CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The state stem cell agency

"Matching Authority" to Advance Stem Cell Science in Discovery and Development towards Therapies

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Presentation will address the following areas

- Brief overview of the application of a “matching” or “match-like” authority at CIRM, the California State Stem Cell Agency
- Considerations that went into the development of its authority – what were the identified advantages and opportunities?
- What are the pitfalls and lessons learned in deploying a match-like authority or requirement?

California Institute for Regenerative Medicine

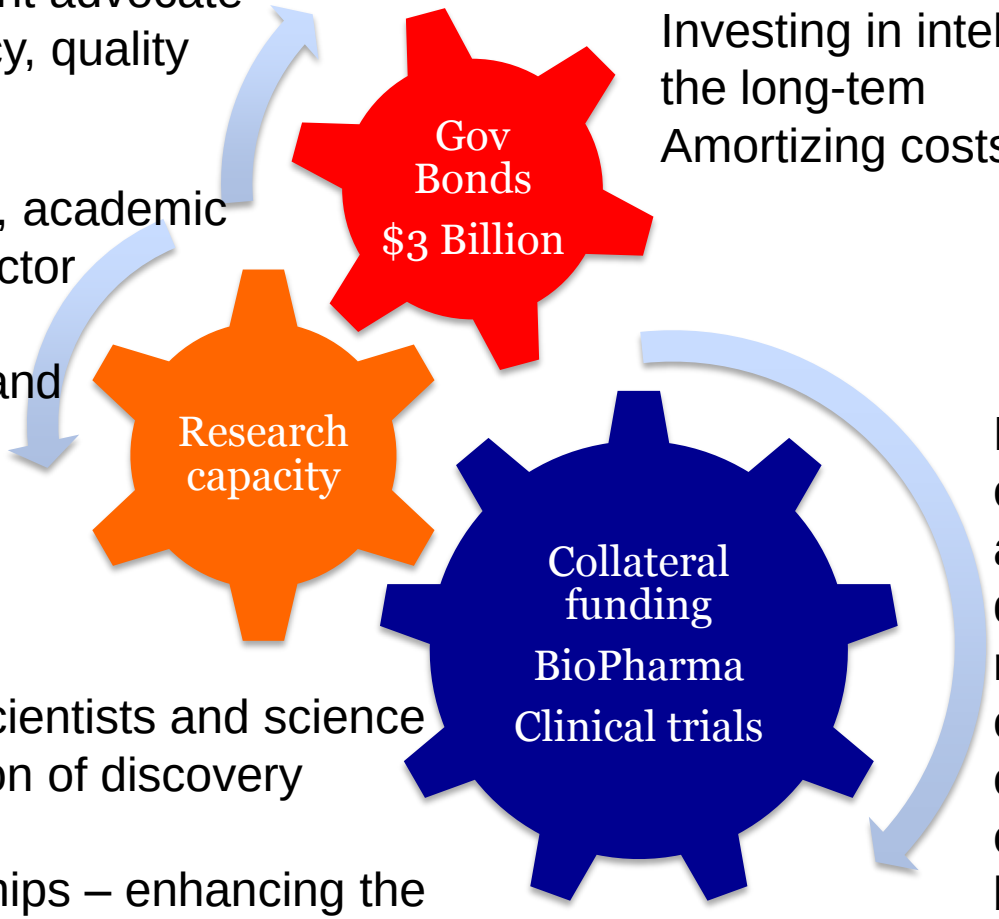
- California taxpayer supported research institute – proposition 71 approved by voters (2004)
- Authorized $3 billion of State Obligation Bonds to fund stem cell research in California (max $300mill/yr) <6% for admin.
- Created an environment that supports both public and private sector research into life-saving and life-improving therapies for patients, based on stem cell science

Funding, partnerships, facilitating pathway into the clinic

Community support, industry and academia support, patient advocate partnership, transparency, quality

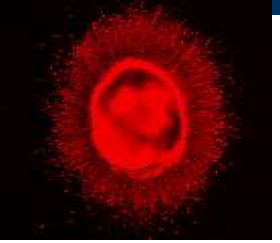
Investing in intellectual capital for the long-tem
Amortizing costs across benefits

Stimulus to California, academic and biotechnology sector
Building institutional research excellence and collaborations



Economic benefits of patient cures and
quality of life, reduced health care costs, commercialization concurrent benefit but not sole driver

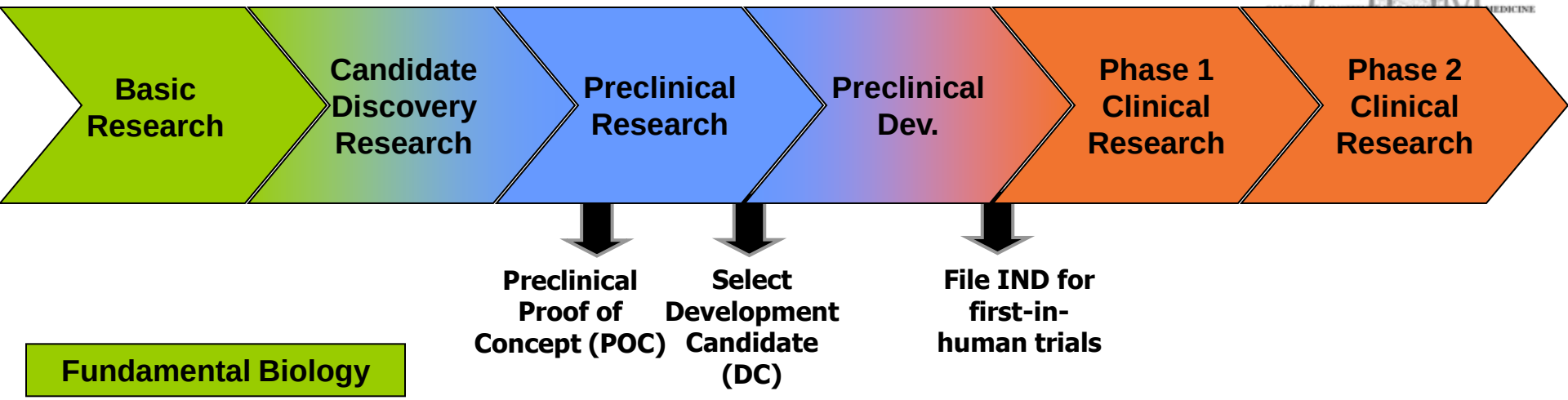
Supporting the best scientists and science
Encouraging translation of discovery to clinical opportunity
International partnerships – enhancing the best - critical to success



CIRM activities towards our scientific mission

- 453 research and facilities awards
- 59 Institutes/Companies with CIRM awards
- 12 new institutes and centers of regenerative medicine ~$1 B ($271M from CIRM – remainder of $1 B from outside CIRM)
- $1.3 B allocated
- Over 1000 major scientific papers published (28% high impact journals)
- Over 130 major stem cell researchers relocated in California
- 62 Translational programs across spectrum of diseases
  - 14 Disease Teams (preclinical) awarded – up to $20 M/award aimed for first-in-human trials within 4yrs;
- New Disease Teams and Strategic Partnerships in 2012

Programs cover product development spectrum – matching opportunities



Fundamental Biology

Early Translational Research I,II,III

Disease Team Research I

Disease Team Research II

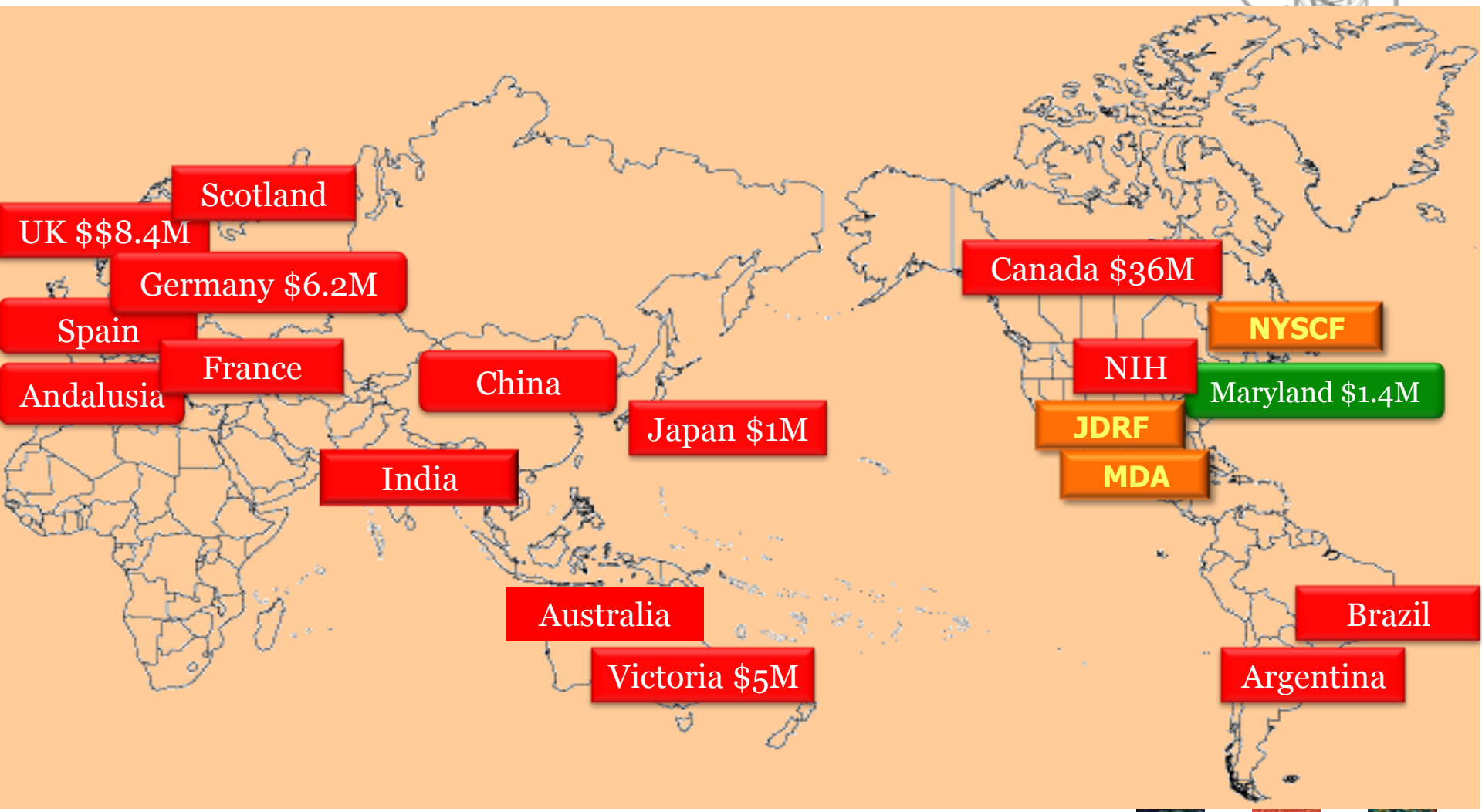
Tools & Technologies

Targeted Clinical Development

Strategic Partnership I

Transplantation Immunology

CIRM's Collaborative Funding Network – Leveraging Opportunities



Brief overview of CIRM's utilization of a "matching" or "match-like" authority

- State-of-the-art facilities
- Translational and development research programs
- Collaborative Funding Programs across entire product development spectrum
- "Matching" or leveraging with public and private institutions, foundations, industry, other government agencies

“Matching” in developing state-of-the-art research facilities

- 12 State-of-the-art facilities CIRM $271M and Institution, donors up to $1B
- One-time, space development/renovation costs for capital project proposals in 1of 3 categories:
  - Institutes: stem cell research in: 1) basic and discovery; 2) preclinical; and 3) preclinical development and clinical.
  - Centers of Excellence: stem cell research includes 2 of the 3 research elements.
  - Special Programs: stem cell research includes 1 of the 3 research elements.
- Matching Funds and Leverage: Applicants required to match at least 20% of CIRM grant amount. Funding from other sources above cash match was considered “Project Leverage” and was part of the basis for the competitive evaluation.

“Matching” in translational/development programs

- Disease Teams I - 14 Teams, up to $20M/award over 4 years
  - Preclinical research, and development; goal of filing IND to enter first-in-human clinical trials
  - Matching not required; matching provided by one company; 5 teams had leveraged $ through collaborative funding partners for partnered research in other countries
  - Mutually agreed upon milestones (Go – No Go/Progress) before CIRM $ released, with interval evaluation at key milestones by external experts - Clinical Development Advisor panel

“Matching” in translational/development programs

- Disease Teams II – Up to $20M/award over 4 years; Grants Working Group reviewed applications, and recommendations to ICOC in July 2012, for final decision
  - Preclinical development with goal of filing IND to enter first-in-human clinical trials and/or conduct and completion of clinical trials;
  - Matching is a review criteria and prioritized (expected from biotech/pharma, at least 1:1, highly recommended for non-profits to partner with industry/other investors to obtain match)
  - Mutually agreed upon milestones and process of evaluation; funding disbursements as in DTI

“Matching” in translational/development programs

- Targeted Clinical Development (clinical trials):
  - Completion of clinical trial
  - Required at least 1:1 match up to $25M over 3 years; Mutually agreed upon milestones before CIRM $ released – Go-No Go/progress
- Strategic Partnership Fund I covers “valley of death” or “bridge to cures” development e.g., IND enabling and completion of early phase clinical trial(s) and/or completion of early phase clinical trial(s):
  - Goal is to attract industry engagement and investment in CIRM-funded research;
  - Requires evidence of commercial validation (e.g., financial strength of applicant or co-funding from industry or VC partner) with required 1:1 match of total CIRM dollars (up to $10M over 4 yrs), with industry $ all going to direct costs; milestones, evaluation

“Leveraging” across product development spectrum with Collaborative Funding Partners

- $138 Million in total commitments to CIRM RFAs by CFPs
- 20 Collaborative research teams successfully competed
- $60+ Million actual amounts awarded by CFPs to date
- $200 million(Approx) in CFP + CIRM awards to date

Partner Participation in CIRM RFAs

RFA	Funding Partner	Grants Awarded
Basic Biology II and III	Japan Germany	1 1
Immunology	Victoria Germany	2
Early Translation I	Victoria	4
Early Translation II	Germany Maryland	4 2 (Supplement)
Early Translation III	Japan, China, Australia, Germany	Pending
Disease Team I	Canada United Kingdom Germany Spain	2 2 1 (Supplement)
Disease Team Therapy Development	Canada, Andalucia, Germany	Pending

Collaborative Project Example

Basic Biology Award

PI: Anderson (Univ. of California, Irvine)

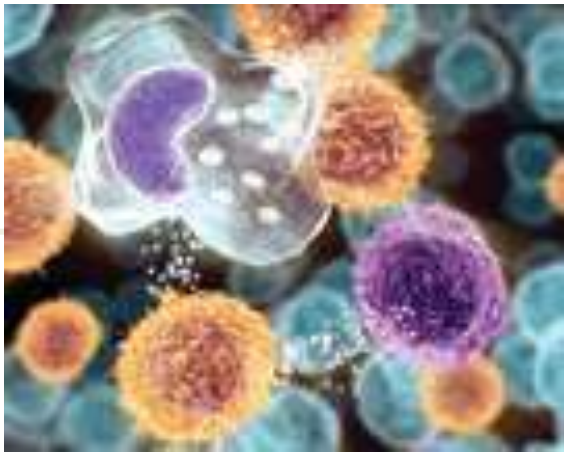
Partner PI: Nakamura (Keio University, Tokyo)

CFP: JST (Japan)

Project Focus: Microenvironmental influences on repair potential of neural stem cells (NSCs) in spinal cord injury

Approach: Analyze the effects of stem cell source and inflammatory microenvironment on NSC differentiation, migration, engraftment, and tumorigenicity using in vitro and animal models

Collaborative Project Example



Stem Cell Transplantation Immunology Award

PI: Weinberg (Stanford University)

Partner PI: Bernard (Monash University, Australia)

CFP: Victoria (Australia)

Project Focus: Generation of a new thymic microenvironment to induce immune tolerance

Approach: Use of embryonic stem cell (ESC) -derived thymic epithelial cells to generate new microenvironment and assess immune responses against ESC and iPSC derived cells

Collaborative Project Example

Early Translation II Award

PI: Isseroff (University of California, Davis)

Partner PI: Machens (Technical University of Munich)

CFP: BMBF (Germany)

Project Focus: Improved option for patients with non-healing diabetic foot ulcers

Approach: Use of allogenic mesenchymal stem cells on a scaffold, preconditioned to maximize reparative properties

Collaborative Project Example

Disease Team Award

PI: Weissman (Stanford University)

Partner PI: Vyas (University of Oxford)

CFP: MRC (United Kingdom)

Project Focus: Leukemic Stem Cells in Hematologic Malignancy (AML)

Approach: Monoclonal antibody against CD47 – antigen that is expressed on LSC and inhibits their phagocytosis by macrophage

CFP Program

- The CFP Network 20 participants across the globe
  - North America: NIH; Maryland; Canada
  - South America: Brazil, Argentina
  - EU: UK, Germany, France, Spain, Scotland, Andalucia
  - Asia-Pacific: Japan, China, India, Victoria, Australia
  - Foundations: JDRF; NYSCF, MDA, Keystone
  - Pending discussions:
    - Countries: Netherlands, Sweden, Singapore, Korea and Israel
    - Foundations: ALS, Cure Huntington's, Foundation Fighting Blindness, Michael J, Fox, National MS, etc.
- Value Proposition Elements:
  - Link California scientists with peers around the world via participation in CIRM RFAs
    - Proposed teams compete in peer review
    - 20 jointly funded projects already underway
    - Total budget of about $200 million
    - Overall productivity assessment - unique teams, good progress to date, combining strengths across borders



Considerations that went into developing "matching" –advantages and opportunities

- Leveraging of CIRM investment
- Sharing risk
- Enabling critical early development programs for therapies
- Financial disbursements linked to progress on mutually agreed upon milestones
- Engaging industry early in development process, to ensure industry commitment to follow-on-financing of later stage clinical development if milestones met
- Global presence – facilitate collaborative work with best investigators in the world – collaborative funding partner program, structured primarily with state or national government funding agency through MOU

Potential pitfalls and lessons learned in deploying a match-like authority

- Academics, non-profits may not be able to compete, or are challenged, in meeting match requirements on early stage research
- Small biotechs, start-ups, are challenged in a very difficult economic environment for innovative technologies (scientific, regulatory, business risk)
- Requires proactive role with encouraging, facilitating partnering, collaborations between academics and industry
- Initiatives that engage industry need to consider timeframes conducive to development and movement towards commercialization
- Helping academics with resources, skill sets that can attract industry partners and investment, VCs



Lessons learned – translational programs driven by science and evidence needed on regulatory pathway

- Prior to award
  - mutually agreed upon Go, no go and progress milestones, success criteria
  - During the conduct of research
    - Interactive ongoing discussions between CIRM scientists and funded research team
    - Updates on interval progress on bi-annual to quarterly basis and overall annual progress updates
    - clinical development advisor meetings yearly/ key milestones (DT1 at 12-18 month milestones)
  - CIRM/FDA webinars, educational roundtables, conferences, seminars