

Concluding remarks

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Tumor immunosurveillance

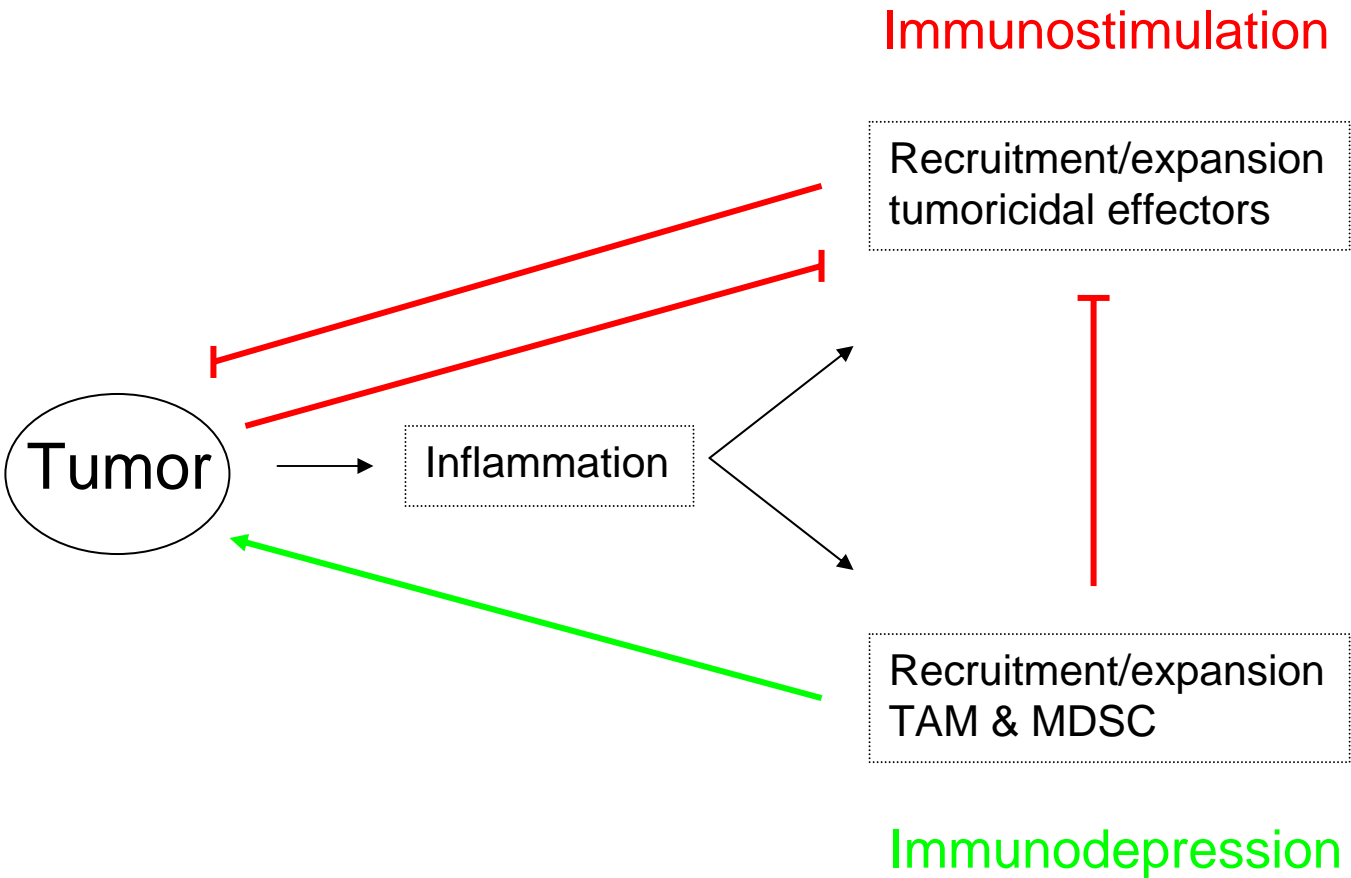
- Tumor-specific immunity

- Preclinical models (chemically- or virally-induced tumors)
- Human studies
 - In vitro tumor recognition and elimination by T cells
 - Ex vivo immune correlates with prognostic value in some cancers
 - Partial or (rare) complete clinical responses induced by therapeutic vaccines

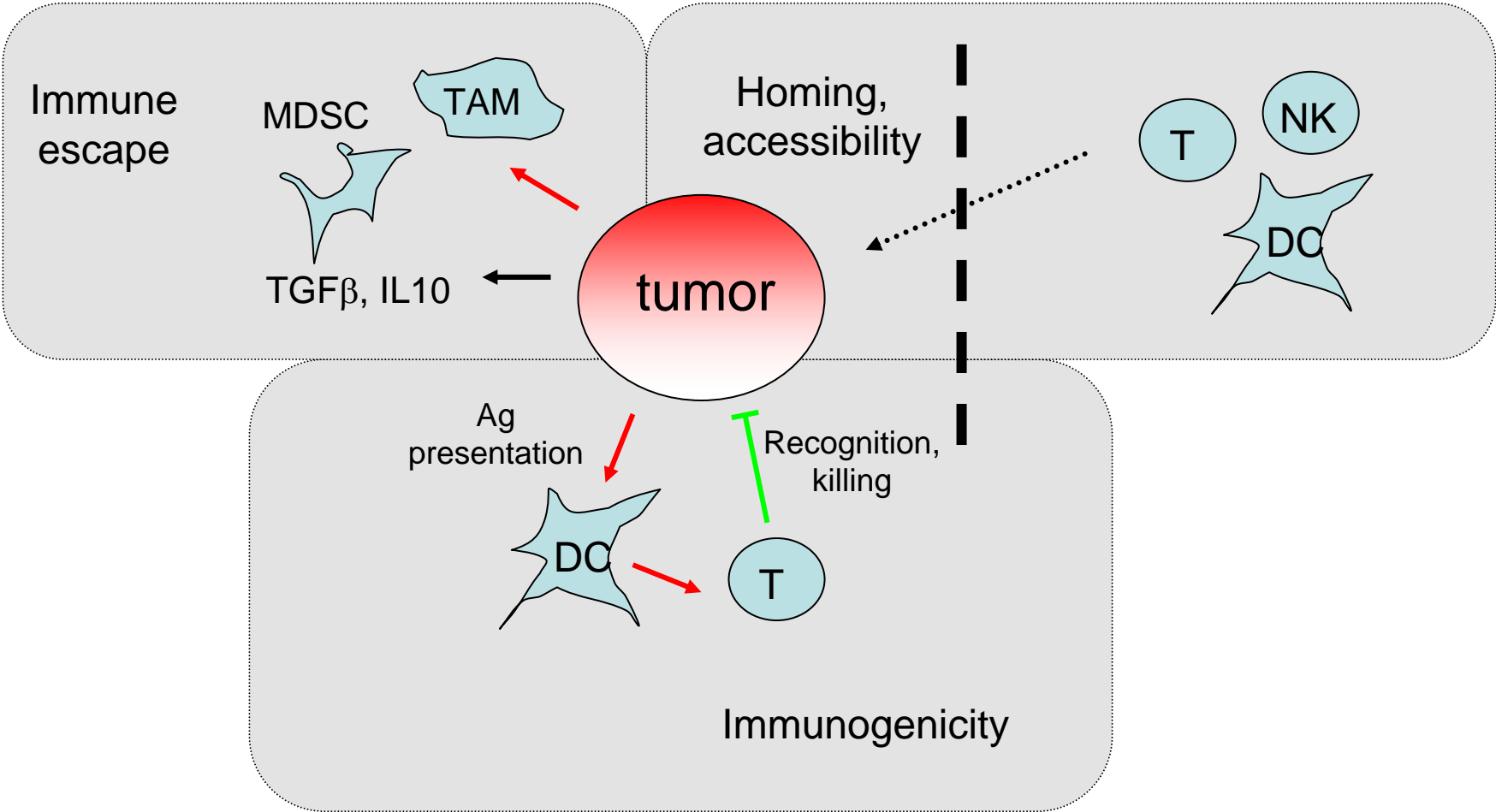
- Cancer immunotherapy

- Tumor clearance through restoration / enhancement of tumor-specific T cell responses
- Varied strategies - complex mechanisms

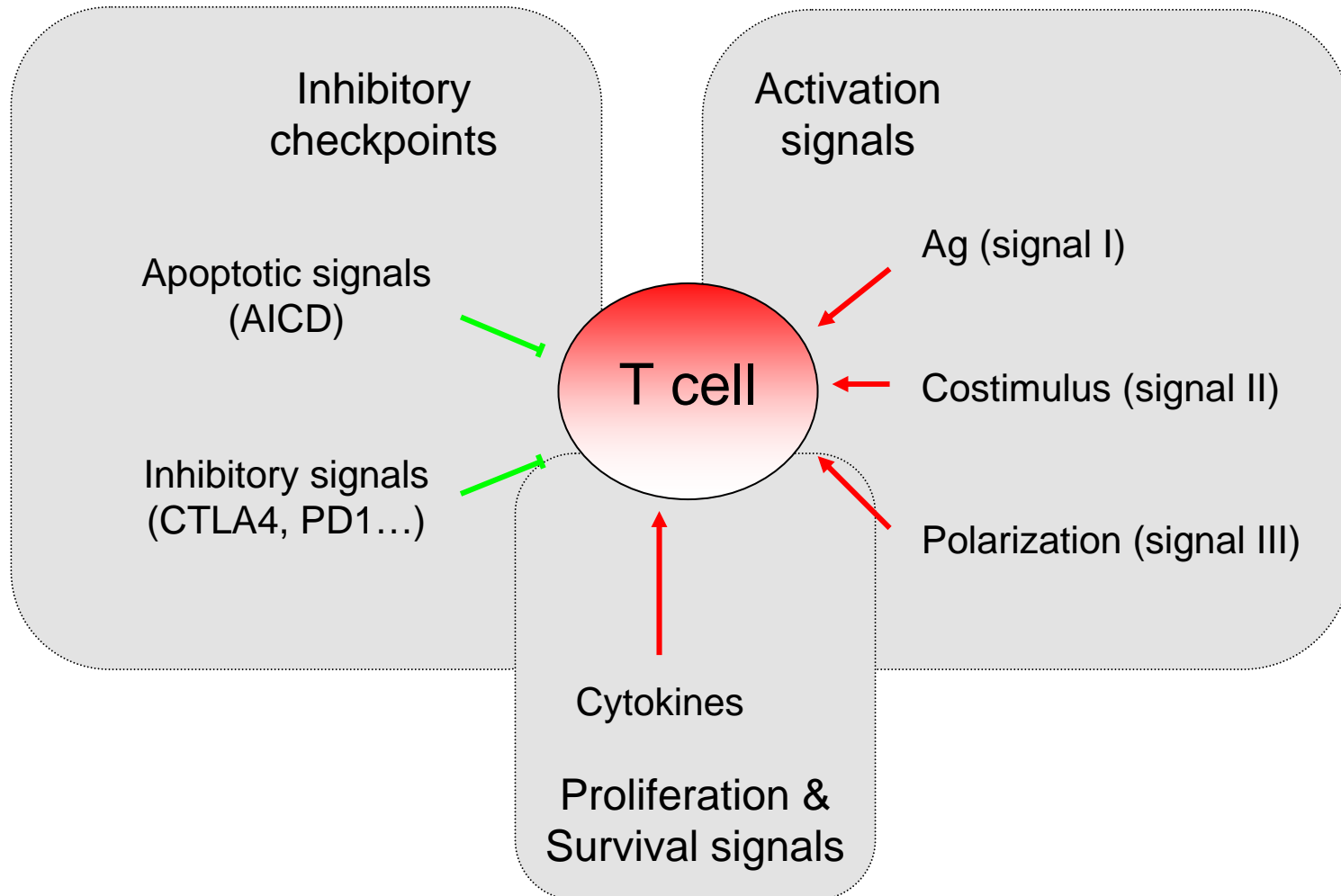
A balance between immunostimulation and immunosuppression



Key parameters : tumor side



Key parameters : T cell side



Why so many failures ?

- Extreme complexity
- Empirism
- Improper clinical setting (late stage, large tumor burden...)

But room for optimism

- Detailed understanding of immune cell activation and tumor recognition
- Rational design of new adoptive / active immunotherapies with promising results
- Unrecognized immune-mediated effects of conventional therapies

Immune markers

- **New prognostic immune markers**
 - Evidence for an immune control
 - Improved therapeutic handling (chemotherapy, immunotherapy...)
- **Challenges & perspectives**
 - Still cumbersome approaches, reproducibility and standardization issues
 - Relevant for local immune responses only
 - Restricted set of tumors
 - Likely heterogeneous from one tumor to another

Adoptive T cell transfer

- **Allogeneic setting (bone marrow transplantation)**
 - Proven efficacy (GvT in allo-BMT) but life threatening side effects (GvH)
 - Broadened indications (improved immunosuppression, reduced intensity conditioning)
 - Key issue : GvH control
 - Distinction GvT vs GvH effectors
 - In vitro depletion protocols
 - Improved / targeted immunosuppression (anti-CD25, anti-TNF α , NK cell transfer...)

Adoptive T cell transfer

- **Autologous setting**
 - Tumor-specific T cell lines and clones (native or gene-modified)
 - Improved standardization of clinical grade in vitro expansion protocols
 - Proven efficacy in late stage metastatic melanoma
 - Challenges
 - Still isolated examples
 - Need for lymphodepletion ?
 - viable business model ? (complex process / tailored therapy / not centralized)
 - Implementation at the academic level (functional T cell reprogramming, high tumor burden)

Active immunotherapy

- DC adoptive transfer
 - Fine modalities of DC expansion/activation/functional polarization
 - Strong induction of systemic T cell responses
 - Some remarkable clinical responses (melanoma...)
- But...
 - Standardization difficult
 - Tumor antigen loading (extracts, RNA, DNA, peptides, immune complexes)
 - In vivo homing and survival
 - Lack of broadly available adjuvants / DC stimulators
 - Pharmaceutical development tricky

Non-cell cancer vaccines

- **State of the art**
 - Composition
 - > 300 tumor antigens characterized
 - Cell extracts, peptides, proteins, DNA, vectors
 - Adjuvants (IFA, Alun, TLR ligands...)
 - Delivery
 - In vivo DC targeting of defined Ag (fusion proteins, immune complexes, long peptides...) (*preclinical*)
 - Available bacterial/viral vectors enhancing tumor immunogenicity and/or triggering systemic response against vaccinal Ag
 - Pharmacodynamics & clinical efficacy
 - Proof of immunogenicity in vivo
 - Preventive vaccines (eg HPV-induced cancers)
 - Therapeutic vaccines : some PR or even CR but still scarce responses

Non-cell cancer vaccines

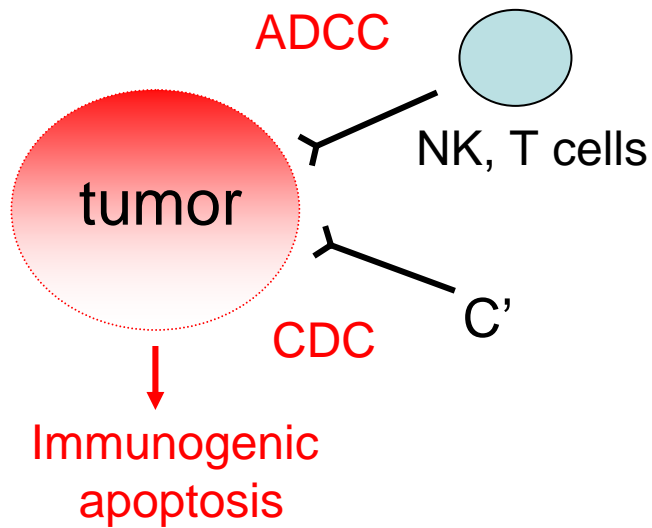
- Current limitations (I)
 - Selection criteria of tumor Ag
 - tumor specificity, distribution and expression
 - mandatory or not for tumor survival
 - CD4 vs CD8 epitopes
 - Lack of consensual immune correlate predictive of clinical response
 - Tumor-specific T cell frequency, affinity, function ?
 - epitope spreading

Cancer vaccines

- **Current limitations (II)**

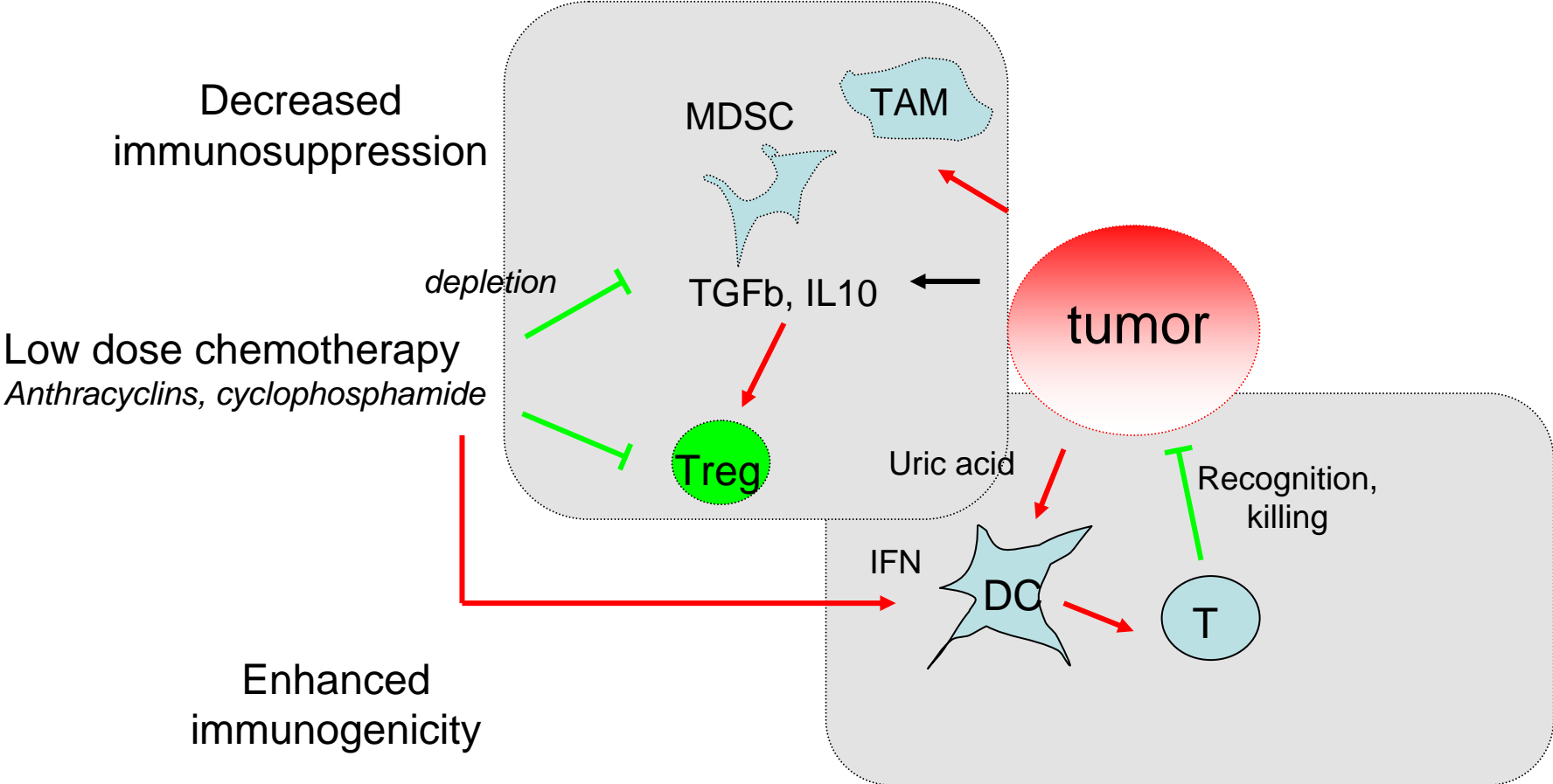
- Need to block tumor-induced immunosuppression and inhibitory checkpoints
 - mAb against CD25, CTLA4, PD1, CD40...
- Complex therapeutic setting
 - Early disease stage (regulatory issues, strong competition with many targeted approaches...)
 - Patients with low tumor burden (lengthy trials, sensitive surrogate markers...)
 - Need for combination approaches using compounds with limited availability

Targeted therapies



- Clinical efficacy
 - Follicular lymphoma : Rituximab
 - Breast cancer : Trastuzumab
 - Colon cancer : Cetuximab...
 - Ab targeting of toxic compounds
- Perspectives
 - New best-in-class Ab with enhanced FcR affinity
 - Combination with immune adjuvants (eg GM-CSF)

Conventional chemo/radiotherapy and tumor-specific immunity



Conventional chemo/radiotherapy and tumor-specific immunity

- Perspectives

- Improved therapeutic settings : combination treatments (eg with DC activators : CD40 agonists, GM-CSF, TLR ligands...)
- Validation in larger retro/prospective studies
- Early disease stage, sequential approaches (low tumor burden)
- New immune markers predictive of response to chemotherapy (immune gene polymorphisms ...)

What's next ?

- Promising compounds with yet limited availability and no proven efficacy yet as monotherapy (NCI 2007 ranking)
 - T cell growth factors (IL15, IL7)
 - T cell checkpoint inhibitors (anti-PD1, PD1L)
 - APC stimulators (anti-CD40, CD40L)
 - Enzyme inhibitors (1-CH3-Trp)
 - T cell costimulators (anti-4-1-BB)
 - DC growth factors (Flt3L)
 - Vaccine adjuvants (IL12, CpG, MPL, polyI:C, Resiquimod...)
- Probably poorly active as monotherapy but synergistic action in multi-component approaches
 - key IP/ regulatory issues : compatibility with pharmaceutical model ?
 - POC obtained through academic programs ?