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Targeting Lin28: Insights into Biology and Advances with AI-Driven Drug Development

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ABSTRACT

Lin28, a conserved RNA-binding protein, promotes cancer stem cell features, epithelial-to-mesenchymal transition, and treatment resistance. Lin28 operates through canonical and non-canonical pathways, contributing to its diverse biological functions. In the canonical pathway, Lin28 binds directly to pre-Let-7 microRNA, blocking its maturation and promoting its degradation. This Let-7-dependent pathway influences cellular processes by regulating Let-7 target mRNAs, which are involved in proliferation, differentiation, and metabolism. In contrast, the non-canonical pathway is Let-7-independent and involves Lin28 interacting directly with specific DNA regions, mRNAs, or proteins. Through these interactions, Lin28 regulates translation, RNA stability, and other cellular processes, often contributing to tumor progression and treatment resistance. These distinct pathways highlight the complexity of Lin28 in cancer biology and its potential as a therapeutic target. We highlight computational drug discovery advances targeting Lin28 utilizing virtual screening and machine learning. Generative artificial intelligence provides an opportunity to develop inhibitors for challenging targets like Lin28 by designing novel molecules tailored to such unconventional targets. This work integrates current knowledge and technology to demonstrate the therapeutic potential of Lin28 and outline future techniques to overcome RNA-binding protein targeting challenges.

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Introduction

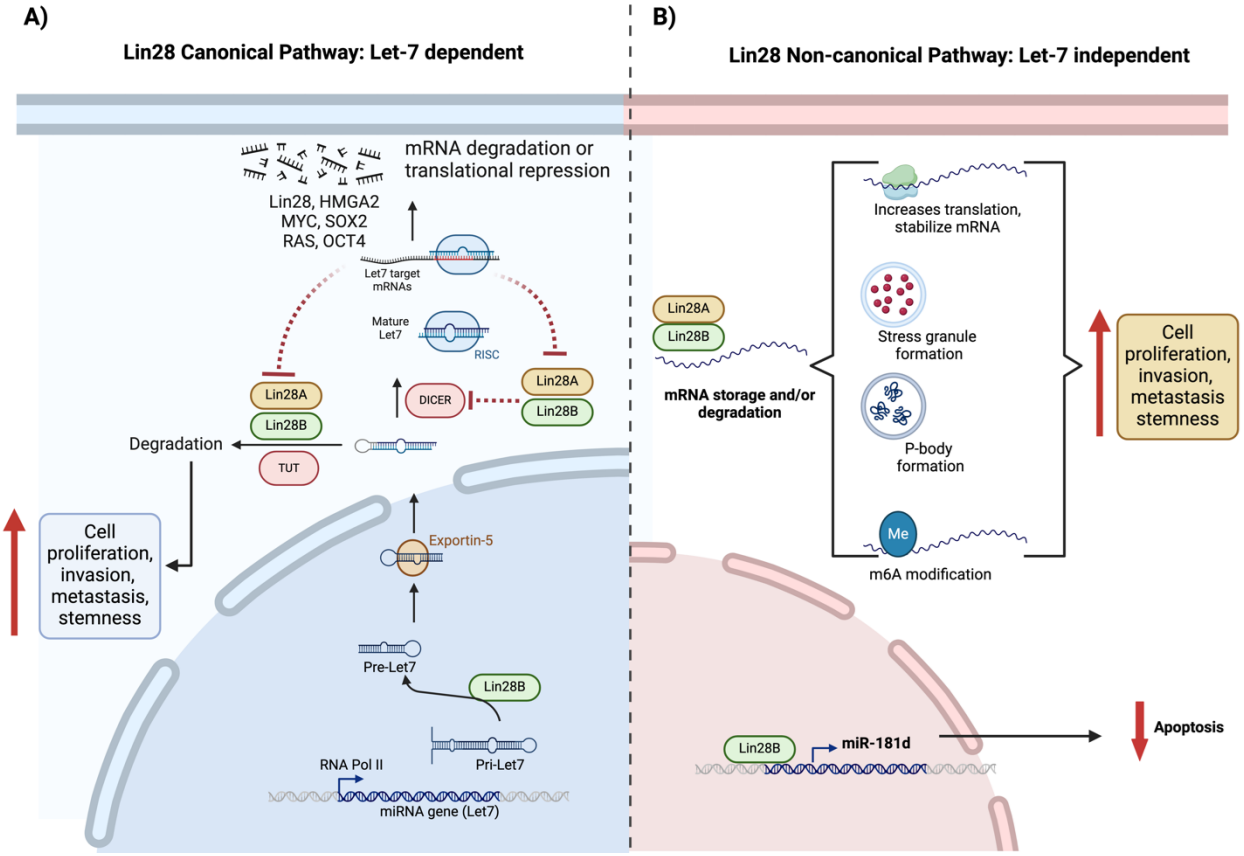
Cancer has high cellular heterogeneity; hence, tumor subpopulations respond differently to treatment. This variety at genomic, transcriptome, and RNA processing levels helps produce therapy-resistant tumor cells with co-existing phenotypes. Designing effective medicines is difficult due to tumor heterogeneity. Lin28, an RNA-binding protein that regulates cellular processes, drives cancer stem cell (CSC) phenotypes, epithelial-to-mesenchymal transition, tumor growth and resistance [1]. Lin28 inhibits Let-7, promoting tumor cell plasticity, which enables cells to adapt to therapy-induced stress, increasing their aggressiveness and resistance, as observed in prostate cancer [2]. In addition to controlling Let-7, Lin28 has been demonstrated to directly interact with mRNAs to promote translation and regulate gene expression independently of Let-7. These additional methods, though not yet fully understood, may provide insight into the role of Lin28 in cancer biology.

This review examines Lin28's roles in cancer progression, focuses on its traditional pathway through Let-7 control and its emergent, less well-characterized functions. We address how Lin28 drives prostate cancer stemness, metastasis, and therapy resistance, and current breakthroughs in targeting Lin28 with small compounds to suppress CSC characteristics and overcome treatment resistance. RNA-binding proteins (RBPs) are notoriously difficultly targeted, making Lin28 targeting become a challenge. Small-molecule inhibitors and computational drug design are promising but need refining to increase potency and specificity, and to decrease off-target effects. Lin28 is an appealing therapeutic target because of its pivotal involvement in tumor plasticity and development. Understanding its complete spectrum of actions could lead to the development of more effective cancer treatments.

Biological Roles of Lin28

Lin28 is a conserved RNA-binding protein, existing as two isoforms, Lin28A and Lin28B, that regulate gene expression through canonical or non-canonical pathways [3]. While its canonical function

Figure 1: Lin28 biological pathways [10]. A) Lin28 canonical pathway (Let-7 dependent). This pathway is Let-7 dependent and illustrates how Lin28 binds to pri-Let-7 and pre-Let-7 microRNA, blocking its maturation and promoting its degradation. The inhibition of Let-7 leads to downstream effects on its target genes, regulating processes such as proliferation, differentiation, and metabolism. B) Lin28 non-canonical pathway (Let-7 independent). This pathway is Let-7 independent, highlighting the direct interactions of Lin28 with mRNAs and proteins. These interactions influence various cellular processes, including translation and metabolic regulation, independent of Let-7. TUT: TUTase; RISC: RNA-induced silencing complex; m6A: N6-Methyladenosine; Me: Methylation.



is to regulate Let-7 microRNA (miRNA) maturation and degradation, Lin28 also plays diverse roles in regulating mRNA translation, stress responses, and long non-coding RNAs [4]. These functions have significant implications for stem cell biology, development, and diseases, particularly cancer.

Canonical Pathways: Regulation of Let-7 miRNA Biogenesis

The canonical Lin28 function involves the suppression of Let-7 miRNA maturation, a mechanism essential for its control of pluripotency and carcinogenic pathways. Within the nucleus, Lin28B associates with pri-Let-7, inhibiting its processing by the Drosha/DGCR8 complex, thereby impeding the early phase of Let-7 development. Within the cytoplasm, Lin28A and Lin28B associate with pre-Let-7 and enlist the Tutase4/7 enzyme, which polyuridylates pre-Let-7, signaling it for breakdown by exonucleases such as Dis3l2 [5–9]. Thus, Lin28 inhibits Let-7 by either blocking its biogenesis or promoting its degradation, disrupting the regulatory functions of Let-7 and leading to the derepression of key oncogenes such as Myc, Ras, and HMGA2 [7]. This results in enhanced cell proliferation, survival, tumorigenesis, and the maintenance of stem-like characteristics [8, 9]. In contrast, Let-7 miRNAs act as tumor suppressors and are essential regulators of differentiation by downregulating pluripotency-associated proteins like Sox2, Oct4, and Lin28 [1]. The interaction between Lin28 and Let-7 forms a tightly controlled feedback loop that regulates cell fate, stemness, and oncogenic potential (Figure 1A).

Previous research highlights the critical role of the Lin28/Let-7 axis in the development of CSC phenotypes, particularly through mechanisms involving oncogene upregulation and treatment resistance [11–14]. Low levels of Let-7 promote the upregulation of

key oncogenes such as HMGA2 and RAS, enhancing self-renewal and suppressing differentiation in breast and pancreatic cancers [14]. Similarly, the suppression of Let-7 has been linked to increased expression of pluripotency genes (e.g., Sox2, Oct4, Nanog), contributing to therapy resistance and metastasis [12]. Additionally, aberrant regulation of several signaling pathways, including Wnt/β-catenin, NOTCH/hedgehog, and STAT3/NFκB, has been associated with the Lin28/Let-7 axis in promoting CSC phenotypes and metastatic potential [11]. In breast cancer, for example, Let-7-induced suppression of the Wnt pathway reduces CSC renewal and resistance to therapies like tamoxifen [15]. In lung and esophageal cancers, Let-7-mediated inhibition of these pathways has similarly suppressed EMT and enhanced re-sensitization to chemotherapy [16, 17]. Overall, the Lin28/Let-7 axis plays a key role in regulating CSC biology and could serve as a valuable target for addressing therapy resistance and metastatic progression in cancer.

Non-Canonical Pathways: Let-7-Independent Roles of Lin28

While Lin28 primarily regulates Let-7 microRNA production, growing data underscore its extensive roles in other physiological processes, including mRNA translation, RNA stability, stress response, and metabolic regulation. These non-canonical functions are essential for proper development, cellular differentiation, and cancer progression.

Lin28 directly interacts with mRNAs, including OCT4, to recruit RNA helicase A, thereby augmenting translation and preserving pluripotency in embryonic stem cells [18]. In response to stress, Lin28 assembles stress granules with G3BP1 and YB-1 to stabilize mRNAs and inhibit superfluous translation, thus promoting cell survival [19, 20]. In P-bodies, Lin28 facilitates RNA breakdown, thereby enhancing its influence on RNA metabolism [21]. Furthermore, LIN28 regulates mRNA methylation at m6A sites, affecting stability, splicing, and translation to control gene expression [22].

In addition to RNA metabolism, Lin28 facilitates fatty acid production and tumor proliferation by augmenting the translation of SREBP-1 and SCAP mRNA in hepatic cancer cells [23]. It also engages with the IGF2-mTOR pathway, binding mRNAs such as IGF1R and AKT to modulate cell survival, growth, and differentiation [24]. Additionally, Lin28 affects cell cycle progression by regulating genes like CDK2 and Cyclin B, which are crucial for both normal and cancerous cell growth [25]. It also influences alternative splicing via splicing factors such as TIA-1 and hnRNPF, independent of Let-7 regulation [26].

Despite RNA-related functions, Lin28b acts as a DNA-binding protein by interacting with the promoter region of miR-181d, thereby enhancing its expression. This subsequently inhibits PDCD4 by targeting its 3' UTR, thus promoting the proliferation of chronic myeloid leukemia cells [27]. These diverse roles position Lin28 as a crucial regulator of gene expression, connecting development, metabolism, and illness. Its considerable effect highlights its importance beyond Let-7 control (Figure 1B).

Challenges in Targeting RNA-Binding Proteins

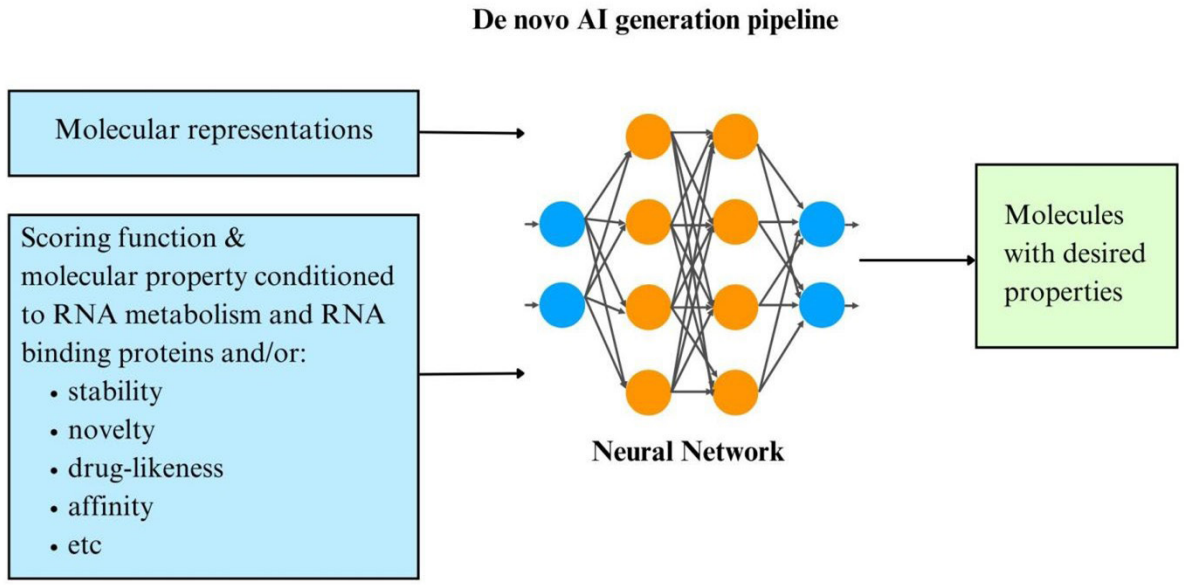
RBPs, including Lin28, are challenging drug targets due to their structural and functional characteristics [28]. Unlike enzymes or receptors with well-defined binding pockets, RBPs typically feature shallow, dynamic, and disordered RNA-binding surfaces [29]. These dynamic interactions, spread over broad regions, lack the deep, pocket-like geometries suitable for small-molecule binding, complicating virtual screening (VS) and drug design [29]. Additionally, RBPs typically interact with diverse RNA sequences and structures, making selective targeting difficult and further increasing the risk of off-target effects [28].

Computer-Aided Drug Development and Artificial Intelligence (AI) for Lin28 Targeting

Despite these difficulties, Lin28 has been consensually validated as a therapeutic target with the potential to block Lin28-RNA interactions for tumor suppression [30–32]. Over the past decades, drug discovery campaigns targeting Lin28 and other RNA-binding proteins have heavily relied on traditional computer-aided drug design (CADD) techniques, such as VS [33, 34]. Molecular docking, a cornerstone of structure-based VS, offers a computationally efficient alternative to labor-intensive wet lab screening for libraries containing millions of molecules and has been consistently applied to Lin28 inhibitor screening in multiple studies [31, 32].

Although traditional in-silico methods have played a crucial role in the early-stage exploration of RBPs, particularly through the screening of existing chemical libraries, these approaches are inherently limited by the size and diversity of available datasets, making brute-force screening impractical [1, 31, 32].

Figure 2. De novo AI generation pipeline illustrating a generalized approach for using generative AI in conditional neural networks. A molecular representation is input into the neural network, which is optimized using a scoring function. The neural network then generates de novo molecules based on the input template, with the process enhanced by the scoring function.



Applications of AI in Drug Development

Machine learning (ML), in particular, has emerged as a valuable tool across various stages of drug discovery, offering the capability to efficiently process and analyze vast datasets [35–37]. For example, Deep Docking, a deep neural network enhanced with active learning, was utilized to identify inhibitors of Lin28 [32, 38]. An active learning algorithm of Deep Docking allowed screening of a billion-scale library with enhanced training of a model on better-docked compounds and eliminating predicted poor binders. In a recent study, graph neural networks (GNNs) were applied for virtual screening of a chemical library against another RNA target [39].

ML offers a transformative solution by reducing the computational burden of exhaustive screening, but its effectiveness still remains tied to the limitations of the pre-existing datasets it analyzes [40]. In contrast, generative AI approaches represent a revolutionary advance in VS. Generative AI refers to AI systems that create new data (de novo), such as molecular structures, by learning patterns from existing datasets [40]. Generative AI models are initially trained on collections of compounds and their known biological properties, enabling them to generate novel molecular candidates that align with specific pharmacological profiles (Figure 2). Contrary to traditional VS methods, generative AI efficiently explores chemical space while simultaneously optimizing compound properties and minimizing the time and costs associated with traditional experimental screening. This is particularly crucial when working with unconventional or difficult-to-screen targets [40, 41]. Instead of searching vast datasets for specific types of molecules, generative AI delivers molecules tailored to desired characteristics, enabling a more targeted and efficient approach to drug discovery [40, 41]. As a result, generative AI significantly accelerates and democratizes the drug discovery process. The application of AI in targeting RBPs is increasingly in demand, particularly as traditional drug discovery methods often struggle with these challenging targets [41], as de novo design offers a highly efficient solution when conventional approaches fail. Unlike traditional techniques that rely on predefined datasets or well-defined binding pockets, generative AI excels in designing novel molecules tailored to complex or unconventional targets, such as the shallow and dynamic surfaces typical of RBPs [42].

Success Stories and Recent Advances

In recent years, the use of generative AI with diverse molecular representations, architectures, and applications for addressing target design challenges has grown exponentially [43]. De novo drug design has emerged as a powerful approach for generating novel chemical structures with desired molecular profiles, such as specific biological activities. Among

the most used architectures in deep generative models are neural networks (NNs), variational autoencoders (VAEs), generative adversarial networks (GANs), transformers, and hybrid reinforcement learning models. Such models can learn the underlying patterns within molecular representations, enabling the generation of novel chemicals with tailored properties [44, 45].

Generative AI is increasingly contributing to drug discovery, with recent advancements leading to AI-designed molecules reaching clinical trials. For instance, AI has successfully been applied to develop drugs targeting serotonin receptors (serotonin 1A receptor and serotonin 2A receptor), demonstrating its potential to identify novel therapeutic candidates within relevant chemical spaces [39, 43]. A small molecule generated through AI-based methods, a 5-HT1A agonist and 5-HT2A antagonist, selectively targeting 5-HT1A and 5-HT2A serotonin receptors, has progressed to clinical trials, highlighting the practical applicability of AI in identifying promising therapeutic agents [46]. Moreover, in 2024, AI-predicted inhibitors for the anti-fibrotic target TNIK, which exhibit desirable drug-like properties and anti-fibrotic activity, were validated in phase I clinical trial. The AI-driven platform was configured to produce small-molecule structures capable of forming hydrogen bonds with the Cys108-NH of the TNIK hinge region [47].

Future directions

The past few years have seen a rapid surge in the adoption of generative models, utilizing various molecular representations, architectural frameworks, and approaches to tackle complex target design challenges. Recent studies of Lin28 have identified numerous promising lead structures that now require a customized approach for lead optimization [30, 32]. For RBPs, traditional methods at this stage offer limited benefits. In contrast, generative AI provides an efficient solution by enhancing specific properties and tailoring molecules to exhibit the desired chemical characteristics, making it the preferred approach for advancing these leads [48].

The development of AI-driven drug discovery for RBPs, such as Lin28, still faces challenges arising from the complexity of RNA-protein interactions. One of the challenges is data limitation. The lack of large, high-quality datasets for RBP-ligand interactions limits the effectiveness of AI [48]. RNA-protein interactions are dynamic, making it difficult for AI models to accurately predict and design small molecules that modulate these interactions [48].

To address these issues, hybrid AI models integrating structural and sequence-based information, alongside molecular dynamics simulations, could improve the prediction accuracy for RBP-targeted small molecules [48]. Multi-objective optimization and transfer learning approaches can enhance specificity and reduce off-target effects [48]. Finally, AI predictions must be validated through iterative feedback with high-throughput screening and real-time experimental testing to refine models [48].

To tackle the challenges of targeting RBPs, such as Lin28, AI-driven optimization should prioritize specific objectives, such as increasing binding affinity to Lin28 and improving pharmacokinetic properties, guided by experimental data from lead compounds. Emerging de novo design approaches, such as diffusion models, offer the potential to design molecules directly within target binding sites, expanding the capabilities of de novo drug design for complicated targets [49]. Additionally, experimental validation of AI-generated candidates remains a critical step to ensure the practical applicability and effectiveness of these innovative methodologies [48].

Ethical approval:

Not applicable.

Conflict of interest:

The authors declare no conflict of interest.

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References

1. Lin Z, Radaeva M, Cherkasov A, Dong X. **Lin28 Regulates Cancer Cell Stemness for Tumour Progression.** Cancers (Basel). 2022 Sep 24;14(19):4640. doi: 10.3390/cancers14194640. PMID: 36230562; PMCID: PMC9564245.
2. Lovnicki J, Gan Y, Feng T, Li Y, Xie N, Ho CH, Lee AR, Chen X, Nappi L, Han B, Fazli L, Huang J, Gleave ME, Dong X. **LIN28B promotes the de-**

velopment of neuroendocrine prostate cancer. J Clin Invest. 2020 Oct 1;130(10):5338-5348. doi: 10.1172/JCI135373. PMID: 32634132; PMCID: PMC7524485.

3. Maklad A, Sedeeq M, Chan KM, Gueven N, Azimi I. **Exploring Lin28 proteins: Unravelling structure and functions with emphasis on nervous system malignancies.** Life Sci. 2023 Dec 15;335:122275. doi: 10.1016/j.lfs.2023.122275. Epub 2023 Nov 19. PMID: 37984514.
4. Cotino-Nájera S, García-Villa E, Cruz-Rosales S, Gariglio P, Díaz-Chávez J. **The role of Lin28A and Lin28B in cancer beyond Let-7.** FEBS Lett. 2024 Dec;598(24):2963-2979. doi: 10.1002/1873-3468.15004. Epub 2024 Aug 16. PMID: 39152528; PMCID: PMC11665955.
5. Nam Y, Chen C, Gregory RI, Chou JJ, Sliz P. **Molecular basis for interaction of let-7 microRNAs with Lin28.** Cell. 2011 Nov 23;147(5):1080-91. doi: 10.1016/j.cell.2011.10.020. Epub 2011 Nov 10. PMID: 22078496; PMCID: PMC3277843.
6. Piskounova E, Polytarchou C, Thornton JE, LaPierre RJ, Pothoulakis C, Hagan JP, Iliopoulos D, Gregory RI. **Lin28A and Lin28B inhibit let-7 microRNA biogenesis by distinct mechanisms.** Cell. 2011 Nov 23;147(5):1066-79. doi: 10.1016/j.cell.2011.10.039. PMID: 22118463; PMCID: PMC3227872.
7. Balzeau J, Menezes MR, Cao S, Hagan JP. **The LIN28/let-7 Pathway in Cancer.** Front Genet. 2017 Mar 28;8:31. doi: 10.3389/fgene.2017.00031. PMID: 28400788; PMCID: PMC5368188.
8. Shyh-Chang N, Daley GQ. **Lin28: primal regulator of growth and metabolism in stem cells.** Cell Stem Cell. 2013 Apr 4;12(4):395-406. doi: 10.1016/j.stem.2013.03.005. PMID: 23561442; PMCID: PMC3652335.
9. Alam M, Ahmad R, Rajabi H, Kufe D. **MUC1-C Induces the LIN28B→LET-7→HMGA2 Axis to Regulate Self-Renewal in NSCLC.** Mol Cancer Res. 2015 Mar;13(3):449-60. doi: 10.1158/1541-7786.MCR-14-0363. Epub 2014 Nov 3. PMID: 25368430; PMCID: PMC4369171.
10. Matias-Barrios, VM. Lin28 biological pathways. Created in BioRender. 2024. https://BioRender.com/y03u835
11. Ma Y, Shen N, Wicha MS, Luo M. **The Roles of the Let-7 Family of MicroRNAs in the Regulation of Cancer Stemness.** Cells. 2021 Sep 14;10(9):2415. doi: 10.3390/cells10092415. PMID: 34572067; PMCID: PMC8469079.
12. Bao, B., Ali, S., Ahmad, A., Li, Y., Banerjee, S., Kong, D., Aboukameel, A., Mohammad, R., Van Buren, E., Azmi, A. S., & Sarkar, F. H. **Differentially expressed miRNAs in cancer-stem-like cells: Markers for tumor cell aggressiveness of pancreatic cancer.** Stem Cells and Development, 2014, 23(16), 1947. https://doi.org/10.1089/scd.2013.0551
13. Yang X, Cai H, Liang Y, Chen L, Wang X, Si R, Qu K, Jiang Z, Ma B, Miao C, Li J, Wang B, Gao P. **Inhibition of c-Myc by let-7b mimic reverses mutidrug resistance in gastric cancer cells.** Oncol Rep. 2015 Apr;33(4):1723-30. doi: 10.3892/or.2015.3757. Epub 2015 Jan 28. PMID: 25633261.
14. Yu F, Yao H, Zhu P, Zhang X, Pan Q, Gong C, Huang Y, Hu X, Su F, Lieberman J, Song E. **let-7 regulates self renewal and tumorigenicity of breast cancer cells.** Cell. 2007 Dec 14;131(6):1109-23. doi: 10.1016/j.cell.2007.10.054. PMID: 18083101.
15. Li X, Liang T, Chen SS, Wang M, Wang R, Li K, Wang JC, Xu CW, Du N, Qin S, Ren H. **Matrine suppression of self-renewal was dependent on regulation of LIN28A/Let-7 pathway in breast cancer stem cells.** J Cell Biochem. 2020 Mar;121(3):2139-2149. doi: 10.1002/jcb.29396. Epub 2019 Oct 8. PMID: 31595560.
16. Ahmad A, Maitah MY, Ginnebaugh KR, Li Y, Bao B, Gadgeel SM, Sarkar FH. **Inhibition of Hedgehog signaling sensitizes NSCLC cells to standard therapies through modulation of EMT-regulating miRNAs.** J Hematol Oncol. 2013 Oct 7;6(1):77. doi: 10.1186/1756-8722-6-77. PMID: 24199791; PMCID: PMC3852827.
17. Pang Y, Liu J, Li X, Zhang Y, Zhang B, Zhang J, Du N, Xu C, Liang R, Ren H, Tang SC, Sun X. **Nano Let-7b sensitization of eliminating esophageal cancer stem-like cells is dependent on blockade of Wnt activation of symmetric division.** Int J Oncol. 2017 Oct;51(4):1077-1088. doi: 10.3892/ijo.2017.4104. Epub 2017 Aug 29. PMID: 28902370; PMCID: PMC5592862.
18. Qiu C, Ma Y, Wang J, Peng S, Huang Y. **Lin28-mediated post-transcriptional regulation of Oct4 expression in human embryonic stem cells.** Nucleic Acids Res. 2010 Mar;38(4):1240-8. doi: 10.1093/nar/gkp1071. Epub 2009 Dec 4. PMID: 19966271; PMCID: PMC2831306.
19. Samsonova A, El Hage K, Desforges B, Joshi V, Clément MJ, Lambert G, Henrie H, Babault N, Craveur P, Maroun RC, Steiner E, Bouhss

A, Maucuer A, Lyabin DN, Ovchinnikov LP, Hamon L, Pastré D. **Lin28, a major translation reprogramming factor, gains access to YB-1-packaged mRNA through its cold-shock domain.** Commun Biol. 2021 Mar 19;4(1):359. doi: 10.1038/s42003-021-01862-3. PMID: 33742080; PMCID: PMC7979924.

20. Song D, Chen Y, Wang P, Cheng Y, Shyh-Chang N. **Lin28a forms an RNA-binding complex with Igf2bp3 to regulate m6A-modified stress response genes in stress granules of muscle stem cells.** Cell Prolif. 2024 Dec;57(12):e13707. doi: 10.1111/cpr.13707. Epub 2024 Jul 17. PMID: 39021312; PMCID: PMC11628740.
21. Balzer E, Moss EG. **Localization of the developmental timing regulator Lin28 to mRNP complexes, P-bodies and stress granules.** RNA Biol. 2007 Jan-Mar;4(1):16-25. doi: 10.4161/rna.4.1.4364. Epub 2007 Apr 30. PMID: 17617744.
22. Sun L, Fazal FM, Li P, Broughton JP, Lee B, Tang L, Huang W, Kool ET, Chang HY, Zhang QC. **RNA structure maps across mammalian cellular compartments.** Nat Struct Mol Biol. 2019 Apr;26(4):322-330. doi: 10.1038/s41594-019-0200-7. Epub 2019 Mar 18. PMID: 30886404; PMCID: PMC6640855.
23. Zhang Y, Li C, Hu C, Wu Q, Cai Y, Xing S, Lu H, Wang L, Huang D, Sun L, Li T, He X, Zhong X, Wang J, Gao P, Smith ZJ, Jia W, Zhang H. **Lin28 enhances de novo fatty acid synthesis to promote cancer progression via SREBP-1.** EMBO Rep. 2019 Oct 4;20(10):e48115. doi: 10.15252/embr.201948115. Epub 2019 Aug 5. PMID: 31379107; PMCID: PMC6776893.
24. Yang M, Yang SL, Herrlinger S, Liang C, Dzieciatkowska M, Hansen KC, Desai R, Nagy A, Niswander L, Moss EG, Chen JF. **Lin28 promotes the proliferative capacity of neural progenitor cells in brain development.** Development. 2015 May 1;142(9):1616-27. doi: 10.1242/dev.120543. PMID: 25922525; PMCID: PMC4419280.
25. Xiong H, Zhao W, Wang J, Seifer BJ, Ye C, Chen Y, Jia Y, Chen C, Shen J, Wang L, Sui X, Zhou J. **Oncogenic mechanisms of Lin28 in breast cancer: new functions and therapeutic opportunities.** Oncotarget. 2017 Apr 11;8(15):25721-25735. doi: 10.18632/oncotarget.14891. PMID: 28147339; PMCID: PMC5421965.
26. Yang J, Bennett BD, Luo S, Inoue K, Grimm SA, Schroth GP, Bushel PR, Kinyamu HK, Archer TK. **LIN28A Modulates Splicing and Gene Expression Programs in Breast Cancer Cells.** Mol Cell Biol. 2015 Sep;35(18):3225-43. doi: 10.1128/MCB.00426-15. Epub 2015 Jul 6. PMID: 26149387; PMCID: PMC4539381.
27. Zhou M, Yin X, Zhang L, Cui Z, Jiang X, Ji Q, Ma S, Chen C. **RNA-Binding Protein Lin28B Promotes Chronic Myeloid Leukemia Blast Crisis by Transcriptionally Upregulating miR-181d.** Mol Cancer Res. 2024 Oct 2;22(10):932-942. doi: 10.1158/1541-7786.MCR-23-0928. PMID: 38847604.
28. Julio AR, Backus KM. **New approaches to target RNA binding proteins.** Curr Opin Chem Biol. 2021 Jun;62:13-23. doi: 10.1016/j.cbpa.2020.12.006. Epub 2021 Jan 31. PMID: 33535093; PMCID: PMC8823266.
29. Jolma A, Zhang J, Mondragón E, Morgunova E, Kivioja T, Laverty KU, Yin Y, Zhu F, Bourenkov G, Morris Q, Hughes TR, Maher LJ 3rd, Taipale J. **Binding specificities of human RNA-binding proteins toward structured and linear RNA sequences.** Genome Res. 2020 Jul;30(7):962-973. doi: 10.1101/gr.258848.119. Epub 2020 Jul 23. PMID: 32703884; PMCID: PMC7397871.
30. Matias-Barrios, V. M., Radaeva, M., Rosellinny, G., Jia, Q., Xie, N., Smith, J., Gleave, M., Lallous, N., Cherkasov, A., Ibrahim, H., Villanueva, M., Straus, S., & Dong, X. **Developing novel Lin28 inhibitors by computer aided drug design. Cell Death Discovery.** Forthcoming 2024.
31. Roos M, Pradère U, Ngondo RP, Behera A, Allegrini S, Civenni G, Zagalak JA, Marchand JR, Menzi M, Towbin H, Scheuermann J, Neri D, Caflisch A, Catapano CV, Ciaudo C, Hall J. **A Small-Molecule Inhibitor of Lin28.** ACS Chem Biol. 2016 Oct 21;11(10):2773-2781. doi: 10.1021/acschembio.6b00232. Epub 2016 Aug 22. PMID: 27548809.
32. Radaeva M, Ho CH, Xie N, Zhang S, Lee J, Liu L, Lallous N, Cherkasov A, Dong X. **Discovery of Novel Lin28 Inhibitors to Suppress Cancer Cell Stemness.** Cancers (Basel). 2022 Nov 19;14(22):5687. doi: 10.3390/cancers14225687. PMID: 36428779; PMCID: PMC9688808.
33. Wu P. **Inhibition of RNA-binding proteins with small molecules.** Nat Rev Chem. 2020 Sep;4(9):441-458. doi: 10.1038/s41570-020-0201-4. Epub 2020 Jul 15. PMID: 37127961.
34. Murgueitio MS, Rakers C, Frank A, Wolber G. **Balancing Inflammation: Computational Design**

of Small-Molecule Toll-like Receptor Modulators. Trends Pharmacol Sci. 2017 Feb;38(2):155-168. doi: 10.1016/j.tips.2016.10.007. Epub 2016 Nov 15. PMID: 27863853.

35. Popova M, Isayev O, Tropsha A. **Deep reinforcement learning for de novo drug design.** Sci Adv. 2018 Jul 25;4(7):eaap7885. doi: 10.1126/sciadv.aap7885. PMID: 30050984; PMCID: PMC6059760.
36. Pu L, Naderi M, Liu T, Wu HC, Mukhopadhyay S, Brylinski M. **eToxPred: a machine learning-based approach to estimate the toxicity of drug candidates.** BMC Pharmacol Toxicol. 2019 Jan 8;20(1):2. doi: 10.1186/s40360-018-0282-6. PMID: 30621790; PMCID: PMC6325674.
37. Van Vleet TR, Liguori MJ, Lynch JJ 3rd, Rao M, Warder S. **Screening Strategies and Methods for Better Off-Target Liability Prediction and Identification of Small-Molecule Pharmaceuticals.** SLAS Discov. 2019 Jan;24(1):1-24. doi: 10.1177/2472555218799713. Epub 2018 Sep 10. PMID: 30196745.
38. Ton AT, Gentile F, Hsing M, Ban F, Cherkasov A. **Rapid Identification of Potential Inhibitors of SARS-CoV-2 Main Protease by Deep Docking of 1.3 Billion Compounds.** Mol Inform. 2020 Aug;39(8):e2000028. doi: 10.1002/minf.202000028. Epub 2020 Mar 23. PMID: 32162456; PMCID: PMC7228259.
39. Haga CL, Yang XD, Gheit IS, Phinney DG. **Graph neural networks for the identification of novel inhibitors of a small RNA.** SLAS Discov. 2023 Dec;28(8):402-409. doi: 10.1016/j.slasd.2023.10.002. Epub 2023 Oct 14. PMID: 37839522.
40. Tang X, Dai H, Knight E, Wu F, Li Y, Li T, Gerstein M. **A survey of generative AI for de novo drug design: new frontiers in molecule and protein generation.** Brief Bioinform. 2024. https://doi.org/10.1093/BIB/BBAE338
41. Morishita EC, Nakamura S. **Recent applications of artificial intelligence in RNA-targeted small molecule drug discovery.** Expert Opin Drug Discov. 2024 Apr;19(4):415-431. doi: 10.1080/17460441.2024.2313455. Epub 2024 Feb 6. PMID: 38321848.
42. Wang M, Wang Z, Sun H, Wang J, Shen C, Weng G, Chai X, Li H, Cao D, Hou T. **Deep learning approaches for de novo drug design: An overview.** Curr Opin Struct Biol. 2022 Feb;72:135-144. doi: 10.1016/j.sbi.2021.10.001. Epub 2021 Nov 22. PMID: 34823138.
43. Cerchia C, Lavecchia A. **New avenues in artificial-intelligence-assisted drug discovery.** Drug Discov Today. 2023 Apr;28(4):103516. doi: 10.1016/j.drudis.2023.103516. Epub 2023 Feb 2. PMID: 36736583.
44. Agu PC, Obulose CN. **Piquing artificial intelligence towards drug discovery: Tools, techniques, and applications.** Drug Dev Res. 2024 Apr;85(2):e22159. doi: 10.1002/ddr.22159. PMID: 38375772.
45. Domenico A, Nicola G, Daniela T, Fulvio C, Nicola A, Orazio N. **De Novo Drug Design of Targeted Chemical Libraries Based on Artificial Intelligence and Pair-Based Multiobjective Optimization.** J Chem Inf Model. 2020 Oct 26;60(10):4582-4593. doi: 10.1021/acs.jcim.0c00517. Epub 2020 Sep 9. PMID: 32845150.
46. Jayatunga MKP, Xie W, Ruder L, Schulze U, Meier C. **AI in small-molecule drug discovery: a coming wave?** Nat Rev Drug Discov. 2022 Mar;21(3):175-176. doi: 10.1038/d41573-022-00025-1. PMID: 35132242.
47. Ren F, Aliper A, Chen J, Zhao H, Rao S, Kuppe C, Ozerov IV, Zhang M, Witte K, Kruse C, Aladinskiy V, Ivanenkov Y, Polykovskiy D, Fu Y, Babin E, Qiao J, Liang X, Mou Z, Wang H, Pun FW, Torres-Ayuso P, Veviorskiy A, Song D, Liu S, Zhang B, Naumov V, Ding X, Kukharenko A, Izumchenko E, Zhavoronkov A. **A small-molecule TNIK inhibitor targets fibrosis in preclinical and clinical models**. Nat Biotechnol. 2024 Mar 8. doi: 10.1038/s41587-024-02143-0. Epub ahead of print. PMID: 38459338.
48. Meyers J, Fabian B, Brown N. **De novo molecular design and generative models**. Drug Discov Today. 2021 Nov;26(11):2707-2715. doi: 10.1016/j.drudis.2021.05.019. Epub 2021 Jun 1. PMID: 34082136.
49. Alakhdar A, Poczos B, Washburn N. **Diffusion Models in De Novo Drug Design**. J Chem Inf Model. 2024 Oct 14;64(19):7238-7256. doi: 10.1021/acs.jcim.4c01107. Epub 2024 Sep 25. PMID: 39322943; PMCID: PMC11481093.