A
MASTERS RESEARCH PROJECT REPORT
ON
PHARMACOPHORE MODELING FOR LEUKEMIA

By

Mahesh Sharma

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A MASTERS RESEARCH PROJECT REPORT ON PHARMACOPHORE MODELING FOR LEUKEMIA

SIKKIM MANIPAL UNIVERSITY

MASTERS IN BIOINFORMATICS

DIRECTOR
WEB UNIV.

GUIDE
PRADYUT KRUMAR MOHANTY

DEDICATION

The support, patience and encouragement which were rendered by my family members were valuable and will be always remembered. Moreover, I am very much thankful to all my friends for their timely support during my dissertation.

Finally, I would like to thank my University for giving me the opportunity to complete this project work as a pleasure in my whole life.

DECLARATION

I AM MAHESH SHARMA HERE BY DECLARE THAT THE WORK DONE IN THE PROJECT " PHARMACOPHORE MODELING FOR LEUKMIA " BY ME AND this is not published and submitted at any other university or copy FROM ANY OTHER resource

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CERTIFICATE

This is to certify that I (MAHESH SHARMA) student of M.Sc. Bioinformatics 4th semester have carried out project PHARMACOPHORE MODELING FOR LEUKEMIA, at web univ, south ext . This is being submitted as minor project for the 4th semester of M.Sc Bioinformatics fulfill of requirement of M.Sc. BI .

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Sign. of Project Guide	**Sign. of Candidate**
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First of all I thanking to my family for their support to carryout the project and I thank to my institute that they permit me to this project work and thank to all my friends for their kind help during this project.

With the blessing of almighty ishwar and his grace I thank to my teachers for helping to overcome difficulties during this project.

At the outset, I express my sincere thank to my project guide Mr. Pradyut Kumar Mohanty for valuable Guidance, help and encouragement to complete this dissertation successfully.

I thank to all the people knowingly or unknowingly assisting in this project work.

MAHESH SHARMA

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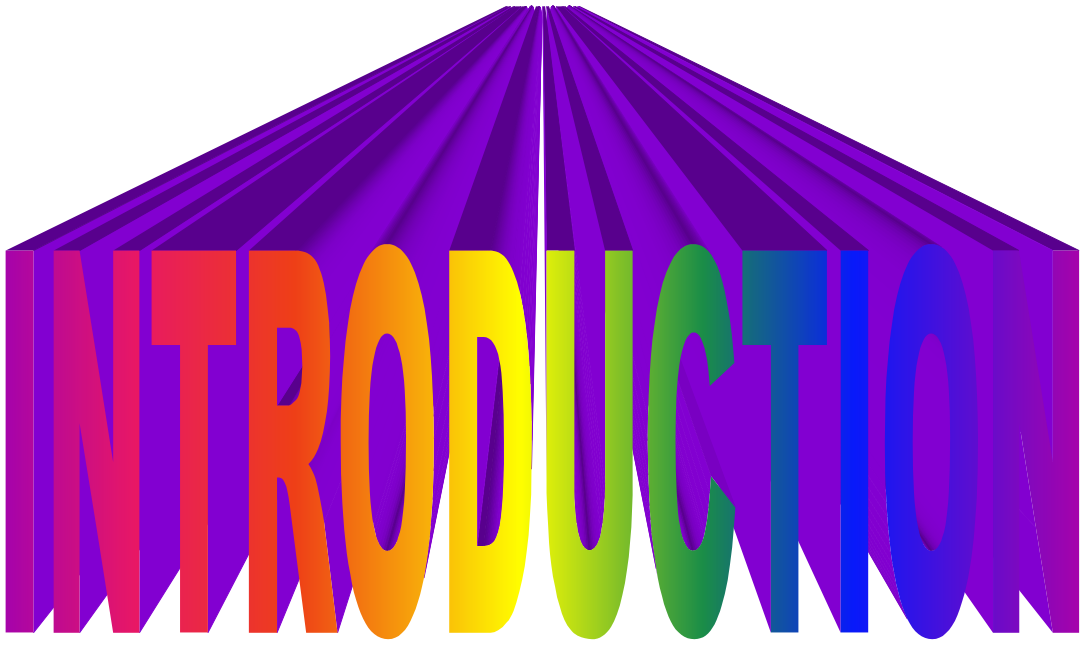

INTRODUCTION

INTRODUCTION

In this advanced age of the genomics and proteomics there are many more complications are also present. and now we can relate all the complications to there genetic levels. and this very interesting that we found the various relation of the complication to their genetic constitution.

In this project work we are concentrating on the leukemia which is the very advanced complication in this time and the work entitled to the pharmacophore modeling. that is the main part for the drug design for the diagnosis and the cure of the disease. this is the disease that is cause due to the metabolic imbalance or we can say that the some change in the genetic constitution.

A pharmacophore is a specific, three dimensional map of biological properties common to all active conformations of a set of ligands which exhibit a particular activity. conceptually, a pharmacophore is a distillation of the functional attributes of ligands which accomplish a specific task. pharmacophores are conceptual templates for drug design. once it is extracted from a set of ligands, a pharmacophore can be used as a model for the design of other molecules that can accomplish the same activity. for example, consider the inhibitors of thermolysin in the following figure. these small molecules have between 5 and 11 torsional degress of freedom,

generating a few hundred distinct, low energy conformations. of these configurations, only a handful are functionally active in the inhibition of thermolysin. the pharmacophore, a 3 to 5 point abstraction, must be congruent to the functional components of at least one active conformation for each inhibitor, in order to represent the entire set.

So due to this work we are now concentrating on the work o the pharmacophore modeling or we can say that pharmacophore analysis. in this project work we are limited the work to the modeling the pharmacophore on the basis of the software called ligand scout. and we are just studying the five protein that are related to the leukemia and just analyse the pharmacophore on the basis of the receptor and discuss it on the report the property of the ligand compounds.


ABOUT LEUKEMIA

ABOUT LEUKEMIA

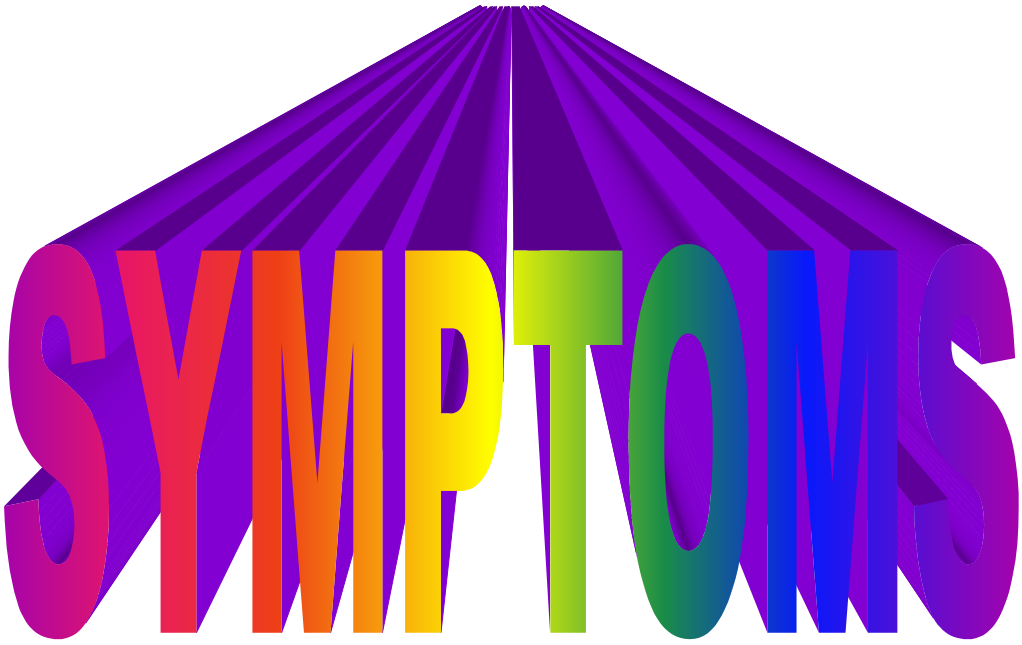
Leukemia, any of several types of cancers that affect blood cells, including oxygen-carrying red cells; certain infection-fighting white cells, such as granulocytes, macrophages and lymphocytes; and platelets, which aid in blood clotting. According to the American Cancer Society, leukemia is the sixth leading cause of cancer deaths among men and the seventh leading cause of cancer deaths among women. Each year in the United States about 31,000 new cases of leukemia are diagnosed and the disease causes an estimated 22,000 deaths. It accounts for about one-third of all cancers in children under age 15.

Blood cells are made in the bone marrow, the spongy tissue in the center of bones. A leukemia begins when an immature blood cell in the marrow, known as a progenitor cell, becomes cancerous, dividing uncontrollably and overriding the body's normal restrictions on cell division. Over time, the marrow becomes crowded with cancerous cells, all of them descendants of the first abnormal cell. The malignant cells may also accumulate in a patient's lymph nodes, spleen, and elsewhere. At the time of diagnosis, up to a trillion leukemic cells may be present in the body.

The mass of leukemic cells in the marrow suppresses the production of healthy blood cells, giving rise to the symptoms typical of leukemia.

Pale skin, fatigue, and shortness of breath are signs of anemia, a decrease in the concentration of red cells in the blood. Nose bleeds, gum bleeding, a tendency to bruise easily, and pinhead-sized red spots on the skin reflect the decrease in the concentration of platelets in the blood. A lack of functional white cells makes patients with leukemia prone to infection.

Leukemia was first described by European physicians during the mid-19th century. During autopsies, physicians noted cases of profoundly elevated white cell counts—today we know that many of these white cells were nonfunctional leukemic cells—and very low red cell counts. For this reason, the condition was referred to as weisses blut (German for “white blood”). Later, the term leukemia (Greek leukos, “white”; haima, “blood”) was applied to the disease.


SYMPTOMS

SYMPTOMS

Damage to the bone marrow, by way of displacing the normal bone marrow cells with higher numbers of immature white blood cells, results in a lack of blood platelets, which are important in the blood clotting process. This means people with leukemia may become bruised, bleed excessively, or develop pinprick bleeds (petechiae).

White blood cells, which are involved in fighting pathogens, may be suppressed or dysfunctional. This could cause the patient's immune system to be unable to fight off a simple infection or to start attacking other body cells.

Finally, the red blood cell deficiency leads to anemia, which may cause dyspnea. All symptoms can be attributed to other diseases; for diagnosis, blood tests and a bone marrow examination are required.

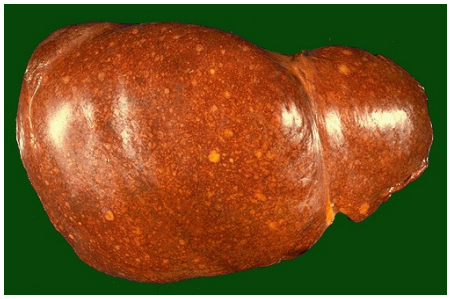
Some other related symptoms:

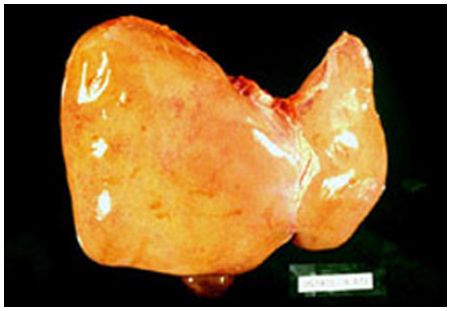
- Fever, chills, night sweats and other flu-like symptoms
- Weakness and fatigue
- Frequent mood swings[citation needed]
- Loss of appetite and/or weight
- Swollen or bleeding gums
- Neurological symptoms (headache)
- Enlarged liver and spleen
- Frequent infection
- Bone pain
- Joint pain

- Dizziness
- Swollen tonsils

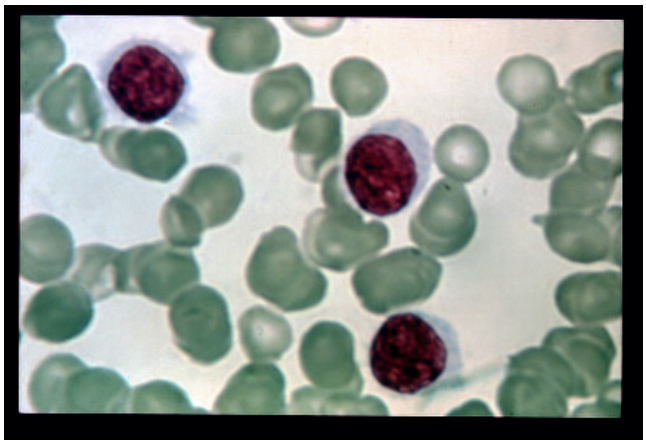
The word leukemia, which means 'white blood', is derived from the disease's namesake high white blood cell counts that most leukemia patients have before treatment. The high number of white blood cells are apparent when a blood sample is viewed under a microscope. Frequently, these extra white blood cells are immature or dysfunctional. The excessive number of cells can also interfere with the normal function of other cells.

Some leukemia patients do not have high white blood cell counts visible during a regular blood count. This less-common condition is called aleukemia. The bone marrow still contains cancerous white blood cells which disrupt the normal production of blood cells. However, the leukemic cells are staying in the marrow instead of entering the bloodstream, where they would be visible in a blood test. For an aleukemic patient, the white blood cell counts in the bloodstream can be normal or low. Aleukemia can occur in any of the four major types of leukemia, and is particularly common in hairy cell leukemia.





- **Enlarged liver and spleen**



- **hairy cell leukemia.**


CAUSES

CAUSES

In most cases of leukemia, the cause is unknown, but physicians have identified four known causes of certain types of leukemia. Intensive radiation exposure or moderately intense exposure for long periods increases the risk of acute and chronic myelocytic leukemia and acute lymphocytic leukemia, but not chronic lymphocytic leukemia. The high rate of leukemia among Japanese survivors of the atomic bomb detonations at Hiroshima and Nagasaki at the end of World War II dramatically demonstrated the role of high-dose radiation in causing leukemia.

In the late 1970s, a study first touched off concern that electromagnetic fields from power lines might be creating an increased cancer risk among children. This article from the July 1997 edition of the Encarta Yearbook reports on the results of a recent large study on this subject, and the continued debate over this issue

Exposure to certain chemicals can also cause leukemia. Workers exposed to benzene over long periods have an increased risk of developing acute myelocytic leukemia. Tobacco smoking appears to increase the incidence of this form of leukemia. Chemotherapy drugs used to treat breast cancer, ovarian cancer, lymphomas, and certain other cancers also increase a patient's risk of later developing acute myelocytic leukemia.

Two viruses, human T-cell leukemia viruses (HTLV) I and II, are known to cause T-cell leukemia, a very rare form of lymphocytic leukemia, in humans. However, only a small percentage of people who are infected with these viruses develop cancer. Although virus-related leukemia is rare in humans, it is quite common in other animal species, such as cats, chickens, and mice.

Genetic factors may also contribute to the development of leukemia. Some inherited conditions, such as Down syndrome, increase a person's risk of developing leukemia. In addition, scientists have identified rare clusters of leukemia in several members of the same family, presumably due to an inherited genetic mutation.

Causing Agent and Risk Factors

1. Benzene exposure
2. Chromosome error
3. Down syndrome
4. Gene therapy causing leukemia like illness
5. Human T-cell leukemia virus
6. Phenytoin
7. Radiation exposure
8. Viruses

Benzene Exposure:

Industrial society has introduced or increased human exposure to thousands of chemicals in the environment. Examples are inorganic materials such as lead, mercury, arsenic, cadmium, and asbestos, and organic substances such as polychlorinated biphenyls (PCBs), vinyl chloride, and the pesticide DDT. Of particular concern is the delayed potential for these chemicals to produce cancer, as in the cases of lung cancer and mesothelioma caused by asbestos, liver cancer caused by vinyl chloride, and leukemia caused by benzene. Minamata disease, caused by food contaminated with mercury, and Yusho disease, from food contaminated with chlorinated furans, are examples of acute toxic illnesses occurring in nonoccupational settings.

CHROMOSOME ERROR:

Humans have 23 pairs of chromosomes, with a diploid number of 46. Scientists number these chromosome pairs according to their size—the largest is chromosome 1 and the smallest is chromosome 23. In human chromosomes, errors may occur that give rise to embryos with more or less genetic material, sometimes resulting in developmental disabilities or health problems. In a process called nondisjunction, paired members of chromosomes fail to separate from one another during meiosis. Nondisjunction can lead to a condition known as Down syndrome, in which a person inherits three copies of chromosome 21. Another

condition that may result from nondisjunction is Turner syndrome, a disorder in which a female inherits only a single X chromosome.

Genetic errors occur if part of a chromosome is either missing or duplicated. Chromosomes sometimes undergo changes called translocations, in which part of one chromosome breaks off and attaches to another chromosome. A translocation involving chromosomes 9 and 22 is linked to a type of leukemia called chronic myelogenic leukemia. On the sex chromosomes, problems arise in men when an abnormal gene is present on the X chromosome. With no healthy gene found on the Y chromosome to override the abnormal gene, disease may result. For example, men who inherit a mutated gene that causes hemophilia from their mother on the X chromosome will develop this bleeding disorder since they are missing a normal version of the gene on their Y chromosome.

DOWN SYNDROME:-

People with Down syndrome are subject to a variety of medical conditions. Heart abnormalities that may require surgery are present in about half of all Down syndrome cases. Thyroid problems (underproduction or overproduction of thyroid hormones) affect 10 to 20 percent of people with Down syndrome, but these problems respond well to treatment. The risk of acute leukemia is somewhat increased, although treatment is successful in the majority of cases.

GENE THERAPY CAUSING LEUKEMIA LIKE ILLNESS:

Although gene therapy offers seemingly limitless possibilities, researchers have been thwarted by many technical problems. There has only been one successful clinical trial using gene therapy—in April 2000 French researchers reported the successful use of gene therapy to treat two female infants with severe combined immunodeficiency disease (SCID), a deadly inherited disease that impairs the immune system. But even this success was marred when each child later developed a rare leukemia-like illness, thought to be a result of gene therapy. Most clinical trials of gene therapy have not resulted in enough improvement in the patient's underlying condition to consider it an unqualified success and to justify treating large numbers of people. The extraordinary potential of gene therapy has also raised alarms among critics who warn that the technology could go too far. They note, for example, that gene therapy could offer wealthy families opportunities for genetic enhancement unavailable to the poor. More troubling still for some critics is gene therapy's potential to narrow the human gene pool, producing unknown, and possibly harmful, consequences.

HUMAN T-CELL LEUKEMIA VIRUS:-

HTLV, or human T-cell leukemia virus, either of two viruses now known to cause certain forms of human blood-cell cancer. HTLV-I and HTLV-II were first identified in the late 1970s. They cause cancer by

attacking the cells known as T lymphocytes, causing the cells to proliferate uncontrollably and to invade various tissues. Both HTLVs are viruses of the retrovirus type, distinguished from other viruses because they code their genetic instructions in RNA instead of DNA molecules. Another retrovirus in 1983 and 1984 was linked with cases of acquired immunodeficiency syndrome, or AIDS, and was tentatively labeled HTLV-III by the U.S. research team that isolated the virus. The French research team that isolated an apparently identical virus, however, objected to this classification, and by common agreement the virus that causes AIDS is now known as the human immunodeficiency virus, or HIV.

PHENYTOIN:-

Patients with impaired liver function, diabetes, or heart disease should use this drug with caution. Although long-term use of phenytoin is common, it may be associated with the development of cancers in the lymphatic system or the bone marrow (leukemia). Pregnant women or those nursing an infant should not take this drug. Children who take it should be monitored with particular care.

RADIATION EXPOSURE:-

Radiation effects biological:

The most important late effect of radiation exposure, however, is an increased incidence of leukemia and other cancers. Statistically

significant increases in leukemia and of cancers of the thyroid, the lung, and the female breast have been demonstrated in populations exposed to relatively high doses (greater than 1 gray).

Radioactive fallout:

Once 90Sr enters the body, part of it is excreted and the remainder is deposited in newly formed bone along with calcium. In young bone the 90Sr and calcium are continually being replaced as the bone grows. In adult bone little replacement occurs; little 90Sr is deposited and its removal is quite slow. The amount of 90Sr remaining in bone depends on the quantities of 90Sr and calcium in the diet during periods of bone growth. The long retention time of 90Sr in bone is the basis for its potential hazard. In animal experiments and in human cases of radium poisoning where sufficient amounts of radioactive material are deposited in bone, a higher incidence of leukemia and bone cancer is seen. Current levels of 90Sr in humans are far too low for such effects to be observed.

VIRUSES:-

HTLV

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RETROVIRUS

The first human retrovirus was discovered in 1980. Known as human T-cell leukemia virus (HTLV), it exists in two forms, HTLV-I and HTLV-II, and appears to cause certain types of lymphoma (cancer of the lymphatic system) and leukemia. In 1983 a third and quite different human retrovirus was discovered in patients suffering from a new immune deficiency disease (an illness that damages the immune system). Initially labeled HTLV-III, it was renamed HIV in 1986 and has since gained worldwide notoriety as the cause of AIDS.


GENETIC CAUSE

GENETIC CAUSES

Genetic Disorders and Family History

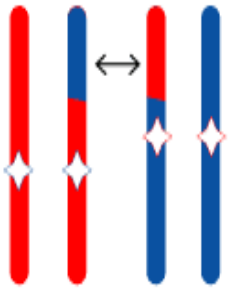
People who have an immediate family member with the disease (children, siblings or parents) are at two to four times greater risk than people with no family history of the disease. For a child whose identical twin develops the disease before six years of age, the risk is 20 to 25 percent higher than in the general population.

Certain genetic disorders also increase the likelihood of developing this cancer. The abnormal chromosomes that cause Down's syndrome, for instance, raise the chance of developing the disease. Damage to chromosomes also occurs in Fanconi's anemia, an inherited bone marrow disorder. As with Down's syndrome, people living with Fanconi's anemia have a higher than normal risk of blood cancer.

Translocation of Chromosomes

Leukemia is sometimes associated with translocation of chromosomes. At its simplest, translocation occurs when a portion of one chromosome switches position with another chromosome. The "Philadelphia" chromosome, which occurs due to a translocation between chromosomes 9 and 22, is often found in cases of chronic myelogenous leukemia (CML). Translocation prevents cells from maturing normally

and gives them a growth advantage over neighboring cells. These immature cells then begin to "crowd out" normal cells.



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DIAGNOSIS

DIAGNOSIS

Once the physician suspects that a patient's blood is abnormal, blood and bone marrow tests are performed to rule out leukemia. Additional tissue samples may be needed to confirm the diagnosis or to help plan treatment

Blood Tests To diagnose leukemia, a number of blood tests are performed. These tests are used to evaluate the type and quantity of blood cells that are present, the blood chemistry, and other factors.

Full blood count—Full blood count is used to establish the numbers of different blood cell types within the circulation. Low numbers of red or white blood cells are described as anemia or leukopenia, respectively. Low numbers of "young" red blood cells (reticulocytes) are described as reticulocytopenia. High leukocyte or reticulocyte counts are called leukocytosis or reticulocytosis, respectively. A lack of mature neutrophils (bacteria-destroying white blood cells) is known as neutropenia or granulocytopenia. Thrombocytopenia is the term used for a low number of blood-clotting platelets, and thrombocytosis refers to a high number of platelets.

Differential blood count—Differential blood count is used to determine the relative proportion of blood cell types within the bloodstream. In particular, the percentage of immature leukemic "blast" cells is noted. People with acute leukemia (either acute lymphocytic leukemia [ALL]

or acute myelogenous leukemia [AML]) often have too many leukocytes (white blood cells), too few erythrocytes (red blood cells) and/or too few platelets. Often many of the leukocytes in these individuals are immature "blast" cells.

Hematocrit assay—Hematocrit assay is used to determine the proportion of the blood that is occupied by erythrocytes (red blood cells); normal men: 46% (39.8 - 52.2); normal women: 40.9% (34.9 - 46.9).

Hemoglobin level —Hemoglobin level is used to evaluate the amount of oxygen-carrying pigment in the erythrocytes; normal men: 15.5 g/dl blood (13.3 - 17.7); normal women: 13.7 g/dl blood (11.7 - 15.7).

Blood coagulation—Blood coagulation variables are used to determine whether there are problems with clotting. Such variables include prothrombin time, partial prothrombin time (PPT), clotting time, coagulation factors II, V, VII, IX, X, XI, and XII, plasminogen, and plasminogen activator.

Blood morphology and staining—Blood morphology and staining is used to identify abnormalities in cell shape, structure, and the condition of the cell nucleus. Some abnormalities common to red blood cells include anisocytosis (excessive variations in size), poikilocytosis (abnormal red blood cell shapes), and macrocytosis (abnormally large cells). Neutrophils often show nuclear and cell-based abnormalities, as

well as loss of granulation. Platelets may show giant forms that are deficient in granules.

Blood chemistry—Blood chemistry is used to measure the type and amount of enzymes, minerals, and other substances within the blood. Typical tests include measuring the serum enzyme lactic dehydrogenase; measuring the leukocyte enzyme alkaline phophatase, especially for the diagnosis of chronic myelogenous leukemia, or CML; measuring serum vitamin B12, which can be increased to roughly 15 times normal in CML patients; and measuring serum levels of calcium, potassium, phosphate, and uric acid (excess uric acid in the blood, or hyperuricemia, is common in lymphocytic leukemia and lymphoma). These tests are used to identify kidney or liver damage that may be caused by leukemic cell breakdown or by drugs used for chemotherapy.

Bone Marrow Tests The bone marrow is sampled by a technique known as bone marrow aspiration. During this procedure, a thin hollow needle with a syringe attachment is used to suction up (aspirate) a teaspoon-sized sample of liquid bone marrow from the back of the hip bone. A larger needle then is employed to obtain a bone marrow biopsy ("core" biopsy), which removes roughly a 1/16 inch cylindrical piece of bone marrow from the hip site. After the bone marrow samples are obtained, they are examined by many physician specialists, including a pathologist (disease diagnosis specialist, who examines samples under a microscope), hematologist (blood specialist), and oncologist (cancer specialist).

Microscopic examination—Microscopic examaination is performed on samples of the bone marrow, as well as any samples of the blood, cerebrospinal fluid, or lymph node tissue. The bone marrow cells are evaluated according to their size, shape, and content of granules (cellular enzymes that help some leukocytes to destroy germs).

Then they are classified with respect to maturity:

1. Mature cells are normal cells of the circulating blood, which are functional infection-fighters that can no longer reproduce.
2. Immature cells are undeveloped blood cells that, although poor infection-fighters, are still able to reproduce.
3. Blast cells are the most immature form of bone marrow cells.

The samples also are categorized according to their number of cells (cellularity), because abnormal tissue may contain appropriate proportions of blood-forming (hematopoietic) versus fat cells. Hypercellular marrow holds too many hematopoietic cells, whereas hypocellular marrow holds too few hematopoietic cells.

Cytochemistry—Identification of the chemical components of cells is conducted to distinguish different types of leukemia. Cytochemical tests often use special colored dyes (stains) that are only visible under a microscope. For example, one stain turns the granules of most acute myelogenous leukemia (AML) cells black, although acute lymphocytic leukemia (ALL) cells are unaffected by this substance. Leukocyte alkaline phosphate (LAP) or neutrophil alkaline phophatase (NAP)

tests formerly have been used to distinguish CML from other types of leukemia and noncancerous blood disorders; however, these assays no longer are considered particularly helpful in diagnosis, except in the absence of cytogenetic (cell genetic material) or other studies.

Flow cytometry—Flow cytometry is a computer-assisted technique in which bone marrow or other cells are treated with special antibodies and then are placed in front of a laser beam. Some types of leukemia cells contain special binding molecules called receptors that cause the antibodies to "label" (stick to) them. Laser treatment makes the antibody-coated cells fluorescent. The light that is given off undergoes computer measurement and analysis. The leukemia cells are counted and categorized by this method.

Immunocytochemistry—Immunocytochemistry, like flow cytometry, uses antibodies to treat the bone marrow or biopsy samples. Yet unlike flow cytometry, computers and lasers are not needed for this procedure. Instead, the sample is prepared so that specific types of cells undergo a color change that can be identified under a microscope. Immunocytochemistry allows the pathologist to identify specific types of leukemia.

Cytogenetic studies—Cytogenetic studies employ a variety of techniques for cell culture, slide-making, and preparation of chromosomes (genetic material). Bone marrow aspirate is the preferred tissue for most blood disorders; however, if unavailable, blood samples

may be used if there are enough circulating blast cells. In cases of chronic lymphocytic leukemia (CLL), blood samples are essential; in lymphoma cases, lymph node samples will provide more information.

Researchers have found that leukemia cells often contain genetic defects known as translocations, inversions, deletions, and additions. Translocations are genetic errors that result when parts of two chromosomes are exchanged. Inversions are produced when part of a chromosome becomes inverted (upside down) and the order of its genetic material is reversed. Deletions occur when part of a chromosome is missing, and additions are caused by duplications of all or part of a chromosome.

Chronic myelogenous leukemia (CML)— CML was the first type of cancer to show a consistent cytogenetic abnormality. This abnormality—a translocation between chromosomes 9 and 22 (written as t [9;22])—is known as the Philadelphia chromosome (Ph1). The Philadelphia chromosome causes uncontrolled reproduction and proliferation of all types of white blood cells and platelets.

Immunophenotyping—Immunophenotyping is the classification of cell types according to their immunologic characteristics. With the development of a form of testing known as monoclonal antibody (MAb) technology, types of leukemia cell lines are now better defined. Numerous antibody reagants have been identified; reagents are substances used to create chemical reactions. Some reagants recognize

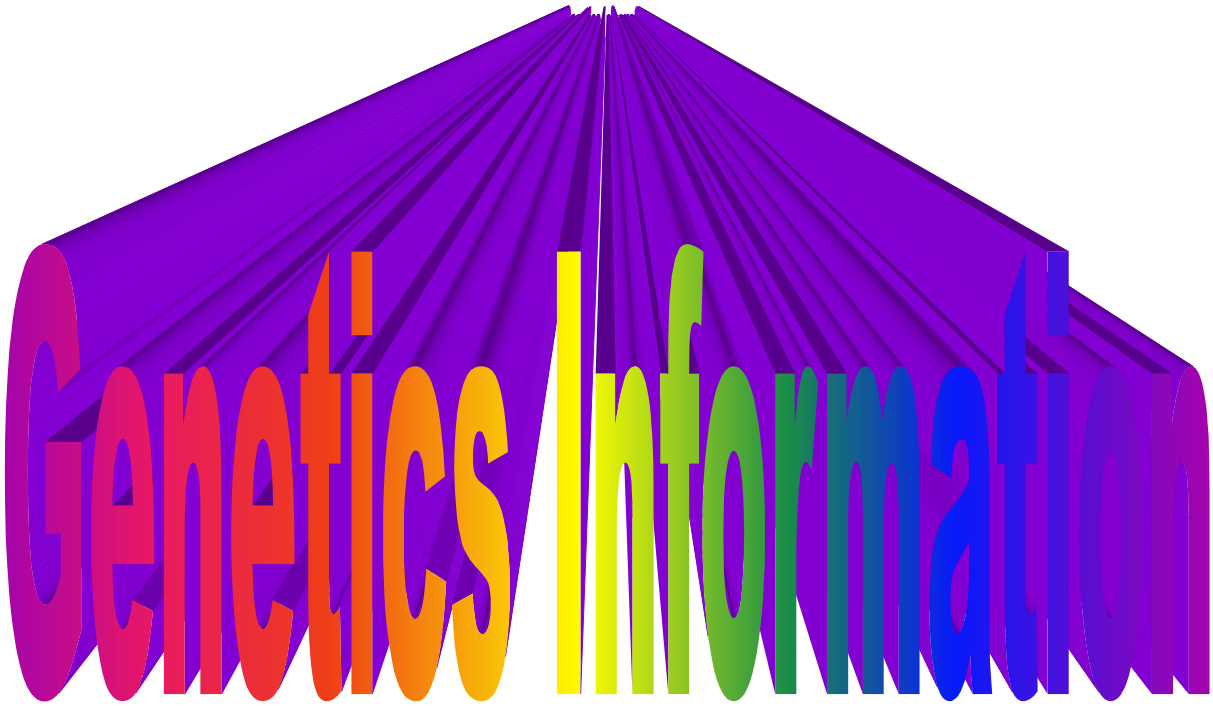
specific "clusters of differentiation" (CD); for example, CD79 recognizes B-cells, CD3 recognizes T-cells, and antimyeloperoxidase recognizes myeloid cells. Other useful, but less specific reagants are CD19, CD22,CD5, CD7, CD13, CD33, glycophorin, and CD61.

Imaging Studies Imaging studies may be used to determine whether the leukemia has invaded other organs within the body.

Such studies include:

- X-rays to see whether there are enlarged lymph nodes in the chest, a localized mass in the lungs, or evidence of spread to the outer bones or joints.
- Computed tomography (CT or CAT) scan is a computer-assisted x-ray that produces cross-sectional images of the body. CT scans are not often used in leukemia patients unless the physician suspects that the disease has spread. In such cases, CT scans may detect changes in the lymph nodes around the heart, trachea (windpipe), or abdomen. Lymph node enlargement is more common in patients with acute or chronic lymphocytic leukemia (ALL, CLL).
- Magnetic resonance imaging (MRI) scan is a procedure that uses electromagnets and radio waves to create computer-generated pictures of the internal organs. MRI may be used if the physician suspects that leukemia involves the brain or lungs.

- Radionuclide (radioactive atom) scanning may be performed to rule out nonleukemic disorders in patients who complain of bone pain. The radiologist injects the patient with a radioactive chemical (e.g., gallium-67), which will accumulate in areas of infection or malignancy and can be viewed with a special camera. This procedure is not used for patients who already have been diagnosed with leukemia.
- Ultrasound is an imaging method based on the principle that solids reflect sound waves in a manner that can be converted into a picture. During ultrasound, a transducer "probe" releases high-frequency sound waves that bounce off the internal organs, are collected, and are transmitted onto a video screen to create a picture called a sonogram. Ultrasound may be conducted to check the kidneys for leukemia-related damage.

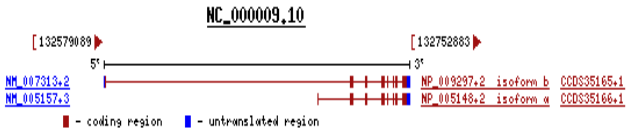

Genetics Informatich

GENETICS INFORMATION
ABL1

Official Symbol	ABL1 provided by HGNC
Official Full Name	v-abl Abelson murine leukemia viral oncogene homolog 1 provided by HGNC
Primary source	HGNC:76
Locus tag	RP11-83J21.1
See related	Ensembl:ENSG00000097007; HPRD:01809; MIM:189980
Gene type	protein coding
RefSeq status	Reviewed
Organism	*Homo sapiens*
Lineage	*Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo*
Also known as	ABL; JTK7; p150; c-ABL; v-abl; bcr/abl
Summary	The ABL1 protooncogene encodes a cytoplasmic and nuclear protein tyrosine kinase that has been implicated in processes of cell differentiation, cell division, cell adhesion, and stress response. Activity of c-Abl protein is negatively regulated by its SH3 domain, and deletion of the SH3 domain turns ABL1 into an oncogene. The t (9;22) translocation results in the head-to-tail fusion of the BCR (MIM:151410) and ABL1 genes present in many cases of chronic myelogeneous leukemia. The DNA-binding activity of the ubiquitously expressed ABL1 tyrosine kinase is regulated by CDC2-mediated phosphorylation, suggesting a cell cycle function for ABL1. The ABL1 gene is expressed as either a 6- or 7-kb mRNA transcript, with alternatively spliced first exons spliced to the common exons 2-11.

Genomic regions, transcripts, and products

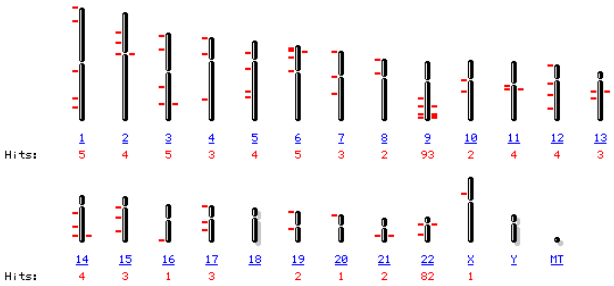
Go to reference sequence details



Genomic context

chromosome: 9; Location: 9q34.1

See ABL1 in MapViewer



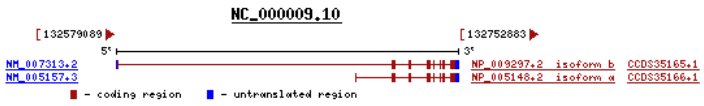
Search results for query "25[gene_id]": 236 hits

Hits shown: 1 - 100 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y MT

Chr	Assembly	Match	Map element	Type	Maps
1	reference	all matches			
		Chronic myeloid leukemia, aberrant translocation	t(1;9;22)(p34;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(1;9;22)(q42;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(1;9;22)(q21;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(1;9;22)(p36;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(1;9;22)(q32;q34;q11)	Breakpoint	Mitelman
2	reference	all matches			
		Chronic myeloid leukemia, aberrant translocation	t(2;9;22)(p13;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(2;9;22)(q11;q34;q11)	Breakpoint	Mitelman
		Acute lymphoblastic leukemia/lymphoblastic lymphoma	t(2;9)(q11;q34)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(2;9;22)(p21;q34;q11)	Breakpoint	Mitelman
3	reference	all matches			
		t(3;9;22)(p25;q34;q11) : Chronic myeloid leukemia, aberrant...	t(3;9;22)(p25;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(3;17;9;22)(q26;q21;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(3;9;22)(q26;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(3;9;22)(q21;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(3;9;22)(p21;q34;q11)	Breakpoint	Mitelman
4	reference	all matches			
		Chronic myeloid leukemia, aberrant translocation	t(4;9;22)(p16;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(4;9;22)(p14;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(4;9;22)(q31;q34;q11)	Breakpoint	Mitelman
5	reference	all matches			
		Chronic myeloid leukemia, aberrant translocation	t(5;9;22)(q31;q34;q11)	Breakpoint	Mitelman
		Chronic myeloid leukemia, aberrant translocation	t(5;9;22)(q13;q34;q11)	Breakpoint	Mitelman

Genomic regions, transcripts, and products

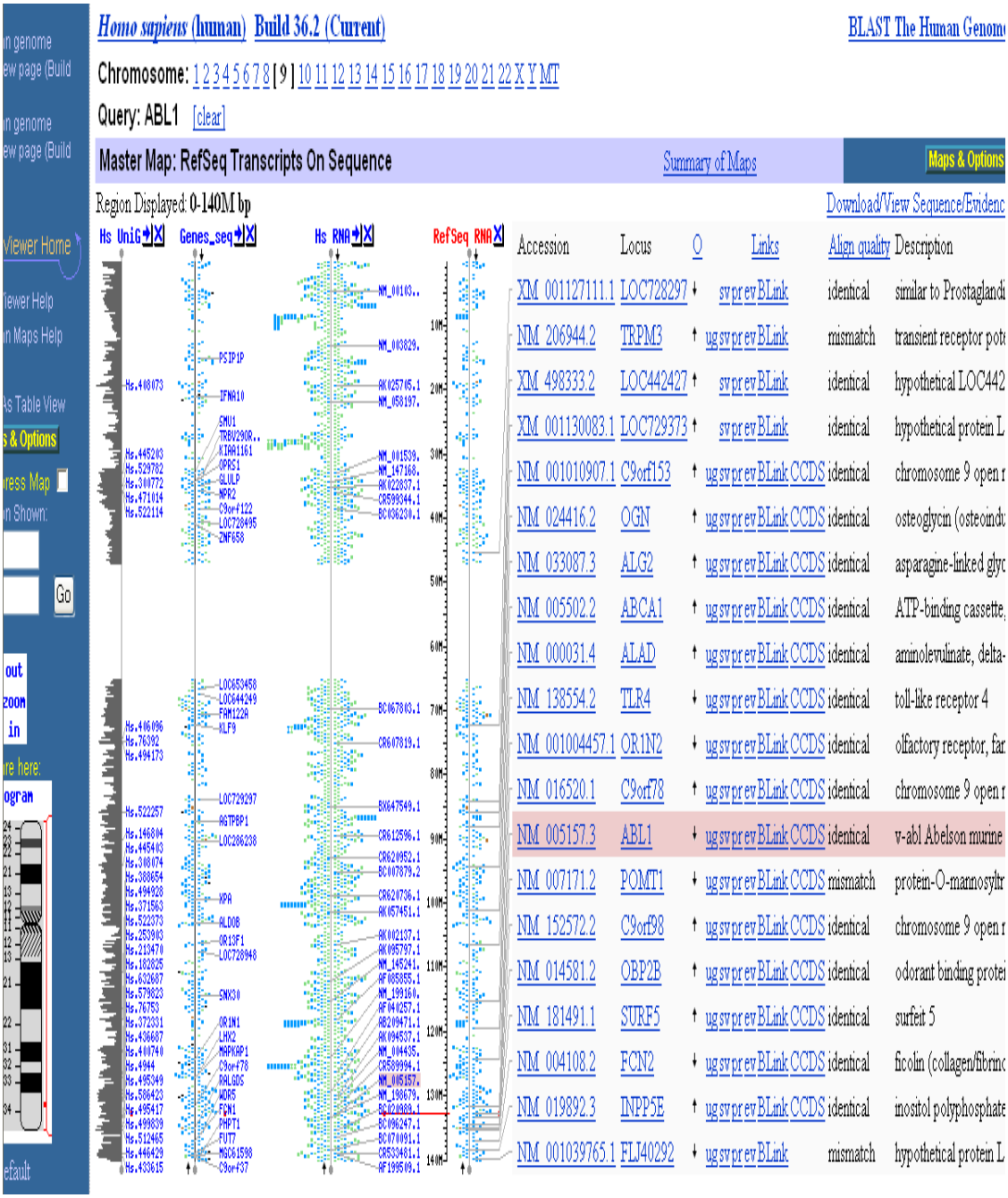
Go to reference sequence details

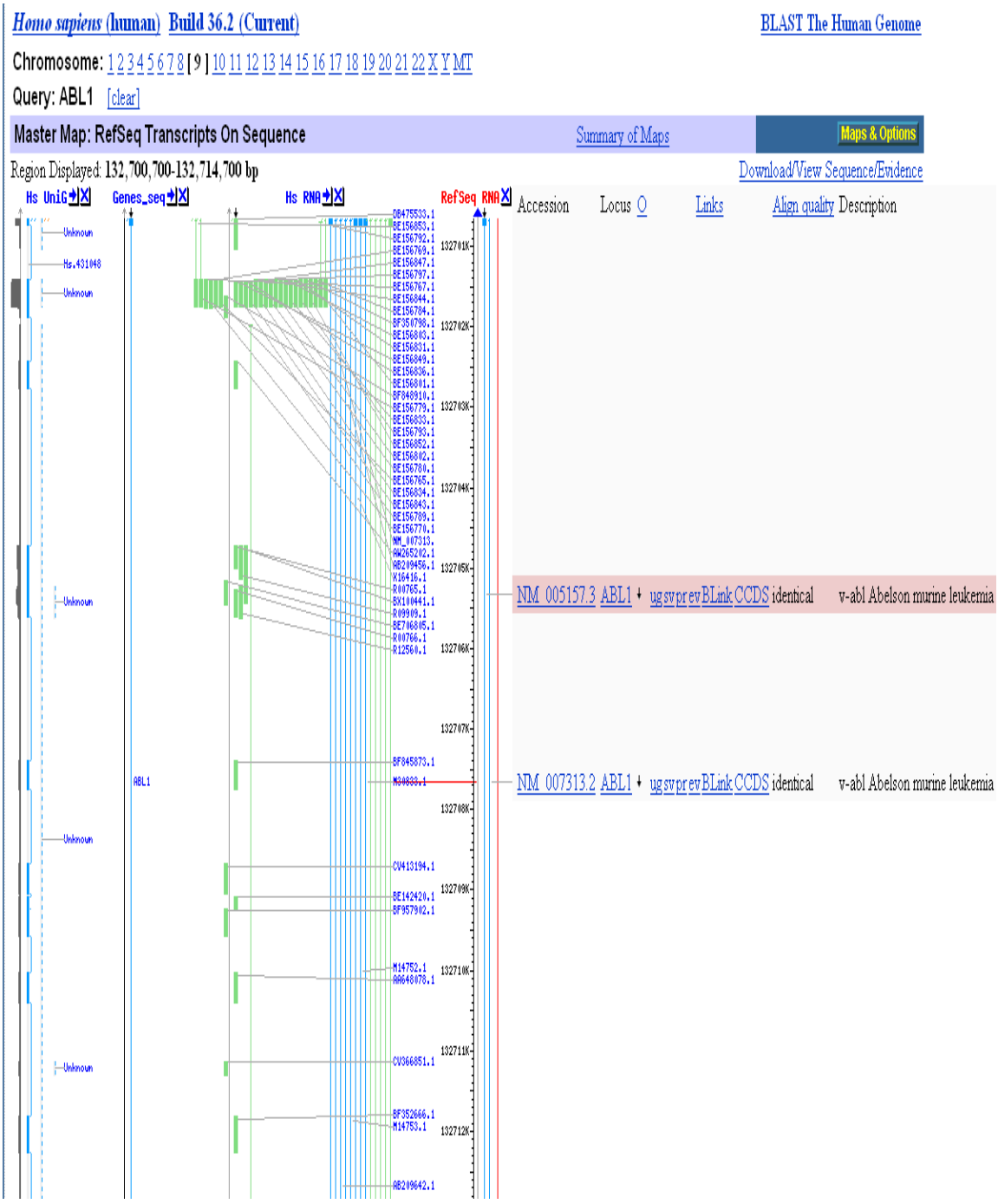


Genomic context

chromosome: 9; Location: 9q34.1

See ABL1 in MapViewer


Homo sapiens (human) Build 36.2 (Current)
BLAST The Human Genome
Chromosome: 1 2 3 4 5 6 7 8 [9] 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y MT
Query: ABL1 [clear]
Master Map: RefSeq Transcripts On Sequence
Summary of Maps
Maps & Options
Region Displayed: 0-140M bp
Download/View Sequence/Evidenc
Hs UniG
Genes_seq
Hs RNA
RefSeq RNA
Accession Locus Q Links Align quality Description
XM_001127111.1 LOC728297 sv pr ev BLink identical similar to Prostaglandi
NM_206944.2 TRPM3 ug sv pr ev BLink mismatch transient receptor pote
XM_498333.2 LOC442427 sv pr ev BLink identical hypothetical LOC442
XM_001130083.1 LOC729373 sv pr ev BLink identical hypothetical protein L
NM_001010907.1 C9orf153 ug sv pr ev BLink CCDS identical chromosome 9 open r
NM_024416.2 OGN ug sv pr ev BLink CCDS identical osteoglycin (osteoindu
NM_033087.3 ALG2 ug sv pr ev BLink CCDS identical asparagine-linked glyc
NM_005502.2 ABCA1 ug sv pr ev BLink CCDS identical ATP-binding cassette,
NM_000031.4 ALAD ug sv pr ev BLink CCDS identical aminolevulinate, delta-
NM_138554.2 TLR4 ug sv pr ev BLink CCDS identical toll-like receptor 4
NM_001004457.1 OR1N2 ug sv pr ev BLink CCDS identical olfactory receptor, fam
NM_016520.1 C9orf78 ug sv pr ev BLink CCDS identical chromosome 9 open r
NM_005157.3 ABL1 ug sv pr ev BLink CCDS identical v-abl Abelson murine
NM_007171.2 POMT1 ug sv pr ev BLink CCDS mismatch protein-O-mannosylt
NM_152572.2 C9orf98 ug sv pr ev BLink CCDS identical chromosome 9 open r
NM_014581.2 OBP2B ug sv pr ev BLink CCDS identical odorant binding prote
NM_181491.1 SURF5 ug sv pr ev BLink CCDS identical surfeit 5
NM_004108.2 FCN2 ug sv pr ev BLink CCDS identical ficolin (collagen/fibrino
NM_019892.3 INPP5E ug sv pr ev BLink CCDS identical inositol polyphosphate
NM_001039765.1 FLJ40292 ug sv pr ev BLink mismatch hypothetical protein L


Homo sapiens (human) Build 36.2 (Current)
BLAST The Human Genome
Chromosome: 1 2 3 4 5 6 7 8 [9] 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y MT
Query: ABL1 [clear]
Master Map: RefSeq Transcripts On Sequence
Summary of Maps
Maps & Options
Region Displayed: 132,700,700-132,714,700 bp
Download/View Sequence/Evidence
Hs UniG
Genes_seq
Hs RNA
RefSeq RNA
Accession
Locus
O
Links
Align quality
Description
NM_005157.3 ABL1 + ug sv pr ev BLink CCDS identical v-abl Abelson murine leukemia
NM_007313.2 ABL1 + ug sv pr ev BLink CCDS identical v-abl Abelson murine leukemia

GENETICS INFORMATION
AFF1

1: AFF1 AF4/FMR2 family, member 1 [*Homo sapiens*]

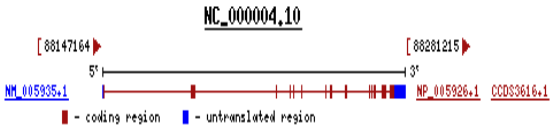
GeneID: 4299 updated 13-Nov-2007

Summary

Official Symbol	AFF1 provided by HGNC
Official Full Name	AF4/FMR2 family, member 1 provided by HGNC
Primary source	HGNC:7135
See related	Ensembl:ENSG00000172493; HPRD:08871; MIM:159557
Gene type	protein coding
RefSeq status	Validated
Organism	*Homo sapiens*
Lineage	*Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo*
Also known as	AF4; AF-4; PBM1; MLLT2; AF4-MLL; MLL/AF4; MGC134969
Summary	DISCONTINUED: The record for PBM1 has been withdrawn by HGNC.

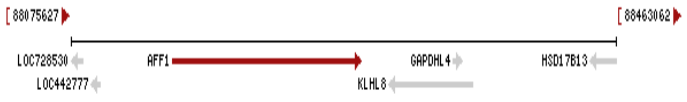
Genomic regions, transcripts, and products

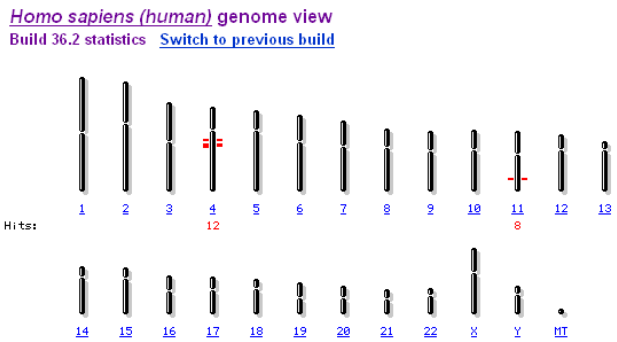
Go to reference sequence details



Genomic context

chromosome: 4; Location: 4q21 See AFF1 in MapViewer





Search results for query "4299[gene_id]": 20 hits

Chr	Assembly	Match	Map element	Type	Maps
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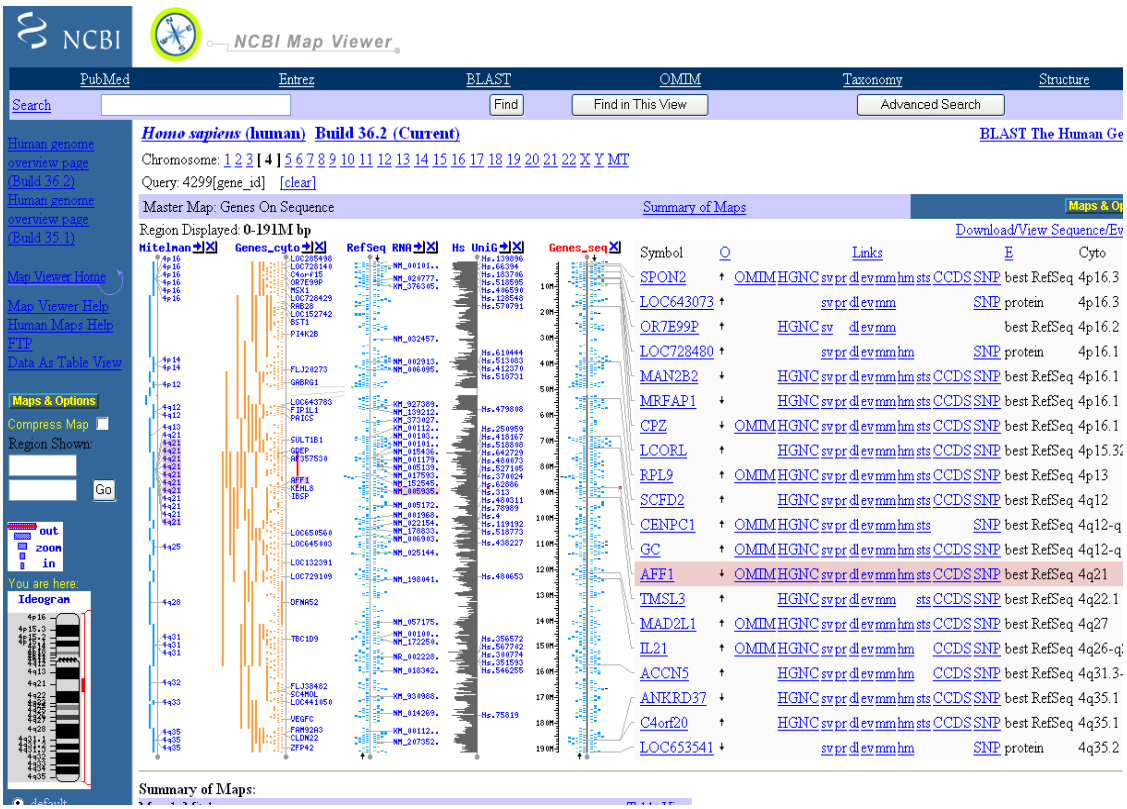
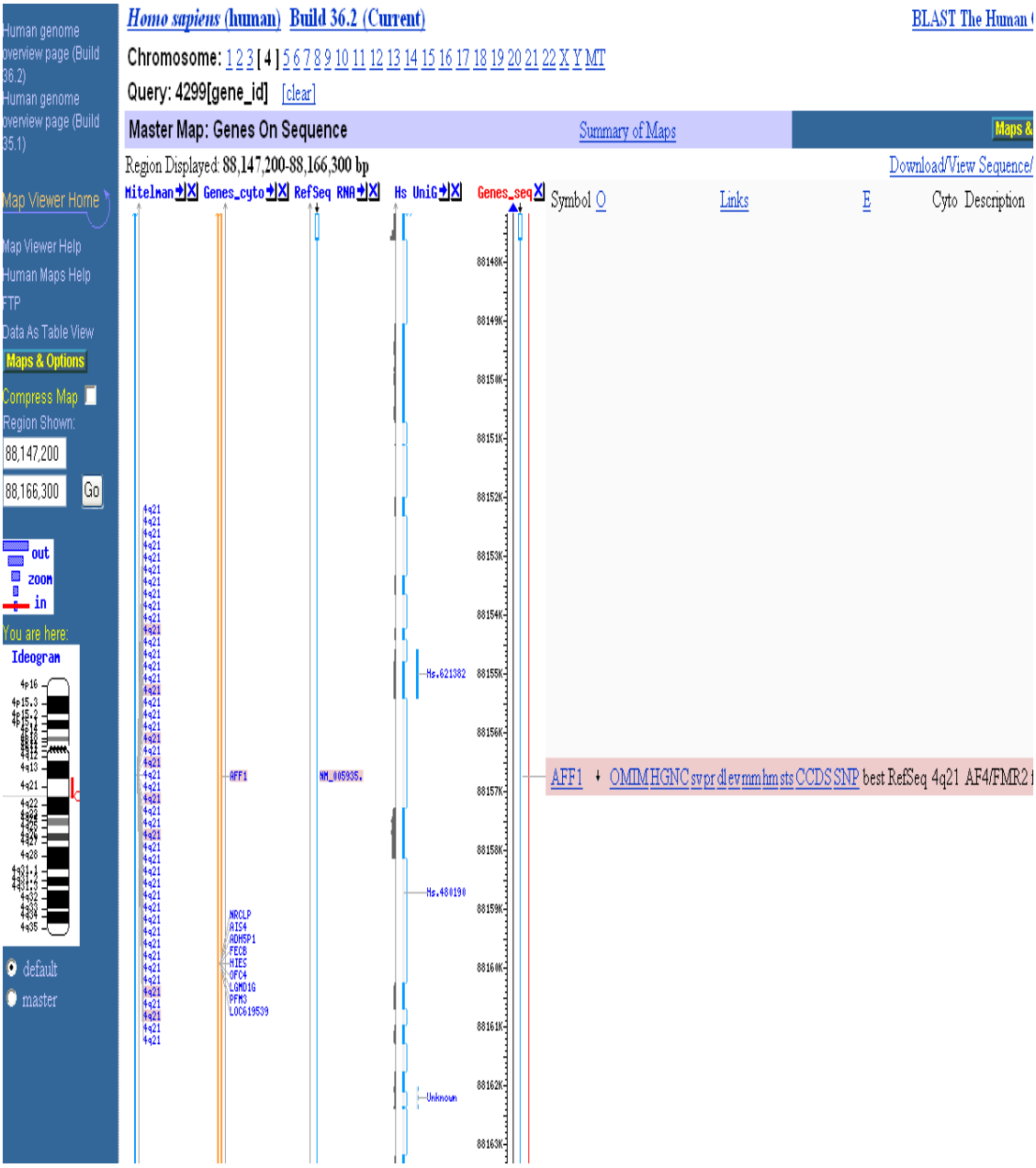
		Homo sapiens AF4/FMR2 family, member 1 (AFF1), mRNA	NM_005935.1	TRANSCRIPT	RefSeq RNA
		Acute myeloblastic leukemia with minimal differentiation (FAB... (7 hits)	t(4;11)(q21;q23)	Breakpoint	Mitelman
		Acute lymphoblastic leukemia/lymphoblastic lymphoma	ins(4;11)(q21;q23q23)	Breakpoint	Mitelman
		pre-B-cell monocytic leukemia partner 1	AFF1	Gene	Genes_cyto | Genes_seq
4	Celera	all matches			
		Homo sapiens AF4/FMR2 family, member 1 (AFF1), mRNA	NM_005935.1	TRANSCRIPT	RefSeq RNA
		pre-B-cell monocytic leukemia partner 1	AFF1	GENE	Genes_seq
11	reference	all matches			
		Acute lymphoblastic leukemia/lymphoblastic lymphoma (7 hits)	t(4;11)(q21;q23)	Breakpoint	Mitelman
		Acute lymphoblastic leukemia/lymphoblastic lymphoma	ins(4;11)(q21;q23q23)	Breakpoint	Mitelman




Human genome overview page (Build 36.2)
Human genome overview page (Build 35.1)
Map Viewer Home
Map Viewer Help
Human Maps Help
FTP
Data As Table View
Maps & Options
Compress Map
Region Shown:
88,147,200
88,166,300
Go
out
zoom
in
You are here:
Ideogram
default
master
Homo sapiens (human) Build 36.2 (Current)
BLAST The Human
Chromosome: 1 2 3 [4] 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y MT
Query: 4299[gene_id] [clear]
Master Map: Genes On Sequence
Summary of Maps
Region Displayed: 88,147,200-88,166,300 bp
Download/View Sequence
Mitelman
Genes_cyto
RefSeq RNA
Hs UniG
Genes_seq
Symbol
Links
Cyto Description
AFF1
NM_005935.
Hs.621382
Hs.480190
Unknown
AFF1 OMIM HGNC swpr dlev mmhm sts CCDS SNP best RefSeq 4q21 AF4/FMR2

GENETICS INFORMATION
MKL1

1: MKL1 megakaryoblastic leukemia (translocation) 1 [*Homo sapiens*]

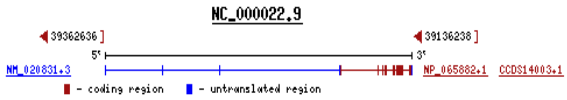
GeneID: 57591 updated 09-Dec-2007

Summary

Official Symbol	MKL1 provided by HGNC
Official Full Name	megakaryoblastic leukemia (translocation) 1 provided by HGNC
Primary source	HGNC:14334
See related	Ensembl:ENSG00000196588; HPRD:10445; MIM:606078
Gene type	protein coding
RefSeq status	Validated
Organism	*Homo sapiens*
Lineage	*Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo*
Also known as	MAL; BSAC; MRTF-A
Summary	The protein encoded by this gene interacts with the transcription factor myocardin, a key regulator of smooth muscle cell differentiation. The encoded protein is predominantly nuclear and may help transduce signals from the cytoskeleton to the nucleus. This gene is involved in a specific translocation event that creates a fusion of this gene and the RNA-binding motif protein-15 gene. This translocation has been associated with acute megakaryocytic leukemia.

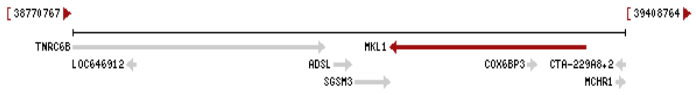
Genomic regions, transcripts, and products

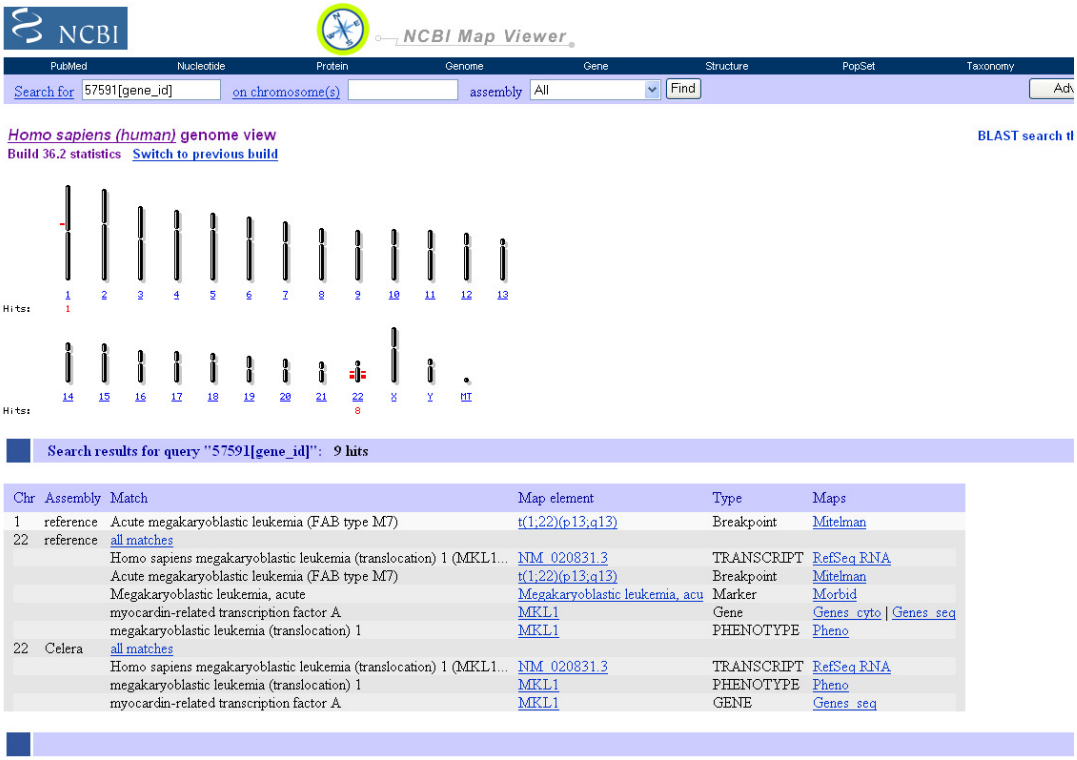
(minus strand) Go to reference sequence details

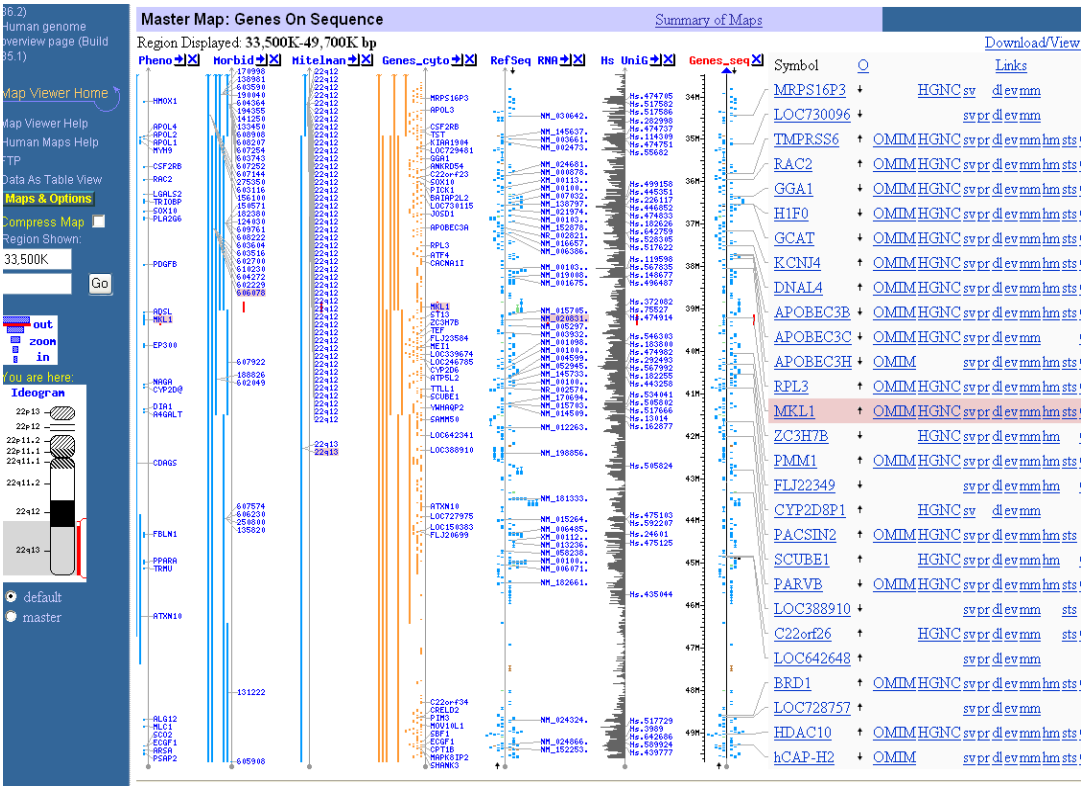


Genomic context

chromosome: 22; Location: 22q13 See MKL1 in MapViewer




NCBI
NCBI Map Viewer
PubMed Nucleotide Protein Genome Gene Structure PopSet Taxonomy
Search for 57591[gene_id] on chromosome(s) assembly All Find
Homo sapiens (human) genome view
Build 36.2 statistics Switch to previous build
BLAST search tl
Search results for query "57591[gene_id]": 9 hits
Chr Assembly Match Map element Type Maps
1 reference Acute megakaryoblastic leukemia (FAB type M7) t(1;22)(p13;q13) Breakpoint Mitelman
22 reference all matches
Homo sapiens megakaryoblastic leukemia (translocation) 1 (MKL1... NM_020831.3 TRANSCRIPT RefSeq RNA
Acute megakaryoblastic leukemia (FAB type M7) t(1;22)(p13;q13) Breakpoint Mitelman
Megakaryoblastic leukemia, acute Megakaryoblastic leukemia, acu Marker Morbid
myocardin-related transcription factor A MKL1 Gene Genes_cyto | Genes_seq
megakaryoblastic leukemia (translocation) 1 MKL1 PHENOTYPE Pheno
22 Celera all matches
Homo sapiens megakaryoblastic leukemia (translocation) 1 (MKL1... NM_020831.3 TRANSCRIPT RefSeq RNA
megakaryoblastic leukemia (translocation) 1 MKL1 PHENOTYPE Pheno
myocardin-related transcription factor A MKL1 GENE Genes_seq


Master Map: Genes On Sequence
Summary of Maps
Region Displayed: 33,500K-49,700K bp
Download/View
Pheno Morbid Mitelman Genes_cyto RefSeq RNA Hs UniG Genes_seq
Symbol O Links
MRPS16P3 HGNC sv dl ev mm
LOC730096 sv pr dl ev mm
TMPRSS6 OMIM HGNC sv pr dl ev mm hm sts
RAC2 OMIM HGNC sv pr dl ev mm hm sts
GGA1 OMIM HGNC sv pr dl ev mm hm sts
H1F0 OMIM HGNC sv pr dl ev mm hm sts
GCAT OMIM HGNC sv pr dl ev mm hm sts
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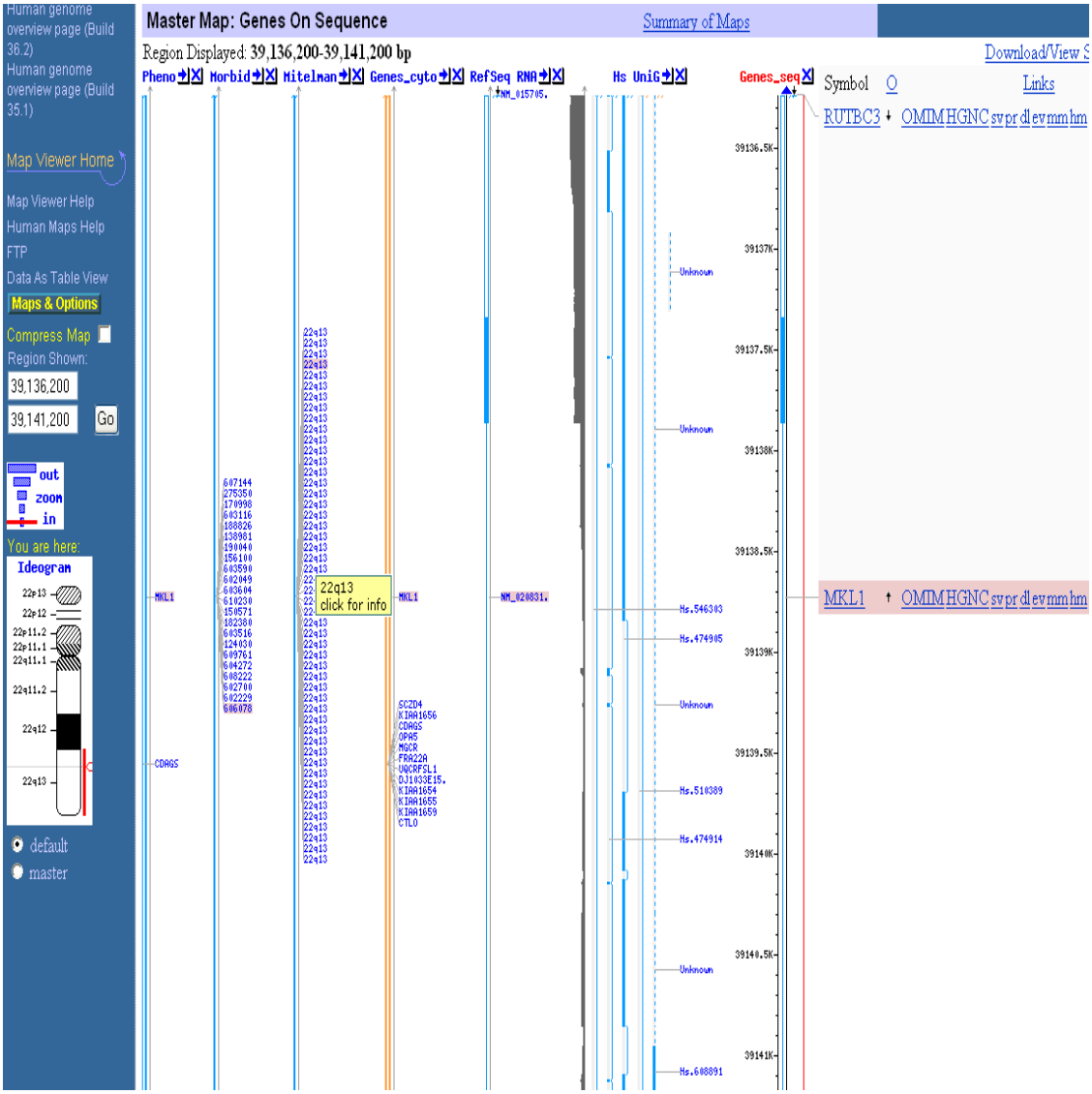
DNAL4 OMIM HGNC sv pr dl ev mm hm sts
APOBEC3B OMIM HGNC sv pr dl ev mm hm sts
APOBEC3C OMIM HGNC sv pr dl ev mm
APOBEC3H OMIM sv pr dl ev mm hm sts
RPL3 OMIM HGNC sv pr dl ev mm hm sts
MKL1 OMIM HGNC sv pr dl ev mm hm sts
ZC3H7B HGNC sv pr dl ev mm hm
PMM1 OMIM HGNC sv pr dl ev mm hm sts
FLJ22349 sv pr dl ev mm hm
CYP2D8P1 HGNC sv dl ev mm
PACSIN2 OMIM HGNC sv pr dl ev mm hm sts
SCUBE1 HGNC sv pr dl ev mm hm
PARVB OMIM HGNC sv pr dl ev mm hm sts
LOC388910 sv pr dl ev mm sts
C22orf26 HGNC sv pr dl ev mm sts
LOC642648 sv pr dl ev mm
BRD1 OMIM HGNC sv pr dl ev mm hm sts
LOC728757 sv pr dl ev mm
HDAC10 OMIM HGNC sv pr dl ev mm hm sts
hCAP-H2 OMIM sv pr dl ev mm hm sts
Human genome overview page (Build 35.1)
Map Viewer Home
Map Viewer Help
Human Maps Help
FTP
Data As Table View
Maps & Options
Compress Map
Region Shown:
33,500K
Go
out
zoom
in
You are here:
Ideogram
default
master

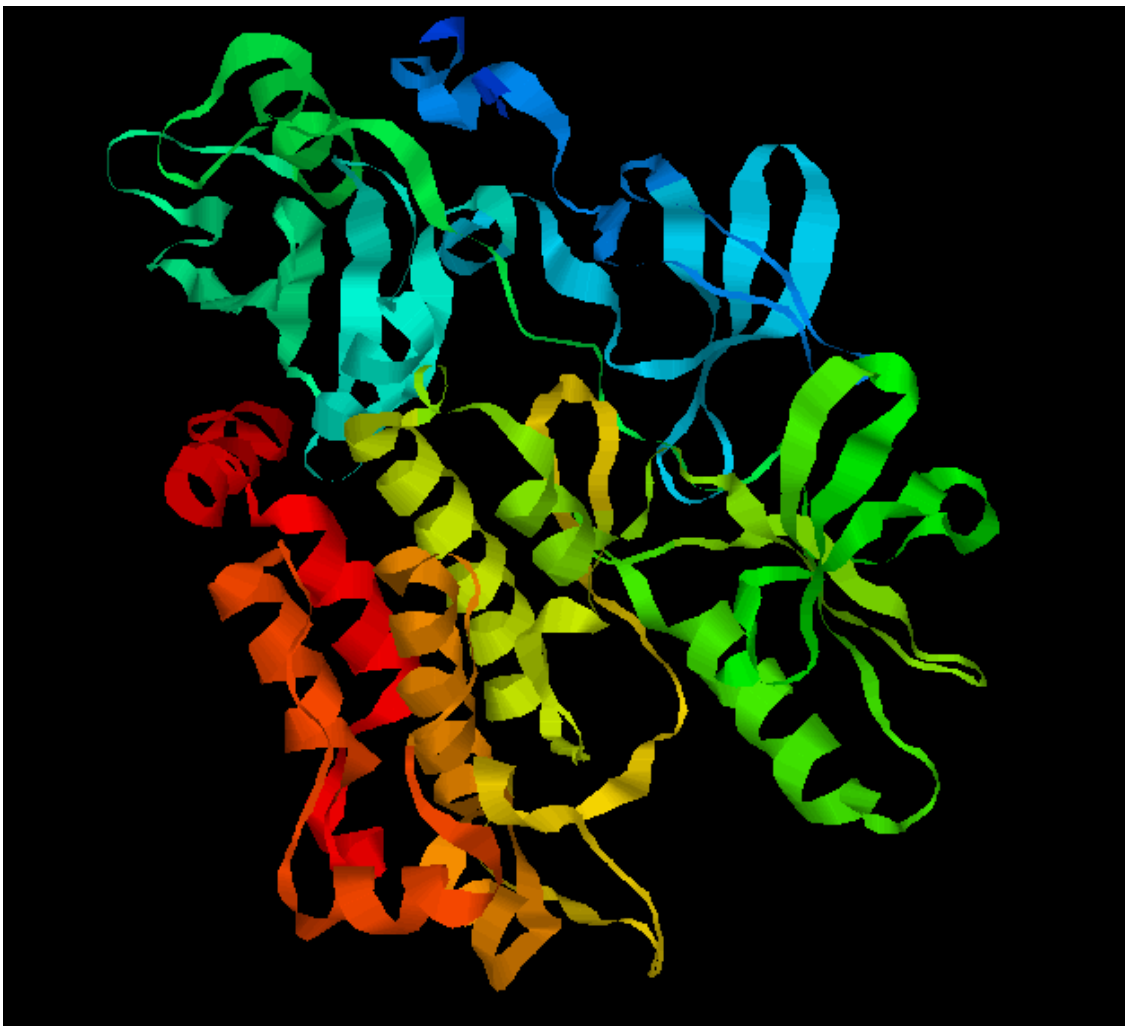

Human genome overview page (Build 36.2)
Human genome overview page (Build 35.1)
Map Viewer Home
Map Viewer Help
Human Maps Help
FTP
Data As Table View
Maps & Options
Compress Map
Region Shown:
39,136,200
39,141,200
Go
out
zoom
in
You are here:
Ideogram
default
master
Master Map: Genes On Sequence
Summary of Maps
Region Displayed: 39,136,200-39,141,200 bp
Download/View S
Pheno
Morbid
Mitelman
Genes_cyto
RefSeq RNA
Hs UniG
Genes_seq
Symbol
Links
RUTBC3
OMIM HGNC sv pr dl ev mm hm
MKL1
22q13
click for info
Unknown
Hs.546303
Hs.474905
Hs.510389
Hs.474914
Hs.608891
39136.5K
39137K
39137.5K
39138K
39138.5K
39139K
39139.5K
39140K
39140.5K
39141K


PROTEIN OF INTEREST

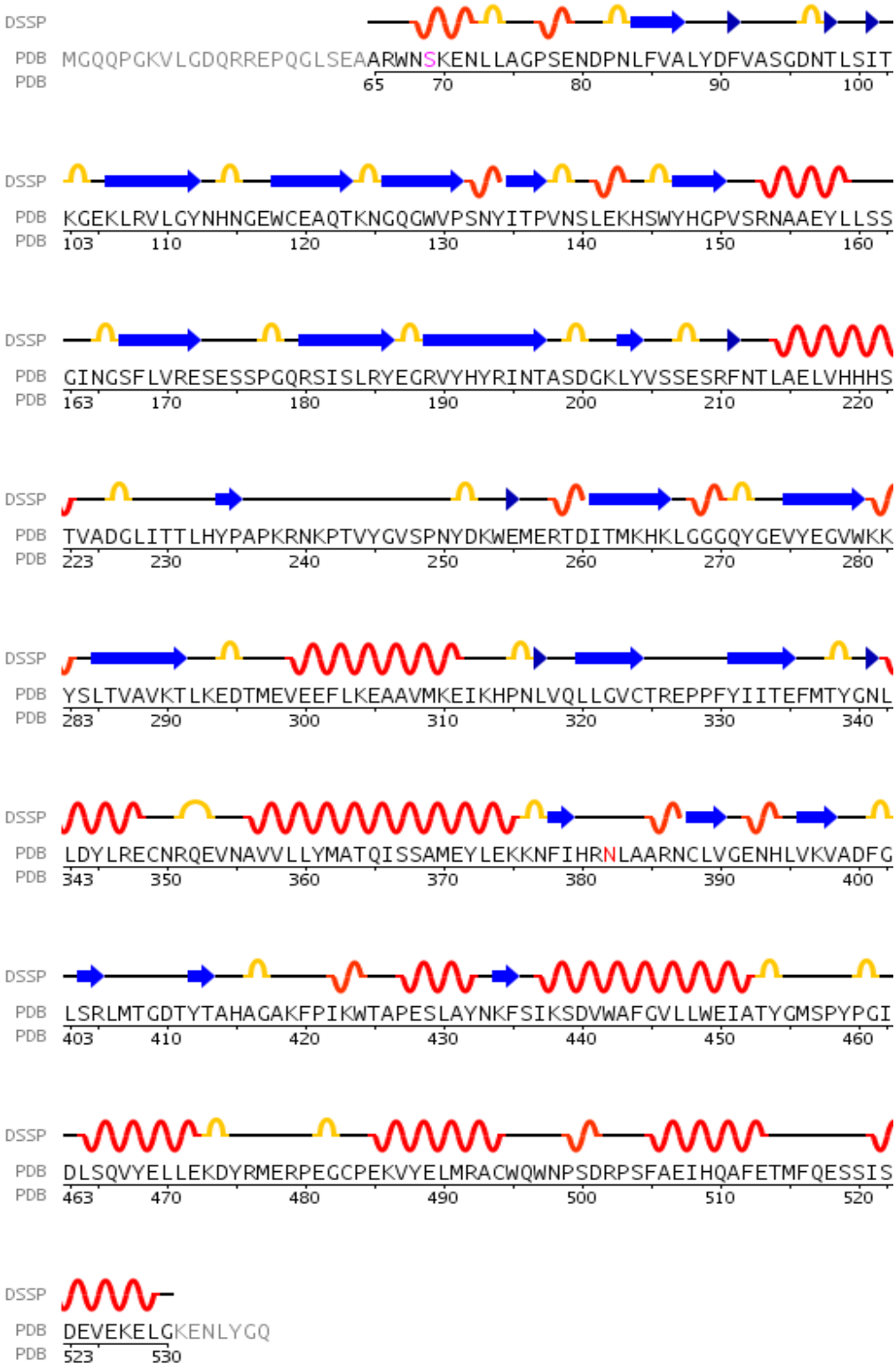
PROTEIN OF INTEREST

2fo0

ENTRY NAME	ABL1_HUMAN New! **View this entry in our Beta site**
ACCESSION NUMBERS	P00519; Q13869; Q13870; Q16133; Q45F09
Integrated into Swiss-Prot on	1986-07-21
Sequence was last modified on	2006-01-24 (Sequence version 4)
Annotations were last modified on	2007-12-04 (Entry version 122)
NAME AND ORIGIN OF THE PROTEIN	
PROTEIN NAME	Proto-oncogene tyrosine-protein kinase ABL1
Synonyms	EC 2.7.10.2 p150 c-ABL Abelson murine leukemia viral oncogene homolog 1
GENE NAME	Name: ABL1 Synonym: ABL; JTK7
SOURCE ORGANISM	Homo sapiens
TAXONOMY ID	9606 [NCBI, NEWT]
LINEAGE	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
PROTEIN EXISTENCE	Evidence at protein level



2Fo0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PDB 65 70 80 90 100
DSSP
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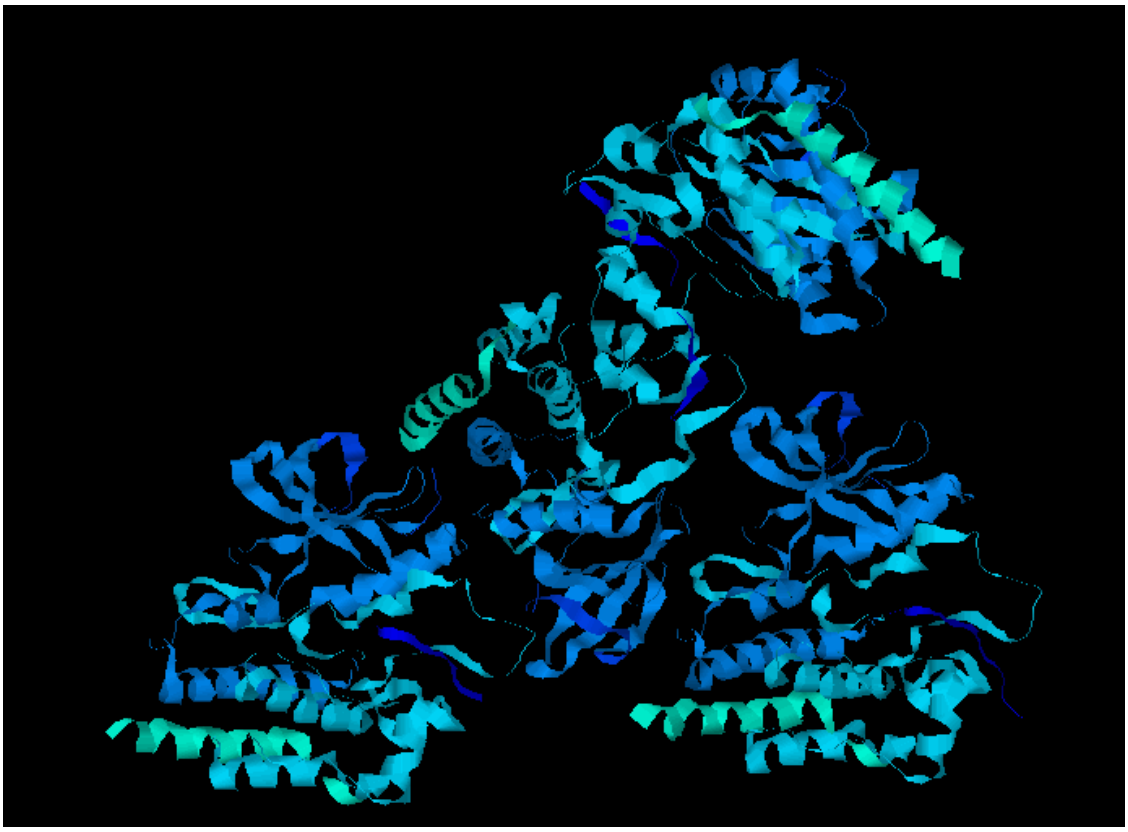
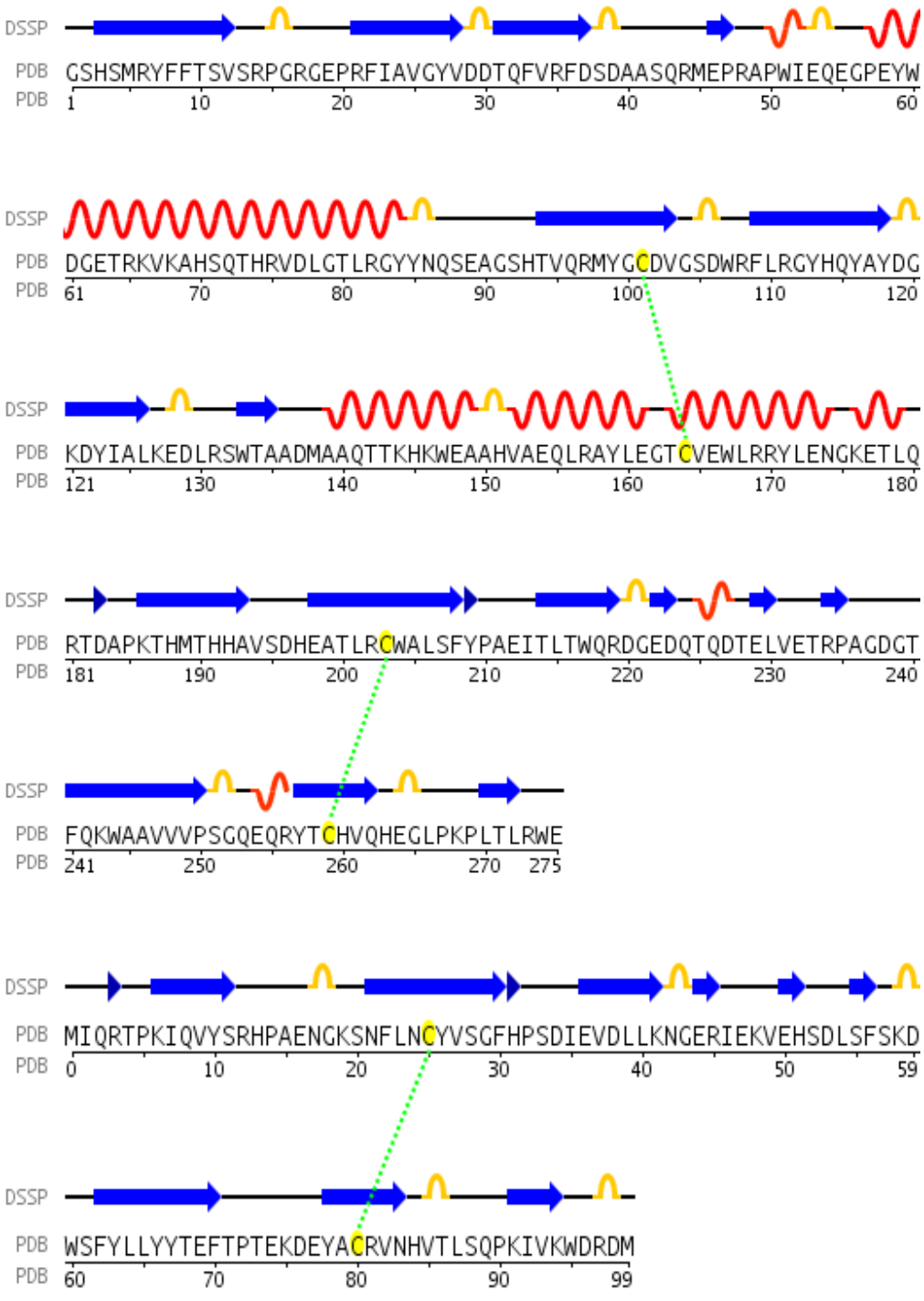
PDB 103 110 120 130 140 150 160
DSSP
PDB GINGSFLVRESESSPGQRSISLRYEGRVYHYRINTASDGKLYVSSESRFNTLAELVHHHS
PDB 163 170 180 190 200 210 220
DSSP
PDB TVADGLITTLHYPAPKRNKPTVYGVSPNYDKWEMERTDITMKHKLGGGQYGEVYEGVWKK
PDB 223 230 240 250 260 270 280
DSSP
PDB YSLTVAVKTLKEDTMEVEEFLKEAAVMKEIKHPNLVQLLGVCTREPPFYIITEFMTYGNL
PDB 283 290 300 310 320 330 340
DSSP
PDB LDYLRECNRQEVNAVVLLYMATQISSAMEYLEKKNFIHRNLAARNCLVGENHLVKVADFG
PDB 343 350 360 370 380 390 400
DSSP
PDB LSRLMTGDTYTAHAGAKFPIKWTAPESLAYNKFSIKSDVWAFGVLLWEIATYGMSPYPGI
PDB 403 410 420 430 440 450 460
DSSP
PDB DLSQVYELLEKDYRMERPEGCPEKVYELMRACWQWNPSDRPSFAEIHQAFETMFQESSIS
PDB 463 470 480 490 500 510 520
DSSP
PDB DEVEKELGKENLYGQ
PDB 523 530

2GLT

ENTRY NAME	ABL1_HUMAN New! **View this entry in our Beta site**
ACCESSION NUMBERS	P00519; Q13869; Q13870; Q16133; Q45F09
Integrated into Swiss-Prot on	1986-07-21
Sequence was last modified on	2006-01-24 (Sequence version 4)
Annotations were last modified on	2007-12-04 (Entry version 122)
NAME AND ORIGIN OF THE PROTEIN	
PROTEIN NAME	Proto-oncogene tyrosine-protein kinase ABL1
Synonyms	EC 2.7.10.2 p150 c-ABL Abelson murine leukemia viral oncogene homolog 1
GENE NAME	Name: ABL1 Synonym: ABL; JTK7
SOURCE ORGANISM	Homo sapiens
TAXONOMY ID	9606 [NCBI, NEWT]
LINEAGE	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
PROTEIN EXISTENCE	Evidence at protein level



2GLT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DSSP
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PDB 181 190 200 210 220 230 240
DSSP
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DSSP
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PDB 60 70 80 90 99

2GQG

ENTRY NAME	ABL1_HUMAN New! **View this entry in our Beta site**
ACCESSION NUMBERS	P00519; Q13869; Q13870; Q16133; Q45F09
Integrated into Swiss-Prot on	1986-07-21
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GENE NAME	Name: ABL1 Synonym: ABL; JTK7
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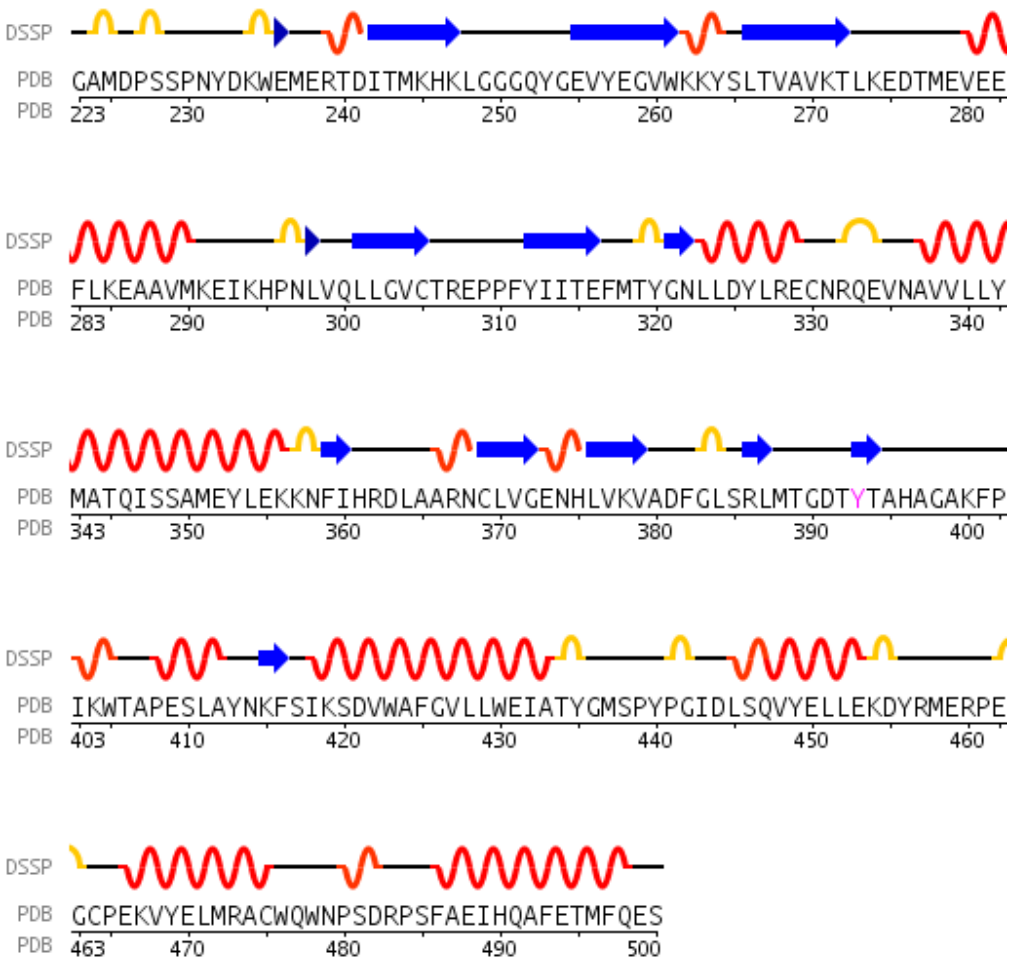
TAXONOMY ID	9606 [NCBI, NEWT]
LINEAGE	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
PROTEIN EXISTENCE	Evidence at protein level

2GQG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PDB 283 290 300 310 320 330 340
DSSP
PDB MATQISSAMEYLEKKNFIHRDLAARNCLVGENHLVKVADFGLSRLMTGDTYTAHAGAKFP
PDB 343 350 360 370 380 390 400
DSSP
PDB IKWTAPESLAYNKFSIKSDVWAFGVLLWEIATYGMSPYPGIDLSQVYELLEKDYRMERPE
PDB 403 410 420 430 440 450 460
DSSP
PDB GCPEKVYELMRACWQWNPSDRPSFAEIHQAFETMFQES
PDB 463 470 480 490 500

2HYY

ENTRY NAME	ABL1_HUMAN New! **View this entry in our Beta site**
ACCESSION NUMBERS	P00519; Q13869; Q13870; Q16133; Q45F09
Integrated into Swiss-Prot on	1986-07-21
Sequence was last modified on	2006-01-24 (Sequence version 4)
Annotations were last modified on	2007-12-04 (Entry version 122)
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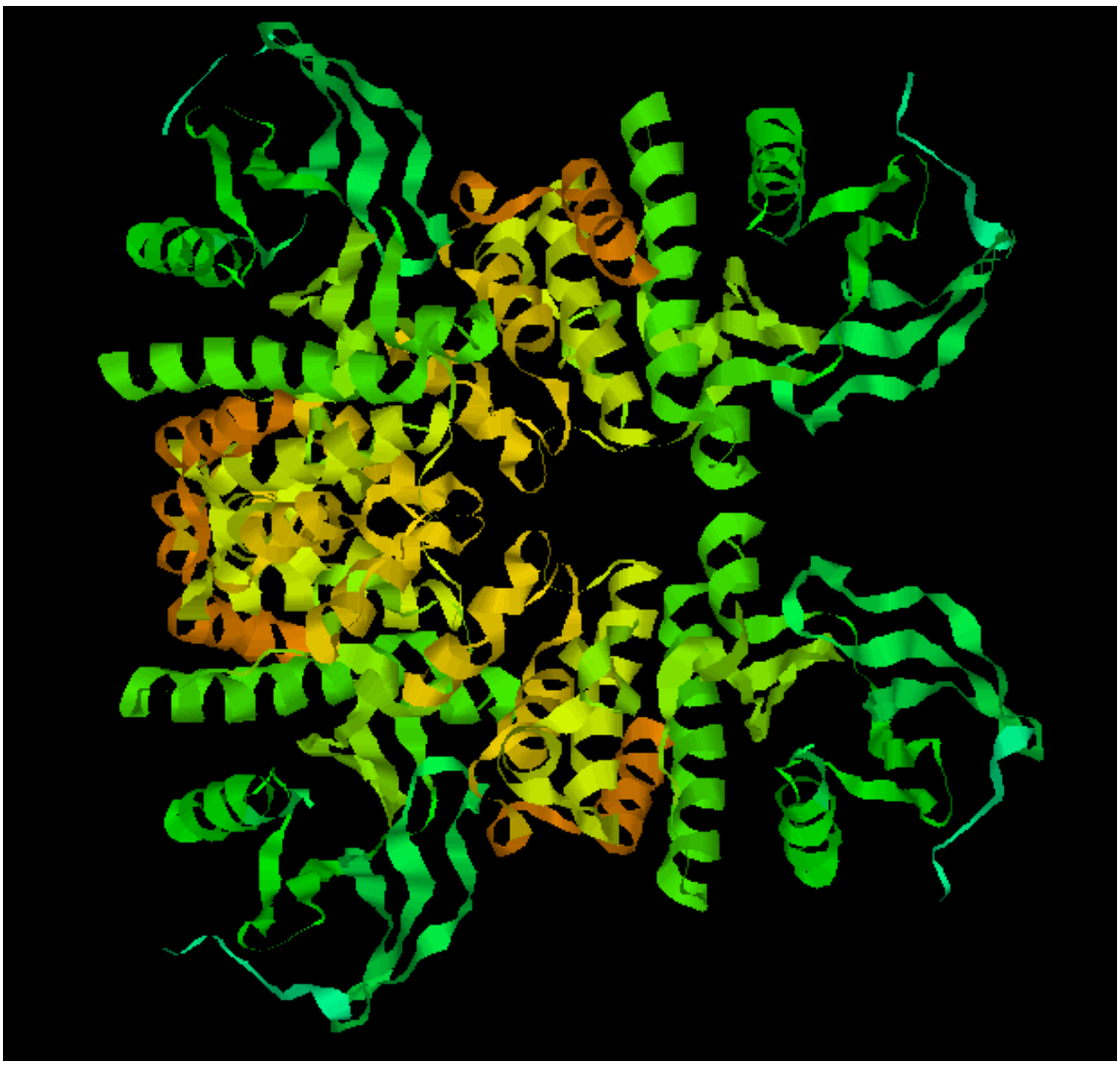
Synonyms	EC 2.7.10.2 p150 c-ABL Abelson murine leukemia viral oncogene homolog 1
GENE NAME	Name: ABL1 Synonym: ABL; JTK7
SOURCE ORGANISM	Homo sapiens
TAXONOMY ID	9606 [NCBI, NEWT]
LINEAGE	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
PROTEIN EXISTENCE	Evidence at protein level



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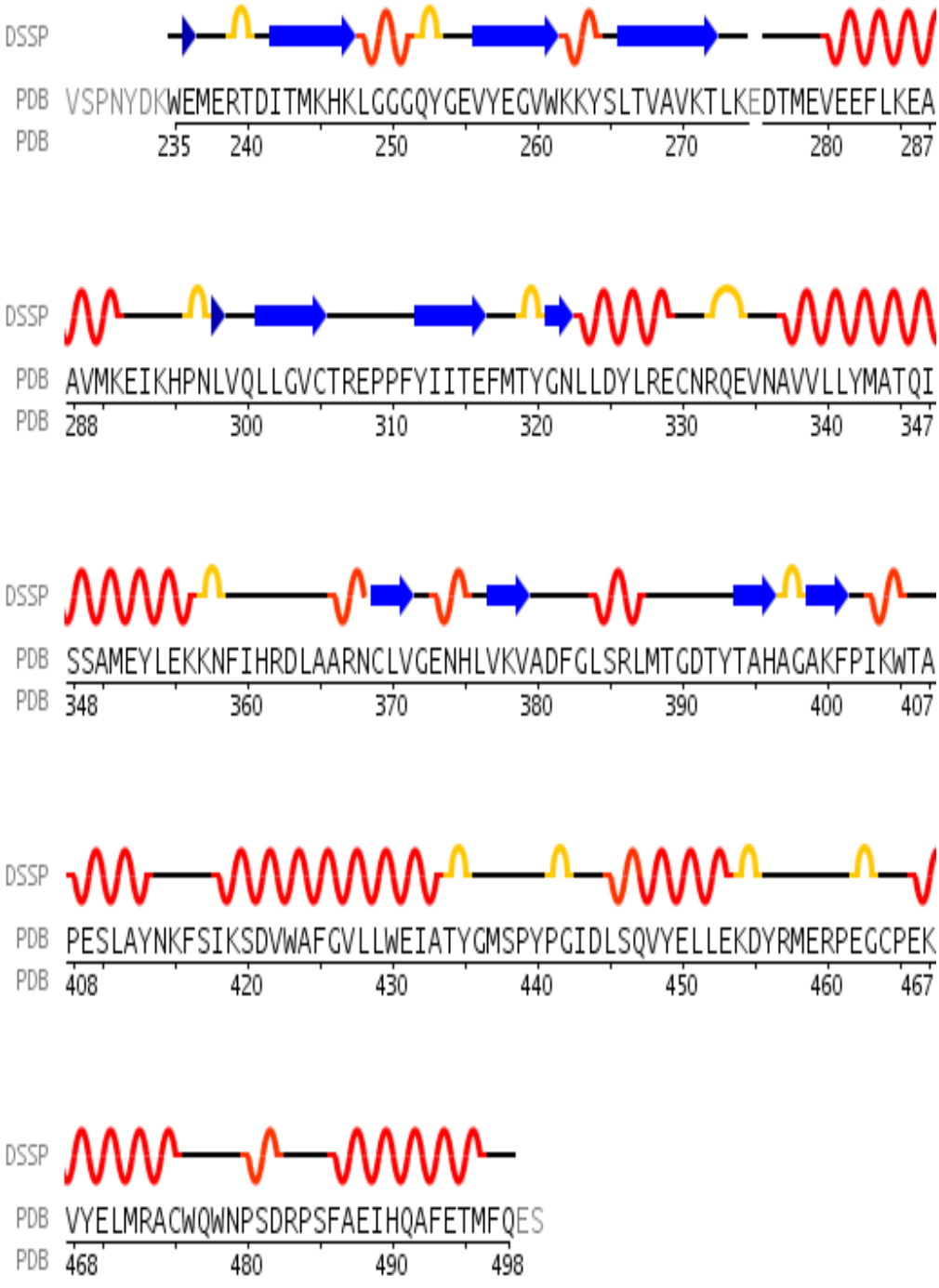
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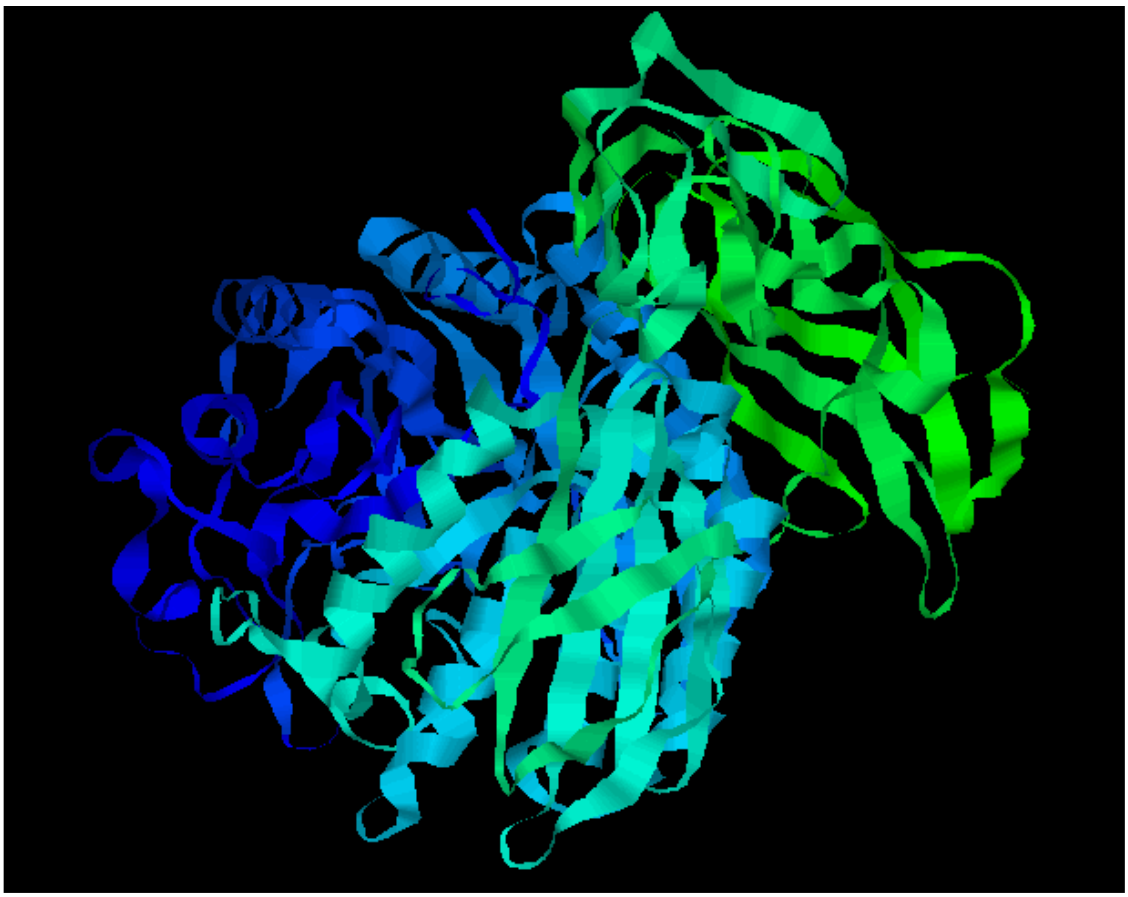
PDB 288 300 310 320 330 340 347
DSSP
PDB SSAMEYLEKKNFIHRDLAARNCLVGENHLVKVADFGLSRLMTGDTYTAHAGAKFPIKWTA
PDB 348 360 370 380 390 400 407
DSSP
PDB PESLAYNKFSIKSDVWAFGVLLWEIATYGMSPYPGIDLSQVYELLEKDYRMERPEGCPEK
PDB 408 420 430 440 450 460 467
DSSP
PDB VYELMRACWQWNPSDRPSFAEIHQAFETMFQES
PDB 468 480 490 498

GENE AFF1

1D3C

ENTRY NAME	CDGT2_BACCI New! **View this entry in our Beta site**
ACCESSION NUMBER	P43379
Integrated into Swiss-Prot on	1995-11-01
Sequence was last modified on	1995-11-01 (Sequence version 1)
Annotations were last modified on	2007-11-13 (Entry version 69)
NAME AND ORIGIN OF THE PROTEIN	
PROTEIN NAME	Cyclomaltodextrin glucanotransferase precursor
Synonyms	EC 2.4.1.19 Cyclodextrin-glycosyltransferase CGTase
GENE NAME	cgt
SOURCE ORGANISM	Bacillus circulans
TAXONOMY ID	1397 [NCBI, NEWT]
LINEAGE	Bacteria; Firmicutes; Bacillales; Bacillaceae; Bacillus
PROTEIN EXISTENCE	Evidence at protein level



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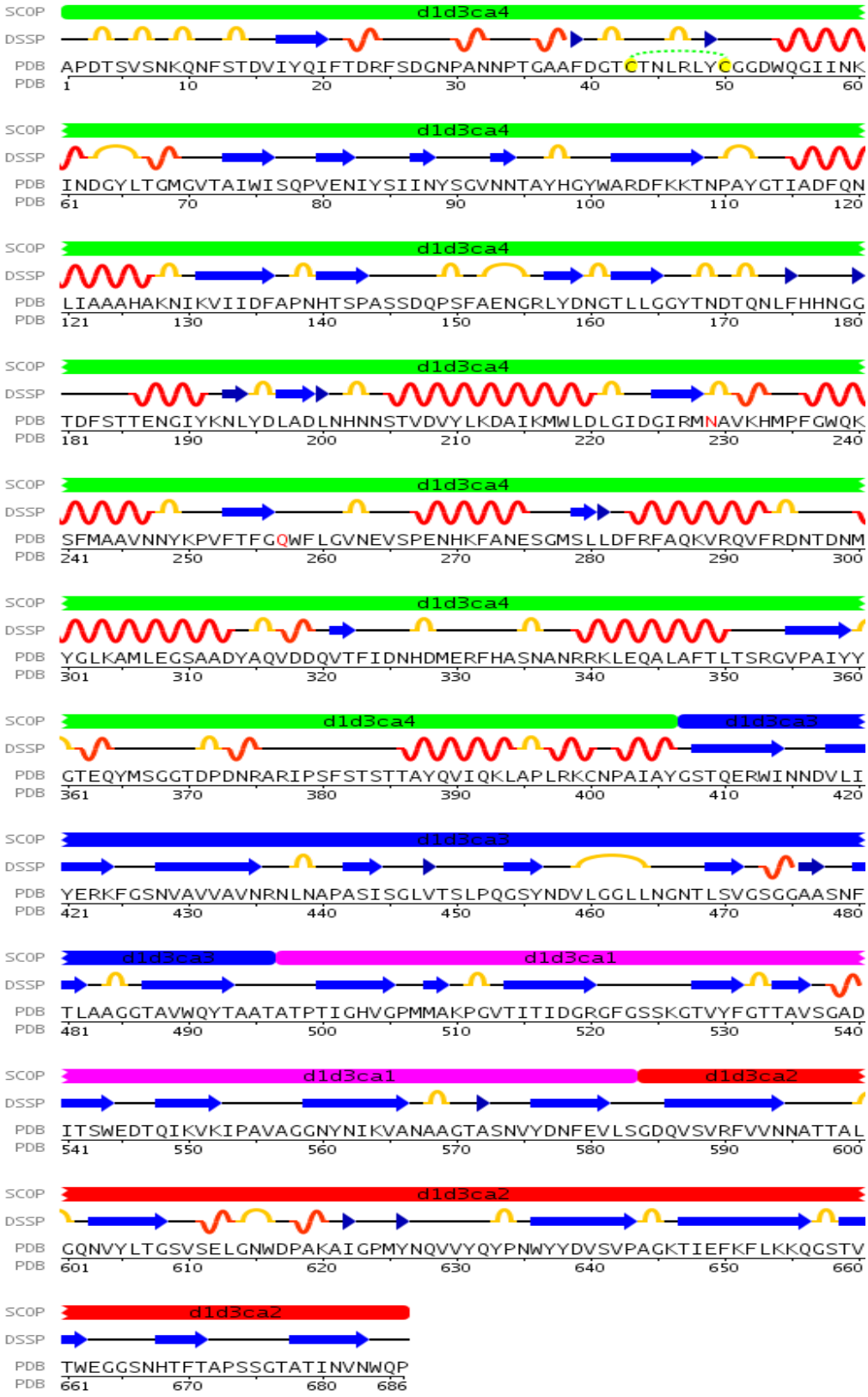
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PDB 1 10 20 30 40 50 60
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DSSP
PDB INDGYLTGMGVTAIWISQPVENIYSIINYSGVNNTAYHGYWARDFKKTNPAYGTIADFQN
PDB 61 70 80 90 100 110 120
SCOP d1d3ca4
DSSP
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PDB 121 130 140 150 160 170 180
SCOP d1d3ca4
DSSP
PDB TDFSTTENGIYKNLYDLADLNHNNSTVDVYLKDAIKMWLDLGIDGIRMNAVKHMPFGWQK
PDB 181 190 200 210 220 230 240
SCOP d1d3ca4
DSSP
PDB SFMAAVNNYKPVFTFGQWFLGVNEVSPENHKFANESGMSLLDFRFAQKVRQVFRDNTDNM
PDB 241 250 260 270 280 290 300
SCOP d1d3ca4
DSSP
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PDB 301 310 320 330 340 350 360
SCOP d1d3ca4 d1d3ca3
DSSP
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PDB 361 370 380 390 400 410 420
SCOP d1d3ca3
DSSP
PDB YERKFGSNVAVVAVNRNLNAPASISGLVTSLPQGSYNDVLGGLLNGNTLSVGSGGAASNF
PDB 421 430 440 450 460 470 480
SCOP d1d3ca3 d1d3ca1
DSSP
PDB TLAAGGTAVWQYTAATATPTIGHVGPMMAKPGVTITIDGRGFGSSKGTVYFGTTAVSGAD
PDB 481 490 500 510 520 530 540
SCOP d1d3ca1 d1d3ca2
DSSP
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PDB 541 550 560 570 580 590 600
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PDB 601 610 620 630 640 650 660
SCOP d1d3ca2
DSSP
PDB TWEGGSNHTFTAPSSGTATINVNWQP
PDB 661 670 680 686


About Software

Software used:-

- **LIGAND SCOUT**
- **RASMOL**
- **HEX**

about the software

Introduction to LigandScout

LigandScout is a powerful structure-based pharmacophore generator based on a sophisticated and customizable ligand-macromolecule complex interpretation algorithm.

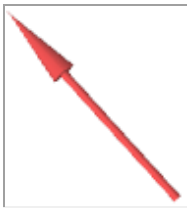
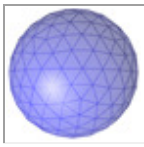
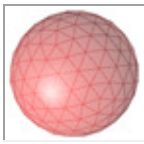
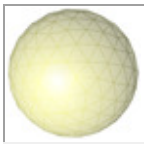
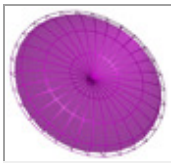
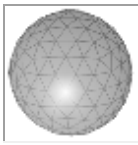
LigandScout extracts and interprets ligands and their macromolecular environment from PDB files and automatically creates and visualizes advanced 3D pharmacophore models supporting multiple features per heavy atom to broaden the scope of a single model. A wide range of powerful editing tools lets you generate customized, highly specific pharmacophores within a few seconds. Excluded volume recognition drastically increases selectivity by considering sterical characteristics of the binding site.

This manual provides an exhaustive documentation of all LigandScout features and gives workflow guidelines for the generation of structure-based pharmacophores and the preparation for external virtual screening applications

Pharmacophore analysis

Pharmacophore Feature Definitions

LigandScout provides the follwing pharmacophore features for automated pharmacophore generation:

Pharmacophore Feature	Depiction in LigandScout
Hydrogen Bond Donor	
Hydrogen Bond Acceptor	
Positive Ionizable Area	
Negative Ionizable Area	
Hydrophobic Interactions	
Aromatic Ring	
Excluded Volume	

Starting the Automated Pharmacophore Generation Procedure

In Active Site View, simply press F9 on your keyboard to start the analysis. Alternatively, you may also use the *Create Pharmacophore*  button or the *Create Pharmacophore* command in the *Pharmacophore* menu. LigandScout will calculate the pharmacophore model within seconds.

LigandScout is designed for the retrieval of automatically created advanced 3D pharmacophore models supporting multiple features per heavy atom to broaden the scope of a single model. However, not all external in-silico screening applications support the wealth of pharmacophore feature handling which is incorporated into LigandScout.

If you are using the software-packages Catalyst or MOE, it is recommended to use the Create Simplified Pharmacophore routines to achieve best compatibility to these external software applications.

You may also reduce advanced pharmacophores for Catalyst or MOE by manually deleting features. In this case, it is recommended to first delete features interacting with water molecules and then to erase features that have unfavorable distances and angles. Try to obtain the best feature(s) for every heavy atom. You may also use literature to sort out interactions. Tutorials on pharmacophore preparation for Catalyst and MOE provide more detailed information on this issue.

Please note that simplified pharmacophores are less restrictive and do not represent LigandScout's full capacity of pharmacophore generation.

Aligning Pharmacophores and Molecules

LigandScout supports alignments of pharmacophores and molecules in arbitrary combinations. Alignments are always performed pairwise no matter how many elements are to be aligned. Therefore, it is necessary to mark one structure as reference element. In case the user did not specify a reference element explicitely, LigandScout will automatically

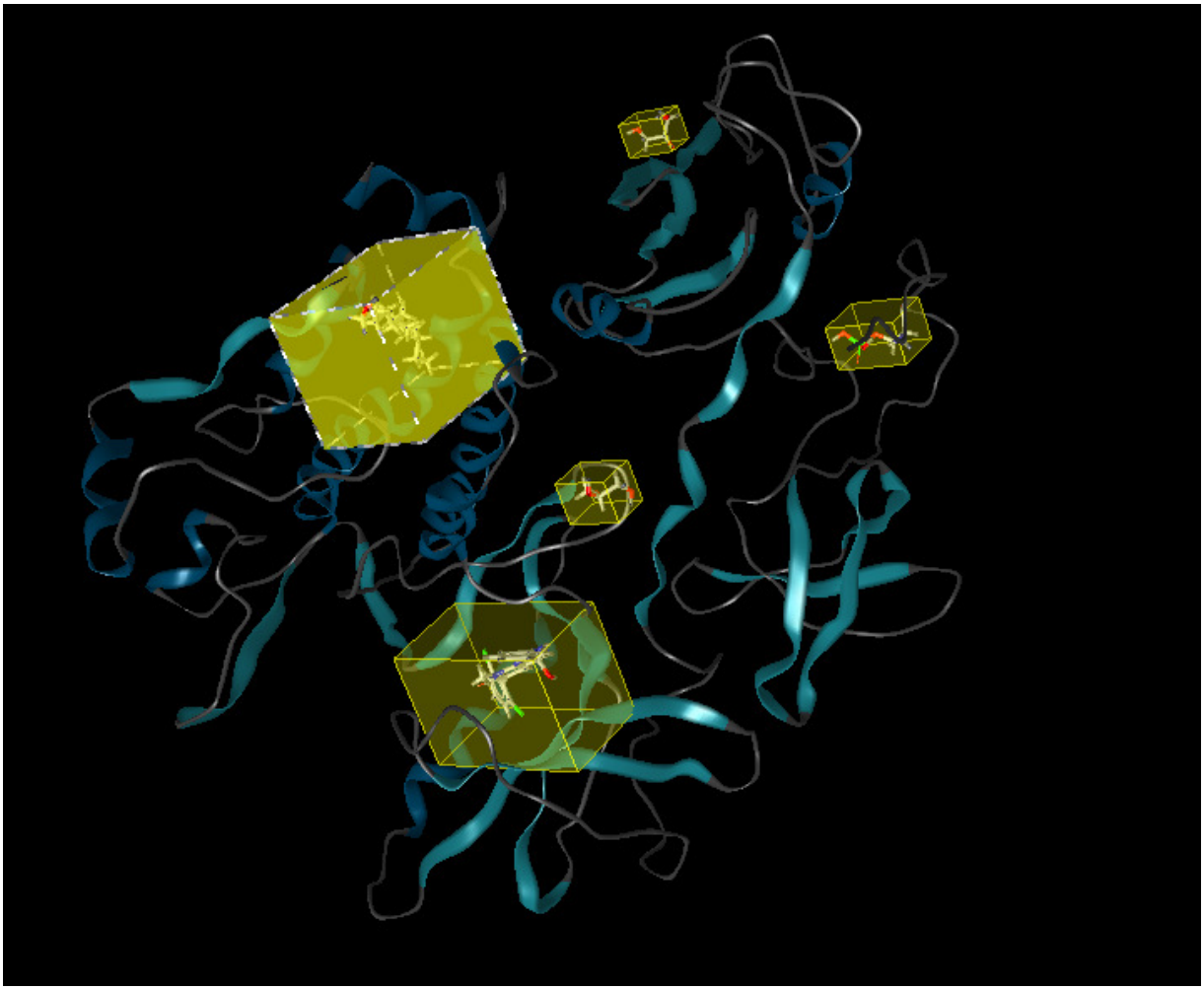
choose one element from the set of selected elements. All other selected elements will be aligned to this reference element.

A single alignment is based on matched chemical features (feature pairs) where one feature must be of the reference element's feature set and the other must be from the feature set of the element to be aligned to the reference element. For pharmacophores these chemical features are given explicitely. However, for molecules these features have to be derived during the alignment algorithm and for the sake of clarity these are not visible to the user.

There are various ways to adjust the alignment algorithm. Please have a look at the Preferences/Alignment Settings for details. Please refer to the PDB Panel or the Bookmark Panel to get more information of how to add pharmacophores and molecules to the alignment list. For more information on possible interactions in the alignment view please have a look at the Alignment Panel.


Pharmacophore analysis

2FO0



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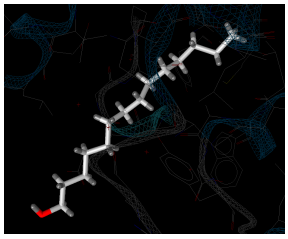
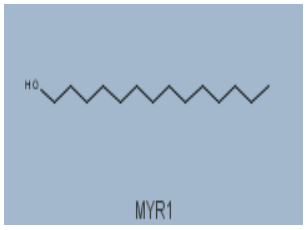
Class*:* Transferase
Source*:* Homo Sapiens, Human
Resolution*:* 2.2
Deposition date*:* Jan 12, 2006
Experimental type*:* X-Ray Diffraction

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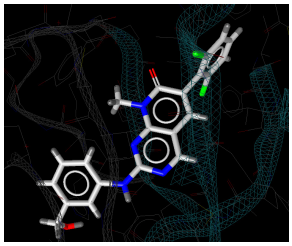
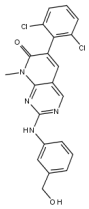
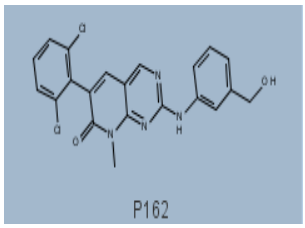
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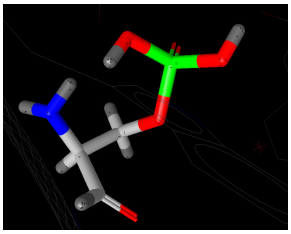
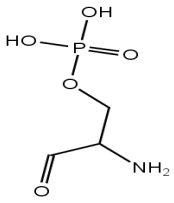
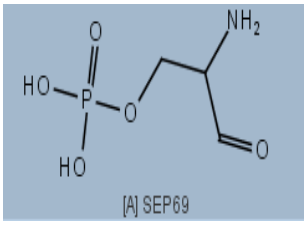
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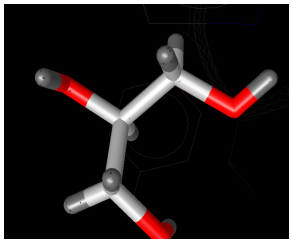
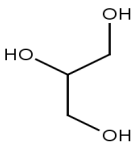
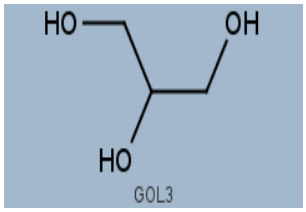
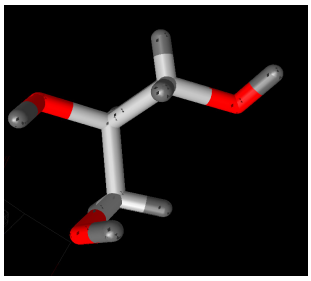
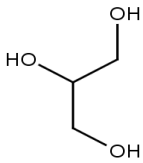
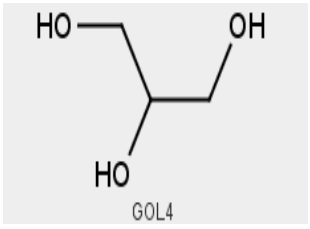



GOL3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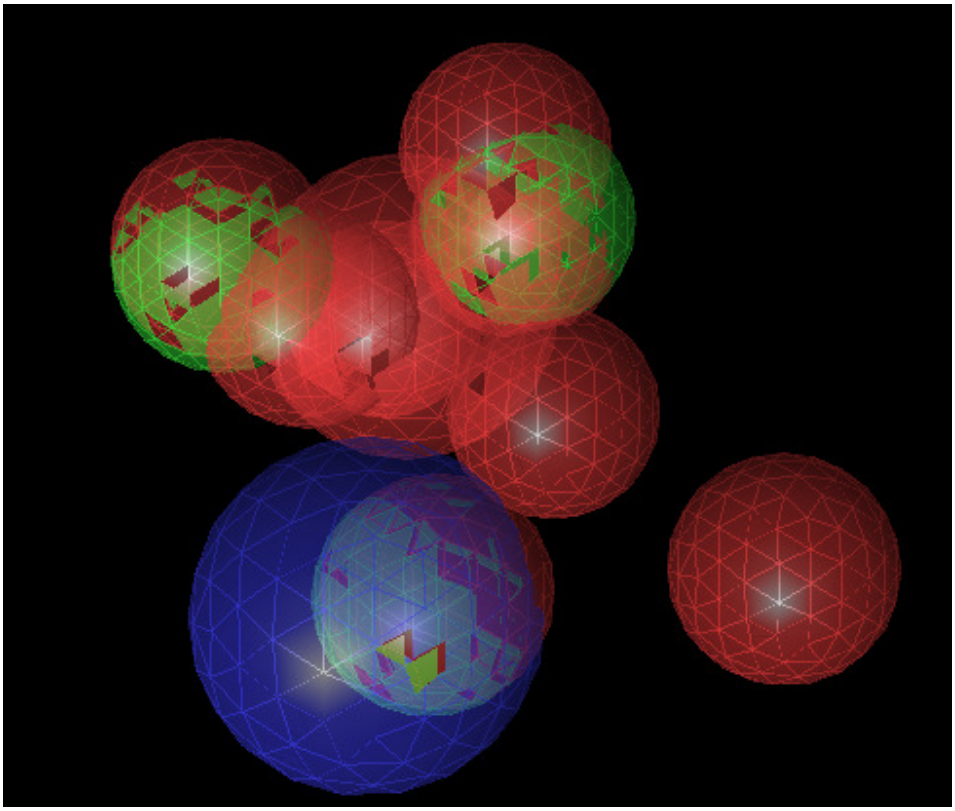
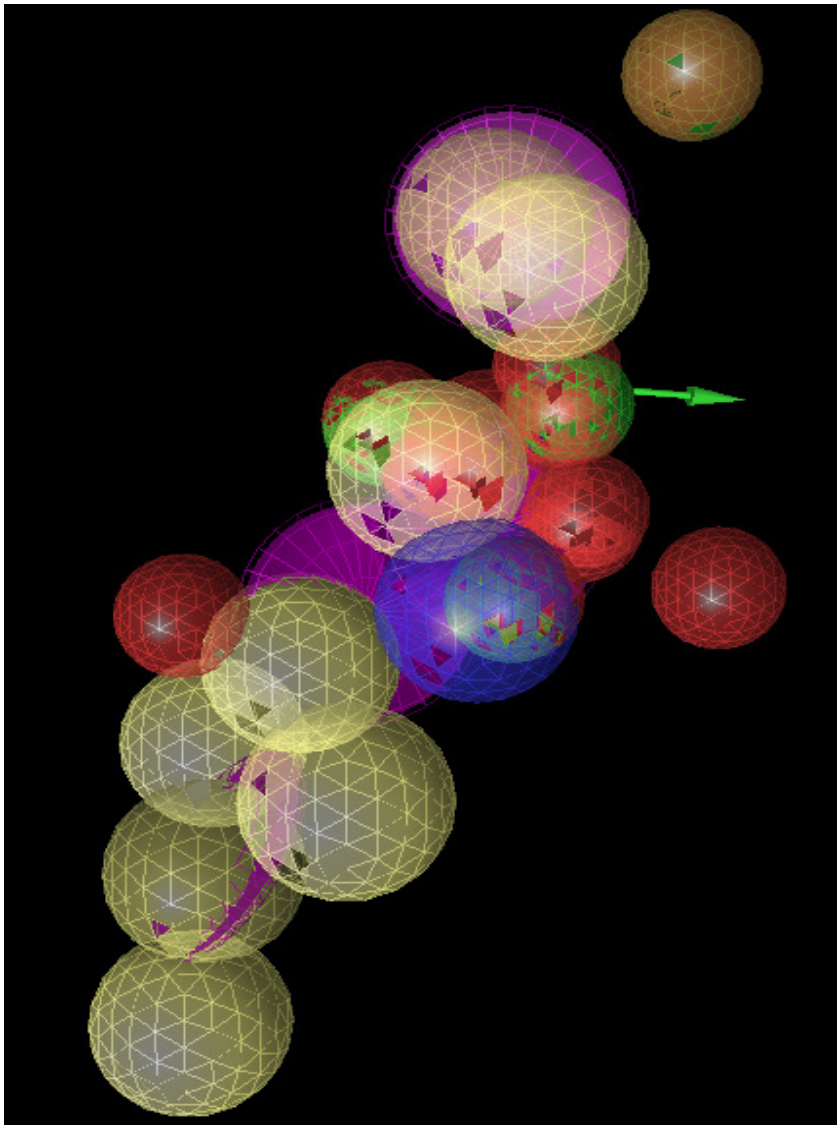


First merged structure after alignment

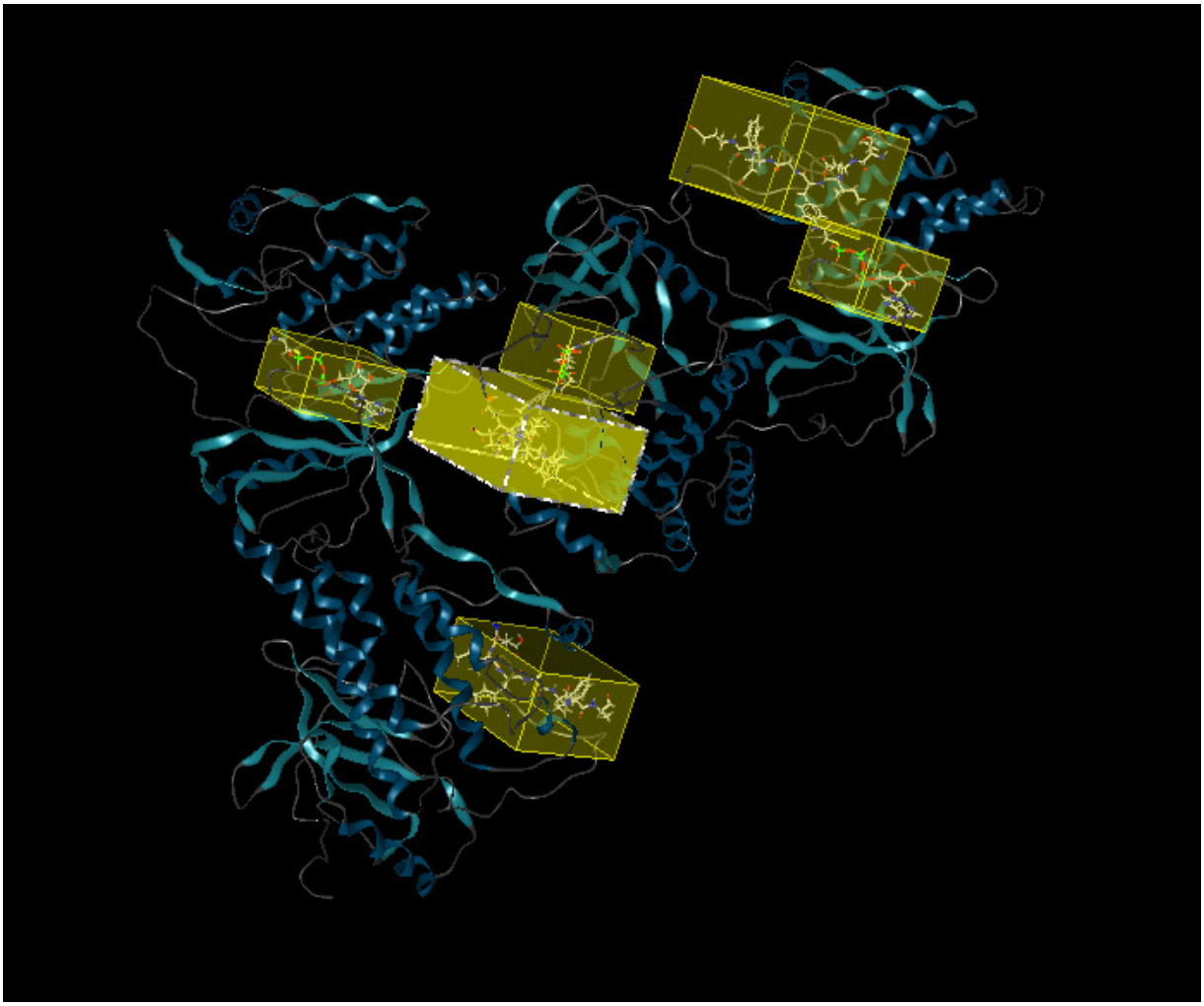
In this structure the merged structure we found that the negatively charged areas are more than the positively charged areas but there are no hydrophobic centers are absent at the first time sharing but there is a large positively charge area that I think will reduce the effect of the pharmacophore formed.



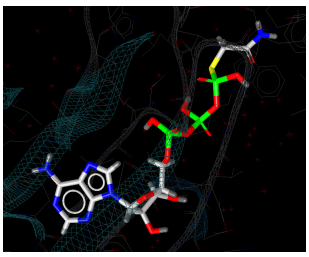
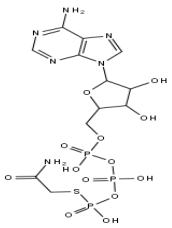
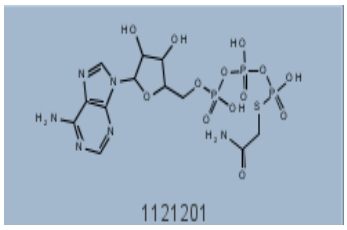
second merged structure after multiple times of alignment and filteration

but in the second case after the filteration due to the multiple sharing of the molecules the structure generate some of the hydrophobic regions and that are the site make us confirm that the molecules are having the ability to be the pharmacophore and the this shared structure generates the single hydrogen donor site so we can say that the molecule having the less possibility to form the pharmacophore so that the molecule generated in this is less active than the first one

2G1T



Title*:* A Src-Like Inactive Conformation In The Abl Tyrosine Kinase Domain
Class*:* Transferase
Source*:* Homo Sapiens, Human
Resolution*:* 1.8
Deposition date*:* Feb 14, 2006
Experimental type*:* X-Ray Diffraction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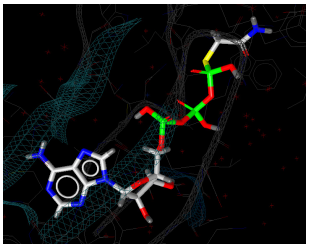
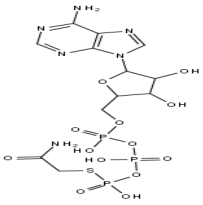
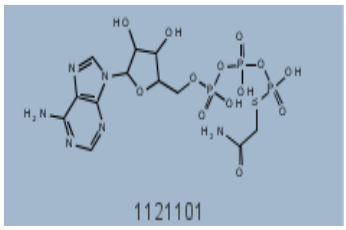
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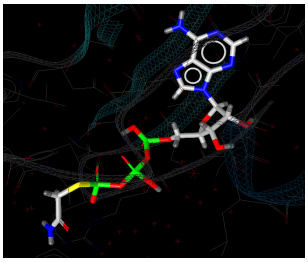
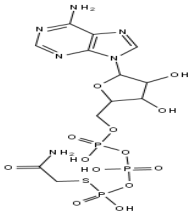
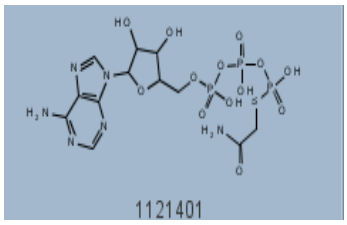
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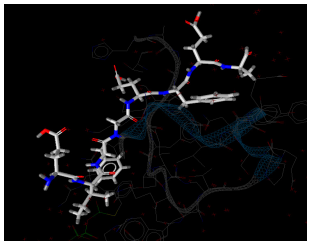
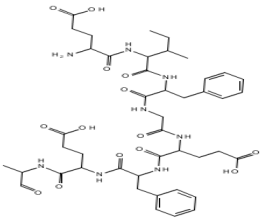
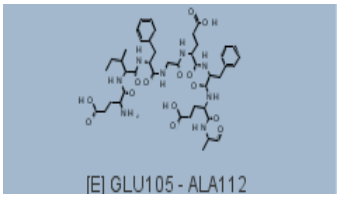
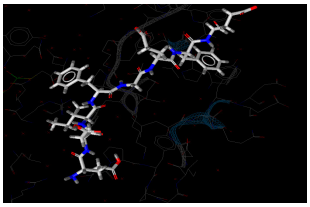
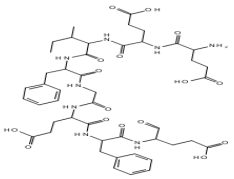
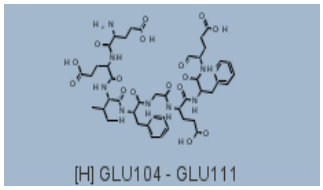
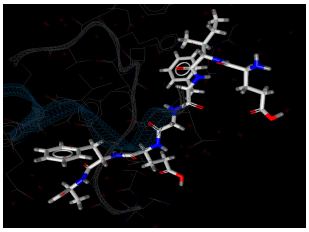
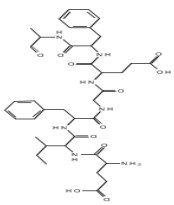
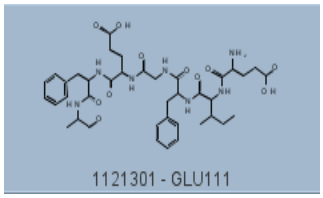
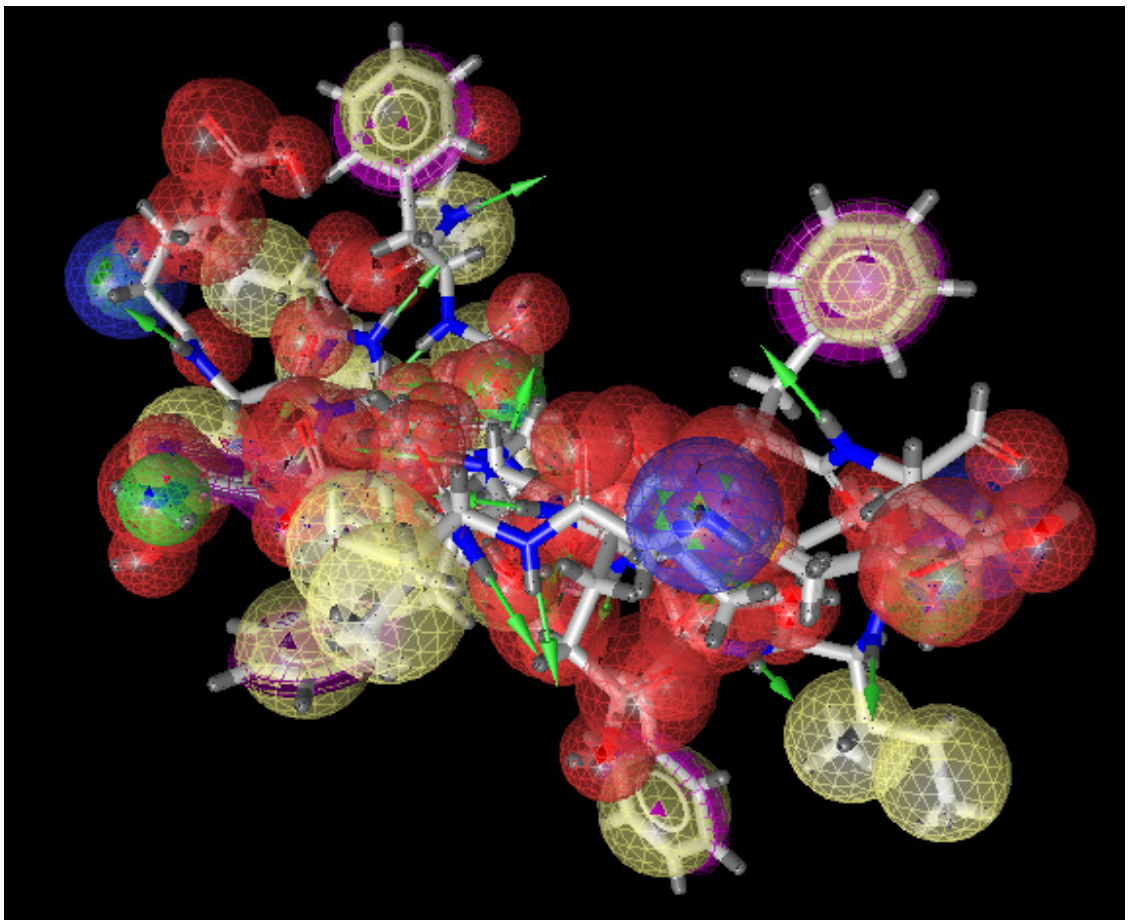



[E] GLU105 - ALA112




[H] GLU104 - GLU111

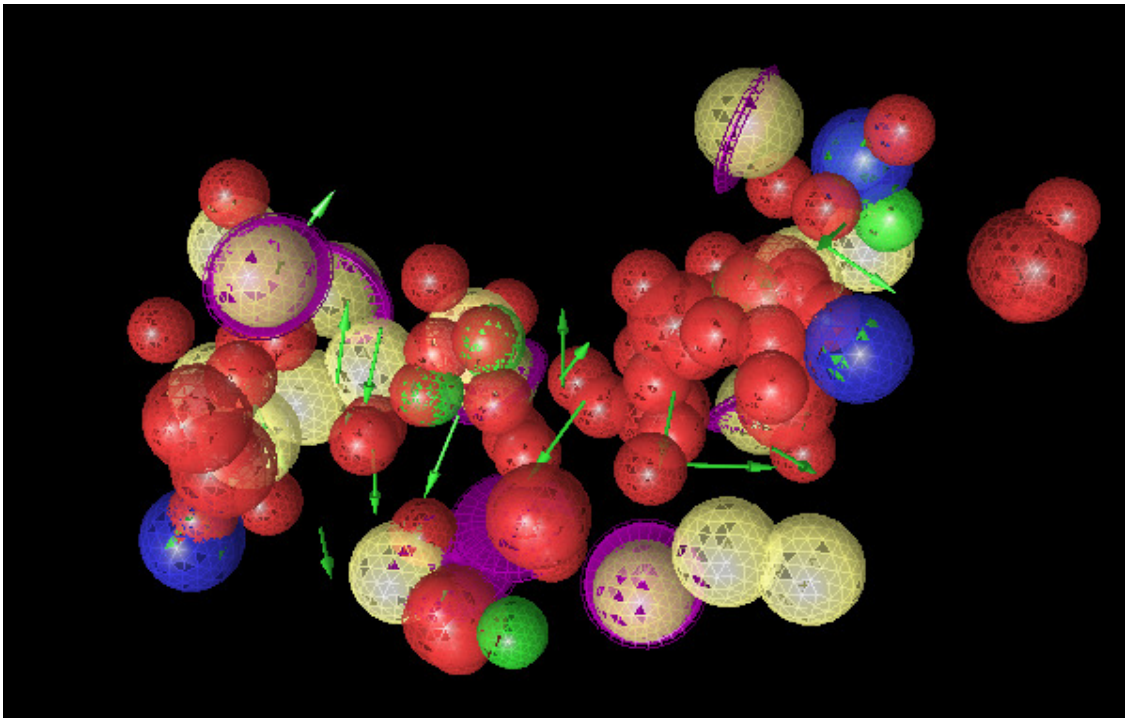



1121301 - GLU111

first merged structure after alignment



the merged structure geneated from the multiple time merging so that the error will be reduced

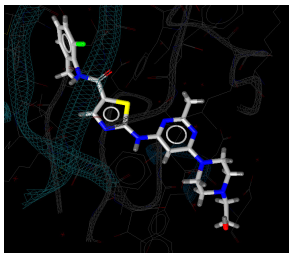
these are the structure generated from the ligand molecule after the alignment and the structure are generated according to the common features in the molecules that are generated through the software. here in the case of the pharmacophore models the structure with the more negativele ionizable areas are the more prone towards the formation of the stable bond between the ligand and the receptor and that have the more ability to form donate the hydrogen that the greeen arrow that is the representation of the area and that property is helping the molecule to form the hydrogen bond with the receptor**.**

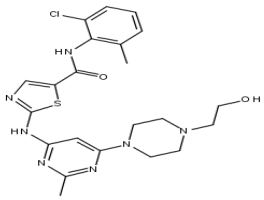


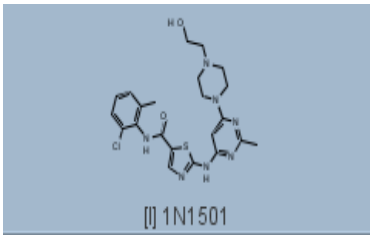
In the second part we are just share the structure till the further no sharing will drawn from that it will confirm that the structure are drawn are the confirmed that will have no further modification and we find that the hydrophobic and the negatively charged center are more densed and the hydrogen donors are the more efficient in the case of these shared structure and give the confirmations that the ligand have the following types of thew structure will be the best fit and the more viable according to me.the aromatic rings and the positive ionized areas are the least conformational sites and play a very low rate of pharmacophore activity. But the question is that the presence of these groups are also the vital part because the energy minimization and the compactibility will maintained.

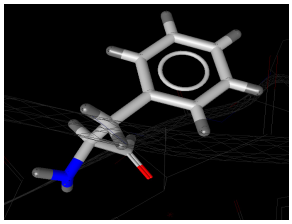
2GQG

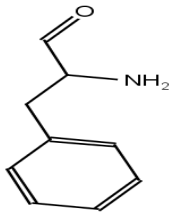
Title*:* X-Ray Crystal Structure Of Dasatinib (Bms-354825) Bound To Activated Abl Kinase Domain
Class*:* Transferase
Source*:* Homo Sapiens, Human
Resolution*:* 2.4
Deposition date*:* Apr 20, 2006
Experimental type*:* X-Ray Diffraction

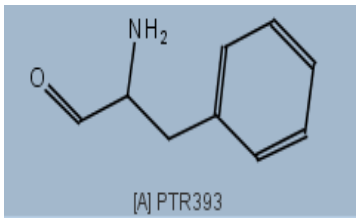


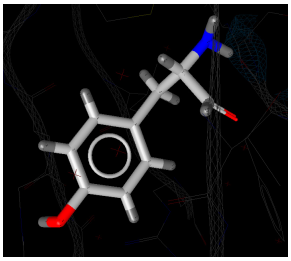


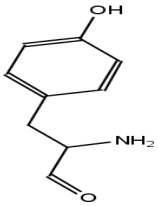

[I] 1N1501

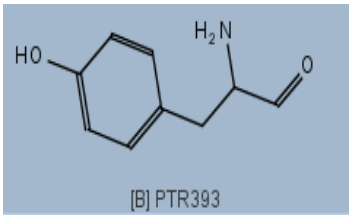


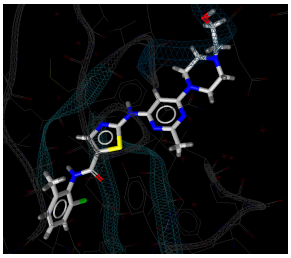

O
NH2

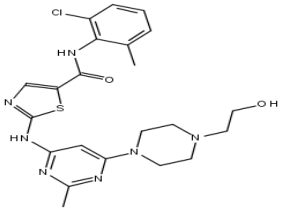

NH2
O
[A] PTR393

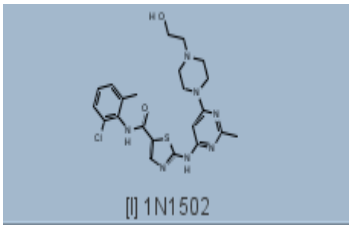


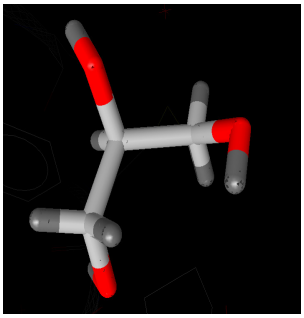

OH
NH2
O

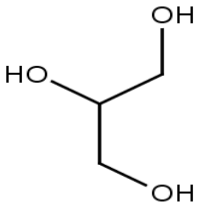

HO
H2N
O
[B] PTR393

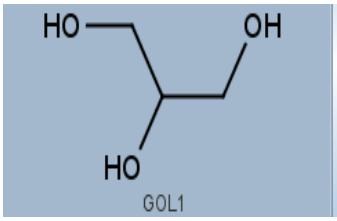


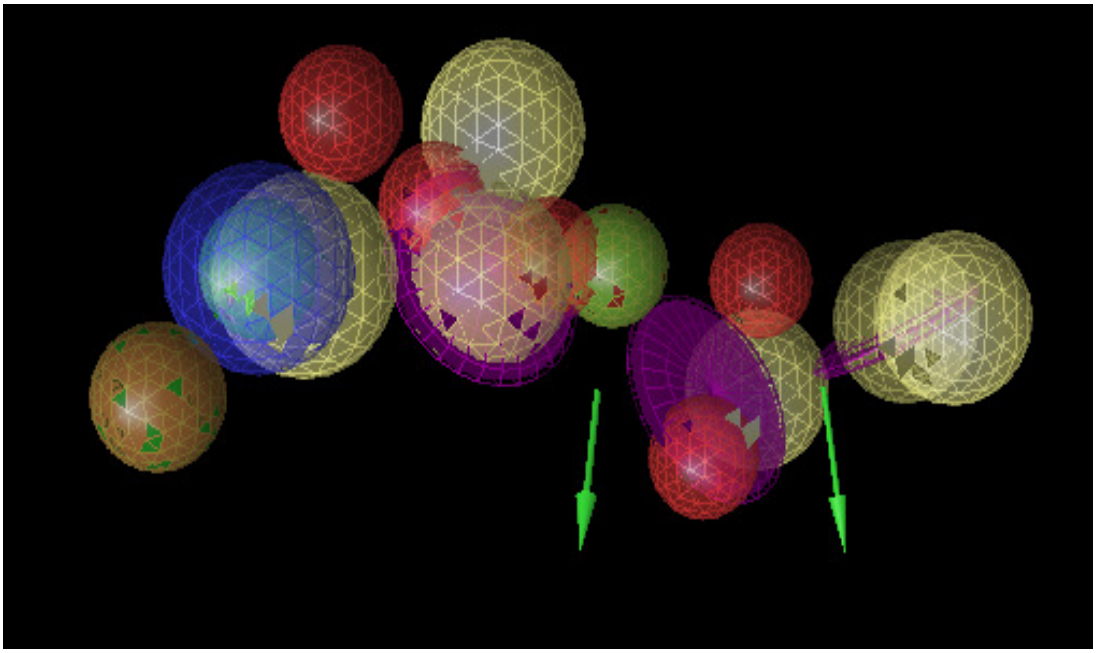

Cl
HN
O
N
S
HN
N
N
N
OH


HO
Cl
[I] 1N1502



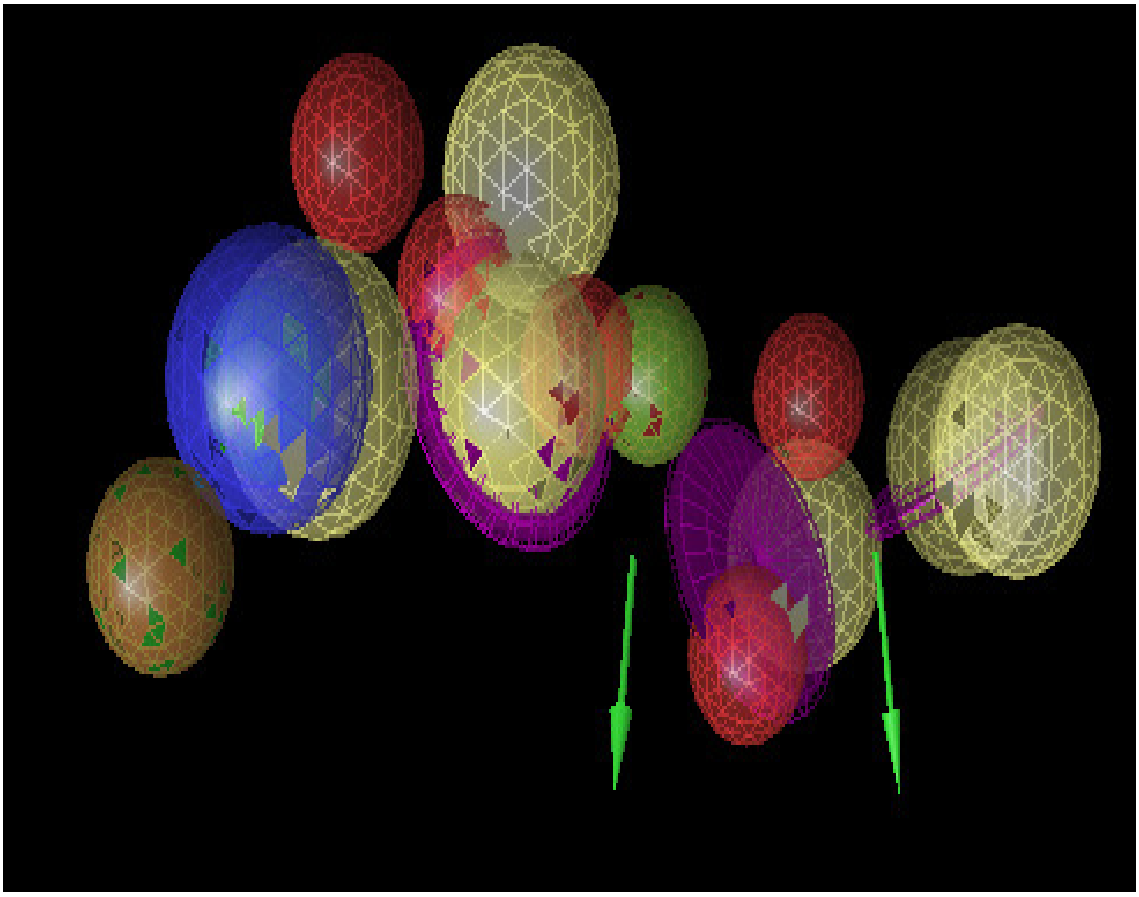

OH
HO
OH


HO
OH
HO
GOL1



After the first alignment and the shared structure generated

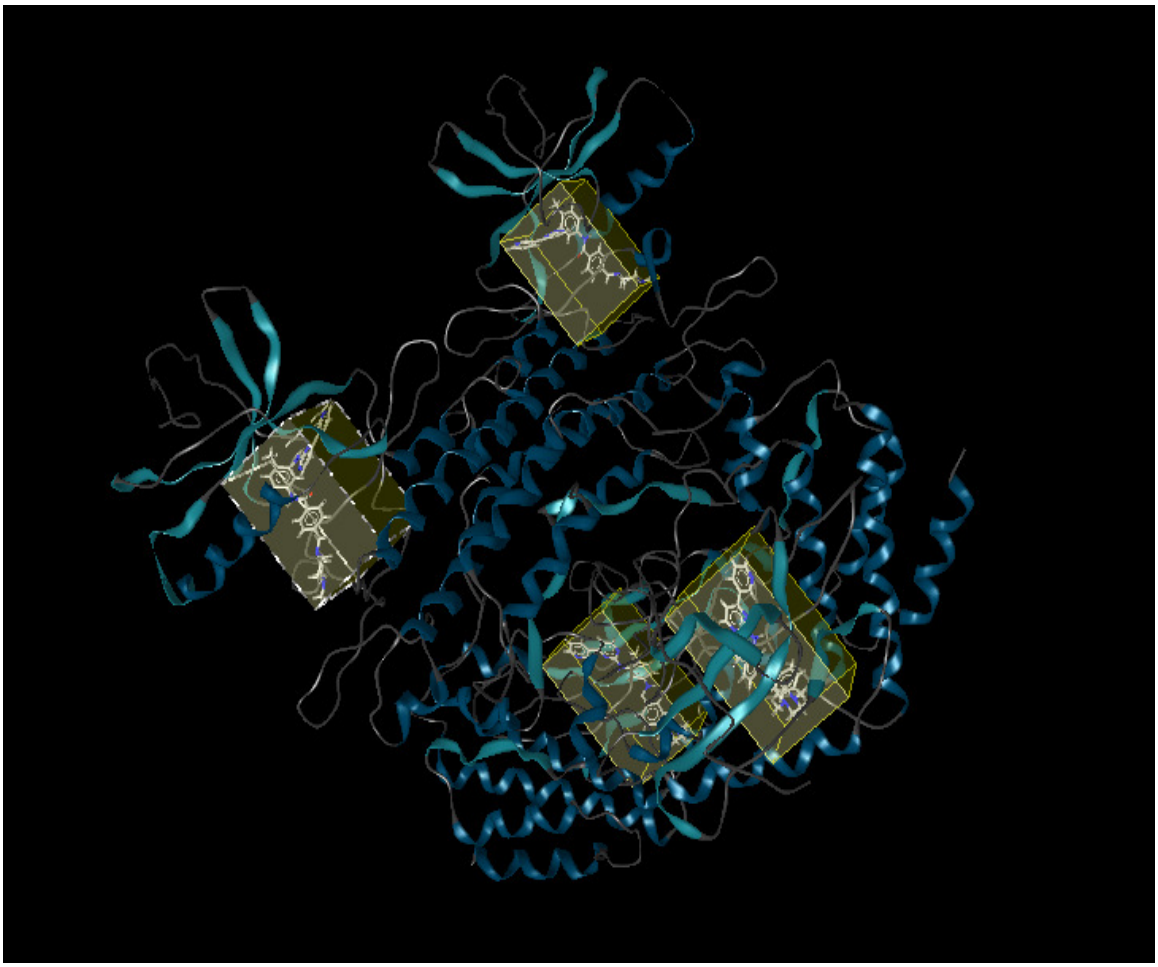
After the first sharing of the ligand molecules the structure generated is the good areas of pharmacophoric activity, but the problem is that the hydrophobic areas are presents at the distance regions and that are having the intermediate positively charged areas and also the aromatic rings and also having the hydrogen donor areas that are the ability to form the pharmacophore center but due to the different group that are discussed the energy is become very less but thing is that the ability of the pharmacophore is more than the previous one.



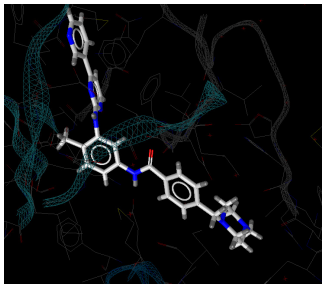
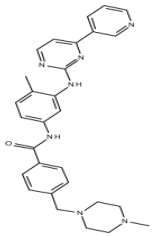
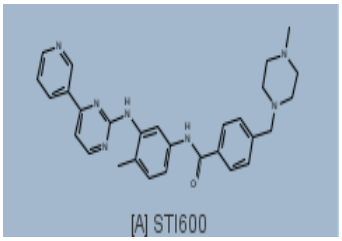
After the multiple time alignment and merged the shared structures

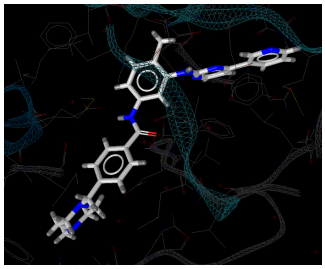
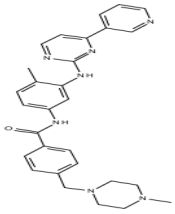
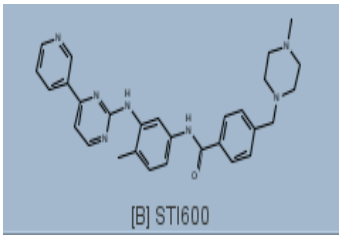
After the filtration by the sharing of the molecules again and again the change is only a few so that the molecule is as it is.

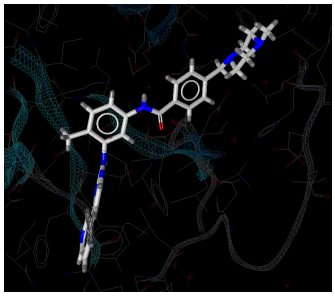
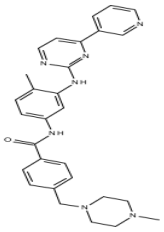
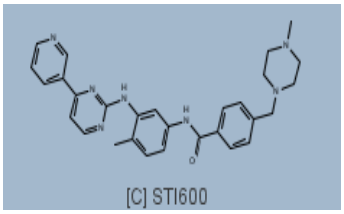
2HYY

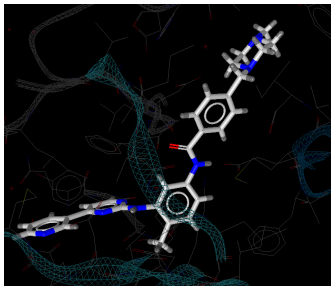
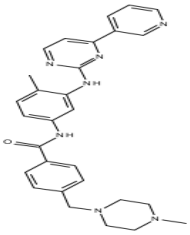
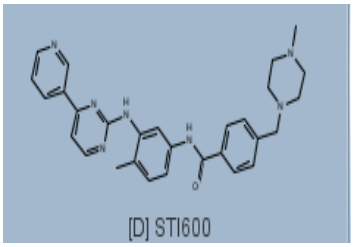


Title*:* Human Abl Kinase Domain In Complex With Imatinib (Sti571, Glivec)
Class*:* Transferase
Source*:* Homo Sapiens, Human
Resolution*:* 2.4
Deposition date*:* Aug 08, 2006
Experimental type*:* X-Ray Diffraction




[A] STI600




[B] STI600




[C] STI600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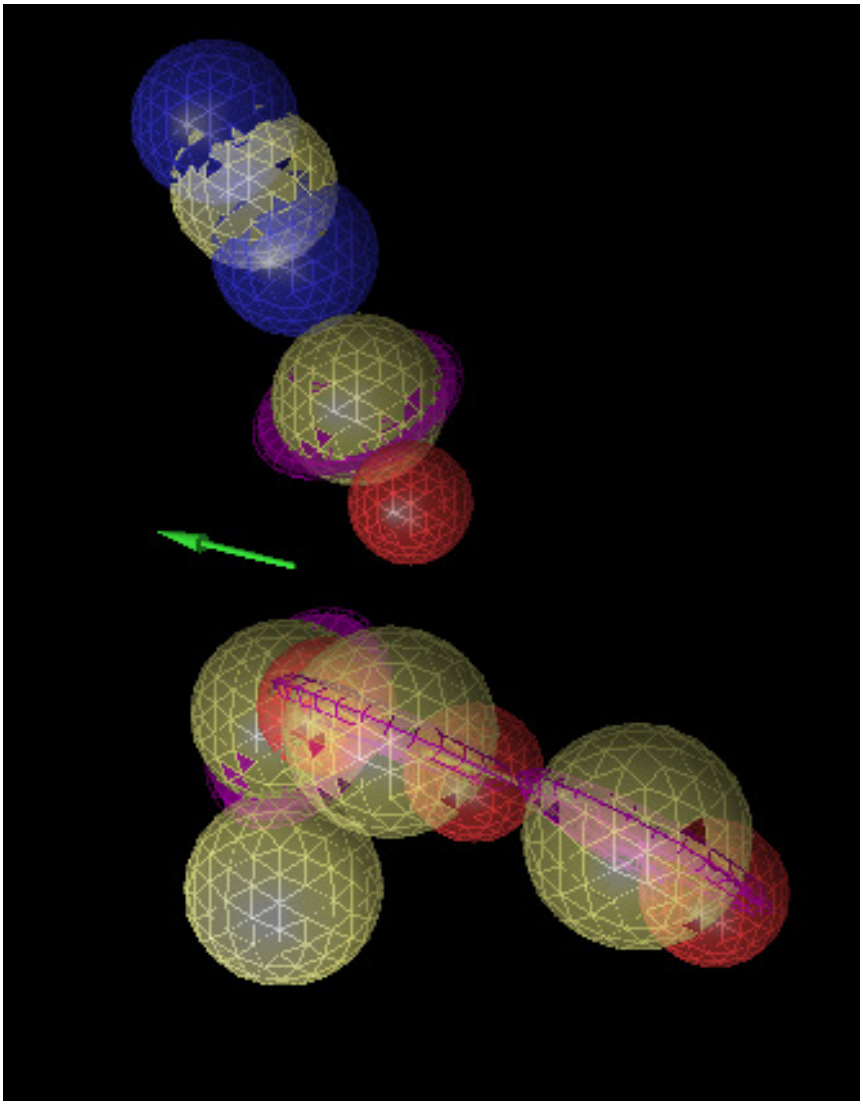
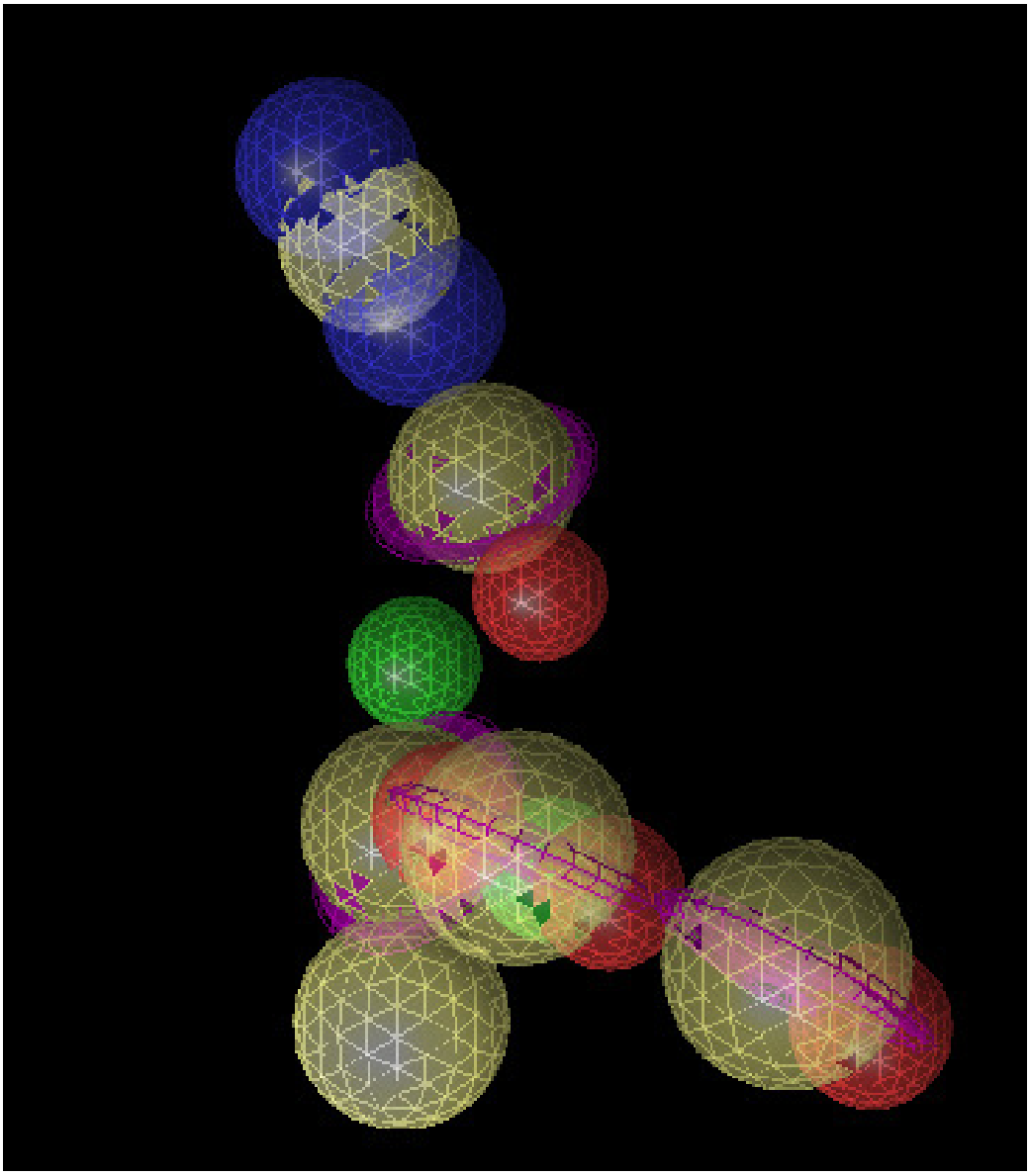


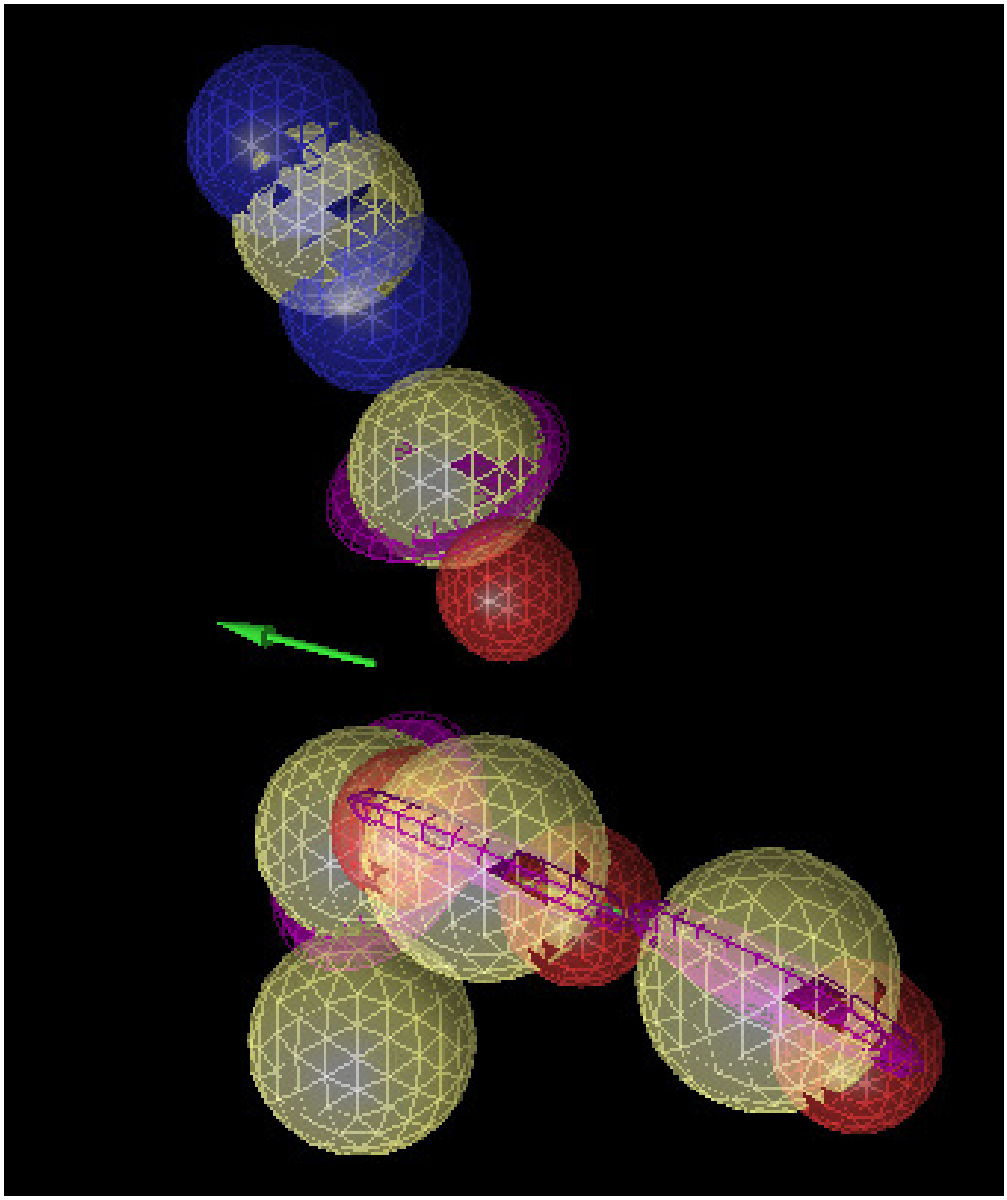
Shared structure after the first alignment

In this the shared structure generated is the structure with the more hydrophobic area and the single hydrogen donor area.



Merged structure after firdt alignment

Merged structure are showing something different that the hydrogen donor region disappears and the hydrophobic and the positive charged areas are going to merge and decrease the reate of the pharmacophoric activity.



Merged structure after the filteration through the multiple sharing

After the multiple sharing there is the slight difference in the first time shared structure and the structure have the reappearance of the hydrogen donor so that the property become some what same as the first shared structure.


DISCUSSION

DISCUSSION

From the above study of the four proteins we found that the proteins are having the difference in the receptor percentage and the molecules are the ability to form the drug molecule. We found that the protein molecule that is the 2G1T is the best one for the pharmacophore modeling and the 2GQG is the next to that and the other twos are 2FO0 and 2HYY are having the less if we make it in the order then the molecule of the pharmacophoric activity will be

2G1T > 2GQG > 2FO0 > 2HYY


CONCLUSION

CONCLUSION

from the above study of the molecules of protein we found the pharmacophore cores and that are the main regions for the drug activity study of the particular compound and the further study of these pharmacophore sites are helpful for the formation of the drug molecule. we are using the software which designing the pharmacophore on the basis of the pharmacophore activity. hydrogen donor activity and the molecule with the best donor of the hydrogen have the ability to form the pharmacophore.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REFERENCE

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October, 2012 after coming from Cambridge (UK) to India, I have started working with Government Registered Organization SIFS INDIA where I use to deal with various types of Forensic Services: such as Forensic Education, Forensic Investigation, Forensic Training, Forensic Internship, Forensic Research, Security Services, and Scientific Equipment Department. In SIFS INDIA, I have experience of taking fingerprints from dead bodies, criminals and suspect, from crime scenes, Police Clearance Certificate (PCC) for private organizations, visa immigrations and for FBI on real cases. In addition, I have also given my expert reports, expert opinions after analyzing many hand writing, signature and fingerprints cases, also MMS cases, case of motor vehicle identification, and case of voice forgery reorganization.