



PORTFOLIO REVIEW OF CLINICAL CANDIDATES

BOSTON, MA – WEDNESDAY, JUNE 19, 2019

OVERVIEW

Barth Syndrome Foundation has reached an important milestone in our mission to accelerate treatments and find a cure for Barth syndrome. Presently, three therapeutic ideas are at the cusp of clinical trial implementation:

1. Gene augmentation therapy (AAV9) with Dr. Barry Byrne;
2. Enzyme replacement therapy (ERT) with Dr. Michael Chin; and
3. ALCAT1 inhibitor therapy with Dr. Roger Shi.

Clinical trials will be required to test the safety and efficacy of these potential therapies in order for affected individuals to one day be able to access life-changing options. Beyond the technical and partnering challenges to advance these products, BSF must consider the limited number of affected individuals eligible for participating in clinical trials, the anticipated therapeutic burden and benefit of each proposed therapy, the competitive landscape of therapeutic possibilities, and the capital requirements for BSF to de-risk the development programs.

MEETING PURPOSE

BSF seeks to understand specific ways, within the next 1-3 years, that the Foundation can strategically advance the above listed clinical candidates through collaborative efforts with the principal investigators (PIs), their academic institutions, and commercial partners¹. To achieve this goal, PIs will present on several different considerations that will impact the clinical development of their potential therapies. Topics include:

- Target Product Profile (TPP)
- Scientific successes (e.g., milestones, publications, partnerships, etc.)
- Scientific Gap Analysis
- Key roadblocks/hurdles (technical and partnering challenges, clinical pathway uncertainty, etc.)
- Differentiated products with same clinical targets (competitor landscape)
- Product development pathway and estimated timelines
- Financing required to reach commercialization
- Regulatory strategy
- Reimbursement strategy
- BSF's suggested role short term (next 1-3 years) & mid term (> 3 years)

¹ **DISCLOSURE:** To foster BSF's values of transparency and collaboration, all participants must have signed and returned BSF's policy on confidentiality and disclosed conflicts of interest in order to participate in this meeting.

ANTICIPATED OUTPUTS

BSF will incorporate both scientific and business considerations of clinical candidates into its strategic planning to guide BSF's allocation of its limited resources, including funds, staff time, and, most importantly, participants in clinical trials. We seek to understand the potential and the risk of each approach and weigh that in the context of potential impact to individuals with Barth syndrome. Our goal is to translate these considerations into actionable steps and magnify the value that BSF brings to the research and development of therapies targeting Barth syndrome.

INTRODUCTION TO GENE THERAPY

William Pu, MD

Professor, Pediatrics
Associate, Cardiology, Boston Children's Hospital
Harvard Medical School
Boston, MA



William Pu, MD, is the Director of Basic and Translational Cardiovascular Research in the Department of Cardiology at Boston Children's Hospital, and the Aldo R. Castañeda Professor of Pediatrics at Harvard Medical School. Dr. Pu has broad expertise in cardiac biology that includes cardiac development, heart failure, cardiac regeneration, and in vitro cardiac disease modeling. His lab has made fundamental discoveries in gene regulation in developing and diseased hearts, particularly in the area of transcriptional regulation. Many of these discoveries are the result of innovative approaches to studying heart development and disease, often involving multidisciplinary collaborations that draw on advances in other fields. His lab is currently engaged in research projects on the genetic causes of inherited heart diseases and gene therapy for Barth syndrome and CPVT.

Dr. Pu has completed his combined BS-MS degree at Yale University and obtained his MD degree from the Harvard Medical School/MIT Science and Technology Program in 1993. He trained in Pediatrics and Pediatric Cardiology at Boston Children's Hospital. He received his training in basic research in the laboratories of Kevin Struhl, David Clapham, and Seigo Izumo. He established an independent research lab at Boston Children's in 2004.

PRINCIPAL INVESTIGATORS

Barry Byrne, MD, PhD

Director, UF Powell Gene Therapy Center
 Professor, Pediatrics and Molecular Genetics & Microbiology
 Associate Chair, Pediatrics
 University of Florida
 Gainesville, FL



Dr. Barry J. Byrne is a clinician scientist interested in a variety of rare diseases, with specific attention to developing therapies for inherited muscle disease. As a pediatric cardiologist, his focus is on conditions that lead to skeletal muscle weakness, cardiac dysfunction, and respiratory dysfunction. His research team has made significant contributions to the understanding and treatment of Pompe disease, a type of muscular dystrophy resulting from abnormal glycogen accumulation in the muscle. His current research has focused on developing new therapies using the missing cellular protein or the corrective gene to restore muscle function in Pompe and other inherited myopathies.

Dr. Byrne is the Associate Chair of Pediatrics and Director of the Powell Gene Therapy Center at the University of Florida. After obtaining a BS degree in Chemistry from Denison University, he pursued his medical education, as well as a PhD in Microbiology and Immunology, at the University of Illinois. He completed his Pediatric Residency, Cardiology Fellowship training, and Post-Doctoral training in Biological Chemistry at Johns Hopkins University. Joining the University of Florida in 1997, he has served in a variety of clinical, research, and educational roles, and is now the Earl and Christy Powell University Chair in Genetics.

Dr. Byrne's research is aimed at understanding types of inherited muscle disease that lead to heart and skeletal muscle dysfunction. His current research focus is aimed to help those affected by Pompe disease, an autosomal recessive lysosomal storage disease, and Barth syndrome, a chromosomal X-linked defect. Dr. Byrne and colleagues are taking two approaches to the problem. The first approach is vector replacement using rAAV, a recombinant virus vector constructed from adeno associated virus (AAV). Second, the Byrne lab is using protein-replacement therapy in an effort to treat deficiencies caused by genetic disorders with specific supplementation. Dr. Byrne is a former member of the SMAB of BSF, and he and his colleagues have been multiple BSF Research Grant Program awardees.

Christina Pacak, PhD

Assistant Professor
 University of Florida
 Gainesville, FL

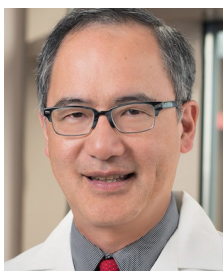


Christina A. Pacak earned her PhD in 2006 from the University of Florida Medical School Interdisciplinary Program in Biomedical Sciences where her thesis focused on the development of AAV-mediated gene delivery for heart and skeletal muscle. She completed a postdoctoral research fellowship at Boston Children's Hospital and Harvard Medical School where she worked on cardiac tissue engineering methodologies and helped to develop mitochondrial transplantation therapies. In 2014 Dr. Pacak returned to UF as an Assistant Professor in the Department of Pediatrics. The overall theme of the Pacak lab research program is to gain a greater understanding of disorders that affect mitochondrial

function. Studies are focused on the investigation of and therapeutic development for rare diseases. The lab applies mechanistic knowledge gained from these studies to understand broader concepts such as the role of mitochondria in cardiac dysfunction and neurodegeneration that are highly relevant to many common health disorders.

Michael T. Chin, MD, PhD

Research Director, Hypertrophic Cardiomyopathy (HCM) Center and Research Institute
Principal Investigator, Molecular Cardiology Research Institute (MCRI)
CardioVascular Center (CVC), and the Division of Cardiology
Tufts Medical Center
Boston, MA



Michael T. Chin, MD, PhD, is the Research Director of the Hypertrophic Cardiomyopathy (HCM) Center and Research Institute at Tufts Medical Center and a Principal Investigator in the Molecular Cardiology Research Institute (MCRI). In his role as the HCM Research Director, Dr. Chin identifies basic pathways

influencing the development of hypertrophy and fibrosis and the attendant electrical instability, with the goals of illuminating potential new treatment paradigms and drug targets for HCM. In the MCRI, Dr. Chin investigates mechanisms and treatments for other genetic causes of heart failure and exploring epigenetic mechanisms by which air pollution causes cardiac failure.

Dr. Chin is trained as a virologist, molecular biologist, biochemist, and cardiologist, studying the molecular biology of the cardiovascular system while also caring for patients. His research interest is in understanding the genetic basis of cardiovascular disease, with a focus on how regulation of gene expression affects cardiovascular disease phenotypes, and a goal to develop therapeutic agents that can ameliorate pathological phenotypes and thus provide treatments for cardiovascular diseases. The activities of the Chin Lab include developing an enzyme replacement therapy for a genetic cardiomyopathy disorder, Barth syndrome, and identifying molecular pathways that regulate cardiac sensitivity to developmental diesel exhaust exposure. His lab also has expertise in analyzing developmental phenotypes in genetically modified mice, differentiating embryonic stem cells to cardiomyocytes, culturing primary vascular, cardiac, and embryonic cells for gain and loss of function studies, assessing for cardiac hypertrophy and heart failure in vitro and in vivo, as well as

TransCellular Therapeutics (TCT) is a private early stage biopharmaceutical company focused on developing novel protein-based therapies for the treatment of inherited diseases for which there are few alternative therapies. TCT engineers these proteins so that they are able to travel from the bloodstream across the cell membrane into the cell, where they correct metabolic defects, thereby returning normal function to the cell and organ system.

TCT's first goal is to develop an enzyme replacement therapy for Barth syndrome, a genetic disorder characterized by mutations in the *tafazzin* gene.

TCT was founded in 2015 by Michael Chin. To date the company has been funded through grants from various institutions. Dr Chin has nearly 20 years of experience in caring for patients and in supervising a research group studying the molecular biology of the cardiovascular system. Craig W. Philips has over 30 years of pharmaceutical industry experience with both large and small pharma. He has extensive experience with corporate strategy, partnering and business development, and preclinical and clinical oversight.

experience in measuring mitochondrial respiration, skeletal muscle contraction, and mouse treadmill exercise performance.

Dr. Chin completed medical school and a PhD at the University of Rochester. He then went on to do a Residency at The Johns Hopkins Hospital, a Post-Doctoral Research Fellowship at the National Institute on Aging, and a Fellowship in Cardiovascular Diseases at Brigham and Women's Hospital. Dr. Chin is a member of the American Society for Clinical Investigation and the Editorial Board for the Journal of Molecular and Cellular Cardiology. He has served on NIH and AHA Study Sections and has received awards for his work at every stage of his career.

Dr. Chin is a multiple awardee of the BSF Research Grant Program.

Yuguang (Roger) Shi, PhD

Joe R. & Teresa Lozano Long Distinguished Chair in Metabolic Biology
 Professor of Pharmacology
 Barshop Institute for Longevity and Aging Studies
 University of Texas Health Science Center at San Antonio
 San Antonio, TX



Dr. Yuguang (Roger) Shi's lab focuses on translational aspects of aging-related metabolic diseases using molecular, cellular, metabolic, and transgenic approaches. His work has recently identified a critical missing link between mitochondrial dysfunction in aging and the onset of various aging-related diseases, paving the way for the development of novel treatment for these pathogenic conditions.

Dr. Shi is also uncovering novel signaling pathways that regulate glucose-sensing by pancreatic beta cells, since a loss of glucose responsiveness by pancreatic beta cells is a major pathological event that triggers the onset of Type 2 diabetes. The lab is recruiting graduate students and postdoctoral fellows.

Dr. Shi is a multiple BSF Research Grant Program awardee.

Perenna is an early stage biotech company targeting mitochondrial dysfunction for the treatment of aging-related diseases. The company has developed a number of highly potent (with IC50 of 10nM) ALCAT1 inhibitors and completed proof of concept studies in various animal models (heart failure, Alzheimer's, Parkinson, and diabetic complications). The company plans to file the first IND on Barth syndrome as an orphan disease after testing the ALCAT1 inhibitors in TAZ knockout mice.

CLINICAL CANDIDATES

Gene Augmentation Therapy

Drs. Byrne, Christina Pacak, and Todd Cade are critical to this therapeutic approach, both in design and clinical implementation. Dr. Byrne has direct medical experience with gene therapy clinical trials. Preclinical work with a knockdown mouse model of Barth syndrome has demonstrated reversal of the mouse phenotype in both of the two major Barth syndrome pathologies of cardiac dysfunction and fatigue/muscular strength. The AAV serotype 9 vector with the human *tafazzin* mini-gene (*tafazzin* gene dysfunction causes Barth syndrome) using a *desmin* promoter is the vector anticipated to be used clinically by this team. Dr. Byrne's position as Director of the Powell Gene Therapy Center at the University of Florida, his connections with the gene therapy industry, his advisory relationship with the FDA, particularly with the head of CBER, and his team's concentration on Barth syndrome clinical and preclinical research should be noted.

Enzyme Replacement Therapy ("ERT")

Dr. Chin has developed a recombinant DNA system in *E. coli* to produce, purify, and refold human *tafazzin* protein with an attached C-terminal cell penetrating peptide. This would be the material used for therapy. He has tested this system in cellular models and reversed the monolysocardiolipin:cardiolipin ("MLCL:CL") ratio – a distinctive biochemical test for the diagnosis of Barth syndrome – and showed transport of the recombinant protein into the mitochondria. Initial but preliminary results in the heart-specific knockout mouse model of Barth syndrome revealed at the 2018 BSF Conference showed an improvement of some of the dysfunctional cardiac parameters with enzyme treatment. Mitochondrial morphology (a common dysfunction in Barth syndrome) also improved as did the MLCL:CL ratio, which gives confidence that the recombinant protein is getting into the mitochondria. Dr. Chin has formed a biotech company called Transcellular Therapeutics with the intent to deliver ERT, and Barth syndrome will be its first indication.

ALCAT1 inhibitors

Dr. Shi discovered the ALCAT1 gene as one of three enzymes that alter cardiolipin (cardiolipin is uniquely associated with Barth syndrome). ALCAT1 appears to be a negative influence on the function of the mitochondria, and that disrupting this gene's function causes a positive reversal in the phenotype of several animal models of human disease like heart failure, Alzheimer's, Parkinson's, and diabetic complications. In genetic crosses of the knockdown mouse model of Barth syndrome with the ALCAT KO line, the cardiac phenotype of the Barth mouse was reversed. Dr. Shi has recently developed orally-available inhibitors of the ALCAT1 enzyme that show efficacy in a mouse model of Parkinson's disease. Dr. Shi believes that a test of his orally-available compounds with the mouse model of Barth syndrome would have similar positive results as his genetic experiments would suggest. Dr. Shi has formed an early stage biotech company called Perenna to exploit his work with ALCAT1 inhibitors, and he intends to file an IND for a Barth syndrome indication.

MEETING FORMAT

Our aim is to review each program and have the investigators describe the clinical and development outlook based on their work. We will keep each project presentation to 40 minutes, allow the invited reviewers and the SMAB members present to ask questions to the presenters, followed by open questioning by all present at the meeting. Each presenter will only be present for their 80-minute discussion as the presenters may choose to share confidential results and plans with the group.

AGENDA

- 8:00-9:00 Introductions and meeting goal review
- 9:00-9:30 William Pu: Introduction to gene therapy (25-minute presentation, 5-minute Q&A)
- 9:30-10:50 Presenter 1 (40-minute presentation, 40-minute Q&A)
- 10:55-12:15 Presenter 2 (40-minute presentation, 40-minute Q&A)
- 12:15-1:15 Lunch
- 1:20-2:40 Presenter 3 (40-minute presentation, 40-minute Q&A)
- 2:45-4:00 SMAB and Reviewers discussion of 3 clinical opportunities (guided discussion each project one at a time, up to 25 minutes each)
- 4:00-5:00 Open discussion and wrap-up

ADVISORS

MODERATOR

Julia Greenstein, PhD

Consultant
Life Science Advisors
Boston, MA



Julia Greenstein leads Life Science Advisors, consulting for the biotech and academic community as well as in the area of medical and scientific philanthropy. Previously she was Vice President for Research Strategy at JDRF, serving in a variety of roles over 12 years beginning in the Beta Cell portfolio and in a variety of roles in the Cure and Prevention portfolios.

Previously she was CEO of Immerge BioTherapeutics, Inc., a Novartis Pharma/BioTransplant JV, and has held the roles CSO at BioTransplant and VP of Discovery Research at ImmuLogic Pharmaceutical Corp.

She received her PhD in Microbiology from University of Rochester Medical School. She did postdoctoral training at the University of Rochester Medical School and the Dana-Farber Cancer Institute of Harvard Medical School and was an Assistant Professor at the Dana-Farber Cancer Institute.

In addition, she serves on the Board of Directors of The Sage Colleges and is on the University of Rochester Regional Cabinet.

EXTERNAL REVIEWERS

Adam Chicco, PhD

Associate Professor of Biomedical Sciences
Colorado State University
Fort Collins, CO



Adam Chicco is an Associate Professor of Biomedical Sciences and Director of the Cardiovascular Research Center at Colorado State University in Fort Collins, CO. His research focuses on the pathogenic links between cardiac phospholipid remodeling, polyunsaturated fatty acid (PUFA) metabolism, and mitochondrial function in the development of cardiometabolic diseases. In particular, he has a longstanding interest in the physiological impacts of altered cardiolipin acyl composition in the settings of heart failure, diabetes, and Barth syndrome. His work in these areas has been continuously funded by NIH, the American Heart Association, USDA, and/or private foundations since 2005, and has recently expanded to include fruitful collaborations in the fields of developmental biology, immunology, and environmental adaptation.

Dr. Chicco received his PhD in Physiology from University of Northern Colorado and postdoctoral training with Russell Moore in molecular/cellular cardiology at the University of Colorado Boulder. Since then, he has reviewed hundreds of manuscripts for journals in the fields of physiology, cardiology, endocrinology, and biochemistry, and reviewed grants for multiple domestic and international organizations. He is a Fellow of the Basic Cardiovascular Sciences Council of the American Heart Association, and has been a regular member of the AHA Basic Cell Biology – Membrane and Subcellular Organelle (MSO) grant review committee since 2010, serving as Chair of the national MSO Transformational Project Award committee since 2018. Dr. Chicco is a past recipient and ad hoc reviewer of Barth Syndrome Foundation grants, and has been a speaker at three biennial BSF Scientific & Medical Conferences.

Philip R. Johnson, MD

CSO

Limelight Bio, Inc.

Philadelphia, PA



Dr. Philip R. Johnson received his undergraduate and medical degrees from the University of North Carolina at Chapel Hill, followed by a Pediatric Residency and an Infectious Diseases Fellowship at Vanderbilt University. After fellowship training, he worked at the National Institutes of Health in Bethesda, MD, and Columbus (Ohio) Children's Hospital for 20 years before assuming the role of Chief Scientific Officer and Executive Vice President at the Children's Hospital of Philadelphia in 2005. In his role as Chief Scientific Officer, Dr. Johnson oversaw the research enterprise at Children's Hospital that supported over 2,000 faculty and staff engaged in a wide array of basic, clinical, and translational research activities. Dr. Johnson has received several national honors, including election to the American Pediatric Society and being named a Fellow of the American Association for the Advancement of Science and a Fellow of the American Academy of Microbiology.

Dr. Johnson is currently listed as the CSO of Limelight Bio, Inc. Limelight Bio, Inc. is an emerging biotech company developing novel gene therapies that greatly expand the utility of clinically validated AAV vectors to enable the treatment of debilitating inherited diseases that cannot be addressed by current technologies, such as those caused by mutations in large genes and autosomal dominant inheritance patterns. Limelight was founded by experienced scientific leaders from the University of Pennsylvania and backed by Apple Tree Partners, a leading life science venture capital firm.

Human Gene Therapy, VOL. 27, NO. 1 | Research Articles



Recombinant Adeno-Associated Virus Vector Genomes Take the Form of Long-Lived, Transcriptionally Competent Episomes in Human Muscle

Bruce C. Schnepf, Jeffrey D. Chulay, Guo-Jie Ye, Terence R. Flotte, Bruce C. Trapnell, and Philip R. Johnson

Published Online: 2 Dec 2015 | <https://doi.org/10.1089/hum.2015.136>

R. Mark Payne, MD

Professor of Pediatrics
Indiana University School of Medicine
Indianapolis, IN



Dr. R. Mark Payne received his MD from University of Texas School of Medicine, Houston. He completed his Residency in Pediatrics, his Pediatric Cardiology Fellowship, and a Research Fellowship in Molecular

Biology at the Children's Hospital at Washington University School of Medicine, St

Louis. He is certified by the American Board of Pediatrics in Cardiology and is a Fellow of the American Academy of Pediatrics and the American College of Cardiology. Dr. Payne is a tenured Professor of Pediatric Cardiology with a secondary appointment in the Department of Medical and Molecular Genetics. Research in his clinic and laboratory is focused on understanding cardiomyopathies and heart failure in children and developing new therapies to repair or prevent children's heart disease. In his clinic, he sees children and young adults who have congenital heart disease, as well as cardiomyopathies such as Friedreich's Ataxia. He is a Fellow of the American College of Cardiology and a Fellow of the American Academy of Pediatrics.

His lab investigates the role of mitochondrial function in heart disease and is funded by multiple sources, including NIH, AHA, and foundation grants. Previously, while at Wake Forest University, Dr. Payne conducted extensive research of TAT-transduction technology and was the inventor on the patent, Non-viral Delivery of Proteins to Mitochondria. Dr. Payne also works closely with the patient advocacy group, Friedreich's Ataxia Research Alliance (FARA), as a scientific advisor, and has significant experience in working with large and small pharmaceutical organizations in basic and clinical research.

Dr. Payne is a co-founder of Chondrial Therapeutics and currently serves as the company's Chief Scientific Officer. A renowned scientist and practicing physician, Dr. Payne brings to Chondrial a longstanding scientific focus on protein targeting to mitochondria and a dedication to treating cardiomyopathies of childhood, including Friedreich's Ataxia.

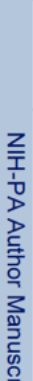

Dr. Payne has served as an external reviewer for the BSF Research Grant Program over the years.

JCI insight

Nicotinamide mononucleotide requires SIRT3 to improve cardiac function and bioenergetics in a Friedreich's ataxia cardiomyopathy model

Angelical S. Martin, ... , R. Mark Payne, Matthew D. Hirschey

JCI Insight. 2017;2(14):e93885. <https://doi.org/10.1172/jci.insight.93885>.

		NIH Public Access Author Manuscript <i>Prog Pediatr Cardiol</i> . Author manuscript: available in PMC 2012 May 1.
	Published in final edited form as: <i>Prog Pediatr Cardiol</i> . 2011 May ; 31(2): 103–109. doi:10.1016/j.ppedcard.2011.02.007.	
The Heart in Friedreich's Ataxia: Basic Findings and Clinical Implications		
R Mark Payne* Riley Heart Research Center, Wells Center for Pediatric Research, Indiana University School of Medicine, Indianapolis, IN, 46202		

Charles P. Venditti, MD, PhD

Senior Investigator

National Human Genome Research Institute, NIH

Bethesda, MD



Dr. Charles P. Venditti received an SB from the Massachusetts Institute of Technology in 1988 and was an MD, PhD scholarship recipient at Penn State University. After graduation in 1996, he completed a Pediatrics Residency at Massachusetts General Hospital/Harvard Medical School (1996-1999) and a combined Clinical and Biochemical Genetics Fellowship (1999-2003) at the Children's Hospital of Philadelphia/University of Pennsylvania School of Medicine. After his fellowship, he joined NHGRI as a member of the Physician-Scientist Development Program (2003-2008) and then as a tenure-track investigator in the Genetics and Molecular Biology Branch (2008-current).

He is board-certified in Pediatrics, Clinical Genetics, and Biochemical Genetics and is an attending physician at the Mark O. Hatfield Clinical Center at NIH, where he has initiated a translational research program to study the natural history and clinical phenotype(s) of the hereditary methylmalonic acidemias (MMA) and cobalamin metabolic disorders. The clinical research studies are paralleled by laboratory investigations that have focused on the development of experimental systems to study the genetics, genomics, and biochemistry of organic acid metabolism in model organisms, including roundworms, mice, and zebrafish. Using a translational research approach, Dr. Venditti and his colleagues have published a number of papers that connect disease pathophysiology in MMA to mitochondrial dysfunction and prove the efficacy of gene therapy as a treatment for both methylmalonic acidemia and propionic acidemia.

In 2009, he was the recipient of a Presidential Early Career Award for Scientists and Engineers (PECASE), the U.S. government's highest honor for early-career scientists. Other awards include selection as an Outstanding New Investigator from the American Society of Gene and Cell Therapy in 2010 and election into the American Society of Clinical Investigation (ASCI) in 2012. Dr. Venditti is a member of numerous professional organizations in the fields of inborn errors of metabolism, genetics, and gene therapy and serves on the medical advisory board of the Organic Acid Association (OAA).

Dr. Venditti has served as an external reviewer for the BSF Research Grant Program over the years.

JCI The Journal of Clinical Investigation

Vector design influences hepatic genotoxicity after adeno-associated virus gene therapy

Randy J. Chandler, ... , Shawn M. Burgess, Charles P. Venditti

J Clin Invest. 2015;125(2):870-880. <https://doi.org/10.1172/JCI79213>.

https://www.youtube.com/watch?time_continue=1&v=IEpUwiVHj1E