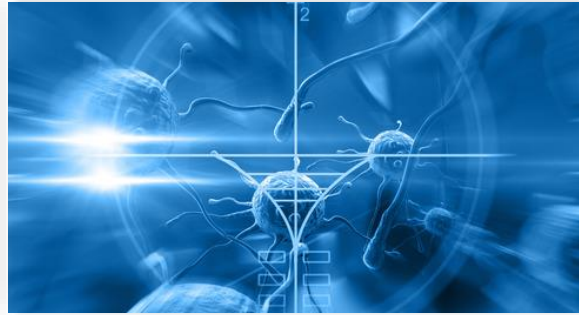


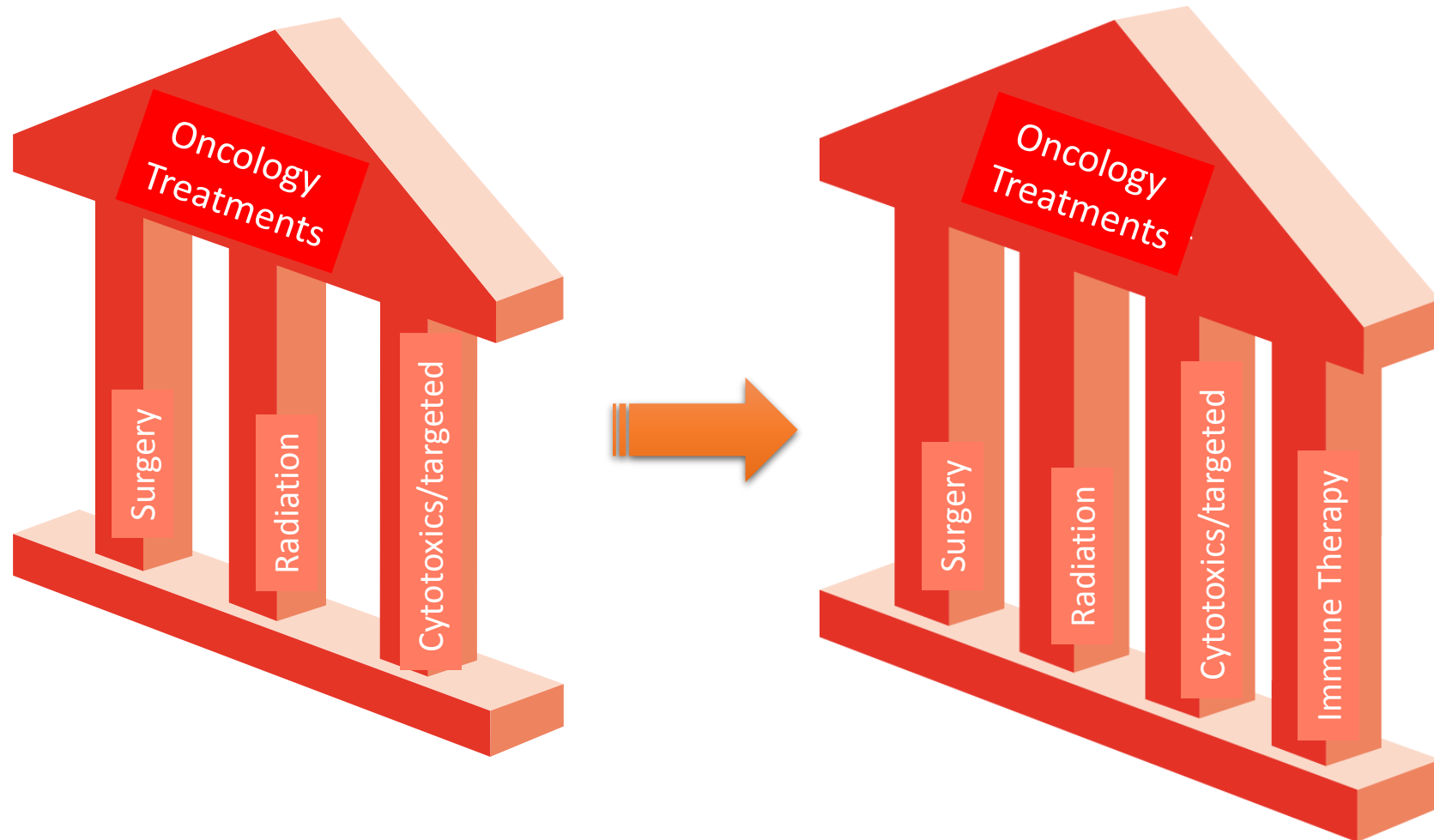
# CELLULAR IMMUNOTHERAPY | Challenges from Bench to Bedside



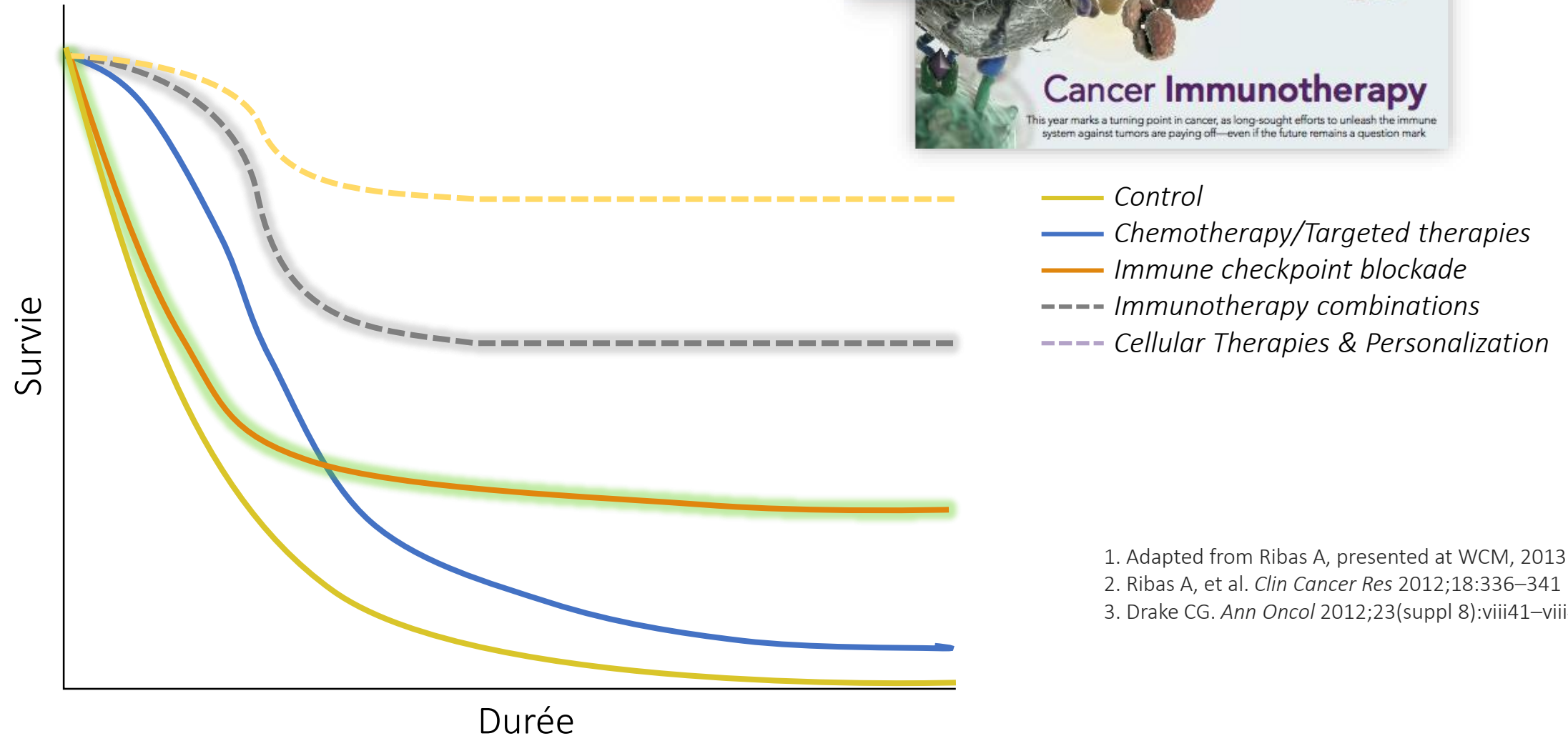
**Prof. Lana E. Kandalaft**

Cheffe de service du Centre de thérapies expérimentales,  
Département d'Oncologie, CHUV  
Institut Ludwig de Recherche sur le Cancer

# Evolution of Oncologic Treatments



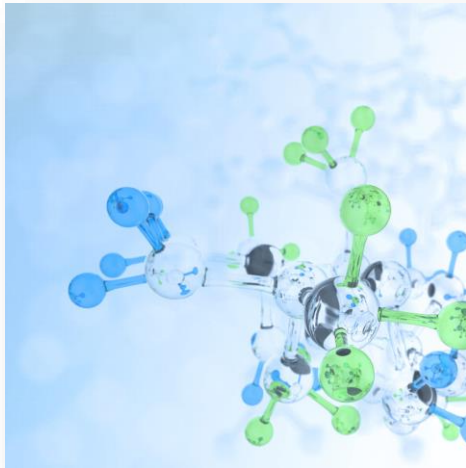
# « L'avancée la plus significative »



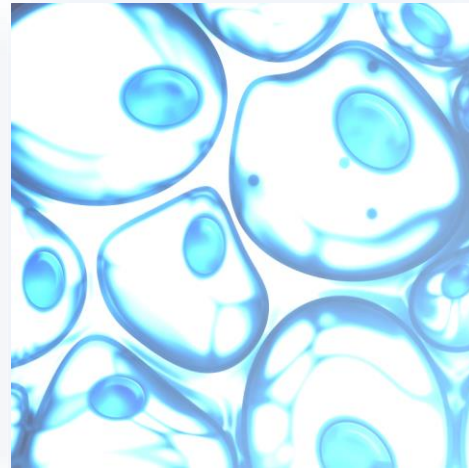
1. Adapted from Ribas A, presented at WCM, 2013
2. Ribas A, et al. *Clin Cancer Res* 2012;18:336–341
3. Drake CG. *Ann Oncol* 2012;23(suppl 8):viii41–viii46

# l'immunothérapie revisitée | Il existe 2 formes d'immunothérapie

dont



une qui  
s'appuie sur  
les molécules

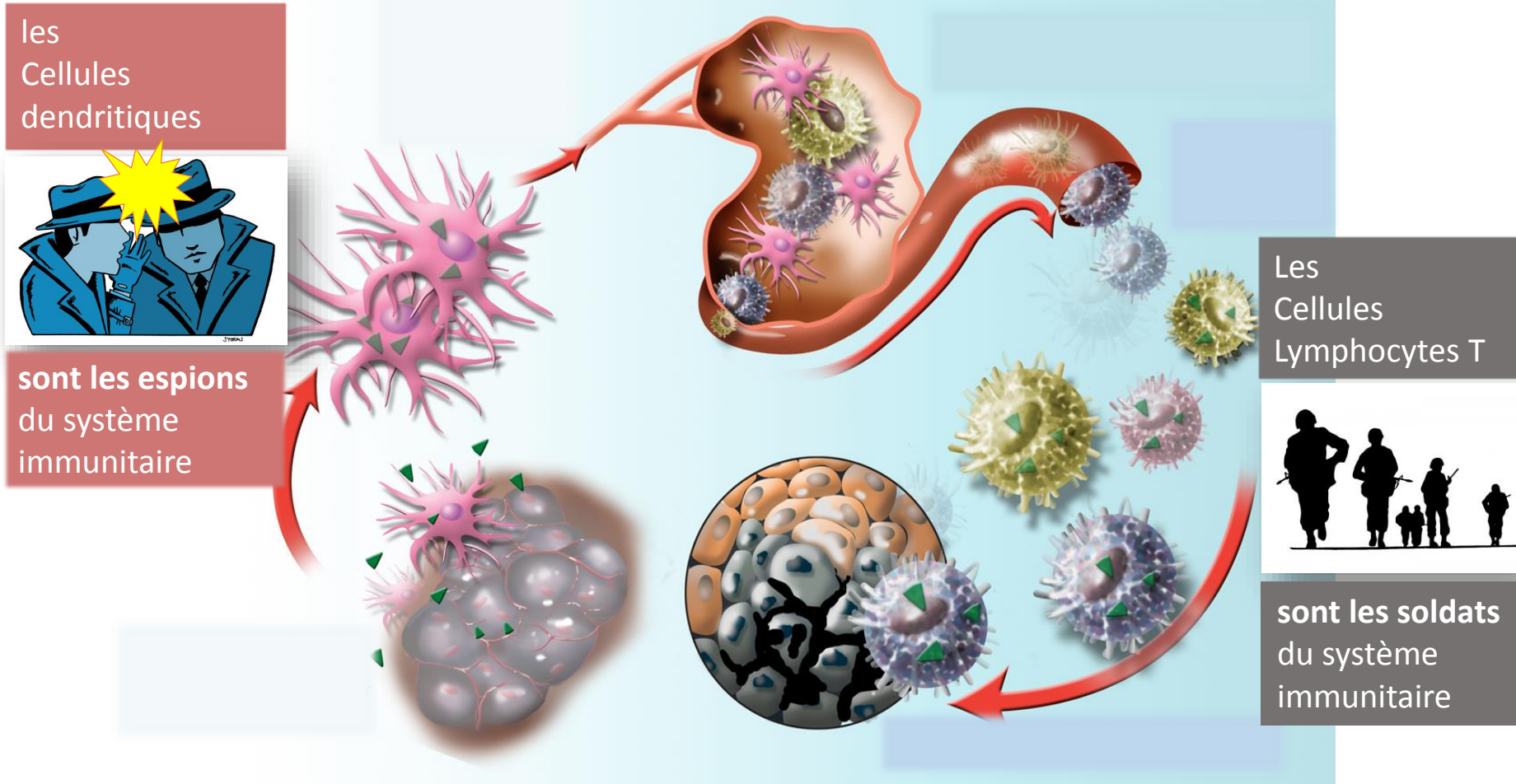


une qui s'appuie  
sur les **cellules**

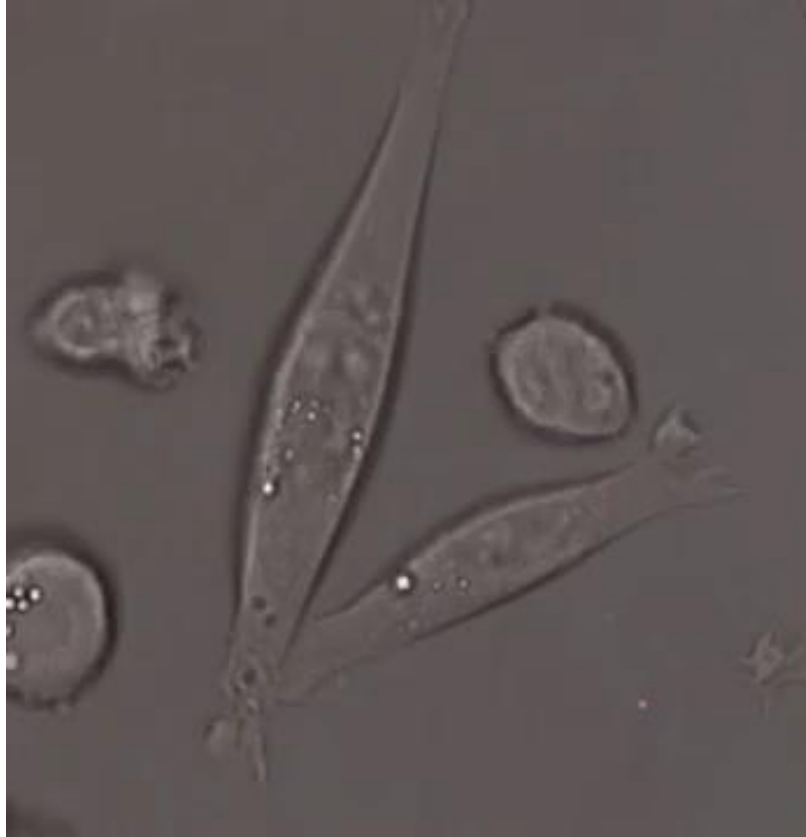
**les thérapies**  
à base de  
cellules lymphocytes T  
(déjà présentées/)

**les vaccins**  
à base de cellules  
tumoraux ou  
dendritiques

# l'immunothérapie revisitée | Les principaux protagonistes et leur rôle

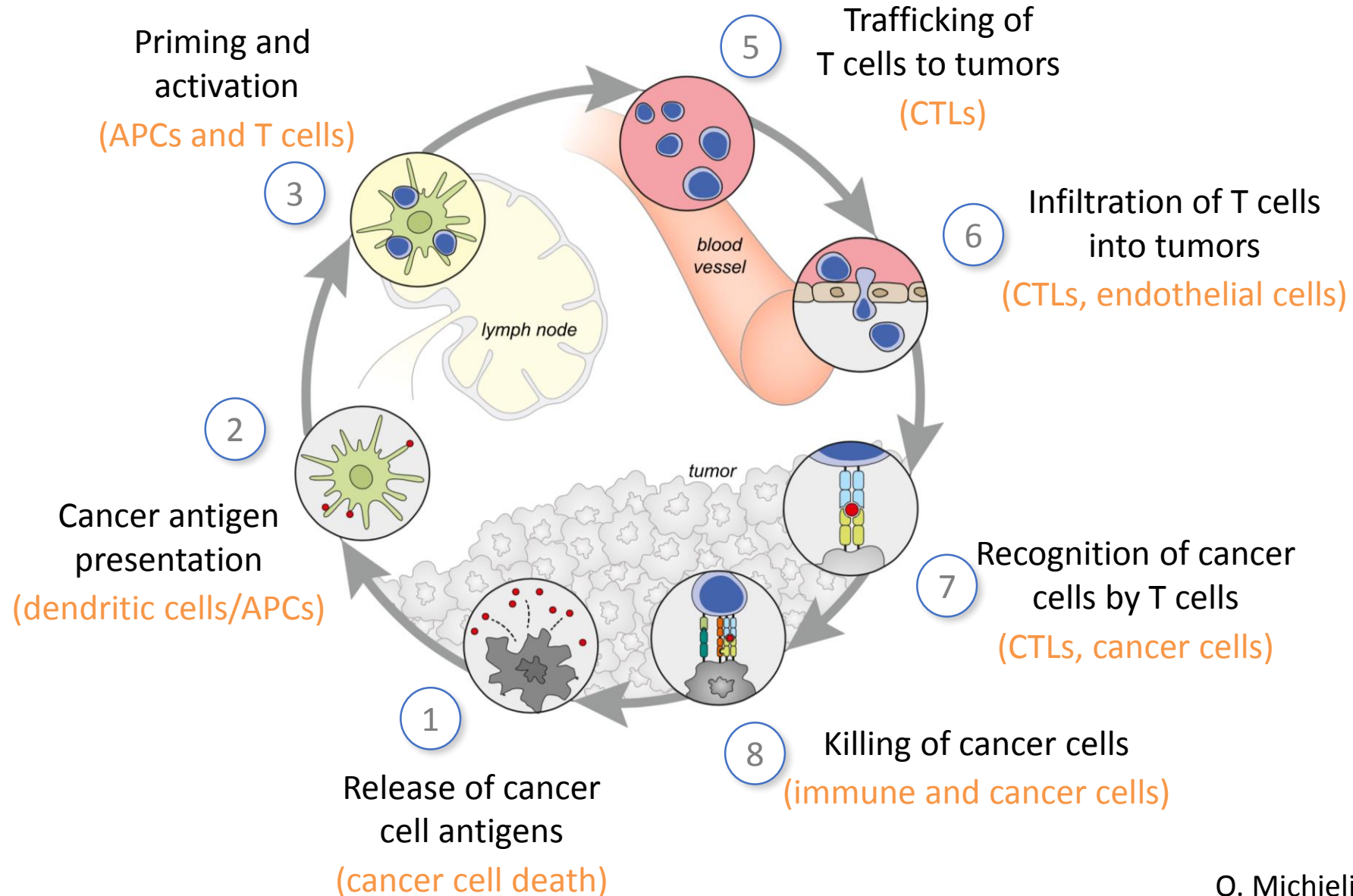


The ultimate Goal is cancer killing





# The Cancer Immunity Cycle: Many Steps To Manage



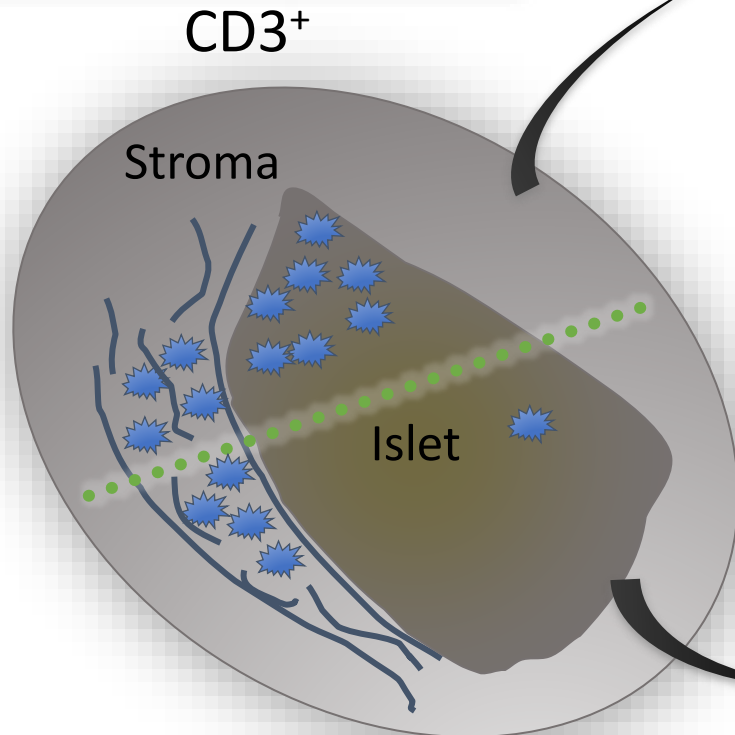
# Does the immune system of a cancer patient play a role in survival? Are Patients different?

The NEW ENGLAND JOURNAL of MEDICINE

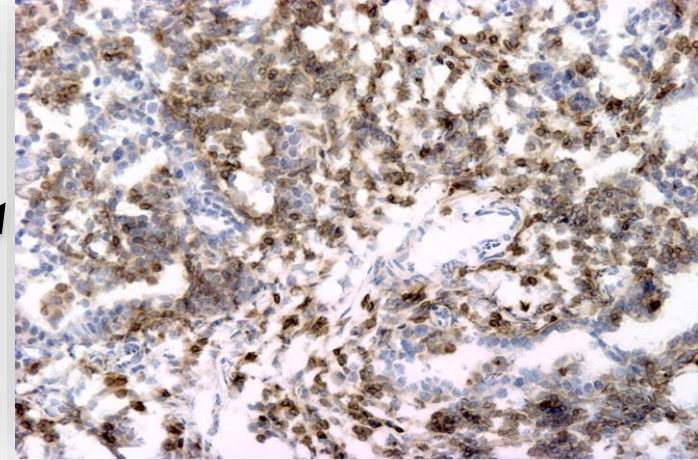
ORIGINAL ARTICLE

### Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

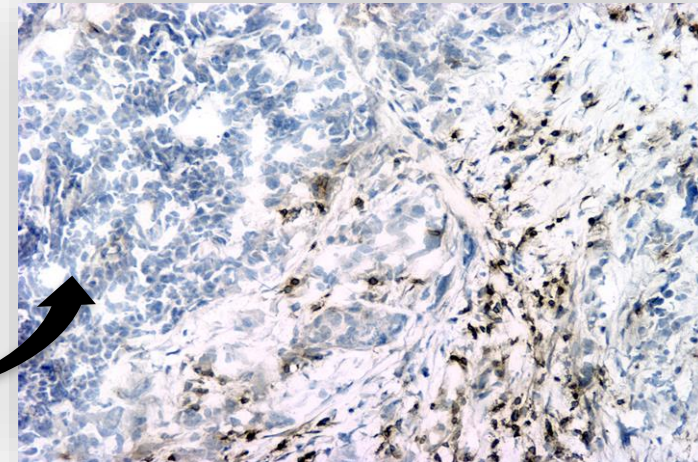
Lin Zhang, M.D., Jose R. Conejo-Garcia, M.D., Ph.D.,  
Dionyssios Katsaros, M.D., Ph.D., Phyllis A. Gimotty, Ph.D.,  
Marco Massobrio, M.D., Giorgia Regnani, M.D.,  
Antonios Makrigiannakis, M.D., Ph.D., Heidi Gray, M.D.,  
Katia Schlienger, M.D., Ph.D., Michael N. Liebman, Ph.D.,  
Stephen C. Rubin, M.D., and George Coukos, M.D., Ph.D.



TIL Present  
55%

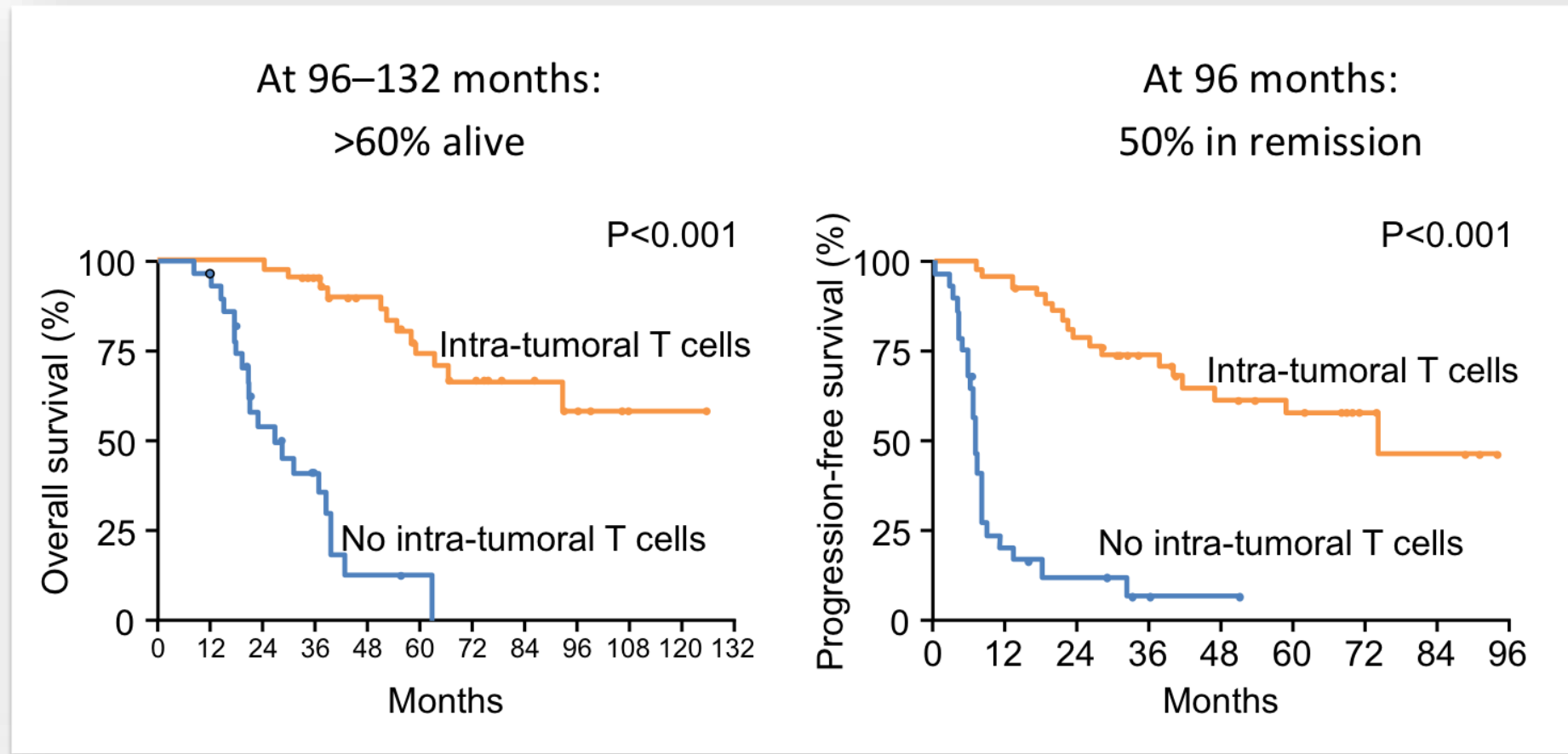


TIL Absent  
40%

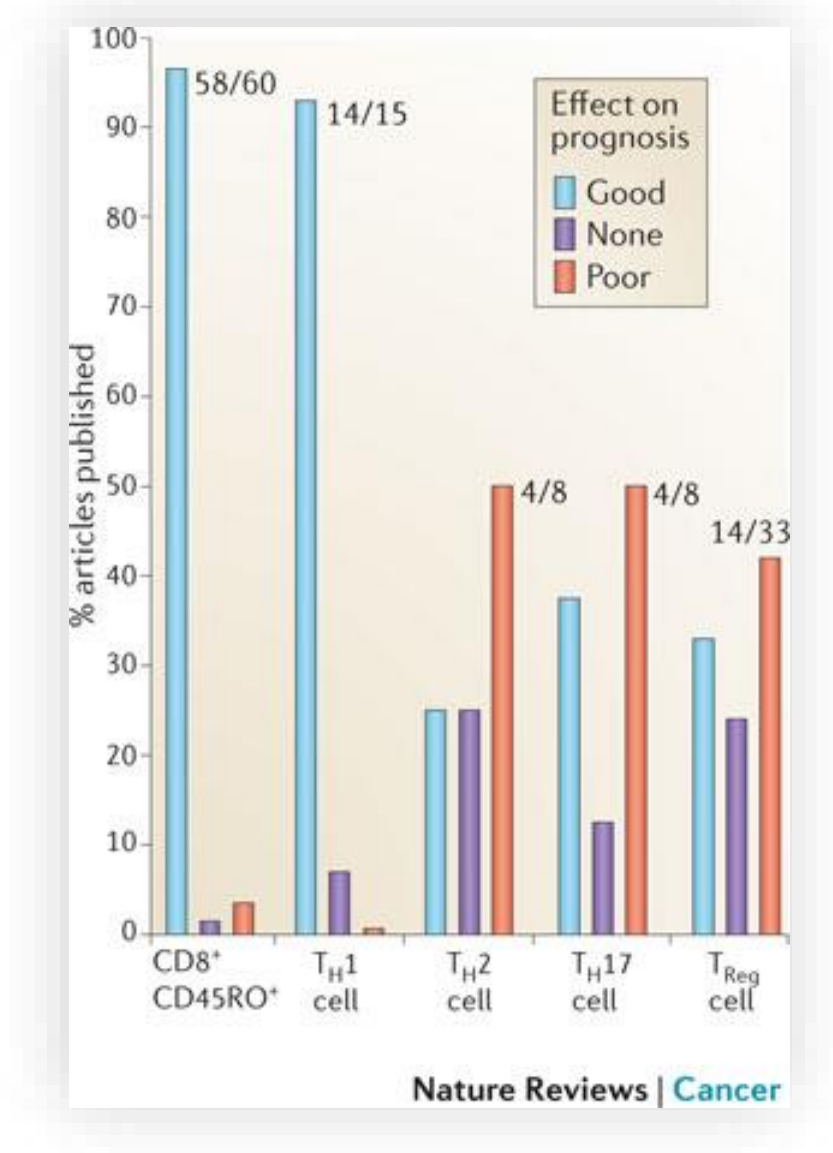




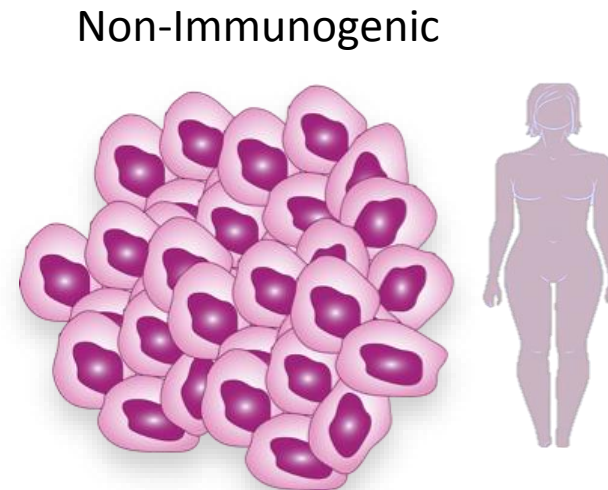
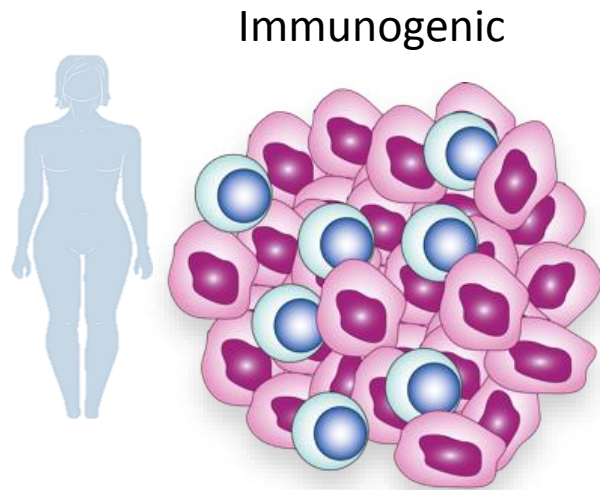
After CR with chemotherapy, only patients with TILs survive or are in remission long-term



T cell infiltrate is associated with better prognosis in most cancer types



# Two immunophenotypes of ovarian cancer ( Also applies to other cancers)

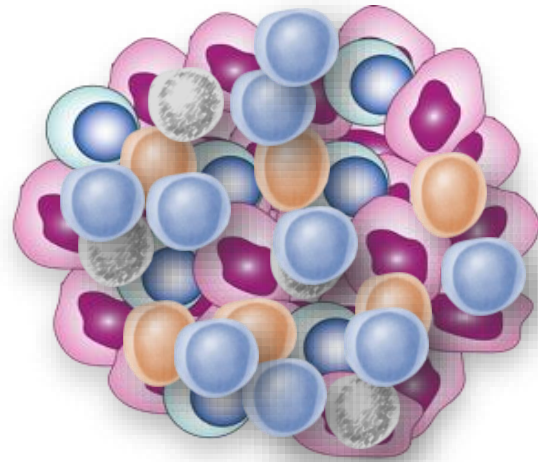
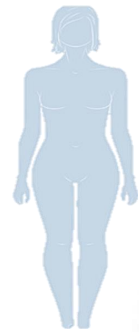


HOT

COLD



# What do we know about the “immunogenic subtype”?



T-regulatory cells

Myeloid cells

IL-10

TGF-B

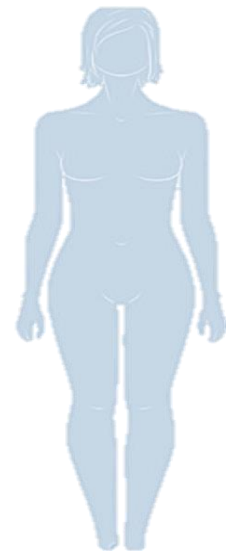
IDO

COX

PDL-1

## Pharmacological Intervention

- Checkpoint Inhibitors
- Cyclophosphamide
- IDO inhibitor
- Aspirin

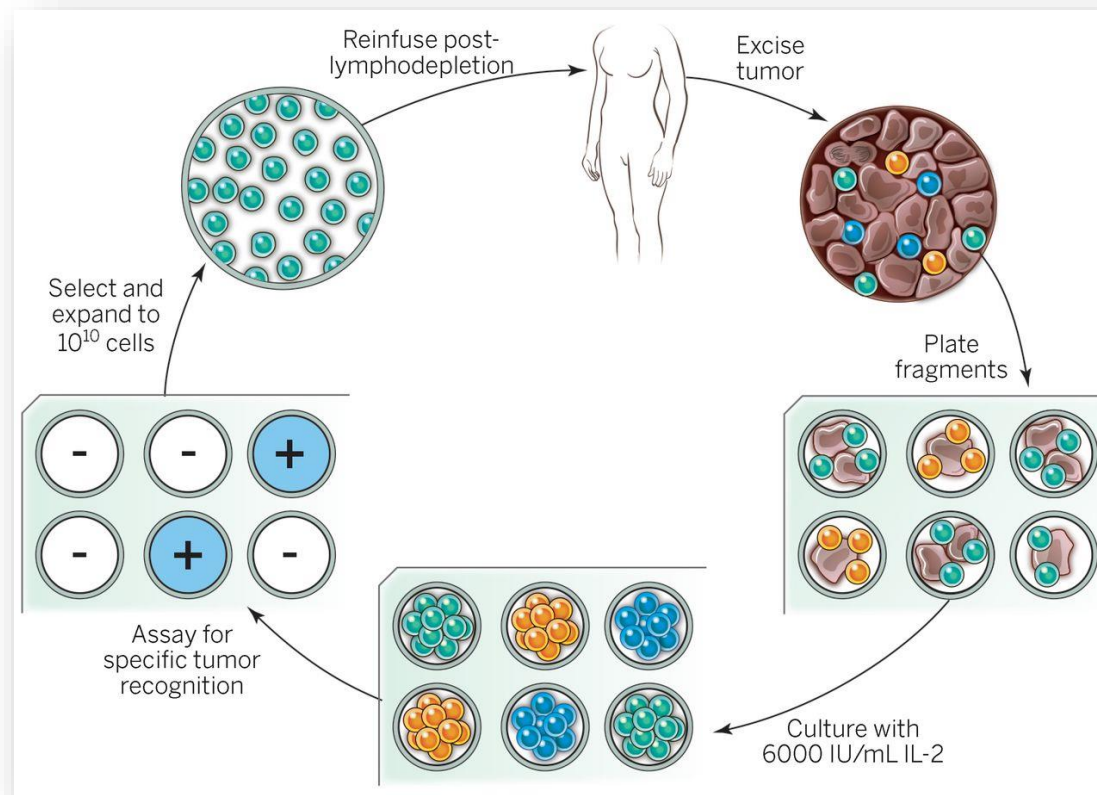


# Types of Cellular Therapy and Patients' Subtypes



# OPTION 1- Natural “completely personal” TILs

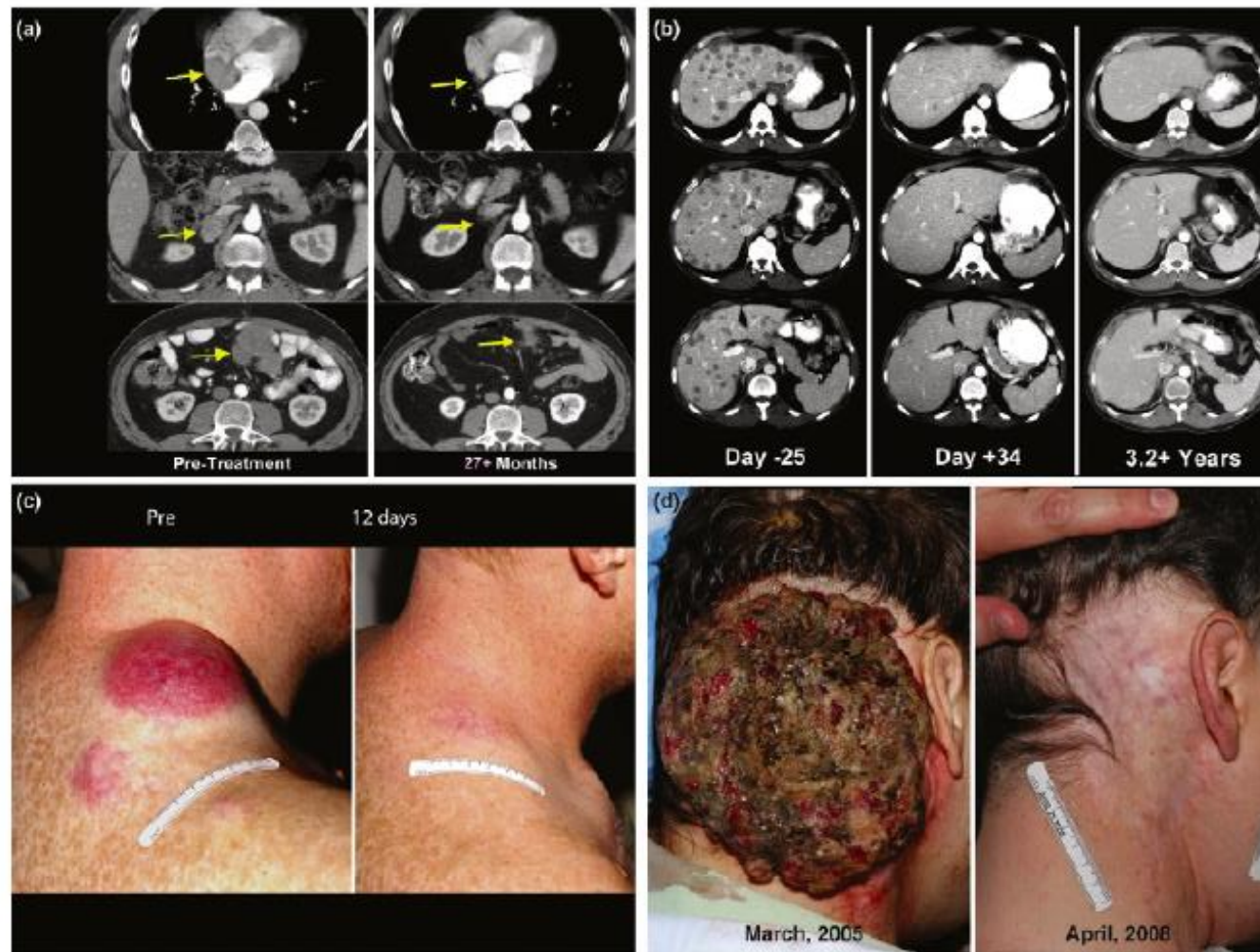
## The generation of anti-tumour T cells used for adoptive cell therapy



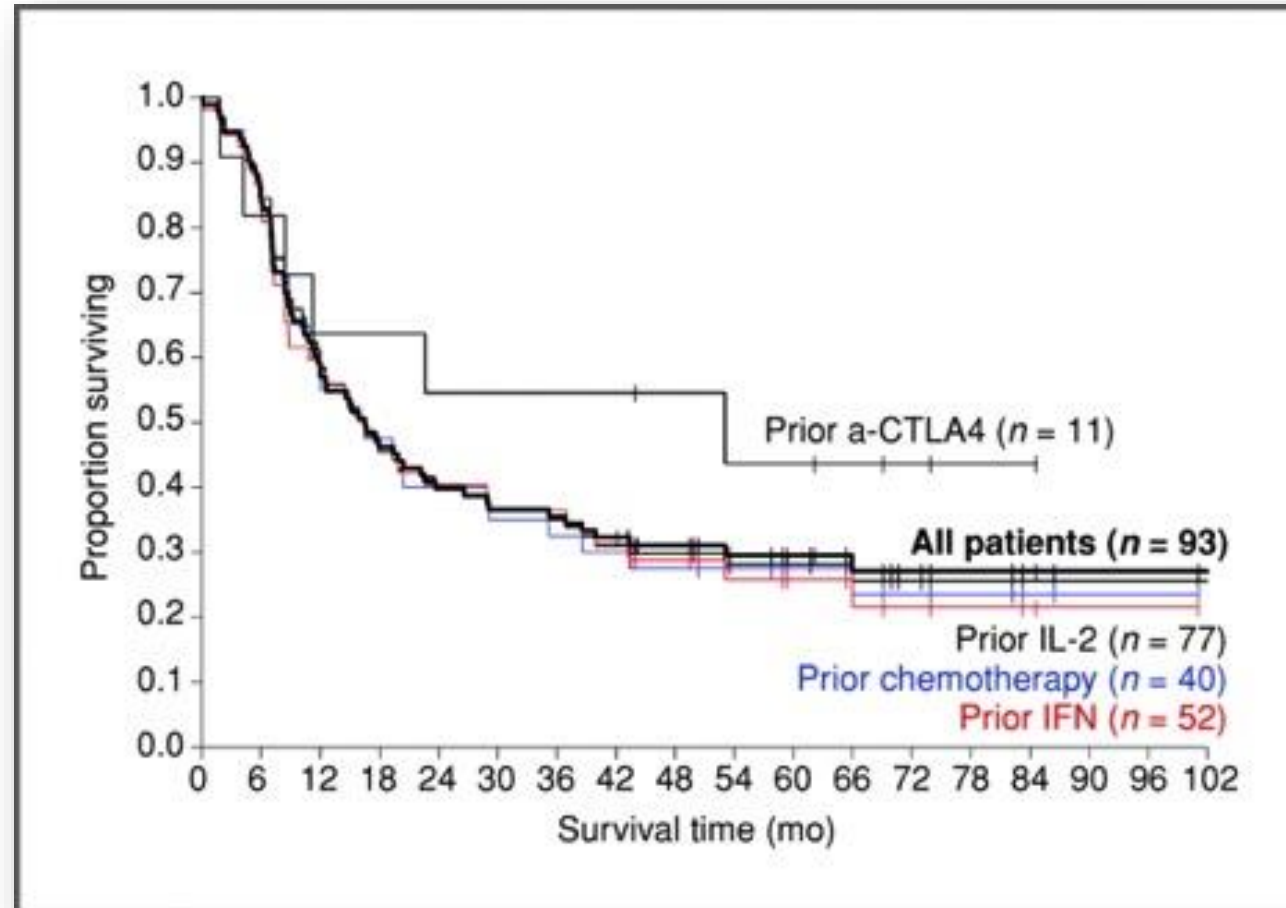
# TILS are powerful: Compelling Results in Late Stage Disease



# TILs: Regressions in Late-Stage Disease



# TILs: Durable Responses in Advanced Melanoma



19 of 20 complete responders are ongoing to >10 years

# Challenges of TIL Therapy

- Patients have to undergo surgery- Tissue needs to be stored PROPERLY
- T cells are functionally 'exhausted'
- TILs are of unknown antigen specificity
- Need for IL-2 and lymphodepletion (toxic)



# Overcoming the Challenges

Cancer Therapy: Clinical

Clinical  
Cancer  
Research

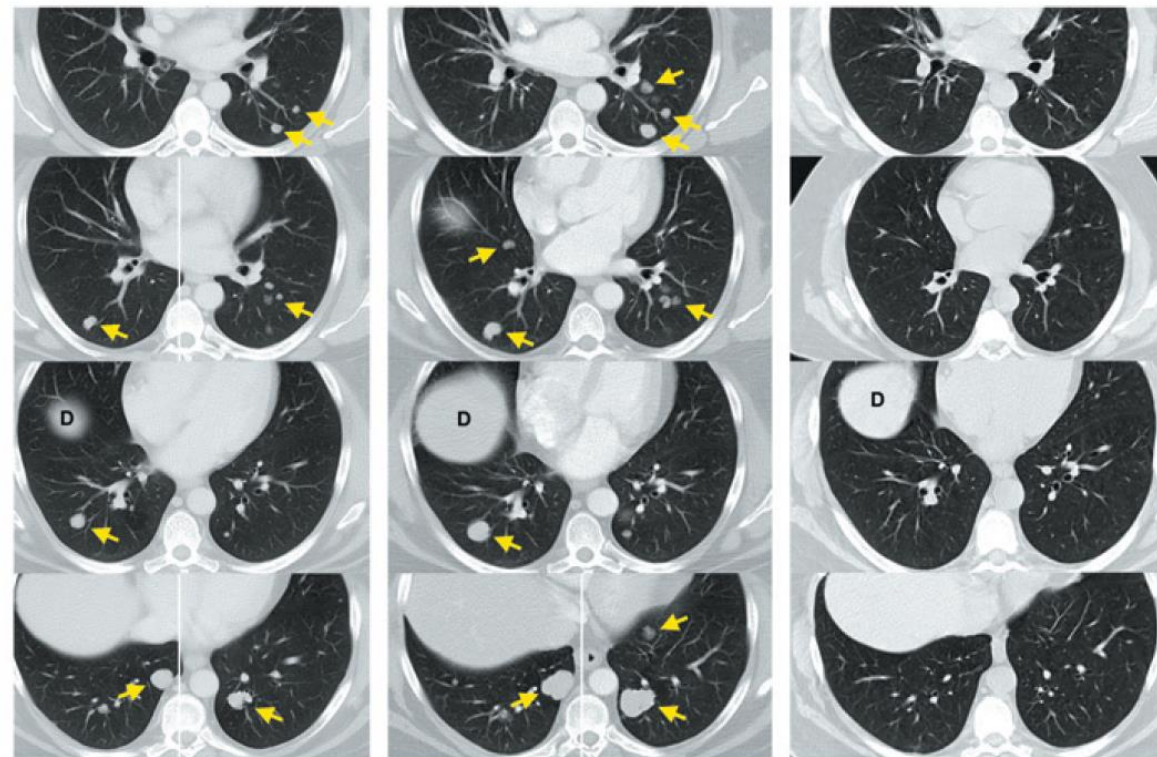
## Tumor-Infiltrating Lymphocytes Genetically Engineered with an Inducible Gene Encoding Interleukin-12 for the Immunotherapy of Metastatic Melanoma

Patient had previously been treated with **30 billion conventional nontransduced TILs**, plus 7 doses of IL2 (720,000 IU/kg) and tumors progressed.

Using TILs expanded from the same original culture, the patient was retreated with a culture of **3 × 100 million NFAT.IL12 gene-modified TILs**

and has an ongoing **complete regression at 38 months** of disease metastatic to lung and lymph nodes

Patient 9 (CR 38+)



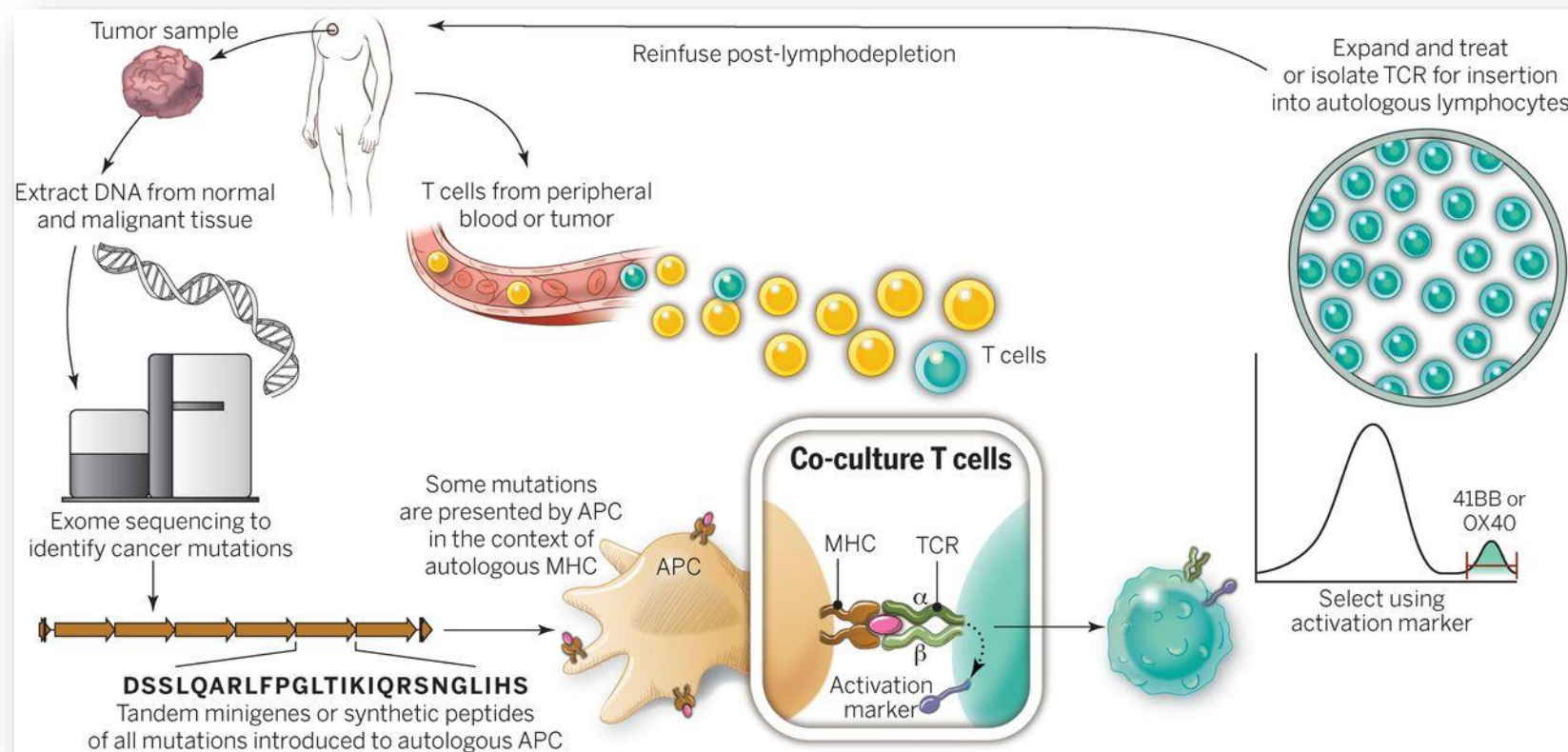
Pretreatment

After conventional TIL + IL2

2 y after TIL-IL12

# Overcoming the Challenges

A “blueprint” for the treatment of patients with T cells recognizing tumor-specific mutations.



# Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer

Eric Tran,<sup>1</sup> Simon Turcotte,<sup>1\*</sup> Alena Gros,<sup>1</sup> Paul F. Robbins,<sup>1</sup> Yong-Chen Lu,<sup>1</sup> Mark E. Dudley,<sup>1†</sup> John R. Wunderlich,<sup>1</sup> Robert P. Somerville,<sup>1</sup> Katherine Hogan,<sup>1</sup> Christian S. Hinrichs,<sup>1</sup> Maria R. Parkhurst,<sup>1</sup> James C. Yang,<sup>1</sup> Steven A. Rosenberg<sup>1‡</sup>

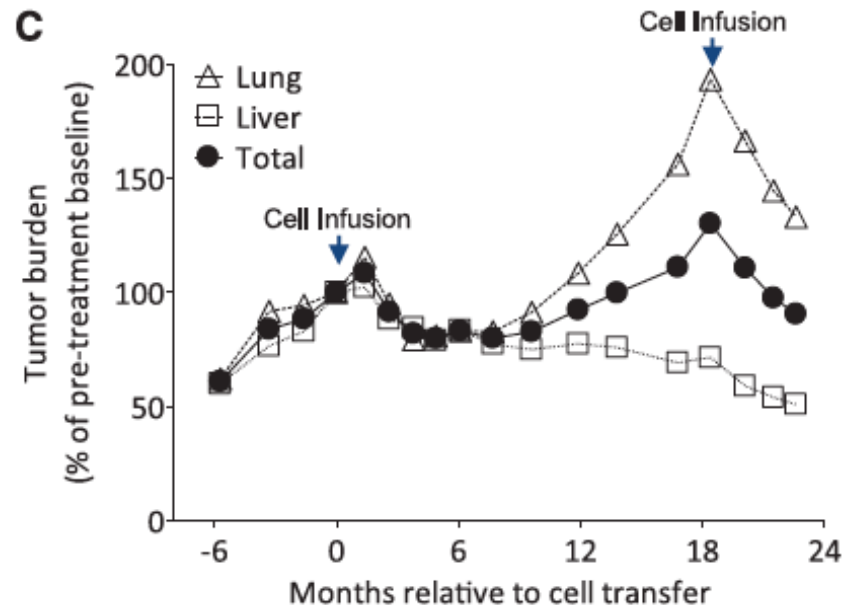
Patient with *metastatic cholangiocarcinoma*

Identified a *T cell* contained (CD4+ T helper 1 (TH1) cells) recognizing a *mutation in erbb2* interacting protein (ERBB2IP) expressed by the cancer.

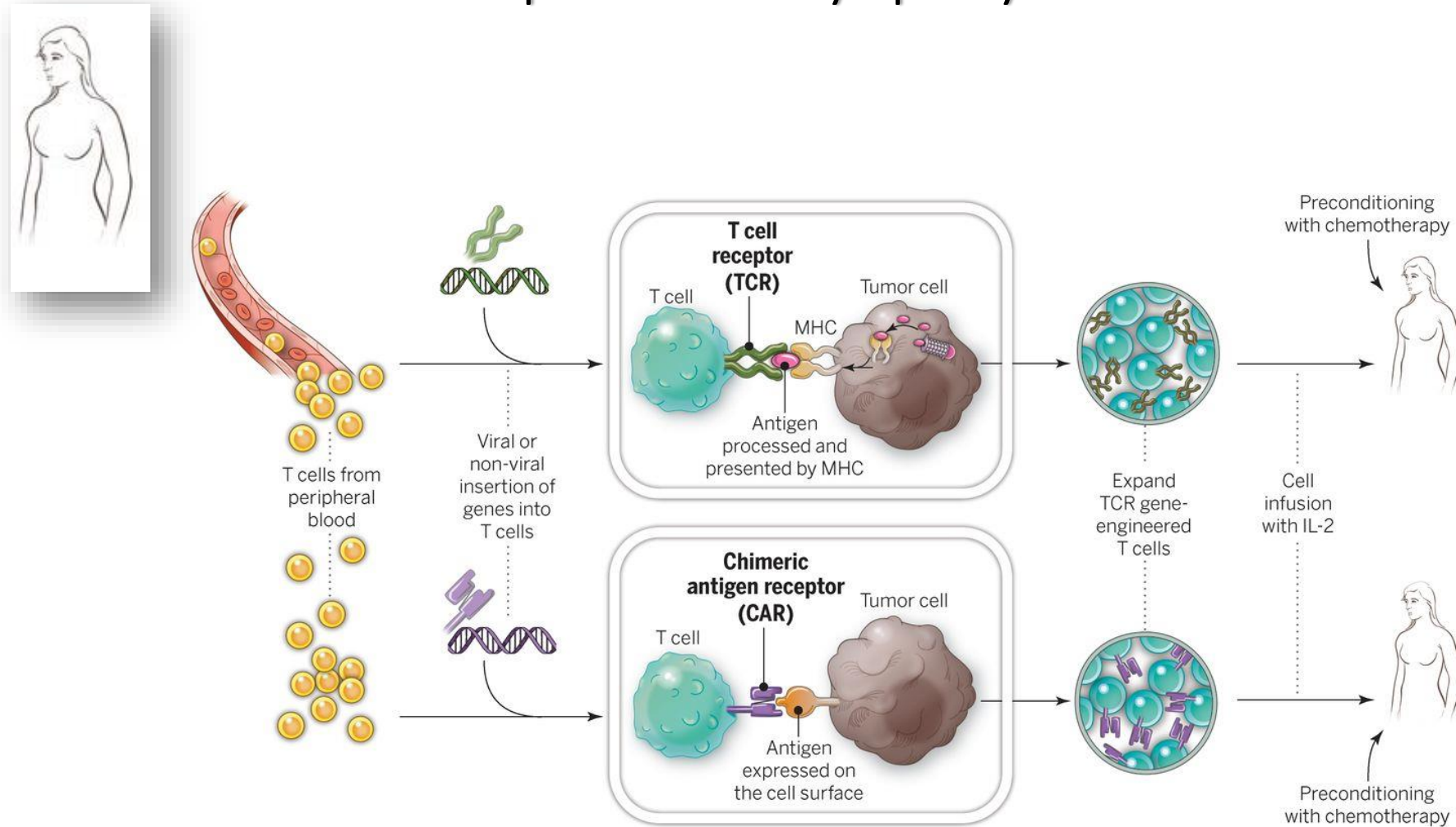
ACT of TIL containing about 25% of the mutation-specific T-cells

*the patient achieved a decrease in target lesions with prolonged stabilization of disease.*

The patient was retreated with a >95% pure population of mutation-reactive T cells



# OPTION 2: Adoptive T cell Therapy with Genetically Engineered Peripheral Blood Lymphocytes.





## La leucémie

### Cell therapy shows remarkable ability to eradicate cancer in clinical study



Science Translational Medicine

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RESEARCH ARTICLE | CANCER



Efficacy and Toxicity Management of 19-28z CAR T Cell Therapy in B Cell Acute Lymphoblastic Leukemia

En 2014, la plus grande étude clinique de patients avec une leucémie avancée annonçait que **88 % des patients avaient bénéficié d'une rémission totale** après avoir traité avec des versions génétiquement modifiées de leur propres cellules immunitaires.



# The CD19 CAR T Cell Success Story for relapsed ALL and CLL



Emily Whitehead

- Complete remission and long-term responses in up to 90% of **acute lymphoblastic leukemia (ALL)** patients ( both adult and pediatric)
- And in > 50% of **chronic lymphocytic leukemia (CLL)** patients.
- On target side effects include B cell aplasia and cytokine release syndrome.



FDA News Release

# FDA approval brings first gene therapy to the United States

*CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia*

- SHARE
- TWEET
- LINKEDIN
- PIN IT
- EMAIL
- PRINT

For Immediate Release

August 30, 2017

## Novartis seeks European approval for cell therapy Kymriah

Reuters Staff 2 MIN READ

ZURICH (Reuters) - Swiss drugmaker Novartis has submitted its cell therapy Kymriah for European approval in two forms of blood cancer, seeking to expand the use of a new treatment it hopes will eventually become a \$1 billion-a-year seller.

REUTERS Novartis seeks European approval for cell therapy Kymriah



### Your Journey

Before, During & After Treatment

### Cancer Types

Overview

Bladder

Brain

# CAR T-Cell Therapy Yescarta Approved to Treat Non-Hodgkin Lymphoma

*Yescarta was granted FDA approval for use in adults with relapsed or refractory non-Hodgkin lymphoma. This is only the second CAR T-cell therapy ever approved.*

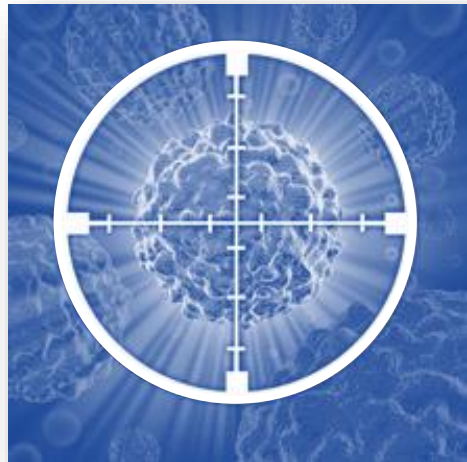
BY BETH INCOLLINGO

PUBLISHED: OCTOBER 18, 2017

## Les vaccins

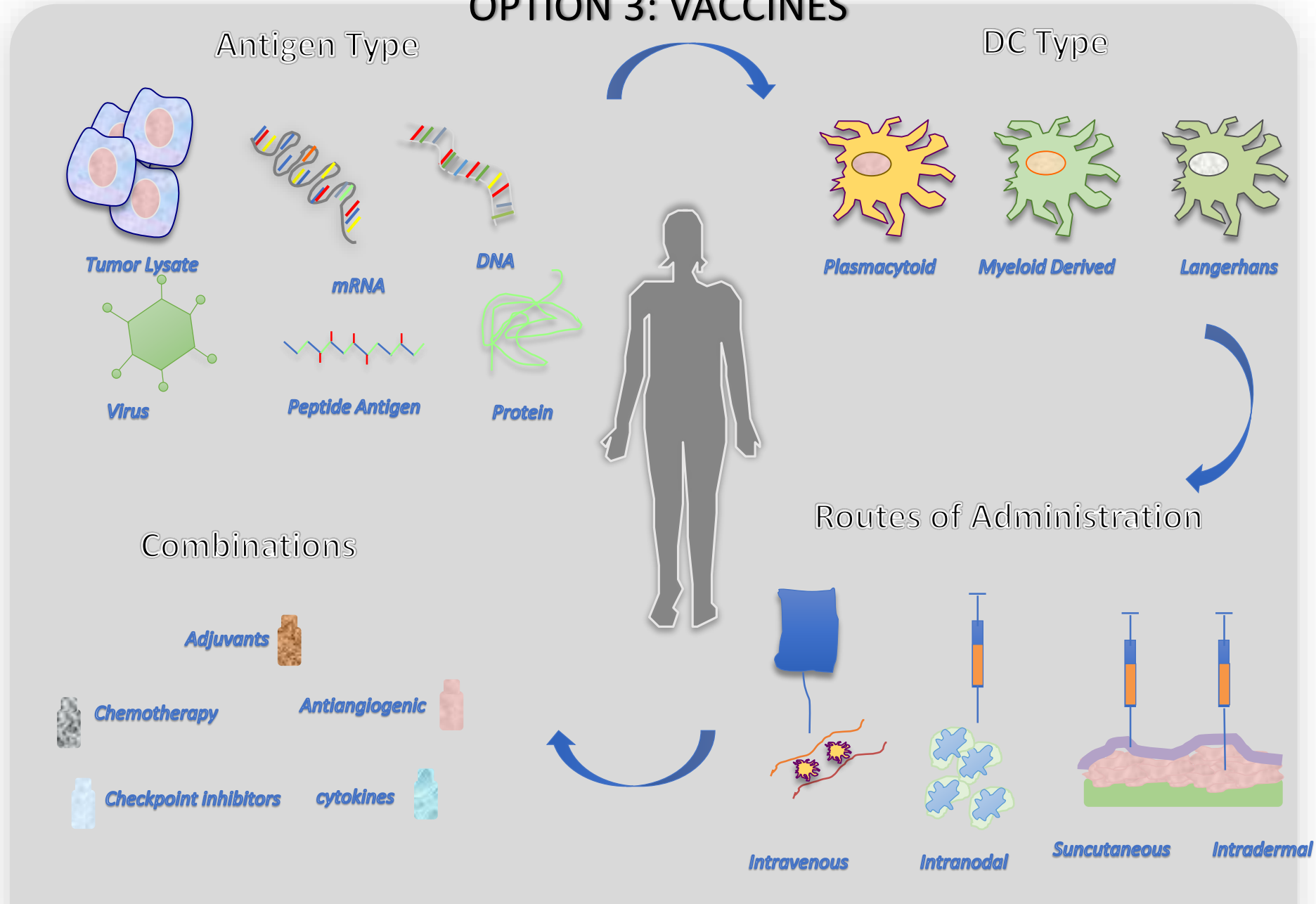
### Au-delà de la prévention

On associe souvent le vaccin à la prévention, mais il faut savoir qu'il peut être aussi utilisé dans un cadre thérapeutique.



Le vaccin vient stimuler les cellules T pour aiguïser leur agressivité contre les cellules cancéreuses.

# OPTION 3: VACCINES



## Les vaccins

Il existe différents types de vaccins

La meilleure approche est le **vaccin personnalisé**.



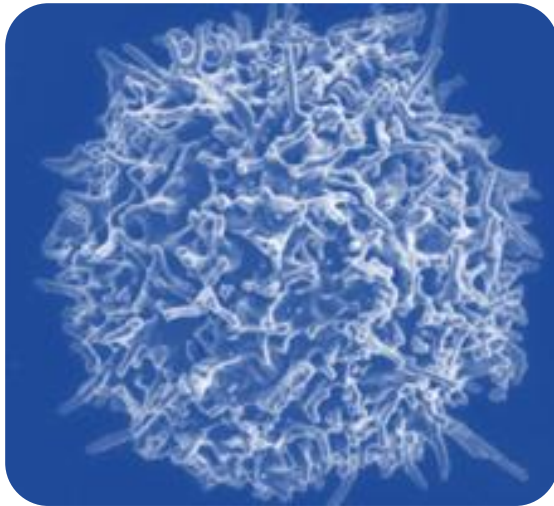
Ceci parce que chaque tumeur est aussi différente et individuelle qu'une empreinte digitale.



## Les vaccins

# La création d'un vaccin personnalisé

à partir de la  
tumeur du  
patient



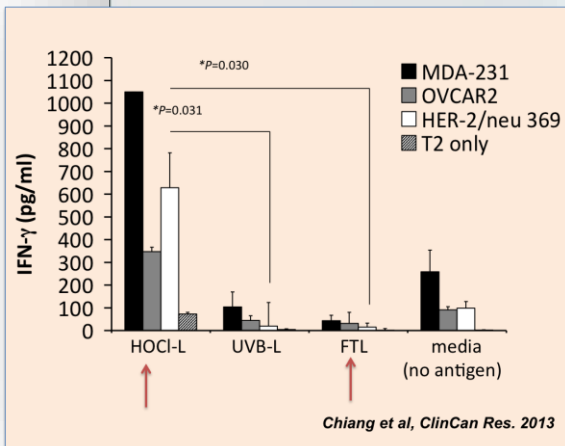
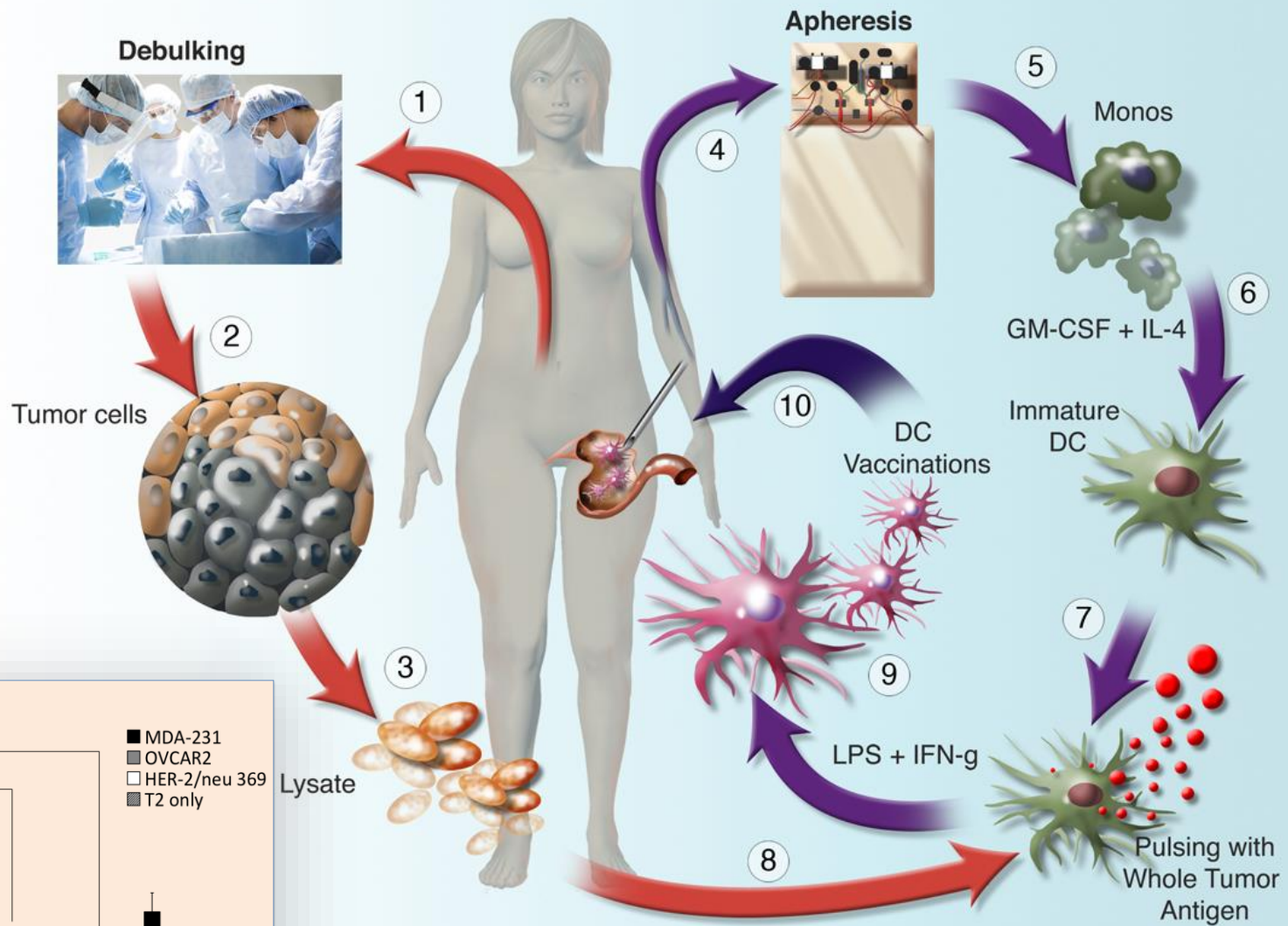
On va créer le vaccin directement à partir du tissu tumoral

à partir  
**d'informations**  
prélevées de la tumeur



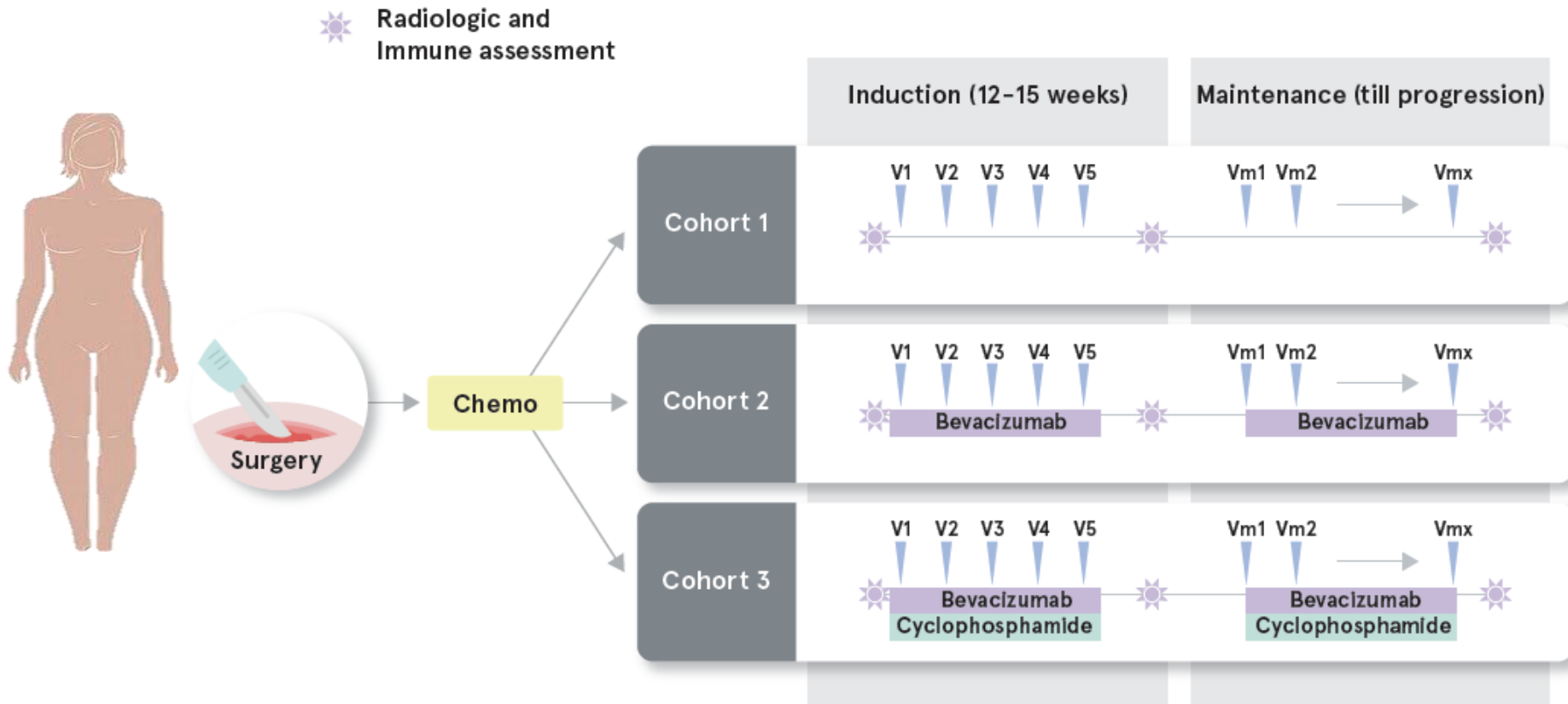
On récolte d'abord des informations sur la tumeur et à partir de ces informations on synthétise un vaccin

# Whole Tumor Antigen Dendritic Cell Vaccine Study

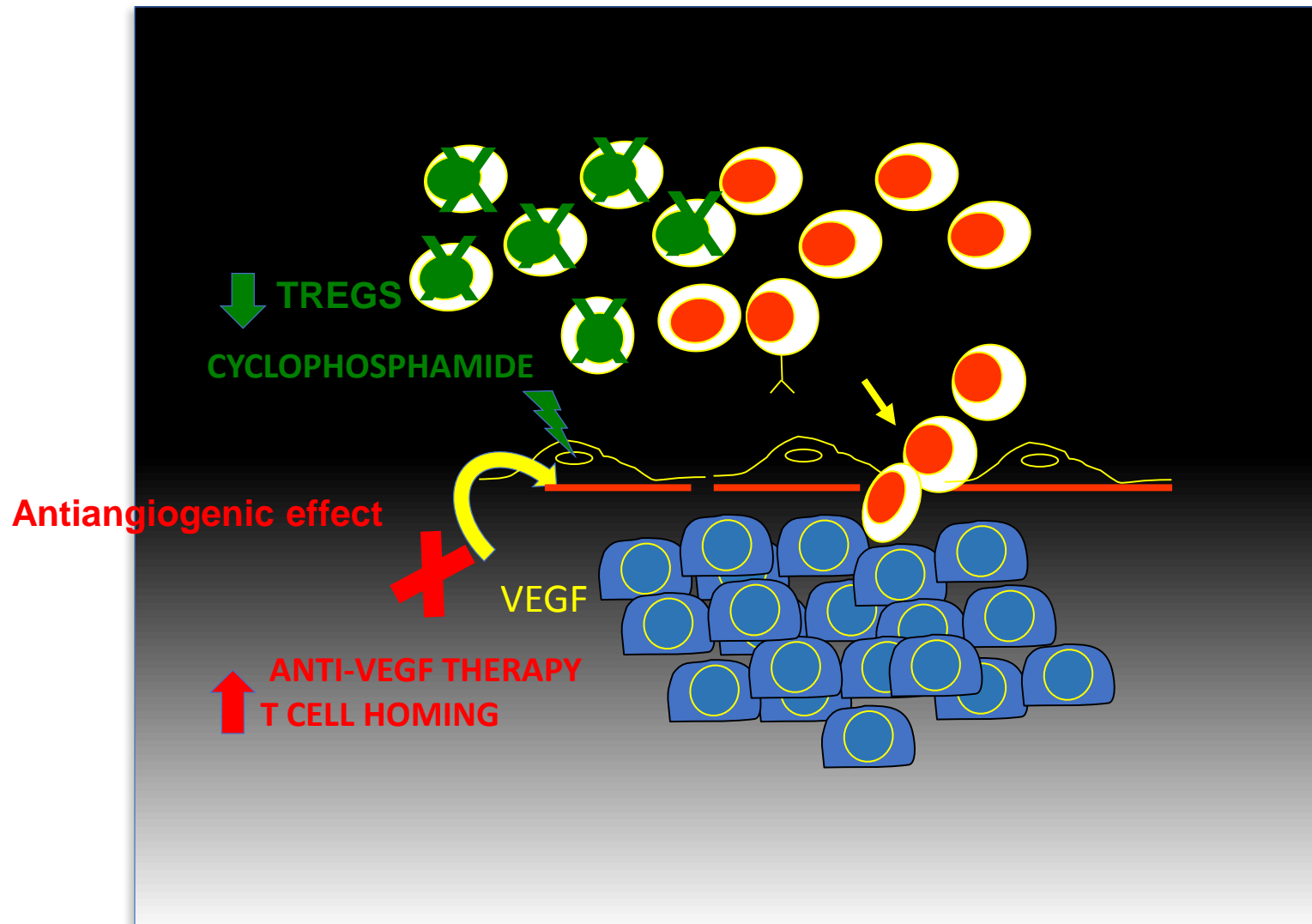


Cheryl Chiang

# A Pilot Clinical Trial of Dendritic Cell Vaccine Loaded with Autologous Tumor for Recurrent Ovarian, Primary Peritoneal OR Fallopian Tube cancer

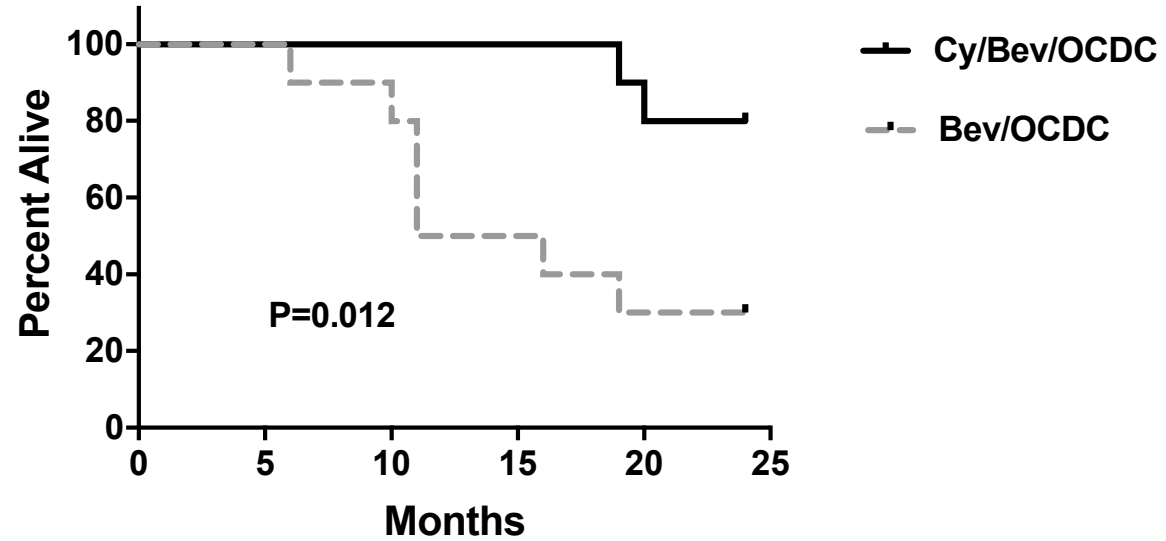
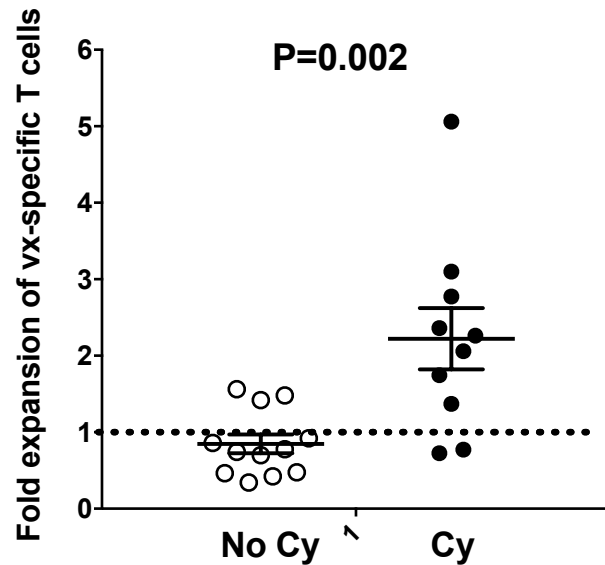


# Combining Vaccines with antiangiogenesis therapy and metronomic chemotherapy



# Vaccines must be combined with other drugs

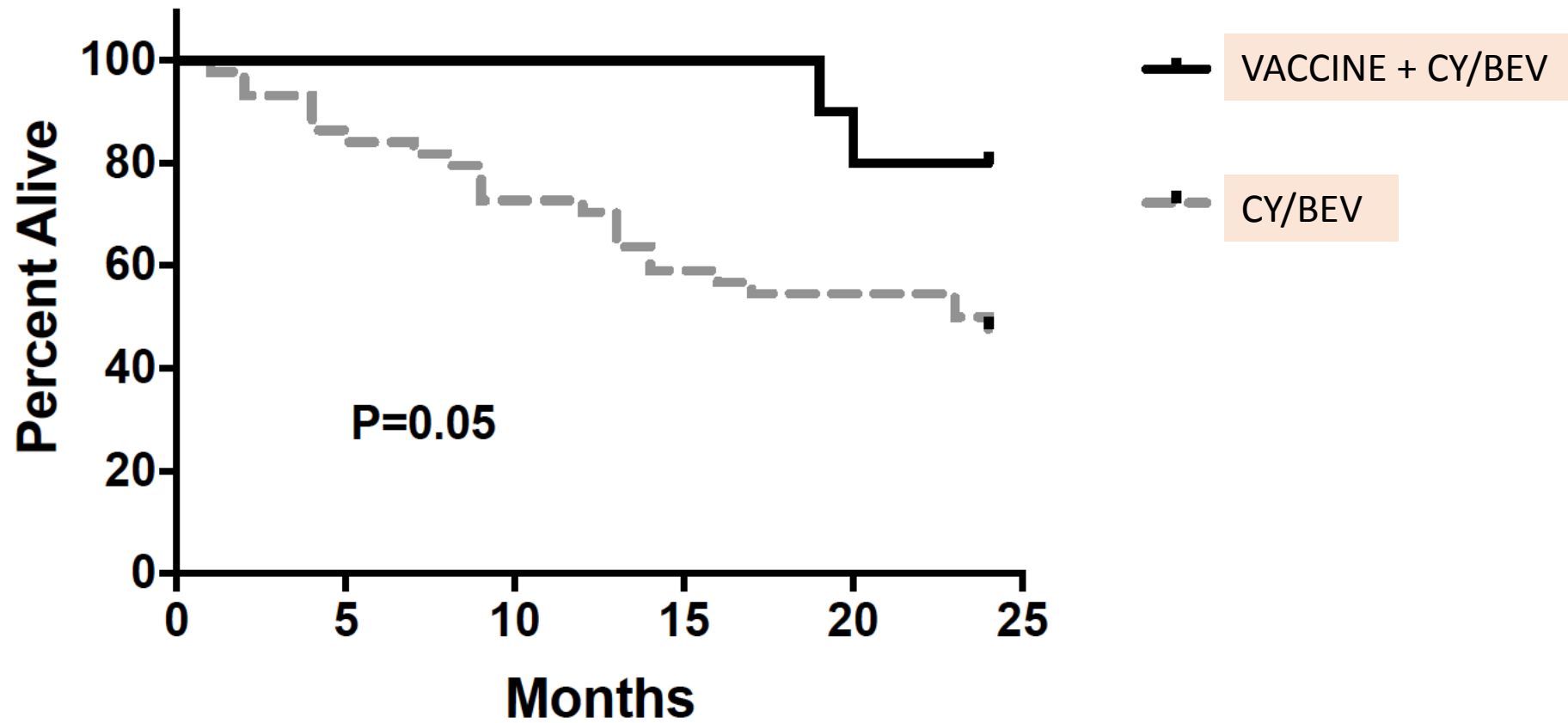
## Increased Immune response and survival in patients treated with cyclophosphamide



Eran Ophir  
Urania Dafni  
Alice Destailats

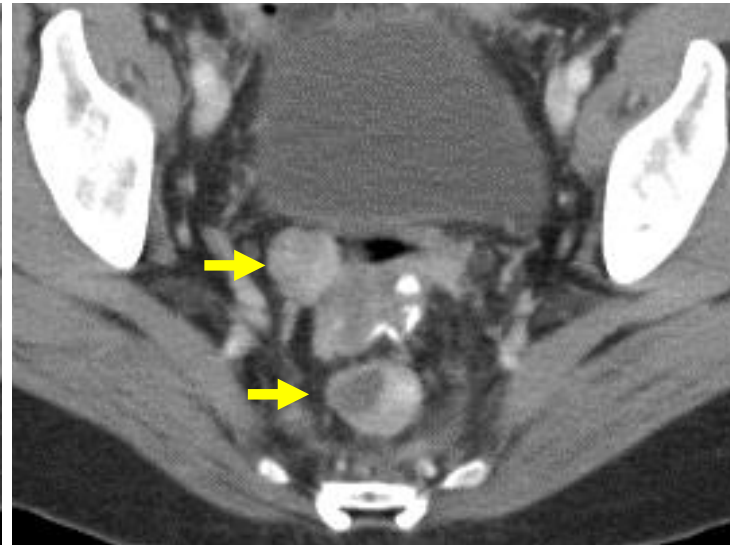


# Vaccine In combination with Standard of Care has Benefit

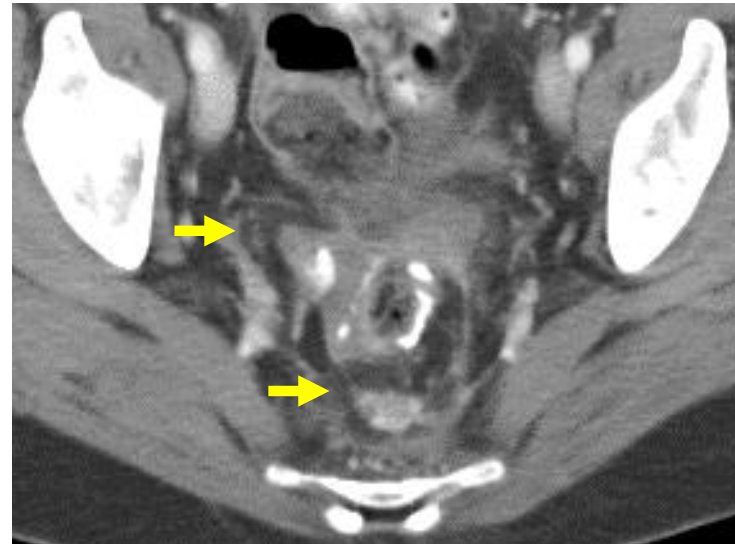


# Vaccine induced T cell response correlates with clinical benefit

Pre-treatment

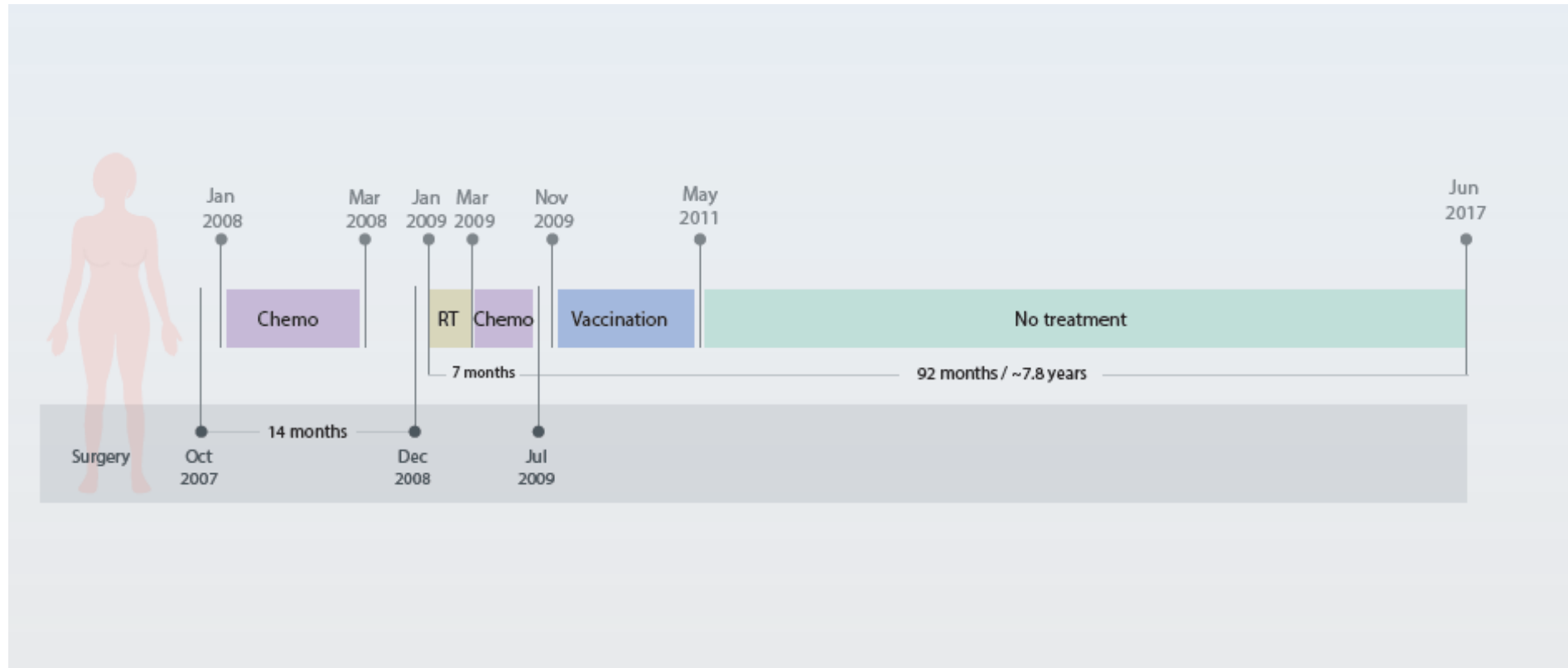


Post-treatment



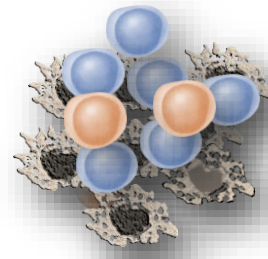
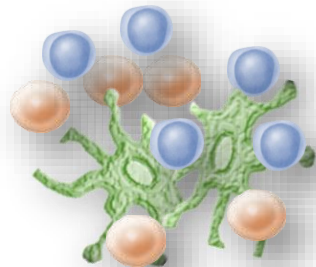
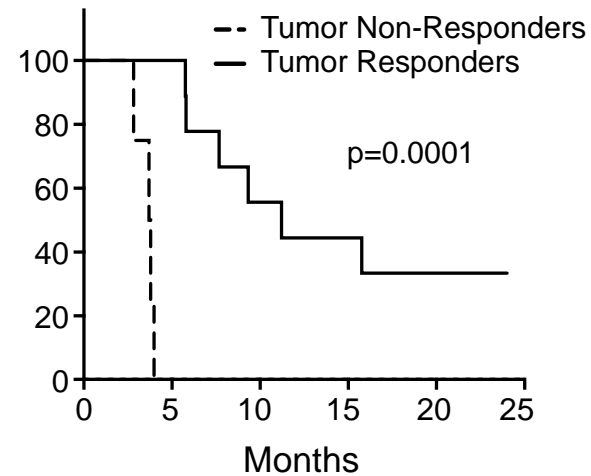
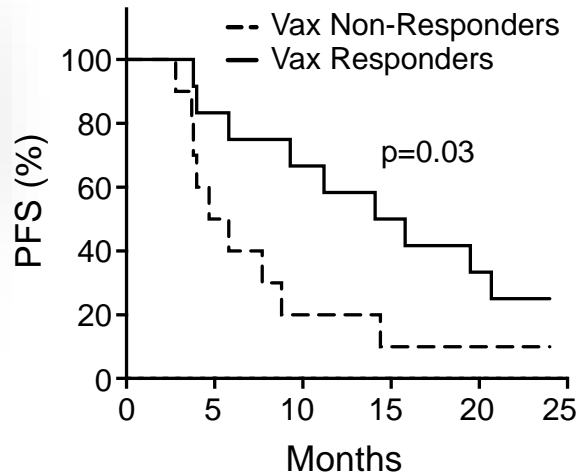
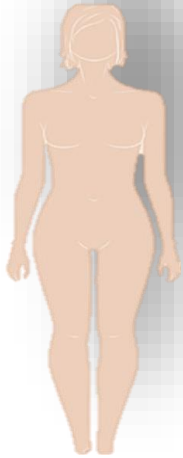
right pelvic and presacral implants regressing

# Vaccine induced T cell response specific correlates with clinical benefit



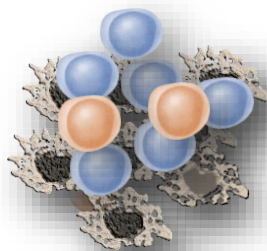
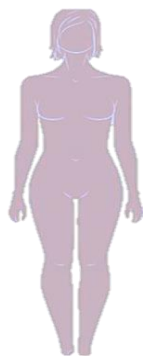
Around 71 % of our patients experienced remission inversion

# Response to vaccine is associated with improved PFS

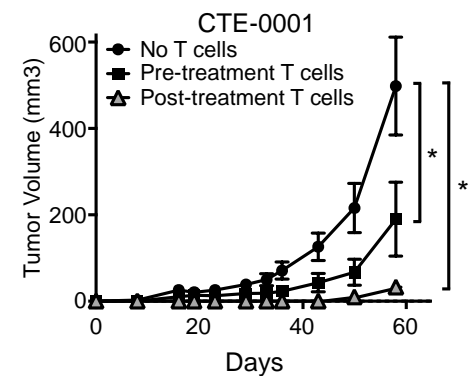
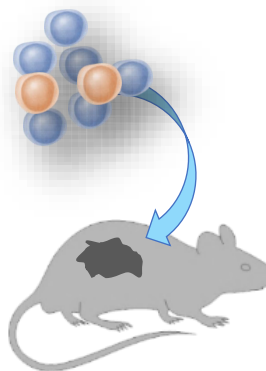
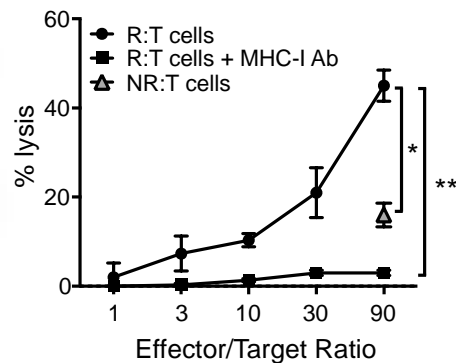
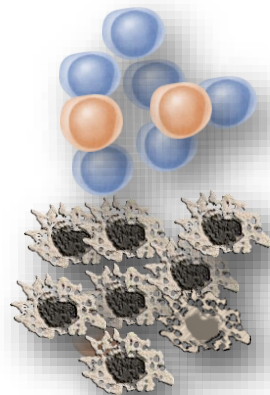
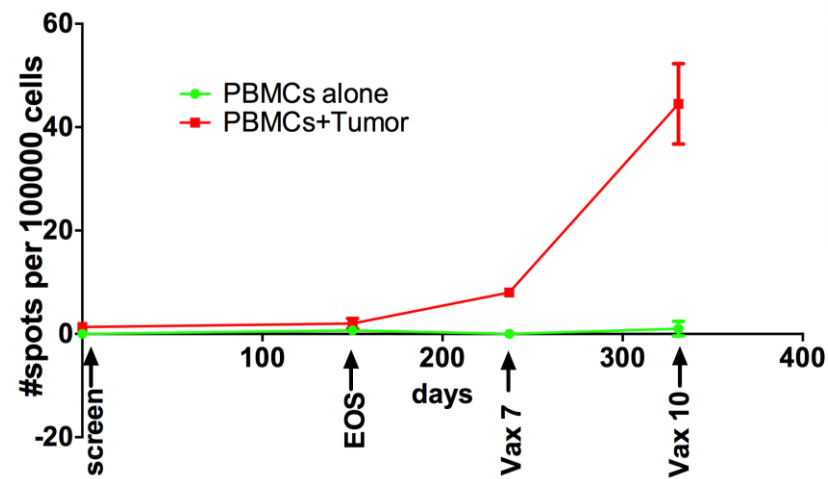


Eran Ophir  
Janos Tanyi

# Vaccine induced T cell response specific to autologous tumor antigen and achieved Tumor killing



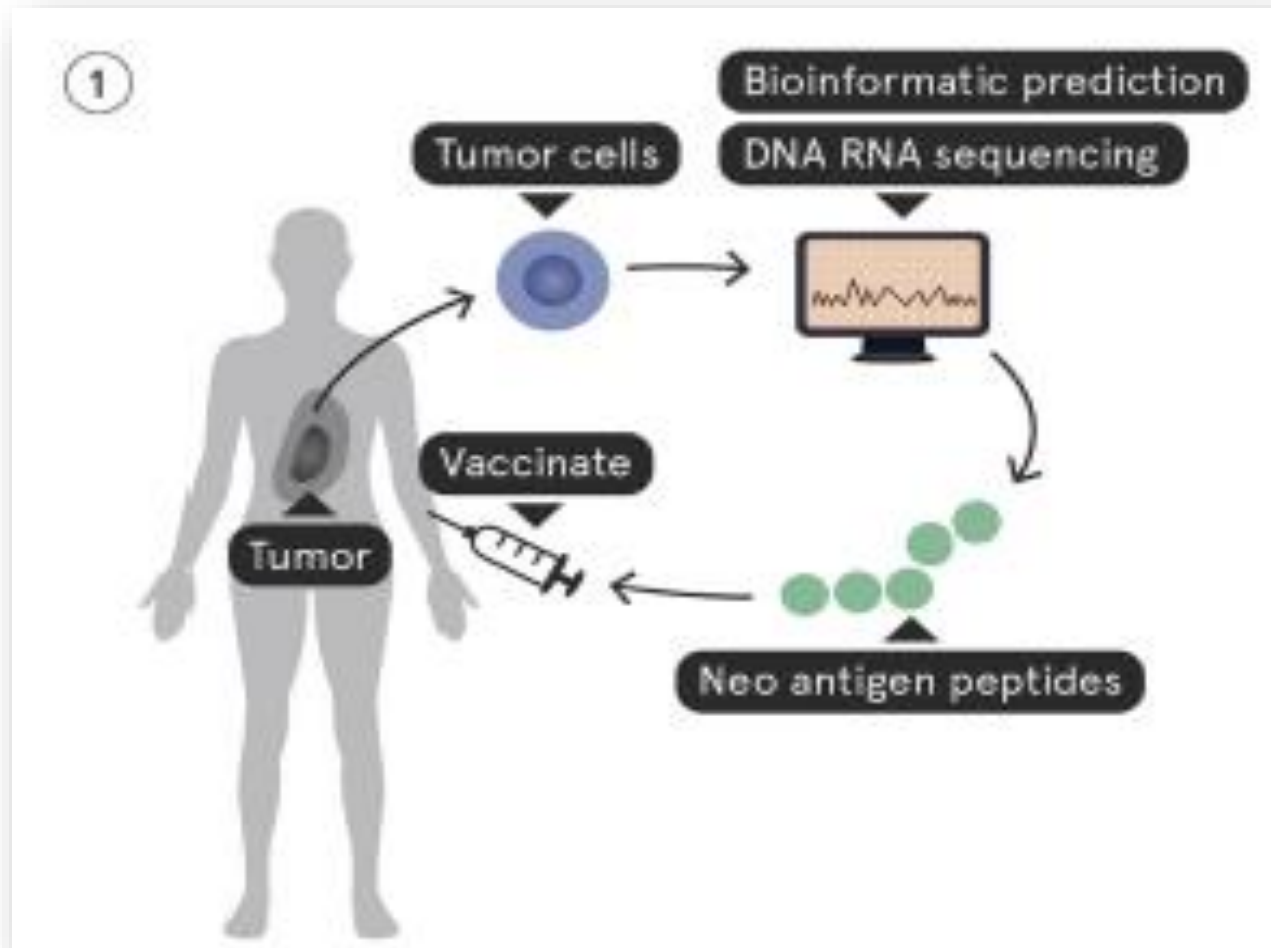
PBMC



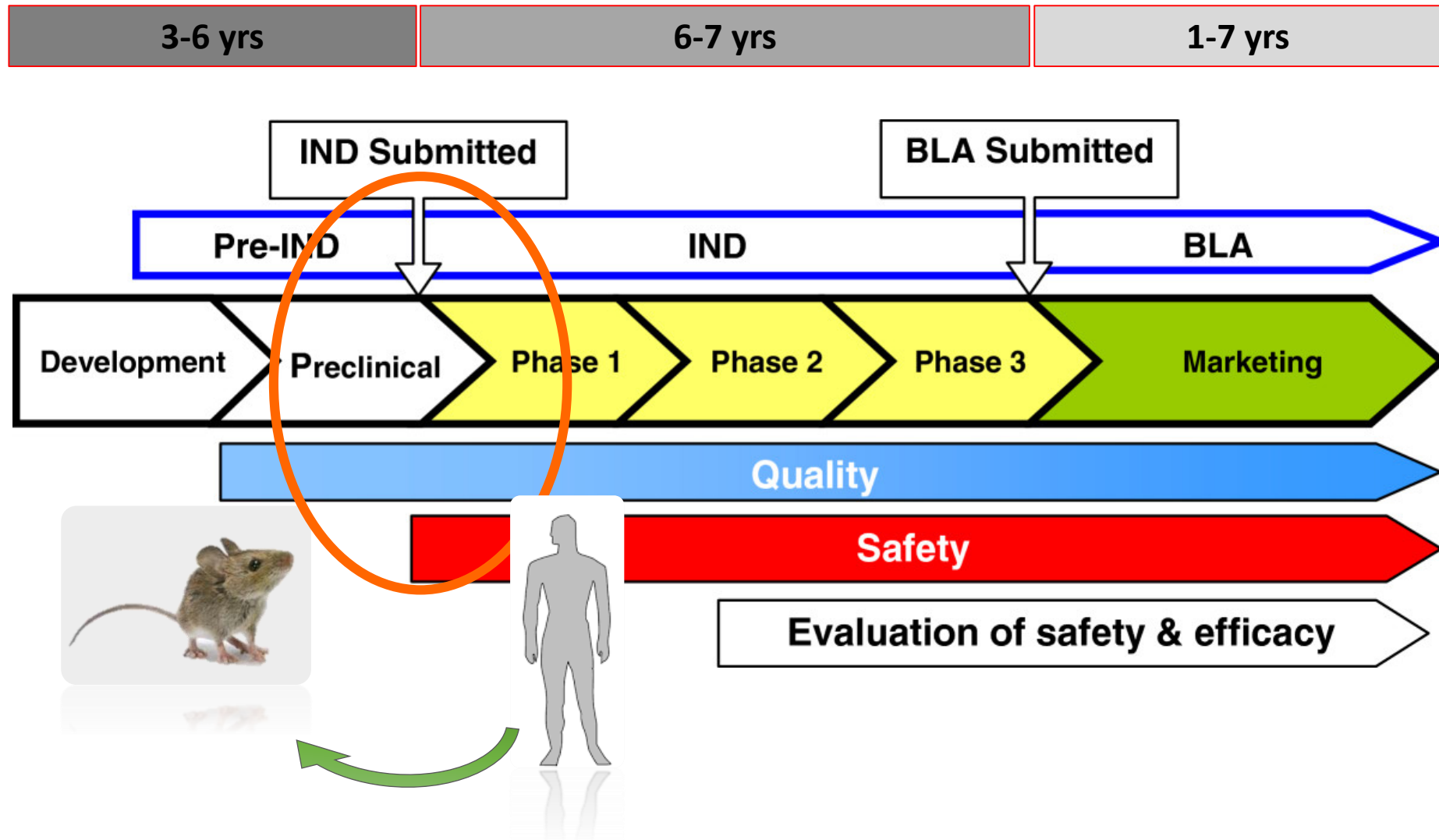
Eran Ophir



# A Personalized NeoAntigen Vaccine



# Biological product development overview



Adapted from Vatsan et al. *Journal for ImmunoTherapy of Cancer* 2013 1:5 doi:10.1186/2051-1426-1-5

le pré-requis de l'immunothérapie cellulaire

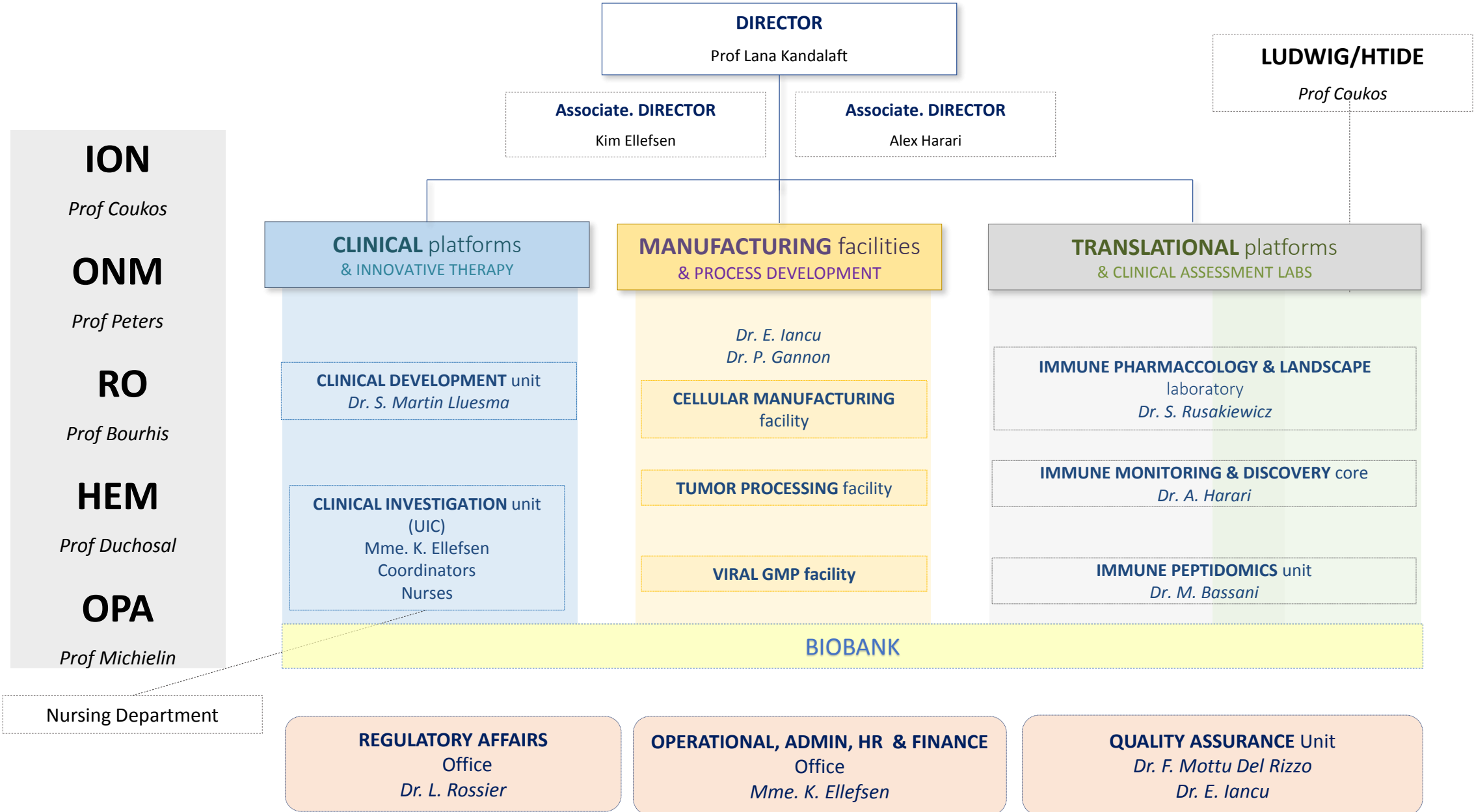
Une structure qui est le pour amener l'innovation  
efficacement



du laboratoire...

...au chevet du patient

# Centre de thérapies expérimentales (CTE) | structure



# TIL protocol that we developed in collaboration with ION and ONM



*Créer le concept*



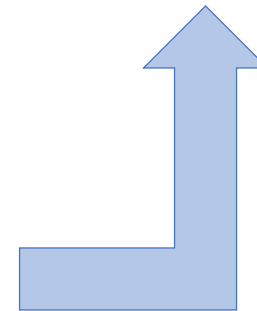
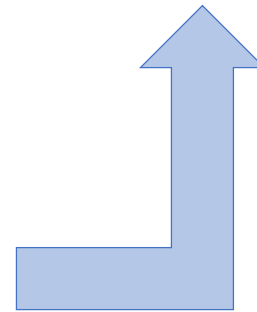
*Ecrire le protocole  
et compiler le  
dossier*



*Soumettre à la CE et à  
Swissmedic*



*Opérationnaliser le  
protocole avec les  
partenaires du DO  
et du CHUV*



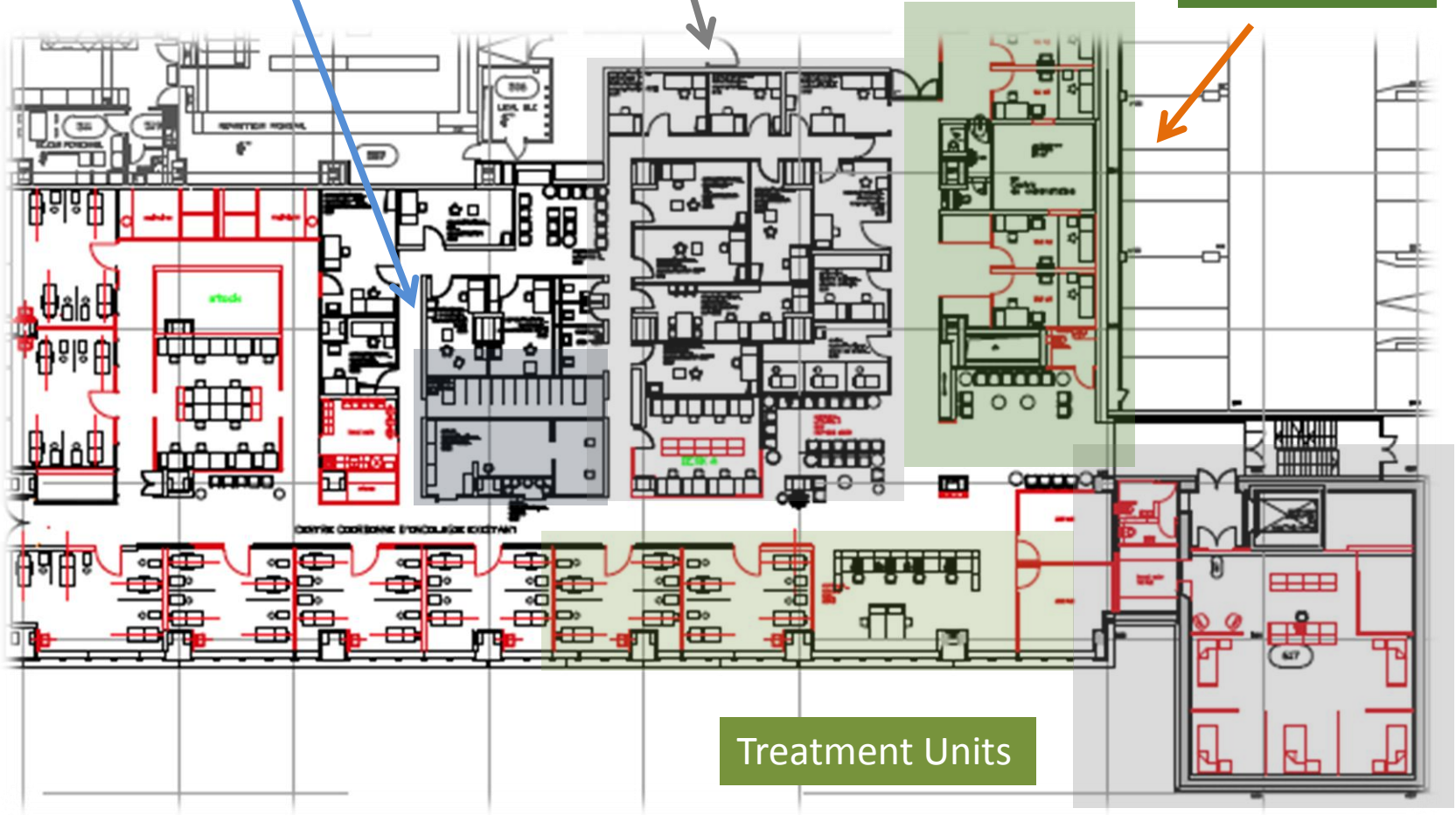


# Unit for Innovative Therapies/Phase I (1,400 m<sup>2</sup>)

Investigational Pharmacy

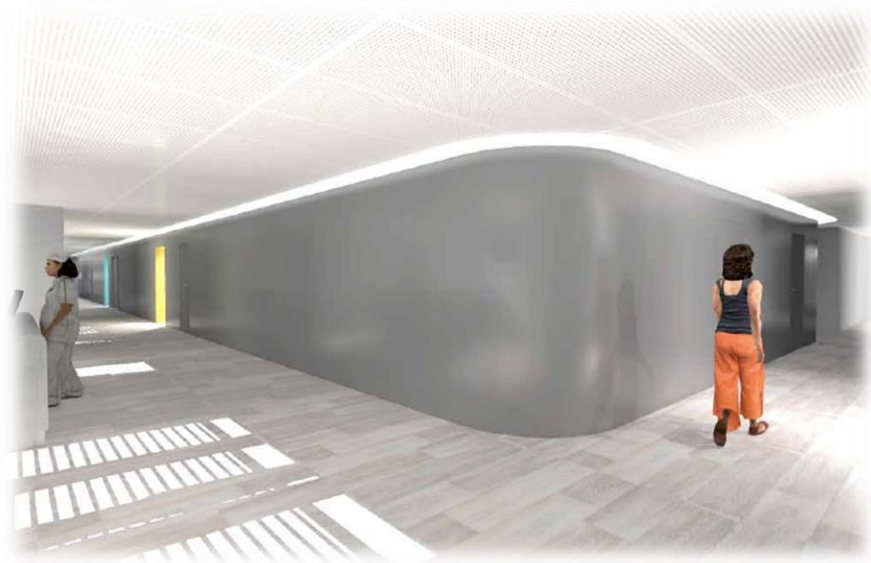
On-site Clinical Investigational Unit

Exam Rooms

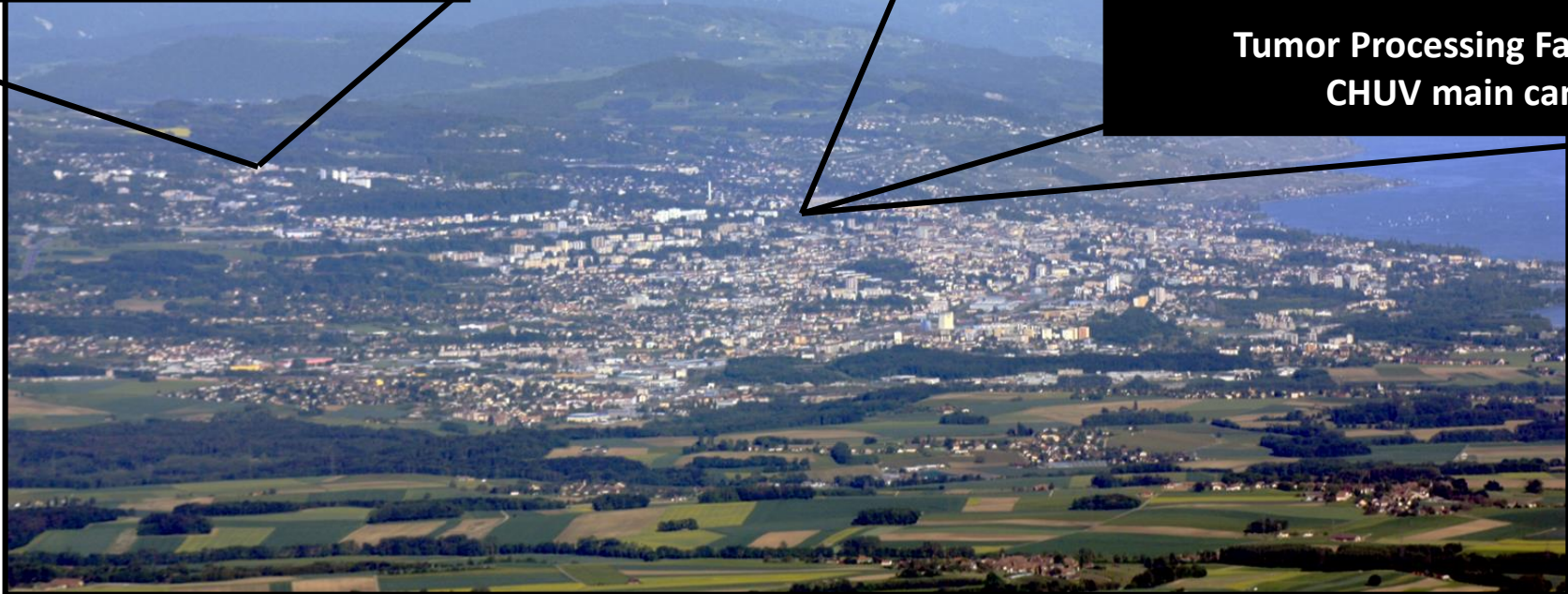
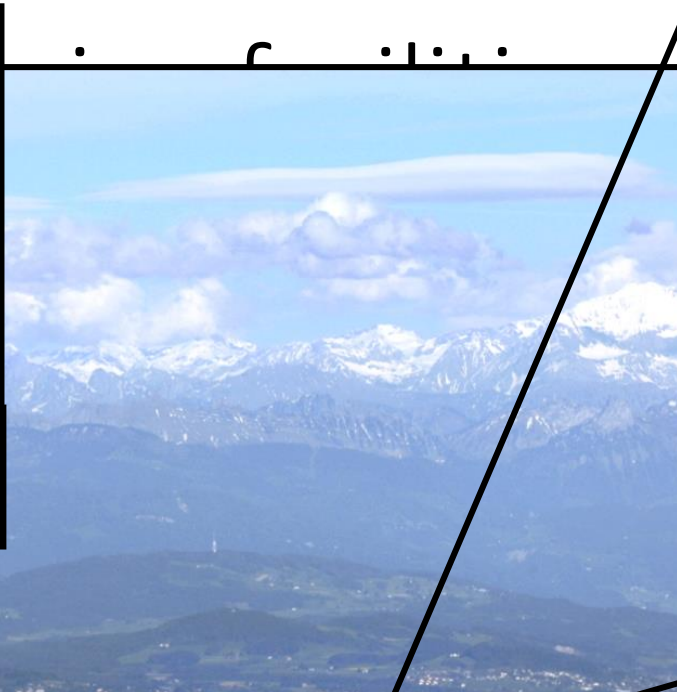


Treatment Units

2017-2018







# GMP manufacturing facilities | CMF



© Matthieu Gafsou



© Matthieu Gafsou



Production

© Matthieu Gafsou



QC Lab

© Matthieu Gafsou

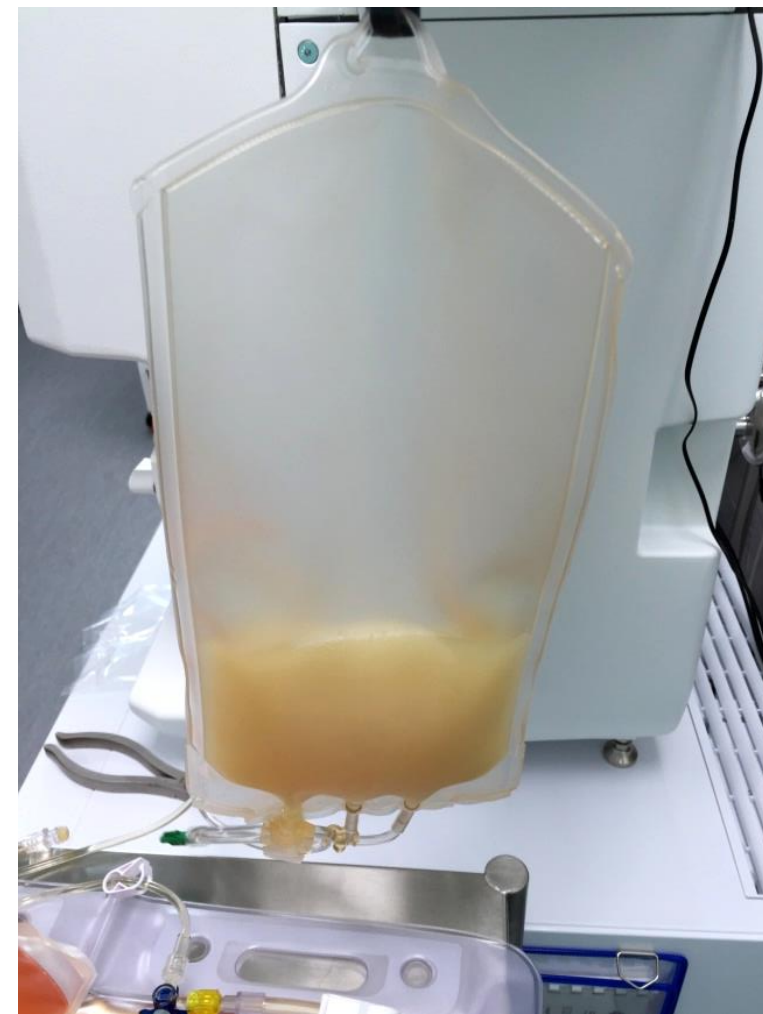


PD Lab

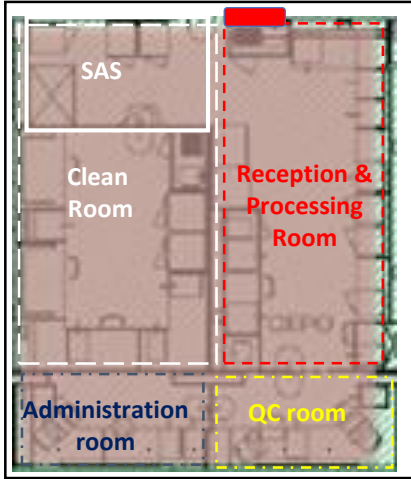
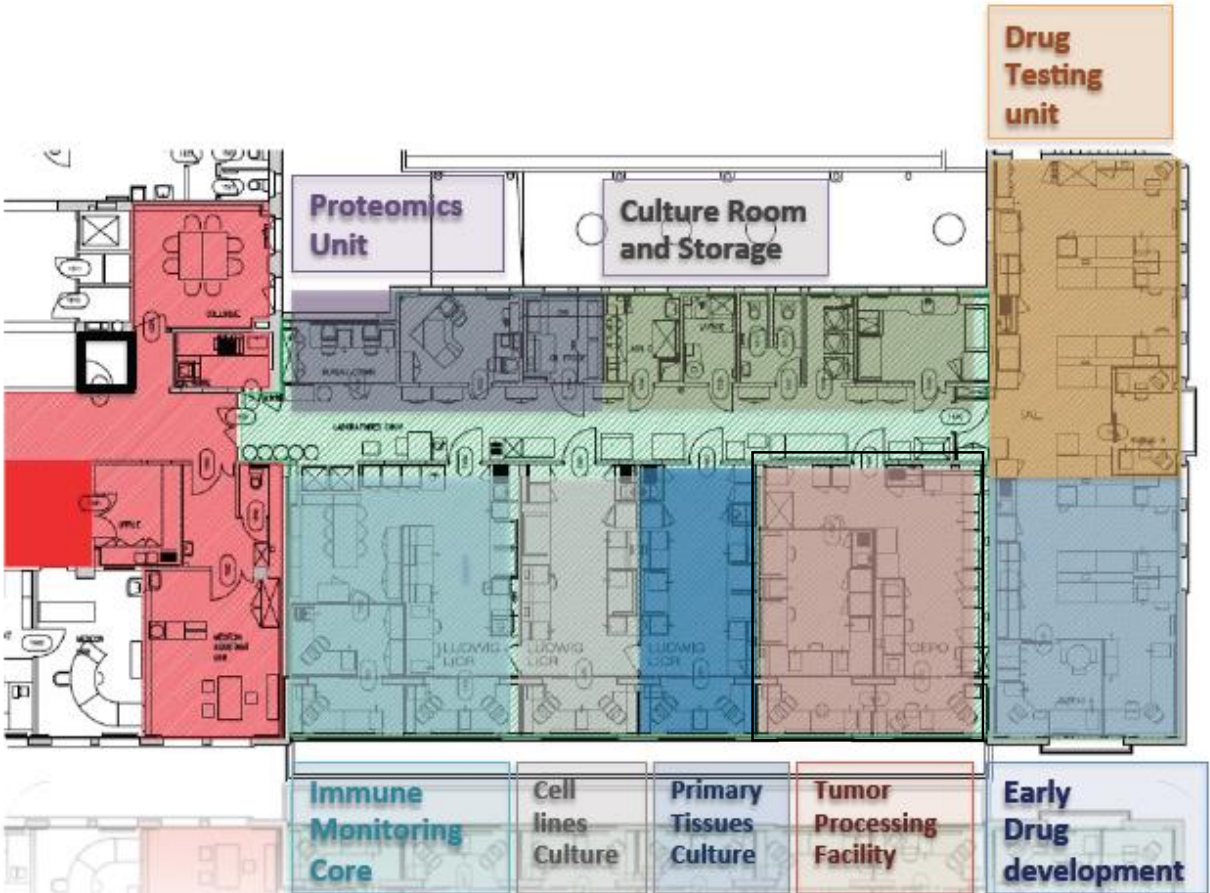
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# Melanoma TIL program



# CTE - Translational Core Facility (760 m<sup>2</sup>)





Merci de votre  
attention !

Questions?