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HIV Cure: Global Overview of bNAb’s Patents and Related Scientific Publications

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Abstract

Introduction: This article provides a global overview of patent deposits for broadly neutralizing antibodies (bNAbs), which have emerged as a key strategy for HIV Cure and future HIV vaccines. Scientific and technological barriers to the discovery of an effective HIV vaccine in the last 40 years have raised concerns on the potential for relevant advances in this area. Nevertheless, recent breakthrough studies have identified novel immune pathways for new innovative HIV vaccine and HIV Cure strategies.

Areas covered: In our patent study, we have identified in a global scale, in the last decade, a sharp increase in the number of bNAb’s patent deposits related to HIV prevention and treatment strategies, reaching 90 bNAb's in 2017, protected by 184 different patent deposits. Refining our patent search to the different stages of bNAb’s development has also allowed us to identify 12 of them already at clinical stage of research (VRC01, 10E8, 3BNC117, 10-1074, 2G12, 2F5, KD-247, 4E10, PG9, PGDM1400, PGT121 and VRC07). We describe these recent breakthroughs and discuss the prospects and limitations of these novel strategies.

Expert opinion: Our results indicate the intellectual property outcomes of a scientific revolution in this field, expressing innovative modifications in antibodies to increase their potency and half-life, which have resulted in extremely potent antibodies that could provide novel preventive and therapeutic HIV strategies.

Keywords: bNAb's, HIV cure, HIV vaccine, intellectual property, patents
Article Highlights

- This review analyzes the temporal evolution of patent deposits that focus on bNABs for HIV prevention and/or cure.
- The analysis reveals new prospects to the development of processes and products such as new therapeutic methods to induce immune response, new bNABs, new polypeptides, new analytical method for HIV, new vaccines and new compositions.
- The United States are the top center for the R&D of bNAB-related technologies, more than 90% of patent priority.
- From the 90 bNAbs identified, only 12 are in clinical trials to treat HIV.
- The patent documents examined for bNAbs in clinical trials indicate promising and exciting scientific and technological advances.
1. Introduction

Despite significant global efforts, since the onset of the AIDS pandemics in the mid-1980’s, to develop HIV vaccines and other HIV Cure strategies, such as immunotherapy, some constraining factors have contributed to skepticism on the prospects for relevant advances in this area: genetic variation of the virus, with high viral replication and mutation rates; difficulties in determining the correlates of immune protection; pathogenesis, with integration of the virus to the genome, making it difficult to prevent or eliminate the infection; animal models, with differences in the Main Histocompatibility Complex (MHC) between human and non-human primates, limiting the predictive value of studies in monkeys, until their validation in clinical trials.

Moreover, the high genetic diversity of HIV-1 envelope glycoprotein remains a big challenge for the development of an effective vaccine [1,2]. These barriers might explain why historically the diverse innovative approaches for HIV vaccine and immunotherapy have not worked for HIV-1.

Nevertheless, for the first time since the onset of the pandemics, there is now renewed optimism and hope for a clinically effective HIV vaccine, with the development of new immunogens based upon broadly neutralizing antibodies (bNAbs) and their target sites.

In more than a decade, since a previous vaccine trial in Thailand showed a modest 31% efficacy, there is now expectation for an HIV vaccine efficacy superior to 50%, in two ongoing multicentric trials with HIV vaccines, described here, based on bNAbs and target sites and incorporating new methodological strategies, such as mosaic
technology. This strategy combines immune-stimulating proteins from different global strains of the virus, with a bioinformatically derived set of gene sequences encoding whole HIV proteins designed to match those made by the majority of circulating HIV strains worldwide. [3,4,5] In this strategy, the viral vectors are combined with other components, such as soluble proteins, to form mosaic-based prime-boost vaccine regimens, aiming to produce stronger and longer-lasting immunity to HIV.

Patents have proved to be a valuable source of information on these breakthroughs and are also a crucial indicator of scientific and technological progress in this area. The focus of our patent study was therefore to describe and analyze the promising applications of bNAbs reaching clinical trial up to January 2018 and related scientific literature and to provide background information on this evolution since the pioneer antibody researches from 1987 up to 2004, when the term “bNAbs” emerged for the first time in patent documents.

2. Overview

The identification of the first generation of bNAbs, 2G12, b12, 2F5 and 4E10, provided significant breakthroughs in understanding mechanisms involved in the relations between HIV and bNAbs. However, these advances were constrained by technological limitations, with the first HIV bNAbs, b12 and 2F5, isolated using phage display and human hybridoma electrofusion. Recently, new high-throughput neutralization assays emerged as a major factor in changing this scenario, contributing to the analysis of mAb and serum activity against large panels of viruses [2,6]. Large numbers of HIV-infected donors were included in the International AIDS Vaccine Initiative (IAVI) Protocol G and C studies, allowing scientists to identify those which were exceptionally potent and with neutralization broad sera, to identify specificities in these responses and then to
isolate bNAbs from these individuals. A more rigorous serum analysis was favored by the standardization of the TZM-bl neutralization assay and the definition of neutralization sensitivity tiers. [6]

Moreover, these crucial advances in identification and selection of donors with the most potent and broad anti-HIV serum neutralization were favored by new methods for the rapid generation of human antibodies from these donors [6,7,8] such as single B-cell culture combined with high throughut neutralization screening and flow cytometry based sorting of single B cells using HIV envelope protein bait, allowing new promising targets for HIV vaccines [6,9,10,11,12].

In 2009, with the description of bNAbs PG9 and PG16, a scientific revolution emerged, with a new generation of bNAbs supported by the development of new analytical tools, such as structural tools, crystallography and cryo-electron microscopy, which have been crucial for the advance in the field. The ability to identify new bNAbs has drastically improved in the last decade and the knowledge of the molecular details of specific interactions in broad and potent neutralization of HIV has significantly increased [2,6]. New knowledge and new tools allowed the design of better strategies to deal with the complexity in which existing bNAbs families target their shared epitopes in different ways.

3. Method
The study was conducted in four steps. First, a search in scientific literature, including articles, congress and seminar abstract. Second, a search in an electronic resource, Broadly Neutralizing Antibodies Electronic Resource of Sanford Burnham Medical Research Institute (website: www. bnaber.org, date of search January 23 2018),
identified a list of 90 bNAbs. Third, a search on patents deposits related to this list, conducted in two data bases: Derwent Innovation Index and Thomson Reuters Integrity, both available in the CAPES’ site*. The patent search related the name of each bNAbs with the words “HIV”, “AIDS”, “Human immunodeficiency virus infection” or “Acquired Immune Deficiency Syndrome”. All the period of both databases was considered: in Derwent Innovation Index from 1963 to January 2018 and in Thomson Reuters Integrity from 1988 to January 2018. Fourth, after the identification of the patent documents related to each of the 90 bNAbs, a new search in three data bases has been made to identify the stages of development: 1. Thomson Reuters Integrity, which indicates the stages for a developing a pharmaceutical process or product – study of biological activity, pre-clinical phase, phase I, phase II, phase III or phase IV; 2. Clinical Trials website (https://clinicaltrials.gov/ct2/home) which details information on the studies, such as date and number of volunteers; 3. International Clinical Trials Registry Platform, a World Health Organization (WHO) website (http://apps.who.int/trialsearch/Default.aspx). We were able to identify 31 bNAbs in at least one of these three databases, according to their different stages of research: 12 bNAbs were in biological tests, 7 in pre-clinical stage and 12 in clinical stage (Table 1). Based on literature review and patent documents, this article shows highlights about the futures development in bNAbs.

4. Classes of bNAbs

The four first generation bNAbs were identified in the last three decades: 2G12[13], b12[14], 2F5[15] and 4E10[16]. From 2009, a new generation of extremely potent

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* Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) is a periodicals portal provided by the Brazilian government to public universities and research centers of excellence in the country
antibodies, with broad reactivity and potential for high neutralization emerged from breakthrough studies on the humoral responses of HIV-positive individuals [2,6]. Recent results of a comparative study [17] have indicated the superior efficacy of bNabs when compared to non-neutralizing antibodies in preventing mucosal acquisition [6]. Recent advances in next-generation sequencing of antibody-gene transcripts are providing genetic records of the development of neutralizing antibodies, providing an understanding of the naïve B cell repertoire, of somatic hypermutation, and of the resulting antibody features that are critical to effective HIV-1 neutralization. An ontogeny and structure-based system of antibody classification has been proposed [6,18]. The trimeric HIV envelope spike (gp 120 and gp 41) has binding sites for bNabs (Figure 1).

According to the binding site at the trimeric envelope spike, five major classes of bNabs have been identified to date: those targeting the trimer apex, high-mannose patch, CD4-binding site, gp120-gp41 interface, and MPER. We present below some bNabs in these classes:

4.1. Trimer apex-binding Abs – PG9 and PG16

The first class of bNabs targeting a shared site, but with subtle differences in the exact epitope bound, is the trimer apex-binding Abs. Pioneer examples are PG9 and PG16, which bind to a novel trimer-prefering, glycan-dependent bNAb epitope. [2,6,10]

4.2. High-mannose patch: 2G12, PGT121, PGT128 and PGT135

The second class of bNabs is made up of those binding the high-mannose patch on the gp120 subunit of the Env trimer. This class has been identified by screening single B-cell cultures, which have led to the isolation of the PGT121 PGT128, and PGT135 families from three individual donors. [6,11]

4.3. CD4-binding site: b12, 3BNC117, VRC01, N6
The third class of bNAbs target the CD4-binding site and have been predominantly isolated by a binding-based selection using proteins designed to isolate bNAbs from donors where this specificity is apparent in the serum neutralization profile (those related to the CD4 binding site, b12, 3BNC117[9] and the VRC01[12]. This approach surpasses the need to screen thousands of individual B-cell culture supernatants and allows a more streamlined process for isolating bNAbs. The first CD4-binding site bNAb isolated, apart from b12, was VRC01, which partially mimics the binding of CD4 to its receptor site. Other highly potent bNAbs have recently been identified, such as N6, an exceptionally broad and potent neutralizing antibody to HIV capable of neutralizing up to 98% of global isolates [19], considered so far the best bNAb in this class targeting the CD4 binding site, but its patents are recent and still protected by confidentiality. For this reason patent holders for this bNAbs could not be identified.

4.4. gp120-gp41 interface

The fourth class of bNAb is a highly divergent set, derived from multiple donors by a variety of methods, but all members of the class target the gp120-gp41 interface. Here we have the trimer specific gp120–gp41 interface bnAbs like PGT151 [11] and 35O22 [20] and the gp41 membrane-proximal external region (MPER), such as 10E8 bNAb[21].

4.5. MPER: 10E8, 2F5 and 4E

The fifth class of bNAbs are those which target the MPER: 10E8, selected by single B-cell culture and screening for neutralization[21]; 2F5[15] and 4E10, isolated by a hybridoma approach[16].

5. Patent Documents
Despite the relevance of patent documents as an important complementary source of scientific information and a crucial indicator of scientific and technological progress, we have identified a major gap in the related scientific literature on intellectual property in this area: publications on patents related to HIV cure, HIV vaccines and bNAbs are scarce or virtually non-existent. In contrast, our findings in patent documents indicate a rapidly changing scenario in this research field, with recent scientific breakthroughs, highlighting the need for new patent studies on the topic.

In our study, a sharp increase in bNAbs’ patent deposits related to HIV/AIDS has been identified worldwide in the last decade, reaching 90 bNAbs from 1987 to 2017 (Figure 2) which are protected by a total of 184 patent deposits.

It should also be noted that patent deposit information for 2014, 2015 and 2016 in Figure 2 and in Figure 3 is not complete due to indexation in the patent database and to the period of confidentiality in patent documents (up to 18 months). As described in the methodology, the search strategy in the patent bases was based on the names of the 90 “bNAbs” quoted on the Broadly Neutralizing Antibodies Electronic Resource website combined with the terms associated with HIV. We identified 184 patent deposits for only 72 antibodies.

The term “bNAB” has appeared in patent documents only from 2004, with a growing trend of deposits afterwards (65 documents). The analysis of these documents allowed to identify that the 72 antibodies currently treated as “broadly neutralizing” have been subject of patenting since 1987, however identified with the terms “antibodies” (Ab) (35 documents), “monoclonal antibodies” (mAb) (39 documents), “neutralizing monoclonal antibodies” (NmAb) (45 documents). The temporal evolution of these deposits, according to this antibody terminology, is presented in Figure 3.
It should be noted that the years 2014, 2015 and 2016 are not complete due to indexing in the database and period of secrecy of the documents.

To claim the rights of a patent it is necessary that the invention meets the 3 basic requirements: novelty, inventive step and industrial application. Therefore, the claim for a new bNAB can only be performed once. The remaining documents of each new bNAB refer to new treatment methods to induce an immune response whose mechanism of action is mainly vaccines; novel compositions containing bNAbs to treat or prevent HIV; new polypeptides; new diagnostic methods for detecting HIV; new protein envelopes among others. It should also be noted that almost 60% of all the deposits are focused on the production of vaccines for the cure or treatment of HIV.

Based on only the 65 documents (Figure 3) in which the antibodies are explicitly referred to as bNABs, and considering the first country of deposit, a very high concentration of patents referring specifically to bNAbs has been identified in a few countries, with the US accounting for 59 patent deposits and ranking in the first position in bNAbs’ patent deposits (~91%), followed by China with 4 deposits. European Patent Office and United Kingdom have one document each as countries of priority, meaning the country of origin of the technology.

In our search, we identified recent patent deposits, from 2008, that have emerged as important breakthroughs and contributed to the development of new conceptual and methodological approaches, such as:

- New therapeutic method to induce immune response (2008-2009): US8105600 (Producing an immune response comprises administering to a mammal a purified antibody-antigen complex useful as prophylactic and therapeutic vaccines for infectious diseases of AIDS or HIV, where the antigen is an HIV envelope protein) [22]; US2008102073 (Producing immune response by
administering to a mammal a purified antibody-antigen complex dissociated from polyclonal anti-HIV sera bound to glycoprotein spikes on HIV envelopes, or mixture of broadly neutralizing antibodies and HIV) [23] and WO2009137632 (New immunogen for vaccinating against and treating HIV infection comprises HIV gap protein 41 polypeptide translationally linked to antibody fraction crystallizable receptor ligand – priority number US20080126662) [24].

- New bNAB (2012): EP2408476 (New isolated human monoclonal antibody that neutralizes HIV-1 virus in vitro, useful for treatment of HIV infection, is obtained by screening memory B cell cultures from a donor sample for broad neutralization activity against HIV-1 species) [25]

- New polypeptide (2011-2014): US2011124842 (New polypeptide having a helical structure, useful for identifying or designing compounds used in diagnostic, pharmaceutical, immunogenic, immunological or vaccine compositions for detection, treatment and/or prevention of HIV infections) [26] and WO2014089152 (New polypeptide selected from specific amino acid sequences is used for preventing or treating an HIV-1 infection in a subject) [27]

- New analytical method for HIV (2010): WO2010040136 (Analyzing intra-patient HIV virus variation to identify amino acid residues of HIV envelope glycoproteins that affect sensitivity or resistance to neutralizing antibodies, involves testing pseudovirions obtained from patient sample – priority number US20080195112) [28]

- New vaccine (2010): WO2010042919 (Vaccine used for eliciting desired antibody against HIV antigen and cancer antigen comprises primary immunogen have intermediate degree of somatic mutational diversity, and secondary
immunogen contains epitope of desired target antibody – priority number US20080104706) [29]

- New composition (2001-2013): US9890207 (Composition used for preventing or treating an HIV infection or an HIV-related disease, comprises anti-CD4 binding site potent VRC01-like antibody composition) [30] and WO2011036560 (Composition, useful to treat viral infections e.g. HIV and infections caused by e.g. Hepatitis-B, Human Papilloma Virus and Bovine Viral diarrhea Virus, comprises a glycoconjugate containing sugar moieties bound to a multivalent support – priority number US20090277326) [31].

6. Clinical Trials: bNAbs for HIV/Aids Treatment

From the 90 bNAbs identified, only 12 are in clinical trials to evaluate the safety, tolerability, pharmacokinetics and/or antiviral activity, according to Clinical Trials and International Clinical Trials or International Clinical Trials Registry Platform (Table 2). Table 3 provides more detailed information on these 12 multipatented bNAbs in Clinical Trials, according to the number of patent documents, clinical trials and sponsors. It should be noted that information has been provided up to January 2018 and for this reason some new bNAbs might have been submitted recently to clinical trials or current bNAbs could have entered a new phase in these trials.

A good example of promising vaccine candidate – VCR01

In phase II VCR01 Clinical trials had already 32 distinct patent documents in 18 ongoing clinical trials. VRC01 focuses its binding onto a conformationally invariant domain that is the site of initial CD4 attachment, which allows the antibody to overcome the glycan and conformational masking that diminishes the neutralization
potency of most CD4-binding-site antibodies. The epitopes recognized by these antibodies suggest potential immunogens that can inform vaccine design. [12]

Although our patent search refers only to VRC01 Phase II trials, National Institutes of Health (NIH) is now conducting, after a long preparation, a new efficacy Phase III trial with a vaccine candidate using VRC01. It has proved to be an extremely potent monoclonal antibody, with great breadth and potential for neutralization, that targets the highly conserved CD4 binding site.

This multi-country AMP trial (Antibody Mediated Prevention Study), conducted jointly by NIAID’s HVTN and HPTN (HVTN 704/HPTN 085) is the first study to evaluate the efficacy of a bNAb (VRC01) in reducing acquisition of HIV infection among at risk populations. HPTN 085 is a Phase 2b clinical trial to evaluate the safety and efficacy of VRC01, testing whether regular infusion of VRC01 in participants can provide protection against HIV. The clinical trial is a randomized, double-blind, placebo-controlled, multi-center, global effort conducted in the U.S., Brazil, and Peru and will enroll 2700 men or transgender persons (TG) who have sex with men or TG persons. Study participants will be randomized to receive VRC01 or placebo by intravenous (IV) infusion every eight weeks. Infusions will continue for 72 weeks for HIV-uninfected participants in all groups, with follow up for 20 additional weeks. A parallel study, HVTN 703/HPTN 081, will be initiated later in sub-Saharan Africa and will enroll 1500 sexually active women.

This trial is testing a passive administration strategy: rather than relying on the immune system to provide antibodies, the antibody itself is directly injected into the susceptible individual. The expectation is that a low dose will provide a sufficient concentration of antibody in vivo to protect against infections. This result would open the door for
creating a marketable subcutaneous or intramuscular injection that would protect against HIV infection.

The main reason for its selection far ahead of other candidates is VCR01’s power against many HIV strains, which results from its ability to target one of a few conserved areas on the viral surface [32]. This discovery has inspired efforts to devise a vaccine that could train the immune system to make antibodies with a similarly broad neutralizing ability [33]. It also raised the possibility that direct infusions of bNAbs might benefit HIV-infected people unable to produce these antibodies themselves.

Researchers at the NIAID’s Vaccine Research Center had previously evaluated VRC01 in 23 HIV-infected people, including 15 who were taking ART and eight who were not. Those treated with ART received two VRC01 infusions 28 days apart. Those with untreated HIV received a single infusion. The average participant was 35 years old, most were college educated, and about 80 percent were male. This antibody treatment proved safe in all participants [34]. It did significantly reduce levels of free-floating virus in the bloodstreams of six of the eight ART-untreated individuals, although the treatment didn’t appear to lower the latent HIV reservoir of cell-associated DNA. The reductions, from 12-to-59 fold, persisted for an extended period of time. A remarkable finding was that in two of these six, the antibody reduced free-floating HIV to undetectable levels for about three weeks, as the VRC01 remained at therapeutic concentrations. The two ART-untreated individuals who didn’t respond to the antibody, they were found to carry viral strains that were more resistant or less sensitive to VRC01. Also, the antibody didn’t have any apparent added benefit for 15 participants who were already taking effective ART.

The findings are very promising, but many challenges persist and they indicate that it will take more than VRC01 alone to treat chronic HIV infection [33]. It’s possible that
the antibody could have a more potent effect in people who are newly infected with the virus.

Another early phase trial to test this notion is set to begin soon in sub-Saharan Africa. There is also evidence indicating that VRC01 infusions delivered prior to HIV exposure might prevent infection. Clinical studies of VRC01 infusion in healthy adults at high risk of infection are expected to begin this year in the U.S. and sub-Saharan Africa, and an early phase safety study in exposed infants is currently recruiting patients in locations around the world.

7. Future developments: N6 and trispecific engineered bNAb

N6, an HIV-specific bNAb still protected by patent confidentiality, is one of the most recent antibodies isolated by researchers at the US National Institute of Allergy and Infectious Diseases (NIAID) [19] and is considered the best in the CD4 binding site class, in terms of neutralization breadth. It potently neutralized 98% of HIV-1 isolates, including 16 of 20 that were resistant to other members of its class. N6 is five to ten times more potent than VRC01 and therefore it has emerged as an attractive candidate for passive administration, since less antibody would need to persist for the protective effect to be sustained. [3]

N6 evolved a mode of recognition such that its binding was not impacted by the loss of individual contacts across the immunoglobulin heavy chain. It evolved from an early intermediate within a VRC01-class antibody lineage. Structural analysis revealed that its orientation permitted it to avoid steric clashes with glycans, which is a common mechanism of resistance. [19]

Researchers found that these uncommon and unique features circumvent mechanisms of resistance to the VRC01 class, indicating that N6 can achieve potent, near-pan
neutralization of HIV-1, making it an attractive candidate for use in therapy and prophylaxis. [19]

The method of isolation used is micro-culture of peripheral blood B cells. N6 rotates the CDRL3 (Light Chain Complementary-Determining Region 3), enabling it to bind to some of the highly resistant HIV isolates that have changes at the V5 loop and therefore to maintain its potency against some of these isolates. Another feature is that N6 is better able to tolerate point mutations, since its binding is more spread across the various regions of the antibody. These two features together drastically improve the breadth of N6 and its ability to neutralize resistant isolates. [3]

These findings are recent and therefore still protected by patent confidentiality. For this reason, although scientific evidence indicates that this is a very promising bNAb, the only patent of this N6 bNAbs had a priority request in 2015 from the US Department of Health and Human Services.

In addition, a research funded by NIAID/NIH in collaboration with Sanofi and IAVI has recently developed another breakthrough strategy which proved successful in monkeys combining in a single engineered molecule parts of the bNAbs VCR01, PGDM1400 and 10E8v4, binding to three independent targets. Infusions of this trispecific engineered antibody have completely protected eight monkeys from infection with two strains of SHIV [35] and a phase I clinical trial is expected to test antibody’s safety and effects in healthy people.

8. Conclusions

The results of our patent study on bNAbs and analysis of related literature indicate important breakthroughs in this successful area of research, renewing optimism on the possibility to develop new HIV vaccine candidates and new HIV cure strategies. The
field is advancing rapidly due to new analytical tools and to the emergence of novel scientific and technological approaches. These advances highlight the need to explore bNAbs patents as a valuable complementary source of strategic information on innovation in this area. A better understanding of patent documents can contribute to technological prospects for bNAbs development, to the modelling of future scenarios for HIV vaccines, drugs and diagnostic tools and finally to support strengthening local scientific and technological capacity of scientists and manufacturers in emerging countries, increasing their participation in the development of HIV Cure strategies.

The crucial scientific and technological information identified in our review also stresses the need for incorporating intellectual property and patent information into international scientific and technological networks, stimulating support from international organizations, governments and enterprises to this promising area of research. They also evidence the need to minimize the high concentration of patent holders, notably the US, increasing the participation of emerging developing countries in this new field of research and development. Access to multipatented HIV vaccines in developing countries is also a major issue to be discussed [36].

These results also evidence the need to recognize limitations in this area of research. Additional and more in-depth evaluations will be necessary to further investigate knowledge gaps in HIV prevention and treatment, such as escape mechanisms related to viral mutation, correlates of protection and the inability to measure germinal center (GC) and T follicular cell (Tfh) responses in humans and non-human primates in vaccine studies and clinical trials. [37]

Nevertheless, despite these constraints, bNAbs have proved to be an exciting and promising field of research. Our patent review indicates its enormous potential for new developments of innovative vaccine and immunotherapeutic strategies.
9. Expert Opinion

Although the patent documents examined here for bNAbs in clinical trials indicate promising and exciting scientific and technological advances, it not possible at this point to tell whether they will be translated into effective vaccine or HIV cure candidates. The target with the two ongoing clinical trials with VCR01 (phase IIb and III) is to overcome existing scientific and technological barriers and to develop a clinically effective vaccine with more than 50% efficacy, improved safety and good tolerability profile, with reduced adverse effects and would be a breakthrough when compared with the previous efficacy of 31% of the HIV vaccine in the Thailand trial. Although a goal to develop a new HIV vaccine with more than 70% efficacy would be more acceptable, a pioneer modeling study has indicated that even a modestly efficacious vaccine, with 50% efficacy, provided to 30% of the population would reduce new annual infections by 34% (seventeen million infections avoided) over fifteen years and result in substantial financial savings. [38] Another modeling study conducted in Brazil confirmed these conclusions, indicating a significant impact of 50% efficacy vaccine, particularly with targeted vaccination strategies focused in more vulnerable at risk-groups. [39]

In addition, other constraints, such as bringing the new preventive and therapeutic products into the health market, have proved to be great challenges. Despite these constraints, some patent documents selected in our study have indicated important breakthroughs from 2008 and allow us to anticipate promising prospects to the development of new processes and products for HIV prevention and cure in a near future:

• New bNAB obtained by screening memory B cell cultures from a donor sample for broad neutralization activity against HIV-1 species (2012): EP2408476 [25]


• New vaccine for eliciting desired antibody against HIV antigen and cancer antigen (2010): WO2010042919 [29]


Moreover, it finally should be stressed that our patent study has not just contributed to the identification and description of these scientific breakthroughs, but has provided, from its translational medicine perspective, a focus on patent documents for bNAbs with a potential for translation into new vaccines and immunotherapy, with information up to January 2018 for 12 bNAbs in Clinical Trials: VCR-01, 10E8, 3BNC117, 10-1074, 2G12, 2F5, 4E10, KD-247, PG9, PGDM1400, PGT12, VRC07 (Table 3).

VCR-01 has raised expectations and recently entered phase IIb and III trials, but many issues remain still to be clarified, with indications that that the antibody could have a more potent effect in people who are newly infected with the virus and that it will take probably more than VRC01 alone to treat chronic HIV infection. [33]

Another strategy has also raised optimism: a trispecific engineered antibody, combining in a single engineered molecule parts of the bNAbs VCR01, PGDM1400 and 10E8v4, binding to three independent targets, which has completely protected eight monkeys from infection with two strains of SHIV [35] A phase I clinical trial is now conceived.
In addition, some studies have provided evidence that another bNAb, N6, can achieve very potent, near-pan neutralization of HIV-1 [19], making it an attractive vaccine candidate. However, it is still protected by patent confidentiality and its only patent document had a priority request in 2015 from the US Department of Health and Human Services.

It should also be noted that other innovative HIV Cure strategies, such as “kick and kill” and “gene editing” have emerged as important breakthroughs and are complementary, increasingly incorporating the outcomes of bNAbs research.

Finally, it is important to stress that the association in our study of information from patent documents with data from related scientific literature was of great support to our patent analysis, allowing us to fill the information gaps with complementary scientific information when patent documents were protected by confidentiality. In this area of research, with rapid emergence of new breakthroughs and innovations, this proved to be a successful methodological strategy.

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Papers of special note have been highlighted as: * of interest ** of considerable interest


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prophylactic and therapeutic vaccines for infectious diseases of AIDS or HIV, where the antigen is an HIV envelope protein. US8105600 (2009).

23. The International Aids Vaccine Initiative (IAVI). Producing immune response by administering to a mammal a purified antibody-antigen complex dissociated from polyclonal anti-HIV sera bound to glycoprotein spikes on HIV envelopes, or mixture of broadly neutralizing antibodies and HIV. US2008102073 (2008).


27. University of Maryland. New polypeptide selected from specific amino acid sequences is used for preventing or treating an HIV-1 infection in a subject. WO2014089152 (2014).


30. Rockefeller University and California Institute of Technology. Composition used for preventing or treating an HIV infection or an HIV-related disease, comprises anti-CD4 binding site potent VRC01-like antibody composition. US9890207 (2018).

31. Novartis Ag. Composition, useful to treat viral infections e.g. HIV and infections caused by e.g. Hepatitis-B, Human Papilloma Virus and Bovine Viral diarrhea Virus, comprises a glycoconjugate containing sugar moieties bound to a multivalent support. WO2011036560 (2011).


Table 1: List of 31 identified bNABs according to stage of research

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<tr>
<th>bNAB</th>
<th>Phase</th>
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<tbody>
<tr>
<td>3BNC60</td>
<td>Biological Testing</td>
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<tr>
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<td>Biological Testing</td>
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<tr>
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Source: Clinical Trials and International Clinical Trials and International Clinical Trials Registry Platform, January 2018.

Table 2: bNAbs at clinical stage – HIV/AIDS

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<td>VRC07</td>
<td>Phase I</td>
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Source: Clinical Trials and International Clinical Trials and International Clinical Trials Registry Platform, January 2018.

Table 3. Number of bNAbs in clinical trial by December 2016, with number of patent documents, clinical trials and sponsors

<table>
<thead>
<tr>
<th>bNAbs/ Phase</th>
<th>Main applicants and number of patent documents</th>
<th>First Patent Applicant - Year</th>
<th>Number of Clinical Trials and Sponsors</th>
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<tbody>
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<td>VRC01 Phase II</td>
<td>Partnership: Rockefeller Univ and California Inst of Technology (4)</td>
<td>IBC Pharm Inc - 2006</td>
<td>16 - National Institute of Allergy and Infectious Diseases (NIAID) 1 - LeafBio, Inc. 1 - Nittaya Phanuphak</td>
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<td>10E8 Phase II</td>
<td>US Dept Health &amp; Human Services (2) Aaron Diamond AIDS Research Center (2) Univ Rockefeller (2)</td>
<td>US Dept Health &amp; Human Services - 2011</td>
<td>3 - Hospital Clinic of Barcelona 2 - Bavarian Nordic 2 - Beijing 302 Hospital 1 - Bavarian Nordic and NIH 1 - NIAID, HIV Vaccine Trials Network, Bill and Melinda Gates Foundation, Medical Research Council, Sanofi Pasteur and Novartis Vaccines 1 - Bavarian Nordic and NIH 1 - Kirby Institute and Thai Red Cross AIDS Research Centre 1 - IrsiCaixa, Germans Trias i Pujol Hospital, Fundacion Lluita Contra la SIDA, Hospital Clinic of Barcelona, Hospital de Sant Pau, HIVACAT, University of Oxford and BCN-Checkpoint 1 - Crucell Holland BV, US Military HIV Research Program, NIAID and Beth Israel Deaconess Medical Center</td>
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<tr>
<td>3BNC117 Phase II</td>
<td>Partnership: Univ Rockefeller e California Inst of Technology (4) Univ Rockefeller (3)</td>
<td>Univ Rockefeller e California Inst of Technology - 2011</td>
<td>3 - Rockefeller University 1 - Dept. of Infectious Diseases, Aarhus University Hospital</td>
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<td>10-1074 Phase I</td>
<td>Univ Rockefeller (4)</td>
<td>Univ Rockefeller e California Inst of Technology - 2012</td>
<td>3 - Rockefeller University</td>
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<tr>
<td>bNAbs/Phase</td>
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<td>2G12 Phase II</td>
<td>Int AIDS Vaccine Initiative (6)</td>
<td>Xoma Corp - 1989</td>
<td>1 - Rockefeller University and European Commission 1 - Rockefeller University</td>
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<td>IAVI (6)</td>
<td>Polimun Sci Immunobiologische Forsch Gmb - 1987</td>
<td>1 - Rockefeller University</td>
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<td>PGDM1400 Phase I</td>
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<td>Cornell Univ, Scripps Research Institute and International AIDS Vaccine Initiative - 2014</td>
<td>1 – International AIDS Vaccine Initiative</td>
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<td>PGT121 Phase I</td>
<td>Partnership: IAVI and Scripps Res Inst (2) Univ Brandeis (2) Univ Rockefeller (2)</td>
<td>Univ Louisville - 2013</td>
<td>2 – International AIDS Vaccine Initiative</td>
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<tr>
<td>VRC07 Phase I</td>
<td>US Dept Health &amp; Human Services (2)</td>
<td>US Dept Health &amp; Human Services - 2011</td>
<td>3 – National Institute of Allergy and Infectious Diseases</td>
</tr>
</tbody>
</table>

Source: Clinical Trials and International Clinical Trials and International Clinical Trials Registry Platform, June 2016
Figure 1. HIV envelope trimeric spike: binding sites and broadly neutralizing antibodies.

Source: Adapted from Fuchs and Desrosiers (2016) [5]

Figure 2: Evolution of Patent Deposits bNAbs – AIDS, 1987-2016

Source: Federal University of Rio de Janeiro, School of Chemistry Information System on the Chemical Industry (SIQUIM®); Derwent Innovation Index and Thomas Reuters Integrity.

*“bNAb” had been identified with other terms in patent documents since 1987 ((Ab, monoclonal antibodies (mAb) neutralizing monoclonal antibodies (NmAb). From 2004 on, technological advances
and scientific breakthroughs, providing new knowledge on bNAbs’ and HIV-1 entry mechanisms, allowed the identification in these documents of their broadly neutralizing properties.

**Figure 3: Evolution of bNAbs’ patent deposits according to Ab terminology -AIDS, 1987-2016**

![Figure 3: Evolution of bNAbs’ patent deposits according to Ab terminology -AIDS, 1987-2016](image)

Source: Federal University of Rio de Janeiro, School of Chemistry Information System on the Chemical Industry (SIQUIM); Derwent Innovation Index and Thomas Reuters Integrity.