Role of Immunogenic Cell Death in Shaping Immune Response to Cancer

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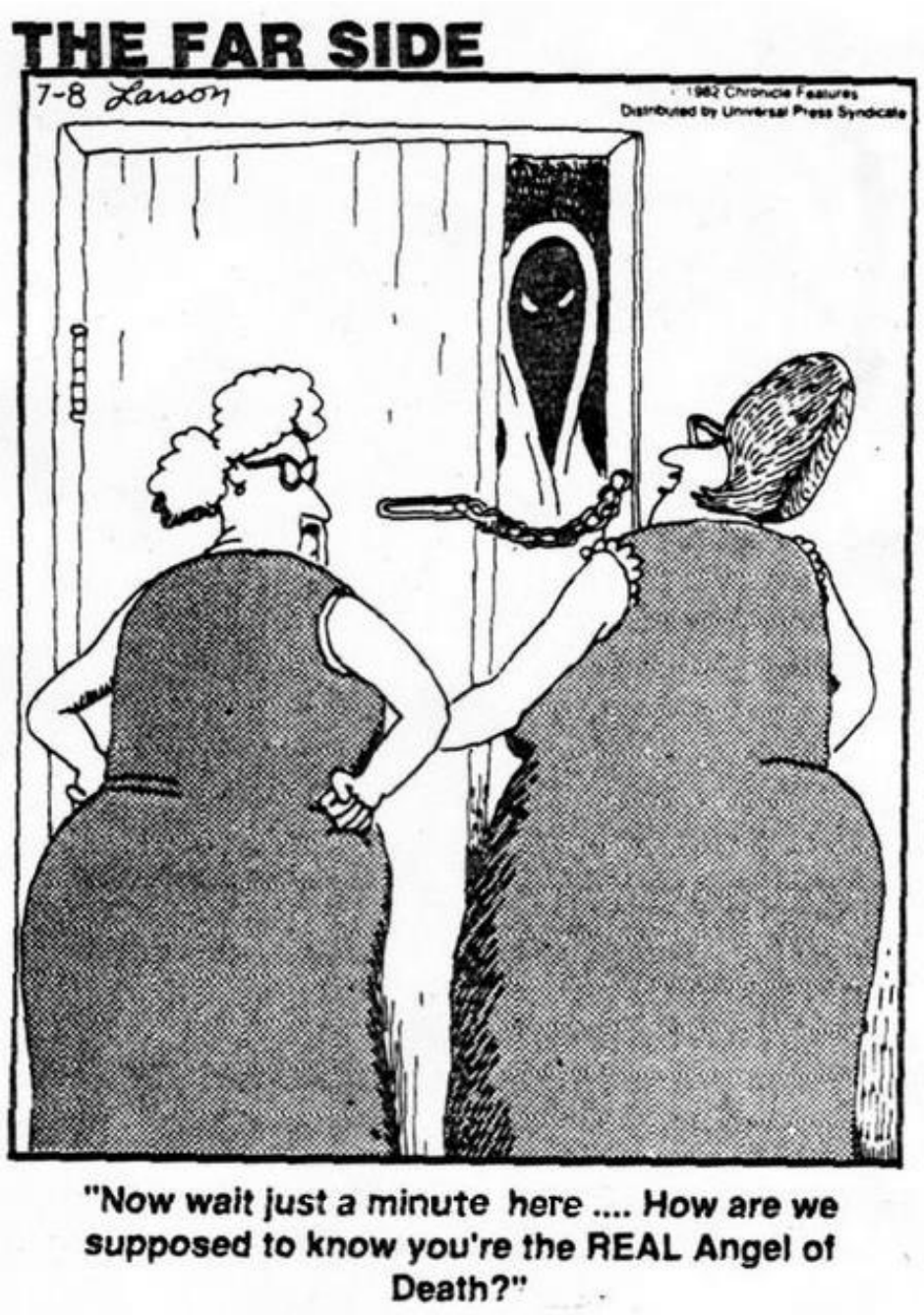
Disclosures

- NanoString Employee and Stockholder

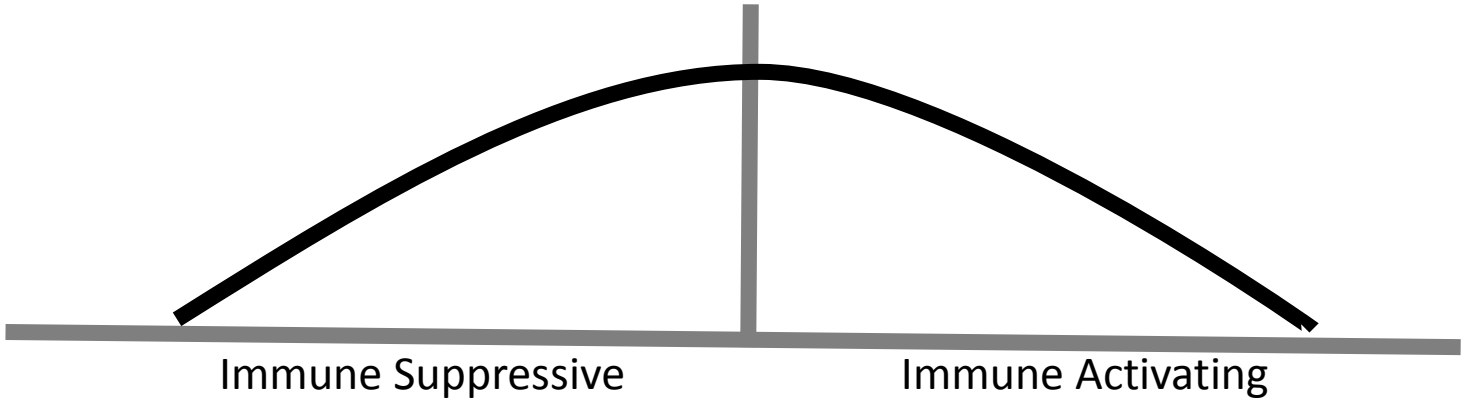
Definition of ICD

Spatiotemporally defined secretion of danger signals (including damage-associated molecular patterns (DAMPs)) from stressed cells in the tumor microenvironment that elevates the immunogenic potential of dying cells to activate protective immunological memory

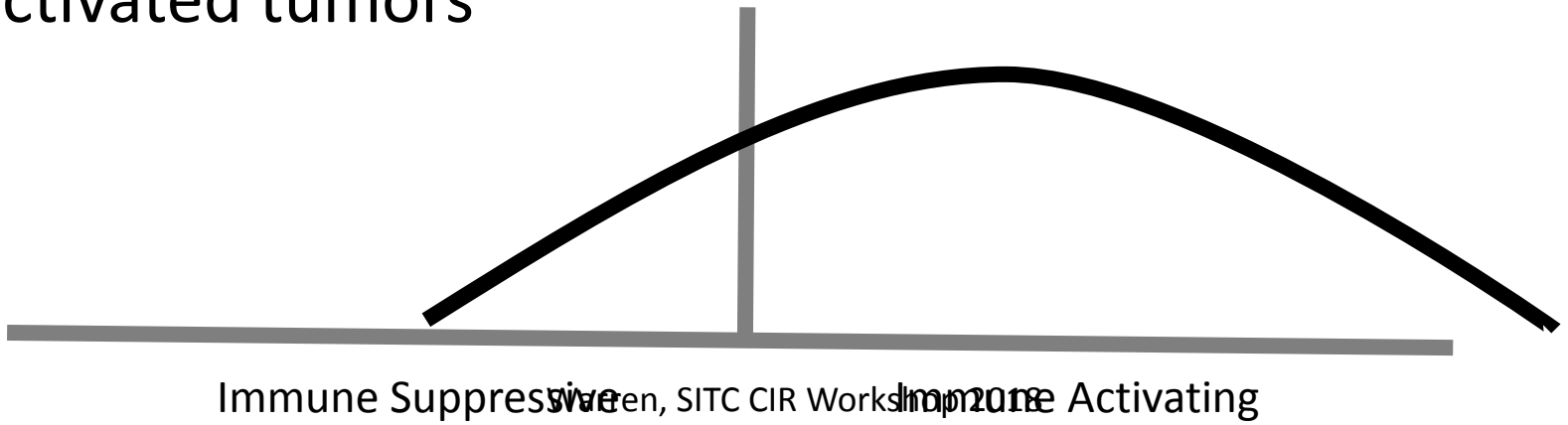


Goal of ICD: Shift Immune Response to State of Activation

- Untreated/nonresponding tumors



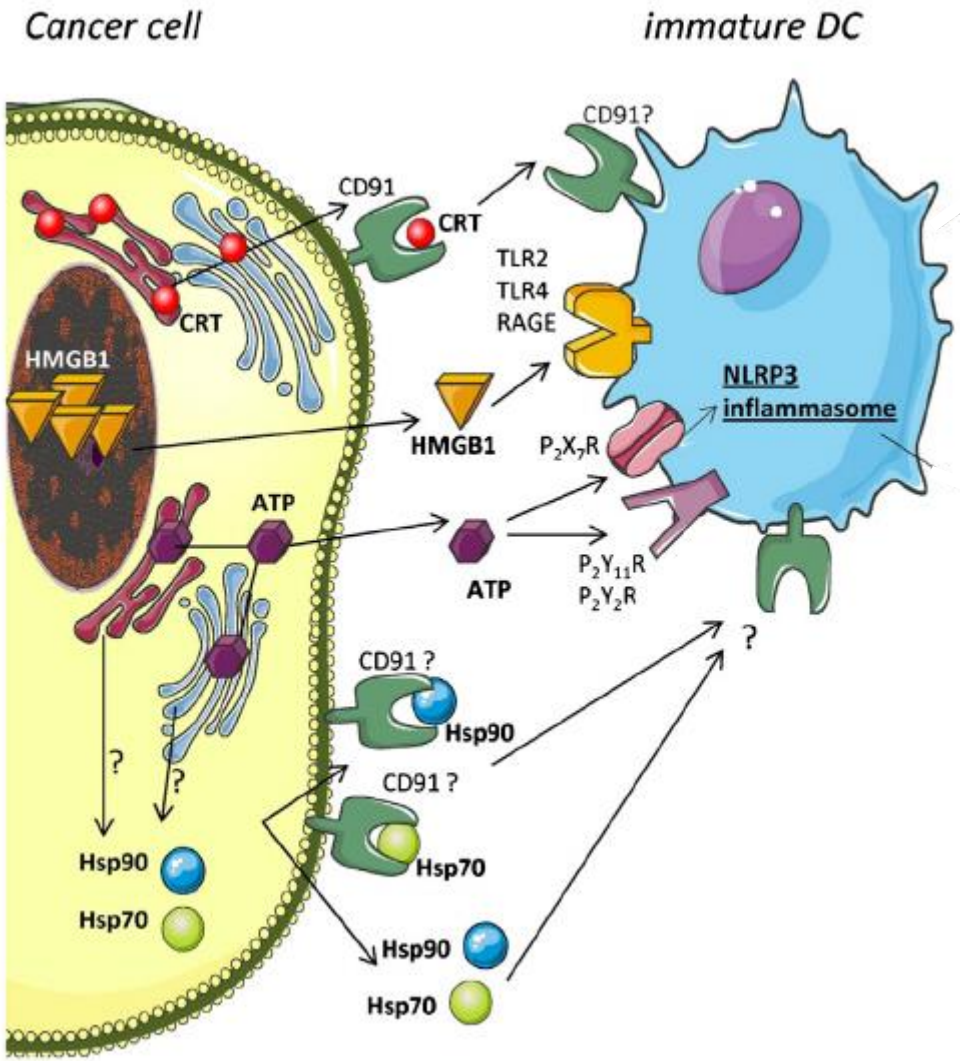
- ICD activated tumors



Overview of Discussion

- Definition and key features of ICD in tumor responsiveness
- Consequences of inducing ICD
- Measuring ICD
- Manipulating ICD therapeutically

Immunogenic Cell Death



How does the molecular events triggers by various cell death pathways shape subsequent immunogenicity?

- Timing, location, subcellular compartment of ligands can effect immunological activity
  - E.g. low vs hi ATP
  - E.g. ecto-CalR vs secreted CalR

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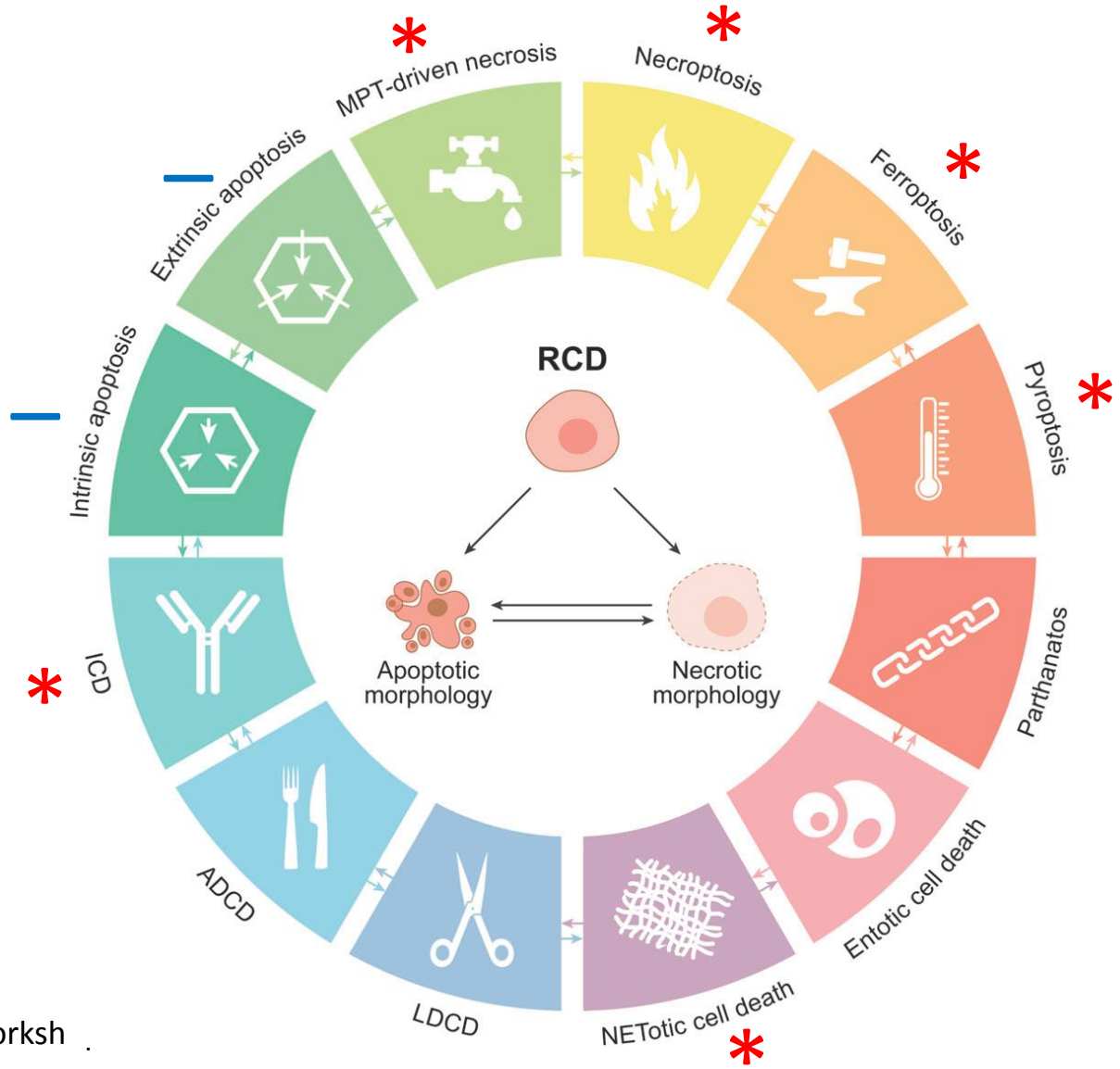
Dudek Cytokine and Growth Factor Res 2013

Immunogenic Cell Death

Which cell death pathways can induce immunogencity?

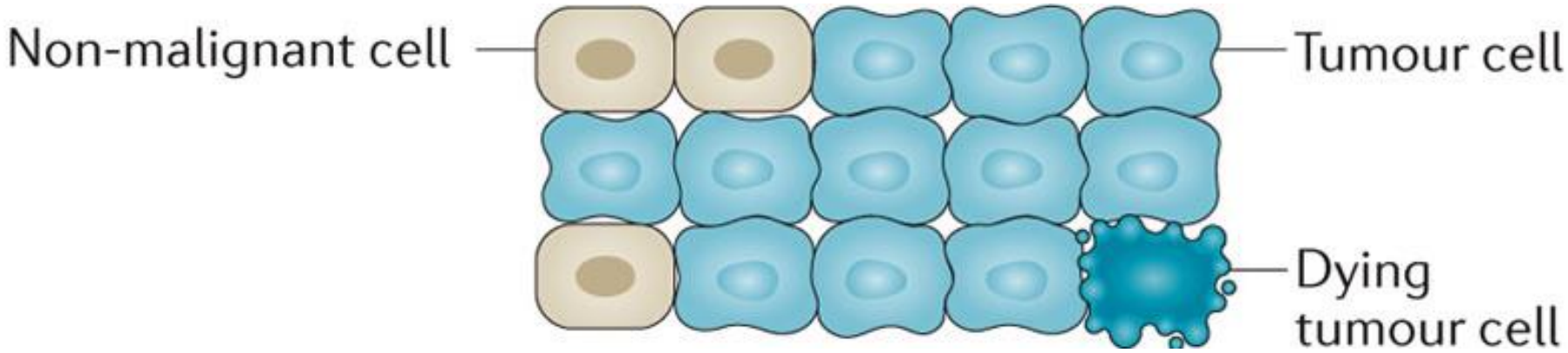
What is (are) the threshold(s) for triggering productive immune responses?

What are the environmental conditions that are required to initiate immune responses?



Galluzzi Nat Rev Immunol. 2016

Tumor microenvironment is more than just cancer cells



- ICD inducing agents will have effects on stromal tissue as well that will shape immune responses
- How does autophagy/disordered survival prior to ICD shape immune responses?
- Importance of Intact TME to understand consequences of ICD

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Galluzzi Nat Rev Clin Onc 2017

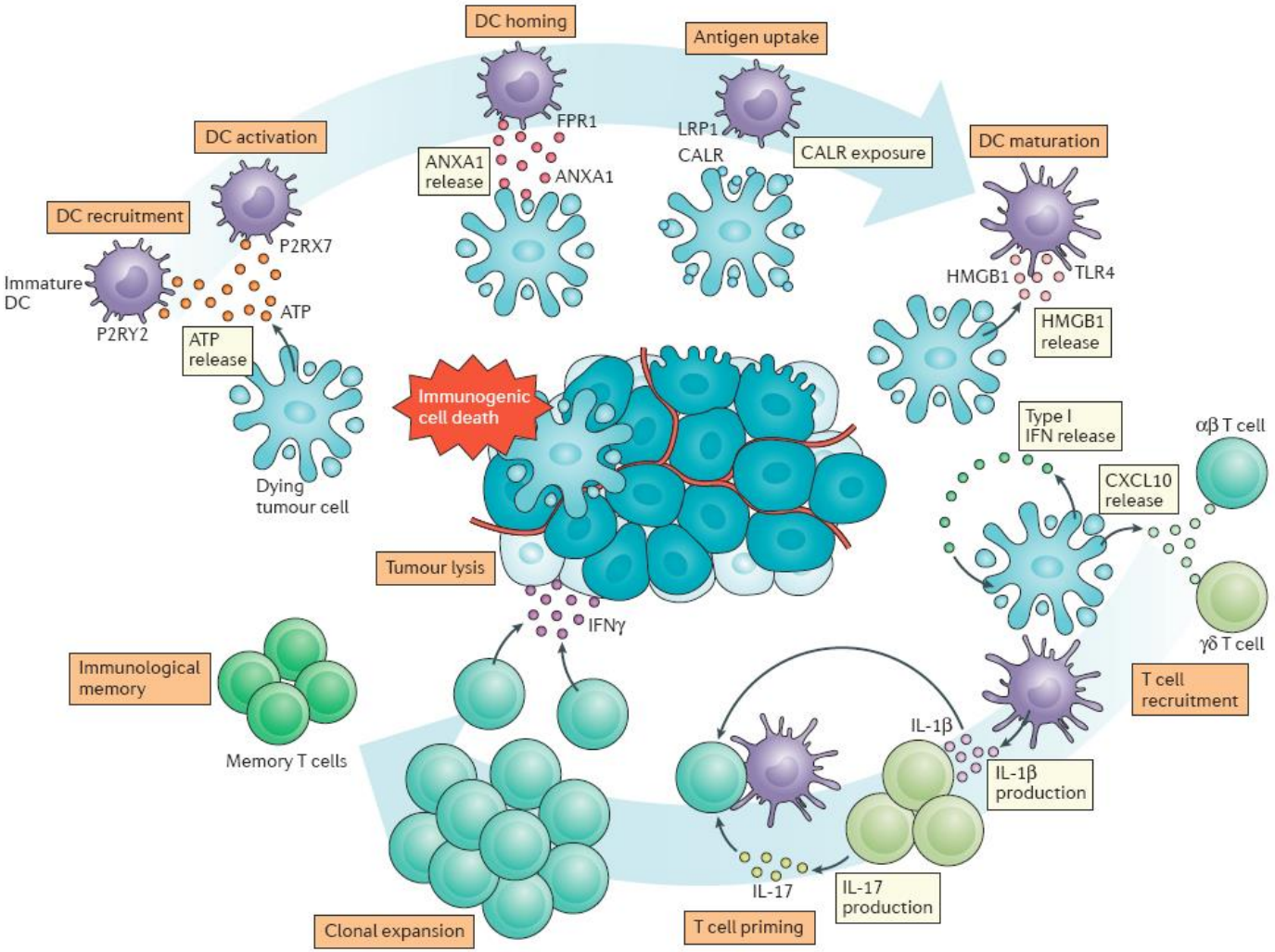
Threshold of ICD

- Different tumors have different thresholds for when cell death can become immunogenic
- Heterogeneity of tumors (location, stage, cellular makeup) can all shape response to ICD
- Threshold influenced by pretreatment and established tolerance – could lead to different treatment paths
- Therapies must be effective in majority of a defined population in order to be tractably developed

How can we measure cell death in vivo?

- Transient event – cells may display many death indicators without truly dying. But, dead cells are quickly eliminated from environment

Immunological consequences of ICD



- Is ICD <u>required</u> to initiate anti-tumor immune responses that generate long lasting memory?

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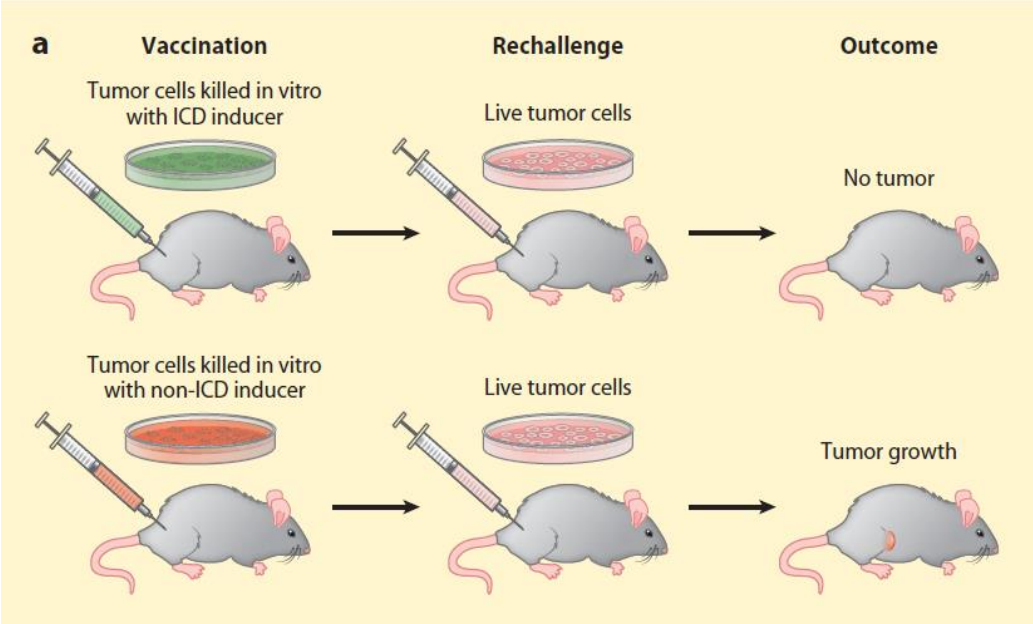
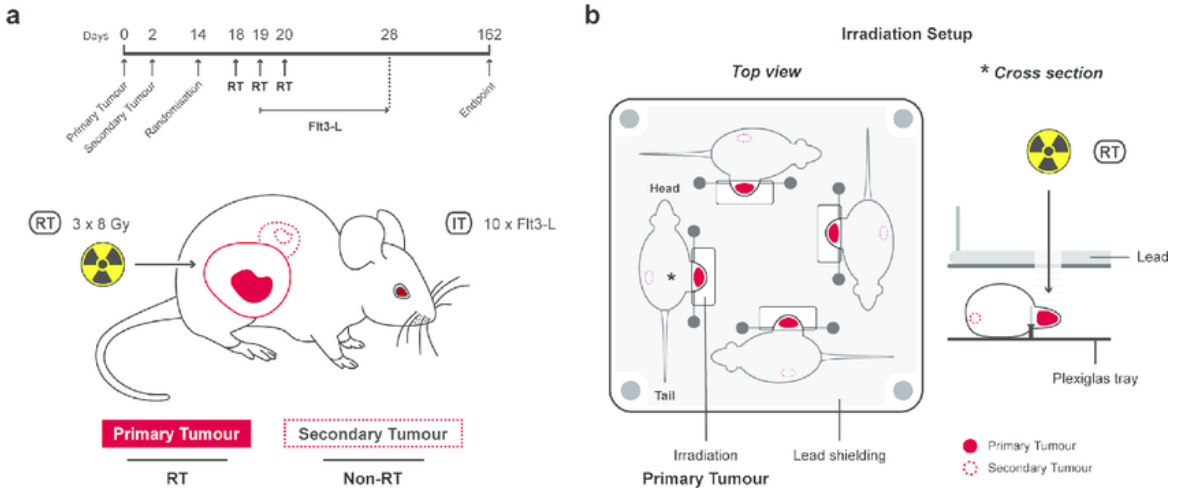
Measuring ICD in vivo



Vaccination Model: Dying cells induced into naïve mouse



Abscopal Model: Restricted to localized therapies

- Need for models that will allow us to evaluate cell death in context of established tumor-immune stalemate

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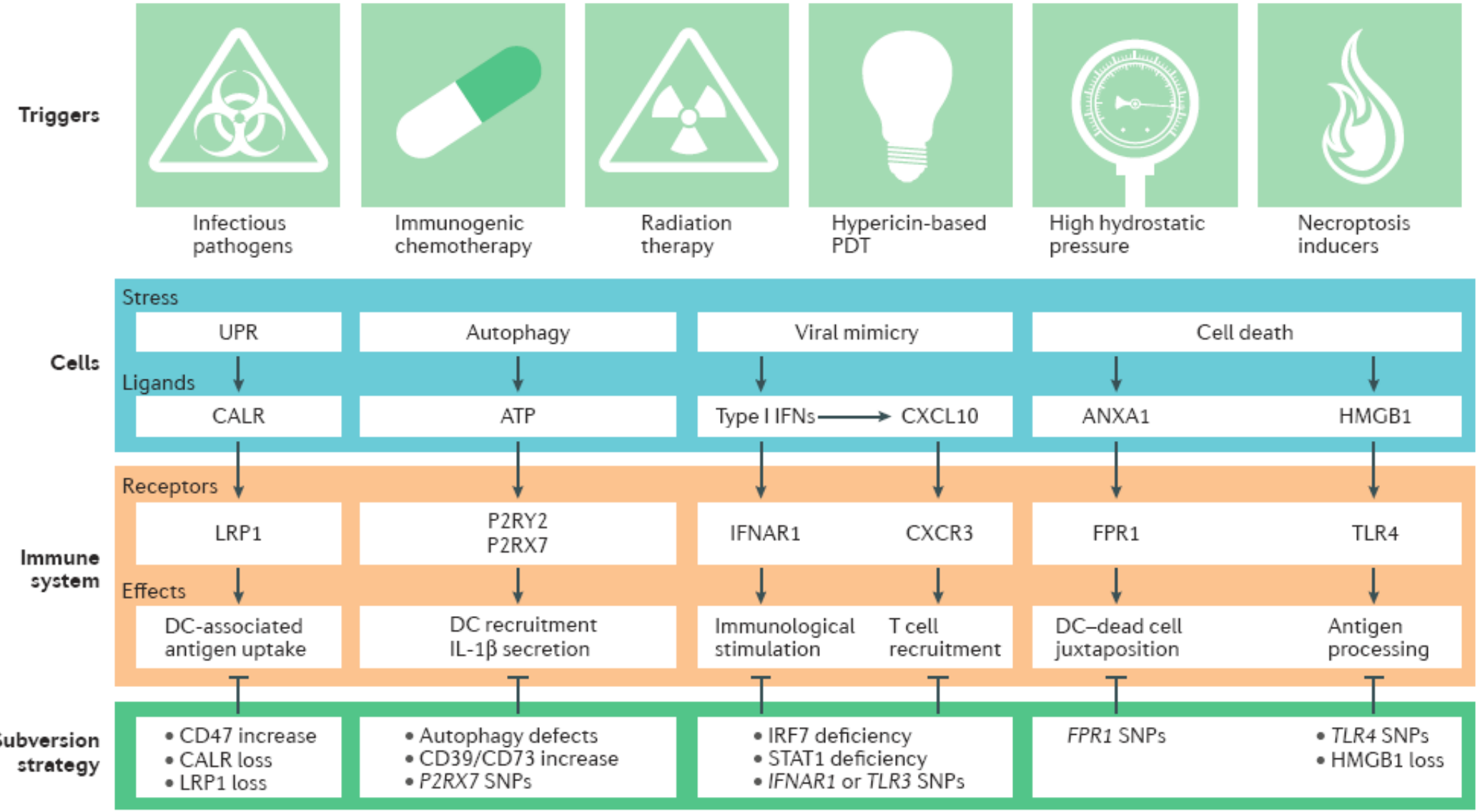
Kroemer, Galluzzi et al. – Annu Rev Immunol 2013
Habets et al. – PLoS One 2016

Autophagy

- How will intrinsic autophagy effect ICD?
- Can we leverage autophagic activity to enhance ICD?
  - Dependent on organ/clinical context
  - Autophagy of stroma can affect tumor survival and sensitivity to ICD
    - If stromal autophagy feeds tumor; inhibit autophagy
- Easy ways to modulate autophagy? Patients not eating before chemo

Induction of ICD



Galluzzi 2016
NR Immunol

Therapeutic manipulation of ICD

- What are the best therapeutic approaches to induce ICD?
  - How does one compare to the other?
- How can we improve them?
  - Timing, dose, fractionation, combinations
  - Often, optimal dose for ICD not the same as MTD
- How does ICD shape response to IO therapeutic agents? Does ICD change in response to IO or non-IO cancer treatment?

Robust Biomarker Strategy

Biomarkers to Capture:

- Amount and type of cell damage
- Ligands releases
- Abundance, identity and location of immune cells
- Functional immune response

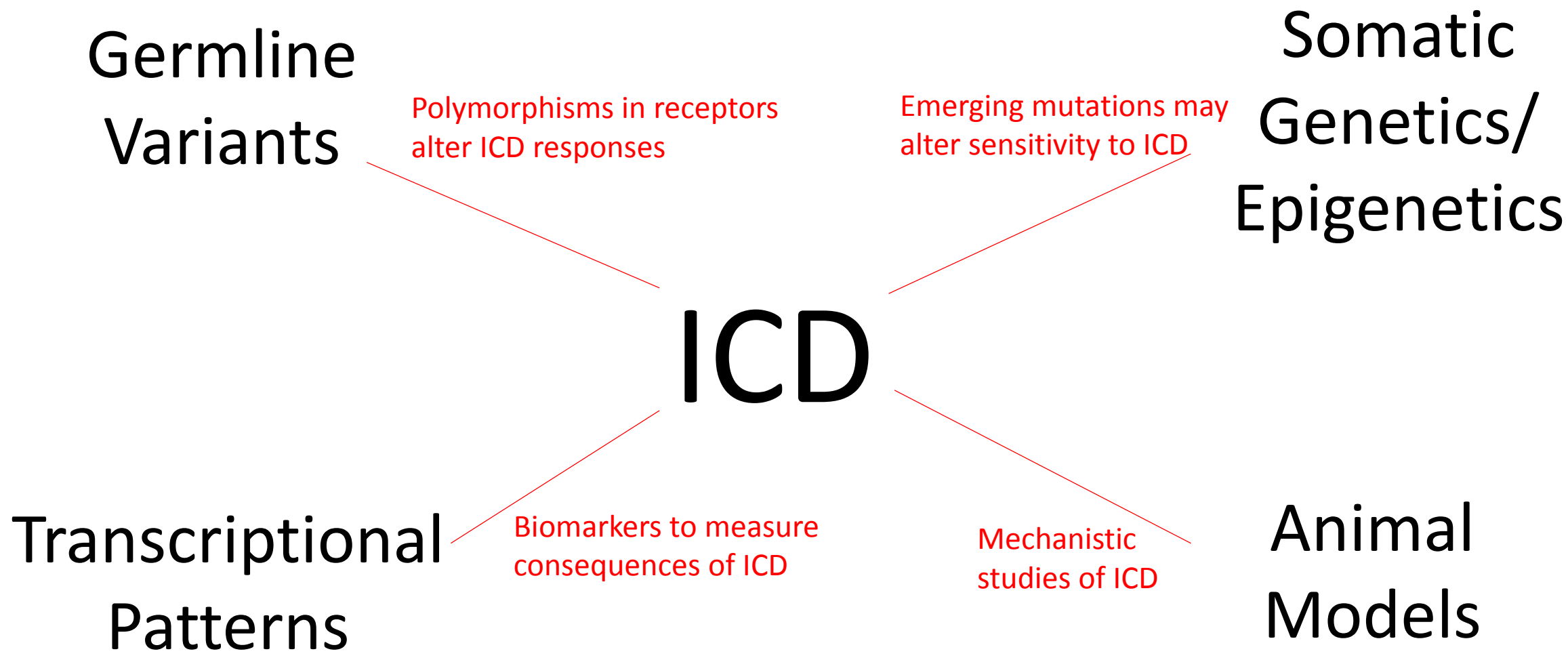
Routinely incorporate biomarkers into early phase clinical trials

Use biomarkers for reverse translational biology

Key Recommendations

- Establish better animal models, especially for therapeutics development
  - In vitro cultures fail b/c dose often nonphysiological
- Develop strategies to measure cell death in vivo
  - How to capture a transient event?
- Measure upstream and downstream markers of ICD
  - Especially events that drive final immune response
- Standardize biomarker panels to run across clinical trials and in animal models
  - Peripheral and local biomarkers
  - Biomarkers upstream of immune cells

ICD Intersection with Other Working Groups



Thanks

ICD Faculty
- Lorenzo Galluzzi
- Howard Kaufman
- Michael Lotze

Working Group 4 Participants

SITC Cancer Immune Response Steering Committee

SITC Staff!

Challenges for the Field

- Establish *in vitro* and *in vivo* models of ICD to characterize molecular components of ICD initiation (e.g. *in vitro* reconstitution of ICD activation) and cellular models of immune response (e.g. via *in vivo* imaging)

- Design and execute studies to permit direct, in vivo comparison of different mechanisms of inducing ICD and consequences on anti-tumor immunity

- Identify gold-standard biomarkers of ICD and incorporate into routine clinical trials testing

Initiation of ICD

- How (and when) is ICD initiated in tumors? What changes occur within the tumor AND immune cells upon initial activation of ICD to propagate the signal?

- Are there changes in abundance or localization of activating ligands? Which receptors are critical for the process? Which signals and antigen delivery need to be coordinated? Which antigen presenting cells (CD141+BATF3+ DCs?) are necessary within the tumor microenvironment?

- What types of cell death initiate ICD? Does the type of cell death influence the distribution or context of neoantigens presented within tumors? What are the immunologic consequences of apoptosis, necrosis, netosis, pyroptosis, necroptosis, ferroptosis, and autosis?

- How does programmed cell survival (autophagy) promote the disordered tumor microenvironment (TME)?

Monitoring effects of ICD

- Are their biomarkers of ICD that can be leveraged in translational research?
- What are the peripheral blood biomarkers associated with initiation of ICD or evidence that an immunogenic response has been provoked? (e.g. CD8:Treg ratio; neutrophil: lymphocyte ratio; T-cell repertoire and dominant personal clonotypes)
- Can circulating cell free DNA/RNA be used to monitor for ICD in response to therapy? Are there biophysical characteristics of tumor-associated DNA (size, associated histones/HMGB1, etc) that can be exploited as indicators of ICD?
- How will biomarkers of ICD be leveraged to improve therapeutics development or change treatment options for patients?

ICD Shaping of Immune Response

- How does ICD shape the balance between tolerogenic and inflammatory immune response?
- What are the cells involved in initiating and responding to ICD?
- Which signals promote immune reactivity and effective adaptive immune response? Which signals promote wound healing and a pro-tumorigenic response?
- Does the character or function of ICD evolve from nascent, early tumors to tumors which are detectable by patients and physicians?
- Are there signals detectable in the peripheral blood T-cells or serum which signal ICD and tumor presence for early detection and following tumor response to treatment?