

Kidneeds – a research fund dedicated to finding a treatment for Dense Deposit Disease (DDD)

www.medicine.uiowa.edu/kidneeds

The things a man has to have are hope and confidence in himself against odds, and sometimes he needs somebody, his pal or his motherClark Gable

The phone line crackled and her voice was tense as she said, “Mom, we’re somewhere in Nebraska and there’s a tornado very close. Can you find out where it is?” I jokingly responded, while bringing up AAA and Weather Channel screens, “Jenna what are the chances you’d be hit a second time by a tornado”. Pause. “Exactly my point,” she replied.

Fact:
Your chances of getting DDD are between 1:500,000 and 1:1,000,000.

Fact:
Your chances of being struck by a tornado are between 1:60,000 and 1:2,000,000 depending on sources.

Yep, better pull that tornado tracker up pretty quickly.

The other odds we cannot ignore are the odds against finding a treatment for Dense Deposit Disease. Compared to the \$1,400,000,000 that has gone into finding a treatment for Juvenile Diabetes since 1970, the \$85,000,000 awarded annually for cystic fibrosis research and the billions and billions awarded annually by the government for cancer research, a small grassroots foundation that operates without paid administrators and has funding designated only for research — like Kidneeds — stands overwhelming odds **against** ever finding

a treatment or cure for a complex disease like DDD. But does that mean we shouldn’t try? Not trying is not an option.

Fortunately, Kidneeds has had the support of many people who have been willing to embrace that decision. The people who have stood beside our family and the families of those with a loved one with DDD, understand that there are compromises the human spirit cannot endure. These people have done all they can to help better our chances of success.

2009-2010 has been incredibly busy. 99% of our income comes from individuals who know one person with DDD. Yet we funded \$250,000 in new research. Our understanding of the DDD disease mechanism is rapidly advancing with the help of the funded research and extensive research done by unpaid scientists. We continue to identify new at-risk gene associations, find new variants of the disease, enroll record numbers of patients in our epidemiology database, and work on creating and testing novel treatments.

In January 2010, in an amazing collaboration of industry, government and academics, a team at the University of Iowa got approval for an FDA drug trial to treat a young 8-year-old DDD patient with the first drug ever tested for DDD. In June 2010, it was approved for trial

in a second patient. There is still a long way to go, but who would have believed we could get to this point so quickly in the face of staggering odds against this success?

Jenna, for one.

It is not in accepting the odds, but in defying those odds that lifetime friendships are forged and “miracles” are created. Miracles grow out of long hours in the lab, from a drug company reaching out and taking a risk, from FDA administrators trusting a researcher, friends cooking, biking, running, cruising, golfing, playing music and selling lemonade in order to raise research money, and from scientists who tirelessly donate their time and expertise, some without being funded, because they refuse to believe it can’t be done. The successes of this year belong to all of you who have contributed your time, money, expertise, guidance and participation in the research so that we can learn more about DDD.

Mary Chapin Carpenter wrote: *“I take my chances, I don’t cling to remorse or regret.”*

Thank you to everyone who has taken a chance on Kidneeds. It might just be the year the odds break in our favor.

Lynne Lanning

Fall 2010 Changes

- > www.medicine.uiowa.edu/kidneeds
- > **New Address for :**
- > **Greater Cedar Rapids Community Foundation**
324 3rd St. SE, Cedar Rapids, IA 52401
- > **Due to new laws, please make your donation checks payable to: GCRCF, kidneeds or put Kidneeds in the memo section.**

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Richard and Lynne

Research Findings 2009-2010

1. Paul Morgan, Cardiff, Wales

Grant Title: Measuring C3 Nephritic factors (C3Nefs)

Background: C3Nefs are antibodies found in most persons with DDD. These antibodies are believed to play a major role in complement dysregulation, which is the pathophysiological basis underlying DDD.

Accomplishments: Despite obvious clinical need, current assays for C3 nephritic factors (C3Nefs) are not fit for purpose. They are highly variable between laboratories, often technically demanding, not standardized, and unproven in terms of sensitivity and specificity for detection of C3Nefs. Little or no attention is given to the likely inter-individual variability in these antibodies, their properties and their levels in the circulation. As a consequence, there is an unmet need for a robust assay or set of assays that provide a sensitive, specific and quantitative measure of C3Nefs in patients with DDD. This assay should be easily translated into a routine immunology laboratory environment.

Dr Morgan's team has shown that the alternative pathway C3 convertase (called C3bBb) can be assembled on plastic and provides a suitable substrate for identifying C3Nefs. These scientists are now optimizing these assays to provide in a reproducible manner qualitative and quantitative data on C3Nef in patient samples, to identify and eliminate factors that interfere in the assays and to develop standards and standard operating procedures (SOPs) that enable the sharing of assays between laboratories. An SOP has been written for the C3-properdin cleavage assay and the assay has now been taken over by the routine Immunology Laboratory at the University Hospital without problems.

2. Claire Harris, Cardiff, Wales

Grant Title: Understanding the mechanisms by which C3 nephritic factors cause renal disease

Background: Major defects in complement regulation result in severe organ damage, particularly affecting the kidney. Partial or complete deficiency of the plasma regulator, complement factor H (CFH), predisposes to severe renal disease and can lead to DDD. Lack of CFH results in uncontrolled activation of the complement alternative pathway (AP) in the blood stream and on cell surfaces. A similar phenomenon of uncontrolled AP activation is caused by C3Nefs. C3Nefs were originally described in 1969 as a factor in plasma responsible for C3 cleavage in a patient with MPGN. They were subsequently characterized as an autoantibody to the C3 convertase. C3Nefs cause loss of control of the AP by stabilizing C3 convertase. Although C3Nefs have been extensively studied over 4 decades, their precise role in DDD remains unclear.

Accomplishments: Dr Harris' team has shown that C3Nefs are incredibly variable and that their overall effect depends on their ability to stabilize C3 convertase, their dependence on properdin, their resistance to innate control mechanisms (such as CFH) and their level in the blood stream. They also found that most C3Nefs in their cohort bound to the assembled enzyme only. They stabilized the C3 convertase to different extents, with one subgroup extending half-life by ~10-fold and others extending half-life by 100-fold (several hours). An additional finding was that some C3Nefs have little effect on the rate at which the C3 convertase cleaves C3 to nascent C3b while others dramatically increased the amount of C3b that is generated. Finally, Dr Harris' team has found that most C3Nefs prevent innate control mechanisms (such as CFH) from working effectively. However, many C3Nefs can still be controlled membrane-associated regulators like CR1. This finding may be important in the development of a treatment for DDD.

3. Jessy Alexander, Chicago, IL, USA

Grant Title: Role of Complement Factor H in DDD

Background: Humans and mice have identical complement cascades, with few differences. One such difference is that immune adherence is performed by CR1 on red blood cells (RBCs) in humans but by CFH on platelets in mice. To generate a

The MPGN survey and DDD Facebook Group

In 2010, we entered our 122th DDD survey into the database., making the U of I MPGN survey database the largest collection of DDD data generated by patients. When new patients are diagnosed, they have many questions. These questions would be impossible to answer without the help of everyone who has taken the time to enter their data into the database. Dr. Der Fa Lu and her research team are finishing 6 months of data analysis for publication. Dr. Lu, at the University of Iowa College of Nursing, has donated thousands of hours to help collect and analyze data so that we can give families the most accurate data available. We are also very grateful for the help of Dr. Nick Street, Mikyung Moon, PhD candidate, Timothy Van Fossen and Chen Yang for their volunteer work on behalf of DDD families.

Once the article is published, summaries and information will

be sent to the participants. Others wishing the information can contact mpgn@uiowa.edu to make a request. Please note we are volunteers and the email is checked on a weekly basis. The summary will not be available until after January so please submit requests after that date.

If you haven't completed the database, please consider doing so. It is only by working together that we can move forward. You can fill in the database at: <https://mpgn.nursing.uiowa.edu>.

You will notice that we have an invitation-only Family Group on Facebook. This is a meeting place for patients or families-of-patients under 18 years of age.

For security purposes, you can not join the group unless you have completed the survey. Although many relatives are very supportive, at the suggestion of some DDD patients, we limit the DDD Facebook Group Membership to the patient or the parents of the patient. We hope you understand.

Research Findings (cont)

mouse model closer to human DDD, Dr Alexander and her group bred mice lacking CFH (*Cfh*^{-/-} mice) with genetically engineered transgenic mice that express human CR1 on RBCs. These mice are called *CR1huTg/Cfh*^{-/-} mice.

Accomplishments: Absence of CFH in *Cfh*^{-/-} mice causes loss of complement regulation and results in the generate proinflammatory products such as C3a, C3b, C5a and C5b-9, which may be important factors in DDD. Once C5a is formed, it is immediately broken down by the enzyme, carboxypeptidase. To determine the role of C5a in DDD, *Cfh*^{-/-} mice with chronic serum sickness (CSS) were treated with Plummers reagent (a carboxypeptidase inhibitor that leads to substantial increase in circulating C5a) and the results were compared to control mice. Decreased kidney function and increased deposition of immune complexes containing both C3 and IgG in kidneys of mice treated with Plummers reagent suggests an important role for C5a in *Cfh*^{-/-} kidney pathology. Treatment with the C5a receptor antagonist, C5aRa prior to and during induction of CSS, decreased kidney damage as determined by a decreased urinary albumin-to-creatinine ratio consistent with a key role for circulating C5a to dictate outcome in DDD. These findings present the possibility that C5aR inhibition may be a therapeutic option for DDD.

4. Josh Thurman, Denver, CO, USA

Grant Title: Non-Invasive Detection of Glomerular C3 in a Mouse Model of Dense Deposit Disease

Background: One of the most difficult aspects of treating patients with renal disease is assessing disease activity and determining whether a patient is responding to therapy. The gold standard for diagnosing and monitoring renal disease is a kidney biopsy. Biopsies, which represent just a small piece of kidney tissue, are studied in many different ways and used to infer what is happening to both kidneys. In DDD, immunofluorescence studies will always be positive for a protein called C3. Dr Thurman's group is focusing on non-invasively measuring renal disease in DDD patients by using nanoparticles (called CR2-targeted nanoparticles) to bind to C3 within the kidney. The nanoparticles can be detected by magnetic resonance imaging (MRI). If this procedure complements a renal biopsy, it may be possible to monitor disease activity more closely and throughout both kidneys.

Accomplishments: After having shown that CR2-targeted nanoparticles are detectable by MRI in the mouse model of DDD, Dr Thurman's group has started to test different doses and time-points to determine the optimal means of delivery. They are also developing alternative targeting proteins that may be superior to CR2 in sticking to C3, thus improving sensitivity. To determine whether nanoparticles + MRI can distinguish active from inactive disease, the two. They will then induce a disease flare in the disease-free mice to monitor what happens.

5. Johan van der Vlag, Nijmegen, The Netherlands

Grant Title: The Role of Glomerular Glycosaminoglycans in Dense Deposit Disease

Background: Heparan sulfate proteoglycans (HSPGs) are important molecules in the extracellular matrix that belong to the family of negatively charged glycosaminoglycans (GAG) and non-sulfated hyaluronan. They consist of a core protein to which are attached heparan sulfate (HS) sugar side chains, which creates immense diversity - the potential structural diversity of an average chain of 100 disaccharides residues is calculated to be 48^{100} . This structural diversity affects binding of many different proteins including growth factors, chemokines, cytokines, enzymes and, of relevance to DDD, complement factors.

Accomplishments: Dr Van der Vlag's group has analyzed glomerular expression of HS and heparanase (the enzyme that destroys HSPGs) in renal biopsies from DDD patients (n=6), DDD patients with DDD who have a renal transplant and have recurrence of disease (n=6), and DDD patients who have a renal transplant and do not have recurrence of disease (n=3). Also studied were human kidneys from healthy controls (n=5). It appears that glomerular HS expression in DDD patients and in DDD patients with recurrent disease in their transplants is significantly decreased as compared to expression in healthy controls. In addition, in these groups heparanase expression is significantly increased. In contrast, in DDD patients who are transplanted but do not have recurrent DDD, the decrease in glomerular HS expression and the increase in heparanase expression are not significant. Dr Van der Vlag's group has also looked at complement binding to mouse glomerular endothelial cells and has found that binding of CFH and variants of this protein is differentially mediated by HS.

Clinical Trials — We hope to begin a clinical trial in the next 1-2 years based on preliminary results in one child who has been treated with a new complement-inhibiting drug in a small FDA-approved study. The clinical trial would likely involve patients in Europe and North America. Please up-date us on your interest in participating and on your health status by a quick email to kidneedsmpgn@yahoo.com.

Face-to-Face & Family-to-Family

Last year, we met with three families in England who had children in renal failure. We also met with the Tullys, members of the Board-of-Directors of Kidneeds. The Tullys provide excellent guidance and support for Kidneeds. In August, we held our annual Family Meeting in Iowa City to present Updates on DDD Research. Attendees also participated in research opportunities. On nearly a monthly basis, we met with patients and families who travel to Iowa City to learn more about DDD and participate in our push for a cure. Families are always welcome to contact us with questions about the disease and on-going research opportunities (kidneedsmpgn@yahoo.com or richard-smith@uiowa.edu). If you would be interested in hosting a Kidneeds family meeting, please contact Lynne Lanning at kidneedsmpgn@yahoo.com.

Fundraisers



One enchanted evening
Cruising on the Thames for Kidneeds



Peter Tearse
4th Annual Lemonade Stand for Kidneeds



Nikki and David Yates
Kidney Classic Golfing Tournament



Richard (left) and Jenna Smith and
Fabrizio Spoletti



The Kane's 'World Run Day'



Ken and Anne Pickett helped with the
Kidney Classic. Their nephew has DDD.

David and Nikki Yates (IL) held their Second Annual KidneyClassic on Sept 11, 2010 at the Whitetail Ridge Golf Club in Yorkville, IL. Seventy-three golfers participated in a 4-man scramble during the day with prizes awarded for the best foursome, longest putt and closest-to-the-pin. Afterwards, 100 gathered for dinner, cocktails, DJ and a silent auction. The event raised \$20,500 for Kidneeds.

Steve McGuire's EnduroCure Ride (IA) for Kidneeds raised \$40,000. While not being able to complete the full 2412 mile race, Steve crossed the continental divide several times and hundreds of people tuned in daily to watch his blue dot move down the Great Divide Race, keenly waiting for the daily update on progress. It was an amazing effort.

Hope Tully (England) 'Cruising for Kidneeds' was held on April 24, 2010 in London. Guests cruised on the Thames River, enjoying views of the London night skyline as the background for an evening of dinner, music, dancing and casino. A live and silent auction of fabulous donated prizes completed a fun,

magical evening. The event was organized by Hope Tully and her London-based friends. The evening raised almost GBP 35,000 (\$55,000) for DDD research.

Sean Tully (England) recently published a book titled 'Restoring Confidence in the Financial System', and is donating a portion of the proceeds from the sale of the book to Kidneeds.

Peter Tearse's (IA) 'Fourth Annual Lemonade Stand' was in August. Pete weathered the withering Iowa heat to help find a cure for his neighbor.

Fabrizio Spoletti's (Italy) 'Third Annual Friendship Drive' for Kidneeds raised thousands of dollars for DDD research. Fabrizio has also established an Italian not-for-profit that will raise money to support Kidneeds DDD efforts. And as Kidneeds goes even more global, Fabrizio is translating Kidneeds' information and the database survey into Italian to engender a greater exchange of information.

Karen Williams (PA) and the Kane family's 'World Run Day Second Event' was held last November in Pennsylvania. Many of the Kane family and friends turned out and raised close to \$20,000 for DDD research.

The Third World Run is scheduled for November 7 in

Bensalem, PA. Contact Karen at: kane-comp@optonline.net or visit <http://www.active.com/donate/TommyKane2010>

Jenna Smith (IA) and Hands Jewelers. After almost 10 years of carrying Jenna's Jewelry and giving all proceeds to Kidneeds, Hands is without inventory to sell. Jenna has moved to Oregon to pursue her Masters of Architecture. Many thanks to Hands for years of supporting Jenna and her efforts to find a cure for DDD.

Carol Personte (NY) is already planning the next 'Golfing for Kidneeds Tournament' in Webster, NY for the fall, 2011.

Cartridge and Cell Phone Recycling Fundraiser continues to bring in DDD research money.

Donations

Thank you to everyone who is helping us find a treatment for DDD. Remember that 100% of your donations go directly to research. If you would like to donate, visit:

<http://www.medicine.uiowa.edu/kidneeds/>
or go directly to:

<https://npo.networkforgood.org/Donate/Donate.aspx?npoSubscriptionId=1000011>