

ACCELERATE **CHICAGO**

Craft software with confidence in 2026

From Data to Discovery

How AI is Finding Hidden Cures – and Making them Human



Introduction

I'm the CEO at TXI

I am one of the co-organizers of this week's conference
(thank you to TriFork and Slalom for organizing)

I am one of the board members of Rare Hopes.

Disclosures

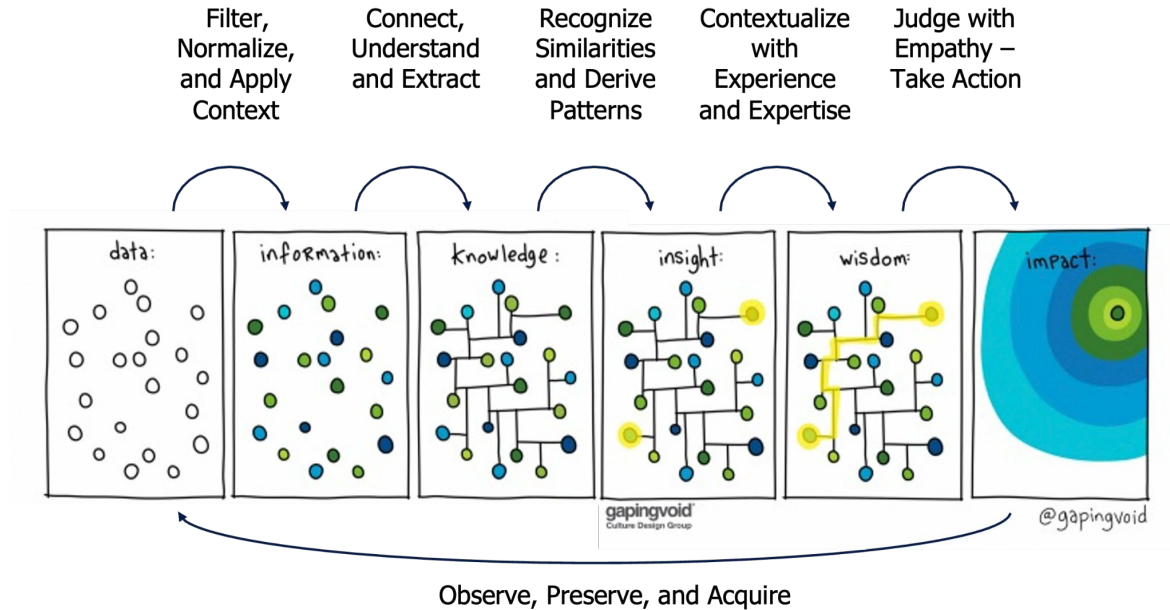
I am a full-time employee and shareholder in AbbVie.

I am the President and Founder of Rare Hopes NFP, a non-profit organization targeting the use of knowledge to generate and release hypotheses for drug repurposing in the treatment of rare diseases.

AbbVie and RareHopes share no affiliation.

The opinions expressed are my own and are not official statements or representative of AbbVie.

How Data Becomes Knowledge



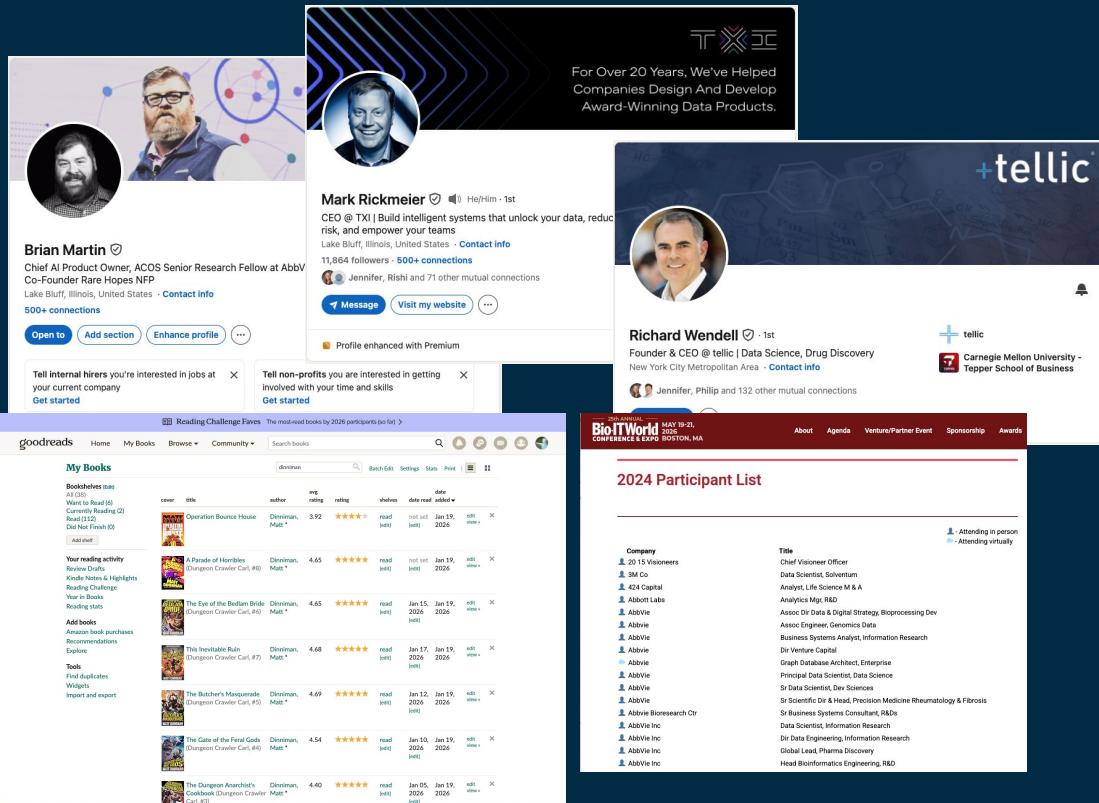
What is a knowledge graph?

Nodes: store details about entities, such as people, places, objects, or institutions.

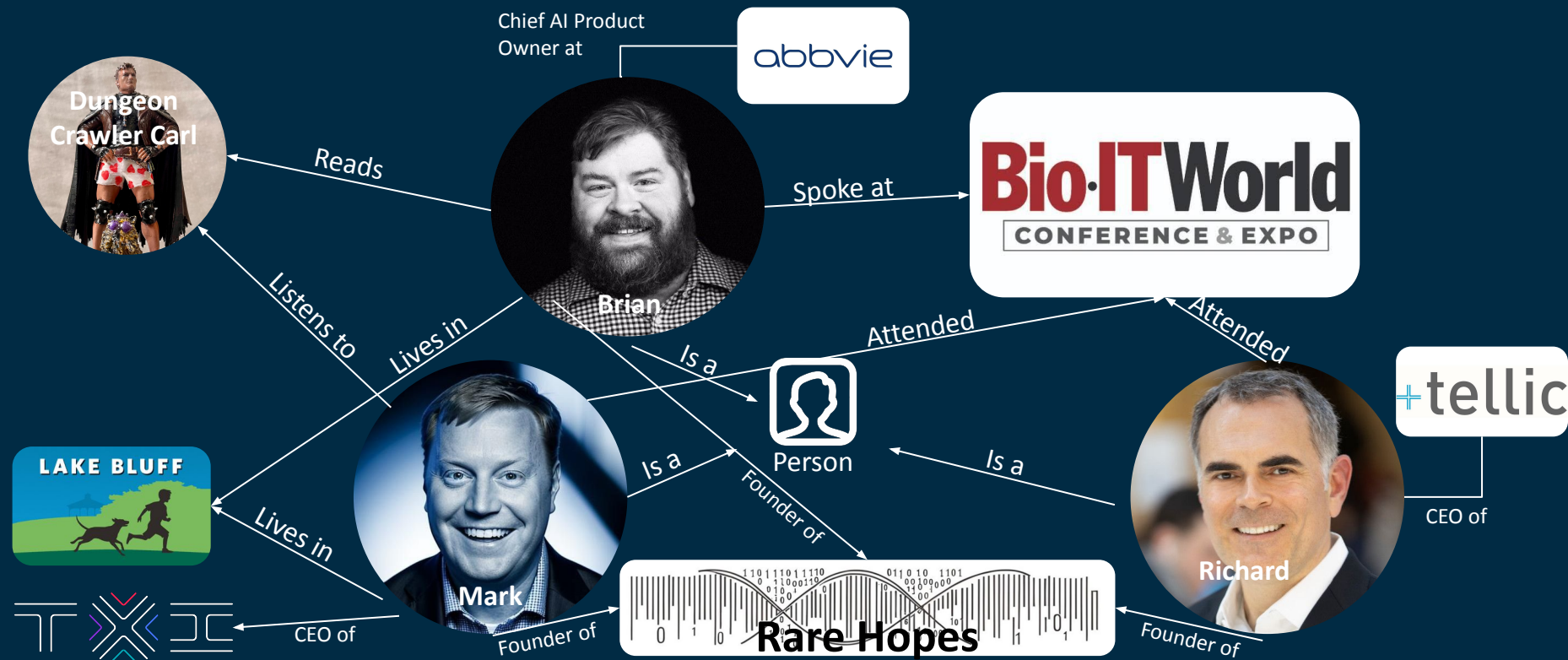
Relationships (or Edges): The link between two nodes that shows how they are related. Like nodes, each relationship has a label identifying the relationship type and may optionally have one or more properties.

Organizing principle: a framework that organizes nodes and relationships. Unlike many data designs, knowledge graphs can easily incorporate multiple organizing principles.

Data



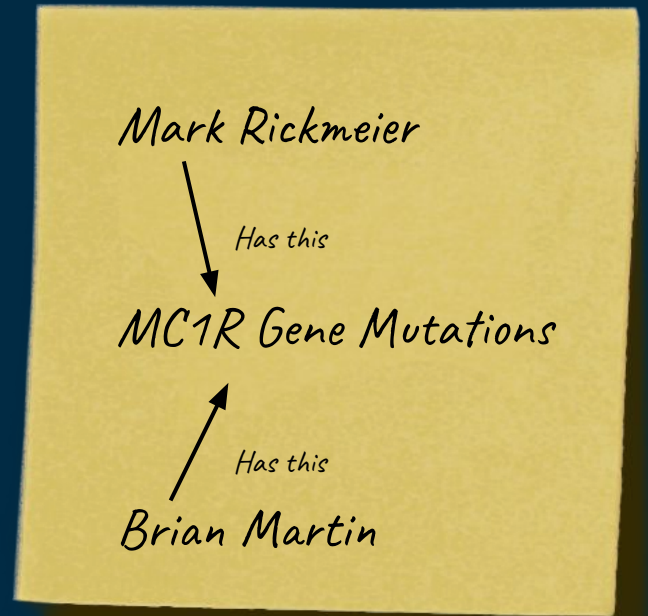
Knowledge



Now you try...

Part of the benefit of this conference is building connections and community.

Turn the people near you and find 3-5 ways that you connect and can build your network.



Now you try...

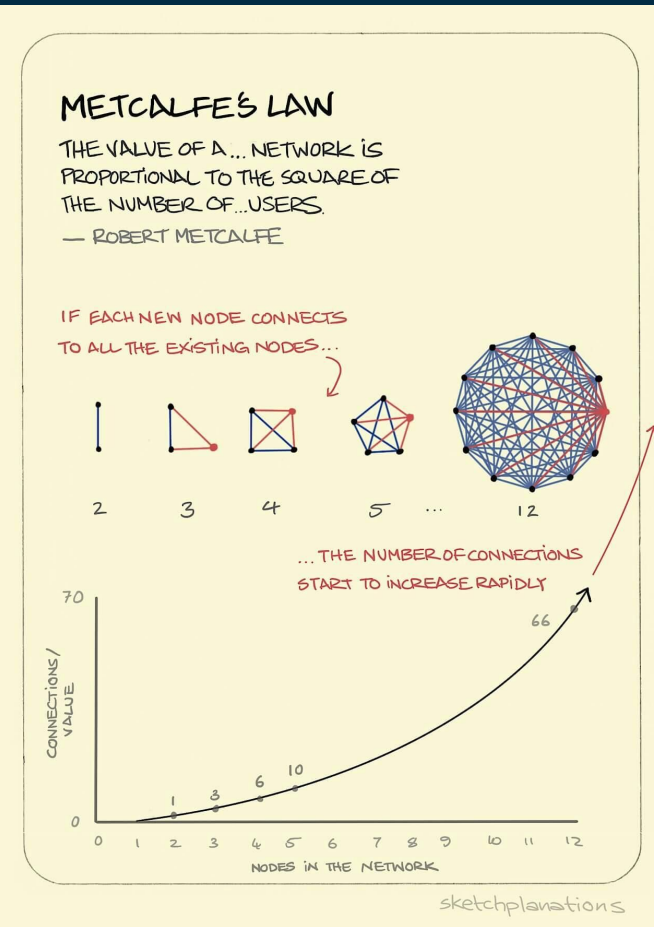
Part of the benefit of this conference is building connections and community.

Turn the people near you and find 3-5 ways that you connect and can build your network.



Metcalfe's Law

Let's apply it to our knowledge of human medicine and biology...



The Rare Hope...

What if a disease is so rare that it will never receive the significant investment of time and resources necessary to research and develop a treatment?

What if an approved, on-market drug can be connected to an existing rare disease through public literature and evidence?

What if we could put the power of AI and graphs to work to make these type of hypotheses and evidence available to doctors and researchers?



A new life conceived...

It's 1998 - somewhere in the world, a new life begins.

A girl will be born, with her whole life ahead of her.

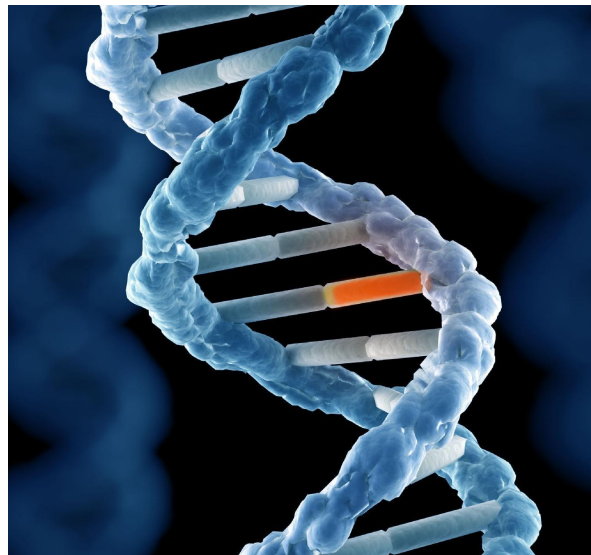


patient



An undetected mutation...

Unbeknownst to anyone, her DNA has experienced from either an inherited condition or a spontaneous mutation, a variation in chromosome 17q24.2 found in the human gene PRKAR1A.



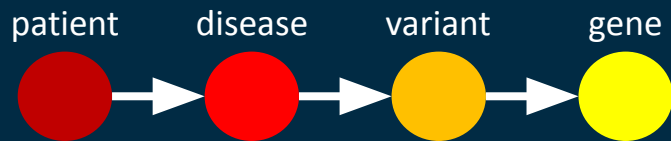
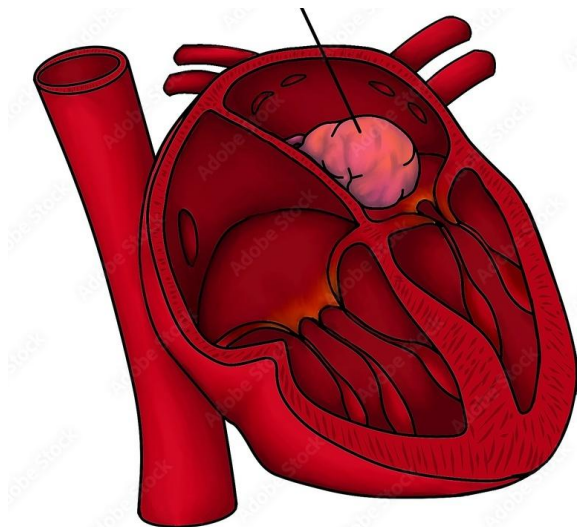
A rare disease...

First described in 1985, Carney Complex is a disorder which causes the growth of small benign tumors in various parts of the body. These tumors range from simple aesthetic nuisance to potentially life threatening.

Carney Complex is in most cases caused by this specific mutation of the PRKAR1A gene.

She is now one of less than 650 individuals ever reported.

There is no approved treatment known.

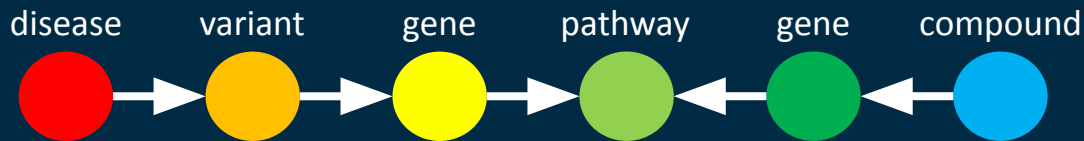
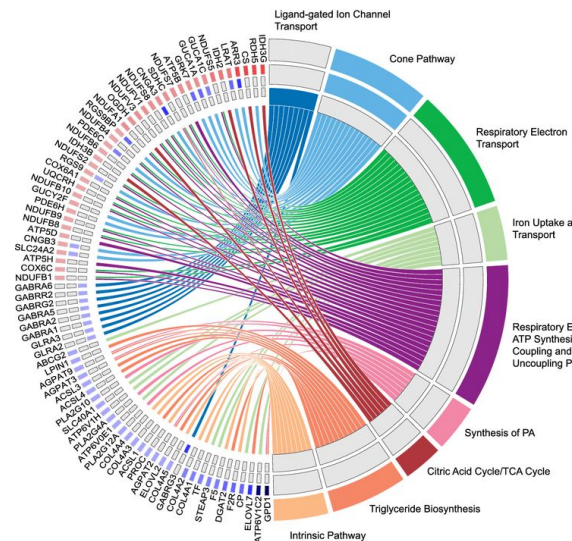


In the neighborhood...

The PRKAR1A gene acts as a catalyst for another gene called PRKACA as part of the cAMP signaling pathway – which has connections to oncology as a known cancer related gene.

Back in 2014, a single paper pointed out the potential for PRKACA inhibitors as a treatment of other diseases similar to Carney Complex.

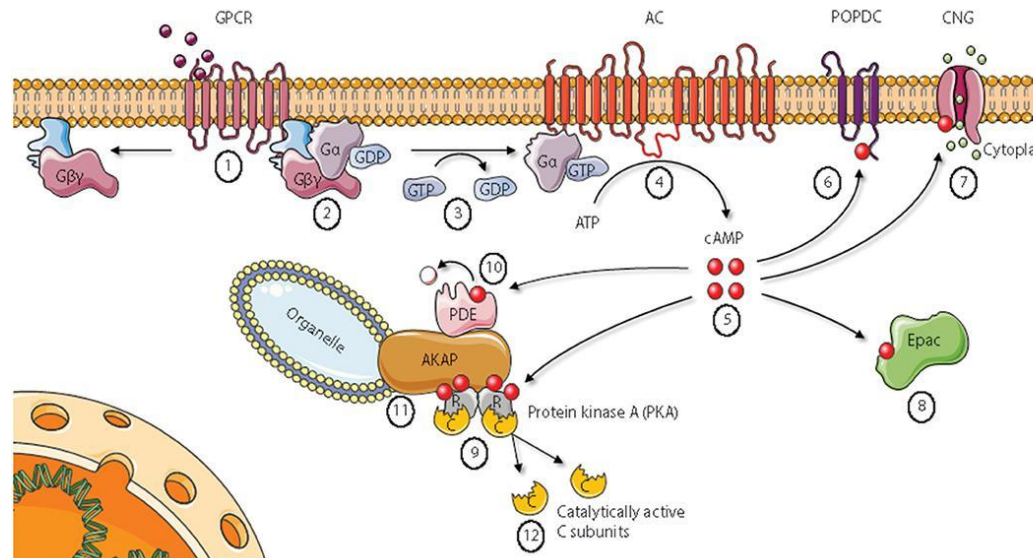
No further research has been identified on this association.



Heading in the right direction...

PRKAR1A and PRKACA are related by sharing a pathway called the cAMP PKA subunit.

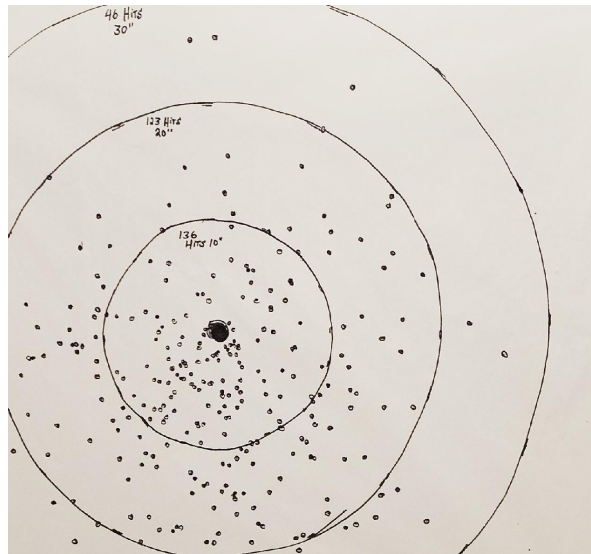
This means if you can affect PRKACA in the right way, you can impact the potential issues with PRKAR1A's failure to perform its role in regulating things.



Unrelated research...

A 2019 Nature publication includes research shared as
"Chemical proteomics reveals target selectivity of clinical JAK inhibitors in human primary cells"

In the study, researchers examined how selective the JAK inhibitor class of compounds are within the JAK family of genes. They found lots of off-target activity of these drugs against other genes, but activity against JAK1/2 was the purpose of the study.

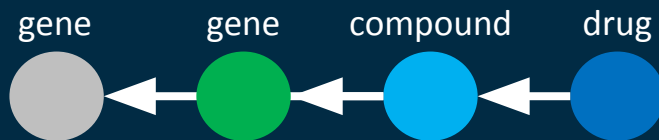
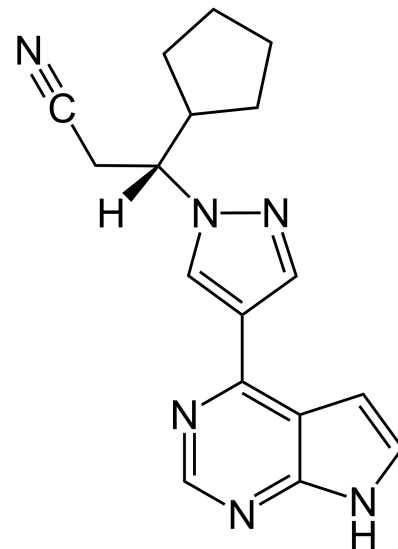


An existing drug...

Enter Ruxolitinib - a JAK1 inhibitor.

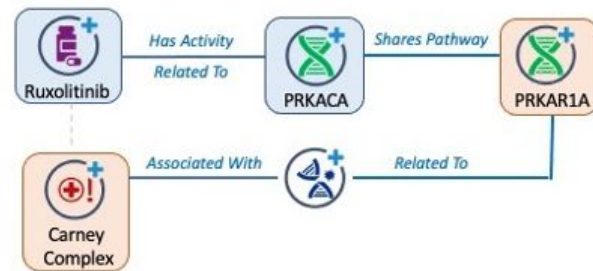
Not designed, targeted, or tested for endocrine tumor conditions, it was first approved in 2011 for the treatment of myelofibrosis.

However, that unrelated research from 2019 shows it has off-target activity against PRKACA.



Potential...

So, if Ruxolitinib as an approved JAK inhibitor compound also affects PRKACA and causes an effect through the cAMP pathway on PRKAR1A which mitigates the impact of the variant in chromosome 17q24.2, could it enable the patient's body to catalyze proteins correctly and prevent the formation of tumors?



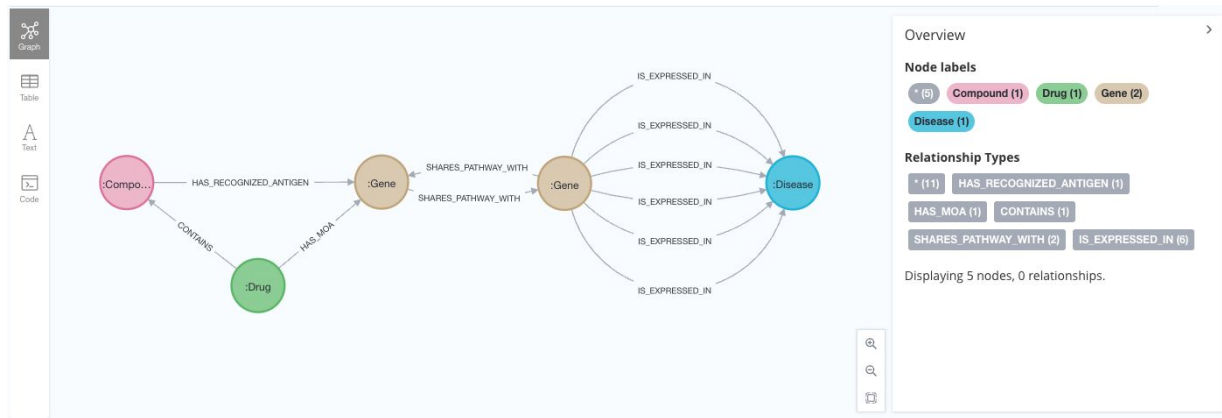
It works.

MATCH

```
(d:Drug)-[r1:CONTAINS]->(c:Compound),  
(c)-[r2:HAS_ACTIVITY_AGAINST]->(g1:Gene),  
(g1)-[r3:SHARES_PATHWAY_WITH]-(g2:Gene),  
(g2)-[r4:HAS_VARIANT]->(v:Variant),  
(v)-[r5:ASSOCIATED_WITH]->(di:Disease)
```

WHERE

```
r1.STRENGTH>0 and r1.CONFIDENCE=1.0 and  
r2.STRENGTH>3 and r2.CONFIDENCE>0.8 and  
r3.STRENGTH>0 and r3.CONFIDENCE>0.7 and  
r4.STRENGTH>0 and r4.CONFIDENCE>0.5 and  
r5.STRENGTH>0 and r5.CONFIDENCE>0.5 and  
di.PREFERRED_NAME='Carney Complex' and  
d.MAX_PHASE>3 and  
NOT EXISTS (d)-[:APPROVED_TREATMENT]-(di)
```



= 1 result: d.PREFERRED_NAME='RUXOLITINIB'



Closing the loop...

A doctor or researcher, armed with sufficient evidence and belief, can consider and pursue the potential of an off-label use of the drug or provide their own knowledge on why the hypothesis of a treatment might be invalid.

A community space where that knowledge can be captured and shared creates an opportunity to close the loop on a hypothesis.

References

1. Maryam Lotfi Shahreza, Nasser Ghadiri, Sayed Rasoul Mousavi, Jaleh Varshosaz, James R Green, A review of network-based approaches to drug repositioning, *Briefings in Bioinformatics*, Volume 19, Issue 5, September 2018, Pages 878–892, <https://doi.org/10.1093/bib/bbx017>
2. Chi Heem Wong, Kien Wei Siah, Andrew W Lo, Estimation of clinical trial success rates and related parameters, *Biostatistics*, Volume 20, Issue 2, April 2019, Pages 273–286, <https://doi.org/10.1093/biostatistics/kxx069>
3. Naylor S, Schonfeld JM. Therapeutic Drug Repurposing, Repositioning and Rescue - Part 1: Overview Drug Discovery World Winter 2014/15 49.
4. Cha, Y et al. "Drug repurposing from the perspective of pharmaceutical companies." *British journal of pharmacology* vol. 175,2 (2018): 168-180.
5. ... drug repositioning, *Mol Biosyst* 2013;9:1268 –
6. ... ch to prediction and population-based *Nat. Commun.* 9:2691 (2018).
7. ... framework for identifying drug-repurposing (2019) (2021)
8. ... h genetic support twice as likely to be act of genetic support for drug mechanisms *PLoS genetics* vol. 15,12 e1008489. 12 Dec.
9. ... Nicoletti P, Shen Y, Floratos A, Sham PC, Li nseau P. The support of human genetic *Nat Genet.* 47(8):856-60. (2015)
10. ... e Diseases" *Trends Pharmacol Sci* 42(4):255-
11. ... : PRKAR1A: Normal and Abnormal Functions")
12. ... f a novel mutation of the PRKAR1A gene in a icant osteoporosis and recurrent fractures."
13. ... ics reveals target selectivity of clinical Jak e 9:14159 (2019)
14. ... e Main Protein Kinase A Catalytic Subunit (PRKACA), a Likely Oncogene, and Cortisol-Producing Tumors" *J Clin Endocrinol Metab* 99(10):3629–3633 (2014)
15. Shi, J.G. et al "The pharmacokinetics, pharmacodynamics, and safety of orally dosed INCB018424 phosphate in healthy volunteers." *J Clin Pharmacol* 51(12):1644-54 (2011)



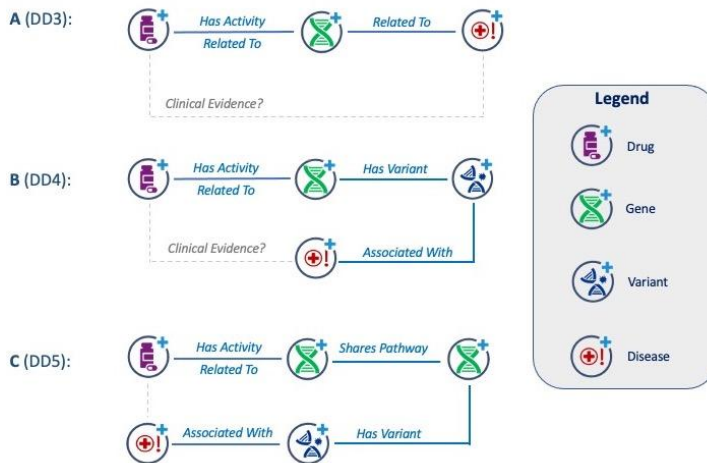
And so much more...

MATCH

```
(d:Drug)-[r1:CONTAINS]->(c:Compound),
(c)-[r2:HAS_ACTIVITY_AGAINST]->(g1:Gene),
(g1)-[r3:SHARES_PATHWAY_WITH]-(g2:Gene),
(g2)-[r4:HAS_VARIANT]->(v:Variant),
(v)-[r5:ASSOCIATED_WITH]->(di:Disease)
```

WHERE

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r1.STRENGTH>0 and r1.CONFIDENCE=1.0 and
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r3.STRENGTH>0 and r3.CONFIDENCE>0.7 and
r4.STRENGTH>0 and r4.CONFIDENCE>0.5 and
r5.STRENGTH>0 and r5.CONFIDENCE>0.5 and
di.PREFERRED_NAME='Carney Complex' and
d.MAX_PHASE>3 and
NOT EXISTS (d)-[:APPROVED_TREATMENT]-(di)
```



<https://www.biorxiv.org/content/10.1101/2022.12.20.521235v1>

> 800,000 drug+disease hypotheses



The platform...

The screenshot shows the 'Rare Hopes' website. At the top, there is a navigation bar with the 'Rare Hopes' logo on the left, a 'Log in' link in the center, and a 'Get Started' button on the right. Below the navigation bar, a purple banner contains the text 'From Research to Hope' with a small icon. The main content area is divided into two columns. The left column features a large heading 'Advancing Therapeutic Discovery for Rare Diseases' in white and blue text, followed by a paragraph: 'By mapping the connections between genes and diseases in a powerful knowledge graph, we uncover new paths for treatment—bringing rare disease research closer to real hope for patients and families.' At the bottom of this column is a 'Search by Disease' button. The right column has a heading 'Hope for Every Patient, Every Family' followed by a paragraph: 'Behind every rare disease is a person with hopes, dreams, and the determination to find answers.' Below this text is a 3x4 grid of images. The grid contains 12 squares; 6 of them show portraits of diverse individuals (a baby, a woman, a man, and two other children), while the other 6 squares are solid purple. Small, colorful star-like icons are scattered around the grid.

Rare Hopes

Log in

Get Started

From Research to Hope

Advancing Therapeutic Discovery for Rare Diseases

By mapping the connections between genes and diseases in a powerful knowledge graph, we uncover new paths for treatment—bringing rare disease research closer to real hope for patients and families.

Search by Disease

Hope for Every Patient, Every Family

Behind every rare disease is a person with hopes, dreams, and the determination to find answers.

The platform...

 Rare Hopes

From Research to Hope

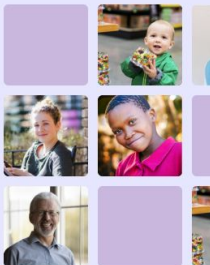
Advancing Therapeutic Discovery for Rare Diseases

By mapping the connections between genes and diseases in a powerful knowledge graph, we uncover new paths for treatment—bringing rare disease research closer to real hope for patients and families.

Search by Disease

Hope for Every Patient

Behind every rare disease is a story of dreams, and the determination to make a difference.



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Carney Complex (CNC)

Carney Complex (CNC). CNC is a rare multiple endocrine neoplasia (MEN) syndrome inherited in an autosomal-dominant manner and characterized by cardiac and noncardiac myxomatous tumors, multiple endocrine tumors, and distinctive pigmented lesions of the skin. According to the National Organization for Rare Diseases (NORD), approximately 600 affected individuals have been reported since the disorder was first described in the medical literature in 1985.

PRKACA Gene Relationship



```
graph LR; A[Carney Complex] --- B[PRKAR1A]; B --- C[PRKACA]; C --- D[Drug]
```

Carney Complex is caused by inactivating mutations in PRKAR1A, which normally regulates the catalytic subunit PRKACA. Loss of PRKAR1A function leads to uncontrolled PRKACA activity and excessive PKA-dependent CAMP signaling, driving the disease pathophysiology including multiple endocrine neoplasias and hypercortisolism. While PRKACA has been recognized as a therapeutic target for Carney Complex since 2014, no specific inhibitors have been developed. However, there is evidence suggesting compelling drug repurposing opportunities.

Select a drug to review potential repurposing hypotheses:

★ High Interest
Ruxolitinib →

★ High Interest
Baricitinib →

★ New
Kaideninib →

For professionals...

[← Back](#)

Carney Complex - Ruxolitinib Treatment Research

[Graph](#)

Carney Complex - PRKAR1A



Inactivating mutations in the Protein Kinase cAMP-Dependent Type I Regulatory Subunit Alpha (PRKAR1A) protein are known to be associated with the development of Carney Complex and other Multiple Endocrine Neoplasia (MEN) syndromes

References

- Bossis I, Stratakis CA.
[Minireview: PRKAR1A: normal and abnormal functions.](#)
Endocrinology. 2004;145(12):5452-5458.
- Papanastasiou L, Fountoulakis S, Voulgaris N, et al.
[Identification of a novel mutation of the PRKAR1A gene in a patient with Carney complex with significant osteoporosis and recurrent fractures.](#)
Hormones (Athens). 2016;15(1):129-135.

Annotations ☒ Private

[Post](#)

PRKAR1A - PRKACA



PRKACA may be highly relevant to therapeutic intervention within this pathway. PRKAR1A is a protein, and the inactivating mutations in PRKAR1A disrupt the interaction with PRKACA and lead to catalytic activity of the PRKACA oncogene. It has been further demonstrated that mutations in PRKAR1A that disrupt binding to the PRKAR1A regulatory domain also increase PKA-dependent cAMP signaling and in patients with Cushing Syndrome and other adrenocortical disorders.

These pieces of genetic evidence support the potential of PRKACA inhibitors in the treatment of Carney Complex and other forms of hypercortisolism, and in fact the use of small molecule PRKACA inhibitors in this field was postulated as far back as 2014.

Stratakis CA.
[Minireview: PRKAR1A: normal and abnormal functions.](#)
Endocrinology. 2004;145(12):5452-5458.

Stratakis CA. E pluribus unum?
[Protein kinase A catalytic subunit \(PRKACA\), a likely oncogene, and cortisol-producing tumors.](#)
Endocrinol Metab. 2014;99(10):3629-3633.

Ruxolitinib



Genetic evidence for off-target activity of Ruxolitinib against PRKACA (protein kinase A catalytic subunit) in a proteomics profiling using kinobeads revealed that ruxolitinib binds to PRKACA as an off-target. When profiled against 250 protein kinases in human PBMC lysates using dose-dependent competition quantitative mass spectrometry, ruxolitinib was found to have multiple off-targets beyond its PKA family targets. PRKACA, a member of the AGC kinase family, was specifically identified as one of the off-targets shared between ruxolitinib and baricitinib (which have the same pyrazole-quinoline core).

For families...

 Rare Hopes

AboutTeamFAQ

Get Started

 Supporting 10K Rare Diseases

Find Hope in Research

By mapping the connections between genes and rare diseases in a powerful knowledge graph, we uncover new paths for treatment. Discover the latest scientific developments.

Search by Disease



For families...

 Rare Hopes

AboutTeamFAQ

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[← Back](#)

Carney Complex (CNC)

Very Rare Disease

Carney Complex (CNC). CNC is a rare multiple endocrine neoplasia (MEN) syndrome inherited in an autosomal-dominant manner and characterized by cardiac and noncardiac myxomatous tumors, multiple endocrine tumors, and distinctive pigmented lesions of the skin. According to the National Organization for Rare Diseases (NORD), approximately 600 affected individuals have been reported since the disorder was first described in the medical literature in 1985.

Quick Facts

Gene: PRKARCA

Prevalence: <750

Primary Effect: Spotty skin pigmentation

TreatmentsResearchersKnowledge Graph

Potential Treatment Hypothesis

Carney Complex is a rare disease caused by subunit PRKACA. Loss of PRKAR1A function signaling, driving the disease pathophysiology.

While PRKACA has been recognized as a target for treatment, no treatment has been developed. However, there is evidence that...

Treatments

★ High Interest

Ruxolitinib

Carney Complex

PRKAR1A

PRKACA

TreatmentsResearchersKnowledge Graph

Leading Researchers

Professionals who have taken lead in researching deeper into this disease.

SC

Dr. Sarah Chen

Baylor Scott & White

NeurologyGene Therapy

PublicationsContact

AC

Alan Chen, PhD

NIH

NeurologyGene Therapy

PublicationsContact

RB

Rolf Brian

Rare Hopes

NeurologyGene Therapy

Contact

Why is this topic relevant to this community?

Chicago coming together to make Rare Hopes happen... bigger than any one company or individual.

Networks are key to this kind of innovation (what we can do together).

Communities like this are critical for networks to form.

What happens if we reduce not just silos in our data, but also in our networks?

Sam
Smith

Cameron
Silver

Gilad
Shanan

Jason
Duff

Maria
Daskalakis

Alek
Shnayder

Brianna
Workman

Hana
Worku

Kevin
Schreck

Emily
Xue

Grace
Rowan

Jay
Flood

Mike
Jansen

Riley
Collins

Ben
Lopata

Claudia
Sohn

Ivan
Parra

Lauren
Ebels

Neil
Bertz

Tessa
Wilhelm

Eero
Pikat

Darin
Langone

Jen
Proos

Danielle
Smith

Phil
Borel

Jared
Currie

Pedro
Lopez

Kajal
Jain

KC
Laney



Follow
Rare Hopes NFP



Sharing hope for those with rare and
neglected diseases.



Support
Rare Hopes NFP

zelle

Grateful for support from all of our partners

CLOUDERA



Rare Hopes NFP is a registered 501(c)(3) organization. Donations are tax-deductible to the fullest extent permitted by law. EIN: 93-3126918

QUESTIONS?

ASK ME IN THE APP



**PLEASE RATE
MY SESSION**