# F31 Specific Aims: Designing your 1-Page "Elevator" Pitch

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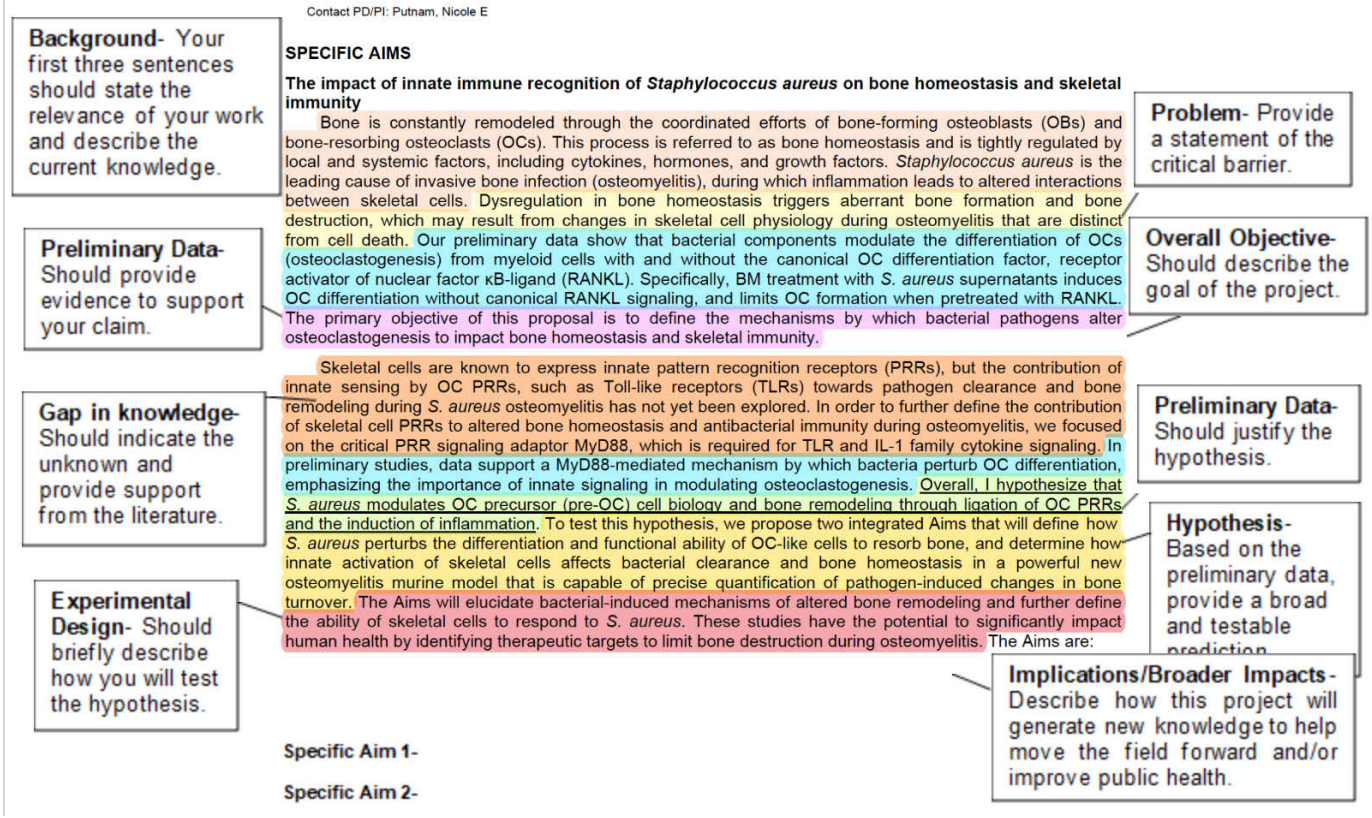
The specific aims page is one of the most important documents of your NIH NRSA F31 fellowship application since it will be used by the Scientific Review Officer (SRO) to select three (3) reviewers for your application. It can be shared with the Program Officer to gauge the institute's potential enthusiasm for the project prior to submission. The specific aims page will mostly likely be the only document read by all the members of your assigned Scientific Review Group. This document is an annotated guide of the introductory paragraphs of a successful application.



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**SPECIFIC AIMS**

**The impact of innate immune recognition of *Staphylococcus aureus* on bone homeostasis and skeletal immunity**

Bone is constantly remodeled through the coordinated efforts of bone-forming osteoblasts (OBs) and bone-resorbing osteoclasts (OCs). This process is referred to as bone homeostasis and is tightly regulated by local and systemic factors, including cytokines, hormones, and growth factors. *Staphylococcus aureus* is the leading cause of invasive bone infection (osteomyelitis), during which inflammation leads to altered interactions between skeletal cells. Dysregulation in bone homeostasis triggers aberrant bone formation and bone destruction, which may result from changes in skeletal cell physiology during osteomyelitis that are distinct from cell death. Our preliminary data show that bacterial components modulate the differentiation of OCs (osteoclastogenesis) from myeloid cells with and without the canonical OC differentiation factor, receptor activator of nuclear factor κB-ligand (RANKL). Specifically, BM treatment with *S. aureus* supernatants induces OC differentiation without canonical RANKL signaling, and limits OC formation when pretreated with RANKL. The primary objective of this proposal is to define the mechanisms by which bacterial pathogens alter osteoclastogenesis to impact bone homeostasis and skeletal immunity.

Skeletal cells are known to express innate pattern recognition receptors (PRRs), but the contribution of innate sensing by OC PRRs, such as Toll-like receptors (TLRs) towards pathogen clearance and bone remodeling during *S. aureus* osteomyelitis has not yet been explored. In order to further define the contribution of skeletal cell PRRs to altered bone homeostasis and antibacterial immunity during osteomyelitis, we focused on the critical PRR signaling adaptor MyD88, which is required for TLR and IL-1 family cytokine signaling. In preliminary studies, data support a MyD88-mediated mechanism by which bacteria perturb OC differentiation, emphasizing the importance of innate signaling in modulating osteoclastogenesis. Overall, I hypothesize that *S. aureus* modulates OC precursor (pre-OC) cell biology and bone remodeling through ligation of OC PRRs and the induction of inflammation. To test this hypothesis, we propose two integrated Aims that will define how *S. aureus* perturbs the differentiation and functional ability of OC-like cells to resorb bone, and determine how innate activation of skeletal cells affects bacterial clearance and bone homeostasis in a powerful new osteomyelitis murine model that is capable of precise quantification of pathogen-induced changes in bone turnover. The Aims will elucidate bacterial-induced mechanisms of altered bone remodeling and further define the ability of skeletal cells to respond to *S. aureus*. These studies have the potential to significantly impact human health by identifying therapeutic targets to limit bone destruction during osteomyelitis. The Aims are:

**Specific Aim 1-**

**Specific Aim 2-**



**Specific Aims-** Each aim should state the objective for the proposed experiments. Aims should be stated broadly and should be open-ended. Each aim should first provide the rationale/justification followed by the working hypothesis. The hypothesis should be followed by a brief description of the model system and how it will be tested. In addition, you could add a brief statement that describes the payoff or expected outcomes of the proposed experiments. To avoid having the proposal deemed as overly ambitious, only two specific aims are recommended.

**Final Paragraph (Optional)-** The final paragraph should discuss the implications and broader impacts of this work. Also, it could discuss the technical skills/expertise that the trainee (you) will develop by executing this research plan and how they will support the applicant's long-term career goals.

Relevant Resources

1. GWL Tips for Writing a NRSA F31 Style Fellowship in the Natural Sciences
2. NIH Grant Applications- The Anatomy of a Specific Aims Page
3. NIH How to Make Your Grant Proposal "Sellable"
4. NIAID three F31 Sample Applications