# *Progress of cancer immunotherapy and its future perspectives*

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# *Cancer immunotherapy*

## *Current status and future perspectives*

- **Cancer immunotherapy is now a promising therapy !**
  - **Durable responses for advanced cancer patients with multiple cancer types**
  - **Immune-checkpoint blockade (PD-1/PD-L1, CTLA4)**
  - **T-cell based adoptive cell therapy (TIL, TCR/CAR-T cells)**

- **The clinical issues to be solved;**
  - **Identification of biomarkers for personalized therapy**
    - **Selection of appropriate patients / Selection of appropriate immunotherapy**
  - **Development of combination immunotherapy particularly for non-responsive patients to the current immunotherapy**

- **Further understanding of immunopathology of cancer particularly in tumor microenvironment and it's modulation !**
  - **Individual difference of immune status in cancer patients**
  - **It's correlation with response to various cancer therapies**
  - **Multiple mechanisms of immune-evasion;** ***Appropriate interventions !***
  - ***Personalized immunotherapy based on the immune-evaluation!***
  - ***Combination immunotherapy targeting multiple key regulation points!***

# Cancer immunotherapy

**Active immunization (Cancer vaccines)**

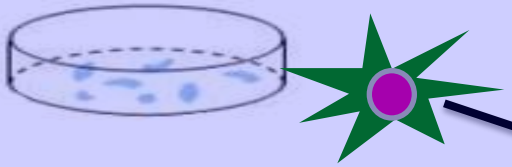
- Prophylactic vaccines for microbes
- Adjuvant vaccines to prevent relapse
- Immunotherapy to reduce tumors

**Passive immunotherapy**
**Adoptive immunotherapy**

**Non-specific immunomodulators**
(BCG, OK432, PSK, etc)

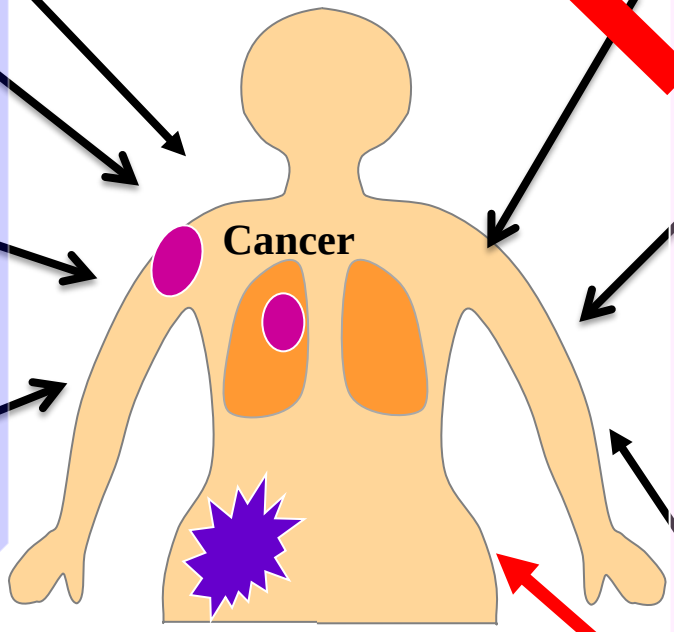
**Tumor Ags**
(peptides, proteins, DNA etc)

**Tumor extracted Ags**



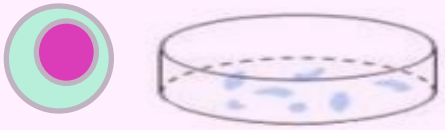
**Dendritic cells pulsed with tumor Ags**

**Modified cancer cells**




**Anti-tumor mAb**

**Tumor Ag reactive T-cells**



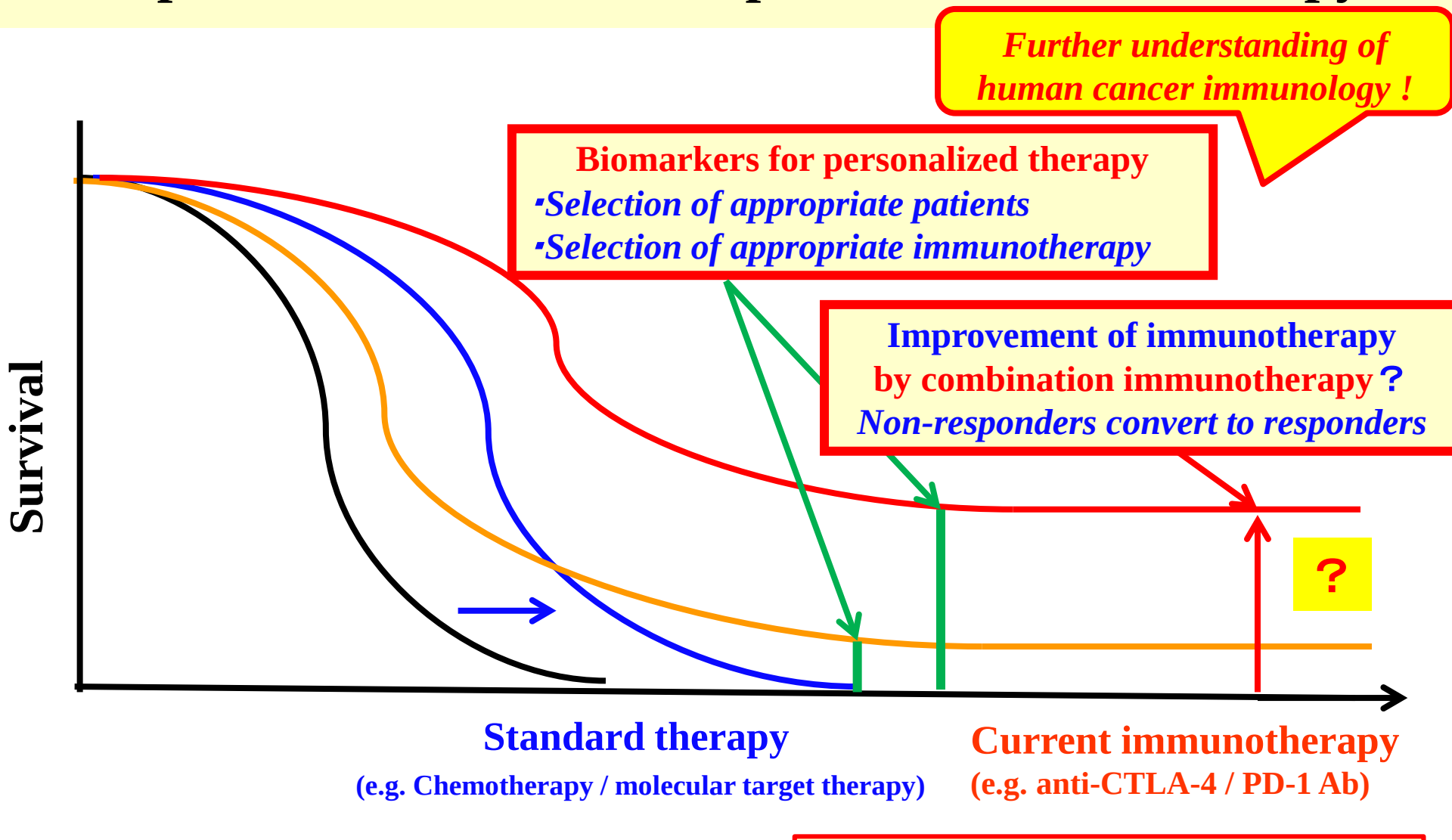
**PBMC**
＋Tumor Ags
＋Cytokines
＋TCR/CAR transduction

**TIL**
＋Cytokines

**Allogeneic lymphocytes**
（Allo-BMT、DLI）

**Reversal of immunosuppression**
**(PD-1/PD-L1, etc)**

# Important issues for development of immunotherapy

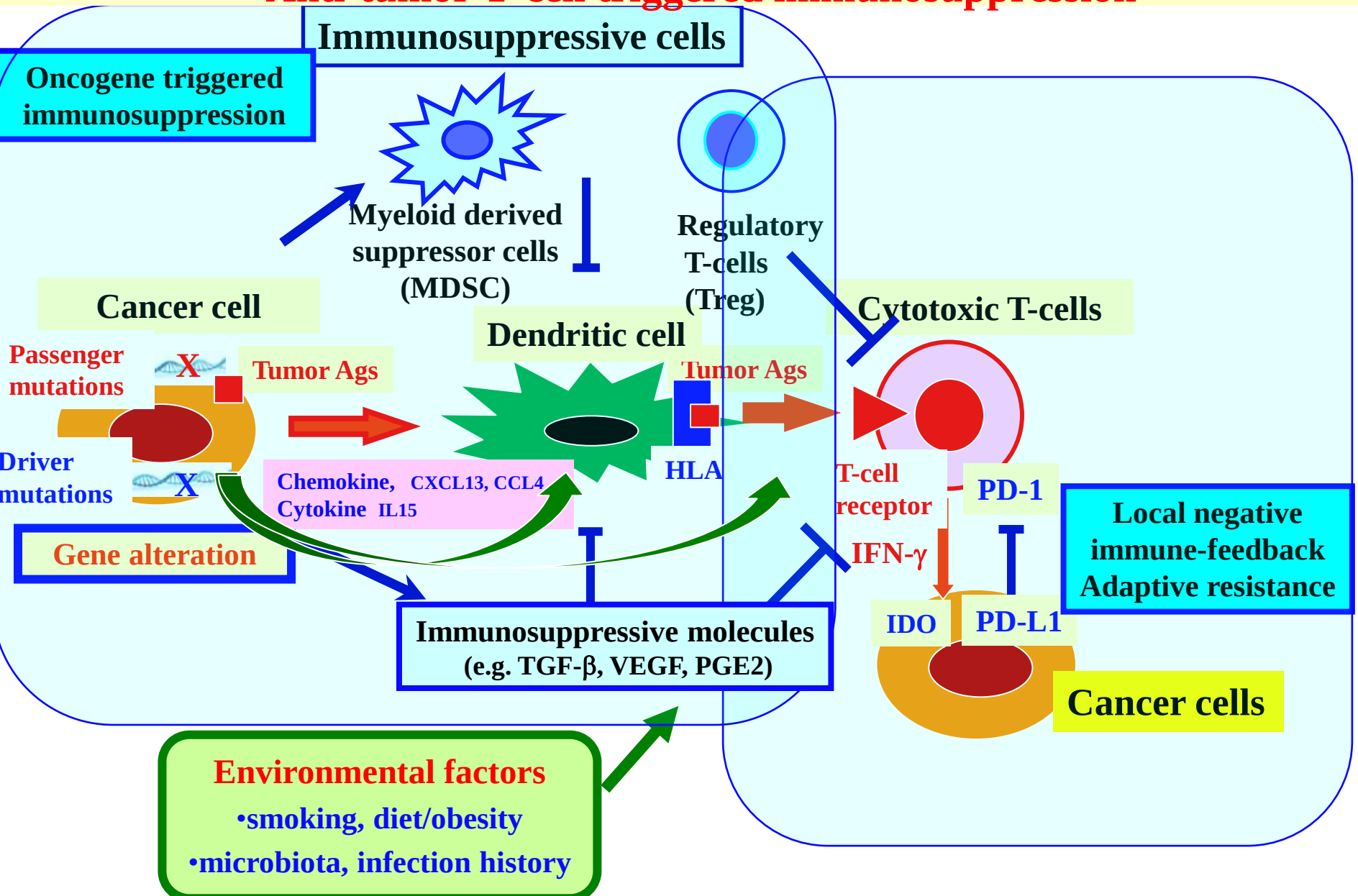



**Immunomonitoring methods ?**

**Clinical evaluation ?**
***irRC, irRECIST, delayed clinical effects***

# Positive and negative immune responses to cancer

- Oncogene triggered immunosuppression
- Anti-tumor T-cell triggered immunosuppression



# Immunotherapy using Ab specific for targets on T-cells

## Anti-PD-1Ab（Nivolumab）

| | Response rate |
|---|---|
| Melanoma | 26/94 (28%) |
| RCC | 9/33 (27%) |
| Lung cancer | 14/76 (18%) |

**Durable responses (over 1 year or more) in 20 of 31 (65%) responders**

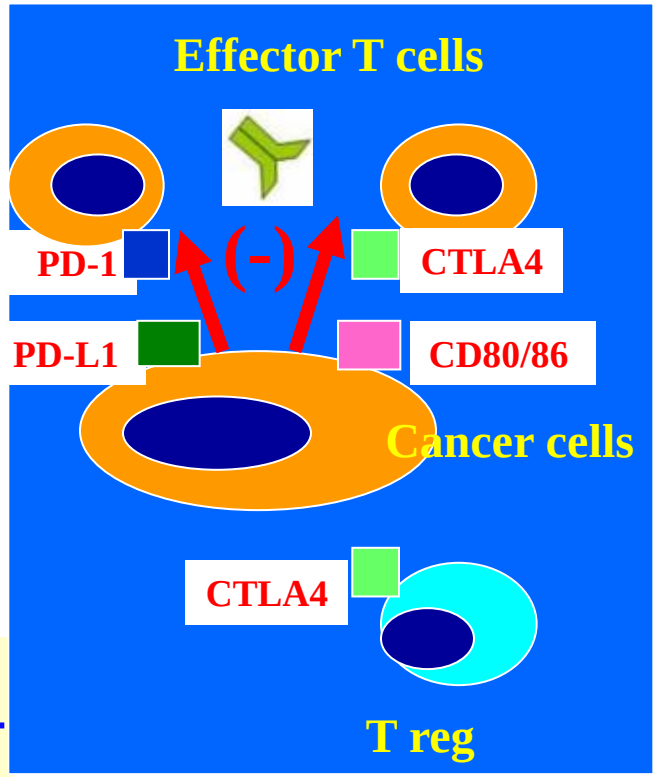
*Topalian SL, et al, NEJM 2012*

## Anti-PD-L1Ab

| | Response rate |
|---|---|
| Melanoma | 3/16 (19%) |
| RCC | 2/17 (12%) |
| Lung cancer | 4/15 (16%) |

**Less immune-adverse effects than anti-CTLA4 Ab**

*Brahmer JR et al, NEJM 2012*




## Anti-CTLA4 Ab
## （Ipilimumab）

- Median Survival: 10mo vs 6.4mo (n=676)

*Hodi FS, et al, NEJM 2010*

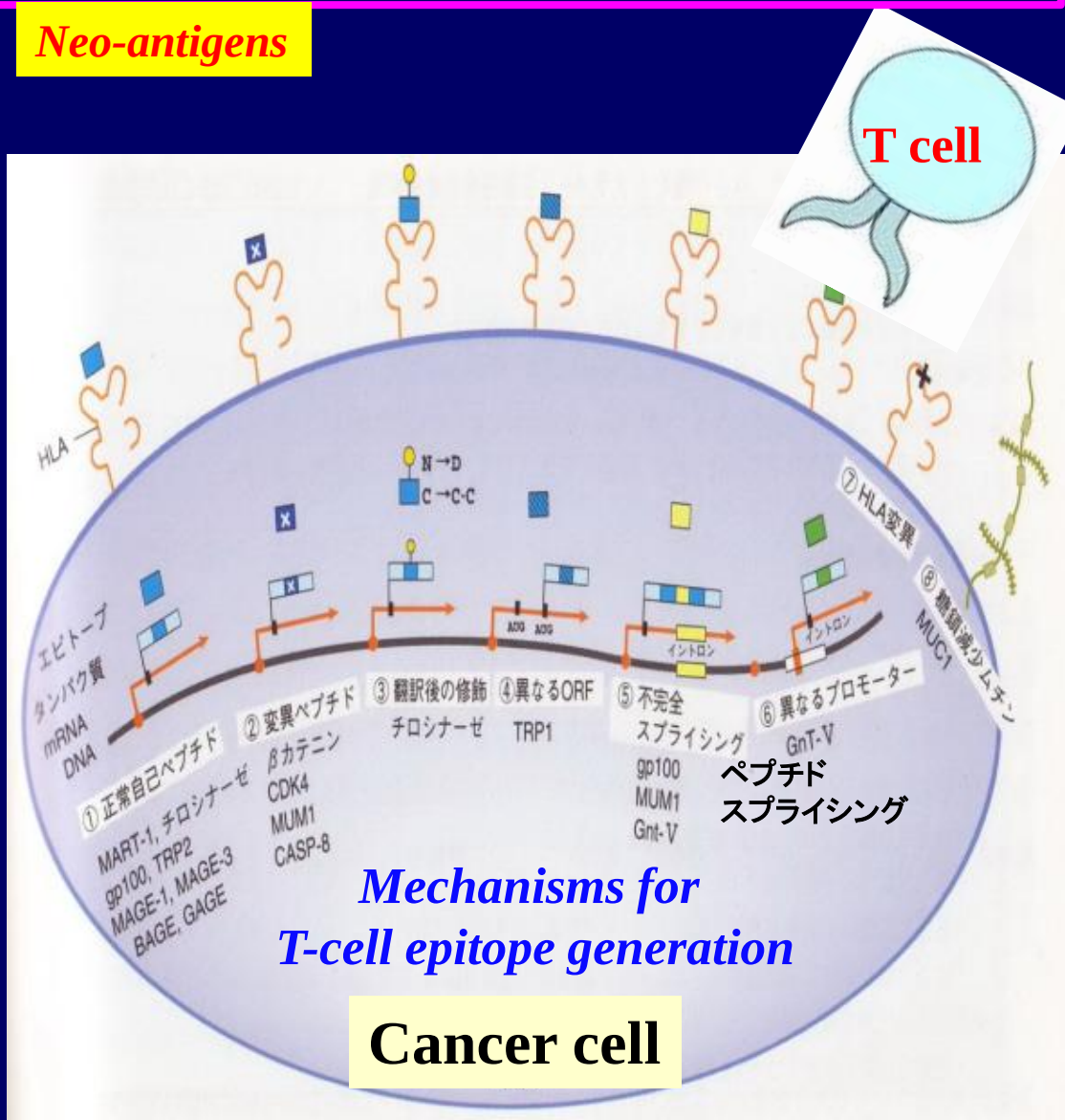
***CTLA-4/Treg is involved in peripheral tolerance —> More autoimmune AE***

# Human tumor antigens recognized by tumor infiltrating T-cells

- **Mutated antigens derived from DNA alterations in cancer cells (β-catenin, etc) SYLDSGIHS(F) －＞acquire HLA-binding**

***Neo-antigens***

- **Viral related antigens**
  **(HPV-E6/E7)**
- **Cancer-testis antigens**
  **(MAGEs, NY-ESO-1)**
- **Tissue specific antigens**
  **(MART-1/Melan-A, gp100)**
- **Over-expressed antigens**
- **Allo-antigens**
- **Others**



# Novel personalized immunotherapy targeting individual mutations

**Identification of mutations by exomic-sequencing of autologous cancer cells**

**Prediction of HLA binding peptides by computer argorithsms**

**Confirmation of T cell epitopes by**

- ***in vitro* peptide induction of T cells**
- **immunization of HLA transgenic mice**
- **using HLA tetramers**

- **Active immunization with peptides / mRNA**
- **ACT with TIL / TCR-transduced T cells**

# Issues to be solved in the immuno-checkpoint blockade

- **When used ?** Advanced cancer, frontline treatment, adjuvant setting
- **When stopped ?** How long should be used? (high cost, economical issues)
- **Personalized immunotherapy**
  - Unresponsive cancer: pancreas ca., MSS-CRC, myeloma, prostate ca,
  - Non-responders convert to responders

  *Biomarkers (PD-L1 exp, $CD8^+$T cell infiltration, DNA mutations, MDSC, Treg, etc) through systematic analysis of clinical trials (Omics, microbiota, immuno-analysis)

  *Pretreatment, early on-treatment

  *Biomarkers can be new treatment targets

- **Combination immunotherapy with personalized interventions**
  - Immunogenic cancer cell death, adjuvant, vaccine, immune-regulators
  - Enhanced anti-tumor effects w/o increase of adverse effects ?
  - Which combination ? Concurrent vs sequential ?
  - Combination of chemotherapy / molecular target therapy

    w/ checkpoint blockade: high immunogenic mutation (melanoma, NSCLC)

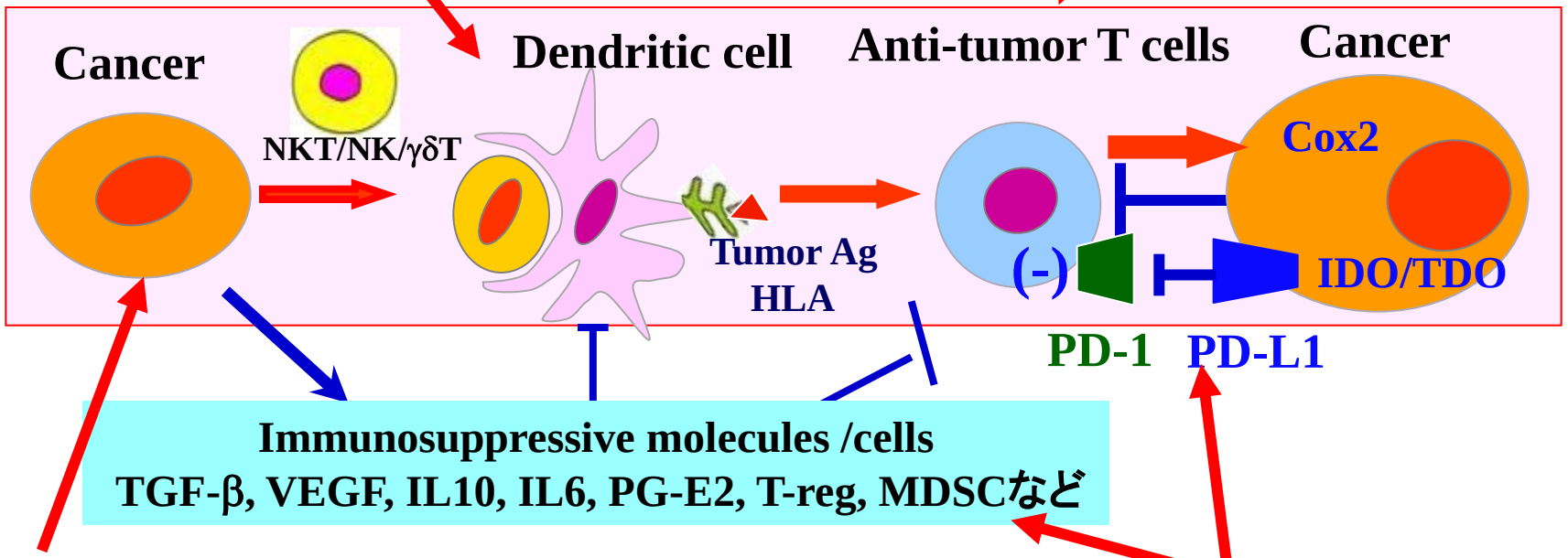
    w/ ACT: less immunogenic leukemia, NSCLC, etc,

# Combined immunotherapy targeting multiple key regulation points in anti-tumor T cell response

**Tumor antigen vaccine**
Mutated Ags
Cancer stem cell Ags

**Augmentation of dendritic cell function**
Adjuvant (TLR3, STING), Ab (CD40 agonist)

**T-cell activation / expantion**
Cytokines (IL2,IL7,IL15,IL21)
Agonist Ab (4-1BB, OX40)など

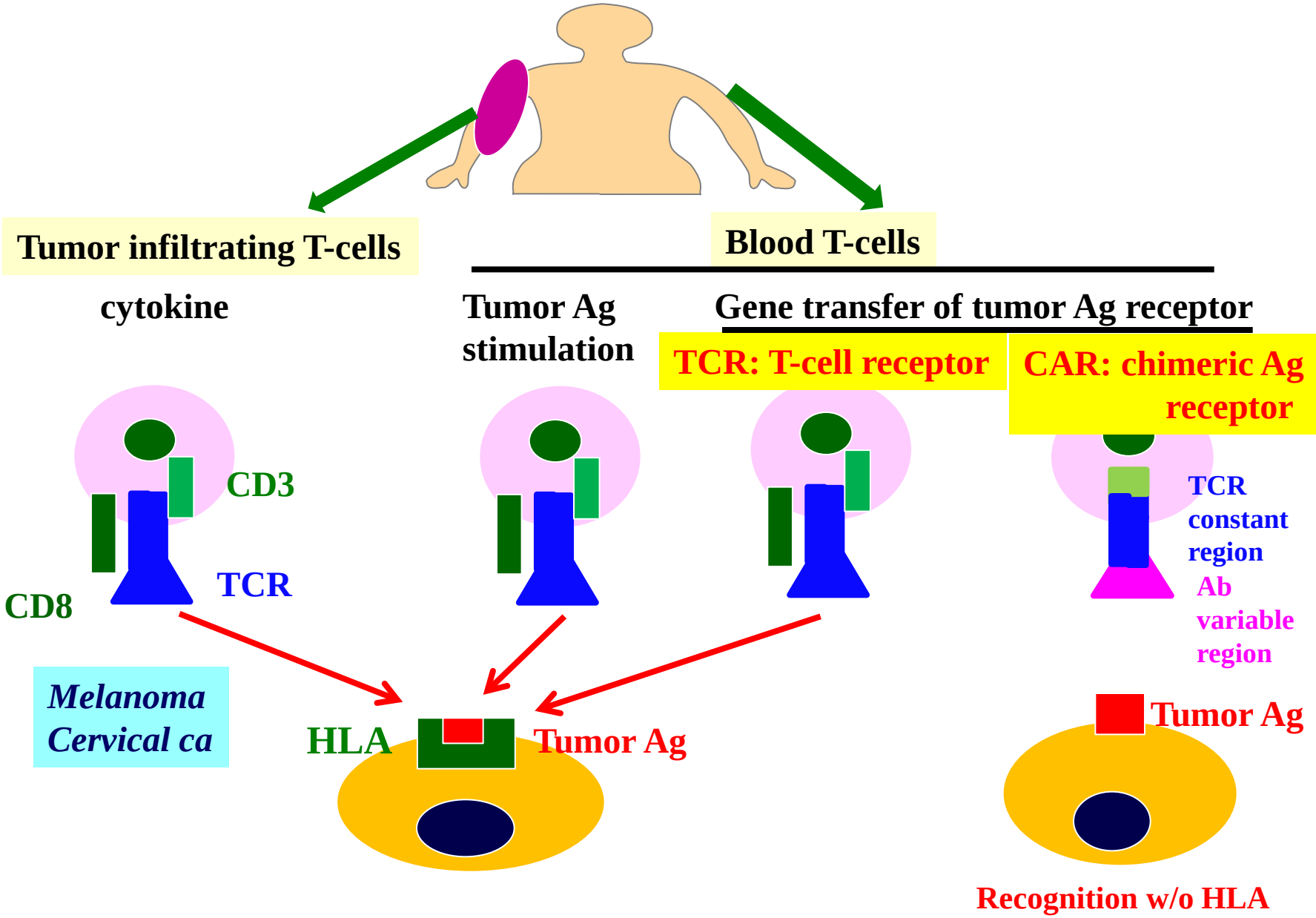



**Immunosuppressive molecules /cells**
TGF-β, VEGF, IL10, IL6, PG-E2, T-reg, MDSCなど

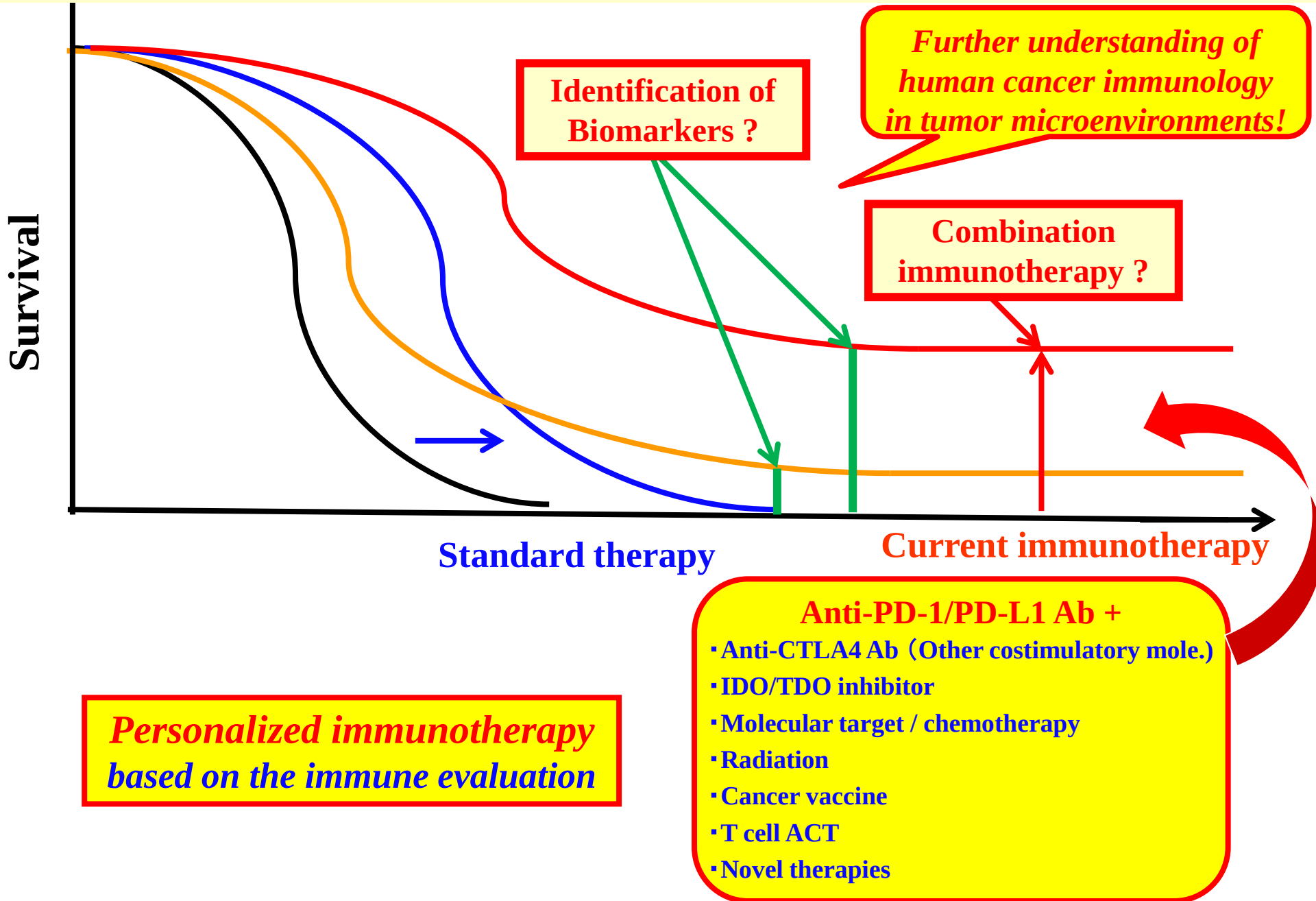
***in site* tumor destruction**
***<Immunogenic cell death>***
Chemotherapy・Ab・physical・Virus, etc

**Reversal of immunosuppression**
Signal inhibitors, Chemotherapy, IDO inhibitor,
Ab（CTLA4, PD-1, LAG3, CCR4, TIM3, TIGIT）, RNAi, etc

# Adoptive cellular immunotherapy using tumor antigen specific *ex vivo* cultured T-cells



# *Important issues to be solved for developing effective immunotherapy*




***Personalized immunotherapy based on the immune evaluation***

# 日本における個別化・複合がん免疫療法開発の課題

## ＊日本での複合免疫療法の臨床試験実施と病態解析研究を！

・複合免疫療法臨床試験のための企業間連携はすでに進んでいる！

・新たな産学官連携の構築が必要（win-win situation, high cost, 得意分野）！

### -アカデミアシーズ・ノウハウの効率的な企業への受け渡し

・日本医療研究開発機構(AMED)（Japan Cancer Research Project）でのシーズ開発

・複合免疫療法の医師主導臨床試験の実施を！　（AMEDにも期待？）

・企業にとって　真に有用なシーズ、適切な組み合わせ、評価法と対策の提言！

### –企業治験におけるアカデミアによる病態解析（治療効果・副作用機序）

・治験段階での免疫学的解析ー＞次のステップのためのシーズ（診断・治療標的）！

・治験の空洞化問題　（臨床研究中核病院）

・企業にとって　真に有用な評価法、臨床データとその解釈、さらにその検証！

・全国レベルでのがん患者ネットワークの構築、臨床検体収集システム、
各種システム生物学的解析拠点体制の構築　　＜AMEDへの期待！＞

・米国NCIの全国ネットワーク　（e.g. 肺癌変異シークエンスシステム）

・米国GoogleのCancer Immunotherapy開発への参画？

・日本における産官学コンソーシアムの確立　（議論の場の提供）

＜米国SITC / CRI, EU-CIMT＞

# 新しい医療の健全な均てん化・教育

- 異なる治療効果判定基準
  - RECISTだけでは不十分(irRCやirRECISTの併用)
- 化学療法や分子標的治療薬とは異なる副作用と対策
  - 免疫性副作用(皮膚炎、甲状腺炎、腸炎、肝炎など)
  - 間質性肺炎や下垂体炎、筋無力症などの重篤、致死的な副作用
  - 適正使用ガイドが作成されており、医療従事者は十分に熟知する必要
- 多職種医療チームへの教育
  - ガイドライン
  - 医師はもちろんのこと、がんチーム医療において、
    薬剤師、看護師など広く各職種への教育体制も重要