A Three-dimensional *In Vitro* Model of Breast Cancer: Toward Replacing the Need for Animal Experiments

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**Summary** — While the events leading to breast cancer development are not fully understood, a pre-invasive lesion, ductal carcinoma *in situ* (DCIS), is recognised as the main precursor of invasive disease. Understanding how pre-invasive lesions develop into invasive breast cancer is critical, since currently there is no way of predicting which tumours are likely to progress, leading to unnecessary surgical intervention or chemotherapy. With a lack of good animal models able to mimic DCIS progression in a laboratory setting, there has been a shift toward developing *in vitro* human models which more accurately represent human disease. By manipulating individual cell populations in these models, we can recapitulate the complex cellular interactions involved in disease progression, an essential step in understanding breast cancer behaviour.

**Key words**: 3-D model, breast cancer, *in vitro*, three-dimensional model.

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**Introduction**

Breast cancer progresses through a well-recognised pre-invasive form, ductal carcinoma *in situ* (DCIS), which accounts for 40% of all screen-detected cancers (1). DCIS is characterised by hyperproliferation of the tumour cells within the central lumen area of the tissue, but the myoepithelial layer and basement membrane remain predominantly intact. In invasive carcinoma, the myoepithelial cell layer is lost, and the tumour cells penetrate the basement membrane and invade into the surrounding stroma. Understanding the biology of how this happens is crucial, since, if left untreated, 25–30% of patients will go on to develop invasive carcinoma, which can lead to metastasis (2). Currently, there is no way of predicting which patients are likely to suffer from invasive cancer, which causes difficulties when deciding on treatment regimes. The patient may undergo a wide local excision, followed by chemotherapy/radiotherapy or, in some cases, a total mastectomy. For some patients, this could constitute excessive treatment, because the tumour is confined to the breast tissue and may never progress to an invasive state. With no way of predicting whether this will be the case for a particular patient, deciding on suitable treatments is complicated. With this in mind, recent work has involved the exploration of *in vitro* model systems. The aim is to understand the biology of tumour invasion, with a view to helping to predict the behaviour of individual cancers and, thus, reveal potential new targets for therapy.

**Current Models for Studying Breast Cancer**

Current models for studying DCIS include animal models or simple human cultures, usually involving one or two cell types. Xenograft models, whereby human cells are injected into the mammary fat pad or the flank of immunocompromised mice or rats, allow formation of a human tumour within the complex microenvironment of a whole organism (3, 4). Having a complex environment can also be a disadvantage, since this added complexity leads to difficulties in ascertaining whether some of the effects seen constitute a mouse response to human cells. In addition, although the lesions formed appear to resemble human DCIS, histological differences are revealed on closer inspection, and the pattern of metastasis observed is different to that seen in the human disease (5).

In transgenic models, genes of interest can be knocked-in or knocked-out, resulting in spontaneous tumour development. This allows the study of the cancer pathway, from initiation to invasion and metastasis, but it is hampered by the obvious physiological differences between humans and rodents. Of particular relevance to breast cancer are differences seen in the mammary stroma, which plays a critical role in cancer progression (6). A further restriction with animal models is the difficulty involved in manipulating the cells *in vivo*. The advantage of a human *in vitro* system is the ability to manipulate a particular cell of interest