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Atypical translation mechanism of selenoprotein mRNPs

Anne-Sophie Gribling-Burrer, Laurence Wurth, Michael Leichter, Séverine Massenet, Franck Martin, Gilbert Eriani, Christine Allmang

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Atypical translation and maturation mechanism of selenoprotein mRNPs



Gribling AS, Wurth L, Leichter M, Massenet S*, Martin F, Eriani G and Allmang C

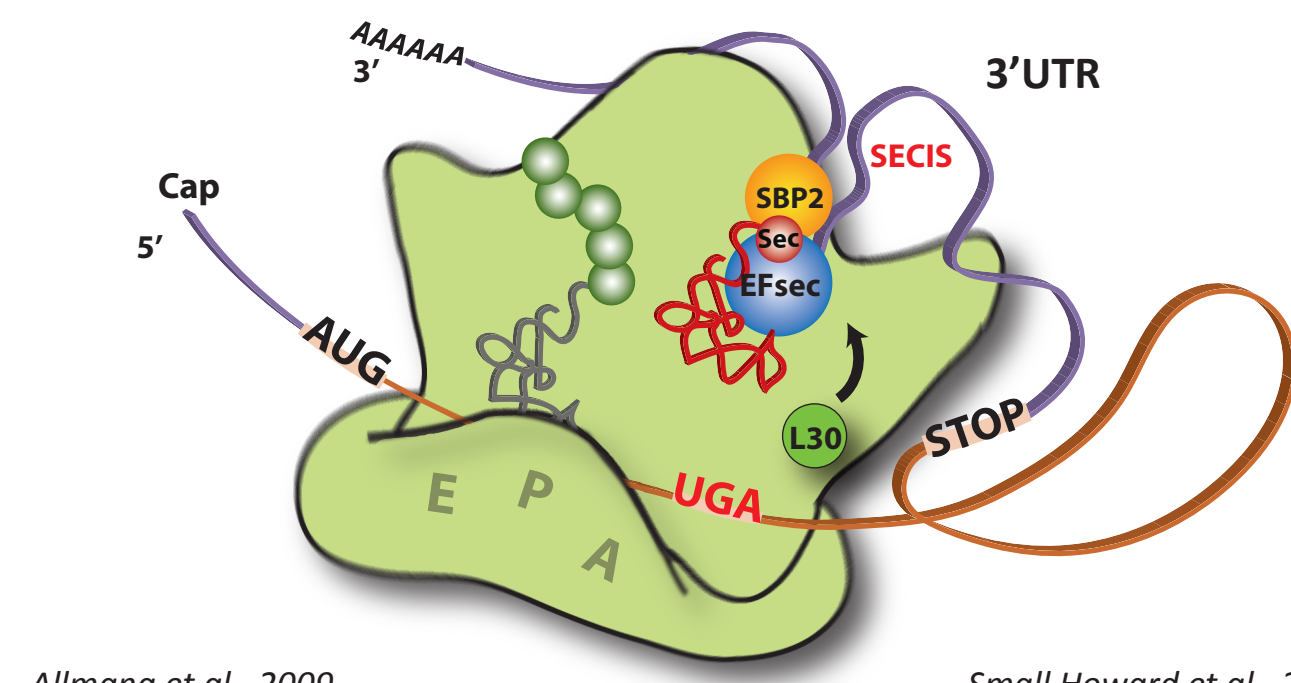
University of Strasbourg, CNRS, Architecture and Reactivity of RNA, Strasbourg, France ;

*University of Lorraine, CNRS, Ingénierie Moléculaire et Physiopathologie Articulaire (IMoPA), Vandoeuvre-lès-Nancy, France

c.allmang@ibmc-cnrs.unistra.fr



Selenoprotein synthesis, a complex mechanism of co-translational recoding

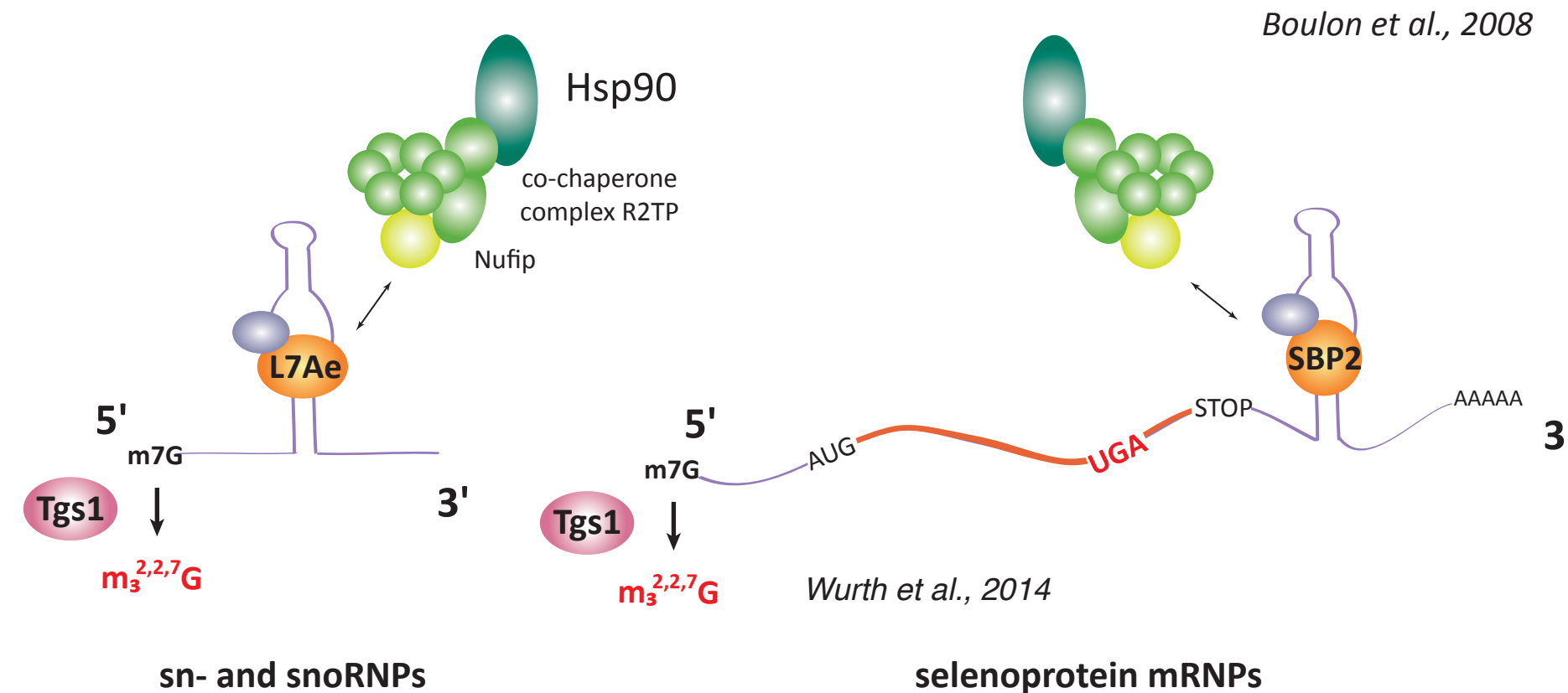


Allmang et al., 2009
Chavatte et al., 2005

Small Howard et al., 2006
Copeland et al., 2009

Selenoproteins, key players of oxidative stress protection, are synthesized by co-translational recoding mechanisms of in-frame UGA codons. In mammals, this process is governed by the recruitment of dedicated factors to a hairpin structure, called Selenocysteine Insertion Sequences (SECIS), in the 3'UTR of selenoprotein mRNAs. Essential in this process is the SECIS binding protein 2 (SBP2) that binds the SECIS RNA and recruits translation and assembly factors to the mRNA.

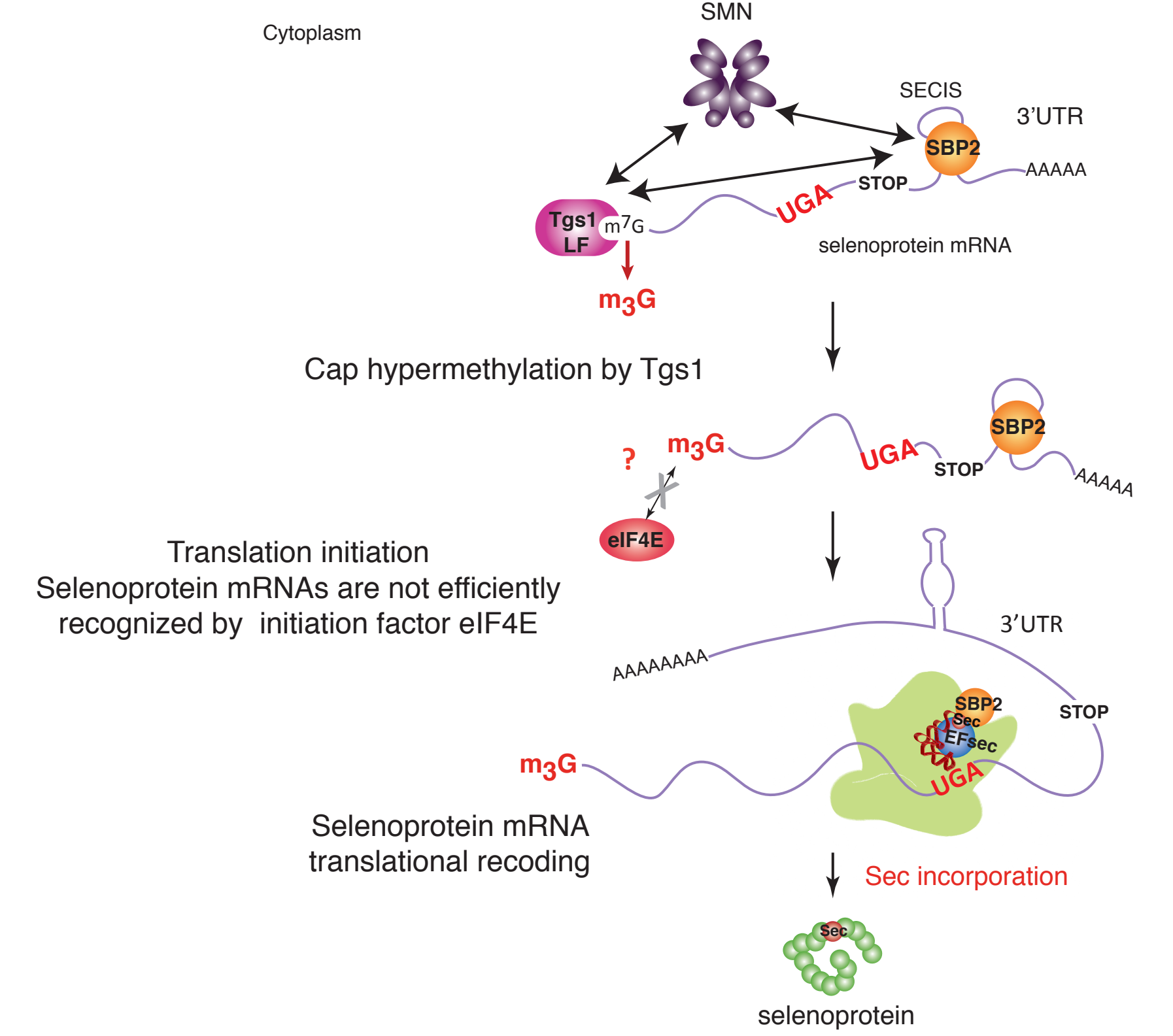
Selenoprotein mRNA assembly and processing : similarities with sn(o)RNPs



SBP2 shares a common RNA binding domain with core proteins of small non-coding RNPs. Selenoprotein mRNA assembly in the 3'UTR is similar to that of snRNPs (splicing) or snoRNPs (ribosome biosynthesis) and involves a complex linked to the HSP90 chaperone (Boulon et al., 2008).

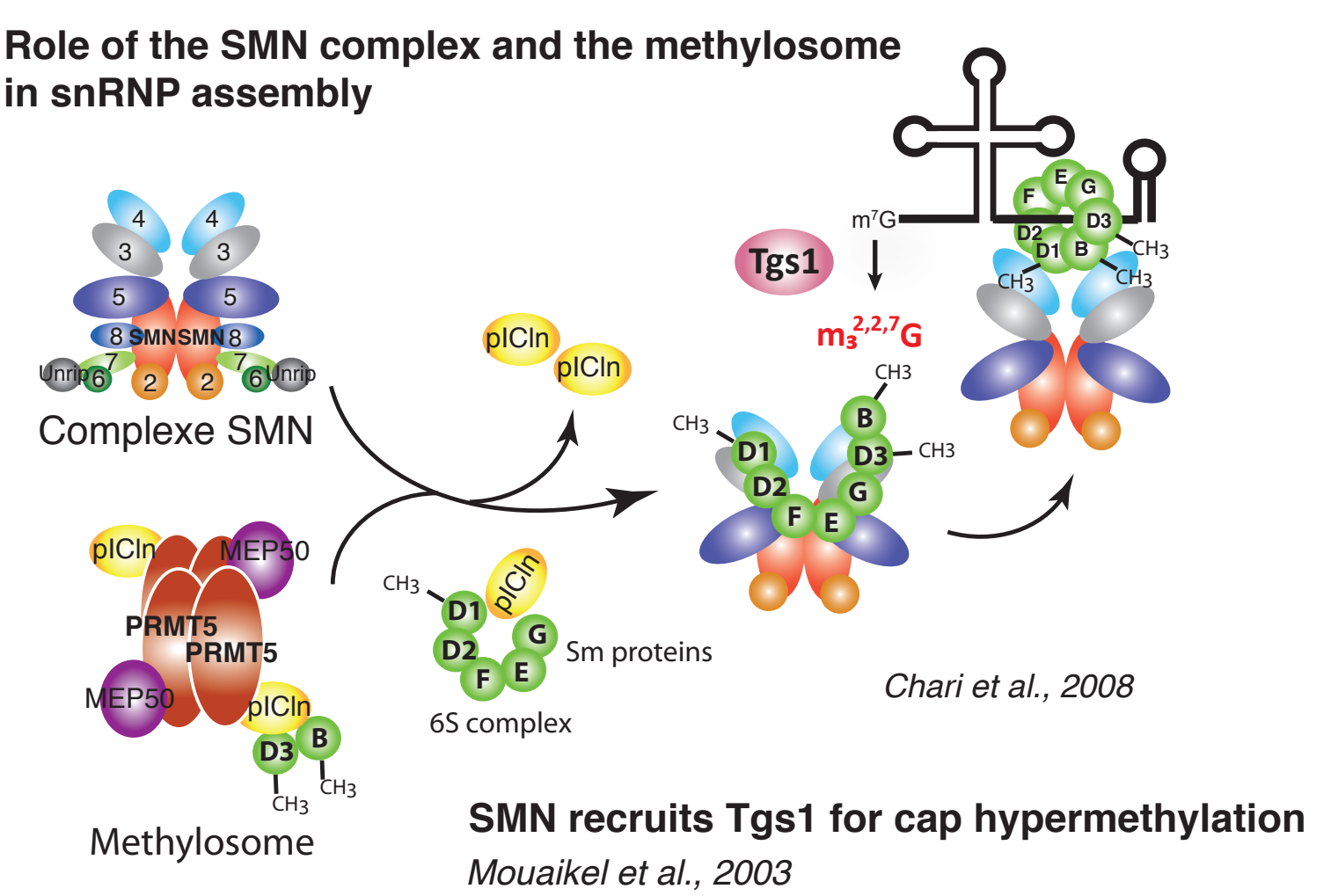
We have demonstrated that several selenoprotein mRNAs, unlike most mammalian mRNAs, bear a hypermethylated $m_3,2,7G$ cap instead of a classical 7-methylguanosine (m_7G) cap and undergo a similar 5' end maturation pathway than non-coding RNAs (Wurth et al. 2014). The trimethylguanosinesynthase 1 (Tgs1) hypermethylates the cap of selenoprotein mRNAs and is recruited by the assembly chaperone Survival of Motor Neuron (SMN) devoted to sn- and snoRNP maturation.

The cap of selenoprotein mRNAs is hypermethylated



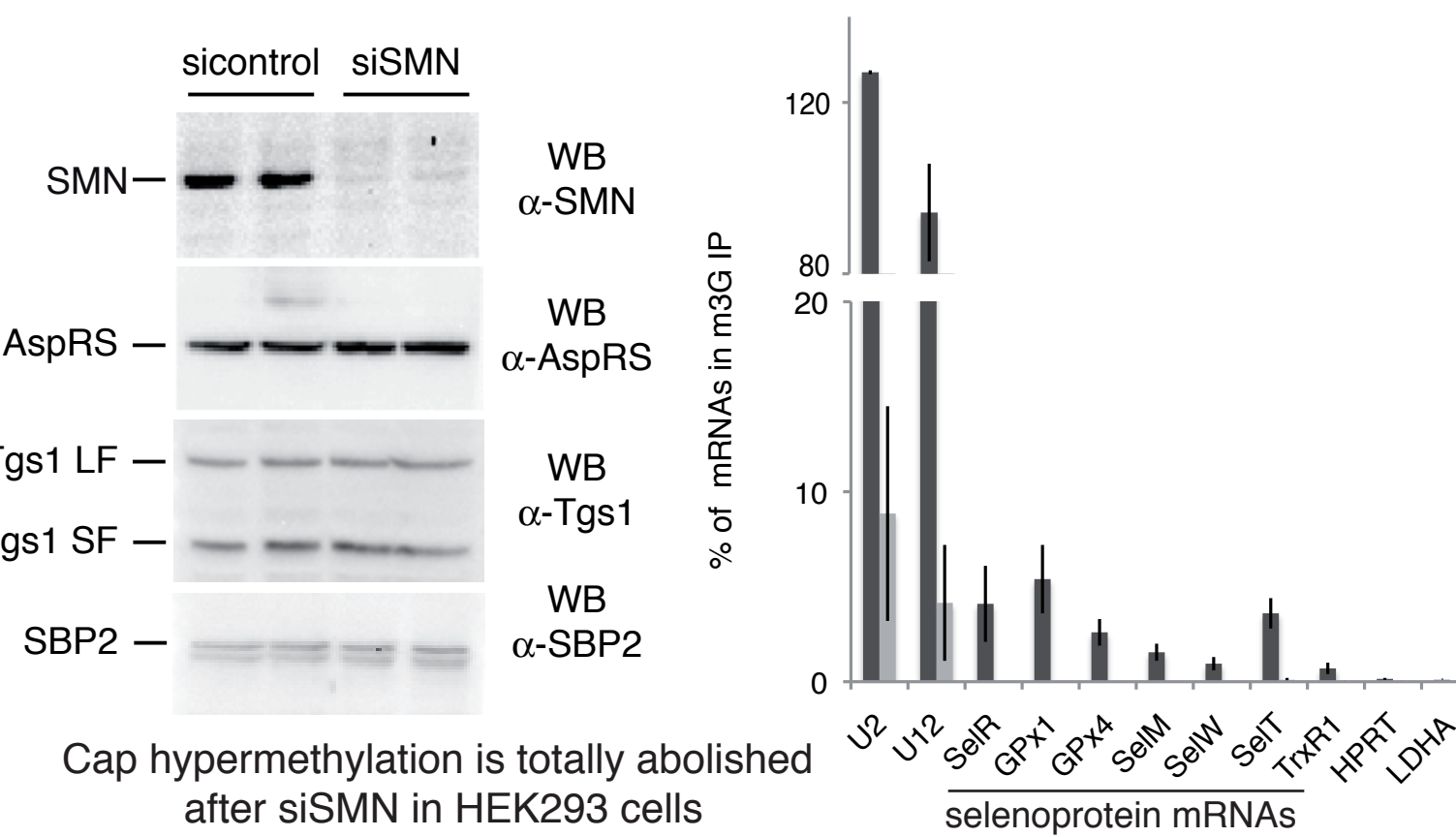
Wurth L (1), Gribling-Burrer A.S (1), Verheggen C, Leichter M, Takeuchi A, Baudrey S, Martin F, Krol A, Bertrand E and Allmang C. Nucleic Acids Res. 2014, 42, 8663-8677. (1) Contributed equally.

Aim: Determine the implication of the SMN complex and the methylosome in the cap maturation and expression of selenoprotein mRNAs



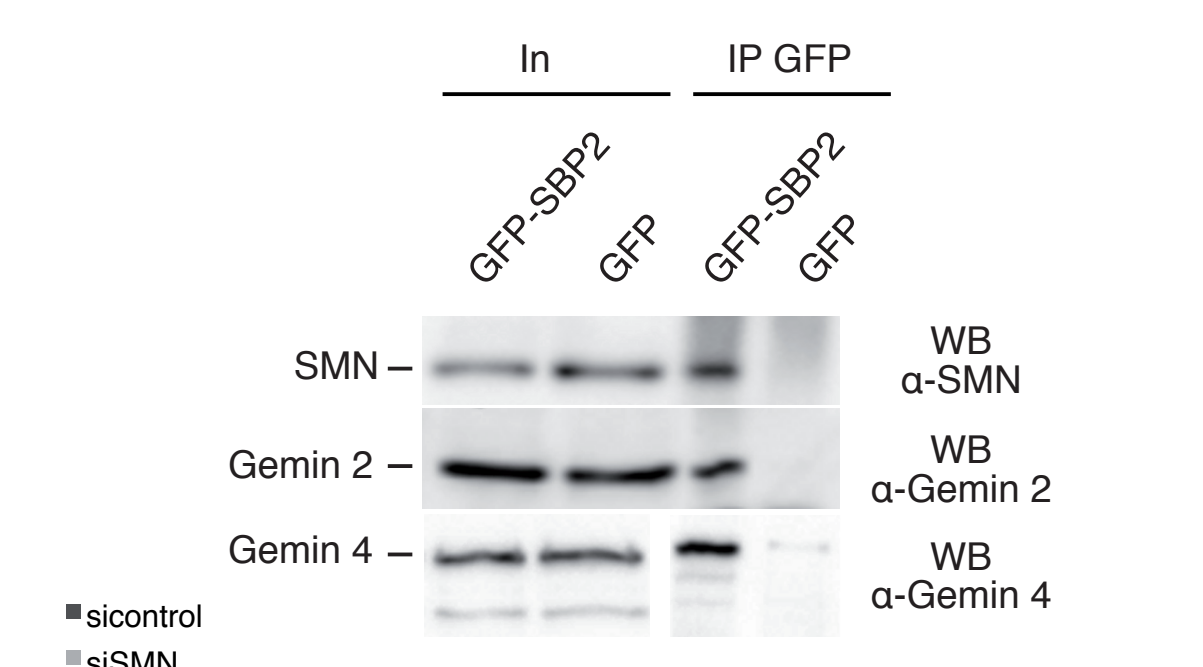
SMN recruits Tgs1 for cap hypermethylation
Mouaikel et al., 2003

SMN is required for cap hypermethylation of selenoprotein mRNAs



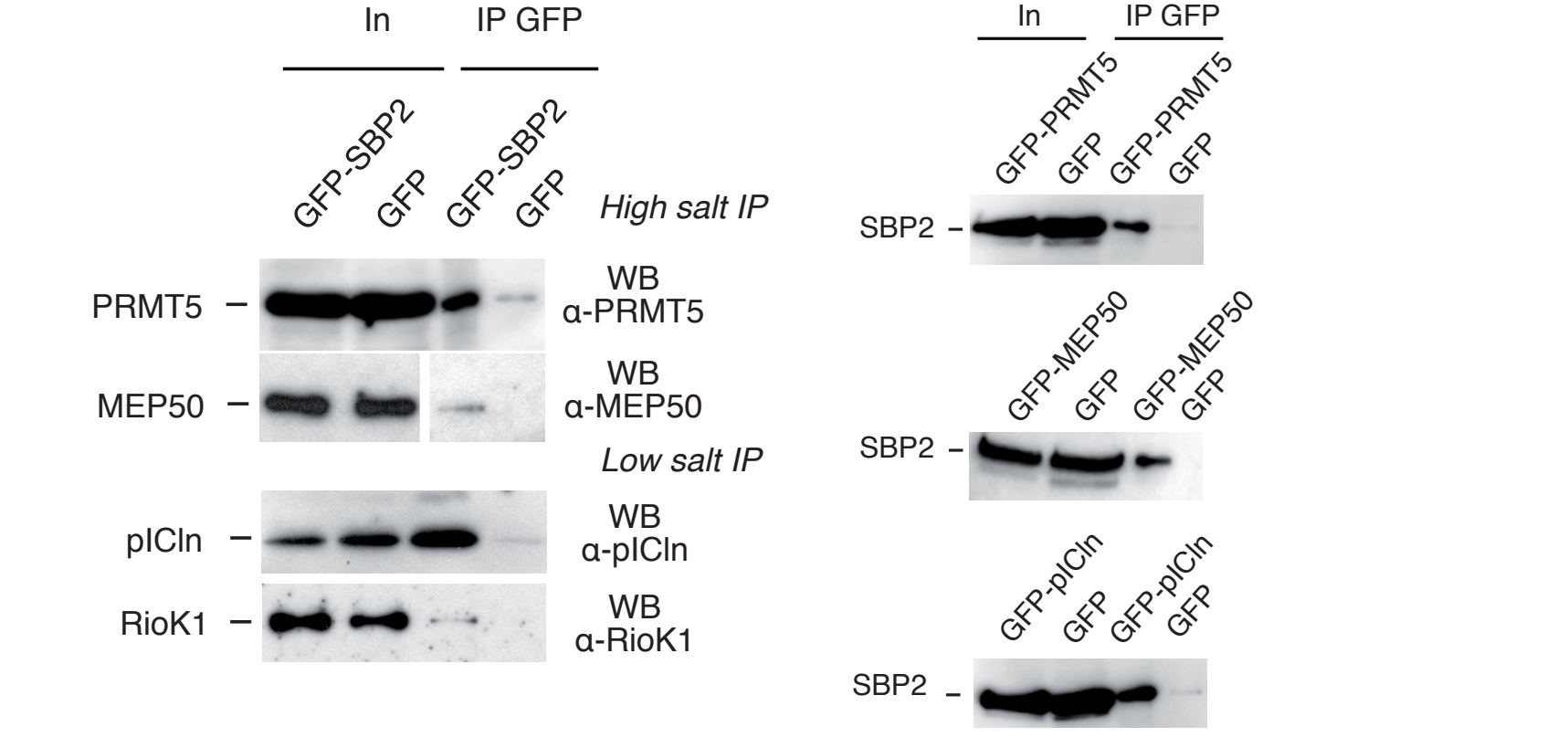
Cap hypermethylation is totally abolished after siSMN in HEK293 cells

The SMN complex interacts with SBP2



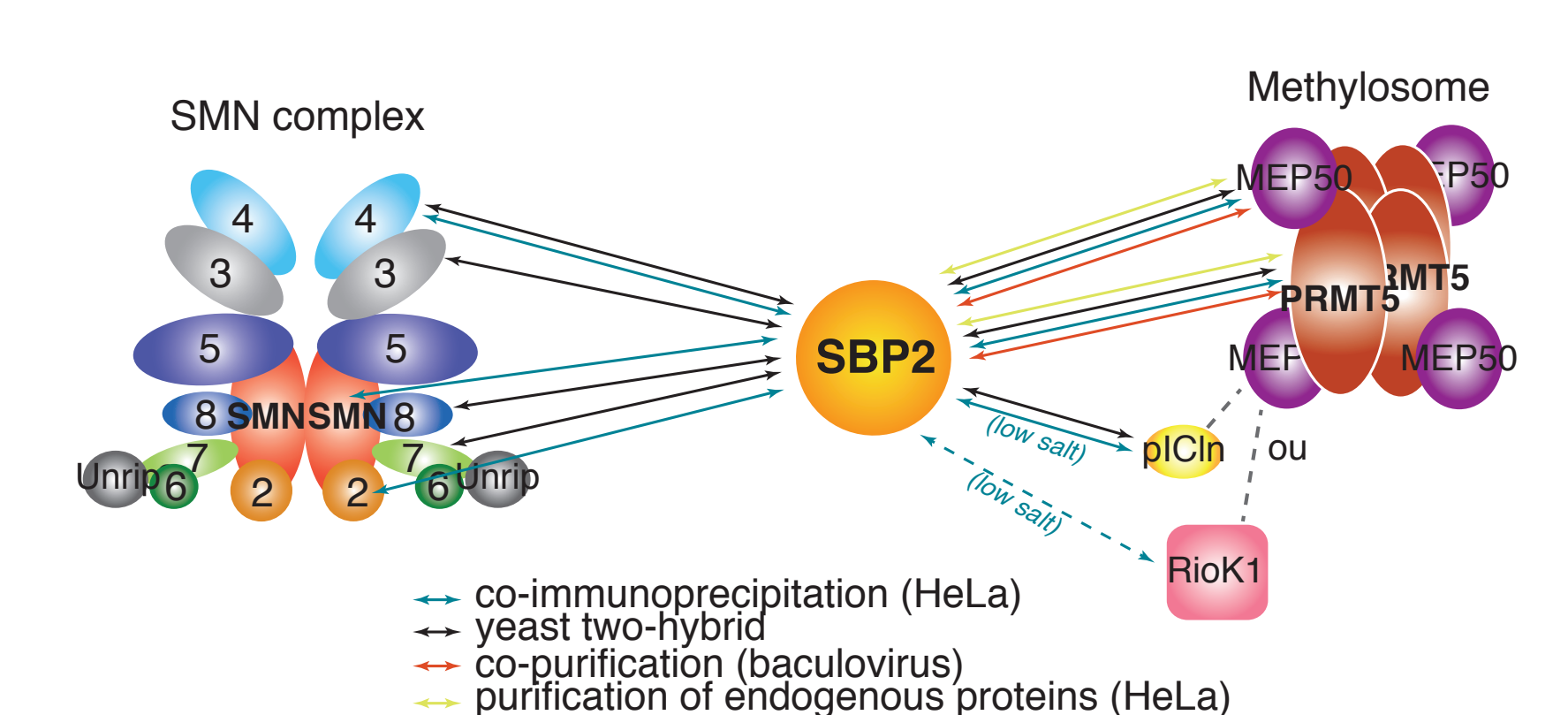
Transfections and co-immunoprecipitation in HEK293 cells

Components of the methylosome interact with SBP2



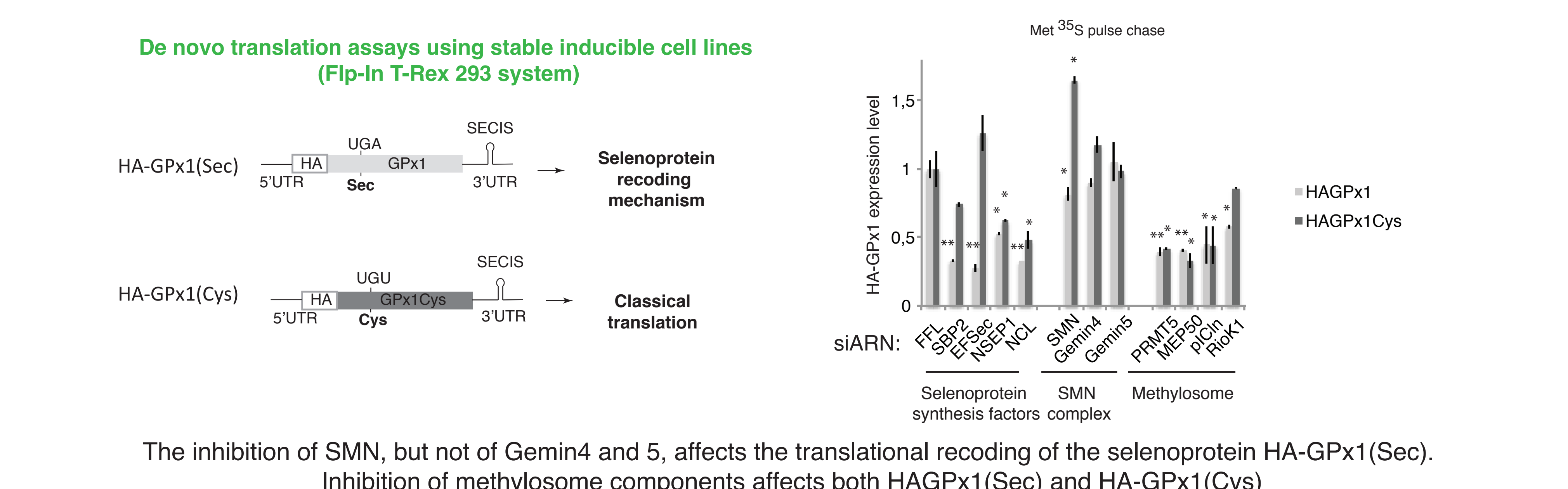
Transfections and co-immunoprecipitation in HEK293 cells

Interaction network between SBP2 and the components of the SMN and methylosome complex

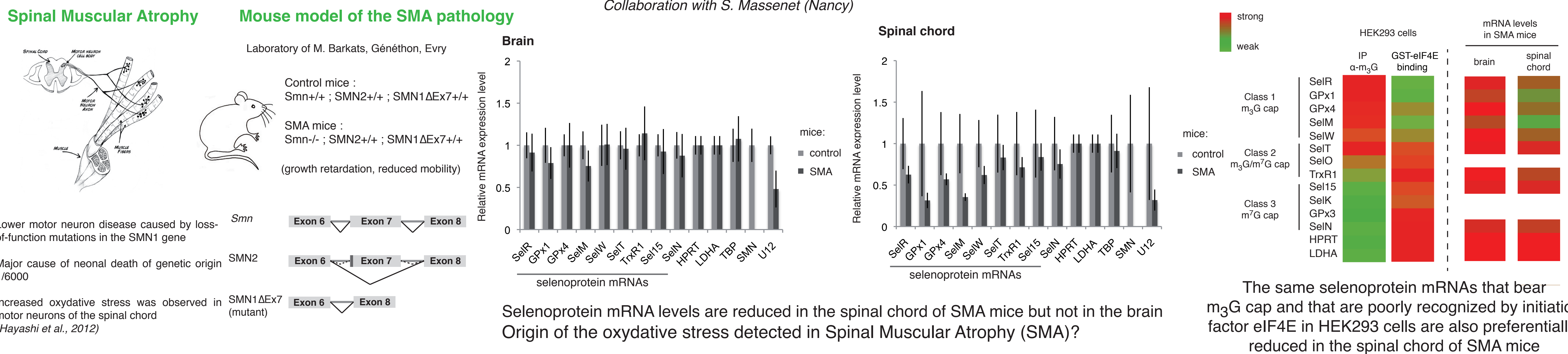


co-immunoprecipitation (HeLa)
yeast two-hybrid
co-purification (baculovirus)
purification of endogenous proteins (HeLa)

Inhibition of SMN and of methylosome components has a functional impact on HA-Gpx1 selenoprotein synthesis *in vivo*



Functional role of SMN in selenoprotein synthesis. The Spinal Muscular Atrophy (SMA) pathology leads to reduced levels of selenoprotein mRNAs in the spinal cord



Summary

