Does Inhibiting the Discoidin Domain Receptor 1 Collagen Receptor Prevent Renal Fibrosis Due to Alport Syndrome?

BMED 3600 Final Proposal

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11/24/2014

1. SPECIFIC AIMS

Alport syndrome (AS) is an inherited form of kidney inflammation caused by a mutation in the gene coding for the connective tissue known as collagen. Although rare, affecting only one in 20,000 people (Sayers et al., 1999), it is a disease that can greatly affect the quality of life; many times it leads to end-stage renal disease (ESRD) as early as age 20 and hearing loss before the age of 30. 80% of AS cases are X-linked due to mutations in the COL4A5 gene (Kashtan et al., 2011). In general, these gene mutations lead to improper production or assembly of the type IV collagen network, which in turn affects the assembly of basement membranes in the kidney, inner ear, and eye (Kashtan et al., 2011). When mutations prevent proper collagen fiber formation in the kidney, the membrane is unable to filter waste products from the blood, leading to hematuria and albuminuria. Glomerular podocytes (visceral epithelial cells), the functional cells of the glomerular basement membrane (GBM), detect these changes due to AS. Current treatments focus only on treating the signs and symptoms and not the root cause of Alport Syndrome (Kashtan et al., 2011).

Our goal is to evaluate potential treatment options by targeting the cause of GBM degradation rather than the aftereffects. Based on cancer studies, we believe that two drugs currently used for cancer treatment, Imatinib and Ponatinib, could be repurposed to inhibit signals coming from the damaged GBM just as it inhibits signals coming from tumors (Day et al., 2008). These drugs are tyrosine kinase inhibitors (TKIs) that suppress tyrosine kinase signaling through ATP inhibition. We seek to gain a greater understanding of the signaling pathways engaged in AS so that future research may be able to eliminate AS entirely. Armed with the knowledge that the Discoidin Domain Receptor 1 (DDR1) pathway is critical to GBM degradation, we hypothesize, based on prior research (Gross et al., 2010; Xu et al., 2011), that manipulating the DDR1 pathway will increase the quality of life for AS patients in the future.

***Specific Aim 1*: Determine the effect of Imatinib & Ponatinib on COL4A3 -/- mice.** It is hypothesized that Imatinib and Ponatinib will decrease fibrotic buildup on the GBM and decrease proteinuria and albuminuria in the urine, indicating slower degradation of the GBM. Earlier drug intervention is expected to result in a longer lifespan.

***Specific Aim 2*: Determine if the negative effects associated with the DDR1 pathway in AS patients are a result of MMP-12 activity and whether CCR-2 activation is an intermediary between the DDR1 and MMP-12.** It is hypothesized that preventing DDR1 expression will lead to a decrease in CCR2 activation and MMP-12 expression. Preventing CCR2 activation would yield to a decrease in MMP-12 expression. Preventing both DDR1 and CCR2 activation would yield a more significant decrease in MMP-12 expression than strictly preventing activation of only CCR2.

We expect the proposed experiments will show the efficacy of TKIs in treating AS, so that further research can move towards AS treatment in humans. Because a number of TKIs are already approved for human use in cancer treatment, the difficulty in bringing them to market for AS treatment should be low. We further expect to gain a deeper understanding of the underlying signaling pathways involved in AS progression. This would allow further research into methods of targeted AS treatment.

2. RESEARCH STRATEGY

2.1 Significance

The significance of this study is to gain an understanding for how AS progresses in glomerular podocytes by establishing the missing links in current research of involved signaling pathways to provide evidence for further research and future interventions.

AS significantly decreases the quality of life in patients, as the disease leads to ESRD, ocular failure, and auditory failure. While there are viable surgeries which correct the ocular failure and hearing aids to improve auditory performance, the effects of ESRD necessitate that the patient be on kidney dialysis for the rest of his or her life, and in some cases, a kidney transplant is necessary. Because at current there is no viable cure for ESRD, the best option is only to prevent the disease from progressing. This grant proposal is significant because we propose to fill in the gaps in current research, allowing a better understanding of the AS signalling pathways which will lead to new interventions making it possible for future AS patients to obtain a higher quality of life.

Type IV collagen, the most essential protein in the basement membrane, forms meshlike structures providing cross-links with other components of the extracellular matrix (ECM) (Yeh et al., 2012). The type IV collagen creates a network of large molecules with interrupted triple-helical stretches, also known as alpha chains. The COL4A3, COL4A4, and COL4A5 genes code for α3, α4, or α5 chains of type IV collagen (Kashtan et al., 2001; Saxena, Maheshwari, & Dadhich, 2013). Evidence suggests that in AS, the failure of α3, α4, or α5 chains to form prevents the necessary changes from a fetal state, where α1 and α2 chains predominate in the GBM, to a more robust network, which combines α2, α3, and α4; this process is known as isotope switching. The lack of this more robust network development leads to a vulnerable and porous GBM that can be attacked by proteolytic enzymes, leading to membrane thickening, splitting, and damage (Gross et al., 2010). Due to the porosity, it is believed the system overcompensates for the lack of α3, α4, and α5 chains needed to build a proper type IV collagen network by developing more α1 and α2 chains.

The system also activates the DDR1 collagen receptor that recruits type V and type VI collagen as well as growth factors. Normal type IV collagen occupies subendothelial space; however due to the initial porosity, type V and type VI collagen expand to fill the gaps in the GBM (Kashtan et al., 2001; Saxena, Maheshwari, & Dadhich, 2013). Inhibiting the transmembrane receptor DDR1 on the GBM using tyrosine kinase inhibitors can decrease the promotion of growth factors and proinflammatory cytokines; the downstream effects of this therapy can stop GBM degradation.

2.2 Innovation

Our study is innovative because we are exploring the possibility of repurposing a drug to treat AS patients in addition to filling gaps in the DDR1 signaling pathway.

The two drugs we are testing, Imatinib and Ponatinib, are drugs which are currently used to treat chronic myeloid leukemia; they however have an off target effect of inhibiting signaling by the DDR1 receptor, which causes many downstream effects. Because Imatinib and Ponatinib are FDA approved cancer drugs with known toxicities, the difficulty in bringing them to market when compared to novel treatments is significantly mitigated. This approach is innovative

because it uses a preexisting cancer drug to treat the cause of AS instead of its effects. By understanding the pathway that causes degradation of the GBM, it is possible to identify locations further down the pathway that could have the same desired effect without activating other pathways that may be activated by DDR1. The current DDR1-CCR2-MMP12 pathway is loosely pieced together by current research, but the direct effects and magnitudes of activation are unknown. By examining every part of the pathway and its ultimate effects on the GBM, we can determine the best location to target in the pathway.

Understanding the signaling pathway for the DDR1 receptor is key to understanding the progression of the disease. Inhibiting the DDR1 receptor has the potential to impede the progression of renal failure and halt the progression of AS by decreasing the promotion of growth factors and proinflammatory cytokines; the downstream effects of this therapy can stop GBM degradation (Licht, 2012). Another benefit of inhibiting the DDR1 receptor is the consequent inhibition of the expression of Matrix Metalloproteinases (MMPs) in fibroblasts. MMPs are proteases that function to remodel the ECM through maintaining balance between degradation and synthesis. If the GBM is already vulnerable, like those of patients with AS, the GBM is more susceptible to degradation by MMPs and further increase in the inflammatory and growth factor recruiting response (Lenz, Elliot, & Stetler-Stevenson, 2000). Inhibiting the DDR1 receptor will knock out one of the two collagen receptors responsible for recruiting the factors that result in fibrosis in patients with damaged GBMs due to mutated collagen IV, effectively decreasing the damage to the GBM.

2.3 Experimental Approach

Drug Background

Imatinib and Ponatinib are tyrosine kinase inhibitors which were designed to target the Abl portion of Bcr-Abl, an oncogene which has important implications in the survival and growth of certain cancers. These drugs work by attaching themselves near the ATP binding site on Abl in order to prevent ATP activation. Both drugs are FDA approved for the treatment of certain leukemias, gastrointestinal stromal tumors, and certain cases of dermatofibrosarcoma protuberans. A common off target effect is the inhibition of DDR1 that prevents activation of the signaling cascade to recruit matrix proteins (Canning et al., 2014; Kim et al., 2013). Because both drugs are approved for human use with known toxicology profiles and manufacturing methodologies, the difficulty in bringing them to market is significantly mitigated when compared to a completely novel chemical. This provides a very attractive opportunity to positively affect AS patients at a minimal cost.

Previous Studies

Previous studies have shown that double-KO mice (collagen IV gene and DDR1) lived 47% longer and showed improved renal function compared to AS animals with 100% DDR1 expression (Gross et al., 2010). Another study proposed that the inhibition of tyrosine kinase receptors reduces matrix accumulation and inflammation in the GBM (Grimminger, Schermuly, & Ghofrani, 2010). Currently, AS is treated using a combination of ACE inhibitors and renin-angiotensin blockade (Savige, 2014). However, these treatments do not slow the progression of AS because it treats the signs and symptoms at a very broad level (Savige, 2014). There are multiple drugs being tested as TKIs, but have not been FDA approved for AS treatment specifically.

The use of Imatinib over time has been shown to be met with resistance, particularly in the instance of Bcr-Abl (Gorre et al., 2001). This occurs as the result of a mutation to a gatekeeper portion of the Bcr-Abl, which prevents Imatinib from binding to and therefore blocking the ATP binding site on Bcr-Abl. DDR1 has a similar structure and therefore has the potential to develop a resistance through the same mechanism (Canning et al., 2014). Ponatinib is the second generation Abl inhibitor which does not suffer from drug resistance; it is, however, less specific than Imatinib (Canning et al., 2014) and has been connected to life threatening cardiovascular complications.

***Specific Aim 1*: Determine the effect of Imatinib & Ponatinib on *COL4A3* -/- mice.**

Purpose: To determine what minimal dose of Imatinib and Ponatinib is required to see statistically significant improvement in the GBM. These doses will be administered with a difference in AS intervention periods. *It is hypothesized that Imatinib and Ponatinib will decrease fibrotic buildup on the GBM and decrease proteinuria and albuminuria in the urine, which indicates a slower degradation of the GBM. Earlier drug intervention is expected to result in a longer lifespan.*

Experimental Approach 1: 105 COL4A3 -/- mice and 15 normal mice will be used in this experiment. At four weeks of age, three groups of 15 COL4A3 -/- mice will be administered with a daily dose of 10mg/kg, 25mg/kg, and 50mg/kg dose of Imatinib respectively until death[TAM1] . An identical protocol will be performed with a daily dose of 5mg/kg, 15mg/kg, and 30mg/kg of Ponatinib. After death, the GBM will be inspected using transmission electron microscopy (TEM). Each GBM will be compared to the normal mice GBM and nonintervention COL4A3 -/- mice GBM to measure the extent of GBM damage. The electron microscopy should demonstrate thickening and splitting of the GBM. To further elucidate the antifibrotic effects of DDR1 loss, both fibronectin (to represent scar-tissue) and EHS-laminin (to represent extracellular matrix deposition) can be immunostained. These two are markers for severe glomerular scarring and matrix deposition that are a consequence of AS (Gross et al., 2010). Protein and blood in urine will be measured on a daily basis until death. Samples of urine will be obtained from mice, fractionated on an 8% acrylamide gel, and stained with Coomassie blue. This will measure the severity of proteinuria. Careful microscopic review of the urine sample will measure hematuria.

	No drug	**Imatnib (mg/kg)**			**Ponatinib (mg/kg)**		
Mice	**0**	**10**	**25**	**50**	**5**	**15**	**30**
COL4A3-	15 mice	15 mice	15 mice	15 mice	15 mice	15 mice	15 mice
WT	15 mice	15 mice	15 mice	15 mice	15 mice	15 mice	15 mice

Table 1: Experiment 1 treatment plan

Experimental Approach 2: Using experiment 1, an appropriate dosage of Imatinib and Ponatinib [TAM1] will be administered to 90 COL4A3 -/- mice. This experiment will measure the success rate of drug intervention at different stages of AS. At four weeks of age, two groups of 25 mice will be administered a daily dose of either Imatinib or Ponatinib. After a week, five mice from each drug group will be sacrificed and the GBM will be inspected to detect improvements due to drug intervention. The other remaining mice will be sacrificed after three, five, eight, and ten

weeks in groups of 5 for GBM inspection. At eight weeks of age, another two groups of 15 mice start a daily regimen of either Imatinib or Ponatinib. These mice will be sacrificed after one, four, and six weeks in groups of five. At twelve weeks of age, two groups of five mice will start a daily regimen of either Imatinib or Ponatinib. These mice will be sacrificed after two weeks. All of the GBM will be compared to normal mice GBM and nonintervention COL4A3 -/- mice GBM using TEM.

	Time of sacrifice (weeks after birth)				
Start of drug regimen (weeks after birth)	**5 weeks**	**7 weeks**	**9 weeks**	**12 weeks**	**14 weeks**
4 weeks	5 mice	5 mice	5 mice	5 mice	5 mice
8 weeks	-	-	5 mice	5 mice	5 mice
12 weeks	-	-	-	-	5 mice

Table 1: Specific Aim 1 Experiment 2 treatment plan

Expected Results: Ponatinib has been shown to target DDR-1 receptors more than Imatinib, with significantly less side effects. It is expected that Ponatinib be more effective during early intervention, and decrease exponentially in effectiveness as intervention is delayed. This drug therapy has been shown to decrease GBM degradation; however it does not repair previous damage. It is expected that the median dosage be appropriate - previous research has shown that the highest dose is borderline harmful, while the lowest dose is bare minimum. Imatinib has been approved by the FDA and been used in cancer patients, while Ponatinib has yet to undergo human trials and FDA approval. A statistical analysis using a two-way ANOVA will be used to determine if there are statistical differences in each group.
Alternative Method: If gross problems with Imatinib and Ponatinib present itself during these trials, alternative drugs may be explored using similar experimental design. DDR-1-IN-1 dihydrochloride is in its early stages of design; it is a chemical which is specifically designed to be highly selective to DDR-1 and DDR-2 (Kim et al., 2013). It does this by inhibiting the auto-phosphorylation of the targeted receptors. However, this experiment would have to be expanded to include the development of a drug delivery system.

Specific Aim 2: **To determine if the negative effects associated with the DDR1 pathway in AS patients are a result of MMP-12 activity and whether CCR-2 activation is an intermediary to the DDR1 to MMP-12.**
Purpose: To determine if the DDR1 pathway associated with MMP-12 is the primary pathway that causes renal fibrosis. *It is hypothesized that preventing DDR1 expression by -/- will lead to a decrease in CCR2 activation and MMP-12 expression. Preventing DDR1, TGF-B, and NFKB activation by -/- in 3 separate experiments would yield to a decrease in MMP-12 expression.*
Experimental Approach 1: For each row illustrated in Table 3, 15 healthy glomerular podocyte dishes and 15 COL4A3 -/- glomerular podocyte cell dishes will be developed for each group, after which the concentrations of each protein will be measured via western blot analysis. The groups will then be compared to specifically answer the questions in the "Why" column which

together will allow a more exact characterization of the MMP12 pathway, which leads to GBM damage.

Experimental Approach 2: 15 COL4A3/DDR1 -/- podocyte dishes, 15 COL4A3/CCR2 -/- podocyte dishes, 15 COL4A3/DDR1/CCR2 -/- podocyte dishes, and 15 normal podocyte dishes will be used in this experiment. MMP-12 levels will be measured and compared amongst all four test groups to determine the effectiveness of removing DDR1, CCR2, or both DDR1 and CCR2 from the signaling pathway. MMP-12 levels will be measured over several weeks followed by histological analysis.

Group 1	Group 2	Measure	Why
DDR1 -/- & CCR2-/-	CCR2 -/-	MMP12	Does DDR1 have pathways not through CCR2 to promote MMP-12?
CCR2 -/- & MMP12 -/-	CCR2 -/-	DDR1 & MMP12	Is there feedback from MMP12 to DDR1?
CCR2 -/- & MMP12 -/-	MMP12 -/-	DDR1 & MMP12	Is there feedback from CCR2 to DDR1?
MMP-12 -/-	None	CCR2 & MMP12	Does MMP-12 feedback to CCR2?
DDR1 -/- & CCR2 -/-	None	MMP12	Is there a pathway to MMP12 not having to do with DDR1 and CCR2?
MMP12 -/-	MMP12 -/- & DDR1 -/-	CCR-2 & MMP12	What effect does DDR1 have on CCR-2?

Table 2: Specific Aim 2 Experimental Approach 1

Expected Results: It is expected that the results will reinforce our proposed signaling pathway outlined in Figure 1 and determine if there is actually a link where there are question marks. For example, a decrease in DDR1 expression is expected to lead to a decrease in MMP-12 levels (as demonstrated through western blotting concentration levels). It is also expected to see possible feedback which is not currently accounted and possible alternative pathways for DDR1 activation to lead to MMP-12 expression.

Alternative Method: If time permits, we will use a proteomics-based approach to interrogate the signaling pathway further, attempting to build intermediaries, which are currently unaccounted for, into the proposed pathway. In addition, we will attempt to look into the mathematical effects of changing the various protein concentrations to develop a mathematical model of the pathway.

3. ESTIMATED TIME LINE

The first experiment in the first specific aim requires the AS mice to live out the full length of their lives. We will allow the normal mice to live until we can find a statistically significant difference in the lifespan and quality of life (albuminuria and hematuria). In a previous study, the average lifespan for AS mice without treatment was 71 days but previous treatments with other drugs have shown AS mice can live up to 150 days (Gross et al., 2003). The second experiment requires mice to start the drug regimen and be sacrificed at predetermined time intervals so that the GBM can be inspected. Different groups of mice will begin to undergo treatment after 4, 8, and 12 weeks of life and be sacrificed 5, 7, 9, 12, and 14 weeks after beginning treatment.

In specific aim 2, cells will be cultivated in petri dishes. Podocytes will be matured for 1 week before the experiment begins. This experiment can be performed during our specific aim 1 experimentation. The experiments proposed in this grant will take a total of 21 weeks minimum.

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