FreeNovation – A funding program of the Novartis Research Foundation

FreeNovation 2023: Can your project idea change biomedical research?

- RNA: Mechanism, drug, target
- Beyond AlphaFold: Targeting dynamic states
- 3D and 4D genome

Submit your application by 15th April 2023!

Exploring New Avenues in Research Funding

Many scientific breakthroughs have occurred not because success was predictable, but thanks to the pioneering spirit of people who gave free rein to their creativity. But there is little room for free creativity and bold, untried ideas these days. This is why the Novartis Research Foundation *(Novartis Forschungsstiftung)* promotes offbeat project proposals with its FreeNovation program. It calls on researchers in Switzerland to submit proposals that are hard to fund by conventional programs.

This kind of research funding by a Swiss foundation is unique in the field of life sciences in Switzerland. With this program, the Novartis Research Foundation wants to encourage unconventional thinking and further enhance the attractiveness of Switzerland as a research location.

An opportunity for people and ideas

Researchers with a doctorate or equivalent that are employed at a reputable healthcare or healthcare-related organization, university, university hospital, or university of applied sciences are eligible to apply. The projects will be selected by a top-class review panel under the leadership of Prof. em. Gerd Folkers, ETH Zürich, Chairman of the Board of the Novartis Research Foundation.

To ensure that both unusual ideas as well as younger scientists without a research track-record have a place in this funding program, the selection process is anonymized: What counts is the originality of the research approach and its potential to achieve something new. Ideas that involve interdisciplinary research are encouraged. Results from preliminary studies are not a prerequisite. Scientific risk-taking is encouraged.

The results of the funded projects shall be published and made available to the public without patent protection. FreeNovation is all about exploring new avenues, venturing into new dimensions, and further strengthening Switzerland's research landscape.

For the 2023 call for proposals, the Novartis Research Foundation is making available up to a total of CHF 2.7 million for a maximum of 15 projects. Each project can be funded with up to CHF 180,000. This will allow the researchers to pursue their objectives over a period of 18 months.

Guidelines for Applicants and the link to submit proposal are available on www.freenovation.ch

RNA: Mechanism, drug, target

The resounding success of RNA as a corona vaccine raised the attention to this class of molecules to the highest attention. However, this is only the tip of the iceberg, the potential for biomedicine is even broader.

RNA as a mechanism: There is still a lot about RNA that is not understood: What is the function of non-coding RNAs? Why does nature use miRNAs and not siRNAs? Why is e.g., miR-122 so important in the liver but not in other cell types? What role do mRNA modifications play in translation? How are mRNAs transported, e.g., in motor neurons, where the destination can be meters away from the cell nucleus? A comprehensive analysis or a systemic perspective could open up new insights into the mechanisms of a wide range of diseases, from neurodegeneration to metabolic disorders or cancer.

RNA as therapeutics: How could the duration of action be extended so that, e.g., only one treatment per year is needed? How could the effect be enhanced so that a much lower dose is sufficient? How could RNA be addressed to target specific organs?

RNA as a target: How could the biological function of cellular RNA be modulated? Are there completely different approaches than RNA editing with Cas13 systems? Small molecules that also have good medicinal chemistry properties have been difficult to find, but do such compounds exist anyway?

Are you inspired to submit a proposal? - We are very much looking forward to it!

Beyond AlphaFold: Targeting dynamic states

AlphaFold has revolutionized the prediction of three-dimensional structures of proteins. It is designed to model single structures and does this with remarkable accuracy and reliability. All problems solved? Of course not. Further developments to include protein complexes or to model the consequences of mutations are already underway. And more challenges are still out there: Many proteins bind co-factors or are influenced by their native environment, be it intra- or extracellular or a membrane. Proteins are flexible and adopt multiple conformations. Many are even intrinsically disordered yet adopt transient residual structures. How can we model such dynamic states? How can transient conformations be trapped? How can we get better predictive models of protein-protein or protein-ligand interfaces that have not co-evolved?

In a biomedical context, is it possible to train models of a drug binding to the many proteins it encounters in a cell and derive biological, including toxic, effects? On a fundamental level, are there novel ways to determine the entropy of water binding, a rather elusive problem? Or let’s revert the question: Is it possible to develop algorithms that define the data that would be needed for such predictions?

Only a couple of years ago, the success of AlphaFold was a dream. What are your ideas to target dynamic states of proteins, predict drug effect and toxicity based on target and off-target binding, or to predict the database content that would make these predictions possible?

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3D and 4D Genome

The linear DNA sequence as well as chemical modifications of the DNA and associated histones are insufficient to explain gene regulation, and good predictive models for gene regulation are currently lacking. Furthermore, how the spatial genome architecture (3D) and temporal genome changes (4D) contribute is unclear. Detailed mechanistic insights, and understanding of the structure, dynamics and regulation of the genome in normal as well as the pathologies are timely and exciting open questions in cell biology!

How are 3D folding and dynamics related to gene expression? What happens at the level of large topological domains and how is this mirrored locally on the level of the chromatin? What role do condensates play in this process? How do transcriptional activators or suppressors work in atomic detail? How do dynamic 3D contacts affect transcriptional output? What is the order of events leading to gene activation or repression following transcription factor binding? In all these complex binding events, what is cause, what is consequence? And will a deeper mechanistic understanding of these processes help decipher gene regulation?

On the multicellular level, the 3D genome architecture differs from cell to cell. To what extent is this controlled, regulated, or stochastic? How does cell-to-cell variability affect the development and signalling between of cells? Are individual differences in 3D/4D genome organisation between individuals useful to explain the emergence and course of human diseases? How is the aging process reflected in the 4D genome?

Direct structural determination using cryo-electron tomography in the cell nucleus of mammals remain technically challenging. What are new ideas how to significantly improve the visualization of the dynamic structure of chromatin? How can molecular “omics” data and cellular images be integrated, ideally at the single-cell level?

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