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Turning transient structures into drug targets

Start-up Sibylla Biotech has developed a drug-discovery platform to look for protein folding intermediates to target therapeutically.

Elie Dolgin

Lidia Pieri is chief executive of Sibylla Biotech, which looks for intermediate structures

during protein folding to target therapeutically. Credit: Studio Bravi Fotografia/Verona

Sibylla Biotech is a spin-off from the University of Trento, Italy; the National Institute for Nuclear Physics, Rome; and the University of Perugia, Italy. The company is one of the final eight for The Spinoff Prize 2021.

Last year, as northern Italy became a global epicentre for the COVID-19 pandemic, scientists at Sibylla Biotech jumped into action. From their base in Trento — not far from the hardest-hit region, where hospitals were overrun with severely ill people and physicians had few effective treatments — the researchers put all their effort into combating the coronavirus SARS-CoV-2.

They focused on one target in particular: a key receptor protein through which the virus enters human cells. But instead of looking for drugs that block the protein's final form, they searched for folding intermediates — transient structures along the protein-maturation pathway that might be more amenable to inhibition with existing therapeutics.

The approach hinges on a proprietary drug-discovery platform developed by two of Sibylla's founders, biochemist Emiliano Biasini and theoretical physicist Pietro Faccioli, both at the University of Trento.

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Because folding intermediates exist for only a fraction of a second, they can be hard to study in the laboratory. But through advanced algorithms and computational simulations, Biasini and Faccioli devised a way to accurately model the folding trajectory of proteins and, in so doing, to find short-lived shapes that bind to drugs with high affinity.

The technique has the power to turn proteins that researchers thought couldn't be pharmacologically targeted into targets. Although these proteins, when fully folded, are not easily bound by drugs, their intermediate forms might not be so impregnable.

The method requires a lot of computational power, which could slow down a new drug-discovery programme. But in March 2020, with Italy in lockdown and most scientific research on hold, the country's National Institute for Nuclear Physics (INFN) — better known for studies of subatomic particles than for protein dynamics — offered its high-performance-computing facilities to Sibylla.

The researchers were used to working with a smaller computer cluster, one that is to drug discovery what a budget-friendly family car is to motor transport — slow and steady. With the INFN machines, Biasini says, "we basically got to drive a Ferrari for two weeks".

In short order, the company discovered a new structural target for taking on COVID-19. Molecular simulations revealed a transitory form of the receptor protein that could be blocked with several drugs previously developed to treat other conditions, including schizophrenia and malaria.

On a good track

In cell culture, an antimalarial agent called artefenomel proved to be especially potent against SARS-CoV-2, a finding that Sibylla's scientists immediately made public in the hope that another group might take the compound into human trials.

None have as yet. But the company's paper, published as a preprint[1], served another purpose. It demonstrated to the research community that Sibylla was not

a one-trick pony.

Biasini and Faccioli have also shown[2] that their drug-discovery technique — termed pharmacological protein inactivation by folding intermediate targeting, or PPI-FIT — can find therapeutics for prion diseases, a group of fatal neurodegenerative disorders caused by structurally abnormal proteins (see 'Targeting a folding intermediate').

Targeting a folding intermediate

With the COVID-19 project, the team "demonstrated that this approach could also work with other proteins", says Roberto Chiesa, a cell biologist at the Mario Negri Institute for Pharmacological Research in Milan, Italy, who is not affiliated with Sibylla (although Biasini trained in his lab).

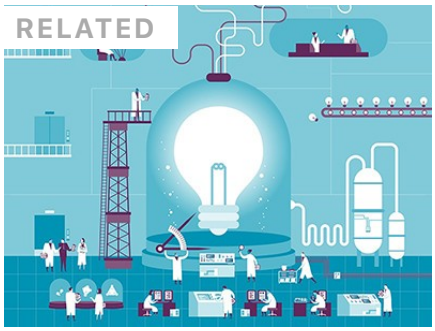
The company has used its proprietary methods to identify drug candidates directed against the protein KRAS, one of the most challenging targets in oncology. The company also has its sights set on cyclin D1, a protein that drives the progression of many tumour types.

And, in May, Sibylla announced a drug-discovery collaboration with the Japanese firm Takeda Pharmaceutical Company. "I think that they are on a good track," says Chiesa.

Meeting of minds

Sibylla's origins trace back to a 2016 thesis defence. Giovanni Spagnolli, then a master's student at the University of Trento, had taken algorithms, devised in Faccioli's lab for simulating protein-folding pathways and applied them to his study of how various modifications along the process might affect protein

function[3].



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Spagnolli needed an internal examiner with expertise in protein biology to critically evaluate the work. Biasini, who had joined the University of Trento a year earlier, agreed to serve as a referee.

"I was blown away by the master's thesis presentation," Biasini recalls. Although much of the mathematics went over his head — "the equations were like hieroglyphics to me," he concedes — Biasini immediately saw the potential for applying the theoretical framework developed by Faccioli's group to his own research interest of prion diseases.

The next day, Biasini knocked on Faccioli's office door, expecting a quick chat. It turned into a long conversation that has since evolved into an even longer collaboration, one that continues to this day. And with Spagnolli as their PhD student, the scientists soon came up with PPI-FIT. The idea was to modulate protein expression by targeting folding intermediates with small-molecule drugs.

If Faccioli's computational methods were correct, they reasoned, the scientists should be able to find compounds that bind and stabilize these transient protein conformations along the folding pathway. Then, part of the cell's quality-control machinery — either the lysosome or proteasome, which are involved in the breakdown of misfolded proteins — would recognize the stabilized structure as aberrant, and send it off for degradation, thereby lowering the expression of the undesired, target protein.

If the strategy proved successful, it would not just validate the model — it would represent a brand-new drug-discovery model. "At that point," says Biasini, "it was

eureka!”

Into the fold

The concept worked. The PPI-FIT simulations identified four compounds predicted to tightly bind a folding intermediate of the human prion protein. Lab experiments confirmed that the most promising molecule selectively decreased prion levels — by as much as 80%.

The results “show pretty convincingly that the drug really does bind a folding intermediate”, says Amir Bitran, a biophysics PhD student at Harvard University in Cambridge, Massachusetts, who is also developing protein-folding models to inform drug development. “I find this a compelling proof of concept, which has the potential to lead to real treatments.”

Biasini is now following up on the prion-related findings in his academic lab. He and Faccioli — together with Maria Letizia Barreca, a medicinal chemist at the University of Perugia, Italy, and Graziano Lolli, a structural biologist at the University of Trento — formed Sibylla to take advantage of PPI-FIT technology for drug discovery for other diseases. Spagnolli, another co-founder, leads the research efforts at the company. Lidia Pieri, an astroparticle physicist by training (and Faccioli’s wife) is chief executive.

“We challenged the complexity of drug discovery with the cross-disciplinary knowledge of our academic founders,” Pieri says. “And we started a mind-blowing path of innovation, transferring that knowledge into a company.”

Now, for Sibylla — named after the oracle in Greek legend whose prophecies often came true — onlookers are predicting big things to come for the company.

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UPDATES & CORRECTIONS

Correction 08 July 2021: An earlier version of this story misstated what the company is pursuing and failed to mention one of the institutes the company spun off from.

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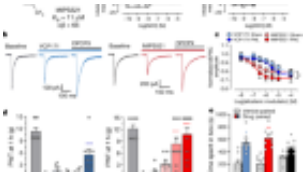

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