35. Drug Discovery and Development

1 unit, Minkui Luo, October 20, 2025

Timeline for Drug Discovery and Development
Target Identification and Verification
Lead Generation
    Rational design (structure-based/mechanism-based/molecular modeling and docking)
    Sources of compounds for high-throughput screening
From Lead to Small-molecule Drugs
    Hit-to-lead development
    Pharmacology and toxicology issues
Macromolecule Drugs: Peptide/Proteins and Nuclei Acids
Limitation and Future of Early-stage Drug Development
Overview of Preclinical & Clinical Study
Preclinical Study: Proof of Principle for Efficacy, Safety & Feasibility
Clinical Trail: Phase 0
Clinical Trail: Phase I for Safety
Clinical Trail: Phase II for Efficacy
Clinical Trail: Phase III for Broader Impact
Phase IV or Post Marketing Surveillance Trail

Papers for discussion

Engstrom, L. D.; Aranda, R.; Waters, L.; Moya, K.; Bowcut, V.; Vegar, L.; Trinh, D.; Hebbert, A.; Smith, C. R.; Kulyk, S.; et al. “MRTX1719 Is an MTA-Cooperative PRMT5 Inhibitor That Exhibits Synthetic Lethality in Preclinical Models and Patients with MTAP-Deleted Cancer”, *Cancer Disc.* **2023**, *13*, 2412.

Background

Gershell, L. J.; Atkins, J. H. "A brief history of novel drug discovery technologies." *Nature Rev. Drug Disc.* **2003**, *2*, 321-327. (Review paper)

Additional

Kalev P, Hyer ML, Gross S, Konteatis Z, Chen CC, Fletcher M, Lein M, Aguado-Fraile E, Frank V, Barnett A, Mandley E, Goldford J, Chen Y, Sellers K, Hayes S, Lizotte K, Quang P, Tuncay Y, Clasquin M, Peters R, Weier J, Simone E, Murtie J, Liu W, Nagaraja R, Dang L, Sui Z, Biller SA, Travins J, Marks KM, Marjon K., “MAT2A Inhibition Blocks the Growth of MTAP-Deleted Cancer Cells by Reducing PRMT5-Dependent mRNA Splicing and Inducing DNA Damage”, *Cancer Cell*, **2021**, 39, *209-224*.

Kryukov GV, Wilson FH, Ruth JR, Paulk J, Tsherniak A, Marlow SE, Vazquez F, Weir BA, Fitzgerald ME, Tanaka M, Bielski CM, Scott JM, Dennis C, Cowley GS, Boehm JS, Root DE, Golub TR, Clish CB, Bradner JE, Hahn WC, Garraway LA., “MTAP deletion confers enhanced dependency on the PRMT5 arginine methyltransferase in cancer cells”, Science **2016**, *351*,1214-8.

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