Cerenis™
THERAPEUTICS

The HDL Company

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Presentation to the HDL Workshop | May 9th, 2018 at San Francisco

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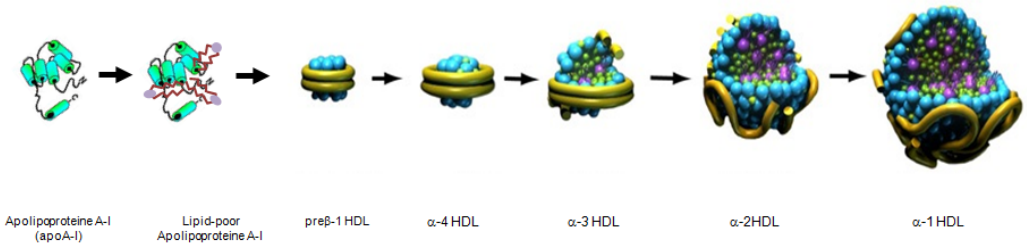
Cerenis™ THERAPEUTICS

Section I

ApoA-I and HDL, Nature's Universal Targeting Delivery Systems

ApoA-I and HDL, Nature's Universal Targeting Delivery Systems From Atherosclerosis to Cancer

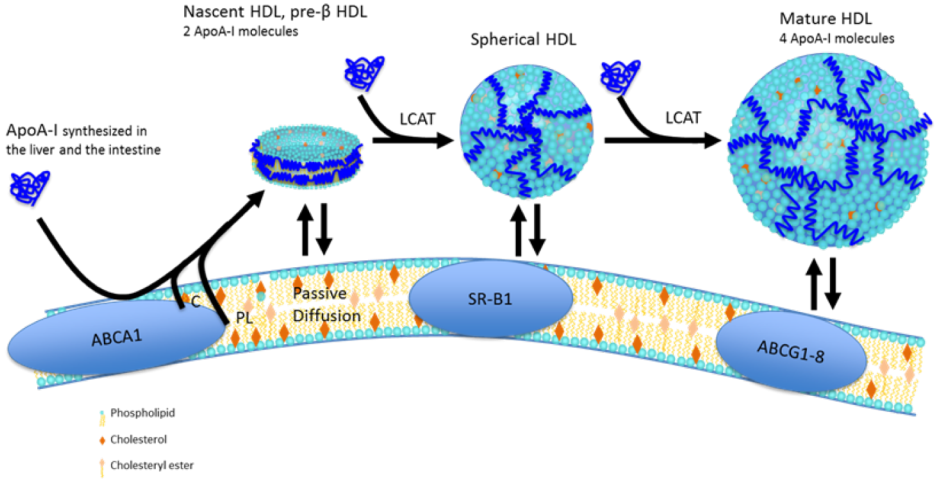
- **The term HDL groups together different classes characterized by the number of molecules of apoA-I, composition, size and morphology. In addition HDL range from lipid-poor apoA-I to spherical HDL containing four molecules of apoA-I, as well as discoidal HDL containing two molecules of apoA-I.**



- **HDLs are universal natural transporters in the blood as well as the lymph, a key compartment for the immune response. HDL, which is responsible for reverse lipid transport, transports lipids as well as nucleic acids such as micro-RNA that are regulators of gene expression, antioxidants (lutein, tocopherols, zeaxanthin) and xenobiotics (drugs and toxins).**
- **ApoA-I is a flexible protein capable of structuring and solubilizing a whole group of apolar and/or amphiphilic molecules and adapting to different nanoparticle sizes/morphologies. ApoA-I is a protein that does not contain cysteine (no formation of disulfide bridge) or glycosylation site and which is soluble in organic solvents.**

ApoA-I and HDLs Interact with Multiple Cellular Receptors

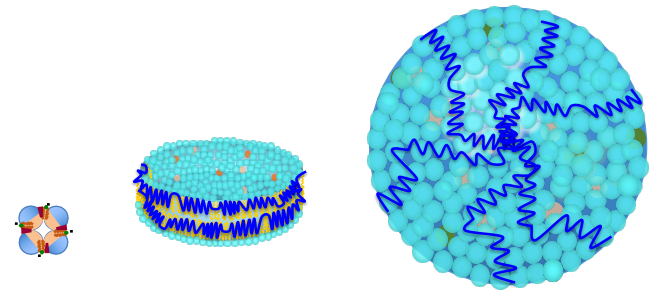
- Pre-beta-1 HDLs (preβ-1 HDL) are comprised of small complexes of lipid-poor apoA-I, interacting with different receptors such as ABCA1, ABCG1 and cubulin. Pre-beta HDLs are discoidal nanoparticles (two-dimensional structure) containing two molecules of apoA-I, capable of mobilizing and transporting apolar molecules and amphiphilic molecules.
- Spherical HDLs (three-dimensional structure) are nanoparticles containing 3 to 4 molecules of apoA-I (offering a maximum load capacity). The core of the particle can accommodate a large number of apolar molecules such as triglycerides and cholesterol esters, whilst the external surface can accommodate amphiphilic molecules and less apolar molecules such as miRNA.
- Lipid-poor apoA-1 is the natural ligand to ABCA1 receptors. Discoidal and spherical HDL interact with numerous receptors, especially the SR-BI receptor.



HDL RECEPTORS ARE EXPRESSED IN MANY TISSUES INCLUDING PATHOLOGIC TISSUES AND IMMUNE CELLS

- Cancer cells over-express HDL receptors (SR-BI receptors) as their proliferation is highly dependent on a constant flux of molecules transported by HDL
- Key immune cells such as Lymphocytes, dendritic cells, monocytes and macrophages express HDL receptors
- SR-BI receptors have a higher affinity for charged HDL (Cerenis has a patent on charged HDL)

HDL, the Perfect Stealth Targeting Drug Delivery Vehicle



Cargomer®
(few nm)

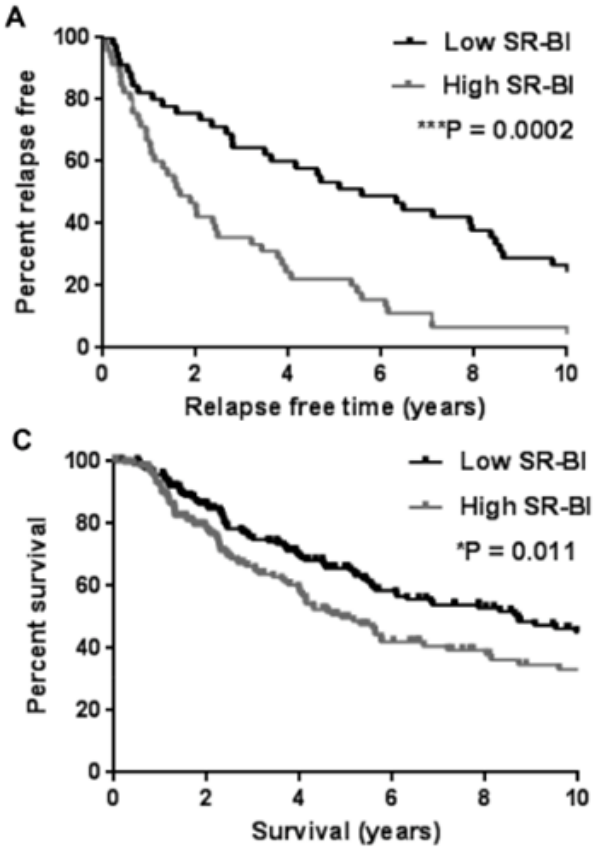
Discoidal HDL
(7-9nm)

Spherical HDL
(10-20nm)

- **The small size of HDLs allows to address all compartments (blood and lymph) and tissues including tumors.**
- **HDLs allows direct access to the immune cells (dendritic cells, lymphocytes) by circulating in the lymph and accessing lymph nodes.**
- **Upon recognition by the receptors, HDL are not degraded in the lysosomal pathway. After endocytosis, HDL is either rapidly recycled through the endosomal recycling compartment (ERC) and resecreted or transported to multivesicular bodies (MVBs)**
- **Endogenous HDLs have been the subject of a large amount of research on their use as vectors for delivery of active substances such as anti-cancer molecules, peptide or non-peptide antigens, nuclear acids (micro-RNA, interfering RNA, antisense oligonucleotide, etc.) , markers (fluorescent or radioactive) and others (vitamins, anti-oxidants).**
- **Once the load is delivered, the remaining apoA-I is rapidly and safely integrated in the natural lipoprotein metabolism pathways leading to no accumulation of empty carrier.**
- **ApoA-I and HDL offers the opportunity to have a carrier with adaptive capacity**
- **ApoA-I provides built in targeting properties to target specific cells, tissues or tumors.**

SR-BI Receptors Play a Key Role in Cancer Cell Proliferation

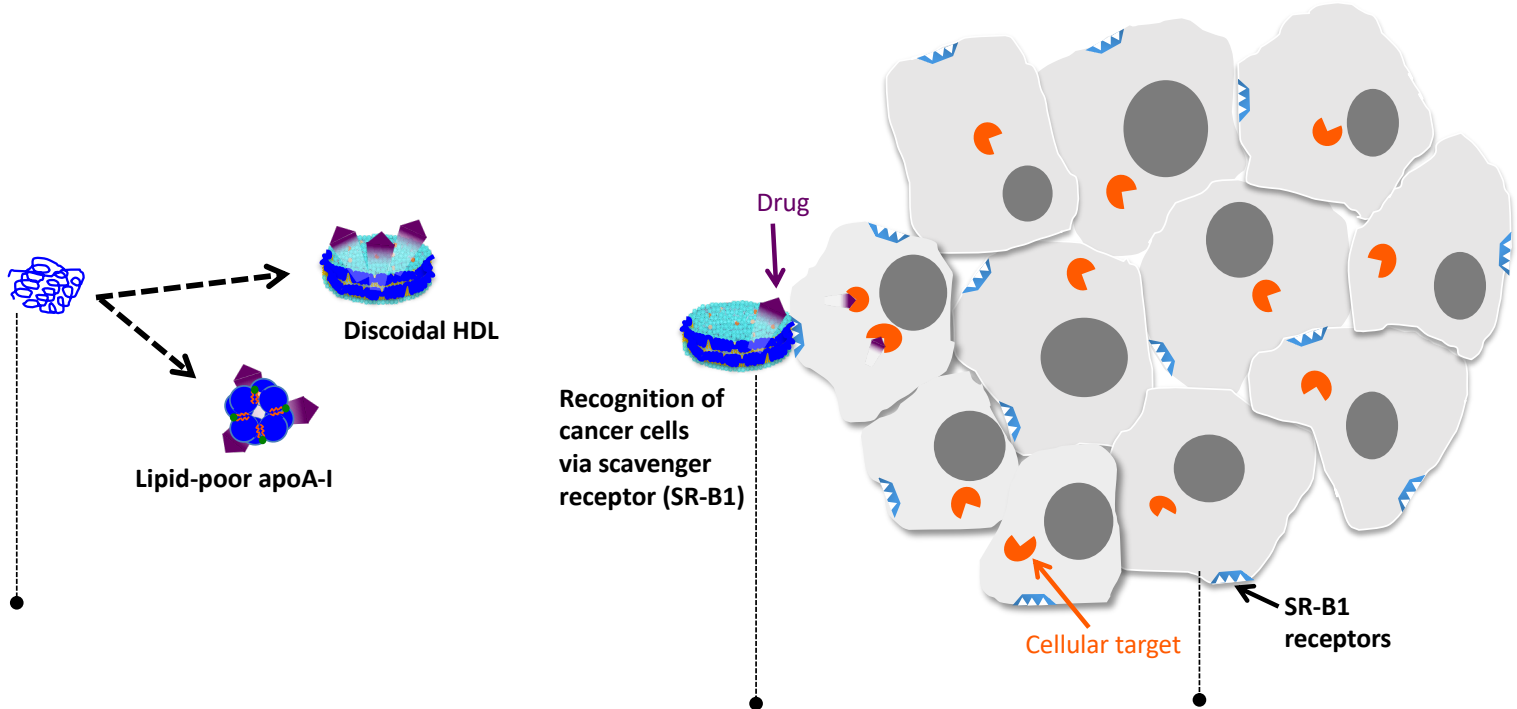
- Melanoma can be an aggressive and fatal form of skin cancer with the prevalence rising significantly over the last decade
- Once the disease is metastatic patients have a very poor prognosis
- Melanoma patients with high SR-BI expression, displayed a significantly earlier time of tumor reoccurence compared to patients with low SR-BI expression (A). In addition patients with high SR-BI have a significant poorer outcome (C)



* Mikula et al.* (Medical University Vienna, Austria) : Mol Cancer Res. 2017 Oct 3. pii: molcanres.0292.2017. doi: 10.1158/1541-7786.MCR-17-0292.

HDL DRUG DELIVERY TARGETING HDL RECEPTORS SUCH AS SR-BI MIGHT REPRESENT A HIGHLY EFFECTIVE WAY TO TREAT CANCERS LIKE METASTATIC MELANOMA

HDL Particles are Perfect Delivery Vehicles Able to Selectively Bring Cell Killing Agents to Cancer Cells



ApoA-I

Biocompatible, major structural protein of HDL

Nano HDL particles

Ability to transport highly water insoluble constituents in the core region

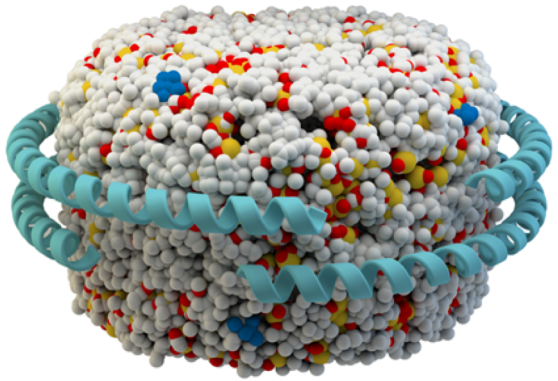
Tumor

SR-B1 are HDL receptors essential to cell homeostasis, proliferation and growth

HDL'S BIOLOGICAL FEATURES SUPPORT THE SAFETY PROFILE OF THE TECHNOLOGY

CER-001, A Recombinant Human Apolipoprotein A-I Pre-Beta HDL Mimetic

- **CER-001 is composed of recombinant human Apolipoprotein A-I and phospholipid containing Sphingomyelin (Sph) and dipalmitoyl phosphatidylglycerol (DPPG).**
- **The protein-to-phospholipid ratio is 1:2.7 and contains 97% Sph and 3% DPPG**
- **CER-001 is a reconstituted High Density Lipoprotein (HDL) with its negative charge. It mimics biological properties of natural HDL when injected intravenously.**
- **CER-001 is currently in phase III clinical trial for treatment of HDL deficiencies (TANGO trial) and in phase II clinical trial (TARGET) for imaging tumor in patient with esophageal cancer**



CER-001 (recombinant HDL particle)

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Section II

CERENIS HDL in Chemotherapy

Chemotherapy: CER-Paclitaxel, a Discoïdal HDL Containing Paclitaxel

Background

- **Paclitaxel (Taxol®) is an anti-cancer (antineoplastic" or "cytotoxic) chemotherapy drug. It is a plant alkaloid, a taxane and an antimicrotubule agent. Cremophor the formulation vehicle used to solubilize paclitaxel is associated with serious side-effect and poor tolerability.**
- **Abraxane® is an albumin-bound paclitaxel, a better tolerated formulation than Taxol®**

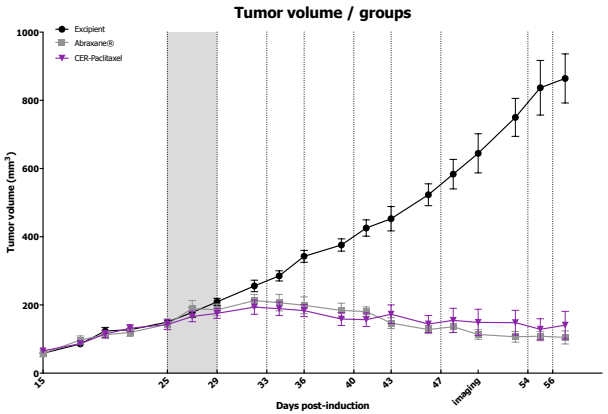
HDL nanoparticle

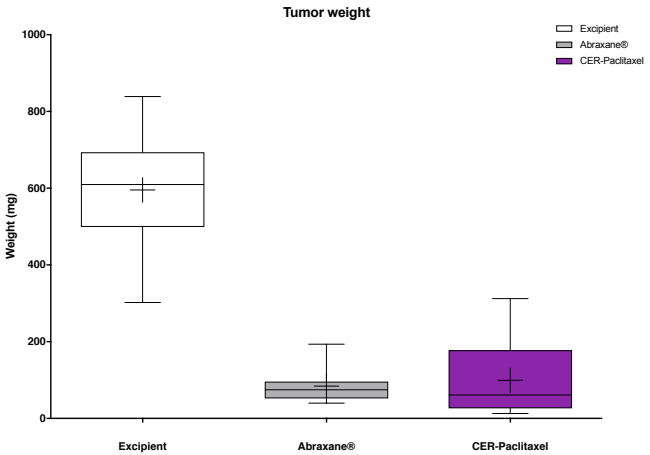
Paclitaxel was embedded in a recombinant human apoA-I pre-beta HDL particle (CER-Paclitaxel)

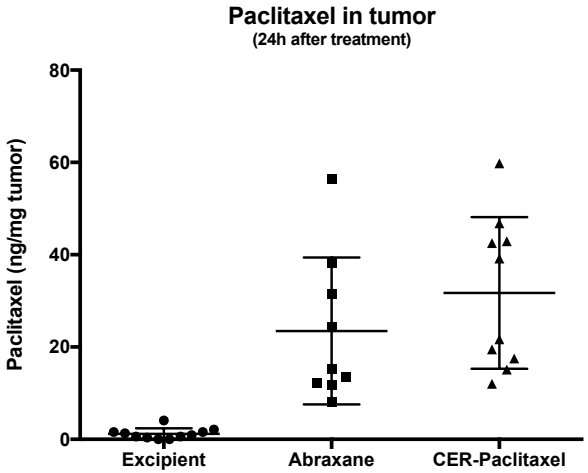
Study design

- **Tumors were induced by xenografting human breast adenocarcinoma cells (Orthotopic xenograft of MDA-MB-231 cells) in NOD-SCID mice**
- **When tumors reach about 150mm^3, test items were administered iv daily for five consecutive days and then twice weekly**
  - Group 1: Control group
  - Group 2: Abraxane®
  - Group 3 : CER-Paclitaxel

Recombinant human apoA-I Pre beta HDL demonstrates excellent targeted Paclitaxel delivery in Xenograft Murine Model of Human Breast Cancer







HDL NANOPARTICLES TRAPPING OF CHEMOTHERAPEUTIC AGENTS PROVIDES:

- **ENHANCED STABILITY.**
- **TARGETED DELIVERY FOR BETTER EFFICACY**
- **BETTER TOLERABILITY**

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Section III

Cargomers® in Immuno-Oncology and Gene Therapy

Apolipoprotein A-I (lipid-free apoA-I)

Human lipid-free ApoA-I exhibits a reversible association-dissociation equilibrium. ApoA-I association is concentration, ionic strength, pH and temperature dependent. Lipid binding will displace equilibrium. Charged lipids will displace equilibrium in favor of dissociation

Random coil apoA-I

folded apoA-I (mainly helical structures)

Multimeric apoA-I (mainly helical structures)

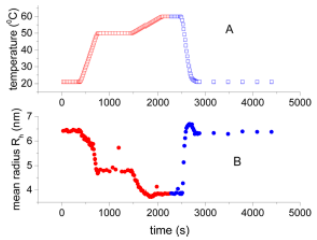


Figure 1. DLS temperature scan of an Apo A-1 solution of concentration 1 mg/mL (35.5 μM) in PBS buffer. (A) Temperature as a function of time (red □) heating and (blue □) cooling). (B) Variation of the average hydrodynamic radius R_h with heating (red ●) and cooling (blue ●).

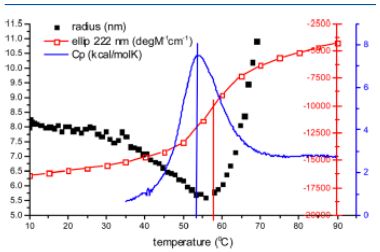


Figure 6. Thermal unfolding of Apo A-1 solution of concentration 2.7 mg/mL (95.7 μM, PBS buffer) measured with differential scanning calorimetry (blue solid line), dynamic light scattering (□), and circular dichroism spectroscopy (red □).

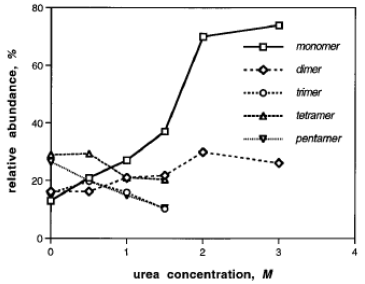
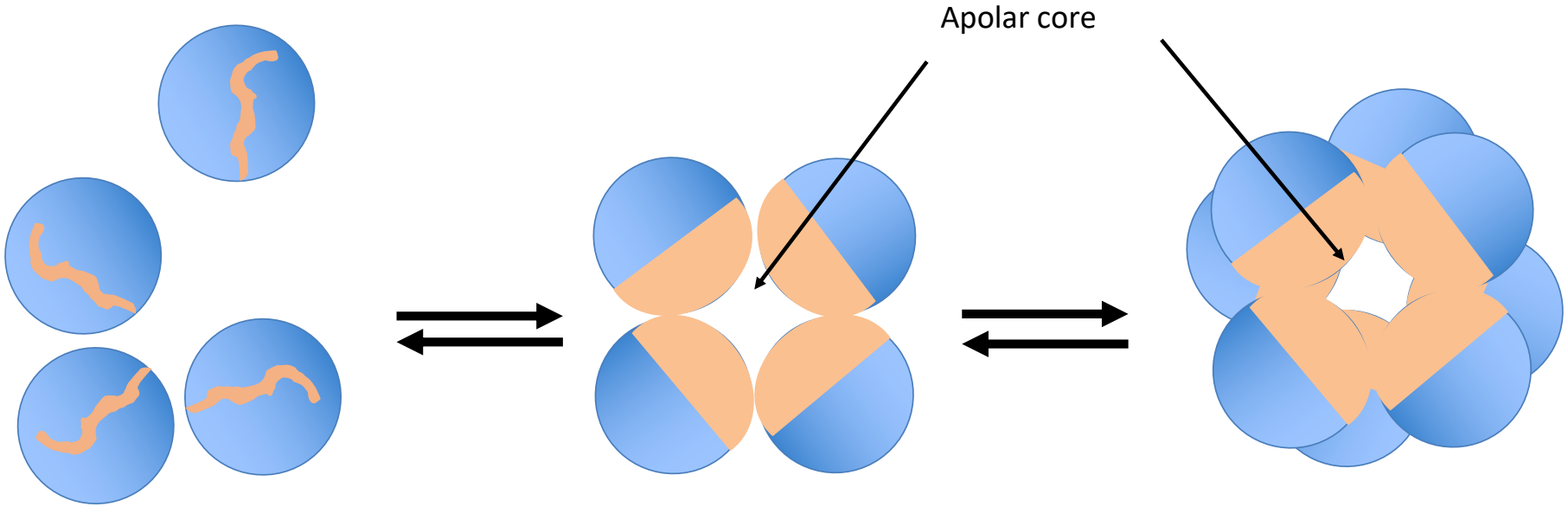


FIGURE 5: Distribution of apoA-I species as a function of the urea concentration, calculated from the densitometry of the SDS–PAGE pattern of a cross-linked sample.

Schönfeld H-J *et al.* J. Phys. Chem. B 2016, 120, 1228-1235
Gianazza E *et al.*, Biochemistry 1997, 36, 7898-7905

MULTIMERIC APOA-I CONTAINS 2 TO 8 MONOMERIC APOA-I.

ApoA-I Multimers



Monomeric form of ApoA-I is in equilibrium with multimeric forms

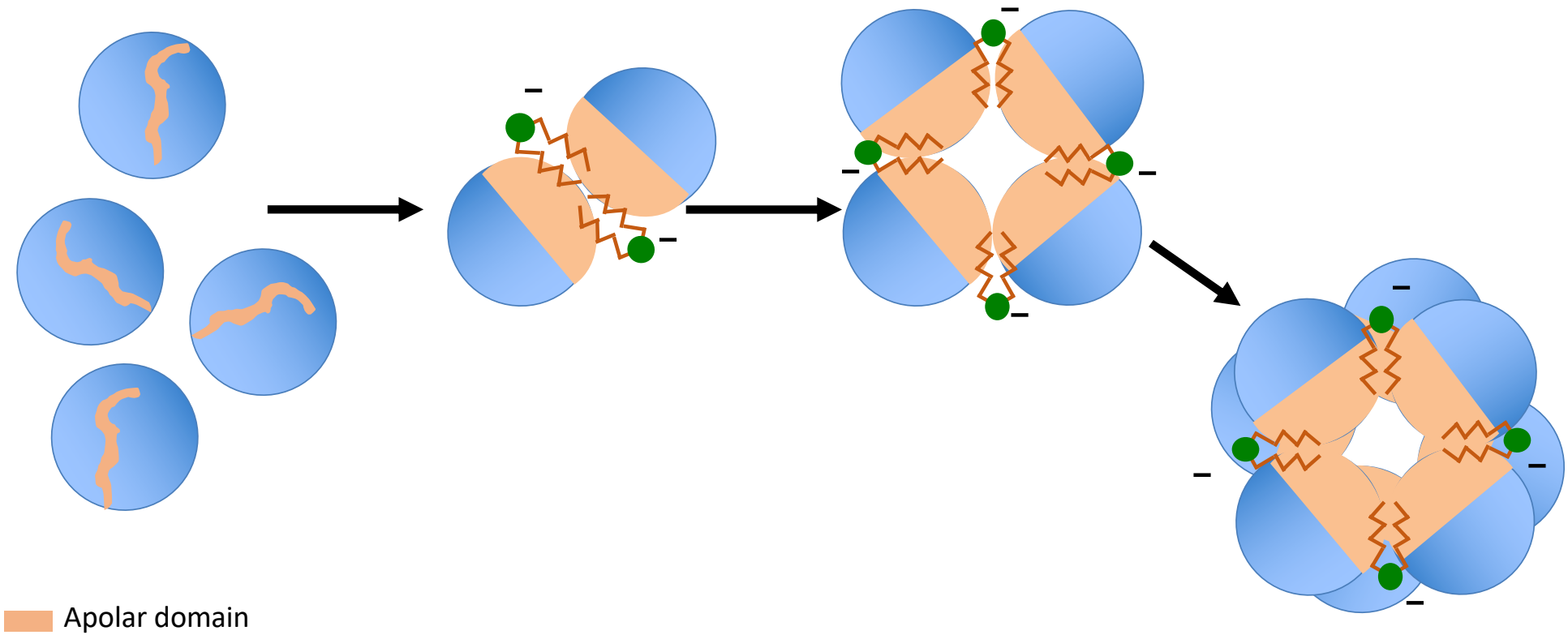
Monomeric form of Apolipoprotein A-I (random coil, helicity increases as apolar molecules bind to the monomer

Tetrameric form of Apolipoprotein A-I (helicity increases as multimers are formed)

Octomeric form of Apolipoprotein A-I

In water based solutions, apolipoprotein A-I has a tendency to aggregate in order to minimize the exposure of apolar residues to the hydrophilic solvent. This is why, apoA-I can easily form insoluble aggregates that are difficult to dissociate

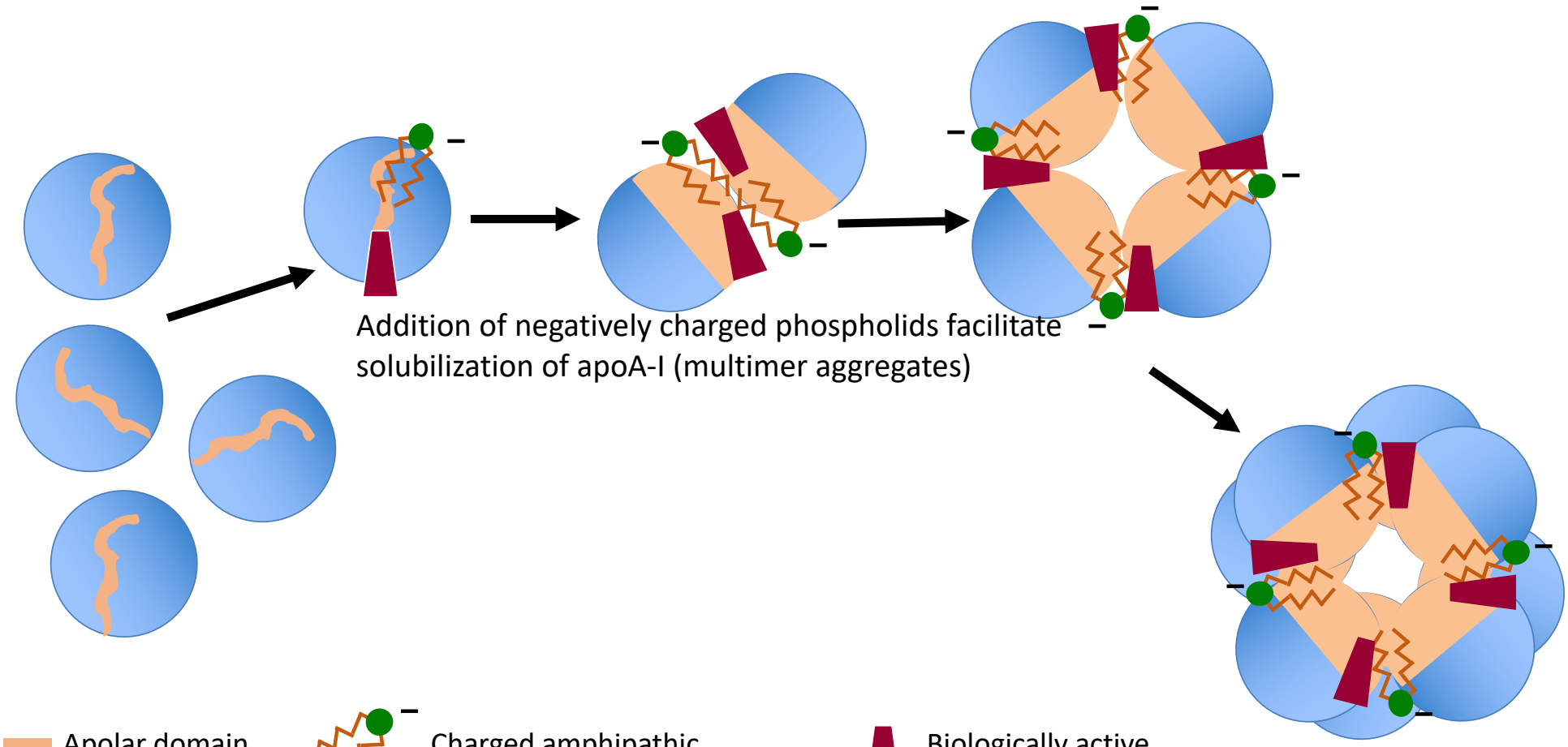
Addition of Negatively Charged Phospholids Facilitate Solubilization of apoA-I (multimer aggregates)



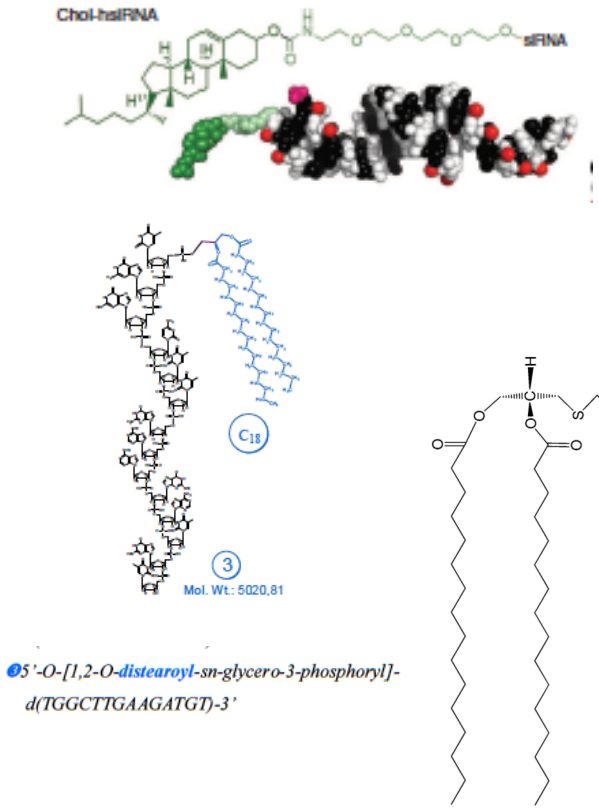
Apolar domain

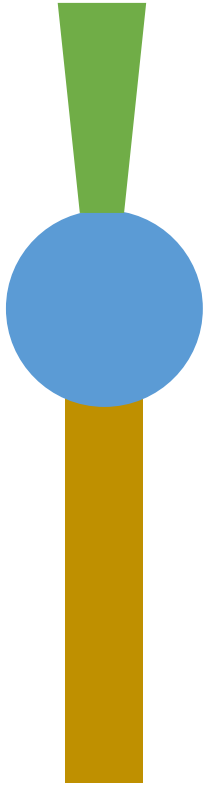
In water based solutions, apolipoprotein A-I has a tendency to form unsoluble aggregates and to precipitate. Addition of few charged molecules (charged phospholipids for instance) can facilitate solubilization.

Cargomers® (non-covalent multimeric form of apoA-I) to carry and deliver biologically active molecules



Examples of Anchors





A bioactive molecule: peptide antigen, Nucleic acid, sugar, etc.

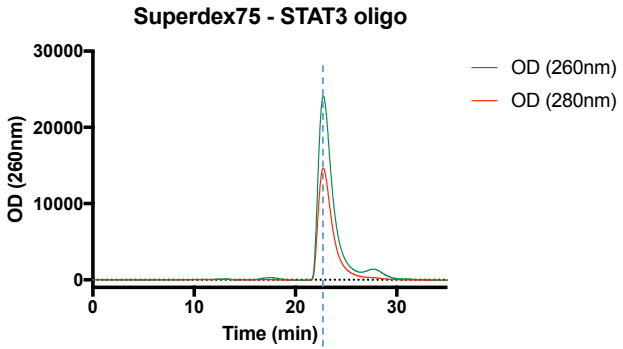
A functionalized linker

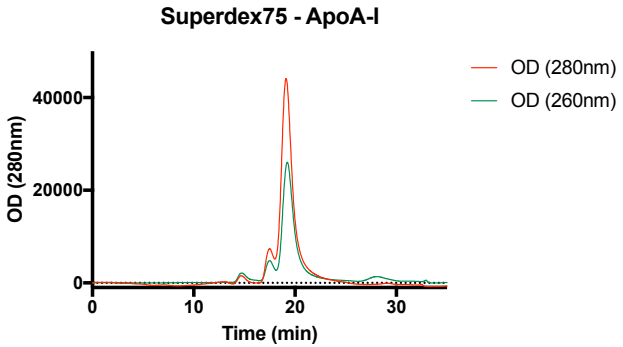
Apolar molecule: PL, TG, Cholesterol, etc.

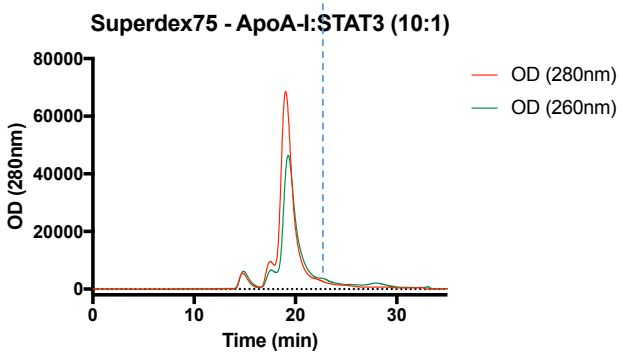
Cargomers® , ApoA-I Multimer Nanoparticles

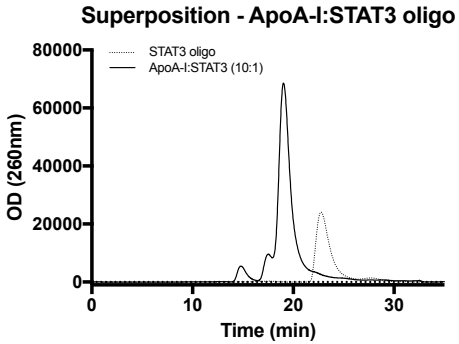
- **Cargomers® , are proprietary nanoparticles measuring a few nanometers, comprised essentially of multimeric apoA-I.**
- **Cargomers® are designed to deliver biologically active molecules and and target specific cells, tumors or tissues**
- **The Cargomers® represents an ideal furtive, perfectly biocompatible targeting vehicle. They integrate into the metabolism of natural HDL and do not leave any accumulation of ingredients once the active substance is delivered, unlike other preparations.**
- **Their size of a few nanometers facilitates penetration and access to a variety of biological compartments such as blood, lymph, tumors, etc.**
- **Cerenis manufacturing process for apoA-I or CER-001 is easily adaptable to incorporate different active substances (antigens, nucleic acids (siRNA, ASOs) and therapeutic agents) in Cargomer® or different HDL-based vectors.**
- **Preclinical experiments have validated the benefit of the Cargomers® in immuno-oncology as well as gene therapy**
- **Cargomers® are part of Cerenis' proprietary Targeted Drug Delivery platform. An innovative proprietary technology leveraging the natural properties of apoA-I and HDL to specifically target and deliver active pharmaceutical ingredients**
  - Cerenis unique and broad IP covers composition of matter and methods of use (indications).
  - The platform benefits from the ApoA-I and HDL commercially viable and proprietary large scale manufacturing processes

Cargomer® with Nucleic Acid (Antisense Oligonucleotide, STAT3)

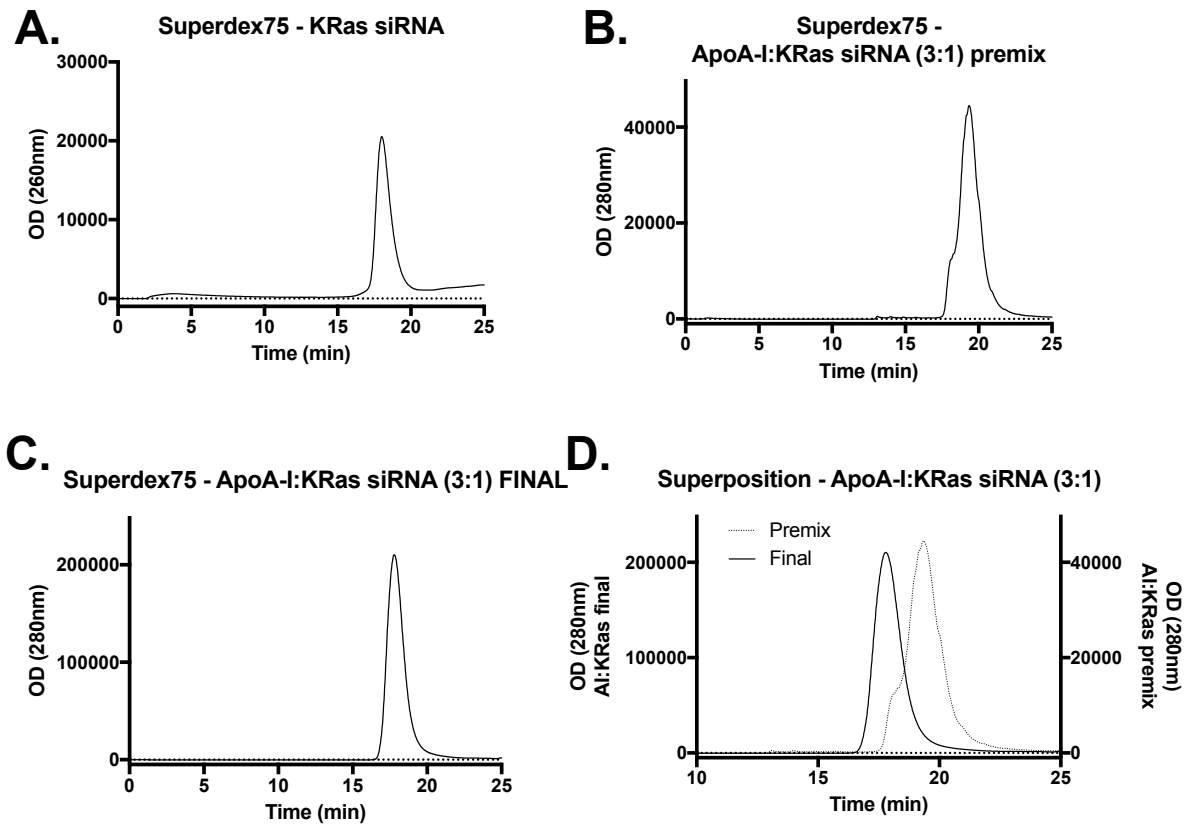




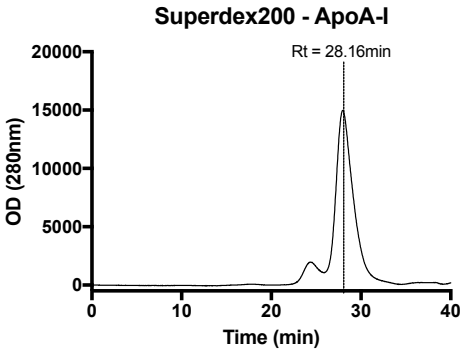


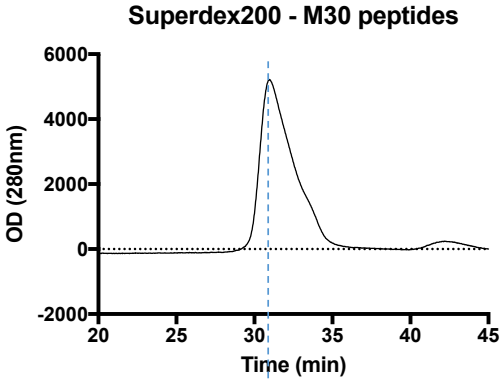


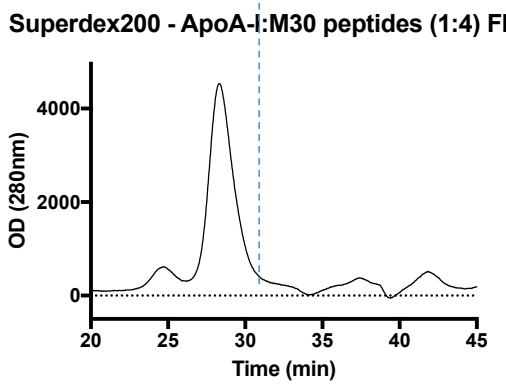
Cargomer® with Nucleic Acid (Silencing RNA, siRNA$_{KRAS}$)



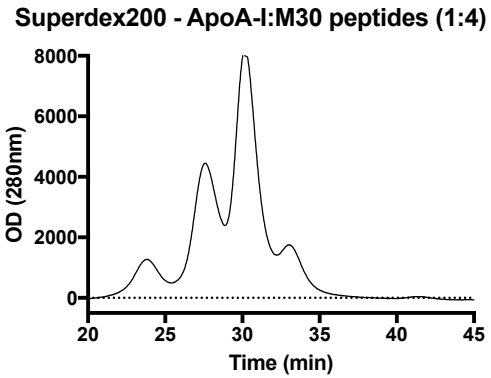
Cargomer® with Peptide (Melanoma Antigen)







Heat dissociation



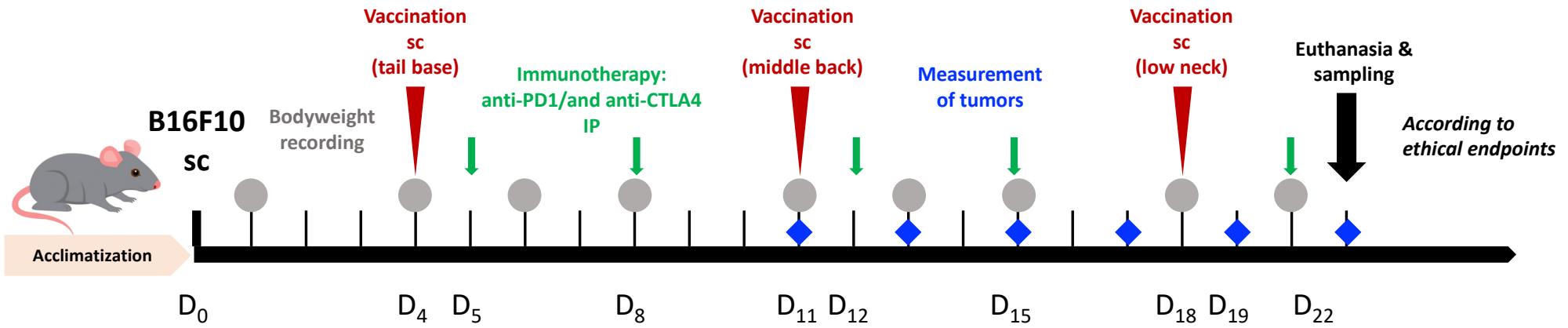
Success of Immuno-Oncology and Remaining Challenges

- **In the battle against cancer, immunotherapy is proving to be the most promising avenue of research.**
- **Checkpoint inhibitors (Yervoy®, Keytruda® and Opdivo®) have led to striking clinical success generating a regain of interest**

- **Cllinical experience has identified remaining challenges**
  - Check point inhibitors augment preexisting immunity
  - Low response rate (below 30%)

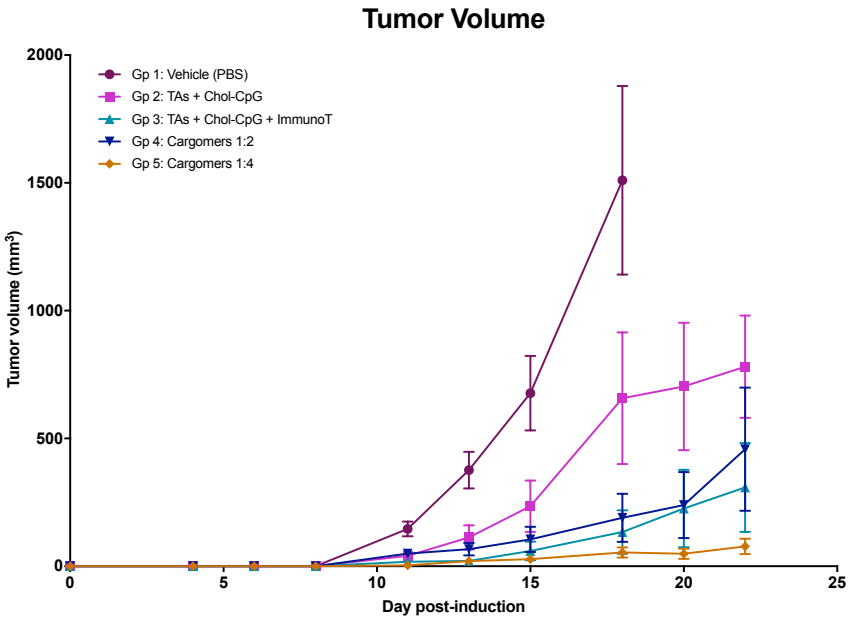
- **Scientists are looking for ways to boost immunity directed to cancer cells expressing specific antigens**

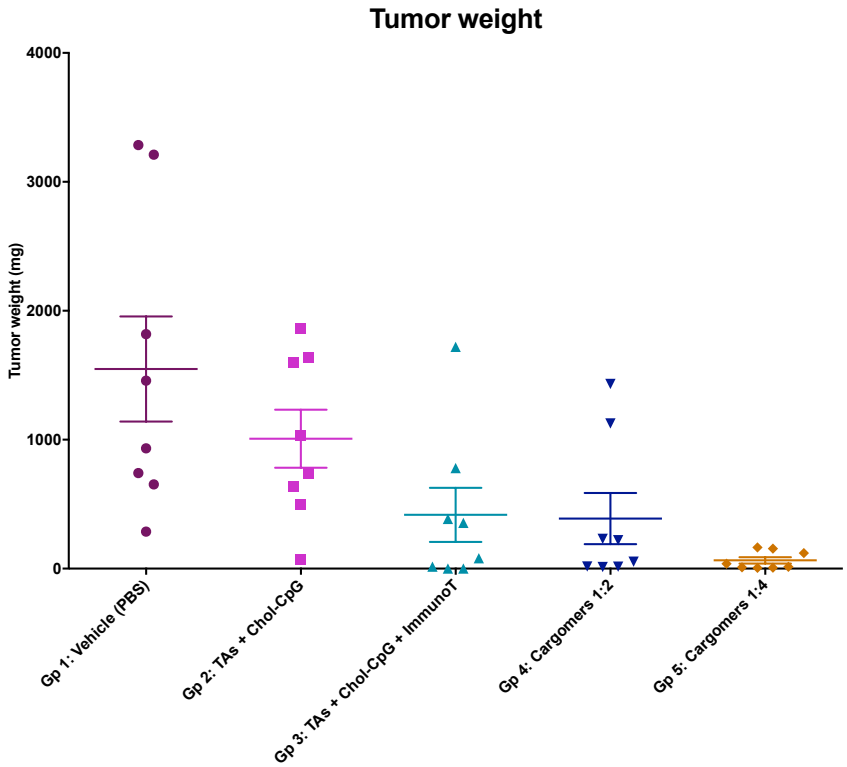
Study Design (syngeneic mouse melanoma model)



- Tumor is induced by implanting B16F10 murine melanoma cells
- Vaccination are performed once a week for 3 weeks (at days 4, 11, 18) by subcutaneous route. Immunotherapy is performed twice a week for 3 weeks (at days 5, 8, 12, 15, 19 &22). Immunotherapy consists in anti-CTLA4 (100 ug per mouse) and anti-PD1 (100 ug per mouse) antibodies administration by intraperitoneal route (final volume 0.2ml in PBS per mouse).
- Four groups:
    - Group 1: vehicle
    - Group 2: Tumor antigens + Chol-CpG
    - Group 3: Tumor antigens + Chol-CpG +immunotherapy (anti-PD1 and anti-CTL4)
    - Group 4: Cargomers (Tumor antigens, ratio 1:2, + Chol-CpG)
    - Group 5: Cargomers (Tumor antigens, ratio 1:4, + Chol-CpG)

Cargomer® Demonstrate Excellent Antigen Delivery and Presentation





CARGOMER® INDUCE AN IMMUNE RESPONSE PREVENTING TUMOR GROWTH.
CARGOMER ® 1:4 IS THE MOST POTENT AND DOES NOT REQUIRE CHECK POINT INHIBITION.

Cerenis™ THERAPEUTICS

Section IV

TARGET, a clinical study testing HDL targeting of tumors with HDL (^{89}Zn CER-001)

TARGET, a Clinical Study Testing HDL Targeting of Tumors with HDL (^{89}Zn CER-001)

Study initiated to evaluate HDL nanoparticles in patients with esophageal cancer

1. First ever performed clinical study testing the potential of labelled HDL to visualize and target tumors in cancer patients.
2. Aim of the TARGET study: assess the concentrations of Zirconium 89 (89Zr) labeled CER-001 in tumor tissue.
3. Secondary objective: evaluate the biodistribution of 89Zr labeled CER 001, the correlation between 89Zr-labeled CER-001 and tumor microcirculation.

TARGET STUDY WILL SUPPORT THE OPPORTUNITY TO TREAT CANCER PATIENTS USING HDL NANOPARTICLES AS A SPECIFIC DRUG DELIVERY PLATFORM TARGETING TUMORS

ApoA-I and HDL, Nature's Universal Targeted Delivery Systems

From Atherosclerosis to Cancer

- **Study of apoA-I and HDL in atherosclerosis has generated a lot of knowledge on nature's universal targeting delivery system**
- **HDL Targeted Drug Delivery represents a great opportunity in immuno-oncology, gene therapy and chemotherapy**
- **Cerenis has developed an innovative proprietary technology leveraging the natural properties of apoA-I and HDL to specifically target and deliver active pharmaceutical ingredients**

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THERAPEUTICS

The HDL Company

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Presentation to the HDL Workshop | May 9th, 2018 at San Francisco