Challenge Questions
NIBR Global Scholars Program 2023

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

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NGSP areas and Challenge Questions

1. **Biologics, Gene Therapy**
   - 1.1. Significantly improve protein production for all non mAb/Fc therapeutic proteins
   - 1.2. Technologies enabling assessment of oligonucleotide-conjugate modalities
   - 1.3. Rapid characterization of new biotherapeutic modalities at the micron scale
   - 1.4. Next generation delivery of gene therapies

2. **Complex Models**
   - 2.1. Complex cellular disease models
   - 2.2. Transformative technologies to increase drug safety

3. **Disease Mechanisms**
   - 3.1. Mechanisms of disease progression in multiple sclerosis (MS)
   - 3.2. Therapeutic approaches to restore immune tolerance in autoimmune diseases and food allergy
   - 3.3. Weight loss in age-related obesity through increased energy expenditure
   - 3.4. Podocytopathies: towards novel mechanistic understanding and therapeutic interventions to preserve kidney structural integrity
   - 3.5. Neurodegenerative Diseases: Huntington's, Parkinson's, and Alzheimer's
   - 3.6. Molecular mechanisms of neuroinflammation in age-related neurodegeneration

4. **Protein & Drug Design**
   - 4.1. Leveraging next generation protein and structure-based drug design
   - 4.2. Optimizing production of therapeutic proteins via AI assisted predictions

5. **Regenerative Medicine**
   - 5.1. Restoring cell and tissue function in diseases of aging
   - 5.2. Regeneration: Restoration of organ function

6. **Tissue/Cell Specific Targeting & Characterization**
   - 6.1. Glycosylation-tags for targeting biologicals to specific cells and tissues
   - 6.2. Cell and tissue-specific targeting
   - 6.3. True single cell spatial proteomics

7. **Oncology & Immuno-oncology**
   - 7.1. Prediction of novel Oncology targets
   - 7.2. Novel relevant disease models for prostate cancer
   - 7.3. Novel targets and approaches for targeting RAS driven tumors
   - 7.4. Advancing the understanding and applications of Radio Ligand Therapy (RLT)
   - 7.5. Tumor cell immunogenicity & innate immunity activation

Each area & Challenge Question is hyperlinked to the corresponding page

1

Biologics, Gene Therapy

1.1 Significantly improve protein production for all non mAb/Fc therapeutic proteins

Challenge question:

Significantly improve protein production process efficiency in microbial and eukaryotic systems using a traceless cleavable tag system that boosts expression, enables high capacity and selective purification, and utilizes novel proteolytic tag traceless cleavage (i.e., no leftover tag/linker residues).

Potential solutions:

Novel universal and developable affinity tag and cleavage system (protease) that significantly enhances protein expression and production yields in all commonly used expression cell systems

- Tag enhances solubility and does not interfere with folding, structure or activity of target protein
- Affinity resin design with high dynamic binding capacity, high selectivity, mild elution conditions, and hundreds of resin use cycles
- Traceless tag cleavage via selective and highly active engineered protease or self-cleavage independent of target sequence, generating a native protein
- Suitability for developable bioprocess scale cleavage system, protease, affinity ligand and resin manufacturing

Out of scope:

Use of existing, non-selective or low activity protease systems.

1.2 Technologies enabling assessment of oligonucleotide-conjugate modalities

Challenge question: Targeted delivery of oligonucleotide therapeutics requires conjugation to other molecules like proteins and diverse chemical entities. The formed conjugate modalities show de-novo (quality) attributes, which can't be addressed by available analytical methods. We are looking into elucidation of these new attributes and establishment of appropriate assessment technologies.
Potential solutions: Establishment of state-of-the-art technologies for quantitative analysis of oligonucleotide-conjugates in buffers and biological matrices assessing colloidal, physical and chemical stabilities. Hereby, high-throughput and low material consumption solutions are in scope, e.g., microfluids-based.
Out of scope: MS-only based technologies

1.3 Rapid characterization of new biotherapeutic modalities at the micron scale

Challenge question:

Production of new biotherapeutic modalities brings many open questions on characterization. Analytical data is needed to support molecular design, process optimization, candidate selection and mechanism investigation. To better support all these activities, we need characterization methods which can work with low sample consumption and low purity, with the possibility to model/predict the behaviors based on a minimal sample volume. Ideally the technique integrates multiple quality attributes, e.g., particle separation, sizing, biomarker detection, and quantification on one single microfluidic chip, requiring only a few microliters of nontreated sample and operating in a time scale of minutes.

Potential solutions:

- Establish analytical methods integrating multiple quality attributes
- Significant reduction of sample consumption compared to current methods
- Possibility to collect the generated data for building up prediction models

Out of scope:

Methods which require licensing from a third-party

1.4 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

2

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, heart, eye.

Novel focused technical solutions allowing image-based cell/organoid sorting as well as innovative ideas to culture and screen these cellular models are encouraged.

Send us your big, bold ideas on 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 safety studies and anticipate adverse events emerging in clinical trials and the real world?

Potential solutions:

Compelling algorithms for quantum computers to predict immune-mediated adverse safety events of drugs

- Artificial intelligence algorithms to accurately predict adverse safety events based on drug epitope(s)
- 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

- Model drug-microbiome interplay, i.e., 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 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 physiological 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

3

Disease Mechanisms

3.1 Mechanisms of disease progression in multiple sclerosis (MS)

Challenge question:

Available drugs for MS only treat immunological aspects of MS. Currently, there are insufficient therapeutic options for stopping or even reverting “silent” progression in MS in absence of relapses.

We want to investigate the molecular/cellular pathomechanisms responsible for the progression in MS independent of relapse, and whether there are determinants differentiating fast from slow progressors, including genetics.

Potential solutions:

- Novel approaches that enable molecular analysis of autopsy CNS tissue or CSF from MS patients and their interconnection with mechanistic in vitro/in vivo analyses, ideally in conjunction with genetic/pharmacologic perturbation
- Successful proposals will enable an integrated suite of molecular observations and mechanistic analyses for the discovery of:
  1. Pathomechanisms driving progression in MS
  2. Novel neuro/axonal/glia targets to halt or reverse progression
  3. Novel preclinical assay/model systems for drug discovery with translatable value

Out of scope:

Sole focus on animal models, mere provision of human biosamples; biosamples with poor clinical annotation and no longitudinal clinical follow-up

3.2 Therapeutic approaches to restore immune tolerance in autoimmune diseases and food allergy

Challenge questions:

Food allergy and autoimmune diseases such as vitiligo are characterized by disrupted B- and/or T-cell tolerance. This calls for therapeutic approaches restoring tolerance, e.g., by modulating effector and/or regulatory T or B cells. Are there unique features marking pathogenic B or T cells? Which human Treg/Breg subsets or functional properties are required to restore tolerance? How to identify novel therapeutic targets or strategies to achieve durable clinical remission?

Potential solutions:

- New insights by characterization of pathogenic and regulatory B and T cells in inflammatory skin diseases and food allergy in humans, as well as translational animal and cellular models.
- Novel approaches and therapeutic targets to modulate subsets and/or properties of human Tregs required for restoration of tolerance.
- Novel approaches with potential for long lasting clinical remission via modulation/depletion of pathogenic cells without systemic immunosuppression (e.g., T cell exhaustion, tissue-specific methods).
- Approaches enabling tissue-specific tolerance induction or tissue regeneration, e.g., via TCR- or CAR-engineered Tregs/T cells combining antigen-specificity with signaling domains conferring “regulatory” rather than solely stimulatory effects.

Out of scope:

In vitro screens of Foxp3 induction or stabilization.

3.3 Weight loss in age-related obesity through increased energy expenditure

Challenge question:

Which molecular mechanisms exist that can be safely targeted to increase cellular energy expenditure and thereby combat age-related obesity?

Obesity is a major accelerator of known age-related diseases, enhancing cellular ageing phenotypes. Elderly obese subjects have reduced skeletal muscle mass and most interventions aiming to induce weight loss further reduce muscle mass leading to a vicious cycle of increasing weakness, reduced energy expenditure and altered cellular metabolism across multiple organs.

Identifying molecular mechanisms that can block this vicious cycle by inducing weight loss while preserving or enhancing skeletal muscle mass, function and energy expenditure are expected to have transformative disease-modifying potential to fight age-related obesity, restore glycemic control and address associated systemic co-morbidities.

Potential solutions:

- Identification of novel entry points for drug discovery targeting age-related obesity via increased energy expenditure
- Validation via complex translational in vitro / ex vivo assay systems and/or preclinical animal models and/or human genetics
- Safety aspects should be taken into consideration

Out of scope:

Longstanding literature targets and targets with known liabilities (i.e., systemic toxicity) without proposed mitigation plans

3.4 Podocytopathies: towards novel mechanistic understanding and therapeutic interventions to preserve kidney structural integrity

Challenge question:

The major hallmarks of all proteinuric kidney diseases is direct or indirect podocyte injury and the breakdown of the glomerular filtration barrier. Loss of structural integrity and glomerular obsolescence are the key disease features but the underlying pathomechanisms promoting glomerular, tubular, and vascular damage and loss are not well understood.

Are there any new genetic, environmental or structure–function insights into root causes of podocytes and glomerular function loss that may pave the way to new candidate therapeutic targets for kidney disease?

Potential solutions:

- New genetic, epigenetic, transcriptional, immunological, infectious and toxic causes of podocyte injury and glomerular dysfunction. Focus on preserving specialized cellular functionality and survival
- Preferably genetically or omics-linked biological proof of causality
- Next-generation pre-clinical models (including patient-derived 3D cell systems) that decisively improve translatability to humans or faithfully mimic disease progression

Out of scope:

Targets from preclinical models only and without human link to disease causality (whether human multi omics- or genetics-based).

3.5 Neurodegenerative Diseases: Huntington's, Parkinson's, and Alzheimer's

Challenge question:

To date, there are no cures for many neurodegenerative disease, including Huntington's (HD), Parkinson's (PD), and Alzheimer's (AD). We seek to discover and develop next generation therapies for these devastating neurodegenerative diseases, but require a better understanding of the core drivers of these conditions in order to develop impactful treatments. Identification and validation of early (prodromal) markers would be highly impactful.

Potential solutions:

Of key interest are:

- Novel biological insights into, or therapeutics targeting, protein misfolding (in HD, PD)
- Neuronal metabolic stressors (mitochondrial dysfunction, endosomal/lysosomal dysfunction)
- Identification of the core genetic drivers of neurodegeneration and neuroinflammatory response

Out of scope:

- Projects focusing on known biology or previously explored approaches to treating neurodegenerative disease e.g., Amyloid based approaches in AD
- Therapies principally addressing symptoms e.g., L-dopa treatments in PD

3.6 Molecular mechanisms of neuroinflammation in age-related neurodegeneration

Challenge question:

What is the contribution of neuroinflammation and microglia and/or astrocyte subpopulations to age-related neurodegenerative diseases?

Neuroinflammation is a hallmark of age-related neurodegenerative diseases such as Alzheimer's Disease (AD), Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS), as well as a key factor in progressive Multiple Sclerosis (pMS). This prompts the question whether age-related chronic low-grade inflammation contributes to the failure of the aging CNS to regenerate and whether normalizing associated cellular states of inflammatory microglia and/or astrocyte subpopulations would slow or reverse age-related neurodegeneration.

Successful proposals will deepen the mechanistic understanding of microglia and astrocyte subpopulations in neuroinflammation aiming at the discovery of novel therapeutic targets/pathways and/or assay systems via unbiased genetic or drug-based screening approaches.

Potential solutions:

- Novel approaches to define the cellular states of neuroinflammatory microglia and/or astrocyte subpopulations in age-related neurodegenerative diseases such as AD, PD, ALS and pMS
- Validation via complex translational in vitro / ex vivo assay systems and/or preclinical animal models and/or human genetics

Out of scope:

Previously published approaches and targets with known liabilities (i.e., systemic toxicity) without proposed mitigation plans

4

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 or molecular properties including first-principle methods
- Methods to enable design of proteins for enhanced stability and 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

4.2 Optimizing production of therapeutic proteins via AI assisted predictions

Challenge question:

To improve the success and timelines for the production of therapeutic proteins we are looking for AI-based methods to predict the following:

- Recombination events within different cell lines of different origin from DNA/RNA sequences
- Expression and secretion capacity from amino acid sequences for non-antibody proteins
- Optimal signal peptide / protein-of-interest combinations
- Post-translational modifications (e.g., O-glycosylation and N-glycosylation heterogeneity, truncations)
- AAV/LVV packaging efficiencies

Such AI-based methods should optimize current protein production methodologies.

Potential solutions:

- AI algorithms with proven correlation of predicted and actual sequence properties
- Preferred validation: In vitro data with sufficient statistical relevance
- Reduction of experimental assessment requirements, improved productivity, production stability and developability

Out of scope:

Repurposed drug, human tissue procurement, etc. AI based protein/protein interaction/ affinity predictions

5

Regenerative Medicine

5.1 Restoring cell and tissue function in diseases of aging

Challenge question:

Which common molecular mechanisms underlie diseases of aging and how can they be safely targeted for novel drug discovery to restore tissue function and homeostasis?

More than 30% of known human diseases are age-related and thus likely share in part common etiology and/or systemic components that contribute to disease onset and progression with age across the spectrum of age-related immune, neurodegenerative and cardiovascular diseases.

Uncovering the underlying common molecular disease drivers as well as specific biological differences to allow selective targeting of age-related diseases may enable the discovery of novel and safe drug entry points to restore cellular and tissue function in elderly patients.

Potential solutions:

- Identification of novel entry points for drug discovery with expected synergy across the spectrum of age-related diseases or highly specific molecular mechanisms, pathways, or targets for selected diseases of aging
- Validation via complex translational in vitro / ex vivo assay systems and/or preclinical animal models and/or human genetics
- Safety aspects should be taken into consideration

Out of scope:

Longstanding literature targets and targets with known liabilities (i.e., oncogenicity) without proposed mitigation plans

5.2 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., skin, liver, kidney, 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, 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 proposed mitigation plans
- Approaches that only impact cell proliferation without restoring their specialized functionality

6

Tissue/Cell Specific Targeting & Characterization

6.1 Glycosylation-tags for targeting biologicals to specific cells and tissues

Challenge question:

Biotherapeutics tagged with certain glycans bind selectively to tissue-specific receptors (e.g., ASGPR) and allow targeted delivery (e.g., to hepatocytes). We are looking for novel glycosylation structures and their cognate cell-specific receptors or disease-specific markers (including extracellular proteins) to target kidney, heart, brain, tumor, eye or to overcome biological barriers (e.g., intravascular, endothelial, blood-brain barrier).

Potential solutions:

- Specific mechanism, pathway, or technology: validated glycan structures for tissue-specific delivery of biologics (e.g., receptor-mediated)
- Preferred validation through in vivo biodistribution studies
- Insights into the potential immunogenicity of unnatural/rare glycan structures
- Enable tissue-targeting of recombinant proteins and therefore additional functionality beyond alternative targeting moieties. Also, an enrichment of recombinant proteins in target tissues could be beneficial.

Out of scope:

- Glycans not produced by glyco-enzymes
- Liver-targeting

6.2 Cell and tissue-specific targeting

Challenge questions:

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., liver, kidney, heart, brain, tumor, 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, CAR-T, etc.

Out of scope:

ADCs, nanoparticles, liposomes, known receptors (e.g., ASGR)

6.3 True single cell spatial proteomics

Challenge questions:

Current spatial 'omics platforms are aimed at transcriptomics and a small set of immune-focused proteins with well-characterized antibodies. A true single-cell spatial proteomics platform that enables "unbiased" profiling would allow deeper insight into human disease mechanisms and faster identification of therapeutic targets

A true single cell spatial proteomics platform would address numerous gaps: dearth of precision protein profiling platforms, disconnects between transcript and protein levels, limitations of sample pooling vs. resolution, longer times to turn transcriptomic data into preclinically validated targets

Potential solutions:

- True single cell resolution (i.e., profiling of individual cells, not regions of interest or pooled cells)
- Able to resolve thousands of proteins (superior to current standard of 500-1000)
- Can profile hundreds to thousands of cells (superior to a few hundred cells)
- Works on preserved (e.g., fixed and/or frozen) human samples, not just cell culture or animal models

Out of scope:

Single cell transcriptomics, pooled approaches, antibody-based hashing approaches, lipidomics, metabolomics

7

Oncology & Immuno-oncology

7.1 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 rates 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
- Differentiation between cellular localization in tumor vs normal cells or tissue
- Differentiation between cell states
- Differentiation between sensitive and resistant states

The above provide a new avenue for directed tumor targeting with advanced analytical methods applied to newly available preclinical and clinical data.

Out of scope:

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

7.2 Novel relevant disease models for prostate cancer

Challenge question:

- Currently, no single pre-clinical model encompasses the entire spectrum of human prostate cancer progression faithfully.
- Novel surrogate models that would enable the study of this disease are needed, as are models that would allow the study of drug resistance.

Potential solutions:

- Identification of technological solutions that allow characterization and scaling of patient samples would be of great interest
- Models that retain the essential markers and that recapitulate the diversity of the disease
- Increased understanding of the disease and options to develop and test new therapies preclinically

Out of scope:

Known and tried approaches

7.3 Novel targets and approaches for targeting RAS driven tumors

Challenge question:

- Approximately 1/3 of human cancers are driven by mutations in RAS genes, but as of yet only KRAS-G12C inhibitors (Sotorasib and Adagrasib) have been approved for clinical use, leaving other RAS mutant onco-alleles orphan of targeted therapies
- KRAS G12C inhibitors are active clinically but tumors often relapse rapidly. A better understanding of the underlying resistance mechanisms is warranted to allow the development of orthogonal MoA for RAS direct inhibition as well as identifying most adapted combination companions to maximize efficacy

Potential solutions:

- Identification of KRAS G12D or G12V inhibitors either through onco-allele selective or pan-inhibition direct RAS binding, either through known or novel (yet to be discovered) binding pockets
- Development and implementation of technologies (e.g., barcoding) to better define resistance mechanisms, allowing new combination therapies.
- Preferred validation in relevant biochemical or cellular models
- For approaches targeting resistance and orthogonal combinations, avoidance of enhancing known MAPK pathway on-target toxicities

Out of scope:

Technologies / MoAs that are not differentiated from current SwII pocket binders.

7.4 Advancing the understanding and applications of Radio Ligand Therapy (RLT)

Challenge question:

- Advancing the understanding and applications of Radio Ligand Therapy (RLT)
- RTL is an effective platform that has the potential to address many types of cancer

Potential solutions:

We are looking to expand the therapeutic applications of RLT through the identification of:

- New tumor and/or tumor microenvironment (TME) specific targets, ideally providing data of specific tumor and/or TME expression versus other tissues especially kidney and bone marrow.
- Novel disease models for predicting RLT response and resistance.
- New combinations of RLT with other cancer therapies that demonstrate improved responses in tumors and are potentially translatable. Plans to mitigate potential toxicities upon combination treatment.

Out of scope:

DDR pathway inhibitors when considering combinations.

7.5 Tumor cell immunogenicity & innate immunity activation

Challenge questions:

Immune check point blockade faces a major challenge of being ineffective against “cold” tumors. How can we:

- turn “cold” unresponsive into “hot” responsive tumors in the context of check point inhibitors?
- activate innate immunity to elicit an integrated immune response against cancer?
- identify and/or develop novel sensitizers for immunotherapy?

Potential solutions:

- 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.
- Identification or development of novel combinations for immunotherapy.

Disease indications: Breast, Lung, Hematological, and Prostate.

Out of scope:

Known & tried experimental approaches