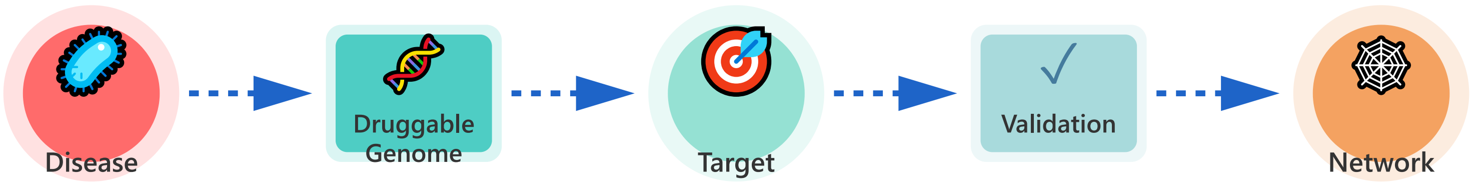
Target Identification



Disease mechanisms
Understanding biological pathways

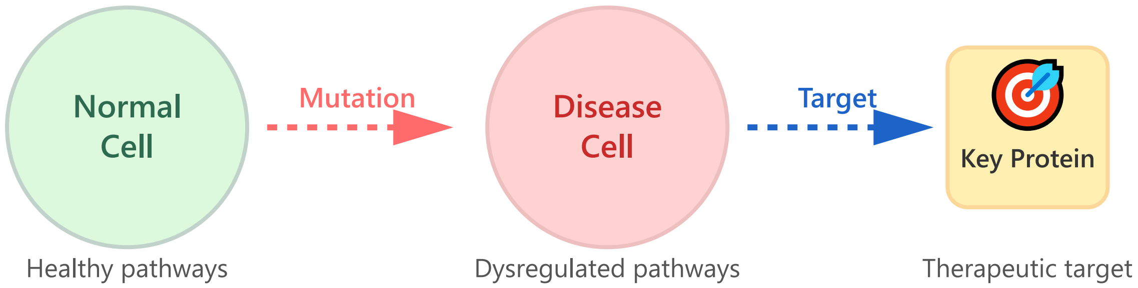
Druggable genome
Identifying targetable proteins

Target validation
Confirming therapeutic relevance

Genetic evidence
Human genetics support

Network approaches
Systems biology integration

1. Disease Mechanisms



Understanding Disease Biology

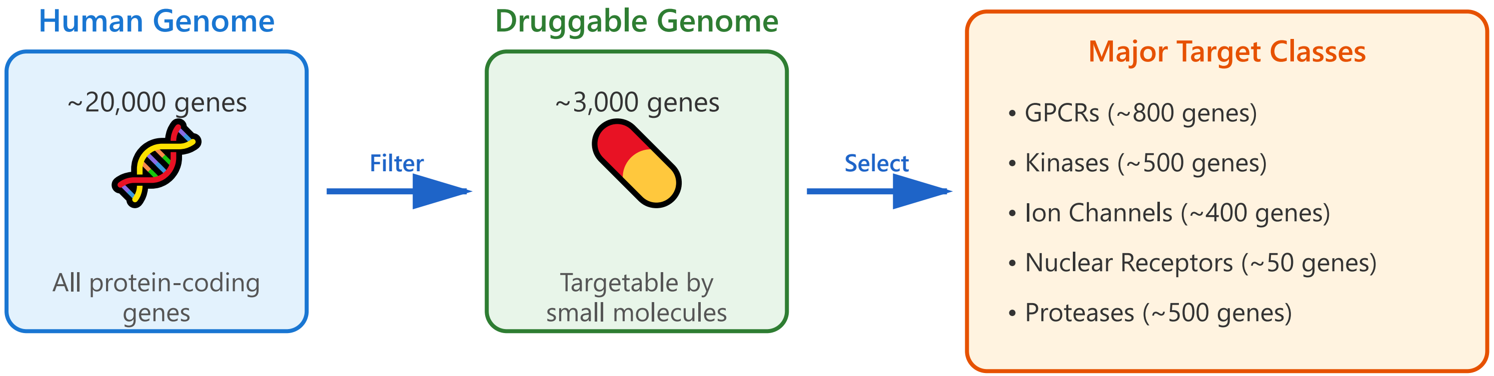
Disease mechanisms reveal how normal biological processes become disrupted, leading to pathological states. This understanding is fundamental for identifying potential therapeutic interventions.

- **Pathway Analysis:** Identifying critical signaling cascades and metabolic pathways altered in disease
- **Molecular Profiling:** Using omics technologies (genomics, transcriptomics, proteomics) to map disease signatures
- **Disease Models:** Developing cell and animal models to study disease progression

Example: Cancer Target Identification

In HER2-positive breast cancer, amplification of the ERBB2 gene leads to overexpression of HER2 protein on cell surfaces. This drives uncontrolled cell proliferation through constant activation of growth signaling pathways. HER2 was identified as a therapeutic target, leading to the development of trastuzumab (Herceptin), which blocks HER2 signaling and has dramatically improved patient outcomes.

2. Druggable Genome



Identifying Targetable Proteins

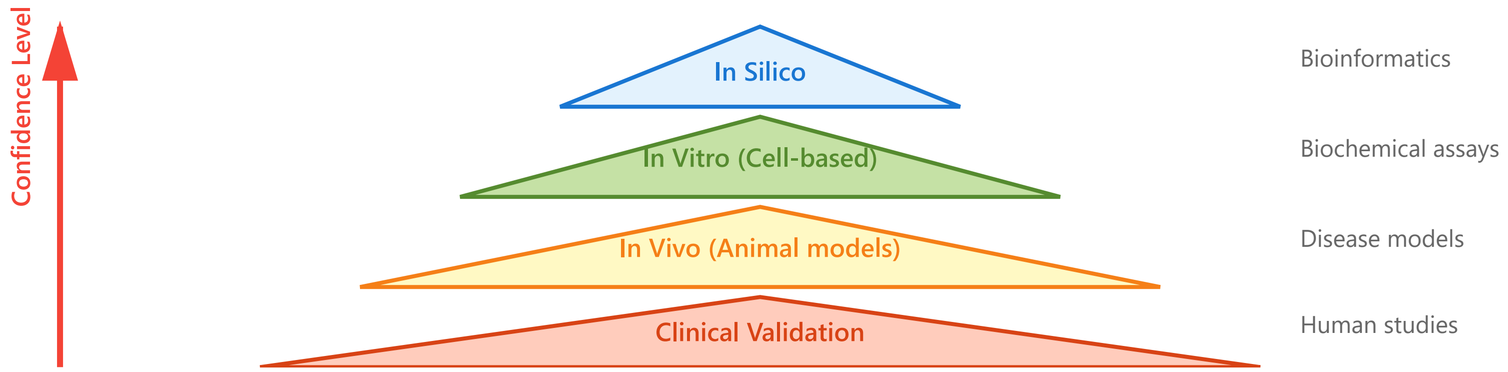
The druggable genome represents the subset of human genes whose protein products can be modulated by drug-like small molecules or biologics. These proteins typically have binding pockets suitable for drug interaction.

- **Structural Features:** Presence of binding sites accessible to small molecules or antibodies
- **Functional Importance:** Critical role in disease-relevant biological processes
- **Chemical Tractability:** Ability to be modulated by drug-like compounds with acceptable properties

Example: Protein Kinases as Drug Targets

Protein kinases represent one of the most successful druggable target classes. Imatinib (Gleevec) targets the BCR-ABL kinase in chronic myeloid leukemia. The ATP-binding pocket of kinases provides an ideal site for small molecule inhibitors. Over 70 kinase inhibitors have been approved, demonstrating the druggability of this protein family.

3. Target Validation



Confirming Therapeutic Relevance

Target validation is the process of demonstrating that modulating a specific target will produce the desired therapeutic effect. This reduces the risk of failure in later drug development stages.

- **Genetic Approaches:** Using CRISPR, RNAi, or knockout models to assess target function
- **Chemical Validation:** Using tool compounds or existing drugs to probe target effects
- **Biomarker Studies:** Identifying measurable indicators of target engagement and efficacy
- **Clinical Evidence:** Human genetic data linking target to disease outcomes

Example: PCSK9 Validation

PCSK9 was validated as a target for cholesterol lowering through multiple lines of evidence: (1) Human genetics showed loss-of-function mutations in PCSK9 associated with low LDL-cholesterol and reduced cardiovascular risk; (2) Animal studies confirmed that PCSK9 knockout reduced cholesterol; (3) Mechanistic studies revealed PCSK9 promotes degradation of LDL receptors. This strong validation supported development of PCSK9 inhibitors, now approved for high cholesterol treatment.

4. Genetic Evidence

GWAS

Genome-wide association studies

Population variants

Rare Variants

Exome/genome sequencing studies

Loss/gain function

Mendelian

Family-based inheritance patterns

Causal mutations

Pharmacogenetics

Drug response genetics studies

Target validation

Human Genetics Support

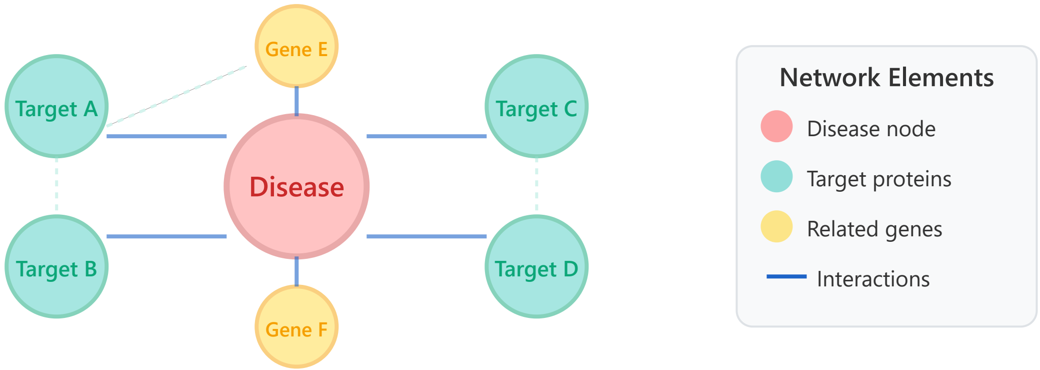
Human genetic evidence provides powerful validation for drug targets. Drugs with genetic support are twice as likely to succeed in clinical development compared to those without such evidence.

- **Natural Experiments:** Human genetic variants that mimic drug effects predict therapeutic outcomes
- **Disease Association:** Genetic variants in target genes linked to disease risk or protection
- **Dose-Response Relationships:** Correlation between variant effect size and phenotype severity
- **Safety Insights:** Rare individuals with loss-of-function variants reveal safety profile

Example: APOC3 and Triglycerides

Human genetics revealed that loss-of-function mutations in APOC3 are associated with 40% lower triglyceride levels and 40% reduced risk of coronary heart disease. Importantly, individuals with these mutations show no adverse effects, suggesting that inhibiting APOC3 would be safe and effective. This genetic evidence strongly supported development of antisense oligonucleotides targeting APOC3, with volanesorsen approved for familial chylomicronemia syndrome.

5. Network Approaches



Systems Biology Integration

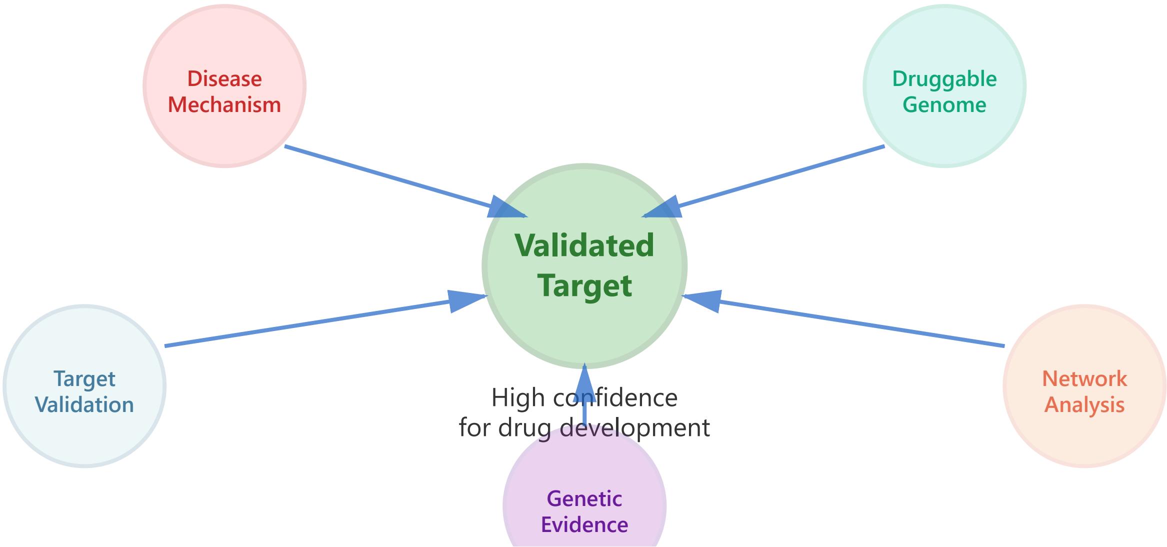
Network approaches analyze biological systems as interconnected networks rather than isolated components. This reveals disease mechanisms and identifies optimal intervention points that traditional reductionist approaches might miss.

- **Protein-Protein Interactions:** Mapping physical and functional relationships between proteins
- **Pathway Enrichment:** Identifying overrepresented biological processes in disease networks
- **Network Topology:** Finding hub proteins and key regulatory nodes as potential targets
- **Multi-omics Integration:** Combining genomic, transcriptomic, proteomic, and metabolomic data

Example: Alzheimer's Disease Network Analysis

Network analysis of Alzheimer's disease brain tissue revealed that while APP and PSEN1 mutations are well-known causes, network hub proteins like TYROBP and TREM2 in microglial cells play critical roles in disease progression. This network approach identified novel immune-related targets beyond the traditional amyloid hypothesis. TREM2 variants were subsequently found to increase Alzheimer's risk, validating the network prediction and opening new therapeutic avenues targeting neuroinflammation.

Integration of Target Identification Strategies



Success in target identification requires convergent evidence from multiple complementary approaches

Best Practices for Target Selection

- **Multiple Lines of Evidence:** Targets supported by several independent validation methods have higher success rates
- **Human Genetic Support:** Prioritize targets with strong human genetic evidence linking them to disease
- **Druggability Assessment:** Consider structural features and chemical tractability early in the process
- **Safety Considerations:** Evaluate potential on-target and off-target effects using available data
- **Biomarker Strategy:** Develop measurable endpoints for target engagement and pharmacodynamic effects