# SELECTED OPPORTUNITIES IN NUCLEIC ACID-BASED THERAPEUTICS

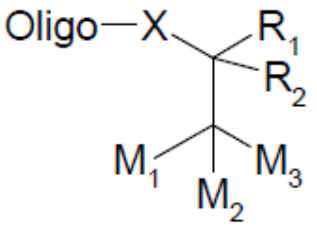
Hydrophobically modified antisense conjugates as New Chemical Entity to improve delivery and efficacy of nucleic acids (CHIM13035/ 13061)

# HYDROPHOBICALLY MODIFIED ANTISENSE CONJUGATES AS NEW CHEMICAL ENTITY TO IMPROVE DELIVERY AND EFFICACY OF NUCLEIC ACIDS - CHIM13035/13061

## Product factsheet

*POC In vivo*

- **Technology:**
  - Lipid conjugate antisense OligoNucleotides (**LON**) comprising a triple alkyl chain or a ketal group




- **Target:**
  - Any antisense oligonucleotide or any nucleic acids

- **Application:**
  - for use to improve antisens oligonucleotide delivery and efficacy (alone or in combination with a drug)
  - LONs self-assemble into micelles, which are prone to host drug molecules within their hydrophobic cores: for instance Paclitaxel

- **POC:** Lipid conjugate Antisens Oligonucleotide (**L-ASO**) are capable of inhibiting prostate cancer in vivo and have no toxicity in mice
  - The addition of a lipid chain on the 5' part of the antisense oligonucleotide enables inhibiting specifically "UD protein" protein, even in the absence of the transfection agent.
  - The specific inhibition of "UD protein" protein with LASO enabled inhibiting the growth of the PC-3 cells (Castration Resistant prostate cancer cell line).
  - Lipid modification strongly enhances the ability of ASO to reduce "UD protein" expression leading to a strong reduction of tumor progression in a murin xenograft model of Castration Resistant prostate cancer

- **Patent and publication:**
  - WO2014195754 A1 filed on 05 June 2013
  - WO2014195755 A1 filed on 05 June 2013
  - Karaki S *et al*. (2017) J Control Release, 258:1-9
  - Aimé A *et al*. (2013) Bioconjugate Chem. 24 (8), pp 1345–1355 ;
  - Patwa *et al*. (2011) Chem. Soc. Reviews, 40, 5844……

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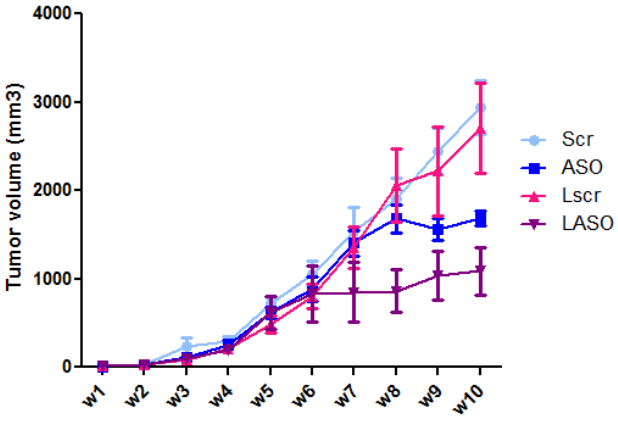
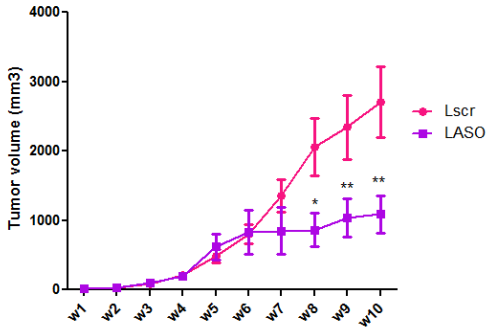
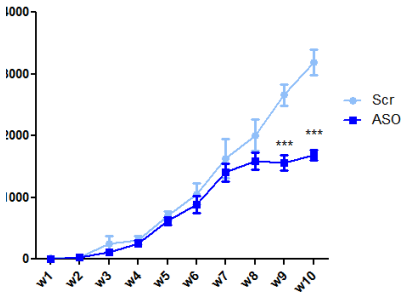
## Proof of concept

*POC In vivo*

**L-ASO directed against « undisclosed » mRNA is more efficient than ASO to inhibit prostate cancer progression, in vivo**

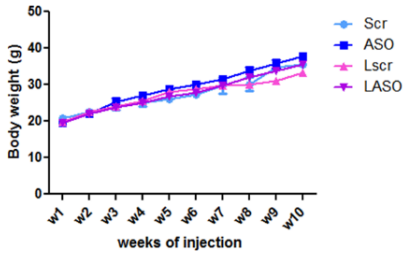



Animals: mice xenografted with PC3 (hormono- resistant) cells, 8 animals/ group
Treatment: IP injection; 10mg/kg; daily injection for 7 days, then 3 injections/ week for 9 weeks.

- **Treatment with ASOs and L-ASOs doesn't induce toxicity**




| | Scr | ASO | LScr | LASO |
|---|---|---|---|---|
| Body weight | Normal | Normal | Normal | Normal |
| Diarrhea | Neg | Neg | Neg | Neg |
| Respiration | Normal | Normal | Normal | Normal |
| Agresivity | Neg | Neg | Neg | Neg |
| Mobility | "+/-" | "+" | "+/-" | "+" |

Renal toxicity evaluation

| | Leucocytes | Nitrite | Protein | pH | Blood | Ketone | Glucose |
|---|---|---|---|---|---|---|---|
| Scr | Neg | Neg | Neg- trace | 6 | Trace 10ery/µL | Neg | Neg |
| ASO | Neg- Trace | Neg | Neg- trace | 6 | Trace 10ery/µL | Neg | Neg |
| Lscr | Neg- trace | Neg | Neg- trace | 6 | Trace 10ery/µL | Neg | Neg |
| Laso | Neg | Neg | Neg- trace | 6 | Trace 10ery/µL | Neg | Neg |



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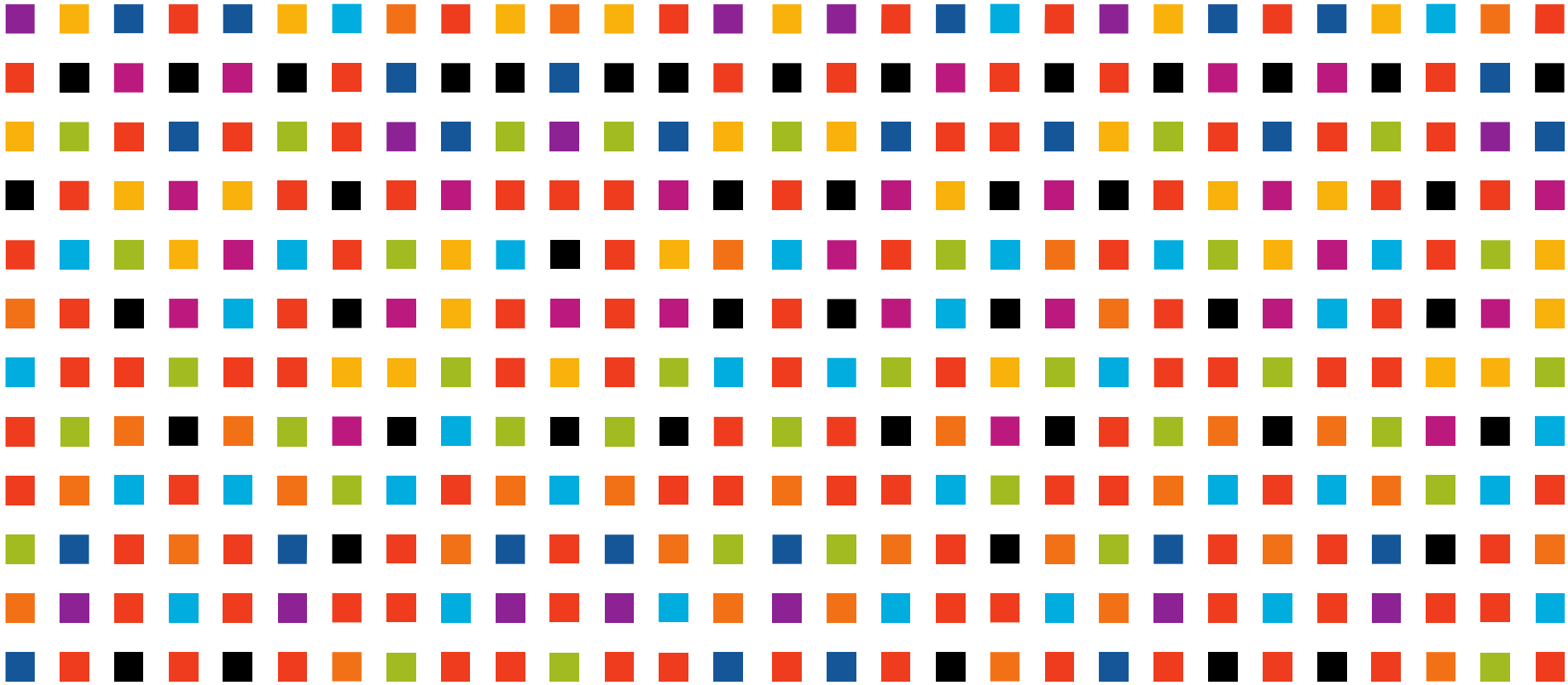

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