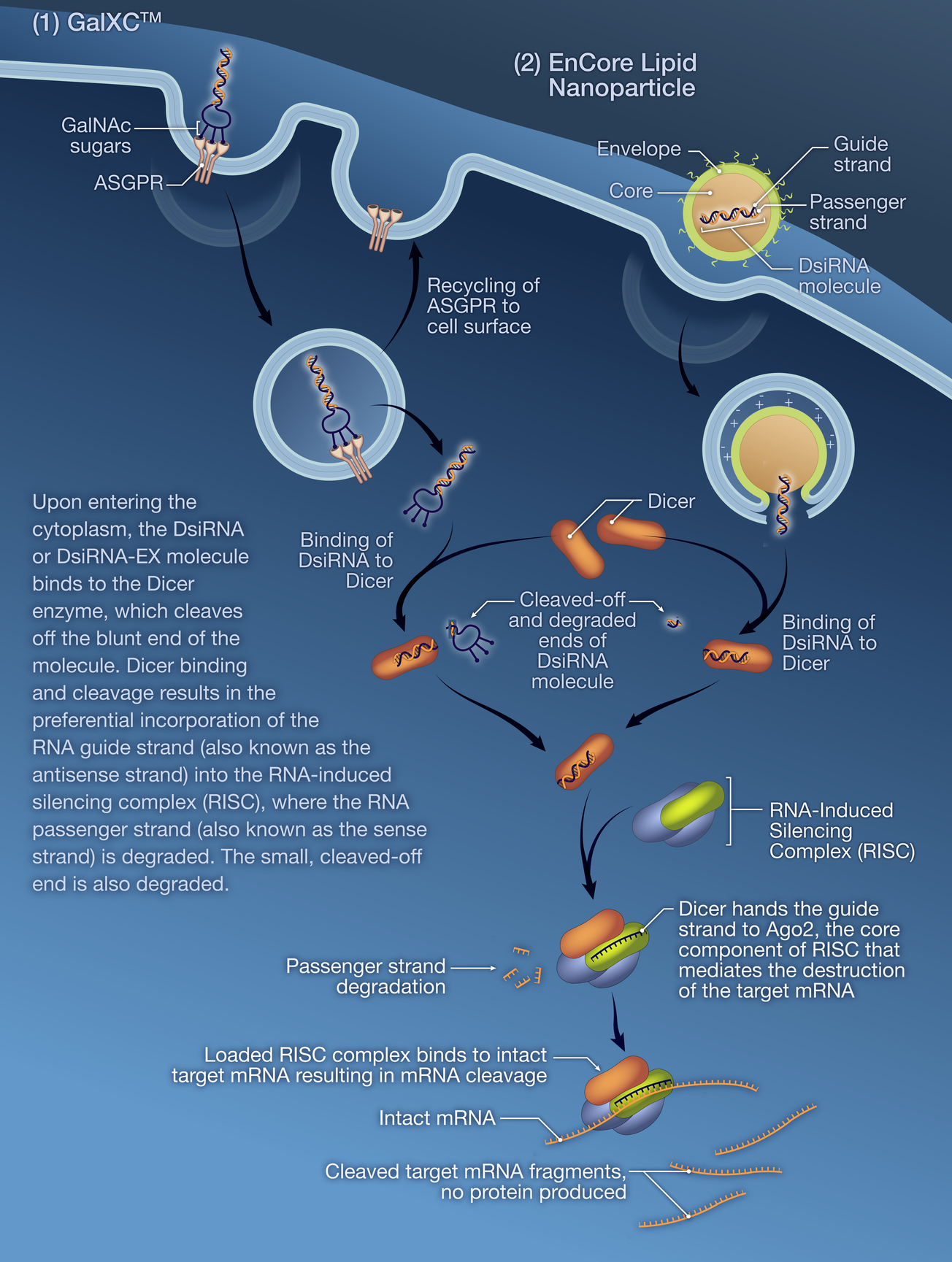
RNAi In Action

Dicerna has created two types of delivery platforms for use with our Dicer substrates.

Our subcutaneous injection delivery platform is optimized for the treatment of liver diseases and makes use of our proprietary GalXC™ technology, which allows us to attach N-acetyl galactosamine (GalNAc) sugars to our DsiRNA-EX molecules, yielding multiple effective and proprietary conjugate delivery configurations.. The GalNAc sugars mediate delivery to hepatocytes (a specific type of liver cell) via the highly expressed asialoglycoprotein receptor (ASGPR) on the surface of the cell and are internalized into the cell via endosomes. This process allows the GalXC conjugates access to the RNAi machinery within the cells. Within the endosome, the ASGPR releases the GalXC and recycles to the cell surface, enabling delivery of the GalXC into the cytoplasm of the cell (hepatocytes in the liver).

Our other delivery platform is optimized for intravenous administration for the treatment of solid tumors. EnCore™ incorporates our DsiRNATM (Dicer substrate short-interfering RNA) and DsiRNA-EX molecules within lipid nanoparticles (LNPs), which consist of a lipid-DsiRNA core surrounded by an outer envelope of additional lipids. EnCore LNPs are internalized inside the cell and fuse with the endosomal membrane through intermingling of the positively charged Encore lipids with the negatively charged endosome lipids. The LNP protects the RNAi payload by preventing its breakdown in the bloodstream. Release of the RNAi payload into the cytoplasm allows the molecule to exert its therapeutic effect.



Upon entering the cytoplasm, the DsiRNA or DsiRNA-EX molecule binds to the Dicer enzyme, which cleaves off the blunt end of the molecule. Dicer binding and cleavage results in the preferential incorporation of the RNA guide strand (also known as the antisense strand) into the RNA-induced silencing complex (RISC), where the RNA passenger strand (also known as the sense strand) is degraded. The small, cleaved-off end is also degraded.