Varda Rotter/ WIS

Summary of past scientific achievements:

The field of p53 underwent major conceptual revolutions, when a protein with an ambiguous relevance to cancer, discovered 30 years ago, became one of the major interests of cancer research. Rotter's scientific career is closely connected with the p53 field and as an active pioneering member in this community; she was able to make several seminal contributions that reshaped the field. Below are listed the main significant contributions made by Varda Rotter:

Pioneering work in identifying p53 and its relevance to cancer:

p53 was first discovered as a non-viral 54KDa protein expressed in SV40-transformed cells. At that time she was a Post-Doc fellow in the laboratory of the Nobel laureate David Baltimore at MIT, where she independently discovered a 50KDa protein that was expressed at high levels in cells transformed by the *abl* oncogene. As she identified one of the first p53-specific monoclonal antibodies; a critical tool in the early work on this protein, she was able to show that, regardless of their etiology, all transformed cells expressed an identical p53 protein.

Rotter returned to the Weizmann Institute and established her own laboratory on 1981. In 1983, she was the first to show that high p53 levels are frequently detected in human and mouse tumors, and she suggested using p53 immuno-staining as a tumor specific marker. Staining of tumor sections for p53 is indeed commonly used today in many medical centers worldwide, and has been shown to have a prognostic value. In her studies, Rotter focused on structural aspects of p53 including the identification and characterization of alternative sliced forms and unique isoforms of p53. She identified and characterized a variety of human p53 non-producer cell lines that were central for studying the function of p53 and its chromosomal localization.

Mutant p53 gain of function:

Perhaps the most seminal aspect of Rotter's contribution to the p53 field is the establishment of the paradigm that mutant p53 has a gain of function in carcinogenesis. In a series of important studies starting with a seminal paper in *Cell* (1984), she was the first to demonstrate that introduction of p53 (known today as mutant p53) into p53-null cells significantly facilitated their oncogenic activity *in vivo* and *in vitro.* This study was further substantiated by a *Nature* paper, in which an *in vitro* model of transformation was utilized to assess the oncogenic activity of mutant p53. These findings practically kick-started the whole field of mutant p53 gain-of-function, in which she may be considered as one of the most prominent figures worldwide. Some more recent major contributions to this field from her research include the realization that tumor-associated mutant p53 isoforms promote cancer through their transcriptional activity (2001 and subsequent publications), and that a major component of their oncogenic activity involves the ability to render tumor cells more resistant to apoptosis. In recent years, Rotter was leading successfully the quest to identify genes whose modulation underlies mutant p53 gain-of-function, and these findings are having major impact on mutant p53 research.

Over the past years, much of Rotter's research activity has focused on the establishment of *in vitro* models for studying the role of p53 in cancer progression. These efforts yielded a number of different novel types of malignant transformation models of great potential. Furthermore, through extensive gene expression analysis and adoption of system biology approaches, she made and continues to make important contributions to the understanding of the molecular mechanisms that underlie distinct steps in the conversion of normal cells into fully malignant cells.

Role of p53 in development, differentiation and stem cell:

Along the years, her laboratory re-examined the role of p53 in cell differentiation and development by using several models of cell differentiation. More recently she focused on understanding the role of p53 in the life of stem cells. Her early studies show that p53 is central in regulating cell reprogramming and, in agreement with others; we found that wild type p53 exerts a negative control on stem cell reprogramming. Her more recent novel data shows that p53 plays a pivotal role in preventing malignant transformation of induced pluripotent stem cells and that mutant p53 exerts a gain of function activity in inducing cancer stem cell. These observations are of great relevance for understanding the role of mutant p53 in cancer development at large and in LI-Fraumeni in particular.