Sonenberg, N., Morgan, M.A., Merrick, W.C., and Shatkin, A.J. (1978). A polypeptide in eukaryotic initiation factors that cross-links specifically to the 5'-terminal cap in mRNA. Proc. Natl. Acad. Sci. USA 75, 4843-4847.

This is the first demonstration of a polypeptide recognizing the cap structure which can specifically stimulate cap-dependent translation of mRNAs. This work led to the identification and cloning of eIF4E, the eukaryotic mRNA cap binding protein.

Pelletier, J., and Sonenberg, N. (1988). Internal initiation of translation of eukaryotic mRNA directed by a sequence derived from poliovirus RNA. Nature. 334, 320-325.

This article documented for the first time the existence of an internal ribosome entry site (IRES) on a eukaryotic mRNA. Until this publication, it was generally accepted that ribosomes access the eukaryotic mRNA only through the 5' end. This finding led to extensive research, which resulted in showing that IRESes function in viruses (Poliovirus, HCV, etc.), and cellular mRNAs that play important roles in inflammation, apoptosis and growth control.

Edery, I., Petryshyn, R., and Sonenberg, N. (1989). Activation of double-stranded RNA dependent kinase (dsI) by the TAR region of HIV-1 mRNA: a novel translational control mechanism. Cell 56, 303-312.

This is the first example (HIV TAR) of an mRNA secondary structure that activates the double-stranded RNA activated protein kinase (PKR). Other mRNAs were subsequently found to exhibit such an activity. This finding was shown to explain many aspects of the interferon response in cells.

Lazaris-Karatzas, A., Montine K.S., and Sonenberg, N. (l990). Malignant transformation by a eukaryotic initiation factor subunit that binds to mRNA 5' cap. Nature 345, 544-547.

This is the first demonstration that eIF4E exhibits the properties of a proto-oncogene. This research led many groups to examine the status of eIF4E in human cancers, and it was found that eIF4E is over-expressed in 50% of breast, prostate and colon cancers. There is now considerable interest from biotech and pharmaceutical companies to screen for inhibitors of eIF4E as anti-cancer agents.

Koromilas, A.E., Roy, S., Barber, N.G., Katze, M.G., and Sonenberg, N. (1992). Malignant transformation by a mutant of the IFN-inducible dsRNA-dependent protein kinase. Science 257, 1685-1690.

This paper showed for the first time that the dsRNA-activated kinase (PKR) exhibits properties of a tumor suppressor gene. This paper triggered an extensive research effort that resulted in showing that PKR suppresses cell growth and contributes to tumorigenesis.

Pause, A., Belsham, G.J., Gingras, A-C., Donzé, O., Lin, T-A., Lawrence, J.C. Jr., and Sonenberg, N. (1994) Insulin-dependent stimulation of protein synthesis via phosphorylation of a novel regulator of 5'-cap function. Nature 371, 762-767.

The first demonstration of the existence of a family of eIF4E-binding proteins (4E-BPs), which repress translation and inhibit cell growth. Our group and many others showed that the 4E-BPs activity is regulated by phosphorylation, which is mediated through the PI3-kinase - AKT/PKB - FRAP/mTOR signaling pathway. 4E-BPs were also demonstrated by us to function as negative regulators of cell growth.

Craig, A.W.B., Haghighat, A., Yu, A.T.K., and Sonenberg, N. (1998) Interaction of polyadenylate-binding protein with the eIF4G homologue PAIP enhances translation. Nature 392, 520-523.

The first demonstration of a protein which interacts with PABP and controls translation. This serves as a paradigm for other proteins which bind to PABP to control translation.

Pyronnet, S., Pradayrol, L., and Sonenberg, N. (2000) A cell cycle-dependent internal ribosome entry site. Molecular Cell 5, 607-616.

The first demonstration of an IRES that functions in a cell-cycle dependent manner. This result predicts that a certain class of mRNAs is translated only at G2/M, when cap-dependent translation is inhibited. This has important implications for understanding the control of the cell cycle.

Tsukiyama-Kohara, K., Poulin, F., Kohara M., DeMaria, C.T., Cheng, A., Wu, Z., Gingras, A-C., Katsume, A., Elchelby, M., Spiegelman, B.M., Harper, M-E., Tremblay, M.L., and Sonenberg, N. (2001). Adipose tissue reduction in mice lacking the translational inhibitor 4E-BP1. Nature Med. 7, 1128-1132.

This is the first paper that describes a 'knock-out' mouse for a gene involved in ribosome recruitment to mRNA. The phenotype exhibiting adipose tissue reduction points to a direct link between metabolism and ribosome recruitment. These results could shed new light on the molecular basis of obesity.

Gingras, A-C., Raught, B., Gygi, S.P., Niedzwiecka, A., Miron, M., Burley, S.K., Polakiewicz, R.D., Wyslouch-Cieszynska, A., Aebersold, R., and Sonenberg, N. (2001) Hierarchical phosphorylation of the translation inhibitor 4E-BP1. Genes Develop. 15, 2852-2864.

This paper describes the importance of a hierarchical phosphorylation mechanism for the regulation of the downstream TOR targets, 4E-BP1.

Khaleghpour, K., Kahvejian, A., De Crescenzo, G., Roy, G., Svitkine, Y.V., Imataka, H., O'Connor-McCourt, M., and Sonenberg, N. (2001) Dual interactions of the translational repressor Paip2 with Poly(A) binding protein. Mol. Cell. Biol. 21, 5200-5213.

This article describes a novel human PABP-interacting protein (Paip2) which acts as a repressor of translation. The paper demonstrates the interplay between PABP interacting proteins to regulate translation.

Cho, P.F., Poulin, F., Cho-Park, Y.A., Cho-Park, I.B., Chicoine, J.D., Lasko, P., and Sonenberg, N. (2005) A new paradigm for translational control: inhibition via 5'-3' mRNA tethering by bicoid and the eIF4E cognate 4EHP. Cell 121, 411-423.

This paper describes a new translational control mechanism that operates to effect body polarity during *Drosophila* development.

Costa-Mattioli, M., Gobert, D., Harding, H., Herdy, B., Azzi, M., Bruno, M., Bidinosti, M., Ben Mamou, C., Marcinkiewicz, E., Yoshida, M., Imataka, H., Cuello, A.C., Seidah, N., Sossin, W., Lacaille, J-C., Ron, D., Nader, K., and Sonenberg, N. (2005) Translational control of hippocampal synaptic plasticity and memory by the eIF2α kinase GCN2. Nature 436(7054), 1166-1173.

Using a knock-out mouse strain for the eIF2α kinase GCN2 we demonstrate that translational control of the ATF4 transcriptional repressor plays a major role in learning and memory. This is the first genetic demonstration of a role of translational control in learning and memory.

Mathonnet, G., Fabian, M.R., Svitkin, Y.V., Parsyan, A., Huck, L., Murata, T., Biffo, S., Merrick, W.C., Darzynkiewicz, E., Pillai, R.S., Filipowicz, W., Duchaine, T.F., and Sonenberg, N. (2007) MicroRNA inhibition of translation initiation *in vitro* by targeting the cap-binding complex eIF4F. Science 317, 1764-1767.

We developed an *in vitro* system from mammalian cells which recapitulates the repression of mRNA by microRNAs. We showed that microRNAs inhibit cap-dependent translation initiation. This system will allow a biochemical analysis of miRNA mechanism of action.

Costa-Mattioli, M., Gobert, D., Stern, E., Gamache, K., Colina, R., Cuello, C., Sossin, W., Kaufman, R., Pelletier, J., Rosenblum, K., Krnjevic, K., Lacaille, J-C., Nader, K., and Sonenberg, N. (2007) eIF2α phosphorylation bidirectionally regulates the switch from short to long-term synaptic plasticity and memory. Cell 129(1), 195-206.

A combined genetic and pharmacological approach was used to unequivocally delineate the importance of translational control in learning and memory, directly via the regulation of eIF2α phosphorylation. Phosphorylation of eIF2α at Serine 51 thus represents a critical event in the formation of long-term memories.

Colina, R., Costa-Mattioli, M., Dowling, R.J.O., Jaramillo, M., Tai, L-H., Breitback, C.J., Martineau, Y., Larsson, O., Rong, L., Svitkin, Y.V., Makrigiannis, A.P., Bell, J.C., and Sonenberg, N. (2008) Translational control of the innate immune response through IRF-7. Nature 452(7185), 323-328.

This paper demonstrates how signaling through mTOR to 4E-BP affects interferon production and virus replication by translational control of IRF-7 mRNA.

Fabian, M.R., Mathonnet, G., Sundermeier, T., Mathys, H., Zipprich, J.T., Svitkin, Y.V., Rivas, F., Jinek, M., Wohlschlegel, J., Doudna, J.A., Chen, C-Y.A., Shyu, A-B., Yates, J.R. III, Hannon, G.J., Filipowicz, W., Duchaine, T.F., and Sonenberg N. (2009) Mammalian miRNA RISC recruits CAF1 and PABP to affect PABP-dependent deadenylation. Molecular Cell. 35(6), 868-880.

This paper describes the discovery of the mechanisms by which RNA-induced silencing complex (RISC) interact with the polyA tail to cause deadenylation.

Bidinosti, M., Ran, I., Sanchez-Carbente, M.R., Martineau, Y., Gingras, A-C., Gkogkas, C., Raught, B., Bramham, C., Sossin, W.S., Costa-Mattioli, M., DesGroseillers, L., Lacaille, J-C., and Sonenberg, N. (2010) Postnatal deamidation of 4E-BP2 in brain enhances its association with raptor and alters kinetics of excitatory synaptic transmission. Mol Cell. 37(6), 797-808.

A novel and brain-specific posttranslational modification of the translation repressor 4E-BP2 was identified. Deamidation of 4E-BP2, which occurs during early postnatal development, is a compensatory mechanism for attenuated upstream signaling in neurons and is important for synaptic function.

Dowling, R.J.O., Topisirovic, I., Alain, T., Bidinosti, M., Fonseca, B.D., Petroulakis, E., Wang, X., Larsson, O., Selvaraj, A., Liu, Y., Kozma, S.C., Thomas, G., and Sonenberg, N. (2010) mTORC1-mediated cell proliferation but not cell growth, controlled by the 4E-BPs. Science 328, 1172-1176.

This study shows for the first time that control of cell growth and proliferation by mTOR in mammalian cells function independently. 4E-BPs mediate proliferation control, whereas S6Ks mediate cell growth control.

Furic, L., Rong, L., Larsson, O., Koumakpayi, I.H., Yoshida, K., Brueschke, A., Petroulakis, E., Robichaud, N., Pollak, M., Gaboury, L.A., Pandolfi, P.P., Saad, F., and Sonenberg, N. (2010) eIF4E phosphorylation promotes tumorigenesis and is associated with prostate cancer progression. Proc Natl Acad Sci, USA 107(32), 14134-14139.

In this study we generated for the first time a "knock-in" mouse expressing non-phosphorylatable eIF4E, which we used to perform genome-wide analysis of phosphorylated eIF4E-regulated genes and studied the role of eIF4E phosphorylation in tumor formation. Our findings establish eIF4E phosphorylation as a critical event in tumorigenesis and raises the possibility that chemical compounds that prevent the phosphorylation of eIF4E could act as anticancer drugs.

Gkogkas, C.G., Khoutorsky, A., Ran, I., Rampakakis, E., Nevarko, T., Weatherill, D.B., Vasuta, C., Yee, S., Truitt, M., Dallaire, P., Major, F., Lasko, P., Ruggero, D., Nader, K., Lacaille, J.C., and Sonenberg, N. (2013) Autism-related deficits via dysregulated eIF4E-dependent translational control. Nature 493(7432), 371-377. In this study, we showed for the first time that exaggerated cap-dependent protein synthesis of neuroligins through genetic deletion of 4E-BP2 in mice induces an imbalance of excitatory to inhibitory (E/I) synaptic transmission and in turn engenders core autism-like phenotypes. Pharmacological inhibition of cap-dependent translation or lentivirus-mediated knockdown of neuroligins restore the E/I balance and reverse the autism-like behaviors. This study provides a unifying molecular mechanism to explain how exaggerated cap-dependent translation can lead to the development of Autism Spectrum Disorders.