

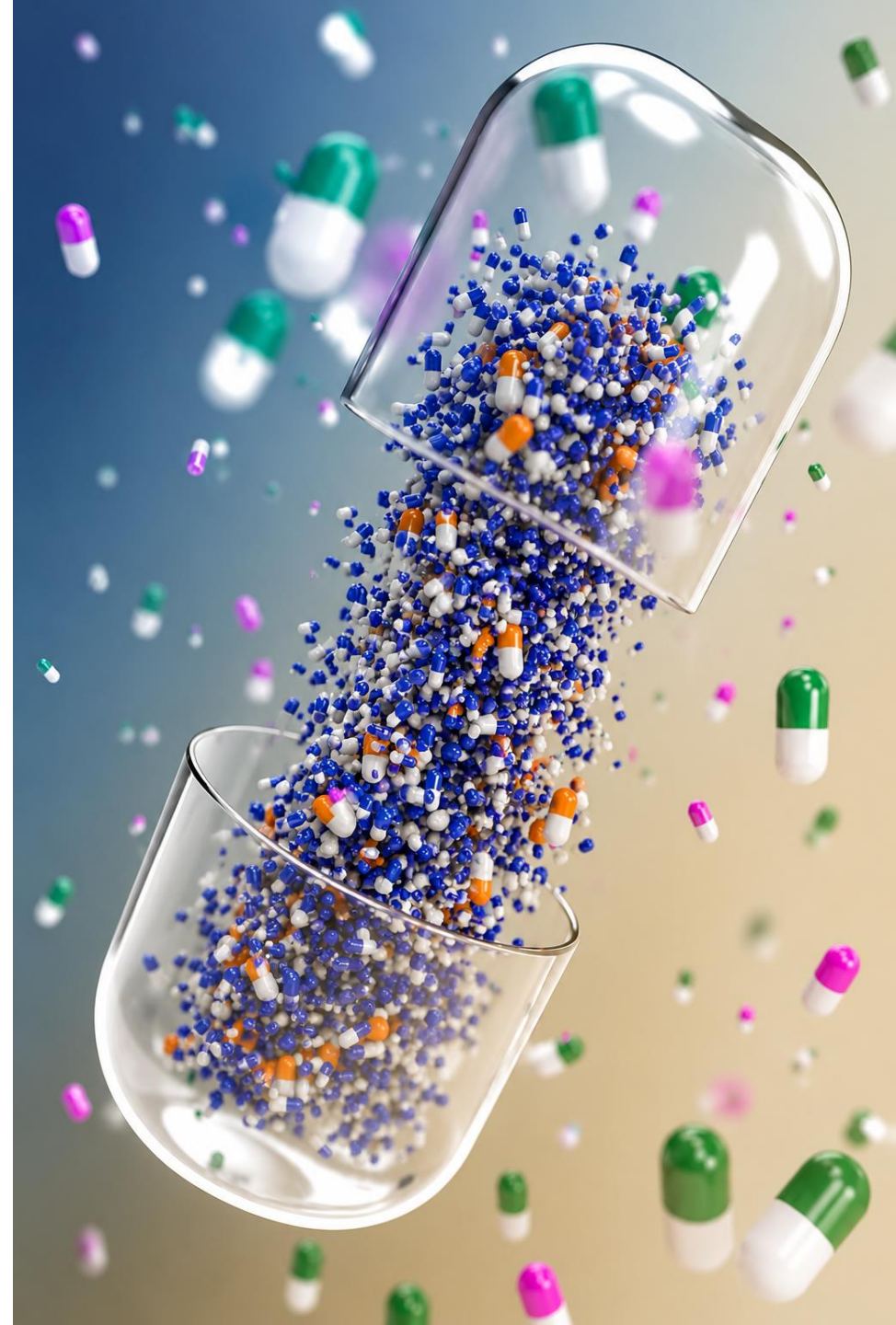
Immunosuppressive Drugs: What's New and What Remains Challenging?

From Broad Immunosuppression to Precision Immune Modulation

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The Therapeutic Paradox

Immunosuppression Is a Balancing Act

Under-Immunosuppression

- Disease relapse / loss of disease control
- Acute or chronic graft rejection
- Alloimmune activation
- Graft-versus-host disease (GVHD)

Over-Immunosuppression

- Opportunistic infections & viral reactivation
- Secondary malignancies
- Organ toxicity
- Metabolic complications

The therapeutic window is **dynamic—not fixed**. It varies with **disease biology**, time after transplantation, concomitant therapies, age and comorbidities, pharmacogenomics, and immune status.



The right drug at the wrong exposure can become the wrong treatment!

Pharmacologic Landscape

Where Do Immunosuppressive Drugs Act?

Target	Drug Class	Representative Agents
Gene transcription	Corticosteroids	Prednisone, methylprednisolone
Calcineurin–NFAT	Calcineurin inhibitors	Tacrolimus, cyclosporine
Nucleotide synthesis	Antimetabolites	Mycophenolate, azathioprine
mTOR	mTOR inhibitors	Sirolimus, everolimus
JAK–STAT	JAK inhibitors	Ruxolitinib, baricitinib, tofacitinib
T-cell costimulation	Costimulation blockade	Belatacept
Lymphocyte depletion	Antibodies	ATG, alemtuzumab
B-cell axis	Targeted biologics	Rituximab, anti-CD38 strategies

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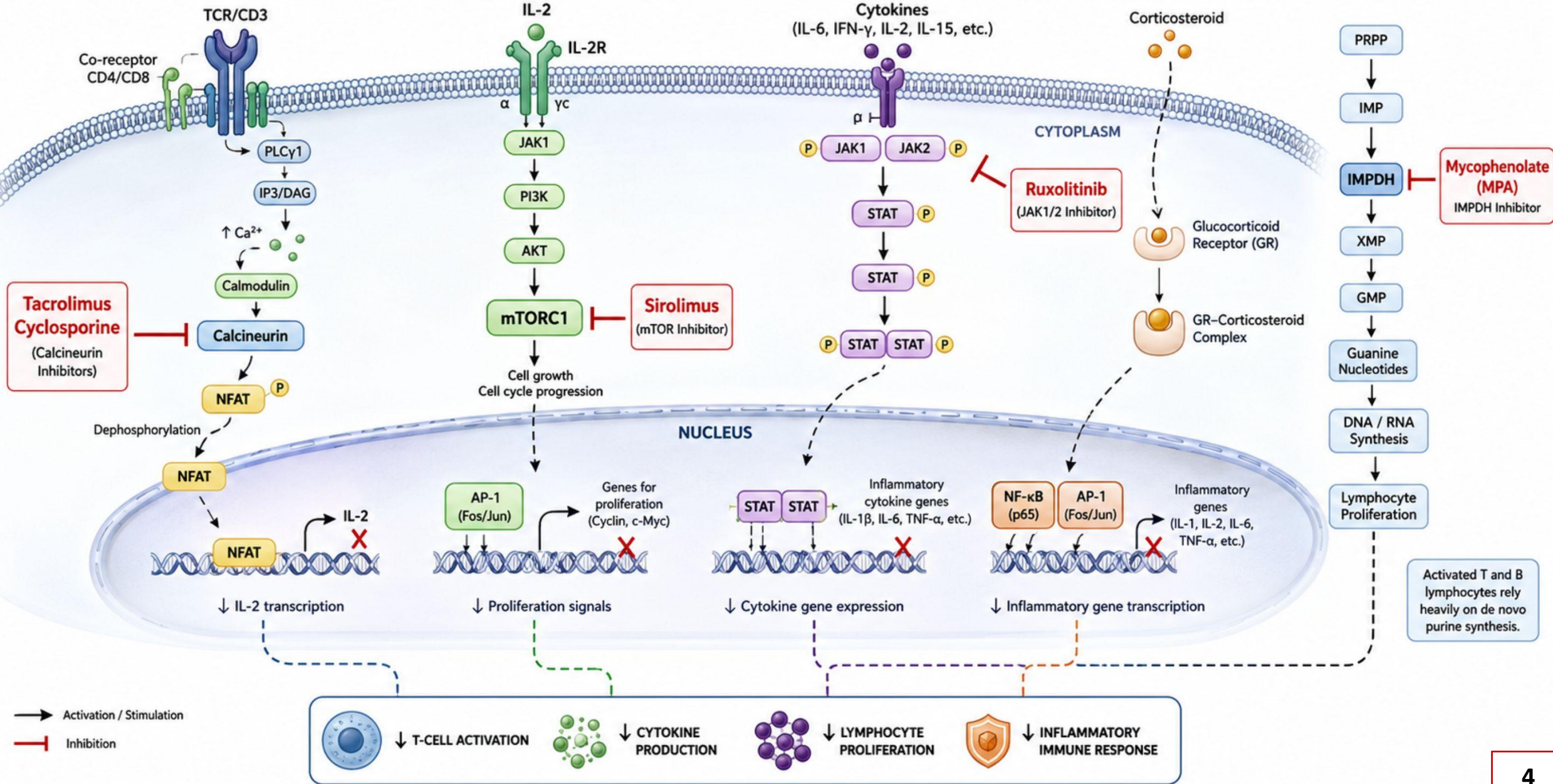
1. CALCINEURIN PATHWAY (TCR SIGNALING)

2. IL-2R / mTOR PATHWAY (PROLIFERATION SIGNAL)

5. JAK-STAT PATHWAY (CYTOKINE SIGNALING)

3. CORTICOSTEROIDS (NUCLEAR EFFECTS)

4. PURINE SYNTHESIS PATHWAY (DE NOVO)





Clinical Applications: One Toolbox, Different Goals

Immunosuppression Across Specialties

Solid Organ Transplantation

Prevention and treatment of rejection. CNI + antimetabolite ± corticosteroid remains the standard backbone, with increasing interest in CNI minimization and avoidance strategies.

Hematopoietic Cell Transplantation

GVHD prophylaxis and treatment (acute and chronic). JAK inhibitors—particularly ruxolitinib—have substantially expanded therapeutic options in steroid-refractory GVHD.

Autoimmune & Inflammatory Disease

SLE, vasculitis, inflammatory myopathies, IBD, and rheumatoid arthritis. Dose intensity and target exposure differ meaningfully from transplant contexts.

Hematology / Oncology

Immune cytopenias, GVHD, and immune-mediated toxicities following cellular therapies. Emerging indications continue to expand the clinical scope.

Same drugs—very different therapeutic objectives, exposure targets, and toxicity thresholds.

Combination Therapy: Why Not Use One Drug?

Multi-Pathway Immunosuppression

Rationale for Combination

- Target multiple stages of lymphocyte activation simultaneously
- Achieve synergistic efficacy at lower individual drug exposures
- Reduce reliance on high concentrations of any single toxic agent

Typical Transplant Regimen

CNI + Antimetabolite + Corticosteroid ± induction immunosuppression
immunosuppression (ATG, basiliximab)

Complexity Created

- Cumulative infection risk across agents
- Drug-drug interactions (PK and PD)
- Overlapping myelotoxicity
- Renal and metabolic toxicity
- Increasing regimen complexity and adherence burden

📌 Clinical principle: Combination therapy improves efficacy—but **exponentially increases** management complexity.

Pharmacokinetics: Why Exposure Matters

Dose $\neq$ Exposure $\neq$ Biological Effect

Tacrolimus: The Prototype

- Narrow therapeutic index with wide inter- and inpatient variability
- CYP3A4/CYP3A5 metabolism; P-glycoprotein-mediated transport
- Major food interactions (grapefruit) and extensive drug interactions

Key Factors Modifying Exposure

- CYP3A5 genotype, age, hematocrit
- Hepatic function, diarrhea/GI dysfunction
- Adherence and concomitant medications

Clinical Implication

A "standard dose" does not produce a standard exposure. Inpatient variability is increasingly recognized as an independent risk factor for rejection and toxicity.

Model-informed and Bayesian dosing approaches are progressively supplanting empirical dose adjustment as the evidence base matures.

Drug–Drug Interactions

Think CYP3A Before Changing the Dose

↑ CNI / Sirolimus Exposure

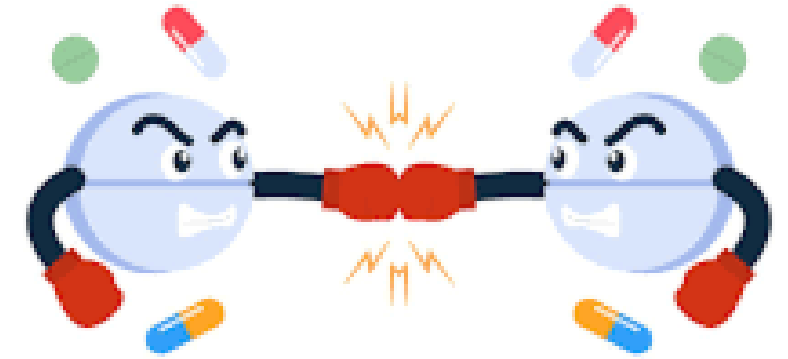
- Azole antifungals (fluconazole, voriconazole, posaconazole)
- Macrolide antibiotics
- Ritonavir-containing regimens
- Some calcium-channel blockers (diltiazem, verapamil)
- Grapefruit and grapefruit juice

↓ Exposure

- Rifampin (major inducer)
- Carbamazepine, phenytoin
- St. John's wort

Other Critical Interactions

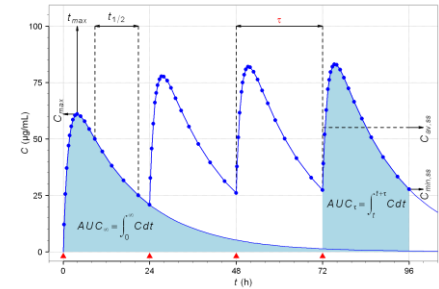
- **Mycophenolate:** Antacids, GI factors, and enterohepatic recirculation disruptors alter absorption
- **JAK inhibitors:** CYP-dependent interactions vary by agent and isoform selectivity



⚠ A new antimicrobial prescription may effectively constitute an immunosuppressant dose change—monitor concentrations proactively.

Therapeutic Drug Monitoring

From Conventional TDM to Model-Informed Precision Dosing



1

Trough Monitoring

Tacrolimus, cyclosporine, sirolimus/everolimus. Widely used but limited to a single time point.

2

AUC-Guided Dosing

MPA AUC in selected settings; abbreviated sampling strategies to estimate full exposure.

3

Population PK / Bayesian

Integrates prior patient data and individual observations for individualized dose optimization.

4

Pharmacogenomics & AI

CYP3A5 genotyping, C/D ratios, and AI-assisted dosing to refine precision further.

Tacrolimus whole-blood trough does not perfectly represent intracellular exposure. CYP3A phenotype characterization and concentration/dose ratios help identify patients with unusually high dose requirements—an area of active investigation.

Toxicity: Know the Signature



Drug / Class	Toxicity Signature
Corticosteroids	Infection, hyperglycemia, osteoporosis, psychiatric & metabolic effects
Tacrolimus / Cyclosporine	Nephrotoxicity, hypertension, neurotoxicity, metabolic toxicity
Mycophenolate	GI toxicity, leukopenia, anemia
Azathioprine	Myelosuppression, hepatotoxicity
mTOR Inhibitors	Dyslipidemia, cytopenia, proteinuria, impaired wound healing
JAK Inhibitors	Infection, herpes zoster, cytopenia ± thrombotic/cardiovascular concerns
Lymphocyte-Depleting Antibodies	Infusion reactions, profound immunosuppression, opportunistic infection

Tacrolimus-associated renal, neurologic, and metabolic toxicity and mycophenolate-associated GI and hematologic toxicity remain the most frequent practical limitations encountered in clinical practice.

The Infectious & Oncologic Price

When Immune Control Becomes Immune Deficiency

Major Infectious Concerns

- CMV & EBV reactivation
- BK polyomavirus nephropathy
- HSV / VZV
- Pneumocystis jirovecii pneumonia
- Invasive fungal infections
- Tuberculosis / HBV reactivation in appropriate risk settings

Malignancy Risk

- Post-transplant lymphoproliferative disorders (PTLD)
- Skin malignancies (SCC, Merkel cell)
- Virus-associated cancers (EBV, HHV-8)

The Competing Hazard

Reducing immunosuppression may improve infection and malignancy control—but simultaneously risks **rejection, GVHD, or autoimmune flare**. Infection and rejection are **competing hazards**.



Beyond Immunosuppression: Immune Reset?

Could We Eventually Stop Chronic Immunosuppression?

Traditional Model

Disease

**Chronic
Immunosuppression**

Chronic Toxicity

Emerging Model

**Targeted Immune
Depletion /
Reprogramming**

**Immune
Reconstitution**

Durable Remission?

Strategies Under Investigation

- CAR-T cells in refractory autoimmune disease
- CAR-Treg strategies for transplant tolerance
- Regulatory T-cell therapy
- Hematopoietic chimerism
- Tolerance induction protocols

❏ CAR-based approaches have shown early signals of drug-free remission in refractory autoimmune disease, but evidence remains preliminary. Toxicity, durability, manufacturing scale, and equitable access remain unresolved.

The Future of Immunosuppression: From Immune Suppression to Immune Reprogramming



Next Generation Immunosuppressive Strategies

1. Precision Small Molecules

- **Selective JAK inhibitors & TYK2 inhibitors**
- More pathway-specific immune modulation with improved safety profiles
- Targeting IL-12/IL-23, type I interferon and cytokine signaling pathways

2. Advanced Targeted Biologics

- Next-generation **costimulation blockade** (CD28, CD40–CD40L, OX40, ICOS pathways)
- More selective inhibition of alloimmune activation while preserving immune surveillance

3. Cellular Immunotherapies: "Living Drugs"

- Regulatory T-cell (Treg) therapy
- Antigen-specific Tregs and **CAR-Tregs**
- Promoting immune regulation rather than global suppression

4. CAR-Based Immune Reset

- CAR-T approaches beyond oncology
- Targeted depletion of pathogenic B cells in autoimmune diseases
- Potential for durable, drug-free remission

5. Tolerance Induction & Immune Reprogramming

- Hematopoietic chimerism
- Antigen-specific tolerance strategies
- Restoration of immune tolerance instead of lifelong immunosuppression

6. Biomarker-Driven Precision Immunosuppression

- Immune profiling & single-cell technologies
- Donor-derived cell-free DNA and molecular biomarkers
- Pharmacogenomics + AI-assisted dosing



SUMMARY

Immunosuppression in 2026: Five Principles

01

Exposure, Not Dose

Immunosuppression is fundamentally an **exposure problem**—variability in PK, pharmacogenomics, and drug interactions defines outcomes more than the nominal dose prescribed.

02

Combination Is Powerful but Complex

Multi-agent regimens achieve synergistic efficacy, but toxicity, interactions, and cumulative immunodeficiency define their limits.

03

TDM Is Evolving

Therapeutic drug monitoring is advancing toward **precision dosing**—integrating pharmacogenomics, population PK, and Bayesian forecasting beyond empirical trough targets.

04

Pathway-Selective Modulation

The field is shifting from broad immune suppression toward **targeted interruption of specific immune circuits**—costimulation blockade, JAK inhibition, and B-cell axis strategies.

05

Toward Tolerance

The ultimate goal may not be better lifelong immunosuppression—but **restoration of immune tolerance** through cellular reprogramming and interventions.

"The future of immunosuppression is not simply to suppress more—it is to suppress smarter, selectively, and eventually, perhaps, temporarily."

Thank You

