

# Regeneration Roadmap: database resources for regenerative biology

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## ABSTRACT

Regeneration plays an instrumental role in biological development and damage repair by constructing and replacing cells, tissues, and organs. Since regenerative capacity declines with age, promoting regeneration is heralded as a potential strategy for delaying aging. On this premise, mechanisms that regulate regeneration have been extensively studied across species and in different tissues. However, an open and comprehensive database collecting and standardizing the abundant data generated in regeneration research, such as high-throughput sequencing data, remains to be developed. In this work, we constructed Regeneration Roadmap to systematically and comprehensively collect such information over 2.38 million data entries across 11 species and 36 tissues, including regeneration-related genes, bulk and single-cell transcriptomics, epigenomics, and pharmacogenomics data. In this database, users can explore regulatory and expression changes of regeneration-associated genes in different species and tissues. Regeneration Roadmap provides the

research community with a long-awaited and valuable data resource featuring convenient computing and visualizing tools, which is publicly available at <https://ngdc.cncb.ac.cn/regeneration/index>.

## INTRODUCTION

Regenerative processes renew and reconstruct damaged cells, tissues, organs and even entire body parts in all living organisms. In both acute injury and continuous environmental stress settings, regeneration ensures organismal survival and homeostasis (1–5). However, with age increasing, regenerative capacity declines, and a gradual loss of function attributes to the well-documented reduced regenerative capacity of the stem/progenitor cell pool (6–9). Consequently, enhancing stem cell function is viewed as a potential mechanism for driving regeneration and delaying aging (10). More broadly, translation of the fundamental principles governing regeneration holds significant promise for treating complex human diseases, especially degenerative diseases related to aging (11,12).

The application of high-throughput omics technologies (including RNA-seq, scRNA-seq, ChIP-seq and ATAC-seq) has accumulated multidimensional data at an unprece-

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**Table 1.** The URL links for each module in the Regeneration Roadmap database

Module	Website
Homepage	<a href="https://ngdc.cnbc.ac.cn/regeneration/index">https://ngdc.cnbc.ac.cn/regeneration/index</a>
Regeneration-related Genes	<a href="https://ngdc.cnbc.ac.cn/regeneration/regeneration_related_genes">https://ngdc.cnbc.ac.cn/regeneration/regeneration_related_genes</a>
Transcriptomics	<a href="https://ngdc.cnbc.ac.cn/regeneration/rna-seq">https://ngdc.cnbc.ac.cn/regeneration/rna-seq</a>
Single-cell Transcriptomics	<a href="https://ngdc.cnbc.ac.cn/regeneration/single-cell">https://ngdc.cnbc.ac.cn/regeneration/single-cell</a>
Epigenomics	<a href="https://ngdc.cnbc.ac.cn/regeneration/epigenomics">https://ngdc.cnbc.ac.cn/regeneration/epigenomics</a>
Pharmacogenomics	<a href="https://ngdc.cnbc.ac.cn/regeneration/regeneration-drugs">https://ngdc.cnbc.ac.cn/regeneration/regeneration-drugs</a>

mented scale and depth in the field of regeneration (13–16). To date, omics technologies have been leveraged to study stem cell self-renewal, fate determination and organ regeneration, enabling pioneering large-scale analyses of regeneration-related molecular programs and regulatory mechanisms across species (14,17–22). However, such regeneration-related data and information are presently scattered across project-specific data depositions, preventing a full realization of their collective impact. As regeneration multi-omics studies from a broad spectrum of regeneration models are increasingly emerging, aggregating such data into a database has become an urgent need for the field.

Current regeneration-related databases, including RE-Gene (23), LimbformDB (24), NvERTx (25) and Myo-REG (26), are primarily knowledge databases that consolidate the published literature on regeneration-associated genes or signal pathways. Although databases with experimental data have been published, no database exists that allows users to upload regeneration multi-omics data, perform an interactive query, joint analysis and visualize such shared data. To propel the regenerative biology field and fully utilize the accumulating high-throughput sequencing data, we built Regeneration Roadmap, a comprehensive regeneration database for storing, managing, and integrating multi-omics sequencing data across multiple species.

The scope of Regeneration Roadmap is to enable an understanding of regeneration processes across species and tissues. The database encompasses data sets collected from the published literature and retrieved from existing databases on wide-ranging regeneration models under different physiological or pathological conditions. In aggregate, Regeneration Roadmap now comprises a spectrum of regeneration-related omics data, including transcriptomics, single-cell transcriptomics, epigenomics, and pharmacogenomics. In addition, we provide search, visualization, and download functions for regeneration gene sets named Genes Archived in Regeneration Roadmap (GARR), which are manually collected from the literature of regeneration. Hence, Regeneration Roadmap provides users with interactive and user-friendly functionalities that enable exploration of specific gene expression changes and the construction of regulatory networks associated with regeneration.

## DATABASE CONTENT

The current implementation of Regeneration Roadmap includes four modules: transcriptomics, single-cell transcriptomics, epigenomics, and pharmacogenomics (Table 1 and Figure 1). Furthermore, we have manually curated a collection of regeneration-related genes, hereafter referred to as GARR. The GARR section presently includes 553

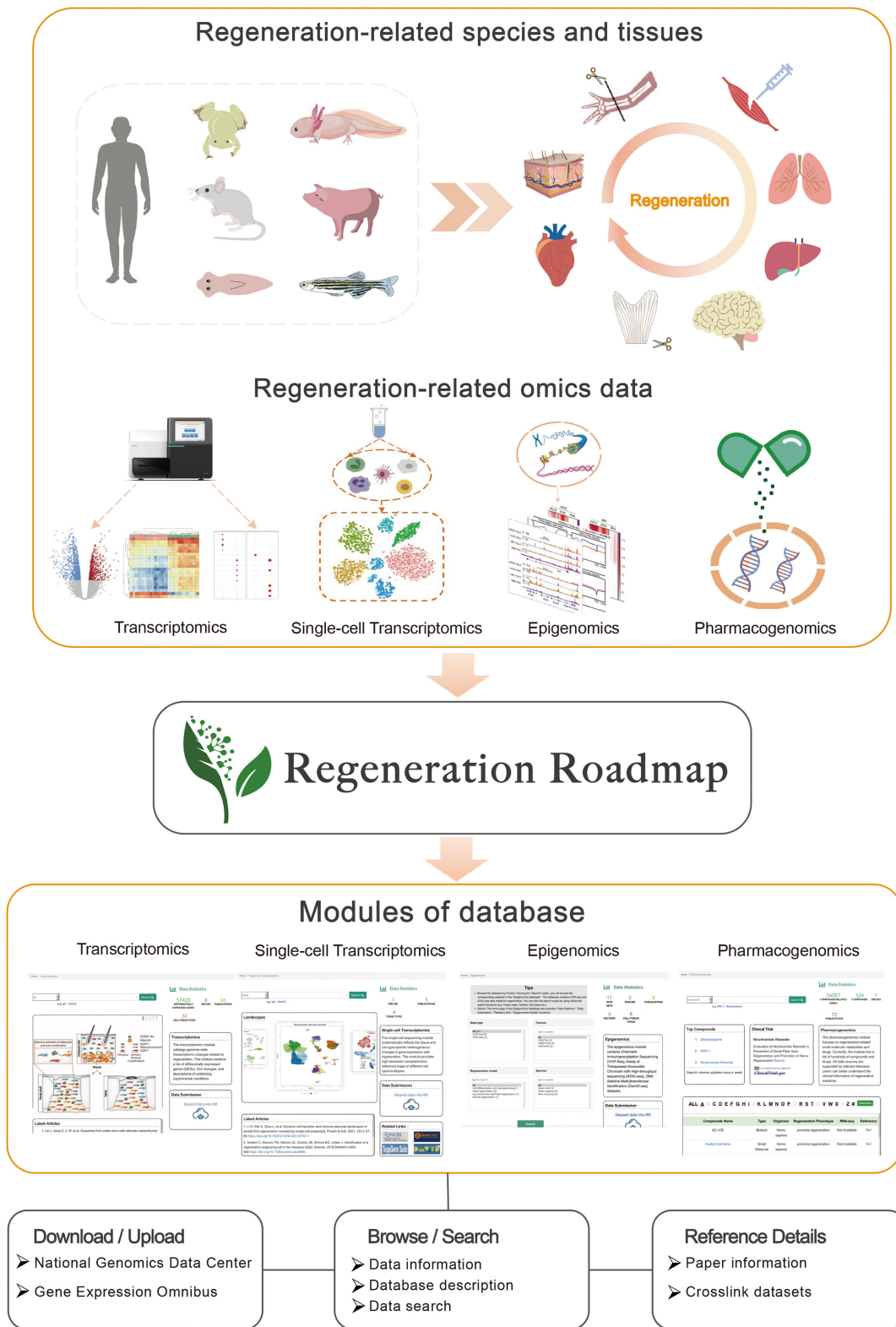
regeneration-related genes from 7 species across 24 different tissues. The gene sets span typical regeneration processes, including planarian regeneration (27), zebrafish lateral regeneration (28), newt limb and heart regeneration (29), human pancreatic islet (30) and liver regeneration (31). Each gene in GARR has been attributed to these regeneration processes. Therefore, GARR provides a benchmark section for Regeneration Roadmap to help our users better interpret the biological implications of regeneration-related genes.

### Transcriptomics module

The transcriptomics module currently contains more than 57 400 differentially expressed genes (DEGs) totally which were identified during regeneration or regeneration intervention across eight species. Users can find the genes they are interested in through the convenient keyword search function. For example, *lepb* is highly induced in both regenerating hearts and fins of zebrafish as revealed by the transcriptome analysis, and it is easy to explore the expression changes of this gene in other species or tissues across our database (2). In addition, users can also click on one picture of the corresponding data set to view and download all DEGs in this article, as well as basic gene descriptions from RefSeq (32) and gene ontology obtained from AmiGO (33). Over time, we will continue to collect more high-quality regeneration research data sets as these become available, and users are encouraged to upload their data to the database as well. Thus, in this module, we have integrated a large amount of RNA sequencing data from published regeneration research articles, making it possible to cross-check the expression changes of any gene during the regeneration process.

### Single-cell transcriptomics module

This module encompasses single-cell resolution gene expression changes during axolotl limb regeneration (20,34), xenopus tail regeneration (13), planarian whole-body regeneration (35), and mouse and human prostate regeneration (36). It contains more than 689 000 cells during regeneration across 6 species. For example, single-cell transcriptomics analysis of axolotl limb regeneration recently revealed gene expression changes and could be explored easily in our database (20). In this module, users can view the newly published regeneration-related single-cell data sets in the ‘Landscapes’ scroll bar. When users click on an atlas, they will go to the sub-page of the data set. From that point on, users can easily explore the gene expression patterns of specific cell types, visualize these in an interactive interface and download information about DEGs. Alternatively,



**Figure 1.** Overview of the Regeneration Roadmap database. The current implementation of Regeneration Roadmap includes four modules: transcriptomics, single-cell transcriptomics, epigenomics, and pharmacogenomics. The Genes Archived in Regeneration Roadmap (GARR), a collection of regeneration-related genes, has been manually curated.

users can search for genes of interest in the search column, and quickly find the relevant information at single-cell resolution by selecting species and tissues. Moreover, we also provide a single-cell data upload portal to facilitate users to upload their single-cell sequencing data to our website. Altogether, by collecting datasets from multi-organ single-cell transcriptomes, this module provides a valuable resource for the regeneration research community for assessing common and specific regeneration mechanisms in different organs across species.

### Epigenomics module

This module allows users to query epigenomic information during regeneration or regeneration intervention across six tissues from 11 datasets. It currently contains largely Chromatin Immunoprecipitation Sequencing (ChIP-Seq) data that identifies how specific regeneration-related loci are regulated by histone modifications and transcription factors (37–39). It also contains Assay for Transposase-Accessible Chromatin Sequencing (ATAC-seq) data, one of the most powerful approaches for genome-wide chromatin accessibility profiling (40). These data can visualize enrichment changes of a transcription factor or chromatin modification at a specific gene locus during regeneration. For example, ChIP-seq of the histone modifications H3K27Ac, H3K27me3 and H3K4me3 recently revealed the importance of epigenomics during adult zebrafish muscle regeneration *in vivo* (38). Furthermore, this module will be expanded to include a broader range of epigenetic data, including DNA methylation, DamID-seq (DNA adenine methyltransferase identification) and R-loop mapping. All data included in this module originate from published high-quality datasets on regeneration research, and datasets will be updated continuously. We manually annotated the dataset in the dataset display page, including the data types, regeneration modes, species, factors, and literature information involved, and supported advanced search functions for further screening. Users can easily visualize these data with WashU Epigenome Browser on our website (41). Users can also input specific gene coordinates simultaneously to show target enrichment data at the specified genomic loci. In conclusion, this module aims to provide a systematic platform to support further research on epigenomic regulation of regenerative processes.

### Pharmacogenomics module

The pharmacogenomics module allows users to query compounds related to regeneration, providing summary data of regeneration-related small molecule compounds, targets, pathways, and their roles in the regeneration process. The module currently lists 124 compounds, including dibenzazepine (42) and nicotinamide riboside (43), as well as RNA-seq datasets from drug therapy analyses, revealing gene expression changes caused by specific regeneration-promoting drugs. The data is primarily curated from the published literature and the DrugBank database (44). On the pharmacogenomics module homepage, users can browse through the ‘Top small molecules’ function, which

lists compounds with high search volumes; and ‘Clinical Trials’, which presents clinical trial data for compounds related to regeneration. Importantly, users can easily search by the name of the drugs and related genes to access detailed information about specific compounds. If a corresponding RNA-seq dataset is available, a link will be provided in the gene expression tables. As the first database containing information about regeneration-related compounds, we provide a comprehensive list of identified regeneration-promoting compounds to date and include information on gene regulation and expression changes caused by the drugs.

### CONCLUDING REMARKS

As a process relying on stem cell self-renewal, differentiation and tissue reconstruction in all living organisms, regeneration is central to physiological processes such as development and tissue damage repair. Since the decline of stem cell regenerative function is a hallmark of the aging process, boosting stem cell self-renewal capacity to drive regeneration can thereby potentially delay aging and/or mitigate aging phenotypes. With the application of high-throughput omics technology (including RNA-seq, scRNA-seq, ChIP-seq and ATAC-seq) in regeneration studies, researchers stand to discover unknown biological events that occur during regeneration processes and that can be targeted therapeutically. To pave the way towards these goals, we constructed Regeneration Roadmap—a multi-species and multi-omics database for regenerative biology that spans (i) currently over 2.38 million data entries across 11 species and 36 tissues, which will be updated continually to display high-quality regeneration omics data and improved functionalities, including four modules on transcriptomics, single-cell transcriptomics, epigenomics and pharmacogenomics; (ii) a collection of 533 regeneration-related genes, GARR, that characterize typical regeneration processes from seven species and 24 different tissues, where each gene has been attributed to corresponding regeneration processes and (iii) a user-friendly website through which to explore and share data and resources, and users can quickly search for information related to regeneration across species or tissues. With the combined efforts of our users and our team, the database will be updated continuously to add high-quality omics data from the ever-growing regeneration research and will stay open and freely available to the public. It also provides the functions for the interactive query, joint analysis, and visualization of such shared data. In the future, we will continue to add more bioinformatic tools. Regeneration Roadmap is bound to become an important resource for the regeneration field but also for the broader life science community.

### DATA AVAILABILITY

All data in Regeneration Roadmap is available to the researchers (<https://ngdc.cncb.ac.cn/regeneration/index>). Users can directly download the search results in the corresponding module without registration or login (Table 1).



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