Philanthropic Opportunities for LHON

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Overview

LHON Collective engaged the Milken Institute's Science Philanthropy Accelerator for Research and Collaboration (SPARC) in 2023 to evaluate challenges and opportunities in the Leber hereditary optic neuropathy (LHON) field. Specifically, SPARC assessed where philanthropic investment in research and development could have the greatest impact in transforming the LHON therapeutic landscape. SPARC conducted a systems-based review of the current LHON research ecosystem using a detailed analysis that integrated knowledge from the peer-reviewed scientific literature, interviews with nearly 70 subject matter experts, analysis of government and nonprofit funding trends, and a two-day scientific retreat held in February 2024. Through this analysis, we identified four high-priority opportunities where philanthropic investment and partnership could have a transformative impact:

(1) Collect natural history data and biological samples in open-access repositories
(2) Develop research tools for the field, beginning with models
(3) Fund basic discovery and drug repurposing research to advance the therapeutic development pipeline
(4) Invest in platform tools and technologies to align with other disease areas and raise awareness of LHON

A brief description of each opportunity follows, including information on the resources required (i.e., investment budget, operational considerations, timelines) to unlock that opportunity and achieve its objectives. Advancing any of the priority areas identified will help create favorable conditions to accelerate research and discovery in LHON therapeutics. Some opportunities have overlapping objectives; all are important factors for de-risking translational research and attracting industry partners to bring more and better therapeutics to market.

LHON Opportunity Map

(1) Collect natural history data and biological samples in open-access repositories

Patient data and biological samples are the foundation for understanding a disease, its underlying cause(s), natural progression, and informing hypothesis-driven research and clinical trial design. In LHON, biological samples are rare and the patient data that exist are fragmented across clinics and patient registries around the world. Among the existing patient data and biological samples, most have been collected without consensus standards or protocols. In our engagement with the LHON field, the need for a coordinated, large, prospective, standardized data set that includes clinician-reported data, patient-reported data, and biological samples—from affected and unaffected carriers—has been a recurrent theme.

LHON Collective has the opportunity to support the build of global repositories to collect clinician and patient-reported data and biological samples from affected and unaffected carriers using common data standards and consensus protocols for collection. Data may include demographics, clinical assessments, symptoms, quality of life surveys, environmental exposures, and other external factors that may modify disease course. Linked patient-derived biological samples could include post-mortem eye tissue, blood, saliva, urine, buccal, or skin and be used to generate genomic data (or other omics data, e.g., metabolomics) and patient-derived cell or organoid models. Post-mortem human tissues, including eyes, optic nerve, and brain, also have the potential to serve as critical resources to generate omics data, pathology data, or organoid models specifically from the affected cells and microenvironment. These tissues will most efficiently be collected in partnership with brain banks that recognize the value of collecting eye tissue along with brain tissue. Any data or resources resulting from banked tissue should be shared either through the LHON repository or in another manner that provides open access to researchers. The goal would be to establish a comprehensive repository anchored on foundational data-sharing agreements and systems; the repository data and samples would be made available for research. Through central support and management by LHON Collective, the organization can ensure that researchers around the world have streamlined access to the samples and data, preventing hold-ups based on individual institution policies or competitiveness.

Investing in such a repository will reduce duplication of efforts and data fragmentation and improve the consistency and completeness of the data, which are prerequisites for high-quality research. Patient and clinical data will be used for natural history studies to better understand the course of the disease and to identify secondary factors that predict penetrance and severity, reveal disease subtypes, find biomarkers with clinical and research applications, and inform clinical trial design and outcome measures. Achieving this objective will improve the field's understanding of the natural disease course and provide patient data as a baseline against which to validate disease models, compare therapeutic interventions, develop data-driven treatment strategies, and foster collaboration among clinicians, researchers, and industry stakeholders.

Approaches to building repositories

Following extensive brainstorming during the 2024 LHON retreat, we recommend establishing a unified framework for data and biological sample collection within open-access repositories. Such an initiative will meet the critical need for standardization, increased sample sizes, and greater diversity of samples from affected and unaffected carriers. Formalizing the collection process for both existing data that are currently siloed by institution and geography and new data and biological samples is paramount for conducting comprehensive analyses. Centralizing these resources in regional repositories offers the highest likelihood that the data and biological samples can be linked for downstream research. This nontrivial task necessitates cooperation and endorsement from multiple stakeholder groups, regulatory approval, and data security and privacy considerations.

To establish comprehensive patient data repositories and biorepositories, globally, we recommend the following activities:

1. Establish unified protocols and standards for harvesting, processing, and storing LHON-relevant post-mortem tissues, including the brain, optic nerve, and eyes, within existing brain banks. Cellular and molecular research for LHON is challenging due to limited adequate animal and cellular models. There is a significant opportunity to build out banks of

applicable post-mortem tissue for research purposes. With the need for high-quality fixed and frozen tissue specimens for research, specialized banks will be key for the standardized collection, characterization, storage, and distribution of eye tissue for research purposes. As the eye is part of the brain, brain banks are the optimal frameworks in which to collect eye tissue. In recognition of this, brain banks such as the Netherlands Brain Bank collect postmortem eyes for investigation of eye diseases such as age-related macular degeneration. A key opportunity in leveraging specialized brain banks lies in the fact that many operate within networks to enhance collaborations, optimize protocols, and increase the ability to fill requests for tissue for research. Examples of successful brain bank networks include BrainNet Europe, UK Brain Bank Network, The National Alzheimer's Coordinating Centre, NIH NeuroBioBank, and the Australian Brain Bank Network. Notably, the NIH NeuroBioBank combines human post-mortem brain tissue and related biospecimens with medical records and clinical data sets (when available) as well as access to quality metrics and best practices for tissue collection and processing used by each site, combining all critical data types into one open access repository. This framework could serve as a model for LHON Collective to move toward. Alternatively, LHON Collective and partners could advocate for inclusion of eye tissue within the NIH NeuroBioBank. Most brain banks operate according to best practice guidelines which will need to be established in collaboration with neuro-ophthalmologists should brain banks expand tissues collected to include eyes. Critical needs associated with supporting brain banks and ensuring efficient expansion of tissue types collected include:

1. Establishing effective methods of donor recruitment;
2. Careful training and coordination by brain bank staff to ensure appropriate consent to collect tissue;
3. Defining and ensuring standardized tissue collection methods that ensure optimal tissue quality considering the immediate and future uses of the tissue (for example, rapid autopsy and freezing of the optic nerve for pathological and genomic analysis);
4. Identifying critical data collection methods that will enable rapid digitization of biological sample data so that human tissue is saved and resulting data can be readily shared through an established LHON data repository (for example, performing DNA and RNA analysis on specific cells or tissues and openly sharing resulting data within a data repository will reduce duplicate requests for tissue to perform such analyses);
5. Performing standardized pathological assessment of the tissue collected; and
6. Defining a process for tissue requests and disbursement

The development, implementation, and maintenance of a brain bank are extremely costly. Estimates of the cost of brain banking vary between $10,000 and $30,000 per specimen banked and are predominantly related to personnel costs. Importantly, leveraging existing infrastructure and patient autopsies to add new tissue types rather than building independent eye tissue banks has the potential to greatly reduce the cost of collecting eye tissue. Moreover, other eye diseases will benefit from the inclusion of eye tissue collection in brain banks. Additionally, there is evidence that ocular changes precede neurodegenerative diseases such as Alzheimer's disease, and researchers are developing eye scan techniques to detect Alzheimer's disease before major symptoms appear. There is potential for eyes to enable identification of banked brains from patients earlier in the neurodegenerative process, enabling study of pre-symptomatic stages of the disease, a critical time in the development of neurodegenerative diseases. Expansion of brain banking to include eyes is an opportunity to collaborate with organizations that support research efforts for eye and neurodegenerative diseases.

According to their 990, in 2023, the Miracles In Sight non-profit eye bank funded approximately:

- $1.7M in surgical recovery and preservation of donor ocular tissue
- $4.8M in testing, evaluation, and distribution of tissue for transplant and research
- $1.9M in the screening, disclosure, authorization, and tissue recovery process

That year, the organization facilitated over 3,200 donations. Based on these values, the per-donation cost for eyes can be estimated at approximately $2,500. The ultimate cost will vary depending on the type of tissue collected, the analysis

performed on the tissue, and the processing and preservation of the tissue. Importantly, if eye donations can be aligned with brain donations, there is potential to share surgical recovery and screening costs and further reduce the cost of eye banking.

2a. Identify and gather existing patient data worldwide to build a unified retrospective data set. Existing data can be used as a baseline to set standards and consensus protocols and identify data gaps that should be addressed in future data collection. The most immediate way to do this is to build a data committee to landscape the current data ecosystem and conduct a data needs assessment. A data committee will prepare a template and request investigators/institutions with existing data contribute to its completion. A cost estimate for assessing the data landscape includes $1,000 per contributor to ensure timely and accurate sharing of available data, $1,000 per member of a data committee to support time spent on identifying the information to be requested of data contributors and coordinate a landscape analysis and development of a publication, and approximately $2,000 to publish the data landscape as a consensus statement and call to action for the field to standardize data and biological sample collection. Overall, this effort should not exceed $25,000 and the final cost will be dependent on the number of institutions that collect LHON patient data and/or biosamples.

2b. Establish open-access data and biorepositories across global regions to gather longitudinal clinician and patient-reported data alongside biological samples from both affected and unaffected carriers. Researchers should use standardized data practices and consensus protocols (2a) for collection of new data to fill LHON data gaps and increase data quantity. The amount of capital required for establishing and maintaining repositories for patient data and biological samples will vary based on location, the number of patients and samples involved, and the project's stage; initial setup and data and sample collection typically incur higher costs compared to ongoing maintenance. Leveraging existing repositories with established sharing policies and infrastructure would significantly reduce the cost of collecting, storing, and sharing data. Based on the data landscape performed (2a), there is the potential for LHON Collective to identify data and/or biorepositories that are already collecting and sharing patient data and biosamples from LHON or other mitochondrial diseases or optic neuropathies with the potential to expand with dedicated funding. An open or targeted grant funding opportunity has the potential to optimize LHON data and sample collection without requiring the costly initial build of repository infrastructure. We recommend a funding opportunity of up to $500,000 to support the expansion of one or two existing repositories to fill data and sample gaps for LHON. This opportunity is not an immediate requirement if preceded by the development of a brain bank. Once processing and digitization of brain bank tissues is initiated and investigators begin to collect molecular patient data, tissue samples for model development, and process post-mortem tissue donations, an open-access repository that can collect and share samples, models, and data will be beneficial to the research community. Additionally, this opportunity can be scaled up over time or allow for the selection of additional global sites within a network to further enhance the volume of data and samples collected.

The collection, storage, and sharing of patient data requires care in consenting and collection, safeguards on data storage, and establishment of frameworks and systems that ensure patient protection from concerns such as identification and discrimination. Below, we consider two different options for the collection of LHON patient and carrier data:

- Solidify and optimize LHON Collective's **partnership with RARE-X** to manage data from multiple sources and identify a biorepository partner (recommended)
- **Partner with a research institution** to establish a patient data and biorepository

Both of the above options include a biorepository component, as outlined above. What differentiates the options is the type of organization that holds the patient data; either RARE-X, an organization with a preexisting relationship with LHON Collective and has an existing framework for collection of both patient-supplied and clinical data, or an institution or collaborative network capable of holding both data and biosamples.

Partnership with RARE-X

Based on current LHON Collective relationships and efforts, we recommend that LHON Collective prioritizes collection of patient clinical and natural history data in partnership with RARE-X. RARE-X collects research-grade data from patients using disease ontologies (i.e., controlled vocabularies for standardization) based on consultation with clinicians. RARE-X can

collect both patient-reported and clinician-reported data, but they do not have the infrastructure to store or manage biosamples. In our conversations with RARE-X, we discussed two major hindrances to data collection in the LHON community: (1) lack of funding to build out a data collection platform accessible to patients with low or no vision and (2) lack of consensus among experts on the most useful data to collect. The LHON Data Collection Program at RARE-X has collected data from more than 120 LHON patients around the world, and addressing the previously noted challenges has the potential to significantly increase the number of participants in the repository. RARE-X is a philanthropy-funded organization, and we recommend that LHON Collective provide targeted support and connections to experts in the field to create a LHON data and patient advisory committee to rapidly scale the expansion of the RARE-X LHON database. This database has the potential to provide information on patient trajectory, LHON plus symptoms, and natural history. All of which will be important to industry as clinical trials are pursued. Patient enrollment, therapeutic window, and endpoints can all be bolstered with enough appropriate data. As such, there is potential for industry to support efforts with RARE-X once preliminary benefit has been demonstrated. Compensation for advisory committee time should be provided by LHON Collective (approximately $1,000 per advisor for up to eight advisors). Appropriate contributions toward improvements in RARE-X platform accessibility and the addition of data types as determined by the advisory committee will need to be determined in collaboration with RARE-X. Information on individual organizational contributions toward RARE-X efforts are not listed in their 990 but estimates of improving accessibility range from $3,000 to $50,000. We would anticipate funding support to RARE-X not to exceed $50,000.

If LHON Collective is interested in pursuing RARE-X as a patient data repository, a biological sample repository site will need to be identified as biosamples are collected from patients. As RARE-X collaborates with the Broad Institute on data collection, data governance, and data sharing, it may be worth exploring options for building a biorepository at the Broad Institute or another organization with the capabilities to analyze and store samples and leverage or link RARE-X data. The appropriate partner could either be identified using a targeted grant mechanism or through field-wide discussion at repository-focused meetings.

Partner with a research institution

Academic medical centers and research institutes have the necessary infrastructure, expertise, and access to diverse patient populations to effectively collect, manage, and analyze patient data and biological samples. Patients and clinicians trust reputable institutions, which helps to lower one of the primary barriers to participation in research. As outlined above (2b), a research institution or network with the capability to house both clinical data and biosamples and data resulting from molecular assessment of those samples could be selected from among the institutions that are currently collecting LHON patient and tissues and express the capacity to expand their efforts with dedicated funding.

Considerations

To ensure efficient management and maximize impact, we recommend, as a first step, partnering with other eye disease and neurodegenerative disease organizations to expand tissue collection within either a single or network of brain banks to include eye, optic nerve, and other appropriate tissue as identified by researchers. The brain bank can serve as a foundation for tissue collection but will benefit from additional funding to support tissue processing, pathological analysis, storage, and distribution. As a first step, we recommend identifying brain banks with the willingness and capabilities to collect, process, and store eye tissue. Standardized collection methods can be established and a core set of analyses for tissue can be identified. Once a critical mass of healthy and affected and/or carrier eyes are banked, clustered DNA, RNA, pathology, and other analyses identified as important by researchers can be performed and data can be digitized and shared with researchers broadly. Digitization of data will ensure the protection of critical biosamples for future analyses as molecular technologies evolve. Moreover, a linked data repository will be necessary as tissues are processed and data are digitized. There is significant potential for digitized pathology to provide ample data that can be processed and analyzed using artificial intelligence methods.

In concert with brain bank efforts, we recommend convening clinicians and investigators experienced in LHON patient data collection to establish consensus guidelines and protocols for patient data and biological sample collection. This convening

may also be used to prioritize sample and data collection, set clinical leads who will be responsible for protocol development for each sample or data type, and weigh biorepository and data network requirements to establish specific criteria for participation to vet potential partners. As natural history data will be an immediate benefit to industry, it will be a key need for early funding streams. Early optimization of the RARE-X platform for the collection of LHON data will enable expansion of that data set. Early successes, such as benefits to patient recruitment for clinical trials or identification of meaningful endpoints will signal the utility of this resource to industry and likely result in additional supportive funding from that sector.

Once the LHON data landscape has been clarified and data collection priorities have been set, established repositories can be identified through either a competitive or targeted application process to receive funding for LHON-specific efforts to support data and biosample expansion. Ultimately, any new therapeutic development will benefit from patient samples, so in establishing repositories, a stipulation of funding should be that data and samples are accessible to both academia and industry.

Data management and curation are essential to the quality and utility of a repository. Challenges often arise with data and sample sharing between clinicians and scientists, potentially necessitating funding for multiple centers in different geographic regions. The complexity of data management will escalate with the addition of more centers, necessitating an increase in the number of regulatory sponsors and data access agreements. It can be challenging for investigators outside a medical center or research institute to access internal data and biological samples for research; it is imperative that data sharing and access agreements guarantee open access.

Partnering with a pharmaceutical company as a financial sponsor or co-funder may be worth pursuing. Leveraging NIH programs for natural history studies may offer additional financial support for investigators in subsequent phases of research.

(2) Develop research tools for the field, beginning with models

Model systems are the backbone of an efficient and productive therapeutics pipeline. Cell and animal models, organoids, and human tissues each contribute something unique along the path from basic discovery through preclinical development. Perturbation experiments in models can demonstrate how mutations and other genetic variations or secondary factors impact biochemistry and drive pathogenic mechanisms. Such experiments lead to a better understanding of the disease and make it possible to figure out how to counteract disease mechanisms to prevent, treat, or reverse a disease process and—further down the path—to assess safety and efficacy of experimental therapeutics. The LHON field has developed fibroblasts, cybrids, patient-derived induced pluripotent stem cell (iPSC) models, and a handful of mouse models, each recapitulating some aspect of the disease, to study Complex I biochemistry and the effects of select therapeutics. However, there is consensus among academic investigators and drug developers that more and better-suited models are needed, including those derived from human eyes and retinas, to support an efficient and productive end-to-end research and development therapeutics pipeline for LHON.

LHON Collective can play a pivotal role in supporting a global disease model research network to catalog and characterize existing *in vitro* and *in vivo* models and develop and validate new models of LHON. New models would cover more mutations and types of genetic variation and expand available model systems, e.g., zebrafish, organoids, *in silico* models, and *ex vivo* models. The goal would be to establish a core set of well-characterized and validated LHON models that recapitulate all key aspects of the disease, including bilateral loss of vision, variable penetrance, and male preponderance. Models would be made openly available to the research and drug development communities to support mechanistic and translational research.

A disease model research network will be able to determine the strengths, opportunities, and needs for models to support a productive therapeutic pipeline and ensure the core set of models are representative of LHON patients. Development of new models will further support basic discovery, compound screening, mechanism of action studies, and preclinical testing. Achieving these objectives will accelerate therapeutic discovery and development by helping identify disease mechanisms,

drug targets, and biomarkers, and enabling rapid testing of hypotheses and validation of early discoveries and experimental therapeutics across a variety of systems. Importantly, a thorough understanding of mechanism of disease and factors that contribute to conversion will pave the way to developing preventative measures. Prevention is a strategy not often pursued by industry but has the potential to revolutionize the patient experience. LHON could serve as a model for prioritizing prevention, given the incomplete penetrance of disease and the potential for recovery seen in some patients.

Approach to developing a global disease model network

Creating a comprehensive and reliable set of LHON models requires collaborative efforts within global research networks. Global research networks serve as a conduit for sharing expertise and resources for advancing a disease area. Such networks can take various forms: they may be formal entities with a centralized agenda and distributed work plans or informal collaborations among independent investigators or collaborative working groups with aligned research interests and goals. Participation in these networks offers opportunities to coordinate efforts, share resources, and validate research findings—a particularly vital aspect in model development. For a LHON model to be useful, first, it must accurately recapitulate one or more clinical or pathological features of LHON, second, the molecular and cellular mechanisms underlying these features must be determined, and only then can a model be validated for use in drug development. Sharing knowledge and resources across a disease model network while moving through these stages can yield significant benefits. It not only reduces costs and accelerates the pace of research but also offers valuable insights into various aspects of the biology of disease.

Based on our evaluation of the LHON field's readiness for discovery and translation, we recommend funding grants for precompetitive collaboration to serve as the foundation for establishing a global research network dedicated to disease models. A disease model network will meet the critical need for more and better-suited models to support a therapeutic development pipeline. Given the diverse array of models anticipated to be required to faithfully replicate the clinical manifestations and pathological features of LHON, and the varying expertise necessary for their development, a research network is the most streamlined approach. Through sharing knowledge and expertise, the network will create a core set of validated models that capture disease heterogeneity and meet the needs of investigators doing experimental work from discovery through preclinical development.

The amount of capital required to establish a global disease model network will vary significantly based on the complexity of the model systems involved. Several LHON investigators shared that there are unpublished mouse model(s) that have not yet been shared with the research community during our one-on-one discussions. Based on these reports and the high value of these models for the field, we recommend initially focusing on the characterization and validation of existing mouse models and building out human tissue bank(s), zebrafish, and organoid models, all of which are scalable and amenable to high-throughput screening. Supporting a network of three to four investigators dedicated to model development would significantly benefit the field. While the amounts awarded may vary, we recommend up to $100,000 per investigator, per year with expectations of model development commensurate with the grant size. To start, we recommend funding three grants per year with 2-year terms corresponding to an annual budget of up to $300,000 and totaling up to $600,000. Eventually, this can build to an optimized grant program that funds four grants per year with 3-year terms, corresponding to an annual budget of $400,000 and totaling $1.2M.

A reasonable timeline to establish a disease model network is on the order of 6 months. Creating a competitive grant process will require assembling a Scientific Advisory Board (SAB) and putting out an open call for grant proposals that will be vetted by peer review and LHON Collective leadership. Model development and characterization will take 2-3 years.

Considerations

The long-term vision for a global LHON model research network is a diverse group of researchers that are pursuing the development and validation of a variety of disease models and shares data and findings about those models freely. In addition to providing funding to develop and validate these models, the program should prioritize funding terms that

requires sharing and collaboration as well as budget to bring investigators together to foster greater resource and knowledge sharing. Additionally, we recommend prioritizing an advisory committee to provide long-term oversight, direction, and input on the selected projects.

(3) Fund basic discovery and drug repurposing research to advance the therapeutic development pipeline

Basic discovery (e.g., mechanisms of pathogenesis) and drug repurposing research have complementary roles to play in the drug discovery process. Mechanistic research provides the foundational knowledge for identifying key molecular pathways that drive disease and/or promote resilience and may point to biomarkers and drug targets, inform therapeutic strategies, and contribute to our understanding of other mitochondrial diseases or forms of neurodegeneration. Mechanistic knowledge can also be used in drug repurposing to select compound libraries and the most appropriate screening assays to conduct high-throughput small molecule screens. These screens use disease models, e.g., fibroblasts or zebrafish, biochemical assays, and computational methods to systematically identify existing small molecule compounds for activity against the mechanisms that drive disease. While investigators know *what* is happening to cause vision loss in LHON, the underlying mechanisms of how and why it is happening have not been discovered yet. During the LHON Scientific Retreat, the field acknowledged many gaps in mechanistic understanding, including those related to:

- Retinal ganglion cell (RGC) structure and function and the contribution of their microenvironment to health and disease
- Mechanisms of RGC cell death
- Mitobiogenesis and mitophagy
- Inflammation
- Neuroprotection
- Identification of biomarkers (risk of conversion, disease progression, target discovery, treatment efficacy, recovery)

LHON Collective can play a key role in supporting foundational basic discovery and drug repurposing research. This funding will create a collaborative, interdisciplinary research ecosystem where investigators are focused on the most critical early discovery knowledge gaps in the field. The goal would be catalyzing a productive and diversified therapeutic pipeline that offers more and better treatment options to prevent, halt, and reverse vision loss in LHON patients by creating a research network dedicated to unraveling the complex biological mechanisms underlying disease and identifying drug targets and potential drug candidates more efficiently. In addition to predicting what will work, such a knowledgebase will contribute to understanding translational failures putting a cycle of continuous improvement in motion.

Our funding analysis demonstrated that government funding for LHON research outside of gene therapy is limited and small one-off grants from foundations have not been sufficient to fill the gaps. This was confirmed as we heard from investigators around the world that a major barrier to progress in LHON research is access to sufficient and sustained funding. Developing a strategic funding mechanism to support foundational research and drug repurposing sets the stage for data-driven therapeutic discovery and expedited translation. Achieving this objective will create an efficiency loop where mechanistic research informs high-throughput drug screening, and drug candidates identified by high-throughput screens can be validated by and inform mechanistic studies.

Approach to developing a funding mechanism

Basic science and interdisciplinary collaboration are often what lead to breakthroughs and paradigm shifts in a field—getting there requires reliable funding. We outline a funding approach that would foster interdisciplinary collaboration and commitment to shared goals to advance foundational research and drive therapeutic development.

Research consortium

Grant programs allow for complete assessment of the capabilities of a team and vetting and refinement of project ideas. Additionally, they are an effective way to identify the most suitable members to build a focused research consortium. A research consortium is a formalized collaboration built on a shared set of research objectives and goals. Members of a consortium can be individuals, institutions, and government or industry stakeholders. Consortia are beneficial to researchers because they provide opportunities to collaborate with people and institutions that may otherwise be outside their own professional networks. For funders, especially those with a research agenda, consortia are beneficial because the framework fosters cooperation across diverse stakeholders to promote speed and efficiency, and an opportunity to set and enforce data collection and sharing standards. Consortia can also provide training, skill building, and mentorship opportunities to young investigators to increase capacity and build a talent pipeline within the field.

Grantmakers intending to build a consortium can choose to open applications to all investigators and institutions or to restrict eligibility to a pre-selected applicant pool. An open application will naturally be more competitive and attract applicants with a diversity of experiences and scientific backgrounds who may bring innovative ideas to the field. A targeted solicitation should be used when it is clear that there are leaders in the field that are most appropriate for the program's priorities. Investigators awarded grants in this framework will be required to abide by data collection and sharing standards and participate in the consortium to contribute to and benefit from knowledge and resource sharing.

Based on our evaluation of the LHON field's readiness for discovery and translation, a grant-based research consortium will meet the critical need for funding to support basic discovery, address the many gaps in mechanistic knowledge, and build a collaborative, interdisciplinary research ecosystem to catalyze drug discovery and repurposing research. Most grants provide two to five years of funding, depending on the goals of the program. Considerations for building a grant-based research consortium include:

(1) Scientific scope and applicant eligibility
(2) Scientific advisory board and strategic management
(3) Scientific review and selection process
(4) Community building within the funded investigator cohort
(5) Partnerships and agreements to support translation

The amount of capital required to support a grant program varies depending on the scientific scope, duration, and number of grantees awarded per cycle. Awarding five grants would be impactful for the field with the possibility to scale over time based on the evolving research landscape and patient needs. The amounts awarded may vary. We recommend $150,000 per grant, per year, over three years. This corresponds to an initial annual program budget of $750,000. In addition to direct grant funding, budgetary considerations should include compensation for an SAB (ranging from $2,000 - $5,000 per person, per year, depending on their engagement and scope of the program), peer reviewers (typically compensated at a rate of $100 per grant reviewed for their service), and an estimated $50,000 for an optional funded investigator meeting.

A grant program could be launched as early as the fall of 2024, following the establishment of an SAB that will work with LHON Collective to set the scope and refine the scientific strategy. If launched in the fall, we would expect funded research projects to commence in Q3 of 2025.

Considerations

We recommend taking a grant-based research consortium approach for LHON because the field has historically been small and self-contained. A consortium offers a way to integrate new investigators, ideas, and technologies, fostering innovation and expanding the research community's capabilities. Using a grant program to build the consortium enables investigator-led projects to drive the science while allowing for flexibility and a diversity of approaches in addressing key research questions. As the research landscape evolves and LHON Collective matures, there may be future opportunities to shape projects more directly in alignment with internal scientific strategies.

This is an opportunity to spearhead the development of the first LHON research program. To maximize the impact of this initiative, LHON Collective may want to join forces and networks with one or more other funders, in which case exploring potential partnerships and foundational synergies should happen during the development phase.

It is important to note that basic discovery and drug repurposing research both rely on a variety of model systems. Discovering a drug candidate without appropriate models for validation and preclinical testing will bring development to a stop. Another option would be to collapse the second the third opportunities to create a single consortium with three internal tracks: (1) model systems, (2) disease mechanisms, and (3) drug repurposing.

(4) Invest in platform tools and technologies to align with other diseases and raise awareness of LHON

Academic scientists and biotechnology companies are working on pan-disease tools and technologies that could reinvent the research and discovery pipeline and therapeutic landscape. For LHON, this includes optimizing the delivery of gene therapies, gene editing, cellular reprogramming, cell replacement therapy, and AI for drug discovery and development. LHON is in the sights of a few gene therapy and gene editing endeavors, but as a rare disease, it may not have the name recognition or market potential on its own to attract scientists and companies looking for use cases for their technologies. LHON does, however, sit within multiple disease families, including mitochondrial diseases, optic neuropathies, and neurodegeneration, that together comprise a significantly larger patient population to become a compelling use case and entry point for multi-indication therapeutics.

LHON Collective has the ability to either invest in platform technologies and/or highlight these platforms among organizations and funders who might mutually benefit from their development. Investing in these areas will ensure that these research tools and treatments are available to the LHON field and patient community. The goal would be to accelerate and harness emerging biotechnologies by forging mutually beneficial relationships with their developers. This relationship may include financial support for preclinical or clinical development and easing the path to translation and commercialization by providing access to patients and patient data. Investments have the potential to create financial returns while also supporting the advancement of therapeutic interventions for LHON and aligned diseases.

During the LHON Program Retreat in 2024, participants highlighted and prioritized promising therapeutic modalities with significant potential to benefit LHON and other diseases if optimized for efficacy and safety. These included:

- Gene editing (CRISPR vs zinc finger nucleases, for example)
- Regulation of mitochondrial dynamics (biogenesis, axonal transport, mitophagy)
- Regenerative medicine, including cell-targeted gene therapy to reprogram muller glial cells into retinal ganglion cells
- Retinal ganglion cell therapy
- Gene therapy with improved and proven RGC tropism, mitochondrial import, and integration of wild-type protein into the protein complexes of the electron transport chain (this may involve development of new viral vectors, new mechanisms for gene expression, or new delivery methods)

Investing in platform tools and technologies and aligning with various disease areas can increase efficiency and cost-effectiveness, broaden therapeutic options, and position LHON as the gateway to addressing unmet medical needs across diseases, thereby benefiting multiple patient populations simultaneously. Achieving these objectives will advance scientific knowledge and potentially bring new therapies to market and/or overcome current limitations of therapeutics in development not only for LHON but also for related diseases. This approach not only establishes credibility and a positive reputation but also attracts more investors and other stakeholders for future endeavors.

Approaches to investing in multi-indication therapeutics

Investing in innovative tools and technologies requires matching the funding mechanism to the situation, vetting partnerships, and balancing financial risk and return. We outline three approaches to provide financial support to biotechnology companies or other product-driven research initiatives:

- **Grants** to fund product-driven preclinical research
- **Contracts** to fund specific research and development tasks
- **Equity investments** to accelerate research and development with the possibility of financial returns

Grants

Companies and other research organizations or initiatives are eligible to apply for grants (see Grant program). Grants can be used to fund a wide variety of research, from basic research to clinical trials. Grants that fund research with a clear path to translation, commercialization, or clinical application may include language that requires sharing intellectual property (IP) and/or right of first refusal to buy or license any resulting products.

Funding for these activities could easily fit within a scientific funding program as outlined in priority three. Initiatives such as the Gilbert Family research initiatives have utilized a mix of grants to academic institutions and biotech companies to accelerate research in the field.

Contracts

Contracts are agreements with companies and other research organizations to perform specific research and development tasks. Contracts typically have a defined scope of work and set deliverables, milestones, and financial terms. Examples of research activities funded by contracts could include creating a novel cell or animal disease model using a proprietary gene editing technology, leveraging an AI tool to predict drug efficacy, optimizing the formulation of an experimental therapeutic, or conducting a clinical trial.

Similarly, contract or project-based funding to a biotech company can be used as an approach to several of the aims above. Within our recent portfolios, BD2 has utilized a blend of grants and milestone-based contracts to provide targeted tools and services to the research consortium.

Equity Investments

Investments can also be made directly in a company (or through a vehicle like a venture philanthropy fund) in exchange for an equity stake. This comes with the potential for financial returns and input into business decisions. In therapeutic research and development, equity investments are often made in promising drug candidates and platform technologies to accelerate their development and commercialization. Investing in the earliest stages and getting to proof-of-concept can attract follow-on investors from venture capital, biotech, or pharmaceutical companies.

Based on our interactions with investigators and clinicians in LHON, and those in aligned biology and disease areas, building partnerships through investment will meet the critical need for bringing novel tools and technologies to a field that, historically, has been constrained by a lack of capacity to innovate due to its small size and limited access to funding. Key examples include optimized vectors for gene therapy, innovative therapeutic delivery methods, and novel cell therapy options. Investments in companies or research initiatives that are pursuing a commercial product require a different level of due diligence than funding discovery or knowledge-generating research to ensure the deal is fair and mutually beneficial. Figuring out at which stage to invest and what type of investment to make will depend on the needs of the recipient and the funder; investments can be used for preclinical and clinical research, regulatory approval, and commercialization efforts. We recommend establishing a global advisory board that has a business advisory committee and a mission alignment committee for governance over investment decisions. Alternatively, LHON Collective could leverage an

established venture program with aligned goals, such as The Mito Fund at UMDF, to assist with diligence and funding strategy.

The amount of capital required to invest in biotechnology companies and other product-driven research initiatives will vary based on the stage of the research. Early-stage or seed funding, typically directed toward proof-of-concept studies, requires smaller investments compared to clinical trials and commercialization efforts. While some nonprofit disease foundations have cited investments in the range of $200K to $2M, there are no strict upper or lower limits. Non-repayable grants usually come with a predetermined dollar amount, while contracts for specific deliverables may be negotiable but typically have a baseline cost. Equity investments are tailored to each case, involving calculated risk assessment and negotiation.

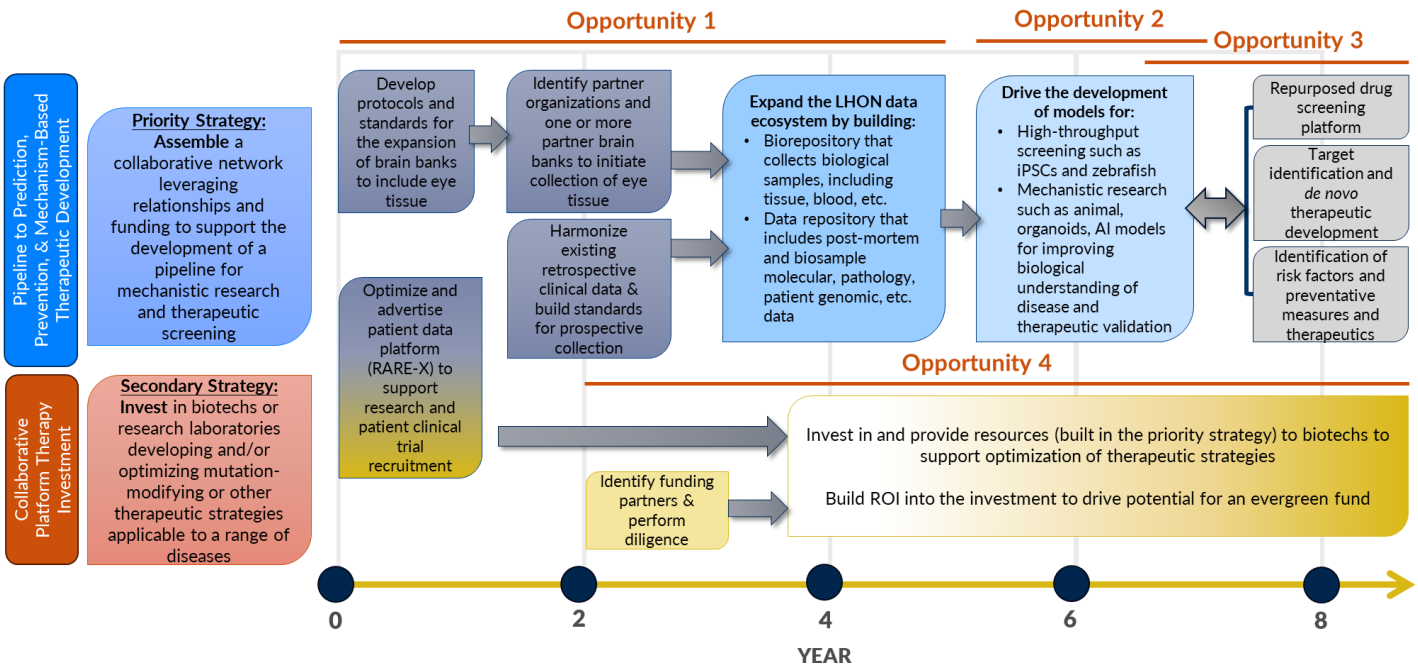
Select investments can be made immediately following due diligence. Establishing a global advisory board to weigh in on a broader investment strategy could take several months to a year and would require defining the purpose and responsibilities of the board, recruiting advisors with a diversity of expertise, and establishing operating procedures. Investment decisions can advance quickly following these steps, offering the potential for more immediate impact despite the acknowledged risks.

Considerations

Investing philanthropic dollars in for-profit companies or product-driven research requires decision-making that is informed by diverse perspectives and grounded in the realities of the field; an advisory board should be comprised of people who can deliver these perspectives. Beyond vetting scientific feasibility, investments in product-driven research also require considering regulatory requirements and market dynamics to mitigate risk. Additionally, prioritizing capacity-building initiatives and collaborative partnerships can multiply resources and expertise, strengthening LHON's Collective's ability to drive impactful investments. Lastly, guiding investment decisions towards initiatives that not only generate financial returns but also advance the foundation's broader philanthropic goal to bring more and better therapeutics to LHON patients is critical for long-term alignment.

Conclusions and next steps

LHON Collective has the opportunity to become the global hub of a sustainable, interdisciplinary, patient-centric research ecosystem. Four high-priority opportunities where philanthropic investment and partnership could have a transformative impact have been outlined. Important to the development of LHON Collective's strategy is understanding how the components of each opportunity might build on one another. For example, while biorepositories are natural pipelines for iPSC model development, there is an opportunity to build partnerships between existing repositories, for example, BRAIN UK and RARE-X to support patient-derived tissue and cell models while also simultaneously supporting the development of zebrafish models, which are not dependent on patient samples. This would shorten the runway to drug screening and therapeutic development by producing important foundational research and drug development tools as the LHON research ecosystem is capable. The below graphic outlines the anticipated timeline and order of program build based on the foundational opportunities presented in this opportunity map. Determining which partners to leverage and when, as LHON Collective leads the build-out of a research and therapeutic development pipeline, will be another key part of the strategy. Leveraging existing frameworks and developing partnerships to align on the opportunities presented will accelerate progress with the potential to increase the scope and scale of the research ecosystem.



A key component of each of these opportunities is building out appropriate expertise and consensus to drive efforts in a manner that will maximally benefit the research ecosystem. Once LHON Collective has identified strategic priorities, a scientific advisory board should be convened to provide insight into optimizing the identified strategy of the organization. Next steps will likely require consensus-building to drive aligned efforts across clinical and research sites and across countries. These processes can be taken on over a six-month period, enabling rapid implementation of a well-defined strategy with ample buy-in from the research community.