

Targeted Investments in Excellence (TIE) Progress Report

MicroRNA genes in the diagnosis, prognosis, prevention and therapy of cancer

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1. Executive Summary:

We have received the TIE funding only in March 2007, and it is May 2007, thus it is difficult to fully describe how the TIE initiative is advancing the goals of the Academic Plan and contributing to our overarching goal of becoming one of the world's top public universities. Despite this caveat we have made tremendous progress in our Program, as indicated by numerous publications in top scientific journals. The TIE funds are being spent to advance our research program on the involvement of microRNA genes in human diseases, in particular cancer. Several breakthroughs have been achieved and have been reported in very high impact scientific journals.

2. Accomplishments to date:

(a) Publications:

1. Bloomston M, Volinia S, and Croce CM. MicroRNA expression patterns differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis. JAMA, 297:1901-1908, 2007.
2. Georgantas RW III, Hildreth R, Morisot S, Alder J, Liu C-G, Heimfeld S, Croce CM, Calin GA and Civin CI. CD34+ Hematopoietic stem-progenitor cell microRNA expression and function. A circuit diagram of differentiation control. Proc. Natl. Acad. Sci., USA, 104:2750-2755, 2007.
3. Garzon R, Pichiorri F, Palumbo T, Visentini M, Aqeilan R, Cimmino A, Wang H, Sun H, Volinia S, Alder H, Calin GA, Liu CG, Andreeff M and Croce CM. MicroRNA gene expression during retinoic acid-induced differentiation of human acute promyelocytic leukemia. Oncogene. 2007 Jan 29; Epub ahead of print.
4. Issaeva I, Zonis Y, Rozovskala T, Orlovsky K, Croce CM, Nakamura T, Mazo A, Eisenbach L and Canaani E. Knockdown of ALR (MLL2) reveals ALR target genes and leads to alterations in cell adhesion and growth. Mol Cell Biol. 27:1889-1903, 2007.
5. Bottoni A, Zatelli MC, Ferracin M, Tagliati F, Piccin D, Vignali C, Calin GA, Negrini M, Croce CM, Degli Uberti EC. Identification of differentially expressed microRNAs by microarray: A possible role for microRNA genes in pituitary adenomas. J. Cell Physiol., 210:370-377, 2007.
6. Donati V, Fontanini G, Dell'Omodrane M, Prati MC, Nuti S, Lucchi M, Mussi A, Fabbri M, Basolo F, Croce CM and Aqeilan RI. WW Domain-containing oxidoreductase expression in different histologic types and subtypes of non-small cell lung cancer. Clin Cancer Res., 13:884-891, 2007.
7. Aqeilan R, Trapasso F, Hussain S, Costinean S, Marshall D, Pekarsky Y, Hagan JP, Zanesi N, Kaou M, Stein GS, Lian JB and Croce CM. Targeted deletion of Wwox reveals a tumor suppressor function. Proc. Natl. Acad. Sci., USA, 104:3949-3954, 2007.

8. Kulshreshtha R, Ferracin M, Wojcik SE, Garzon R, Alder H, Agosto-Perez FJ, Davuluri R, Liu C-G, Croce CM, Negrini M, Calin GA and Ivan M. A microRNA signature of hypoxia. Molec and Cellular Biol., 27:1859-1867, 2007.
9. Vecchione A, Baldassarre G, Ishii H, Nicoloso MS, Beletti B, Petrocca F, Zanesi N, Fong LYY, Battista S, Guarnieri D, Baffa R, Alder H, Farber JL, Donovan PJ, and Croce CM. Fez1/Lzts1 absence impairs Cdk1/Cdc25C interaction during mitosis and predisposes to cancer development. Cancer Cell, 11:275-289, 2007.
10. De Flora S, D'Agostini F, Izzotti A, Zanesi N, Croce CM and Balansky R. Molecular and cytogenetical alterations induced by environmental cigarette smoke in mice heterozygous for Fhit. Cancer Res., 67:1001-1006, 2007.
11. Pekarsky Y, Zanesi N, Aqeilan RI and Croce CM. Animal models for Chronic Lymphocytic Leukemia. J. Cell Biochem., 100:1109-1118, 2007.
12. Sevignani C, Calin GA, Nnadi SC, Shimizu M, Davuluri RV, Hyslop T, Demant P, Croce CM and Siracusa LD. MicroRNA genes are frequently located near mouse cancer susceptibility loci. Proc. Natl. Acad. Sci., USA, 104:8017-8022, 2007.
13. Aqeilan RI and Croce CM. WWOX in biological control and tumorigenesis. J Cell Physiol. 2007 Apr 25; [Epub ahead of print]
14. Fabbri M, Garzon R, Cimmino A, Liu Z, Callegari E, Liu S, Alter H, Costinean S, Fernandez-Cymering, Volinia S, Guler G, Morrison CD, Chan KK, Marcucci G, Calin GA, Huebner K and Croce CM. miR29 family targets DNMT3A and DNMT3B and induces global DNA hypomethylation and reactivation of tumor suppressor genes. Nature, submitted 2007.
15. Care A, Catalucci D, Felicetti F, Bonci D, Addario A, Gallo P, Bang ML, Segnalini P, Gu , Dalton ND, Elia L, Latronico MV, Hoydal M, Autore C, Russo MA, Dorn GW 2nd, Ellingsen O, Ruiz-Lozano P, Peterson KL, Croce CM, Peschle C, and Condorelli G. microRNA-133 controls cardiac hypertrophy. Nat Med. 13:613-8, 2007.
16. Blower PE, Verducci JS, Lin S, Zhou J, Ghung J-H, Dai Z, Liu C-G, Reinhold W, Lorenzi PL, Kaldjian EP, Croce CM, Weinstein JN and Sadee W. MicroRNA expression profiles for the NCI-60 cancer cell panel. Mol. Cancer Ther. 6:1483-1491, 2007.
17. Nakamura T, Canaani E, and Croce, CM. Oncogenic All1 fusion proteins target Drosha-mediated micro RNA processing. Proc. Natl. Acad. Sci., USA, accepted for publication 2007.
18. Nakanishi H, Nakamura T, Canaani E, Croce M. De-regulated expression of *EphA7* in leukemia cells carrying chimeric *ALL1* genes causes ERK2 phosphorylation. Proc. Natl. Acad. Sci., USA, submitted 2007.
19. Croce, CM. Oncogenes and human cancer. New Eng. J Med. 2007 Review, in press.

(b) Professional Presentations:

We have been invited to present papers and chair sessions at the Annual Meeting of the American Association of Cancer Research in Los Angeles and at the Annual meeting of the American Association for Clinical Oncology in Chicago. We have also

been invited to speak at several workshops organized by the NIH and NCI; to Gordon Conferences; and to Keystone meetings. Dr. Croce will also chair the next Keystone meeting (June 2007) on "*microRNAs and Cancer*". Dr. Croce has also been invited to numerous international congresses in the USA, Israel, Australia, England, the Netherlands, Germany, France, Spain, Austria, Sweden, Denmark and Italy.

(c) Faculty and Staff Honors and Awards:

Dr. Croce has received the 2007 Henry M. Stratton Medal by the American Society of Hematology. This is one of the highest honors for American hematologists.

(d,e,f,g,h,i) Because of the very short period of support (three months) it is impossible to provide credible information of these points.

3. Implementation Issues:

During the time of support, we did not encounter any implementation issues.