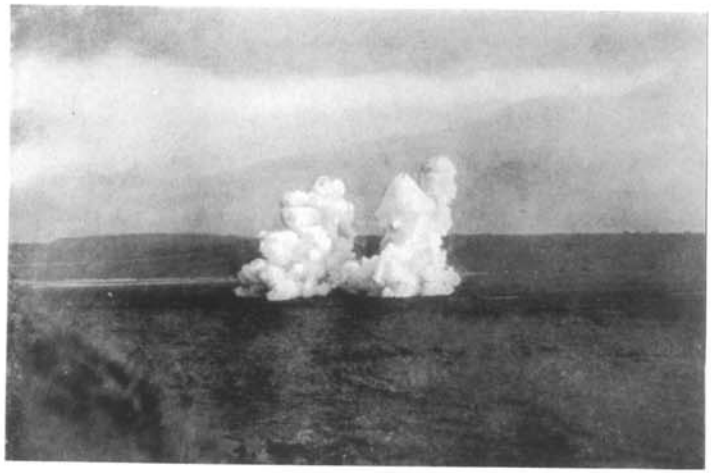
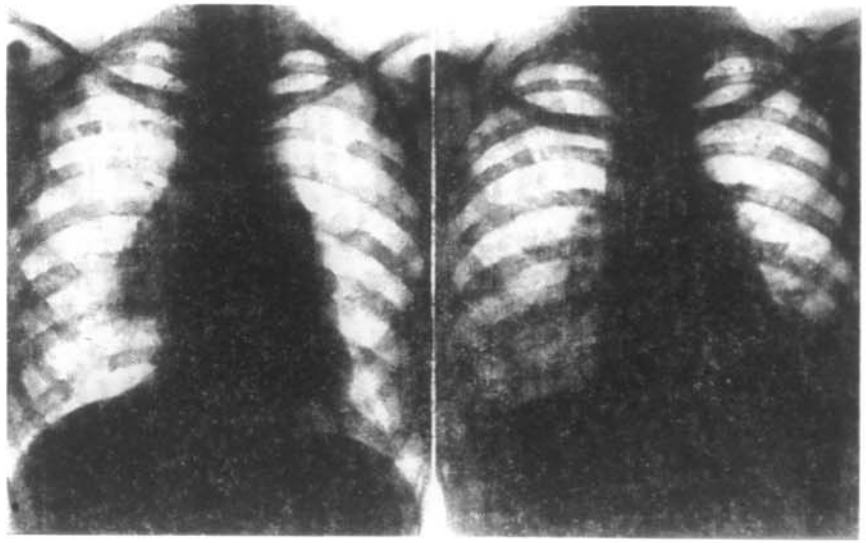
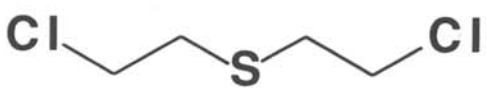
A PERSONAL HISTORY OF DNA DAMAGE AND REPAIR RESEARCH 1960-2005

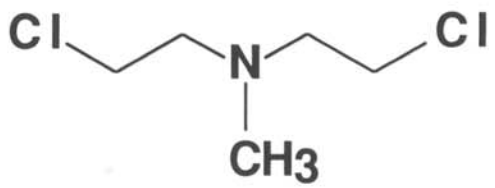
DR. KURT KOHN
LABORATORY OF MOLECULAR PHARMACOLOGY
CENTER FOR CANCER RESEARCH
NATIONAL CANCER INSTITUTE

From historical review: Kohn KW (1996) *Cancer Res.* 56: 5533-46.









SCIENCE

Vol. 103, No. 2675 Friday, April 5, 1946

The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides

Alfred Gilman, Major, and Frederick S. Philips, 1st Lieutenant, SnC, AUS

Pharmacology Section, Medical Division, CWS, Edgewood Arsenal, Maryland

AT THE CONCLUSION OF WORLD WAR I the theory was generally accepted that mustard gas exerted its vesicant action by releasing hydrochloric acid intracellularly. A few isolated reports appeared describing remote systemic effects of mustard gas on hematopoietic tissues (*1–3*), the gastrointestinal tract (*3–5*), and electrolyte and fluid balance (*3*). Although in the interim between wars the adverse effects of mustard gas on leucopoietic tissues (*6–8*) and on the growth of experimental tumors (*9*) received some attention, biological research on chemical warfare agents remained relatively quiescent. With the advent of World War II research on war gases was resumed, and the newer knowledge and technics of a quarter of a century of trials have also been made of the possible value of the nitrogen mustards in the treatment of neoplasms, in particular those of lymphoid tissue.

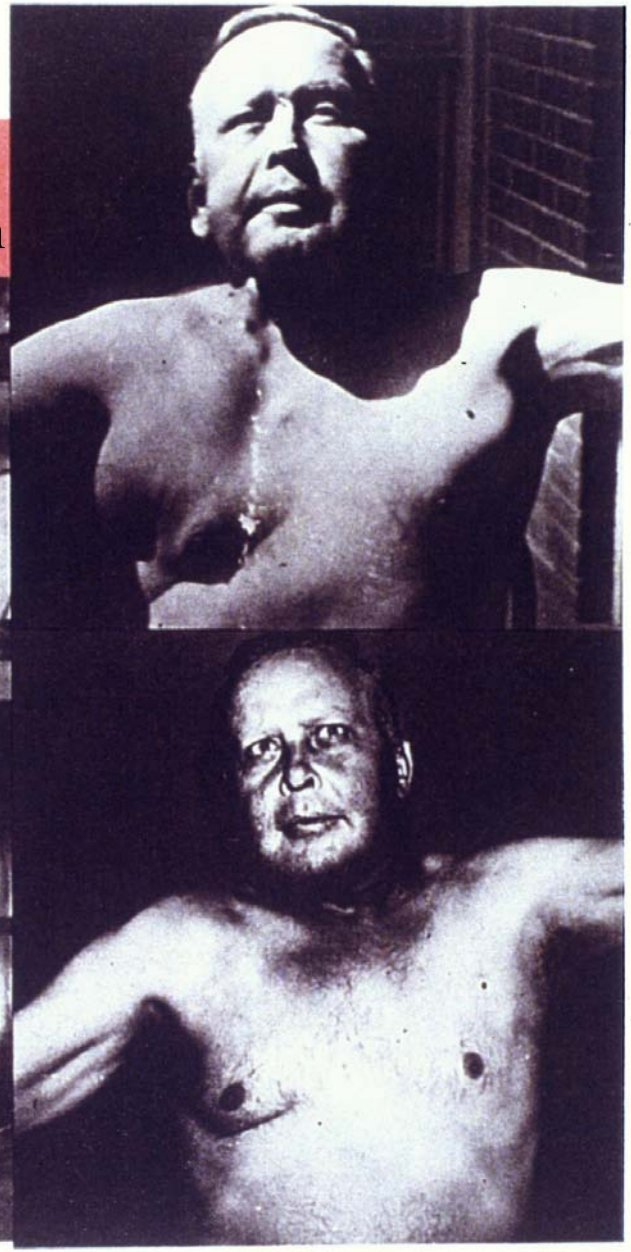
The fact that agents classified as "confidential" were involved in the above studies has heretofore precluded the possibility of presenting the results in the open literature. This report reviews briefly the contributions which have focused attention on the cellular actions of the mustard compounds and gives a general description of their systemic effects as well as a preliminary statement of their possible clinical applications. Because of space limitations important contributions of many investigators will have to go unmentioned.

First lymphoma patient before & after treatment with nitrogen mustard

Alfred Gilman

Louis Goodman

Alfred Gilman and Louis Goodman, circa 1942

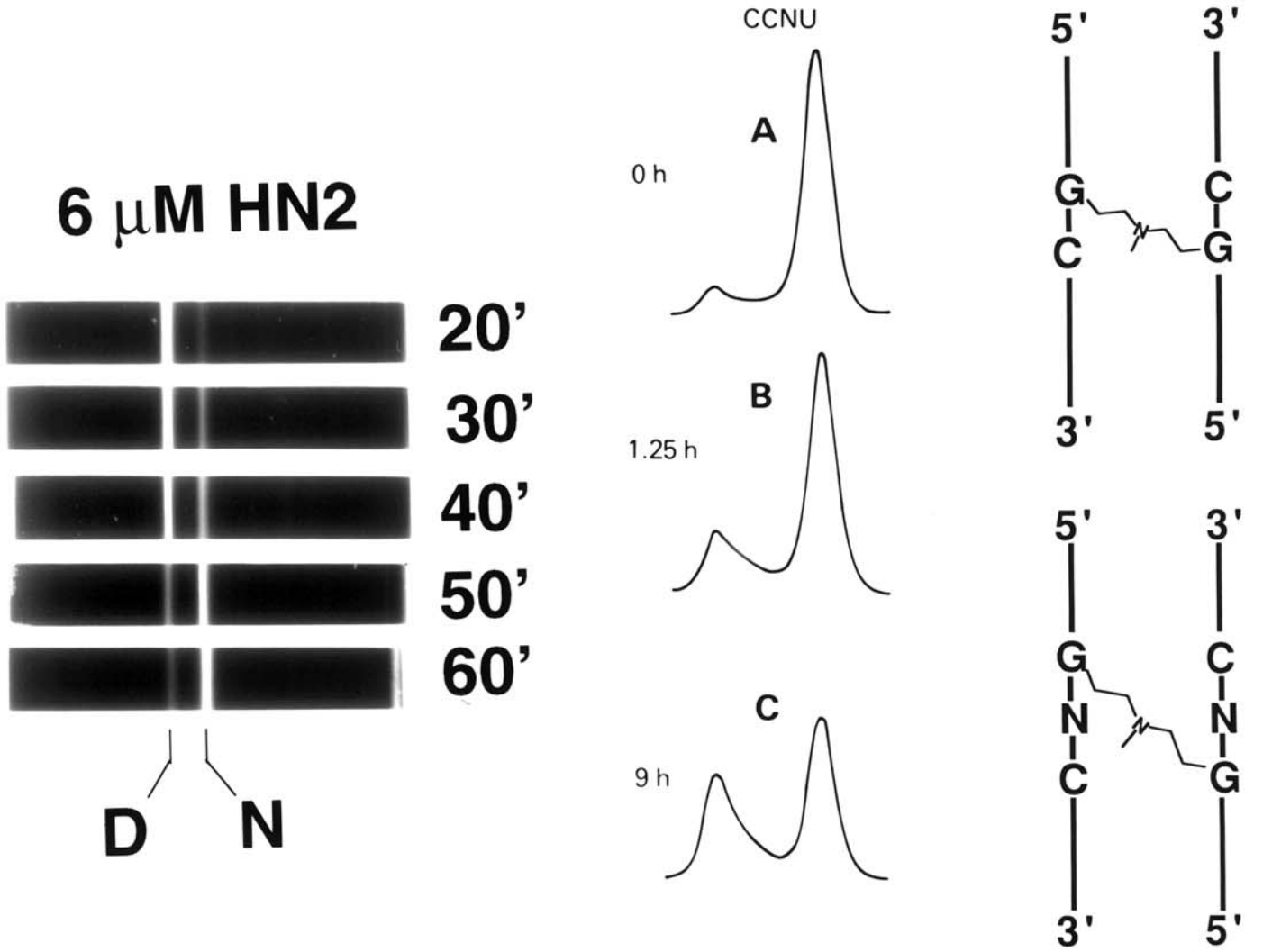


First patient with lymphosarcoma treated with nitrogen mustard, photographed before and after therapy. Note reduction in lymph nodes and facial edema.

circa 1942

From: Michael B. Shimkin "Contrary to Nature" PHS, NIH 1977

Cf: Kohn KW, Spears CL, Doty P (1966) *J. Mol. Biol.* 19: 266-288.



Proceedings of the National Academy of Sciences of the United States of America

CROSS-LINKING AND REPAIR OF DNA IN SENSITIVE AND RESISTANT STRAINS OF E. COLI TREATED WITH NITROGEN MUSTARD

By Kurt W. Kohn, Neal H. Steigbigel, and Carlos L. Spears

LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

Communicated by Paul Doty, March 23, 1965

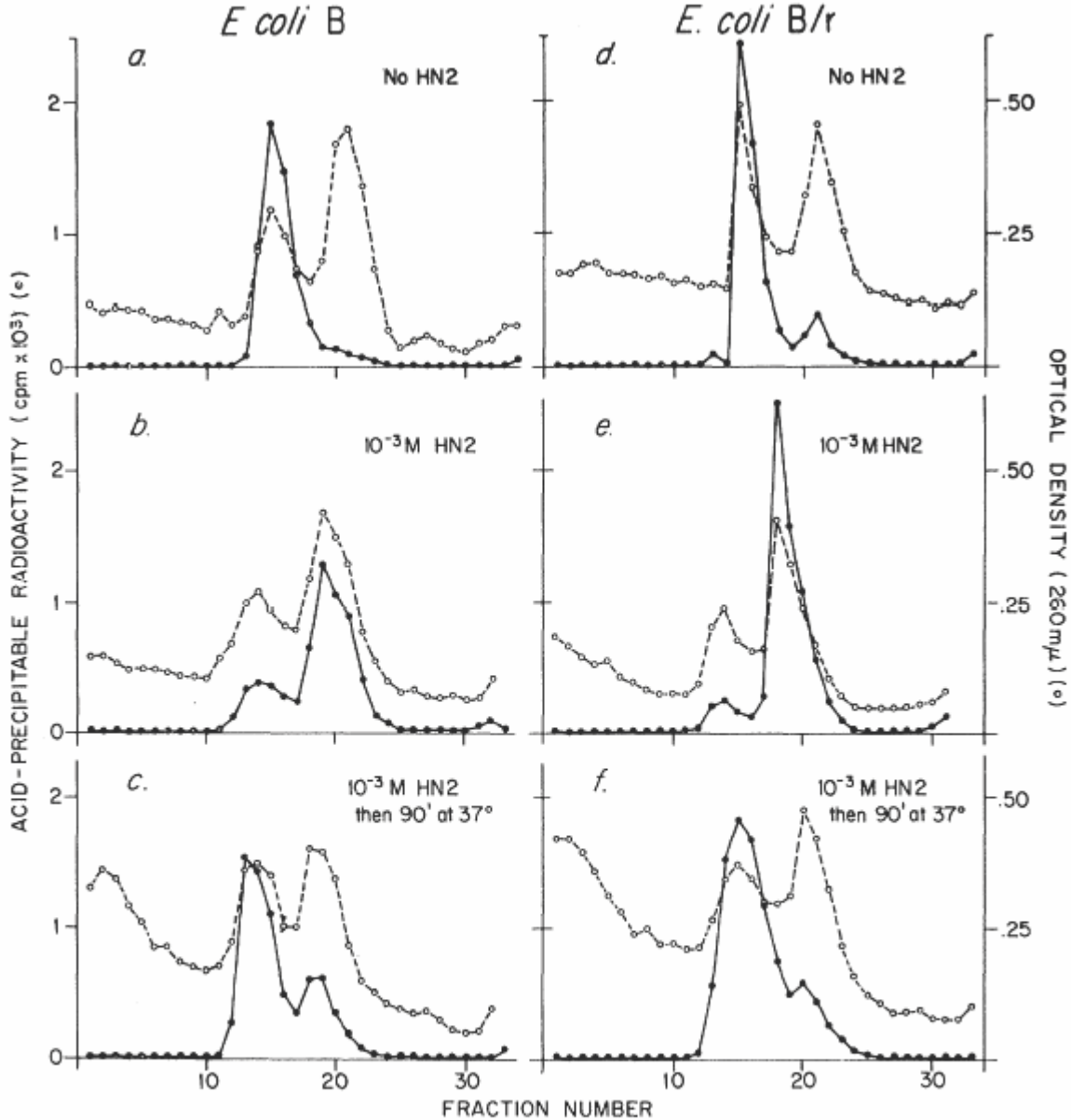


FIG. 3.—Effect of HN2 on denaturability of labeled DNA in *E. coli* B (Hill) (*a–c*) and B/r (ORNL) (*d–f*). Optical density curves (dashed) represent the distribution of the excess unlabeled *E. coli* DNA mixed with the cells prior to NaOH treatment (see text). Right and left bands define the positions of native and denatured DNA, respectively.

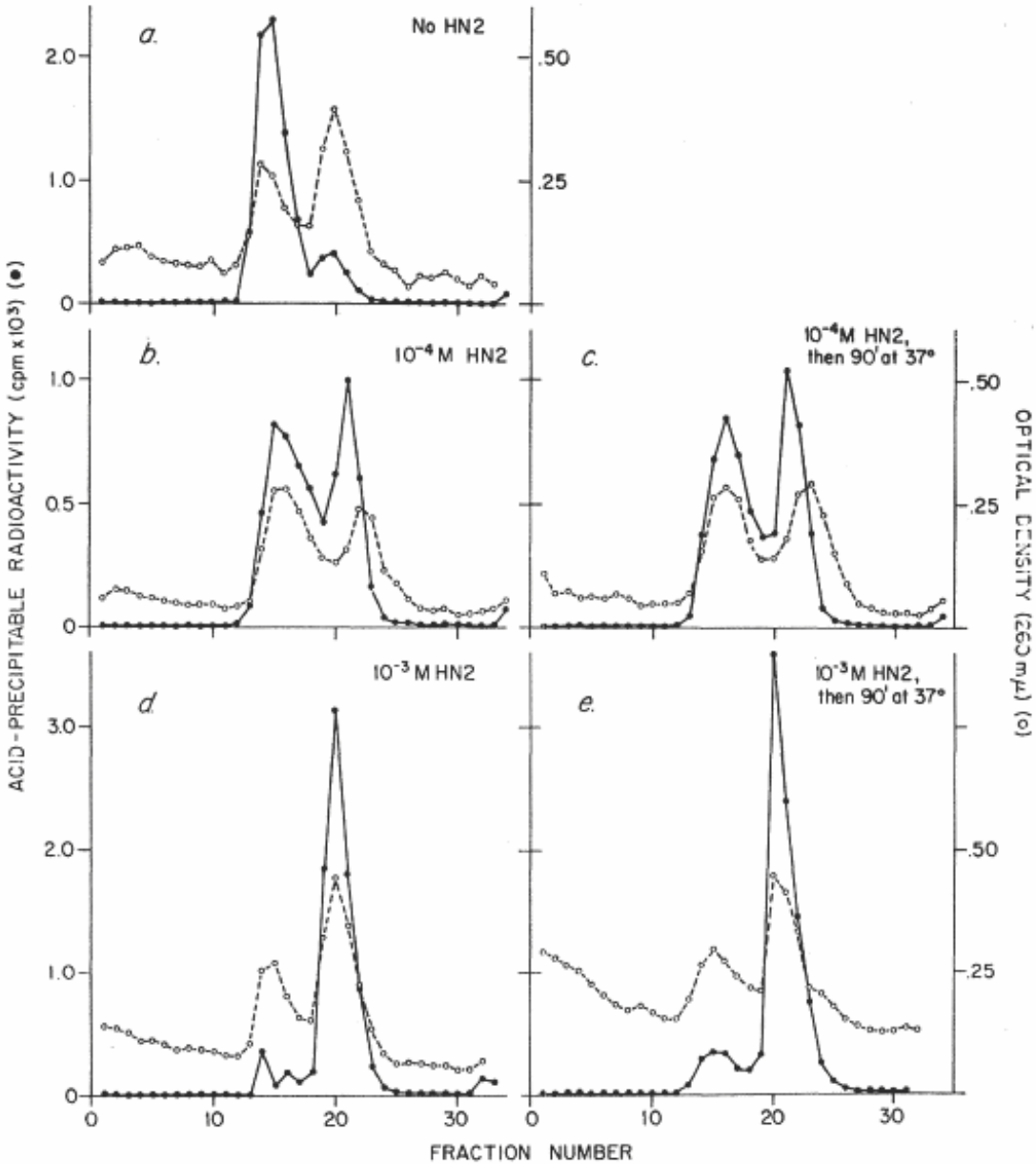
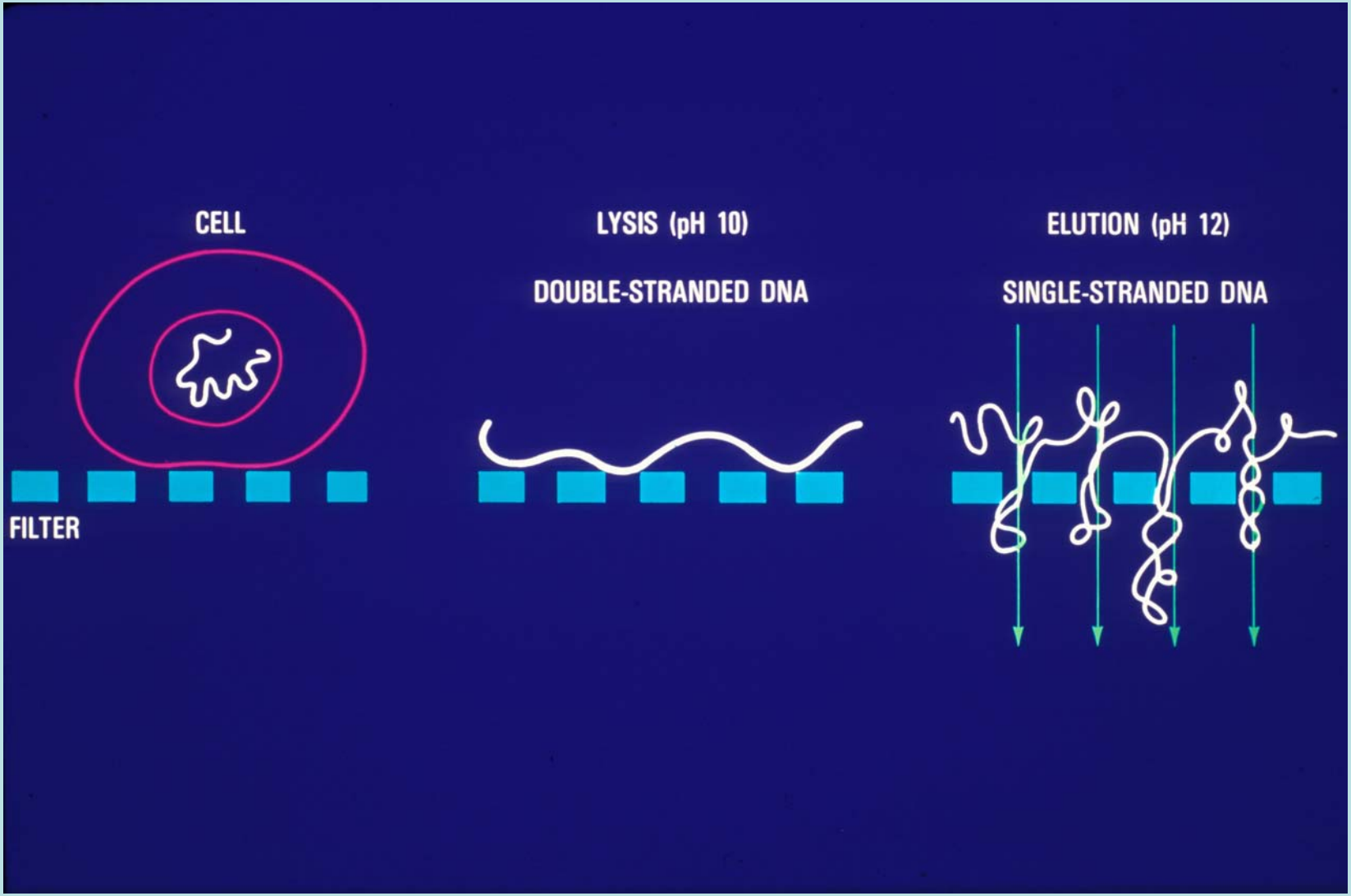
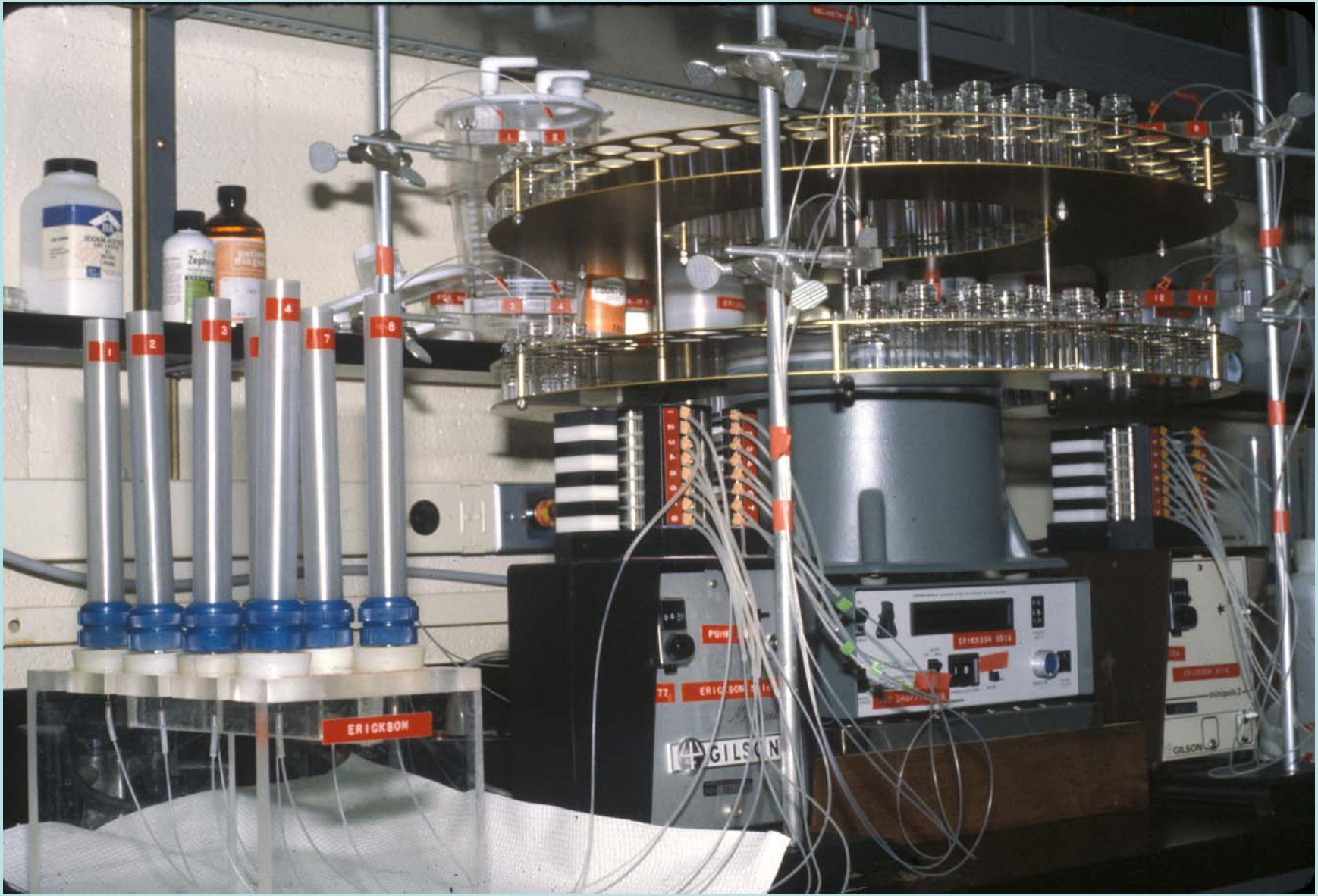


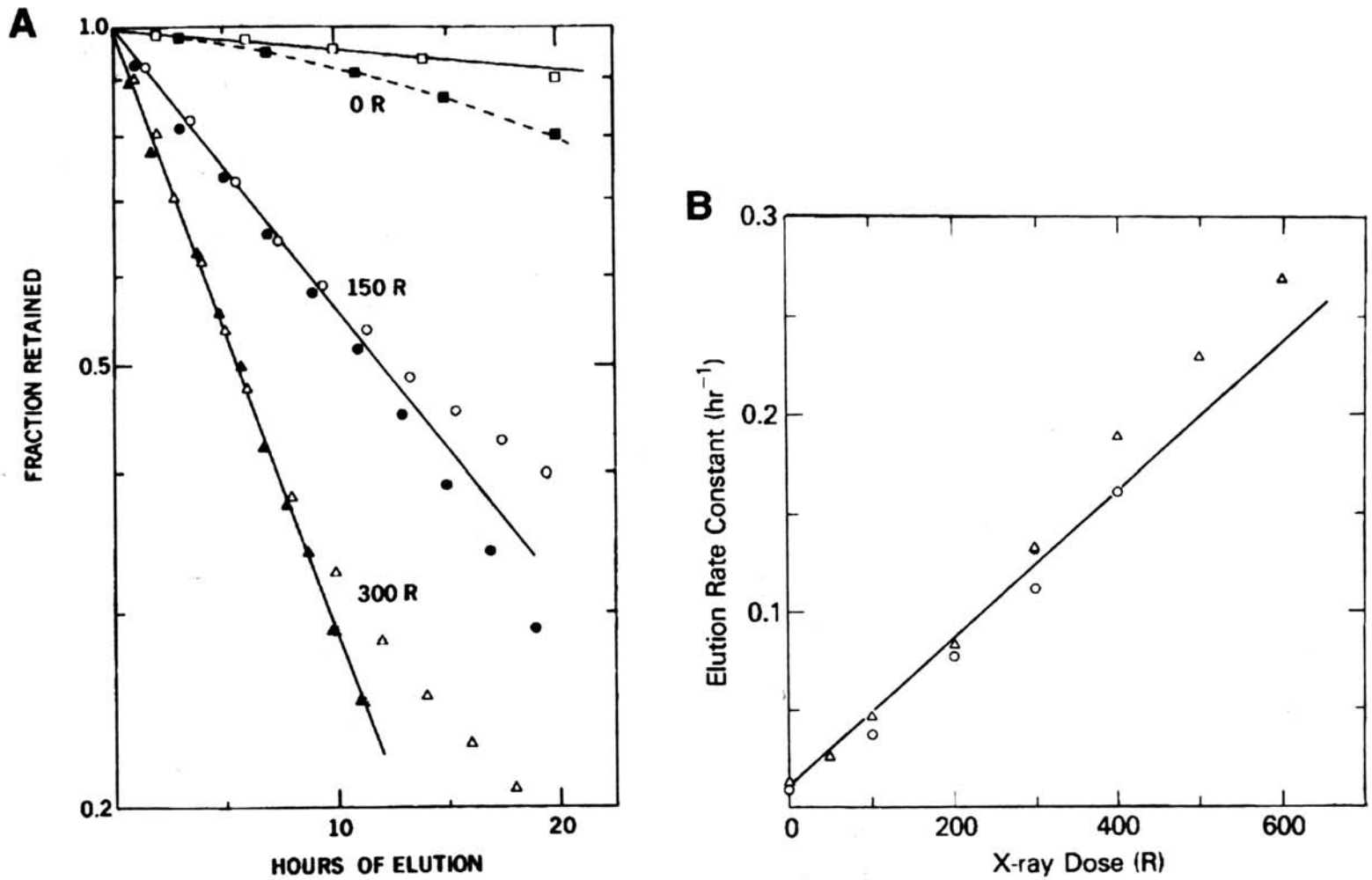
FIG. 4.—Effect of HN2 on denaturability of labeled DNA in *E. coli* Bs_1 (see text and caption to Fig. 3). (The HN2-treated portion of the reference DNA used for *b* and *c* was unintentionally treated with a 10-fold higher concentration of HN2 than used for the other experiments. This explains the shift of this band towards lower densities.[2])


CELL
LYSIS (pH 10)
DOUBLE-STRANDED DNA
ELUTION (pH 12)
SINGLE-STRANDED DNA
FILTER

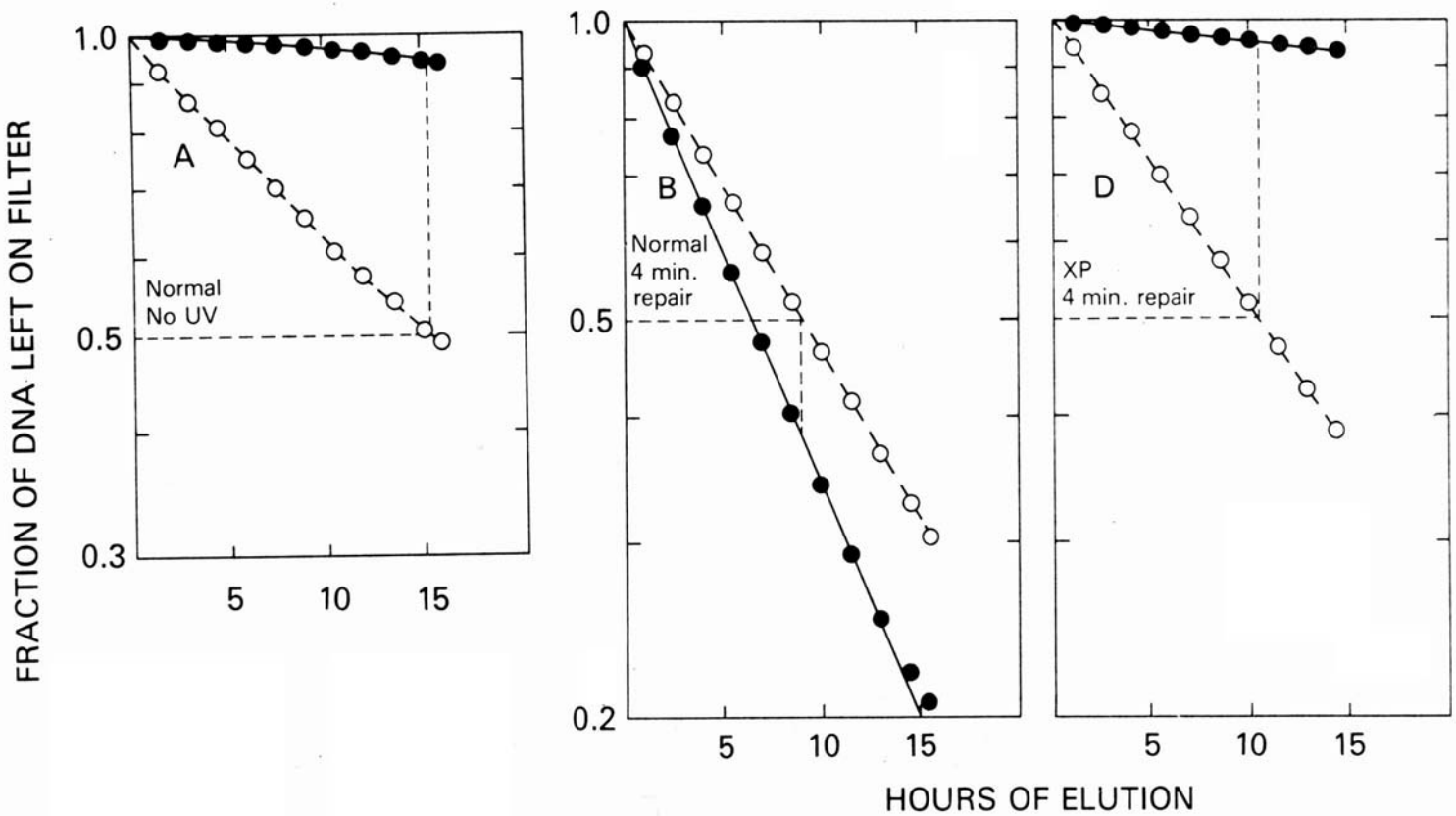


ALKALINE ELUTION APPARATUS

From historical review: Kohn KW (1996) *BioEssays* 18(6): 505-513.

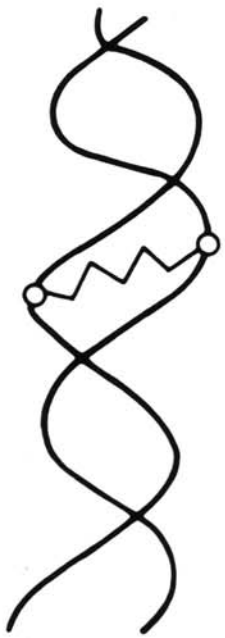


Fornace AJ, Jr, Kohn KW, Kann HE, Jr. DNA single-strand breaks during repair of UV damage in human fibroblasts and abnormalities of repair in xeroderma pigmentosum. Proc. Natl. Acad. Sci. USA *73*: 39-43, 1976.

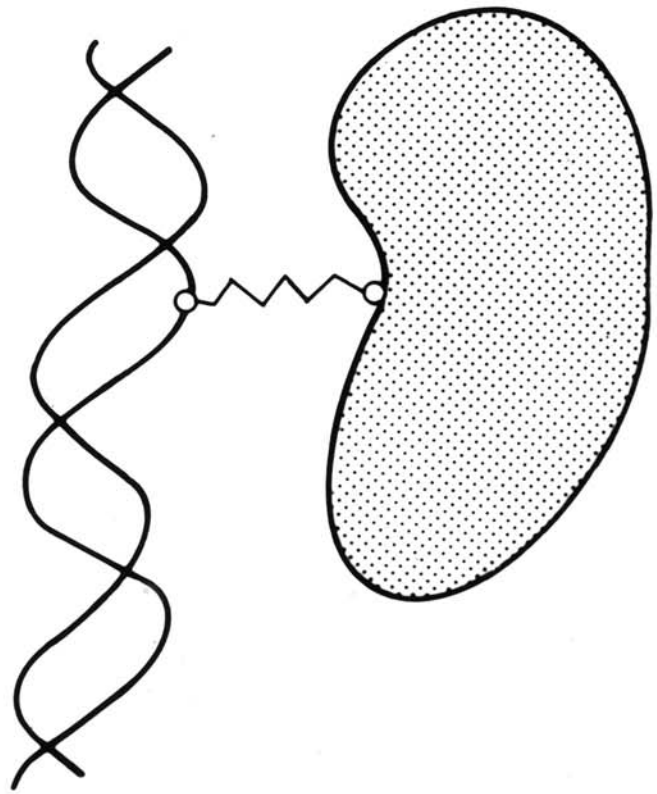


Fornace AJ, Jr. and Kohn, KW. DNA-protein crosslinking by ultraviolet radiation in normal human and xeroderma pigmentosum fibroblasts. Biochim. Biophys. Acta *435*: 95-103, 1976.

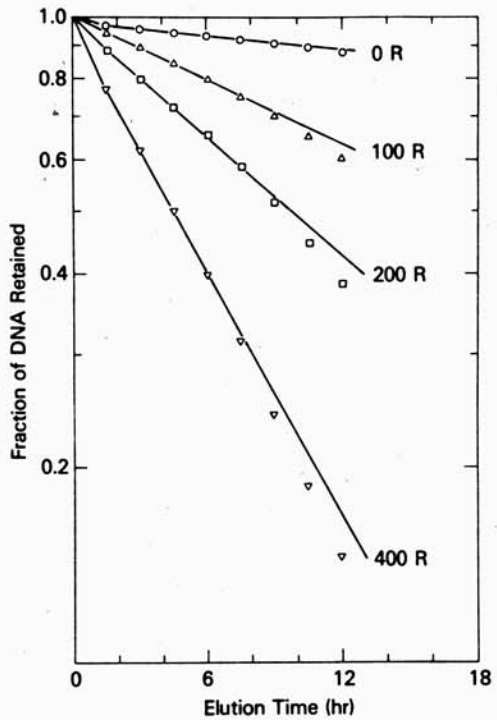
INTERSTRAND
CROSSLINK

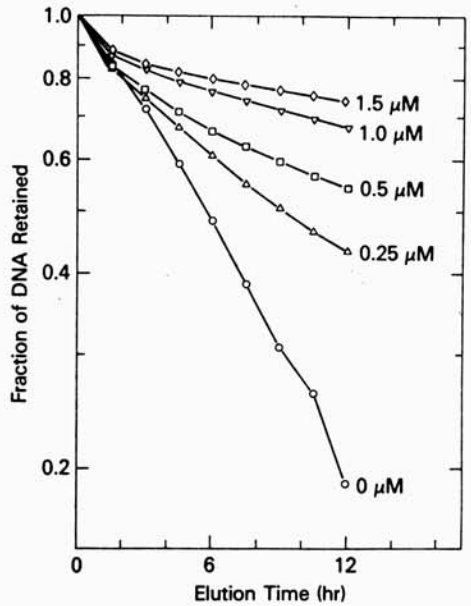


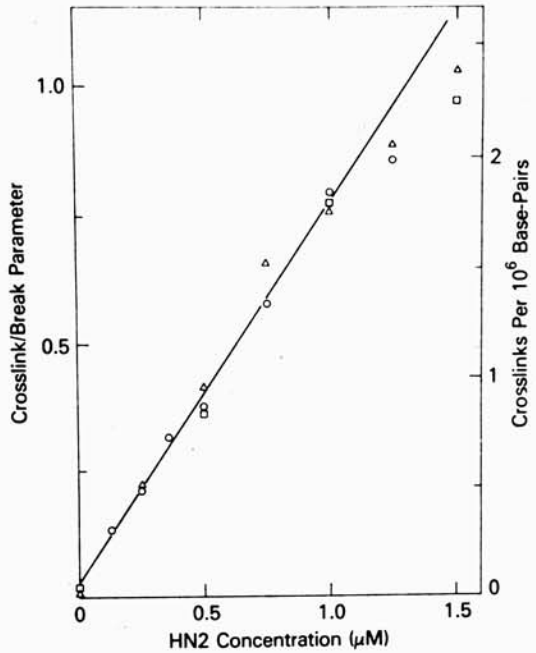
DNA-PROTEIN
CROSSLINK



Kohn KW, Erickson LC, Ewig RA, Friedman CA (1976) *Biochemistry* 15: 4629-37.







DNA damage/repair researchers after fellowship in the Laboratory of Molecular Pharmacology 1965-1995

Clinical Associates/Fellows

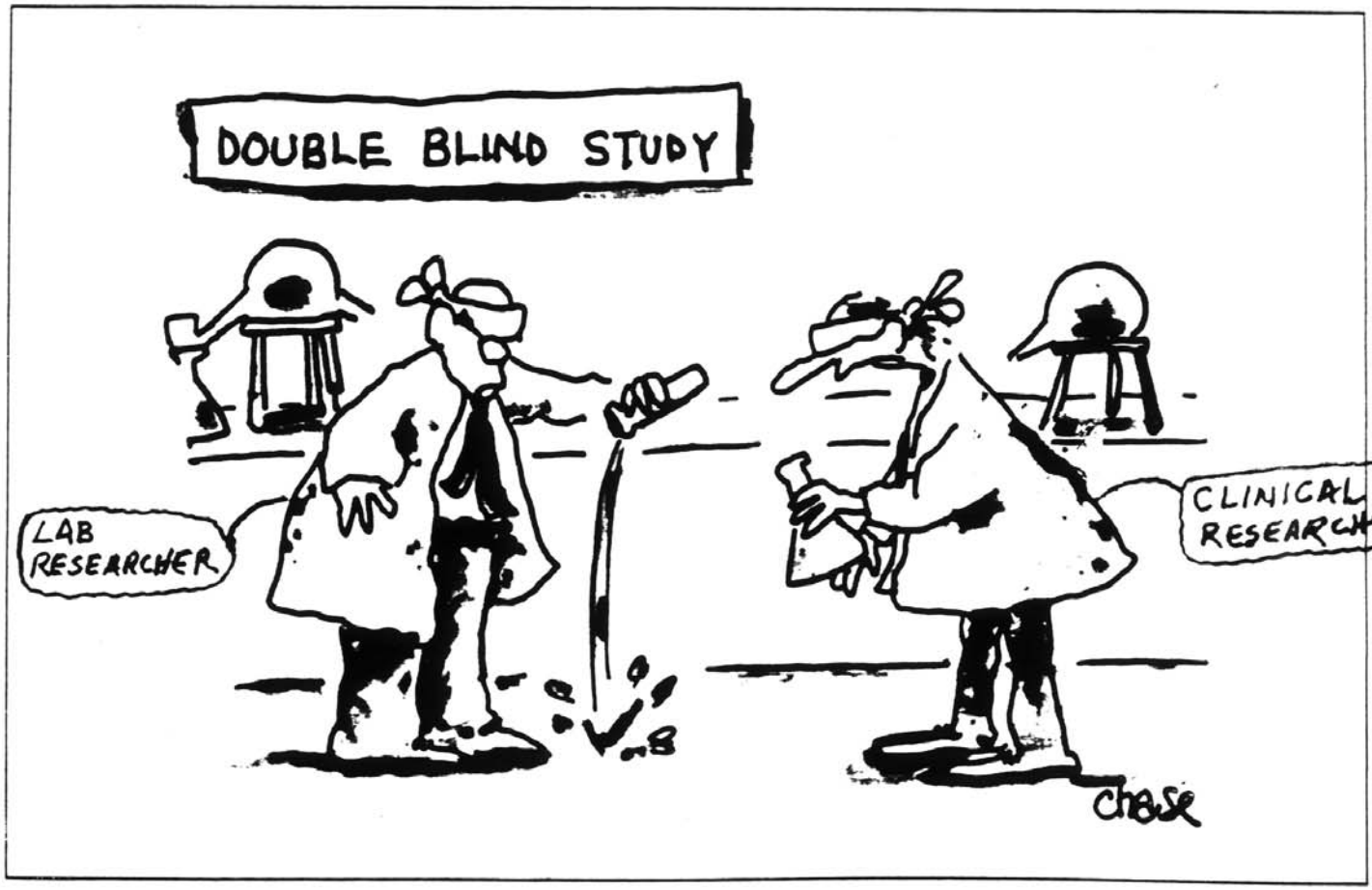
Herbert E. Kann, Jr.
Albert J. Fornace, Jr.
Leonard Zwelling
Warren Ross
Yves Pommier
Jonathan M. Ducore
Kenneth Micetich
Maurizio D'Incalci
Guy Laurent
Vilhelm A. Bohr
Karsten Wassermann

Research Associates/Post-docs

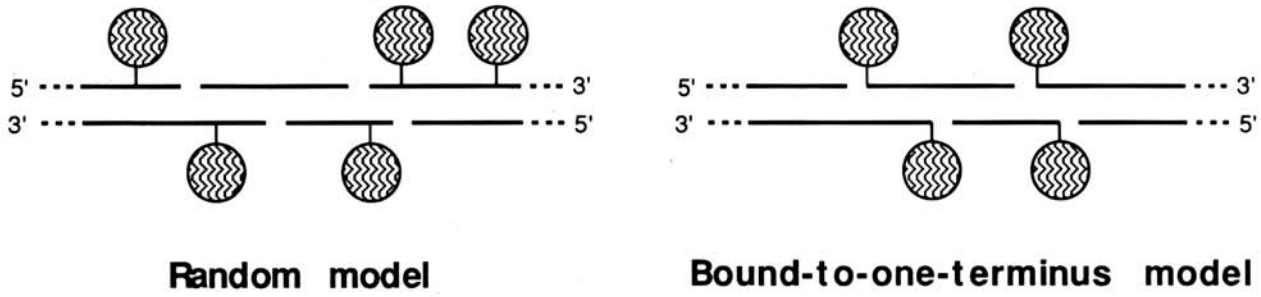
Leonard C. Erickson
Neil W. Gibson
John A. Hartley
Matthews Bradley
Jan Filipski
Michael R. Mattern
Leszek Szmigiero
William B. Mattes
Judith Markovits
Christine Jaxel
Giovanni Capranico
Richard Bertrand
Patrick M. O'Connor
Francois Leteurtre

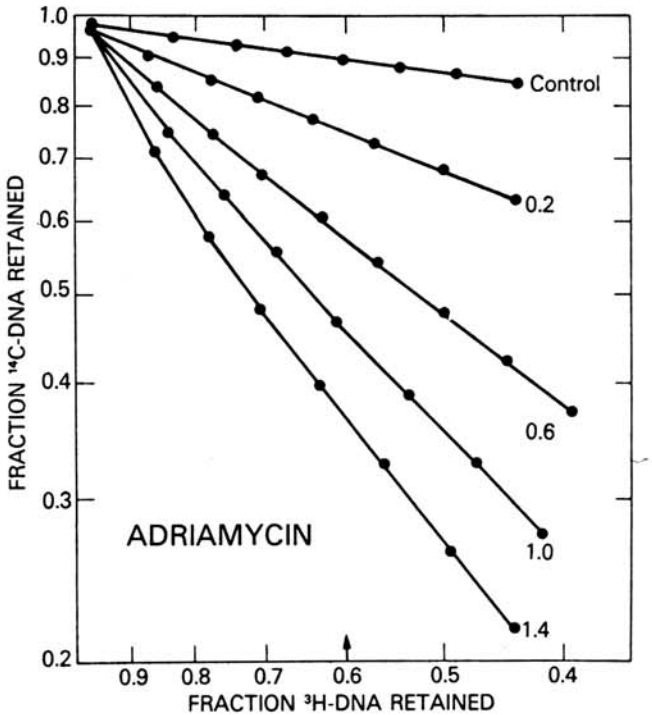
LABORATORY OF MOLECULAR PHARMACOLOGY 1985

LABORATORY OF MOLECULAR PHARMACOLOGY 1987

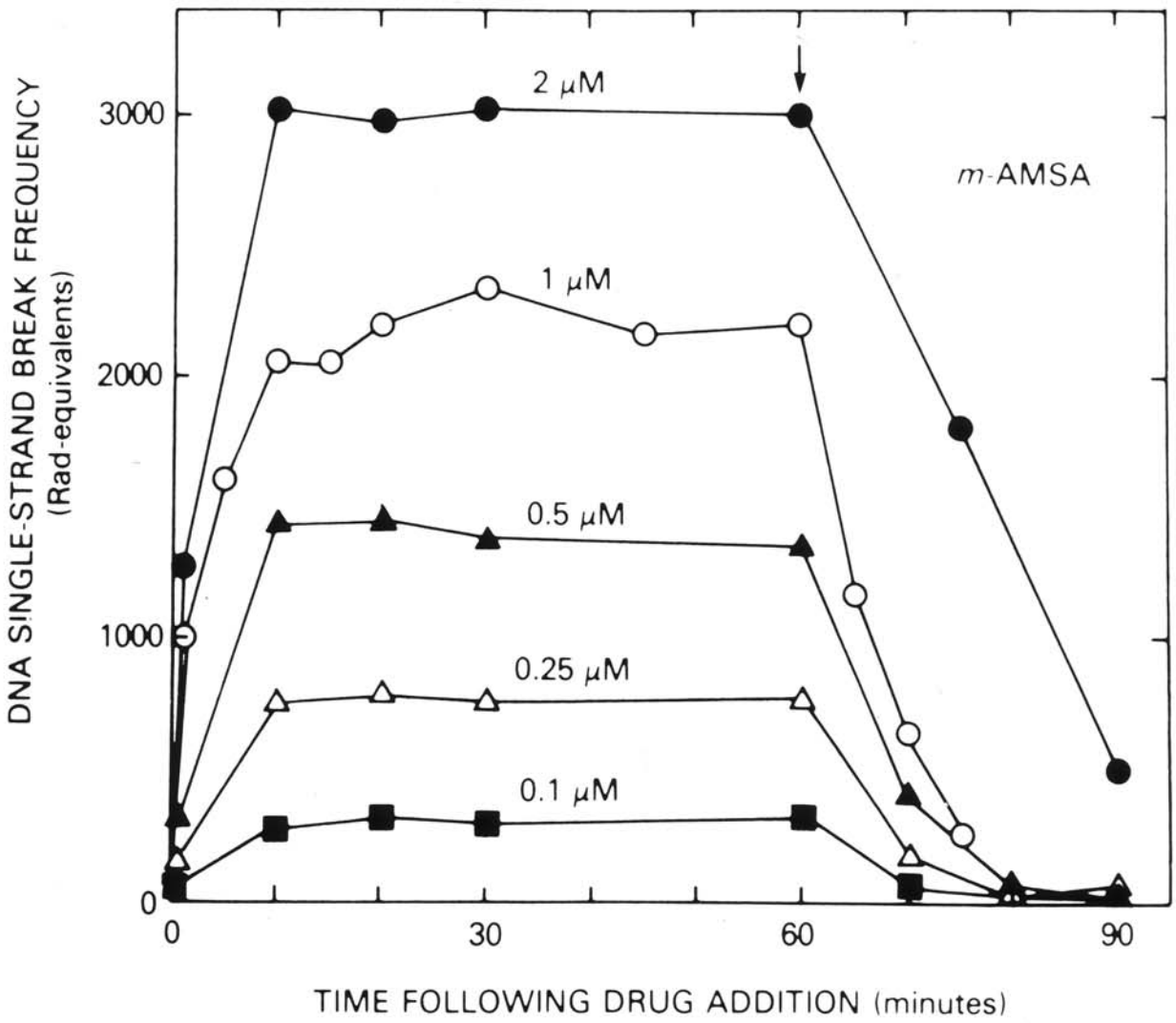

DOUBLE BLIND STUDY
LAB RESEARCHER
CLINICAL RESEARCHER
chase

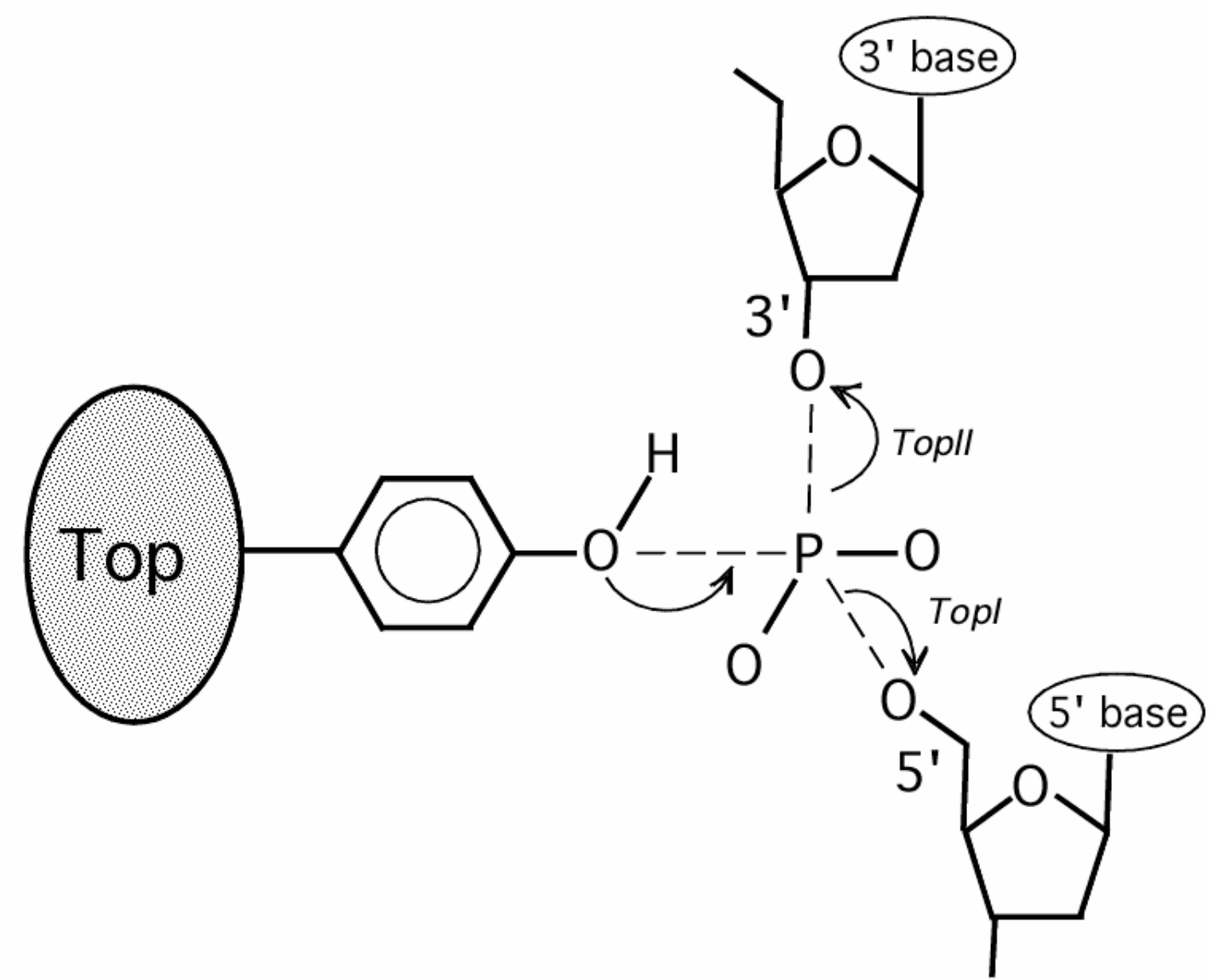
Ross WE, Glaubiger DL, Kohn KW (1978). *Biochim. Biophys. Acta 519:* 23-30.



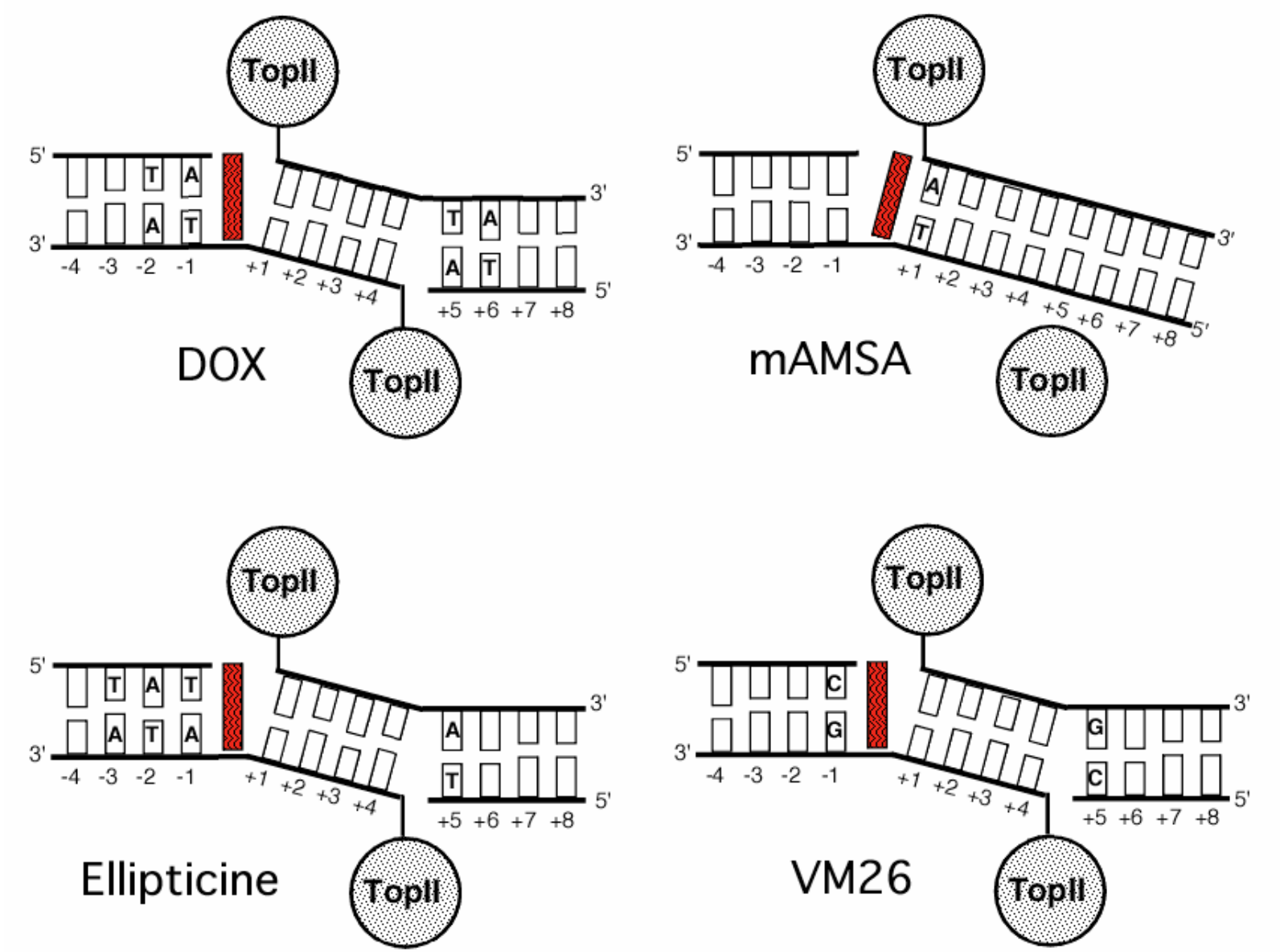


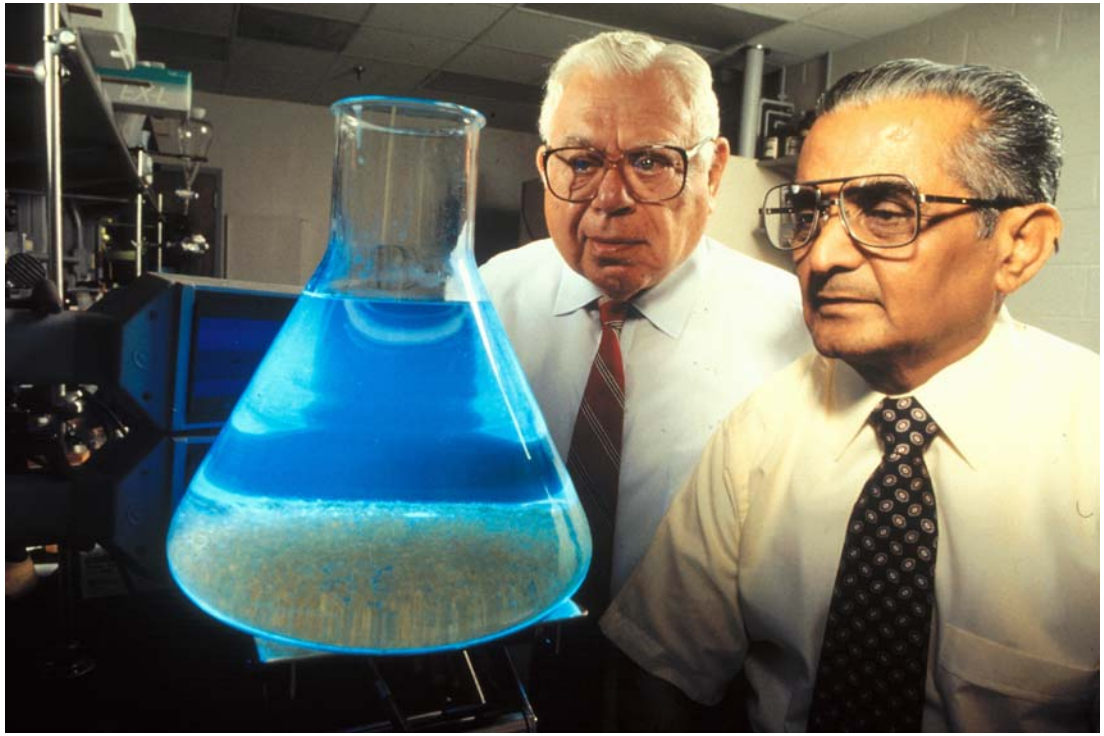
Zwelling LA, Michaels S, Erickson LC, Ungerleider RS, Nichols M, Kohn KW. *Biochemistry* 20: 6553-6563 (1981).

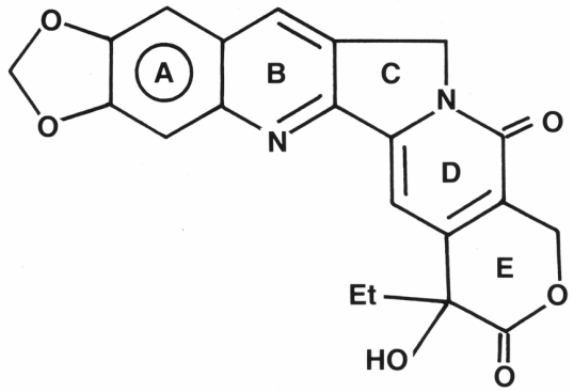



3' base
O
3'
O
TopII
H
Top
O
P
O
O
TopI
O
5' base
5'
O

Capranico G, Kohn KW, Pommier Y (1990). Local sequence requirements for DNA cleavage by mammalian topoisomerase II in the presence of doxorubicin. *Nucl. Acids Res.* 18: 6611-19.





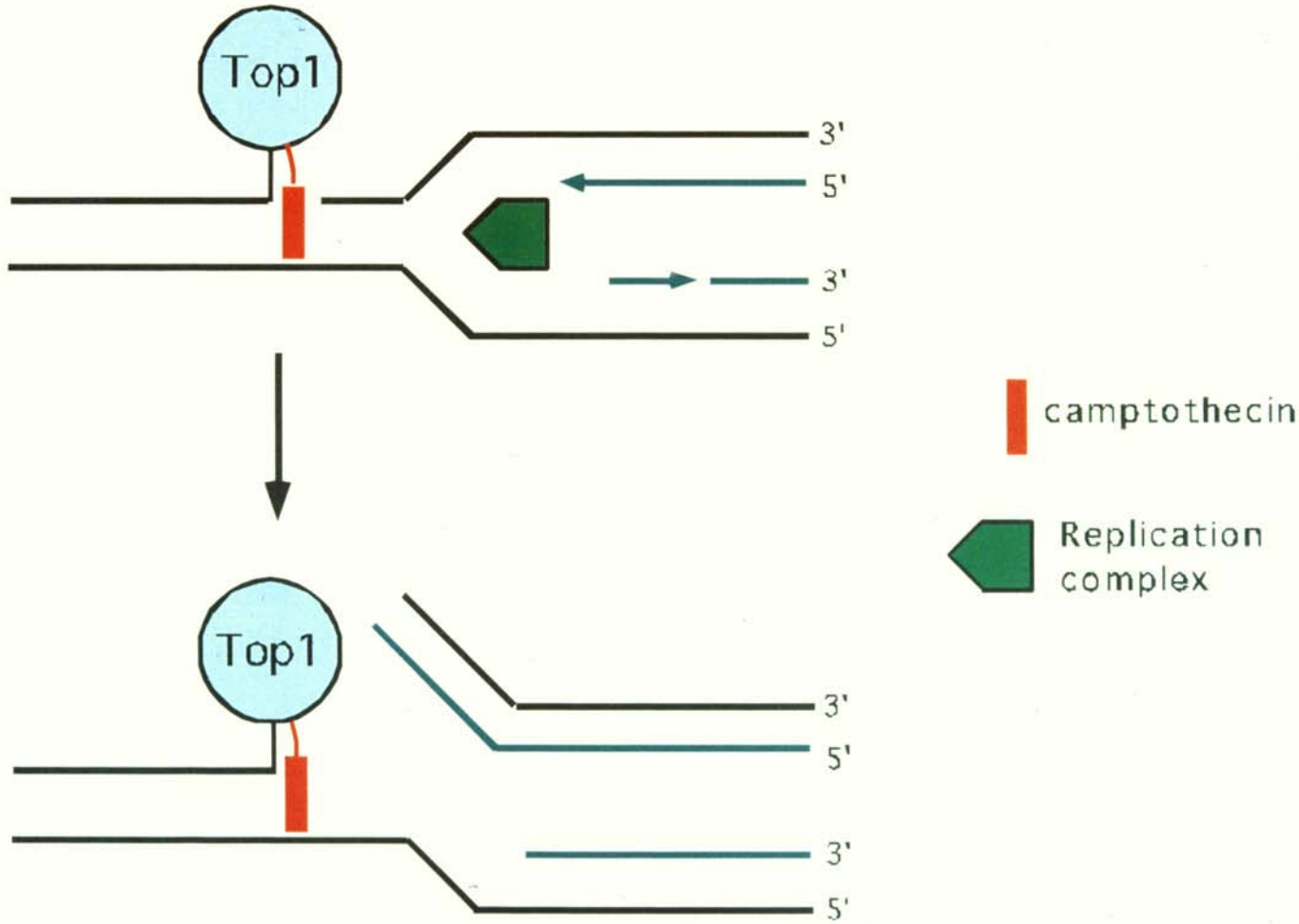


10,11-methylenedioxy-(RS)-Camptothecin
(MDO-CPT)

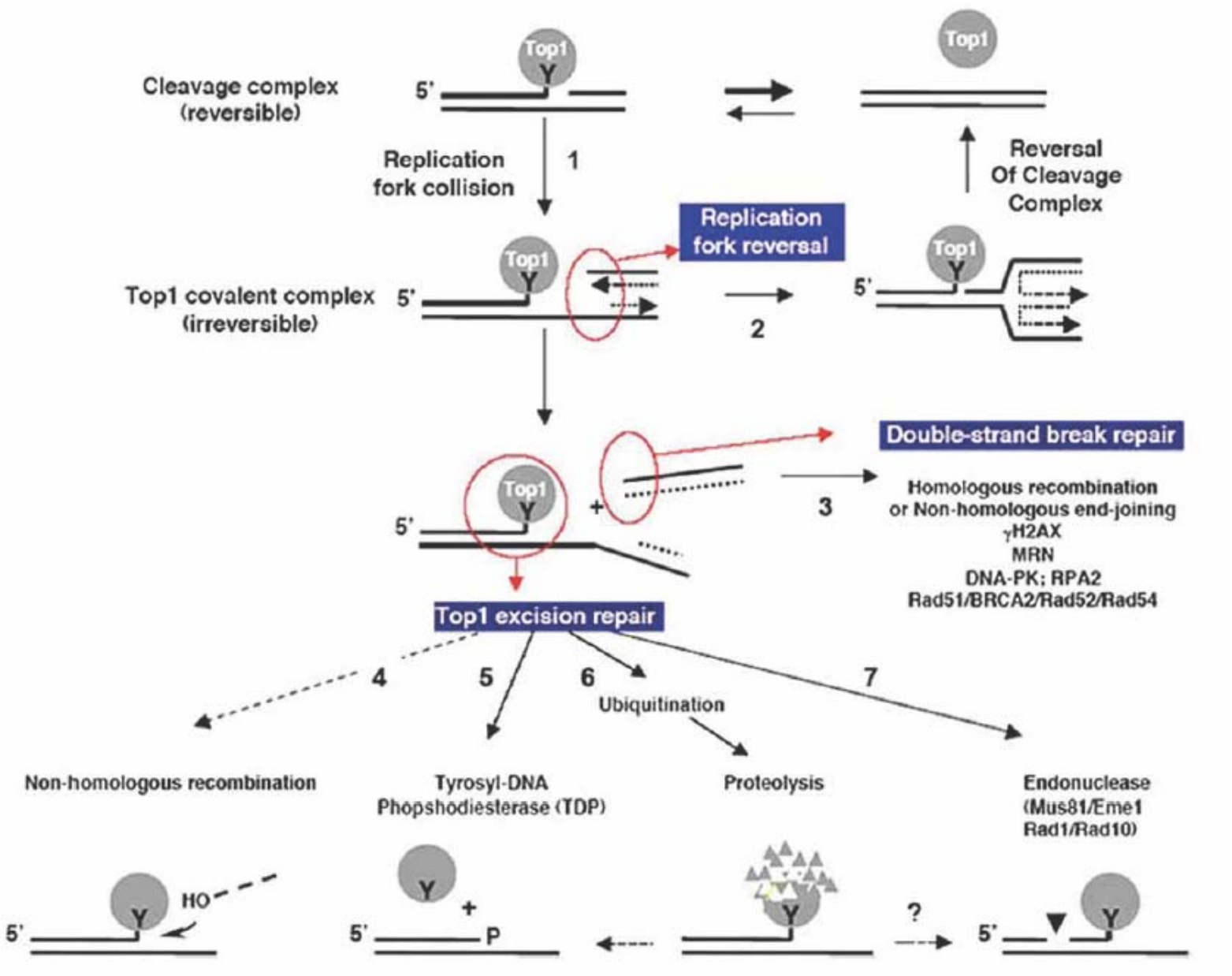
Monroe Wall

Mansukh Wani

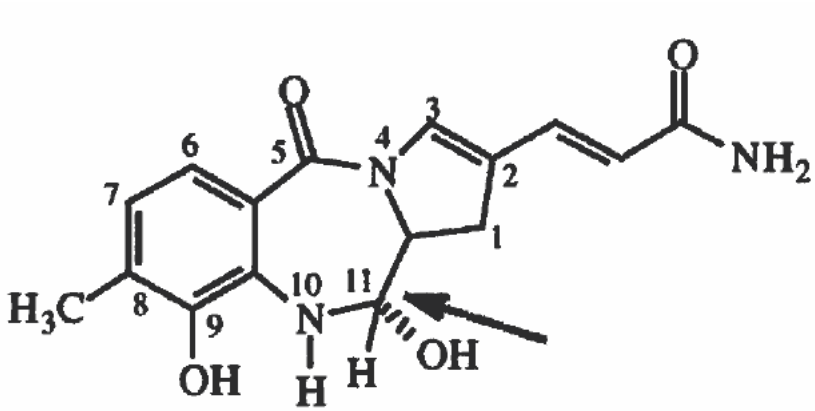
DNA Replication-Encounter (DRE) Lesion



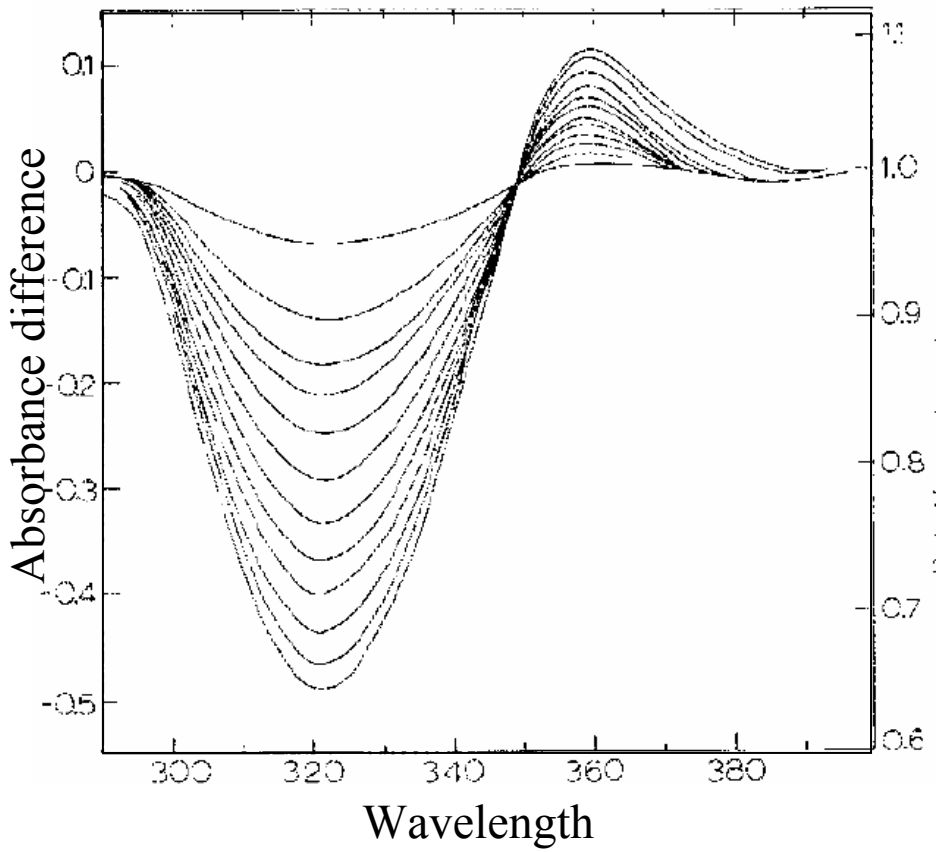
Pommier Y (2004) *Curr. Med. Chem. - Anticancer Agents* 4: 429-434.

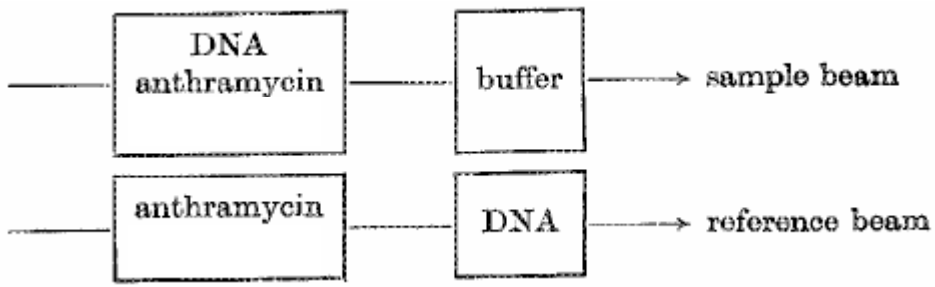


Kohn KW, Bono V, Kann HE *BBA 155:* 121 (1968)
Kohn KW & Spears CL *J.Mol.Biol. 51:* 551 (1970)

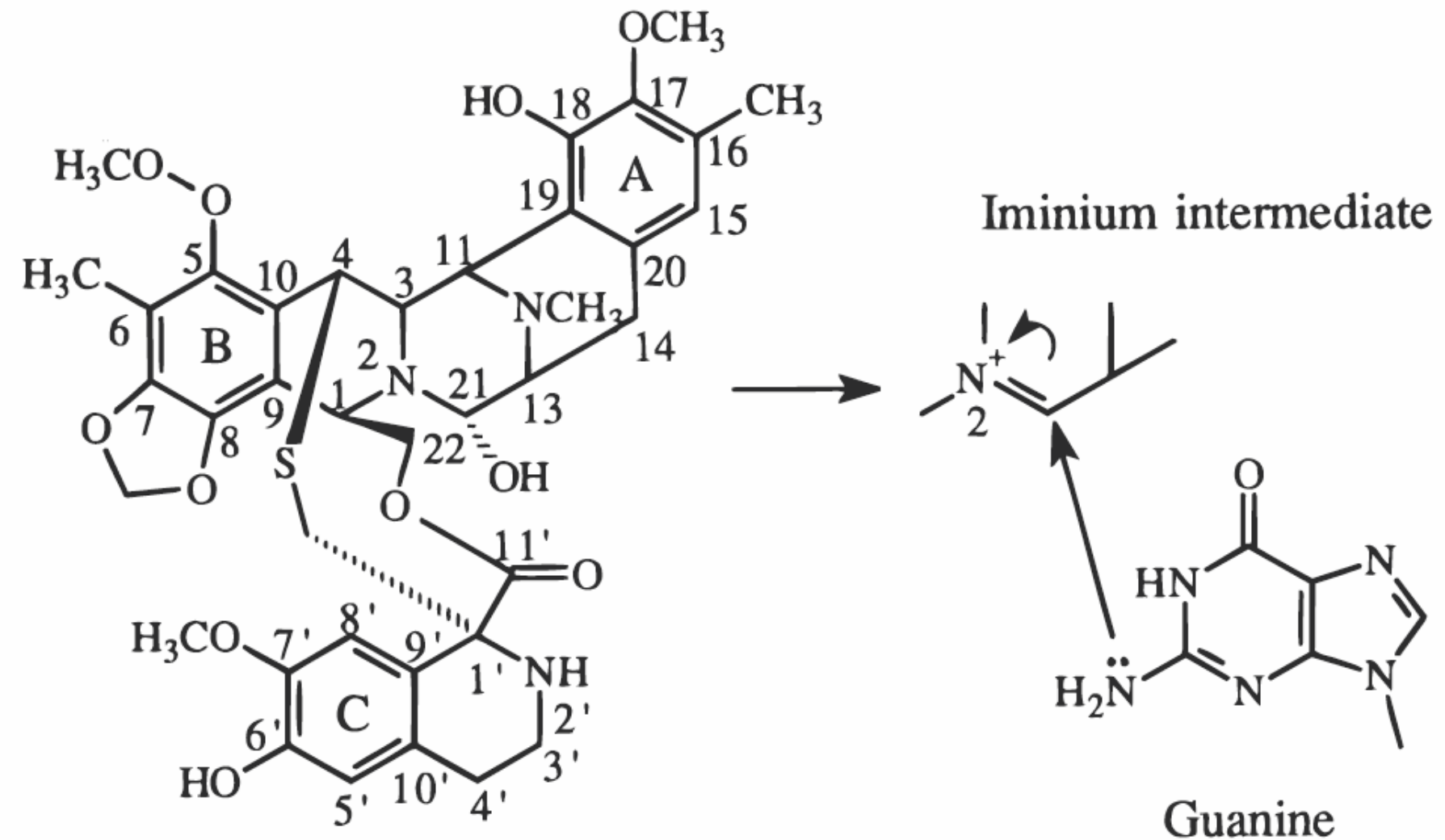


Anthramycin





Pommier et al. *Biochemistry* 35: 13303 (1996)



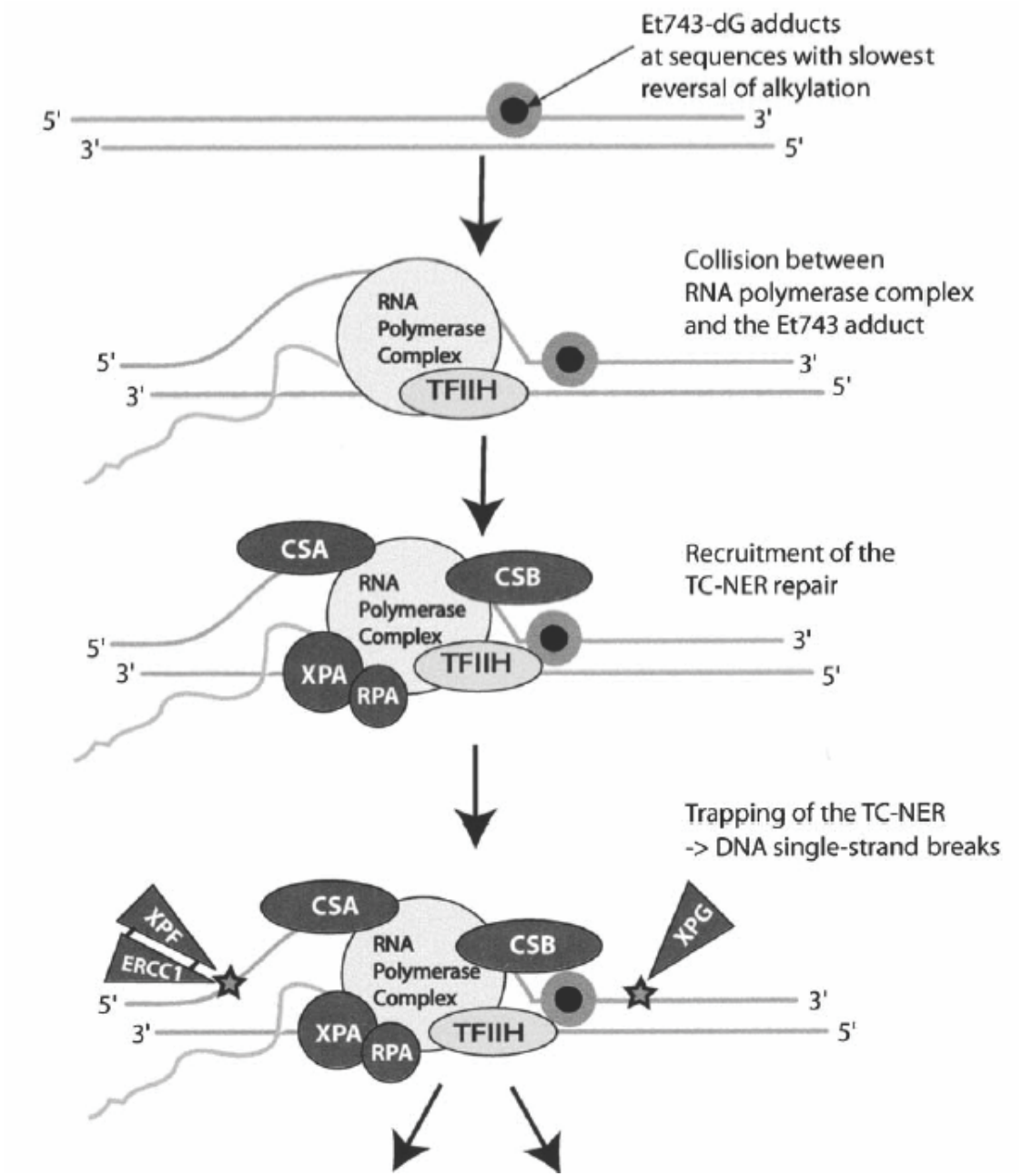
Takebayashi et al *Nature Medicine* 7: 961 (2001)

Table 1 Determinants of Et 743 cytotoxicity in fibroblast cell lines

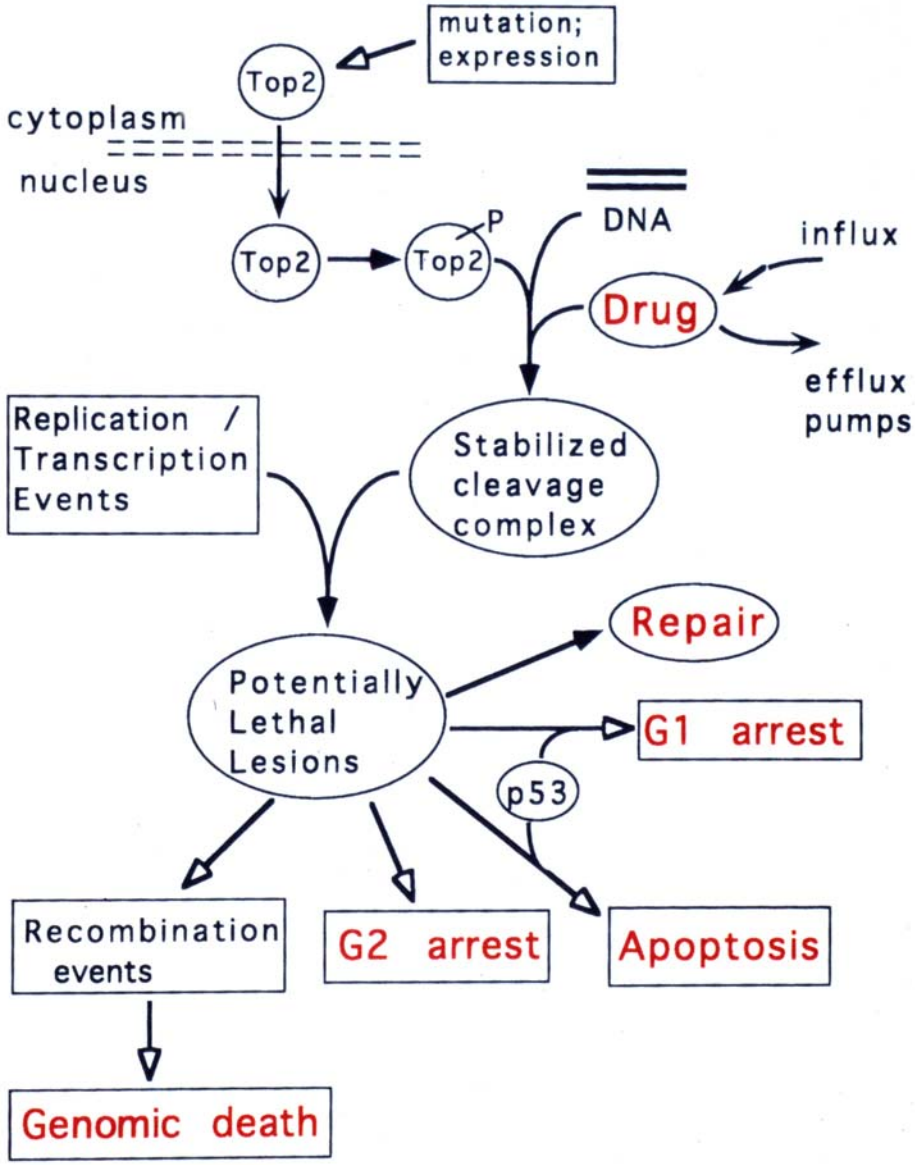
	NER			
	GG	TC	DNA SSBs	Et743 cytotoxicity
Normal fibroblasts	+	+	+	+
XPA, XPD, XPF, XPG	–	–	–*	–
XPA- and XPD-complemented	+	+	+	+
XPC	–	+	+	+
XPC-complemented	+	+	+	+
CSA, CSB	+	–	–	–

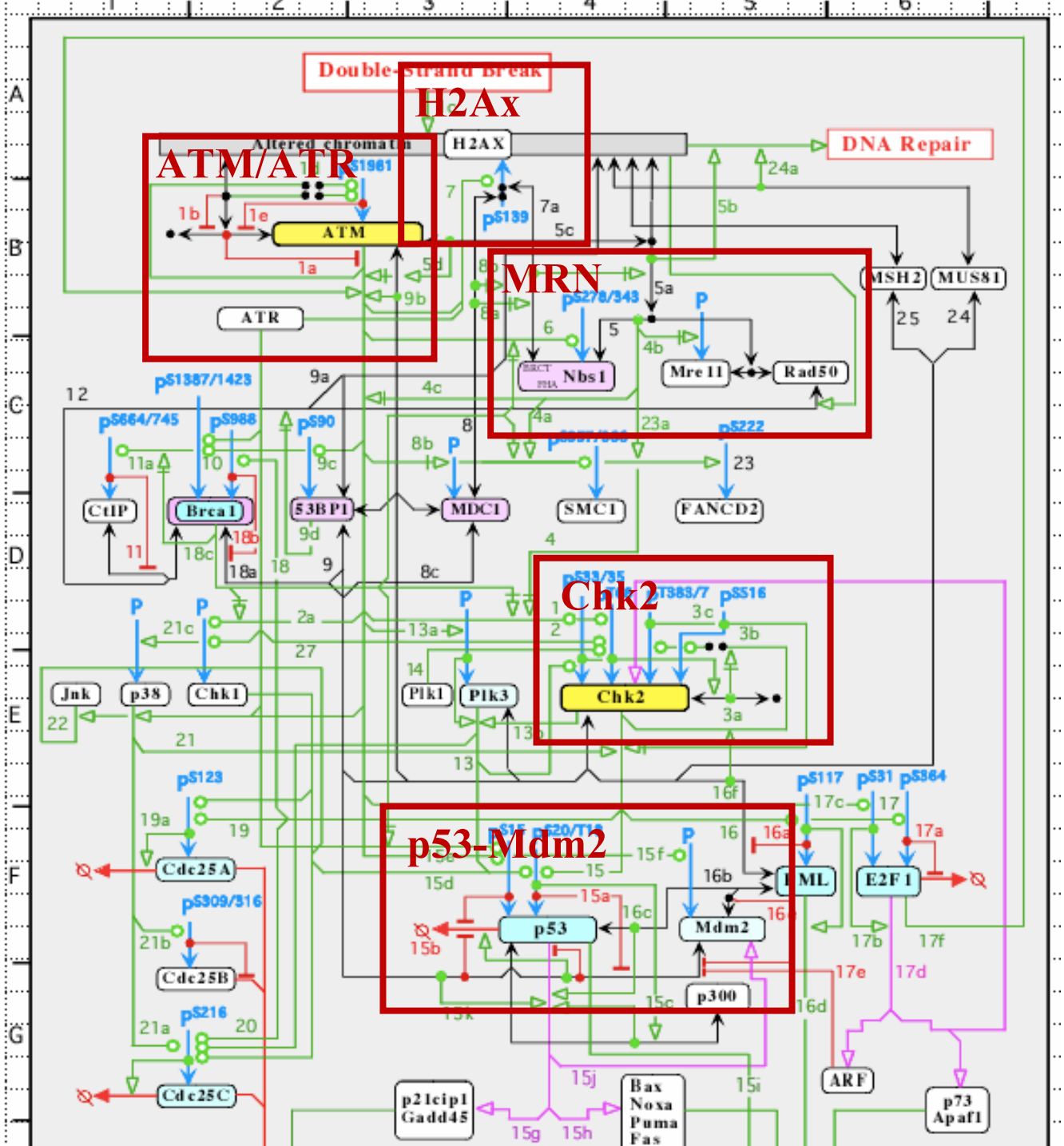
– and + signs indicate either deficiency or proficiency in the repair sub-pathway, sensitivity or resistance to Et743, or absence or presence of significant Et743-induced DNA SSBs measured by the alkaline elution technique (see Fig. 5). *, SSBs were not determined for XPG and XPF cell lines.

Aune GJ, Furuta T, Pommier Y *Anti-cancer Drugs* 13: 545 (2002)

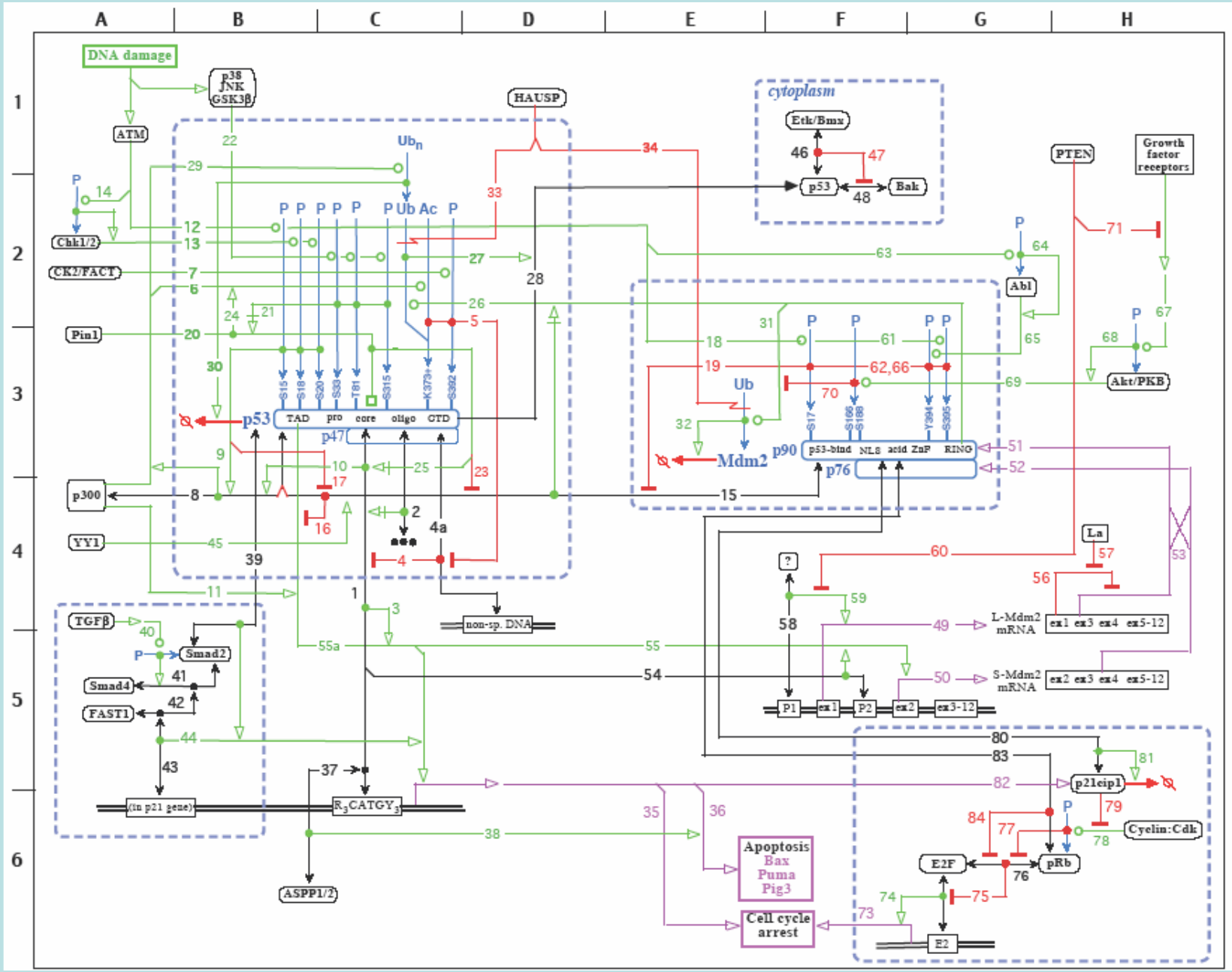


DETERMINANTS OF DRUG SENSITIVITY

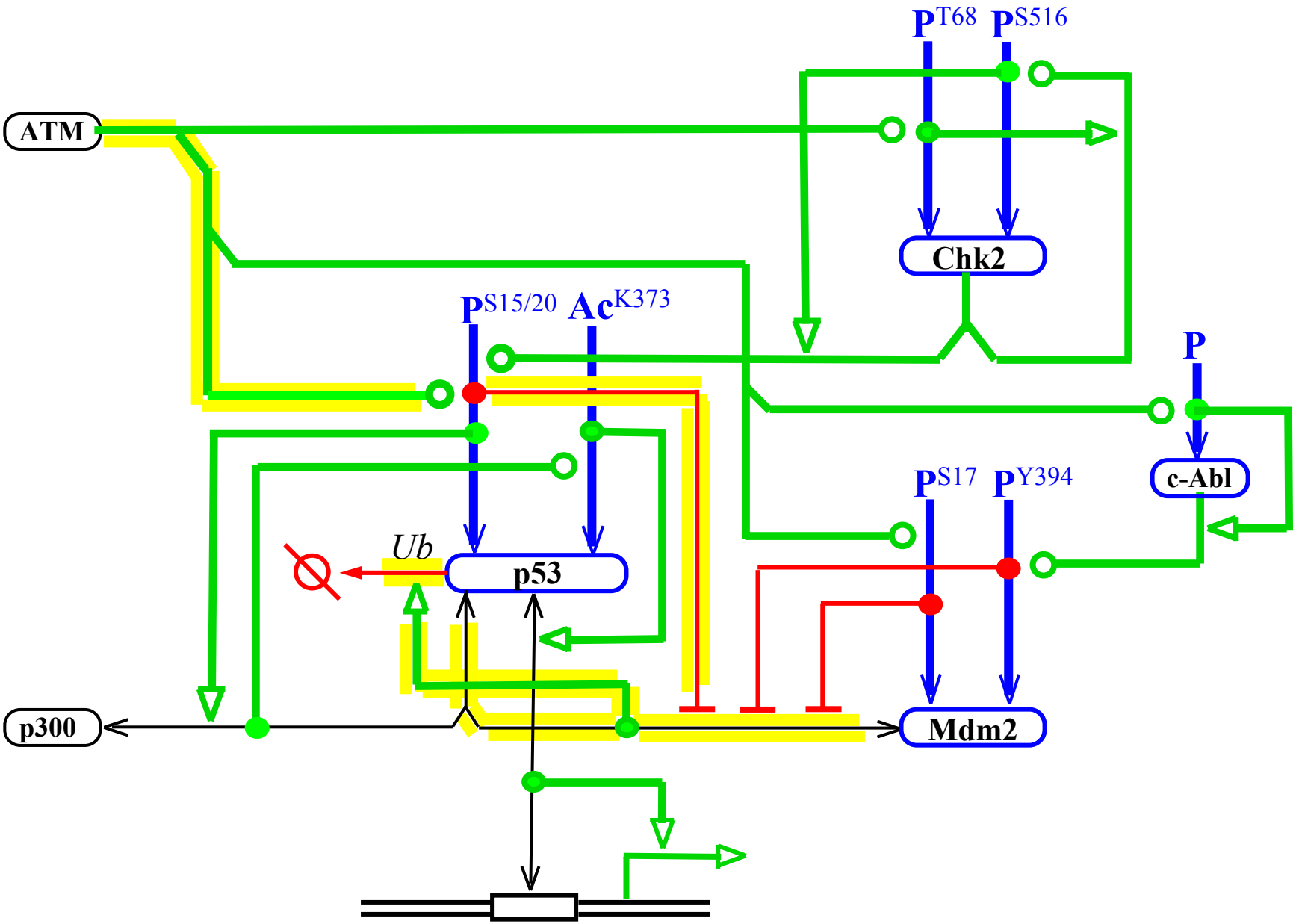



Double-Strand Break
H2Ax
ATM/ATR
MRN
Chk2
p53-Mdm2
Altered chromatin
H2AX
DNA Repair
ATM
ATR
Nbs1
Mre11
Rad50
MSH2
MUS81
CtIP
Brca1
53BP1
MDC1
SMC1
FANCD2
Jnk
p38
Chk1
Plk1
Plk3
Chk2
Cdc25A
Cdc25B
Cdc25C
p53
Mdm2
p300
E2F1
ARF
p21cip1
Gadd45
Bax
Noxa
Puma
Fas
p73
Apaf1
pS1981
pS139
pS278/343
pS1387/1423
pS664/745
pS988
pS90
pS222
pS123
pS309/316
pS216
pS117
pS31
pS364

Kohn KW & Pommier Y (2005). *BBRC* 331(3): 816-827.



http://discover.nci.nih.gov



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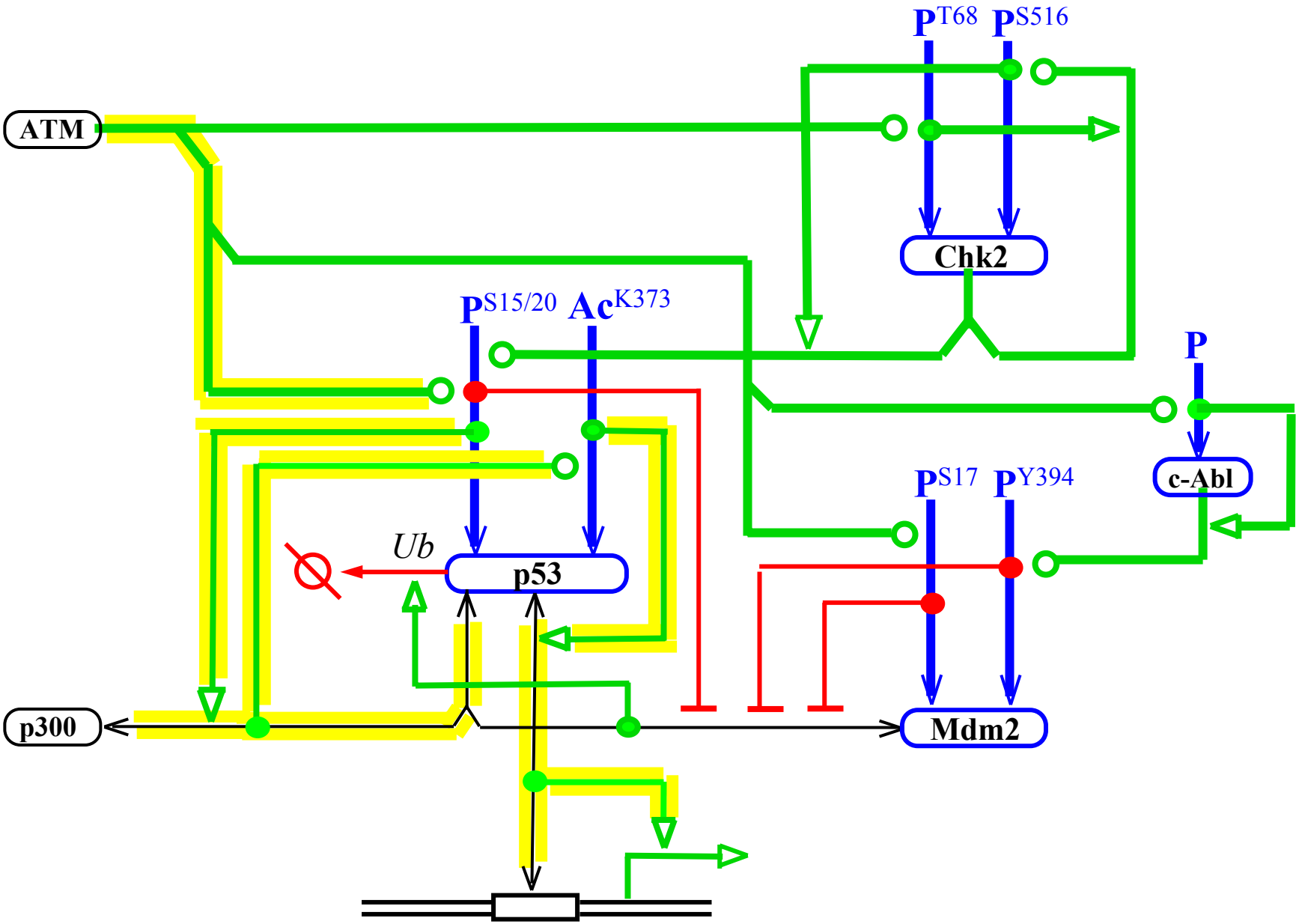

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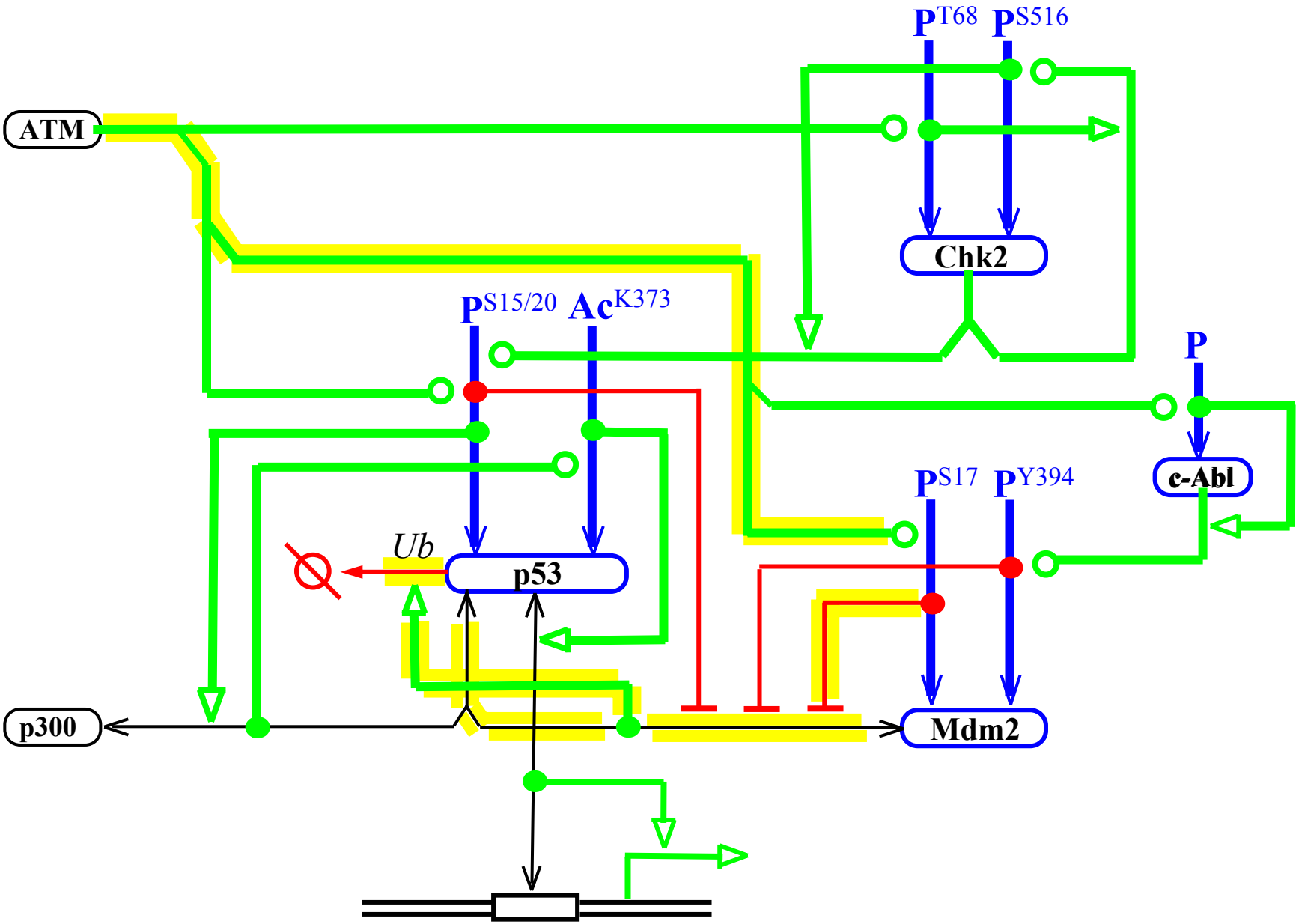

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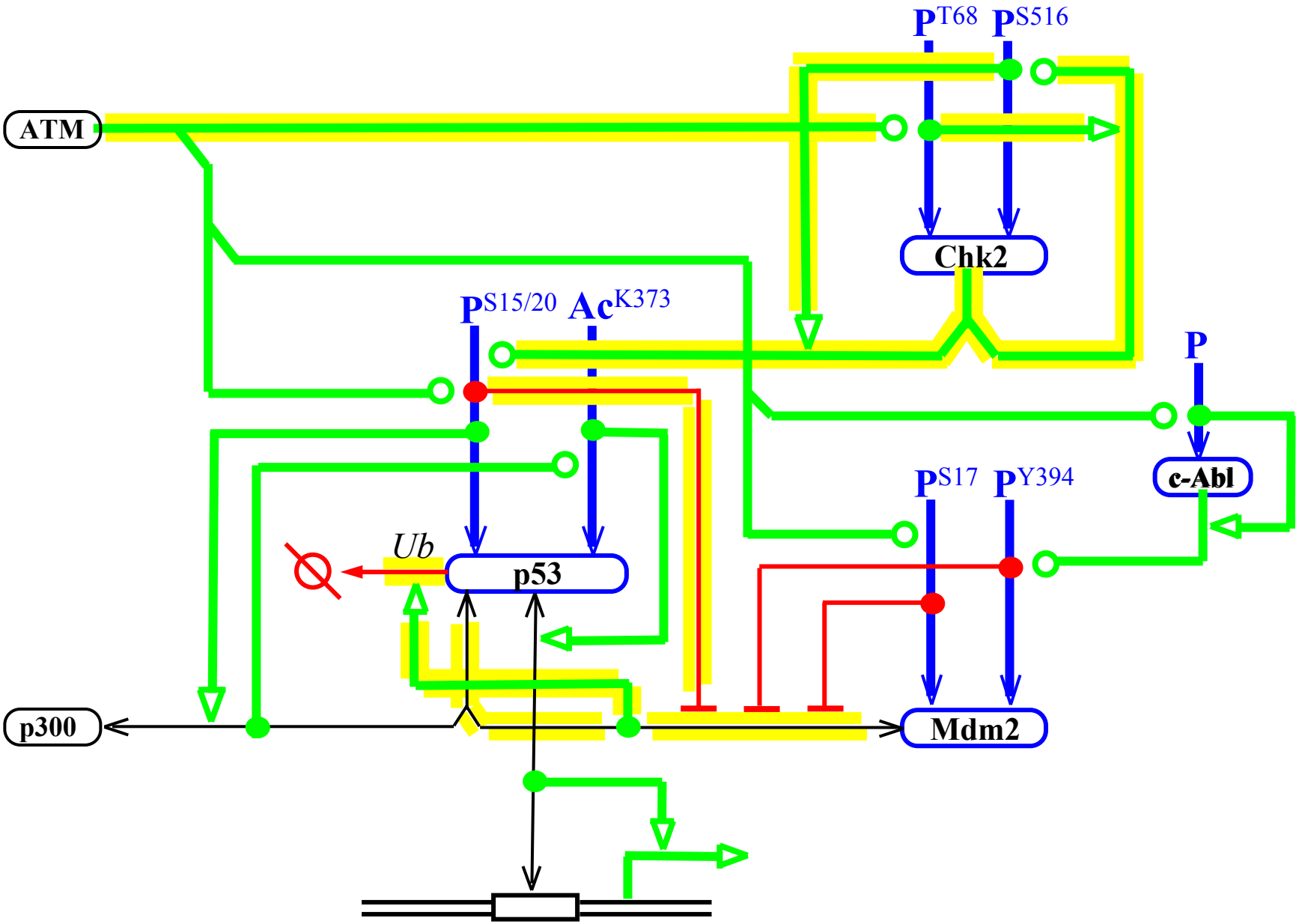
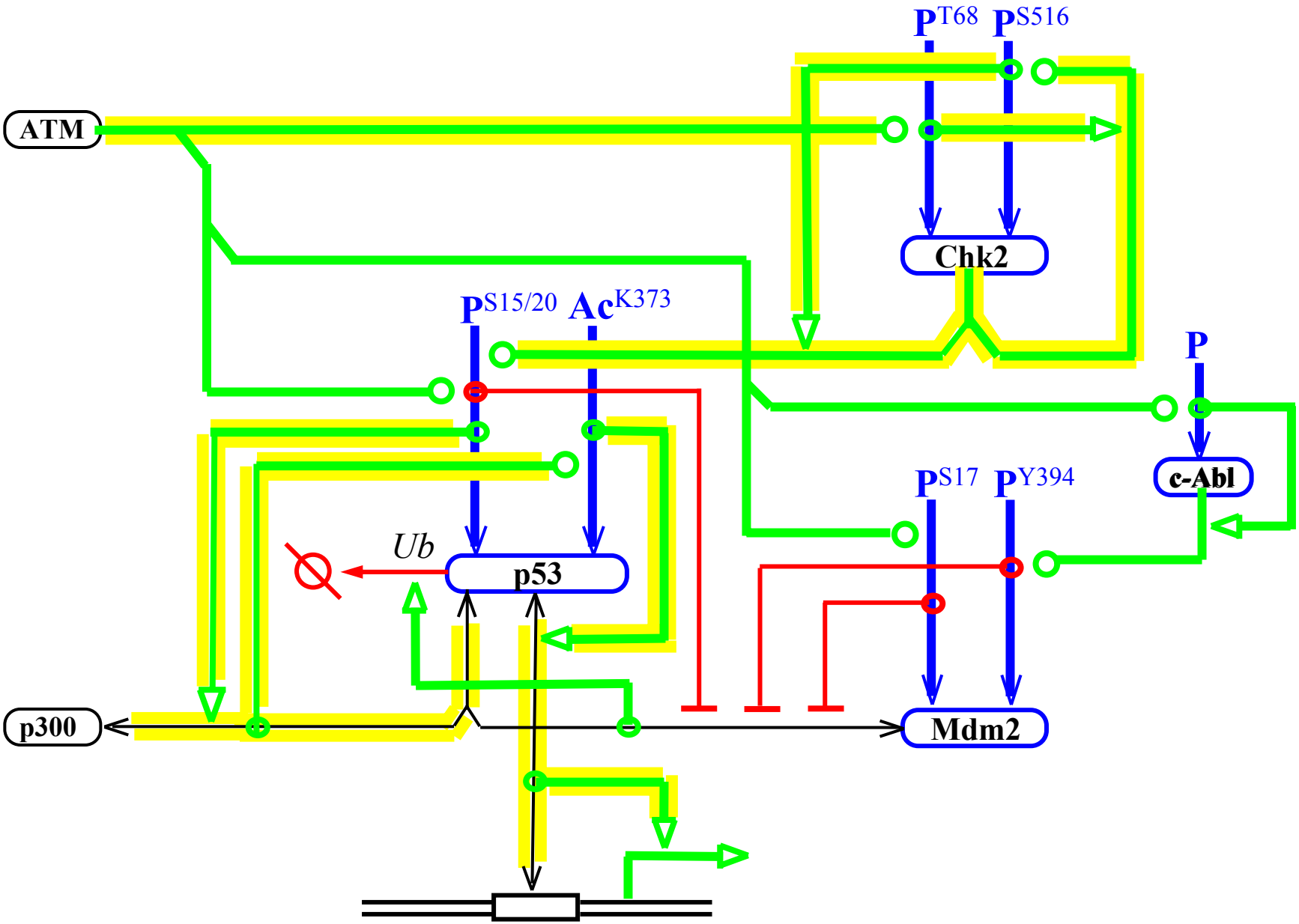
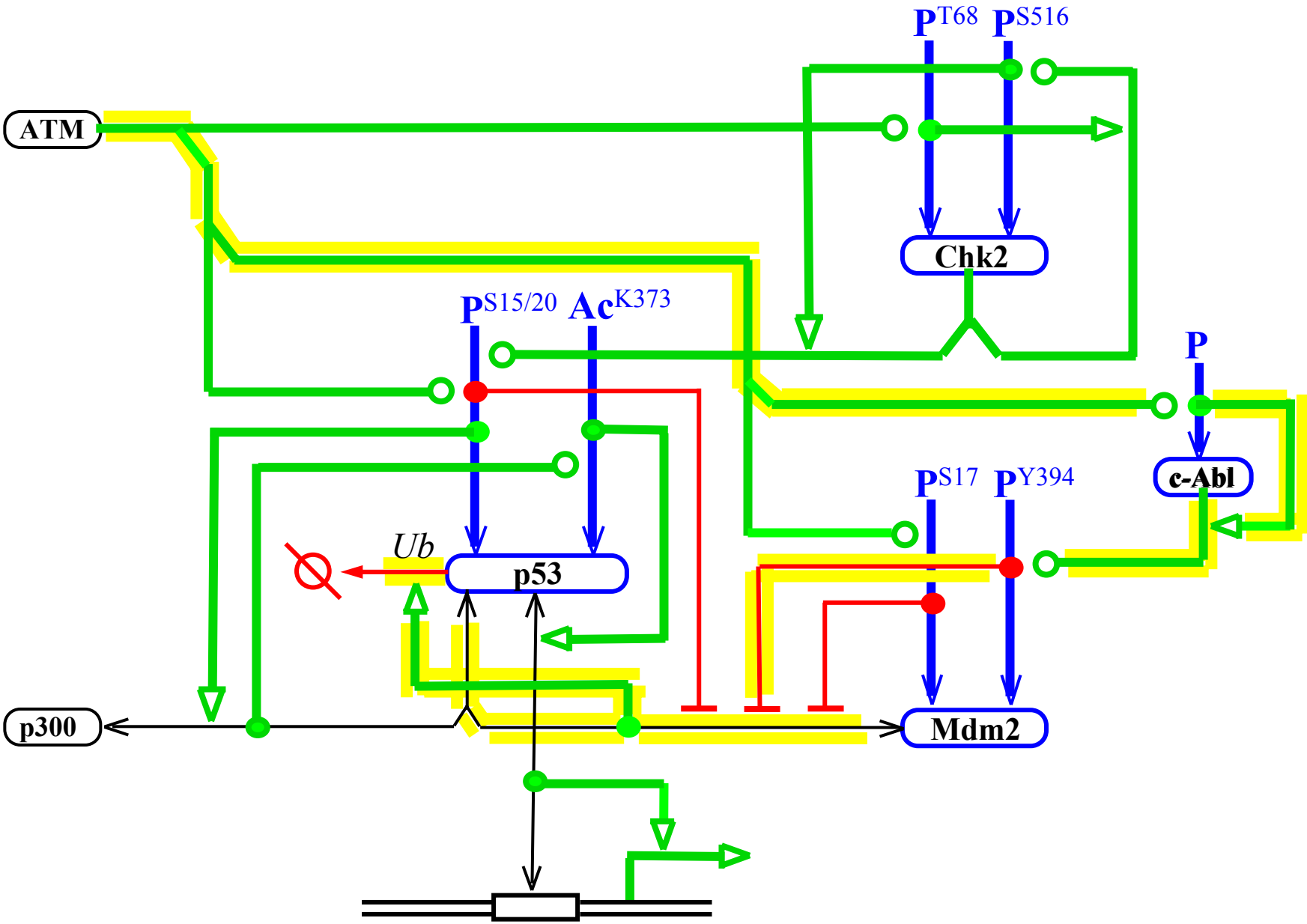


ATM &(*T68P*) >Chk2 &(*S516P*) >Chk2 *&(S20P*) >p53 : >p300 &(*Ac*) >p53*g* [6+]



http://discover.nci.nih.gov



Cancer Research
December 15, 1996 Volume 56 • Number 24

Edouard Manet's GARE SAINT-LAZARE -- Juliet Wilson-Bareau