EURYI Awards 2004

Press Information

Dr. Reuven AGAMI

– Biomedicine –

Project:

Genome wide search for DNA damage checkpoint functions in human cells

DNA damage induces cellular pathways that set off a rapid and long-lasting cell cycle arrest that is required for proper repair mechanisms. Genes that participate in these pathways or regulate the activity, stability or the expression of their constituents, affect also the sensitivity of cells to DNA damage. The inappropriate activation or the loss of such a response ultimately leads to deregulated cellular growth, induction of genomic instability and cancer.

Recently, we have developed a vector based system that creates persistent loss-of-function phenotypes in mammalian cells by continuous production of short interfering (si)RNAs. Intriguingly, this system consents to perform genome wide loss-of-function and synthetic lethal screens in mammalian cells. Indeed, a collection to suppress up to 8000 human genes was recently built in our institute and is being further expanded. Here, we propose to use RNAi libraries to screen for novel regulators of DNA damage pathways. As proof of principle we used primary human cells exposed to ionizing radiation. Under optimal conditions, these cells ceased to proliferate for at least two weeks but continued to grow uninterruptedly when we silenced the expression of either p53 itself, its target p21CIP1 or genes that regulate p53 activity or stability. We then introduced the RNAi library to the primary human cells and indeed obtained clear rescuing activity.

From this, we intend to identify genes that participate in the cellular survival to damaged DNA. We are also developing a novel synthetic lethal screen called SAGS (Sequential Analysis of Gene Suppression) to identify genes that synergize with DNA damage in cell killing. The identification of novel genes whose function modulates cellular toxicity induced by DNA damage will not only deepen our understanding of how genotoxic agents work but will also open new opportunities to screen for potent drugs that sensitize tumours to conventional cancer therapy.

Comments:

This project will open new approaches to study cancer, and will act as proof of concept for the study of many other diseases.

The candidate is a recognized world leader in the exciting area of RNAi with an outstanding publication record. He has already moved many different research areas by his contribution to the development of new methodologies.

Any flaw in the ability of our body to repair DNA will lead to cancer. The candidate will develop the latest technologies to uncover new pathways in this process.

The host institution is a leader in cancer research with the advantage of having access to cancer material, important in this study.

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Current institution: The Netherlands Cancer Institute
New institution: The Netherlands Cancer Institute

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