Targeted Delivery of microRNAs OligoNucleotide Therapeutics to Cure Metabolic Pandemics and Ovarian Cancer

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SUMMARY

Structure: AptamiR is a US modular Biotechnology Company currently executing the pre-clinical development of its OligoNucleotide Therapeutics (ONTs) drug candidates.

Mission: Develop safe, effective and convenient ONTs drugs to cure unmet medical needs:

- **Treat fat accumulation, inflammation and necrosis** to cure obesity, dyslipidemia, diabetes and MAFLD, without altering brain functions, but improving patients' quality of life
- Develop microRNAs-based ONTs **to treat Ovarian Cancer**

Strategy: Use the pleiotropic concept of One Drug-Multiple Targets by developing microRNA-based ONTs for complex diseases like obesity, MAFLD and ovarian cancer.

Accomplishments to date: Proofs of efficacy for our first generation microRNA ONTs were achieved in primary cultures of human cells and in specific animal models.

Goal for the next 24 months:

- Complete the pre-IND and IND phases for our new generation 2.5 of targeting miR-22-3p Antagomirs to **treat Metabolic Pandemics**
- Achieve the pre-clinical selection of the targeting microRNA ONT drug candidates to **cure Epithelial Ovarian Cancer**

Gap to achieve this goal: Secure Series B financing ($10M)

End Goal:

- Help patients live longer, productive and healthier lives while reducing healthcare costs
- Develop safe, effective, and convenient treatments for:
  - the metabolic pandemics Obesity, diabetes, and MAFLD
  - the deadly Epithelial ovarian cancer

TARGET PRODUCT PROFILE OF APTAMIR GENERATION 2.5 ONTS

1. Use the **pleiotropic** concept of One Drug-Multiple Targets to develop **microRNA-based ONTs** which simultaneously modulate several target genes involved in complex diseases
2. **Maintain resistance to nucleases and proteases/peptidases**
3. **Eliminate potential toxicities** by replacing Phosphorothioate and Locked Nucleic Acid modifications by a **Peptide Nucleic Acid (PNA) backbone**
4. **Avoid chirality**
5. **Limit protein binding**
6. **Conjugate the ONT** to a **fatty acid** or **peptide or folic acid** for preferential targeted delivery to adipocytes or ovarian cancer cells of a greatly reduced effective dose with an extended duration of action (**Mean Residence Time**)
7. **Subcutaneous administration of bi-annual doses of metabolic ONTs to improve patients' compliance**
8. **Intra-peritoneal administration of ovarian Cancer ONTs to treat Ovarian Cancers and their Tumor Microenvironment**

REFERENCES

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2. M. Thibonnier & C. Esau, Metabolic benefits of microRNA-22 inhibition. **Nucleic Acid Therapeutics**, 104-116, 2019
3. M. Thibonnier, C. Esau, S. Ghosh, E. Wargent & C. Stocker. Metabolic and energetic benefits of microRNA-22 inhibition. **BMJ Open Diabetes Res Care** 2020 Oct;8(1). pii: 8/1/e001478. doi: 10.1136/bmjdrc-2020-001478.
4. Thibonnier M, Ghosh S, Blanchard A. Effects of a short-term cold exposure on circulating microRNAs and metabolic parameters in healthy adult subjects. **J Cell Mol Med.** 2021;00:1–15. doi:10.1111/ jcmm.17121
5. M. Thibonnier & C. Esau. Metabolic and Energetic Benefits of microRNA-22 Inhibition. **Oligonucleotide Therapeutics Society**, October 13-16, 2019, Munich, Germany
6. M. Thibonnier. Oligonucleotide Therapeutics with a Peptide Nucleic Acid Backbone to Treat Metabolic Pandemics. **TIDES USA**, September 20-23, 2021, Boston, MA, USA
7. **USPTO Application 17/656,901 "**MICRORNA OLIGONUCLEOTIDE THERAPEUTICS FOR OVARIAN CANCER" filed on 29 March 2022

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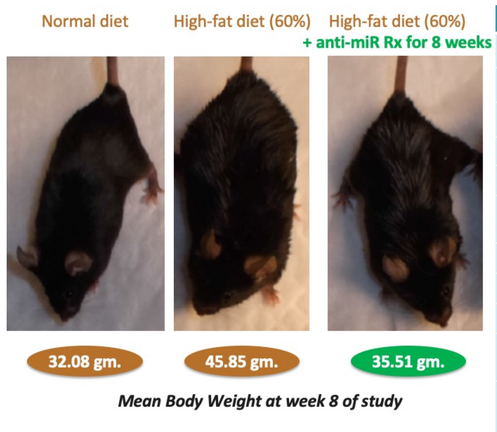
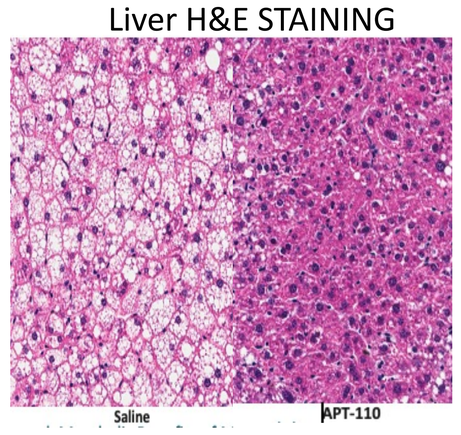
RESULTS

A. AptamiR first generation miR-22-3p antagomir APT-110 (single stranded 18-mer with PS and LNA modifications) **reduced fat mass and liver steatosis while improving metabolic parameters in obese mice:**

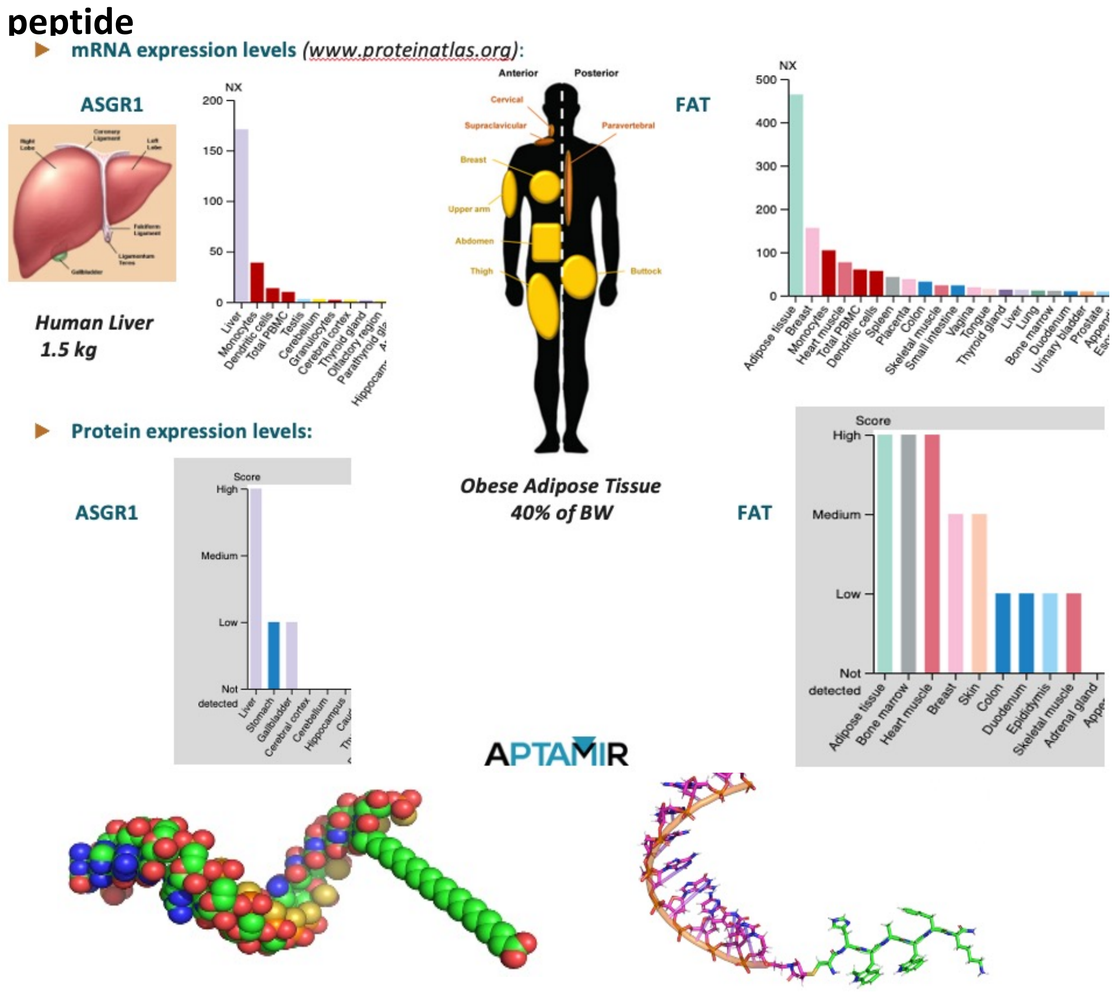


Results	
Body Weight	Reduced
Fat Mass	Reduced
Lean Mass	Unchanged
Cholesterol	Improved
Glucose	Improved
Insulin Sensitivity	Preserved
Liver Tests	Normal
Temperature	Normal
Appetite	Unchanged
Energy Expenditure	Increased
Liver Steatosis	Reduced

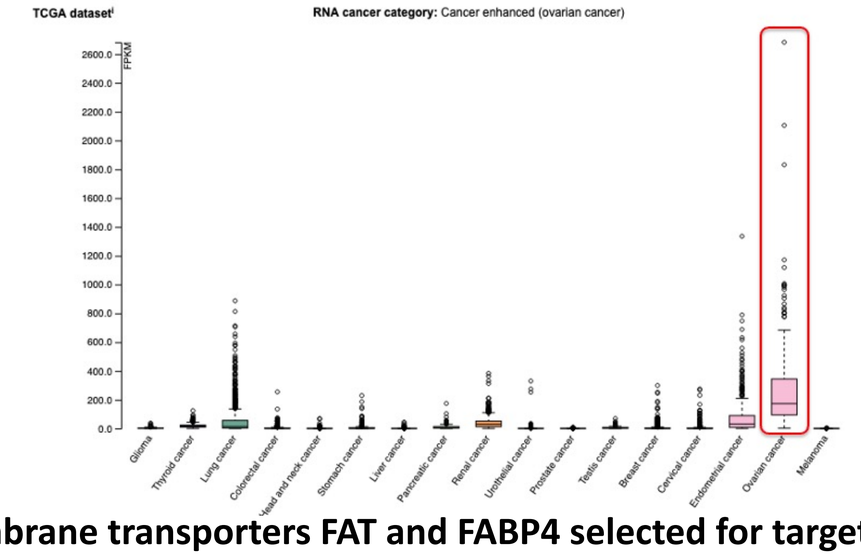


B. Targeted Delivery of AptamiR Generation 2.5 ONTs

1. Membrane Fatty Acid Translocase (FAT) transporter selected for targeted delivery to adipocytes and metabolic organs of ONTs coupled to a fatty acid or a peptide

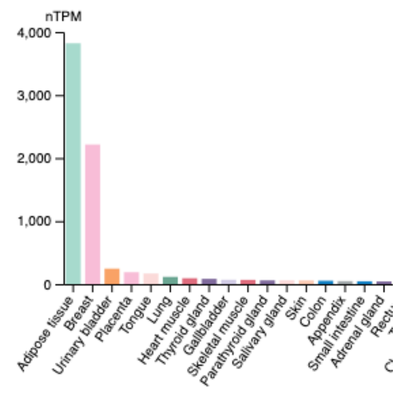


2. Membrane Folic Acid Receptor Alpha (FOLR1) selected for targeted delivery to Ovarian Cancer cells of ONTs coupled to folic acid or a peptide



3. Membrane transporters FAT and FABP4 selected for targeted delivery to the adipocyte-rich Ovarian Cancer microenvironment of ONTs coupled to a fatty acid or a peptide

FABP4 tissue specific expression



FDA EXPEDITED PROGRAMS

An effective therapy for High Grade Serous Ovarian Cancer should qualify for FDA Expedited Programs based on the following criteria: **Serious Condition**, **Available Therapies** and **Unmet Medical Need.**