Journal scan

Discovery of small molecule splicing modulators of survival motor neuron-2 for the treatment of spinal muscular atrophy

Spinal muscular atrophy (SMA) is a rare neuromuscular disorder caused by the deletion or mutation of the survival motor neuron-1 (SMN1) gene. A second closely related gene survival motor neuron-2 (SMN2) in humans codes for a less stable SMN protein. In this article, the authors have targeted RNA biology for the discovery of LMI070/branaplam, a small molecule stabilising the interaction between the spliceosome and SMN2 pre-mRNA. Optimisation of the hit molecule for its potency, bioavailability, and safety led to the discovery of Branaplam (1), a pyridazine SMN2 pre-mRNA splicing modulator. This was tested in a severe mouse SMA model and was found to increase the full-length SMN RNA and protein levels. This, in turn, leads to extended survival. Currently, Branaplam is used in clinical studies for SMA.

COMMENT

SMA is a leading cause of death among infants and toddlers due to the loss of function of SMN1 and SMN2. Truncated and unstable SMN2 protein is synthesised with the exclusion of exon7 from the mature RNA transcript due to a single-nucleotide mutation in exon7. Cheung *et al.* in 2018 using NSC34 cell line expressing SMN2 minigene and mice model proposed an efficacious small molecule (Branaplam) against SMA targeting RNA which has advanced to human clinical trials. The study opens avenues to develop novel therapeutic agents in the field of phenotypic drug discovery for various diseases by targeting RNA.

Cheung AK, Hurley B, Kerrigan R, Shu L, Chin D, Shen Y, *et al.* Discovery of small molecule splicing modulators of survival motor neuron-2 (SMN2) for the treatment of spinal muscular atrophy (SMA). J Med Chem 2018;61:11021-36.

Cationic silver nanoclusters as potent antimicrobials against multidrug-resistant bacteria

Long-term subtherapeutic clinical treatment of infectious diseases often leads to bacterial multidrug resistance (MDR). In this article, the authors have utilised the nanoscale engineering of metal nanoparticles technique to selectively kill MDR pathogenic bacteria. This works on the antimicrobial activity of silver with the selective toxicity of branched polyethylenimine-functionalised silver nanoclusters (bPEI − Ag NCs). In this study, the minimum inhibitory concentration of bPEI − Ag NCs was determined against 12 uropathogenic MDR strains and was studied against PEI and AgNO3 alone. Using cell viability and haemolysis assays, the biocompatibility of bPEI − Ag NCs with human fibroblasts and red blood cells was assessed and was found to have selective toxicity against MDR bacteria.

COMMENT

Huma *et al.* in 2018 selected 12 uropathogenic and 2 nonpathogenic multidrug-resistant strains for antimicrobial development studies. In general, ATPases or enzymes involved in peptidoglycan synthesis can be targeted to design antimicrobials towards superbugs. In this study, the authors targeted bacteria through membrane disruption. The authors synthesized blue fluorescent cationic silver nanoparticle clusters coated with bPEI which was characterized using optical measurements and electron microscopic techniques. These nanoclusters disrupted membrane of the superbug and exhibited minimal haemolysis against RBC, host cells and thus showing them to be useful as potential antimicrobial agents for uropathogenic MDR. The silver nanoclusters may be used as broad-spectrum antimicrobials in the future.

Huma ZE, Gupta A, Javed I, Das R, Hussain SZ, Mumtaz S, *et al.* Cationic silver nanoclusters as potent antimicrobials against multidrug-resistant bacteria. ACS Omega 2018;3:16721-7.

Salivary and gut microbiomes play a significant role in *in vitro* oral bioaccessibility, biotransformation and intestinal absorption of arsenic from food

Inorganic arsenic is toxic to humans even at very low concentrations. The gut microbiome has been shown to play an important role in maintaining the intestinal barrier integrity and thus arsenokinetics. While earlier studies concentrated on colonic bacteria, the authors of this study concentrated on the microbial component present in the oral environment as well. The authors described a modified setup of the human simulator of the gut microbial ecosystem (SHIME). This involved four sequential gastrointestinal reactors (oral, stomach, small intestine and colon). Natural sources such as arsenic-containing rice, mussels, and nori seaweed were digested in the presence of microorganisms. Using high-performance liquid chromatography/mass spectrometry, the authors determined the *in vitro* oral bioaccessibility, bioavailability, and metabolism of arsenic species. An increase in soluble arsenic in the gastric digestion stage was observed for mussel and nori samples, with no coincidence impact observed in the small intestinal and colonic digestion stages. Following digestion with salivary microorganisms, the simulated small intestinal absorption of arsenic was found to be increased in all food matrices (1.2–2.7-fold higher). Apart from the arsenosugars found in mussels and nori, the authors did not find any significant transformation of the arsenic species. In the small intestinal digestion stage, the original oxo forms were converted to the thioxo analogues. The findings of this study throw light on the metabolism and oral bioavailability of arsenic during human digestion, including the role of oral and intestinal bacteria in the assessment of the risk of dietary arsenic.

COMMENT

Calatayud *et al.* 2018 in their study examined the levels of toxic inorganic arsenic and other forms in different food sources, their bioaccessibility and intestinal absorption in human SHIME. In this study, they found following four major arsenosugars: Oxoas-sugar-glycerol, oxoAs-sugar-phosphoryl glycerol, thioxoAs-sugar-glycerol, and thioxoAs-sugar-phosphoryl glycerol; their biotransformation levels in three different food sources, three different regions of the body in the presence and absence of oral microbiota. Salivary bacteria increase the apparent permeable coefficient and cellular uptake of arsenic from digested food matrices in the small intestine. Authors evaluated the metabolic potential of the microbiome and their influence as determinants of oral arsenic bioaccessibility and intestinal transport. The work is useful to assess the toxic effects of arsenic and the model proposed has direct implications for toxicity studies and risk assessment.

Calatayud M, Xiong C, Du Laing G, Raber G, Francesconi K, van de Wiele T, *et al.* Salivary and gut microbiomes play a significant role in *in vitro* oral bioaccessibility, biotransformation and intestinal absorption of arsenic from food. Environ Sci Technol 2018;52:14422-35.

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