Website address:
https://www.gesundheitsindustrie-bw.de/en/article/press-release/after-embl-umlautbio-and-its-potential-role-drug-development

After EMBL: Umlaut.bio and its potential role in drug development

Alumnus Bastian Linder discusses the origin of this start-up and how a tRNA mechanism is helping scientists understand the importance and use of various RNA modifications as they pertain to disease.

With just two dots above a letter, the German umlaut can instantly change a word's pronunciation, its quantity (singular to plural), or even its meaning. Now, an EMBL start-up, Umlaut.bio, has provided an outlet for alumnus Bastian Linder and other scientists to address the modifications that change the 'letters' of transfer RNA molecules.

Just like DNA, RNA is built of nucleotides, which are considered the 'letters' of the genetic code. At the heart of Umlaut.bio is a mechanism its scientists discovered, by which chemically modified versions of nucleotides, such as m6A and mcm5s2U, exert their function. As the biotech company founders chose a name, it reflected on how these modified nucleotides can likewise be considered the umlauts of the genetic alphabet.

After a paper published this year in Cell about the science at the core of Umlaut.bio, we caught up with Linder, who serves as the company's chief scientific officer, to find out more about this start-up, its focus on transfer RNA (tRNA), and the contribution it hopes to make in how we treat disease in the future.

Tell me about Umlaut.bio.

The idea for Umlaut.bio was basically born at EMBL in Lars Steinmetz's lab. At Umlaut.bio, we create therapeutic molecules that address this novel, widespread biological mechanism that we discovered. Whenever cells switch from a normal state to becoming a cancer cell or an activated immune cell, for example, this mechanism plays a major role. We hope to prevent this transition or reverse this transition by inhibiting chemical modifications that occur in tRNA. There are actually a lot of disease areas where this might be helpful.

Where did the idea begin?

It first started with related discoveries in messenger RNA (mRNA). Modifications there affected gene regulation. Scientists had observed before how the molecules that decode and modify mRNA were involved in a lot of biological processes. Our mechanism, for the first time, offered a good explanation of how these things regulate gene expression and cancer from the tRNA side.

When and why did you first get interested in RNA and, more specifically, mRNA and tRNA?

During my diploma studies, I was planning to do neuroscience research, and a lot of neurodegenerative diseases originate from errors in RNA metabolic factors. In particular, I was drawn to localised translation that happens only at the synapse if it's activated. Somehow, I got caught up in the molecular machines that underlie this form of mRNA-centred gene regulation. So, during my diploma thesis and later in my PhD, I worked on splicing factors, proteins that are critical for the generation of mature mRNAs.

Since the beginning of my PhD thesis, I was also searching for novel RNA regulatory mechanisms. Samie Jaffrey's lab at Weill Cornell Medical College, USA, was among the first to show that m6A, a common chemical modification on mRNA is not static, but dynamically regulated. The idea was that RNA methylation might regulate gene expression in much the same way that DNA methylation does, and so that was where I decided to do my postdoc.

What was the focus of this work?

At the Jaffrey Lab, I developed a method to map m6A modifications with single-nucleotide precision. Before that, people only

roughly knew where these things were, but not the precise nucleotides modified on the mRNA. The thinking in the field was that once we established this method, it would tell us what exactly the modification was doing.

In 2012, researchers had started mapping nucleotides, but not down to single-nucleotide levels. However, they could identify specific mRNAs and specific regions of those mRNAs. The distribution didn't look random, so we began to believe it was connected to a function. And then another paper showed cellular enzymatic activity that could reverse m6A modifications. This was the start of 'epitranscriptomics' – the study of chemical modifications on RNA and their regulatory roles. This was exactly what I wanted to do, and I continue to do now.

How did you make the transition from studying mRNAs to tRNAs?

That happened in Lars Steinmetz's lab. Transfer RNA's job is basically to carry the right amino acid to the ribosome while the cell builds a protein, matching the mRNA's code to the protein's building blocks. The Steinmetz group was using yeast cells, so the idea was that we'd try to flip m6A on and off in yeast cells to see what would happen.

Unfortunately, the yeast strains used in the m6A field simply didn't work, but that led us to analyse already available human data. We switched from yeast cells to HEK cells (Human Embryonic Kidney cells), so then we were also able to study the implications for disease. We looked at the signalling pathways under this system's control, and this is how a cancer connection arose.

You had a paper published in Cell this summer. Is it an important one?

I'd say it's the foundation of our scientific hypothesis. It pulls together the different parts of the puzzle we've gathered along the way.

I met Sebastian Leidel, an expert in tRNA modifications and a group leader at University of Bern, Switzerland, who became a co-corresponding author. When he learned I was working with human cells, he offered to collaborate with ribosome profiling data from cells lacking a tRNA modification. I could then provide the map of where m6A is located in those cells. We could compare a series of mRNA positions that have m6A with those that don't. By reviewing the two datasets together, we could see where a specific modification on the tRNA side functionally interacted with the mRNA modification. And that was the starting point.

While difficult to prove mechanistically, when we finally saw this connection, we realised it was both an interesting and novel way to regulate genes, which could potentially translate into novel therapeutics.

These days, people talk a lot about epitranscriptomics, but they often just mean m6A in mRNA-modified nucleotides. Our study provided an opportunity to more deeply understand tRNA modifications, too. The tRNAs are the most modified RNAs in the cell. And while they'd been studied in some measure for probably half a century, we could now probe them in ways not possible before. We showed that they were part of the epitranscriptome, and it is a cross-functional system. This is why our paper received a bit of attention.

What do you enjoy most about this work?

Solving puzzles definitely is a big part of what makes this interesting. But I really enjoy being here at Umlaut.bio. We're at the forefront of this field. There are still so many unknowns, and we're pushing the science behind it. I am always amused when investors at a board meeting encourage us to study RNA decay even as we're in the business to develop drugs. It's refreshing to see that this basic research is important and needs to be done.

How did the idea of a start-up arise?

The idea was born from the discovery of this gene regulatory mechanism that seemed so fundamental, but also useful for different disease indications. Scientists had already been developing drugs that addressed the mRNA side of the pathway. Researchers had been looking at the consequences of perturbing the m6A system for a specific phenotype related to heart cells, for example, or neurodegeneration or cancer.

By now, hundreds of papers have described those m6A impacts, but the mechanistic basis of this involvement was often still quite hypothetical in many cases, and most importantly, they were only looking at one half of the m6A mechanism. They didn't understand the tRNA portion of this. There was an entrepreneurial opportunity here. Samie had founded a company that targeted m6A, and Lars also had this entrepreneurial mindset. So, together , with support from EMBLEM – the technology transfer partner and commercial arm of EMBL – , we applied for and received financing via the EMBL Technology Development Fund.

What's your day-to-day work like now?

I co-founded Umlaut.bio with Karsten Fischer, who is essentially the business guy based in Switzerland at our Swiss subsidiary. I'm the Chief Scientific Officer and the Managing Director here in Heidelberg. As a Biolabs incubator, we get a lot of help with things like biological safety and lab organisation. However, not everything is taken care of by someone else, so I have organisational and managerial responsibilities. But I still enjoy analysing data. Without that, we would not have uncovered the mechanism that has helped us build Umlaut.bio, and it now allows us to navigate this unknown area of biology.

What are your expectations for Umlaut.bio?

It's been a challenging time for biotech start-ups. A lot of investors are more interested in companies with more near-term clinical applications; they're concerned about a timely return on investment. I feel like Umlaut.bio will survive this 'biotech winter', and I'm optimistic for the long-term. More and more people are realising that these tRNA modifications offer very interesting opportunities for drug development, and we are at the forefront of this field.

You sound pretty busy. What do you do in your free time, when/if you have it?

Easy question. I spend time with my family – travelling, hiking, and just being able to do things together.

Publication:
tRNA modifications tune m6A-dependent mRNA decay , Linder B., et al., Cell 10 July 2025
DOI: 10.1016/j.cell.2025.04.013

Press release

05-Sept-2025
Source: European Molecular Biology Lab (EMBL)

Further information

- European Molecular Biology Laboratory