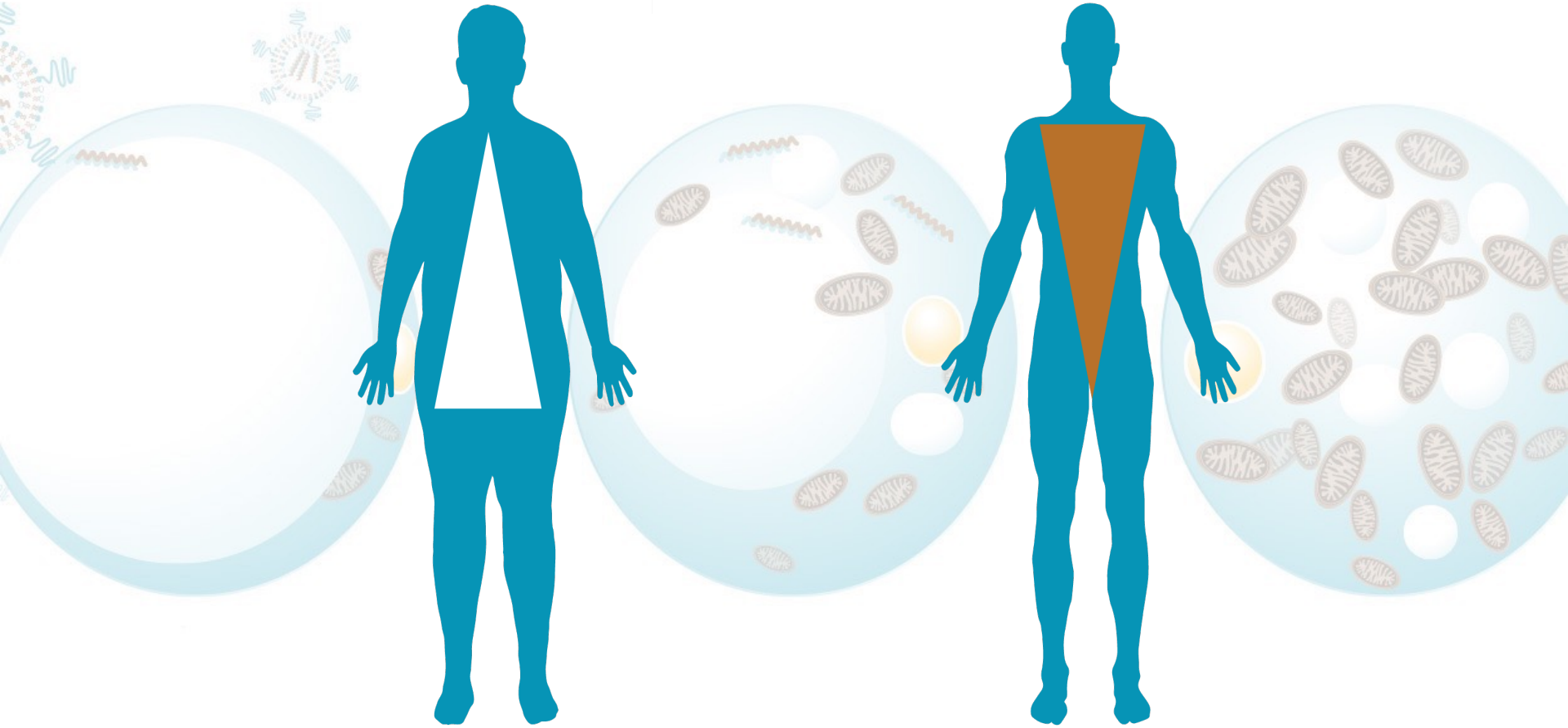
APTAMIR

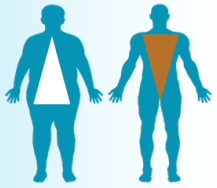


Investment Opportunity

Marc Thibonnier, M.D., M.Sc.

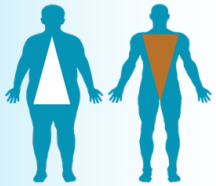
Founder & President

June 2021



AptamiR Therapeutics Summary

- **Structure:** AptamiR is a US modular Biotechnology Company currently developing pre-clinical drug candidates
- **Mission:** Treat ***fat accumulation, inflammation and necrosis*** to cure related cardiometabolic disorders (dyslipidemia, diabetes and metabolic dysfunction-associated fatty liver disease (MAFLD)), without altering brain functions, but improving patients quality of life
- **Strategy:** Transform fat-storing cells (white adipocytes) into fat-burning cells ("browning effect") to increase lipid oxidation, mitochondrial activity and energy expenditure
- **Accomplishment to date:** Proofs of efficacy for our first generation of Oligonucleotide Therapeutics (ONTs) targeting microRNAs were achieved ***in vitro*** **in primary cultures of human adipocytes** and ***in vivo*** in animal models of obesity and fatty liver disease
- **Goal for the next 24 months:** Complete the pre-IND and IND phases for our second generation of targeting miR-22-3p Antagomirs to treat the ***Metabolic Pandemics*** obesity, diabetes and fatty liver disease
- **Gap to achieve this goal:** Secure the first tranche ($5M) of Series B financing
- **Major milestone:** Initiate within 2 years the clinical studies for the lead miR-22-3p antagomir drug candidate of the second generation
- **End goal:** Help patients live longer and healthier lives while reducing healthcare costs



The Problem

- **Obesity and Metabolic Dysfunction Associated Fatty Liver Disease** (MAFLD) are growing and costly pandemics in need of safe, effective and convenient therapies

- **Obesity**
  - **Affects one third of the world population, including millions of children**
  - The economic burden of obesity on the healthcare systems is significant and growing (e.g. $190 billion or nearly 21% of annual medical spending in the United States)
  - Currently approved drugs offer limited efficacy with significant side effect profile and adverse events
  - Pharmacotherapy treatment rates of obesity are very low (<10%)
  - **Obesity worsens morbidity and mortality from COVID-19** (www.cdc.gov/obesity/data/obesity-and-covid-19.html)
  - **Adipocyte membranes are rich in the ACE2 docking protein for the SARS-CoV2 virus**
  - **The adipose tissues are a very large site of replication, refuge and shedding for that virus**

- **MAFLD**
  - **Affects 25% of the global adult population**, ranging from 14% in Africa to 32% in the Middle East
  - Prevalence of liver steatosis is 76% in obese patients
  - Lifetime costs of treatment of NASH in the United States in 2017 was $223 billion
  - Currently there is no approved drug for MAFLD in the context of multiple recent clinical failures of drug candidates

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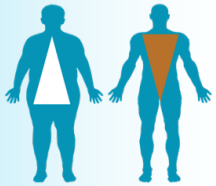


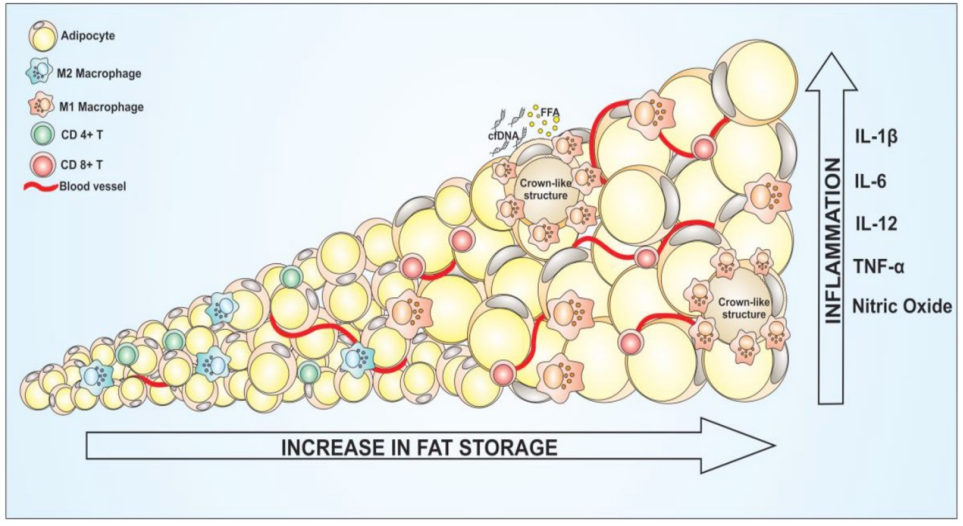
The Market

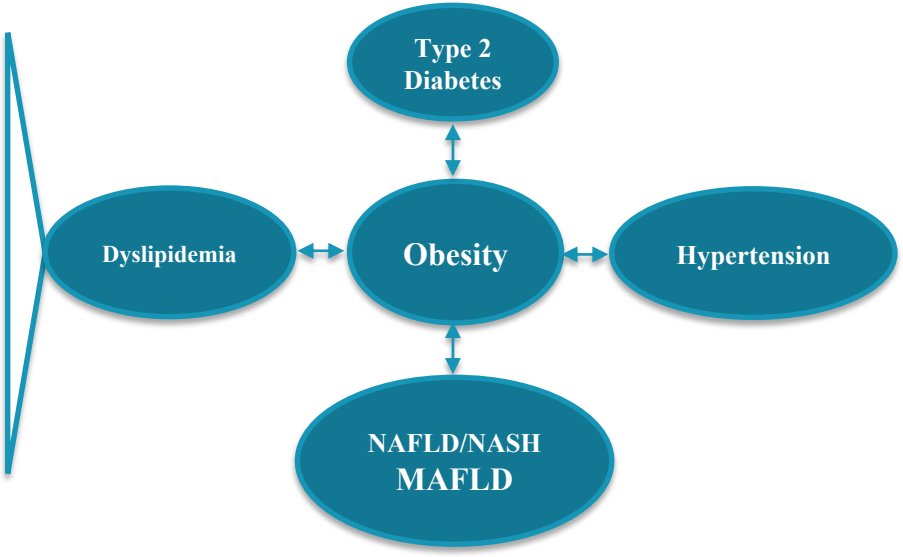
- **Obesity**
  - The US weight loss and diet control market was estimated to be **$66 Billion in 2017**
  - Annual **low productivity costs** in the US related to obesity are estimated to be **$75 Billion**
  - A safe and effective therapy to treat obesity (>10% weight loss) could reach global sales of **~$20 Billion**

- **MAFLD**
  - Significant unmet medical need for a safe and effective treatment
  - The MAFLD market is expected to reach **$21 Billion globally by 2025**

Disruptive Therapeutic Approach

Fat accumulation, inflammation and necrosis cause several cardio-metabolic disorders including lipotoxicity, dyslipidemia, insulin resistance, diabetes, liver steatosis, inflammation and fibrosis





https://www.ncbi.nlm.nih.gov/pubmed/31262098

- Obesity and associated cardio-metabolic disorders are **multifactorial** diseases that cannot be easily controlled by classical therapeutic agents (Mechanism of Action: one drug-one target or one drug-two/three targets)
- Several small molecule drug candidates have failed to reach the market for obesity or MAFLD
- AptamiR's approach uses a **pleiotropic** concept (One Drug-Multiple Targets) by developing oligonucleotide therapeutics targeting **microRNAs,** as they simultaneously modulate many target genes involved in lipid oxidation, mitochondrial activity and energy expenditure.

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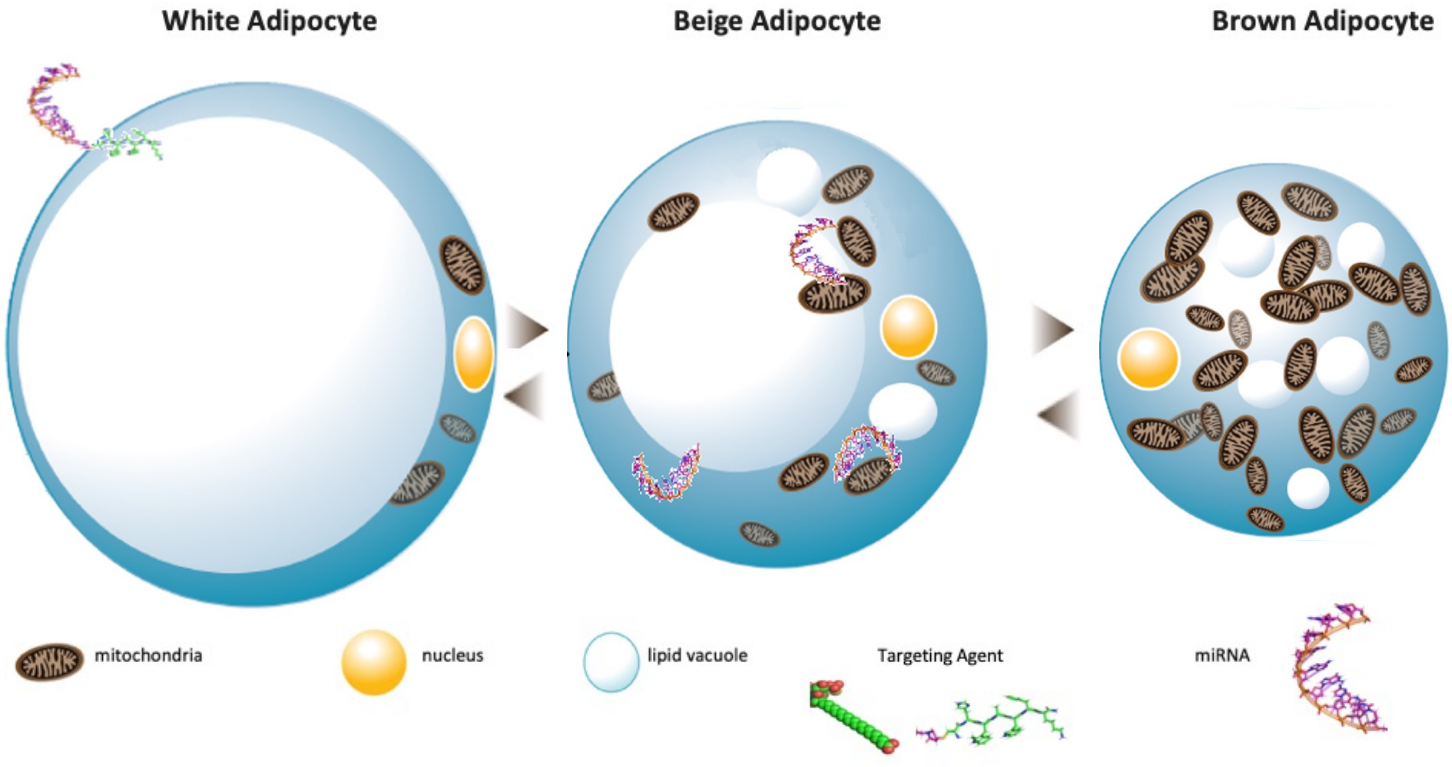
AptamiR Strategy & Technology

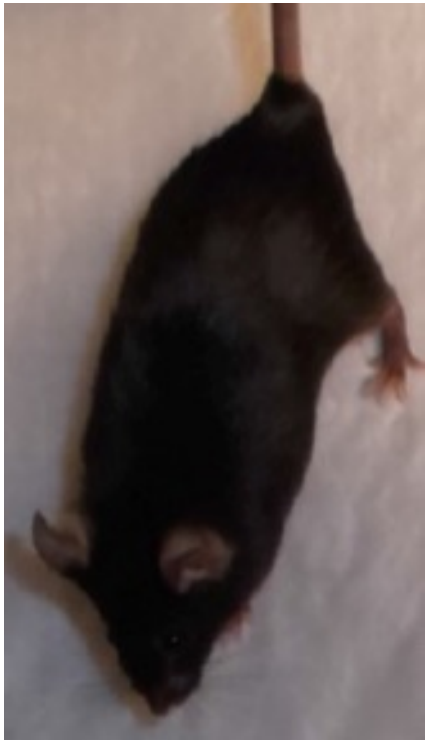
Development of microRNA-derived Drugs (Oligonucleotide Therapeutics, ONTs):

- Designed to be preferentially delivered to adipocytes and hepatocytes via the membrane Fatty Acid Translocase (FAT) transporter
- Transforming subcutaneous lipid-storing fat cells (White Adipocytes) into calories-burning fat cells (”Browning Effect”)
- Reducing fat accumulation and body weight
- Correcting lipotoxicity and dyslipidemia
- Improving insulin sensitivity and Type 2 Diabetes Mellitus
- Reversing liver steatosis, inflammation and fibrosis



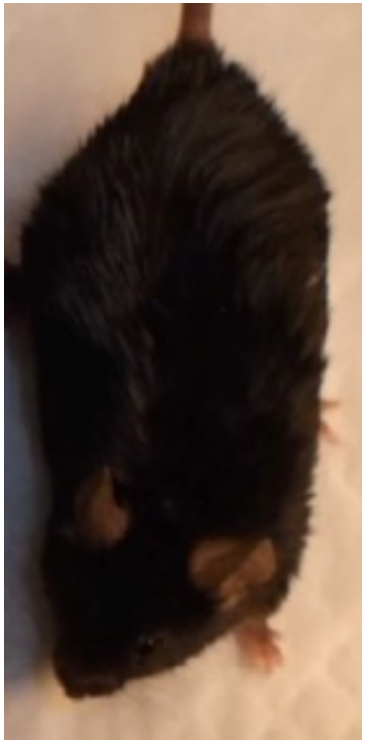
AptamiR first drug candidate reduces fat mass and improves metabolic parameters in obese mice

Normal diet



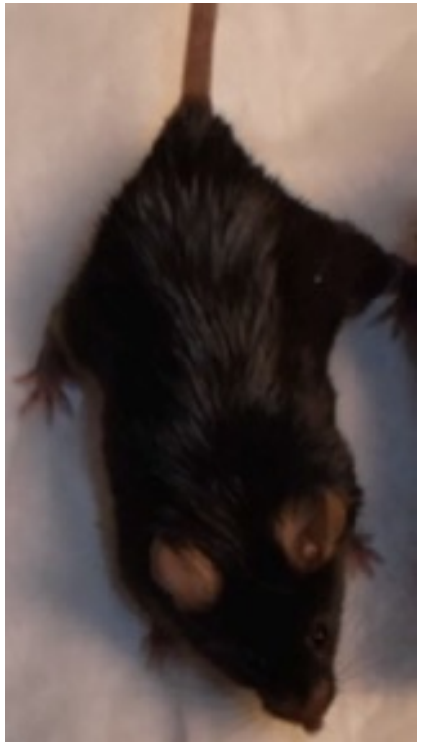
32.08 gm.

High-fat diet (60%)



45.85 gm.

High-fat diet (60%) **+ anti-miR Rx for 8 week**



35.51 gm.

Mean Body Weight at week 8 of study

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**

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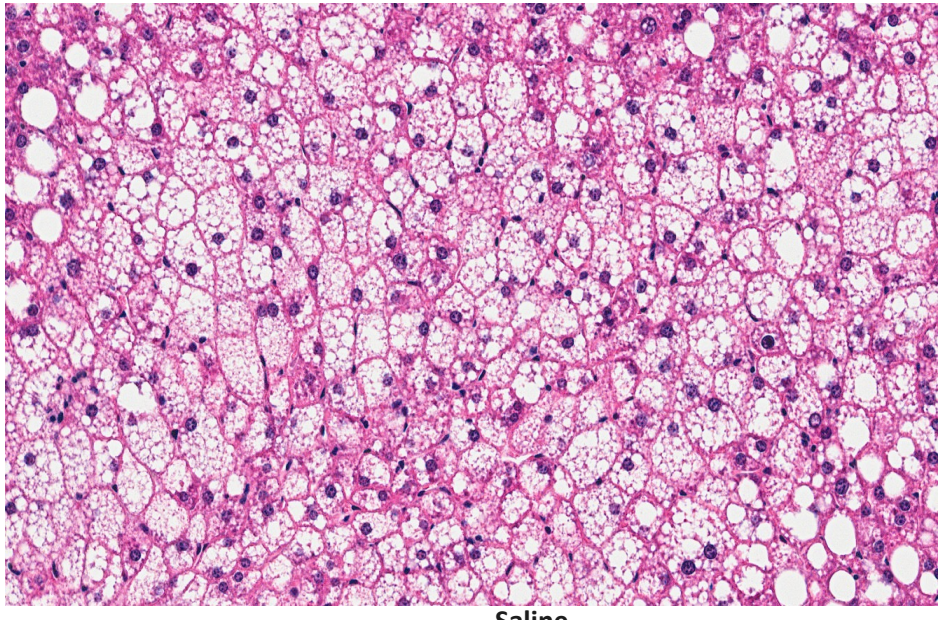
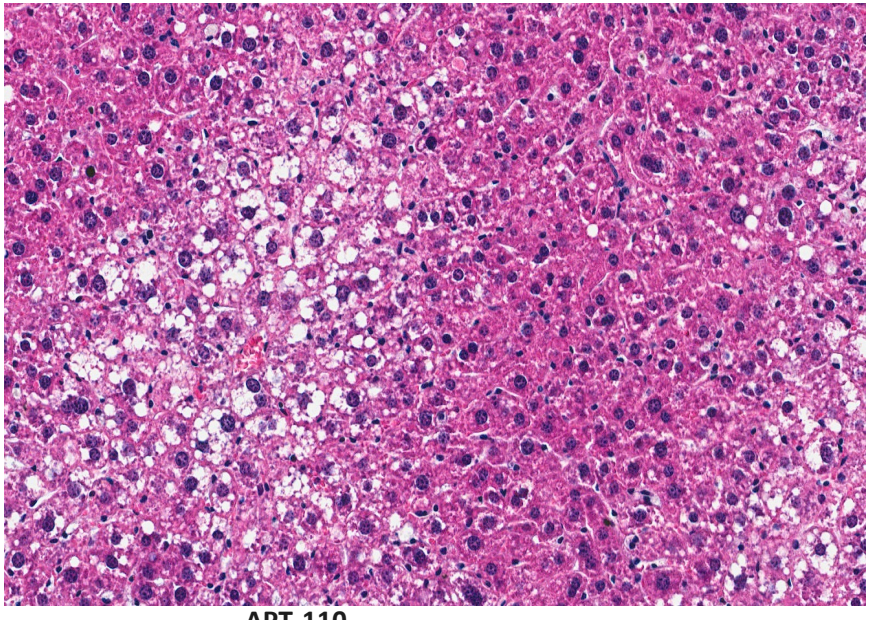
AptamiR miR-22 Antagomir Reduces Liver Fat Accumulation in DIO Mice

- Treatment for **12 weeks** with the miR-22-3p antagomir APT-110 produced a marked reduction in fatty infiltration of the liver (H&E staining):



Saline



APT-110

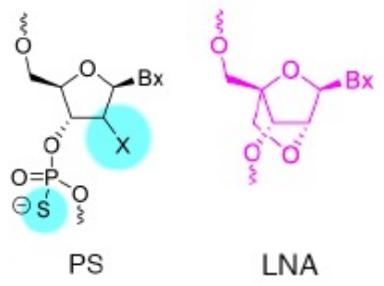
- Thibonnier, M. et al. Metabolic Benefits of MicroRNA-22 Inhibition, Nucleic Acid Ther., 30(2), 104-116, 2020
- Thibonnier, M. et al. Metabolic and Energetic Benefits of MicroRNA-22 Inhibition, BMJ Open Diabetes Res. Care, 8, 2020

- Elevated circulating miR-22-3p is a biomarker of NAFLD, in relation to activity score (NAS) and Steatosis Activity Fibrosis (SAF): Scientific Reports, 8:10606, 2018; BMC Genomics, 19:188, 2018
- Hepatic miR-22 overexpression enhances diet and alcohol-induced steatosis whereas reducing miR-22 level improves alcoholic steatosis in mouse models: JHEP Rep. 2020;2(2), 100093
- miR-22 promotes the development of liver cirrhosis through BMP7 suppression: Cell Physiol. Biochem. 2015;36:1026-1036
- miR-22 modulates the expression of lipogenesis-related genes and promotes hepatic steatosis in vitro: FEBS Open Bio 2021;322-332. "***miR-22 inhibitors may have potential as candidate drugs for NASH and obesity***"

Toxicity of the 1st Generation of ONTs

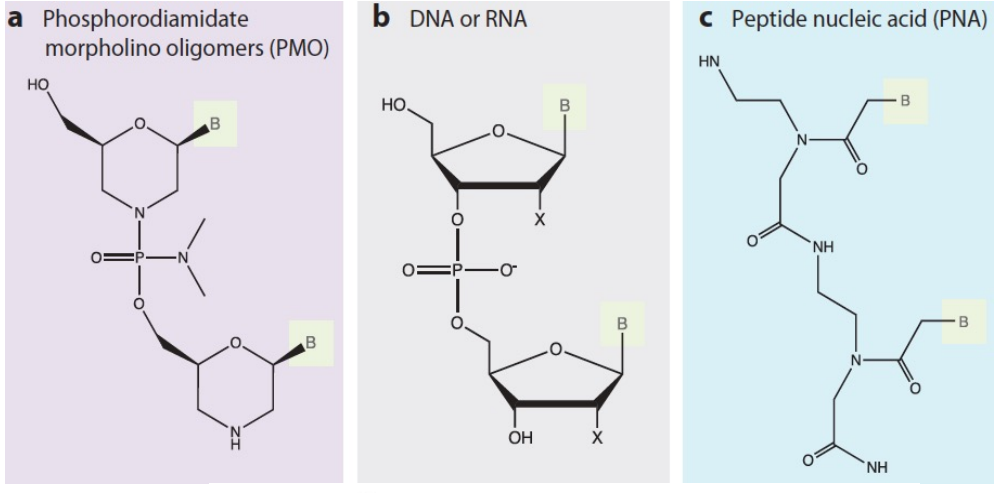
The First Generation of ONTs (ASOs, siRNAs & miRNAs) developed by AptamiR and other Biotechnology Companies were found to trigger at supra-therapeutic doses in Non-Human Primates:

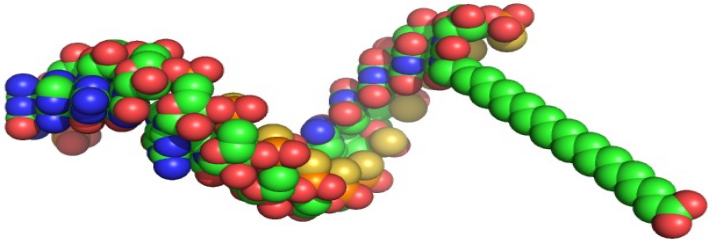
- Transient activation of blood platelets and the complement pathway in relation to Phosphorothioate (PS) backbone modifications
- Hepatic and renal toxicity in relation to Locked Nucleic Acid (LNA) sugar modifications

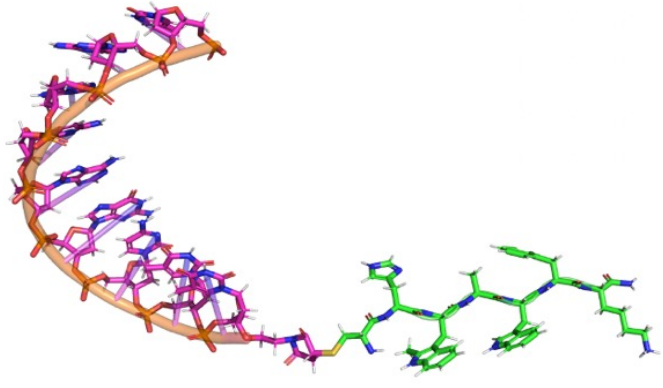


Our Second Generation of ONTs was designed to eliminate this toxicity by:

- Replacing PS by PNA or PMO backbone modifications
- Conjugating the ONT to a fatty acid or short peptide for enhanced targeted delivery to adipocytes of a greatly reduced effective dose with an extended duration of action in target tissues







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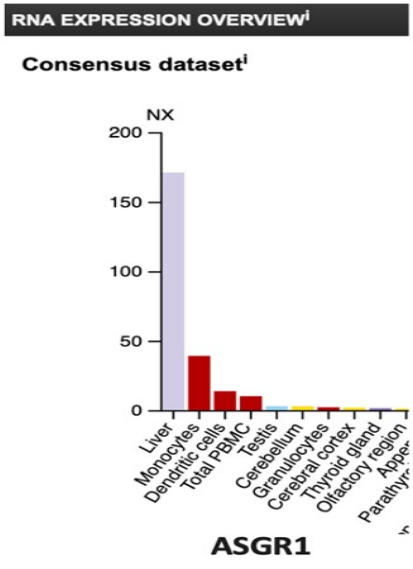
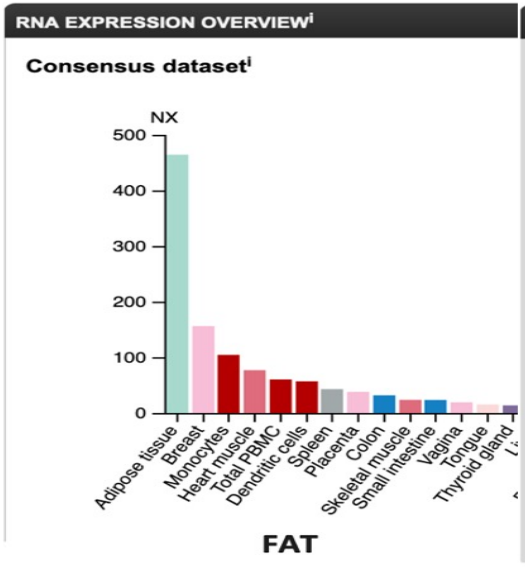
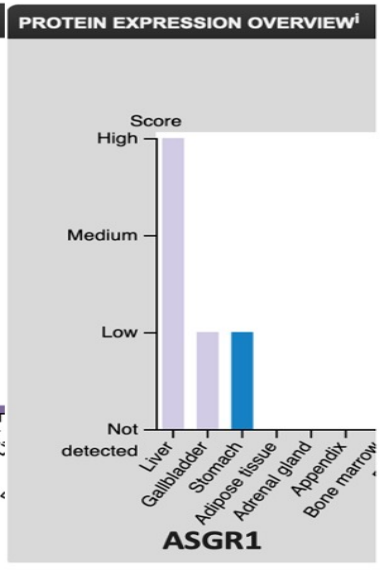
Targeted Delivery of the 2nd Generation of ONTs

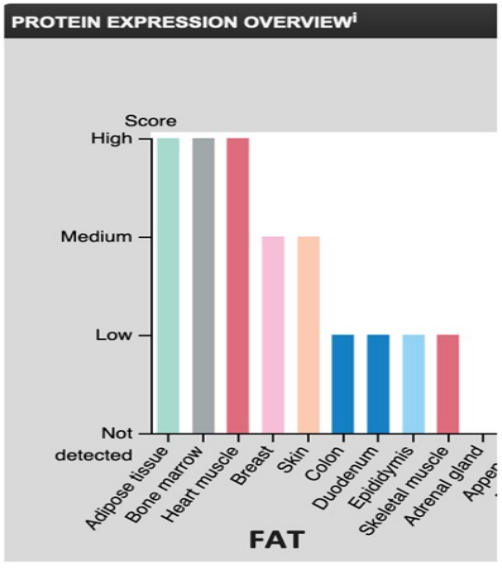
Selection of the membrane Fatty Acid Translocase (FAT) transporter for targeted delivery of ONTs to adipocytes and metabolic organs

- mRNA and protein expression levels of FAT are very high in human adipose tissues (the Asialoglycoprotein receptor 1, ASGR1 used for targeted delivery to the liver is used as a reference)









- Conjugating our ONTs to a fatty acid or short peptide allows enhanced targeted delivery of a much reduced effective dose with a significantly longer duration of action
- As the average obese male patient weighs around 200 lbs with 40% being adipose tissue, there is a huge amount of FAT available at the surface of adipose tissues to transport inside the adipocytes our second generation of miR-22-3p antagomir coupled to a fatty acid or a peptide.
- Consequently, the effective dose for our second generation of drugs should be much lower with a greatly improved safety and PK/PD profile, especially the mean residence time inside the targeted cells

AptamiR IP & Assets Development Stage

Patent Portfolio	Subject Matter	Date of Publication/Issue
WO 2013/159091 A3	MicroRNA modulators of thermogenesis	Published in 2013
US 9,034,839; 9,453,224; 9,803,203 and 10,253,319	MicroRNA modulators of thermogenesis	Issued in 2015-2019
US 2015-0216892-A1	Cell-specific delivery of miRNA modulators for the treatment of obesity and related disorders	Published in 2015
WO 2017/187426 and US 0127736	Inhibition of miR-22 miRNA by APT-110	Issued in 2017-2019
WO 2020/051398 A1	Metabolic benefits of short miR-22 miRNA antagomirs therapies	Published in 2020
WO 2020/010059 A1	Targeted delivery of therapeutics agents to human adipocytes	Published in 2020
EP 2839005	MicroRNA modulators of thermogenesis	Granted in 2021

Current Development Stage

Our second generation of miR-22-3p antagomirs is now ready to be tested:

- In vitro in primary cultures of **human adipocytes**
- In vivo in animal models of obesity and fatty liver disease
- In toxicology studies in mice and Non Human Primates

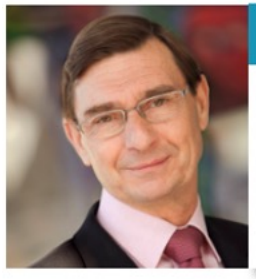
AptamiR Experienced Team

Marc Thibonnier, M.D, M.Sc., Founder & President

- **Founded AptamiR in 2012**
- Academic career at CWRU and Stanford University
- Senior management positions at Pharmaceutical (Bayer, BMS, GSK) and two Biotechnology Startup Companies
- Holds an M.D. degree from Université Pierre et Marie Curie, and a M.Sc. in Pharmacology from UCSF

Philippe Camus, Chairman of the Board

- **Chairman of AptamiR since 2012**
- Former Chairman of the Board at Alcatel–Lucent and Senior Adviser at Evercore Partners
- Former CEO of EADS and co-managing partner at Lagardère
- Graduated from Ecole Normale Supérieure and Institut d'Etudes Politiques de Paris



Jean-Pierre Lehner, M.D., Board Director

- **Director of AptamiR since 2015**
- Retired Chief Medical Officer of Sanofi, with previous positions notably at Roussel
- CEO of JPL Pharma Consulting and Board Member of several biotech and R&D companies
- Cardiologist with M.D. degree from University of Paris School of Medicine

ADVISORS

- **Bernard Poussot**: Retired Chairman, CEO & President of Wyeth, Board Director of Roche
- **Daniel Ricquier, Ph.D.**: Discoverer of UCP1 and Member of the French Academy of Sciences
- **André Ulmann, M.D., Ph.D.**: Chairman of HRA Pharma, Former Developer of RU-486
- **Huntington Willard, Ph.D.**: Founding Director, Geisinger National Precision Heath and Howard Hughes Medical Institute Professor, Former Founding Director of the Duke Institute for Genome Sciences and Policy, and Chairman of Genetics at C.W.R.U.

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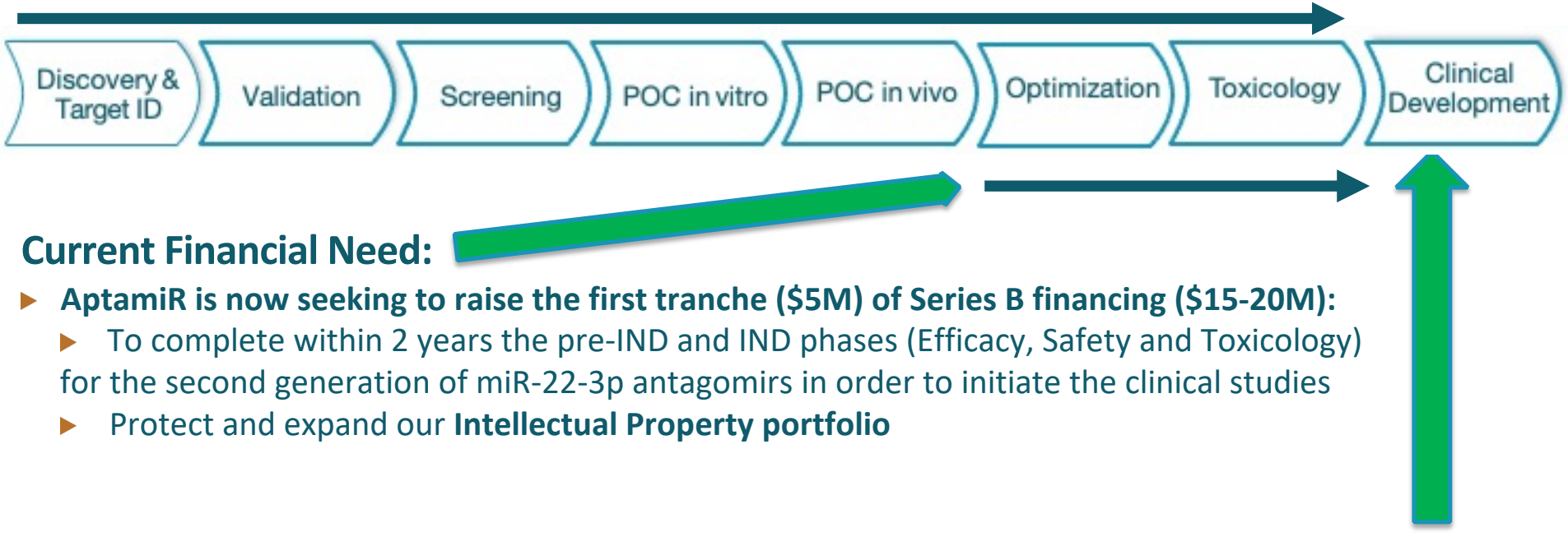
Financial Need and Use of Proceeds

- **Development of the *1st Generation of miR-22-3p AntagomiRs (APT-110) from Discovery to Toxicology ($7M spent)* proved the concepts** that:
  - miR-22 is a good metabolic target and
  - antagonizing miR-22 reduces fat mass, body weight, dyslipidemia, insulin resistance and fatty liver:



Current Financial Need:

- **AptamiR is now seeking to raise the first tranche ($5M) of Series B financing ($15-20M):**
  - To complete within 2 years the pre-IND and IND phases (Efficacy, Safety and Toxicology) for the second generation of miR-22-3p antagomirs in order to initiate the clinical studies
  - Protect and expand our **Intellectual Property portfolio**

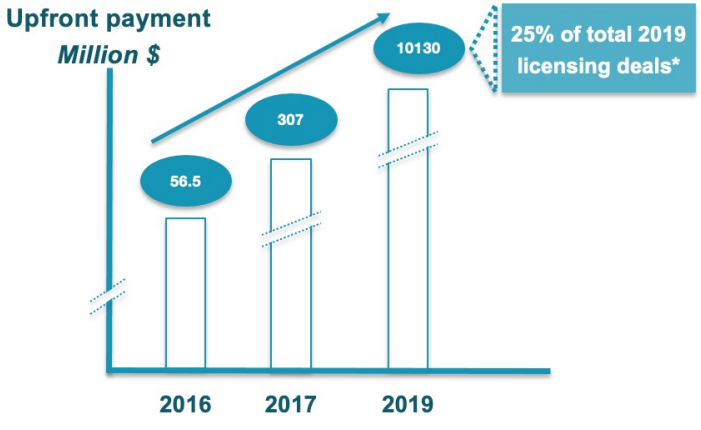
Several Pharmaceutical Companies have expressed interest for **Out-Licensing /Partnership** at the initiation of clinical trials

AptamiR Current Valuation

- Benchmarking versus executed ONT licensing deals -

Deal #	1	2	3	4	5	6	7	8	9	10
Year	2016	2017	2018	2018	2018	2019	2019	2019	2019	2020
Therapeutic area/ Indication	Cardiovascular	NASH	Orphan diseases- multiple targets	Cardio-metabolic, neuro degeneration	Chronic Hepatitis B	NASH	Chronic Hepatitis B	Liver cardio-metabolic diseases	Cholesterol reduction	Alpha-1 Antitrypsin-Associated Liver Disease
Out-licensor	Arrowhead	Dicerna	Dicerna	Dicerna	Arrowhead	Dicerna	Dicerna	Dicerna	The Medicines Company	Arrowhead
In-licensor	Amgen	BI	Alexion	Eli Lilly	Janssen	BI	Roche	Novo- Nordisk	Novartis	Takeda
Development stage	Pre-Clinical	Discovery	Discovery	Discovery	Phase I/II	Pre-Clinical	Phase I	Discovery	Regulatory	Phase II
Upfront (M$)	56.5	10	37	20 per target	250	5	200	225	9700 (acquisition)	300
Milestones (M$)	617	201	105 per target	350 per target	3500	Undisclosed	1470	375.5 per target	NA	$740M
Royalties	Double digit	Double digit	Double digit	Double digit	Undisclosed	Undisclosed	Undisclosed	Undisclosed	NA	Profit sharing 50/50 in USA

Licensing deal activity for Oligonucleotide Therapeutic assets



* The top 15 biopharma licensing deals of 2019, Fierce Biotech, Mar 23, 2020

APTAMIR Valuation