AMDCC Annual Report (2011)

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Abstract: The Animal Models of Diabetic Complications Consortium (AMDCC) and the Mouse Metabolic Phenotyping Centers (MMPC) are two multi-center initiatives funded by the NIH. During the current five year funding cycle, the AMDCC had the primary responsibility of developing and characterizing animal models that mimic human diabetic complications. The AMDCC consists of 8 animal engineering centers, 3 phenotyping cores and 1 coordinating and bioinformatics unit (CBU) with investigators from 14 separate institutions. Oversight of the consortium comes from both the NIH and an External Advisory Committee (EAC). My laboratory is the current CBU for the AMDCC and is responsible for organizing the activities of the consortium, including the administrative responsibilities as well as the development of the informatics infrastructure required to store, disseminate and analyze the data generated by the AMDCC. In contrast, the MMPCs were charged with providing the scientific community with standardized, high quality metabolic and physiologic phenotyping services for the mouse. The MMPC provides state-of-the-art technologies to investigators for a fee, with their services including characterization of mouse metabolism, blood composition (including hormones), energy balance, eating and exercise, organ function and morphology, physiology and histology. Officially, these two consortia had no interaction or coordination of activities with regard to their respective missions. As part of the renewal of these two consortia, the NIH has decided to integrate and coordinate their activities. In order to facilitate this interaction, one CBU will be responsible for creating and maintaining the administrative, scientific and informatics infrastructure necessary to organize and facilitate their operations. The goal of this proposal is to provide that infrastructure. We will build upon the success of the current AMDCC CBU infrastructure to provide both the AMDCC and MMPC with a robust and comprehensive service oriented solution that supports both the common and unique aspects of each entity. Specifically, we will: 1) Provide Support for the Administrative and Coordinating Activities; and 2) Create and Maintain the Informatics Infrastructure Necessary to Support the Activities of both Consortia.

1. Program Accomplishments:

Throughout this period, my group has been responsible for coordinating and supporting consortia activities for both the AMDCC and MMPC. Specifically, we were responsible for both the annual Steering Committee meetings and monthly Steering Committee conference calls, organizing workshops and training sessions for consortia members, providing travel funds and itinerary support for the External Advisory Board (EAB) and invited guests, providing agendas and minutes of the meetings and conference calls, fiscal and review oversight for the funding programs and designing and creating the informatics infrastructure to support the activities of the membership as well as the data generated by both consortia.

AMDCC/MMPC Coordinating Unit

Administration. The administrative effort of the AMDCC and MMPC CBU has been primarily focused on providing coordination and support for the meetings, workshops, conference calls and funding programs. The AMDCC Steering Committee (SC) meets twice a year and the MMPC SC meets once a year to discuss the progress and direction of the consortia with their EAB and NIH staff. Both meetings are two days long with the full Steering Committee, EAB and NIH program directors meeting for the first day and a half followed by the EAB and NIH staff meeting for a few hours afterwards to discuss consortium progress. The CBU is responsible for determining the meeting dates, organizing the agenda, providing travel funds and itinerary support for the EAB and invited guests, organizing and compiling any correspondence between the EAB and the SC, and working with the NIH staff to determine the hotel location. Due to NIH restrictions, the AMDCC meetings are always held in Bethesda or Baltimore, MD while the MMPC meetings are held at one of the funded centers. The travel support for the EAB members includes; airline itineraries, help with hotel reservations and reimbursement of travel expenses. We coordinated 8 of these meetings for the AMDCC and 6 for the MMPC (includes joint meetings between AMDCC and MMPC) during this last funding cycle.

In addition to the semi-annual meetings, we also coordinate and support the monthly SC conference calls. The AMDCC call is scheduled to occur the first Wednesday of each month at 2:00 PM EST and the MMPC monthly call is the last Thursday of the month at 3PM EST. In addition to normal agenda items, the AMDCC selects one investigator each month to present new and interesting data from their laboratory. As the CBU we are responsible for preparing the agenda, scheduling the speaker list and taking the minutes for each call.

During this second project period, we held 12 different training workshops for the AMDCC/MMPC member investigators. The purpose of the workshops were to train the membership in website navigation, data entry and data analysis. The CBU visited the MGHC, AMDCC Pathobiology Sites and the MMPC Centers to train their entire staff. In addition, the CBU produced the workshops as web based training videos with full sound and graphics. The videos were placed on the private side of the portal where members could train new personnel or have a refresher course. Although the members were pleased with the workshops, investigators may have additional questions or needs beyond the scope of the workshop. Therefore, we also provide a web based conference system for the consortium members

(www.gotomeeting.com). This system allows the CBU to remotely run workshops, consult with the membership and troubleshoot problems. A conference can be started on-the-fly or scheduled in advance. This system is firewall friendly and allows the moderator to release control to any of the connected users to present data or show their desktop. Between the two consortia, we hold 1-2 web conferences a month to work with the consortium members.

Lastly, we are responsible for creating and maintaining the reporting mechanisms to the EAB and NIH staff. We developed the software to generate website activity summary reports to monitor how much data is being uploaded to the servers by the membership. We developed an interface on the private side of each portal for the entire membership to generate these reports for either individual investigators or specific AMDCC/MMPC centers.

Communication As the CBU, we provide more than one way for the membership to communicate and disseminate information. The typical medium for communication between members is email. To support the structure of the consortia, we provide our membership with a number of mailing list email addresses or ListServs. Mailing lists provide a convenient way for people to communicate with a group of individuals by allowing them to use one email address to send correspondence to a group of individuals. The AMDCC/MMPC CBU maintains 24 different ListServ lists for consortium members. Most of these correspond to the various subcommittees in the two consortia to allow private communication. The membership to these lists is maintained and automated using the AMDCC/MMPC Websites via the object model we created (see Bioinformatics Infrastructure below).

In addition to the ListServ, we often require a mechanism to survey or question the membership concerning the various activities of the AMDCC or MMPC. For example, choosing dates for meetings or voting on funding program applications by the EAB and Steering Committee. To accomplish these tasks, we use a web based product called SelectSurvey.NET to manage all the questionnaires and surveys (www.classapps.com). This product provides an easy and quick way to produce web based questionnaires and surveys as well as the statistical evaluation of the results. For determining committee conference call or meeting dates and times we use Doodle polls (www.doodle.com). This free website provides a simple interface to collect dates and times for meetings and conference calls and includes a reporting tool.

Funding Programs Both the AMDCC and MMPC have opportunity pools used to fund research related to each of the consortia. As the CBU, we were responsible for both the review process as well as the fiscal oversight of the funded applications (awards are subcontracts from the CBU). The MMPC had two funding programs, a Pilot and Feasibility (P&F) Program and the MICROMouse program while the AMDCC has only a P&F Program. The MMPC P&F program was originally solicited once a year but was subsequently folded into the MICROMouse program which accepts applications throughout the year and is reviewed quarterly. The AMDCC P&F program is solicited once a year. To manage the review process and fiscal oversight, we developed a software solution to streamline the process of application submission/review and application tracking. To do this we created an extensive infrastructure to store, manage and organize the funding program activities of both consortia. This required us to develop the database schema, object model and web pages to deal with this information and workflow. To help manage the application and review process, automated emails are sent out by the system to the investigators, reviewers and program staff at key points during the submission/review

workflow as well as post-award activities (e.g. progress report reminders). Once an application is awarded, the system tracks the invoices and progress reports submitted by the applicants. During this last funding cycle, we organized 20 separate review cycles for the MMPC (15) and AMDCC (5). These 20 solicitations received a total of 109 applications (AMDCC=55, MMPC=54) and the CBU funded and tracked 51 applications (AMDCC=24, MMPC=27).

Over the last 4 years, we have created a robust and comprehensive infrastructure to coordinate and interact with the AMDCC and MMPC members. This includes the personnel and software necessary to communicate effectively.

AMDCC/MMPC Bioinformatics Infrastructure

Our programming paradigm is to develop software systems based on a 3-tier architecture, where we create the presentation layer, business logic and data layer into separate software systems. These systems have been developed to minimize maintenance, but provide a robust scalable model for future growth and interactions at the national level with other organism databases. A description of the software and object/data model design and implementation diagrams can be viewed at http://www.amdcc.org/bioinformatics/ bioinformatics.aspx.

During this current funding period, we were focused on the re-design and creation of the infrastructure to support multiple consortia. This effort required that we re-write the AMDCC and MMPC websites and redesign the object model and database schema. These design changes are technological advancements for the websites as a whole while others are more functional additions and enhancements. The following sections describe these changes in more detail.

.NET 1.1 to .NET 2.0 to .NET 4.0 The most significant change we undertook during this cycle was to convert the entire code base from the .NET 1.1 to .NET 2.0 frameworks. The previous website application was written during the first funding cycle used .NET 1.1. While this website was quite functional, there were a number of limitations of the .NET 1.1 application model that made maintenance and future enhancements of a multi-consortium system more cumbersome. The most significant advantages are the ability to use object factories and master pages, which allows us to re-use code more efficiently. Figure 2 illustrates the changes made to the system. The .NET framework is a high performance scalable programming paradigm that provides

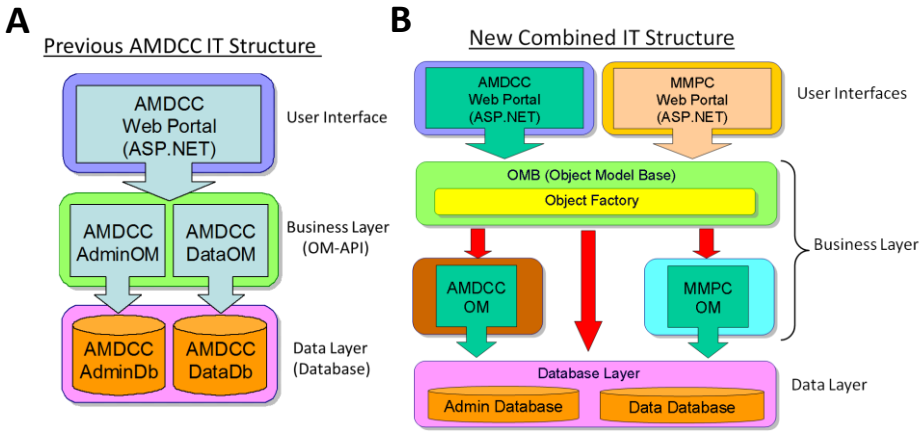

Figure 1. Infrastructure re-design. **A**) Previous IT structure used for the AMDCC. **B**) Current infrastructure design to support multiple consortia. The OMB provides the **same interface and functionality to both portals**. This allows for all common functionality to be implemented in the OMB code base and prevents code from having to be duplicated and separately maintained for each portal. The OMB also allows its functionality to be overridden and/or customized through the concept of Object Factories.

technologies to easily create web applications (ASP.NET) and Web Services (HTTP/SOAP). My laboratory exclusively writes our web applications in C#. The most significant advantage of C# and ASP.NET are that these technologies are strongly-typed fully object-oriented languages with full support for inheritance and polymorphism. We completed the transition to .NET 2.0 during the first year of the funding cycle.

Over the last five years, the .NET framework has evolved through several versions (.NET 2.0 => .NET 3.0 => .NET 3.5 => .NET 4.0). Some of the advantages of the .NET 4.0 framework include better memory management via improved garbage collection, better support for parallel computing and faster execution times due to an improved compiler. We wanted to take advantage of the parallel computing aspect for future data analysis algorithms as well as speed up the sites responsiveness. Over the last six months, we ported the .NET 2.0 codebase to a .NET 4.0 codebase and have deployed it to the production servers.

Software System Re-Design In implementing the .NET 1.1 to .NET 2.0 transition, we re-wrote the entire portal system for both consortia including the web portal, object model and database schema. We developed a common object model base class that can be inherited by both consortium specific APIs (Figure 1). This is ideal since a large fraction of the objects and implementation are identical between the two consortia, allowing us to maintain one code base for both consortia. The common base class is inherited by each of the AMDCC and MMPC specific APIs, with the differences between the consortia being coded at level of these APIs. This object model covers the entire spectrum of objects necessary to support both the AMDCC and MMPC: all the scientific objects (experiments, strains, models, protocols, assays, histology, etc.); consortium specific objects (MMPC catalogs, tests, center cores, etc.); and the administrative objects (members, clients, laboratories, meetings, security, privileges, etc.). The complete re-write of the object model to support multiple consortia required coding 384 total objects with more than 800 properties.

Database Schema The original AMDCC database did not have the concept of multiple consortia built into the schema. To support both consortia, we developed a unified database schema that can accommodate multiple consortia. This required a re-write of both the administrative data schema and the scientific data schema. The schema for the administrative database can maintain separate consortium memberships, meetings, security privileges, and security groups. With respect to the scientific data, we unified the phenotype assays while allowing consortium specific data for their experiments such as measurements, mouse strains, laboratory animals, histology, protocols, and publications. For the MMPC, we added the data objects to support the creation of a dynamic catalog of tests available for the consortium as well as support for external clients of the MMPC. The newly completed administrative and data schemas are stored using SQL Server 2008 and required 267 tables, 1052 stored procedures, 203 views, 141 functions and 65 triggers.

Web Applications During this cycle, we also re-wrote both the AMDCC and MMPC web portals. We took advantage of master pages that allow us to create one page that contains the header and footer for the consortium and inject page specific code when needed. Because a good portion of the two web portals have similar content, we can unify the code execution using UserControls where the content display is the same. The advantage of this is we only maintain one code base for both web portals, so any change that is made will be inherited by both portals automatically. Consortium specific rendering differences are coded at the level of

the UserControls by passing a consortium ID to the control during the rendering process. The web portals accommodate both public and member driven interactions (private). We are on the fourth generation design of the AMDCC web portal and second generation for the MMPC and are continually adding content to the websites for both the public and the members.

Ontologies/Controlled Vocabulary. We use controlled vocabularies extensively throughout the websites. All drop down boxes used during data entry or data query use either existing controlled vocabularies or ones developed by the consortia. We populated our ontology table with Gene Ontology terms and anatomy terms from the Computational Biology and Informatics Laboratory (University of Pennsylvania). For mice, we use the Standard Anatomical Nomenclature Database at the University of Edinburgh to relate these terms to developmental (Theiler) stages. In addition, we imported mouse gene information from the Mouse Genome Informatics database at the Jackson Laboratories for those genes currently associated with GO terms. This enables searches using the gene name, symbol, or GO concept. We have programs for automatic, scheduled retrieval and import of externally maintained data (such as GO). Note that we do not reproduce these databases; rather, we import enough information to permit structured data entry and searches. Should users require further details about a term or gene, we provide hyperlinks to the appropriate web resource. The ontologies required for microarray data exchange were imported from Chris Stoeckert's work in the MGED Ontology Workgroup. The AMDCC/MMPC CBU has been careful to align our vocabulary with existing groups whenever possible

Security Model We built a role based security model to manage application security. The model requires that we assign members to groups based on their roles in the consortium. Each group has privileges associated with it. Thus, members inherit privileges based on their group membership. This security layer is called every time a member tries to perform a privileged action. We worked with the consortia Steering Committees to determine what information is public and what should be kept private. All experimental data entered into the system is tagged with a public release date determined by the policies of the consortium that controls the data. Investigators are notified 2 weeks in advance when their data is about to be released. This was done to avoid potential publishing problems by releasing data before manuscripts have been accepted.

Because we built a robust security model, we are able to tailor the web sites based on the user and their privileges. By default, all users are considered "public" unless a member logs onto the system. All the web pages generate their options, look and feel and information based on the user's personal profile (e.g. My AMDCC). If the general public comes to the site, they will only see what has been released to the public.

Data Entities and Organization Because the AMDCC/MMPC generates both quantitative and qualitative data, one of the technical challenges of creating the web portals was to develop an organization of the data and web site that would accommodate the diversity of data and experimental designs being captured. For example, an AMDCC investigator evaluating a diabetic cardiovascular model may expose a mouse strain to a specific concentration of streptozotozin (STZ, e.g. 20 mg/kg body weight) at different times (e.g. 0 and 5 days) while being fed a high fat diet and take blood glucose and total cholesterol measurements at timed intervals (e.g. 0, 4,8,12 weeks post STZ) followed by *post mortem* En Face staining of the aortic root and the quantitation of the lesions. This example has a number

of experimental factors (independent variables) as well as quantitative measurements and image data. To provide the scientific community with a comprehensive system that is contextual and flexible, we developed a software architecture that unifies and captures these various experimental entities. We are only listing some of the data entities supported by the software.

- *Experiments* All data entry into both consortia is done in the context of an "Experiment". The Experiment domain is quite generic and provides a unifying structure to integrate the heterogeneous data types collected by the members of the consortia. This domain allows users to specify animals, protocols, assays and *independent variables* used in an experiment. Of note is the ability to define the independent variables (termed Experimental Factors in the portal). This provides a mechanism for the phenotype data to be defined in precise terms, such as taking samples at timed intervals or varying dosage of drugs. This becomes extremely useful for analysis and provides clear ways to compare data across different experiments. An "experiment" captures animal level data and links concrete results, such as phenotype assay measurements, histology, images and gene expression data. For example, quantitative data from a phenotype assay (e.g. aortic root lesion size) can be tied to a histology image (e.g. En face staining of the aortic root) from the same animal. Because we capture both the independent variables and the animal level data, one has the opportunity to partition the data in a variety of ways based on specific query options.
- *Strains* Strains can be defined based on how they were created and their genetic manipulations. Because the genetic manipulations of the strains can be extensive, we created a flexible genotype class to capture more detailed genetic information for the strains created. The genotype class can be used to precisely define any genetic manipulation, including genomic segment mice, transgenics (regulatory elements can be defined separately from the gene), cre/lox mice and all the standard manipulations (eg. knockout, knockin, point mutations, etc).
- *Protocols and Publications* One of the products of each consortium are the protocols developed by the membership. Protocols can be attached to virtually any entity in the system and are conceptually grouped (eg. array manufacturing, diabetes induction, staining, breeding, etc.). All the publications generated by consortium members are added to the system and searchable by the public.
- *Histology Images* The web portals also provide the infrastructure for the AMDCC/MMPC investigators to upload any histology images associated with their experiments. The image can be viewed using a flash viewer, associated with a specific animal/experiment, and annotated with the magnification, staining protocols, sample dates, slide prep dates, and macroscopic and microscopic descriptions.
- MMPC Catalogs, Tests and Orders As a service oriented consortium, the MMPC maintains a catalog of services and tests that can be purchased from each of the MMPC Centers. In order to provide the most up to date information to the public, we created the data and object models to support a dynamic MMPC catalog of tests that can be downloaded or searched from the MMPC website. The catalog can be searched using catalog number, center, center core, test category or keyword. The catalog maintains a list of the tests, their titles and descriptions and pricing information where available. We also created a series of

web services that provide electronic access to the MMPC catalog information. Using the web services, the individual MMPC centers can maintain their catalog information on the National MMPC site, but still have it displayed on their custom center site's look and feel. This allows both the National and individual MMPC sites to remain in sync with respect to their catalog information.

In addition to the catalog, we also created the software system to track the orders requested by the clients of the MMPC Centers. The system tracks the status of an order and links the order to the experimental data generated for that client, providing the MMPC Centers a way to distribute the results to their clients via the website.

Data Analysis A number of analytical tools have been incorporated into the web portals in order to facilitate data analysis. We wanted to provide not only the tools, but also automated analysis of the data where appropriate. One of the common features to all of the interfaces for these tools is that one can filter the data to be analyzed or viewed. Filtering is accomplished via the creation of a DataSet or at run time using common options to filter based on assay, strain, sex, age and any independent variable available for that data. The run time options are tailored to the kind of tool being used. Both websites currently support these types of automated analyses:

- Basic statistics: This interface provides the public and membership with an easy and flexible way to calculate basic statistical information for ad-hoc and saved datasets or individual experiments and tests.
- T Test: This interface provides an unpaired T Test to assess whether two groups of animals are significantly different from each other.
- ANOVA: This interface supports automated One Way and Two Way ANOVA analyses for both balanced and unbalanced experimental designs. The Two Way ANOVA currently only looks for Strain by Sex interactions. In addition, we use a Tukey HSD correction when calculating the p values for all pairwise comparisons to account for multiple tests.
- Correlations: This interface allows the users to quantify the relationship between two or more assays. The algorithm calculates the Pearson correlation coefficient, R squared and covariance as well as provides a plot of the data with the regression line.

Data Visualization In addition to analytical tools, we provide visualization tools for the membership and public. Specifically,

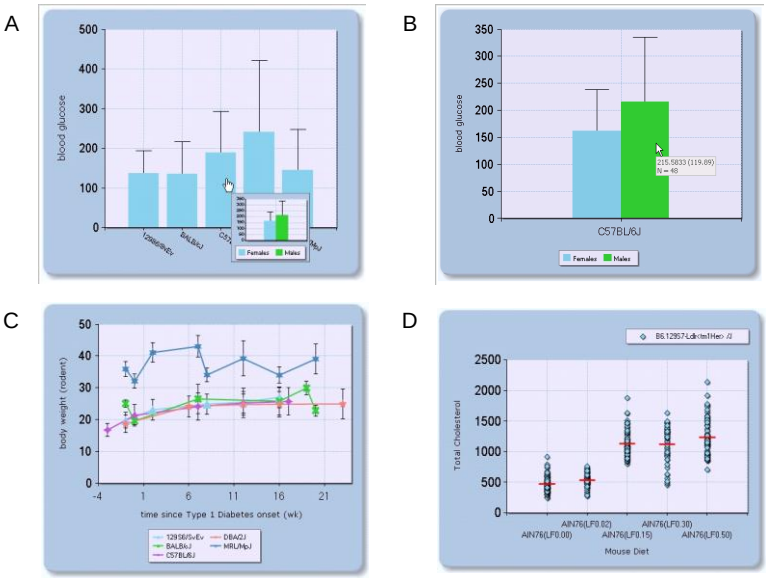

Figure 2 On-the-fly charting **A)** Column charts for comparing strains. If the data contains male and female data, a preview is shown during mouse over. **B)** Detail male/female data from panel A. Tooltip shows mean, SD and N. **C)**. Line chart where each line is a different strain. **D)** XY Plot with categorical data (mouse diet).

we have developed a number of user interfaces to allow users to create charts on-the-fly based on any filter criteria. Like the analytical tools described above, one can chart data from a DataSet or an individual experiment. We currently have three charting options for the portal; column charts, line charts and X-Y plots. All of the charts generate error bars when appropriate and are fully configurable (e.g. editable titles and axis labels). Additionally, we use tooltips extensively so that details of each data point can be seen simply by moving the mouse pointer over the data point (Figure 2).

Data Search and Retrieval One of the key aspects of the web portals is the ability to search and download the data generated by the public and members. We provide data search pages for all the data entities in the system as well as the ability to create ad-hoc datasets using these data entities as filtering options. The data entities covered by the individual search pages include; Animals, Assays, Complications, Experiments, Histology, Investigators, Microarrays, Models, Publications, Protocols and Strains. Each of these pages provides the user with the appropriate filtering options for that data entity.

Data from an individual experiment can be downloaded as an Excel spreadsheet by simply navigating to the Experiment Definition page for the Experiment and clicking on the Browse Data link at the top of the page. To search and download data from multiple experiments simultaneously, users can explore the data using the DataSet search page. A DataSet is a generic class used to construct complicated data queries across all the data generated by consortium members, thus providing a mechanism for higher order analysis (e.g. meta analysis). Investigators can build sophisticated queries using all the objects in the object model. We use SearchCriteriaGroup (SCG) objects to build the queries. One can use as many SCGs as necessary to define the query, giving them the ability to combine all the available objects to build complicated queries. For example, one can build a query to extract all the assays performed on C57BL/6 mice with blood glucose measurements > 200 mg/dl for at least 4 weeks post diabetes onset and induced with STZ 20 mg/kg body weight and fed on a high fat diet starting at 4 weeks of age for 3 months. *Ad-hoc* datasets can be downloaded as an Excel spreadsheet or used by the analysis and visualization tools at the web portal.

Web Services Both the AMDCC and MMPC web services layer exposes classes and methods of the CBU object models which can be used by users to interact with each consortium specific object model using custom built applications or machine-to-machine interfaces. Details about the interfaces are provided to users through an XML document called a Web Services Description Language (WSDL) document.

Over the remaining months of this last year we will continue to improve the sites usability and will work with the AMDCC Pathobiology Center PIs to make sure they upload their data to the AMDCC web portal before then end of the funding period. In addition, we will begin planning the transition from the Animal Models of Diabetic Complications Consortium to the Diabetic Complications Consortium. This will include a redesign of the key aspects of the portal, including logo design and update of all the documentation.

2. **Collaborations:**

Although the CBU does not technically collaborate with the AMDCC Pathobiology Sites, it continues to provide support and the infrastructure for each of the sites to accomplish the mission of the AMDCC.

With respect to groups outside of the AMDCC, the CBU currently collaborates with the Beta Cell Biology Consortium (www.bcbc.org) and the Nuclear Receptor Consortium (www.nursa.org) in a project called dkCOIN, the NIDDK Consortium Interconnectivity Network. This project is designed to develop the tools and infrastructure to allow NIDDK funded consortia to share data between consortia. The initial pilot project started in November 2009 with a workshop between the principals of each of the consortia to discuss how to move forward with this initiative. Over the last year, we have develop the policies, protocols, software, database schema and web portal (www.dkcoin.org) to allow each of the consortia to share information regarding the resources available at each of the NIDDK funded consortia. We will continue this work.

3. **Address previous EAC comments:**

- Monthly calls with NIH program staff are beneficial and should continue.

  Response: The CBU will continue to have monthly AMDCC conference calls to review the web portal and develop plans for the future functionality of the web site.

- Summer student program is highly valuable and merits continuation. Additional efforts must be made to engage the community.

  Response: After authorization from the NIDDK Program staff, the CBU is soliciting another funding cycle for the Summer Student program during the 2011 funding solicitations.

- Several valuable resources and weblinks (from NIA, NHLBI, NCI, NIAID, JDRF, KOMP, etc.) were identified during the SC meeting. Every effort should be made to make these easily accessible via the AMDCC website.

  Response: The CBU thanks the EAC for this suggestion. In response, we implemented a web resource page that can be accessed via the AMDCC Home Page that provides links to external resources organized into these categories: 'Basic Research Networks & Resources'; 'Research Sample & Data Repositories'; 'Clinical Trials & Networks'; and ' Clinical Information & Data Repositories'. The total number of resources identified in this page is 55.

  Web Resource page: http://www.amdcc.org/shared/webResources.aspx

- The KOMP/IMPC allows individual investigators to nominate genes (http://komp.org/phenotype/nomination.php). The CBU is encouraged to lead an effort to work with the consortium to nominate new strains for creation and phenotyping.

Prioritization methods could include literature searches, genetics studies, omic studies, network analyses, etc.

Response: We thank the EAC for this suggestion. The CBU will begin to organize a similar effort that was undertaken during the first few months of the current AMDCC funding cycle where each of the AMDCC Pathobiology sites identified specific mouse models that should be created by the AMDCC and rank them. We would suggest a similar activity with the AMDCC investigators regarding genes that should be knocked out with respect to the Diabetic Complications being studied and develop a list of genes to be nominated to the KOMP project with their rationale.

- The website is a work in progress. In both the individual PI data and consortial data, more work is required to improve the access and meaning of the information pulled up. It's not always clear who has done what. For example, in searching for nerve conduction velocities some are motor, some sensory tail, some listed as sural. Age of mice and duration of diabetes for each of these values are not readily available. Nor are nerve temperature values. We were unable to bring up summary graphs. We also tried to bring up data on a number of models, but were unable. It was unclear which boxes needed to be ticked off to generate data. Are sural sensory conduction velocities actually being done or are these truly sciatic-tibial sensory conduction? No SNAP amplitudes or CMAP amplitudes are given. A single Table I was able to bring up did not list n numbers, age of mice, standard errors, etc. Much of the Table was unpopulated. This very public interface must be improved.

  Response: The CBU is very concerned that the EAC had these difficulties with the web portal. One of the difficulties of designing the web portal is that the CBU comes at the data in a defined way and it is difficult to anticipate how individuals unfamiliar with the site and data organization will approach the web portal. In response to this, the CBU would suggest that it organize a standing internal committee that meets regularly to review the web portal from the perspective of the user and determine the best way to present the data to the general public. We will begin to identify local individuals with expertise in phenotyping and studying Diabetic Complications and start the process of web portal organization.

  With respect to the neuropathy measurements indicated in the above comment, the CBU will work with the investigators responsible for the neuropathy phenotyping to determine the baseline information that needs to be uploaded for experiments involving neuropathy phenotyping. Unfortunately, the Neuropathy Committee has not developed validation criteria for Diabetic Neuropathy so there aren't always baseline assays defined. Meaning, investigators don't always provide the same information between laboratories. We will work with these investigators to make sure they all agree on some basic level of information that must be uploaded with adding data for these measurements.

- Dr. McIndoe needs to ensure that lay descriptions for all models are added to the

website ASAP.

Response: The CBU is working with Ed Leiter at the Jackson Laboratory to provide the lay descriptions for the strains.

- The web site continues to be improved. The model centric concept is probably the best for now. The pilot project program seems very successful and well administered.

  Response: The CBU thanks the EAC for this comment. We have started the 2011 P&F solicitations and will continue to work on the web portal to make is useful to the scientific community.

- The integration of several resources is a new challenge and may not be trivial, but also has great potential for adding value to the AMDCC.

  Response: The CBU is currently part of the initial working group for a new pilot project sponsored by the NIDDK called dkCOIN initiative. We have been working over the last year to integrate meta-data information from other NIDDK funding consortia into the AMDCC site and vice versa. dkCOIN is the NIDDK Consortium Interconnectivity Network (www.dkcoin.org) and was established to begin the process of integrating and collating the data generated from NIDDK funded centers and consortia. We will continue to work on this initiative in collaboration with the other NIDDK funded consortia.

- The summer student projects are a great idea and we are looking forward to seeing the results. This will likely lead to further improvements of the site as well as give us a first impression of the possibility for meta-analyses. We strongly encourage the consortium to solicit additional summer student opportunities in 2011 and beyond.

  Response: The CBU has continued solicitation for the Summer Student program for the 2011 cycle.

- We need to be doing more with the eyes and other tissues being generated by JAX. Perhaps the consortium should solicit/advertise via website?

  Response: The CBU will work with the NIDDK Program Officers to determine what resources should be dedicated to the diabetic complications that are under represented.

- Dr. McIndoe's team continues to try to make the AMDCC website more user friendly. Connectivity with the MMPCs, indeed maintaining their website will certainly improve cooperation and utility of both resources. The added ARRA funding should ensure the durability and integration of the related programs. Continued encouragement from Dr. McIndoe to have the AMDCC investigators upload data is appreciated. However, more needs to be done to ensure that all data is uploaded and available to the community.

The use of novel approaches such as "GoToMeeting" should improve user compliance.

Response: The CBU continues to work with all the AMDCC investigators to ensure their data is uploaded into the system. We schedule multiple monthly conference call and web conferences with the staff of the AMDCC investigators to either help them with the data upload or provide extended training on how to organized data for experiments that are complicated (ie many independent variables).

- The EAC recognizes that the website has become an extremely useful tool for investigators from around the globe to find assays and protocols relevant to diabetic complications. However, it was also noted that many of these documents have not been updated in several years. The SC is strongly encouraged to routinely review these documents to ensure that they are up-to-date and that new protocols are added as needed. This should include discussions with the AMDCC P&F awardees who provide additional expertise in areas such as retinopathy, uropathy, neuropathy, wound healing, etc. We encourage the full consortium to identify any such gaps and to work with Dr. McIndoe fill them.

  Response: The CBU will work with consortial investigators from the various sub committees to review the current state of the protocols and make changes as necessary. This will dove tail nicely with the switch to the DCC for the third funding cycle as many of the protocols will need to be updated with the new DCC look and feel.

- Below is a list of your AMDCC publications from the website. Should any publications be added or subtracted?

  Response: None of the publications need to added or subtracted, they are up to date.

1. ParaSAM: A parallelized version of the significance analysis of microarrays algorithm.
   Ashok Sharma, Jieping Zhao, Robert Podolsky, and Richard A. McIndoe
   Bioinformatics (Oxford, England), 2010
2. Mouse Models of Diabetic Nephropathy:A Midstream Analysis from the Animal Models of Diabetic Complications Consortium
   Frank C. Brosius IIIa, Charles E. Alpersb, Erwin P. Bottingerc, Matthew D. Breyerd, ThomasM. Coffmane, Susan B. Gurleye, Raymond C. Harrisf, Masao Kakokig, Matthias Kretzler, Edward H. Leiterh, Moshe Levii, Richard A. McIndoej, Kumar Sharmak, Oliver Smithiesg, Katalin Susztakl, Nobuyuki Takahashig, Takamune Takahashif
   Journal of the American Society of Nephrology : JASN, 2009 (20(12)), 2503 - 2512
3. A modified hyper plane clustering algorithm allows for efficient and accurate clustering of extremely large datasets.
   Sharma A, Podolsky R, Zhao J, McIndoe RA.
   Bioinformatics (Oxford, England), 2009
4. ParaKMeans: Implementation of a Parallelized K-means algorithm Suitable for General Laboratory Use.

Piotr Kraj, Ashok Sharma, Nikhil Garge, Robert Podolsky, and Richard A McIndoe
BMC bioinformatics [electronic resource], 2008 (9), 200

5. Recipes for Creating Animal Models of Diabetic Cardiovascular Disease
   Willa Hsueh, E. Dale Abel, Jan L. Breslow, Nobuyo Maeda, Richard C. Davis, Edward A. Fisher, Hayes Dansky, Donald A. McClain, Richard McIndoe, Momtaz K. Wassef, Cristina Rabadan-Diehl, Ira J. Goldberg
   Circulation research, 2007 (100), 1415 - 1427
6. caBIONet – A .NET wrapper to access and process genomic data stored at the National Cancer Institute's Center for Bioinformatics databases
   Piotr Kraj and Richard A. McIndoe
   Bioinformatics (Oxford, England), 2005 (21), 3456 - 3458