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The Retinal Ganglion Cell Repopulation, Stem Cell Transplantation, and Optic Nerve Regeneration Consortium

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Purpose: The Retinal Ganglion Cell (RGC) Repopulation, Stem Cell Transplantation, and Optic Nerve Regeneration (RReSTORe) consortium was founded in 2021 to help address the numerous scientific and clinical obstacles that impede development of vision-restorative treatments for patients with optic neuropathies. The goals of the RReSTORe consortium are: (1) to define and prioritize the most critical challenges and questions related to RGC regeneration; (2) to brainstorm innovative tools and experimental approaches to meet these challenges; and (3) to foster opportunities for collaborative scientific research among diverse investigators.

Design and Participants: The RReSTORe consortium currently includes > 220 members spanning all career stages worldwide and is directed by an organizing committee comprised of 15 leading scientists and physician-scientists of diverse backgrounds.

Methods: Herein, we describe the structure and organization of the RReSTORe consortium, its activities to date, and the perceived impact that the consortium has had on the field based on a survey of participants.

Results: In addition to helping propel the field of regenerative medicine as applied to optic neuropathies, the RReSTORe consortium serves as a framework for developing large collaborative groups aimed at tackling audacious goals that may be expanded beyond ophthalmology and vision science.

Conclusions: The development of innovative interventions capable of restoring vision for patients suffering from optic neuropathy would be transformative for the ophthalmology field, and may set the stage for functional restoration in other central nervous system disorders. By coordinating large-scale, international collaborations among scientists with diverse and complementary expertise, we are confident that the RReSTORe consortium will help to accelerate the field toward clinical translation.

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Supplemental material available at www.ophthalmologyscience.org.

Optic neuropathies, regardless of their specific origin and pathophysiology, cause vision loss through a final common pathway: degeneration of retinal ganglion cells (RGCs) and their axons. Retinal ganglion cells are the projection neurons of the retina which transmit visual information to subcortical nuclei in the brain via their axons, which form the optic nerves and optic tracts. After injury, RGCs are spontaneously repopulated in some species of fish, amphibians, and birds; mammals, however, lack this inherent regenerative capacity throughout the central nervous system, including in the retina, rendering functional loss from trauma or neurodegenerative conditions permanent.[1–3] Scientific approaches to restoring lost vision in optic neuropathies include transplantation of pluripotent stem cell-derived RGCs,[4–7] induction of endogenous RGC regeneration through glial transdifferentiation,[8,9] and development of visual cortical prostheses.[10] The former 2 approaches hold considerable conceptual and scientific overlap and have been designated by the National Eye Institute (NEI) as priority areas of research through the Audacious Goals Initiative.[11] Given the numerous conceptual, scientific, and logistical barriers to achieving RGC repopulation throughout the visual pathway in human patients, several funding bodies including the NEI (https://www.nei.nih.gov/), the Glaucoma Research Foundation (http://glaucoma.org), and the Gilbert Family Foundation (https://gilbertfamilyfoundation.org/) have developed specific mechanisms to promote collaborative efforts among independent laboratories to tackle this goal through project grants. Though regular meetings are held among the investigators who work on those projects, the scope of

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inclusion is limited to those who are directly involved in the funded research. We hypothesize that to advance the field more rapidly toward clinical translation, it may be beneficial to foster open discussions and scientific collaboration among a wider range of interested parties, both in person and virtually.

The Retinal Ganglion Cell Repopulation, Stem Cell Transplantation, and Optic Nerve Regeneration (RReSTORe) consortium (http://rrestore.info) was founded in 2021 to fill a perceived gap in formal international communication and collaboration among researchers capable of providing critical input into the complicated task of restoring vision for patients with optic neuropathies. The premise of the RReSTORe consortium is that regular focused attention to this challenge, paid by diverse investigators of all career stages who hold complementary expertise, would help to unify scientific efforts toward solving key problems that stifle the field. Critically, this initiative aims to nucleate collaborations capable of generating innovative and effective approaches that restore functional eye-to-brain connectivity.

The RReSTORe consortium was developed by an organizing committee composed of 15 established scientists in the field of visual neuroscience, with intentional inclusion of investigators from diverse personal and scientific backgrounds and career stages. The initial steps of building the consortium have proceeded through 3 developmental phases. In phase I, participants worked through an iterative consensus-based process to define the most pressing questions and challenges that need to be addressed to bring vision-restorative treatments for optic neuropathy to clinical translation. Phase II included a 1-day hybrid workshop during which breakout sessions dedicated to specific topics of discussion were held, with an aim to brainstorm innovative tools and experimental approaches to meet these challenges while fostering opportunities for collaborative scientific investigation among diverse investigators. Now in phase III, the RReSTORe consortium holds regular virtual and in-person symposia dedicated to key topics in RGC repopulation while preparing for its next in-person workshop.

Herein, we describe the organization, structure, and activities of the RReSTORe consortium in detail. In addition, we present the results of a participant survey aimed at quantifying the perceived impact of the consortium over the course of its first year. We intend for this detailed description of the consortium to be informative not only to those actively working in the field of optic nerve regeneration, but also to those considering the development of similar large-scale international consortia aimed at achieving audacious goals in ophthalmology and vision science.

Methods

Organizing Committee

The RReSTORe organizing committee was formed through direct conversations among colleagues working in the field of regenerative medicine and developmental neuroscience as applied to ophthalmology and vision science. After the assembly of a small group of like-minded investigators (T.V.J., P.B., C.A.M., J.L.G., and D.Z.), the organizing committee was expanded to a total of 15 scientists with consideration directed specifically at gender balance; career stage balance; inclusion of basic, translational, and clinical scientists; and a strong track record of mentorship of trainees and junior scientists (Appendix S1, available at www.ophthalmologyscience.org). The organizing committee met virtually approximately once per month through the concept-building phase of development, which lasted for 6 months.

General Membership

Invitations to participate in the RReSTORe consortium were disseminated broadly and prioritized inclusion. Our goal was to unify a diverse group of scientists with a shared interest in RGC repopulation and optic nerve regeneration. To that end, invitations were sent to society listservs, university graduate programs, and funding agencies, with encouragement for broad dissemination. A primary goal of RReSTORe has been to encourage and help develop the careers of trainees and early-stage investigators, based on the premise that the goals of the consortium may take years to attain and the investigators making key contributions in the future may only be in early stages of career development at this time. Therefore, we created 2 types of scientific membership: *Senior Investigators* included independent scientists with their own laboratories and *Emerging Vision Scientists* (EVSs) included trainees of all stages and junior faculty within the first 5 years of their first academic appointment. Identifying EVSs, as such, enabled us to create additional opportunities for involvement of this important class of participants (see below). We also invited representatives from agencies and foundations that fund eye and vision research. Inclusion as a participant in the RReSTORe consortium was open to anyone who responded with interest. Applicants were asked to provide contact information, basic demographic information (age, gender, underrepresented minority [URM] in science and medicine status) and a brief description of what he/she/they felt was the most pressing question or challenge in vision restoration for optic neuropathy.

Subtopic Discussion Groups

Given the depth and breadth of scientific expertise needed to attain functional RGC repopulation in models of optic neuropathy, we divided the content for discussion and areas of potential collaboration into 5 subtopic discussion groups (SDGs, Fig 1). Two or 3 organizing committee members were assigned to lead each of the SDGs, based on their scientific expertise. The RReSTORe participants self-selected to contribute to 2 SDGs each.

Phase I: Iterative Consensus Building to Identify and Prioritize Questions and Challenges Relevant to Functional RGC Population

To collate a comprehensive list of topics to be addressed by the consortium, the membership engaged in a process of iterative consensus building from January through April, 2022 (Fig 2). The process began with a 1-hour virtual webinar held on January 24, 2022, during which time the goals and organization of the consortium as well as instructions for phase I were disseminated to the membership. At that time, a 3-week request for submissions was opened, wherein each participant was asked to submit $\geq$ 1 discussion topic for each of the 2 SGDs to which they had self-selected and that was relevant to vision restoration for optic neuropathy. Participants provided a 1-sentence descriptor and a 2- to 4-sentence summary of their submitted topic including an explanation of its importance to the field.

After the initial call for submissions, organizing committee members reviewed all entries. Organizing committee members were masked to the identity and career stage of all submitters to

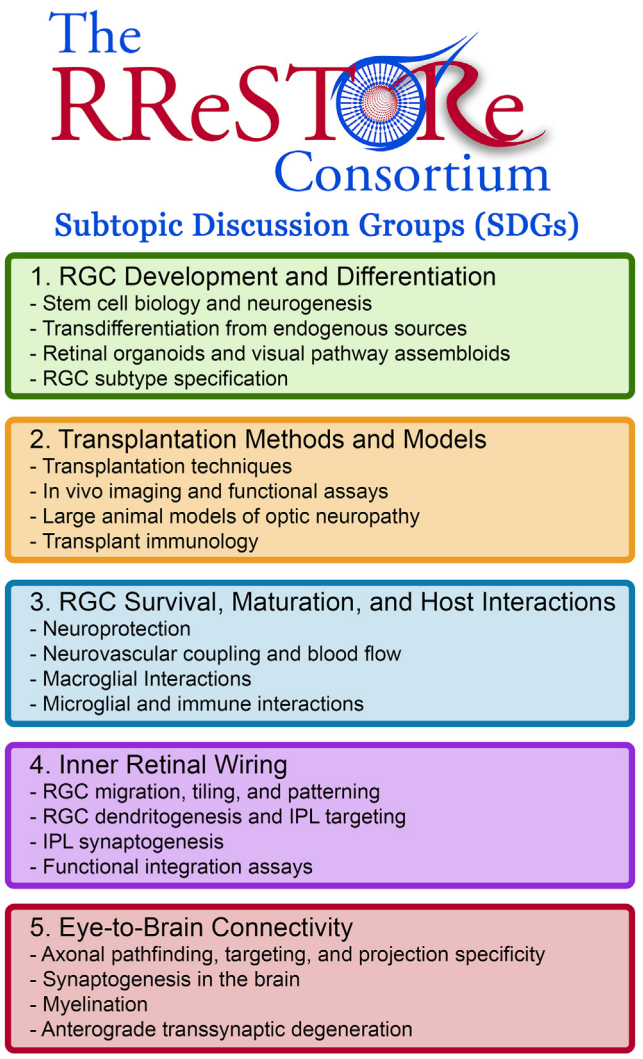


Figure 1. Subtopic discussion subgroups. The Retinal Ganglion Cell Repopulation, Stem Cell Transplantation, and Optic Nerve Regeneration (RReSTORe) consortium is conceptually divided into 5 subtopic discussion subgroups (SDGs). Examples of topics pertinent to each SDG are provided. IPL = inner plexiform layer; RGC = retinal ganglion cell.

reduce the risk of bias for or against specific ideas. Duplicate or highly overlapping submissions were distilled into unique topics and assignment of topics to specific SDGs was made to minimize content overlap between SDGs. A collated list of discussion topics summarizing some of the most important unanswered questions and challenges in the field of optic nerve regeneration (Appendix S2, available at www.ophthalmologyscience.org) was then redistributed to the membership, organized by SDG and with removal of identifiers pertaining to submitting participants. During a review period of 3 weeks, participants were asked to review the proposed topics within their self-selected SDGs. For each submitted question/challenge, members were asked to: (1) rate their level of enthusiasm for that topic on a 10-point Likert scale; and (2) provide written feedback on the perceived value (or lack thereof) of addressing the question/challenge(s) raised in that submission. Based on the enthusiasm scores and written feedback from participants, the organizing committee selected the top 5 topics for each SDG to be discussed in detail at the 2022 RReSTORe workshop (Appendix S3, available at www.ophthalmologyscience.org).

Phase II: The RReSTORe Workshop

On April 30, 2022, the RReSTORe workshop was held in Denver, Colorado, immediately preceding the annual meeting of the Association for Research in Vision and Ophthalmology. Participants were encouraged to attend in-person and the majority of attendees were present on-site, though a hybrid option was made available. The schedule included a 30-minute introductory and orientation session with all participants, followed by a series of small group discussions held concurrently by each of the 5 SDGs. The introductory session set expectations regarding professionalism in interactions, encouraged open discussion and data sharing, and highlighted the EVS participants by encouraging the more senior participants to meet and have discussions with the more junior participants.

Each SDG participated in 5 separate discussions, each centered on 1 specific topic identified in phase I (earlier) and lasting for 60 minutes. Discussions began with a 10-minute introduction by 1 or 2 invited experts in the field who provided background information necessary to engage in high level discussions about the topic at hand. The remaining 50 minutes were spent on in-depth discussion among the participants, led by 2 moderators. Moderators were specifically asked to encourage active participation from the EVSs. Thus, a total of 25 small group discussions were held over 5 hours, with each of the 5 SDGs running their sessions simultaneously. Participants were free to attend the SDG topic discussion of their preference. Each SDG was attended by 2 EVSs that were designated as scribes, to take notes during discussions. Video and audio recording of breakout discussions were not permitted, to promote an open and uninhibited environment for discussions and sharing of data and experience. Participants were able to share unpublished data in person or through the virtual meeting platform.

Time for informal discussions was built into the schedule and included 15 minutes between each small group discussion and 1 hour for lunch. At the end of the day, all participants reassembled for a 45-minute summary session, during which time moderators from each SDG reviewed the most salient points raised during the day's discussions. The workshop concluded with a 30-minute closing session, which informed participants of plans for the future. These plans included a series of virtual discussion sessions and symposia (phase III).

For those not able to attend the RReSTORe workshop in person, a virtual option consisted of live-stream webcasts of the opening and closing plenary sessions, and each of the 25 small group discussions. Virtual participants were able to view a wide-field camera feed of the room and/or slides presented via PowerPoint. They were also able to participate in discussions through audio-feed or an online chat that was monitored by the moderators. The opening and closing sessions of the workshop, which included all participants, were video recorded and are available on the RReSTORe website (below).

To ensure that EVSs would have the resources necessary to attend the RReSTORe workshop in person, funding for travel grants was provided by several bodies including the NEI (R13EY034018), The Glaucoma Foundation, the Glaucoma Research Foundation, the BrightFocus Foundation, and the Gilbert Family Foundation. Emerging vision scientists applied for travel grants by providing contact and demographic information (including self-identification as an URM), submitting a curriculum vitae (CV), and describing in $<$ 100 words: (1) how participation in RReSTORe would contribute to their research career; and (2) what they think is the most important challenge, question, or area to be studied to advance clinical translational of vision restoration

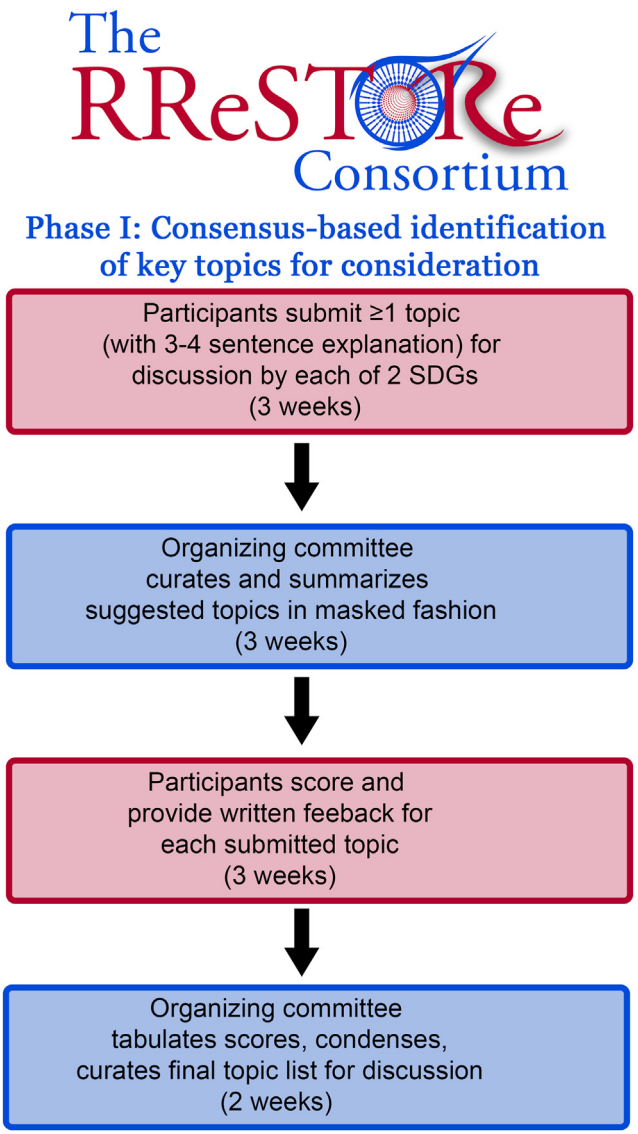


Figure 2. Workflow for phase I: consensus-based identification of key topics for discussion. Tasks performed by the organizing committee (blue) and the membership (red) are described, along with relevant timelines. RReSTORe = Retinal Ganglion Cell Repopulation, Stem Cell Transplantation, and Optic Nerve Regeneration; SDG = subtopic discussion subgroup.

therapies for optic neuropathy. The RReSTORe organizing committee members reviewed the entries stratified by training stage. Students, postdoctoral fellows, and junior faculty were reviewed separately. Committee members with conflicts of interest recused themselves from reviewing individual abstracts. At least 2 organizing committee members scored each application on 5-point Likert scale and the top applications within each training category were awarded travel grants.

Phase III: Virtual Discussion Series

To maintain collaborative momentum after the workshop, RReSTORe has hosted a series of live virtual discussions focused on key topics from the workshop that were found to be of particularly high interest. Discussion sessions are held via Zoom and are led by ≥ 1 senior investigators with expertise in the selected topic(s). Participants join discussions via the meeting function (rather than the webinar function), to encourage active participation during a 45-minute presentation followed by a 45-minute discussion session. Virtual discussions are video recorded and are available on the RReSTORe website (below).

RReSTORe Website

To provide a single location in which to curate information about the RReSTORe consortium, announcements about upcoming events, and recordings of virtual meetings, a website was created (http://rrestore.info). The website is updated regularly with the names of members, announcements, video recordings of virtual discussions, and milestone achievements of the consortium.

Participant Survey

To gauge the impact of the RReSTORe workshop for individual participants, an online survey was administered using Qualtrics. Survey questions are listed in Appendix S4 (available at www.ophthalmologyscience.org). Participation in the survey was invited on October 25, 2022, and reminders were sent 3 times before closing the survey on February 13, 2023. The survey compiled some demographic data but was permitted to be anonymous for submission of responses related to the participant's experience in the RReSTORe workshop. At the end of the survey, participants were given an option to contribute toward a white paper manuscript describing the discussions held at the RReSTORe workshop, which collected optional contact information. Differences in Likert scale question responses were compared between senior investigators and EVSs using 2-tailed, unpaired *t* tests.

Summary of RReSTORe Workshop Discussions

After the RReSTORe workshop, each of the 10 EVS scribes (2 per SDG) were asked to compile their notes from the meeting. These EVSs were then asked to work in pairs to draft a 3- to 5-page summary of the discussions from the SDG in which they participated, with organizing committee SDG leaders serving as active mentors in this process. The EVSs were then asked to combine their summaries into a comprehensive white paper that described the content of the RReSTORe workshop discussions, and focused on outstanding questions that remain to be answered or key technical or experimental challenges that need to be overcome to propel the field forward.

Phase I: Iterative Consensus Building to Identify and Prioritize Questions and Challenges Relevant to Functional RGC Repopulation

After collection of question/challenge submissions from RReSTORe participants, organizing committee members collated submissions in a masked manner and merged similar questions/challenges together. In total, we received 183 submissions, of which 102 came from EVSs and 81 came from senior investigators. Narrowly focused but related questions were combined to develop more general topics that could support ≥ 60 minutes of intense discussion, often with several subquestions. The final list of collated questions/challenges is presented in Appendix S2.

The list of curated topics was then returned to participants who were asked to rate their level of enthusiasm for that topic on a 10-point Likert scale and to provide comments and suggestions for revision. Subtopic discussion groups 1, 3, and 4 presented 5 potential topics each, whereas SDGs 2 and 5 presented 7 potential topics. In general, enthusiasm for all potential topics was high, with mean enthusiasm scores ranging from 7.0 to 8.4 (Fig 3). Within each SDG, there were no significant differences in enthusiasm

scores when comparing individual topics ($P > 0.05$ by 1-way analysis of variance for all SDGs). In addition, the scores generated by senior investigators and EVSs were similar for every topic proposed ($P > 0.05$ by 2-tailed, unpaired t test for all topics).

Based on these results, the organizing committee selected the 5 highest-scored topics for each SDG and further revised the content based on the feedback from participants. These served as the agenda for discussions at the RReSTORe workshop on April 30, 2022 (Appendix S3).

Phase II: The RReSTORe Workshop

A survey evaluating the experience of participants at the RReSTORe workshop was completed by 165 people, representing 76% of RReSTORe members at the time. The respondents included 97 men (59%) and 68 women (41%). The ages of participants ranged from < 25 years old to > 61 years old (Fig 4A). In total, 36 (22%) respondents self-identified as URM in science and/or medicine, 115 (70%) did not self-identify as URM, and 14 (8%) preferred not to answer. There were 28 respondents (17%) who were based outside of the United States, including in Australia, Belgium, Canada, China, France, Pakistan, Qatar, Romania, Spain, Sweden, Ukraine, and the United Kingdom.

Participants in the workshop included 158 vision scientists, 6 representatives from grant funding agencies or foundations, and 1 representative from industry. Of the vision scientists, 74 (47%) identified as established, independent investigators and 84 (53%) as EVSs. Among independent investigators, 8 were assistant professors, 19 were associate professors, and 43 were full professors, with an additional 4 listing their rank as senior scientist, senior research associate, or medical doctor. Among EVSs, there were 11 graduate students, 4 medical students, 34 postdoctoral research fellows, 2 clinical residents, 3 research associates, 5 lecturers or instructors, and 25 assistant professors within 5 years of their initial appointment.

We awarded a total of 46 travel grants to the 69 EVSs who applied, a 66.7% funding rate.

Participants engaged 2 SDGs each, and SDGs contained a range of participants, from 48 in SDG #4 (Inner Retinal Wiring) to 87 in SDG #3 (RGC Survival, Maturation, and Host Interactions; Fig 4B).

One hundred twenty-seven of the survey respondents participated in phase I of RReSTORe by submitting ideas for questions and topics to be discussed at the workshop, submitting comments or criticisms on proposed lists of topics, and voting for the final list of discussion topics. One hundred three respondents attended the RReSTORe workshop in person and 35 participants attended virtually.

Survey respondents were then asked a series of questions to evaluate their opinion of the content at the RReSTORe workshop. Respondents overwhelmingly agreed that "discussions at the RReSTORe workshop covered the most relevant questions and challenges related to RGC repopulation and vision restoration for optic neuropathy" (Fig 5A). Most respondents also agreed that discussions at the RReSTORe workshop "raised new questions that are important for the field to consider" (Fig 5B) and that they "helped to generate new and innovative ideas for addressing important questions and challenges in the field" (Fig 5C).

Survey respondents were then asked about the perceived value of the workshop to their own work and careers. Most respondents felt that participation in the RReSTORe workshop "facilitated engagement in new scientific collaborations" (106/135 responses, Fig 5D), or "prompted new scientific questions, experiments, and/or research areas that I will explore in my own work" (114/134 responses, Fig 5E).

Survey respondents were asked about the scientific and collaborative environment at the RReSTORe workshop. Most respondents agreed that the RReSTORe workshop "fostered an open and inclusive atmosphere" (128/135 responses, Fig 5F). Among independent investigators, the majority agreed that the RReSTORe workshop "enabled me to interact with and develop relationships with EVSs in the field" (45/56 responses, Fig 5G) and among EVSs, the majority agreed that the RReSTORe workshop "enabled me to interact with and develop relationships with senior investigators in the field" (66/72 responses, Fig 5H). Emerging vision scientists also felt overwhelmingly that "participating in the RReSTORe workshop was valuable to my future career in vision science" (70/72 responses, Fig 5I). All respondents indicated that they were planning to continue their participation in the RReSTORe consortium (Fig 5J).

Phase III: Virtual Discussion Series

To date, 3 virtual discussion symposia have been held by the RReSTORe consortium. On September 22, 2022, the topic of discussion was "Lessons learned from photoreceptor and RPE transplantation" and was led by Drs. Ed Stone, Budd Tucker, and Ian Han (University of Iowa) and Dr Kapil Bharti (NEI). On January 4, 2023 the topic of discussion was "Updates on RGC repopulation from endogenous sources," led by Dr Levi Todd (University of Washington). On June 6, 2023, the topic was "Transsynaptic degeneration at visual centers in optic neuropathy: implications for regeneration" led by Drs. Josh Morgan and Phil Williams (Washington University School of Medicine in St. Louis). Video recordings from each discussion are available on the RReSTORe website.

One-Year Impact on Scientific Experimentation and Collaboration

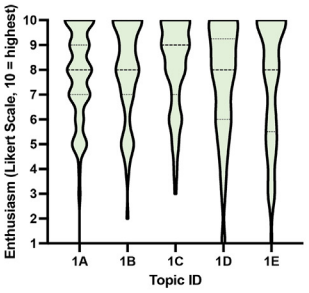
Respondents were asked open-ended questions about new collaborations or avenues of scientific research taking place within their laboratories which they directly attributed to their participation in RReSTORe. Among the 165 respondents, 43 described new ideas, experiments, or projects that they planned to pursue within their laboratories as a result of participation in RReSTORe. There were 26 investigators who acknowledged a new collaboration that arose from participation, and 7 who felt that RReSTORe had helped strengthen existing collaborations. Four new research grants have been submitted since the in-person RReSTORe meeting. In addition, 2 members noted having organized local conferences on the topic of vision restoration for optic neuropathy after participating in RReSTORe.

Discussion

The RReSTORe consortium was established to encourage thought sharing and experimental collaboration among an international group of scientists with diverse backgrounds and expertise. Though sharing of preliminary research findings within a consortium may run the risk of unverified results driving future experimental directions, open discussion of late-breaking science in this context has the benefit of speeding dissemination of important data to those best positioned to act on it while also providing a forum for real-time peer-review of such data. In describing the structure and early impact of this consortium, we hope to substantiate the enthusiasm that exists within the scientific community for the development of prospective treatments capable of restoring vision for patients with optic neuropathy. Moreover, we aim to detail the methodologies we employed to

Proposed discussion topics

A



SDG #1: RGC Development and Differentiation

1A: What is the current state of the RGC development and differentiation field?

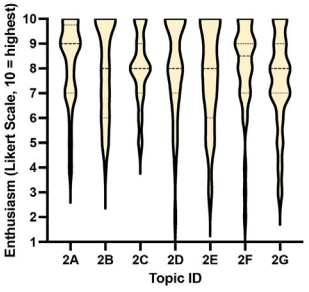
1B: How do RGCs develop normally in various species, and how can this information be leveraged for therapeutic RGC repopulation?

1C: What are the relative strengths and weaknesses of approaches to creating new RGCs and how can we improve upon current methods?

1D: How can we create and engineer RGCs for successful transplantation?

1E: How can we leverage Muller glial transdifferentiation for RGC replacement?

B



SDG #2: Transplantation Methods and Models

2A: What preclinical models will be needed to adequately study RGC repopulation?

2B: What are the optimal sources and characteristics of RGCs for transplantation?

2C: To what extent does the host immune response affect donor RGC survival and engraftment?

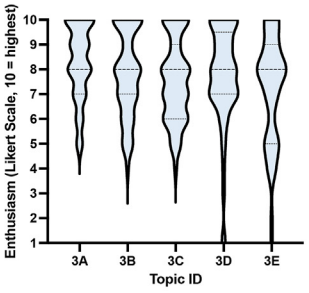
2D: What surgical transplantation strategies will maximize RGC survival and engraftment?

2E: What are the relative strengths and weaknesses of RGC transplantation vs endogenous transdifferentiation?

2F: What should be the outcomes or metrics by which RGC repopulation success is evaluated?

2G: Moving beyond the ILM: what modifications of the host recipient visual pathway will augment RGC engraftment?

C



SDG #3: RGC Survival, Maturation, and Host Interactions

3A: What are the RGC-intrinsic factors that affect long-term survival following injury and transplantation?

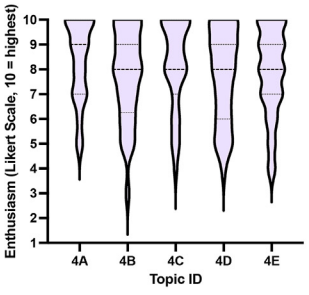
3B: How can we modify the recipient retinal environment to augment donor RGC survival?

3C: What is the best way to assess appropriate maturation and functional integration of repopulated RGCs?

3D: What is the role of other retinal or optic nerve cells in driving RGC transplantation efficacy?

3E: What are the clinical and translational considerations for successful RGC transplantation, integration, and function?

D



SDG #4: Inner retinal wiring

4A: What are the RGC-specific intrinsic signals required for successful integration and connectivity to inner retinal circuitries?

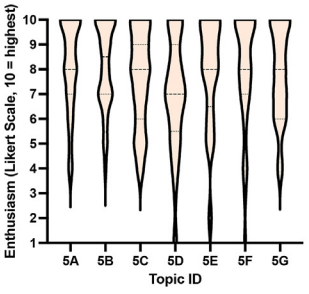
4B: What are the local microenvironmental (RGC-extrinsic) signals required for successful integration and connectivity to inner retinal circuitries?

4C: The diseased RGC: how do optic nerve injuries alter endogenous RGC structure and connectivity in the IPL, and what are the implications for RGC repopulation?

4D: The diseased IPL: How does the IPL environment change in optic neuropathy and how will this affect integration of repopulated RGCs?

4E: Studying and modulating the host retina: Can we modify the inner retinal environment to enhance functional integration of repopulated RGCs?

E



SDG #5: Eye-to-brain connectivity

5A: How can we get axons to regenerate long distances?

5B: How do we direct axons to navigate to their appropriate targets to maintain topographic maps?

5C: Are regenerated synpases in the brain anatomically/functionally normal?

5D: Are there particular central targets or RGC subtypes that need to be prioritized?

5E: What is the best model(s) to study regeneration of RGCs and how can we leverage collaborative endeavors to produce better models?

5F: What role do glia play in axonal regeneration?

5G: Is there a critical period for regeneration of connections to occur?

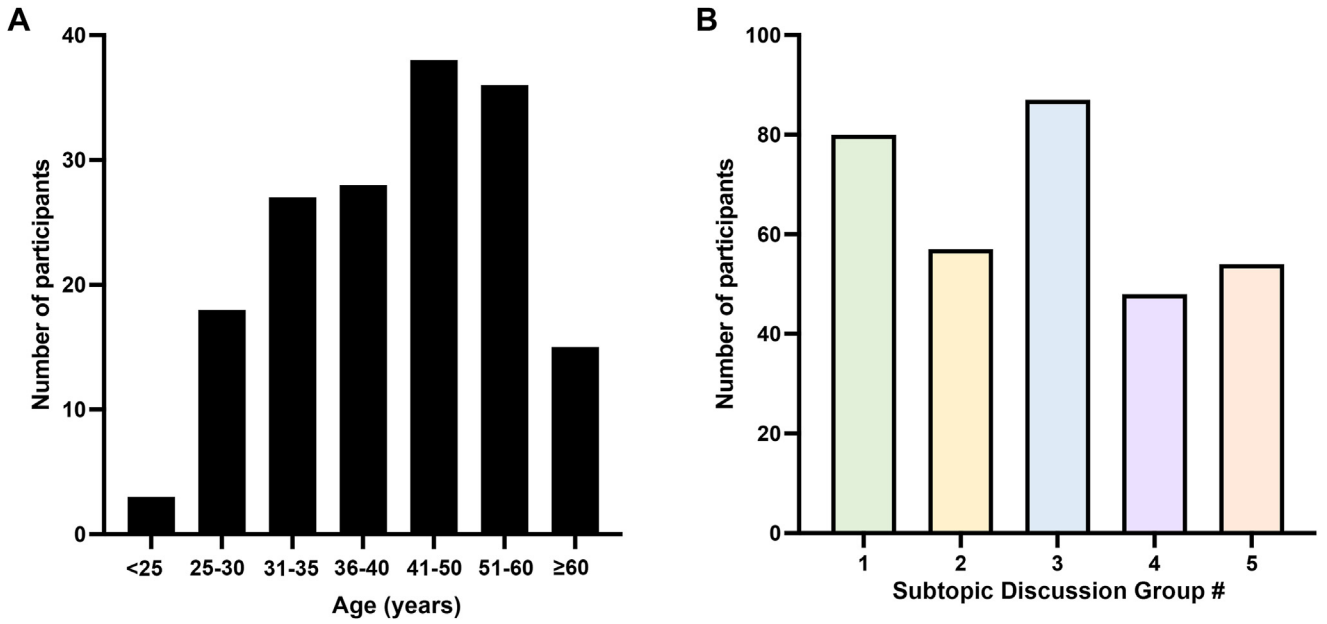


Figure 4. Age and subtopic discussion group (SDG) membership of survey respondents. **A,** To maintain anonymity, age was binned by 5 or 10 years. **B,** Refer to Figure 1 for SDG names and example topics.

construct a robust and unbiased collaborative group that effectively helps to establish new experimental approaches and ideas capable of propelling the field while also supporting the early career development of EVSs. We anticipate that investigators interested in establishing similar consortia focused on achieving other audacious goals in ophthalmology, vision science, and/or neuroscience may be inspired or learn from our experience.

Large research consortia have been successful in advancing cutting-edge biomedical science across many emerging disciplines.[12] Differences in structure and activities among consortia are largely related to their unique goals and scientific areas of focus. For example, the International Human Epigenome Consortium (www.ihec-epigenomes.org) began in 2009 and established goals to "coordinate the production of reference maps of human epigenomes for key cellular states relevant to health and diseases, to facilitate rapid distribution of the data to the research community, and to accelerate translation of this new knowledge to improve human health."[13] Over the subsequent 8 years, the International Human Epigenome Consortium generated > 7000 data sets relevant to their work, analyses of which were described in a series of 41 seminal papers published in coordinated fashion.[14] The SARS-CoV-2 Assessment of Viral Evolution Program[15] was established to explore emerging viral variants and their impact on immunity and vaccine protection, and has provided timely data related to coronavirus viral evolution and resistance tracking.[16–20] It is clear that large research consortia have the potential to make significant impacts in their fields. We hope that by engaging in regular data sharing and experimental brainstorming, and by fostering opportunities for large-scale collaboration, RReSTORe will contribute similar levels of success to ophthalmology and vision research.

Recent advances in several fields, including developmental neuroscience, stem cell biology, biomedical engineering, optics, electrophysiology, gene therapy, and molecular biology have now converged to the point that vision restoration for optic neuropathy may be feasible. Indeed, it is likely that successful therapeutic paradigms that restore vision loss from optic neuropathy in human patients will require input from these and other scientific fields. Given the breadth and depth of the contributions required from these disciplines, it is certain that collaboration among experts with diverse expertise will be necessary as the field advances. For instance, the RReSTORe consortium has identified development of biocompatible scaffolds for epiretinal implantation of RGCs as a priority area of focus. Designing, fabricating, validating, and implanting such scaffolds will require cooperation among biomedical engineers and material scientists, stem cell biologists,

Figure 3. Enthusiasm scores for proposed discussion topics in phase I. After curation and summary of all submitted discussion topics submitted by Retinal Ganglion Cell Repopulation, Stem Cell Transplantation, and Optic Nerve Regeneration (RReSTORe) members (see Appendix S2 for full descriptions and subtopics), members reviewed the proposed topics and submitted enthusiasm scores, based on a 10-point Likert Scale where 1 represented no enthusiasm and 10 represented highest possible enthusiasm. **A,** Topics for subtopic discussion group (SDG) #1: Retinal Ganglion Cell (RGC) Development and Differentiation. **B,** Topics for SDG #2: Transplantation Methods and Models. **C,** Topics for SDG #3: RGC Survival, Maturation, and Host Interactions. **D,** Topics for SDG #4: Inner Retinal Wiring. **E,** Topics for SDG #5: Eye-to-Brain Connectivity. Violin plots of enthusiasm scores are shown. Dashed lines, median. Dotted lines, interquartile range. ILM = internal limiting membrane; IPL = inner plexiform layer.

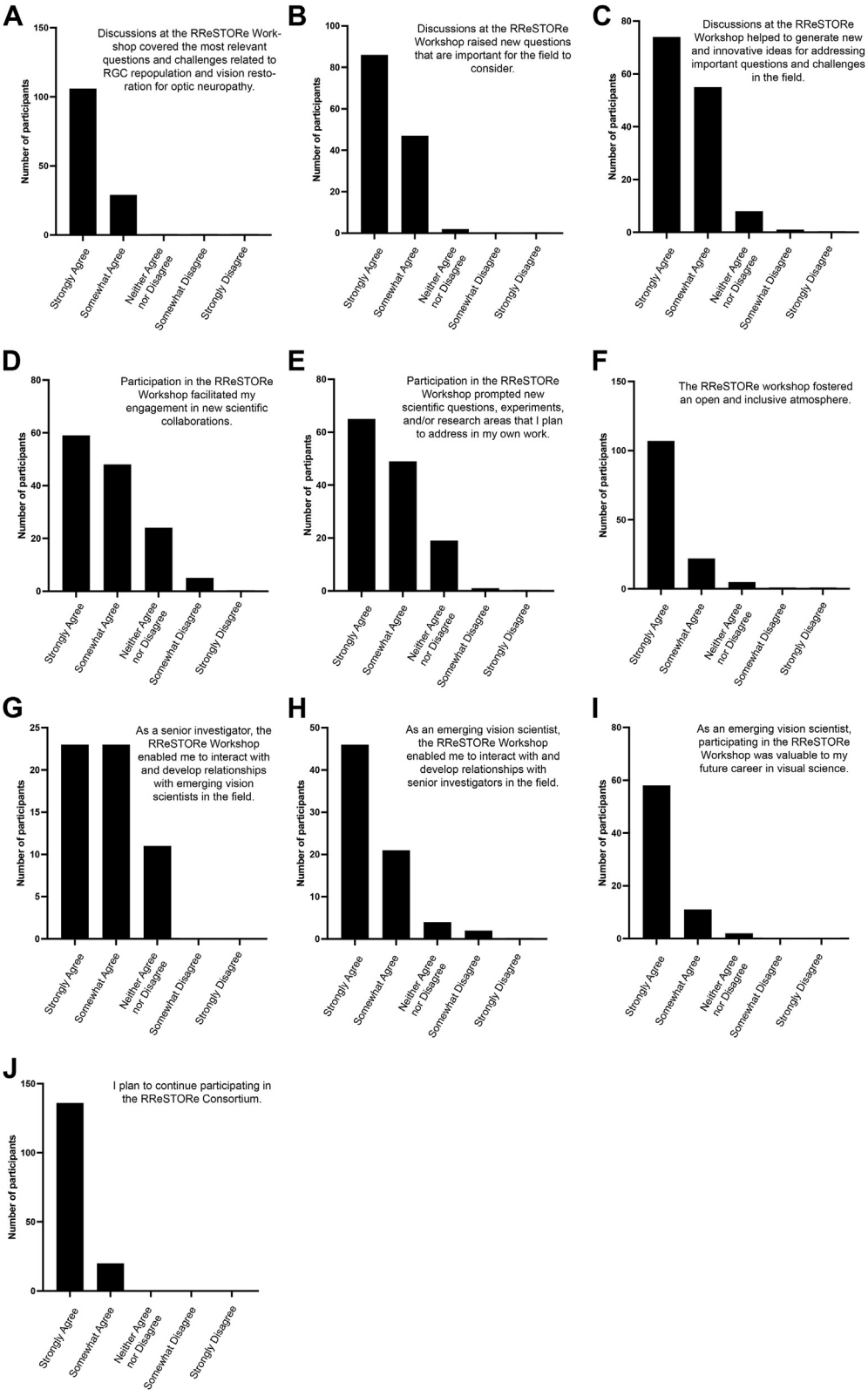


Figure 5. Results from 1-year impact survey. Respondents were asked to rate their level of agreement with the indicated statements (**A**-**J**) on a 5-point Likert scale, with 1 representing "strongly disagree" and 5 representing "strong agree." Refer to Appendix S4 for survey questions. RGC = retinal ganglion cell; RReSTORe = Retinal Ganglion Cell Repopulation, Stem Cell Transplantation, and Optic Nerve Regeneration.

neuroscientists, and vitreoretinal surgeons. Another area of priority research is the in vivo visualization of transplanted neurons, which will require input from optical engineers, neuroscientists, and molecular biologists. Fostering these new collaborations is therefore a top priority for the RReSTORe consortium. To that end, we were pleased to receive feedback in our 1-year survey suggesting that dozens of new collaborations and several new grant applications were generated over the past year, and the participants who disclosed those activities in large part attributed the success of developing these new collaborations and grant proposals to their participation in RReSTORe. Formalizing an approach to support collaborations through seed funding will be a major goal of the consortium in the immediate future.

A central tenet in designing the RReSTORe consortium has been to encourage involvement from EVSs while supporting their career development and research efforts. Indeed, as the goals of the consortium and the regenerative medicine field are ambitious, we anticipate it will take several years before the first clinically applicable techniques for RGC replacement become available. Moreover, it is likely that techniques to optimize the function of diverse RGC subtypes with an array of function-specific intraretinal and central circuits will evolve over decades. Therefore, supporting the interest, training, and careers of early-stage investigators in this field is a critical investment into the future of our work. We employed several strategies to help achieve these goals. First, we sent calls for participation widely to and requested dissemination from national and international research societies, funding agencies that award career development grants, and graduate programs in biomedical science. Second, we provided travel grants to EVSs who wished to attend the RReSTORe workshop in person. Third, we specifically encouraged EVSs to participate in discussions and for more senior members of the consortium to reach out to and meet EVSs during the workshop. Fourth, we established specific roles for EVSs such as taking notes during the workshop discussions and translating their notes into a comprehensive review paper on the subject of vision restoration for optic neuropathy, with dedicated mentorship from Organizing Committee members. As the consortium continues to evolve, we aim to create leadership and organizational positions in which EVSs can serve. By encouraging involvement from EVSs and providing early career support, we hope that these future leaders in the field will dedicate at least a portion of their work to the scientific goals established by the RReSTORe consortium.

The RReSTORe consortium recognizes and embraces the importance of diversity, inclusion, and equity in all scientific endeavors. We recognize that increased diversity reduces implicit bias and increases the heterogeneity of opinions expressed during discussion. Studies have shown that manuscripts written by scientific teams with gender diverse authors have significantly higher citation rates than those with gender homogeneous authorships.[21] We believe that racial diversity similarly results in higher quality science. Ensuring gender equity and inclusion of underrepresented minorities is, and will continue to be, a principle at the foundation of our consortium.

It is critical that RReSTORe continues to highlight the importance of sustainability. Although many scientific research consortia have made significant contributions to advance their respective fields, there are examples of others that have, unfortunately, failed to live up to expectations. By learning from the experiences of other consortia, we aim to ensure sustainability and long-term goal attainment for RReSTORe. In analyzing $>$ 50 research consortia and large collaborative research organizations, Cutcher-Greshenfeld et al[12] identified key traits of successful consortia. These include providing mechanisms for interaction beyond institutional silos in a bottom-up rather than top-down fashion, rigorous engagement of the membership to cultivate a shared vision, adapting to diverse and evolving interests, fostering cooperative endeavors to enable large-scale projects that could not be completed by individual laboratories or small groups of investigators while avoiding duplication of effort, and coevolving with technological advances in science, data analysis and interpretation, and medicine. We have structured RReSTORe to conform to these principles, with regular in-person and virtual meetings that engage investigators of diverse career stage, scientific expertise, personal background, and geographic location; regular requests for feedback from the membership to the Organizing Committee; a consensus-based approach to organizational activities with input provided from the entire membership; plans for structured mechanisms to provide future seed grant funding for collaborations among consortium members; and plans to create a mechanism for rotation of organizing committee members.

The development of innovative interventions capable of restoring vision for patients suffering from optic neuropathy would be transformative for the ophthalmology field and may set the stage for functional restoration in other central nervous system disorders. We are convinced that the field is at an inflection point, where the availability of state-of-the-art technology will make this goal achievable in the coming years. By coordinating large-scale, international collaborations among scientists with diverse and complementary expertise, we are confident that the RReSTORe consortium will help to accelerate the field toward clinical translation.

The RReSTORe consortium invites participation from diverse investigators interested in the topic of RGC repopulation (regardless of career stage, scientific expertise, personal or professional background, or geographic location) to join. For information about joining the consortium, please contact the corresponding author or visit http://rrestore.info.

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Abbreviations and Acronyms:
EVS = emerging vision scientist; **NEI** = National Eye Institute; **RGC** = retinal ganglion cell; **RReSTORe** = Retinal Ganglion Cell Repopulation, Stem Cell Transplantation, and Optic Nerve Regeneration; **SDG** = subtopic discussion group; **URM** = underrepresented minority.

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