NTP Turns to Mechanisms

DNA Breaks, Oxidative Stress and Gene Expression Are on the Agenda

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The U.S. National Toxicology Program (NTP) will soon embark on a new phase of its long-running RF project. Last year, the NTP concluded that RF radiation causes cancer; now it will begin a systematic search for mechanisms to explain how and why the tumors developed. Work is expected to begin by the end of the year.

The research plan is wide-ranging. It includes studies on gene expression, oxidative stress and DNA damage and repair, as well as the possible role played by heat. Other priorities on the NTP agenda are studies on behavior and stress.

We're "optimistic" that we can detect changes in gene expression and identify biomarkers of RF effects, NTP's Michael Wyde told *Microwave News.* Wyde is leading the new project. He will continue to work with John Bucher, the former NTP associate director, who ran its $30 million animal study, which showed "clear evidence" that RF radiation can lead to malignant tumors in male rats.

The NTP has already reported finding more DNA breaks —as detected with the comet assay— among the RF–exposed animals, including in the brain where rats later developed tumors. Those results, presented at a conference two years ago, have been submitted for publication. The paper is currently under peer review, according to Sheena Scruggs in NIEHS' Office of Communications and Public Information. (The NTP and NIEHS are closely connected.)

How Does RF Radiation Cause DNA Breaks?

The fact that the NTP documented DNA damage "adds to the credibility of the animal findings," said Ron Melnick. "It's very

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supportive." Melnick led the team that designed the NTP study; he retired in 2009.

Still missing, however, is how RF radiation causes DNA damage. "The breaks themselves don't tell you anything about the mechanism at work," Henry Lai explained in a recent interview. Twenty-five years ago, Lai and N.P. Singh were the first to show that RF radiation can induce DNA breaks —as it happened, in the brains of rats.

It is generally accepted that RF radiation is in itself not powerful enough to break chemical bonds and therefore unable to directly tear DNA apart. At the outset, Lai and Singh offered two possible mechanisms: oxidative stress and impaired DNA repair. Oxidative stress is shorthand for the sequence of events that follows an increase in the number of free radicals —biologically active molecules that *can* damage DNA. Alternatively, RF radiation may hinder the cell's ability to repair DNA breaks, which occur naturally and not infrequently.

In 1997, two years after their original paper, Lai and Singh followed up with strong evidence implicating oxidative stress. When they treated the rats with melatonin —a natural hormone that neutralizes free radicals— before RF exposure there were no more DNA breaks. If the radiation could indeed generate free radicals, they pointed out, the risks would go beyond cancer to include premature aging as well as Alzheimer's, ALS and other neurological diseases.

"If I were to design the project, I would look at the link between oxidative stress and DNA damage," Melnick said. "That's doable."

A recent review of some 100 journal articles found that more than 90 percent "confirmed that [low-level] RF radiation induces oxidative effects in biological systems." It was published in *Electromagnetic Biology and Medicine* in 2016.

NTP's Wyde said that an important first step will be "to replicate the comet assays" to confirm that RF radiation damages DNA. He cited some uncertainty due to the wide variation in the extent of the breaks seen in the original NTP experiments and the small number of animals used. If the breaks are replicated, Wyde plans to run additional "more specific and robust assays" to evaluate the DNA damage and repair enzymes.

New Smaller Exposure Chambers

For this new phase of the RF project, the NTP has again turned to the IT'IS Foundation in Zurich to design and build new reverberation chambers, which are more compact and less expensive than the room-size units built for the original study. As before, these smaller units will also allow animals to move freely while being exposed to 900 MHz or 1800 MHz radiation. Each can house up to ten animals.

The NTP declined to discuss the new exposure setups, stating only that the information would be posted on the NTP RF website in due course. Niels Kuster, the director of IT'IS, confirmed that four new

chambers have been delivered to the NIEHS/NTP Campus in Research Triangle Park, NC.

For the time being, the NTP is planning only animal studies. When asked whether *in vitro* RF experiments (using living cells) are under consideration, the NTP communications office replied that their feasibility is “still being assessed.”

In a recent posting on its website, the NTP announced that it is in the midst of evaluating the literature on the higher frequencies used in 5G.

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The NTP paper on DNA breaks has been published in *Environmental and Molecular Mutagenesis.* The abstract is here.

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