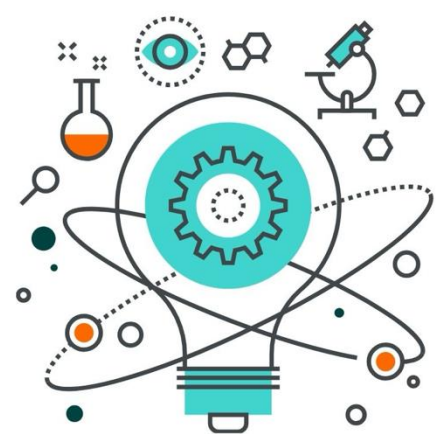




ARC Catalyst Innovation Talks



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WELCOME

Agenda for today

- Opening: **Dr William McCormark**
ARC Hub for Therapeutics Business Development and Training Manager
- Keynote speaker: **Dr Araz Raoof**
ARC Hub for Therapeutics Executive Director
- Live Q&A : **With the help of our colleagues from the Project Management Team**





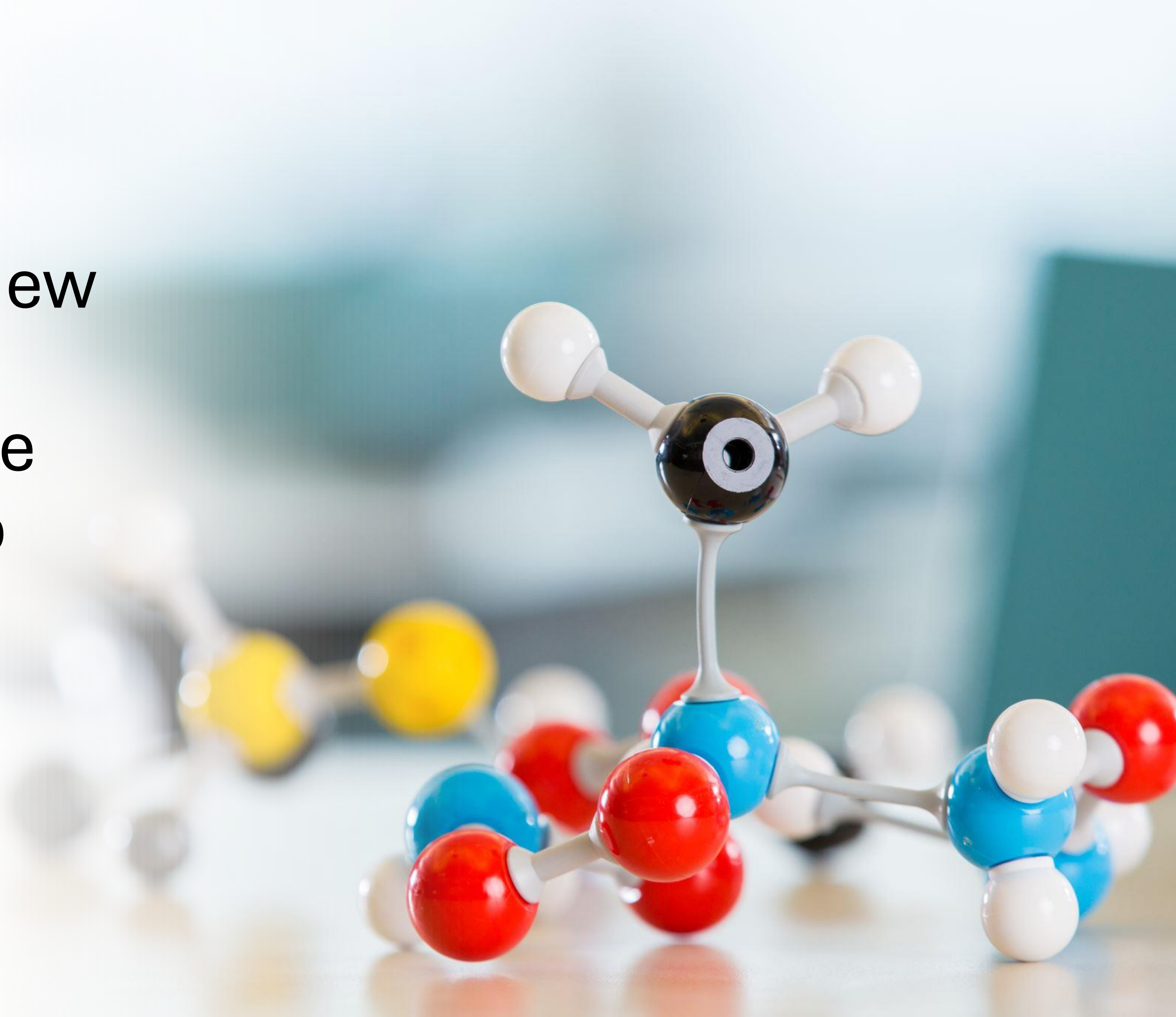
Dr Araz Raoof

“Discovery of New Therapeutics: Small Molecule Approaches to Autoimmunity”.



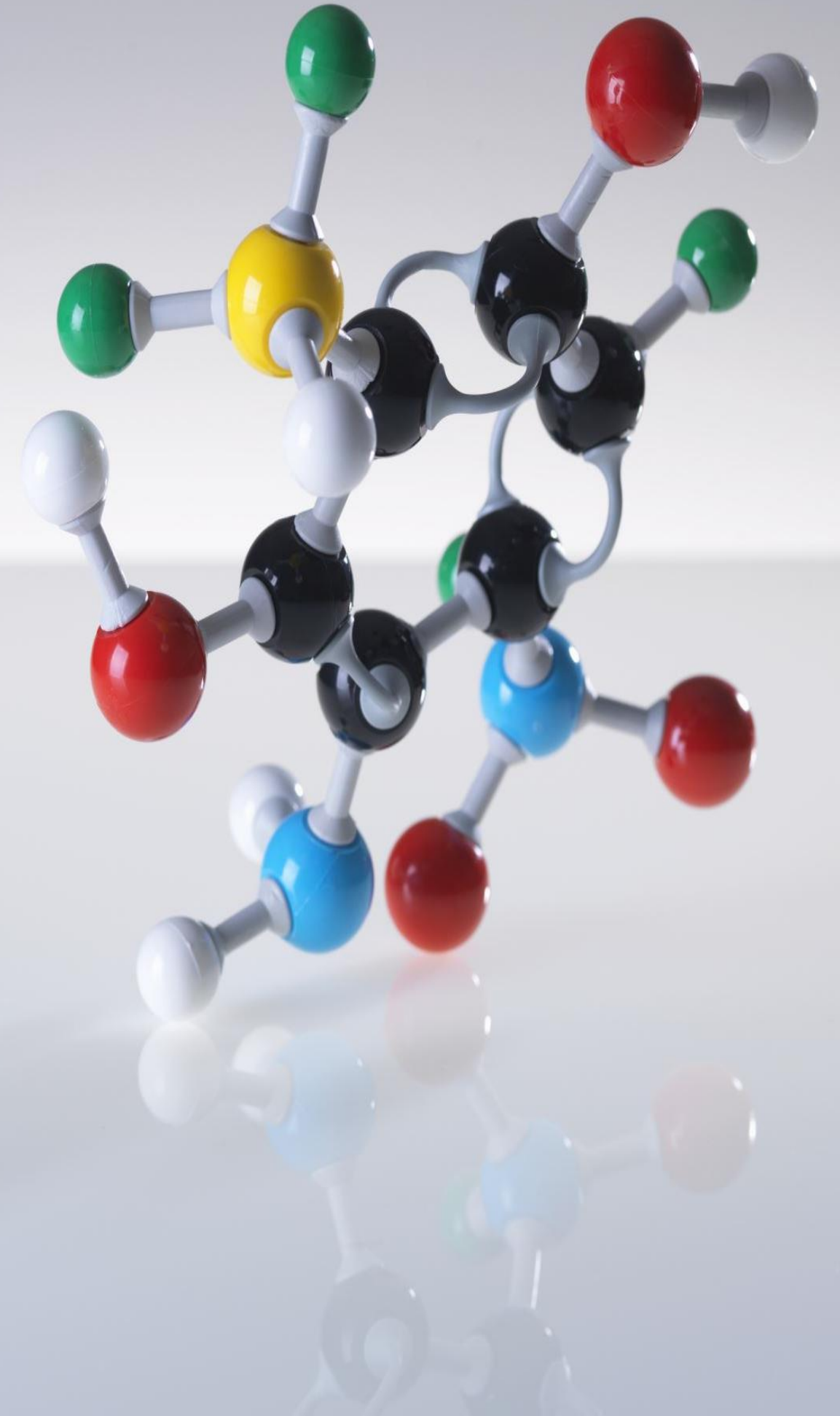
Discovery of New Therapeutics: Small Molecule Approaches to Autoimmunity

Araz Raoof, Ph.D, MBA



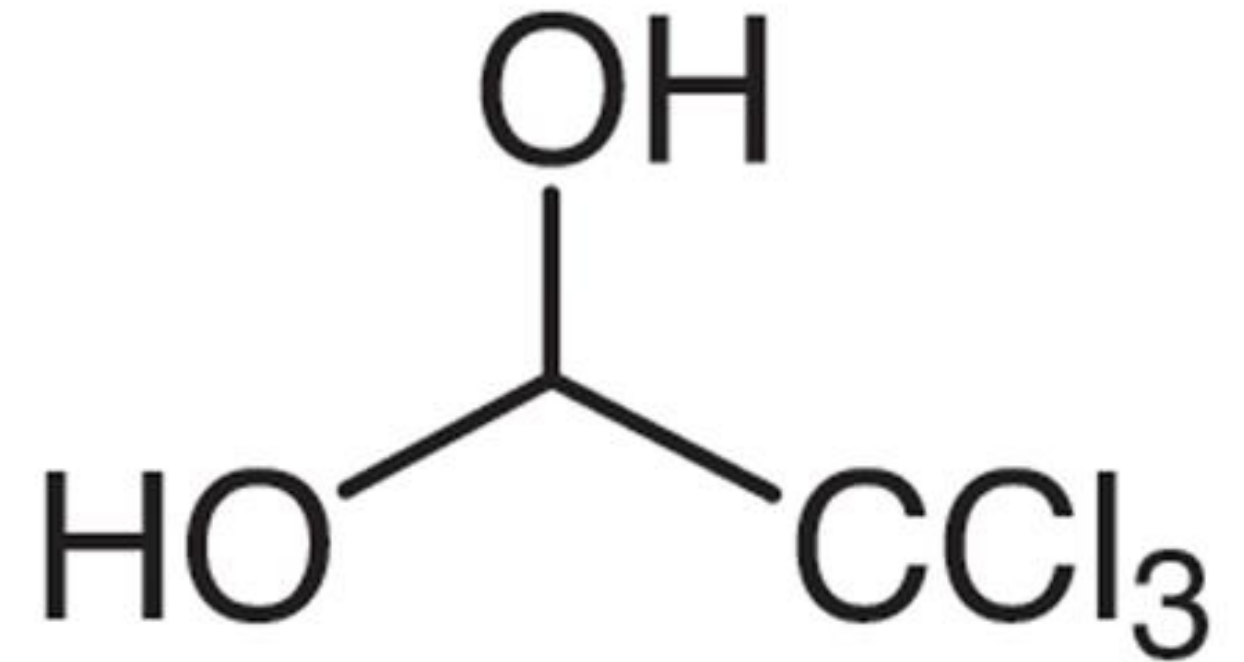
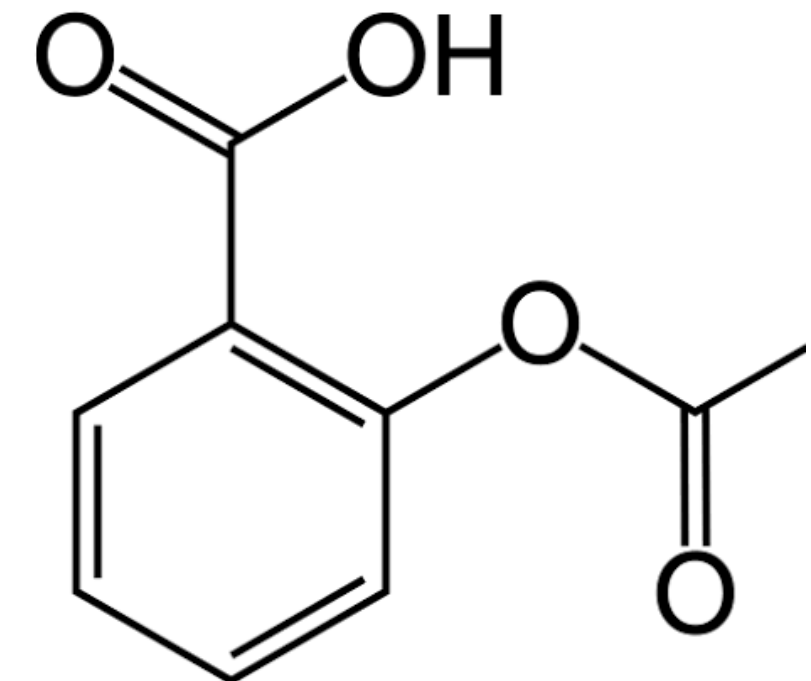
Agenda

- **Small molecule evolution & sub-modalities**
- **Therapeutic scope & discovery principles**
- **Translational approaches & technologies**
- **Autoimmune diseases & undruggable target breakthroughs**



The Dawn of Synthetic Small Molecules

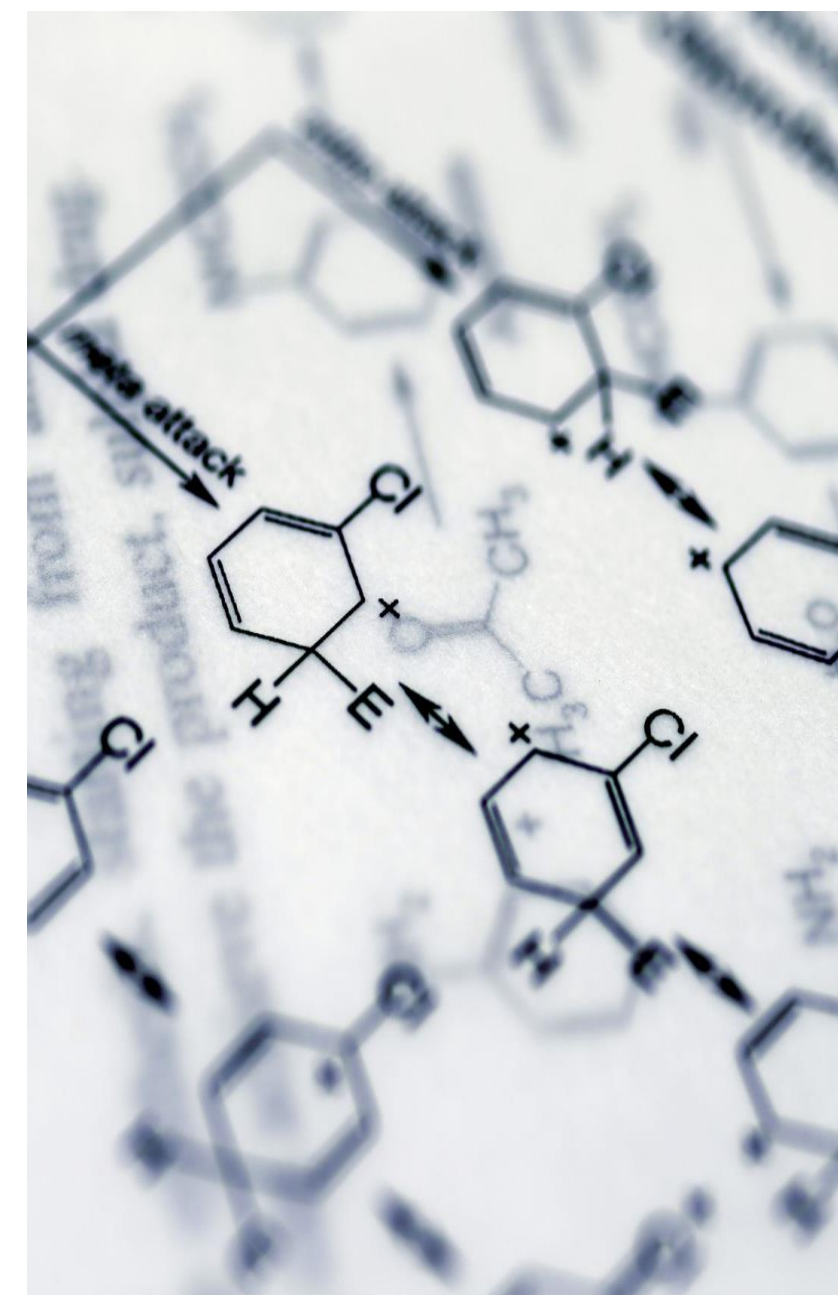
- **Chloral hydrate (1869) sedative & hypnotic**
 - 37 years from initial synthesis to medical introduction
- **Aspirin (1899 - Bayer) nonsteroidal anti-inflammatory**
 - Ancient Sumerians & Egyptians used willow tree bark as pain killer
 - Salicin extraction 18th & 19th century
 - Synthetic prodrug alteration (adding acetyl group to salicylic acid)
 - Prostaglandin biosynthesis inhibition – primary mode of action (1970s)



1

Small Molecules: multiple applications & sub-modalities

- **Occupancy-based (traditional)**
 - Orthosteric inhibitors/activators – binding to active or catalytic site block or trigger substrates binding
 - Allosteric Modulators – binding to distinct site altering protein's native activity or affinity.
 - Covalent inhibitors – permanent chemical bond enabling prolonged duration of action
- **Induced-proximity based**
 - PROTACs – hetro-bifunctional molecules causing degradation
 - Molecular Glues – monovalent forcefully recruit, degrade, interact with neo-substrate proteins
 - Other Chimeras – LYTACs, AUTACs, RIPTACs – direct targeting to different apoptotic pathways
- **Small Molecule-Drug Conjugates (SMDCs)** – target seeking ligand to deliver toxic payload
- **RNA-Targeting Small Molecules**
 - RNA-binders – target highly conserved mRNA, microRNA, non-coding
 - Translation Interdictors – sequence selective locking into ribosome halting selectively pathogenic protein
- **Radiotheranostics** – radioisotop delivery vehicle for precision targeting & personalized therapy
- **Macrocyclic & cyclic peptides** – between large & small (large surface protein targets).



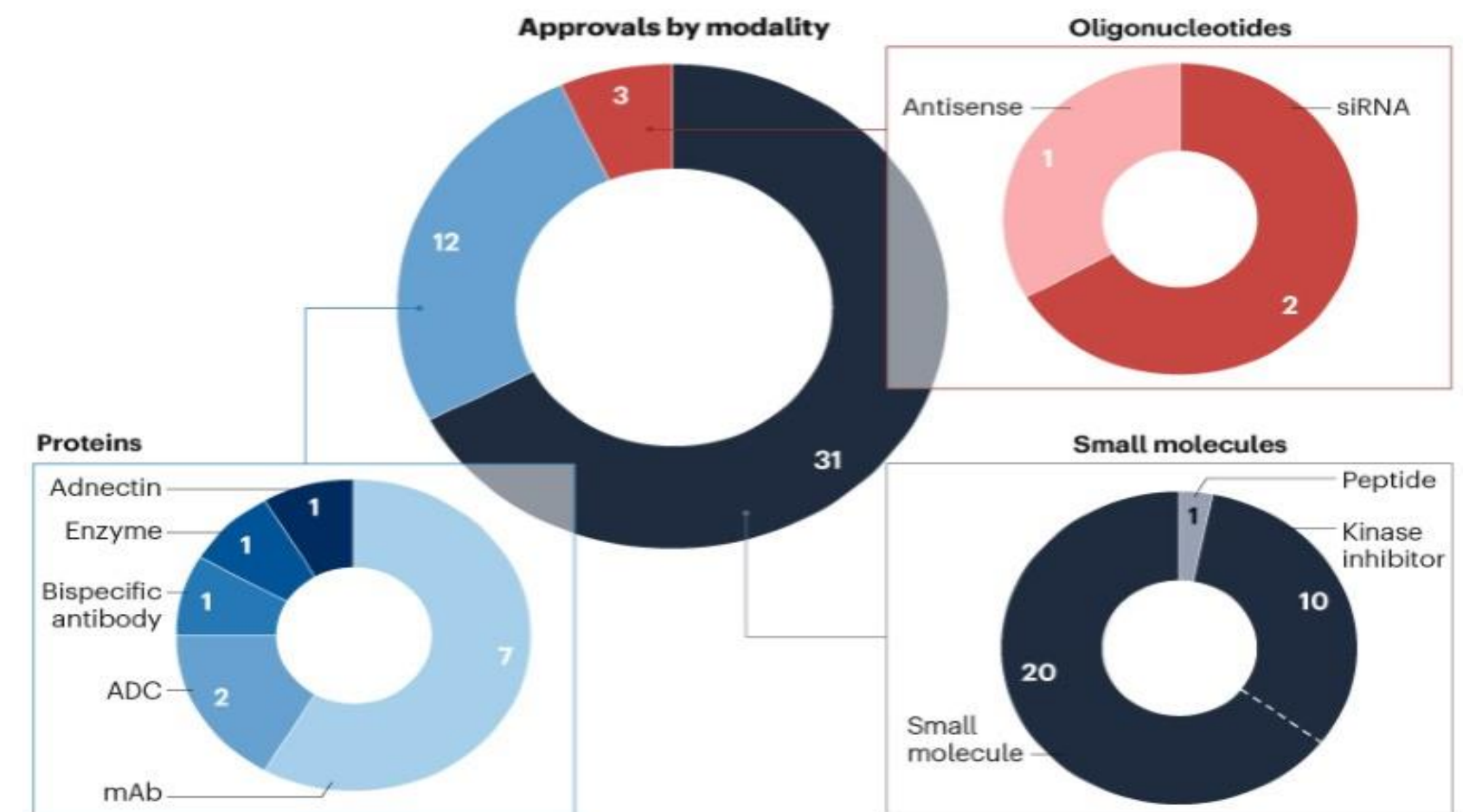
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Small Molecules: multiple applications & sub-modalities

Diverse Biological Target Space

- Enzymes, Receptors, Ion channels, Transporters, (glycol)-lipids, Structural & Scaffold Proteins, Protein-Protein Interactions, (epi)Genetic regulation, etc..
- **Majority of drugs approved are small molecules**
 - Oral administration
 - Intracellular penetration
 - Dosing flexibility
 - Versatile delivery
 - Ideal for multi-drug combination
 - High stability
 - Cost-effective manufacturing

FDA Drugs approved in 2025



Nature Reviews Drug Discovery 2026



The Magic Bullet is Hard to Achieve

‘selective single molecule that targets single mechanism’

- Biological complexity (networks of genes & pathways)
- Disease multi-etiology
- Patient variability
- Pathway redundancy
- Drug resistance
- Off-target interactions (simultaneous impact on multiple cellular pathways)
- Delivery barriers (tissue or subcellular)

New Modalities - New Chemical Design & Engagement Rules

- Beyond Lipinski Rule of 5 (complex targets require different molecules challenging weight and lipophilicity limits)

Lipinski Core Criteria

- Molecular weight: Under 500 Daltons (Da).
 - LogP (lipophilicity): Less than 5 (a measure of fat-versus-water solubility).
 - Hydrogen bond donors: 5 or fewer (such as -OH and -NH groups).
 - Hydrogen bond acceptors: 10 or fewer (such as nitrogen and oxygen atom)
-
- Compound considered "drug-like" if it has no more than one violation of these core criteria
 - Innovation starts when bending the rules...



New Modalities - New Chemical Design & Engagement Rules

- Covalent binders & permanent pocket trapping (two step time dependent mechanisms)
 - Reversible non-covalent target recognition followed by target residue & warhead chemical reaction
 - Common target engagers: nucleophilic amino-acids (cysteine, lysine, serine, histidine)
- PROTACs new metrics for ternary complex formations
 - Precise conformational flexibility (vs tight static binding)
 - Linker length & chemistry (stability, steric clash & intracellular release kinetics)
 - Common linkers:
 - PEG (PEG2, PEG6 or longer improve aqueous solubility),
 - Alkyl chains (12-20 carbon chain –synthetic accessibility & cellular permeability)
 - Rigid motifs (triazoles & alicyclic rings – conformational control & metabolic stability)
- RIPTACs – potential for better selectivity & broader PPI
 - Handcuff – overexpressed cancer specific protein linkage to protein regulator



New Modalities - New Chemical Design & Engagement Rules

- Molecular glues (diverse interaction modality)
 - Surface remodeling
 - Non-covalent (thalidomide) & covalent (expand target space) glues
 - Governed by network of binding equilibrium
 - Cooperative driven thermodynamic affinity (key to enhance affinity between two proteins)
 - Surface exposed moieties – include protruding chemical group to bridge contact with secondary target
 - Modification important for neo-substrate recruitment



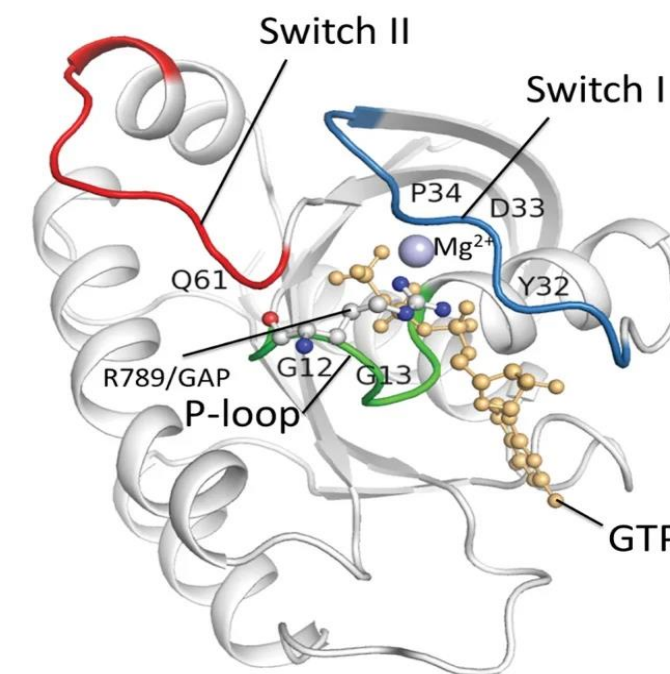
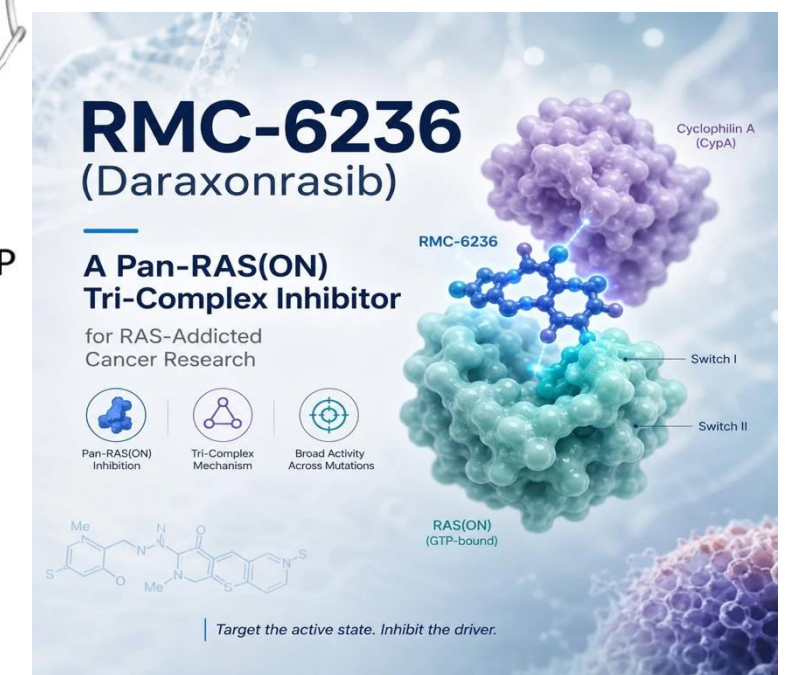
Modality Innovation Expands The Druggable Space

- Approximately 85% of human proteome is classified undruggable ...or yet to be drugged!

- No pockets - smooth flat surface
- Shapeshifting – intrinsically disordered
- Hidden location
- Large interaction surfaces

- Uncrackable KRAS (40 years of research!)

- Identified in 1982
- Breakthrough 2013 – Kevin Shokat UCSF with discovery of mutated protein allosteric pocket Switch II
- 2021 1st FDA drug approval sotorasib – NSCLC
- 2026 daraxonrasib non-covalent molecular glue



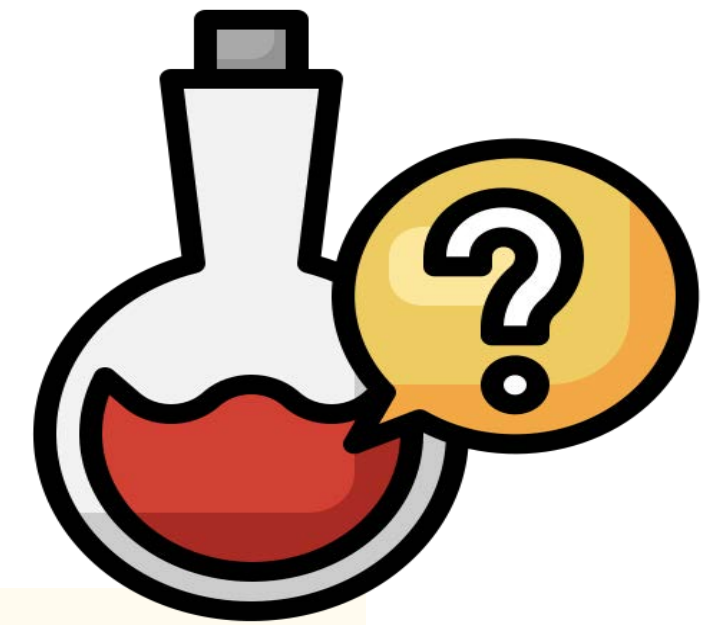
- Binding to chaperon protein cyclophilin A, surface remodeling creating specific binding interface, tri-complex lock to GTP RAS ON protein

Discovery of New Therapeutics

Are we asking the right questions?

What are the underlying biological & chemical principles?

Data volume versus decision quality !!



Biological Principles

- Target Identification (role of data sciences & AI)
- Target Validation (relevance in disease pathophysiology)
- Biological Pathway (interruption of cellular signals)

+

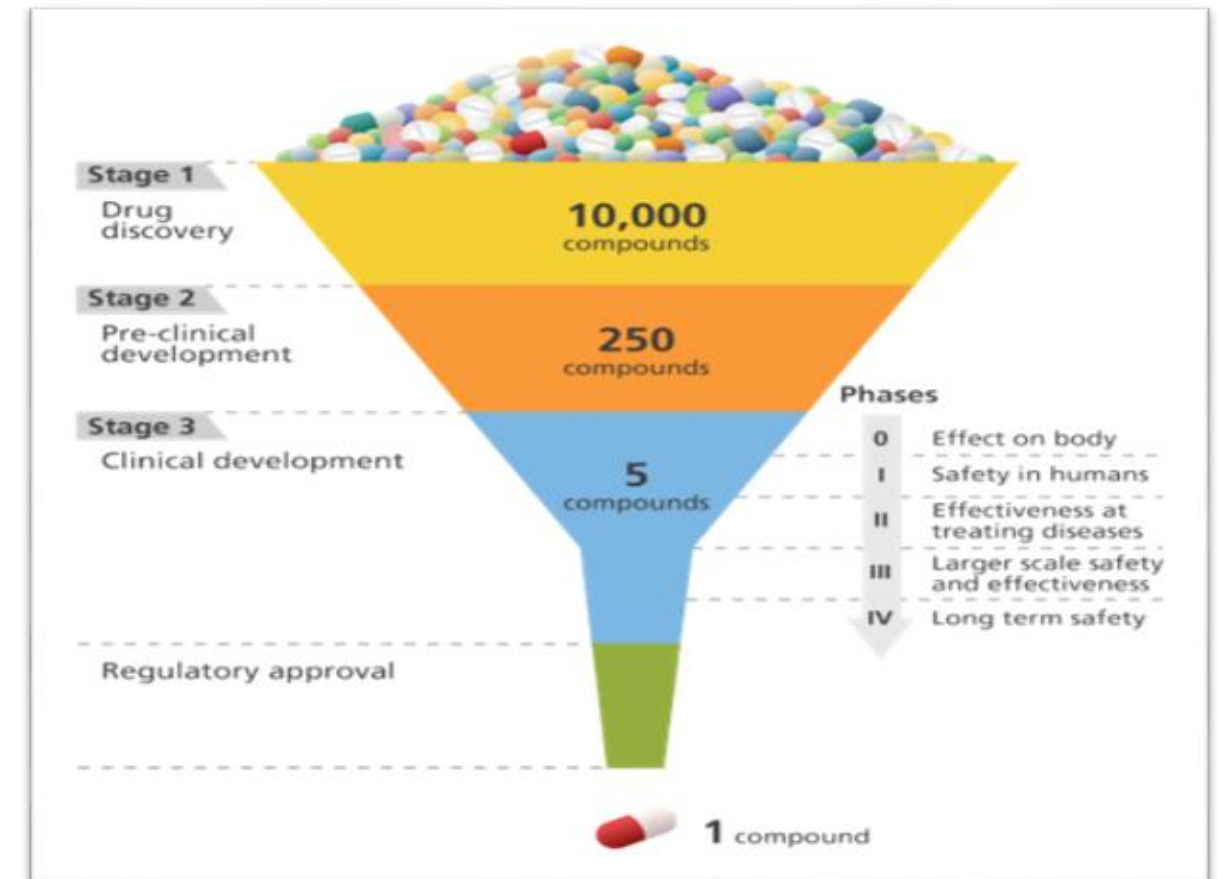
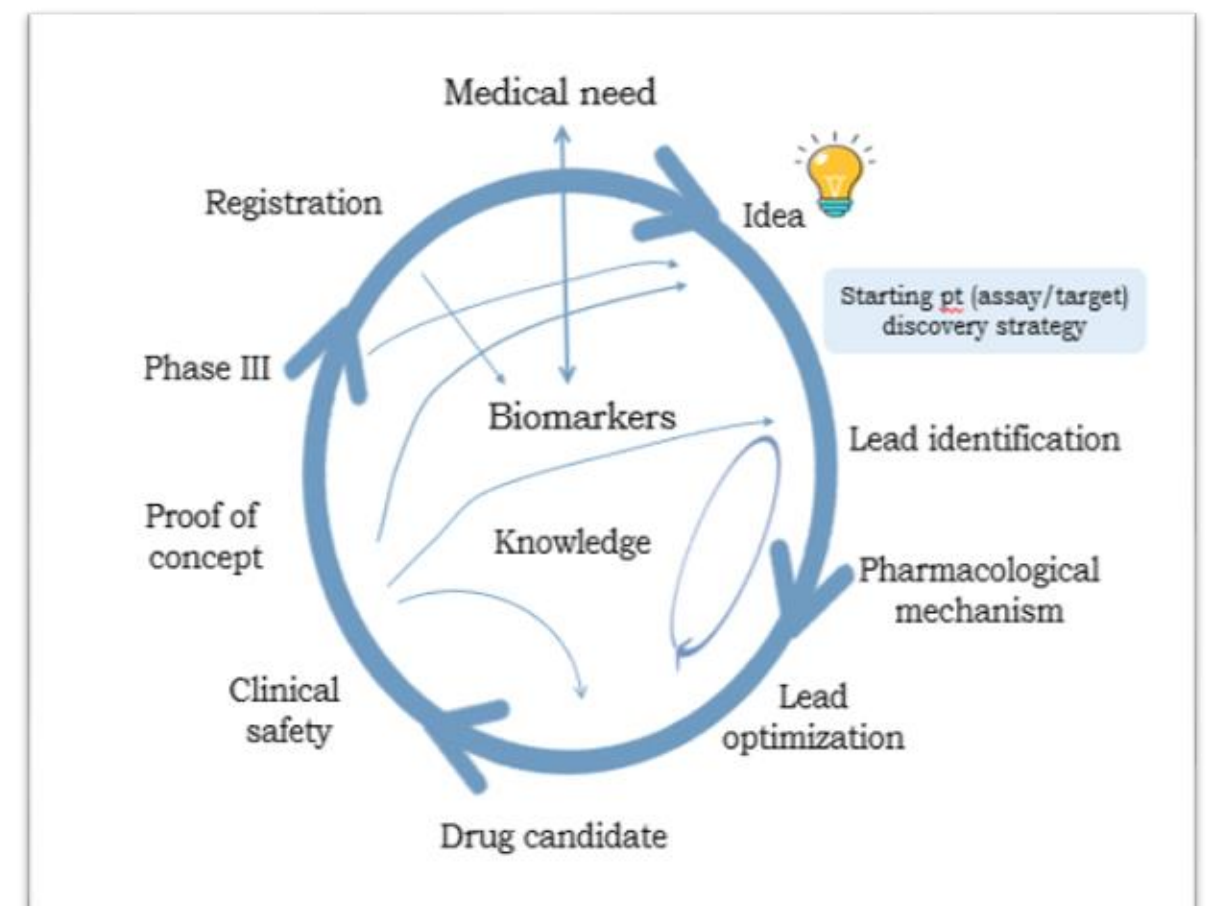
Chemical Principle

- Molecular Design (creativity matters more than tools)
- Molecular Complementarity (chemical properties to match biological target)
- Structural Activity Relationship (understand the drivers)

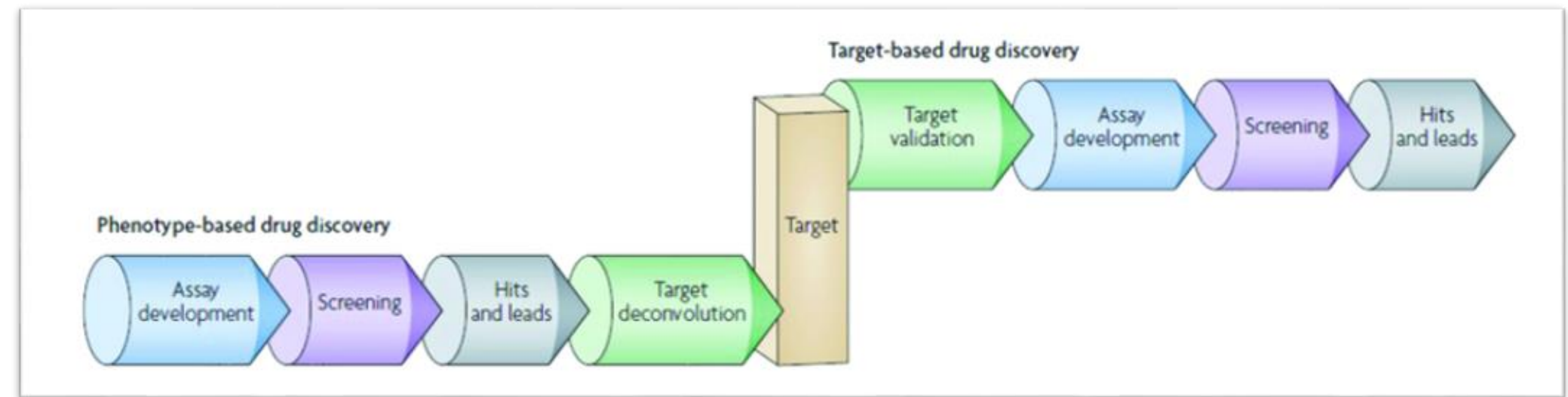
Druggability, Pk/PD & Safety Profile

Drug Discovery Complex Iterative Path

- New modalities require tailor-made approaches & technologies
- PK & ADME properties are guided by Target Product Profile
- Safety profile weighed against treatment benefit & risk
- High regulatory & commercial bar for superior efficacy & safety



Genesis of Discovery Program



Phenotypic

- Pros
 - Physiological relevance (test system dependent)
 - uncover polypharmacology (multiple pathways)
 - Historically 1st in class or new biology
- Cons
 - Target deconvolution
 - Harder to optimize chemistry

Target centric

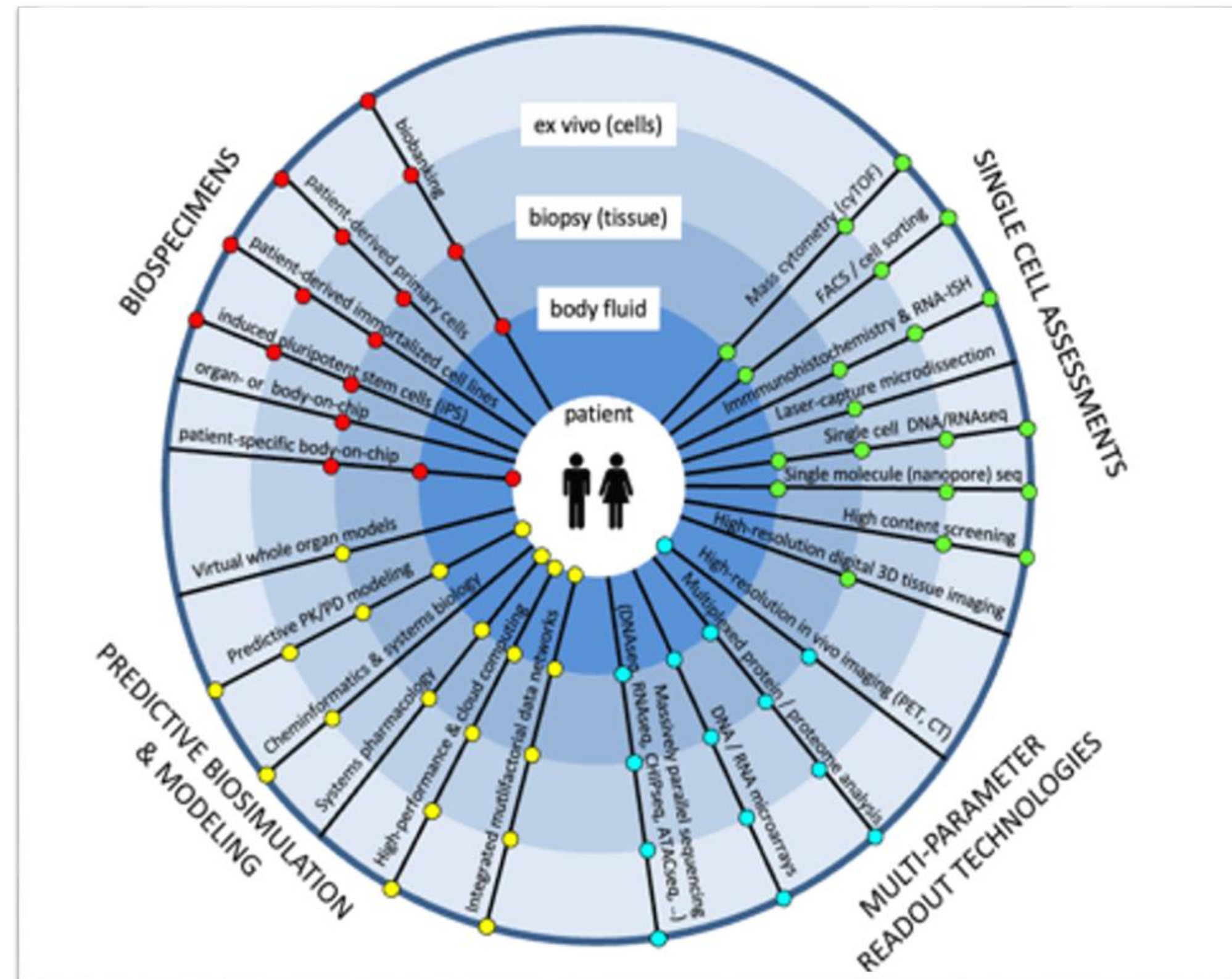
- Pros
 - Clear data interpretation
 - Allow rational drug design
 - Faster structure optimization
 - Better druggability prediction
- Cons
 - Translational risk (disease relevance)
 - Limited to known mechanisms (novelty?)

Hybrid model

- Modern discovery approach influenced by AI & new technologies

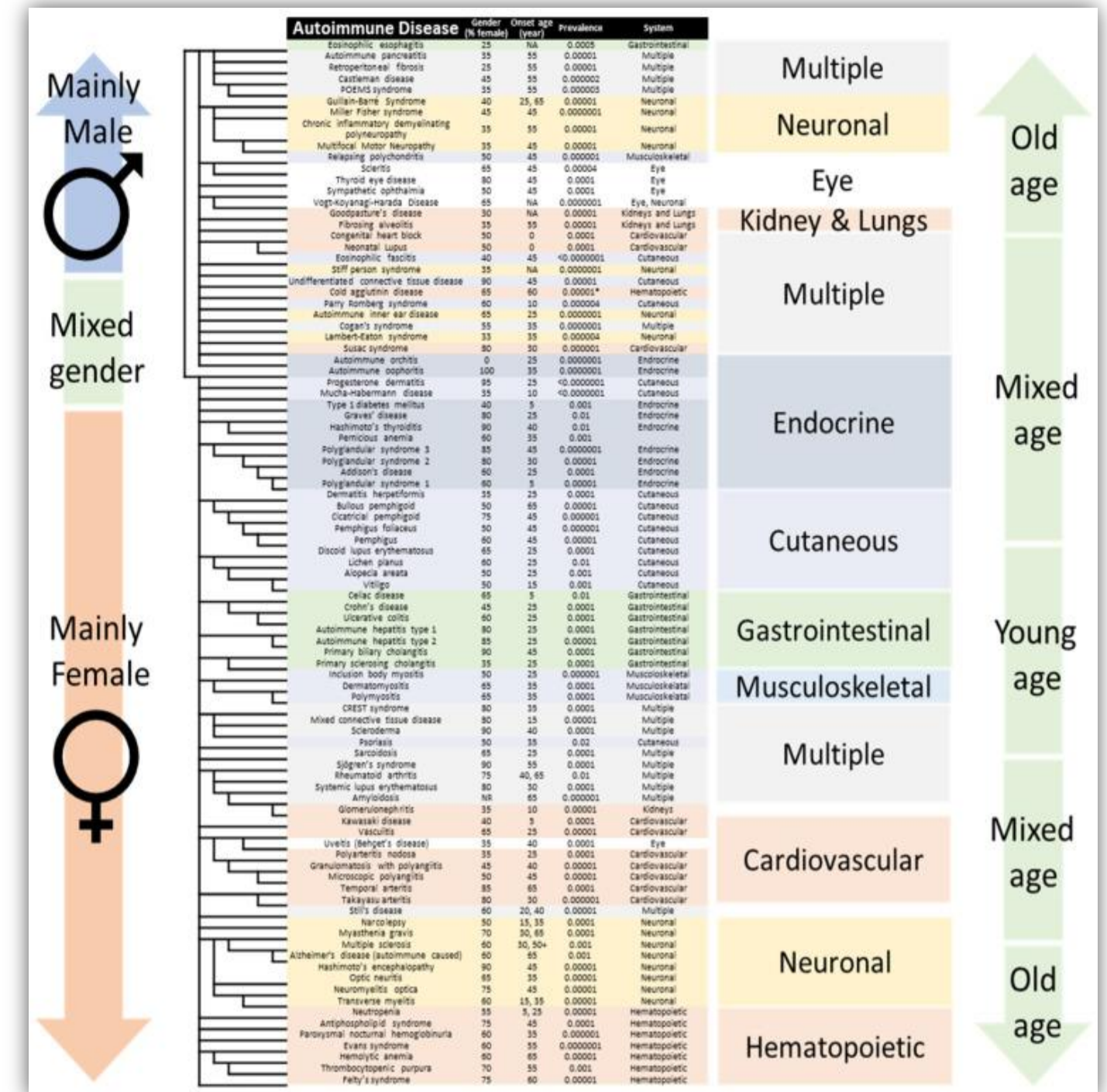
Importance of Translational Tools in Drug Discovery

- Insufficient efficacy remains a key driver for clinical attrition
- Establish disease mechanism at molecular level
 - Patient derived biospecimens, multi-parametric readouts technologies, bio-simulation & modelling, etc..
- Establish the relevance of biology before chemical optimization



Autoimmune Diseases

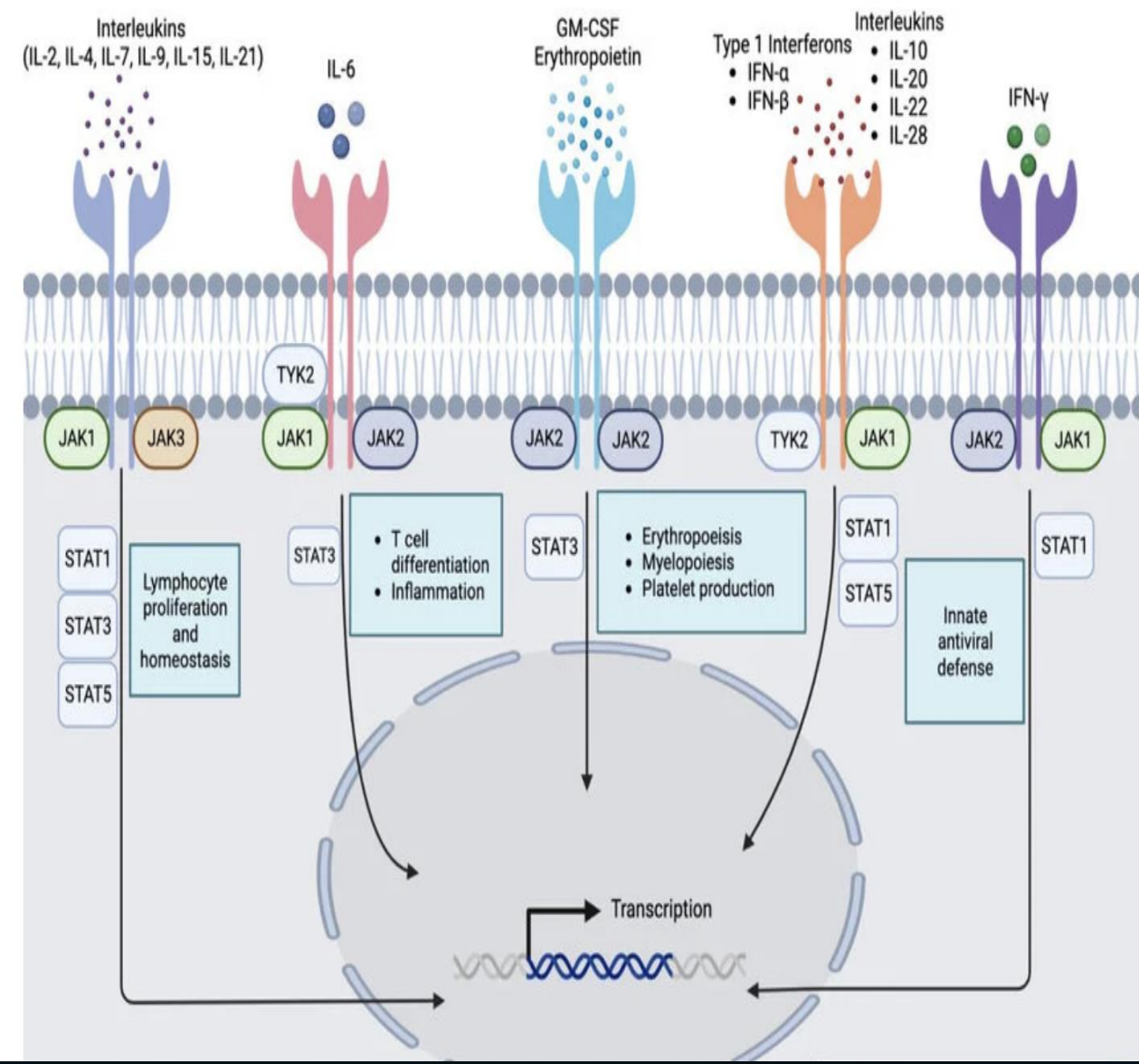
- More than 100 diseases
- Affects 3-5% of population
- Aberrant activation of autoreactive immune cells leading to tissue damage
- Comorbidity & overlapping mechanisms
- Complex pathophysiology: interaction of immunological, genetic & environmental factors



Undruggable Targets in Autoimmune Diseases – TYK2

Selective Pathway Modulation JAK/STAT

- JAK/STAT pathway has a major role in cytokine receptor signaling.
- Non-covalently associated with cytokine receptors, mediate receptor phosphorylation, STAT recruitment & transcription.
- >50 cytokines & growth factors stimulate signaling pathway
- Diverse downstream events - hematopoiesis, immune fitness, tissue repair, inflammation, apoptosis, adipogenesis, etc

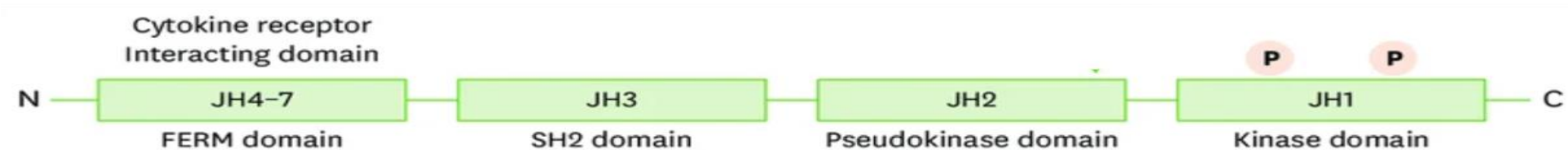


Druggability Challenges

JAK/STAT Pathway

Overlap & Selectivity Issues

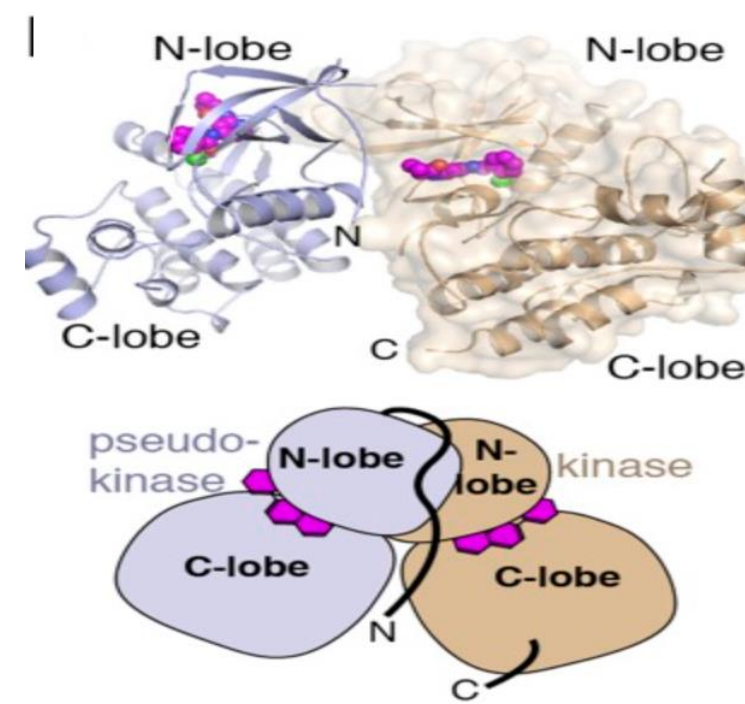
- Conserved JH1 ATP-binding site: methionine is the gate keeper for the ATP binding pocket for all JAK family members (JAK, JAK1, JAK2, JAK3 & TYK2)



- Biochemical assays limitation for selectivity assessment – poor correlation with correlation cellular & in vivo systems
 - Lost of selectivity due to PK/PD
- Class-wide black box warning due to serious adverse events (cardiovascular, thromboembolism, malignancies) leading to usage restriction

Selective Pathway modulation TYK2 allosteric inhibition

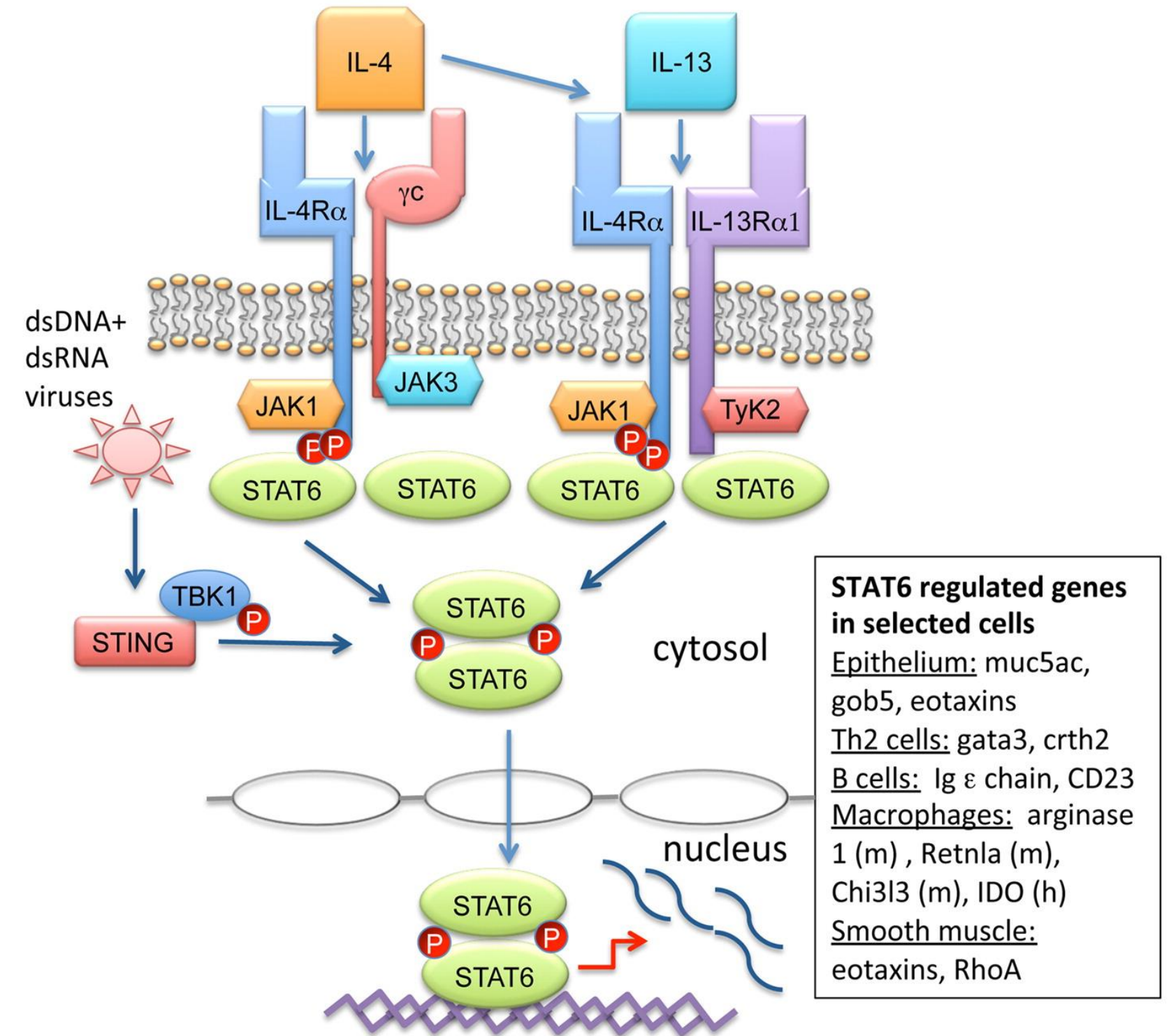
- TYK2 mediates a narrower set of immune pathways (regulates activity of IL12, IL23 & type1 IFN)
- TYK2 JH2 (pseudokinase) is autoinhibitory regulator of the adjacent JH1 catalytic domain.
 - Stabilization of JH2 in autoinhibited conformation prevents JH1 activation & STAT recruitment
- Deucravacitinib first TYK2 allosteric inhibitor approved for plaque psoriasis (2022) & active psoriatic arthritis (2026)
- No black-box warning, label-directed prescreening & targeted monitoring



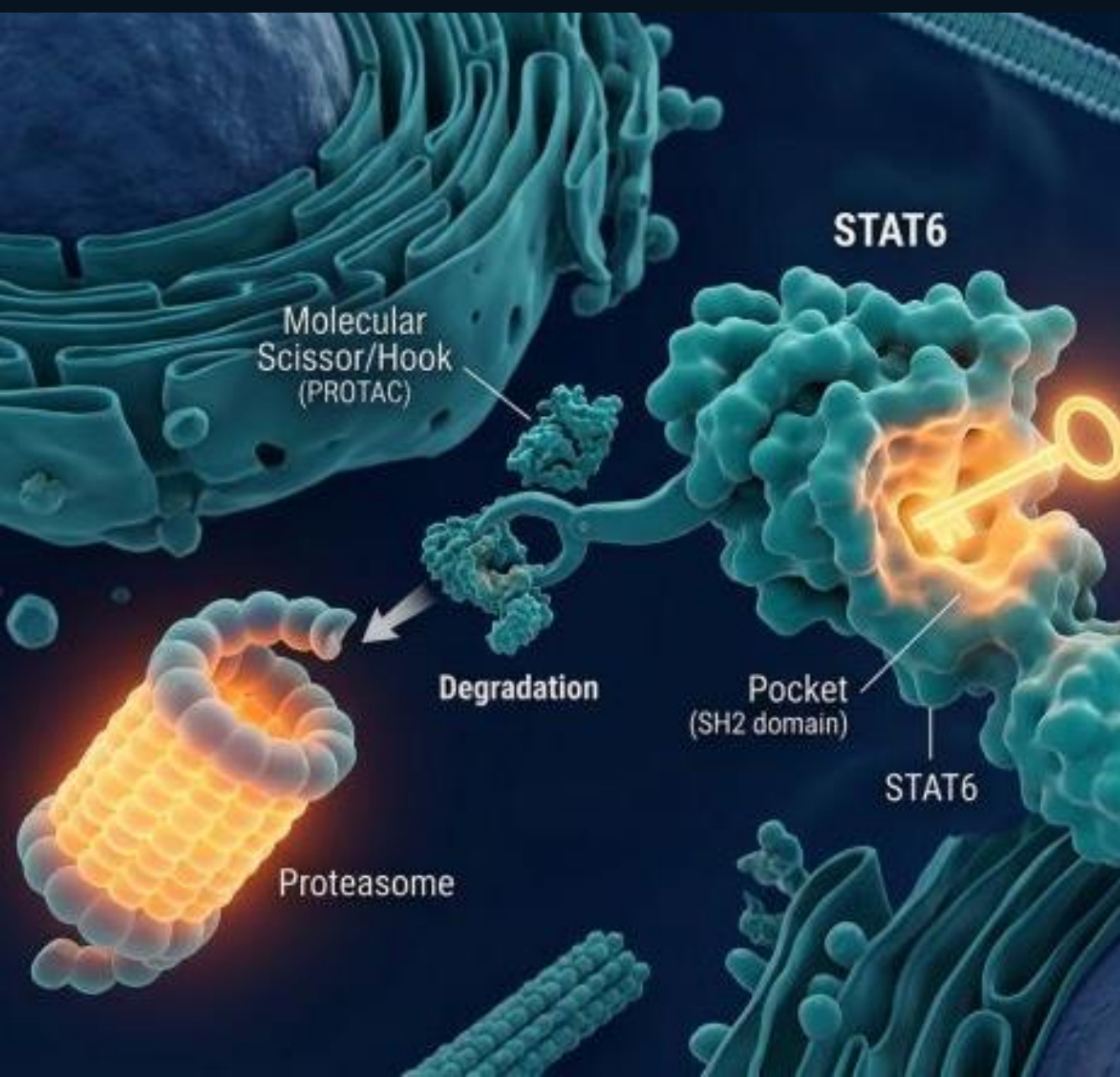
Undruggable Targets in Autoimmune Diseases – STAT6

STAT6 – Downstream signaling IL-4/IL-13

- Mediates type 2 immune response
- Dysregulated in allergic inflammatory (asthma, atopic dermatitis) & oncogenic disease
- Clinically validated pathway
 - Dupilumab (anti-IL4Ra) approval in 2017 for atopic dermatitis (and variety of other diseases asthma, COPD, eosinophilic esophagitis, nasal polyps, etc..)



Undruggable Targets in Autoimmune Diseases – STAT6



Why STAT6 was considered undruggable?

- No enzyme pocket
- Flat PPI interaction surface: SH2 domain which is critical for STAT phosphorylation, activation, homodimerization and signaling
- Diffused Protein-DNA interface – no isolated pocket & tight pocket
- High positive charge DNA domain
- Physical movement (cytoplasm & nucleolus)
- Identifying a ligand to target transcription factors requires significant drug discovery capabilities, proprietary technologies & new chemical approaches.

Undruggable Targets in Autoimmune Diseases

STAT6

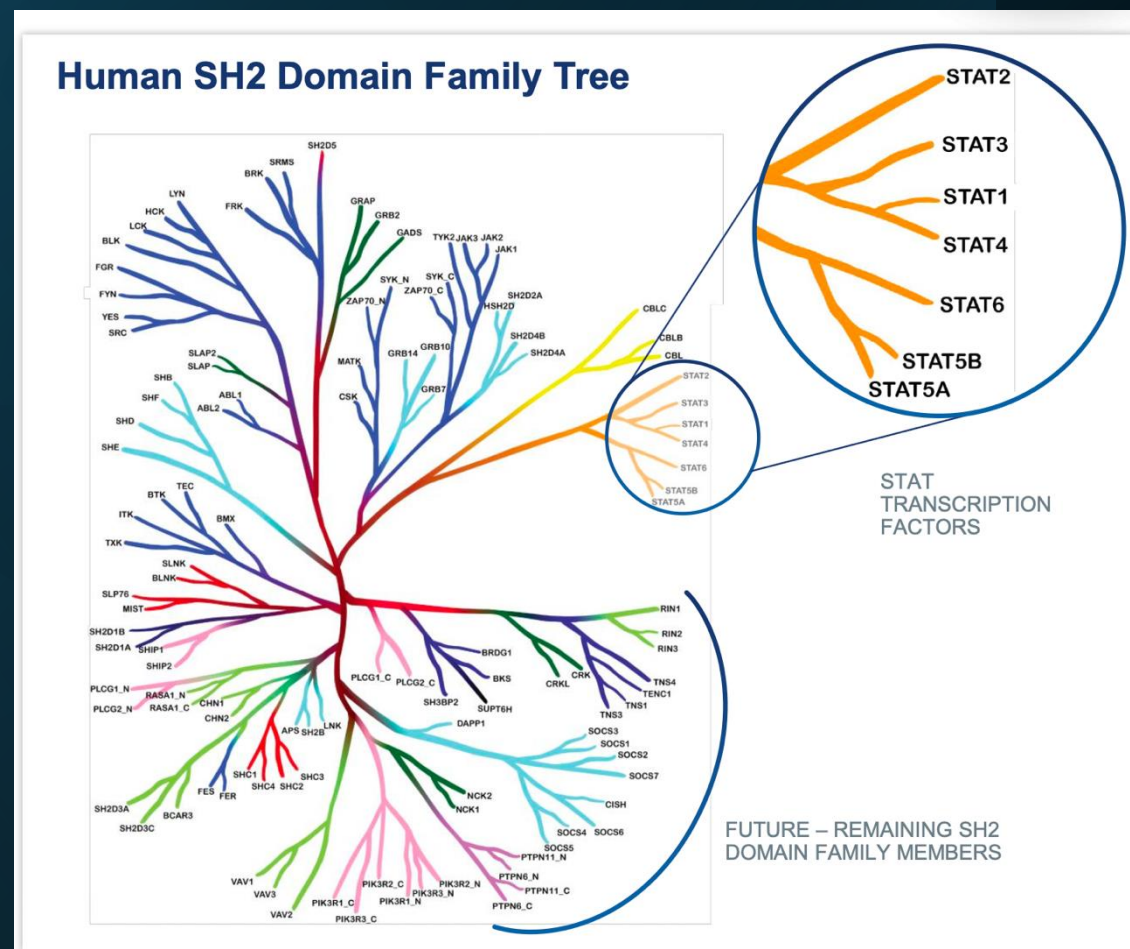
Small Molecule STAT6 Frontrunners

KT-621

- Most advanced first-in-class selective STAT6 PROTAC (cereblon E3 ligase)
- STAT6 reduction (~ 94%) in skin & blood, disease biomarker comparable to dupilumab.
- Advancing to phase 2b (atopic dermatitis), FDA Fast Track Designation December 2025.

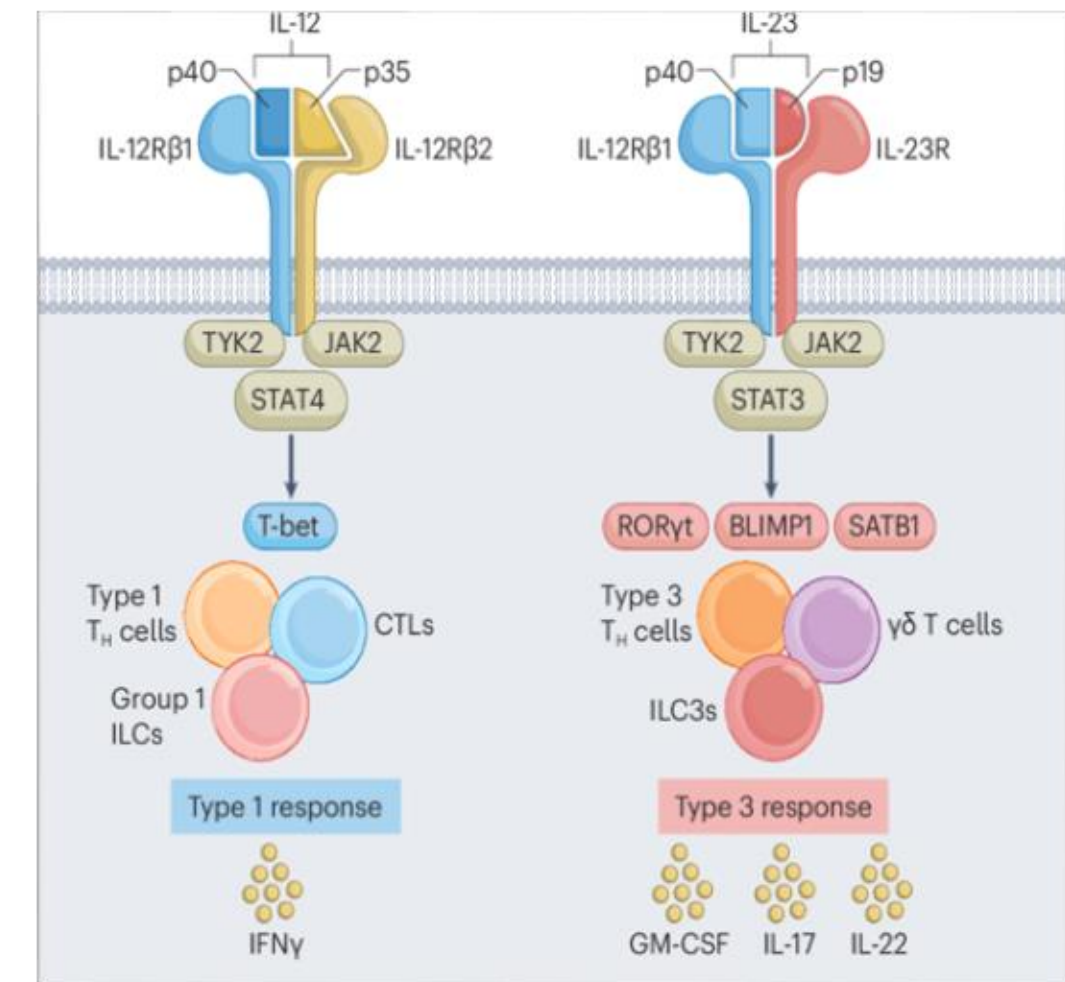
REX-8756

- Selective, reversible orthostatic inhibitor binding to SH2 domain
- IND (2025), First-in-Human dosing (2026)



Undruggable Targets in Autoimmune Diseases – IL23

- Heterodimer cytokine made of P19 (IL23A) & P40 (shared with IL12B) subunits.
- Activation of Th17 and release of proinflammatory cytokines
- Central driver for chronic inflammation in psoriasis, psoriatic arthritis, IBD, MS.
- Clinically validated pathway
 - Multiple biologics blocking P40 (ustekinumab) or selective p19 subunit (guselkumab, risankizumab, mirikizumab).

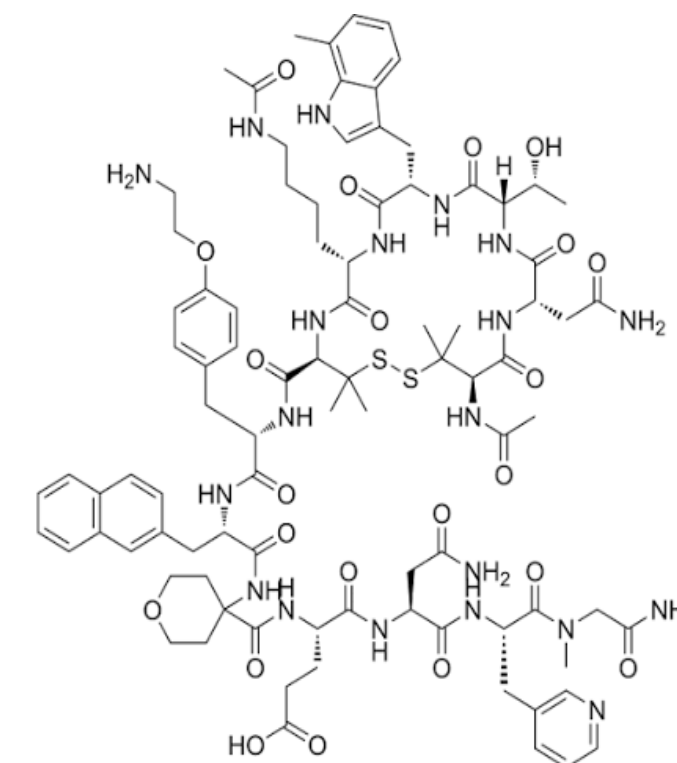


Undruggable Targets in Autoimmune Diseases – IL23

Oral Biologics

Icotrokinra

- Macrocyclic peptide first-in-class oral IL-23 receptor antagonist
 - High molecular weight (1898 Da), single digit picomolar affinity, gut stability, low bioavailability.
 - Single once daily oral tablet (200 mg)
 - Efficacy approaches injectable biologics, FDA approval March 2026 plaque psoriasis.
-
- The most advanced non-antibody approach for interrupting IL23
 - Moving peptides to target classes historically considered unsuitable



Autoimmune Discovery & Future Direction

- Greater target selectivity (fewer off target effects)
- New intracellular targets (data sciences + AI)
- Combination strategy (complementary mechanisms without additive immunosuppression)
- Sustained efficacy & longer remission

Key takeaways

- Discovery of small molecules is complex & evolving
 - New modalities expand the druggable space & intensify molecular design creativity
- Paradigm shift from traditional drug discovery to individualized strategy for execution
- Drugging “undruggable targets” requires time & perseverance

Thank You





Questions & Answers



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Upcoming session 2027 Registration Opening Soon

Caroline Gaynor - Partner at Lightstone Ventures

“VC Maths and How It Impacts Your Fundraising Strategy”.

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 **Please complete our short survey**



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Accelerating Research to Commercialisation



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