Marian Carlson

# The 2009 Genetics Society of America Medal

## Marian Carlson

MARIAN Carlson is the recipient of the 2009 Genetics Society of America Medal in recognition of her many important contributions to our understanding of fundamental aspects of eukaryotic gene expression and cellular growth. The work from Marian's laboratory is an outstanding example of the unique and formidable power of forward genetics. Beginning with a system where little was known, Marian skillfully employed all the tools of yeast genetics to identify previously unknown classes of factors that play widespread roles in gene regulation and that are conserved from yeast to humans. This research, which began with the isolation and analysis of mutations that alter regulation of the *Saccharomyces cerevisiae SUC2* gene, has had a far-reaching impact throughout eukaryotic biology.

How does a yeast geneticist get started in science? In Marian's case, it began with a neurobiology course that she took during her sophomore year at Harvard. Inspired by what she learned, Marian spent the following summer in the laboratory of Nobel Prize winner David Hubel and decided to become a scientist. She did her graduate work in the Department of Biochemistry at Stanford, where she cloned *Drosophila melanogaster* satellite DNA and associated repeated elements.

Marian's entry into the world of yeast genetics began with her postdoc. Interested in studying gene regulation, Marian chose yeast as a system and genetics as an approach. Marian took the Cold Spring Harbor Laboratory yeast course, taught by Gerry Fink and Fred Sherman, which, in her view, provided an important foundation for her research. She then joined David Botstein's lab at MIT, where she embarked on the career for which she has received the 2009 Genetics Society of America Medal. Below is a summary of many of Marian's outstanding contributions.

In David's lab, Marian began her work on studying *SUC2*, the gene encoding invertase, which is required for yeast to use sucrose or raffinose as a carbon source. In low glucose, yeast cells produce both secreted and nonsecreted forms of invertase, while in high glucose only the nonsecreted form is made. Marian's cloning of *SUC2* and analysis of *SUC2* mRNAs revealed two differentially regulated promoters (Carlson and Botstein 1982). While this type of regulation had been previously demonstrated for phage λ, with two promoters differentially controlling λ repressor expression, *SUC2* was one of the first examples of such regulation in eukaryotes.

Marian's work focused on isolating mutations that alter *SUC2* regulation, as a route to understanding glucose repression. The isolation and analysis of these mutants laid the foundation for almost everything that has followed in her research career. Marian isolated mutants that were unable to express *SUC2* and initially identified a new complementation group that was named *SNF1* (*s*ucrose *n*on*f*ermenting) (Carlson *et al.* 1981). *SNF1* came to be the major focus of Marian's research. During her postdoc, and after she became a faculty member at the Columbia University College of Physicians and Surgeons in 1981, she and her lab isolated more *snf* mutants, as well as suppressors of *snf* mutations (*ssn*) (for example, Carlson *et al.* 1984; Neigeborn and Carlson 1984). The suppressor analysis and other phenotypic characterizations divided the *snf* mutants into groups. The first group, *snf1* and *snf4*, appeared to play a role in glucose repression, and the second group, *snf2*, *snf5*, and *snf6*, appeared to play a more general role in transcriptional activation. Another mutation, *snf3*, affected glucose transport and led to greater understanding of this process.

A major contribution of Marian's lab has come from pioneering work on Snf1, a kinase that is understood today to play key roles in both yeast and mammals. A breakthrough in understanding Snf1 function came from the finding from Marian's lab that Snf1 is a protein kinase (Celenza and Carlson 1986), thus providing the first demonstration that protein phosphorylation

plays a role in glucose repression in eukaryotes. Subsequent studies from Marian's lab established that Snf1 acts in a trimeric complex. Snf1, the catalytic member, is referred to as the α-subunit. Three alternative β-subunits were identified by two-hybrid and multicopy suppressor studies (Yang *et al.* 1992, 1994) and were shown to play roles in interactions with substrates, regulation of subcellular localization, and regulation of kinase activity (Vincent and Carlson 1999; Vincent *et al.* 2001; Momcilovic *et al.* 2008). Snf4, the γ-subunit, affects both autoinhibition and activation of Snf1 by phosphorylation (Celenza and Carlson 1989; Jiang and Carlson 1996; Momcilovic *et al.* 2008). The three kinases that phosphorylate Snf1 were identified by Marian's lab (Hong *et al.* 2003) and others (Sutherland *et al.* 2003). The protein phosphatase Reg1-Glc7 plays an antagonistic role in Snf1 regulation (Tu and Carlson 1995). This work, along with other studies from Marian's lab, has shown Snf1 to be a central sensor of carbon stress, other environmental stresses, meiosis, invasive growth, and more.

An important aspect of Snf1 that came out of Marian's work is its remarkable functional conservation in mammalian cells. In 1994, a mammalian gene was identified that encoded an AMP-activated protein kinase (AMPK) that is 46% identical and functionally related to Snf1 (Mitchelhill *et al.* 1994; Woods *et al.* 1994). There is now strong evidence that mammalian AMPK plays a major role in control of energy metabolism, thereby protecting individuals from type 2 diabetes and obesity (reviewed in Kahn *et al.* 2005). The wealth of genetic studies from Marian's lab on yeast Snf1 has provided a framework for a greater understanding of AMPK. Notably, the Snf1-activating kinases led to the identification of the first AMPK-activating kinase. Collaborative studies of the Carlson and Carling labs showed that the mammalian LKB1 tumor suppressor kinase activates AMPK (Hong *et al.* 2003; Woods *et al.* 2003). The *LKB1* gene is mutated in Peutz–Jeghers polyposis and cancer syndrome, and these findings suggested a link between cancer and metabolic control and also between LKB1 and the broader family of AMPK-related kinases. The Carlson and Carling labs, and others, also implicated Ca(2+)/calmodulin-dependent protein kinase kinases as mammalian AMPK-activating kinases (Hong *et al.* 2005; Woods *et al.* 2005).

Marian's studies have also made important impacts in other areas of gene expression. Analysis of the *snf2*, *snf5*, and *snf6* mutants contributed significantly to the identification of the first chromatin-remodeling complex, Swi/Snf. Studies of these genes from Marian's lab provided strong evidence that Snf2, Snf5, and Snf6 act together to play an important and general role in gene activation (Laurent *et al.* 1991; Laurent and Carlson 1992). An additional key study provided the first demonstration that Snf2 possesses a DNA-dependent ATPase activity (Laurent *et al.* 1993). The work from Marian's lab, in conjunction with *swi* mutants isolated in Ira Herskowitz's lab (Stern *et al.* 1984), led to later results from other labs that these proteins were members of the same complex, named Swi/Snf, and that this complex functioned to remodel nucleosomes in an ATP-dependent fashion (reviewed in Sudarsanam and Winston 2000). In addition, her work on Ssn6-Tup1 contributed significantly to the understanding of its role as a global repressor (Carlson *et al.* 1984; Keleher *et al.* 1992; Treitel and Carlson 1995). Finally, her *ssn* suppressors identified many components of the Mediator complex that link transcriptional regulators to RNA polymerase II, and her analysis of these genes provided early evidence for a negative regulatory role for Mediator (Vallier and Carlson 1994; Kuchin *et al.* 1995; Song *et al.* 1996).

In conclusion, Marian has skillfully employed the powerful tools of yeast genetics to open fields that no one even knew existed prior to her work. Her work on Snf1 is an outstanding example of science moved forward, with a combination of genetics and subsequent biochemistry, to understand the cellular roles and the regulation of a critical function in eukaryotes. In recognition of these great accomplishments, the Genetics Society of America is happy to present her with the 2009 Genetics Society of America Medal.

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Fred Winston