Challenge Questions
NIBR Global Scholars Program 2022

The Novartis Institutes for BioMedical Research (NIBR) is seeking to advance science through the NIBR Global Scholars Program (NGSP). For NGSP, NIBR is requesting proposals exploring breakthrough science that is a strategic fit with the NIBR portfolio. The NIBR Challenge Questions are designed to guide you in aligning your proposal with the NIBR portfolio.

Out of scope

Please note that proposals involving the following are out of scope for NGSP:

- generation of new animal or cellular models, except when done within the context of a larger project
- clinical testing of drugs or products in human subjects or any patient intervention
- prospective collection of human samples
- use of human data without informed consent from human subjects for use of their samples in the NGSP research proposal
- use of any identifiable patient data or clinical data
- provision of access to human tissue, except when done within the context of a larger project

NOVARTIS | Reimagining Medicine

NGSP areas and Challenge Questions

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Biologics, Gene Therapy

1.1 Next generation delivery of gene therapies

Challenge question:
Limitations and liabilities of current gene therapies include safety concerns, decreased efficacy upon repeated administration, lack of targeting specificity to most tissues or cells of interest, and design constraints that preclude the use of complex and sophisticated constructs. What novel approaches and methods could address these safety, technical and biological liabilities?

Potential solutions:

- New methodologies or mechanisms that address the following liabilities and limitations in *in vivo* pre-clinical models:
  - systemic safety and immunogenicity
  - delivery of larger and more complex constructs
  - tissue or cell specific targeting
- Preference for technologies that are molecularly understood and/or amenable to platform approaches
- Characterization of novel non-integrating viral systems

Out of scope:

- Delivery technologies without specific targeting ability
- Minor adaptations of broadly-used technologies (i.e., LNPs, AAV9, LVs)
- Methodologies or editing technologies that require licensing from a third party

1.2 Novel genome engineering effectors

Challenge questions:
How can we advance the:

- identification, characterization and optimization of novel genome engineering effectors that permit the precise disruption, correction, or insertion of nucleic acids?
- development of novel cell and gene therapies by addressing the underlying genetic cause of human disease?

Potential solutions:

- Precise and efficient modification (including but not limited to insertion, deletion, correction) of nucleic acids
- Systems with advantages over current genome engineering technologies (smaller size, increased specificity, etc.)
- Lack of associated effector-mediated toxicity
- Open collaborative scientific exchange that benefits from the expertise of the respective teams

Out of scope:
Co-development of therapeutic candidates with academic partner

1.3 Regulatable, tunable gene therapies

Challenge question:
Gene therapy has been applied successfully in treatment of several monogenetic diseases in rare disease spaces. It can potentially be developed to deliver intracellular, extracellular, as well as antibody biologics for a broad range of diseases. Can we develop regulatable technologies to design safe gene therapies that have predictable and tunable transgene expression?

Potential solutions:

- Advances in controlling gene expression in gene therapy vectors with the potential to translate into humans, including broad patient populations
- Specifically for ophthalmology, including Glaucoma and AMD: approaches that overcome the safety concerns associated with long lasting, potentially permanent, one-time treatment natures of non-retrievable gene therapy for developing treatment of non-genetic diseases
- Low molecular weight compounds to control transgenes at the transcriptional, translational or post-translational step

Out of scope:
Work with LMI070

1.4 Specific intracellular delivery of biologics

Challenge question:
Biologics have increasingly become an important therapeutic modality in the treatment of cancer, autoimmunity diseases, and other human diseases. These biologics interact mainly with targets in the extracellular space, e.g., cell-surface structures or soluble factors in serum etc. How can biologics be delivered intracellularly into defined cell compartments like cytosol or nucleus (ideally, in a cell-specific way), thereby opening a whole new target space with functional activity on intracellular targets?

Potential solutions:

- We are open to all ways of intracellular delivery technologies by, e.g., adding structures binding to receptors which assist in intracellular delivery, fusions to proteins or small molecules enhancing cell permeability or via engineered AAV / AV etc.
- Key is that the biologic is finally ending up in the compartment of interest, e.g., cytoplasm or nucleolus and is still functionally active to interact with the target in an agonistic or antagonistic mode of action.

Out of scope:
Approaches using poly-cationic peptides are less preferred due to unspecific, broad cell targeting

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Complex Models

2.1 Complex cellular disease models

Challenge question:
Understanding human biology requires complex cellular model systems. Can we generate organ or tissue models that represent mechanistic aspects of disease, are scalable and robust to allow for genetic or chemical screening?

Potential solutions:
Innovative ideas and solutions to generate complex model systems for organs/tissues that have not been tractable so far, e.g., requiring microfluidics, adding vascularization and/or immune system components.
Basis for the models can be iPS-derived, primary cell-derived or other *in vitro* models that represent some mature organ-specific functions. Examples: peripheral nerve, kidney, liver, lung, heart, eye.
Novel focused technical solutions allowing image-based cell/organoid sorting as well as innovate ideas to culture and screen these cellular models are encouraged.
Send us your big, bold ideas how we can jointly accelerate drug discovery and bring new innovative medicines to patients.

Out of scope:
Classical 2D cultures of primary or iPS-derived cell models.

2.2 Transformative technologies to increase drug safety

Challenge question:
How to explain side effects manifesting after long safety studies and anticipate adverse immunogenicity events emerging in clinical trials and real world?

Potential solutions:

Compelling algorithms for quantum computers to predict immunogenicity of drugs

- Artificial intelligence algorithms to accurately predict TcR-drug epitope-MHC interactions
- *In silico* systems biology to model on-target and off-target drug interactions and pathway activation

Knowledge on microbiome's role in drug-induced toxicity and metabolism

- *In silico* systems biology to model drug-microbiome interplay, i.e., liver tumors/skin rash

Advanced methodologies to investigate genomics, proteomics and epigenetics in paraffin-embedded specimens

- Modern imaging and *in silico* technologies to interrogate tissue expression and modification of genes and proteins in the context of disease environment (e.g., inflammation, cancer, infections) using formalin fixed, paraffin embedded (FFPE) blocks

Novel organoid to investigate complex cell interactions involving cell trafficking and functional compartmentalization

- Technical solutions to generate organotypic models recapitulating mature organ-specific functions, such as kidney, liver, gut, pancreas, lung, peripheral nerves, eye, etc., under physiologic and inflammatory conditions (i.e., including vascularization and adding immune cells and/or microbiota)
- Capabilities to image and sample metabolites and cell components of working organoids during physiological conditions, inflammatory challenge, and drug exposure

Out of scope:

- Established, currently standard bioinformatic and imaging capabilities
- Studies of individual microbes not exploring their role in drug toxicity / safety of the host
- Spheroids and 2D cell cultures

Disease Mechanisms

3.1 Functionalization and validation of GWAS hits for neurological and neuropsychiatry conditions

Challenge question:
GWAS studies have revealed several potential causal genes in neurological and neuropsychiatric diseases. However, the directionality of the genes and precise impact on biology / pathology of the disease remains unclear for many candidate genes identified.

Potential solutions:
Systematic evaluation of the role of candidate causal genes *in vitro* (in iPSC derived human neuronal cells or microglia and in primary mouse neuronal cells), *in vivo* (in engineered mouse models carrying the relevant human orthologue) and recapitulating appropriate pathologies (neurodegeneration, neuroinflammation) and disease (AD, PD, ALS, MS) background.

Out of scope:
N/a

3.2 Longitudinal trajectories of clonal hematopoiesis of indeterminate potential (CHIP)

Challenge questions:

1. What is the natural history of the rate of progression of CHIP over time in human populations and how does the change relate to health maintenance and the development of disease, such as cardiovascular disorders?
2. Can progression of CHIP be more easily measured in patient and participant samples, including when extracted DNA is not available from stored longitudinal samples?

Potential solutions:

- Determination of the rate of progression of CHIP over time, including by stratification of CHIP mutation type
- Relation of the rate of progression of CHIP to baseline clinical characteristics including risk factors for solid tumor and blood cancers and cardiovascular disease and polygenic risk strata
- Relation of the rate of progression of CHIP to incident disease or disease progression, including cardiovascular disorders
- Identification of an alternate assay to evaluate CHIP progression from stored longitudinal samples (e.g., from cell free DNA) where extracted DNA is not available

Out of scope:

De novo collection of human samples for the purpose of this research

3.3 Mechanisms of disease progression in multiple sclerosis (MS)

Challenge question:
Available drugs for MS only delay disease progression. Currently there are only insufficient therapeutic options for MS patients to halt or even reverse progressive disability.
Which molecular switches drive MS progression and differentiate progressive from relapsing remitting MS?

Potential solutions:
Novel approaches that enable molecular analysis of (autopsy/biopsy) CNS tissue or CSF from MS patients and their interconnection with mechanistic *in vitro*/*in vivo* analyses, with or without genetic/pharmacologic perturbation.
Successful proposals will enable an integrated suite of molecular observations and mechanistic analyses, for discovery of:
(1) novel prognostic biomarkers for progression in MS, (2) novel therapeutic targets to halt or reverse progression, and/or (3) novel preclinical assay systems for drug discovery with translatable value.

Out of scope:
Singular focus on animal models, mere provision of human biosamples, biosamples without clinical annotation

3.4 Mechanisms underlying the spread and progression of ALS

Challenge question:
Spreading of pathology and neurodegeneration between CNS regions is a hallmark of ALS and linked to disease progression. What is the contribution of neuroinflammation and / or other pathways to this process?

Potential solutions:
Novel approaches to selectively dissect the mechanisms contributing to pathological spreading and disease progression in ALS, including complex culture systems (e.g., iPS lines, co-culture, slice culture and/or organoid systems), *in vivo* genetic models and/or animal models with compound treatments, and use of patient pathological material (e.g., aggregates).

Successful proposals will (i) deepen the mechanistic understanding of these pathological processes, (ii) reveal novel therapeutic targets/pathways, (iii) enable new assay systems for unbiased genetic or drug-based screening, and (iv) elaborate identification of disease biomarkers to improve translatability of novel therapeutic targets identified.

Out of scope:
Non-mammalian models

3.5 Novel surface T cell antigen targets and innate immunity activation against cancer

Challenge questions:
How can we identify novel surface T cell antigen targets and their cognate T cell receptors?
How can we activate innate immunity to elicit an integrated immune response against cancer?

Potential solutions:
Novel data mining and experimental approaches to identify novel surface antigens, such as spliced transcripts, post translational modifications etc., and their cognate T cell receptors.
Successful proposals will yield new insights into shared antigens and compliment and enable next generation CART therapy.
Novel approaches, new targets, and biological mechanisms to activate innate immunity, to promote tumor immunogenicity, and to elicit a strong integrated immune response against cancer.
Disease indications focus: Pancreatic cancer, Colorectal cancer, Breast cancer, AML, Glioblastoma multiforme, Ovarian cancer, Melanoma.
Seeking only original, unprecedented ideas and unique experimental approaches.

Out of scope:
Published targets

3.6 Paroxysmal/Persistent atrial fibrillation (AF)

Challenge question:
Can we understand AF better, in an effort to define distinct forms of the disease that could serve as the basis for developing anti-AF drugs for distinct patient populations?

Potential solutions:

1. Are there different, discrete sub-populations of paroxysmal / persistent AF patients, identifiable via biomarkers (ECG, circulating, imaging, other)? Can such biomarkers be tied to pathogenic mechanisms at the tissue level?
2. By what mechanism(s) do pulmonary veins produce arrhythmogenic, ectopic firing?

Out of scope:
Post-operative atrial fibrillation is not of strategic interest

3.7 Precision medicine in inflamed CNS tissue

Challenge question:
Tissue microenvironment in chronically inflamed CNS is poorly described as biopsies are not available. Can molecular endotypes of MS (focus on SPMS, PPMS & compare to RRMS) be discovered and linked to clinical phenotypes, enabling targeted intervention and endotype-specific drug discovery in this population of high unmet medical need?

Potential solutions:
- Successful proposals will propose an integrated approach to CNS inflammation, and promise to yield new molecular and mechanistic insights into the molecular definition of SPMS and PPMS, and a comparison to RRMS. This should fuel target hypotheses.
- Looking for an integrated approach, using scRNAseq interlaced with imaging/histology, and follow-up functional studies.
- *In vitro*/*in vivo* validation assays could be available or co-developed.

Out of scope:
- The proposal should focus on inflammatory diseases of the CNS.
- Inflammation of the PNS or degenerative diseases of the CNS are out of scope.

3.8 Prediction of novel oncology targets

Challenge question:
It seems like we have exhausted the oncology target space in terms of gene alterations, at least in sizeable patient populations. Still, many cancer patients do not have a precision medicine treatment option, leaving them with either poor success rate or tremendous adverse events. How do we identify novel ways to predict a safer next generation of targets in oncology?

Potential solutions:
New data science approaches to arrive at a testable hypothesis for potential targets:

- Differentiation between normal and cancer tissue (e.g., leveraging single cell approaches)
- Differentiation between cellular localization in tumor vs normal cells or tissue (e.g., leveraging multiplex imaging)
- Differentiation between cell states (e.g., leveraging post treatment multi-omics)
- Differentiation between resistant and sensitive patients (e.g., leveraging image-based drug screening from patient biopsies)

Successful proposals will describe new avenues for directed tumor targeting, leveraging advanced analytical methods applied to newly generated or newly available preclinical and clinical data.

Out of scope:
Known and tried approaches, especially gene alterations. Approaches solely focused on widely used preclinical models.

3.9 Treg based immune tolerance induction

Challenge questions:
Regulatory T cells are essential for the maintenance of self tolerance and therapeutic approaches modulating or enhancing their numbers and/or function have the potential to restore tolerance in autoimmune disease (AID) and organ transplantation.
What are the relevant human Treg subsets and functional properties required for the effective and durable tolerance induction? How to identify novel therapeutic targets or strategies able to efficiently modulate endogenous human Tregs?

Potential solutions:

- Novel approaches to characterize subsets and properties of human Tregs required for effective tolerance induction
- Methods to identify therapeutic targets suitable for the modulation of endogenous human Tregs in AID and transplantation
- Identification of PD biomarker reflecting the Treg efficacy and stability *in vivo*
- Use organ transplantation as a model to understand and apply therapies allowing the induction of effective functional tolerance

Successful proposals will yield new insights into the biological processes, immunoregulatory properties of different human Treg subsets and application potential in AID or organ transplantation

Out of scope:
In vitro screens relying on Foxp3 induction or stabilization as a readout. Therapeutic approaches based on *ex vivo* expanded Treg subsets

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Protein & Drug Design

4.1 Leveraging next generation protein and structure based drug design

Challenge question:
New developments in computational methods, including protein structure and binding pockets prediction and AI, have the potential to revolutionize the practice and timelines of drug discovery. How can we push the boundaries of these technologies and test what can be achieved?

Potential solutions:
Key areas of interest include, but are not limited by:

- Cryptic pocket prediction and in-depth analysis of allosteric MoA
- Developing fast and accurate geometric 3D machine-learning methods for protein-protein interaction and protein-ligand interaction prediction. Determination of transient protein conformation
- Methods to understand the kinetics of protein folding, and the influence of small molecules. Applications to diseases where protein aggregation or misfolding is implicated
- Effective and reliable methods for computing the energetics of molecular recognition
- Methods to enable design of proteins for enhanced stability, function
- Can we expand structure prediction beyond proteins – e.g., RNA?
- VR: Tools to facilitate drug design in 3D collaborative immersive environments (virtual & augmented reality)

Out of scope:
Commercial software

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Regenerative Medicine

5.1 Cardiac regeneration

Challenge question:
Identify new biological pathways/mechanisms that promote regeneration of functional and anatomically correct myocardium.

Potential solutions:
New biological mechanisms or molecular targets that induce regeneration of functional myocardium following myocardial infarction or other myocardial insults (infection, toxins, remodelling due to haemodynamic stressors) in preclinical models.

Successful proposals will yield new insight into the biological processes that generate new, functional tissue.

Seeking only original, unprecedented ideas and unique experimental approaches.

Out of scope:
Longstanding literature targets

5.2 Inflammation / Regeneration

Challenge question:
How does inflammation impact joint homeostasis and cartilage regeneration in inflamed joints (OA, CPPD, gout and RA)?

Potential solutions:
New biological mechanisms or molecular targets that induce the following in pre-clinical models:

- Regeneration of cartilage lesions/early OA in inflamed joints
- Regenerate cartilage to overcome crystal driven joint degeneration
- Triggering regeneration by reducing inflammation in inflamed joints
- Protecting joints from cartilage degeneration in PsA, RA

Successful proposals will yield new insight into the biological processes that generate new, functional tissue

Seeking only original, unprecedented ideas and unique experimental approaches

Out of scope:
Published targets

5.3 Regeneration: Restoration of organ function

Challenge question:
Biology underlying restoration of specialized cellular functions following acute or chronic damage is only poorly understood, leading to a lack of tools to efficiently address and support organ regeneration. What novel biological pathways, or new nodes along known pathways, can enable pharmacological approaches to heal and functionally restore tissues *in vivo?*

Potential solutions:

- Original, unprecedented ideas to identify or modulate pathways, molecular targets or mechanisms that (re)generate functional tissue, ideally across multiple different organs (e.g., liver, kidney, lung, heart, muscle, etc.)
- Focus on restoring specialized cellular functionality rather than just cellular proliferation
- Compounds, tools, or molecular approaches to restore or maintain viability and function of target tissues or cells of interest
- Regeneration approaches that recapitulate the tissue specific physiological microenvironment
- Pre-clinical models that decisively improve translatability to humans
- Novel biological insights to restore tissue functionality including but not limited to hepatocyte function in liver cirrhosis; alveolar epithelial cell function in idiopathic pulmonary fibrosis; or nephron function in chronic kidney disease or renal failure

Out of scope:

- Targets or approaches well-described in the literature
- Pathways or targets with known liabilities (i.e., oncogenicity) without a proposal to mitigate said liabilities
- Approaches that only impact cell proliferation without restoring their specialized functionality

Tissue Targeting

6.1 Atherosclerotic cardiovascular disease prevention and reversal

Challenge question:
Macrophages play key roles in atherosclerosis progression and regression. Consequently, the manipulation of macrophage functions with the use of small molecules or biomolecules (e.g., siRNA) has significant therapeutic potential in atherosclerosis. Our challenge for you is to identify a method for targeted delivery of siRNA to macrophages in atherosclerotic plaque.

Potential solutions:
- Novel modality that will enable safe and effective targeting of arterial plaque macrophages
- Potential solutions may include a receptor-mediated endocytosis mechanism (e.g., by targeting a plaque macrophage-specific endocytic receptor), targeting plaque-specific endocytosed material, or another novel approach
- Ideally, method will enable infrequent dosing (e.g., monthly, semi-annual, annual)

Out of scope:
Folate receptor and other well-described macrophage receptors (e.g., scavenger receptors)

6.2 Cardiomyocyte specific drug delivery for heart failure

Challenge question:
Identify new methods for delivery of pharmacological agents, siRNA, gene therapy, etc., specifically to cardiomyocytes *in situ*.

Potential solutions:
New biological mechanisms or molecular targets that result in

- Highly selective targeting to cardiomyocytes, including preference for injured cells over healthy
- Enhanced intracellular delivery to cardiomyocytes
- Appropriate release of the agent from the targeting mechanism into the cardiomyocyte cytoplasm
- Mechanisms for efficient transfer across the endothelial barrier

Out of scope:
Unmodified and known receptors that have already been exploited for delivery

6.3 Cell- and tissue- specific targeting

Challenge questions:
Emerging pharmaceutical targets for intractable diseases often suffer from unacceptable safety risks when systemically administered. Specific targeting of pharmacological treatments to diseased cells holds the promise to avoid severe side effects. How might we identify cellular receptors on disease-relevant cells and/or molecular approaches to modify known tissue-specific receptors? What novel technologies can be used to direct molecular modulators to diseased tissue with high specificity?

Potential solutions:

- Molecular profiling approaches to identify novel cell-specific receptors or disease-specific markers amenable to targeting (e.g., lung, liver, kidney, heart, brain, tumour, eye)
- Basic insights to disease-specific cell populations that may lead to novel targeting approaches
- Deep understanding and modelling of tissue/cell targeting principles (e.g., avidity vs. affinity)
- Novel approaches to overcome biological barriers (i.e., intravascular, endothelial, cellular barriers)

Targeting strategies enabling site-directed delivery, reducing unwanted toxicities or enhancing a drug's efficacy:

- Low molecular weight compounds
- Chemistries or other technologies improving biodistribution to key disease tissues in pre-clinical models
- Natural or genetically engineered cells

Cargo may include small molecules, peptides, imaging or radioligand agents, biologics, bi-specifics, RNA, antibody oligo conjugates, CART, etc.

Out of scope:
ADCs, nanoparticles, liposomes, known receptors (e.g., ASGR)

6.4 Mechanistic insights to enable improved CNS tropism of AAV capsids

Challenge question:
CSF-delivery of AAV cargoes is currently a widely employed strategy to deliver gene therapies for a range of neurological disease. Emerging data has highlighted that most CSF-delivered capsids show poor distribution to deeper brain regions, a major limitation to leveraging this approach for a range of CNS indications where delivery to deep brain regions is critical.

Potential solutions:
Systematically identify receptors and other key molecular players involved in the spread and neuronal uptake of AAV capsids to inform design of next generation capsids with improved spread and enhanced neuronal tropism.

Out of scope:
N/a

6.5 Selective targeting of Schwann cells

Challenge question:
There are a range of acquired, inflammatory and inherited neuropathies involving Schwann cell dysfunction with peripheral axon degeneration. Can we selectively harness the close association of Schwann cells with the axons to deliver therapeutics for such conditions?

Potential solutions:
Novel approaches to selectively target Schwann cells with therapeutic agents, including gene therapies, to correct biological mechanisms or molecular targets that induce the following:

- Loss of axon myelination or trophic support
- Axonal degeneration or axon retraction from tissues

Successful proposals will enable the direct targeting of Schwann cells

Out of scope:
Non-targeted approaches