



Daiichi-Sankyo

# *Human iPS/ES Cell Technology and Its Application to Toxicology Testing*



*-Especially focusing on in vitro cardiac function toxicity-*

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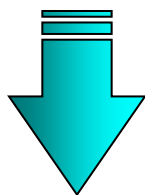
**New Energy and Industrial Technology  
Development Organization (NEDO)**

**JAPAN Independent Government Agency**

## **Critical issue: High rate attrition of new drugs**

**(8/9 clinical candidates fail during Ph I~III)**

**Poor efficacy and safety concerns are major cause of attrition.  
To overcome the species difference is key to the solution.**



### **We need:**

- ***New technologies to predict efficacy and toxicity in humans with improved reliability at an early pre-clinical stages via HTS screening***
- ***To streamline validation of new technologies with collaboration among industry, government, and academia.***

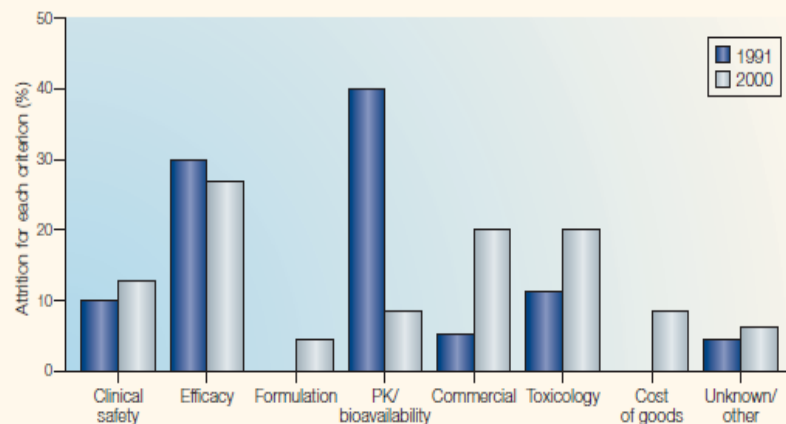
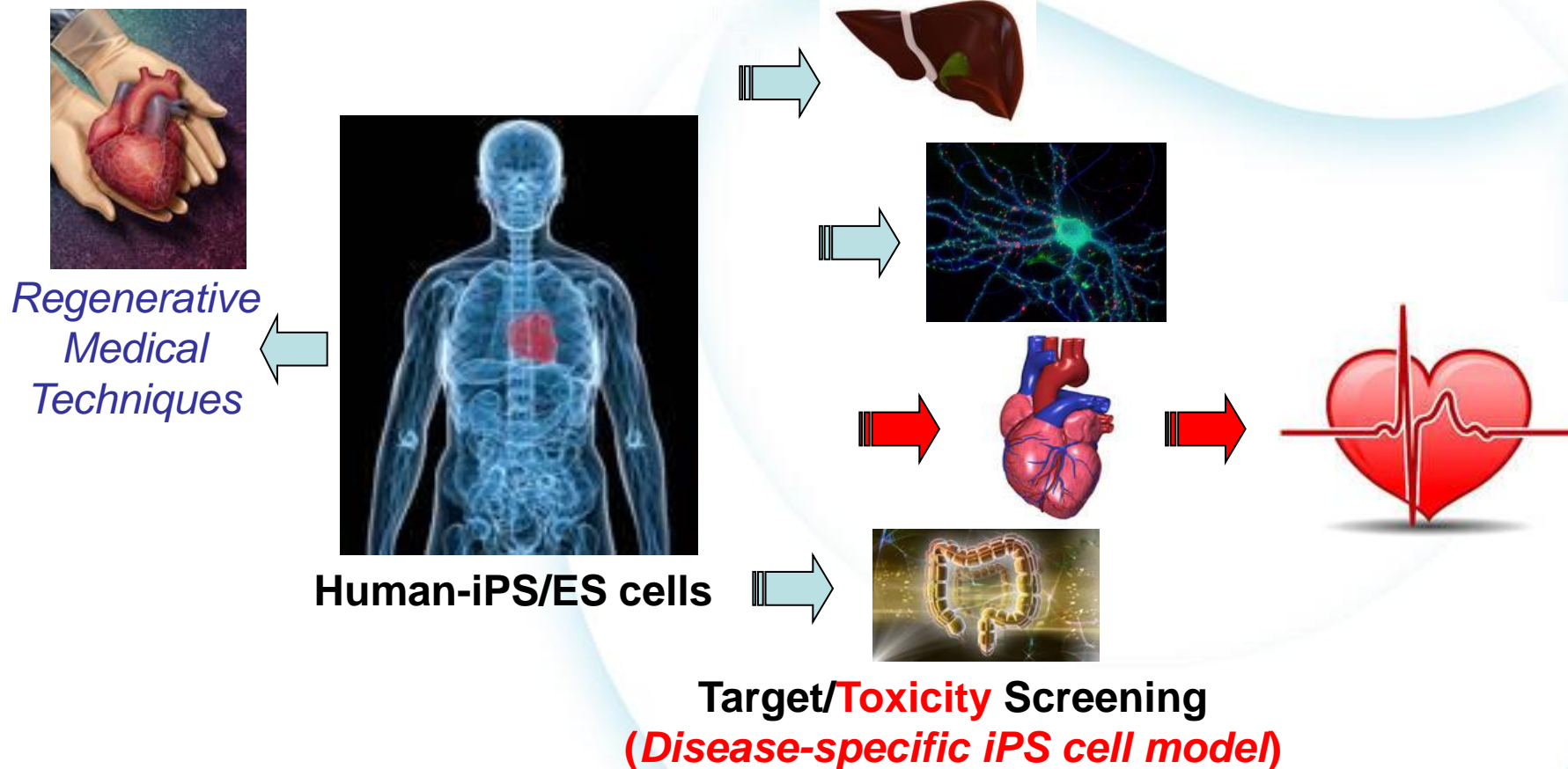


Figure 3 | Reasons for attrition (1991-2000). PK, pharmacokinetics.

# Human-iPS/ES Cell-Based Technology: Potential Platform of Drug Development to Overcome Species Difference



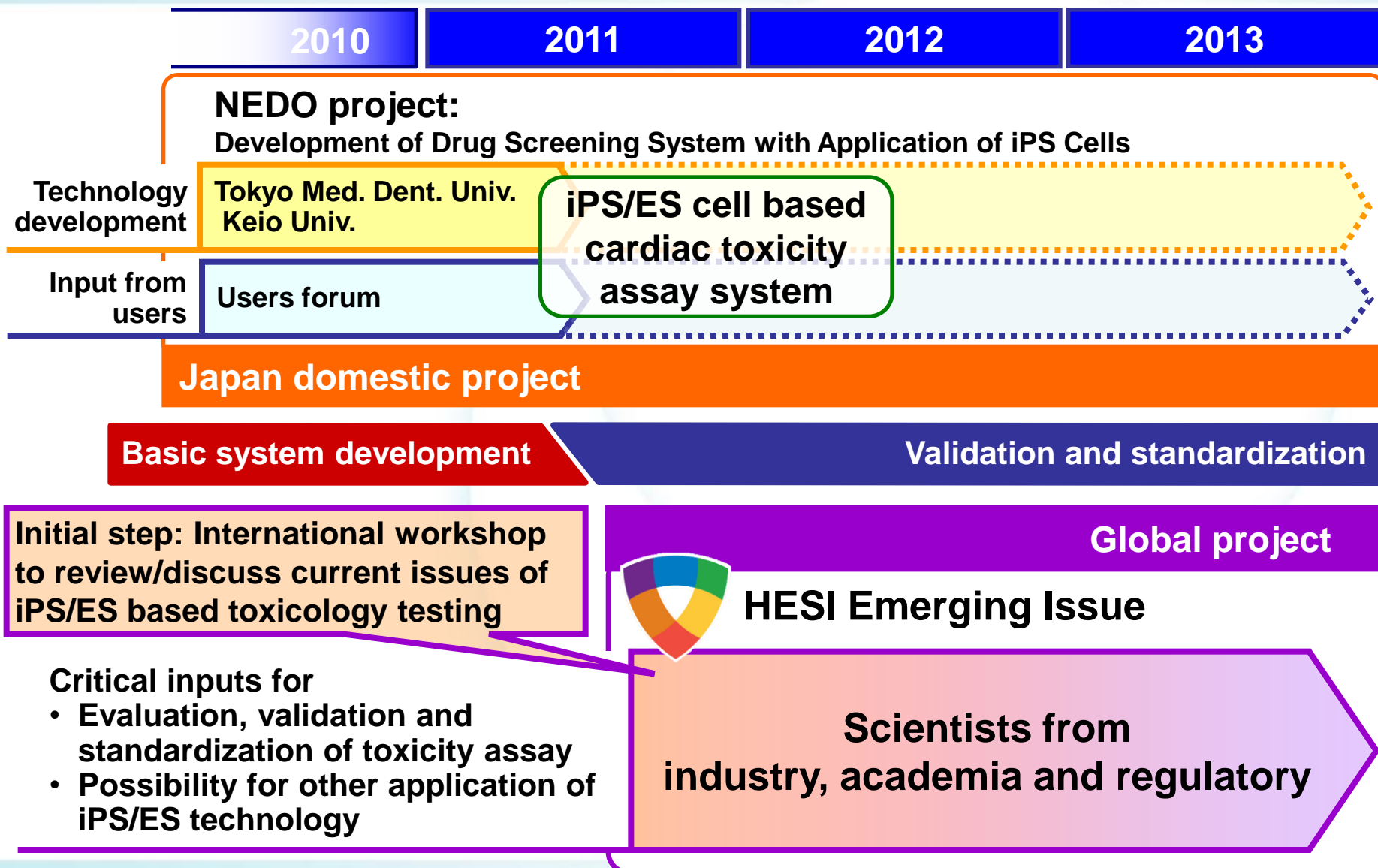
➤ Expected to provide innovative tools for drug development via HTS screening.

## **New Energy and Industrial Development Organization (NEDO)**

A public organization in Japan to promote research and development of industrial, energy and environmental technologies as well as application of the technologies developed

- **Development of Drug Screening System with Application of iPS Cells (2008 to 2013)**
  - **Keio University**
    - Differentiation of iPS cells into cardiomyocytes
  - **Tokyo Medical and Dental University**
    - On-chip single/multiple cell-based model and technology
  - **Users forum: Daiichi Sankyo, Takeda, Astellas, Eisai....**  
**13 Japanese pharmaceuticals and 4 CROs**
    - Input from the expected users

# Preliminary Work Plan



**Industry:  
Applicability in drug screening**

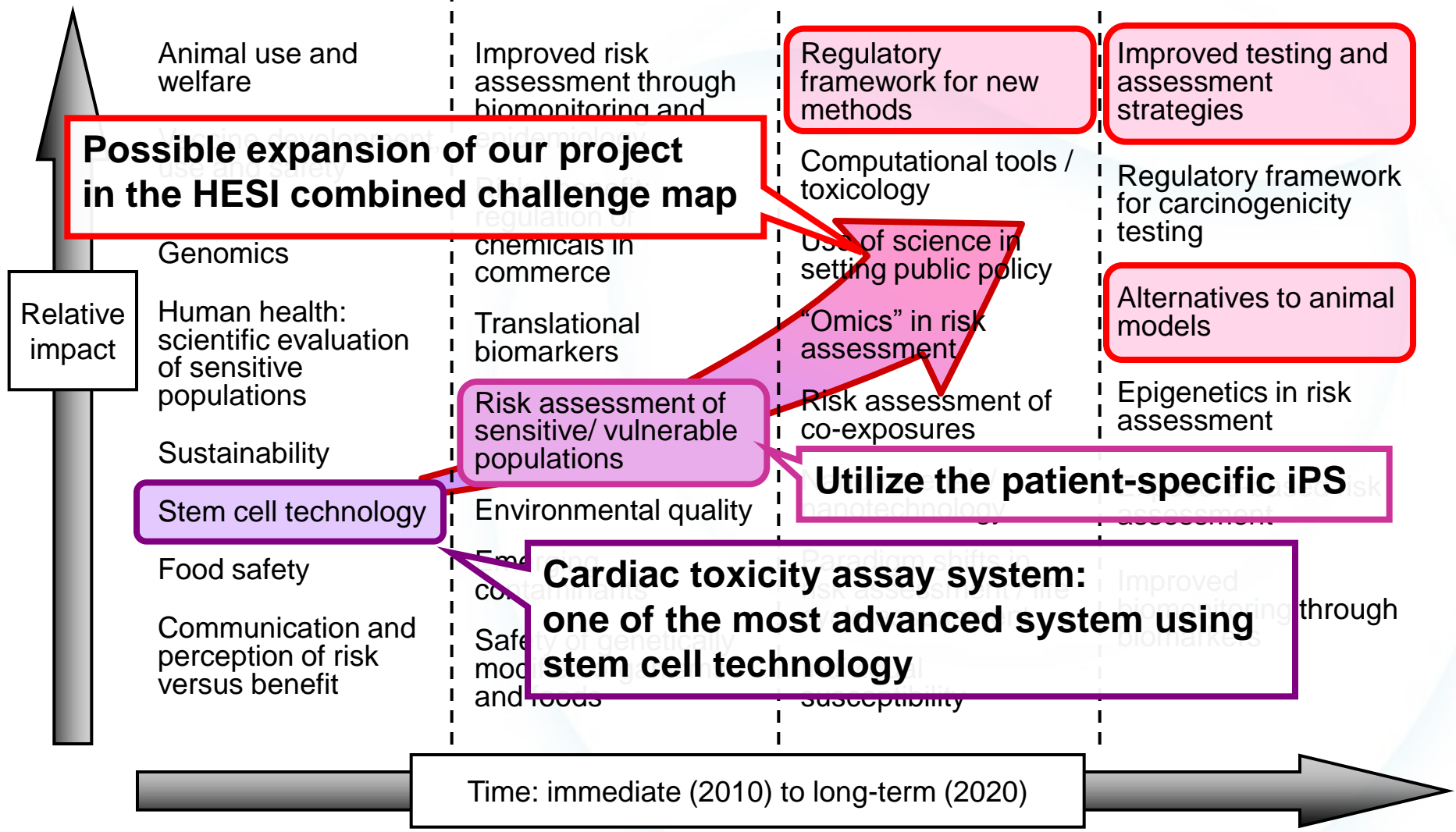
**iPS/ES cell based  
cardiac toxicity  
assay system**

**Government:  
Regulatory perspective**

**Academia:  
Scientific input**

- **Consensus on the protocol of standardization/validation for iPS cell application in cardiac toxicity screening**
- **Basic understanding on applicability of iPS cell in toxicity prediction shared globally among industry, academia and regulatory scientists**
- **Proposal for further researches on application of iPS cells in other toxicity evaluations**

# Position of Our Proposed Project in the HESI Combined Challenges Map



- **New cardiac toxicity assay system with stem cell derived human cardiomyocyte based on the novel technology is now under development.**
  - This technology has the potential to improve the current risk assessment of the pro-arrhythmic potential in the drug development.
- **For validation, standardization and practical application of this assay system, global input from expertise of multidiscipline are needed.**
  - HESI EI project can organize a global forum of tripartite scientists to provide the critical input for further development of this new assay system.
- **This project is expected to be expanded to the full scope of iPS cell technology such as application to other types of toxicities and/or chemicals, and is related to other topics in the HESI combined challenges map.**



**This project can be the first HESI Emerging Issue project of iPS/ES cell technology application.**

**Through this project, a general framework for evaluation of future stem cell technology application will be provided.**

# Appendix

## **Cross validation:**

- Positive/ negative control data collection
- Comparison with current standard assays

... in the global industry-government-academia collaboration

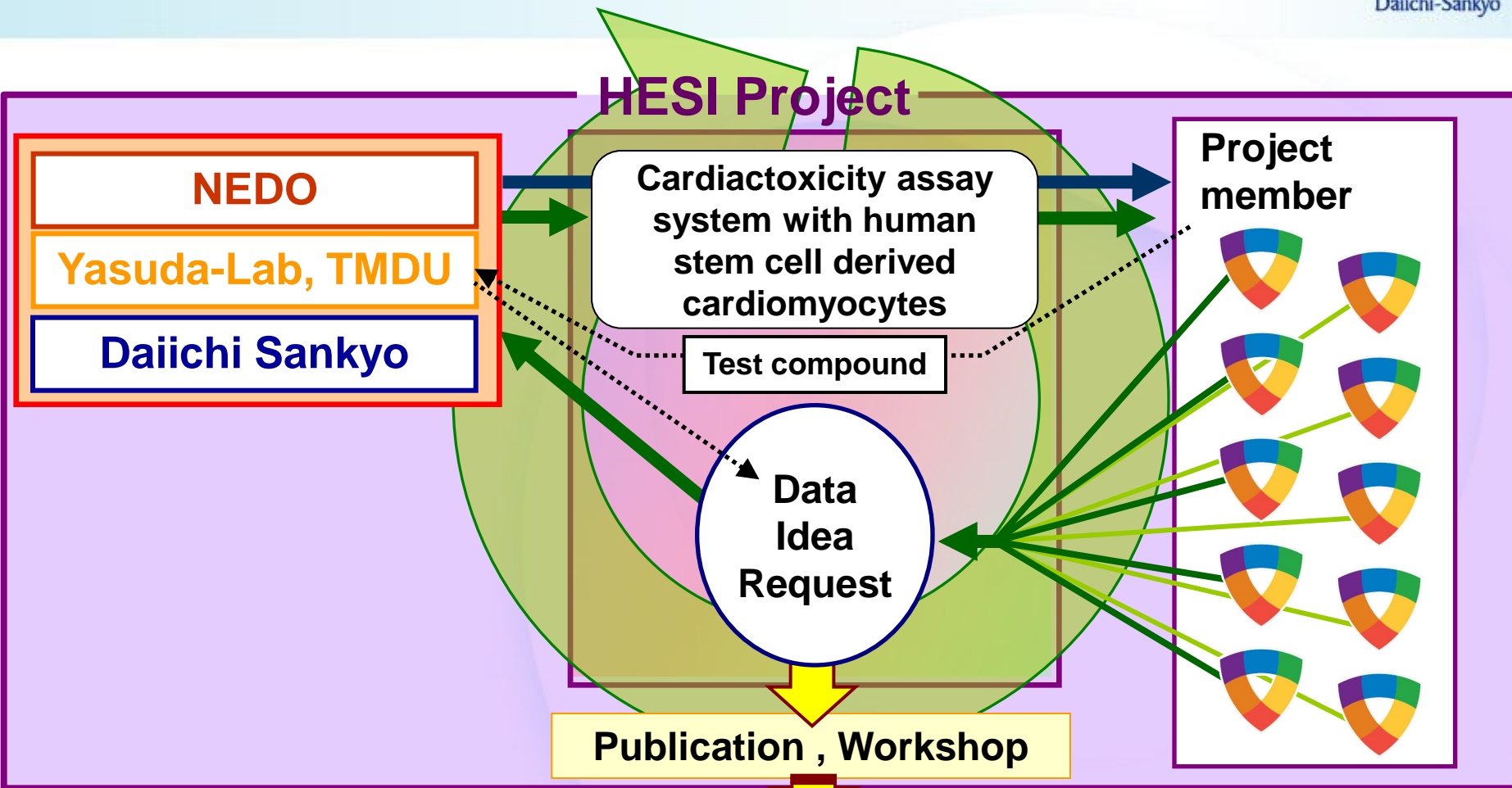
## **Further development:**

- Improvement / refinement of the experimental devices and assay protocol through the cross validation

## **Standardization:**

- **Determination of the specification of the total assay system**
  - Cells: Source of the human cardiomyocytes, Criteria to use in the assay
  - Cell chip: Cells/ electrodes arrangement
  - Field potential recording: Required specification of the recording device
  - Data analysis: Automated analysis software
  - Evaluation: Index of pro-arrhythmic potential

# Framework of the HESI Project



**Final goal: Establishment of the global standard “proarrhythmic risk evaluation system” for the all chemicals**