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Molecular Tridimensional Phenotyping Predicts HIV-1 Protease Inhibitor Resistance

G Pèpe^{1,2}, J Courcambeck², J Durant³, P Dellamonica³, R Boulmé⁴ and P Halfon^{2,5}

1 CNRS ; 2 Molecular Modelling Unit, Genoscience, Marseille, France; 3 CHU Archet, Dept. Infectious Diseases, Nice; 4 Advanced Biological Laboratories, Biomedical Information Unit, Luxembourg and 5 Alphabio, Dept. de Virologie, Marseille, France

BACKGROUND : Drug resistance development is a major limitation for successful highly active antiretroviral therapy. HIV genotyping and phenotyping resistance testing are the most commonly used methods to guide treatment decisions. Clinical interpretation of genotypic tests and determination of the phenotyping test clinical cut off are still limited regardless time consuming and costly. We developed a 3Dimensional molecular computer-based modeling system which rapidly predicts HIV-1 protease drug resistance by measuring the binding energies between a protease mutant (PM) and a protease inhibitor (PI).

METHODS : HIV-1 protease mutants were built from X-ray crystal structure corresponding to each PI complex. The GenMol™ (GM) program (www.3dgenoscience.com) was used to generate amino-acid mutations by energy minimization. The PI-PM binding resulting energy complex was determined after energy refinement. We applied the methodology to ritonavir. (i) We compared the actual predicted GM ritonavir result with genotypic data interpretation (ABL ViroScorer™) for cut-off determination and concordance. (ii), We assessed the correlation between GM ritonavir values and phenotyping results (PhenoSense™, resistance cut-offs of >2.5 fold-resistance (FR) and >10). (iii), We evaluated the baseline GM predictive value on virological outcome at month 3 and 6 among 48 patients from the Viradapt trial who had been adapted with ritonavir.

RESULTS : Based on 129 HIV-1 protease sequences, an energy cut-off value (-91.1) was determined for the GM analysis. (i) Individual predictive interpretation as resistant or susceptible were determined with a good agreement ($k > 0,80$). (ii) Significant correlations between binding energies and ritonavir phenotyping results were found without excluding outliers. Kappa scores were 0.55 and 0.67 for $FR > 2.5$ and $FR > 10$, respectively. The association between $\log_{10}(FR)$ and gm value was $R_s = 0.61$ (Spearman's correlation). (iii) At M3, median GM value of -90.21 and -92.01 was significantly different ($p < 0.01$, Wilcoxon) for virological failure and success, respectively. Identically at M6, median GM value of -90.78 and -92.03 was significantly different ($p < 0.01$). GM values were entered in a logistic model with baseline viral load (bvL) and genotypic-guided treatment covariates. Using cut-offs -91.0 and -90.5, GM predicts a virological outcome in the uni- (odds-ratio=5.09, 95% confidence interval (CI)=1.55-22.58, $p < .01$ (Wald)) and the multivariate (OR=5.89, CI=1.53-22.60, $p < .01$ (bvL-GM) model).

CONCLUSIONS : GenMol™, a novel 3Dimensional molecular modeling method was developed to predict HIV-1 ritonavir drug resistance. 2) Good agreement was reported with genotypic and phenotypic interpretation. 3) Other PIs GM validation is underway 4) Further work is required to empower first findings about GM as an independent predictor of virological outcome in prospective clinical trials.

Abstracts