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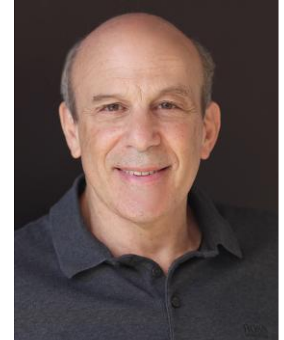
Yeast molecular genetic tricks to study gene regulation



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The Genetics Society of America's (GSA) Edward Novitski Prize is awarded to researchers for extraordinary creativity and intellectual ingenuity in genetics research. Struhl is being recognized for his pioneering work cloning a functional eukaryotic gene in E. coli, defining its promoter and regulatory region, and using random DNA and amino acid sequences to define determinants of specificity. The award also recognizes other key scientific contributions including Struhl's discovery of the sequences and protein interactions required for transcriptional activation and repression and demonstrating the importance of nucleosome-free regions for transcription initiation, among others.

It is hard to believe that my graduate career began 50 years ago. Inspired by Francois Jacob and Jacques Monod, whose brilliant genetic analysis of the *Escherichia coli lac* operon uncovered fundamental principles of gene regulation (Jacob and Monod 1961), my goal was to apply their conceptual approach to eukaryotes. Eukaryotes had three RNA polymerases (Roeder and Rutter 1969), nucleosomes (Kornberg 1974), acetylated histones linked to gene expression (Pogo *et al.* 1966), and mutations that affected regulation of multiple genes (Douglas and Hawthorne 1964), but little else was known. During a day of intense interviews for the PhD program in the famed biochemistry department at Stanford Medical School, I learned about and was awestruck by recombinant DNA technology, which had just begun there. On the spot, I decided to work with Ron Davis and use recombinant DNA to study eukaryotic gene regulation. I never met Edward Novitski, but recognizing his creativity and ingenuity in genetic analysis (Crow *et al.* 2006), this history focuses on novel molecular genetic approaches my laboratory developed to elucidate eukaryotic gene-regulatory mechanisms. It only covers work in yeast and excludes contributions using conventional genetics and biochemistry.

The classical genetic approach of Jacob and Monod was based on obtaining informative mutations in the intact organism. In contradistinction, recombinant DNA enabled "reverse genetics," a term not then used, that involves cloning a gene, making mutations in the cloned DNA, and introducing the altered DNA back into the organism to assess the phenotypes (Struhl 1983). When I started my PhD, one could generate bacteriophage λ or plasmid libraries (called hybrid pools at Stanford) of cloned DNA segments from any genome. However, identifying a defined gene from such libraries was very challenging.

Based on my undergraduate experience with P1 transduction in bacteria, I tried a functional complementation assay in which expression of a defined yeast gene would permit growth of an *E. coli* auxotroph lacking the corresponding enzyme; for a history, see (Struhl 2008). Although viewed by many as very speculative, I isolated the yeast *his3* gene via complementation of the *E. coli hisB463* mutation that inactivated the histidine biosynthetic enzyme IGP dehydratase (Struhl *et al.* 1976). Aside from isolating the first yeast gene, this was the first example of functional expression of a eukaryotic protein in *E. coli* (Atkins 1976). To prove that the cloned DNA truly contained the yeast *his3* gene, I cloned the equivalent DNA fragments from two yeast *his3* mutant strains via plaque filter hybridization. These mutant genes did not complement the *hisB463* mutation, but they could be recombined via a λ phage cross to regenerate the wild-type gene (Struhl and Davis 1977).

The cloned *his3* gene enabled an attempt to transform yeast cells, a critical step for reverse genetic analysis. I tried for a month, but only obtained a single potential transformant that could have been a contaminant. Given this lack of success, I instead made mutations in the cloned DNA hoping to test them if/when other laboratories figured out how to transform yeast. Thus, I was ready to identify *his3* regulatory elements when Gerald Fink's laboratory developed a yeast transformation method (Hinnen *et al.* 1978). The Fink method and my attempts were both based on a spheroplast fusion protocol (van Solingen and van der Plaat 1977), but unfortunately I used a higher molecular weight version of polyethylene glycol.

The original yeast transformation protocol required chromosomal integration and hence was inefficient. Shortly thereafter, (Beggs 1978) and I (Struhl *et al.* 1979) independently discovered that yeast 2μ plasmid sequences confer high-frequency transformation via autonomous replication. Dan Stinchcomb and I then discovered chromosomal DNA replication origins that also permit high-frequency transformation (Stinchcomb *et al.* 1979; Struhl *et al.* 1979). These discoveries allowed me to create yeast/coli shuttle vectors for molecular genetic manipulations in yeast (Struhl *et al.* 1979) and to perform reverse genetic analysis with mutated versions of the *his3* gene (Struhl 1979).

Although reverse genetics is based on generating mutated derivatives of the cloned *his3* gene, few methods were available

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beyond subcloning fragments with restriction endonucleases, and DNA sequencing had not been developed. To circumvent this problem, I used a trick from Sandy Parkinson that involved EDTA-mediated selection of deleted λ derivatives (Parkinson and Huskey 1971) of a λ-*his3* hybrid phage (Struhl and Davis 1980). Importantly, most deleted derivatives are mediated by int-mediated recombination (Parkinson 1971) and have a common endpoint at the λ attachment site. Thus, this set of deletion mutants represented a sequential 5′-deletion analysis of the *his3* regulatory region, leading to the surprising conclusion that sequences >100 bp upstream of the coding region are required for wild-type levels of expression in yeast (Struhl 1981).

Subsequently, I generated a large set of internal deletion mutants by systematically combining 5′ and 3′ deleted fragments via a common restriction site (Struhl 1982b). Analysis of >200 mutated derivatives resulted in early descriptions of basic gene-regulatory elements: upstream elements acting a distance from the promoter (Struhl 1979; 1981); regulatory sites activating gene expression in specific conditions (Struhl 1982a); poly(dA:dT) sequences (Struhl 1985a); functionally distinct TATA elements (Struhl 1986); initiator elements (Chen and Struhl 1985); repression sequences acting upstream of intact promoters (Struhl 1985b). Finally, we created many single base pair substitutions in a localized region using a single degenerate oligonucleotide, leading to the first saturation mutagenesis of a transcriptional regulatory element (Hill *et al.* 1986) and the TATA element (Chen and Struhl 1988).

Genetic evidence suggested the possibility that Gcn4 protein might directly activate transcription of *his3* and other amino acid biosynthetic genes in response to amino acid starvation (Hinnebusch and Fink 1983). To prove this while avoiding the cold room and protein purification, we invented "reverse biochemistry," in which radiopure ^{35}S-labeled proteins are synthesized by in vitro transcription and translation of cloned genes (Hope and Struhl 1985). As assayed by a reverse electrophoretic shift with unlabeled DNA fragments, ^{35}S-Gcn4 binds specifically to promoters of genes regulated by amino acid starvation, (Hope and Struhl 1985). Reverse biochemistry makes it easy to study mutant proteins by simply modifying the DNA template. Aside from showing that DNA-binding is mediated by the C-terminal 60 amino acids, Ian Hope developed a stoichiometry assay involving co-synthesis of differently sized Gcn4 derivatives to demonstrate that Gcn4 binds as a dimer to overlapping and nonidentical half-sites (Hope and Struhl 1987).

Domain swaps to generate chimeric yeast/human proteins demonstrated that dimerization specificity is mediated by the leucine zipper within the DNA-binding domain (Sellers and Struhl 1989) and, in my last experiments, that the Jun oncogene encodes a Gcn4 homolog that binds the same sequences (Struhl 1987) and activates transcription in yeast (Struhl 1988). Jun was the first example of an oncogene that encodes a transcription factor. Deletion analysis of Gcn4 led to the unexpected discovery that transcriptional activation is mediated by short unstructured activation domains that are functionally autonomous and can be encoded by different sequences (Hope *et al.* 1988; Hope and Struhl 1986).

Our laboratory developed novel approaches to study transcriptional activation mechanisms. My first graduate student, Wei Chen, had the idea to use bacteriophage T7 RNA polymerase in yeast as a mechanistic probe, and she demonstrated distinct chromatin-accessibility and protein-protein interaction mechanisms for transcriptional activation (Chen *et al.* 1987). Kinetic analysis of transcription by an altered-specificity TATA-binding protein (TBP) (Strubin and Struhl 1992) showed that activators increase the rate of TBP recruitment to the promoter (Klein and Struhl 1994). Lastly, protein fusions between heterologous DNA-binding domains and general transcription factors result in their artificial recruitment to promoters and transcriptional activation without an activation domain (Chatterjee and Struhl 1995; Keaveney and Struhl 1998). Together, these results indicated that transcriptional regulation in yeast occurs primarily at the level of recruitment of the RNA polymerase II transcription machinery. This was subsequently confirmed by chromatin immunoprecipitation (Kuras and Struhl 1999; Li *et al.* 1999).

Other molecular genetic tricks to study gene regulation are worth noting. First, transcriptional synergy was addressed by analyzing the activity of Fos-Jun heterodimers with one or two activation domains on promoters with one or two binding sites (Oliviero and Struhl 1991). Synergistic enhancement does not depend on the number of acidic activation domains but rather the number of proteins bound to the promoter. Second, to demonstrate that an activation-defective TBP mutant was due to an impaired biochemical interaction with TFIIA, we showed that the mutant phenotype was suppressed by directly fusing TFIIA to TBP (Stargell and Struhl 1995). Third, by measuring expression differences of derivatives in which poly(dA:dT) length was varied by 1–2 bp, we demonstrated that activation by poly(dA:dT) occurs continuously as opposed to stepwise (Iyer and Struhl 1995). As conventional measurements were unsuitable for such subtle effects, we developed a competitive growth assay where strains were mixed, grown under selective conditions that favored higher expression levels, and simultaneously assayed for the relative frequency of the alleles by their different lengths. Fourth, an inducible double-shutoff method that simultaneously represses transcription and degrades an essential protein led to the then controversial finding that TBP-associated proteins (TAFs) are not essential for transcriptional activation (Moqtaderi *et al.* 1996). Fifth, the relationship and distinction between Pol II elongation rate and processivity were clarified with a new transcriptional elongation assay in which Pol II occupancy across a long gene was followed after a rapid shutoff of transcriptional initiation (Mason and Struhl 2005). Sixth, to disentangle direct and indirect effects that inevitably occur in stable knock-out strains, we followed molecular events at promoters regulated by the Cyc8-Tup1 co-repressor complex upon rapid removal of the nonessential Tup1 subunit; this led to a new model for Cyc8-Tup1 function (Wong and Struhl 2011). Seventh, mRNA stabilization and destabilization elements were identified on a transcriptome scale by a deletion strategy that does not rely on mutants but rather on the stability of naturally occurring 3′ isoforms (Geisberg *et al.* 2014).

A completely new way to study biological function began when Arnold Oliphant, then a first-year graduate student, wished to join my laboratory and pursue his radical and creative idea to select functional genetic elements from random-sequence DNA. We termed this functional approach "random selection" to distinguish it from the "natural selection" process of evolution (Oliphant *et al.* 1986). Random-sequence or highly degenerate oligonucleotides are generated by equimolar (or other defined) mixtures of nucleotide precursors and cloned into appropriate DNA molecules, followed by a genetic or biochemical selection for functional sequences. Genetic selections identified *E. coli* promoters (Oliphant and Struhl 1988) and yeast TATA elements (Singer *et al.* 1990), and a biochemical selection (later termed SELEX by others) identified Gcn4 binding sites (Oliphant *et al.* 1989). We also selected for novel β-lactamases with altered enzymatic or other functional properties by recoding the active site of β-lactamase with a highly degenerate oligonucleotide, (Oliphant and Struhl 1989). This approach for selecting proteins with novel functions was reported 5 years

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earlier than related work by Francis Arnold that received the 2018 Nobel Prize in chemistry.

More recently, we developed a functional evolutionary approach to address mechanistic questions independently of evolutionary constraints, something that cannot be done by standard experiments in native organisms. Using functional assays in *Saccharomyces cerevisiae*, evolutionarily irrelevant DNA (e.g. from evolutionarily distant yeast species or random-sequence DNA) is compared either to *S. cerevisiae* genomic DNA in the same cells or to the evolutionarily distant species. This approach yielded insights into nucleosome positioning (Hughes *et al.* 2012), promoter directionality (Jin *et al.* 2017), transcriptional noise, transcriptional initiation, and 3′ end formation (Gvozdenov *et al.* 2023).

Years ago, when Stewart Scherer and I were graduate students in Ron Davis' laboratory, we characterized scientists by whether they played primarily for elegance, technical wizardry, or craftsmanship points. I played for elegance points then, and I still do. Of course, scientific discovery, the goal of any research effort, most commonly employs conventional methods available at the time to address specific questions of interest. While conventional experiments underlie many of my laboratory's contributions, I particularly enjoy designing molecular genetic tricks to gain scientific knowledge in new ways, which is in the spirit of Edward Novitski.

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Conflicts of interest

The author(s) declare no conflict of interest.

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