nature structural & molecular biology

Focusing in on the small

In 2010, *Nature Structural & Molecular Biology* will carry a series of quarterly web features devoted to diverse areas within the journal's scope. As we unveil the first, on RNA silencing, we consider the eloquent argument made by this field for the power of model-organism biology.

One of the pleasures of reading the broad range of manuscripts that we receive at *Nature Structural & Molecular Biology* is the elegance of the miniscule: the ability to see and probe the nuts and bolts of mechanisms in miniature that underlie, for example, the process of getting a piece of cargo from A to B in the cell, or sieving out one ion while ushering another across a membrane, or aiding the correct folding of a protein or RNA. Sometimes being small can prove too obscure: this was the case for RNA-silencing pathways which are mediated by small RNAs. The first hints that small RNA–mediated silencing pathways exist came from pioneering work examining plant defense mechanisms. Meanwhile, two seemingly disparate research paths were pursued in the nematode *Caenorhabditis elegans*, one examining the unexpected ability of exogenously supplied double-stranded (ds)RNA to post-transcriptionally silence endogenous gene expression and the other arising from the effort to define the genes involved in the "Peter Pan–like" heterochronic phenotype, where mutants cycle again and again through particular larval stages. The roads not taken led to the same place, as all three paths converged at a similar mechanistic junction: small RNAs of 21–23 nucleotides and families of processing and effector proteins, Droshas, Dicers and Argonautes, among other key factors.

Although the mechanisms by which the Argonaute proteins mediate silencing and the structures of many of the proteins involved in divergent organisms remain to be defined, it is now clear that this mechanism exists across kingdoms. The classes of small RNAs that exist have since expanded with the emergence of the Piwi-interacting piRNAs, involved in germline function, and other new classes such as the endo-siRNAs. The list of processes affected by small RNAs is also continuing to expand as their targets continue to be defined, predicted, refined and, more recently, 'pulled down'. MicroRNAs in particular have been linked to many basic molecular biological processes, including (but by no means limited to) DNA repair (*Nat. Struct. Mol. Biol.* **16**, 492–498 (2009)) and p53 regulation (*Nat. Struct. Mol. Biol.* **16**, 23–29 (2009)). The latter suggests involvement in disease, and there is evidence for this, though of course the other side of the coin is also true, with there being obvious therapeutic potential in using the RNAi pathway to exogenously manipulate cellular processes.

The volume of research papers being published in this area across journals has expanded at an astonishing rate. Such increases often occur in the wake of the uncovering of such a deeply conserved and highly used molecular biological pathway, but despite this frenzy of activity, much remains unknown. To kick off our quarterly web focuses, we present a special focus on RNA silencing, featuring a Perspective in the current issue by Kai and Pasquinelli, who discuss recent insights and findings indicating that, far from being stable once present, the turnover and stability of microRNAs is regulated. The full web focus will be available at http://www.nature.com/nsmb/focus/rnasilencing and will contain papers from recent and upcoming issues of NSMB, as well as a broad library of papers published in this field at other Nature Publishing Group journals.

Given the unexpected reach of these pathways, it is worth remembering where they were first found. Model-organism biology can be hard to explain to nonscientists (the lack of understanding of the power of model-organism research inherent in the comment by 2008 Vice-Presidential candidate Governor Sarah Palin that taxpayer money was being spent on "projects that have little or nothing to do with the public good. Things like fruit fly research in Paris, France." is not an isolated attitude). The signposts to the small-RNA pathway came from research in just such organisms. In addition, 2010 marks the 30th anniversary of the publication of the landmark paper by Christiane Nüsslein-Volhard and Eric Wieschaus entitled "Mutations affecting segment number and polarity in *Drosophila*." Follow-up work on the mutants described in that paper, as well as the study of orthologs that emerged in other model organisms, was critical to our current understanding of, among other fields, signaling pathways from hedgehog to wingless and beyond—pathways that we now know are linked to cancers as well as to congenital defects in humans. In that sense, the fly screen, like the RNA-silencing work that began in *Arabidopsis thaliana* and *C. elegans*, embodies the power of model-organism research. This has been said before, but it is never too late or too often to defend this sort of basic research. Who knows where the road will lead?

We hope you enjoy this focus and look out for other such focuses, which will highlight distinct and diverse areas and techniques in structural and molecular biology and will appear each quarter throughout the upcoming year, with accompanying specially commissioned print content such as Perspectives. Have a great 2010, and we look forward to receiving your feedback, working with you and meeting you in person at conferences during the year ahead. ■