The Rockefeller University Clinical Scholars (KL2) Program 2006-2016

Supplementary Material

Selected Core Elements of the Clinical Scholars (KL2) Program

Mentored Clinical and Translational Protocol. This is the central component of the curriculum, focusing on the Scholar actually designing, implementing, conducting, analyzing, and reporting a research protocol involving human subjects. The scientific rationale for the study and how it relates to a health need, as well as the laboratory assays that will be conducted in the research protocol, are developed by the Scholars in collaboration with their primary scientific mentor. After selecting a topic for research, the Scholar enters the Protocol Navigation program, which guides the Scholar through the development of a rigorously designed and biostatistically robust protocol that incorporates the elements of Good Clinical Practice (GCP) and focuses on the protection of human subjects and informed consent.[1] A senior Clinical Research Coordinator serves as the Navigation Facilitator and advises the Scholar on developing the protocol, provides education on GCP, and simultaneously expedites the process. Consultations by biostatisticians and bioinformaticians provide valuable information on the analytical features of the protocol. The Community Engaged Research Navigation Program assists the Scholar in understanding the opportunities for interacting or partnering with community patients, advocacy groups, and community clinicians to incorporate their input on research priorities and the design of the study, as well as collaborating with them in patient identification, recruitment, assessment, and follow-up.[2] The Central Recruitment Program provides consultations on optimizing the feasibility of recruiting the required

number of research participants and provides recruitment expertise and an evidence-driven estimate of the length of time required to enroll them under different scenarios.[3]

When the protocol is completed, it is submitted to the ACCTS for scientific review. If the protocol is approved by the ACCTS, the Scholar then presents in person her or his protocol to the IRB and answers questions posed by the IRB members. After IRB approval, the Scholar implements her or his protocol with the advice of the Central Recruitment Program staff and the Research Nursing staff, and assistance from a clinical research coordinator. Shortly after the protocol begins, the Clinical Research Support Office conducts a formal audit of the protocol as part of the Early Audit Program to insure that the protocol is being conducted as approved by the ACCTS and IRB, and that the procedures are in accord with GCP principles. This allows for rapid detection of any deviations, followed by guidance and education of the Scholars, and implementation of corrective actions. After the study is completed, the Scholar analyzes the data with the assistance of her or his mentor and advice from members of the Biostatistics and Research Bioinformatics group. The Clinical Research Support Office provides guidance on compliance with trial registration and data reporting responsibilities. Finally, the Scholar prepares a manuscript for publication and presents the results of the study both locally and at one or more national meetings, including the yearly Translational Science meeting sponsored by the Association for Clinical and Translational Science (ACTS).

Tutorial in Clinical and Translational Science. This weekly tutorial encompasses all of the elements of clinical and translational science, including the regulatory process, bioethics, protocol design, technology transfer, grant and manuscript writing, epidemiology, community-engaged research, entrepreneurship, and mentoring.

Each week a Clinical Scholar presents a topic of her or his choosing after consultation with the Chief Clinical Scholar. Scholars are encouraged to select any topic that relates to their own work and that they believe has general educational value for the other Scholars.

Seminars in Clinical Research and Luncheon Meetings with Speakers. The weekly Seminars in Clinical Research series brings outstanding translational investigators to the campus to discuss their research. Faculty members take turns in hosting the speakers, insuring a wide range of topics. The Clinical Scholars also have the opportunity to host speakers. After the formal presentation, the Scholars and both the Director and Co-Director have lunch with the speaker. This provides an opportunity to obtain additional scientific information and to discuss career development issues and topics that are usually not included in formal presentations, such as those related to mentorship, technology transfer, and conflict of interest.

Biostatistics/Bioinfomatics, Epidemiology, and Research Design. Scholars attend a weekly biostatistics tutorial led by a senior biostatistician focusing on the principles of biostatistics related to clinical and translational science, as well as clinical trial design. These emphasize the biostatical methods currently being employed by the Scholars, along with analysis of their own data. Monthly tutorials in epidemiology focus on review of articles related to Scholars' areas of research, exercises in trial design, identification of potential communities with which to partner and methods to engage the communities, and connecting mechanistic studies with community-developed research priorities.[2] Bioinformatics training and methods for analyzing large electronic health

record data sets to test scientific hypotheses have been added to the tutorials in the past several years.

Pilot Project Grant Writing. Within a few months of joining the program, Scholars are expected to submit a proposal for pilot project funding. This is commonly the Scholar's first experience in grant writing. To maximize the educational value, the format follows the NIH R01 application, albeit with a shorter page limit, so that the applicant can have the experience of compiling all of the relevant materials and approvals that will be required when they seek NIH funding. A Public Health Impact statement is required for every proposal, highlighting the translational nature of all research. Senior Scholars serve as teachers and mentors during this process, insuring that the new Scholars obtain guidance and that the senior Scholars exercise their mentoring skills.

Manuscript and Grant Writing Workshops, Mock Study Sections, and Media Training. To enhance the Scholars' education in writing manuscripts and grants, periodic workshops are arranged, led by outside experts in written communication. Scholars have an opportunity to have their grant proposals for extramural funds reviewed by a Mock Study Section. To help Scholars learn how to communicate their research findings to the public, both directly and via the media, the Scholars periodically participate in media training workshops given by experts.

Graduate School Course. Each Scholar is required to pass a Rockefeller University Graduate School course that is aligned with her or his research interests. In special cases, Scholars can take courses at other institutions to fulfill this requirement.

Team Science training. Team Science training begins immediately upon entry into the program with the Scholar training in GCP and protection of human subjects, and entering the multidisciplinary Protocol Navigation and Community Engaged Research Navigation programs. These programs help the Scholar begin to build relations with patients, advocacy groups, and community based clinicians. They also help the Scholar develop and learn to lead her or his own scientific team, which depending on the specific protocol, will include variable numbers of the experts who comprise the clinical infrastructure (Table 1). Tutorials focusing on leadership skills complement this experience. Specific aspects on how to organize teams, conduct team meetings, and build team spirit are discussed. The team building skills of all Scholars are reviewed periodically at the weekly CCTS Senior Staff meeting and the Director and Co-Director provide informal feedback to Scholars about their team building and leadership skills based on these reviews.

Humanities and Translational Science. Topics related to humanism in medicine are introduced into the program as opportunities arise. These have included, for example: 1. A trip to Ellis Island focused on the medical evaluations performed there early in the 20th century to decide whether immigrants met the medical standards for immigration. In preparation for the visit the Scholars read about the history of the American Eugenics Movement during the same time period and how this affected public policy and immigration legislation. During and after the tour, the Scholars engaged in discussions about the role and responsibility of clinical investigators with regard to public health measures and the responsibility to resist state actions that violate the physician's oath.[4] 2. A dinner meeting with the medical historian Dr. David Oshinsky of NYU Medical School

to discuss the history of clinical research in poliomyelitis as recounted in his award-winning book, *Polio: An American Story*. 3. A dinner meeting with Dr. Jonathan Reiner, the cardiologist who provided medical care to Mr. Dick Cheney before, during, and after his term as Vice President. Dr. Reiner is the author of book *Heart: An American Medical Odyssey*, in which he recounts his experience caring for Mr. Cheney and the development of the translational advances in cardiologic care that have benefited Mr. Cheney. 4. Group attendance at the play, *Informed Consent,* which deals with how DNA sequencing studies had a negative impact on the communal cultural identity of members of a Native American tribe. After the play there, was a panel discussion with the playwright, members of the cast, and Rockefeller participants.

Evaluation by Master's Degree Advisory and Review Committee (MARC). The Clinical Scholar's progress is constantly tracked by her or his primary mentor, the Director and Co-Director, and the Scholar's Master's Degree Advisory and Review Committee (MARC), which contains at least three individuals, one of whom is the Scholar's primary mentor. The Scholars choose the other members of their MARCs in consultation with their primary mentors based on the individual's expertise in the scientific discipline being investigated by the Scholar and potential to provide valuable career development advice. Clinical expertise is provided to Scholars with PhD primary mentors by ensuring that at least one physician-scientist serves on the MARC.

Career Development and Individual Development Plans. A preliminary career development plan agreed to by both the applicant and the mentor is required as part of the mentor's letter requesting the admission of the trainee into the program in order to emphasize the centrality of career development as opposed to performing a postdoctoral

research project. All trainees are required to complete an Individual Development Plan (IDP) and they are encouraged to discuss them with their mentor, the program leaders, and members of their MARC. We use the IDP developed by the American Association for the Advancement of Science. Although trainees vary in their perception of the value of the IDP, some trainees have judged it to be extremely valuable in helping them plan to obtain important skills and in identifying their interests. For example, the IDP helped one trainee better appreciate how important it was for him to include opportunities for teaching in his career planning.

Clinical Scholars Graduates Publications and Scientific Programs

Graduates have been lead authors on major publications in the most prestigious journals, including the *New England Journal of Medicine, Cell, Nature, Science, and Proceedings of the National Academy of Sciences (USA)*. They are also leading paradigm changing programs. For example, several Scholars have contributed to the development and clinical evaluation of broadly neutralizing antibodies to HIV-1 cloned from patients' peripheral blood cells to treat and prevent HIV-1 infection.[5-10] Phase 1/2 studies in HIV-1 patients are currently ongoing at the Rockefeller University Hospital.[5,8-10] They have also identified the genetic basis of a number of important disorders,[11-18] opening up new therapeutic pathways; developed a novel metagenomics platform to identify new biologically active compounds synthesized by intestinal bacteria;[19] and called into question whether oral vitamin D repletion is equivalent to vitamin D repletion by ultraviolet light exposure in its effects on cholesterol levels.[20-22] Their studies of the potential role of glutamatergic regulation in age-related neurodegeneration has led to an ongoing clinical

trial of the glutamate modulator riluzole in early Alzheimer disease.[23,24] In addition, they have participated in studies that have refined our understanding of the pathogenesis of psoriasis, psoriatic arthritis, and atopic dermatitis, leading to more targeted and effective therapies.[25-34] The broad international representation of Clinical Scholars studying dermatologic disorders has contributed to their ability to identify the basis for the differences in manifestations of psoriasis and atopic dermatitis in Asian and European-American populations, with important therapeutic implications.[35,36]

Moreover, they have defined the impact of primary HIV-1 infection on neurocognition,[37] contributed to U.S. policies on HIV prevention and treatment based on the principles of implementation science,[38-42] developed a novel automated light scattering device to improve the accuracy and reproducibility of identifying malignant skin lesions,[43] improved the methodology for clinical micro-RNA diagnostics,[44-46] developed novel methods for modeling host interactions with hepatitis B virus using primary iPS cell-derived hepatocytic cells,[47] defined how interferon γ-dependent tissue homeostasis is co-opted by tumors to evade immune recognition,[48] and dissected the mechanism of B cell affinity selection after influenza vaccination, with important implications for improving vaccine strategies.[49] They have also developed ontology-backed phenotyping instruments to obtain granular bleeding history data[50,51] and defined the role of the electroencephalogram (EEG) in evaluating patients in the minimally conscious state.[52,53]

References

1. Brassil D, Kost RG, Dowd KA, Hurley AM, Rainer TL, Coller BS. The Rockefeller University Navigation Program: a structured multidisciplinary protocol development and educational program to advance translational research. *Clin Transl Sci*. 2014;7(1):12-19.

2. Kost RG, Leinberger-Jabari A, Evering TH, et al. Helping basic scientists engage with community partners to enrich and accelerate translational research. *Acad Med*. 2017;92(3):374-379.

3. Kost RG, Corregano LM, Rainer TL, Melendez C, Coller BS. A data-rich recruitment core to support translational clinical research. *ClinTransl Sci*. 2015;8(2):91-99.

4. Coller BS. The physician-scientist, the state, and the oath: thoughts for our times. *J Clin Invest*. 2006;116(10):2567-2570.

5. Caskey M, Schoofs T, Gruell H, et al. Antibody 10-1074 suppresses viremia in HIV-1-infected individuals. *Nat Med*. 2017;23(2):185-191.

6. Caskey M, Klein F, Nussenzweig MC. Broadly Neutralizing Antibodies for HIV-1 Prevention or Immunotherapy. *N Engl J Med*. 2016;375(21):2019-2021.

7. Lorenzi JC, Cohen YZ, Cohn LB, et al. Paired quantitative and qualitative assessment of the replication-competent HIV-1 reservoir and comparison with integrated proviral DNA. *Proc Natl Acad Sci U S A*. 2016;113(49):E7908-E7916.

8. Lu CL, Murakowski DK, Bournazos S, et al. Enhanced clearance of HIV-1-infected cells by broadly neutralizing antibodies against HIV-1 in vivo. *Science*. 2016;352(6288):1001-1004.

9. Schoofs T, Klein F, Braunschweig M, et al. HIV-1 therapy with monoclonal antibody 3BNC117 elicits host immune responses against HIV-1. *Science*. 2016;352(6288):997-1001.

10. Caskey M, Klein F, Lorenzi JC, et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. *Nature*. 2015;522(7557):487-491.

11. Bogunovic D, Byun M, Durfee LA, et al. Mycobacterial disease and impaired IFN-gamma immunity in humans with inherited ISG15 deficiency. *Science*. 2012;337(6102):1684-1688.

12. Kong XF, Bousfiha A, Rouissi A, et al. A novel homozygous p.R1105X mutation of the AP4E1 gene in twins with hereditary spastic paraplegia and mycobacterial disease. *PLoS ONE*. 2013;8(3):e58286.

13. Kreins AY, Ciancanelli MJ, Okada S, et al. Human TYK2 deficiency: Mycobacterial and viral infections without hyper-IgE syndrome. *J Exp Med*. 2015,212(10):1641-1662..

14. Dobbs K, Dominguez CC, Zhang SY, et al. Inherited DOCK2 Deficiency in Patients with Early-Onset Invasive Infections. *N Engl J Med*. 2015;372(25):2409-2422.

15. Guo Y, Audry M, Ciancanelli M, et al. Herpes simplex virus encephalitis in a patient with complete TLR3 deficiency: TLR3 is otherwise redundant in protective immunity. *J Exp Med*. 2011;208(10):2083-2098.

16. Zhang SY, Herman M, Ciancanelli MJ, et al. TLR3 immunity to infection in mice and humans. *Curr Opin Immunol*. 2013;25(1):19-33.

17. Lim HK, Seppanen M, Hautala T, et al. TLR3 deficiency in herpes simplex encephalitis: high allelic heterogeneity and recurrence risk. *Neurology*. 2014;83(21):1888-1897.

18. Sambuughin N, Goldfarb LG, Sivtseva TM, et al. Adult-onset autosomal dominant spastic paraplegia linked to a GTPase-effector domain mutation of dynamin 2. *BMC Neurol*. 2015;15:223.

19. Cohen LJ, Kang HS, Chu J, et al. Functional metagenomic discovery of bacterial effectors in the human microbiome and isolation of commendamide, a GPCR G2A/132 agonist. *Proc Natl AcadSci US A*. 2015,112(35):E4825-4834.

20. Ponda MP, Huang X, Odeh MA, Breslow JL, Kaufman HW. Vitamin D may not improve lipid levels: a serial clinical laboratory data study. *Circulation*. 2012;126(3):270-277.

21. Ponda MP, Dowd K, Finkielstein D, Holt PR, Breslow JL. The short-term effects of vitamin D repletion on cholesterol: a randomized, placebo-controlled trial. *Arterioscler Thromb Vasc Biol*. 2012;32(10):2510-2515.

22. Ponda MP, Liang Y, Kim J, et al. A randomized clinical trial in vitamin D-deficient adults comparing replenishment with oral vitamin D3 with narrow-band UV type B light: effects on cholesterol and the transcriptional profiles of skin and blood. *Am J Clin Nutr*. 2017;105(5):1230-1238.

23. Pereira AC, Lambert HK, Grossman YS, et al. Glutamatergic regulation prevents hippocampal-dependent age-related cognitive decline through dendritic spine clustering. *Proc Natl Acad Sci US A*. 2014;111(52):18733-18738.

24. Pereira AC, Gray JD, Kogan JF, et al. Age and Alzheimer's disease gene expression profiles reversed by the glutamate modulator riluzole. *Mol Psychiatry*. 2017;22(2):296-305.

25. Nograles KE, Zaba LC, Guttman-Yassky E, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol*. 2008;159(5):1092-1102.

26. Guttman-Yassky E, Lowes MA, Fuentes-Duculan J, et al. Low expression of the IL-23/Th17 pathway in atopic dermatitis compared to psoriasis. *J Immunol*. 2008;181(10):7420-7427.

27. Nograles KE, Zaba LC, Shemer A, et al. IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. *J Allergy Clin Immunol*. 2009;123(6):1244-1252 e1242.

28. Belasco J, Louie JS, Gulati N, et al. Comparative genomic profiling of synovium versus skin lesions in psoriatic arthritis. *Arthritis Rheumatol*. 2015;67(4):934-944.

29. Zaba LC, Suarez-Farinas M, Fuentes-Duculan J, et al. Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. *J Allergy Clin Immunol*. 2009;124(5):1022-1010 e1021-1395.

30. Fujita H, Nograles KE, Kikuchi T, Gonzalez J, Carucci JA, Krueger JG. Human Langerhans cells induce distinct IL-22-producing CD4+ T cells lacking IL-17 production. *Proc Natl Acad Sci U S A*. 2009;106(51):21795-21800.

31. Czarnowicki T, Krueger JG, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. *J Allergy Clin Immunol*. 2017;139(6):1723-1734.

32. Czarnowicki T, Esaki H, Gonzalez J, et al. Alterations in B-cell subsets in pediatric patients with early atopic dermatitis. *J Allergy Clin Immunol*. 2017;140(1):134-144 e139.

33. Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis--part I: clinical and pathologic concepts. *J Allergy Clin Immunol*. 2011;127(5):1110-1118.

34. Kim J, Krueger JG. Highly effective new treatments for psoriasis target the IL-23/Type 17 T cell autoimmune axis. *Annu Rev Med*. 2017;68:255-269.

35. Kim J, Nadella P, Kim DJ, et al. Histological stratification of thick and thin plaque psoriasis explores molecular phenotypes with clinical Iiplications. *PLoS One*. 2015;10(7):e0132454.

36. Kim J, Oh CH, Jeon J, et al. Molecular phenotyping small (Asian) versus large (Western) plaque psoriasis shows common activation of IL-17 pathway genes but different regulatory gene sets. *J Invest Dermatol*. 2016;136(1):161-172.

37. Evering TH, Applebaum A, La Mar M, Garmon D, Dorfman D, Markowitz M. Rates of non-confounded HIV-associated neurocognitive disorders in men initiating combination antiretroviral therapy during primary infection. *AIDS*. 2016;30(2):203-210.

38. Sturke R, Harmston C, Simonds RJ, et al. A multi-disciplinary approach to implementation science: the NIH-PEPFAR PMTCT implementation science alliance. *J Acquir Immune Defic Syndr*. 2014;67 Suppl 2:S163-167.

39. Mahler HR, Kileo B, Curran K, et al. Voluntary medical male circumcision: matching demand and supply with quality and efficiency in a high-volume campaign in Iringa Region, Tanzania. *PLoS Med*. 2011;8(11):e1001131.

40. Bertrand JT, Rech D, Omondi Aduda D, et al. Systematic monitoring of voluntary medical male circumcision scale-up: adoption of efficiency elements in Kenya, South Africa, Tanzania, and Zimbabwe. *PLoS One*. 2014;9(5):e82518.

41. Rech D, Bertrand JT, Thomas N, et al. Surgical efficiencies and quality in the performance of voluntary medical male circumcision (VMMC) procedures in Kenya, South Africa, Tanzania, and Zimbabwe. *PLoS One*. 2014;9(5):e84271.

42. Kripke K, Chen PA, Vazzano A, et al. Cost and impact of voluntary medical male circumcision in South Africa: Focusing the program on specific age groups and provinces. *PLoS One*. 2016;11(7):e0157071.

43. Gareau DS, Correa da Rosa J, Yagerman S, et al. Digital imaging biomarkers feed machine learning for melanoma screening. *Exp Dermatol*. 2017,26(7):615-618..

44. Gustafson D, Tyryshkin K, Renwick N. microRNA-guided diagnostics in clinical samples. *Best Pract Res Clin Endocrinol Metab*. 2016;30(5):563-575.

45. Renwick N, Cekan P, Bognanni C, Tuschl T. Multiplexed miRNA fluorescence in situ hybridization for formalin-fixed paraffin-embedded tissues. *Methods Mol Biol*. 2014;1211:171-187.

46. Hafner M, Renwick N, Brown M, et al. RNA-ligase-dependent biases in miRNA representation in deep-sequenced small RNA cDNA libraries. *RNA*. 2011;17(9):1697-1712.

47. Shlomai A, Schwartz RE, Ramanan V, et al. Modeling host interactions with hepatitis B virus using primary and induced pluripotent stem cell-derived hepatocellular systems. *Proc Natl Acad Sci U S A*. 2014;111(33):12193-12198.

48. Nirschl CJ, Suarez-Farinas M, Izar B, et al. IFNgamma-Dependent tissue-immune homeostasis Is co-opted in the tumor microenvironment. *Cell*. 2017;170(1):127-141 e115.

49. Wang TT, Maamary J, Tan GS, et al. Anti-HA Glycoforms Drive B Cell Affinity Selection and Determine Influenza Vaccine Efficacy. *Cell*. 2015;162(1):160-169.

50. Mauer AC, Barbour EM, Khazanov NA, Levenkova N, Mollah SA, Coller BS. Creating an ontology-based human phenotyping system: the Rockefeller University bleeding history experience. *Clin Transl Sci*. 2009;2:382-385.

51. Mauer AC, Khazanov NA, Levenkova N, et al. Impact of sex, age, race, ethnicity and aspirin use on bleeding symptoms in healthy adults. *J Thromb Haemost*. 2011;9(1):100-108.

52. Forgacs PB, Conte MM, Fridman EA, Voss HU, Victor JD, Schiff ND. Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. *Ann Neurol*. 2014;76(6):869-879.

53. Forgacs PB, Conte MM, Fridman EA, Voss HU, Victor JD, Schiff ND. A proposed role for routine EEGs in patients with consciousness disorders. *Ann Neurol*. 2015;77(1):185-186.

Supplementary Table 1

CCTS Protocol Conduct Support
Community Partnership Support
Participant Recruitment
Clinical Research Coordination
Research Nursing and Hospitalist
Bionutrition
Research Pharmacy
Regulatory Support
Data Organization and Protection
Biostatistics/Bioinformatics and Research Design
Biostatistical/Bionformatical Analysis
Auditing and Monitoring

Supplementary Table 2

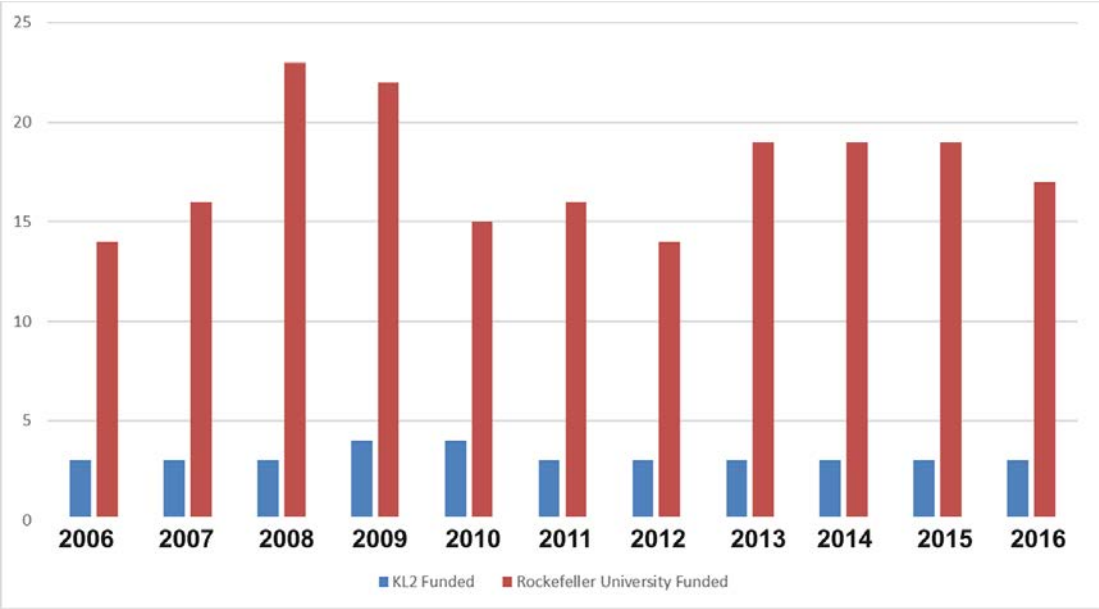
Clinical Scholars' Areas of Focus	
Bioengineering	1
Dermatology	4
Endocrinology	3
Epidemiology	1
Gastroenterology	4
Genetics	2
Hematology	1
Hepatology	1
Immunology	2
Infectious Diseases	6
Metabolism	2
Nephrology	2
Neurology	2
Oncology	1
Pathology	1
Pediatrics	1
Pulmonary	1
Rheumatology	4
Surgery	1

Supplementary Table 3

U.S. Institutions Where Clinical Scholar Graduates Hold Faculty Appointments
Harvard Medical School
Icahn School of Medicine at Mount Sinai
Memorial Sloan Kettering
New York University
Northwestern University
Stanford School of Medicine
University of Pennsylvania
University of Pittsburgh
Weil Cornell Medical College

Supplementary Figure 1

Number of Clinical Scholars Supported by CTSA KL2 Funds or Rockefeller University Funds 2006-2016



Supplementary Figure 1. Number of Clinical Scho9alrs Supported by CTSA KL2 Funds or Rockefeller University Funds 2006-2016. The number of Clinical Scholars supported each year by CTSA KL2 funding (blue) or Rockefeller University funding (red). The latter includes funds from an endowment and additional philanthropic support.