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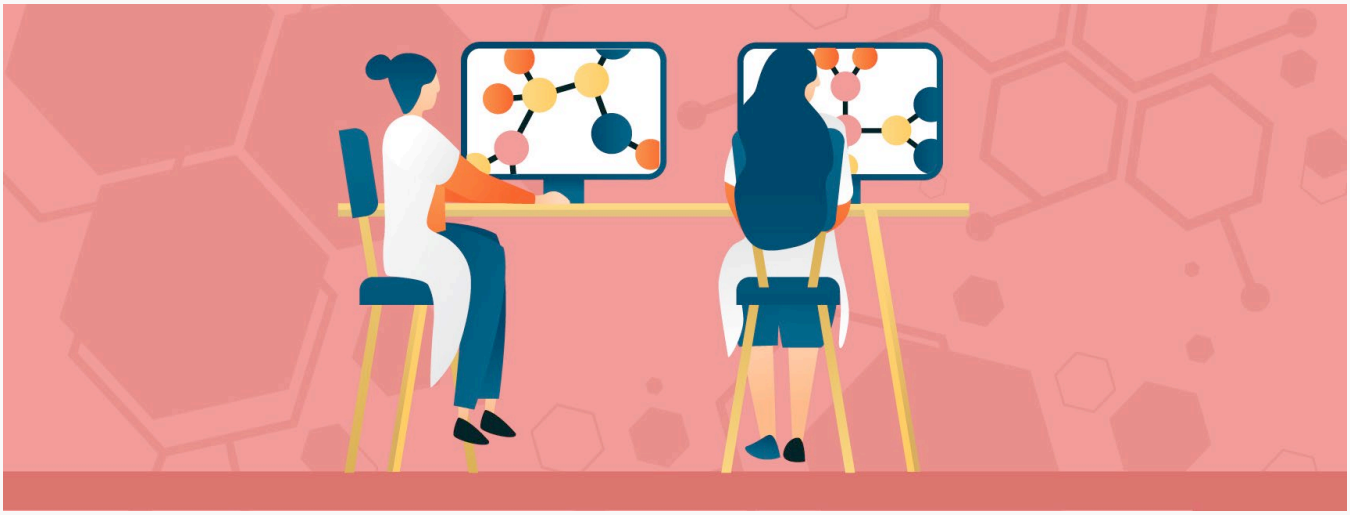

BIOCENTURY & GETTY IMAGES

EMERGING COMPANY PROFILE

Neoleukin emerges with a de novo approach to improving biologics

BY ALLISON JOHNSON, SENIOR WRITER

With a platform to design proteins from scratch, Neoleukin is making a new class of biologics that resemble their endogenous protein counterparts in structure, but not in sequence. The strategy gives the company a clean slate to improve function and reduce toxicity without the constraints built in by nature.

A spinout of David Baker's lab at University of Washington's Institute for Protein Design, the company debuted in January with a Nature paper describing a *de novo* IL-2 protein that resembled the endogenous cytokine in 3-D structure, but had a different amino acid sequence and better preclinical efficacy and toxicity in mouse models of melanoma or colon cancer.

Baker is director of University of Washington's Institute for Protein Design and professor of biochemistry and a Howard Hughes Medical Institute investigator.

The company's suite of computational programs enables it to begin with a defined target protein shape that drives the desired function, generate natural amino acid sequences that can fill that shape, then optimize the protein's function.

The concept behind the platform is that if a structure can be replicated *de novo*, "you can get the same function that the natural protein has but with a different sequence," Neoleukin Co-founder, VP and Head of Research Daniel-Adriano Silva told BioCentury.

Neoleukin's IL-2 shares less than 15% of its sequence with endogenous IL-2.

A protein's final 3-D conformation is the consequence of evolutionary pressure that required it to go through various intermediate conformations that need to be thermodynamically stable. But by going directly to the final conformation, Neoleukin does not need to consider those transition states, and can optimize the sequence to produce the protein shape it wants.

Gutting the original amino acid sequence allows Neoleukin to add properties such as increased stability that could make

a compound a better biologic than the natural protein, and dial out properties such as unwanted protein-protein interactions.

"You can modify it to tune affinity, to tune half-life, to turn it from an agonist to an antagonist, to make it conditionally active. There's a lot of things you can do with *de novo* proteins," said CEO Jonathan Drachman. Drachman served as senior advisor for innovation at Seattle Genetics Inc., where he was CMO and EVP of R&D until last year.

Neoleukin is applying its platform to other undisclosed cytokines and proteins involved in cancer and autoimmune disease.

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JONATHAN DRACHMAN, NEOLEUKIN

Selectivity, and then some

Neoleukin sees the key differentiator of its IL-2 as the ability to selectively stimulate the intermediate affinity IL-2 receptor while avoiding the high affinity receptor.

The immunostimulatory benefits of IL-2 come from its ability to promote proliferation and activation of CD8+ T cells and NK cells via the intermediate affinity receptor, which comprises IL2Rβ and IL2Rγ.

The severe toxicities that have plagued the only approved IL-2 therapy, Proleukin aldesleukin from Novartis AG, are thought to be driven by the high affinity IL-2R, which contains CD25 (also referred to as IL2Rα) as well as IL2Rβ and IL2Rγ.

Neoleukin is one of several companies aiming to prevent the CD25-IL-2 interaction: at least nine IL-2 therapies in the clinic are engineered to avoid binding CD25 (see "Clever Pegylation Payoff").

But while most other strategies mask the CD25 binding domain, Neoleukin removed the structure responsible for CD25 interaction.

That makes Neoleukin the only company with an IL-2 that can't bind to CD25 at all, according to Drachman.

When Neoleukin designed its IL-2 protein *de novo*, it only included the structures necessary to bind IL2Rβ and IL2Rγ.

Drachman described Neoleukin's IL-2 as "a completely new molecule that has all the good parts of IL-2 without the part that is the greatest limitation: the binding to the alpha chain [CD25]."

NEOLEUKIN THERAPEUTICS INC.SEATTLE, WASH.
Technology: Platform to create optimized biologics by *de novo* protein design

Disease focus: Cancer, inflammation

Clinical status: Preclinical

Founded: 2018 by Daniel Adriano-Silva, Umut Ulge, Carl Walkey, Alfredo Quijano Rubio, Jonathan Drachman, and David Baker

University collaborators: None

Corporate partners: None

Number of employees: 8

Funds raised: Undisclosed

Investors: Undisclosed

CEO: Jonathan Drachman

Patents: None issued

The molecule has other features that could help it against competitors, including the ability to activate IL-15 signaling in NK cells and higher stability, both of which were possible to engineer because Neoleukin wasn't limited to the properties inherent to the original sequence of IL-2.

Because IL-2 and IL-15 both signal via IL2Rβ, IL-2 therapies can cause some level of IL-15 pathway activation.

Drachman said Neoleukin is the only company he's aware of whose IL-2 therapy elicits full IL-15 pathway activation, and consequently, full activation of an additional arm of the immune system via NK cells.

Neoleukin's IL-2 is also uniquely stable outside of the body, according to co-founder Carl Walkey, a senior fellow at the Institute for Protein Design.

"Based on our experience with it as a research compound, we can keep it on the bench at room temperature and as long as it's free of bacterial contamination, it can last for weeks without losing potency," Walkey said. It can also be heated for an hour without losing any activity.

"That opens up a whole new set of interesting applications and ways of delivering this to patients and eliminating cold chain transport. It's unprecedented for a biologic," said Walkey.

VP of Translational Medicine Umut Ulge added that there will be other ways to leverage the advantages of *de novo* proteins. "The stability of the proteins may allow you new types of formulations and new types of bioavailabilities."

Avoiding immunogenicity

One concern with proteins created *de novo* or with synthetic elements is that the body's immune system may see them as foreign and attack the molecule and anything else that looks like it.

Ulge said the company can't know with certainty whether its IL-2 will be immunogenic until it's tested in patients, but Neoleukin thinks the chances of eliciting an immune reaction are low.

"One thing the molecule has going for it is that it's so compact and so stable and hydrophilic, it's just not as likely as unstable or hydrophobic proteins to be taken up non-specifically and presented by the immune system," said Drachman.

Even if Neoleukin's IL-2 caused an immune reaction, Drachman said "it's extraordinarily unlikely to cross react with anything else in your body, so it's unlikely to cause an autoimmune effect or neutralize your own IL-2."

He added Neoleukin has ways to cope with immunogenicity if it did occur, including the tools to predict which epitopes elicit the reaction and removing them from the protein's sequence.

Neoleukin has raised undisclosed seed funding from undisclosed investors.

Associate Editor Karen Tkach Tuzman contributed to this report.

COMPANIES AND INSTITUTIONS MENTIONED

Neoleukin Therapeutics Inc., Seattle, Wash.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Seattle Genetics Inc. (NASDAQ:SGEN), Bothell, Wash.
University of Washington, Seattle, Wash.

TARGETS

CD25 (IL-2α)- Interleukin-2 receptor alpha chain
IL-2 - Interleukin-2
IL2Rβ (CD122) - Interleukin-2 receptor beta chain
IL2Rγ (CD132) - Interleukin-2 receptor gamma chain

BIOCENTURY INC.

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