The innate immune system and cancer

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Society for Immunotherapy of Cancer

The following relationships exist related to this presentation:

None.

Outline

- **Innate immune system - definitions**
  - Pattern recognition receptors
  - Dendritic cells
  - NK cells
- **Innate immune sensing of cancer**
  - Inflamed versus non-inflamed cancers
  - Danger associated molecular patterns
  - Type I interferon
- **Manipulating innate immunity to combat cancer**
  - DC-based vaccines
  - Sipuleucel-T

Innate immunity

- Innate immune system
  - Provides initial recognition of self vs non-self
  - Comprised of *cells* (granulocytes, monocytes, dendritic cells and NK cells) and *proteins* (complement)
  - Recognizes non-self via pathogen-associated molecular patterns (PAMPs)
    - conserved structures (i.e. LPS, nucleic acids) in microbes
  - Pattern recognition receptors (PRRs) expressed on innate immune cells recognize PAMPs
  - Necessary for priming adaptive immune responses
  - Does not provide immunological memory (unlike the adaptive immune system)

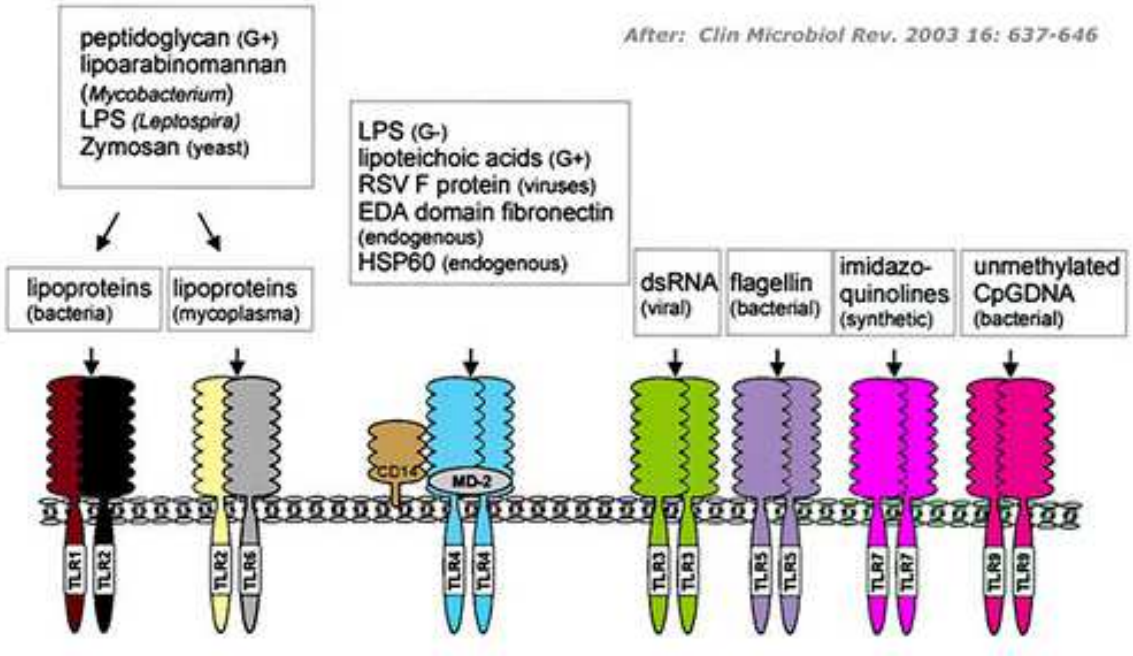
Innate immunity – on the front line of host defense

- Classes of PRRs
  - Toll-like receptors
  - NOD proteins
  - C-type lectin receptors
- Differential expression of PRRs on innate immune cells determines "functionality"

Receptor characteristic	Innate immunity	Adaptive immunity
Specificity inherited in the genome	Yes	No
Expressed by all cells of a particular type (e.g. macrophages)	Yes	No
Triggers immediate response	Yes	No
Recognizes broad classes of pathogens	Yes	No
Interacts with a range of molecular structures of a given type	Yes	No
Encoded in multiple gene segments	No	Yes
Requires gene rearrangement	No	Yes
Clonal distribution	No	Yes
Able to discriminate between even closely related molecular structures	No	Yes

Figure 2-13 Immunobiology, 7ed. (© Garland Science 2008)

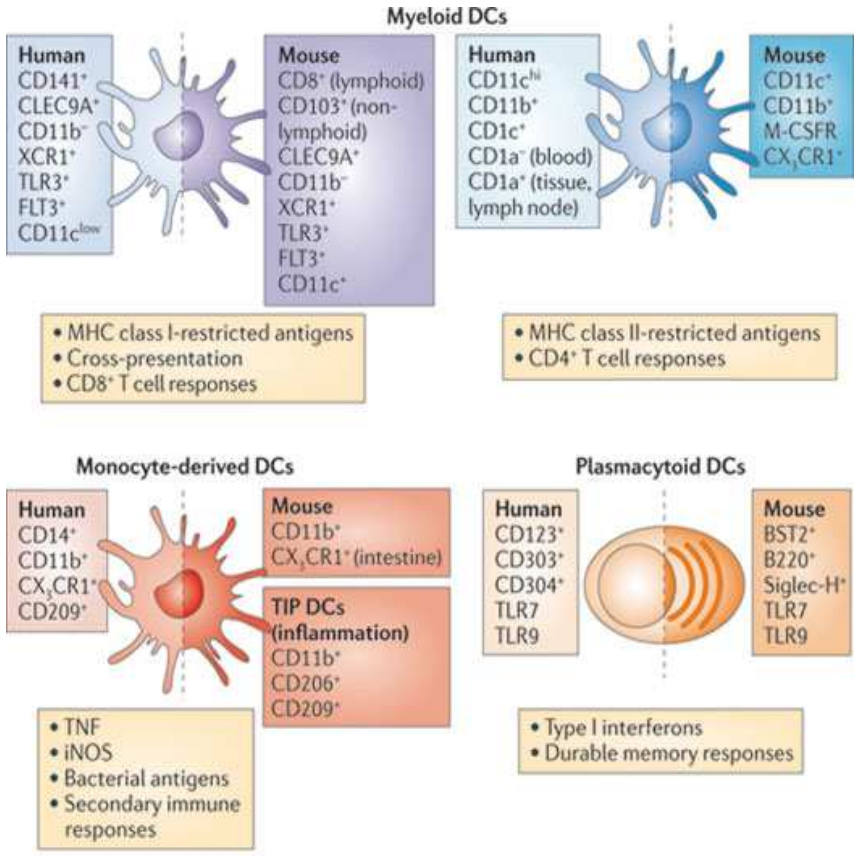
Innate immunity – the Toll-like Receptors



- TLRs originally described in Drosophila
  - Bruce Beutler received Nobel prize in 2011 for discovering that LPS bound TLR4
- 10 expressed TLR genes in humans
- Present on extracellular or intracellular membranes
- Binding of TLR by ligand induces signalling through MyD88 adaptor protein
  - leads to NF-kB activation
  - upregulation of MHC molecules
  - costimulatory molecules
  - cytokines (TNF-α, IFN-β, IL-12) and chemokines

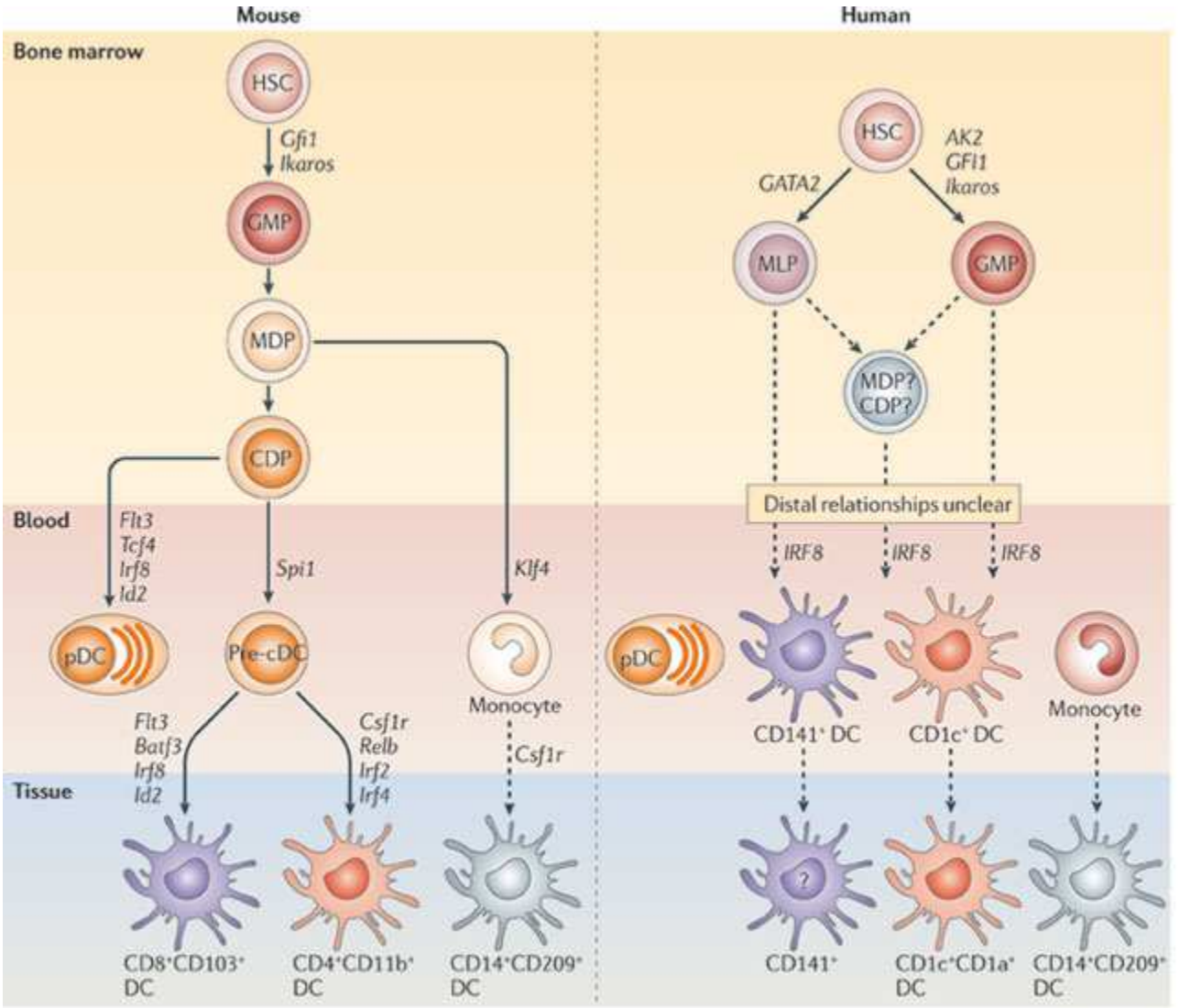
Innate immunity – dendritic cells

- Ralph Steinman (1970s)
  - DCs - hematopoietic cells specially equipped for antigen presentation and T cell activation
  - Nobel prize in 2011 for discovery of DC
- DC classified functionally in 2 groups
  - Conventional DC
    - Antigen presentation
    - T cell activation
  - Plasmacytoid DC
    - Type I IFN production
    - Important for immune responses against viruses



Colin et al. Nat Rev Immunol 2011

Dendritic cells – development

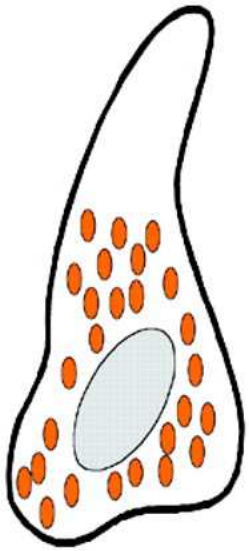


Colin et al. Nat Rev Immunol 2011

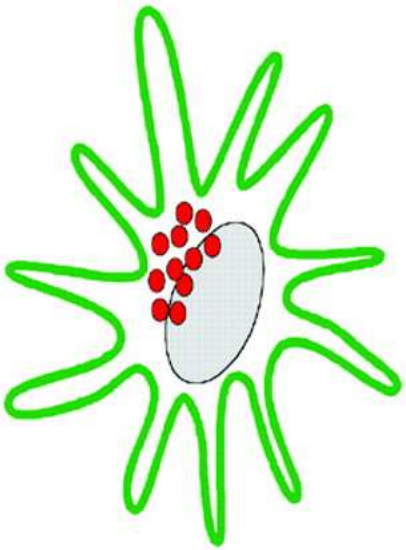
Dendritic cell activation

- DC receive signals through PRRs and other receptors (i.e. CD40) to become activated
  - Activation/licensing of DC results in:
    - MHC upregulation
    - Upregulation of costimulatory and cell adhesion molecules
    - Production of pro-inlfammatory cytokines (IL-12, TNF-α, type I IFNs
    - Alteration of chemokine receptor expression
    - Migration (to site of inflammation)
  - Only licensed DC will fully activate naïve T cells
  - Non-licensed DC can induce peripheral tolerance (T cell deletion or anergy)

Dendritic cell activation



Microbial products
TNF family



IMMATURE DC
capture of antigens

- adsorptive uptake, eg, DEC-205, FcR
- macropinocytosis
- phagocytosis: microbes, dying cells

MATURE DC
stimulation of T cell immunity

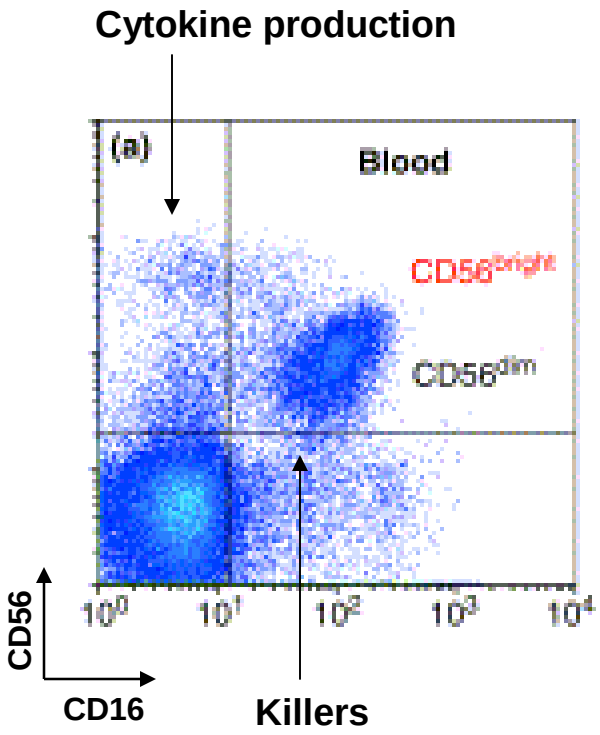
- CD40, CD86
- CCR7
- IL-12
- High MHC - peptide

TOLERANCE IMMUNITY

Steinman. PNAS 2002

Innate immunity – NK cells

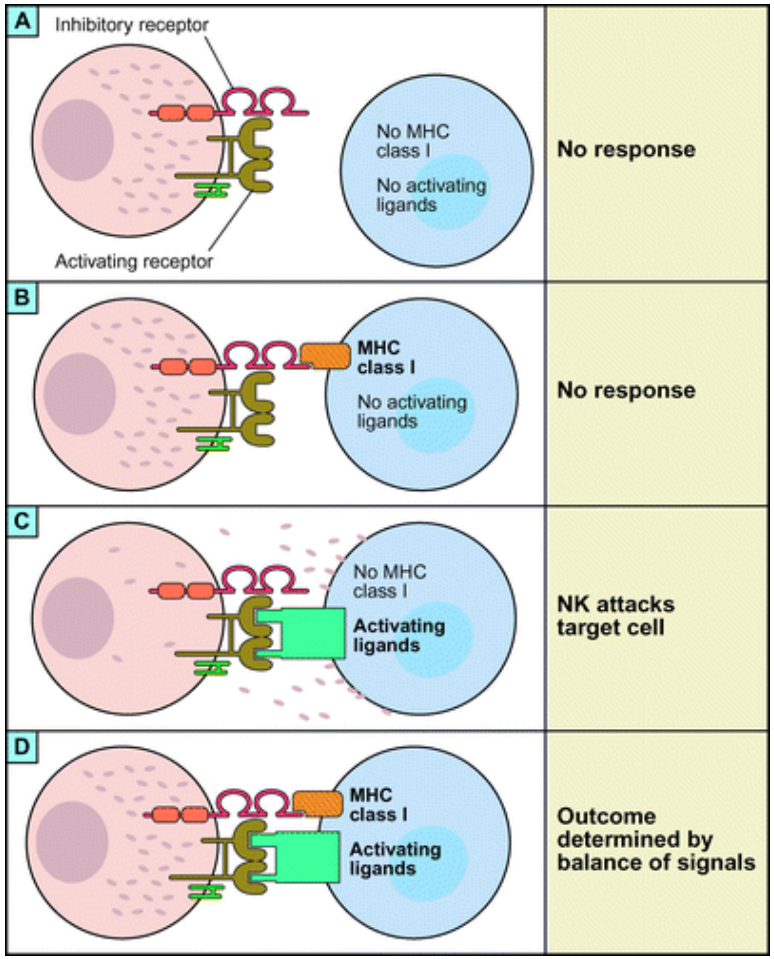
- Natural killer cells
  (NK cells – $CD3^{-}CD56^{+}CD16^{+/-}$ lymphocytes)
  - Develop in bone marrow from CLP
  - Circulate in blood
  - Able to kill lymphoid tumor cell lines in vitro without prior activation
  - Mechanism of killing – secretion of cytotoxic granules containing perforin and granzymes
    - Also express Fc receptors - effectors of ADCC
  - Important for early host recognition of infected host cells
    - HSV and Leishmania
  - NK cells are “activated” in response to Type I IFNs, TNF-α and IL-12
    - killing capacity and production of IFN-γ



Cooper et al. Trends Imunol 2004

Innate immunity – NK cell receptors

- 2 families of NK receptors
  - Killer lectin-like receptors (KLRs)
  - Killer cell Ig-like receptors (KIRs)
- Both KLRs and KIRs can act as activating or inhibitory receptors
  - Makes the study of NK cell activation complicated
  - Further complicated by the fact that KIR genes are also polymorphic
- Missing self hypothesis:
  - NK cells do not kill self cells due to MHC class I expression (MHC = major histocompatibility complex)
  - NK cell do kill target cells which lack MHC class I



Lanier L. Ann Rev Immunol 2005

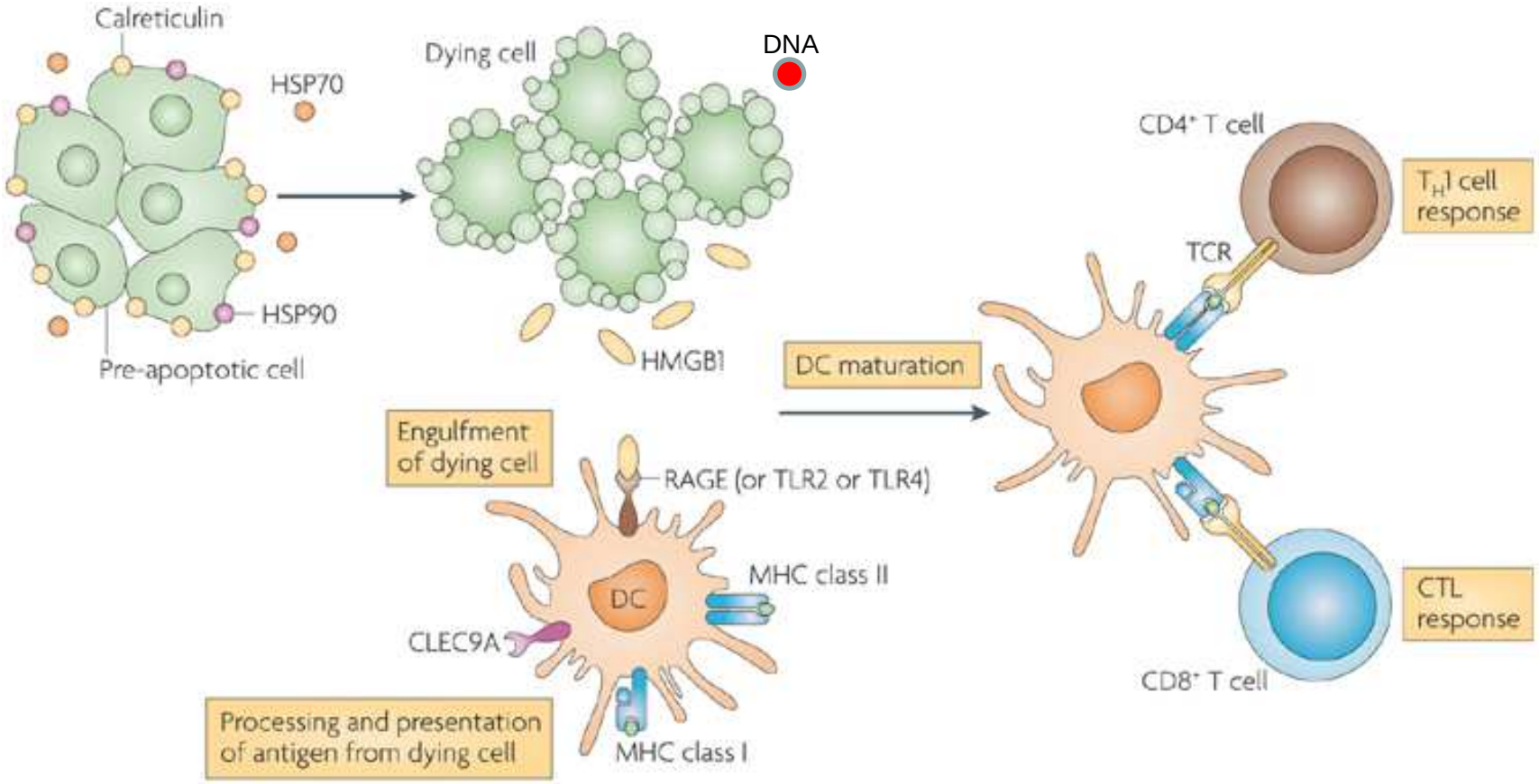
Innate immunity – NK cells and cancer

- NKG2D – Activating C-type lectin receptor on NK cells
  - Recognizes RAE proteins and MICA and MICB
    - RAE and MICA/B - MHC class I-like molecules expressed on virally-infected cells and some malignant cells
    - Recognition by NKG2D is a “danger” signal, resulting in “costimulation” of NK cells
    - Leads to lysis of targets and production of IFN-γ
- KIRs and graft-versus-leukemia effect following allogeneic SCT
  - Donor vs recipient KIR “incompatibility” provides GVL effect
    - Ruggeri et al Science 2002.
  - Similar analyses have confirmed that KIR mismatched allo-grafts led to decreased risk of AML relapse following alloSCT
  - Ongoing studies are evaluating the efficacy of adoptive KIR-mismatched NK cell therapy in myeloid leukemias

How cancer is sensed by the innate immune system

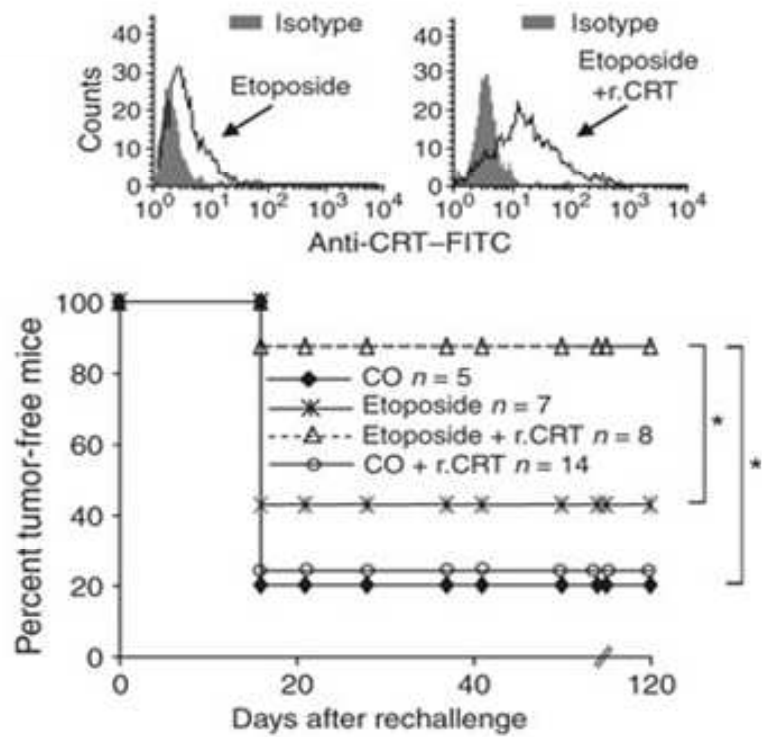
- Question: Most cancers originate in sterile tissues and in the absence of PAMPs.
- How then, are cancer cells “sensed” by the host innate immune system?

Dying cancer cells release “danger” signals

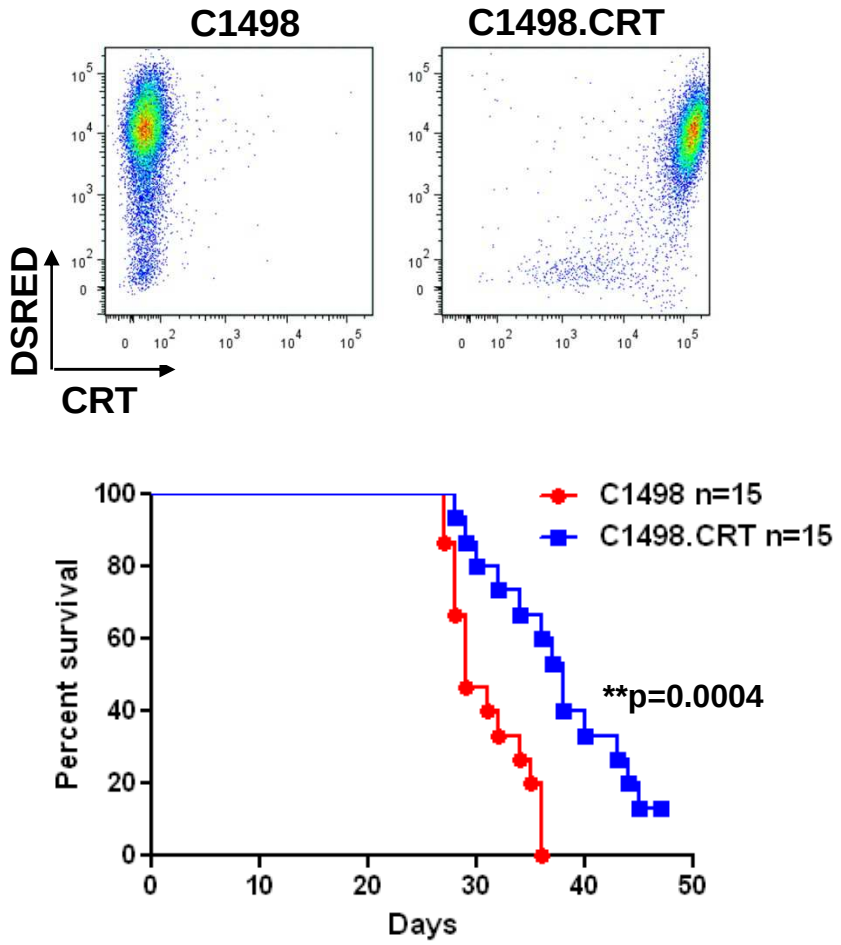


Green D et al. Nat Rev Immunology 2009

Calreticulin translocation in dying cancer cells stimulates immunity



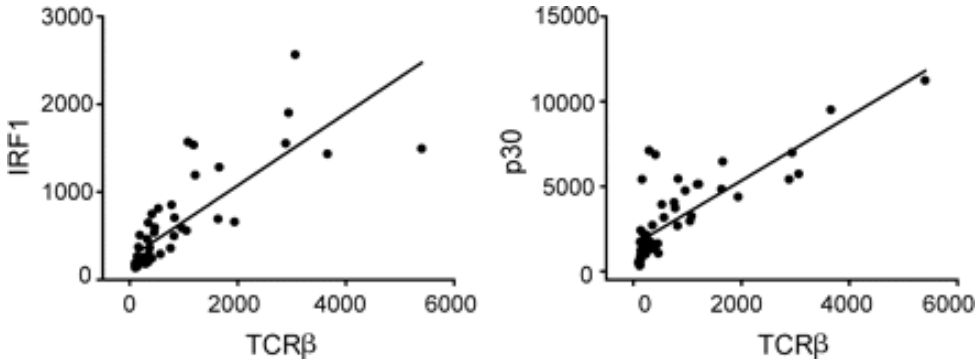
Obeid et al. Nat Medicine 2006

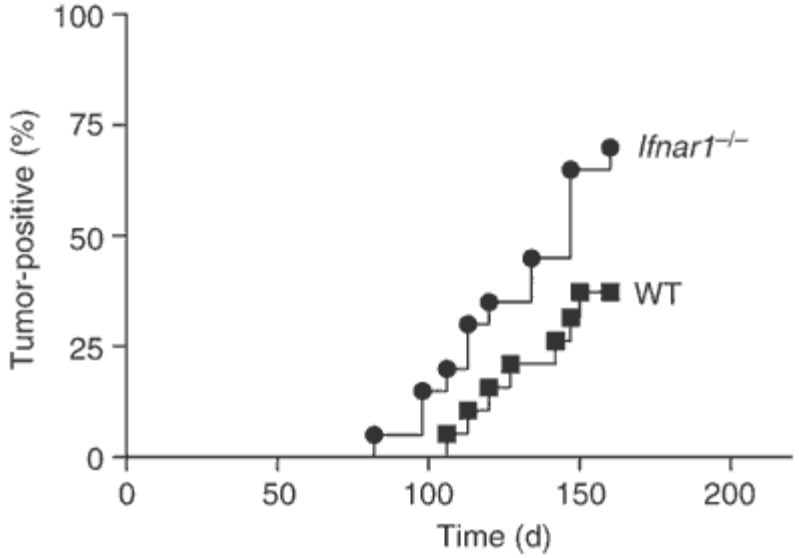


X. Chen - unpublished data

Type I interferons are critical for innate immune sensing of cancers

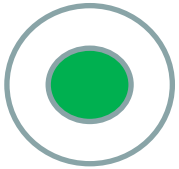
- Melanoma gene profiling showed that tumors infiltrated by $CD8^+$ T cells expressed a type I interferon transcriptional signature
  - Fuertes et al. JEM 2011
- Transplantable tumors fail to induce spontaneous T cell responses in type I IFN-$R^{-/-}$ animals
  - Fuertes et al. JEM 2011
- Increased tumor induction in a carcinogen-induced cancer model (MCA) in type I IFN-$R^{-/-}$ hosts
  - Dunn et al. Nat Immunol 2005
- Functional role of type I IFN signaling mapped to the dendritic cell compartment





How do tumors induce type I IFN by the host?

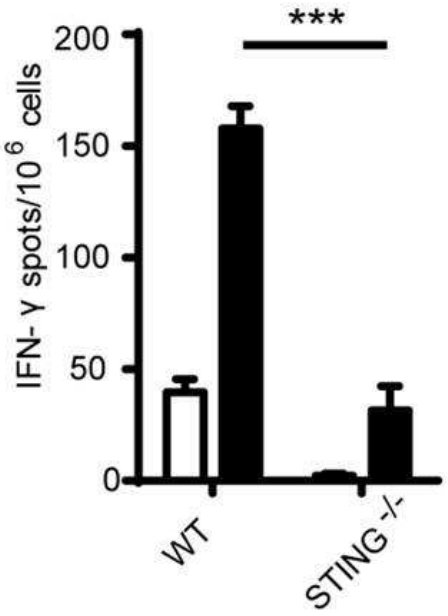
B16 melanoma



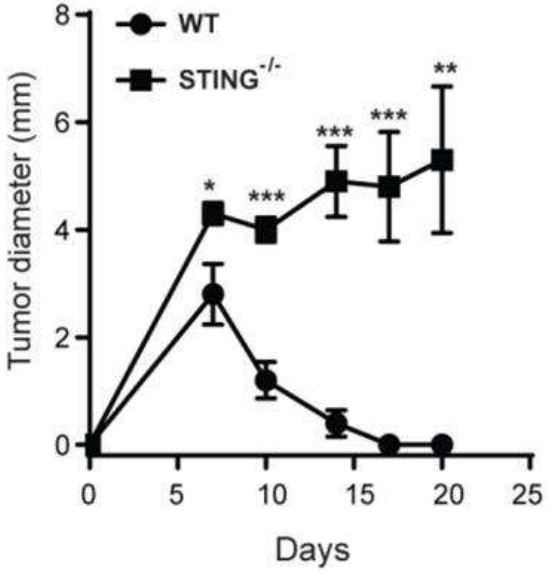
IFN-γ–producing $CD8^+$ T cell number by ELISPOT

- DNA from dying cancer cells may activate a DNA-sensing receptor called STING.
- STING activation leads to downstream induction of IFN-β production
- Decreased T cell responses and increased tumor growth in $STING^{-/-}$ hosts
- Sensing of tumor-derived DNA by host DC may be critical to generate adaptive immunity

T cell responses



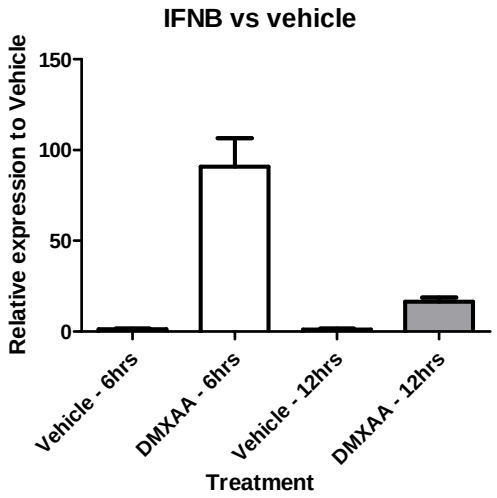
Tumor growth

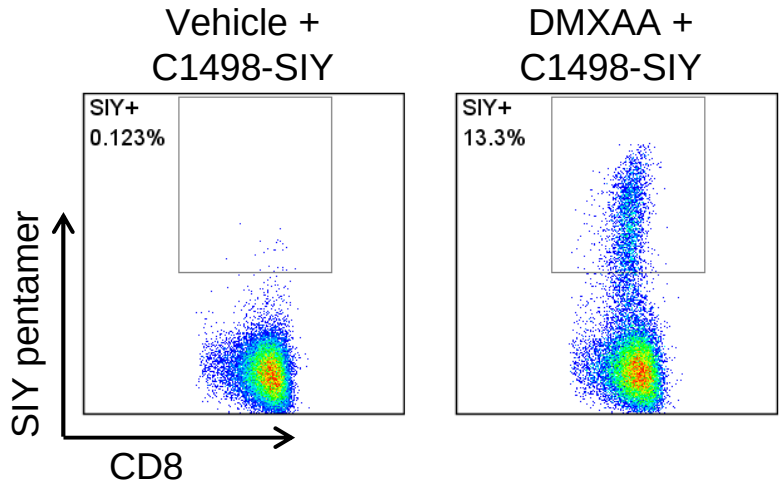


S. Woo –unpublished data

How do tumors induce type I IFN by the host?

- STING agonists (DMXAA) stimulate IFN-β production
  - Leads to host DC activation and enhanced tumor-specific T cell responses
  - STING agonists like DMXAA or cyclic di-nucleotides may be useful as vaccine adjuvants
  - Clinical trials in development

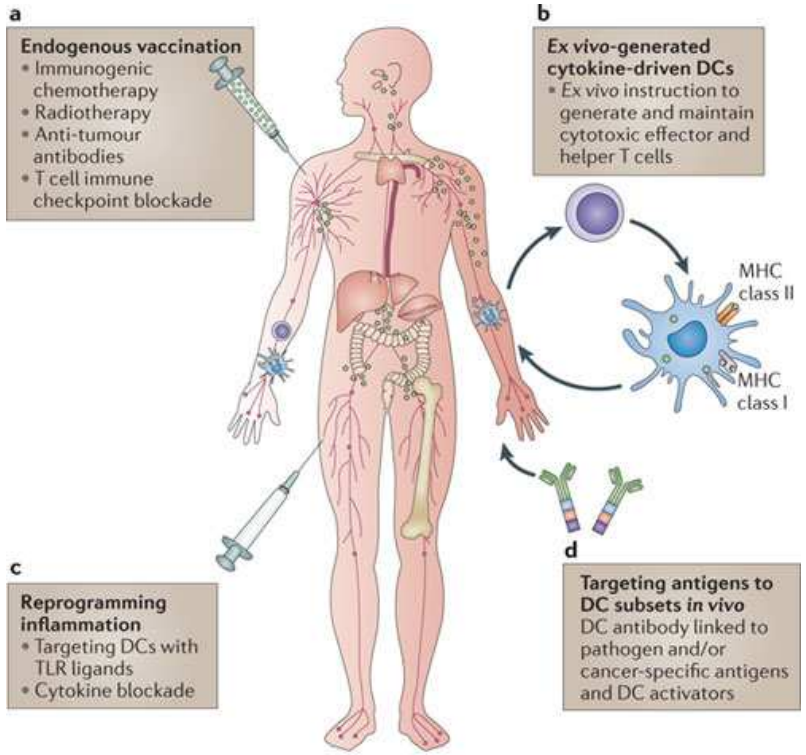




E. Curran – unpublished data

DC-based immunotherapy

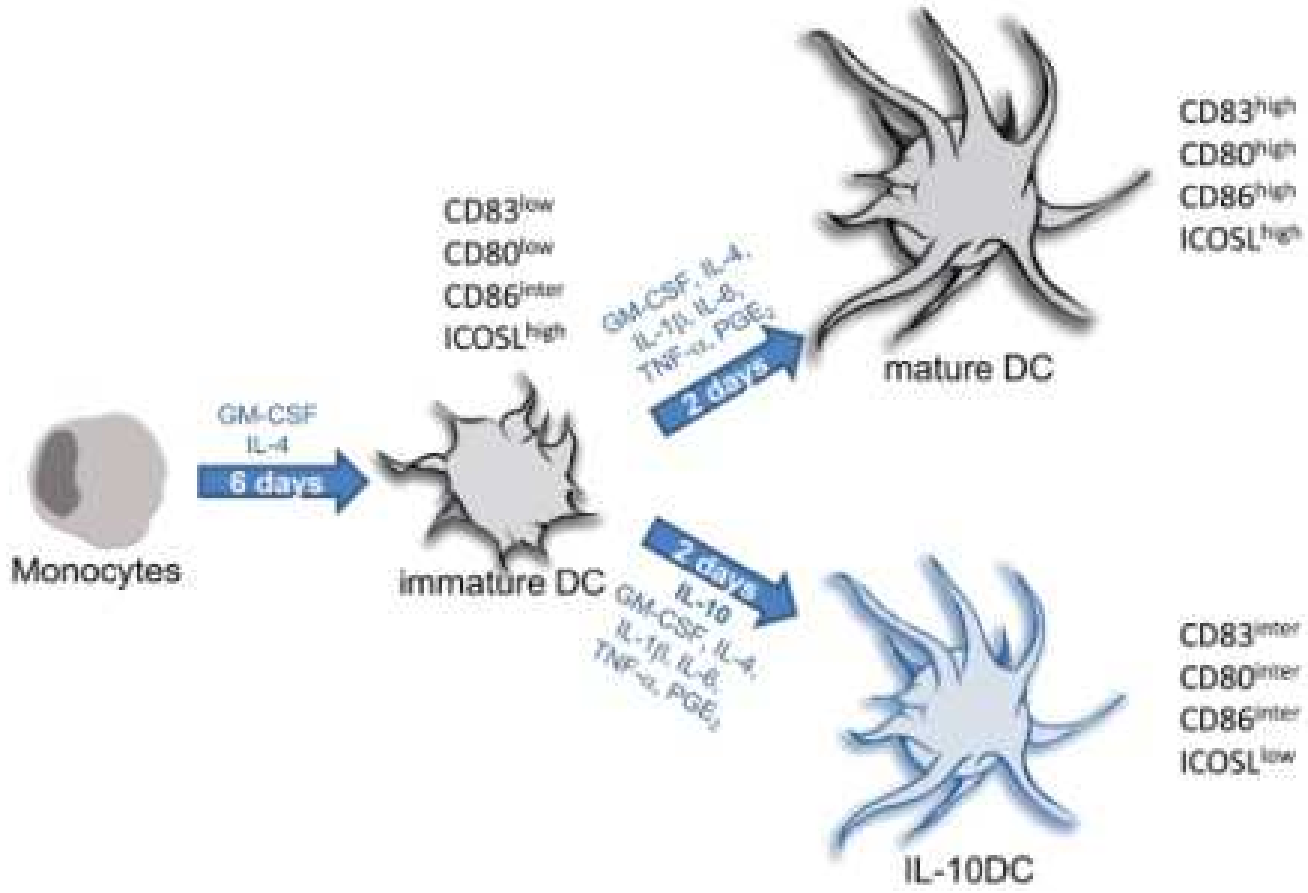
- Targeting DC activation in situ
  - Agonistic anti-CD40 mAbs
    - Beatty et al. Science 2011
  - Type I IFNs
  - TLR agonists (poly(I:C), CpG)
  - Targeting tumor proteins to DCs (DEC205)
  - Chemotherapy, radiation
- Autologous DC vaccines
  - Multiple approaches
  - Limited clinical efficacy
  - Sipuleucel-T as an example



Palucka et al. Nat Rev Cancer 2012

Nature Reviews | Cancer

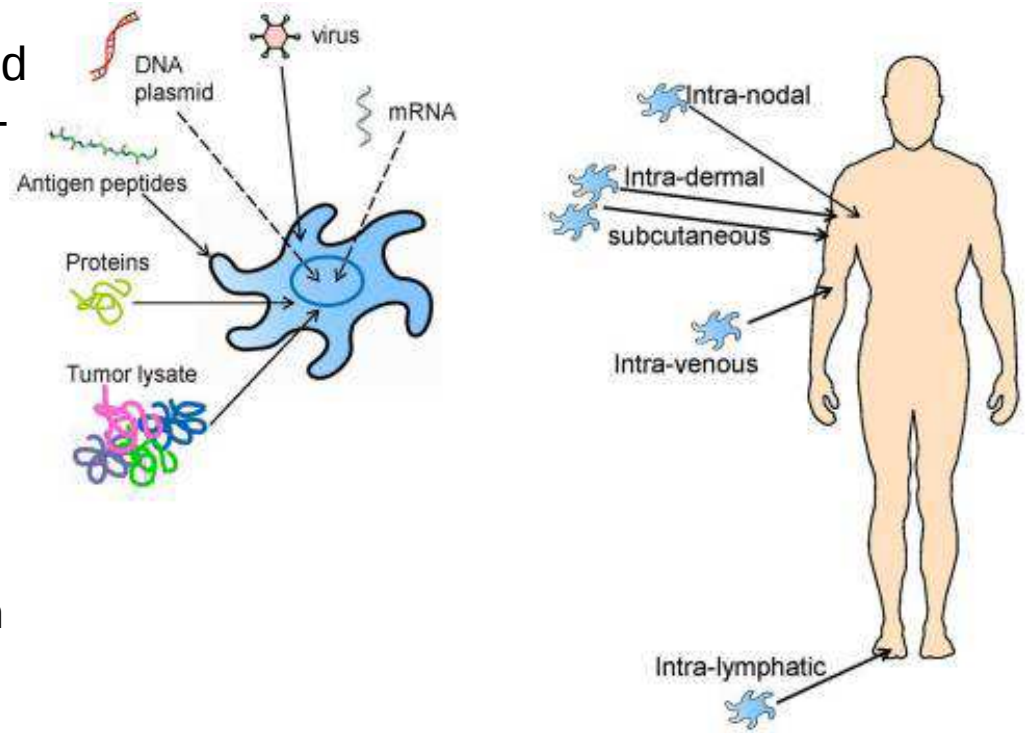
DC vaccines – generating DCs in vitro



Hubo M et al. Frontiers Immunol 2013

DC vaccines – Approaches

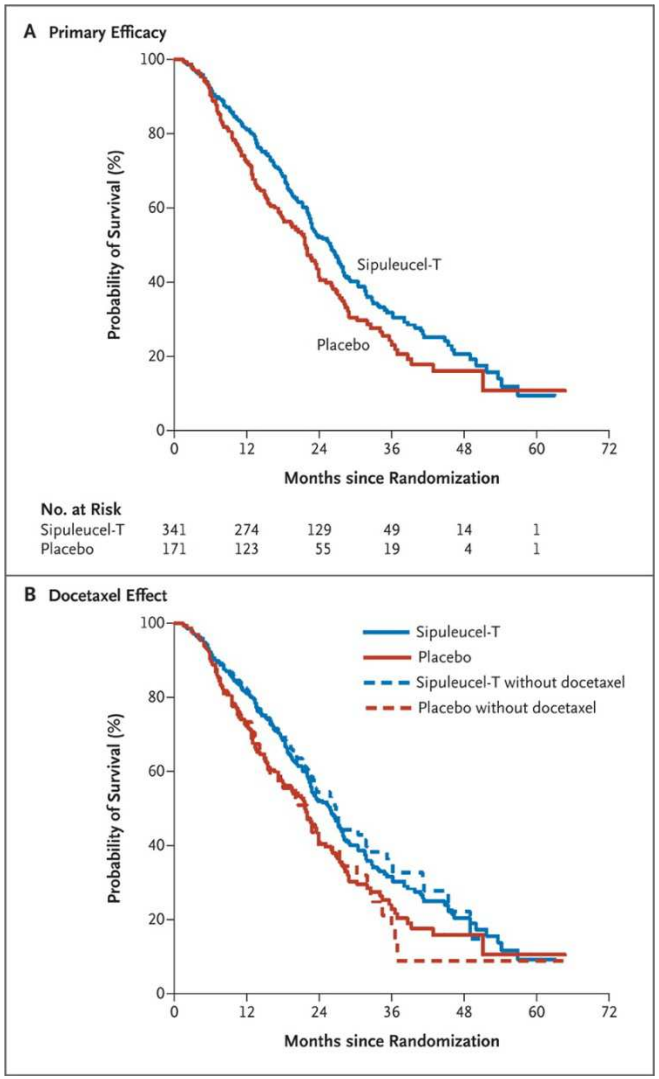
- First DC-based vaccine trial – 1995
- NCI analyzed ORR in vaccinated solid tumor patients on clinical trials (1995-2004)
  - 3.3% (all vaccines)
  - 7.1% (DC-based vaccines)
    - Rosenberg SA Nat Med 2004
- Randomized phase III trial of DTIC v peptide-pulsed DC vaccine for met melanoma stopped early
  - No difference in ORR (<6%) between arms
- Ongoing controversies in DC based immunotherapy
  - Antigen source (what is the best TAA)
  - Route of delivery (SC, ID, lymph node)
  - DC maturation protocol
  - Patient selection (biomarkers of response)



Butterfield, LH. Frontiers Immunol 2013

Sipuleucel-T

- Sipuleucel-T – DC vaccine (sort-of)
  - PBMCs activated with prostatic acid phosphatase (PAP) fused to GM-CSF
  - PBMCs (leukaphereis), cultured with PAP/GM-CSF and re-infused.
  - Patients with castrate-resistant prostate cancer received 3 infusions of Sipuleucel-T or placebo (IMPACT trial)
  - Increased survival by 4 months (How?)
  - Essential no objective tumor responses
  - No difference in PFS
  - FDA approved in 2010 (1st FDA approved cancer vaccine)



Kantoff PW et al. N Engl J Med 2010

Conclusions

- The innate immune system appears to have the capability of sensing a growing cancer in the host
- Danger molecules elaborated by cancer cells can be recognized by innate immune cells (DNA, calreticulin, HSPs, HMGB1)
- Stimulating innate immune cells can enhance anti-tumor immunity
- DC-based vaccines have had limited efficacy as immunotherapy for cancer
  - Combination approaches may prove more useful
- Further understanding of human dendritic cell biology may lead to improved translational applications for DCs in cancer