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14. ABSTRACT

miRNAs are small, non-coding RNAs that are 20-23 nucleotides long and control gene expression by binding to the 3' untranslated region (UTR) of complementary mRNAs, causing degradation or translational repression. miRNAs control essential cellular processes, and their mutation and aberrant expression are associated with and causative of disease. Removal of overexpressed, disease-causing miRNAs is thus a viable therapeutic strategy. Here, our overall objective was to develop small molecules that target miR-21, which has been reported to cause pulmonary fibrosis. Small molecules were designed using the Disney lab identification strategy dubbed Inforna. Compounds that selectively degrade miR-21 were identified. LNAs targeting miRNA-21 or miR-21 targeting small molecules were not found to inhibit lung myofibroblast differentiation or function in cellular models.

15. SUBJECT TERMS
None listed.

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1. INTRODUCTION

MiRNAs are small, non-coding RNAs that are 20-23 nucleotides long and control gene expression by binding to the 3' untranslated region (UTR) of complementary mRNAs, causing degradation or translational repression.[10] They are transcribed as primary transcripts (pri-miRNAs) and often contain multiple miRNAs. Indeed, miRNAs control essential cellular processes, and their mutation and aberrant expression are associated with and causative of disease. Removal of overexpressed, disease-causing miRNAs is thus a viable therapeutic strategy. Here, we are developing small molecules that selectively degrade malfunctioning miRNAs in pursuit of lead medicines and deeper understanding of their function. In particular, we will develop our small molecules against two miRNAs: miR-21, which causes pulmonary fibrosis and polycystic kidney disease (PCKD), and miR-17, the upregulation of which causes PCKD. Importantly, we have successfully developed small molecules against various miRNAs by inhibiting protein binding and hence miRNA biogenesis by blocking binding of the processing enzymes Dicer and Drosha.[11-16] These small molecules were designed using our lead identification strategy dubbed Inforna that identifies privileged interactions between RNA 3-dimensional folds and small molecules and searching for those folds in cellular, disease-causing RNAs. As both miR-21 and miR-17 are upregulated in PCKD, compounds that selectively degrade them could have a synergistic effect. Herein, we report our progress to implement our innovative strategy to effect targeted degradation of miR-21 and miR-17 precursors with small molecules: (i) direct cleavage; and (ii) cleavage by recruiting an endogenous nuclease.

Target selection: miR-21 and miR-17. Various studies have linked miR-21 with both pulmonary[17, 18] and kidney[19] fibrosis. Indeed, miR-21's role in the development of fibrosis has been validated *in vivo*: (i) inactivation of miR-21 with an antagomir oligonucleotide prevents fibrosis; while (ii) its overexpression induces fibrosis.[17, 19] Its downstream targets in the development of pulmonary and kidney fibrosis have been identified.[17-19] Interestingly, miR-21 is expressed at aberrantly high levels in PCKD mouse models and its inhibition with an antagomir reduces the number of cysts observed.[23, 24] This, taken together with the fact that miR-21 can be knocked out in mice without adverse effects,[25] indicates the RNA's suitability as a target for therapeutic intervention against both pulmonary fibrosis and PCKD. The miR-17/92 cluster, in particular miR-17, has also been validated as causative of PCKD in mouse models: (i) forced expression of miR-17 exacerbates cyst formation; and (ii) inhibition with an antagomir alleviates it.[24, 26, 27] The downstream protein targets that mediate miR-17's induction of PCKD have been identified.[26, 27]

Small molecules that directly cleave RNA targets. We recently reported two studies in which small molecules were engineered with the ability to selectively degrade a disease-causing RNA.[5, 7] In both cases, a small molecule was conjugated to bleomycin A5, a derivative of the well-known anti-tumor natural product bleomycin. Interestingly, bleomycin cleaves both DNA[28] and RNA *in vitro*.[29-31] Thus, our studies sought to direct bleomycin to only react with the desired RNA target by conjugating it to a small molecule that selectively binds it. Such an approach has been used for oligonucleotide-bleomycin conjugates to afford selective cleavage of DNA *in vitro*.[29, 31, 32]

We chose bleomycin A5 as the cleaving module as the cationic dimethyl sulfonium in the C-terminal DNA-binding domain has been replaced with a butyl-1,4-diamine side chain. This modification serves two purposes: (i) facile conjugation of the terminal primary amine to RNA-binding modules containing carboxylates. Notably, acylation of the butyl-1,4-diamine side chain (cationic) with a small molecule affords an uncharged linkage; and (ii) reduction of DNA binding affinity[1-3] as the cationic side chain, known to drive binding to DNA, has been acylated and is no longer charged. In addition, it has been shown that increasing the size and hydrophobicity of bleomycin A5's butyl-1,4-diamine side chain further decreases DNA binding affinity and the extent of cleavage.[1-3] Conjugation of an RNA-binding module therefore alters bleomycin A5's binding and cleavage preferences toward RNA, as we have observed in the selective cleavage of two disease-causing RNAs.[4-6] *Importantly, we have shown that this strategy selectively cleaves the RNA that causes myotonic dystrophy type 1 (DM1) in vivo, rescued DM1-associated defects including alleviation of myotonia, normalized the transcriptome, and was selective transcriptome- and proteome-wide (no significant RNA or protein off-targets). Further, no induction of lung fibrosis at a dose range that significantly affected the levels of the RNA target was observed.*[6] Likewise, this strategy was applied to the primary transcript of oncogenic miR-96, which was selectively cleaved by the small molecule-bleomycin conjugate, leading to de-repression of a downstream target, and reversal of phenotype in cancer cells.[5]

2. KEYWORDS

Fibrosis, pulmonary fibrosis, polycystic kidney disease, kidney fibrosis, RNA, microRNA, small molecules, targeted degradation

3. ACCOMPLISHMENTS

What were the major goals of the project?

Hypothesis & Objectives: Understanding how to target pathways that involve RNA with small molecules is in its infancy, but such investigations are needed to pursue new avenues in therapeutic development. We submit our proposed studies are *highly* innovative as they design and deliver selective small molecules that act at the level of RNA that could revolutionize our ability to treat pulmonary fibrosis and PCKD. We have discovered two novel means to eliminate disease-causing RNAs by endowing small molecules with the ability to cleave their target directly[4, 5, 7] or by directing endogenous nucleases to cleave them.[8, 9] To test the hypotheses that new therapeutic paradigms for pulmonary fibrosis and PCKD can be developed by selectively cleaving RNAs operating in these disease axes, we propose the following **Specific Aims**, supported by our published work and preliminary data.

Specific Aims & Study Design: In *Aim 1*, we will fully characterize small molecules that directly cleave miR-17, the upregulation of which causes PCKD. These rigorous studies include evaluating our small molecule cleaver and the simple binding compound from which it was derived in cellular models of PCKD and patient-derived cells for: (i) reducing levels of mature miR-17; (ii) de-repressing of its downstream target; and (iii) reduction of cysts. Transcriptome- and proteome-wide studies on the effect of compound treatment will inform lead optimization. The optimal compound will be carried forward to *in vivo* studies proposed in Aim 3. In parallel, we will develop and fully characterize a RIBOTAC against miR-17. In *Aim 2*, we turn our attention to the selective cleavage of miR-21. As summarized in our description of Aim 1, we will fully evaluate our lead small molecule that targets miR-21 and its RIBOTAC in cells derived from PCKD and pulmonary fibrosis patients, including rescue of phenotype and transcriptome- and proteome-wide studies to identify off-targets. In parallel, we will develop the corresponding small molecule that directly cleaves miR-21. Finally, in *Aim 3*, we will evaluate the therapeutic potential of the three most optimal compounds emerging from Aims 1 & 2 for improving PCKD and lung fibrosis *in vivo*. Interestingly, anti-miR-17 and anti-miR-21 compounds could have a synergistic effect on PCKD, which also will be explored.

What was accomplished under these goals?

In this section, we report progress related to Site 2 (partnering PI, Lairson) activities related to **Specific Aims 2a and 3**

Specific Aim 2: Develop and study small molecules that cleave pre-miR-21, the upregulation of which causes PCKD and lung fibrosis.

Aim 2a: Fully evaluate TGP-21 and the TGP-21-C1-3 RIBOTAC in cellular models of PCKD and lung fibrosis, including transcriptome- and proteome-wide studies to identify off-targets.

Major Task 2: Comprehensive cellular evaluation of **TGP-21**, **TGP-21 RIBOTAC**, and **TGP-21-Bleo** in human pulmonary fibroblasts – cytokine-induced fibrosis and in human idiopathic pulmonary fibrosis patient-derived cells (months 1-24)

Subtask 4: Complete transcriptome- and proteome-wide selectivity studies.

Specific Aim 3: Study the optimal compounds emerging from Aims 1 & 2 for improving PCKD and lung fibrosis in vivo.

Major Task 1: Complete DMPK studies

Background: Despite the diversity of diseases and triggers that can initiate a fibrotic process in a given tissue or organ, common biochemical and cellular mechanisms occur in all instances studied to date.[20-22] Following injury or inflammatory insult, resident fibroblasts (in some cases recruited bone marrow-derived circulating fibrocytes or epithelial cells that have undergone an EMT) are activated and "transdifferentiate" into □-smooth muscle actin (α-SMA) expressing myofibroblasts that secrete the extracellular matrix (ECM) components required for wound repair. Transforming growth factor-□1 (TGF-□1) mediated Smad-signaling commonly drives the transdifferentiation of resident fibroblasts to myofibroblasts and stimulates production of ECM components in the latter populations.[22] Platelet-derived growth factor (PDGF) also serves as a common pro-fibrotic cytokine that drives cell activation and proliferation.[22] Validation that the therapeutic approach of inhibiting myofibroblast differentiation/activation is relevant to human fibrosis related diseases is derived from the demonstrated clinical efficacy of pirfenidone in the treatment of idiopathic pulmonary fibrosis. Pirfenidone has well established anti-fibrotic properties in multiple cell-based and animal models of fibrosis.[20] The mechanism of action of this drug is direct inhibition of fibrogenic factor (TGF-β1) production. Cell based assays demonstrate that pirfenidone inhibits myofibroblast transdifferentiation, proliferation and TGF- β1 induced collagen production.[20] The anti-fibrotic activity of pirfenidone has been established using animal models of cardiac, renal, lung and hepatic fibrosis.

Here, we propose to deactivate signaling pathways that promote pulmonary fibrosis by targeting an RNA that operates in many of them, miR-21. Upon injury or in idiopathic pulmonary fibrosis (IPF), TGF-1□□is upregulated, activating transcription of miR-21. Two miR-21 mediated axes have been shown to operate in pulmonary fibrosis, direct repression of Smad7[17] and Spry1 (Sprouty RTK signaling antagonist 1).[17, 33, 34] Spry1 is a negative regulator of Erk activation, which promotes fibrosis via TGF-1β and creates a feedback loop that amplifies fibrogenesis.[82, 83] Smad7 is an antagonist of TGF-1β signaling, and its miR-21 mediated repression further amplifies the miR-21-TGF-1β circuit.[17] The miR-21-PTEN circuit has been investigated in cardiac fibrosis,[35] the axis has not been characterized in pulmonary fibrosis. However, PTEN expression has been shown to be protective in experimental lung fibrosis.[36] Our studies will allow us to fully define the miR-21-PTEN circuit in the development of pulmonary fibrosis.

A distinctive feature of miR-21 expression is that it is primarily upregulated in cyst epithelial cells and not normal tubules, thus representing a unique opportunity for a precision medicine approach to selectively target PCKD.[23, 24] Further, miR-21 is also involved in pulmonary fibrosis and is highly upregulated in myofibroblasts of pulmonary fibrosis lung patients.[17, 18] In lung fibrosis, lung epithelial cells must first undergo epithelial to mesenchymal transition (EMT), followed by differentiation to fibroblasts, and the production of excess extracellular matrix (ECM) proteins resulting in fibrotic tissues.[22] In fibrotic tissues, increased miR-21 results in the transcription of ECM proteins (fibronectin, collagen) and increased production of TGF-1β, a prototypical EMT/differentiation marker, and α-smooth muscle actin (α-SMA), a marker for fibrogenic cell activity.[22] As we have already demonstrated that **TGP-21** and **TGP-21 RIBOTAC** can inhibit breast cancer proliferation and invasive phenotypes caused by miR-21 in breast cancer, herein we report on our progress to develop our miR-21-targeting compounds to rescue PCKD and pulmonary fibrosis phenotypes in patient-derived cells. Overall, these studies will provide chemical tools to study and suppress the pathobiology and molecular mechanisms of these diseases and candidate precision medicines. Notably, unlike the structural differences observed in and adjacent to the pre-miR-17 Dicer site, mouse and human miR-21 are identical. We therefore expect similar activity in both mouse miMDC2 and human WT-7-9 and WT-7-12 cells.

Progress.

Aim 2a: Fully evaluate TGP-21 and the TGP-21-C1-3 RIBOTAC in cellular models of PCKD and lung fibrosis, including transcriptome- and proteome-wide studies to identify off-targets.

Major Task 2: Comprehensive cellular evaluation of **TGP-21**, **TGP-21 RIBOTAC**, and **TGP-21-Bleo** in human pulmonary fibroblasts – cytokine-induced fibrosis and in human idiopathic pulmonary fibrosis patient-derived cells (months 1-24)

Subtask 4: Complete transcriptome- and proteome-wide selectivity studies.

We are using a highly optimized phenotypic myofibroblast differentiation assay, involving serum starved and TGF-b stimulated primary human lung fibroblast, to characterize the potential anti-fibrotic activity of miR-targeting and/or degrading small molecules. Western blot analysis of a-smooth muscle actin (aSMA) expression levels, indicative of induced myofibroblast differentiation, or high content imaging-based immunofluorescent analysis of aSMA intensity and myofibroblast morphological features, are used to quantitatively assess the ability of small molecule or genetic perturbations to inhibit cytokine-induced myofibroblast differentiation. In the previous reporting period, in our work related to Aim 2 and Major task 2 associated with evaluating miR-21-targeting small molecules in human pulmonary fibroblasts, we described observed paradoxical findings when working with dovitinib-based miR-21 targeting agents (i.e., Dovetinib, DOV3 and DOV4). The parent dovitinib molecule was found to induce myofibroblast differentiation, presumably via off-target kinase inhibitory function (e.g., PDGFR, an essential modulator of fibroblast proliferation and differentiation-inhibiting pathway). This result was observed in replicated experiments and confounds the interpretation of any miR-21-dependent anti-fibrotic activity and also eliminates the potential utility of anti-miR-21 compounds based on this scaffold. We also described an identified potential limitation of targeting miR-related mechanisms using our established assay format, based on the relative kinetics of miR degradation versus differentiation. To address these issues, in this reporting period we have re-optimized our assay to facilitate evaluation miR-dependent mechanisms (i.e., miR target degradation and impact on downstream proteome-level changes), by pre-incubating compounds or antagomirs for 24 hours prior to TGF-β stimulation. While the overall dynamic range is lower with this assay format (e.g., Fig. 1A versus Fig. 1B, DMSO +/- TGF-β), statistically significant differences in differentiation efficiency are detectable (Fig 1B).

To address the observed pro-differentiation effect of dovitinib and dovitinib-based compounds that target miR21, in this period we focused our efforts characterizing the activity of the alternative miR21 targeting small molecule TGP-21 and miR21 degrading derivatives thereof (i.e., TGP-21-C1-3 RIBOTAC). To date, this class of compound has not demonstrated appreciable activity in the context of human lung myofibroblast differentiation (Fig. 1B, C). As such, we have focused our efforts on characterizing the alternative targets identified in our completed global RNA-seq and miRNA-seq analysis of unstimulated primary human lung fibroblasts compared to TGF-b stimulated pulmonary myofibroblasts (Fig. 2). As reported previously, based on this analysis, miR-33a-5p, miR-135b-5p and miR-1-3p were identified as being upregulated in differentiated myofibroblasts compared to undifferentiated human lung fibroblasts. In this period, we have validated that levels of mature forms of these miR are significantly upregulated in lung myofibroblasts (fig. 3A and 3B), and that LNAs targeting 3p, 33a or 135b inhibit levels of myofibroblast differentiation (fig. 3C). Consistent with these findings, miR33 deficient mice are protected from kidney fibrosis (Price et al. (2019) JCI Insight. 4: e131302) and miR-135b-5p is a known regulator of TGF signaling (Wang et al. (2021) Aging. 13: 13211). We are now focused on further characterizing these exciting and novel findings, by evaluating 3p, 33a and 135b targeting LNAs and antagomirs in our orthogonal imaging-based assay, and seek to develop small molecule inhibitors and RIBOTAC degraders against these targets as candidate anti-fibrotic agents.

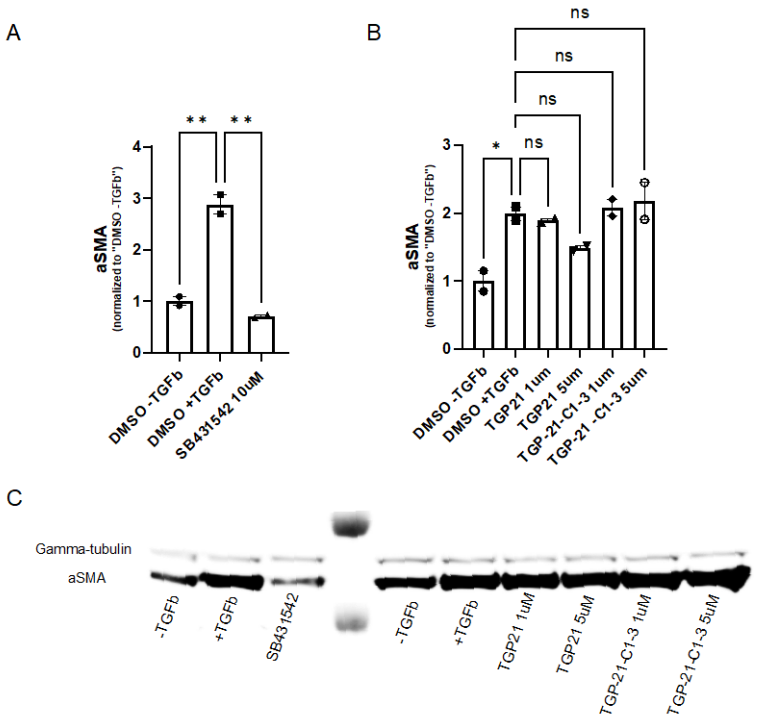

Fig. 1. Human lung myofibroblast differentiation assay results for TGP-21 and TGP-21-C1-3. A) Dynamic range for previously established assay format. B) Newly established assay format involving 24 hour pretreatment with test agents prior to TGF-b stimulation and characterization of miR-21 targeting agents TGP-21 and TGP-21-C1-3. C) Raw Western blot data associated with quantified band intensities shown in panel B.

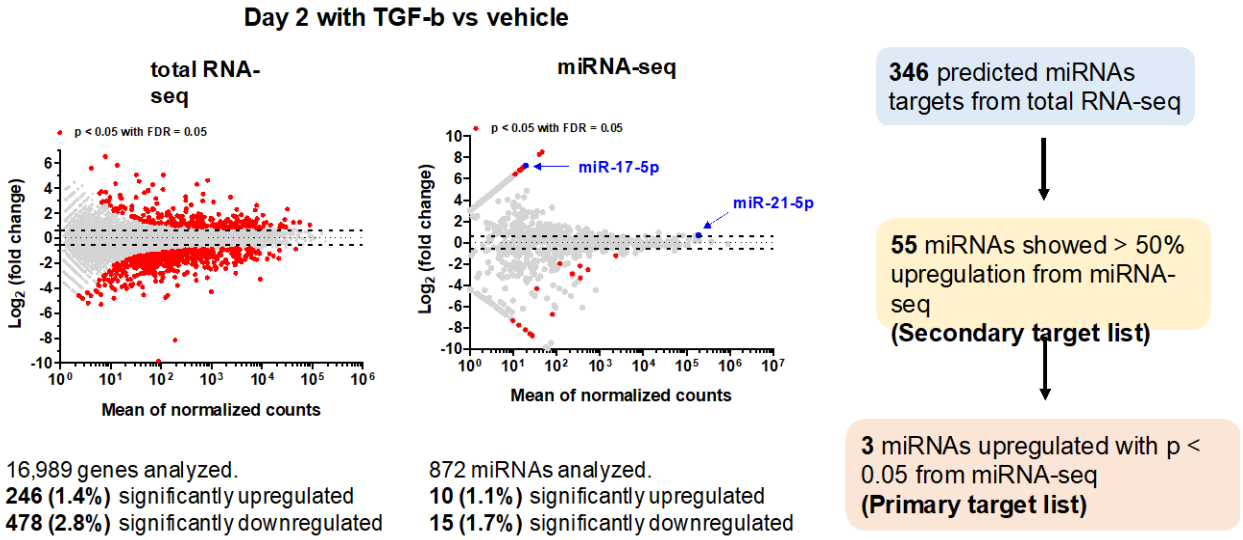

Fig. 2. Global RNA-seq and miRNA-seq analysis of pulmonary myofibroblasts compared to undifferentiated primary human lung fibroblast control.

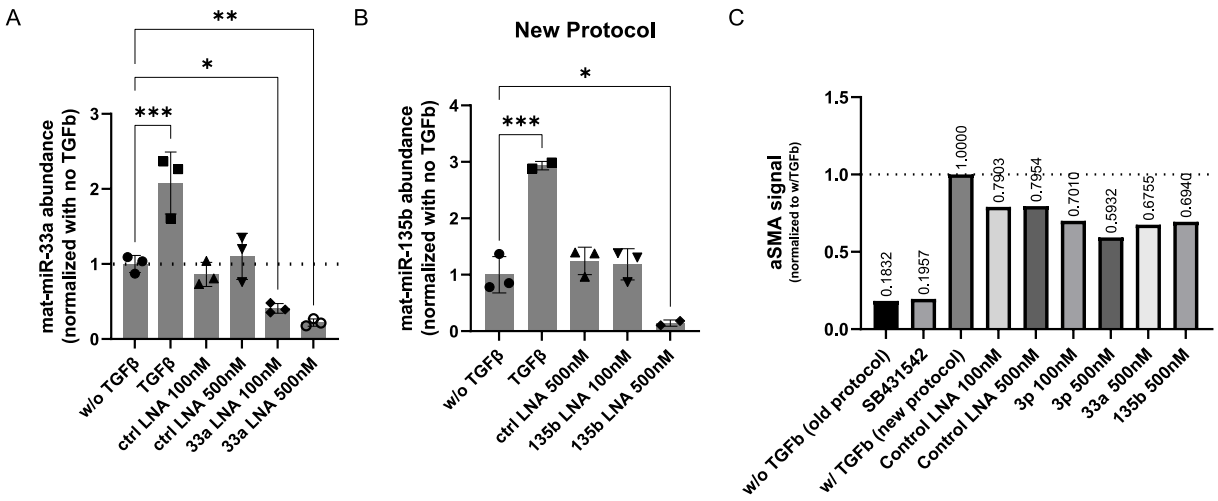

Fig. 3. A, B) Validation of miRNA-seq results and impact of miR-targeting LNAs by qPCR. C) Impact of LNAs targeting identified miRNAs upregulated in primary human lung myofibroblasts on induced differentiated.

Specific Aim 3: Study the optimal compounds emerging from Aims 1 & 2 for improving PCKD and lung fibrosis in vivo.

Based on the lack of observed robust and reproducible activity for miR-targeting LNAs or TGP-21-based small molecules in cellular models of lung myofibroblast differentiation assays, activity in rodent in vivo models of lung fibrosis was not achieved.

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

The Scripps Research Institute (Lairson): Annual performance reviews and Individual Development Plans (IDPs) are widely recognized as effective tools for setting and achieving Ph.D.-level training goals. They also encourage productive communication between trainees and their mentors. The Scripps Research Institute requires graduate students, including Erika James and Stephan Spangenberg, to create and revisit IDPs, and to seek regular feedback on their performance from their mentor (Prof. Luke Lairson). IDP templates are available from the institute's Career and Postdoctoral Services Office website and are provided to trainees as part of their initial onboarding process. The Graduate Student Services Office also arranges biannual IDP workshops to help trainees to interpret self-assessment information, explore career options, and set goals using myIDP from AAAS/ScienceCareers.org. Prof. Lairson worked with Ms. James and Mr. Spangenberg to create their own personalized IDP that encompasses their activities and training related to this project.

How were the results disseminated to communities of interest?

Unfortunately, the observed lack of activity for miR-targeting LNAs or TGP-21-based small molecules in cellular models of lung myofibroblast differentiation assays precludes the publication of our findings in the context of lung fibrosis.

What do you plan to do during the next reporting period to accomplish the goals?
n/a (final technical report)

4. IMPACT

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

The therapeutic modality of choice for RNA targets has long been ASOs. Unfortunately, ASOs suffer from therapeutic liabilities including poor cellular and tissue permeability, and clinical trials of ASOs have been halted due to non-specific activation of the immune system and thrombocytopenia. Therefore, alternative strategies are required not only to study disease pathology but also for therapeutic development. Herein, we have proposed to imbue small molecules with antisense- or CRISPR-like properties to eliminate the RNAs that cause PCKD and pulmonary fibrosis, using a two-pronged strategy – direct cleavage or cleavage by recruiting endogenous nucleases. These studies are potentially paradigm-shifting and could provide a strategy for diseases caused by upregulation of an RNA. Such compounds will be an invaluable resource to study disease pathology and have therapeutic potential. Our studies in the RNA field have indeed influenced the pharmaceutical industry to re-consider RNA as drug targets, as evidenced by investments in this area and additional new drug discovery efforts being deployed. Further, we have identified 12 miRNAs that are upregulated during macrophage polarization or during fibrogenesis of human pulmonary fibrosis, induced by TGF-b.

What was the impact on other disciplines?

Our highly unconventional approach has the potential to establish a completely new paradigm for studying human disease pathology, particularly polycystic kidney disease, which leads to renal fibrosis, and pulmonary fibrosis, each caused by aberrantly expressed miRNAs. Our studies have expanded potential drug targets for their treatment, showing that two miRNAs are druggable with small molecules, either by a simple binding mechanism, direct degradation by conjugation of the natural product bleomycin, or by induced proximity by recruiting an endogenous nuclease. Further, we have identified 12 other miRNA targets that may be implicated in fibrogenesis, helping to define disease pathways.

What was the impact on technology transfer?

Nothing to report from co-Investigator.

What was the impact on society beyond science and technology?

Pharmaceutical companies have traditionally viewed RNA as poor drug targets, with the vast majority of their effort focused on a few classes of protein drug targets. and how they approach tackling diseases caused by RNA. We have expanded the mode of action of drugs from simple binding to binding and cleavage, eliminating aberrantly expressed RNAs directly or by recruiting a cellular protein to degrade it. In total, our studies are opening up new therapeutic pipelines, approaches, and strategies for the treatment of many diseases, which will have a positive impact on human health in the form of precision medicines.

Further, our military personnel are at higher risk for developing both renal and pulmonaray fibrosis. Indeed, a database was created to track military personnel diagnosed with post-deployment chronic pulmonary disease, including lung fibrosis, and two programs, STAMPEDE[37] and STAMPEDE II,[38] were implemented to evaluate lung function pre- and post-deployment. Likewise, higher rates of CKD are observed in Veterans (1 out of 6)[39] than the general population, and CKD has been linked to higher rates of vascular disease, diabetes, and cancer.[40] Thus, understanding how to short-circuit disease processes with drugs would advance new therapeutic paradigms, allowing for a better understanding of disease pathology, and importantly improve our military readiness.

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

Nothing to report

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

Nothing to report

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:

- **Publications, conference papers, and presentations**

Journal Publications

Nothing to report

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

Nothing to report

Other publications, conference papers and presentations.

Nothing to report

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Luke L. Lairson
Project Role: Principal Investigator (Partnering PI)
Researcher Identifier: 0000-0001-8486-1796
Nearest Person Month Worked: 1.00 calendar months
Contribution to Project: Professor Disney oversees all aspects of the Initiating project.
Funding Support: in addition to this award, active awards include CIRM DISC2-13063; R01 NS112482

Name: Erika James
Project Role: Graduate Student, Lairson Lab
Researcher Identifier: N/A
Nearest Person Month Worked: 12.00 calendar months
Contribution to Project: *Completed experimental work associated with Disney Laboratory milestones/tasks*
Funding Support: N/A

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

Luke Lairson
New Awards Received Throughout Budget Period (2022-2023):

Nothing to report

What other organizations were involved as partners?

Organization Name:	The Scripps Research Institute
Location of Organization:	Dept. of Chemistry 10550 North Torrey Pines Road BCC-519 La Jolla, CA 92037
Partner's Contribution:	Collaboration (academic worksite of Partnering PI Luke Lairson)

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: In this collaborative award, Initiating and Partnering PI are submitting individual progress reports. This report reflects progress associated with site 2 activities defined in the established statement of work.

QUAD CHARTS: N/A