NCTR Division of Genetic and Molecular Toxicology

NCTR Science Advisory Board Subcommittee Site Visit Review, March 20-21, 2019
(Rescheduled from December 5-6, 2018)
Report Submitted May 14, 2019

Overview

Review Subcommittee and Expertise

The names and affiliation of the Subcommittee site visit reviewers are provided in Appendix 1. Two members (S. Felter and M. Aschner) of the NCTR Science Advisory Board (SAB) participated in the review and served as chair and co-chair of the subcommittee, respectively. Three additional reviewers participated as subject matters experts in content areas of interest to the Division of Genetic and Molecular Toxicology (DGMT). The Subcommittee members received a written overview of their charge in a memorandum, dated July 19, 2018 from Daniel Acosta, Jr., Ph.D. NCTR Deputy Director for Research and Donna L. Mendrick, Ph.D., Associate Director for Regulatory Activities. The charge memo is attached in Appendix 2.

In advance of the meeting, the Subcommittee site visit reviewers were provided project overviews divided into three thematic areas. A primary reviewer was assigned to each research theme in advance of the meeting. The reviews of each theme area have been written primarily by the assigned experts:

Theme (NCTR lead(s))	**Primary Reviewer**
Current research supporting regulatory acceptance of the Pig-a gene mutation assay (Dobrovolsky)	David Eastmond
New approaches to genetic analysis (Parsons, Revollo, Chen)	Mark Fielden
New biological platforms for evaluating (genetic) toxicity (Wang, Petibone)	Ofelia Olivero

Agenda, Reviewed Materials, and Process

The agenda for the Subcommittee site visit is shown in Appendix 3. Electronic files of materials were provided to reviewers prior to the site visit, and hard copies were provided during the site visit. These included:

- An overview of the DGMT, including the history, mission and strategy, description of personnel and laboratory structure, a list of major equipment, and sources of research funding.

- Information relevant to each of the three themes, including an overview, list of ongoing projects, presentation abstracts and slides, and poster abstracts. A full copy of each poster was also provided to the reviewers during the meeting.
- List of accomplishments and complete projects (FY 2009-FY2016)[1]
- A list of publications from 2010-2018
- *Curriculum Vitae* of DGMT Principal Investigators
- SAB Subcommittee Report from 2009 Review of the Division of Genetic and Reproductive Toxicology, annotated with responses from Division Director Martha Moore
- Examples of how DGMT has responded over the last 10 years to recommendations made by the 2009 SAB Subcommittee.

After welcomes and opening remarks, Dr. Heflich began the scientific session by providing an overview presentation of the Division.

Division of Genetic and Molecular Toxicology: Overview

At the time of the last SAB Subcommittee review in 2009, the Division was called the Division of Genetic and Reproductive Toxicology (DGRT), led by Dr. Martha Moore. The following year, the Division was re-named the Division of Genetic and Molecular Toxicology, to better reflect its research activities. Dr. Heflich has served as Director of the DGMT since 2013, succeeding Dr. Martha Moore. Dr. Mugimane (Manju) Manjanatha became the Division's first Deputy Director in 2017. The DGMT staff includes 11 permanent (GS) research scientists, 10 GS support scientists, 3 FDA staff fellows (one externally supported), 1 FDA visiting scientist (externally supported), 2 administrative personnel, and 7 ORISE post-docs (4 externally supported).

Dr. Heflich described the mission of the DGMT to improve public health by providing FDA with the expertise, tools, and approaches necessary for comprehensive assessment of genetic risk. The goals of the Division are to:

(1) Respond to Agency needs for chemical-specific data (e.g., nanomaterials and tobacco products);

(2) Maintain DGMT's tradition of leadership in regulatory assay development and validation (e.g., Mouse Lymphoma Assay, *Hprt* assay, transgenic rodent assay, and *Pig-a* assay); and

[1] The previous review of this Division was held in 2009; the list of accomplishments and completed projects represents work completed after this review.

(3) Establish new paradigms for regulatory decision making that integrate measures of genetic risk with biomarkers of toxicity.

The Division is in the process of moving to a new location (Building 14), with Phase I of the move having been completed in 2018. Phase II of the move is expected to be completed in 2019. The new location will provide about 8000 sq. ft. of lab space and 4000 sq. ft. of office space. When the move is complete, there will be several common labs in addition to special-purpose labs. The PCR common lab, which is currently distributed among several locations in two different buildings, will all be consolidated into a single lab as part of Phase II. While a list of equipment was provided to the reviewers, this was not discussed during the site visit.

Funding for the DGMT is provided by NCTR and a number of external sources, including FDA Centers (FDA/CDER, FDA/CTP), FDA competitive grants, the National Toxicology Program, and Cooperative Research and Development Agreements (CRADAs). The site visit focused on NCTR-funded projects that have been designed and/or proposed by DGMT scientists.

As with other divisions at the NCTR, some projects undertaken by DGMT originate from ideas/hypotheses by DGMT scientists and are proposed to FDA Product Center scientists, while others are initiated at the request of FDA staff based on needs of one or multiple Product Centers. The DGMT also conducts studies under an interagency agreement with the National Institute of Environmental Health Sciences / National Toxicology Program (NTP). DGMT scientists collaborate with the Product Centers on design and conduct of approved projects to ensure that the results of studies will meet Product Center needs and are most useful to the missions of FDA. An impressive number of publications originating from the DGMT have remained fairly constant at approximately 20-30 per year for the past eight years.

In response to the SAB Subcommittee review in 2009, the DGMT has continued to invest in several research areas (development and validation of new methods and risk assessment approaches for genetic toxicology – e.g., Pig-a assay, Gpt-THA mouse model; development and integration of high throughput methodologies - e.g., CometChip assays; and the cancer biomarkers program – e.g., ACB-PCR, cancer driver mutations). It has also initiated new projects including the development of *in vitro* human test models (*in vitro* organotypic models, metabolically competent human primary cells and cell lines), exploration of germline effects (sperm Pig-a, *in vitro* testes model, *C. elegans* model), and the development of epigenetic endpoints (epiComet chip assay).

The remainder of the agenda was spent hearing presentations and viewing posters grouped into three thematic research areas:

1. Current research supporting regulatory acceptance of the Pig-a gene mutation assay (Dobrovolsky)
2. New approaches to genetic analysis (Parsons, Revollo, Chen)
3. New biological platforms for evaluating (genetic) toxicity (Wang, Petibone)

Review of Theme 1: Supporting FDA regulatory needs in the field of genetic toxicology: collaborative activities providing expertise and conducting applied and original research for the FDA

Current research supporting regulatory acceptance of the Pig-a gene mutation assay

Dr. Dobrovolsky provided an overview of the research that has been conducted on the Pig-a gene mutation assay, a sensitive assay that detects mutations in the X-linked Pig-a gene that has been developed using hematopoietic cells of several mammalian species and humans. The Pig-a assay measures mutant phenotype cells using immunofluorescent staining and flow cytometry and has been shown to be useful in non-clinical safety evaluations for detecting potential mutagens and carcinogens. As an *in vivo* gene mutation assay, it is seen as a valuable test which can be used as a follow-up to positive *in vitro* results and should be able to fill a critical void in the current regulatory testing schemes.

Approximately 5 years ago, a proposal to create a regulatory-compliant test guideline for the Pig-a assay was submitted to the OECD by a consortium led by DGMT scientists. While generally viewed as a promising *in vivo* gene mutation test, a number of concerns were raised by the OECD reviewers that needed to be addressed before the test guideline could be approved by the OECD. Drs. Dobrovolsky, Heflich and other members of the DGMT, in collaboration with outside stakeholders, have taken the lead in addressing the OECD reviewer concerns. These efforts included creating a database of the more than 90 Pig-a mutation studies that have been conducted to date with their results. They have also produced multiple lines of evidence that the flow cytometry-based assays of peripheral blood T-lymphocytes, erythrocytes and granulocytes detect actual mutations in the endogenous Pig-a gene. In addition, they developed a flow cytometry-based *in vitro* Pig-a assay in mouse lymphoma L5178YTk+/- cells and demonstrated that this assay is also an effective detector of mutations affecting the Pig-a gene. Review information requested by the OECD was compiled in a Pig-a Detailed Review Paper which was recently submitted to OECD. Work continues on a retrospective performance analysis, which will need to be submitted to the OECD prior to the beginning of the formal review by the OECD. If all goes according to plan, it is anticipated that the Pig-a OECD test guideline will be approved in 2021. Altogether, the work by the DGMT scientists and

collaborators have confirmed that the Pig-a assay detects true mutants and appears to be suitable for inclusion as a recommended regulatory test.

DGMT scientists are also beginning a study with collaborators at the University of Arkansas that will determine erythrocyte PIG-A mutant frequencies in cancer patients before and after undergoing cisplatin-based antineoplastic chemotherapy. In conjunction with *in vitro* and animal Pig-a mutagenesis studies on cisplatin, this study has the potential to confirm the usefulness of rodent assays for detecting mutations relevant for human risk, as well as provide insights into the potential risks for humans receiving this type of chemotherapy.

The Subcommittee thought that the work that the DGMT has conducted on the Pig-a assay in preparation for the OECD guideline review has provided critical information supporting the validity of this up-and-coming assay and represents a valuable contribution to the genetic toxicology and regulatory fields.

During the poster session, a number of poster presentations were made that were related to Topic 1. The titles of these presentations are listed below.

- Differential genotoxicity mechanisms of silver nanoparticles and silver ions
- Comparative genotoxicity of TEMPO and TEMPO derivatives in mouse lymphoma cells
- Genotoxicity of 2-bromo-3'-chloropropiophenone
- Analysis of vehicle control mutant frequencies in the rat *Pig-a in vivo* gene mutation assay
- Differentiation of whole smoke solution-induced micronuclei using potency ranking by dose-response modeling
- Development of an "Epicomet" assay for the assessment of global DNA methylation status *in vitro* using an endonuclease enzyme, McrBC
- Development of a new transgenic hairless albino mouse model for potential reduction, refinement or replacement of animals used in photocarcinogenesis studies
- *In vivo* genotoxicity study of NNK in Sprague-Dawley Rats
- *In vivo* gene mutation assay for *Pig-a* mutation in bone marrow granulocytes: Use in determining the source of erythrocyte *Pig-a* mutations in ENU-treated and DMBA-treated F344 rats
- Development and characterization of a sperm *Pig-a* gene mutation assay

The studies presented were at various stages of completion; some were at early initial stages whereas others had been completed. In general, the Subcommittee felt that the topics and focus of the research projects were consistent with the DGMT mission and were responsive to FDA Center needs and comments made in the last Subcommittee review. As noted elsewhere, it was not possible to thoroughly review and discuss the posters with their authors given the limited amount of time available for poster viewing. Brief comments are included as feedback to the poster authors. For

some posters, it is recommended that headings and better description to the axes be added to the figures to make them easier to follow in a short amount of time. The Subcommittee was encouraged to see that Benchmark dose analyses had been included in a number of the poster presentations. However, there were considerable inconsistencies in the approaches used (different BMRs, etc.), and the work appeared to be more of an after-thought and not an integral part of the studies. The Subcommittee was also pleased to see that some of the posters tried to understand the mechanisms underlying the genotoxic responses that were seen. We encourage that, in addition to simply performing the tests, mechanistic studies be performed where feasible to help with the broader interpretation of the test results.

Review of Theme 2

The focus of the DGMT on the analysis of both somatic and germline mutations is highly relevant and consistent with its mission. The DGMT researchers are encouraged to continue to evaluate and develop Next Generation Sequencing (NGS) approaches to understand the exact base changes involved with mutation (mutational spectroscopy or spectrum analysis), help determine how diseases progress through the induction and expansion of mutations, and to leverage mutational signatures to associate cause with effect (e.g., particular exposures with disease causing mutation). This technology promises to significantly advance the means by which *in vivo* mutagenesis is evaluated both *in vitro*, *in vivo* and in human populations, which is anticipated to have far reaching implications for hazard identification and risk assessment. It will also be important to address potential risks with new therapeutic modalities, such as gene editing, which is a significant gap.

<u>Cancer driver mutation-based biomarkers for cancer risk (B. Parsons)</u>

The ongoing work by Dr Parsons on cancer driver mutations should help to improve our ability to predict future cancer risk and potentially help improve the translatability of animal data. The DGMT are encouraged to further develop the expertise in error-corrected NGS approaches and apply their experience in validating new mutation assays (e.g., Pig-A assay) to this emerging area of mutagenesis research. Dr Parson's work has helped to establish the importance of variability in cancer driver mutations as a marker of risk. To expand the significance of this work it will be important to address what set of driver mutations will be important to assess for specific tumors of interest, and how these may behave in nonclinical models. The DGMT should continue to avail themselves to both nonclinical rodent models and clinical samples to further test these hypotheses and improve our understanding of the translatability of rodent data. Adopting state of the art

approaches for ultra rare detection of somatic mutations will be key to advance this field, so the DGMT should consider developing experience with other error-corrected sequencing approaches as they become commercially available. It is not clear whether the efforts in this area applied to establishing a model to identify molecularly-targeted therapies that prevent acquired resistance (lung tumor organoid model) was consistent with the DGMT mission, albeit of great interest therapeutically.

Assessment of clonal whole genome sequencing for detection of gene editing induced off-target effects (J Revollo)

The research focused on establishing the unintended genetic side effects of CRISPR-based therapeutics is important for the safety assessment and regulation of these products and represents a significant gap that requires new tools since existing genotoxicity assays do not fully inform the potential risks with the class of drugs. It is acknowledged that detecting rare somatic variants such as INDELs (insertions, deletions) can be difficult to detect with short read sequencing technology and may require single cell cloning and expansion. Careful attention to artefacts that may arise during the expansion phase will be required. One limitation of this approach is the need to source individual cells, which prohibits application to certain cell types. The DGMT should consider exploring methods that can be readily applied to a variety of tissues, models or species and can be incorporated into existing toxicology studies where single cell cloning is not readily feasible. The evaluation of base editing in *E.coli* and germline mutations in *C. elegens* may also be problematic from the perspective of human relevance. Therefore, the use of mammalian models should be prioritized as feasible.

Assessment of mutagenicity of nanomaterials using whole genome sequencing (T Chen)

The efforts to study the mutagenicity of nanomaterials is challenging owing to the physical attributes of these particles and limitations of the Ames assay. The proposed approach of evaluating mutagenesis *in vitro* using whole genome sequencing of clonally selected cells may provide an attractive alternative. The DGMT should consider first establishing an *in vitro* model with appropriate negative and positive controls to characterize the system and establish the methodology prior to investigating and interpreting effects with new compounds such as silver nanoparticles. Initial characterization of the model will also facilitate an understanding of the strengths and limitations of *in vitro* models to predict how the results may translate and how it compares to gold standard approaches using the Ames assay, mouse lymphoma and/or *in vivo* endpoints.

Other recommendations

Considering the many potential applications of NGS to mutation detection in a variety of *in vitro* and *in vivo* models, the DGMT should consider what an ideal minimal *in vitro* and/or *in vivo* test battery may look like that would provide the best characterization of chemical-induced DNA damage from the perspective of understanding mechanism of action and dose response, and which considers animal use. In addition, there should be some consideration for how a new model would replace what is already been used, rather than add to the existing testing burden.

It is acknowledged that epigenetics can play an important role in carcinogenesis and inheritable phenotypes. However simply measuring changes in methylation state with the Epicomet assay may not provide the information needed to fully understand the risk of such changes. There are basic biological questions related to the cause vs effect of epigenetic alterations in tumors, and the degree to which changes, quantitatively and/or qualitatively, induced by a chemical can meaningfully contribute to an understanding of risk with any certainty, particularly in an *in vitro* model. The DGMT should carefully consider the degree to which these basic questions are explored relative to the effort involved and the competing priorities of the Division, and the relative impact of any new assays on risk assessment at this time.

Review of Theme 3: New biological platforms for evaluating (genetic) toxicity (Wang, Petibone)

The models presented by the investigators were developed to address 3 main limitations of existing *in vitro* assays: 1- Tissue/cell specificity of the induced toxicities; 2-three-dimension structure and metabolic capacities and 3-close simulation of the *in vivo* environment. Both models seem to address those limitations and there is potential to improve their capabilities.

Wang's bronchial-epithelium model will be used to detect mutations using the *Pig-a* gene reporter assay with the aim of bridging gaps between *in vitro* and *in vivo* outcomes and limiting testing in animals. Although the method is promising and closer to human scenarios of exposure, a word of caution should be placed. Three-D cultures should be biologically relevant and recapitulate microenvironmental factors that closely mimic *in vivo* situations. One of the components that should not be forgotten is the extracellular matrix (and its ~300 interactive molecules), and of critical importance for the endpoints in question are the infiltrating immune cells that in multiple occasions are the producers of oxidative stress and consequent DNA damage.

The model presented by M. Petibone seeks to address the complex concept of germline mutations by providing a tool that can help with designing studies, dose selection, time of exposure and aid in interpretation of germ line mutations, before moving to *in vivo* models.

It is advisable that the model be developed to obtain sperm cells, that in turn will provide a venue to address a different set of toxicities associated with exposures and associate them with endpoints such as malformations, motility issues, and others.

The investigators have a challenging but exciting time ahead of them optimizing the models and moving forward with the concept of diminishing animal testing.

Overall Subcommittee Review and Suggestions:

1. The primary mission of the DGMT is to advise the FDA Product Centers in the area of genetic and molecular toxicology and related areas, and to perform original and applied research to address the Centers' needs. It is evident from the history of achievement of the DGMT and the materials provided to the Subcommittee that the DGMT provides essential support to the mission of NCTR and FDA overall. DGMT scientists have substantial experience with many of the commonly used genotoxicity assays, and have also been involved in developing the guidelines for these assays. As a result, they serve as a valuable source of information for the FDA Centers on the performance of the various tests and on the interpretation of test results.

2. DGMT scientists are very well-integrated into the broader scientific community. The discussions with the FDA Centers were described as both informal and formal with DGMT members serving on FDA committees. DGMT scientists also serve on expert committees organized by professional societies and international consensus-forming groups where, in a number of cases, DMGT scientists have leadership roles. These activities were seen by the Subcommittee as closely aligning with the mission of the DGMT, and represent a valuable service to the FDA as well as the genetic toxicology and regulatory communities at large.

3. The evolution of the Division over time speaks to its agility and focus on meeting the needs of the Agency. The DGMT is highly effective at providing data needed for genetic risk assessment / product safety assessments, while also strategically investing in research to advance the field. Especially because the field of genetic toxicology is rapidly changing, we encourage the DGMT to revisit its strategic plans on a regular basis, and to ensure there are mechanisms in place to gauge productivity and success towards short and long-term goals.

4. The quality of the science performed by members of the DGMT is outstanding. DGMT scientists use innovative approaches to solve important issues required to advance regulatory science. A

good example of this is the work to evaluate the off-target effects of gene editing therapeutics using NGS approaches, and error corrected NGS to explore the utility of cancer driver mutations as biomarkers of cancer risk. Another example is the DGMT work to demonstrate and confirm that the Pig-A assay is actually measuring mutations, which has made a valuable contribution to the genetic toxicology field and has helped advance regulatory sciences. One caution is to ensure that *where appropriate and feasible*, the research remains hypothesis-driven rather than technique-driven.

5. One area in which we see the DGMT having a unique opportunity to be influential in moving regulatory toxicology forward is in the qualification process of new biomarkers or models, which is currently quite lengthy. The DGMT should consider how their experience in validating the Pig-A assay could be leveraged to help develop guidelines for how new genetic toxicology tools should be qualified for regulatory use. Additionally, DGMT is positioned to improve the qualification process of new biomarkers or models, which is currently quite lengthy.

6. It is important that DGMT consider the external landscape and the need avoid reproducing what is already being developed elsewhere (e.g. human lung and testicular platforms) so as to focus Division resources where significant gaps in the field exist. The Division should also continue to collaborate with consortiums where possible to develop or test approaches that require more resources and/or stakeholder input (e.g. validation of NGS for mutagenesis).

7. DGMT scientists are highly collaborative and have established very effective working relationships with other research and regulatory entities within NCTR, throughout FDA, and with other groups both within and outside of the federal government. Two very recent examples are the collaboration that DGMT scientists established with the University of Arkansas Medical Sciences to adapt the human reticulocyte Pig-a assay for use in monitoring gene mutation in cancer patients receiving platinum-based antineoplastic therapy. Additionally, DGMT signed a Memorandum of Understanding with the State of Arkansas to conduct research on the genotoxicity of the nanomaterial graphene in collaboration with the University of Arkansas at Little Rock.

8. The Subcommittee Site Visit Team greatly appreciates the significant effort made by the DGMT staff to prepare meaningful materials, including presentations and posters, for our evaluation and discussion. We recognize that this work represents only a fraction of the capability and achievements of the DGMT, and as such encourage the NCTR to continue to keep Division reviews focused on those projects for which input is specifically sought, as it is not possible to

conduct a complete review of a Division within one day. More time could be arranged in the schedule to facilitate real-time question and answers, discussion and feedback, particularly during the poster session. With regard to the materials prepared for the site visit, consideration might be given to arranging the publications and achievements in a way that allows the reviewers to more easily connect them with the research areas that are being highlighted (vs. all DGMT publications/achievements being listed in chronological order).

9. The DGMT should consider initiating or enhancing career development programs for postdoctoral fellows to ensure they are being trained not only in the scientific process and techniques, but also in the roles and responsibilities of the NCTR and the FDA Product Centers. Cross-training across divisions or short-term projects across the agency may expand the experience and serve to improve recruitment and retainment. The Division should also consider succession plans for their staff to ensure continued career development and retainment. Given newly established security policies, it will be increasingly important for the DGMT and other NCRT divisions to recruit more domestic scientists or international scientists that reside within the United States. To do this we recommend that the NCTR establish relationships and increase outreach/recruiting efforts with graduate and other training programs to ensure a pipeline of eligible and qualified postdoctoral fellows and early career scientists. Enhancing the diversity of the ORISE fellows will add originality, creativity and innovation.

Appendix 1. Division of Genetic and Molecular Toxicology Subcommittee Site Visit Review Members

Susan P. Felter, Ph.D., Subcommittee Chairwoman and NCTR SAB Member
Research Fellow
Central Product Safety Division
Procter & Gamble Company
Cincinnati, OH

Michael Aschner, Subcommittee Co-Chair and NCTR SAB Member
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David Eastmond, Subject Matter Expert
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Mark Fielden, Subject Matter Expert
Scientific Director
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Amgen Inc.
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Ofelia Olivero, Subject Matter Expert
Chief
Intramural Diversity Workforce Branch
National Cancer Institute
National Institutes of Health
Rockville, MD

U.S. FOOD & DRUG ADMINISTRATION
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

September 17, 2019

To: Science Advisory Board Members to the National Center for Toxicological Research

From: Drs. Donna Mendrick and William Slikker, Jr.

Dear Science Advisory Board Members,

We welcome participation of the Scientific Advisory Board (SAB) in the review of the research conducted at the National Center for Toxicological Research (NCTR) that will occur on December 3-4, 2019. The SAB is comprised of eminent scientists in their fields and NCTR requests that the Board conduct external reviews of its research programs to provide independent scientific guidance, technical advice, and recommendations on strategic direction and mission relevance to the NCTR leadership and program staff. It is anticipated that the SAB will provide objective advice to the NCTR Director, researchers and senior staff on strengths and perceived weaknesses of each aspect of the research program. Because there is insufficient time to present all the ongoing and planned research being conducted at NCTR, summaries of research programs will be provided with some examples of individual projects.

Research projects at NCTR are conducted by senior scientists with the assistance of staff fellows and postdoctoral fellows. These projects may arise in several ways including:

- In response to requests from FDA regulatory centers
- Initiated by NCTR Principal Investigators
- Requested from the National Toxicology Program (since there are reviewed by a multi-government panel in great detail, these studies are not covered in this SAB review)

These projects are critical to the success of NCTR's mission and goals, and the quality of the science must be state-of-the-art, able to withstand critical analysis and worthy of publication in peer-reviewed journals.

Tasks for the SAB:

- What is your evaluation of the research programs being conducted?
- One role for NCTR is to prepare the FDA for new technologies. Please evaluate how NCTR may improve horizon-scanning for emerging sciences and comprehensive safety assessment approaches

U.S. Food and Drug Administration
National Center for Toxicological Research
3900 NCTR Rd.
Jefferson, AR 72079
www.fda.gov

- Identify and discuss critical regulatory, research, scientific issues, trends, and needs in relation to the research capabilities of the NCTR/FDA. (Feedback will be given in open session except for those areas that impact personnel. That feedback will be given in closed sessions.)

We look forward to your visit and review of NCTR's research.

Sincerely,

|signed|

Donna L. Mendrick, Ph.D.
Designated Federal Official and Associate Director for Regulatory Activities

|signed|

William Slikker, Jr, Ph.D.
Director

Appendix 3. Division of DGMT Subcommittee Site Visit Agenda

SAB Subcommittee Review of the Division of Genetic and Molecular Toxicology Research Program – Day 1

All presentations include a minimum of 5-10 min for discussion

Wednesday, March 20, 2019

1:00 – 1:30 p.m.	**Welcome, Introduction to NCTR, Purpose of Review**	
	William Slikker, Jr., Ph.D., NCTR Director	
1:30 – 2:15 p.m.	**Overview of DGMT**	
	Robert H. Heflich, DGMT Director	
	Mugimane G. Manjanatha, DGMT Deputy Director	
2:30 – 3:45 p.m.	Topic 1: **Supporting FDA regulatory needs in the field of genetic toxicology**	
	2:30 – 3:00 p.m.	**Introduction**
		Robert H. Heflich
		Rui Xiong
	3:00 – 3:45 p.m.	**Current research supporting regulatory acceptance of the *Pig-a* gene mutation assay**
		Vasily N. Dobrovolsky
3:45 – 5:00 p.m.	**Break/Poster viewing**	
	Adjourn	
	Dinner (location TBD)	

SAB Subcommittee Review of the Division of Genetic and Molecular Toxicology Research Program – Day 2

Thursday, March 21, 2019

8:30 – 10:20 a.m.	**New approaches to genetic analysis**	
	8:30 – 8:45 a.m.	**Introduction** Robert H. Heflich
	8:45 – 9:30 a.m.	**Cancer driver mutation-based biomarkers for cancer risk assessment: FDA needs, strategy, progress, and planning** Barbara L. Parsons
	9:30 – 9:55 a.m.	**New Project, Using NGS to evaluate the off-target effects of gene-editing** Javier R. Revollo
	9:55 – 10:20 a.m.	**Research Proposal, Assessment of mutagenicity of nanomaterials using whole genome sequencing of mammalian cells expanded from single-cell clones** Tao Chen
	10:20 – 10:40 a.m.	**Break**
10:40 – 12:00 p.m.	**New biological platforms for evaluating (genetic) toxicity**	
	10:40 – 11:00 a.m.	**Introduction** Robert H. Heflich
	11:00 – 11:20 a.m.	**Research Proposal, Genotoxicity Testing in Organotypic Tissue Models: a Potential Alternative of in vivo testing** Yiying Wang
	11:20 – 11:45 a.m.	**Research Proposal, Can an in vitro testicular model be used to evaluate germ cell toxicity?** Dayton M. Petibone
11:45-12:00	**Wrap-up** Robert H. Heflich	
12:00 p.m.	**Open session adjourns**	
12:00 p.m.	**Closed Subcommittee meeting begins**	