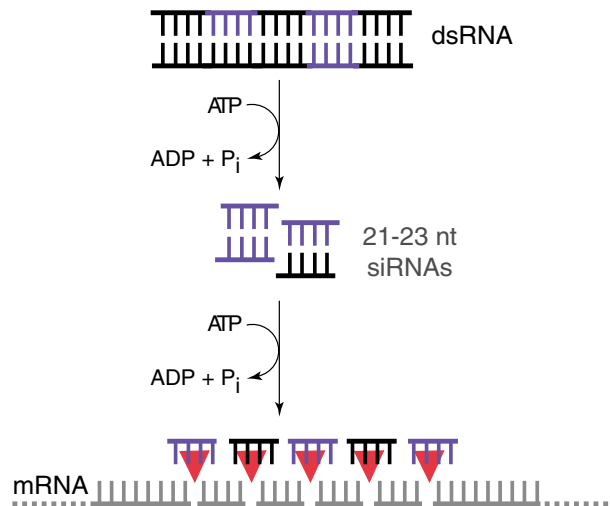


RNA Interference (RNAi)

RNAi is the surprising ability of double-stranded RNA (dsRNA)—but not antisense RNA—to target a corresponding mRNA for destruction. RNAi likely represents an ancient cellular defense against viral infection, a mechanism for preventing the “jumping” of transposons, and perhaps even a pathway by which cells regulate endogenous genes. RNAi has become an important tool for studying gene function in worms, flies, and cultured mammalian cells, and may lead to new drugs to treat human genetic disorders.



A Model for the RNAi pathway.

RNAi begins with cleavage of long dsRNA to 21-23 nt products. These small interfering RNAs (siRNAs) are double-stranded and need to be unwound before they can direct a nuclease (red triangles) to cleave the mRNA.

We use a variety of methods in our quest to understand the mechanism and biological function of RNAi, including tools from biochemistry and chemical biology, as well as genetics and cell biology.

A rotation project is available to explore the mechanisms that underlie the RNAi phenomenon.

Recent Publications on RNAi

Zamore, P.D. (2001). RNA Interference: Listening to the Sound of Silence. *Nature Structural Biology* **8**: 746-750.

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Sharp, P.A. and Zamore, P.D. (2000). Perspective: Molecular Biology. RNA Interference. *Science* **287**: 2431-2433.

Zamore, P.D., Tuschl, T., Sharp, P.A., and Bartel, D.P. (2000). RNAi: double-stranded RNA directs the ATP-dependent cleavage of mRNA at 21 to 23 nucleotide intervals. *Cell* **101**: 25-33.

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Translational Control

In *Drosophila*, mRNA encoding the transcription factor, *hunchback*, is present throughout the embryo, but is translated into protein only in the anterior half of the embryo. Two proteins, NANOS and PUMILIO, are required to repress *hunchback* translation in the posterior half of the fly embryo. PUMILIO binds RNA through a novel RNA-binding motif found in proteins that control developmental decisions in yeast, slime mold, and worms, and is more than 80% identical to a protein of unknown function in humans. A major goal of our laboratory is to learn how PUMILIO and NANOS control *hunchback* mRNA translation and to determine the biological role of the human PUMILIO protein. We are taking biochemical and structural approaches to the study of translational control.

We have recently developed an in vitro system that recapitulates the essential features of translational regulation of *hunchback* by PUMILIO and NANOS. A rotation project is available to use this in vitro system to study translational control in *Drosophila* development.



Structure of the Human PUMILIO RNA-binding domain.

The positively charged concave surface is envisioned to interact with RNA, whereas the convex face binds NANOS protein.

Recent Publications on Translational Control

Wang, X., Zamore, P.D., and Hall, T.M.T. (2001). Crystal Structure of a Pumilio-Homology Domain. *Molecular Cell* **7**: 855-865.

Zamore, P.D., Bartel, D.P., Lehmann, R., and Williamson, J.R. (1999). The PUMILIO-RNA interaction: A single RNA-binding domain monomer recognizes a bipartite target sequence. *Biochemistry* **38**: 596-604.

Zamore, P.D., Williamson, J.R., and Lehmann, R. (1997). The Pumilio protein binds RNA through a conserved domain that defines a new class of RNA-binding proteins. *RNA* **3**: 1421-1433.