Design and Engineering of Trastuzumab emtansine production plant

Part I: Introduction to T-DM1 production process and Upstream of monoclonal antibody Trastuzumab


ABSTRACT
Breast cancer is the most common cancer among women following skin cancer. Specifically, HER2 overexpressing tumours reveal a particularly poor prognosis. For this reason, the aim of this project is to simulate an industrial plant for the production of the antibody drug conjugate Trastuzumab emtansine (T-DM1) which has resulted to be a successful therapy for this type of breast cancer. T-DM1 is composed by a monoclonal antibody (Trastuzumab) produced in CHO DG44 cells and a cytotoxic drug (DM1) produced in Actinomycine pretisium. Therefore, two parallel processes have been designed to produce these two components followed by a mixing step. All simulations have been done using SuperPro Designer®. This part is focused on the T-DM1’s mechanism of action, the annual amount production of the plant, the block diagram and the upstream process of Trastuzumab which includes the genetic engineering as well as the clone selection and the scale-up.

INTRODUCTION

Antibody Drug Conjugates (ADC) are potent biopharmaceutical drugs that combine the selectivity of targeted treatments with the cytotoxic potential of chemotherapy drugs. In this case we design the production plant of Trastuzumab emtansine for the treatment of breast cancer HER2+ cells. This ADC is composed by:

- A highly selective monoclonal antibody (mAb) for a tumour-associated antigen → TRASTUZUMAB
- A potent cytotoxic agent designed to induce mitotic arrest → DM1
- A LINKER stable in circulation that releases the cytotoxic agent in target cells

The objective is to treat the population from Europe and USA. Every year 6.25 × 10^9 new cases are diagnosed, from which the 25% that overexpress HER2 receptor can be treated with this therapy. An average of 3.5 DM1 molecules are bound to 1 molecule of Trastuzumab.

BIOCATALYST: Why CHO cells?

- 1 Able to fold and secrete immunoglobulines.
- 2 Glycosylation pattern similar to humans.
- 3 Adaptable to growing in suspension culture.
- 4 Adaptable to growing in chemically defined and serum-free media.

VECTOR CONSTRUCTION:

TRICISTRONIC VECTOR
- Light chain (LC)
- Heavy chain (HC)
- Internal Ribosome Entry Site (IRES)
- DHFR (polyA)
- Polyadenylation (polyA tail)

Components:
- CHO-DG44
- Deficient in DHFR used as selection marker

SCALE-UP

- The inoculum cell density of all seed train steps was 0.2 × 10^6 cells/mL.
- For animal cells, the transfer volume needs to be minimum 10% of the following equipment and each step has a duration of 3 days.
- Total time = 15 days

REFERENCES