【Grant-in-Aid for Scientific Research (S)】

Science and Engineering (Engineering)

# Title of Project : Integrated platform for mammalian cell-based cell and bioprocess engineering

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Research Area : Process engineering, Biochemical engineering
Keyword : Biopharmaceutical, mammalian cell engineering

## 【Purpose and Background of the Research】

Mammalian cell lines are important host cells for the industrial production of pharmaceutical proteins owing to their capacity for correct folding, assembly and post-translational modification. In particular, Chinese hamster ovary (CHO) cells are the most dependable host cells for the industrial production of therapeutic proteins, such as therapeutic antibodies. Growing demand for therapeutic proteins is promoting the development of technologies to increase the productivity and output quality of CHO expression systems. Ideally, a CHO expression system should exceed g/L levels of production, whilst minimizing cell culture costs. To achieve this, the cultivation of CHO cells requires optimization. In this proposal, we focus on the genomic instability of CHO cells and analyze the instability/heterogeneity of the CHO chromosomes (genome). In particular, we aim to: (1) construct a genomic cell engineering system, (2) analyze the log-term and/or continuous bioprocess involved, and (3) construct an integrated platform for CHO cell-based cell and cell culture engineering.

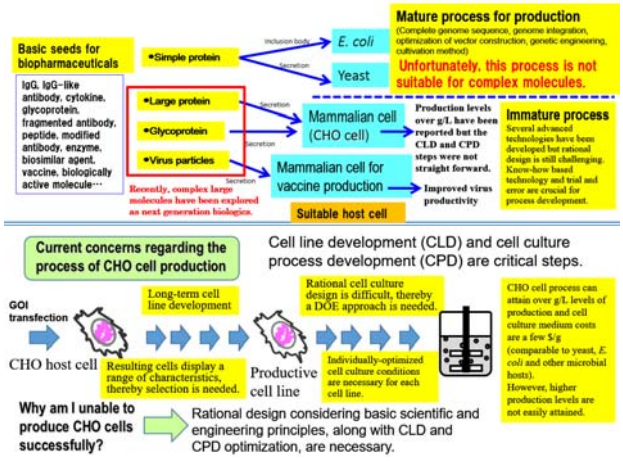


Figure 1 CHO bioprocess for biopharmaceutical production

## 【Research Methods】

The methodology applied in this study can be divided into three sections: (1) cell engineering using target-integration into CHO chromosomes to establish genome-scale cell engineering, (2) construction of an advanced bioprocess on the basis of stability and heterogeneity analysis of the CHO cell genome under log-term and/or continuous operation, and (3) integration between cell engineering and the advanced bioprocess to construct platform technology for CHO cell-based cell and cell culture engineering.

## 【Expected Research Achievements and Scientific Significance】

The genome sequence of CHO cells has been published; however, the instability of the CHO genome means that these sequence data are not always accurate or applicable. Therefore, to construct an integrated platform, we developed a strategy of advanced cell and bioprocess engineering, as illustrated in Figure 1.

## 【Publications Relevant to the Project】

Noriko Yamano, Mai Takahashi, Seyed Mohammad Ali Haghparast, Masayoshi Onitsuka, Toshitaka Kumamoto, Jana Frank, and Takeshi Omasa "Increased recombinant protein production owing to expanded opportunities for vector integration in high chromosome number Chinese hamster ovary cells" Journal of Bioscience and Bioengineering, **122**(2):226-231 (2016).

Yihua Cao, Shuichi Kimura, Takayuki Itoi, Kohsuke Honda, Hisao Ohtake, and Takeshi Omasa "Construction of BAC-based physical map and analysis of chromosome rearrangement in Chinese hamster ovary cell lines" Biotechnology and Bioengineering, **109**(6):1357-1367 (2012).

【Term of Project】 FY2017-2021
【Budget Allocation】 118,400 Thousand Yen

## 【Homepage Address and Other Contact Information】

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