

# **Granulosa Cell Tumors and Immunotherapy for Ovarian Cancer**

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# Immunotherapy : A Renaissance in Cancer Treatment

## Adoptive T Cell Therapy

CANCER IMMUNOTHERAPY OUTLOOK



T cells taken from a leukaemia patient and multiplied in culture are ready for infusion.

### ADOPTIVE CELL THERAPY

## Honing that killer instinct

*Genetically altered immune cells are helping to push life-threatening cancers into remission and generating a buzz.*

BY COURTNEY HUMPHRIES

A few years ago, when Michel Sadelain spoke about adoptive cell transfer (ACT) therapy at cancer meetings, his colleagues were dubious about what seemed a drastic and unconventional approach: harvesting and genetically altering his patient's immune cells to train them to attack her cancer. "I can't tell you how many nearly empty rooms I've spoken to about this technique," says Sadelain, director of the Center for Cell Engineering at Memorial

Sloan-Kettering Cancer Center in New York. The technique harnesses the power of the immune system by recruiting the body's own T cells — immune cells that recognize and marshal an attack against foreign invaders and diseased cells. T cells travel through the body, using their receptors to scan for small bits of protein called antigens on the surface of foreign cells. If an antigen matches the receptors, the T cell activates and launches an attack. In theory, malignant cells should be ideal targets for T cells, but tumours have ways of shielding themselves from an immune attack. With

ACT, scientists tweak the T cells to give them a fighting chance. Sadelain calls them "living drugs".

Pilot studies in the past couple of years have had promising results, leading to increased interest and dozens more clinical trials investigating the technique. Success stories — albeit involving small numbers of patients — tell of people with aggressive cancers whose tumours melted away in days or weeks. In a field where extending life by a few weeks or months is considered a breakthrough, the complete remission of even a few patients is stunning. Sadelain is no longer speaking to empty rooms. Suddenly, he says, ACT has captured the imagination of scientists and pharmaceutical companies as if it were a new approach, rather than a field that has been developing for twenty years.

But there are both scientific and logistic challenges to expanding the use of this therapy. Researchers are still learning to control the cells' potency to ensure they can vanquish cancer without damaging normal tissue — an issue complicated by the fact that many cancer antigens are also found on normal cells. Another problem is that it's not yet clear how to turn ACT into a profitable business model, as harvesting and growing living cells requires much more time and skill than prescribing a drug. So while pharmaceutical companies are licensing proprietary receptors and looking into ways to scale up the process, that's just the start of the endeavour. As with any therapy, the companies still need to embark on large, multi-centre clinical trials to test the effectiveness of the therapies on a broader group of patients. But large trials also require a way to engineer and distribute large quantities of cells, so they will only happen if companies are confident of long-term profitability.

Proponents of the approach say that the possibility of eradicating life-threatening tumours makes these challenges worth tackling. And recent progress in designing ACT therapies that are surprisingly effective is causing many in the field to sit up and take notice.

### BOOSTING THE BODY'S CELLS

There are three strategies for ACT therapies (see 'Cellular attack'); the most-developed of which is the simplest. The tissue surrounding a tumour is likely to contain immune cells with antitumour activity, so doctors take a sample of this tissue and select those T cells that have been primed to attack the cancer. They culture these cells in the lab until they have enough, and re-infuse the cells back to patients along with the T-cell growth factor interleukin-2 (IL-2), which promotes the proliferation of antigen-specific T cells. However, the endogenous immune system has suppressive mechanisms that keep the immune response in check, and these mechanisms also prevent the newly transferred cells from working effectively. So patients must also be treated with drugs or radiation

## Immune Checkpoint Blockade

OUTLOOK CANCER IMMUNOTHERAPY



### DRUG DEVELOPMENT

## Releasing the brakes

*Tumours can put a brake on the immune system, but new therapies work by removing these brakes. Now, researchers have to figure out how to use them most effectively.*

BY KAREN WEINTRAUB

First it was one melanoma patient, a woman named Sharon, who should have died but didn't. Then, several more outlived their prognoses — not just surviving but seeing their tumours shrink dramatically or even disappear. As the successes accumulated, in both individual patients and larger clinical trials, oncologist Antoni Ribas slowly began to accept that the immune treatments he was giving to his cancer patients were making a profound difference. Initially only about one in ten patients improved, but that fraction increased as he and his colleagues tested newer versions of the therapy. Ribas, a tumour immunology researcher, now has dozens of patients, like Sharon, whom he had expected to succumb cancer years ago. His patient load at the Jonsson Comprehensive Cancer Center at the University of California,

Los Angeles (UCLA) used to stay about the same from one year to the next, with new melanoma patients roughly equaling the number who didn't make it. Now, the number of patients is growing.

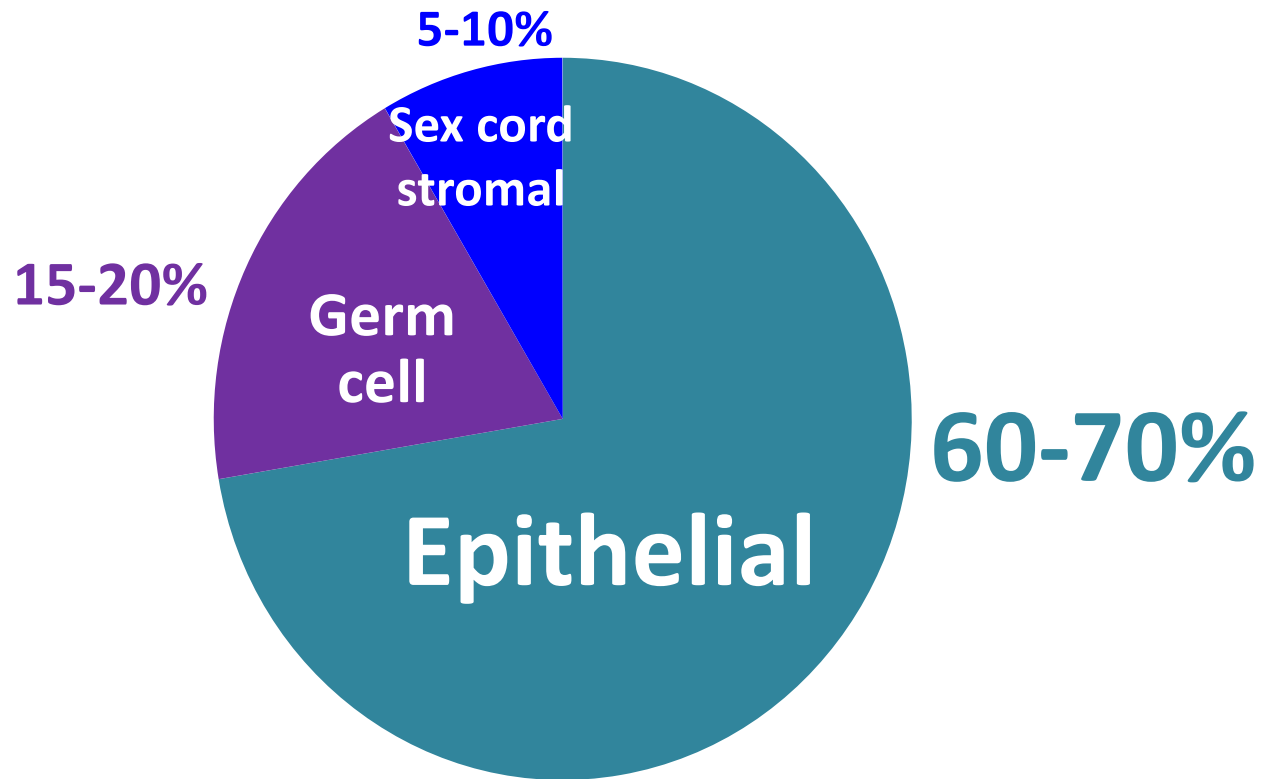
The drugs he uses are known as immune checkpoint blockades and they are designed to circumvent one of the insidious ways in which cancer staves off an immune response. The immune system has a number of checkpoints — mechanisms that help to prevent it from getting out of control and attacking the body's own cells. The checkpoints act much like the brakes on a car: even if the immune system is trying to prompt its T cells into action, the checkpoints suppress the activation. Tumours can turn on these checkpoints and prevent a T-cell attack, but immune checkpoint blockades take the brakes off the T cells, freeing them to fight the malignancy.

When other researchers saw the results of

clinical trials of checkpoint blockades in melanoma, they dismissed them as too narrow to be of much use in other cancers. Melanoma was different, they said, and has a known immune component. Then, in 2012, everything changed. In one study, a checkpoint blockade caused a measurable improvement in 31% of renal cancer patients, and in 18% of patients with lung cancer, which kills more people every year than colon, breast and pancreatic cancers combined. Researchers and drug companies realized that these blockades, also called checkpoint inhibitors, might be as effective in patients with any type of solid tumour as they were in those

with melanoma. **Jedd D. Wolchok**, a medical oncologist at Memorial Sloan-Kettering Cancer Center in New York City, says the lung

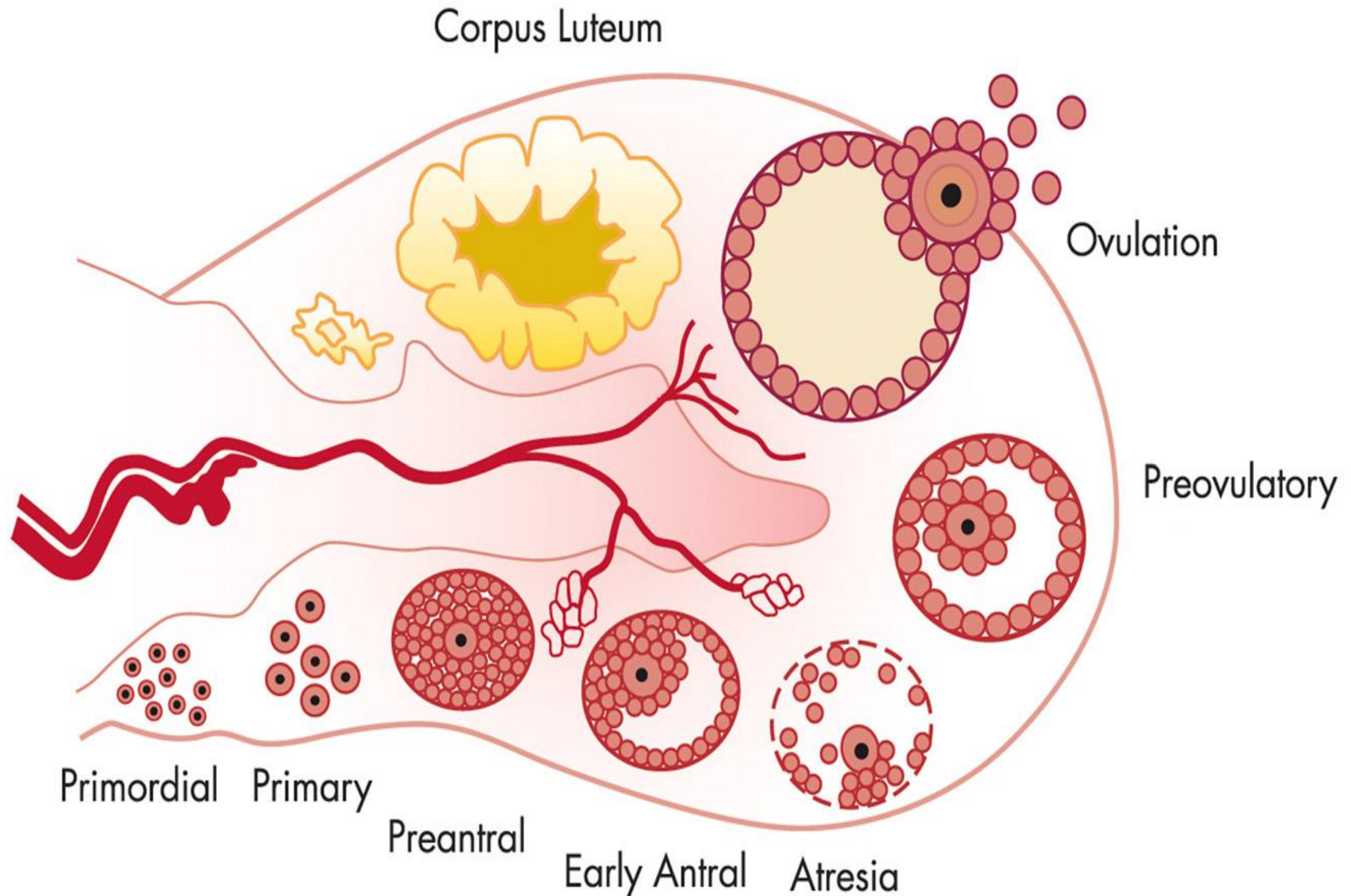
# Types of Ovarian Cancer



**25,000 new cases of ovarian cancer in the US each year  
more than 14,000 deaths**

**1,500-2,000 new cases of Granulosa-Thecal tumors each year**

# What are granulosa cells?



# Granulosa Cell Tumors: Fast Facts

- Include tumors composed of granulosa cells, theca cells, and fibroblasts in varying degrees and combinations.
- GCTs account for approximately 2% of all ovarian tumors:
  - Adult (95%)
  - Juvenile (5%) types based on histologic findings.
  - Both subtypes commonly produce estrogen.
- **Adult GCTs** (AGCTs) usually occur in postmenopausal women and have late recurrences.
- **Juvenile GCTs** (JGCTs) develop in individuals <30 yrs old and often recur within the first 3 years.

# Why and how?

- No clear cause identified
- Genetic studies: point mutation (C402G) in **FOXL2**
  - 100% of 4 adult GCTs
  - Confirmed in an additional 86 of 89 adult GCTs
  - *And 1 in 10 juvenile-type GCTs*
  - Not found in any epithelial ovarian tumors

**This the possibility of identifying  
novel targeted therapies**

# Additional Facts

- AGCTs and JGCTs have very good cure rates due to early stage of disease at diagnosis.
  - >90% diagnosed before spread occurs outside ovary.
  - AGCTs usually are seen in postmenopausal women, with a median age at diagnosis of 52 yrs
- 5-year survival rates usually 90-95% for stage I tumors
  - 25-50% for patients presenting with advanced-stage disease
- AGCTs have a propensity for late recurrence
  - some occur as many as 37 yrs after diagnosis
  - mean survival after the diagnosis of recurrence is 5 yrs
- **Approximately 20% of patients diagnosed with GCTs die of their disease over the course of their lifetime.**

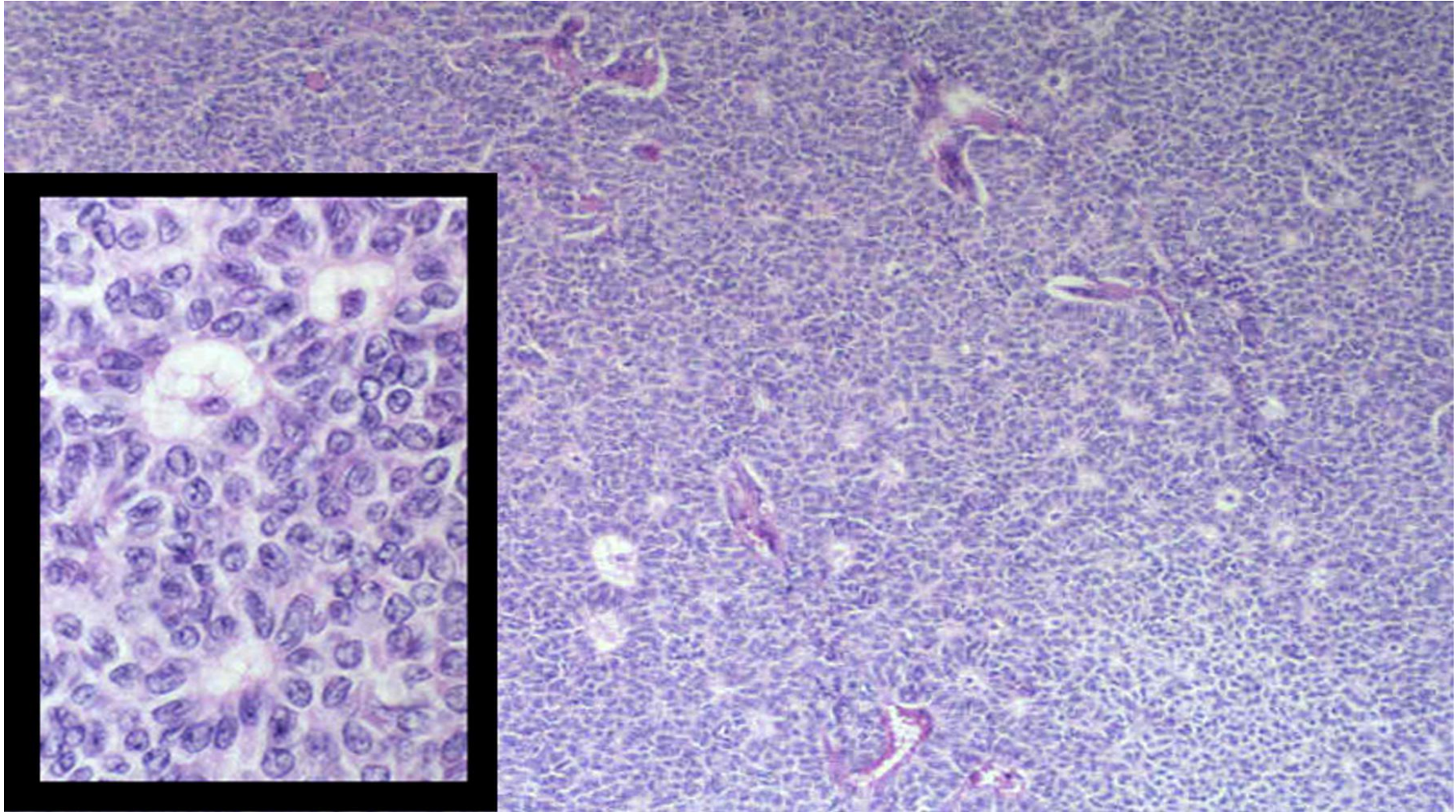
# Signs and Symptoms

- Manifestations of excessive estrogen
  - ~70% of these tumors are **hormonally active**
- Reports of increasing abdominal girth and abdominal discomfort
  - Acute abdominal or pelvic pain may be observed
  - in combination with nausea, vomiting, dizziness, shoulder pain
- **Prepubertal girls:** usually present with precocious pseudopuberty (70-80%) and have secondary sex characteristics at a very early age.
- **Postmenopausal women:** abnormal uterine bleeding, endometrial hyperplasia and/or endometrial carcinoma

# Laboratory studies

- **Prepubertal or <30 yrs old**
  - bhCG, alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), CA125.
- **Reproductive-aged women >30 yrs old**
  - CA125, inhibin, Hormones, if suggested based on clinical findings.
- **Postmenopausal women**
  - CA125, hormones
- **Others**
  - Inhibin A & B; AMH or MIS
- Imaging studies
- Histology (Microscopy)

# Microfollicular pattern; Call-Exner bodies and nuclear grooves



# Treatment

- Surgery; stage is most important prognostic factor
- In younger patients who desire future fertility
  - unilateral salpingo-oophorectomy is usually sufficient
- Current chemotherapy regimens usually multidrug
  - most frequent combination therapy given currently is bleomycin, etoposide, and cisplatin (BEP)
  - carboplatin and paclitaxel for patients with advanced or recurrent chemotherapy-naïve sex cord stromal tumors

**Challenge: recurrent, metastatic disease**  
**But, little research on novel therapies**

# Why harness the immune system against cancer?

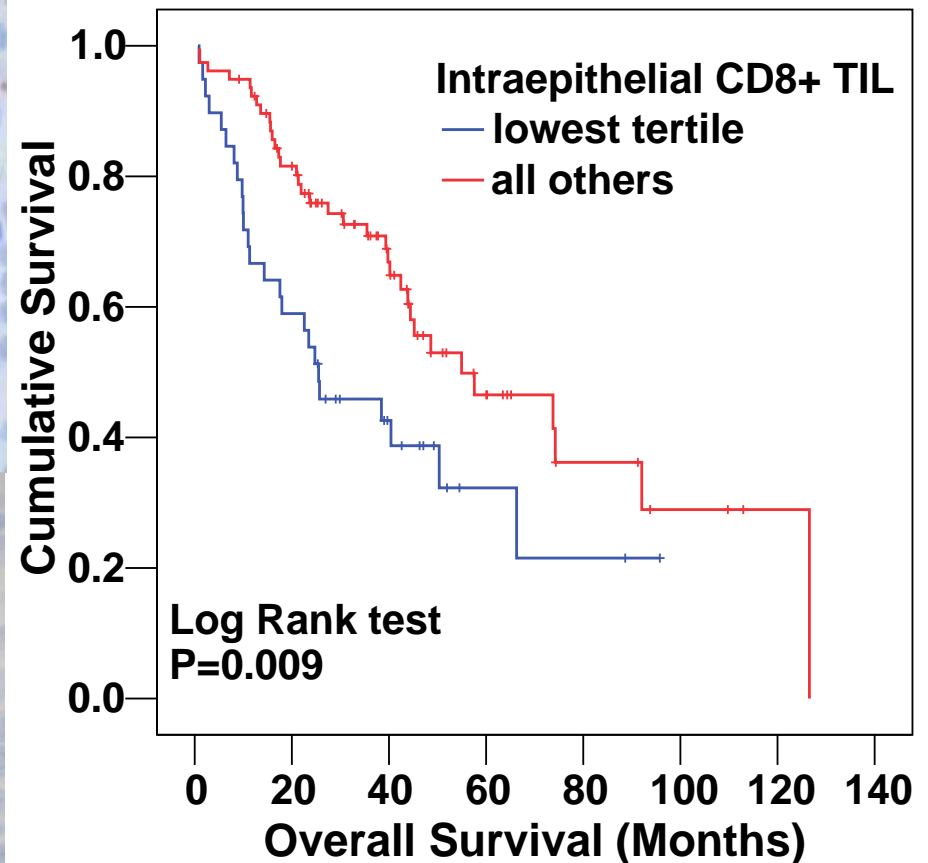
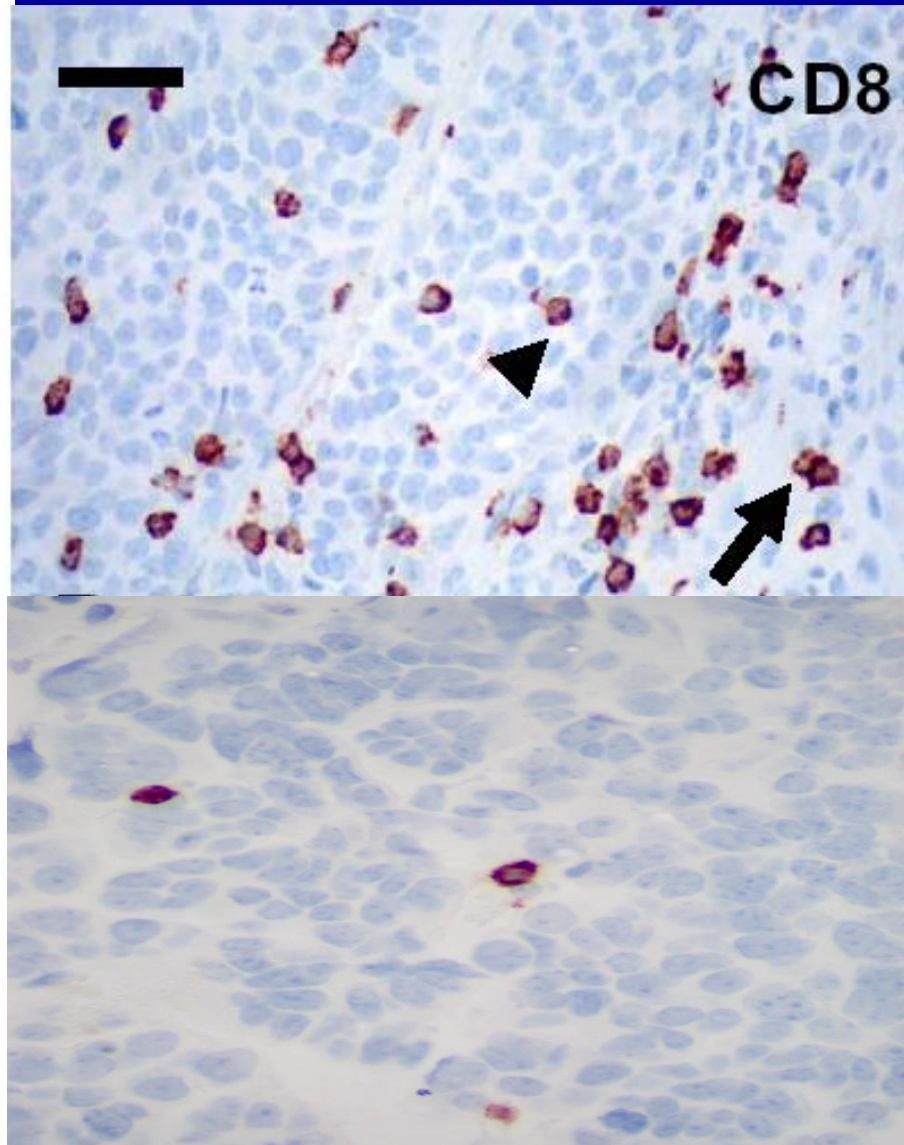
**Vaccination against infectious diseases has proven cheap, safe and extremely successful in preventing illness and death.**

Disease	Baseline 20th century annual morbidity	1998 provisional morbidity	% decrease
Smallpox	48,164	0	100
Diphtheria	175,885	1	100
Pertussis	147,271	6,279	95.7
Tetanus	1,314	34	97.4
Poliomyelitis (paralytic)	16,316	0	100
Measles	503,282	89	100
Mumps	152,209	606	99.6
Rubella	47,745	345	99.3
Congenital rubella syndrome	823	5	99.4
Haemophilus influenzae type b	20,000	54	99.7

# Major advances in the last 10 years

- **Your immune system protects you against cancer.**

# Significance of anti-tumor immunity in ovarian cancer



Median survival: 55 vs 26 months  
Hazard ratio: 0.33 (p = 0.0003)

# Major advances in the last 10 years

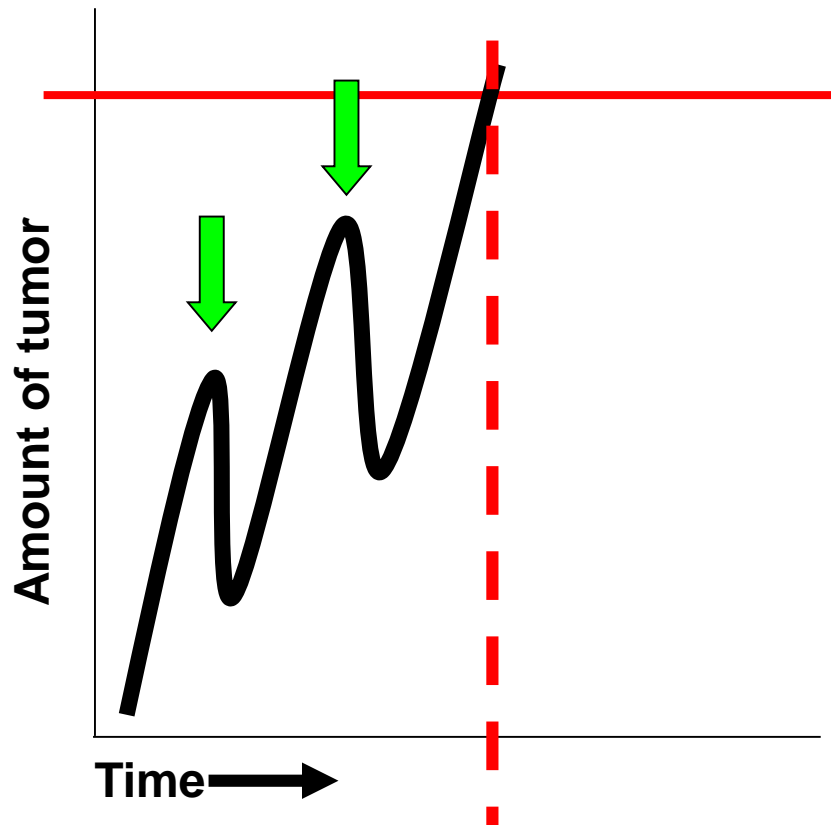
- Your immune system protects you against cancer.
- **Cancer vaccines**
- **Immune checkpoints**
  - CTLA4 and PD-1/PD-L1 pathways



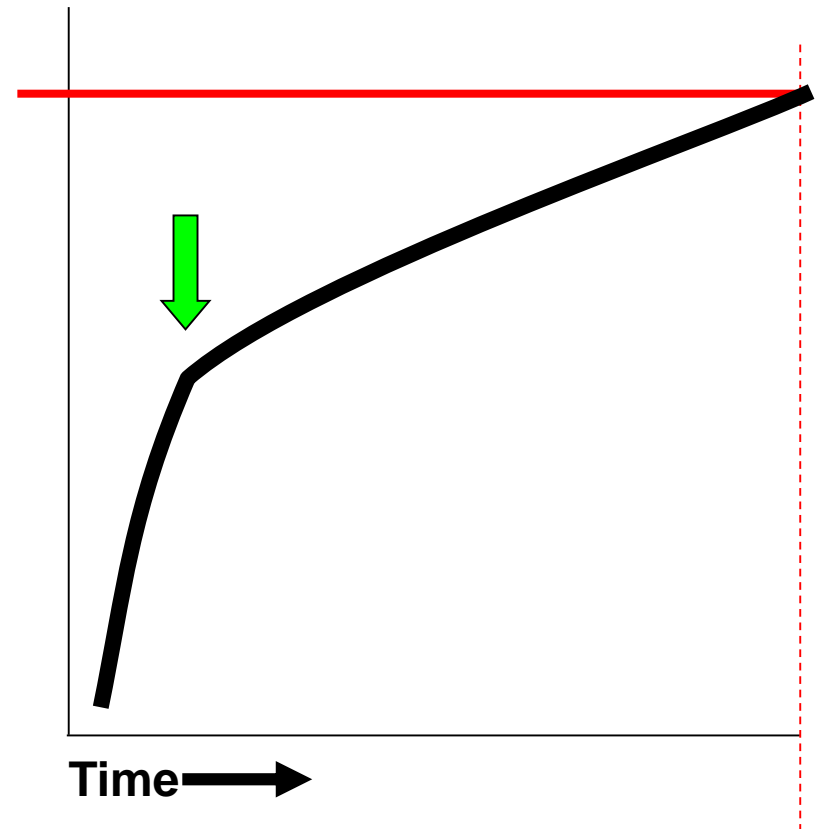
- **Adoptive cellular therapy**

# How cancer vaccines prolong survival

Chemotherapy/radiation therapy



Immunotherapy

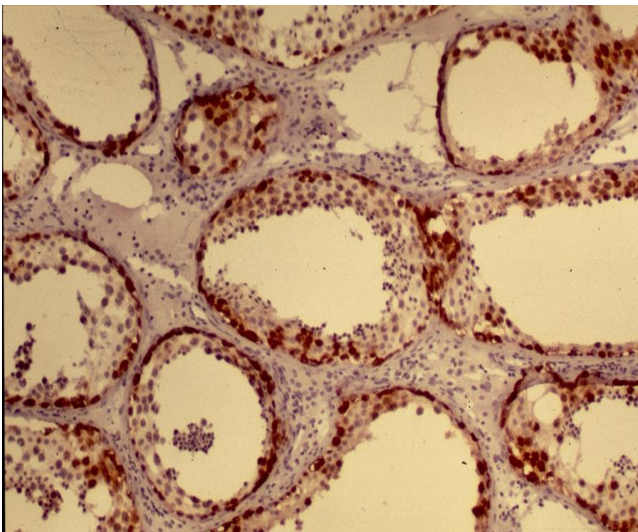


# Which antigens should we target with cancer vaccines?

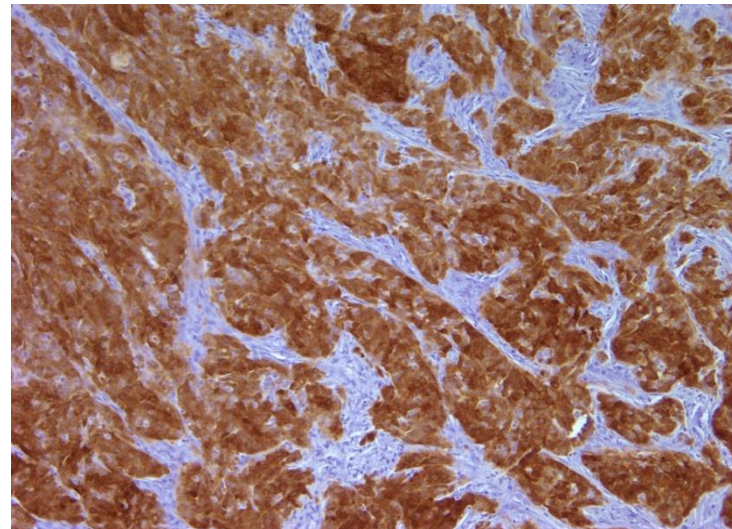
- A protein that is expressed in cancer but NOT in other normal cells of the body.
- Best examples are CANCER TESTIS ANTIGENS, e.g. **NY-ESO-1**.

## NY-ESO-1 expression

**Testis**



**Ovarian Cancer**



# How are lymphocytes “instructed” to attack?

**Antigen Presentation**  
**e.g. NY-ESO-1**

**The Dendritic Cell**  
**presents the antigen**  
**(NY-ESO-1) to a T cell**

**Dendritic  
cell**

**“eats” bacteria  
or NY-ESO-1**

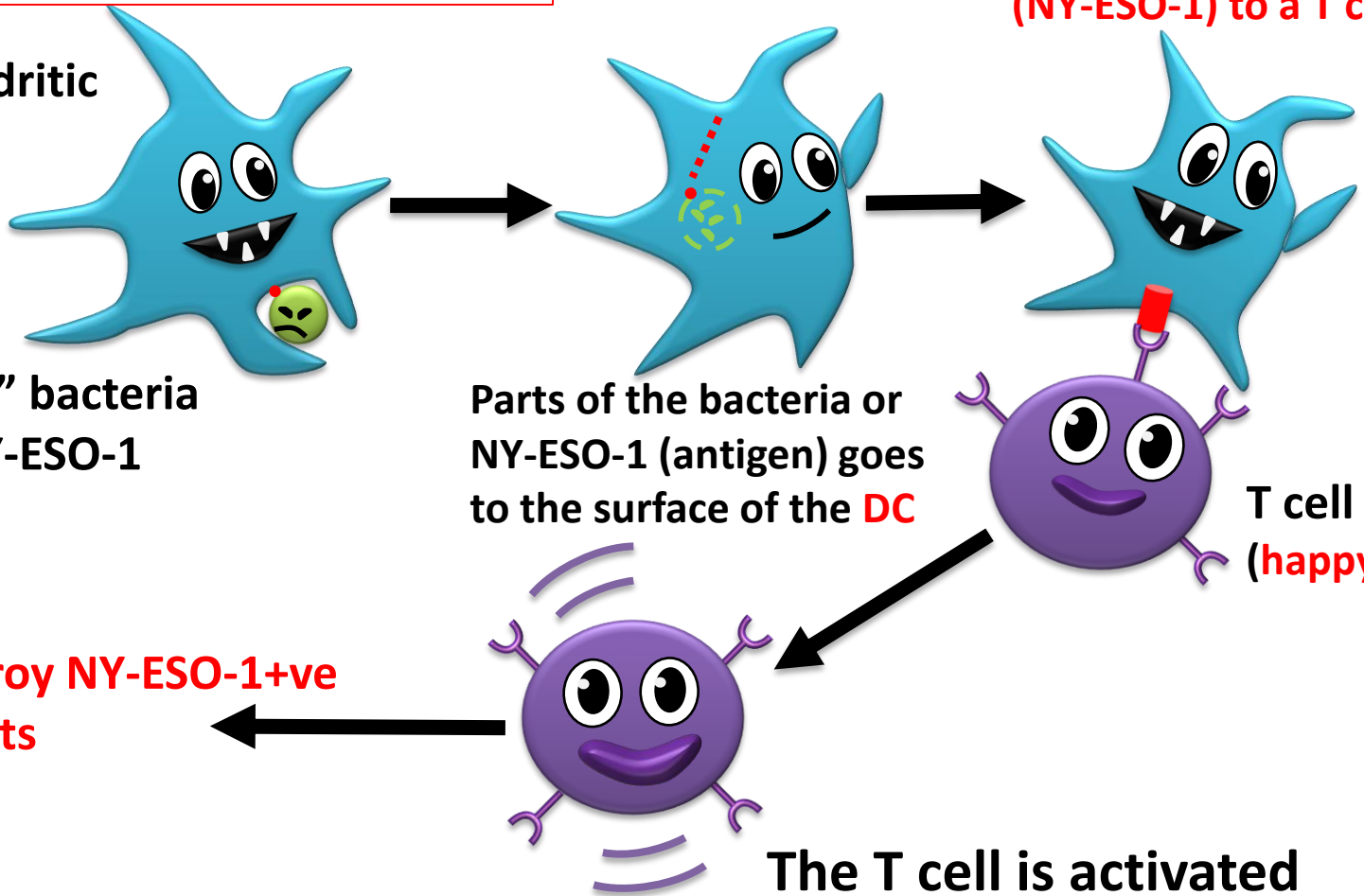
**Parts of the bacteria or  
NY-ESO-1 (antigen) goes  
to the surface of the DC**

**Destroy NY-ESO-1+ve  
targets**

**T cell  
(happy)**

**The T cell is activated**

**The Battle Begins**



# Types of Cancer Immunotherapy

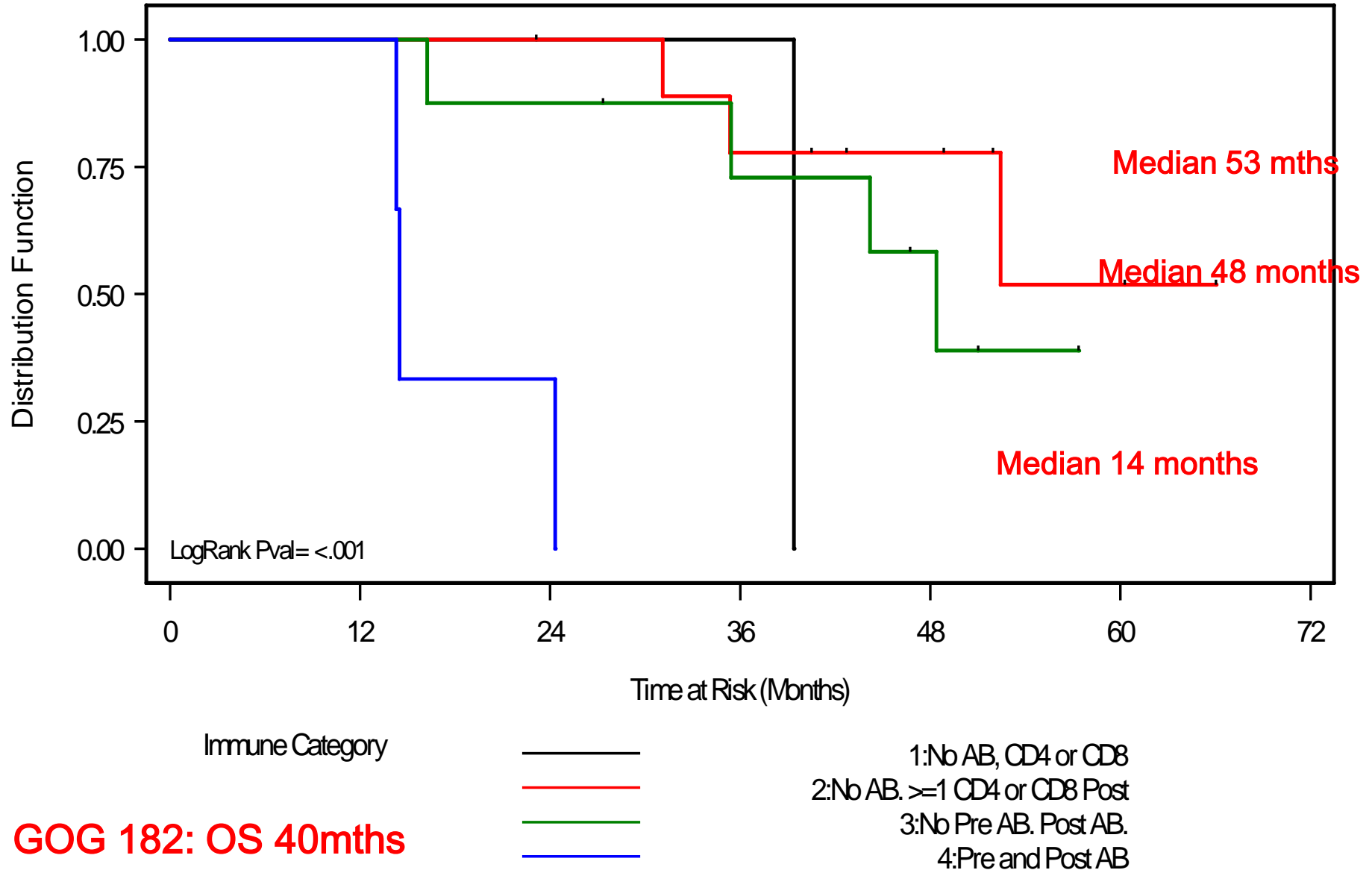
- Antibodies
- Vaccines
- Immune Checkpoint Inhibitors / Modulators
  - CTLA-4, PD-1/PD-L1 Inhibitors
- Cellular therapies
  - Adoptive T cell therapy

# Cancer Vaccines

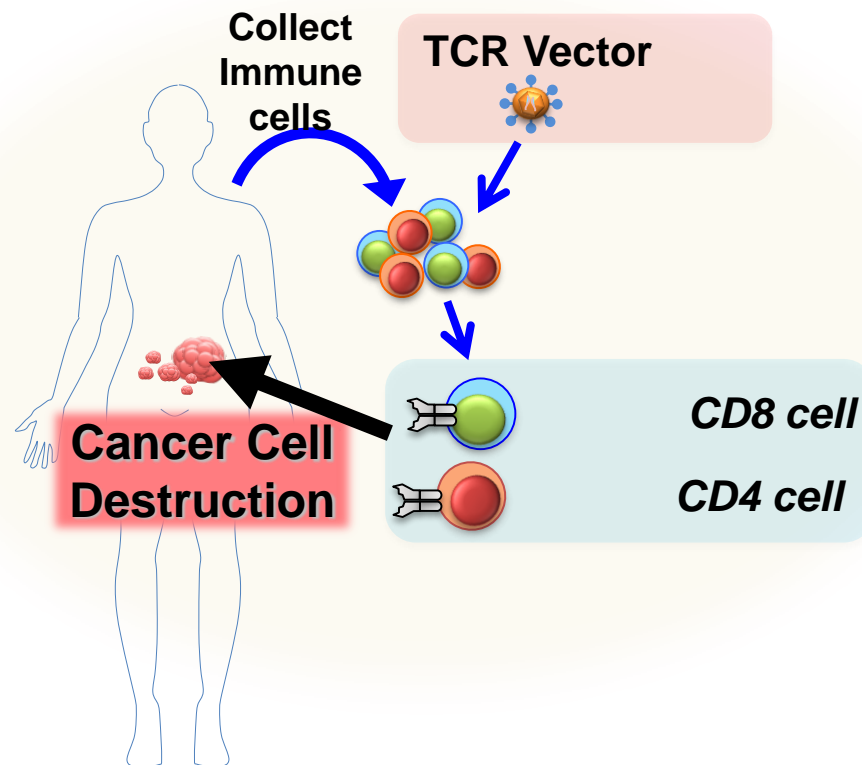
- Fragments of tumor antigen (peptides) + adjuvant (NY-ESO-1)
- Full length antigen protein + adjuvant
- Viruses engineered to express cancer antigen
- Personalized dendritic cells
  - loaded with antigen or tumor lysate
- Combined with other immune modulators

# Phase II Trial: rVaccinia/rFowlpox-NY-ESO-1 vaccination

## Overall Survival by Immune Response Category



*An innovative immunotherapy that specifically targets and kills cancer cells*

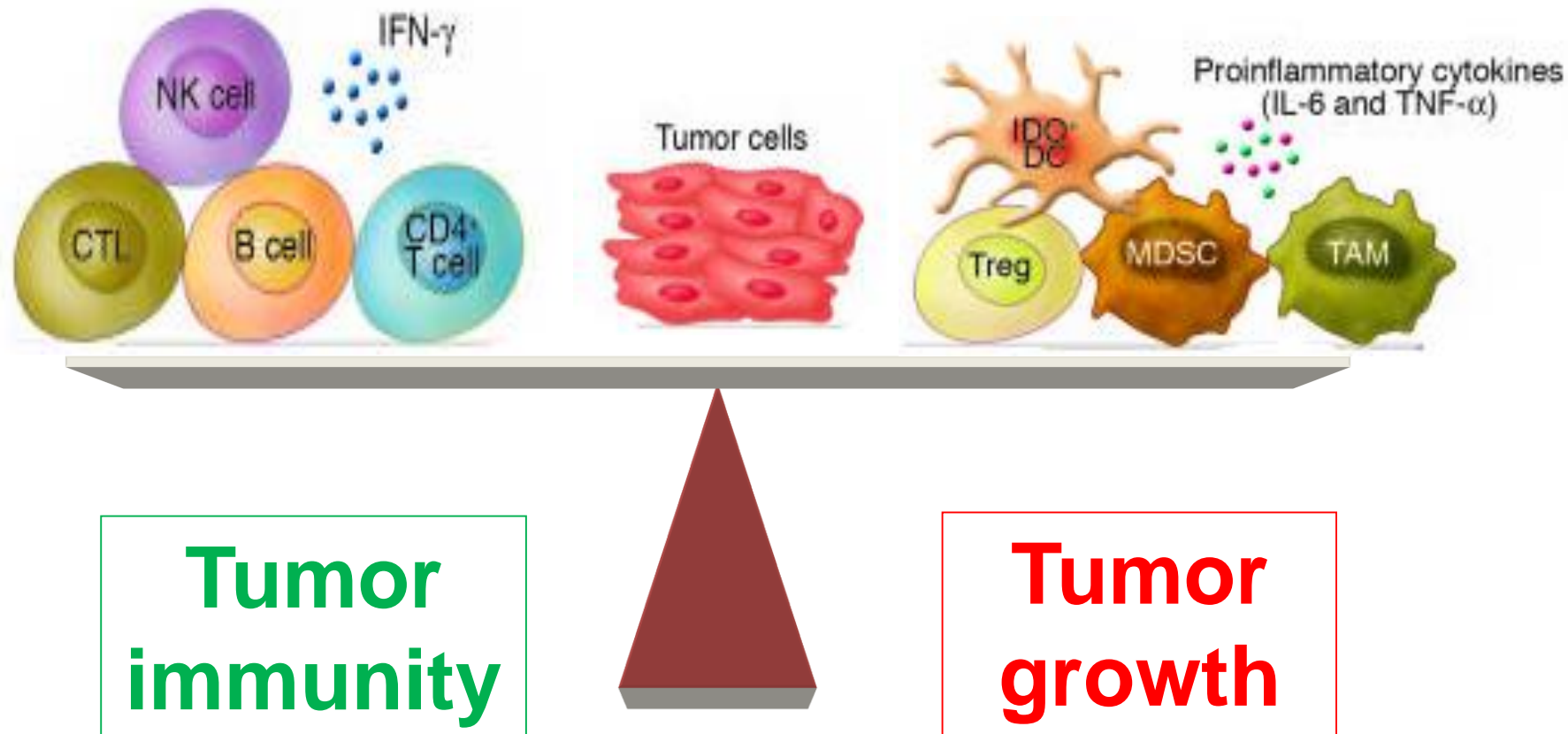


# Manufacturing of T cells

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- Aseptic Manufacturing
- Controlled Manufacturing Environment
  - temperature
  - humidity
  - pressure
  - particulates
  - gases
- Continuous real-time monitoring

# Challenges Confronting Development of Cancer Immunotherapy



**The tumor environment is an immunological battle ground:  
Good vs. Bad**

# Conclusions

- Cancer immunotherapy offers the possibility for long-term cancer remission.
- Cancer immunotherapy may not cause the same side effects as chemotherapy and radiation.
- Vaccines, Immune checkpoint, adoptive T cell therapies (ACT).
- Combination strategies.
  - Vaccines  $\pm$  immune checkpoint; vaccines  $\pm$  ACT
  - Adoptive T cell therapy  $\pm$  immune checkpoint
  - Vaccines  $\pm$  chemotherapy.
- We can apply these same strategies to GCT: collaborations/funding will be required.
- Choosing the right clinical trial.