Biochemical and Biophysical Research Communications 436 (2013) 650–654

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Molecular dynamics study of carbon nanotube as a potential dual-functional inhibitor of HIV-1 integrase

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ARTICLE INFO

Article history:
Received 29 May 2013
Available online 13 June 2013

Keywords:
HIV-1 integrase
Integrase inhibitor
Carbon nanotube
Drug delivery
Molecular dynamics simulation

ABSTRACT

HIV-1 integrase (IN) plays an important role in integrating viral DNA into human genome, which has been considered as the drug target for anti-AIDS therapy. The appearance of drug-resistance mutants urgently requires novel inhibitors that act on non-active site of HIV-1 IN. Nanoparticles have such unique geometrical and chemical properties, which inspires us that nanoparticles like nanotubes may serve as better HIV-1 IN inhibitors than the conventional inhibitors. To test this hypothesis, we performed molecular dynamics (MD) simulation to study the binding of a carbon nanotube (CNT) to a full-length HIV-1 IN. The results showed that the CNT could stably bind to the C-terminal domain (CTD) of HIV-1 IN. The CNT also induced a domain-shift which disrupted the binding channel for viral DNA. Further MD simulation showed that a HIV-1 IN inhibitor, 5ClTEP was successfully sealed inside the uncapped CNT. These results indicate that the CNT may serve as a potential dual-functional HIV-1 IN inhibitor, not only inducing conformation change as an allosteric inhibitor but also carrying small-molecular inhibitors as a drug delivery system.

1. Introduction

Acquired immunodeficiency syndrome (AIDS) is a global pandemic and leading infectious disease caused by human immunodeficiency virus type one (HIV-1). There are three proteins encoded by HIV-1 genome, namely reverse transcriptase (RT), protease (PR), and integrase (IN). Among them, HIV-1 IN plays a key role in the integration of viral DNA into host genome. Two HIV-1 IN monomers first assemble as a homodimer. Then viral DNA binds to the dimer for 3′-processing during which the dimer removes two nucleotides from two DNA strands and leaves 3′ CA-OH ends. After the 3′-processing, two HIV-1 IN dimers recruit other co-factors to form the so-called pre-integration complex (PIC) and carry the processed DNA to the nucleus. Eventually, the 3′ CA-OH ends of the viral DNA are covalently joined to the host DNA via trans-esterification reaction [1]. As a consequence, IN has been considered as an important drug target for anti-AIDS therapy.

In 2007, raltegravir [2] was computationally designed to target the catalytic core domain (CCD) of HIV-1 IN and soon became a leading anti-AIDS drug [3]. Similar drugs such as elvitegravir [4,5], diketo acid (DKA) derivative inhibitors [6,7] had also achieved good clinical results. However, drug-resistance mutants in the CCD have already been found from AIDS patients [8,9]. Thus, to develop novel effective HIV-1 IN inhibitors will have great prospective.

Nanoparticles have been suggested as promising inhibitors because of their unique geometrical and chemical properties, such as highly chemical stability and lower biodegradability [10]. Particularly, nanoparticles such as C60 and nanocarbon tube (CNT) are relatively rigid, and thus could retain their geometrical structures during interaction with biomolecules [11]. Experimental and computational studies have shown that proteins like HIV protease [12], human and bovine serum albumins [13], DNA mismatch repair proteins [14] were ideal targets of nanoparticle drugs. This highlights that nano-scale ligands could also act as effective inhibitors of HIV-1 IN.

To test this hypothesis, here we applied molecular simulation (MD) to examine the interactions between a CNT and a full-length HIV-1 IN. The simulations showed that the CNT could stably bind to the C-terminal domain (CTD) of HIV-1 IN, which has been proved to be the platform for DNA binding [15]. During the binding process, the CNT induced a domain-shift of the CTD and NTD, which disrupted the DNA binding channel of HIV-1 IN. Further MD simulation of the HIV-1 IN inhibitor 5ClTEP [16] showed that the inhibitor molecule was stably sealed in the uncapped CNT. Taken together, this study indicated that the CNT might serve as both an allosteric inhibitor and a delivery system for HIV-1 IN.

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http://dx.doi.org/10.1016/j.bbrc.2013.06.009

2. Materials and methods

2.1. Protein and CNT preparation

The full-length HIV-1 IN was obtained by assembling the available structures of domains from the Protein Data Bank (PDB): 1EX4 (CCD–CTD) and 1K6Y (CCD–NTD). Ligands and ions were removed from both 1EX4 and 1K6Y. Mutations were eliminated in order to obtain native structure. Highly conserved motives like HHCC of NTD (residues 1–45) and DDE of CCD (residues 56–210) were preserved as the linking segments between CCD and CTD were refined by the program MODELLER 9 [17] according to standard modeling protocols [18]. Final model was assessed by the Ramachandran plot to inspect residues distribution [19]. The CNT was generate with chirality of (5,5), with a C–C bond length of 1.42 Å. The diameter of the CNT was 6.8 Å, and the length was 23 Å.

2.2. Molecular dynamics simulation

MD simulations were performed using the GROMACS software package [20], with the Amber99SB force field [21]. First, The CNT-IN system was solvated in a water box containing TIP3P water molecules [22]. The carbon atoms of the CNT were selected as CA, the aromatic and non-polarizable carbon atom particles with 1–4 carbon–carbon interactions were switched on [23]. Then, temperature of the system was gradually heated from 100 K to 300 K and simulated 500 ps in the constant volume (NVT) ensemble for equilibrium. Afterwards, the system was simulated for 100 ns using constant temperature (NPT) ensemble while temperature maintained at 300 K and pressure set as 1 bar, using a time step of 0.002 ps. During the simulation, the periodic boundary condition was used on all sides of the simulation systems. Berendsen thermal coupling was used as the dynamics ensemble. The electrostatic interactions were treated using the PME approach. As for the CNT-inhibitor system, we adjust the water model from TIP3P to TIP4P in order to get a better description of water molecules behavior [24,25]. In addition, 10-ns simulation was considered as proper because the size of CNT-inhibitor system was much smaller than CNT-IN system.

2.3. Trajectory analysis and molecular graphics

Root mean square deviation (RMSD) values of HIV-1 IN and 5ClTEP in our simulations were calculated by the *g_rms* module of GROMACS. To investigate the dynamics of HIV-1 IN residues, root mean square fluctuation (RMSF) values for all 288 HIV-1 IN residues were calculated by the *g_rmsf* module. The search for CNT-binding residues was conducted by our own Python script. Structural data was first extracted every 1 ns from the whole 100 ns simulation. For each snapshot conformation, centroid of the CNT was used as the decoy and 6 Å was set as threshold to search the close residues. The programs PyMOL (http://www.pymol.org) and VMD [26] were used to create the protein structure images in all figures in the study.

3. Results and discussion

3.1. CNT bound to HIV-1 IN CTD

CNTs have been proved to bind to non-polar motifs of proteins. Because of the distribution of hydrophobic residues, all three domains of HIV-1 IN may have equal opportunity for the CNT binding. In addition, there exits a dimerization interface on the HIV-1 IN monomer [27]. To avoid artifacts in the simulation, the (5,5) CNT was placed on the opposite side of the known dimerization interface, with average distance of 49.5 Å from three domains of HIV-1 IN (Fig. 1A). The system was soaked in a water box with NaCl concentration of 150 mM, mimicking biological environment. 100-ns MD simulations were then carried out for both the experimental system and control system which contained only HIV-1 IN. Results showed a conformation reached by the experimental system, which control system could not reach (Fig. 1B). To investigate conformation change of HIV-1 IN during CNT binding, trajectories of the simulation was extracted to calculate the RMSD (root mean square deviation) values of α-carbon atoms of HIV-1 IN with respect to the starting conformation (Fig. 1C).

The RMSD results showed that the conformation of HIV-1 IN became stable after about 25-ns simulation. From 0 to 25 ns, the HIV-1 IN conformation appeared to undergo two conformational changes. The first conformational change was attributed to the interaction between HIV-1 IN and solvent before 5 ns. The second conformational change was induced by the contact with the CNT at about 20 ns (Fig. 1C). After the CNT binding caused the significant conformational change of HIV-1 IN, the whole system reached a stable state from 25 ns to the end of the simulation.

Consistent with the RMSD results, the RMSF results (Fig. 1D) showed that prior to the binding, the HIV-1 IN structure was more flexible than that after the CNT binding, particularly in the CTD part (residues from 270 to 288). This also implied that the CTD played an important role in the CNT binding process.

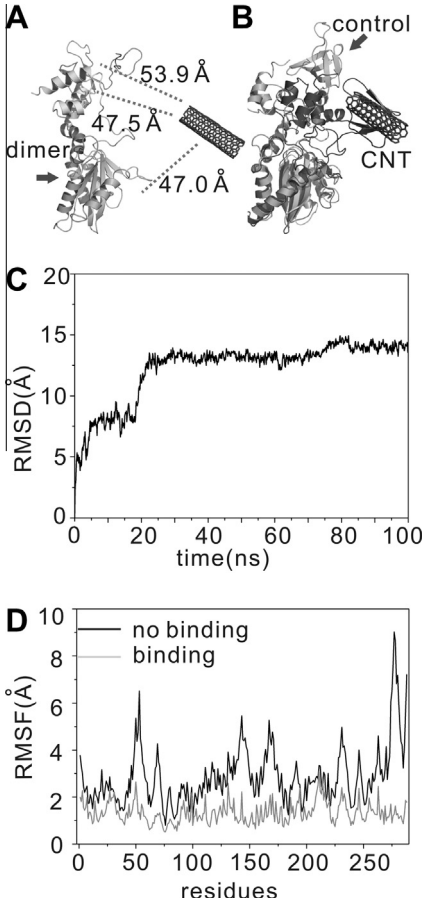

Fig. 1. MD simulation of the CNT and HIV-1 IN system. (A) Starting position of the CNT. The known IN dimer interface is indicated by arrow. Distances between CNT and CTD, NTD, CCD are 53.9 Å, 47.5 Å and 47.0 Å, respectively. (B) Stable conformations of two simulations. (C) Backbone RMSD values of HIV-1 IN in the MD simulation. (D) RMSF values of 288 HIV-1 IN residues before and after CNT binding shown as black and grey lines, respectively.

To further examine the CTD role in the CNT binding, we analyzed the simulation trajectories from 25 to 100 ns by investigating the detailed interactions between the HIV-1 IN residues and the CNT. As expected, we found that the residues in the CTD mainly mediate the CNT binding process, via a channel-like structure formed by residues Tyr227, Asp229, Lys231, Asp232, Lys236, and Lys258. Among those residues, the tryptophan Tyr227 bound to the CNT through hydrophobic interaction between its aromatic ring and the sp^2 carbon ring of the CNT [28]. Residues Lys236 and Lys258 applied their long hydrocarbon chain to 'clamp' the CNT from both sides, similar interactions has been shown in a previous study [29]. Very interesting, residue Arg231 used not only its hydrophobic carbon chain as a platform for the CNT binding, but also its hydrophilic amino group as a barrier to protect the CNT from gliding out of the binding channel (See Supplementary Fig. S1).

3.2. CNT induced domain-shift of HIV-1 IN

Through conformational comparison, we found that the CNT induced a large conformational change of the CTD and NTD during the CNT binding process (Fig. 2A). According to the trajectories analysis, this domain-shift process was mainly divided into three sub-steps: (1) part of the linking helix between the CTD and CCD first released and thereby increased its flexibility; (2) with the help of the linking segment, the CTD bent towards the CNT and at the same time adjusted its surface residues to form the CNT-binding channel; (3) due to the interactions between the CTD and NTD, the NTD also moved in the same direction and towards the CNT. After forming a stable CNT-bind channel, the three domains of HIV-1 IN surrounded the CNT, leading to a compact conformation that is very different from the starting conformation (Fig. 2B).

As mentioned before, HIV-1 IN needs to form a homodimer to carry out its biological function. It has also been confirmed that the HIV-1 IN dimer has a viral DNA binding channel formed by the CCD from one monomer, and the CTD and NTD from the other [30] (Fig. 2C). In our simulation, the domain-shift of HIV-1 IN altered the relative positions of these three domains, especially that of the CTD and NTD. Based on our dimer model, the CNT-binding led the CTD and NTD to the opposite side from original dimerization interface, which made it difficult for two HIV-1 IN monomers to form the DNA-binding channel for the integration activity (Fig. 2D). Thus, the CNT-binding could disrupt the binding of the viral DNA to the HIV-1 IN dimer, and thereby inhibit activity of the HIV-1 IN. Therefore, our MD simulation showed that the CNT could serve as an allosteric inhibitor of HIV-1 IN.

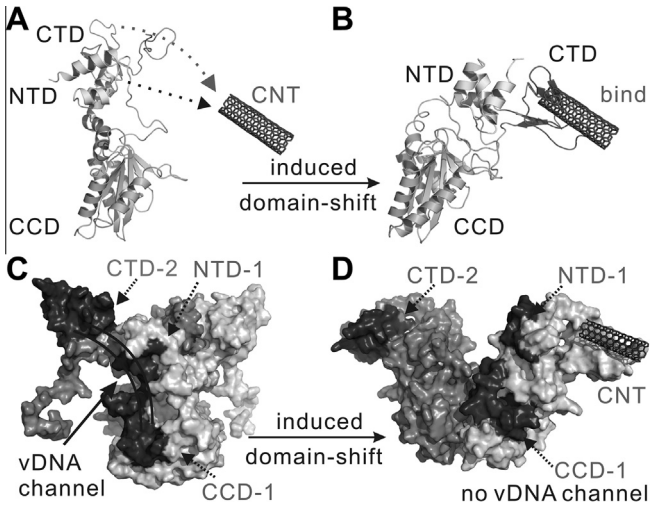

Fig. 2. Domain-shift induced by the CNT-binding. (A) Arrows indicate the move directions of the CTD and NTD. (B) Conformation of HIV-1 IN after the CNT binding. The released linking helix is shown as loop. (C) Arrow indicates viral DNA-binding channel (black surface) of the HIV-1 IN homodimer, consists of CCD-1, NTD-1, and CTD-2, respectively (dash arrow). (D) HIV-1 IN dimer conformation after the CNT binding.

3.3. CNT sealed HIV-1 IN inhibitor

Nanoparticles have been shown to have the capability to deliver drugs to their targets due to their unique properties, especially their cavity for containing small molecules [31]. Meanwhile, our MD simulation above has shown that the CNT could stably bind to the CTD of HIV-1 IN. Based on these, one might use the CNT as a drug delivery system to target HIV-1 IN. To test this hypothesis, further MD simulation was performed to study the capability of the CNT to carry a small-molecular inhibitor. 5ClTEP, a known HIV-1 IN inhibitor that binds to the active site of the CCD, was placed inside the CNT (Fig. 3A) and went through 10-ns simulation.

To examine the behavior of 5ClTEP within the CNT, we calculated its RMSD values with respect to the initial position in the CNT (Fig. 3B). The RMSD results showed that during the period of simulation, 5ClTEP experienced certain fluctuations with respect to its original position. However, 5ClTEP was never observed to move outside of the CNT, even two ends of the CNT were uncapped during the simulation (Fig. 3A). This indicated that 5ClTEP could be stably 'trapped' in the CNT and delivered to a target to which the CNT is able to bind. So the CNT could serve as a drug delivery system of HIV-1 IN. Besides, release of the carried inhibitor from the CNT would become necessary when reaching HIV-1 IN. According to the study by Chaban and Prezhdo [32], such problem might be solved using release-assistant stimuli like carbonic acid (H_2CO_3) to generate substantial pressure to push drug molecules outside of the CNT.

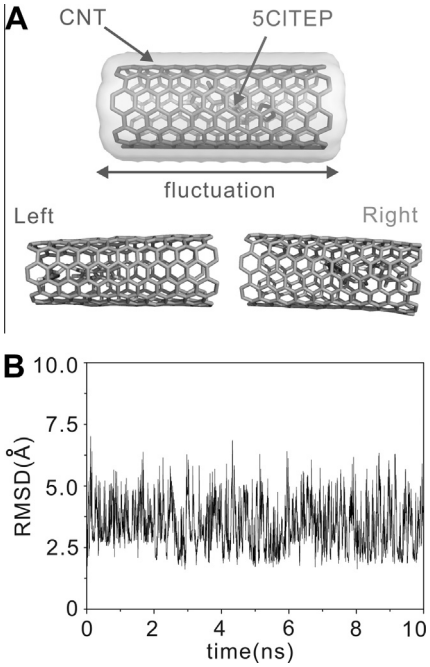

Fig. 3. MD simulation of HIV-1 IN inhibitor 5ClTEP within the CNT. (A) 5ClTEP (grey arrow) is placed into a CNT. Double-headed arrow indicates the fluctuation of 5ClTEP within the CNT. (B) RMSD values of 5ClTEP with respect to its starting position.

3.4. CNT as a dual-functional inhibitor of HIV-1 IN

Simulation results have shown that the CNT could stably bind to the CTD of HIV-1 IN and induce a domain-shift which may influence the viral DNA binding to HIV-1 IN. Meanwhile, it was showed that the CNT could serve as a drug delivery system carrying HIV-1 IN inhibitors. Taken together, our study suggested that the CNT could be a potential dual-functional inhibitor of HIV-1 IN.

When the CNT enters into the infectious cells, it could bind to the CTD of HIV-1 IN monomer. Even after dimerization, HIV-1 IN also exposes the CTD, which may leave a chance for the CNT binding. So there are two identical targets for the CNT before HIV-1 IN enters into the nucleus: monomer and homodimer (Fig. 4A). Based on our results, the CNT could attach to the CTD for a long time period after binding to the HIV-1 IN monomer. Such binding ensures the CNT to release the drug molecule near the HIV-1 IN surface. Consequently, the drug could inhibit the HIV-1 IN active site in a relatively short time. Obviously, such a CNT-based drug delivery system would reduce both the drug dosage and side effects (Fig. 4B).

Furthermore, the CNT would act in an allosteric way when binding to the homodimer. Before the CNT binding, the HIV-1 IN dimer could bind to the viral DNA through a channel consisting of the CCD and NTD from one monomer and the CTD from the other (Fig. 4C). However, if the CNT bound to the HIV-1 IN dimer, it would change the dimer conformation by inducing a domain-shift, which would disrupt the viral DNA binding channel and prevent the viral DNA from binding to the HIV-1 IN dimer (Fig. 4D). Therefore, besides carrying small-molecular inhibitors to the HIV-1 IN surface, the CNT could also serve as an allosteric inhibitor.

Our study strongly implied that the CNT could act as a promising HIV-1 IN inhibitor. Simulation revealed several key residues involved in CNT binding process, especially Arg231, Lys236 and Lys258. So mutations of these three residues might strongly affect the CNT-binding capability of CTD. Since the full-length, native HIV-1 IN may not be obtained easily from crystallization, fragments crystal structure containing CTD could be used to test this prediction. Besides, based on the simulation of 5ClTEP in the CNT sealing, to apply the CNT as a drug delivery tool is of great interest for other HIV-1 IN inhibitors such as L-CA [33], coumarin-like [34], etc.

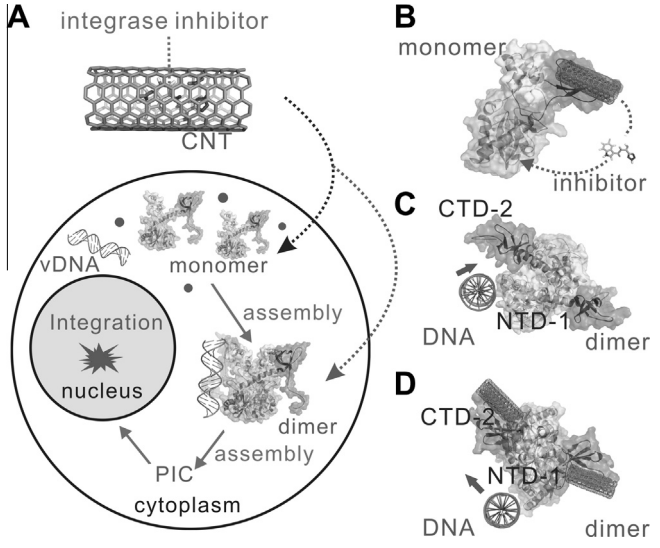

Fig. 4. The CNT serves as a potential dual-functional inhibitor. (A) Two targets of the CNT. Infected cell is shown as a white circle with its nucleus as a grey circle inside. Dash arrows indicate two identical targets of the CNT: HIV-1 IN monomer and homodimer. (B) The CNT serves as a drug delivery system. Arrow indicates that HIV-1 IN inhibitor released from the CNT inhibits the active site of HIV-1 IN. (C) HIV-1 IN dimer before CNT binding. DNA molecule is shown as cartoon. Arrow indicates a channel for DNA binding. (D) HIV-1 IN dimer after CNT binding. DNA molecule and the CNT are shown as cartoon. Arrow indicates the failure of DNA binding to HIV-1 IN dimer.

In summary, we have used MD simulation to verify that the CNT could serve as a potential dual-functional HIV-1 IN inhibitor. Our results showed that the CNT could stably bind to the CTD of HIV-1 IN. The CNT also induced a domain-shift which disrupted the binding channel for the viral DNA and thereby inhibited the HIV-1 IN activity. Further MD simulation showed that the HIV-1 IN inhibitor, 5ClTEP was successfully sealed inside the uncapped CNT. Therefore, we concluded that the CNT could serve as a promising dual-functional HIV-1 IN inhibitor, not only to carry HIV-1 IN inhibitors to the HIV-1 IN surface, but also to act as an allosteric inhibitor by inducing the domain-shift of HIV-1 IN.

Acknowledgments

This study was supported in part by the HI-tech Research and Development Program of China (Grant No. 2008AA02Z311), the Shanghai Leading Academic Discipline (B111), and Shanghai Supercomputer Center (SSC).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2013.06.009.

References

[1] Y. Pommier, A.A. Johnson, C. Marchand, Integrase inhibitors to treat HIV/AIDS, Nat. Rev. Drug. Discov. 4 (2005) 236–248.
[2] B. Grinsztejn, B.Y. Nguyen, C. Katlama, J.M. Gatell, A. Lazzarin, D. Vittecoq, C.J. Gonzalez, J. Chen, C.M. Harvey, R.D. Isaacs, Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial, Lancet 369 (2007) 1261–1269.
[3] J.R. Schames, R.H. Henchman, J.S. Siegel, C.A. Sotriffer, H. Ni, J.A. McCammon, Discovery of a novel binding trench in HIV integrase, J. Med. Chem. 47 (2004) 1879–1881.
[4] M. Sato, T. Motomura, H. Aramaki, T. Matsuda, M. Yamashita, Y. Ito, H. Kawakami, Y. Matsuzaki, W. Watanabe, K. Yamataka, S. Ikeda, E. Kodama, M. Matsuoka, H. Shinkai, Novel HIV-1 integrase inhibitors derived from quinolone antibiotics, J. Med. Chem. 49 (2006) 1506–1508.
[5] K. Shimura, E. Kodama, Y. Sakagami, Y. Matsuzaki, W. Watanabe, K. Yamataka, Y. Watanabe, Y. Ohata, S. Doi, M. Sato, M. Kano, S. Ikeda, M. Matsuoka, Broad antiretroviral activity and resistance profile of the novel human immunodeficiency virus integrase inhibitor elvitegravir (JTK-303/GS-9137), J. Virol. 82 (2008) 764–774.
[6] M. Huang, G.H. Grant, W.G. Richards, Binding modes of diketo-acid inhibitors of HIV-1 integrase: a comparative molecular dynamics simulation study, J. Mol. Graph. Model. 29 (2011) 956–964.
[7] A. Chen, I.T. Weber, R.W. Harrison, J. Leis, Identification of amino acids in HIV-1 and avian sarcoma virus integrase subsites required for specific recognition of the long terminal repeat ends, J. Biol. Chem. 281 (2006) 4173–4182.
[8] D.A. Cooper, R.T. Steigbigel, J.M. Gatell, J.K. Rockstroh, C. Katlama, P. Yeni, A. Lazzarin, B. Clotet, P.N. Kumar, J.E. Eron, M. Schechter, M. Markowitz, M.R. Loutfy, J.L. Lennox, J. Zhao, J. Chen, D.M. Ryan, R.R. Rhodes, J.A. Killar, L.R. Gilde, K.M. Strohmaier, A.R. Meibohm, M.D. Miller, D.J. Hazuda, M.L. Nessly, M.J. DiNubile, R.D. Isaacs, H. Teppler, B.Y. Nguyen, Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection, N. Engl. J. Med. 359 (2008) 355–365.
[9] V. Summa, A. Petrocchi, F. Bonelli, B. Crescenzi, M. Donghi, M. Ferrara, F. Fiore, C. Gardelli, O. Gonzalez Paz, D.J. Hazuda, P. Jones, O. Kinzel, R. Laufer, E. Monteagudo, E. Muraglia, E. Nizi, F. Orvieto, P. Pace, G. Pescatore, R. Scarpelli, K. Stillmock, M.V. Witmer, M. Rowley, Discovery of raltegravir, a potent, selective orally bioavailable HIV-integrase inhibitor for the treatment of HIV-AIDS infection, J. Med. Chem. 51 (2008) 5843–5855.
[10] S.H. Friedman, P.S. Ganapathi, Y. Rubin, G.L. Kenyon, Optimizing the binding of fullerene inhibitors of the HIV-1 protease through predicted increases in hydrophobic desolvation, J. Med. Chem. 41 (1998) 2424–2429.
[11] S. Bosi, T. Da Ros, G. Spalluto, M. Prato, Fullerene derivatives: an attractive tool for biological applications, Eur. J. Med. Chem. 38 (2003) 913–923.

[12] R.F. Schinazi, R. Sijbesma, G. Srdanov, C.L. Hill, F. Wudl, Synthesis and virucidal activity of a water-soluble, configurationally stable, derivatized C60 fullerene, Antimicrob. Agents Chemother. 37 (1993) 1707–1710.
[13] H. Benyamini, A. Shulman-Peleg, H.J. Wolfson, B. Belgorodsky, L. Fadeev, M. Gozin, Interaction of c(60)-fullerene and carboxyfullerene with proteins: docking and binding site alignment, Bioconjug. Chem. 17 (2006) 378–386.
[14] S.K. Gupta, L. Baweja, D. Gurbani, A.K. Pandey, A. Dhawan, Interaction of C60 fullerene with the proteins involved in DNA mismatch repair pathway, J. Biomed. Nanotechnol. 7 (2011) 179–180.
[15] A. Alian, S.L. Griner, V. Chiang, M. Tsiang, G. Jones, G. Birkus, R. Geleziunas, A.D. Leavitt, R.M. Stroud, Catalytically-active complex of HIV-1 integrase with a viral DNA substrate binds anti-integrase drugs, Proc. Natl. Acad. Sci. USA 106 (2009) 8192–8197.
[16] Y. Goldgur, R. Craigie, G.H. Cohen, T. Fujiwara, T. Yoshinaga, T. Fujishita, H. Sugimoto, T. Endo, H. Murai, D.R. Davies, Structure of the HIV-1 integrase catalytic domain complexed with an inhibitor: a platform for antiviral drug design, Proc. Natl. Acad. Sci. USA 96 (1999) 13040–13043.
[17] N. Eswar, B. Webb, M.A. Marti-Renom, M.S. Madhusudhan, D. Eramian, M.Y. Shen, U. Pieper, A. Sali, Comparative protein structure modeling using Modeller, Curr Protoc Bioinformatics 15 (2006) 5.6.1–5.6.30.
[18] A. Sali, T.L. Blundell, Comparative protein modelling by satisfaction of spatial restraints, J. Mol. Biol. 234 (1993) 779–815.
[19] G.N. Ramachandran, V. Sasisekharan, Conformation of polypeptides and proteins, Adv. Protein Chem. 23 (1968) 283–438.
[20] S. Pronk, S. Pall, R. Schulz, P. Larsson, P. Bjelkmar, R. Apostolov, M.R. Shirts, J.C. Smith, P.M. Kasson, D. van der Spoel, B. Hess, E. Lindahl, GROMACS 4.5: a high-throughput and highly parallel open source molecular simulation toolkit, Bioinformatics 29 (2013) 845–854.
[21] V. Hornak, R. Abel, A. Okur, B. Strockbine, A. Roitberg, C. Simmerling, Comparison of multiple Amber force fields and development of improved protein backbone parameters, Proteins 65 (2006) 712–725.
[22] S.E. Feller, D. Yin, R.W. Pastor, A.D. MacKerell Jr., Molecular dynamics simulation of unsaturated lipid bilayers at low hydration: parameterization and comparison with diffraction studies, Biophys. J. 73 (1997) 2269–2279.
[23] A. Alexiadis, S. Kassinos, Molecular simulation of water in carbon nanotubes, Chem. Rev. 108 (2008) 5014–5034.
[24] A. Perez, A. Rubio, A molecular dynamics study of water nucleation using the TIP4P/2005 model, J. Chem. Phys. 135 (2011) 244505.
[25] H. Ye, H. Zhang, Z. Zhang, Y. Zheng, Size and temperature effects on the viscosity of water inside carbon nanotubes, Nanoscale Res. Lett. 6 (2011) 87.
[26] W. Humphrey, A. Dalke, K. Schulten, VMD: visual molecular dynamics, J. Mol. Graph. 14 (33–38) (1996) 27–38.
[27] N.C. Fitzkee, D.A. Torchia, A. Bax, Measuring rapid hydrogen exchange in the homodimeric 36 kDa HIV-1 integrase catalytic core domain, Protein Sci. 20 (2011) 500–512.
[28] H. Xie, E.J. Becraft, R.H. Baughman, A.B. Dalton, G.R. Dieckmann, Ranking the affinity of aromatic residues for carbon nanotubes by using designed surfactant peptides, J. Pept. Sci. 14 (2008) 139–151.
[29] F. Bomboi, A. Bonincontro, C. La Mesa, F. Tardani, Interactions between single-walled carbon nanotubes and lysozyme, J. Colloid Interface Sci. 355 (2011) 342–347.
[30] J.C. Chen, J. Krucinski, L.J. Miercke, J.S. Finer-Moore, A.H. Tang, A.D. Leavitt, R.M. Stroud, Crystal structure of the HIV-1 integrase catalytic core and C-terminal domains: a model for viral DNA binding, Proc. Natl. Acad. Sci. USA 97 (2000) 8233–8238.
[31] S.Y. Madani, N. Naderi, O. Dissanayake, A. Tan, A.M. Seifalian, A new era of cancer treatment: carbon nanotubes as drug delivery tools, Int. J. Nanomed. 6 (2011) 2963–2979.
[32] V.V. Chaban, O.V. Prezhdo, Water boiling inside carbon nanotubes: toward efficient drug release, ACS Nano 5 (2011) 5647–5655.
[33] R.A. Reinke, D.J. Lee, B.R. McDougall, P.J. King, J. Victoria, Y. Mao, X. Lei, M.G. Reinecke, W.E. Robinson Jr., L-chicoric acid inhibits human immunodeficiency virus type 1 integration in vivo and is a noncompetitive but reversible inhibitor of HIV-1 integrase in vitro, Virology 326 (2004) 203–219.
[34] H. Zhao, N. Neamati, H. Hong, A. Mazumder, S. Wang, S. Sunder, G.W. Milne, Y. Pommier, T.R. Burke Jr., Coumarin-based inhibitors of HIV integrase, J. Med. Chem. 40 (1997) 242–249.