3rd International Conference on Influenza and Zoonotic Diseases August 21-22, 2017 Birmingham, UK- C1: How the C1 platform will change the production approach for recombinant vaccines

Ronen Tchelet
Dyadic Inc., USA

Abstract

For over 30 years Dyadic has proven itself, commercially and scientifically, as a high quality and highly productive producer of enzymes and proteins using a proprietary and patented expression system based on the Myceliophthora thermophila fungus, nicknamed C1. The C1 platform technology is a hyper-productive fungal expression system used to develop and manufacture large quantities of desired proteins at industrial scale at significantly lower CapEx and OpEx costs. Since the successful sale of Dyadic industrial biotech business to DuPont for US$75 million on December 31, 2015, we have been focused on applying the C1 technology platform to help enhance the development and manufacturing of biologic vaccines and drugs. We achieved encouraging results; knowledge and experience in vaccine development from our prior research collaboration with Sanofi Pasteur that we believe can be leveraged and built upon with other partners. During the collaboration, meaningful improvements were made to the C1 expression system to produce antigens of interest at high level with potentially better immune response. Dyadic is one of a consortium of companies participating in the EU sponsored ZAPI research program. ZAPI is a program sponsored by the EU suitable for the rapid development and production of vaccines and protocols to fast-track registration of developed products to combat epidemic Zoonotic diseases that have the potential to affect the human population. Insight on the development of antigens by C1 will be presented. Dyadic has also displayed the ability to easily express mAb's. The C1 expression system Dyadic's C1 technology has the potential to change the way in which both animal health and human biotech and pharmaceutical companies bring their biologic vaccines and drugs to market faster, in greater volumes, at lower cost, and with newer beneficial properties, and most importantly save lives. Dyadic believes that our current efforts, with or without potential partners, to successfully express several therapeutic proteins, will validate the C1 technology as one of the vital production platforms for developing and manufacturing biologic vaccines and biopharmaceuticals..

Introduction

During the past few decades, the technology and techniques of recombinant protein expression have been based largely on molecular engineering concepts associated with fundamental aspects of microbiology and cellular biology. One of the major drivers of expression system development has been the ever-increasing demand for large quantities of recombinant monoclonal antibodies, mostly for use in cancer therapy, and the need to produce highly purified and well-defined vaccines against infectious agents, which are sometimes composed exclusively of recombinant viral or bacterial proteins. In parallel with this, molecular biology techniques have gained in sophistication and ease of use, allowing the exploration of novel expression systems. Today, in addition to efficiency, productivity and cost-effectiveness, safety considerations are increasingly demanding, leading to new, stronger regulatory standards in production quality and control, such as the use of alternatives to the traditional antibiotic-based selection system.

In the continuously moving field of expression systems, 2 developmental directions should be considered: the rational re-engineering of existing systems and the identification of completely alternative hosts (a strategy which does not, in itself, exclude engineering steps). In the case of re-engineering, the impact of multi-omics or a system-based biological approach may improve the quality of the expressed protein, such as creating a molecule with a better glycosylation profile. In terms of productivity, considering that the physiological limits of any given system cannot be pushed indefinitely, the solution is more likely to come from new hosts with a naturally extended capacity for very high protein production and secretion. In an ideal situation, these alternative hosts would have a fast doubling time, grow in simple and inexpensive media, and be compatible with linear scale-up, creating the capacity for very large production volumes of secreted protein that is easy to purify and with a molecular structure as close as possible to the natural protein.

Mammalian cell lines: Still in pole position?

Mammalian cell lines are used to manufacture diverse immuno- and biotherapeutic molecules, due to their high and robust productivity of secreted proteins in serum-free medium, and their ability to perform complex post-transcriptional modifications.3 It is also possible for mammalian

cell lines to be used for the production of viral vaccines, for example PER.C6, Vero, CAP, AGE1.CR and EB66,4 but we will focus on 2 commonly used cell lines, the Chinese Hamster Ovary (CHO) and the Human Embryonic Kidney 293 (HEK293) cell lines. Recently these have been stably transfected in order to extend, and possibly to increase, the production of recombinant proteins, and therefore become "non-conventional" expression systems.

Ciliate tetrahymena thermophila: A multi-faceted organism

The sustained and increasing demand for new recombinant proteins has driven interest in alternative and "non-conventional" expression hosts, such as Leishmania tarentolae or Tetrahymena thermophila. The rationale for investigating such concepts is the need for high productivity at an affordable cost, although there may be major regulatory issues associated with these new hosts.

Concluding remarks and perspectives

While expression systems for the production of next generation vaccine proteins and immunotherapeutic molecules are reaching maturity, this does not exclude the possibility of breakthrough innovations in the future. This dynamic field of investigation is continuously challenged by the need for rapid, efficient, robust, safe and cost-effective solutions to fulfill an ever-increasing demand, although the quest for an ideal and universal host vector combination is likely to be endless, and every protein is unique, and would require a dedicated strategy ensuring its optimal expression and biological activity.

The prominent impact of multi-omic approaches and molecular engineering techniques allowing direct intervention in the genome of expression hosts will allow fine-tuning of existing systems, allowing their full potential to be exploited. In parallel, the development of cell-free synthesis on a larger scale, with reliable incorporation of non-natural chemical structures, will open the pathway toward new options to address urgent medical needs.

Note: This work is partially presented at 3rd International Conference on Influenza and Zoonotic Diseases C1: How the C1 platform will change the production approach for recombinant vaccines on August 21-22, 2017.