Corporate Overview

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Rubicon Biotechnology

- Established as a three member California LLC in 2012
- An early stage drug development company located in Orange County, CA
- Two drug technologies currently in-licensed:
  - Fv-Hsp70: Exclusive VA License
  - Modified Annexin Cancer Immunotherapeutic: Exclusive MosaMedix BV License
- Collaborations with leading research and development institutions:
  - UCLA, Mount Sinai Medical Center, UCI, Vanderbilt University, MRI Global, Maastricht University, Syngene International

Mission Statement

To develop novel bio-therapeutics for substantial and practical impact in cardiovascular disease and oncology, and to create high value drug candidates ready for entry into Phase III clinical trials

Rubicon Leadership

Mr. Richard Richieri COO, Process, MFG and CMC	**UCLA 1988 – Chemical Engineering; UCSD 1993 – Masters in Chemical Engineering** • **Process expert with 25 years of experience in biologics development and GMP Manufacturing** • **Consultant to major multi-nationals in technical operations** • **Continues to publish and lecture on bioprocess trends, including disposable bioreactor systems**
Dr. Missag Parseghian CSO, Protein Scientist	**UCLA 1987 – Biology; UCI 1993 – PhD in Molecular Biology and Biochemistry;** **UCI 1993 – 1997 Post-Doctoral Research in Chromatin and Epigenetics** • **Protein expert with 15 years as a biotech executive and R&D Director** • **Established and led the Analytical Methods Department and the Scientific Affairs Department** • **Author of numerous research articles and patent applications**
Dr. Glenn Reynolds CMO, Interventional Cardiologist	**Yale 1978 – Biology; Harvard 1980 – Graduate Biology;** **Boston University 1987 – MD; UCI 1987 – 1991 Internal Medicine;** **UCLA 1991 – 1994 Cardiology; Arizona Heart Institute 1994-1995 – Interventional Cardiology** • **Medical expert with over 20 years as a practicing interventional cardiologist** • **Principal sub-investigator and co-author for the EPIC trial of abciximab (ReoPro)** • **Participant and co-author in clinical research on several cardiovascular surgical techniques** • **Experience in the use of a novel stent graft in severely diseased vein grafts to coronary arteries** • **Implemented new surgical techniques related to pacemaker implantation**

Rubicon's Technologies

At present, we have in-licensed two platform technologies:

1. Fv-Hsp70 from the Department of Veterans Affairs
2. Modified Annexin from MosaMedix B.V.

Fv-Hsp70 is a powerful targeted cytoprotectant which can directly deliver Hsp70 into stressed and dying cells in order to salvage them from death. Our primary indication is myocardial infarction and we believe Fv-Hsp70 will help reduce cellular damage to the heart, thereby improving heart function and reducing morbidity. Other indications include acute lung injury and stroke.

Our Modified Annexin program uses Annexin A5, a natural high-affinity phosphatidylserine (PS)-binding protein discovered by Dr. Chris Reutelingsperger at Maastricht University. Dr. Reutelingsperger modified the annexin so that it will not internalize into the cell, which is the normal physiological response for annexin binding to PS. Phosphatidylserine is exposed on the surface of solid tumors and their blood vessels within the tumor microenvironment, but not on healthy cells. Rubicon's Modified Annexin is able to deliver powerful anti-cancer compounds to a common target found on the surface of tumors and tumor vasculature. Our Modified Annexin Program is undergoing *in vitro* and *in vivo* animal studies for breast cancer, melanoma and metastatic cancer and other solid tumors.

Rubicon's Operational Strategy

Operationally, Rubicon's strategy is to maintain a small internal core team to manage and approve various QA, regulatory and technical tasks with our vetted network of CROs, CMOs and consultants. We will oversee the strategic and day-to-day challenges ahead; all in accordance with regulatory guidelines. Our internal capabilities are complemented by an outstanding group of scientific advisors located in North America and Europe.

We will manage the cGMP production of our clinical candidates at our CMO and will review and approve the analytical testing and clinical protocols. Our goal is to ensure that our external resources are organized and working together to produce a harmonized process.

Our objective is to have a complete program package (intellectual property, GMP supply chain, regulatory documents, etc.) available to potential partners that would meet the high expectations of suitable licensees.

Rubicon's Collaborators

National Institutes of Health
MosaMedix N.V
Maastricht University
Mount Sinai Medical Center
MRI Global
National Cancer Institute
National Heart Lung and Blood Institute
Seacoast Science, Inc.
University of California, Irvine
University of California Los Angeles
Vanderbilt University
Department of Veterans Affairs
Syngene International

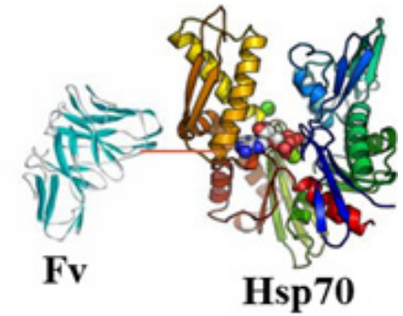
With a strong, experienced core team and world class collaborators, Rubicon is well positioned to develop our two leading-edge platform technologies

TECHNOLOGY SUMMARY

Fv-Hsp70 Program

Fv-Hsp70: Rubicon's Solution to Acute Injuries

Rubicon's Solution: Fv-Hsp70 will target and deliver Hsp72 in therapeutic quantities directly into damaged cells to prevent apoptosis (programmed cell death following cellular injury).



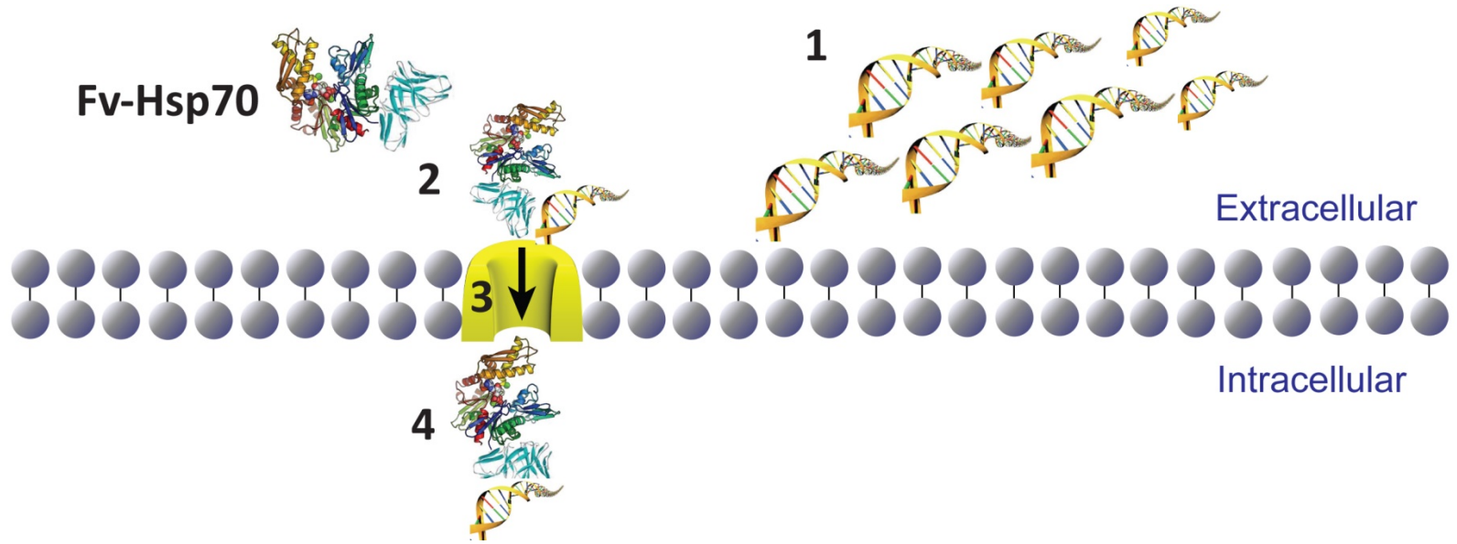
Created at UCLA/VA, Rubicon's clinical candidate, **Fv-Hsp70** is a recombinant fusion protein consisting of a targeting molecule (Fv) linked to an effector (Heat Shock Protein 72; Hsp72). The Fv is a single chain fragment from the 3E10 monoclonal antibody, which targets injured cells specifically. Hsp72 is a critical cellular protein which protects and refolds other proteins.

Fv-Hsp70 can be recombinantly produced at large scale using conventional industrial techniques. The Fv moiety is an antibody fragment that specifically targets the endogenous DNA that is released from cells. The Hsp72 is a "heat shock protein" which helps with the proper folding of new proteins during their synthesis. However, Hsp72 has multiple other roles including, during cell stress, Hsp72 binds to critical proteins that are damaged and become misfolded. It binds to these critical proteins and protects them from aggregation and cellular destruction, thereby inhibiting these processes. Hsp72 also has a dual role binding and inhibiting the activities of several key proteins involved in multiple apoptotic pathways; hence, the increased presence of this protein in a dying cell may rescue its viability.

The protective effects of endogenously produced heat shock protein Hsp72 are well known. Unfortunately, more than 3 hours are required by our cells to initiate production of the endogenous protein, and peak production does not occur until 72 hours after induction. Following a heart attack, stroke or other acute assaults, time is of the essence, as cell damage begins immediately. Our technology will deliver therapeutic amounts of Hsp72 directly into the stressed and damaged cells immediately. Our NIH supported studies, executed at Mount Sinai Medical Center in NYC, have proven Fv-Hsp70 administration will preserve myocardium in a rabbit model of left coronary artery ischemia-reperfusion injury. Furthermore, NIH supported studies have also shown Fv-Hsp70's effectiveness in stroke and acute lung injury.

Fv-Hsp70 Mechanism of Action

(1) There is an abundant exogenous pool of DNA in areas of cell damage e.g. from an infarction or other acute assaults. Fv-Hsp70 binds to the DNA (2) and is transported into stressed cells via the ENT2 channel (3). (4) Once internalized in the cell, the Hsp72 then carries out cell salvage activities by binding to critical proteins that are misfolded and helps the cell avoid apoptosis.



Fv-Hsp70's ability to directly deliver Hsp72 into cells has advantages over small-molecule strategies designed to induce Hsp72 synthesis. For a small molecule approach, the need to evaluate unintended induction of other genes is critical. Add to that complication, induction of Hsp72 synthesis with a small molecule during cell stress requires a significant lag time to take effect, limiting its usefulness as a therapeutic agent. Some inducers require lag times varying from 8 to 24 hours in *in vivo* models, depending on the organ being targeted. Furthermore, induction of Hsp72 is attenuated with aging, dampening the effectiveness of the small molecule strategy in older individuals.

Fv-Hsp70: Proof of Concept Data Summary

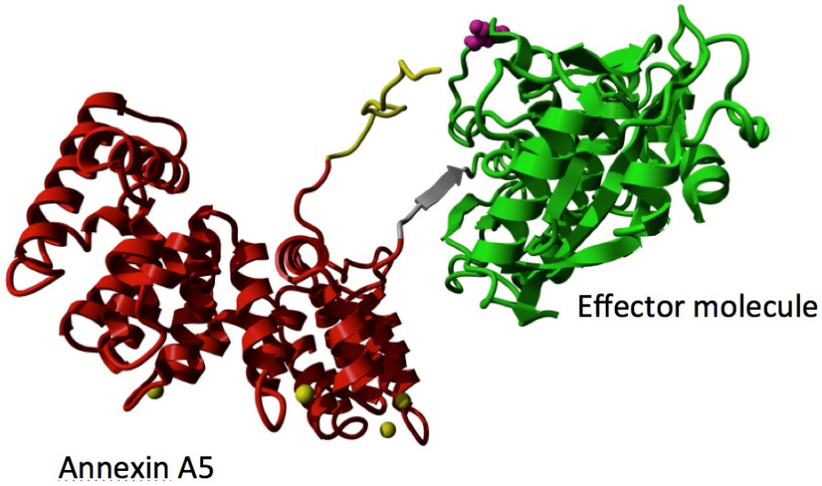
- Compelling animal data is already obtained in heart attack, stroke and acute lung injury models
  - Myocardial Infarction
    - **43%** less cellular damage as assessed by SPECT in the Apex and Area-at-Risk
    - **27%** higher Ejection Fraction (a measure of heart function)
    - **42%** lower levels of Troponin I (a blood marker indicating heart damage)
  - Acute Ischemic Stroke
    - **68%** less infarct volume in Fv-Hsp70 treated animals
    - **5-fold** improvement of motor skills in Fv-Hsp70 treated animals
    - Fv-Hsp70 shown to enter ischemic brain but not the normal brain
  - Acute Lung Injury
    - **3-fold** improvement in survival in Fv-Hsp70 treated animals following phosgene gas exposure
    - Reduced pulmonary congestion, hemorrhage and red mottling
    - Reduced oxidative stress and protein carbonylation

Modified Annexin Program

Modified Annexin for Immunotherapy

Rubicon's Modified Annexin technology will trigger an immunostimulatory response against a tumor by directly binding phosphatidylserine (PS) exposed on the surface of tumor cells and the tumor vasculature.

A myriad of academic studies have demonstrated that cell surface PS can be selectively targeted in the tumor microenvironment.



Anionic phospholipids, like PS, are largely absent from the surface of resting mammalian cells under normal conditions but are prevalent on the surface of living tumor cells and on tumor vasculature. This selective exposure of PS in the tumor microenvironment provides the opportunity to exploit it as a target for the delivery of cancer therapeutics.

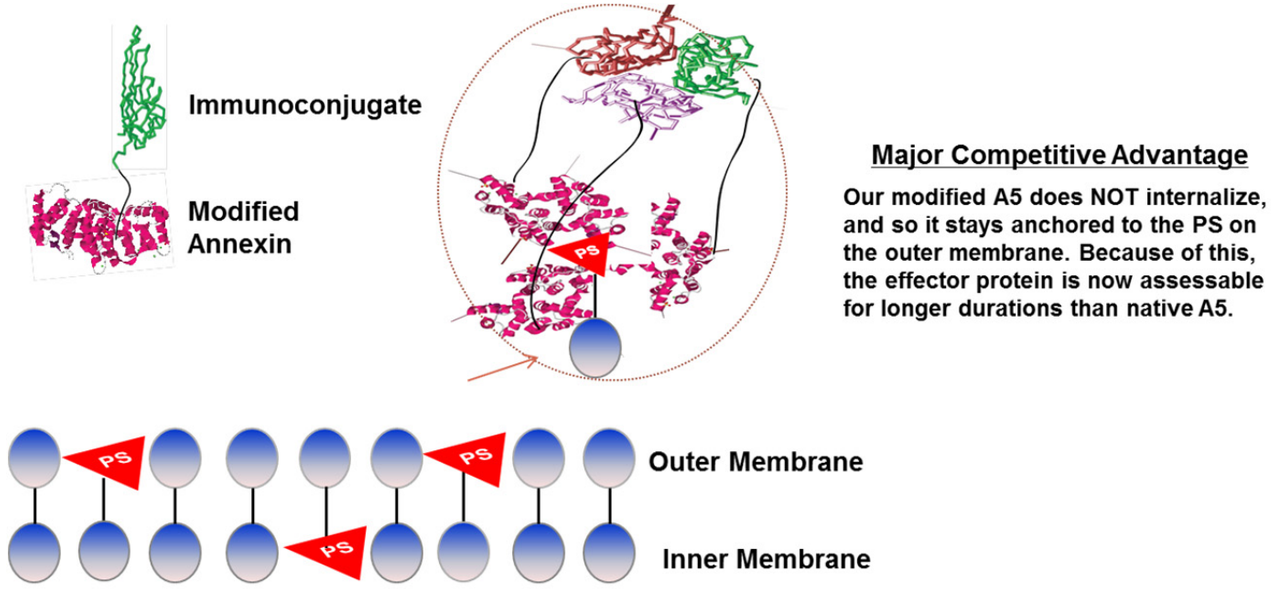
Tumors avoid a full immunological assault by manipulating key "checkpoints" designed to prevent auto-immune disease. Blockading these "checkpoints" has included development and FDA-approval of ipilimumab, an antibody targeting CTLA-4 to inhibit downregulation of T-cell activation. It has also included development of antibodies to disrupt the PD-1/PD-L1 ligand -receptor complex. Yet, these therapies localize not only to tumors but to the general immune system. Cell surface exposure of PS within the tumor environment creates an immunosuppressive checkpoint localized to the tumor so targeting it should be less disruptive to a patient's overall immune system.

The key to specific PS targeting in the tumor microenvironment is to create a reagent that binds specifically and directly to PS. Arming such a PS-specific binding molecule with immuno-stimulatory activity offers a uniquely effective strategy to direct the patient's immune system to the neoplasia.

Our approach uses a Modified Annexin A5 (a.k.a. Annexin V), a protein with an extremely high affinity to PS. Annexin A5 was first discovered by Dr. Chris Reutelingsperger, who has been studying the molecule for 3 decades and has been developing it as an imaging agent in the clinic.

Modified Annexin Mechanism of Action

Rubicon's Modified Annexin Immunotherapy will target a stable, non-shedding target on tumors and tumor vasculature. Our approach uses Annexin A5, a natural high-affinity phosphatidylserine (PS)-binding protein discovered by Dr. Chris Reutelingsperger at Maastricht University. Typically, the problem with molecules binding to phosphatidylserine is that the agent, once bound to PS, can be internalized into the cell, which neutralizes its effectiveness. Dr. Reutelingsperger modified the annexin so that it will not internalize into cells, preventing this problem. PS is exposed on the outer membrane on many different tumor types but not on healthy cells. Rubicon's Modified Annexin is able to deliver powerful immunotherapy compounds to a common target found on the surface of tumors and tumor vasculature.



Modified Annexin Program Status

Rubicon was awarded a grant from the National Cancer Institute (NCI) to study our Modified Annexin technology in a breast cancer animal model. The study is being performed at Vanderbilt University Medical Center under the direction of Dr. Andries Zjilstra, Assistant Professor in the Department of Cancer Biology and the Department of Pathology, Microbiology, and Immunology.

In this proof-of-concept study, balb/c mice were injected with breast cancer cells and the resulting tumor was allowed to grow aggressively. Once the tumor reached a pre-determined size, then the animals was injected with (1) Modified Annexin by itself, (2) Modified Annexin linked to Effector Protein #1, (3) Modified Annexin linked to Effector Protein #2. PBS or saline was used as a control. Experiments were performed using either a single dose or a multiple dose regimen. The tumor size was measured post injection to determine efficacy.

In addition, the Modified Annexin technology was evaluated in melanoma and metastatic breast cancer animal models.

Modified Annexin is also being studied in several *in vitro* tumor cell lines.

Once the proof-of concept data set is completed, then we will determine which effector protein and which indication should be our clinical focus.

Rubicon Summary

- Lead technology, Fv-Hsp70, is ready for clinical development for myocardial infarction
- Fv-Hsp70 is a unique technology to salvage tissue after myocardial infarction
- Myocardial infarction represents a large worldwide market
- Secondary indications for Fv-Hsp70 are also significant value drivers
- Additional non-dilutive funding from NIH, NCI and Defense Countermeasures grants will augment value
- Our second technology under development, Modified Annexin Immunotherapy, is expected to increase company value, given promising preliminary data
- Validation of the Fv-Hsp70 technology is established by publications in major peer-reviewed journals
- Validation of the Fv / 3E10 mechanism of action is evidenced by substantial funding of other biotechnology companies
- Core team and organizational structure in place has demonstrated successful execution in a short time with limited funds
- Detailed clinical development plan for Fv-Hsp70 for myocardial infarction is prepared and ready for execution upon funding

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