AML Landscape Analysis

Sleuth

Modern decision intelligence for the bioeconomy

Executive Summary

AML Landscape Analysis

1. **CROWDED AT THE TOP, FRAGMENTED EVERYWHERE ELSE:** Six validated targets attract intense competition yet account for only 16% of 957 programs. The remaining 65% scatter across 402 targets with limited clinical validation.

2. **SELECTIVITY IS THE CORE CONSTRAINT:** The most pursued AML targets overlap with normal hematopoiesis at the HSC or progenitor level, creating inherent on-target toxicity. Myelosuppression and cytopenias recur across modalities as a direct consequence.

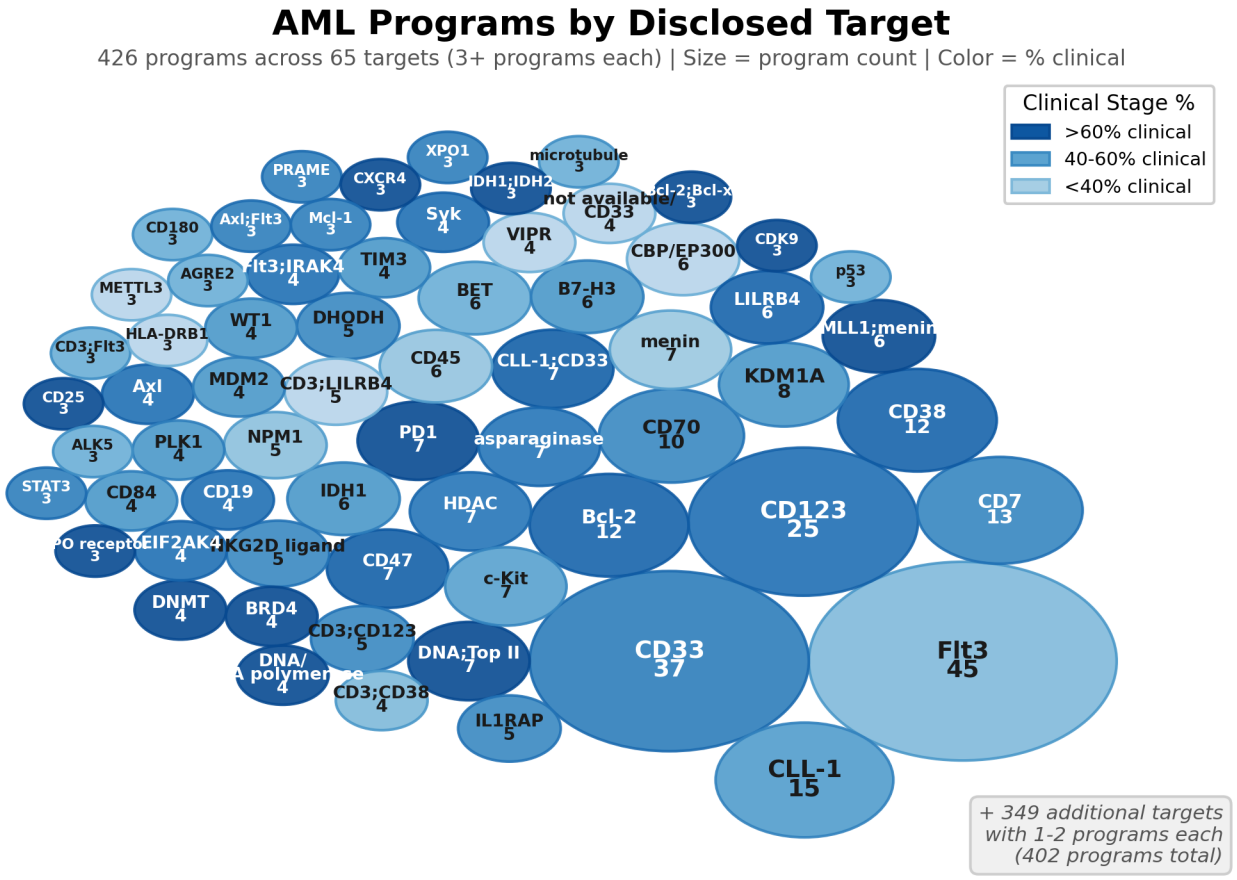
3. **EVIDENCE DOES NOT MATCH CLAIMS:** Only 23% of programs support selectivity claims with protein-level data. Most rely on transcript evidence or inference, meaning the therapeutic window for many targets is assumed rather than demonstrated.

4. **MITIGATION STRATEGIES ARE WORKAROUNDS, NOT SOLUTIONS:** Cell therapies manage toxicity through post-transplant timing and target selection. Small molecules rely on dosing strategies, with 44% citing no explicit mitigation. These approaches compensate for poor targets rather than solving the underlying biology.

5. **WHITESPACE EXISTS FOR HSC-SPARING TARGETS:** Targets with mature-restricted expression and low competitive intensity (LILRB4, PRAME, CD25, Siglec-6) remain underexplored. These represent opportunities for discovery approaches that resolve selectivity upfront rather than engineering around it downstream.

AML targets are fragmented with few validated leaders

Top 6 targets account for only 16% of 957 programs; 402 targets comprise the long tail

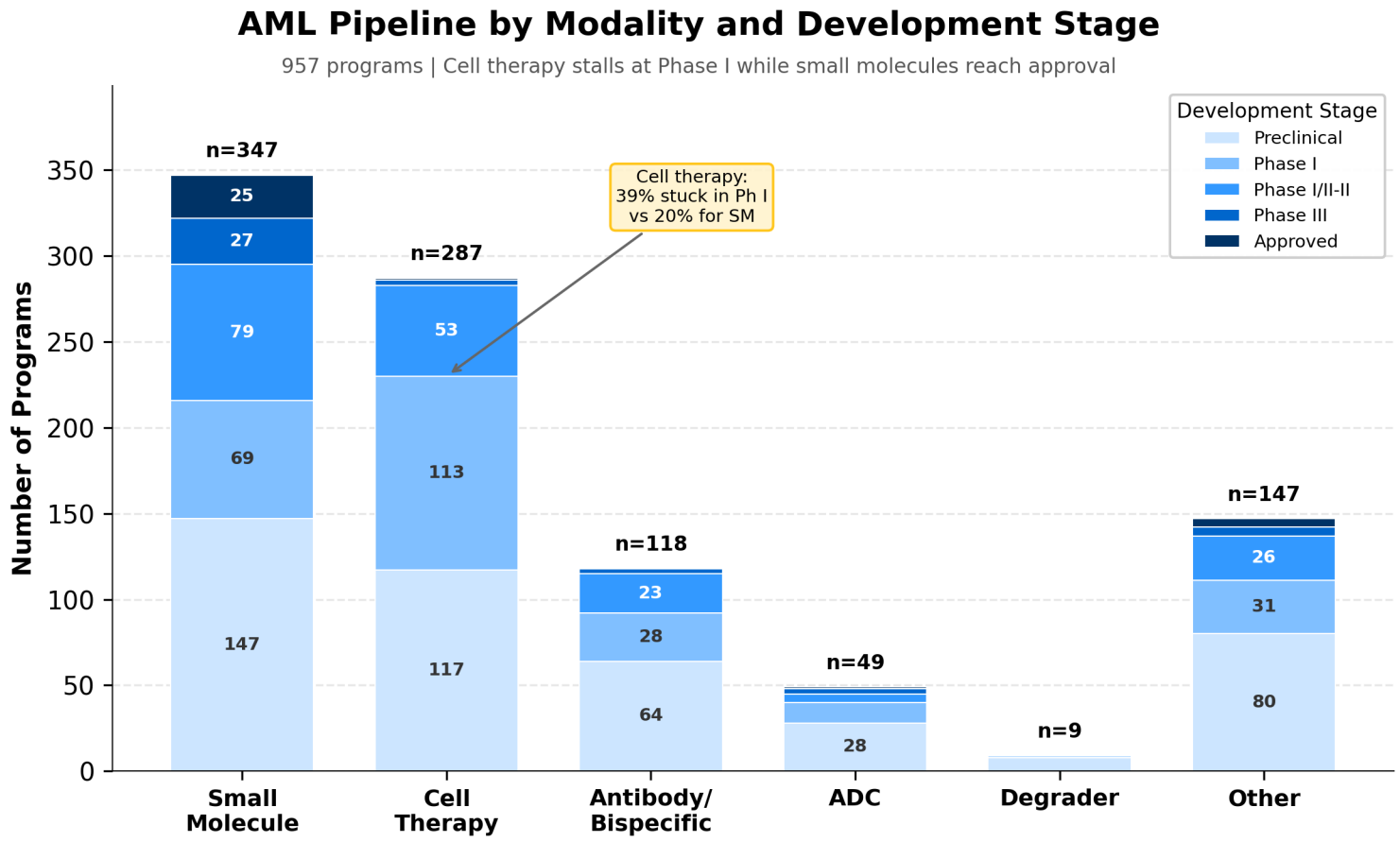


- Six targets (FLT3, CD33, CD123, CLL-1, CD7, Bcl-2) account for just 16% of all programs despite being the most validated in the space
- The long tail dominates. 402 targets with fewer than 5 programs each represent 65% of total activity
- Clinical advancement correlates with target maturity. FLT3 and CD33 show the highest proportion beyond preclinical
- Target fragmentation creates both risk and opportunity as most programs pursue unvalidated biology

Sleuth analysis of 957 AML programs; data as of January 2025

Cell therapy leads volume but trails in clinical maturity

Newer modalities cluster in preclinical; small molecules show balanced phase distribution

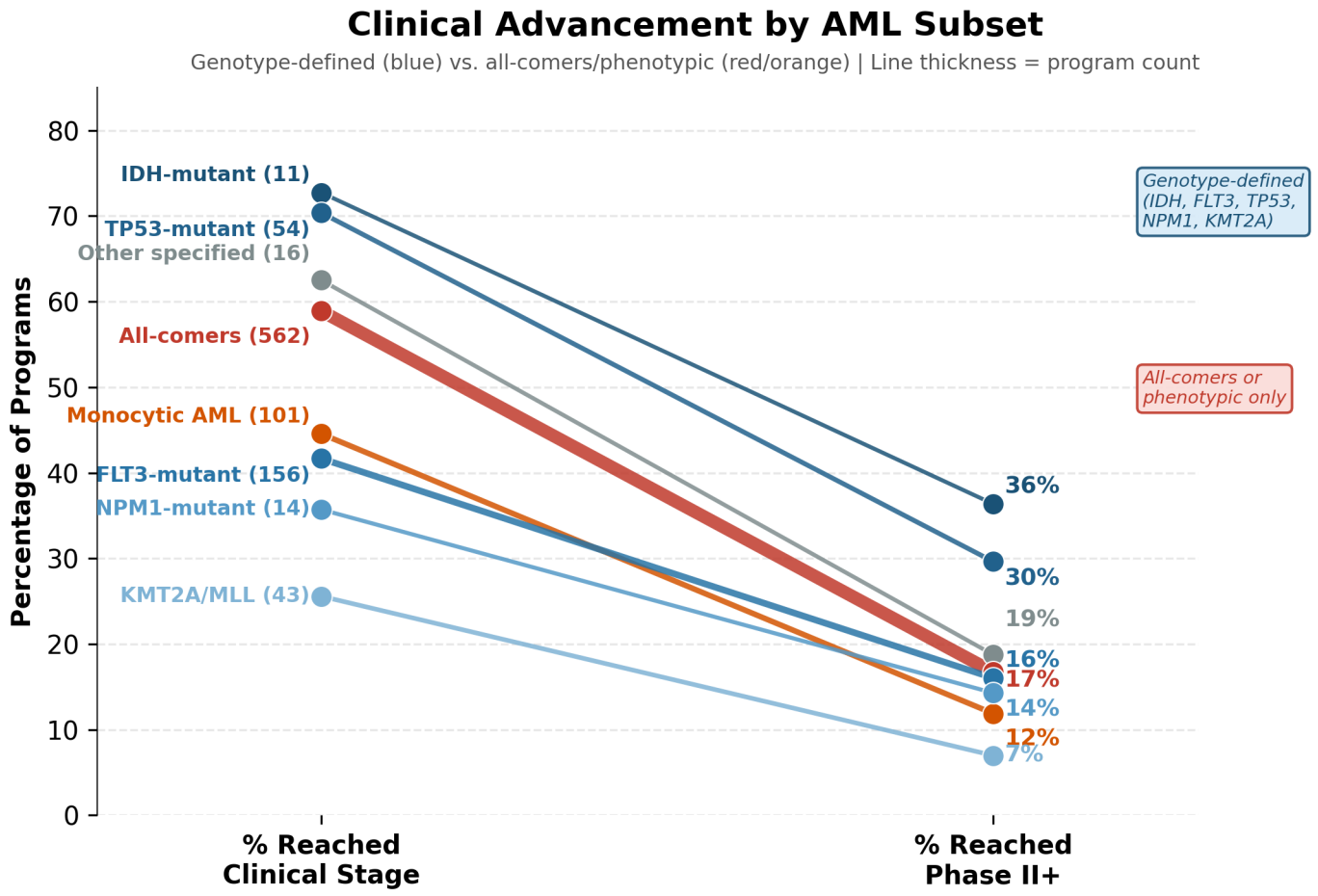


- Cell therapy represents the largest program count (287 programs, 30%) but remains predominantly preclinical
- Small molecules show the most balanced phase distribution, reflecting decades of development history
- ADCs and antibody approaches cluster in early clinical stages, suggesting recent interest but unproven viability
- Preclinical concentration across newer modalities indicates significant attrition risk ahead

Sleuth analysis; phase data reflects global highest phase per program

Molecular segmentation is gaining but broad AML still dominates

Relapsed/refractory remains the primary entry point across programs



- Relapsed/refractory AML remains the dominant population, used as entry point regardless of molecular subtype
- FLT3-mutant and NPM1-mutant populations show increasing concentration, reflecting actionable biomarkers
- TP53-mutant AML attracts growing interest despite poor prognosis as unmet need drives exploration
- Most segmentation remains clinically defined rather than biologically precise

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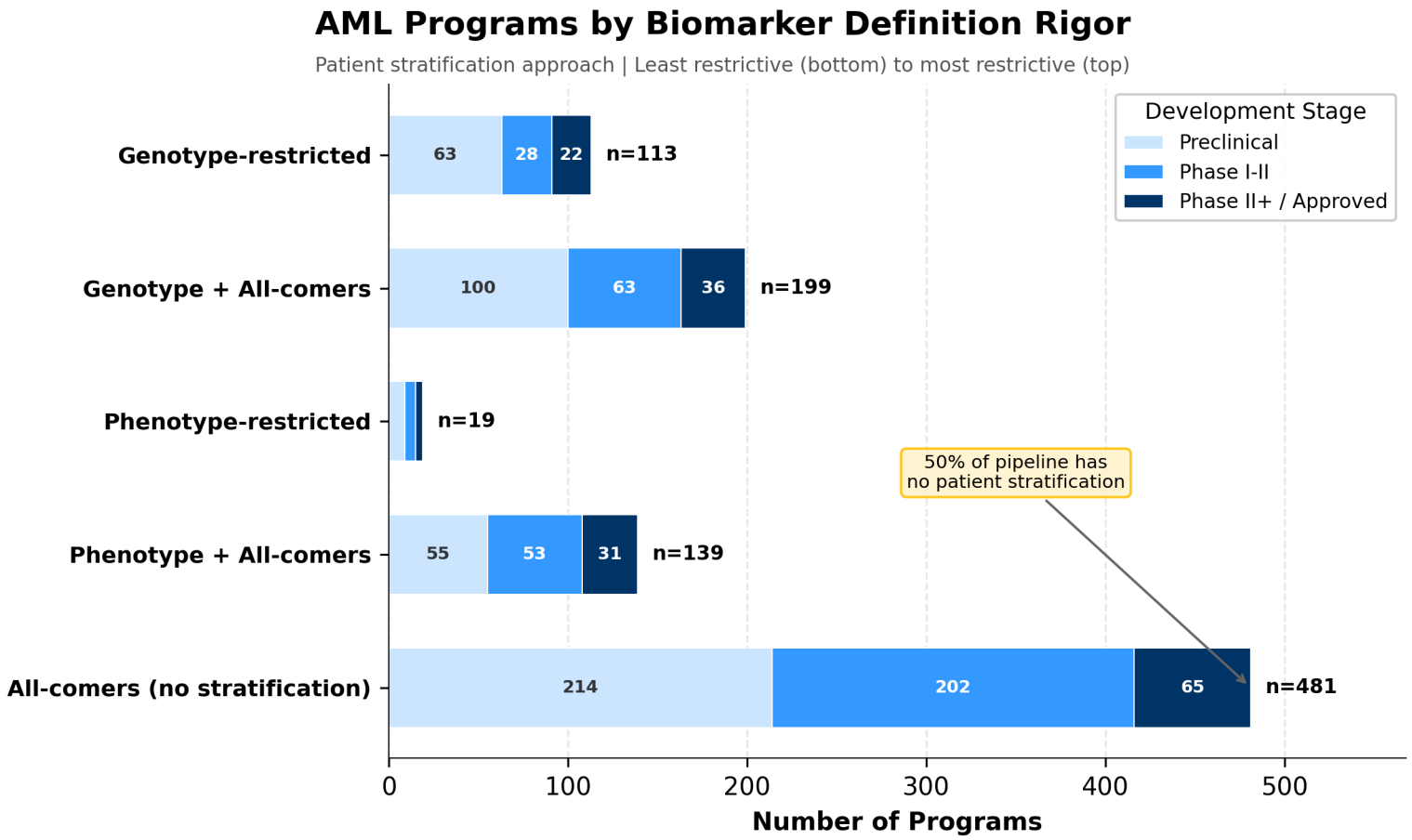
Sleuth analysis; patient population derived from program-level annotations

Biomarker use is expanding but rigor varies widely

62% cite molecular biomarkers; quality ranges from validated diagnostics to exploratory

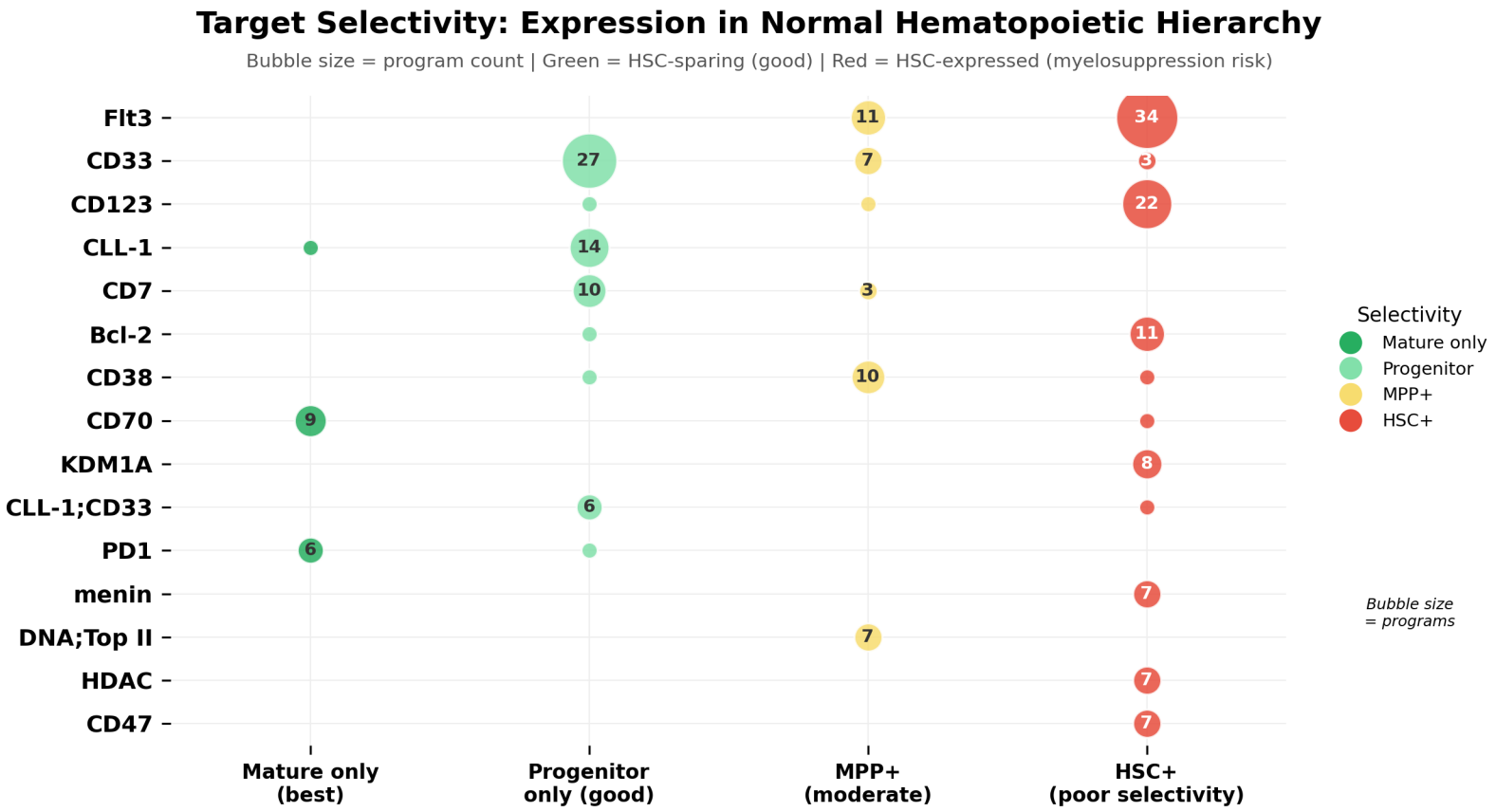


- 62% of programs now specify a molecular or genetic biomarker, up from historical reliance on phenotypic definitions
- Rigor varies significantly from validated companion diagnostics to exploratory associations
- Programs with high specificity cluster around established targets like FLT3 where diagnostics exist
- Emerging targets often lack standardized definitions, creating regulatory and commercial risk

Sleuth analysis; biomarker classification based on reported selection criteria

Most AML targets overlap with HSC or progenitor compartments

Expression in normal hematopoiesis constrains therapeutic windows across modalities



- The most pursued targets (FLT3, CD123, CD33) all show expression in HSC or early progenitors
- Targets restricted to mature compartments remain underexplored despite cleaner therapeutic windows
- HSC/MPP overlap correlates with reported myelosuppression and prolonged cytopenias
- True LSC-selective targets that spare normal hematopoiesis are rare in the current landscape

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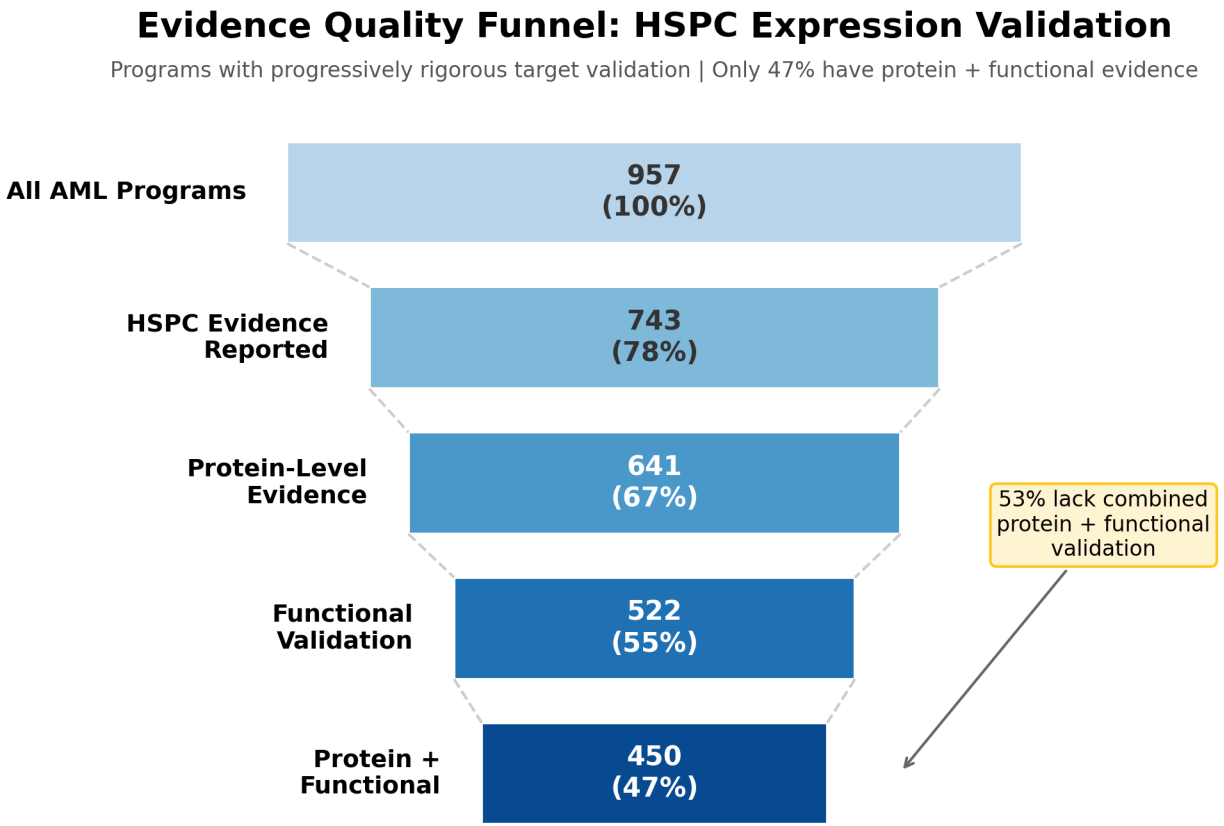
Sleuth analysis; expression data derived from literature and public databases

Selectivity claims lack protein-level validation

Only 23% cite protein-level evidence; 8% show quantitative differential expression

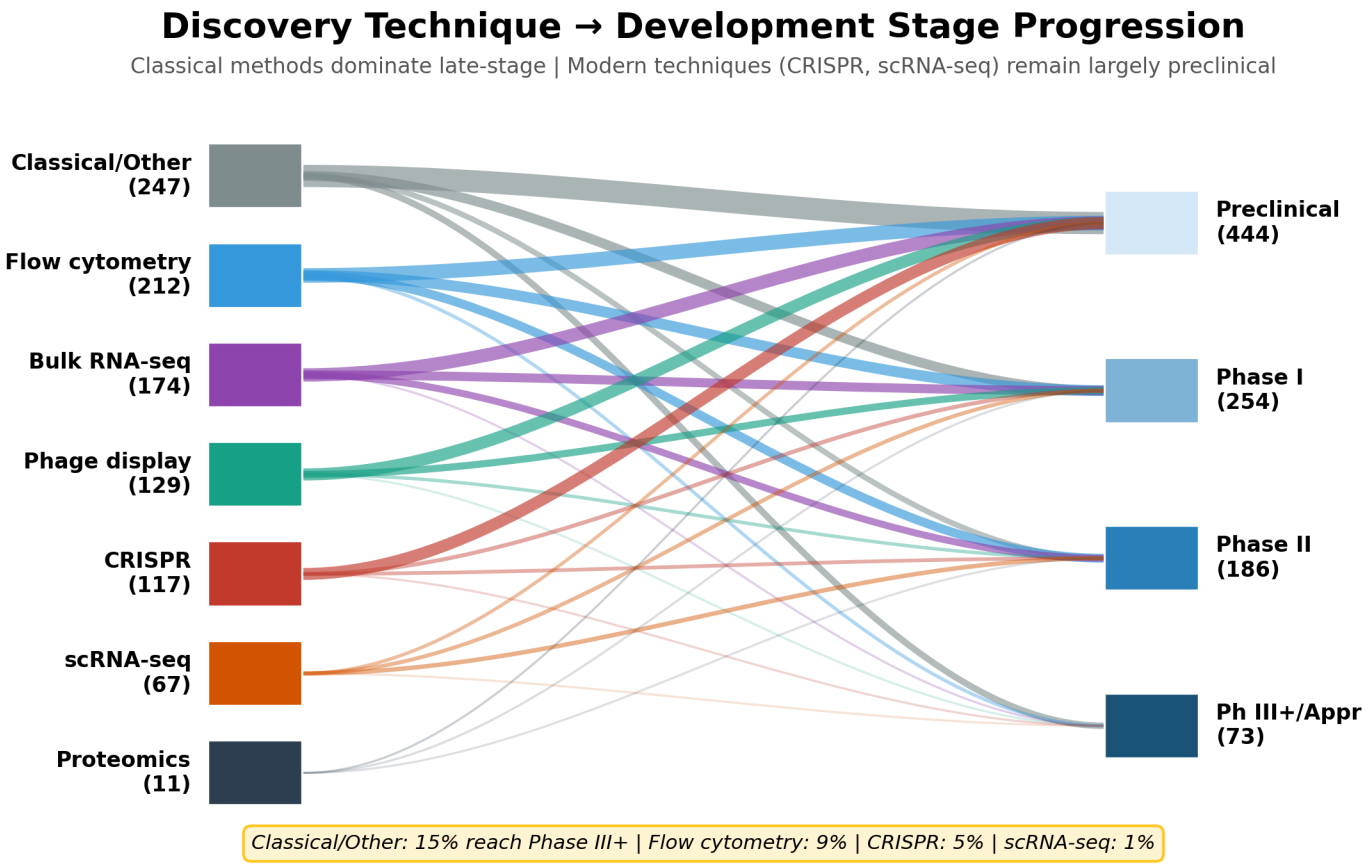


- Only 23% of programs cite protein-level selectivity evidence. Most rely on transcript data
- 8% demonstrate validated differential expression with quantitative metrics
- Flow cytometry and IHC dominate assay methods though standardization remains inconsistent
- The evidence gap suggests many selectivity claims are inferred rather than demonstrated

Sleuth analysis; evidence type classified from reported assay methods

Traditional discovery dominates despite selectivity limitations

Literature mining and functional screens inherit biases toward known targets

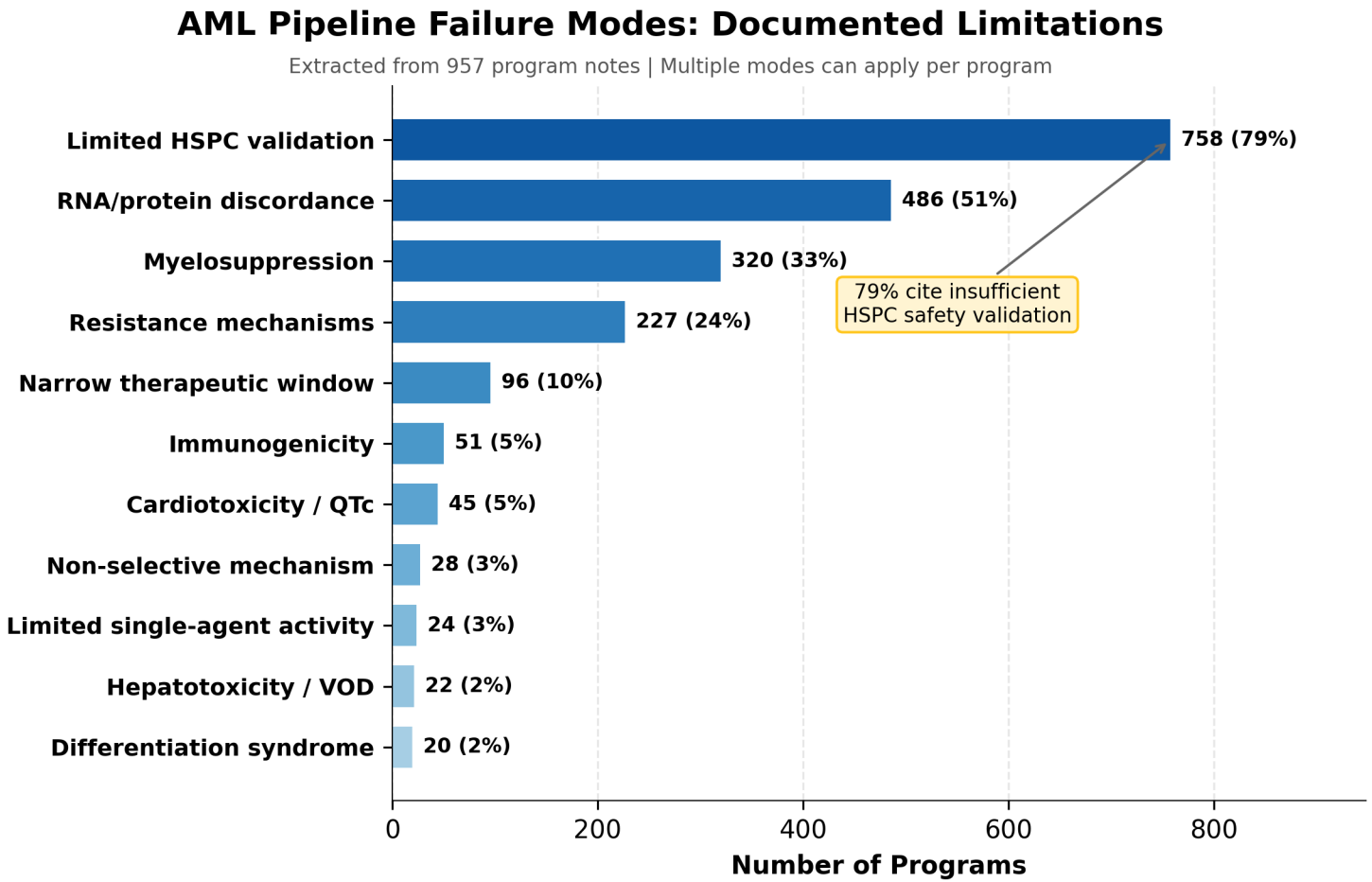


- Literature mining and database analysis remain primary routes, inheriting biases toward known targets
- Single-cell RNA sequencing is emerging but rarely integrated systematically into prioritization
- Functional screens (CRISPR, shRNA) identify dependencies but do not resolve normal tissue expression
- Proteomics-based discovery that could assess protein-level selectivity remains underutilized

Sleuth analysis; discovery methods derived from program disclosures and publications

On-target toxicity and insufficient efficacy drive failures

Myelosuppression appears across modalities; poor response limits advancement



- Myelosuppression and prolonged cytopenias appear across modalities, reflecting shared myeloid antigen targeting
- Insufficient efficacy in unselected populations drives many discontinuations
- CRS and neurotoxicity concentrate in cell therapy and bispecific programs
- Resistance and antigen loss are reported but less frequently cited as primary drivers

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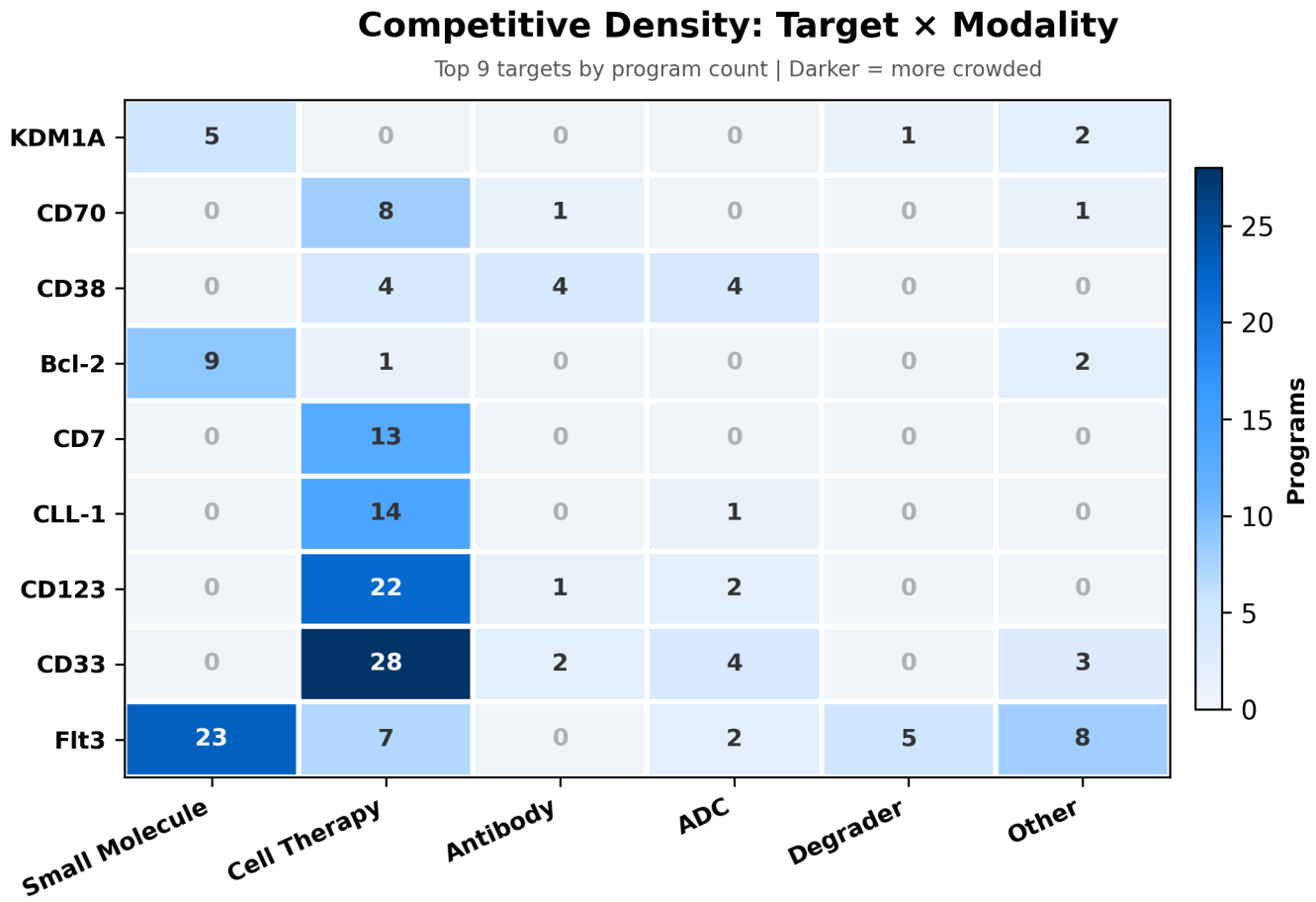
Sleuth analysis; failure modes derived from clinical disclosures and literature

Competition clusters around few target-modality combinations

CD33 and FLT3 attract programs across modalities; many pairings remain unexplored



- CD33 and FLT3 show high density across multiple modalities, creating crowded dynamics
- Cell therapy concentrates heavily on few surface antigens (CD33, CD123, CLL-1)
- Several target-modality combinations remain unexplored, representing whitespace
- Small molecule competition clusters around kinase targets with established druggability

Sleuth analysis; 957 programs mapped to target and modality classifications

High-selectivity, low-competition targets remain underexplored

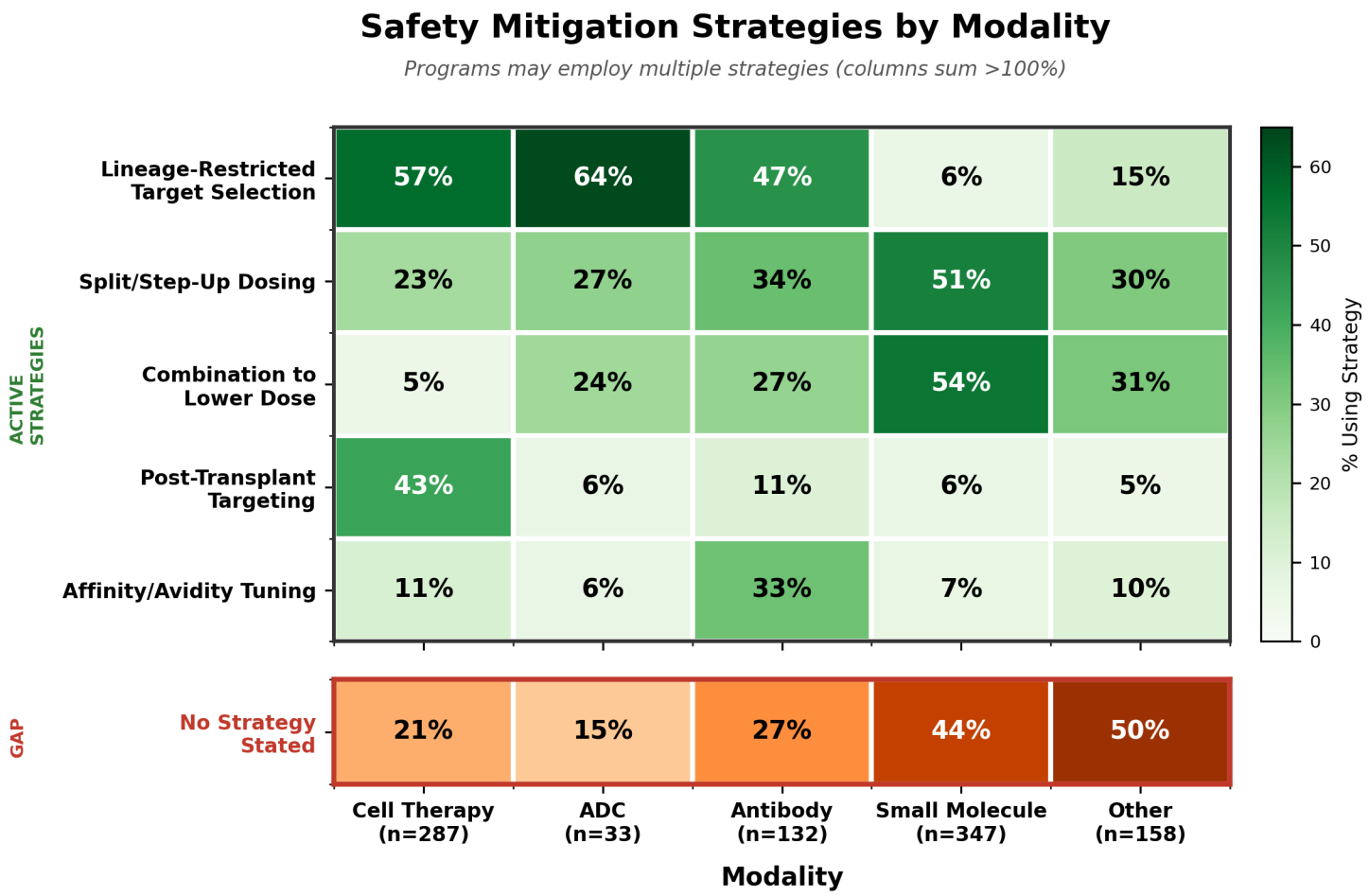
Opportunity scoring identifies mature-restricted targets with limited competitive activity

- Top-ranked targets (LILRB4, PRAME, CD25, Siglec-6) combine mature-restricted expression with limited competition
- These could serve as proof-points for discovery approaches that resolve selectivity upfront
- Established targets like FLT3 and CD123 rank poorly due to HSC overlap and intense competition
- The framework guides prioritization toward biological differentiation aligned with whitespace

Sleuth analysis; opportunity score = HSC selectivity minus competition penalty

Mitigation strategies diverge sharply by modality

Cell therapies rely on target selection and timing; 44% of small molecules cite no strategy



- Cell therapies rely on lineage-restricted target selection (57%) and post-transplant timing (43%)
- Small molecules depend on split dosing (51%) and combination approaches (54%) to manage effects
- 44% of small molecule programs cite no explicit strategy, suggesting implicit toxicity acceptance
- ADCs show highest target selection adoption (64%), consistent with surface antigen dependence

Sleuth analysis; mitigation strategies as reported in program documentation