

## POSTER 5

### PF-68742 IS A LOW MOLECULAR WEIGHT HIV-1 FUSION INHIBITOR THAT TARGETS gp41

Edward J. Murray<sup>1</sup>, Daniel P. Leaman<sup>3</sup>, Hannah Perkins<sup>1</sup>, Graham Rickett<sup>1</sup>, Chris Pickford<sup>1</sup>, Marilyn Lewis<sup>2</sup>, Pat Dorr<sup>1</sup>, Manos Perros<sup>1</sup>, Michael B. Zwick<sup>3</sup>, and Scott Butler<sup>1</sup>

<sup>1</sup>Anti-viral Department, <sup>2</sup>Bioinformatics Department, Pfizer Global Research and Development, Sandwich, Kent, C13 9NJ, United Kingdom; <sup>3</sup>Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, California 92037, USA

The low molecular weight inhibitor PF-68742 (MW 573) was identified from a high throughput screen against HIV-1 fusion. Subsequent studies revealed that the compound is potent against both R5 and X4 isolates in both cell-cell fusion and antiviral assays ( $IC_{50}$  values ~0.2 to 1  $\mu$ M). Time of addition experiments confirmed that PF-68742 is an entry inhibitor and virus pseudotyping experiments identified Env as the sole and specific target for anti-viral action. PF-68742 was not able to block binding of gp120 to CD4 or the binding of gp120:CD4 complexes to CCR5, distinguishing PF-68742 from previously described gp120 antagonists and co-receptor binders such as maraviroc, and indicating that it is likely to block viral entry downstream of co-receptor engagement, possibly through interaction with gp41. Alignment of the sequences of Env from resistant and sensitive strains tested either in cell-cell fusion or pseudotyped virus assays pointed to amino acid position 619 (HXB2 numbering), which is Leucine in 9/9 PF-68742 sensitive isolates, but other, mainly polar side chains in all 8 resistant strains. L619 is in the central ectodomain portion of gp41 that includes the disulfide-loop (DSL) within the principle immunodominant domain (PID). Further site-directed mutagenesis experiments confirmed that altered gp41 sequences in the vicinity of the PID confer complete resistance to PF-68742 and therefore have an important role in its mechanism of action.