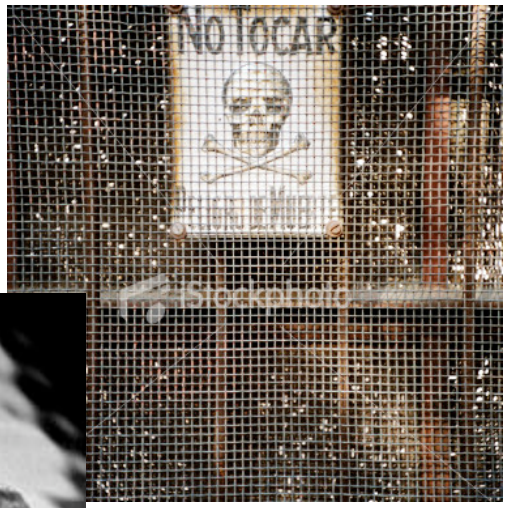
The Danger Theory

What is it?



IN A FULLY H-2 INCOMPATIBLE CHIMERA, T CELLS OF DONOR ORIGIN CAN RESPOND TO MINOR HISTOCOMPATIBILITY ANTIGENS IN ASSOCIATION WITH EITHER DONOR OR HOST H-2 TYPE*

By POLLY MATZINGER and GALADRIEL MIRKWOOD

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Despite much recent interest and effort, the role played by major histocompatibility complex products in the regulation of T-cell responses remains perplexing. In 1972 it was observed that mouse T and B cells would only cooperate in an antibody reponse if they shared certain regions of H-2 (1). Subsequently, H-2 gene products were also found to be involved in cytotoxic T-cell reactions, and it was postulated that the killer T cell must bear H-2 molecules in common with those of its target in order to effect lysis (2–6). Later studies with radiation chimeras showed that this is not the case, but that the H-2 region must be shared between the cells used to stimulate the response and the targets; a killer T cell that was itself H-2 type A, after having grown up in an (A × B)F_1 could be stimulated to lyse H-2 type B virus-infected or trinitrophenyl-modified targets (7–9). Such chimeras were also found to contain A type helper T cells which can cooperate with B type B cells (10). It was then postulated that T-cell precursors "learn" to recognize the H-2 type of the host as self (11). Recent evidence shows that the host H-2 type of a chimera does distinctly influence the specificity of the responding T-cell population (12, 13) and that it is the H-2 type of the thymus that is important (13). Most of this work has been done with semiallogeneic chimeras (e.g., "A" bone marrow into an irradiated [A × B]F_1, or [A × B]F_1 bone marrow into an "A" or [A × C]F_1) where the responses were very strongly restricted by the H-2 type of the host. A small number of completely allogeneic chimeras was tested (e.g., "A" bone marrow into "B") and appeared to be immunoincompetent. The virtually absolute restriction of the semiallogeneic chimeras as well as the immunoincompetence of the fully allogeneic chimeras has led to much speculation and has been quoted as suggestive evidence for the dual recognition model of T-cell receptors (13).

We report here that in contrast to the results with virus-infected mice, fully allogeneic chimeras made by repopulating irradiated BALB/c(H-2^d) mice with BALB.B(H-2^b) bone marrow are well able to respond to minor histocompatibility

* Supported by U. S. Public Health Service grants CA 09174 and AI 08795.

[1] *Abbreviations used in this paper*: B10, C57BL/10Sn; C, BALB/c; C.B, BALB.B; C.K., BALB.K; Con A, concanavalin A; CTL, cytotoxic T lymphocyte; H antigen, histocompatibility antigen.

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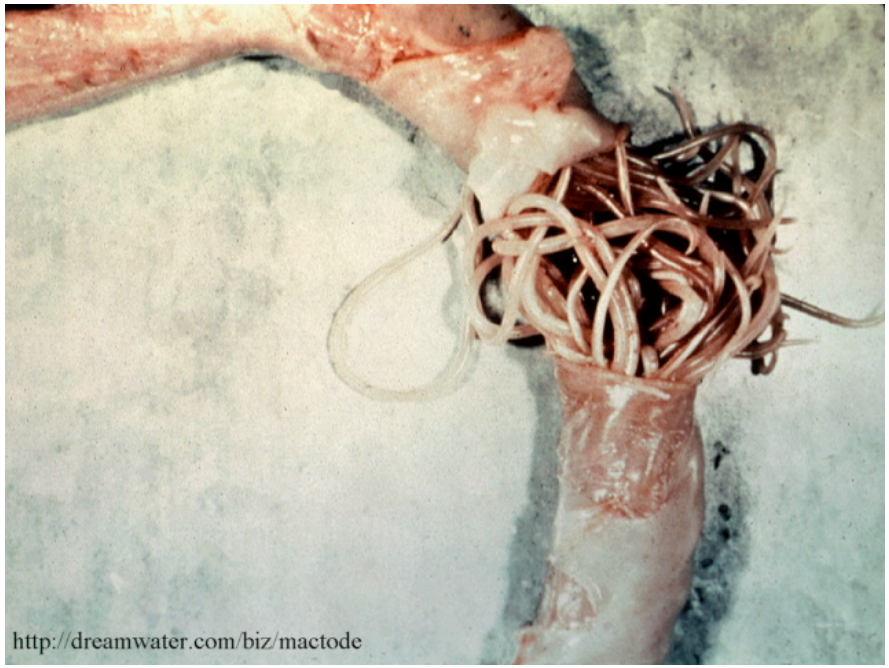
Danger Theory

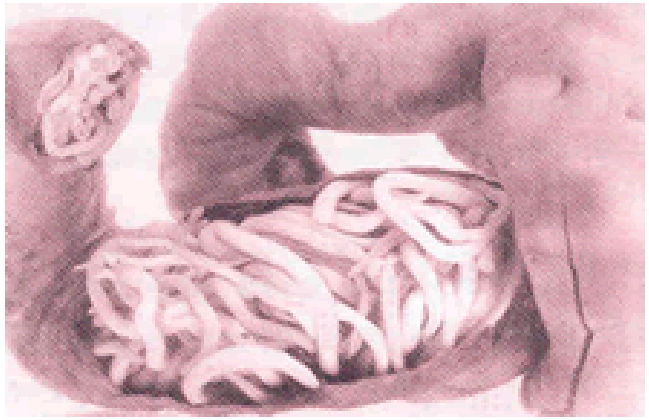
What is self?

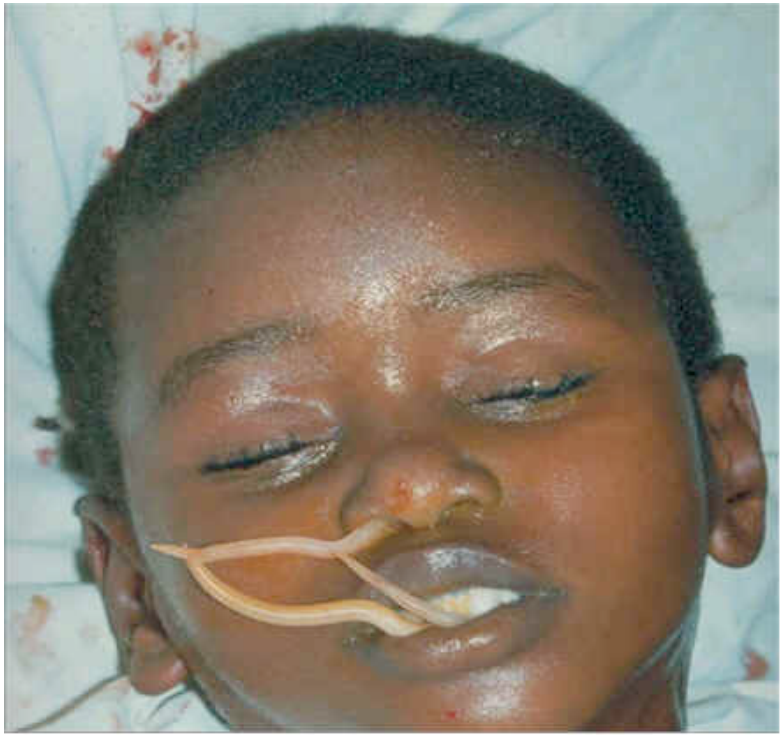
- **Everything encoded by the genome?**
- **Everything under the skin, including structures encoded by commensal genomes.**
- **Any tissue accessible to lymphocytes (excludes privileged sites, *e.g.,* brain, cornea, and testes)?**
- **For T cells the set of peptides complexed with MHC molecules (that don't elicit a response)?**
- **For B cells, cell surface and soluble molecules (to which they would not respond)?**
- **The set of bodily proteins that exist at a concentration above a certain threshold?**

A theory put forth to address many unexplained immunological phenomenon…

- What happens when 'self' changes?
  - Puberty
  - Lactation
  - Aging
- Why are fetuses not rejected?
- Why do we fail to make immune responses to vaccines composed of inert foreign proteins unless we add noxious substances (adjuvants)?
- Why do we fail to reject tumors even though they express new proteins (antigens)? Immune surveillance does not exist.
- Why do most of us harbor autoreactive lymphocytes without any sign of autoimmune disease, while a few individuals succumb (most also carry antibodies reactive to keratin and DNA)?
- Why do we respond to some pathogens and not others?
- Why are some transplants *e.g.*, liver more likely to survive than other types of tissue?
- What mechanism can induce tolerance to antigens found only on skin, kidney, or liver cells?
- How are we tolerant to the 55,000 different bodily proteins, plus 10^{12} potentially different B and T cell idiotypes and still be able to respond to foreign antigens.

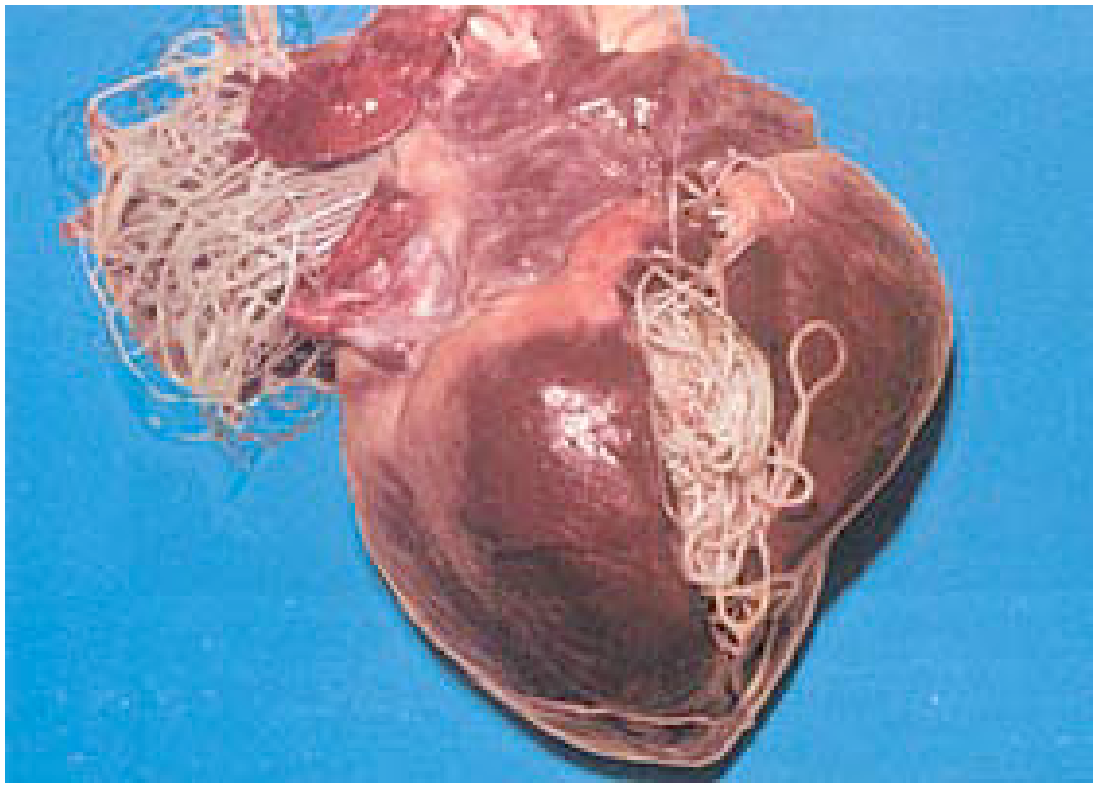




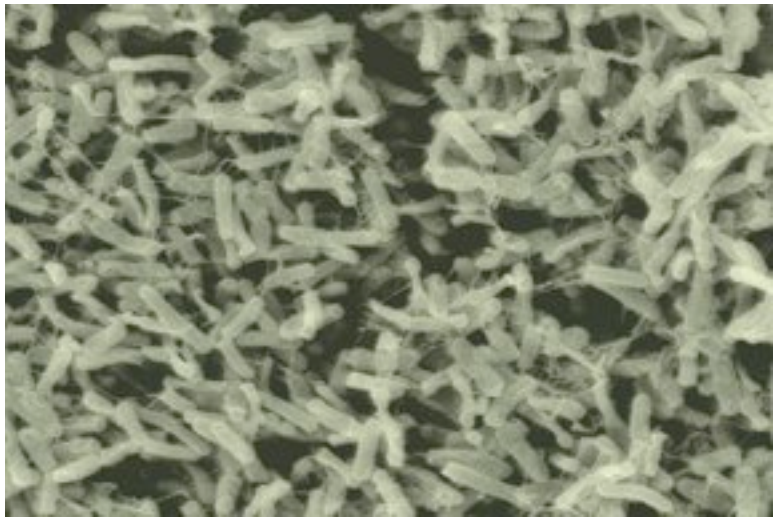


Ascaris lumbricoides

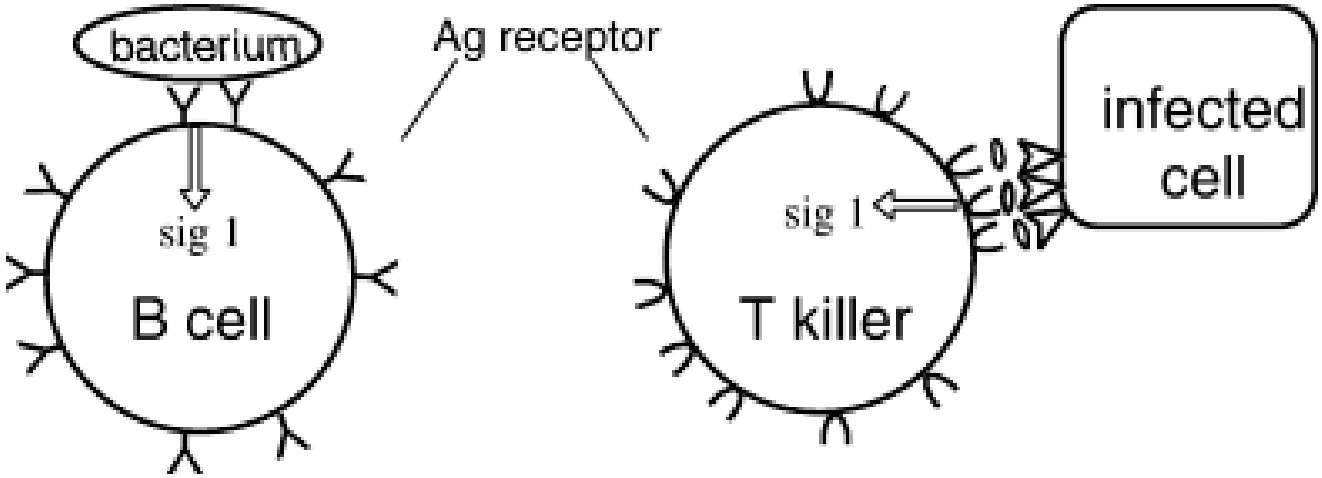
Canine: heartworm



Normal Gut Flora

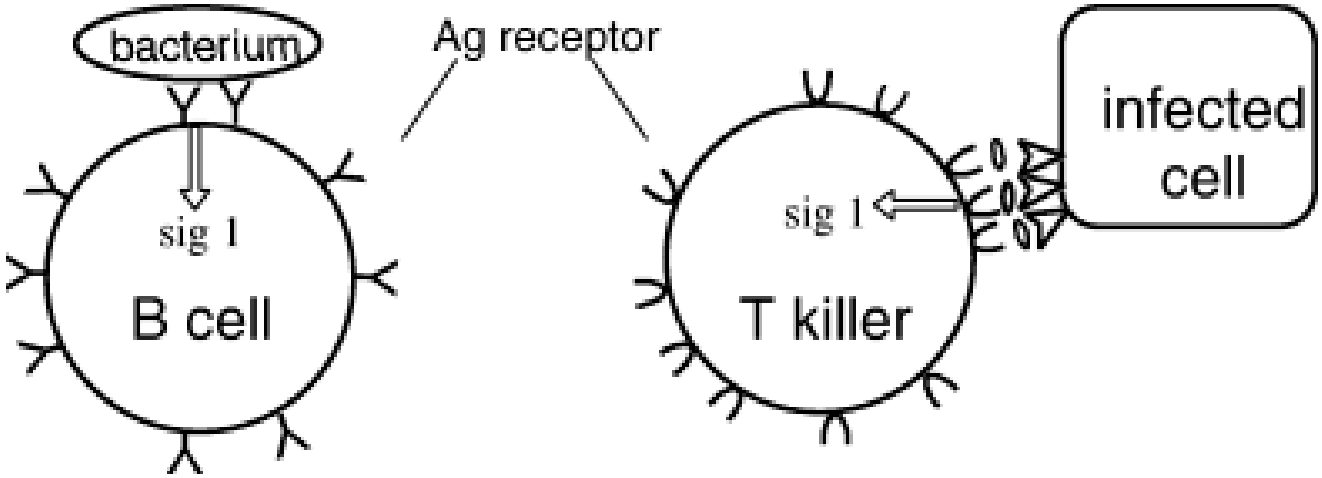


The Evolution of the Danger Theory



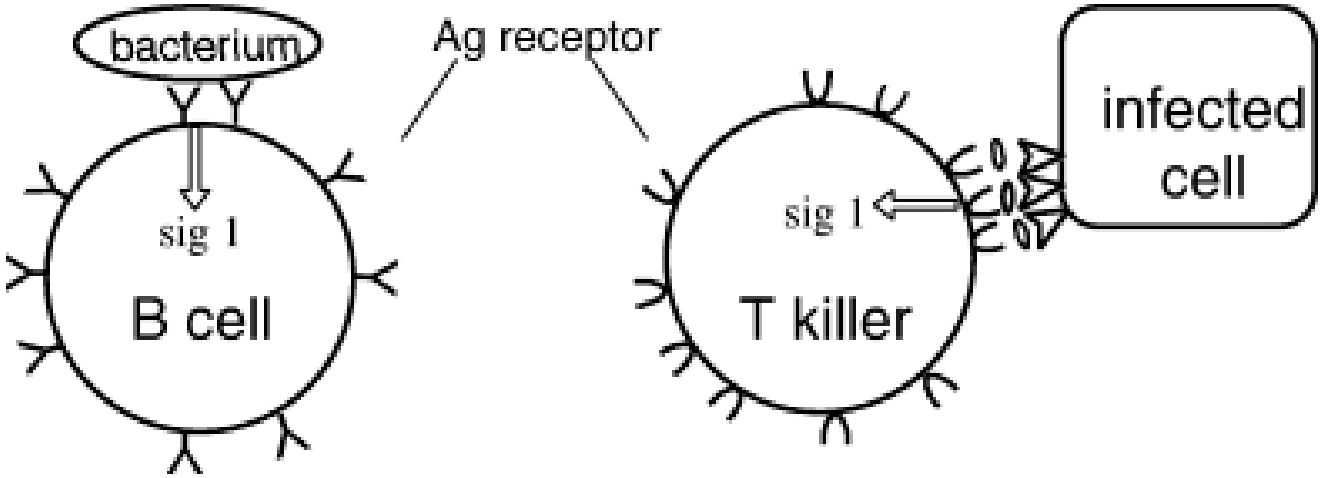
- **Immunology in the traditional sense: anything not me is non self and will therefore be cleared.**
- **The first SNS (Self-Non-Self) model.**
- **1959; Burnet and Medawar**

The Evolution of the Danger Theory



- **This SNS model suggested that...**
- **(i) Each lymphocyte expresses multiple copies of a single surface receptor specific for a foreign entity.**
- **(ii) Signaling through this surface Ab initiates the response.**
- **(iii) Self reactive lymphocytes are deleted early in life (reinforced by Ray Owen's observations in 1945).**

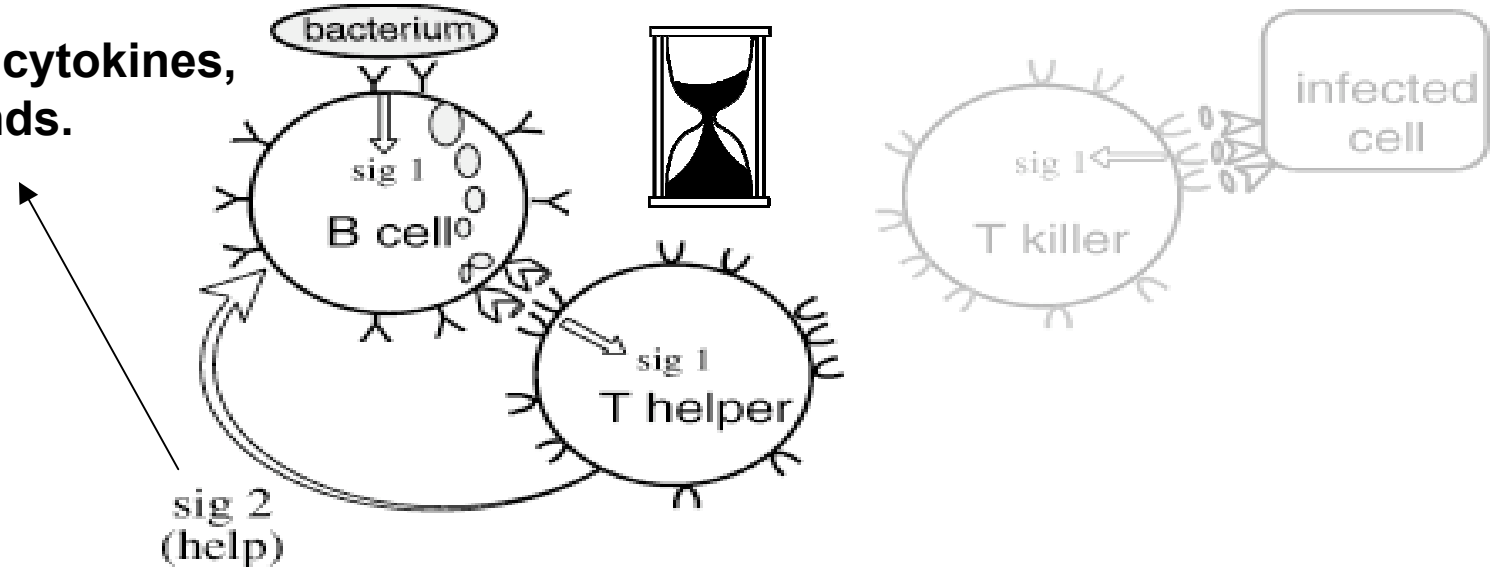
The Evolution of the Danger Theory



- **SUMMARY-The antigen is in control (Burnet): recognition of antigen (Signal 1) leads to B- and T-cell activation.**

Modifications to the SNS…

***e.g.*, cytokines, ligands.**



- **In 1969, Bretscher and Cohn added the 2-signal hypothesis to the SNS model.**
- **New theory proposed that autoimmunity would be rare if 2 cells had to recognize different specificities on the same antigen.**
- **Signal 1/Signal 2**
- **This version of the SNS lasted until 1976…**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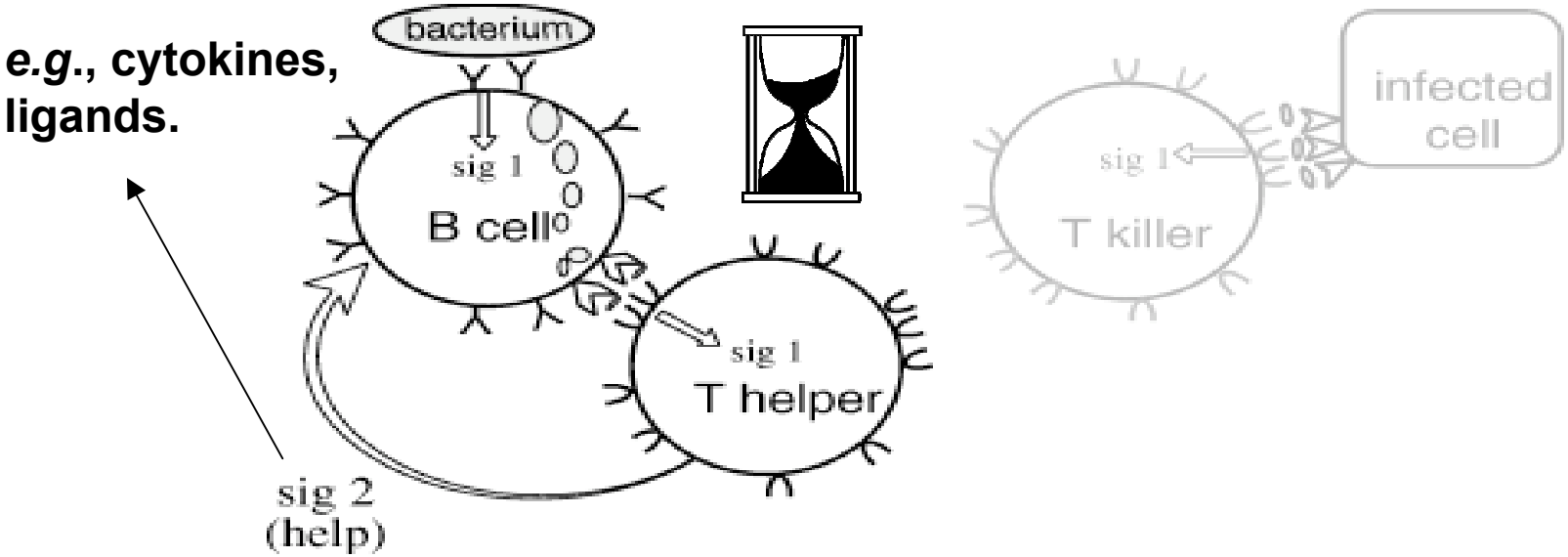
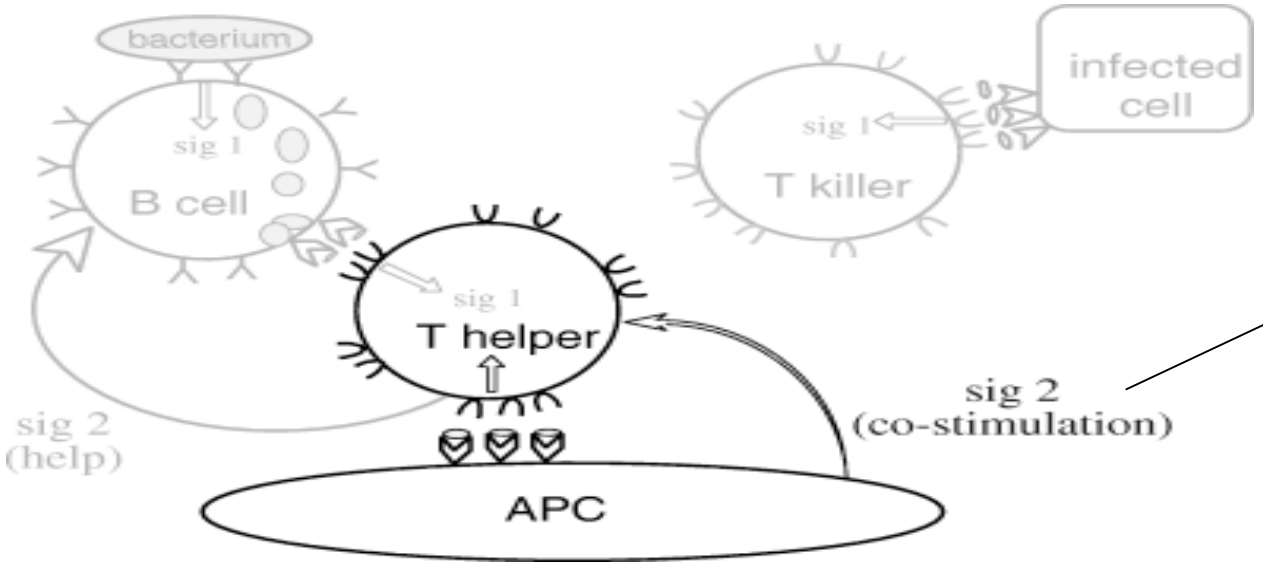
Modifications to the SNS…



- **SUMMARY-The helper cell is in control (Bretscher and Cohn): Signal one leads to B-cell death, but the addition of help (Signal 2) leads to activation.**

Modifications to the SNS…



***e.g.*, cytokines, ligands.**

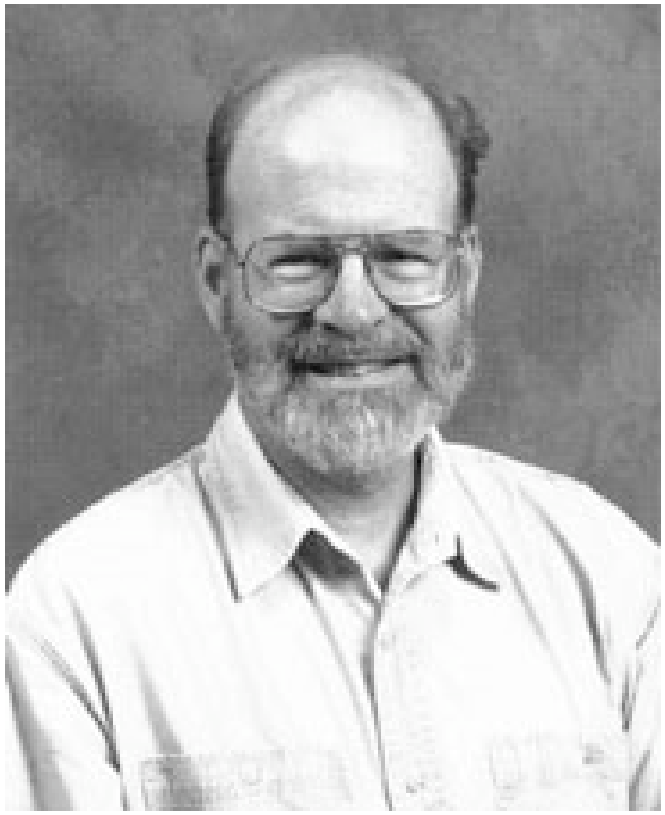
- **Lafferty and Cunningham modified it by adding yet another new cell (the accessory cell or the APC) and a new signal (co-stimulation).**

- **This theory was largely ignored for 13 years because up until now, APCs were believed to be 'non specific' and always active.**

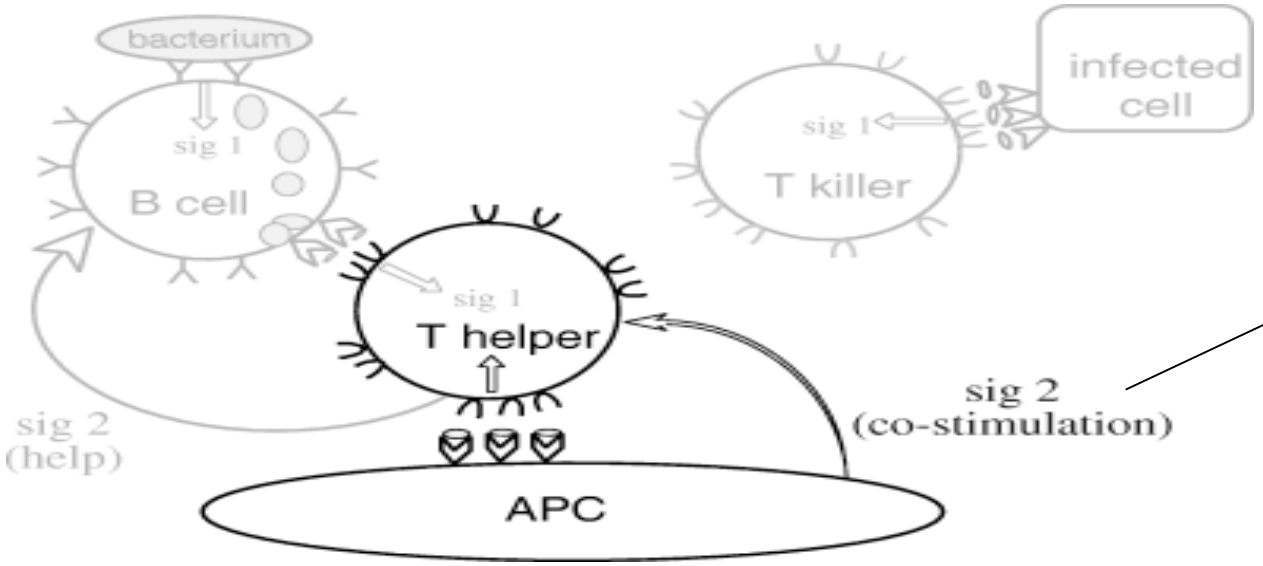
Why was the co-stimulation theory ignored for so long?

- **Co-stimulation by APCs did not fit the SNS model because...**
- **Unlike help (Signal 2), which comes from a population of T-helper cells that are antigen specific (and can be depleted of self-reactive cells), co-stimulation comes from APCs, which cannot distinguish self from non-self (is this true?).**
- **Enter the Infectious Non-self SNS model.**

Charles Janeway
1943-2003



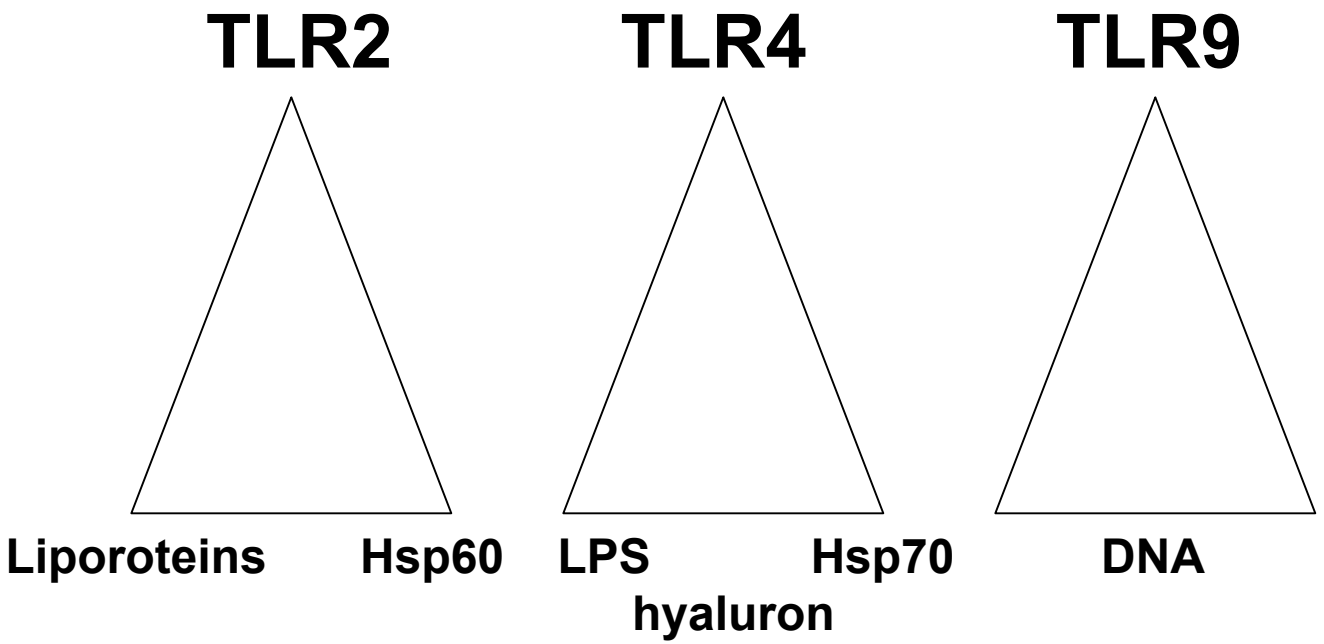
APCs are not non-specific



***e.g.*, cytokines, ligands.**

- **Janeway, 1976.**
- **APCs are not constitutively active.**
- **APCs express pattern recognition receptors (PRRs).**
- **PRRs (Toll-like receptors) recognize bacterial products that will lead to activation and costimulation.**
- **This means that APCs CAN recognize self from nonself...to a point.**

TLRs and SNL



-TLRs recognize both <u>endogenous</u> and <u>exogenous</u> molecules. Why?

-Maybe pathogens have evolved to bind them and not the other way around.

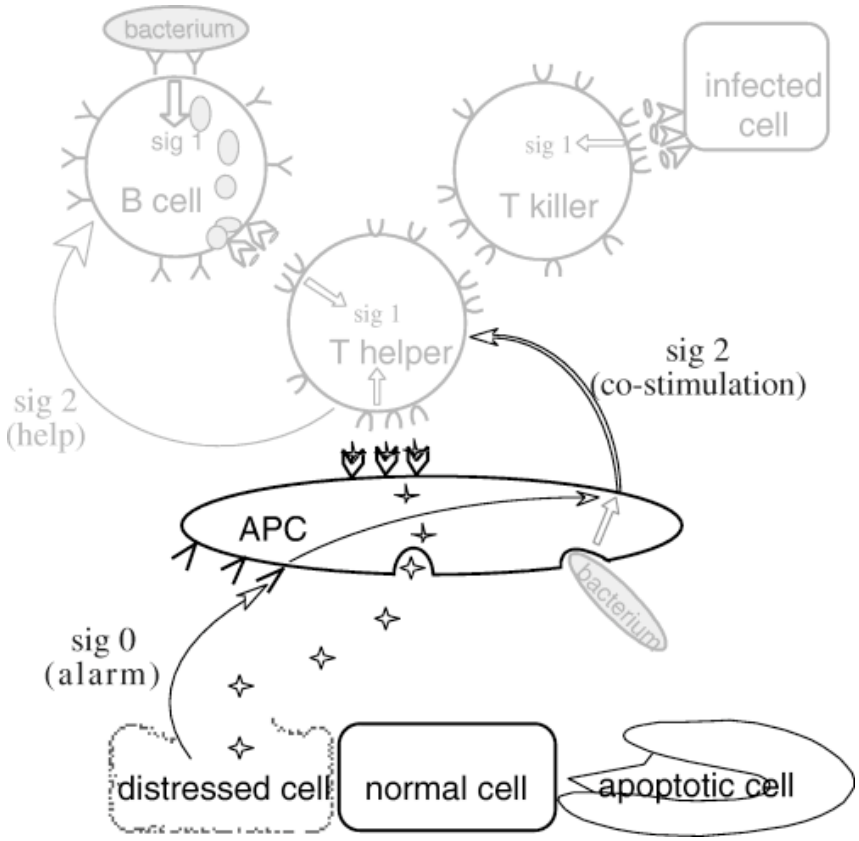
Pathogens-Ligands

• HIV	CD4, CCR5
• Toxoplasma	CCR5
• Streptococcus & Staphylococcus	TCR and Ab-Fc
• Coxsackie virus	ICAM-1
• Rabies virus	N-CAM
• EBV	CR2
• LPS/Apoptotic cells	CD14

The SNS and INS Models

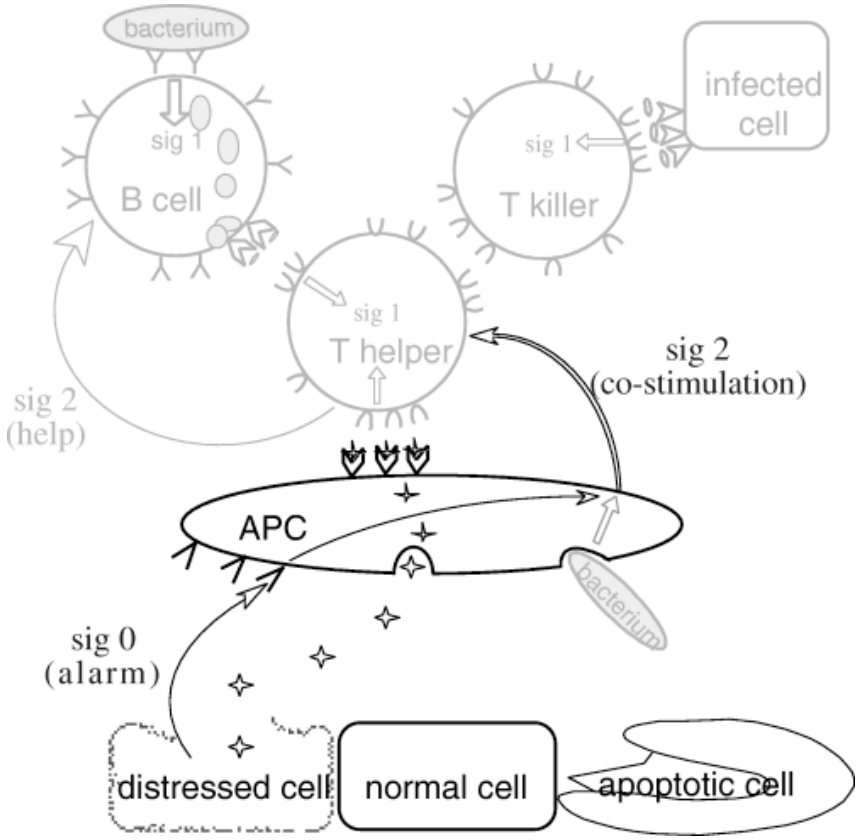
- **The critical event in all of these theories is the recognition of foreign antigen.**
- **What is non-self?**
- **We have spent half a century studying self-non-self discrimination.**
- **Janeway himself pointed out that even with the addition of PRRs the SNS/INS models could not explain the immune response to transplants or tumors, nor the dysfunction(s) that lead to many autoimmune diseases.**

Danger Theory

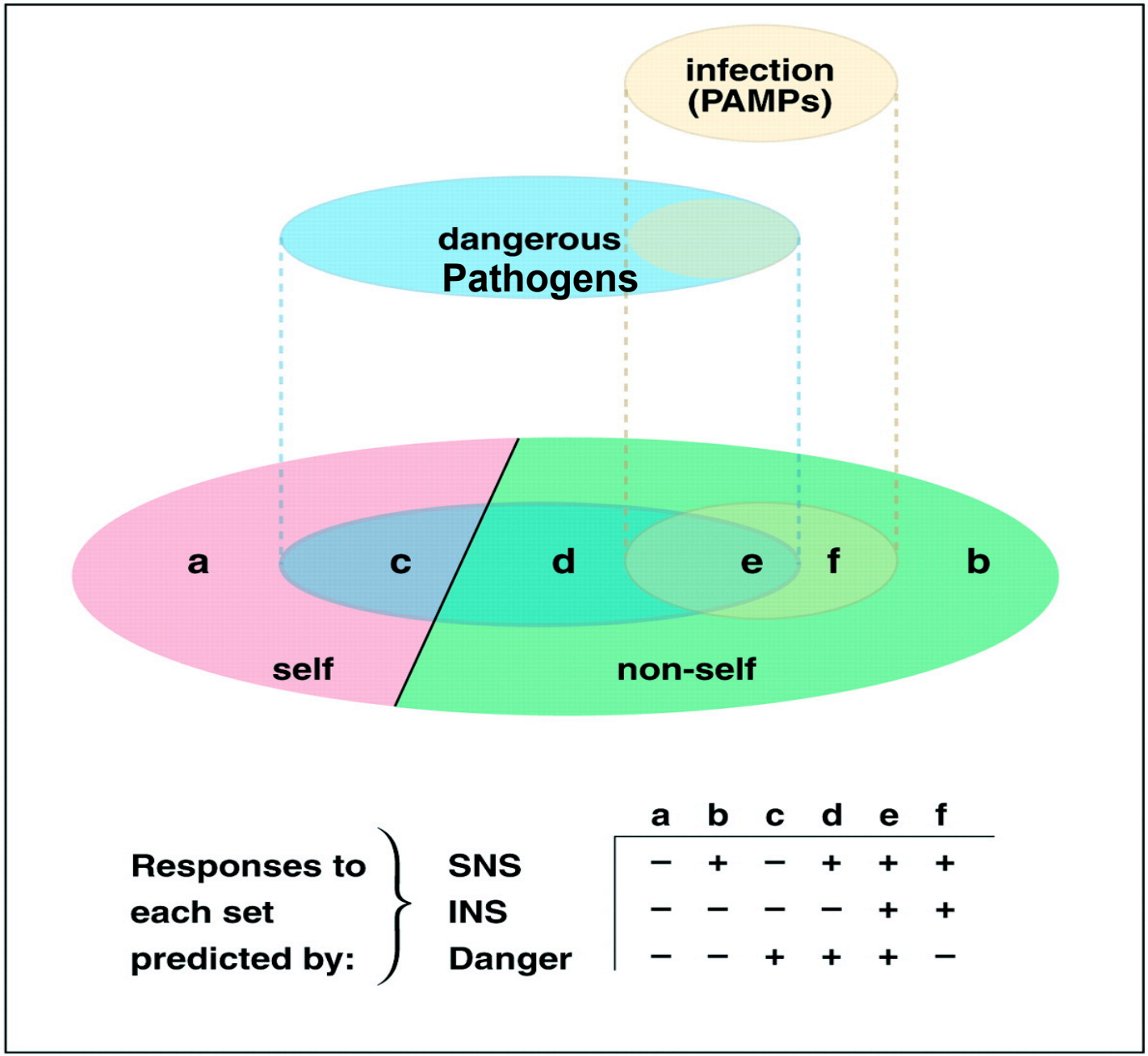


- **Abandons the concept that the immune system is concerned with nonself.**
- **The Danger model is based on the idea that the ultimate controlling signals are endogenous, not exogenous.**

Danger Theory

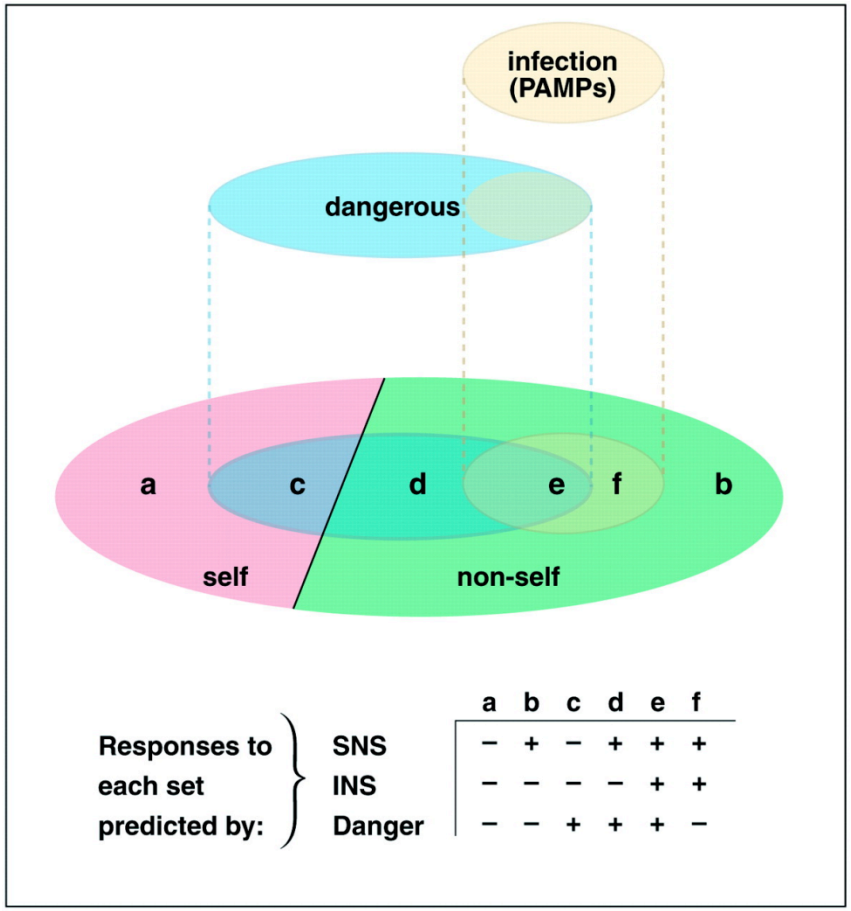


- **SUMMARY-The tissues are in control (Matzinger): APCs receive activating signals from injured cells, but not from healthy cells of from cells dying by normal physiological death.**



Responses to each set predicted by:	a	b	c	d	e	f
SNS	−	+	−	+	+	+
INS	−	−	−	−	+	+
Danger	−	−	+	+	+	−

The Big Picture: Danger Model



- **A) fetuses, milk proteins, aging related changes.**
- **C) mutations**
- **INS predicts neither transplants and fetuses would be rejected.**
- **SNS predicts both should be rejected.**
- **DM predicts that healthy fetuses should not be rejected because the do not send out an alarm. Transplants cannot be performed without surgical and or ischemic damage: danger.**

Rules of the Danger Theory

- **First Law-DIE IF YOU RECEIVE SIGNAL ONE IN THE ABSENCE OF SIGNAL TWO.**
  - **Cells that receive signal one can be rescued by the addition of an appropriate Second signal--- Leading to activation.**
  - **Co-stimulation for T cells**
  - **Help for B cells**
- **Second Law-ACCEPT SIGNAL TWO (ACTIVATING SIGNAL) ONLY FROM APCs.**
- **Third Law-IF ACTIVATED, ONLY NEED SIGNAL 1 AND IT CAN COME FROM ANY CELL TYPE.**

Rules of the Danger Theory: T cells

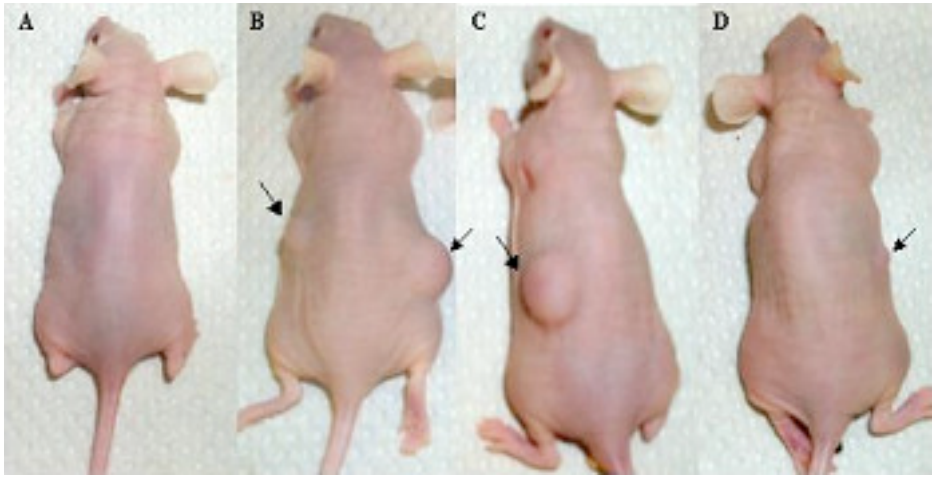
	T cell differentiation state			
	Immature thymocyte	Resting naive T cell	Resting experienced T cell	Activated effector T cell
Potentially activating (or triggering) cells	NONE	DC, Active Mø?	DC Mø B cells Tissue cells	ALL
Tolerizing cells	ALL	B cells, Tissue cells		NONE

Examples of the Danger Theory

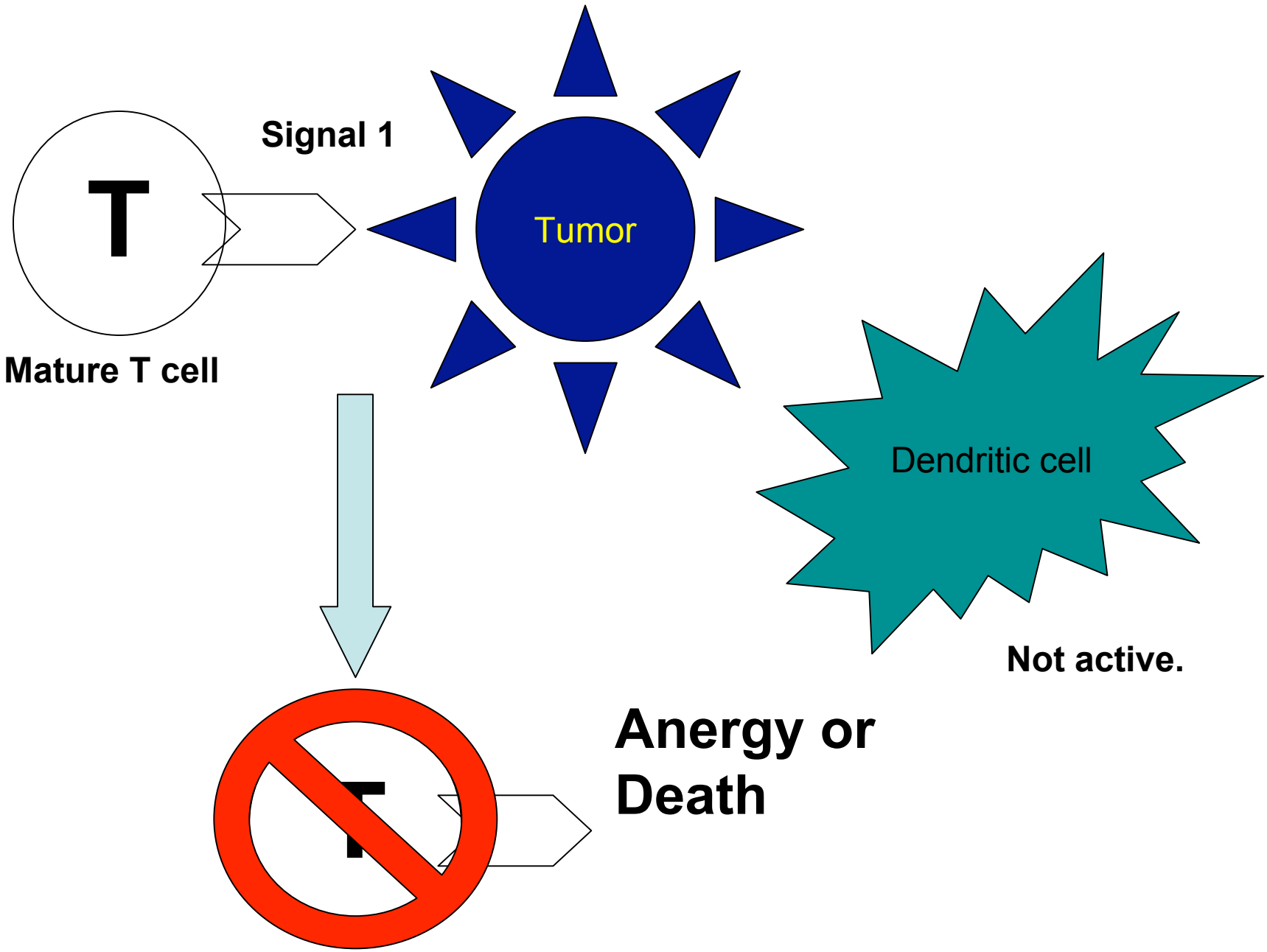
Life Changes

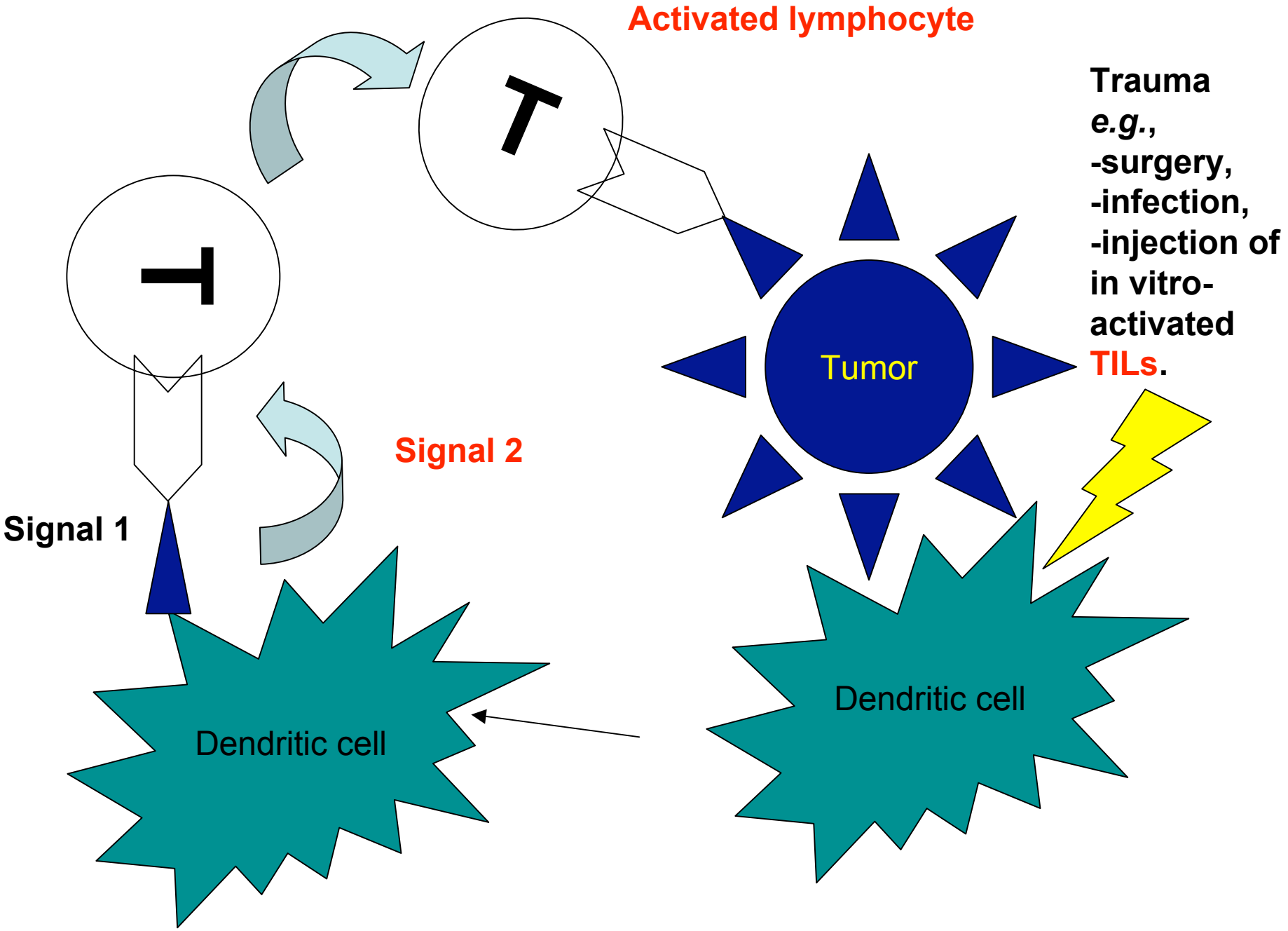
- **Why is there no immune response to the many new proteins associated with lactation, puberty, aging?**
  - **First-They are not associated with tissue damage (death, destruction, distress, danger).**
    - **Danger Signals? Necrotic cell death, heat-shock proteins**
  - **Second-Any T cells or B cells that recognize these 'changes' will receive signal one only (which means?).**

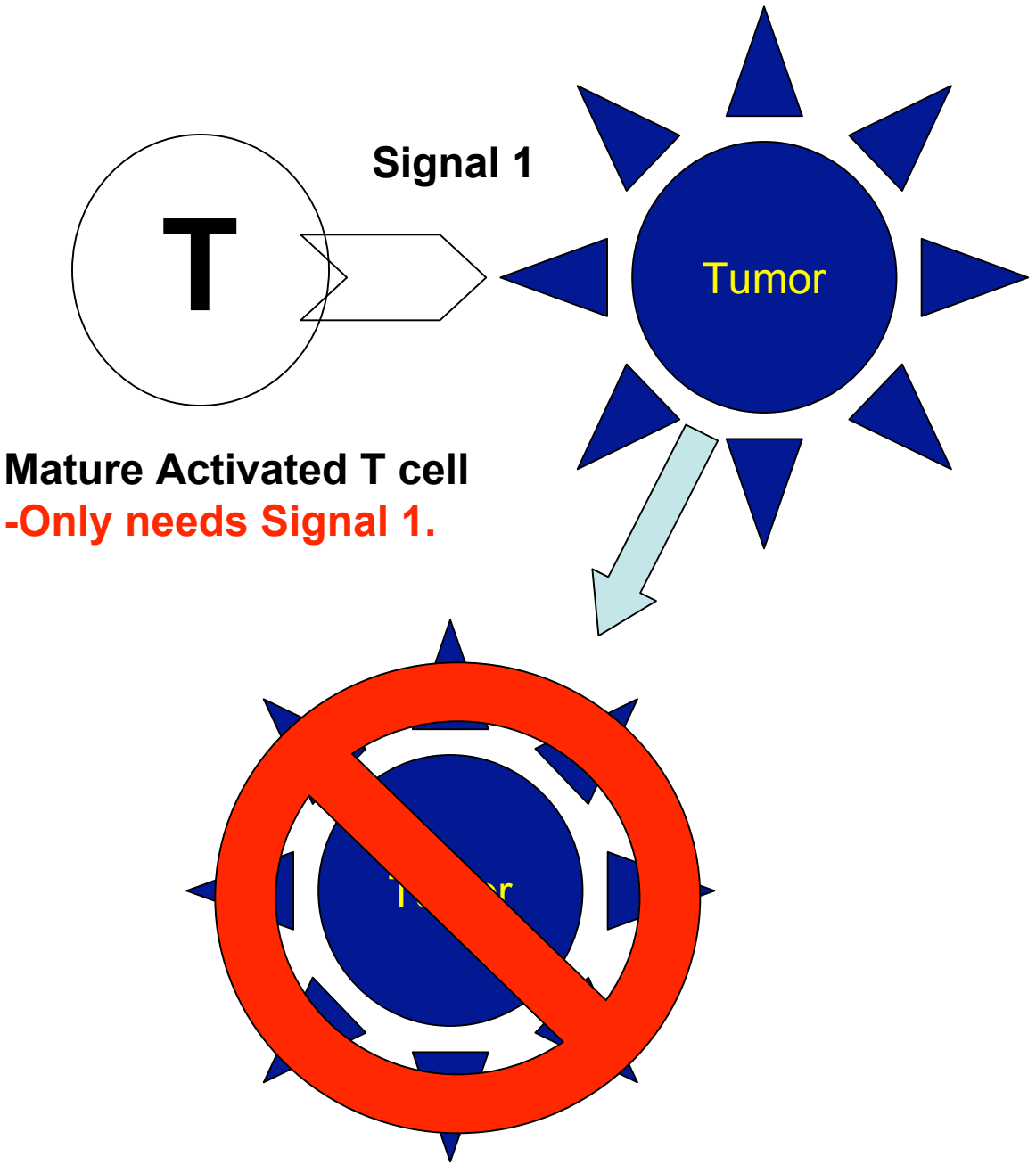
Tumors



- Newly arising tumors may express antigens not expressed by ‘normal’ tissues but this is not enough to alert the immune system.
- No difference between a rapidly dividing cancer cell and a rapidly dividing hematopoietic cell, gut cell, or thymocyte.
- Consequently, as it grows, any tumor unable to deliver Signal two should induce deletion of tumor specific T cells.


Signal 1
T
Tumor
Mature T cell
Dendritic cell
Not active.
T
Anergy or
Death


Activated lymphocyte
Trauma
e.g.,
-surgery,
-infection,
-injection of
in vitro-
activated
TILs.
Tumor
Signal 2
Signal 1
Dendritic cell
Dendritic cell



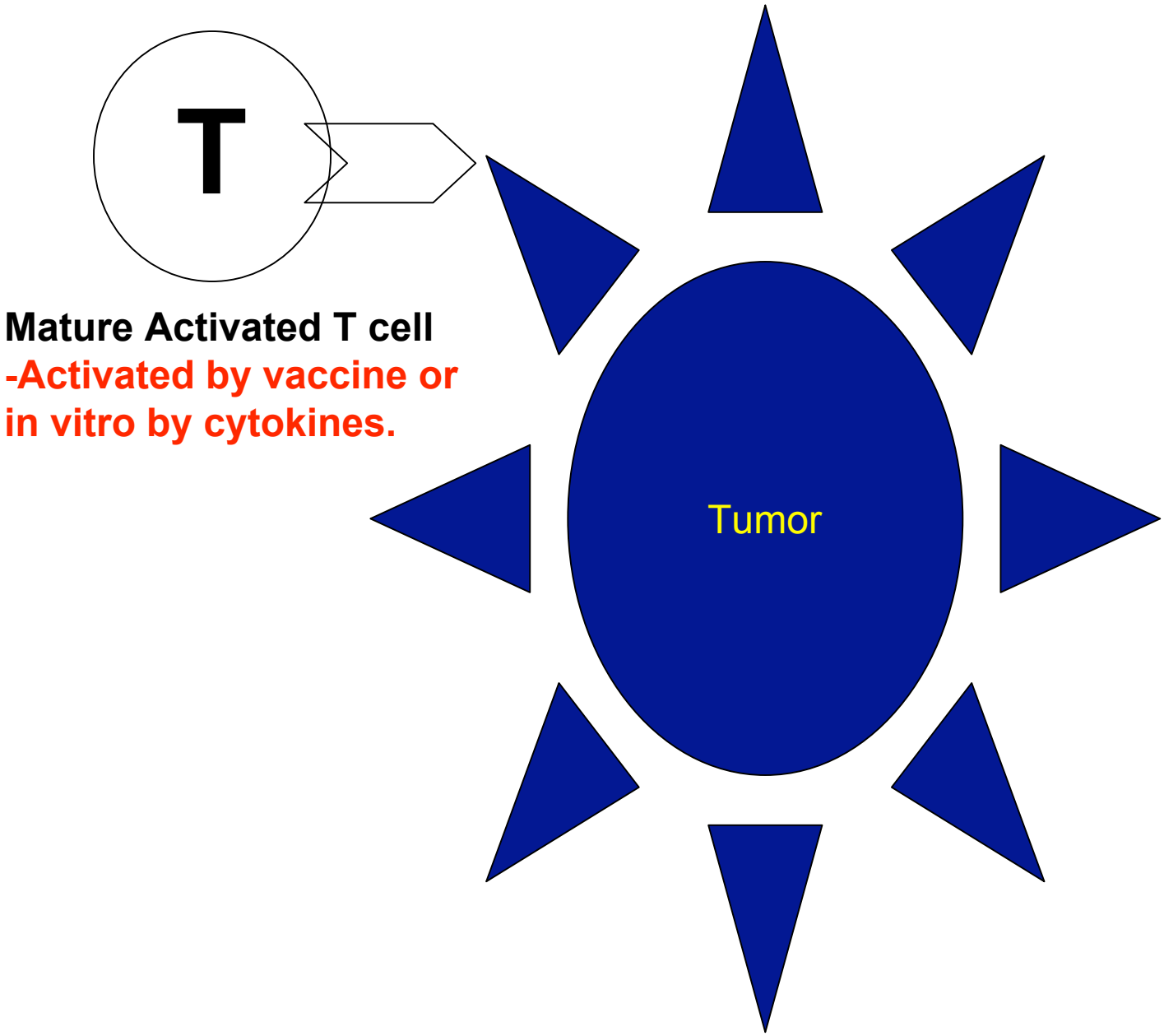
Mature Activated T cell

-Only needs Signal 1.

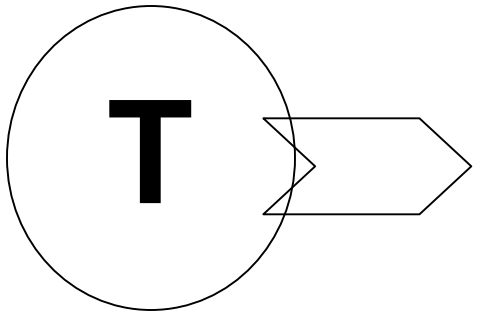
T cell Activation in the Tumor Model

- By trauma (as described).
- Vaccination (tumor vaccine).
- Activation of T cell in vitro.

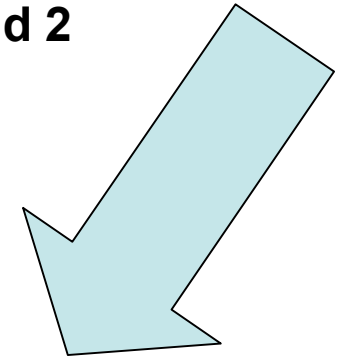
- However...the tumor size will affect the efficacy of these strategies.



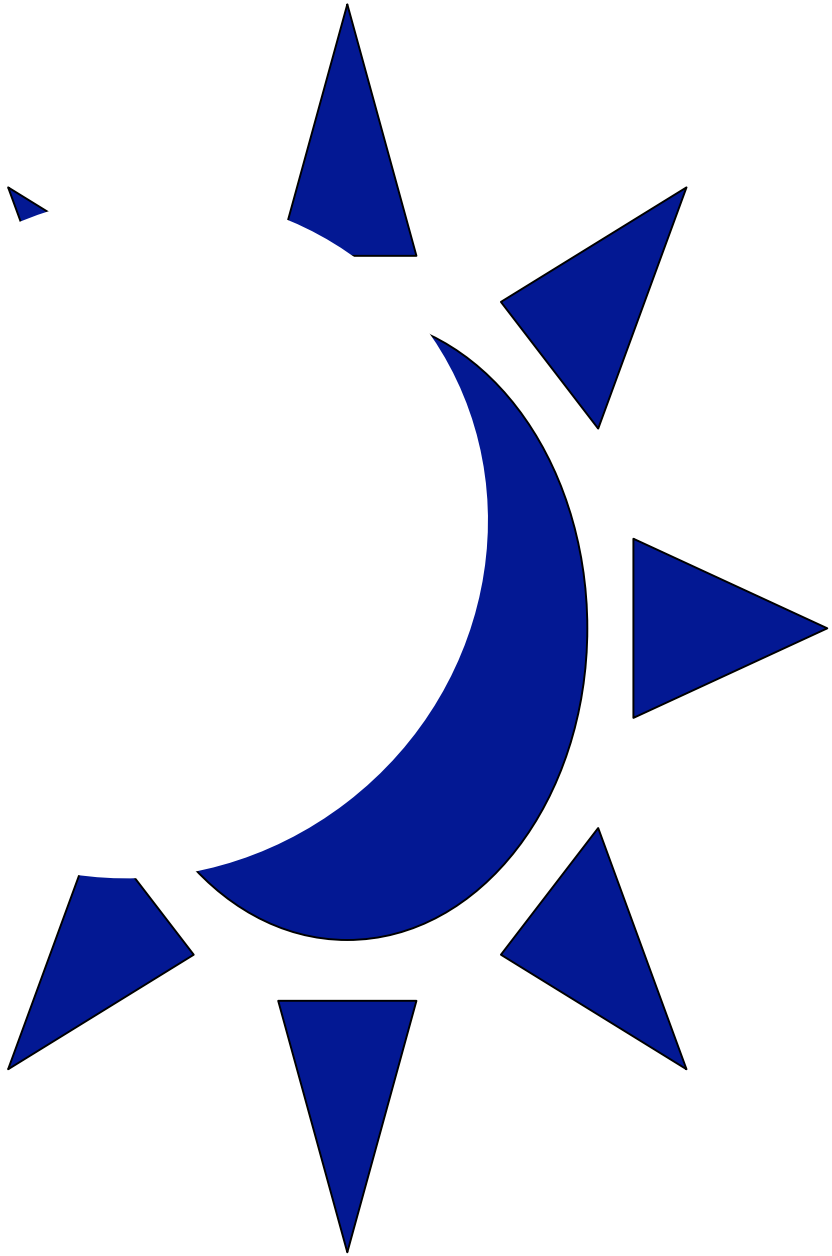
Mature Activated T cell
-Activated by vaccine or in vitro by cytokines.

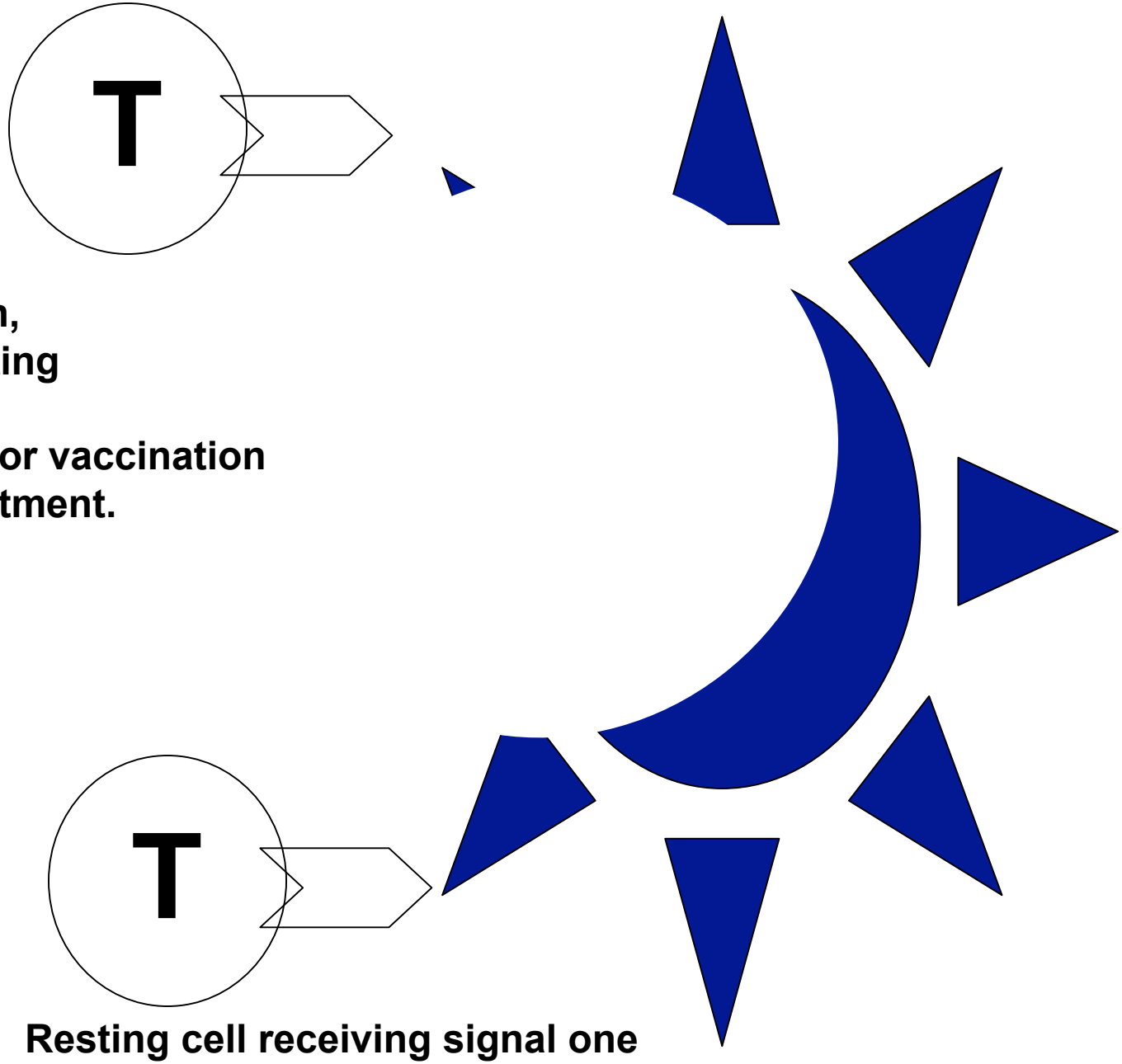


-T cell attacks tumor.
-T cell now needs to be **Re-activated** with Signal 1 and 2



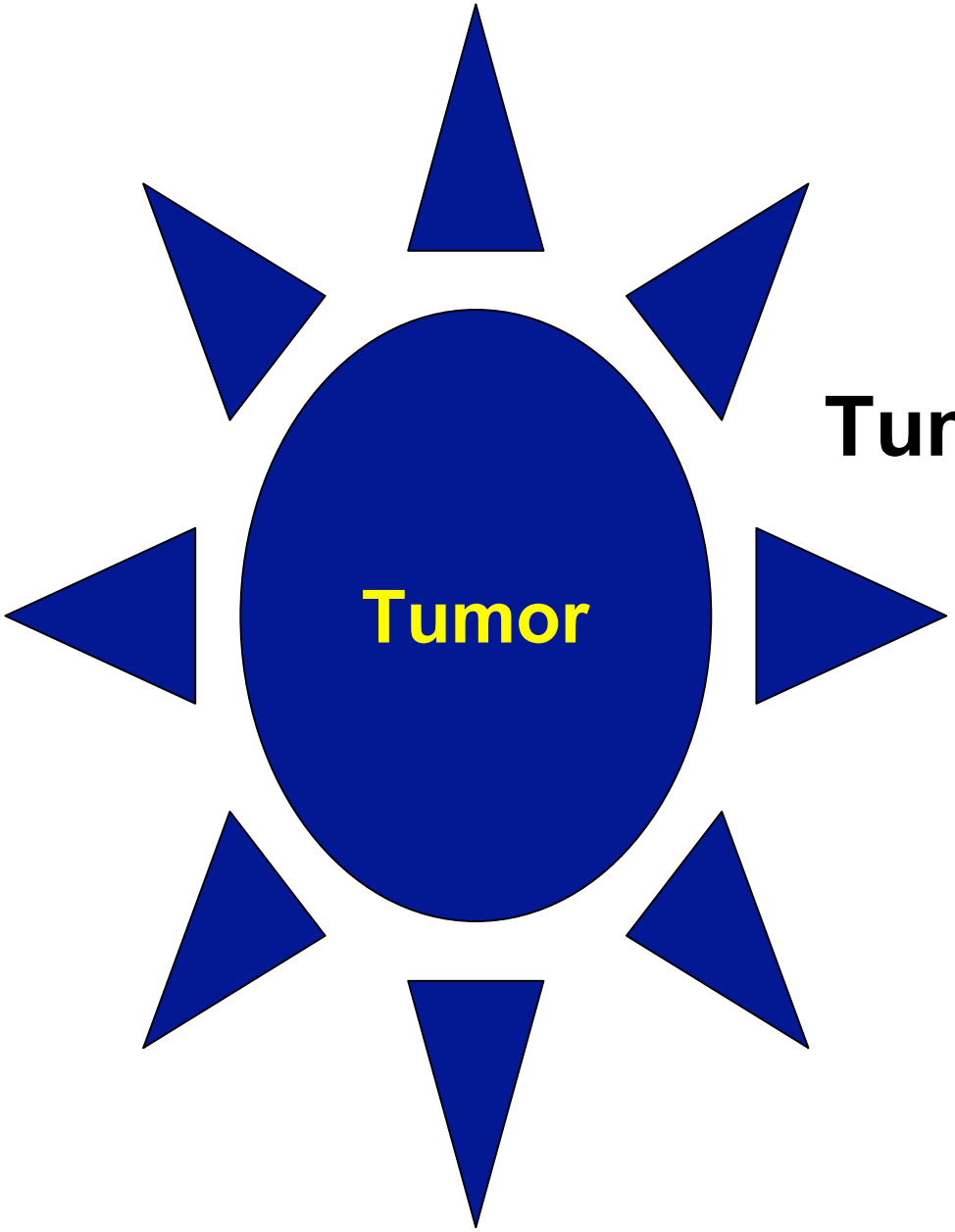
T cell needs APC for reactivation in the lymph node.





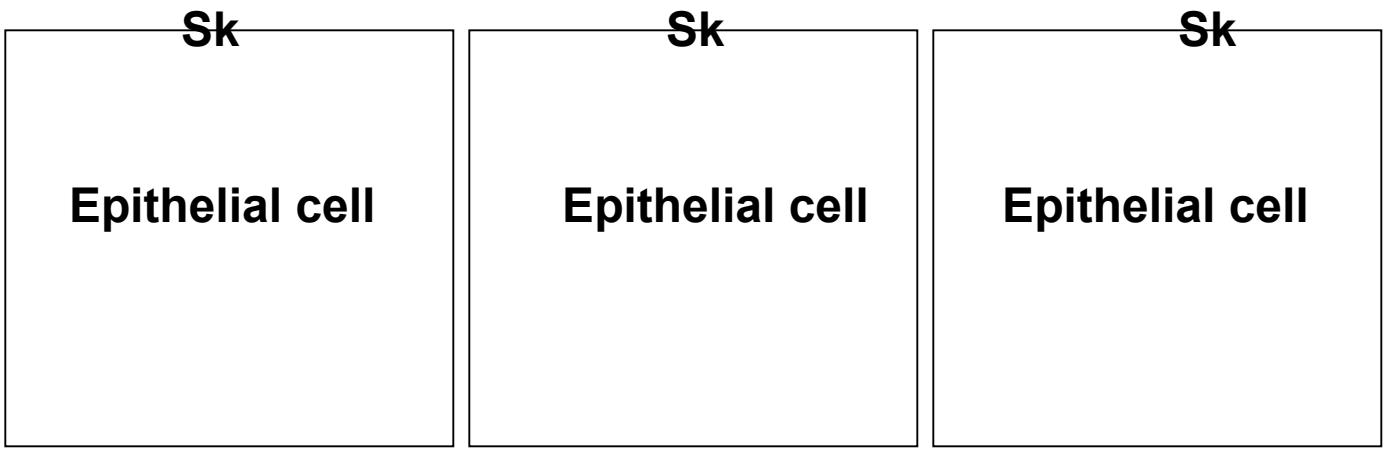
Without reactivation,
T cell goes into resting state.
-Need repeated tumor vaccination or repeated TIL treatment.

Resting cell receiving signal one without Signal 2 will die.



Tumor regenerates.

Viral Infection (Skin)

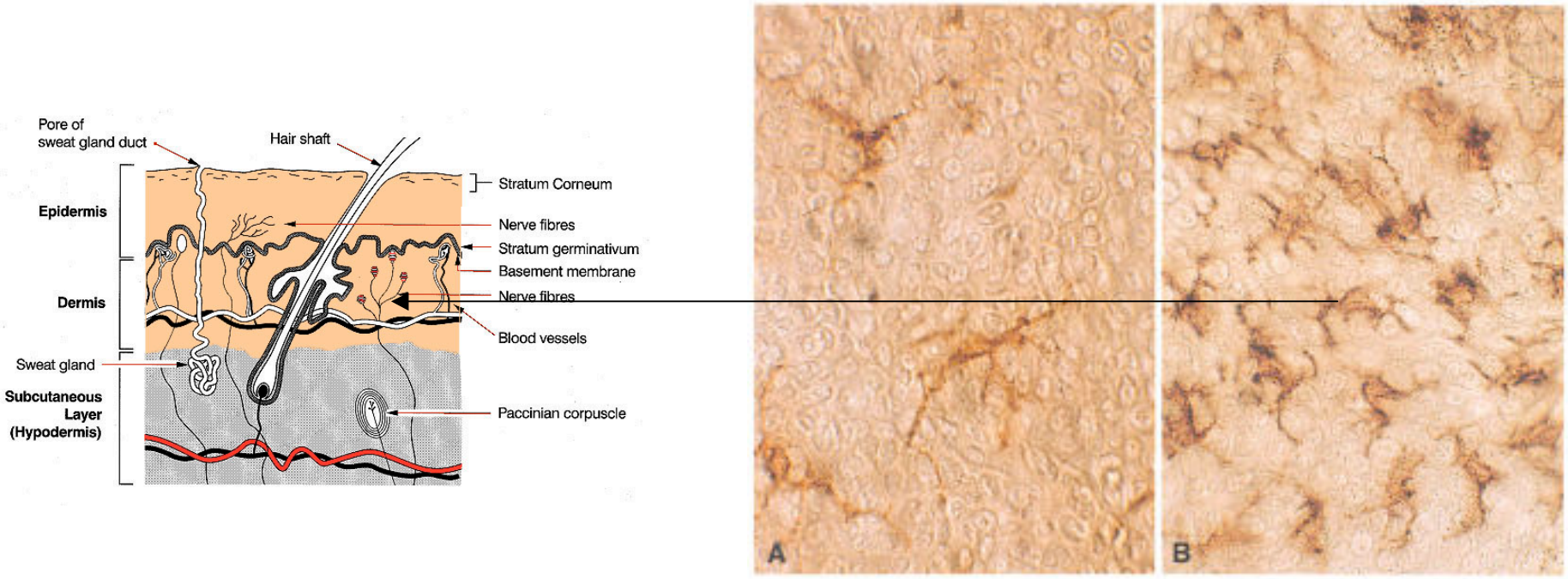


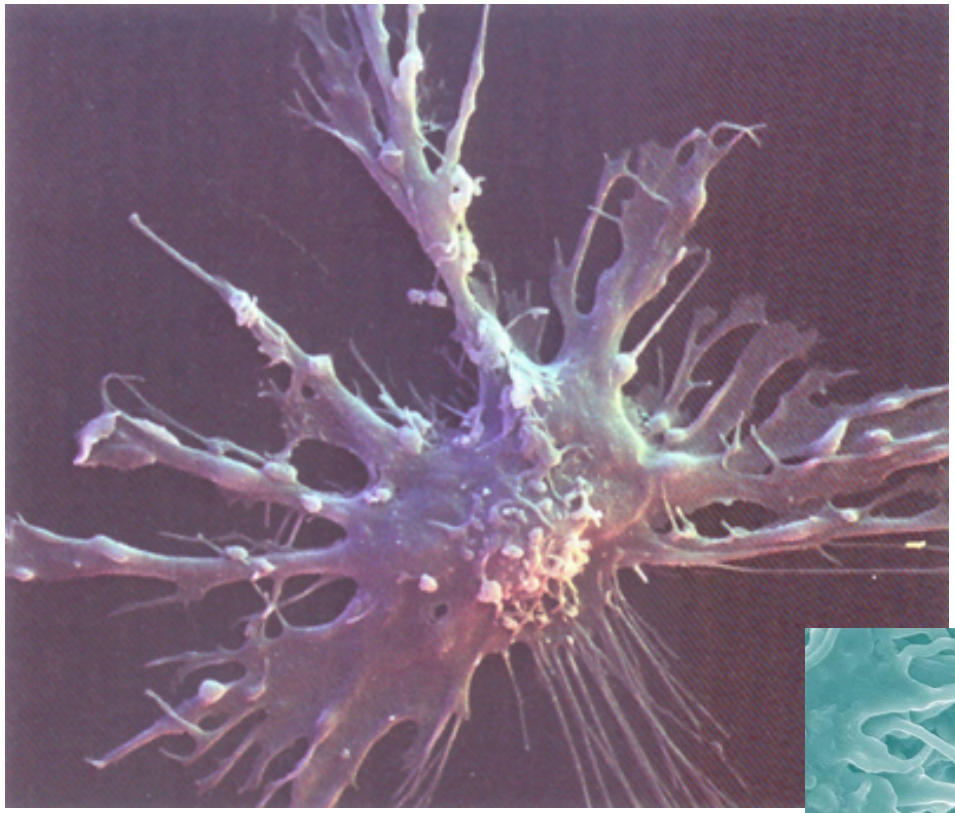
Non infected skin cells expressing self antigen (Sk).

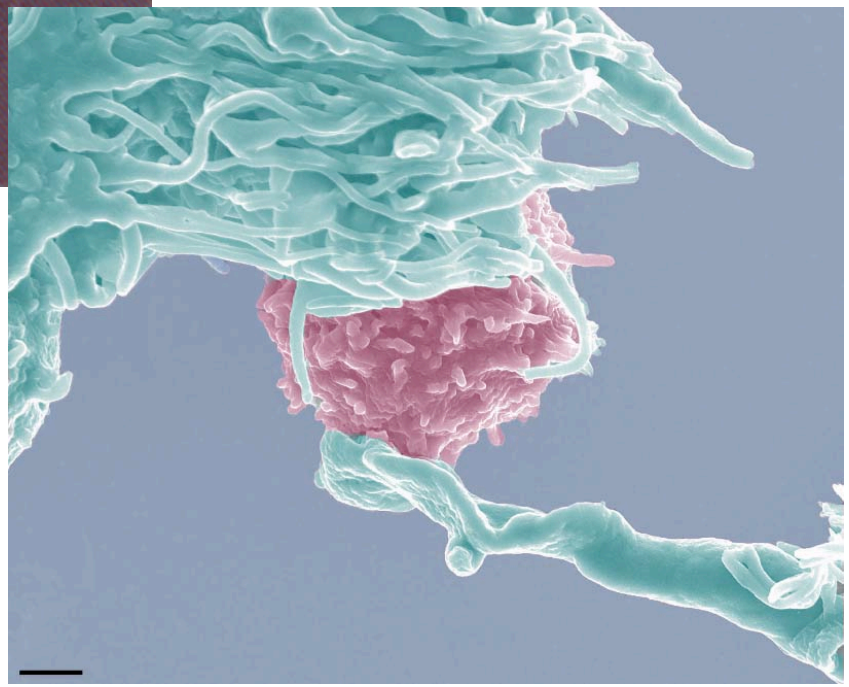
Immune system should always be in ‘off’ mode.

Dendritic cell at work.

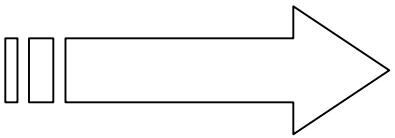
Mounting a Response





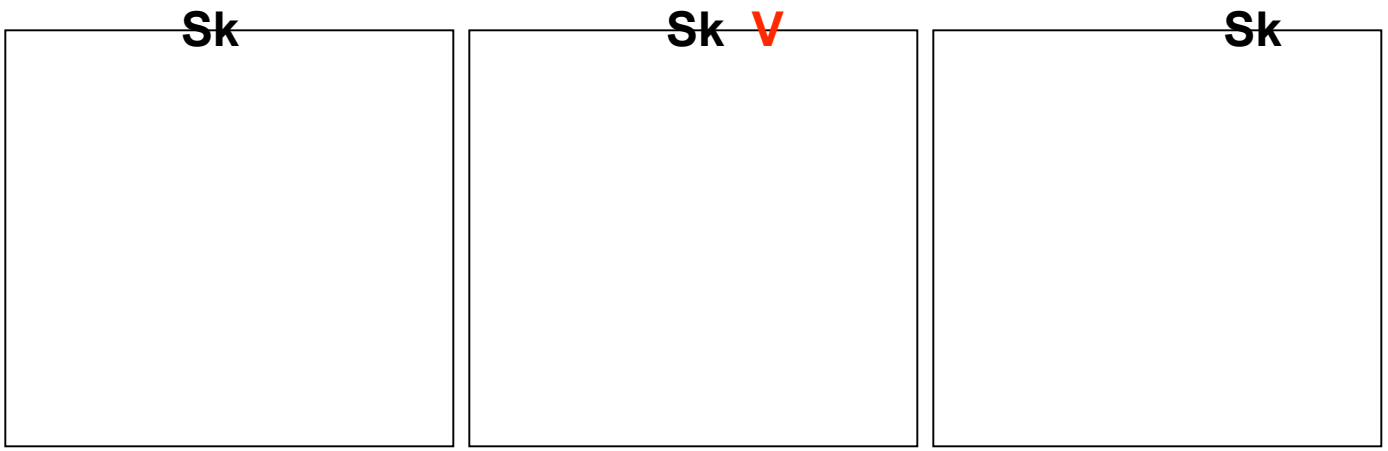


Even though ‘asleep’, dendritic cells sample one cell volume every hour.



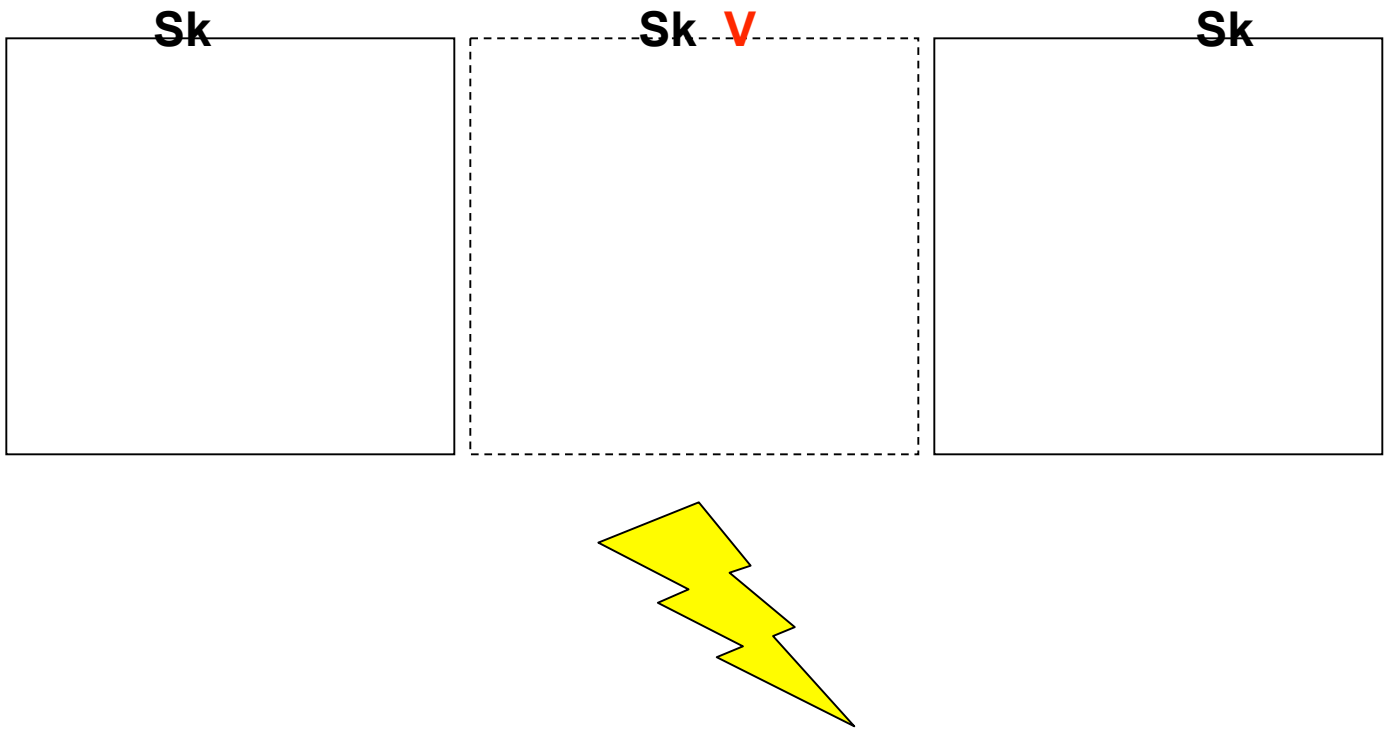
x2

Viral Infection (Skin)

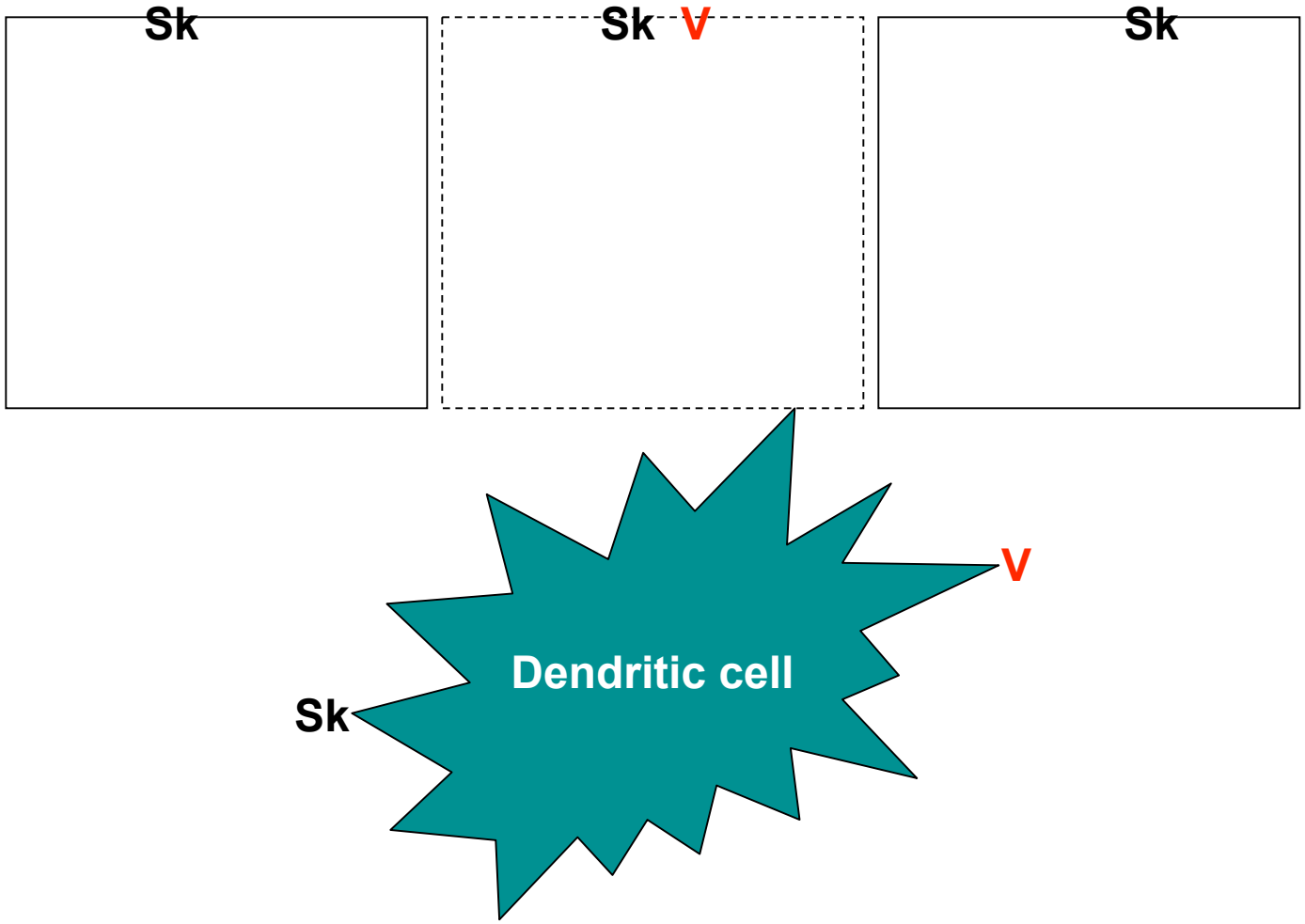


Infected skin cells expressing self antigen and viral antigen (V).

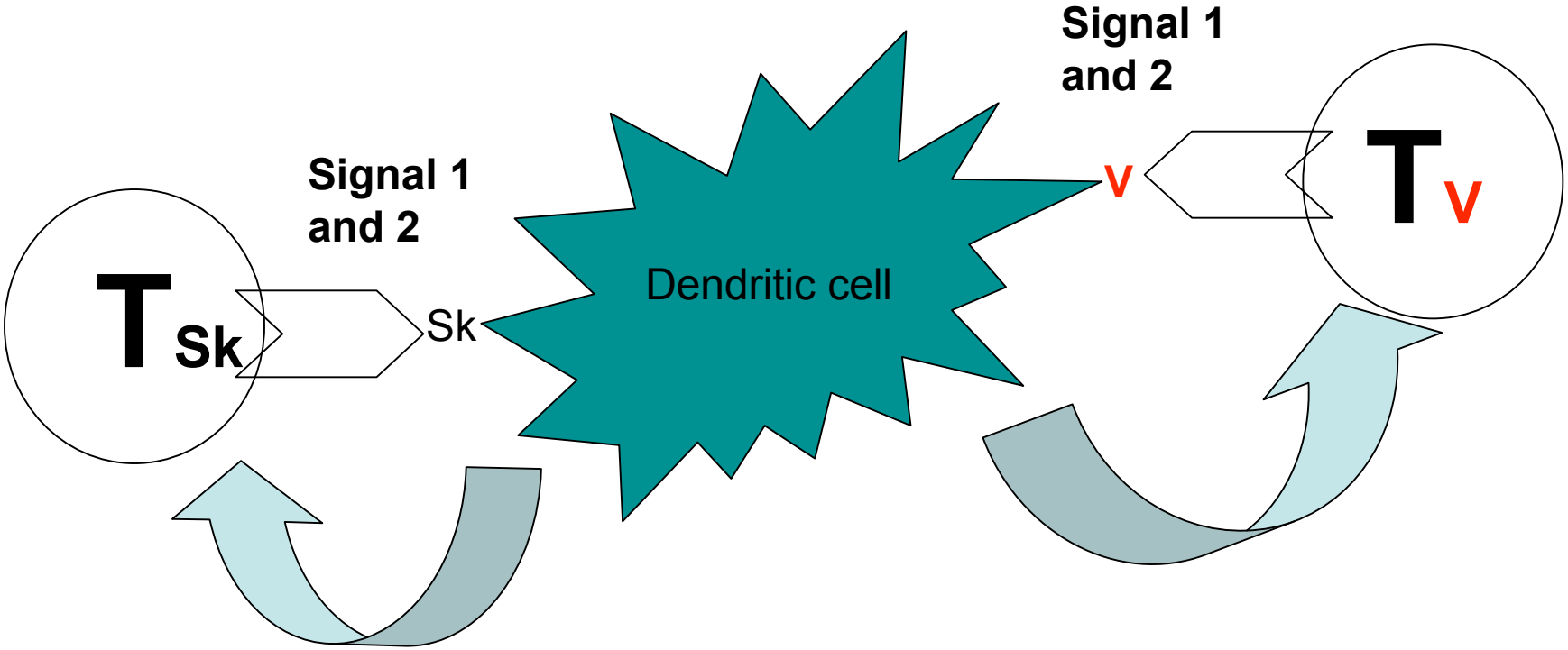
Viral Infection (Skin)



Virally-infected skin cell is lysed, sending out danger signals (necrosis).

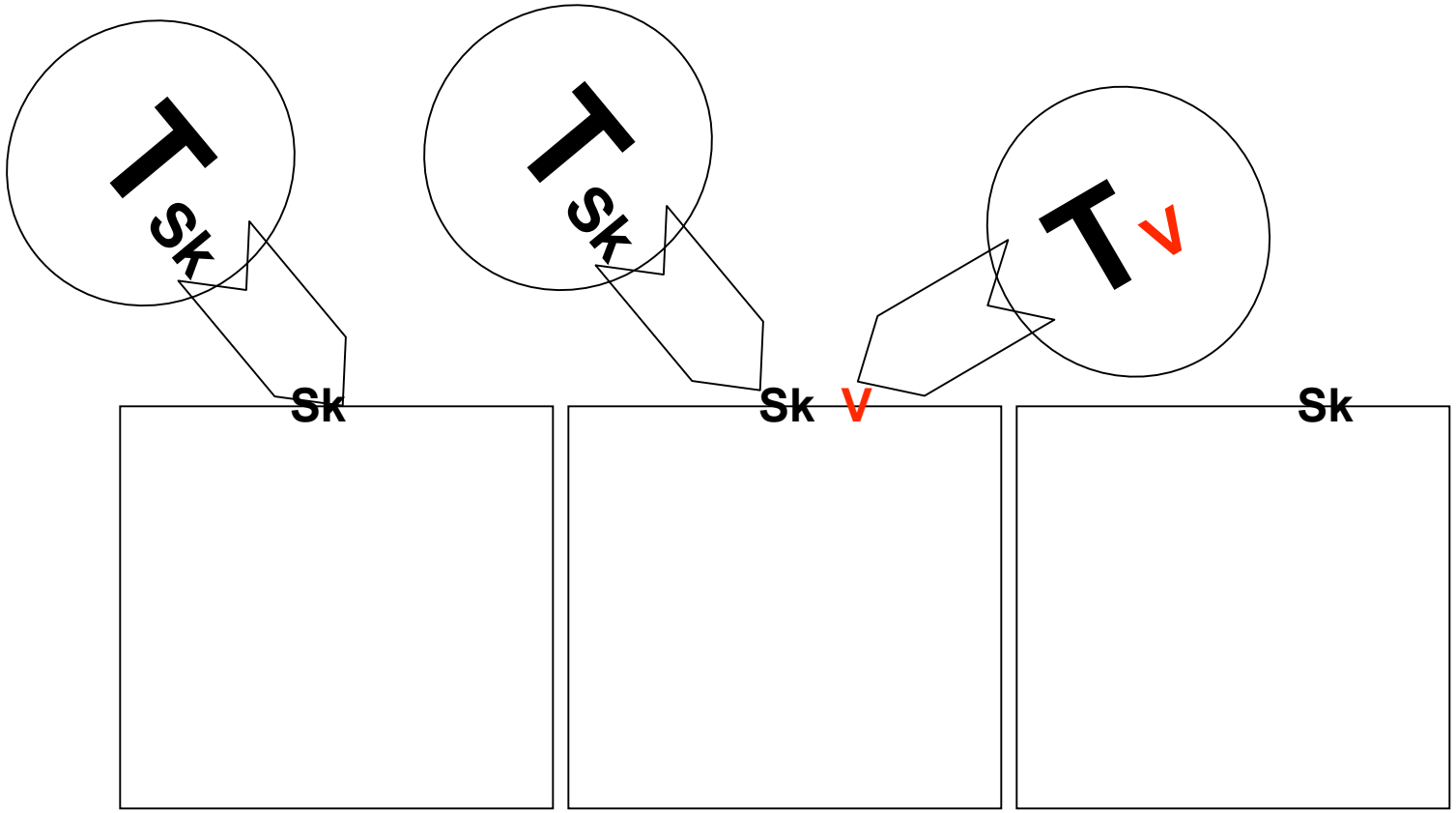


Dendritic cell becomes activated and it picks up both Sk and V antigens and goes to the DLN.

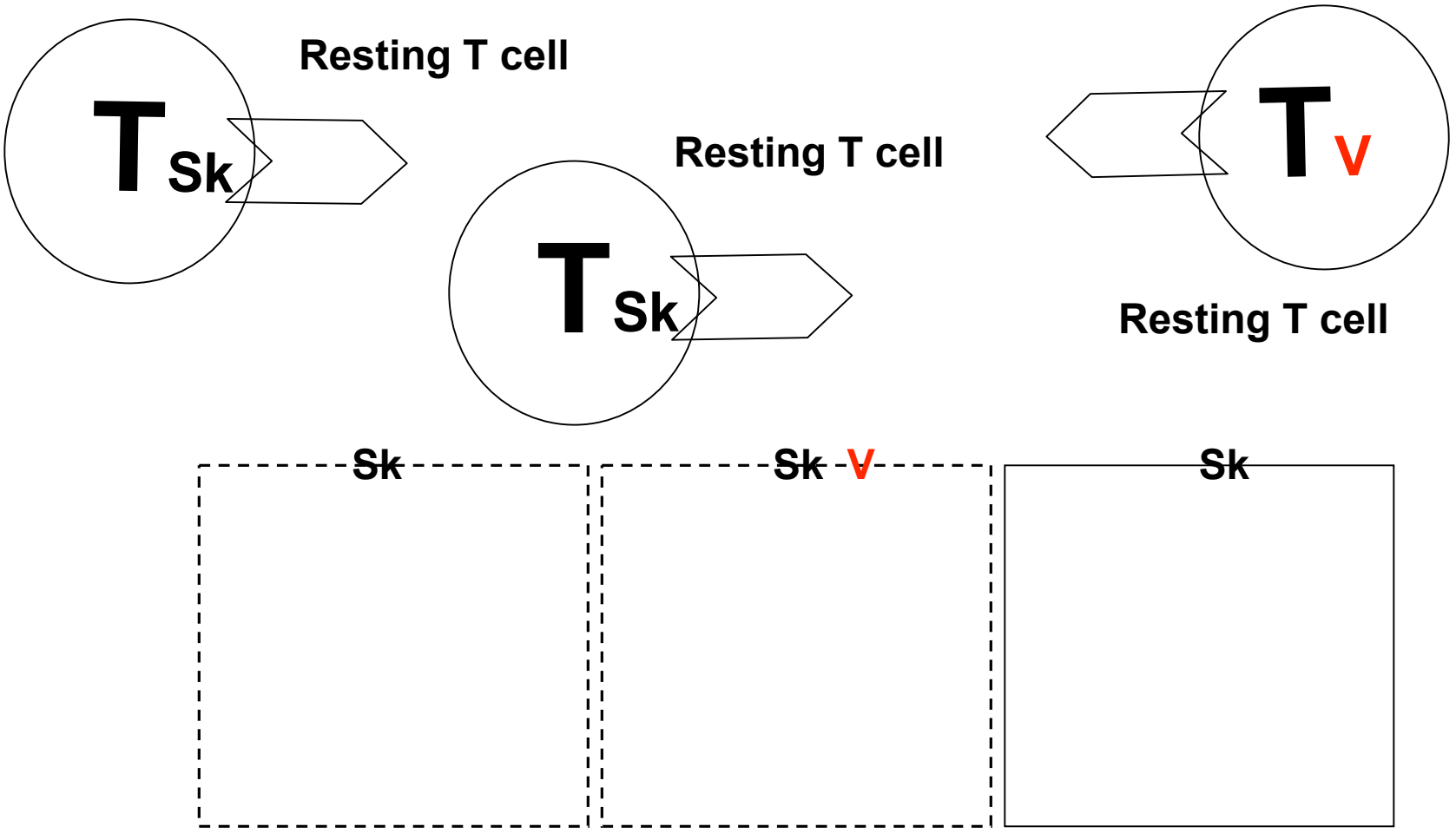


Activated T cells go to the site of infection.

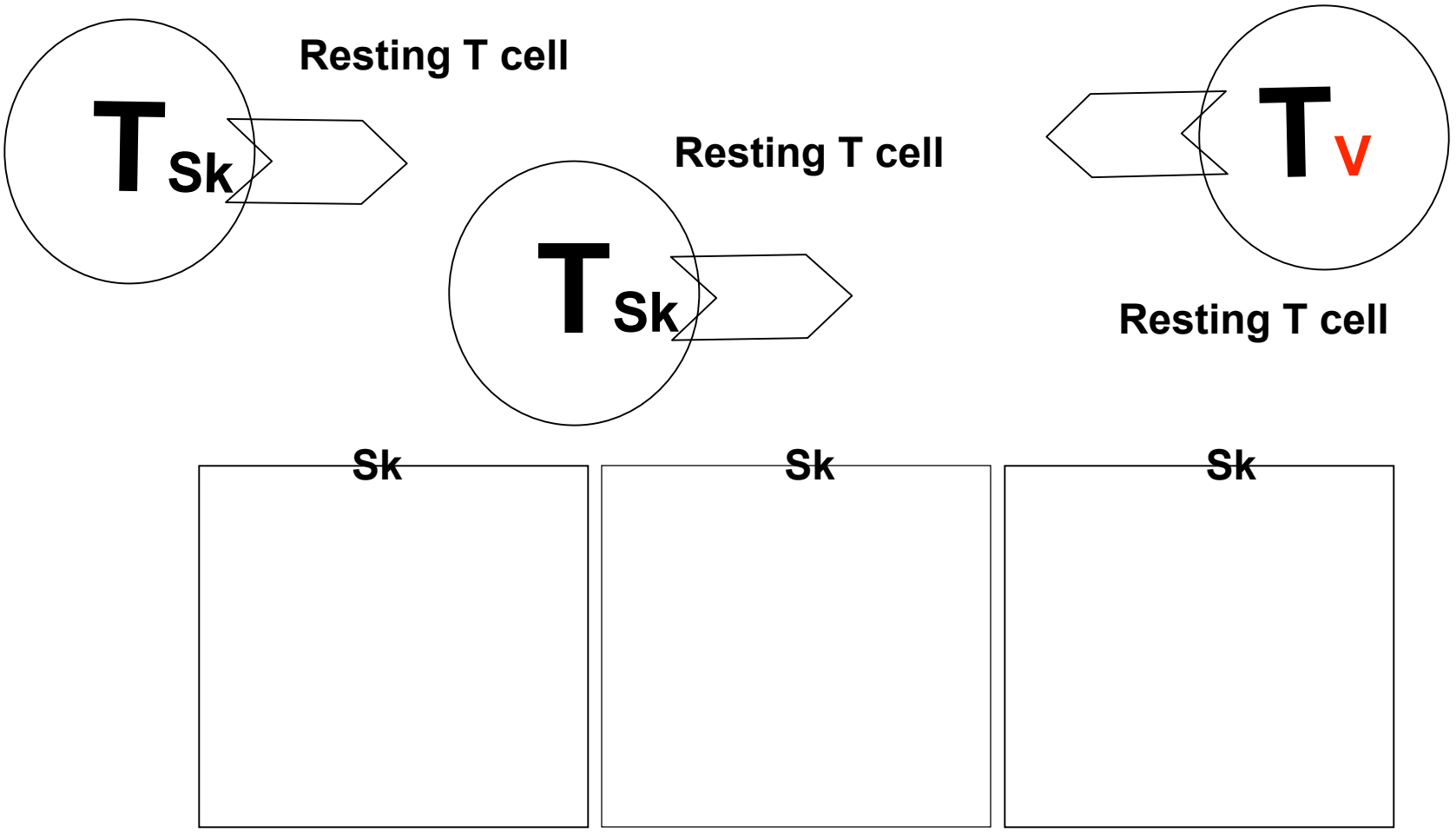
Activated T cells return to the site of infection.



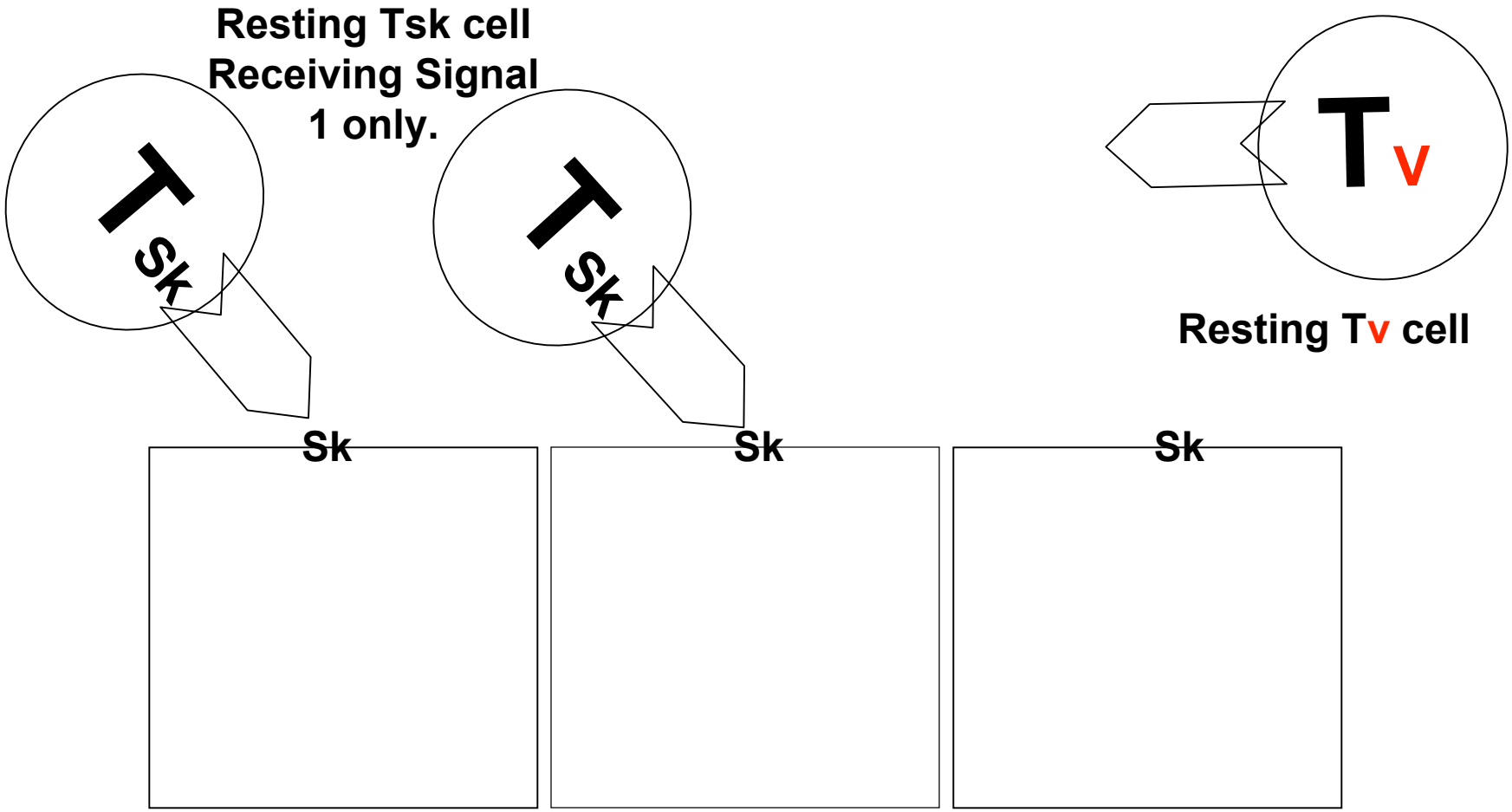
Infected skin cells expressing Self antigen and Viral antigen are lysed by Activated T cells.



After lysing Sk- and V-antigen expressing cells, T cells have to get 'recharged' by Signal 1 and Signal 2.

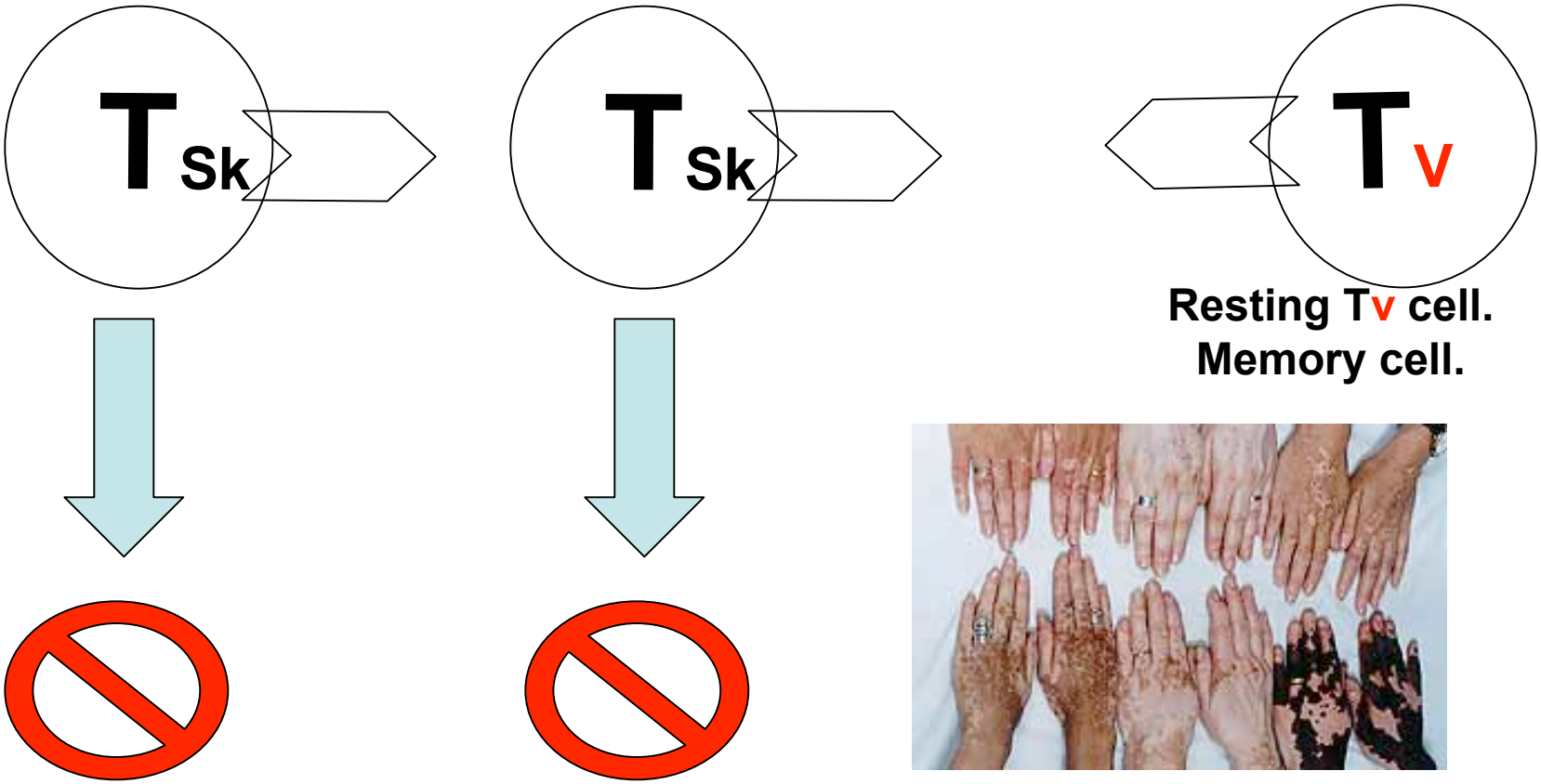


After infection is cleared, no more dendritic cell activation and no more Signal 1 and Signal 2. T cells not active.



After infection is cleared, no more dendritic cell activation and no more Signal 1 and Signal 2 in the DLN.

T cells not active.

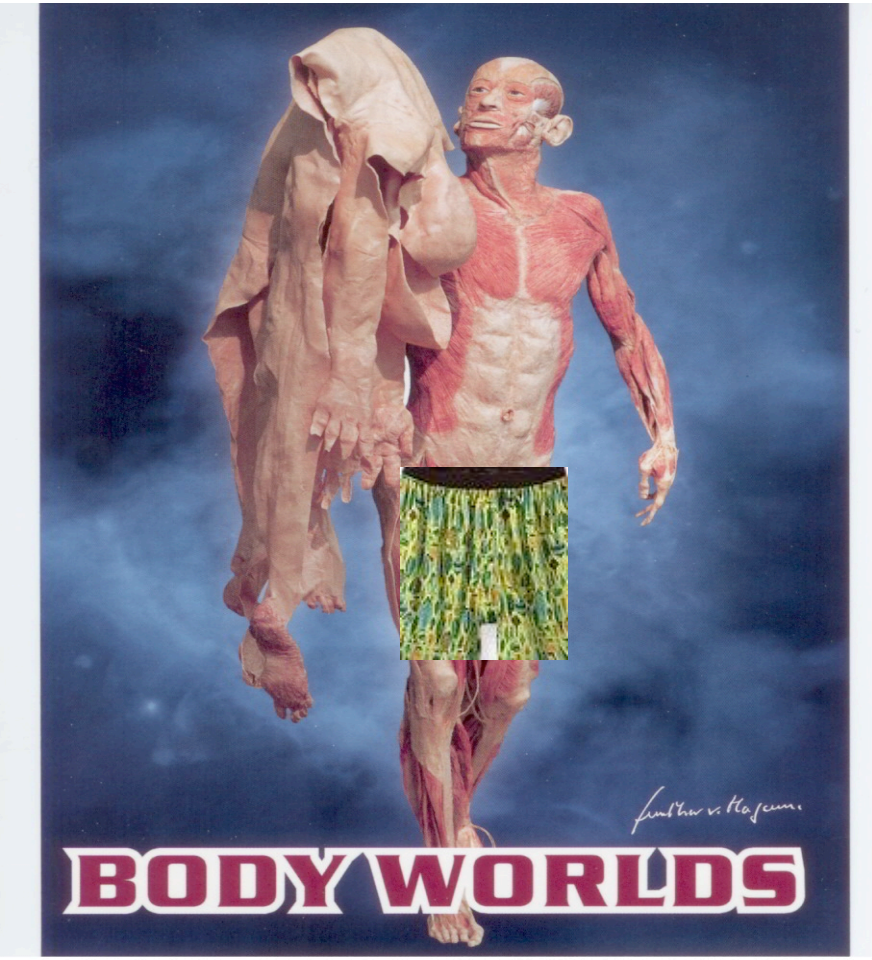


Resting Tv cell.
Memory cell.

Vitiligo-
Associated with spontaneous melanoma remission

Deletion of Tsk (Signal one only) and maintenance of Tv cells. Tolerance established.

Outcome dictated by tissue size.



- **Like the tumor model, the size of the infected tissue defines the outcome *i.e.*, there are infinitely more Sk antigens than V antigens.**

Spontaneous Tumor Regression

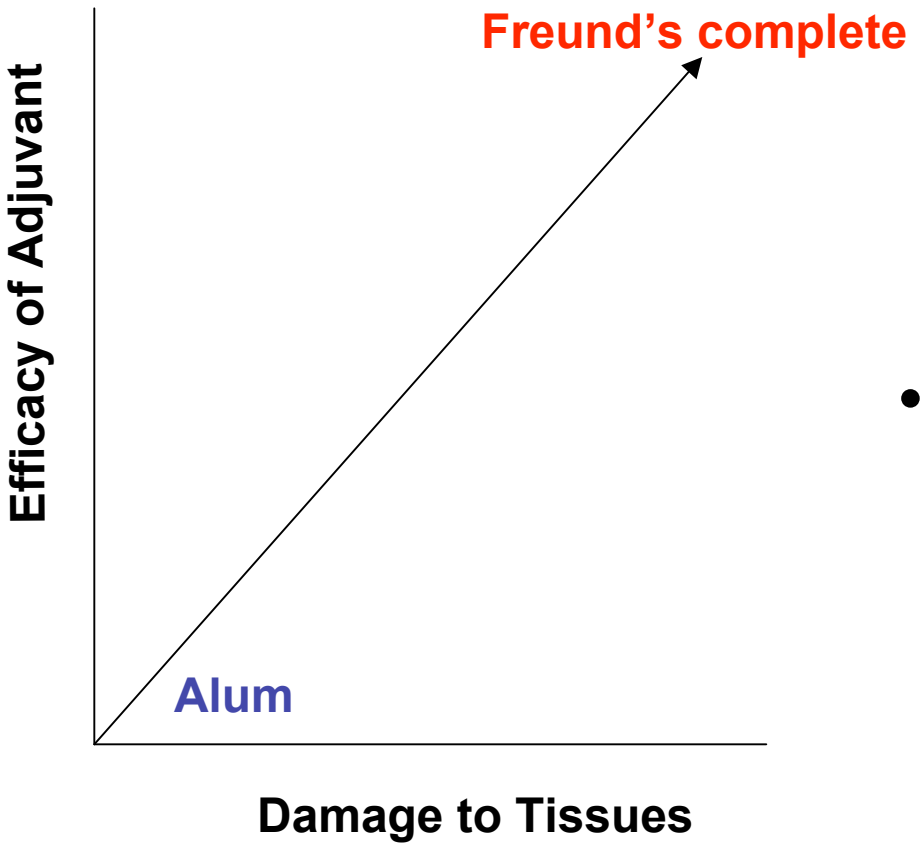
- **Concurrent with acute bacterial infections.**
- **Administration of bacterial vaccines.**
- **Removal of at least some of the tumor or its metastases.**
- **Compiling 449 cases of spontaneous regression most were commonly associated with suppurative infections *e.g.*, *S. pyogenes* (Nautus, 1980).**

Spontaneous Tumor Regression

- **Everson and Cole (1966) reported 176 cases of spontaneous regressions.**
  - **40% of the patients had some type of operative trauma.**
  - **24% excision of the primary tumor was followed by regression of metastases.**

--Both surgery and infection result in tissue-mediated danger signals.

Why so many vaccines (protein) do not work.



- Most do not elicit a danger response, especially those approved for human use *i.e.*, alum.
- Attenuated pathogens, DNA vaccines, elicit danger signals without the need for adjuvants.

Danger and Tissue Transplantation

- **Until the mid-1980s, most attempts to transplant organs were unsuccessful.**
- **Then, cyclosporine A was found to block the activation of the immune system, and soon transplant successes were occurring everywhere.**

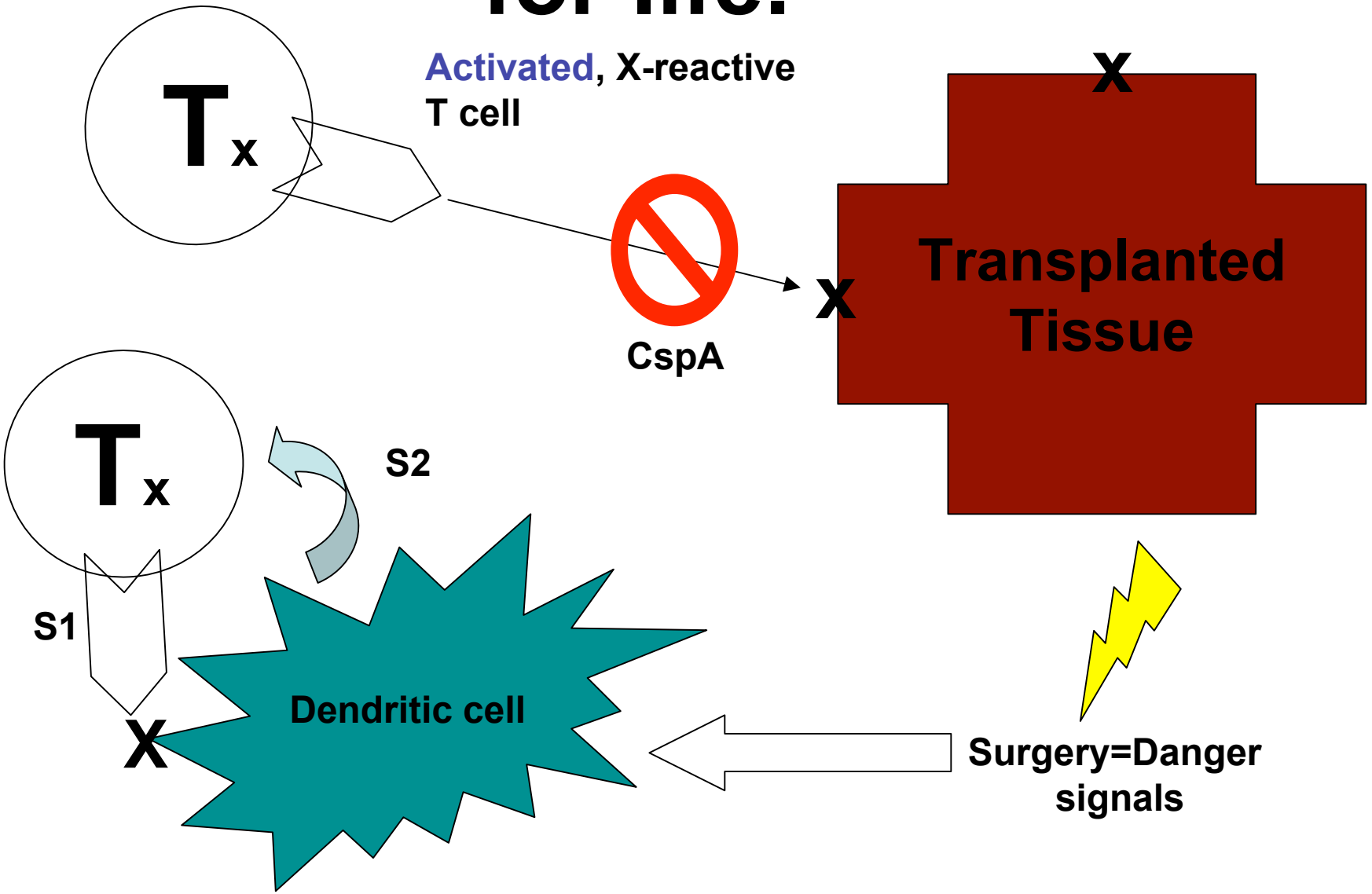
Danger and Tissue Transplantation

- **90-95% transplants lasted longer than 1 year.**
- **However, 40-50% of kidney transplants were lost by 10 years.**
- **30% of patients now on kidney waiting lists have already had one--and lost it.**
- **Patients need to take the drug the rest of their lives, living on the edge of immunosuppression with a constant threat of infections.**

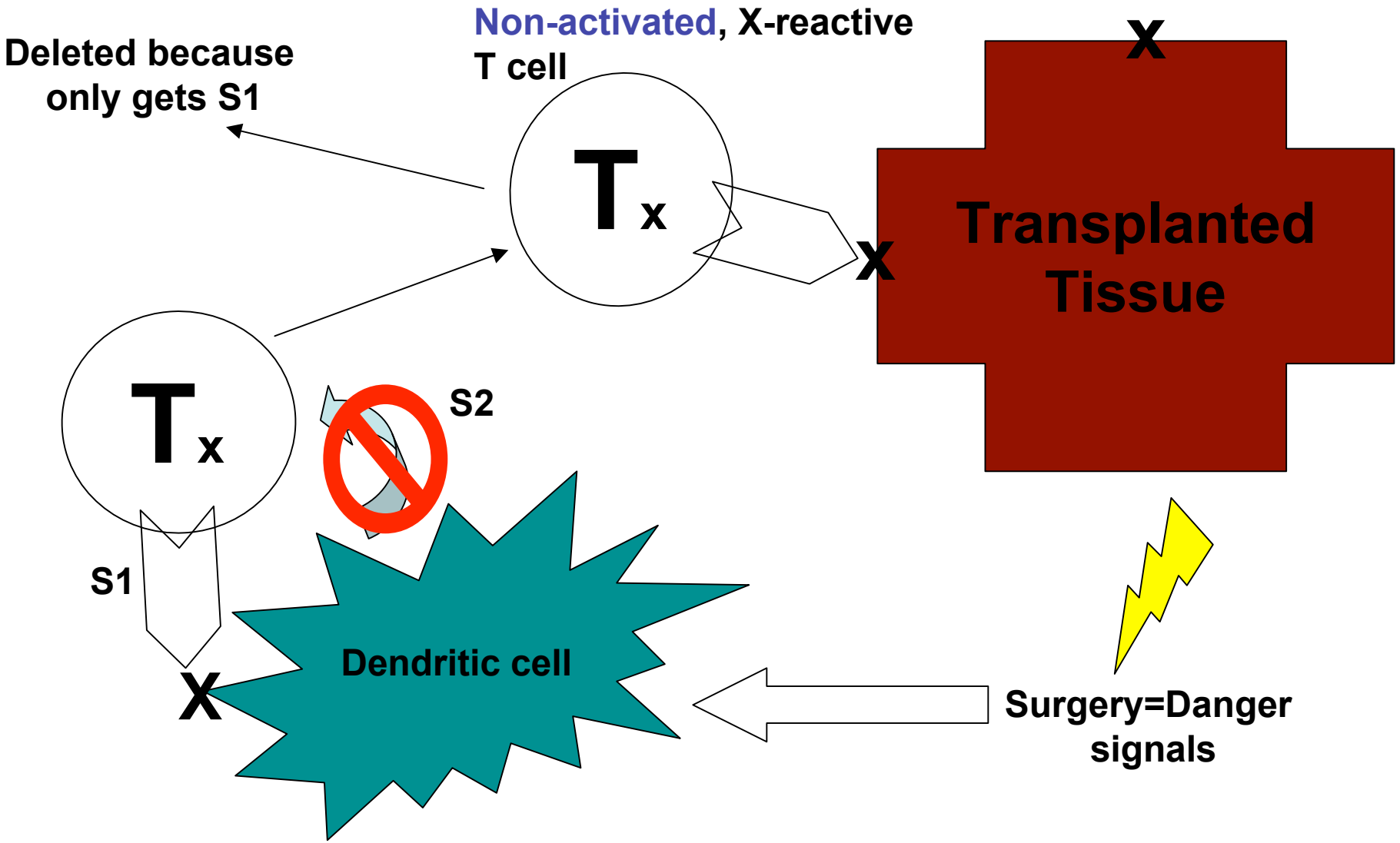
Danger and Tissue Transplantation

- **A better approach came from:**
- **1) Understanding how cyclosporine A works *i.e.*, by blocking signal one.**
- **2) The understanding that the body's normal tolerance mechanism hinges on Signal 2, NOT Signal 1.**

Why you have to take CspA for life.



Alternative strategy to CspA.



Mounting a Response