9th ANNUAL DEPARTMENT OF PATHOLOGY YOUNG INVESTIGATORS’ DAY
POSTER SESSION
Thursday, April 5th, 2007
TURNER CONCOURSE
REGISTRATION FORM

E-mail COMPLETED Registration form and abstract to:
Stacey Morgan (smorgan9@jhmi.edu) on or before
Friday, March 16th, 2007

If you have questions or problems regarding your submission, please contact Stacey
Morgan via e-mail (smorgan9@jhmi.edu)

Applicant’s Name:  ___Xiaobing He _____Degree: ___Ph.D________

Applicant’s Division: ___Urology
Faculty Preceptor:  David M. Berman
(Must hold a primary appointment in Pathology)

Appointment Category: _____House Staff _____Clin Fellow 4 _____Research Fellow

_____Medical Student _____Graduate Student (Program:___________)

Register for: _____Clinical Research 4 _____Translational Research _______Basic Research

Full Poster Title *  Urothelial differentiation in urothelial carcinoma: Identification of
candidate bladder tumor stem cell____________________________________________________

Where has the work been presented?
Meeting Name  2007 annual meeting of United States and Canadian Pathology
Meeting Date  March 24

2007____________________________________________________

Not Previously Presented ______________________________

Where is this work being published? ________________________________________________

Journal Name, Volume, Page, Date _________________________________________________

In Preparation 4 __________________________________________________________________

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Urothelial differentiation in urothelial carcinoma: A bladder cancer stem cell model

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Background:
As few as 2-5% of cells in solid tumors can grow indefinitely and colonize metastatic sites. Such “cancer stem cells” have been partially characterized in tumors from the brain and breast, but little is known about other sites, and no paradigm has been established to identify and isolate carcinoma stem cells. Most epithelia are organized such that the putative stem cell compartment abuts the basement membrane, with more differentiated cell types populating positions closer to the epithelial surface. Here we show that urothelial carcinomas comprise distinct cell populations corresponding to basal (cytokeratin 17+/cytokeratin 20-), intermediate (ck17-/ck20-), and superficial (ck17-/ck20+) cells in normal urothelium. We further demonstrate enhanced tumor forming potential of cells expressing markers of basal differentiation.

Design:
We inoculated human urothelial carcinoma cell lines subcutaneously into immunodeficient mice and analyzed the resulting xenograft tumors by histomorphology, immunohistochemistry, RT-PCR, and flow Cytometry. We used fluorescence activated cell sorting (FACS) to isolate basal-like cells from digested xenografts and tested their tumor forming potential upon reinjection into nude mice.

Results:
In several human urothelial carcinoma xenografts, we noted that tumor cells were organized in distinct layers, with ck17 expressing basal-like cells ringing the basal aspect of tumor nodules, adjacent to tumor stroma, larger ck20 positive cells in the center of the nodule, and ck17-/ck20 cells intercalated in between. By immunohistochemistry, we found coexpression of ck17 in basal cells with a surface receptor predicted to bind to laminin in the basement membrane. Using antibodies against this receptor, we isolated tumor cells from dissociated urothelial carcinoma xenografts with high or low level expression of the receptor. We found equal cell viability for the two populations in vitro. However, when injected subcutaneously into nude mice, receptor bright cells were at least 6-fold more potent in forming tumors than receptor dim cells and gave rise to tumors that were almost 5 times larger. Tumors from receptor-bright cells also recapitulated the morphology and cytokeratin staining pattern of the parental tumor, indicating that the basal-like cells can give rise to the full range of cell types in the original tumor.

Conclusions:
These results indicate a hierarchy of differentiation in cells populating carcinomas that corresponds to different abilities to form tumors. They further implicate the basement membrane as a “niche” in which carcinoma stem cells might be sought. Future studies will pursue the implications of these findings for refining cancer classification, prognosis, and therapy.