Medicine by Design

Grand Questions Program

request for applications (RFA) – phase 1

Phase 1 proposal due date: August 21, 2020

Phase 2 proposal due date: November 13, 2020

Funding period: March 1, 2021 - August 31, 2022

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# INTRODUCTION

Medicine by Design’s **Grand Questions Program** aims to change the future of regenerative medicine through research that addresses some of the field’s biggest unanswered questions. Through this program, Medicine by Design is investing in bold ideas and developing transformative and revolutionary solutions that will be of critical importance to regenerative medicine over the next 20 years. These solutions will enable new therapies that promise dramatically better health outcomes for people around the world, ensuring Toronto and Canada continue to lead this health-care transformation.

Medicine by Design will invest up to $3 million in the Grand Questions Program. Successful teams will receive up to $1 million each over the period of March 1, 2021- August 31, 2022.

Funded by the [Canada First Research Excellence Fund](http://www.cfref-apogee.gc.ca/home-accueil-eng.aspx) (CFREF), Medicine by Design harnesses world-leading regenerative medicine expertise at the University of Toronto and its affiliated hospitals, and encourages creativity, risk-taking and excellence at the convergence of science, engineering and medicine.

# OVERVIEW OF THE GRAND QUESTIONS

Medicine by Design invites researchers to submit proposals outlining how they will address one of the following Grand Questions. These questions have been developed and refined in consultation with investigators at U of T and its affiliated hospitals and Medicine by Design’s Scientific Advisory Board.

1. **Designing Tissues *de novo*** — Can we make tissues that perform better than nature?
2. **Affordability and Accessibility** — How can we make regenerative medicine available to everyone?
3. **New Technology for Cell Tracking** — Can we record the m/RNA/protein/signaling history of a cell?
4. **Physics of Regeneration** — What are the core physio-chemical principles governing organ formation, and can they facilitate organ regeneration?
5. **Senescence and Aging** — How can we turn back the clock, making old cells young again?
6. **Reversing Organ Failure** — Can tissue damage that is considered to be permanent actually be reversed?

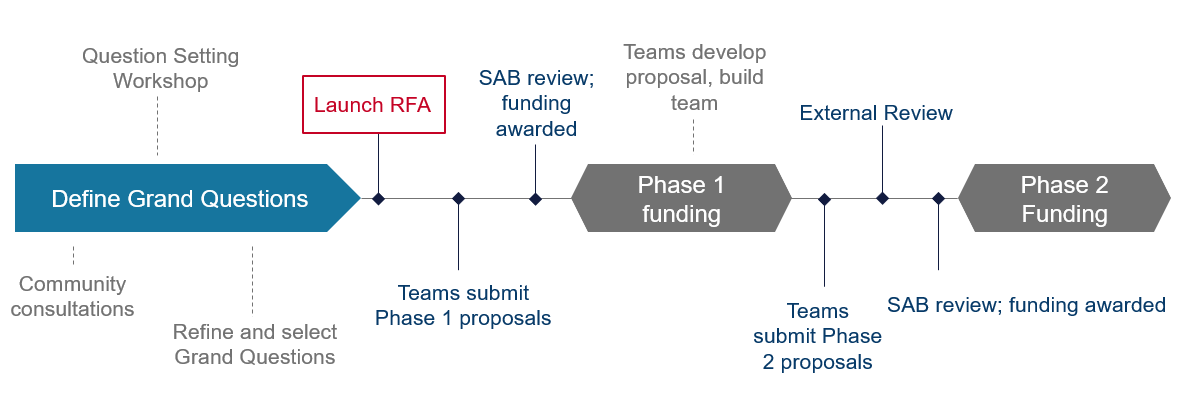
[See pages 5-7 for additional descriptions of the Grand Questions.](#_DESCRIPTIONS_OF_GRAND)

# PROCESS AND TIMELINE

After several earlier idea-generating sessions, the Grand Questions Program was launched in April 2020 with a question-setting workshop that engaged more than 50 investigators from the Medicine by Design community and beyond. During the workshop and in follow-on scientific discussions, the community was asked to identify and describe ambitious research questions that were provocative, non-obvious, and would excite curiosity and inspire progress. In defining these Grand Questions, we have sought inspiration from the [Cancer Research UK’s Grand Challenge](https://www.cancerresearchuk.org/funding-for-researchers/cancer-grand-challenges) and the [NCI Provocative Questions Initiative](https://www.nature.com/articles/481436a) (developed by Harold Varmus). Based on the recommendation of Medicine by Design’s Scientific Advisory Board (SAB), a subset of these Grand Questions form the basis of this RFA.

Research funding for the Grand Questions will include two phases, outlined in the figure below. Teams that are successful at Phase 1 will have access to $10,000 from September to October 2020 to develop the team and the Phase 2 proposal. Teams that are awarded Phase 2 funding will receive up to $1 million each in Phase 2 funding over the period of March 1, 2021, to August 31, 2022.

Multiple teams may submit proposals around the same Grand Question. Not all Grand Questions will receive funding.



**Key dates:**

|  |  |  |
| --- | --- | --- |
| Milestone | Who | Dates |
| Phase 1 proposals due | Applicants | August 21, 2020 |
| Phase 1 proposals reviewed  Successful proposals awarded Phase 1 funding | Medicine by Design’s SAB | September 2020 |
| Teams develop Phase 2 proposals | Applicants | September – November 2020 |
| Phase 2 proposals due | Applicants | November 13, 2020 |
| Phase 2 proposals reviewed by external reviewers  Phase 2 funding awarded to successful proposals | External peer reviewers,  Medicine by Design’s SAB | December 2020 – February 2021 |
| **Funding Period: March 1, 2021 – August 31, 2022** | | |

# ELIGIBILITY

Investigators with a faculty appointment at the University of Toronto are eligible to apply.

Medicine by Design Cycle 2 **lead** principal investigators (PI) are not eligible to be lead PIs for projects funded under this program, but are eligible to be co-PIs. Cycle 2 co-PIs and all other investigators who have previously received Medicine by Design funding are eligible to be lead PIs for this program.

Only one application will be accepted from each lead investigator. Each project may have only one lead PI but there is no limit to the number of co-PIs.

# EQUITY, DIVERSITY, AND INCLUSION

The University of Toronto recognizes that diversity is essential to the creation of a vibrant intellectual community that allows our researchers to maximize their creativity and their contributions. Medicine by Design is therefore strongly committed to diversity in research and especially welcomes applications that engage racialized persons/persons of colour, women, Indigenous/Aboriginal Peoples of North America, persons with disabilities, LGBTQ+ persons, and others who may contribute to the further diversification of ideas.

**All applicants (both lead and co-PIs) are required to answer a self-identification survey.** In completing this survey, applicants may voluntarily self-identify in all applicable groups, or they may log a response indicating that they decline the survey. Self-identification data is important to the University’s ability to accurately identify barriers to inclusion and to develop strategies to eliminate these barriers. Any information directly related to you is confidential and cannot be accessed by the reviewers or the Medicine by Design team. *Aggregated* results as of the closing of this posting may be shared with only a small number of designated senior administrators on a need-to-know basis.

# DESCRIPTIONS OF GRAND QUESTIONS

1. **Designing Tissues *de novo*** **—** **Can we make tissues that perform better than nature?**

Mimicking the function of the native tissue is often the goal of regenerative medicine research and respects evolutionary pressure. But can we do better?

Can we generate cells and/or tissues that will provide function(s) that are enhanced, entirely novel or “borrowed” from nature (i.e. from non-human organisms) for therapeutic purposes?  Examples of new functional properties could include the ability to evade infection by viruses or other pathogens, enhanced vision (widened spectra), improved sense of smell or hearing, avoidance of senescence and neoplasia.

Is there a way we can design robust cells and tissues such that when they and we eventually expire, we do so painlessly and naturally, without having suffered debilitating conditions?

These outcomes could be achieved by creating chimeric cells, combining tissue functions in one novel cell type, or interfacing cells and tissues with electronics or soft robotics. The new cell/tissue could be designed for ad hoc use (i.e. something that could be removed once the outcome has been achieved), or it could be implanted for life.

Since the development of such a cell/tissue has ethical implications, competitive proposals will integrate ethical considerations and engage with bioethicists to create a consensus framework as part of the project. Competitive applications will propose goals that are well beyond the current state of the art.

1. **Affordability and Accessibility** **— How can we make regenerative medicine available to everyone?**

Regenerative medicine and cell-based therapies have the potential to cure otherwise intractable diseases and are among the most promising domains for the delivery of paradigm-changing health care. However, the anticipated cost of these therapies will strain even well-resourced health-care systems. Globally, these costs will pose a much greater challenge, with most people not expected to be able to access the benefits of these technologies. Furthermore, it is expected that such technologies, as currently envisioned, will be hard to implement outside major medical centres.

Reducing the cost of developing and delivering these advanced therapies is critical for patient access, but also for researchers and innovators in the field. Society’s continued investment in research is critical to bringing their products to market. Reducing the barriers to access is a separate but equally critical task.

While some regenerative medicine therapies are based on approaches that do not involve cells, for cell-based therapies can we look to automation, robotics, machine learning or other technologies to simplify their scale-up or scale-out, perhaps making them no more complex than dialysis or chemotherapy?

The development of such technologies will require perspectives from global health practitioners among others with a health accessibility perspective. Therefore, competitive applications will integrate an array of disciplines to inform the team on how best to reach the goal of affordable, accessible regenerative medicine.

1. **New Technology for Cell Tracking** **— Can we record the m/RNA/protein/signaling history of a cell?**

Observing a tissue as it undergoes a dynamic transition (e.g. during development, disease progression or during the integration of regenerated tissue) is challenging, if not impossible, to do using current methods. The capacity to spatially and temporally record cellular signalling events in a multiplexed manner would transform our understanding of the cellular heterogeneity and multicellular information processing that underlies normal and pathological tissue biology.

Can we comprehensively trace the input signals (type, magnitude, duration) that drive cell decision-making in complex multicellular systems undergoing organizational and fate transitions? Can we develop a scalable, high-content and non-destructive technique to log signalling pathways at single-cell resolution in space and time?

1. **Physics of Regeneration** **— What are the core physio-chemical principles governing organ formation, and can they facilitate organ regeneration?**

Tissue engineering currently relies in large part on mimicking normal developmental processes in an *in vitro* setting. Often, small and rapidly developing systems the size of early embryos (e.g. cell aggregates, embryoid bodies and organoids) are used as paradigms for tissue or organ construction. However, to rationally advance the generation of functional post-natal tissues, completely different size and time scales need to be mastered by employing insights and technologies that do not currently exist. During organogenesis, cell differentiation and tissue morphogenesis are spatiotemporally coupled and regulated by biochemical and physical cues.

In contrast to current approaches such as trial-and-error experimentation, it may be more efficient to define conserved physical rules that drive key morphogenetic processes as systems transit to larger sizes and progressively acquire different mechanical features.

Can the physical and chemical principles of embryonic morphogenesis be distilled into core principles and applied to bridge the spatiotemporal gap from organogenesis to the generation of functional organs? Defining these core physical rules and applying them *in vitro* and *in vivo* will require close collaboration between developmental and cell biologists with physicists, mathematicians, and engineers.

1. **Senescence and Aging** — **How can we turn back the clock, making old cells young again?**

Current approaches to reverse aging focus on limiting cell senescence, promoting and ensuring mitochondrial health, rejuvenating factors, epigenetic reprogramming, and modulating the immune and stress environment. Can we vastly improve on current approaches to prevent aging, or develop new concepts and propose novel technologies that in turn will reverse the inevitable process of aging and increase human healthy lifespan?

The goal of this question is to better understand the aging process, identify new mechanisms of aging, and develop strategies that have the potential to reverse it. One approach could be to determine the minimum and maximum heathy lifespan value of a particular species. Is there a master regulator or set point of lifespan value? Does this master regulator influence or even determine metabolic activity and biosynthetic capacity, the ability to repair oxidative and DNA damage and maintain organelle health, telomere erosion and response to stress? An approach to addressing these questions could explore new concepts and propose novel technologies that have the potential to vastly improve on strategies to promote organismal health within the lifespan range and reverse the inevitable process of aging.

Other perspectives include considering whether repairing aged stem cell function not only involves restoring "young" intrinsic repair and epigenetic regulatory pathways, but also requires at the same time repairing the niche and preventing the influence of damaging systemic factors. Alternatively, one can ask if cancer is an inevitable consequence of healthy aging or if we can separate the two.

1. **Reversing Organ Failure** — **Can tissue damage that is considered to be permanent actually be reversed?**

Until very recently, the concept of an irreversibly failing organ was accepted and not challenged. But what if this dogma was wrong? What if the presumed irreversible permanent tissue damage could be reversed, and strategies could be implemented that would allow for organ regeneration?

Is it possible to unravel the path to re-program endogenous cells to clear scar tissue and regenerate parenchyma? Such capability could result in an unprecedented paradigm shift in the clinical management of end-stage organ failure. Physicians would be able to block disease progression (e.g., fibrosis) at earlier stages of disease and ultimately induce functional tissue (organ specific parenchyma) regeneration in both native and transplant organs.

With the global population aging and the incidence of chronic disease rising, reversal of scar tissue and regeneration of parenchyma would have an unprecedented impact on patient survival and quality of life, benefitting healthcare systems globally in an unprecedented way.

Medicine by Design

2020 Grand Questions Awards

# PHASE 1 PROPOSAL

**Submission deadline is August 21, 2020,** **at 5 p.m. ET**.

Please submit two PDF files: the completed Phase 1 proposal, and a combined PDF file of all investigator CVs. Please send the completed document by email to [awards.mbd@utoronto.ca](mailto:awards.mbd@utoronto.ca). Notification of receipt will be sent within one business day.

Self-identification surveys (see section 2 for details) should be sent by email to Andrea Gill ([amk.gill@utoronto.ca](mailto:amk.gill@utoronto.ca)). **Do not copy** Medicine by Design staff or send this form as part of your application package**.**

Successful Phase 1 proposal applicants will be contacted in September 2020 with instructions for submitting the Phase 2 proposal.

## SECTION 1: PROJECT OVERVIEW

**Project Title:**

**Lead PI:**

**Which Grand Question are you addressing?** (Please check only one)

*Please note that applications that do not address a Grand Question from the list below or re-write one of the listed Grand Questions will be considered nonresponsive.*

*Applicants uncertain as to whether their intended project meets the requirements of this RFA are encouraged to contact Michael Sefton (*[*michael.sefton@utoronto.ca*](mailto:michael.sefton@utoronto.ca)*) or Allison Brown (allisonl.brown@utoronto.ca).*

**Designing Tissues *de novo*** — Can we make tissues that perform better than nature?

**Affordability and Accessibility** — How can we make regenerative medicine available to everyone?

**New Technology for Cell Tracking** — Can we record the (m/RNA/protein/signaling) history of a cell?

**Physics of Regeneration** — What are the core physio-chemical principles governing organ formation, and can they facilitate organ regeneration?

**Senescence and Aging** — How can we turn back the clock, making old cells young again?

**Reversing Organ Failure** — Can tissue damage that is considered to be permanent actually be reversed?

1. **Project Goal(s)**

*The proposed goals must attempt to provide definitive, comprehensive, and thorough research answers to the problem or portions of the problem presented by the chosen Grand Question.*

(Maximum 1 page)

* 1. Define the overarching goal(s) of the project and indicate how achieving them will yield far-reaching advances within the context of the selected Grand Question. The goals of this project should extend beyond the funding period of this competition (March 1, 2021- August 31, 2022)
  2. Highlight how the goal(s) extend well beyond the next steps of ongoing research efforts within the team and the scientific community more broadly.

1. **Approach**

*The proposed research approach should be creative and original with high potential for transformative impact on current concepts and paradigms in regenerative medicine research. The approach should not focus on specific diseases unless the findings are applicable to multiple diseases. Approaches should be ambitious and have an element of “strategic infeasibility” (i.e., be high-risk).*

(Maximum 1 page)

* 1. Briefly describe the proposed approach to addressing this Grand Question.
  2. How will the proposed research take advantage of new and emerging technologies to address the previously intractable challenges associated with this Grand Question?
  3. How is the proposed approach distinct from the current state-of-the-art?
  4. How will the approach take an ambitious, long-term view while also yielding nearer-term feasibility with impactful results?

1. **Impact**

*If successfully completed, the proposed research should have the potential to redefine the field of regenerative medicine over the next 20-30 years. The research should have wide-reaching impact, beyond a specific disease or tissue-focussed project.*

*Short-term aims should pursue ambitious, non-incremental progress. Long-term aims should chart provocative, new, non-obvious paths that differ from where the field is already headed.*

(Maximum 1/2 page)

* 1. Provide both short-term (5-year) and long-term (20-year) aims for the project beyond the end of the initial funding period.
  2. Outline the expected impact of successful completion of these aims on the field of regenerative medicine.

## SECTION 2: PROJECT TEAM

*Project team should be multi-disciplinary and multi-institutional with investigators at a mix of career stages.*

*Project teams may include Canadian or international advisors or scholars in residence to complement Toronto-based investigators. Only individuals with University of Toronto appointments are eligible to receive research funding from Medicine by Design; however travel costs and honoraria can be provided as part of Phase 2 funding. Judicious use of this mechanism for international engagement is expected to add value to a well-crafted team.*

*Note: Team members identified in Phase 1 may change prior to submission of the corresponding Phase 2 proposal.*

(Maximum 1 page)

1. Why is your team well positioned to address the selected Grand Question? Describe the combined disciplines and expertise in your proposal and outline the integration of expertise towards achieving the objectives of the project.
2. How is this team configuration new or different from existing Medicine by Design research teams?

Highlight equity, diversity, and inclusion (EDI) considerations that were relevant to team assembly. Describe processes used to engage diverse team members, including those from under-represented groups, and/or describe how the team incorporates expertise in EDI. Please **do not** disclose demographic information or identify team members.

1. Justify your choice of non-Toronto collaborators and explain their role in the project.

LEAD PRINCIPAL INVESTIGATOR (must hold faculty appointment at U of T):

|  |  |
| --- | --- |
| Name: | E-mail Address: |
| Position & Institution: | |

CO- PRINCIPAL INVESTIGATORS (must hold faculty appointment at U of T):

Please add rows as needed.

|  |  |  |
| --- | --- | --- |
| Name | Position & Institution | Email |
| 1. |  |  |
| Role in project: | | |
| 2. |  |  |
| Role in project: | | |

## SUPPORTING DOCUMENTATION

1. Attach a **single PDF file with CVs** for all investigators requesting funding from Medicine by Design. CVs can be in any format (e.g. CIHR Biosketch), but each CV must be less than 8 pages.
2. All applicants (both lead and co-PIs) are required to answer a **self-identification survey**. Please fill out the survey found at this link (<https://mbd.utoronto.ca/wp-content/uploads/2020/07/MbD_Self-ID_Form_July2020.pdf>) and either use the button in the form, or **send by email to Andrea Gill** ([amk.gill@utoronto.ca](mailto:amk.gill@utoronto.ca)). **Do not copy** Medicine by Design staff or send this form as part of your application package**.**

In completing this survey, applicants may voluntarily self-identify in all applicable groups, or they may log a response indicating that they decline the survey. Self-identification data is important to the University’s ability to accurately identify barriers to inclusion and to develop strategies to eliminate these barriers. Any information directly related to you is confidential and cannot be accessed by the reviewers or the Medicine by Design team. *Aggregated* results as of the closing of this posting may be shared with only a small number of designated senior administrators on a need-to-know basis.

## SECTION 3: BUDGET

***Phase 1:*** *Teams that are successful at Phase 1 will have access to $10,000 from September to October 2020 to develop the team and the Phase 2 proposal.* *Examples of eligible expenses include: workshop facilitation (in-person or online), fees for proposal development support (including writing/illustration), and travel costs (should travel be feasible).*

***Phase 2:*** *Teams that are awarded Phase 2 funding will receive up to $1 million each over the period of March 1, 2021, to August 31, 2022.*

(Maximum 1/2 page)

1. Please provide the estimated costs of planned activities (e.g. workshops) during Phase 1 to assemble the team and to develop a Phase 2 proposal.
2. Please indicate the approximate amount of Phase 2 funding that will be allocated to each team member. This budget allocation may change in the Phase 2 proposal as required.

## SECTION 4: RECOMMENDED POTENTIAL REVIEWERS

Phase 1 proposals will be reviewed by Medicine by Design’s Scientific Advisory Board. Phase 2 proposals will be reviewed externally.

Please recommend at least two international reviewers that you believe have the expertise to review your application and are not involved in the application. Reviewers cannot be affiliated with the University of Toronto, University of Toronto affiliated hospitals, or have been a collaborator in the last 6 years.

|  |  |  |  |
| --- | --- | --- | --- |
| Name | Position & Institution | Email | Expertise |
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# APPENDIX A: PHASE 1 PROPOSAL REVIEW CRITERIA

SECTION 1: PROJECT OVERVIEW

1. **Project Goal(s)**

* The proposed goals provide definitive, comprehensive, and thorough research answers that will yield far-reaching advances to the problem or portions of the problem presented by the chosen Grand Question.
* The proposed goals go well beyond the next steps of ongoing research efforts within the team and the scientific community more broadly.

1. **Approach**

* The proposed research approach is:
  + creative and original with high potential for transformative impact on current concepts and paradigms in regenerative medicine research;
  + ambitious with an element of “strategic infeasibility” (i.e., be high-risk); and
  + distinct from the current state-of-the-art.
* The approach balances a longer-term view while also yielding nearer-term feasibility.

1. **Impact**

* If successfully completed, the proposed research should have the potential to redefine regenerative medicine over the next 20 to 30 years. The research should have wide-reaching impact, beyond a specific disease or tissue-focussed project.
* Short-term research aims should aim for ambitious, non-incremental progress. Long-term research aims should chart provocative, new, non-obvious paths that differ from where the field is already headed.

SECTION 2: PROJECT TEAM

* Project team is multi-disciplinary and multi-institutional with investigators at a mix of career stages.
* Project team has diverse scientific expertise and is well equipped to tackle the objectives of the project.
* Project team is new or different from existing Medicine by Design research teams.
* Project teams took equity, diversity and inclusion (EDI) into consideration when recruiting members.
* Strong teams will include Canadian or international advisors or scholars-in-residence, with well-defined and critical roles in both the Phase 2 proposal development and project execution.

SECTION 3: BUDGET

* Team has planned suitable activities for effective Phase 2 proposal development and for use of Phase 1 proposal development funds.
* Suggested Phase 2 budget allocations for each team member are reflective of their involvement in the project.