Cancer and the Immune system

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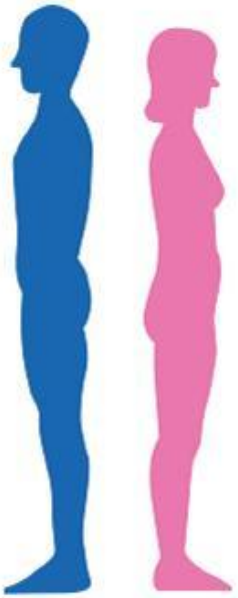
Ten leading Cancer types in USA, 2014

Estimated New Cases*

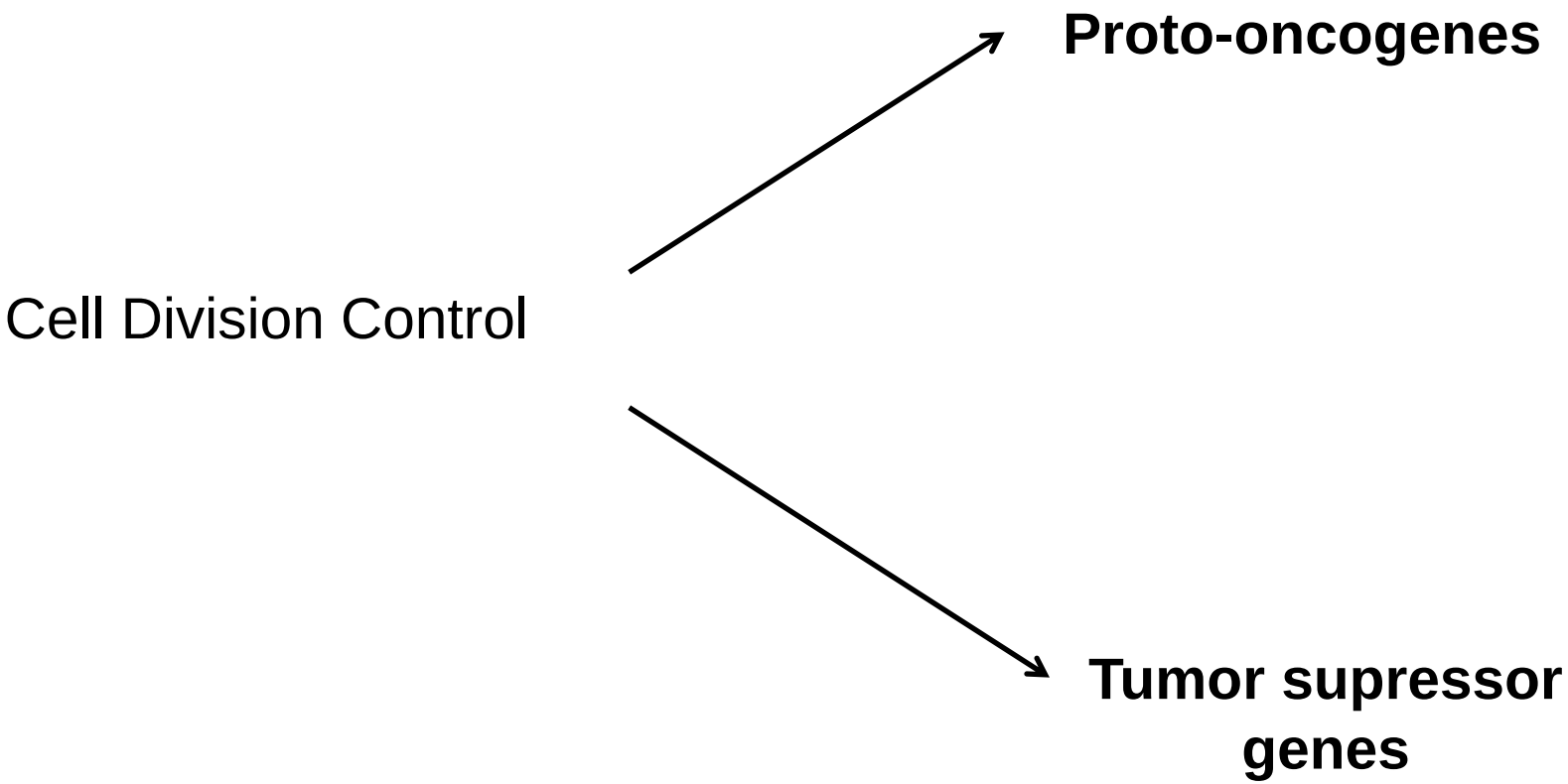
Males				Females		
Prostate	233,000	27%		Breast	232,670	29%
Lung & bronchus	116,000	14%		Lung & bronchus	108,210	13%
Colorectum	71,830	8%		Colorectum	65,000	8%
Urinary bladder	56,390	7%		Uterine corpus	52,630	6%
Melanoma of the skin	43,890	5%		Thyroid	47,790	6%
Kidney & renal pelvis	39,140	5%		Non-Hodgkin lymphoma	32,530	4%
Non-Hodgkin lymphoma	38,270	4%		Melanoma of the skin	32,210	4%
Oral cavity & pharynx	30,220	4%		Kidney & renal pelvis	24,780	3%
Leukemia	30,100	4%		Pancreas	22,890	3%
Liver & intrahepatic bile duct	24,600	3%		Leukemia	22,280	3%
All Sites	**855,220**	**100%**		**All Sites**	**810,320**	**100%**



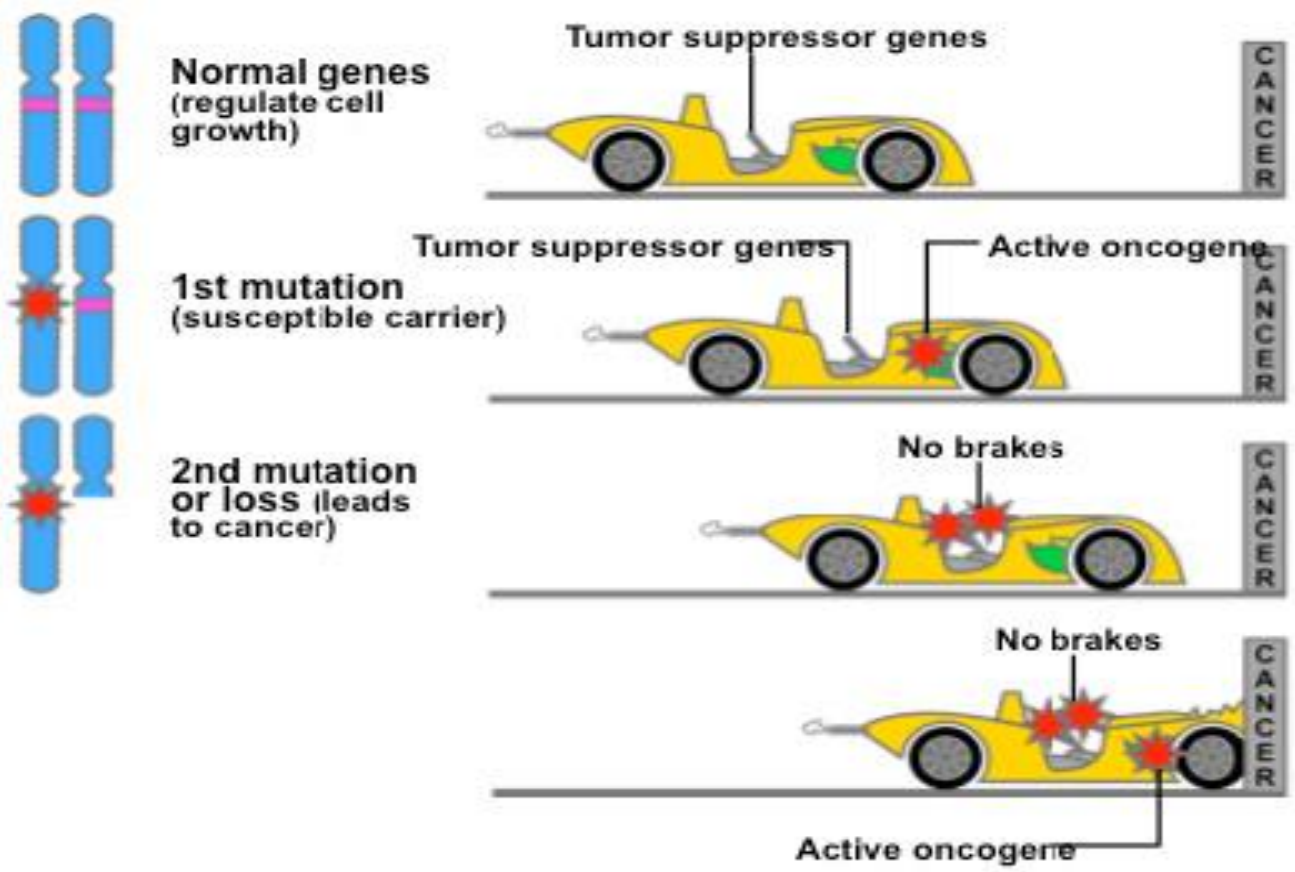
1 in 3 people get Cancer!!

Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014 Jan;64(1):9-29)

Cancer is a Control System Problem

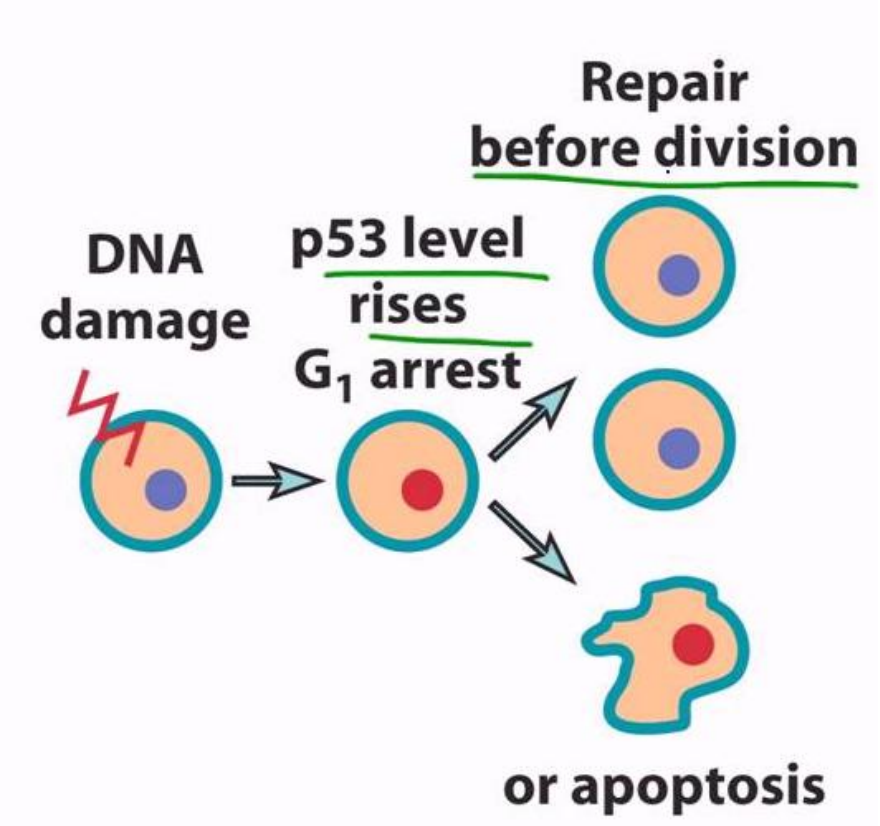


How Cancer Develops



A gene, which when mutated, can cause a cell to proliferate inappropriately is called a **Proto-oncogene**, and the mutated version is called an **oncogene**.

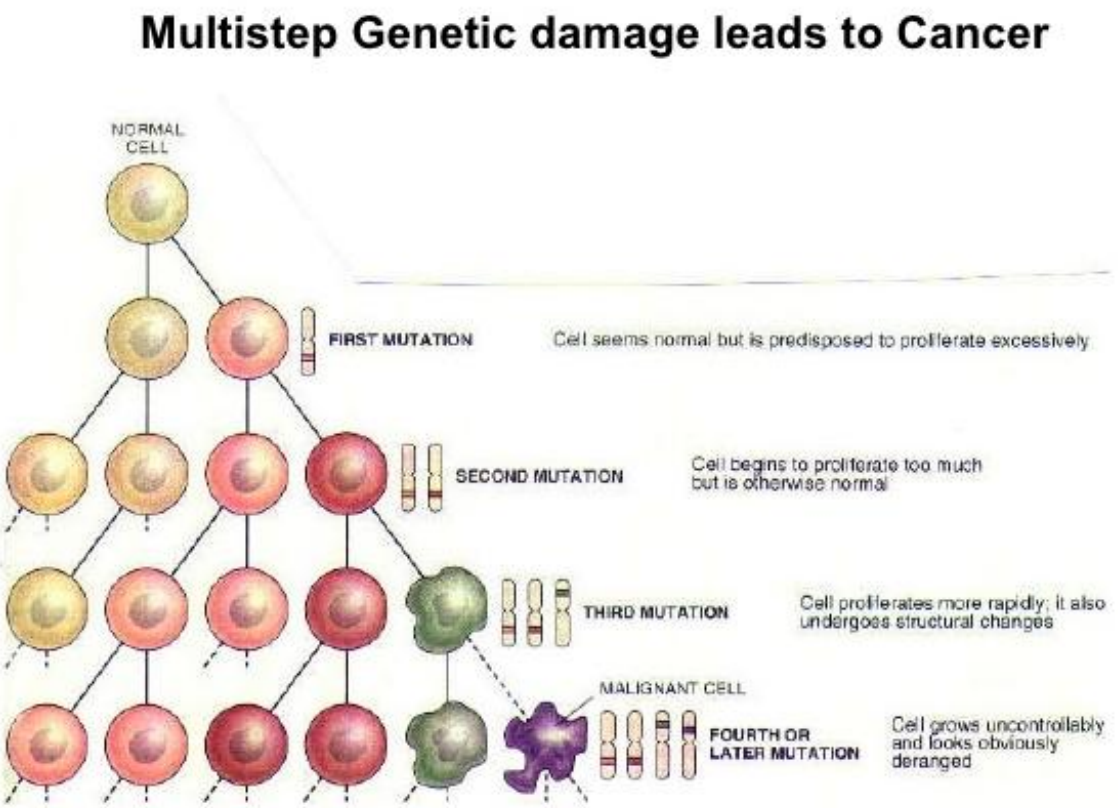
Tumor Suppressor Genes



Tumor suppressor genes such as **p53**, help safeguard against uncontrolled cell growth. They allow time for **DNA repair mechanisms** to work, or if overwhelmed push cells towards **apoptosis**.

P53 is mutated in the majority of cancers. Mice lacking p53 die of cancer in few months.

Cancer is a Multi-step Process



Cancer is a multi-step process (4-7 mutations required).
Cancer is a disease of age.
Cancerous cells mutate a lot and are genetically unstable (One step ahead of the immune system).

Classification of Cancer Cells

Major types of cancer

- Carcinoma
  - Derived from epithelial cells, which line surface of skin and organs, digestive tract, airways and mammary ducts
  - Most common cancer type (89-90% of all reported cases)
- Sarcoma
  - Derived from mesenchymal tissue – muscle, bone, cartilage, fat, connective tissues
- Hematopoietic
  - Leukemia – derived from white blood cells or their precursors
  - Lymphoma – involves cells of the lymphatic system
  - Myelomas – involves white blood cells responsible for the production of antibodies (B lymphocytes or B-cells)

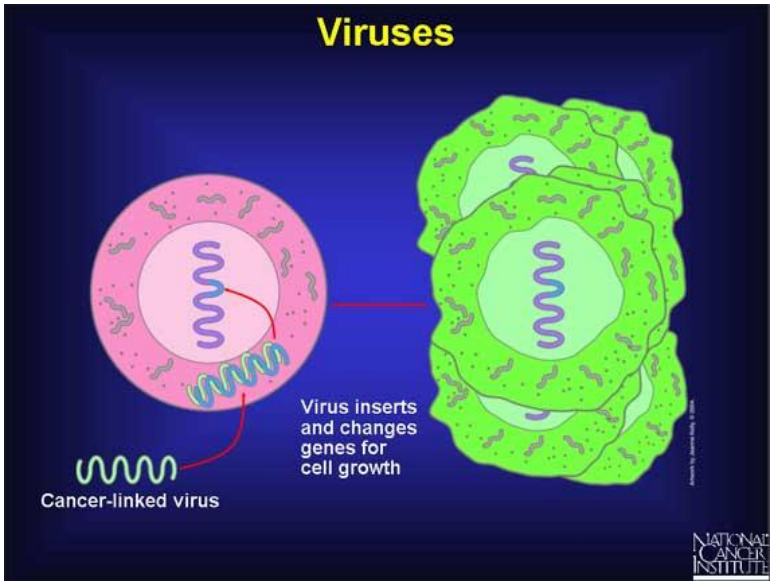
Spontaneous vs. Virus-induced

Most human tumors are spontaneous, because they arise when a single cell accumulates a collection of mutations that causes it to develop cancerous properties.

Natural process, carcinogens, radiation, smoking, fatty diet, etc...

In other tumors, a viral infection can help accelerate the process, by interfering with cell's safeguard systems.

Ex: Cervical Cancer
Liver Cancer



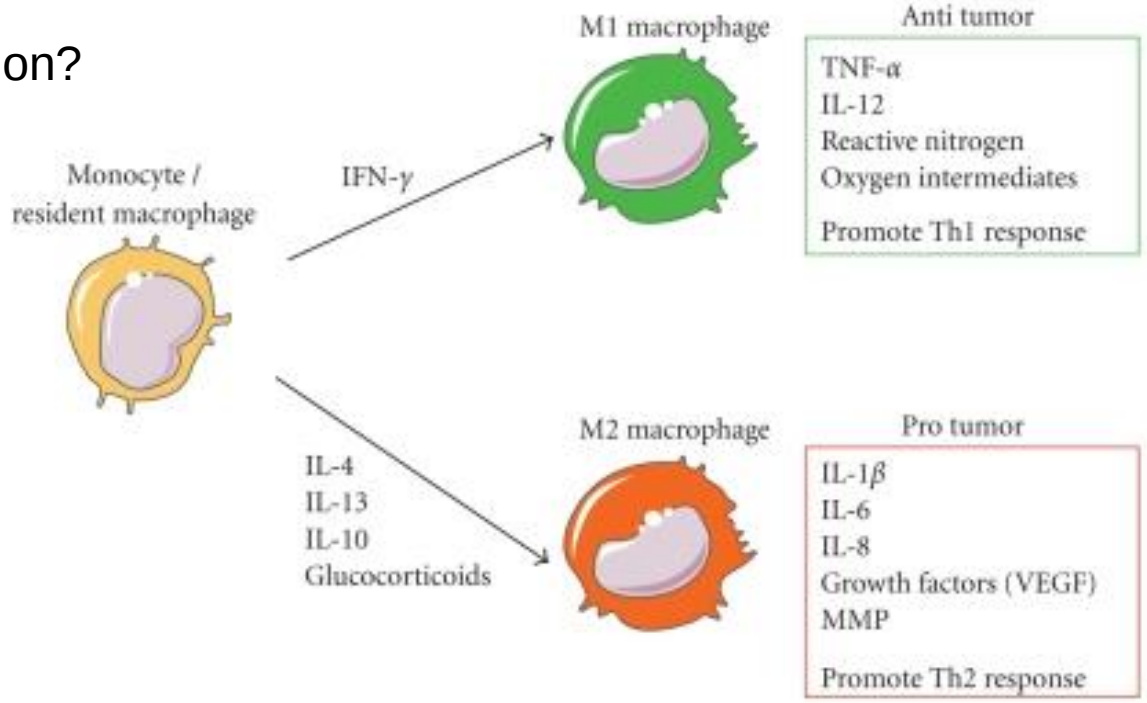
Immune Surveillance against Cancer

Mφ secreting TNF have the ability to kill tumors.

Mφ are found in tissues and are therefore in an ideal location to fight solid tumors. (BCG use in bladder cancer)

Mφ have versatile receptors that allows them to differentiate normal cells from abnormal ones (Phosphatidylserine, etc..)

Polarization?

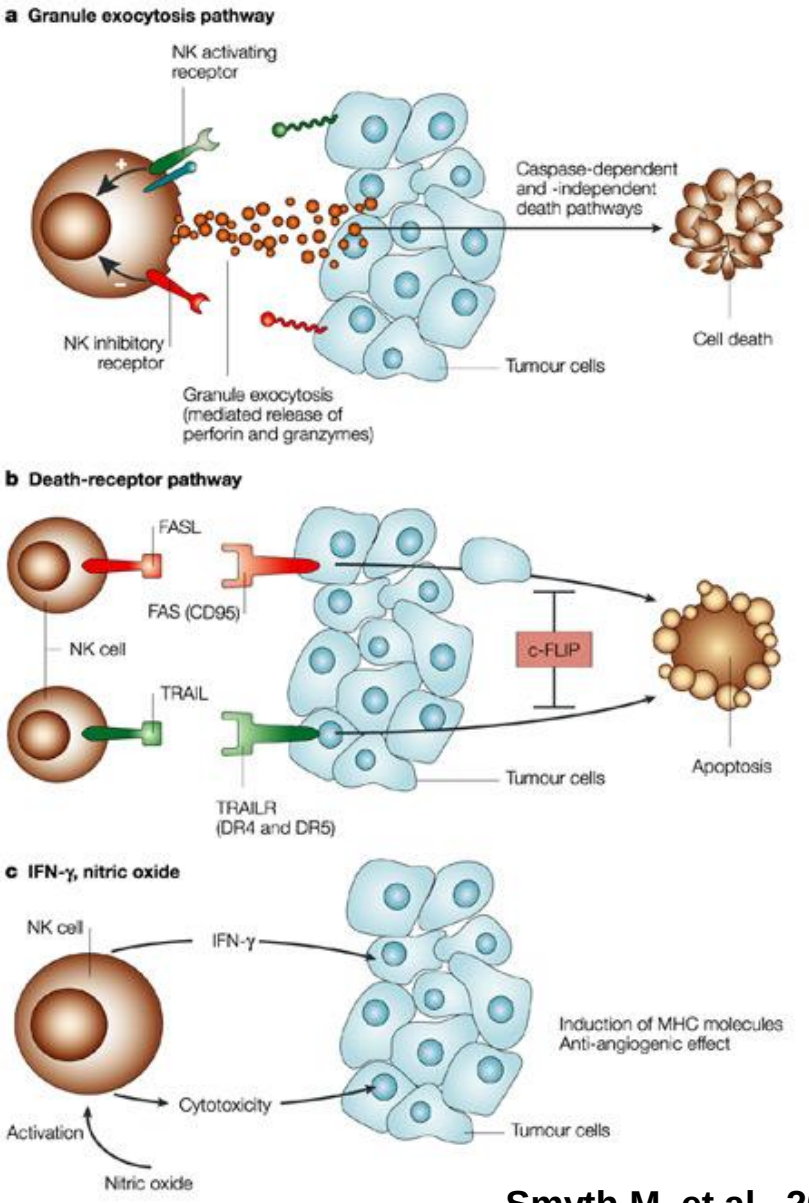


NK cells and Cancer

NK cells have a license to kill

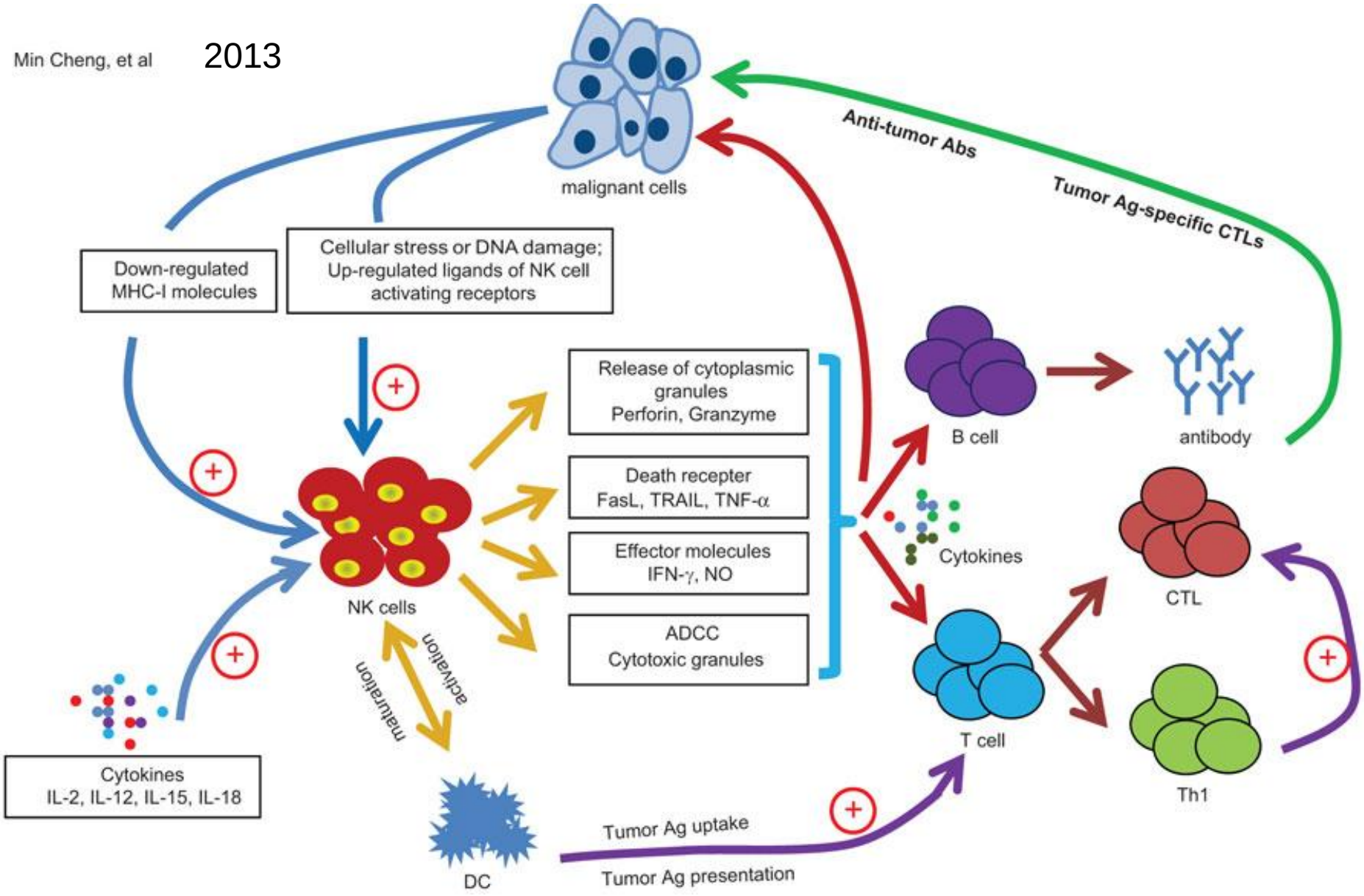
Can recognize variable targets

Traficking issue??



Smyth M. et al., 2002

Min Cheng, et al 2013

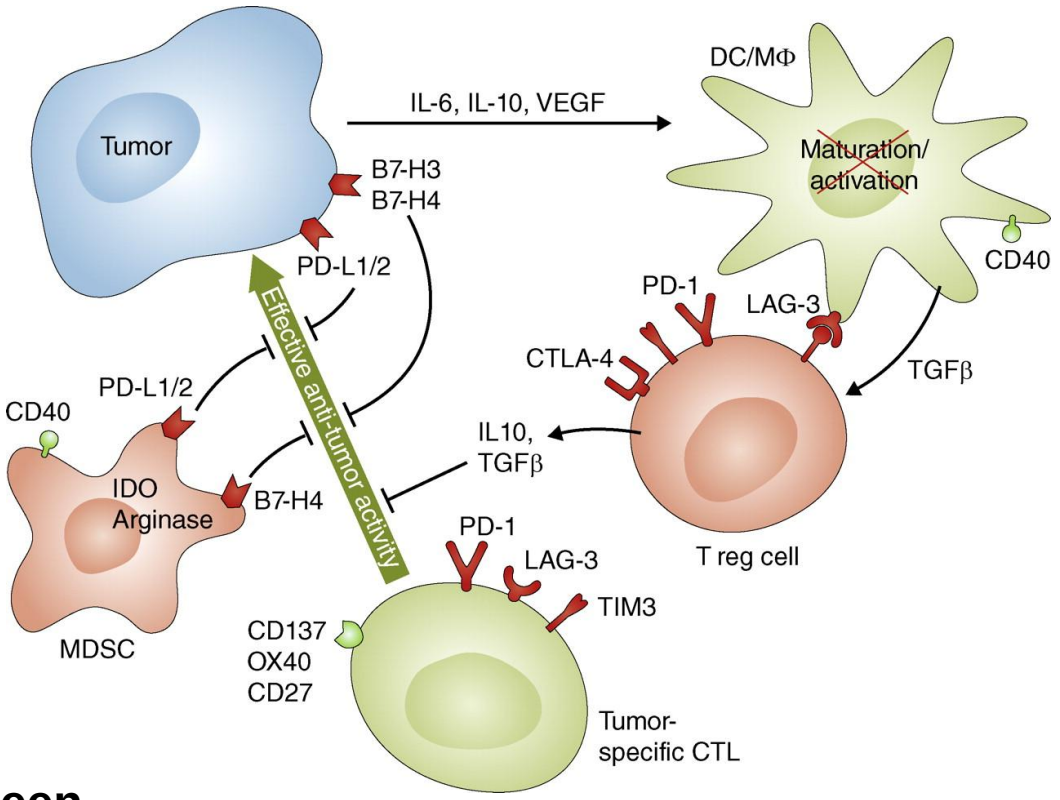


CTLs and Cancer

Naive CTLs normally do not got to tissues

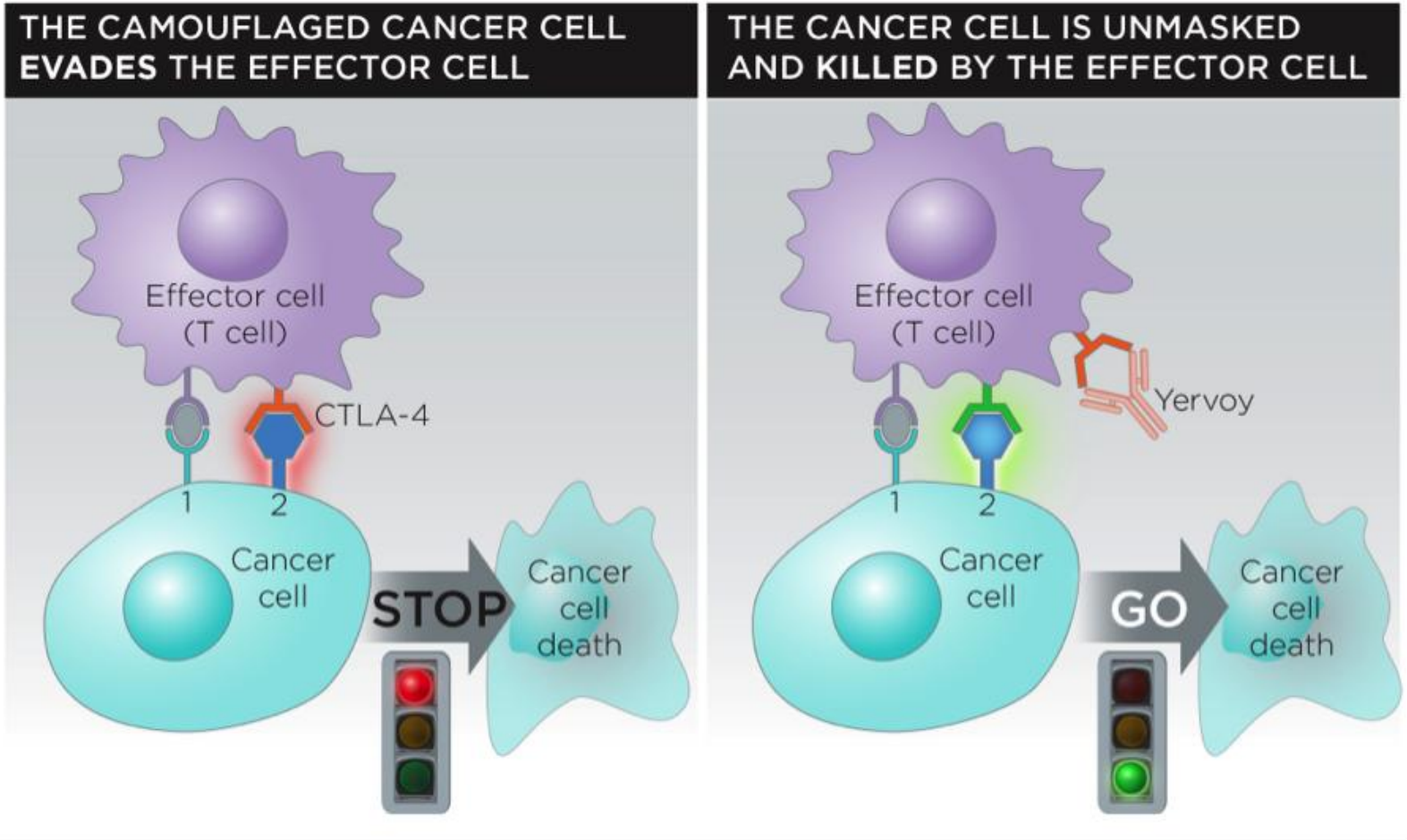
Even if they do, no co-stimulation.

Immune cells at cancer site will further suppress CTLs.

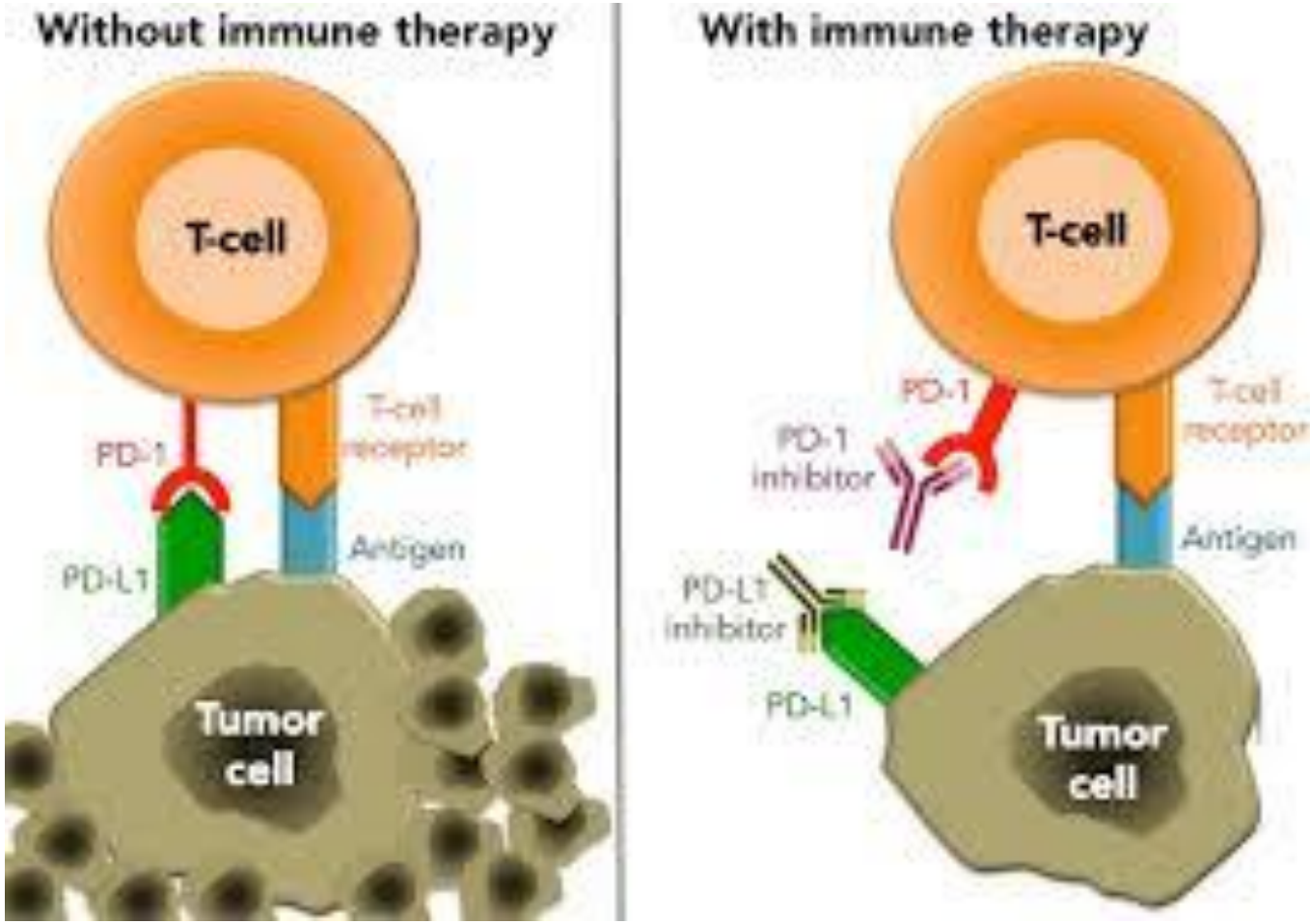


There is a serious conflict between tolerance preservation to self, and the need to provide surveillance against tumors arising in tissues.

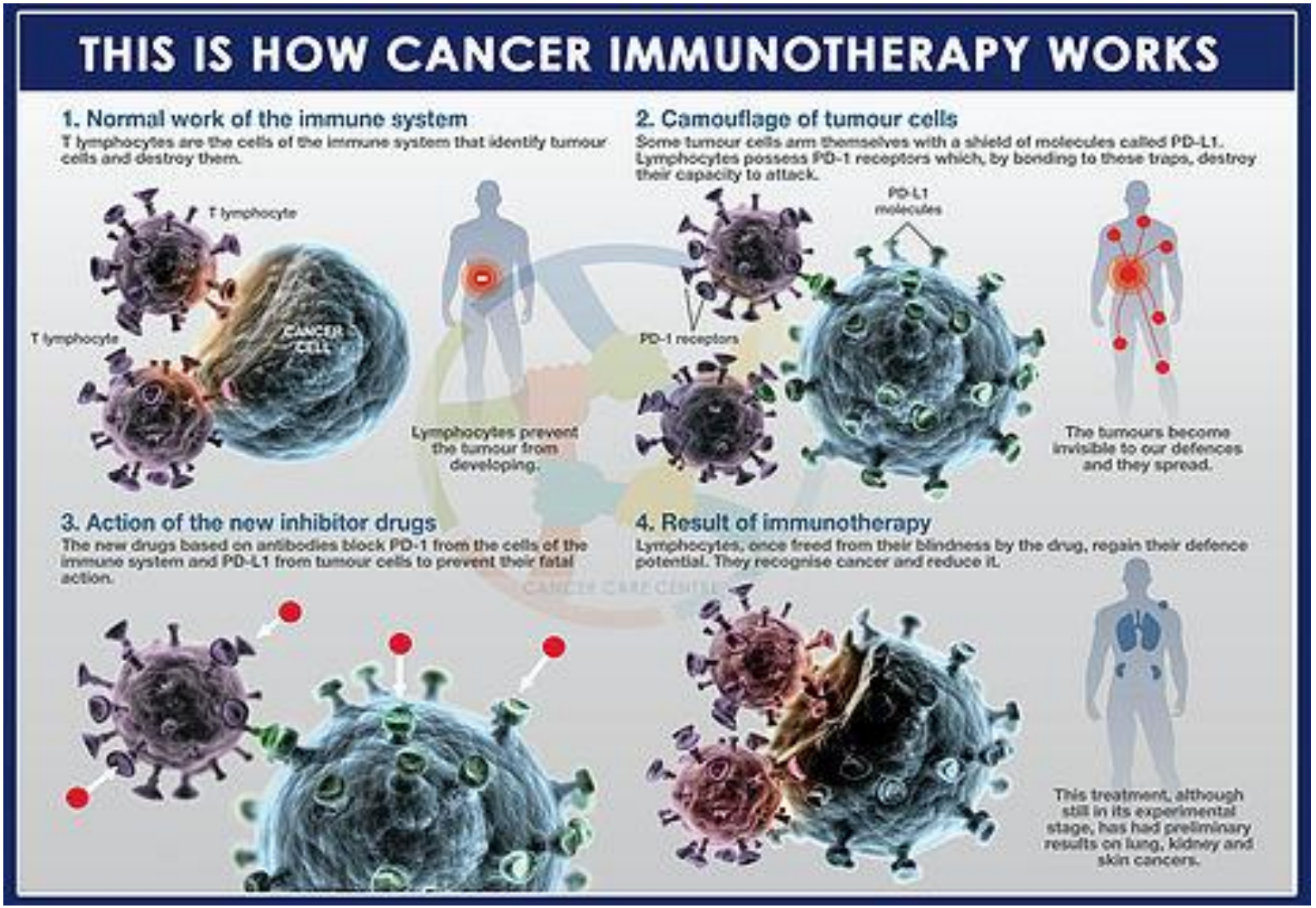
CTLA-4 targeted Immunotherapy



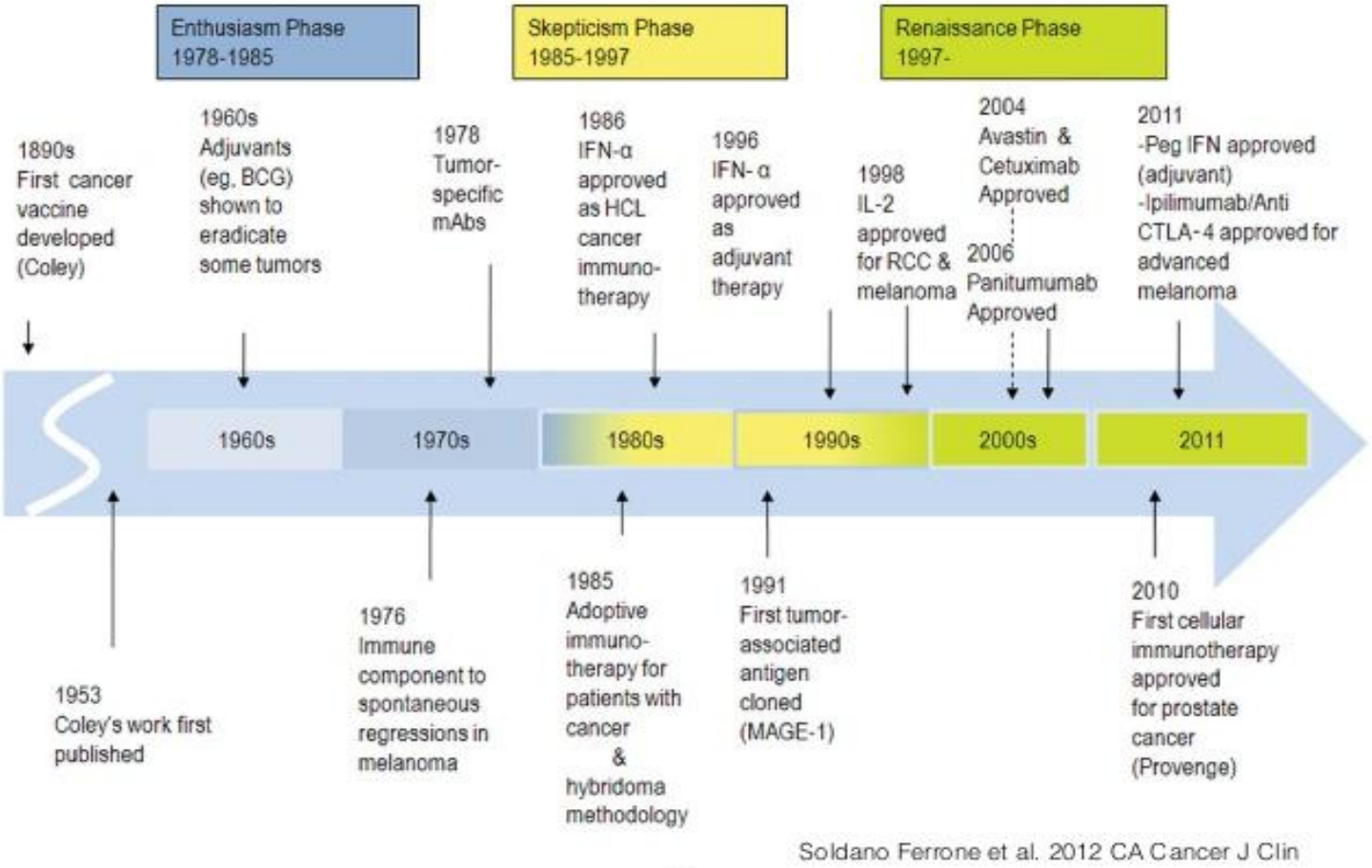
PD-1 targetted Immunotherapy



Cancer Immunotherapy



Cancer Immunotherapy over the years



Soldano Ferrone et al. 2012 CA Cancer J Clin

Cancer Vaccines

Prevention Vaccines:

Hepatitis B vaccine since 1982, Effective!

HPV vaccine (GSK)- Cervical Cancer (HPV16,18) High risk strains
HPV vaccine (Merck) also includes HPV 6,11 responsible for genital warts in both men and women. Low risk strains, why include them?

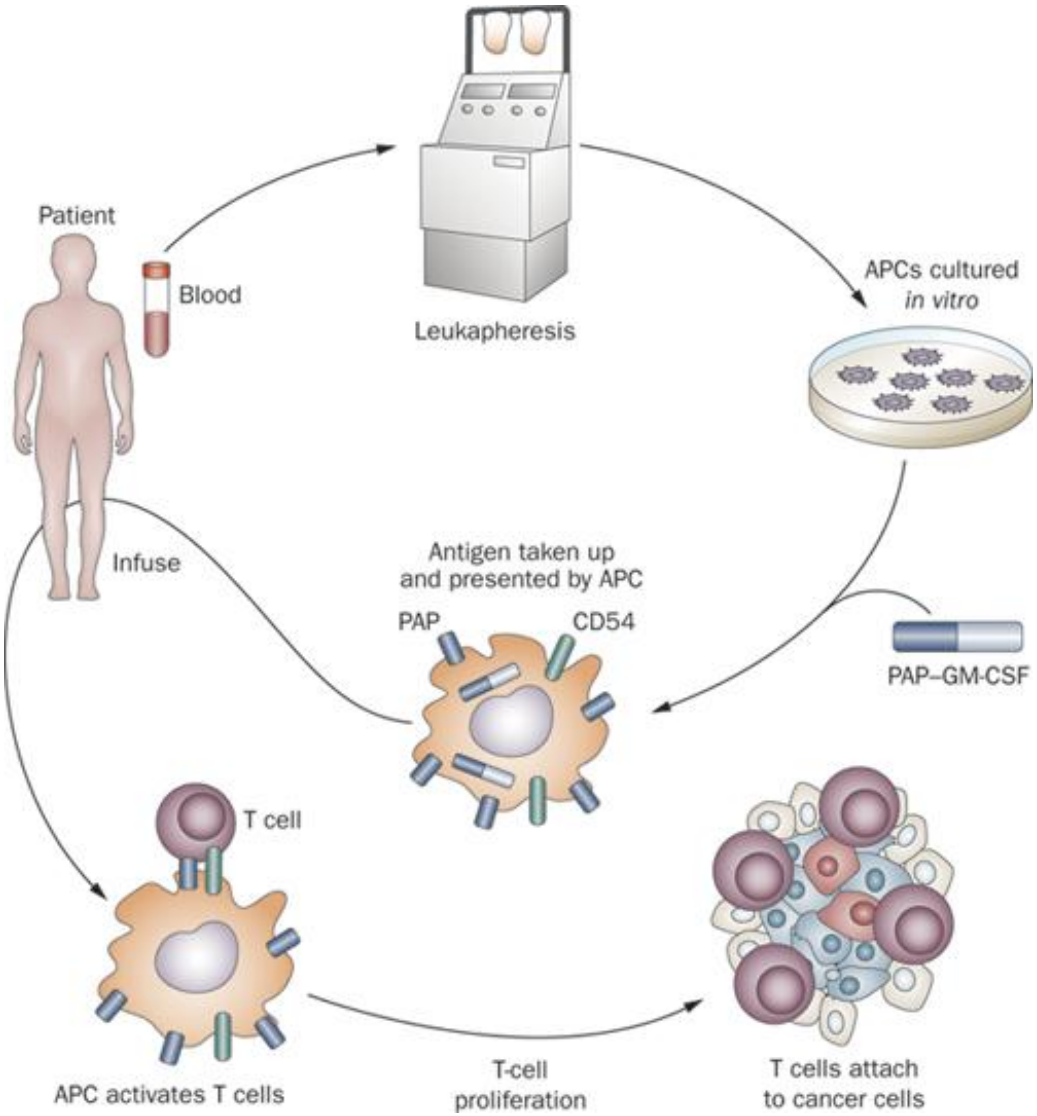
Treatment Vaccines:

Boosting immune cells using cancer antigens to attack tumor. (+/- adjuvant)

Mostly used in research clinical trials.

Recently, FDA approved Sipuleucel-T for men with metastatic prostate cancer.

Sipuleucel-T mode of Action



Questions?????