FRAXA Funding Priorities for 2012

As always, we try to maintain flexibility in our approach to research funding, and so we are willing to consider proposals for a wide range of fragile X studies. However, to avoid disappointment for prospective applicants, we offer these guidelines for the kinds of research proposals that are assigned highest priority in our grant-making process. Please remember that FRAXA's only goal is to develop enhanced treatments for fragile X, so all applications must pass through the filter of "translational relevance."

RFA: Translational Research - Identifying New Targets for Fragile X Therapeutics

Since trials of mGluR5 antagonists are well underway with a number of pharmaceutical companies, preclinical studies of mGluR5 antagonists are no longer high priority for FRAXA. mGluR5 is now exceptionally well validated as a treatment target in fragile X. Investigations of mGluR (and other GPCR) linked signaling pathways in fragile X animal models are still of interest to us, but only to the extent that they have the potential to identify other new treatment targets.

When planning research in relevant signaling pathways, it is worth remembering the pharma dictum that "kinases don't make good targets." While it is relatively easy to identify many kinases in any given pathways which could be points of therapeutic intervention, in practice it is often very difficult to develop drugs which target the kinases under study with any useful degree of specificity. There may be exceptions, and a bit of background research on the part of the applicant may show that potentially useful drugs are in development for a particular kinase.

Phosphorylases are generally even more problematic as drug targets, according to our pharma scientific advisors, and for many of the same reasons; they are ubiquitous. For this reason, we assign highest priority to investigations of targets which are CNS-specific. Potential applicants are well advised to keep these practical considerations in mind when developing a proposal to FRAXA, since we now have quite a bit of experience in dealing with these issues, and they are important factors in our decisions.

RFA: Preclinical Validation Methods

FRAXA has funded an enormous amount of high-quality research over the years, and this research has generated many important findings, both basic and translational. Most of these leads still need to be followed up. Several FRAXA grantees have identified long lists of mRNAs bound by, and presumably regulated by, FMRP, but we note with some dismay that few applicants propose to follow the leads generated by other groups.

One of the main roadblocks in developing new treatments for fragile X is the difficulty of validating putative treatment targets in animal models (especially the knockout mouse.) Currently, the gold standard for validation is the audiogenic seizure paradigm in the fmr1 KO mouse. Successfully validated drug classes for fragile X, such as mGluR5 antagonists and GSK3 inhibitors, have shown potent effects in this

paradigm. However, this assay uses far too many mice to be practical for most labs, and it is susceptible to false positives with known anticonvulsants.

We have a great unmet need for improved methods for preclinical validation of potential therapeutics in fragile X animal models. We need better ways to test compounds quickly and cheaply. These could be live-animal models, cell based, or in vitro, but they must have relevance to the mechanism of disease in fragile X. We are not prepared to fund a long, speculative development process -- we expect that the successful applicant will begin utilizing this model and testing compounds as part of the proposed work, and that the project itself will validate new therapeutic strategies.

We also have a great need for labs willing to perform preclinical validation of candidate compounds (or even genetic rescue) on an ongoing basis. Many universities have onerous Intellectual Property policies which preclude effective pharma collaborations, or even contract research of any kind, so please consult with your Technology Transfer office before applying.

RFA: Clinical Trials

Our highest priority will always be clinical trials; no other type of research has the potential to immediately improve the lives of people affected by fragile X. However, we do have important preferences for the kinds of clinical research we fund. We prefer to fund novel treatment approaches with the potential for disease-modifying effects. We recognize that is not practical to demonstrate disease modification during the course of most clinical trials, and that behavioral improvement will typically serve as a proxy. However, this model is only valid if there is evidence of disease modifying effects in fragile X animal models (see Preclinical Validation, above.) Thus, we are reluctant to fund clinical trials involving therapeutic strategies which have not undergone some form of preclinical validation. We encourage clinicians to collaborate with translational research groups to validate prospective therapeutics in animal models of fragile X prior to applying for major funding of clinical trials.

We hope these guidelines are helpful.

FRAXA Research Priorities

As fragile X research races ahead, FRAXA Research Foundation's funding priorities continue to change. At the same time as more highly talented scientists become interested in fragile X, NIH funding remains flat. This has resulted in a financial crunch that has prompted record numbers of applications to FRAXA, for larger average amounts than ever before. These factors, combined with no growth in FRAXA income, have resulted in a dramatic increase in competition for FRAXA grants. We anticipate being forced to reject many excellent applications, and we appreciate the frustration this may cause in the research community.

It may be of some help, therefore, to summarize FRAXA's current funding priorities, so that applicants will better understand what we are looking for. The purpose of this is not to discourage or disparage any kind of scientific inquiry; rather it is to inform the research community of the rather specific needs and interests of our foundation. We are committed to a single goal: helping children with fragile X in the near term, by funding the most appropriate biomedical research.

First and foremost, FRAXA funds translational research which may lead to routine medical treatment of fragile X syndrome. For the foreseeable future, we have decided not to fund any investigation of the various aspects of carrier status for premutations of FMR1. This means we do not fund FXTAS or POF research, or studies of possible cognitive or psychiatric effects of the premutation. These are all areas of great scientific interest, and these conditions may well cause significant morbidity. However, these conditions involve distinct mechanisms of disease from classical fragile X syndrome, which is the subject of our mission. Furthermore, studies of the basic mechanisms of disease in fragile X have been so remarkably fruitful that we feel it is imperative to pursue the leads generated by previous FRAXA-funded research.

FRAXA Priorities

1. Clinical Trials in Fragile X Subjects
   a) investigational new drugs (i.e. mGluR5 antagonists)
   b) available agents with disease specific effects (i.e. lithium)
   c) available agents with general effects (i.e. aripiprazole)

2. Preclinical Research
   a) animal testing of compounds which affect mGluR pathways
   b) enhanced cognitive/behavioral testing paradigms
   c) pharmacologic challenge testing (live animal)
   d) enhanced animal models

3. Translational Research (…just a few examples…)
   a) comparative studies of FMRP pathways in WT vs KO, preferably with rescue protocol (i.e. via double KO, siRNA, transgenics, etc.)
   b) pharmacology and electrophysiology (in slices, cell culture, etc.)
   c) proteomics, preferably with a functional component, since we are dealing with a defect in synaptic plasticity

Topics of Less Interest to FRAXA

1. Mechanisms of Trinucleotide Repeat Expansion
   (no viable near-term treatment is likely based on this line of inquiry)

2. Gene Reactivation Strategies
   (our consultants agree that commercially viable treatments based on these mechanisms are not likely in the near term)
   a) basic methylation mechanisms
   b) demethylation strategies
   c) histone deacetylase inhibition strategies

3. Basic Studies of Normal Pathways
   a) studies of synaptic plasticity in non-fragile X systems
   b) regulation of dendritic morphology in non-fragile X systems
   c) regulation of dendritic protein synthesis in non-fragile X systems
   d) RNAi mechanisms (though RNAi may be a powerful tool to study disease)
   e) studies of proteins/pathways with parallel function to FMRP (need some pilot data showing ***interaction*** with FMRP pathways)

4. Epidemiology and Phenomenology
   a) population studies of fragile X prevalence
   b) neuropsychology/traits of fragile X individuals (except as possible outcome measures for clinical trials)

5. Carrier (Premutation) Pathology
   a) cognitive/psychiatric profiling
   b) FXTAS
   c) premature ovarian failure

We attach highest priority to research projects with potential for near-term benefit for individuals with fragile X. Thus, human trials of therapeutic agents in fragile X subjects are a top priority, for both available and investigational compounds. Studies examining preclinical efficacy of potential therapeutics in the fragile X mouse model, based on previous basic mechanisms of disease research in fragile X, are also a very high priority. Translational studies in any of the accepted model systems of fragile X are also high priority, especially if they incorporate rescue paradigms. The term "translational research" is broadly used nowadays, so we define it here as research which can identify or test potential therapeutic targets in the disease pathways.

Specific topics which we feel are "too basic" for FRAXA funding at this point include basic mechanisms of trinucleotide expansion, general studies of RNAi pathways, and determinants of spine morphogenesis. We are at, or very near, the point where FRAXA-funded research projects will need to be done primarily in animal models of fragile X. It has been our experience that simply studying normal pathways in normal animals does not yield an accurate or complete picture of the abnormalities encountered in fragile X. The absence of FMRP causes multiple subtle changes in cells, and studies of one aspect of the normal function of FMRP often ignore other functions. The most productive research projects to date have involved functional assessments of FMR1 null tissues compared to normal tissues; electrophysiologic and pharmacologic studies have been especially productive, with much more potential remaining in these disciplines. Incorporation of rescue paradigms into proposed studies greatly enhances the competitiveness of applications. Attempted reversal of a phenotype via rational pharmacologic or genetic manipulation holds great appeal for us.

We frequently receive applications seeking funding for study of pathways which parallel the function of FMRP. Studies of genes and gene products which interact with FMRP are unlikely to be funded without pilot data, and there must be some suggestion of therapeutic implications from greater understanding of this interaction. For example, MAP1b mRNA is a target of FMRP; in the absence of FMRP, MAP1b is elevated (as are many other things). Several excellent FRAXA-funded studies have shown that inhibition of MAP1b function by pharmacologic or genetic means can rescue a wide range of fragile X phenotypes. This interests us greatly. On the other hand, FMRP is known to participate in interactions with RNAi machinery, and preliminary studies suggest that microRNA's may enhance recognition and translational regulation of mRNAs by FMRP. However, since this mechanism is absent in fragile X syndrome, the details are not a high priority for FRAXA (although we fully appreciate its importance to the general fund of knowledge). More important (to us) is an understanding of which proteins are upregulated or downregulated, and under what circumstances this occurs.

This summary is not meant to be exhaustive and we will update it as often as necessary. We are always willing to discuss exceptions. As always, feel free to ask us about our priorities -- we're happy to discuss this at any time.

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