Drugging the undruggable

- mutation-specific targeting of RAS oncogenes

Value proposition and Field of application

Our splice-switching oligonucleotides (SSOs) target the RAS oncogenes and mediate exon 2 skipping, resulting in significant reduction in cancer cell growth and proliferation. The mutation-specific SSOs preferentially target the allele with the oncogenic mutation, thus reducing side effects.

Technological description

More than 30% of all human tumors have mutations leading to constitutively active RAS proteins. RAS oncogenes have therefore long been in the searchlight of industry. So far, they have remained “undruggable”.

We have developed splice-switching oligonucleotides (SSOs) to target H-RAS, N-RAS and K-RAS directly, thereby decreasing RAS signaling. The result is decreased proliferation or growth, which we have demonstrated in several cancer cell types (bladder – T24, pancreatic – MiaPaca22, colorectal – SW620, lung – NCI-H1792, NCI-H358, NCI-H23 etc.).

Furthermore, RAS is also a relevant target in certain other diseases, eg. Costollo syndrome.

Importantly, we have developed mutation-specific SSOs that mediate exon 2 skipping preferentially from the allele with the oncogenic mutation, thus reducing side effects.

SSOs have significant advances over existing therapeutic approaches:

- SSOs target gene-specific sequences, which ensures that side-effects are minimal.
- In sharp contrast to other antisense technologies, SSOs are chemically modified to ensure superior long-term stability. They can be further modified for enhanced cellular uptake and specific cancer cell targeting.
- Contrary to RNAi, SSOs do not depend on the cellular RISC/RNase H or other cellular systems mediating mRNA degradation.

Some SSOs are already approved (e.g. SPINRAZA® and EXONDYS 51™) and there is a large range of chemically modified nucleotides available for the design of stable, bioavailable and non-toxic SSOs.

The main hurdle is delivery of the SSOs to the cancer cells.

We are looking for a partner with delivery expertise. By combining our unique expertise in targeting the RAS genes with expertise in oligonucleotide delivery, we can create a platform for generating treatment for many cancer patients that currently are left without (good) treatment options.

Current state of development

Our in vitro and in vivo data show that:

- HRAS, NRAS and KRAS are all susceptible to SSO-mediated exon skipping
- SSOs cause exon skipping in vivo
- Exon skipping is mutation specific

Our SSOs have shown effect in:

- several cancer cell types *in vitro* (for example: bladder, pancreatic, colorectal, lung)
- a mouse model of colon cancer
- a mouse model of lung cancer (preliminary data)

- Professor Brage Storstein Andresen
  - 30 years' experience in human genetics, RNA splicing and antisense technology
  - >140 scientific papers
  - 4 patent applications on SSO-mediated splicing therapy
- SDU Business developer, Liv Thomsen, PhD

Intellectual property rights

Patent family: WO2015091525A1; priority date: 16 December 2013
Patent granted in US: US10266828

Owner: SDU

Business opportunity and Call to action

We are looking for a partner with experience in delivery of antisense oligonucleotides to cancer cells.

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