



**HAL**  
open science

## Atypical translation mechanism of selenoprotein mRNPs

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

### ► To cite this version:

Anne-Sophie Gribling-Burrer, Laurence Wurth, Michael Leichter, Séverine Massenet, Franck Martin, et al.. Atypical translation mechanism of selenoprotein mRNPs. Colloque SifrARN 2016, Mar 2016, Toulouse, France. hal-03550134

**HAL Id: hal-03550134**

**<https://hal.science/hal-03550134>**

Submitted on 3 Feb 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



# Atypical translation and maturation mechanism of selenoprotein mRNPs



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

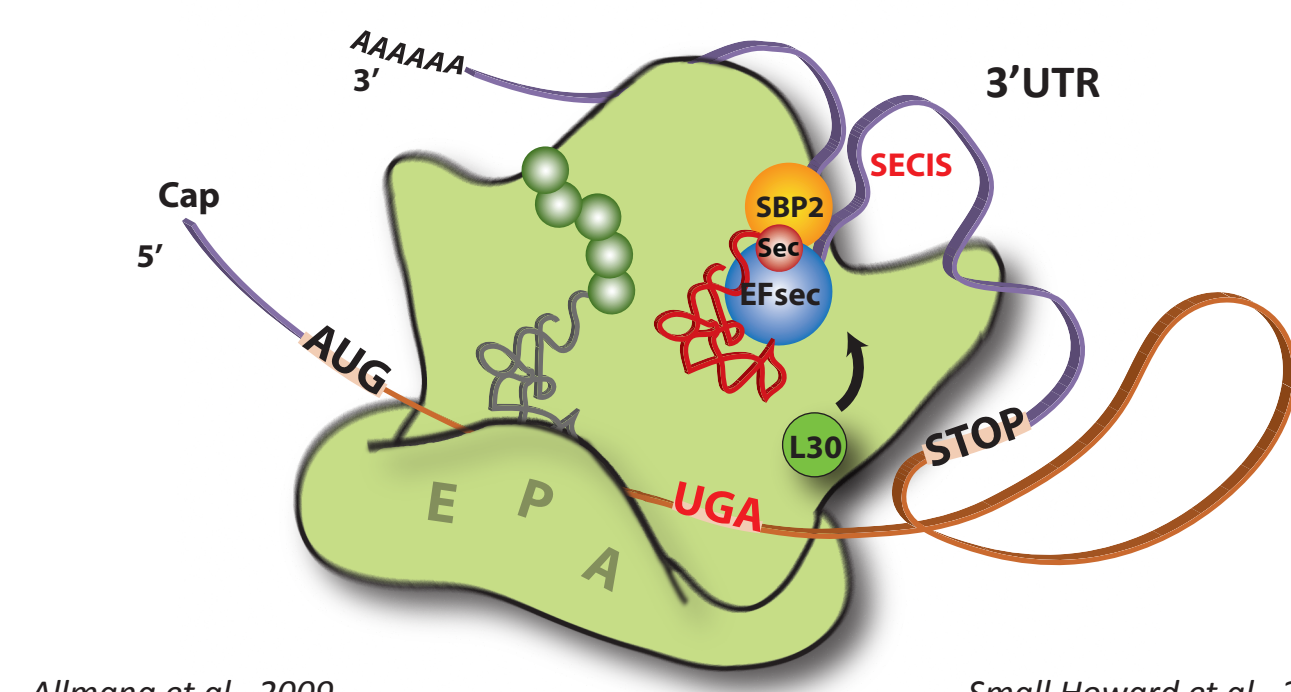
University of Strasbourg, CNRS, Architecture and Reactivity of RNA, Strasbourg, France ;

\*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

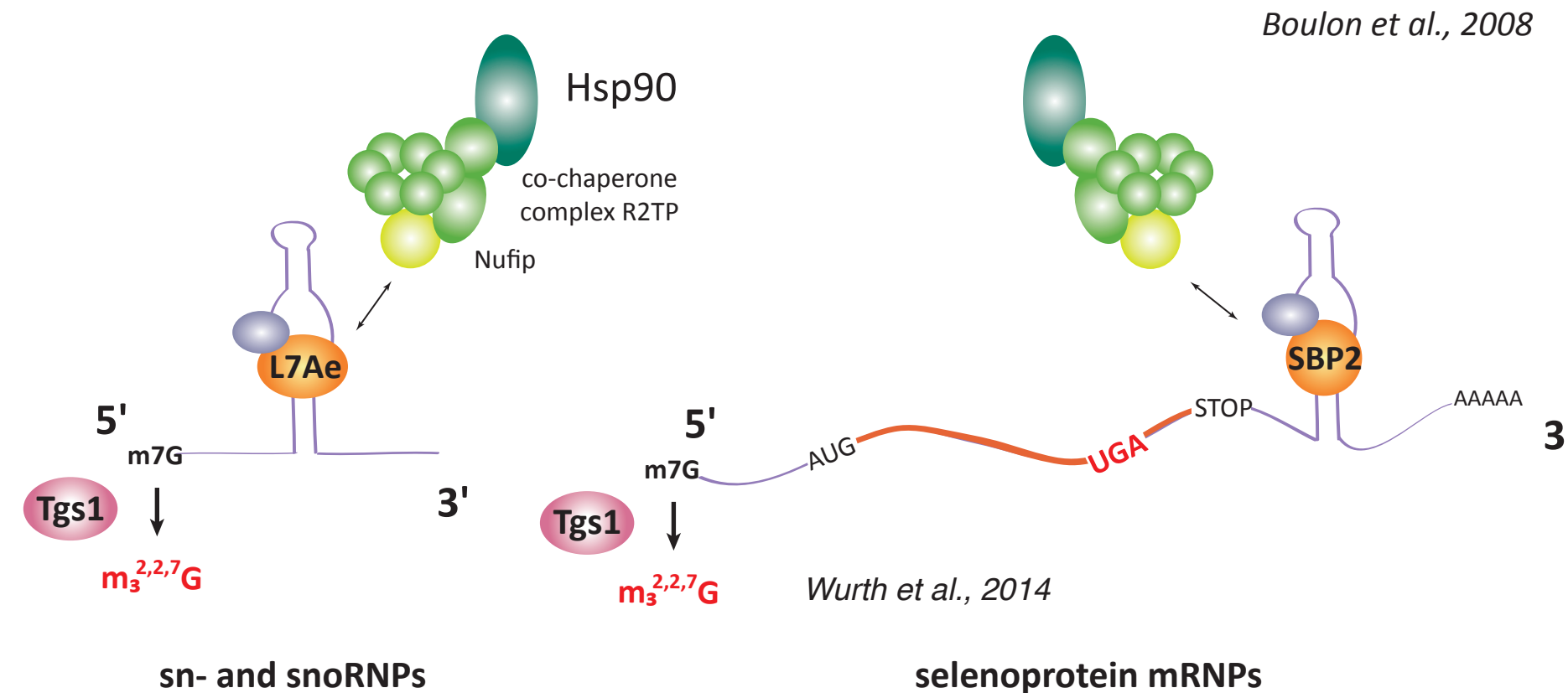


Allmang et al., 2009  
Chavatte et al., 2005

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

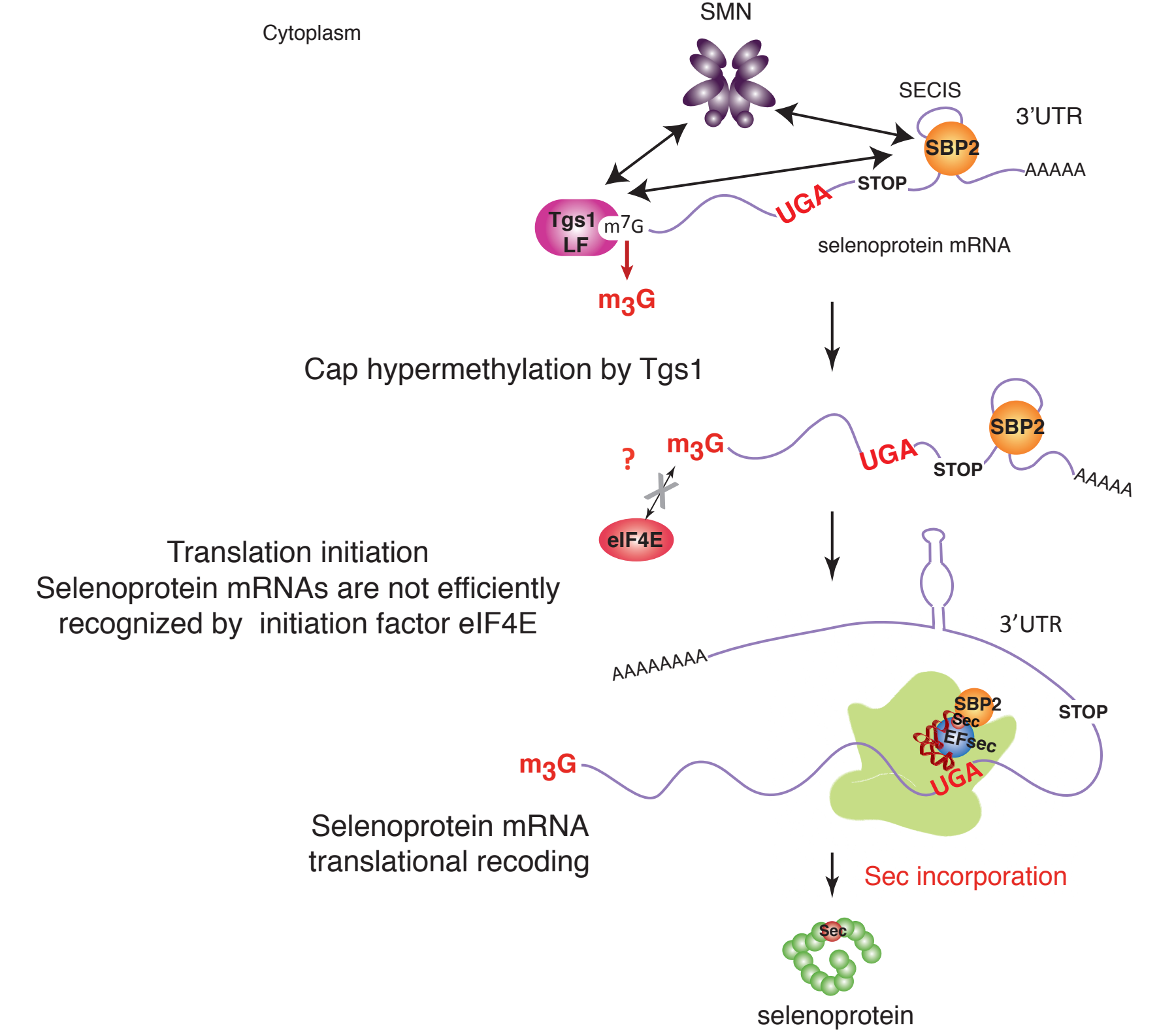


Wurth et al., 2014

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).

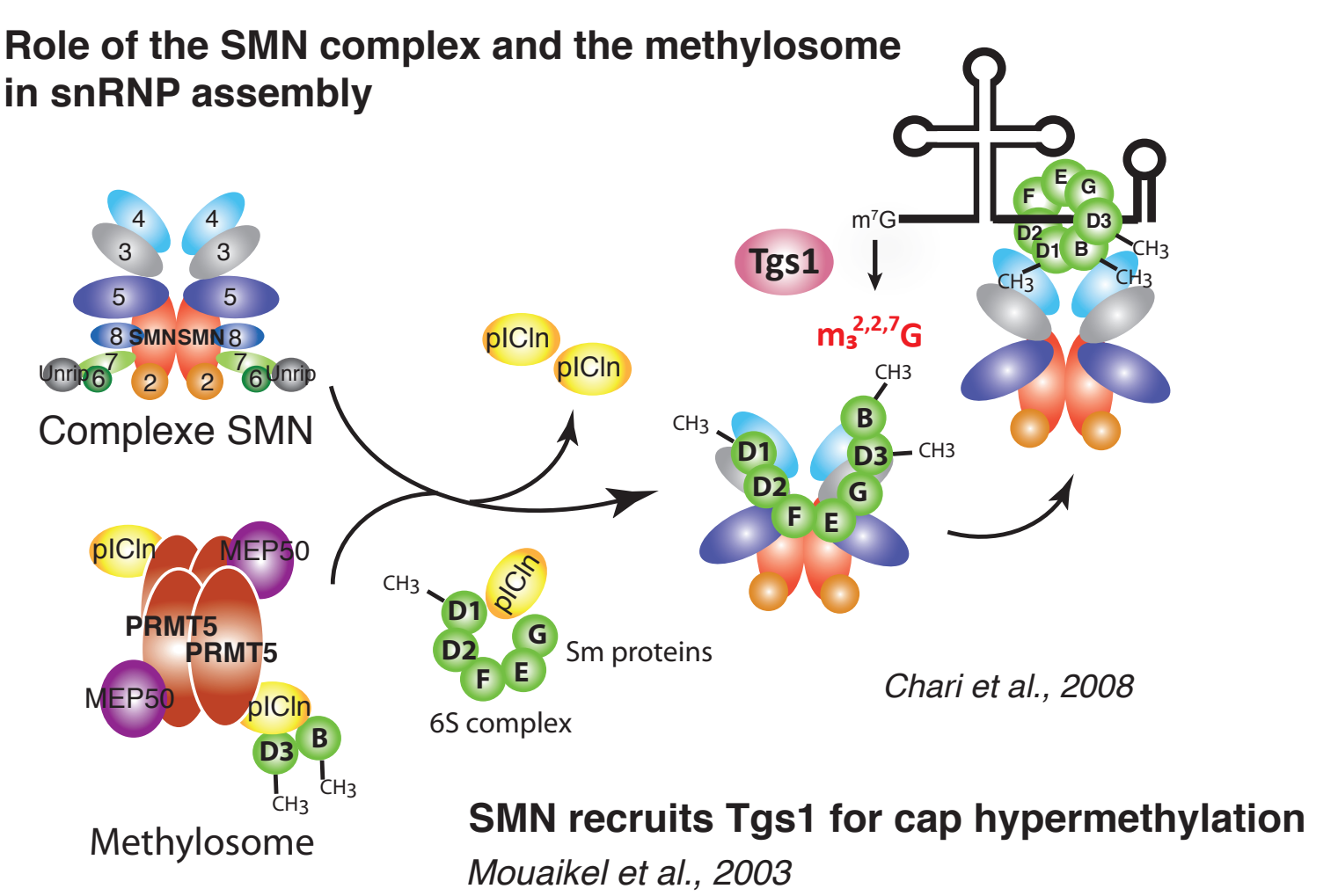
We have demonstrated that several selenoprotein mRNAs, unlike most mammalian mRNAs, bear a hypermethylated m3,2,7G cap instead of a classical 7-methylguanosine (m7G) cap and undergo a similar 5' end maturation pathway than non-coding RNAs (Wurth et al. 2014). The trimethylguanosinesynthase 1 (Tgs1) hypermethylates 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



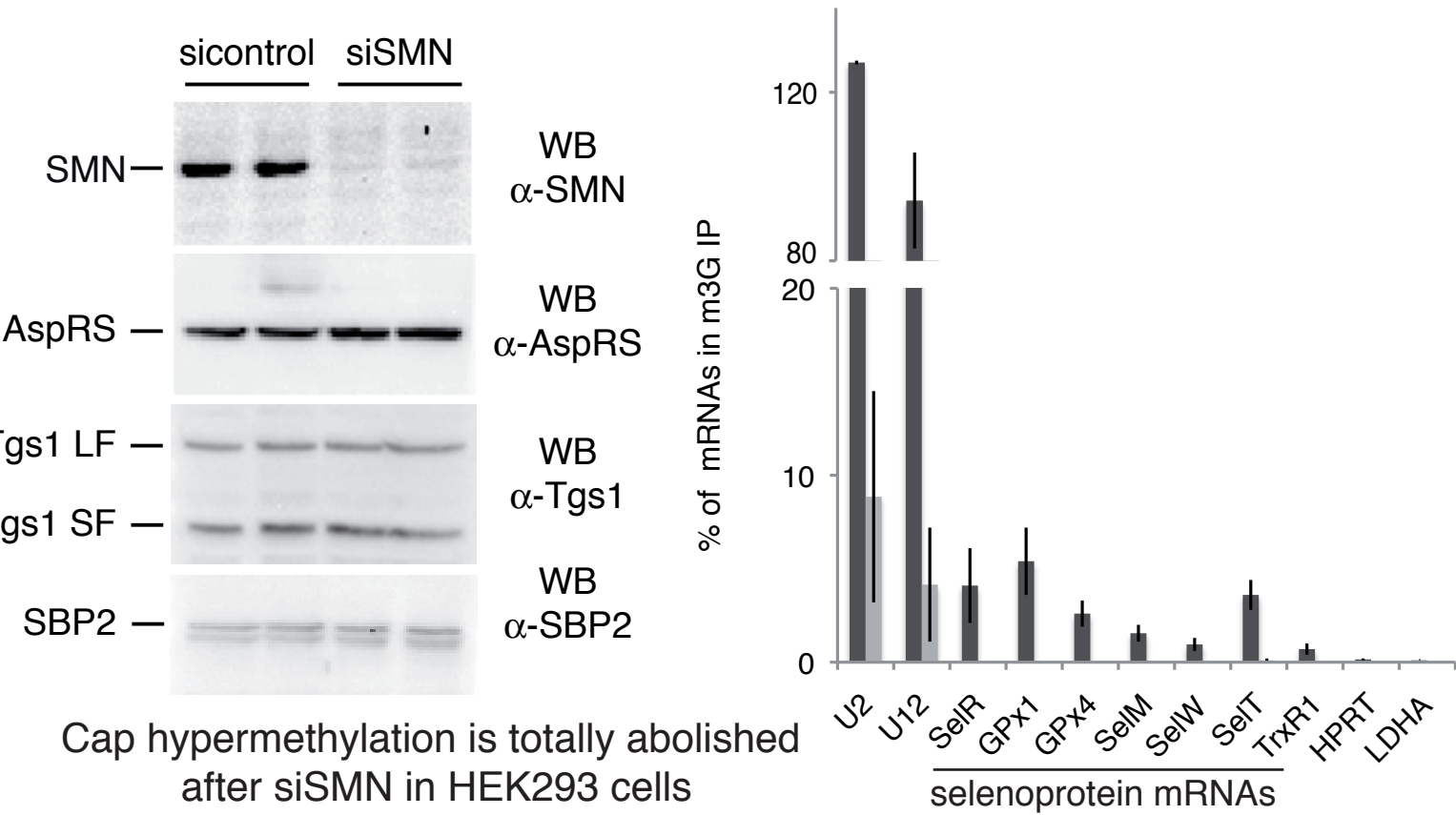
Wurth L (1), Gribling-Burrer A.S (1), Verheggen C, Leichter M, Takeuchi A, Baudrey S, Martin F, Krol A, Bertrand E and Allmang C. Nucleic Acids Res. 2014, 42, 8663-8677. (1) Contributed equally.

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



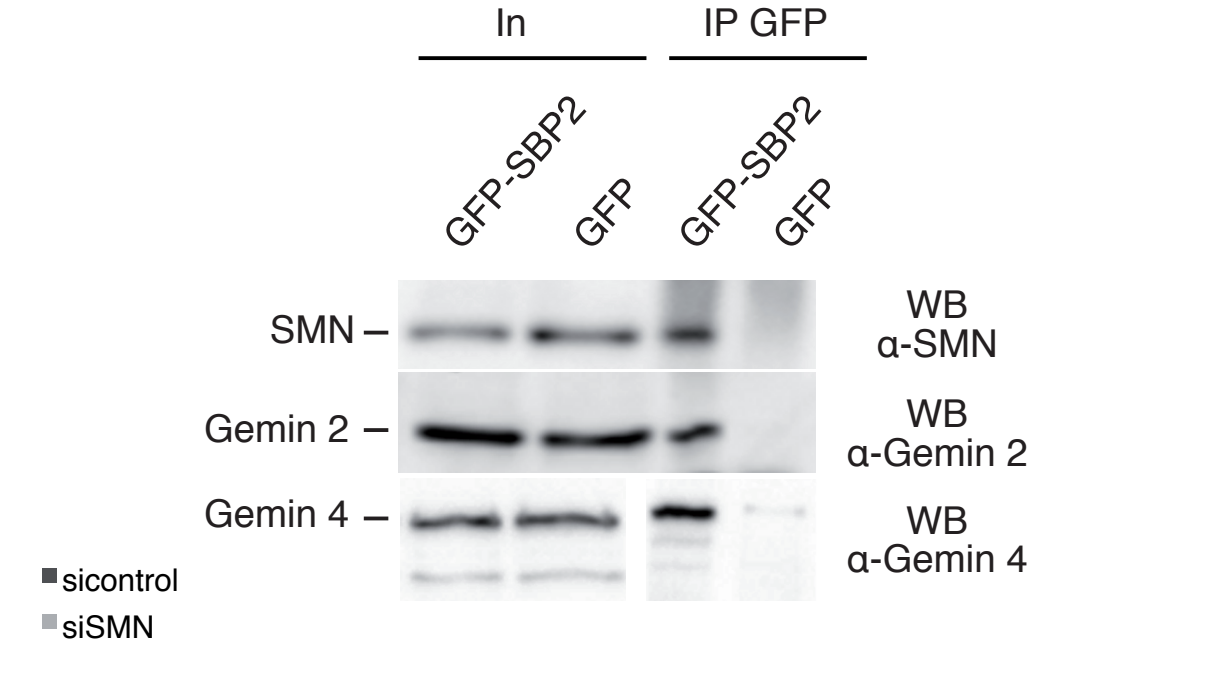
SMN recruits Tgs1 for cap hypermethylation  
Mouaikel et al., 2003

## SMN is required for cap hypermethylation of selenoprotein mRNAs



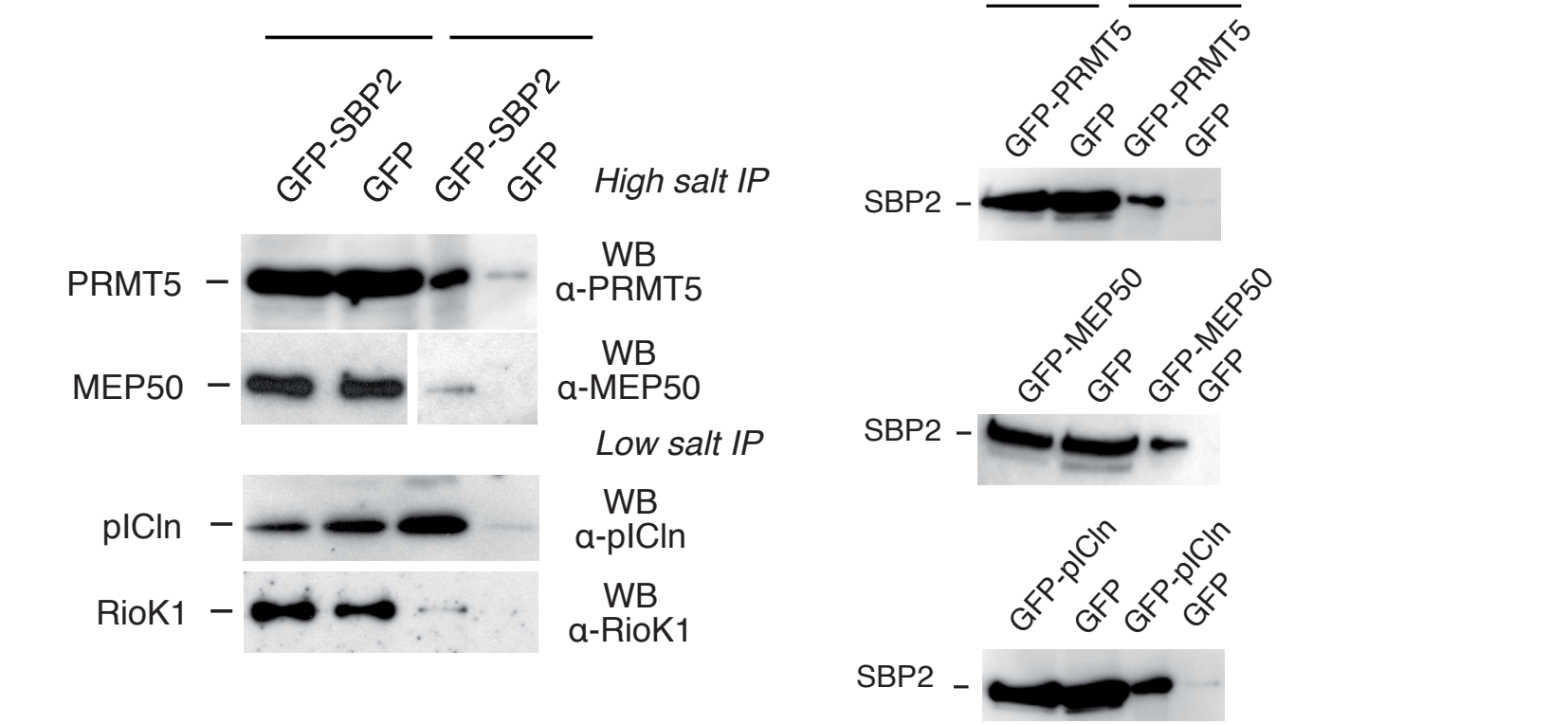
Cap hypermethylation is totally abolished after siSMN in HEK293 cells

## The SMN complex interacts with SBP2



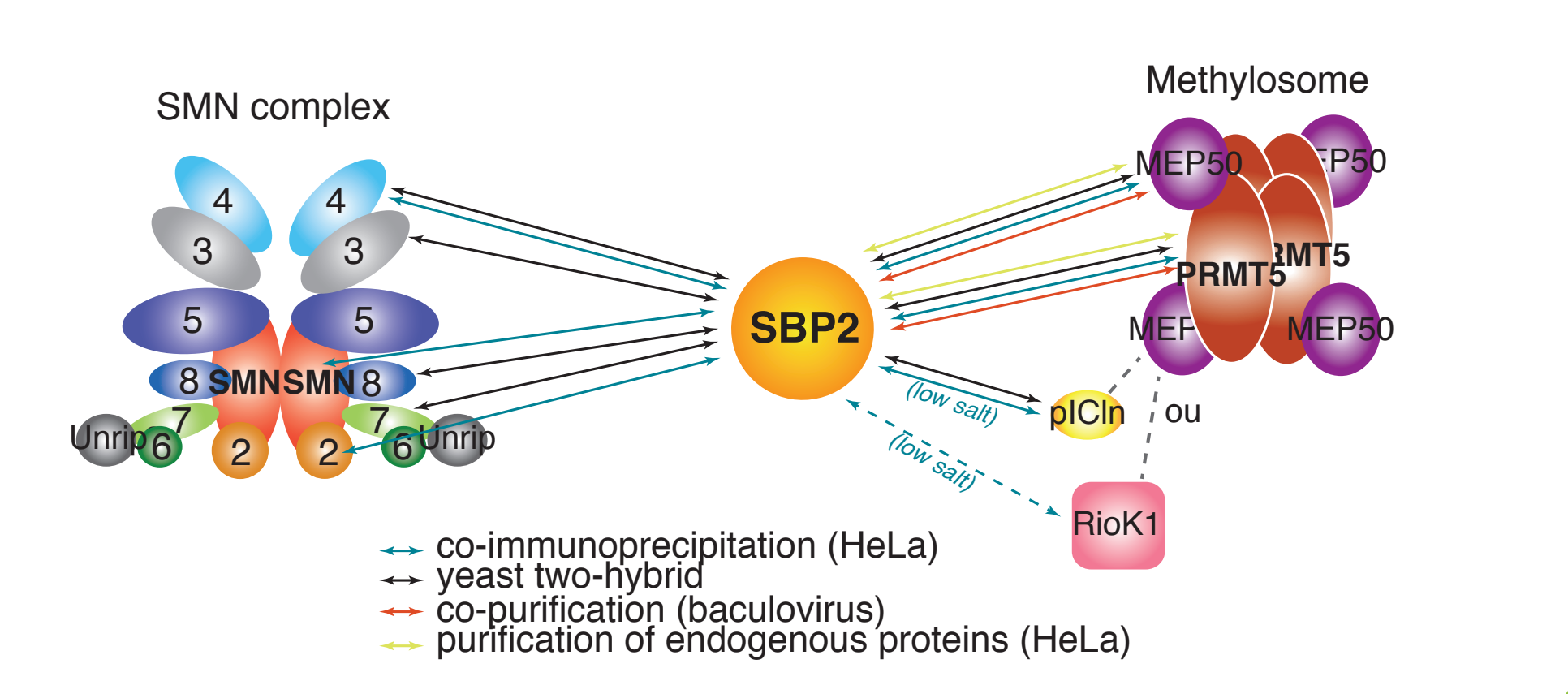
Transfections and co-immunoprecipitation in HEK293 cells

## Components of the methylosome interact with SBP2



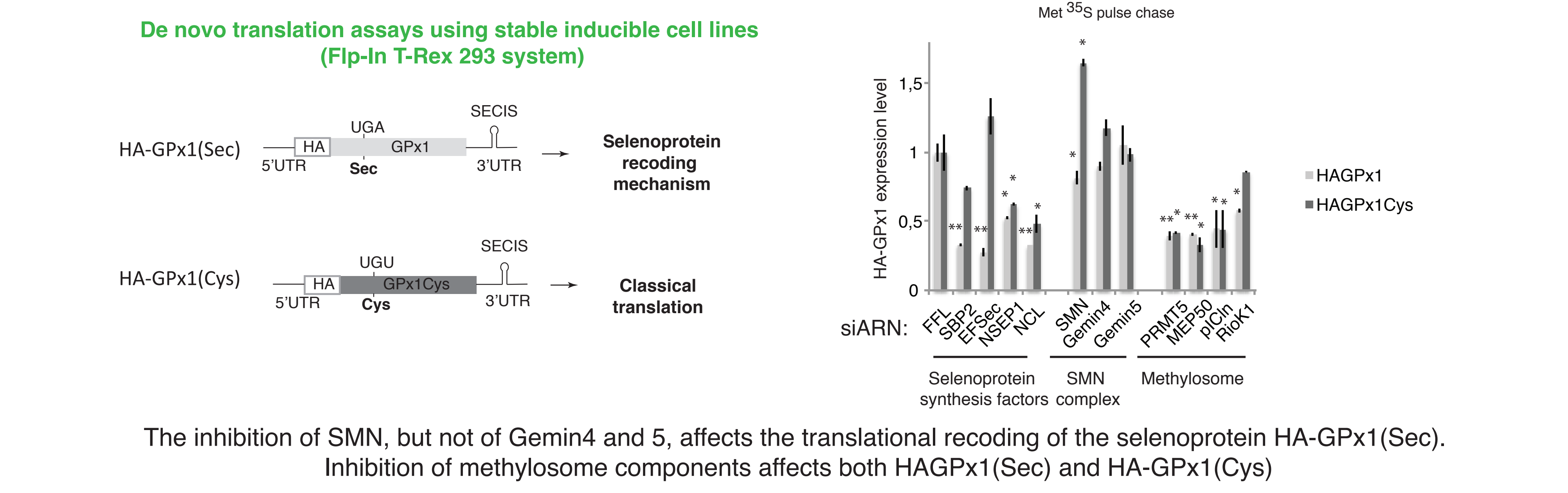
Transfections and co-immunoprecipitation in HEK293 cells

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



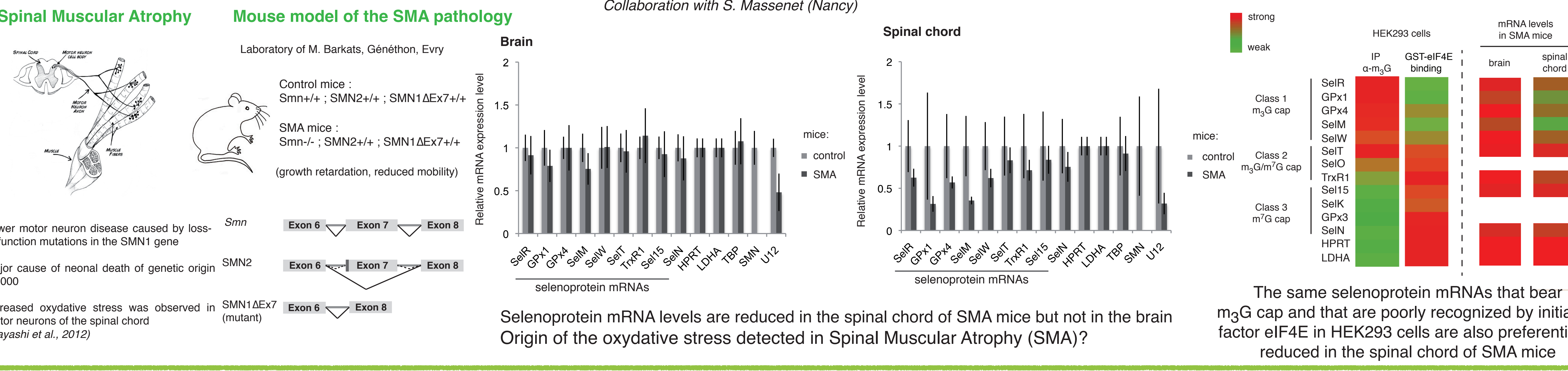
co-immunoprecipitation (HeLa)  
yeast two-hybrid  
co-purification (baculovirus)  
purification of endogenous proteins (HeLa)

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



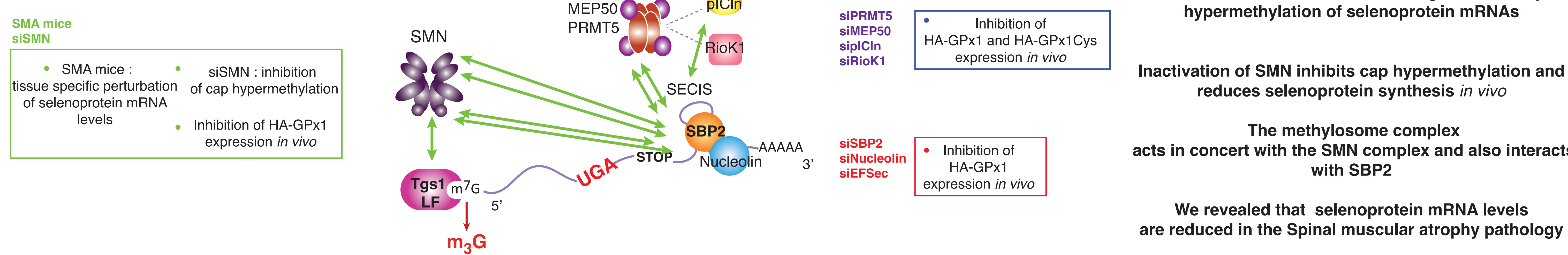
The inhibition of SMN, but not of Gemin4 and 5, affects the translational recoding of the selenoprotein HA-GPx1(Sec). Inhibition of methylosome components affects both HA-GPx1(Sec) and HA-GPx1(Cys)

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



Selenoprotein mRNA levels are reduced in the spinal cord of SMA mice but not in the brain. Origin of the oxidative stress detected in Spinal Muscular Atrophy (SMA)?

## Summary



SMA mice siSMN

- SMA mice : tissue specific perturbation of selenoprotein mRNA levels
- siSMN : inhibition of cap hypermethylation
- Inhibition of HA-GPx1 expression *in vivo*

The entire SMN complex interacts with SBP2 and contributes to the recruitment of Tgs1 for the cap hypermethylation of selenoprotein mRNAs

Inactivation of SMN inhibits cap hypermethylation and reduces selenoprotein synthesis *in vivo*

The methylosome complex acts in concert with the SMN complex and also interacts with SBP2

We revealed that selenoprotein mRNA levels are reduced in the Spinal muscular atrophy pathology