様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

令和　元 年　 ６ 月 １７ 日現在

機関番号：１２６０１
研究種目：基盤研究(C)（一般）
研究期間：2015～2018
課題番号：１５Ｋ０８０１６

研究課題名（和文）承認プロセスを視野に海外ネットワークを活用するバイオベンチャーの創薬支援の模索

研究課題名（英文）Overseas networks to assist Japanese biostartups to develop and register new drugs

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交付決定額（研究期間全体）：（直接経費）　　2,600,000円

研究成果の概要（和文）：本研究では日本のバイオベンチャーが承認プロセスを視野に海外での治験の可能性を求めて海外ネットワークを有効活用するケーススタディーを試みた。治験を中心とする米国食品医薬品局FDA)、欧州医薬品庁(EMA)、英国医薬品庁（MHRA)のような機関からの承認を射程に入れれば、日本国内だけで行う治験計画は現実的とは言えない。これらの治験の設定はCROと呼ばれる開発業務受託機関が行うが、同時に海外の大学を中心とする学術的ネットワークも重要な役割を担っている。本研究では、研究者の科学的知見、新規性に富む検証方法、患者へのアクセスに影響を及ぼす病院との連携など具体的な事例をもとにこの点を検証した。

研究成果の学術的意義や社会的意義
治験に伴う時間や費用は新薬開発にとって大きな障壁であり、治験を有効かつ迅速に行えることは新薬を患者に届けるために極めて重要である。様々な制約を受けている日本のバイオベンチャーにとっては海外ネットワークの存在を無視することは賢明とは言えず、海外の学術機関とどのような協力関係を築くことが治験のプロセスに有効であるかを知るのは喫緊の課題である。特許や資金調達に関する理論は当然ながら重要だが、現実的な側面には対処できない。本研究では海外ネットワークがもたらす極めて現実的な側面をケーススタディーを通じて示したが、このような詳細なモデルを知ることは創薬ベンチャーにとっては大きな一歩を踏み出す助けになる。

研究成果の概要（英文）：This research adopted a case study approach to exploring ways overseas research networks can assist Japanese bioventures to conduct clinical trials for regulatory approval. Clinical trials outside Japan are often necessary to obtain approval from overseas regulatory agencies such as the US FDA, European EMA and the UK MHRA. Contract research organizations (CROs) can perform such trials. However, overseas trials can also be performed in collaboration with academic institutions. This research found that academic collaborators can offer valuable scientific expertise, innovative testing methods, and access to affiliated hospitals that can hasten patient recruitment. Sometimes academic institutions can leverage public research funds, thus reducing overall costs. They can often help select appropriate CROs that conduct some of the research. They often have close ties to regulators who can provide valuable feedback on study design from a regulatory perspective.

研究分野：医薬品開発、臨床試験

キーワード：医薬品開発　臨床試験　薬事承認　レギュラトリーサイエンス　バイオベンチャー　海外ネットワーク　知的財産権　特許

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１．研究開始当初の背景

This research was motivated by previous research by myself and others that indicates the importance of bioventures for the discovery and development of new drugs. However, bioventures do not have the resources of large pharmaceutical companies to conduct preclinical and clinical research to bring their discoveries to patients. Also the cannot rely on Japanese academic ties alone. Having worked in NIH, I am aware of ways that academic institutions help bioventures outside Japan. The purpose of this research was to clarify how such institutions can also help Japanese bioventures, using a case-study approach.

２．研究の目的

The purpose of this research was to clarify, in a practical way, how academic institutions overseas and networks of overseas researchers can help Japanese bioventures.

３．研究の方法

Case study method where the Japanese bioventures are companies I am personally familiar with.

４．研究成果

This research found that academic collaborators can offer valuable scientific expertise, innovative testing methods, and access to affiliated hospitals that can hasten patient recruitment. Sometimes academic institutions can leverage public research funds, thus reducing overall costs. They can often help select appropriate CROs that conduct some of the research. They often have close ties to regulators who can provide valuable feedback on study design from a regulatory perspective.

Details of the research supporting these findings are contained in the two following case studies:

Case study 1

This case study deals with of a novel vaccine delivery system from the laboratories of Prof. Hiroshi Kiyono, Institute of Medical Science, University of Tokyo (IMSUT); Prof. Kazunari Akiyoshi, Kyoto University Department of Chemical Engineering (Polymer Chemistry), and Prof. David Briles, University of Alabama at Birmingham (UAB) Medical School, Department of Microbiology. The lead application for the delivery system is a nasal vaccine for pneumococcal pneumonia, but other applications include immunization against tuberculosis and other mycobacterial diseases.

2015/5/18: Met entire morning in New York City with Dr. Bruce Forrest who used to work for Pfizer and is an expert in pneumococcal drugs. Dr. Forrest knows Dr. Kiyono well and is familiar with his research. Dr. Forrest gave helpful advice regarding the numbers of antigens we should include in the vaccine, how the vaccine compares with currently marketed vaccines, Israeli academic researchers who have who have relevant data, and the pathway to FDA approval. Traveled that evening to Washington DC

2015/5/19: Met with officials in NIH near Washington DC and joined by Dr. Briles by teleconference. This meeting was fruitful because it provided guidance on funding from NIH and also on the types of evidence of immunity we should use for the new vaccine.

2015/5/26: I met officials of PATH in Seattle. PATH is funded mainly by the Gates Foundation, and is one of the main NGO working on behalf of Gates to develop vaccines for children in developing countries. The discussion was helpful, because it clarified the requirements of organizations such as WHO and Unicef in terms of factors such as cost, reliability, ease of administration in developing countries, etc. It also clarified procedures for becoming certified by WHO to treat children in developing countries.

2015/7/20: I met Dr. Terrance Blaschke, Professor at Stanford and Advisor to the Gates Foundation on vaccine development. Dr. Blaschke gave helpful advice on American university vaccine and also pharmaceutical company researchers who are working with Gates to develop vaccines for infectious diseases in developing countries. These contacts will be helpful as possible collaborators in developing a version of the vaccine for children. Traveled to Chicago to meet Dr. Briles

2015/7/21: All day meeting with Dr. Briles. This was helpful because we reviewed correlate of protection assays that are vital for the development of many vaccines, because such assays can greatly shorten the time and expense for Phase 3 trials. UAB has developed such assays for the currently marketed pneumococcal vaccines. Dr. Briles may be able to develop similar assays for the new nasal vaccine, which is based upon protein, rather than polysaccharide antigens. We also discussed possible NIH funding for the research to valid such a new assay. This is an example of how academic research supported by public funds can be very helpful for drug and vaccine development by startups, including Japanese startup.

2016/11/2: Full day of meetings at the Liverpool School of Tropical Medicine (LSTM). LSTM is an important potential collaborator for development of the nasal pneumococcal vaccine. It's researchers are world leaders in mucosal immunity for vaccine discovery. LSTM has the world's only facility to conduct pneumococcal vaccine clinical studies by challenging patients with live pneumococcal bacteria (low dose and antibiotic sensitive). This challenge system is linked to a unique assay LSTM has developed to assess the effectiveness of pneumococcal vaccines, namely measuring whether the vaccines prevent colonization of the bacteria in the oropharynx. LSTM also has links to UK government agencies that can fund early stage human clinical trials and can help in preclinical Chemistry, Manufacturing and Controls (CMC) work. Also, it has links to MHRA, the UK's drug regulatory agency, which can advise on trial designs that and preclinical development (CMC) studies that are required to begin testing in humans. The relationship with LSTM shows how academic institutions can bring valuable resources to drug and vaccine development by Japanese bioventures and also help them obtain regulatory advice.

2016/1/11-13: Biotech Showcase Conference in San Francisco. This conference was a good opportunity to learn about other groups developing mucosal and pneumococcal vaccines and to meet pharmaceutical companies that might be interested in our vaccine and potential investors. In addition, I had another meeting with Dr. Forrest who discussed the pros and cons of developing a mucosal as compared to a normal injectable vaccine, and ways to finance development, including ways that overseas investors might support Japanese university research. On Jan. 14, I flew to San Diego.

2016/1/15: This day we had meetings with a company that can manufacture vaccine antigens according to FDA specified GMP quality. This meeting provided understanding of the CMC process as it applies to our vaccine. These meetings formed the basis for many follow-up discussions with the parent company, Ajinomoto, back in Japan. CMC issues account for one of the largest expenses in pre-clinical drug development, and how to handle CMC processes and validation is an important task for therapeutic bioventures.

2016/4/5-6: Dr. Kiyono, Dr. Yuki (also from IMSUT) and I met Dr. Briles in his lab in UAB. We discussed which antigens to include in the vaccine and also intellectual property matters, including licensing of patents from UAB. We also had discussions with other researchers in UAB Medical School about the in vitro assays that are used to test the efficacy in vitro of current vaccines and whether different assays might be developed to test the efficacy in vitro of protein antigen vaccines such as ours. Again, this showed how university collaborators can mobilize various scientific resources for vaccine/drug development and expedited regulatory approval.

2016/10/6: Met researchers in the not-for-profit Infectious Disease Research Institute (IDRI) in Seattle. These researchers have been developing various tuberculosis (TB) vaccines. The discussions concerned the drug delivery system from Prof Akiyoshi's Kyoto University laboratory and how this might be used to deliver the IDRI vaccine antigens directly to the lung bronchi and alveoli, much as natural infection occurs. The discussions also concerned appropriate antigens, which types of mycobacteria most need new vaccines, adjuvants, and other possible collaborators. These discussions showed the scientific benefits of working with non-profit research institutions such as IDRI, including expanded uses of technologies being developed by bioventures.

2016/12/3: I completed writing a patent application covering the antigens for our pneumococcal vaccine and this application was filed this date in the US PTO. WO2018102774 (A2) (priority number: US201662429782P 20161203)

2016/12/26: A startup, HanaVax, was formed which licensed this and other patents and is carrying forward development.

2017/1/9-12: Biotech Showcase Conference in San Francisco. Like the previous year, this conference was a good opportunity to learn about other groups developing mucosal and pneumococcal vaccines and to meet pharmaceutical companies that might be interested in our vaccine and also potential investors.

2017/2/8-9 Attended US-Japan Cooperative Medical Science Program in Seoul. Many of the sessions were on pneumonia and related respiratory diseases. It was beneficial to speak with vaccine researchers from around the world, to gain a broader perspective on vaccine research that might be relevant to our pneumococcal vaccine -- and on other respiratory diseases that might benefit from our vaccine delivery system.

５．主な発表論文等

〔雑誌論文〕（計　2　件）

Amir Farmanbar, Robert Kneller Sanaz Firouzi. RNA sequencing identifies clonal structure of T-cell repertoires in patients with adult T-cell leukemia/lymphoma. NPJ Genomic Medicine (2019)4:10. Available: https://www.nature.com/articles/s41525-019-0084-9.pdf.

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Robert Kneller〔学会発表〕（計　1　件）

Technology Transfer and the Development of University Biomedical Discoveries – a perspective from Japan. 20 May 2015 talk at the International Scientific Association for Probiotics and Prebiotics, Washington DC.

〔図書〕（計　　件）

〔産業財産権〕

○出願状況（計　1　件）

名称：Pneumococcal vaccine combining seleccted alpha helical domains and proline rich domains of pneumococcal surface protein A
発明者：David Briles, Hiroshi Kiyono, Robert Kneller, Reshmi Mukerji, Kristopher Genschmer, Yoshikazu Yuki
権利者：University of Tokyo and University of Alabama at Birmingham
種類：patent application
番号：WO 2018/202774
出願年：2016
国内外の別： international

○取得状況（計　　件）

名称：
発明者：
権利者：
種類：
番号：
取得年：
国内外の別：

〔その他〕

ホームページ等

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