



SARCOMA FOUNDATION OF AMERICA  
FINAL REPORT

Project Title: A mouse model to examine human  
osteosarcoma therapeutic options

Project Number: SFA08-14

1. Date project was initiated: July 1, 2008
2. Period covered by this report: From July 1, 2008 To June 30, 2009
3. Publications, Abstracts, and Presentations:
  - a. List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts. Each entry must include the author(s), article title, journal [book, editors(s), publisher, volume number, page number(s), and date.]
    - (1) Lay Press:
    - (2) Peer-Reviewed Scientific Journals:

Ma, O., Cai, W.-W., Zender, L., Dayaram, T., Herron, A.J., Lowe, S.W., Man, T.-K., Lau, C.C., and **Donehower, L.A.** (2009). Birc2 (clAP1) and Birc3 (clAP2), Amplified on chromosome 9, collaborate with p53 deficiency in mouse osteosarcoma progression. *Cancer Res.* 69:2559-2567.

Engin, F., Bertin, T., Ma, O., Jiang, M.M., Wang, L., Sutton, R.E., **Donehower, L.A.**, and Lee, B. (2009). Notch signaling contributes to the pathogenesis of human osteosarcomas. *Hum. Mol. Gen.* 18:1464-1470.
    - (3) Invited Articles:
    - (4) Abstracts:
  - b. List presentations made during the last year (international, national, local societies, etc.). Use an asterisk (\*) if presentation produced a manuscript.

4. Provide a brief list of keywords: (limit to 20 words)  
P53, osteosarcoma, mouse cancer model, Birc2, Birc3, MMP-13, Notch signaling, genomic instability, CSF-1 receptor
  
5. Summarize the progress during the period of this report and its impact on your plans for the remainder of the project. Include a summary of the progress toward the achievement of the originally stated aims and list the significant results:

SFA funds were instrumental in furthering our progress on several fronts. First, it enabled us to finish our work on functional analysis of frequently amplified genes in our p53-deficient mouse osteosarcoma model. This work was published in the March 15, 2009 edition of *Cancer Research*. We were able to show that three genes (Birc2, Birc3, and MMP13) are frequently overexpressed in human and mouse osteosarcomas and might serve as viable targets for anti-cancer drugs.

Second, SFA funds were helpful in a collaborative effort with Dr. Brendan Lee's laboratory to show the importance of Notch signaling in osteosarcomas, using our p53-deficient mouse model. This work was recently published in *Human and Molecular Genetics*.

Third, SFA funds were also helpful in initiating an improved p53-deficient mouse osteosarcoma model. Our previous model develop other types of tumors over a time period of 8-24 months. Our improved model has developed only osteosarcomas much earlier in life. Also, we are developing both a non-metastatic and metastatic osteosarcoma model.

Finally, we spent much of our SFA funds to pursue the original aims of the proposal, which were to examine the effects of the CSF-1 receptor on osteosarcoma growth and formation in our mouse osteosarcoma model. The CSF-1R gene is massively overexpressed in mouse and human osteosarcomas and we proposed to determine whether knocking down its expression would slow or reverse osteosarcoma growth. We succeeded in generating lentiviral CSF-1R shRNA vectors that significantly knocked down CSF-1R expression in osteosarcoma cells. Unfortunately, knockdown of CSF-1R in mouse osteosarcoma cells failed to slow the growth of transplanted tumors compared to control vector transduced osteosarcoma cells.

6. In layperson's terms, summarize the progress during the period of this report. Explain any medical significance or implications of your results to date:

During the past year (7/1/2008-6/30/2009), we have worked on developing an osteosarcoma model in the mouse that partially mimics the development of

osteosarcoma in humans. Mice that are defective for the tumor suppressor gene p53 have a strong likelihood of developing osteosarcomas. We isolated osteosarcomas from the p53-deficient mice and looked at changes in how genes behaved in these tumors in comparison with genes in human osteosarcomas. We showed that several genes were likely to be very important in the origin or progression of mouse osteosarcomas and thus likely in human osteosarcomas as well. Ultimately, it may be possible to develop drugs to target these genes in osteosarcomas and thus develop new therapies to delay progression or cure this particular cancer.

Lawrence A. Donehower  
Principal Investigator (signature)

7/31/09  
Date

David Butel  
Department Chair (signature)

8/3/09  
Date