SYSTEMATIC RESEARCH TO FIND OUT THE LINK BETWEEN SARCOMAS AND HUMAN GENES AND TO VALIDATE USING BIOINFORMATICS TOOL

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Thesis submitted to the SASTRA Deemed to be University
in partial fulfillment of the requirements
for the award of the degree of

B. Tech. Bioinformatics

Submitted by

Aparna Venkata Krishnan
122013004

JULY 2022

SCHOOL OF CHEMICAL & BIOTECHNOLOGY

SASTRA
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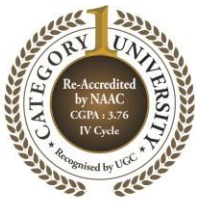

THINK MERIT | THINK TRANSPARENCY | THINK SASTRA

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ABSTRACT

Goliath cell growth (GCT) is a sort of disease that can display complex way of behaving and metastasize. It is recognized by an expansion in mononuclear in the giant cell . There is no extensively held settlement on the best treatment procedure. Albeit most goliath cell tumors are harmless and happen in youthful grown-ups, scarcely any patients foster moderate lung metastases with heartbreaking results. Late advances in pathogenesis understanding are basic to cultivating new medications for this locally alarming fundamental bone development. Clonal deviations brought about by monster cell development of bone (GCTB) are brought about by epigenetic histone changes (especially the G34W change of H3F3A quality), which cause cytogenetic abnormalities. Clonal varieties are inseparably connected to the power of GCTB. In GCTB, "neoplastic" mononuclear stromal cells express key RANKLs as well as different chemokines and cytokines related with monocyte enrolment and "open" multinucleated beast cells (osteoclast beginning). The family member and made practices out of goliath cells of GCTB atomic pathogenesis and sickness science. Later in the novel, the novel spotlights on the latest progressions being developed science and subatomic pathogenesis of GCTB, which ought to be explored and tried for the headway of major treatment. GCT addresses around 5% of all fundamental bone malignant growths. Most of these sores show up in the third and fourth many years of life. Albeit harmless bone growths are seldom deadly, they can cause huge disturbance of the neighborhood hard engineering, which can be particularly dangerous in peri-articular areas..

Specific Contribution:

- Found out the genes involved in the Giant Cell Tumor (Osteoclastoma).
- Finding out the protein-protein interaction.

Specific Learning:

- Finding the link between the genes and the sarcoma.
- How the genes are involved and comparing it with normal human genes

Technical Limitations & Ethical challenges faced:

- Time taken to find the protein-protein interaction.

Keywords*: Giant Cell Tumor (GCT), pathology, H3F3A/H3F3B, GCTB, PyRx, Chimera, PyMol, IDH,*

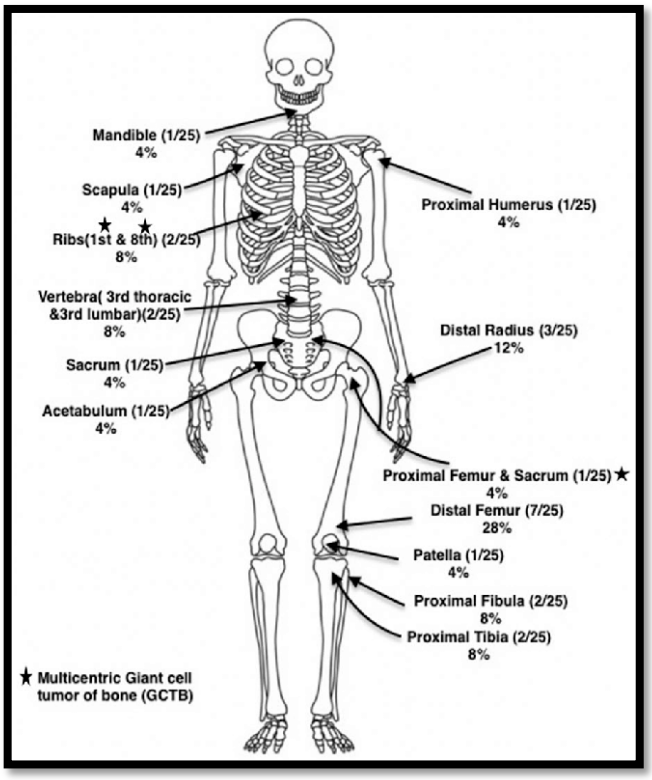
CHAPTER 1

INTRODUCTION

GIANT CELL TUMOR (OSTEOCLASTOMA)

1.1 WHAT IS GCT (GIANT CELL TUMOR)?

Goliath cell growth (GCT) is a kind of disease with the possibility to show complex way of behaving and the capacity to metastasize. It is depicted by an extension of mononuclear stromal cells and the presence of various multi-nucleated goliath cells with homogenous scattering There is no comprehensively held understanding concerning the best treatment procedure assurance. As most goliath cell tumors are innocuous and are arranged near a joint in young adults, despite the way that GCT is designated an innocuous sore, barely any patients cultivate moderate lung metastases with sad outcomes. A goliath Cell Growth of bone is intriguing, forceful non-destructive cancerIt for the most part found in grown-ups between ages 20 and 40 when skeletal bone development is finished. Decisions of chemotherapy and radiotherapy are put something aside for picked cases.Late advances in the comprehension of pathogenesis are chief empowering new medications for this locally upsetting essential bone turn of events. GCT addresses around 5% of all essential bone cancers. In the greater part of the cases these sores happen in the third and fourth many years of life. Albeit seldom deadly, harmless bone growths might be related with a significant aggravation of the neighborhood hard design that can be especially problematic in peri-articular areas. Albeit viewed as harmless cancers of bone, GCT has a moderately high repeat rate.



Anatomical Distribution of the Giant Cell Tumor of Bone

(https://www.researchgate.net/profile/Ziyad-Mohaidat/publication/335444114/figure/fig1/AS:807299408998400@1569486586282/Anatomical-distribution-of-giant-cell-tumors-of-bone-GCTB.png)

1.2 WHAT CAUSES THE GIANT CELL TUMOR?

The exact reason is obscure; the writing talks about the meaning of Paget sicknesses and their relationship to Monster Cell Growth. Paget's bone sickness disturbs the body's ordinary reusing process, in which new bone tissues steadily supplant old bone tissue.

1.3 HOW CAN THE GIANT CELL TUMOR BE DETECTED?

Some of the most common symptoms of a giant cell tumour are as follows: Although symptoms vary greatly from person to person, the following are the most common: - Bone fracture

- Fluid build-up in the joint situated closest to affected bone region
- Swelling
- Pain at the nearest joint

1.4 HOW IS THE GCT BEING DIAGNOSED?

Various tests are performed for various diagnostic purposes, including:

- Biopsy: A test where tissue tests are taken from the body and inspected under a magnifying lens to decide the kind of disease or to affirm the presence of unusual cells in the gathered examples.

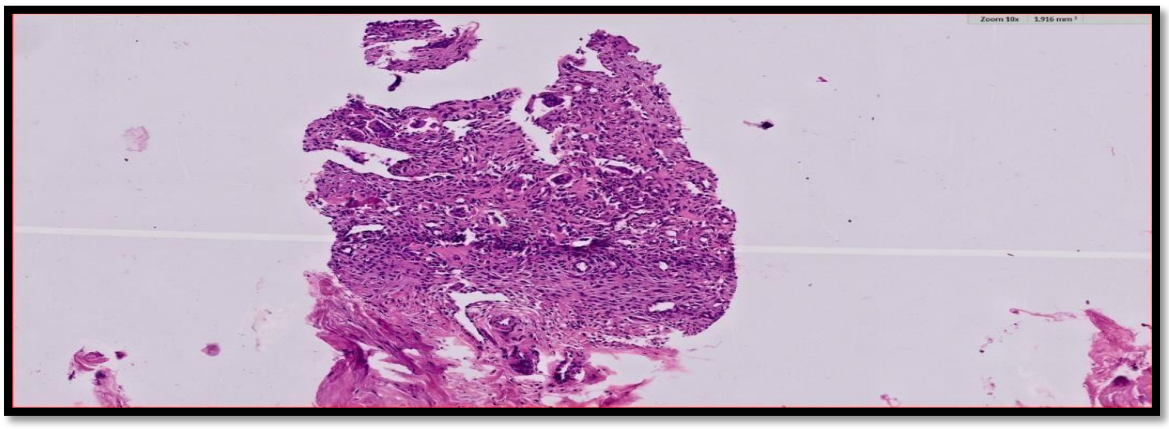


Figure 1

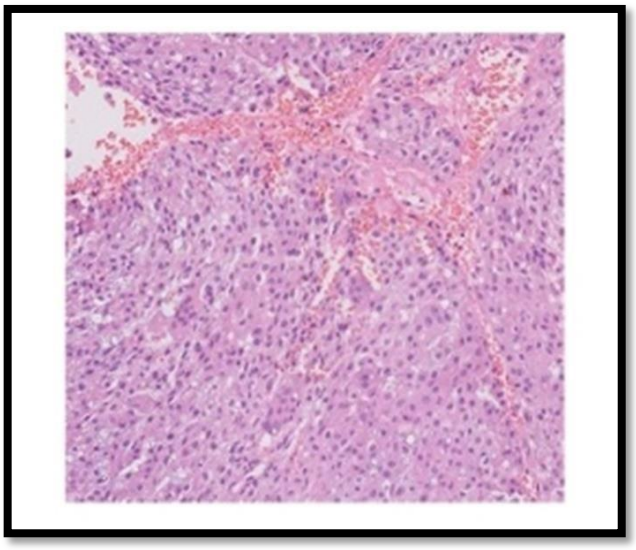


Fig 1.2 Histopathological Images of GCT

- Radionuclide bone malignant growth: An atomic imaging test is utilized to recognize bone illnesses or cancers as well as the reason for agony or irritation.

- X-beams: An indicative test that utilizes electromagnetic energy pillars to make pictures of bone on film.

- Magnetic Reverberation Imaging (X-ray): An indicative system that utilizes huge magnets, radio frequencies, and a PC to address definite pictures of cells.

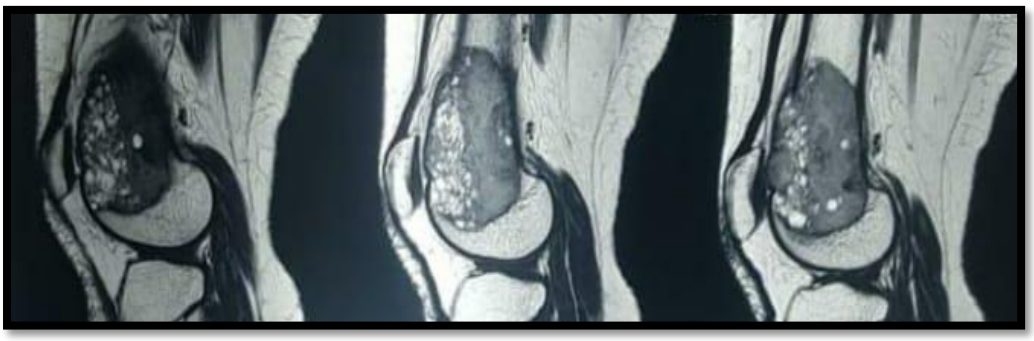


Fig 1.3: MRI Scan representing the GCT in knee region

1.5 WHAT IS THE LIVING PROOF OF DETECTION OF THE GCT?

There are many indicating genes that are liable for the goliath cell growth, some of the genes which are involved are

- *H3F3A / H3F3B*
- *IDH1/IDH2*
- *ZNF687*

1.5.1How do these genes involve clinically?

H3F3A/H3F3B: The H3F3A quality is simply limited to the stromal cell population rather than the osteoclast ancestry cells, indicating that GCT is a mesenchymal neoplasm. Specifically, H3.3 changes were observed among various bone cancers, emphasising the importance of genotyping growths for analytic purposes. Typically, for the same, a biopsy is performed first, followed by DNA Extraction, Genetic Screening, and Allele-Specific Sequencing. The evidence from the literature supports the presence of two heterozygous p. Gly34Trp mutations in the H3F3A gene, with no changes in other coding regions.

IDHI1 and IDH2: Isocitrate dehydrogenase (IDH) is an enzyme that catalyses the oxidative carboxylation of isocitrate to ketoglutarate. The presence of IDH2 R172S mutations in osteosarcomas has been demonstrated using MsMab-1 mAb and direct DNA sequencing. According to the analysis of some samples, 65 percent (approx.) of the GCTB has IDH mutations, whereas GCTB accounts for about 20 percent (approx.) of the typically essential bone cancer in adults. It has also been discovered that somatic IDH2 mutations at the R172 or R140 codon result in extremely high levels of 2-HG production. This is the most common IDH mutation in osteosarcomas (IDH2-R172S).

ZNF687: The ZNF687 is detected in most tissues, including bone, using real-time PCR. ZNF687 contains an amino acid sequence between 938 and 954, according to bioinformatic analysis. With arginine substitutions at positions 937 and 938, ZNF687 may be nuclear imported more effectively.

c.2810C>G mutations were also found in 0.3 percent and 0.6 percent (approximately) of two large cohorts of unrelated people from different ethnic backgrounds.

1.6 CLASSIFICATION:

They are separated into three kinds in view of qualities like Stage I - dormant, Stage II - dynamic, and Stage III - forceful. The developments, both fundamental and discontinuous, are assessed radiographically utilizing the task's Grade I, Grade II, Grade II with crack, and Grade III orders.

- Grade I sickness has a well-marginated breaking point of a dainty edge of mature bone, and the cortex is pure or genuinely diminished in any case not twisted
- Grade II disease has commonly obvious edges yet no radiopaque edge, the united cortex and edge of responsive bone is genuinely petite and fairly broaden but simultaneously present. Grade II bruises with a break are assessed freely

- Grade III relegates a disease with fleecy lines, suggesting a fast and possibly permeative turn of events; the development enlarges into the sensitive tissues, but the fragile tissue mass doesn't follow the type of the bone and isn't confined by a clear shell of open bone

1.7 TREATMENT:

On account of GCT of the bone, resection is one of the treatment choices. The utilization of compound or actual adjuvants, for example, fluid nitrogen, acrylic concrete, phenol, hydrogen peroxide, privately directed chemotherapy, or radiation treatment, to work on their surgery

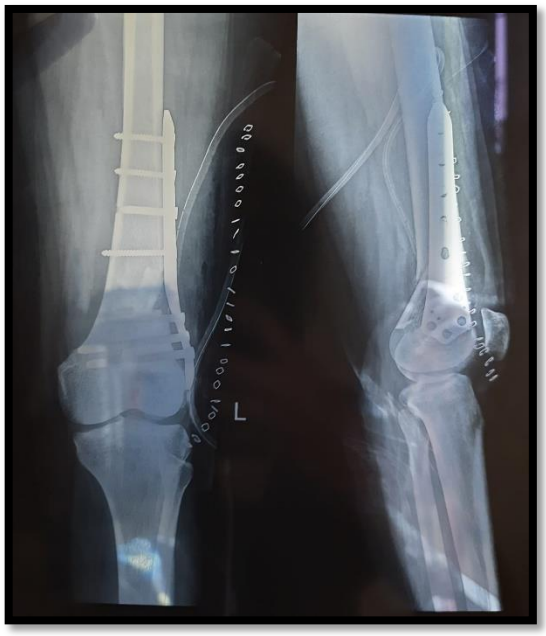


Fig 1.4. Left Distal Femur giant cell tumor (GCT) treated with curettage with bone graft (allograft) with platting (post-op AP view; post-op lateral view).

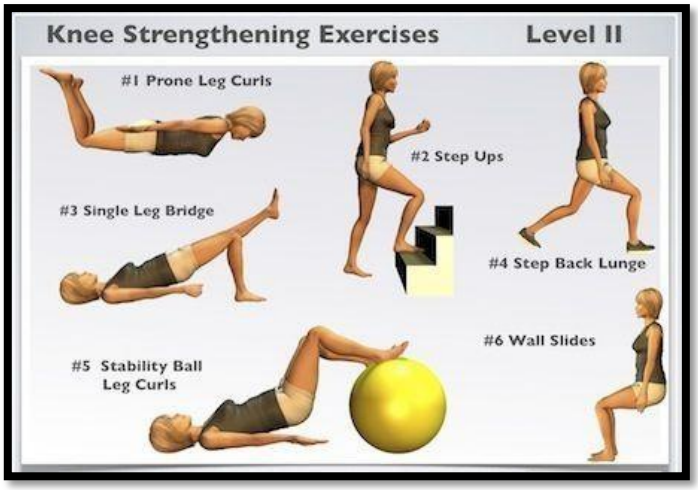


Fig 1.5 Physiotherapy for post-op

(https://i.pinimg.com/originals/36/0e/71/360e71ba77c5a82955a2e3b48a59947c.jpg)

1.8 REVIEW OF LITERATURE:

The distal femur and proximal tibia are normal locations for GCTB events. Its display is frequently proclaimed by torment, enlarging, and an inability to bear eight of the involved limits. GCTB is most common in people between the ages of two and four, but it can occur in older patients as well. The treatment strategy for GCTB is medical procedure. Careful administration has essentially improved over the long haul with the utilisation of cutting-edge imaging to better take into account worked on careful preparation and remaking. The use of adjuvant treatments has aided in decreasing neighbourhood repeat while attempting to keep up with undeniable level appendage capability. (Errani C, Ruggieri P- Cancer Treat Rev2010) ; (Gortzak Y J Bone Joint Surg Br 2010). GCT accounts for 5% of all essential bone cancers and 20% of all harmless skeletal cancers. (. Turcotte RE. Giant cell tumor of bone Orthop Clin North Am 2006, Turcotte RE Clin Orthop Relat Res 2002, Arnold RT RadioGraphics 2011). There is an unusually high prevalence in southern India and China, where GCT treats 20% of all essential bone cancers. When GCT occurs near a joint, it may mimic the tension disintegrations seen in a joint-focused interaction, such as pigmented villonodular synovitis or synovial chondromatosis. GCT of the spine and sacrum is uncommon, accounting for less than 3% of all cases. (Kwon JW - MRI findings of giant cell tumors of the spine 2007, Shankman S - Giant cell tumor of the ischium 1998)

CHAPTER 2

OBJECTIVE

The goal is to break down the ordinary human qualities with the sarcoma qualities and to take the protein connection and decide the most grounded association for the treatment interaction. In this way, the bioinformatics apparatus utilized is PyRx.

PyRX
It is a Virtual Evaluating programming for Computational Prescription Divulgence, that is used to screen libraries of blends against conceivable cure targets. PyRx enables Solid Physicists to run Virtual Screening from any stage and helps clients in each step - from data mean work convenience and assessment of results.

The primary goal is to figure out the limiting proclivity for protein-ligand docking between three receptors and three ligands and to dissect the association.

Different apparatuses are utilized like Fabrication, PyMol which eliminates the non-polar hydrogen particles and water atoms and deposits and save it as PDB record for sub-atomic docking

Chimera: To eliminate the buildups, iotas
PyMol: To eliminate the water particles and the non-polar Hydrogen molecules

CHAPTER 3

MATERIALS AND METHODOLOGY

3.1 MATERIALS:

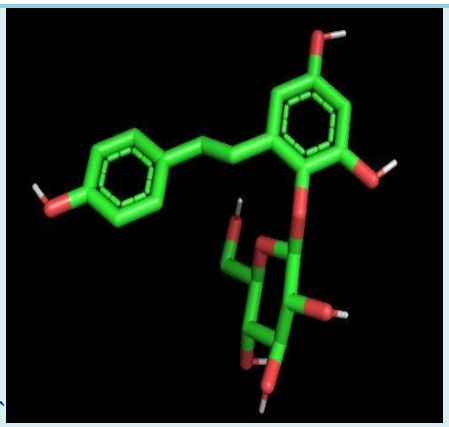
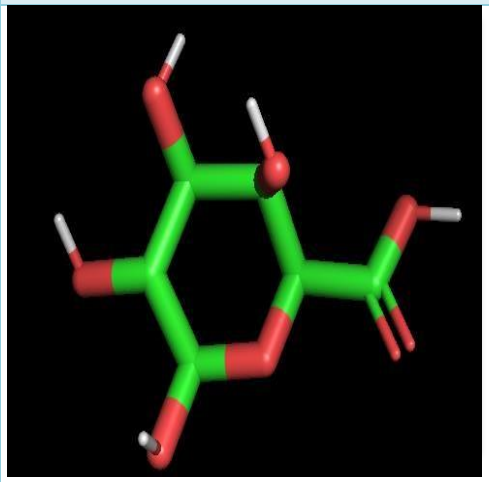
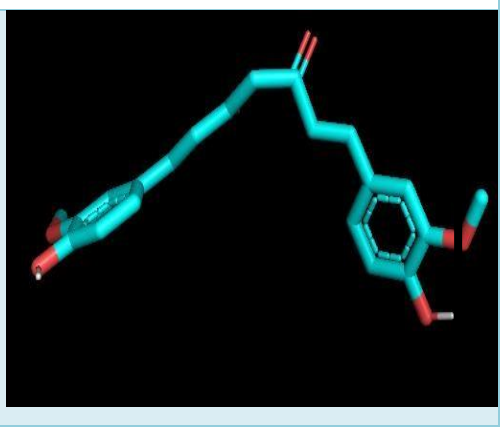
The evidences used to validate the protein-protein interaction are as follows:3 Ligands (plant based phytochemical ligand); 3 Receptors (A Precision CSF1R Therapy for Tenosynovial Giant Cell Tumors), Chimera, PyMol and PyRx.

3.1.1 Ligands:

The ligands are taken from the plant-based Vegetables (a class of vegetables incorporates beans, peas and lentils) and ginger which are the most versatile and nutritious food sources open. Vegetables are low fat, no cholesterol and are wealthy in Folate, Potassium, Iron and Magnesium and including insoluble fats. Ginger is one of the fixings most usually utilized as a flavor for culinary reason as well as restorative reason.

Phytochemicals have exceptional malignant growth avoidance specialist potential and are of fantastic interest due to their beneficial effects on prosperity of individuals, and they give huge clinical benefits to the purchasers.

Table 3.1 Antioxidant-rich phytochemicals with their food and health benefits

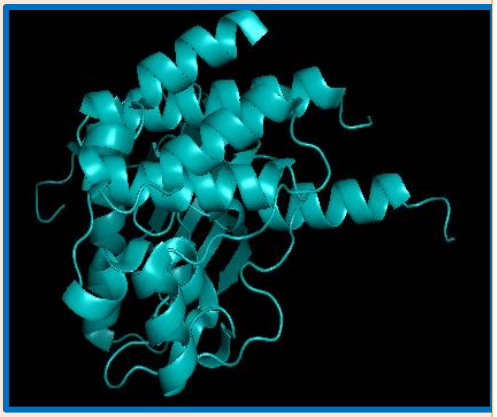
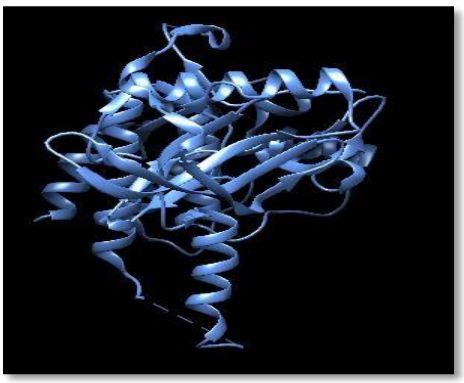
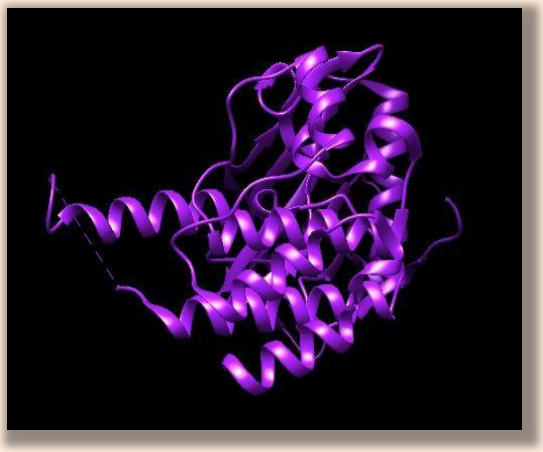
S No.	Phytochemicals	Source	Health Benefits	Figures (3D Structures)
1.	Polyphenols ➢ Flavonoids ➢ Isoflavonoids ➢ Anthocyanidins	Fruits, vegetables, cereals, beverages, chocolates, oil seeds	Action against free radicals, mediated cellular signaling, inflammation etc.	
2.	Polysaccharides	Fruits and vegetables	Antimicrobial, Antiallergic, anti-inflammatory, enhances defense mechanism	
3.	Curcumin	Ginger	Anti-inflammatory,nti-oxidant,antimicrobial and chemo-preventive characteristics of ginger against different types of cancer	

3.1.2 Receptors:

Receptors are protein-based substance structures that get and send signals that can be incorporated into organic frameworks. Receptors are proteins, normally found on cell surfaces, that tight spot to ligands and cause responses in the safe framework

The receptor chosen is CSF1R, and are formulated into the tabular column:

3.2 Receptors and the structure summary

S No.	RECEPTOR NAME	STRCTURE SUMMARY	PYMOL STRCTURE
1.	Vimseltinib: A Precision CSF1R Therapy for Ten synovial Giant Cell Tumor.	PDB ID: 7MFC Crystal structure of SCF1R in complex with Vimseltinib Transferase Inhibitor *Homo sapiens* Trichoplusia ni Yes	`` 
2.	Structure-Guided Blockade of CSF1R Kinase in Ten synovial Giant Cell Tumor	PDB ID: 4R7H Crystal structure of FMS KINASE domain with a small molecule inhibitor, PLX339 Transferase inhibitor *Homo sapiens* Spodoptera frugiperda Yes	
3.	Structure-Guided Blockade of CSF1R Kinase in Ten synovial Giant Cell Tumor	PDB ID: 4R7I Crystal Structure of FMS kinase domain with a small molecular inhibitor, GLEEVEC Transferase Inhibitor *Homo sapiens* Spodoptera frugiperda Yes	

3.1.3 UCSF CHIMERA:

Delusion at UCSF is a program for insightful discernment and examination of subatomic plans and related data, for example, thickness guides, bearings, and progression courses of action. It is allowed to use for non-commercial purposes.

3.1.4 PYMOL:

PyMOL is one of only a few exceptional open-source model representation devices available for use in fundamental science. The Py part of the item's name implies the Program being in the Python language.

3.1.5 PYRX:

PyRx is a Computational Medication Disclosure Virtual Screening programme that can be used to screen libraries of mixtures against potential medication targets. PyRx enables Restorative Physicists to run Virtual Screening from any stage and assists clients at every stage of this cycle - from information arrangement to work accommodation and outcome evaluation.

CHAPTER 4

METHODOLOGY

The methodology starts with the collection of three receptors and three ligands, and using the RCSB website to get the PDB format for the receptors and Pubchem to get the 3D structures of the ligands an save it in sdf format.

Tool 1: UCSF Chimera

To get the receptors and saving the file in the .pdb format

PROCEDURE:

- Open UCSF Chimer tool
- Open the 3D structure of given receptors (Ex. Polyphenols, Polysaccharides and Curcumin)
- Remove the residues
  - Click Select -> Residue -> HOH
  - Click Action ->Atoms / Bonds -> Delete
  - Click Select -> Residue -> Select the given residue
  - Click Action -> Atoms/Bonds -> Delete
- Save as .pdb
  - Click File -> Save PDB -> Dialogue box opens -> Save as Receptor 1.pdb -> Click save

This method is followed for the other two receptors. (*Refer Table 3.1 for 3D Fig)*

Tool 2: PyMol

PROCEDURE:

- Open PyMol
- Click on File -> Open -> Select the PDB Id for the given Ligand (Ex. 7MFC)

- In 7mfc name panel -> Click on Action -> Remove Water molecules
- Again, in 7mfc name panel -> Click on Action -> Click on Hydrogen -> Remove non polar.
- Click on file -> Export Molecule -> Save Molecule dialogue box opens -> Save -> Save as type -> .pdb file -> Ligand 1.pdb -> Save

Hence the ligand is saved in the pdb format and for the other ligands the same procedure has been followed *(Refer 3.2 table for the figure)*

TOOL 3: PyRX

PROCEDURE:

1. Processing of the protein molecule

(i) Preprocessing is complete with the assistance of discovery studio visualizer

(ii) Remove the molecules from the protein

(iii) Remove ligands that are nearly present within the binding sites

2. Preparation of macromolecule

(i) Load the preprocessed protein in PyRx software

(ii) Right click on the macromolecule then choose autodock, choose macromolecule, this protects, enter the pdbqt format

3. Preparation of ligands

(i) Import the library from the visual wizard

(ii) Minimize energy by selecting Reduce All by right clicking on one of these compounds

(iii) After minimizing, right click again on the compounds and select Convert All to file pdbqt ligand

4. Screening Process

(i) Select the number of ligands to be anchored

(ii) Then proceed to set up the grid box covering the binding site

The software performs the docking for each ligand when it's selected

Similarly for the other ligands and receptors are done to get the binding affinity.

CHAPTER 5

RESULTS

The results are going to display at the rock bottom where, the finding of the binding energies of various conformations of the ligands that were docked to simplest protein-ligand docked pose

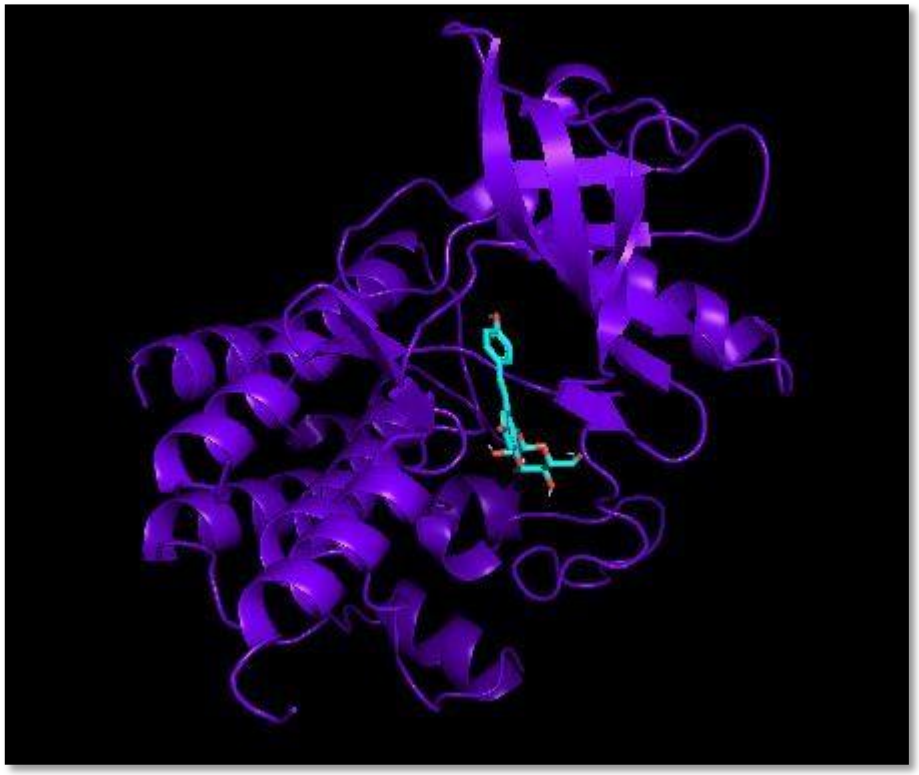


Fig. 5.1(a) The image of CSF1R receptor with Polyphenols

Fig5.1(b) The table representation of Receptor_ligand_1_uff_E=287.67 binding affinity

Ligand	Binding Affinity (Kcal/mol)	Mode	RMSD lower bound	RMSD upper bound

Receptor_Ligand_1_uff_E=287.67	-7.8	0	0.0	0.0
Receptor_Ligand_1_uff_E=287.67	-7.5	1	10.146	14.053
Receptor_Ligand_1_uff_E=287.67	-7.5	2	0.886	2.516
Receptor_Ligand_1_uff_E=287.67	-7.4	3	11.121	16.462
Receptor_Ligand_1_uff_E=287.67	-7.4	4	2.721	5.687
Receptor_Ligand_1_uff_E=287.67	-7.3	5	10.048	15.472
Receptor_Ligand_1_uff_E=287.67	-7.2	6	8.796	11.716
Receptor_Ligand_1_uff_E=287.67	-7.1	7	11.356	16.559
Receptor_Ligand_1_uff_E=287.67	-7.1	8	3.319	5.98

In this the binding affinity between the interaction of Receptor CSF1R and Polyphenols. By comparing all the binding affinity this is the strongest binding

Receptor_Ligand_1_uff_E=287.67	-7.5	1	10.146	14.053

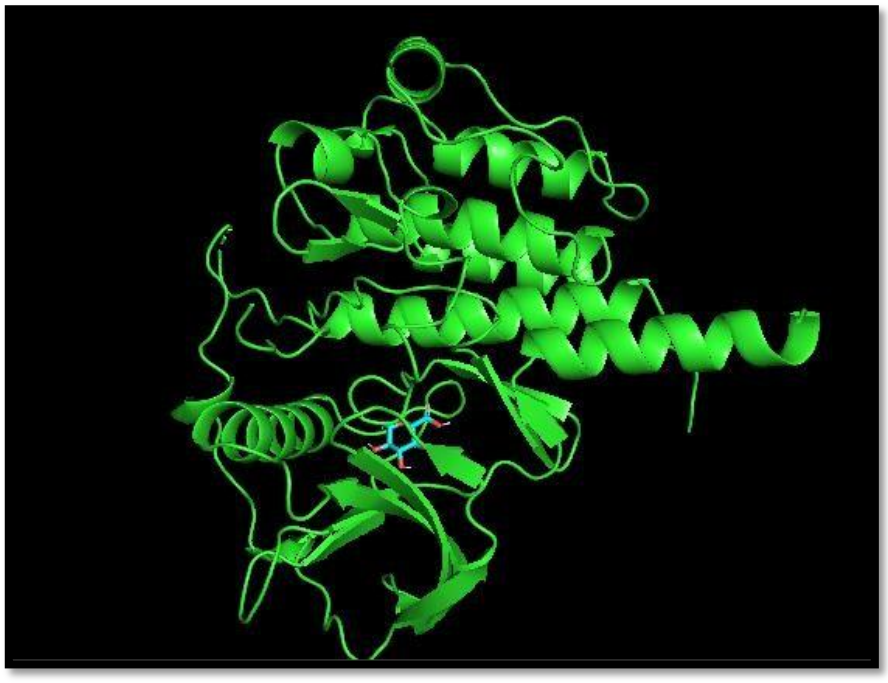


Fig 5.2 (a) The image of CSF1R receptor with polysaccharides

Table 5.2 (b) The table representation of Receptor_2_ligand_2_uff_E=99.34 binding affinity

Ligand	Binding Affinity (Kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
Receptor_2_Ligand_2_uff_E=99.34	**-6.1**	**0**	**0.0**	**0.0**
Receptor_2_Ligand_2_uff_E=99.34	**-5.9**	**1**	**11.97**	**13.076**
Receptor_2_Ligand_2_uff_E=99.34	**-5.5**	**2**	**9.88**	**11.46**
Receptor_2_Ligand_2_uff_E=99.34	**-5.2**	**3**	**12.941**	**14.319**
Receptor_2_Ligand_2_uff_E=99.34	**-5.2**	**4**	**21.664**	**23.747**
Receptor_2_Ligand_2_uff_E=99.34	**-5.1**	**5**	**22.408**	**24.5**
Receptor_2_Ligand_2_uff_E=99.34	**-5.1**	**6**	**11.688**	**14.528**
Receptor_2_Ligand_2_uff_E=99.34	**-5.1**	**7**	**10.234**	**12.157**
Receptor_2_Ligand_2_uff_E=99.34	**-5.0**	**8**	**10.015**	**11.457**

In this the binding affinity between the interaction of Receptor CSF1R and Polysaccharides. By comparing all the binding affinity this is the strongest binding

Receptor_2_Ligand_2_uff_E=99.34	-5.9	1	11.97	13.076

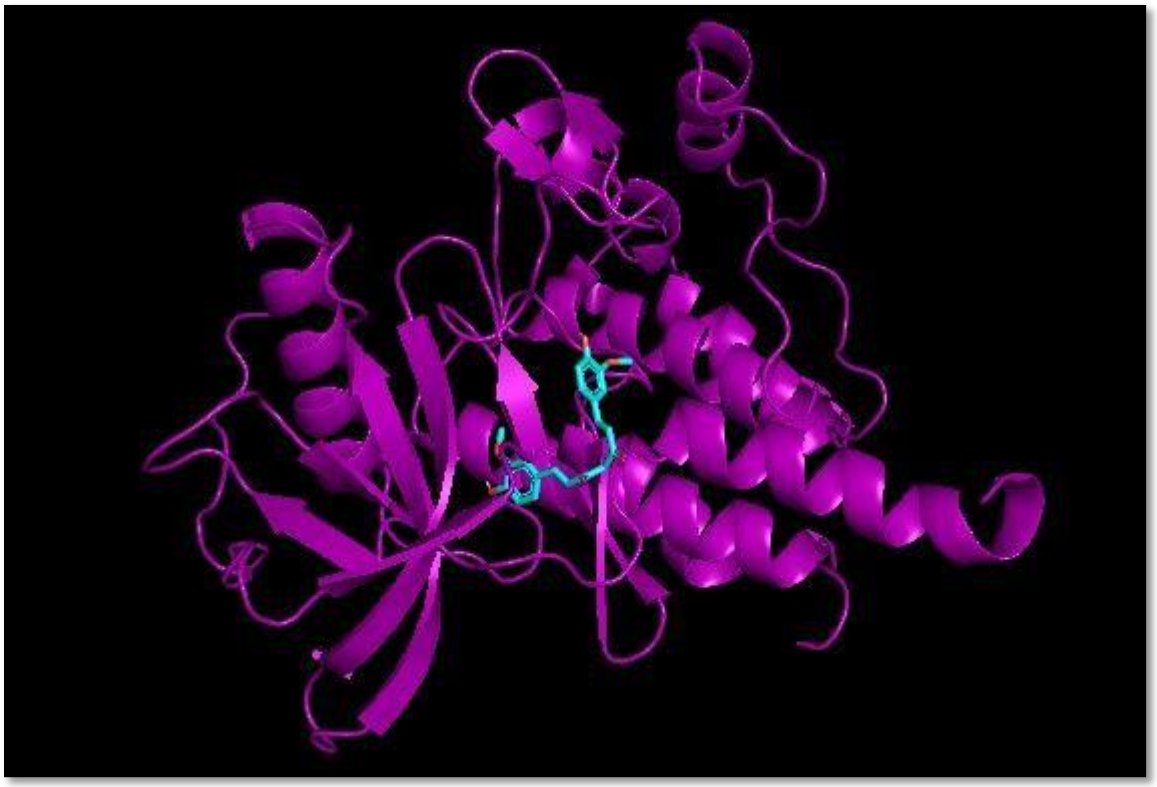


Fig 5.3 (a) The image of CSF1R receptor with Curcumin

Fig 5.3 (b) The table representation of Receptor_3_ligand_3_uff_E=189.08 binding affinity

Ligand	Binding Affinity (Kcal/Mol)	Mode	RMSD lower bound	RMSD upper bound
Receptor_3_Ligand_3_uff_E=189.08	-6.6	8	20.554	24.48
Receptor_3_Ligand_3_uff_E=189.08	-6.6	7	20.293	24.05
Receptor_3_Ligand_3_uff_E=189.08	-6.6	6	3.237	8.504
Receptor_3_Ligand_3_uff_E=189.08	-6.9	5	3.551	10.59
Receptor_3_Ligand_3_uff_E=189.08	-7.0	4	5.86	7.859
Receptor_3_Ligand_3_uff_E=189.08	-7.2	3	4.691	6.677
Receptor_3_Ligand_3_uff_E=189.08	-7.7	2	3.355	10.465
Receptor_3_Ligand_3_uff_E=189.08	-7.8	1	2.048	3.23
Receptor_3_Ligand_3_uff_E=189.08	-7.9	0	0.0	0.0

In this the binding affinity between the interaction of Receptor CSF1R and Polysaccharides. By comparing all the binding affinity this is the strongest binding affinity

Receptor_3_Ligand_3_uff_E=189.08	**-7.8**	**1**	**2.048**	**3.23**

CHAPTER 6
DISCUSSION

The speed of emptied cells and sensitive tissues is close in other respects. Histological similarities probably indicate surprising connections. This is due to the fact that both developments are represented by an amazing number of long osteoclast Goliath cells and histiocytic mononuclear cells. In both progressions, the monocytes appeared to be completely osteoblasts. Both sometimes have abundant vascular systems and may show marked solid metaplasia. H3F3A Gly34 is mutated in Goliath cell disease and we resolved the genetic link between these two new developments by genotyping H3F3A grade sensitive tissue cohorts. None of the 15 Goliath malignancies in vulnerable tissues qualified for class H3F3A, indicating differences between these types of genetic amplification. Of the Gly34 codons of all H3 histone proteins (encoded as GGG, GGC, or GGT), only those with the GGG set are kind enough to completely replace tryptophan (encoded as TGG) with specific nucleotide substitutions. The idea that Goliath cells pose a threat to improvement has its limits. However, the presence of unmixed non-tumor cells (e.g., Goliath osteoclast cells) was unavoidable, despite difficult assessments to promote pain-amplifying tissue and attention could be paid to confirming changes by Sanger sequencing. Second, because HIST2H3A and HIST2H3C clones have unclear coding and extended development and thus share a similar set of keys, the sensitivity to see changes in the two qualities differs from the sensitivity of reduced sensitivity. Finally, disease remnants in sensitive animal tissues may adopt other histone protein disturbances or factors involved in epigenetic pathways, leading to strong bending of subnuclear junctions.

CHAPTER 7

CONCLUSION

Taken together, the researchers isolated the H3F3A genotype and other similar variants of histone H3 from 15 tissues sensitive to Goliath cell growth. The findings suggested that the development of goliath cells in sensitive tissues cannot be genetically distinguished from major partners and that these two types of risky development are best viewed as distinct entities. Further studies are expected to reveal the pathogenesis of soft tissue Goliath cell disease.

CHAPTER 8

ABBREVIATION

- GCT: Giant Cell Tumor
- H3F3A/H3F3B: Histone H3.3 protein
- IDH1/IDH2: Isocitrate dehydrogenase 1/ Isocitrate dehydrogenase 2
- ZNF687: Zinc Finger protein 687
- RANKLs: Receptor activator of nuclear factor kappa-B ligand
- MRI: Magnetic Resonance Imaging
- PCR: Polymerase Chain Reaction
- Post-op: Post Operative
- GCTB: Giant Cell Tumor of the bone
- CSF1R: Colony Stimulating Factor 1 Receptor
- PDB: Protein Data Bank
- RMSD: Root Mean Square Deviation
- HIST2H3A: Histone Cluster 2 H3 family member
- HIST2H3C: Histone Cluster 2 H3 family member

CHAPTER 9

REFERENCES

1. (2013). Clinical practice. Paget's disease of bone. N. Engl. J. Med. 368, 644–650.

2. Roodman, G.D., and Windle, J.J. (2005). Paget disease of bone. J. Clin. Invest. 115, 200–208.

3. Whyte, M.P. (2006). Clinical practice. Paget's disease of bone. N. Engl. J. Med. 355,593–600.

4. Cowan RW, Singh G. Giant cell tumor of bone: a basic science perspective. *Bone.* 2013;52:238–46

5. Czerniak B. Giant cell lesions. In: Czerniak B, editor. Dorfman and Czerniak's bone tumors. 2nd edn. Philadelphia: Elsevier; 2016. p. 692–759.

6. Athanasou NA, Bansal M, Forsyth R, Reid RP, Sapi Z. Giant cell tumour of bone. In: Fletcher CD, Bridge J, Hogendoorn P, et al. editors. Pathology and genetics of tumours of soft tissue and bone. 4th edn. Lyon: IARC Press; 2013. p. 321–4.

7. Campanacci M, Baldini N, Boriani S, Sudanese A. Giant-cell tumour of bone. J Bone Joint Surg Am. 1987;69:106–14.

8. Behjati S, Tarpey PS, Presneau N, Scheipl S, Pillay N, Van Loo P, et al. Distinct H3F3A and H3F3B driver mutations define chondroblastoma and giant cell tumour of bone. Nat Genet. 2013;45:1479–82.

9. Turcotte RE. Giant cell tumor of bone. *Orthop Clin North Am.* 2006;37(1):35–51.

10. Eckardt JJ, Grogan TJ. Giant cell tumor of bone. *Clin Orthop Relat Res.* 1986;204(2):45–58.

11. Desai D, Pandith S, Jeergal PA, Arathi K, Saini R. Fibroblastic variant of osteosarcoma: a challenge in diagnosis & management. Open Dent J 2010;4: 211–217.

12. Kwon JW, Chung HW, Cho EY, et al. MRI findings of giant cell tumors of the spine. AJR Am J Roentgenol 2007;189(1):246–250.

13. Shankman S, Greenspan A, Klein MJ, Lewis MM. Giant cell tumor of the ischium: a report of two cases and review of the literature. Skeletal Radiol 1988;17(1):46–51.
14. Farsad K, Kattapuram SV, Sacknoff R, Ono J, Nielsen GP. Sacral chordoma. RadioGraphics 2009; 29(5):1525–1530.
15. Cooper AS, Travers B. Surgical essays. London, England: Cox Longman & Co, 1818; 178–179. 2. Balke M, Schremper L, Gebert C, et al. Giant cell tumor of bone: treatment and outcome of 214 cases. J Cancer Res Clin Oncol 2008;134(9):969–978
16. Turcotte RE. Giant cell tumor of bone. Orthop Clin North Am 2006;37(1):35–51.
17. Arnold RT, van Holsbeeck MT, Mayer TG, Mott MP, Koch SR. Necrotic giant cell tumor of bone manifesting with pathologic fracture. RadioGraphics 2011;31(1):93–98.
18. Turcotte RE, Wunder JS, Isler MH, et al. Giant cell tumor of long bone: a Canadian Sarcoma Group study. Clin Orthop Relat Res 2002;(397):248–258.
19. Behjati S, Tarpey PS, Presneau N, et al. Distinct H3F3A and H3F3B driver mutations define chondroblastoma and giant cell tumor of bone. Nat Genet 2013;45: 1479–1482.
20. Cleven AH, Hocker S, Briaire-de Bruijn I, et al. Mutation analysis of H3F3A and H3F3B as a diagnostic tool for giant cell tumor of bone and chondroblastoma. Am J Surg Pathol 2015;39:1576–1583.
21. Guo H, Garcia RA, Perle MA, et al. Giant cell tumor of soft tissue with pulmonary metastases: pathologic and cytogenetic study. Pediatr Dev Pathol 2005;8:718–724.
22. 6 Kovacs G, Muller-Brechlin R, Szucs S. Telomeric association in two human renal tumors. Cancer Genet Cytogenet 1987;28:363–366.
23. Sawyer JR, Roloson GJ, Bell JM, et al. Telomeric associations in the progression of chromosome aberrations in pediatric solid tumors. Cancer Genet Cytogenet 1996;90:1–13.
24. Paz-y-Mino C, Sanchez ME, Del Pozo M, et al. Telomeric association in women with breast and uterine cervix cancer. Cancer Genet Cytogenet 1997;98:115–118.
25. Gortzak Y, Kandel R, Deheshi B, et al. The efficacy of chemical adjuvants on giant-cell tumour of bone. An in vitro study. J Bone Joint Surg Br 2010;92(10):1475–1479

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