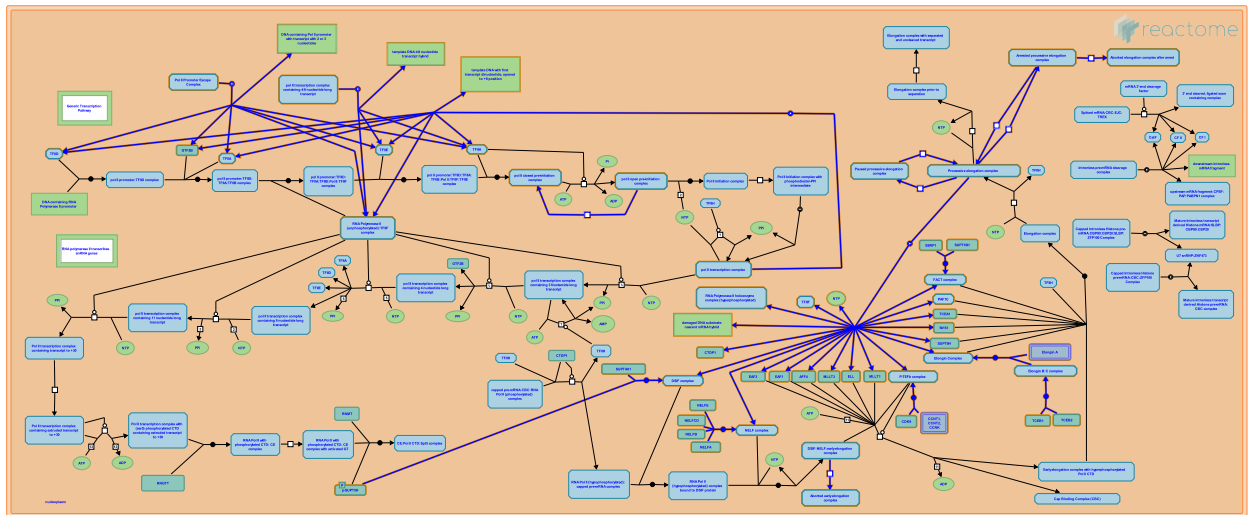


# RNA Polymerase II Pre-transcription

## Events



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook/).

04/05/2024

## Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

## Literature references

- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)
- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

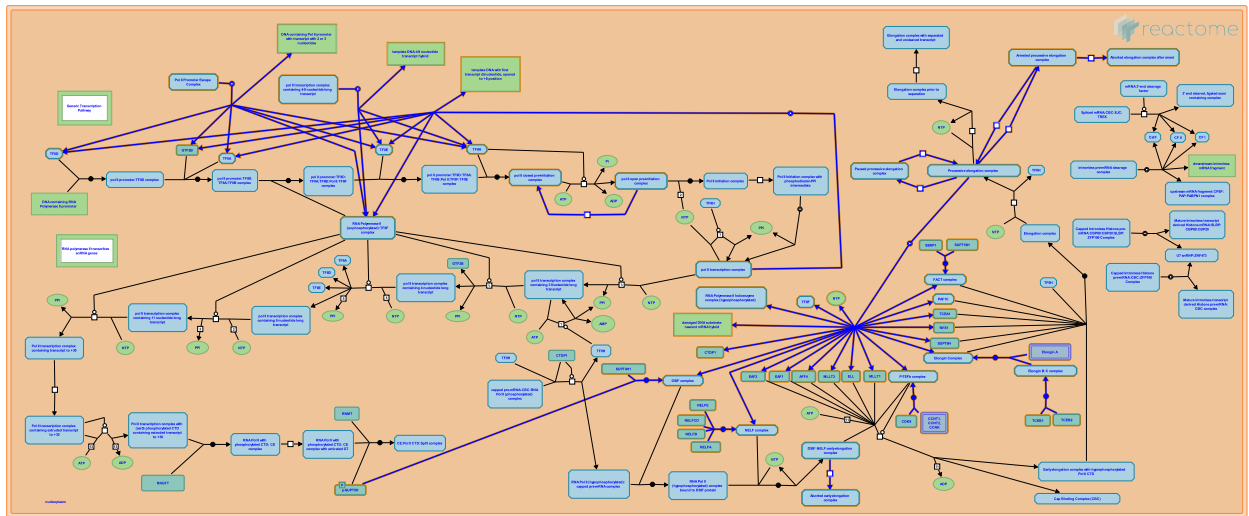
Reactome database release: 88

This document contains 1 pathway and 17 reactions ([see Table of Contents](#))

# RNA Polymerase II Pre-transcription Events ↗

**Stable identifier:** R-HSA-674695

**Compartments:** nucleoplasm



For initiation, Pol II assembles with the general transcription factors TFIIB, TFIID, TFIIE, TFIIF and TFIIH, which are collectively known as the general transcription factors, at promoter DNA to form the pre-initiation complex (PIC). Until the nascent transcript is about 15 nucleotides long, the early transcribing complex is functionally unstable. In the beginning, short RNAs are frequently released and Pol II has to restart transcription (abortive cycling). There is a decline in the level of abortive transcription when the RNA reaches a length of about four nucleotides, and this transition is termed escape commitment

## Literature references

Cramer, P. (2004). Structure and function of RNA polymerase II. *Adv. Protein Chem.*, 67, 1-42. ↗

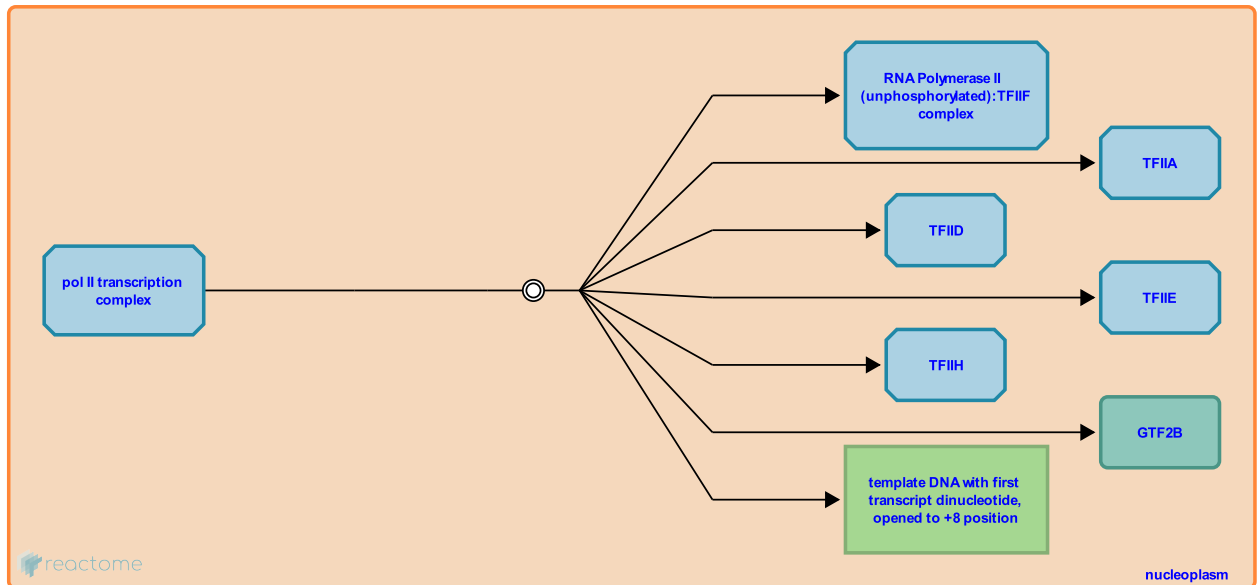
## Abortive initiation after formation of the first phosphodiester bond ↗

**Location:** RNA Polymerase II Pre-transcription Events

**Stable identifier:** R-HSA-73946

**Type:** dissociation

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'pol II transcription complex' is present. At the end of this reaction, 1 molecule of 'TFIIA', 1 molecule of 'TFIIH', 1 molecule of 'TFIIE', 1 molecule of 'TFIID', 1 molecule of 'TFIIB', 1 molecule of 'RNA Polymerase II (unphosphorylated):TFIIF complex', and 1 molecule of 'template DNA with first transcript dinucleotide, opened to +8 position' are present.

This reaction takes place in the 'nucleus'.

### Literature references

Luse, SW., Jacob, GA., Luse, DS. (1991). Abortive initiation is increased only for the weakest members of a set of down mutants of the adenovirus 2 major late promoter. *J Biol Chem*, 266, 22537-44. ↗

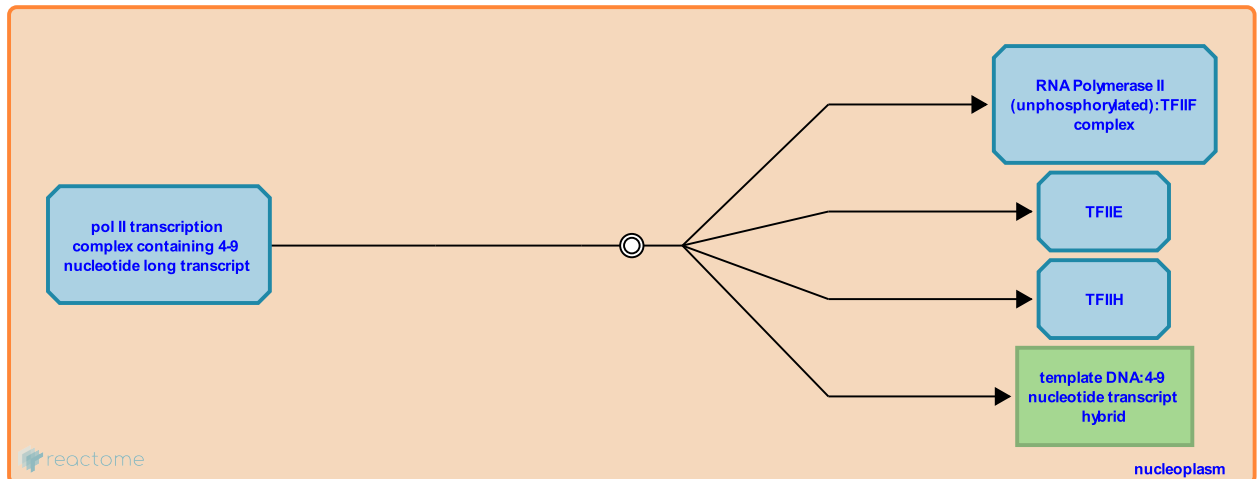
## Abortive Initiation After Second Transition ↗

**Location:** RNA Polymerase II Pre-transcription Events

**Stable identifier:** R-HSA-75891

**Type:** dissociation

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'pol II transcription complex containing 4-9 nucleotide long transcript' is present. At the end of this reaction, 1 molecule of 'template DNA:4-9 nucleotide transcript hybrid', 1 molecule of 'TFIIH', 1 molecule of 'TFIIE', and 1 molecule of 'RNA Polymerase II (unphosphorylated):TFIIF complex' are present.

This reaction takes place in the 'nucleus'.

### Literature references

Luse, SW., Jacob, GA., Luse, DS. (1991). Abortive initiation is increased only for the weakest members of a set of down mutants of the adenovirus 2 major late promoter. *J Biol Chem*, 266, 22537-44. ↗

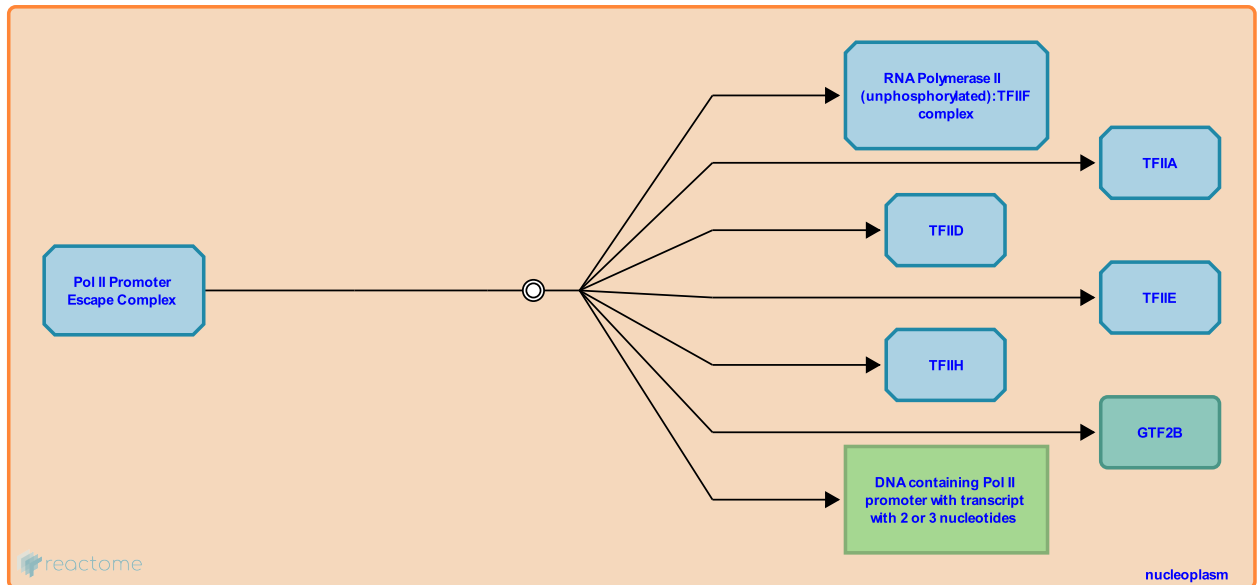
## Abortive Initiation Before Second Transition ↗

**Location:** RNA Polymerase II Pre-transcription Events

**Stable identifier:** R-HSA-75856

**Type:** dissociation

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'Pol II Promoter Escape Complex' is present. At the end of this reaction, 1 molecule of 'TFIIA', 1 molecule of 'TFIIH', 1 molecule of 'TFIIE', 1 molecule of 'TFIID', 1 molecule of 'TFIIB', 1 molecule of 'RNA Polymerase II (unphosphorylated):TFIIF complex', and 1 molecule of 'DNA containing Pol II promoter with transcript with 2 or 3 nucleotides' are present.

This reaction takes place in the 'nucleus'.

### Literature references

Luse, SW., Jacob, GA., Luse, DS. (1991). Abortive initiation is increased only for the weakest members of a set of down mutants of the adenovirus 2 major late promoter. *J Biol Chem*, 266, 22537-44. ↗

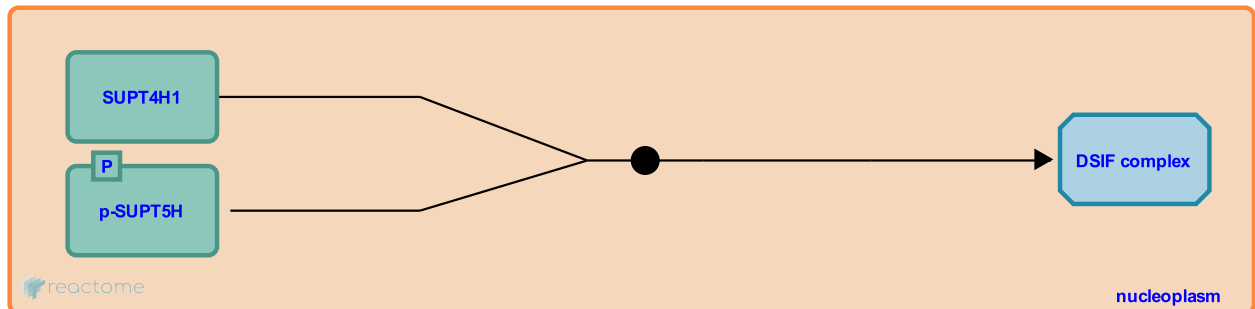
## Formation of DSIF complex ↗

**Location:** RNA Polymerase II Pre-transcription Events

**Stable identifier:** R-HSA-112434

**Type:** binding

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'SUPT5H protein', and 1 molecule of 'SPT4H1 protein' are present. At the end of this reaction, 1 molecule of 'DSIF complex' is present (Wada et al. 1998).

This reaction takes place in the 'nucleus'.

### Literature references

Takagi, T., Buratowski, S., Yano, K., Ferdous, A., Wada, T., Handa, H. et al. (1998). DSIF, a novel transcription elongation factor that regulates RNA polymerase II processivity, is composed of human Spt4 and Spt5 homologs. *Genes Dev*, 12, 343-56. ↗

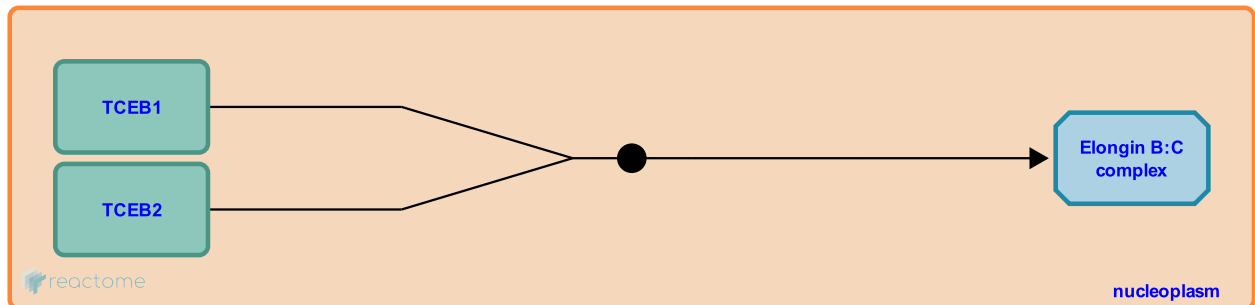
## Formation of Elongin BC complex ↗

**Location:** [RNA Polymerase II Pre-transcription Events](#)

**Stable identifier:** R-HSA-112435

**Type:** binding

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'Elongin B protein', and 1 molecule of 'Elongin C protein' are present. At the end of this reaction, 1 molecule of 'Elongin B:C complex' is present. This reaction takes place in the 'nucleus' (Aso et al., 1995; Duan et al., 1995b; Kibel et al., 1995).

**Followed by:** [Formation of Elongin complex](#)

### Literature references

- Conaway, RC., Conaway, JW., Garrett, KP., Aso, T., Burgess, WH., Chen, DY. et al. (1995). Inhibition of transcription elongation by the VHL tumor suppressor protein. *Science*, 269, 1402-6. ↗
- Conaway, RC., Lane, WS., Conaway, JW., Aso, T. (1995). Elongin (SIII): a multisubunit regulator of elongation by RNA polymerase II. *Science*, 269, 1439-43. ↗
- DeCaprio, JA., Iliopoulos, O., Kaelin, WG., Kibel, A. (1995). Binding of the von Hippel-Lindau tumor suppressor protein to Elongin B and C. *Science*, 269, 1444-6. ↗



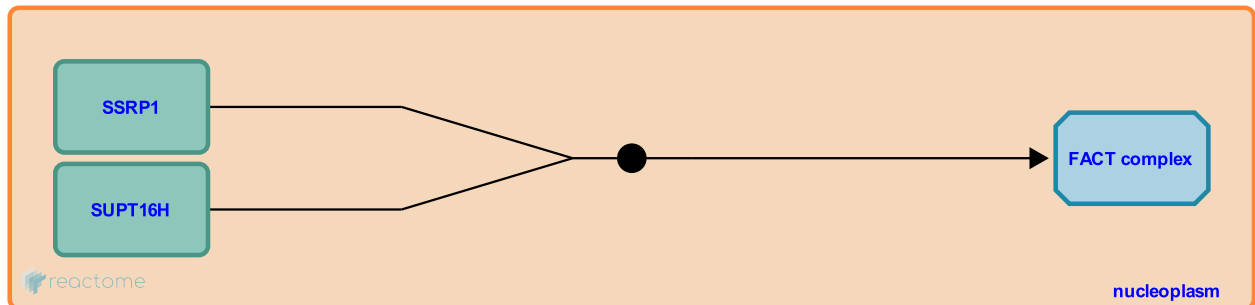
## Formation of FACT complex ↗

**Location:** [RNA Polymerase II Pre-transcription Events](#)

**Stable identifier:** R-HSA-112429

**Type:** binding

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'FACT 140 kDa subunit', and 1 molecule of 'FACT 80 kDa subunit' are present. At the end of this reaction, 1 molecule of 'FACT complex' is present.

This reaction takes place in the 'nucleus' (Kamakaka et al.1993, Orphanides et al.1998).

### Literature references

Kamakaka, RT., Bulger, M., Kadonaga, JT. (1993). Potentiation of RNA polymerase II transcription by Gal4-VP16 during but not after DNA replication and chromatin assembly. *Genes Dev.*, 7, 1779-95. ↗

Chang, CH., Orphanides, G., Reinberg, D., LeRoy, G., Luse, DS. (1998). FACT, a factor that facilitates transcript elongation through nucleosomes. *Cell*, 92, 105-16. ↗

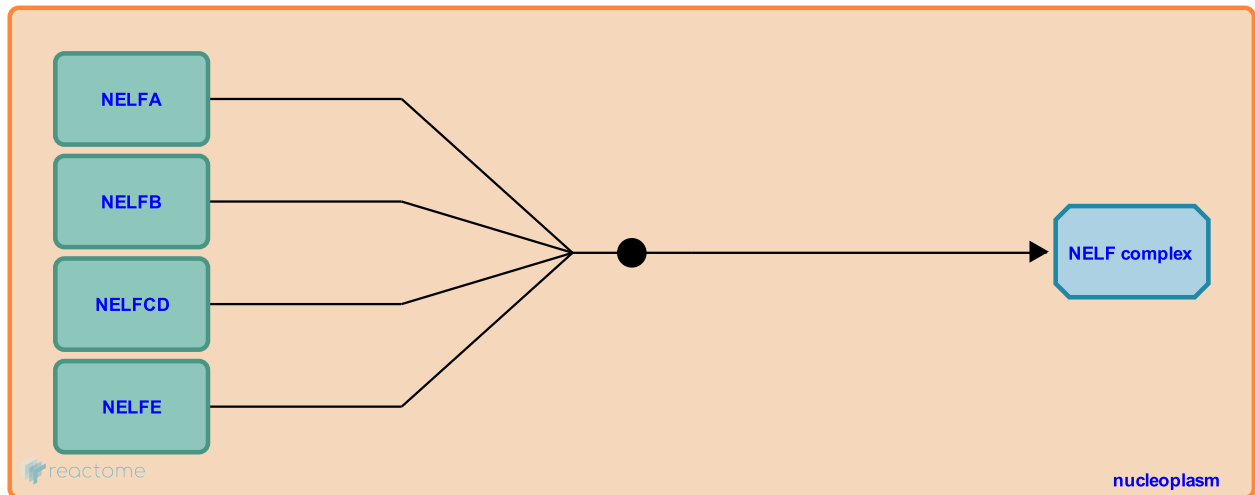
## Formation of NELF complex ↗

**Location:** RNA Polymerase II Pre-transcription Events

**Stable identifier:** R-HSA-112437

**Type:** binding

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'NELF-A protein', 1 molecule of 'RD protein', 1 molecule of 'NELF-B protein', and 1 molecule of 'NELF-C/D protein' are present. At the end of this reaction, 1 molecule of 'NELF complex' is present (Yamaguchi et al. 1999).

This reaction takes place in the 'nucleus'.

### Literature references

Takagi, T., Yano, K., Furuya, A., Wada, T., Handa, H., Hasegawa, J. et al. (1999). NELF, a multisubunit complex containing RD, cooperates with DSIF to repress RNA polymerase II elongation. *Cell*, 97, 41-51. ↗

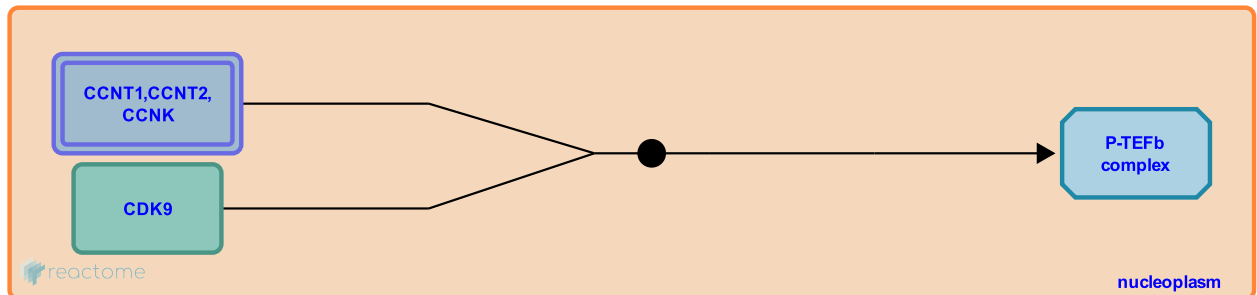
## Formation of P-TEFb complex ↗

**Location:** RNA Polymerase II Pre-transcription Events

**Stable identifier:** R-HSA-112430

**Type:** binding

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'Cdk 9 protein', 1 molecule of 'Cyclin T1', and 1 molecule of 'Cyclin T2' are present. At the end of this reaction, 1 molecule of 'P-TEFb complex' is present.

This reaction takes place in the 'nucleus'.

### Literature references

Taube, R., Peterlin, BM., Fujinaga, K., Lin, X. (2002). P-TEFb containing cyclin K and Cdk9 can activate transcription via RNA. *J. Biol. Chem.*, 277, 16873-8. ↗

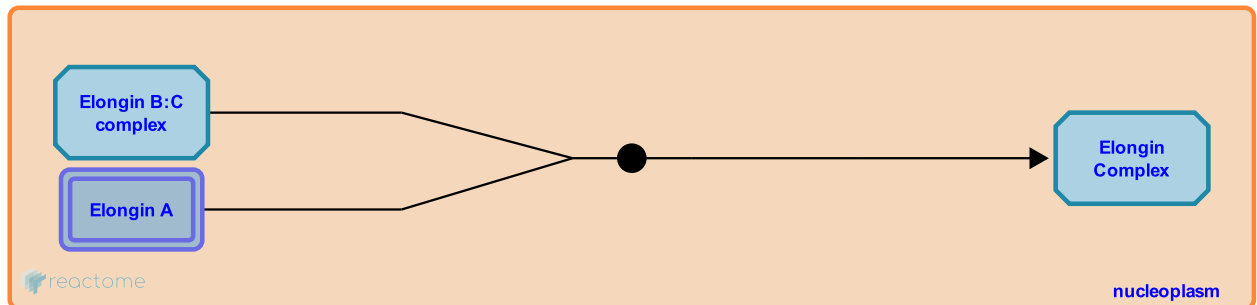
## Formation of Elongin complex ↗

**Location:** RNA Polymerase II Pre-transcription Events

**Stable identifier:** R-HSA-112436

**Type:** binding

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'Elongin A1 protein', and 1 molecule of 'Elongin B:C complex' are present. At the end of this reaction, 1 molecule of 'Elongin Complex' is present.

This reaction takes place in the 'nucleus' (Kibel et al. 1995, Aso et al. 1995, Duan et al. 1995).

**Preceded by:** [Formation of Elongin BC complex](#)

### Literature references

- Conaway, RC., Conaway, JW., Garrett, KP., Aso, T., Burgess, WH., Chen, DY. et al. (1995). Inhibition of transcription elongation by the VHL tumor suppressor protein. *Science*, 269, 1402-6. ↗
- Conaway, RC., Lane, WS., Conaway, JW., Aso, T. (1995). Elongin (SIII): a multisubunit regulator of elongation by RNA polymerase II. *Science*, 269, 1439-43. ↗
- DeCaprio, JA., Iliopoulos, O., Kaelin, WG., Kibel, A. (1995). Binding of the von Hippel-Lindau tumor suppressor protein to Elongin B and C. *Science*, 269, 1444-6. ↗

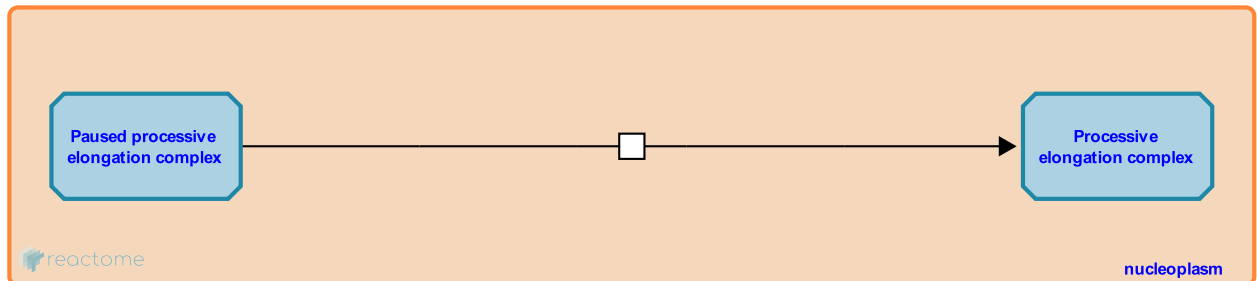
## Resumption of elongation after recovery from pausing ↗

**Location:** [RNA Polymerase II Pre-transcription Events](#)

**Stable identifier:** R-HSA-112392

**Type:** transition

**Compartments:** nucleoplasm



Recovery from pausing occurs spontaneously after a variable length of time as the enzyme spontaneously slides forward again. This renders the transcript's 3'-OH terminus realigned with the catalytic  $Mg^{2+}$  site of the enzyme. TFIIIS is capable of excising the nascent transcript at 2 or 3 nucleotides upstream of the transcript's 3'-end to reinitiate processive elongation (reviewed by Shilatifard et al., 2003).

**Preceded by:** [2-4 nt.backtracking of Pol II complex on the template leading to elongation pausing](#)

### Literature references

Conaway, JW., Shilatifard, A., Conaway, RC. (2003). The RNA polymerase II elongation complex. *Annu Rev Biochem*, 72, 693-715. ↗

### Editions

2004-06-23

Authored

Gopinathrao, G.

## 2-4 nt.backtracking of Pol II complex on the template leading to elongation pausing

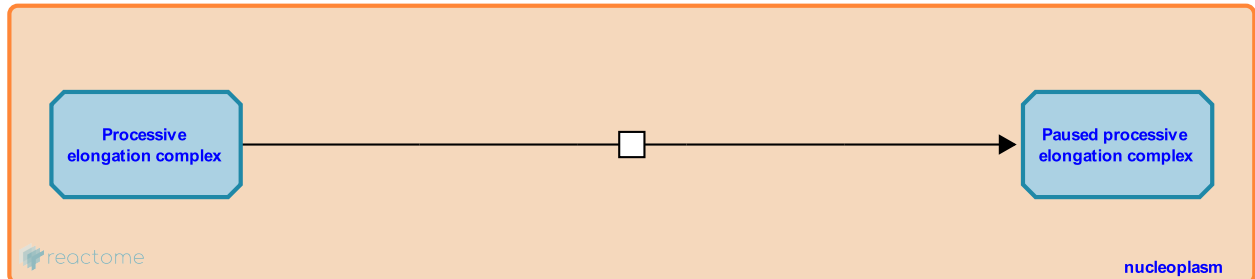


**Location:** [RNA Polymerase II Pre-transcription Events](#)

**Stable identifier:** R-HSA-113411

**Type:** transition

**Compartments:** nucleoplasm



Pol II pausing is believed to result from reversible backtracking of the Pol II enzyme complex by ~2 to 4 nucleotides. This leads to misaligned 3'-OH terminus that is unable to be an acceptor for the incoming NTPs in synthesis of next phosphodiester bond (reviewed by Shilatifard et al., 2003).

**Followed by:** [Resumption of elongation after recovery from pausing](#)

### Literature references

Conaway, JW., Shilatifard, A., Conaway, RC. (2003). The RNA polymerase II elongation complex. *Annu Rev Biochem*, 72, 693-715. [↗](#)

### Editions

2004-06-23

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## 7-14 nt. Backtracking of Pol II complex on the template leading to elongation arrest

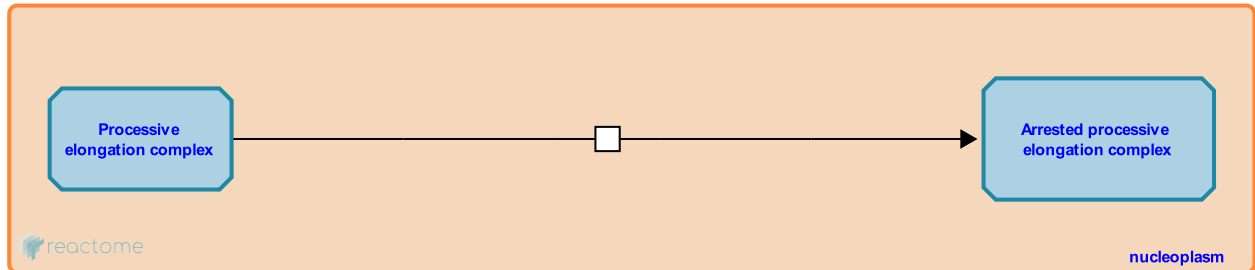


**Location:** [RNA Polymerase II Pre-transcription Events](#)

**Stable identifier:** R-HSA-113414

**Type:** transition

**Compartments:** nucleoplasm



RNA Pol II arrest is believed to be a result of irreversible backsliding of the enzyme by ~7-14 nucleotides. It is suggested that, arrest leads to extrusion of displaced transcripts 3'-end through the small pore near the Mg<sup>2+</sup> ion. Pol II arrest may lead to abortive termination of elongation due to irreversible trapping of the 3'-end of the displaced transcript in the pore (reviewed by Shilatifard et al., 2003).

**Followed by:** [Abortive termination of elongation after arrest](#), [TFIIS-mediated recovery of elongation from arrest](#)

### Literature references

Conaway, JW., Shilatifard, A., Conaway, RC. (2003). The RNA polymerase II elongation complex. *Annu Rev Biochem*, 72, 693-715. [↗](#)

### Editions

2004-06-23

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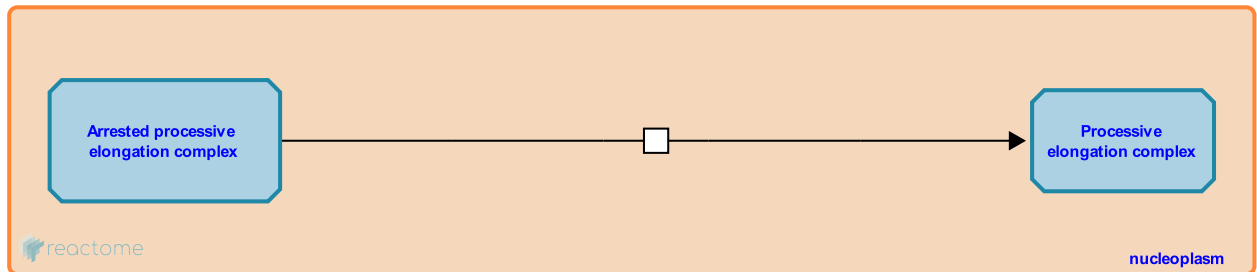
## TFIIS-mediated recovery of elongation from arrest ↗

**Location:** [RNA Polymerase II Pre-transcription Events](#)

**Stable identifier:** R-HSA-113413

**Type:** transition

**Compartments:** nucleoplasm



TFIIS reactivates arrested RNA Pol II directly interacting with the enzyme resulting in endonucleolytic excision of nascent transcript ~7-14 nucleotides upstream of the 3' end. This reaction is catalyzed by the catalytic site and results in the generation of a new 3'-OH terminus that could be used for re-extension from the correctly base paired site (reviewed by Shilatifard et al., 2003).

**Preceded by:** [7-14 nt. Backtracking of Pol II complex on the template leading to elongation arrest](#)

### Literature references

Conaway, JW., Shilatifard, A., Conaway, RC. (2003). The RNA polymerase II elongation complex. *Annu Rev Biochem*, 72, 693-715. ↗

### Editions

2004-06-23

Authored

Gopinathrao, G.



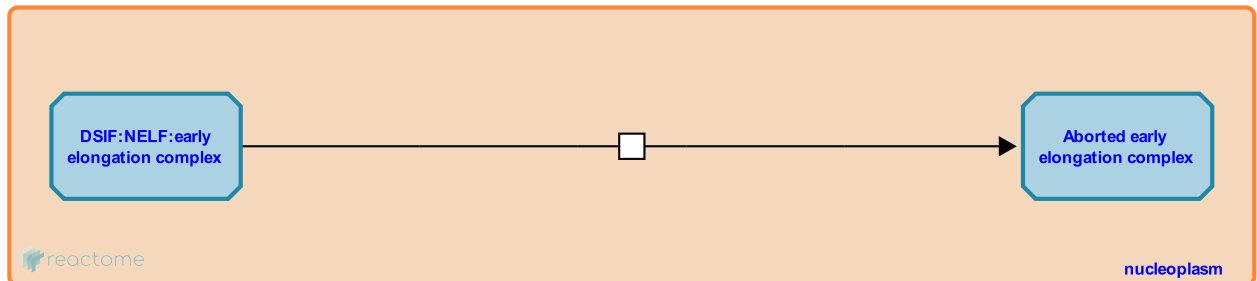
## Abortive termination of early transcription elongation by DSIF:NELF ↗

**Location:** [RNA Polymerase II Pre-transcription Events](#)

**Stable identifier:** R-HSA-113409

**Type:** transition

**Compartments:** nucleoplasm



In the early elongation phase, shorter transcripts typically of ~30 nt in length are generated due to random termination of elongating nascent transcripts. This abortive cessation of elongation has been observed mainly in the presence of DSIF-NELF bound to Pol II complex. (Reviewed in Conaway et al.,2000; Shilatifard et al., 2003 ).

### Literature references

Conaway, JW., Shilatifard, A., Conaway, RC. (2003). The RNA polymerase II elongation complex. *Annu Rev Biochem*, 72, 693-715. ↗

### Editions

2004-04-28

Authored

Gopinathrao, G.

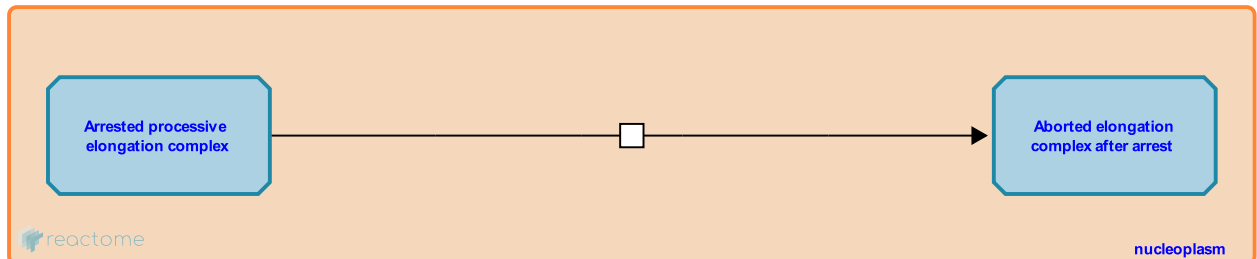
## Abortive termination of elongation after arrest ↗

**Location:** [RNA Polymerase II Pre-transcription Events](#)

**Stable identifier:** R-HSA-112395

**Type:** transition

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'Arrested processive elongation complex' is present. At the end of this reaction, 1 molecule of 'Aborted elongation complex after arrest' is present.

This reaction takes place in the 'nucleus'.

**Preceded by:** [7-14 nt. Backtracking of Pol II complex on the template leading to elongation arrest](#)

### Literature references

Conaway, JW., Shilatifard, A., Conaway, RC. (2003). The RNA polymerase II elongation complex. *Annu Rev Biochem*, 72, 693-715. ↗

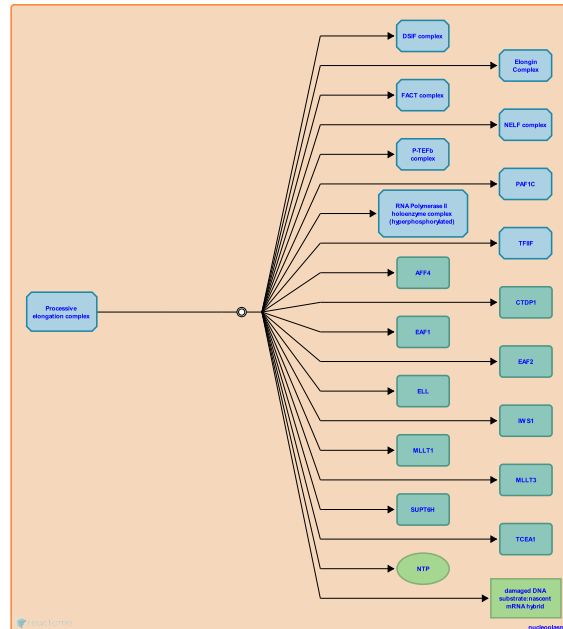
## Elongating transcript encounters a lesion in the template ↗

**Location:** RNA Polymerase II Pre-transcription Events

**Stable identifier:** R-HSA-113429

**Type:** dissociation

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'Processive elongation complex' is present. At the end of this reaction, 1 molecule of 'DSIF complex', 1 molecule of 'FACT complex', 1 molecule of 'RNA Polymerase II holoenzyme complex (hyperphosphorylated)', 1 molecule of 'damaged DNA substrate:nascent mRNA hybrid', 1 molecule of 'Elongin Complex', 1 molecule of 'FCP1P protein', 1 molecule of 'P-TEFb complex', 1 molecule of 'NELF complex', 1 molecule of 'RNA polymerase II elongation factor ELL', 1 molecule of 'NTP', 1 molecule of 'TFIIS protein', and 1 molecule of 'TFIIF' are present.

This reaction takes place in the 'nucleus' (Woudstra et al. 2002).

### Literature references

Jansen, L., Svejstrup, JQ., Brouwer, J., Fellows, J., Gilbert, C., Woudstra, EC. et al. (2002). A Rad26-Def1 complex coordinates repair and RNA pol II proteolysis in response to DNA damage. *Nature*, 415, 929-33. ↗

Reinberg, D., Sims, RJ., Belotserkovskaya, R. (2004). Elongation by RNA polymerase II: the short and long of it. *Genes Dev.*, 18, 2437-68. ↗

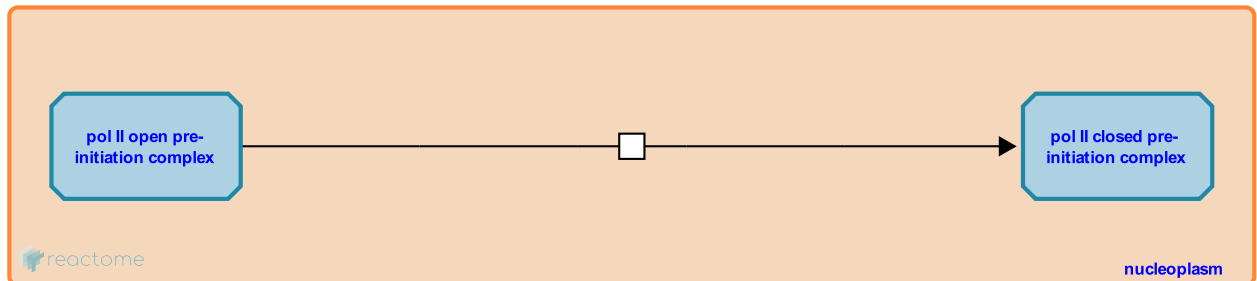
## Fall Back to Closed Pre-initiation Complex [↗](#)

**Location:** [RNA Polymerase II Pre-transcription Events](#)

**Stable identifier:** R-HSA-75862

**Type:** transition

**Compartments:** nucleoplasm



At the beginning of this reaction, 1 molecule of 'pol II open pre-initiation complex' is present. At the end of this reaction, 1 molecule of 'pol II closed pre-initiation complex' is present.

This reaction takes place in the 'nucleus'.

### Literature references

Conaway, JW., Conaway, RC. (1988). ATP activates transcription initiation from promoters by RNA polymerase II in a reversible step prior to RNA synthesis. *J Biol Chem*, 263, 2962-8. [↗](#)

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