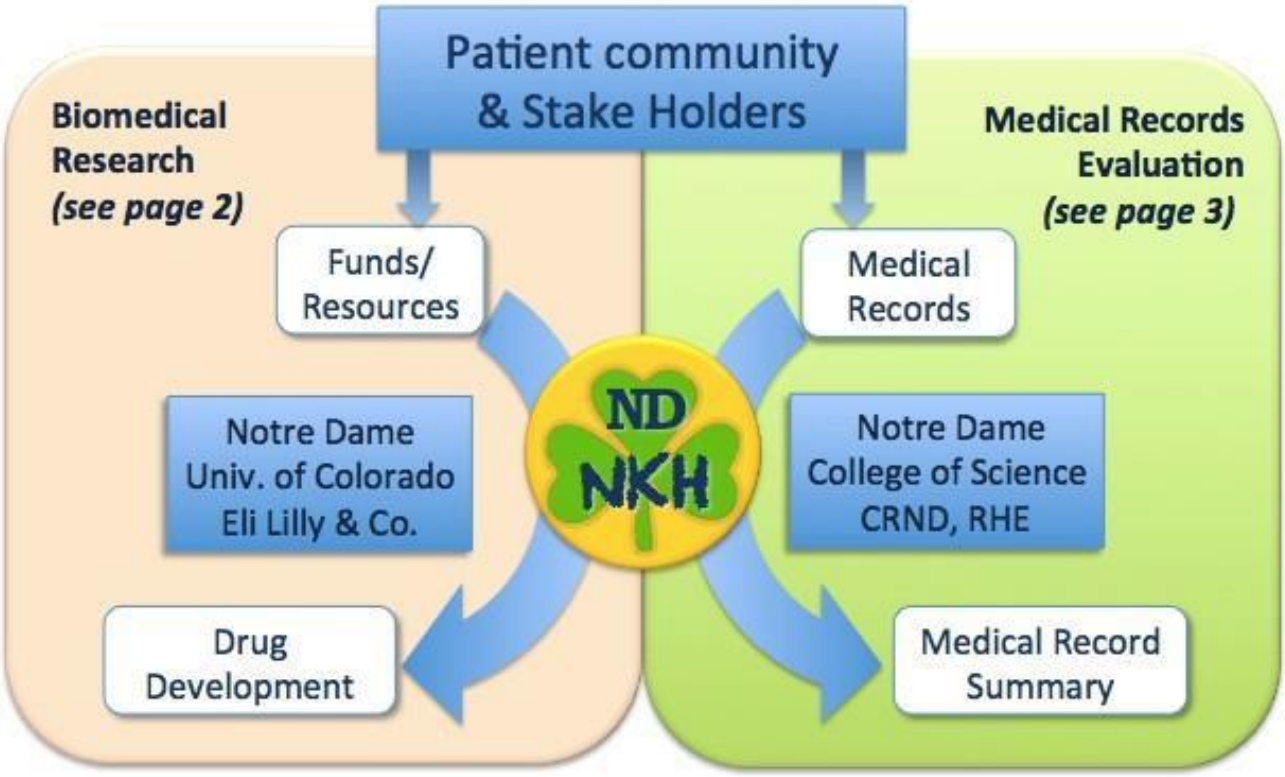
UNIVERSITY OF NOTRE DAME
College of Science

BOLER-PARSEGHIAN
Center for Rare & Neglected Diseases

The ND---NKH Program

ND---NKH is a program developed by the Notre Dame's Boler-Parseghian Center for Rare and Neglected Diseases that aims to develop therapies for NKH and to tailor them in personalized therapies, based on patient medical records. The program builds on collaborative efforts between students, researchers and clinicians from the University of Notre Dame, the University of Colorado, Eli Lilly & Co (one of the first companies to mass produce penicillin, the world's first antibiotic) and the NKH patient community. A summary is provided below. Page 2 describes the laboratory research program and page 3 provides the first step to develop personalized medicines.



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Developing new therapies for the NKH enzyme deficiency

University of Notre Dame College of Science

Boler Parseghian Center for Rare and Neglected Diseases with Eli Lilly & Co, the University of Colorado and NKH patient families.

The main problem with many genetic diseases like NKH is that they result in faulty enzyme function. In most cases, the mutated (faulty) enzyme is unable to take on the normal shape (3-•dimentional structure) that is essential for its proper function.

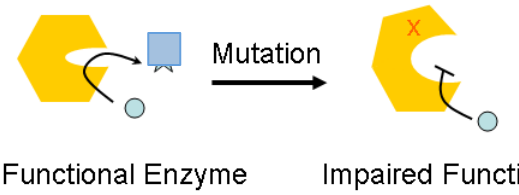

Figure 1: Proper functional P protein with normal 3D structure. Poor/bad function of faulty protein results from mutation.

For example, the normal enzyme in **figure 1** (left such as P protein) converts its substrate (blue circle) to the product (blue square). When there is a mutation in the P protein, it can no longer function properly because it can't take on its proper 3D--- structure. **The goal is to find drugs that can help the P protein take its shape, and restore normal function ultimately to cure the disease.**

One way to do this is to "screen" through hundreds of thousands of molecules and find the few that can make the P protein fully functional again.

To do this we at **Notre Dame's Center for Rare and Neglected Diseases** will develop engineered antibodies, which are proteins that can recognize the proper 3D functional form of the enzyme, but not its faulty form **bearing a patient mutation seen in diseased cells**. This is established in a clinical laboratory to grow cells with the mutation**.** Then 'drug' like molecules from the chemical libraries of **Eli Lilly &Co** can be added to these cells**,** when the drug molecule helps the mutant P protein return to the functional 3D form, the antibody will bind to the enzyme. This binding will trigger a signal that is captured by a microscope camera. In this way we will have identified a new potential drug hit.

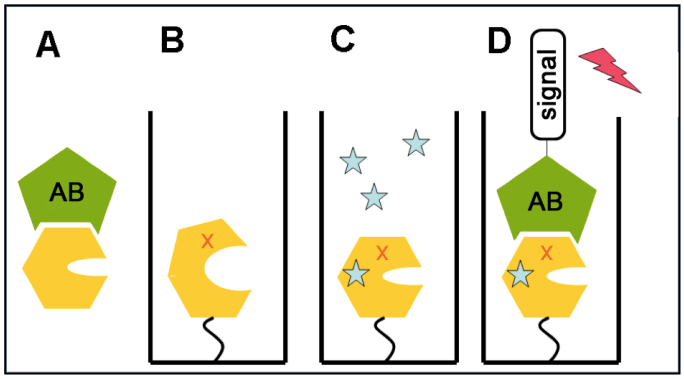

Figure 2: Finding the correctly folded P protein.

For example, in **Figure 2**, the engineered antibody (green) only recognizes the properly folded fully functional enzyme (A), but not the faulty form caused by the mutation (B). If a drug molecule, (blue star), binds the faulty P protein and changes it to its proper shape (C), the engineered antibody will now bind and produce a signal (D) captured by a microscope.

The drug **'hits'** will be converted into **'leads'**, tested for efficacy and safety and developed as new drugs in partnership with **Eli Lilly & Co, clinicians and patient families.**

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Greetings from the Rare Health Exchange (RHE) at the University of Notre Dame! RHE is a rare disease collaborative at the Center for Rare and Neglected Diseases (CRND) in the College of Science. In order to assist you we ask that you participate in our program.

Through course work we train advanced, pre-med students to assess medical records to assist physicians, researchers, and patient families in developing natural histories for rare diseases. The students learn how to analyze your records to identify important clinical symptoms, determine their severity and summarize how they change over time. This helps develop treatment strategies. Students are also trained to obtain the latest information on what is known about the rare disease and available therapies. By participating, students will assess your (or your family member's) medical record and return to you a summary of your clinical history and supply you with a password protected electronic copy of your record. The clinical summary includes important milestones in your (or his/her) clinical history, hospitalizations, procedures and lab results, medication history and a contact list of all health care providers. This summary will assist each physician you visit to understand your full history with the disease and help in creating an effective treatment plan.

If you are interested in participating in our program, we ask that you sign and return this consent form to allow us to view your medical records. Any information that we gather on symptom progression will be de-identified and entered into a database with other de-identified information from other records of your particular disease. This information will help physicians and researchers improve disease management, early diagnosis and accelerate therapeutic research.

With your participation, we can assist you with finding information regarding your disease. We can help identify and approach physicians, clinical centers, support groups, explore current research and find available resources for your disease. Once we have your signed consent form, Nurse Calhoun will initiate the process by calling you.

Best Wishes,

Barbara Calhoun MSN, NP
Outreach Coordinator

Kasturi Haldar
Director, CRND

Patient Name:_____ Parent/Guardian:_____

I give my permission for medical records to be viewed by the following people (check all that apply):

_____ Students at the University of Notre Dame: students will assess de-identified records
_____ Physicians: Physicians will use this information to improve disease management
_____ Researchers: Researchers will use this information to develop new therapeutics

_____ _____
Signature Date

Please email PDF copy of form to bcalhoun@nd.edu and send hard copy to 107 Galvin Life Sciences Center, Notre Dame, IN 46556