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Teaser This review describes the underlying principles, challenges and opportunities in the provision of high-quality cell banks to drive research in drug discovery programmes and the wider scientific community.

Cell banking for pharmaceutical research

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The provision of high-quality eukaryotic cells through robust cell banking processes is essential for the progression of drug discovery projects throughout the pharmaceutical research process. Numerous models exist to meet this aim, and this review describes many of the underlying principles, challenges and opportunities as well as detailing how these have been addressed within AstraZeneca. Crucial aspects discussed include cell line acquisition, cell bank generation, cryopreservation, storage, tracking and distribution. Because quality assurance underpins much of the process, quality control (QC) testing including mycoplasma screening and cell line authentication are also discussed in detail. Furthermore, because many of the underlying principles of cell banking are applicable in non-pharmaceutical settings, it is hoped that this review will prove a useful resource across the wider scientific community.

Jonathan Wrigley is Associate Director of the Cell Reagents & Assay Development group within Discovery Sciences at AstraZeneca, Alderley Park. The group is responsible for the provision of cells, cellular reagents and development of cellular assays for a wide range of therapeutic areas, and one of Jonathan's roles is to lead the AstraZeneca Global Cell Bank. Previously, Jonathan obtained a BSc in Biochemistry and Molecular Biology from the University of Leeds, and subsequently continued his studies there, obtaining a PhD on the biochemical characterisation of retinal degeneration. In 2000, Jonathan joined Merck, Sharp and Dohme, working at the Neuroscience Research Centre in Harlow, during which time he published work on the characterisation and targeting of gamma-secretase for Alzheimer's disease. In 2006 Jonathan joined AstraZeneca, initially leading a team in oncology lead generation and later in the assay sciences group, before moving into his current role in 2011.

Introduction

Eukaryotic cell lines lie at the heart of most drug discovery projects, having a wide range of impacts throughout project progression from initial target validation studies through to clinical candidate selection and subsequent translational studies [1]. They form an essential part of most assay cascades, being key components in primary screens and cellular high throughput screening (HTS) campaigns, phenotypic screens and downstream cellular assays for determining the safety profile and structure-activity relationship (SAR) of lead molecules. This is in addition to their use in bespoke target and compound profiling experiments, mechanism of action studies, safety screening and the generation of engineered cellular systems and cellular reagents. Furthermore, high-quality cells are essential for a range of *in vivo* studies, such as xenograft models which provide a key bridge between *in vitro* studies and the clinical setting.

Owing to their widespread use and impact, it is essential for project scientists to have rapid access to high-quality, well-characterised banks from a wide range of mammalian cell lines. Robust processes need to be put in place that not only meet this aim but also minimise potential

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risks, such as depletion of cell stocks, cross-contamination of cell lines and infection by adventitious agents. When assessed across the global scientific community, the scale of the potential impact of these issues becomes obvious, with 18–36% of cell lines being reported as misidentified or contaminated [2–4], and quality control (QC) testing companies reporting mycoplasma infection rates of around 8% of total samples tested (IDEXX-RADIL data; http://www.idexxbioresearch.com/). Failure to address these issues can have serious impacts on the drug discovery process from the postponement of experiments and interruptions in assay data delivery and the resulting impact on project timelines through to the potential for de-validation of studies as a result of cellular contamination or misidentification [5].

The cell banking process aims to meet these needs through the provision of reliable stocks of cells that can be utilised in a wide variety of research settings. It is therefore important to address considerations, such as the appropriate sourcing of cell lines, best practice for cell culture and optimal cryopreservation methodologies, as well as the supporting infrastructure for robust storage, distribution and data tracking. Together these should ensure optimal cell quality, which is crucial to the entire process and, as such, needs to be appropriately monitored throughout. It is also important to drive towards standardising cell culture best practice, such that cells show consistent performance and responses, irrespective of their location, source and history. Although these fundamental principles need to be maintained, numerous options exist throughout the cell banking process, and this review will discuss many of these alternatives, in addition to describing the model that has been employed within AstraZeneca (AZ).

Cell banking model

The most basic model of cell banking that can be employed involves the acquisition, storage and use of cell lines by individual research groups. Although this offers the advantage of being the simplest model for individual scientists, it generally results in variations in cells and processes between groups, often yielding differing cell quality, and does little to enable widespread access to cell lines throughout the wider organisation. Thus, although the same cell line can be held by different groups within an organisation, it could have been sourced from different suppliers, grown under different culture conditions, with different reagents, from different passage numbers, frozen using different methods and, in some cases, could have become infected with mycoplasma or even a second cell line. Thus, although two groups can hold the same cell line, there could be significant phenotypic differences, making it very hard to compare data between laboratories and potentially resulting in an inability to reproduce data.

An alternative approach is to manage the provision of cells within a research organisation through a centralised capability that is responsible for the acquisition, growth, storage and distribution of cells. This model offers significant advantages in that processes can be standardised such that all cell stocks within the organisation are handled in the same way and to the same quality standards. Additionally, although restrictions on the use and distribution of cells might need to be implemented for some lines, in general the use of central storage facilities with supporting IT infrastructure maximises the access of cellular assets to scientists across the company. Duplication of purchasing and effort is avoided, with associated cost and resource savings; and, because numerous groups can utilise a single bank of cells, data comparison between functions and drug discovery stages should be more consistent. Although such a global model offers benefits as described, it does raise numerous logistical challenges. Within large organisations, the model can often involve large numbers of cell lines and users (often across multiple sites), and as such it is essential to have robust stock management, sample tracking and logistical processes in place.

Such a centralised model has been employed within AZ, whereby the provision of cryopreserved cells is coordinated, as demonstrated in Fig. 1. The Global Cell Bank (GCB) at Alderley Park is responsible for all aspects of cell banking, beginning with acquisition of cell lines from numerous sources and the subsequent generation of a range of cell banks for use by scientists. Rigorous QC testing is performed on all cell banks and, alongside central storage repositories at each site, a single global database holds all the associated cellular metadata, allowing users to view, search and request cell supplies. The final piece in the process is the distribution of cells to scientists locally and, where applicable, globally. In addition to the GCB, local cell banks are based at other AZ sites (Mölndal, Boston and Shanghai), although differing stocks can be held at each site, owing to distribution restrictions on externally sourced cell lines. Importantly, the network of scientists at these banks forms a community for sharing of best practice and learning, to ensure consistency in all aspects of cell banking across the company.

Cell line collections and acquisition

In general, the cell banking process is initiated when a scientist identifies a cell line that is required for use in a specific research study. The first step is for the scientist to access reliable records to determine whether the cell line is already held within the research group or organisation, or needs to be acquired and/or generated from another source. Like most research organisations, AZ holds stock of a large number of cell lines that have been acquired over many years, from internal and external sources. Within different organisations, such collections can vary from just a few key cell lines within individual groups to much larger collections such as those held by the Sanger Institute [6] and the Cancer Cell Line Encyclopaedia initiative [7].

Typically, there is wide variation in the types of cell lines held within a collection, including immortalised cell lines that have not undergone any further genetic engineering, stable cell lines expressing a gene of interest, transiently transfected cells and other cell types such as hybridomas and primary or stem cells. Within AZ approximately 6000 cell lines are held internally, covering a very wide range of cell types and representing a significant biological asset for scientists to utilise. Holding such a centralised collection in conjunction with a means of interrogating a database of the internally held samples enables individual scientists to gain very rapid access to a large number of cell lines. However, even with large collections, owing to the continually evolving nature of research, the library of cell lines held within collections never remains static and new lines are continually required and subsequently being added.

New cell lines can be acquired from a range of sources, depending on their origin and availability. Each year significant numbers

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