Arterez™
Diagnostics and Therapies

Platform Summary

Technology Abstract

Background and Hypothesis

Gene deficient or knockout (KO) mice and rabbits are common models used in the study of atherosclerosis, primarily focusing on cholesterol plaques, which do not reflect the multiple (plexic) nature of cardiovascular disease (CVD). The 'one-drug-one-target' paradigm has produced statins and other therapies for many years, yet they have proved symptom-targeted and at best palliative, thus beginning in 2012, Dr. J.B. Tunac set out to develop curative and preventive treatments for vascular disease by identifying and targeting the multi-factorial root-causes of vascular disease.

Vision and Objective:

To demonstrate that CVD is comprised of multifactor etiology that can be identified, cured and prevented utilizing multi-compound therapies and then to evolve Arterez' platform technologies to develop predictive, preventive and curative solutions for related vascular pathophysiologies such as rheumatoid arthritis and diabetes type II.

Methods and results:

A virtual thromboembolic pathway was constructed to reflect the multiple etiology of CVD. Druggable sites were identified, and nine new chemical entities (NCEs) synthesized to match target sites. A series of 3-NCE combo were then designed to address in toto the thromboembolic pathway. A natural mouse was created to produce plaques and was used as a model to evaluate the curative and/or preventive treatment effect of these NCEs. A 4- panel biomarker, based on glycocalyx disruption was assembled as a histopathology surrogate to monitor plaque formation. Of the 12 series of 3-NCE combos, four were found to be both curative and preventive. One combo was chosen and given the designation Embotricin™. Pre-clinical studies led to an early focus on cardiovascular disease (CVD), however established a root-cause correlation between several vascular pathophysiologies.

Data Conclusion:

CVD and its multiple etiology can be identified, characterized, prevented and cured utilizing combo-drug therapeutics and associated diagnostics marker panels.

Arterēz™ Diagnostics and Therapies

Platform Summary Overview

Dr. J.B. Tunac
Chairman and President
drjoe@arterez.com

Arterēz™ Diagnostics and Therapies

Meet Dr. Joe Tunac

Education

- U of Philippines – BS, Plant Pathology
- So. Dakota State – Masters, Plant Pathology
- Penn State – Microbiology Ph.D. program
- Rutgers, Waksman Institute – Ph.D.
  - Known as the 'world center' for antibiotic research
  - Joe was the 1st student to develop a drug brought to market; Hyrdoheptin, an anti-fungal antibiotic

Professional Career – Senior Scientist

Merck – Director of Research

- Avermectin (Ivomec: 2015 Nobel Prize) 1st billion-dollar drug
- Cefoxitin (*Mefoxin*)
- Primaxin (*Imipenem*)

Parke-Davis/W-Lambert – Director of Antibiotics & Chemotherapy

- Pentostatin (*Nipent*)
- Daunorubicin (*Cerubidine*)
- Vidarabine (*Vira-A*)

Professional Career – Entrepreneur & Founder

Fermical, Ferndale, MI

- Designed and developed Bioreactor
- Designed and licensed the Tunair Labware (flasks)
  - Still sold worldwide today
- Developed anticancer drug (Mitomycin)
  - Licensed to Astex Pharma (ASTX)
  - Sold to Otsuka Pharma for $886M

JJ Pharma, San Ramon, CA

- Anti-arthritis drug development

Acea Biotech, San Francisco, CA

- Developed Anti-fungal (Corifungin)
  - Designated orphan drug by FDA

Farmaceutix, Metamora, MI

- Developed hypothesis and platform for anti-Embolic™ drugs
- Developed diagnostic and biomarker "fingerprint" for CVD
  - All IP now wholly owned by Arterez, Inc.

Arterēz™ Diagnostics and Therapies

About Arterez, Inc.

- Arterez, Inc. is a pharmaceutical company developing therapeutics and diagnostics for vascular diseases. Vascular diseases including CVD are of multiple etiology triggered by environment, lifestyle, and drug usage (xeno), herein referred to as xenoplexic diseases. While chronic disease describes symptoms, xenoplexic describes etiology or root cause.
- Arterez' aspires to develop novel therapeutic and diagnostic solutions designed to be predictive, preventive and curative for vascular disease, beginning with cardiovascular disease (CVD), thus transforming the standard of care.
- Xenoplexic diseases starts with glycocalyx (GCX) disruption. GCX is an extracellular matrix that covers body surfaces, lines internal closed cavities, glands, body tubes and the vascular system.
- GCX disruption and shedding signal the onset of diseases and the multicomponent pattern of debris (detritus) shedding is the basis of our proprietary Glycalyx Detritus Fingerprint™ (GDF) technology.
- Moreover, current drug development platforms are based on the classic "one-gene one-enzyme/disease" strategy, usually targeting the downstream manifestation of a dysfunctional enzyme. Invariably, current drugs are symptom targeted, at best palliative and not curative.
- Thus, Arterez rationally synthesized 9 new chemical entities (NCEs) to target the individual upstream causes, then tested these NCEs in 3-NCE combinations.
- Arterez' first oral drug is Embotricin™, a rationally synthesized combo-drug therapy for CVD targeting the multiple upstream root causes of chronic disease, including glycocalyx disruption, oxidation, and inflammation.
- Arterez' first diagnostic is GlycoCardia™, a multiple 7-marker diagnostic surrogate to measure the efficacy of Embotricin™. This product is the first of many thanks to Arterez' evolving diagnostic fingerprint system, the Glycalyx Detritus Fingerprint™ designed to identify and characterize vascular disease.
- To achieve this, Dr. Tunac designed an Arterial Plaque (TAP) mouse model to mimic the natural progression of CVD in humans and demonstrated arterial plaque formation, prevention and reversal through histopathology. Furthermore, plaques had defined fibrous caps, which mimic humans as opposed to superficial cholesterol plaques generated by gene deficient animal models currently used to study arthrosclerosis, commonly known as the APO-e model.

ComboRX – Arterez' therapeutic platform

Development Background

- Pharmacognosy is the exploitation of secondary metabolites found in natural products, including plants, animals, and microorganisms as sources of pharmaceuticals. Plant extracts were effective due the synergistic effect of complex mixtures of molecules (folk medicine).
- The 'one drug-one target' complements the 'one gene-one enzyme' concept of the early 1940s. Thus, identifying a specific enzyme associated in disease ontology and inhibiting its activity is believed to be an effective strategy in drug development. The Human Genome project promised some 30,000 genes as "druggable" targets, then pared down to 3000 targets (about 10% of the genome), but no significant drugs have yet been developed. Thus, finding the target gene for a 'magic-bullet' has proven to be unsuccessful and >90% of disease risks are due to lifestyle and environmental factors while genetic factors only make a minor contribution.
- Environmental exposures and lifestyle modulate gene expression through epigenetic processes. Genes are basic units of heredity and control body functions. Epigenetics control inheritable changes which can be a cellular (stem cell) or molecular (cell division) phenomenon. DNA modifications form during the oxidative removal of 5mC marks which are temporally stable and elicit distinct biological responses. With regard to CVD and other vascular pathophysiologies, epigenetic changes begin with endothelial dysfunction.

Polypharmacology and diseases

- The 'one drug-one target' was adopted assuming that a drug with a specific target would be absent of off-target side-effects. However, a single drug can be promiscuous, interacting with 6-28 targets. Thus, polypharmacology was born almost 25 years ago to exploit the promiscuity of individual drugs, particularly the development of a single drug acting on multiple targets of a disease pathway, or single drug acting on multiple targets pertaining to multiple disease pathways. Cancer exemplifies polypharmacological drug targeting.
- An extension of polypharmacology is 'systems pharmacology' aimed at targeting biological networks rather than single transduction pathways and the products are referred to as multi-target or systems pharmacology drugs. An evolution of systems polypharmacology is precision medicine which tailors medical treatment with medical decisions, treatments, practices, or products to a subgroup of patients, instead of a one-drug-fits-all model. Thus, diagnostic testing is employed to customize appropriate and optimal therapies based on a patient's genetic content or other molecular or cellular analysis, which includes molecular, imaging, and analytics.

Embotricin™ triple compound oral therapy

Multifactorial ontogeny of CVD

The paradigm for this project begins with disruption of the endothelial glycocalyx that exposes cell membrane to injury creating tiny holes for entry of blood debris leading to plaque formation. This process involves shedding of one or more of its components into the blood. The disrupted components can be restored or rebuilt to its native hydrodynamic thickness within 5 - 7 days, thus the objective is to restore AEG integrity along with treating the associated factors of oxidation and inflammation, which lead to fatal thromboembolism (clotting). In this regard, we constructed a thromboembolic cascade and identified 5 'druggable' targets. Arterez has since developed a 3-combination drug treatment (Embotricin™), which showed curative and preventive effect in pre-clinical models using plaque formation as the primary endpoint.

Development Process

- Based on experience in drug development, we identified substances naturally found or tolerated in the body (mitigates toxicity) with therapeutic activities and used them as building blocks for new chemical entities (NCEs).
- We then rationally 'mixed and matched' to 'synergize their active cores' to enhance activity against chosen targets. Of about 30 combinations, 9 were successfully synthesized per good laboratory practice (GLP) and characterized. These 9 NCEs designated as FTX-compounds, are our drug portfolio to be further developed mimicking polypharmacology as a paradigm to treat CVD and in time, other chronic diseases.
- There is no animal model that represents glycocalyx disruption in relation to CVD. To evaluate FTX drug leads, we developed a natural mouse model that mimics CVD and the thromboembolic cascade. This involves feeding mice with a high fat diet and exposure to a biological and chemical agent like polychlorinated biphenyl (PCB), which resulted in a mouse that produced well-formed subendothelial plaques.
- The complex nature of thromboembolism informed our proprietary approach to administer the FTX-drugs as polypharmacology or combo drugs, administered as a fixed dose. In this regard, we designed several 3-drug combinations and tested them. To maintain objectivity, the protocol was designed by Dr. J. B Tunac and the experiment carried out at Wichita State University, Wichita Kansas, c/o Dr. Paul Wooley and an experienced staff with a preclinical histopathology facility.

Embotricin™ triple compound oral therapy

- Individual compounds showed activity yet were much more pronounced in combination. Results show a range of activities from curative to curative/preventive. For our first drug candidate, we chose the curative/preventive combo drug containing 3 NCEs (FTX-214, -218, and -219) formulated as fixed 1:1:1 ratio with an effective dose of 3.0 mg/kg.
- The activity of the FTX compounds were evaluated by plaque production or reduction per histopathology. Since the mouse coronaries are too small, we focused on histopathology in the brachiocephalic artery, which showed no plaques in the drug treated mouse, while plaques found in the untreated control
- Histopathology is an impractical endpoint in humans. For this reason, we correlated histopathology with a set of biomarkers. These include hyaluronan, heparan SO4, syndecan-1 and plasminogen activator inhibitor 1, a biomarker for clotting. Indeed, glycocalyx component shedding and clotting correlated with plaque formation. Embotricin™ reduced the levels of these biomarkers in the blood, reflecting its curative and preventive effect.

Correlating MRI, histopathology, and biomarkers

Cardiac MRI offers radiation-free arterial imaging to detect stenosis, plaque burden and high-risk plaques. High-risk plaques in the carotid arteries predict stroke and heart attack in the coronaries. CVD is a complex disease thus a combination of histopathology, biomarkers, and in patient-level interactive MRI can best identify vulnerable patients. While MRI is developed in humans, corresponding techniques are lacking in mouse models because of the small tortuous arteries, 3-dimensional branches and rapid movement during the cardiac and breathing cycles. In this regard, we are evaluating our arterial plaque mouse model employing contrast agents including; paramagnetic gadolinium (Gd)-based agents and, superparamagnetic iron-oxide nanoparticles with excellent results.

Arterez arterial plaque model applicable for heart failure (HF)

Heart failure (HF) aka: congestive heart failure (CHF) is a condition in which the heart cannot pump efficiently enough to meet the body's need for blood. Heart failure (HF) is a chronic, complex condition with increasing incidence worldwide, necessitating the development of novel therapeutic strategies. Coronary plaques are known risk factors for CHD by stiffened artery and diastolic dysfunction due to peripheral artery disease (PAD) often resulting in heart failure. Ventricles are primary origin of HF: left ventricle pumps oxygenated blood while right pumps deoxygenated blood to the lungs. In this regard, disrupted glycocalyx trigger coronary plaques, which contribute to myocyte stiffness and reduced ejection fraction volume particularly in the left ventricle.

Embotricin™ triple compound oral therapy

High fat diet and pollutant reduce ejection fraction (EF) using MRI

Most mouse models used to model HF are surgically or genetically altered. Since the Arterez' TAP arterial plaque mouse models AEG disruption and plaque formation (ergo stiffening of heart myocytes), we evaluated this model for ventricular ejection fraction volume. In this regard, the MRI (c/o Dr. Robert Knight, Henry Ford Health System) was used to measure ejection fraction. Briefly, the heart is aligned to the proper orientation then an intra-gate scan is carried out for a CINE presentation (motion sensitive MRI in which a series of static images are obtained at various stages of the cardiac cycle and then played back). The black blood method (blood appears darker than the adjacent tissue) was used. The CINE sequence and software auto detected end diastole/end systole and calculated percent ejection fraction (EF), heart rate (HR) and respiratory rate (RR). This method showed the most reduced EF in the Arterez mouse model. Next is to test Embotricin™ vs HF. Treatment rationale: Embotricin™ restores healthy heart pumping by restoring glycocalyx integrity, eliminating 'tiny' endothelial gaps and debris infiltration (plaque). Thus, by inference restoration of ejection fraction volume equates to plaque elimination.

Embotricin™ cured Corona Virus in pre-clinical studies

Disruption of the glycocalyx is the main entry for the covid-19 virus, akin to the onset of CVD due to glycocalyx disruption. In this regard Embotricin was evaluated vs coronavirus, which was carried out by the Institute for Antiviral Research, Utah State University in Logan, Utah. Briefly, 5-week-old female BALB/C mice were infected with the Severe Acute Respiratory Syndrome-Associated Coronavirus (SARS-CoV-1) Urbani strain and was challenged with Embotricin™. Result: lung viral load ((Log10 /ml) for Embotricin™ ~ was reduced by 17-21% compared to 12% of the control drug Poly (I:C).

This is further proof-of-principle that restoring the integrity of the cell is also a curative approach against infection.

Embotricin™ is non-toxic.

Preliminary toxicology vs mouse of the Embotricin™ components were carried out by Molecular Diagnostic Services. This preliminary tox study indicates that the individual components were non-toxic with an effective dose of 3.0 mg/kg and maximum tolerated dose of ~1,000 mg/kg.

GlycoTRX – Arterez' diagnostic platform

The endothelial glycocalyx (GCX) and disease

As discussed earlier, the GCX is an extracellular matrix that covers the luminal surface of the vascular system. It is a slippery protective coat that lines the endothelium and contains anchoring proteoglycans and members of the syndecan protein family as well as connecting glycosaminoglycans such as heparan sulfate, chondroitin sulfate and hyaluronic acid. Under conditions of oxidation and inflammation, the glycocalyx begins to break down, releasing detritus components, leading to endothelial damage and a cascade of pathological conditions. For example, the release of microparticles, detachment of the pericytes and circulating endothelial cells (CEC); increase in CECs precedes that of established tissue-damage markers like troponins or creatine kinase. CECs counts are extremely low in healthy individual but elevated in patients with diabetic nephropathy (DN), heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), and arterial hypertension (aHT).

Disruption of glycocalyx triggers epithelial and vascular diseases including CVD

The GCX structure is not just a barrier for vascular permeability but contributes to various functions including signal sensing and transmission to the endothelium. Thus, pathological changes to this structure are involved in the development of various diseases.

Detritus parameter - 2012

Dr. J. B. Tunac (US) introduced glycocalyx detritus *(worn off glycocalyx fragments)* as components for a biological fingerprint. Currently, there is no fingerprint system developed for diseases. Thus, the glycocalyx detritus shedding pattern becomes the equivalent to the physical patterns found on fingertips or the nucleotide microsatellite pattern found in DNA bands. The classic fingertip pattern and DNA microsatellite pattern do not diagnose diseases but are used to identify individual humans in forensics or paternity cases. On the other hand, glycocalyx detritus pattern is the first in kind to diagnose diseases, which we believe will bring a new dawn in healthcare. A fingerprinting system for diseases not only increases the accuracy of disease diagnosis but allows for disease identification, classification and staging serving as guide and aide for improved therapies targeting the root causes of vascular disease. Further, hundreds of recent reviews supporting glycocalyx disruption as the root cause of several pathologies and as a basis for diagnostics and therapeutic targets confirms Dr. Tunac's original hypothesis.

GlycoCardia™ therapeutic aide

Preclinical proof of principle: 4-panel glycocalyx detritus

Coronary heart disease (CHD) is a member of the cardiovascular family (CVD) and the leading CVD killer. The characteristic feature of CHD is plaque formation, which results in atherosclerosis or hardening of the arteries. Plaque formation is triggered by glycocalyx disruption and the shedding of glycocalyx detritus, thus the basis for developing a therapeutic aide or companion diagnostic for Embotricin or any drug targeting the endothelial glycocalyx among other multi-factorial root causes.

- Plaque formation is central to CVD and sans histopathology, a diagnostic system is needed to follow plaque formation. Plaque formation is a complex process and there is no single biomarker known to monitor this event. Thus, a panel of biomarkers was conceived.
- The utility of Glycocardia™ was highlighted during the development of Embotricin™ by initially evaluating 4 glycocalyx detritus biomarkers, each clinically confirmed to correlate to vascular disease as a surrogate to monitor drug effect. Untreated mice (no drug compound) were set aside as a control, which showed elevated ELISA blood levels in each of the detritus markers and reduced level corresponding to efficacy of the drug compound.

Clinical proof of principle: 5-panel glycocalyx detritus

Cardiac troponin (cTn), proteins found in skeletal and heart muscle fibers is the most common diagnostic tool in the emergency room (ER). The test is ordered if a person is experiencing possible symptoms such as chest pain (angina), shortness of breath (heart failure), and hypertension (rapid heart rate, lightheadedness, fatigue). Even with the widespread use of cTn assays worldwide, there remains some confusion among clinicians and laboratorians about the timing, frequency, and duration for measuring cTn after patients present with symptoms suggestive of acute coronary syndrome (ACS) highlighting the discrepancy and inherent flaw of single biomarkers. For this reason, blood samples of patients identified with CVD; chest pain [CHD], heart failure [HF] and hypertension [HTN] were collected and tested against an expanded 5-marker panel. Blood levels of these 5 detritus were evaluated by ELISA.

- The levels of the 5 detritus were elevated in each of the diseases. More importantly, each disease produced a unique pattern indicating the potential of establishing a “fingerprint” system for CVD and subsequently other vascular diseases.

GlycoCardia™ therapeutic aide

Clinical proof of principle: 7-panel glycocalyx detritus

To expand the concept of 'fingerprinting' as a diagnostic platform across chronic diseases, with the early focus on development of a diagnostic surrogate to monitor efficacy of Embotricin™, Arterez then developed a 7-detritus biomarker diagnostic panel.

- Blood (IRB) samples were drawn from patients clinically identified with chronic diseases, including; coronary heart disease, heart failure, rheumatoid arthritis, stroke, hypertension, diabetes 2 and alzheimers disease along with a healthy control. These blood samples were analyzed by ELISA for levels of detritus biomarkers. This pilot study proved to be effective in creating distinct patterns or fingerprints of the different family members of CVD tested as well as other associated diseases tested.
- GlycoCardia™ will be developed as a multi-well diagnostic kit to simultaneously measure multiple analytes in a single experiment to enable and accelerate development of proprietary disease algorithms using AI and machine learning for analysis.
- The same 7-detritus panel used as a surrogate diagnostic "fingerprint" to monitor efficacy of targeted treatments can be used as an analytical tool to diagnose and characterize vascular diseases as well (discussed in the next section).

Glycalyx Detritus Fingerprint™ (GDF)

Utility of a fingerprint platform

In perspective, GDF is comprised of biological materials like the biological nature of DNA. In DNA fingerprinting, fragments of DNA are separated on a gel using a technique called electrophoresis while GDF involves analysis and quantitation of gycocalyx detritus shed in the blood stream per ELISA. The usefulness of each diagnostic system depends on a robust library of fingerprints for comparison with unknown samples.

Early onset diagnosis

While developing GlycoCardia™, a therapeutic aide for Embotricin™, the data also proved to be effective in creating distinct patterns or fingerprints of the different family members of CVD tested among other chronic diseases tested. While GlycoCardia™ is our first focus for clinical evaluation of our first therapy, the opportunity to develop the Glycocalyx Detritus Fingerprint™ (GDF) technology for the diagnosis of vascular disease is quite clear. If a disease is detected early when there is no severe damage to the organs, it will be easier to treat. Currently, there is no practical or feasible way of monitoring vascular disease that we now know and can demonstrate begins with disruption to the endothelial glycocalyx and subsequent cascade.

GDF as a viable fingerprint across chronic disease spectrum

Each disease we piloted showed a unique 'fingerprint', which confirms the effectiveness of the GDF as a tool for diagnosing a wide spectrum of chronic diseases. Indeed, while the biomarkers are detected at any stage of the disease cycle and have been used individually or as single markers in the clinic with limited success, there is a sequential rationale for the shedding of these biomarkers, disease is a dynamic process, and a mixture of these biomarkers are present in the milieu at any given time reflecting the stage of the disease or type of disease. In additon, healthy normal shedding of cells releases background levels of detritus, which and if taken individually could be misconstrued to be associated to a certain disease.

As the data set expands within the Arterez Disease Repository database, this will contain various stages of diseases within each person, as a reference to properly identify, diagnose, and treat multiple chronic diseases.

Intellectual Properties

Issued 2019 – US 9,867,842 B2

Methods and Compositions for Reversing Disruption of the Glycocalyx, Inflammation and Oxidative Damage.

Pending – ARTZP003PUS

Drug Treatment and Biomarker Panel Targeted to Diseases due to Multifactorial Ontology of Glycocalyx Disruption

Pending – PCT/US2016/015015

Biomarkers of Vascular Disease

Pending - International PCT

Filed November 2020

- The U.S. Patent Office as the International Searching Authority (ISA) has recently determined that the application contains multiple inventions.

Proprietary draft in process

Natural Arterial Plaque Mouse Model

Issued Trademarks

- Arterez™
- GlycoCardia™
- Embotricin™

Applications in process

- 'Glycalyx Detritus Fingerprint
- Anti-Embolics
- Xenoplexic disease

Available for download: https://www.arterez.com/investors

Arterēz™ Diagnostics and Therapies

Timeline, initial exit and platform expansion

2012-2017

2012
- Dr. J.B. Tunac launches Farmaceutix, LLC (FTX)
- R&D for anti-embolic™ markers & compounds*

2013
- Surrogate markers identified for Development/testing of compounds
- Developed natural arterial plaque mouse model

2014
- Rationally synthesized 9 synthetic compounds
- 3x combo proved to prevent & reverse arterial plaques

2015
- Proved non-toxic up to 20x effective dose
- Engaged firm to assist with Platform development and funding

2016
- New studies launched for Natural model, biomarkers
- Compounds/methods, biomarker patent filed

2017
- FTX acquires control & rights to all intellectual properties
- Patents amended, audit completed, development pathway established

2018-2023

2018
- Arterez launched, FTX IP assigned, team developed
- Website built, new IP filed & issued, providers engaged

2019
- Seed raise, biomarkers added, ELISA & HFHS** studies engaged
- Glycalyx Detritus Fingerprint™ and natural model validated

2020
- 7 disease IRB pilot study, NCE's manufactured to GLP
- ELISA, pre-clinical studies, GAP analysis, planning

2021
- Regulatory dev, $10M capital raise, Pre-IND, GLP scale-up
- Formulation (individual & combo), chronic toxicology, assemble board

2022
- $15M raise, Ph 1 healthy, IND submission, multiplex kit
- IND/Safety approved, choose CRO Investigators, recruit

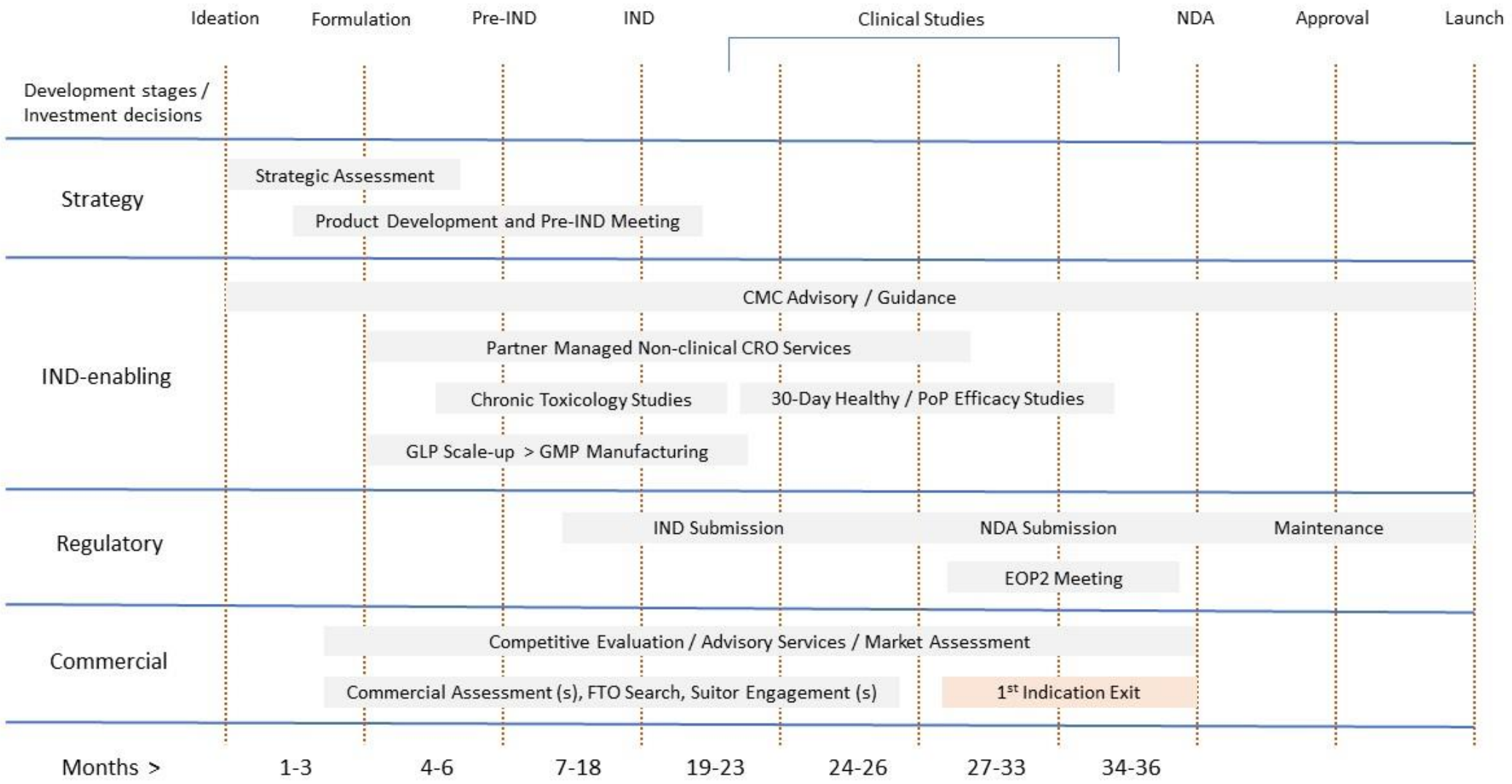
2023
- Complete/continue efficacy studies Consider first indication exit
- IPO to expand platform development vs multiple vascular diseases

*4 surrogate markers identified, 9 compounds designed and rationally synthesized to target multi-factorial root causes of CVD – also proved interesting for other vascular pathophysiologies.

**University Research Study – 7 marker ELISA 32 patients vs HF, HTN, Chest Pain*
***Henry Ford Health Systems (HFHS) MRI translational studies using TAP model.*

Arterēz™ Diagnostics and Therapies

Embotricin™ Development to 1st Exit Gantt



Arterēz™ Diagnostics and Therapies

Clinical strategy; IND and Proof of Principle

Clinical Trials and Regulatory/Business Strategies

At a high level, the novel diagnostic and therapeutic approach that Arterez is pioneering may result in dramatic change in the clinical approach to prevention and therapy of cardiovascular diseases. This has been recognized by scientists worldwide. However finding the correct balance between this goal and what will be efficient and achievable is a dynamic process and ongoing discussion. Our approach is to continue to accrue data, consider all inputs, including from the FDA and EMA to determine our optimal clinical approach while maximizing value and enabling the evolution of the platform.

Concurrent Clinical IND & Proof of Principle Studies

Arterez plans to conduct three in-human efficacy studies concurrently. One will be conducted within the FDA/IND process with defined end-points, while the other two will be proof of principle IRB initiated studies or conducted out of country. Arterez has identified and investigated the clinical pathway in Australia while other countries remain under consideration.

IRB-initiated add/or /FDA IND clinical evaluation of Embotricin™ vs patients with pulmonary hypertension

Projected outcome "Embotricin™ improves HTN in patients, monitored by GlycoCardia^{HT}

IRB-initiated or out of country proof-of-principle clinical evaluation of Embotricin™ vs patients with heart failure

Systolic dysfunction (SD, HFrEF) or diastolic dysfunction (DD, HFpEF)

Compare "GlycoCardia ^{CVD} vs echocardiogram (Doppler) and cardiac magnetic resonance (CMR)

Projected outcome "Embotricin™ improves ventricular ejection fraction, monitored by GlycoCardia^{HF}

IRB-initiated or out of country proof-of-principle clinical evaluation of Embotricin™ vs patients with coronary artery disease

Compare GlycoCardia ^{CVD} vs arteriographic imaging techniques, e.g.,CCTA (coronary computed tomography angiography), MRA (magnetic resonance angiography) or MRI (magnetic resonance imaging)

Projected outcome "Embotricin™ reduces plaque in CHD patients, monitored by GlycoCardia^{CHD}

Arterēz™ Diagnostics and Therapies

THANK YOU FOR
YOUR CONSIDERATION

www.Arterez.com