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**Sent:** Tuesday, July 28, 2009 3:14 AM  
**To:** m-meagher@tamu.edu  
**Cc:** Giroir, Brett; Wallis, Deeann; Webb, Ray; Carlson, David; rfinnell@ibt.tmc.edu; Diedrich, Guy  
**Subject:** Misconceptions about TIGM  
**Attachments:** Science article.pdf

Dear Dr. Meagher,

I heard your comments about TIGM and its gene-trap asset yesterday at the faculty forum with Dr. Giroir, and I wanted to take this opportunity to introduce myself, and to provide additional information that might help you and other faculty members understand more about TIGM and its operations. Clearly, it would have been helpful if I could have participated in this meeting, given that Dr. Giroir has only recently arrived in College Station (1 yr) and TIGM's inception dates back several years before his arrival. Furthermore, he has several time consuming activities and he is not involved in the day to day management of TIGM, so it was unrealistic to think he was in a position to address any and all questions related to the institute. Unfortunately I was out of the country and the issues were of such a nature that the CPI did not want to wait until I returned.

You raised two concerns that I would like to try to address in this email message. I would also like to encourage you to contact me *any time* you would like to know something about TIGM. My office is in Houston (713-677-7777) but I will be doing research out of the country for the rest of August. Once back, feel free to call my cell phone (713 291 1553) if you have any concerns. You can also contact Dr. Deeann Wallis at (979 218 7586). Deeann is a TIGM scientist currently based in College Station and she can probably tell you more about TIGM than you care to know.

#### First issue: Gene-Trap Technology

I have often heard it said that TIGM didn't get the NIH KOMP award because our gene trap technology was old and why would TAMUS invest thoughtlessly in such antiquated technology. I believe you also made the comment that TIGM's application was not responsive to the KOMP RFA. While most of us would agree that a conditional ready clone has more potential value than straight, "conventional" knockout alleles, there are several reasons why the C57 ES cell asset produced for TIGM by Lexicon, has conventional, rather than conditional ready clones.

First, the RFA that TIGM responded to from the NIH **specifically requested conventional** over conditional clones. If you read the RFA, and I trust that you have since you specifically commented on this point, then you would see that the request was for a straight (conventional) knockout with a reporter in C57BL/6 ES cells. That is it. While the scientific community, of which I am a part, would have preferred that NIH invest in a conditional asset, that is NOT what the RFA **requested**. So TIGM was absolutely responding to the RFA. The fact that TIGM barely existed (I was the only TIGM member, devoting 25% of my effort at the time of the submission), we had no track record which, as you know from submitting grant proposals to NIH, weighs heavily upon the reviewers. Yes, we could pretty much guarantee a successful outcome to Francis Collins, as we were in the position to put up the 273,000 ES cell clones from the 129 OmniBank 1 gene-trap library, up to 3000 already made Lexicon knockout mice, and the 350,000 C57 ES cell clone gene-trap library that was under construction. But we lacked credibility as we had no reputation for shipping products to end users, which is one reason why TIGM has been so active sending out products to the international and national research community so to obtain a good reputation and be in

better position for new large-scale opportunities as they arise. One could speculate endlessly about the other reasons why TIGM did not get the KOMP RFA (see the attached *Science* article), but that is really only self-serving and no good can come of it at this point in time. Suffice to say that the review and its outcome were highly irregular, prompting Francis Collins and his senior KOMP staff to fly to Houston to try to explain to us in person why we were not funded. I don't know about you, but when my NIH applications are not funded, my program officer doesn't spontaneously call me and jump on a plane to talk to me in person about it. Quite the contrary, they are usually hard to find. This was unusual. That is all I can really say.

Secondly, getting back to the gene-trap issues, during the random process of gene trapping, it appears that the conventional clones are far more efficient at trapping than the conditional ready ones. Thus, even though the vectors are now in existence, and the vectors created by NORCOM in Canada based upon a design from Bill Skarnes of the Sanger Center/EUCOMM are really very cool with lots of great features, they are not being utilized to generate gene-trap libraries by the other groups involved in the IKMC. In fact, the EU pulled funding from the EUCOMM gene-trap effort. They believe that the TIGM asset made by Lexicon was sufficient. All current IKMC efforts funded by NIH (KOMP), EUCOMM and NORCOM rely upon high-throughput gene targeting approaches. These are slower and as a result, we find ourselves with more genome coverage than any other organization. This will remain true for another few years, I believe.

Finally, it is important to realize that condition-ready clones made into mice will only behave in a tissue-specific manner **IF** there is a cre-driver (line) available to take advantage of the vector design. Since my neuroscience colleagues tell me that they need 5000 cre-lines just for the brain, and only 400 total cre lines exist at this time in the WORLD, the vast majority of genetically modified ES cell clones made by the IKMC members will only make null alleles, thus being indistinguishable from the TIGM asset. So it is absolutely true that there are more advanced vector designs than the one that Lexicon used to create the C57 asset that TIGM maintains. But to say that the TIGM resource is antiquated technology is not being intellectually honest. I do not think that was your intent, which is why it is important to explain all the facts. With time, there will be more Cre lines, as the EU has the CREATE program to do just that. But now, the numbers are limited.

When the Lexicon production was nearing completion, I was able to convince them to switch to a conditional-ready vector and so TIGM does maintain about 2000 genes that are theoretically conditional ready. We are working with a few of these now to see if they work as expected. The TAMUS faculty have access to these ES cell clones as well.

Your second major concern was about how the decision was made to go after this Texas Enterprise Fund award. I certainly do not know when the conversations began, as I was a faculty member brought in to give my input sometime long after the process had already started. I had my own opinions as to whether or not TAMUS should get involved and what other options might have been explored. It was a decision made by individuals with the best intentions in mind. I can only imagine that people accept administrative roles with the understanding that they are empowered to make decisions. It is not always possible to get ground-up consensus before going forward with a plan. In my opinion, no one would be crazy enough to take on the headache of governance if every last matter was to be vetted by all concerned stakeholders. Sometimes one has to react to opportunities. Apparently TIGM represented such an opportunity. There were probably plenty of others in the 100 years before TIGM and there will be plenty more after TIGM. Well-intended administrators can pay lip service to the need for ground up buy-in, but sometimes it is not possible. Again, this is merely my speculation.

I hope this helps address some of your questions. If you have others, you can email me anytime or contact Dr. Wallis in College Station. With kindest regards, I remain

Sincerely yours,  
Rick

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