October 29, 2011 a Kidneeds’ Family Conference was held in Iowa City, Iowa. Families from 10 different states in the US and from England attended. Lectures by nephrologists, scientists and a social worker from UIHC covered the disease process, treatment protocols for children and adults, social implication of the disease, available resources, and transplantation and dialysis. There was also a ‘question and answer’ period. In the evening, patients and families gathered to share stories, fears and hopes. Evelyn Weirich, known for her Cinco de Mayo Enchiladafest for Kidneeds graciously prepared dinner for everyone. For audio and PowerPoint presentations of the meeting please visit the Kidneeds’ website: www.healthcare.uiowa.edu/kidneeds
A Drug Trial for DDD is Starting

At the end of August, the Food and Drug Administration (FDA) approved a drug trial to test CDX-1135 in pediatric and adult patients with Dense Deposit Disease (DDD). This is the FIRST-EVER drug trial for DDD patients using a drug specifically designed for DDD. The drug targets the complement system at the level of the C3 convertase.

What is CDX-1135?

CDX-1135 is a drug made by Celldex (CDX). They have numbered it 1135. In earlier work done in laboratories and in mice and in one patient with DDD, it was called TP10. It is also known as soluble CR1 or sCR1. CDX-1135, TP10 and sCR1 are all the same thing.

What is the title of the study?

It is called: A Pilot, Open-label Multicenter Clinical Trial of CDX-1135 in Pediatric and Adult Patients with Dense Deposit Disease. It is called a pilot study because we don’t know whether it will work and we don’t know the dose of CDX-1135 to use. It is ‘open-label’ meaning that everyone in the study will receive CDX-1135. No one will receive placebo. It is a multicenter trial because DDD is a rare disease and many centers will have to participate to complete the study.

Who is eligible?

To be included in this study, a patient with DDD must meet the following criteria:

Patient and/or parent/legal guardian (as appropriate) must be willing and able to give written informed consent indicating that the patient or parent/legal guardian has been informed of and agreed with all pertinent aspects of the study, and is willing to comply with all study requirements and procedures; if also applicable, the patient must be willing to give written informed assent.

Non-pregnant female and male patients from all racial and ethnic groups, four (4) years of age or older

Patient must have DDD as confirmed by renal biopsy within six months of enrollment (confirmation by University of Iowa investigators is required). If you have not had a biopsy within six months and you are otherwise eligible, you will need another biopsy.

Blood studies must show:

1. Serum creatinine level must be abnormal (>97 percentile for age or <80 ml/min using the Cockroft Gault equation for adults).
2. 24 hour urine protein must be >1000 mg/day, or the urine protein:creatinine ratio must be >1.0
3. Hemoglobin ≥ 9.0 g/dL
4. Platelet count ≥ 100,000/mm³
5. Alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 3.0 x ULN

Both male and female patients of childbearing potential enrolled in this trial must use adequate birth control measures. Patients and/or partners who are surgically sterile or postmenopausal are exempt from this requirement.

Patient must be willing and able to comply with study procedures including

1. Vaccination against meningitis, hemophilus and pneumococci at least 2 weeks prior to starting the Induction Period
2. Agree to a renal biopsy at Week 13 (half-way through the study) and at the conclusion of the study. Patient must wear an identification bracelet indicating their diagnosis and treatment with CDX-1135 and warning of possibly overwhelming infection with certain bacteria during the study.

Certain medications (eg, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers) must be at a stable dose for at least four weeks prior to first dose of CDX-1135.

I don't know what some of these things mean. What should I do?

Take this information to your doctor and ask you doctor whether you qualify. You or your doctor can also email Dr Richard Smith (Richard-smith@uiowa.edu) or Dr Carla Nester at (Carla-nester@uiowa.edu).

Who is NOT eligible for the study?

Patients who have any of the following are NOT eligible for the study:

1. Patients on dialysis or patients with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73 m² for over a four-week period prior to the Screening Period
2. Patients with an active or untreated systemic bacterial infection that in the opinion of Drs Smith and/or Nester preclude treatment with CDX-1135
3. Pregnancy or lactation
4. Rituximab therapy, unless discontinued with B cell levels and immunoglobulin levels normalized by study entry
5. Patients on immunosuppressive therapies (except for low dose steroids ≤10 mg of dexamethasone or equivalent per day) given for non-DDD related conditions such as asthma. Patients on steroids for DDD must complete a taper prior to study entry.
6. Patients who have received any complement inhibitor within 3 months of study entry
7. Patients who have received any other investigational drug or device or experimental procedures beginning four weeks prior to study enrollment
8. Patients who have had a renal transplant
9. Patients who have a preexisting condition with a reported association as a potential cause of DDD (i.e., Monoclonal Gammopathy of Undetermined Significance [MGUS])
10. Patients with another glomerular disease that may interfere with the interpretation of study results
11. Malignancy except for adequately treated and cured basal or squamous cell skin cancer, curatively treated in situ disease, or other cancer from which the patient has been disease-free for ≥ 5 years
12. Patients with myocardial infarction (MI) within 1 year of screening, congestive heart failure, arrhythmia persistent on medication at screening or clinically evident chronic lung disease
13. Patients who have human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C infection
14. Any medical or psychological condition that would increase the patient’s risk by participation in this study or would interfere with interpretation of the study
I don’t know what some of these things mean. What should I do?

Again, take this information to your doctor and ask you doctor whether you qualify. You or your doctor can also email Dr Richard Smith (Richard-smith@uiowa.edu) or Dr Carla Nester at (Carla-nester@uiowa.edu).

It doesn’t seem fair to exclude transplant patients. My transplant is not working well and I would like to participate. Why can’t I?

We considered this point a long time but decided not to include transplant patients at this time because we need to have very rigid inclusion and exclusion criteria to know whether CDX-1135 will work. We are sorry everyone cannot be included in the initial study.

How many patients can be included?

The study will enroll five patients only. During the study, a Data Monitoring and Safety Committee (DMSC) will review safety data on a periodic basis, based on the rate of patient enrollment and emergence of safety data. Unplanned safety review meetings of the DMSC may be called at any time if earlier review of safety data is warranted.

What would make you stop the study?

If any of the following criteria are met, further enrollment into the trial will be halted and the data reviewed with the DMSC. The trial will only be reopened after a mutually agreed plan is defined with the DMSC.

CDX-1135 does not work in the first three patients. This means that during the Induction Period (the first 4 weeks) we are unable to show that CDX-1135 normalizes C3, C3 breakdown products or alternative pathway complement activity.

Any of the following toxicities in more than one patient:

1. Dose-limiting toxicity defined as any Grade 3 or higher drug-related adverse event (AE)
2. Grade 3 or higher infection caused by encapsulated bacteria, not responsive to appropriate medical intervention within 24 hours
3. Drug-related death

Do you mean that CDX-1135 is really unsafe?

We think it is safe, but CDX-1135 has NEVER been given to a patient for 26 weeks, which will be the length of the study. The longest it has been given to a patient is two weeks. The person who received it was a child with DDD who was on dialysis at the time.

We wanted to see whether CDX-1135 would do anything. It increased the patient’s C3 and normalized her CRP. There were no adverse effects of CDX-1135 in this patient. CDX-1135 has also been used in several other studies in a large number of patients undergoing heart surgery. These patients received CDX-1135 during surgery and did not receive multiple doses. There were no adverse effects attributable to CDX-1135 in these patients either. However, it is important to remember that the current study is different as the proposed treatment will be for 26 weeks. CDX-1135 has never been used in patients for this length of time.

Why could I be asked to leave the study?

You would be asked to leave the study if:

1. Your kidney function got worse, meaning that the CDX-1135 wasn’t working.
2. You developed toxicity defined as any Grade 3 or higher Adverse Event (AE) attributed to CDX-1135 or any Grade 3 infection caused by encapsulated bacteria, not responsive to appropriate medical intervention within 24 hours.
3. The study is terminated for other reasons (say for example, you are the 4th patient enrolled and we don’t see a response in the first 3 patients – we would then stop the study).
4. You want to stop or your legal representative wants you to stop.
5. We think your participation would be bad for your health or wellbeing.
6. You don’t follow the study rules.
So how does the study work?

You receive CDX-1135 two times each week intravenously (through a vein) for a total of 26 weeks. Before starting CDX-1135, there is a **4-week screening period** to ensure that you qualify for the study and really want to be in the study. After the screening period, the **26-week treatment period** starts. The 26-week treatment period is divided into an **Induction Period** of up to 4 weeks and then a **Maintenance Period** which allows for continued treatment for up to **26 weeks**.

**How will you know if CDX-1135 works?**

At the end of the 26-week treatment period, we will consider CDX-1135 as having worked if:

1. Your proteinuria has dropped by at least 50% or to a level of <2 g/day
2. Your serum creatinine has improved by 25% or more.

**Okay. So tell me about the 4-week screening period. What is that?**

The screening period is the time we evaluate whether you are eligible for the study. If you and your kidney doctor believe that you meet eligibility criteria for this study, you and/or your kidney doctor should contact Drs. Smith and Nester. You will be invited to the University of Iowa to meet the study team and review the study design and requirements. During this visit, additional tests may be done, such as an eye examination to check for drusen. If you have not been vaccinated, you will be given the meningococcal, pneumococcal and hemophilus influenzae vaccines.

**Why do I have to come to Iowa?**

Because the study is complicated and you need to be evaluated in Iowa to see whether you qualify and to review the study in detail with Drs. Smith and Nester. If you are enrolled in the study, you need to return to Iowa for the **Induction Period** (see below).

**Okay, but that’s expensive?**

Your travel and medical expenses related to the drug trial will be covered. Full details on what IS and what IS NOT covered are being determined.

**So then what comes after the screening period, if I am accepted for the study?**

The treatment period, which is divided into the **Induction Period** of up to 4 weeks and then the **Maintenance Period**.

**What is the Induction Period?**

The **Induction Period** is when you first start getting CDX-1135. This is done at the University of Iowa on a twice-a-week basis and can last a maximum of 4 weeks. You have to come to Iowa because we will be doing complement studies immediately before and after you get CDX-1135 to see whether we need to change the dose. It is possible that each person in the study will require a different maintenance dose of CDX-1135. The first two doses you receive will be 5 mg/kg, with dose-escalation in 5 mg/kg increments for each dose thereafter, up to a maximum dose of 30 mg/kg. We will stop increasing the dose when:

Your C3, C3 breakdown products or alternative pathway complement activity is normal. At that time, you will get one more dose of CDX-1135 dose at the same level and then move to the **Maintenance Period**.

You have reached the dose level of 30 mg/kg without normalizing C3, C3 breakdown products or alternative pathway complement activity. If that happens, you will receive one more dose of CDX-1135 at 30 mg/kg.

1. If nothing happens after the second dose at 30 mg/kg, treatment will be stopped.
2. If C3, C3 breakdown products or alternative pathway complement activity normalizes, you will move to the **Maintenance Period**.

**So I could be in Iowa for 4 weeks? What about school and expenses?**

We can arrange a school curriculum for you and help with school expenses. The exact amount of money that will be provided is being determined.
Okay, so the *Induction Period* is done. What is the *Maintenance Period*?

The *Maintenance Period* starts when we have figured out the best dose of CDX-1135 for you. You will continue to receive CDX-1135 by vein twice a week. The first week of the *Maintenance Period* will be completed at University of Iowa. The remaining weeks of *Maintenance Period* can be completed your hometown by your own nephrologist. To make this possible, while you are at Iowa during the *Induction Period*, we will work with your nephrologist and home institution to get the required IRB approvals and appropriate home institution-specific patient consent/assent for you to complete the study there.

What else happens during the *Maintenance Period*?

It is possible that the dose required for maintenance may be significantly lower than that required during the *Induction Period*. During the *Maintenance Period* we will try to identify the lowest dose of CDX-1135 that provides ongoing control of C3 activation. The *Maintenance Period* will allow for dose decreases to 2 mg/kg, which is lower than the starting dose in the *Induction Period*. Complement studies will be collected on each dosing day and analyzed on a weekly basis at University of Iowa during the *Maintenance Period*. The *Maintenance Period* will be continued until either:

1. The study treatment period of 26 weeks ends;
2. The study is discontinued for any of the reasons described earlier.

Who pays for the CDX-1135 and visits to my nephrologist/kidney clinic when I go back home?

The study will pay for the visits and tests done because you are getting CDX-1135.

So if it is working, I won’t want to stop. What happens then?

You may be able to receive extended treatment under a separate extension protocol.

Well I’m interested but pretty confused. What should I do?

Email either Dr Richard Smith ([Richard-smith@uiowa.edu](mailto:Richard-smith@uiowa.edu)) or Dr Carla Nester at ([Carla-nester@uiowa.edu](mailto:Carla-nester@uiowa.edu)). If you would like one of them to call you back, include your phone number. It would also be a good idea to discuss this study with your nephrologist.

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**BENEFITS—2012**

**Emma Gibbs**— was selected to carry the Olympic torch in Peterborough, England. She asked people to donate money to Kidneeds if they wanted to hold the Torch. Emma’s brother Alex has DDD and is on dialysis.

**Julie Gibbs**— and her sister have started ‘Art in the Heart’ an original new Peterborough shop and gallery that is one of the great tourist attractions in Cambridgeshire. The charity it supports is Kidneeds. Visit [http://www.artintheheart.co.uk/default.html](http://www.artintheheart.co.uk/default.html).

**David Abraham**— held a raffle near his home of Leicester, England for Kidneeds. David has been on dialysis a couple of years and recently started doing home dialysis with NxStage.

**David Yates and Nikki Miljavec**— held their fourth golfing benefit for Kidneeds, near Chicago, Illinois, with great success despite the one storm of the summer for Iowa and Illinois, which knocked out power and dampened the tournament.

**Toyota of Iowa City**— supporters of Kidneeds since its inception, gave a large donation to Kidneeds on behalf of Jenna Smith.

**Mary Jo Yates and several people at the UI School of Art and Art History**— have been helping with the cartridge and cell-phone recycling fundraiser.

**Rose Kane and Family**— held their very successful 4th Annual World Day run/walk for Kidneeds in Bensalem, PA. They also held the 4th Tommy Kane Strikeout Benefit for Kidneeds. Thanks for all the hard work.

**Chelsea Nunn and Kickball Team**— her team took second place in a kickball tournament and donated their winning to Kidneeds. Chelsea’s brother has DDD.