

GRANT PROPOSAL WRITING: A CASE STUDY OF AN INTERNATIONAL
POSTDOCTORAL RESEARCHER

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Chapter One: Introduction

Grant writing has been studied by numerous investigators; however, after an exhaustive review of the literature, there yet remains a need for published studies examining the systematic process of writing a grant from the initial rough draft and following through the steps leading to the finished proposal within the community of international postdocs who work in medical research laboratories. In the current case study, the objective was to study an international postdoc's process of copies that included retention of his/her original texts leading up to the final proposal. After finding a successful candidate who was willing to volunteer her proposal for examination, the data were collected and subjected to rigorous evaluation. Since the literature emphasizes the importance of gathering ethnographic data (Kern, 2006), a brief, informal interview was held at the same time as the data were collected. One of the primary benefits of obtaining ethnographic data is to place in perspective how the grant writer approached the writing process and what her perceptions were about the data she submitted. Such reflective information is invaluable when, after rigorous evaluation of the data, one attempts to make sense of the findings. Following the evaluation, a questionnaire was sent to the subject that asked for specific clarification and provided an excellent ethnographic tool for contextualizing the conclusions of the current study.

Although more studies need to be done among international postdocs, one of the key problems facing investigators is the busy schedule and the intense pressure placed upon a principle investigator (PI) to produce and publish research as well as write grant proposals to fund the laboratory. Even with their busy schedules, many PIs are usually willing to take time to participate in data gathering once they are satisfied that an

investigator does not require of them excessive time requirements. Many universities across the country provide laboratory space and fund research and many of those laboratories are staffed with international postdocs; thus, university laboratories provide a rich environment for finding additional subjects and data.

Among the universities with medical schools, cancer research typically carries tremendous importance and requires many hours of work to complete projects. The competitiveness for grants by various research laboratories appears to be the reason why so many postdocs are so busy with research that they prefer not to participate in additional studies (personal interview, August 15, 2007). As just one example of how important cancer research is, the website for Indiana University School of Medicine stated that grant funding for 2006 was over \$220 million and that approximately 1,200 investigators worked on medical research studies. That number suggests a healthy research enterprise at Indiana University (IU) and other universities across the country have a similar oncological research focus. New construction at IU is evidenced by the planned opening of a lab-research complex in late 2008, housing an additional 118 new laboratories. The IU Medical School's website conservatively estimates that by 2010, \$500 million in grants will be awarded to IU just in cancer research alone (Indiana University Cancer Center, 2007). As these figures demonstrate, grants provide tremendous income potential and stress the importance of writing successful grants, not only within the IU School of Medicine, but also within medical education and research programs across the nation. Connor and Mbaye (2004) note that research labs across the country employ international postdocs, yet this population remains unexamined.

Therefore, investigators who wish to pursue studies about the grant writing process among international postdocs have a very large pool of potential subjects.

Grant writing remains the medium of exchange and selection between funding agencies and researchers and thus provides the large pool of subjects from which to choose for studying the grant writing process. As research enterprises expand and competition for funding increases, the field for potential growth of English for Specific Purposes (ESP) cannot be underestimated as many of those who write grants are non-native speakers (NNS). Although other investigators focused on how proposals *were* written by North American native speakers (NANS), this study focuses on how studies *are* written by an international postdoc. By studying how the process takes place, both second language (L2) instructors and L2 learners can benefit from the findings of the current study; nonetheless, more study is needed because little is known about how international postdocs prepare texts in L2 English, nor how the epistemological process in the medical research laboratories helps to acculturate writers of grant proposals. It is critical that this populations' grant writing strategies and competencies be examined. The present study will expand upon the previous research by investigating the grant writing processes of an L2 English writer as she goes through the various steps of grant writing.

Chapter Two: Literature review

2.1 Overview

This section will review existing research exploring several threads of the social construction of knowledge in scientific writing and the grant proposal writing process. Beginning as far back as the 1970's, researchers began to lay an important foundation to build understanding about how scientific texts are written. Those first researchers were sociologists and psychologists who were then followed by linguists and sociolinguists.

Secondly, the internationalization of English will be explored. Swales (1990) stated the predominance of scientific writing occurs in English. Such demand places a heavy emphasis on English taught in a foreign language (EFL), English as a second language (ESL), English for specific purposes (ESP), and English for academic purposes (EAP); it provides a substantial reason why postdocs are obligated to publish in English. The internationalization of English is also greatly impacted by the publishing process and relevant literature related to this process will be reviewed.

The final section considers research methodologies used to study the grant writing process. It is necessary to review these methodologies because no previous studies provide an existing model for the current study to replicate. As such, the study will merge applicable methods from the studies reviewed. Thus, the following comprehensive review of the literature demonstrates little is known about either the production or the process of writing grant proposal texts in L2 English by international postdocs.

2.2 Social construction of knowledge

One of the first authors in the field of sociology to publish research on scientific writing was Gieryn (1978), who investigated how a community of scientists established a “problem choice” for research. He defined “problem area” as an area within an accepted knowledge of a field or specialty (p. 97). He further defined “problem choice,” as a choice made by an individual researcher who selected or identified a specific issue within a problem area (p. 97). “For purposes of empirical investigation, a defining characteristic of a problem choice is taken as the publication of a scientific paper whose subject is within the substantive or technical scope of a problem area” (p. 98). Gieryn’s paper began a line of study looking at what scientists write and why they write it. He concluded with a question of how “various patterns of change...differ among scientific disciplines with their ...social structures...” and how these patterns interact within communities of scientists (p. 110). Although Gieryn’s view was strictly from a sociological discipline, his comments apply to succeeding studies within the field of sociolinguistics as he constructed a foundation for scientific investigation by describing writing as products of social activity.

Following Gieryn, it was not until the mid 1980’s when Bazerman (1984) added to the social construction of knowledge by inquiring about scientific texts as a unique and specific genre. To do so, he examined textual artifacts from a 1923 physics publication including the author’s notes and previous work that led up to the final publication. Bazerman argued that specific social situations and authorial controls identify scientific text and “advance the author’s interests” (p. 39). He addressed and disproved previously held beliefs that “scientific texts simply ...report on nature” (p. 39). Bazerman focused

on contextual forces that constrained and directed procedures of scientific argumentation: how science is shaped into a linguistic object or text, how the author showed personal identification when required for purposes of the audience's understanding, and how authors textually react to potential objections of the audience.

Overall, Bazerman identified elements of scientific writing that continue to shape the genre of research papers; his work focused attention on social awareness on the part of the author as it affected the presentation of a text for other scientists to read, duplicate, and perhaps disagree or reformulate the hypothesis. The elements of his work have been extended by further research in how scientific papers are written from start to finish. Although his work examined textual artifacts, his methodology utilized original authorial notes documenting changes in the process of publication. Bazerman used them to gain understanding about the development of scientific genres. The current study will utilize a similar methodology, studying the original texts, documenting changes, and holding interviews with the author rather than using authorial notes.

Following Bazerman's work, Rymer (1988) provided a case study¹ of how one eminent scientist composed journal articles. She agreed with Bazerman (1984) who stated scientific texts are products of social activity (p. 212), and with Myers' (1990) assertion that writing grant proposals builds relationships (p. 213). Rymer² disagreed with Myers claim that "the grant proposal is the most persuasive document scientists write..." (p. 214) and claimed "the journal paper, [is] a genre that is, in fact, also very persuasive,

¹ Rymer's article focused heavily on using follow-up interviews after taped responses of the scientists while he wrote the article and articulated aloud his thinking process.

² Rymer's work built others' work, yet her textual criticism of another researcher/author causes reader confusion. Considering that the field was wide open for study, that new territory and wider definitions were being worked out for several disciplines simultaneously, and that there were plenty of subjects to study in all the scientific fields, Rymer's remarks about Myers seem somewhat arrogant and ill-informed; especially true when both individuals were attempting to provide similar research.

but is the more so when it seems not to be” (p. 214). Rymer observed that experienced scientists use a wide range of composing strategies and through revision they seek excellence (p. 229).

Rymer sought to answer this question: What was the process scientists used to write? Was it random or did they carefully plan with an outline? She discovered that many scientists sat down to write without even articulating a hypothesis—it was the writing process that forced them to arrive at a hypothesis. Without the hypothesis clearly in mind at the outset, it created difficulty for some of the scientists because it required extensive revisions (p. 239). It frequently occurred to the writers that they discovered new meaning in their research once they had a written text. Rymer later commented, “Many scientists do discover some of what they know...while they are drafting. [T]he very act of composing can be instrumental, ...giving form and shape to their [paper], ...finding out what their results mean, ...what they know scientifically, and ...the direction of future research (p. 243).” What is of interest here is that the question she posed might well be asked as data are collected in the present study: Did the preparation of the grant proposal help redefine the research?

During the same year that Rymer published her study, Bazerman (1988) also published his studies of scientific texts. His was a monumental study that provided a historical documentation of scientific writing (speech acts) beginning with Sir Francis Bacon and the Royal Society of 1665 (p. 59) up to the modern scientific journals of the 1980’s. He identified themes from Aristotelian thinking still reflected in current scientific literature. To perform his study, he examined hundreds of the Royal Society’s scientific experimental reports (p. 7). Bazerman carefully documented how each century left its

mark on the emerging development of scientific writing (p. 8) as it evolved into its current genre. Years later, he wrote an introduction in Ann Blakeslee's (2001) book and commented on his research, "[L]earning to communicate with one's peers is at the very core of learning to be a scientist, and is at the very core of making meaningful contributions, as Latour (1987), Myers (1990) and I (1998) suggested" (p. xiii). It was through such a deliberate process of social interactions that scientists learned to write to a specific audience of other scientists, which has direct implications for studying the grant writing process.

By establishing the importance of "scientific writing," Bazerman (1988) included and supported Kuhn's "observation of communal interaction in the production of knowledge" (p. 4, note #3). Bazerman extended that idea to expand his position that social interaction and the structure of language influenced the historical, scientific production of texts and that the rhetorical moment was framed by that text (p. 5). At the end of the book, Bazerman examined how readers (pp. 132-133) read texts and interpret them. He favored Vygotsky's position of "the role of language in human activity, society, and consciousness" (p. 302) as it played out in the rhetoric and social interactions of scientists when they met at symposiums, conferences, or read and responded to published articles. "Language is a tool" that facilitates "cooperative activities" because scientists share not only meanings of words in their "syntactical operations but how those generalized words apply" in the text and to a responding action from the reader (p. 304).

Bazerman also described the introduction of "gatekeepers" (pp. 130-136) and editors as part of the "new social dynamics" of the developing scientific journal. No longer were scientific experiments performed in front of peers at the Royal Society;

instead, experiments were discussed in journals. Although less visible to the readers, the early journals had editors who selected the materials for publication. Such a position required respect in the professional community and by the 1750s, editors became part of the scientific journals' gatekeepers. Besides controlling the subjects published, they provided feedback to writers who desired publication; thus, a scientific rhetoric gradually became commonly accepted. The present study will investigate how much influence the referees had, if any, in shaping the final grant proposal in their role of gatekeepers.

In recent years, the social impact of scientific writing was heavily influenced by experimental psychologists (p. 259) and the American Psychological Association's Publication Manual (*APA Manual*), which had immense influence on the construction and organization of manuscripts—the final word in editors' prescriptive demands in the presentation of scientific texts. Thus, scientific rhetoric evolved from social influences that included the activities of the participants in the peer review process as well as the readers; thus, most scientific communities participate in an evolving genre over which the *APA Manual's* influence extends, including medical research publications and grant proposals as demonstrated in the data for the current study.

In an attempt to explore that evolving genre, Myers (1990) provided an excellent contribution to the advancement of the body of knowledge about how scientific texts are shaped. Myers made a salient comment about texts: "Texts hold still and texts are portable" (p. 6). However, he was quick to point out, "...texts change meaning whenever they change context" (pp. 6-7). Later, he concluded that texts do not transport the context of their initial creation because the social interactions inherent inside the text are invisible to the reader. Thus, Myers approached texts with a claim that they be "read as processes"

(p. 6). He briefly discussed oral discussions and their contribution to the literature only from the standpoint that they are carefully transcribed and written down for “transport and making them stand still” (p. 6).

Although Myers approached the study of his subjects, Bloch’s and Crews,’ writings as textual artifacts, he conducted his interviews with the scientists to determine context. He made an interesting point, “Finding conventional terms for unconventional research is not just an exercise in rhetoric—it changes the research” (p. 60). Considering that he published his work in 1990, his comment begs an excellent question: How does this observation interact with the writing process or knowledge development of international postdocs? Might they have difficulty with specific nuances in the refinement of academic meanings ascribed to specific syntactical constructions? Myers noted a syntax gap in Bloch’s grant proposal because Bloch, a native speaker, was unable to connect methodologies between two sentences and the journal referees noted the inconsistency in the rejected manuscript (p. 54). Myers made several noteworthy comments following his endeavor

to find textual evidence for the social nature of that discourse... or linguistic features that might figure in social negotiation. [Myers stated his limitations:] What brings a feature to my attention is the difference between a text and its revised version, a text and a comment on it, and two texts for different audiences (p. 40).

He finalized his two case studies with the following justification, “One advantage of starting with cases rather than norms is that it is not my job to look for this somewhere else, for the typical science and the typical scientific text. I can begin with the material at hand”³ (p. 40).

In order for Myers to document how information became “accepted scientific literature” he referred to the data from his second subject’s (Crews) first submission for a journal publication. The entire article was broken down into separate components, published individually, and then Crews waited until his articles were cited by other authors in an effort to gauge the acceptability of his new research. Although Bloch followed the same publishing strategy, his articles required extensive revisions from peer reviews; then, he waited to find acceptability within the scientific community through citation. Myers quipped, “What is not printed cannot be cited” (p. 96).

One of the conclusions Myers offered was “[al]though historians can locate classic papers in retrospect, the success or failure of a claim seldom hinges on one article” (p. 98). Myers suggested many articles, over time, if sufficiently cited and used by the local community of scientists, could then build from “last year’s wild speculation [to] become this year’s plausible hypothesis and next year’s basic assumption” (p. 98). Myers concluded, when no one picks up a published claim, then by ignoring it, it “disappear[s] into the morass of scientific publications” (p. 101).

³ Although his comment was bold and described his limitations, it was a clear refutation of other critics of the 1980’s, whose previous experience in sociology would never allow one or two subjects as a valid, scientific study. In a sense, Myers was joining Bazerman’s and Mishler’s work which was expanding sociological studies into exploring texts as a means of discovery about social interaction in specific communities or academic disciplines. These studies became not only part of the foundation for post-modern sociolinguistic methodology, but validated qualitative case studies.

His ultimate conclusion for the evaluation of texts as it applied to his research was 1) look for the rhetorical; 2) reconstruct the social context; 3) look for related texts; 4) look for the source of authority; and 5) look for any links between scientific language and everyday uses of language” (pp. 255-258). Thus, Myers provided insight and justification for the social construction of scientific knowledge in his case study. However, he was not alone in establishing and defining a new field of research. Bazerman, Rymer, Myers, and Mishler (1990), a psychologist, were all working independently to investigate how scientific knowledge was being shaped.

Mishler’s (1990) seminal argument paper departed from the previously accepted rigor of scientific discourse because it established a new definition of *validation*, which is currently reflected in research papers across genres. His argument further established new territory in scientific experimental discourse as he defined validation “...as the social construction of knowledge” [that relies upon the] “relevant community of scientists [who] evaluate reported findings [and]...rely on them for their own work” (p. 417). Mishler defended a new paradigm, which he defined as a type of “...‘scientific inquiry’ [wherein] a ‘validity judgment’ is an ‘inductive summary’ of all [previously] available information [which is] central to the process” (p. 418). Ultimately, researchers now benefit from Mishler’s work because scientific papers reflect “...rhetorical strategies” ...of normal science [that] are embedded in complex networks of concepts, linguistic and technical practices, and an established framework of norms and values” (p. 420).

Mishler stressed the existence of complex social processes that provide “a context-based explication ...of how observations are transformed into data and findings, and how interpretations are grounded” as a community of scientists share “exemplars

through which [they] confirm and validate [their] collective work” (p. 423)⁴. Thus, Mishler’s work could apply to sociolinguists (as well as all scientists) who rely heavily on interviews of subjects in their studies because his inductive approach validated the personal interview (tape-recorded, transcribed (p. 429)) so that others could analyze and interpret the data. The personal interview was no longer stigmatized as antidotal and non-scientific. He defended “what is being told now...[and it] is not a weakness, but rather a hallmark of interpretive research in which the key problem is understanding how individuals interpret events and experiences....” (p. 427). The methodology of the present study relies on Mishler’s precedent, justifying the interview process. Mishler’s work gave credibility to “inquiry-guided research that... features such studies [as] ethnographies, case studies and textual analyses...” (p. 434). Mishler’s work directly applies to the study of grant writing and how it occurs. He summarized,

...research scientists turn out to resemble craftspersons [whose] competence depends on apprenticeship training, continued practice, and experience-based, contextual knowledge of the specific methods applicable to a phenomenon of interest.... The discovery, testing, and validation of findings is embedded in cultural and linguistic practices” (p. 435).

Mishler also defended the validity of case studies based on the “general theoretical significance [that] depended upon whether or not the particular texts are representative samples of a general class of texts...” (p. 437). His reference to craftspersons is an apt analogy to postdocs as they enter a specific field with its

⁴ The six exemplars Mishler discussed (p. 423) have become so established in the literature, that by the time Connor (2000) identified the nine rhetorical moves in a grant proposal, Mishler’s influence is present.

own epistemology, which must be acquired through practice in grant writing to achieve final success. This very process is the focus of the current study.

Several years later and having reflected on Mishler's research, Bazerman (1994) proposed

a vision of how people create...meaning and value within structured discursive fields and...act within highly articulated social systems. [He explained that] the action is accomplished through performance of genres that have highly specific, systematically contextual requirements and well defined consequences for further generically-shaped social acts (p. 79).

In developing his argument, Bazerman likened genres as "important levers" that society "must recognize, use and construct...to create consequential social action" (p. 79). He contended that the whole system works through its genres and our willing participation in them "create[s] highly consequential meanings in highly articulated and developed systems" (p. 79) and thus, "it gives insight into the way other less explicit socio-textual systems work" (p. 80). His view provides a theoretical basis for identification of genres as they function within an organized society. To extend this theoretical position, Bazerman used U.S. patents as a sample genre for his argument to explain how

genres rely on our being able to recognize them and to some degree understand the meanings they instantiate within the systems of which they are part. A textual form which is not recognized as being of a type, having a particular force, would have no status nor social value as a genre. A genre exists only in the recognitions and attributions of the users... (p. 82).

The social interaction between users and readers of a specific genre is "real and consequential [because] all exist in the realm of social fact constructed by the maintenance of the patent system[']s forms (genres) by which it is enacted" (p. 82). The current study will attempt to document those interactions.

Bazerman chose speech acts to describe his analysis of the patent application process but he completely redefined them as “related and evolving genres.” He further asserted the genres did not fit a mathematical equation, but rather, as acts that had contextual occurrence, based on Austin’s (1962) and Searle’s (1969) previous work, stating that it gave the patent genre “a stable illocutionary force with the legal system...” (pp. 84-5). Thus, it would be possible to ascribe “speech acts” to some of the research papers⁵, but more likely to grant proposals since they are written to persuade the reader as justification for funding⁶.

Bazerman made an interesting point about two types of genres. First, he addressed those that are “single acts...[that] can be filed away purely for the record...[where] the text becomes dead or a black box and exists only in its consequences” (p. 90). Secondly, the other texts, in order “to have force [they] must constantly be reread...” such as poetry and philosophy (p. 90). Questions might arise about old research that is antiquated, or grant proposals that were funded, filed, and after the funding process, forgotten in the “black box.” Myers (1990) referred to the same concept when scientific papers are ignored by the scientific community.

Bazerman summarized by stating, “What we have, in essence, is a complex web of interrelated genres where each participant makes a recognizable act or move in some recognizable genre, which then may be followed by a certain range of appropriate generic responses by others” (pp. 96-7). Bazerman’s observations could easily translate to grant proposals. As he observed the evolution of the patent granting process, he made a

⁵ In this instance, finding evidence of “speech acts” would make an interesting study in light of Bazerman’s redefined terminology.

⁶ Technically, application for a patent is not that different from the rigor of form for a grant proposal.

comment that could easily apply to research papers and grant proposals. “Yet every potential lawyer, in order to play the game, must learn the forms of currently available moves through extensive education and apprenticeship activities” (p. 97). Bazerman’s statement reinforces Blakeslee (2001), Adolphs (2005), and Li (2006) who suggested postdoctoral laboratory researchers enter into a type of unique mentorship or apprenticeship—the epistemology of the research lab and its written genre. Bazerman further introduced the written genre as the notion of systems of genre. These are interrelated genres that interact with each other in specific settings. Only a limited range of genres may appropriately follow upon another in particular settings, because the success conditions of the actions of each require various states of affairs to exist (pp. 97-8).

Bazerman further developed his argument by stating there were conditions which “successfully identify the generic utterance appropriate for our needs at each point...which constitute[s] the perfected act” (p. 98). Some of those “appropriate utterances” were identified later as moves by Connor and Mauranen, (1999) and Connor, (2000). They advanced the theoretical frame explored by Bazerman when he stated, “This notion of systems of genres extends the concept of genre set...” (p. 98). It represented an entire range of texts required as in all of a tax accountant’s work. That type of interaction would “...embody the full history of speech events as intertextual occurrences, but attending to the way that all the intertext is instantiated in generic form establishing the current act in relation to prior acts” (p. 99). Although Bazerman studied native speakers, clearly, one could extrapolate that notion to the genre set of the research lab and the grant proposal.

Bazerman stated that genre understanding and usage is related to “*kairos*, or timeliness” (p. 99). How writers grasp an entire discursive system as it operates through generic turns becomes the means by which we

locate ourselves, our potential speech acts, and the criteria our utterances should seek to meet; we can start to understand what we can achieve rhetorically at any moment, and what we cannot, and how. ...[t]hrough an understanding of the genres available to us at any time we can understand the roles and relationships open to us” (p. 99). Thus, when we are put on the spot, we must act, and in acting we must act generically if others are to understand our act and accept it as valid. Without a shared sense of genre [then] others would not know what kind of thing we were doing (p. 100).

His point stresses the need for researchers to understand fully the genre of both the research paper for journal publication and how a grant proposal is successfully written; each become an integral social interaction and learning process. It also provides pedagogical implications for EAP/ESP.

One recent study adding to the research and the construction of knowledge was Kern’s (2006) study of computer assisted language learning. Kern’s article tied together linguistic studies and new technologies, as they apply to ESL/EAP pedagogy and application of previous theories, and studies on the effectiveness of “language labs.” He discussed computer integration using an example from one area, the cell phone. It not only transmits voice, but includes taking movies, still pictures, sending text messaging, voice mail, chat rooms, and providing a platform for group discussion—all of which “enable new forms of discourse, ...authorship, ...identity construction, and new ways to form, choose, and maintain learning communities and affinity groups that cross national boundaries” (pp. 183-4).

The current study will address questions about computer influence in the preparation of the grant proposal; Kern connected the new technologies as pertinent to

applied second language acquisition (SLA) theories and suggested that those theories could be analyzed best through the utilization of “multiple perspectives and paradigms to best inform [SLA] understanding and future research” (p. 188). Kern, citing a question posed by Zhao (2003), stated that the issue was not the “effective or ineffective” use of technology, but correct identification of the “ways in which the technology is used” (p. 189).

Kern also addressed the cultural issues surrounding the use of the computer. His conclusions indicated that “computer environments have their specific cultures, [and] ...computer cultures are subject to transformation...by users⁷” (p. 191). Thus, computer usage could have an effect upon production of texts in a grant proposal. Kern concluded, success of ESL & SLA depends upon the student’s “ability not only to read and write comprehensible language but also the ability to negotiate new roles and identities. Identity construction and socialization are inherently intertwined with language and can have either a facilitating effect or a constraining effect on the resources learners acquire and use” (p. 198). Kern’s study of social interaction identified a problem without the face-to-face ethnographic assessment of the content/context learning; thus, he emphasized a clear need for ethnographic methodologies employed by the current study.

2.3 Internationalization of English

Numerous authors acknowledge the fact that English has become the *lingua franca* of international communication (e.g., Crystal, 1997; Graddol, 2004; Tardy, 2004;

⁷ Postdocs using a computer would, by this definition, have their own culture associated with its use, impacted by L1 or L2. To adequately assess the perspective of the researcher, that issue needs to be addressed.

Seidlhofer, 2003; Canagarajah, 2006). David Graddol (2004) based his argument around languages found in the United Nations demographic data, the observable political unification of the new world order, and the huge population growth in China and India. In his view, English as a *lingua franca* will diminish over the next 50 years; that statement differs from other authors looking at the future of language. Graddol lamented the loss of languages,⁸ while suggesting new languages would develop to replace old ones in the large cities. The salient point of Graddol's paper was the suggestion that all new world citizens should become multilingual, or at least bilingual. Otherwise, he expressed a negative view about the future of English to the exclusion of "specialized domains such as the scientific article" which he referred to as an institutionalized genre. The only way Graddol's ideas will reach the grant writing genre is for a global internationalization of Englishes and a complete restructuring of journal and grant requirements.

Regardless of the imminent demise of Graddol's English, other authors are convinced that English is here to stay. Tardy (2004) addressed English as an international language of science (EILS). She referred to the current literature as an indicator that English can be seen as a "neutral *lingua franca* or [as Canagarajah and others see it] ...an insidiously dominating [worldwide] force" (p. 247). She studied international graduate students who were struggling with writing in English as L2 for publishing in scientific journals. The application of her study validated EAP as long as English remains the *lingua franca* of scientific literature.

Tardy expressly noted that the ascendance of the internet as an internationally accepted medium of communication magnified the importance of English for both

⁸ Shades of Canagarajah as she suggests the rejection of English as a cannibalistic destroyer of dying languages.

reading and publishing scientific articles. She attempted to resolve how applied linguists can both understand the “co-existing roles of English” (p. 248) and the “next generation” of scientists. Tardy explicitly identified the gatekeepers of the respected journals as the bastion of control for keeping academic English in a “stranglehold” (p. 250). She concluded that within a frame of pragmatics, if scientific publishing is desired, all writers must conform to EILS.

In her study, Tardy listed the number of international graduate students who were her primary users of EILS (p. 251). The overwhelming percentage (86%) of her study group was from Asia. Although she did not appear to ascribe cultural issues⁹ as a point of concern in her study, a purely linguistic interpretation of data does not present the whole picture. It is concerning for researchers that her study could provide a bias from a linguistic evaluation in that textual relics provide neither cultural understanding nor intent of the writer¹⁰.

Tardy, in her discussion, made a salient point for EAP. She suggested less fluent writers deserve an opportunity to become published when their research is important. However, that would place more stress on the gatekeepers; yet, at the same time, would bring some diversity into the publishing community. Some of her pragmatic conclusions echoed Canagarajah as she referred to the “vulgar pragmatism” of “EAP instruction” and its “inequities that learners face” (p. 265).

Seidlhofer (2003) offered a salient view on pragmatics and language, distancing herself from Canagarajah (1999), Pennycook (1994), and Phillipson (1992) as evidenced

⁹ Albeit, she alluded to politically important issues.

¹⁰ Tardy’s questionnaire (p. 265-6) attempted to define linguistic background only. I wonder if she had submitted her questionnaire to sociolinguists, perhaps there might have been other questions to bring cultural balance into the study.

by her view that she presented the “era in which a kind of functional realism and pragmatic view seems to establish itself” (p. 12). Seidlhofer attempted to set the stage for and defend English as an international language (EIL) for the EU because its existence is an undisputed “econocultural fact...[for two reasons: 1] utilitarian...for international business,...[2] idealistic...[for] cross-cultural communication and mutual understanding” (p. 12). Seidlhofer argued for a pragmatic acceptance of EIL since English was currently in wide acceptance not only across the scientific community, EILS, but also in the business world. Tardy contended that EIL would become acceptable across the EU, spoken by various speakers, and each would use their own version of English. She saw EIL as an opportunity to focus on communication between speakers but not necessarily requiring the prescriptive grammars frequently attributed to current EFL or ESL instruction that is still entrenched in the EU’s educational system. Even though EIL discussion began in the early 1990’s, it still lacks widespread acceptance and appears unlikely to become an immediate change agent affecting medical texts or research and grant proposal genres. Although business entities might be affected through international communication, it would appear to have little bearing on the present study.

Among the voices who despair, claiming English is running other languages into extinction is Canagarajah (2006). Pragmatically, he acknowledged, “English is here to stay as an international language for communication.” He divided World English (WE) and Metropolitan English (ME) as two distinct worlds where he defined ME as elitist while WE took on the multidimensional, trans-cultural, trans-national language, which comprises many varieties of Englishes. He focused on an essay by Horner and Trimbur, (2002) that identified English as a global *lingua franca* from an internationalist

perspective, since it is taught world wide as a unidirectional, monolingual compositional competence. Canagarajah raised questions of who controls the power in decision making regarding English and what changes might be made? He echoed Seidlhofer, (2006) as she presented her case for International English for the EU. However, there appears little support from the gatekeepers of the scientific journals to support such a move in the near future, enhancing the need for the current study.

Within a framework of accommodation theory, Canagarajah suggested some pedagogical benefits that included less attention to prescriptive grammars and more about communication of ideas. Canagarajah did not address postdocs' needs for EAP/ESP as applied to research papers and grant proposals; yet he concluded the gatekeepers must relax their standards of academic English across all journal publications. Apparently, he would prefer to see less successful writers of EAP find a voice and acceptance in the prestigious journals so that slowly, the vernacular or *vulgate* would be allowed and find equal acceptance in the "revised academic" register. As a student of history, I find that desire slightly naïve in the politically charged environment of medical research journals where change evolves slowly.

2.4 Internationals in the publishing process

International graduate students, post docs, and research lab scientists comprise a large portion of the research production at a major Midwest university where the present study is situated; it includes engineering, computer engineering, cancer research, and the medical sciences. Since the conclusions of the current study could have implications for

EAP/ESP, Belcher (2006) presented a global overview of ESP by providing a historical context for ESP. She documented various researchers and theorists who gave ESP its broad definition while at the same time presenting the arguments of its antagonists such as Canagarajah (2006), Pennycook (1997), and Phillipson (1992). Belcher argued that perhaps English for occupational purposes (EOP) and ESP could stand at least a face-lift, if not a revised makeover. She did not discount Dudley-Evans and St. John (1998), but rather, she called for revising and updating the ESP textbooks. Belcher made suggestions for new areas of study using internet, email, and text messaging.

Belcher seemed to accept the current, widely divergent definitions of ESP as long as EAP and EOP are included as part of the broader view of ESP. Although ESP is the specific area providing internationals with preparation for grant writing, it would appear easier for one to define what ESP is not, as opposed to what it is. Nevertheless, Belcher strongly supported keeping a primary tenet of ESP, the ongoing needs assessment and its continual, weekly updating so that learner needs would be met in real time, regardless whether it met the requirements of the agencies paying for the ESP or not (p. 144). In Lee and Swales (2006), the same theme arises; weekly updating of needs assessment is an ongoing process for ESP. In both studies, there was direct application to internationals preparing to write grant proposals or research papers.

One of the areas Belcher suggested ESP could incorporate into a structured pedagogy related to recent ethnographic work that would broaden (p. 146) the ESP classroom instruction. Belcher also suggested that ESP forum be broadened to include new venues for publication (p. 150). She cited difficulties of publication for International English from World Englishes that do not meet the current gatekeeper biases (p. 150).

The establishment of the Internet for publishing articles of interest in local ESP is fascinating. Part of the criticism of ESP was that the local was not allowed a voice in the peer reviewed journals (p. 151). Belcher cited Seidlhofer (2001), arguing strongly for decentered ESP by “uncoupling English from its native speakers holds the exciting, if uncomfortable, prospect of bringing up for reappraisal just about every issue and tenet in language teaching which the profession has been traditionally concerned with” (p. 151). If such an idea were to become broadly accepted, it would have an immediate positive effect for internationals publishing research and writing grant proposals.

In a different study, Blakeslee (2001) provided insight into the cooperative interactions of three native English-speaking physicists, whose objectives were to publish for an interdisciplinary audience. Although her study applied to native English speakers, her data revealed language between the chemists, physicists, and biologists were dissimilar and that dissimilarity created misunderstanding. That difference highlighted the difficulties internationals have in gaining competency in the medical sciences and emphasized the need for an improved epistemological process as postdocs are acculturated into the U.S. grant writing genre sets. Those difficulties Blakeslee’s work identified have application in the current study.

Through situated cognition and activity theory (pp. 83, 102-3) Blakeslee documented how knowledge was attained regarding a domain’s discursive practices. Her study revealed the efforts of the physicists to engage others in a knowledge that they believed was reliable, true, and useful. The problem that occurred for the physicists was to bridge the gap and interact with different audiences, effectively convincing other disciplines of science that their knowledge was worthwhile and applied across

disciplines. In this interactive process, Blakeslee provided insight into the process with personal interviews, reviews of the textual artifacts as they evolved, and how the physicists could provide an effective rhetorical strategy that engaged their multidisciplinary audience (p. 83). Further, she gave readers an inside view as to how scientific information is written before becoming a textual artifact. Likewise, she gave students of composition, technical and scientific writing, and rhetorical theory a better understanding of how to define an audience and cooperatively write a manuscript for a multidisciplinary audience.

Blakeslee made an observation that is of epistemological note: "...knowing how to adapt one's writing to a particular community entails more than having a body of [fixed and retained] knowledge...[but] rather, it is a tool or a skill that requires continual updating as communities shift and change...." (p. 35). Blakeslee suggested that her descriptive data analyzes how direct interactions with actual audience members occurred and provided insight into knowing and reaching an audience through social interaction. One of the shortcomings she identified in the interaction process was in the interest of efficiency because the physicists did not do all they could have done to fully bridge the gap. Her study indicated it might take years to attain the quality of activity required for a multidisciplinary acceptance, "which raises the important question of whether there are ways to speed up such processes or whether they simply require this slow cumulative experience" (p. 36). Thus, writers seeking a different audience may find it difficult to become an accepted voice in other scientific forums (p. 46). Although her subjects were native speakers attempting to address different scientific disciplines, she identified a critical issue that affects internationals who struggle in L2 English. Considering the

difficulties some native speakers have in communicating, it only exacerbates the difficulties non-native speakers face when attempting to gain competencies in a scientific discipline, acquire L2 writing skills that demonstrate those competencies, and master the prescriptive genre of the grant proposal. Clearly, the present study has relevance.

An interesting dynamic Blakeslee's study discovered about a postdoc physicist, who was new to his field, was that he had not fully gained the "language of physicists." Her finding validates the importance of apprenticeship in the epistemological process, which is learned through social interaction within a specific community as well as the practice of rhetorical application in a specific genre, physics. Although her subject, a statistical physicist, could successfully communicate mathematically, he chose to engage in work as postdoc in a biology lab to learn their language. Blakeslee noted that he had not fully acquired the language of his own community, physics (p. 49). She commented, audiences were "complex, dynamic entities that can never be known completely... and entail some level of abstraction" (p. 50). However, even if the audience appears somewhat abstract, it becomes "an integrated and [an] integral component of an author's larger [dynamic] rhetorical process" (p. 50). After this discussion, Blakeslee concluded,

Writing is a social process that involves envisioned as well as real, interactionally experienced audiences. ...[A]uthors' interactions with audiences are affected by ...time and efficiency; willingness and capability to change; ethos and status; genre and type of acceptance sought; duration and intensity or depth of experience within one's own or a different community; and inherent skill. ...My findings also suggest the importance of interaction both for knowing ...and how to ...influence that audience, ...when it is not the same community as the author (p. 51).

In another, but unrelated case study, Adolphs (2005) examined how international students in England became acculturated and competent in local, non-standard British English. He documented difficulties the students had in learning "native-speaker"

English, which was very different from “BBC English” and considered “standard English” (p. 129). Adolphs concluded that in the “acculturation process” the international students became “more aware of the concept of ‘native speaker’” as a variety of English and “became more critical of conforming to native speaker norms” (p. 129). The study identified the desire of the international students to be able to be successfully understood in just a simple task, such as to call for a taxi and to be understood. Adolphs’ study established that “native speaker¹¹” was essentially an identity with a local variety of English and that his subjects became more critical in “re-defining their language learning goals with greater focus on mutual intelligibility in an international context” (p. 130). Although Adolphs did not address EFL pedagogy, the experiences of his subjects indicated that their training in “standard BBC English” did not prepare them for conversational success in local varieties/accents of English.

The difficulties international postdocs might have in determining local Englishes appears as a global theme for ESL/EFL/EAP. John Flowerdew (2005) and Swales (1990) addressed these issues as it pertained to academic research and the non-native English speakers (NNES) who found it difficult to publish in English journals. In one example, after China assumed control over Hong Kong, Cantonese speakers were free to attend Hong Kong Universities; yet they were speakers who had little exposure to native English speakers and perhaps less likely to feel comfortable publishing in English.

¹¹ It is indeed interesting that the same issues confront most non-native speakers to any English speaking country. Native speaker English has too many local varieties from which to choose, thus making a specific variety the absolute standard or norm. It leads me to wonder if North American Standard English is defined by the international media giants. Another question would equate to Chinese; many can read and write the characters, but Mandarin and Cantonese are only two varieties of the same language: which one is the native speaker Chinese?

Flowerdew listed four research objectives¹² for his quantitative study in which he included a pilot survey that was administered, revised, and sent out to 2300 academics, of whom, 717 responded at a 31% return rate (p. 69). Flowerdew accepted that response as good. One of the noteworthy findings was that a “majority felt confident... [publishing] a paper in English, [but] a (larger) majority also believed there to be prejudice against NNES on the part of editors and referees” (p. 69). A result like that justifies the current study.

In his study, Flowerdew referred to his own research from 1999 to “ground” his 2004 study regarding the interview process and described his efforts not to “lead” the subjects. Because the subjects had already completed the quantitative survey first, their thinking was “already grounded” (p. 70) and the questions remained general in order to obtain the broadest possible response. Performing research and publishing findings required significant time and Flowerdew used ATLAS.ti software to load data, sort it, and resort into various categories. His research goal was to find “commonalities and differences within the group of participants” (p. 71).

¹² Flowerdew listed four research objectives:

1. Investigate in Hong Kong:
 - a. publication rates by educational and professional writers
 - b. attitudes toward publishing in academic English (L2) by Cantonese (L1) speakers (p. 67)
2. Identify key problems for academic Cantonese L1 speakers from the perspective of writers, editors, and journal referees (p. 67)
3. Identify key strategies used by academic Cantonese L1 writers for publication in English (p. 68)
4. Investigate in Hong Kong (p. 68)
 - a. attitudes of journal editors and referees to submissions from NNES
 - b. feedback given from the referees’ report forms

Flowerdew's interviews with editors included four question areas.¹³ He followed up with the editors several times after the initial interview to improve and solidify his findings. In the follow-up of writers, he used the grounded research theory to apply his data and determine findings (p. 74). As mentioned in other articles, participation of case study subjects required considerable commitment of time and energy, which Flowerdew referred to as legitimate peripheral participation theory¹⁴ (p. 74). "Since the participant was seeking access to the international discourse community of scholars, but from a disadvantaged position [in] Hong Kong, [Flowerdew applied] the application of discourse community theory" (p. 75). In the current study, it is expected that data collected might assist international postdocs to gain more rapid access to the discourse community and help them acquire the grant genre.

In a slightly different study, Lee and Swales (2006), presented how a corpus of self-compiled data from each international graduate student actually helped all of them work through some of the primary difficulties they had in writing English. Although they chose to call it EAP, it appeared more like ESP since the size of the study group was

¹³ Flowerdew's interviews with editors included four question areas:

1. What means the term, *non-native speaker*
2. Attitudes of editors and reviewers to NNES contributions
3. Problematic aspects of NNES contributions
 - a. "surface" errors
 - b. absence of authorial voice
 - c. parochialism
 - d. nativized varieties of English
4. Positive attributes of NNES contributors
 - a. awareness of cross-linguistic and cross-cultural issues
 - b. objectivity of "outsider" perspectives
 - c. an international perspective
 - d. a testing mechanism for the dominant theories of the "centre"
 - e. access to research sites and data where NES's would be intrusive
 - f. alerting "centre" scholars to research undertaken on the "periphery"

¹⁴ Fascinating comment in that Lee & Swales (2006) discussed the same phenomenon, but did not tie in peripheral participation theory or activity theory.

small and individual planning guided each student in areas of his/her own weakness¹⁵. Lee and Swales documented how much work was required from the students in the study, but the final product seemed to satisfy everyone because each member in the study gained writing confidence. For students using their own corpora and placing it into Wordsmith, Lee and Swales concluded that it empowered the students, built confidence, and allowed for stylistic writing that was strictly individual and yet acceptable academic English and extended across disciplines¹⁶ (p. 71). Although judged extremely effective, the limited time constraints of postdocs working long hours in research labs leaves Lee and Swales methods unrealistic for adoption in the current study. Hence, the effectiveness of the current study design attempts to limit the amount of time required from the postdocs in order for them to become willing to participate in the present study.

2.5 Review of methodologies

In a review of the literature, there are very few published articles focusing on postdocs in the U. S. who are working in university research laboratories. In the absence of previous studies about how postdocs write grant proposals, a method that would adapt to the current study was used by Connor and Asenavage (1994), who used Faigley and Witte's (1981) Taxonomy of Revisions in order to catalogue revisions of student writing

¹⁵ Some of the principles of structured learning Lee discussed in his study were observed by this author in ICIC's Postdoc Program. Lee's honesty was apparent in that he admitted that the "planned" lesson was sometimes scrapped and they moved on in a different direction that met the needs of the study group. Noteworthy was his coining of JITM (just in time materials) (p. 62). It showed how researchers must think on their feet quickly and why they must listen to what the students need—not what the instructor planned.

¹⁶ Even for NS, a similar program could apply to the problem the biologists had trying to interact with the physicists in Blakeslee (2001).

in a social context. Although the current case study does not include the social dynamics of a classroom, the grant writing process does involve social dynamics as it pertains to writing to a specific audience of grant reviewers or referees. Based upon a review of the literature (Connor, 2000; Tardy, 2003; Lee and Swales, 2006), grant writing occupies a niche in the social construction of knowledge. Gieryn (1978), Bazerman (1984, 1988, 1985), Rymer (1988), and Mishler (1990) also discuss the importance of the social construction of texts wherein the preparation of a grant proposal for referee responses might well be considered as a social activity, e.g. writing for other readers, that contributes to the community of knowledge. However, the missing piece that has not been well studied is how international postdocs, as contributing members of that discourse community, prepare written grants and what processes are required in the acts of writing.

Building her research upon previous studies (e. g., Connor & Mauranen, 1999; Connor, et al., 1995) Connor (2000) effectively identified specific rhetorical moves found in U.S. grant proposals, some of which were not found in EU grants (Connor & Mauranen, 1999). Although these moves were linked to funded grants, unfunded grants were not studied. In her study, Connor included ethnographic data from recorded and transcribed interviews with the authors to determine if the identified moves corresponded with the conscious efforts of the authors. Through writer/researcher interaction, interpretative data were presented that indicated social interaction throughout the grant writing process allowed the proposal writers, all native speakers, to define and redefine their objectives and write grants to meet a successful funding criteria.

Connor's study identified variations in grant proposal requirements, the moves that are found in successful grants for the U.S., and why the authors chose the specific moves. Connor established a wider context for the grant genre and provided interview evidence that grant proposals represent a much wider, socially interactive genre system. She suggested that more research is needed for understanding the complex interactions of the genre system. Blakeslee (2001) and Tardy (2003) provided similar follow-up studies, and the current study attempts to add to what is known about how grant proposals are written by internationals in L2.

Tardy (2003) also studied the grant writing process and contributed not only to the social construction of knowledge, but provided specific methodologies, textual analysis, and ethnographic interviews that are relevant to the current study. Her research investigated the grant writing process as it reflected not only persuasive rhetoric, but as it became a genre system. Her case study sought to determine what genres and communities of practice interact to make up the genre system of grant-funding, what those roles might be, and what type of knowledge is required to participate in text genres as well as how writers use and develop that knowledge (p. 13). Although the subjects of her study were two native English speaking researchers who were successful in grant funding, her research techniques have direct application to this study. She used personal interviews and examined their texts, while documenting the two researchers' processes in the production of texts. Her data revealed the importance of the social context, how it contributed to the subject's knowledge, and how those requirements varied extensively among funding agencies.

In her study, Tardy (2003) cited Paré's (2000) study of interns who were social workers, whose written documents provided evidence for how knowledge was built within a selected community of writers. Paré suggested that the interns developed a genre set and she (Tardy) connected that "to activity theory, illustrating how writers acquire knowledge...by collaboration...[where] novices coparticipate with experts within an activity system that 'produces, reproduces, and applies the community's knowledge'" (p. 12). Thus, Tardy (2003) connects activity theory as an "umbrella concept that encompasses the theory of situated learning, which posits that learning and knowing occur through participation in activities" (p. 12). By making that theoretical connection, her work is pertinent to my study because she applied an epistemological approach using ethnographic and linguistic studies to explain the intertextual and interdiscursive nature of the grant genre. Since she noted that "writers' composing and interacting with the "other" throughout the grant writing process could be further investigated, it is the objective of this study to discover some of the processes required by internationals to produce successful grants. Because she identified a gap in the literature and collected data to demonstrate that the writers' strategies changed over time in the writing process, perhaps my study might identify what strategies are successful for internationals writing grants.

In another study, Connor and Mbaye (2004) posited that postdocs represent a large group for which little is known regarding their sociolinguistic acculturation in North American academic English. Their study identified language and communication as a common problem postdocs encountered. Connor and Mbaye also raised questions about the seeming absence of "postdoc training programs" (p. 287) to minimize the socio-

cultural demands placed upon postdocs working in U.S. university research labs. Data from Connor and Mbaye's study indicated that previous EFL/ESL training had not adequately prepared the postdocs for successful "socialization in the context of work" (p. 287).

Connor and Mbaye's study provided adequate evidence of a gap in the literature and they set out to discover how international postdocs acculturate into the research labs and cultural surroundings of the American universities. Connor and Mbaye agreed with previous authors that social development of language and communication is well established [e.g., Mishler (1990), Myers (1990), Bazerman (1984, 1988, & 1994) and Tardy (2003)]. Connor and Mbaye addressed the current apprenticeship program (p. 282) postdocs undergo and they questioned how the interactions occur 'between a supervisor and a postdoc, collaboration between the two in research ethics, and in ideologies' (p. 282). The questions raised are applicable to the current study as they noted, "competencies the postdoc requires in [a] lab have academic literacy ramifications which are highly socio-cultural" (p. 282).

One important finding from Connor and Mbaye's data is relevant to my case study because, as they aptly concluded,

language and communication rank high among the problems encountered by the respondents... This new finding, in relation to problems encountered by international postdocs, supports our assumption that language proficiency and communication skills are a potential source of problems in the context of the U.S. research lab. [They suggested] postdocs would benefit from explicit training in how to respond to the language, communication, and socio-cultural demands of their positions in U.S. universities and research labs [by] designing and implementing postdoc training programs that would minimize the impact of these specific problems... and incorporate conscientious attempts to achieve socialization in the context of work (p. 285 & 287).

Connor and Mbaye's study provides a basis for this case study because they not only identified a gap, but they revealed little is known about how grants are developed and written in L2 English. Their study provided specific methodologies, textual analysis, and collection of ethnographic data, which can be used in the current study. They also established the need for research exploring how the epistemological process establishes itself in a research lab for writing grants.

In a recent study, Li (2006) studied a computer science doctoral student whose first paper was written in Chinese and later translated/written in English for an international Computer Engineering (CE) conference. Li documented the process toward publication, difficulties encountered by a novice writer, and final success for publication. That process included the epistemological characteristics of the international CE community, the journal gatekeepers of China, the difficulties of writing outside one's L1, and negotiation of changes in the text to obtain publication. Besides the textual artifacts, Li used email correspondence with other members of the CE community, journal reviewers' comments, and personal interviews with the student. Her study provides strong support for the methodologies chosen for the current study.

Li developed a strong theoretical basis for her study and performed a review of the literature that focused on substantiating epistemological development of the student writer. She provided samples of the student's work to illustrate that development as the student learned how to match the required genre of CE as it was codified in the CE literature; however, Li did not document how much mentoring influence was Li's in her student's work. Other authors (e. g., Myers, 1990; Bazerman, 1988; Blakeslee, 2001; Gieryn, 1978; and Mishler, 1990) have indicated that social interaction within discourse

communities is an ongoing process as language within that community continues to evolve. Other members of that community read each other's work and provide meaningful feedback at symposiums and conventions that reinforces the element of social interaction and maintains connection among its members. When Li, the researcher, became a part of the CE discourse community (for her study), she chose to become a mentor to her student as she made corrections and suggestions. What might appear troublesome to some investigators begs the question: Why Li did not view her direct involvement with the student as part of that social interaction and heuristically adjust her approach? Application to the current study requires careful consideration that the appropriate researcher/subject distance is maintained, all changes documented, and sources of change identified.

Chapter Three: The Study

3.1 Context of the research

Many studies using a thorough textual analysis apply contrastive rhetoric (Connor, 1994), corpus development (Lee & Swales, 2006), and linguistic textual analysis (Bazerman, 1988); however, the best theoretical framework to establish the current study, based on the lack of previous research, requires a grounded theory approach (Strauss & Corbin, 1990). Grounded theory is flexible, requires continuous observation and collection of data, and requires a recursive and on-going analysis as data are collected. If patterns in data are observed, a trial hypothesis is formed, tested, and if proven valid, provides the researcher with a new theory.

In order to meet the grounded theory criteria, I included written observational notes and collected ethnographic data from personal interviews with the subject. Because the current study found changes made to the original grant proposal, Faigley and Witte's (1981) taxonomy of revisions, as used by Connor and Asenavage (1994), have been applied in this study. Following the study design of Connor and Asenavage, revisions were tagged and quantified. Additionally, since the granting institution's requirements were very specific, I also analyzed the data to determine if all the requirements were met. Subsequent to the compilation of revisions and analysis of the grant requirements, an interview process with the subject was performed to determine why the changes were made; answers and observations were noted, as grounded theory requires.

3.2 Goals

This study addresses the following research questions:

1. How does an international grant proposal writer in a research laboratory meet the funding agency's guidelines and reviewers' comments?
2. What, if any, epistemological processes guide the writing process in the research laboratory from either peers or the Principle Investigator?
3. What were the sources influencing changes in the text?
4. Were textual changes initiated by the author or from others?

3.3 Situating the case study and collection of the data

Documents were collected and a complete textual analysis was performed on each one. The analysis captured changes between drafts and these were identified according to Faigley and Witte's (1981) Taxonomy of Revisions. An attempt to capture metacognitive and metadiscoursal data by personal interview with the grant's author was made after the analysis of the data was completed in order to gain a better understanding from the author's point of view, why she added, removed, or modified texts. The author's explanation for changes might provide an ethnographic explanation of her approach and understanding of the grant writing process. Specific interview questions were based on an analysis of revisions and the IRB protocols were followed at all times. After analyzing data from the textual artifacts and performing and analyzing the interview data, a discussion of the findings and possible implications follow.

The subject for this case study was a Principal Investigator and an International Postdoctoral researcher in a large, Midwest University Research Center. For purposes of anonymity, she will be referred to as Dr. Kye. Her first language, L1, is Mandarin, her second language, L2, is Japanese, and her third language, L3, is English. Recently, Dr. Kye wrote a grant proposal to fund research in her laboratory. The process involved two steps in the grant application: her first submission to the Department of Defense with the results from the reviewers and her second, revised grant proposal, which was funded.

The data Dr. Kye provided were on a CD ROM and it consisted of three grant proposals sent to the Department of Defense (DOD), herein referred to as Grant I, Grant II, Grant III, and the RSFG Reviewers' Comments for Grant I. The third and most important grant application was approved by the DOD. Also provided on the CD ROM was a personal Biosketch of Dr. Kye; however, for purposes of protecting identity, it has been removed from this study. Although it was mentioned by the RSFG Reviewers, it has no bearing on the outcome of the grants being studied here.

3.4 Analysis and tabulation of the data

In order to assess, identify, and accurately tag all changes, Microsoft Word 2007 was used to compare Grant I to Grant II and Grant I to Grant III. The changes from Grant I and II were then copied one paragraph at a time and pasted into Appendix A in a box on the left hand column. The changes from Grant I and III were also copied and pasted into Appendix B, into a box on the left column one paragraph per box. In the right column in both Appendices, each box analyzes and categorizes the revisions based on the

Taxonomy of Revisions proposed by Faigley and Witte (1981) (p. 403). In my study, it seemed appropriate to replicate the usage of the Taxonomy by Connor and Asenavage (1994) in their study of student writings.

Faigley and Witte (1981) suggest two primary levels of changes or revisions that occur in a text, those “that affect the meaning of the text and those that do not” (p. 401). Their common objective was to develop a simple taxonomy that could be replicated by other readers of the same text. In order to accomplish that objective, Faigley and Witte developed a system to “sort the changes which affect meaning from those which leave meaning intact” (pp. 401-402). Consequently, they developed a Taxonomy of Revisions “based on *whether new information is brought to the text or whether old information is removed in such a way that it cannot be recovered through drawing inferences*” (p. 402). From that working definition, they defined the left branch of the taxonomy as “*Surface Changes,*” while the right branch represented “*Meaning Changes,*” which involves the “adding of new content or the deletion of existing content” (p. 402).

Within the two branches of the taxonomy, each revision is divided into two subsections where the Surface Changes split into “*Formal Changes and Meaning-Preserving Changes.*” Within the Formal Changes, Faigley and Witte (1981) define copyediting such as “*spelling, tense, number, and modality; abbreviations, punctuation, and format*” (p. 402); none of those significantly change the meaning of the text. In my study, the data revealed many of these surface changes were made between revisions of each grant version. Although *Meaning-Preserving Changes* were found in the data, they were very few in number and consisted of “changes that paraphrase the concepts in the text but do

not alter them” or where sentences were combined as Faigley and Witte (1981) defined the *Meaning-Preserving Changes*.

Although the left fork of the taxonomy identifies the surface changes, my data contained significant *Text-Base Changes* under the right fork of the taxonomy. That branch is divided into two sections as well. On the left side are *Microstructure Changes*, while on the right side are *Macrostructure Changes*. The data for my study of three grant proposals provided many instances of *Macrostructure Changes*, which Faigley and Witte define as altering the summary of a text because it comprises a major revision (p. 404). “In contrast, *Microstructure Changes* [are] meaning change[s] that [do] not affect a summary of the text” (p.405). They further state, “Meaning Changes affect the concepts in a text” (p. 404) both at the micro and macro levels. These types of *Macrostructure Changes* were reflected clearly in the data as the focus and direction of the grant process changed and a new grant, requiring a very different approach in research methodology, was written using very little information from the first two grants.

Besides just classifying revisions, the data provide an interesting evolution from the first proposal to the second proposal. A careful analysis of the Referee’s Comments provides an extrinsic explanation for the exhaustive compilation of revisions between Grant I and II. However, Grant III was hastily revised from the first two grants because the grant writer was informed of a slightly different, but new category for grant proposals. Consequently, she then resubmitted the revised Grant III to the Department of Defense, where it was subsequently approved (personal interview, August 15, 2007). At first glance, it did not appear that anything remained from Grant I. However, after a through analysis of Grant III, and by using Microsoft Word 2007’s compare documents,

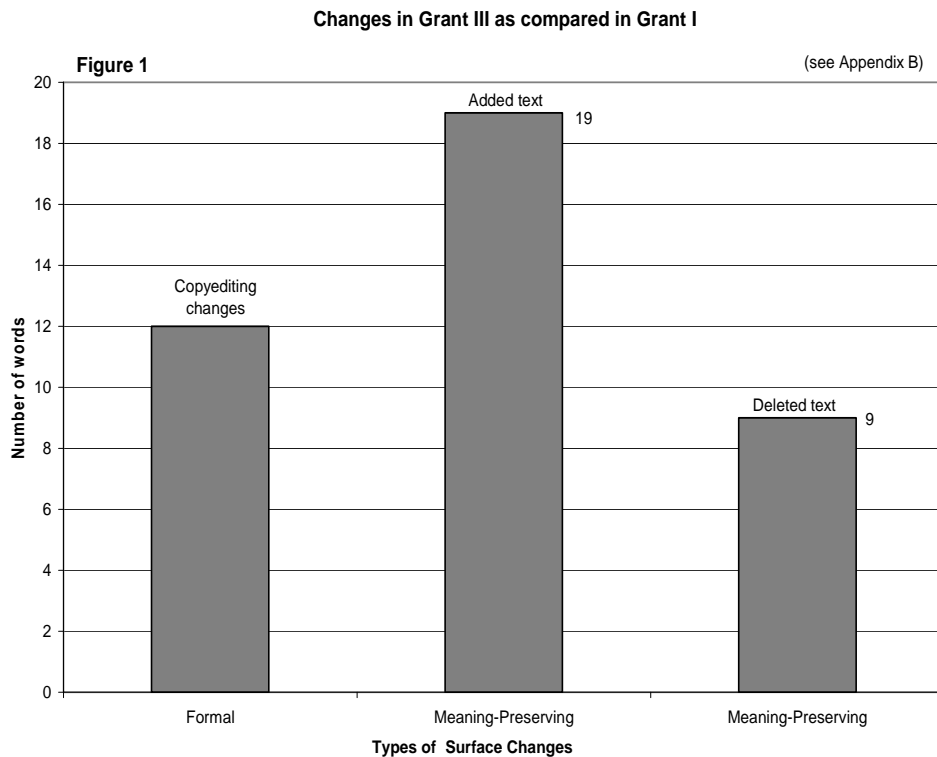
the comparison revealed that nearly two pages, approximately 858 words, of Grant I survived the revision, even though the focus of the study changed significantly (personal interview, August 15, 2007).

3.5 Data analysis and discussion

Although the initial objective of this study was to obtain grant proposal writing samples that demonstrated a full evolutionary cycle from the very beginning of the process to the finished product, the data provided for this study did not quite fulfill those expectations. Instead, the subject of this study provided three grant proposals that were finished products before submission to the granting agency. Earlier versions that might have contained evidence of second language interference were not available for collection. However, the data from the first two grants do provide evidence for how a grant proposal was revised based upon the Referee's Comments, which were provided as part of the data. During a brief interview with the grant's author, it was explained that at the time of Grant II submission, she was contacted by one of the Referees who mentioned that the Department of Defense (DOD) was looking for a similar study, although it needed to have a completely different laboratory approach (personal interview, August 15, 2007). Consequently, there was a rushed revision and Grant III became the grant that won acceptance and was funded (personal interview, August 15, 2007).

The data were thoroughly analyzed and versions of each of the three grants were compared to each other using MS Word 2007 software's compare documents creating Appendix A and B. At first, Grant III did not appear to contain any text from Grant I;

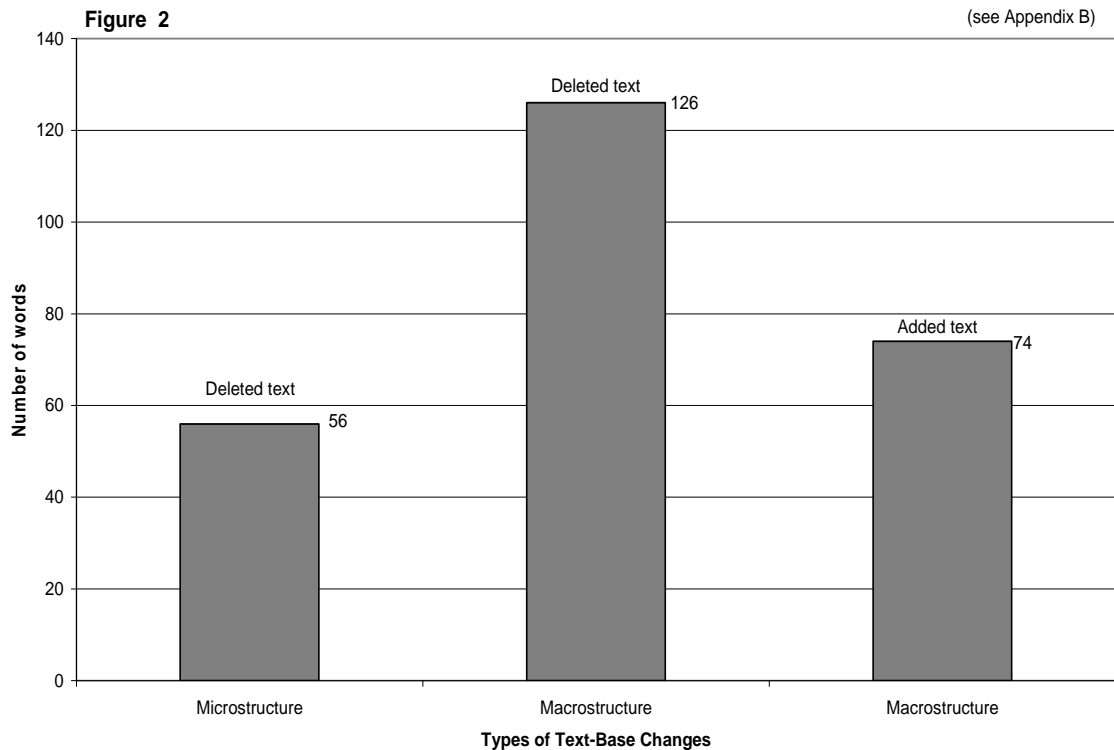
however, by comparing documents, one nearly intact section remained in Grant III. In Figure 1, the Taxonomy of Revisions shows that there were 12 copyedits, which occurred in five places within the surviving text from Grant I.



The meaning preserving changes included 19 words, but amounted to only four locations with the text. Deleted text only occurred in one spot amounting to nine words. Analyzing the changes, they appeared to remain consistent with the requirements for the new focus of Grant III; thus, section changes and table and figure numbers were the primary copyedits performed. Another change was that the writing style changed to reflect APA style by inclusion of the author and year instead of numbers, formerly associated with MLA style.

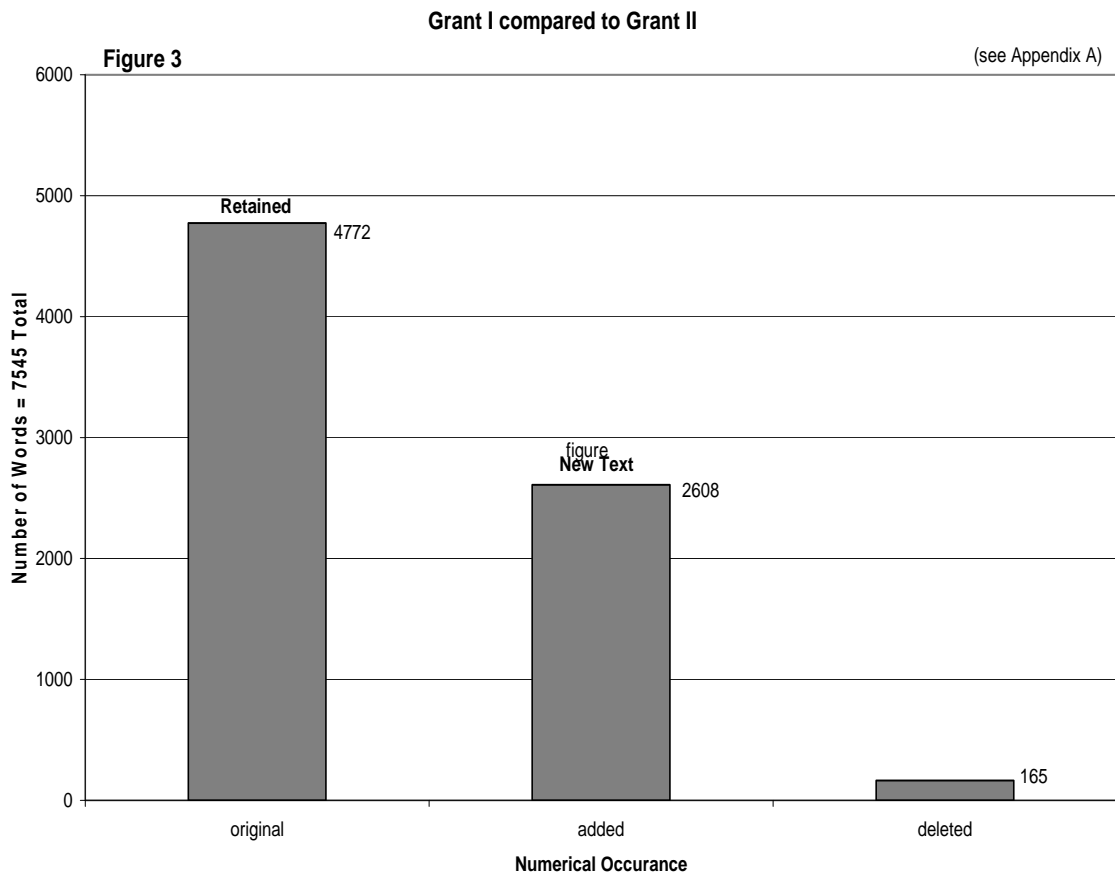
In Figure 2, the text-based changes are reflected as two types; added text (74 words) and deleted text (182 words). Although that might seem like a high number, only three macrostructure level changes were made; meanwhile, only one microstructure level change was made. All the revisions appeared consistent with the new direction of Grant III and thus, text deleted from Grant I did not fit the new study design. After a close analysis, the added text appears to connect previous text with the information provided in tables and figures as it pertains to the new focus of Grant III. Since the Grant III was

Changes in Grant III as compared in Grant I



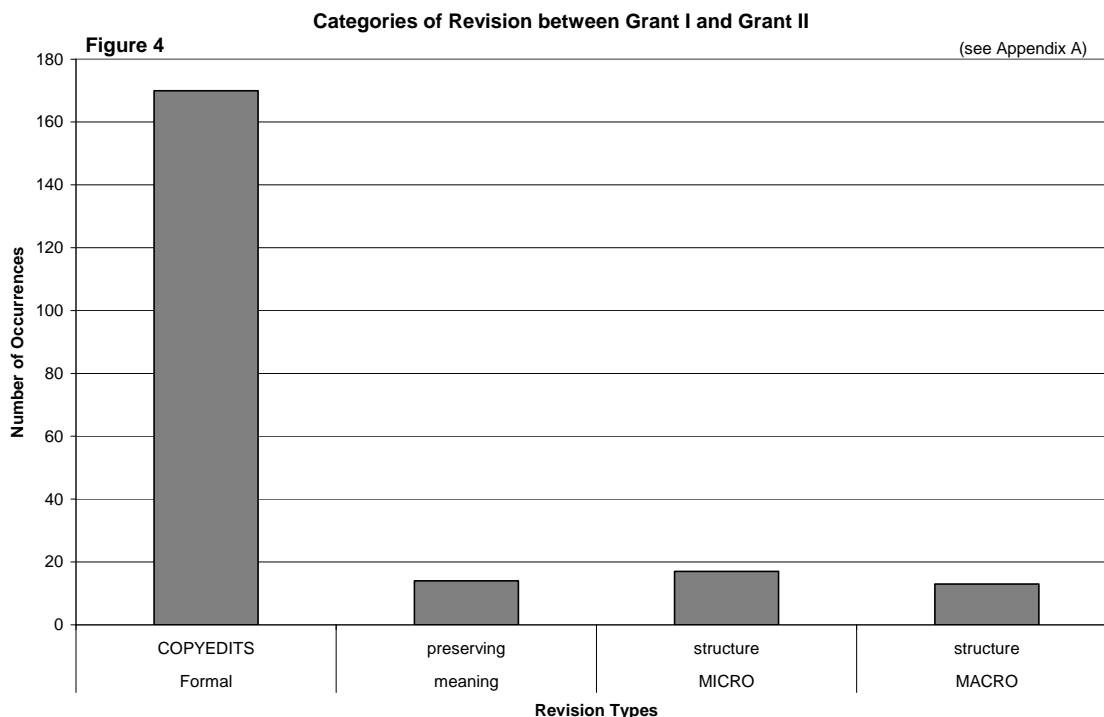
approved, it could be assumed that these changes were adequate for the overall success of the grant. It could also be concluded that the retention of this one section from Grant I, and modified for Grant III, provides the primary research rationale for the entire study: The collection and testing of Osteoclasts from femurs of rats.

Although Grant III was the winning grant, its unique redesign notwithstanding, much can be learned from looking at differences between Grant I and II, since they reflect the opinions and values of the Referees whose job it is to accept or deny grant approval. In Figure 3, the total number of words that appeared in Grant I amounted to 4772.



Nevertheless, to meet the new suggestions from the Referees, 2308 words were added to satisfy that request. Only 165 words were deleted from Grant I in one block deletion defined as a macrostructure change. Additionally, it is worth noting that although track changes were used extensively in all three copies provided for my data, sources for those changes remain anonymous, in that no one's computer can be identified as to who was responsible for the changes.

Appearing in Figure 4 are a significant number of copyedits, most of which reflect



the Referee's comments because they wanted APA style references. They also expressed that OCL be spelled out as Osteoclast. There were also other abbreviations, which were spelled out as well; most of copyedits are relegated to that type of change. There were only nine instances of meaning preserving changes and they were usually tense related or marked changes of measurements for the study's design. Eight microstructure changes occurred and that reflected the Referee's comments for change and inclusion of other studies related to this study. Thirteen macrostructure changes were made and all of those were block insertions of new material answering with information pertinent to the Referee's request for more information related to other studies.

3.6 Qualitative data and discussion of further data via the interview

Since both of the grant applications were final drafts, the data were incomplete as originally envisioned for purposes of this study. Thus, in the absence of the expected data, the current data provide an opportunity to assess uniquely different objectives. Unfortunately, the initial objectives were thwarted in an effort to quantify linguistic errors that might have been found by the writer as her text evolved between drafts. Had there been differences between drafts, then the next step would have been to ask the writer how she determined those corrections were needed. Instead, a new set of questions can be posed, answered, and provide a framework of acquisition for future studies to find the original data that this study sought.

Although some qualitative assessments could be made between the first and last drafts, which were based upon the first interview with the subject (personal interview, August 15, 2007), the data failed to meet the initial expectations of this study. However, the data provide an opportunity to observe the social interaction and construction of knowledge between Dr. Kye and the RSFG Reviewer's comments. After analyzing Grant I and Grant II, as well as analyzing the RSFG Reviewer's comments, the analysis reveals Dr. Kye's changes were specific to the Reviewers' requests for clarification. During our initial interview (personal interview, August 15, 2007), Dr. Kye mentioned that she had made changes related specifically to reviewer comments. Although those suggestions might be noteworthy for a different or expanded case study, they are not the focus of this study. One of the Reviewers commented that the length of the grant proposal did not meet the specific space requirements; hence, Dr. Kye was required to summarize and delete in order to meet the format and still maintain comprehensibility. Another

observation relates to the specific meaning preserving changes noted in the writing style change to APA for the in-text citations; the change was in response to the Reviewers' comments. Previously, in Grant I, Dr. Kye used a different style for the in-text references.

3.7 The Questionnaire

A written questionnaire (see Appendix C) was emailed to Dr. Kye (personal communication, June 13, 2008). Her response was helpful in confirming my interpretation of the data and verified the suppositions made after the thorough analysis. She expressed the need for other researchers to practice grant writing extensively because is it a very difficult genre in which to write successfully. She stated that some of the linguistic and grammatical problems are not quite as difficult for her because she relied on the word processor help with spell check and formal English grammar. She indicated that the one section that remained nearly complete in all three versions of the grants was copied from a previous research paper she had written. In response to a question about her preference in writing a grant proposal or a research paper, she heartily preferred writing research papers because they are less stressful to her. What the questionnaire revealed about the data collected was that the word processor was the key in providing correct grammar and spelling and voided the need for multiple revisions on her part.

Chapter Four: Conclusion

4.1 Summary of the study

Many published studies focus on grants; some determine linguistic features that define specific moves required for successful grants, while others have clearly defined the social construction of knowledge and appropriate genre of each scientific community. However, none focuses on the actual writing process from inception of the first draft to the finished proposal. After a thorough review of the literature, a gap exists in not only understanding how international postdocs prepare a written grant proposal, but also in identifying what revision and editing steps might be taken as the grant is written. The initial goal of the present study was to find a subject's written grant that would yield data from the inception of the process to the final, approved grant. When the data were obtained during an initial meeting with Dr. Kye, an informal personal interview was also held to obtain ethnographic information. Following that meeting, the data were subjected to a rigorous analysis. As previously noted in the review of the literature, evidence is contained in the reviewers' comments that are a section of the data, which cannot be included in the Appendix because the Institutional Review Board (IRB) protects personal information and identification. The reviewer's comments validate previous studies (e.g., Gieryn, 1978; Latour, 1987; Bazerman, 1984, 1988; Rymer, 1988; Myers, 1990; and Blakeslee, 2001) which discuss the social construction of scientific writing and the social influence among members of specific research communities.

Additionally, the value of ethnographic data also provide evidence of the internationalization of English (e.g., Blakeslee, 2001; Adolphs, 2005; Flowerdew, 2005;

Belcher, 2006; and Lee & Swales, 2006) as represented by Dr. Kye's third language, English, and her decision to utilize selected sections of her previously published journal article in the grant proposal. Ethnographic information obtained from the initial interview (personal interview, August 15, 2007) confirmed the difficulties she found in publishing an article in English as well as writing in L3 English for the grant proposal.

In order to categorize the data and to find evidence for a community of influence as well as L3 writing difficulties, a systematic, methodological approach involved identifying the three grant proposals and labeling them Grant I, Grant II, Grant III, and studying reviewers' comments. Additional to the initial interview and following the thorough analysis, a questionnaire was submitted by email to Dr. Kye in order to obtain specific ethnographic data that might strengthen and confirm the findings.

4.2 Major findings

As the Principle Investigator (PI), Dr. Kye is responsible for obtaining grants to fund her research laboratory. During the first informal interview, as a new PI, she discussed how her current research took a different approach from her previous research. She stated that English is her third language (L3), Japanese is her second language (L2), and Mandarin is her first language (L1). In both the interview and the questionnaire, she indicated that being tri-lingual was beneficial, but that it did not make writing grants any easier for her in L3 English. Although the data provided much insight into the social process of writing and the influences within her scientific community, the data failed to reveal a systematic development containing original drafts. Thus, the goal of this study to

find consecutive drafts was thwarted by computer software and its capacity to correct errors systematically as she typed.

During the collection of the data and in the informal interview (personal interview, August 15, 2007), she shared some of the details explaining how her third grant became funded. That process confirms the findings of other authors (e. g., Myers, 1990; Bazerman, 1988; Blakeslee, 2001; Gieryn, 1978; and Mishler, 1990), who indicate that social interaction within discourse communities is an ongoing process as language within that community continues to evolve. Other members of that community read each other's work and provide meaningful feedback at symposiums and conventions that reinforces the element of social interaction and maintains connection among its members. It was at a symposium where Dr. Kye met one of the DOD reviewers of her first grant. As she related during the initial personal interview, he suggested a different approach for Dr. Kye to take with her grant proposal. He suggested that her research was important and suggested revisions so that it could qualify for a specific niche the DOD wanted. Additionally, he told her about a new PI funding category and that she should apply under that section. After the symposium, she returned to her laboratory and completely revised the third grant to meet those new requirements. That change is documented in Appendix B and Grant III was funded. Thus, social interaction and networking can be strongly linked to the success of her grant proposal.

Another finding relates to Rymer's (1988) suggestion that the preparation of the grant proposal might redefine the research. In a sense, the comments from the referees did in fact provide a redefined, revised Grant II. Likewise, the meeting at the symposium connects the complete revision and change in the research question for Grant III.

Although Rymer was taking her conclusions in a slightly different direction, the research she observed by the two scientists was developed by sitting down and writing, by defining their goals, and by changing them as they progressed. Based on the data for my study, I think it entails a combination of not only writing, but also, a social interaction with one's peers to define and redefine one's research objectives.

Completely unrelated to social interaction, Kern's (2006) study concentrates on the use of new technologies such as the Internet and computer influences; Kern suggested that technology might affect SLA theories as well as how language is produced. In the present study, answers on the questionnaire clearly indicated Dr. Kye used the tools of the word processor to identify and check both spelling and grammar. Therefore, Kern's observation was verified because Dr. Kye did not have a series of rough drafts; instead, as Kern noted, software can affect the outcomes of L2 or L3 language production. In the questionnaire, Dr. Kye indicated she made immediate changes (see Appendix C, question 4), thus, the software eliminated L2 or L3 errors long before the final grant was even printed. What is more disappointing to the researcher in the collection of data is that when files are reopened, those files are saved over, thus eliminating any systematic collection of successive drafts. Although Dr. Kye said, in her initial interview (personal interview, August 15, 2007), that she was accustomed to using software as an aide to her writing, she stated on the questionnaire that English grammar was difficult for her to master for both research papers and grant proposals.

Another comment worth noting was Dr. Kye's advice to other international postdocs who are writing grant proposals; she stated, "They need to have lots of practice and read more" (see Appendix C). She also indicated she prefers writing research articles

rather than writing grant proposals. The reason that question arose is that in all three grants, there was one contiguous section that never changed in content. I suspected it was copied from a previous research article; therefore, I asked about that section. Indeed, it was the case; she needed to keep that article as a unit because it was the basis of her entire osteoclast research on tibial fractures, which provided the basis for future research (see Appendix B). Using Faigley and Witte's (1981) Taxonomy of Revisions, the only changes made to the research article were surface changes and the loss of a couple figures and charts. Observing the research article, I asked her in the questionnaire if she preferred writing grants or research papers. Her response was clear, "I'd choose to write for a journal publication, because the grant proposal does need to look at a big picture and this is relatively hard for a beginner" (see Appendix C, question 9).

4.3 Limitations

In the present study, one of the limitations is availability of data beyond finished documents. With the advent of word processors and the related software that checks for and corrects spelling and grammar, there is no allowance for the researcher to see or document the errors as the writer progresses. Additionally, at the initial interview, Dr. Kye stated that the grant proposals had already passed the eyes of a medical grant reviewer working for the medical research community. Hence, any errors that might have survived the software were screened and edited out before becoming part of the data for this study. Although the large medical center with many research laboratories might have

great research potential for a case study like this one, availability, access, and time constraints on the international postdocs extremely limit the subject pool.

4.4 Implications

Perhaps one of the most interesting implications for pedagogical application arising from this study was Dr. Kye's response to the questionnaire for suggestions to other postdocs, "start to practice writing earlier and more" (see Appendix C, question 8). Although the response to a different question was related to her preference for writing for journal publications, it is noteworthy that current SLA theory strongly encourages using authentic and relevant materials and the appropriate tools. L2 instructors and L2 learners, in order to engage all those advantages, need to practice authentic grant writing and include the use of computer software tools as aids in the writing process, as previously noted by Kern (2006). Since these "tools" are available, ESP instruction can encourage their use; additionally, it would allow for less attention to grammar and provide more productive time to implement Dr. Kye's suggestion, "because the grant proposal does need to look at a big picture and this is relatively hard for a beginner" (see Appendix C, question 9). Therefore, L2 instructors have a major tool to help them teach writing skills that master most of the spelling and grammar issues by using appropriate computer software. L2 instructors can also focus pedagogical units towards helping L2 learners view a "big picture." Such instruction predicated the L2 instructor have some, albeit limited, content knowledge to convey successfully and specifically to postdoc L2

learners, the appropriate big picture concepts; hence, the need for ESP and a relatively firm grasp of the content area.

L2 instructors should also consider pedagogical adjustment to grant writers' needs in effectively summarizing and cutting materials, such as research articles, to fit a specific space. Dr. Kye's comment about finding it difficult to make her research article fit the limited space, (see Appendix C, question 10) is indeed worthy of consideration if L2 instructors prepare internationals to write grants, but fail to teach summarization skills that still maintain the key points. If possible, using the L2 learner's own published research articles is the best possible choice for teaching the summarization process since one's own work is most difficult to edit for fixed space, as Dr. Kye agreed.

Another issue that the present study noted is the need for L2 instructors to teach the importance of networking. The initial interview (personal interview, August 15, 2007) confirmed this key element in Dr. Kye's successful, third attempt. Had it not been for her networking at previous conventions, the opportunity to rewrite her Grant II to fit the new requirements would not likely have occurred. Utilization of conventions, seminars, professional group meetings, and email contact are critical in keeping lines of communication open.

A final and important point is Dr. Kye's comment, "read more" (see Appendix C, question 3), that she suggested for novice grant writers. That has definite pedagogical implications for L2 instructors and gives L2 learners a first-hand suggestion to read in the journal publications directed at their specific discipline. For the instructors, that requires some degree of content knowledge in order to design ESP learning modules that include authentic and relevant materials that would satisfy current SLA theory. This author's

observations validate Dr. Kye's comment, even for North American native speakers who are unacquainted with the medical and academic genre: read more in journals of one's specific scientific discipline.

4.5 Concluding thoughts

Grant writing is not easy for native speakers of English, let alone internationals who are writing in their L2. Although computer software helps eliminate some grammar and spelling problems, effectively grasping the big picture and understanding the application process are frequently challenging for all grant writers. The current study has potential teaching and learning implications for L2 instructors and L2 learners alike. Extensive reading and significant practice writing for the grant genre, specific to a scientific discipline, are important objectives in any pedagogic endeavor. L2 instructors of ESP can use a comprehensive needs analysis to assess and help L2 learners become successful by carefully choosing appropriate teaching strategies to focus on what the "big picture" is for each student's grant proposal. Although content knowledge on the part of the instructors is not absolute, it is helpful to have some understanding of the specific discipline of each of the L2 students.

Lastly, the skills of summarization and editing to fit a limited space, which are required in most grant applications, are skills best performed with practice. Even though native English speakers sometimes have difficulty summarizing, L2 learners must acquire that skill in order to be successful; L2 instructors can effectively reinforce those skills by using research papers the students have previously written and published. Besides

summarization skills, learning to network with peers within the specific scientific discipline also needs to be emphasized. Networking can be taught as another form of communication that requires cultural understanding within the context of the specific scientific discipline.

Since this study was limited to final grant applications, perhaps other researchers could replicate the goals of this study by obtaining, in advance, permission from international postdocs to save each of the individual steps of the writing process and avoid saved-over files, as well as files reviewed by writing specialists to remove errors. I hope this study opens the door to further studies that might provide a better window of understanding in the systematic writing process of a grant proposal.

Appendix A

This table contains the text of the second grant proposal, Grant II, February 2007. It was compared to the original grant proposal, Grant I, April 2006. Also included is the abstract for Grant II.

Note: Pages 1, and 3-8 have been deleted from the first grant proposal to comply with my IRB for this case study. Grant I was the only one that contained personal and budget information; therefore, only the texts of the two grants are being compared against each other.

| <p style="text-align: center;"><u>Legend</u></p> <p><i>Italics</i> indicate text surviving from the original grant proposal April 2006. Highlighted text denotes text or numbers added to the original proposal. Strikeout text denotes text deleted from the original grant proposal prior to February 2007.</p> | <p style="text-align: center;"><u>Theoretical rationale</u></p> <p>In this column, Faigley and Witte's (1981) (p. 403) Taxonomy of Revision Changes is used to categorize revisions.</p> |
|---|--|
| <p><i>Background.</i></p> <p>NF1 patients have a high incidence of skeletal abnormalities. <i>Neurofibromatosis type 1 (NF1) is a common, autosomal-dominant disorder caused by mutations in the NF1 tumor suppressor gene. Individuals with NF1 have a high incidence of both malignant as well as non-malignant complications.</i> Many laboratories are pursuing concentrated efforts to understand the pathogenesis of the peripheral and central nervous system tumors that affect a wide range of NF1 patients {Zhu, 2002 #11; Wallace, 1990 #373; Wallace, 2001 #450; Atit, 2000 #61; Atit, 1999 #85; Rutkowski, 2000 #322; Bajenaru, 2003 #10; Ingram, 2001 #7; Ingram, 2000 #9; Yang, 2003 #4; Johannessen, 2005 #59; Cichowski, 2001 #129}. However, less effort to date has been focused on understanding the molecular mechanisms underlying the pathogenesis of many of the non-malignant manifestations of NF1, particularly the skeletal manifestations that cumulatively affect up to 50% of all NF1 patients {Crawford, 1986 #42; Crawford, 1989 #935; Marques, 1951 #1018; Sbihi, 1980 #1017; Kuorilehto, 2006 #1019; Kuorilehto, 2004 #1; Kuorilehto, 2005 #12}.</p> | <p><u>Text-based Macrostructure Changes:</u> The first retained sentence with one meaning preserving change describes the primary thesis of both proposals. However, based on reviewer's comments, the added text reflects the requirement for more information about previous research as it intends to extend findings of this study to answer questions and build on previous studies.</p> |

Preliminary data

Nfl^{+/-} mice have increased osteoclast progenitors. Osteoclasts are tissue-specific, differentiated, monocyte/macrophage progeny, which have bone resorptive activity. In a preliminary study, we quantitated the number of macrophage and osteoclast progenitors per femur in *Nfl*^{+/-} and WT mice *in vivo* by establishing clonogenic assays that promote the growth of monocyte/macrophage progenitors (colony forming unit-macrophage CFU-M) and osteoclast (TRAP+ CFU-M) progenitors. Following culture in semisolid media, we scored the number of osteoclast and macrophage progenitor colonies per femur. Osteoclast progenitors were identified by staining the colonies with tartate resistant acid phosphatase (TRAP), which stain colonies as dark red (Figure 1a, right panel), while macrophage progenitors lacking TRAP activity appear yellow (Figure 1a, left panel). In five independent experiments, we show that *Nfl*^{+/-} mice have significantly higher numbers of macrophage progenitors (Figure 1b) and osteoclast progenitors (Figure 1c) per femur as compared to WT mice. Thus, haploinsufficiency of *Nfl* results in an increase in progenitors that have the potential to mature into fully differentiated osteoclasts.

Text-based Microstructure Changes:

In this sample, some of the original grant is adequate for older data; however, newer studies have changed the amount and importance of recent experiments. Those have been added to the text to increase the importance of identifying haploinsufficiency of *Nfl* results within the osteoclasts. This was a connection marked by the reviewers as a deficiency of the first grant proposal.

Figure 1 a.

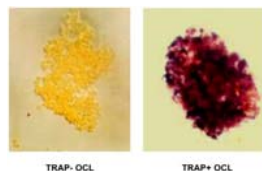


Figure 1b.

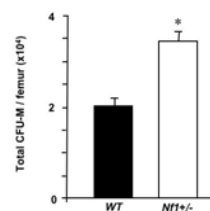


Figure 1c.

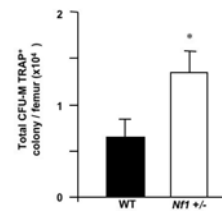
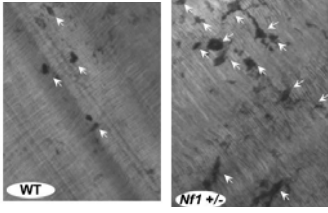
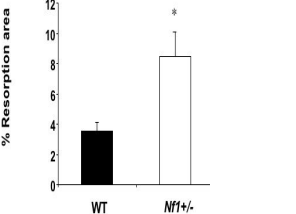
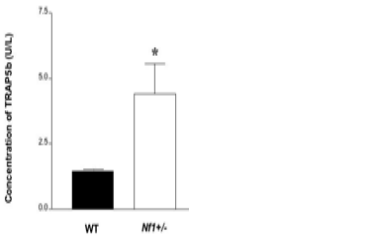


Figure 1 (a-c). *Nfl*^{+/-} mice have increased osteoclast progenitors and osteoclasts *in vivo*. Clonogenic assays in methylcellulose culture were established to analyze the progenitor of OCL, CFU-M (a). *Nfl*^{+/-} mice have increased total CFU-M / femur (b) and increased TRAP positive CFU-M / femur (c). (*P<0.01).

Surface Meaning Preserving Changes:

Adding text helps to explain Figures 1a-c. One Formal Change for copyediting is noted at the bottom in order to identify the proper charge.

| | |
|---|---|
| <p><i>Nf1</i> +/- mice have increased multinucleated osteoclasts in vivo. Given the increase in osteoclast progenitors in <i>Nf1</i> +/- mice, we next compared the number of mature osteoclasts in <i>Nf1</i> +/- mice <i>in vivo</i>. The femurs of 7-8 week old syngeneic <i>Nf1</i> +/- and WT mice were decalcified, and histological sections from the distal metaphysis were stained for the osteoclast enzyme, TRAP. Strikingly, there is a marked increase in the number of multinucleated osteoclasts per unit trabecular surface (Figure 2 a), and in the size of individual osteoclasts among <i>Nf1</i> +/- mice (Figure 2 b).</p> | <p><u>Text-Base Microstructure Changes:</u> The older data was correct, but necessitated adding more information about the potential benefits of the study as requested by the reviewers.</p> |
| <p><i>Nf1</i> +/- osteoclasts have increased capability to resorb bone in vitro and in vivo. The high incidence of lower bone mineral density, osteopenia, and osteoporosis in <i>NF1</i> patients {Illes, 2001 #53; Kuorilehto, 2005 #12; Lammert, 2005 #13} strongly suggest that an overactive bone resorptive process exists <i>in vivo</i>. Given that osteoclasts form a specialized cell-extracellular matrix to initiate degradation of bone matrix by secreting proteinases {Boyle, 2003 #24}, we hypothesize that <i>NF1</i> osteoclasts have increased osteoclast resorption activity. This process can be assessed <i>in vitro</i> by culturing osteoclasts on bone slices (dentin) and examining the number and area of bone “pits” that are resorbed. Our preliminary studies from four independent experiments indicate that the mean area of resorption by <i>Nf1</i> +/- osteoclasts in all experiments was significantly greater than pits generated by WT controls (Figure 3a, b). We next tested whether <i>Nf1</i> +/- osteoclasts have increased activity <i>in vivo</i> by measuring serum TRAP5b activity, an established measure of osteoclast lytic activity. The results from five individual age- and sex-matched mice indicate that serum from <i>Nf1</i> +/- mice has a significantly higher concentration of TRAP5b activity as compared to that in WT mice (Figure 3c). Collectively, these functional data demonstrate that <i>Nf1</i> +/- mice osteoclasts have an increase in lytic activity both <i>in vitro</i> and <i>in vivo</i>.</p> | <p><u>Text-Base Microstructure Changes:</u> Noteworthy are changes reflecting APA style in-text citations now found in the second revision. The older data was correct, but necessitated adding more information about the potential benefits of the study as requested by the reviewers.</p> |

| <p>Figure 3a.</p>  | <p>Figure 3b.</p>  <table border="1"> <thead> <tr> <th>Genotype</th> <th>% Resorption area</th> </tr> </thead> <tbody> <tr> <td>WT</td> <td>~3.5</td> </tr> <tr> <td>Nf1^{+/-}</td> <td>~8.5*</td> </tr> </tbody> </table> | Genotype | % Resorption area | WT | ~3.5 | Nf1 ^{+/-} | ~8.5* | <p>Figure 3c.</p>  <table border="1"> <thead> <tr> <th>Genotype</th> <th>Concentration of TRAP5b (U/L)</th> </tr> </thead> <tbody> <tr> <td>WT</td> <td>~1.5</td> </tr> <tr> <td>Nf1^{+/-}</td> <td>~4.5*</td> </tr> </tbody> </table> | Genotype | Concentration of TRAP5b (U/L) | WT | ~1.5 | Nf1 ^{+/-} | ~4.5* | <p><u>Surface Meaning Preserving Changes:</u> Adding text helps to explain Figures 3a-c. An answer to reviewers' comments further defines the process.</p> |
|--|---|----------|--|----|------|--------------------|-------|---|----------|-------------------------------|----|------|--------------------|-------|--|
| Genotype | % Resorption area | | | | | | | | | | | | | | |
| WT | ~3.5 | | | | | | | | | | | | | | |
| Nf1 ^{+/-} | ~8.5* | | | | | | | | | | | | | | |
| Genotype | Concentration of TRAP5b (U/L) | | | | | | | | | | | | | | |
| WT | ~1.5 | | | | | | | | | | | | | | |
| Nf1 ^{+/-} | ~4.5* | | | | | | | | | | | | | | |
| <p>Figure 3 (a-c). <i>Nf1</i>^{+/-} osteoclasts have increased bone resorb capability. Representative photomicroscopy of a bone section following completion of a pit assay is shown (Figure 3 a). The area of absorption was calculated using software that measures defined areas at sections as well as the area of a pit so that the % of resorption per unit area can be calculated (Figure 3 b). The concentration of TRAP5b in serum was shown in Figure 3 c. (*<i>P</i><0.0).</p> | | | <p><u>Text-Base Microstructure Changes:</u> The older data was correct, but necessitated adding expanded information explaining what happens in the osteoclasts as requested by the reviewers.</p> | | | | | | | | | | | | |
| <p><i>Nf1</i>^{+/-} osteoclasts have increased activation of Ras and PI3-K. M-CSF is a potent growth factor that promotes osteoclast differentiation by binding to its receptor (<i>c-fms</i>) and activating <i>p21^{ras}</i> {Guidez, 1998 #50}. Though heterozygosity of <i>Nf1</i> alters <i>p21^{ras}</i> activity in mast cells, it remains unclear whether heterozygous loss of <i>Nf1</i> is sufficient to induce an increase in <i>p21^{ras}</i> activity in other myeloid lineages. To investigate whether heterozygous loss of <i>Nf1</i> alters <i>p21^{ras}</i> activity in osteoclasts, osteoclasts from <i>Nf1</i>^{+/-} and WT mice were stimulated with M-CSF and assayed for changes in <i>p21^{ras}</i>-GTP levels with a GST-fusion of the <i>p21^{ras}</i> binding domain of Raf-1 kinase in an effector pull-down assay. In four independent experiments, <i>Nf1</i>^{+/-} osteoclasts had higher M-CSF-mediated <i>p21^{ras}</i>-GTP levels compared to WT cells. A representative experiment is shown in Figure 4a. Given that Ras is at the apex of a series of signal transduction cascades that control a range of cellular functions in osteoclasts, the genetic evidence indicates that activation of PI3-kinase is important for bone resorption by osteoclasts {Takeshita, 2002 #16}, we next compared Akt phosphorylation, a sensitive measure of PI3-K activity, in <i>Nf1</i>^{+/-} and WT osteoclasts. An increase in M-CSF mediated Akt phosphorylation was observed in <i>Nf1</i>^{+/-} osteoclasts (Figure 4b) as compared to WT controls.</p> | | | | | | | | | | | | | | | |

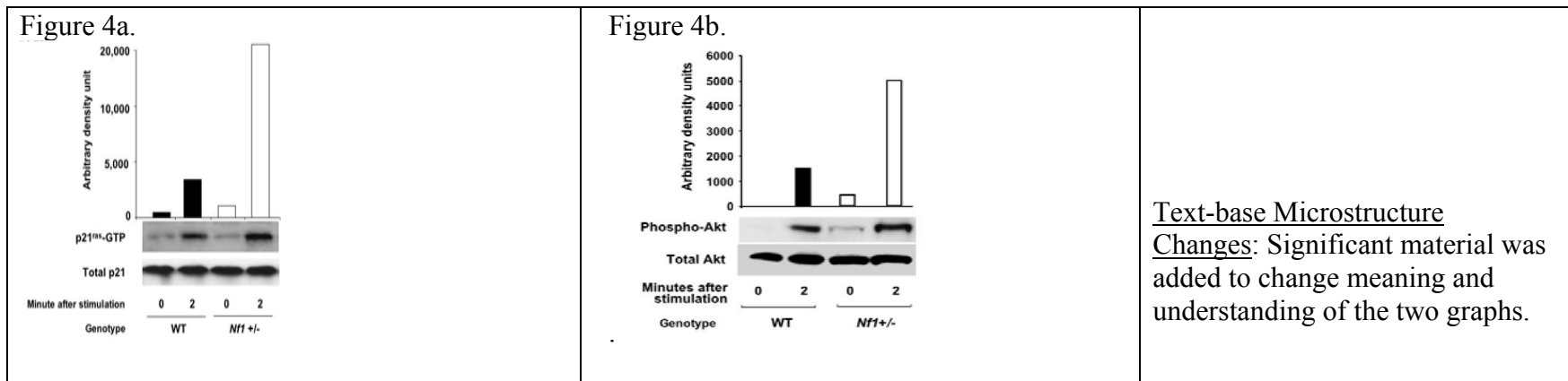
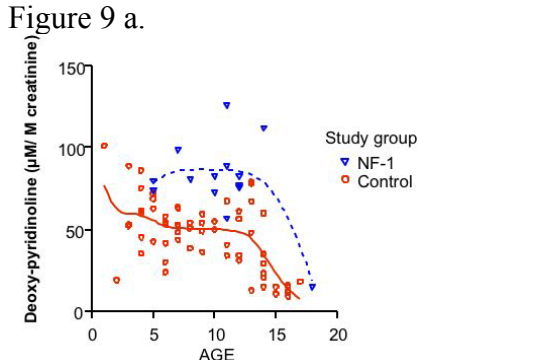
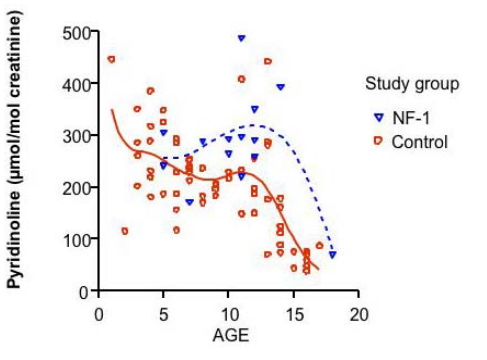


Figure 4 (a, b). *Nf1* +/- osteoclasts have hyperactivity of Ras and Akt. *Ras activity* in WT and *Nf1* +/- osteoclasts was measured at basal levels and 2 minutes following stimulation with M-CSF (Figure 4 a). *Akt phosphorylation* was measured at basal levels and at 2 minutes following stimulation with M-CSF (Figure 4 b).

NF1 patients have increased collagen degradation products in urine consistent with increased osteoclast activity: The urinary excretion of pyridinium cross-links (pyridinoline and deoxyypyridinoline), which are the cross-linked N-telopeptides of type I collagen {Rosen, 1994 #1051}, have been used as indicators of bone resorption. They are abundant in bone and cartilage but lacking in skin and soft tissue with deoxyypyridinoline located primarily in bone {Pasquali, 1997 #1052}. They are formed during collagen maturation and then excreted in the urine in free and peptide bound forms. In Dr. Stevenson's preliminary study, urinary pyridinium cross-link levels (pyridinoline and deoxyypyridinoline) from the first morning void for 2 consecutive days have been measured in 59 NF1 patients and compared to data from healthy age-matched controls. Statistical analysis on the first 14 patients using an analysis of variance showed statistically significant differences for pyridinoline and deoxyypyridinoline ($p < 0.001$) with an increase in values in NF1 individuals compared to controls (Figure 9 a, b). This study suggests that the increased bone resorption may be due to increased osteoclast activity in NF1 patients.

Text-based Macrostructure Changes: Other than the competed title, little of the original material remains in this paragraph and shows how extensive the grant had to be revised based on the reviewers' comments.

| | | |
|---|--|--|
| <p>Figure 9 a.</p>  | <p>Figure 9b.</p>  | <p>No changes were made to either the tables or the explanation.</p> |
| <p>Preliminary evidence that changes in <i>Nf1</i>+/- osteoclasts are conserved in human NF1 osteoclasts. Given known species-specific differences in the biology of the human and murine myeloid lineages {Okumura, 2003 #1053}, we next examined whether the alterations of osteoclast biological functions observed in murine <i>Nf1</i>+/- osteoclasts are conserved in NF1 patients. Peripheral mononuclear cells were stimulated with M-CSF and RANKL to differentiate blood monocytes into osteoclasts as previously described {Shinoda, 2003 #66}. Neurofibromin levels in osteoclasts from NF1 patients were approximately 50% of the level found in control individuals. A representative Western from 2 patients and 2 unaffected controls are shown (Figure 10a). Though the total peripheral white blood cell counts of the two groups were similar (data not shown), the number of osteoclasts that were formed from mononuclear cells of NF1 patients was significantly higher than that of unaffected control individuals (Figure 10b). In addition, NF1 osteoclasts formed more and bigger osteoclasts than WT cells (Figure 10c, upper panel and lower panel).</p> | | <p><u>Text-based Macrostructure</u> <u>Changes:</u> Based on newer studies the information was added here. In part, it also reflects the reviewers' comments that current data from the most recent studies be presented.</p> |

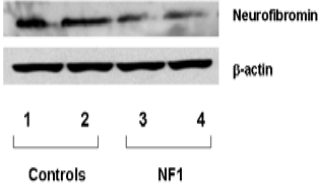
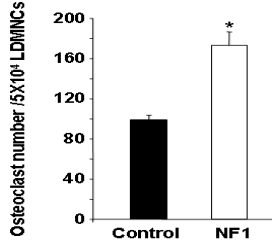
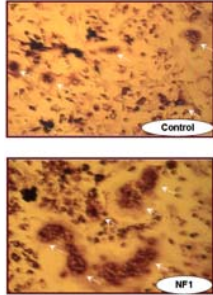
| <p>Figure 10 a</p>  | <p>Figure 10 b.</p>  <table border="1"> <thead> <tr> <th>Group</th> <th>Osteoclast number / 15X10⁴ LDMNCs</th> </tr> </thead> <tbody> <tr> <td>Control</td> <td>~100</td> </tr> <tr> <td>NF1</td> <td>~175*</td> </tr> </tbody> </table> | Group | Osteoclast number / 15X10 ⁴ LDMNCs | Control | ~100 | NF1 | ~175* | <p>Figure 10 c</p>  | <p><u>Text-based Macrostructure</u> <u>Changes:</u> Based on newer studies the information was added here. In part, it also reflects the reviewers' comments that current data from the most recent studies be presented.</p> |
|---|--|-------|---|---------|------|-----|-------|--|--|
| Group | Osteoclast number / 15X10 ⁴ LDMNCs | | | | | | | | |
| Control | ~100 | | | | | | | | |
| NF1 | ~175* | | | | | | | | |
| <p>Figure 10 a-c. Osteoclasts generated from peripheral blood mononuclear cells of NF1 patients have less level of neurofibromin (a), increased number of OCLs following stimulation with M-SCF and RANKL for 14 days (b). Representative photomicrographs of differentiated osteoclasts from healthy control are shown in Figure 10c, upper panel and Figure 10c, lower panel.</p> | | | <p><u>Text-based Macrostructure</u> <u>Changes:</u> The added information reflects the reviewers' comments that current data and a specific focus on osteoclasts be presented.</p> | | | | | | |
| <p>NF1 osteoclasts have increased Akt phosphorylation. Given that murine <i>Nf1</i> +/- osteoclasts have increased Akt phosphorylation, we next evaluated the Akt phosphorylation from human NF1 osteoclasts to see if there is a conservation of the biochemical activation between the two species. Our preliminary studies on two NF1 patients indicate that osteoclasts from these individuals have increased Akt phosphorylation following M-CSF stimulation as compared to the osteoclasts from two age and sex matched healthy controls (Figure 11). Addition of Ly294002, a Pan- PI3-K inhibitor, diminished Akt phosphorylation in both genotypes of osteoclasts from healthy controls and NF1 patients. In other studies discussed in detail in Appendix A, we found that addition of this inhibitor to osteoclasts from NF1 patients inhibited cytoskeletal functions including migration, adhesion, and pit formation. Studies proposed in Aim 1 of the application propose to use siRNAs to further validate this target.</p> | | | <p><u>Text-based Macrostructure</u> <u>Changes:</u> The added information reflects the reviewers' comments that current data and a specific focus on osteoclasts be presented.</p> | | | | | | |

Figure 11.

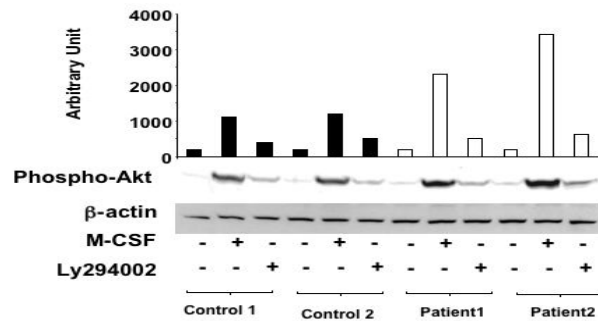


Figure 11.

Osteoclasts from NF1 patients have increased Akt phosphorylation. This Figure shows Akt phosphorylation of osteoclasts from two healthy controls and 2 NF1 patients following M-CSF stimulation. PI3-K inhibitor, Ly294002, significantly reduces the Akt phosphorylation in osteoclasts from both healthy controls and NF1 patients.

Text-based Macrostructure

Changes: The added information reflects the reviewers' comments that current data and a specific focus on osteoclasts be presented.

Study Design.

Aim 1: To evaluate the role of the Ras-PI3K signaling axis in modulating murine (*Nf1*^{+/-}) and human NF1 osteoclasts.

Rationale: Our rationale for conducting the mechanistic studies proposed in this application are based on emerging clinical data that NF1 patients have a significantly higher incidence of osteoporosis and osteopenia {Illes, 2001 #53; Kuorilehto, 2005 #12; Lammert, 2005 #13} and clinical observations that individuals with NF1 have defects in skeletal repair. We hypothesize that haploinsufficiency of *NF1* (*Nf1*) results in a gain in function in osteoclasts leading to hyperactivation of Ras activity in osteoclasts and that haploinsufficiency of NF1 causes intrinsic defects in skeletal formation and remodeling. Preliminary *in vitro* and *in vivo* data in *Nf1*^{+/-} mice and from NF1 patients support this hypothesis. In addition, though bisphosphonates are non-specific agents that inhibit osteoclast function, these agents have modest biological effects in preserving or restoring bone integrity {Solomon, 2002 #1054}. For that reason recent basic studies have focused on identifying more efficacious and specific molecular targets to treat and/or prevent these manifestations {Raisz, 2005 #1050}.

Text-based Macrostructure

Changes: The added information reflects the reviewers' comments that current focus and rationale be revised.

Previous studies by Dr. Shannon's laboratory {Donovan, 2002 #15} and studies from our group {Ingram, 2001 #7; Yang, 2003 #4; Hiatt, 2004 #3} have provided evidence that the Ras-PI3-K axis provides a gain in function in other lineages of *Nf1*^{+/-} and *Nf1*^{-/-} myeloid cells. In addition, Krystal and colleagues have shown that hyperactivation of PI3-K in mice containing a homozygous disruption of the hematopoietic restricted protein Src homology-2-containing inositol-5-phosphatase (SHIP) are severely osteoporotic due to increased numbers and osteolytic activity of hyper-resorptive osteoclasts {Takeshita, 2002 #16}. In preliminary studies, we have demonstrated that hyperactivation of Ras-PI3 pathway modulates a gain in function in osteoclasts *in vitro* that would in turn be anticipated to promote alterations in skeletal cell-cell interactions and accelerated skeletal bone resorption in adult mice. Studies proposed here are designed to conduct genetic intercrosses to verify that the gain in function through this signaling axis is sufficient to correct these osteoclast functions *in vivo* in adult mice. Complementary studies proposed in Aim 2 of the application will test whether genetic correction of this signaling axis is sufficient to correct these pathological changes in skeletal dynamics. In contrast to the *p85α* knockout strain that was utilized in preliminary studies, the proposed *p85α* knockout mice contain a disruption of 1 of two alternatively spliced *p85α* transcripts and thus are viable {Munugalavadla, 2005 #74; Haneline, 2005 #17}. These mice are commercially available from Jackson Laboratories and our colleague Dr. Ingram has already established the intercross of this line with *Nf1*^{+/-} mice for other purposes and provided them to us (see letter of collaboration). In addition, Drs. Ingram and Kapur have also established that genetic loss of *p85α* in this strain of mice reduces macrophage growth and migration {Munugalavadla, 2005 #74}. The obvious advantage of this particular intercross is that we can evaluate the role of *p85α* on individual lineages and at the whole organ level in the adult skeleton.

Text-based Macrostructure Changes:
The added information reflects the reviewers' comments that current focus and rationale be revised.

Absolute numbers of osteoclasts and multinucleated osteoclasts will be scored and their function examined in vivo. Bone mineral content (BMC) and density (BMD) of the whole body (excluding skull), will be evaluated using peripheral dual-energy X-ray absorptiometry (pDXA). A particular focus of these studies will be on the spine and the femoral and tibial diaphysis that is clinically relevant in patients. Geometric properties of femoral mid-diaphysis, trabecular bone volume fraction and microarchitecture in the femoral distal metaphysis will be evaluated using high-resolution desktop microcomputed tomography imaging systems. Complementary studies proposed in Aim 2 of the application will evaluate skeletal biomechanics both under basal conditions and in the context of bone remodeling using a controlled fracture model.

*In addition to the studies in mice, we propose to conduct parallel studies in osteoclast function and activation in the human system. Studies by others {Fujikawa, 1996 #1055; Udagawa, 1990 #1056} have shown that blood monocytes are the endogenous precursors that home to bone and complete their terminal differentiation program to become osteoclasts. There are also many experimental models indicating a close functional association between the activity of *in vitro* differentiated osteoclasts and the functional activity of osteoclasts from those same genotypes *in vivo* {Wada, 2005 #76; Chellaiah, 2000 #1057;*

Text-based Microstructure Changes:

The added information reflects the reviewers' comments that current focus and rationale be revised, but it does not change meaning as much as it shifts emphasis on answering the reviewers' comments requesting other studies to be cited as they relate to osteoclasts.

Takatsuka, 1998 #1058; Takeshita, 2002 #16}. Therefore evaluation of NF1 osteoclast functions *in vitro* may serve as an indicator for the activity *in vivo* in patients. We propose to conduct these studies in the context of an already funded NIH K23 award to Dr. Stevenson (Drs. Viskochil and Clapp- sponsors) where he is evaluating the bone mineral density and urinary collagen degradation products in children with NF1 and in age-matched controls. As presented in preliminary studies, urinary collagen degradation products (pyridinium urinary cross-links) are an indirect measure of osteoclast activity *in vivo*. Dr. Stevenson is finding that there is an association between the reduced bone mineral density in NF1 patients and an increase in urinary collagen degradation products. Consistent with these observations, in a small survey, we have found that osteoclasts differentiated from NF1 patient peripheral blood monocytes/macrophages, have increased lytic activity as compared to unaffected age and sex matched controls. Here we propose to obtain 10-20 mLs of blood from NF1 patients and age and sex matched controls in Dr. Stevenson's study and evaluate whether there is an increased lytic activity in osteoclasts from the NF1 individuals compared to unaffected age- and sex-matched controls. We will also correlate the association between the activity of osteoclasts and the bone mineral density and bone mineral content using DXA and pQCT imaging modalities from NF1 patients with and without osseous abnormalities. Finally, to evaluate whether the biochemical pathways between mice and men have been conserved, we will add siRNAs that inhibit PI3-K that were given to us and previously validated by our collaborator Dr. David Ingram (see letter of collaboration).

Collectively, these studies provide the first cellular and biochemical evidence for a NF1 haploinsufficient phenotype in osteoclasts and in the evaluation of the consequences of Nf1 haploinsufficiency on skeletal biomechanics.

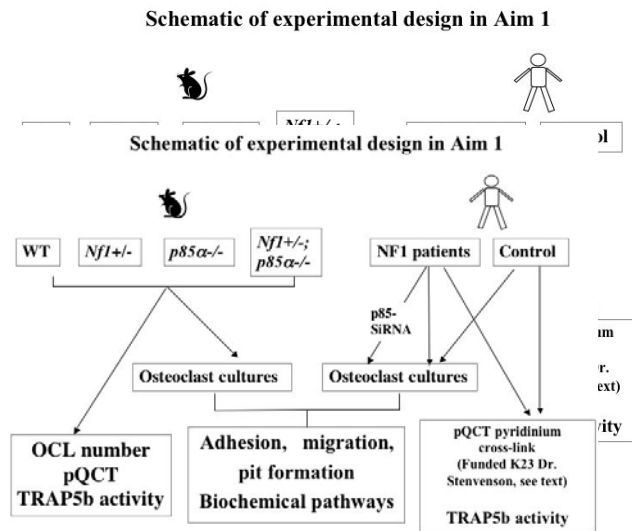
Text-based Microstructure Changes:

The added information reflects the reviewers' comments that current focus and rationale be revised, but it does not change meaning as much as it shifts emphasis on answering the reviewers' comments requesting other studies to be cited as they relate to osteoclasts. Citation of Dr. David Ingram's letter of collaboration is evidence for that request.

Experimental design and methodology – Aim 1

A schematic outlining the experimental design of this aim is shown in the right panel. Below, we describe the techniques and measurements proposed for this project, and the rationale for using each method. A more detailed description of each technique is provided in the appendices (published and submitted papers) currently in use by the investigators of this application.

In the initial studies in mice, 10-12 mice of each sex and genotype will be evaluated. Particularly for the pQCT studies in this aim and for the bone biomechanics studies proposed in Aim 2, cohorts of this size are utilized to control for in vivo variability from animal to animal. Data from all experiments are maintained in a database that is backed up on a University supercomputer server daily. In all instances, the investigator scoring the experiments is experimentally blinded to the F2 intercrossed group.



Surface Meaning Preserving Changes: Here, the words help to clarify thoughts but do not change meaning.

A. Evaluation of osteoclast functions in murine.

(1) Generation of experimental intercrosses. All mice utilized in these experiments are inbred in a C57BL/6 strain. The intercross strategy used to generate experimental animals are indicated below:

Nfl^{+/-}; *p85*[□] ^{-/-} mice have been generated by Dr. Ingram and provided to us.

F0: *Nfl*^{+/-}; *p85*[□] ^{+/+} X *Nfl*^{+/+}; *p85*[□] ^{+/-}. *F1*: *Nfl*^{+/-}; *p85*[□] ^{+/-}, *Nfl*^{+/+}; *p85*[□] ^{+/-}

Intercross of *F1* *Nfl*^{+/-}; *p85*[□] ^{+/-} X *Nfl*^{+/+}; *p85*[□] ^{+/-} to generate the following four desired *F2* experimental groups: \supseteq *WT* $\not\subset$ *Nfl*^{+/+}; *p85*[□] ^{-/-} \subset *Nfl*^{+/-}; *p85*[□] ^{+/+} \subseteq *Nfl*^{+/-}; *p85*[□] ^{-/-}.

From this cross 1/2 of all newborn mice are nullizygous at the *p85*[□] locus and *WT* or *Nfl*^{+/-} at the *Nfl* locus. We obtain approximately 1 *Nfl*^{+/-}; *p85*[□] ^{-/-} per liter and 1 *Nfl*^{+/+}; *p85*[□] ^{-/-} per litter. Given the requirements to have age and sex controlled mice in these studies, we estimate that we will need to generate a breeding stock of approximately 25 dams and 12 males from the *F1* cross.

Surface Formal Changes: Emphasis is on the osteoclast. That could qualify as contextual meaning preservation. The letter and numbering system changes are merely copyediting.

| | |
|---|---|
| <p>(2) Histomorphometric determination of osteoclast numbers. Though preliminary studies evaluated the role of Class I_A-PI3K from osteoclasts generated from fetal liver, this intercross will allow evaluation of the role of Class I_A-PI3K on osteoclast maturation and development in the adult skeleton. The femurs of 12 week old syngeneic <i>Nf1</i>^{+/-} and <i>WT</i> mice will be decalcified, and histological sections from the distal metaphysis will be stained for the osteoclast enzyme, TRAP. The number of multinucleated osteoclasts per unit trabecular surface will be counted, and the size of individual osteoclasts will also be scored under microscope with a QImaging camera and QCapture-Pro software (Version 5.1, Fryer Company Inc., Cincinnati, OH). Mice of each genotype and each sex will be evaluated to identify any individual or variability associated with sex. Genotypic differences will be examined using analysis of variance with a <i>p</i><0.05 being considered significant. Assuming a 50% difference in numbers of multinucleated osteoclasts amongst the <i>Nf1</i>^{+/-}, and <i>Nf1</i>^{+/-}; <i>p85α</i>^{-/-} genotypes or between <i>Nf1</i>^{+/-} and <i>WT</i> genotypes (which is a conservative estimate given differences amongst the groups in preliminary studies), we estimate that we will have a Power of 0.85 with the size of the treatment groups (10-12/genotype/sex) that are being utilized. A <i>p</i>-value <0.05 will be considered statistically significant.</p> | <p><u>Surface Formal Changes:</u> Emphasis is on the osteoclast. That could qualify as contextual meaning preservation. The letter and numbering system changes are merely copyediting.</p> |
| <p>(3) Isolation and culture of osteoclasts from <i>Nf1</i>^{+/-} mice. As <i>p85α</i> is a key biochemical target in monocyte/macrophages {Munugalavadla, 2005 #74}, the circulating precursors of osteoclasts {Fujikawa, 1996 #1055; Udagawa, 1990 #1056}, and since in preliminary studies genetic disruption of <i>p85α</i> reduces the biological activity of <i>Nf1</i>^{+/-} osteoclasts (Figure 5a-c), studies here will be conducted to verify that the cellular functions and biochemical activities observed in fetal liver cells of the F2 intercross are maintained in osteoclasts isolated from adult tissue and in an independent knockout line. Osteoclasts will be cultured as previous described by others {Suda, 1997 #28} and as in Appendix A.</p> | <p><u>Surface Formal Changes:</u> Emphasis is on the osteoclast. However, a bigger copyediting issue is the sudden change from references by numbers (usually associated with MLA Style) now appearing in APA Style as in-text citations.</p> |

| | |
|--|--|
| <p>(4) Osteoclast migration assay. Bone resorption by osteoclasts is linked to the migration and adherence of these cells to a local bone surface. To examine whether haploinsufficiency of <i>NF1</i> (<i>Nf1</i>) alters migration in osteoclasts, purified populations of TRAP positive cells from <i>NF1</i> patients or <i>Nf1</i>^{+/-} mice will be generated and migration of osteoclasts will be evaluated using a transwell assay as described with minor modifications {Yang, 2000 #20}. Briefly, aliquots of mononuclear cells previously cultured in M-CSF and RANKL for 6 days will be scored to identify TRAP (+) cells. Equivalent numbers of TRAP (+) cells (1X10⁴ /well) will then be loaded onto the upper chamber of transwells and allowed to migrate through a 8 μm pore size polycarbonate filter coated with vitronectin for 15 hours in a humidified incubator at 37 °C to M-CSF (30 ng/ml), 0.1% BSA in α-MEM placed in the bottom chamber. The cells migrated to the bottom of the filter will be stained with for TRAP activity. The number of TRAP-positive cells in per field will be counted using an image-analyzing system (Empire Imaging Systems, Plattsburgh, NY). As above, five independent experiments per treatment group will be evaluated and statistical differences among the 4 F2 populations will be determined using analysis of variance with a p value of < 0.05 being considered significant.</p> | <p><u>Surface Formal Changes:</u> Emphasis is on the osteoclast. However, copyediting continues. One preposition change occurred after the initial grant was rewritten but not identity of the changer.</p> |
| <p>(5). Osteoclast adhesion assay. Since monocytes adhere to skeleton via α_vβ3 integrins prior to forming polykarons and initiating bone resorption {McHugh, 2000 #36; Nakamura, 1999 #70}, we will examine whether haploinsufficiency of <i>NF1</i> (<i>Nf1</i>) alters cell adhesion. To evaluate the adherent capability of osteoclasts, a single cell suspension of osteoclast precursors (1 x 10⁵ cells/ml) will be put into a 24-well plate coated with vitronectin 20 μg/ml (Takara Inc. Shiga, Japan) supplemented with M-CSF (30 ng/ml). After 10 or 60 minutes, non-attached cells will be gently washed away, and attached cells will be fixed and stained for TRAP, then counted for per field cell numbers. Five independent experiments per treatment group will be evaluated, and statistical differences among the four F2 populations will be determined using analysis of variance with a p value < 0.05 being considered significant.</p> | <p><u>Surface Formal Changes:</u> Emphasis is on the osteoclast. However, copyediting continues. Grey highlight indicated changes made to this text but no ownership of who made the changes. They are not in the original, but were added to this copy.</p> |

| | |
|---|---|
| <p>(6). Bone resorption assay. Following adhesion, osteoclasts form a specialized cell-extracellular matrix to initiate degradation of bone matrix by secreting proteinases {Boyle, 2003 #24}. This function is assessed in vitro by culturing osteoclasts on dentine slices and examining the number and area of “pits” that are resorbed as previously described with minor modifications {Shinoda, 2003 #66}. Single cell suspensions of purified osteoclasts will be seeded onto dentine slices {Takeshita, 2002 #16} (ALPCO Diagnostic, Windham, NH) and incubated at 37 °C, 5% CO₂ in the presence of M-CSF and RANKL. Dentine slices will be then rinsed with PBS and left overnight in 1 M ammonium hydroxide to remove all cells. The slices will be washed in PBS and stained with 1% toluidine blue in 0.5% sodium tetraborate solution. For human pit assays, mononuclear cells will be collected from peripheral blood of NF1 patients or controls and cultured on dentine slices for 14 days and then processed with 1% toluidine blue in 0.5% sodium tetraborate solution. The number of resorptive areas or “pits” per low power field on each bone slice will be counted using reflective light microscopy. The area (mm²) of each pit will be evaluated by measuring width x length using QCapture Pro (Version 5.1) by an investigator who will be blinded to the experimental groups. Five independent experiments per treatment group will be evaluated. As discussed above, statistical differences among the four F2 populations will be determined using analysis of variance with a p value < 0.05 being considered significant.</p> | <p><u>Surface Formal Changes:</u> Emphasis is on the osteoclast. Note the copyediting still includes APA changes for in-text citations.</p> |
| <p>(7) TRAP5b measurement. To examine whether Nf1 +/- osteoclasts have increased activity in vivo, serum TRAP5b activity {Janckila, 2001 #72}, an established measure of osteoclast lytic activity will be measured in all experimental groups using a solid phase immunofixed-enzyme activity assay, which is a rapid and specific determination of bone resorption rate in vivo as described in Appendix A. The levels of TRAP5b activity in serum will be measured according to the manufacturer’s instructions (SBA Sciences, IDA) and compared to age and sex-matched wildtype controls.</p> | <p><u>Surface Formal Changes:</u> Emphasis is on the osteoclast. Note the copyediting still includes APA changes for in-text citations.</p> |

(8) Evaluation of Erk and Akt phosphorylation. *In order to correlate the gain in Nf1 +/- osteoclasts with biochemical pathways, Western blot will be performed to measure the phosphorylation of Erk and Akt. Phosphorylation of Akt kinase will be determined by depriving osteoclasts of serum and growth factors for 3 hours and followed by stimulation with 30 ng/ml M-CSF for various amounts of time. Cells will be washed twice with PBS containing 1 mM sodium orthovanadate and lysed in nonionic lysis buffer (20 mM Tris/HCl, 137 mM NaCl, 1 mM EGTA, 1% Triton X-100, 10% glycerol, 1.5 mM MgCl₂, and complete protease inhibitors (Amersham Pharmacia Biotech, Piscataway, NJ). The protein lysates will be equalized for protein concentration using the bicinchoninic acid (BCA) assay (Pierce Chemical Co.), and equal loading of protein in these assays will be confirmed by Western blot. The membranes will be developed with antibodies specific to phosphorylated proteins of Erk1/2 and Akt (Cell Signaling Technology). Densitometry of individual bands will be conducted using NIH Image software.*

(9) Ras activation assay. *To evaluate the Ras-GTP activity, osteoclasts will be deprived of serum and growth factors for 18 hours and stimulated at various amounts of time with 30 ng/ml M-CSF. Ras activation will be subsequently determined using Ras activation assay kits that focus on Ras binding domain of Raf1 (Upstate Biotechnology). Studies will be conducted according to the manufacturer's protocol and as previously described {Ingram, 2000 #9; Ingram, 2001 #7}.*

Surface Formal Changes: Emphasis is on the osteoclast. Note the copyediting still includes APA changes for in-text citations.

(10) Proof of concept that *Nf1* haploinsufficient osteoclast gains-in-function are mediated by hyperactivated Ras. *NF1* has 60 exons and has in certain contexts been found to have both Ras and Ras independent effects. To verify that the gain in function in *Nf1*^{+/-} osteoclasts is mediated by hyperactivation of Ras, the following experiments are proposed. Myeloid progenitors will be transduced with a retrovirus encoding the GTPase related domains of *NF1* and an EGFP selectable marker as we've done in previous studies {Venkatachalam, 1998 #62}. Following retroviral transduction, transduced progenitors will be sorted using fluorescence cytometry and purified populations of transduced myeloid progenitor cells (*Sca1*⁺, *Kit*⁺ *Lin*⁻, EGFP⁺) will be differentiated into osteoclasts. Ras-GTP, Akt and Erk activity as well as migration, adhesion, and pit formation will be examined in the transduced cells. Comparisons will be made to an equivalent population of *Nf1*^{+/-} cells and WT cells transduced with a reporter gene. A third population of *Nf1*^{+/-} cells will be transduced with a retrovirus encoding a GRD transgene that contains a point mutation that renders the GAP domains of *NF1* inactive. These constructs were originally developed in Dr. Clapp's laboratory (Hiatt, JBC2001) and have been previously used by us and others. The prediction is that retroviral transduction of the GAP domains corrects Ras activity the elevated Akt and Erk effectors, and corresponding cellular functions in the *Nf1*^{+/-} osteoclasts. Additional proof of a Ras specific effect anticipated is that cells transduced with a cDNA containing a known patient point mutation that lacks GAP activity will retain hyperactive Ras and hyperactive osteoclast functions.

Surface Formal Changes: Emphasis is on the osteoclast. Note the copyediting still includes APA changes for in-text citations.

B. Evaluation of osteoclast functions in NF1 patients.

(1) Isolation and culture of osteoclasts. Using a previously established method {Fujikawa, 1996 #1055; Fujikawa, 2001 #21} to generate primary osteoclasts for in vitro cellular and biochemical determinations, we will compare the cellular and biochemical activity of NF1 osteoclasts to unaffected controls. We will also correlate the respective activities in NF1 individuals with and without an osseous dysplasia (long bone dysplasia, sphenoid wing dysplasia, and/or scoliosis) with bone mineral density and bone mineral content in those individuals. Dr. Stevenson will recruit NF1 patients and collect 10-20 mL peripheral blood, and ship the specimens to us by Fedex. We have previously established that travel by this method does not impair myeloid progenitor or myeloid cell function. Once we get the specimens, we will isolate mononuclear cells from the peripheral blood following Ficoll-Hypaque separation and differentiated into osteoclasts as previously described {Fujikawa, 2001 #21} and as accomplished in Appendix A. Differentiated osteoclasts will then be utilized in in vitro cellular and biochemical assays. Osteoclast cultures will be assessed under a Nikon TE2000-S microscope (Nikon Inc.), and images will be taken by a QImaging camera and QCapture-Pro software (Fryer Company Inc., Cincinnati, OH).

Surface Formal Changes: Emphasis is on the osteoclast. Note the copyediting still includes APA changes for in-text citations. BMD is now written out as bone mineral density. Likewise, peripheral blood is not spelled out instead of appearing as PB.

(2) Evaluate the biological functions of osteoclasts from NF1 patients. Based on our preliminary studies in Appendix A, we will focus our efforts on examining three sensitive, readily quantifiable and easily reproducible assays that can be conducted from osteoclasts generated from small samples of blood. Here we propose to score the absolute numbers of osteoclasts that are formed in vitro as one measurement. We will then utilize defined numbers of those osteoclasts to conduct two functional assays that are integral to osteoclast function. Specifically, we will measure $\alpha_v\beta_3$ mediated osteoclast adhesion to skeletal matrix. In addition, we will add a defined number of osteoclasts to dentine slices and score the area of pit formation as described in preliminary studies, in Appendix A and above. A common source of fetal calf serum, growth factors, and use of commercial media will be utilized to prevent any trivial non-genotypic variability. The data will be utilized to make the following comparisons. First, we will validate in this large population of patients that osteoclasts from NF1 patients have increased cytoskeletal functions that promote lytic bone activity as compared to unaffected controls. Second, we will evaluate whether the increased propensity to form osteoclasts and to have an increase in osteoclast activity correlates with an increase in collagen degradation products in the urine of NF1 patients with an osseous dysplasia. Finally, we will evaluate whether an increase in osteoclast lytic activity in NF1 patients with an osseous dysplasia correlates with bone mineral density. Based on preliminary studies in Nf1 +/- mice and in data from human patients, we predict that with 27 NF1 individuals and 27 unaffected controls in a 1:1 age and gender matched case: control design we will have sufficient power (1-beta-error) = 80% and a 1-sided alpha error of <0.05 to detect a 50% difference in experimental groups. Forty-one NF1 individuals and a comparable number of unaffected controls are required to achieve the 40% effect size. We plan to enroll a sufficient number of patients (50/group) to achieve a 40% effect size.

Surface Formal Changes: Emphasis is on the osteoclast in this paragraph shows how important the change from OCL's to osteoclasts became.

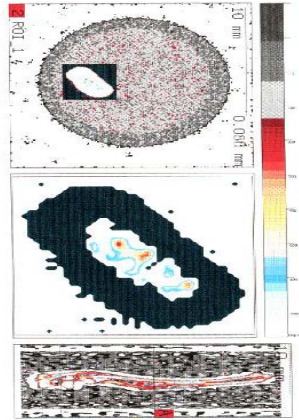
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| <p>(3) Understand biochemical signal pathway(s) that affect(s) the biological functions of osteoclasts from NF1 patients. We will evaluate the role of Class 1_A-PI3-K in controlling osteoclast adhesion and lytic activity by using siRNAs previously utilized by our collaborator, Dr. Ingram from 6-7 selected specimens. In his studies in endothelial cells he found that these particular sequences reduced Akt phosphorylation by approximately 50% and though this level of genetic silencing reduced cytoskeletal functions, it did not induce apoptosis (personal communication, David Ingram to FC-Yang). In studies proposed here, specific siRNAs to p85 or scramble control sequences will be added to osteoclasts 48 hours prior to use and at 2 day intervals afterwards. From one aliquot of cells, M-CSF mediated Akt phosphorylation will be examined to verify that the siRNAs are having an effect on the biochemical target. A reduction of Akt by 50-75% as compared to cells transfected with the scramble sequences will be considered significant. The remainder of the osteoclasts will be utilized to measure the impact of PI3-K activity on adhesion and pit formation respectively. Analyses will be conducted as described above for murine osteoclasts. A $p < 0.05$ difference in adhesion or pit formation will be considered a statistically significant reduction in biological activity.</p> | <p><u>Surface Formal Changes:</u> In this paragraph, emphasis is on spelling out the word, osteoclast; it reveals another change requested by the grant reviewers in their comments.</p> |
| <p>(4) TRAP5b measurement. To examine whether NF1 osteoclasts have increased activity in vivo, serum TRAP5b activity {Janckila, 2001 #72}, an established measure of osteoclast lytic activity will be measured in all experimental groups using a solid phase immunofixed-enzyme activity assay, which is a rapid and specific determination of bone resorption rate in vivo. The levels of TRAP5b activity in serum will be measured according to the manufacturer's instructions (SBA Sciences, IDA).</p> | <p><u>Surface Formal Changes:</u> Emphasis is on the osteoclast and proper APA in-text citations.</p> |

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| <p>C. Determination of bone mineral density and bone mineral content in <i>Nf1</i>+/- mice</p> <p>(1) Overview.</p> <p>While it is becoming increasingly clear that patients harboring <i>NF1</i> mutations have deficient bone mass and strength, it remains unclear whether the <i>Nf1</i> mouse model recapitulates the tissue- and organ-level phenotype observed in NF1 patients. Characterization of the skeletal phenotype exhibited by the <i>Nf1</i> haploinsufficient mice will be executed using a multifaceted approach, owing to complex ways in which bone metabolic disturbances can be manifest in the skeleton. To this end, we have assembled an extensive and complementary battery of assays to be conducted in this aim and in aim 2 that measure: (1) the amount of bone in the entire skeleton, (2) the amount of bone at discrete, biomechanically relevant sites throughout the skeleton, (3) the volumetric density of the bone tissue, (4) the architectural integrity of the trabecular bone network at the long bone ends, (5) the structural (geometric) properties of long bone diaphyses, based on engineering (beam theory) principles, and (6) the biomechanical properties of different skeletal elements, both at the material and structural levels. These measurements are routinely used by Dr. Robling, a co-investigator on this application.</p> | <p><u>Text-based Macrostructure Changes:</u> The added information reflects the reviewers' comments that current focus and rationale be revised.</p> <p><u>Surface Formal Change</u> occurred with spelling out bone mineral density.</p> |
| <p>(2). Dual-energy X-ray absorptiometry. <i>In order to ascertain whether <i>Nf1</i>+/- mice have less bone mass, we will begin by measuring bone mineral content (BMC; mg) and areal bone mineral density (aBMD, mg/cm²) using a miniature dual-energy X-ray absorptiometry instrument (pDXA, or pixiMUS) designed for analyzing mouse skeletons (GE-Lunar Corp., Madison, WI, USA) (Figure 12 a). We will begin by analyzing BMC and aBMD in the entire skeleton, (excluding the skull). Subsequently, we will probe individual skeletal regions (lumbar spine L1-L5, central femoral diaphysis, entire lower extremity) for site specific differences in BMC and aBMD. The regional analysis should help us to detect site specific differences not yielded by the whole body scans, and will allow us to compare sites analogous to those manifest clinically in NF1 patients. For example, the observation that NF1 patients are more prone to developing scoliosis and exhibit decreased hip and spine bone density will be addressed in the mouse model by specifically monitoring those sites. Based on our preliminary data, and on data published by other labs, we anticipate that the <i>Nf1</i> haploinsufficient skeleton will exhibit reduced aBMD and BMC, particularly in the femur, distal tibia, and spine.</i></p> | <p><u>Surface Meaning Preserving Changes:</u> The addition of a qualifying sentence clarifies what will be addressed in the study. A requirement from the reviewers' comments.</p> |

Figure 12 a.



Figure 12 b.



Surface Formal Change occurred with spelling out bone mineral density.

Figure 12 (a-b). Dual energy X-ray absorptiometry (DEXA) will be used to measure whole body and regional bone mineral density (BMD) and content (BMC) (a). Peripheral quantitative computed tomography (pQCT) will be used to measure true volumetric bone density in the distal femur (a trabecular bone site) and the midshaft femur (a cortical site) (b).

(3) Quantitative computed tomography.

Our next step in assessing the phenotype of the Nf1 haploinsufficient mouse skeleton will be to examine the volumetric density of the mineralized skeletal tissue using peripheral quantitative computed tomography (pQCT; Norland-Stratec GmbH, Pforzeim, Germany). With this instrument, we will probe the cortical and trabecular envelopes separately, a procedure not possible with DEXA. Specifically, we will collect two slices through the midshaft femur, (a cortical site), two slices through the distal femur at 85% of the total length (a trabecular site), and two slices through the 5th lumbar vertebra (a second trabecular site). For the trabecular sites, we will use the “peel mode” in the Stratec software to remove the cortical shell and analyze the trabecular compartment separately. The pQCT measurements will yield trabecular volumetric BMD (vBMD), cortical BMD, and total vBMD. These measurements will allow us to assess potential mineralization and bone mass deficiencies in the Nf1 haploinsufficient skeleton. Furthermore, we will be able to probe specific sites of the skeleton (and compartments within each site) that are of clinical importance in NF1 patients. It should be noted that Dr. Stevenson is obtaining similar measurements in children with NF1 (and in controls) in a K23 application; therefore our design for these studies has a parallel element in the clinical realm. We expect to find reduced vBMD in the femur and spine in Nf1 haploinsufficient mice, particularly in the trabecular compartment. Our hypothesis is based on the observation that osteoclast phenotypes are typically more robust in trabecular bone.

Surface Formal Change
emphasizing osteoclast spelled
out.

C) Anticipated results and alternatives. Given our previous studies that *Nf1*^{+/-} mice have increased osteoclast numbers and elevated functions that functionally lead to increased lytic activity, together with evidence in osteoclasts isolated from fetal liver cells that leads to a correction of these functions, we hypothesize that osteoclasts from *Nf1*^{+/-}; *p85α*^{-/-} mice will have a correction of osteoclast numbers in the femur, tibia, and vertebrae. We also predict that at the tissue level we will see a decrease in volumetric bone mineral density in *Nf1*^{+/-} mice, analogous to what Dr. Stevenson is observing in preliminary studies in children with NF1. If a decrease in vBMD is observed in *Nf1*^{+/-} mice, then the prediction is that *Nf1*^{+/-}; *p85α*^{-/-} mice will have a correction of this skeletal defect. We also predict that the pathological increase in osteoclast proliferation and cytoskeletal functions that promote gross and subtle microscopic changes in skeletal density detected by pQCT and DXA and that these measurements will be corrected in intercrossed mice that contain both a genetic disruptions of *p85α* and *Nf1*^{+/-} (*Nf1*^{+/-}; *p85α*^{-/-}) mice.

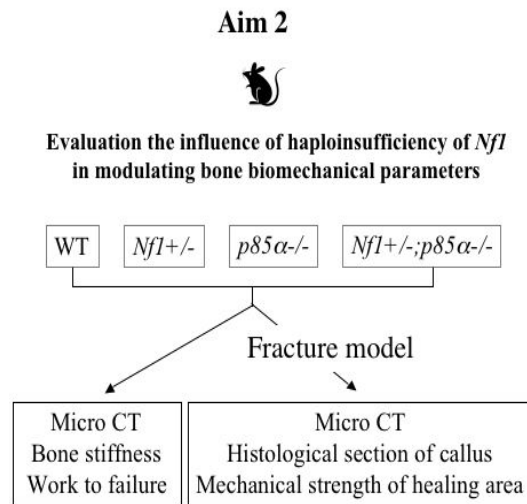
The prediction is that human osteoclasts generated from peripheral blood monocyte precursor cells will have increased adhesion, migration, and pit formation in response to M-CSF as compared to unaffected controls. We also predict that NF1 patients have increased TRAP5b levels in serum as compared to normal individuals. Similarly, the prediction is that osteoclasts from NF1 patients will have an increase in Akt phosphorylation following M-CSF stimulation as compared to normal individuals. It is possible that there will be greater variability in the NF1 patients as compared to genetically engineered inbred mice. The sample size that we are utilizing was chosen to allow sufficient statistical power to deal with this possibility. Further, to analyze the results in this experiment, we anticipate utilizing both parametric and nonparametric analyses. Dr. Stevenson and I will elicit the support of a biostatistician dedicated to support investigators in the IU Cancer Center. Though it's hard to predict with accuracy how sensitively the in vitro measurements will correlate with changes in bone mineral density and bone mineral content on an individual basis, we will assess whether the increase in osteoclast numbers and function can correlate with a reduction in bone mineral density and bone mineral content in NF1 individuals with and without an osseous dysplasia. The design provides a unique opportunity to compare the impact of NF1 haploinsufficiency on osteoclast activity and bone density in humans and in an experimental murine model. The use of established siRNAs or an intercross that genetically disrupts Class I_A-PI3K provides an important proof of concept to test the role of a molecular target in contributing to the hypothesized gain in function.

Surface Formal Change:

The spelling out of osteoclast as well as peripheral blood (formerly “PB”) still reflects the grant reviewers’ comments are influencing the revisions.

Aim 2: To evaluate the influence of haploinsufficiency of Nf1 in modulating bone biomechanical parameters in Nf1+/- mice.

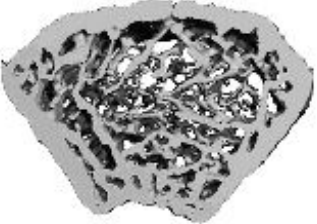

1). Rationale: Studies in Aim 1 focus on elucidation of cellular and biochemical functions in osteoclasts that promote skeletal degradation and noninvasive measurements of bone mineral density and content in both human NF1 patients and Nf1+/- mice. Studies here allow provocative testing of the murine model that cannot be conducted in humans to test the role of Nf1 haploinsufficiency on skeletal strength and bone remodeling. In preliminary studies we have provided preliminary evidence that haploinsufficiency of Nf1 does in fact alter skeletal strength and integrity. Studies here will allow further validation of this concept and determination whether correction of PI3-K activity is sufficient to correct this skeletal tissue vivo. Furthermore, the controlled fracture model proposed in these studies provides a rigorous preclinical platform to evaluate the role of haploinsufficiency of Nf1 on bone remodeling, the basic mechanistic process utilized in mice and men to repair and generate new bone. Furthermore, this will allow determination of the role of PI3-K in modulating the correction of this process.



in

Text-based Macrostructure Changes:
The added information reflects the reviewers' comments that current focus and rationale be revised.

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| <p>2). Experimental design: The experimental design in this aim is shown in right panel. The detailed methodologies are outlined below.</p> | <p><u>Surface Formal Change</u></p> |
| <p>(1) Examination of trabecular bone architecture. Following the bone mineral density and mass measurements obtained in Aim 1, we will explore the trabecular bone architecture in the <i>Nfl</i> haploinsufficient skeleton as well as the <i>Nfl</i> +/- mice that are genetically disrupted of Class I_A-PI3-K sub unit (<i>Nfl</i> +/-; <i>p85</i>^{-/-} mice), using a series of 3-D histomorphometric measurements collected on a desktop micro-computed tomographer (μCT; Scanco Inc., Basserdorf, Switzerland.). A representative photograph of this type of measurement is shown in Figure 13. The architecture of trabecular bone is strongly influenced by osteoclastic activity; slight imbalances in resorption vs. formation are often manifest in trabecular bone as changes in the thickness of individual trabeculae, the spacing of trabeculae, the number of trabecular struts, and in the anisotropy of the network. We will measure these variables in the distal femur and lumbar spine trabecular compartment by collecting 100 high resolution (9 μm) CT slices through the distal femoral metaphysis and through the L5 vertebral body, and reconstructing them to 3-D structures using the Scanco software. In addition to the trabecular bone work, we will also use the microCT to image the femoral midshaft. These midshaft scans will allow us to determine the amount of cortical bone, and the geometric distribution of that bone (second moments of area), which are strongly related to the bending and torsional strength. In light of preliminary data, we predict that the <i>Nfl</i> mice will exhibit reduced trabecular bone architectural properties, and perhaps less geometrically advantageous diaphyses.</p> <p>Briefly, these measurements are collected in the following fashion. Biomechanical properties of the left femur and radius from 12-week-old mice will be tested in three-point bending using a materials testing machine (Jandel Scientific, Corte Madera, CA, USA). Bones will be resected, cleaned, and stored in saline-soaked gauze at -20°C. Prior to testing, the bones will be brought to room temperature slowly in a temperature-controlled saline bath. The bones will be positioned posterior side down across the lower supports of the testing machine, which will be 15 mm apart. Load will be applied to the midshaft using a crosshead speed of 20 mm/min. The load vs. displacement data will be recorded by TestWorks software, version 4.06, which calculates the following mechanical parameters from load-displacement curves: ultimate force (F_u), stiffness (S), and work to failure (U). Data will be normalized using μCT-derived cross-sectional geometric properties to obtain intrinsic material properties, including ultimate stress, elastic modulus and toughness, which are independent of bone size and shape.</p> | <p><u>Surface Formal Change</u> in spelling out bone mineral density and adding Switzerland. What remains a mystery is where the deleted text came from since it did not come from the original grant. Yet it is noted in the track changes as having been deleted. As such, it would qualify as a <u>Macrostructure Change</u>.</p> |

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| <p>Figure 13 a.</p>  | <p>Figure 13 b.</p>  | <p><i>Figure 13 (a, b). (a) Micro-computed tomography (μCT) will be used to measure trabecular architecture in the reconstructed distal femur from 100 consecutive tomo-graphs collected at the metaphysis. (b) μCT will also be used to derive geometric properties at the midshaft femur.</i></p> | <p>No changes in this figure.</p> |
| <p><i>Detailed methods of these procedures are outlined. Briefly, for geometric properties of femoral shaft, a single transverse slice through the mid-diaphysis will be taken at 9-μm resolution. Each mid-diaphysis slice is imported into Scion Image v4.0.2 (Scion Corporation, Frederick, MD, USA), in which the geometric properties are calculated using standard and customized macros. Geometric properties include cortical area (CA; mm^2), total area (TA; mm^2), and the maximum (I_{MAX}, mm^4) and minimum (I_{MIN}, mm^4) cross-sectional moments of inertia (CSMI). In addition, we will calculate polar moment of inertia I_P as the sum of I_{MAX} and I_{MIN}. The CSMI estimates a beam's (in this case, a bone diaphysis) capacity to resist torsion and bending. For evaluation of the trabecular envelope at the femoral distal metaphysis, each specimen is scanned with a slice increment of 9 μm. CT images are reconstructed, filtered ($\sigma= 0.8$ and support = 1.0), and thresholded (22% of maximum possible gray scale value) using routine procedures. Scanning for the femur begins at 15% of the total femur length, measured.</i></p> | | | <p>No changes in this figure.</p> |

(3) Fracture model: *Fracture repair is a complex physiological process during which osteoblasts and osteoclasts in the surrounding fracture region mounts a repair process that restores mechanical integrity and an anatomical configuration of the injured bone (Figure 15) . After the initial bony union, there is a prolonged phase of callus remodeling to restore the anatomical configuration. It has become widely recognized that many of the cellular and biochemical processes that occur during fracture healing correspond to those that take place during skeletal development. In addition, the process of fracture repair is an effective and sensitive measurement of bone remodeling {Bruder, 1994 #1059; Jacobson, 1997 #1060; Ferguson, 1999 #1061}.*

Figure 15.



Lateral radiograph of a 16 wk-old C57BL/6 mouse that had undergone unilateral tibial fracture and pinning 4 weeks earlier. Note the fracture callus that has bridged the defect, which has already begun to remodel.

Surface Formal Changes: the osteoclast is spelled out and the APA for in-text references has been corrected.

(3). Anticipated results and alternative. We hypothesize that the ultimate force (F_u), stiffness (S), and work to failure (U) in the tibia, femur, and vertebrae of unmanipulated, age and sex controlled $Nf1$ +/- mice will be reduced as compared to WT controls. Since osteoclast phenotypes have a particular predilection to reduce trabecular bone, the prediction is that $Nf1$ +/- mice will have a reduction in trabecular bone as measured by micro-CT. We hypothesize that genetic correction of hyperactivation of PI3-K will correct this skeletal deficit.

In the fracture model, the prediction is that callus bone mineral density will be significantly reduced in the fractures of $Nf1$ +/- mice as compared to the callus formation in WT control mice. We also predict that histological analysis of the fractures will reveal that $Nf1$ +/- mice have a (1) delay in endochondral bone formation, (2) increased numbers of osteoclasts around the trabecula, and (3) potentially a persistence of the fracture line along with increased cartilage, indicative of a delay in healing. Furthermore, we hypothesize that there will be both an absolute decrease in the amount of trabeculated bone in the fracture of $Nf1$ +/- mice, and the organization of the trabeculae will be less organized. These histologic changes will be associated with clear quantitative reductions in ultimate force and a reduction in work to failure to fracture observed in $Nf1$ +/- mice as compared to WT controls. Evaluation of the fractures from mice that are mutant at the $p85\alpha$ locus will allow examination of PI3-K on modulating this effect of remodeling of osteoclast function.

Surface Formal Changes: the osteoclast is spelled out as copyediting.

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| <p>Given the preliminary studies, we believe that the proposed studies have a high likelihood of success in demonstrating clear biomechanical differences in the skeleton of the <i>Nf1</i> +/- mouse as compared to syngeneic controls. Our colleagues Drs. Kapur and Ingram have previously established that monocytes from the <i>p85α</i> -/- line proposed in these studies do have reduced M-CSF mediated migration as compared to WT monocytes, so we do not believe that will be a complication. Since <i>Rac1</i> and <i>Rac2</i> are the downstream effector of Class 1_A-PI3K, and are key effectors in modulating multiple biological functions, including migration and adhesion, in hematopoietic lineages (see Appendix 3), while we are performing the proposed studies, we will also take an alternative approach to evaluate the role of <i>Rac1</i> and/ or <i>Rac2</i> in modulating the cytoskeletal processes including migration, adhesion and bone resorption in <i>Nf1</i> +/- mice. We do have both <i>Rac1</i> conditional knockout mice and <i>Rac2</i> -/- mice available that could be utilized for purposes of this application.</p> | <p><u>Text-based Macrostructure Changes:</u> The added information reflects the reviewers' comments and effectively attempts to convince the reviewers that their objections have been met.</p> |
| <p>Finally, it is unlikely but still possible that we will need to modify the proposed fracture experiments. Based on previous experiments by Dr. Robling, we predict that examination of the fractures 1 month after surgery will provide meaningful differences in bone turnover and repair. However, if in those studies we do not observe significant differences, we would propose to conduct a series of experiments where we evaluate the repair of the fractures using a longitudinal design such that we evaluate the repair at 4-10 weeks following injury.</p> | <p><u>Surface Formal Change:</u> Added concluding marker.</p> |

Appendix B

This table situates the location of the only surviving text from the original grant proposal, Grant I, April 2006, that is found in the third and final grant proposal for the Department of Defense dated May 2007.

ORIGINAL GRANT PROPOSAL: Starting 6 lines up from the bottom of page 15, on the left hand side, see: **Section: Aim 2, (2) Skeletal Biomechanics** [bold in original text].

FINAL GRANT PROPOSAL: Starting 2 lines below Figure 8A 8B on page 8, starting near the right margin, see: **(6) Skeletal Biomechanics** [bold and italics in the original].

| <u>Legend</u> | <u>Theoretical rationale</u> |
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| <p><i>Italics</i> indicate text surviving from the original grant proposal April 2006. Highlighted text denotes text or numbers added to the original proposal. Strikethrough text denotes text deleted from the original grant proposal prior to February 2007.</p> | <p>In this column, Faigley and Witte's (1981) (p. 403) Taxonomy of Revision Changes is used to categorize revisions.</p> |
| <p>"...will assess one of the most clinically relevant manifestations of reduced bone mass, which is reduced bone strength (i.e., increased risk of fracture). To assess whether the <i>Nf1</i> mouse bones suffer from impaired mechanical integrity, we will conduct biomechanical tests of the femur, radius, and L5 vertebrae. We will break the femur and radius samples in 3-point bending using a miniature material testing machine equipped with a very sensitive load cell (0.05N resolution) as outlined in (Figure 14) (Figure 9A). The L5 vertebral bodies will be tested in axial compression on the same machine. All tests are conducted under saline irrigation at room temperature. From the tests, we will be able to extract elastic and plastic properties of the bone samples, including the amount of force required to break the bones, the energy absorbed prior to failure, and the stiffness of the samples. We will also derive material properties (flexural modulus, ultimate stress, and others) using the geometric properties of the bone shafts collected from the μCT" (p.1).</p> | <p><u>Meaning Preserving Surface Changes:</u> ... as outlined in (Figure 14)" was deleted from original text. Since Figure 9A is an illustration, deletion of "as outlined in" does not accurately describe an illustration or pictured representation of a procedure. <u>Formal Surface Changes:</u> Change was made to reflect new numbering for figure 14, (Figure 9A). Both are surface feature revisions and do not change meaning.</p> |

Figure 10



Lateral radiograph of a 16 wk-old C57BL/6 mouse that had undergone unilateral tibial fracture and pinning 4 weeks earlier. Note the fracture callus that has bridged the defect, which has already begun to remodel.

Briefly, ~~these measurements are collected in the following fashion.~~ biomechanical properties of the left femur and radius from 12-week-old mice will be tested in ~~three~~ 3-point bending using a materials testing machine (Jandel Scientific, Corte Madera, CA USA). Bones will be resected, ~~cleaned~~, and stored in saline-soaked gauze at -20°C. Prior to testing, the bones will be brought to room temperature slowly in a temperature-controlled saline bath. The bones will be positioned posterior side down across the lower supports of the testing machine, which will be 15 mm apart. Load will be applied to the midshaft using a crosshead speed of 20 mm/min. The load vs. displacement data will be recorded by TestWorks software to calculate the following mechanical parameters from load-displacement curves: ultimate force (Fu), stiffness (S), and work to failure (U). (p. 2a)

Meaning Preserving Surface Changes:

The deleted phrase does not describe the process of bone testing; hence, its retention would add confusion to the process of bone testing. (9 words deleted)

Removal of ~~cleaned~~, also preserves meaning in the context, since cleaned refers to the deleted collecting process.

Formal Surface Changes:

Changing “~~three~~” to 3, removal of USA, and changing the figure number from 15 to 10 are evidence of copyediting.

(7) **Fracture model:** Fracture repair is a complex physiological process during which OBLs and OCLs in the surrounding fracture region mounts a repair process that restores mechanical integrity and an anatomical configuration of the injured bone (Figure 10). After the initial bony union, there is a prolonged phase of callus remodeling to restore the anatomical configuration. It has become widely recognized that many of the cellular and biochemical processes that occur during fracture healing correspond to those that take place during skeletal development. In addition, the process of fracture repair is an effective and sensitive measurement of bone remodeling⁴⁶⁻⁴⁸. (p. 2b)

Formal Surface Changes:

Section 7 and Figure 10 provide evidence of copyediting.

Text-Based Change (or omission in this case) under Microstructure Changes:

The original proposal used numerical referencing; the final DOD proposal was changed to reflect strict APA guidelines. Therefore, the inclusion of the original reference “46-48” is an APA style in-text citation error. The text should have read: (Bruder, et al., 1994; Jacobson, et al., 1997; & Ferguson, et al., 1999).

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|---|---|
| <p>Using surgical techniques that These studies are established in Dr. Robling’s laboratory conducted by initially preparing 12-week-old adult male mice with an intraperitoneal injection of 60–80 mg/kg ketamine and approved by 7.5 mg/kg xylazine. The surgical site is prepared by shaving and the IU Animal care committee, area is cleaned with 70% EtOH and novalsen. Using sterile technique, a 1 cm incision is made over the middle third of the medial surface of the tibia, tibia. A a cortical defect is made using a 26-gauge needle, medial to the tibial tuberosity and at 45° to the long axis of the tibia. A a 0.15 mm intramedullary rod is then inserted into the upper third of the medullary canal through the cortical defect.</p> <p>(p. 3a)</p> | <p><u>Text-Based Change, Microstructure Changes:</u> Textual deletion (56 words) remains consistent with the initial changes and retains contextual agreement regarding how testing will be performed, not how samples are collected.</p> <p><u>Formal Surface Changes:</u> By adding “and,” adding small case “a” are copy editing as text is modified to agree with the above testing procedure.</p> |
| <p>The skin and muscle are then retracted using two 26-gauge needles, after which the tibia is osteotomized proximal to the tibia-fibular junction using a dremel saw with a diamond blade under saline irrigation. Care is taken not to disrupt the fibula and to not scrape the periosteum. It is important to leave the fibula intact to improve stability of the fracture. After the fracture is created the intramedullary rod is fed down the fracture site to the base of the tibia, after which the fracture is examined to ensure the fracture site is stable with no excessive rotation. The wound is then closed using 4-0 nylon sutures. To reduce post-operative pain a subcutaneous injection of buprenorphine 0.1–0.5 mg/kg is administered up to 48 hours post-surgery. After 4 weeks, the animals are sacrificed and the tibiae are dissected free and stored in 70% EtOH for processing. μCT/MicroCT is used to visualize the fracture site to check for callus bridging, and histological sections are cut to assess the degree of union/healing. We also will break a subset of the fractured tibias using torsional loads, to assess changes in mechanical strength of the healed fracture in the different genotypes described.</p> <p>(p.3b)</p> | <p><u>Text-Based Change, Macrostructure Changes:</u> Major removal of text (126 words) is again consistent with the above deletions to emphasize testing procedures, not how bones are collected and stored. There was also a new constraint added to the third proposal, which did not previously exist with proposals one and two. There was a strict limit on the number of words allowable. Therefore, only the absolute minimum to convey process was used here.</p> |

3) (4). **Anticipated results.** Given our previous studies that *Nf1*^{+/-} mice have increased OCL numbers and elevated functions that lead to increased bone resorptive activity, together with evidence of *Nf1*^{f/-Peri+} mice have reduced somatic size, we hypothesize that OCLs from *Nf1*^{f/-Peri+} mice will have an increased OCL numbers in the femur, tibia, and vertebrae. We also predict that we will see a decrease in vBMD and reduced trabecular bone architectural properties in *Nf1*^{f/-Peri+} mice. In addition, we ~~alternatives:~~ We hypothesize that the ultimate force (Fu), stiffness (S), and work to failure (U) in the tibia, femur, and vertebrae of unmanipulated, age and sex controlled *Nf1*^{f/-Peri+} ~~*Nf1*^{+/-}~~ mice will be reduced as compared to WT, *Nf1*^{+/-}, or *Nf1*^{f/Peri+} controls. Since OCL phenotypes have a particular predilection to reduce trabecular bone, the prediction is that *Nf1*^{f/-Peri+} ~~*Nf1*^{+/-}~~ mice will have an enhanced bone turnover and a reduction in trabecular bone as measured by μ CT (p.4).

Text-Based Change, Macrostructure Changes:

This addition reflects the changed audience for the third grant, the Department of Defense (DOD). Thus, the added text enhances the desirability of this study to be funded based on the objectives of the DOD referees.

Formal Surface Changes: Evidence of copyediting is observed in the changes in the types of measurement

Appendix C

1. What single difficulty in writing seems to repeat itself while writing in English?

Grammar.

2. Is it easy to identify linguistic problems during the writing process?

Yes.

3. What strategies work best for you to use to overcome linguistic problems?

Writing more and reading more.

4. When do you usually find and identify errors during the writing process?

Find the red error dashed lines automatically show by software.

5. When you read other international postdocs' papers:

a) Do you find errors? *Yes.*

b) Do the errors you notice also appear in your writing as well?

Sometimes.

6. Since you already write in several languages, does that make composing research articles and grants in English easier? *Yes.*

7. Generally, APA is the style format for science papers. It appeared that the first grant proposal used MLA. Was the style change difficult to adjust?

No. It is not difficult.

8. Since you have written several funded grants, what advice would you offer to novice international postdocs who want to write a grant proposal?

I would suggest that they start to practice writing earlier and more.

9. If you could choose between writing for a journal publication or a grant proposal, which would you prefer and why?

I'd choose to write for a journal publication, because the grant proposal does need to look at a big picture and this is relatively hard for a beginner.

10. It appeared that space requirements for the grant proposal were restrictive. Did you find it difficult to edit and shorten the grant without losing your intentional meanings and explanations?

Yes. At beginning, I did find it difficult to shorten the grant.

11. I found one section of the first grant that reappeared in the third, approved grant, with minimal changes. Was that material about extracting the OCLs from the tibial fracture from an original research paper that you had previously written?

Yes. It was the case.

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Curriculum Vitae

Clyde William Strickland

Teaching experience

- 8/04 -- present Adjunct instructor for Freshman English Composition (W-131) at IUPUI
- 10/06 -- 2/07 ESP instructor for Afghans; preparing students for the written TESOL essays
- 8/06 -- 5/07 Assistant to ICIC's EAP and Intercultural Communication for international postdoctoral researchers at IUPUI
- 8/02 -- 5/05 Instructor at Ivy Tech State College, Indianapolis: English Composition 101
- 3/00 -- 5/04 Instructor, machine shop, Ivy Tech State College, Indianapolis, IN Teaching Blueprint Reading, Shop Math, Shop Theory, Measuring Instruments, and Machine Shop for NTMA workforce retraining.

Skilled trade experience (Retired after 33 years)

- 1971 -- 1999 Available on request

Education

MA: English, IUPUI, October, 2008

TESOL Certificate, IUPUI, December, 2007

MA: Vocational Education, Ball State University, Muncie, IN, 1994

BA: Art Design & English Literature, University of California at Los Angeles, 1966

Presentations

- 2006: Poster presenter at the Fourth Conference on Intercultural Rhetoric and Discourse