

Three-dimensional Structure Prediction of the Human LMTK3 Catalytic Domain in DYG-in Conformation

Loubna Allam^{1,2*}, Wiame Lakhilili¹, Zineb Tarhda¹, Jihane Akachar¹, Fatima Ghrifi¹, Hamid El Amri² and Azeddine Ibrahim¹

¹Biotechnology Laboratory (Medbiotech), Rabat Medical and Pharmacy School, MedBiotech Center, Mohammed V University in Rabat, Rabat, Morocco

²Genetics Laboratory of Royal Gendarmery, Rabat, Morocco

Abstract

Lemur Tyrosine Kinase 3 (LMTK3) plays a key role in the regulation of a Estrogen Receptor (ER α) activity. It has been defined as an essential actor involved in the endocrine resistance process in breast cancer patients accelerating the dispersion and invasion of tumor cells which are the first steps of the metastatic process. In the absence of a crystallized structure of LMTK3 and in order to study its inhibition, we generated its tridimensional structure. We constructed the LMTK3 kinase in its active state (DYG-in) using the homology modeling approach. The evaluation of the generated model by several tools indicated the reliability of the predicted 3D structure and the good quality of the stereochemical characteristics model were confirmed by the PROCHECK tool. In conclusion, the docking approach used to study LMTK3-ATP interaction allows us to determine key residues of the ATP binding site that may be useful in the design of potential competitive ATP inhibitors of human LMTK3.

Keywords: Homology Modelling; LMTK3 Kinase; Docking; ATP; Binding Site

Introduction

Cells having multi-drug resistance are characterized by high expression of membrane proteins [1]. In breast cancer cases, inhibition by anti-estrogen in particular by tamoxifen modifies the estrogens response and its resistance is a complex problem requiring the discovery of new regulatory therapeutic targets. These effectors could modulate estrogen receptor (ER) pathways, responsible for the development of mammary gland hemostasis and the growth of the majority of breast tumors. This resistance, also, involves a powerful regulator, the lemur tyrosine kinase3 (LMTK3), which is overexpressed in more aggressive forms of breast cancer [2,3]. More recently, important efforts have been concentrated on the discovery of the LMTK3 protein role in cell growth, survival, motility, and cell proliferation leading to its involvement in multiple cancer types [4-7]. The 3D structure prediction of LMTK3 binding site could be a first step towards understanding the role played by this protein in metastasis and development of different cancers.

The functional state of a kinase protein can be characterized by the DFG motif position (Asp-Phe-Gly), preserved in most kinases and rarely by the D [LWY] G.(8) LMTK3 is one of the rare kinases proteins with DYG motifs flexible in their activation loop [9] and can reveal a conformational heterogeneity between the active (state in) and inactive (state out) conformations [9]. Some kinases with in an active state (DFG-in) were shown to allow the ATP molecule to bind to a highly conserved pocket, located in depth between the two lobes and forms hydrogen bonds with the "hinge" region [10,11]. Therefore, inhibiting the activity of these kinases, requires the use of small molecules preventing the attachment of ATP to the hinge (ATP pocket region).

Lemur tyrosine kinase (LMTK3) is a member of the LMTK family, located in the position 13.33 of the 19q chromosome. It has 1460 amino acids (a.a) with a catalytic domain of 279 amino acids located between 133 and 411. This kinase appears to serine-threonine-tyrosine kinases family [12-14] which has been defined as an essential actor involved in endocrine resistance process [15]. Furthermore, the overexpression of LMTK3 accelerates the dispersion and invasion of tumor cells which are the first steps of the metastatic process [15]. Giamas et al. claim that

this protein plays a key role in the regulation of a estrogen receptor (ER α) activity [16] by positively regulating the Estrogen Receptor1 gene (ESR1) transcription. LMTK3 improves this transcriptional activation by inhibiting protein kinase C (PKC), responsible for AKT phosphorylation which phosphorylates Forkhead box protein O3 (FOXO3), inducing an increased in the transcriptional activity of ER α [3]. LMTK3 can also directly phosphorylate the ER α protein, by protecting it from the proteasomal degradation mediated by ubiquitin (UB) [16]. Stebbing et al. [2] Reported that the inhibition of LMTK3 kinase after tamoxifen resistance in breast cancer patients, resulted in the re-sensibilization to tamoxifen and suggested that LMTK3 kinase was involved in the resistance of the endocrine system and could be considered as a promising therapeutic target.

In absence of its crystallized structure, we used in silico approaches to generate the LMTK3 kinase 3D structure and study its inhibition mechanism. We constructed the LMTK3 kinase in its active conformation (DYG-in) based on homology modelling approach and evaluated the generated structure. Thereafter, we determined the binding mechanism of ATP molecule with the LMTK3 kinase by studying their interaction using molecular docking approach.

Materials and methods

Sequence extraction and template Selection

The primary structure of the LMTK3 catalytic domain was extracted in its FASTA format from UniProt database (www.uniprot.org) (ID: Q96Q04).

In order to verify the identity between the proposed template and

*Corresponding author: Loubna Allam, Biotechnology Laboratory, Rabat, 10000, Morocco, Tel: +212 537 77 2850; Fax: 212 53 777 3701; E-mail: allamloubna09@gmail.com

Received April 10, 2017; Accepted May 22, 2017; Published May 29, 2017

Citation: Allam L, Lakhilili W, Tarhda Z, Akachar J, Ghrifi F, et al. (2017) Three-dimensional Structure Prediction of the Human LMTK3 Catalytic Domain in DYG-in Conformation. J Biomol Res Ther 6: 151. doi:10.4172/2167-7956.1000151

Copyright: © 2017 Allam L, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

the LMTK3 sequence, we used Blast program (Basic Local Alignment Search Tool) [17] (<http://blast.ncbi.nlm.nih.gov/Blast.cgi>).

Homology modelling

The generation of LMTK3 kinase model by homology modelling approach was based on Swiss Model server [18] (<http://swissmodel.expasy.org/workspace>).

Evaluation of the predicted model

The physical and chemical evaluation of the predicted model used three servers:

Prosa server [19] (<https://prosa.services.came.sbg.ac.at>), can determine the structural model quality based on a Z-score.

ProQ server [20,21] (<http://www.sbc.su.se/~bjornw/ProQ/ProQ.cgi>) evaluates the structure of correct proteins, represented by LGscore and MaxSub scores.

SAVES (Structural Analysis and Verification Server) (<http://nihserver.mbi.ucla.edu/SAVES/>), runs three programs, the Verify-3D program which analyze the compatibility between the atoms of the 3D structure [21,22]. Errat program which analyzes the statistics of the unbound interactions between different atoms types, and allow the determination of the 3D structure overall quality [23] and PROCHECK program, which verifies the stereochemical quality of the predicted 3D structure of LMTK3 using residue-by-residue analysis and the entire geometry of the structure, by constructing a Ramachandran plot [24].

Besides the physic-chemical evaluation we were study the binding of ATP molecule with LMTK3 kinase using molecular docking for validate its active site.

Docking methodology

The molecular docking approach was used for two reasons; the first one was the evaluation of the LMTK3 binding site, and the second was the study of the inhibition of LMTK3 using the inhibitors of InsR.

MGL tools 1.5.6 with AutoGrid4 and AutoDock vina (Scripps) [25] were used for determined the interaction between LMTK3 and ligands. The visualization of the results were done by PyMol software [26].

The docking strategy implicated two steps: 1) firstly, preparation of elements for docking. The docking by Autodock vina requires inputs into “.pdbqt” format. The Mgltools transform the ligands in.Mol2 format and receptor in.pdb format on.pdbqt format. The same tool was

also used to determine the docking box on the receptor. 2) secondly, the docking itself followed by visualization by PyMol.

Ligands selection

ATP molecule and inhibitors used in this research were extracted from PDB database [27].

In the absence of LMTK3 kinase inhibitors with an experimental activity, we selected two inhibitors of InsR kinase. Details of these molecules are in [Table I].

Results

Sequence alignment and Model generation

Among the templates proposed by Swiss-Model server, we selected the protein with the most resolution (2.60Å). The insulin receptor (InsR: ID: 1rqq) had the highest identity percent with the LMTK3 kinase. As illustrate in [Figure 1] the alignment between LMTK3 kinase in DYG-in conformation and InsR primary sequence using Blast program reveled an identity of 37%. [Figure 2] shows the generated model of LMTK3 kinase with different key parts and [Figure 3] demonstrate the visualized superposition between the model of LMTK3 kinase and the resolved 3D structure of the template. The RMS of this superposition was 0.329Å which confirms the high identity between the superposed proteins.

Evaluation and validation of the structural model

The quality of the predicted model was performed by PROCHECK server presented by Ramachandran diagram which allows the viewing of the distribution of torsion angles phi and psi in the 3D structure. The Ramachandran graph in [Figure 4] revealed the presence of a large number of helices segments of the model regrouped around psi ~ -50 and phi ~ -50 with 90% of residues (217 amino acids) in the most favored region, 7.9% of residues (19 amino acids) in the supplementarily permitted region, 1.2% of residues (3 amino acids) in the generously allowed region and 0.8% (2 amino acids) in the disallowed region. [Figure 5] showed that two residues (His221 and Thr71) were found in disallowed region are to very long distances from the pocket the

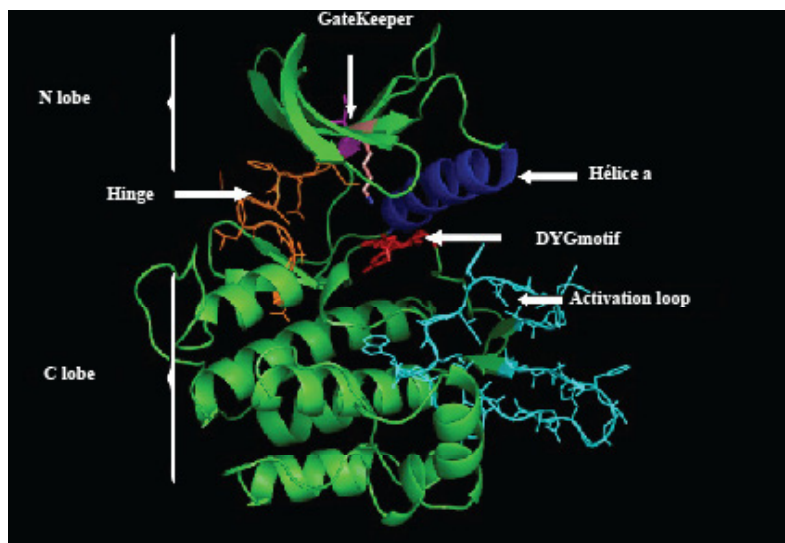
Ligands ID PDB	Receptor ID PDB	Resolution (Å)
112	1rqq ^a	2.6 Å
IR1	4IBM	1.8 Å

Note: ^a1rqq is the template used to generate the model. LMTK3: Lemur Tyrosine Kinase 3; PDB: Protein Data Bank; 3D: Three-dimensional

Table 1: Ligands used to assess 3D model of de LMTK3 DYG-in.

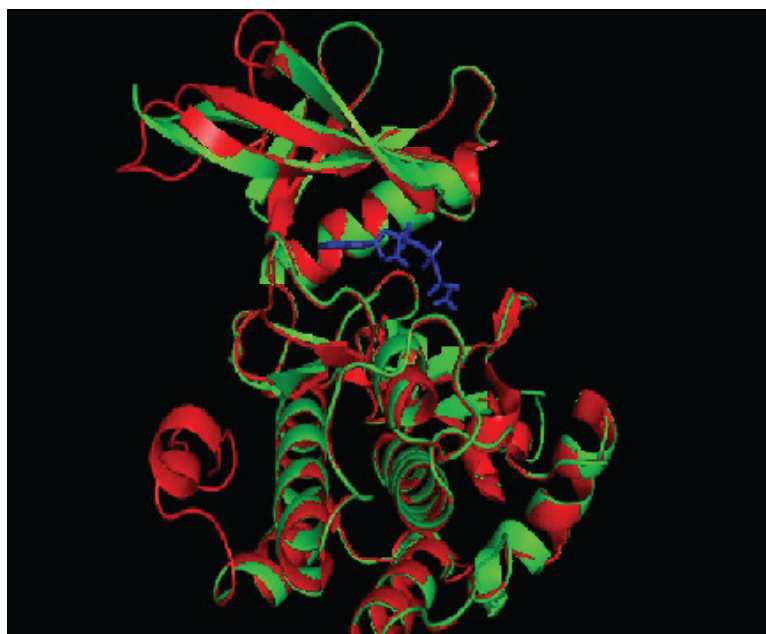
LMTK3	1	LSYLQEIGSGWFGKVLG---EIFSDYTPAQVVKELRASAGPLEQRKFISEAQPYRSLQ	57
InsR	1	++ L+E+G G FG V G +I +V VK + SA E+ +F++EA +	60
LMTK3	58	HPNVLQCLGLCVETLPFLLIHEFCQLGDLKRYLRAQRPPPEGLSPELPPRDLRTLQRMGLE	117
InsR	61	+V++ LG+ + P L++ME GDLK YLR+ RP +P PP L+ +M E	128
LMTK3	118	CHHVRLLGVSXGQPTLVVMEMLMAHGDLKSYLRSLRPEAENPGRPPPTLQENIQMAAE	128
LMTK3	118	IARGLAHLHSHVYVHSDLALRNCLLTSDLTVRIGDYGLAHSNYKEDYYLTPERLWIPLRW	177
InsR	121	IA G+A+L++ +VH DLA RNC++ D TV+IGD+G+ Y+ DYY + +P+RW	180
LMTK3	178	IADGMAYLNAKKFVHRDLAARNCMVAHDFTVKIGDFGMTRDIYETDYRKGKGLLPVRW	180
LMTK3	178	APEL L + G F + S++WS GV LWE+ QPY+ LS+E+VL FV+ +	237
InsR	181	MAPELKD--GVF----TTSSDVMWSFGVWVLEITSLAEQPYQGLSNEQVLFKFMVMDGGY-	232
LMTK3	238	KLARPRKLKPYADYVYDILQSCWR-PPAQRPS	268
InsR	233	L +P P + D+++ CW+ P RP+ -LDQPD-NCP--ERVTDLMRMCKQFNPKMRPT	260

Figure 1: Sequence alignment between LMTK3 and InsR. LMTK3: Lemur Tyrosine Kinase 3; InsR: Insulin Receptor.



Note: The N-lobe at the top and the hinge is colored in orange; the C-lobe is at the bottom of the figure, the alpha helix C in blue and the activation loop in cyan. The residue of the gatekeeper and the residue Lys32 which is involved in catalysis and the DYG motif are represented by sticks. LMTK3: Lemur Tyrosine Kinase 3; 3D: Three-dimensional

Figure 2: Constructed 3D model of LMTK3DYG-in catalytic domain generated by Swiss Model server.



Note: The RMS between the predicted model and template is 0.329 Å

Figure 3: LMTK3 Predictive model aligned to the InsR template (red: template; green: model; blue: ligand). LMTK3: Lemur Tyrosine Kinase 3; InsR: Insulin Receptor.

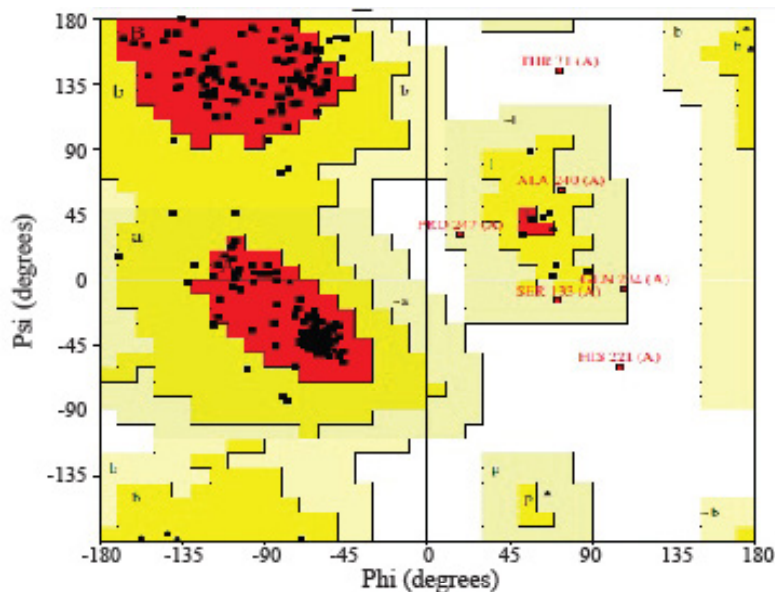
predicted model. [Figure 6] shows the global quality of the predicted model by Prosa program with a similar quality index to the experimental protein, represented by the Zscore of -7.070.

The use of the ProQ program of our model allowed us to show that the LGscore was of $4.480 > 1.5$ and the MaxSub was of $0.421 > 0.1$ validating our predicted model. The overall quality factor obtained by the Errat program of the LMTK3 DYG-in 3D structure was calculated with error analysis and the modeled structure was proven to have a good quality factor of 82.625%.

In [Figure 7], the Verify-3D analysis showed that 76.26% of the LMTK3-DYG-in residues have an average of $3D-1D > 0.2$ score confirming the compatibility of the 3D structure and the primary sequence of LMTK3.

Docking analysis

Our molecular docking generated 9 conformations for one ligand and the orientation selection was based on the position of the most appropriate conformation in the model to form a stable complex. The



Plot statistics

Residues in most favoured region [A,B,L]	217	90.0%
Residues in additional allowed regions [a,b,l]	19	7.9%
Residues in generously allowed regions [~a,~b,~,~p]	3	1.2%
Residues in disallowed regions	2	0.8%

Number of non-glycine and non-proline residues	241	100.0%
Number of end -residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangle)	16	
Number of proline residues	19	

Total Number of residues	278	

Based on an analysis of 118 structures and resolution of at least 2.0 Angstrom and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured Regions.

Figure 4: Ramachandran plot of structural 3D model of LMTK3 DYG-in. Gly: Glycine; LMTK3: Lemur Tyrosine Kinase 3; Pro: Proline; 3D: Three-dimensional.

best one with less binding affinity of Kcal/mol was selected and the PyMol software [Table II] was used to visualize the binding sites on the basis of the hydrogen bonds between the ATP atoms and the atoms of LMTK3-DYG-in predicted model. [Figure 8] shows the interaction mode of our predicted model with ATP molecule which was located in the LMTK3 binding site.

[Figure 9A] presents the superposition between the used inhibitors and ATP molecule in the catalytic site of LMTK3 model in their DYG-in conformation. [Figure 9B] and [Figure 9C] show the superposition result between the complex of our model and docked ligand 112 and the used template 1rqq complexed with their ligand extracted from PDB database.

Discussion

In this study, we used the homology modeling approach to determine the three dimensional structure of the LMTK3 catalytic domain. We evaluated different models based on the 37% sequence identity between the target and the template, and superposition of LMTK3 DYG-in predicted model with the InsR experimental template structure. The validation was performed by physical and chemical tools such as Prosa

servers, ProQ, Verify-3D, Errat and PROCHECK and asserted the reliability of our predicted model. The second evaluation of the model was done by studying the interaction of the predicted model with ATP molecule and inhibitors of the template using the docking approach, and which showed a good binding scores. Docking analysis demonstrated that ATP molecule and the used inhibitors were co-located at the same position in the binding pocket of LMTK3 in DYG-in conformation. The ATP has bounded by their adenine cycle to the key residues of the pocket forming the three hydrogen bonds within the model hinge (Glu79 and Cys81). The ribose and triphosphate groups of ATP were bound with the rest of the key residues of the binding site (Arg138, Asn139 and Lys32). Therefore, these results led to the identification of functional sites on LMTK3 and revealed the presence of residues, which may play a major role during ligand-protein interactions.

The protein kinase LMTK3 is which has a key role in the regulation of a estrogen receptor (ER α) activity [16]. It is also involved in the process of endocrine resistance and it is overexpressed in the more aggressive forms of breast cancer [2,3]. Thus, LMTK3 is considered as an interesting target [2] requiring the development of new inhibitors used as therapeutic molecules for treating the listed diseases.

The crystal structure of LMTK3 kinase is not elucidated, however, Anbarasu et al. developed a 3D structure of LMTK3 in their DYG-out conformation [28]. Their computational reports provided information on the structure-function relationship of LMTK3 with the ATP molecule and identified The critical residues Tyr185 and Asp284 found in the ATP binding cavity to be used in designing potential inhibitors on human LMTK3 [29].

The present study was done in order to complete this structural study and since we have no indication on the LMTK3 adopted conformation, and that DFG-in is the most used in the Protein Data Bank (PDB), and seen that 70% of mammalian structural kinome are in the DFG-in conformation, 22% are intermediate and 3% are apo-DFG-out [8]. We decided therefore to study LMTK3 kinase in their DYG-in conformation since both of the DYG-in and DYG-out conformations might actually co-exist for the LMTK3 in a dynamic equilibrium [9].

Developing inhibitors to the LMTK3-ATP binding site appears to be crucial to propose any therapeutical approach and allow the design of a new inhibitors series showing a broad antiproliferative effect on solid and liquid tumors. Anbarasu et al. [29] were the first to develop novel LMTK3 inhibitors and identify lead candidates. However, the proposed lead molecules did not dock on the LMTK3-ATP site of the in-model developed in our study (data not shown). This may be explained by the location of the ATP binding pocket on the model-out [28] and the one identified in our study for the model-in.

In conclusion, this study allowed us to validate a model that can be used in designing of new ATP-competitive LMTK3 inhibitors targeting the ATP binding pocket. The QSAR appears to be the adequate approach to identify new and more effective molecules targeting LMTK3 kinase, which will subsequently be tested biologically. This study could be of great value in developing methods to improve inhibitors that supplement treatment with Tamoxifen to treat “correct” tumors.

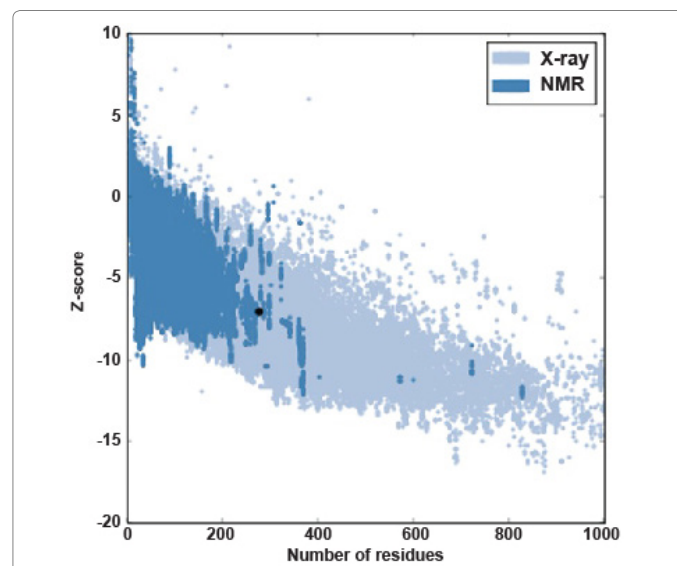
Acknowledgments

This work was carried out under National Funding from the Moroccan Ministry of Higher Education and Scientific Research (PPR program) to AI. This work was also supported by a grant from the NIH for H3Africa ABioNet to AI.



Note: The LMTK3 DYG-in model is in red, residues are in Green and ligand in blue. LMTK3: Lemur Tyrosine Kinase 3

Figure 5: Position of the Thr71 and His221 found in the disallowed region in Ramachandran plot.



Note: The value of the index was represented by the Z-score. LMTK3: Lemur Tyrosine Kinase 3

Figure 6: Quality Index of LMTK3 catalytic domain model generated by the server Prosa.

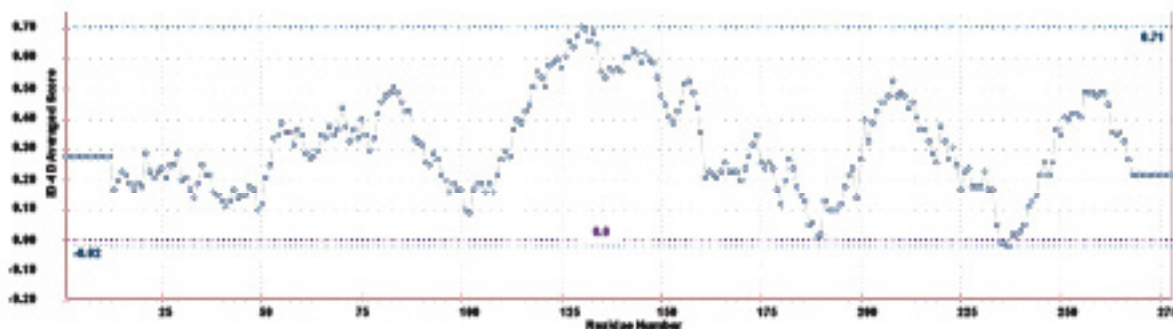
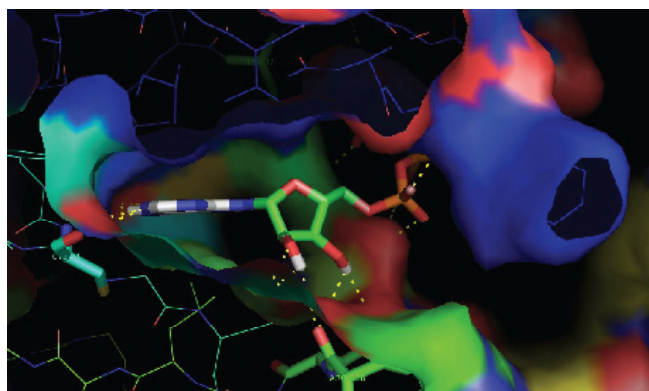


Figure 7: VERIFY-3D plot analysis of computed LMTK3-DYG-in model. LMTK3: Lemur Tyrosine Kinase 3; 3D: Three-dimensional.

S. No.	Residue	Protein atom	ATP atom	ATP source	Bond length (Å)
1	Glu 79	O	1N H	Adenine	2.49
2	Glu 79	O	2N H	Adenine	3.57
3	Cys81	N	NH	Adenine	3.01
4	Cys81	O	N	Adenine	3.36
5	Cys81	N	N	Adenine	3.66
6	Asp85	OD1	OH	Ribose	3.54
7	Asp85	OD1	OH	Ribose	3.29
8	Arg138	O	OH	Ribose	3.22
9	Arg138	O	OH	Ribose	2.93
10	Asn139	OD1	OH	Ribose	3.30
11	Asp152	OD2	OA	Phosphate	3.13
12	Asp152	OD2	OB	Phosphate	3.50
13	Lys32	NZ	OG	Phosphate	3.34
14	Glu33	O	OG	Phosphate	3.26

LMTK3: Lemur Tyrosine Kinase 3; ATP: adenosine triphosphate; 3D: Three-dimensional

Table 2: Molecular docking of human LMTK3 DYG-in with ATP.



Note: The complex LMTK3-ATP is superposed on the template 1rqq. PDB: Protein Data Bank; ATP: Adenosine Triphosphate

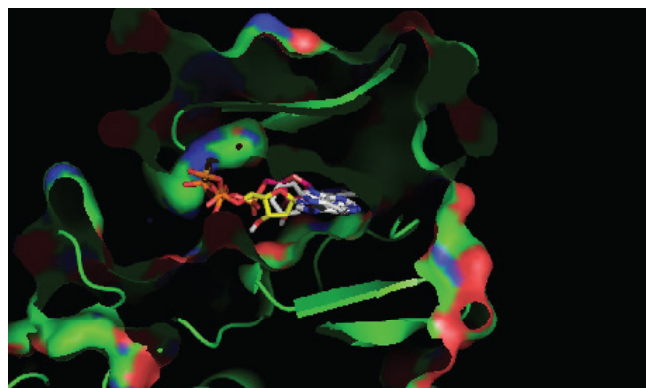
Figure 8: The LMTK3 DYG-in model docked with ATP extracted from PDB.

Disclosure

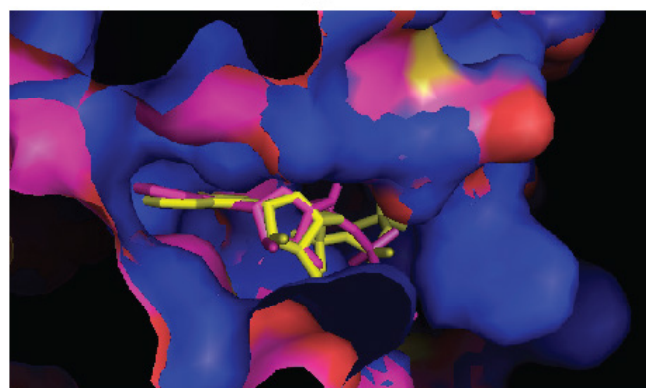
The authors report no conflicts of interest in this work.

References

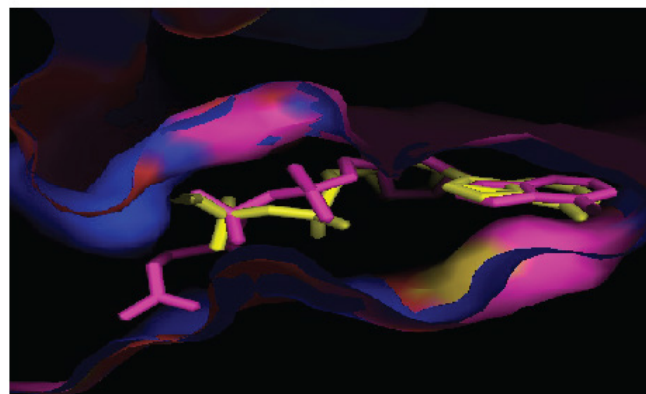
- Rumsby MG, Drew L, Warr JR (1998) Protein kinases and multidrug resistance. *Cytotechnology* 27: 203.
- Stebbing J, Filipovic A, Lit LC, Blighe K, Grothey A, et al. (2013) LMTK3 is implicated in endocrine resistance via multiple signaling pathways. *Oncogene* 32: 3371-3380.
- Stebbing J, Filipovic A, Ellis IO, Green AR, D'Silva TR, et al. (2012) LMTK3 expression in breast cancer: association with tumor phenotype and clinical outcome. *Breast Cancer Res Treat* 132: 537-544.
- Tyner JW, Deininger MW, Loriaux, et al. (2009) RNAi screen for rapid therapeutic target identification in leukemia patients. *Proc Natl Acad Sci U S A* 106: 8695-8700.
- Wakatsuki T, LaBonte MJ, Bohanes, PO, et al. (2013) Prognostic role of lemur tyrosine kinase-3 germline polymorphisms in adjuvant gastric cancer in Japan and the United States. *Mol Cancer Ther* 12: 2261-2272.
- Naik S, Dothager RS, Marasa J, Lewis CL, Piwnica-Worms D (2009) Vascular endothelial growth factor receptor-1 is synthetic lethal to aberrant β -catenin activation in colon cancer. *Clin. Cancer Res.* 15:7529-37.
- Shi H, Wu J, Ji, et al. (2013) Serum lemur tyrosine kinase 3 expression in colorectal cancer patients predicts cancer progression and prognosis. *Med Oncol* 30: 754.
- Kufareva I, Abagyan R (2008) Type-II kinase inhibitor docking, screening, and profiling using modified structures of active kinase states. *J Med Chem* 51: 7921-7932.



(A)



(B)



(C)

Note: The model LMTK3 with the docked ligands is perfectly superposed on the 1rqq template. The model is in blue, the InsR (PDB ID: 1rqq) in pink, docked ligand (PDB ID: 112) in yellow and the InsR crystallized ligand (112) was in pink. PDB: Protein Data Bank; ATP: Adenosine Triphosphate; LMTK3: Lemur Tyrosine Kinase 3

Figure 9: Docking of template inhibitors in to the constructed 3D model. (A) Two docked ligands superimposed to ATP in the catalytic site of the DYG-in model. (B) The model built with a docked ligand superposed at the template 1rqq and its ligand. (C) The model built with a docked ligand superposed at the template 1rqq and its ligand.

9. Levinson, NM, Kuchment, O, Shen, et al. (2006) A Src-like inactive conformation in the abl tyrosine kinase domain. *PLoS Biol* 4: e144.
10. Knighton DR, Zheng, J (1991) Crystal Structure of the Catalytic Subunit of Cyclic Adenosine Monophosphate-Dependent Protein Kinase. *Sci* 253: 407.
11. Hanks SK, Quinn AM, Hunter, et al. (1988) The protein kinase family: conserved features and deduced phylogeny of the catalytic domains. *Sci* 241: 42-52.
12. Inoue T, Kon T, Ohkura, et al. (2008) BREK/LMTK2 is a myosin VI-binding protein involved in endosomal membrane trafficking. *Genes Cells* 13: 483-495.
13. Robinson DR, Yi-Mi W, Su-Fang, et al. (2000) The protein tyrosine kinase family of the human genome. *Oncogene* 19: 5548.
14. Tomomura M, Morita N, Yoshikawa F, Konishi A, Akiyama H, et al. (2007) Structural and functional analysis of the apoptosis-associated tyrosine kinase (AATYK) family. *Neuroscience* 148: 510-521.
15. Xu Y, Zhang H, Giamas G (2014) Targeting lemurs against cancer metastasis.
16. Giamas G, Filipović A, Jacob, et al. (2011) Kinome screening for regulators of the estrogen receptor identifies LMTK3 as a new therapeutic target in breast cancer. *Nat Med* 17: 715-719.
17. Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ (1990) Basic local alignment search tool. *J Mol Biol* 215: 403-410.
18. Schwede T, Kopp J, Guex N, & Peitsch MC (2003) SWISS-MODEL: an automated protein homology-modeling server. *Nucleic Acids Res* 31: 3381-3385.
19. Sippl MJ (1993) Recognition of errors in three-dimensional structures of proteins. *Proteins: Struct, Funct, Bioinf* 17: 355-362.
20. Wallner B, Elofsson A (2003) Can correct protein models be identified?. *Protein Sci* 12: 1073-1086.
21. Luthy R, Bowie JU, Eisenberg D (1992) Assessment of protein models with three-dimensional profiles. *Nature* 356: 83.
22. Bowie J, Luthy R, Eisenberg D (1991) A method to identify protein sequences that fold into a known three-dimensional structure. *Sci* 253: 164-170.
23. Colovos C, Yeates TO (1993) Verification of protein structures: patterns of nonbonded atomic interactions. *Protein Sci* 2: 1511-1519.
24. Laskowski RA, MacArthur MW, Moss DS, & Thornton JM (1993) PROCHECK: a program to check the stereochemical quality of protein structures. *J Appl Crystallogr* 26: 283-291.
25. Trott O & Olson, AJ (2010) AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem* 31: 455-461.
26. Delano W. The PyMOL Molecular Graphics System 1.01. Available from www.pymol.sourceforge.net; 2009.
27. Westbrook J, Feng Z, Chen L, Yang H, Berman, et al. (2003) The protein data bank and structural genomics. *Nucleic Acids Res* 31: 489-491
28. Anbarasu K, Jayanthi S (2014) Structural modeling and molecular dynamics studies on the human LMTK3 domain and the mechanism of ATP binding. *Mol Biosyst* 10: 1139-1145.
29. Anbarasu K, Jayanthi S (2017) Designing and optimization of novel human LMTK3 inhibitors against breast cancer—a computational approach. *J Recept Signal Transduct* 37: 51-59.

Citation: Allam L, Lakhilili W, Tarhda Z, Akachar J, Ghrifi F, et al. (2017) Three-dimensional Structure Prediction of the Human LMTK3 Catalytic Domain in DYG-in Conformation. *J Biomol Res Ther* 6: 151. doi:[10.4172/2167-7956.1000151](https://doi.org/10.4172/2167-7956.1000151)

OMICS International: Publication Benefits & Features

Unique features:

- Increased global visibility of articles through worldwide distribution and indexing
- Showcasing recent research output in a timely and updated manner
- Special issues on the current trends of scientific research

Special features:

- 700 Open Access Journals
- 50,000 Editorial team
- Rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, EBSCO, Index Copernicus, Google Scholar etc.
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://www.omicsgroup.org/journals/submission>