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Research Article

DISCOVERY OF REPURPOSED FDA APPROVED THERAPEUTIC DRUGS AGAINST SARS COV2 OMICRON VARIANT

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ABSTRACT

The mutations present in the spike protein of omicron, a new variant of SARS CoV2 favours the high transmission of Covid in fection. To control the rate of infection finding an effective alternative drug can be beneficial. In our work, we have repurposed 1930 FDA approved drugs in which best top five lead compounds based on their GOLD score are Telotris tetethyl, Oxyglutatione, Pentamidinium, Clindamycin palmitate, Pentagastrin having GOLD score 53.2481, 52.7613, 52.7513, 52.5499, 52.5473. These compounds were selected for further molecular interactions & visualization studies with the spike region of omicron. The homology modelling of the spike protein with 30 induced mutations were carried out and the quality of the modelled structure was found to be reasonably good with 80% of its residue falling in the accepted region of Ramachandran plot. The frustration analysis of the protein and ligand complexes were analysed to find the contribution of residues in overall functioning of the protein.

Keywords: Omicron, Pymol, Covid-19, Polycistronic, Substitution mutation, Receptor binding domain.

1. INTRODUCTION

The outbreak of coronavirus disease declared as pandemic on 11th march 2020. Corona viruses are highly diverse, enveloped ssRNA viruses it belongs to positive ribonucleic acid family and has the potential to infect the diseases in several species like bats, pangolian & humans which lead to severe acute respiratory syndrome [1]. The genome size of the virus is 29881bp which codes 9860 amino acid, the RNA has 5' cap, polyadenylated tail and is polycistronic [2]. Genes encoding nucleocapsid, spike and membrane proteins forms the structural framework whereas RNA dependent RNA polymerase, 3-chymotrypsin like protease & papain like protease are the nonstructural component of SARS CoV-2 [3]. Among all the structural protein spike protein (S) 1273 amino acids in length is very crucial for the infection and transmission of the diseases since it interacts and binds with the angiotensin converting enzyme-2 (ACE-2) receptors expressed majorly in the respiratory tract of the host [4]. The spike protein mainly consists of two subunits, Subunit 1 (S1) encompasses N-terminal domain (NTD) & Receptor binding domain whereas Subunit 2 (S2) consist of two hepta peptide repeats and fusion peptide. The first mutant following the Covid-19 spread from the origin city wuhan in December 2019 was identified as D614G, may be responsible for the 1st wave of Covid-19 [4]. Thereafter many SARS CoV variants have been identified worldwide. The mutations analyzed from the sequence retrieved from Global Initiative on Sharing All Influenza Data (GISAID) revealed that SARS CoV -2 are mildly detrimental since the deleterious mutations are less in number as compared to low effect amino acid changes [5]. These variants are categorized based on their fatality, transmission and infection. A group of experts established by WHO named as Technical advisory group on SARS-CoV-2 Virus Evolution (TAG-EV) closely monitoring the emergence and evolution of SARS-CoV-2 [6] has put forward the nomenclature and classified them as variants of interest (VOI). These variants shows increased transmissibility due to newly incorporated genetic changes, can escape diagnostic and host immunity, has increased predominance whereas variants of concern (VOC) includes all the characteristics of VOI along with decreased vaccine impact and increased virulence [7]. They belong to the lineage B.1.351, B.1.1.7 & P.1 [8]. B.1.617.2 also known as delta variants is a sub lineage of B.1.617 and it can be a reason for the second wave of Covid-19 in India [8]. With the advent of

the corona pandemic, this virus has evolved from time to time as Alpha, Beta, Gamma, Delta and the Omicron. Omicron, a new variant appeared in November 2021 [9], initially it was named as B.1.1.529 and later included in VOC called as Omicron (B.1.1.529). One of the largely accepted hypothesis for its emergence is that it might have evolved in immune compromised chronically infected covid-19 patients who provide a long term suitable environment for the virus to adapt [10]. This virus was firstly identified in Botswana, within a month omicron infected cases were reported from all over South Africa & the world [11]. The remarkable number of mutations and its astonishing characteristics features has gained the attention of the scientists across the world. The omicron neutralization by monoclonal antibodies, convalescent serum and vaccine effect is low in comparison to delta variant and the parent SARS-CoV-2 [12]. However the experimental trial suggests that the third vaccine booster can increase the neutralization [13]. Though the austerity of this new variant is low, the transmissibility rate is significantly high [14]. There are more than 30 mutations present only in the spike protein [11] deletion mutations at position Δ69-70, Δ143-145, Δ211, substitution mutation A67V, T95I, G142D, L212I, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F. The mutations occur in the region 319-541 residue contain receptor binding domain (RBD) such as G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y provides a tolerable advantage for the transmission and infectivity [15].

2. EXPERIMENTAL

2.1. Structural refinement and mutagenesis

PDB structure of SARS Cov2 (PDB ID-6VYB) was retrieved from Protein data bank [16]. Structural refinement like removal of heteroatoms, water molecules and extra cofactors were done by Pymol [17]. Structure and sequence gap were filled by Swiss PDB viewer [18]. 30 mutations were induced in the respective positions as reported in the template spike protein of omicron variant by using Pymol [17].

2.2. Energy minimization

The mutant spike protein structures were minimized for a time scale of 10ns simulation using gromacs force field with a leap-frog integrator [19]. The minimized structures were used for molecular docking studies.

2.3. Protein frustration analysis

The localized energetic frustration analysis of configurational and mutational spike proteins were done by frustratometer [20].

2.4. Molecular interactions Studies

1930 FDA approved drugs were repurposed against minimized spike protein of omicron variant using genetic algorithm preset gold_P450 [21]. Ritnovir used as a control in docking studies. Visualization of the best complexes were done by Ligplot [22] and Pymol.

3. RESULTS AND DISCUSSION

3.1. Structural refinement and mutagenesis of spike protein

Representation of the spike protein of omicron showing N terminal domain (NTD), receptor binding domain (RBD), Fusion peptide (FP), heptad repeat (HR), repeat (HR), transmembrane (TM). Substitution mutations in the receptor binding domain and other region of spike protein is shown in the figure 1. Red sphere shows positions of various newly substituted mutations labelled with the amino acid residues. There are 15 mutations exclusively in the RBD region. The other 14 mutations were present in the rest region of spike protein with their respective position shown in purple colored sphere.

3.2. Energy minimization & Homology modelling

The overall quality of homology modelled structure of the spike protein in omicron strain (fig. 2) is considerable since 80 % of its residue fall under accepted region of Ramachandran plot. Minimal disturbed regions which are not a part of the active pocket of the modelled protein belongs to the loop region of the protein.

3.3. Frustration index measures for SARS CoV2 and omicron spike protein

The frustration index measures how favourable a particular contact is relative to sets of possible interactions. Figs. 3 & 4 depicts the local frustration map the green coloured area is minimally frustrated whereas grey and red is neutral and highly frustrated region. In omicron strain the spike protein is highly frustrated than the native SARS CoV2 spike protein which confirms the instability of omicron spike protein. Figs. 5 & 6 represents the local frustration index, Figure 7 & 8 Illustrate the density of contacts in sequence space, Figure 9 & 10 Shows fraction of contacts in each frustration class.

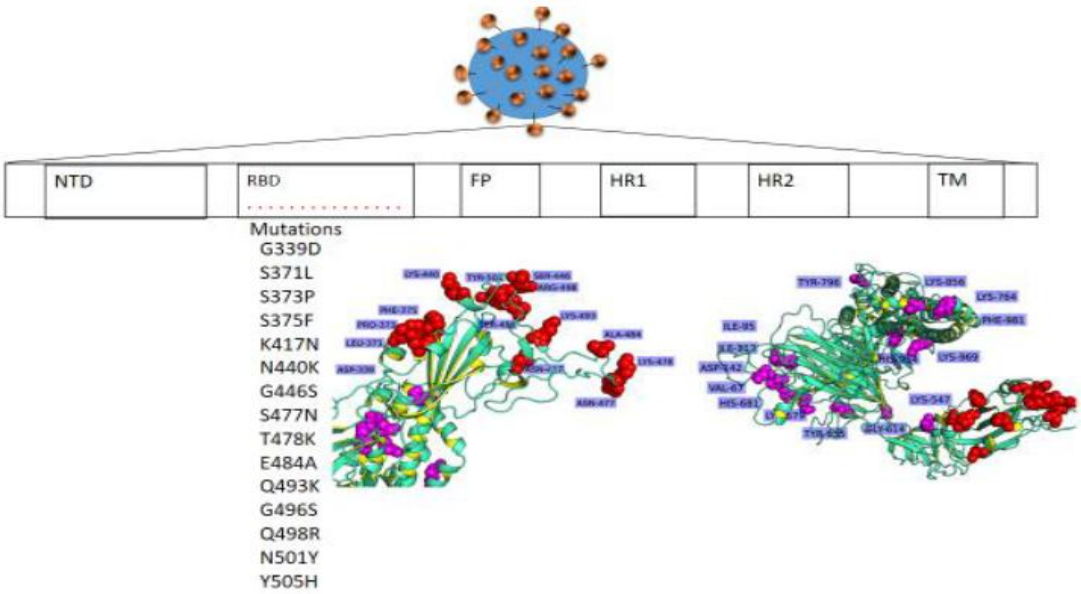


Fig. 1: Mutations in the receptor binding domain and other region of spike protein

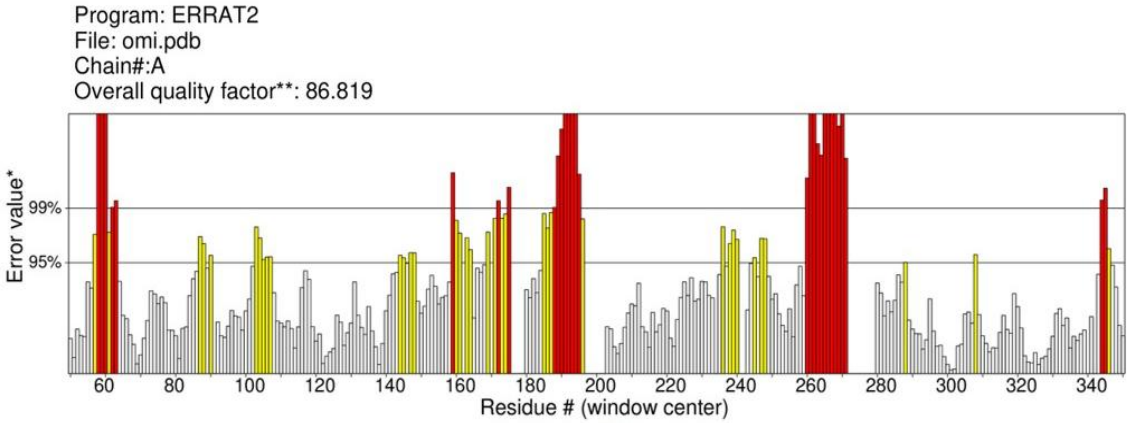


Fig. 2: The ERRAT value of around 87 percent for the overall quality of the homology modelled structure of spike protein of omicron

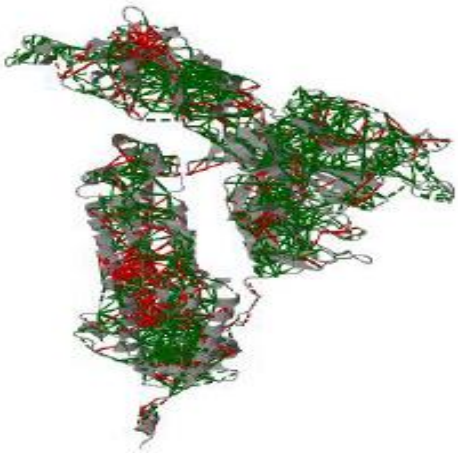


Fig. 3: SARS CoV2 spike protein

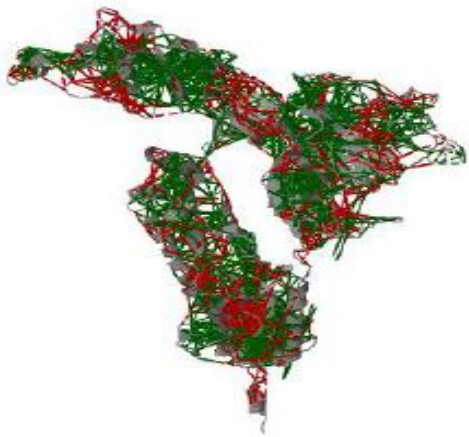


Fig. 4: Omicron spike protein

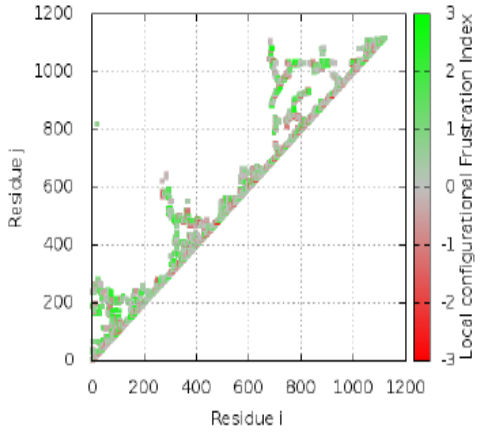


Fig. 5

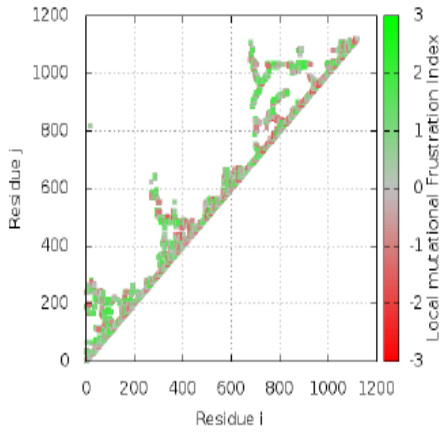


Fig. 6

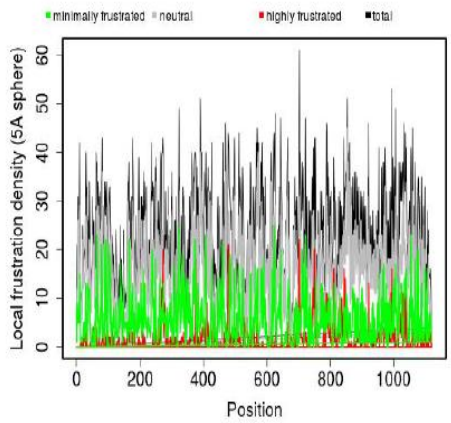


Fig. 7

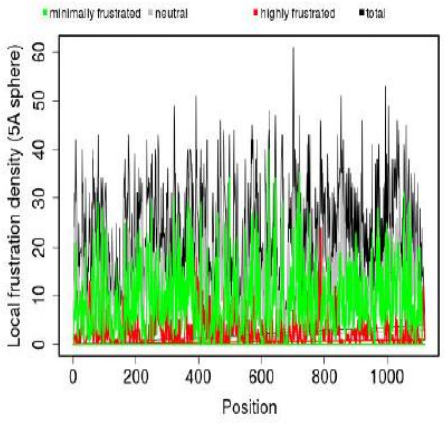


Fig. 8

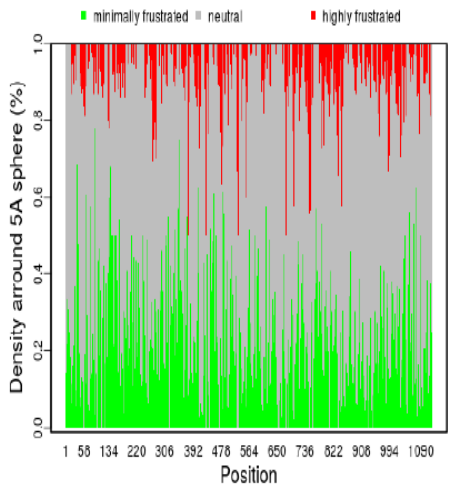


Fig. 9

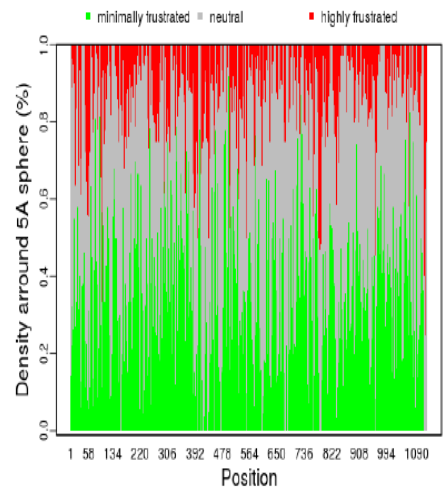
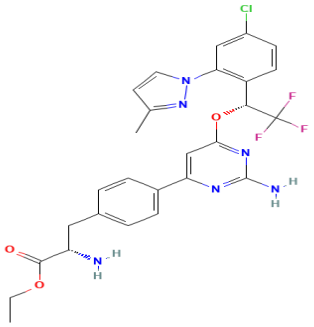
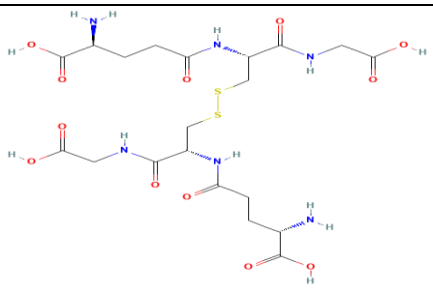
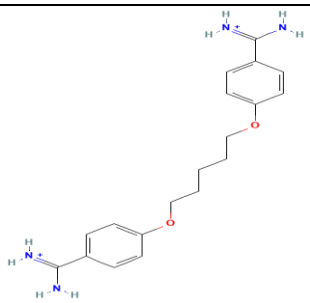
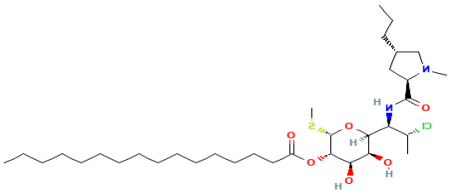
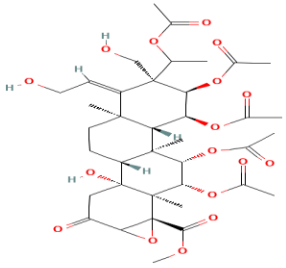
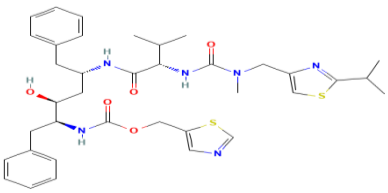


Fig. 10

Figs. 5, 7, 9 shows frustration index, residue wise contact map and fraction of contact in each frustration class of native structure of spike protein, similarly Figure 6, 8 & 10 represents the same for omicron spike protein

Table 1: The standard Ritonavir & top five lead compounds based on their GOLD score

Sl. No	Compound name	Pubchem id	Gold score	Structure
1	Telotris tetethyl	25181577	53.2481	
2	Oxyglutatione	65359	52.7613	
3	Pentamidinium	22956467	52.7513	
4	Clindamycin palmitate	16052039	52.5499	
5	Pentagastrin	9853754	52.5473	
6	Ritonavir	392622	45.79	

3.4. Molecular interactions and visualization

Pentaminidium is shown to interact non covalantly with the amino acid residues such as proline-500, valine-335, lysine-501, at the active pocket of the protein, similarly the drug molecule telotris tetethyl shows non covalent interactions with the arginine-330, aspargine-307, threonine-306 amino acid residue of the active pocket. Figure 11 & 12 shows molecular interactions between active site of mutated spike protein and the top selected compounds as mentioned in the table 1.

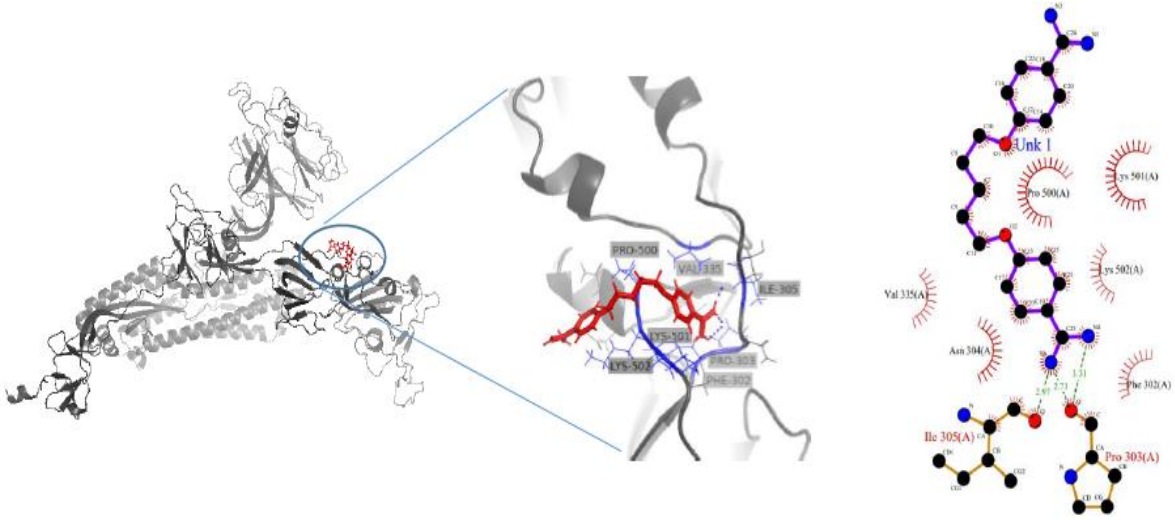


Fig. 11: Molecular interaction between Pentaminidium and active site of mutant spike protein

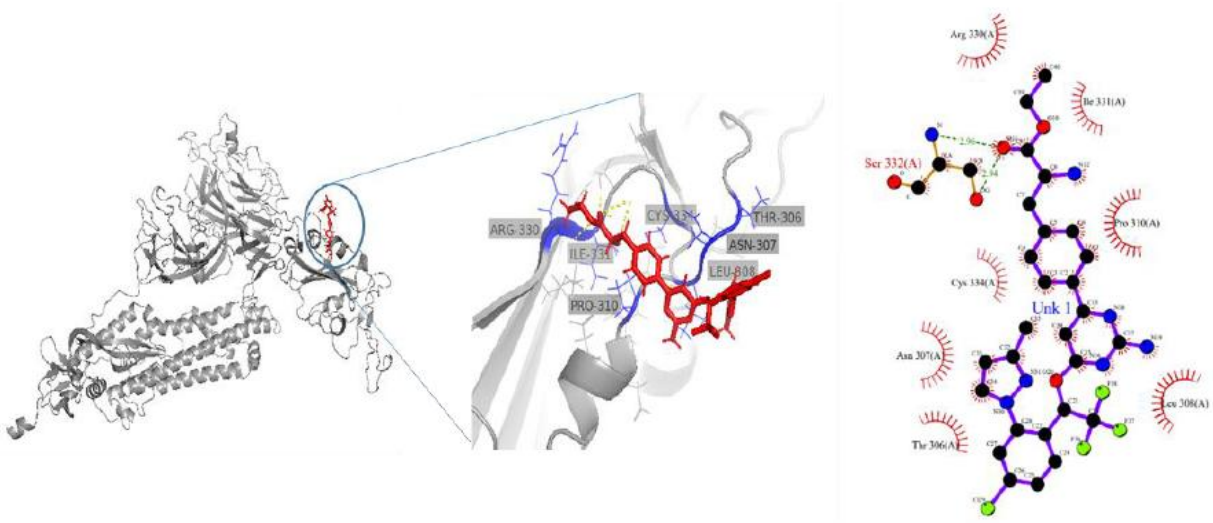


Fig. 12: Molecular interaction between telotris tetethyl and active site of mutant spike protein

4. CONCLUSION

Though the severity of this new omicron variant is low, the transmissibility rate is much higher may be due to the presence of thirty mutations in the spike region. Apart from other controlling measures like vaccine development and antibody production which takes relatively more time, identification of an effective drug is much preferred at this time. A potential drug molecule could effectively bind to the mutant spike protein and may not allow the spike protein to bind with the ACE2 receptor thereby impeding the viral entry and reduce the severity of the diseases. However a drug needs to be further validated with wet lab experiments followed by clinical trials to prove its efficacy. The drug Pentaminidium and telotris tetethyl being FDA approved drugs has an excellent chance to progress without major toxicity issues.

5. ACKNOWLEDGMENT

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Conflict of interest

None declared

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