An algorithm for precision medicine

Matt Might, Ph.D. | matt.might.net | @mattmight
This is a personal talk. This talk may not reflect the views of the President or the administration.
But, it used to.
Disclaimer
A story
An algorithm
Data-driven medicine
Might’s Conjecture
The greatest drug of the 21st century is data.
data-driven medicine?
data-driven
often genome-guided
right drug to right patient
\[ f : \text{person} \rightarrow \text{pill} \]
\( \hat{f} : \) \[\text{human} \rightarrow \{ \text{pill}, \text{microscope} \} \]
“undiagnosed island”
Step 0: Collect data
Step 1: Diagnose
Step 1.1: Sequence
[Need, Shashi, et al. JMG 2012]
NGLY1
NGLY1
“first”
“only”
“n = 1”
How do you know?
Step 1.2: Interpret variants
Dr. Hudson Freeze, Sanford-Burnham-Prebys
“almost certainly”
“not actionable”
Science becomes action.
Science becomes medicine.
Step 2: Science
“Let’s do Science.”
“Let’s stand on shoulders of giants.”
PubMed: shoulders of giants?
“We’re gonna need more giants.”
“the cure”
Step 2.1: Grow $n$
1 in millions
“Let’s find the others.”
So, I wrote a blog post.
Hunting down my son's killer

I found my son's killer.

It took three years.

But we did it.

Not quite like this.
GIZMODO

Hunting Down My Son's Killer

Hacker News
Hunting down my son's killer - Matt Might
matt.might.net/articles/my-sons-killer/

We discovered that my son inherited two different (thus-far-unique) mutations in the same gene—the NGLY1 gene—which encodes the enzyme N-glycanase 1.
What can $n = 59$ do?
(Does it scale?)
Reaching out

This page is for parents, doctors, or researchers who may know of other children like our son, Milo. If you know of a similar case, please get in touch with us. The more cases we have, the more opportunities we will have to improve our understanding of his condition and facilitate research that can help him and others.

Find out more

- [What this site is for](#)
- [Case study:](#)

Finding others like our Milo

Currently, at age 3, Milo’s primary challenges are global developmental delay and significant hypotonia. He has had surgical repairs for a minor cleft in his soft palate, for ptosis, for C1 stenosis, for a tethered
Participant Web Pages

How do you get beyond n=1?

To help find patients with the same or similar condition, the Undiagnosed Diseases Network (UDN) is creating public web pages about participants in the study. Ideally healthcare providers, researchers, and families who know similar patients will find these pages on the Internet. Connecting these individuals with UDN participants provides the hope of getting beyond n=1.

For more information, visit udnconnect.org!

Kim Splinter  Rachel Ramoni  Cecilia Estevez
Step 2.2: Natural history
Natural History Study for Disorders of Glycosylation

National Institutes of Health
Step 2.3: Natural experiments
Step 3: Therapeutics
Step 3.1: Assays
Step 3.2: Models
Nutritional Yeast Flakes

Premium - Unsweetened - Fortified

Gluten Free

Wonderful Nutty Flavor
Non-GMO

Net wt. 22 oz. (624 g)
Step 3.3: Replace protein
Human NGLY1 full length protein (ab163212)

<table>
<thead>
<tr>
<th>Size</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 µg</td>
<td>$402</td>
</tr>
</tbody>
</table>

Order now and get it on Tuesday February 10, 2015

ADD TO BASKET
Or Request quote for bulk purchase

**Overview**

- **Product name**: Human NGLY1 full length protein

**Description**

- **Nature**: Recombinant
- **Source**: Wheat germ
- **Amino Acid Sequence**
  - **Species**: Human
Step 3.4: Metabolic diets
Can you give B?

Can you restrict A?
PKU? Restrict.
CDG-MPI? Give.
NGLY1?
A congeneric disorder of disglycosylation: Biochemical characterization of Nglycanase 1 deficiency in patient fibroblasts

Ping He, Jeff E Grotke, Bobby G Ng, Murat Gune, Hamad Jaffer-Nejad, Peter Creuswelly, Gregory M Ennis, and Hudson H Freeze

In the cytosol (17). Recent evidence suggests that a nonlysosomal degradation pathway exists for these cytosolic free glycans (17). In the cytosol (17). Degradation was evident in yeast; Ngly1−/− MEF cells. The unconventional deglycosylation reaction was found to be catalyzed by the cytosolic endo-N-acetylglucosaminidase (ENGase), generating aggregation-prone N-GlcNAc protein. The ENGase deglycosylation in cells lacking Ngly1 was restored by the additional knockdown of ENGase gene. Thus, our study underscores the functional importance of Ngly1 in the ERAD process and provides a potential mechanism underlying the phenotypic consequences of a newly emerging genetic disorder caused by mutation of the human Ngly1 gene.

Engly1−/− MEF cells were identified by MS analysis, demonstrating that the ENGase-mediated degradation process involves cytosolic endo-N-acetylglucosaminidase (ENGase) activity (18, 19). Although the ENGase is believed to be involved in the catabolism of cytosolic free oligosaccharides, recent evidence shows that it can deglycosylate glycoproteins in vivo to generate N-GlcNAc-bearing proteins in Arabidopsis thaliana (20), raising the possibility that this enzyme may also act as a deglycosylating enzyme for nonglycosylated glycoproteins in the cytosol (18, 21, 22) (Fig. 1 A).

Recent patients harboring mutations in the Ngly1 gene, an ortholog of the cytoplasmic PNGase in mammalian cells (23), have been described (24, 25). Although this observation emphasizes the functional importance of this protein in mammalian cells, mechanistic insights into the phenotypic consequences of these mutations remain unclarified. In this study, we established an ERAD model substrate, RTAΔΔ in 26S proteasomal degradation. Moreover, the occurrence of N-GlcNAc-modified RTAΔΔ in Ngly1−/− MEF cells was identified by MS analysis, demonstrating that the ENGase-mediated degradation process involves cytosolic endo-N-acetylglucosaminidase (ENGase) activity. ENGase catalyzes the deglycosylation of RTAΔΔ in cells with defects in the endoplasmic reticulum-associated degradation (ERAD) process, which is caused by an unexpected deglycosylating activity of endo-N-acetylglucosaminidase (18, 19). Our study clearly points to the critical role of Ngly1 even in cytosolic events of the ERAD process by controlling the conformation/solubility of proteins. This study may also provide a potential mechanism for explaining the pathogenesis of a human genetic disorder caused by mutations in the Ngly1 gene.
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That’s great, but…
Clement Chow, Ph.D.
survival

without GlcNAc  with GlcNAc
computer science

biology & medicine
Toward therapeutics for NGLY1 deficiency
+ RNAi for NGLY1
+ RNAi for NGLY1
+ RNAi for NGLY1 & ENGase
+ RNAi for NGLY1 & ENGase
computer science

biology & medicine
computer science

biology & medicine
Step 3.5: Virtual screening
70 compounds!
14 FDA approved!
1 works in the lab!
PREVACID® 24HR
Lansoprazole delayed-release capsules 15 mg / acid reducer

May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours

Clinically Proven To Treat Frequent Heartburn

14 CAPSULES
ONE 14-DAY COURSE OF TREATMENT

Sodium Free
Repurposing of Proton Pump Inhibitors as First Identified Small Molecule Inhibitors of Endo-β-N-acetylglucosaminidase (ENGase) for the Treatment of Rare NGLY1 Genetic Disease

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

ABSTRACT

N-glycanase deficiency, or NGLY1 deficiency, is an extremely rare human genetic disease. N-glycanase, encoded by the gene NGLY1, is an important enzyme involved in protein deglycosylation of misfolded proteins. Deglycosylation of misfolded proteins precedes the endoplasmic reticulum (ER)-associated degradation (ERAD) process. NGLY1 patients produce little or no N-glycanase (Ngly1), and the symptoms include global developmental delay, frequent seizures, complex hyperkinetic movement disorder, difficulty in swallowing/aspiration, liver dysfunction, and a lack of tears. Unfortunately, there has not been any therapeutic option available for this rare disease so far. Recently, a proposed molecular mechanism for NGLY1 deficiency suggested that endo-β-N-acetylglucosaminidase (ENGase) inhibitors may be promising therapeutics for NGLY1 patients. Herein, we performed structure-based virtual screening of FDA-approved drug database on this ENGase target to enable repurposing of existing drugs. Several Proton Pump Inhibitors (PPIs), a series of substituted 1H-Benz[d]imidazole, and 1H-imidazo[4,5-b] pyridines, among other scaffolds, have been identified as potent ENGase inhibitors. An electrophoretic mobility shift assay was employed to assess the inhibition of ENGase activity by these PPIs. Our efforts led to the discovery of Rabeprazole Sodium as the most promising hit with an IC\(_{50}\) of 4.47±0.44 μM. This is the first report that describes the discovery of small molecule ENGase inhibitors, which can potentially be used for the treatment of human NGLY1 deficiency.
Step 4: Medicinal chemistry
Step 5: Clinical trials
How is Bertrand?
Recap
The algorithm
sequencing ➔ web / wikipedia
 sequencing ➔ gene experts
 sequencing ➔ functional studies
web / wikipedia

gene experts

functional studies

interpretation
natural history

interpretation

crowd-screening

gain of function

partial loss of function

total loss of function

change of function
total loss of function

- model organisms
- structural analysis
- enzyme synthesis
- stem cell creation
- gene therapy
- metabolic diet
- assay development
gain of function

- RNA downregulation
- inhibitor / antagonist
- model organism
- dietary changes
change

- proteomics
- structural analysis
- model organism
- transcriptomics
clinical trials
clinical trials
But, will it scale?
5 diseases; 12 months
Next?
“not actionable”
Thank you! Questions?

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