Generative AI in Cancer: Improving Therapies Against Common Oncogenic Drivers

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Abstract

As early-onset cancer becomes increasingly common, the need for innovative therapeutic approaches in targeted therapy grows. Generative AI has emerged as a powerful tool for *de novo* drug design, offering the potential to create targeted therapies against challenging cancer driver mutations. These mutations, including *TP53*, *KRAS*, and *EGFR*, often confer gain-of-function effects that drive cancer progression and are notoriously difficult to target due to their unique biochemical properties. This review summarizes the shift from conventional drug design towards newfound generative AI models, highlighting their ability to optimize binding affinity, anticancer properties, and generate novel molecules against previously "undruggable" targets. This review explores how generative AI is revolutionizing the fight against prevalent cancer driver mutations, paving the way for personalized and effective cancer treatments.

Introduction

Cancer, a leading cause of death worldwide, is characterized by the uncontrolled growth and spread of mutated, abnormal cells.[1] Genetic mutations that confer growth and survival advantages to these transformed cells and remain central to disease progression are known as cancer “driver” mutations.[2] Gain-of-function (GOF) drivers, in particular, are mutations that result in new or enhanced functionality of the resulting protein.[3] Despite their known significance in cancer initiation and progression, historically, GOF driver mutations have been challenging to target therapeutically. This is due to their diverse biochemical properties granting high resistance to conventional treatments and latency evading immune detection.[4] Fortunately, the advent of generative artificial intelligence (genAI) invites new possibilities for drug discovery with the potential to design novel molecules, enabling precise and effective inhibition of GOF mutant activity.

The current methods in drug design make the research and development process laborious and ineffective, with FDA approvals being granted to only 4% of preclinical drugs.[5] Mass expansions of online data make it clear that conventional drug design methods lack the means to overcome complications associated with targeting GOF driver mutations. Standard methods, such as ligand based drug design, fragment based drug design, and structure based drug design, are limited to existing molecules and rely on inefficient “trial and error” to manage safety and toxicity or demonstrate clinical promise. Given its recent entrance into the biopharmaceutical space, AI-derived drugs have yet to reach FDA approval. However, in today’s technology-driven age of information, burgeoning collaboration amongst scientists, open source data, and expanding repositories of physicochemical and biological knowledge invite a deeper understanding of drug design. With continual growth and understanding of this technology, integration of generative AI is poised to improve and expedite cancer drug discovery.[6]

This review focuses on three of the most prevalent driver mutations in cancer: *TP53*, *KRAS*, and *EGFR*. This paper covers the role of these proteins in cancer progression, the challenges associated with targeting them, and the potential of generative AI to overcome these challenges. This work provides an overview of current generative AI models and their applications in drug design, highlighting the benefits and limitations of this approach. Finally, this review explores

future directions in precision medicine, emphasizing the role of generative AI in personalized therapies for cancer.

Discussion

Understanding Cancer Driver Mutations

Compared to passenger mutations which show no bearing on cancer progression, cancer driver mutations can be classified as either GOF or loss-of-function (LOF) mutations; mutations either promote cancer growth (oncogenes) or impede anticancer mechanisms (tumor suppressor genes). GOF mutations lead to excessive or aberrant protein activity, often granting new functions.[7] While in contrast, LOF mutations typically result in decreased or a complete loss of normal function, such as an inability to regulate the cell cycle (Figure 1). In general, it is simpler to turn GOF protein activity off than it is to restore original LOF protein function; this is because restoration of function is difficult when target proteins are not even expressed.

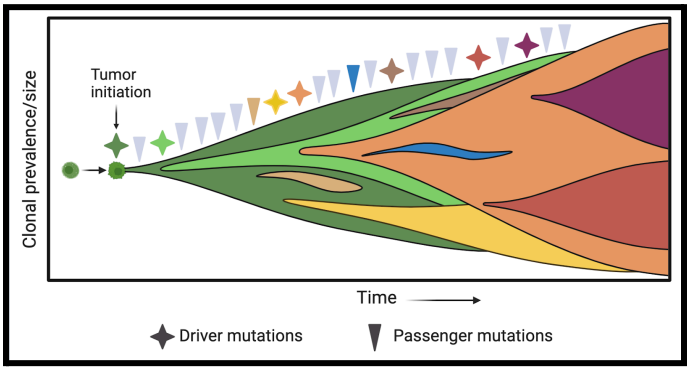

Figure 1. Visual of tumor growth and evolution as a result of driver mutations. Demonstrates neutrality of passenger mutations. (Source: Mishra, J., 2024, BioRender)

The most frequently mutated drivers in human cancers include *KRAS* (25-30%, majority being GOF), *EGFR* (6-7% GOF overall, 30% in non-small cell lung cancer [NSCLC]), and *TP53* (50-60% in all cancers, 30% of these being GOF).[8–11] Therapeutically, GOF mutations are generally attacked via targeted drug inhibition, with the goal of diminishing or deactivating the gained oncogenic function.[12] While conceptually straightforward, these mutations present significant challenges due to the high level of heterogeneity, or variation, amongst cancer cells.[4] Even within a single protein, like KRAS or EGFR, different GOF mutations can exhibit distinct behaviors; mutated DNA sequences result in altered protein folding and functions including varying drug binding sites, responses to tumor microenvironment, and sensitivity to targeted therapies. For example, EGFR exhibits point mutations (EGFR 21), deletions (EGFR 19), and insertions (exon 20) — the exon 20 insertion has higher drug resistance, making it difficult to develop a single drug that effectively targets all variants.[13,14] Despite these obstacles, scientists continue to explore strategies against these oncogenic drivers, developing small molecule inhibitors that can bind to the mutated active or allosteric site(s). The goal is to design molecules that can readily penetrate cellular membranes and inhibit the oncogenic activity of these proteins.

KRAS: the "Undruggable" Mutation

Kirsten rat sarcoma virus (KRAS) is the most frequently mutated oncogene in human cancers. In healthy, non-mutated cells, KRAS plays a crucial role in cell signaling pathways that promote cell growth and survival in response to growth factors. Mutations in *KRAS*, particularly those that lock the protein in an active state, lead to uncontrolled cell proliferation and tumor growth. Many cancers resort to activating the KRAS pathway as a method of circumventing certain targeted therapies.[15]

KRAS has long been considered an "undruggable" target due to its smooth surface and lack of obvious binding pockets for drug molecules. The clearest binding site is monopolized by GTP, shifting drug developers' focus to targeting allosteric sites.[16] Recent advances in drug discovery, including the use of computational modeling and fragment-based drug design, have led to the development of several promising KRAS inhibitors. Small molecule inhibitors such as sotorasib and adagrasib have shown moderate efficacy in clinical trials, reaching response rates up to 34% and 32%, respectively, in KRAS G12C–mutated NSCLC tumors. Thus, such treatments have room to improve in terms of response rates and efficacy.[17,18]

The National Cancer Institute's RAS Initiative continues to drive research efforts to develop more effective and selective KRAS inhibitors. The NCI's slow progress in discovering compounds that inhibit KRAS — due to KRAS' unique shape and high rate of resistance to therapy — demonstrates the drawbacks of current drug design methods.[19] Despite the challenges, targeting KRAS remains a high priority due to its central role in cancer development and its ability to drive resistance to other targeted therapies.

EGFR: an Optimistic Example

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that plays a key role in cell growth and survival by activating future RAS, RAF, MEK, and MAPK pathways. Mutations in EGFR, which often lead to constitutive activation of the receptor, are common in several cancers, especially NSCLC.[20]

Targeting EGFR with tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of EGFR-mutant lung cancer. First-line treatments like osimertinib, afatinib, and dacomitinib have significantly improved outcomes for patients with these mutations. However, resistance to TKIs often develop, highlighting the need for new therapeutic strategies. Ongoing efforts to develop next-generation TKIs can integrate AI-driven anti-cancer drug design algorithms which accelerate the identification and optimization of EGFR inhibitors. For instance, gefitinib, lapatinib, and erlotinib were designed through AI models to inhibit EGFR, EGFR-mediated signaling, and intracellular phosphorylation, respectively.[21] Offering hope for more effective and personalized treatments, advanced generative AI can target rarer EGFR mutant subtypes, side effects, acquired drug resistance, and unexplainable absence of response.

TP53: the Guardian of the Genome

The *TP53* gene, often referred to as the "guardian of the genome," encodes the p53 protein, a master regulator of the cell cycle and a critical tumor suppressor. P53 has a wide array of functions, including: cell cycle arrest, apoptosis, and regulation of metabolism, immune systems, and cellular defense mechanisms.[22] P53 halts cell division in response to DNA damage, allowing for repair. P53 achieves this by increasing production of p21, which inhibits cyclin-dependent kinases (CDKs) responsible for cell cycle progression. In apoptosis, p53

triggers programmed cell death in irreparably damaged cells, increasing the expression of death receptors, namely DR5.

Mutations in *TP53* are the most common genetic alteration in human cancers, occurring in over 50% of cases. These mutations can be LOF or GOF, with approximately 30% of missense mutations resulting in GOF. GOF p53 mutations not only lose their tumor-suppressive abilities but can also acquire new oncogenic functions, promoting cell proliferation, migration, and resistance to apoptosis and chemotherapy.

While no FDA-approved drugs directly target mutant p53, several compounds are under investigation. COTI-2, designed to inhibit mutant p53, has shown promising results in preclinical studies. APR-246, a drug that restores wild-type p53 function, is also being evaluated in clinical trials.[11] However, these drugs are still in early stages of development, and personalized treatment approaches remain challenging due to the wide variety of *TP53* mutations and their diverse effects on cancer cells.

KRAS, EGFR, and TP53 all play vital roles in normal cellular processes, hence why their mutations accelerate cancer cell proliferation. Most driver mutations do not currently have approved treatments, and conventional drug design practices are inadequate to target them. Despite properties making these proteins difficult to drug, commotion within the scientific community has brought generative AI to the forefront of drug discovery. Generative AI serves as a promising tool for designing cancer treatment, reducing time and cost.

Generative AI in Targeted Cancer Therapeutics

At its core, artificial intelligence (AI) is a technology-enabled tool that allows machines to perform complex tasks. AI is being continually leveraged across industries such as finance, business, engineering, and medicine, leveraging an advantage in situations where humans are often error-prone. For example, in medical practices, AI-enabled tools can assist healthcare professionals with disease diagnosis, evaluate patient health records, and predict which treatment course will be most suitable and effective for a given case. Machine learning (ML) is a subcategory of AI capturing an ability for computers to learn and think like humans. ML uses data to make predictions by either reproducing predetermined patterns (supervised learning) or identifying general trends within datasets on its own (unsupervised learning).[23] Unsupervised learning — where parameters are not predetermined or labeled beforehand — allows computers to predict outcomes without explicit parameters and instructions being set. A more specific category of unsupervised ML is deep learning, a method using neural networks (Figure 2). These neural networks are inspired by the neurons in the human brain, seeking to mimic how human neurons fire when thinking.[24]

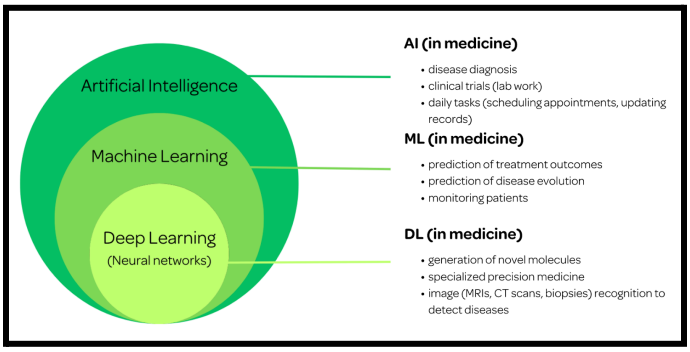

Figure 2. Hierarchy of AI and instances of each level seen in present-day medicine. (Created with Canva)

Unique compounds for cancer patients are designed with generative AI models or generative adversarial networks (GANs). GANs push past human limitations in drug discovery by designing molecules and predicting the new drug's characteristics. The AI tool comprises two neural networks that toggle back and forth to generate and improve produced compounds.[25] Each generative AI model has a different goal and target protein. For example in medicine, the goal might be inhibition of a specific protein, drug repurposing, or polypharmacology. Polypharmacological drugs simultaneously bind to multiple targets whilst reducing resistance buildup and improving pharmacokinetics such as movement, absorption, and distribution throughout the body. This section discusses the current generative AI models being utilized in cancer research.

Current Landscape of Generative AI in Cancer Research and Development

Generative AI specializes in five main aspects of anticancer drug design: target identification, hit identification, *de novo* drug design, drug repurposing, and drug reactions (Figure 3).[26]

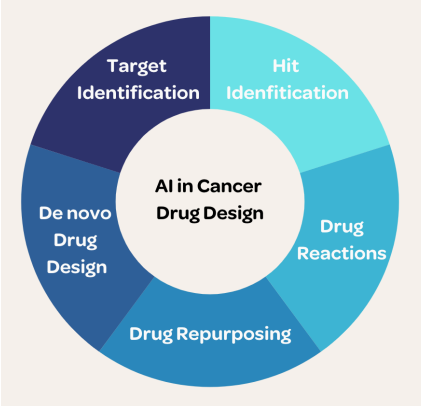

Figure 3. Key aspects of AI in anticancer drug design. (Created with Canva)

With cost and speed being the greatest challenges in modern drug design, GANs offer specialized drug design where treatments often successfully enter phase 2/3 for clinical trials.[27] Generative AI has two main purposes in drug design: discovering *de novo* treatments and repurposing existing drugs, both of which aim to overcome the difficulty in targeting and treating cancer driver mutations. Established above are several intrinsic properties, such as flat surfaces

and shallow binding sites, that make *TP53*, KRAS, and EGFR challenging to target. Instead of finding drugs serendipitously, which requires years of follow-up testing and validation, generative AI enables decisions to improve safety and efficacy *a priori* (Figure 4).

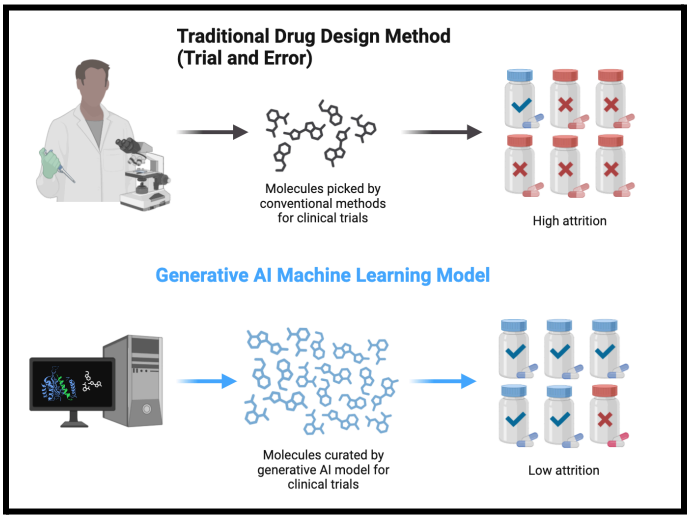

Figure 4. Traditional vs. generative AI drug design workflow. (Created with Biorender)

Target and hit identification relates to the docking and binding of therapeutic drugs to target proteins, and generative AI systems optimize drugs for compatibility of binding affinity and docking accuracy as well as absorption, distribution, metabolism, secretion, and toxicity (ADMET). For instance, one of the most widely used generative AI docking simulations is Autodock Vina (used in POLYGON). Autodock Vina and other AI programs overcome 3D barriers by gathering different types of data from separate sources that best inform models to predict position and orientation of ligand docking. Models are trained on known protein-ligand interactions and 2D representations of drugs and targets. Each predicted ligand is scored based on binding accuracy, and programs are consequently reinforced. These scoring functions predict binding affinity constants like IC50, Kd (dissociation constant), and Ki (inhibition constant).

Accuracy of ligand docking is dependent on shape complementary and compatibility of the selective inhibitors' shape (Figure 5). For GOF driver mutations where protein function changes, it is difficult to predict target structures that lack rigidity, hence why generative AI can be leveraged to fine-tune minute details in compounds that are key for increased selectivity and binding of drugs. Binding of ligands also relies on electrostatic complementarity: the interactions between polar groups, charged groups, and solvents.[28] Less polar molecules, naturally, have more targets, putting cancer mutations at a disadvantage since "undruggable" mutations have shallow pockets which have undesirable polarity.[29] KRAS and GOF *TP53* are known for lacking a clear active site target and deep allosteric sites as well.[30] Generative AI models can be trained to classify and predict narrower binding selectivity for more polar and charged groups.

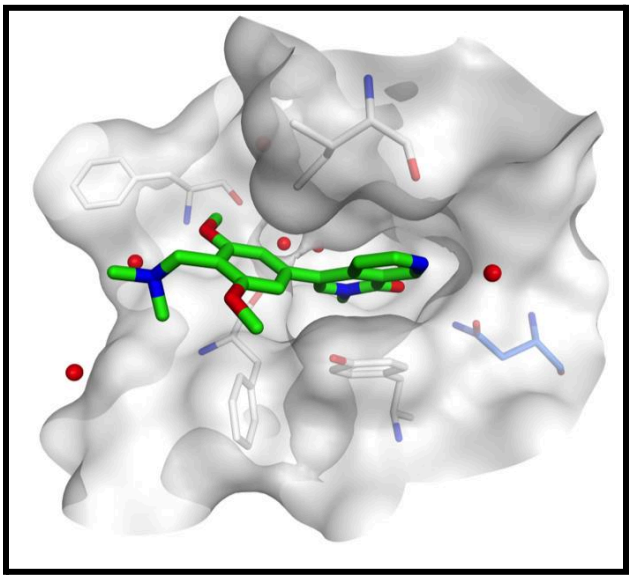

Figure 5. Atomic resolution imaging of the fit of a ligand inside its corresponding binding pocket. (Adapted from Cold Spring Harbor Laboratory, 2016)

Depending on the target driver mutation, GANs have different parameters to optimize physicochemical properties or ADMET properties. While optimizing combinations of characteristics is still elusive, improved AI imaging of hydrogen bonds and computer analysis of boiling points, melting points, and vapor pressure can expand the capacity of generative AI to consider multiple properties.[27]

One popular AI framework for unsupervised learning to inform biological content and structure is known as a variational autoencoder (VAE). In the context of drug design, VAEs are most useful in generating novel chemical structures. The VAE framework translates 3D biological structures into a computer-readable format.[31] By taking in molecules and mapping them in their corresponding 2D chemical representation, protein structures are made biologically interpretable to computers, allowing computers to experiment with designing unique compounds *in silico*.

Once researchers construct the VAE to generate a feasible compound, computer developers train the GAN to optimize these outputs by the means of reinforcement learning (RL). RL has been adopted for unsupervised learning and is iterative — desired characteristics are rewarded and undesired characteristics are discriminated against.[32] GANs can generate drugs that do not have undesirable properties, components, or elements. In RL, computers designing new molecules for cancer treatment are set to maximize drug likeness or desirability of certain molecular properties, ligand efficiency, and solubility.[33] This enables capture of desirable targets in drugs that can also be readily-formulated in a lab. For drug developers, these AI tools enable multiple assessment integration, prioritizing crucial metrics such as ADMET properties.

One of the most widely-used generative AI models for biologists is AlphaFold2 (AF2). Cancer researchers have been utilizing AF2 to aid novel protein-based therapeutic design in cancers such as liver cancer.[34] Developed in 2021 at the University of Toronto, AF2 predicts the 3D shape of proteins based solely on amino acids from an input DNA sequence. AF2 is especially useful in predicting the structure of unknown proteins and chemically-complex molecules.

Specifically, it enables the identification of the 3D molecular structure of proteins with intrinsically disordered regions or regions lacking a fixed conformation, which are notoriously difficult to target therapeutically.[35] The ability to predict the shape of proteins with over 90% accuracy, understand the nature of protein folding, and predict unknown target structures or mutated proteins with disrupted function significantly aids *de novo* drug design. Within a month, cancer researchers using AF2 to scan and predict structurally vulnerable targets in liver cells designed and synthesized a drug for use against CDK20 with strong correlation to liver cancer progression.[36]

In 2024, UC San Diego developed its own platform called POLYGON (POLYpharmacology Generative Optimization Network) to design drugs against synthetically lethal targets in cancer: MEK1 and mTOR. Synthetic lethals are proteins in which inhibition of both, as opposed to one or the other, results in cancer cell death.[37] The attention surrounding POLYGON is due to the promise of polypharmacology reducing side effects that are associated with current combination therapy; combination therapy is the mixing of five or more drugs for a patient at one time, increasing risk of toxicity and unpredictable drug-drug interactions. Until recently, companies targeted a single cancer biomarker and found therapeutic compounds exclusively through serendipity, however generative AI is a new outlet for more systematic discovery of drugs with pharmacological promise. POLYGON, at the time of publication, reported an accuracy of 81.9% in dual activity prediction for generated molecules. Out of hundreds of newly synthesized molecules, POLYGON predicted the top 32 that would best inhibit MEK1 and mTOR, reducing phosphorylation by over 50% and testing off-target inhibition to ensure safety. POLYGON falls short in optimization of ADMET properties, though. There is also room for improvement in selectivity of targets and minimization of side effects. Despite the potential of generative AI in drug design, humans are still necessary in following clinical trials to test the safety and efficacy of the treatment.[38]

Even more recently in 2024, Zapata AI came out with quantum enhanced generative AI models to design a KRAS inhibitor *in silico.* Zapata AI has revolutionized generative AI by using quantum inspired ML strategies on classical computers to model how quantum computers function.[5] Quantum mechanics are especially proficient in performing enhanced ML capabilities too complex for current AI to solve. This can include formulating drugs with more desirable properties, evaluating complex internal and external conditions, and high resolution imaging of 3D structures which can take months for classical computers. Zapata AI synthesized 15 molecules, two of which were novel compounds and demonstrated significantly higher binding affinity to KRAS.[39] This promising outcome paves the way for discovering more molecules with enhanced binding to difficult to drug targets like driver mutations. Because quantum technology is still relatively unexplored, there is still a challenge in creating highly successful molecules with GAN models like Zapata AI's.

Additional Use Cases for Generative AI in Cancer

High quality imaging of tumor microenvironments (TME) can also be accomplished by GANs to optimize affinity between ligands and targets. This optimization is complex, though — TMEs vary per cell due to unique interactions with nearby cells and proteins.[40] Affinity is determined by chemical structures of molecules which GANs can quickly learn through collection of thorough data. Generative AI models then assess which chemical attributes are most useful to maximize binding affinity.

Drug repurposing is another avenue that researchers are incorporating generative AI into to find new therapeutic uses for pre-existing drugs. Approval of repurposed drugs is much more efficient since drugs may automatically progress to phase 2 of clinical trials. Creativity to discover new purposes for pre-existing drugs is inhibited due to predetermined cancers these treatments are first approved for. However, GANs have the capacity to evaluate whether drugs can be repurposed for a different target. Utilizing known drug-target interactions and chemical structures, GANs recognize that similar drugs are associated with similar disease profiles, leveraging established biological knowledge to be specific to each patients' DNA sequence or mutation.

Generative AI models including AF2, POLYGON, and Zapata AI each have their own goals and targets, creating drugs that cater to a specific cancer protein. Difficult to drug proteins like KRAS, EGFR, and *TP53* all have intrinsic properties that make them unfit for ligand binding, but generative AI has the means to overcome these properties and design novel molecules with the highest binding affinity and predicted docking accuracy. *De novo* drug design takes advantage of generative AI's ability to create novel molecules with favorable traits such as absorption or metabolism. Further exploration of biological AI can greatly aid anticancer drug development, advancing precision medicine to contain and treat cancer for every patient's unique case.

Challenges and Limitations

Generative AI models must be trained before they can generate valuable outputs. This training informs AI about existing drug-protein interactions from which the AI learns patterns and generates novel cancer drugs. The data that is used to educate generative AI must be diverse, though, posing the challenge of obtaining high quality data. In theory, high-quality, comprehensive training data will provide accurate chemical structures, mutated DNA sequences, and solid imaging of protein structure. The reality, however, is that human specimens serving as the source of this data can oftentimes be messy and incomplete, making it difficult to define and discern what might be considered "good" data from poor-quality, non-informative, "bad" data. A cost effective and user-friendly solution to overcoming such limitations is open source databases specific for anticancer therapeutics such as chEMBL and the Protein Structure Database. Routine maintenance and updates of databases must be consistent, though, otherwise data can unexplainably degrade, causing predictions to drift or biases to occur. The scientific research community is poised to have a high quantity of training data to help further refine these models, however, emphasis on accurate recording and reproducibility are evermore important as open sourcing may invite data that is not adequate.

Another limitation is the "black box" concept in AI, relating to the lack of reasoning behind how AI predicts outcomes. Since humans can not interpret the underlying biological mechanisms of AI, generated outcomes lack reliability.[41] Explainable AI exists to ethically explain predictions (prediction accuracy) and educate humans on how AI makes decisions (decision understanding).[42] Explainable AI models like LIME test and understand why computers give certain outputs and explain it to users.[43] Clinical adoption and usage of generative AI tools is enhanced when humans trust the expertise and logic behind AI.

Mode collapse is another challenge in generative AI models where produced outputs become limited in variety. Lack of diversity in datasets constrains the diversity of outputs, resulting in inadequate compounds for binding responses and effective treatment. What mode collapse looks like is ambiguous, making it especially troublesome to identify and deal with. To

reintroduce variation in generated outcomes, GANs can be altered to disfavor molecules that are too similar to previously curated molecules, promoting variety again.

Future Directions and Conclusion

While this review highlights the application of genAI drug design against GOF driver mutations, other cancer-associated mutations, such as LOF driver and passenger mutations, present an additional opportunity for genAI-enabled drug development. For select driver mutations such as *TP53*, proteins can exhibit both LOF and GOF. Integration of CRISPR technology to correct altered DNA sequences and generative AI to design *de novo* drugs facilitates repair of LOF driver mutations.[27] Fixing LOF mutations subsequently turns tumor suppressor genes back "on," resuming regulation of the cell cycle to check cancer. There are few treatments currently under clinical trials that correct mutated proteins, and generative AI would immensely improve drug design and success of such restoration treatment.

Passenger mutations, "neutral" genetic mutations which on their own do not contribute to carcinogenesis, make up 97% of mutations in the human body. Yet a key barrier to effective treatment, and one attributed heavily to passenger mutations, is intratumoral heterogeneity. This is a phenomenon where different cancer cells within the same tumor may not respond similarly to a particular therapy. Indeed, recent studies found that passenger mutations may contribute to cancer evolution and drug resistance.[4,44] These mutations increase cancer cells' fitness by promoting a pro-tumor environment for cancer to evolve and persist. Using generative AI to target driver mutations to slow cancer progression and target passenger mutations to prevent and slow cancer resistance provides increasingly efficacious personalized treatment. Future investigation of LOF and passenger mutation targeting through GANs is another promising outlet to combat cancers.

The excitement surrounding AI-enabled tools remains evident in the biopharmaceutical industry, with investors writing large checks for AI-driven biotechnology companies. These companies aim to produce less expensive medicine through fusion of AI, data generation, and drug design. These startups enable AI to optimize daily work, predict toxicity and drug efficacy, and generate new ML models. Billions of dollars of funding are now being funneled into companies harnessing cutting-edge AI technology for their drug discovery process, such as Xaira Therapeutics and Formation Bio.[45,46] The backlog of current treatments is due to how expensive drug development is, and biotech companies close this gap between candidate drugs and FDA approval through increased appliance of AI.

Strong momentum from academics to develop AI mediated tools in healthcare presents generative AI as a powerful tool in drug design, particularly for targeting "undruggable" driver mutations in cancer. Despite challenges of data limitations and interpretability, AI's ability to process vast datasets and uncover hidden patterns makes it invaluable for drug discovery. Future research should focus on addressing these challenges, expanding AI applications to LOF and passenger mutations, and developing patient-specific models for personalized treatment. The growing investment in AI-driven biotech startups further underscores its potential to revolutionize cancer therapy. As AI continues to advance, we can anticipate a future where effective treatments for even the most challenging cancers become a reality.

References

(1) *How does cancer start?* https://www.cancerresearchuk.org/about-cancer/what-is-cancer/how-cancer-starts (accessed 2024-06-29).
(2) Ostroverkhova, D.; Przytycka, T. M.; Panchenko, A. R. Cancer Driver Mutations: Predictions and Reality. *Trends Mol. Med.* **2023**, *29* (7), 554–566. https://doi.org/10.1016/j.molmed.2023.03.007.
(3) Li, Y.; Zhang, Y.; Li, X.; Yi, S.; Xu, J. Gain-of-Function Mutations: An Emerging Advantage for Cancer Biology. *Trends Biochem. Sci.* **2019**, *44* (8), 659–674. https://doi.org/10.1016/j.tibs.2019.03.009.
(4) F, A.; H, A.-L.; S, C.-F.; S, T.; A, H.-P.; E, J.-L.; A, B.; V, I.; C, C. Passenger Mutations in Cancer Evolution. *Cancer Rep. Rev.* **2019**, *3* (3). https://doi.org/10.15761/crr.1000188.
(5) Kao, P.-Y.; Yang, Y.-C.; Chiang, W.-Y.; Hsiao, J.-Y.; Cao, Y.; Aliper, A.; Ren, F.; Aspuru-Guzik, A.; Zhavoronkov, A.; Hsieh, M.-H.; Lin, Y.-C. Exploring the Advantages of Quantum Generative Adversarial Networks in Generative Chemistry. *J. Chem. Inf. Model.* **2023**, *63* (11), 3307–3318. https://doi.org/10.1021/acs.jcim.3c00562.
(6) BPM, I. *Exploring the Power of Generative AI in Drug Discovery*. https://www.infosysbpm.com/blogs/generative-ai/exploring-the-power-of-generative-ai-in-drug-discovery.html#:~:text=Generative%20AI%20drugs%20are%20essentially,interactions%2C%20and%20clinical%20trial%20results (accessed 2024-06-29).
(7) Rougvie, A. E. Brenner's Encyclopedia of Genetics (Second Edition). *Artic. Titles: H* **2013**, No. Science2261984, 442–445. https://doi.org/10.1016/b978-0-12-374984-0.00700-2.
(8) Ellis, R. R. *EGFR Mutations in NSCLC: What Does It Mean?* https://www.webmd.com/lung-cancer/egfr-mutations-defined-nsclc (accessed 2024-07-24).
(9) *Can Targeted Therapy for KRAS Mutations Double as Part of Immunotherapy?* https://www.cancer.gov/news-events/cancer-currents-blog/2022/kras-targeted-drugs-as-immunotherapy (accessed 2024-07-24).
(10) Baugh, E. H.; Ke, H.; Levine, A. J.; Bonneau, R. A.; Chan, C. S. Why Are There Hotspot Mutations in the TP53 Gene in Human *Cancers*? *Cell Death Differ.* **2018**, *25* (1), 154–160. https://doi.org/10.1038/cdd.2017.180.
(11) Roszkowska, K. A.; Piecuch, A.; Sady, M.; Gajewski, Z.; Flis, S. Gain of Function (GOF) Mutant P53 in Cancer—Current Therapeutic Approaches. *Int. J. Mol. Sci.* **2022**, *23* (21), 13287. https://doi.org/10.3390/ijms232113287.
(12) Waarts, M. R.; Stonestrom, A. J.; Park, Y. C.; Levine, R. L. Targeting Mutations in Cancer. *J. Clin. Investig.* **2022**, *132* (8), e154943. https://doi.org/10.1172/jci154943.
(13) Kazandjian, D.; Blumenthal, G. M.; Yuan, W.; He, K.; Keegan, P.; Pazdur, R. FDA Approval of Gefitinib for the Treatment of Patients with Metastatic EGFR Mutation–Positive Non–Small Cell Lung Cancer. *Clin. Cancer Res.* **2016**, *22* (6), 1307–1312. https://doi.org/10.1158/1078-0432.ccr-15-2266.
(*14*) *EGFR and Lung Cancer*. https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/symptoms-diagnosis/biomarker-testing/egfr (accessed 2024-07-05).
(15) Holderfield, M.; Lee, B. J.; Jiang, J.; Tomlinson, A.; Seamon, K. J.; Mira, A.; Patrucco, E.; Goodhart, G.; Dilly, J.; Gindin, Y.; Dinglasan, N.; Wang, Y.; Lai, L. P.; Cai, S.; Jiang, L.; Nasholm, N.; Shifrin, N.; Blaj, C.; Shah, H.; Evans, J. W.; Montazer, N.; Lai, O.; Shi, J.; Ahler, E.; Quintana, E.; Chang, S.; Salvador, A.; Marquez, A.; Cregg, J.; Liu, Y.; Milin, A.; Chen, A.; Ziv, T. B.;

Parsons, D.; Knox, J. E.; Klomp, J. E.; Roth, J.; Rees, M.; Ronan, M.; Cuevas-Navarro, A.; Hu, F.; Lito, P.; Santamaria, D.; Aguirre, A. J.; Waters, A. M.; Der, C. J.; Ambrogio, C.; Wang, Z.; Gill, A. L.; Koltun, E. S.; Smith, J. A. M.; Wildes, D.; Singh, M. Concurrent Inhibition of Oncogenic and Wild-Type RAS-GTP for Cancer Therapy. *Nature* **2024**, *629* (8013), 919–926. https://doi.org/10.1038/s41586-024-07205-6.
(16) Huang, L.; Guo, Z.; Wang, F.; Fu, L. KRAS Mutation: From Undruggable to Druggable in Cancer. *Signal Transduct. Target. Ther.* **2021**, *6* (1), 386. https://doi.org/10.1038/s41392-021-00780-4.
(17) Goodman, A. *Second-Line Therapy With Adagrasib in KRAS G12C–Mutated Non–Small Cell Lung Cancer*. https://ascopost.com/issues/july-10-2024/second-line-therapy-with-adagrasib-in-kras-g12c-mutated-non-small-cell-lung-cancer/#:~:text=Adagrasib%20remained%20superior%20to%20docetaxel,adagrasib%20vs%2050%25%20for%20docetaxel. (accessed 2024-08-20).
(18) Zhou, K. I.; Lin, C.; Tseng, C.-L.; Ramnath, N.; Dowell, J. E.; Kelley, M. J. Brief Report: Real-World Efficacy and Safety of Sotorasib in U.S. Veterans with KRAS G12C-Mutated NSCLC. *JTO Clin. Res. Rep.* **2024**, *5* (5), 100670. https://doi.org/10.1016/j.jtocrr.2024.100670.
(19) *RAS Initiative Drug Screening and Preclinical Research*. https://www.cancer.gov/research/key-initiatives/ras/research-teams/drug-screening (accessed 2024-07-03).
(20) Danesi, R.; Fogli, S.; Indraccolo, S.; Re, M. D.; Tos, A. P. D.; Leoncini, L.; Antonuzzo, L.; Bonanno, L.; Guarneri, V.; Pierini, A.; Amunni, G.; Conte, P. Druggable Targets Meet Oncogenic Drivers: Opportunities and Limitations of Target-Based Classification of Tumors and the Role of Molecular Tumor Boards. *ESMO Open* **2021**, *6* (2), 100040. https://doi.org/10.1016/j.esmoop.2020.100040.
(21) Paliwal, A.; Alam, M. A.; Sharma, P.; Jain, S.; Dhoundiyal, S. Revolutionizing Cancer Research and Drug Discovery: The Role of Artificial Intelligence and Machine Learning. *Curr. Cancer Ther. Rev.* **2024**, *20*. https://doi.org/10.2174/0115733947288355240305080236.
(22) Alvarado-Ortiz, E.; Cruz-López, K. G. de la; Becerril-Rico, J.; Sarabia-Sánchez, M. A.; Ortiz-Sánchez, E.; García-Carrancá, A. Mutant P53 Gain-of-Function: Role in Cancer Development, Progression, and Therapeutic Approaches. *Front. Cell Dev. Biol.* **2021**, *8*, 607670. https://doi.org/10.3389/fcell.2020.607670.
(23) Brown, S. *Machine learning, explained*. https://mitsloan.mit.edu/ideas-made-to-matter/machine-learning-explained (accessed 2024-07-04).
(24) *What are Neural Networks and How Do They Work With Generative AI*. https://shelf.io/blog/neural-networks-and-how-they-work-with-generative-ai/ (accessed 2024-06-30).
(25) *Generative AI vs. Neural Networks: Exploring the Landscape*. https://dasha.ai/en-us/blog/generative-ai-vs-neural-networks-exploring-the-landscape (accessed 2024-06-30).
(26) Wang, L.; Song, Y.; Wang, H.; Zhang, X.; Wang, M.; He, J.; Li, S.; Zhang, L.; Li, K.; Cao, L. Advances of Artificial Intelligence in Anti-Cancer Drug Design: A Review of the Past Decade. *Pharmaceuticals* **2023**, *16* (2), 253. https://doi.org/10.3390/ph16020253.
(27) Duo, L.; Liu, Y.; Ren, J.; Tang, B.; Hirst, J. D. Artificial Intelligence for Small Molecule Anticancer Drug Discovery. *Expert Opin. Drug Discov.* **2024**, *19* (*8*), 933–948. https://doi.org/10.1080/17460441.2024.2367014.

(28) Huggins, D. J.; Sherman, W.; Tidor, B. Rational Approaches to Improving Selectivity in Drug Design. *J. Med. Chem.* **2012**, *55* (4), 1424–1444. https://doi.org/10.1021/jm2010332.
(29) Xie, X.; Yu, T.; Li, X.; Zhang, N.; Foster, L. J.; Peng, C.; Huang, W.; He, G. Recent Advances in Targeting the "Undruggable" Proteins: From Drug Discovery to Clinical Trials. Signal Transduct. Target. Ther. 2023, 8 (1), 335. https://doi.org/10.1038/s41392-023-01589-z.
(30) Dolma, L.; Muller, P. A. J. GOF Mutant P53 in Cancers: A Therapeutic Challenge. Cancers 2022, 14 (20), 5091. https://doi.org/10.3390/cancers14205091.
(31) Chen, H.; Engkvist, O.; Wang, Y.; Olivecrona, M.; Blaschke, T. The Rise of Deep Learning in Drug Discovery. *Drug Discov. Today* **2018**, *23* (6), 1241–1250. https://doi.org/10.1016/j.drudis.2018.01.039.
(32) Gillis, A. S. *What is reinforcement learning?* https://www.techtarget.com/searchenterpriseai/definition/reinforcement-learning (accessed 2024-07-01).
(33) Bickerton, G. R.; Paolini, G. V.; Besnard, J.; Muresan, S.; Hopkins, A. L. Quantifying the Chemical Beauty of Drugs. *Nat. Chem.* **2012**, *4* (2), 90–98. https://doi.org/10.1038/nchem.1243.
(34) Warner, E. *Researchers use AI-powered database to design potential cancer drug in 30 days*. https://www.utoronto.ca/news/researchers-use-ai-powered-database-design-potential-cancer-drug-30-days (accessed 2024-06-06).
(35) *Strengths and limitations of AlphaFold2*. https://www.ebi.ac.uk/training/online/courses/alphafold/an-introductory-guide-to-its-strengths-and-limitations/strengths-and-limitations-of-alphafold/ (accessed 2024-07-10).
(36) Jiang, K. *U of T researchers used AI to discover a potential new cancer drug — in less than a month*. https://www.thestar.com/news/canada/u-of-t-researchers-used-ai-to-discover-a-potential-new-cancer-drug-in-less/article_6400a3cc-f9b7-5eb9-b966-a91c071362f9.html (accessed 2024-06-20).
(37) *Simulated chemistry: New AI platform designs tomorrow's cancer drugs*. https://www.sciencedaily.com/releases/2024/05/240506131601.htm (accessed 2024-06-21).
(38) Munson, B. P.; Chen, M.; Bogosian, A.; Kreisberg, J. F.; Licon, K.; Abagyan, R.; Kuenzi, B. M.; Ideker, T. De Novo Generation of Multi-Target Compounds Using Deep Generative Chemistry. *Nat. Commun.* **2024**, *15* (1), 3636. https://doi.org/10.1038/s41467-024-47120-y.
(39) *For the First Time, Quantum-Enhanced Generative AI Generates Viable Cancer Drug Candidates*. https://zapata.ai/news/for-the-first-time-quantum-enhanced-generative-ai-generates-viable-cancer-drug-candidates/ (accessed 2024-06-30).
(40) Bhinder, B.; Gilvary, C.; Madhukar, N. S.; Elemento, O. Artificial Intelligence in Cancer Research and Precision Medicine. *Cancer Discov.* **2021**, *11* (4), 900–915. https://doi.org/10.1158/2159-8290.cd-21-0090.
(41) Lorenzo, G.; Ahmed, S. R.; Hormuth, D. A.; Vaughn, B.; Kalpathy-Cramer, J.; Solorio, L.; Yankeelov, T. E.; Gomez, H. Patient-Specific, Mechanistic Models of Tumor Growth Incorporating Artificial Intelligence and Big Data. *arXiv* **2023**. https://doi.org/10.48550/arxiv.2308.14925.
(42) *What is explainable AI?* https://www.ibm.com/topics/explainable-ai (accessed 2024-07-02).
(43) Molnar, C. *Interpretable Machine Learning: A Guide For Making Black Box Models Explainable*; Independently published, 2022.
(44) Wodarz, D.; Newell, A. C.; Komarova, N. L. Passenger Mutations Can Accelerate Tumour

Suppressor Gene Inactivation in Cancer Evolution. *J. R. Soc. Interface* **2018**, *15* (143), 20170967. https://doi.org/10.1098/rsif.2017.0967.
(45) *Our Technology Platform*. https://www.formation.bio/technology (accessed 2024-07-11).
(46) Armstrong, A. *New AI drug discovery powerhouse Xaira rises with $1B in funding*. https://www.fiercebiotech.com/biotech/new-ai-drug-discovery-powerhouse-xaira-rises-1b-funding (accessed 2024-08-16).