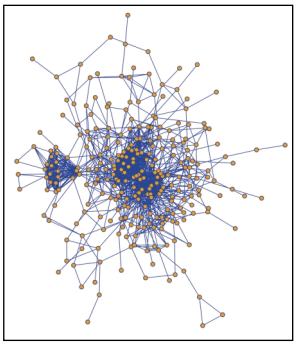
pathway—similar to the way in which workers perform together on an assembly line. It follows that if a signal transduction pathway (cascade) is conserved across species, then the proteins and their function within that cascade must be conserved as well.

Protein Pathways take every open reading frame (ORF) in an organism's genome and compare them to ORFs in 77 other genomes, creating a "profile" of organisms containing a specific homolog. ORFs with similar profiles, or ORFs that are at similar locations in multiple genomes, often represent proteins working within the same cascade. If any of these proteins is homologous with a protein of known function, then a broad role can be assigned to the whole class.



Protein pathways in *Mycoplasma genitalium*.

Sequential steps in a metabolic pathway are usually catalyzed by separate enzymes, but on some occasions these enzymes fuse to form a meta-enzyme that catalyzes multiple steps. The Rosetta stone technique searches for proteins that were once separate domains within a meta-enzyme, but whose DNA sequence was split during evolution. By searching completed genomes for such "Rosetta stones"—relic sequences in which homologs for two separate genes exist within a single ORF—Protein Pathways researchers can identify proteins that are functionally related and could bind to one another.

As a testament to the effectiveness of the phylogenetic profiling and Rosetta stone technologies, Protein Pathways has identified 59 drug targets unique to *Mycobacterium tuberculosis*, two of which were already are targets for existing antibiotics. Pellegrini says that although Protein Pathways has no desire to develop the antimicrobials, the firm will inevitably move into drug development: "We have already combined the analysis of microarrays with comparative genomics for the yeast genome, and we were able to extract a great deal of additional functional data." Unfortunately, phylogenetic profiling still has limited application to the human genome as a result of the lack of completed vertebrate genomic sequences for comparison.

Protein Pathways will initially generate revenue by selling subscriptions to its internally developed proprietary microbial protein interactions database, Prolinks. The company currently has one collaboration—UroGenesys (Santa Monica, CA)—to identify new therapeutic candidates from UroGenesys's database of prostate cancer–associated antigens. *AB*

PTC Therapeutics

Targeting therapeutics against RNA translation.

The process by which DNA is transcribed to messenger RNA (mRNA), which is then translated into protein, is central to our understanding of molecular biology. Although DNA transcription is a well-established target for drug development, in the relatively new field of RNA targeting there have been few advances in our understanding of what happens after transcription, specifically during translation. PTC Therapeutics aims to identify points of intervention in RNA translation as novel drug targets.

Founded: 1998
Founders: Robert Swanson, Peter Svennilson, Allan Jacobson, Tariq Rana, Stuart Peltz (chief executive officer)
Employees: 45
Financing to date: $16.2 million
Location: South Plainfield, NJ
http://www.ptcbio.com

PTC Therapeutics has developed three proprietary technologies to screen for, and identify, small-molecule drug targets within the RNA translation process. First, targeted ribonucleic acid chemistry (TRAC) identifies molecules that bind with high specificity to RNA and modulate RNA function. TRAC is performed under physiological conditions allowing RNAs of interest to retain their native structures, facilitating the identification of molecules that modulate function. PTC also has RNA-Screen Translation and RNA-Screen Turnover platforms that identify, respectively, molecules that modulate different aspects of the translation process, and those that affect specific steps in the turnover and processing of cellular RNA. Molecules identified by the RNA-Screen Turnover platform can promote either substantial increases or decreases in RNA levels. The initial technologies were developed by Peltz and colleagues at the University of Medicine and Dentistry of New Jersey (Piscataway, NJ), during the early 1990s, and were licensed to PTC Therapeutics.

PTC Therapeutics is hoping to develop orally active drugs to treat a variety of diseases including cystic fibrosis and Duchenne muscular dystrophy—both inherited diseases arising from nonsense genetic mutations that lead to the synthesis of an mRNA that contains an inappropriate stop codon. The premature stop codon results in the synthesis of a truncated protein, which may be inactive or insufficient for normal function. In addition, most common cancers result from frameshift and nonsense mutations in regulatory genes (e.g., *p53*, *BRCA1*, *BRCA2*, and *APC*). Suppressing the effects of these mutations by restoring RNA translation can inhibit blood vessel formation, boost antitumor immune responses, and induce apoptosis in the cancer cells.

RNA targeting is also being tried against HIV, against hepatitis C, and also in the search for new antibacterial and antifungal drugs. For example, PTC Therapeutics is using its TRAC platform to find inhibitors for Tat–TAR, the interaction between a viral protein and RNA structure that is essential for replication of HIV-1 virus.

PTC's main collaborator to date has been Tularik (S. San Francisco, CA). Together the companies have developed high-throughput screens for over 700,000 compounds in both cell-based and *in vitro* assays, and lead candidates have been identified and characterized in secondary assays. Other companies focusing on RNA and the post-transcription process include the emerging company Message Pharmaceuticals (Malvern, PA), as well as Boulder, Colorado–based Ribozyme Pharmaceuticals and its spinoff, Atugen. *MF*