

Decline of Immune Responses and Immunologic Memory

Contraction, persistence, and antigen-specific recall

Dr Abu Suraih Sakhri

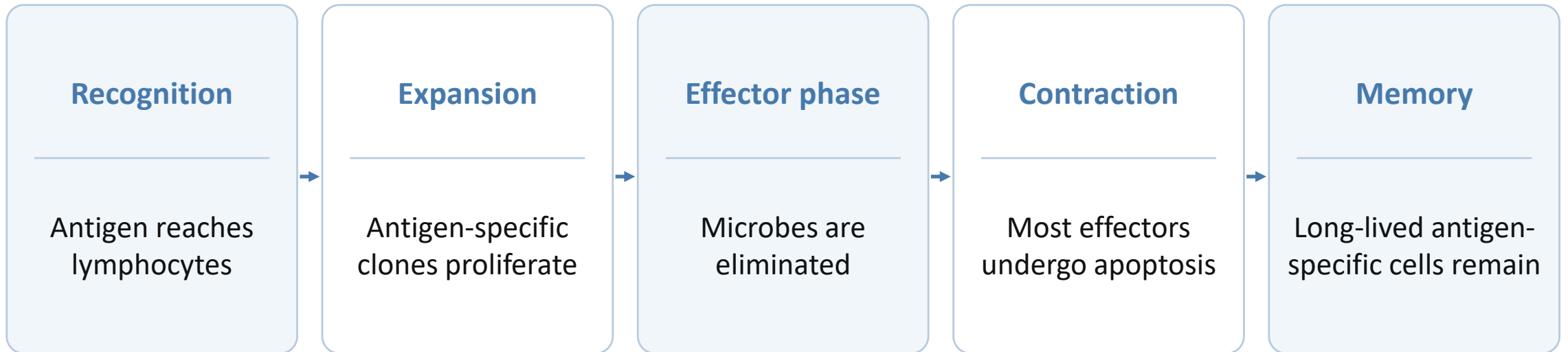
MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain how antigen clearance initiates contraction of an immune response.
- Distinguish apoptotic loss of effector lymphocytes from persistence of memory cells.
- Trace the generation of T-cell and B-cell memory from primary lymphocyte activation.
- Connect memory-cell abundance and responsiveness with vaccination and recall immunity.

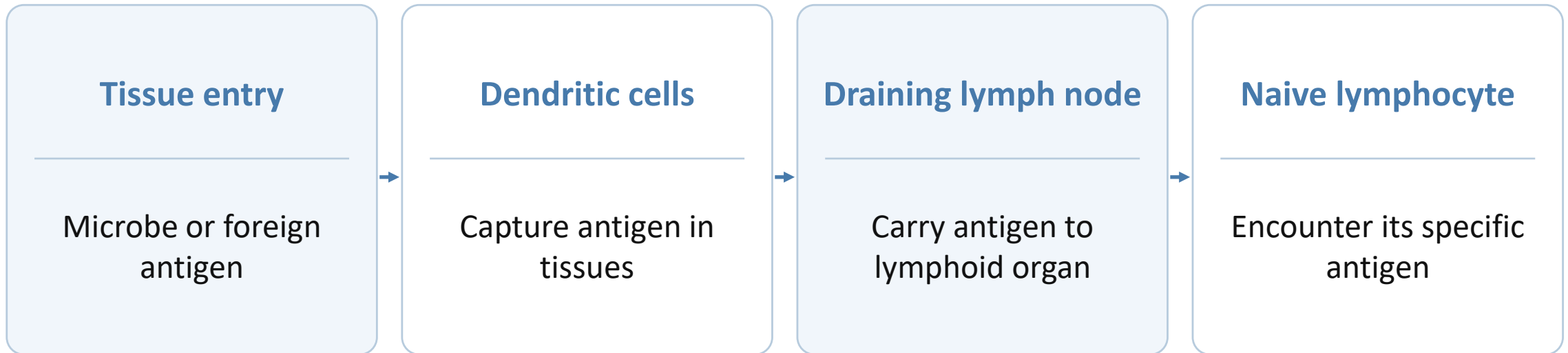
Adaptive responses follow an ordered sequence



The naive antigen-specific pool is initially limited

- Before antigen encounter, only a small pool of naive lymphocytes recognizes that particular antigen.
- Antigen capture and concentration in lymphoid organs increases the chance of productive recognition.
- Primary activation expands this antigen-specific pool before most effector cells are lost.
- After contraction, surviving memory cells outnumber the corresponding preimmune naive population.

Antigens are concentrated in lymphoid tissues



T and B lymphocytes recognize antigen differently

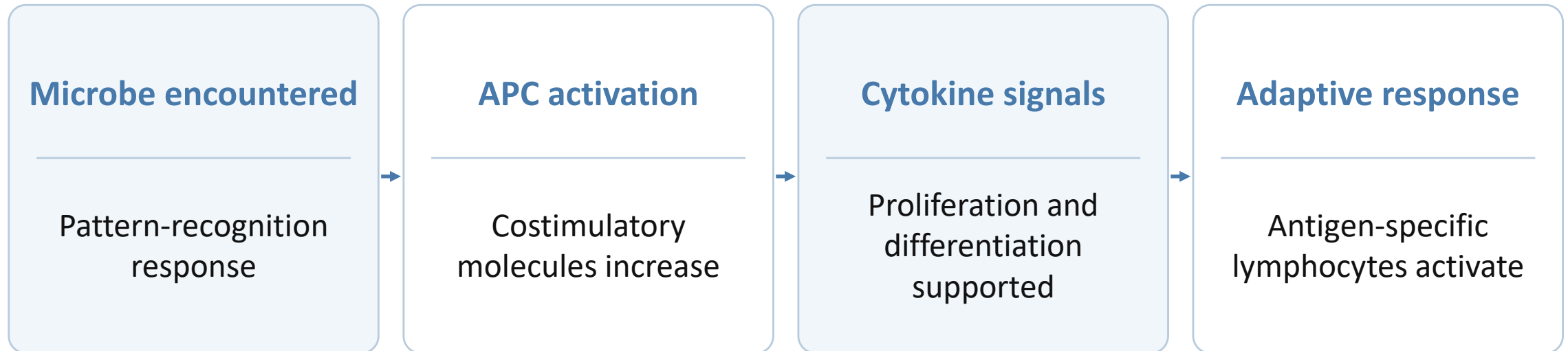
T lymphocyte

1. Recognizes a peptide displayed with MHC on an antigen-presenting cell.
2. Antigen presentation and costimulation promote activation.
3. Generates effector and memory T cells.

B lymphocyte

1. Membrane immunoglobulin recognizes antigen directly.
2. Recognizes proteins, polysaccharides, or lipids.
3. Generates antibody-secreting cells and memory cells.

Innate signals prepare adaptive immunity



Naive T-cell activation requires cooperating signals

Signal 1: Specificity

1. T-cell receptor detects peptide–MHC.
2. Determines which clone is selected.
3. Recognition alone is not the complete activation context.

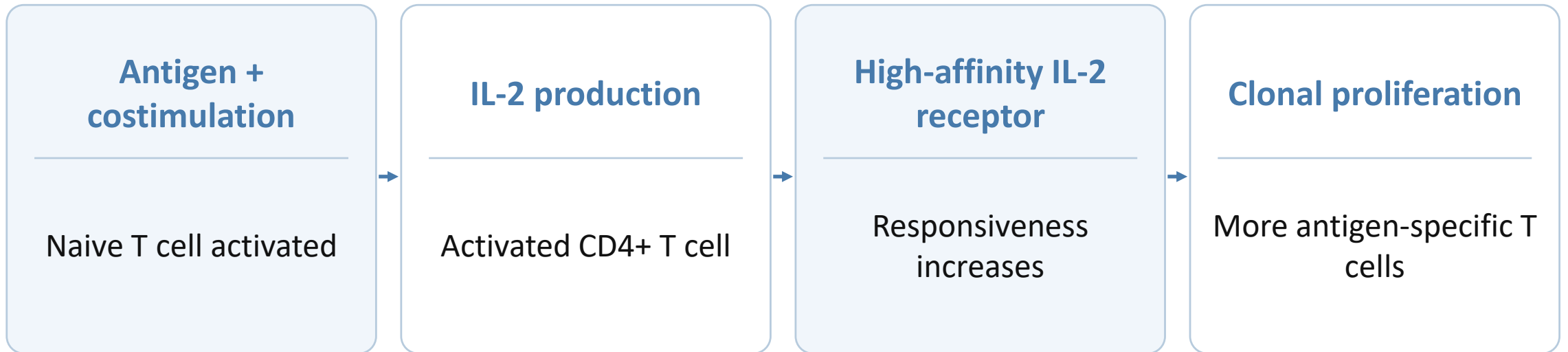
Signal 2: Costimulation

1. APC B7 (CD80/CD86) engages CD28 on naive T cells.
2. Generated during innate activation to microbes.
3. Supports effective lymphocyte activation.

Costimulation links adaptive defense to danger

- Microbes stimulate innate immune cells before a full adaptive response develops.
- Activated APCs express B7 proteins and release cytokines.
- This couples antigen recognition to the presence of a biologically relevant stimulus.
- Homeostatic immune regulation limits inappropriate responses after activation signals resolve.

IL-2 forms an amplification loop in activated T cells



Clonal expansion creates the effector population

- Antigen-stimulated T cells proliferate in secondary lymphoid organs.
- The expanded population contains many cells of the same antigen specificity.
- Expansion provides sufficient effector cells to reach sites of infection.
- This expansion precedes the decline that occurs after microbial elimination.

Activation produces more than one cell fate

Activated antigen-specific lymphocyte

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graph TD; A[Activated antigen-specific lymphocyte] --> B[Effector progeny]; A --> C[Memory progeny];
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Effector progeny

Immediate microbe control
Predominantly short-lived

Memory progeny

Persist after infection
Respond on re-exposure

CD4+ T cells coordinate antimicrobial defenses

Th1

IFN- γ helps activate macrophages

Th2

IL-5 activates eosinophils against helminths

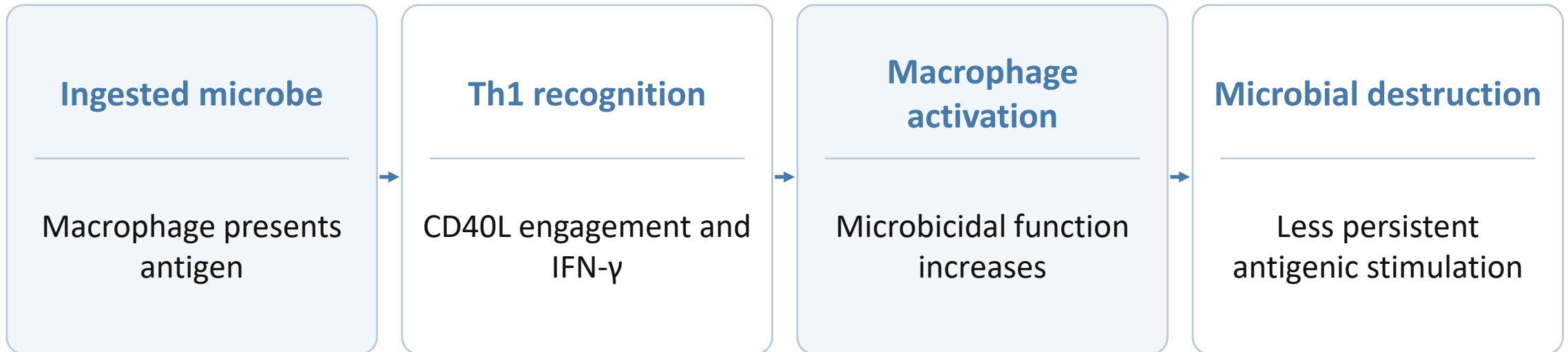
Th17

IL-17 promotes recruitment of neutrophils and monocytes

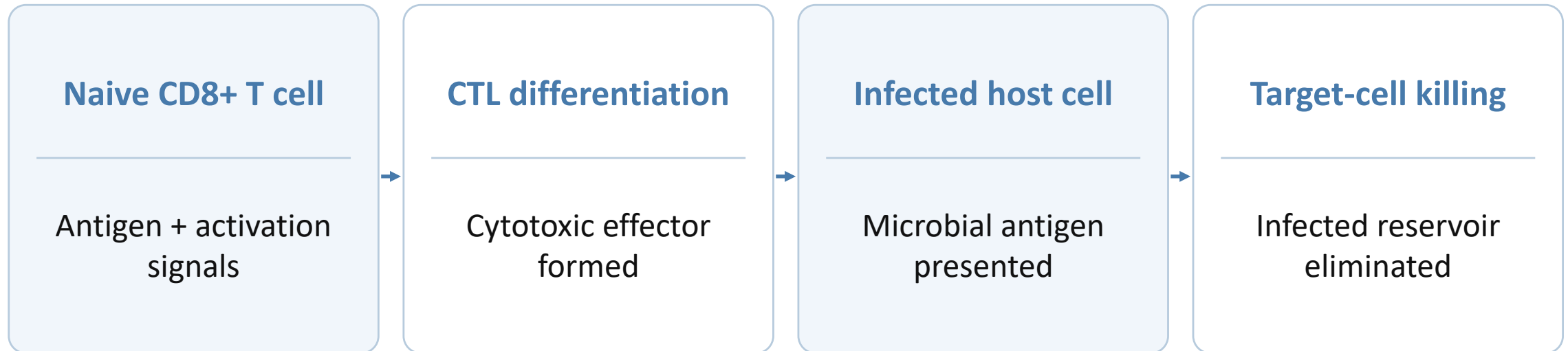
Tfh

Provide help for B-cell antibody production

Th1 cells help macrophages eliminate ingested microbes



CD8+ cytotoxic lymphocytes remove infected reservoirs



Effector T cells leave lymphoid organs for tissues

- Naive T cells are activated in secondary lymphoid organs.
- Effector T cells migrate into the circulation and toward sites of infection.
- CD4+ subsets coordinate local antimicrobial responses.
- CD8+ CTLs kill infected cells containing cytosolic microbes.

Antigen elimination uses complementary arms

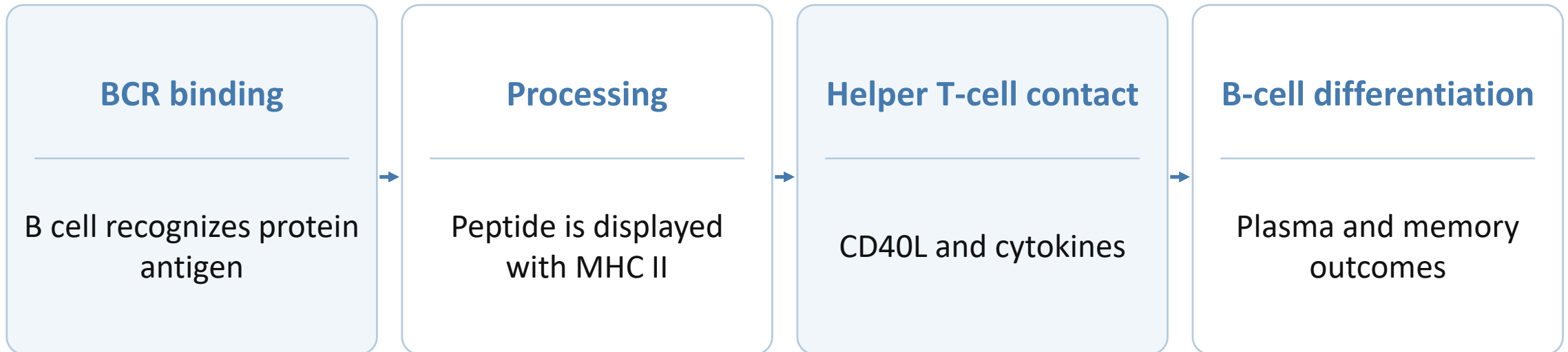
Cell-mediated defense

1. CD4+ effectors stimulate phagocytes and recruit leukocytes.
2. CD8+ CTLs kill microbe-harboring host cells.
3. Especially important for intracellular microbes.

Humoral defense

1. Plasma cells release antigen-specific antibodies.
2. Antibodies neutralize, opsonize, and activate complement.
3. Especially important for extracellular microbes.

Protein-antigen B-cell responses require T-cell help



CD40L and cytokines cooperate in B-cell activation

- Antigen-specific B cells internalize bound protein and display peptide–MHC II.
- Activated helper T cells recognize the displayed peptide.
- CD40L on T cells engages CD40 on the B cell; Cytokines provide additional help.
- These signals support proliferation, class switching, affinity maturation, and differentiation.

T-independent responses take a different route

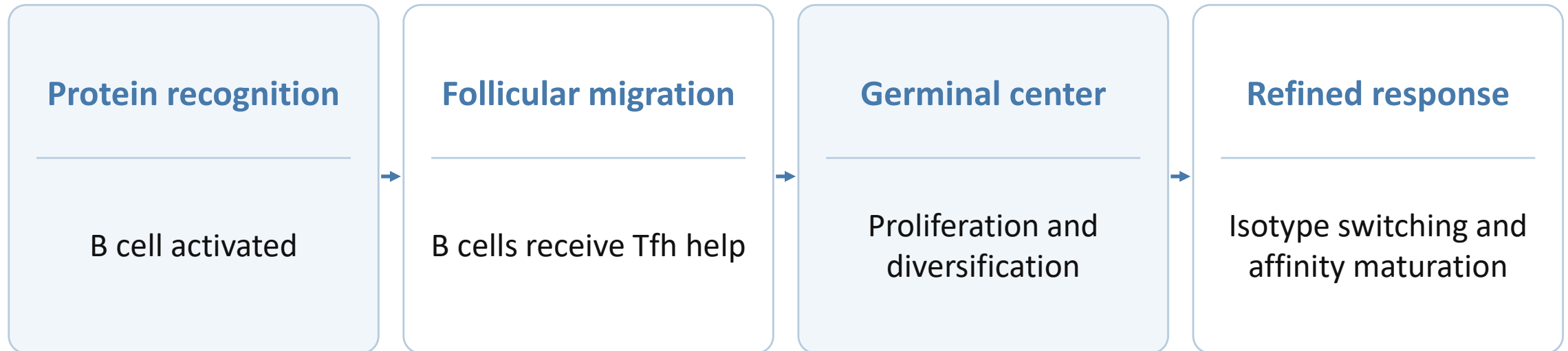
T-dependent protein response

1. Needs helper T-cell interaction.
2. Can undergo class switching and affinity maturation.
3. Supports generation of long-lived memory cells.

T-independent response

1. Multivalent polysaccharide or lipid antigens can cross-link BCRs.
2. Does not require conventional T-cell help.
3. Produces mainly IgM of relatively low affinity.

Germinal centers refine the antibody response



Isotype switching changes antibody function

- Tfh-derived signals support switching from the initial antibody heavy-chain class.
- Protein-antigen responses may generate IgG, IgA, or IgE.
- Changed isotype alters effector function without changing the targeted antigen specificity.
- This broadens the functional repertoire of the humoral response.

Affinity maturation improves antibody quality

- Tfh help supports the production of antibodies with progressively higher affinity.
- This process occurs in the context of the germinal-center response.
- Higher affinity improves antigen binding compared with earlier antibody products.
- Affinity maturation as an important goal of vaccination.

Activated B cells generate distinct long-term outputs

Antigen-stimulated B lymphocyte

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graph TD; A[Antigen-stimulated B lymphocyte] --> B[Antibody-secreting plasma cell]; A --> C[Memory B lymphocyte];
```

Antibody-secreting plasma cell

Immediate antibody secretion
Some persist in bone marrow

Memory B lymphocyte

Antigen-specific reserve
Participates in later response

Antibodies eliminate microbes through several mechanisms

Neutralization

Blocks microbes from infecting cells

Opsonization

IgG coats microbes for Fc-receptor
phagocytosis

Complement

IgG and IgM activate the classical pathway

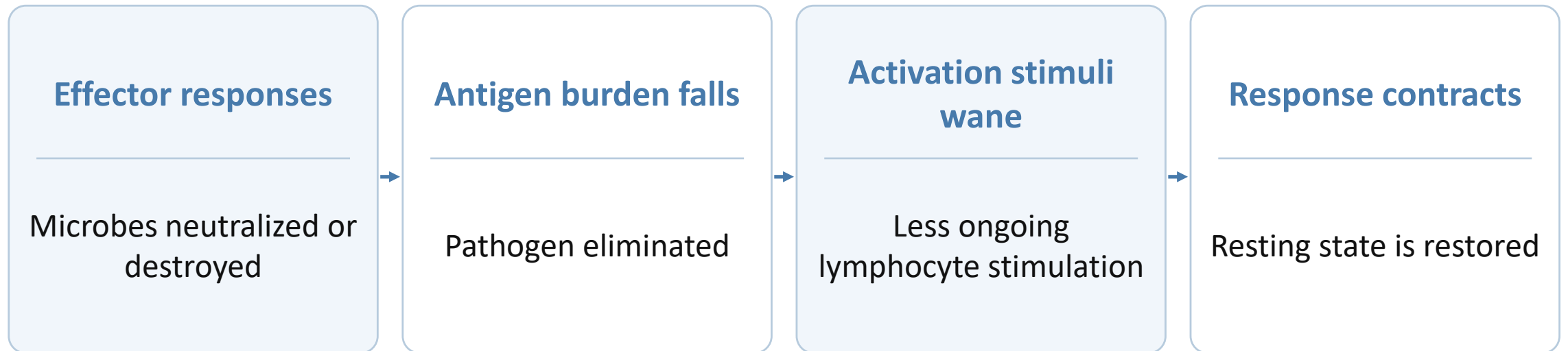
Specialized sites

IgA neutralizes microbes at mucosa

Long-lived plasma cells sustain antibody secretion

- Each plasma cell secretes antibody matching the original B-cell antigen specificity.
- Some plasma cells generated in germinal centers migrate to the bone marrow.
- These cells may continue to produce antibodies for months or years.
- This persistent secretion is distinct from the rapid activation of memory lymphocytes on re-exposure.

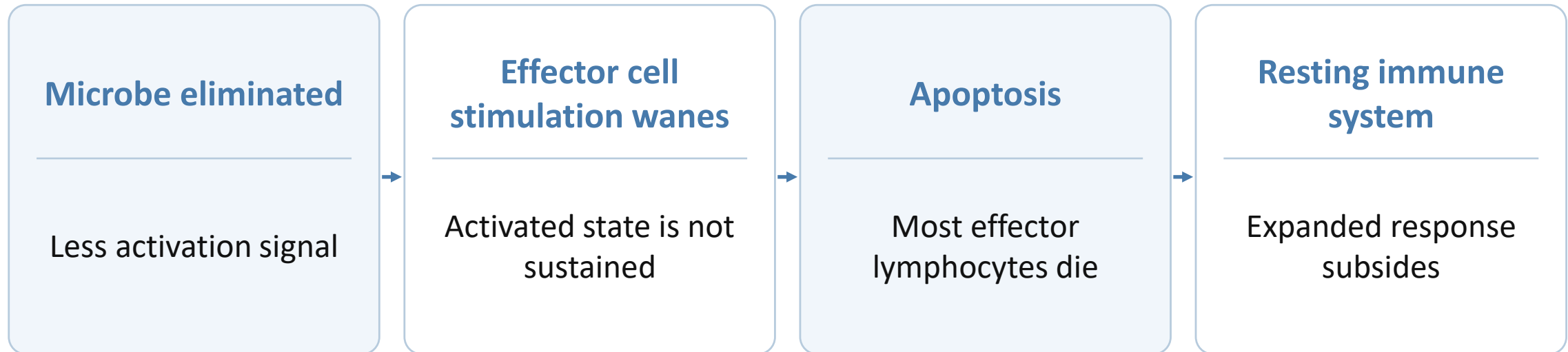
Clearance of the microbe changes the immune environment



Immune contraction begins after pathogen elimination

- The decline of the response to elimination of infectious microbes.
- With the microbe absent, stimuli that sustained lymphocyte activation decrease.
- The population of activated effector lymphocytes therefore becomes much smaller.
- Contraction is an expected endpoint of successful immune defense.

Most effector lymphocytes are removed by apoptosis



Apoptosis explains decline without erasing specificity

- Apoptosis removes much of the expanded effector-cell population.
- The contraction phase is selective: It does not eliminate every antigen-specific descendant.
- Some activated lymphocytes have already differentiated into long-lived memory cells.
- Preserved memory allows a new response if the same antigen is encountered again.

Contraction is not equivalent to immune failure

Physiologic contraction

1. Follows successful pathogen clearance.
2. Most effector cells undergo apoptosis.
3. An antigen-specific memory population remains.

Loss of protective immunity

1. Not implied by falling effector-cell numbers.
2. Cannot be diagnosed from contraction alone.
3. Requires separate evidence of impaired protection.

The response follows a qualitative population sequence



The immune system returns toward a resting state

- Persistent activation is unnecessary once the original microbial threat is eliminated.
- Declining activation stimuli accompany widespread effector-cell apoptosis.
- The previously enlarged effector population shrinks.
- A reduced resting-state population coexists with long-lived antigen-specific memory.

Effector loss and memory survival coexist

Expanded antigen-specific population

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graph TD; A[Expanded antigen-specific population] --> B[Majority: Effector-cell death]; A --> C[Minority: Long-lived survivors];
```

Majority: Effector-cell death

Apoptosis after clearance
Response returns to baseline activity

Minority: Long-lived survivors

Memory cells remain
Ability to respond again is retained

Memory is generated during the primary response

- Lymphocyte activation produces effector cells and a memory-cell population.
- Memory-cell development begins during the initial encounter, not only after all effectors die.
- Surviving cells persist after the infectious episode resolves.
- The subsequent contraction therefore leaves a lasting change in the antigen-specific repertoire.

Immunologic memory is antigen-specific persistence

- Memory lymphocytes are long-lived descendants generated by antigen-driven activation.
- They are specific for an antigen encountered previously.
- They persist in the circulation, secondary lymphoid organs, and peripheral tissues.
- They respond faster and more effectively than naive cells after renewed exposure.

Memory cells form an expanded antigen-specific pool

Before first encounter

1. Relatively few naive lymphocytes have the relevant specificity.
2. A full primary activation and expansion process is needed.
3. The immune system has not yet expanded this clone.

After resolved encounter

1. A larger number of antigen-specific memory cells remain.
2. These cells are available for a subsequent challenge.
3. This numerical advantage contributes to recall responsiveness.

Memory persists across multiple anatomic compartments

Secondary lymphoid organs

Sites where antigen-specific cells are concentrated

Circulation

Cells can remain within the recirculating compartment

Peripheral tissues

Long-lived cells can persist near potential entry sites

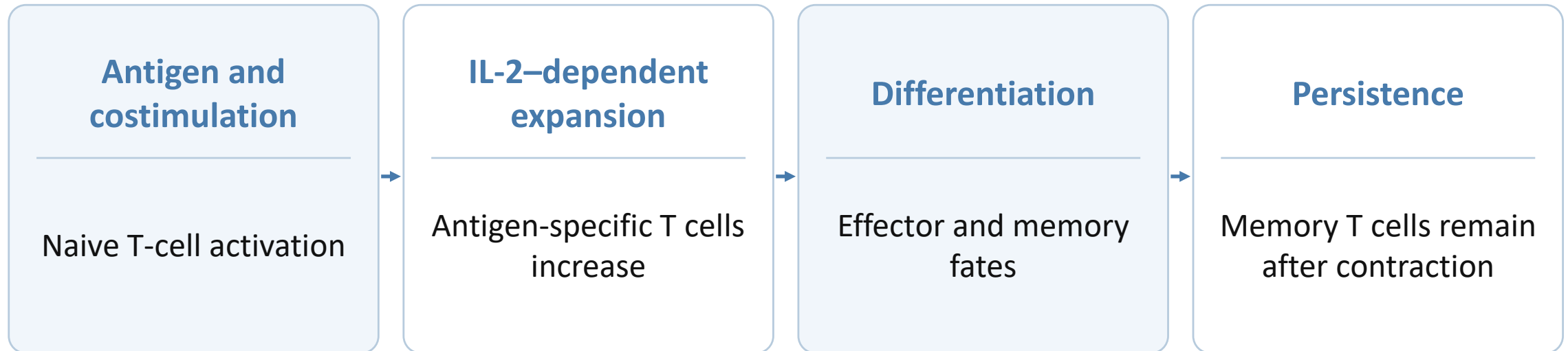
Lymphoid organs are both induction and memory sites

- Naive lymphocytes encounter concentrated antigens in secondary lymphoid organs.
- Clonal activation and differentiation occur within these sites.
- Some generated memory cells continue to reside in secondary lymphoid organs.
- Thus an organ involved in priming may also harbor antigen-specific memory.

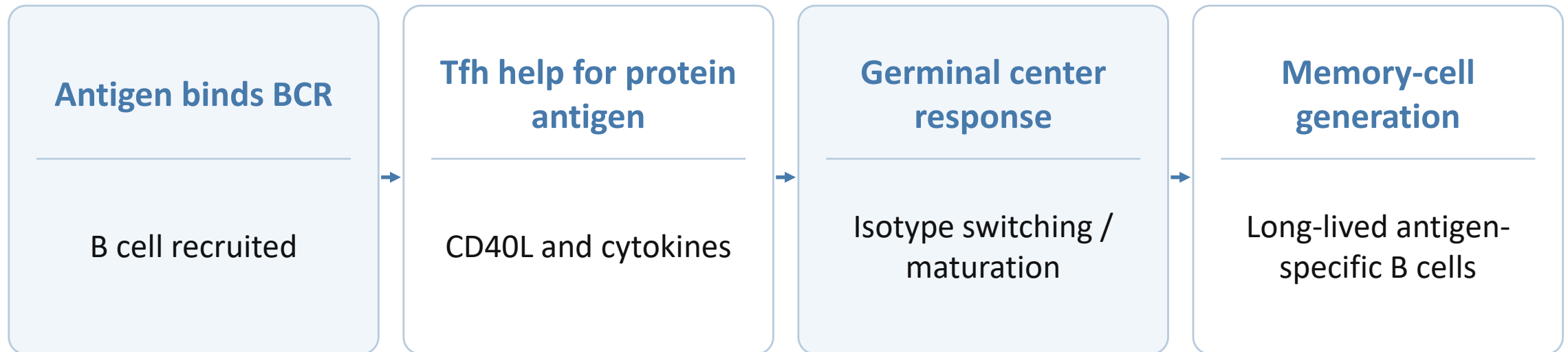
Memory also extends beyond lymph nodes

- Robbins explicitly identifies the circulation and peripheral tissues as memory-cell locations.
- This distribution distinguishes persistent memory from a response confined to the original lymphoid site.
- The text does not assign all memory cells to one fixed anatomic compartment.
- Location and long-term survival are separate features of memory.

Memory T cells arise during T-cell activation



Memory B cells arise with the humoral response



Memory cells and long-lived plasma cells are different

Memory lymphocyte

1. Persistent antigen-specific cell population.
2. Rapid and effective response after re-exposure.
3. Defined by capacity for recall.

Long-lived plasma cell

1. Can reside in bone marrow for months or years.
2. Continuously secretes antigen-specific antibody.
3. Provides ongoing antibody production.

Protection can involve both recall and ongoing antibody

Preexisting antibody

Long-lived plasma cells may maintain secretion

Memory B-cell reserve

Antigen-specific cells persist for subsequent activation

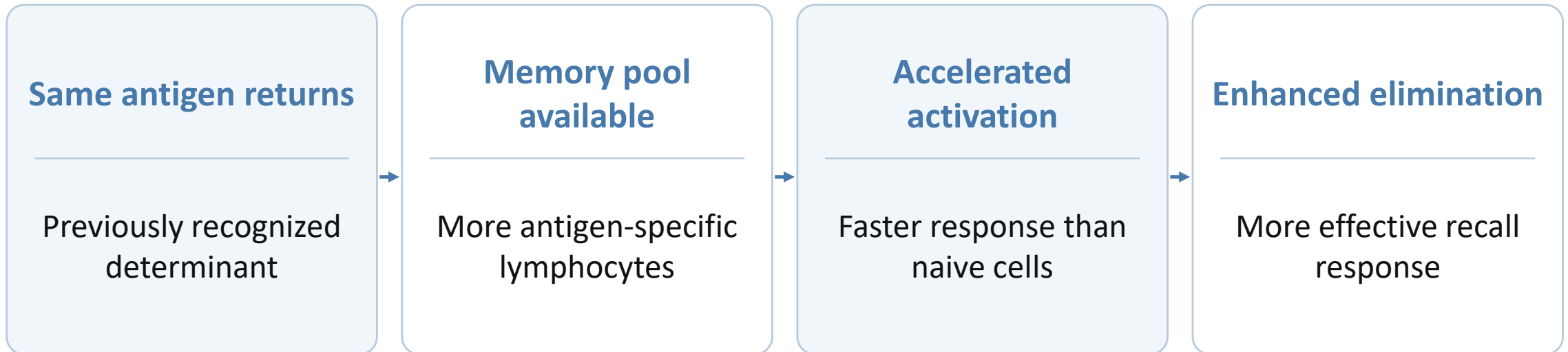
Memory T-cell reserve

Antigen-specific T lymphocytes persist

Re-exposure

A faster, more effective antigen-specific response becomes possible

Second exposure encounters an altered immune repertoire



Primary and secondary responses are conceptually distinct

Primary antigen exposure

1. Starts with relatively few antigen-specific naive cells.
2. Requires activation, proliferation, and differentiation.
3. Generates effector and memory populations.

Subsequent exposure

1. Recruits an expanded antigen-specific memory pool.
2. Response is faster than with naive cells.
3. Response is more effective than the primary naive-cell response.

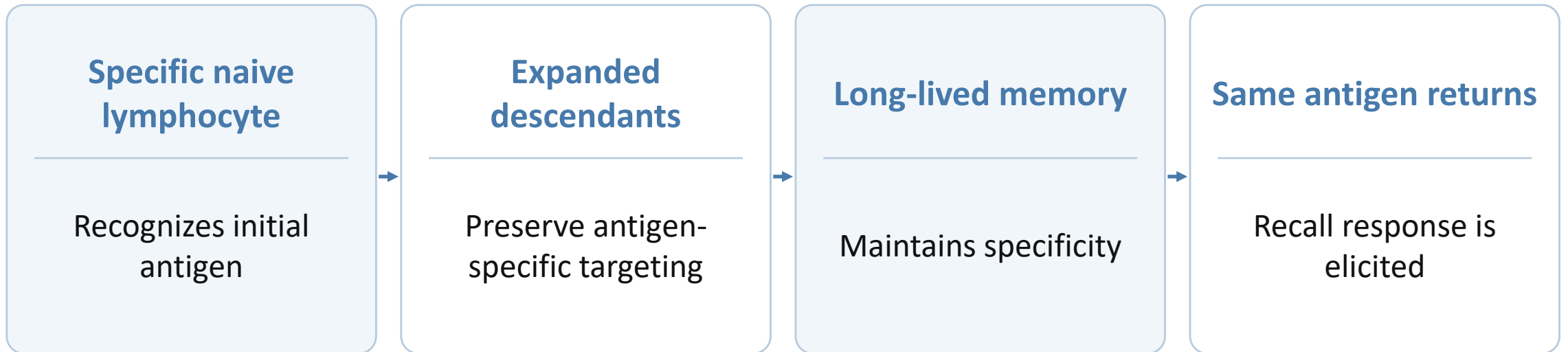
Numerical memory is one basis of faster recall

- Primary exposure increases the number of cells specific for the encountered antigen.
- After effector contraction, memory cells remain more numerous than the original naive pool.
- On re-exposure, more relevant lymphocytes are immediately available to participate.
- Both higher cell number and greater responsiveness as distinguishing features.

Recall is faster and more effective—not merely larger

- Memory lymphocytes differ functionally from the naive cells from which the response began.
- Robbins explicitly describes more rapid responses when memory cells encounter antigen again.
- The secondary response is also described as more effective.
- No numerical fold-change or time-to-response is specified in the supplied section.

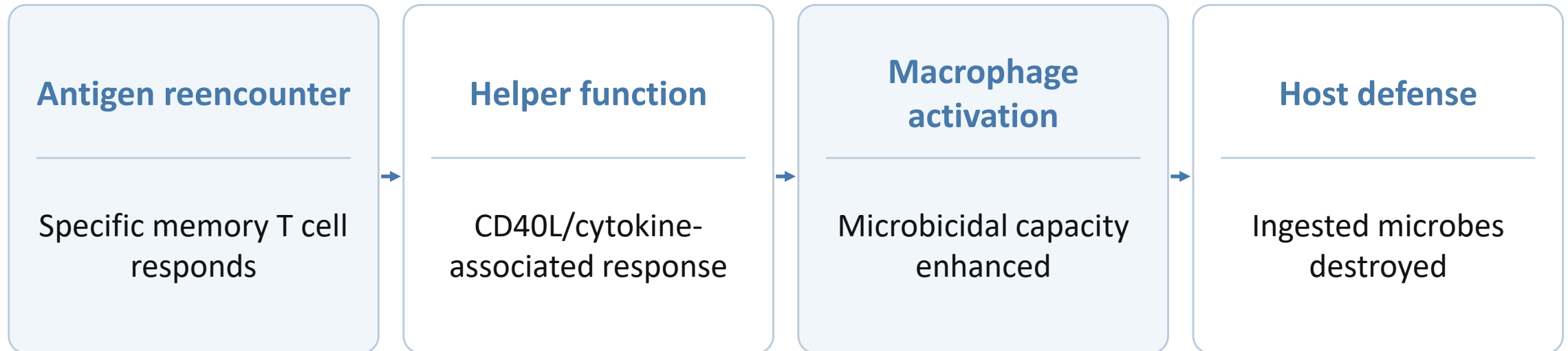
Antigen specificity is retained across the response



Memory T cells support later cell-mediated responses

- Initial T-cell priming generates effectors and long-lived memory lymphocytes.
- Differentiated T-cell effectors include helper and cytotoxic populations.
- The core Robbins account establishes memory T-cell persistence and faster recall, not a detailed memory-subset taxonomy.
- Memory-cell reactivation is distinct from ongoing effector activity after pathogen clearance.

Memory CD4+ responses can reengage phagocyte defense



Memory and CD8+ cytotoxic defense are complementary

- The initial CD8+ response generates cytotoxic T lymphocytes capable of killing infected cells.
- The general lymphocyte activation sequence also produces memory T cells.
- If the same antigen is encountered again, memory is associated with accelerated responsiveness.
- The source does not provide a quantitative cytotoxic-memory time course.

A memory B-cell pool complements humoral maturation

- B-cell activation yields antibody-producing cells and long-lived memory cells.
- Protein-antigen responses can undergo class switching and affinity maturation with T-cell help.
- Germinal-center processes improve the quality and variety of the antibody response.
- Memory B-cell persistence provides a cellular component of later humoral responsiveness.

Persistent antibody is not identical to memory

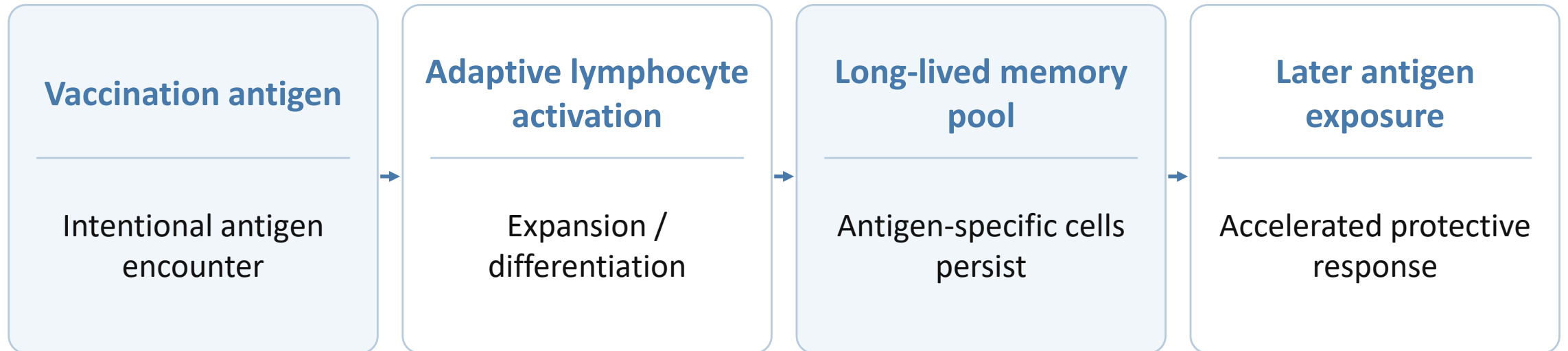
Antibody persistence

1. Antibody can continue to be secreted by long-lived plasma cells.
2. Can be present between exposures.
3. A soluble effector mechanism.

Immunologic memory

1. Long-lived antigen-specific lymphocytes remain.
2. Manifested as enhanced response to subsequent antigen.
3. A persistent cellular capability.

Vaccination uses the ability to generate memory



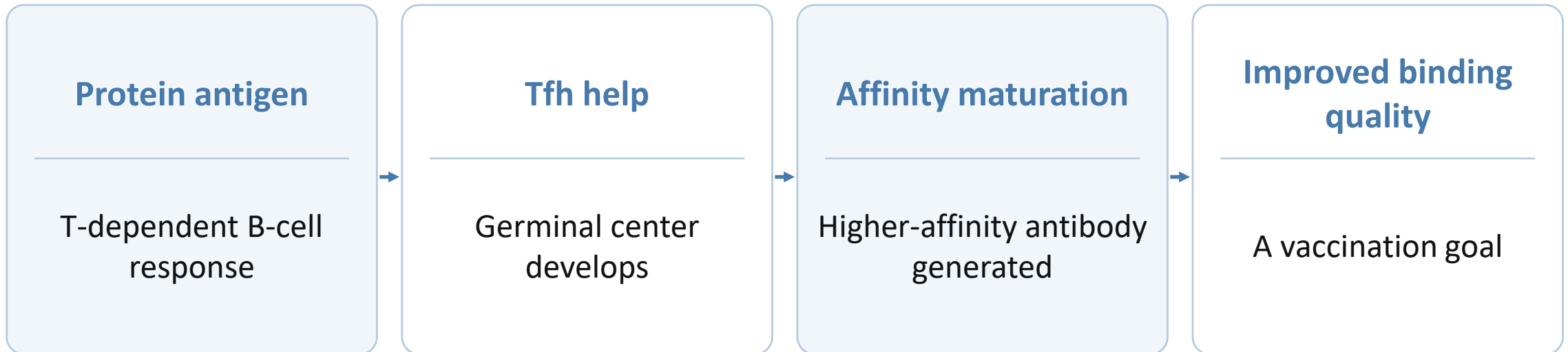
Adjuvants provide innate activation in immunization

- Adjuvants as microbial mimics administered with protein antigens.
- They stimulate innate immune responses in the vaccination setting.
- Innate activation increases APC costimulators and cytokine signals.
- These events help initiate the adaptive response from which memory develops.

Antibody class switching broadens vaccine responses

- Protein antigens can induce T-dependent germinal-center responses.
- Tfh help permits B cells to produce antibody isotypes beyond the initial IgM-dominated response.
- IgG, IgA, and IgE have different biological functions.
- The textbook relates germinal-center refinement to effective humoral immunity.

Affinity maturation is a stated vaccination objective



Vaccination prepares the system before natural exposure

Without previous immunization

1. A newly encountered antigen recruits its small naive-specific pool.
2. Clonal expansion and differentiation must begin.
3. Memory is created during the primary response.

After successful immunologic priming

1. An expanded antigen-specific memory pool already exists.
2. Recall is faster and more effective on re-exposure.
3. This is the textbook basis for vaccine effectiveness.

Vaccination engages cellular and humoral principles

Antigen recognition

Selection of specific T or B lymphocytes

Innate support

APC maturation and costimulation

Effector differentiation

Cell-mediated or antibody-mediated mechanisms

Memory generation

Long-lived antigen-specific reserve

Natural infection and immunization share core steps

Pathogen-driven response

1. Microbe provides antigen and innate stimulation.
2. Effector cells act to eliminate infection.
3. Memory remains after contraction.

Immunization with antigen/adjuvant

1. Antigen plus adjuvant can stimulate innate and adaptive signals.
2. Intentional priming creates an antigen-specific response.
3. Generated memory supports subsequent recall.

Two arms of immunity can contribute to recall protection

Cellular arm

1. Memory T lymphocytes persist.
2. Relevant effector programs include helper functions and CTL activity.
3. Supports antigen-specific cellular defense.

Humoral arm

1. Memory B lymphocytes persist.
2. Long-lived plasma cells can continue secreting antibody.
3. Antibodies neutralize or target microbes for elimination.

Case: Response to a previously encountered pathogen

A person recovers from an infection. Several months later the same pathogen is encountered again. Why can the response differ?

Mechanistic answer

- Primary exposure generated memory lymphocytes before contraction.
- The antigen-specific memory pool is larger than the original naive pool.
- The recalled response is faster and more effective.

Case: Comparing two antibody responses

One antigen is a protein; Another is a multivalent polysaccharide. Which response has the textbook mechanisms for class switching and affinity maturation?

Mechanistic answer

- Protein responses recruit helper T-cell signals through CD40L and cytokines.
- Germinal centers support class switching and affinity maturation.
- T-independent polysaccharide responses mainly produce low-affinity IgM.

Case: Antibodies persist after clinical recovery

**Antigen-specific antibodies are detectable long after an infection has resolved.
Must there be ongoing infection or active effector-cell expansion?**

Mechanistic answer

- No. Some long-lived plasma cells continue secreting antibodies in bone marrow.
- Antibody secretion can persist while most effector lymphocytes have contracted.
- Cellular memory is a related but distinct form of long-term immunity.

Resolve three common conceptual errors

“Contraction deletes immunity”

Incorrect: Memory cells survive effector apoptosis

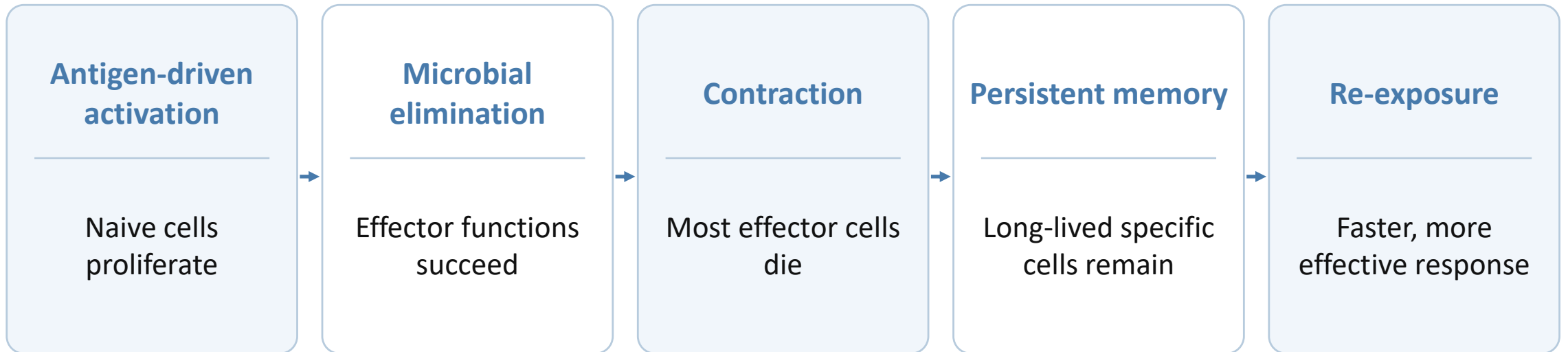
“Memory is simply residual effector activity”

Incorrect: Persistent antigen-specific cells remain after resting state returns

“Persistent antibody proves ongoing infection”

Incorrect: Long-lived plasma cells can secrete after infection resolves

Integrate contraction, memory, and recall



Core principles to retain

- Contraction is the normal decline in effector lymphocyte numbers after antigen elimination.
- Apoptosis removes most effectors as activation stimuli wane.
- Long-lived antigen-specific memory lymphocytes persist in lymphoid organs, blood, and tissues.
- Memory cells are more numerous than the preimmune naive pool and respond faster and more effectively.
- Vaccination exploits the generation of this persistent antigen-specific reserve.

Principal reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).

Chapter 6: Diseases of the Immune System.

Core section: “Decline of Immune Responses and Immunologic Memory” (p. 179).

Supporting sections: “Overview of Lymphocyte Activation and Immune Responses” and preceding T-cell/humoral immunity discussions (pp. 177–179).