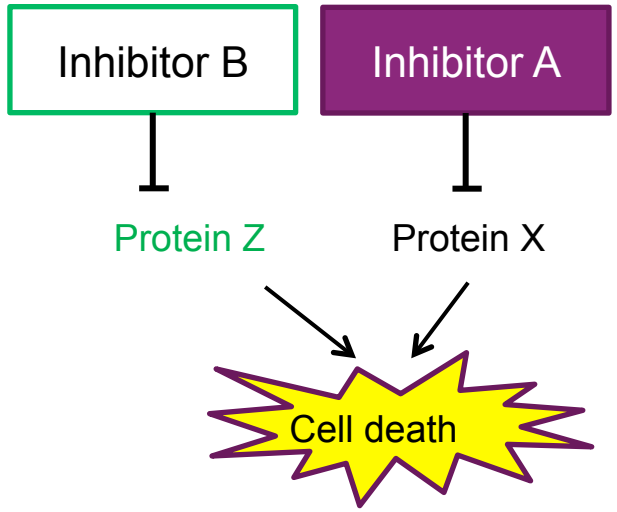


Looking for new Targeted Therapies against CCRCC

Mono-targeted Therapy



Combinational Targeted Therapy



Synthetic lethality

Where to find novel potential targets?

Response to Growth Factors

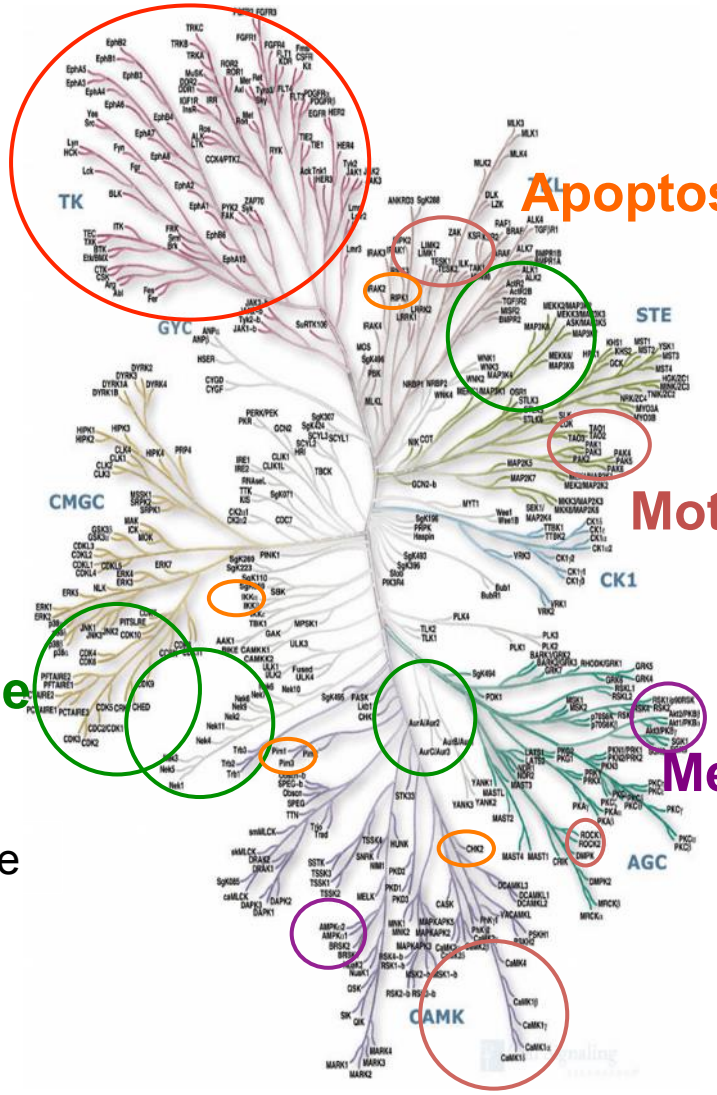
Apoptosis

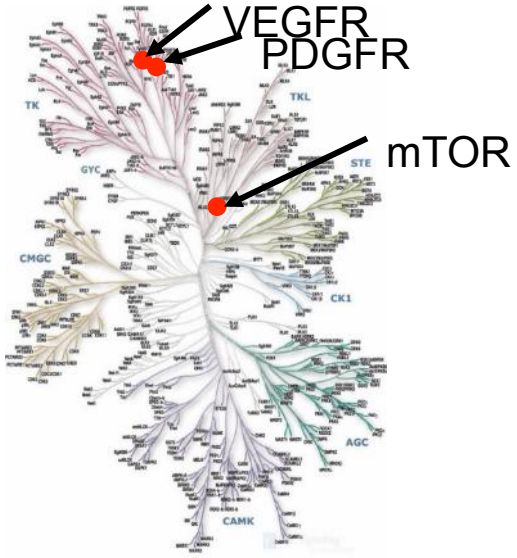
Motility

Cell Cycle

Metabolism

Human Kinome





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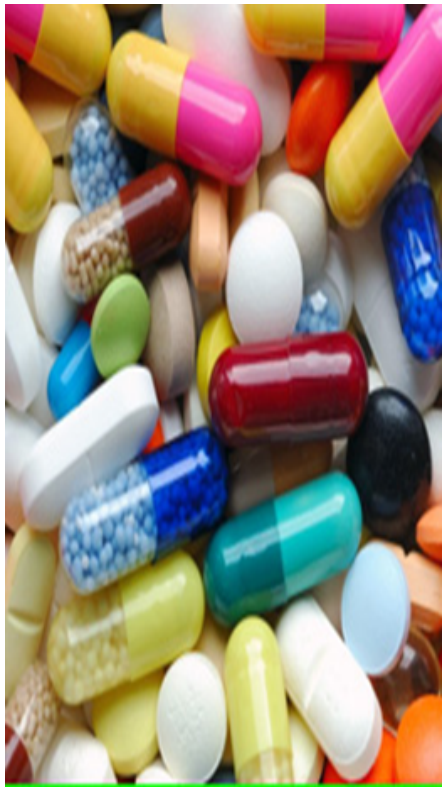
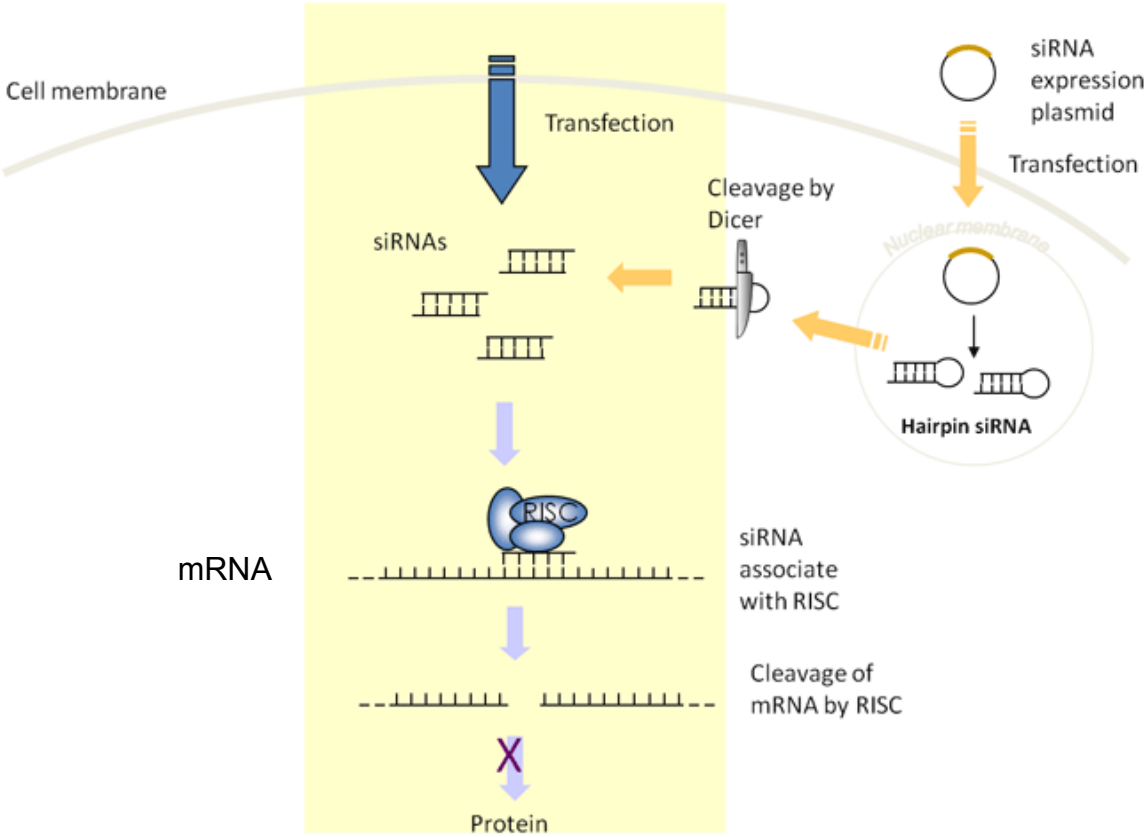
How to inhibit novel potential targets?

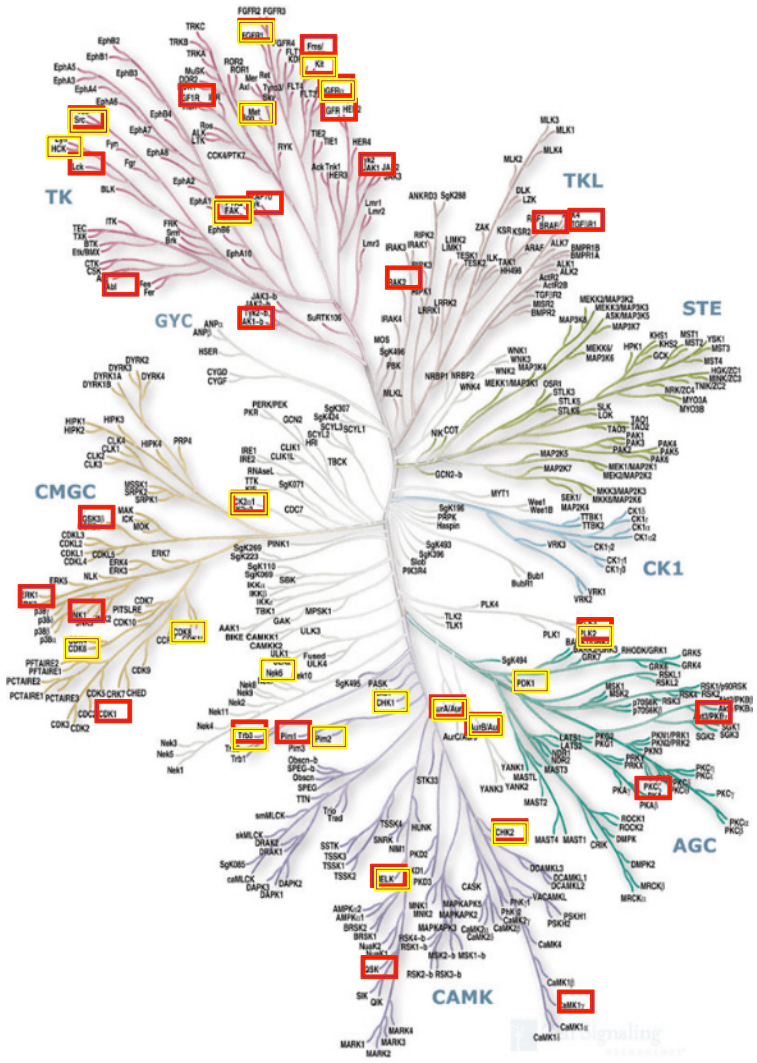
Chemicals



RNA interference



Chemo-genomic Screening

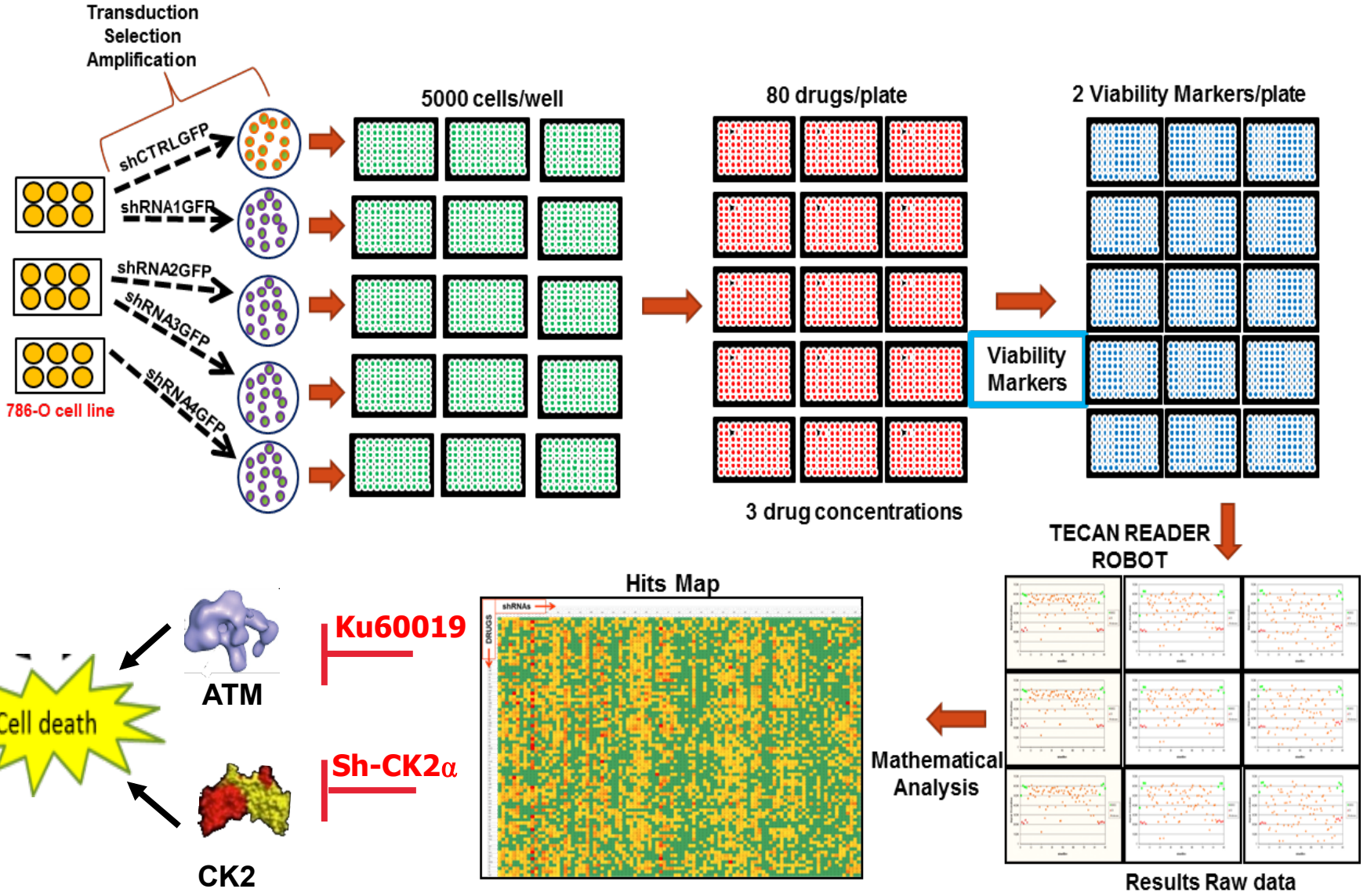


Drug targets

Gene targets

36 shRNA cell lines treated with 80 drugs

Chemo-genomic Screening Method



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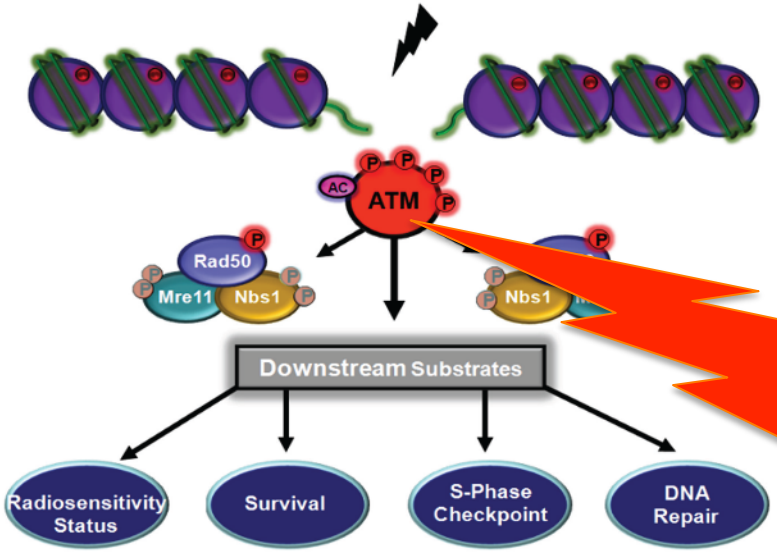
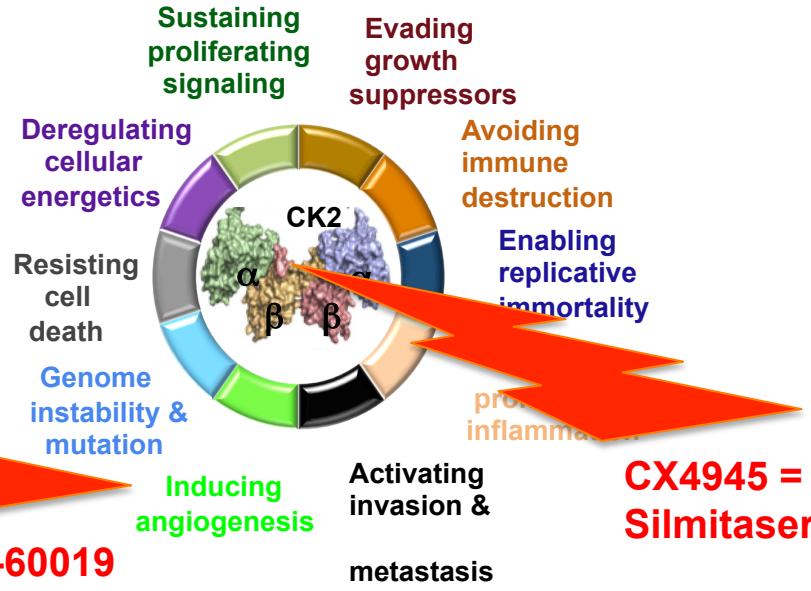
ATM and CK2

Ataxia telangiectasia mutated (ATM) is a serine/ threonine protein kinase that is recruited and activated by DNA double-strand breaks



CK2 is a multifunctional and pleitropic protein kinase

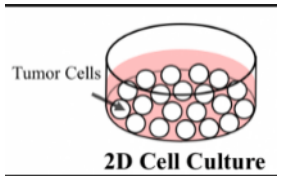


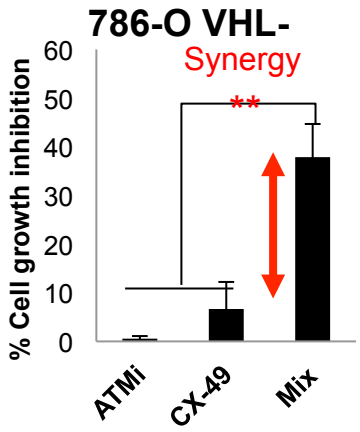
CK2α is overexpressed and its activity is enhanced in multiple forms of human cancers

CK2 phosphorylated many substrates that are involved in the different hallmarks of cancer processes (Bob Weinberg) an in particular in the genome instability pathway CK2 phosphorylates proteins involved in DNA damage recognition.

RESULTS
2D culture and spheroids

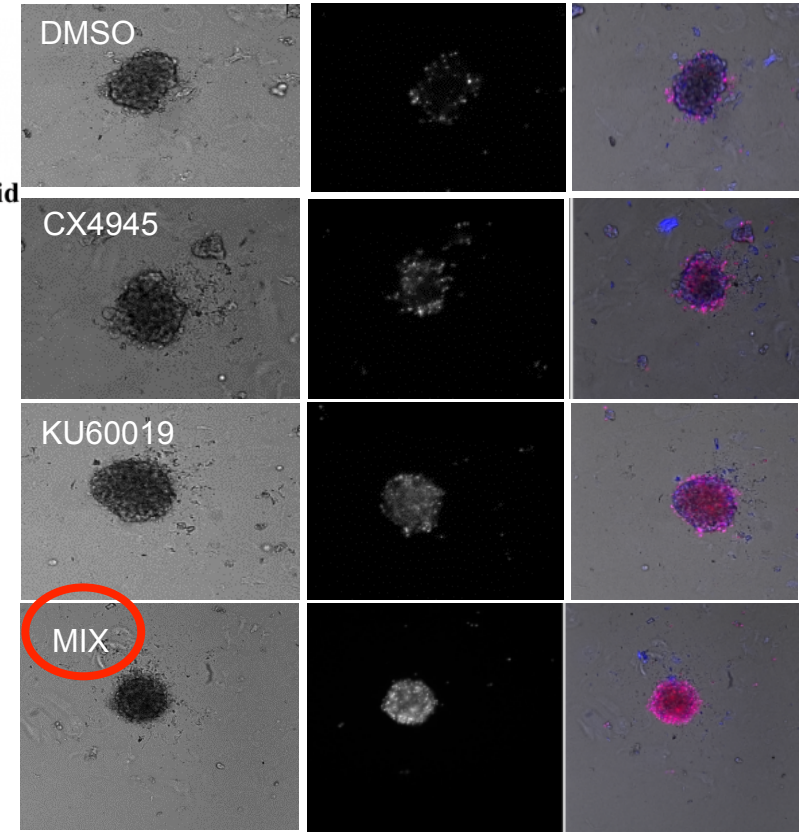
2D cell culture





3D cell culture

ArrayScan^{VTI}
(ThermoScientific)



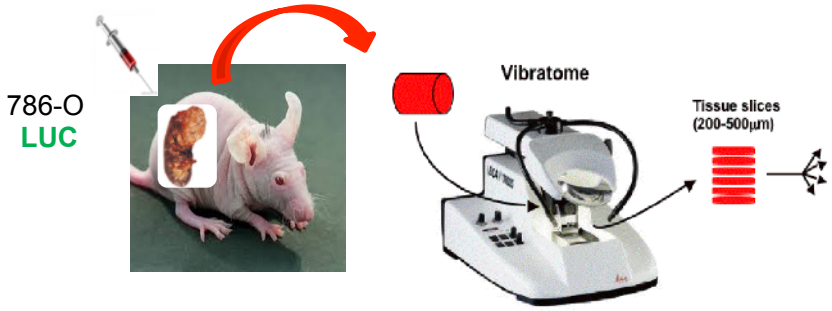
Tissue slice culture

- Advantages :
  - Preserve the 3D architecture and micro-environement of tumor
  - *In vivo-like* condition
  - Price
  - Rapidity of response to drugs
- Disadvantages :
  - Access of human tissue
  - Vibratome dissection
  - Culture Difficulty
- Limits :
  - Representativity and heterogeneity

Technical

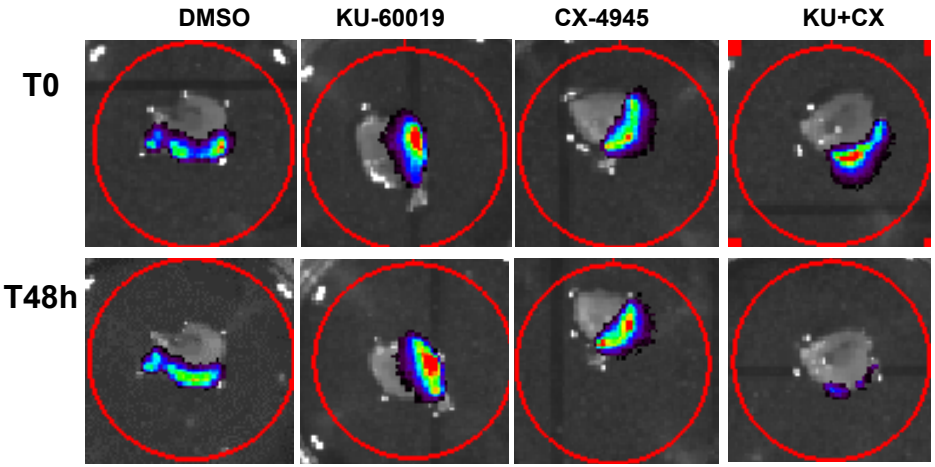
- Prelevement of tumor sample at the hospital
- Inclusion in agarose before vibratome dissection
- Culture in presence of differents drugs
- Quantitative analysis of viability using fluorescence

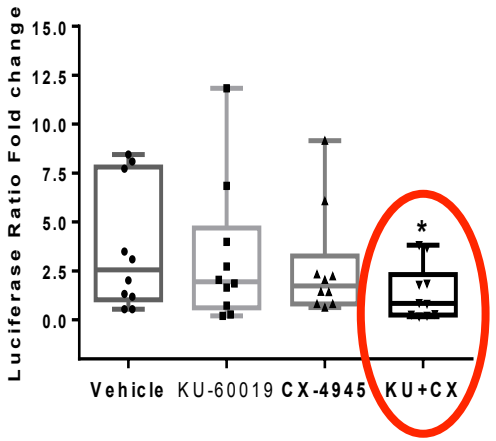
RESULTS
Organotyopic culture



+ ttts
48H

IVIS imager





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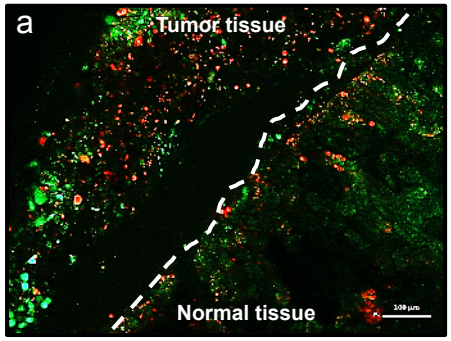
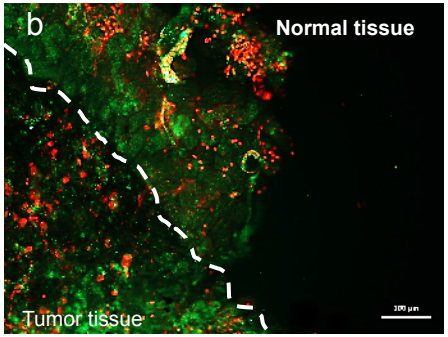
RESULTS
Organotyopic culture

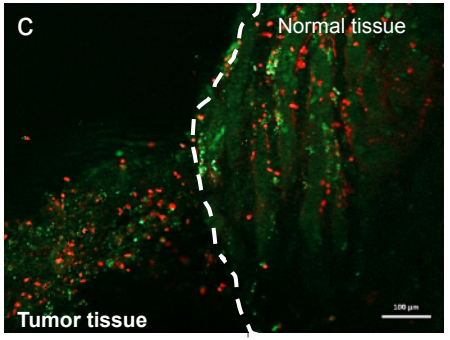
Vehicle

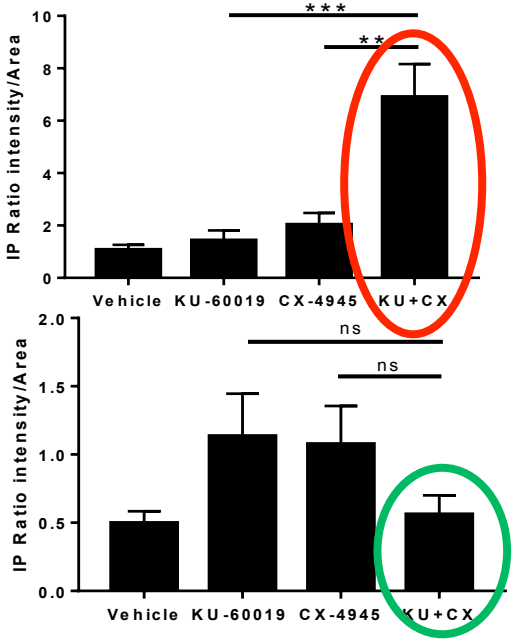


KU-60019



CX-4945

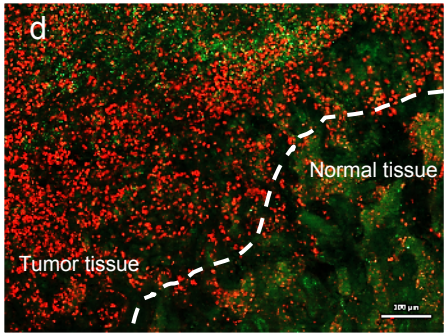




Tumor

Normal Tissue

KU + CX



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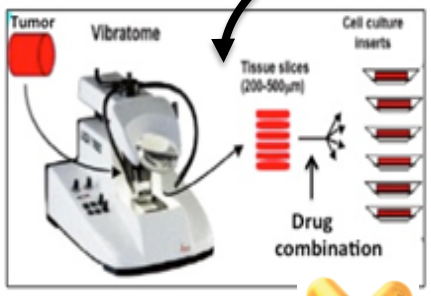
Summary

Partner 1
Urologie
CHUGA
J-L Descotes

Parter 2
INSERM U1036
CEA Grenoble
O Filhol

Renal tumor

Patient clinical data

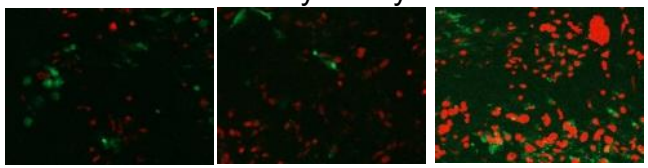


COMBOREIN

Preclinical study on 100 kidney tumors

3 days

Viability assay



CTRL | Pazopanib | KU + CX

Molecular Analysis

Responders / non-responder

Our Project

- Prove that tumor slice culture system is available to assess drug response in kidney cancer

- Confirm the supperiority of our combination of drugs

- Develop a personalized medicine

Thanks

Thanks you for your attention