The current paradigm of cancer treatment targets not only intracellular molecules, but also the cell membrane and external environment simultaneously, and this requires the use of versatile materials that can detect targets and function directly in each process from the transcriptional to the post-translational stage. In this regard, nucleic acid-based therapy that functions beyond mere regulation of gene expression and protein synthesis, such as antisense oligonucleotide, ribozymes, short interfering RNAs and aptamers, is emerging and represents new trials of cancer treatment with their high specificity, targeted delivery, functional and structural diversity, production at low cost, and minimizing toxicity. Trans-splicing ribozyme (Rz) has the advantage of dual therapeutic efficacy and specificity as well as transcriptional control. Rz enables to sense and reprogram target RNA into therapeutic transgene such as herpes simplex virus thymidine kinase (HSVtk) and thereby becomes a good sensing device for detection of cancer cells, judging from transgene expression. We have demonstrated that Rz might be an effective theragnostic tool in combination with noninvasive imaging method from the function of PAUF-targeting Rz in pancreatic cancer and hTERT targeting Rz in hepatocellular carcinoma. As another nucleic acid-based therapeutics, aptamers that are short-lengthed single-stranded nucleic acid (DNA or RNA) with high specificity, high affinity to targets have recently emerged as reliable and promising targeting agent. As another nucleic acid-based therapeutics, aptamers have unique interaction mode with target protein by recognizing its three-dimensional structure like as antibody, not by complementary nucleotide sequences, thereby they target secretory molecules in tumor microenvironment as well as cell surface receptors. We have showed that VEGF targeting aptamer and PAUF targeting aptamer had the neutralizing effect to target molecules, respectively. In addition, aptamer-antibody complex, designated an “Oligobody” showed that aptamers could function as an antibody delivery tool, which might overcome the therapeutic limitations of aptamers due to poor pharmacokinetics for systemic delivery. We have proved this concept from Pegatinib-antibody complex or HER2 targeting aptamer-antibody complex study. Moreover, we verified that cancer targeting aptamers could be used deliver therapeutic payloads to cancer cells to achieve tumor killing effect and further utilized as diagnostic agents by conjugation with imaging probe, based on the advantages of with high affinity and specificity against cell surface biomarker, well tissue penetration, and easy conjugation/modification. Collectively, it is sure that various nucleic acid-based drugs might be the new driving strategy for cancer theragnostics to lead the clinical use.