

TREAT-ARCA

EJP RD JTC 2020, JUNE 2021-MAY 2024



TEAM COMPOSITION



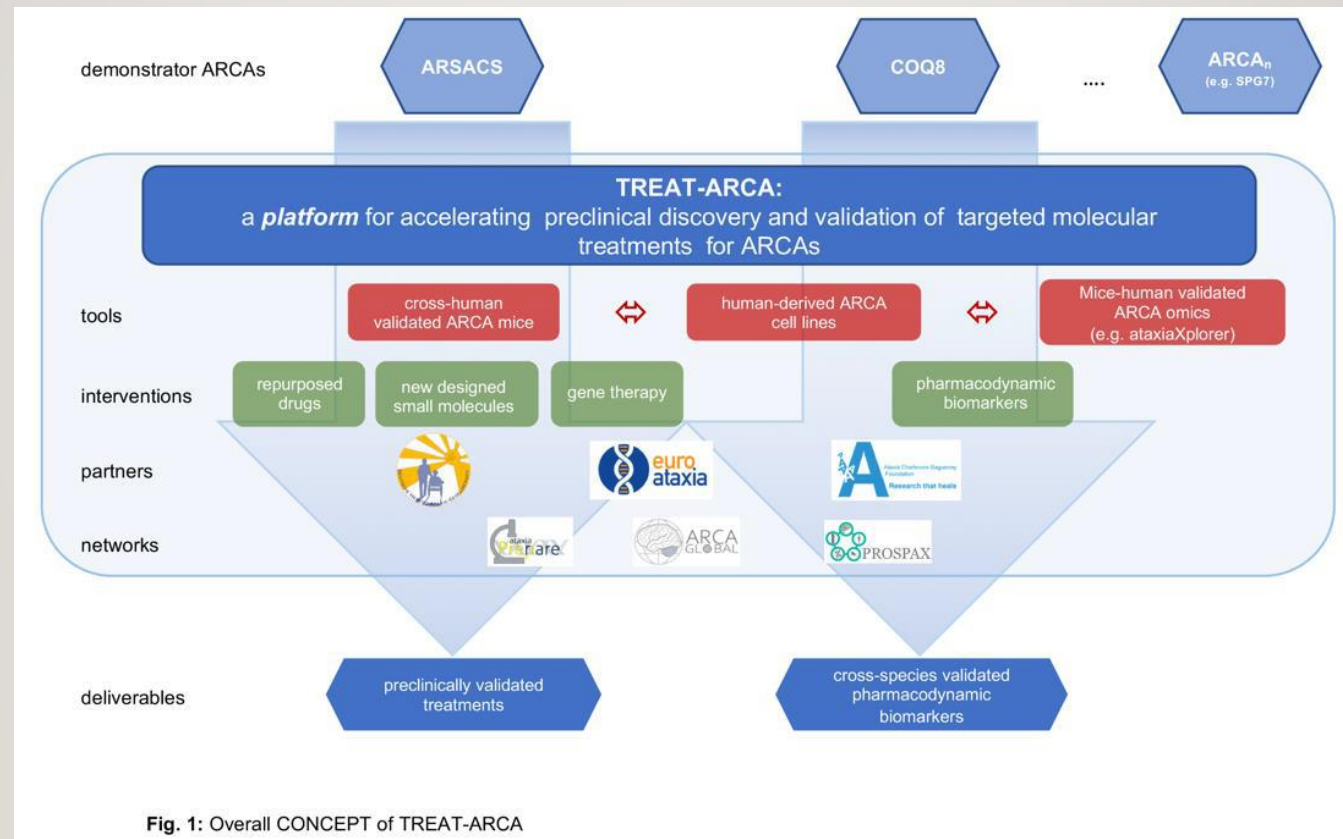
CHALLENGES FOR TREAT-ARCA

- ***Developing ARCA disease models closely mimicking the human condition and suitable for therapy development.***
- ***Development of novel ARCA therapies in pre-clinical proof-of-principle studies including repurposing drugs, small molecules, and gene therapies.***
- ***Development of pharmacodynamic biomarkers in close-to-human models.***

PRELIMINARY STUDIES SUPPORTING THE PROPOSAL

- ***Ca²⁺ and mitochondrial dysregulation in ARSACS – and its rescue by Ceftriaxone***
- ***Neurofilament bundling in ARSACS and its rescue by the novel small molecule UMI51***
- ***Ca²⁺ and mitochondrial dysregulation in COQ8A-ataxia and its rescue by CoQ10***
- ***OMICS identification of dysregulated pathways in ARSACS and COQ8A-ataxia to identify new biomarkers***
- ***Integrating cross-species OMICS and charting an ataxia treatabologomics interactome by the ataxiaXplorer to identify common dysregulated pathways and biomarkers***

PROJECT OVERVIEW

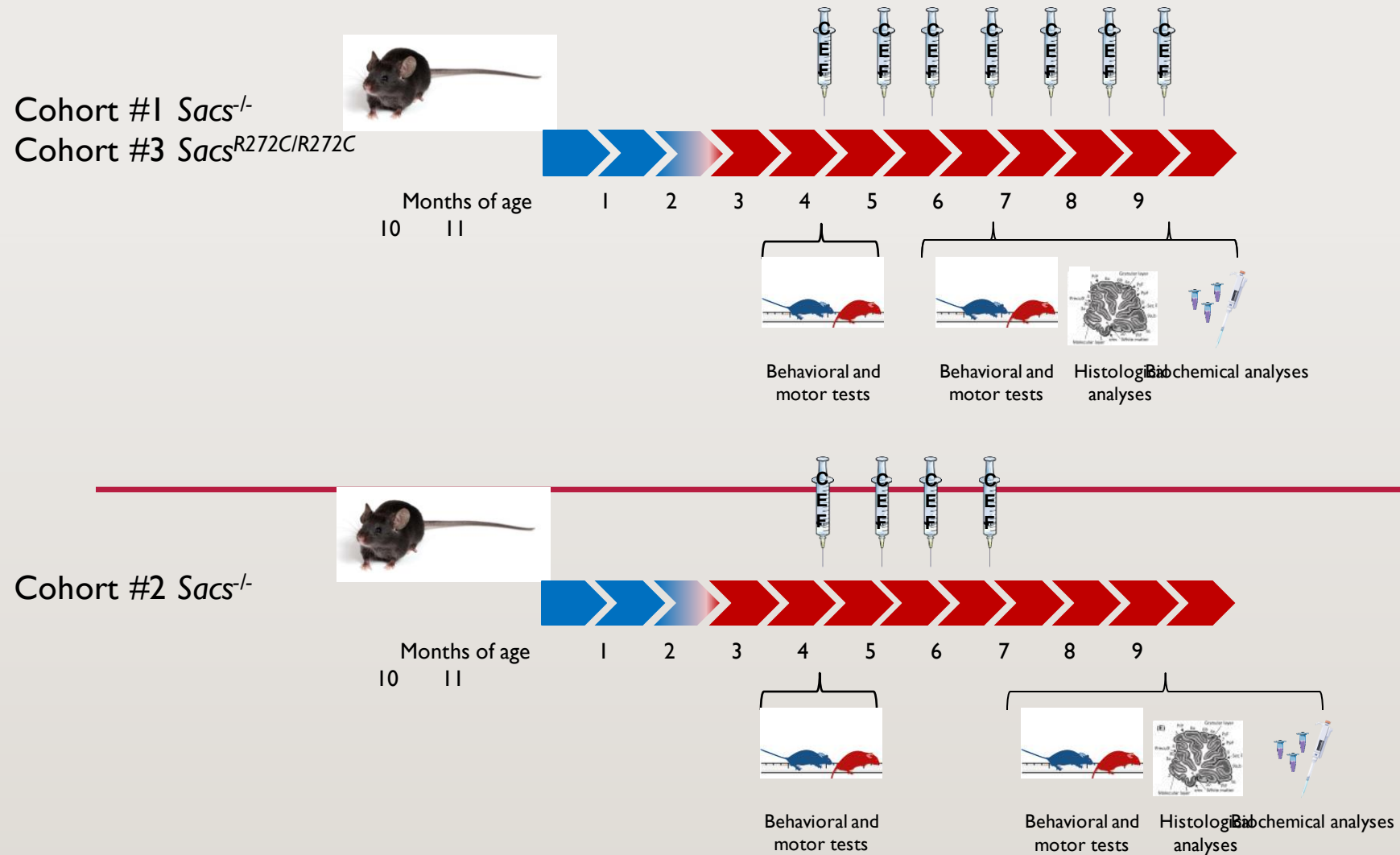


AIMS FOR TREAT-ARCA

- 1 ARSACS (Ceftriaxone) and COQ8A-ataxia (Ceftriaxone, CoQ10 compound - Ubiquinol) in pre-clinical mouse trials**
- 2 To develop and validate the efficacy of a novel small molecule for ARSACS (UMI91) and of a novel gene therapy for COQ8A-ataxia in pre-clinical mouse trials**
- 3 To identify and validate pharmacodynamics biomarkers for ARSACS and COQ8A treatments by cross-species cross-OMICS and complementary targeted approaches, to prepare them trial-readiness in human trials, and to launch a dynamic open-science ataxia treataboloomics interactome**
- 4 Project management, project dissemination, and innovation management activities**

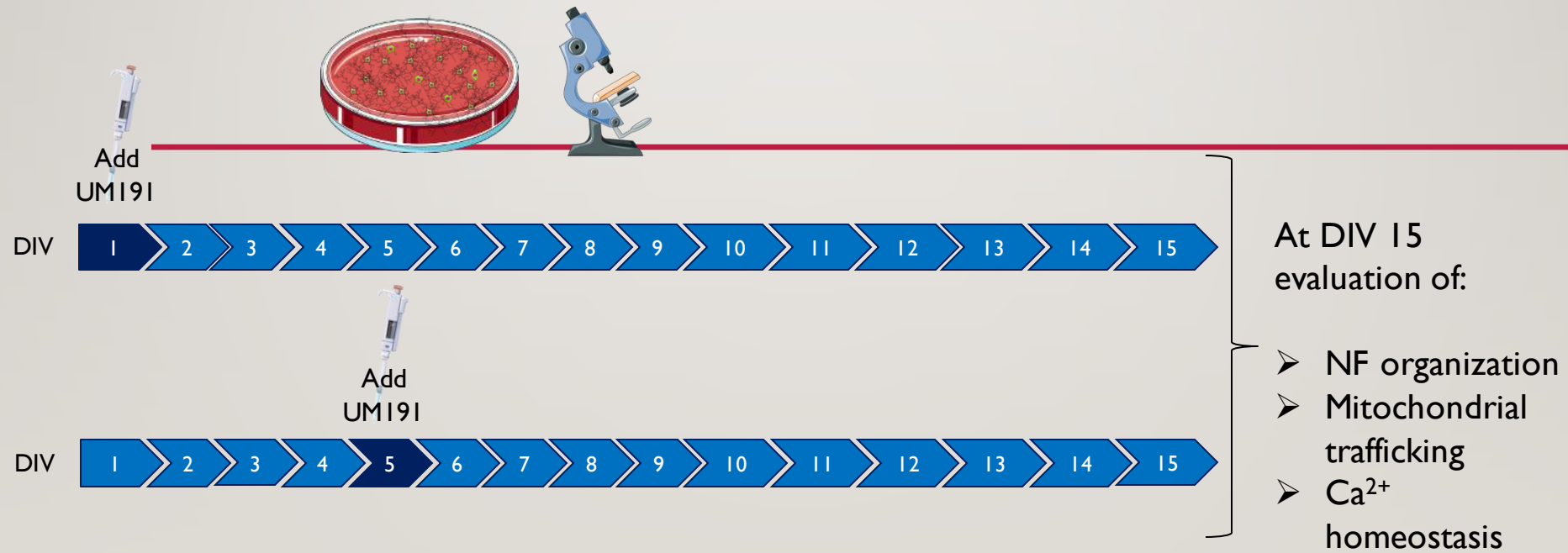
AIM I : Pre-clinical trials

Post-symptomatic Ceftriaxone treatment in ARSACS mouse model



WPI_Task I.I: Demonstrating the therapeutic efficacy of Ceftriaxone in *Sacs*^{-/-} (KO) mice and validating it in *Sacs*^{R272C/R272C} (KI) mice.

Aim 2: validate the efficacy of a novel small molecule Cytoskeletal remodelling in *Sacs*^{-/-} primary PNs



WP2_Task 2.1.1: Searching for UMI91 target and demonstrating its effect on cytoskeletal organization and mitochondrial function in *Sacs*^{-/-} primary PNs.

AIM3: IDENTIFY AND VALIDATE PHARMACODYNAMICS BIOMARKERS

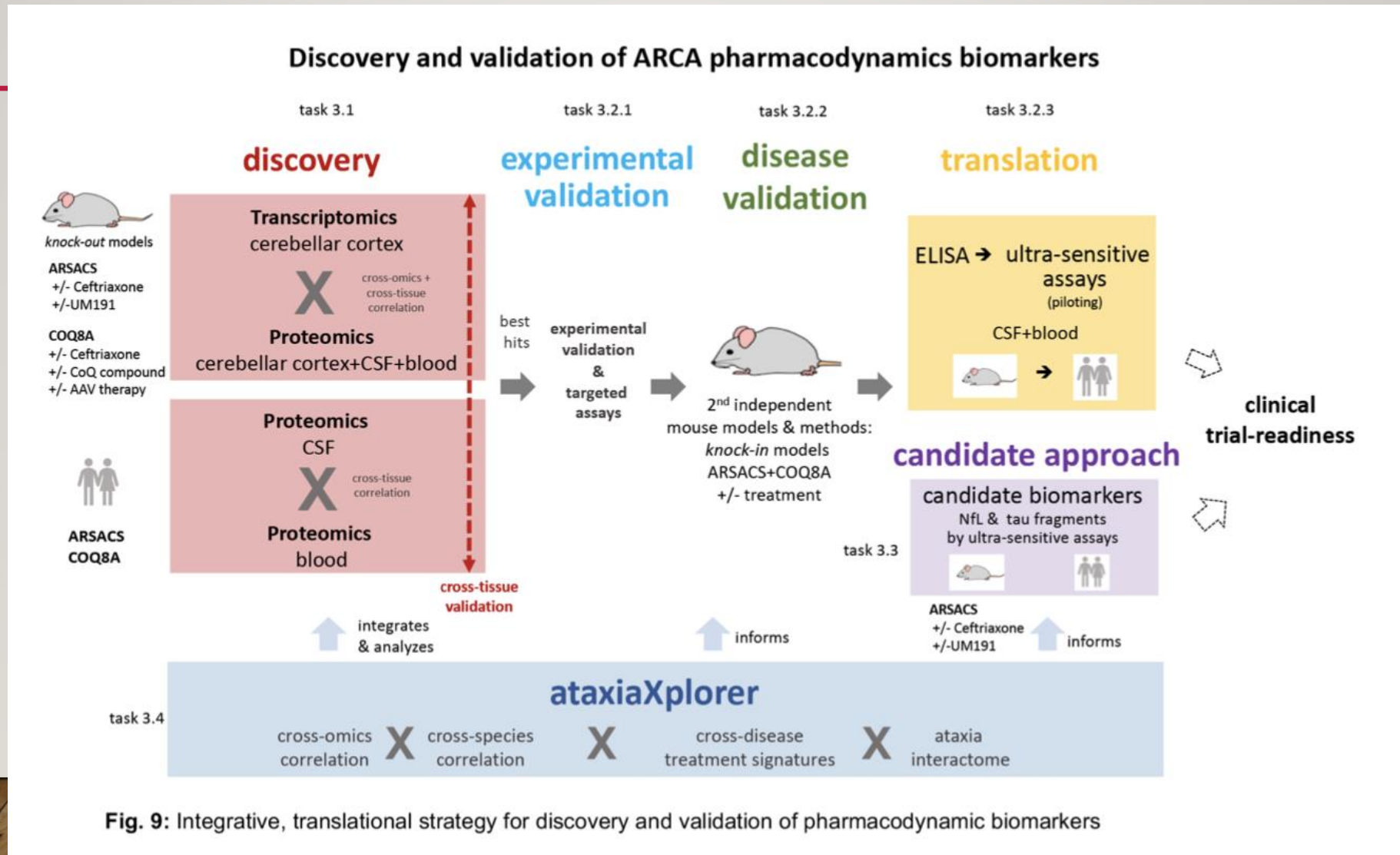
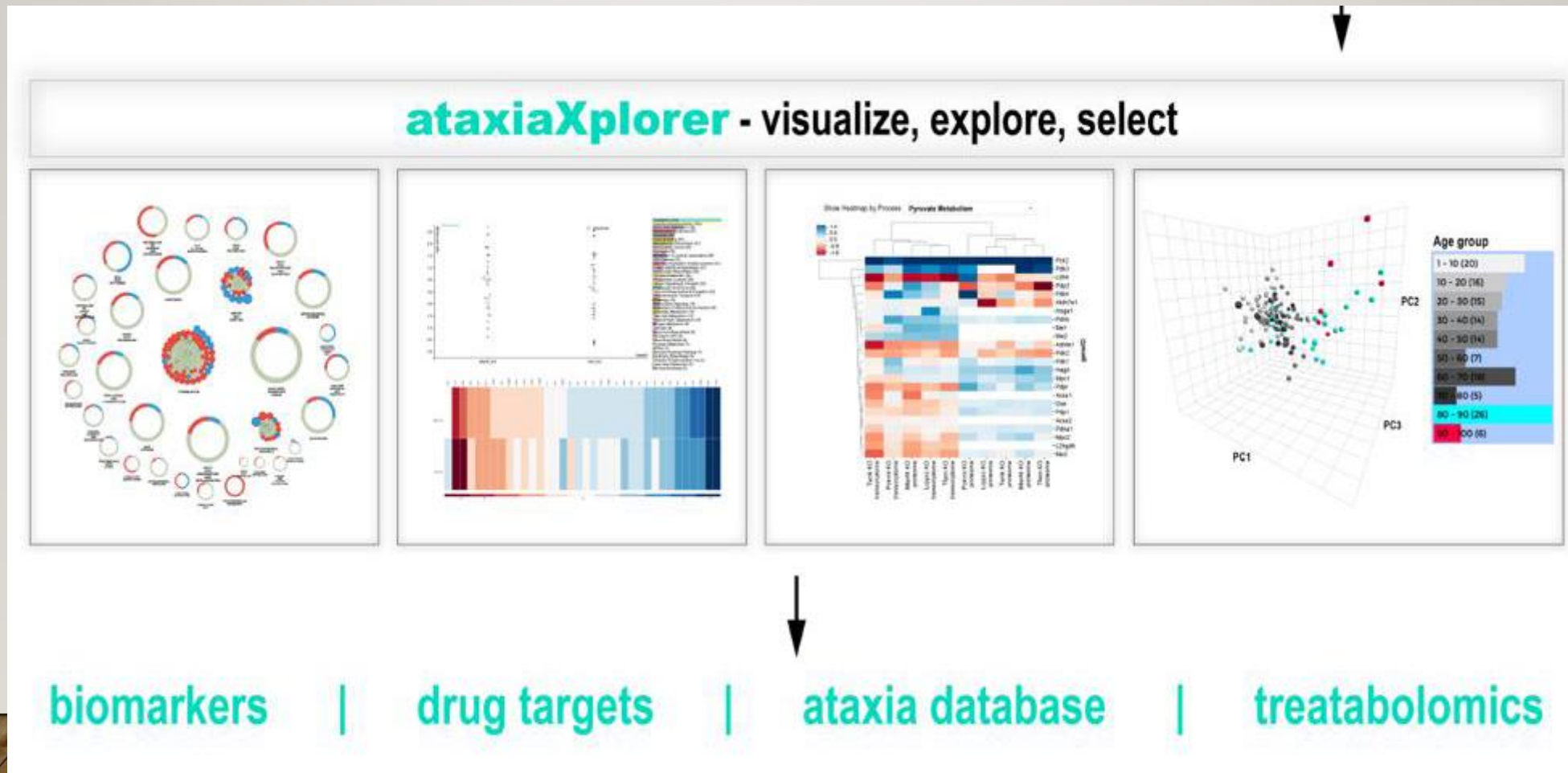


Fig. 9: Integrative, translational strategy for discovery and validation of pharmacodynamic biomarkers

AIM3: GENERATION OF THE ATAXIAXPLORER PLATFORM



AIM 4: PROJECT MANAGEMENT, PROJECT DISSEMINATION, AND INNOVATION MANAGEMENT ACTIVITIES

