

2. Background.

2.1. Rationale, Overview and Objectives

2.1a. Rationale: This is a new proposal which will develop a pre-doctoral training program in Translational and Molecular sciences (TMS). The last decade has seen significant emphasis being placed, at a national level and at UAB, on translational research being a central feature of biomedical related research activities and training. This is exemplified by the emergence of many 'translational science' specific journals and the establishment of the National Center for Advancing Translational Sciences (NCATS) by the NIH. The challenges facing academic research institutions are adapting traditional training paradigms for students in clinical and basic science programs, and integrating into them, a significant and meaningful translational research element. The focus of this proposal are graduate students, who are a significant driving force in biomedical research. Enhancing their training is essential to ensure their competitiveness and readiness for the current and future workforce. However, the emphasis on molecular biology and other related disciplines in recent decades has led to deficit in instruction and training to PhD students in pathologic mechanisms and knowledge of disease processes, and more importantly in translational medicine. Effective translation of any finding requires a bridge between basic and clinical investigators. While there are many programs that encourage physicians to engage in biomedical research, relatively few exist for PhD graduates. As a consequence, we feel that too few PhD graduates are entering the workforce with sufficient knowledge / training to effectively translate molecular advances into clinical practice. A major challenge in effective training in translational sciences for pre-doctoral students is the need to incorporate multiple disciplines and concepts ranging from understanding disease mechanisms, understanding of how findings may be translated in academia or industry, to understanding regulatory oversight procedures and rules. This broad range of disciplines cannot be mastered by any one individual, and thus emphasize the importance of team science based learning. *This proposal addresses this need with our goal being to provide training that provides the necessary skills for the next generation of PhD biomedical scientists to incorporate translational objectives into their research and prepare them for current and future biomedical research work requirements.*

For this proposal, we build upon our recent experiences in translational training programs for pre-doctoral students. Over the last 10 years via a Med into Grad program supported by the Howard Hughes Medical Institute, we have developed and implemented a program that was based on the recognition that there is a premium in the current work place (in all sectors, academia, industry and government) for a scientist's ability to translate key concepts from basic research to the development of novel therapies or biomedical devices. Our experiences gained during this program provide the foundation for the current application, the goals of which are to: i) provide didactic instruction in disease-oriented research and in all aspects of drug discovery, ii) to provide hands-on training in the translational research oversight and regulation, iii) to broaden the mentor base for translational research, iv) to empower PhD students to incorporate translational research elements into their research projects, v) introduce trainees to clinically relevant experiences and patient contact opportunities that pertain to their research, vi) foster interactions of trainees with the UAB Center for Clinical and Translational Science (CCTS) trainees and educational programs in order to catalyze further interactions between fellows and faculty across the UAB health science campus, vii) provide enrichment opportunities and training that will position our students to meet the diverse requirements of the current workplace.

2.1b. Overview of Program: Our overarching philosophy is to create an environment in which students will receive high quality training and mentoring and which instills in them the skills and confidence to pursue research projects that have a strong translational focus and potential to impact human health and disease. Our approach is to provide a didactic framework, that comprises required classes and electives that allow for a customized curriculum with a focus on translational science, and integrate into this, meaningful clinical experiences. These experiences will be customized to complement student dissertation research projects. The goal is to provide opportunities for students to couple learning activities in the classroom and the clinic, with their research. To accomplish this goal, we feel it is important to capture students early in their training. We propose to enroll students into the program starting at the beginning of year 2, which coincides with their starting in a lab to pursue their dissertation research. We propose a 2 year program, over which time the program will provide stipend, and over which time the majority of the training will occur. Our goal is that by capturing students earlier in their research project, we can better train students and empower them to integrate translational research as a key element in their research. In addition to didactic elements, enrichment activities and significant clinical experiences will occur over this time period and which will provide career development opportunities and advice for translational research geared for the current job market. We note that the current proposal differs from our existing Med into Grad program, which is a year 1, and 1 year program.

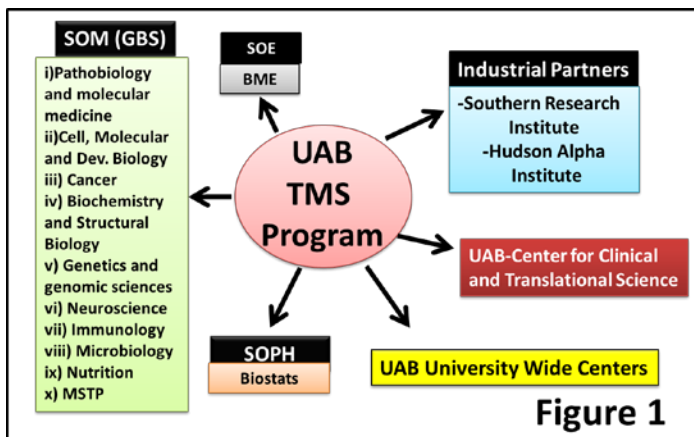


Figure 1 shows how the proposed training program will interface with UAB graduate programs. We anticipate that graduate students applying to the TMS training program will be from Schools of Medicine (Graduate Biomedical Sciences (GBS program which comprises 8 themes (i – viii in Figure), the MSTP program, and the Department of Nutrition Sciences), Public Health (Biostatistics) and School of Engineering (Biomedical Engineering). Typically in Year 1, students matriculate through common and department or theme specific core / foundation courses together with completing lab-rotations, culminating with entering a lab for their dissertation research. Only students who have successfully completed year 1 and been accepted into

a lab will be eligible for the TMS training program. Prospective preceptors may be members of any theme or department across campus. In addition, the TMS program will partner with UAB University Wide Centers that provide disease focused logistical, intellectual and training expertise including the Center for Clinical and Translational Science, and with industrial partners at the Southern Research Institute (SRI) and Hudson Alpha Institute. **Industrial partners provide expertise in drug discovery and personalized medicine concepts, and are integral and unique components in the training program discussed below.**

2.1c: Our experiences and the need for a Pre-doctoral Translational and Molecular Medicine Training Program Our experiences with the Med into Grad program have been extremely positive with significant impact on graduate student recruitment and training at our institution. Most importantly, the feedback from students in the Med into Grad program is overwhelmingly encouraging and the current application stems largely from existing students indicating that a graduate training program in translational sciences has been, and will continue to be key in their overall training and future careers. This is also reflected by the Med into Grad program (2006-current) (i) Increasing our recruiting competitiveness regionally and nationally; (ii) Increasing minority recruitment; (iii) Facilitating reorganization of the UAB SOM graduate curriculum to the current GBS format (described below); (iv) Facilitating interactions among scientists at UAB and Southern Research Institute (SRI); (v) Increasing physician participation in graduate education; (vi) Increasing integration of graduate training with CTSA training opportunities and (vii) development of a Certificate in Translational and Molecular Sciences and an associated Eminent Speaker Series. Specifically:

i) Increased Quantity and Quality of Applicants and Matriculants. **Table A** shows the number of TGE applicants and number of students enrolled into the Med into Grad program since 2006. **Importantly, the number of applications to the Med into Grad program has remained >100 over the last 3 years emphasizing the high level of student interest in receiving training in translational research. Thus there is a clear need for the program outlined in this application.** Further comparison between students in our current translational research program compared to JHS graduates over the last 10y that the average matriculation times are 5.2y and 5.9y respectively indicating that the translational research program is associated with a stronger caliber of student. Furthermore, 47% of our Med into Grad students vs, 32% of GBS students received a pre-doctoral fellowship (from NIH, AHA, NSF and others). Moreover, of the 16 Med into Grad program students who have graduated with their PhD and the 4 who are defending their thesis in the next semester, the mean number of publications was 4.2 ± 2.1 (STDEV) with a mean impact factor of 5.2 ± 2.4 (STDEV). Moreover, trainees were first author on 38% of these publications (with a mean of 1.6 first author publications per student, minimum-maximum range being 1-3). To date, 16 HMG students have graduated with their PhD and 2 with MS. Of the 16 PhD's 11 (69%) are pursuing post-doctoral research, 2 (12.5%) are researchers in industry including 1 as a vice president of research 2 (12.5%) are university or college faculty with teaching as their primary job and 1(6.3%) is stay at home mother. Of the 2 students who left with a MS one joined another PhD program (Ophthalmology) and the other journalism. Thus of the PhD graduates ~80% went into research as their immediate next career step. We note that the Med into Grad program is a one year program only; however, students participate in program enrichment and training exercises throughout their entire training, which we feel has played an important role in the impressive metrics indicated above **ii) Increased Minority Recruitment.** Also shown in **Table A** one positive impact of the Med into Grad program has been strengthening of enrolment of diversity students. Since 2010, 15.4% (mean) of TGE enrollees in Med

into Grad are diversity students compared to 14.7% for all pre-docs in participating programs, **Table 7A**). Further details of recruitment, retention and support of diversity students is provided below in section 4. **iii). Integration of Institutional PhD Training.** Our goal for making translational research a central component of doctoral training (and development of our Med into Grad program) facilitated consolidation of biomedically based graduate programs at UAB in 2006, including reconfiguration of formerly department-based programs to 8 multi-disciplinary, trans-departmental, trans-school tracks with a single entry mechanism and collectively referred to as the GBS (outlined in Figure 1). **iv) Facilitated UAB and Southern Research Institute (SRI) Interactions.** SRI, a contiguous UAB-affiliate contract drug-development company encourages students to perform lab rotations and provides insight into the workings of modern drug discovery, allowing fellows to follow the pipeline from target selection to drug discovery to FDA approval. A course on drug discovery and high-throughput screening was developed as a result of our Med into Grad program and is an integral part of the proposed training program. Importantly, SRI faculty oversee and teach this course and SRI faculty are involved in mentoring our students. **v). Increased Physician Involvement in Graduate Education.** A natural consequence of implementing our Med into Grad program has been the recruitment of clinical and basic researchers for teaching and enrichment exercises and clinical demonstrations. In other words, the translational training program has become a vehicle for bringing clinicians and basic scientists together and providing unique opportunities for trainees to interact with these faculty. We refer to course description HMG702 as an example of how this will continue in the current proposal. **vi). Integration of UAB Center for Clinical and Translational Science (CCTS) Educational Programs with Pre-doctoral training programs.** Med into Grad students have participated in multiple CCTS activities including didactic components related to biomedical regulatory issues, scientific writing, career placement and mechanisms to facilitate collaboration of nascent projects. **vii). Development of translational training program specific activities.** We have recently developed a Certificate program in Translational and Molecular sciences (approved by the UAB Board of Trustees, Summer 2012). Open to any pre-doctoral student on campus, this certificate formally recognizes formal training in translation research (described in more detail in program plan below). In addition, with financial support from the School of Medicine, and with the goal of partnering with different Departments and Centers at UAB, through the Certificate program, we have also recently developed a new Eminent Speaker Series, the goal of which is to bring leading translational scientists to UAB to share their research and provide an unique training opportunity for our students. Consistent with our philosophy of empowering students during their training, this seminar series is organized by the students (described below).

TABLE A	# of Med into Grad applicants / enrolled / diversity	% of minority in the Med into Grad Program
Year		
06-07	20 / 6 / 1	16.66%
07-08	40 / 6 / 1	16.66%
08-09	31 / 8 / 2	25%
09-10	37 / 8 / 0	0.00
10-11	99 / 12 / 1	8.33%
11-12	137 / 5 / 0	0.00
12-13	163 / 10 / 2	20%
13-14	111 / 10 / 3	30%
Totals (06-current)	638 / 65 / 10	14.6%

We note that our Med into Grad program ends in 2014 and is a year 1 program that is directly involved in student recruitment / enrollment. The current new TMS program application differs significantly and will follow a year 2/3 model. The synopsis provided above underscores our experiences in translational research training and the positive impact these have had on pre-doctoral training at our institution. This proposal builds upon these experiences and addresses a pressing need, indicated by the increasing number of applicants to our Med into Grad program (**Table A, data for TGE students only are shown**), to provide translational research training to the next generation of biomedical scientists. We also note that the UAB Graduate School provides 64 graduate fellowships via the GBS, per year for pre-doctoral students that ends after the first year of training. Support for subsequent years is the

responsibility of faculty mentors in whose labs students are performing their dissertation research. In addition, due to the current focus from the NIH on translational research coupled with the reality that resources available via the traditional RO1 investigator initiated mechanism for supporting pre-doctoral students are at relatively low levels, *we feel that a training grant that provides student stipends and couples it with translational research training is timely and needed.*

2.1d. Relationship to other Training programs and need for TMS program at UAB: We have carefully considered overlap between existing training grants and the current TMS proposal. However, all current training programs at UAB are focused on a specific disease or area. While some of these incorporate translational elements in their training program, these are limited to the disease focus. Currently there are no

programs focused exclusively on translational research which couple the broad training required in the fundamentals of translational research with significant clinical experiences. Our goal is to provide a strong foundation in the varying elements that comprise translational research that trainees can use throughout their careers and in any disease setting. Moreover, at the end of year 1, students select mentors and are then supported by funds from the individual laboratories. Within the SOM, SOPH, and SOE-affiliated departmental or theme graduate programs from which trainees are likely to be selected (**Figure 1 and Table 7A**), there are currently 370 (304 TGE) (data based on Fall 2013 registration JHS/SOM=287 (246 TGE), BME=40 (29 TGE), Biostatistics=22 (15 TGE) and Nutrition=21 (14 TGE)) graduate students in training. At UAB there are 17 active NIH predoctoral TGs with 85 total predoctoral training slots (Table 3) (note 14 of these are for MSTP, 5 for DAST, 5 for UAB Biostatistics and 4 for school of nursing). Amongst the 42 preceptors in this proposal, 37 are associated with the 17 predoctoral training grants (Table 3). Our program's faculty have mentored 155 predoctoral trainees over the past 10 years, with 61 current mentees (Table 5A). From this total, 68.2% would have been appropriate candidates for the proposed program. Currently, of the 279 total students affiliated with participating departments / themes (Table 1), 61 (22% of total) are in participating faculty labs with 48 (79%) being TGE. Despite this only a small number of these trainees (16%) receive NIH training grant support. Clearly there is a need to expand the number of institutional NRSA training opportunities for the UAB trainees interested in translational research.

MD/PhD and DMD/PhD programs are designed to prepare students for careers that combine laboratory investigation of disease mechanisms with the practice and teaching of clinical medicine in an academic setting, which could be considered to overlapping with the current application. However, the curriculum which is an integrated educational program, is composed of three phases: the preclinical phase (2 years comprised of core graduate curricula as well as the basic sciences curriculum of the Medical School. Students select their thesis laboratories and complete their requirements for their PhD), the research phase (usually 3.5 to 4.5 years), and the clinical phase (14-18 months). Our NIH NIGMS MSTP T32 (Lorenz PI) supports MSTP students during their first two integrated UASOM/UAB GBS years. If a trainee from either of these programs is selected for appointment to the TMS TG, he/she would be supported in the first 2 years of their research phase.

Finally, our institutional Center for Clinical and Translational Sciences (CCTS) is heavily involved in translational training including for pre-doctoral trainees via the TL1 mechanism that provides stipend support for 1 year and a 50 hour didactic program. This program is limited to 1-2 trainees per year however and does not include unique features associated with the proposed TMS program.

2.1e. Objectives: The overall training objectives are to provide a strong foundation in the diverse principles that comprise translational research that trainees can use throughout their careers, and in any research or regulatory setting. Specifically, our goals are to i) provide funding support that will attract outstanding graduate students interested in pursuing a career in which translational research is a central aspect, ii) to provide an outstanding training environment that effectively prepares the students for the current and future biomedical workforce, iii) develop skills required for hypothesis-driven experimental design and critical thinking to evaluate hypotheses and data, with a view to develop scientists that can ultimately lead cutting edge research programs including aspects of presentation skills, personnel management and project development, iv) provide training and experiences so that students have the confidence and skills to effectively communicate with physicians and other translational researchers, v) attract more physicians into graduate training and education. To assess these objectives, we will consult with oversight committee and set targets at the onset of the program. We anticipate these will be that trainees graduate in 5 years, with an average of 4 publications (minimum 1 as first author) and 85% initial placement in a career utilizing unique skills / experiences learned during TMS training. We also expect >75% of the publications to have a translational / clinical emphasis. See section 3.6 for discussion regarding evaluation of these objectives.

2.2. Environment for Research & Training at UAB

2.2a. UAB is a comprehensive urban university with a nationally recognized academic health center. UAB is the largest single employer in the state, with more than 23,000 employees. UAB's 2010 Economic Impact Study, which was conducted by the nationally respected firm Tripp-Umbach, calculated UAB's impact on the state of Alabama at \$4.6 billion. Much of UAB's impact is generated by technology transfer-taking basic research discoveries to the marketplace. A total of 18,568 students (undergraduate through doctoral levels) were enrolled as of fall 2013. The graduate student population is 67% female and 18.5% are minority ethnicities. UAB is among 51 public and private universities (and the only Alabama university) classified by The Carnegie Foundation for both "very high research activity" and "community engagement", and has been

named four consecutive years to the President's Higher Education Community Service Honor Roll, the highest federal recognition a university can achieve for civic engagement and service-learning. UAB has been cited four consecutive years among the top 10 universities nationally for diversity in *The Princeton Review* and is ranked 21st nationally in funding from the National Institutes of Health and 31st in total federal research funding and is considered among the top 100 universities internationally for life sciences according to Academic Ranking of World Universities. UAB occupies more than 85 square blocks in downtown Birmingham with over 250 buildings and 13 million square feet of research, teaching, administrative, and office space.

2.2b. Interdisciplinary Research Centers and the UAB Research Environment: The research environment at UAB is collaborative and independent of departmental affiliation. Major and unique elements of this culture are the multidisciplinary Research Centers. These are a cross-school, multi-investigator groups with a specific research focus which have an independent budget and administrative structure from Departments. They provide a rich training environment for trainees (e.g. by sponsoring seminars and workshops), and opportunities to develop cross-disciplinary projects with minimal boundaries (e.g. by providing pilot and feasibility funding opportunities for pursuit of novel hypotheses, approximate annual total of awards is \$3 million). In addition, centers expand basic and translational research opportunities with some centers providing core facilities employing cutting edge methodology and instrumentation. Proposed TMS preceptors have multiple center appointments greatly increasing interactions across departments, divisions, and schools. A list of Centers and their descriptions associated with TMS faculty is provided in Appendix 1. Additional support for the research enterprise comes through the University of Alabama Health Services Foundation (UAHSF) General Endowment Fund (GEF). UAHSF provides nearly \$2 million in annual grants for shared capital equipment and for establishing/enhancing core facilities that benefit the UAB research community. The HSF grants are available to any university faculty member who obtains sponsorship and approval of one of the departmental chairs. These grants support studies in one of four specific categories: Patient-Oriented Research, Laboratory Research, Clinical Care Initiatives, or Medical Education Initiatives. Many of the proposed TMS faculty have received awards from Centers and UAHSF.

2.2c. Teaching Facilities: UAB has recently renovated/constructed several buildings that improved facilities and resources for trainees. This includes small interactive classrooms that facilitate problem-oriented small group discussion courses and journal clubs. A prime example is the new Shelby Interdisciplinary Biomedical Research Building which houses the GBS offices and has 26 classrooms across 12 floors. GBS and affiliated themes have established websites that are continually updated with programmatic and university-wide information. This includes lecture notes and presentations, prior exams and study guides, and information on upcoming scientific meetings and seminars/workshops offered by departments and centers (<http://www.uab.edu/gbs/>). With the size of UAB, these resources are critically important for helping students keep informed about upcoming events. Moreover, in 2011 UAB developed a Center for Teaching and Learning (CTL) which offers workshops, assistance and help with technology to assist faculty with teaching including with new teaching paradigms (e.g flipped classrooms) (www.uab.edu/ctl).

2.2d. Research Facilities: The facilities at UAB are continuing to expand to meet the scientific and clinical research needs of faculty and student population. Below is a short description of the main research buildings in which TMS faculty members are located. See **Appendix 2** for a partial map of the university and location of TMS faculty mentors and GBS graduate offices. The state-of-the-art Shelby Interdisciplinary Biomedical Research Building opened in 2006. It is 12 stories tall with 340,000 square feet of space. The facility in the heart of UAB's campus and Academic Medical Center, includes research laboratories, research support areas including a state-of-the art microscopy area, offices, administrative space for graduate programs, and conference and class rooms. Shelby also has lounge space dedicated to GBS students for small group study sessions. Programs in neuroscience, immunology, bone biology, diabetes and Biomedical Engineering are housed in this building. It is also has the Office of Postdoctoral Education, the Graduate Program for Biomedical Sciences (GBS) and thematic administrative personnel. The Charles A. McCallum Basic Health Sciences Education and Research Building (MCLM) was completed in 1985 and has 177,000 square feet of research space. Kaul Human Genetics Building (KHGB) is a \$37.6 million, 145,000 square foot facility that is home to the Howell and Elizabeth Ann Heflin Center for Human Genetics and the UAB Department of Human Genetics. Volker Hall Education and Research Tower (VHCLM) is a 500,000 square foot building that is the primary teaching facilities for students involved in pathology graduate and health science programs. Other TMS faculty members are located in, Bevil Research Building (BRB), Biomedical Research Building II (BBR2), Boshell Diabetes Building (BDB), Center for Biophysical Sciences and Engineering, CBSE, Civitan

International Research Center (CIRC), Ryals Public Health Building (RPHB), School of Dentistry Building (SDB), Spain Rehabilitation Center (SRC), Tinsley Harrison Tower (THT), Webb Nutrition Science Building (Webb), Worrel Building (WORB), and the Zeigler Research Building (ZRB).

2.2e. Shared Core Resources: UAB has an extensive network of Core facilities supported by University-Wide Interdisciplinary Research Centers. There are currently more than 60 shared core research facilities available to TMS trainees and faculty mentors. These research core facilities are essential to the research/training infrastructure of UAB, and are a tremendous resource.

2.2f UAB commitment to career development: Training programs are in place for students, fellows, and faculty, and an aggressive plan has been implemented for further improvements including the enhancement activities organized by the Office of Postdoctoral Education (OPE) for the interest of graduate students and postdocs. These include grant and scientific workshops, industrial and academic roundtables where visiting professors, scientists and industrial leaders visit with students and fellows to discuss career paths and opportunities. In addition UAB's Professional Development Program was established to foster the development of graduate students, postdoctoral fellows, and visiting scholars to promote their success in an increasingly competitive world for scientists and academicians. The program targets the enhancement of skills in the areas of professional presentations, university teaching, publishing, interdisciplinary collaboration, and fellowship and grant writing. The program offers semester-long credit courses as well as day-long workshops in a various areas such as: (i) Career Support & Advancement; (ii) Academic & Grant Writing; (iii) Teaching at the College Level; (iv) Presentation & Discussion Skills; and, for international scholars, (v) Academic English for Internationals and (vi) Pronunciation & Accent Improvement. These and other career development programs are discussed further in section 3.7 below.

2.3 Industrial Collaborators

2.3a: Southern Research Institute - Collaborating Institution (<http://www.southernresearch.org/life-sciences>). SRI is located adjacent to the medical campus and receives approx. \$40,000,000 sponsored research money. SRI is located 1 block away from the PI office and GBS offices. SRI Pharmaceutical Division scientists are faculty within the UAB graduate school and participate as instructors, research mentors, and core leaders, providing expertise in drug discovery and oversight of the Vocabulary in Drug Discovery Research course that will be one of the required courses in this training grant proposal. SRI has a history of collaborations with UAB in the life sciences and has provided contract research for both public and private sector clients, including major national and international pharmaceutical and biotechnology companies, the NIH, and the DoD. Through the Vocabulary in Drug Discovery Research course, SRI scientists provide insight in modern drug discovery, allowing TMS fellows to follow the pipeline of drug discovery from target selection to FDA approval. Additionally, fellows observe elements of large-scale, federally sponsored programs such as the NIAID-funded Antimicrobial Acquisition and Coordinating Facility (AACF). SRI has a successful track-record in drug discovery and development. It has discovered more anti-cancer drugs than any other research organization globally, with six FDA-approved anti-cancer drugs and seven additional compounds in late stage preclinical development or clinical trials. SRI has tested more than 80% of all other FDA approved cancer drugs and 75% of all FDA approved anti-viral drugs. SRI staff are involved in all stages of the drug development process prior to the clinical testing, including medicinal chemistry, high throughput screening of new targets, basic drug action research, determination of drug efficacy, and preclinical pharmacodynamic / toxicology evaluation. SRI holds significant NIH Roadmap funding for its Molecular Libraries Screening Center and Specialized Biocontainment Screening Center.

2.3b The HudsonAlpha Institute of Biotechnology (<http://www.hudsonalpha.org/>) is a non-profit, academic-style research institute dedicated to basic and applied research in genomics and genetics. The Institute, which opened in April 2008, is housed in a four-story, 270,000 square foot building that has the capacity to house up to 700-800 scientists and staff. It is in Huntsville, Alabama, on the grounds of Cummings Research Park, a half-mile from the University of Alabama at Huntsville and next to the headquarters of NASA and a large number of engineering and computer science firms. The building houses well-equipped state-of-the-art laboratories, numerous small- and medium-sized conference rooms, as well as a library, auditorium and conference center. The Institute is comprised of nine large laboratories with space for 15 to 18 Faculty Investigators, and is situated in the North Wing of the building and comprises almost half of the square footage. The remaining half, in the South Wing, houses the HudsonAlpha Genome Sequencing Center (formerly the Stanford Human Genome Center) and 16 biotechnology companies, all of which are involved in

research, development or production related to genomics. A laboratory classroom for high school and college students, as well as teachers, is used to support an extensive education outreach program that is led by scientist/educator Dr. Neil Lamb, and is outfitted for distance education programs that originate from the Institute. High-definition video conferencing is placed throughout the building to connect our scientists and educators with colleagues, teachers and students in other locations.