—In reply

We agree with Fidler and Kripke that primary tumor cells are genetically heterogeneous. The relationship of this heterogeneity to the metastatic phenotype, however, is unclear. Although poorly metastatic cell lines can give rise to highly metastatic progeny after *in vitro* selection and transplantation, such experiments do not prove the existence of metastatic heterogeneity *in vivo*. Our microarray-based studies in human tumors support a model in which the propensity to metastasize reflects the predominant genetic state of a primary tumor rather than the emergence of rare cells with the metastatic phenotype. Our microarray experiments are only able to detect subsets of cells comprising a significant portion of the tumor.

It is formally possible, as Fidler and Kripke suggest, that the metastasis gene-expression signature that we observed is actually a composite signature resulting from distinct subsets in the tumor, with each subset expressing a portion of the metastasis signature. This interpretation, however, would require independent clonal expansion of multiple cells in the tumor, with each cell expressing a portion of the metastasis signature. The selective advantage of such various partial metastatic phenotypes is not obvious. We therefore favor the more parsimonious explanation that the mechanism of transformation of primary tumors dictates metastatic behavior.

Our results could also be explained by the mechanism proposed by Hunter, Welch & Liu, whereby host genetic background could be important in cancer metastasis. In this regard, they refer to an analysis of our recently reported 17-gene metastasis expression signature in transgene-induced mouse tumors arising in varying genetic backgrounds. Their findings, though difficult to evaluate without full review of the data, are of substantial interest, particularly the finding that primary tumors associated with metastases largely express the conserved 17-gene expression program due to these background differences. These findings raise the possibility that genetic modifiers in humans may influence the expression of metastasis programs.

The potential presence of such modifiers has important implications but does not demand another model of metastasis. Indeed, their results are consistent with our view that metastatic behavior is established early in the pathogenesis of tumors and is reflected in the bulk of primary tumors. The extent to which the metastasis program in human tumors is governed by tumor cell intrinsic factors as opposed to host cell factors must now be determined.

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Assessing the impact of biobanks

Human biobanks are essential to genomics research[1]. Although large population collections (for example, the ones in Iceland, Estonia, Latvia, Sweden and the UK; refs. 2–4 and *Nat. Genet.* **33**, 325, 2003) have attracted the most attention, a recent European survey of 147 research institutions[5] shows that these are only part of the picture. Collections of human biological samples have been gathered over years by medical doctors and researchers, often as a side activity without a designated budget. These individuals usually manage their resources within their institutions and control who has access to it.

As biobanking activity increases, there is a trend to officially recognize and fund this activity and a need to establish formal guidelines not only for how biobanks should be maintained but also for assessing their value (see http://www1.oecd.org/publications/e-book/9301041E.pdf). Several meetings and workshops in the past two years have taken steps to establish standards for the quality of collections and the management of ethical issues, including consent procedures and protection of personal data (refs. 6–9 and see http://www.eshg.org/Banking%20background%20consult.pdf). New ethical frameworks are even being proposed[10]. An issue that still needs to be addressed is how to allow broad and free access to the samples contained in biobanks and, at the same time, protect the rights of researchers or institutions that developed the collection and allow long-term recognition of their contributions[5,11]. When a collection becomes available to new users, there is fear that the effort to establish and maintain the collection will no longer be recognized. Part of the problem is that currently there is no standardized way to quantify the degree to which a biobank is used and to link its use to the impact of the scientific discoveries that arise from it.

The ways in which use of a biobank is acknowledged in a published report vary considerably. Original biobankers may be included as co-authors on a paper[12], even if they were not intellectually or actively involved in the study, or they may be cited in the acknowledgments. Sources of samples may be cited in the Methods, or the references may include the first paper that described the resource. When giving access to their resources, some institutions ask to be cited in a particular way or require that any results be entered in their database to increase its value to future users.

Biobanks become known to scientists by word-of-mouth and through the scientific literature; in general, scientists working in a given field know which biobanks provide useful information and which ones do not. But this knowledge does not necessarily extend outside specialized fields. Another problem is that several biobanks do not share their resources because the time and effort involved are not compensated by any recognition of the biobank's value, especially if an individual who wants access to the biobank is from a different field. When searching for financial support, biobankers must document the usefulness of sharing their resources. Setting up a quantitative parameter to measure the value of a biobank would address many of these issues.