2009

# JST-CIRM Research Collaboration Program RFA

**Attention:**
**This is only an English translation of JST's original RFA for the JST-CIRM Research Collaboration, not an RFA itself.**
**Please be sure that you need to refer to the original RFA written in Japanese to know the exact terms and conditions designated by the JST's regulations.**

## 1. Objectives

For a major step forwards finding new practical applications of iPS cell, collaboration between Japan and California is relevant as it will certainly accelerate comprehensive research activities and maximize their research potential.
Based on this understanding, JST and CIRM*[1)], as funding agencies representing Japan and California respectively, will work together to establish and support Japan - California joint research projects.

*1) The California Institute for Regenerative Medicine ("CIRM")

The statewide ballot measure, which provided $3 billion in funding for stem cell research at California universities and research institutions, was approved by California voters in November, 2004, and called for the establishment of a new state agency to make grants and provide loans for stem cell research, research facilities and other vital research opportunities in early 2005.
The mission of CIRM is to support and advance stem cell research and regenerative medicine under the highest ethical and medical standards for the discovery and development of cures, therapies, diagnostics and research technologies to relieve human suffering from chronic disease and injury.
On November 18, 2008, JST and CIRM signed MOU on collaboration on stem cell research in order to conduct joint research and develop fostering exchange programs such as scientific seminars and conferences. Based on the above MOU, JST and CIRM are facilitating joint research and research exchange in the field of stem cell research including iPS cell etc.

CIRM URL：http://www.cirm.ca.gov/

## 2. The basic scheme to provide funding for JST-CIRM teams

According to their own rules and regulations, JST and CIRM will provide the research fund to the research teams in Japan and California respectively. In other words, JST provides support to Japanese researchers as a part of JST's Basic Research Program*[2)], and CIRM provides support to Californian researchers utilizing the framework of Basic Biology Award II*[3)]. In this scheme, JST follows its own application call and evaluation process while CIRM follows its own, too.

*2) Outline of JST's Basic Research Program

The purpose of the Basic Research Program is to promote basic research in strategically prioritized fields and create innovative technologies that will lead to the future growth of science and technology and the creation of new industries, as part of a system for encouraging innovation that will lead to social and economical reforms.
In line with national science and technology policies, as well as social and economic needs, the government (MEXT) sets targets that are expected to have a major social impact, and JST establishes research areas that are to be promoted and research supervisors who will act as head of research areas under the strategic sector.
Research supervisors promote basic researches aiming to bring out the seeds of innovative technology in order to achieve the strategic objectives.

*3） Basic Biology Award II
For further details, please refer to: http://www.cirm.ca.gov/RFA_09-02

## 3. Definition of Terms

Terms in this guideline are defined as follows:

3-1. Joint Research Project: a collaborative research project which is carried out by Japanese and California scientists pursuing joint research theme.
3-2. Joint Research Team: a team which is constituted of one Japanese research team and one California research team.
* In case a researcher belongs to two institutions, one in California and one in Japan, that researcher is not qualified to be a member of the team on either side.
3-3. Research Director: researcher who will act as the leader of the Japanese research team. Applications to JST should be submitted by Research Directors.
3-4. Research Group: Each Japanese and California research team can be composed of several research groups.
3-5. Group leader: researcher who will act as the leader of the above group.

## 4. Application and Evaluation Process

JST calls for the application for this program under the national strategic goal "Creation of Innovative Basic Medical Technologies by Stem Cell Manufacturing and Control Based on

Cell Reprogramming" with the designated research area and research supervisor. CIRM utilizes the scheme of its own program, Basic Biology Awards, in the selection and evaluation process for the collaboration with JST.
In order for the application to be considered as the one for a JST/CIRM research team, Japanese researchers should apply for JST on one side while at the same time Californian researchers for CIRM on the other.

Both JST and CIRM go through two application steps, pre-application and full-application. Research proposals submitted to JST and CIRM in the pre-application process will be evaluated by the two agencies respectively, and only the proposals selected by both agencies will be invited to the second stage, full-application.
In the full-application step, the applicants will send applications to each corresponding agency. The full application documents submitted to each agency will be evaluated by JST and CIRM separately and respectively, as in pre-application.

## 5. Eligibility to Apply for JST

The researchers who belong to a research institution in Japan are eligible to apply for the program. This program is designed for researchers who fully understand its objectives and are able to propose to conduct joint research by establishing international cooperative relationship and complementing each other's project on stem cell research in the close coordination with California researchers.
Each applicant can submit only one proposal.

## 6. Eligible Research Proposals

In this collaborative program, the proposals should focus on studies into the basic molecular mechanisms that control the generation and the regulation of human pluripotent stem cells with a particular emphasis on the recently developed cellular reprogramming technologies.

Cooperating with CIRM's Basic Biology Award II (http://www.cirm.ca.gov/RFA_09-02), JST promotes research into the basic biology of iPS cells and other relevant stem cells.
Preferred research areas for collaborative projects include:

- Analysis of molecular mechanisms of cellular reprogramming.
- Molecular basis of human pluripotent stem cell self renewal.

- Characterization of molecular mechanisms of human pluripotent stem cell differentiation.

With a view to meeting one of the national strategy objectives, “Creation of Innovative Basic Medical Technologies by Stem Cell Manufacturing and Control Based on Cell Reprogramming”, JST is seeking the above collaborative research proposals.

JST hopes that joint research projects will elucidate basic mechanisms that provide a foundation for studies leading to innovative Translational Research such as analysis of molecular and cellular mechanisms of disease, toxicology assays based on the use of pluripotent stem cells, etc. in the future.

## 7. Research Supervisor

Research Supervisor will be committed to the program in the following:
Selection of research theme; coordination of research plan (including budget, team arrangement); exchanging views with research directors; advice; evaluation; other necessary research management.

## 8. Budget for the Joint Research Project

8-1. JST

The total budget for one project through the research period is considered to be around 20 to 80 million Yen on annual average. Budget of a project can vary in each year, depending on the content of activities.

Please make a proposal for the most appropriate budget to achieve the research goals. In principle, the above budget shall be appropriated as direct cost as part of what JST calls “commissioned research cost”, and the total amount will be administrated by the research institution that a research director or a group leader belong to. Overhead up to 30% of direct cost will be paid separately to the institution by JST.

Budget items include equipments, consumables, personnel cost and other expenses needed. Due to budget limitations of this program, amounts may be adjusted in each fiscal year, by a consultation with the Research Supervisor based on the research plan of the year.

8-2. CIRM will support funding within the Basic Biology Award II.

Please see the RFA (http://www.cirm.ca.gov/RFA_09-02) for details:

## 9. Joint Research Period

The joint research period shall be for a maximum of 3 years.
The commencing date is expected after April, 2010, however it may be changed according to conditions in CIRM's evaluation process etc.

## 10. Evaluation Process

The evaluation will be carried out in two steps, pre-application and full-application.
Only the selected pre-application proposals are invited to the second stage, full-application
Both Pre-application and Full-application will be evaluated by JST and CIRM respectively.
JST will go through evaluation process with peer reviewers under the guidance of the Research Supervisor. Please refer to Basic Biology Awards II for the details for the evaluation by CIRM: http://www.cirm.ca.gov/RFA_09-02

10-1. JST Evaluation Criteria
The following evaluation criteria will be applied to each proposed project:
1) Conformity with Program Aims and Designated Research Fields
The proposed activity shall conform to the aims of the program and the research fields that the program designates. In addition, the proposed activities shall be supported by the applicants' institutions utilizing their resources available.
2) Significance of Research
- Opening up of a new field or new advances in science and technology through the creation of new scientific knowledge in an existing research field.
- Having a strong impact on science and technology to achieve steady growth and sustainability.

3) Effectiveness of Collaboration Activities
- Having effective consequences on the achievement of the research goals through collaboration

4) Capability of Research Director
The research directors shall have the insight or experience necessary for pursuing the activity and the ability to manage the cooperation and reach the project goals during this program's period of support.
5) Appropriateness of Plan

The plan shall be appropriate from the perspectives of collaboration environment and the research scale.

10-2. Announcement of Selection
The result of the pre-application will be notified in writing around October, 2009, and the final decision regarding the selection of research project will be around April, 2010. The time of announcement is subject to change due to the progress of evaluation on both JST and CIRM sides.

## 11. Number of Proposals to be Selected

A certain number of joint research projects will be selected.

## 12. Administration of Budget

12-1. Contract between a Japanese Team and JST (for Japanese applicants only)
Support will be provided according to a contract for commissioned research concluded between JST and a university or public research institute, etc. (hereinafter referred to as the "institution").
The participating researchers should consult with the department in charge of their institution for the appropriate administration of the allocated budget based on the contract.
As for the contract between the Japanese institution and JST, it stipulates the Article 19 of Industrial Technology Enhancement Act be applied to patents or other intellectual property rights generated as a result of this project, and that these can be the properties of the institution with which the researcher is affiliated.

12-2. Contract between California Team and CIRM
All Grants awards made by CIRM will be subject to CIRM regulations.
Please see the RFA (http://www.cirm.ca.gov/RFA_09-02) for details:

12-3. Research Agreements between Teams
Entering into a contract for management of intellectual property issues may be envisioned between the Japanese institutions and the California institutions for the implementation of actual research activities. For intellectual property rights issues, please refer to the section [13. Intellectual Property Rights] as described below (page 8)

12-4. Funding Expenses

Funding provided within this call is intended to support a complete joint research project for Japanese teams.

Research expense (direct cost) needed for the joint research project may be spent for the following items:

1) Goods: expense for facilities, equipment and consumable supplies.

2) Travel: travel expense for research directors and research associates (team members); or for the researchers who are invited to attend special events to pursue the goals of research project.

3) Personnel expense:

Salaries: in principle, salary for newly hired fixed-term and full time employees on annual salary base (researcher, technical staff etc.) to carry out the research project.

Fees: fees for fixed-term employees on an hourly wage for data reduction work etc. (technical staff, research support staff etc.), lecture fees etc.

4) Other: Other cost needed for joint research project as follows:

Publication of research results (submission fee, printing etc.)

Equipment leasing, books, transportation

* If you have difficulties in judging appropriateness of the cost, please contact JST.
* JST requests for research institutions to administrate the budget in a flexible and efficient manner, since the funding is financed from the national treasury, appropriate administration is strongly requested by establishing certain rules and guidelines such as contract for commissioned research and description of business processing etc.
* Overhead up to 30% of the direct cost will be paid separately to the institution by JST.

Funding for California portion of a JST-CIRM team will be supported according to the CIRM regulations. Please see the details: CIRM Basic Biology Award II RFA (http://www.cirm.ca.gov/RFA_09-02)

## 13. Intellectual Property Rights

As for the contract between the Japanese institution and JST, it stipulates the Article 19 of Industrial Technology Enhancement Act be applied to patents or other intellectual property rights generated as a result of this project, and that these can be the properties of the institution with which the researcher is affiliated.

A contract to deal with intellectual property issues must be concluded between the Japanese institutions and the California institutions for the implementation of actual

research activities.
When agreement is concluded between the two parties, a copy of signed written agreement which indicates the contents should be submitted to both JST and CIRM prior to start of funding.

As for application for intellectual property rights jointly made by Japan and California institutions in the process of joint research, the applicants funded by JST are required to comply with terms and conditions set in CIRM's regulations in addition to a contract for commissioned research concluded between JST and the institution. Please refer to the below URL for more details of CIRM's regulations:
http://www.cirm.ca.gov/cirm/Regulations
(For intellectual property rights, please see chapter 3 and 4 of the CIRM regulations)

With regards to products based on intellectual property rights which are jointly held by Japan and California institutions, it is required to comply with the following CIRM regulations concerning access and pricing when the products are commercialized and sold in California. For the details, please refer:
http://www.cirm.ca.gov/reg/pdf/Reg100407_IP_RevShare_Profit_Org.pdf

## 14. Report

14-1. Annual Progress Report (Only for Japanese Research Director)
At the end of each fiscal year, the Research Director shall promptly submit a progress report on the status of research, and the institution with which the Research Director and Group Leader are affiliated shall promptly submit a financial report on supported expenses.

14-2. Final Report
After completion of the period of Joint Research Project, research directors shall promptly submit to JST a final report, in addition to a financial report, on the research activities. The report shall include a general summary compiled jointly by both of the Japanese and the California research groups, which California researchers are requested to submit to CIRM. If papers describing results of research are presented to academic journals, societies and so on, please attach copies of such papers to the final report.

## 15. Responsibilities of Japanese Research Directors after Proposals are Approved

After the proposal has been approved, research directors and group leaders shall observe the following rules when carrying out the joint research and spending the research fund.

15-1. Promotion and Management of Research

Research directors are responsible for the management of the research project as a whole including the research planning and implementation, working with the counterpart in California.

They shall prepare a research report and submit it to the research supervisor and JST, and be responsive to their evaluation. They also have to submit research progress reports as designated by research supervisors.

15-2. They are responsible for the appropriate management of research budget of the whole research team by working closely with the institutions they belong to. Research directors and group leaders are expected to consider seriously the research and work environment and conditions for the researchers employed through JST funding.

15-3. How research results should be handled

The research results should be published in and outside of Japan in every possible way with the consideration into the fact that the fund comes from the national government and intellectual property rights as well.

When publishing the research results in papers and etc., it should be stated that they were brought about from JST's Basic Research Programs.

They may be advised to make a presentation of their research results at workshops or symposiums held by JST in and outside Japan, together with other researchers.

The acquisitions of intellectual property rights are strongly encouraged. The application for Intellectual property rights shall be made by research institutions, based on the research agreement between researchers and JST.

15-4. Research directors have to follow the research agreement and other relevant rules of JST.

15-5. Please note that JST provide some items of information such as the name of researchers, research budget, and etc., to e-Rad and other government data base. Research directors may be asked to provide other necessary information regarding the

research.

15-6. They have to cooperate for the evaluation of the project as part of JST's Basic Research Program, the investigation of the budget allocation, and the auditing of the national treasury.

15-7. They may be asked to provide necessary information and accept interviews for the follow-up evaluation which is carried out a while after the research period is over.

## 16. The Application and Evaluation Process

The application procedure consists of two stages: First, applicants must submit a PreApplication that will be subjected to an initial review (as described in the RFA). For this stage, Japanese teams should submit their PreApps in Japanese and English to JST, whereas California applicants must submit their pre-application in English to CIRM. It is important to note that the submission to CIRM by the California team is due September 3, 2009 and should include description of the Japanese contribution to the overall effort. The deadline for submission to the JST (by the Japanese research director), however. will be **September 15, 2009** in order to allow extra time to prepare the text in both languages. After the initial review by JST and CIRM of their respective submissions, the applicants with the most promising and responsive proposals will be invited to submit Full Applications. Full-Applications should be prepared collaboratively by the Japanese and California teams and must be submitted in parallel to both JST and CIRM.

16-1. Pre-application

16-1-1. Application process

**Applicants of Japan Team shall submit pre-application to JST no later than September 15, 2009 (Japan standard time).**

California applicants must submit a pre-application describing the joint project to CIRM by 5:00 (PDT) on September 3, 2009.

Japanese applicants have to write pre-application (in Japanese and English) using the application form set by JST through the cross-ministerial R&D management system (online application system) (http://www.e-rad.go.jp/index.html).

California researchers should submit proposals as described in the CIRM Basic Biology Awards II RFA (http://www.cirm.ca.gov/RFA_09-02).

16-1-2. Evaluation Process for Pre-Application

Pre-application will be evaluated by JST and CIRM respectively. JST will select members of the evaluation committee consisting of peers to review all proposals. Please refer to the details for pre-application of CIRM Basic Biology Awards II RFA.

The result of selection will be notified to applicants in writing around the end of October, 2009. Applicants whose projects are judged as the most promising, competitive and responsive pre-application by both sides will be invited to submit a full-application.

16-2. Full-Application

16-2-1. Application Process

Full-application may be submitted only by Japanese/California applicants who are explicitly invited to participate in the second stage of submission following the positive evaluation of their pre-application. In the second stage, joint proposals should be submitted by Japanese/California applicants. The details for JST full-application process such as application forms (in Japanese and English), submission instructions, and deadlines will be provided at the time of notice of results of the pre-application review.

Please see CIRM Basic Biology Award II RFA for details.

16-2-2. Evaluation Procedure for Full-Application

Full-application will be evaluated by JST and CIRM respectively. JST will select members of the evaluation committee consisting of experts to review all proposals.

Applicants whose projects are judged as the most promising, competitive and responsive full-application by both sides will be approved.

The result of selection will be notified to applicants in writing around April, 2010.

*JST will not accept the change of a research theme or contents once the proposal goes on to the stage of a full-application.

## 17. Strategic Goal

1. Title

Creating fundamental technologies for advanced medicine through generation and regulation of stem cells, based on cellular reprogramming (Set in FY2008)

2. Content

Cellular reprogramming that can turn differentiated cells into pluripotent stem cells draw attention as potential means to realize pioneering advanced medicine. A Japanese researcher brought about major breakthroughs in this field in 2006 and 2007. The strategic sector aims at advancing and simplifying the reprogramming technologies, based on molecular biological mechanisms of the reprogramming process. In addition, using the technologies, stem cells that could be generated from somatic cells of patients or healthy persons will be given to elucidate pathological mechanisms and to establish fundamental technology such as new therapy strategies and methods to detect and test side effects of drugs.

3. Policy position (relationship with "Science and Technology Basic Plan" and "Strategic Prioritized Science and Technology")
The strategic sector is relevant to "Science and technology for reconstruction of complex systems of life" within the "Strategic Prioritized Science and Technology" field of life sciences in the plan. Specifically, this strategic sector is also relevant to "Research for understanding higher-level control mechanisms in living organisms," listed in the content of Research and Development.

4. Position of this research project among research promotion measures in relevant research fields, differences from other related measures, and differences in effects of policy
This strategic sector focuses on research aiming to develop the cellular reprogramming technology, followed by applying the technology to elucidation of pathological mechanisms of congenital diseases and development of detecting and testing methods for side effects of drugs. Research subjects under the strategic sector are different from those of other projects, the "Project for realization of regenerative medicine (Ministry of Education, Culture, Sports, Science and Technology, since 2003)," which aims to establish cell therapies and tissue transplantation using stem cells. The research phase of this strategic sector is different from that of a project supported by Grants-in-Aid for Scientific Research (Grant-in-Aid for Specially Promoted Research "Molecular basis of nuclear reprogramming"), which focuses on scientifically elucidation of the molecular mechanism of reprogramming by 4 essential factors.

5. Achievements and goals expected; and reasons, urgency, and need for priority from specialists and industries over other Strategic Prioritized Science and Technology
The objective of the strategic sector is to establish fundamental technology which can help elucidating pathological mechanisms of congenital diseases, studying new therapy strategy

and detecting and testing side effects of drugs through advancing and simplifying the cellular reprogramming technology and establishing disease model from patients' somatic cells. Concrete goals are as follows:

[Examples of short-term goals]
- Establishment of a reprogramming technology with less genomic stress, by precisely introducing the pluripotency factors into genome, or by using of chemical compounds
- Elucidation of pathological mechanisms through disease model from somatic cells of patients or healthy persons

[Examples of medium-term goals]
- Identification of candidate compounds for drug discovery by using the above-mentioned disease model cells, and establishment of fundamental technology for gene therapy
-Finding of methods for detecting side effects of drugs, such as arrhythmia, using pluripotent stem cells from healthy persons

By 2006, 132 stem cell institutes had been established worldwide. At present, researchers in these institutes are trying to establish human induced pluripotent stem (iPS) cells after the success in Japan, bringing severe competitions in the field. It is thus necessary for Japan to keep the position as one of the world's leader in the field by steady implementation of these research themes.

6. Scientific justification for the research and development goals
Advances in related fields of individual research are summarized as follows:
The importance of human disease model cells has been recognized so far, even in the stages of basic research prior to clinical research. Progress in stem cell biology prompted research and development of reprogramming technologies in Europe and the United States that generate disease model cells from patients' own cells, namely "therapeutic cloning". However, this research is confronted with some obstacles, including ethical controversy concerns due to the use of human embryonic stem (ES) cells and low efficiency of generation by nuclear transfer or cell fusion techniques.
In 2006, a Japanese researcher succeeded in establishing iPS cells that are close to ES cells from murine fibroblasts by introducing 4 defined factors, and in 2007, successfully established human iPS cells. These achievements reduced the aforementioned ethical problems, and brought a major breakthrough in reprogramming research. Japanese stem cell research, conducted mainly in universities, maintains internationally-recognized high

levels of researchers, equipments, and publications through Grants-in-Aid for Scientific Research and the "Project for realization of regenerative medicine".
Utilizing the high potential of stem cell research in Japan, this strategic sector will enhance the development of new therapies and preventive medicines required in an aging Japanese society through promoting the basic research based on the reprogramming technology. In addition, stem cell research itself is expected to develop as a major research field, comprising - based on the view of stem cells - all areas including developmental and regenerative biology, pathology, and age-related tissue impairment.

7. Considerations in achieving the research and development goals (research team organization, etc.)
To achieve the goal of this strategic sector, it is advised to take a team-oriented research approach in which a team consisted of researchers with abundant clinical findings of diseases and researchers with excellent cellular analysis technologies such as flow cytometry. In addition, individual research will also be necessary to effectively develop cellular reprogramming technologies based on molecular biological mechanisms. Individual research projects will be conducted mainly by young researchers who have new ideas, such as direct induction of stem cells or progenitor cells of various tissues from skin cells or tissue stem cells without necessity of iPS cell stage.
Advances are made quickly in the field of stem cell research worldwide, and the competition to acquire intellectual property rights is fierce. Although Japan currently holds the second-largest number of patents concerning stem cells after the U.S., the number of acquired patents has tended to decrease recently. In the researches implemented in this strategic sector, attention should be paid to patent acquisition as well as patent quality, in view of the stem cell patents applied in the U.S. and other countries. Moreover, it will be necessary to pay attention to bioethical appropriateness of each research project, because human cells will be used.

(Reference) Political goals to be achieved in this project
More recently, iPS cells have been obtained by reprogramming of human somatic cells via introduction using retrovirus vectors of 3 factors, Oct3/4, Sox2, and Klf4.
In the strategic sector, research on targeted introduction of genes and control of the number of genes to be introduced into single cells will be conducted at first, through genomics, chromosome structure, and especially epigenetics analyses of the cellular reprogramming mechanism. High-throughput screening of reprogramming-inducing compounds will also be conducted to achieve precise control of introduction factors as well as simplifying of

generation methods. With effective use of advanced reprogramming technologies, iPS cells will be generated from somatic cells of patients with congenital disease and will be differentiated into disease model cells for elucidation of pathological mechanisms. On the basis of findings obtained from these activities, fundamental technologies for identifying candidate compounds for disease-controlling drug and detecting side effects of drugs using iPS cells derived from healthy persons.

* Ministry of Education, Culture, Sports, Science and Technology (MEXT) set up “the comprehensive strategy for the promotion of iPS cells research”, and the iPS cell research programs are in progress all over the country at many levels and from many perspectives. As part of the efforts, MEXT established “The iPS Research Network” involving the research institutions and researchers participating in the MEXT-funded and JST-funded iPS cell research programs. This network stipulates its own rules and regulations regarding intellectual property rights, publication of research results, and confidentiality, is expected to function efficiently for the total promotion of iPS cell research through the permission of sharing among members of intellectual property rights and materials.
As this collaboration program constitutes the “Network”, the selected researchers are, as a rule, required to join the “Network”, and asked to go with the national policy objectives described in the government’s comprehensive strategy. (This rule does not apply to researchers or institutions on the CIRM side.)

* Research Supervisor:
Dr. Ryozo NAGAI (Dept. of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Professor and Chairman)

* Position of the strategic goal in this joint research program
With a view to meeting one of the national strategy objectives “Creation of Innovative Basic Medical Technologies by Stem Cell Manufacturing and Control Based on Cell Reprogramming”, JST is seeking research proposals.
On the Japan side of a collaboration team, the proposals should focus on the research of iPS cells derived from the cellular reprogramming technologies.
Concrete goals to be expected in future as follows:

- The establishment of patient-derived pluripotent stem cells of intractable diseases.
- The development of disease models by using of patient-derived pluripotent stem cells to understand the pathology of the disease at molecular level.

- The development of in vitro models to predict and/or evaluate side-effects of drugs based on the use of iPS technology.

It is strongly advised that both Japan and California research teams work together to achieve their common goals, by complementing the work of each other and maintaining the good cooperative relationship through the research period.