May 17th, 2019

NAGMSC Working Group on Sepsis

Final Report

Contents

Working Group Membership

Alfred Ayala, PhD
Professor of Surgery
Division of Surgical Research/Department of Surgery,
Rhode Island Hospital/Brown University
Providence, Rhode Island

Craig Coopersmith, MD
Professor of Surgery
Interim Director, Emory Critical Care Center
Emory University
Atlanta, Georgia

Monica Kraft, MD (Co-Chair)
Professor and Chair, Department of Medicine
University of Arizona College of Medicine
Tucson, Arizona

Vincent Liu, MD MSc
Research Scientist
Kaiser Permanente Division of Research
Oakland, California

Nuala J. Meyer, MD MS
Associate Professor of Medicine
Pulmonary, Allergy, and Critical Care Division
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania

Guy Padbury, PhD
Senior Vice President
Preclinical Development
Merck Research Laboratories
West Point, Pennsylvania

Polly E. Parsons MD
E.L. Amidon Chair and Professor of Medicine
Robert M. Larner MD College of Medicine at the University of Vermont
Burlington, Vermont

Ronald M. Przygodzki, MD
Director, Genomic Medicine R&D
Office of Research and Development
Department of Veterans Affairs
Washington, DC

John G Younger, MD (Co-Chair)
Director and Chief Technology Officer
Akadeum Life Sciences, Inc.
Ann Arbor, Michigan

Executive Summary

Sepsis, a rapidly progressive and frequently lethal disease, is a major killer of Americans. CDC estimates indicate 270,000 deaths annually. One-in-three inpatient deaths are due to sepsis. There are no accepted specific treatments for sepsis other than anti-infectives. Despite decades of intensive study of the underlying mechanisms of this condition, no new drug or significantly new diagnostic technology has emerged. Dozens of prospective trials of agents or strategies targeting the inflammatory basis of sepsis have failed.

Across all NIH institutes and centers in 2019, NIGMS provides the most research support for this field (approximately $40M), with NIAID and NHLBI being the second and third largest contributors. NIGMS has on occasion supported prospective clinical trials in the area, although it mainly supports fundamental, preclinical work as well as non-trial based human studies.

The NAGMSC Working Group on Sepsis was convened in the Summer of 2018 to advise NIGMS leadership regarding its extramural portfolio of research grants studying fundamental and clinical aspects of sepsis. The Group concluded that NIGMS is well positioned to play a unique role in the study of this condition within the NIH Institutes and Centers. In part this was due to NIGMS being unaffiliated with a specific organ system or patient population. Important opportunities were noted in both fundamental and clinical contexts. However, the Group strongly felt that given the complexity of managing and monitoring large-scale clinical trials, NIGMS was not currently configured to support definitive (e.g., Phase III) clinical studies outside of a partnership with another Institute or sponsor. Exclusion of sole sponsorship of such trials was not endorsed, but the Group acknowledged that NIGMS should conduct such trials only rare circumstances.

Several recommendations were made. Chief among them was rebalancing the NIGMS sepsis research portfolio to include a more clinical focus. There is need for better understanding of the heterogeneity and complexity of the clinical illness including the host response and to more effectively classify patients quickly. Progress in how to endotype septic patients offers near-term promise of better care, improving the design and conduct of clinical trials, and more informed fundamental research. Further recommendations were directed to preclinical research efforts, clinical informatic and biomarker research, and improved alignment of NIGMS funded research with the needs of the early stage pharmaceutical and biotech companies necessary for creating new treatments.

Lastly, the Group noted that cultural silos existed not just between fundamental and clinical scientists studying sepsis but existed also between Institutes within the NIH. Funding for sepsis research is fragmented across a number of Institutes with no apparent organizing authority. This is unacceptable for a disease as common and lethal as sepsis and quite distinct from how other major killers (e.g., cancer, heart disease) are approached. The Group strongly recommended conversations at higher administrative levels to consider how best to organize sepsis research in the United States and what role NIGMS would play in such a plan.

Recommendations

Global Recommendation 1: NIGMS should significantly expand its support of clinical research related to sepsis

- Support the collection, biobanking, and distribution of biospecimens and data sets to clinical and basic science investigators.
- Support the development of clinical informatic and biomarker tools to better identify, and assess the complexity and heterogeneity of the disease including the host response in order to endotype patients and study participants.
- Emphasize the importance of materials from ill patients in mechanistic research programs, including clinical data sets and clinical materials.

Global Recommendation 2: NIGMS should broaden its collaborations with other institutes to support clinical trials in sepsis

- Support the development of tools that directly enhance clinical research and clinical care of septic patients.
- Support 'proof of principle' trials wherein a fundamental disease mechanism is evaluated in a small-scale human trial structure. Endpoints may include surrogate biomarker response and not necessarily clinical outcomes. Priority of such work should be given to mechanisms deemed to be of high translational promise

Global Recommendation 3: NIGMS should independently sponsor definitive clinical trials only in extraordinary circumstances

- In most instances, NIGMS should not independently support definitive clinical trials (e.g., Phase II clinical studies or later) or support trial-planning grants for which follow-on funding has not been definitively established elsewhere.
- Instances where sponsorship could be warranted include studies for which there is broad agreement of otherwise unmet societal need and instances providing a unique opportunity to gather data that will likely significantly improve understanding of the underlying mechanism.

Global Recommendation 4: NIGMS should work with the Center for Scientific Review to ensure the availability of reviewer expertise

- Expertise is needed in a broad array of methodologies, including mechanistic, discovery, traditional clinical, and clinical informatic approaches.

Global Recommendation 5: NIGMS leadership should engage the Office of the Director to conduct a higher-level review of how the NIH can best coordinate efforts across institutes and more fully define NIGMS's role in that effort in order to translate tax dollars into cures.

_____

Regarding preclinical sepsis research, NIGMS should:
- Support the standardization of animal models and the development of models that more closely mimic (1) non-immunological aspects of sepsis and (2) important co-morbidities in human sepsis.
- Encourage use of human clinical material as a necessary means of confirming observations in nonhuman models.
- Support the use of discovery science, computational, as well as cell-culture and organoid-type methods in preclinical sepsis research.
- Evaluate current and new models in part by their ability to provide readouts relevant to the specific translational development of new diagnostic methods and therapies.

Regarding clinical sepsis research, NIGMS should:
- Support clinical research approaches that improve human disease identification, staging, and endotyping.
- Work with current NIGMS-sponsored researchers to identify and catalog extant clinical data sets and biospecimens for use in new research.
- Work with other stakeholder institutes (e.g., NHLBI, NIAID, NICHD) to sponsor a workshop to identify best practices and research priorities related to the use of electronic health records and other technologies to identify and stage septic patients for the purposes of supporting care and clinical trials.

Regarding efforts to translate discoveries into new diagnostics and therapies, NIGMS should:
- Proactively partner with other stakeholder institutes, early-stage pharma and biotech companies, and early-stage investors to identify unmet needs relevant to the translation of NIGMS funded discoveries into the nation's pharmaceutical and biotech development pipeline.
- Support the use of preclinical research endpoints that specifically align with drug discovery, distinct from mechanism discovery, and that address feasibility needs of early stage biotech companies and investors.
- Support research that improves the rapid identification and characterization of septic patients to improve the efficiency of early trials of new sepsis treatments.

Working Group Methods

The Working Group's efforts included an internal review of historical trends of NIH funding of sepsis research, the types of work currently supported by NIGMS, and the composition of the investigator pool carrying out the work. Contemporaneously, a call for public comment was made via Request for Information NOT-GM-18-039 'Strategies for Advancing Sepsis Research Supported by NIGMS.'

The results of these activities were summarized and presented at a face-to-face meeting of Institute leadership, the Working Group, and shareholders from other Institutes in the Autumn of 2019. Three SWOT (Strengths-Weaknesses-Opportunities-Threats) breakout analyses were conducted, focusing on preclinical model systems, clinical heterogeneity and endotyping, and the translation of fundamental research into new diagnostic tools and therapies.

The results of those efforts were combined and reviewed across the Group. In the spring, in two additional conference calls, the recommendations presented here were generated.

SWOT Analyses

Preclinical Model Systems

Analysis performed primarily by Drs. Ayala, Coopersmith, and Przygodzki, then reviewed by the Group.

Strengths

- Focus on a set of related murine models (used in 80% of NIGMS funded proposals looking at sepsis) has provided a platform for standardization across investigators and access to sophisticated methods (e.g., conditional knock-outs, transgenic organisms).
- Almost half of funded grants propose some type of analysis on clinical material.
- NIGMS has a track record of dual-institute RFAs that have drawn broad interest by applicants (e.g., with NHLBI, Blood and Vascular Systems Response to Sepsis)
- Sepsis shares with many other illnesses important pathophysiologic, and especially immunological, features. Discoveries supported through NIGMS sepsis awards have and will continue to provide important information about many other human diseases.
- NIGMS has supported important work in alternative experimental approaches (e.g., microfluidic, organ-on-a-chip, mathematical) that are expected to increase in importance and utility

Weaknesses

- A heavy emphasis on a small number of related murine models may prioritize precision (e.g., reproducibility) over accuracy (e.g., relevance to human syndrome). Generally, lack of experimental diversity limits the robustness of the program.
- While providing a generally reproducible model of global immune dysregulation, the cecal ligation and puncture model does not share the inciting pathophysiology of most human sepsis and is demonstrably difficult to standardize across operators and laboratories.
- Cecal ligation by its nature casts a surgical, rather than medical, subspecialty perspective on sepsis, casting doubt on its utility in studying the majority of human experience.
- Important comorbidities (age, diabetes, pre-existing organ failure, malignancy) and life-sustaining acute therapies (mechanical ventilation, renal replacement therapy) are difficult to incorporate into existing models of disease.
- Animal systems become more expensive - in some cases by orders of magnitude - as animal size and model fidelity to the human syndrome increase.
- Similarly, more complex and therefore more heterogeneous model systems become more expensive due to inflated sample size requirements.
- Subtyping (endotyping) human sepsis remains an underdeveloped science, complicating attempts to match animal systems with patient illness patterns.
- Reliance on investigator-initiated science is a valuable strategy only to the extent that submissions are being motivated by the clinical unmet needs. Experimental models and endpoints pursued because of perceived reviewer expectations threaten the close connection many NIGMS investigators have with clinical sepsis.

Opportunities

- Physician-scientists, and particularly those still practicing, are a significant part of the institute's PI portfolio and bring valuable understanding of clinical reality.
- NIGMS-funded investigators have been very proactive in efforts to improve the preclinical modeling of sepsis (e.g., the 2017 Wiggers-Bernard Conference)
- There are ample opportunities for collaboration and joint program development with governmental agencies (e.g., Departments of Defense, Veterans Affairs), private corporations (e.g., Jackson Laboratories), and philanthropic organizations (e.g. Gates Foundation) for various subsets of the sepsis problem
- Discovery approaches (e.g., -omics, big data) remain ripe for use in characterizing preclinical sepsis and better mapping models to human disease.
- Non-immunological aspects of sepsis (e.g., neurocognitive, cardiovascular) are relatively understudied and a natural entre into cross-institutional collaborations.
- The field is hungry to develop, and receive endorsement for, standardized model systems
- Diagnostic programs have the opportunity to impact clinical care on a much shorter timeline than mechanistic or early-phase therapeutic studies.

- The utility of rodent models as a path to new therapies or diagnostics faces substantial doubt in the broader scientific community.
- The lack of standardized but affordable alternative models may limit the institute's capacity to migrate towards more translatable research.
- Access to human material for study is widespread but far from universal
- The lack of consensus around clinical phenotype necessarily limits the value of experimental work performed on material obtained from human septic patients.

Clinical Heterogeneity and Endotyping

Analysis performed primarily by Drs. Kraft, Meyer, and Liu, then reviewed by the Group.

Strengths

- Because NIGMS is not focused on a particular organ system, it is uniquely positioned to pursue questions around the wide heterogeneity of organ involvement in sepsis.
- NIGMS has a strong track record of valuing mechanistic studies in sepsis and supporting a broad collection of scientific approaches in pursuit of those studies, including animal systems, work on human samples, and computational and biostatical strategies.
- The institute's sepsis portfolio includes genetic, immunological, and computational expertise that lend themselves to a variety of new approaches to better understand and stratify the heterogeneity encountered in clinical sepsis.

Weaknesses

- Historical emphasis on a small set of animal systems has not captured what is known of the complex background upon which clinical sepsis is typically encountered
- Animal models appear to have evolved to better address increasingly mechanistic phenomena but have not evolved to deliver to translational and clinical researchers actionable findings.
- Limitations in the budget of individual projects has limited the ability of translational researchers to capture sufficiently large patient cohorts to make meaningful discoveries.
- Discovery arms (e.g., genomic, proteomic, or banking goals) have not been consistently encouraged or funded, limiting the impact of the small number of clinical project the institute supports.
- The research community is not aware of what, if any, deposited or archived samples and data that NIGMS has available for study (e.g., GLUE grant data sets, samples)
- Clinical pheno- and endo-typing, which have been foundational tasks in the study of cancer, asthma, and other diseases, have not yet received emphasis from NIGMS.

- In large part by design, NIGMS lacks a trial network or structure to efficiently collect large data sets or evaluate new diagnostic, algorithmic, or therapeutic approaches.

Opportunities

- As NIGMS is not tied to a particular organ system or patient population, it is ideally suited to support studies of heterogeneity and stratification that intrinsically acknowledge the variability involvement of particular organ systems or populations. Such work would not find another obvious home within the NIH but impacts the work done by all other institutes in the field
- NIGMS has existing relationships and has co-developed RFAs with other institutes in sepsis.
- Similarly, NIGMS can justify the creation of resources and data or tissue repositories that extend beyond specific organ-based research
- While not possessing the clinical trial infrastructure needed to examine new approaches in sepsis, it is well resourced and has ample expertise in supporting mechanistic parallel work in later phase clinical trials carried out in other institutes.

Threats

- Issues around heterogeneity, stratification, and staging of sepsis are fundamental blocks to further progress in the field that imperil efforts by other institutes as well as industry
- The recognized reviewer pool typically tasked with evaluating sepsis proposals (e.g., Surgery, Anesthesia, and Trauma) possess deep mechanistic understanding but insufficient expertise in the design and interpretation of clinical phenotyping and endotyping.
- Investigators with translation, clinical informatic, and biostatistical expertise may not be submitting grant proposals to NIGMS because of perceived difficulty in receiving quality reviews

Translation of Research into New Diagnostics and Therapies

Analyses performed primarily by Drs. Padbury, Parsons, and Younger, then reviewed by the Group.

Strengths
- The institute has made a long-standing commitment to increase understanding of the pathophysiology of human sepsis and into developing new therapies.
- Physician scientists with active clinical practice are well-represented in the NIGMS sepsis portfolio. Broad interaction with the clinical problem provides deep understanding of what aspects of the condition are in greatest need, and what approaches are more or less likely to be fruitful.

- NIGMS supports an active SBIR/STTR program through which translation activities could be accelerated.

Weaknesses
- Few members of the NIGMS investigator portfolio have first-hand experience translating basic science discoveries towards clinical application
- The features which make a therapeutic or diagnostic target attractive to industry are not broadly understood by investigators in the portfolio
- The relevance of the most frequently studied model systems are in question, raising concerns that current 'best practice' may not be a reliable tool in making translatable discoveries
- The institute's stance on human studies and clinical trials is ambiguous, and may be driving investigators to the 'safe cover' of mechanistic studies rather than towards translational opportunities.

Opportunities
- The burden of disease both nationally and globally is enormous, and not likely to decline in the near term; new discoveries have the potential for major impact
- The development of new biologicals, particularly in immuno-oncology, may provide an early stage development road map for sepsis investigators within the GM portfolio
- Experience in adjacent diseases provides clinical and development expertise that can be leveraged in the creation of new sepsis treatments.

Threats
- Pharma's historical experience with new drugs for sepsis is very poor and creates a substantial headwind to the translation of any new candidates into the development pipeline. More specifically, it may be very difficult to financially justify the pursuit of a sepsis candidate therapy given the combination of negative past experience and the uncertainties around the design and conduct of confirmatory human sepsis trials, as the syndrome is poorly phenotyped.
- The review process used by NIGMS via the Center for Scientific Review may not be well positioned for the receipt of translatable proposals. Applicants know 'what works' at study section and are 'writing to the reviewer' rather than writing to the clinical problem. Without translationally experienced reviewers in the room, this may pose a systematic bias against proposals seeking primarily to develop therapies and diagnostics rather than pursue disease mechanism.
- Few members of the most commonly employed study sections for the NIGMS sepsis portfolio bring translational expertise. Note an important distinction between clinical experience (clinicians are well-represented at study section) and translational experience.
- Tribalism within the sepsis field may prevent investigators from other fields applying for sepsis related funding.

- GM's efforts suffer by a lack of an intentional cross-institutional division of labor related to sepsis research. No fewer than 4 institutes (NIGMS, NHLBI, NIAID, NICHD) support the work.

Appendix I: Request for Information NOT-GM-18-039

Below is the complete final analysis of RFI responses as performed by the NIGMS team and provided to the Working Group.

RFI Executive Summary

Of the 55 responses received, most identified the heterogeneity of sepsis as a disease, lack of relevance of animal models, and the paucity of team science approaches being leveraged as major barriers to advancing the state of sepsis research. Commonly cited research gaps included studies focused on work to better identify sepsis in patients through biomarker development and the use of big data / machine learning approaches, research to improve the translatability of animal models, and an increased focus on specific subtypes of sepsis, including pediatric sepsis, aging / comorbidity studies, and long-term implications of sepsis. The general perception was that mouse models had both drawbacks and benefits. Benefits primarily centered around the cecal ligation and puncture model's strength in capturing characteristics of short-term infection while drawbacks cited a lack of more nuanced characteristics of the disease which ultimately present challenges in translation of the findings. Most respondents agreed that the NIGMS focus in sepsis research should be in fundamental discoveries, with many emphasizing the need for cross-disciplinary team research being needed to ensure the translatability of findings. Many of the comments suggested the need for resources such as biobanks, clinical databases, and the need for shared resources to promote team science and conduct work in larger animal models.

RFI Background and Methodology

On July 23, 2018, the National Institute of General Medical Sciences (NIGMS) issued a Request for Information (RFI) on Strategies for Advancing Sepsis Research Supported by NIGMS (NOT-GM-18-039). In the RFI, NIGMS identified 5 key topics for respondents to address to help inform the direction of its sepsis research portfolio: barriers hindering advancement in sepsis research; gaps in currently supported sepsis research; the utility of current animal models; the appropriate mix of fundamental and clinical research; and the need (if any) for shared resources. Responses were received from 55 stakeholders such as sepsis researchers, professional societies including the American Thoracic Society and the National Association for Biomedical Research, and other interested parties. These responses were coded by a pair of NIGMS analysts based on major themes and subthemes identified in an initial scan of all responses. Results reflect the most common themes addressed by respondents, with exemplar quotes incorporated to provide context to these themes.

RFI Findings

Topics 1 and 2 – Barriers and Gaps in Sepsis Research

   The barriers and gaps in sepsis research are interrelated, and many respondents provided information about both across these two prompts. As part of the analysis, we consolidated responses to these two prompts, and used the following definitions to categorize comments as either "barriers" or

"gaps" in the NIGMS sepsis portfolio. Barriers were defined as unresolved problems, perceived shortcomings, or as-yet-unavailable platforms or technologies that require resolution or creation to move currently pursued research topics forward. Gaps were defined as underexplored areas of research that are currently feasible, but not typically explored through NIGMS-funded efforts.

Among barriers, comments focused on the heterogeneity and imprecise definition of sepsis; the need for lower cost diagnostics such as biomarker panels; the paucity of support for research, especially team science approaches involving interdisciplinary teams; difficulties in obtaining samples for research; and a lack of relevant models for sepsis. Sepsis was typically described as a constellation of specific conditions that lead to similar presentations and end results, but which suffer from being erroneously considered a monolithic disease. Analogies to cancer were somewhat common: *"It becomes clear not to expect one treatment to cure all types of cancer. Likewise, clinical trials and research in sepsis should focus on specific conditions and subpopulations of patients…"* Even the clinical definition of sepsis was deemed to be imprecise for purposes of advancing research: "…*the misdiagnosis of sepsis in research is* [a] *more serious problem that confounds epidemiology studies and entry into clinical trials hampers development and study of treatments*." To address this, the development of specific biomarker panels, and the reduction of cost of such diagnostics was noted as a barrier to adequately capturing the disease state, and subclassifying for potential treatments. In many cases, challenges were noted in translating fundamental research to clinical practice, with a strong emphasis on the need for team science: *"Sepsis need to be tackled by teams made of medical doctors, biologists, veterinarians, biotechnologists, bioengineers, bioinformaticians."* Related to the issue of collaboration, some respondents noted the difficulty associated with obtaining research samples: *"Basic/translational scientists have limited access to clinical samples which often lack of* [sic] *standardized procedures for reliable sample processing which can impact the quality of molecular analyses."* The detailed concerns about relevant models of sepsis are addressed in topic 3 but were commonly mentioned as a barrier to further research.

Regarding unexplored opportunities in the sepsis research portfolio, respondents communicated gaps in research that can lead to improvements in animal models; an additional need for clinical studies, especially focused on pediatric populations and understanding complexities associated with aging and comorbid populations; the importance of studying long-term sepsis and the associated recovery process; and the potential for precision medicine research, including the use of big data and machine learning. As with the benefits and drawbacks of current models, suggestions for model improvements are also addressed in further detail in topic 3. Many respondents stressed the importance of clinical studies to ensure viability of findings: *"… sepsis is a uniquely human disease."* Specifically, commenters noted the importance of pediatric populations: (*"There are significant gaps in early identification and treatment of pediatric sepsis, especially in previously healthy children."*) and disentangling the many challenges connected with studying the disease in aging populations*: "… improvements have not been as dramatic as seen in trauma, due in part to the greater complexity of the problem (older patients, more comorbidities, more complex underlying disease)."* In addition, research focused on better capturing the longer-term effects of sepsis, rather than the earliest stages of the disease, were deemed worthy of further exploration. Specifically, respondents suggested that NIGMS invest in additional research on post-sepsis syndrome and continued organ dysfunction (beyond 28 days) as well as septic progression beyond the acute (24 hour) phase of the disease. Finally, in keeping with earlier comments about the establishment of cost-effective biomarker panels as a barrier to sepsis research, respondents suggested that sepsis, like many other conditions, could benefit from a precision

medicine approach. Through better understanding of subtypes of sepsis (aided by better indicators), respondents suggested that big data and machine learning approaches could be employed to improve diagnoses and subsequent treatments: *"Improved patient stratification by clinical parameters (enhance [sic] by machine-learning techniques) and precision medicine biomarkers are needed to determine which patients are likely to respond specific therapies at different time points in the different trajectories of sepsis."*

Topic 3 – Benefits and Drawbacks of Mouse Models, Alternative Models

Benefits and drawbacks of animal models were mentioned in responses to every topic but are aggregated here. Among these comments were suggestions for the improvement of mouse models of sepsis and the use of alternate animals in sepsis research. "*The cecal ligation and puncture (CLP) model of polymicrobial sepsis* [in inbred mouse strains] *is considered the gold standard for experimental sepsis research and has been widely used in mouse and rat models. The advantages of the CLP model include the ability to modify the severity of sepsis* […], *the ability to mimic the hemodynamic, metabolic, and immunologic changes that occur in human sepsis.*" In addition, their inexpensive nature – compared with large animal models or human trials – was lauded. Conversely, many other respondents had a dubious or negative view of the current rodent models: "*Mouse models are some of the worst models for sepsis research.*" Some respondents suggested, "*mice have significant physiological differences and results* [should] *be confirmed in other mammal species with an immune, metabolic and cardiovascular systems closer to humans*." Differences in model techniques and methods, inflammatory response to infection, and organ function and response were all cited as difficulties with the mouse model. Multiple respondents urged the diversification of mice to include broader age groups (very young and aged mice), mice with comorbidities (metabolic or cardiovascular disfunction), 'humanized' mice, and mice which had previously been challenged with bacterial infections. Finally, treatments for mice were suggested to mimic human treatment regimens, including antibiotic and fluid replacement therapies, treatment for pain relief, and surgery to remove necrotic tissues.

Non-murine animal models were suggested for use in sepsis research. "*Using large animal animals* [sic] *(such as sheep and pig) for models of local infection (e.g., peritonitis) could be more relevant for clinical polymicrobial sepsis than the CLP mouse model.*" Even with these benefits, it was noted that some aspects of the condition (such as pulmonary artery pressure responses) could not be adequately mimicked in large animal models. Suggestions for shared resources to enable these models are included in Topic 5. Also mentioned were non-human primate models, rats, and simpler models like zebrafish and drosophila, though it was noted that alternate animal models may *"lack genomic and other data that were presumed to be a problem with mouse.*"

Finally, several respondents suggested *in silico* studies, three dimensional organotypic cultures, and cell models as alternatives to traditional animal models for sepsis.

The consensus was that any of the models – animal, cell, or computational – run a significant risk of not resulting in therapies that translate to the bedside due to the barriers and gaps outlined in Topics 1 and 2. Some respondents felt that less emphasis should be placed on such models because "no ideal model exists," and others felt that meaningful work could still be pursued by focusing on improving the existing models.

Topic 4 – Balance of Fundamental and Clinical Research

While the recommended balance between fundamental and clinical research varied, the majority of respondents agreed that the NIGMS portfolio of sepsis research should be balanced between the two, but somewhat favoring fundamental research. Many responses stressed the importance of blending research across fundamental and clinical lines, to assure translatability of the results: "*it is extremely important to balance fundamental and clinical sepsis research studies, or studies that propose a combination of the two.*" These comments also included the previously mentioned need for interdisciplinarity as a key aspect of the research being pursued. Finally, some responses indicated the importance of a balance of support mechanisms, ranging from single investigator R01s to larger team efforts such as P50s and RM1s.

Topic 5 – Potential Resources Needed for Advancing Sepsis Research

Respondents generally agreed that there are needs in the sepsis community that may best be served through the development and use of common resources. Such resources include biobanks, electronic health record (EHR) data or clinical databases, shared resources for conducting work on larger animal models, and resources for conducting team science on sepsis. Biobanks and EHR/clinical databases fill the need for researchers to gain access to valuable samples or data that are otherwise difficult to obtain on sepsis populations. Some cited challenges to overcome: "*Technology to manage multicenter studies leveraging the electronic health record is still underdeveloped,*" while others noted resources in development that could be used: "*A shared repository for resources, such as the national sepsis database being proposed by HHS's new division, DRIVe, should only serve to remove barriers for sepsis research and should be supported.*" In addressing ways to improve models, larger animal models require more robust infrastructure to pursue research questions and may be amenable to multiple researchers working with samples from the same animal. Aligning with many other comments about the need for increased interdisciplinarity and team approaches to sepsis research, respondents stressed that mechanisms and resources for conducting such team work would be important for progress in the field.

RFI Other Comments

The most common additional comments beyond the prompted topics included suggestions for NIGMS to provide increased support for sepsis research. Some respondents perceived that NIGMS does not adequately communicate its investments in sepsis research: "*The mission statement of the NIGMS … is not worded appropriately to be inclusive of research that includes inflammation and sepsis.*" some respondents proposed that research support be provided in specific requests for applications targeted towards sepsis research, with the mechanisms for such support comprising the breadth of the current NIGMS portfolio of grant mechanisms.

RFI Summary

Overall, respondents identified a number of challenges present in the current approaches to sepsis research, with varied reactions about ways to improve the impact of work in the field. These opinions will be thoughtfully considered by NIGMS as it moves forward in outlining a plan to advance sepsis research supported by the Institute.

Appendix II: NIGMS and NIH Sepsis Funding Analytics

As foundational work for this report, analysts within NIGMS examined in detail funding patterns within NIGMS and across the NIH for the past several years, including the quantity and features of funded and unfunded proposals, the characteristics of the principle investigators of these awards, and to a limited extent the scientific content of the work. The latter examined primarily the inclusion of human subjects and the types of preclinical models being studied. The result of these analyses were not a separate written report, but rather a collection of slides addressing questions that had arisen either among the analytic team or by Working Group members. The slides are included here.

NIGMS Sepsis Portfolio Analysis

Sepsis Working Group of Council

November 2018

Drs. Claire Schulkey and Jake Basson

NIGMS Provided the Most Money to Septicemia Research of All NIH Institutes (NIH RePORT 2014-2018)*
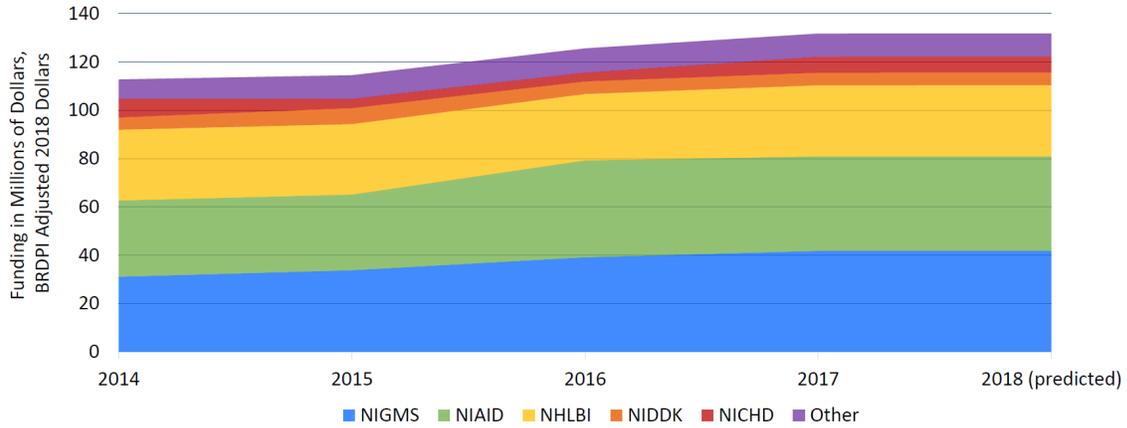
*RePORT data is publicly reported federal spending and not directly comparable to RCDC-identified sepsis estimates

NIH Septicemia Funding (NIH RePORT 2008-2018)
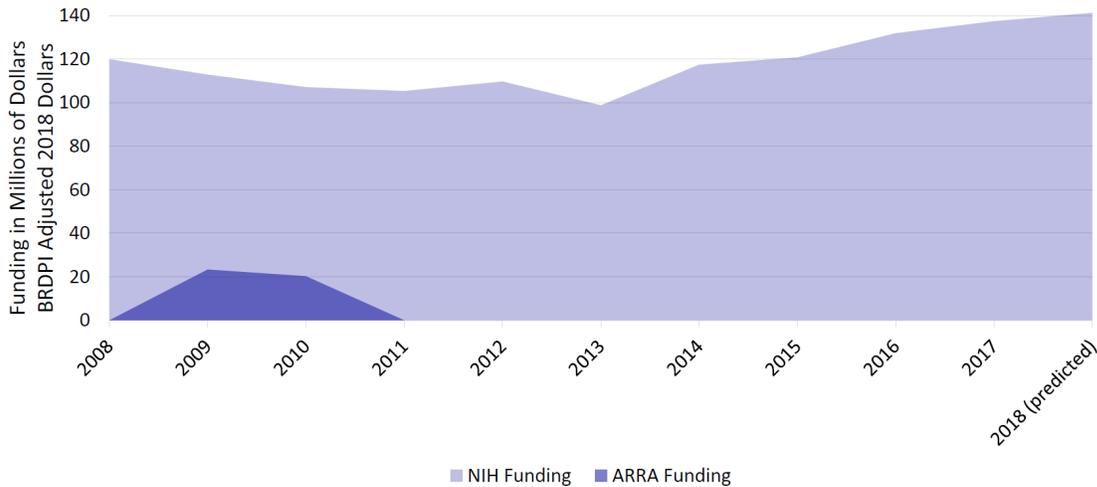
Sepsis Relevance was Defined in Two Ways

Sepsis Relevant Applications within NIGMS: Applications which contain "sepsis" or related terms in the title, or which have a weighted Research, Condition, and Disease Categorization (RCDC) score of at least 100. NIGMS applications included in this classification have been individually examined and determined to contain sepsis relevant studies or training.

RCDC Sepsis Applications across NIH: Applications with an unweighted Research, Condition, and Disease (RCDC) score of at least 30. This definition allows a broad identification of potentially relevant sepsis applications across all NIH Institutes, but likely contains many more false positives.

NIGMS Septicemia Funding Remains Between 1% and 2% of Total Research and Center Funding*
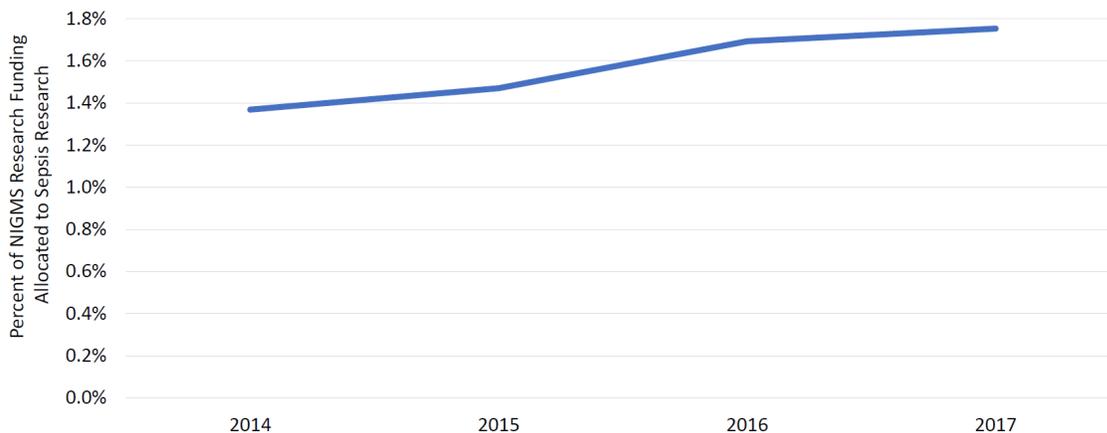
*Data obtained from NIH Office of Budget

NIGMS Funded Primarily
# R01's in Sepsis Research
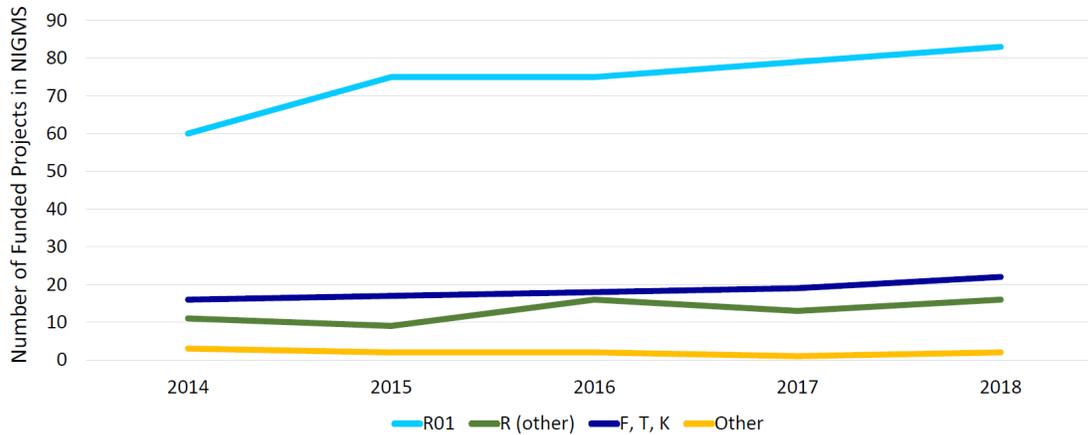
Submission Rate and Award Rate of Sepsis Relevant
Applications in NIGMS were Closely Linked
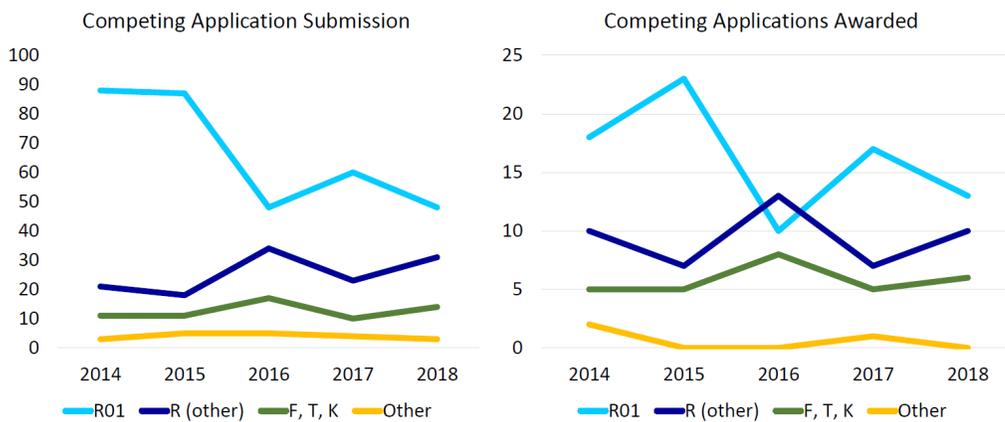
# Success Rates of NIGMS Sepsis Relevant R01 Applications Averaged 24%

Success Rate of All NIGMS and NIGMS Sepsis Applications

Y-axis: Success Rate of R01 Applications by FY

Sepsis Average = 24%

Legend: All NIGMS, Sepsis Applications
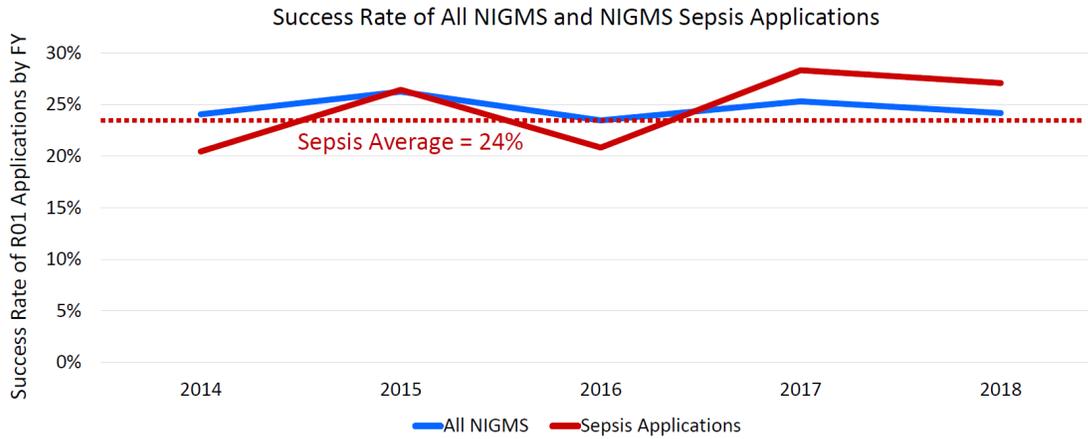
Number of PIs Who Submitted NIGMS Grants in Sepsis Only Versus Submission in Multiple Fields FY 2014-2018

28%

72%

Legend: Sepsis Only, Multiple Fields
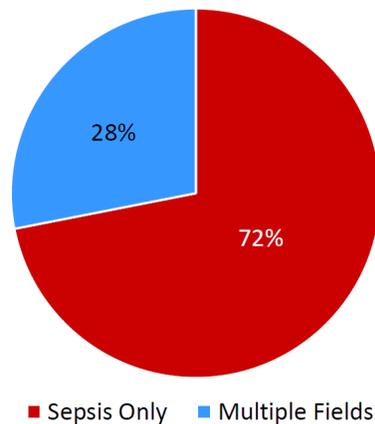
Women Were Approximately a Quarter of the PIs in NIGMS Who Submitted Sepsis Relevant Applications FY 2014-2018

	Men	Women
Applicants	283	84
Applicant Proportion	77%	23%
Funded	175	46
Proportion Funded by Gender	62%	55%
Unfunded	108	38
Proportion Unfunded by Gender	38%	45%

# Sepsis Applications were Predominately Submitted by White and Asian Researchers in NIGMS FY 2014-2018

- White
- Asian
- Other[*]
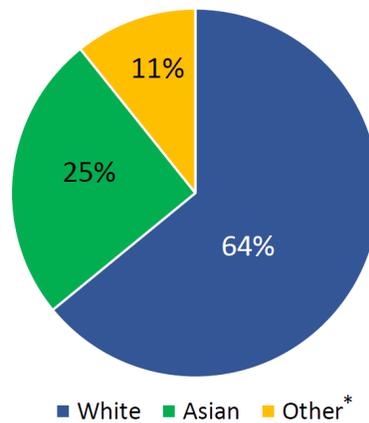
*Other includes all other racial groups as well as those with unknown or withheld racial status

NIGMS Applicants Under 41 Years of Age Made up
~24% of Sepsis Applicants
FY 2014-2018

Age of PIs at Time of Submission of Competing Applications to NIGMS
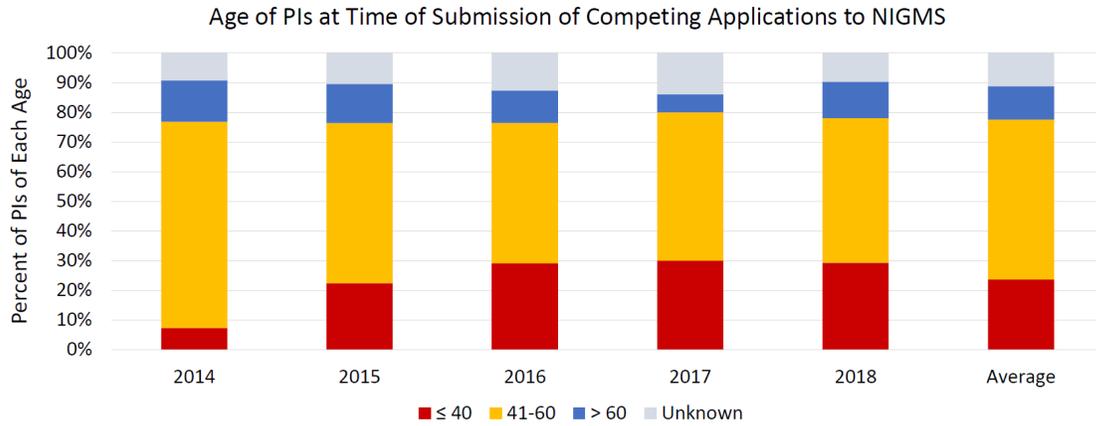
# Degrees of NIGMS Investigators Who Submitted
## Sepsis Relevant Applications
FY 2014-2018
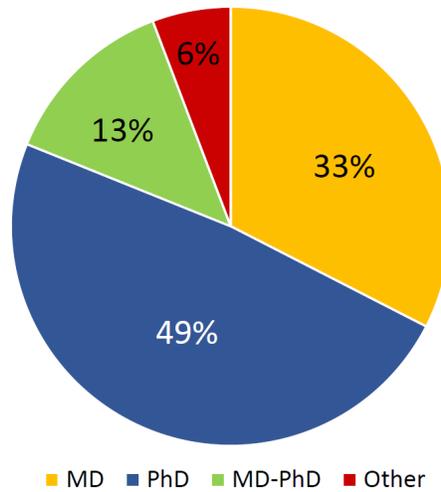
Board Certifications Obtained by NIGMS Applicants Submitting Sepsis Relevant Grant Applications FY 2014-2018

17% of PI's had identifiable medical board certifications

Board certifications identified included Surgery, Critical Care/Emergency Medicine, Internal Medicine, and organ specific care (cardiovascular, nephrology, neurology)

- Organ/Disease specific care
- Critical Care/Emergency Medicine
- Internal Medicine
- Surgery
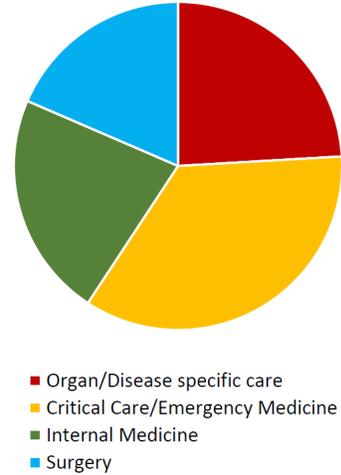
The Majority of NIGMS Sepsis Applications Come From Investigators at Institutions of Higher Education

- Independent hospitals
- Institution of higher education
- Other
- Other health, human resrces, environment/community serv org
- Research organization, institute, foundation, lab, etc.
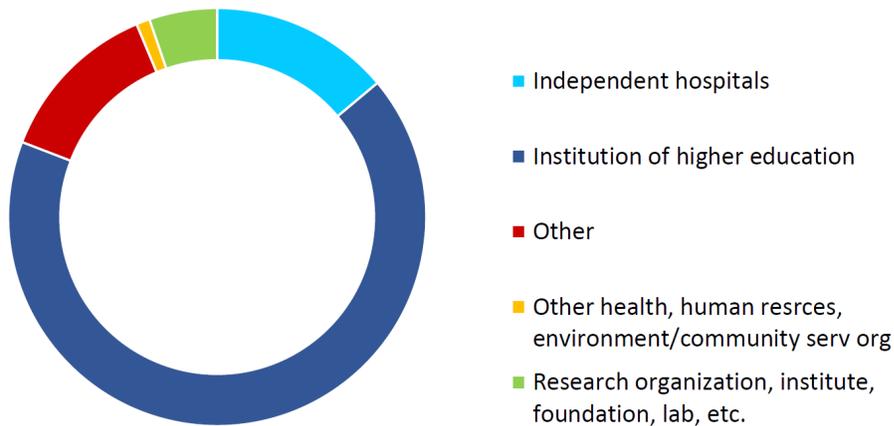
Internal Medicine and Surgery Were the Most Frequent Departments Listed by NIGMS Applicants*
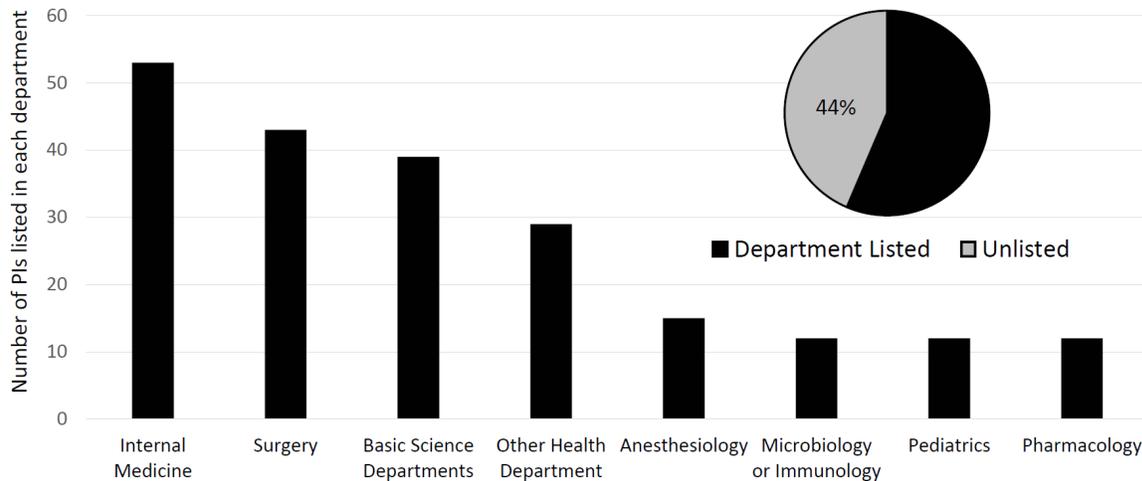
Support for Computational and Clinical Informatics Projects in NIGMS was a Small Portion of Total Sepsis Funding FY 2014-2018

< 3% of applications are computational or clinical informatics projects

27% of applications in computational and clinical informatics are funded – **similar to the 24% success rates of all sepsis applications and 24.6% success rate for all NIGMS applications in this time period**

Computational and clinical informatics projects are ~2% of all funded applications – 4 projects total between 2014 and 2018

Grants Which Include Human Subjects and Vertebrate Animal Work Were Identified Through NIH Administrative Codes

Individual review of sepsis relevant grants across all NIH institutes is extremely labor intensive, so administrative tags are used to approximate the number of NIH studies using human subjects and animal models.

Human Subject Involvement Codes indicate that human subjects OR human materials such as blood or tissue samples will be used, and IRB approval is needed prior to funding of an application

Human Inclusion Monitoring Codes indicate that human subjects will be prospectively recruited for a study

Vertebrate Animal Codes indicate that live vertebrate animals are used but not the purpose or number of animals

Human Subjects Involvement Codes Appeared at Similar Rates in NIGMS and All NIH[*] FY 2014-2018

All NIH

4%

42%

NIGMS

4%

41%

■ No Human Subjects   ■ Human Subjects Involved   ■ Extant/Public Human Data Used
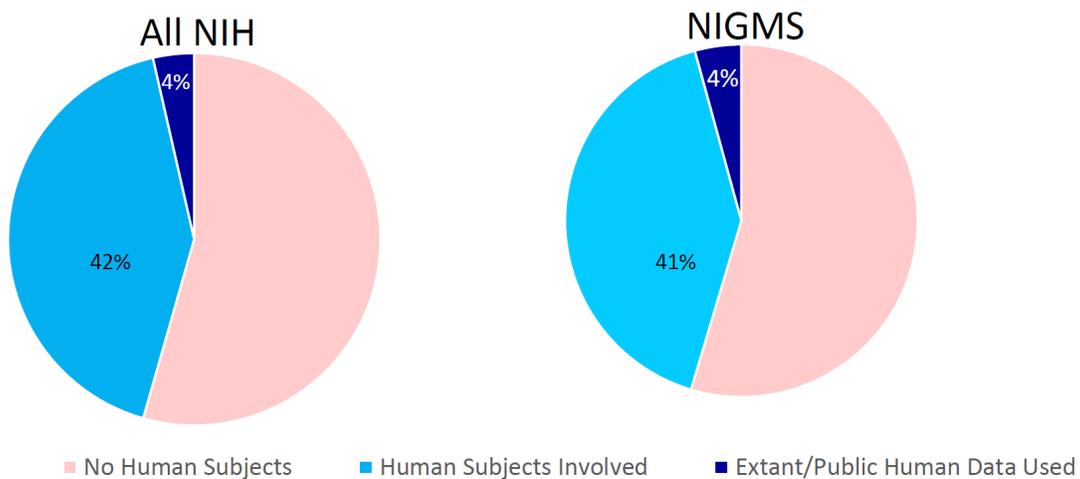
Human Inclusion Monitoring Codes Indicate **Prospective Recruitment** of Human Participants*for Studies Other than Clinical Trials at NIH
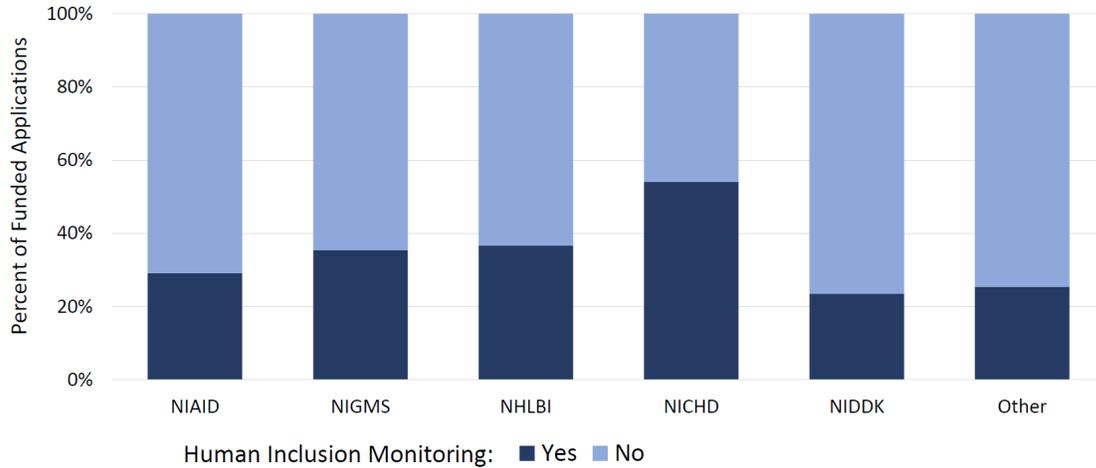
Vertebrate Animal Codes Indicate **Live** Vertebrate Animal Models were Used* FY 2014-2018
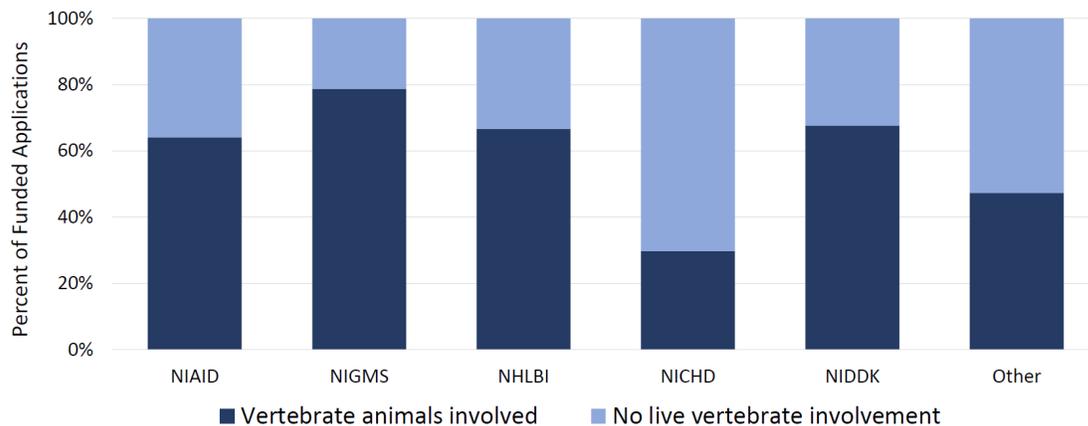
Most Funded NIH RCDC Sepsis Applications [*] (87%) Included Human or Animal Studies

Number of Funded Applications

- Vertebrate Animals Involved
- Human Subject Involved
- Human AND Vertebrate Animals Involved
- No Human or Vertebrate Animals Involved
- Extant/Public Human Data Only
- Extant/Public Human Data AND Vertebrate Animals Involved
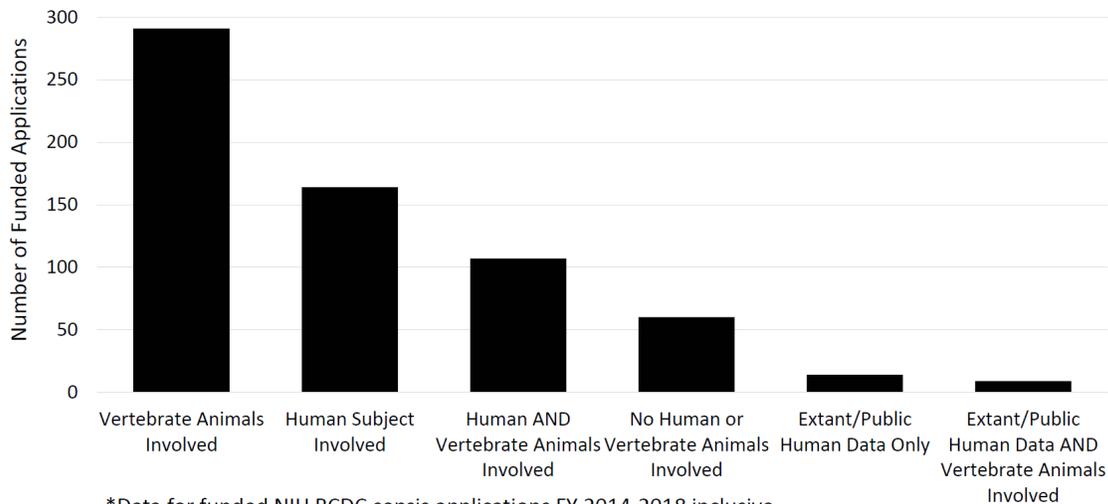
*Data for funded NIH RCDC sepsis applications FY 2014-2018 inclusive

64 Sepsis Clinical Trials Funded by the NIH Were Listed in Clinicaltrials.gov*

Number of Clinical Trials

- Completed
- Active
- Terminated or Unknown
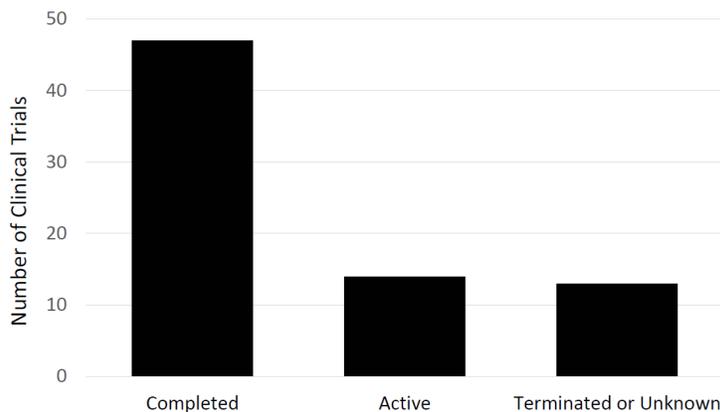
Active Clinical Trials funded by NIGMS

Rapid Administration of Carnitine in sEpsis (RACE), Active, not recruiting
Initiated 2012
NCT01665092

Kidney Response to Sepsis Affects Angiogenic Balance and Likelihood of CCI and PICS Recruiting
Initiated 2014
NCT02276066

Study of Early Enteral Dextrose in Sepsis (SEEDS) Recruiting, initiated 2018
NCT03454087

Detailed Examination of NIGMS Portfolio Showed Similar Trends in Animal and Human Subject Use

Dr. Jake Basson **reviewed** over 400 applications (primarily R01's) identified as sepsis relevant through individual examination.

Applications were **classified** as including Human subjects, including a model organism, including bioinformatics work, or including none of the above.

Applications including model organisms were classified as mouse/not mouse work, and those without mouse work identified non-mouse model organisms in use.

This data is highly reliable, but requires significant time and expertise to properly code, hence its execution on only the NIGMS grant applications.

Majority of Reviewed NIGMS Applications Involved Model Organisms or Human Studies
FY 2014-2018
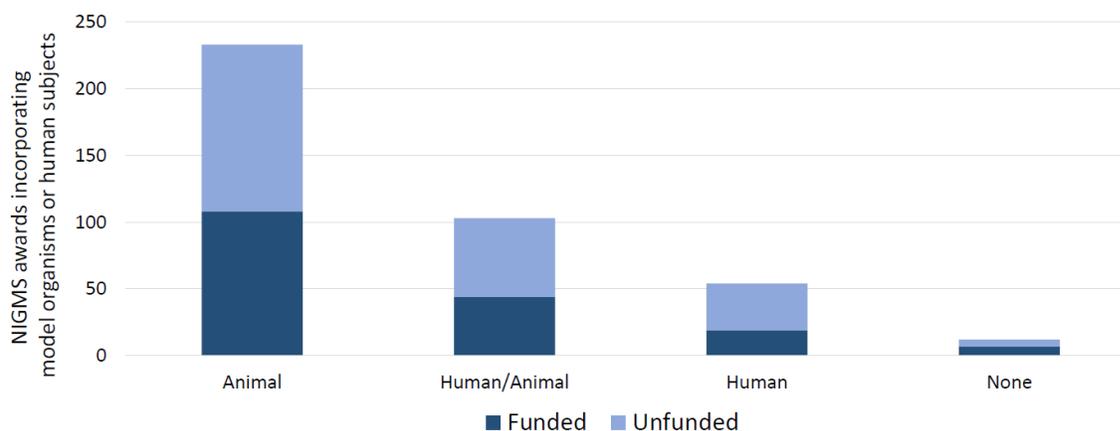
Majority of Reviewed NIGMS Applications Involved Model Organisms or Human Studies
FY 2014-2018

- 6 applications involved bioinformatics, algorithm, or device development

- 3 applications involved human biospecimens or other de-identified human samples

Mouse Studies Comprised 78% of All NIGMS Applications Involving Model Organisms
FY 2014-2018
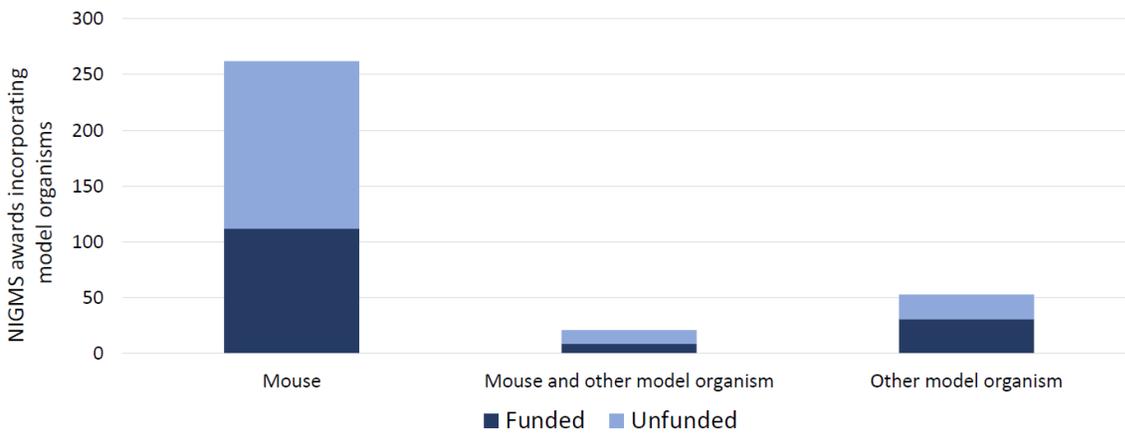
Mouse Studies Comprised 78% of All
NIGMS Applications Involving Model Organisms
FY 2014-2018

Non-Mouse model organism use included:

Baboon, C. elegans, dog, guinea pig, pig, rabbit, rat, sheep, and zebrafish with rat occurring the most frequently behind mouse

Multiple specific pathogen species were mentioned including:

E. faecalis, E. faecium, E. coli, K. pneumoniae, L. pneumophila, M. abscessus,

M. avium, M. chelonae, M. fascicularis, M. intracellulare, MRSA, P. aeruginosa,

S. aureus, S. enterica, S. enterococcus, S. epidermidis, S. iniae, S. Minnesota,

S. pneumoniae, S. pyogenes, T. mentagrophytes, T. rubrum