The terminology of teratocarcinomas and teratomas

To the editor:

In their paper in the January issue entitled 'Isolation of amniotic stem cell lines with potential for therapy', De Coppi *et al.*[1] claim that embryonic stem (ES) cells "grow as teratocarcinomas when implanted *in vivo*." This disagrees both with standard histopathological classification of germ cell neoplasms and with terminology previously used in the field to define ES cell–derived tissues.

Historically, the term teratocarcinoma has been used by pathologists to specifically define a malignant testicular germ cell tumor that is composed of teratoma and embryonal carcinoma. This neoplasm is associated with a malignant phenotype[2,3], including the potential for distant metastasis[4], local invasion and marked cytogenetic defects, as well as serial transplantability in experimental systems[5–7]. Teratocarcinomas are malignant tumors and may cause death due to invasion and metastasis if left untreated.

A more correct term for the experimental tissue masses formed by human ES cells is mature teratomas. Mature teratomas and ES cell–derived teratoma-like masses contain differentiated derivatives of all three embryonic germ layers and differ from teratocarcinomas in that they are considered benign[2,6,8], do not invade adjacent tissues or metastasize to distant organs and typically do not reoccur after surgical removal[9,10]. Owing to their developmental potency, ES cell–derived masses that form in immunodeficient animals are referred to as teratomas by most other authors in the field[11]. That said, to a purist, neither term is correct, as both teratocarcinomas and teratomas are naturally occurring neoplasms that arise as a result of specific, acquired genetic and epigenetic alterations.

In contrast, experimental human ES cell–based 'lumps' result from disorganized but normal tissue generation and are a manifestation of a failed attempt, resulting from ectopic implantation, to form an embryo by ES cells that are genetically normal. Referring to the ES cell–derived tissue masses as teratocarcinomas (neoplastic tumors) is not only ontologically inaccurate: in view of the heated debate surrounding the conduct of human ES cell research, failing to make this important distinction could also have political implications.

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1. De Coppi, P. *et al. Nat. Biotechnol.* **25**, 100–106 (2007).
2. Martin, G.R. & Evans, M.J. *Cell* **2**, 163–172 (1974).
3. Cooper, M. *Med. Humanit.* **30**, 12–22 (2004).
4. Andrews, P.W. *Phil. Trans. R. Soc. Lond. B Biol. Sci.* **357**, 405–417 (2002).
5. Kleinsmith, L.J. & Pierce, G.B. Jr. *Cancer Res.* **24**, 1544–1551 (1964).
6. Martin, G.R. *Cell* **5**, 229–243 (1975).
7. Zwaka, T.P. & Thomson, J.A. *Development* **132**, 227–233 (2005).
8. Isaacs, H. Jr. *J. Pediatr. Surg.* **39**, 1003–1013 (2004).
9. Lopes, M.A., Pereira, C.M., da Cruz Perez, D.E., Vargas, P.A. & de Almeida, O.P. *Oral. Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.* **100**, 598–602 (2005).
10. Heerema-McKenney, A., Harrison, M.R., Bratton, B., Farrell, J. & Zaloudek, C. *Am. J. Surg. Pathol.* **29**, 29–38 (2005).
11. Brivanlou, A.H. *et al. Science* **300**, 913–916 (2003).

Anthony Atala and Mark Furth respond:

We used the term 'teratocarcinoma' in our paper because it accurately reflects observations and language from some of the original reports on ES cells that we cited. For instance, in her seminal paper from 1981, Martin[1] describes "a method...for isolating and establishing pluripotent cell lines with the properties of teratocarcinoma stem cells directly from normal early mouse embryos *in vitro*." She characterizes the tumor type formed after injection of ES cells into athymic mice as follows: "In most cases, a typical teratocarcinoma, containing derivatives of all three primary germ layers, formed within 6 weeks." Furthermore, she documents the presence of undifferentiated stem cells within tumors formed from ES cell clones. This may help to explain Martin's choice of the term teratocarcinoma, rather than teratoma, as it was one of the key criteria used by original workers in the field, including Stevens[2].

Evans and Kaufman[3] also use the term 'teratocarcinomas' to refer to tumors formed by mouse ES cells and ectopically implanted embryos. Moreover, they retain this terminology when reporting the efficient formation of germline chimeras from ES cells ("embryo-derived teratocarcinoma cell lines") but not EC cells[4]. In 1995, Thomson *et al.*[5], like us, used the term teratocarcinoma—not teratoma—when citing the prior mouse ES cell literature and observed that "when injected into severe combined immunodeficient mice, R278.5 [primate ES] cells consistently differentiate into derivatives of all three embryonic germ layers."

Three years later, Thomson and coworkers chose to refer to tumors formed after injection of human ES cells into immune deficient mice as teratomas[6]; however, a survey of the subsequent literature reveals that even among leaders in the field, the distinction between the terms seems subtle at best. For instance, Andrews and colleagues[7] use the term teratoma to describe tumors formed by most human ES cells, but report the production of malignant teratocarcinoma tumors by "culture adapted" human ES cells that, nonetheless, retain the ability to generate differentiated cell types corresponding to the three germ layers[7]. Andrews[8] has also, on occasion, described tumors formed by cancer-derived human embryonal carcinoma (EC) cells as teratomas rather than teratocarcinomas[8]. Elsewhere, Solter[9] refers to a human ES cell–derived tumor as a teratocarcinoma. In contrast, Schuldiner