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SYMPOSIUM

A Report of the James Watson Lecture at Yale University

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In March 2012, Nobel Prize winner James Watson gave a seminar at Yale University entitled "Driven by Ideas." In his lecture, Watson discussed his personal vision for the future of science, specifically addressing how the scientific community should approach developing anticancer agents. He discussed the use of glycolytic inhibitors as anticancer agents due to the Warburg effect, as well as the benefits of metformin and anti-inflammatory drugs to help prevent cancer. He also compared drugs that target cell proliferation instead of targeting cell growth. Additionally, Watson commented on the mechanisms for how research should be conducted in the laboratory.

James Watson, who won the Nobel Prize in Physiology or Medicine in 1962 with Francis Crick for their 1953 discovery of the structure of DNA, discussed his personal vision for the future of science at a seminar sponsored by the Yale Cancer Center and Molecular Virology Program in March 2012. His talk, titled "Driven by Ideas," emphasized cancer research, how scientists should conduct research, and which questions the scientific community should focus on investigating.

Watson's interest in studying cancer began when he participated in a course about tumor viruses, given by Salvador Luria, who would later become Watson's PhD advisor at Indiana University. Watson said it was quite intriguing for him to learn how DNA tumor viruses cause cancer by "carrying" genes that turn on the cell cycle in the infected host cells.

Watson presented a variety of metaphors to describe how scientists should view studying cancer. For example, he

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claimed that researchers should treat the cancer cell as a "sick man" and not "Superman," as cancer cells exhibit constitutively active cell growth and glycolytic metabolism, known as the Warburg effect, which makes cancer cells inherently metabolically vulnerable to cell-killing agents (see Pelicano et al. [1] for a review of glycolytic inhibitors as anticancer mechanisms). Thus, Watson claimed that a cancer cell should be "killed the right way" by attacking what he called the "Achilles heel" of that cell. For example, a study was conducted to reduce tumor size in rats by depleting ATP levels, indicating that lowering glycolytic metabolism in cancer cells could be a useful therapeutic mechanism [2]. In this study, there was a significant reduction in tumor size of implanted rat gliomas after injection of apyrase, an enzyme that depletes ATP levels [2].

Watson discussed how cancer treatments could instead be focused on targeting glycolytic metabolism. He mentioned studies showing that metformin, which is used for treating diabetes and is currently the most prescribed drug, can reduce cancer risk by selectively killing highly glycolytic p53-deficient cancer cells [3]. Metformin, an indirect activator of AMPK, has been shown to suppress oxidative phosphorylation in the mitochondria, which then causes cells to increase glycolysis rates as an alternative ATP-producing mechanism; however, metformin-treated p53-deficient cells are unable to carry out this conversion [3]. Watson explained that this demonstrates how scientists can work toward stopping cancer by decreasing insulin levels and glycolysis with this diabetes treatment.

Watson emphasized that cancer cells also secrete large amounts of the anti-inflammatory interleukin IL-6, which then activates STAT3 and MYC [4]. These factors block apoptosis during inflammation and consequently maintain growth when persistently activated in tumor cells [4]. Watson claimed that more research should be focused on anti-inflammatory drugs to help prevent cancer, mentioning as an aside that he takes ibuprofen every day as a preventive measure. Watson alluded to the benefits of taking a daily aspirin or ibuprofen; for example, one study has shown that taking a daily aspirin for at least 5 years reduces cancer risk [5].

Furthermore, Watson claimed that anticancer drugs should be targeted against factors that promote cell proliferation, like MYC, rather than developing drugs that would be more toxic by targeting signal transduction pathways that promote cell growth, such as RAS-MEK or PI3K-AKT. Watson envisions the future of anticancer drugs to be primarily non-toxic chemical agents, such as metformin, as well endostatin and thrombospondin, which are broad-spectrum angiogenesis inhibitors. In this way, he hopes these drugs can be administered in a simple pill, similar to taking antibiotics.

Lastly, in order to reach these goals, Watson commented on the mechanisms of how research should be done, namely that more RNAi screens should be conducted to identify these "Achilles heels" of cancer cells. In this way, researchers can utilize an unbiased approach to scan the whole human genome for the appropriate oncogenic factors to target. Additionally, to facilitate this type of research, Watson explained that research laboratories could be "semi-industrialized," which could involve having more labs work together to create a larger collaborative community with a streamlined approach to designating different projects to researchers. This reorganization of laboratory structure, Watson said, would enable scientists to "act like a war against cancer is on."

In addition to describing his ideas regarding "curing 'incurable' cancer," Watson also appealed to all scientists, emphasizing the importance of spending as much time thinking about how to conduct research as the time given to conducting the experiments themselves.

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