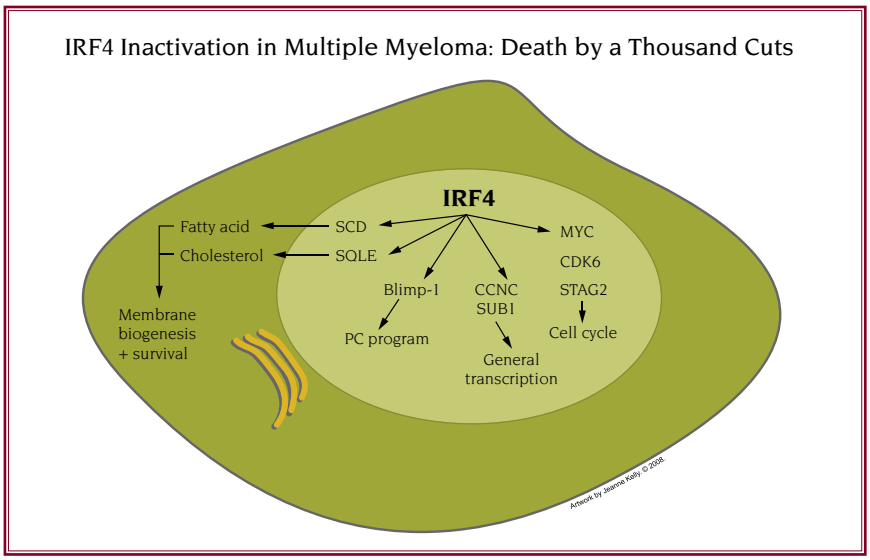
# Achilles' (Other) Heel:

## Non-Oncogene Addiction in Multiple Myeloma

*Oncogene addiction has been regarded as the Achilles' heel of cancer, based on the idea that silencing an oncogene's expression will prove lethal in certain cancers.*[1] *However, new research suggests that multiple myeloma—a cancer of antibody-producing plasma cells—may have a fatal vulnerability that is better described as a "non-oncogene addiction."*




(*Image: J. Kelly*)

Multiple myeloma cells' survival depends on the ability of the transcription factor IRF4 to activate genes that are quiescent in healthy plasma cells. This dependency suggests that, just as some cancers are said to have an "oncogene addiction," myeloma cells have a "non-oncogene addiction."

There is no curative treatment for the many subtypes of multiple myeloma, each of which utilizes distinct oncogenic pathways. Thus, developing therapeutic alternatives not based on type-specific oncogenes is very attractive to clinicians and researchers. Recent research highlighting the role of the protein IRF4 in the survival of myeloma cells suggests that this protein may provide a therapeutic target for all myeloma subtypes.

In the July 2008 issue of *Nature*, a team of NCI and NIH researchers, led by Staff Scientist Arthur Shaffer III, Ph.D., and Deputy Chief Louis Staudt, M.D., Ph.D., of CCR's Metabolism Department, reported results of a study utilizing small hairpin RNAs (shRNAs) to identify potential drug targets for multiple myeloma. The team observed that silencing the gene *IRF4* killed 10 different cell line models representing many subtypes of myeloma. Importantly, most of these myeloma models lacked any genetic abnormality in *IRF4* but were nevertheless completely dependent upon *IRF4* for survival, a phenomenon that the investigators characterized as "non-oncogene addiction."

In normal lymphocytes, IRF4 is a transcription factor, helping to initiate responses to foreign antigens and to generate plasma cells. To understand the molecular basis for *IRF4* addiction in multiple myeloma, the investigators characterized the repertoire of genes that are activated by IRF4 in myeloma cells. They found that IRF4 turns on genes in myeloma cells that are also induced during normal lymphocyte activation but are silenced in healthy plasma cells, from which myeloma is derived. Thus, *IRF4* controls an aberrant regulatory network in multiple myeloma.

Staudt, Shaffer, and their collaborators found a peculiar relationship between *IRF4* and the oncogene *MYC*, which has a prominent role in myeloma pathogenesis. In their experiments, silencing *IRF4* suppressed *MYC* expression and, conversely, silencing *MYC* suppressed *IRF4* expression. Their observations suggest a model in which *IRF4* and *MYC* reinforce the expression of each other in a cycle that perpetuates cancer cell proliferation and survival.

The findings suggest that blocking *IRF4* expression may be an attractive and broadly applicable therapeutic option for the many subtypes of multiple myeloma. More generally, the phenomenon of non-oncogene addiction promises to provide a new range of therapeutic targets in cancer.

*To learn more about Dr. Staudt's research on hematologic malignancies, please see "Making Sense of Lymphoma: The Definition Makes a Difference" in CCR Connections, Vol. 1, No. 2, or visit his CCR Web site at http://ccr.cancer.gov/staff/staff.asp?profileid=5780.*

[1] *Weinstein, B. Addiction to oncogenes—the Achilles heal of cancer. Science.* 2002;297:63-64.