The guidelines for using cell lines in biomedical research, published recently in BJC (Geraghty et al, 2014), include a pioneering safety warning about human-to-human cancer transmission through cancer cells, a route that we will call extracorporeal metastasis (XM). Because XM has been tacitly dismissed as implausible in everyday laboratory practice, if considered at all, we emphasise the warning by reviewing the underlying evidence and preventive measures.

Our review is not intended to suggest the possibility of XM (Box 1) as assessed previously (Murgia et al, 2006; Rebbeck et al, 2009; Belov, 2011), in which cancer is sexually transmitted (Rebbeck et al, 2009), and Tasmanian devils, in which cancer is transmitted from a patient to the surgeon who pricked his hand during surgery (Cavallo et al, 2011), it should not come as a surprise that XM happens in human tumors under particular circumstances.

The possibility of XM in humans was first tested half a century ago in experiments that now appear medieval and that involved inoculating human cancer tissues or cancer cell lines into healthy individuals or into cancer patients (Moore et al, 1957; Langer, 1964; Brunschwig et al, 1965). Most inoculants failed to survive but some persisted, metastasising into local lymph nodes or recurring after the primary tumours caused by the inoculation had been excised (Moore et al, 1957; Langer, 1964). In another experiment, a slice of melanoma transplanted from a patient into her 80-year-old mother killed the recipient 451 days later by disseminated metastases, although the initial implant was resected 21 days after the implantation and the patient was treated with chemotherapy (Scalon et al, 1965).

The implications of these now-unthinkable experiments became clear once organ transplantation became common and XM (especially by melanoma) through transplanted organs became a serious problem, as even organs free of overt cancerous tumours can still transmit cancer, apparently by harbouring disseminated or circulating cancer cells from the donor (Strauss and Thomas, 2010; Desai and Neuberger, 2014). This problem has been minimised by screening donors, but not yet eliminated (Desai and Neuberger, 2014). The risk of XM seems to apply to transplanted organs from donors who previously had cancer, at least to immunocompetent recipients (Yang et al, 2010), perhaps because cancer cells do not survive or adhere to the plastic containers during processing and storage of blood (Matsui et al, 2008; Simanovsky et al, 2008; Brennen et al, 2013).

Unfortunately, XM is not limited to immunocompromised individuals and does not require organ transplant to occur. In one reported case, a sarcoma was transmitted from a patient to the surgeon who pricked his hand during surgery (Gartner et al, 1996). The transmission was noticed and documented only because the pathologist who examined the patient’s tumour also happened to examine the surgeon’s tumour and noticed that their histopathology was remarkably similar, which prompted the investigation. A similar accident occurred in a laboratory at the National Institutes of Health (USA), where a homocentric meningitis virus transmitted to monkeys by respiratory droplets caused a meningitis-like illness in humans (Cavallo et al, 2011). A similar accident occurred in a laboratory at the National Institutes of Health (USA), where an agent transmitted from a patient to the laboratory worker who handled his tissue culture was the agent from a patient to the laboratory worker who handled his tissue culture was the agent from a patient to the laboratory worker who handled his tissue culture.

In our experience, the possibility of XM is generally unknown to laboratory researchers, as it is not reviewed during their safety training, or is dismissed as implausible. Yet, without awareness, the risk of accidental XM in the laboratory may increase in the future as more cancer cell lines are established, and the lines that are already in use continue to evolve. Thousands of human cell lines have been established over the last 50 years (Barretina et al, 2012) by exploiting cancer tissues, which, despite human cell lines, are believed to be an exception because, despite their unusual nature, the immune response is usually tested only in the studies that are concerned directly with this question.

Out of an abundance of caution, we propose two actions to minimise the risk of XM in the laboratory. First, the notion that cancer cells themselves are potential pathogens should be included into routine laboratory safety training. Second, cancer cell lines, perhaps starting with those provided commercially and bought for research, should be tested in vitro for their ability to evade immune responses in humans. The lines that show potential for immune evasion should be labelled accordingly and used with all due care.

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Barretina J, Caponigro G, Starnesky N, Venkataram K, Margolin AA, Kim S, Wilson CJ, Loughlin T, Kryukov GV, Shih YM, Shi H, Gordon B, Stojanov P, Cibulskis K, Cline TM, Dresdner G, Meehan SA, Lee C, Carloni Y, Pan D, Harshman J, Kalyana-Sundaram S, Demirer T,发现自己在前文中所提到的，我们没有意识到XM的 possibility. In this case, the XM was noticed, documented and communicated to the laboratory worker, implying that these two reported cases of transmission may be more common, but by no means extraordinarily rare in the operating room or the laboratory. These include the occurrence of XM in humans (Chung et al, 1957; Langer, 1964; Barretina et al, 2012) by exploiting cancer tissues, which, despite human cell lines, are believed to be an exception because, despite their unusual nature, the immune response is usually tested only in the studies that are concerned directly with this question.

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Comment on: 'Evaluation of chemoresponse assays as predictive markers’

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Sir,

We read with great interest the recent Short Communication by Korn and Freidlin (2015), which considers hypothetical examples challenging the ‘match/mismatch’ analysis presented in Tian et al (2014). In Tian et al (2014), we proposed and applied a novel match/mismatch analysis approach for evaluating the predictive value of a chemoresponse assay from an observational study, by investigating the assay’s association with outcome. The match analysis was performed using the assay result for the administered therapy (assayed therapy = administered chemotherapy); the mismatch analysis was performed using the assay result for a randomly selected therapy from all assayed treatments for a given patient, not necessarily matching the administered therapy (assayed therapy ≠ administered chemotherapy). If the match association is stronger than mismatch association, then the association is potentially drug specific and the assay may have predictive value. Using three examples in which a hypothetical chemoresponse assay is assumed to have only prognostic value, Korn and Freidlin (2015) have indicated that this analytical method may incorrectly conclude that the assay has predictive properties.

We agree with Korn and Freidlin (2015) that the match/mismatch method employed in Tian et al (2014) should be applied in limited circumstances and likely cannot be generalised to all chemoresponse, or more generally to all predictive biomarker assessment studies. As Korn and Freidlin (2015) point out, in situations where either (1) the treatments being considered have meaningful differences in efficacy in the unselected population or (2) specific treatment selection for a given patient is based on factors that have prognostic importance, the match/mismatch approach is inappropriate. However, we believe that neither of these cases are present in the clinical situation of recurrent ovarian cancer considered in the study by Rutherford et al (2013). Specifically, in their hypothetical examples 2 and 3, Korn and Freidlin (2015) assumed different efficacies across treatments. This is inconsistent with the clinical situation in recurrent ovarian cancer (to which the match/mismatch analysis was applied), where more than ten different drugs are recommended, but evidence from clinical trials fail to demonstrate that any one is superior to any other (National Comprehensive Cancer Network, 2014). In their hypothetical example 1, Korn and Freidlin (2015) assumed similar treatment effects for drugs A and B, but they also assumed that the patients treated by drug A were different from those treated by drug B in terms of patient prognostic profiles. In Korn and Freidlin’s (2015) example, due to differences in subpopulations (pattern of assay results and sampling fraction can also be different), the match/mismatch analysis method is indeed inappropriate. However, in the study by Tian et al (2014), 15 drugs and drug combinations were evaluated and, as such, the heterogeneous pattern of assay results across treatments was far more complex than Korn and Freidlin’s (2015) example that included two drugs. In addition, although it is possible that the treatment groups differ in prognostic profile, it is more likely, as demonstrated in clinical practice, that patients with similar prognoses have multiple therapeutic options, and there are no clear prognostic factors which dictate treatment decisions for individual patients. Taking all of these considerations together, after resampling, the likelihood that patients included in the mismatch analysis have similar prognostic profiles (on average), compared with those included in the match analysis, is quite high. Table 1 shows the comparison of patient prognostic profiles between match and mismatch analyses in the study by Tian et al (2014), demonstrating strong similarity between the two analysis groups. For the mismatch analysis used in Tian et al (2014), patients with heterogeneous patterns of in vitro response were assigned either ‘sensitivity’ (S) or ‘resistance’ (R) assay results by resampling. For match analysis, 28.6% were treated with an S drug and 71.4% were treated with an R drug, with mean multiple drug

**Table 1. Comparison of prognostic profiles between match and mismatch analyses (sensitivity vs resistance)**

|                     | Match analysis | Mismatch analysis* |
|---------------------|----------------|--------------------|
| **Sensitivity**     |                |                    |
| (28.6%)             | 0.68           | 0.10               |
| **Resistance**      |                |                    |
| (71.4%)             | 0.71           | 0.11               |
| **MDRI**            |                |                    |
| (74.8%)             |                |                    |
| Age (mean, years)   | 57.3           | 63.3               |
| ECOG PS (%)         |                |                    |
| 0                   | 68.0           | 70.6               |
| 1 or 2              | 32.0           | 29.4               |
| **Cell type (%)**   |                |                    |
| Serous              | 65.3           | 69.0               |
| Others              | 34.7           | 31.0               |
| **Tumour grade (%)**|                |                    |
| 1 or 2              | 15.9           | 23.3               |
| 3 or 4              | 84.1           | 76.7               |
| **TFI (%)**         |                |                    |
| < 6 months          | 38.7           | 47.1               |
| ≥ 6 months          | 61.3           | 52.9               |

**Abbreviations: MDRI = multiple drug response index; TFI = treatment-free interval.**

*Mismatch analysis: results representing the averages of 3000 simulations.

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