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THE DEVELOPMENT OF RITONAVIR

1. This statement summarizes my personal knowledge regarding the manner in which ritonavir, a protease inhibitor used to treat HIV/AIDS, was conceived or first actually reduced to practice in the performance of federal grants.
2. The information in this statement is based on personal knowledge obtained while directing research and development of protease inhibitors for Abbott Laboratories between 1987-1991 and in subsequent involvement in research and development of medicines in related fields.
3. My personal knowledge and professional opinion is that ritonavir was conceived in the performance of grants from the National Cooperative Drug Discovery Group for AIDS (NCDDG-AIDS), administered by the National Institute of Allergy and Infectious Diseases, NIH, in the Department of Health and Human Services.
4. In 1988, Abbott received a grant from the NCDDG-AIDS to research potential medicines to inhibit the spread of HIV by blocking a viral-encoded enzyme, HIV protease. The purpose of NCDDG-AIDS was to bring together the efforts of government, industry and academia to promote pre-clinical research efforts needed to translate basic research findings on HIV into novel antiretroviral

therapies. The NCDDG-AIDS program was a response to the national health crisis that HIV/AIDS represented in the 1980's in the US, and a recognition that R&D support from the pharmaceutical industry would be essential to the rapid development of new and effective antiviral drugs. .

5. Using research funding from the NCDDG-AIDS grant to Abbott, I led a team of researchers that performed new research into potential medicines that would inhibit the spread of HIV by blocking a viral-encoded enzyme, HIV protease. This was an entirely new area of research that, prior to receiving Federal funding, was not supported by Abbott as a full-fledged R&D project. Rather, it was given 'pilot project' status, and received minimal internal funding support. Abbott believed at the time that the market potential for AIDS drugs was too small to justify a major R&D expenditure. The award of the NCDDG-AIDS grant gave the HIV project a much-needed funding boost. In my experience and professional opinion, this research would probably not have been brought to a successful outcome without the involvement of the federal government and its funding.

6. The research I and my project team performed at Abbott led to the design, synthesis and identification of the first structure-based HIV protease inhibitor, A77003 that entered clinical trials around 1992. The A77003 compound is a precursor of ritonavir, sharing the same symmetry-based core that was developed under the NCDDG-AIDS grant. Abbott holds a patent on compounds that contain this core structure and variants of the core structure, and that claim numerous HIV protease inhibiting compounds including A77003 and ritonavir.

7. A77003 was formulated for intravenous administration. At that time, there was no oral formulation option for a protease inhibitor. Abbott was unwilling to fund the clinical development of A77003 on its own because it was concerned that an

intravenous compound would not generate sufficient profits to justify its investment. The National Cancer Institute and National Institute for Allergies and Infectious Diseases saw the potential benefit of this new medicine, however, and agreed to fund and to conduct the necessary pre-clinical and clinical development of the compound. In return, Abbott agreed to manufacture and provide the necessary drug quantities for the studies.

8. In 1991, I left Abbott and moved to the NCI to establish a structure-based drug design research program. The NCDDG-AIDS grant continued to fund Abbott's protease project until it expired in 1993. To the best of my knowledge, further research at Abbott conducted under the NCDDG-AIDS grant led to the development of another protease inhibiting compound with a symmetry-based core, known as ABT-538. I led the team that designed, synthesized and identified A-77003 and which led to the elaboration of ABT-538. ABT-538 is an orally bioavailable analogue of A77003 and, while it was synthesized after my departure from Abbott, I believe that the compound was conceived of in performance of the same NCDDG-AIDS grant.

9. In or around 1995, I received a sample of ABT-538 from my former colleagues at Abbott to perform structural and biochemical studies relating to its drug resistance profile. I had previously collaborated with Abbott on evaluating the structures of several of Abbott's protease inhibitors with the target enzyme, HIV protease. It was my belief that these collaborative studies were performed with Abbott's knowledge and were done under the support of the NCDDG-AIDS. In addition, the studies in my laboratory were funded under a research contract with the NCI which was appropriately acknowledged in joint or sole publications.

10. Ritonavir was approved for widespread treatment of HIV in 1996. Ritonavir was conceived in the performance of grants from NCDDG-AIDS, as I am informed is noted on its patents.

11. Due to the adverse side effect profile of ritonavir, Abbott developed a less noxious analog – Lopinavir. Abbott found that the co-administration of sub-therapeutic amounts of ritonavir with lopinavir resulted in higher sustained concentrations of lopinavir in the bloodstream. Abbott eventually developed and received FDA approval for the co-formulation of ritonavir and lopinavir, commonly referred to as Kaletra™.

12. Lopinavir is a key component of Kaletra, a combination of ritonavir and lopinavir. Kaletra is the latest and most effective version of Abbott's protease inhibiting compounds with a symmetry-based core. Lopinavir, ritonavir, and A77003 share the same symmetry-based core structure developed under the 1988 NCDDG-AIDS grant.

13. In addition to its antiviral activity, ritonavir has the unexpected property of inhibiting its own metabolism, which explains its long half-life in the body's circulation relative to other protease inhibitors. In effect, it "boosts" its own pharmacokinetic profile, making it last longer. Because of its ability to inhibit common drug metabolism processes, ritonavir is commonly co-prescribed in antiviral regimes that contain a protease inhibitor. In low, sub-therapeutic doses, ritonavir effectively "boosts" the pharmacokinetic profile of the active protease inhibitor. To my knowledge, ritonavir is frequently prescribed as an "off label" pharmacokinetic boosting agent in many HAART regimens in which a different protease inhibitor is used as the drug of choice.

14. Ritonavir can be prescribed as the main protease inhibitor in HAART, as a co-formulated boosting agent in Abbott's Kaletra, or as an off-label boosting agent with other FDA-approved protease inhibtors, including saquinavir, indinavir, nelfinavir, amprenavir, atazanavir and fosamprenavir (a recently approved prodrug of amprenavir).