



Using Research to Make ALS Livable
Jan 23, 2022

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What **Livable** Means

People with ALS will have a fundamentally different experience than they have today.

- Longer lives
- Improved quality of life
- Preventing loved ones from getting ALS

Find New Treatments and Cures

- More trials and research participation
- More focused research

Optimize Current Treatments and Care

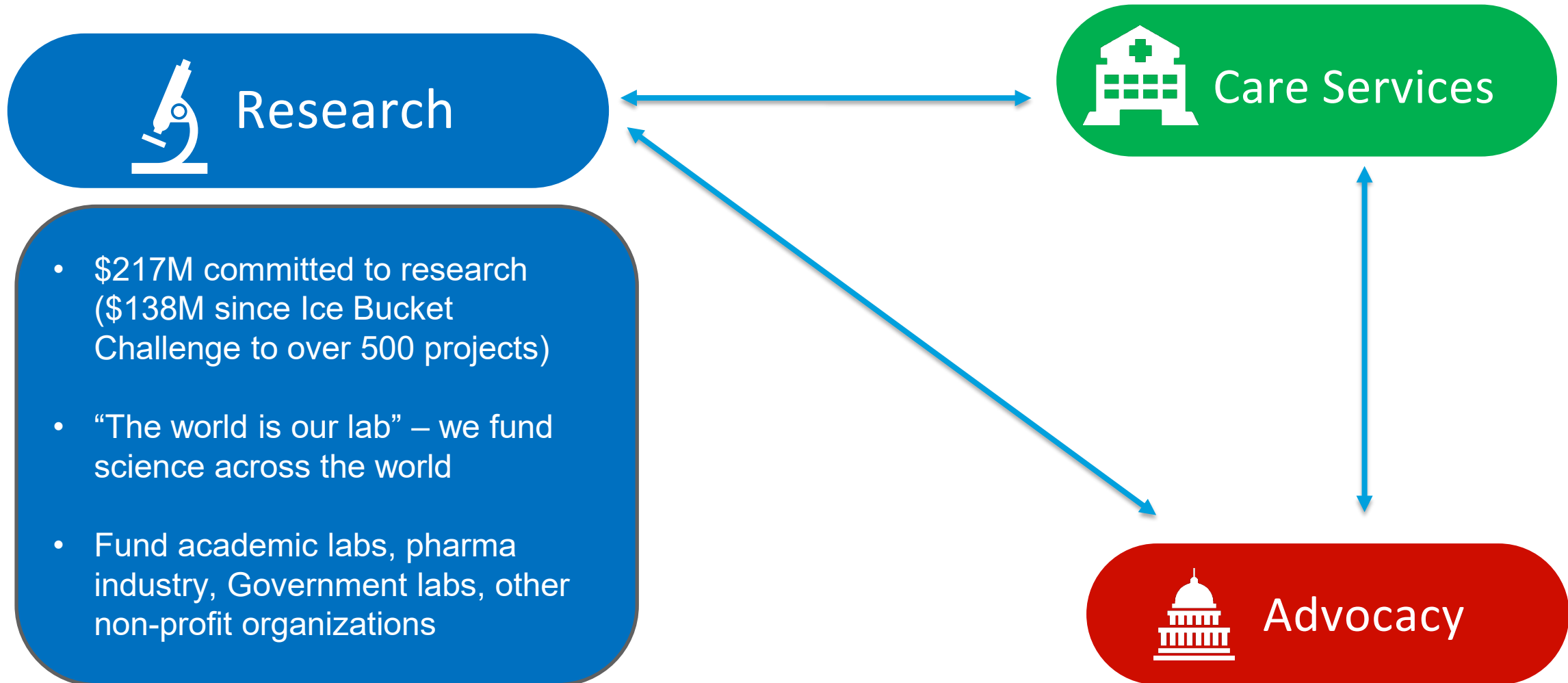
- Improve and deliver state of the art care
- Improve Assistive technology

Prevent or Delay the Harms Associated with ALS

- Identify Risk Factors
- Treat as early as possible
- Discover new preventative treatments



The ALS Association is the Largest Philanthropic Research Funder in the World



Research Projects get Selected Through a Rigorous, Transparent and Deliberative Process



Letter of Intent

- Short proposal (elevator pitch, 1-2 pages)
- Criteria: Scope, priority for the Association, novelty of the idea



Full Proposal

- Full proposal (8-12 pages), peer-reviewed by independent external experts
- Criteria: Scientific plan, team, budget, feasibility



Research Committee

- Volunteers comprised of people living with ALS, caregivers, scientists, clinicians, business professionals
- Provides final approval for funding and budget



Grant Project

- Milestone-based payments
- Collaboration, data sharing, specimen sharing, publications, follow-on funding

Research Committee – Role & Structure

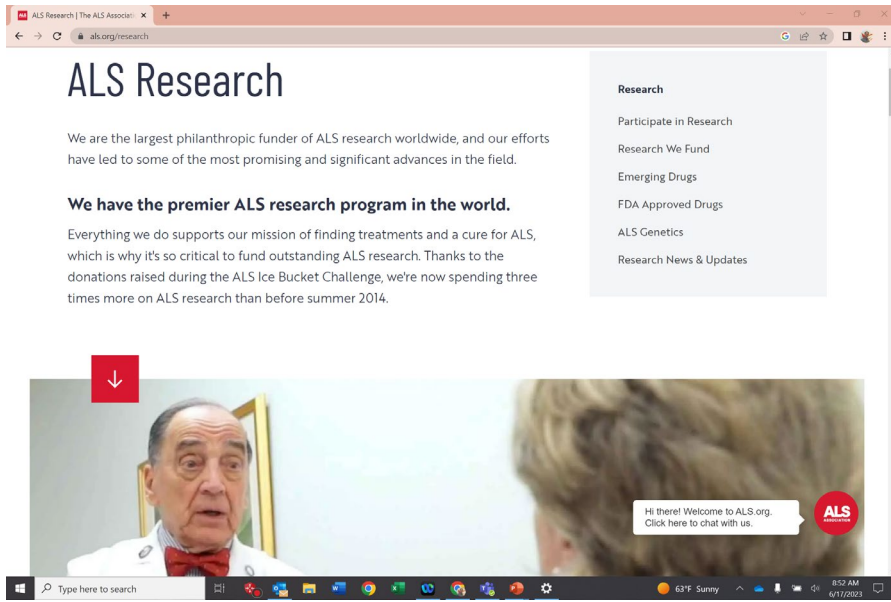
Dr. Joel Shamaskin – Research Committee Member

Role

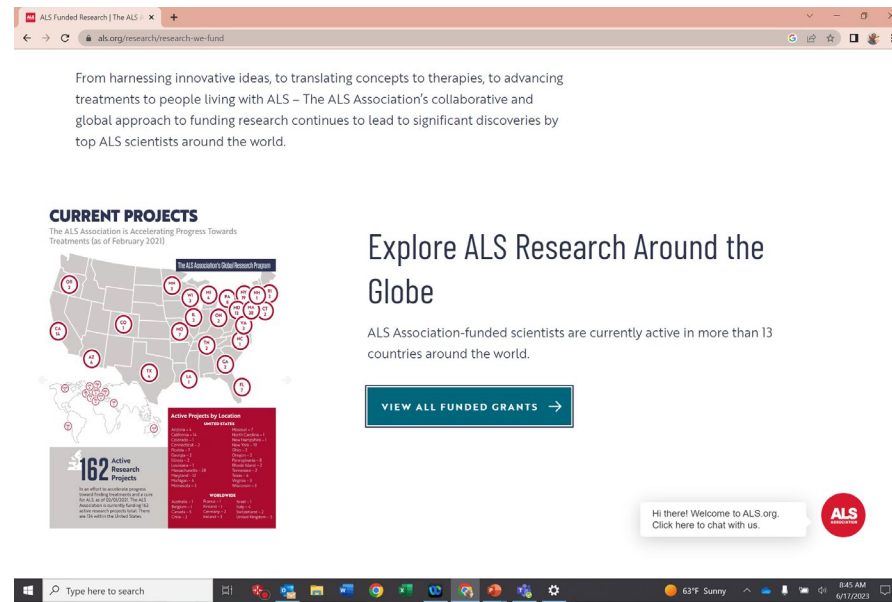
- The Research Committee will make recommendations to the Board of Trustees regarding ALS research-related strategy, direction and policy.
- The Research Committee will recommend and monitor The Association's annual ALS research budget, annual spending and funding parameters for ALS research-related programs and initiatives.
- The Research Committee will provide advice and feedback on new strategic avenues and funding programs.
- The Research Committee votes and approves research projects.

Structure/Cadence

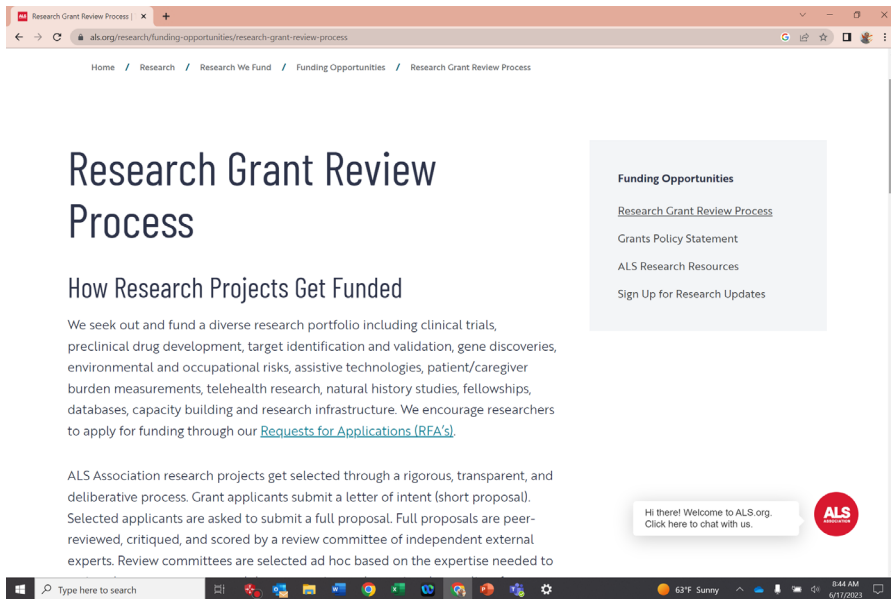
- Volunteers comprised of people living with ALS, caregivers, scientists, clinicians, business professionals
- Monthly hourly meetings
- Agenda: Programmatic and budgetary updates, RFA approval, project approvals, discussion/feedback



<https://www.als.org/research>



<https://www.als.org/research/research-we-fund>



<https://www.als.org/research/funding-opportunities/research-grant-review-process>



<https://www.als.org/research/funding-opportunities>

ALS Research Ecosystem



Currently ~165 active projects and ~\$52.5M committed across 14 countries

Drug Development

Biology and Genetics of ALS

Preclinical Drug Development

Phase I

Phase II

Phase III

Drug Approval

Risks and Causes of ALS

Biomarker Development

Academia

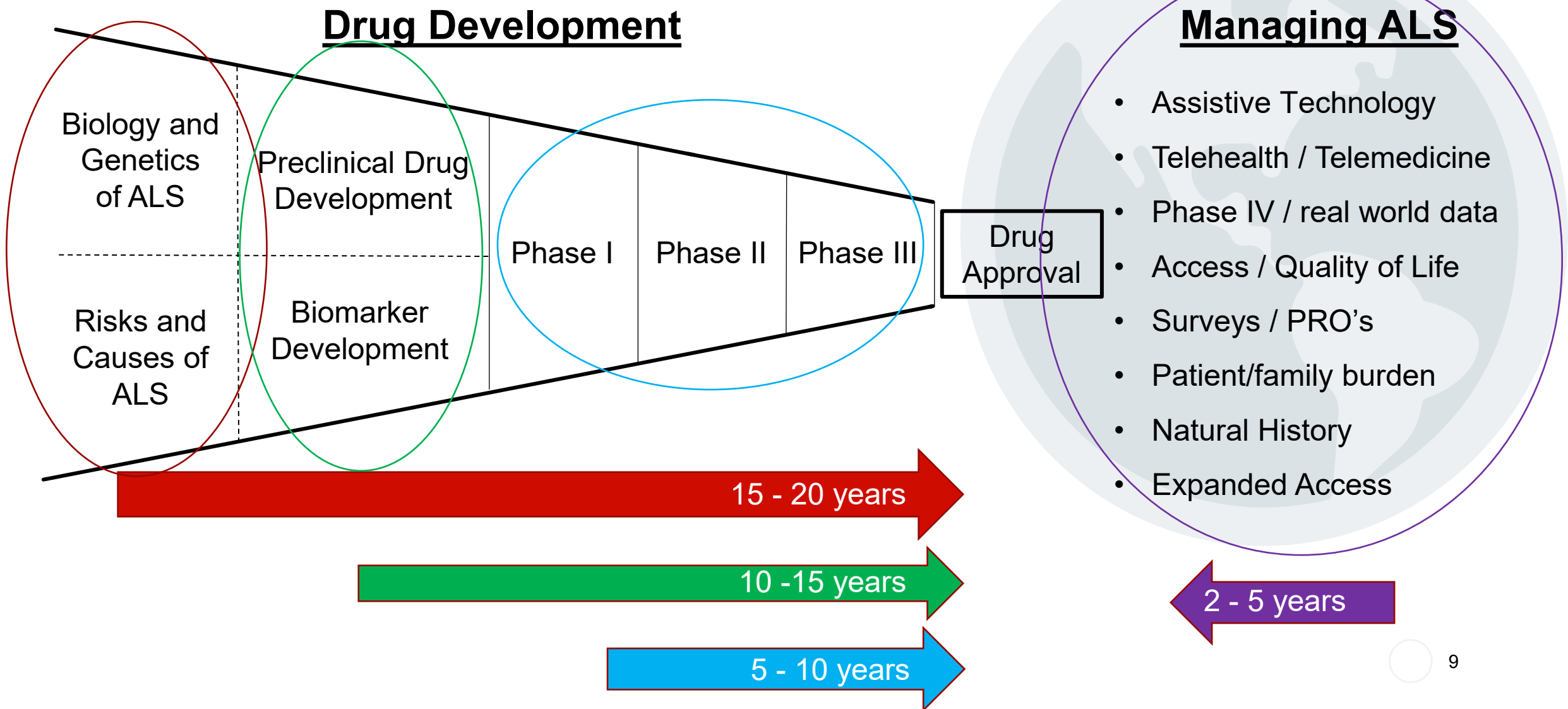
Industry

Managing ALS

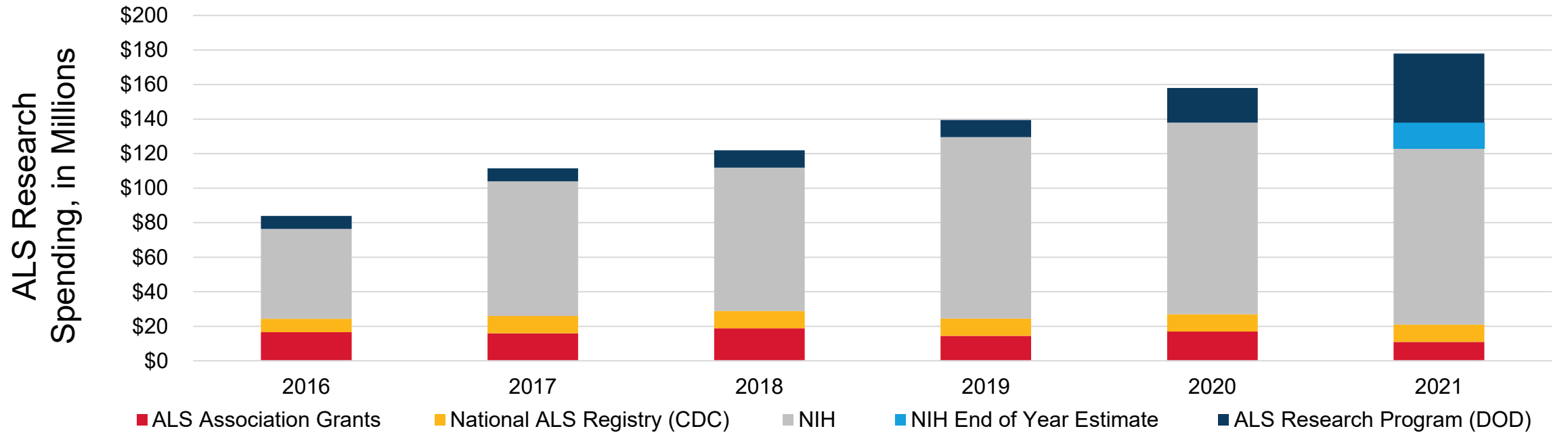
- Assistive Technology
- Telehealth / Telemedicine
- Phase IV / real world data
- Access / Quality of Life
- Surveys / PRO's
- Patient/family burden
- Natural History
- Expanded Access

Infrastructure, Specimens, Data, Tools, Training

Time to Impact on People with ALS



Government Funding for ALS (post IBC)



CONGRESSIONAL FUNDING OF ALS RESEARCH (2022)

NIH: \$120M Research

Drug Development

Biology and Genetics of ALS

Risks and Causes of ALS

Preclinical Drug Development

Biomarker Development

Phase I

Phase II

Phase III

Drug Approval

DOD: \$40M

CDC: \$10M

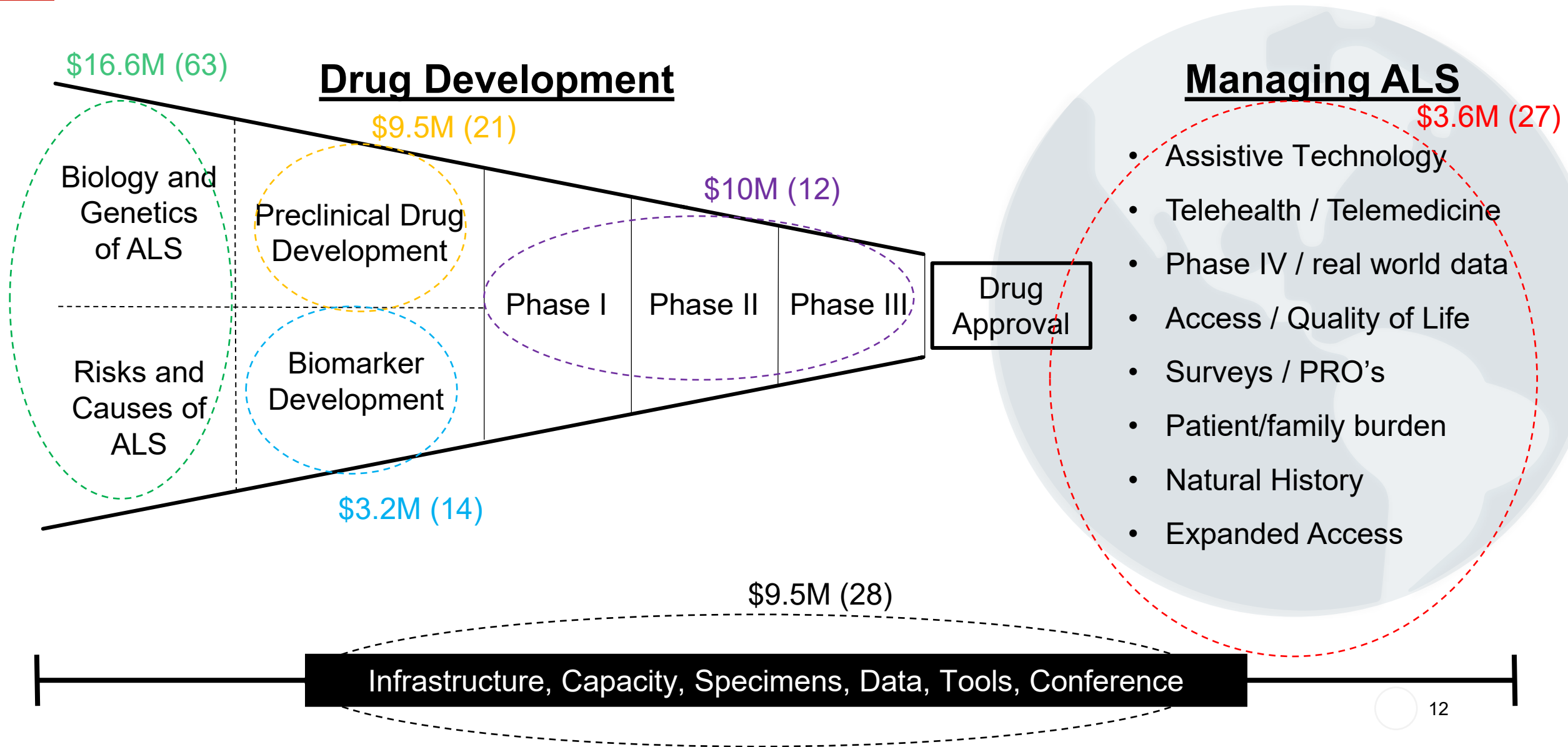
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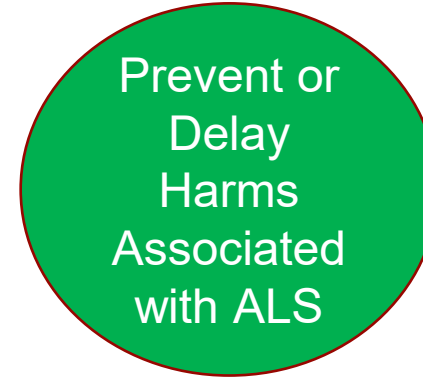
FDA: \$5M

Infrastructure, Specimens, Data, Tools, Training

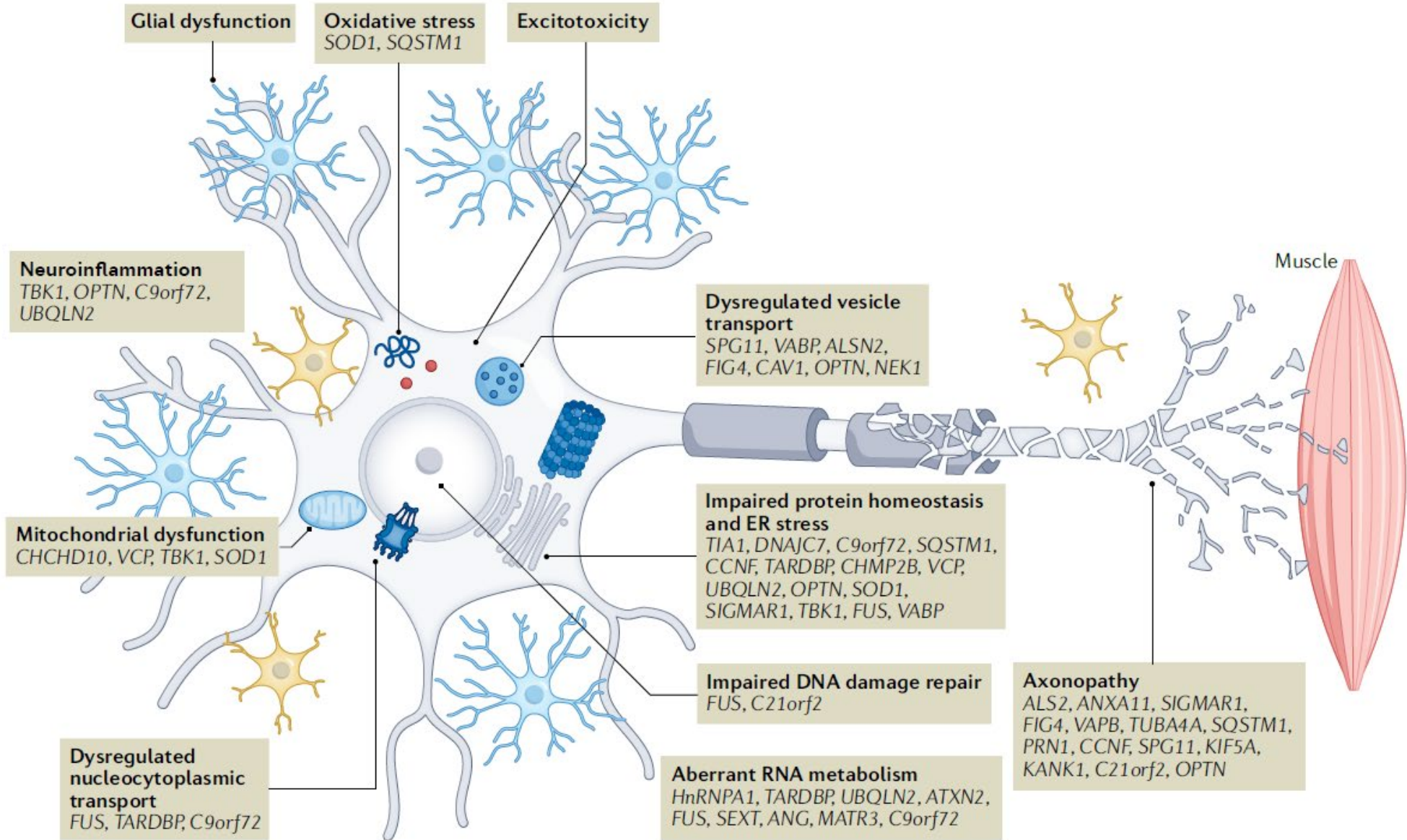
Current Research Portfolio (165 projects = \$552.5M)



Funding Programs Align with Strategic Priorities



ALS Pathophysiology, Genetics and Risk Factors



Major Targets and Pathways for Therapeutic Development

Cell therapies

- Clinical trials
- Neuronata-R MSCs
 - NurOwn MSC-astrocyte like cells
 - AstroRx
 - RAPA-501 T cell therapy

Multiple targets

- Clinical trial
- AMX0035

- Preclinical
- M102-S(+)-apomorphine

Genetic therapies

- Clinical trials
- SOD1 ASO (Tofersen)
 - C9orf72 ASOs (BIIB-078, WVE-004)
 - FUS ASO (ION-363)
 - Ataxin2 ASO (ION-541)

- Preclinical
- AAV5 C9orf72 repeat expansion
 - Progranulin neurotrophic factor
 - Cryptic exon splicing in STMN2 (QRL-201)
 - AAV-FUS (CTx-FUS)
 - Censavudine reverse transcriptase inhibitor targeting transposon activation

Oxidative stress

- Clinical trials
- Edaravone
 - Verdiperstat

Mitochondrial function

- Clinical trials
- AMX0035
 - TUDCA alone

Proteostasis

- Clinical trials
- Trametinib MAPK inhibitor
 - eIF2B activator (DNL-343)
 - Bosutinib autophagy promoter

- Preclinical
- eIF2B activator
 - Ataxin 2 inhibitor

Troponin activator

- Clinical trials
- Reldesemtiv – Fast type 2 skeletal muscle troponin activator

Neuroinflammation

- Clinical trials
- Zilucplan C5 inhibitor
 - Aldesleukin rIL-2
 - IgG4 C1q mAb
 - Anti-CD40 ligand mAb
 - CSF1R blocker (BLZ-945)
 - Pegcetacoplan C3 regulator
 - RIPK1 inhibitor (DNL-788)
 - Masitinib
 - Ibudilast

Glutamate toxicity

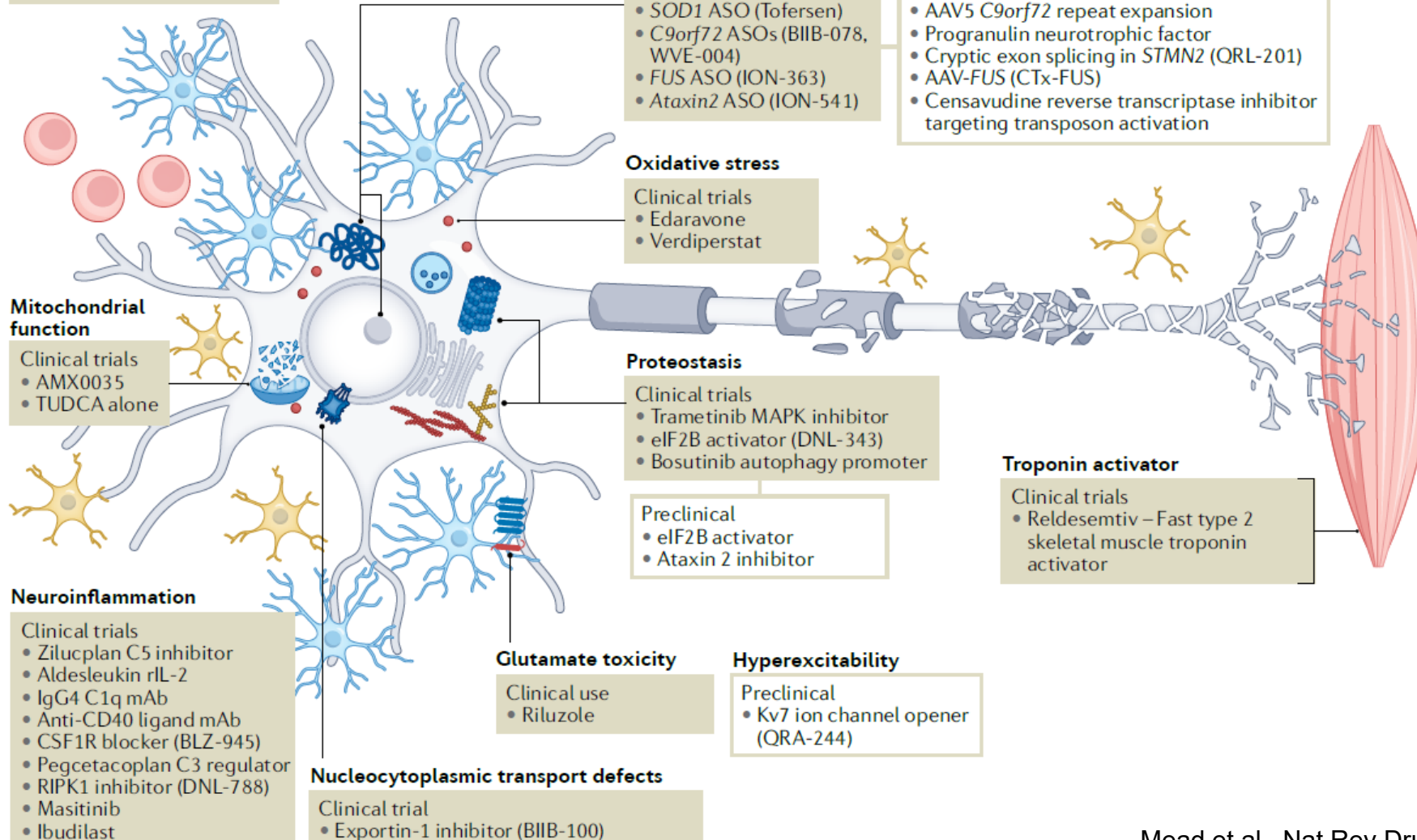
- Clinical use
- Riluzole

Hyperexcitability

- Preclinical
- Kv7 ion channel opener (QRA-244)

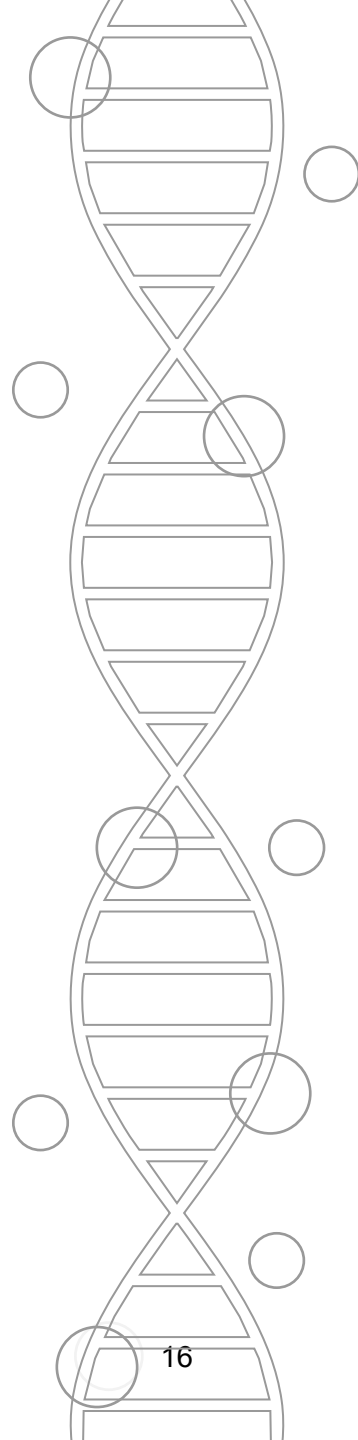
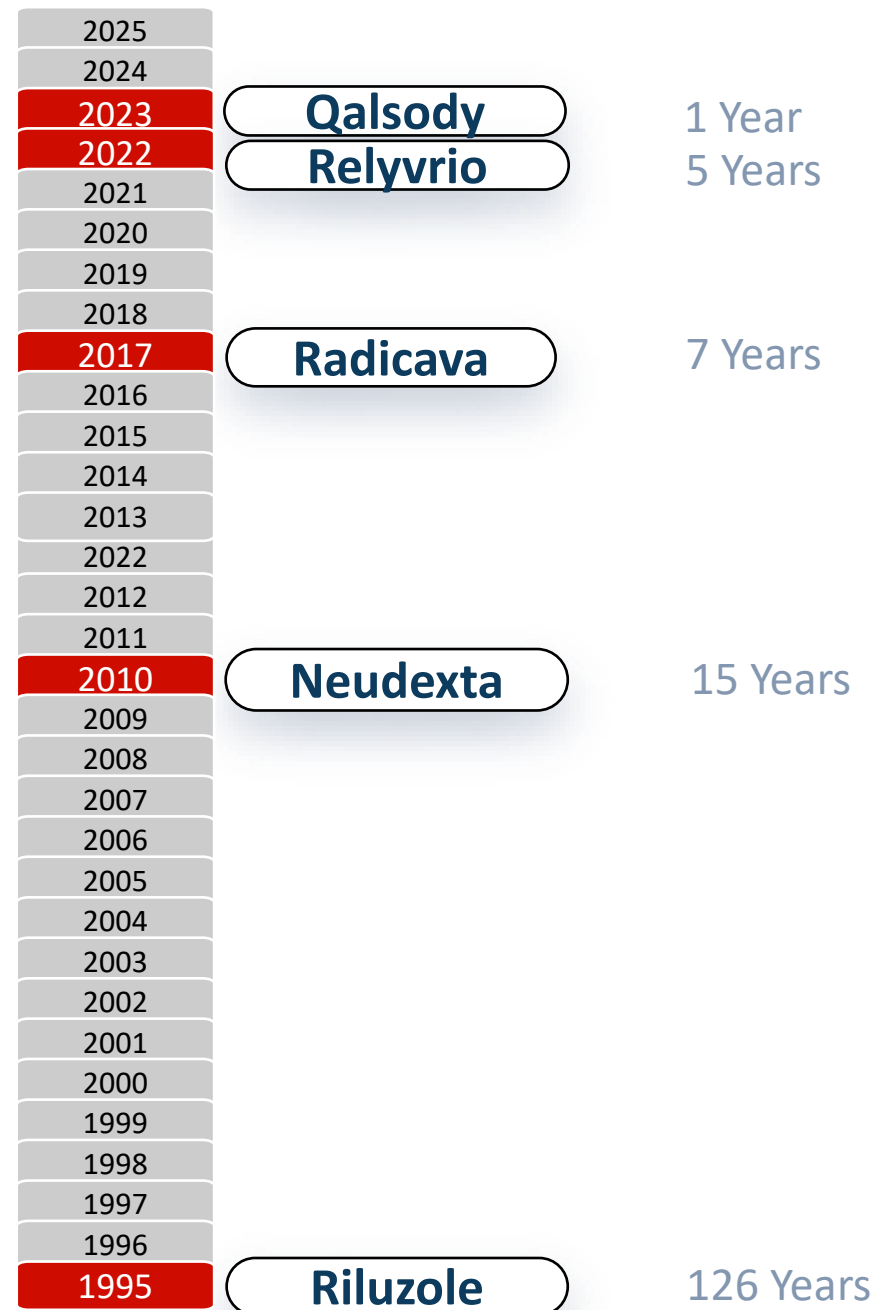
Nucleocytoplasmic transport defects

- Clinical trial
- Exportin-1 inhibitor (BIIB-100)



Accelerating Progress

- ALS was first identified in 1869
- Treatment options are improving at an increasing pace
- We have much more work to do



Impact of ALS Association Research Funding

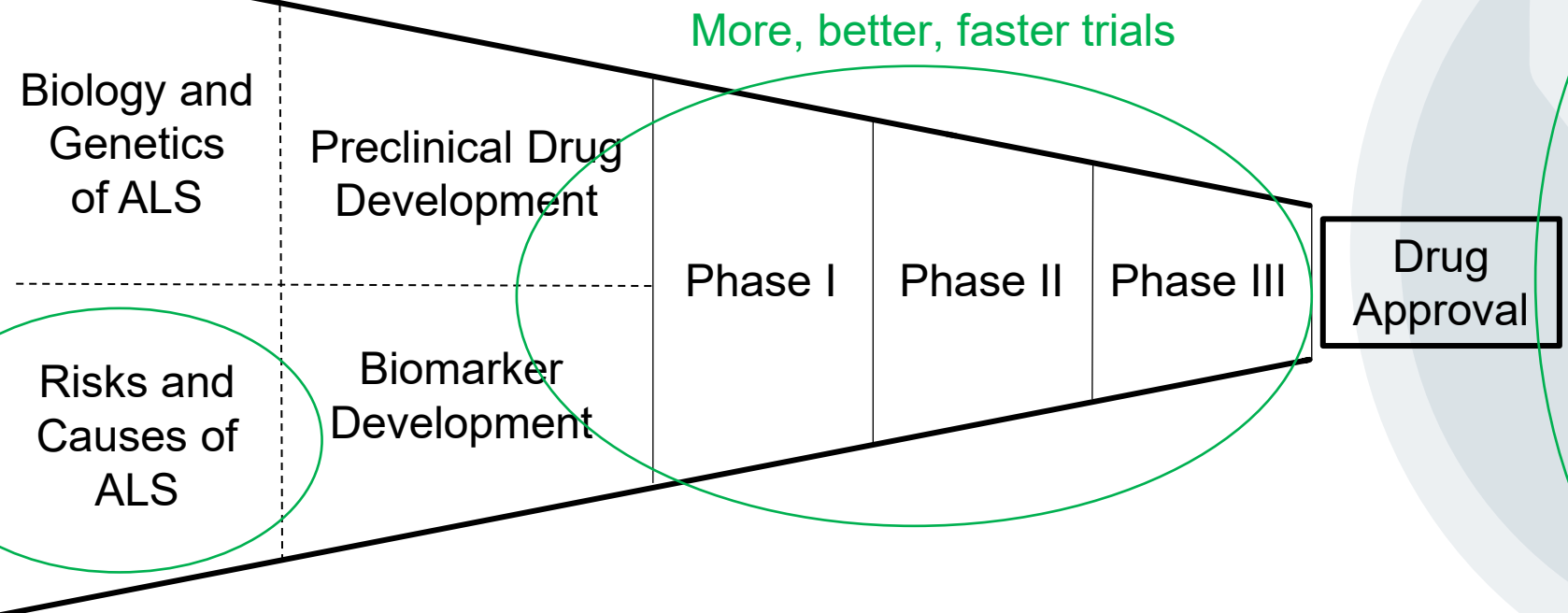
- 2 funded drug programs received FDA approval
 - Relyvrio and Qalsody
- 3-fold funding leverage
 - \$40M of funding led to \$120M of follow-on funding
- 95 fellows trained in ALS research in last 20 years
 - More than 75 percent remain in ALS ecosystem
- Funding to largest gene sequencing initiatives have led to 40 new genes linked to ALS
 - Qalsody approved, therapies against 10 other genes are in development
- Funding of critical infrastructure has enabled more, faster and better clinical trials
 - Trial awards, NEALS, Pro-ACT, trial capacity, trial match, biobank support
- Greater engagement with ALS community has resulted in tools and solutions to tackle challenges
 - Roundtable, ALS Focus, ThinkALS, CDC registry, ALS journey map

Research Funding Priorities to make ALS Livable

Improve Quality of Life and Quality of Care

Coordination > Collaboration

Drug Development



Managing ALS

- Assistive Technology
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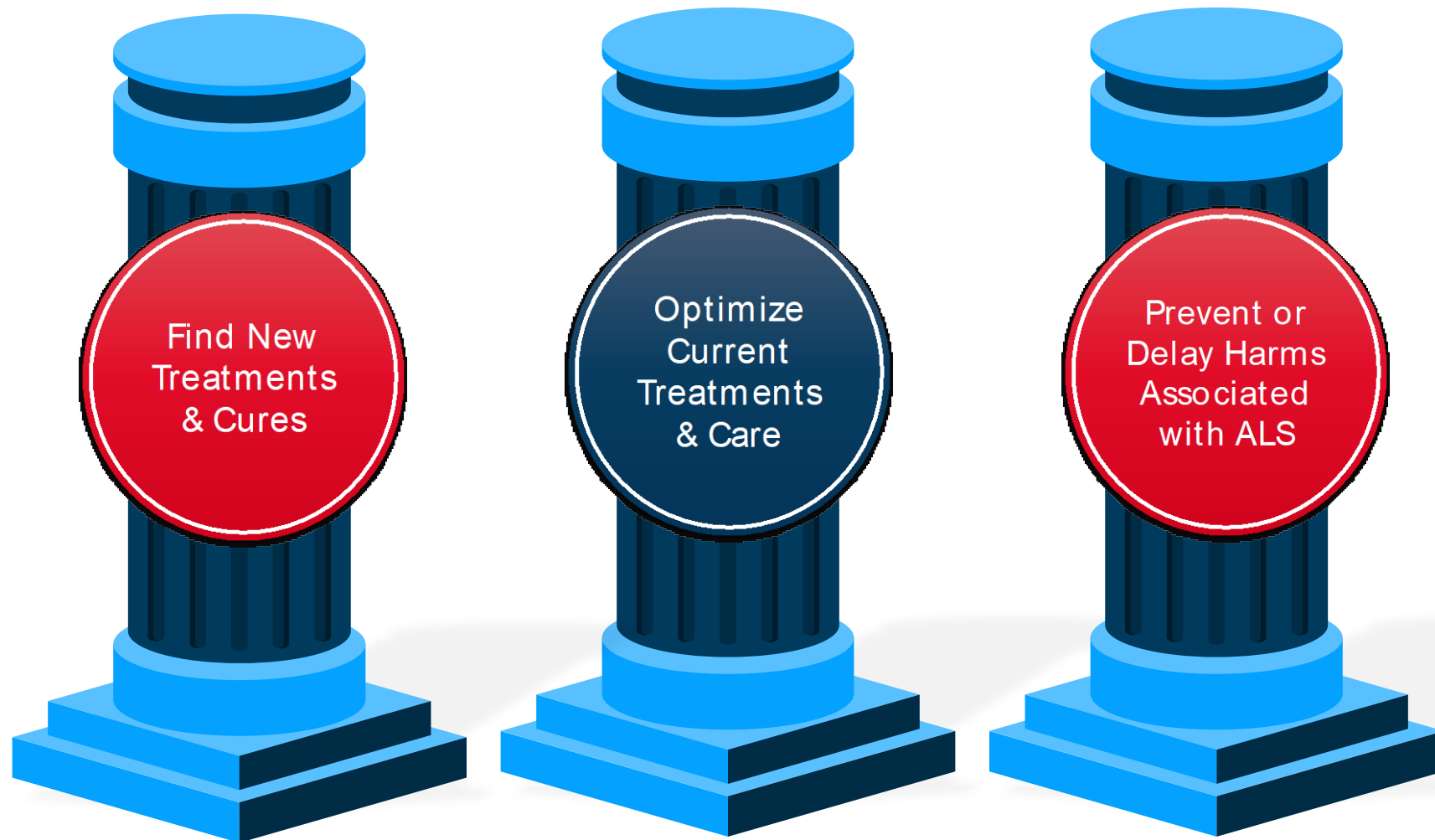
Infrastructure, Specimens, Data, Tools, Training



Appendix

Research Funding Priorities to make ALS Livable

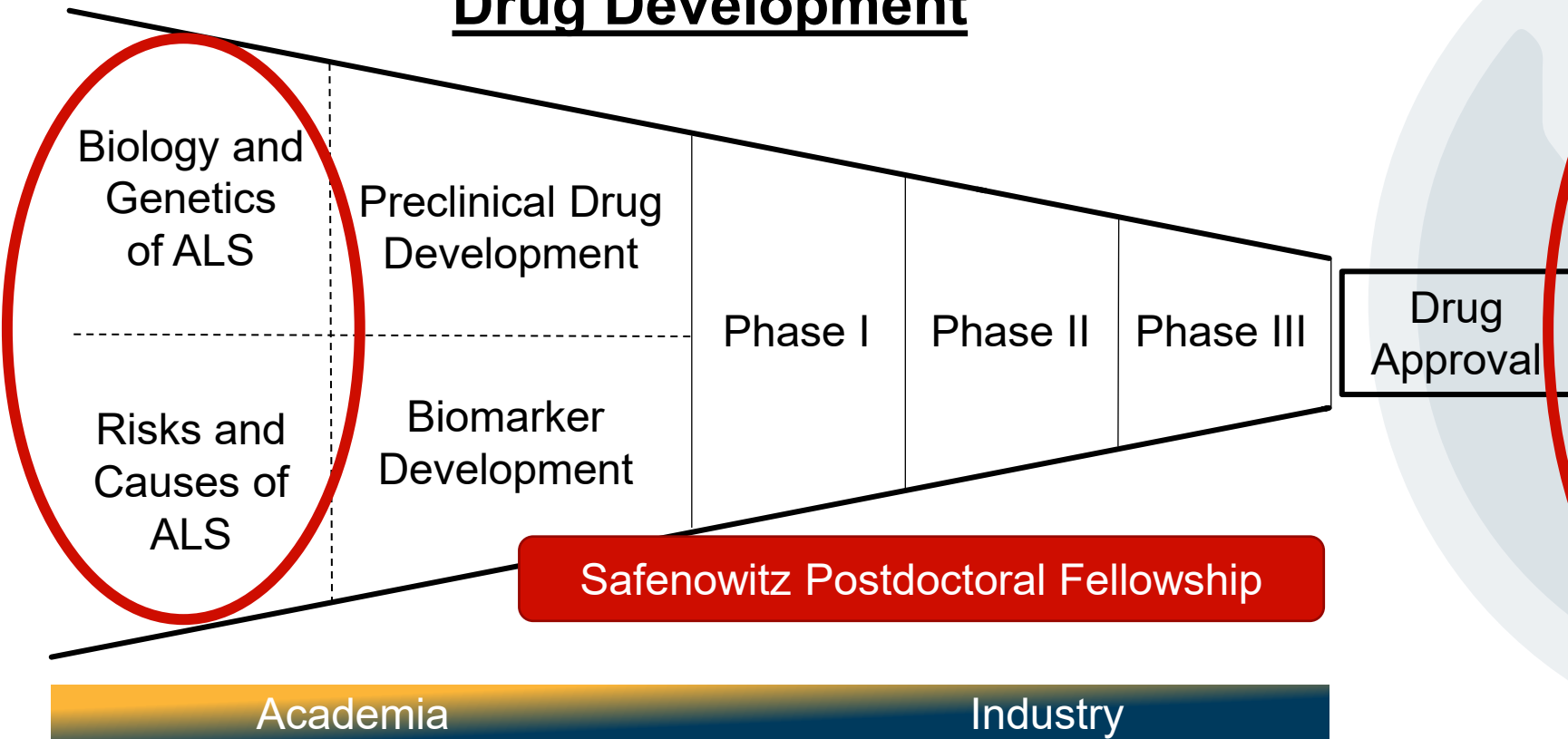
- Improve quality of care – make it efficient, accessible and affordable
- Develop, validate and commercialize assistive technology – to allow people with ALS to interact with the world in the way they want
- Shepherd drug discovery programs towards clinical trials and to make trials better and faster
- Improve staffing and capacity across the ecosystem with focus on new/junior investigators and trial personnel
- Translate identified risks into prevention approaches to reduce incidence and delay onset of ALS
- Improve quality of life and health – reduce isolation, stigma and burdens of ALS



We're Making ALS Livable While We Work To Cure It

ALS Research Ecosystem

Drug Development



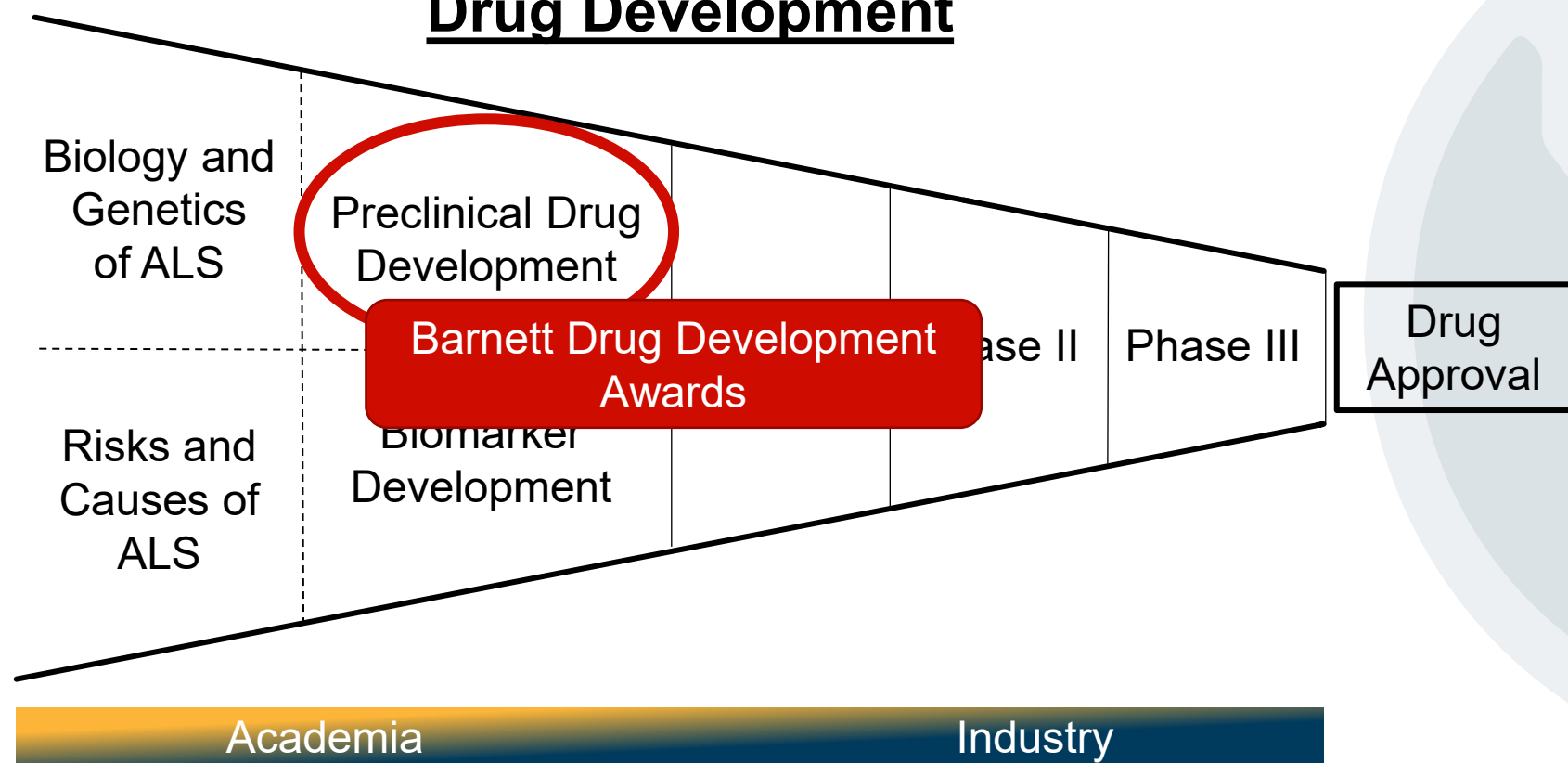
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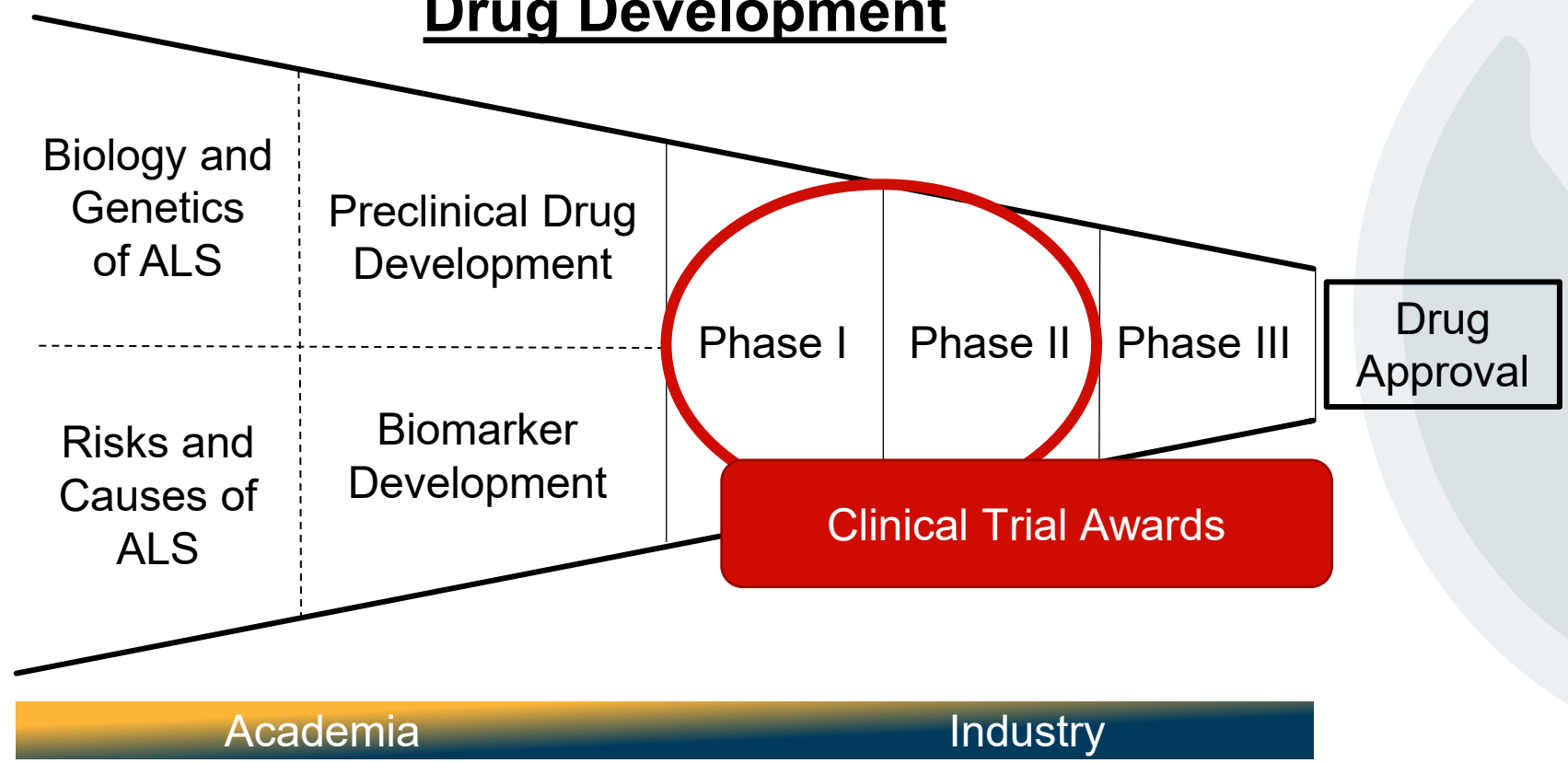
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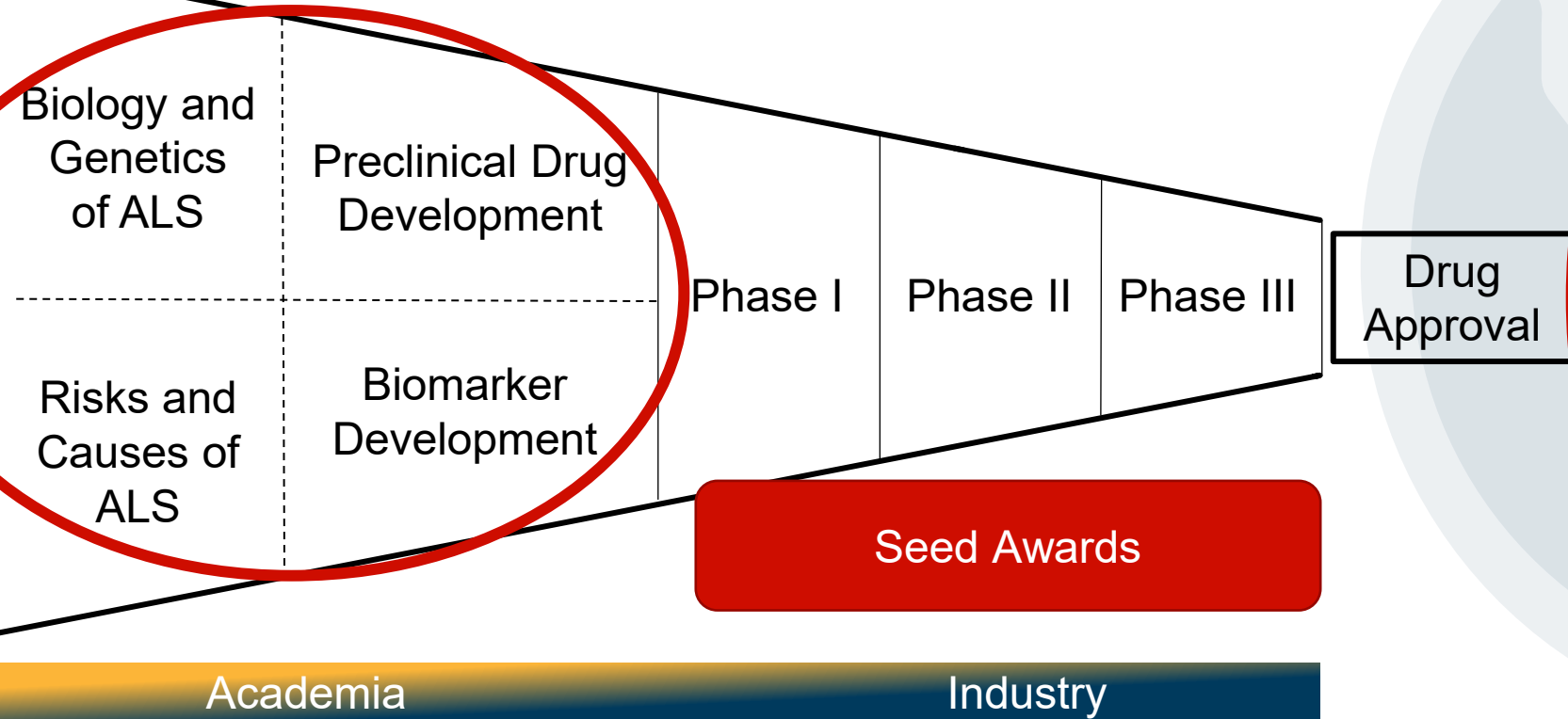
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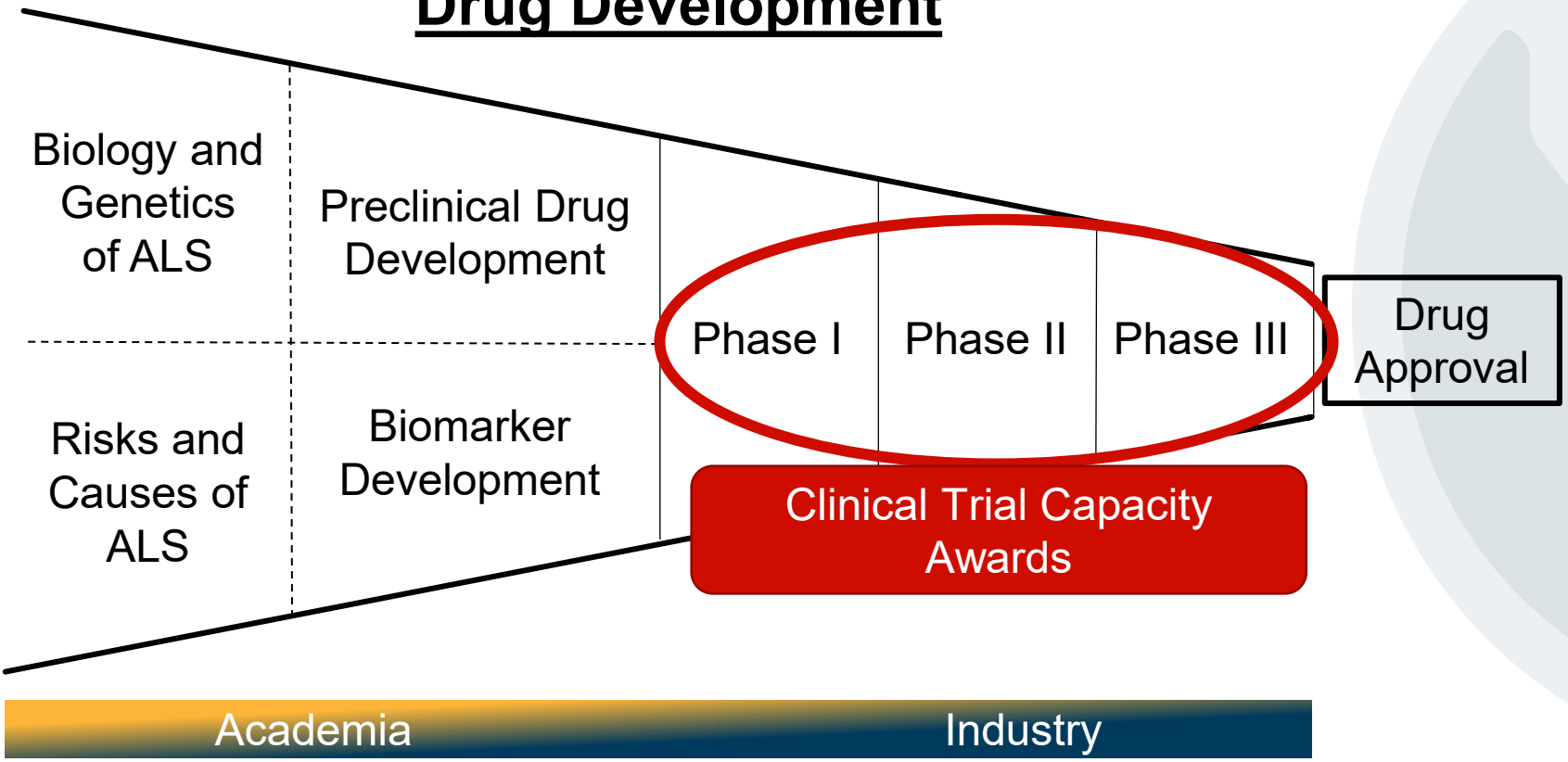
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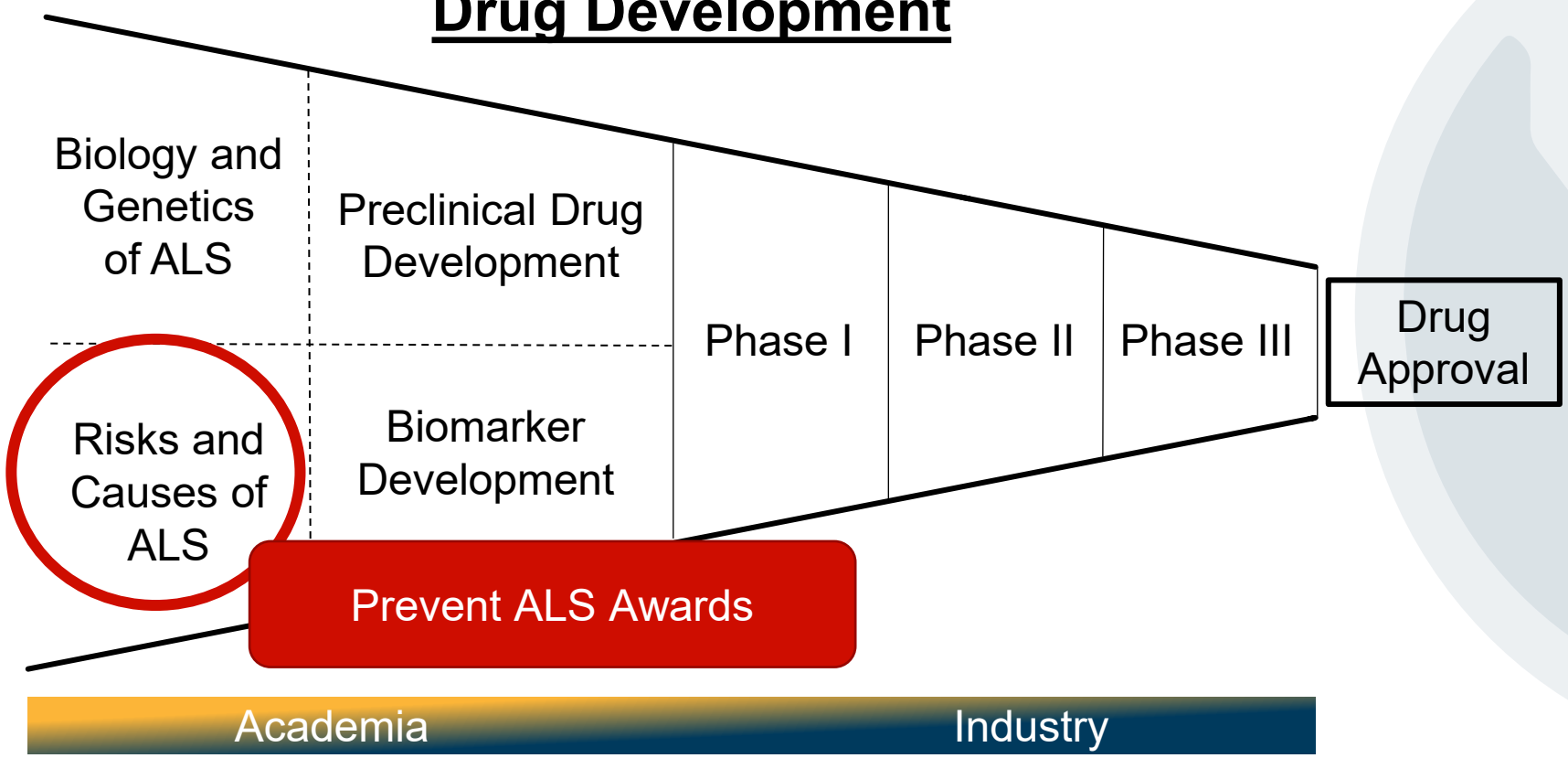
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Drug Development



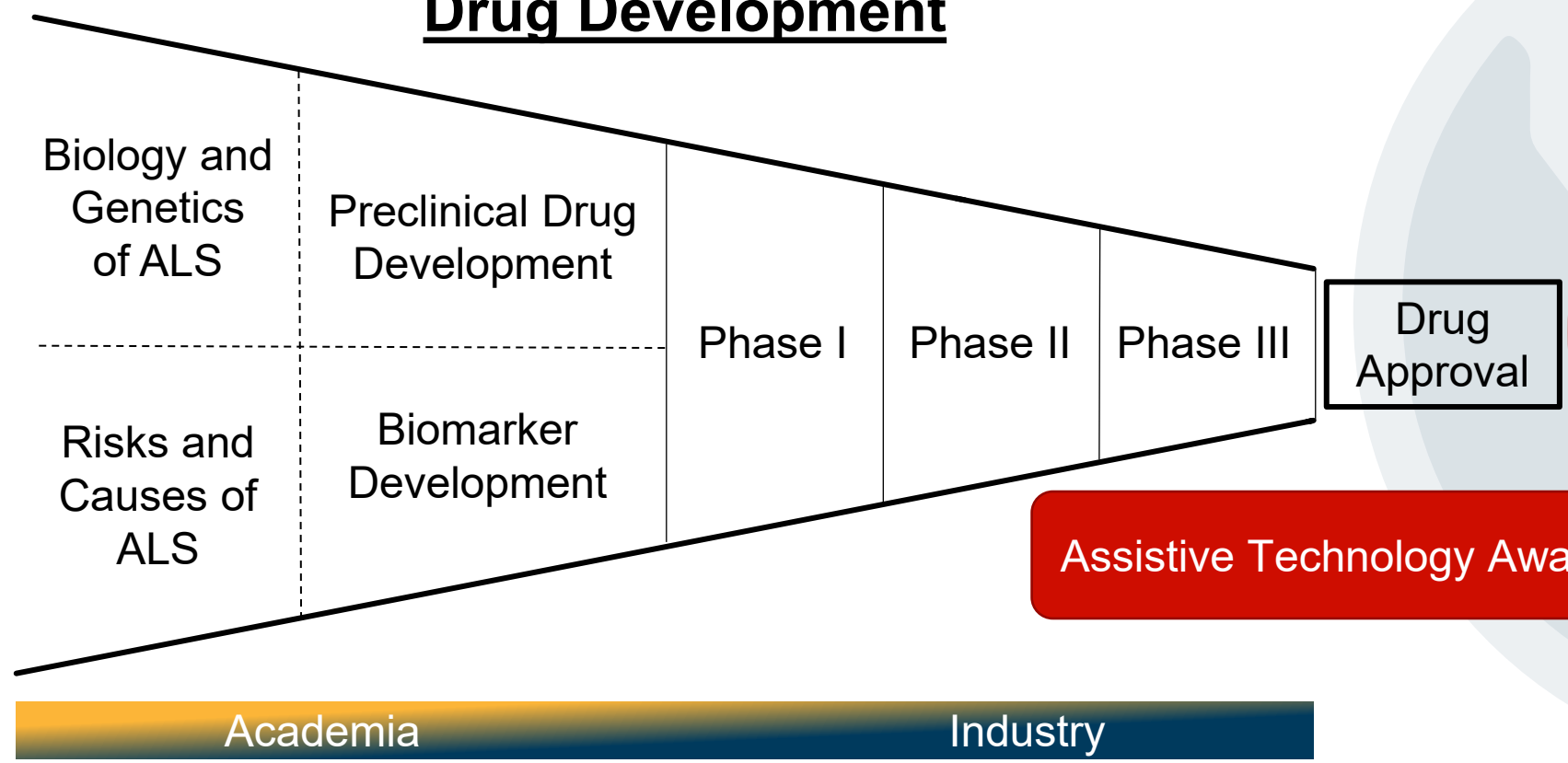
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ALS Research Ecosystem

Drug Development



Assistive Technology Awards

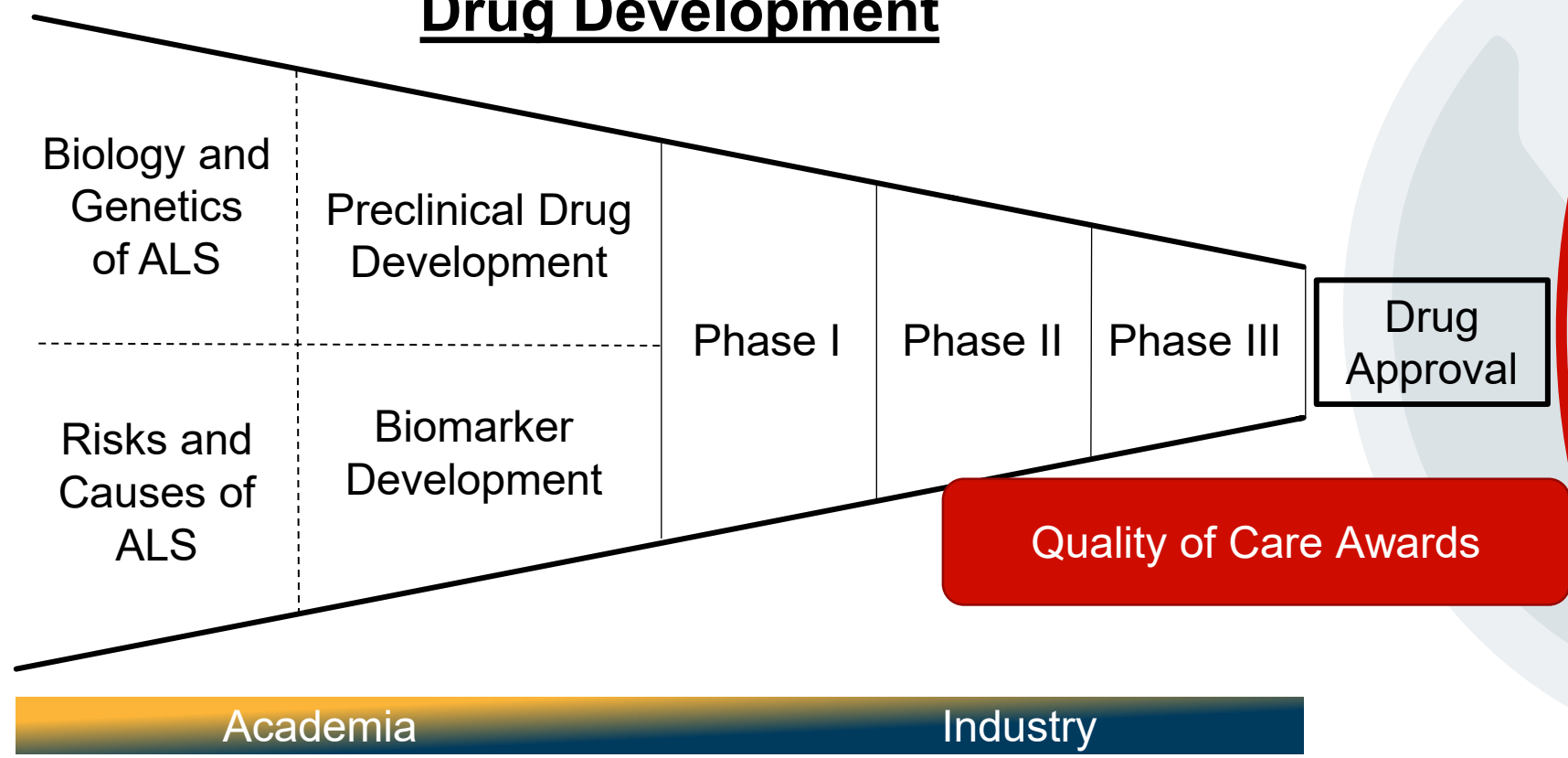
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Safenowitz Postdoctoral Fellowship (2022 commitment = \$900,000)

Support Young Researchers at a Pivotal Stage of Their Careers

- Established program, launched annually
 - Each postdoctoral researcher receives up to \$150,000 in funding over 2 years
 - Expect to fund 6-8 postdoctoral researchers per year
- Research projects span ALS research from basic research to assistive technologies
 - Funded postdoctoral researchers are likely to continue to work in ALS
- More than 40 Fellowships and \$5M in funding awarded since 2015. Over 70% postdocs continue research in ALS.
- For more information see July 8th Connecting ALS Podcast with Dr. Jill Yersak
 - <https://www.connectingals.org/episodes>
 - "Recruiting New Researchers to the Search for Treatments..."

Barnett Drug Development Awards (2022 commitment = \$3M)

Bridge the Gap Between Academic Research and Commercial Development

- Established program, launched annually since 2015
 - Each project can receive up to \$500k in funding over 2 years
 - Expect to fund ~6 projects per year moving forward
- Supports preclinical assessment of therapeutics for ALS
 - Funds activities including safety testing, dose finding, manufacturing scale-up, etc
 - If successful, results support IND filing and initiation of Phase 1 clinical trials
- More than 30 programs and \$10M in funding awarded since 2015. We are seeing a 6-fold leverage with 5 therapeutics already in the clinic.
- For more information see October 28th Connecting ALS Podcast with Dr. Kuldip Dave
 - <https://www.connectingals.org/episodes>
 - "Developing New Drugs..."

Clinical Trial Awards (2022 commitment = \$4M)

Generating More Shots on Goal by Funding Clinical Trials

- New RFA, first launched Fall 2021
 - Each project can receive up to \$1M in funding over 3 years
 - Expect to fund ~4 projects per year
- Supports early-stage clinical trials of new therapeutics
 - Phase 1 or Phase 2a trials exploring safety, dosing or biomarkers
 - If successful, results are used to kickstart larger efficacy trials (Phase 2b or 3)
 - Often driven by a handoff from small biotech to large pharma
- Strong interest from the therapeutic development community
 - 13 Letters of Intent received
 - Top 4 clinical trials awarded end of 2021, with 2 of them already enrolling

Seed Awards (2022 commitment = \$500,000)

Planting the Seeds of Scientific Innovation

- New RFA, will launch in 2022
 - Each project can receive up to \$50k in funding for 1 year
 - Expect to fund ~10 projects starting in 2022
- Supports early development of innovative research ideas
 - Fund novel projects where early go / no-go data needs to be generated
 - Final milestone of all projects: use the data you've generated to apply to large follow-on funding opportunities
- Leverage the structure of large funders
 - NIH spends >10X ALSA's research budget on ALS research annually, but requires significant preliminary data before funding large awards
 - DoD spends >5X ALSA's research budget, commercial investment (though generally later stage) exceeds NIH and DoD budgets combined

Clinical Trial Capacity Awards (2022 commitment = \$4.5M)

Better Clinical Trials Make Drug Development Better For All

- New RFA, will launch in 2022
 - Each project can receive up to \$400k in funding over 4 years
 - Expect to fund ~12 sites starting in 2022
- Supports establishment of new clinical trial sites and improvement of existing ones
 - Funding can be used for personnel, equipment, training – whatever is needed to increase clinical trial capacity
- Benefits across the ALS drug development ecosystem
 - More trial access for patients (especially in underserved geographies)
 - More diverse patient population
 - Easier and faster clinical trials induce additional commercial investment in ALS

Prevent ALS Awards (2022 commitment = \$1.5M)

Reducing the Number of People Who Get ALS

- New RFA, will launch in 2022
 - Each project can receive up to \$300k in funding over 2 years
 - Expect to fund ~5 projects starting in 2022
- Supports identification and validation of risk factors
 - Non-genetic factors (like environmental, occupational or lifestyle factors) contribute to risk of ALS, but it is not clear how much any one factor contributes
 - If successful, results would be used to pursue pharmacological, behavioral or societal interventions that reduce risk
- Long term goals require early investment
 - The projects we support and partners we engage will change as risk factors are identified – start building evidence and exploring potential partnerships now

Quality Improvement Awards (2022 commitment = \$150,000)

Identify Best Practices for Delivering Care

- New RFA, will launch in 2022
 - Each project can receive up to \$25k in funding over 1 year
 - Expect to fund ~6 projects starting in 2022
- Supports program evaluation for care delivery
 - Collaborative award where ALS Association staff work with researchers to evaluate a new or ongoing care delivery program
 - Diverse programs eligible – from outreach campaigns to workflow design to physical resources and more
- Once identified, successful programs can be implemented across our national network