

# TREAT-ARCA

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EJP RD JTC 2020, JUNE 2021-MAY 2024



# TEAM COMPOSITION

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# CHALLENGES FOR TREAT-ARCA

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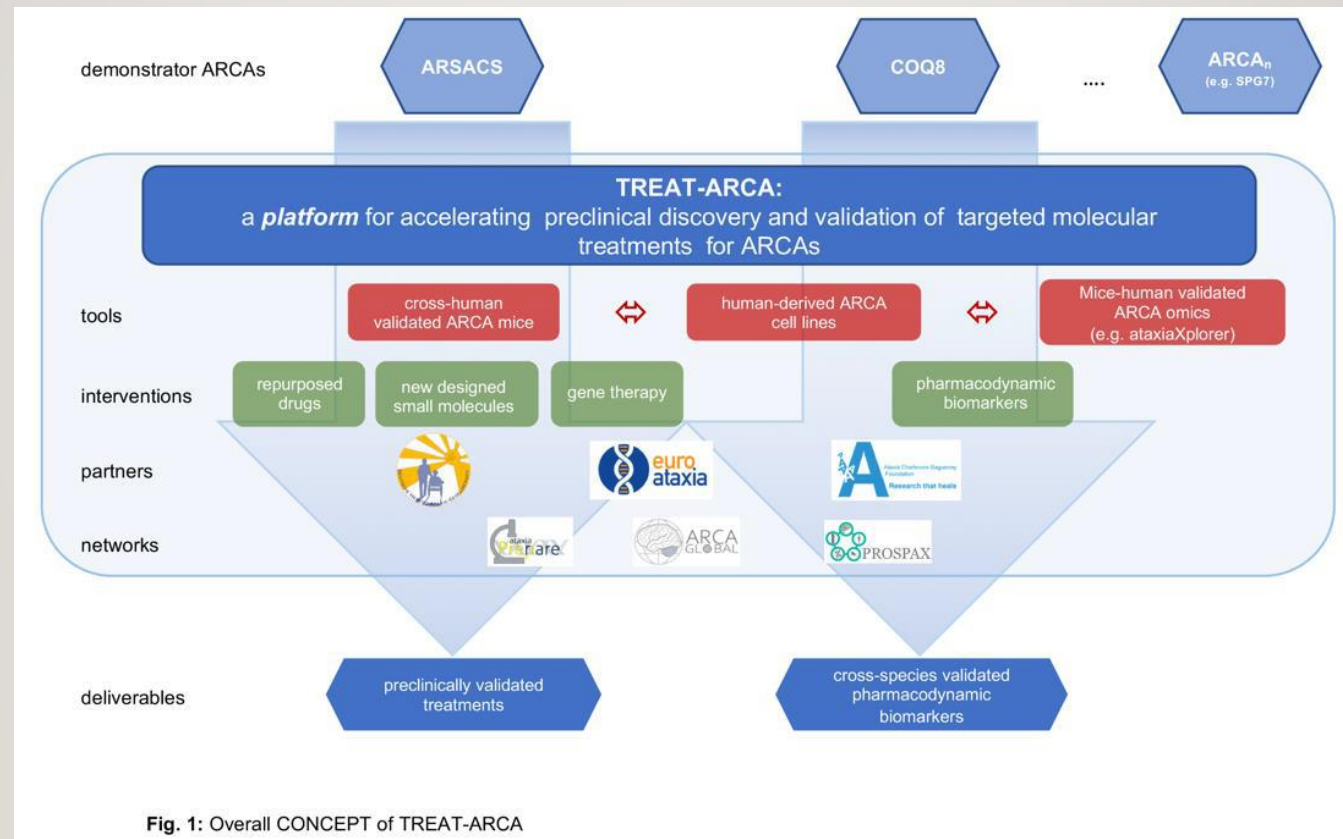
- ***Developing ARCA disease models closely mimicking the human condition and suitable for therapy development.***
- ***Development of novel ARCA therapies in pre-clinical proof-of-principle studies including repurposing drugs, small molecules, and gene therapies.***
- ***Development of pharmacodynamic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

# **PRELIMINARY STUDIES SUPPORTING THE PROPOSAL**

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- ***Ca<sup>2+</sup> and mitochondrial dysregulation in ARSACS – and its rescue by Ceftriaxone***
- ***Neurofilament bundling in ARSACS and its rescue by the novel small molecule UMI51***
- ***Ca<sup>2+</sup> 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



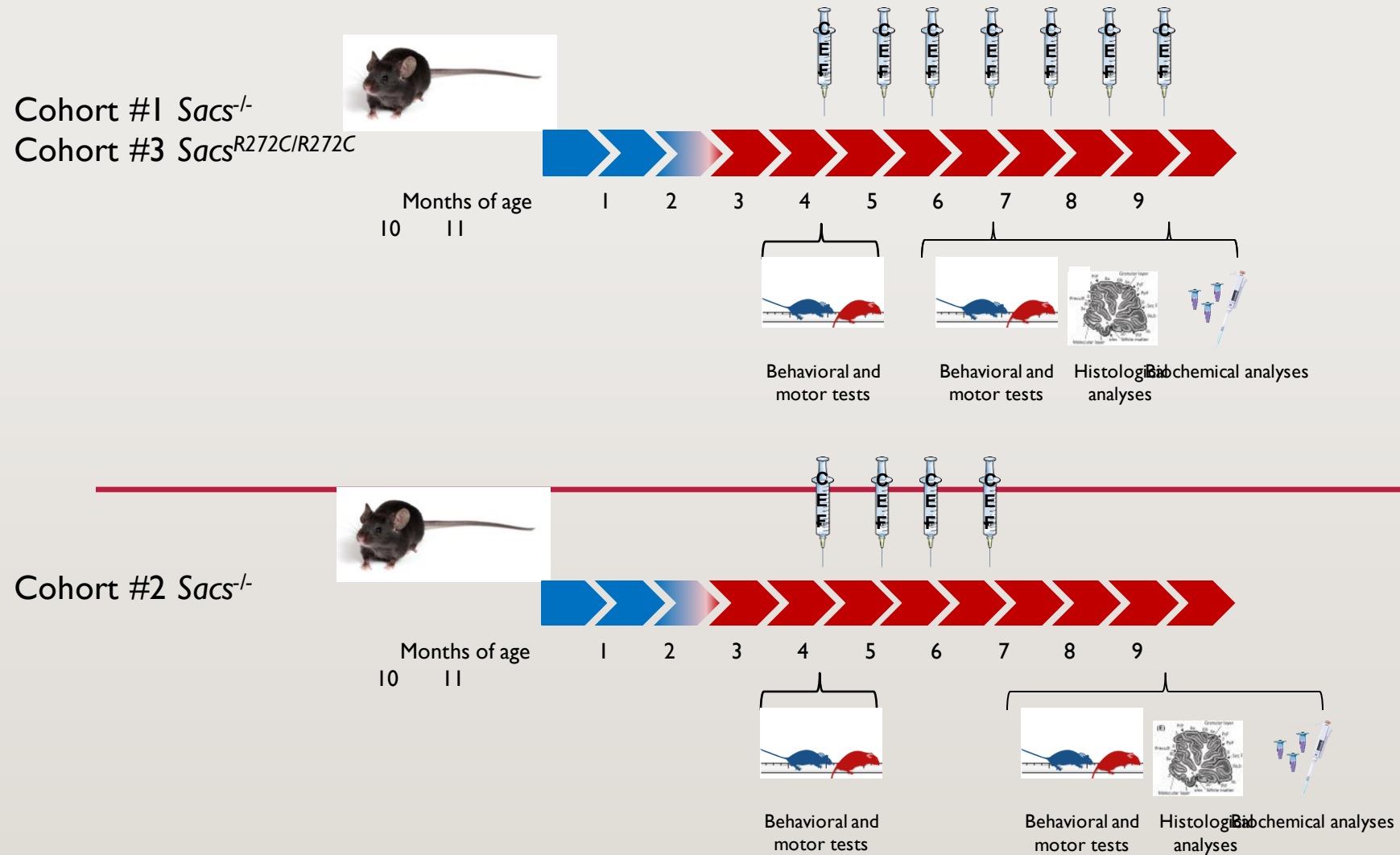
# AIMS FOR TREAT-ARCA

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- 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 treatabologomics interactome**
- 4 Project management, project dissemination, and innovation management activities**

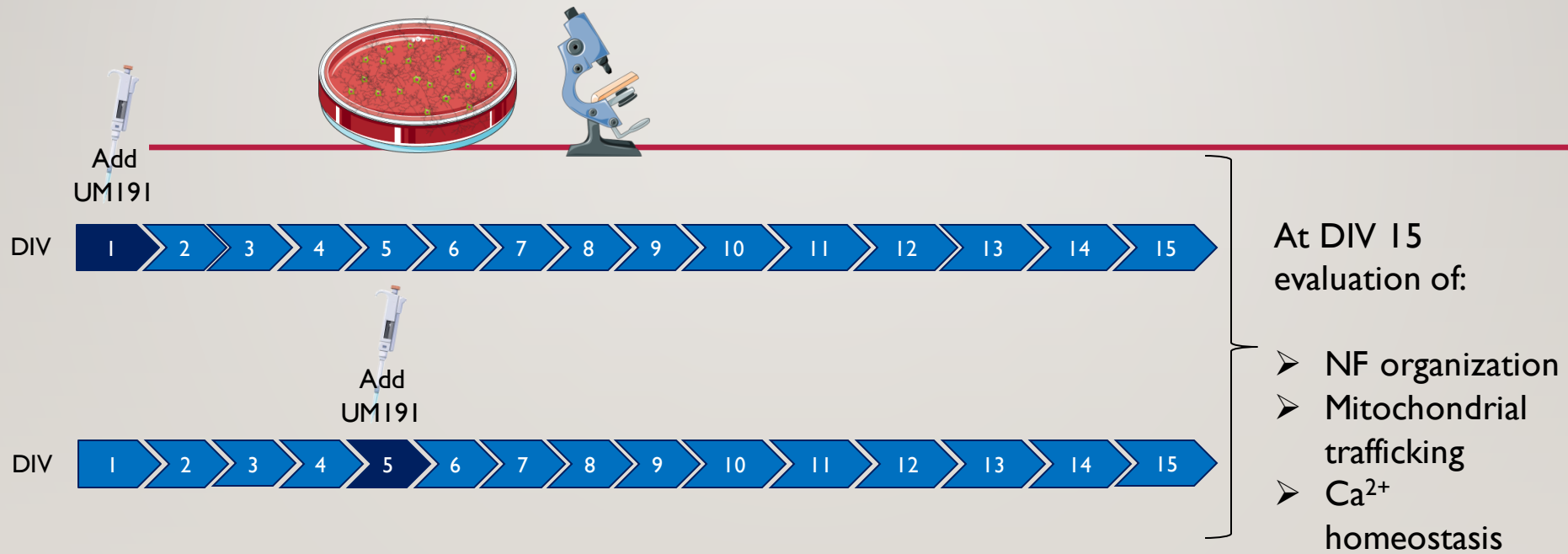
# AIM I : Pre-clinical trials

## Post-symptomatic Ceftriaxone treatment in ARSACS mouse model



**WPI\_Task I.I: Demonstrating the therapeutic efficacy of Ceftriaxone in *Sacs*<sup>-/-</sup> (KO) mice and validating it in *Sacs*<sup>R272C/R272C</sup> (KI) mice.**

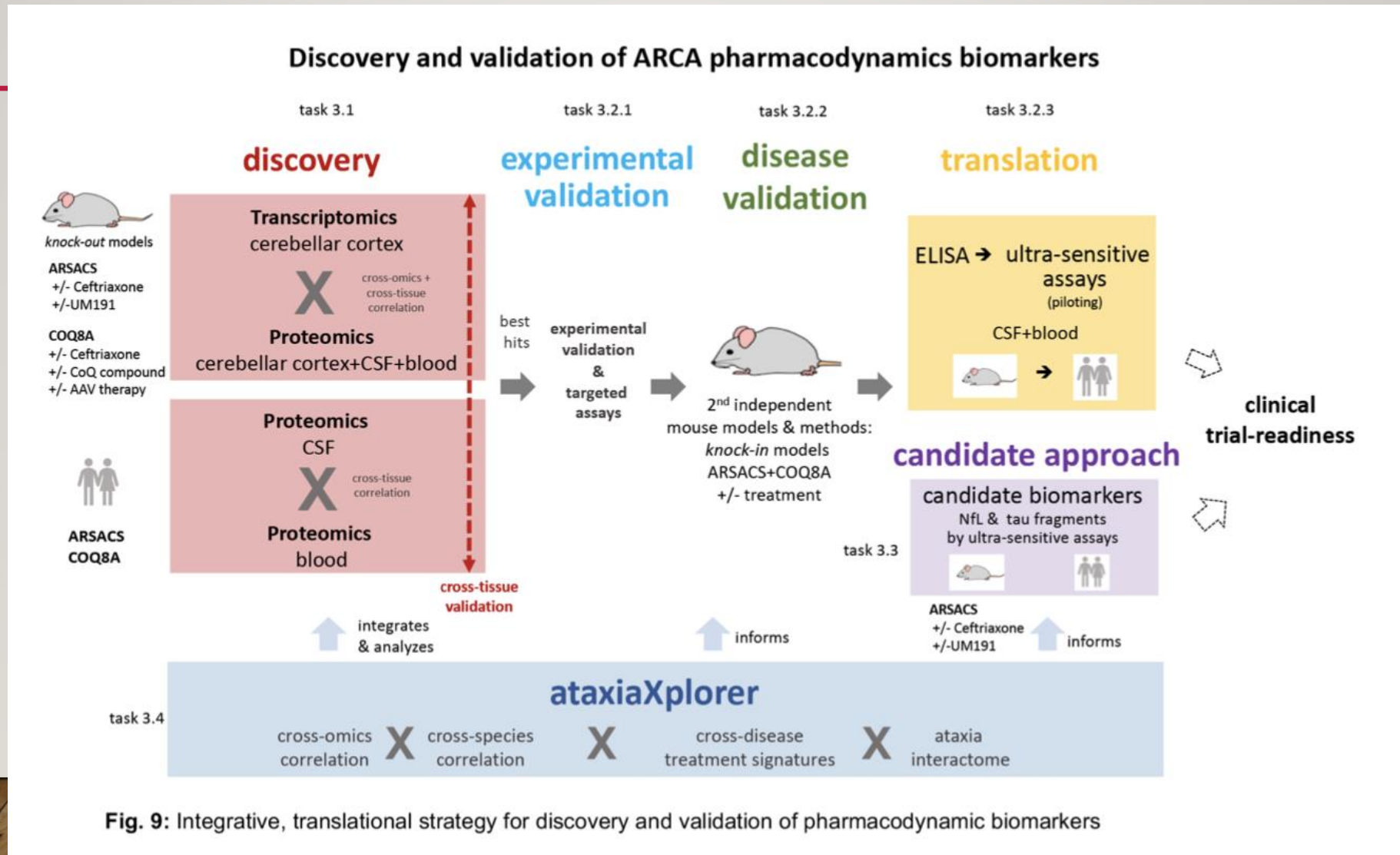
## Aim 2: validate the efficacy of a novel small molecule Cytoskeletal remodelling in *Sacs*<sup>-/-</sup> primary PNs



**WP2\_Task 2.1.1: Searching for UMI91 target and demonstrating its effect on cytoskeletal organization and mitochondrial function in *Sacs*<sup>-/-</sup> primary PNs.**

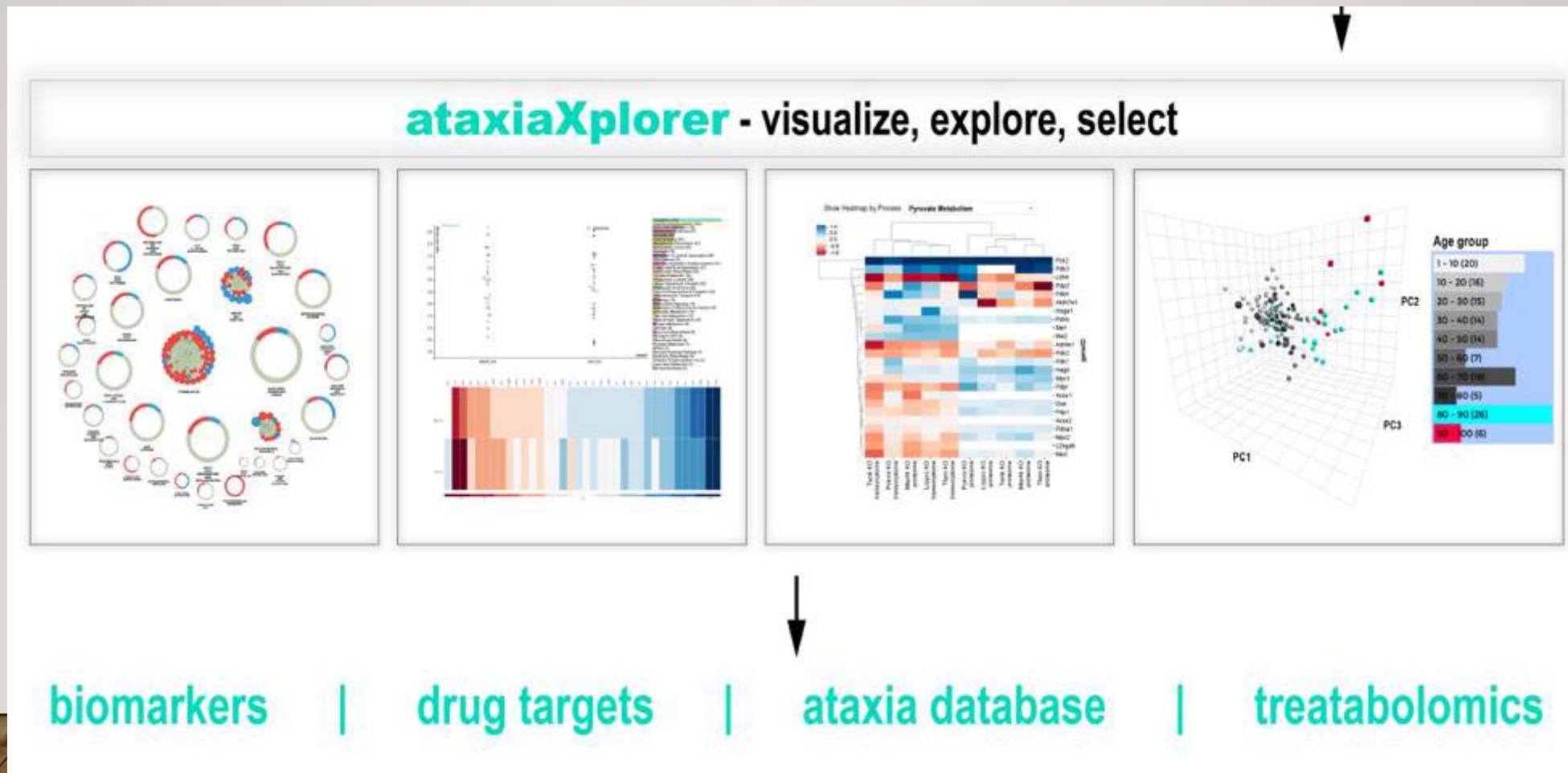


# AIM3: IDENTIFY AND VALIDATE PHARMACODYNAMICS BIOMARKERS



**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

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