Cord blood: a source of anti-tumour specific T cell clones?

2ο Συμπόσιο για Πρωτοπαθείς Ανοσοανεπάρκειες Παιδιατρική Ανοσολογία

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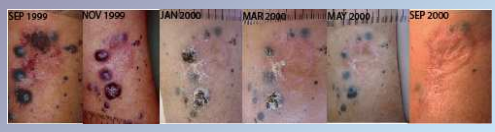
The reasoning for cancer immunotherapy……..

Most approaches targeting rapidly dividing cells, also affect normal cells and result in side effects that limit treatment

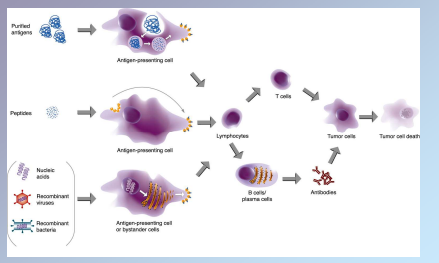
Harnessing the immune system to precisely target cancer cells without harming normal cells represents the challenge of <u>Cancer Immunotherapy</u>

The ultimate goal of cancer immunotherapy……..

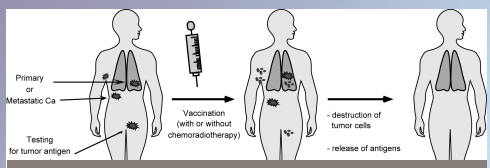


Anti-cancer vaccination

Cancer vaccine modalities



Cancer vaccine principles

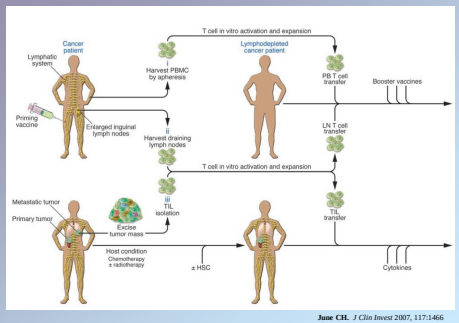


Thorough analysis of

pre-existing anti-tumor T cell responses

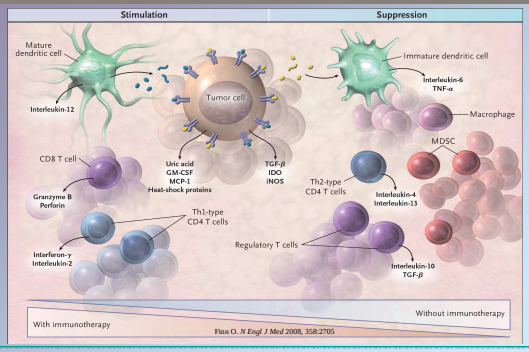
Karanikas V, Germenis A. *J BUON.* 2009; 14: S153-S157

Adoptive T cell cancer therapy



June CH. *J Clin Invest* 2007, 117:1466

Significance of cancer immunotherapy



20 years of cancer immunotherapy……..

	Clinical response	T cell response
Group A	+	+
Group B	–	–
Group C	+	–
Group D	–	+

All trials

(antigen, immunostimulant, age, sex, type of Ca etc)

< 3-5% of vaccinated patients present with short lived regressions

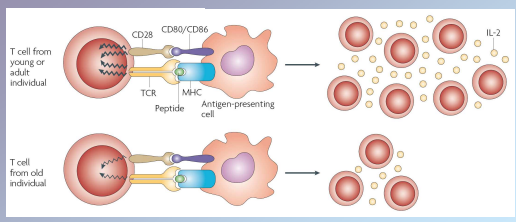
Rosenberg SA. *Nat Med* 2004, 10:909

20 years of cancer immunotherapy…….

Immunosenescence

Senescence of CD8 T cells

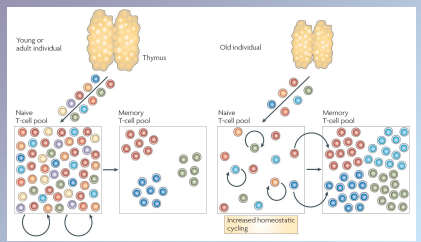
Antigen recognition



TcR and co-stimulatory molecule signalling

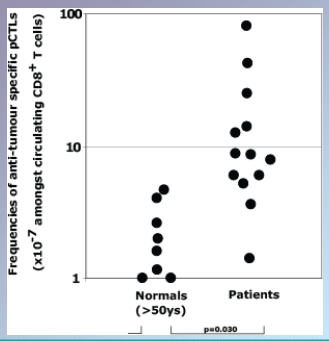
Senescence of CD8 T cells

T cell number



- thymic involution
- decline of naive T-cell numbers
- reduction in T-cell repertoire diversity
- memory inflation

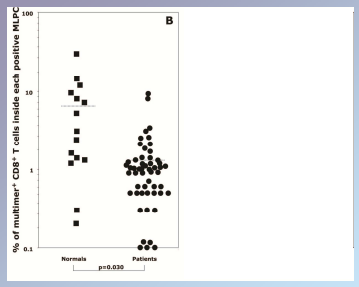
Senescence of CD8 T cells



Patients with cancer, have x10 more pCTL than healthy subjects of same age

Karanikas etal, *Immunology and Cell Biology*, 2010

Senescence of CD8 T cells



CD8 T cell clones of healthy individuals

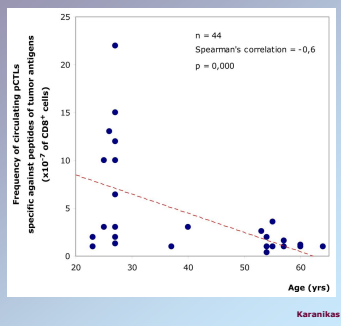
Multiply better

and

Bind to MHC-peptide stronger

Karanikas etal, *Immunology and Cell Biology*, 2010

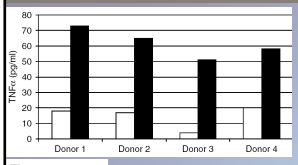
Senescence of CD8 T cells

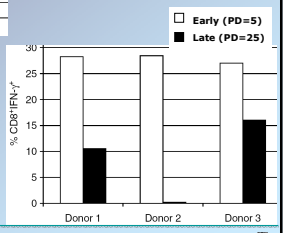


Karanikas etal, *Unpublished*

T cell replicative senescence

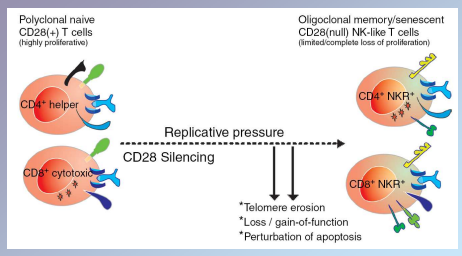
Antigen specific division



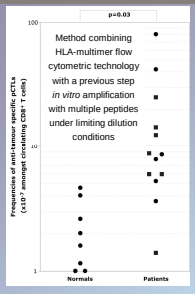


Effros RB et al. *Immunol Rev* 2005, 205:147

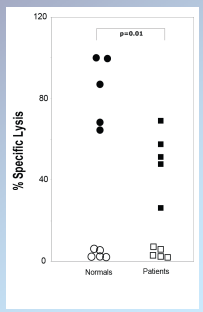
T cell replicative senescence



T cell replicative senescence



Karanikas etal, *Immunology and Cell Biology*, 2010



^{51}Cr-cytotoxicity assay of CTL-clones against peptide-baded targets

What does the future hold for cancer immunotherapy?

The **FUTURE** of cancer immunotherapy

"YOUNG" *(allogeneic)* ***lymphocytes***

promise to be more efficient
in combating homologous tumors

than

the senescent host lymphocytes

Germenis A, Karanikas V. *J Reprod Immunol, 2010; 85:47-50*

The **FUTURE** of cancer immunotherapy

A. Can allogeneic lymphocytes combat homologous tumors?

Trials	# of pts	Response rate % (CR/PR/MR)	
Childs, 2000	19	53% (**3**/7/0)	RCC
Bregni, 2002	7	57% (0/4/0)	
Pedrazzoli, 2002	7	0% (0/0/0)	
Rini, 2004	12	33% (0/4)	
Hentschke, 2003	10	30% (0/3)	
Ueno, 2003	15	47% (**1**/2/4)	
Bregni, 2002	6	33% (0/2)	BREAST
Ueno, 2003	8	38% (**2**/0/1)	
Carella, 2002	17	25% (**3**/1/0)	
Bishop, 2004	16	38% (0/2/4)	

Clinical trials on RIST HSCT for RCC

Modified from **Lundqvist A and Childs R.** *J Immunother* 2005, 28:281

The **FUTURE** of cancer immunotherapy

B. Can antigen-specific T cells be primed/expanded from naïve UCB lymphocytes?

- **Successful attempts have been made in expanding functionally active virus-specific T cells of neonatal origin that target CMV, adenovirus and EBV from naïve UCB T cell populations**

  Sun Q et al.. *Cell Immunol* 1999, 195:81
  Park KD et al. *Blood* 2006, 108:1770
  Hanley PJ. *Blood* (in press)

- **UCB lymphocytes can be expanded in vitro by approximately 1000-fold with a phenotype and function equivalent to those of expanded peripheral blood lymphocytes**

  Azuma H et al.. *Exp Hematol* 2002, 30:346

The **FUTURE** of cancer immunotherapy

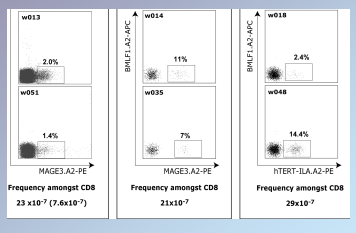
C. Can tumor-specific T cells be primed and expanded from naïve UCB lymphocytes?

- **Her2/*neu*-specific CTLs have been generated from UCB effective against human breast cancer cells**

  Wang P et al.. *Breast Cancer Res Treat* 2004, 83:15

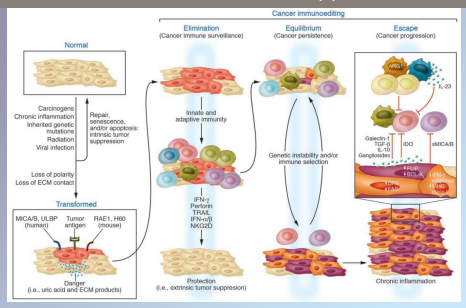
The **FUTURE** of cancer immunotherapy

C. Can tumor-specific T cells be primed and expanded from naïve UCB lymphocytes?



Karanikas V et al. (unpublished data)

The **FUTURE** of cancer immunotherapy



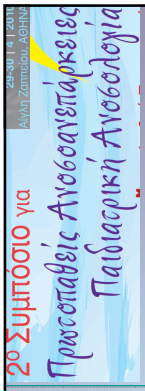
Cancer results from the development of a tumor cell escape phenotype sculpted by the immune system (during immunosurveillance)

The **FUTURE** of cancer immunotherapy

The issue……..

tumor immunogenicity against ***adoptively transferred*** *homologous* ***UCB lymphocytes****,*

might be ***sufficiently different*** *to when the tumors are seen by the host immune system*



Cord blood can be a source of anti-tumour specific T cell clones

Thank you for your attention

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