（様式 10）

【16am0101021j0005】
平成 29 年 5 月 29 日

平成28年度医療研究開発推進事業費補助金
（創薬等ライフサイエンス研究支援基盤事業）補助事業成果報告書

I. 基本情報

事　業　名：創薬等ライフサイエンス研究支援基盤事業（創薬等支援技術基盤プラットフォーム事業）
Platform Project for Supporting Drug Discovery and Life Science Research
(Platform for Drug discovery, Informatics, and Structural life science)

補助事業課題名：（日本語）動物細胞発現系を用いた高難度タンパク質生産支援と、糖鎖工学・抗体工学を用いたその高度化（高付加価値抗体作製と糖鎖細胞工学）
（英　語）High-throughput recombinant production of glycoproteins and their binders using mammalian expression system (Production of high-level antibody and glycan-cell engineering)

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

II. 成果の概要（総括研究報告）

本課題では、創薬等に重要なタンパク質の構造機能解析を飛躍的に加速するために、ヒトタンパク質などの困難なターゲットの発現精製を動物細胞発現系を利用して生産するパイプラインを構築・提供し、高度な発現精製技術の共有とさらなる技術革新によるソリューションを確立するとともに、新規高付加価値分子の創成、試料評価法の改善、糖タンパク質生産用細胞株の樹立などを通して将来のさらなる汎用化、共有化、および高難度ターゲットの構造解析や医薬開発に大きく寄与する新規技術を開発し、「支援」と「高度化」をすることを目的とした。

支援については、平成 25 年度までに、当初予定の支援業務項目において依頼に応えられる体制の整備をすべてで完了した。平成 28 年度までに、19 件の支援課題を担当し、予定通

りにすべて終了した。正式支援終了後も、平成 28 年度末までに自主的支援を合計 9 件行った。特に、最も得意とする抗体改変技術を用いて、支援依頼者が数十年間解決できなかった課題に短期間に応えることができた。また、1,000 mg を超える抗体を培養・精製する支援も複数実施した。高難度抗体作製支援案件についても、新規抗体を複数樹立した。抗体作製支援においては、複数の重要なステップがある。まず、各支援案件についてのコンサルティングを実施するが、メールや電話だけでなく、実際に研究室を訪問した。各施設において、抗体作製に関するセミナーを行った他、依頼案件に関する詳細な打ち合せを実施した。困難な案件に関しては、途中で追加の打ち合せを行い、終了時に今後の方針について議論も行った。しかしながら、支援依頼者から提供して頂いた抗原に対して、全く抗体価が上がらない案件もあり、モノクローナル抗体樹立まで至らなかった案件も 2 例経験した。そのような案件に対しても、単なる失敗ということで終了とせず、今後の抗体作製のために必要な抗原作製法のアドバイスを継続して実施した。

高度化については、東北大学が作製したオリジナル性の高い PA タグシステムが、代表機関と分担機関の高度な連携によって極めて優れたシステムとして完成した。この成果は、論文や学会で発表しただけでなく、複数の支援案件に活用した。さらに、平成 26 年度に PA タグを企業導出し、支援を通さなくても PA タグを利用できるようになった。また、平成 28 年度後半には、PA タグに対する抗体（NZ-1）などを抗体バンクとして管理し、引き続き支援ができる体制を構築した。新規高付加価値バインダーの創成においては、東北大学の独自技術としてがん特異的抗体（CasMab）を作製する CasMab 法を開発した。CasMab 法を用いることにより、がん細胞と正常細胞に同じ膜タンパク質が発現していても、がん細胞に特異的な抗体を作製することが可能となった。ポドプラニンなどのムチン型膜タンパク質に対して CasMab を作製し、複数の論文で発表した。すでに、CasMab 法を用いた抗体作製のコンサルティングを開始している。我が国独自の「糖鎖均一化発現細胞」の樹立については、当初はノックダウンの系により実施することを検討していたが、事業開始後、効率の良い TALEN の系を導入することに成功し、予想以上に早く GnT1 ノックアウト細胞株の樹立に成功した。その後、CRISPR/Cas9 によるノックアウト技術も導入し、当初計画よりも効率的に糖鎖均一化発現細胞の作製に成功した。合計 30 種類以上のノックアウト細胞を樹立し、細胞バンクを東北大学に設置した。

Until 2013, we developed the supporting system for antibody production. Until 2016, we officially supported 19 projects and successfully finished them. Additionally, we supported 9 projects by ourselves in 2016. Using our original antibody-engineering and antibody-producing techniques, we helped many researchers to accomplish their projects.

There are many important steps for antibody production. At first, we visited the researchers and discussed in details before starting experiments. Although we tried our best to produce monoclonal antibodies against membrane proteins such as GPCR, we could not always develop high-quality antibodies. However, we continued to support those researchers to solve the problems together. Sometimes, we produced more than 1,000 mg of monoclonal antibodies (mAbs) for clinical study.

In this project, we developed a novel affinity tag system designated as the PA tag system. This system is composed of a rat anti-human podoplanin monoclonal antibody (mAb; clone NZ-1) and PA tag derived from the platelet aggregation-stimulating (PLAG) domain of human podoplanin. NZ-1 possesses high affinity and specificity for the PA tag, and the NZ-1/PA tag complex dissociates in the presence of the epitope peptide, indicating that the PA tag system is suitable for protein purification. We successfully purified many proteins, including soluble proteins and membrane proteins using the PA tag system. The PA tag system is very useful not only for protein purification but also for protein detection systems such as Western blot and flow cytometric analyses. We developed "Antibody Bank" in Tohoku University, and will continue to provide researchers with PA tag system.

We recently established a novel method to produce cancer-specific mAb (CasMab). The CasMab method is the platform to develop mAbs, which could attack only cancer cells. This method is useful for not only producing CasMabs against novel targets but also replace the existing mAbs into the side effect-free ones. We can try to develop antibody drugs again against many targets, which were excluded from antibody-drug candidates.

We produced many glycan-deficient cell lines using CRISPR/Cas9 system. For example, GnT1-knockout cell lines of HEK-293T are very useful for the production of glycan-homogenous proteins, which can lead to the successful analysis of protein structure. We could produce more than 30 cell lines, and developed "Cell Bank" in Tohoku University.

III. 成果の外部への発表

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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

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