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TREATMENT OF COLORECTAL CANCER USING NANOTECHNOLOGY

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Abstract

Bioinformatics was tasked to support the first flow generated by Nano biotechnology at the early stages of development. This challenge requires the adaptation of classical bioinformatics tools, and also computational chemistry tools, to store, standardize, analyze and visualize the information generated in Nano biotechnology. Therefore, bioinformatics and computational chemistry have been merged to develop a new sub-discipline called Nano informatics. This review depicts some new requirements such as the development of new drug designing, modelling, simulation and visualization of Nano drug particle in the treatment of cancer. Bioinformatics, Nano technology and chemo informatics plays the beneficial role in the treatment of cancer. Using bioinformatics tools and software's we can able to predict the protein whose structure is not predicted, this was achieved using PUBMED and PDB [protein data bank] databases. Chemo informatics plays a role in designing a drug. Here the two drug compound Aspirin +Cystaphos which is used in treatment of cancer are identified using PUBCHEM database, these two compounds are combined in the drug design software's chemsketch, and a new chemical compound is obtained. Then the protein and designed ligand is docked using molecular docking techniques its binding affinity towards the ligand and receptor should be 74% can be used effectively. In addition to this for easy drug delivery system we use PAMAM dendrimer, ethylenediamine core, generation 0.0 solution, high degree of branching, multivalency, globular architecture and well-defined molecular weight, make them promising new scaffolds for drug delivery.

Keyword*:*

Ligand-Receptor preparation, Docking, Ligand-Receptor interaction, Virtual Screening.

Introduction

CRC is one of the most prevalent cancer types worldwide, colorectal cancer (CRC) occurs when malignant (cancer) cells form in the tissues of the bowel (colon or rectum). The majority of cancers occurring in the colon or rectum are adenocarcinomas, cancers that originate in glandular tissue, and account for 95 percent of all large bowel tumors. Most colorectal cancers do not cause any symptoms in the early stages, so they can grow 'silently' for years while the patient feels perfectly healthy. When clinical symptoms occur, the tumor is often at an advanced stage. The five-year survival rate of people diagnosed with stage I colorectal cancer, where the tumor is confined to the organ in which it started, is 74 percent.

Treating Colorectal Cancer

- Treatment options depend on the stage of the cancer.
- Once colorectal cancer has metastasized to another part of the body, the chances of being cured dramatically decline. Chemotherapy, radiotherapy and surgery are all options for mCRC, however chemotherapy is often supplemented with the use of biologic therapies.

CASPASE9

Caspases exist as inactive proenzymes which undergo proteolytic processing at conserved aspartic residues to produce two subunits, large and small, that dimerize to form the active enzyme. This protein can undergo autoproteolytic processing and activation by the apoptosome, a protein complex of cytochrome c and the apoptotic peptidase activating factor 1; this step is thought to be one of the earliest in the caspase activation cascade.

This protein is thought to play a central role in apoptosis and to be a tumor suppressor. Alternative splicing results in multiple transcript variants. Sequential activation of caspases plays a central role in the execution-phase of cell apoptosis.

Dendrimer as a Nanoparticle for Drug Delivery in Cancer

The field of oncology could soon be revolutionized by novel strategies for diagnosis and therapy employing dendrimer-based nanotherapeutics. Several aspects of cancer therapy would be involved. This might involve novel contrast agents targeted specifically to cancer cells. Dendrimers can also be being applied to a variety of cancer therapies to improve their safety and efficacy. Further applications of dendrimers in photodynamic therapy, boron neutron capture therapy,

and gene therapy for cancer are being examined. An evaluation of this new technologies will detail what advantage dendrimer based therapeutics might have over conventional cancer drugs.

Tools and Database Used

NCBI

The National Center for Biotechnology Information (NCBI) is part of the United States National Library for Medicine (NLM), a branch of National Institute of Health. The NCBI houses a series of databases relevant to biotechnology and biomedicine. All the databases are available online through the Entrez search engine.

Drug Bank

The Drug Bank database is a unique bioinformatics and cheminformatics resource that combines detailed drug data with comprehensive drug target information. The database contains 7759 drug entries including 1600 FDA-approved small molecule drugs, 160 FDA-approved biotech (protein/peptide) drugs, 89 nutraceuticals and over 6000 experimental drugs.

Chemsketch

For structure drawing and creating a .mol file ACD/ChemSketch Freeware is a drawing package that allows you to draw chemical structures including organics, organometallics, polymers, and Markush structures. It also includes features such as calculation of molecular properties

Swiss-Model

SWISS-MODEL is a structural bioinformatics web-server dedicated to homology modeling of protein 3D structures. Homology modeling is currently the most accurate method to generate reliable three-dimensional protein structure models and is routinely used in many practical applications. Homology (or comparative) modelling methods make use of experimental protein structures ("templates") to build models for evolutionary related proteins ("targets").

Ramachandran Plot Server

A Ramachandran plot (also known as a Ramachandran diagram or a [φ,ψ] plot), originally developed in 1963 by G. N. Ramachandran, C. Ramakrishnan, and V. Sasisekharan, is a way to visualize backbone dihedral angles ψ against φ of amino acid residues in protein structure. One is to show in theory which values, or conformations, of the ψ and φ angles are possible for an amino-acid residue in a protein.

MGL Tool

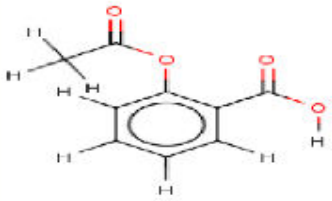
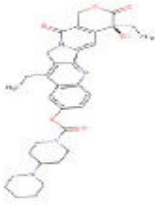
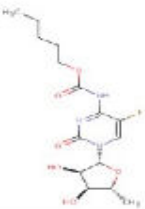
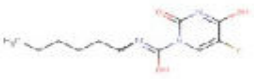
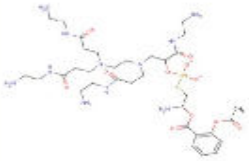
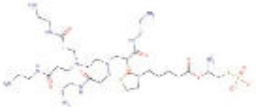
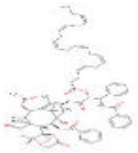
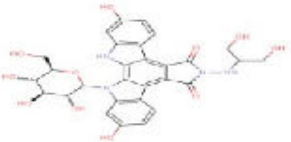
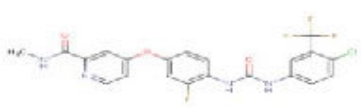
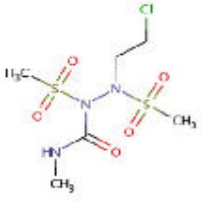
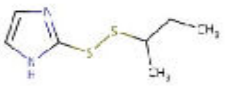
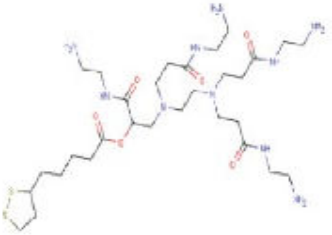
This tool is used for docking. Auto Dock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure. TheAuto Dock 4 comprises three major improvements:

1. The docking results are more accurate and reliable.
2. It can optionally model flexibility in the target macromolecule.
3. It enables Auto Dock's use in evaluating protein-protein interactions.

iGEM DOCK

iGEMDOCK - A Graphical Environment for Recognizing Pharmacological Interactions and Virtual Screening. Pharmacological interactions are useful for identifying lead compounds and understanding ligand binding mechanisms for a therapeutic target. Moreover, most docking programs loosely coupled the stages of structure-based virtual screening (VS) from preparations through to post-screening analysis. An integrated VS environment, which provides the friendly interface to seamlessly combine different-stage programs for VS and identifying the pharmacological interactions from screening compounds, is valuable for drug discovery.

Results: Ligands

Aspirin 	Irinotecan 	Capetacitabine 	Carmafur 
Cystaphos+Aspirin+Dendrimer 	Cystaphos+Thiotic acid+Dendrimer 	DHA-Paclitaxel 	Edotecarin 
Regorafenib 	VNP 40101M 	PX-12 	Thiotic acid+Dendrimer 

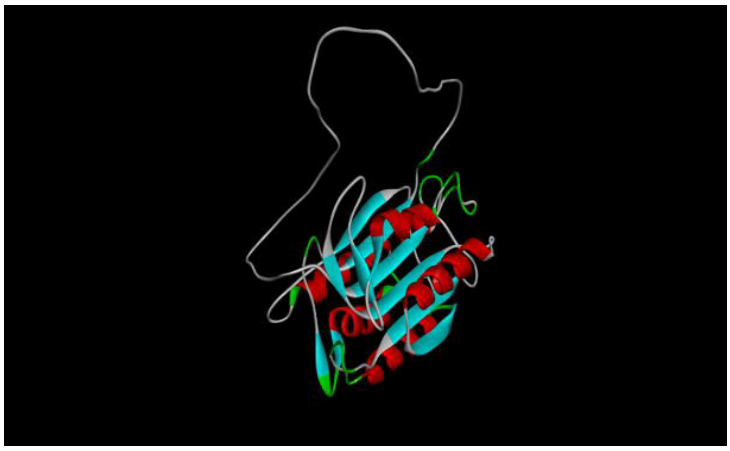
Target Protein Preparation

Protein Sequence - CASP9_Human

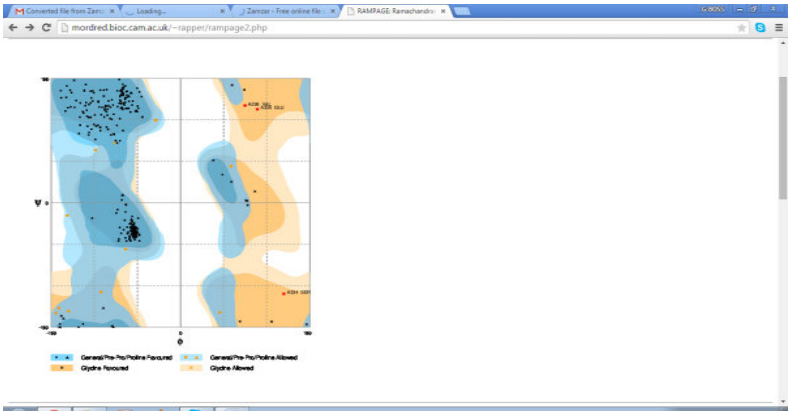
>gi|13623673|gb|AAH06463.1| Caspase 9, apoptosis-related cysteine peptidase [Homo sapiens]

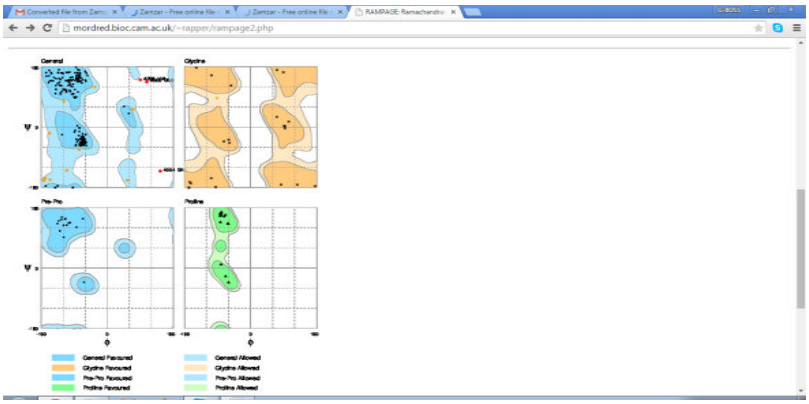
MDEADRRLLRRCRLRLVEELQVDQLWDALLSRELFRPHMIEDIQRAGSGSRRDQARQLIIDLETRGSQAL
PLFISCLEDTGQDMLASFLRTNRQAAKLSKPTLENLTPVVLRPEIRKPEVLRPETPRPVDIGSGGFGDVG
ALESLRGNADLAYILSMEPCGHCLIINNVNFCRESGLRTRTGSNIDCEKLRRRFSSLHFMVEVKGDLTAK
KMVLALLELAQQDHGALDCCVVVILSHGCQASHLQFPGAVYGTDGCPVSVEKIVNIFNGTSCPSLGGKPK
LFFIQACGGEQKDHGFEVASTSPEDESPGSNPEPDATPFQEGLRTFDQLDAISSLPTPSDIFVSYSTFPG
FVSWRDPKSGSWYVETLDDIFEQWAHSEDLQSLLLRVANAVSVKGIYKQMPGCFNFLRKKLFFKTS.

Modelled Protein:



Ramachandran Plot Results





EVALUATION OF RESIDUES

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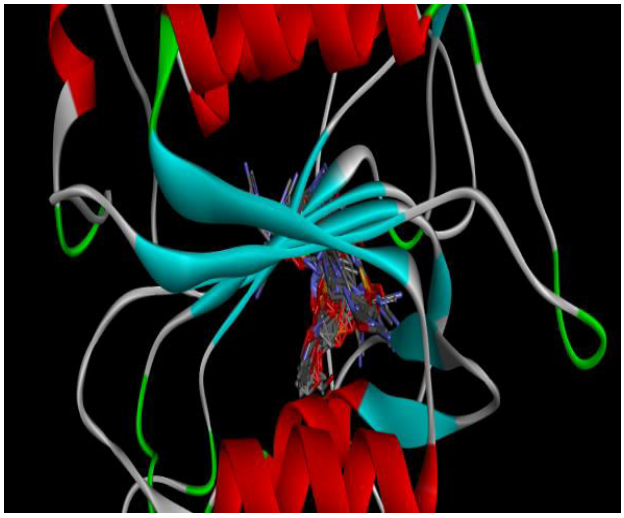
Residue [A 147 :GLY] ( -91.80,  86.91) in Allowed region
Residue [A 155 :LEU] (-117.98,  76.27) in Allowed region
Residue [A 198 :HIS] (  70.30,  53.06) in Allowed region
Residue [A 244 :LEU] ( -76.33, -66.97) in Allowed region
Residue [A 296 :PHE] (-155.68,-156.77) in Allowed region
Residue [A 316 :ALA] (-172.83,-159.63) in Allowed region
Residue [A 320 :GLN] (-169.14,-152.28) in Allowed region
Residue [A 324 :ARG] (  54.93,-158.59) in Allowed region
Residue [A 325 :THR] (-157.49, -18.39) in Allowed region
Residue [A 329 :LEU] (-110.48,-129.04) in Allowed region
Residue [A 330 :ASP] ( -34.35, 119.52) in Allowed region
Residue [A 298 :VAL] (  89.93, 140.68) in Outlier region
Residue [A 306 :GLU] ( 107.17, 135.43) in Outlier region
Residue [A 334 :SER] ( 143.99,-131.65) in Outlier region
Number of residues in favoured region(~98.0%expected):258(94.9%)
Number of residues in allowed region(~2.0% expected)  :11 (4.0%)
Number of residues in outlier region             :    3 (  1.1%)
```

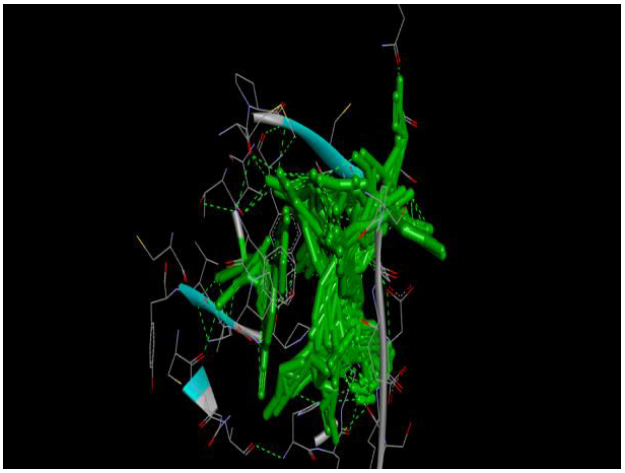
Docking Results

LIGANDS	BINDING ENERGY	RUN
Cystaphos+Aspirin+Dendrimer	-3850410.00	9
Thiotic acid+Dendrimer	-12.96	9
Aspirin	-13264271.00	8
Cystaphos+Dendrimer	-2788755.50	8
DHA-Paclitaxel	-13.81	8
Irinotecan	-11.52	8
Carmafur	-7.60	8
PX-12	-4.99	8
VNP4010M	-1361042.65	6
Capecitabine	-9.73	6
Regorafenib	-5064645.50	5
Cystaphos+Thiotic acid+Dendrimer	-3948114.75	5

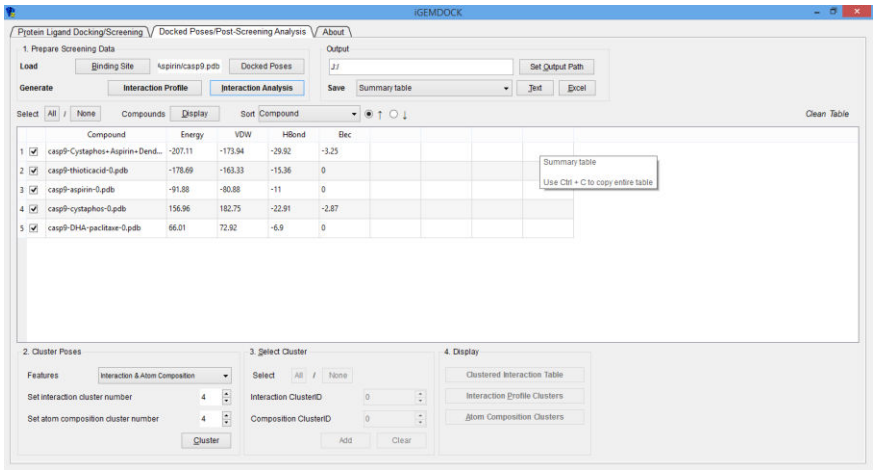
Docked Protein



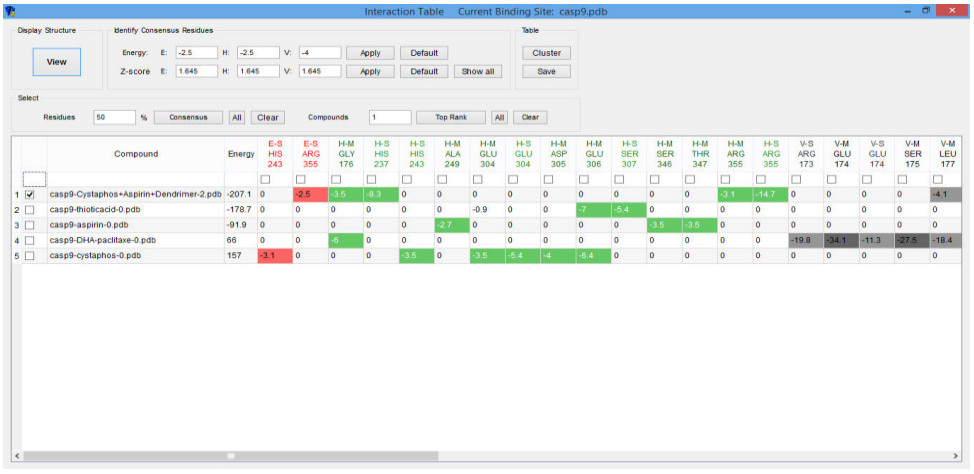
Protein-Ligand Interaction



Virtual Screening Result



Interaction Scores



Discussion

Previous studies found that aspirin are more active to the colorectal treatment and the chemical compound cystaphos acts as an adjuvant for the treatment of Readiotherapy against breastcancer. Thus a combined compound along with the nano

particle PAMAM dendrimer ethylene diamine solution core generation 0.0 is used for the binding of compound to the ligand binding site of the protein.Now then these chemicals along with 12 other compounds are made to dock to see find a better results and efficacy to use against colorectal cancer. Now, the first the protein casp9 protein is modelled using Swiss-model and validated using Ramachandran plot server. From the result is that our modelled protein has 258 (94.9%) in favoured region.Then the 12 ligand with dendrimer loaded for some compounds are retrieved from the Drug Bank database drawn using chemsketch tool. Then they are made for the docking process. From the result we have found that cystaphos+Aspirin +Dendrimer has a higher binding affinity with lowest binding energy of -3850410.00 k cal per mol binding energy with more runs than the normally used compound Aspirin which has a binding energy of about-13264271.00 k cal per mol with 8 runs. For further confirmation top 5 molecules with lowest binding energies are passed for the virtual screening process.And from the result it is clear that Cystaphos+Aspirin+Dendrimer has the highest energy of about -207.1 k cal/mol.

Conclusion

As then from the binding energy results it is clear that the compound of Cystaphos+Aspirin+Dendrimer has a higher binding affinity with lower binding energy comparing to the normal compound Aspirin and so it is predicted that the can act more effectively to the Casp9 protein. As the compound acts more precisely the compound can be made to our further project study will be of to prepare a nano particle, and its physio-chemical study, analysis of protein and ligand interaction in cell lines, pharmacokinetics and Animal studies etc.

Reference

1. Shapiro JA, Seeff LC, Thompson TD, et al. Colorectal cancer test use from the 2005 National Health Interview Survey. Cancer Epidemiology, Biomarkers & Prevention. 2008 Jul; 17(7):1623–30.
2. US Preventive Services Task Force Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Annals of Internal Medicine. 2008 Nov 4; 149(9):627–37.
3. Flossmann E, Roth well PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet. 2007 May 12; 369(9573):1603–13.
4. Thun MJ, Namboodiri MM, Heath CW. Aspirin use and reduced risk of fatal colon cancer. The New England Journal of Medicine. 1991 Dec 5; 325(23):1593–6.

5. Jacobs EJ, Thun MJ, Bain EB, et al. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. The New England Journal of Medicine. 2007 Apr 18; 99(8):608–15.

6. Chan AT, Giovannucci EL, Meyerhardt JA, et al. Aspirin dose and duration of use and risk of colorectal cancer in men. Gastroenterology. 2008 Jan; 134(1):21–8.

7. Chan AT, Giovannucci EL, Meyerhardt JA, et al. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA. 2005 Aug 24;294(8):914–23.

8. Ruder EH, Laiyemo AO, Graubard BI, et al. Non-steroidal anti-inflammatory drugs and colorectal cancer risk in a large, prospective cohort. The American Journal of Gastroenterology. 2011 Jul;106(7):1340–50.

9. Chan AT, Manson JE, Feskanich D, et al. Long-term aspirin use and mortality in women. Archives of Internal Medicine. 2007 Mar 26;167(6):562–72.

10. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA.2009 Aug 12; 302(6):649–58.

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