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COMPUTER-AIDED DRUG DESIGN METHOD USED FOR ANTICANCER DRUG DISCOVERY AND DESIGN

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ABSTRACT:
The process of creating a new medication is difficult, costly, time-consuming, and hazardous. The traditional drug discovery process is thought to require up to 15 years and more than USD 1 billion before a new medication is ready for the market. Thankfully, new methods have recently emerged, altering this situation. To improve the effectiveness of the drug development process, numerous innovative tools and approaches have been created, and computational techniques are now an essential part of many drug discovery initiatives. Many discovery efforts employ strategies like ligand- or structure-based virtual screening, which range from hit identification to lead optimization. In the case of developing possible anticancer medications as well as potential drugs, various computer approaches have shown to be highly influential throughout time and have yielded valuable insights into the field of cancer research. Concept of rational design is discussed in this article, and showcase a few of the most exemplary molecules discovered through its application.
KEYWORDS: Cancer, Lead optimization, Virtual Screening, Rational design,ligand.

INTRODUCTION:

Cancer is a complicated illness with a wide range of potential causes. Numerous variables might affect the disease's development and spread. Normal cells may develop into tumor cells as a result of inherited and environmental variables interacting. These tumor cells can then proliferate, infiltrate nearby tissues, and spread to other organs[1]. In an effort to reduce the incidence of cancer, several therapeutic techniques, including chemotherapy and radiation, have been developed over time. Certain tumors have been successfully treated with these medicines; nevertheless, these therapeutic methods have drawbacks, including limited effectiveness, toxicity, and drug resistance. Furthermore, many cancer therapies are not tailored to the specific requirements of each patient, which results in less than ideal results[2].

COMPUTER-AIDED DRUG DISCOVERY AND DESIGN:

Enabled the analysis of atomic processes in naturally occurring chemicals and medicines, the resolution of 3D structures, the optimization and development of novel chemical compounds, and the simulation of chemical systems. The process of finding new drugs has been more effective than it has ever been because to the development of new methodologies. Many

compounds have been submitted for clinical testing, and some of them have even received FDA approval[3]. Figure.1 are explain the HTS. The creation and development of novel anti-cancer medications has increasingly relied on computational techniques, such as computer-aided drug design (CADD). Researchers can uncover compounds that may be good treatment candidates for a variety of disorders, including cancer, by using computational tools and methodologies to simulate and predict the interactions between possible drug molecules and biological targets[4]. Computational techniques were used in the development of many FDA-approved anticancer medicines. Using structure-based design, crizotinib—a medication used to treat lung, lymphoma, and esophageal cancers—was discovered. The FDA authorized axitinib in 2012 to treat patients with advanced renal cell carcinoma; this medicine was also found utilizing computational techniques for structure-based drug discovery[5].

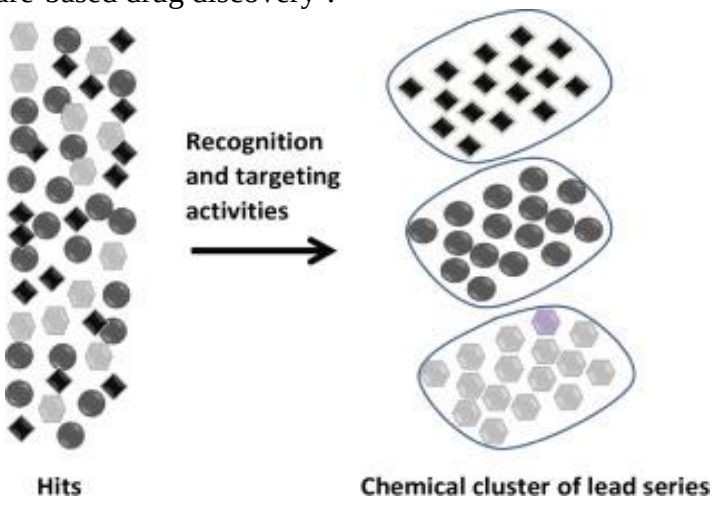

Fig. 1. High Throughtputscreening(HTS)

Biologically identifying a potential target to which ligand binding might result in antimicrobial action is the first step in the procedure. In SDBB, the target's three-dimensional structure may be determined via X-ray crystallography, nuclear magnetic resonance (NMR), or homology modeling. The procedures for CADD SBDD screening that follow are based on this. When the target 3D structure is not available, LBDD is used. The main focus is on creating a SAR, which will provide information on how to modify the lead chemical to enhance its activity. Figure 2 shows how the SAR is further developed using data from chemical synthesis and biological assays, which in turn improve the compounds in terms of activity and ADME (absorption, disposition, metabolism, and excretion) considerations. This process begins with CADD methods, which are used to create compounds[5].

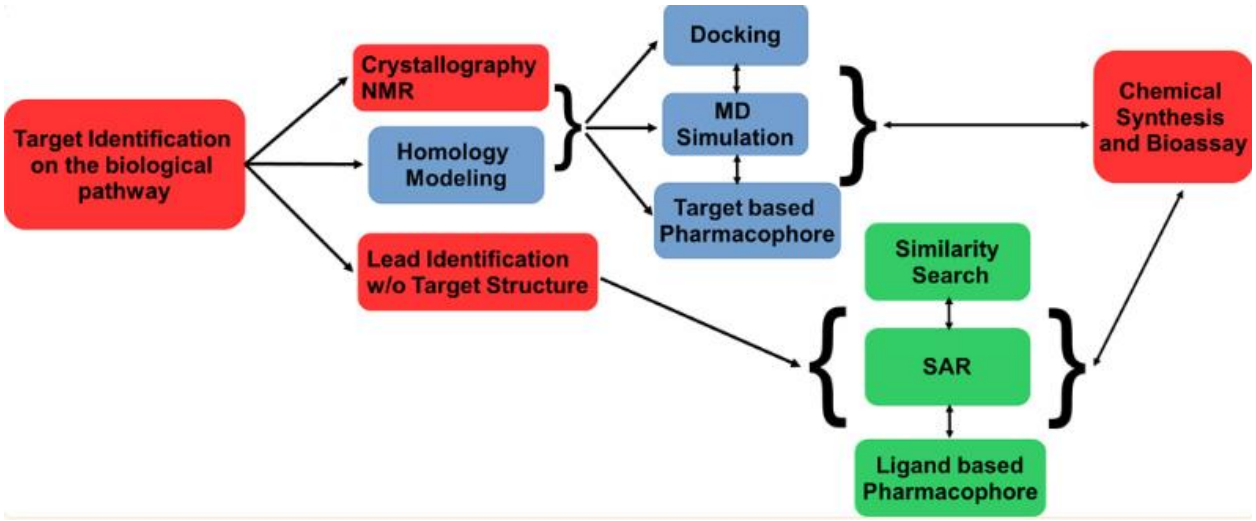

Fig. 2. Target to lead identification

ANTI-CANCER DRUG TARGET PREDICTION:

There are about 30,000 genes in humans, and of those, 6,000–8,000 are thought to be viable pharmacological targets. But there are less than 400 encoded until now, proteins are useful in development of drugs[6,7].

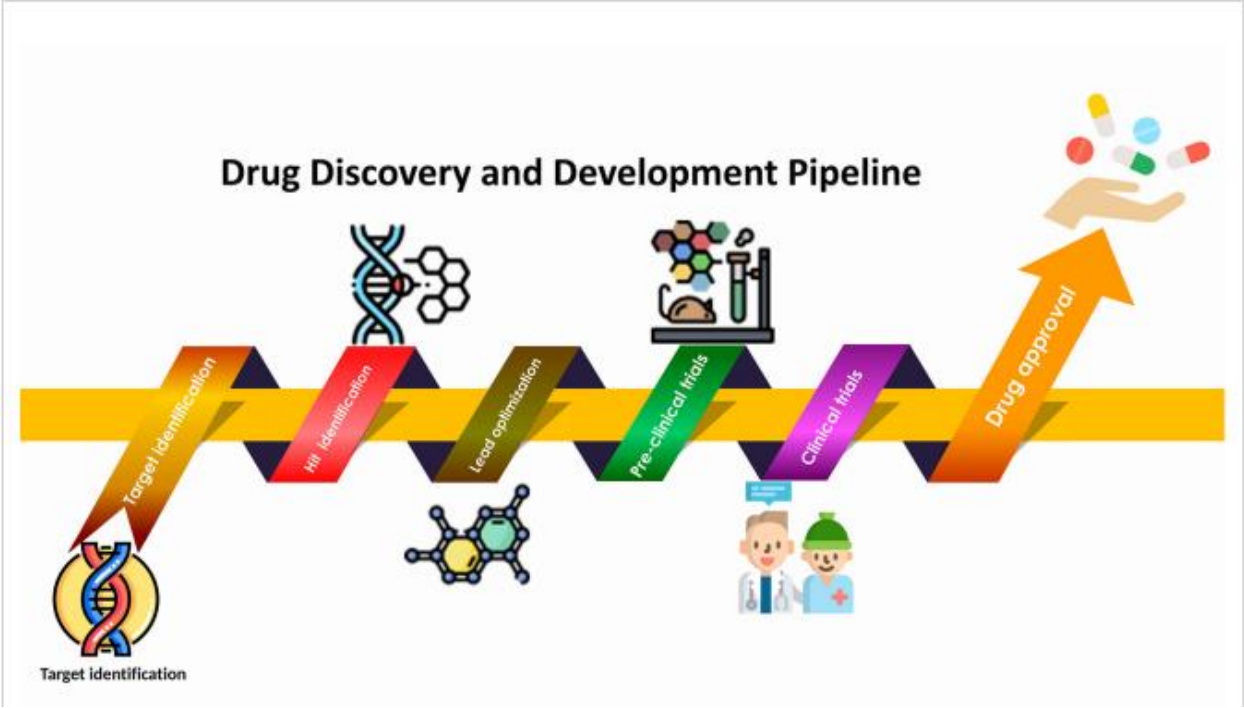

Fig.3.Target identification to drug approval pathway.

Traditional drug discovery typically adheres to paradigm of "one molecule - one target - one disease," often neglecting the interactions between drugs and proteins. However, it's crucial to recognize that many complex diseases are associated with a variety of target proteins has been overlooked[8-10]. Numerous interactive web servers with a medication target have been developed

to date, offering a variety of prediction tools and drug-target databases. ML-based models and network-based models in particular have become vital instruments. Chen et al.'s review provides an overview of the various computational models enlisted in Table 1 that are available for this application. Interestingly, we were drawn approach proposed by Campillos et al. that determines whether or not all medications have same binding sites for their target proteins by comparing the side effects of the drugs[11]. Multiple anticancer drug is discovered by using these techniques which mention in Table 2.

Table 1. Computational tools

COMPUTATIONAL TOOLS	WEBSITE	REFRENCES
PHARMMAPPER	https://www.lilab-ecust.cn/pharmmapper/	[7]
SEA	https://omictools.com/sea2-tool	[7]
CHEMMAPPER	https://omitools.com/chemmapper-tool	[7]

Table.2.Anticancer drug developed through using computational techniques[15-21].

S/N	Target	Therapeutic area	FDA Year of approval	Name	Refrences
1	VEGFR inhibitor	Renal cell carcinoma	2012	Axitinib	[15]
2	HGFR, ALK and cMET inhibitor	Lung cancer, Lymphoma and esophageal cancer	2011	Crizotinib	[16]
3	EGFR inhibitor	Advanced or metastatic non-small cell lung cancer (NSCLC)	2015	gefitinib	[17]
4	EGFR kinase inhibitors	Pancreatic cancer, NSCLC	2004	Erlotinib	[18]
5	ERBB2)/EGFR inhibitor	Breast cancer	2007	Lapatinib	[19]
6	Inhibitor of androgen synthesis	Metastatic castration-resistant prostate cancer	2011	Abiraterone	[20]
7	Tyrosine kinase inhibitors	Chronic myeloid leukemia	2003	Imatinib	[21]

Methods:

Ligand based methods:

Because potential targets' 3D structures are unavailable, pharmacophore approaches have emerged as a significant tool in drug discovery. Approaches like Quantitative Structure-Activity Relationship and pharmacophore modeling understand dynamics of target-ligand interactions, leading to development of predictive models that may be appropriate for lead optimization and discovery. Models of active ligands interacting with targets of interest are basis of ligand-based design techniques, which aim to anticipate novel chemical entities exhibiting comparable

activity. A new drug's success is justified by pointing to characteristics of existing ligands, or molecular similarity, which states that it is more probable that activity profiles of compounds with strong structural similarity would be comparable. This technique, which is seen as a side way to finding new drugs, is typically employed in situations where the target's 3D structure is either unknown or unpredictable[12]. One or more active molecules that have been identified may be screened using a small molecule library in a number of ways using key patterns. For a small price, you can compare a reference molecule or collection of molecules to an extensive chemical library using physicochemical properties such as volume, geometry, molecular weight, surface areas, atom types, dipole moment, molar refractivity, polarizability, octanol-water partition coefficient (log P), electronegativity, planar structures, or solvation properties. Any of these can be derived from experimental measurements or theoretical models. A simplified symbolic model of molecule allows for quick completion of this activity. Various types of molecular representation allow for further classification of these descriptors, which can be expressed as little strings that show if certain attributes are present or not. These descriptors include constitutional, count, fingerprint, list, surface and volume, quantum-chemical, descriptors. An further ligand-based strategy that outperforms molecular descriptors is use of a ligand-based pharmacophore model. To build a pharmacophore model, next step in using molecular descriptors is to include two D or three D structure of these molecules with collection of known active chemicals. QSAR and pharmacophore modeling have emerged as crucial drug discovery techniques to address dearth of 3D structures for potential therapeutic targets. Lead identification and optimization prediction models are made feasible by disclosure of target-ligand interactions[13]. Pharmaceutical industry optimizes drug pharmacokinetic properties such as absorption, distribution, metabolism, excretion, and toxicity by screening ligand-based approaches for discovering drugs to identify novel ligands with exciting biological activity. Predicted on idea that biological effects of molecules with comparable structures, these methods predict similar chemical entities using the structure of known ligands. These techniques examine the known ligands' 2D or 3D structures when they interact with target molecule. Aim is to eliminate unnecessary information while capturing physicochemical properties required for desired interactions[14].

Structure based methods:

Three-dimensional structural analysis of biological molecules is needed for structure-based drug design. Significant advancements in this field have been made possible by NMR and X-ray crystallography are examples of biomolecular spectroscopy methods, which have greatly enhanced structural data about the medicinal aim. Using structural target knowledge, this method predicts whether a new compound will bind highly affinity at the site where interaction changes how protein works and has a medicinal impact. To model interacting with any of the chemical library's small molecules, target is used as a mold. These tactics make advantage of biochemical information on ligand-receptor interaction to increase the effects of known ligands with little chemical changes[13]. Structure-based pharmacophore modeling, molecular docking, and molecular dynamics are utilized to investigate. A key method for increasing effectiveness of currently available anticancer medications and creating novel ones is structure-based pharmacophore (SBP) modeling. This approach creates pharmacophore models by utilizing a protein's three-dimensional structure as well as chemical characteristics of ligands that bind to it. These models shed light on critical molecular characteristics that affect binding, which can be used to improve binding qualities and optimize drug design. Drug development and discovery

tools that use structure-based pharmacophores are becoming more important. They make it possible to conduct extensive structural chemogenomics research to find novel proteins' ligands or novel ligand targets[14]. Bcl-2 protein-targeting anticancer medications have been developed using structure-based pharmacophore modeling. Cancer cells often exhibit elevated levels of Bcl-2, a protein that plays a pivotal role in controlling cell death and survival. It has been determined that Bcl-2 inhibition is a viable therapeutic approach for management of cancer. Applying structure-based pharmacophore modeling led to creation of novel drugs that attach to Bcl-2 protein and cause cancer cells to die[15]. Multiple anticancer drug is discovered by using these techniques which mention in Table 2. **Table.2.Anticancer drug developed through using computational techniques[15-21]**.

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Molecular docking:

Atomic-scale drug-target interaction analysis is possible with MD simulation. By looking at structural changes brought on by genetic mutations, it aids in the investigation of drug resistance, prediction, and discovery. With femtosecond accuracy, MD simulation predicts motion of every atom found in a molecule, such as a protein using a comprehensive model of interatomic interactions. It is possible to study protein folding, ligand binding, and conformational change. The ability of MD simulations to predict the atomic-level reactions of biomolecules to ligand addition or removal, phosphorylation, protonation, and mutations is significant. To increase accuracy, nuclear magnetic resonance (NMR) and X-ray crystallography are frequently combined with MD simulations[22].The three most widely used molecular dynamics software packages are GROMACS, AMBER and NAMD. DESMOND simulation is now a vital software tool for researching interactions and dynamics. The molecular interactions between drugs and their targets, such as those involving proteins and ligands,

proteins and DNA, can be studied thanks to DESMOND's simulation capabilities. Information can be used to develop new medications and drug candidates as well as enhance the safety, effectiveness, and specificity of currently available medications. In DESMOND, the system dynamics equations are solved via integrator algorithms. When simulating large, complex systems in DESMOND, Verlet and speed most common verlet integrator techniques frequently utilized. DESMOND uses force fields to simulate atom-to-atom interactions. Force fields use the locations of atoms to calculate their potential energy. CHARMM, GROMACS and AMBER, force fields are used by DESMOND. User-friendly interface, superior performance, flexibility, robustness, and ability to interface with other applications of DESMOND. MD simulations were used to study the interactions between imatinib and BCR-ABL, revealing the key structural and dynamic characteristics of the binding site. Using this understanding, imatinib derivatives with improved BCR-ABL binding properties and selectivity were created, leading to an extremely effective and focused CML treatment [23].

Structure-Based Pharmacophore Mapping:

Over last few decades, pharmacophore mapping has emerged as a leading tool in fight for new pharmaceuticals. Pharmacophore modeling has been enhanced by several structure-based methodologies; It is widely utilized in de novo design, lead optimization, and virtual screening[23]. Another practical approach is the structure-based pharmacophore . There are two categories of SBP modeling approaches that are based on the ligand structures that are currently available: technique based on target-ligand complex and technique based on target-binding site (devoid of ligand). Finding the protein's ligand-binding pocket and evaluating the primary ligand-protein interactions are both made easier by target-ligand complex technique[24].

Possible Function of Certain tiny Molecules as Anticancer Medications:

In preceding segment, we deliberated on identification and application of computer-based rational drug design techniques for purpose of designing experiments and, above all, for clarifying structure-activity interactions that aid in development of new drugs and improvement of existing ones. By using these methods, small-molecular-weight drugs have been developed with specific goal of targeting cancer cells and blocking chemicals or processes that allow unregulated cell growth and division. Here, we classify small compounds according to methods in which they promote cancer development and survival: by inducing cell cycle arrest, apoptosis, or angiogenesis inhibition or by changing signaling pathways that do just that. The set of processes a cell goes through during its growth and division is known as the cell cycle. The cell cycle is strictly controlled in normal cells, and there are checkpoints to guarantee correct development and stop the build-up of genetic errors. Nevertheless, the regular control of the cell cycle is frequently compromised in cancerous cells, resulting in unchecked cell proliferation and division. Numerous things, including alterations in cellular signaling, replicative stress, and damage to DNA, can cause this. It has been demonstrated that cell cycle arrest is essential to the onset and management of cancer. Development of molecules capable of inducing cancer cells experiencing a cell cycle halt as Fig.2. is a significant advancement in treatment of cancer. This medication acts by replenishing regular control of cell cycle in cancerous cells or by specifically addressing cell cycle elements that are disturbed in cancerous cells[25].

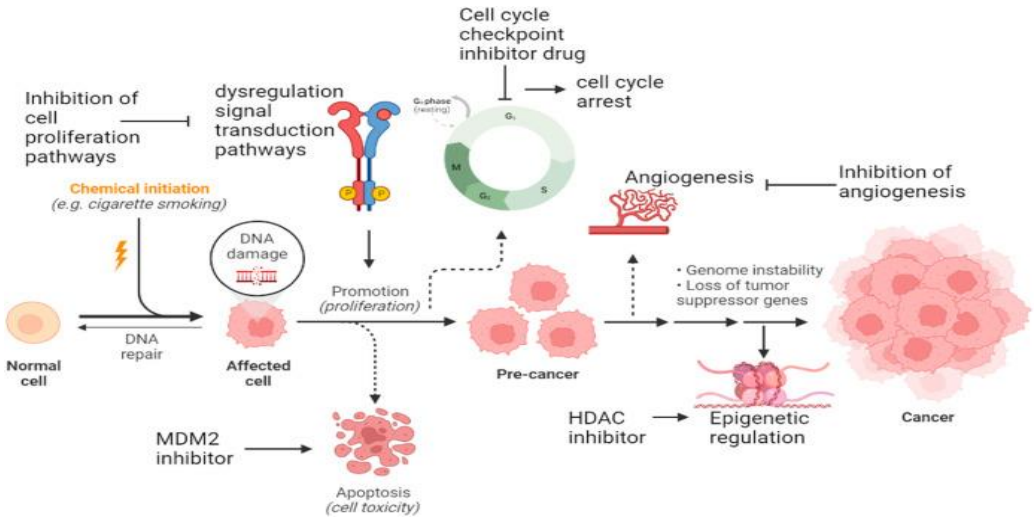

Fig.2.Pathway through at which anticancer drug act.

Objective of study:

The aim of employing computational approaches in the search for anticancer drugs is to harness the potential of computer-based techniques and models to expedite and improve the process of finding and creating new drugs that combat cancer.With the use of computational techniques, scientists can quickly examine enormous volumes of chemical and biological data. This shortens the time needed to move promising drug candidates through clinical trials and speeds up the drug discovery process.The cost of traditional drug discovery can be very high. The cost of screening and testing compounds can be decreased by computational methods, which lowers the cost of developing anticancer medications. Researchers can create medications with high specificity for cancer cells while minimizing harm to healthy cells, lowering side effects, and enhancing the effectiveness of treatment with the aid of computational tools.The use of computational methods makes it possible to forecast how a potentialdrug will interact with particular molecular targets, like cancer-development-related proteins or enzymes, to help identify potential treatment candidates.

Discussion:

It turns out that creating new anticancer medications is a very complex, expensive, and time-consuming process. With the benefit that much less time, money, and resources must be invested in technology, CADDD is growing in significance. With explosion of data on genomes, protein structures, and small compounds, computational techniques are finding their way into almost every step of drug development and discovery process. Computationally rationally created chemical compounds may, in light of target molecule's three-dimensional structure, have a stronger affinity for it. Numerous successful uses of structure-based drug design have been documented in recent years. The identification of p53 upregulated modulator of p53 is an intriguing structure-based pharmacophore modeling apoptosis inhibitors. A member of the Bcl-2 protein family, PUMA is a pro-apoptotic protein. Tumor suppressor p53 controls its expression. Apoptosis deficiency caused by PUMA ablation or inhibition underlies elevated cancer development risks as well as treatment resistance. This cancer treatment target interacts with every member of the known antiapoptotic Bcl-2 family, having a vital part in cell death caused by the mitochondria.

Through the investigation of BH3-only protein binding to Bcl-2-like protein, We could find tiny substances that alter these relationships and prevent apoptosis. Research efforts have smostly been focused on creating Bcl-2 family inhibitors that replicate the pro-apoptotic BH3 domains' actions. Researchers have used high-throughput screening of libraries of natural and synthetic products, computational modeling, and structure-based design to locate these compounds.The drug discovery process can now proceed more quickly thanks to the quick and affordable synthesis and screening of large libraries of compounds made possible by the rapid advancements in CADDD technologies and methodologies. These methods have been effectively used in a number of projects searching for better or newer medicines over previous many years. To show how useful applications are, we have a look at a few of them that deal with in silico target prediction, hits detection, and leads optimization.

Conclusion:

In search for novel cancer treatments, computer-aided drug design has emerged as a crucial tool. To forecast efficacy of small compounds against cancer-related biological targets, it integrates computational models and simulations with experimental data. This allows for quick discovery of possible medication candidates and improvement of their qualities to increase effectiveness and decrease side effects. development of multi-target medications, which simultaneously target several biological targets, of small molecule activity against particular biological targets, and of molecular mechanisms of action of tiny compounds in cancer are all examples of computational methods that have been utilized in cancer drug discovery. Current predictive models have their limits, and CADD still needs more advanced models to account for complicated interaction between several biological targets and pathways in cancer, among other issues. Nevertheless, CADD has been successful in discovering novel cancer treatments. Furthermore, there are limits and potential for erroneous predictions when drug development predictive techniques are primarily based on transcriptome profiles of cancer cell lines. We should expect CADD to keep playing a vital role in the search for novel cancer treatments going forward. More precise and focused cancer treatments may be possible with help of big data integration, this include tumor samples from patients as well as information from high-throughput testing techniques. This could lead to improved predictive approaches in drug development. Future CADD efforts aimed at designing effective anticancer treatments will likely hinge on creation of increasingly accurate computer models that can capture the intricate relationship between cancer's many biological targets and pathways.

Future prospect:

The future prospects of computer-aided drug design (CADD) in developing anticancer drugs are quite promising. CADD helps in identifying specific molecular targets that are crucial for cancer cell survival or proliferation. This enables the design of drugs that selectively inhibit these targets, leading to more effective and less toxic treatments compared to traditional chemotherapy. With advances in computational algorithms and increased computing power, virtual screening techniques can efficiently analyze large chemical libraries to identify potential drug candidates. This accelerates the drug discovery process by prioritizing compounds with high binding affinity and specificity for the target. CADD can facilitate the identification of existing drugs or compounds that can be repurposed for anticancer activity. By analyzing molecular interactions and pharmacological properties, researchers can uncover

new uses for drugs that were originally developed for other indications, saving time and resources in drug development.

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