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TITLE: The Therapeutic Effect of the Antitumor Drug 11beta and Related Molecules on Polycystic Kidney Disease

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14. ABSTRACT:

This project aims to develop and validate synthetic multifunctional compounds as therapeutics for polycystic kidney disease (PKD). In collaboration with the Essigmann lab at MIT, we have shown that two parent compounds, 11B-dichloro and 11B-dipropyl, are effective in preventing and delaying cyst growth in two different orthologous mouse models of PKD. To guide the development of new compounds, the mechanism by which 11B compounds achieve their efficacy and selectivity against cystic cells is being investigated. One arm of the project focuses on the synthesis of new molecules in the 11B family, which will inform, through structure-activity studies, the key molecular features required for activity and provide additional hints about mechanism of action. A second arm of the project focuses on the development of a cell culture model that can be used to screen the new molecules for improved efficacy and selectivity; such molecules will be then validated in the established PKD mouse models and pave the way towards their preclinical and clinical development. During the last funding period, we successfully synthesized 0.5 g of 11B-dipropyl which is beginning testing in the adult onset model of PKD. We produced and studied novel epithelial cell line models of 11B action. We established potentially novel roles for mitochondrial function and the unfolded protein response in PKD pathogenesis and 11B action.

15. SUBJECT TERMS
Polycystic kidney disease, ADPKD, PKD1, polycystin1, therapeutic, apoptosis, mitochondria, reactive oxygen species, unfolded protein response

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Table of Contents

1. INTRODUCTION

This project aims to develop and validate synthetic multifunctional compounds as therapeutics for polycystic kidney disease (PKD). In collaboration with the Essigmann lab at MIT, we have shown that two parent compounds, 11B-dichloro and 11B-dipropyl, are effective in preventing and delaying cyst growth in two different orthologous mouse models of PKD. To guide the development of new compounds, the mechanism by which 11B compounds achieve their efficacy and selectivity against cystic cells is being investigated. One arm of the project focuses on the synthesis of new molecules in the 11B family, which will inform, through structure-activity studies, the key molecular features required for activity and provide additional hints about mechanism of action. A second arm of the project focuses on the development of a cell culture model that can be used to screen the new molecules for improved efficacy and selectivity; such molecules will be then validated in the established PKD mouse models and pave the way towards their preclinical and clinical development. During the last funding period, we successfully synthesized 0.5 g of 11B-dipropyl which is beginning testing in the adult onset model of PKD. We produced and studied novel epithelial cell line models of 11B action. We established potentially novel roles for mitochondrial function and the unfolded protein response in PKD pathogenesis and 11B action.

2. KEYWORDS

Polycystic kidney disease, cystic disease, ADPKD, *PKD1*, *PKD2*, therapeutic, polycystin-1, apoptosis, mitochondria, reactive oxygen species, unfolded protein response, mouse model.

3. ACCOMPLISHMENTS

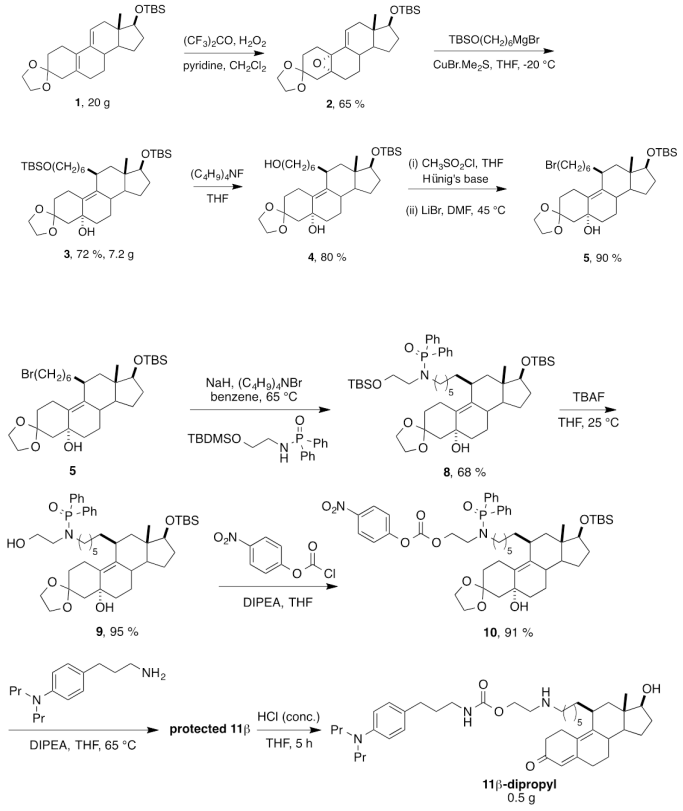

Figure 1. The chemical synthesis scheme for 11B-dipropyl. The percentages under each compound denote the typical yield of the transformation. The amounts under certain compounds denote the amounts available on hand as of September 29, 2016.

What were the major goals of the project?

Our major goals were:

- Synthesize 0.5 grams of 11B-dipropyl (completed August 2016)
- Test 11B-dipropyl in the adult onset PKD mouse model (10% completed).
- Synthesize analogs with different linkers and/or alkyl substituents (50% completed).
- Establish a cell culture model to evaluate efficacy and selectivity of 11B-compounds (completed September 2016)
- Using the cell culture model, investigate the role of apoptosis, mitochondrial metabolism and UPR in the toxicity and anti-PKD effects of 11B compounds (20% completed).
- Using the cell culture model, evaluate the efficacy and selectivity of the 11B analogs (10% completed).

What was accomplished under these goals?

a. Synthesis of 11B-dipropyl (Essigmann, MIT)

11B-dipropyl was synthesized using the scheme outlined in Figure 1. After a number of small scale trials to optimize the conditions

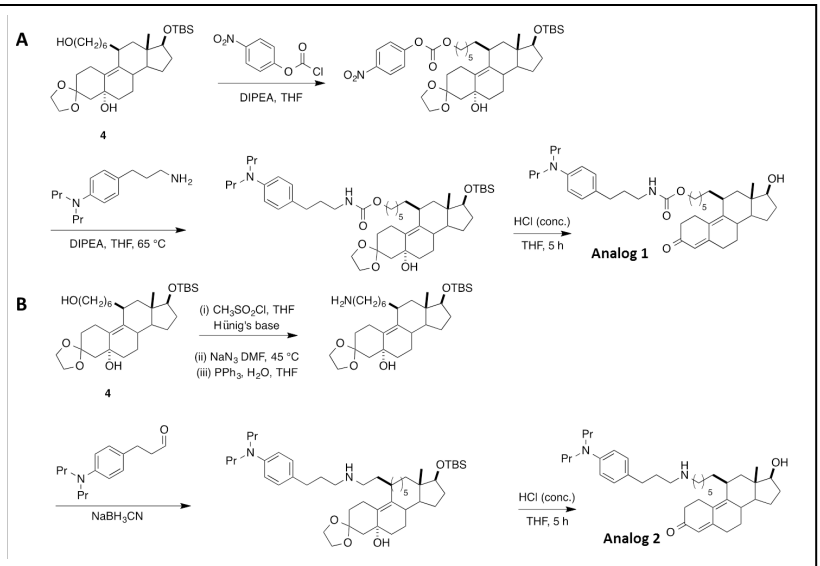

Figure 2. Chemical synthesis schemes for 11B-dipropyl derivatives with simplified linkers. A) The synthesis scheme for analog 1, which features a linker with only the carbamate moiety. B) The synthesis scheme for analog 2, which features a linker with only the secondary amine moiety.

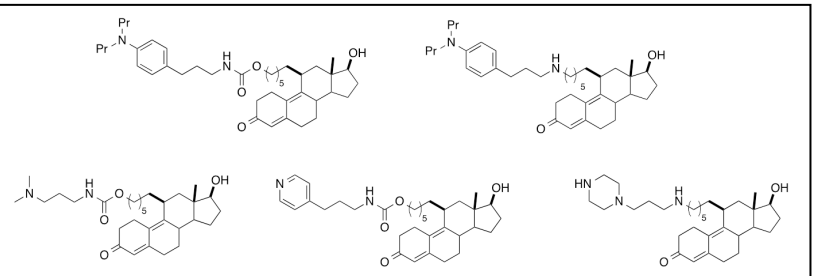

Figure 3. Chemical structures of the11B-dipropyl analogs currently in the synthesis pipeline, which will be used for structure-activity studies.

for each of the steps, larger scale syntheses were performed to obtain ~0.5 grams of 11B-dipropyl. The compound was characterized by ^{1}H-NMR, ^{13}C-NMR, MS and UV-Vis.

As explained in Section 5 (Changes/Problems), an improved strategy for the synthesis of the dipropyl-aniline-amine portion had to be designed in order to obtain reasonable yields.

A number of intermediates (**1** [20 g], **3** [7.2 g], protected ethanol-amine [8 g] and the dipropyl-aniline-amine [4.2 g]) were synthesized in larger quantities. These will constitute the precursors for the majority of the 11B-dipropyl derivatives proposed. The synthesis schemes of two such derivatives, featuring simplified linkers are depicted in Figure 2. These two syntheses are underway, with products expected within 1-2 month. Additional derivatives planned for the next funding period are shown in Figure 3.

b. Probing the mechanism of toxicity of 11B compounds in cell culture (Essigmann, MIT; Somlo, Yale)

Work from the Somlo and Essigmann labs has shown that 11B compounds (specifically 11B-dichloro) kill cells by deregulating mitochondrial respiration, which leads to increased oxidative stress and by increasing the level of ER stress, which manifests as the unfolded protein response (UPR). Either of these perturbations may be influencing and promoting the other, with the end result being cell death by apoptosis.

Before the development of the LLC-PK cell line model (Somlo group, Yale; see below), the Essigmann group performed studies on the mechanism of toxicity of 11B-dichloro on the conditionally immortalized PH2 (Pkd1+/- heterozygous) and PN24 (Pkd1-/- null) cell lines made by the Somlo group from *Pkd1* conditional mouse models. During the course of the first year, the Somlo group used CRISPR/Cas9 technology to further modify the PN24 cell line to knockout XBP1. Efficiency of the knockout was validated by sequencing of genomic DNA and absence of XBP1s (the active spliced form) following stress with tunicamycin (data not shown). This double mutant (Pkd1-/-; Xbp1-/-), called PN10, was used to evaluate the role of the Ire1α/XBP1 branch of the unfolded protein response (UPR) in 11B activity.

The toxicity of 11B-dichloro was evaluated in cell culture, using the above-mentioned cell lines (Essigmann lab). The cells were initially cultured at the permissible temperature (33 °C), then re-plated at 37 °C, in the absence of interferon gamma, conditions in which turn off the large T transgene and allow the cells differentiate into a more epithelial phenotype. The monolayers thus formed were then

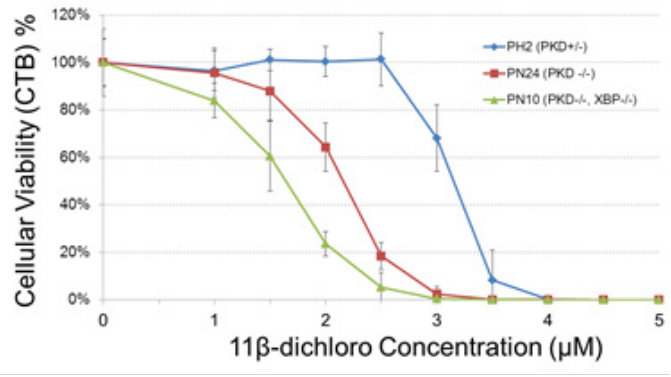

Figure 4. Dose response curves of *Pkd1* cell lines to 11B-dichloro.

exposed to 11B-dichloro doses ranging from 0-5 μM for 24 hours, and the cell viability was then analyzed with CellTiter-Blue (Promega). We found that Pkd1-/- cells are more sensitive to 11B than Pkd1+/- PH2 cells, and that the double mutant PN10 cells (Pkd1-/-; Xbp1-/-) are even more sensitive than the single Pkd1 mutant PN24 cells (Figure 4). The IC50 values were: PH2 (~3.3 μM), PN24 (~2.3 μM), PN10 (~1.6 μM). These findings demonstrate that UPR, through the activity of XBP1, plays a modulatory role in the toxicity of 11B-dichloro. The Somlo group is performing the in vivo correlate of these studies. We have produced *Pkd1*$^{fl/fl}$*; Xbp1*$^{fl/fl}$*; Pkhd1-Cre* (DKO) mice and control *Pkd1*$^{fl/fl}$*; Pkhd1-Cre* (SKO) mice. We are treating these with 11B-dichloro and vehicle to determine whether in vivo apoptotic response of cyst cells to 11B is dependent on XBP1 activation.

Next the Essigmann group investigated two aspects of 11B-dichloro toxicity: generation of reactive oxygen species, and calcium imbalance. To test whether the generation of oxidative stress plays a role in the toxicity of 11B compounds in *Pkd1* mutant cells, we co-treated the cells with the antioxidants N-acetyl cysteine (NAC) and vitamin E. Both Pkd1+/- and Pkd1-/- cell lines showed decreased sensitivity to 11B-dichloro in the presence of either NAC or vitamin E.

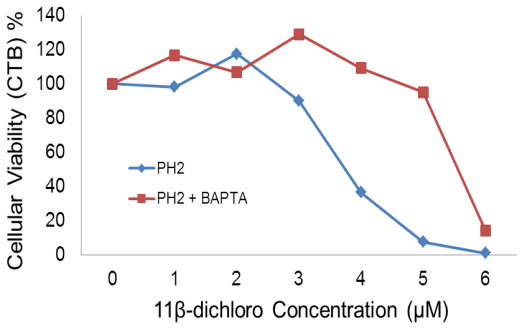

Figure 5. Effect of intracellular calcium on 11B-dichloro toxicity. Co-treatment with calcium chelator BAPTA-AM ameliorates 11B toxicity.

Earlier studies on 11B-dichloro found that lower doses of the compound increase the intracellular calcium concentration. To test whether this increase in calcium concentration is required for 11B toxicity, we exposed the cells to the drug in the presence of the intracellular calcium chelator BAPTA-AM, a substance that should buffer drastic changes in the calcium concentration. Our preliminary results show that by chelating the intracellular calcium, the toxicity of 11B-dichloro is reduced (Figure 5; Essigmann group). These data suggest that deregulation of calcium homeostasis may play a role in the toxicity of the drug – and may help connect, mechanistically, the effects of 11B on mitochondria with the effects on the endoplasmic reticulum and subsequent UPR.

We also made some headway in elucidating the basis for the selectivity of 11B compounds towards Pkd1-/- cells. Our previous work indicated that 11B compounds localize in the mitochondria, where they inhibit the activity of complex I of the electron transport chain, thus generating reactive oxygen species, and setting in motion the cell stress response that culminates with apoptosis. A joint brainstorming session between the teams at MIT and Yale raised the possibility that the altered mitochondrial metabolism of Pkd1-/- cells may be due to a change in the number of mitochondria/cell as well as their functional competency.

Since the in vivo models of kidney cysts represent the most certain relevant surrogate phenotypes for human ADPKD, the effect of *Pkd1* inactivation on the mitochondrial biogenesis status was investigated *in vivo* (Somlo group) in the adult *Pkd1* inactivation model at an early cystic stage (*Pkd1*$^{flox/flox}$*;Pax8-rtTA;TetO-Cre;* 12 weeks old). We found that the mitochondrial marker Tom20 was significantly upregulated as seen by immunoblotting (Figure 6). Next the Somlo lab examined via qPCR whether there was a difference in the relative ratio of copies of *ND1,* a subunit of complex I encoded on the

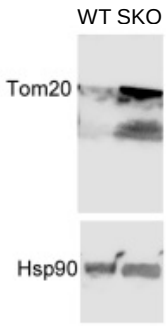

Figure 6. The mitochondrial marker Tom20 is upregulated in *Pkd1flox/flox;Pax8-rtTA;TetO-Cre* (SKO) vs. WT kidney tissue lysates. Hsp90 serves as loading control.

mitochondrial genome, to the number of copies of *HPRT* encoded nuclear genome in kidney tissue DNA from WT and *Pkd1* SKO knockout kidneys (*Pkd1*$^{flox/flox}$*;Pax8-rtTA;TetO-Cre;* 8 weeks old). The 8 week time point is a pre-cystic stage such that there is no increase in cyst lining cell mass; this is expected to be an indication of an early cell autonomous phenotype in the knockout cells. There was ~2 fold increase in the copies of *ND1* normalized to *HPRT* in *Pkd1* SKO compared to WT kidney DNA (Figure 7) suggesting that there is ~2-fold increase in the number of mtDNA per Pkd1 knockout cell. Kidney tissue is mosaic with many cell types and only a minority (<50%) of these cells have Cre activity due to *Pax8rtTA* induction. These cells are largely proximal tubule and distal nephron, which have the largest baseline complement of mitochondria due to their energy needs, so changes in the mitochondrial content in these cells will manifest as global changes in whole kidney mitochondrial content. Mitochondrial staining in tissue sections of cystic and control kidneys confirmed that the increased mitochondrial burden arose from cyst cells (data not shown). The Essigmann group examined the number of copies of *ND1* relative to the number of copies *HPRT*. Preliminary data show that Pkd1-/- cells have a 1.3-fold increase in the number of mitochondrial chromosome copies (Figure 8), which is consistent with an increase in the number of mitochondria seen in the in vivo models and suggest that the cell lines are likely useful surrogates in evaluating phenotypes relevant to energy metabolism and 11B function that extend to the in vivo models.

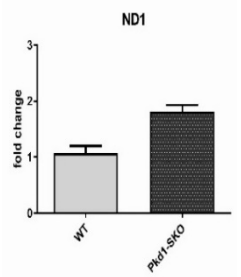

Figure 7. The expression of the mitochondrial DNA marker *ND1* is increased ~2 fold in *Pkd1* knockout kidneys (*P* = 0.041; t-test).

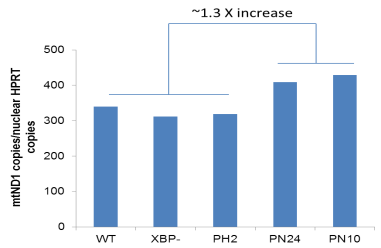

Figure 8. Relative number of mitochondrial genomes in *Pkd1-/-* cells, relative to wild-type cells.

c. Development of a cell culture model to evaluate 11B compounds. (Somlo, Yale; Essigmann, MIT).

The Somlo group developed the well characterized LLC-PK1 (ATCC CL-101) kidney epithelial cell line as a cell culture model for testing 11B compounds activity. The advantages of this line over cell lines noted above are: i) a generally available and well characterized kidney epithelium cell line; ii) the cells exhibit contact growth inhibition, which allows formation of stable monolayers, without the need to inactivate a growth-driving oncogene (e.g. SV40); iii) these cells readily form cilia in cell culture; iv) they are easy to culture under standard conditions. The Somlo lab then employed CRISPR/Cas9 technology to generate two isogenic cell lines (2 independent clones for each) derived from LLC-PK1 in which either *Pkd1* or *Pkd2* genes were deleted as well as an isogenic control cell line in which Cas9 is stably expressed but no gRNAs were introduced leaving it wild type for both *Pkd1* and *Pkd2*. The control and the two mutant cell lines were then evaluated in cell culture by the Essigmann team at MIT.

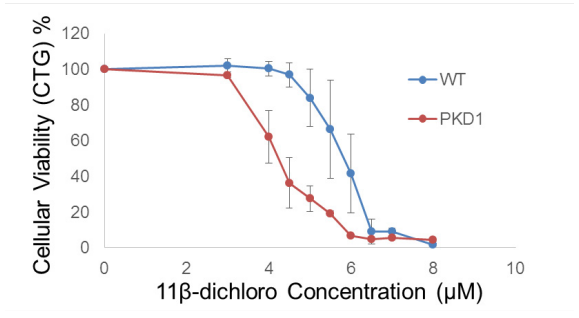

Figure 9. Dose responses to 11B-dichloro of LLC-PK1 cell lines (WT and Pkd1-/-).

Preliminary work with the LLC-PK1 cell lines showed that they could be a good cell culture model for 11B compounds sensitivity and specificity. A dose response with 11B-dichloro showed that the *Pkd1* knockout is more sensitive to compound than the wild-type parent line (Figure 9). The cellular viability in this

case was measured using the CellTiter-Glo reagent from Promega, which gives a luminescent signal proportional to the amount of ATP present in each well. For reasons that are currently under investigation, the CellTiter-Blue reagent we used for measuring the viability in other cell lines (see above) did not work with the LLC-PK cell lines.

What opportunities for training and professional development has the project provided?

A postdoctoral research scientist, Sakunchai Khumsubdee was supported by the project. Sorin Fedeles and Rachel Gallagher, associate research scientists were in part supported by this project. A Northeastern Coop undergraduate student (Jake Campolo) and two undergraduate students from MIT's Undergraduate Research Opportunities Program (UROP) (Michelle Huang and Leandra Zimmermann) contributed to the project.

How were the results disseminated to communities of interest?

Results from this project were disseminated in the form of oral and poster presentations at the 2015 and 2016 (upcoming) annual meetings of the American Society of Nephrology. The titles of the published abstracts are included in Section 6. The data were also presented in seminars a Yale as part of the PKD Center meetings that involve investigators, fellows and students from the Departments of Medicine, Genetics, Pediatrics and Physiology.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period, we will continue our work to investigate the mechanism of action of 11B compounds against Pkd mutant cells (both *Pkd1* and *Pkd2*) in cell culture, and their efficacy in animal models of PKD, including notably the adult onset inducible models. We will complete the synthesis of the proposed 11B analogs (Essigmann, MIT). We will test these analogs in the cell culture models we recently established to evaluate efficacy and selectivity for PKD -/- cells (Essigmann, MIT). We will complete the testing of the efficacy of 11B-dipropyl in the adult *Pkd1* inactivation model (*Pkd1*$^{flox/flox}$*;Pax8-rtta;TetO-Cre;* 12 weeks old) mouse model (Somlo, Yale). We will test the best 11B analogs in the early onset PKD mouse model (*Pkd1*$^{fl/fl}$*; Pkhd1-Cre*) to validate their in vivo activity. We will perform metabolic evaluation of mitochondrial function in cystic models with and without 11B treatment.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

This project is likely to make an impact in the area of therapeutics targeted at polycystic kidney disease (PKD). The 11B compounds show great efficacy in preventing cystic growth in mouse models, suggesting that they can be developed into clinical candidates. Furthermore, the 11B compounds work by inducing apoptosis in cystic cells, a mechanism of action that is relatively unique in the field of PKD.

What was the impact on other disciplines?

The 11B compounds that will be developed in this project for treating PKD are likely to have an impact for the treatment of other diseases, including cystic diseases in other organs (i.e. liver) or proliferative diseases (i.e. cancer). In the future, they may be explored as therapeutic agents in recessive ciliopathy disorders related to PKD.

What was the impact on technology transfer?

The new 11B compounds and derivatives synthesized in this project have the potential to qualify for composition of matter and use patents for treating PKD and related cystic diseases.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change.

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them.

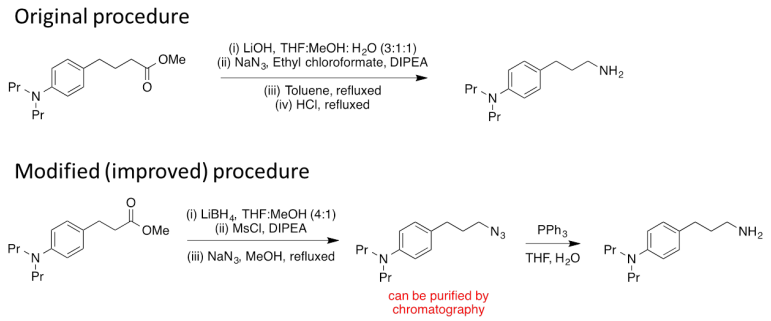

Figure 12. Modification to the synthesis of the dipropyl-aniline-amine. The improved procedure generates a pure product and improved yield.

The synthesis of the 11B-dipropyl compound took longer than previously anticipated. Several steps in the procedure produced yields that were too low, due to formation of side products which led to an inefficient recovery of the desired material. Specifically, the originally proposed strategy for the synthesis of the dipropyl-aniline-amine (Figure 12) produced an impure amine product and low yield. We developed a new procedure, in which the final step is the Staudinger reduction of azide with triphenylphosphine, which generates a very clean amine product in high yield.

Changes that had a significant impact on expenditures.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.

Significant changes in use or care of human subjects.

Nothing to report.

Significant changes in use or care of vertebrate animals.

Nothing to report.

Significant changes in use of biohazards and/or select agents.

Nothing to report.

6. PRODUCTS:

Journal publications.

A manuscript that includes most of the preliminary data outlined in the proposal for this award, as well as some of the more recent data, is currently in preparation. The manuscript acknowledges the federal support received.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers, and presentations.

American Society of Nephrology published abstracts:

1. Fedeles, S., Ishikawa Y., Gallagher R., Lee AH., Somlo S. Genetic interaction between *XBP1* and *Pkd1* modulates cyst progression in ADPKD. 2016, *J.Am.Soc.Nephrol.* (27); 211-12A

2. Fedeles, S., Fedeles, B., Ishikawa, Y., Essigmann, J., Somlo S. 11β inhibits cyst progression in an adult ADPKD model. 2015, *J.Am.Soc.Nephrol.* (26); 347-48A

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

The non-provisional patent application 14/515,441, entitled “Methods for treating polycystic kidney disease and polycystic liver disease” was filed jointly by MIT and Yale on October 15, 2014. While this application was filed prior to the start of the funding for this project, it covers a broad range of compounds that could be used to treat polycystic kidney disease. Most of the compounds that are being synthesized as part of this project may be covered by this patent application.

Other Products

Nothing to report.

7. Participants and Other Collaborating Organizations

Name:	*Somlo, Stefan*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2.4*
Contribution to Project:	*Overall supervisory responsibility for the Yale site providing oversight of the project progress at Yale as well as ensuing coordination with the MIT site. Reviewing results, experimental design and quality control on a weekly basis and discussion of results particularly in the context of PKD.*
Funding Support:	

Name:	*Fedeles, Sorin*
Project Role:	*Associate Research Scientist*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
Contribution to Project:	*Performance of experiments including those related to mitochondrial biology in vivo and unfolded protein response studies.*
Funding Support:	

Name:	*Gallagher, Anna-Rachel*
Project Role:	*Associate Research Scientist*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
Contribution to Project:	Performance of experiments including treatment of mice with 11B compounds, analyzing cell lines.
Funding Support:	

Name:	*Tian, Xin*
Project Role:	*Associate Research Scientist*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3*
Contribution to Project:	Mouse colony management for the PKD models used for the study.
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Updated Other Support Pages are included in the Appendix 1.

What other organizations were involved as partners?

This is a COLLABORATIVE AWARD. Our collaboration partner is Stefan Somlo at Yale University.

Details are below:

- **Organization Name:** Massachusetts Institute of Technology
- **Location of Organization:** Cambridge, MA, USA.
- **Partner's contribution to the projec**t
- **Financial support** None
- **In-kind support** Synthesis of compound used in the study
- **Facilities** None
- **Collaboration** Compound synthesis and quality control; cell studies on mechanism of action of compounds; cell studies on mitochondrial function
- **Personnel exchanges** None
- **Other** None

8 SPECIAL REPORTING REQUIREMENTS

This is a COLLABORATIVE AWARD. An independent report from BOTH the initiating PI and Collaborating PI will be provided. The current report is from the Initiating PI (Stefan Somlo). Given the collaborative nature of the work, experiments that involve materials and expertise provided by both institutions are included in this report. The reports are therefore very similar. Throughout the report, the responsible PI and the site where the work was performed is included.

9. APPENDICES:

Appendix 1: Stefan Somlo Updated Other Support Pages

Title:	**Mouse Models of Polycystic Kidney Disease**
Effort:	0.6 calendar months
Supporting Agency:	NIH/NIDDK
Grants Officer:	Krystle Nicholson, nicholsonk@niddk.nih.gov
Performance Period:	06/15/98 – 08/31/17 (NCE)
Level of Funding:	$362,138 Total Costs
Project Goals:	The major goal of this project is to establish the mechanisms of *in vivo* cyst formation in orthologous gene models of ADPKD.
Specific Aims:	The specific aims of this project are (1) to define the in vivo mechanisms of non-cell autonomous cyst formation in PKD and (2) to define the mechanisms of EGFR and MAPK/ERK activation and their role in non-cell autonomous cyst formation.
Overlap:	None

Title:	**Mechanisms of Polycystin and Cilia Function in ADPKD**
Effort:	2.4 calendar months
Supporting Agency:	NIH/NIDDK
Grants Officer:	Krystle Nicholson, nicholsonk@niddk.nih.gov
Performance Period:	09/20/13 – 05/31/18
Level of Funding:	$362,138 Total Costs
Project Goals:	The major goal of this project is to determine the relationship between cilia and polycystin function in polycystic kidney disease.
Specific Aims:	The specific aims of this project are (1) to define the determinants of cyst progression whose activity following inactivation of polycystins is modulated by the presence or absence of intact cilia and (2) to determine the functional interplay between polycystins, cilia and α5β1 integrin in mechanisms of cyst progression.
Overlap:	None

Title:	**George M. O'Brien Kidney Center at Yale** ***Core B*: Mouse Genetics and Cell Line Core**
Effort:	1.2 calendar months
Supporting Agency:	NIH/NIDDK
Grants Officer:	Amanda Linehan, linehana@mail.nih.gov
Performance Period:	09/01/08 – 07/31/18
Level of Funding:	$304,187 Total Costs
Project Goals:	This is a Core Center aimed at providing physiology, mouse and human genetic resource support to facilitate translational and clinical research projects that will advance the study of kidney diseases.
Specific Aims:	The specific aims of this project are (1) to provide services for modification of genes of interest in bacterial artificial chromosome (BAS) for use in transgenic mice (2) to provide services for isolation of primary tubule cells and cell lines from specific nephron segments of mutant mouse strains (3) the generation of conditional knockout and knockin gene targeting strategies and constructs and (4) the education and general resources for investigators in mouse genetic applications.
Overlap:	None

Title:	**Developing Therapies for Polycystic Kidney Disease**
Effort:	0.6 calendar months
Supporting Agency:	Lillian Goldman Charitable Trust
Grants Officer:	R Scott Johnston (Hollan & Knight LLP), scott.johnston@hklaw.com
Performance Period:	03/14/14 – 3/13/17
Level of Funding:	$200,000 Total Costs
Project Goals:	The major goal of this project is to translate basic scientific investigations into therapeutic target discovery.
Specific Aims:	The specific aims of this project are (1) to determine whether polycystic kidney disease is reversible and (2) to determine whether chaperone therapy is effective in ADPKD resulting from partial loss of function of polycystin-1 due to missense mutations.
Overlap	None

Title:	**Cellular Energy Pathways as Novel Targets for the Therapy of Autosomal Dominant Polycystic Kidney Disease**
Effort:	0.36 calendar months
Supporting Agency:	Department of Defense
Grants Officer:	Susan Dellinger, susan.m.dellinger.civ@mail.mil
Performance Period:	09/01/15 – 08/31/18
Level of Funding:	$50,000 Total Costs (Collaborating Investigator)
Project Goals:	The major goals of this project are to explore in cell culture and animal models the potential therapeutic utility of modulating cellular energy pathways in the setting of polycystic kidney disease.
Specific Aims:	The specific aims of this project are (1) to assess whether PDH kinase inhibition or AMPK activation, alone or in combination, corrects the perturbed energy metabolism in ADPKD cells and slows cyst growth in vitro and in vivo and (2) to measure candidate metabolomic biomarkers and screen for additional biomarkers that correlate with disease severity and progression in ADPKD mice and cells and that are modulated by reduction of PDH kinase activity or AMPK activation. Dr. Somlo's role in the project is to oversee the animal models for the in vivo studies.
Overlap	None