Unravel Biosciences Presentation Summary
Speakers: Richard Novak and Frederic Vigneault

How patient-driven drug discovery is accelerating a path to treatment for SPATA5 and SPATA5L1 mutations

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The Problem

Families dealing with rare diseases like SPATA5 and SPATA5L1 Disorders often face long confusing diagnostic journeys, few or no treatment options, and little research that directly reflects their individual child's biology.

Unravel Biosciences is trying to change this by building treatments *starting with the patient*, not with the disease label.

What Unravel Does (simplified)

They study RNA, not just DNA.

- DNA holds genetic information that tells you what might happen
- RNA shows what's actually happening at that moment in the body and changes day to day with things like illness, stress, diet, medication, sleep

Unravel's approach of looking at DNA and RNA gives a more accurate picture of **what's going wrong in the cells right now**.

"Google Maps for Biology" Approach

Imagine the body as a huge biological road map. A disease causes traffic jams or roadblocks. Unravel's software ("BioNAV") tries to:

- Detect where the roadblocks are
- Predict which drugs could clear the traffic
- Test those drugs in model organisms
- Then design new drugs if needed

Unravel Partners Directly with Patients

Using at-home nasal swabs, they collected:

- RNA data from **19 SPATA patients**
- RNA data from **18 healthy family members**

This creates a scientific “datamine” that allows them to compare patterns.

Key Findings (so far) in the SPATA Study

1. There are two subgroups of SPATA patients.
    a. One large group
    b. One smaller group

These groups do **not** differ by their SPATA5/SPATA5L1 gene expression. Instead, they differ in:

- **mitochondrial metabolism** (energy production)
- **fatty acid metabolism**
- **immune system / inflammation pathways**, especially the **IL-17 pathway**

This suggests SPATA has **distinct biological subtypes**, which may explain why kids have different severities.

What does this mean?

Future treatments may work better if tailored to the patient’s subgroup. SO, we must figure out what the true differentiating factor is and how to determine what subgroup each child is in before treating.

SPATA Tadpole Models

Why Tadpoles?

- They share many genes with humans
- You can test drugs on them quickly
- They show behaviors similar to neurological symptoms

Tadpoles were genetically engineered to mimic SPATA5 and SPATA5L1 Disorders. The tadpoles showed:

- Developmental delay, Smaller brains, Lower survival, Seizures, Balance issues, Abnormal swimming

These match symptoms seen in children with SPATA-related disorders.

****Please do not be alarmed by "lower survival." Please keep in mind that, while tadpoles are good models of humans, they are not humans. These tadpoles are also what we call "knockout" models meaning they are completely missing one copy of the gene. Our children do not have total copies missing, so some of the symptoms shown in the tadpoles are exaggerated.*

Drug Testing Results (Early But Promising)

High-ranked predicted drugs (from the RNA analysis)

- improved tadpole survival and behavior

Low-ranked drugs

- made symptoms worse

This gives early confirmation that their prediction system (BioNAV) is working properly.

What's Next?

Unravel is now:

- Narrowing down the best drug candidates for each SPATA subgroup
- Testing them in the tadpole models
- Preparing to move forward toward potential clinical use

Long-term plan:

- Validate the best drug candidates in tadpoles
- Move the safest, strongest ones into **patient testing**
- Use subgroup biomarkers to match patients to the right treatment

Why This Matters

For the first time, SPATA5 and SPATA5L1 have:

- A biological explanation for different severities
- Potential treatment targets identified
- Live disease models
- Early drug candidates showing benefit

This is a major step toward **real, personalized treatments** for SPATA disorders.