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## **1974-1979 THE EARLY YEARS: MAPPING TRANSCRIPTS, PROMOTERS, AND INTRONS**

**1974 - Phil Sharp starts his lab at MIT next to the labs of Hopkins, Baltimore, Weinberg and Housman; Richard Nixon resigns as President over Watergate scandal**

**1975 - concerns about the safety of recombinant DNA research are addressed at the Asilomar Conference**

**1976 - The Concorde enters service as the only supersonic passenger jet; Jimmy Carter elected president**

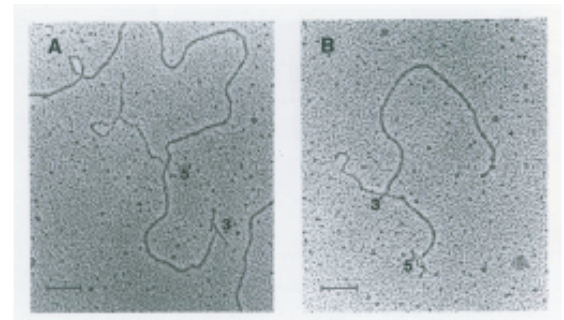
**1977 - Star Wars premieres; Elvis Presley dies**

**1978 - first test tube baby born; Phil co-founds Biogen**

**1979 - Soviet Union invades Afghanistan**

**Heteroduplex mapping of transcripts and replication intermediates by EM of adenovirus and retroviruses. *J. Vir* 1975; *Virology* 1976; *Cell* 1976, 1978, 1979**

**Discovery of adenovirus introns. *PNAS* 1977  
UV mapping of adenovirus promoters. *Cell* 1977  
S1 nuclease protection assay. *Cell* 1977**



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## 1980-1984 DEVELOPING IN VITRO SYSTEMS FOR STUDYING GENE EXPRESSION

**1980 - Ronald Reagan elected President; Mt. St. Helens erupts. John Lennon killed by crazed fan.**

**1981 - first New York Times article appears on mysterious illness, later named AIDS**

**1982 - first artificial heart; FDA approves first genetically engineered human drug; Arnold Schwarzenegger stars in "Conan the Barbarian"**

**1983 - Phil is elected to NAS and AAAS**

**1984 - Reagan elected to second term; Whitehead Institute construction completed; Phil becomes director of Center for Cancer Research; Macintosh computer debuts after "1984" Super Bowl ad**

**Splicing is modular in its choice of 5' and 3' substrates.** *Nature 1981; J Mol Appl Genet. 1983*  
**Transcription regulation by proteins from SV40, adenovirus, and poliovirus.** *Cell 1981; Cell 1981; Nature 1983*

**Structural analysis of tubulin genes and pseudogenes to understand the evolution of the genome.** *J Mol Biol. 1981; Nature 1982*

**Nonsense suppression can be used to control the expression of genes in mammalian cells.** *PNAS 1982; Cell 1982; Cell 1987*

**Adenovirus Capsid formation as a model for protein assembly in mammalian cells.** *Cell 1982*

**Gene amplification with DHFR.** *J Mol Biol. 1982; MCB 1983*

**Development of Adenovirus as an effective expression vector.** *NAR 1983; NAR 1984*

**Transcription initiation in vitro.** *PNAS 1980; JMB 1982; Methods Enz. 1983*

**Intron splicing in vitro.** *PNAS 1983; Nature 1984*

**snRNPs are required for splicing.** *Cell, 1983*

**The mRNA cap stimulates in vitro splicing.** *Cell 1984*

**Transcription requires multiple basal factors: separation of factors, template commitment, and initiation.** *JBC 1982; 1984; 1984 Science 1984; Nature 1985*

**In vitro system and requirements cleavage and polyadenylation.** *Cell 1984, Cell 1985*



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## **1985-1999 PURIFICATION, FUNCTIONAL CHARACTERIZATION, AND CLONING OF FACTORS AND INTERMEDIATES**

**1985 - Mikhail Gorbachev becomes leader of Soviet Union**

**1986 - Phil wins General Motors Research Foundation Alfred P. Sloan, Jr. Prize for Cancer Research and the Gairdner Foundation International Award**

**1987 - Dow Jones Industrial Average loses 22% of its value in one day**

**1988 - George H. W. Bush elected President; Phil wins Lasker Basic Medical Research Award**

**1989 - Berlin Wall falls**

**1990 - Hubble Space Telescope is launched**

**Trans-splicing of introns.** *Cell*, 1985

**Identification of regulatory transcription factor MLTF/USF.** *Cell* 1985

**Identification of the spliceosome and its mechanism of assembly.** *Cell* 1985; *Science* 1986; *Cell* 1986; *Genes Dev* 1987; *PNAS* 1988

**Immortalization of primary cells by Large T antigen.** *J. Virol.* 1986; *MCB* 1986

**Role of hnRNP proteins in splicing.** *Science* 1986

**Use of "gel shift" to identify transcription factors.** *Nature* 1986



**MLTF binds and activates cellular promoters.** *Genes Dev.* 1987; *Science* 1987

**Polyadenylation-specific complexes.** *Genes Dev.* 1987; *MCB* 1988

**Human and yeast CCAAT box factors are interchangeable.** *Cell* 1988; *Cell* 1988

**Lambda expression system for cloning DNA binding factors.** *Cell* 1988

**Identification, purification, and cloning of yeast TBP.** *Nature* 1988; *Cell* 1989.

**Oct-2 gene cloned.** *Science* 1988

**POU-homeodomain of Oct proteins identified.** *Genes Dev.* 1988; *Genes Dev.* 1988

**Assembly pathway of the RNA polymerase II initiation complex.** *Cell* 1989

**Identification and cloning of polypyrimidine tract binding protein.** *Genes Dev.* 1989; 1991

**HIV Rev protein connected to mRNA splicing and export.** *Cell* 1989; *Science* 1990; *Cell* 1991

**Oct1 complexes with Herpes virus TIF(vp16) and host cell factor C1.** *EMBO J* 1989; *Genes Dev.* 1990; *Genes Dev.* 1992

**In vitro transactivation by Tat via elongation.** *Cell* 1990; *EMBO J.* 1991



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**1991 - Soviet Union breaks into 15 separate nations; Operation Desert Storm sends U.S. troops into Kuwait and Iraq. Phil becomes Biology Department Chair**

**1992 - William Jefferson Clinton elected president; riots sweep Los Angeles after Rodney King verdict**

**1993 - Phil wins Nobel Prize for Medicine; other winners include Toni Morrison for Literature, Nelson Mandela and F.W. deClerk for Peace**

**1994 - Nelson Mandela elected president of South Africa; Sharp Lab Reunion celebrating Phil's 50th birthday; construction of MIT Biology Building completed**

**1995 - O.J. Simpson found not guilty of double homicide**

**1996 - Atlanta hosts Summer Olympics**

**1997 - Dolly the sheep cloned; Princess Diana dies in automobile accident**

**1998 - Good Friday peace accords in Northern Ireland**

**1999 - U.S. Women's Soccer Team wins World Cup; Clinton Impeachment Trial**

**Discovery and characterization of "B-TFIID".** *Genes Dev 1991;PNAS 1992*  
**TFEB, MYC, and the Helix-loop-helix family of transcription factors.** *Genes Dev 1991;PNAS 1992;Cell 1993*

**Stereochemistry of splicing.** *Science 1992;Nature 1993*

**TFIIE and TFIIH are necessary for DNA unwinding.** *Cell 1993*

**Crosslinking of proteins to the branch site during splicing.** *Genes Dev 1994*  
**Bypass of the requirement for UI-snRNP.** *Science 1994;Genes Dev 1995*

**Structure-based transcription factor design.** *Science 1995;PNAS 1995*  
**A role for HMG-2 and Topo I in TFIID-TFIIA complex assembly.** *Genes Dev 1995;1997*

**Characterization and cloning of Tat-SFI, a TAT cofactor.** *Science 1996*  
**Bulged-duplex model for branch site nucleophile selection.** *Genes Dev 1996*  
**Oct1-OcaB co-complex and structure.** *Genes Dev 1996;Genes Dev 1999*  
**Computational analysis of U2/UI2 introns.** *Cell 1997;Mol Cell 1998*



**SRmI60, a coactivator of pre-mRNA splicing.** *Genes Dev 1999*  
**In vitro system for ubiquitination of RNA polymerase II.** *PNAS 1999,PNAS 2002*  
**Studies of X-chromosome inactivation.** *PNAS 1999;JBC 2000*



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## 2000-PRESENT NEW APPROACHES: RNAi AND COMPUTATIONAL METHODS

**2000** - In a controversial election, George W. Bush becomes President; Phil becomes director of the McGovern Institute

**2001** - The human genome sequence is published; simultaneous terrorist attacks in New York, Washington D.C., and Pennsylvania kill thousands.

**2002** - U.S. led military coalition topples Afghanistan's Taliban government; East Timor becomes the newest independent country. Patriots win their first Super Bowl; Phil co-founds Alnylam Pharmaceuticals

**2003** - Arnold Schwarzenegger elected governor of California.

**2004** - Sharp Lab 30th reunion; Patriots win Super Bowl again; Red Sox finally go all the way????

**In vitro system for RNAi.** *Genes Dev 1999; Cell 2000*

**Computer prediction of exonic splicing enhancers.** *Science 2002*  
**siRNA inhibition of HIV-1.** *Nature Medicine 2002*



**siRNAs can function as miRNAs.** *Genes Dev 2003*

**Oct-1 knockout and analysis.** *MCB 2004; PNAS 2004; PNAS 2004*

