Cleveland Clinic Innovations

PRODUCT
Gapmer Antisense Oligonucleotide (ASO) Targeting APE2

INDICATION
Cancers that are commonly treated with cisplatin

VALUE PROPOSITION
- Protect kidney function in cisplatin treatment

DEVELOPMENT STAGE
Preclinical in vivo efficacy in cisplatin induced-AKI mouse model

INTELLECTUAL PROPERTY
US Patent Application Submitted

RELATED PUBLICATIONS
Hu Y… **Zhao J**. Cisplatin-mediated upregulation of apurinic/apyrimidinic endonuclease 2 (APE2) binding to myosin heavy-chain 9 (MYH9) provokes mitochondrial fragmentation and acute kidney injury. Cancer Research. 2021 Feb 1;81(3):713-723.

CONTACT INFORMATION
Saqib Sachani, PhD MBA
Director, Business Development and Licensing

sachans@ccf.org

IDF 2019-309

Antisense oligo to treat Acute Kidney Injury

Jianjun Zhao MD, PhD, Jianhong Lin MD, PhD

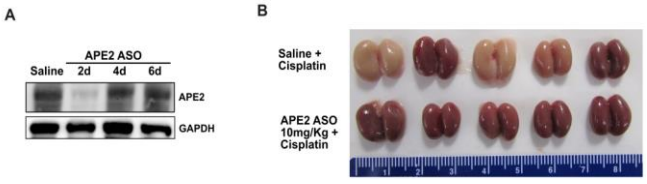
UNMET NEED
Cisplatin is a cornerstone in the treatment of various cancers, such as testicular, ovarian, bladder, and lung cancers. However, its clinical use is significantly hampered by nephrotoxicity, which is a major dose-limiting factor. Approximately 30% of patients receiving cisplatin experience some degree of acute kidney injury (AKI). This renal damage not only affects patient outcomes but also restricts the ability to administer optimal doses of cisplatin, thereby compromising its efficacy in cancer treatment.

SOLUTION
Researchers at Cleveland Clinic have developed a targeted therapeutic strategy to mitigate cisplatin-induced nephrotoxicity by addressing the underlying mechanism of injury. Cisplatin leads to the overexpression of APE2 (Apurinic/Apyrimidinic Endonuclease 2), which interacts with MYH9. This interaction triggers mitochondrial fission and activates cell-death pathways, ultimately resulting in kidney injury. The solution involves the delivery of APE2 gapmer antisense oligonucleotides (ASOs) specifically to proximal tubule cells, which are primarily affected by cisplatin toxicity. By selectively suppressing APE2 expression, this approach aims to decrease the nephrotoxic effects associated with cisplatin treatment.

ASO Composition: The ASOs consist of a gapmer DNA structure flanked by 2' O-methyl (2'OMe) modified nucleotides, designed to enhance stability and binding affinity to the target mRNA.

Safety Profile: Systemic delivery methods for 2'OMeASO drugs have demonstrated a favorable safety profile in kidney gene therapy applications, suggesting that they can be effectively used without significant adverse effects.

Mechanism of Action: By targeting the key etiological molecule, APE2, this therapeutic strategy aims to inhibit the side effects of cisplatin while preserving its pharmacological benefits. This dual action not only enhances the safety of cisplatin treatment but may also improve overall cancer treatment outcomes by allowing for higher or more frequent dosing without the associated renal complications.



APE2 ASO treatment protects against cisplatin-induced acute kidney injury in mice. Male C57B6 mice were subjected to cisplatin-induced acute kidney injury (AKI) and treated with a single IV injection of APE2 ASO at a dose of 10mg/kg. **(A)** APE2 expression level was assessed by western blot analysis at different time points. APE2 ASO effectively knocked down APE2 expression within 24 hours, which returned to normal levels by day 4 post-injection. **(B)** Macroscopic images of the kidneys were taken 3 days after cisplatin treatment. The kidneys from the saline-treated group were visibly shrunken, while the kidneys from the APE2 ASO-treated group appeared larger and healthier.