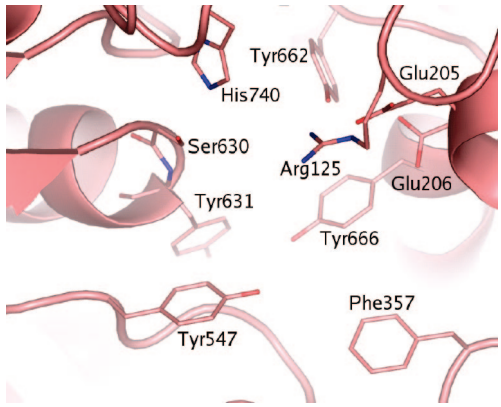
Additions and Corrections

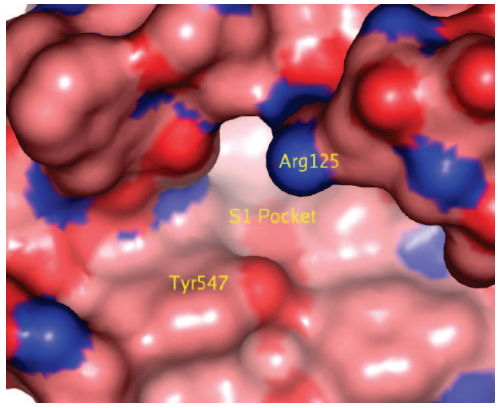
2007, Volume 50

Jun Feng, Zhiyuan Zhang, Michael B. Wallace, Jeffrey A. Stafford, Stephen W. Kaldor, Daniel B. Kassel, Marc Navre, Lihong Shi, Robert J. Skene, Tomoko Asakawa, Koji Takeuchi, Rongda Xu, David R. Webb, and Stephen L. Gwaltney II*: Discovery of Alogliptin: A Potent, Selective, Bioavailable, and Efficacious Inhibitor of Dipeptidyl Peptidase IV.

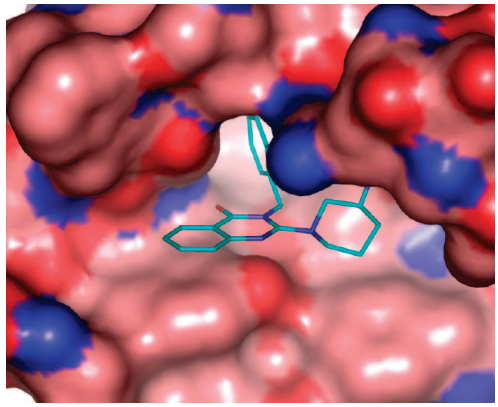
Page 2297. The image in Figure 1 should be replaced with the following image:



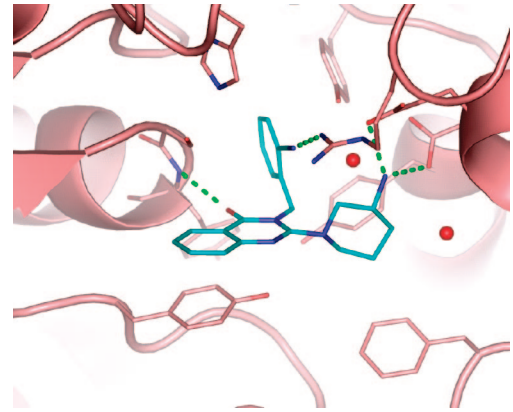
The image in Figure 2 should be replaced with the following image:



Page 2298. The image in Figure 4 should be replaced with the following image:



The image in Figure 5 should be replaced with the following image:



Page 2300. Reference 11 should read as follows. (11) Early work on a cocrystal of **1a** has already appeared in the following: Gwaltney, S. L., II; Aertgeerts, K.; Feng, J.; Kaldor, S. W.; Kassel, D. B.; Manuel, M.; Navre, M.; Prasad, G. S.; Shi, L.; Skene, R. J.; Stafford, J. A.; Wallace, M.; Xu, R.; Ye, S.; Zhang, Z.; Webb, D. R. Design and synthesis of potent, selective, and orally efficacious DPP4 inhibitors accelerated by high-throughput structural biology. Presented at the 231st National Meeting of the American Chemical Society, Atlanta, GA, March 26−30, 2006; MEDI-018. Figure 4 depicts a recently obtained cocrystal structure (PDB code 2ONC).

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Amnon Hoffman,* Bashir Qadri, Julia Frant, Yiffat Katz, Sudhakar R. Bhusare, Eli Breuer,* Rivka Hadar, and Reuven Reich*: Carbamoylphosphonate Matrix Metalloproteinase Inhibitors 6: *cis*-2-Aminocyclohexylcarbamoylphosphonic Acid, A Novel Orally Active Antimetastatic Matrix Metalloproteinase-2 Selective Inhibitor—Synthesis and Pharmacodynamic and Pharmacokinetic Analysis.

Page 1408. The paragraph in right-hand-side column, starting with the words “The pharmacodynamics...” should be replaced by the following paragraph.

The pharmacodynamics of *cis*-ACCP (i.e., concentration−effect relationship) has been found to be nonlinear. The magnitude of inhibition (i.e., reduction of enzyme activity and tumor cell invasion) is concentration-dependent up to a certain concentration. This concentration of *cis*-ACCP, defined as MIC, required for neutralizing the actual amount of MMP-2 in the animal was verified experimentally by zymography and was found to be 12 ng/mL (see below paragraph for details about the MIC). Any *cis*-ACCP concentration that exceeds this value will provide the maximal antimetastatic/MMP-inhibitory activity. Thus, the maximal inhibition of MMP-2 will be maintained as long as the concentrations in the blood and the extracellular fluid are above MIC. This explains

the prolonged action observed following single daily administrations either orally or intraperitoneally. It also allows predicting the kinetics of action of this MMP inhibitor following various modes of administration based on the concentration−time profile that would be obtained. In contrast, in in vitro studies, i.e., cellular invasion experiments, a much higher concentration of *cis*-ACCP was used (50 μM). This concentration is at least 10-fold above the IC_{50} value, and it guarantees above 70% inhibition of the cellular invasion in vitro.

The minimum inhibitory concentration (MIC) of *cis*-ACCP, defined as the lowest concentration of the inhibitor that will inhibit the enzyme secreted by 50 000 B16F10 cells injected into each mouse, was established as follows. From a dose response curve of recombinant human MMP-2 preparation, it was estimated that 50 000 B16F10 cells secrete daily approximately 100 pg of MMP-2. Dilution of this amount into the mouse circulatory fluids (5 mL) results in an approximate concentration of 20 pg/mL MMP-2. The concentration of *cis*-ACCP required for neutralizing the activity of this amount of MMP-2 was verified experimentally by applying MMP-2 (20−5 pg) to zymography in the absence and presence of *cis*-ACCP and was found to be 12 ng/mL or 50 nM. In view of the literature, this amount of MMP in the mouse's circulation is probably an overestimation, since only a very low percentage (0.1−1%) of the injected cells survive and capable of secreting MMPs and of forming metastatic loci. See the following: (a) Fidler, I. J. Metastasis: quantitative analysis of distribution and fate of tumor emboli labeled with ^{125}I-5-iodo-2′-deoxyuridine. *J. Natl. Cancer Inst.* **l970,** *45*, 773−782. (b) Fidler, I. J. The relationship of embolic homogeneity, number, size and viability to the incidence of experimental metastasis. *Eur. J. Cancer* **l973**, *9*, 223−227.

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