

### **Cardiovascular Program – Theme # 3: Arrhythmias**

#### **Introduction:**

Cardiac arrhythmias are a major public health burden. There are 250,000 - 400,000 sudden cardiac deaths (SCD) in the US every year, accounting for up to 20% of all deaths in adults; the majority of these are due to ventricular fibrillation. In addition, approximately 2.5 million Americans now suffer atrial fibrillation (AF), a number that is expected to surpass 5 million by 2050. AF is associated with increased risk for stroke, heart failure, and death, and AF incidence increases in the presence of structural heart disease and with age. Strong evidence indicates that risk for both SCD and AF includes a prominent genetic component, and that the arrhythmias arise as a result of the dynamic interplay among a susceptible substrate, proximate triggers, upstream modulators, and perpetuators.

Despite dramatic advances in the therapy of some arrhythmias, contemporary treatment approaches to AF and SCD continue to be seriously limited. Use of ICDs in primary prevention of SCD is life-saving, but inefficient and costly as currently applied. Ion channel blocking antiarrhythmics have not reduced mortality, and proarrhythmia with these agents, as well as with a wide range of drugs developed for non-cardiovascular indications, is an increasing problem clinically and in drug development.

Contemporary arrhythmia management reflects improved understanding of mechanisms and the development of new technologies. Studies of genetic arrhythmia syndromes have demonstrated the speed at which progress can be made in the development of a personalized approach to therapy that exploits the partnership between clinical and basic science. This paradigm highlights the potential for new approaches to provide predictive, personalized, and preemptive strategies for effective antiarrhythmic interventions in large populations at risk. We present here highly inter-related priority recommendations for research in cardiac arrhythmias that focus on ***investigator-initiated interdisciplinary approaches, that integrate genetics, molecular, cellular, systems and clinical approaches, to delineate risk factors and mechanisms, and thereby improve therapy.***

#### **Recommendations:**

##### **1. Improve methods to identify patients at risk and causally-related biomarkers.**

Identification of patients at risk for AF and SCD remains a challenge. Studies are needed not only of electrophysiologic remodeling but of the modulatory effects of aging, autonomic function, reactive oxygen species, and inflammatory and metabolic factors in arrhythmia risk. Delineating the relationships between triggers and substrates in the initiation and perpetuation of arrhythmias is required. Biomarkers of risk should be sought in the general population and in defined patient cohorts at risk, such as those with coronary disease, hypertension, heart failure, or congenital heart disease. These markers may be genetic or environmental, and their interplay may be highly dynamic. New methods to identify and analyze dynamic risk over short (seconds to minutes) and long (weeks to months) time frames are needed. Ethnic- and gender-specific risk should be explored. Exploration of risk will require generation of new cohorts and analyses of existing datasets. In both cases, databases that include all acquired phenotypic information should be developed and retention of samples for subsequent analysis (e.g. at the genomic or proteomic levels) should be encouraged.

## **2. Delineate mechanisms that bridge molecular events to systems biology.**

Identification of genetic and environmental factors that place patients at risk for arrhythmias should be integrated into experimental studies that link events from the molecular to the systems level. "Molecular" includes inter- and intra-molecular interactions and control of gene expression; "systems" includes organ level physiology, intact animals, and clinical populations. Improved computational models are required to extend understanding and to help interpret effects of physiologic, pathophysiologic, or pharmacologic perturbations in such complex systems. To enhance the link in exploring remodeling and integration from molecule to system levels, better cellular and *in vivo* experimental models are needed; including the development of novel genetically altered mammalian models.

## **3. Develop new therapies based on improved understanding of mechanisms.**

Identification of new genetic, molecular, cellular, and tissue mechanisms should result in new targets for effective and safe drug therapies, and, along with advances in imaging, in improved approaches to ablation. Clinical studies pointing toward antiarrhythmic effects of pleotropic therapies (e.g. statins, aldosterone blockers, or fish oil) are also clues to new targets for intervention. Thus, large clinical trials should incorporate AF and SCD endpoints. Research into novel therapies should focus on (a) drug development; (b) cell/gene-based therapy and tissue engineering; and (c) improvement in development and use of devices and ablation to prevent or inhibit arrhythmic electrical activity. Ion channels remain key drug targets, and research should extend to channel modulation via targeting of upstream regulatory cascades and channel motifs that control activity via allosteric interactions. Drug development should be accompanied by research into novel delivery systems (exploiting, for example, advances in nanotechnology) to increase specificity of delivery and dosage. Potential areas well suited for cell/gene based therapy include biological pacemakers, AV node repair/bypass, and treatment and/or reversal of disease-induced myocardial remodeling and tachyarrhythmias. Evaluation of new therapies should include a cost analysis. Studies are required in children and adults with congenital heart disease as these present increasing challenges in ethics, counseling, and management.

## **4. Develop a centralized, patient-based, dynamic resource that will facilitate the identification of genetic and other biomarkers that confer high risk phenotypes and variable responses to therapeutic interventions in patients with rhythm disturbances.**

While investigation of rare diseases has provided a starting point for the development of personalized approaches to disease management, a continuing challenge is accumulation of sufficiently large numbers of subjects to conduct appropriately powered research. To address this, a national core facility that functions as a centralized laboratory for genotyping and as a repository for genetic and relevant clinical data related to cardiac arrhythmias should be established and maintained by the NHLBI. The data in this core facility should be accessible as a resource for NHLBI-supported researchers involved in phenotype-genotype studies of cardiac arrhythmias. Within the context of this resource, we recommend a commitment to the development of bioinformatics that will enable management and distribution of these data and materials. This effort requires active involvement of biostatisticians and statistical geneticists to assess complex probabilistic issues involved in the long-term clinical course. This unique resource, which could be extended to other areas in cardiovascular genetics, has a high probability of: 1) enhancing the joint involvement of basic scientists, clinical investigators, biostatisticians, and statistical geneticists in the investigation of complex probabilistic risk mechanisms related to arrhythmic events; and 2) expediting scientific advancement of risk assessment and effective therapeutics for prevention of SCD and AF during the next decade.

09/29/06

Business Operations  
National Heart, Lung, and Blood Institute  
Level 1 Strategic Planning Working Group  
June 29-30, 2006

**Cardiovascular Program – Theme # 3: Arrhythmias**

**Recommendations:**

The business operations discussion occurred during the working lunch on day one of the meeting. The group discussed the 7 areas identified by the Cardiovascular Executive Planning Committee. Priority ranking sheets were collected at the start of day two. A Cumulative Response table is appended.

**1. Streamline CSR review procedures.** The working group recommended that streamlined review procedures, shorter grant applications, and shorter turnaround times should be a high priority for CSR and should not be limited to only senior investigators. This recommendation was added as a separate item for prioritization and is included at the end of the Cumulative Response Table.

**Additional Business Operations Areas and Other Recommendations:**

**2. Hold an NIH (NHLBI) summit with industry.** The idea of a summit with industry seemed to resonate with the group. A summit might explore the idea that NIH Institutes should have more control over the science, i.e., control over trial design (and not only the access to the data); perhaps the FDA should be involved in that they only approve devices that had been vetted through the NIH or another science-focused agency (see below).

**3. Promote synergy between NIH and FDA to take advantage of NIH scientific expertise in the design and evaluation of clinical trials that are required as part of new drug or device applications.** In the age of ever increasing complexity in drug and device trial design and implementation, it seems that some improved efficiency and synergy could be realized by sister agencies such as the NIH and FDA. With the FDA's appropriate focus on regulatory and surveillance concerns, it seems that institutes of the NIH might be well-positioned to assist in the design and evaluation of clinical trials that are required as part of new drug or device applications. This would include, but not be limited to, robust statistical design, analysis and interpretation, recommendations regarding minimal clinical data to be collected and standardization of data formats. This could help to streamline the drug/device approval process and improve reporting and analysis of untoward events. Unanticipated benefits of such cooperation might be the generation of biological data repositories and generation of a venue for reporting negative studies that often do not appear in the medical literature.

**4. Form disease-based CSR study sections, to cover two-three main diseases, comprised of diverse experts with a strong clinical or research interest in the disease being studied.** Since many future grants will likely combine population-based approaches and molecular/genetic science, it will be important to create study sections that have a balance of diverse expertise in methods (epidemiologists, geneticists, basic scientists) so that these grants can be adequately evaluated. In addition, some amount of clinical expertise on the problem being studied is extremely important so that the significance of grants can be evaluated.

**5. Mandate a minimum effort for PIs with multiple awards.** Perhaps an assessment of the percent effort devoted to each grant should be performed.

**Group 3 Arrhythmias Cumulative Response Table**

	High	Medium	Low	Mean Priority Rank
1. Create streamlined procedures for renewing grants for established investigators, including a briefer application and greater emphasis on prior productivity	7	1	9	4.6
2. Funding and Award Mechanisms Junior Faculty	16	2		1.4
3. Create incentives and mechanisms for cross-Institute and interagency funding of large projects	3	9	4	4.1
4. Review the NHLBI pre-approval process for investigator-initiated grants with direct costs >\$500K in any year and the process for Institute-initiated programs (RFAs, RFPs):	2	8	6	5.6
5. Create a mechanism to provide infrastructure support for large observational studies to facilitate addition of ancillary studies. Create mechanisms to assure that the data and samples from the core studies are made available to the wider scientific community as a resource for further research	8	7	1	3.5
6. Issues related to CSR and study sections	5	7	3	3.9
7. Dissemination and communication of advances and discoveries and resources made by NHLBI-Supported Investigators	3	4	8	4.8

Streamlined review procedures and shorter turnaround times for all investigators; without priority for senior investigators.	16	1		1.6
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Note: Data represents cumulative responses from 18 priority/ranking sheets collected at the meeting with some items omitted by individual respondents.

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