Henipavirus Vaccine Development

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Abstract

The henipaviruses, Hendra virus and Nipah virus, belong to the family Paramyxoviridae which has long been a source of highly contagious pathogens for both humans and animals. Some notable paramyxoviruses such as measles virus have spilled over from animals into humans to cause significant morbidity and mortality. Since 1994 the henipaviruses have periodically emerged from their animal reservoir in flying foxes to cause disease in human and animal populations. The recent emergence of these viruses coupled with the high mortality rate associated with henipavirus infections and the lack of any licensed prophylactic or therapeutic treatments, makes them agents of particular concern in the area of both human and agricultural biodefense. Advances in our understanding of henipavirus infection and pathogenesis has led to the development of several promising vaccine candidates making it likely that vaccines for henipavirus infections may be available in the near future.

Keywords: Henipavirus; Vaccine; Hendra virus; Nipah virus

Introduction

The history of the interaction of man and animals is one involving a constant exchange of microorganisms; according to one survey an estimated 61% of human infections are caused by zoonotic organisms that have transferred from animals to humans [1]. The vast majority of new pathogens recognised in humans since 2001 are zoonotic [2] including those causing very high impact infections such as acquired immunodeficiency syndrome (AIDS), a result of infection with human immunodeficiency virus type-1 (HIV-1) [3], and severe acute respiratory syndrome (SARS) [4-6]. Plague is perhaps one of the best known and most terrifying of the zoonoses. The causative agent, the bacterium Yersinia pestis, is carried by rodents. The first recorded outbreaks were in the 6th and 7th centuries, and later the most notable one in the 14th century when, by some estimates, half the population of Europe died. The devastation caused by the natural spread of zoonotic agents such as these into human populations provides an insight into the destructive potential of deliberately introduced pathogens, particularly those to which humans have had little or no previous exposure, and for which there are no therapeutic treatments.

The use of biological agents as weapons is a time honoured tradition in the field of human conflict. Perhaps the earliest recorded instance is the catapulting of plague-ridden bodies into cities in the 14th century [7]. In World War I horses and mules were deliberately infected with glanders and anthrax [8], both agents capable of infecting humans as well as horses. More recently, in 2001, anthrax spores were posted in the United States mail and infected 22 people, of whom 11 contracted pulmonary anthrax and 5 died [9].

The virus family Paramyxoviridae, consisting of viruses possessing non-segmented, single stranded negative sense RNA genomes, is also the source of several highly contagious pathogens such as measles virus and mumps virus in humans and canine distemper virus in dogs [10]. Measles virus is most closely related to the etiologic agent of “cattle plague”, rinderpest virus, and is thought to have been acquired from this species at the time of domestication of cattle, possibly around the 11th to 12th century [11]. On contact with naïve populations in the Americas in the 16th century the measles virus is reported to have killed 50% of certain human populations as well as two thirds of the population of Cuba in 1529. Some hundreds of years after measles virus is thought to have crossed into man, the paramyxoviruses as a group have continued to be a source of emerging zoonotic infections: two new additions to the paramyxovirus family, Nipah virus (NiV) and Hendra virus (HeV) emerged to cause infections among humans at the end of the last century. HeV and NiV were assigned to a new genus, the henipaviruses [12-14], based in part on both their broad host range and ability to cause mortalities in both humans and animals and their unique and distinctly large genomes size – 18,234 nucleotides for HeV [12], and 18,246 or 18,252 nucleotides for NiV Malaysia and NiV Bangladesh respectively [15,16] – which are approximately 15% larger than other paramyxovirus genomes.

Epidemiology of henipavirus infections

The source of these new henipavirus infections was not immediately apparent. In the first outbreak in 1994, HeV infected and caused mortalities in horses and humans [17]. In an effort to determine the reservoir species for HeV, a serological survey was carried out in eastern Queensland with sera collected from 46 species including 34 species of wildlife. No antibody was detected in this initial survey, but in a second survey targeting flying foxes and birds, antibodies capable of neutralizing HeV were detected in the 4 mainland species of pteropid bats found in eastern Australia [18] and virus was subsequently isolated from the reproductive tract and urine of wild-caught bats [19]. NiV appeared some 4 years later in an outbreak that primarily affected pigs and humans in peninsular Malaysia and Singapore [20], and was later shown to be closely related to HeV by immunological and molecular analyses [21,22]. Pteropid bats were the suspected reservoir host based on the similarities between HeV and NiV. Again surveillance of animal species identified neutralizing antibody to NiV mainly in flying foxes (Pteropus sp). Virus was isolated from urine of these animals and from partially eaten fruit [23] under trees in which bats foraged.

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For both HeV and NiV a major mechanism of spillover infection is thought to be contamination of food sources by bats; such as pasture underneath fruit trees for horses in Queensland or contaminated date palm sap or fruits consumed by humans in Asia. Since 1994 there have been 31 outbreaks of HeV, unusually 17 of these have occurred in 2011 (Table 1). On each occasion, horses have been infected and, in 5 of these, transmission to humans has occurred. Although the number of known human infections is small, the mortality rate is high with 4 deaths recorded among 7 cases. In all instances the infection of humans has been through horses infected with HeV and no known cases of direct transmission from bats to humans have been reported [24]. In nature, HeV has so far only been isolated from bats, humans and horses, although other mammals replicate virus following exposure under laboratory conditions.

Since 1998 NiV has re-emerged more than a dozen times in Bangladesh and neighbouring parts of India (Table 2) and these outbreaks differed from the initial emergence of NiV in Malaysia. In the Malaysian outbreak the disease appeared to be largely encephalitic with respiratory signs recorded in only a small percentage of patients [25]. While there was no clinical evidence of human-to-human transmission, abnormal cerebral magnetic resonance imaging was seen in a nurse with asymptomatic NiV infection, indicating that human-to-human spread may occur [26]. The mortality rate was approximately 40% [27]. By comparison the later episodes of human NiV infection in Bangladesh and India were characterized by a higher mortality rate and clear evidence of human-to-human spread [28-33]. Respiratory symptoms were more severe and the fatality rate approached 70% [34]. In the Faridpur outbreak in Bangladesh in 2004, 75% of patients developed respiratory difficulty and the associated fatality rate was 73% [35]. In addition, patients with respiratory symptoms were more likely to transmit the virus [36], and the case for the role of respiratory secretions in the human-to-human spread was further strengthened by the identification of NiV RNA in the respiratory secretions of infected patients [16,37]. In the most recent emergence of NiV in Bangladesh in early 2011, the mortality rate has exceeded 75% [38]. NiV infects humans, bats, pigs and dogs [39] in nature, and like HeV, other mammals replicate virus following exposure under laboratory conditions.

**Viral infection**

One of the distinguishing characteristics of the henipaviruses in comparison to all other paramyxoviruses is the ability to induce severe disease across a broad range of vertebrate hosts. Some of the reasons for this became clear with the identification of ephrin-B2 and ephrin-B3 as the host cell receptors for these viruses [40-43]. Ephrins act as a ligand for their receptors, Eph molecules, and both are members a large family of tyrosine kinase receptors. Both the ephrin ligands and their Eph receptor partners are highly conserved and evolutionarily ancient bi-

| Date       | Location         | Horses no. cases | Humans deaths/no. cases | Reference |
|------------|------------------|------------------|-------------------------|-----------|
| 1994 Aug   | Mackay, QLD      | 2                | 1/1 (100%)              | [75]      |
| 1994 Sept  | Hendra, QLD      | 20               | 1/2 (50%)               | [17]      |
| 1999 Jan   | Trinity Beach, QLD | 1               | 0/0                     | [99]      |
| 2004 Oct   | Gordonvale, QLD  | 1                | 0/1                     | [100]     |
| 2004 Dec   | Townsville, QLD | 1                | 0/0                     | [101]     |
| 2006 June  | Peachester, QLD  | 1                | 0/0                     | [100]     |
| 2006 Oct   | Murwillumbah, NSW | 1               | 0/0                     | [102]     |
| 2007 June  | Peachester, QLD  | 1                | 0/0                     | [103]     |
| 2007 July  | Clifton Beach, QLD | 1             | 0/0                     | [104]     |
| 2008 July  | Redlands, QLD    | 5                | 1/2 (50%)               | [105]     |
| 2008 July  | Prosperpine, QLD | 3                | 0/0                     | [106]     |
| 2008 July  | Rockhampton, QLD | 3                | 1/1 (100%)              | [107]     |
| 2009 Sept  | Bowen, QLD       | 3                | 0/0                     | [108]     |
| 2010 May   | Tewantin, QLD    | 1                | 0/0                     | [109]     |
| 2011 June  | Logan Reserve, QLD | 1             | 0/0                     | [110]     |
| 2011, June | Kerry, QLD       | 1                | 0/0                     | [111]     |
| 2011, June | McLeans Ridge, NSW | 2            | 0/0                     | [112]     |
| 2011, July | Mt Aflord, QLD   | 3+ 1 dog         | 0/0                     | [113,114] |
| 2011, July | Utingan, NSW     | 1                | 0/0                     | [115]     |
| 2011, July | Park Ridge, QLD  | 1                | 0/0                     | [116]     |
| 2011, July | Kuranda, QLD     | 1                | 0/0                     | [117]     |
| 2011, July | Hervey Bay, QLD  | 1                | 0/0                     | [118]     |
| 2011, July | Cooroy, NSW      | 1                | 0/0                     | [119]     |
| 2011, July | Boondall, QLD    | 1                | 0/0                     | [118]     |
| 2011, July | Chinchilla, QLD  | 1                | 0/0                     | [120]     |
| 2011, July | Mullumbimby, NSW | 1                | 0/0                     | [121]     |
| 2011, August| Newrybar, NSW    | 1                | 0/0                     | [122]     |
| 2011, August| Pimlico, NSW     | 2                | 0/0                     | [122]     |
| 2011, August| Mullumbimby, NSW | 1                | 0/0                     | [122]     |
| 2011, August| Currimbin Valley, QLD | 1   | 0/0                     | [123]     |

Total 64 47 (57%)

Based on Smith et al. [124].

**Table 1**: Hendra virus outbreaks in Australia, August 1994-August 2011.
number of lower order species such as Ephrins have been found in all mammalian species examined and in a systems through regulation of cell migration and tissue assembly [53].

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**Viral pathogenesis**

The utilisation of ephrin-B2 and ephrin-B3 as the receptor on the host cell leads to fundamental similarities in the disease processes caused by HeV and NiV regardless of the species infected. Principally, tropism for the vascular endothelium is responsible for the widespread vasculitis seen in humans, monkeys, horses, hamsters, cats and ferrets infected with HeV [62-65]; and in humans, pigs, guinea pigs, cats, hamsters, ferrets and monkeys infected with NiV [66-70]. Viral tropism for neurons is reflected in the common finding of central nervous system (CNS) neuronal infection which may or may not result in encephalitis. Autopsy of fatally infected NiV patients, and isolation directional signalling cell surface molecules [44,45]. Sequencing of the ephrin-B2 and ephrin-B3 genes of the human, pig, horse, cat, dog and bats showed over 95% identity at the amino acid level [46]. Binding of ephrins to the Eph receptor facilitates communication between cells by triggering cellular signalling pathways that regulate cell movement, positioning and adhesion (reviewed in [47]). They are expressed on most human tissues [48], but are most highly expressed on neurons, arterial endothelial cells and smooth muscle reflecting their role in development of the nervous and cardiovascular systems and in erythropoiesis [49-52]. Ephrins also play a role in many adult organ systems through regulation of cell migration and tissue assembly [53]. Ephrins have been found in all mammalian species examined and in a number of lower order species such as C. elegans [54]. However, ephrin expression alone is not sufficient to confer susceptibility to henipavirus infection. Mice have so far proved to be refractory to systemic infection despite expressing ephrin B2 [55], suggesting that other factors such as the ability of the host cell to replicate the virus or co-receptors may be important [14].

Similar to other paramyxoviruses, henipavirus infection of the host cell is mediated by two membrane anchored surface glycoproteins- and HeV and NiV possess an attachment (G) and fusion (F) glycoprotein (Figure 1) [18,56]. The G glycoprotein is present as tetramer anchored in the lipid membrane of the virus [57] which appears to be associated with the trimeric F glycoprotein prior to receptor binding [43]. The F glycoprotein is a typical class I viral fusion glycoprotein and its activity is dependent on the cleavage of the inactive F0 glycoprotein into two subunits, F1 and F2 by the proteolytic enzyme Cathepsin L [58]. Following binding of G to its ephrin receptors, conformational changes are speculated to occur within the G glycoprotein oligomer (reviewed in [59]). The receptor engagement of the G glycoprotein in turn triggers a conformational change in the F glycoprotein, the exact details of which remain ill-defined, leading to the exposure of the fusion peptide which inserts into the juxtaposed-host cell membrane to form a physical link between the viral and cellular membranes. This is followed by a dramatic refolding of the F glycoprotein structure and association of its two α-helical heptad repeat domains referred to as the 6-helix bundle formation which is believed to facilitate the merger of the viral and cellular membranes [59-61] (reviewed in [60]). The end result of the fusion process is entry of the nucleocapsid in to the cytoplasm of the cell and the onset of viral replication.

**Table 2:** Nipah virus outbreaks in Bangladesh, India, Malaysia and Singapore, September 1998 to May 2011.

| Date                  | Location                  | Human deaths/no cases | Reference |
|-----------------------|----------------------------|-----------------------|-----------|
| 1998 Sept-1999 April  | Malaysia, Singapore       | 105/265 (40%)         | [20]      |
| 2001 Jan – Feb        | India                     | 67/92 (74%)           | [29]      |
| 2001 April – May      | Bangladesh                | 9/13 (69%)            | [31]      |
| 2003 Jan              | Bangladesh                | 8/12 (67%)            | [31]      |
| 2004 Jan – Feb        | Bangladesh                | 23/31 (74%)           | [125]     |
| 2004 Feb - April      | Bangladesh                | 27/36 (73%)           | [35]      |
| 2005 Jan              | Bangladesh                | 11/12 (92%)           | [126,127] |
| 2007 Feb - May        | India                     | 5/50 (10%)            | [128]     |
| 2007 March - April    | Bangladesh                | 5/8 (63%)             | [129]     |
| 2007 Jan – Feb        | Bangladesh                | 3/7 (43%)             | [129]     |
| 2008 Feb - March      | Bangladesh                | 8/9 (89%)             | [130]     |
| 2010 Jan              | Bangladesh                | 3/3 (100%)            | [131]     |
| 2011 Jan              | Bangladesh                | 4/5 (80%)             | [132]     |
| 2011 Feb              | Bangladesh                | 21 deaths uncertain   | [133]     |
| **Total excluding Malaysia** |                      | **194/278 (70%)**     |           |

Figure 1: Henipavirus structure. A diagrammatic representation of the henipavirus particle indicating the six structural proteins associated with the virion and highlighting the two membrane glycoproteins, F and G that serve as vaccine target antigens.
of virus from nasopharyngeal secretions of human patients infected with NiV [37] suggested that respiratory and lymphoid tissues could be the primary site of virus replication, followed by a viraemic phase [71]. Outcomes of virus infection studies in ferrets are consistent with this. Recently, ferrets were treated with a cross reactive and henipavirus neutralizing human monoclonal antibody (mAb) specific for the HeV G glycoprotein [72,73] to evaluate the therapeutic benefit of passively administered antiviral mAb on an otherwise lethal HeV infection scenario. Passive immunotherapy with mAb m102.4 reduced viral replication sufficiently to prevent lethal disease. However, viral RNA was detected in the nasal washes and oral swabs and at post mortem viral genome was detected in the retropharyngeal lymph nodes that drain the nasal cavity even where genome was not detected in any other tissues. These results suggested that the primary site of HeV replication could well be in the respiratory and lymphoid tissues, in accordance with observations made for NIV [71] and the well characterized paramyxovirus, measles [74].

In the viraemic phase, viral antigen was found in the endothelial cells of small blood vessels and in arteriolar smooth muscle, with viral infection leading to systemic vasculitis including in the CNS (reviewed in [65,70]). Multinucleated syncytial endothelial cells were also seen both in HeV infections [17,75] and in the initial NiV outbreak in Malaysia, and are considered by some authors to be diagnostic of henipavirus infection [71]. The route of viral infection to the brain is thought to be via infection of endothelium, with local extension to neurons following infarction and resulting injury to nervous tissue [14]. In pigs exposed to NiV, anterograde infection of the brain has also been proposed [76] and data derived from experimentally infected ferrets also supports the possibility of this scenario under certain conditions (J. Pallister and D. Middleton, unpublished results).

Persistent infection with virus is thought to be responsible for henipavirus disease recurring sometime after an apparent recovery from a previous infection. In the initial NiV outbreak in Malaysia, 7.5% of those who survived acute encephalitis suffered recurrent neurological disease known as relapsed encephalitis and 3.4% suffered late-onset encephalitis where neurological manifestations were first seen some time after recovery from an acute non encephalitic or asymptomatic infection [25,77]. Both outcomes were reportedly due to recrudescence and rapid replication of virus that persisted following the initial infection [14,77] although NiV was not isolated from the neurological tissues of these patients [77]. A similar disease pattern occurred in a Mackay farmer who initially contracted HeV from infected horses. He recovered from the initial infection but developed encephalitis and died 13 months later. Again no virus was isolated from the brain although PCR, immunohistochemistry and electron microscopy indicated the presence of HeV [75].

In a small number of cases, an acute measles virus infection can also lead to a persistent infection which in turn leads to the development of subacute sclerosing pan-encephalitis (SSPE). SSPE is a progressive neurological disorder of children and young adults [78,79] characterized by severe demyelination and infection of neurons leading to death. The disease appears on average 7-10 years post an acute infection with measles [80], but is now rare in western countries where it has largely been eliminated by vaccination [81]. The hallmark of viruses that persist to cause SSPE is the accumulation of mutations, particularly in the M protein and the cytoplasmic tail of the F protein; both proteins that play an integral role in viral budding [10,82]. In all SSPE measles strains the F glycoprotein loses the carboxy-terminal pentadecapeptide that is highly conserved in morbilliviruses and thought to be involved in budding [82]. In addition, the M protein is severely reduced or lacking in these viruses [83,84] and rapid post-translational degradation of the M protein was shown to lead to defects in virus budding [85]. Together these observations have led to the suggestion that defective viral budding is a mechanism of persistence.

Threat to biosecurity

Henipaviruses have been classified as category C priority pathogens and Biosafety Level-4 (BSL-4) agents by the Centers for Disease Control and Prevention (CDC), and the National Institute of Allergy and Infectious Diseases (NIAID). The NIAID Strategic Plan for Biodefense Research (NIAID Biodefense Research Agenda) encompasses emerging animal pathogens considered as potential bioterrorists - like NIV which is designated as the example pathogen defining category C agents [86]. Some of the reasons for inclusion of henipaviruses are (i) the high mortality rate associated with henipavirus infection (greater than 50%) (ii) the absence of vaccines and post-exposure treatments - one of the reasons that these agents have been designated as Biosafety Level 4 (BSL-4) organisms (iii) there has been no co-evolution of humans and henipaviruses that might reduce the virulence of the infection in humans (iv) carriage of these viruses by wildlife and their relative ease of propagation means that the agent is theoretically accessible from nature (v) their very broad host range amongst mammalian species and (vi) possible confusion with other more common ailments leading to delayed diagnosis.

Vaccine development

The recent emergence of these viruses and the sporadic nature of disease outbreaks have made the development and testing of vaccines and therapeutics for henipavirus infections a low commercial priority. However, the development of such countermeasures is a crucial component of any preparedness plan against an outbreak or emergence whether deliberate or natural. Vaccines have been used very successfully to control other well known and debilitating paramyxovirus infections including measles and mumps infection of humans and rinderpest virus infection of cattle. Vaccination with an attenuated live measles virus vaccine began in 1963 and was highly successful in reducing the infection rate with measles virus. In the United States alone, the first 20 years of vaccination is estimated to have prevented 52 million cases of the disease, 17,400 cases of mental retardation and 5200 deaths [87]. As a result of vaccination the United States has been declared free of endemic measles [88]. Importantly, an historic announcement in May 2011 declared rinderpest as the first animal disease ever to be eradicated by humankind [89]. Vaccination was a central plank of the campaign to eradicate the virus.

Successful resistance to paramyxovirus infection that is conferred by vaccination is commonly mediated by an adaptive immune response to viral surface proteins/glycoproteins [90] particularly for infections associated with a viraemic phase such as those caused by the measles virus and the mumps virus [91,92]. Consequently, vaccine development for the henipaviruses has focused on the viral F and G envelope glycoproteins either expressed in a recombinant virus or as a recombinant subunit immunogen.

Hamsters vaccinated with recombinant vaccinia viruses encoding NIV G or F were protected against a lethal challenge with NIV. However a strong anamnestic response to the challenge virus suggested that vaccination did not prevent virus replication [93]. Similarly, pigs vaccinated with canarypox viruses encoding either NIV G or F were...
protected against a lethal NiV infection and although virus was not reisolated from any tissues low levels of viral RNA were detected in several samples [94].

Several studies have also been carried out with a HeV recombinant soluble G glycoprotein (sG)-based subunit immunogen (HeVsG). In one experimental study, cats survived a lethal NiV challenge with no clinical signs [95] and the data supported the development of sterilizing immunity in this animal model. In a second study carried out in cats, virus was reisolated from one vaccinated animal and viral RNA was detected in the brains of several animals receiving the two highest doses of vaccine [96]. The authors speculated that the detection of genome in the brain in the face of significant levels of neutralizing antibody prior to challenge indicated that ‘a persistent infection might occur despite pre-existing immunity’. In a vaccine antigen dose sparing study, ferrets immunized with HeVsG survived an otherwise lethal HeV challenge. Here, all vaccine antigen doses prevented clinical disease and there was no anamnestic antibody response detected following challenge, nor could any challenge virus be reisolated from any animal [97]. While all three of these studies utilized HeVsG as the vaccine immunogen, variations in adjuvant used, immunogen dose and challenge virus dose make it difficult to directly compare the experimental outcomes. However, the results of two of three studies indicate that it is possible to prevent establishment of a HeV infection by vaccination, and indeed all three studies indicated that vaccination could prevent clinical illness.

Development of an effective vaccine ideally requires an understanding of how the agent in question interacts with the host to cause disease. Anterograde infection of the brain has been proposed in henipavirus infection, as well as infection via the systemic route. In addition to preventing systemic disease, an ideal vaccine would prevent infection of the CNS by either route and thus eliminate the possibility of recrudescence CNS disease – vaccination against mesaeles virus did reduce the incidence of persistent infection manifested as SSPE. Clinical trials of a potential vaccine against a BSL-4 agent could not be carried out in humans; instead there is a requirement by the U.S. FDA that candidate vaccines be tested in at least two different animal models [98]. Relevant animal models that reproduce the nervous and systemic aspects of henipavirus infection and a thorough understanding of henipavirus pathogenesis in these animal models will be essential to this activity. To this end, the development of a model for henipavirus infection in a non-human primate (African green monkey) was an important step, and indeed disease progression mediated by either HeV or NiV in these animals essentially mirrors that seen in humans [64,69]. Other species that may be suitable include golden hamsters, ferrets and cats [70].

The strategy for the deployment of successful therapeutics is relatively straightforward but a successful vaccine may be deployed differently in different circumstances. While the outbreaks caused by henipviruses remain sporadic in nature and involve relatively small numbers of people and animals (except in the NiV outbreak in Malaysia where over one million pigs were culled), mass vaccination is unlikely to be a viable approach. Vaccination of select human populations at risk (where over one million pigs were culled), mass vaccination is unlikely to be feasible because of the large number of people and animals involved. In the initial NiV outbreaks in Malaysia and Singapore. Should the nature of henipavirus outbreaks change or bioterrorism involving these agents become a reality then mass vaccination may become a viable option.

Conclusions

Experience with paramyxoviruses indicates that the opportunity for significant reduction in transmission risk by vaccination is great. There is potential for recrudescence of the virus but the potential for sterilizing immunity seen with some HeVsG candidate vaccines may circumvent this risk – as mesaeles vaccine reduced the incidence of the persistent infection manifested as SSPE. The challenges in developing a vaccine against a BSL-4 agent are significant but not insurmountable. The requirement to carry out challenge experiments at BSL-4 imposes constraints on the speed with which the preliminary vaccine work can be conducted, and the process is further complicated by the rigorous testing required prior to release of a vaccine for human use. However, vaccine development is progressing and, in conclusion, it would seem that vaccines for henipavirus infections are likely to be available in the foreseeable future.

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