

PERSPECTIVE

Transduction, Transcription, and Translation: a practical framework for the pediatric pulmonary specialist for diagnosing and treating inborn errors of immunity

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ABSTRACT

The expanding number of recognized inborn errors of immunity (IEIs), together with rapid advances in biologic, gene, and RNA-based therapies, has increased the diagnostic and conceptual complexity faced by practicing pediatric pulmonary specialists.

This article introduces a practical, biologically grounded framework – Transduction, Transcription, and Translation (“the Three T’s”) – to aid clinicians in understanding, classifying, and diagnosing IEIs.

The work is a conceptual synthesis of classic and contemporary IEIs based on the stage at which immune communication fails.

IEIs can be categorized as disorders of signal reception (Transduction), immune program selection (Transcription), or protein execution (Translation). Mapping disorders to this framework clarifies diagnostic reasoning and therapeutic implications. In conclusion, the Three-T framework offers a clinically intuitive model for interpreting immune dysfunction and may facilitate the integration of emerging targeted therapies.

IMPACT STATEMENT

The “Three-T” framework provides pediatric pulmonary specialists with a practical conceptual model for localizing immune dysfunction in inborn errors of immunity. The model facilitates diagnostic reasoning and helps clinicians integrate emerging biologic, gene, and RNA-based therapies into clinical practice.

INTRODUCTION

In recent years, the field of clinical immunology has undergone a remarkable expansion. New inborn errors of immunity are described annually, and therapeutic options now include targeted biologics, small-molecule inhibitors, gene therapy, and RNA-based approaches (1-3). While these advances have transformed patient care, they have also created a growing challenge for the practicing pediatric pulmonary specialist: how to integrate molecular mechanism, clinical phenotype, and therapeutic strategy into a coherent diagnostic framework (4).

Traditional classifications of IEIs – based on affected cell lineages or immune pathways – remain valuable; however, they do not always provide clinicians with an intuitive way to localize where immune function fails. To address this need, I pro-

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KEY WORDS

Transduction; transcription; translation; inborn errors; immunity.

pose a simple pedagogical model based on the fundamental flow of biological information.

Transduction → Transcription → Translation

The conceptual basis of the Three-T framework was introduced in earlier textbook work (5); however, it is not intended as a rigid or exhaustive classification system, but rather as a practical guide to aid clinical reasoning. This “Three-T” framework conceptualizes immunity as a process of communication, allowing the pediatric pulmonary specialist to ask a sequence of practical questions: “Can the immune system hear the signal? Can it choose the correct response? Can it execute that response?”.

WHY A LANGUAGE-BASED MODEL MATTERS NOW

Advances in immunology increasingly manipulate information rather than cells or organs (6). Gene therapy edits

genetic instructions, mRNA therapeutics deliver executable messages, and biologics block or amplify specific signals. In this context, IEs are best understood not simply as missing components, but as failures in how immune information is received, interpreted, or executed. The Three-T framework aligns naturally with these developments by framing immunity as a communicative process, allowing the clinician to reason mechanistically while remaining grounded in clinical phenotype.

THE THREE T'S: THE GRAMMAR OF THE IMMUNE SYSTEM

All immune responses, whether innate or adaptive, follow a common informational pathway (**Figure 1**):

- 1) Transduction: extracellular signals are received by surface or intracellular receptors.

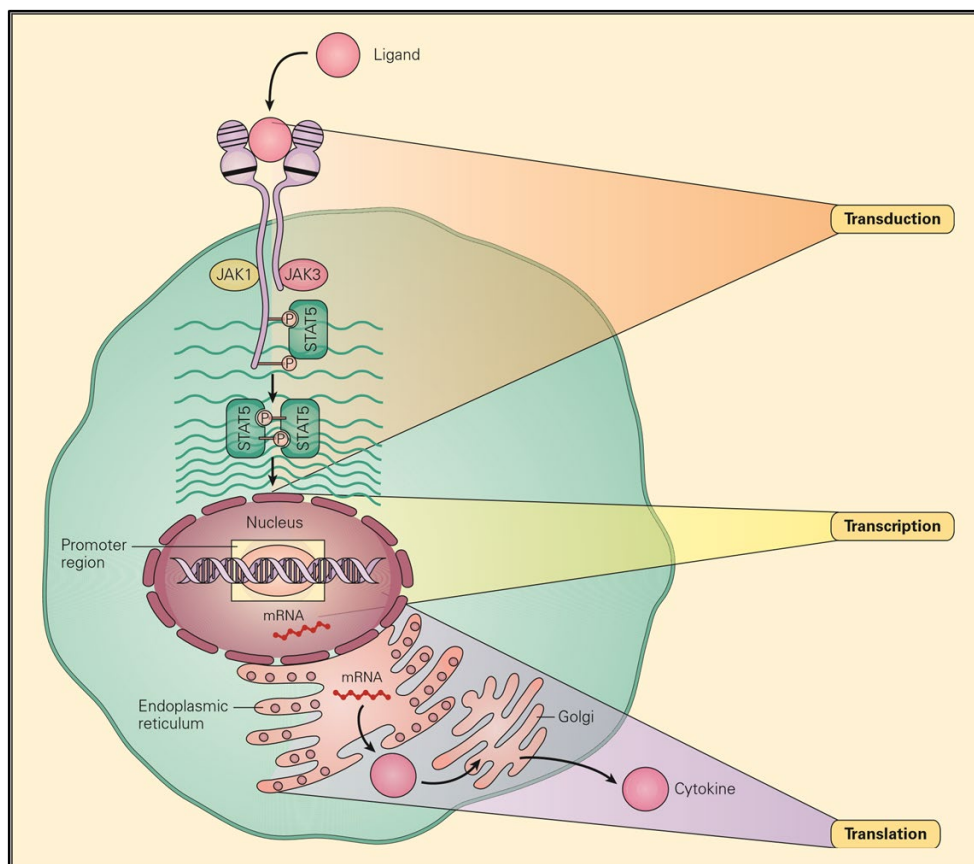


Figure 1. Schematic representations of the “Three Ts” of molecular signaling.

Transduction: from the Latin transducere, meaning “to lead across”. It is the process by which a signal is conveyed from outside the cell to its interior, initiating a cascade of molecular events. Transcription: from the Latin transcribere, “to write across”. It occurs within the cell nucleus, where that signal is converted from DNA into a written molecular message: mRNA. Translation: from the Latin transferre, “to carry across”. It interprets that message to produce the proteins that sustain every heartbeat, immune response, and act of cellular repair. (Reproduced with permission from Reference 5).

2) Transcription: intracellular signaling pathways activate nuclear programs that determine immune cell fate and function.

3) Translation: genetic instructions are converted into functional proteins that execute immune responses. Failure at any of these stages produces characteristic clinical patterns. Framing IEIs within this sequence allows clinicians to localize immune dysfunction conceptually before identifying specific genetic defects.

TRANSDUCTION DEFECTS: WHEN THE IMMUNE SYSTEM CANNOT HEAR

Representative example: IFNAR2 deficiency

In disorders of transduction, immune signals are generated normally but cannot be received. IFNAR2 deficiency exemplifies this category. Despite normal production of type I interferons during viral infection, defective interferon receptor signaling prevents activation of antiviral programs. Clinically, this manifests as severe viral infections and intolerance to live viral vaccines. Conceptually, this represents immune deafness: the message exists, but the receiver is broken.

TRANSCRIPTION DEFECTS: WHEN THE WRONG IMMUNE PROGRAM IS WRITTEN

Representative examples: Activated PI3K- δ syndrome (APDS) and common variable immunodeficiency (CVID)

Transcription defects occur when immune signals are received but interpreted incorrectly. In APDS, gain-of-function mutations in PI3K signaling lead to constitutive pathway activation, resulting in immune dysregulation, lymphoproliferation, and allergic disease. The immune system repeatedly selects inappropriate transcriptional programs. Similarly, CVID often reflects impaired B-cell differentiation and class-switch recombination rather than absence of immune signals or proteins. These disorders represent immune misinterpretation: the signal is heard, but the wrong instructions are written.

TRANSLATION DEFECTS: WHEN IMMUNE EXECUTION FAILS

Translation defects are particularly familiar to allergist-immunologists and account for many classic IEIs. Examples include:

- Severe combined immunodeficiency (SCID): absence of functional immune cell output.
- X-linked agammaglobulinemia (XLA): failure to produce functional BTK protein, resulting in absent antibody production.
- Chronic granulomatous disease (CGD): nonfunctional NADPH oxidase despite intact transcription.
- Wiskott-Aldrich syndrome: defective cytoskeletal protein leading to impaired immune synapse formation.
- DOCK8 deficiency: failure to generate effective protein output from a large, complex gene.

In these disorders, immune intent exists, but execution fails – representing a loss of immune fluency.

THE THREE T'S AS A DIAGNOSTIC FRAMEWORK

Clinically, the Three-T model serves as a practical diagnostic framework rather than a rigid classification system. When faced with a patient with recurrent infection, immune dysregulation or allergy, the clinician may first ask:

- Transduction: are immune signals being received at all?
- Transcription: is immune decision-making biased or inappropriate?
- Translation: is the immune system capable of executing its intended response?

This approach localizes immune failure conceptually before molecular confirmation, guiding both diagnostic testing and therapeutic expectations.

THERAPIES MAP TO THE THREE T'S

The Three T's have relevance not only to diagnosis but also to therapy. Modern immunologic treatments act at distinct stages of immune communication, reinforcing the practical value of this framework for treatment selection (**Table 1**).

Integrating the framework: classic IEIs mapped to the Three-T hypothesis

Table 2 illustrates how selected classic and contemporary IEIs align naturally within the Three-T framework, providing a unifying visual model for diagnostic reasoning and teaching.

WHY TRANSLATION DEFECTS DOMINATE CLASSIC IEIS

Many of the IEIs most familiar to pediatric pulmonary specialist – SCID, X-linked agammaglobulinemia, chronic

Table 1. Alignment of major immunologic therapies with the Three-T framework.

Therapeutic Class	Example	Dominant T*
Biologics	Anti-cytokines, receptor blockade	Transduction
Small-molecule inhibitors	Tyrosine kinase inhibitors	Transcription
Gene therapy	mRNA, protein replacement	Translation

*Dominant T" refers to the primary molecular stage of the 'Three T's' targeted by the respective therapeutic class.

Table 2. Classic inborn errors of immunity mapped to the Three-T framework.

IEI	Dominant T	Core Failure	Conceptual Label
IFNAR2 deficiency	Transduction	Signal not received	Immune deafness
APDS	Transcription	Constitutive signaling bias	Misinterpretation
CVID	Transcription	Faulty B-cell differentiation	Miswritten script
SCID	Translation	No immune output	Global loss of fluency
XLA	Translation	Absent BTK protein	Failed antibody translation
CGD	Translation	Nonfunctional enzyme	Silent execution
WAS	Translation	Cytoskeletal defect	Broken grammar
DOCK8 deficiency	Translation	Protein instability	Incomplete sentencing

granulomatous disease, and Wiskott-Aldrich syndrome – are disorders of translation. In these conditions, immune intent exists, but protein execution fails. In contrast, newly recognized IEIs increasingly affect immune sensing and transcriptional logic, reflecting advances in molecular diagnostics and population genetics. The Three-T framework naturally accommodates both, bridging classic teaching with contemporary discovery.

CLINICAL IMPLICATIONS FOR THE PRACTICING PEDIATRIC PULMONARY SPECIALIST

The Three-T framework offers practical advantages:

- Guides diagnostic thinking before genetic testing.
- Clarifies why targeted therapies succeed or fail.
- Facilitates communication with patients and trainees.
- Bridges classic IEIs with modern gene and RNA therapies.

CONCLUSIONS

Inborn errors of immunity are not random failures of the immune system; they are failures of communication. By framing immune dysfunction as breakdowns in transduction, transcription, or translation, clinicians gain a practical and intuitive tool for diagnosis and education. As immunology advances, restoring immune meaning

– rather than simply correcting components – may be the central therapeutic goal.

COMPLIANCE WITH ETHICAL STANDARDS

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JAB contributed entirely to the work.

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Human studies and subjects

N/A.

Data sharing and data accessibility

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

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