Neutralizing antibodies against botulinum toxins A,B,E

Sprawozdania

Informacje na temat projektu

ANTIBOTABE

Identyfikator umowy o grant: 241832

Status
Projekt zamknięty

Data rozpoczęcia Data zakończenia
1 Września 2010 28 Lutego 2015

Finansowanie w ramach
FP7-SECURITY

Całkowity budżet
€ 3 896 416,21

Wkład UE
€ 2 966 386

Koordynowany przez
MINISTERE DE LA DEFENSE
Francja

Final Report Summary - ANTIBOTABE (Neutralizing antibodies against botulinum toxins A,B,E)

Executive Summary:

Background
Despite great successes in the prevention and control of communicable diseases in Europe, there are several rare infections that may cause severe morbidity and/or mortality for which existing treatment is not always readily available. If outbreaks of such diseases occur with unexpectedly high numbers of cases, Member States may face difficulties in providing vaccines or treatment. Botulism is one of these, a rare but serious paralytic illness caused by a neurotoxin. The classic symptoms of botulism include progressive flaccid paralysis, double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. If untreated, these symptoms may progress to cause paralysis of the respiratory muscles, arms, legs, and trunk, potentially leading to the death by asphyxiation. The respiratory failure and paralysis that occur with severe botulism may require the treatment in an intensive care, under mechanical ventilation for weeks or months, plus intensive medical and nursing care. Botulinum neurotoxins (BoNT) can be treated with an antitoxin which blocks the action of toxin circulating in the blood.
Botulinum toxins (BoNT) are mainly produced by Clostridium botulinum. Eight serotypes are known (designated A to H), but the serotypes A, B and E (rarely F and H) are responsible for human botulism. BoNT/A is the most potent toxin known for human with mean lethal dose (LD 50) estimated at 1 ng.kg⁻¹. Beside natural intoxications (e.g. contaminated food), botulinum neurotoxin can also be used as a biowarfare agent. The botulinum neurotoxin is classified as a category A (highest) agent according to the Center for Disease Control and Prevention (CDC).

Current situation
Botulism is mainly treated with equine antitoxin (animal serum). These products are poorly tolerated; it can cause serum sickness and the efficacy and quality rely on extensive testing during the batch to batch evaluation process. In addition, existing producers are reluctant to continue production, considering the significant side effects and the associated product liability, coupled with a small market size. Botulinum antitoxin price estimates are between 2000 and 5000 €/treatment + costs for hospitalization. Several countries hold stockpiles of serum for both civilian and military use, but shortages are likely to occur. A massive outbreak of botulism in Thailand in March 2006 tested international capacity to respond to a public health emergency. Botulism poisoning due to contaminated food caused illness in 209 villagers, of whom 134 persons were hospitalized and 42 required mechanical ventilation. A global search for botulism antitoxin began, involving international agencies, embassies, national laboratories, airlines and commercial organizations in seven countries. Antitoxin was obtained for treatment of only 90 patients.

The aim of AntibotABE
The aim was the development of a cocktail of neutralizing human-like antibodies against the most frequent Botulinum neurotoxins: BoNT/A, B and E. These drugs aim to protect EU civilians and soldiers of the national armies in case of natural intoxications or bioterrorism. Advantages compared to existing drugs: less side effects, standardized recombinant product, simpler non animal derived production process, longer shelf-life.

Results of the consortium
Macaques were immunized with the recombinant heavy or the light chain of BoNT/A, B or E. Six immune antibody phage-display libraries were successfully generated and antibodies against all six targets selected and further analyzed. Three antibodies directed against the light chains and inhibiting the toxin in vitro and neutralizing the toxin ex vivo were generated. Two antibodies directed against the heavy-chain and neutralizing the toxin ex vivo were generated. No antibodies neutralizing the heavy chain of BoNT/E were generated. Four neutralizing antibodies against BoNT/A and B heavy and light chain and one neutralizing antibody against BoNT/E light chain were germline-humanized and produced as IgG. These five IgGs were protective in non-lethal and lethal in vivo assays in mice and showed a strong synergistic effect when combining an anti-heavy and an anti-light chain antibody directed against the same BoNT serotype. AntibotABE thus developed successfully a recombinant, protective human-like antibody cocktail against A, B and E botulinum toxins.
Currently, the clinical and regulatory development of the antibodies is planned. It is intended to develop one (combination of the five antibodies) or three drugs (combinations of two antibodies against BoNT/A, and BoNT/B heavy and light chains respectively, and one single antibody against BoNT/E).
Botulism is a potentially life-threatening disease generally associated with foodborne poisoning caused by intoxication with botulinum neurotoxins (BoNTs) that are secreted by Clostridium botulinum and certain other Clostridium spp. or by colonization of the gastrointestinal tract by BoNT-producing clostridia. Botulism is characterized by a flaccid muscle paralysis. To date, 8 serologically distinct serotypes (designated A to H) of BoNT are known. The BoNT serotypes A, B, E, (rarely F and H) are mainly responsible for human botulism. In the past, several cases of botulism caused by BoNT/A, B and E have been reported worldwide. BoNT/F causes only 1% of food poisoning-related cases of botulism. In 2013, a new botulinum neurotoxin serotype, BoNT/H, has been reported that causes human botulism. Due to the high toxicity, BoNTs are classified as category A agents by the Center for Disease Control and Prevention (CDC) and are among the six agents with the highest risk of potential use as bioweapons. The Soviet Union and Iraq were suspected to weaponize BoNTs and the Japanese cult AUM Shinrikyo attempted to use it for bioterrorism. Furthermore, the risk of contamination of the food chain by BoNTs has been highlighted by several scenarios.

BoNT/A and BoNT/B are considered to be the most toxic substances for human currently known, with a human mean lethal dose (LD50) estimated between 1 and 10 ng.kg-1 by intravenous, subcutaneous, intra-peritoneal and intramuscular routes; between 10 and 21 ng.kg-1 by pulmonary route and at 1 µg.kg-1 by oral route. BoNT/E-related intoxications are more scarce than those related to BoNT/A and BoNT/B, but the LD50 of BoNT/E is estimated to be as low as that of BoNT/A, equal to 1.1 ng.kg-1 in mice and monkeys (by intravenous, subcutaneous and intraperitoneal route.

All BoNT serotypes are synthesized as a 150 kDa single-chain progenitor toxin which normally is subsequently activated by a clostridial protease to generate a disulfide bond-linked structure containing a 50 kDa light chain and a 100 kDa heavy chain. The heavy chain contains two functional domains (HC and HN) that are required for toxin uptake into nerve cells by receptor-mediated endocytosis and for the translocation of the light chain across the membrane into the neuronal cytosol. In a final step, the catalytic domain of the light chain (a zinc endopeptidase), cleaves the SNARE complex proteins (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) which are involved in the fusion of synaptic vesicles with the presynaptic membrane and inhibits the neurotransmitter release, thereby causing flaccid paralysis, which requires intensive hospitalization.

Project objectives
Currently the treatment of botulism consists of non-specific medical care and passive immunization with antibodies, such as equine antitoxins (Botulismus antitoxin Behring, Novartis), botulinum immune globulins (BabyBIG®) or the new heptavalent equine anti-toxin serum consisting of Fab and F(ab')2 (HBAT) (www.cdc.gov). The human serum stock of BabyBIG® is limited and the equine serum may cause hypersensitivity and serum sickness. The rationale behind this antitoxin treatment is the removal of the toxin from the bloodstream before it can be taken up by neurons or the inhibition of its translocation by binding to the HN domain of BoNT. Immunotherapeutic treatments are no longer effective once the toxin has bound and is taken up into the neuron, and such treatments cannot be used to reverse paralysis. Antibodies, however, may be useful for the direct neutralization of the proteolytic activity of the light chain to prevent cleavage of the SNARE complex. The human IgG 4LCA directed against the light chain of BoNT/A, isolated by the hybridoma technology, has been shown to neutralize the proteolytic activity of the light chain in vitro and to display protective activity in vivo.

The project objective was the development of germlines humanized IgGs against the botulinum toxins A, B,
The project objective was the development of germline humanized IgGs against the botulinum toxins A, B and E for the treatment of botulism. For this purpose, macaques were immunized with the recombinant heavy or light chains of BoNT, followed by the generation of immune antibody gene libraries and selection of antibody fragments (scFv) by the phage display technology. This approach was successfully applied jointly by IRBA-CRSSA and TUBS in several projects, including the development of anti-ricin and anti-anthrax antibodies. In this project antibodies against all three serotypes were successfully generated, by targeting five out of six target antigens; no antibody neutralizing BoNT/E by targeting its heavy chain was identified. All five neutralizing antibodies were successfully germline humanized and converted to IgG, the final product. The five IgGs are neutralizing in vivo in the mice protection assay, alone or in combination (when the antibody directed against the heavy and light chain of a serotype were combined). When combining the antibodies directed against the heavy and light chain of a same serotype, a synergistic effect was observed, resulting in improved (lower IgG concentrations necessary) in vivo protection. The anti-E light chain antibody alone showed a strong protection, with only nanograms of the IgG required for the in vivo BoNT/E neutralization; a second neutralizing antibody was not necessary to efficiently neutralized BoNT/E. The objective to develop germline humanized antibodies which are protective in vivo against BoNT/A, B and E was achieved. These five antibody lead candidates can be further clinically developed as therapeutic.

Project Results:
Figure 1: Illustration of the AntiBotABE work flow.
The figure 1 illustrates the complete workflow of the AntiBotABE project. The description of the main results is given in the order of the anti-BoNT antibody development workflow.

1. Macaque immunization and antibody gene library construction
In this project six macaques were immunized with either the light chain or the heavy chain of botulinum toxin (BoNT) A, B or E. As example, the immunization schema for BoNT/A heavy chain is shown in figure 2.
All six macaques showed a good antibody titer. As example, the antibody titres of BoNT/A heavy chain were 1:800,000 for BoNT/A1 heavy chain and 1:310,000 for BoNT/A1 holotoxin.
Afterwards, immune antibody gene libraries were constructed. An overview is given in table 1.
Six macaque immune libraries were successfully constructed.

2. Selection of anti-BoNT scFv and biochemical analysis
The selection of antibody fragments (scFv) was performed by the phage-display technology against the holotoxin or the recombinant BoNT light or heavy chain. After each panning, at least 100 clones were analyzed in vitro by ELISA or surface plasmon resonance. An example for a screening ELISA with soluble scFv is given in figure 3.
From all libraries a panel of binders were isolated and validated, e.g. 22 DNA sequence unique scFv were analyzed from the pHAL32 BoNT/A light chain library or 85 unique binders from BoNT/E light chain library. In most cases, the affinities were directly measured, e.g. for BoNT/A heavy chain 24 scFv had a better affinity than 10 nm (best anti-BoNT/A heavy chain clone: 1.3 nM).
The sequences of the antibodies were analyzed to determine the closest human germline genes and to calculate the Germinality Index (identity of macaque framework region with the corresponding human counterpart). An example for this analysis is given in table 2.
The kind of epitope (conformational/non-conformational) were further analyzed. In addition the epitope of the non-neutralizing antibody SEM95-C6 was determined by epitope mapping (figure 4). The epitope of the neutralizing antibodies, of particular biodefense interest, were not mapped.

3. In vitro inhibition analysis of the antibodies directed against the light chains of BoNT
The selected antibody fragments (scFv or scFv-Fc) directed against the light chains of BoNT/A, B or E were characterized in vitro in the SNARE endopeptidase assay, to evaluate the inhibition capacity of these antibody fragments. Antibody fragments inhibiting the endopeptidase activity were identified for all three BoNT light chains.
An example for this assay is given in figure 5 and the corresponding 50% inhibition concentrations (IC50) and the molar ratios are given in table 3 for nine antibodies of interest.

In case of SEM120-IIIC4, the antibody is inhibiting the BoNT/A endopeptides with a 1:1 stoichiometry related to binding domains (scFv-Fc and IgG have two binding domains)! Antibodies inhibiting the endopeptidase activity of each of three botulinum toxins were successfully identified.

4. Ex vivo neutralization analysis of the anti-BoNT antibodies
In a next step, the neutralization capacity was analyzed ex vivo in a mouse phrenic nerve hemidiaphragm assay. The results of this assay are closely correlated with the results obtained in the in vivo protection assays. The antibodies were analyzed as scFv-Fc or scFv. An example is given in figure 6 for the neutralization of BoNT/A by targeting its light chain.

The 50% paralysis (of the muscle) time was measured to evaluate the efficiency of the antibodies. An example for the evaluated paralysis time is given in table 4.

The antibody fragments generated against five of six BoNT chains were neutralizing ex vivo. None of 44 antibodies generated against BoNT/E heavy chain were neutralizing in this assay, even when tested in combination with a non-competitive antibody targeting BoNT/E-HC. However, neutralizing antibodies generated against BoNT/E light chain are available and neutralize efficiently BoNT/E.
On the basis of affinity, in vitro inhibition and the ex vivo neutralization experiments five antibody fragments were chosen for germline humanization and IgG development. The selected antibodies for further development are given in table 5.

5. Germline humanization of the neutralizing antibodies
To minimize potential immunogenicity of the antibodies as therapeutic a germline humanization was performed. The framework regions of the macaque antibodies were compared with the corresponding human germline genes, to identify the closest human germline genes. Figure 7 shows the amino acid comparison of the anti-BoNT/B heavy chain VH (variable antibody domain) B2 7 with the corresponding human germline gene.

The amino acid differences in the framework regions were rated according to their biochemical differences in very similar, similar, dissimilar and very dissimilar, to predict if their mutation will be problematic for the
in very similar, similar, dissimilar and very dissimilar, to predict if their mutation will be problematic for the structure of the antibody. Figure 8 shows these analysis for VH and VL of B2-7. The germinality index was also calculated, to quantify the proximity of the antibodies of interest with the human antibodies, and thus to predict the tolerance of the antibodies of interest.

Several variants of humanization were generated for each antibody of interest. Each of them was characterized to identify the most humanized variant which preserve the affinity of the parental antibody. As example, the results of the humanization of SEM120-IIIC1 (anti-BoNT/A light chain) are given in Figure 9.

This figure represents the reactivity of the antibody variant against BoNT/A light chain or against BSA (negative control). For the VH domain, only very similar and similar amino acids can exchanged. Indeed, if dissimilar amino acids were exchanged, affinity of the generated antibody variant was strongly degraded. For the VL, all amino acids diverging from the human germline sequence were completely germline humanized without loss of affinity (= all macaque amino acid can be exchanged to the human ones).

Similarly, for the other four selected antibodies, for VH only the very similar and similar exchanges were realized. Finally, all five antibodies were successfully germline humanized.

6. IgG production
The five germline humanized antibody fragments were converted from scFv-Fc or scFv to IgG (human IgG1). The IgGs were expressed using proprietary LFB vectors and rat YB2/0-EMABling® cells, which have a low fucosylation rate. This cell lines is compatible with Good Manufacturing Process (GMP) production of recombinant therapeutics. The IgGs were finally analyzed by antigen ELISA to compare potential loss of affinity due to the conversion.
An example of expression as IgG is given for B2.7 in Figure 10.

All five antibodies were successfully produced as IgG.

7. Analysis of the in vivo protection
The produced IgGs were used for in vivo protection studies in mice. Two kind of in vivo assays were performed: the non-lethal in vivo paralysis assay and the lethal in vivo assay. The paralysis assay works with a non-lethal toxin concentration (0.4 LD50) rates the development of an abdominal ptosis. An example for this non-lethal protection assay with the antibodies directed against the heavy and light chain of BoNT/A is given in Figure 11.

As shown in Figure 11, hu8SEM120-IIIC1 (anti-light chain) shows a slight protection, whereas hu8A1HC38 (anti-heavy chain) shows a good protection up to 100% protection with antibody concentrations superior to 10 µg.mL-1. When both antibodies were tested in combination, 100% protective was achieved whatever the antibody concentration was. Concerning the protection against BoNT/E, the hu8B2.7 (anti-heavy chain) was partially protective, hu8BLC3 (anti-light chain) was fully protective in higher concentrations and a synergistic effect was seen when combining both antibodies resulting in 100% protection. The anti-BoNT/E light chain antibody is 100% protective alone with antibody concentrations of 10 ng/mice and higher.
The lethal in vivo assays were performed with 5 mL50 of botulinum toxins mixed with one antibody or with a combination of the two antibodies directed against the two chains of a serotype, and subsequently injected intraperitoneally. The results of the lethal mouse protection assay are given in the three following tables (Table 6 to Table 8).

The anti-BoNT/A heavy chain antibody hu8-AHC38 is fully protective when using 25 µg of the antibody per mice. Surprisingly, the protection is lower with lower antibody concentrations. The anti-BoNT/A light chain antibody hu8-SEM120-IIIC1 is partially protective with the higher concentrations and not protective at 250 ng/mice. When using both antibodies in combination, even with 2.5 µg of each antibody per mice the antibodies are fully protective and partially protective with 250 ng/mice. The antibody combination is also protective against other analyzed BoNT/A subtypes. These results are in accordance with the in vivo paralysis experiments.

Weak or no neutralization of BoNT/B with the antibody hu8-B2.7 (anti-heavy chain) alone was observed against this subtype. The anti-light chain antibody hu8BLC3 is fully protective with 25 µg/mice and partially protective for lower concentrations. Both antibodies in combination are fully protective for 2.5 µg/mice and partially protective for lower concentrations. The antibody combination is also protective against other analyzed BoNT/B subtypes. These results are also in accordance with the non-lethal paralysis assays.

In case of the anti-BoNT/E light chain antibody hu8ELC18 alone is fully protective with 2.5 ng/mice! This impressive efficacy was also seen in the paralysis assays.

The combination of the two antibodies directed against the heavy and the light chain of BoNT/A or B is very efficient in the in vivo animal model. In case of BoNT/E, the efficacy of the anti-light chain antibody alone is striking.

8. Summary
Macaques were immunized with the heavy or the light chain of BoNT/A, B or E. Six immune antibody phage display libraries were successfully generated and antibodies against all six targets were isolated and characterized. Against all three BoNT light chains, in vitro inhibiting and ex vivo neutralizing antibodies were generated. Against two of three heavy chains ex vivo neutralizing antibodies were generated. Concerning BoNT/E heavy chain, all selected antibodies were not neutralizing. Four neutralizing antibodies against BoNT/A and B heavy and light chain and one neutralizing antibody against BoNT/E light chain were germline-humanized and produced as IgG. These IgGs were protective in non-lethal and lethal in vivo mice assay and showed a strong synergistic effect when the antibodies directed against the heavy and light chain of BoNT/A or B where combined. AntibotABE thus developed successfully a recombinant, protective human-like antibody cocktail composed of five antibodies directed against BoNT/A, B and E.

The output is summarized in the table 9.

Currently, the clinical and regulatory development of the antibodies is planned. It is intended to develop three drugs: combinations of two antibodies against BoNT/A heavy and light chains, of two antibodies directed against BoNT/B heavy and light chains, and one antibody against BoNT/E. These three drugs can also be used as one combined drug directed against all three BoNT/A, B and E.
Potential Impact:
The expected impacts of ANTIBOTABE were the following:

• Immediate “Scientific” impact: to demonstrate the development feasibility and the potency of recombinant antibody for the neutralization of toxins. This impact has been reached with the development of the IgG targeting the two chains (HC / LC) of the toxins which was the first of a kind development. The potency of this approach has been demonstrated and disseminated among the scientific community.

• Mid-term “Market/economic” impact: To foster a market for anti-BoNT A, B and E. This long-term impact will require several additional steps which are described in the ANTIBOTABE dissemination and exploitation plan.

• Long-term “Societal” impact: Recombinant antibodies used as therapeutic drugs against toxins could lead to important societal impact:
  o Safer than current drugs based on animal derived products, recombinant antibodies led to less side effects and to therefore to an economy for public health systems;
  o The non-animal origin of recombinant antibodies is an important acceptance factor for what regards societal aspects;
  o The production cost is lower and the shelf life is higher than current products which makes recombinant antibodies a cheaper and safer product than existing ones.

Immediate “Scientific” impact:

The ANTIBOTABE consortium has developed a unique strategy and a know-how which could be re-used for other target. The workflow is summarized in the figure 12.

One of the project impacts will be the duplication of this workflow for other targets. This strategy particularly fits with toxins-related diseases: Cyanobacterial toxins, Diptheria toxin, marine toxins (Scombrotoxic fish poisoning, Ciguatera poisoning, Paralytic shellfish poisoning, Neurotoxic shellfish poisoning, Amnesic shellfish poisoning) etc. The ANTIBOTABE consortium has already initiated new collaboration on some of these targets.

The potential impact on public health is important, however the financial support requested to move a research result up to a marketable product will be important and it is the main obstacle of this impact achievement.

The scientific impact success can also be measured with the high number of presentation of ANTIBOTABE in scientific congresses. ANTIBOTABE was presented 27 times in talk or posters in worldwide congresses (Europe, US, China, Australia). In addition 4 scientific papers were published by the consortium members in scientific journals. Five further publications are submitted/in preparation.

Mid-term “Market/economic” impact:

The ultimate goal of ANTIBOTABE, going beyond the project, being to develop and register, as a single-drug or as three different drugs, recombinant monoclonal antibodies aiming to prevent and treat botulism. Two areas can be targeted:
- Accidental botulism: the frequency of accidental botulism (mainly food intoxication) is very low (51 cases in France between 2010 and 2012, according to an INVS report (Mazuet C. et al, BEH, February 2014) and adequately treated with marketed products (polyclonal Ig). It cannot be considered for a main potential market.

Identification of the causes of accidental botulism:
Botulism is reported as a rare disease (www.orphanet.org). Global prevalence is less than 1/1,000,000. Annual incidence in Western countries is estimated at 1/2,000,000.

Table 10 describe the main accidental botulism cases.
- Botulism as a CBRN threat: botulism toxin is considered as a biological threat (part of the chemical, biological, radiological and nuclear –“CBRN”- threat) in the context of bioterrorism or biowarfare. The national authorities’ interest for stockpiles of Anti-BoNT to be used in case these cases can be considered as the main potential market.

BoNTs are part of the “dirty dozen” agents listed in Europe, and are classified by the CDC among the six highest-risk threat agents for bioterrorism (CDC category A agent) both due to their toxicity and their ability to be produced and disseminated. In the past, BoNTs were experienced on humans by Unit 731 of the Japanese army in Manchuria, in 1930’s. The US produced BoNT during the Second World War and the program was ended in 1970. Despite the 1972 Biological and Toxin Weapons Convention they signed, at least the Soviet Union and Iraq produced BoNT for potential use as a weapon. The Soviet Union tested those toxins and a former Russian scientist reported that BoNT-coding genes have been inserted in other bacteria. In Iraq, after the 1991 Persian Gulf War, it was recognised that 19000 litres of concentrated BoNT were produced, a quantity of toxin sufficient to kill the entire human population. More recently, the Japanese cult Aum Shinrikyo attempted to use BoNT for terrorism but failed, possibly due to the difficulties of the aerosolization technique. Voluntary dissemination of botulinum toxins by pulmonary or oral route (for instance, utilizing refrigerated milk as a vehicle, as recently investigated by Wein and Liu) can contaminate large number of people and put a severe stress on already over-burdened hospital systems, requiring intensive care for as long as six weeks in the absence of specific neutralizing therapeutics.

Current competitors on the market
See table 11.

Other competitors (not yet on the market)
Nineteen products are under evaluation. None of them are marketed, 1 is registered in Europe and approved in US, 2 are under clinical development and the majority are still in discovery phase. Among these products, 8 are monoclonal antibodies or derivatives (antibody fragments), 5 are vaccines and 4 are from other class of molecules (small molecules).

The companies developing the products against Botulinum toxin are private companies (14 products) and public institutions (3 products) with a major implication of the US government. The majority of the products registered or under evaluation is only efficient on botulinum toxin A, some recognize botulinum toxin A & B and only few more than 2 strains. NP-018 an equine-derived product developed by Cangene Corp recognize strains A, B, C, D, E, F &G.

Concluding SWOT for the ANTIBOTABE results market exploitation
Strength:
The main strength of ANTIBOTABE is the quality of the results. The efficiency and specificity of ANTIBOTABE results have been proven. The ANTIBOTABE antibodies are super-humanized, nearing the human antibodies and thus avoiding all the side effect of current polyclonal equine products. The high quality of the results is due to the high quality of the consortium which include key opinion leader (KOL) on botulism and a pharma industry able to perform all the requested development up to a marketable product.

Weakness:
Due to the high cost, the consortium doesn’t have the financial capacity to support the whole marketable product development. A financial support is mandatory.
Other toxins subtypes such as F, G will not be targeted by our product but these types are so rare that it can’t be considered as a CBRN threat.

Threat:
Competitors are numerous as described above. However ANTIBOTABE results have a clear competitive advantage and are the most promising due to the efficacy, the wide range of targeted subtypes and the advanced stage of development.
Some competitor products exist on the market but have many drawbacks due to their equine origins or prices.

Opportunity:
CBRN threats are still a concern for the EU Member States. The current counter measures are not satisfactory and many countries are interested to foster their arsenal against CBRN.
EDA has a limited budget but is willing to strengthen a common European defence strategy. A cooperative project between Member States and initiated by EDA could be the first stone of a common European defence strategy. ANTIBOTABE should bet on this and try to proactively foster the Member States’ interests for the development of the project results.
The H2020 programme with a high budget (70 billion on the 2014-2020 period) might be considered as a source of funding. However the scope and the dimension of the whole development appear to exceed the budget per project allowed in H2020. In addition, the success rate of H2020 proposal in health thematic (below 3%) is not motivating.

Potential impact per partner:
Beside the impact of ANTIBOTABE results, the consortium members have identified a set of impact directly linked to their participation to ANTIBOTABE and listed in table 12.

List of Websites:
www.antibotabe.com
Jean-Nicolas Tournier - tel: + 33 4 76 63 75 16 - jean-nicolas.tournier@irba.fr
Michael Hust (scientific coordinator) - Tel: +49-531-391-5760 - m.hust@tu-bs.de
Olivier de Bardonneche (Project manager) - Tel: +33 4 86 110 184 - o.debardonneche@absiskey.com

Ostatnia aktualizacja: 23 Grudnia 2015
Numer rekordu: 173825