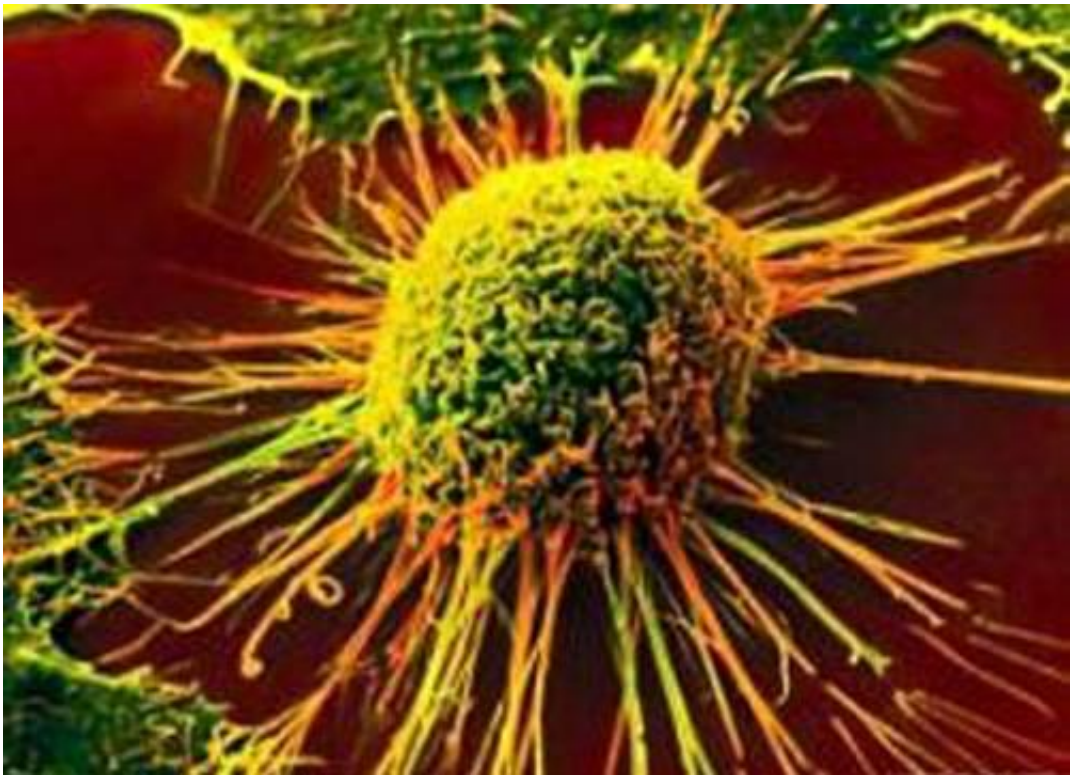
Exciting results from cancer immunoagent study

July 20 2015, by Christopher Packham



(Medical Xpress)—Cancer therapies have improved incrementally over the years, but cancer treatment largely remains analogous to forest fire suppression, in which the spread of fire is contained with deliberate controlled burns in surrounding greenery. The goal of oncology research is the development of therapies and pharmaceuticals that treat cancerous

cells while leaving normal, healthy cells intact.

Researchers have recently focused on a nucleocytoplasmic protein called nucleolin (NCL), a cellular Swiss Army knife involved in multiple biological processes including ribosomal assembly, chromatin decondensation, transcription, nucleo-cytoplasmic import-export, and chromatin remodeling. Because NCL is frequently up-regulated in cancer and in cancer-associated endothelial cells compared with healthy tissues, a group of researchers at Ohio State University conducted a study of NCL as a target for antineoplastic therapies. They've recently published the results of their study in the *Proceedings of the National Academy of Sciences*.

The researchers isolated a fully human single-chain fragment variable (scFv) antibody called 4LB5 which binds with high affinity to NCL. The antibody interferes with NCL and its regulated micro-RNAs (miRNA), and the researchers report that in vitro, the activities of 4LB5 result in a marked decrease in cancer cell viability and proliferation.

Further, they report that it is the only fragment variable antibody found to display dramatic reduction of the growth of orthotopic breast cancer tumors in vivo. They induced tumor growth in mice, which were then treated with either intraperitoneal injections of 4LB5 or a control buffer. Two weeks after treatment, the 4LB5-treated mice showed a clear reduction in breast tumor size compared to control mice, based on results from an in vivo imaging system. Examination revealed reduced cellularity and the development of necrosis following treatment, and the tumors exhibited reduced proliferation compared to those in control animals.

The researchers note that "we did not observe alteration of health conditions and body weight in scFv-treated mice, suggesting that 4LB5 was not toxic for normal cells." It's also important to note that the chosen

cancer cell lines are associated with a breast cancer phenotype that is well known to be extremely invasive.

A hypothetical oncologist's wish list would include a therapy that selectively targets cancer cells, leaves normal cells intact, and suppresses migration, and it's hard to argue that 4LB5 isn't a promising candidate. Checking off another item on that wish list, the researchers also demonstrated that 4LB5 induces apoptosis (cell death) in cancer cells. They performed a flow-cytometric analysis of of various cell lines treated with 4LB5 in vivo, and all of the cell lines showed evidence of dead cells within 72 hours of treatment. "Overall, these data indicate the NCL inhibition by 4LB5 treatment results in decreased cell viability and activation of programmed cell death," the authors write.

The researchers also suggest that 4LB5 could be improved or modified to serve as a novel tool for diagnostics, noting that because it translocates into the cytoplasm following NCL binding, it could be used as a vehicle to shuttle various kind of antitumoral molecules directly into cancer cells, thereby enhancing the effectiveness of these drugs while diminishing side effects. Though practical therapies based on this research are likely to be years away, the study's results are unusually exciting and present a promising avenue for further investigations.

More information: "Human anti-nucleolin recombinant immunoagent for cancer therapy." *PNAS* 2015 ; published ahead of print July 13, 2015, DOI: 10.1073/pnas.1507087112

Abstract
Nucleolin (NCL) is a nucleocytoplasmic protein involved in many biological processes, such as ribosomal assembly, rRNA processing, and mRNA stabilization. NCL also regulates the biogenesis of specific microRNAs (miRNAs) involved in tumor development and aggressiveness. Interestingly, NCL is expressed on the surface of actively

proliferating cancer cells, but not on their normal counterparts. Therefore, NCL is an attractive target for antineoplastic treatments. Taking advantage of phage-display technology, we engineered a fully human single-chain fragment variable, named 4LB5. This immunoagent binds NCL on the cell surface, it is translocated into the cytoplasm of target cells, and it abrogates the biogenesis of NCL-dependent miRNAs. Binding of 4LB5 to NCL on the cell surface of a variety of breast cancer and hepatocellular carcinoma cell lines, but not to normal-like MCF-10a breast cells, dramatically reduces cancer cell viability and proliferation. Finally, in orthotopic breast cancer mouse models, 4LB5 administration results in a significant reduction of the tumor volume without evident side effects. In summary, here we describe, to our knowledge, the first anti-NCL single-chain fragment variable displaying antineoplastic activity against established solid tumors, which could represent the prototype of novel immune-based NCL-targeting drugs with clinical potential as diagnostic and therapeutic tools in a wide variety of human cancers.

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