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Sequencing the Genome of the Domestic Cat

Felis catus

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Introduction

Domestic cats and their wild relatives of the Family Felidae (37 species) have fascinated humankind for nearly a hundred centuries, appearing continually in archeological remains, art, and literature. Cat domestication, originally a defense against rodent infestation of a rapidly expanding agrarian society, led to the worship and deification of cats in Egyptian culture, vilification and subjugation by Christian superstition during the Dark Ages, followed by recent artificial selection of fancy breeds as house pets (18). Our personal adulation for cats and dogs has produced a veterinary medical surveillance unchallenged by any mammalian species except humans. The baseline of hereditary and infectious disease descriptions in cats offers a fertile platform for modeling homologous diseases in man. This bio-medical relevance combined with several biological advantages make a strong case for assessing the whole genome sequence (WGS) of this species.

In the following White Paper we propose the development of a 6X assembled whole genome sequence for the domestic cat, as is currently determined for mouse and rat, and has been nominated recently for chimpanzee, cattle and dog. The domestic cat has served as a powerful laboratory model for neuroscience, reproduction, comparative anatomy and development, monogenic plus complex hereditary human disease homologues, and for numerous fatal infectious disease agents related to human pathogens (86, 90). Nonetheless, advances in each of these areas has lingered behind rat and mouse during the genomics era, but would be surely invigorated by an imperative for assessing an unabridged genome sequence. The cat has played a leading role in the field of comparative genomics having already yielded moderately dense gene maps (1800 markers, 1.8cM average marker density), PAC, BAC, flow-sorted autosome and Y-chromosome libraries, and a bio-resource repository of nearly 10,000 tissue specimens including 300 established cell lines (10, 75, 76, 86, 87). The conservative retention of ancestral genome organization and syntenic parallels between the feline and human genomes (in contrast to markedly reshuffled genomes of mouse, rat, and dog) has placed the cat-human genomic similarities as baseline for discerning the whole genome organization of all placental mammals. (75, 87).

The case for a WGS of the feline genome is predicated on biomedical relevance and application to human health (including enzymatic, transplantation and gene therapy), on basic science potential in a number of biological disciplines, on the available genomic resources, and on the established informativeness of feline comparative biology. In Section I, we highlight examples and potential of feline models for hereditary and infectious disease, for comparative inference on human/mouse gene annotation, and for basic evolutionary perception. In Section II we address the strategic issues around sequencing the cat genome. These include the status of available feline genomic resources, the breadth of the research community, the experimental potential, rationales and empirical strategies for WGS, and other funding organizations that have pledged their support for aspects of the feline genome project. Finally, we include letters of endorsement from the feline and comparative genomics communities and from representatives of the public's enthusiastic support for this project.

I. BIOLOGICAL AND BIOMEDICAL RATIONALE FOR THE CAT WGS

A. The Cat and Infectious Diseases

Perhaps the strongest argument for a WGS of the cat is its potential for informing the interplay of host genes and infectious agents. Numerous feline viruses and other microbes have been described in detail leading to fruitful biomedical discoveries. When one considers that the implication of susceptibility-resistance genes in man is in its infancy (for viral diseases like AIDS and hepatitis), while infectious agents are considered to be one of the primary agents of mortality and natural selection (2, 46, 85), the development of a WGS for a species rich with natural history experimental opportunities like the domestic cat seems critical to reveal the details of host-pathogen interaction and adaptation.

Consider that feline leukemia virus, FeLV, originally discovered in 1964, led to the revelation of downstream promotional neoplastic transformation and the characterization of over one hundred genomic "oncogenes" which have informed our understanding of human cancers (47). Further, chronic FeLV carriers (5-30% of FeLV infections) succumb to various cancers and immunodeficiency mediated sequelae that are poorly understood from an immunogenetic perspective. A feline WGS would allow genomic identification of immunological, receptor, and host defenses against these chronic diseases.

Feline immunodeficiency virus (FIV) provides the single naturally occurring animal model for HIV-AIDS pathogenesis. (African monkeys endemic with SIV are resistant to disease, while native Asian macaques succumb)(98, 123). FIV is the genetic cousin to HIV; the cause of AIDS, a disease for which there is no vaccine and no curative therapy. The FIV model has been under utilized – largely due to lack of two things: precise immunological reagents and advanced high resolution genomic tools (123). Although more and more reagents have been developed, the pace of this development would be greatly accelerated by achieving a WGS of the cat.

There are three areas where the FIV model could be of immense help in our understanding of HIV-1 disease: 1) to determine why lentivirus (the HIV/FIV family) immunity is so weak compared to immunity to other types of retroviruses and other cell associated viruses, which is prerequisite for effective vaccines; 2) to resolve the pathogenic process for immunodeficiency disease, so that we will be better able to design adjunctive therapies for either retarding the collapse of immune system or actually reconstituting it once effective antiviral therapy has been applied; and 3) to help resolve the role of cellular genetic factors in collaborating or facilitating HIV/FIV mediated AIDS progression. Curiously, over twenty wild cat species (including lions, cheetahs, ocelots, pumas, leopards and others) are endemic with their own monophyletic strain of FIV (16, 23). Yet, in contrast to domestic cats, the circulating FIV strains do not appear to cause acute immunodeficiency in the wild cats, likely a consequence of host genomic adaptation toward genetic resistance to pathogenic FIV. Resolution of the acquired genetic resistance mechanisms would be greatly accelerated by a cat WGS, and would lead to new cellular avenues for development of HIV/FIV therapy.

There are a number of other feline infectious agents that have been intensely studied. A coronavirus, feline infectious peritonitis virus (FIPV), causes a fatal immune-mediated peritonitis in domestic cats and in the 1980s led to annihilation of several captive cheetah colonies as a consequence of historic genetic homogenization of their immune systems (89, 97). In the mid-1970s feline panleucopenia (distemper) virus cultivated in a cat vaccine factory abruptly jumped from cats to become a hyper-virulent strain in the world's dogs (93). That virus transfer fostered a global epidemic of neurological distemper disease that went on to kill millions of puppies before a canine vaccine was developed. In 1994, a virulent strain of canine distemper virus, a relative of human measles, emerged from a domestic dog reservoir to kill a third of the large lion population in Tanzania's Serengeti ecosystem (107). Add to the list verified cat-specific agents ranging from alpha herpesvirus, a relative of human herpes-simplex, toxoplasmosis, cryptococcus, plague, Q-fever, chlamydiosis

and rotavirus infections, ehrlichiosis, calicivirus infection, poxvirus infection, and mycobacteriosis (4). Cats are also highly resistant to anthrax, which has obvious implications. All of these infections, and more, could prove valuable to biomedical research, providing we have a better working knowledge of the innate and adaptive immune system of the cat. Such knowledge will be greatly facilitated by the cat WGS.

B. The Cat as a Model for Human Hereditary Disease Pathology, Diagnostics, and Therapy.

There are approximately 70 million cats in the United States and several times that number worldwide. Actually overpopulation of feral cats is considered a serious nuisance in many countries (5, 7, 12, 94). The reasons for the large population of cats include mankind's fascination and domestication of the species plus a relatively high fecundity, features that increase the cat's potential as a genomic model for medical and biological application. The world's veterinary schools produce thousands of practitioners each year, most of whom carefully document genetic and chronic diseases analogous or homologous to human maladies. The result is a comprehensive veterinary literature which has described some 258 feline genetic diseases (http://www.angis.org.au/ Databases/BIRX/omia/).

Fifty presently recognized breeds of cat descend from moderate degrees of inbreeding and artificial selection that has contributed to numerous hereditary pathologies. Reported disorders reflect spontaneous mutations that cause congenital abnormalities, inborn errors of metabolism, susceptibility to immune disorders and infectious disease, many bearing strong phenotypic and/or genotypic homology to human hereditary pathologies. Physiological study of these feline hereditary diseases provides a strong comparative medicine opportunity for prevention, diagnostic and treatment studies in a laboratory setting. Most physiological studies are not possible in children, while large numbers of affected cats allow extensive insights into pathogenic mechanisms and gene background influence, a key requirement for disease understanding and therapy evaluation.

Specific mutations have been characterized in ten feline genes that lead to genetic disease: GM1- and GM2-gangliosidosis, glycogen storage disease type IV, hyperlipoproteinemia alpha-mannosidosis, muccopolysaccharidosis-I, -VI, -VII, muscular dystrophy and Niemann-Pick disease (6, 11, 31, 39, 40, 43, 51, 71, 124, 131). As many disorders have been well characterized on a phenotypic or biochemical level, including several high frequency human diseases: spinal muscular atrophy (38), progressive retinal atrophy (77-79), hypertrophic cardiomyopathy (61), polycystic kidney disease (13), and mucolipidosis (14).

Debilitating neurological abnormalities caused by mutations in genes for lysosomal storage enzymes have numerous homologues in cats. The mucopolysaccharidoses types I, VI, and VII- and β-mannosidosis disorders in cats result from deficient activities of the enzymes alpha-L-iduronidase (IDUA), arylsulfatase B (ARSB), glucuronidase (GUSB) and β-mannosidase, respectively (28, 49, 50, 57, 81, 115). Enzyme deficiencies for these genes lead to analogous phenotypic abnormalities in human and cat, including mental retardation, growth abnormalities and shortened life span (28, 49, 50, 57, 81, 115). Effective therapies tested in cats have played important roles in evaluating correctional strategies for human health, including enzyme replacement, bone marrow transplantation and gene therapy (42, 48, 64, 112, 117, 126).

The cat MPSI model has provided an ideal system to study mechanisms of brain neurodegeneration and neural-directed strategies, especially given the large body of pre-existing literature on cat neurology (1, 22, 60, 127). Affected MPS VI cats (Maroteaux-Lamy disease) respond to allogenic bone marrow transplantation from normal cats (41). *In vitro* studies have demonstrated retroviral-mediated correction of MPS VI fibroblasts, chondrocytes and bone marrow cells in both humans and cat (36). In MPS VII cats, enzymatic activity has been restored in fibroblasts by retroviral gene transfer of rat beta-glucuronidase cDNA (40). As GUSB is an essential housekeeping enzyme, this feline model is important to examine exogenous genes and gene product delivery to

a variety of tissue types, and could prove especially valuable due to extensive research conducted on the anatomy and physiology of the cat central nervous and visual systems.

The feline α-mannosidase deficiency syndrome has served as a powerful model for bone marrow transplantation (BMT) of lysosomal storage diseases, showing appreciable restoration of α-mannosidase activity in brain tissue of affected Persian cats (48, 117). These results have provided direct evidence of the efficacy of BMT as corrective strategy for neuronal storage diseases of the CNS and the potential of using haematopoietic stem cells as corrective strategy for lysosomal storage disorders.

Cats with lysosomal neurodegenerative GM1 and GM2 gangliosidoses have been invaluable in characterizing the pathobiology, molecular biology and therapeutic strategies for these diseases. Whereas acid beta-galactosidase deficiency in GM1 has been corrected in human fibroblasts by retroviral mediated gene transfer (108) and limited success has been reported in felines reducing GM2 neuronal storage following feline bone marrow therapy (117), gene therapy of the CNS presents a challenging front as corrective retroviral constructs require mitotically dividing cells for integration and expression (24).

Lipoprotein lipase (LPL) is a crucial enzyme involved in the regulation of lipoprotein and lipid metabolism (17). LPL-deficient cats share a nearly identical phenotype to the human mutational deficiency involving severe pancreatitis, chylomicronenia, and failure to thrive (43). Of the numerous animal models for LPL deficiency examined including mouse, the cat most closely resembles the lipoprotein pattern and lipid transport system of humans (43). Liver directed adenovirus mediated gene therapy in LPL deficient cats has demonstrated the efficacy of this strategy to significantly improve lipoprotein metabolism and marks an important advance in the development of LPL directed gene therapy (64). Additionally this feline model offers great potential as an *in vivo* system to examine increased triglyceride levels associated with LPL deficiency on atherosclerosis (43).

Thus, cats have proved invaluable mode for three treatment regiments: 1) direct enzyme replacement which has been tested in MPS I (59) and VI (15, 20, 21, 29, 30) prior to the recent initiation of clinical trials in children, 2) bone marrow transplantation (MPS-VI, α-mannosidosis, GM1 gangliosidocis) (32, 42, 48, 117); and 3) gene therapy (MPS-VI, MPSVII, GM1 gangliosidocis (36, 40, 108, 129, 130, 132), and *in vivo* testing for lipoprotein lipase deficiency and MPS VI (53, 110). Since most feline genetic disease models were identified by a candidate gene approach, genome scans are presently underway for hereditary syndromes for which the candidate approach has failed: spinal muscular atrophy (Laboratory of Genomic Diversity, NCI), retinal atrophy (University of Missouri) and a host of hereditary anomalies for which veterinary pedigrees have been assembled. These genomic searches would benefit enormously from a whole genome sequence of the cat.

There are certain practical advantages to a domestic cat model as well. Cats breed well in a captive setting, and domestication dating back to 6-8000 years ago has produced nearly 50 recognized breeds which have experienced moderate levels of inbreeding and artificial selection across their recent ancestry (18, 37, 52). The breeds provide recent phylogenetic lineages that capture different combinations of coat color, coat length, patterning, appearance, and behavior traits suitable for genetic analysis. Modern breeds reflect different combinations at around twelve monogenic coat color trait loci, most with homologous counterparts in coat color genes of mouse and other domestic species (105). Gene homologues of pigmentation loci in other mammalian species have been implicated in anemia, sterility, neurological, and metabolic disorders (8, 9, 56). The history of modest inbreeding in cat breeds supplies important populations ideal for linkage disequilibrium mapping of complex quantitative characters as have also been recognized in dog breeds (92). A 6X WGS combined with existing cat pedigrees offer a rare opportunity to interpret a large body of hereditary trait inference.

C. The Cat as a Model for Human Reproduction

Detailed studies of reproductive physiology, endocrinology, and behavior of cats have been undertaken for over 25 years (120). Description of sperm capacitation, oocyte and embryo metabolism, oocyte harvest, and gamete interactions has led to applications in artificial insemination, in vitro fertilization, embryo maturation, and embryo transfer (3, 33, 34, 44, 54, 111). The cat has proved an extraordinary model for in vitro maturation (IVM) of oocytes, (45, 114). Human fertility clinics are turning to IVM to bypass or reduce invasive hormonal treatments required for aspirating mature oocytes (116, 118). These procedures have been extended to non-domestic Felidae species allowing successful assisted reproduction in cheetahs, tigers, lions, ocelots and several other wild cat species (54, 120). More recently, the fruits of decades of extensive empirical reproductive studies led to the birth of the first cloned domestic cat kitten via nuclear transfer (109). This landmark advance, based on accumulated cat reproduction research, nearly ensures the likelihood of stem cell gene-knockout and gene transfer technology for this species. These powerful methodologies are under development in several laboratories including those of present authors (Stephen J. O'Brien and David E. Wildt).

Particularly fascinating has been the high prevalence of teratospermia that occurs among male domestic cats and for entire species (cheetahs and clouded leopards) or subspecies (Asian lions and Florida Panthers) (101, 106, 120-122). Teratospermia, the production of high proportions of pleiomorphic (or malformed) spermatozoa, is a primary cause of infertility in humans (25, 128). The cat research has identified novel mechanisms associated with failed fertility (55, 100-103, 120) pointing to high priority areas of study and therapy for human counterparts. Finally, there are remarkable distinctions in reproductive-behavioral traits among each of the Felidae species highlighting the rapid co-evolution of genes that specify reproductive compatibility and isolation mechanisms among species.

D. Informing the Human Sequence: Gene Annotation and Comparative Genomics

An important argument for comparative genome sequence information is annotation of the human genome. Distant evolutionary comparisons of the human sequence with pufferfish, zebrafish and chicken will reveal highly conserved coding regions missed by gene annotation software, in addition to conserved non-coding regulatory regions. Representative mammalian WGS will be even more informative for detecting rapidly evolving non-coding regulatory regions invisible to more distant species alignments. Murid genomes (mouse and rat) clearly have significantly higher rates of nucleotide substitution than most other mammalian species (63, 72)**;** this factor alone will hamper the ability of the mouse and rat genomes to identify the majority of conserved regulatory elements in mammalian genomes. On the basis of nucleotide homology alone the cat is more similar to the majority of human homologues than either is to mouse or rat, owing to its overall slower than average nucleotide substitution rate. Therefore the cat WGS will provide an additional and potentially more powerful source for human, and mammalian-wide, gene and non-coding regulatory element annotation than either of the murid species.

The cat genome (along with dog and cow) represents a phylogenetic outgroup species to both human and mouse genomes, as documented by exhaustive independent mammalian phylogenetic analysis (66, 72, 73). The cat has evolved from the mammal superorder Laurasiatheria, one of four super-ordinal clades that predated the radiation of modern placental mammals (73, 84). The three mammalian species already scheduled for finished WGS, human, rat, and mouse, are all members of a single different clade, Euarchontoglires. Thus, the cat genome would represent a significant extension of the genomic diversity present among mammals. Considering preliminary human-mouse sequence comparisons, the rate of lineage specific gene-birth and gene-death might be rapid: on the order of one every 200,000 years in mammals (27). Thus, multiple whole genome

sequences from different mammalian orders provide the opportunity for discovering not only the minimal set of common mammalian genes, but also novel genes with unique functions specific to either lineage.

A provocative glimpse of multi-species genome sequence comparisons has been achieved with the recent full sequence comparison of the major histocompatibility complex (MHC) class II sequence of human *HLA*, mouse *H-2*, and domestic cat *FLA* (133). The human *HLA* region consists of 224 genes of which 128 are expressed while 96 are pseudogenes. Nearly half of the *HLA* genes play a role in immune defenses and about 50% of the HLA sequences consist of repetitive elements (LINES, SINES, LTRs and STRs). Sequence alignment of human, mouse and cat MHC class II region homologues revealed several fascinating evolutionary features including 50% differences in MHC segment size (mouse – 500kbp, cat – 750kbp, human – 1000kbp), pseudogene accumulation (humans have 27, cats 7, and mice 5 pseudogenes) gene loss (cats lose *DP* and *DQ*), gene gain (7 DR genes in cats) and repeat disposition (133). The extinction of *DP* and *DQ* gene function in the cat is a likely explanation for the rather inefficient humoral response to embryonic antigens in pregnant females (99) or to graft rejection in domestic cats (125). The prospect of a cat WGS would allow similar full genome analysis of the complete human, mouse, rat and other genomes for both the non-coding and coding comparisons unavailable using EST based genomic approaches.

The cat possesses distinct advantages from a comparative genomics perspective. The feline genome, composed of 19 chromosome pairs, is extensively conserved in gene order/content (conserved synteny based on comparative mapping and ZOO-FISH) among other Felidae species, among other carnivore species, and indeed across many placental mammals (70, 80, 83, 87, 104, 119). Ordered RH gene map comparisons reveal that the extent of chromosome segment conservation between the cat and human genomes is among the highest observed between mammalian orders (87) (76, 104, 119). For example, the feline genome assembly is 2-3 times less rearranged relative to the human genome than are the genomes of murid rodent species (mouse and rats) (76, 87). In mammals, there seems to have been an extremely slow or default rate of chromosome translocation exchange as seen between cats and humans, but punctuated occasionally by rare lineage specific global chromosome reshufflings as found in gibbons, bears, dogs, and murid rodents. The remarkable co-linear parallel of the cat and human genomes provides an opportunity to inspect rather long stretches of conserved synteny between the two species, as well as the patterns and details of global genome reorganizations that are apparent in lineages of the WGS candidates such as the dog, rat, and mouse.

E. The Cat as a Model of Comparative Anatomy and Physiology

The cat has served the scientific community as a powerful animal model of classical research in anatomy, physiology, and neurology. A vast literature detailing intricate aspects of the feline central nervous and visual systems, anatomy and physiology provide a powerful comparative database to humans (1, 22, 60, 67, 95, 127). In the field of vision research detailed knowledge has been gained through elaborate investigations including physiological and morphological aspects of the cat retina, and the cat is a preferred model for opthamological research, based on eyes that approximate the size of humans, and tolerance for intra-ocular surgery (as opposed to the dog) (78). In spite of the extensive physiological, morphological and neurological research advances, these studies await genetic integration, a proposed consequence of the WGS assembly of the cat.

F. Why WGS for cat in the wake of dog and cow?

In September 2002 the dog and cow were added to the list of high priority species for whole genome sequencing by NHGRI. We applaud this decision and support the initiatives, while recognizing that the question arises – why develop a cat WGS in the same context? Many of the same advantages of the dog are shared with

the cat: lots of animals, human affinity, extensive medical surveillance, high public enthusiasm, breeds as partial inbred strains, well developed linkage and physical gene maps, representative of distinct super-ordinal clade, several hundred described genetic diseases homologous to human disorders (437 for dog, 261 for cat), and proven opportunities for gene therapy development. Nonetheless, as for the arguments to support an additional murid rodent (e.g., rat) or an additional fruit fly (e.g. *Drosophila pseudoobscura*), both the differences between cat and dog plus their similarities lend support to the case for a cat WGS. Specific strengths for the cat model consideration follow:

1. The infectious disease background, literature, and research on cats are extensive including successful vaccines for distemper, FeLV, and promising FIV vaccines.
2. Of the 258 naturally occurring human hereditary models, nearly one-third do not exist in mouse or dog.
3. Reproductive baseline research in cats is more advanced than dogs, which translates to the promise of cloning, embryonic stem cells, germline transgenesis, gene therapy and gene knockout technologies.
4. The feline genome organization, like humans, is primitive, reflecting ancestral gene order association; mouse, rat, and dog descend from global genome reorganization. Feline genome organization is also much more conserved relative to human than the moderately reshuffled cattle genome (75,76).
5. The 37 species of Felidae, less than 12 million years old, have a vast network of behavior-ecological surveillance which can be assessed from a genomic perspective with assembly of a cat WGS. Genomic resources (map, PCR primers, STR loci) transfer readily among Felidae species for an expanding evolutionary perspective.
6. Bioresources for domestic cat and other Felidae species are extensive. The NIH-NCI Laboratory of Genomic Diversity repository (available to the public domain) lists 31,327 Felidae tissue specimens including 2,564 viable cell lines, of which 346 are from the domestic cat.

Cats, dogs and cattle each have enormous biological, biomedical and basic science potential and their nomination by NHGRI as high priority would assure their expansive development in many arenas of biomedical and biological inquiry.

II. STRATEGIC ISSUES: CURRENT RESEARCH IN FELINE MODELS

A. Size and Current Funding Status of Feline Genomics

The research efforts ongoing in feline models are considerable. The CRISP database of US Federal grants utilizing cats number 467, compared to 248 for chicken, 244 for cow, and 592 for dogs. A search of PubMed for papers using cats yielded 115,658 hits while ‘cat and genetics’ produced 11,654 citations. Ongoing support for feline genomics has been achieved from the Cat Fanciers’ Association, The Winn Feline Foundation, Morris Animal Foundation, Nestle-Purina and several conservation and pet agencies. We anticipate continuing support and enhanced enthusiasm with the nomination of domestic cat for whole genome sequencing. A recent conference in May 2002 entitled “Recent Advances in Feline and Canine Genomics” in St. Louis, MO brought together over one hundred cat and dog researchers to discuss the latest advances in this rapidly advancing area. The list of papers presented at this symposium is presented in the Appendix of this White Paper.

B. Status of Feline Genomic Resources. Progress in Assembling the Feline Gene Map

The domestic cat carries 18 autosomal pairs, X and Y chromosomes, in a genome containing around 3 x 10^9 nucleotides, comparable to the human genome. First and second generation linkage and radiation hybrid physical maps have been developed (68, 69, 76, 113) to produce a feline genetic map integrating 1) comparative anchor – Type I coding genes for alignment with human and mouse genomes, 2.) Type II microsatellite loci placed on average 5 cM apart and 3.) selected genes with important phenotypes (68, 69, 76). The genomic resources assembled by the feline genomic community are listed in Table 1 and discussed below.

Table 1. Developed Feline Genome Project Resources (May 2002)

	Resource	Citation
I.	Somatic cell hybrid panel, and framework physical map	(82, 88)
II.	Interspecies backcross (ISB) genetic linkage map	(69)
III.	Nestle-Purina intraspecies reference pedigree	(35)
IV.	5000-rad radiation hybrid panel and map, 1.8cM density, 1881 loci	(74, 76)
V.	Arrayed BAC and PAC libraries	(10, 133)
VI.	Domestic cat Y-chromosome cosmid library	Unpublished
VII.	Flow sorted feline chromosome libraries: comparative chromosome paint map	(90, 104, 119)
VIII.	Tissue/cell line DNA repository of 31,327 exotic and domestic feline specimens	(58, 96)
IX.	Domestic cat breed forensic database 40 breeds, 11 multiplexed, optimized STRs, 1 Y chromosome STS	(19)
X	Complete sequence	
	a. mtDNA genome	(62, 65, 91, 133)
	b. MHC-FLA	
	c. FIV	

1. Radiation Hybrid Map. The current feline 5000 rad RH map contains 784 Type I coding gene markers (density = 4.3 cM/Type I marker) and 1086 Type II microsatellite markers (density = 3.5 cM/marker). The current integrated RH-linkage map contains a total of 1881 markers with an average interval of 1.8 cM. The integrated gene map provides a powerful tool for both tracking cat phenotypes and comparing the processes that mould genome organizations that determined the evolution of mammals (75, 87, 90).

2. Linkage Map. An interspecies backcross pedigree (ISB) between the domestic cat and Asian leopard cat (*Prionailurus bengalensis*) was constructed to maximize the chance of obtaining genetic variants between Type I loci, as was demonstrated in building the mouse gene map (26, 68, 69). To date, 248 microsatellites and 81 Type I markers are mapped on the linkage map. The sex-averaged length of the feline genome was estimated from the ISB at 3,300 cM, with an average density of 8 cM (69). An intra-specific pedigree, developed in collaboration with Nestlé-Purina utilizes 256 cats with 483 meiosis. A total of 705 microsatellite loci are currently being mapped on this pedigree, which will provide an average density of one marker per 4.7 cM.

3. Genomic libraries. Three large insert libraries have been constructed for the domestic cat. **1)** A 2X genome equivalent PAC library was constructed from a normal male domestic cat, composed of 91,900 P1 clones with an average insert size of 80 kb (10). **2)** An improved BAC library was constructed, consisting of 234,349 BACs with an average insert size of 137 kb and 10.6 fold redundancy, derived from a male domestic cat (10). These resources have been applied successfully to a number of projects, including creation of 3 Mb BAC/PAC contig of the entire feline MHC and complete sequencing of class II and class I regions, and isolation of clones for genomic regions surrounding the *PKD*1and *PKD*2, *ASIP* and *MC1R* loci (35, 133). **3)** A domestic cat Y chromosome cosmid library has been constructed, with 4.3X coverage and arrayed in 3648 clones. Current efforts are towards developing a contig map of the euchromatic portion of the Y chromosome in collaboration with the NCI-Frederick Molecular Technology Laboratory.

C. The Cat's Role in Therapy for Genetic Disease (see also Section I-A)

The development of therapeutic strategies for genetic diseases, and enzyme deficiency disorders in particular, requires testing in animals. Cats have several advantages for this purpose: a) the background genetic heterogeneity between relative non-inbred cats is similar to the genetic diversity of affected human populations, b) selective breeding produces adequate numbers of affected individuals homozygous for the mutant allele as well as normal siblings for matched treatment and control groups, c) relatively large numbers of affected animals can be produced, allowing individual variability to be documented, against which changes during therapy can be evaluated, d) cats are long-lived (>5 years) and are large enough to allow magnetic resonance imaging and repeated sampling, f) cats require individual clinical care similar to human patients, g) having models with multisystem pathology, including CNS disease, allows evaluation of therapy on a variety of tissues and organs.

D. Sequencing Strategy

The feline genome has a haploid content approximately equivalent to the human 3 x 10^9 bp of DNA distributed over 18 autosomes plus the X and Y sex chromosomes. The Whitehead Center for Genome Research has expressed a strong interest in supporting the sequencing of the feline genome. The proposal outlined by the Whitehead Institute will involve a whole genome shotgun sequencing (WGS) approach designed to yield a long-range, high-quality assembly covering >95% of the cat genome. The approach for the feline genome will be analogous to that employed for the mouse genome, which resulted in an assembly consisting of 89 ultracontigs placed on the 20 mouse chromosomes and covering ~96% of the genome. Similarly, for cat we propose collecting a total of 40 million paired-end reads generated from different vectors and insert sizes (2, 4, 6 & 10kb plasmid libraries, 40kb fosmid library, and 200 kb BAC library). The use of different library sizes should hopefully minimize cloning bias and to allow a hierarchical linking approach in the assembly process. Genomic libraries will be created by random shear, with the possible exception of the BAC library. In the latter case two libraries will be generated using different enzymes. Paired-end sequencing will be undertaken followed by whole genome assembly using the ARACHNE software, in addition to other existing WGS assembly programs. Using the described breakdown of insert sizes would result in an approximate 6-fold sequence coverage (Phred-20) and a 50-fold physical coverage of the cat genome allowing for a sequencing pass rate of approximately 80%. This procedure should result in an assembly with >95% coverage of the genome, with long-range continuity achieved by linkage and orientation of the WGS supercontigs to existing feline genetic and radiation hybrid maps.

E. A Moderate Resolution SNP Map Resource

The wave of new high throughput genotyping technologies under development for human genetics assures that single nucleotide polymorphic (SNP) mapping and population assessment will be powerful genetic currency for developed model species. To anticipate their many applications and to complement the genome sequence, including coding genes, repeats and STRs, we propose to generate a moderate coverage SNP map resource of the cat by sequencing six distinct breeds: American Shorthair, Norwegian Forest Cat, Oriental Shorthair, Manx, Japanese Bobtail, and Scottish Fold. The six breeds have been selected for maximum heterozygosity based on STR assessment (available for 25 breeds in a related forensic based assessment (see Appendix 3)). Specifically, we propose generating 100,000 reads from each breed, resulting in approximately 25,000 novel SNPs for each breed given an average SNP rate of 1/1,000 bp and that approximately 50% of reads can be placed uniquely in the genome. This methodology has proven successfully for defining SNPs in three inbred mouse strains and we expect it to work well for the cat. The SNP screen would generate approximately 250,000 SNPs with an average spacing of ~10 kb across the genome.

F. Decision Making Process to Select Breed/Animal to Sequence

Of the approximate 50 cat breeds, most are moderately inbred based upon genome heterozygosity estimates of 52-81% estimated recently for 22 microsatellite loci (see Appendix 3). As an approach to diminishing variation, a member of an Abyssinian pedigree inbred for 15 generations, with fewer than ten founders (77) will be selected as a sequencing subject.

CONCLUSIONS

The feline genome project, now entering its third decade and armed with a broad array of advanced genomic resources, has positioned the domestic cat and its charismatic wild relatives to make substantive contributions to a number of biomedical and basic biological disciplines. Over 258 hereditary pathologies have been reported in the domestic cat largely due to intensive medical surveillance of cats by the veterinary profession (84, 86). These feline models have been important in elucidating molecular pathogenesis and are playing a critical role in evaluating and optimizing therapeutic strategies prior to clinical trials in humans. With continued development of a 6X WGS, characterization of many hereditary pathologies in the domestic cat could be anticipated in the future. The feline model shows continued promise for resolution, diagnostics, vaccine development and treatment of human infectious disease. The identification of FIV in domestic cats offers a viable model for HIV pathogenesis as it provides the only known naturally occurring model for human AIDS. As the Human Genomic Sequencing Consortium winds down with the drafts of the human, mouse and rat genomes, other species are lining up to reap the benefits of WGS comparisons (84). We believe the discussions laid forth here present a compelling case for the domestic cat as one of the next mammalian species for whole genome sequencing.

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Sequencing the Genome of the Domestic Cat

Appendices:

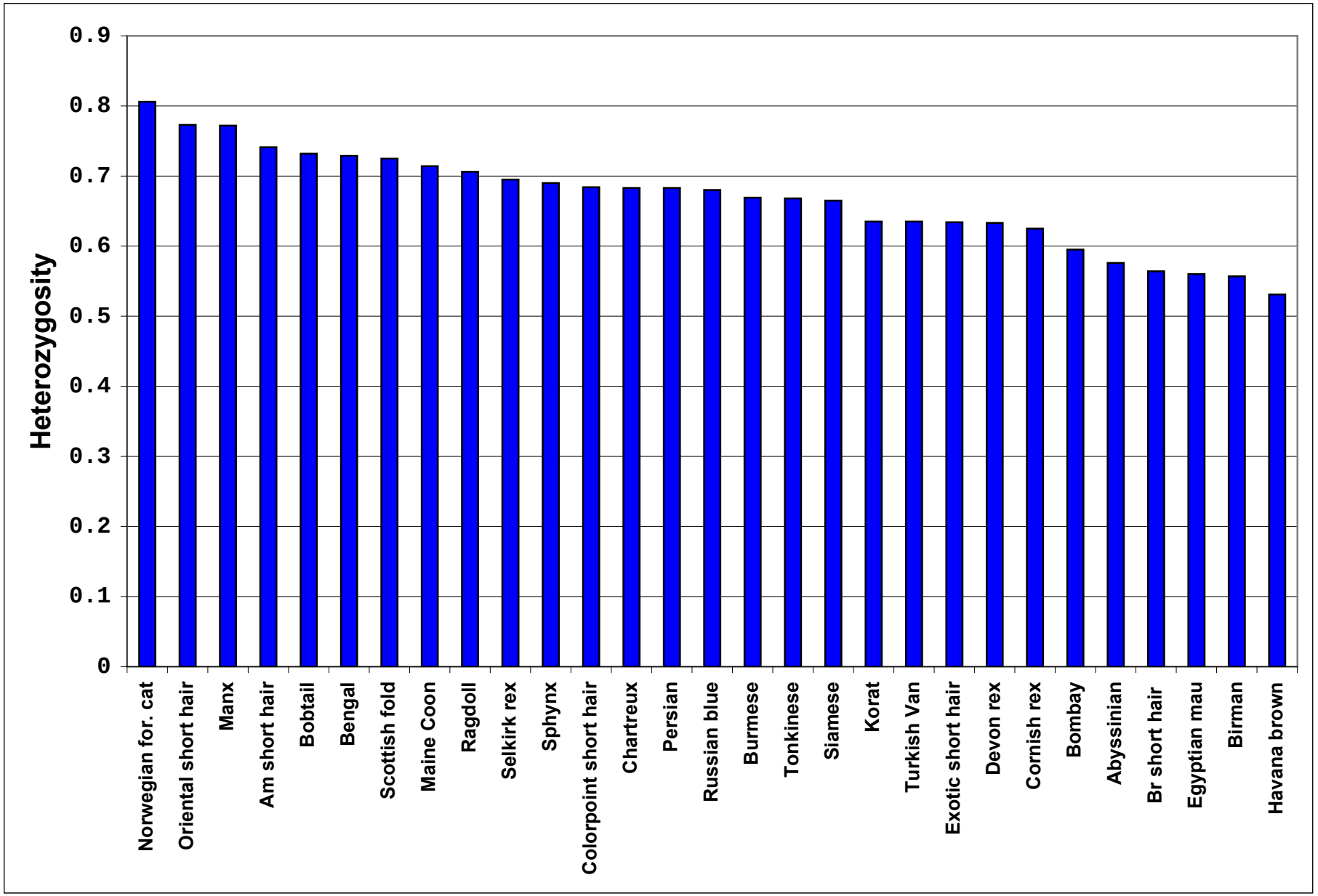
Appendix I Table of Cat Breed STR Heterozygosities

Appendix II Agenda Advances in Canine and Feline Genomics
St. Louis, MO
May 16-19, 2002

Appendix III The Feline and Comparative Genomics Community
Letters of Support

1. Donald F. Patterson
2. Michael B. Gorin
3. Henry J. Baker
4. John C. Fyfe
5. Stephen P. DiBartola
6. C.A. Buffington
7. Lawrence E. Mathes
8. Kristina Narfstrom
9 Mark Westhusin
10. Hajime Tsujimoto
11. Frank Nicholas
12. William G. Nash
13. Malcolm A. Ferguson-Smith
    Fengtang Yang
14. Hilary Helmrich
15. Thomas H. Dent
16. Roger Wyse
17. Neal G. Copeland
18. Elaine Ostrander
19. James E. Womack
20. Jeffrey Rogers
21. Mary Anna Thrall

Average Locus Heterozygosity in 29 Cat Breeds for 22 STR Loci



ADVANCES IN CANINE AND FELINE GENOMICS

Comparative Genome Anatomy and Genetic Disease

May 16-19, 2002
Millennium Hotel
St, Louis, MO

Thursday May 16, 2002

5:00pm – 8:00pm **Opening Reception/Registration**

Friday May 17, 2002

7:30am-8:30am **Registration/Breakfast**

8:30am Welcome – Stephen O'Brien
National Cancer Institute at Frederick, MD

8:45am Nestlé Purina Welcome - Steve Hannah
Nestlé Purina PetCare Company

8:55am **Keynote Speaker:**
An Overview of Comparative Genomics from the Corral Fence
James Womack
Texas A&M University

Session 1: Genomic Maps and Markers in Cats and Dogs
Moderator: Stephen O'Brien

Morning Session

9:40am High Resolution RH Mapping of the Dog Genome and its Application to the Positional Cloning of Cancer Genes
Elaine Ostrander
Fred Hutchinson Cancer Research Center

10:00am Cat Genomics Overview and the Status of the Genetic Linkage Map in the Domestic Cat
Marilyn Menotti-Raymond
National Cancer Institute at Frederick, MD

10:20am Comparison of the Efficiency of the Multimap and TSP/CONCORDE programs in the Construction of an RH map of the Canine Genome
Francis Galibert
Centre National de la Recherche Scientifique

10:40am **Break**

11:10 A second generation radiation hybrid map of the feline genome
William Murphy
National Cancer Institute at Frederick, MD

11:30 The Frequency and Usefulness of Single Nucleotide Polymorphisms (SNPs) in the Dog Genome
Patrick Venta
Michigan State University

12:00pm **Lunch**

ADVANCES IN CANINE AND FELINE GENOMICS

Comparative Genome Anatomy and Genetic Disease

May 16-19, 2002
Millennium Hotel
St, Louis, MO

Friday May 17, 2002

Session 2: Large Scale Genomic Analysis
Moderator: William Murphy

1:00pm — Large Scale Sequencing of Feline Major Histocompatibility Complex
Naoya Yuhki
National Cancer Institute at Frederick, MD

1:20pm — Canine MHC
John L. Wagner
Thomas Johnson University

1:40pm — Sequencing and Analysis of Canine ESTs
Richard McCombie

Session 3: Animal Models of Hereditary Disease
Moderator: Don Patterson

Afternoon Session

2:00pm — Overview of Genetic Disease Testing
Urs Giger
University of Pennsylvania

2:20pm — The Dog as a Model for Identifying the Gene Defects Underlying Diseases That Are Genetically Complex: Lesion-Specific Genetic Defects in Cardiovascular Development
Don Patterson
University of Pennsylvania

2:40pm — Whole Genome Linkage Studies of Conotruncal Defects in the CTD Line of Keeshond Dogs
Petra Werner
University of Pennsylvania

3:00pm — **Break**

3:30pm — Retinal Disease in Cats: An Update on the Abyssinian Mutant
Kristina Narfström
University of Missouri-Columbia

3:50 — Inherited Motor Neuron Disease in Domestic Cats Similar to Spinal Muscular Atrophy Type III
John C. Fyfe
Michigan State University

ADVANCES IN CANINE AND FELINE GENOMICS

Comparative Genome Anatomy and Genetic Disease

May 16-19, 2002
Millennium Hotel
St, Louis, MO

Afternoon Session - Continued

Friday May 17, 2002

Session 3: Continued

4:10pm	Genetics of Cancer in Dogs ***Elaine Ostrander*** Fred Hutchinson Cancer Research Center
4:30pm	Familial Canine Dilated Cardiomyopathy ***Kathyrn Meurs*** Ohio State University
4:50pm	Heterogeneity in Cystinuria ***Paula Henthorn*** University of Pennsylvania
6:30pm – 9:00pm	**Welcome Reception – Nestlé Purina PetCare Company**

ADVANCES IN CANINE AND FELINE GENOMICS

Comparative Genome Anatomy and Genetic Disease

May 16-19, 2002
Millennium Hotel
St, Louis, MO

Morning Session

Saturday May 18, 2002

7:30am-8:30am **Breakfast**

Morning Session:

Moderator: Urs Giger

8:30am AKC/CHF Welcome
Erika Werne
American Kennel Club Canine Health Foundation

8:40am Winn Feline Foundation Welcome
Janet Wolf
Winn Feline Foundation

8:55am **Keynote Speaker:**
Promise of Comparative Genomics in Mammals
Stephen O'Brien
National Cancer Institute at Frederick, MD

Session 4: Evolutionary History of Cats and Dogs I
Moderator: Marilyn Raymond

9:40am Genetic Diversity of Domestic Cat Breeds
Leslie Lyons
University of California at Davis

10:00am History of the Development of Purebred Dog Breeds
Debra Lynch
American Kennel Club

10:20am **Break**

10:50am Felidae Evolution
Warren Johnson
National Cancer Institute at Frederick, MD

11:10am Coat Color Genetics in the Felidae
Eduardo Eizirik
National Cancer Institute at Frederick, MD

Session 5: Comparative Carnivore Genomics Moderator: Steve Hannah

11:30am Carnivore Chromosome Painting
Bill Nash
H&W Cytogenetic Services

11:50am A Genome-Scale Comparative Chromosome Map Between Domestic Cat and Dog Based on Reciprocal Chromosome Painting
Fengtang Yang

ADVANCES IN CANINE AND FELINE GENOMICS

Comparative Genome Anatomy and Genetic Disease

May 16-19, 2002
Millennium Hotel
St, Louis, MO

University of Cambridge

Saturday, May 18, 2002

12:10 Canine Cytogenetics – Application to Genome Mapping and Cancer
Matthew Breen
Fred Hutchinson Cancer Research Center

12:30pm **Lunch**

Session 6: Genetic Mapping and Molecular Characterization
Moderator: Urs Giger

Afternoon Session

2:00pm Inheritance of Epilepsy in Dogs
Anita Oberbauer
University of California at Davis

2:20pm Identification of a New Copper Metabolism Gene by Positional Cloning in a Purebred Dog Population
Bart van de Sluis
University Medical Center Utrecht

2:40pm Inherited Retinal Diseases in Dogs
Gus Aguirre
Cornell University

3:00pm Progress in QTL Mapping of Canine Hip Dysplasia
Rory Todhunter
Cornell University

3:20pm Statistical Analyses on Addison's Disease
Thomas Famula
University of California at Davis

3:40pm Compulsive Tail Chasing in Bull Terriers
Alice Moon-Fanelli
Tufts University

4:00pm **Poster Viewing Session**

6:30pm – 11:00pm **Riverboat Cruise and Dinner**

UNIVERSITY of PENNSYLVANIA

The School of Veterinary Medicine
Center for Comparative Medical Genetics
3900 Delancey Street
Philadelphia, PA 19104-6010

Donald F. Patterson, DVM, DSc
Phone: (215) 898-8894
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Stephen J. O'Brien, CSO
Laboratory of Genomic Diversity
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, Maryland 21702-1201

October 8, 2002

Dear Steve:

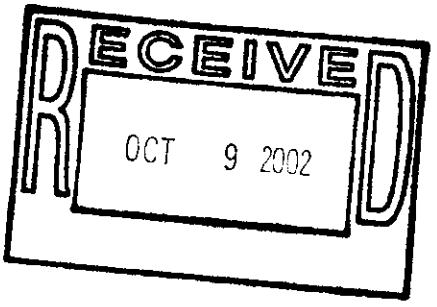
I am writing to tell you how delighted I am to hear of the initiative to propose a full genome sequence project for the cat!

I am very aware of the importance of this initiative in adding to knowledge in general biology and evolution and believe this is reason enough to put the cat in a priority position for whole genome sequencing. However, because of my own long-term interest in the field of comparative medical genetics, I need to say that, through the medium of modern veterinary medicine and its many clinical specialties, the cat, along with the dog, is the most medically scrutinized of mammals other than man. Having a whole genome sequence of the cat will add immensely to its already well-recognized value as a model for human genetic diseases. As you know, the breeding of purebred cats creates a series of partially inbred genetic isolates (breeds), each with its own group of simple recessive and genetically complex diseases. A large number are already known, including congenital heart defects, musculo-skeletal disorders, retinal degenerations, inherited metabolic diseases such as the mucopolysaccharidoses, porphyrias and hemolytic anemias due to inborn errors of erythrocyte metabolism. Many genetic disorders in the cat, such as congenital heart defects, hold the promise of revealing the genes that underlie now poorly understood birth defects with complex inheritance in humans.

The cat genome sequencing project will have many payoffs for the medical, behavioral and evolutionary sciences as well as for the health of companion cats. I look forward to them.

Sincerely,

Donald F. Patterson, DVM, DSc
Professor Emeritus of Medical Genetics, Veterinary School
Professor Emeritus of Human Genetics, School of Medicine



University of Pittsburgh

School of Medicine
Department of Ophthalmology

The Eye & Ear Institute
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Pittsburgh, Pennsylvania 15213
412-647-2205
Fax: 412-647-5119
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Michael B. Gorin, M.D., Ph.D.
Associate Professor and
Interim Chairman

September 11, 2002

Stephen J. O'Brien, Ph.D.
Chief, Laboratory of Genomic Diversity
National Cancer Institute
Frederick, Maryland 21702-1201

Dear Dr. O'Brien

I wish to express my enthusiastic support for the effort to undertake the genomic sequencing of the cat. The cat has been one of the premier models for the study of vision development and ocular disease. Though not as heavily used for genetic diseases as mice, the cat offers unique opportunities to study hereditary ocular disorders and provide a suitable animal model for therapeutic trials. The feline eye, being larger than that of rodents and rabbits, is much more amenable to the surgical interventions that are typically used for human treatments. As laboratory animals, cats are far less costly and easier to work with than dogs, pigs and primates. Unlike the dog, the cat eye better tolerates intraocular surgery with less inflammatory response and excellent long term results.

For years I have collaborated with investigators to study the molecular genetics of a recessive retinal degeneration in Abyssinian cats. While the identification of the gene has been elusive, much of the difficulty has been the lack of comparable genomic information that we have for the mouse and human. Despite these limitations, the effort has continued and this particular cat model is already being heavily used for gene therapy studies. The identification of the causative gene for this animal would be enormously helpful in identifying the comparable human gene. Without such animal studies, the human gene may well be unidentifiable directly because of the genetic heterogeneity of recessive retinitis pigmentosa. An added benefit of sequencing the cat genome would be its value in the study of genetic evolution and the identification of conserved regions that would aid in the identification of biologically relevant gene variants that may be implicated in common and complex genetic disorders. Investigators are increasingly using cross species conservation as an argument for biologically relevant variations.

I wish you the very best in convincing the NIH of the importance of this undertaking. As one who confronts the effects of genetic disorders on the eye sight of my patients on a daily basis, I have a real appreciation for the potential benefits that would come from this particular effort.

Sincerely yours,

Michael B. Gorin, M.D. Ph.D.
Interim Chairman – Department of Ophthalmology
Founding Director – Center for Human Genetics and Integrative Biology
University of Pittsburgh
Associate Professor – Departments of Ophthalmology and Human Genetics

Auburn University

Auburn University, Alabama 36849-5525

Scott-Ritchey Research Center
College of Veterinary Medicine

Telephone: (334) 844-5951
FAX: 844-5850

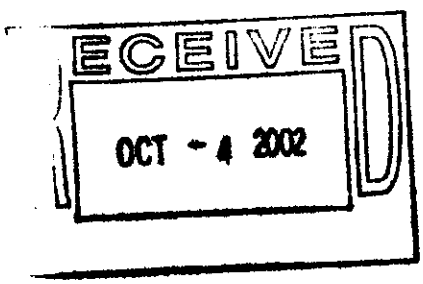
October 2. 2002

Dr. Stephen J. O'Brien
Laboratory of Genomic Diversity
National Cancer Institute
Fredrick Cancer Research and Development Center
Frederick, MD 21702-1201

Dear Steve:

It is a pleasure to support your proposal to sequence the domestic cat genome. For 30 years, I have studied naturally occurring cat models of human inherited diseases with special emphasis on degenerative nervous system diseases typical of the gangliosidoses and other lysosomal diseases. My laboratory has identified four distinct ganglioside storage diseases in domestic cats, sequenced the genes for the pivotal enzymes and identified mutations responsible for these diseases. I am currently the principal investigator of two NIH funded projects studying mesenchymal stem cell transplantation therapy and viral vectored gene therapy of the gangliosidoses using these feline models.

No one underestimates the enormous value of transgenic and knockout mouse models. But in years past, the enthusiasm for this technology suppressed interest and support for naturally occurring models of inherited diseases in non-inbred rodent "large animal" models of human diseases. It is now abundantly clear that the promise that transgenic mouse models would solve all animal model needs was unrealistic. In my area of research, knockout mouse models do not resemble the human counterparts and are not useful for research on the gangliosidoses. Fortunately, more and more scientists recognize the limitations of mouse models for some research and the urgent need to catch up on development of authentic inherited disease models in cats, dogs and other non-rodent species. As you are well aware, the lack of much information about the cat genome has been a substantial hindrance to progress of our research. If you multiply our limitations by the hundreds of feline models which are available for biomedical research, the gravity of the problem becomes substantial. Although we were able to overcome some limitations through substantial individual effort, the availability of reagents and basic information about the cat genome remains a significant limitation. Therefore, a national investment in sequencing the cat genome would open many doors for investigators who are already working on cat models and in fact, will encourage involvement of new investigators in this exciting area. For these reasons and all of the compelling arguments made in our position paper, I strongly encourage investment in sequencing the cat genome.



Cordially,

Dr. Henry J. Baker, Professor and Director

MICHIGAN STATE UNIVERSITY COLLEGE OF VETERINARY MEDICINE

John C. Fyfe, D.V.M., Ph.D.
Laboratory of Comparative Medical Genetics
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TEL: (517) 355-6463, ext 1559

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and Small Animal Clinical Sciences

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October 2, 2002

Stephen J. O'Brien, CSO
Laboratory of Genomic Diversity
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, Maryland 21702-1201

Dear ~~Dr. O'~~Brien, Steve

My colleagues at MSU and I enthusiastically support your efforts to get NHGRI support for producing a 6X assembled whole genome sequence of the domestic cat. In addition to my personal affinity for cats and my desire, as a veterinarian, to have all possible resources to enhance the quality of life of cats, the source of my enthusiasm for this project is the large degree to which the utility of feline models of human genetic disease will be enhanced. There are some 150 feline disorders that are phenotypically homologous to human genetic diseases, but we know the underlying gene defect of only about a dozen. As you know, my laboratory has determined the molecular bases of feline mucopolysaccharidosis VII and type IV glycogen storage disease, but both of those disorders were enzymopathies, and detailed investigation of each of them strongly suggested candidate genes based on functional data. We do not have such luxury for most feline disorders, including the spinal muscular atrophy (SMA) currently under investigation here with NIH grant support (HD39888).

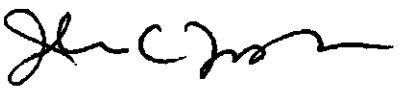
Feline SMA is a degenerative disorder of spinal motor neurons that is phenotypically very similar to type III SMA of humans caused by mutations of the survival of motor neuron gene (SMN). Human SMA is the most common inherited disorder lethal to infants. For this reason, we considered the feline SMN gene as a comparative functional candidate gene for the disorder, but it was excluded because an SMN marker segregated independently of the disease in a linkage analysis. Similarly, we excluded the IGHMBP2 gene, a gene involved in other forms of human SMA. We were greatly aided in these efforts by the feline genome map resources developed in the Laboratory of Genomic Diversity. Thus, we are presently conducting a genome scan for linkage of the disorder to markers of the integrated genome map developed there.

Our concurrent experience in the investigation of a dog disorder homologous to Imerslund-Gräsbeck syndrome, for which we have close linkage (4.6 cM) to a CFA 8 marker, indicates that when we find a marker linked to feline SMA, feline genome sequence will be invaluable. In what we characterize as a comparative positional-candidate gene approach to disease gene discovery, we will be developing new markers for genes in the linked region and looking to the sequenced human, (dog?), and mouse genomes for analysis of genes in the minimal region of linkage. A fully sequenced cat genome will make this effort and others like it far more efficient than we are currently experiencing in our dog work.

Of course, our dog work will be greatly enhanced by the sequenced dog genome which appears to be just beyond the horizon. We are getting a taste of it from the 1X dog sequence we access through a collaborative agreement with The Institute for Genome Research, but that taste just makes it more obvious how valuable the fully sequenced genome will be. Marker development in sequenced regions obviates the need to guess at PCR primer sequences or to clone and sequence target regions. A cat genome sequence, but not the forthcoming dog sequence, will similarly boost efforts to uncover the molecular basis of feline models of human genetic disease such as our SMA model. I particularly look forward to such genome sequence data being available in freely accessible databases rather than in proprietary forms.

Obviously a cat genome sequence will have great value in many areas of genetic investigation outside my own. I think you have hit all the important points in your white paper proposal and have made a good case for funding of this project. Best of luck to us all.

Sincerely,



John C. Fyfe

Department of Veterinary
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Veterinary Hospital
601 Vernon L. Tharp Street
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Small Animal Clinic 614-292-3551
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October 3, 2002

Stephen J. O'Brien, CSO
Laboratory of Genomic Diversity
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, Maryland 21702-1201

Dear Dr. O'Brien,

With this letter I would like to express my wholehearted support of your project to sequence the feline genome. My training is primarily as an academic clinician, and in 25 years I have stumbled across 2 genetic diseases of cats: familial amyloidosis in Abyssinian cats and polycystic kidney disease in Persian cats. I have tried my best to obtain extramural research support to study the genetic basis of these diseases as animal models for familial Mediterranean fever and autosomal dominant polycystic kidney disease in humans, but have largely been unsuccessful. I believe that with access to more information about feline genetics I would have been more successful in my efforts. I believe that spontaneous animal models of human disease remain an important avenue of basic research. Not all aspects of a naturally-occurring genetic disease can be satisfactorily studied using knock-out mouse models. Consequently, I am in strong support of your work to advance knowledge about the feline genome. I've attached a list of publications about the two diseases mentioned in this letter.

Sincerely,

Stephen P. DiBartola, DVM
Professor

Biller, D. S., D. J. Chew, et al. (1990). "Polycystic kidney disease in a family of Persian cats." Journal of the American Veterinary Medical Association 196(8): 1288-1290.

Biller, D. S., S. P. DiBartola, et al. (1996). "Inheritance of polycystic kidney disease in Persian cats." Journal of Heredity 87(1-5).

Boyce, J. T., S. P. DiBartola, et al. (1984). "Familial renal amyloidosis in Abyssinian cats." Veterinary Pathology 21: 33-38.

Chew, D. J., S. P. DiBartola, et al. (1982). "Renal amyloidosis in related Abyssinian cats." Journal of the American Veterinary Medical Association 181(2): 139-142.

DiBartola, S. P., M. D. Benson, et al. (1985). "Isolation and characterization of amyloid protein AA in the Abyssinian cat." Laboratory Investigation 52(5): 485-489.

DiBartola, S. P., R. L. Hill, et al. (1985). "Pedigree analysis of Abyssinian cats with familial amyloidosis." American Journal of Veterinary Research 47(12): 2666-2668.

DiBartola, S. P., M. J. Tarr, et al. (1986). "Tissue distribution of amyloid deposits in Abyssinian cats with familial amyloidosis." Journal of Comparative Pathology 96: 387-398.

Eaton, K. A., D. S. Biller, et al. (1997). "Autosomal dominant polycystic kidney disease in Persian and Persian-cross cats." Veterinary Pathology 34: 117-126.

OHIO STATE UNIVERSITY
HEALTH SCIENCES CENTER

Department of Veterinary Clinical Sciences

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3 October 2002

Stephen J. O'Brien, CSO
Laboratory of Genomic Diversity
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, Maryland 21702-1201

Dear Dr. O'Brien,

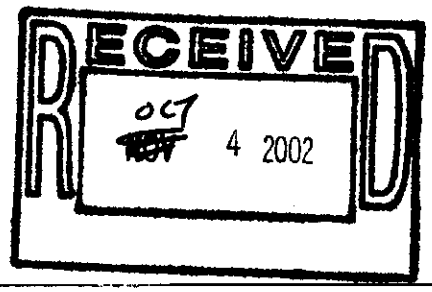
I am *profoundly* enthusiastic about your efforts to sequence the cat genome. My research focuses on the neuroendocrinology of a chronic visceral pain syndrome in humans, interstitial cystitis. For the past 10 years, I have studied a naturally occurring model of this common a chronic condition that occurs in domestic cats. I have been assisted in my efforts through collaborations with scientists from NIH to UCLA and many points in between, and with NIH support for myself and many of my colleagues. Most recently, this model became part of a newly funded Specialized Center of Research to explore the role of sex and gender factors in women's increased risk to develop a wide range of visceral disorders.

One persistent limitation to this model is the availability of cat-specific molecular probes for many of the molecules of interest to us. This added level of complexity has delayed some avenues of investigation, and complicated others. There also has been the recent, exciting finding of a new genetic syndrome involving panic disorder and interstitial cystitis. Since the neuroendocrine abnormalities we find in the cats mirror that found in some panic disorder patients, this model may provide an opportunity to identify some of the common features of "psycho" and "somatic" disorders. Theses studies are urgently needed, and the value of having a genome map of the cat for such investigations is clear.

Cats provided information that resulted in some of the major scientific breakthroughs of the 20th century; knowledge of their genome will help ensure that they continue to teach us about ourselves.

Sincerely,

C. A. Tony Buffington, DVM, PhD, DACVN
Professor of Veterinary Clinical Sciences



College of Veterinary Medicine
Department of Veterinary Biosciences

1925 Coffey Road
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FAX: (614) 292-6473

October 4, 2002

Dr. Stephen J. O'Brien, CSO
Laboratory of Genomic Diversity
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, Maryland 21702-1201

Dear Dr. O'Brien,

It is with great enthusiasm that I write this letter of support for your proposal to develop a whole genome sequence of the domestic cat. Your laboratory has lead the field in feline genetics and is arguably the most capable to organize the feline genomic project. Your white paper has presented a strong case for this effort in the area of animal models for genetic and infectious diseases. I would add the important contribution that a complete genomic map of the cat could make to cancer biology and therapy in animals and man. For example mammary carcinoma, one of the leading causes of death in cats, has a close histological resemblance human breast cancer. Histological similarities between cat and man also are found for head and neck cancers such as oral squamous carcinoma and ultra violet light-associated dermal squamous cell carcinomas. As you know, the value of defining the genetic relatedness of animal cancers to that of man is the potential use of the animal models to explore mechanisms of disease and evaluate the feasibility of novel treatment regimens such as gene therapy and drug intervention. My own studies on the immune response of cats to FIV infection as a model for AIDS will gain from applying genomic array screening to experimental and clinical samples.

Please keep me informed as the cat genome project progresses and allow me to assist you in any way that I can.

Best wishes

Lawrence E. Mathes, Ph.D.
Professor
Director, Center for Retrovirus Research
Director, RNA Oncogenic Virus Program
OSU Comprehensive Cancer Center

College of Veterinary Medicine
University of Missouri-Columbia

Veterinary Medical Teaching Hospital
Clydesdale Hall
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FAX (573) 884-5444

October 5, 2002

Dr. Stephen J. O'Brien, Chief
Laboratory of Genomic Diversity
National Cancer Institute
Building 560, room 21-105
Frederick, MD 21702-1201

Dear Stephen O'Brien,

I am writing to express my sincere support of the Laboratory of Genomic Diversity, National Cancer Institute, for a publicly supported sequencing of the cat genome. Such genomic sequencing will permit the active community of research scientists who use the cat as an animal model to greatly accelerate the pace of their research. The information gathered will be of great importance for both comparative genomics and the biomedical sciences.

Being a representative for the active researchers in the field of comparative hereditary retinal degenerative diseases and its treatment I can certainly endorse the importance of mapping the cat genome. I have been involved in research concerning the hereditary rod cone degenerative disease in the Abyssinian cat model, a recessively inherited disease that is similar to human Retinitis Pigmentosa (RP). I found this disease in cats and have been investigating it since more than 20 years. Many important basic science studies have been performed in the cat, especially in the field of visual anatomy and physiology. I use this vast scientific knowledge on a regular basis in my research. The last 10 years I have been involved in various collaborative projects, and one of the most important projects that we are currently working with together with Steve O'Brien's lab, is aimed at finding the genetic defect in the Abyssinian cat mutant. This project would be greatly enhanced and speeded up if the cat genome was sequenced.

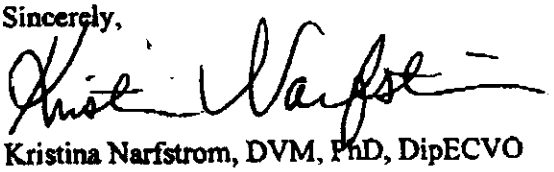
As soon as the genetic defect has been elucidated in the cat, I wish to continue with research regarding treatment modalities. I was also the person responsible for finding the Briard dog model in Sweden, some 14 years ago. This defect was found to be a RPE65 null mutation, and an excellent model for human Leber's congenital amaurosis. Gene

transfer treatment in my lab has been shown by electrophysiologic and morphologic studies (reported at the dog and cat molecular meeting at St.Louis and at ARVO 2002) to be extremely effective in this severe canine retinal dystrophy. Day light and some dim light functional vision is partially restored, which gives hope for treatment of the human counterpart. My wish is to continue with similar research using the Abyssinian cat with the hope of, in the future, elucidate ways of restoring vision in humans affected by diseases similar to the Abyssinian hereditary photoreceptor disorder, namely RP. The example, using RPE65 null mutation dogs and alleviating a defect of the retinal pigment epithelium, brings hope to the vast community of RP patients awaiting treatment.

Thus, increased knowledge of the cat genome, and subsequent gene mutation identification in cat models of human disease, can be expected to give similarly good results. I hope that the importance of this project will be recognized so that the cat genome can be sequenced for the sake of comparative genomics and for the importance in development of treatment and cures not only for blinding diseases but also for other debilitating diseases both affecting cat and human.

Thank you for the opportunity to enthusiastically endorse sequencing of the feline genome!

Sincerely,



Kristina Narfstrom, DVM, PhD, DipECVO
The Ruth M. Kraeuchi Missouri Endowed Professor of Veterinary Ophthalmology

TEXAS A&M UNIVERSITY
College of Veterinary Medicine
Department of Veterinary Physiology & Pharmacology

October 8, 2002

Dr. Stephen J. O'Brien, Chief
Laboratory of Genomic Diversity
National Cancer Institute
Building 560, Room 21-105
Frederick, MD 21702-1201

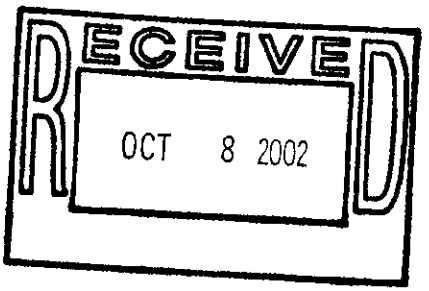
Dear Dr. O'Brien,

The purpose of this letter is to provide my enthusiastic support for your proposal to complete a full genome sequence in the cat. As you know cats represent an important animal model for biomedical research. In our laboratory we have utilized cats for studies involving reproductive physiology and developmental biology. In addition we have invested considerable time into developing technology for producing genetically identical cats by embryo splitting and somatic cell cloning. As cats acquire FIV, which has similarities to HIV, It is our hope to someday use these animals for developing new treatments/vaccines for the treatment of AIDS. Complete sequence information would no doubt be extremely helpful for some of the studies we have in mind for the future.

Please do not hesitate to contact me should you require additional information regarding my support for this important work. Good luck with your proposal.

Sincerely yours,

Mark Westhusin
Associate Professor
College of Veterinary Medicine
Texas A&M University,
College Station, Texas 77843-4466



THE UNIVERSITY OF TOKYO

Department of Veterinary Internal Medicine
Graduate School of Agricultural and Life Sciences
The University of Tokyo
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October 7, 2002

Dr. Stephen J. O'Brien
Laboratory of Genomic Diversity
National Cancer Institute, Frederick Cancer Research and Development Center
Frederick, Maryland 21702-1201, U.S.A.
FAX: 301-846-1296

Dear Steve,

I have heard that you are planning a full genome sequence project for the genome of domestic cat. From my standpoint as a researcher on the molecular pathogenesis of various diseases in animals, I believe that the full genome sequencing project for the genome of domestic cat is worth doing.

The population of domestic cats is more than 10 % of the population of humans in many countries. Their health conditions are closely observed by humans who are taking care of them. Life span of domestic cats is generally 10 to 15 years, shorter than one fifth of the life span of humans. From these reasons, many people believe that cat is a very good animal model for health problems.

The full genome sequencing project for the genome of domestic cat will provide a useful information for keeping a good health in humans as well as in domestic cats.

Sincerely,

Hajime Tsujimoto, DVM & PhD, Professor

The University of Sydney

Reprogen
Faculty of Veterinary Science

NSW 2006 AUSTRALIA

Frank Nicholas
Professor of Animal Genetics

Gunn Building B19
Telephone +61 2 9351 2184
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email frankn@vetsci.usyd.edu.au

Stephen J. O'Brien, CSO
Laboratory of Genomic Diversity
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, Maryland 21702-1201

7 October 2002

Whole Genome Sequence for the Domestic Cat

Dear Steve,

I write in very strong support of the proposal to sequence the domestic cat.

As you know, for the last 25 years I have been compiling *Mendelian Inheritance in Animals*, the domestic-animal equivalent of Victor McKusick's *Mendelian Inheritance in Man*. And since 1995, this resource has been available on the Internet as Online Mendelian Inheritance in Animals (OMIA) (http://www.angis.org.au/omia/), hyperlinked in both directions to Online Mendelian Inheritance in Man (OMIM). The cat is one of the major species in OMIA, and details on each of the disorders listed in your white paper can be found there, as can direct links to the relevant sections of OMIM, for any feline disorder that is a model for a human disorder.

The above paragraph establishes my long-standing activity in comparative genomics. It also highlights that just as OMIM is proving to be an invaluable tool in deciphering the human genome (specifically by providing information on phenotypes that can be related to particular sequences), **the homologous phenotypic tool (i.e. OMIA) already exists for the proposed sequencing of the domestic cat.**

I fully agree with, and strongly support, all the arguments raised in the white paper. In particular I highlight the important point about the far greater similarity between the human and feline genomes than between human and rodent genomes.

I applaud the efforts of you and your colleagues in preparing this proposal. It has my full and unequivocal support

Yours sincerely

Frank Nicholas

H&W Cytogenetic Services, Inc.
12148 ENFIELD LANE LOVETTSVILLE, VA 20180 (540) 822-4067

October 6, 2002

Dr. Stephen J. O'Brien, CSO
Laboratory of Genomic Diversity
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, Maryland 21702-1201

Dear Dr. O'Brien:

I recently read your review article entitled "The Feline Genome Project" and strongly concur with your evaluation of the biomedical relevance and basic science potential of a whole genome sequence of the domestic cat. My own research over the last decade has focused on the process of chromosome evolution in Carnivores using standard and molecular cytogenetic techniques. As a result of these efforts and others I think it is fair to say that chromosome evolution in Carnivores is better understood than in any other mammalian group.

The karyotypes of the felids and canids encompass the full range of chromosome changes seen over evolutionary time in this order. The karyotypes of all 37 species of the *Felidae* are highly conserved relative to one another and the ancestral carnivore karyotype. Canid karyotypes on the other hand have undergone a series of extensive and now, well defined chromosomal rearrangements. Felids and canids appear to have had fairly similar evolutionary histories, so why then do their chromosomes behave so differently and what are the biological implications underlying these differences?

A whole genome sequence of the cat and dog would be an enormously powerful resource for answering these kinds of questions. This comparative approach is certain to reveal important insights regarding the interdependence of chromosome function and chromosome structure. For example, currently the functional relevance of the non-coding DNA, which makes up to 90% of the mammalian genome is still largely a black box. It is becoming increasingly clear, however that this DNA has important epigenetic consequences in terms of chromatin modification and remodeling in the orchestration of gene activities during development. A comparative study of how this part of the genome changes over evolutionary time relative to chromosome structure and gene function is essential.

For these and many other reasons I think the whole genome sequence of the domestic cat would be invaluable.

Sincerely yours,

William G Nash

William G. Nash, Ph.D.
President and Director
H & W Cytogenetic Services, Inc.

UNIVERSITY OF CAMBRIDGE

Professor M. A. Ferguson-Smith, FRS
Tel: +44 1223 766496
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Email: maf12@mole.bio.cam.ac.uk

Centre for Veterinary Science
Department of Clinical Veterinary Medicine
Madingley Road, Cambridge
CB3 OES, UK

Stephen J. O'Brien, CSO
Laboratory of Genomic Diversity
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, Maryland 21702-1201
USA

7th Oct. 2002

Dear Dr. O'Brien

We are delighted to hear about your proposal to sequence the genome of the domestic cat.

As first proposed by you and colleagues about two decades ago and later confirmed by comparative gene mapping and chromosome painting, the cat genome is highly conserved and closely resembles the ancestral karyotype of eutherian mammals. Its highly conserved genome makes the cat an important species for comparative genomics and evolutionary studies. Although comparative chromosome painting and gene mapping are highly informative in revealing the conservation of gene synteny and linkage, genome-wide comparative sequencing holds the key to elucidate the full history of genome evolution and underlying molecular mechanisms that have driven genome evolution. With the near completion of human and mouse genome sequencing projects, the genomes of rat, cattle and dog have been put onto the priority list. But it is worth mentioning that the genomes of the mouse, rat and dog, and to a lesser extent cattle, are highly rearranged and represent "atypical" genomes in mammals. The availability of the whole genome sequence of the cat will help to elucidate the evolutionary history of the human genome and to aid the ongoing human genome annotation efforts. The cat is also one of the most common companion animals and much could be learned about feline genetic disorders and genetic susceptibility were its DNA sequence known.

Our group, in collaboration with colleagues in Russia and China, has recently undertaken a project to map the chromosomal rearrangements which occurred during carnivore species radiation by cross-species chromosome painting. A series

of comparative chromosome maps have been established with the cat genome as the reference. Our project will benefit greatly from your endeavor in sequencing the cat genome.

As one of world's leading centre for feline genetics and comparative genomics, your laboratory is best placed for such a project. We strongly support this venture and wish you every success in securing the necessary funding.

Yours sincerely,

Malcolm A. Ferguson-Smith

Fengtang Yang

THE WINN FELINE FOUNDATION

For the Health and Well-Being of Cats.

Janet C. Wolf, Secretary • 293 Landing Road, Newport, NJ 08345 • 609-447-4068

October 5, 2002

Stephen J. O'Brien, CSO
Laboratory of Genomic Diversity
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, MD 21702-1201

Dear Steve:

The Winn Feline Foundation enthusiastically supports the effort of the Laboratory on Genomic Diversity and its colleagues in their effort to obtain funds for the sequencing of the genome of the domestic cat.

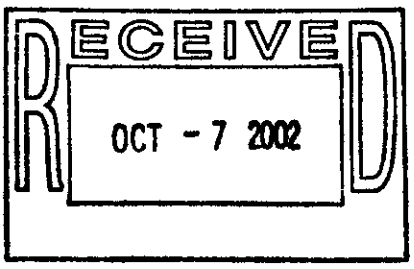
The Winn Foundation is a not for profit [501(c)(3)] organization that funds programs exclusively dedicated to the health of cats. We are limited to grants of $15,000 per year and have funded proposals to research specific genetic disorders of the cat including cleft palate, familial amyloidosis, hypertrophic cardiomyopathy, polycystic kidney disease, Burmese cranio-facial defect as well as genetic diversity research in a variety of pedigreed cats. We have funded studies in FeLV and FIV (including the original pilot program at the University of California at Davis) that have particular relevance to felines of all varieties as well as humans.

The Foundation and its donors will work with and continue to contribute samples needed for this important project.

We wish you every success in this endeavor and we are available to help in any way.

Very truly yours,

Hilary Helmrich
President



THE CAT FANCIERS' ASSOCIATION, INC.

World's Largest Registry of Pedigreed Cats
1805 Atlantic Avenue
PO Box 1005
Manasquan, NJ 08736-0805
732-528-9797 Phone • 732-528-7391 Fax
Web Address: http://www.cfainc.org

October 3, 2002

Fax: 301-846-1686 Rejax 10-8-02

Stephen J. O'Brien, CSO
Laboratory of Genomic Diversity
National Cancer Institute
Federick Cancer Research & Development Ctr
Frederick MD 21702-1201

Dear Dr. O'Brien:

I am pleased that we have this opportunity to write in support of the funding of the project to determine the full genome sequencing of the domestic cat. For over 15 years, the domestic cat has been America's most popular pet with estimates ranging from 65 to 70 million pet cats in America. The Cat Fanciers' Association, the world's largest registry of pedigreed cats, has supported research benefiting the health of cats through its affiliate The Winn Feline Foundation Foundation. Our funded projects most often benefit all domestic cats both pedigreed or not.

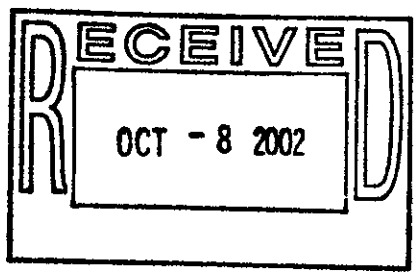
Over 30 million American households find the companionship of cats to be a rewarding experience. The mapping of the feline genome and the inherent positive effect for both human and feline medicine will only enhance the experience to the benefit of both species.

The Cat Fanciers' Association is fully committed to the welfare of all cats. The results and the benefits of the feline genome mapping project will be leveraged by the publication of news of this important project by CFA and The Winn Feline Foundation and through the funding of new health studies by those millions of Americans who value these wonderful little creatures for the companionship and joy they bring to our lives.

Sincerely,

Thomas H. Dent
Executive Director

THD/dlv



Alliance for Animal Genome Research

One Embarcadero Center, Suite 2700
San Francisco, CA 94104
EIN: 94-3390928

7 October 2002

Stephen J. O'Brien, CSO
Laboratory of Genomic Diversity
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, MD 21702-1201

Dear Dr. O'Brien:

On behalf of the Alliance for Animal Genome Research, I am writing to express the strong support of the Alliance for the "White Paper" that will be submitted to the National Human Genome Research Institute proposing to sequence the domestic cat genome, *Felis catus*. As you know, the Alliance, a nonprofit organization, represents the companion animal, livestock, and poultry scientific and industry communities.

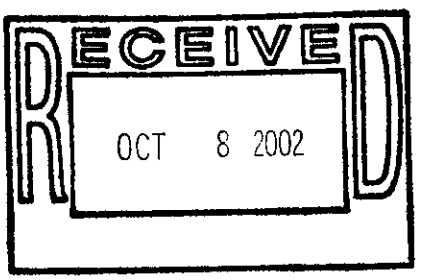
The Alliance believes that the sequence of the feline genome will provide the scientific community with critical, unique knowledge that will have a significant impact on both human and animal health. The domestic cat is a valuable veterinary model for several hundred human hereditary and infectious diseases. Many of the human genetic diseases that are found in the domestic cat are not found in rodent strains and having the genome sequence of the domestic cat will yield critical knowledge about human genetic diseases.

We, strongly, support the sequencing of the feline genome. If there is any way the Alliance can be of assistance in this important effort, please do not hesitate to contact me, or Kellye Eversole, the executive director of the Alliance.

Sincerely

Roger Wyse

Roger Wyse
Chairman
Alliance for Animal Genome Research



Phone: 415 591 5416 Fax: 415 591 5401

DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
Frederick Cancer Research
and Development Center
Email: copeland@ncifcrf.gov

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Phone : (301) 846-1266
FAX : (301) 846- 6666

October 9, 2002

Dr. Stephen J. O'Brien
Laboratory of Genomic Diversity
National Cancer Institute-Frederick
Frederick, Maryland 21702-1201

Dear Steve,

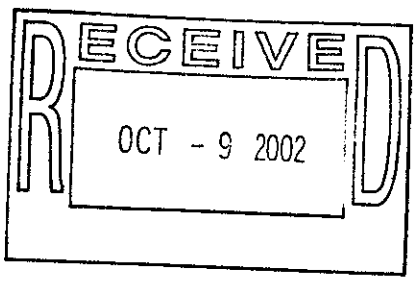
It is a special pleasure to write a letter expressing my strong support of your quest to have the cat considered as high priority for a full genome sequence. It is very clear form the parallel and overlapping aspects of our careers that comparative genomics is a powerful approach to understanding and applying the lessons of genome organization to health, medicine and basic science. The mouse genome sequence has expanded considerably the insight of rodent models and I am certain the veterinary cat model will also enjoy a strong renaissance by the acquisition of a whole genome sequence,.

The mouse and rodent genetics community may also benefit by the continued increase in mammal species representation particularly in annotation of conundrums developed by two-dimensional mouse-human alignments. Of course the medical, infectious disease and neurological opportunities will also be immensely improved.

After mouse I can think of no better candidate for comparative genomics and wish you the greatest success in your application.

Yours sincerely,

Neal G. Copeland, Ph.D.
Director, Mouse Cancer Genetics
Program
National Cancer Institute-Frederick



FRED HUTCHINSON CANCER RESEARCH CENTER

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Human Biology Division &
Clinical Research Division
1100 Fairview Ave. N., D4-100
Seattle, WA 98109-1024
Tel: 206-667-6979
Fax: 206-667-6396
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October 3, 2002

Stephen J. O'Brien, Ph.D.
Laboratory of Genomic Diversity
National Cancer Institute
Frederick, Maryland 21702-1201
Telephone: 301-846-1296

Dear Steve:

I'm writing to express my heartfelt enthusiasm for your white paper that proposes sequencing of the cat genome. As you know I've recently led an effort to generate a similar paper for the dog genome, and it seems to me that our dog work is nicely complemented in many ways by the cat work that has been the focus of your laboratory for so many years.

It is important to state up front that sequencing of both the dog and cat genomes are important, and that detailed sequence analysis of both organisms stands to make a profound contribution to our understanding of the genetics of mammalian disease. The cat, in particular, is a terrific resource for tackling the genetics of neuromuscular and metabolic diseases. I'm most impressed, however, by the utility of the cat for the study of viral and other types of infectious disease. This is not an area where the dog stands to make a major contribution, and it is a place where new genetic systems are needed. Your work on feline retroviruses has been important in this regard and I sincerely hope the review committee has a chance to examine your seminal findings to date.

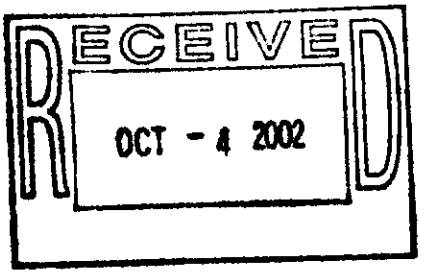
After reading your white paper I was pleased to note that you have all the resources in place to readily exploit the cat sequence as it is generated. High quality meiotic linkage and RH maps are assembled. In addition, you have good quality BAC and PAC libraries. Your studies on synteny between the cat and human genomes are fairly far along, and it seems that as such you will be able to rapidly take studies from the realm of "linked marker" to "positional cloning" in short order.

I was delighted also to note that Eric Lander is enthusiastic about sequencing the cat genome. It would be ideal if we stay well coordinated as the sequencing efforts commence. I'm sure that significant cost savings can be achieved for informatics, data base development, and sequence analysis if we do so. I note that you are also interested in developing a SNP resource for the cat, and propose, as we did, to do 100,000 reads each in 10 distinct breeds. Any resources developed for analysis of the dog SNP data will almost certainly work equally well for cat---and vice versa. Assuming your white paper is met with high enthusiasm, I look forward to our collaboration and constant communication as we proceed along these avenues.

In summary, if there is anything at all I can do to be of help to you at this early stage please do not hesitate to contact me. The availability of high quality sequence from both key domestic species is exciting, and is sure to facilitate our understanding of human biology and disease in many ways. Please keep me posted.

Warmest regards,

Elaine Ostrander, Ph.D.
Member, Divisions of Clinical Research and Human Biology
Fred Hutchinson Cancer Research Center



TEXAS A&M UNIVERSITY
College of Veterinary Medicine
Department of Pathobiology

October 7, 2002

Dr. Stephen J. O'Brien, CSO
Laboratory of Genome Diversity
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, MD 21702-1201

Dear Dr. O'Brien:

I fully support your proposal to the NIH for sequencing the genome of the domestic cat. Because of its importance as a companion animal, the domestic cat has a rich history in veterinary medicine and consequently a rich database of inherited diseases and predisposition to complex diseases. Thanks largely to your laboratory and your network of collaborators, the status of feline genomics is equal to or greater than that of most other domestic animals. There is little doubt that the NIH will gain a great return on its investment in a complete sequence of this important animal genome. As an animal genome scientist and also as current president of the International Society for Animal Genetics, I endorse your proposal with great enthusiasm.

Sincerely,

James E. Womack, Ph.D.
Distinguished Professor

JEW:mlj

Southwest Regional Primate Research Center

Jeffrey A. Rogers, Ph.D.
Leader, Genetics Group

October 3, 2002

Dr. Stephen J. O'Brien
National Cancer Institute
Building 560
NCI-Frederick
Frederick, MD 21702

Dear Steve,

I am writing to express my enthusiastic support for a national effort to generate whole genome DNA sequence information for the domestic cat (*Felis catus*). This sequencing effort is clearly justified, based on the importance of cats as animal models for human health and disease. As the National Human Genome Research Institute evaluates various species as candidates for whole genome sequencing, I hope that they will consider the diverse research applications that use cats as model organisms. As you and your colleagues have clearly shown, domestic cats can be used effectively in studies related to infectious disease and pathogenesis, as well as hematology and cardiovascular disorders. This species is also valuable in studies of the central nervous system, cancer and other aspects of physiology and metabolism that are directly relevant to human diseases.

In addition to the value of genomic data in studies of specific diseases, information on the cat genome will be important in efforts to understand the evolution of the human genome. There will be elements within the mammalian genome that evolve at different rates and undergo different types of molecular change. Having the cat genome sequence to compare to human, mouse, rat and other mammals, including other nonhuman primates, will provide new insights into the early differentiation of the mammalian genome, and place the human genome into its proper scientific context.

I strongly support your effort to see the cat designated as a High Priority species for genome sequencing, and I urge the NHGRI to recognize the tremendous value this work would have for a wide range of biomedical research programs

.

With best wishes,

Jeffrey Rogers

Jeffrey Rogers, Ph.D.

Mailing Address: P.O. Box 760549, San Antonio, Texas 78245-0549 ■ Shipping Address: 7620 NW Loop 410, San Antonio, Texas 78227-5301
Telephone: (210) 258-9532 ■ FAX: (210) 670-3316 ■ E-Mail: jrogers@darwin.sfbr.org ■ www.srprc.org

Colorado State University

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http://www.cvmbs.colostate.edu/mip/

Stephen J. O'Brien, Chief
Laboratory of Genomic Diversity
National Cancer Institute
Building 560, Room 21-105
Frederick, MD 21702-1201

Dear Steve,

I am writing to offer my unequivocal and enthusiastic support for your efforts to have the domestic cat nominated as a high priority for full genome sequencing by NHGRI this year. The cat has enormous potential for bio-medical application as well as for veterinary advances that inform basic biology. The animal is abundant, modestly expensive and highly studied for hereditary and infectious diseases. In addition the advances in reproduction technology nearly assure that the cat will soon enjoy stem cell technology, cloning and transgenesis and knock out genomic technology. For all these reasons I strongly endorse the approval of your proposal the achieve a full genome sequence as soon as possible.

Sincerely,

Mary Anna Thrall, DVM, MS. Diplomate, ACVP
Professor, Department of Microbiology, Immunology, and Pathology