RNA folding during transcription
(Co-transcriptional folding)

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RNA folds into cool tertiary structures

tRNA
~25 KDa

P RNA
~115 KDa

ribosome
> $10^3$ kDa
(Biophysics) Mg$^{2+}$-initiated RNA folding versus
(Biology) transcription-initiated RNA folding

**Mg$^{2+}$-initiated**

- 5' RNA
- 3' RNA
- Native structure

**Transcription-initiated**

- 5' RNA
- RNA polymerase
- DNA template
- Native structure
The obvious problem spots: Long-range helices
Things that matter in folding during transcription

**Polarity**

RNA polymerase

5’

**Speed**

Interstate

County road

**Pausing**

County road

Take CR

1

2

3

(1) Location.

(2) Timing.

(3) Interaction with RNA polymerase?

Timing is everything.
Folding of *E. coli* RNase P RNA

![Diagram showing folding mechanisms and speed comparison]

- **Cognate**
- **non-cognate** (same speed, different pause)

**Speed doesn’t matter.**
Mg$^{2+}$-initiated folding even slower.
Big-time Pausing

Its location: right after the 5' portion of all long-range helices!
Pausing at 119 matters to folding
An extensive paused complex structure forms (structural mapping and phylogeny)

Core of the structure is phylogenetically conserved . . .

Structure of the paused complex matters ....
Why should this non-native structure help folding?

Prevents super-stable non-native structure from forming.

It’s labile, easy to undo for native structure when downstream partners are transcribed.

Provides a topological benefit for the order of strand invasions.
Recap

Long-range helix: cool for native structure, not cool for folding.....

Non-native structure in folding: can be good, can be bad; devils are in the details ..... 

Pausing matters: location, location, location ..... 

(Poster) Two other non-coding RNAs need pausing, too. 
(Poster) Pause sites are conserved in related bacteria species.

Evolutionary cross-talk? 
Non-coding RNA sequence/structure co-evolves with the properties of their transcribing RNA polymerase?

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