CONTRIBUTI PER PROGETTI DI COLLABORAZIONE SCIENTIFICA INTERNAZIONALE

ENTE DI RICERCA RICHIEDENTE:

Centro Servizi Interdipartimentale Stazione per la Tecnologia Animale - Università degli Studi di Roma "Tor Vergata"

TELEFONO 06 72596396 FAX 06 72596037 CITTA' Roma

INDIRIZZO Via Montpellier E-MAIL mattei@uniroma2.it

REFERENTE SCIENTIFICO: Maurizio Mattei

IL PROGETTO

TITOLO DEL PROGETTO:

Anti-tuberculosis and anti-hepatitis B vaccination based on BCG-HBsAg co-formulation: pre-clinical and phase I study.

DESCRIZIONE SINTETICA DELL'IDEA PROGETTUALE DI COLLABORAZIONE INTERNAZIONALE

(max 6.000 caratteri):
Obiettivi, scambio di competenze con l'unità di ricerca internazionale, modalità di attuazione, risultati attesi)

In Hepatitis B infection, vaccine-induced neutralizing antibodies play an important role in protecting young infants from infection and the control of viral replication also involves helper T lymphocytes. BCG vaccine is recommended at birth and remains the only tuberculosis vaccine available for field usage. Evaluation of BCG vaccine immunogenicity demonstrated that human newborns make strong Th1 responses to BCG detectable as long as one year suggesting immunological memory response. Moreover, it has been shown that BCG may be a useful Th1 inducing adjuvant at birth in humans [Marchant A, 1999; Vekemans J 2001; Ota MO 2002). It markedly increases the primary immune response to Hepatitis B vaccine in newborns and may have influence on infant memory responses [Ota MO 2006]. Because immunization at birth generally primes to subsequent vaccine doses, new combinations of vaccines are an important public health endeavour.
Recently, E.F. Carniel and co-workers demonstrated that intradermal Recombinant Hepatitis B combined with BCG at birth as first dose of vaccine, induce antibody response specific for Hepatitis B as well as the conventional Hepatitis B vaccine, indicating safety and immunogenicity of this vaccine in newborn.

The University of Rome Tor Vergata and its spin-off Research Drug Development (ReDD), in the context of the internationalisation of the research in the Region Lazio, is developing a new co-formulation of BCG and Hepatitis vaccines with antigens coming from new companies such as Cuban Center for Genetic Engineering and Biotechnology (Havana, Cuba) and Bulgarian BulBio-NCIPD (Sofia, Bulgaria). Although these 2 vaccines are used for many years separately, this co-formulation product imposes a new detailed control of immunogenic characteristic and possible adverse effects.

The objective of this project is to develop vaccine specific for Hepatitis B and tuberculosis by a co-formulation of BCG and recombinant HBsAg where BCG has also an adjuvant role. The use of this vaccine is intended for paediatric use in countries where vaccination against tuberculosis and hepatitis B are or should be planned during the first day of life.
Specifically, this project is aimed to

- exclude any toxic effect of BCG-rHBsAg combination when administered together at the same site and time;
- exclude any interference of HBsAg on the BCG-induced immunisation and viceversa;
- confirm immunogenicity of HBsAg-BCG compared to HBsAg and BCG injected in different sites and to conventional HBV vaccine.

The r-HBsAg-BCG co-formulation will be obtained with BCG by Bulgarian BulBio-NCIPD (Sofia, Bulgaria) and r-HBsAg by Cuban Center for Genetic Engineering and Biotechnology (Havana, Cuba). The co-formulation will be prepared at BulBio-NCIPD. The r-HBsAg is the recombinant protein used in formulation of conventional anti-hepatitis B vaccine called Heberbiovac distributed in Cuba and licensed by WHO. BCG producted by BulBio is also licensed by WHO and the production facilities, the quality of the products and the quality management system of the company meet the standards of the European Legislation.
Pre-clinical study and phase I study will be performed at Animal Facility of University of Rome "Tor Vergata" and at Policlinico "Tor Vergata" respectively. The phase II trial will be performed at Center St. Camille of Ouagadougou, Burkina Faso.

The pre-clinical studies of present multi-antigenic BCG-HBV vaccine will be performed in mice and is based on the administration of of BCG and rHBsAg co-formulation without aluminium adjuvant inoculated in the same site. Control group will receive BCG and HBsAg separately, or conventional HBV vaccine alone or BCG alone.

Local and systemic reactions will be monitored as usually performed for BCG vaccination (hypersensitivity reactions, abscesses at the injection site, and localised lymphoadenopathy, usually self limiting). Toxicity evaluation include clinical monitoring before and after vaccination, with additional follow up evaluations.

Immunogenicity of vaccine will be assessed by analysing antigen specific CD8 and CD4 producing IFNg measured by intracellular staining (ICS) and antigen specific proliferation. The presence anti-HBsAg IgM, IgG and IgA antibody response are tested in the sera by ELISA.
Sera from immunised mice will be tested for the presence of anti-BCG and anti-HBsAg antibody response. In particular, in order to confirm that the administration of rHBsAg with BCG does not modify anti-BCG immune response, western blotting will be performed to test the presence of IgM, IgG, IgA specific for BCG proteins. Moreover, the DTH reaction to PPD will be evaluated before sacrificing the animals to establish the efficacy of BCG vaccination.

The phase I study will be performed in healthy volunteers. Subjects will be selected between healthy adults between 18 and 45 years of age. Volunteers will be recruited into the study after obtaining written informed consent. Individuals will be eligible if they had no history of hepatitis B nor tuberculosis infection or immunization with hepatitis B vaccine or BCG.

Thirty volunteers will be divided in three groups and they will receive an intradermal (id) injection of BCG-rHBsAg co-formulation without adjuvant in the same site. A control group will receive BCG id and rHBsAg intramuscular (im) in two different site. The last group will receive conventional HBV vaccine im alone. All volunteers will receive first and second boosting after 2 and 6 months after priming with conventional Hepatitis B vaccine Heberbiovac.
Adverse events will be actively recorded until 30 days after each dose. Clinical laboratory evaluation include complete blood and platelets count; measurement of levels of blood urea nitrogen, creatinine, ALT, AST; Anti-HBs and anti-HBc antibody titers will be evaluated using corresponding ELISA kits before and after priming, after first and second boosting. At the same time will be evaluated the cellular response to HBsAg in terms of proliferation and cytokine production as described for pre-clinical study.

The probability to obtain positive results is high and on the basis of these results the project will advance to a phase II study in Ouagadougou by vaccination of newborns.

The main advantages of this co-formulation are the ability to induce an effective cellular immune response in newborn, the decrease of costs and troubles of two distinct vaccine injection and the spread of vaccination against hepatitis B in Africa that actually is low with respect to anti-tuberculosis vaccination (30% vs 85% respectively).

The project is also intended to obtain the proof of concept for a model of vaccine able to induce immune response against several pathogen by using BCG as adjuvant in countries where tuberculosis and infections such as HIV and of course HBV, are widespread.
These vaccination platform may allow a change in the current immunization program overall in developing countries with high rate of vertical HBV transmission and tuberculosis infection, decreasing the number of injections, increasing parent compliance, improving timely vaccination and reducing cost.

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DURATA DEL PROGETTO

Data inizio	Data (stimata) di conclusione
Giugno 2008	**Dicembre 2008**

PREVISIONE DEI COSTI

Collaborazione scientifica in attività di ricerca	
Personale ricercatore universitario Personale a contratto (assegno di ricerca annuale)	**10.000** **18000**
Missioni e viaggi	**4.000**
Materiali di consumo	**28.000**
TOTALE COSTI AMMISSIBILI – Collaborazione	**60.000**
Eventuali studi di fattibilità	
Personale quali tecnologi ed esperti in validazione tecnico-scientifica	**10.000**
Missioni per eventi internazionali	
Analisi di mercato	**10.000**
TOTALE COSTI AMMISSIBILI – Studi	**20.000**
TOTALE COSTO PROGETTO	**80.000**

COPERTURA FINANZIARIA

CONTRIBUTO RICHIESTO (max 75% costo totale)	60.000
RISORSE PROPRIE (personale universitario, missioni, 20% materiale di consumo)	20.000

MODALITA' DI EROGAZIONE DEL CONTRIBUTO

Il contributo sarà erogato secondo il seguente schema:

- 50% a titolo di anticipazione
- 40% a titolo di ulteriore anticipo dopo aver effettuato e saldato spese per un importo pari al 80% dell'anticipo ricevuto previa presentazione di rendicontazione amministrativa e subordinatamente all'accertamento dell'ammissibilità da parte della Filas S.p.A.
- 10% a saldo dopo l'invio della relazione conclusiva sul progetto, previa presentazione di rendicontazione amministrativa dell'intero progetto e subordinatamente all'accertamento dell'ammissibilità da parte della Filas S.p.A.

COORDINATE BANCARIE

Banca:	BANCA DI ROMA, AGENZIA 75						
Indirizzo:	VIA ORAZIO RAIMONDO, 18 – 00173 ROMA						
C/C n.	**5021472**	ABI	3002	CAB	03255	CIN	
IBAN:	IT64T0300203255000005021472						
Intestazione del c/c:	CENTRO DI SERVIZI INTERDIPARTIMENTALE – STAZIONE PER LA TECNOLOGIA ANIMALE						