# HIV And Molecular Immunity: Prospects for the AIDS Vaccine

*Omar Bagasra*
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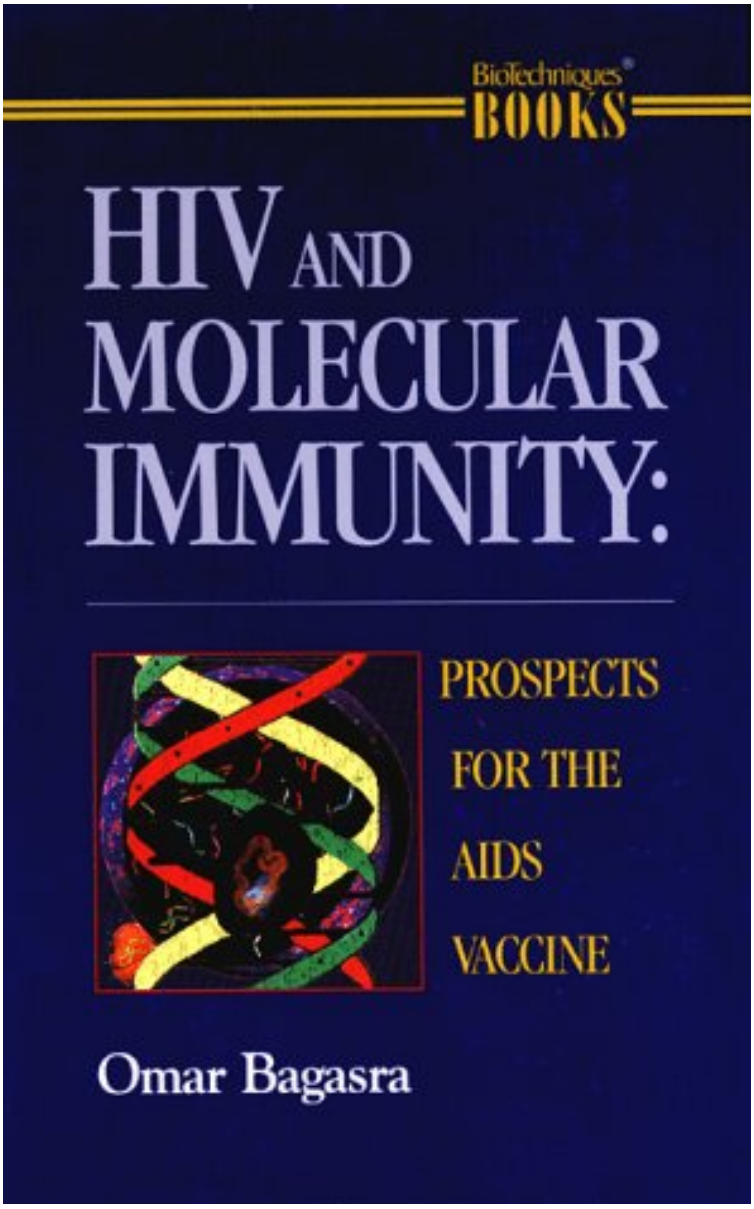




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**Omar Bagasra : HIV And Molecular Immunity: Prospects for the AIDS Vaccine** before purchasing it in order to gage whether or not it would be worth my time, and all praised HIV And Molecular Immunity: Prospects for the AIDS Vaccine:

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Pages 131-132 The HIV X-FileHIV and Molecular Immunity:Prospects for the AIDS Vaccine By Omar Bagasra Natick, MA: EatonPublishing (1999). 198 pp. ....Almost two decades ago, fourpreviously healthy individuals presenting with mysteriousimmunodeficiency were reported (Gottlieb et al., N. Engl. J. Med. 305,1425-1431, 1981). Two years later, international scientists isolated anovel retrovirus as the probable cause of an expanding acquired immunedeficiency syndrome (AIDS) epidemic (Gallo et al., Science 220,865-867, 1983; Barre-Sinoussi et al., Science 220, 868-871,1983). Today, we are still grappling to devise effective vaccinesagainst the human immunodeficiency virus (HIV).HIV rapidly infectsand destroys CD4+ T lymphocytes, likely following delivery fromperipheral tissues or mucosal membranes to the secondary lymphoidorgans by dendritic cells. Vaccine research and development strategieshave therefore tended toward bolstering humoral immunity (Hl) and/orcell-mediated immunity (CMI) to ensure that good defenses are alreadyin line before HIV attempts to breach them (reviewed by Heilman andBaltimore, Nat. Med. 4, 532-534, 1998). In general, Hl approachesfocus on producing antibody responses that can specifically neutralizeviral particles or block their entry into host cells, while CMIapproaches focus on drawing the attention of CD8+ cytotoxic Tlymphocytes (CTL) to virally infected cells. A common obstacle tothese approaches has been the unexpected variability of HIV epitopesboth in the population and arising by mutagenesis.Unfortunately,the roles played by the adaptive immune responses (Hl and CMI) in thecourse of HIV infection remain incompletely, and often inconsistently,defined. We know, for instance, that individuals infected with HIVexhibit both of these responses in widely varying degrees throughoutthe disease course. Not surprisingly, infected individuals exhibitextremes of illness: some succumb rapidly while others advance soslowly (surviving asymptomatically more than 10 years after infection)as to be termed long-term nonprogressors. Even among infants born toHlV-infected mothers, accounts have surfaced for identical twins inwhich one child progresses rapidly to AIDS while the other child doesnot (Goedert, Acta Paediatr. Suppl. 421, 56-59, 1997). Manypossibilities have been explored to explain phenomena such as these,from differences in certain chemokine receptors (Liu et al., Cell 86,367-377, 1996; Martin et al., Science 282, 1907-1911, 1998) to humanleukocyte antigen allotypes expressed among patients (Carrington etal., Science 283, 1748-1752, 1999). At best, they appear to explainsome but not all observed immune responses (or lack thereof) toHIV. The clinical face of AIDS therefore seems nearly as diverse asthe viral quasispecies that define the infection of any givenindividual.In light of such inconsistencies, Omar Bagasra contendsin his book HIV and Molecular Immunity: Prospects for the AIDS Vaccinethat pursuit of vaccines against HIV is currently advancing with onlyone eye open. He argues that "the research efforts onretroviruses over the past 10-15 years have focused on the mechanismsof disease production by these pathogens. Now it is time to exploremechanisms by which infected hosts defend themselves. The mainpostulate of this book is that evolution has created some sort ofintracellular protective mechanism to specifically battleretroviruses" (p. 5).Basagra's text is not merely a critiqueof the trials and tribulations faced by HIV/AIDS researchers in theircollective quest for answers and, ultimately, a vaccine. The book isinstead a highly personal treatise that describes a new theory ofimmunity based upon (as he admits in the preface, p. x) years ofcollecting and dissecting anomalous findings To be blunt, it is thestuff of an established scientist's dreams ... andnightmares.Throughout, Bagasra reiterates the existence of anas-yet-undescribed "third arm" of immunity, which hedistinguishes from both Hl and CMI, capable of controlling HIVinfection at the molecular level. This hypothesized "molecularimmunity" depends upon expression of protective RNAs produced byCD8+ T lymphocytes or natural killer cells that can neutralize viralcDNA prior to nuclear transport and integration. He bases his theoryon evidence drawn largely from studies of nonhuman primates infectedwith various simian immunodeficiency viruses (SlVs); many monkeysinfected with strains of SIV that typically infect a different monkeyspecies (and to which the former monkeys have not been previouslyexposed) tend to respond similarly as humans infected with HIV. Nodisease is demonstrated, however, upon infection with the concordantstrain, or the virus common to a given population of monkeys. Bagasrathus builds his idea around an evolutionarily naive state of thesusceptible host. This is thought to confer susceptibility topathogenic infection only in distant host /retroviruscombinations. Assuming HIV has arisen from recombination events amongvarious SIV strains (the precise origins of which remain unknown,though in chapter 2 the author suggests it occurred during Africanpolio vaccine trials), humans therefore serve as ideally naive hostsin which HIV can fully unleash its pathogenic potential.But whypropose an entirely novel arm of immunity to account for protectionfrom HIV infection?: "The obvious reason for the evolution of adifferent protective mechanism is that retroviruses are geneticparasites that penetrate into the host genome much faster than Hl orCMI can develop protective barriers" (p. 77). Considering this,rapid disease progression might be expected in 100% of clinical casesif antibodies and cytolytic CTL were the only defenses againstinfection, but we know that this does not occur. Bagasra discusses atlength the high content of potential retroviral sequence elementsoccupying the diverse human genome. He then asserts that they mayhave been specifically retained over time, rather than excised, toplay an active role in the immune system (serving as the source ofproposed protective RNAs produced by CTL). Like browsing through a mugshot book at police headquarters, RNAs transcribed from these regionsmight "recognize" (form complexes with) the genetic materialof invading retroviruses such as HIV and cripple their abilities topropagate, depending strongly upon the initial infecting dose. Hasthis been directly proven? No, but the theory is certainly not withoutappeal.Despite sounding vaguely like X-Files Agent Fox Mulder withhis proposal, Bagasra's concept does appear to overlap someobservations regarding the

natural control of HIV infection aside fromconventionally recognized Hl and CMI contributions. For example,ongoing studies have demonstrated that a soluble CD8- T cell antiviralfactor (CAF) can potentially control or even prevent infection by HIV(reviewed by Levy et al., Immunol. Today 17, 217-224, 1996; Stranfordet al., Proc. Natl. Acad. Sci. USA 96,1030-1035,1999). Briefly, theCTL associated CAF-suppressive effect (1 ) is observed independentlyof the p-chemokines RANTES, MIP-1a, and MIP-1 b; (2) is not restrictedby the major histocompatibility complex; and (3) acts at the level oftranscription following viral integration. In conducting similarstudies,Bagasra's results argue that this soluble factor is RNA(due to the fact that in vitro protective activity is lost when RNaseis included in the assays) and that it completely prevents nuclearpenetration by HIV (chapter 4). However, as Brander and Walkerappropriately caution us regarding CTL responses to HIV(Curr. Opin. Immunol. 11, 451-459,1999), "the relativecontributions of cytolytic and noncytolytic effector mechanisms invivo remain elusive."Overall, HIV and Molecular Immunity:Prospects for the AIDS Vaccine is a well-researched (with more than800 references cited) and bold presentation of a novel concept. Whilemost of the support is indirect and nonphysiological in nature, anyonewith an interest in HIV vaccine development will benefit from thedetailed historical accounts and stimulating perspective offered byBagasra in describing his theory of molecular immunity. Althoughflowing in a much less organized manner than the chapters in the tableof contents promised (the text is often as stream-of-consciousness asa chat over coffee in the lunchroom), the book can definitely berecommended to the patient reader. Anyone who completes it will bestrongly persuaded that preventive vaccine strategies should aim tobarricade viral transcription and integration, while therapeuticvaccination should aim to tap the host's innate abilities (if theyexist) to control viral replication.In any case, the truth is outthere ... somewhere. We just need to keep both of our eyes open torecognize it.....

How old is the AIDS virus (HIV-1) and where did it come from? Is it the result of a recombinant event in simian immunodeficiency viruses (SIVs)? Why do SIVs naturally occur in a variety of nonhuman African primates without inducing AIDS in their natural hosts? HIV-1 has devastated human society, although chimpanzees carry an SIV that is genetically almost identical to HIV-1 but causes no known illness in these great apes. How are Chimpanzees immune to HIV-1? Can humans acquire this immunity? Why do most newborns infected with HIV-1 in utero or during birth become long-term non-progressors while 20% rapidly develop AIDS and die in less than a year? Why are some adults asymptomatic for over 10 years after infection? Dr. Omar Bagasra, an eminent molecular biologist, immunologist, and retrovirologist, has considered these puzzling questions for more than a decade and now offers intriguing new possibilities for the nature of human immunity and the development of an effective AIDS vaccine. This book is a provocative personal treatise on the origin, evolution and etiology of HIV-1 supported by a wealth of peer-reviewed scientific references. The compelling ideas presented in this volume will have an important bearing on HIV vaccine development and current lentiviral gene therapy protocols. It is a must read for anyone interested in the development of a safe AIDS vaccine.

(From the Foreword by Dr. Luc Montagnier) "Dr. Omar Bagasra is not only a skillful, innovative laboratory researcher; he is also a discerning scholar who explores novel ideas. (This book) is, I believe, a comprehensive reflection of his provocative theory ...on the mechanisms of natural immunity against retroviruses, as well as on the origin and evolu-tion of the AIDS virus. ...The reader will find in this book, together with many novel concepts, a wealth of scientific information in the field of HIV research."