The story of p53

This presentation was prepared

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The history of p53 as seen by Varda Rotter

Presented at the 12th p53 workshop in New Zealand

12th International p53 Workshop DUNEDIN NEW ZEALAND







The p 5 3 25th anniversary



The story of p53

Pre-history -1979

Name: The non-viral antigen 54K

A keen of Large Tantigen-makes a complex

Name: Cancer Associated p53

Expresessed in Methylcholantrn transformed

fibroblasts

Name: p50

Expressed in retroviral transformed cells

Baptized as p53!!!

History: 1979-1989

The STRUCTURAL period!
Bulding of tools to study the gene and the protein!

Function: ONCOGENE! (no-kosher)

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The STRUCTURAL period!
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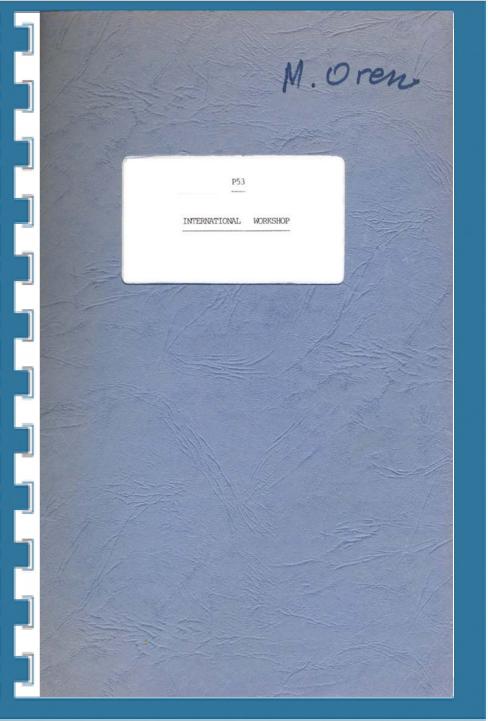




The first p53 workshop

The Marie Curie Memorial Foundation Research Institute The Chart Oxted, Surrey

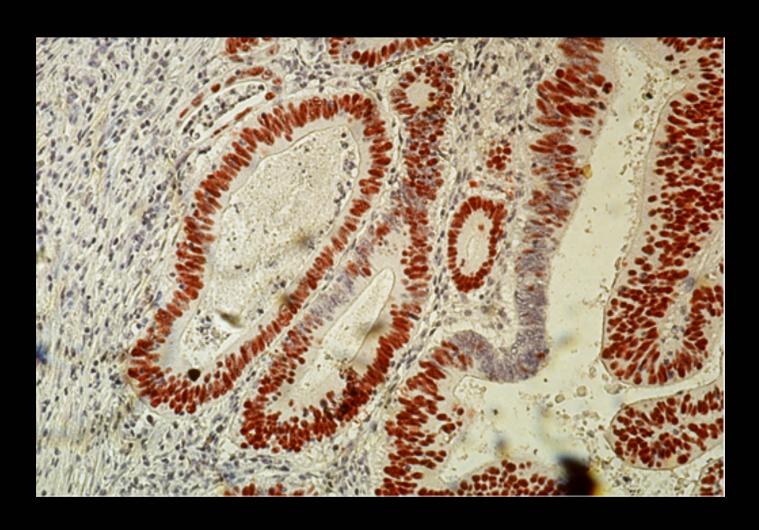
The clonning "saga"





p53 is a tumor marker: p53 protein expression in Small

p53 protein expression in Small Intestinal Carcinoma



6-12 October, 1983



NEWS AND VEWS-

Oncogenic intelligence

The rasmatazz of cancer genes

from Peter Newmark

ing fields, has gradually broken up into a large number of sub-specialities, with little real cohesion between many of them. In the course of the last few months, however, researchers in at least three separate areas - RNA viruses. DNA viruses and growth factors - have found common cause through a series of revelations on the nature and action of oncogenes. The recent Cold Spring Harbour* conference on cell proliferation and change, dedicated to Mary Lasker, brought many of the major workers together

Particular impetus has come from the discovery that a partial sequence of platelet-derived growth factor (PDGF) is nearly identical to that deduced for the product of the six oncogene of simian saccoma virus (see Nature 304, 35: 1983 and Science 221, 275: 1983). One prediction of the homology was that the cellular six gene would encode PDGF and some evidence in support of that prediction was forthcoming. S. Aaronson (National Institutes of Health) reported a pulse-chase study of the proteins that could be immunoprecipitated from simian sarcoma virus-infected cells with antibodies against synthetic peptides corresponding to the amino and carboxy termini of the viral sit gene product. The original product seemed to form dimers which were then processed through a series of molecules whose sizes resembled that of PDGF in various states of processing, M. Waterfield (Imperial Cancer Research Fund, London) added evidence that viral sin-producing cells contain PDGF-like biological activity and that the human cellular sir gene encodes a poptide that differs by only two amino acids (one perhaps a species difference and the other an error) from one of the peptides of PDGF.

So where does that leave PDGF? Is it a growth factor when released in its peoper context by platelets and a tumour growth factor when released in the wrong place and at the wrong time? Or will the viral six gene product turn out to be different enough from PDGF to account for their different properties? Whatever the answer, platelets contain a 'S-transforming growth factor' (8-TGF) that is clearly different from PDGF (M. Sporn, National Institutes of Health). The \$-TGF (which, together with an a-TGF, transforms certain cell types in vitro) does not bind to the PDGF receptor and PDGF does not act as a \$-TGF in the transforming assay. Moreover, the aminoterminal sequence of \$FTGF is not that of

By contrast, a-TGFs bind to the epider-

*Element Cold Spring Harbor Conference on Cell Problemation and Career, 8-15 September.

Cancer research. like other rapidly grow- ; mal growth factor (EGF) recenter and EGF acts as an a-TGF in the cell transformation assay. Nevertheless, the newly

completed sequence of a rat a-TGF shows

it only to resemble ECE in the position of

its eysteine residues (G. Todaro, Oncoren,

Although the experiments are under way, neither E. Ruley (Cold Spring Harbor) nor H. Land (MIT) could set say whether any of the growth factors could replace one of the oncogenes in their powerful systems of cooperative transformation of primary rodent cells (see Nature 364, 596 and 602: 1983). Nov. with the cloned genes unavailable to them, have they yet been able to test the transforming genes of chicken and now human (Nature 365, 112; 1983) B-cell lymphomas described by A. Diamond (Dana-Farber Cancer Institutel: a positive result would dispel some of the hesitancy in accepting these as transforming genes, Surprisingly, D. Spandidos (Beatson Institute, Glasgow) claimed that transformation of primary cells does not necessarily need the cooperation of two oncogenes. Instead he claimed that many types of rodent cell could be transformed by the EJ-Ha-rus gene alone, when it was in a very high-expression vector, containing both a viral long terminal repeat and a simian virus 40 enhancer. Chinese hamster lung cells transformed by that vector formed tumours in nude mice. Others will want to test this carefully.

As to the possible functions of the p21 protein products of the ray gene family, only J. Feramisco (Cold Spring Harbor) had any specific suggestion. Starting from the fact that the p21 proteins are localized on the inner surface of the platma membrane of cells and are GTP-binding, he suggested that they may play a part in regulating the binding of growth factors to

"MARY Lasker is the kind of lady you might as well say yes to the first time". said Benno Schmidt at a dinner held after the meeting in her honour. Amongst those who have said yes in their time are numerous members of congress persuaded by her to put their vote behind the National Institutes of Health and the National Cancer Act of 1971. The Lanker drive against cancer began in 1945 when Mary and her husband Albert (who made a fortune with an advertising agency) decided to apply business methods to the American Cancer Society, They chose and half-paid for a new campaign director on condition that 25 per cent of the income went to basic research. The Lasker wealth also provides the annual Lasker awards, next best thing to a Nobel prize in medicine according to many Americans.

their recentors, in a manner reminiscent of the regulation of adenylate-cyclase through its GTP-binding subunit. Although Feramisco attempted to support his proposal with data on the stimulation of EGF binding by GTP in transformed cells and on stimulation of p21 phosphorylation in response to EGF binding, as yet the story is intriguing rather than convincing. Conorivably the study of our gene activation and function will be made easier by the adyear of seemingly excellent animal models. such as that described by M. Barbacid (National fastitutes of Health), in which all the mammary tumours induced in rate by a single dose of the carcinogen nitrosomethylurea contained a Ha-res transfor-

ming gene with the same point mutation in

NATURE WAS NOT A CATTORNEY PRO

Since both Ruley and Land have shown that the Elapone of adenovirus can serve as well as the muc sene (from the MC29 tumour virus or mouse plasmacytoma cells) in cooperating with the EJ-Ha-ser to transform primary cells, one question is whether they use the same mechanism, as is suggested by the sequence homology betwoen Ela and the central two-thirds of mye described by R. Rabston (University of California, San Francisco). A positive, but tentative, answer to the question was delivered by R. Kingston (MIT) who presented evidence that both Ele and muc-(from a plasmacytoma) were able to increase the expression of dihydrofolate reductase when either was co-transfected with the dibudeofolate reductase some attached to a heat shock gene promoter into CHO cells, T. Maniatis (Harvard Universitv) described similar experiments with E1a from which it was clear that the Ela gene

translagations between the muc. carrying chromosome and that carrying the gene for an immunoglobulin light or heavy chain eene. Only one example was reported (A. Hayday, MIT) in support of the attractive hypothesis that transcription of myc genes is increased in lymphoma cells because translocation brings them under the influence of the enhancer sequence recently located within immunoglobulin genes. For the vast majority of cases, where the truncated myc and the enhancer are on different chromosomes (see for example M. Neuberger and F. Calabi. Nature 303, 240: 1981). Hayday had an alternative explanation. Pointing out that the non-coding exon and the first coding exon of the myc gene share a highly homologous stretch of sequence, he proposed that the equivalent homologous sequences in the gene's messenger RNA would base-pair in-

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Another way of looking at it was P. Leder's (Harvard Medical School), whose own data and others (M. Cole, St Louis University School of Medicine and C. Croce. Wistar Institute) showed that transcription of the normal cellular myc gene was negligible in the face of high expression of the truncated allele. Perhaps, suggested Leder, truncation of the gene derepresses it by removing the site of action of a trans-acting suppressor; and perhaps the normal allele is suppressed by the high level of transcripts from the derepressed

hibiting translation; however, after trunca-

tion of the gene, base-pairing would be

eliminated. leading to increased myc gene

products

To end with the topic of tumourassociated proteins. Peter Rigby (Imperial

Finally Varda Rotter presented data that raised questions concerning the importance of the p53 protein which started life as a proposed marker of tumour cells, but later came to be considered as a cell cycle protein (see Nature 303, 660; 1983). From her sequence of the p53 gene of a transformed cell line that does not produce p53 it is clear that all but the amino terminus of the p53 coding sequence has been replaced by a Moloney virus-like sequence. If one transformed cell type can survive without p53, how essential is it for anything?

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The second p53 meeting

Centre d'Information Scientifque De L'A.R.C. Villejuif Paris

The p53 genome era

VARDA ROTTER.

P53 INTERNATIONAL WORKSHOP

APRIL 29 AND 30, 1987 29 ET 30 AVRIL, 1987

AT

CENTRE D'INFORMATION SCIENTIFIQUE DE L'A.R.C. RUE CAMILLE DESMOULINS

94800 VILLEJUIF

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2

MARIE CURIE MEMORIAL FOUNDATION RESEARCH INSTITUTE

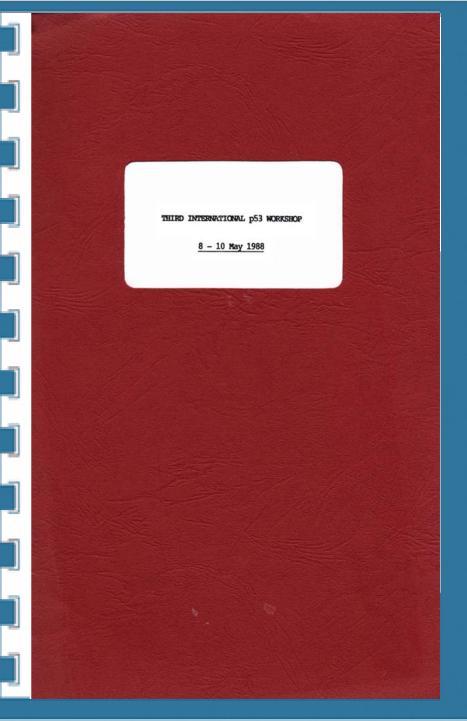
(THE CHART, OXTED, U.K.)



The third p53 workshop

The Marie Curie Memorial Foundation Research Institute The Chart Oxted, Surrey

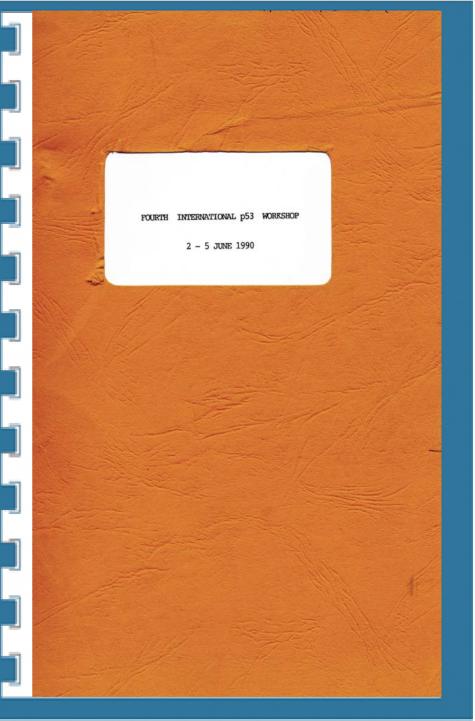
Still an ugly duckling!!
We are still very
confused!



The fourth p53 workshop

The Marie Curie Memorial Foundation Research Institute The Chart Oxted, Surrey

Turning into a beautiful Swan!!
Am I tumor Suppressor gene???



History: 1990 critical year in the history of p53!!

- *There is a wild type p53 protein and there are many mutant p53 proteins!!
- *Different half life of the proteins
- *Different activities

The story of p53

History: 1990-date

Wild type p53 is a tumor suppressor gene!!

Based on: in vitro studies Clinical evidences K/O mice!

Did we study all those years the mutant p53 proteins??



The 6th BIG DEAL of ONCOGENES



The fifth p53 workshop

Princeton University
PRINCETON
U.S.A

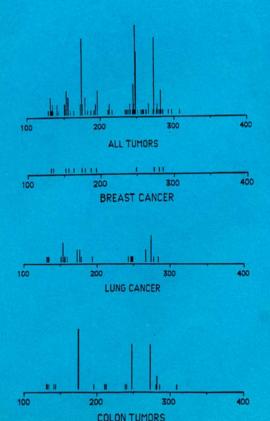
A beautiful Swan Indeed!

A bona-fida tumor suppressor!

*in vivo significance:
in mouse and man!
What about K/O mice?
*Transcription factor
*Apoptosis!!

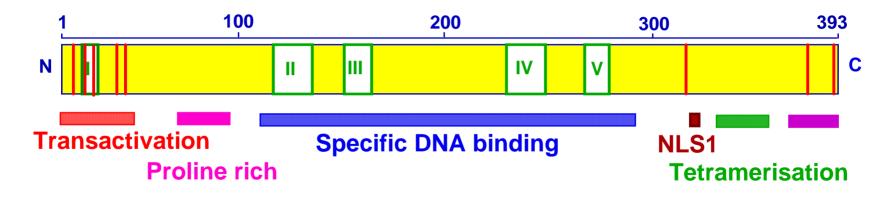
The Fifth Annual p53 Workshop

P53 POINT MUTATIONS IN HUMAN TUMORS



The story of p53

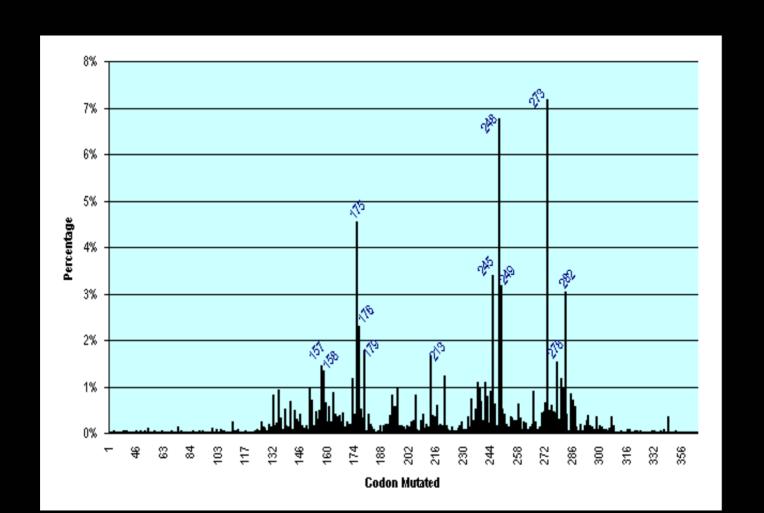
History: 1992-date
The "domain" periods
A transcription factor!!



Negative regulation of DNA binding

Protein-protein interactions, Transcriptional repression apoptosis

Spectrum of p53 mutation in human tumors IARC Database



6th p53 workshop Tibirias, Israel 1992



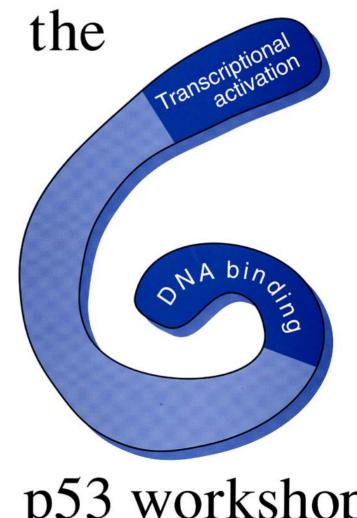
The Sixth p53 workshop

The Weizmann Institute Rehovot, Israel

The Sea of Galille, Israel

Functional Domains! Finally it makes sense!!

A new partner: mdm2 The love loop! To be or not to be



p53 workshop

1-5 November 1992, Tiberias, Israel



AMERICAN AMOCRATION FOR THE AMPLICATION FOR THE SCHOOL SCHOOL

Science

24 Discharge 1993 Vol. 262 • Pages 1945-2108

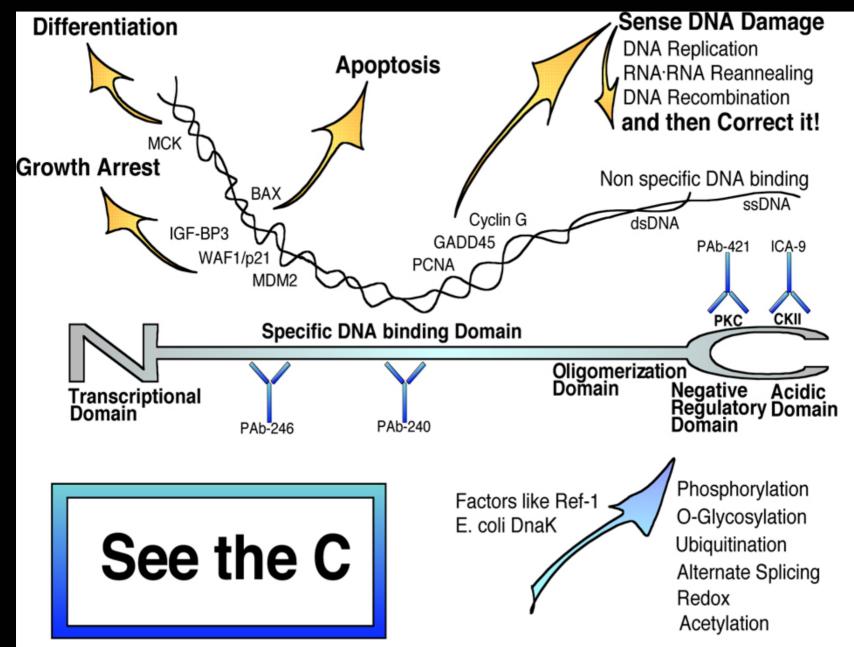
p53 Molecule of the Year

A Genetic Key to Cancer,

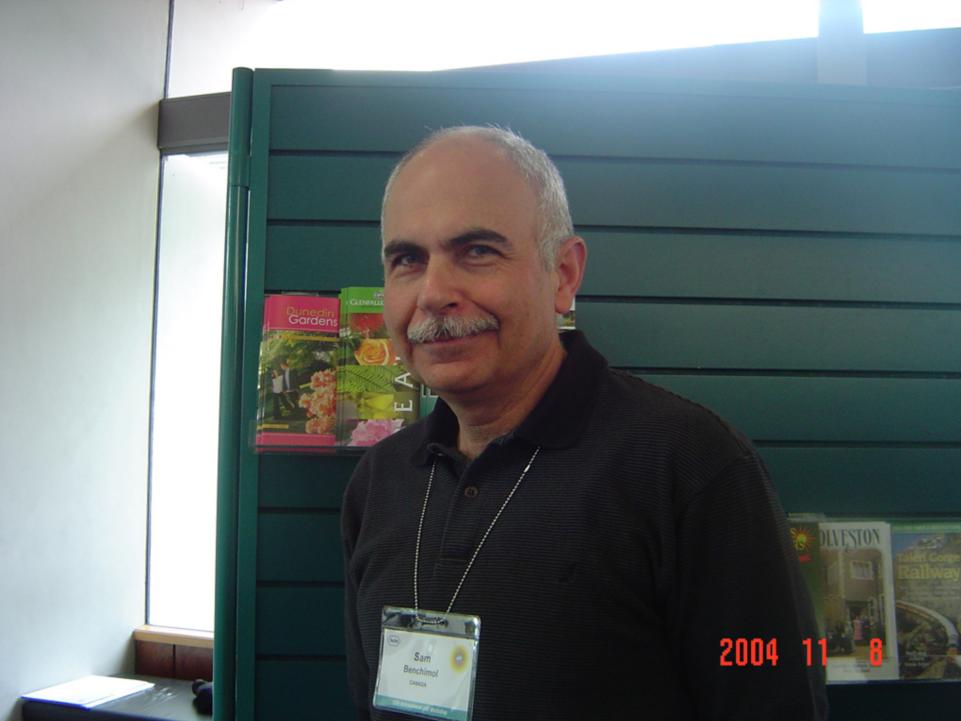


The DNA binding period!

Binding Specific p53 consensus sequences
Non-specific DNA sequences



Wolkowicz PZ



The seventh p53 workshop

Toronto, Canada Muskoka

Just more good news:

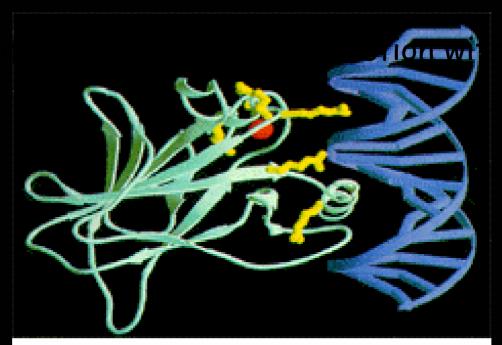
*p53-DNA Crystals appeared!!

*K/O mice-grow tumors!!

*Germ line p53 mutations!!

7th p53 Workshop

Program and Abstracts



The structure of the core domain of the p53 protein (light blue) bound to DNA (dark blue) The six most frequently mutated amino acids in human cancers are shown in yellow - all are residues important for p53 binding to DNA. Red ball: zinc atom. [Reproduced from Cho, Y., et al. (1994) Science, 265, 346-355, with kind permission.]

Clinical data make sense!!!

Varda Rotter, Weizmann Institute of Science, Rehovot, Israel



The eight p53 workshop
Dundee
Scotland

P53-based therapy?

More about the p53-mdm2 Relationship!!

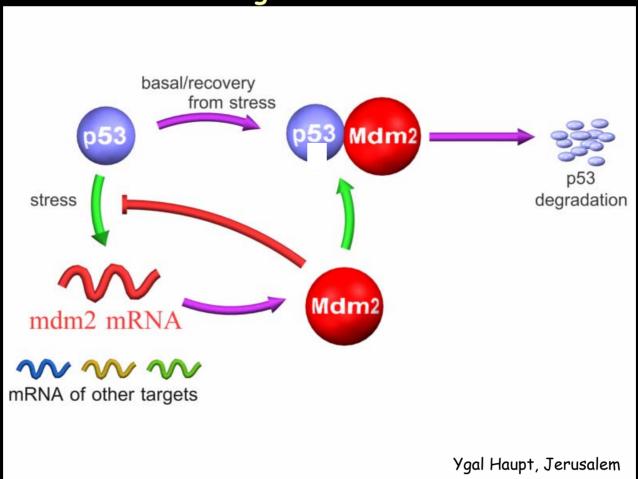
8th International p53 Workshop



Dundee, Scotland 5th-9th July, 1996



Mdm2 inhibits p53 activities and promotes it for proteasomal degradation



How the p53-Mdm2 auto-regulatory loop is interrupted in response to stress?

The ninth p53 workshop

Elunda Beach Crete Greece

A wonderful meeting almost every one agrees with everyone!

Are we ready for the clinical trials?

9th p53 Workshop

Elounda Beach

Crete

Greece

May 9-13, 1998

The story of p53

Finally p53 finds a FAMILIA!

p73

P63







The story of p53

p53 gene therapy







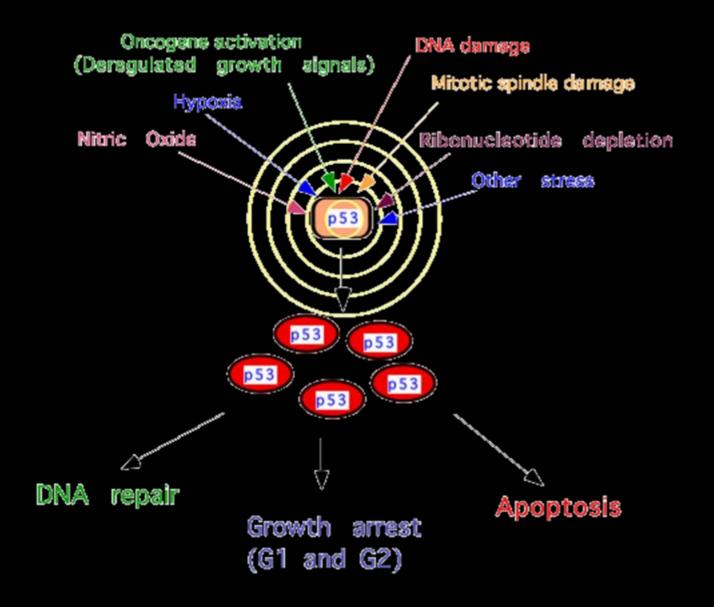
The tenth p53 workshop Monteray USA

10th International p53 Workshop

Major Sponsorship provided by:

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UCSF Comprehensive Cancer Center
UCSF Program in Cell Cycle Disregulation
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Barcelona

A great meeting organized by Carlos Cordon-Cardo and Carol Privas
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Abstracts

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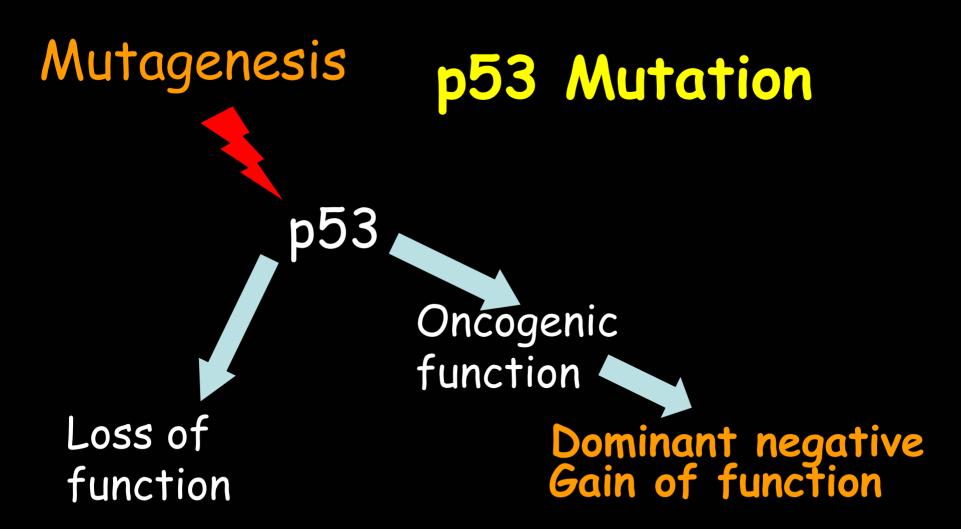
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So where are we today???



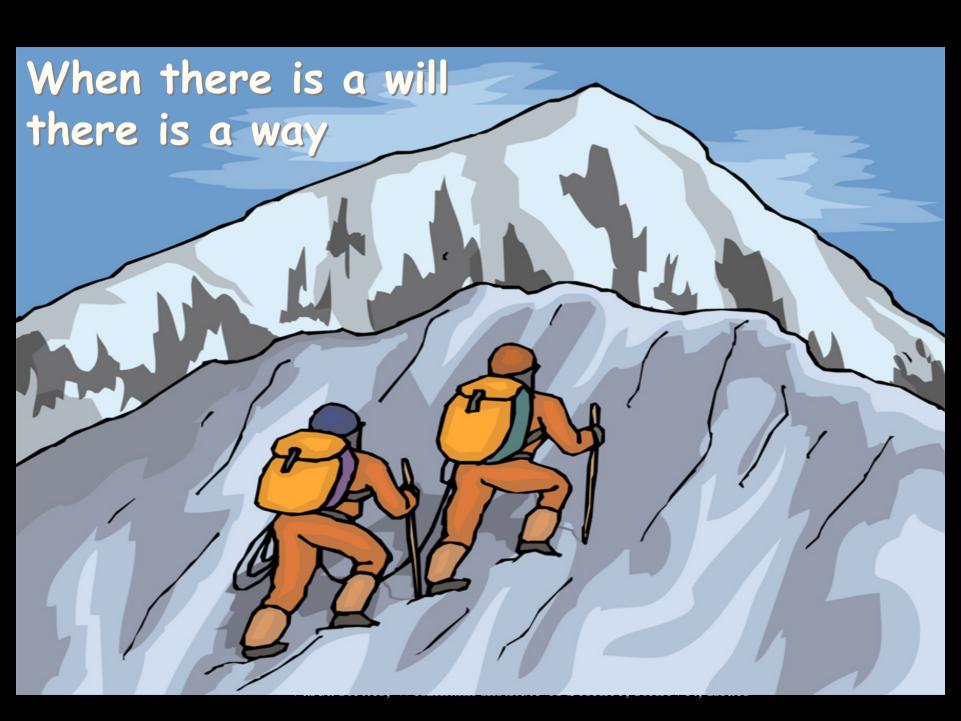








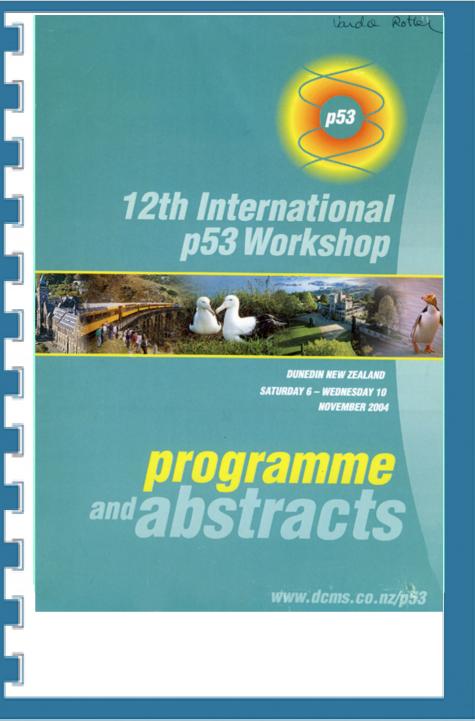




New -Zealand

A great meeting organized by Antony Braithwaite

Dunedin, New Zealand



USA

Jill Brgonetti
Carlos Cardon-Cardo
Wei Gu
Scott Lowe
Arnold J. Levine
Jim Manfredi
Ute Moll
Carlo Privesa





Jill Bargonetti
Carlos Cordon-Cardo
Wei Gu
Scott Lowe
Arnold J. Levine
Jim Manfredi
Ute Moll
Carol Prives (Chair)

Antony Braithwaite Curtis Harris David Lane Moshe Oren Varda Rotter Yoichi Taya