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Details of the Collaborative Activity

2020-21

Name of the Collaborating Institute: Division of Molecular Microbiology and Immunology, CSIR-Central Drug Research Institute, Lucknow, India

Name of the Collaborating Department with YDU: Yenepoya Research Center

Activities:

- **Joint Research and Publications**

Joint research was undertaken with Division of Molecular Microbiology and Immunology, CSIR-Central Drug Research Institute, Lucknow.

1. Divya Lakshmanan M, Shabeer AH. Ligand Binding Domain of Estrogen Receptor Alpha preserve a Conserved Structural Architecture Similar to Bacterial Taxis Receptors. *Frontiers in Ecology and Evolution*. 2021https://doi.org/10.3389/fevo.2021.681913

2. Divya L M, Shabeer Ali H, Prajosh P, Sreejith K Conformers of a novel lipopeptide antibiotic, Kannurin inhibits SARS-Cov2 replication via interfering with RNA-dependent-RNA polymerase activation and function. *International Journal of Computational Biology and Drug Design*. (2021) DOI: 10.1504/IJCBDD.2021.10042390

ATTESTED
Dr.Gangadhara Somayaji K.S.
Registrar
Yenepoya(Deemed to be University)
University Road, Deralakatte
Mangalore- 575 018, Karnataka

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Ligand Binding Domain of Estrogen Receptor Alpha Preserve a Conserved Structural Architecture Similar to Bacterial Taxis Receptors

Divya Lakshmanan Mangalath[1]* *and Shabeer Ali Hassan Mohammed*[2,3]

[1] *Cancer Research and Therapeutics, Yenepoya Research Centre, Yenepoya University, Mangalore, India,* [2] *Division of Molecular Microbiology and Immunology, CSIR-Central Drug Research Institute, Lucknow, India,* [3] *Department of Biotechnology and Microbiology, Kannur University, Kannur, India*

It remains a mystery why estrogen hormone receptors (ERs), which are highly specific toward its endogenous hormones, are responsive to chemically distinct exogenous agents. Does it indicate that ERs are environmentally regulated? Here, we speculate that ERs would have some common structural features with prokaryotic taxis receptor responsive toward environmental signals. This study addresses the low specificity and high responsiveness of ERs toward chemically distinct exogenous substances, from an evolutionary point of view. Here, we compared the ligand binding domain (LBD) of ER alpha (α) with the LBDs of prokaryotic taxis receptors to check if LBDs share any structural similarity. Interestingly, a high degree of similarity in the domain structural fold architecture of ERα and bacterial taxis receptors was observed. The pharmacophore modeling focused on ligand molecules of both receptors suggest that these ligands share common pharmacophore features. The molecular docking studies suggest that the natural ligands of bacterial chemotaxis receptors exhibit strong interaction with human ER as well. Although phylogenetic analysis proved that these proteins are unrelated, they would have evolved independently, suggesting a possibility of convergent molecular evolution. Nevertheless, a remarkable sequence divergence was seen between these proteins even when they shared common domain structural folds and common ligand-based pharmacophore features, suggesting that the protein architecture remains conserved within the structure for a specific function irrespective of sequence identity.

Keywords: estrogen receptor, ligand binding domain, taxis receptors, domain architecture, nuclear hormone receptor

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Ernesto Mollo,
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Reviewed by:
Taisen Iguchi,
Graduate University for Advanced Studies (Sokendai), Japan
Michael Baker,
University of California, San Diego, United States

***Correspondence:**
Divya Lakshmanan Mangalath
divyalmangalath@gmail.com;
divya@yenepoya.edu.in

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HIGHLIGHTS

- ER-LBD shares structural folds with bacterial chemotaxis receptor LBD.
- Domain architecture is preserved by conserved structural folds, irrespective of sequence identity.
- Ligands for ER and bacterial chemotaxis receptors share common pharmacophore features.
- Ligands of bacterial chemotaxis receptors interacted with human ER and vice versa.

ATTESTED
Dr.Gangadhara Somayaji K.S.
Registrar
Yenepoya(Deemed to be University)
University Road, Deralakatte
Mangalore- 575 018, Karnataka

Conformers of a novel lipopeptide antibiotic, Kannurin inhibits SARS-Cov2 replication via interfering with RNA-dependent-RNA polymerase activation and function

H. Shabeer Ali

Division of Molecular Parasitology and Immunology,
CSIR-Central Drug Research Institute,
Lucknow, Uttarpradesh, 226031, India
Email: shabeer.m@cdri.res.in

P. Prajosh and K. Sreejith

Department of Biotechnology and Microbiology,
Kannur University,
Kerala, 670 661, India
Email: prajoshpalanthara@gmail.com
Email: sreejithkrishnan@hotmail.com

M. Divya Lakshmanan*

Molecular Biology Division,
Yenepoya Research Centre,
Yenepoya (Deemed to be University),
Deralakatte, Mangalore, 575018, Karnataka, India
Email: divyalmangalath@gmail.com
*Corresponding author

Abstract: The key component 'nsp12' of RNA-dependent-RNA polymerase of Corona virus is considered as a primary target for drug intervention purposes. The broad spectrum antimicrobial lipopeptide Kannurin revealed favourable interactions against nsp12 in preliminary in silico experiment. Among the different target sites on nsp12 selected for docking study, the cyclic form of Kannurin was found to interact with the residues Phe 407, Leu 544 and Lys 511 present in the finger subdomain of nsp12 that are facilitating the binding of nsp7 and nsp8 cofactors. Hence it is proposed that Kannurin can act by inhibiting the binding of cofactors with nsp12 and ultimately leading to its inactivation. The second mechanism is by the interaction of linear form of Kannurin with the palm subdomain cavity, specifically with the residue Arg 555 that involved in receiving the incoming nucleotides during replication. The mechanism is closely related to the action of 'Remdesivir'.

Keywords: SARS-COV; Kannurin; lipopeptide; nsp12; nsp7; nsp8.

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ATTESTED
Dr.Gangadhara Somayaji K.S.
Registrar
Yenepoya(Deemed to be University)
University Road, Deralakatte
Mangalore- 575 018, Karnataka