***et al.*[10] use teratoma for tumors formed by human ES cells. However, they report that ES cell lines consistently can be cultured from these tumors, demonstrating that stem cells are still present—a criterion that could justify the alternative terminology, as employed by earlier workers[1–4]. In a more extreme example, Erdo *et al.*[11] report the formation of "highly malignant teratocarcinomas" by mouse ES cells injected into mouse brain. They support the nomenclature by noting that "tumor growth was highly invasive and micrometastases outside the tumor were repeatedly detected[11]".**

What is clear, regardless of the terminology used, is that potential tumorigenicity must be evaluated directly before the clinical application of any stem cell—embryonic, amniotic or adult—in regenerative medicine. The more important issue remains assuring the safety of patients.

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To the editor:

We appreciate the opportunity to respond to preprint copies of correspondence from Lensch and Ince and the response from Atala and Furth.

From our point of view, most of the problems and controversies mentioned in this correspondence have arisen from the inconsistent usage of the terms teratoma and teratocarcinoma by many scientists working in this field. Thus, we encourage the editors of *Nature Biotechnology* to standardize the terminology, at least for human embryonic stem (ES) cell–derived xenografts .

In our view, the term teratocarcinoma should be used only for malignant tumors, which in this context are malignant by virtue of the continued presence of stem cells—the embryonal carcinoma (EC) cells[1]. EC cells, as suggested by almost all studies on mouse- and human-derived cells, are the malignant equivalents or cognates of ES cells[2]. Any pathologist trained to identify human EC cells should be able to distinguish malignant teratocarcinomas from benign teratomas, which are defined as tumors composed only of somatic tissues and devoid of EC cells. In an experimental setting, the malignancy of a tumor due to the presence of morphologically identifiable EC cells can be tested by re-transplantation to a new host.

The distinction between teratomas and teratocarcinomas is crucial, especially for the future usage of ES cells in human medicine. Using xenografting as an essential preclinical safety control, one could predict that the ES cell lines that form only teratomas are 'benign' or 'safe' for human usage, whereas the cell lines that produce teratocarcinomas are 'malignant' and not safe for injection into humans[3]. Thus, we would discourage the indiscriminate usage of terms 'teratoma' and 'teratocarcinoma', even though in the past some eminent scientists have used those term interchangeably and even as synonyms. Previous imprecision is, in our opinion, not a valid justification for future use of a confusing terminology.

A minor but not insurmountable problem pertains to the usage of 'teratocarcinoma' for tumors produced from human ES cells. Even though the term 'teratocarcinoma' has been used as a synonym for malignant teratoma in mice for more than four decades, most leaders in human pathology have consistently refused to accept it. In the recent consensus book on human testicular tumors compiled by the experts of the World Health Organization (WHO; Geneva, Switzerland)[4], the term teratocarcinoma is mentioned only in passing for the animal model of human germ cell tumors. Because the work on human ES cells is, in a sense, a continuation of the experiments first performed on mouse ES cells and teratocarcinoma-derived EC cells, we feel that the term 'teratocarcinoma' will be more readily accepted by laboratory researchers than diagnostic pathologists. At least it is less cumbersome than the WHO-recommended term "mixed embryonal carcinoma and teratoma" or indeed the British classification "malignant teratoma intermediate[4]".

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***Nature Biotechnology* responds:**

A survey of the literature indicates no consensus on how to distinguish the terms 'teratoma' and 'teratocarcinoma'. The term 'teratocarcinoma' is used as a synonym for human tumors clinically known as "teratoma with embryonal carcinoma" (according to the World Health Organization) or "teratoma intermediate" (according to the British classification of germ cell tumors). Some pathologists include these tumors in the group of testicular 'nonseminomas' (also known as 'nonseminomatous germ cell tumors (NSGCT)') or use imprecise terms, such as 'malignant teratoma'. The somatic tissues in teratocarcinoma may be fully differentiated (equivalent to adult tissue) or only partially differentiated (corresponding to immature tissues in fetal organs).

On the basis of the above exchange and after expert consultation, *Nature Biotechnology* will adopt the term 'teratocarcinoma' to describe malignant tumors comprising both somatic tissues and undifferentiated malignant stem cells, identifiable as EC cells. EC cells are malignant equivalents of ES cells. Human EC cells should be identifiable microscopically according to the pathologic and immunohistochemical criteria used to identify human EC cells in malignant germ cell tumors of the ovary or testis or extragonadal sites. In an experimental setting, the malignancy of a tumor due to the presence of morphologically identifiable undifferentiated EC cells may be defined by their ability to form a new tumor after transplantation to a new host.

We will apply the term 'teratoma' only to tumors composed of normal, 'benign' somatic tissue and their immature (fetal) precursors derived from more than one of the three embryonic germ layers (ectoderm, mesoderm and endoderm). Teratomas comprising nonproliferating somatic tissue may be further labeled as 'benign', 'mature' or 'fully differentiated'. Teratomas composed of immature, proliferating fetal-like tissues may be labeled 'immature'.

It should be noted that almost all tumors produced in immunosuppressed mice from xenografted human ES cells have proven to be teratomas. Some data suggest that teratocarcinomas may occasionally be produced from human ES cells upon xenografting, but these tumors have not been fully documented.