



# KHYBER MEDICAL UNIVERSITY

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## APPLICATION FORM FOR SUBMISSION OF RESEARCH PROPOSALS TO KMU-AS&RB

Serial No (for office use): \_\_\_\_\_

Date of submission: 7/12/2017

Name of the Institute: IBMS, Khyber medical university peshawar

Date of Registration with institute: Feb, 2016 Session: 2016-2018

Program/Specialty: M.phil Biochemistry Semester: 4th

Name: Lubna Bibi

Fathers Name: Muhammad Faeem

Contact No: 03405812338 Email: Lubna.chemist1@yahoo.com

Name & Designation of Supervisor: Roshan Ali, Assistant professor

Type of Participants: Humans  Animals  Others (specify): \_\_\_\_\_

Status of Submission: 1) Fresh  2) Revised: \_\_\_\_\_ Duration of Data collection: \_\_\_\_\_

Title of the project: Virtual screening and Docking studies of Ebola virus viral Uprotein

### Please tick the following checklist before submission:

- Work plan/Gantt Chart attached: Yes/No
- Proposal attached as per format provided by KMU-AS&RB: Yes/No
- Approved by Graduate Committee: Yes/No
- Ethical Approval obtained: Yes No In process
- KMU dues submitted and up to date: Yes/No
- Covering Letter Attached: Yes/No
- 20 copies of proposals and all supplementary documents attached: Yes/No
- Plagiarism Certificate attached: Yes/No
- Course Completion certificate attached: Yes/No

[Signature]  
7/12/17

[Signature]  
Candidate Signature:

Supervisor Signature and Stamp:

No.KMU/IBMS/2017/ 10819

Date: 08/11/2017

**TO WHOM IT MAY CONCERN**

It is certified that Miss. Lubna Bibi D/o Muhammad Faheem, MPhil Scholar of Biochemistry at Institute of Basic Medical Sciences, Khyber Medical University Peshawar, has successfully completed her course work for session Spring 2016. As per KMU rules, for the requirement of degree of MPhil, she has to undertake research project. Whenever the project is completed, she will write her thesis, which will be evaluated by two external examiners and at the end she will have a viva voce examination. After completion of the above mentioned requirements, the candidate will be awarded degree of MPhil, accordingly.

A handwritten signature in black ink, appearing to read 'Dr. Jawad Ahmed', is written over a horizontal line.

(Dr. Jawad Ahmed)  
Director IBMS

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### CHECK LIST:

1	Has the basic editing of the proposal been done to a satisfactory level (font, spelling mistakes, English grammar and basic editing of the proposal)?	✓
2	Has the supervisor signed the document before submitting to the committee members?	✓
3	Has the rationale of the study been clearly discussed?	✓
4	Has the sample size been justified for the selected research question?	✓
5	Statistics: Have statistics been appropriately explained in the context of the proposal to answer the research question?	-
6	Are references complete, consistent and uniform? Are references in Vancouver style?	✓
7	Has the budget been elaborated with cost break-ups?	✓
8	Has the Gantt chart been included in the document?	✓
9	Has the supervisor seen and approved the Power Point Presentation of the student?	✓
10	Consent form (English/Urdu) and patient information sheet attached? (if required)	-
11	Plagiarism report: Is this report attached with the document and is the similarity index less than 20%?	✓
12	For reports with similarity index less than 20%, has it been checked that no more than 7% similarity is from a single source?	✓

Supervisor Name: Roshan Ali

Supervisor Signature:



# RESEARCH PROPOSAL

New for GSC  / Revised for GSC

Virtual Screening and Docking Studies of Ebola Virus Viral Protein 40



SUBMITTED BY:

LUBNA BIBI  
M.Phil Scholar (Biochemistry).

RESEARCH SUPERVISOR:

ROSHAN ALI  
Assistant Professor, Molecular Biology &  
Genetics, IBMS, KMU, Peshawar

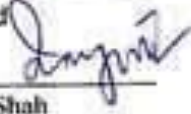
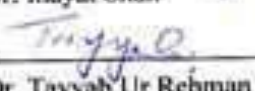
CO-SUPERVISOR:

Dr. Niaz Ali

Student Email: lubna.chemist1@yahoo.com  
Supervisor Email: roshanali.ibms@kmu.edu.pk

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INSTITUTE OF BASIC MEDICAL SCIENCES,  
KHYBER MEDICAL UNIVERSITY, PESHAWAR  
(November 2017)

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1	Has the basic editing of the proposal been done to a satisfactory level (font, spelling mistakes, English grammar and basic editing of the proposal)?	✓
2	Has the supervisor signed the document before submitting to the committee members?	✓
3	Has the rationale of the study been clearly discussed?	✓
4	Has the sample size been justified for the selected research question?	✓
5	Statistics: Have statistics been appropriately explained in the context of the proposal to answer the research question?	-
6	Are references complete, consistent and uniform? Are references in Vancouver style?	✓
7	Has the budget been elaborated with cost break-ups?	✓
8	Has the Gantt chart been included in the document?	✓
9	Has the supervisor seen and approved the Power Point Presentation of the student?	✓
10	Consent form (English/Urdu) and patient information sheet attached? (if required)	-
11	Plagiarism report: Is this report attached with the document and is the similarity index less than 20%?	✓
12	For reports with similarity index less than 20%, has it been checked that no more than 7% similarity is from a single source?	✓

Supervisor Name: Roshan Ali

Supervisor Signature:



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**RESEARCH PROPOSAL**

**Virtual Screening and Docking Studies of Ebola Virus Viral Protein 40**

<b>Name of Candidate:</b>	Lubna Bibi
<b>Name of Supervisor:</b>	Roshan Ali
<b>Duration of Project:</b>	Six months.
<b>Institute:</b>	Khyber Medical University
<b>Budget Required:</b>	Rs 50,000

<b>Name &amp; Signature of Student/Scholar:</b>	Lubna Bibi
<b>Name &amp; Signature of the Supervisor:</b>	Roshan Ali 
<b>Name &amp; Signature of Head of Institute:</b>	Prof. Dr. Jawad Ahmad 



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### 1. TITLE:

Virtual screening and docking studies of Ebola virus viral protein 40

### 2. INTRODUCTION:

A virus is an infective agent which reproduces only inside the living cells and infects all life forms. The pathogenic viruses cause serious diseases like Hepatitis, AIDS, Chikungunya, Dengue, Encephalitis, Influenza, Herpes, Malaria, Tuberculosis, Tetanus, Polio, Measles and Small pox. Most of them are difficult to treat or have no treatment at all (1). Among these, one of the deadliest virus is Ebola virus which is a member of Filoviridae family which is filamentous, lipid enveloped, single stranded negative sense RNA virus (2, 3). Ebola virus causes severe hemorrhagic fever, bleeding diathesis, focal necrosis of liver, kidney and spleen, sudden shock. The mortality rate of Ebola virus infection is up to 90% (4). Initial symptoms are muscle aches, fever, fatigue, exhaustion, and dizziness (5).

In 1976, Ebola virus was originated in the village of Yambuku, in Zaire close to the Ebola river (6). Ebola epidemics in 2014 is one of the main viral epidemics in history that affected four major areas in West Africa. These regions include Guinea, Liberia, Sierra Leone and Nigeria (7). In Pakistan, WHO declared that Ebola virus is spreading across the globe so Pakistan can be affected by Ebola virus disease (8).

Ebola virus's genome contains seven virion structural proteins (VP) VP35, VP40, VP30, VP24, glycoprotein (GP), nucleoproteins (NP), and RNA- dependent RNA polymerase (L) (9, 10). Post translational cleavage of GP will produce GP1 and GP2 subunits by pro-protein furin (11). GP1 is responsible for the attachment of Ebola virus to host cell while GP2 facilitates fusion of viral membranes and host cell (12, 13). The secondary matrix protein, VP24 helps in viral binding and also responsible for the suppression of host interferon activity (14). VP30 and VP35 proteins cause the suppression of host immune system and tolerate host immune responses (15). NP is responsible for the replication of Ebola virus and supports the attachment of viral proteins within the nucleocapsid (16). The VP40 is a matrix protein which helps in virus budding and assembly (17).

Although many potential drug candidates have been identified for the control of Ebola virus that include peptides, small molecule inhibitors, monoclonal antibodies, recombinant DNA vectors as well as repurposing of existing drugs (18). However no FDA-licensed drug is available for the treatment of Ebola virus infection (19). Structure and ligand based strategies are under trial for the development of novel potent inhibitors against various target proteins of Ebola virus but the identification of more potent compounds is still needed.

As VP40 plays a prominent role in the life cycle of the Ebola virus, it is considered as a key target for antiviral treatment which results in an urgent need to develop effective antiviral inhibitors against vp40 that display good safety profiles in a short duration. Vp40 is located below the viral envelope and is responsible for viral maturation and maintaining structural integrity (20). Crystal structure of VP40 at 1.6 Å resolution is available in protein data bank under the accession codes 1H2C, 3TCQ (21).

Drug discovery is a time consuming, expensive and prolonged method. As compare to the wet-lab discovery method, computational approach is less time consuming and cost effective (22). One of the computational approaches to drug discovery is target based virtual screening. The aim of this study is to identify the potential inhibitors for Ebola virus VP40 by target based virtual screening methods.

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### 3. OBJECTIVE:

To find out potential inhibitors for Ebola virus vp40 by using structure based virtual screening approach.

### 4. OPERATIONAL DEFINITIONS:

**Structure based virtual screening:** A technique which is used to virtually screen libraries of compounds for identification of potential inhibitors against a target protein.

**3D Ligand Binding Site:** Binding site of a ligand predict from 3D ligand binding site.

**Drug Discovery Studio Visualizer:** This tool share, visualize, and analyze the structure of proteins.

**Protein Data Bank:** A database that gives information about the structures of biomolecules e.g. proteins, nucleic acids and other complex moieties.

**CASTp:** This tool determines the active site of 3D structures of proteins.

**PubChem:** It gives the detail about structural, functional and properties of drugs and other compounds.

**UCSF Chimera tool:** UCSF chimera tool analyses the interaction of structures and sequences.

**PyRx tool:** It is a tool used to find out the libraries of drugs against a target.

**AutoDock Vina:** With the help of this tool ligand dock with target protein.

**LigPlot plus:** This tool is used to analyses the ligand-protein complex interactions and to plot the interactions in two dimensional planes.

### 5. HYPOTHESIS:

Several potential drug candidates may be identified through Virtual screening for Ebola virus's vp40 that may result in a significant reduction in terms of cost and time.

### 6. MATERIALS AND METHODS

**6b. Study Settings:** Bioinformatics Lab, IBMS, KMU.

**6a. Study Design:** Computational approach



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**6c. Study Duration:** Six months**6d. Sample Size:** All the small drug like molecules available in Zinc Database**6e. Sampling Technique:** Computational**7. SAMPLE SELECTION:****7a. inclusion criteria:**

1. Vp 40 structure with water molecules in its active site with high resolution
2. Compounds that are lead like
3. Molecules that will follow Lipinski's Rule of five
4. Molecules that obeys the rule of three
5. Compounds with proper ADME properties

**7b. Exclusion Criteria:**

1. Structures with low resolution
2. Complex lead molecules
3. Filtration of toxic compounds

**8. DATA COLLECTION PROCEDURE:**

1. **Protein 3D Structure Retrieval:** The three-dimensional structures of Ebola virus vp40 will be downloaded from the RCSB Protein Data Bank (23).
2. **Protein Structure Optimization:** Discovery Studio Visualizer will be used for the optimization of 3D structure of target protein.
3. **Protein Binding Site:** The binding site of target protein will be predicted by using different tools i.e. Discovery Studio, CastP (24), FINDSITE (25) and 3D LigandSite (26).
4. **Structure based virtual screening:** Using the structure based virtual screening; the possible ligand molecules for the active site of the Ebola virus target protein will be screened. For this purpose, FINDSITE<sup>COMb</sup> (27) FINDSITE-LHM (28), ZincPharmer (29), pep:MMs:MIMIC (30), dockblaster (31), iscreen (32), iStar'sidock (33, 34), e-LEA3D (35) and MTiOpenScreen (36) will be used.

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5. **Creation of Ligand Library:** A library will be created by downloading ligands that will be identified by methods mentioned in step 4. The ligand molecules, identified by various methods will be given preference.
6. **Separation of Drug-like Compound:** Whether the selected compounds are drug like or not will be analyzed using MLViS: machine learning-based virtual screening tool (37).
7. **Ligand Optimization:** The ligands will be optimized using UCSF Chimera (38) tool.
8. **Ligand Format Conversion to PDBQT:** PyRx (39) tool convert the format of the ligand to PDBQT format.
9. **Identification of Potential Lead Molecules:** By using PyRx, the library will be screened against target protein of Ebola virus.
10. **Selection of the Inhibitor for Further Analysis:** Ligands with highest binding affinity and lowest energy will be counted as potential inhibitors.
11. **Docking of Ligand to Protein:** Docking of the protein to ligand will be carried out using AutoDockVina (40).
12. **Ligand Protein Interaction Analysis:** The interaction analysis will be done using Discovery Studio Visualizer and LigPlot Plus (41).
13. **Visualization:** All the visualization of the structures will be carried out using Discovery Studio Visualizer (35).

### 9. Data Analysis Procedure

Analysis of the interaction and structures will be carried out with Ligplot Plus, Autodockvina, Pyrx, and Discovery Studio Visualizer

**10. BIBLIOGRAPHY:**

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**ANNEXE:**

**Annexure I: Proforma: Not applicable**

**Annexure II: Consent form (English): Not applicable**

**Annexure III: Plan of work (Gantt Chart)**

**11. Plan of Work**

Steps/months	1st	2nd	3rd	4th	5th	6th
Retrieval of structure, optimization and analysis of its binding site.						
Virtual screening, library creation and conversion of format						
Identification, selection and comparison of potent molecules						
Interaction analysis and visualization.						
Thesis writing						
Thesis submission						

**Annexure IV: Estimated cost of work: Not applicable**

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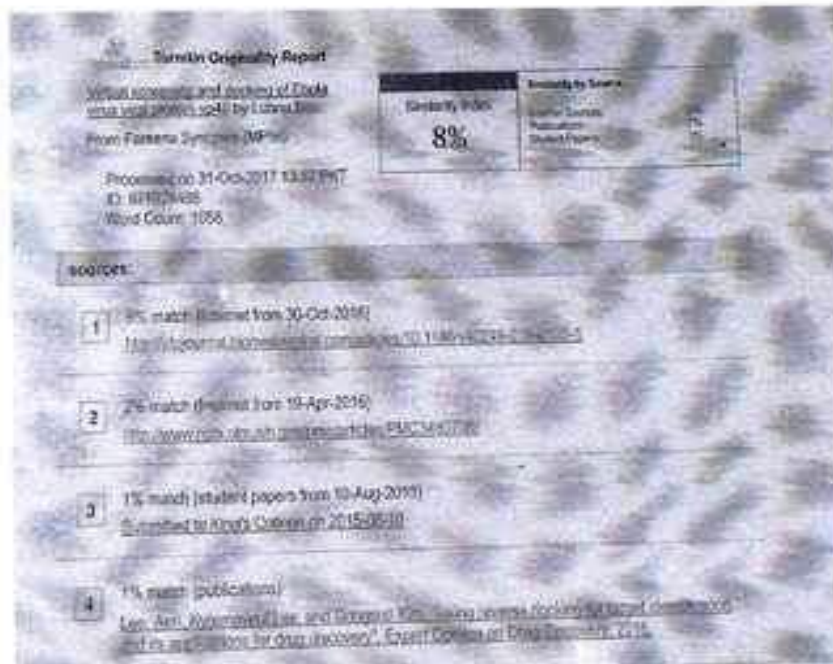
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**Budget List:**

S. No	Good Needs	Estimated Price
1.	Laptop	50,000

**Turnitin Originality Report:**



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