Proposal for a Ph.D. Program in Human Genetics

Rationale

Genetics is the study of variations in and transmission of hereditary material from generation to generation and how this information is translated into biological function. Genetics utilizes multiple techniques to understand the variation, transmission and function of hereditary material from the molecular level to the population level. Because of the pervasive impact of genetic variation on biological function, genetics has become a unifying theme for much research in the biological and biomedical sciences and can serve as a focus for the study of virtually all biological processes and systems. Genetics plays ever increasing role in elucidation of the cellular and molecular mechanisms of human disease and birth defects, as well as in their prevention, diagnosis and therapy. In addition to the use of genetics to study biomedical questions posed by other fields, genetics encompasses an important set of questions as to how the information content of a set of relatively simple molecules can be translated into complex organisms, how variation at the molecular level can cause differences among individuals in terms of normal variation and disease processes, and how this variation within and among populations can be used to explain differences in disease prevalence.

In recent years, human genetics, as a subfield of genetics, has contributed significantly to our understanding of disease processes. This explosion in the growth of knowledge as an outcome of genetic analysis and the successfully completed Human Genome Project will increase over the foreseeable future. It is expected that the addition of a Ph.D. program in Human Genetics will enable Vanderbilt University to become a key player in this explosion of knowledge, both nationally and internationally, by attracting and training the best students interested in human genetic research and serving as a focus for the recruitment of new faculty interested in training students in genetics.

The goal of the proposed Ph.D. program in Human Genetics is to encourage the training of students to explore the questions motivated by genetic research in general and particularly as they apply to human disease. This curriculum will also teach students within the program as well as students in other disciplines how to use the tools of genetics to answer a variety of important biological questions. The resources for such a program are already largely in place. The establishment of such a program will serve to focus these resources into a cohesive program that can serve to unify human genetic research at Vanderbilt and provide common direction for investigators interested in training graduate students in genetics.

The current lack of a Human Genetics graduate program requires students in human genetics laboratories to create ad hoc training programs that can be less than optimal. In addition, despite the tremendous faculty expertise that exists at Vanderbilt, not having a Human Genetics PhD program can discourage excellent potential students from matriculating here because other programs in the nation offer a more visible and cohesive training program.

The addition of a Ph.D. in Human Genetics will provide Vanderbilt with an important opportunity that will unify divergent elements of genetics training into a single coherent

program, providing vision and direction for future of genetics research and training. The specific benefits of a Ph.D. program in Human Genetics include:

1. strengthening, complementing, and expanding existing coursework
2. strengthening current training programs in genetics
3. increasing the visibility of genetics research and training at Vanderbilt
4. increasing the number and quality of applicants to the graduate program
5. improving faculty research

Training Objectives

The overall goal of the Human Genetics Ph.D. degree program is to provide students with a solid foundation for a career in genetics research and teaching. Training will be available in human genetic analysis and in genetic analysis of model systems that contribute to our understanding of human disease. The training will combine a prescribed set of basic courses intended to ground students in the fundamentals of genetic analyses, the basics of human genetics, a set of elective courses designed to meet individual needs, and a rigorous research experience that will contribute to the field of genetics. Students completing the requirements of the PhD program in Human Genetics will have demonstrated mastery of knowledge in genetics and contributed substantial and original scientific knowledge to the field.

The specific objectives are:

1. To consolidate and enhance graduate training and research on the genetic basis of human disease that is currently scattered among multiple departments;
2. To provide students with an integrated and comprehensive academic curriculum designed for a concentrated program of study in Human Genetics;
3. To ensure that the existing critical mass of faculty in genetic analysis will interact synergistically in their efforts to provide students with firsthand knowledge of emerging concepts and "state of the art" technology in the rapidly evolving field of Human Genetics.

The proposed Ph.D. program will provide students with options for the study of human genetics from several perspectives, ranging from genetic epidemiology to molecular genetics/genomics of model organisms and disease states, and will build on the training that students receive in the Interdisciplinary Graduate Program in the Biomedical Sciences (IGP).

It is important to note that the intent of the training program is not to train students who only use one or a few techniques of genetics to address a wide variety of biological questions, but to train students who address questions fundamental to the discipline of Human Genetics. These areas include: 1) the characterization and implications of genetic variation; 2) the transmission of genetic information within and across populations; 3)

genomic structure and function; 4) how genetic variation is translated into phenotypes; and 5) the genetic basis of human disease.

Relationship to the Interdisciplinary Graduate Program in the Biomedical Sciences (IGP)

Students in the Human Genetics Ph.D. program will enter graduate studies as do current IGP students. All entering graduate students in the IGP (~80 students) are admitted uncommitted to a specific department or Ph.D. program and take the two semester IGP course (Bioregulation I and II), which covers the fundamentals of biochemistry, cell biology, genetics, and molecular biology as well as an introduction to several integrated themes, including intracellular signaling, neuroscience and the molecular basis of human disease.

At the end of two semesters of coursework and after laboratory rotations students must choose a Ph.D. degree program. Currently, there are 10 Ph.D. degree programs that participate as part of the IGP: Biochemistry, Biological Sciences, Cancer Biology, Cell and Developmental Biology, Microbiology and Immunology, Molecular Physiology and Biophysics, Neuroscience, Pathology, and Pharmacology. Human Genetics will be the 11th program.

Academic Curriculum for the Genetics PhD

Ph.D. students in Human Genetics are required to complete a minimum of 29 credit hours of formal coursework, consisting of 23 hours of required coursework and 6 hours of electives. One of the required courses will be a statistics course to be chosen from several currently available on campus and approved by the Program faculty. Students will take a minimum of 6 hours of didactic classes per semester during their first two years of study. It is expected that during the second year at least one semester will exceed this minimum in order to complete the required courses prior to year 3 of study. The electives will come from an approved list of advanced genetics courses, several of which are listed below. In individual cases, other courses approved by the Director of Graduate Studies and a student's committee can serve as electives. The choice of these courses will be based on the individual student's research interests. A sample course schedule is listed in Appendix III.

Students may take one of two paths in their training. These paths diverge in the Spring semester of the second year when it is expected that students who are more focused on population and/or statistical genetics will opt for courses that emphasize statistical and population approaches and students more interested in functional studies will take courses that emphasize molecular genetics/genomics. Other specific needs of students can be met with the electives, or in very rare cases students with the support of their mentors can petition to replace **one** required course with another one suited to their research needs.

Courses summaries are included in this document (Appendix 1).

All Students

Required Courses - Fall, Year 1

Bioregulation I (6)

Required Courses - Spring, Year 1

Bioregulation II (3)
Fundamentals of Genetics (3)

Required Courses - Fall, Year 2

Human Genetics I (MPB 340) (3)
Tutorials in Human Genetics I (1)

Required Courses - Spring, Year 2

Human Genetics II (3)*
Tutorials in Statistical and Population Genetics II (1)*

OR

*Genetics of Model Organisms** (2)
Regulation of Gene Transcription (MPB 332)(2)

Also Required
Statistics
For example, Introduction to Statistics (e.g., BioSci 270)

Advanced Genetics Course Electives (see Appendix 1)
Human Genetics II (3) (For Molecular Genetics Track)*
Medical Genetics (Genetics 520-5040 or Medical Genetics at Meharry Medical College)(3)
Evolutionary Genetics (BioSci 246)(3)
*Genetics of Model Organisms**
Neurogenetics (Neuroscience 376) (3)
Regulation of Gene Transcription (MPB 332)(2) (For Human Genetics Track)

Bioinformatics (Foundations of Bioinformatics and Computational Biology) (Bioinf 310) (3)
Immunology (BioSci 226)
Mol Developmental Biology (Cell Bio 341)
Microbial Genetics (Micro/BioSci 328)
Molecular Evolution (BioSci 247)
Advanced Molecular Genetics (BioSci 266)
*Analytical Proteomics (*Bchm 352)
Seminar in Ecology and Evolutionary Biology (BioSci 336)
Molecular Structure and Function (Bchm 301)
Genetics and Public Policy¶
*Statistical Genetics (3)**
Developmental Biology (BioSci 340)(3)
Advanced Developmental Biology (BioSci 342)(3)

* - Indicates a course not currently offered
¶ - Currently offered as a non-credit six hour seminar

Academic Performance

All students must maintain an overall B (3.0) grade point average (GPA) in their didactic coursework. Student progress will be monitored by the Director of Graduate Studies (DGS), who will meet with each student at least once per semester. If a student's GPA drops below 3.0, he/she will be placed on academic probation. If the GPA is still below 3.0 after two more semesters, the Oversight Committee will evaluate the student's overall performance, and he/she may be dismissed from the program.

Continued financial support is contingent upon maintaining an overall GPA of 3.0 and taking a full course load each semester.

Ph.D. Qualifying Examination

To qualify for candidacy, a student must complete all of the required first and second year courses, must be in good academic standing (GPA $\geq$3.0), and must pass an oral candidacy examination. The qualifying examination will be taken by the end of the summer between the second and third years of entry into the graduate school. The candidacy examination will have two parts. The first is to defend a 10-15 page written proposal on the student's thesis research. The second part of the examination will cover general knowledge pertinent to the student's field of research.

The first aim of the examination is to test a student's ability to demonstrate his or her capacity to think critically and to design experiments that will both test hypotheses and contribute to the understanding of basic genetic principles. The second aim is to insure sufficient general knowledge in the area of genetics to allow the student to place his or her own research into proper perspective, and to determine if the student has the

knowledge and comprehension of genetics to define important future areas of investigation. The examining committee will decide upon the division of the questioning.

The examining committee will be chosen by the DGS after consultation with the Oversight Committee. It will consist of 4 members of the Human Genetics training faculty, one faculty from outside the training program, and the DGS and/or his representative (*ex officio*). One of the Human Genetics training program faculty will be chosen by the committee as the chair of the examining committee. The student's supervisor will not be included in the examining committee. There will be three possible outcomes of the examination:

1) Pass;
2) Conditional Pass – Specific conditions and time requirements to meet the conditions will be determined by the committee with approval of the DGS;
3) Fail.

In the case of failure, the student will be given up to 4 months to retake the examination. The examining committee with approval of the DGS will determine the date of the second examination. Failure to pass a second examination will result in dismissal from the Ph.D. program. In this case, a plan for a terminal master's degree may be developed.

On satisfactory completion of the oral examination, the student will be admitted to candidacy.

Dissertation Committee

Once a student has achieved candidacy for the Ph.D. degree, he/she will select a dissertation advisory committee that will be chaired by a faculty member other than the research mentor. The committee will be chosen in consultation with the DGS and the student's advisor. The committee must include at least 2 members of the Human Genetics faculty other than the mentor and at least one faculty member from another discipline who is not a member of the Human Genetics program faculty. The DGS will serve as an *ex officio* member of the committee if he/she is not an official member of the committee. Committees should include at least 5 faculty members, including the mentor. The student should meet with his or her thesis committee for the first time no later than January of the third year and then once every six months. Thesis committees will serve as a resource for direction and assistance.

The role of the Dissertation committee is to guide the development of the student's research and career development, but the thesis advisor is primarily responsible for guidance of the student's research and training. The Dissertation committee is responsible for administering the final Ph.D. examination and will determine whether the candidate has presented an acceptable thesis. A summary of all committee meetings will be written by the student and approved by the committee. Copies of the summary will be sent to all committee members and the DGS and become a part of each student's

permanent record. The chair of the Dissertation Committee will inform the DGS in writing of the results of the final examination, including completion of any required revisions. If all other requirements are satisfied, the DGS will notify the Dean of the Graduate School that the student has completed the requirements for the Ph.D. degree.

Candidates for the Ph.D. degree in Human Genetics must present an acceptable dissertation that adds to or modifies what was previously known. The requirements of the Graduate School, as described in the Graduate School Bulletin, must be followed when preparing the thesis. Professional achievement must also be evident and should include the presentation of research work at a national meeting(s). Prior to the thesis defense the student **MUST** have at least one first authored publication (or one in press) in a peer reviewed scientific journal.

Rotations

Laboratory Rotations

During the IGP component of training, each student will be required to complete a minimum of three laboratory rotations with different faculty members, chosen after consulting the faculty members involved. The purposes of these rotations are to provide an early opportunity for research experience and for exposure to multiple methods of research inquiry, areas of research investigation, and technology. This early exposure will also help students decide if they are comfortable in a particular research environment and thereby aid in choosing a research mentor/laboratory for their thesis research. The rotations also provide the faculty an opportunity to observe and evaluate the student's performance and motivation in a research setting.

Each rotation will last for 8 weeks. An 8-week interval was chosen to fit the academic calendar, but it is usually sufficient to determine if the research program and lab culture are compatible with the student's interests and professional objectives. In addition, it is adequate time for a faulty member to judge whether the student will meet the faculty member's expectations.

It is expected that the three rotations will form the basis of matching students with their thesis advisors. However, should a match not be made on the basis of the first three rotations, a fourth rotation will be permitted during the summer between the first and second years of graduate training. In order for a student to be admitted to the Human Genetics Ph.D. program, the selected advisor must be a member of the program's training faculty.

Clinical Rotation (Optional but strongly recommended)

Each Ph.D. student will be encouraged to complete a minimum of one clinical genetics rotation. The purpose of this experience is to expose the students to issues related to the utility of genetics for the diagnosis, treatment, and prevention of human diseases. Although not a formal program requirement, it is expected that students will participate

unless a strong justification for not doing so is given to the DGS by both the student and his or her mentor.

The options include the following 3 rotations:

1) Genetics Clinical Rotation: During a one-month rotation, students will attend four genetics clinics with faculty from the Division of Medical Genetics, Department of Pediatrics. Students will be assigned a patient for each clinic and will be expected to research the patient's genetic problem and its implications. Following a meeting with the assigned patient, and in consultation with a clinician the students will produce a short write up about that problem based on a standard format similar to that found in GeneClinics. The students will also be asked to discuss and consider the social, ethical, and legal issues involved in the case. The outpatient genetics clinic at Vanderbilt is held 3 times per week and sees over 1500 patients each year, thereby providing a wide range of opportunities for these students.

2) Molecular Diagnostic Lab Rotation: During a one-month rotation, graduate students will attend four sessions in which they gain experience in the molecular genetics lab. During the rotation graduate students will be exposed to 1) key procedures in molecular genetics, 2) methods of diagnosing molecular alterations and recording and reporting molecular results and 3) assessing risks for abnormal and normal results. They will review and interpret lab results and participate in preparation of reports as well as discussing selected results and reports in small group conferences.

3) Newborn Screening Lab Rotation: During a two-day rotation, graduate students will gain experience in newborn screening by a rotation through the Tennessee Newborn Screening Lab. During the rotation graduate students will be exposed to 1) key procedures in newborn screening, 2) methods of recording and reporting results and 3) assessing risks for abnormal and normal results. They will review and interpret lab results and participate in preparation of reports as well as discussing selected results and reports in small group conferences

Additional Requirements

To help students become effective teachers, all students will be strongly encouraged to participate in the teaching of a course or seminar. A variety of teaching opportunities will be made available to students. Students can chose from a list teaching opportunities to be maintained by the DGS that will include teaching in undergraduate, graduate, and professional courses. In addition, opportunities will be developed to allow students to teach or present in local middle or high schools. This latter opportunity should be viewed as an opportunity to educate society at large about the importance of genetics research and its potential to help us understand and change the world around us.

At Vanderbilt, choices will vary among students, but will include leading in class literature discussions, performing activities as a teaching assistant in undergraduate laboratories/courses, or designing and presenting supplemental material in lower level

courses. For example, an advanced graduate student can assist instructors in required or elective courses for the program in the selection of literature for discussion, lead the discussions and participate in the developments of examinations on this material. The specific activities will be approved by the DGS following consultation with the Oversight Committee and the student's mentor, but will not exceed the equivalent of being a teaching assistant for one semester course.

Students in the Human Genetics Ph.D. degree program will be required to attend the Genetic Interest Group (GIG). GIG will be taken as a 1 credit hour Pass/Fail course with grades based solely on student attendance. No unexcused absences will be permitted.

GIG is held every Thursday at noon, and currently has a rotating format, with a research seminar on the first Thursday of the month, interesting clinical cases on the second Thursday, directed conversations on a topic of particular interest on the third Thursday, and a discussion of two current journal articles on the fourth Thursday. This has proven an excellent format for lively discussions and occasional strong debate on a broad spectrum of current topics, from genetic control of circadian rhythms in slime mold to ethical issues in patenting human genetic tests.

In addition to attending and participating in the discussions at GIG all students will be required to present their research progress once each year after admission to the program. Each presentation will consist of a 20-minute talk followed by questions from the audience. This experience will serve to train in students in oral presentation of their research and to provide increased input from the Vanderbilt genetics community regarding the research project.

Length of Training

Students and advisors should aim for completion of graduate studies within a period of three years after passing their qualifying examinations. Most students will be able to meet this expectation. All students are expected to graduate within six years of matriculating as graduate students at Vanderbilt. If this is not the case, the student will be required to submit a formal petition to the Oversight Committee to grant an extension. The petition must include an explanation for the inability to complete training within six years and a projected time for degree requirement completion. If an extension is recommended by the Oversight Committee, the DGS will petition the Dean of Graduate School for the extension.

Faculty

Faculty in the Departments of Biological Sciences, Biochemistry, Cancer Biology, Cell & Developmental Biology, Medicine, Molecular Physiology and Biophysics, Microbiology and Immunology, Pathology, Pediatrics, and Pharmacology will direct graduate training. The faculty in these departments have both strong research programs and extensive experience in graduate student training. Faculty are to be chosen on the basis of their

area of research expertise and their willingness to train students in the prescribed program. The program Oversight Committee will review the Curriculum vitae of all interested faculty and determine their eligibility based on criteria given below. A roster of faculty, their department affiliations, and general areas of research interest is given in Appendix 2.

The diverse faculty represented in the training program offer a wide variety of research and training opportunities for potential Human Genetics graduate students as well as emphases on different aspects of genetics research ranging from statistical and population genetics to the molecular basis of human disease.

Importantly, many of the faculty on the roster are already interacting in order to leverage their individual strengths to solve current research problems in genetics. The establishment of a Ph.D. program in Human Genetics will only serve to strengthen these collaborations and the research programs at Vanderbilt. The existing collaborative interactions of the faculty will also serve to provide an opportunity for students to have co-mentors who can bring particular expertise to aid student's research development.

In the future, additional training faculty will be added based on the following criteria:

1) Area of research interest;
2) An active research laboratory with peer-reviewed support, or start-up funds;
3) A track record in training graduate students. For young faculty, potential to train students effectively will be considered sufficient to become members of the training faculty, but these faculty will be periodically counseled on the responsibilities and duties of a thesis advisor;
4) Active participation in Ph.D. related courses, seminars or other program activities.

All training faculty in the program will be required to teach in at least one **required** course every other year, although teaching in a required course every year will be strongly encouraged. It is expected that all faculty will teach in an elective course every year. All appointments of training faculty in the Ph.D. program will be for a four year period. By the end of the appointment period all faculty will be re-evaluated and either re-appointed or removed from the program. Criteria for removal or reappointment will be the same as for initial appointment, as well as, fulfilling teaching requirements.

Administrative Structure

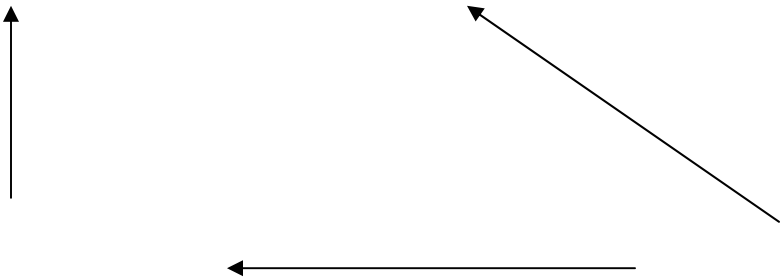
The Ph.D. Program will be administered by the DGS in close consultation with an Oversight Committee. As the faculty will be from multiple departments, centers, divisions and schools, this Ph.D. program will represent a truly trans-institutional program that will serve as the educational focus for Human Genetics training across the campus. Additionally, it is expected that the development of this program and the resulting interactions among faculty from across the campus will serve to foster new and productive faculty collaborations. Because of the trans-institutional nature of this

program, financial support will be provided through a budget for the Ph.D. program administered by the DGS in consultation with the Oversight Committee. At present there is currently a Genetics training grant that supports three Vanderbilt Ph.D. students. It is expected that in the future this grant will support students who are in the Human Genetics Ph.D. program. With the establishment of a trans-institutional Ph.D. program in Human Genetics, we plan to seek funding for additional student support from a variety of external sources.

As indicated in the diagram below, the Director of Graduate Studies will be advised by an Oversight Committee. Additionally, the Oversight Committee will evaluate student progress based on reports from the Dissertation committees.

The DGS will be responsible for overseeing all aspects of the Ph.D. program. He will do so with the help of the Oversight Committee (described below). The DGS will be the official spokesman for the Ph.D. program and will serve as its representative in matters related to University policy and programs. The DGS will be responsible for the maintenance of high standards in the academic program, including the continuing evaluation of all required and elective courses in the program, the qualifications and diversity of the faculty. The DGS will initiate and coordinate recruitment activities and will be also responsible for identifying and applying for (or assisting others in applying for) internal and external support for graduate training in Human Genetics.

Director of Graduate Studies
(Scott M. Williams, Associate Professor of Medicine)



Oversight Committee **Dissertation Committees**

In addition, the DGS will be responsible for monitoring the progress of each student throughout his or her training. He will have the most frequent contact with the students and will be responsible for explaining the program requirements to the students as well as monitoring their performance in course work. The DGS will also serve as a student advocate when personal problems arise and in hopefully rare cases of faculty irresponsibility or misconduct.

The Oversight Committee will also serve multiple roles. Included in its roles are:

1) The admissions committee, evaluating applicants for the Ph.D. program. The committee will also recommend which students should be supported by training grants and which by institutional funds;
2) An advisory committee on student-related issues, including monitoring student progress, performance, and welfare. The Committee along with the DGS will assess each student's performance at the end of the second year, and determine whether each student will remain in the program. The Committee will also meet with each student once each subsequent year at which time the student will outline his/her research progress and other training activities. This is intended to maintain formal contact with each student, thereby providing encouragement and suggesting modifications of research direction. However, it should be noted that the Committee, while overseeing the progress of all Program students will not provide the kind of individualized attention that the Dissertation Committee is required to do. The Committee's purpose instead is to make sure that the goals of the program are met in a more general sense.
3) Advisory committee on policy changes for the program. This will include the addition of and removal of courses from the program and the addition of tracks to the program;
4) Selection and evaluation of program faculty based on the criteria above.

The Oversight Committee will be composed of a broad spectrum of faculty representing all of the areas of genetics included in the training program and will be capable of advising the DGS on all program and research related topics pertinent to student training.

Pool of Applicants and Admission

The recent sequencing of the human genome, as well as, that of many model organism genomes, has been a focus of the growth of research in genetics. As an expression of this growth there currently exist over 100 programs in and/or departments of genetics or human genetics at universities across the United States, including some of the nation's most prestigious institutions such as the Universities of Chicago, Pennsylvania, Washington, and Wisconsin, Duke, Yale, Harvard, Columbia, and Cornell. The existence of such programs speaks both to the current demand for such programs and the need to develop such a program at Vanderbilt in order to provide a training mechanism capable of attracting the best students interested in the field of Human Genetics to our campus. There is no question that the lack of an existing Ph.D. program in any area of genetics at Vanderbilt has caused us to lose outstanding prospective graduate students to other institutions that may not have as many opportunities for quality research in genetics. Establishment of such a program will allow Vanderbilt to compete successfully for such students, many of whom are already committed as undergraduates to career paths in Genetics.

As an example of the growth of genetics as a field, the number of abstracts at the annual meeting of the American Society of Human Genetics (ASHG) has more than doubled

from 1149 in 1990 to 2702 in 2003. This substantial increase is also reflected in the number of members of the ASHG that has grown from 6494 in May, 1999 to 9038 in January, 2004. This number includes student members. These data speak to the recent expansion in research in Human Genetics. The Genetics Society of America, which includes researchers working on a wide variety of taxa and problems, has expanded in membership over the same period from 4218 to 5005. These numbers represent a ~20% to almost 50% increase in a four year time period and emphasizes the continued growth in these disciplines.

All entering graduate students in the IGP are admitted as uncommitted to a specific department or program, and many make their choice only at the end of two semesters of study after they are able to explore various programs. These students represent a highly qualified pool of students for recruitment into Human Genetics. It is expected that the addition of a Ph.D. program in Human Genetics will serve to increase both the number and quality of the overall pool of graduate students not only for this program but for all programs. Obviously, some students originally interested in the Human Genetics program will choose other programs while some who had not considered this program initially will choose Human Genetics. The result is that students will be better served by having this program as an option. For those who choose to pursue a Human Genetics Ph.D. the program will allow them to tailor their training programs more effectively to their major interests as opposed to forcing them into already existing excellent but not particularly well-fitting training programs.

Each year the IGP program arranges for each Ph.D. granting program or department to meet separately with students to introduce its graduate training program to the first year class in order to facilitate recruitment of students into their programs. In the future, students will also meet with the DGS and faculty in the Human Genetics Ph.D. program for an introduction to the opportunities in genetics training at Vanderbilt. In the past three years we have successfully recruited 11 students into labs focused on human genetics. Five of these have been funded by our training grant. We are hopeful that with the establishment of a Ph.D. program and the success of our past and present trainees we will be able to secure funding for both a renewal and expansion of this grant.

Official admission into the Human Genetics Ph.D. program will take place at the end of the second semester of graduate school, when the students have completed the IGP component of their training. This will insure that the students have had an opportunity to review the requirements and expectations of our degree program and are committed to fulfilling the goals of the program. Acceptance into the Human Genetics Ph.D. program depends on satisfactory performance in the first two semesters and completion of all IGP requirements. Acceptance will also depend on the recommendation of a thesis advisor who is part of the Human Genetics program faculty.

Financial Support

Stipends and tuition allowances are awarded to students on the basis of academic merit. Stipend levels are set by the Steering committee of the IGP in consultation with the department chairs. Stipends for 2004-2005 will be $22,000.

The first two semesters of support (while students are in the IGP) are provided by funds from the Graduate School. Following the first year, multiple avenues of support will be available. For United States citizens or permanent residents training grant slots are currently available, in which case most of the tuition (60%) is covered by the training grant(s) and the remainder by tuition remission. For foreign students support will come from research grants with tuition remission. Alternative sources of support include faculty research grants for all students and individual fellowships from extramural sources. Financial support for senior students (years 4 and above) will be the responsibility of the thesis advisor. Financial support may be withdrawn from a student whose cumulative GPA is less than 3.0 at the end of two semesters or whose performance is deemed otherwise inadequate as described elsewhere in this document.

Administrative costs are designed to be minimal and will be supported by the Genetics training grant and the Dean's office. Support staff will be provided through the BRET office. No financial support will be requested from participating departments.

Periodic Evaluation of Program

After three years and every five years thereafter, the DGS will convene a committee of external experts to evaluate the Ph.D. program, including the quality of the academic program and course work and the performance of the students as judged by research and publication quality. In addition, training grant applications to external sources such as NIH and NSF serve as a continuing source of external evaluation by experts in the field.

Conclusion

Critical resources (faculty, courses, seminars, pool of interested applicants, training grant support) are already in place for the development of a new trans-institutional Ph.D. program devoted to training students to explore fundamental problems in genetics. These existing key elements of a Human Genetics training program include already existing tutorials, lab rotations, training support, and courses. However, the individual components of this training program have not been coordinated into a cohesive training entity. The creation of this program will provide unity to Human Genetics at Vanderbilt, as well as, formal recognition and vision for this rapidly expanding scientific field. It will also provide the structure and financial support necessary to foster the continued growth of Human Genetics at Vanderbilt. It will also serve to bring together faculty to focus efforts on this increasingly important discipline, and bring Vanderbilt on a par with the top medical and graduate schools that already have genetics programs in place.

Appendix 1.
Brief Course Descriptions

Bio 246 Evolutionary Genetics This course covers basic population and quantitative genetic principles and then moves into more advanced (and more conceptual) 'special' topics such as the nature and origin of species, conservation genetics, and the evolutionary consequences of genetic modification and transgene escape. Prerequisite: Bio 205 (Evolution) and BSCI 210 (Principles of Genetics).

Bio 266. **Advanced Molecular Genetics**. Principles of classical and molecular genetic analysis: mutation and recombination, mapping, and the application of genetic methodology to the study of complex systems. Special emphasis on modern genomic approaches. Prerequisite: 210. FALL. [3] Friedman.

BCHM 352 Analytical Proteomics This course will introduce students to analytical proteomics methods and approaches through lectures, directed readings, and group and individual data analysis exercises. Topics include a) characteristics of proteomes and protein diversity; b) mass spectrometry approaches to protein and peptide analysis; c) protein and peptide separation methods; d) bioinformatics tools for identification of proteins from MS data; e) quantitative proteomics methods; f) applications of proteomics in common experimental designs; g) tissue proteome profiling and imaging approaches. SPRING [2] Liebler, Caprioli, Link

MP&B 332. Regulation of Gene Transcription. Factors affecting DNA/protein interactions. The most recent findings on how such interactions are established within the chromosomal environment and how those interactions affect gene activity. Hormonal and developmental aspects of gene control within the context of protein/DNA interactions. Prerequisite: BCHM 321 or consent of instructor. SPRING, ODD NUMBERED YEARS. [2] Stein and Staff.

MP&B 340. Human Genetics. Designed to cover background and latest advances in human genetics. Topics will include an overview of mutational mechanisms, cytogenetics (detection and description of chromosomal abnormalities), biochemical genetics (gene defects in biochemical pathways), molecular genetics (gene structure, function, and expression), population genetics (heritability, quantitative traits, variance analysis), disease gene discovery (study design, statistical and molecular techniques), and genetic epidemiology (genetic linkage analysis, association studies, gene-gene and gene-environment interaction). Topics will be discussed with reference to specific human genetic diseases. Prerequisite: consent of instructor. SPRING. [3] Haines, Sutcliffe, and Staff.

MP&B 345. Cellular and Molecular Neuroscience. (Also listed as Cell and Developmental Biology 345, Neuroscience 345, Pharmacology 345) Students are exposed to fundamental concepts and techniques in molecular and cellular

neuroscience and provided with a theoretical context for experimental analysis of brain function. The course is divided into four modules. Module I: Biophysics and Biochemistry of Synaptic Transmission reviews biophysical and molecular concepts relating to membrane excitability, action potential generation and propagation, and the molecular basis of chemical signaling at synapses. Module II: Synaptic Integration and Plasticity discusses mechanisms and models of synaptic integration and plasticity and concentrates on how molecular changes translate into altered synaptic strength and gene expression programs that underlie short and long-term plasticity. Module III: Neural Development examines historical and current concepts in neural pattern formation, neural migration, axon guidance and synapse formation. Module IV: Neural Diseases and Disease Models focuses on specific brain disorders such as epilepsy, depression, schizophrenia, and Alzheimer's disease and current models used to investigate their origin and/or treatment. This course combines faculty lecture with discussion of original articles, with an emphasis on student participation. SPRING. [4] Blakely, Carter, and Staff.

MP&B 385. Fundamentals of Genetic Analysis. This course is designed to accomplish three goals: 1) Introduce students to critical topics of genetic research, 2) introduce students to important areas of genetic research not covered in first year coursework, and 3) promote an understanding of classical genetic analysis by learning genetics using the original literature. Emphases will be placed on research problems that utilize the full power of genetic analysis. FALL. [4] Williams and Staff.

M&IM 328. Microbes and Immunity. A lecture series on selected topics. The course may be taken once in each of the following subject areas for a maximum total credit of 8 hours.

M&IM 328 1. Microbial Genetics. (Also listed as Biological Sciences 328) The genetics of bacteria and yeast and their use in molecular biology as an experimental tool. Prerequisite: IGP 300a. FALL. [2] Graham (Biological Sciences), Fang.

BioSci 340. Developmental Biology Genetic, molecular, and cellular mechanisms underlying development of eukaryotic organisms, with emphasis on insects and vertebrate animals. Topics include regulation of gene expression during developmental processes, specification of embryonic polarity, generation and patterning of germ layers, organogenesis, axonal specificity, evolution of chordate body plan. FALL [3] Solnica-Krezel, Zwiebel (Biological Sciences).

BioSci 342. Advanced Developmental Biology Cellular and molecular regulation of the morphogenetic processes that shape vertebrate tissues and organs. Emphasis on development of digestive, respiratory, hematopoietic, cardiovascular, urogenital, sensory and nervous systems. Where appropriate, correlation to invertebrate development and reference to evolutionary changes in organ structure and

function. SPRING [3] Appel (Biological Sciences), Bader (Medicine and Cell & Developmental Biology).

NEURO 376. Neurogenetics. This advanced course covers Mendelian genetics including relationships between mutational mechanisms and inheritance patterns. Topics highlighting genetics of neurological phenotypes will be discussed. Prerequisite: 345, 346, or consent of instructor. SPRING, SECOND MODULE. [2] Sutcliffe.

MIB 320. Graduate Seminar in Biological Sciences. May be taken for credit more than once. FALL, SPRING. [1]

MIB 390. Special Topics and Advanced Techniques in Biological Sciences. Specialized laboratory experiments, open to a limited number of properly qualified students. Admission to course, hours, and credit by arrangement. FALL, SPRING. [2–4] Graham and Staff.

BCHM 301. Molecular Structure and Function. This course considers the use of structural biological methods to answer important questions of function in systems involving two interacting species. Topical examples of protein-protein, protein-ligand, and protein-nucleic acid interactions are considered. Each example illustrates the use of multiple complementary approaches, which may include mutagenesis, kinetic, chemical, spectroscopic, and diffraction methods. SPRING. [3] Armstrong, Beth, Caprioli, Chazin, Guengerich, Marnett.

BCHM 302. Advanced Biochemistry, Cell Biology, and Genetics. Advanced concepts in genetics and cell biology will be reviewed using a combination of lectures based on textbooks and discussion sections based on manuscripts. Prerequisite: IGP core course or consent of instructor. FALL. [3] Carpenter, Hiebert, Cortez.

BCHM 305. Biochemical Basis of Human Disease. The molecular basis of diseases and basic biological processes will be discussed. Biological processes to be covered include cancer, neurobiology, apoptosis, tumor suppressors, oncogenes, cell cycle control, molecular toxicology, DNA damage, RNA processing, and metabolism as it relates to disease. Prerequisite: IGP core course or consent of instructor. SPRING. [3] Hiebert and Staff.

MP&B 325. Physical Measurements on Biological Systems. (Also listed as Physics 325 and Biomedical Engineering 325) A survey of the state of the art in quantitative physical measurement techniques applied to cellular or molecular physiology. Topics include the basis for generation, measurement, and control of the transmembrane potential; electrochemical instrumentation; optical spectroscopy and imaging; x-ray diffraction for determination of macromolecular structure; magnetic resonance spectroscopy and imaging. One lecture and one recitation. Prerequisite: modern physics course or consent of instructor. FALL, ODD NUMBERED YEARS. [3] Wikswo.

Tutorials in Human Genetics. The class meets once weekly. Graduate students critically evaluate research publications in areas of active research in the program (e.g., molecular basis of human disease, role of genetic variation on expression of human phenotypes, role of model organism in the dissection of disease processes FALL Mortlock, Summar, Canter

Tutorials in Statistical/Population Genetics. The class meets once weekly. Graduate students critically evaluate research publications in areas of genetic analyses (e.g., methods of linkage analyses, statistical tests for genetic association, genetic structure of human populations, patterns of linkage disequilibrium in the human genome) SPRING Haines, Li, Moore, Ritchie, Williams

Appendix II
Faculty Roster

Appendix III.
Sample Course Schedule

Year 1	**Total Credits**
Fall	
Bioregulation I (Biomed 300a) 6 credits Laboratory Rotations 2 credits	8
Spring	
Bioregulation II (Biomed 300b) 3 credits Fundementals of Genetic Analysis (MPB 385) 3 credits Laboratory Rotations - 2 credits	8
Year 2	
Fall	
Human Genetics I (MPB 340) 3 credits Tutorials in Human Genetics – 1 credit Introduction to Mathematical Statistics (Math 218) 3 credits Research - 5 credits	12
Spring	
Human Genetics II (3 credits) Tutorials in Statistical and Population Genetics II (1 credit) Evolutionary Genetics (Bio 246) 3 credits Research - 5 credits	12
Year 3	
Fall	
Found of Bioinformatics and Comp Biology (Bioinf 310) 3 credits Research 9 credits	12
Spring	
Research	12
Year 4	
Fall	
Research	8
Total Credits	**72**

Tentative Syllabus
Human Genetics II
Department Molecular Physiology and Biophysics
Instructors
J. Moore, J. Haines, C. Li, S. Williams, M. Ritchie

I. Structure of Genetic Variation in Human Populations
    A. Hardy Weinberg Law
    B. Role of Genetic Drift and Selection in the Genetic Structure of Human Populations
    C. Measures of population differentiation
    D. Meaning of heritability

II. Identifying Genes that Cause/Predispose to Disease
    A. Linkage analysis
        i. Resemblance between relatives and inbreeding effects
        ii. Two point LOD scores
            1. Effects of locus and Allelic heterogeneity
        iii. Multipoint LOD score
        iv. Non parametric linkage analysis
        v. Quantitative Trait Loci mapping
        vi. Family based association
            1. Transmission disequilibrium
            2. Sibship vs. multiplex analyses
    B. Association/ Case-Control Analysis
        i. The role of candidate genes in genetic analysis
        ii. Single locus genetic effects
        iii. Multilocus models of complex disease
        iv. Role of stratification and genomic controls
        v. Admixture mapping

III. Structure of the Genome
    A. The meaning of linkage disequilibrium
        i. Role of recombination
        ii. Role of selection
        iii. Role of finite populations
    B. Haplotypes and disease gene discovery

Tentative Syllabus
Genetics of Model Organisms
Instructors
M. Southard-Smith, D. Mortlock, L. Solnica-Krezel

I. Genetic analysis of yeast, *Saccharomyces cerevisiae*

A. Introduction to yeast a model genetic system
B. Genetic screens using yeast
C. Mutagenesis, complementation tests, segregation tests, allelism tests
D. Examples: cell type determination, mating type switching, and SWI mutants
E. Genetic analysis of asymmetric gene expression and cell lineage determination in yeast

II. Genetic analysis of the nematode *Caenorhabditis elegans*

A. Introduction to *C. elegans* and its use in the genetic analysis of development
B. Mutagenesis, simple mutant screens, mapping, complementation testing
C. Genetic analysis of early embryogenesis
D. Maternal effect mutations and screens
E. Genes required for the emergence of asymmetry
F. Determination of founder cell fate by localized gene products

III. Genetic analysis of *Drosophila melanogaster*

A. Introduction and history of *Drosophila* genetics
B. Phenotypic mutants and screens
C. Transgenic manipulation, transposons, RNA interference
D. Clonal analysis
E. Examples of key discoveries through fly genetics (e.g. HOX genes, signaling pathways)

IV. Genetic analysis of *Arabidopsis*

A. Introduction to plant genetics and *Arabidopsis* as a model system
B. Methods and screens using Arabidopsis
C. Examples: Flower developmental mutants, genes relevant to agricultural crops
D. Comparison of plant and animal genomes

V. Genetic analysis of the mouse, *Mus Domesticus*

A. Introduction to *Mus* and its use in the genetic analysis, terminology
B. Mouse genetics, inbred strains, congenic lines, genome sequence, and mutant alleles
C. Mapping simple Mendelian traits, mapping resources, crosses, and RI strains

D. Statistical analysis for mapping simple traits, software packages and approaches

E. Dissection of complex genetics traits: approaches, examples, and strategies

F. Statistical analysis for QTL/modifier mapping, software packages and approaches

G. Mutagenesis and mutant screening in mice

H. "Functional" genomics:

i. Transgene and targeted mutagenesis, and conditional "knockouts"

ii. Mouse genomics and comparative sequence analysis

VI. Genetics analysis of the zebrafish, *Danio rerio*

A. Introduction to zebrafish as a genetic model system; life cycle and embryology

B. Mutant screens, complementation tests, and TILLING

C. Organogenesis

D. Examples: genetic manipulation of zebrafish to dissect specific problems in development (e.g. neural patterning, convergent extension)

E. Evolution of vertebrate genomes: fish/mammal genome comparisons