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Yves Brun
Systems Biology/Microbiology Faculty Search
Department of Biology
Indiana University
Jordan Hall 142
1001 E. 3rd St.
Bloomington, IN 47405-7005

Dear Dr. Brun:

I would like to recommend Jesse Wright for a tenure track position at Indiana University. Jesse has been a post-doc here for the past five years, during which he has made three important contributions to our studies of virulence regulation and its clinical implications in *Staphylococcus aureus.*

1) He began by encouraging us to apply for the IVIS (in vivo imaging) system and used it to demonstrate *agr* expression, trans-activation and inhibition in vivo. These results were published in the PNAS. 2) He then developed a luciferase-based agar plate test for *agr* group specificity, which eventually led to a publication in Mol. Micro, proposing an interesting hypothesis on *agr* evolution. 3) He also created a series of AgrC chimeras and used these to localize the apparent binding site for the AIP to the distal region of the AgrC receptor domain. One of his chimeras had the remarkable property of being activated by all of the AIP variants that we had previously synthesized, including those that were inhibitors for all four of the *S. aureus agr* groups. These findings were also published in PNAS. Jesse initiated the first two of these, the third had been outlined in an existing grant application.

Jesse is a highly motivated and productive member of the lab, demonstrating great independence, initiative, and creativity. He is a fully fledged young scientist ready to establish an independent research program and I am sure he will have a highly successful career at IU.

Sincerely yours,

Richard P. Novick, M.D.

Tom W. Muir
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Dear Committee Members: 9/28/05

I am writing in strong support of Dr. Jesse Wright's who is applying for a junior faculty position in your department. Dr. Wright is currently a postdoctoral associate in Richard Novick's group at NYU Medical Center. The Muir and Novick groups have a long-standing collaboration on studying the molecular details of virulence regulation in *Staphylococci* by the *agr* global regulon. As part of this on-going research, Jesse has for the last ~4 years been working closely with a series of graduate students in my group, and indeed has spend a great deal of time in my laboratory at Rockefeller. I have had numerous interactions with Jesse during this period and so feel qualified to comment on his abilities.

For several years now, we have been trying to understand the molecular mechanism by which small, secreted cyclic peptides produced by *Staph* bacteria can act either as agonists of virulence expression with respect to their own specificity group, or as antagonists of virulence in all other groups. Understanding these processes, we hope, will provide important insights into the pathogenesis of this organism and may uncover novel strategies for therapeutic intervention. While substantial progress has been made in both these goals, there remain several important unresolved questions. For his part, Jesse became interested in characterizing which parts of the autoinducing peptides (AIPs) interact with which parts of the histidine kinase receptor, AgrC. His approach to this problem has been to prepare various chimeric receptors using genetic techniques and then to ask how these respond to various AIP analogs, prepared chemically. This interdisciplinary approach to this problem has been quite productive; to date there have been three papers published on this part of the work. Using essentially double mutant-cycle type analyses, Jesse was able to deduce the likely binding orientation of the peptide in the receptor binding pocket. The success of this work was due, in part, to a very productive partnership formed between Dr. Wright and students in my group, but also to Jesse's impressive ability to analyze and interpret a large amount of seemingly contradictory data; Jesse was able to make sense of this while the rest of us were to say the least confused! Jesse's theories predict that certain peptides will bind more or less tightly to certain chimeric receptors; so far these predictions have held up beautifully to experimentation. Throughout this period, I have also been very impressed by Jesse's willingness, and ability, to learn new areas; his background is in microbial genetics, yet he has become familiar with the synthesis and characterization of moderately complex peptides, as well as molecular pharmacology experiments on the AgrC receptor.

Concurrently with the above work, Dr. Wright has developed a luciferase-based reporter of agr activation and used this to monitor activation and inactivation of agr quorum sensing in vivo using a mouse model of *S. aureus* infection. The results of these experiments have been, to say the least, surprising and in some respects raise more

questions than they answer. In essence, Jesse's reporter system has revealed a rhythmic nature to the agr response *in vivo* such that the virulence response is rapidly triggered after initial infection, declines into a prolonged eclipsed phase and then is reactivated during abscess formation. Remarkably, inhibition of the initial burst phase (using suitable peptides) is sufficient to prevent reactivation of the agr response days later, even though the peptide has half-life of a few hours in serum. This has led to the idea that the exoproteins released during the initial burst-phase somehow protect the bacteria from attack by host neutrophils and that this permits eventual tissue necrosis and abscess formation. Of course, many questions remain regarding the nature of the eclipsed-phase and will be the subject of future studies.

Over the last year or so, Jesse has become increasingly interested in the evolution of the staphylococci, to the point where he wants to pursue this in his own research laboratory. As you will see from his research proposal, Dr. Wright's program will be largely focused on exploring the role Agr in the social behaviors and genetic landscape of the staphylococci. This is a fascinating and potentially fruitful area of research and, importantly, one where he will be able to carve out a niche for himself. I have no doubt that he has, the drive, intelligence and creativity to succeed in this area. His communication skills (both written and verbal) are first rate, and he has an easy-going personality that makes him a pleasure to be around. Overall, I think Dr. Wright compares favorably with the very best postdocs I have worked with here at Rockefeller over the years, many of whom have gone on to faculty positions in the US and elsewhere. Consequently, I fully support his application and I hope you will give it serious consideration. Please don't hesitate to contact me should you have any questions.

Sincerely,

Tom Muir
Salomon Professor of Chemistry