

Identification of HIV-1 Matrix Determinants of Fitness Compensation in a Protease Inhibitor Resistant Virus



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Introduction



We have previously shown :

Gag from a multi drug resistant virus confers reduced PI susceptibility

Gag increases the PI resistance of resistant protease

(Also Dam *et al. PLoS Path.* 2009)

Amino terminal 'half' of Gag (matrix and part capsid) can confer more PI resistance, with out CSM than the carboxyl terminal 'half' (with CSM)

Introduction



PI resistant protease has reduced replication capacity (RC)

RC can be improved by mutations in protease and in Gag

We have previously shown :

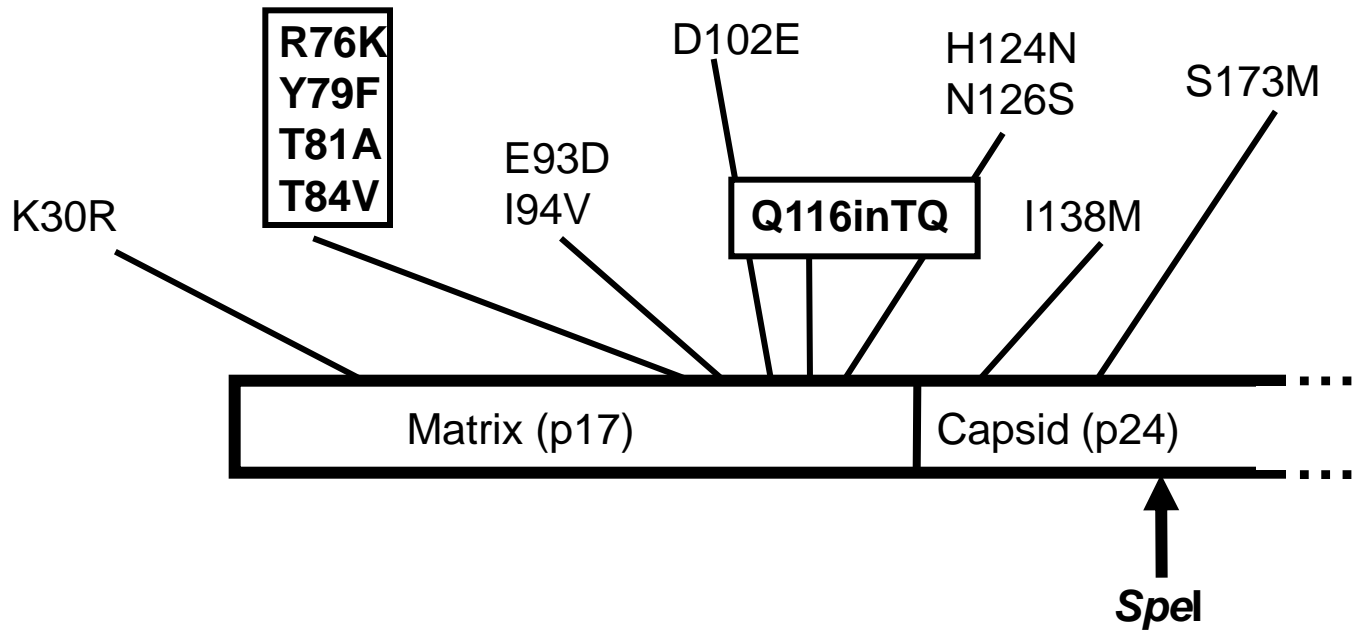
Protease alone leads to a 95% drop in replication capacity (RC)

- Full length Gag from the same virus rescues RC
- Segments of Gag can also rescue RC independently

Thus matrix MA and part of capsid can rescue the RC of multi drug resistant protease

Which mutations in MA are involved in this rescue?

Mutant Matrix, Capsid and Protease



Major Protease Mutations: L33F, M46I, I54V, V82A

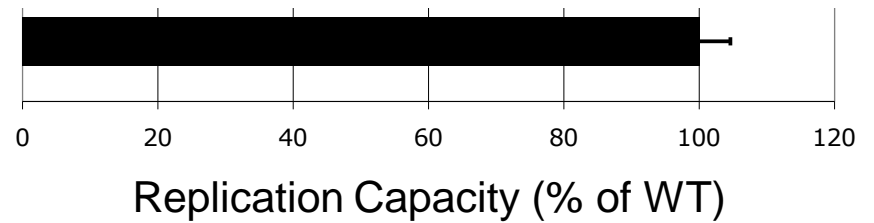
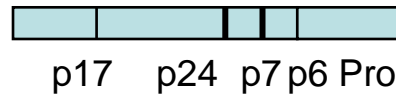
Minor Protease Mutations: L10V, L24I, K55R, L63P

Other Protease Mutations: I13V, M36QNL, G57K, I62V, I64V, L76V

Role of 116 insertion




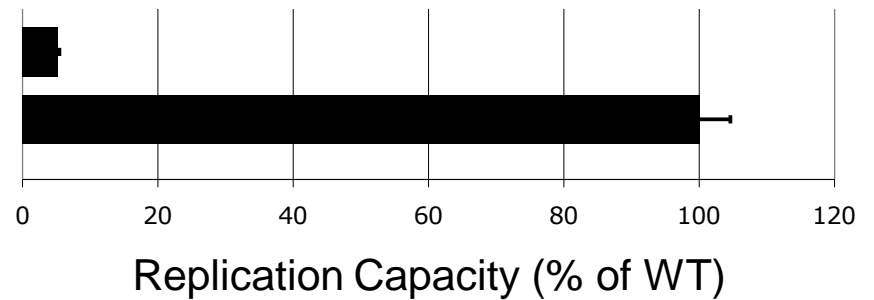
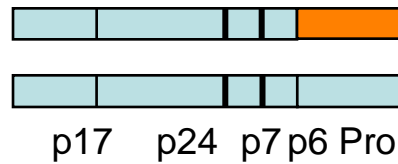
 **WT**
 **Mutant**



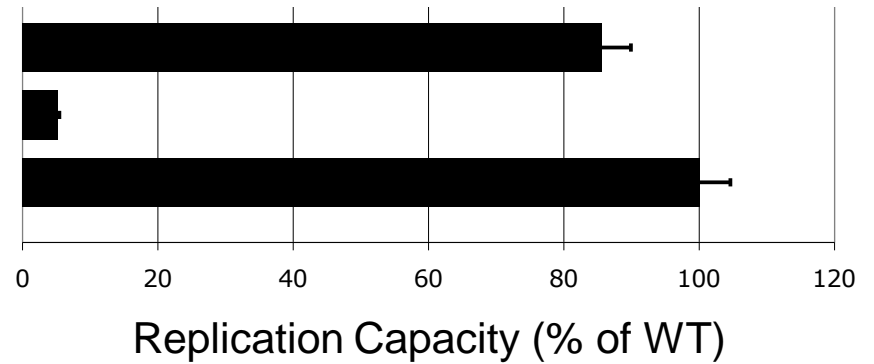
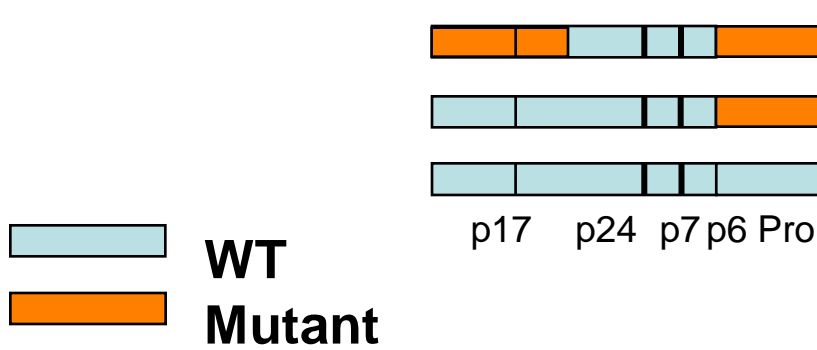
Role of 116 insertion



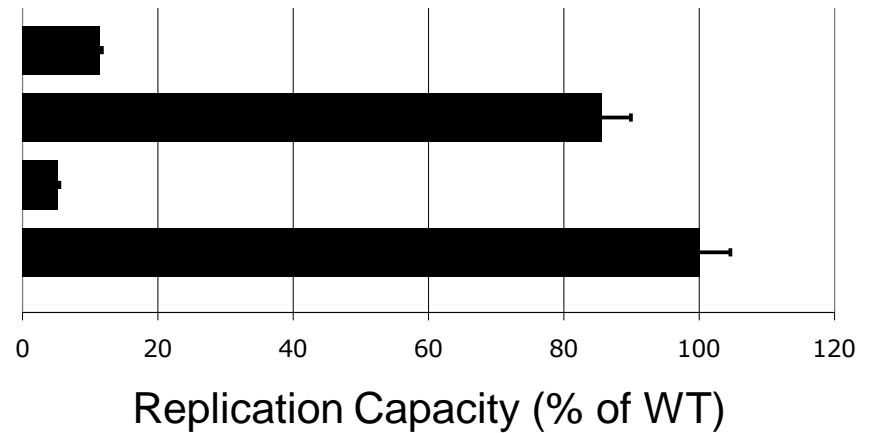
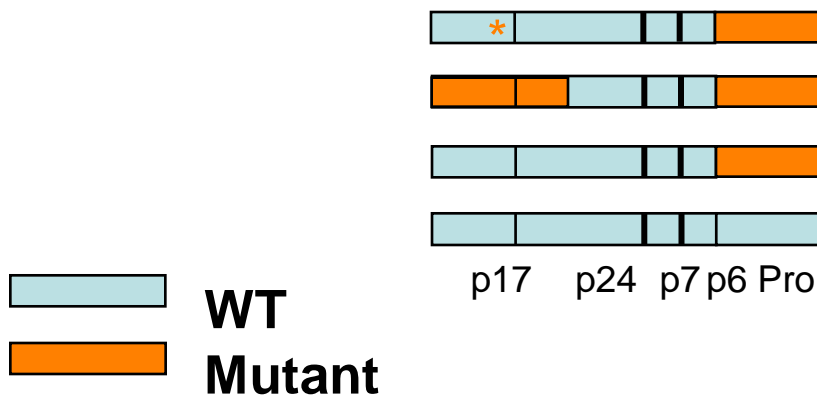
 **WT**
 **Mutant**



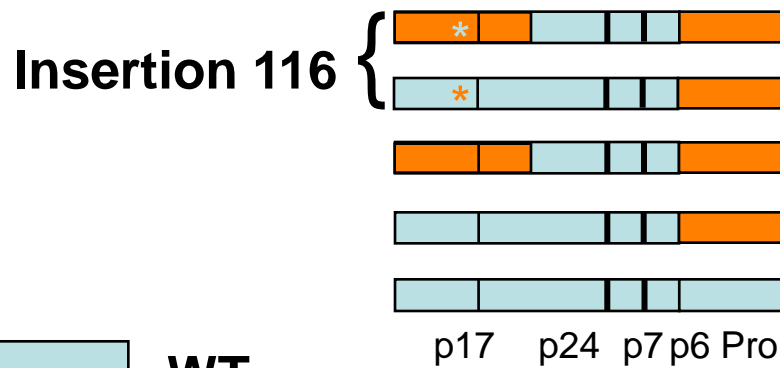
Role of 116 insertion



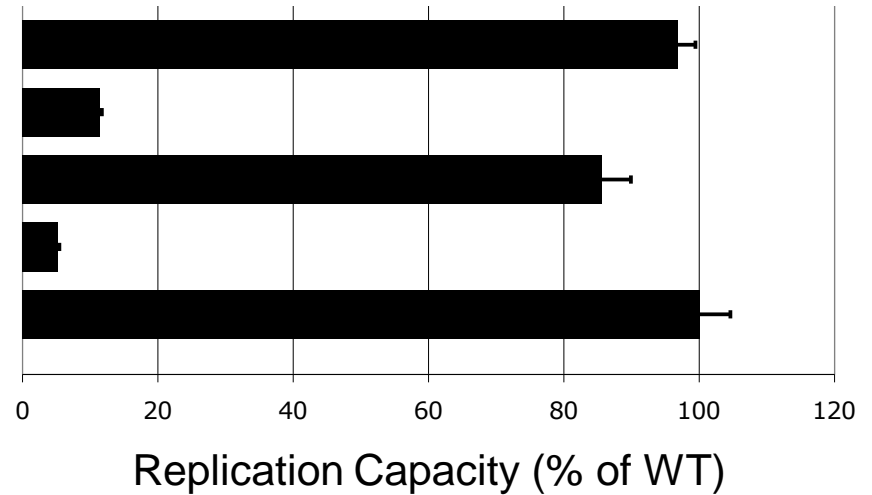
Role of 116 insertion



Role of 116 insertion



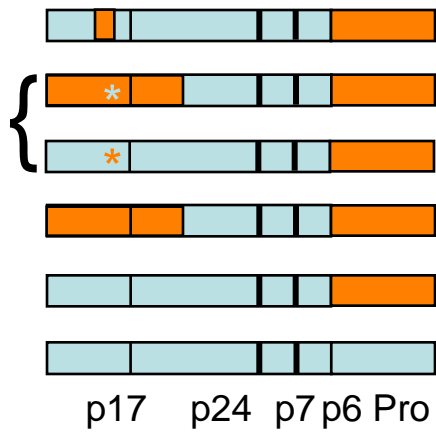
 **WT**
 **Mutant**



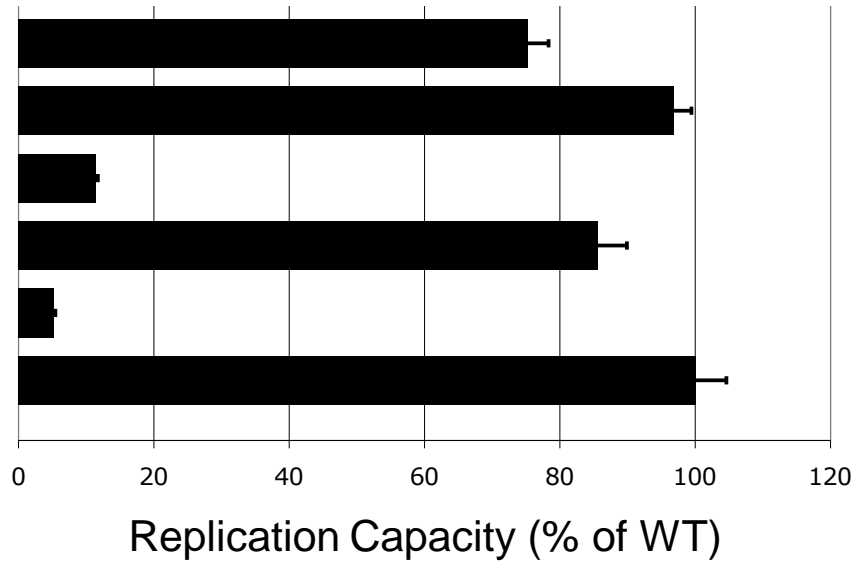
Role of 76, 79 & 81 mutations



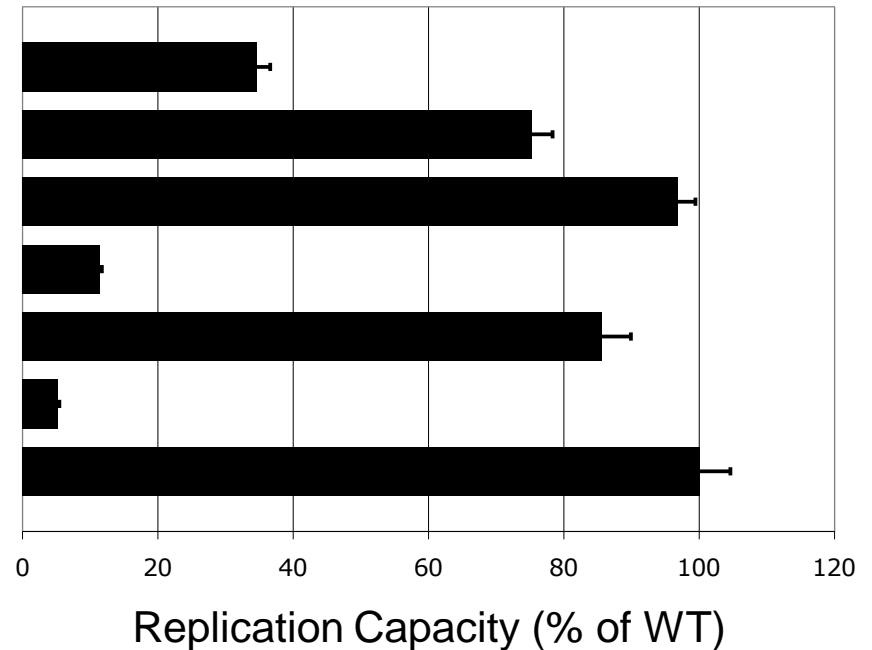
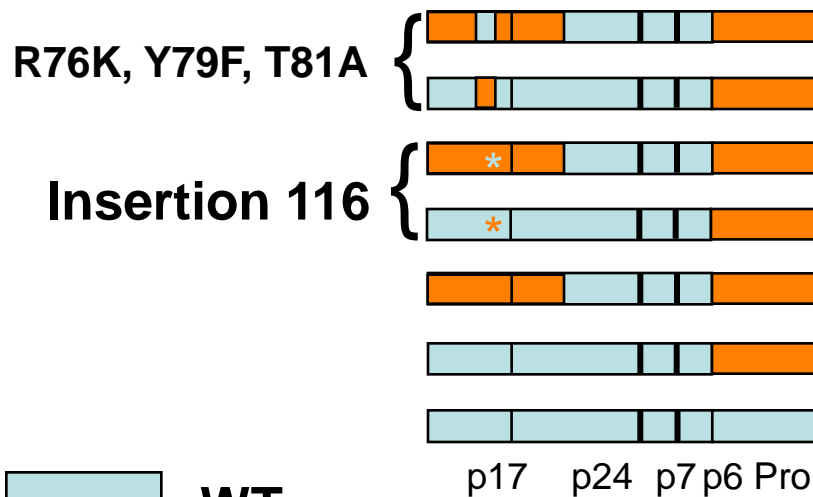
Insertion 116



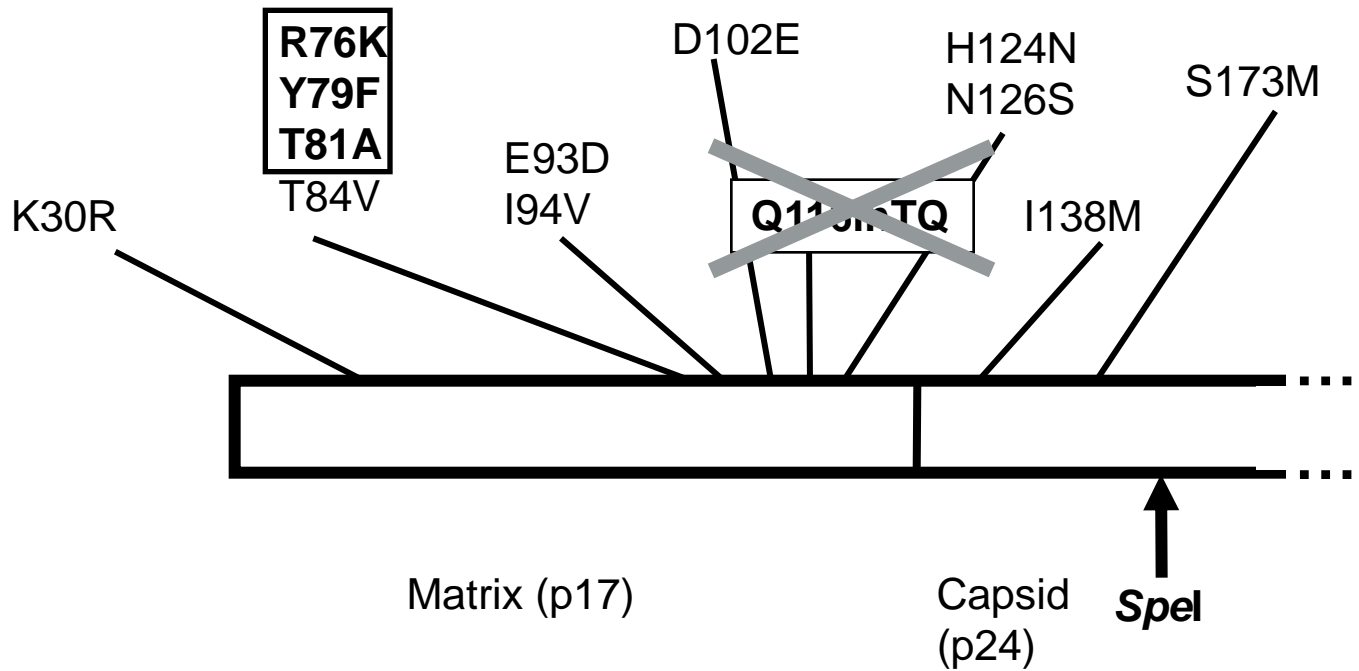
 WT
 Mutant



Role of 76, 79 & 81 mutations

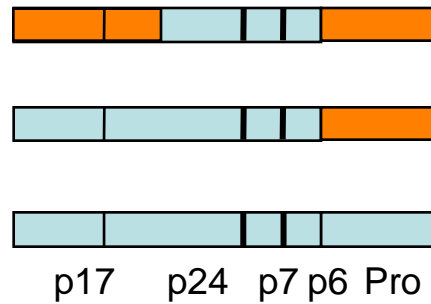


Mutant Matrix and Capsid

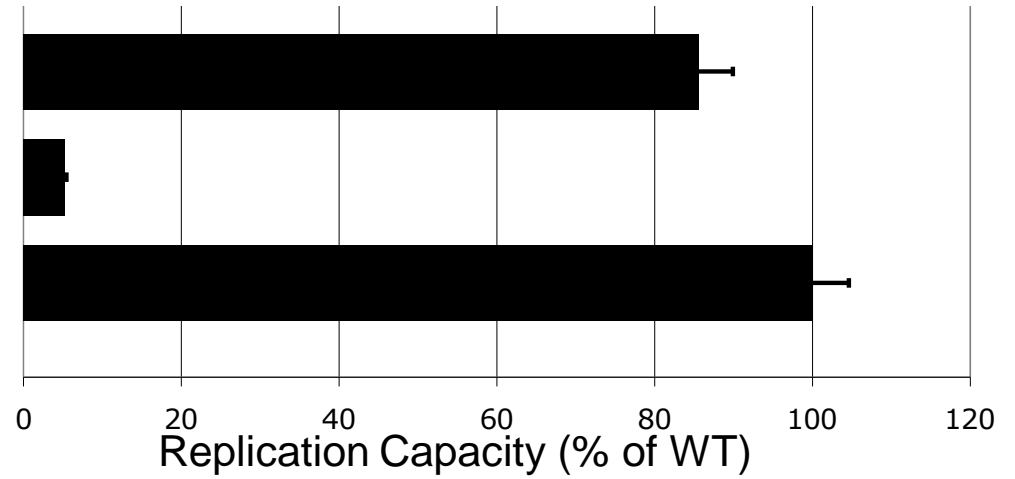


Insertion in Matrix at position 116 does not significantly contribute
R76K, Y79F & T81A rescue the RC of Mutant protease
What is the role of each...?

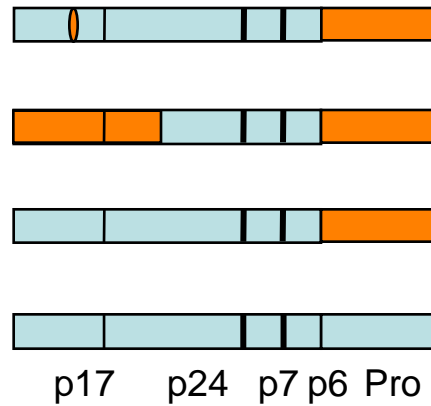
Role of MA T81A



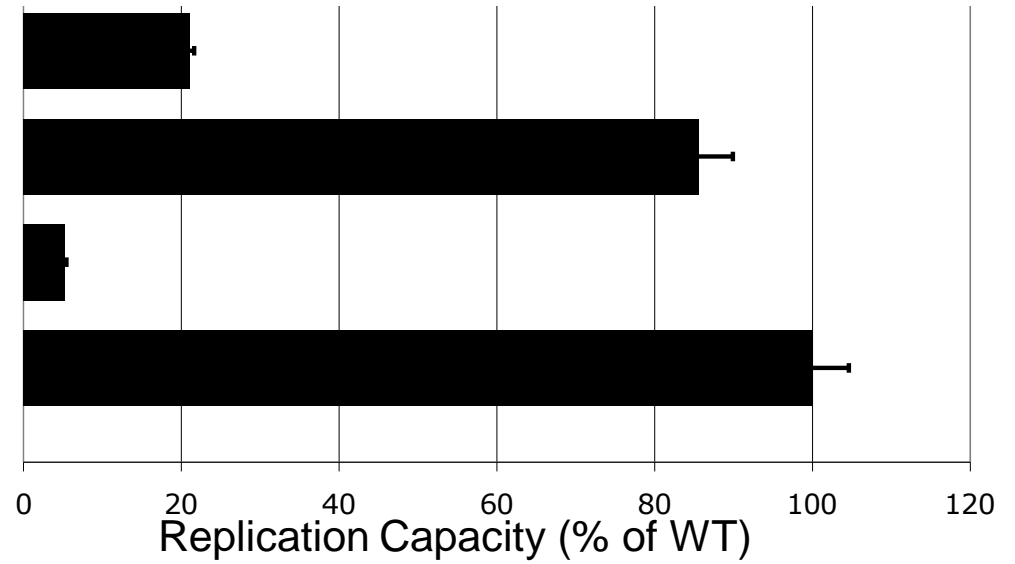
 **WT**
 **Mutant**



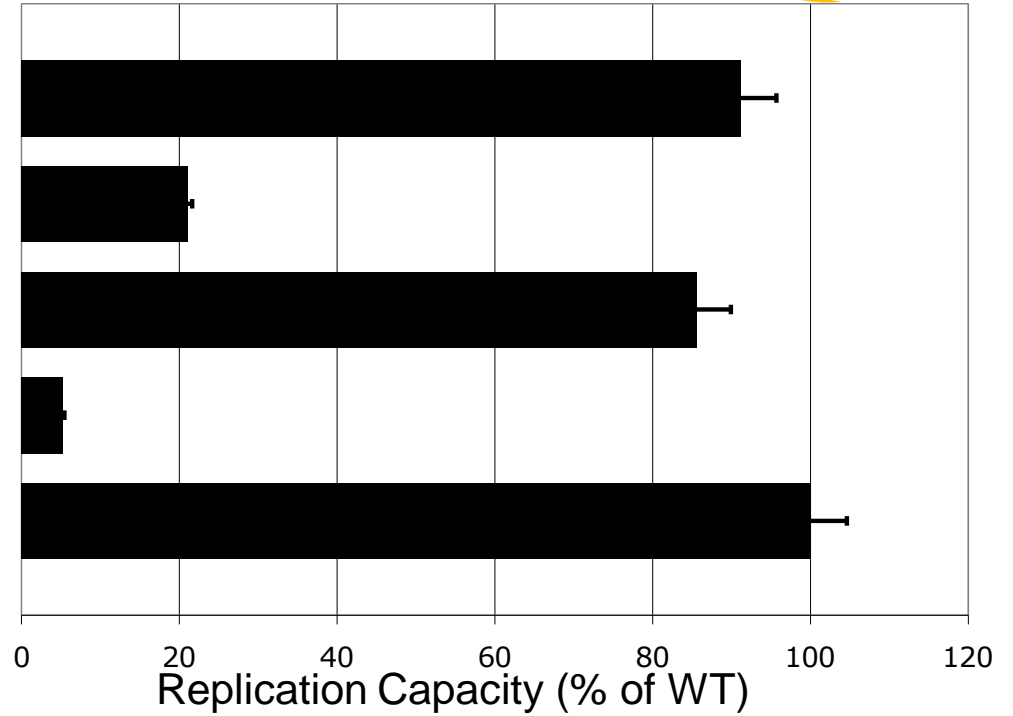
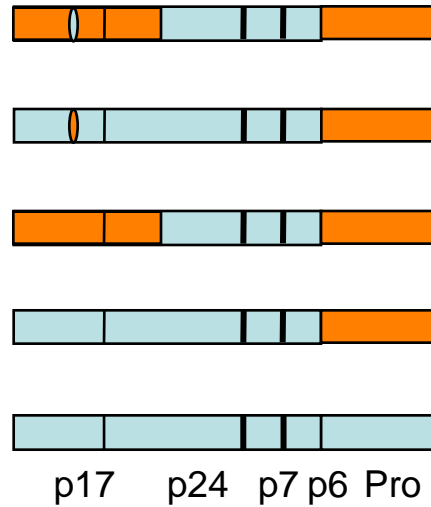
Role of MA T81A



 **WT**
 **Mutant**



Role of MA T81A



Change at 81 alone has a minor effect

Summary



MA & part CA can rescue RC of Mutant protease

Insertion 116 in MA not important

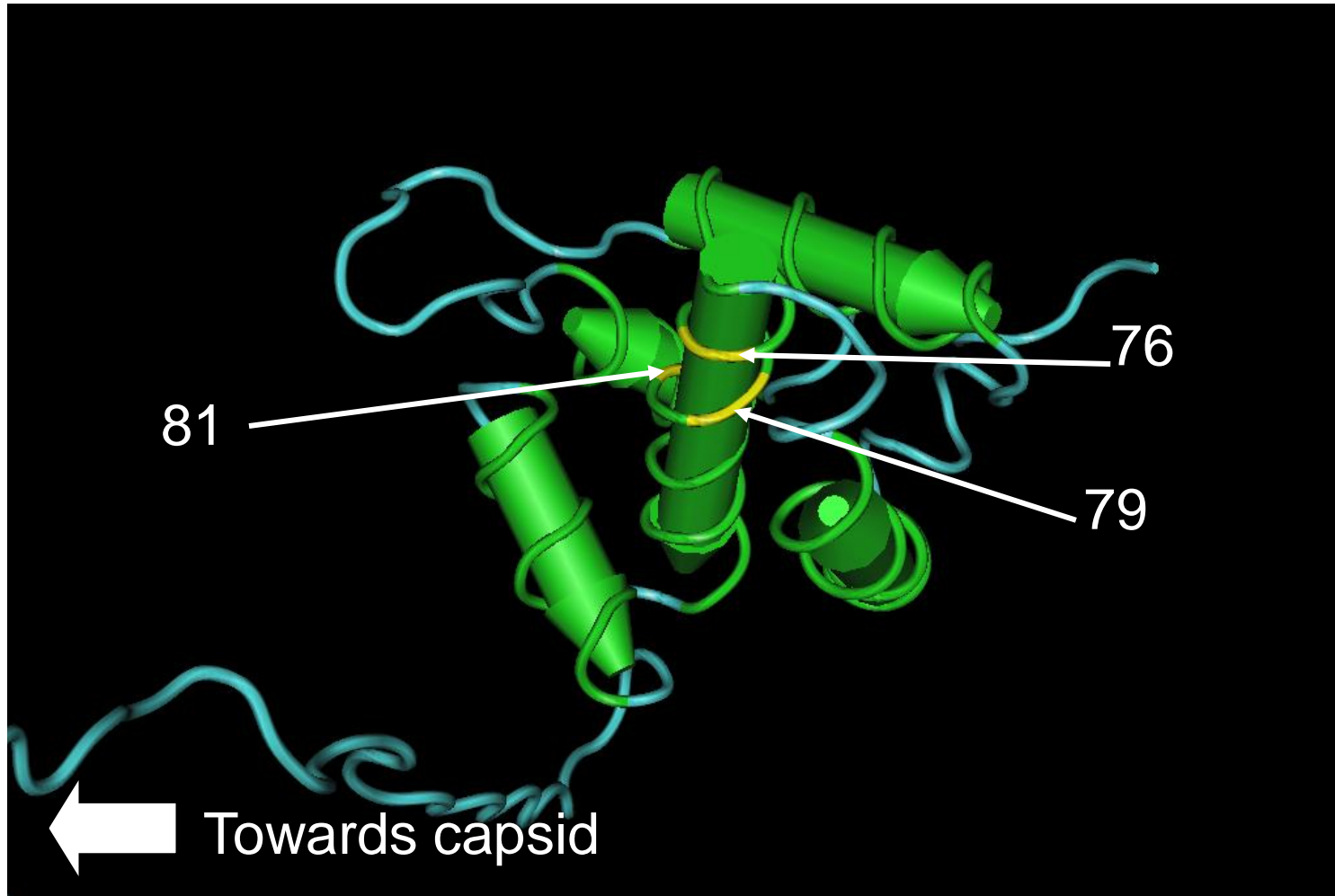
Changes at 76, 79 and 81 are sufficient for rescue

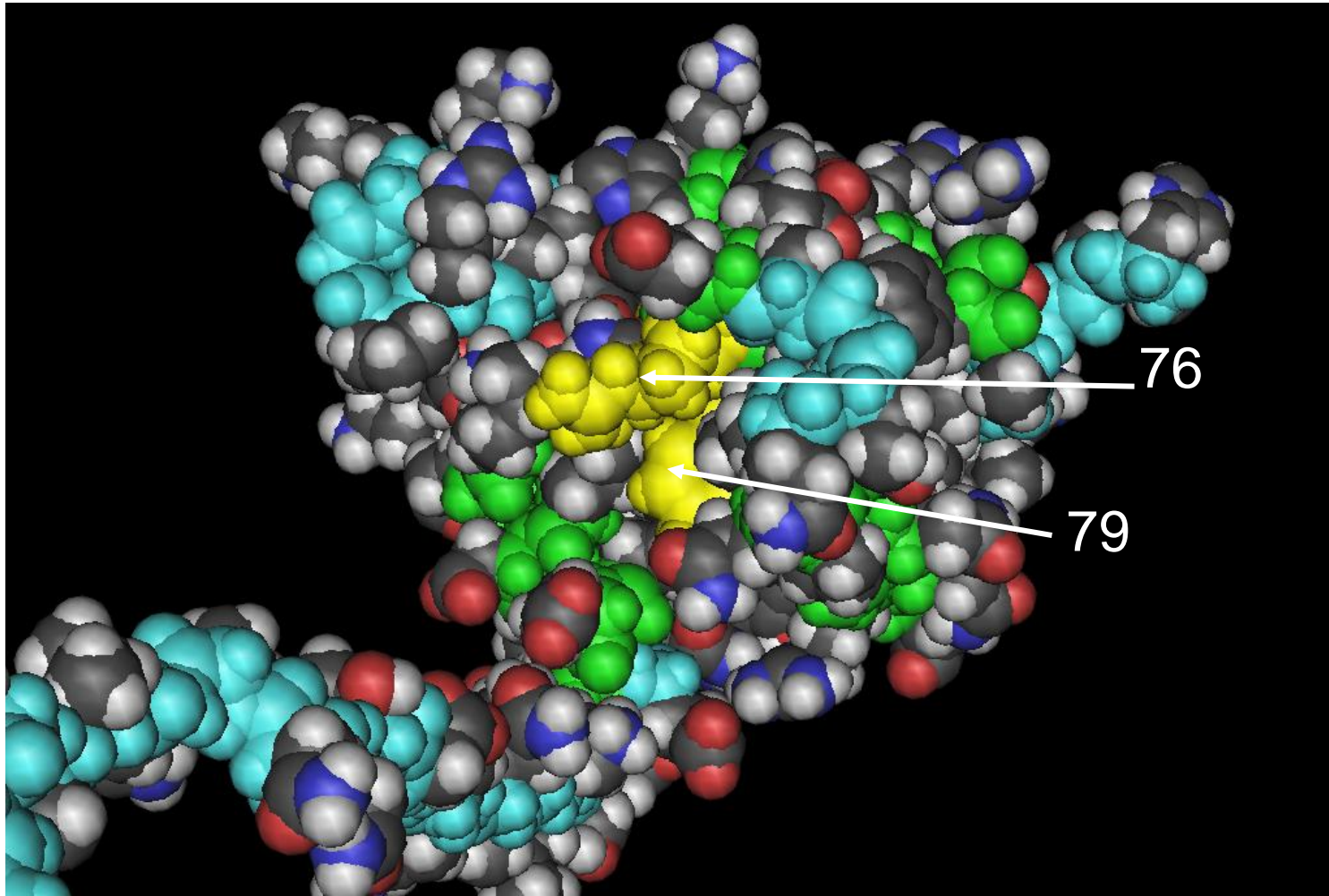
Single change at 81 is not sufficient for rescue

does have a small effect

Is not required for function of Mutant MA and part CA







Acknowledgements



Deenan Pillay

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UCL