RUNX1 Research Program

Request for Proposals

Overview:

RUNX1 Research Program (RRP) is requesting proposals from investigators who are interested in sharing existing clinical and sequencing datasets from research-consented *RUNX1*-FPD individuals/families in an ethics-approved database called the "Inherited Hematological Conditions Database: IHCSdb." This collaborative multi-institutional effort will enable comprehensive retrospective analyses across a large, diverse patient population cohort. Furthermore, the data collected will be made accessible to scientists, clinicians and other interested research groups.

Background:

RRP is a non-profit organization with a mission to improve the quality of life and prevent blood cancer in patients with *RUNX1* familial platelet disorder (*RUNX1*-FPD). RRP previously funded the RUNX1 databse (https://runx1db.runx1-fpd.org/), the world's largest and only interactive public web-based international collaborative database. This centralized repository of germline *RUNX1* variant information, associated next-generation sequencing data and expert-curated variant information is expanding to include clinical data. Additionally, the platform will also be made available for the collection of data for other hereditary hematologic malignancies, hence the new name IHCsdb. Detailed information about the database can be found in Appendix A.

Purpose:

RRP recognizes that collecting and entering clinical and genomic patient data across multiple timepoints requires significant time and focused effort. Thus, RRP aims to provide financial support to allow clinicians and researchers to dedicate time toward this effort. RRP is interested in supporting investigators who are committed to improving our understanding of *RUNX1*-FPD. There are three tiers of support designed to reflect the volume of information entered per patient medical record. Tier 1 will provide $250 per patient report, Tier 2 will provide $500 per patient report and Tier 3 will provide $750 per patient report. Criteria for each tier are listed below.

Tier 1:

Per Patient:

- Enter general patient clinical metadata (listed as required in Table 1)
- Include between 1-4 clinical timepoints

- Upload de-identified PDFs that contain data requested in Table 1 instead of abstracting and entering data into fields for the clinical and treatment records.

Tier 2:

Per Patient:

- Enter general patient clinical metadata (listed as required in Table 1)
- Include between 1-4 clinical timepoints
- Enter complete data into the relevant fields for clinical and treatment records. PDFs may be uploaded in addition to entering data in the fields.

Or

- Data requirements as per Tier 1 if ≥5 clinical timepoints

Tier 3:

Per Patient:

- Enter general patient clinical metadata (listed as required in Table 1)
- Include ≥4 clinical timepoints
- Enter complete data into the relevant fields for clinical and treatment records. PDFs may be uploaded in addition, but all data fields must be complete to entering data in the fields.

Table 1:

Metadata Categories	Key Data Fields
Consent information: *Must enter into database.	- Investigator email - HREC approval # - Study Site - Specific consent requirements (Yes/No) - DUO Data Use Permissions - Total number of patients - Do you confirm that the patient/patients have signed appropriate consent required for their de-identified data to be stored in the database? (Yes/No) - Acknowledgement of consent requirements
Case Management: *Only required for the proband.	- Is this individual the index case (Yes/No) - If a family – upload a de-identified pedigree at a minimum - Family history: Enter clinical phenotype terms i.e. MDS, Thrombocytopenia etc. - Publications: Enter pubmed ID and patient reference if previously published
Patient Info:	- Family ID - Patient ID - Is patient in the NIH Natural History study (Yes/No/Unknown) - Patient Clinical group: o Patient Broad Group (relating to hematological condition) - dropdown menu o Select relevant subcategories defining condition selected o Select outcomes 3 years after diagnosis (if applicable) – dropdown menu

	- Patient demographics:
	  o Broad affected Status
	  o Sex
	  o Year of birth
	  o Life status
	  o Ethnicity (if available)

<u>Germline Variant:</u>	- Germline Gene Symbol - Clingen allele ID (if known) - Allele origin - Tissue used for testing - Reference genome - Variant coordinate

<u>Clinical Record:</u>	- Clinical record date
	- Disease status at time of report (broad)
	- Clinical diagnosis/Findings:
	  o Enter a brief clinical summary for the patient
	  o Enter at least one clinical term: i.e. AML
	- Upload de-identified PDF of clinical records for any of the clinical categories:
	  o History, Exam, CBC, diff, platelets, coagulation profile, general path, other bloods, BM exam, cytogenetics/Molecular status/BM flow

<u>Treatment Record:</u>	- Date treatment started - Patient age category – dropdown menu - Disease being treated - Select Record contents: Supportive care, Medications, Transfusions, Chemotherapy, Stem cell transplant, clinical trials, and other treatments - Fill in basic information or upload a de-identified pdf with details of the treatment

<u>Somatic Analysis:</u>	- If somatic data is available, at a minimum:
	  o Select disease stage of somatic analysis (dropdown menu)
	  o Age of individual
	  o Either fill in variant details or upload a de-identified pdf with details

Application Guidelines:

1. Submit an application in PDF form that is typed, **<u>single-spaced, 11-point Arial type with one inch margins</u>**.

2. Submit the materials listed below, in the order they are listed:

   - **Grant Application Cover Page**
     - Applicant/PI Name, Title, Institution, Department, Mailing Address, Phone, Email

- Institutional Signatory Name, Title, Department, Mailing Address, Phone, Email
- Financial Officer Name, Title, Department, Mailing Address, Phone, Email
- Institutional Review Board (IRB) Contact, Title, Mailing Address, Phone, Email

- **Applicant Experience**
  - Summary of the Applicant/PI's clinical experience diagnosing and managing *RUNX1*-FPD patients, including descriptions of key members of their local clinical team and their expertise. The summary should also include interest in participating in *RUNX1*-FPD research enabled by the data collected in the IHCSdb, as well as any future research endeavors expanding beyond *RUNX1*-FPD.
- **Patient Data Details**
  - Details on the number and comprehensiveness of medical records from *RUNX1*-FPD individuals and families who have been consented to share their de-identified data for research. Please indicate how many individuals are still under care at the institution to date.
- **Confirmation of Local Ethics Approval (i.e. IRB-Approval)**
  - Applicant/PI must acknowledge that each identified patient record has an associated research consent form that includes the sharing of personal and health information with researchers and research databases. If the applicant/PI plans on consenting new patients for research to participate in this IHCsdb initiative then they may use the electronic consent within the database.
- **Timeline**
  - Provide specifics on the level of data entry (Tier 1, 2 or 3) planned for each patient record.
  - Define the total time needed to complete data entry for the entire cohort identified. Please provide the number of complete records that can be successfully entered within quarter-year blocks.
- **Budget Requested**
  - Based on the defined funding levels (Tier 1, 2, 3) calculate the total funding requested over the total time period, as well as the total spend per quarter.

Application Deadline: April 30, 2024 at 8:00 pm PT.

- **Email a single PDF document to info@runx1-fpd.org with cc to kkorgan@runx1-fpd.org**

Appendix A

Inherited Hematological Conditions Database: IHCSdb

A collaborative clinical and genomics database for inherited hematological conditions

Database vision: *C*ollaboration between clinicians, diagnosticians and researchers, both nationally and internationally is imperative to facilitate accurate diagnosis, define clinical spectrums, understand genotype-phenotype relationships, and develop effective molecular monitoring and treatment strategies in rare disorders such as *RUNX1*-FPD and other inherited hematological conditions (IHCS). The database will act as a centralized resource for the collation, curation and continued accumulation of patient clinical and genomics data from individuals with inherited hematological conditions, providing a rich cohort that can be analyzed to better define our understanding of these disorders and develop better treatments and therapies for patients.

Specific Purpose: To collect existing clinical and sequencing datasets from individuals/families with germline mutations in known inherited hematological conditions predisposition genes, with the aim of allowing a comprehensive analysis and an accessible format for continued access and addition to the data for scientists, clinicians and other interested parties.

Database Structure: The IHCS-database structure consists of two interconnecting databases: A custom-designed REDCap Clinical database linked to the existing VariantGrid (VG) driven RUNX1db genomics repository and mutation registry (https://runx1db.runx1-fpd.org/snpdb/data) allowing linkage of clinical data/snapshots to patient genetic data.

> **The Clinical Database** is stored as a REDCap (Research Electronic Data Capture) database. REDCap is a secure, web-based application for data capture in research studies (Harris et al., 2009). The database is based on the Framework for Responsible Sharing of Genomic and Health Related Data, established by The Global Alliance for Genomics and Health (GA4GH)(Sept 2019).
>
> **The Genomics database** is a custom-designed cloud-based portal for the housing and analysis of de-identified genomics data. The database is housed as a virtual machine (VM) on a cloud-based server, with a set Security Group for each VM, allowing us to secure access and specify who can directly access the files on the system.

The IHCSdb specifics:

Contributing to the database:

1. Clinicians, diagnosticians and/or researchers **(Approved Investigators)** wanting to submit patient data will be responsible for ensuring that the patients have given informed consent to participate in research which includes the sharing of personal and health information with

researchers and research databases. This includes appropriate ethics approval from local institutions.

2. Data used in the database falls under: Secondary use of stored data, when the intended use falls within the scope of the original (broad) informed consent (According to the International Ethical Guidelines for Health-related Research Involving Humans Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)).
3. Consent forms and associated local institutional ethics approvals will be housed on a REDCap database forming the "study management registry". These will be reviewed and approved by the database custodian prior to approval for investigators to deposit de-identified patient data to the IHCS-database.
4. New patients can be recruited using the database-specific consent form.
5. Once Investigator access is approved, investigators will be able to input patient de-identified data including demographic, clinical data, and genetic testing via the REDCap survey function or REDCap form. All use of data will be related to the subject's anonymous identifier held by the local institutional investigator submitting the data.

Accessing the database: The database follows a controlled-access sharing model. Bona fide researchers will have the ability to access the de-identified data housed in the database. This will allow researchers to interrogate and query the data for the advancement of their research. Future uses of this data shall have the purpose of advancing the human understanding of Inherited hematological conditions and all related and potentially related factors and information.

- Data access will follow the registered access policy model as set out by the GA4GH (S. O. Dyke et al., 2016; S. O. M. Dyke et al., 2018) and will be limited to bona fide researchers.

- Applications for access to and use of data held in the database will be considered by the Database Management Committee.

- Such applications will be reviewed by the committee for verification of user identity and training and required to sign an online agreement to data use conditions to maintain the security of the data provided and an assurance that it will not be passed to any third party.

- Use of data from the database for research purposes will have its own ethics approval granted by a duly constituted HREC and its own site authorisation by the relevant Research Governance Officer. Applications should refer to the database by name and ethics approval number.

Publication of results: All contributing investigators will have the opportunity to lead analysis of data housed in the database and drive manuscript development. Results published in peer-reviewed journals will include authorship by the investigators who have made significant contributions to the conduct of the study. Principal investigators will review the final authorship of any publication. Any publications, presentations or documents relating to this study, distributed outside of the database management committee will be reviewed and approved by the principal investigators.

Appendix B

Inherited Hematological Conditions Database: IHCSdb

Overview of Survey Structure and Collection Criteria

The IHCSdb survey is composed of 7 sub-surveys as defined by different REDCap collection instruments as outlined below:

Data Dictionary Codebook

Inherited Hematological Conditions Database (PID: 86)

27/02/2024 1:56pm

Instruments	Codes for Missing Data

	#	Variable / Field Name	Field Label *Field Note*	Field Attributes (Field Type, Validation, Choices, Calculations, etc.)	
Instrument: **Consent** (consent)			Enabled as survey		[collapsed]
Instrument: **Database custodian user review** (database_custodian_user_review)					[collapsed]
Instrument: **Case Management** (case_management)			Enabled as survey		[collapsed]
Instrument: **Patient Metadata** (patient_metadata)			Enabled as survey		[collapsed]
Instrument: **Germline Variant** (germline_variant)			Enabled as survey		[collapsed]
Instrument: **Clinical Record** (clinical_record)			Enabled as survey		[collapsed]
Instrument: **Treatment Record** (treatment_record)			Enabled as survey		[collapsed]
Instrument: **Somatic Analysis** (somatic_variants)			Enabled as survey		[collapsed]

A detailed list of the IHCSdb sub-surveys and the collection fields are available at the following link:

https://drive.google.com/drive/folders/1kWomKePumqNAk6VhDyU1iezOkK7itFdQ?usp=sharing