
# Resverlogix Corp.

## Corporate Update

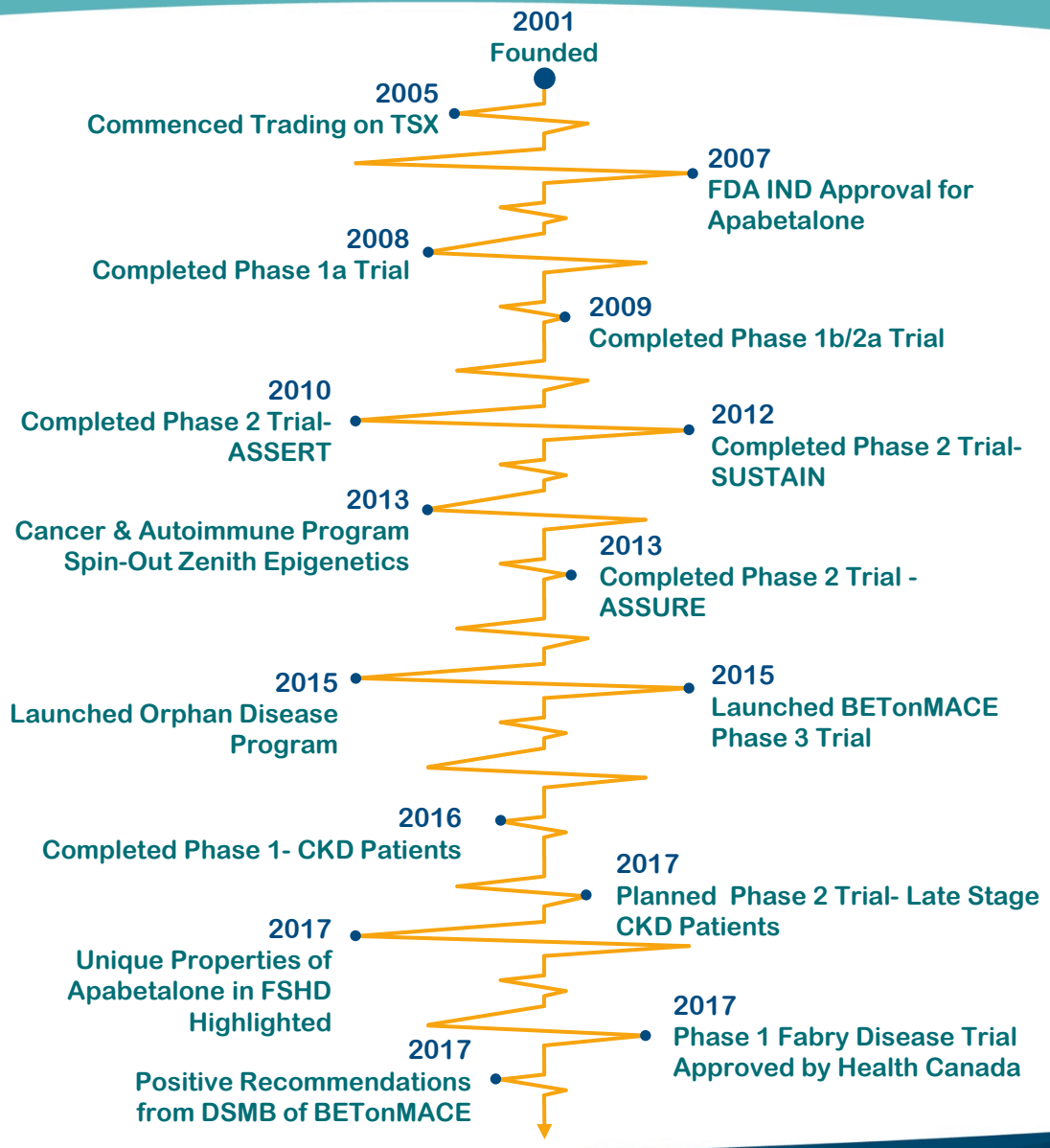
May, 2018 Calgary, AB & San Francisco, CA

# Forward Looking Statements

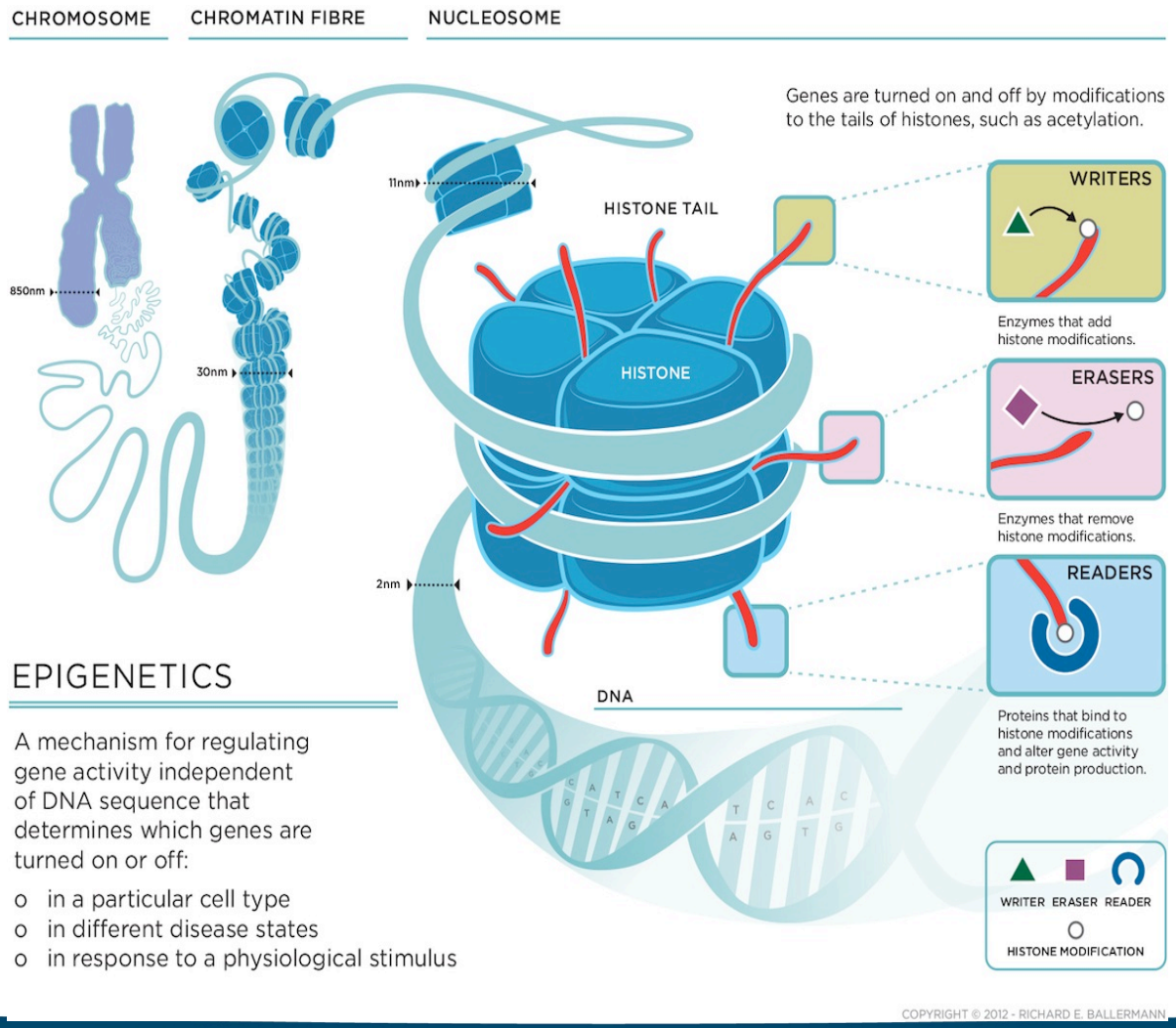
This presentation may contain certain forward-looking information as defined under applicable Canadian securities legislation, that are not based on historical fact, including without limitation statements containing the words "believes", "anticipates", "plans", "intends", "will", "should", "expects", "continue", "estimate", "forecasts" and other similar expressions. In particular, this presentation includes forward looking information relating to the Company's clinical trials and the potential role of apabetalone in the treatment of CVD, DM, chronic kidney disease, Orphan diseases, and peripheral artery disease. Our actual results, events or developments could be materially different from those expressed or implied by these forward-looking statements. We can give no assurance that any of the events or expectations will occur or be realized. By their nature, forward-looking statements are subject to numerous assumptions and risk factors including those discussed in our Annual Information Form and most recent MD&A which are incorporated herein by reference and are available through SEDAR at www.sedar.com. The forward-looking statements contained in this presentation are expressly qualified by this cautionary statement and are made as of the date hereof. The Company disclaims any intention and has no obligation or responsibility, except as required by law, to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

# About Resverlogix

- Resverlogix Corp. (TSX:RVX) is a Calgary and San Francisco based clinical stage biotechnology company focused on the development of apabetalone
- Apabetalone (RVX-208) is a first-in-class small molecule selective BET bromodomain inhibitor, which acts via an epigenetic mechanism that can turn disease-causing genes off, returning them to a quiescent state
- Apabetalone was the only selective BET bromodomain inhibitor in clinical trials for the past 10 years
  - Discovered & synthesized in 2006
  - Selected using a cell based screen for Apolipoprotein A-I

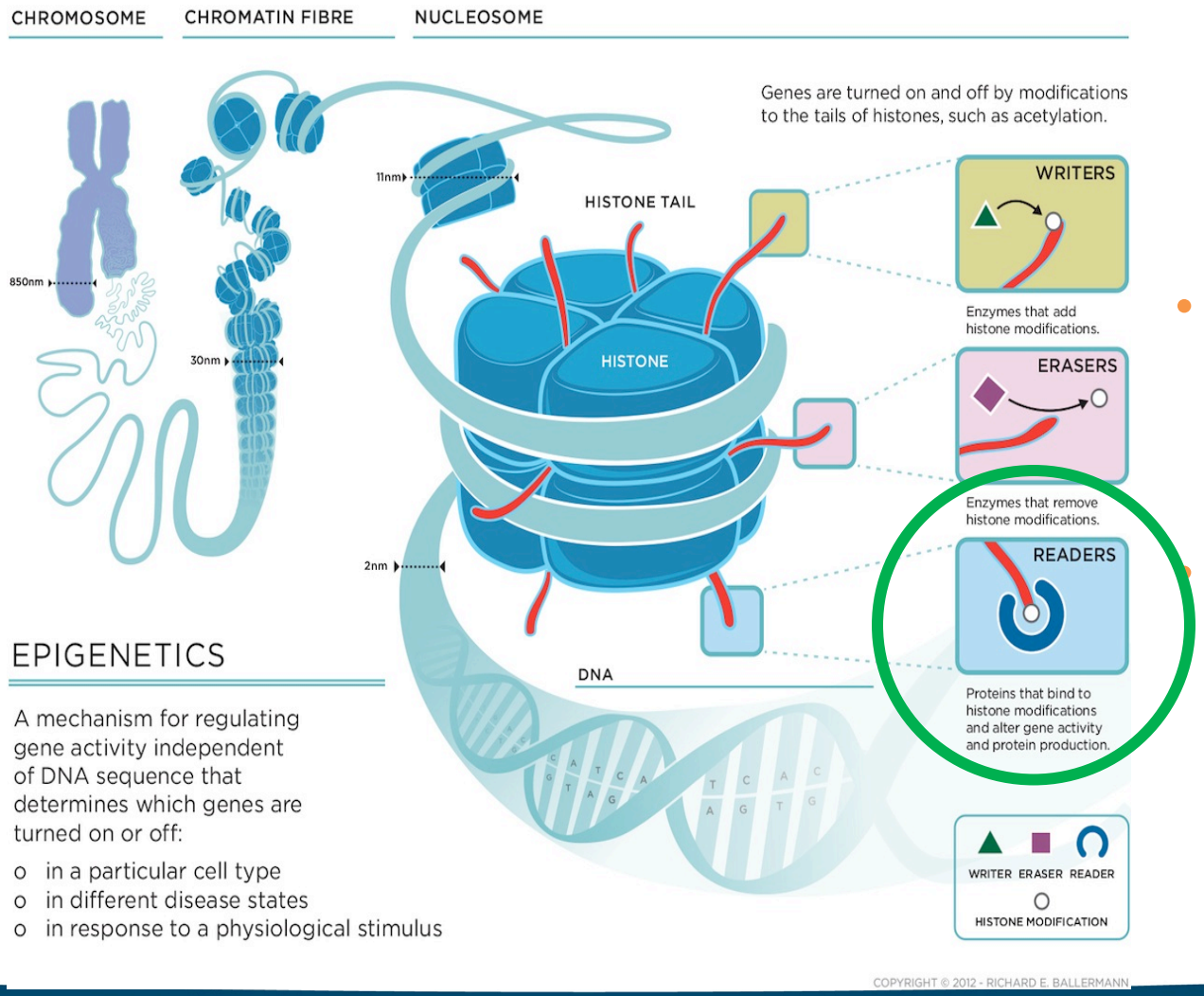


# Epigenetics



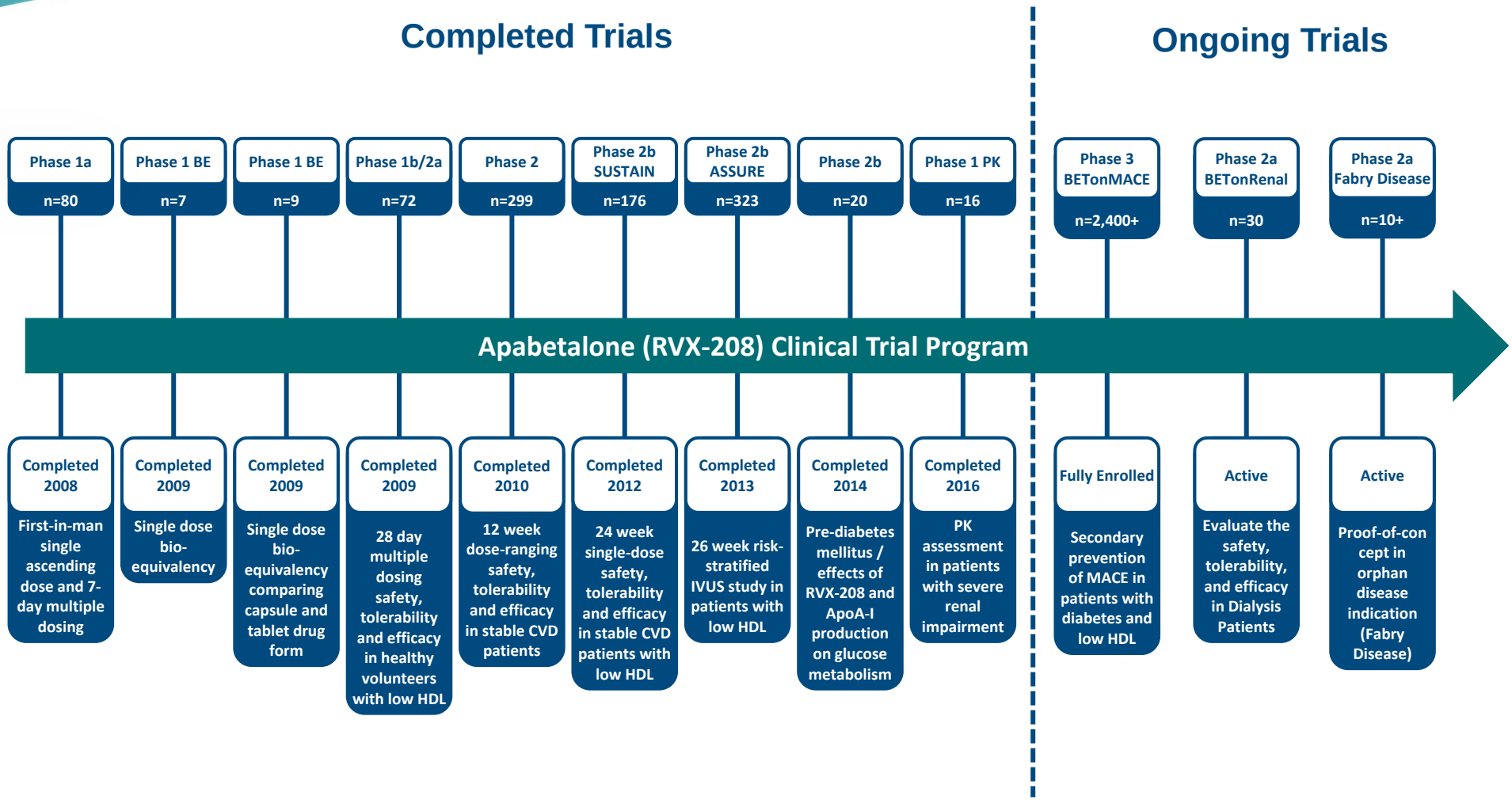

- The epigenetic code refers to modifications to chromatin components that regulate its activity
- Turning genes on or off is regulated by these modifications
- BET (Bromodomain and Extraterminal Domain) proteins recognize these modifications and turn genes on

# Epigenetics




- The epigenetic code refers to modifications to chromatin components that regulate its activity
- Turning genes on or off is regulated by these modifications
- BET (Bromodomain and Extraterminal Domain) proteins recognize these modifications and turn genes on

# Apabetalone Clinical Trials to Date



# BET Literature Impact Growing CVD and Renal Risk

RESVERLOGIX

OPEN ACCESS Freely available online

PLOS ONE

## RVX-208, an Inducer of ApoA-I in … Bromodomain Antagonist

Data in Brief 8 (2016) 1280–1288

Contents lists available at ScienceDirect

ELSEVIER

Data Article

Data on gene and pr… induced by apabetal… treated human whol… primary hepatocytes

Sylwia Wasiak [a], Dean Gil… Christopher Halliday [a], Ka… Kevin G. McLure [a], Peter R… Ewelina Kulikowski [a], Jan … Norman C. Wong [a,*]

[a] Resverlogix Corp., Calgary, Canada
[b] Resverlogix Corp., San Francisco, USA

Am J Cardiovasc Drugs
DOI 10.1007/s40256-017-0250-3

CrossMark

ORIGINAL RESEARCH ARTICLE

## Selective BET Protein Inhibition with Apabetalone and Cardiovascular Events: A Pooled Analysis of Trials in Patients with Coronary Artery Disease

KI REPORTS ISN

Kidney International Reports

Articles & Issues ~ For Authors ~ For Readers ~ For Advertisers ~ Companion Journals ~

All Content ~ Search Advanced Search

< Previous Article | Articles in Press | Next Article >

Article in Press

## Benefit of Apabetalone on Plasma Proteins in Renal Disease

Sylwia Wasiak[5], Laura M. Tsujikawa[5], Christopher Halliday, Stephanie C. Stotz, Dean Gilham, Ravi Jahagirdar, Kamyar Kalantar-Zadeh, Richard Robson[6], Michael Sweeney, Jan O. Johansson, Norman C. Wong, Ewelina Kulikowski

atherosclerosis

…otic cardiovascular …ys that contribute to

CrossMark

…pher Halliday [a], …sson [b], Michael Sweeney [b],

J. of Cardiovasc. Trans. Res.
DOI 10.1007/s12265-017-9755-z

ORIGINAL ARTICLE

## Downregulation of the Complement Cascade In Vitro, in Mice and in Patients with Cardiovascular Disease by the BET Protein Inhibitor Apabetalone (RVX-208)

Sylwia Wasiak [1] · Dean Gilham [1] · Laura M. Tsujikawa [1] · Christopher Halliday [1] · Cyrus Calosing [1] · Ravi Jahagirdar [1] · Jan Johansson [2] · Michael Sweeney [2] · Norman C. Wong [1] · Ewelina Kulikowski [1]

Received: 21 December 2016 / Accepted: 17 May 2017
© The Author(s) 2017. This article is an open access publication

…, Has Therapeutic Effects …ation and Autoimmune Disease

Ravi Jahagirdar, Sarah Attwell, Suzana Marusic, Alison Bendele, Narmada Shenoy, Kevin G. McLure, Dean Gilham, Karen Norek, Henrik C. Hansen, Raymond Yu, Jennifer Tobin, Gregory S. Wagner, Peter R. Young, Norman C. W. Wong, and Ewelina Kulikowski

*Resverlogix Corporation, Calgary, Alberta, Canada (R.J., S.A., K.G.M., D.G., K.N., H.C.H., R.Y., J.T., G.S.W., P.R.Y., N.C.W.W., E.K.); Hooke Laboratories Inc., Lawrence, Massachusetts (S.M.); Bolder BioPATH Inc., Boulder, Colorado (A.B.); and Aravasc Inc., Sunnyvale, California (N.S.)*

# Corporate Overview

- Resverlogix Corp. (TSX:RVX) is a Calgary and San Francisco based clinical stage biotechnology company focused on the development of apabetalone

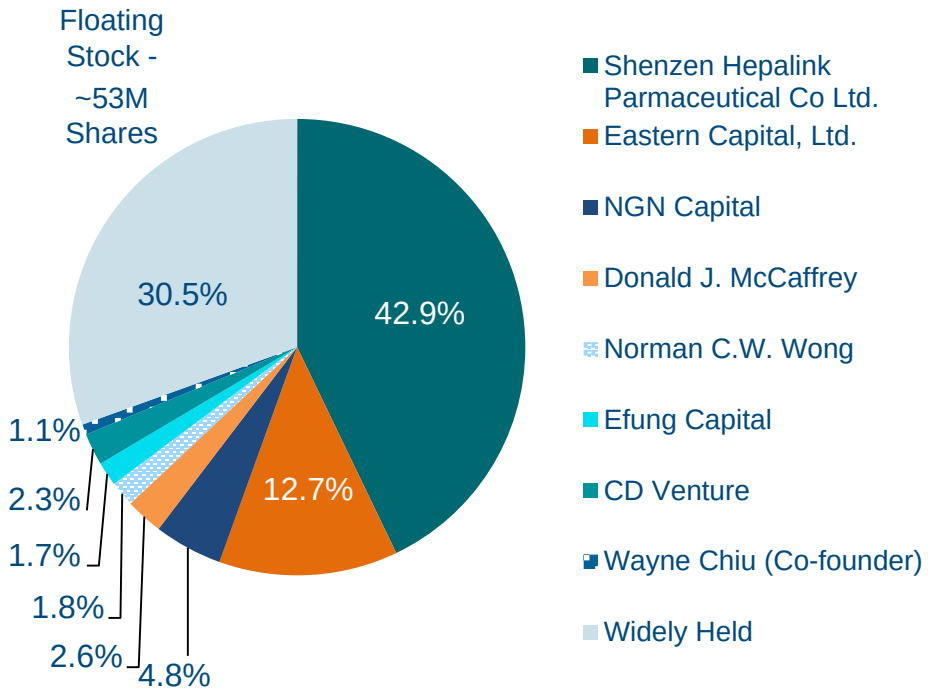
- Apabetalone (RVX-208) is a first-in-class small molecule selective BET bromodomain inhibitor, which acts via an epigenetic mechanism that can turn disease-causing genes off, thereby normalizing gene function
  - Apabetalone was the only selective BET bromodomain inhibitor in clinical trials for the past 10 years

- Resverlogix has initiated clinical trial work for apabetalone in three indications:
  - Cardiovascular Disease (BETonMACE Trial) – Phase 3
  - Chronic Kidney Disease (BETonRENAL Trial) – Phase 2a
  - Fabry's Disease – Phase 2a

# Capitalization and Financial Profile

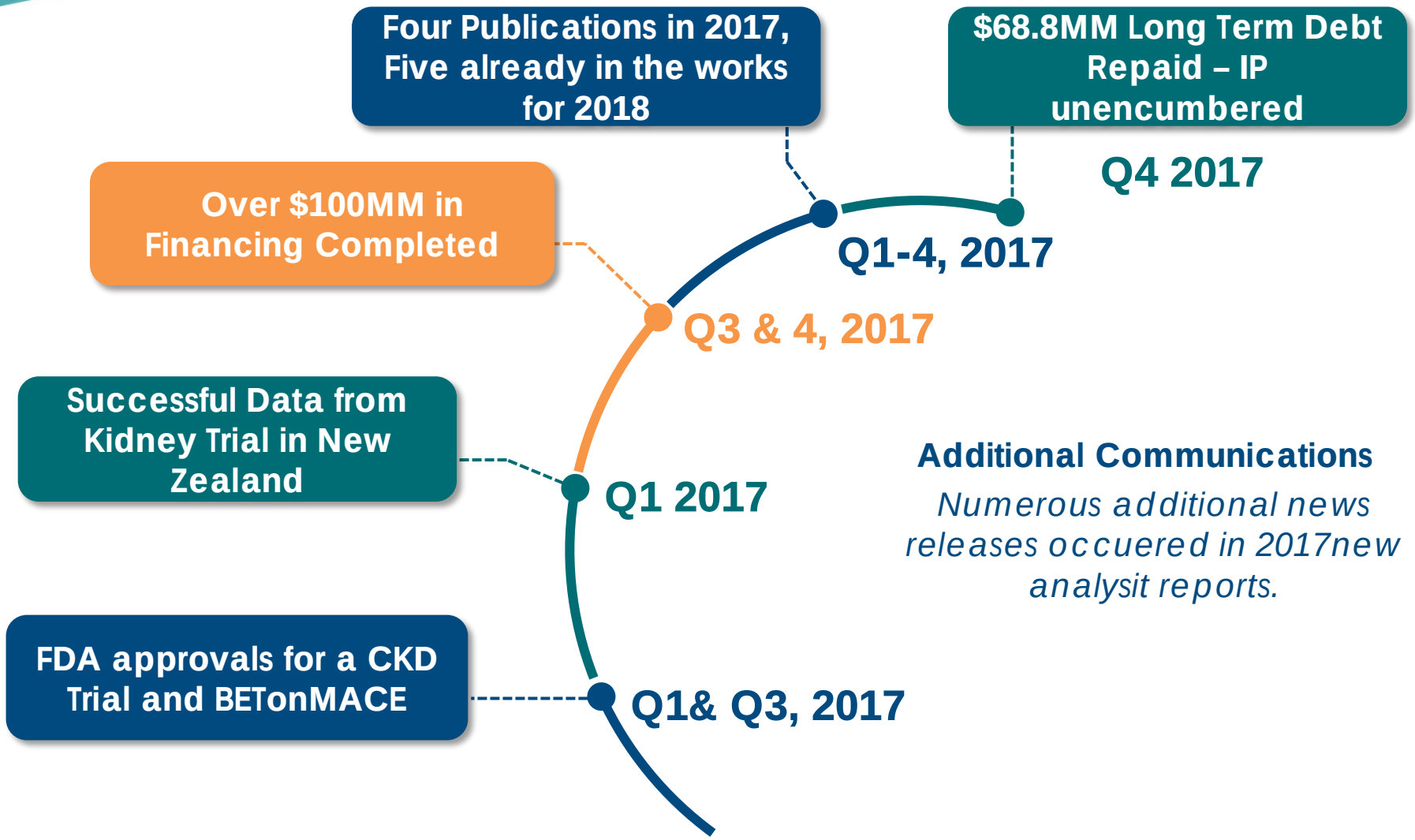
| | |
|---|---|
| **Founded** | **2001** |
| **Ticker** | **TSX: RVX** |
| **Market Cap** | **~C$250MM** |
| **Shares Outstand** | **175.04MM** |
| **Cash Burn (Annual)** | **~C$40.0M** |
| **Finance** | **$30MM USD– Announced April 2018** |

## RVX Top Shareholders




- RVX shareholder base consists of several long term investors who have been supportive over 10 years
- RVX maintains a diversified public market float of approximately 54M shares

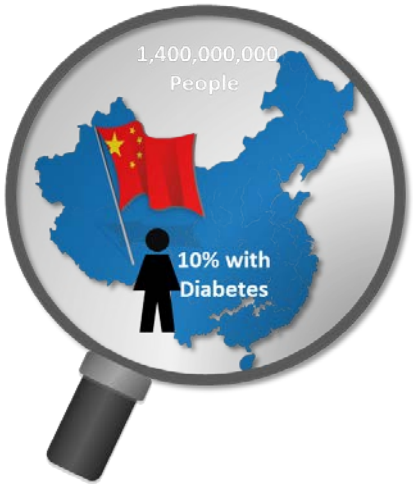
# 2017's Major Accomplishments



# Shenzhen Hepalink Partnership

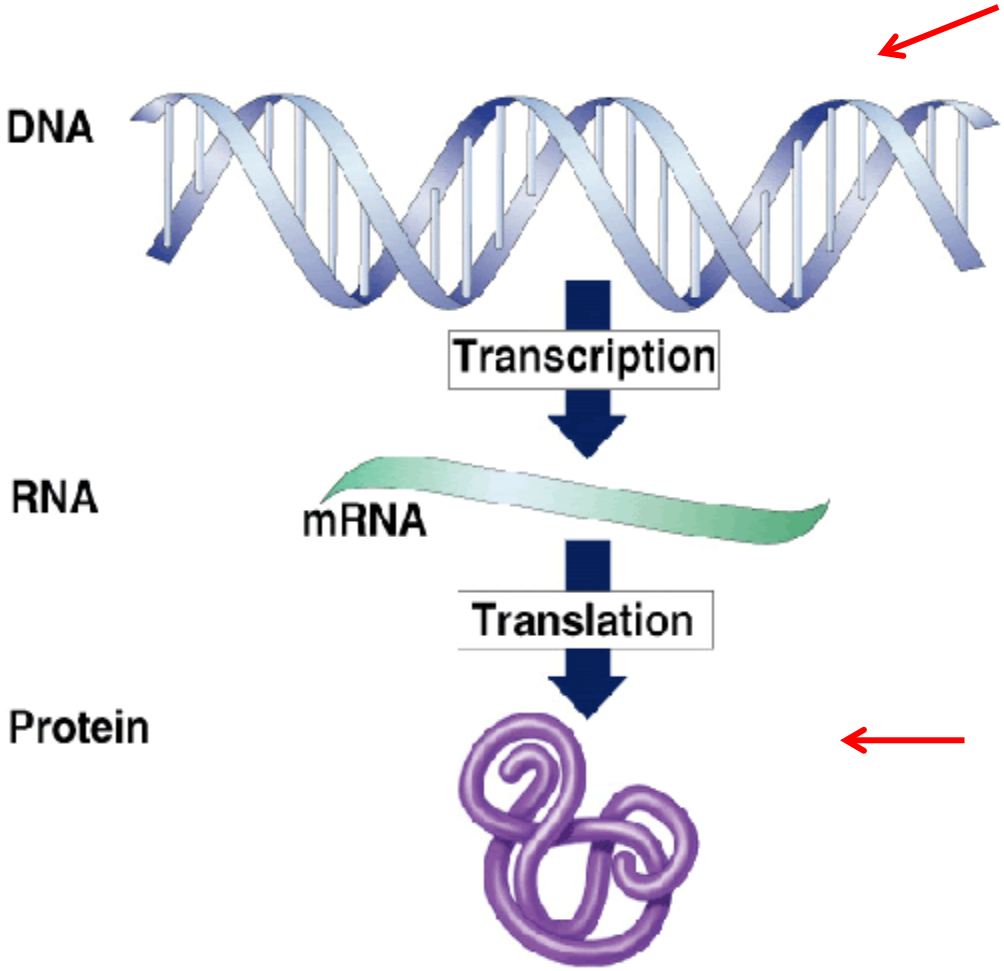
Resverlogix's partnership with Shenzhen Hepalink represents the largest single molecule deal in the history of China

| Resverlogix – Shenzhen Hepalink Exclusive Licensing Agreement | |
|---|---|
| **Compound** | • Apabetalone (RVX-208) |
| **Licensor** | • Resverlogix Corp. |
| **Licensee** | • Shenzhen Hepalink Pharmaceutical Co., Ltd. |
| **Territory** | • China, Hong Kong, Taiwan, and Macau |
| **Indications** | • Any approved indication |
| **Deal Structure** | • US$35M in equity investments in Resverlogix<br>• >US$400M in projected future China sales milestones and licensing royalties |
| **Developmental Costs** | • Shenzhen Hepalink is responsible for all developmental costs for the licensed territories<br>• This includes the cost of additional clinical trials in the licensed territories, regulatory applications, etc. |




# Apabetalone and the BET Platform

# Unique Mechanism of Action




**Genome Editing**

The mechanism is based on cutting and pasting undesired/desired sequences into or out of the DNA, thereby altering the gene sequence and then re-introducing the modified DNA into the body.

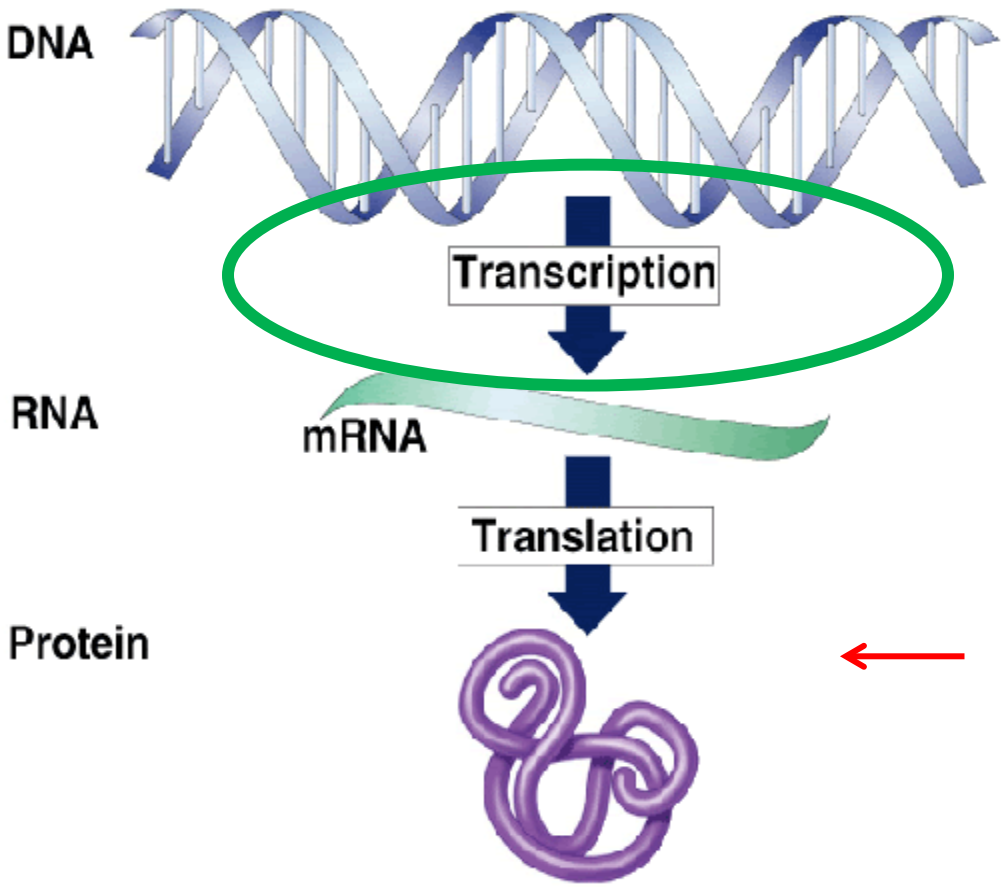
**CRISPR – gene editing within a cell sub population**

**Protein Targeting**

Focus on reducing or blocking the activity of **one** disease protein by using an inhibitor or antibody

**Antibody or Inhibitor – blocks activity of one mediator of disease**

# Unique Mechanism of Action




**Genome Editing**

The mechanism is based on cutting and pasting undesired/desired sequences into or out of the DNA, thereby altering the gene sequence and then re-introducing the modified DNA into the body.

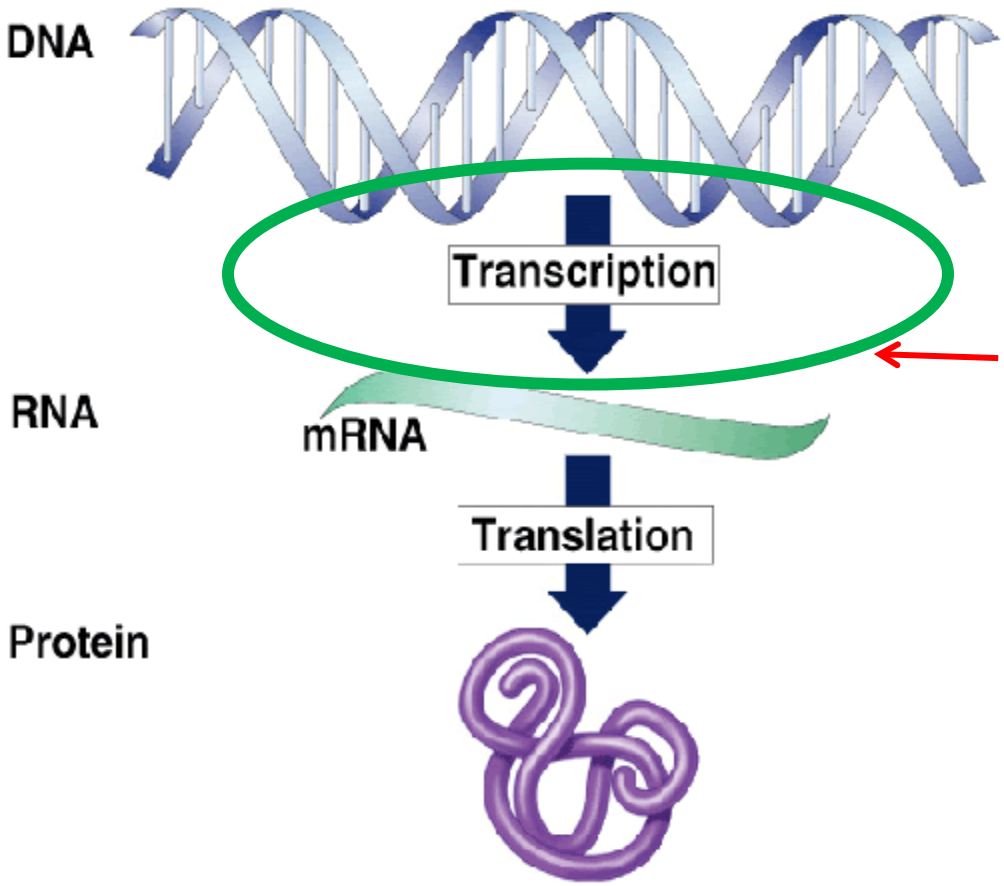
**CRISPR – gene editing within a cell sub population**

**Protein Targeting**

Focus on reducing or blocking the activity of **one** disease protein by using an inhibitor or antibody

**Antibody or Inhibitor – blocks activity of one mediator of disease**

# Unique Mechanism of Action




**Transcriptional Regulation**

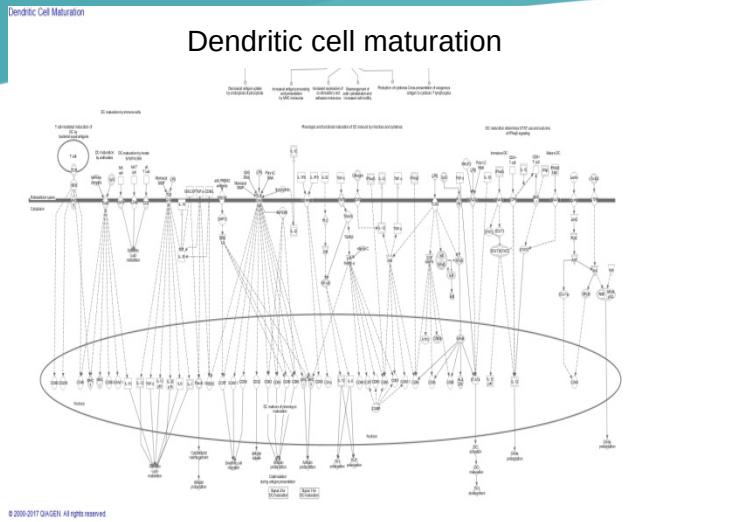
Mechanism is based on changing the levels of disease causing **proteins** by modulating their expression at the gene level

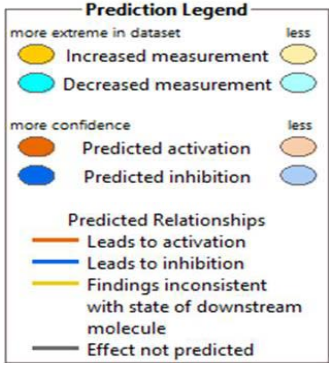
**Apabetalone – reduces expression of disease mediators**

# SOMAscan® Analysis of Plasma Proteome

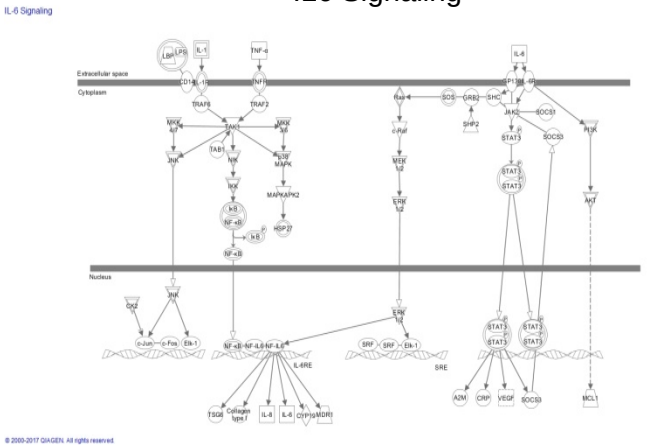
## IPA Canonical Pathways: Top 5 Pathways Upregulated

Dendritic cell maturation

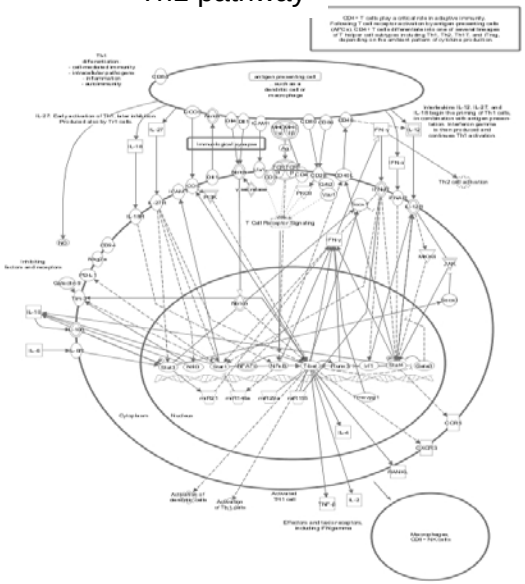




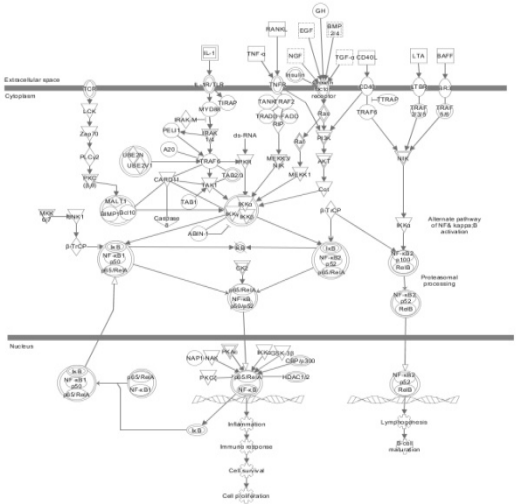

IL6 Signaling



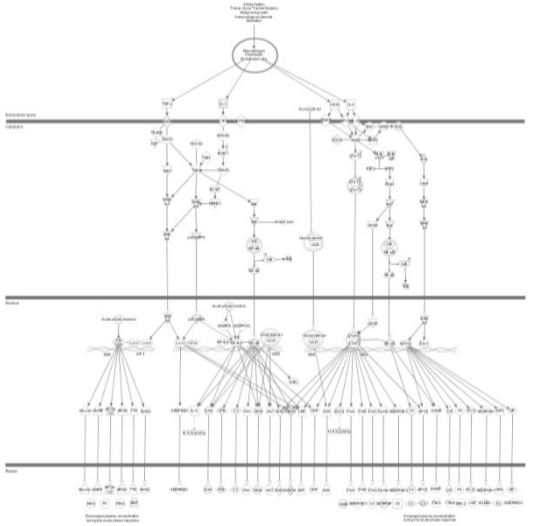
Th1 pathway



NF-kB Signaling



Acute Phase Response



Wasiak et al., 2017

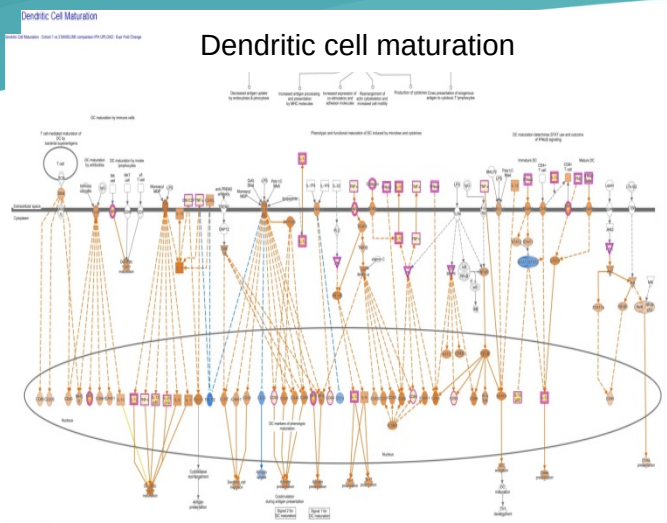
Δ>10% p≤0.05

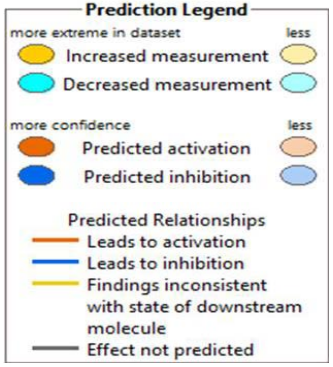
# SOMAscan® Analysis of Plasma Proteome

## IPA Canonical Pathways: Top 5 Pathways Upregulated

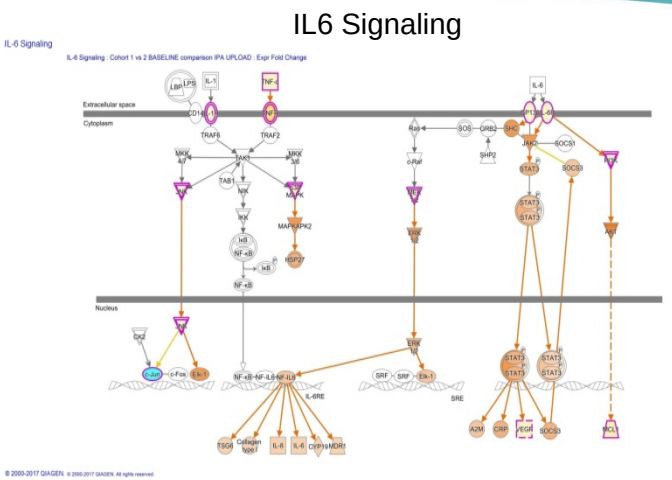
Baseline

Dendritic cell maturation

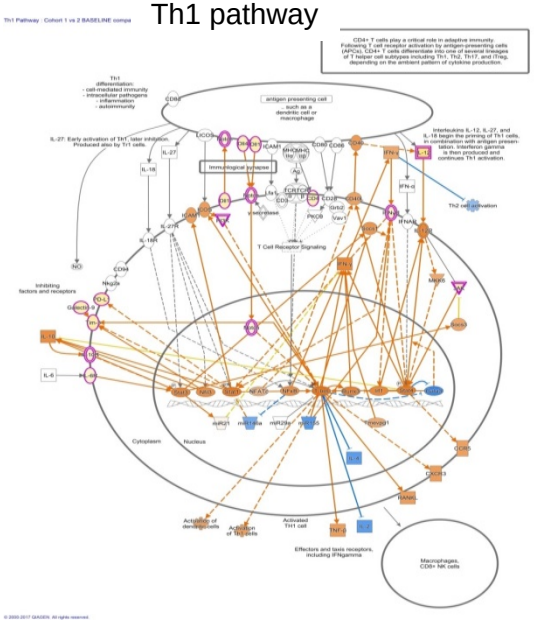




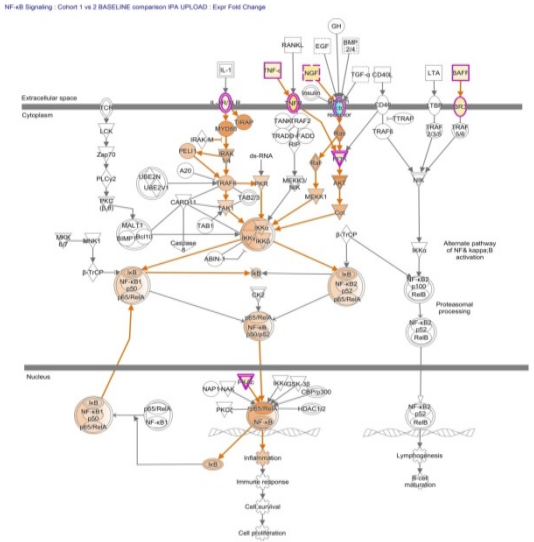

IL6 Signaling



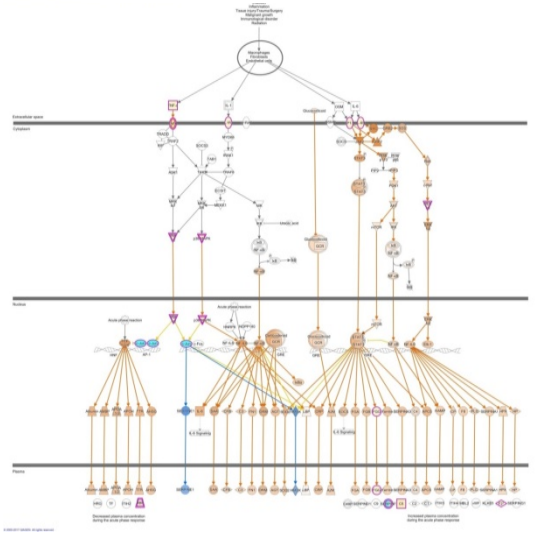
Th1 pathway



NF-kB Signaling



Acute Phase Response



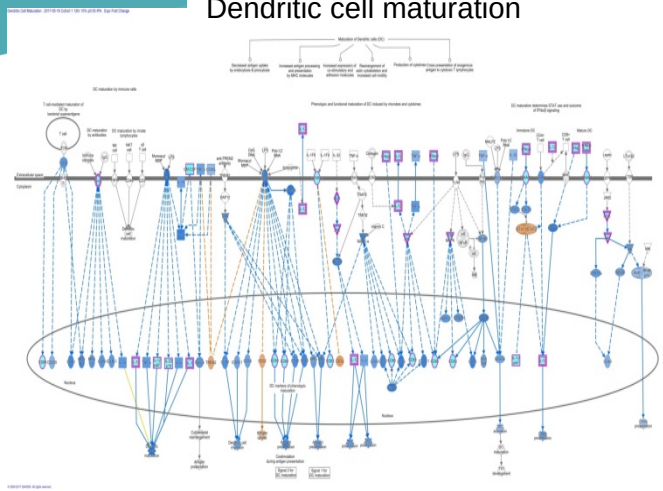
Wasiak et al., 2017

Δ>10% p≤0.05

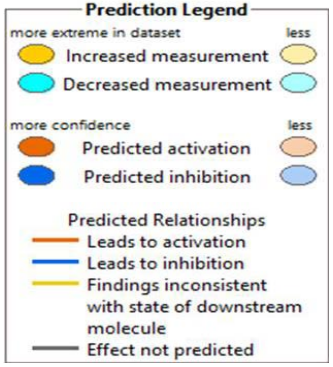
# SOMAscan® Analysis of Plasma Proteome

## IPA Canonical Pathways: Top 5 Pathways Upregulated

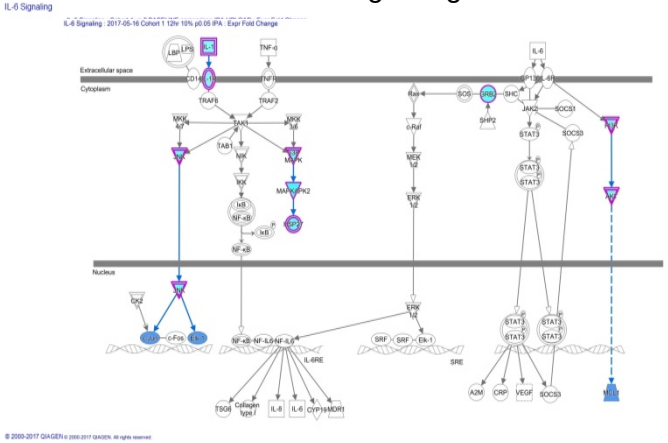
Dendritic cell maturation



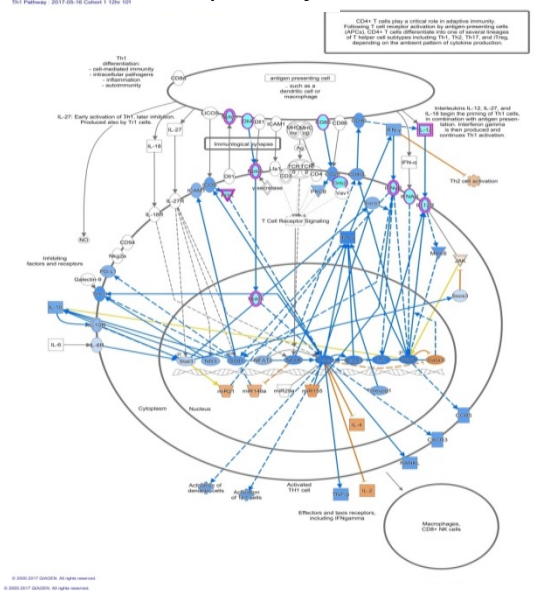
**Apabetalone**



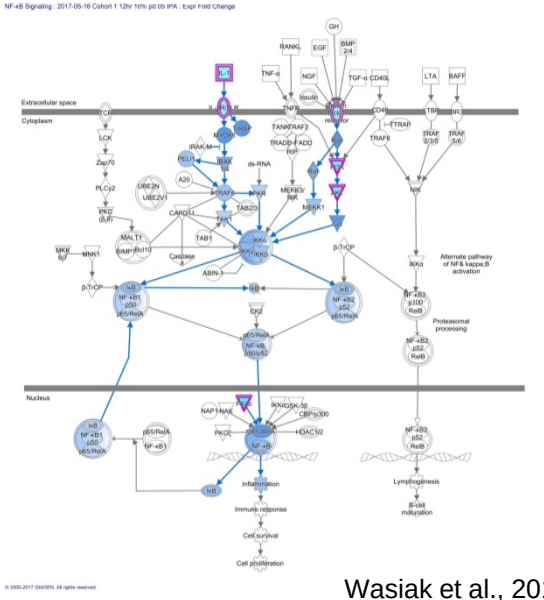

IL6 Signaling



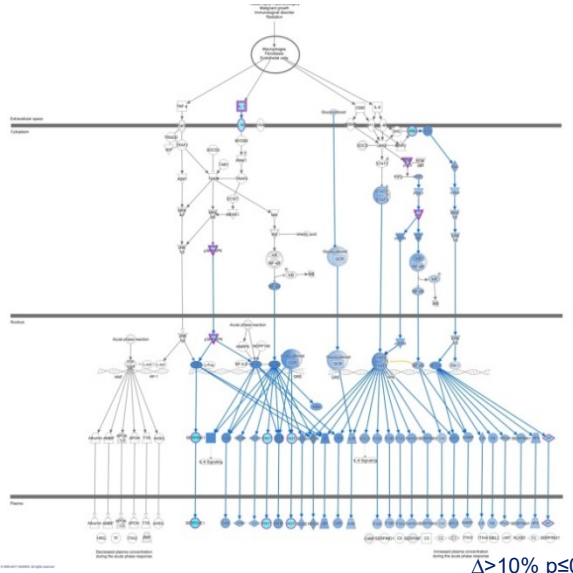
Th1 pathway



NF-kB Signaling



Acute Phase Response



Δ>10% p≤0.05

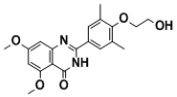
Wasiak et al., 2017

# Differentiation (RVX's BET Platform)

- Resverlogix has discovered compounds that **selectively** bind the bromodomains of BET proteins**.**
  - Bromodomain selectivity: Resverlogix's apabetalone selectively targets BD2
  - BET (BRD2, BRD3, BRD4) protein selectivity: Our expertise in medicinal chemistry and epigenetics allows us to identify small molecules that target one or a specified subset of BET proteins
- Our Phase 2 clinical program provided us with what was **the only blood bank of BET inhibitor-treated patients in the world**
  - In-depth analysis such as proteomics, genomics, and pathway analysis revealed advanced knowledge of BET activities
  - The resulting knowledge from these activities provided a level of sophistication around BET that surpasses that of many others working in this area
- The properties of Resverlogix's molecules **avoid side effects seen with other BETi**
  - BET programs in oncology can tolerate a high degree of side effects due to the nature of the disease being treated
  - Chronic conditions such as cardiovascular disease and renal impairment require treatments with a side-effect profile acceptable for long-term treatment

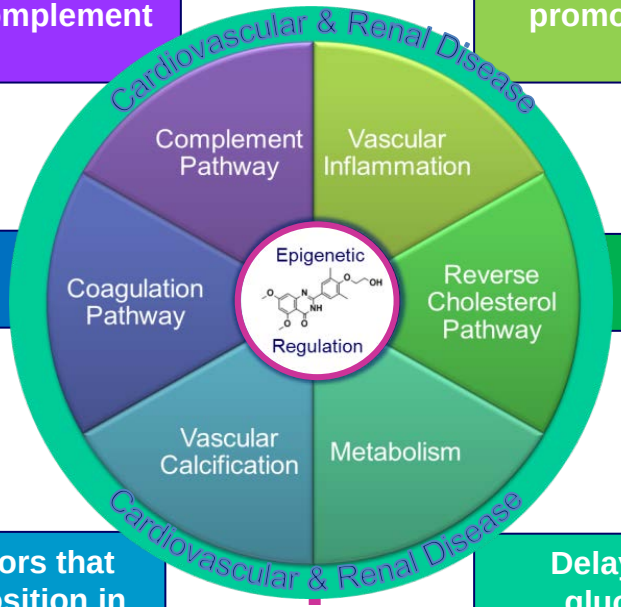
# BET Inhibition Impacts the Pathways that Drive Cardiovascular Disease and Kidney Diseases

Apabetalone, a bromodomain extra-terminal (BET) protein inhibitor, regulates the expression of genes and restores the function of pathways underlying the pathogenesis of CVD and kidney disease



**Reductions in the components and function of the complement cascade**

**Reductions in mediators that promote inflammation of the vasculature**




**Reductions in components of the coagulation cascade**

**Increased ApoA-I, positive effects on lipid content of HDL**

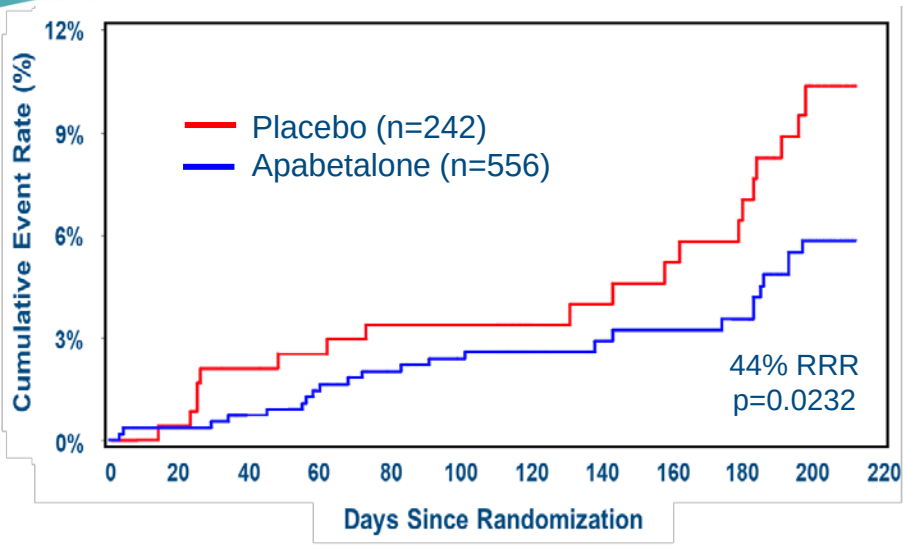
**Reductions in mediators that promote calcium deposition in the vasculature**

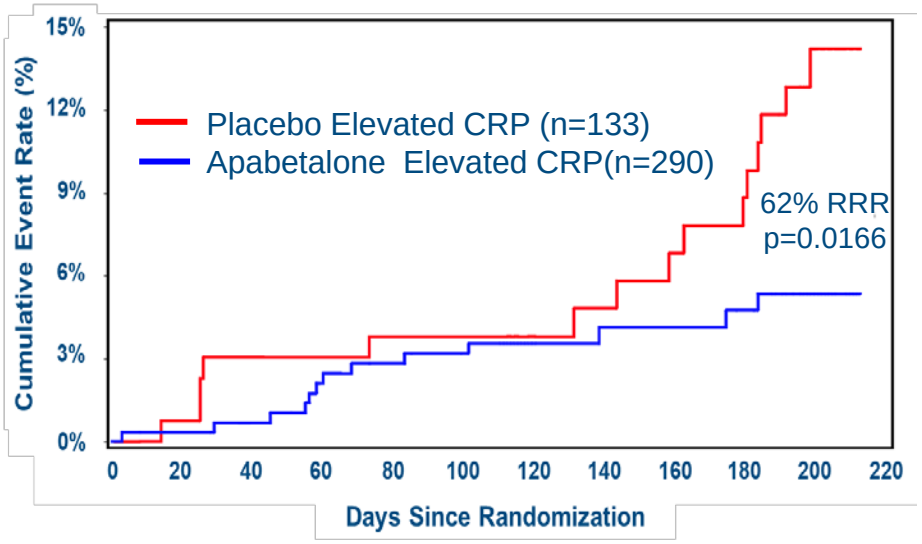
**Delayed and reduced oral glucose absorption and endogenous production**

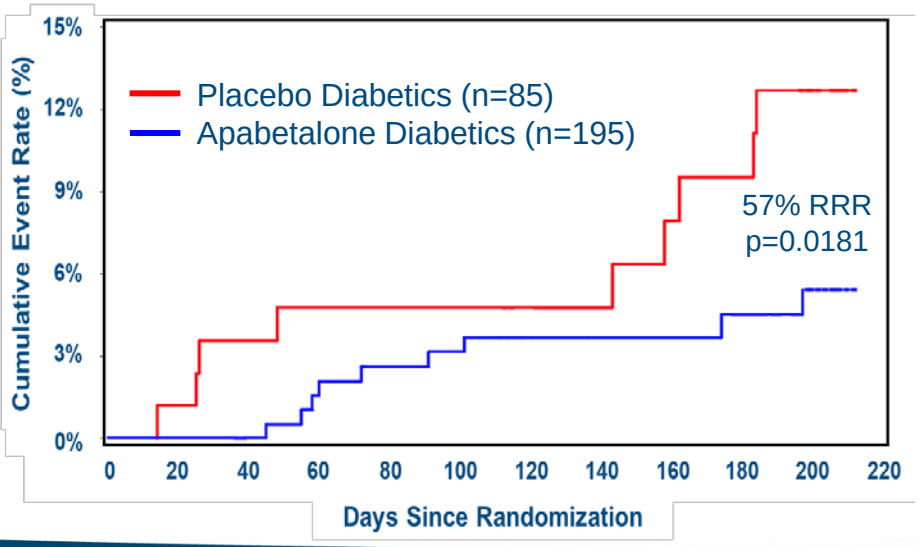
Reduced incidence of MACE


# BETonMACE Clinical Program Overview

# Nicholls et al. 2017 Am J Cardiovasc Drugs




**MACE:** Major Adverse Cardiac Events including: death, myocardial infarction, stroke, coronary revascularization, hospitalization for acute coronary syndrome or heart failure

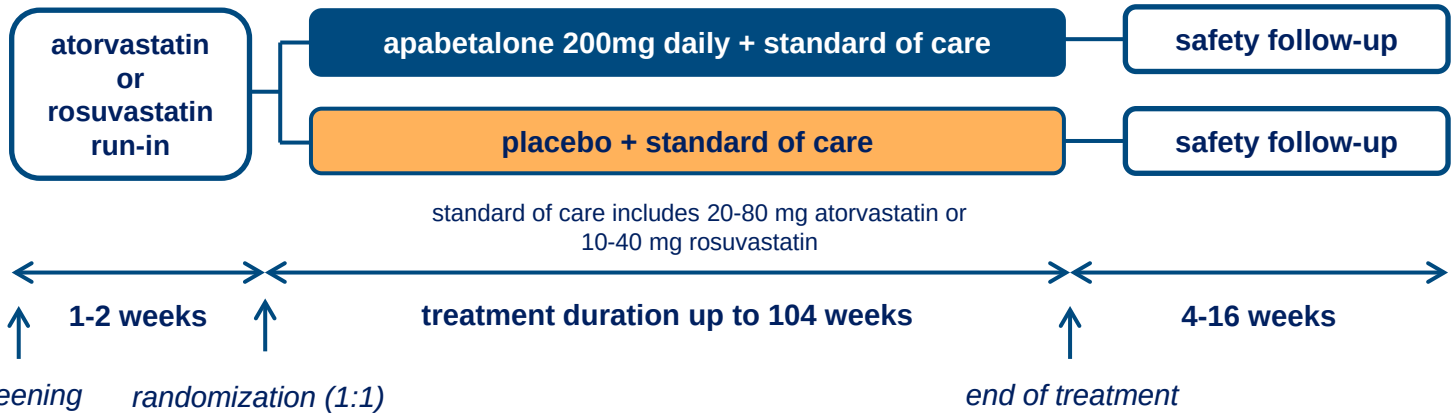
Decrease in MACE was most profound in patients who had a higher level of inflammation such as patients with diabetes

# CVD Program Moving Forward- BETonMACE CV Outcomes Study

BETonMACE
A CARDIOVASCULAR STUDY FOR PEOPLE WITH TYPE 2 DIABETES

**2,400 + subjects**

- double blinded
- 1-2 week statin run-in




**The study is an event-based trial and continues until 250 narrowly defined MACE events have occurred**

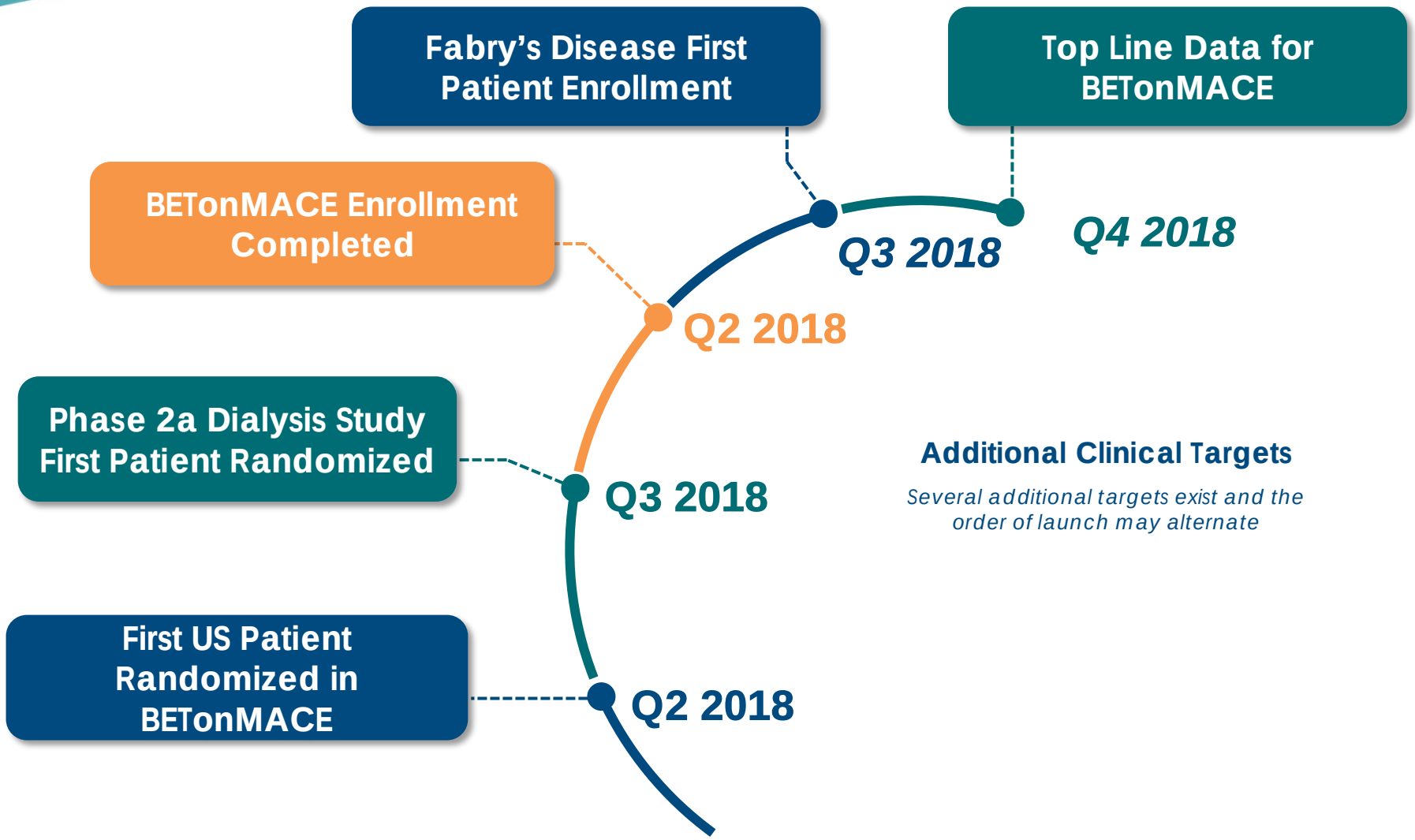
**Key inclusion criteria**

- Type II Diabetes Mellitus
  - HbA1c > 6.5% or history of diabetes medications
- CAD event 7 days - 90 days prior to screening
  - Myocardial infarction (MI), unstable angina or percutaneous coronary intervention
- HDL < 1.04 for males and < 1.17 for females

# BETonMACE Commenced November 2015


Apabetalone has already been tested in over 1,800 patients in 18 countries around the world.

# The Upcoming Clinical Year Estimates




**Additional Clinical Targets**

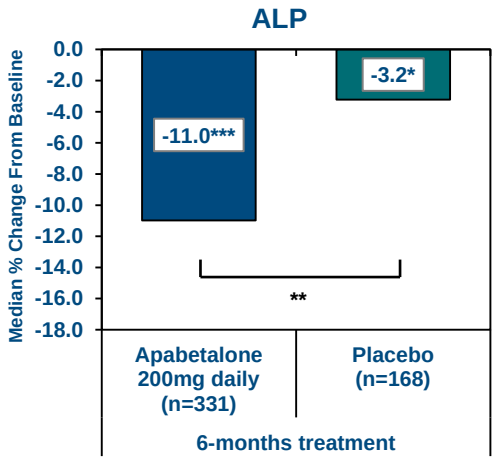
*Several additional targets exist and the order of launch may alternate*


# Chronic Kidney Disease Clinical Program Overview

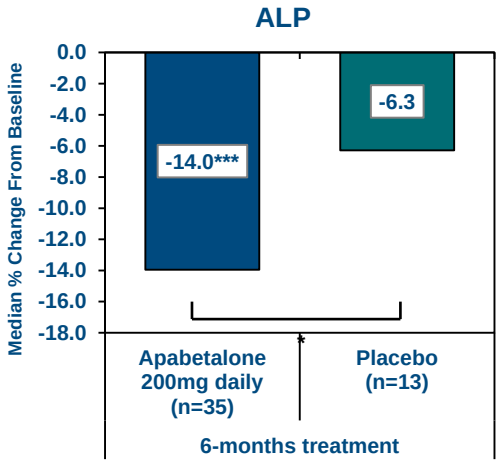
# Rationale for Kidney Disease Program

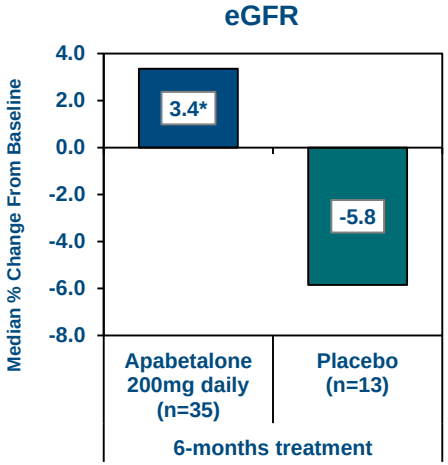
- Apabetalone has demonstrated reductions in alkaline phosphatase (a strong marker of CKD risk) and improvements in eGFR in CKD patients (eGFR < 60 mL/min/1.73m$^2$) with CVD in the phase 2 ASSURE and SUSTAIN trials.

*All Patients*




*Patients With Baseline eGFR<60 mL/min/1.73m2*




*Data Presented in Keynote Address at the 2015 American Society of Nephrology Conference, San Diego*

- Resverlogix believes that BET inhibition and apabetalone may have the potential to improve kidney function, as measured by eGFR, in patients suffering from various stages of kidney disease.
- Resverlogix is currently investigating the potential for expansion into specific kidney indications:
  - CKD (Stages 3a and 3b) patients, with a history of CVD (Phase 3 BETonMACE subgroup)
  - High Risk CKD Patients on Dialysis (Phase 2a BETonRenal study)

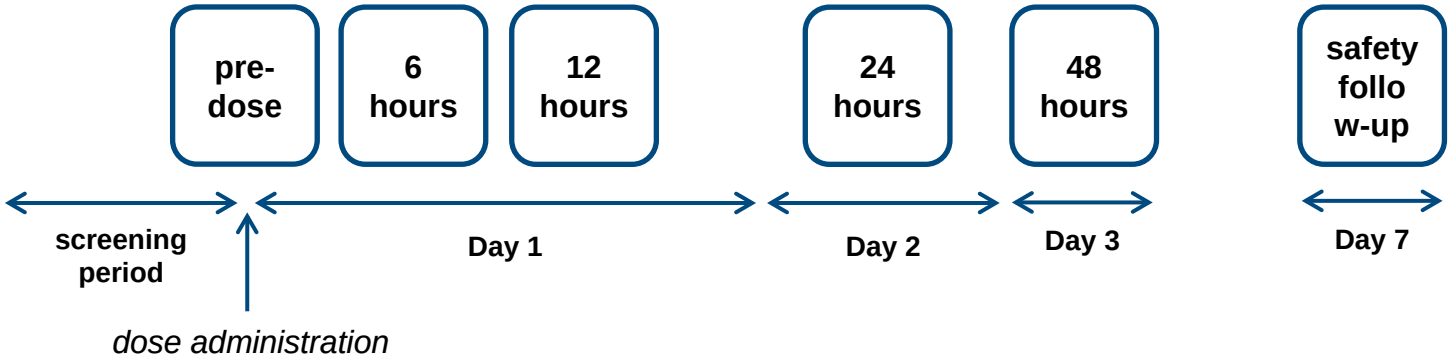
# Kidney Disease: Phase I Study

A Phase I, Open-Label, Parallel Group Study to Evaluate the Safety and Pharmacokinetics of a Single Oral Dose of RVX000222 in Subjects with Severe Renal Impairment

**Cohort 1**
Previously diagnosed with CKD (stage IV) and not on dialysis (eGFR <30 mL/min/1.73m$^2$) N=8

**Cohort 2**
Volunteers matched for age (±10 years), weight (±20%), and gender with the subjects in Cohort 1 (renal impaired subjects); eGFR ≥60 mL/min/1.73m$^2$ N=8

**apabetalone 100mg single dose**



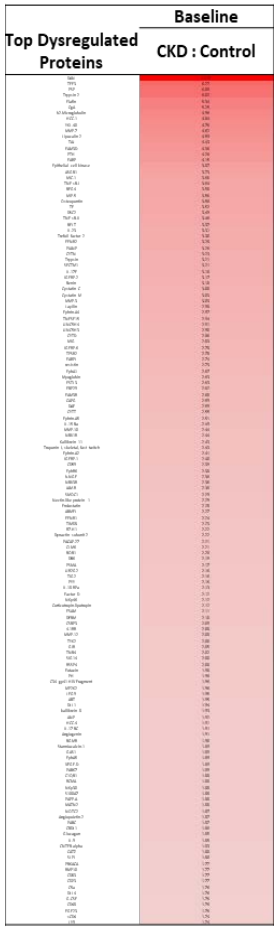

Trial demonstrated that apabetalone has a highly differential effect on protein levels based on disease status, healthy vs sick, reducing a variety of plasma proteins and downregulating pathways activated in the CKD cohort

# CKD Program - Phase 1 Data

## Effect of Apabetalone on Differentially Expressed Proteins

289 proteins were different between the plasma of CKD patients and matched controls (red indicates higher protein levels in CKD/control)

**CKD = Subjects with stage 4 Chronic Kidney Disease**



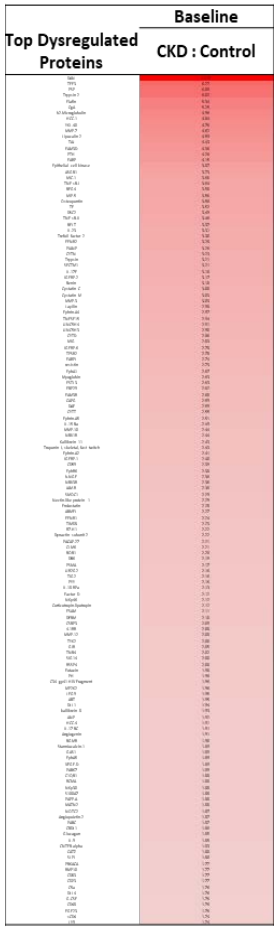

Blue = downregulated;
white = no change;
Red = upregulated

# CKD Program - Phase 1 Data

## Effect of Apabetalone on Differentially Expressed Proteins

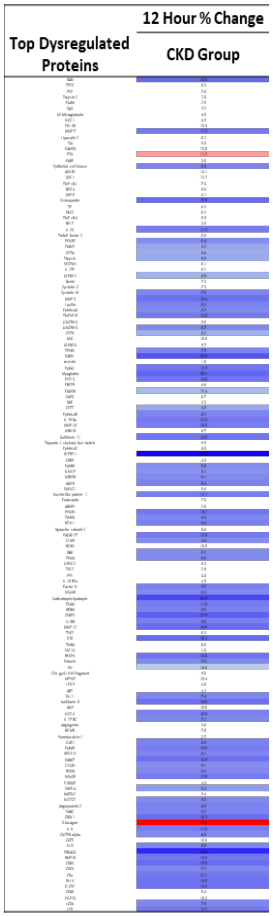
289 proteins were different between the plasma of CKD patients and matched controls (red indicates higher protein levels in CKD/control)

**CKD = Subjects with stage 4 Chronic Kidney Disease**




**100mg Dose Apabetalone**

Blue = downregulated;
white = no change;
Red = upregulated



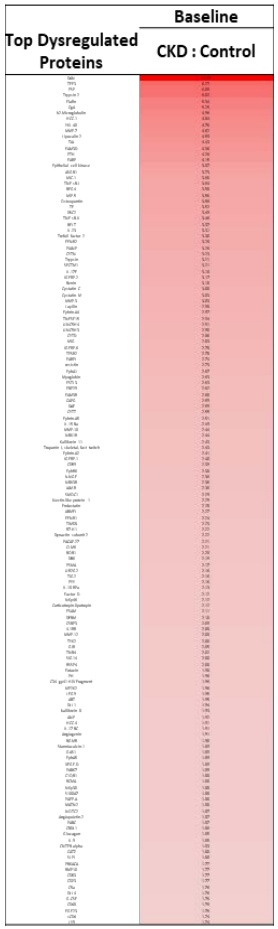
# CKD Program - Phase 1 Data

## Effect of Apabetalone on Differentially Expressed Proteins

289 proteins were different between the plasma of CKD patients and matched controls (red indicates higher protein levels in CKD/control)

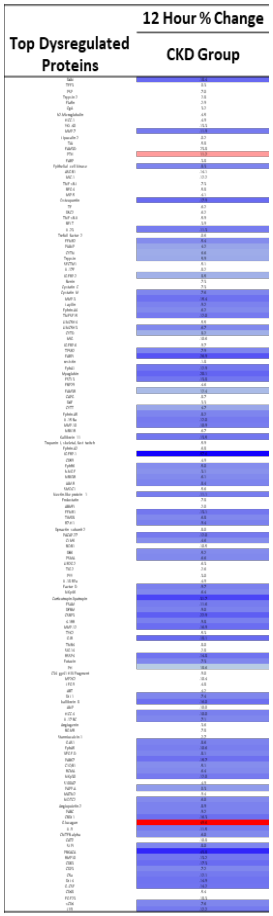
**CKD = Subjects with stage 4 Chronic Kidney Disease**

152 of the 289 differentially expressed proteins in the CKD patients were downregulated at 12 hours following one dose of apabetalone




**100mg Dose Apabetalone**

Blue = downregulated;
white = no change;
Red = upregulated




**In CKD patients, one dose of apabetalone reduced CKD and CVD biomarkers that were dysregulated at baseline**

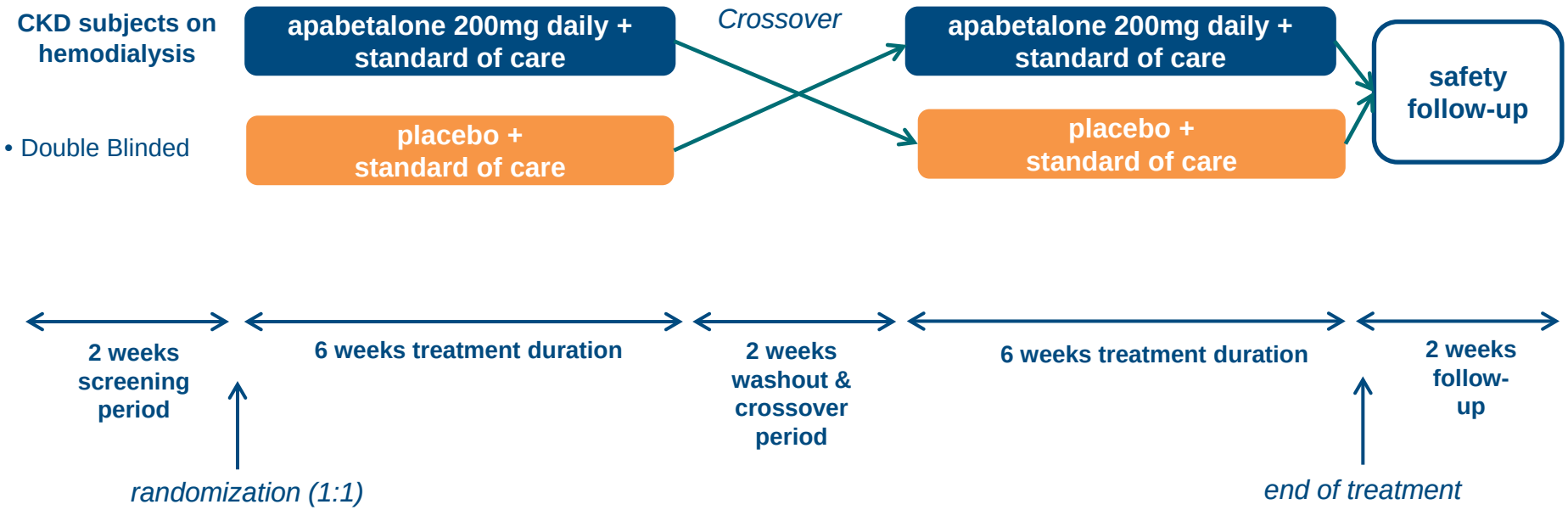
# SOMAscan® Analysis of Plasma Proteome – Phase 1 Trial

## Apabetalone Reduces CVD and CKD Biomarkers

| | Protein Name | Gene Symbol | Subjects with CKD (stage IV) (n=8) treated with 100 mg Apabetalone | | Matched Control Subjects (n=8) treated with 100 mg Apabetalone | |
|---|---|---|---|---|---|---|
| | | | % Δ from baseline at 12h | p-value | % Δ from baseline at 12h | p-value |
| Inflammation | Interleukin-6 | IL6 | | 0.05 | NS | |
| | Interleukin-1 alpha | IL1A | | 0.01 | NS | |
| | Interferon gamma | IFNG | | 0.04 | NS | |
| | TNF receptor superfamily member 1A | TNFRSF1A | | 0.05 | NS | |
| | C-reactive protein | CRP | | 0.04 | NS | |
| | Tumor necrosis factor | TNF | | 0.02 | NS | |
| Cell Adhesion | P-selectin | SELP | | 0.04 | NS | |
| | E-selectin | SELE | | 0.01 | | 0.02 |
| | Intercellular adhesion molecule 1 | ICAM1 | | 0.05 | | 0.04 |
| | Vascular cell adhesion protein 1 | VCAM1 | | 0.01 | NS | |
| Matrix Remodeling Calcification | Fibronectin | FN1 | | 0.02 | NS | |
| | Stromelysin-1 | MMP3 | | 0.02 | NS | |
| | Stromelysin-2 | MMP10 | | 0.02 | NS | |
| | Osteopontin | SPP1 | | 0.01 | | 0.04 |
| Thrombosis | Plasminogen activator inhibitor 1 | SERPINE1 | | 0.04 | NS | |
| | Tissue-type plasminogen activator | PLAT | | 0.01 | NS | |
| | Urokinase-type plasminogen activator | PLAU | | 0.01 | NS | |
| | D-dimer | FGA/B/C | | 0.05 | NS | |
| | Urokinase plasminogen activator surface receptor | PLAUR | | 0.02 | NS | |

Apabetalone reduces markers of inflammation, cell adhesion, matrix remodeling, calcification and thrombosis in the CKD cohort after one dose and 12 hours

# BETonRENAL Dialysis Study Design




- The study is an sequential cross-over trial to evaluate the safety, tolerability, and efficacy of apabetalone in CKD patients on hemodialysis in addition to standard of care
- 30 CKD patients receiving standard regimens of hemodialysis three days per week
- Clinical sites identified and prepared to begin patient enrollment

# Kidney Disease Program Clinical Advisory Board

**Dr. Kamyar Kalantar-Zadeh**
Chair
*UC Irvine Chief Nephrology*

**Prof. Vincent Brandenburg**
Member
*University Hospital RWTH Aachen*

**Dr. Carmine Zoccali**
Member
*University Pisa*

**Dr. Marcello Tonelli**
Member
*University of Calgary Chair Medical Research*

**Dr. Srinivasan Beddhu**
Member
*University of Utah*

**Dr. Mathias Haarhaus**
Member
*Karolinska University Hospital*

# Why Invest in Resverlogix?

- **Phase 3 company** focused on significant unmet need in high-risk CVD patient population with lead therapeutic - **apabetalone**
- **Market leader with significant potential** – targeting high-risk unmet need in several patient groups – Over 10MM patients in top 7 markets
- **Advancing development** of apabetalone in high-risk (dialysis) CKD patients – New phase 2 clinical trials to commence in early 2018
- **Well established safety profile** - to date, over 2,000 patients treated with apabetalone with no significant safety issues
- **Proven track record** of funding development while minimizing shareholder dilution


# Resverlogix Corp.

## Corporate Update

May, 2018 Calgary, AB & San Francisco, CA