（報告様式４）

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I.　基本情報

事　業　名：（日本語）免疫アレルギー疾患等実用化研究事業（移植医療技術開発研究分野）
（英　語）Practical Research Project for Allergic Diseases and Immunology (Research on Technology of Medical Transplantation)

研究開発課題名：（日本語）原発性免疫不全症に対する造血幹細胞移植法の確立
（英　語）Study for optimal hematopoietic stem cell transplantation procedures for primary immunodeficiency

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実 施 期 間：平成２８年４月１日　～　平成２９年３月３１日

分担研究開発課題名：（日本語）患者登録（関東地区統括、PIDJ とのデータベース照合）および移植ガイドライン作成、新たな移植合併症診断法の開発
（英　語）Patients registration (collation with PIDJ in Kanto area), establishment of transplantation guidelines, and development of new diagnostic methods for the transplantation related complications

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分担研究開発課題名：（日本語）患者登録（近畿地区統括）および移植ガイドライン作成、新たな移植合併症治療法の開発
（英　語）Patients registration in Kinki area, and development of new treatment for the transplantation related complications

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分担研究　（日本語）患者登録（東海地区統括）および評価項目の設定、新たな移植合併症治療法の開発
開発課題名：
（英　語）Patients registration in Tokai area, reassessment of the items for evaluation, and development of new treatment for the transplantation related complications

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分担研究　（日本語）患者登録（中四国地区統括）および造血幹細胞移植ガイドラインの評価検討
開発課題名：
（英　語）Patients registration in Chugoku-Shikoku area, and evaluation of the guideline for hematopoietic stem cell transplantation

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分担研究　（日本語）患者登録（北海道地区統括）および造血幹細胞移植前処置の問題点とその対策
開発課題名：
（英　語）Patients registration in Hokkaido area, and analysis of problems regarding conditioning regimen for hematopoietic stem cell transplantation

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分担研究　（日本語）患者登録（関東、東北中部地区統括）および移植データ解析、新たな移植合併症診断・治療法の開発
開発課題名：
（英　語）Patients registration in Kanto, Tohoku, and Chubu area, analysis of the database, and development of new diagnostic and therapeutic methods for the complications of hematopoietic stem cell transplantation

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分担研究　　（日本語）患者登録（東北地区統括）および移植前処置プロトコールの検討
開発課題名：　（英　語）Patients registration in Tohoku area, and analysis of problems regarding conditioning regimen for hematopoietic stem cell transplantation

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II.　成果の概要（総括研究報告）

・　研究開発代表者による報告の場合

原発性免疫不全症は稀な疾患であり、300 種類以上の疾患が含まれ、それぞれの疾患が比較的稀であり、病態が異なっている。重症の免疫不全状態がある場合や悪性疾患等の重症疾患を合併しやすい場合には造血幹細胞移植が適応となるが、原発性免疫不全症では移植前の免疫不全の種類や状態によって、病原体による感染症の早期診断及び治療、造血幹細胞移植のタイミングや移植すべき年齢、前処置やドナーの選択など困難な問題が多い。各々の疾患病態に応じた最適な造血幹細胞移植法を確立し、患者の長期的な QOL を向上させるため、本研究を行った。

2013 年 1 月 1 日から 2014 年 6 月 30 日までの期間（1 年 6 か月）における専門施設での移植症例を解析したところ、1 年 6 か月間での移植症例は、国内で 37 名であり、再移植を含めると 41 回の造血幹細胞移植が行われていた。これに加えて日本造血細胞移植学会の TRUMP を活用した解析を進めた。原発性免疫不全症に対する造血幹細胞移植数は増加傾向にあり、近年新たに同定された免疫不全症である活性化 PI3KD 症候群や MonoMac 症候群、IL-10 受容体欠損症などに対しても造血幹細胞移植が行われている。MonoMac 症候群で難治性抗酸菌感染症を抱えながら造血幹細胞移植を施行した結果、免疫不全状態の改善を得ることができ、さらに抗酸菌感染症を治癒させることが可能であることが新たにわかった。食細胞異常症では、慢性肉芽腫症に対する造血幹細胞移植が最も多いが、重症先天性好中球減少症に対する移植例も増加してきている。ただし、生着不全およびキメリズムが不十分である例があり、ブスルファンを用いた移植前処置が海外から報告され、今後この方法を用いた移植が増加していくものと考えられる。Wiskott-Aldrich 症候群については、完全キメラの達成が極めて重要であることが確認された。また、X-linked thrombocytopenia でも造血幹細胞移植を受けた患者の方が、QOL が良く、長期生存可能であることがわかった。

移植プロトコールについては、T-B+NK+重症複合免疫不全症の移植方法に重要な示唆をあたえるデータを得ることができた。この疾患では、移植前処置なしで移植した場合、細胞性免疫能の獲得が不十分であることが判明した。移植前処置としては、他の重症複合免疫不全症での移植前処置を適応可能であると判断している。また、放射線感受性を有する原発性免疫不全症については、造血幹細胞移植法を作成し、実際に造血幹細胞移植を施行した。EDA-ID、XLP などの他の疾患における移植前処置法を中心とした造血幹細胞移植法について

も、研究を継続している。HLA 一致ドナーが得られない患者に対する移植法として、T 細胞除去法や post transplant CY についても検討を行った。

移植後の免疫能に関しては、移植後の各細胞集団におけるキメリズム解析を、HLA フロー法を用いた解析を行った。疾患遺伝子変異特異的プライマーを用いた droplet digital PCR 法によるキメリズム解析方法について検討し、有用性を確認した。

ブスルファンの投与量の決定には、試験投与後に血中濃度を測定する必要があり、測定解析可能な施設が限られていた。依頼先での測定後に移植施設で統計学的解析を行うことで投与量を設定可能であることがわかり、実際にこの方法を用いた移植例が増加している。各移植施設で血中濃度が測定できるようにすることが今後必要である。移植前処置で用いる抗胸腺細胞グロブリンの至適投与量について、血中濃度を測定し、移植後の EB ウイルス感染症の発症リスクを考慮した至適投与量を設定することができた。

GVHD 治療として非自己の間葉系幹細胞が保険収載されたが、本研究では、自己の間葉系幹細胞を樹立し、GVHD 治療に使用する方法が有効であることを明らかにした。移植後の感染症のモニタリングとして、新たにデジタル PCR によるサイトメガロウイルス検出系およびヘルペスマルチプレックス PCR 法を確立した。10 color FACS、TREC、KREC を用いた免疫再構築評価により、制御性Ｔ細胞、Ｂ細胞の再構築の不良が、重症腸管炎症性 GVHD に繋がっていることを示した。遺伝子修復研究では、Helper-dependent adenovirus/adeno-associated virus (AAV) hybrid vector を用いた homologous recombination による CD34 陽性造血幹細胞を対象とした遺伝子修復が可能であることを明らかにした。ただし、この方法では遺伝子導入効率が低く、これを改善させるために、Crispr/Cas9 システムを用いた研究へ展開した。この方法を用いることにより、遺伝子度入効率を向上させることに成功した。

本研究での成果を基に、各疾患の病態を考慮し、議論した結果、最終的に 11 疾患で造血幹細胞移植ガイドラインを作成し公開した。（http://pidj.rcai.riken.jp/medical_guideline.html）

Primary immunodeficiency (PID) is a syndrome characterized by increased susceptibility to infection. It is composed of more than 300 rare diseases with different clinical manifestations and severity. Hematopoietic stem cell transplantation （ HSCT ） is necessary for patients with uncontrollable severe infections and possible complications such as malignant diseases or intractable autoimmune diseases. Before HSCT, patients' condition should be managed by appropriate treatment and prophylaxis against infections and other complications according to the pathophysiology of each disease. In addition, the timing of HSCT, the type of conditioning and selection of donor for each PID are difficult problems to be solved. This study was conducted to establish the optimal methods for HSCT, which leads to improve survival and QOL of the patients.

We first investigated the results of HSCT during Jan 1, 2013 and June 30 2014. Thirty seven patients received HSCT. In addition, we used TRUMP data from the Japan Society for Hematopoietic Cell Transplantation and collected data from each institute of the member of this study. The number of PID patients who received HSCT has been increasing and the overall survival after HSCT has been improving. Also, we found that the number of HSCT for patients with recently identified PID, such as activated PI3Kδ syndrome, MonoMac syndrome and IL-10 receptor deficiency has been increasing. HSCT led to cure of MonoMac syndrome and uncontrollable mycobacterial infections and hemophagocytic lymphohistiocytosis which accompanied with the PID. Although patients with chronic granulomatous disease were transplanted most often among the phagocytic disorders of PID

category, the opportunity of HSCT in patients with severe congenital neutropenia patients was increasing. On the other hand, there was significant number of patients with phagocytic disorders showing low chimerism after HSCT. More myeloablative regimen might be recommended in these patients to overcome it. For Wiskott-Aldrich syndrome patients, complete chimerism after HSCT was found to be necessary to avoid the development of malignant diseases and autoimmune disorders. We found that patients with X-linked thrombocytopenia had better QOL after HSCT compared with those without HSCT.

In patients with T-B+NK+ severe combined immunodeficiency (SCID), T cell reconstitution was not sufficient without conditioning. Therefore, conditioning chemotherapy is recommended as patients with X-linked SCID, if possible. For patients with radio-sensitive SCID, more reduced intensity conditioning might be useful. For EDA-ID, XLP or other PID, we collected useful information regarding HSCT and discussed about the indication and problems with it. In patients who had no HLA-matched donors, we performed T-cell depleted HSCT or HSCT with post-transplant cyclophosphamide regimen.

We performed immunological and chimerism analysis after HSCT. We found that HLA-flow and droplet digital PCR is useful in assessing the chimerism in each cellular population.

By measuring serum concentration of busulfan after its pilot administration, it can be used at safely and effectively by adjusting the dose in chemotherapy conditioning. This target busulfan should be applied as regular method in near future. Anti-thymocyteglobulin (ATG) is often used in conditioning regimen. On the other hand, the optimal dose of ATG has not been clarified. We investigated correlation between ATG concentration and the incidence of development of EB virus infection after HSCT. We found that the lower dose of ATG did not decrease the incidence of EB virus infection, but correlated with higher incidence of severe GVHD. Therefore, the reduced dose of ATG is not recommended.

Allogenic mesenchymal stem cells are recently used against severe GVHD. On the other hand, the effectiveness of autologous mesenchymal stem cells against GVHD has not been clarified. We established a system to establish autologous mesenchymal stem cells and found that they were effective against severe GVHD.

We found that multiplex PCR applying droplet digital PCR method was useful to detect cytomegalovirus and herpes virus at very early stage of infection after HSCT. Ten color FACS、TREC、KREC were found to be useful to evaluate immunological state after HSCT. By using these methods, we found a correlation between insufficient immunological reconstitution after HSCT and the development of severe intestinal GVHD. We established new gene repair system using helper-dependent adenovirus/adeno-associated virus hybrid vector and Crispr/Cas9, which could effectively and specifically lead to the targeted homologous recombination.

We made a guideline for hematopoietic stem cell transplantation for patients with primary immunodeficiency regarding 11 diseases and published on the web.

（http://pidj.rcai.riken.jp/medical_guideline.html）

III. 成果の外部への発表

（１）学会誌・雑誌等における論文一覧（国内誌　1　　件、国際誌　　54　件）

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（3）「国民との科学・技術対話社会」に対する取り組み

1. 移植ガイドラインの追加掲載，今井耕輔，PIDJ ホームページ 2015/，国内.
2. 患者相談会，野々山恵章，日本免疫不全症研究会，2016/1/23，国内.
3. 患者相談会，高田英俊，九州地区免疫不全症研究会，2016/7/2，国内.
4. 原発性免疫不全症に対する造血幹細胞移植ガイドライン，高田英俊，野々山恵章，平家俊男，小島勢二，村松秀城，小林正夫，有賀 正，今井耕輔，笹原洋二，金兼弘和，石村匡崇．PIDJ ホームページ 2017/ ，国内.

（様式１０）

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平成２８年度医療研究開発推進事業費補助金

（免疫アレルギー疾患等実用化研究事業）成果報告書

平成２８年４月１日付け≪27 医研開 4004 号≫で交付決定のありました平成２８年度医療研究開発推進事業費補助金（免疫アレルギー疾患等実用化研究事業）の平成２８年度における成果について、医療研究開発推進事業費補助金（研究者用）取扱要領第１８条第１項の規定により、下記のとおり報告します。

I.　基本情報

事　業　名：　（日本語）免疫アレルギー疾患等実用化研究事業（移植医療技術開発研究分野）
（英　語）Practical Research Project for Allergic Diseases and Immunology (Research on Technology of Medical Transplantation)

補助事業課題名：　（日本語）原発性免疫不全症に対する造血幹細胞移植法の確立
（英　語）Study for optimal hematopoietic stem cell transplantation procedures for primary immunodeficiency

補助事業担当者　（日本語）防衛医科大学校・教授・野々山恵章
所属 役職 氏名：　（英　語）National Defense Medical College・Professor・Shigeaki Nonoyama

実　施　期　間：　平成 28 年 4 月 1 日　～　平成 29 年 3 月 31 日

分担研究　（日本語）患者登録（関東地区統括、PIDJ とのデータベース照合）および移植ガ
分担課題名：　イドライン作成、新たな移植合併症診断法の開発
（英　語）Patients registration (collation with PIDJ in Kanto area) , establishment of transplantation guidelines, and development of new diagnostic methods for the transplantation related complications.

補助事業分担者　（日本語）防衛医科大学校・教授・野々山恵章
所属 役職 氏名：　（英　語）National Defense Medical College・Professor・Shigeaki Nonoyama

II. 成果の概要（総括研究報告）

研究開発代表者：九州大学大学院医学研究院・高田英俊　総括研究報告を参照。

III. 成果の外部への発表

（1） 学会誌・雑誌等における論文一覧（国内誌　0　件、国際誌　3　件）

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（2） 学会・シンポジウム等における口頭・ポスター発表

1. Kanako Mitsui-Sekinaka, Kohsuke Imai, Satoshi Okada, and Shigeaki Nonoyama. Activated PI3 Kinase Delta Syndrome (APDS)-like immunodeficiency caused by PTEN mutation. ポスター発表, 17th Biennial Meeting of the European Society for Immunodeficiencies (ESID 2016), 2016/9/22-23, 国外.
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（3）「国民との科学・技術対話社会」に対する取り組み

1. 患者相談会，日本免疫不全症研究会（東京），2017/1, 国内
2. 移植ガイドラインの掲載，PIDJ ホームページ，2016/9, 国内

（4）特許出願

特になし。