Joint Science Subcommittee / Neuro Task Force Meeting

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August 16, 2024

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Presentation Overview

1. Pre-read: Background
2. Pre-read: SAF Overview
3. Updates to Goals 1 & 2
4. Goals 3 & 4
5. Discussion/Next Steps

Please note:

To ensure ample time for discussion, the Background and SAF Overview will not be presented during the meeting on August 16th. For those interested, these sections were previously presented at the June 27th ICOC meeting. Please review these slides accordingly. (6:52:15 timepoint)

Goals 1 & 2 were presented at the July 11th Joint Science Subcommittee & Neuro Task Force Meeting. (2:38 timepoint)

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5-Year Strategic Plan (2022-2027) | 3 Themes

Advance World Class Science

- Develop shared resources
- Build knowledge networks

Deliver Real World Solutions

- Advance therapies to marketing approval
- Create a manufacturing partnership network
- Expand Alpha Clinics Network
- Create Community Care Centers of Excellence

Provide Opportunity for All

- Build a diverse and highly skilled workforce
- Deliver a roadmap for access and affordability

Background & Rationale

CIRM must allocate remaining resources to maximize its impact by considering available funds and reviewing past strategies

- CIRM has established itself as a leader in stem cell and regenerative medicine, funding basic research, infrastructure, education/training, and regenerative medicine discovery and clinical development
- Since CIRM's inception, the regenerative medicine field has grown exponentially
- CIRM has finite resources
- Demand for CIRM funding exceeds available resources

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SAF Mandate

- September 2023 Science Subcommittee: Prioritization Kickoff Discussion (BM Fischer-Colbrie)
  - **Outcome:** Ask for CIRM staff to develop an approach and recommendations for prioritization
- March 2024 Science Subcommittee and ICOC: Presented SAF and continued process with September 2024 target for recommendations

The **Strategic Allocation Framework (SAF)** is a structured and data-driven approach to prioritize resource allocation and provide recommendations to the ICOC for continued implementation of CIRM's strategic plan

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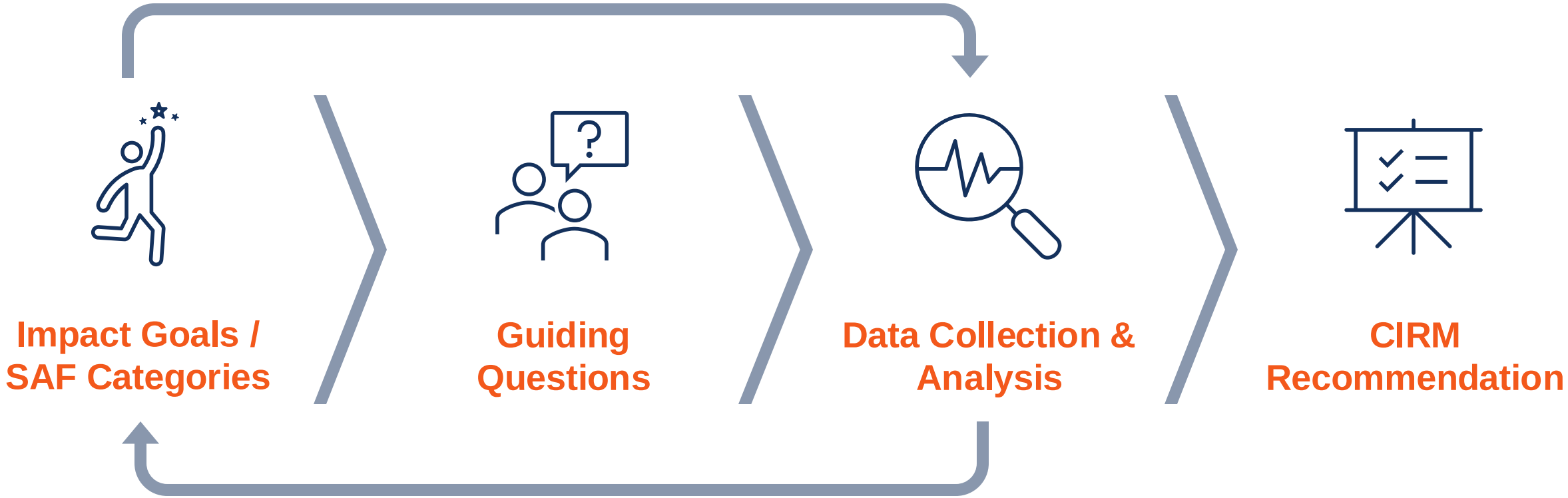
SAF | Design Questions

Determine:

- How can CIRM make the greatest impact on its mission?
- How might CIRM effectively allocate its remaining budget of $3.86B?
  - How might CIRM effectively allocate its remaining Neuro budget of $1.14B?

SAF | Process*

CIRM Staff



*Science Subcommittee, NTF, AAWG will inform specific aspects of the Recommendations

SAF Categories

SAF Categories

1. Cell and Gene Therapy Approvals
2. Accessibility and Affordability of CIRM-Funded Cell and Gene Therapies
3. Discovery of Novel Disease Mechanisms
4. Diverse Workforce Development

*NTF will inform specific aspects of the Recommendations

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CIRM Preliminary* Impact Goals

Accelerating Discovery & Translation

1. **Catalyze** the identification and validation of at least X novel targets and biomarkers, ensuring integration into preclinical or clinical research for diseases in California
2. **Accelerate** development and utilization of X technologies that demonstrate improvements in safety, efficacy, and quality of cell and gene therapies

Cell & Gene Therapy Approvals

3. **Advance** at least X rare disease projects to BLA
4. **Propel** X therapies targeting diseases affecting Californians to late-stage trials

Accessibility & Affordability of CIRM-Funded Cell & Gene Therapies

5. **Ensure** that every CIRM funded project completing a late-stage clinical trial has a strategy that enables access and affordability by all California patients, particularly underserved populations

Diverse Workforce Development

6. **Enhance** the integration and real-world application of training programs through strategic partnerships

**Preliminary Impact Goals to be refined through September ICOC*

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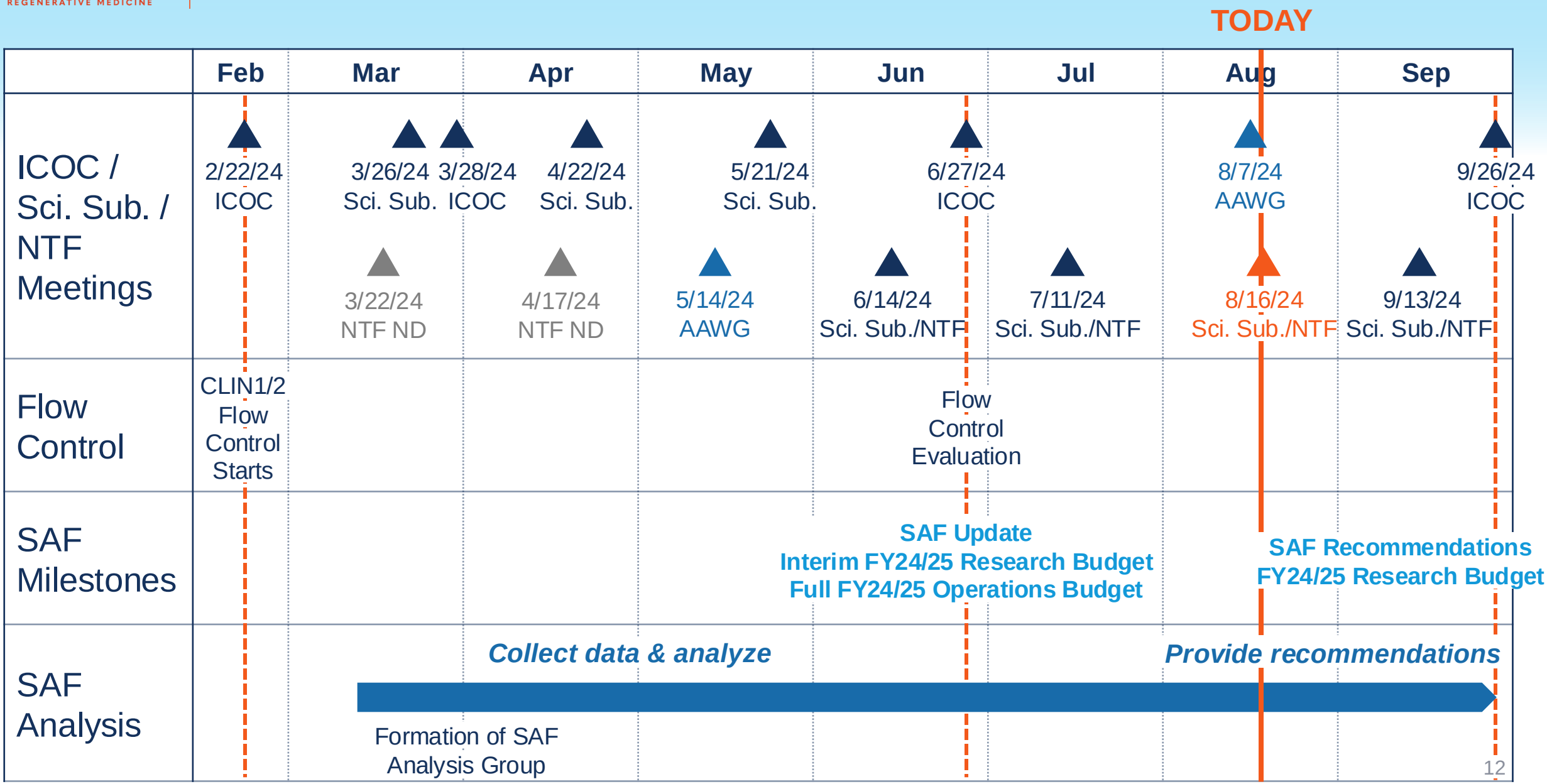
SAF Timeline



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CIRM CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE | Goals 1 & 2

Category: Accelerating Discovery & Translation

Goal 1 - Catalyze the identification and validation of at least X novel targets and biomarkers, ensuring integration into preclinical or clinical research for diseases in California

Goal 2 - Accelerate development and utilization of X technologies that demonstrate improvements in safety, efficacy, or quality of cell and gene therapies

Goal 1 Recommendations

Goal 1 - Catalyze the identification and validation of at least X novel targets and biomarkers, ensuring integration into preclinical or clinical research for diseases in California

Recommendation 1 - DISC4 and DISC5 as Pillars for Discovery funding - Support comprehensive discovery research through structured initiatives DISC4 and DISC5

Approach: Encourage collaborative, multidisciplinary innovation in stem cell and genetic research across diverse disciplines and disease indications with early engagement of industry to address reproducibility and scalability issues

Recommendation 2 - Establish a Data Coordinating and Management Center (DCMC) - Streamline CIRM data management to enhance the utility of cross-disease data

Approach: Fund and develop a central hub for data coordination, facilitating better integration with consortia and research initiatives and enabling data science collaborative efforts via dedicated grants

Recommendations for Goal 2

Goal 2 - Accelerate development and utilization of X technologies that demonstrate improvements in safety, efficacy, or quality of cell and gene therapies

(Pilot) **INFR Technology Platform Program -** Bridge the gap between research and commercialization by fostering partnerships between academic researchers and industry professionals

Approach: Support multi-stakeholder technology incubation programs to achieve defined technology readiness levels thereby facilitating rapid application in cell and gene therapy development

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Preliminary Goals 3 & 4

Category: Cell & Gene Therapy Approvals

Goal 3 - Advance at least X rare disease projects to BLA

Goal 4 - Propel X therapies targeting diseases affecting Californians to late-stage trials

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Objective of Today

Review Preliminary Goals 3 & 4:

1. High-Level Questions
2. Data & Analysis
3. Recommendations
4. Discussion

Preliminary Goal 3 | High Level Questions

Goal 3 - Advance at least X rare disease projects to BLA

High-Level Questions

- **Current Portfolio:**
  - What proportion of the current portfolio supports rare diseases?
  - What proportion of CIRM-funded rare disease grants are likely to attain FDA approval in the next five years?
- **Infrastructure Utilization:**
  - How can CIRM's previous investment in clinical, manufacturing, and patient support infrastructure support this goal?
  - Are there any additional infrastructure investments necessary to support the unique requirements of rare disease therapy development and BLA filings?
- **Approach:**
  - What mechanisms can be adopted to facilitate the scalable development of accessible and sustainable rare diseases therapies?
- **Partnerships:** Are strategic partnerships necessary to achieve this goal?

Preliminary Goal 4 | High Level Questions

Goal 4 - Propel X therapies targeting diseases affecting Californians to late-stage trials

High-Level Questions

- **Disease Impact:** What diseases relevant to CA populations are amenable to CGT therapies?
- **Current Portfolio:**
  - What diseases relevant to California's population have been or are in the current CIRM clinical pipeline?
  - How many have progressed to later stage development?
  - What are the challenges facing the current portfolio?
- **Approach:** What types of enhancements to our funding programs are necessary to address these challenges and optimize the pathway for candidates towards late-stage clinical development?
- **Partnerships:** Are there strategic partnerships necessary to achieve this goal?

SAF Data Sources

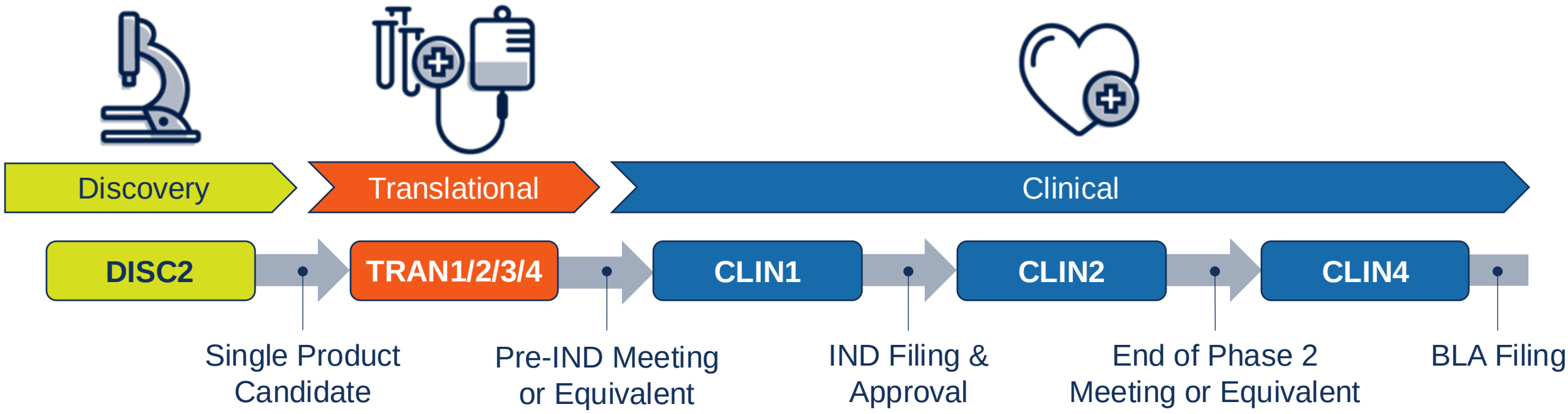
- California department of public health, CDC, Cancer Registry reports
- CIRM internal portfolio data analysis
- CIRM independent research by project leads and science officers
  - Clinical trials
  - Economic burden reports
  - News reports
  - Peer review papers
  - Research articles
- GlobalData database for industry analysis
- IQVIA CA disease landscape analysis
  - Anonymized 1.5B patient claims data past 12 months matched to ICD-10 medical codes
  - Subject matter expert review and insights
  - Health Economics and Outcomes Research (HEOR) data
  - Patient Reported Outcomes (PROs) data
  - NIH funding and Industry pipeline data
- Neuro Task Force survey results and analysis
- Meetings with federal agencies

SAF Data Gathering and Analysis Team

- **Janie Byrum**
- Jim Campanelli
- **Rosa Canet-Avilés** *
- Lila Collins
- **Abla Creasey**
- Uta Grieshammer
- **Dongjin Lee**
- Lisa Kadyk
- Hayley Lam
- **Lisa McGinley**
- Ross Okamura
- **Shyam Patel** *
- **Kelly Shepard**
- **Sara Taylor** *
- Sohel Talib
- Chan Tan
- **Thomas Trinh** *
- Paul Webb
- Daisy Xin

* core team

Current CIRM R&D Pipeline Programs



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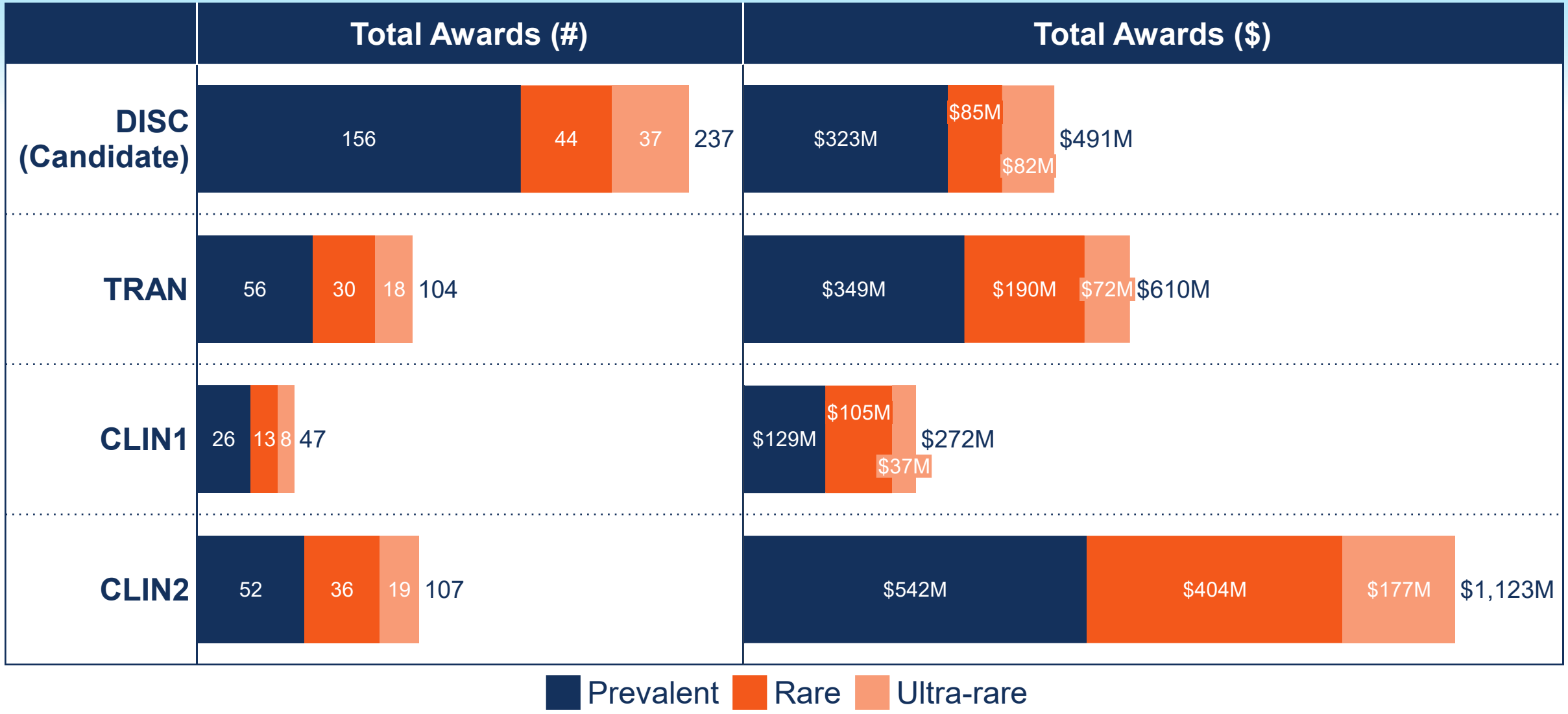
CIRM Historical Portfolio | Prevalent vs. Rare Disease



Source: CIRM Portfolio as of May 2024 excluding Foundational/Basic Research

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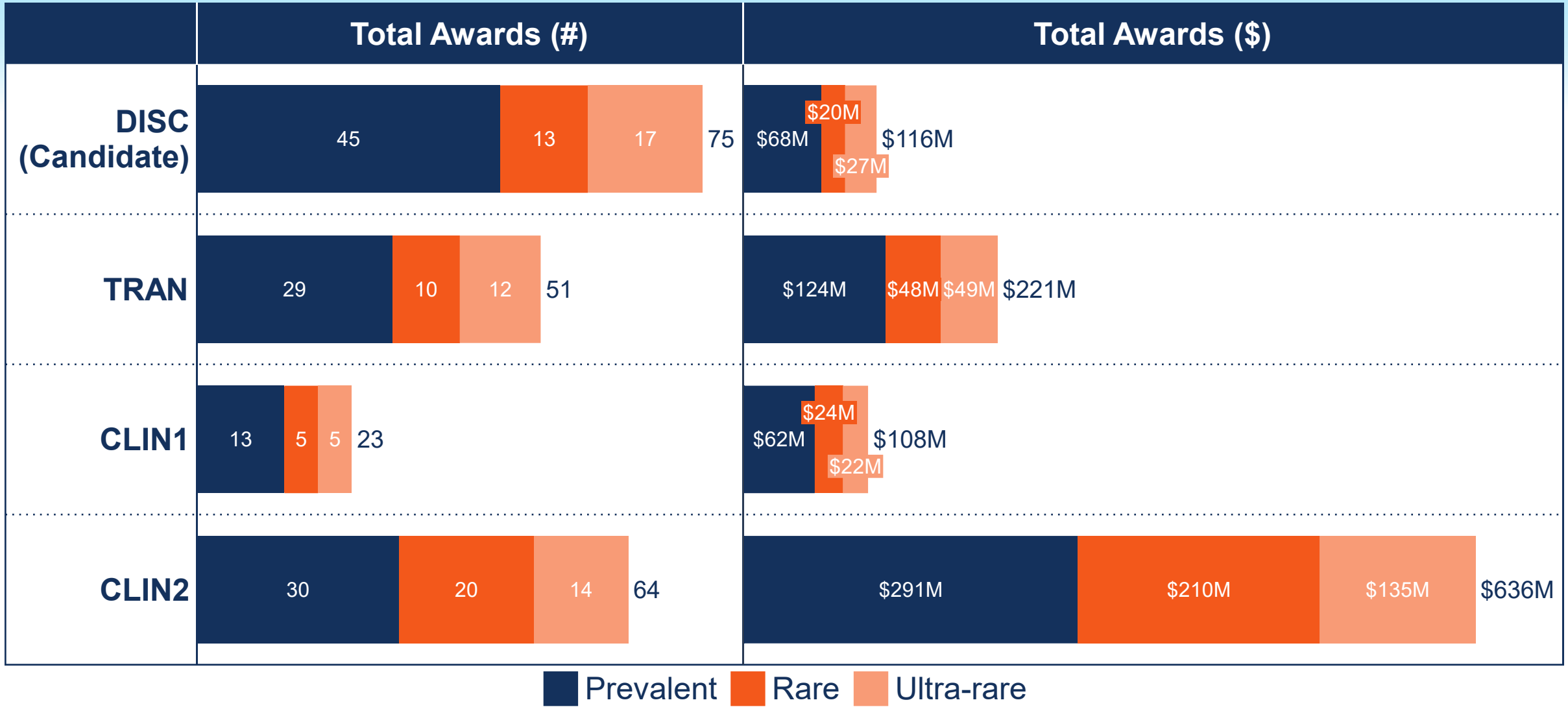
CIRM Active Portfolio | Prevalent vs Rare Disease



Source: CIRM Portfolio as of May 2024 excluding Foundational/Basic Research

Goal 4 | Summary Table 1/2

Disease	Patient Count	CA Economic Burden	Global CGT Pipeline	US Approvals
Hypertension	4,468K	$20.1B	44	0
Type II Diabetes	2,988K	$42.4B	95	0
Depression	1,747K	$33.9B	7	0
Chronic Ischemic Heart Disease & Heart Failure	1,354K	$68.0B	199	0
Asthma	1,154K	$16.0B	51	0
Stroke	892K	$65.1B	110	0
Osteoarthritis (knee)	698K	$5.3B	129	0
Type I Diabetes	290K	$42.4B	164	1
Liver Fibrosis / Cirrhosis	113K	$3.8B	94	0
Alzheimer Disease and Related Dementias	91K	$47.2B	172	0
Multiple Sclerosis	39K	$12.3B	114	0

Goal 4 | Summary Table 2/2

Disease	Patient Count	CA Economic Burden	Global CGT Pipeline	US Approvals
Stroke	892K	$65.1B	110	0
Breast cancer	224K	$4.1B	521	0
Melanoma	202K	$0.8B	412	1
Prostate cancer	152K	$3.2B	254	1
Lung cancer	71K	$3.4B	668	0
Colorectal cancer	67K	$3.4B	330	0

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Challenges and Opportunities in CIRM R&D Pipeline

Prop 14 mandates support for therapies for diseases affecting Californians

Development of gene therapies is costly & time consuming, which makes it difficult to scale for thousands of rare diseases

Approved cell and gene therapies often face patient access challenges

Discovery | Translational | Clinical

DISC2 → **TRAN1/2/3/4** → **CLIN1** → **CLIN2** → **CLIN4**

Single Product Candidate

Pre-IND Meeting or Equivalent

IND Filing & Approval

End of Phase 2 Meeting or Equivalent

BLA Filing

- Discontinuity between early & late translational phases
- Preclinical development of cell and gene therapies can be streamlined as the field matures

Regulatory innovation can enable clinical studies of multiple therapies for multiple diseases via master protocols

Late-stage programs often require extensive investment, especially in CMC, that prevent or delay BLA readiness

Goals 3 & 4

Goal 3 - Advance at least X rare disease projects to BLA

Goal 4 - Propel X therapies targeting diseases affecting Californians to late-stage trials

Goal 3 | Objective & Approach

Goal 3 - **Advance** at least X rare disease projects to BLA

- **Objective**: Advance rare diseases therapies to Biologics License Application and potential approval
- **Approach**: Address late-stage development gaps in the current therapy pipeline and pilot a novel platform-based approach to accelerate and sustain delivery of therapies for rare disease patients

Goal 3 | Recommendations

Goal 3 - Advance at least X rare disease projects to BLA

Accelerate Current Rare Disease Therapy Pipeline

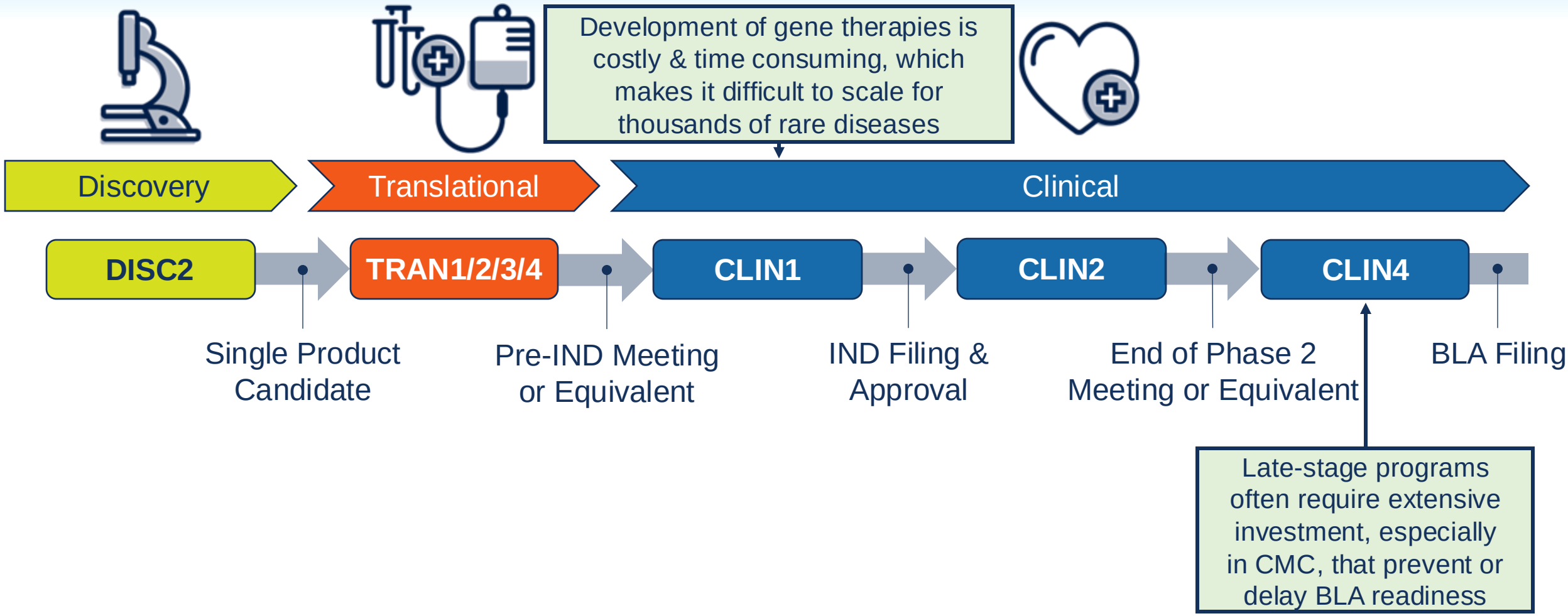
- **Increase and scale** CLIN4 funding to comprehensively address BLA readiness gaps in manufacturing, clinical/non-clinical research, and pre-commercialization*

Pilot Platform-Based Therapy Development

- **Implement pilot platform-based approach** for gene therapy development using life-threatening monogenic neurological disorders as a test case

*Not exclusive to rare disease, but majority of programs near BLA in CIRM's portfolio are in rare disease

Challenges and Opportunities in CIRM R&D Pipeline



Goal 4 | Objective & Approach

Goal 4 - Propel X therapies targeting diseases affecting Californians to late-stage trials

- **Objective**: Accelerate the timeline to clinical proof-of-concept for therapies that target diseases affecting Californians
- **Approach**: Enhance CIRM's therapeutic development funding programs to streamline award mechanisms, to support collaborative approaches, and to facilitate innovation in technologies, research methodologies, and regulatory strategies

Goal 4 | Recommendations

Goal 4 - Propel X therapies targeting diseases affecting Californians to late-stage trials

Streamline Preclinical Development Programs

- **Consolidate DISC2, TRAN1-4, and CLIN1** to accelerate the preclinical development incentivizing multidisciplinary collaborations and rapid progression to IND
- Incorporate **prioritization of innovative therapies for diseases that affect Californians**

Update CLIN2

- Allow for support of emerging **novel clinical trial designs** in CLIN2 program
- Incentivize stage-appropriate **market access strategy** development and **pre-commercialization** activities in CLIN2 program
- Incorporate **prioritization of innovative therapies for diseases that affect Californians**

Challenges and Opportunities in CIRM R&D Pipeline

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Approved cell and gene therapies often face patient access challenges

Discovery | Translational | Clinical

DISC2 → TRAN1/2/3/4 → CLIN1 → CLIN2 → CLIN4

- Single Product Candidate
- Pre-IND Meeting or Equivalent
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- Discontinuity between early & late translational phases
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Regulatory innovation can enable clinical studies of multiple therapies for multiple diseases via master protocols

Proposed Changes to Programs

Current	Proposed
CLIN2 and CLIN4 Programs • Prevalent, rare, and ultra-rare diseases are eligible for the same funding opportunities • **CLIN2** supports individual clinical trials for single candidates and supports a subset of pre-commercialization activities • **CLIN4** funding is insufficient for all activities needed to reach BLA readiness	**Updated Clinical Programs** • **CLIN2** supports innovative clinical trial design and incentivizes market access strategy development & pre-commercialization activities • **CLIN4** funding increases & scales to comprehensively address BLA readiness gaps • Prioritize innovative therapies for diseases that affect Californians **Pilot Rare Disease Platform Program** • Rare and ultra-rare diseases (focus) • Requirement for academic-industry partnership
Multi-Program Preclinical Path • Separate DISC2, TRAN1/2/3/4, CLIN1 Programs with their own applications • Prevalent, rare, and ultra-rare diseases are eligible for the same funding opportunities	**Streamlined Preclinical Program** • Consolidated preclinical program • Prioritize innovative therapies for diseases that affect Californians

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Timeline & Next Steps

Meeting	SAF Topics
June NTF/Science Subcommittee	• SAF Overview - NTF Background • Present Neuro Survey Results – Discussion • Provide a high-level overview of how this fits within Strategic Analysis Framework (SAF)
June ICOC	• Provide an update on the process, aligning with the June NTF/Science Subcommittee • Offer an example of analysis that will inform recommendations
July NTF/Science Subcommittee	• Present four overarching SAF Goals and delve into Goals 1 & 2 • Review relevant data associated with Goal 1 & 2 • Discuss potential recommendations for Goal 1 & 2
August AAWG	• Present updates on Goal 5 • Discuss considerations for Goal 5
August NTF/Science Subcommittee	• Present updates based on feedback received on Goal 1 & 2 • Introduce Goal 3 & 4 and discuss associated data • Discuss potential recommendations for Goals 3 & 4

September NTF/Science Subcommittee	• Full SAF presentation:
	  • Present updates based on feedback received on Goals 1, 2, 3, & 4
	  • Present Goals 5 & 6
	  • Discuss overall recommendations in preparation for September ICOC

September ICOC	• Overall Presentation of SAF recommendations

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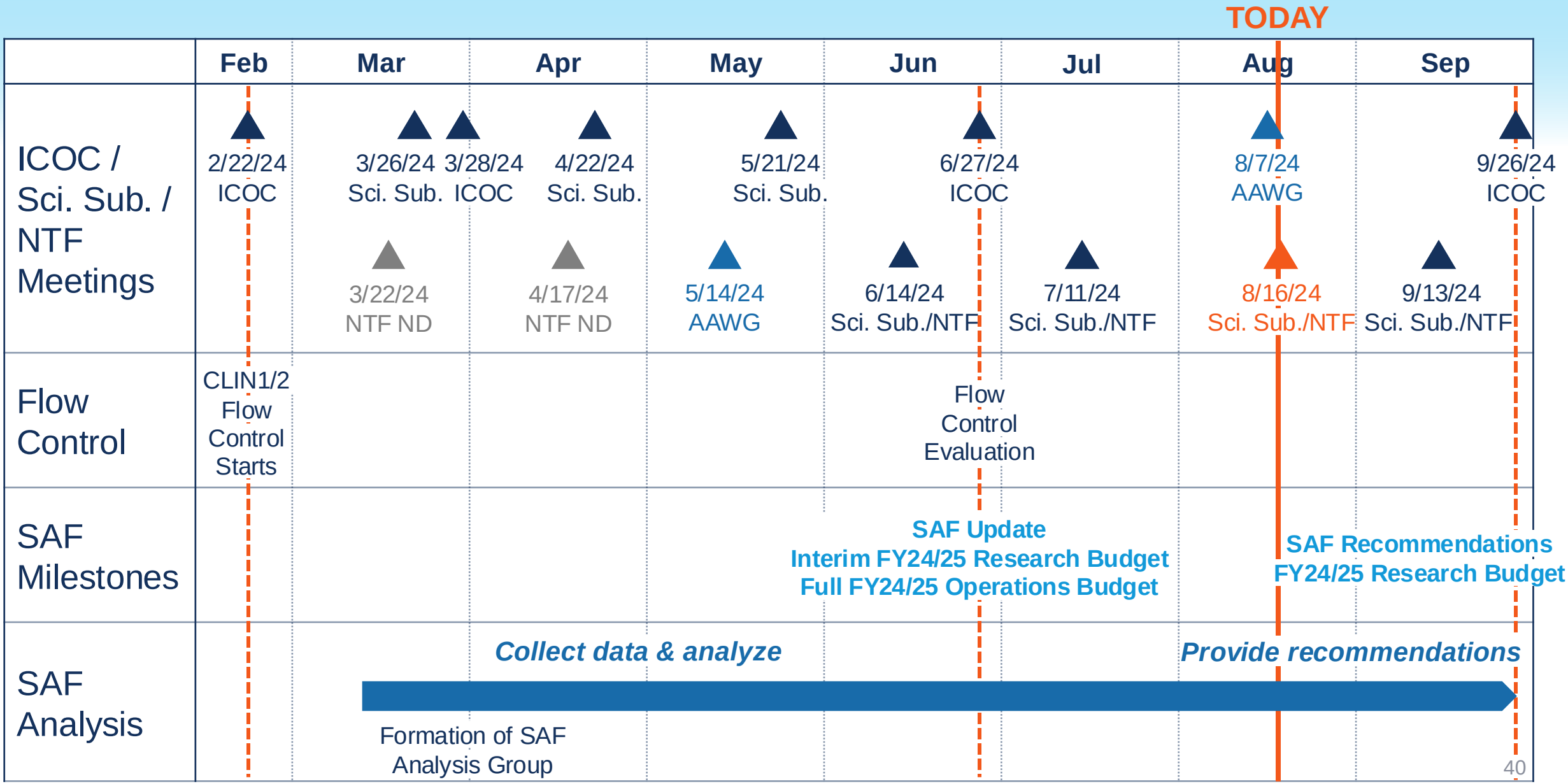
SAF Timeline



Glossary of Terms

- **BLA**: Biologics License Application
- **Master Protocol**: A clinical trial protocol designed with multiple coordinated sub-studies to evaluate one or more investigational drugs for one or more diseases within the overall trial structure
  - **Basket Trial**: A master protocol designed to study a single investigational drug in multiple diseases or disease subtypes
  - **Platform Trial**: A master protocol designed to study multiple investigation drugs in a single disease in a perpetual manner, with therapies allowed to enter or leave the platform based on a decision algorithm
  - **Umbrella Trial**: A master protocol designed to study multiple investigational drugs in the context of a single disease
- **Platform Technology**: A technology that can be incorporated in multiple therapies or that can be used for the research, development and/or manufacture of multiple therapies.
- **Rare Disease**: A disease with a prevalence of <200,000 patients in the US
  - **Ultrarare Disease**: A disease with a prevalence of <10,000 patients in the US