Targeted mRNA degradation by siRNA-induced RNA interference (RNAi) allows for selective manipulation of cellular phenotypes and has great potential to treat human disease. However, due to their size (~14,000 Dalton) and charge, siRNAs have no bio-availability to enter unperturbed cells. Moreover, current delivery approaches fail to deliver siRNAs into the vast majority of cell types, especially primary cells. Here we report a siRNA delivery approach that targets 100% of cells by Peptide Transduction Domain-dsRNA Binding Domain (PTD-DRBD) fusion proteins. DRBDs bind siRNAs in a sequence-independent manner that masks the negative charge, allowing for cationic PTD-mediated siRNA delivery. PTD-DRBD delivered siRNAs induced RNAi responses in 100% of all 14 cell types tested, including fibroblasts, keratinocytes, neuronal cells, hematopoietic lineages and human embryonic stem cells (hESCs). Indeed, PTD-DRBD-siRNA mediated knockdown of the Oct4 pluripotent transcription factor induced hESC differentiation. Taken together, these observations demonstrate a universal siRNA delivery approach by PTD-DRBD fusions.