



CANCER PREVENTION &
RESEARCH INSTITUTE OF TEXAS

**REQUEST FOR
APPLICATIONS**

RFA R-13-IIRA-1

**Individual Investigator
Research Awards**

**Including Targeted Requests for Applications:
Carson Leslie Awards for Pediatric Brain Cancer Research
Hoffman-La Roche Research Awards**

FY 2013

Fiscal Year Award Period
September 1, 2012–August 31, 2013

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ARCHIVE

RFA VERSION HISTORY

Rev 2/16/12 RFA release

Rev 3/8/12 Announcement box revised (p.4)

- Prevention Research applications may be submitted under any Research award mechanism RFA

ARCHIVE

1. ABOUT CPRIT

The State of Texas has established CPRIT; CPRIT may issue \$3 billion in general obligation bonds over 10 years to fund cancer research and prevention.

CPRIT is charged by the Texas Legislature to:

- Create and expedite innovation in the area of cancer research and product or service development, thereby enhancing the potential for a medical or scientific breakthrough in the prevention, treatment, and possible cures for cancer;
- Attract, create, or expand research capabilities of public or private institutions of higher education and other public or private entities that will promote a substantial increase in cancer research and in the creation of high-quality new jobs in the State of Texas; and
- Continue to develop and implement the Texas Cancer Plan by promoting the development and coordination of effective and efficient statewide public and private policies, programs, and services related to cancer and by encouraging cooperative, comprehensive, and complementary planning among the public, private, and volunteer sectors involved in cancer prevention, detection, treatment, and research.

CPRIT believes that the best ideas come from Texas-based researchers, rather than from CPRIT staff. To that end, CPRIT strives to keep RFAs simple and as free from rules and restrictions as possible. **This RFA may and should be used for any kind of research**—basic, translational, clinical, or prevention. CPRIT reviewers are established and accomplished scientists who are encouraged to support excellence and weigh risk against potential gain. CPRIT review committees are constituted broadly. There are no quotas for types or areas of research. Simply stated: CPRIT tries to fund the projects that can make the biggest difference.

2. EXECUTIVE SUMMARY

CPRIT will foster cancer research in Texas by providing financial support for a wide variety of projects relevant to cancer research. This Request for Applications (RFA) solicits applications for innovative research projects addressing critically important questions that will significantly advance knowledge of the causes, prevention, and/or treatment of cancer. CPRIT encourages applications that seek to apply or develop state-of-the-art technologies, tools, and/or resources for cancer research, including those with potential commercialization opportunities. **CPRIT will look with special favor on new approaches to be taken or new areas of investigation to be**

explored by established investigators and on supporting the research programs of the most promising investigators at the beginning of their research careers. Applicants need not be trained specifically in cancer research. Indeed, CPRIT strongly encourages investigators from other fields, including the mathematical, physical, chemical, and engineering sciences, to bring their expertise to bear on the exceptionally challenging problems posed by cancer. CPRIT expects outcomes of supported activities to directly and indirectly benefit subsequent cancer research efforts, cancer public health policy, or the continuum of cancer care—from prevention to treatment and cure. To fulfill this vision, applications may address any topic or issue related to cancer biology, causation, prevention, detection or screening, treatment, or cure.

3. MECHANISM OF SUPPORT

The goal of awards made in response to this RFA is to fund exceptionally innovative research projects with great potential impact that are directed by a single investigator. This award allows experienced or early career-stage cancer researchers the opportunity to explore new methods and approaches for investigating a question of importance that has been inadequately addressed or for which there may be an absence of an established paradigm or technical framework. Successful applicants should be working in a research environment capable of supporting potentially high-impact studies. Access to a clinical environment and interaction with translational cancer physician-scientists are highly desirable.

4. RESEARCH OBJECTIVES

Areas of interest include laboratory research, translational studies, and/or clinical investigations. In that cancers arise from a large number of derangements of basic molecular and cellular functions and in turn cause many alterations in basic biological processes, almost any aspect of biology may be relevant to cancer research, more or less directly. The *degree of relevance* to cancer research will be an important criterion for evaluation of projects for funding by CPRIT. For example, are alterations in the process in question *primarily* responsible for oncogenesis or secondary manifestations of malignant transformation? Will understanding the process or interfering with it offer selective and useful insight into prevention, diagnosis, or treatment of cancer? *Successful applicants for funding from CPRIT will have addressed these questions satisfactorily.*

5. FUNDING INFORMATION

Applicants may request a maximum of \$500,000 in total costs per year for up to 3 years. Exceptions to the \$500,000 per year limit may be requested if extremely well justified (see Section 12.3.11). Applications funded in this cycle will be eligible for competitive renewal. Funds may be used for salary and fringe benefits, research supplies, equipment, clinical costs, and travel to scientific/technical meetings or collaborating institutions. Requests for funds to support construction and/or renovation will not be approved under this funding mechanism. State law limits the amount of award funding that may be spent on indirect costs to no more than 5 percent of the total award amount.

6. TARGETED REQUEST FOR APPLICATIONS

CPRIT has established a partnership with The Carson Leslie Foundation and Hoffman-La Roche to fund applications in specific areas of cancer research. At the time of application submission, applicants will have the opportunity to indicate if their applications are intended as a response to these specific partnerships.

6.1. Carson Leslie Awards for Pediatric Brain Cancer Research

Carson Leslie, a Dallas native, died of medulloblastoma at the age of 17 in 2010. His family has established The Carson Leslie Foundation to raise funds for pediatric brain cancer research (<http://carsonlesliefoundation.org>). Further, one of Carson's last wishes was that his brain be used to enhance understanding of his disease. CPRIT is honored to collaborate with the Carson Leslie Foundation in providing partial funding for this award and in overseeing its administration.

One or a small number of awards will be made if an application or applications are received that meet CPRIT's usual high standards. If no award is made, funds will be held until a suitable application/recipient is found. Applications must be submitted following the procedures and instructions for CPRIT Individual Investigator Research Awards, and applications will be reviewed in the same way, using the same criteria as all other applications submitted to this award mechanism. Both the Carson Leslie Foundation and CPRIT are committed to maintaining very high standards in choosing the recipient(s) of this special award.

Applications may be basic, translational, or clinical in their orientation, but they must be clearly relevant to brain cancer in children and/or adolescents. As noted above, Carson's wish was to donate his brain for research into the causes and treatment of childhood brain cancer. In keeping with his wish, fixed tissue, DNA, and cell lines are available from Carson's tumor. Applications that would benefit scientifically from the use of this material may request access, with justification.

6.2. Hoffman-La Roche Research Awards

Hoffman-La Roche has partnered with CPRIT to provide partial or complete support for research in two specific areas of cancer research. These areas are described in the Appendix (Section 16). Applications must be submitted following the procedures and instructions for CPRIT Individual Investigator Research Awards, and applications will be reviewed in the same way, using the same criteria as all other applications submitted to this award mechanism.

7. KEY DATES

RFA

RFA release February 16, 2012

Application

Online application opens April 12, 2012, 7 a.m. Central Time

Application due May 31, 2012, 3 p.m. Central Time

Application review September/October 2012

Award

Award notification November 2012

Anticipated start date (new awards) December 1, 2012

Anticipated start date (renewal awards) June 1, 2013

8. ELIGIBILITY

- The applicant must be a Texas-based entity. Any not-for-profit institution that conducts research is eligible to apply for funding under this award mechanism.
- A public or private company is not eligible for funding under this award mechanism; these entities must use the appropriate award mechanism(s) under CPRIT's Commercialization Program.

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- The Principal Investigator (PI) must have a doctoral degree, including M.D., Ph.D., D.D.S., D.M.D., Dr.P.H., D.O., D.V.M., or equivalent, and must reside in Texas during the time the research that is the subject of the grant is conducted.
 - A PI may submit only one new or resubmission application under this RFA during this funding cycle. If submitting a renewal application, a PI may submit both a new or resubmission application and a renewal application under this RFA during this funding cycle.
 - Because this award mechanism is intended to support research directed by a single investigator, only one Co-PI may be included. Collaborators should have specific and well-defined roles. This award mechanism should not be used for applications that are better suited for the Multi-Investigator Research Awards mechanism.
 - Collaborations are permitted and encouraged, and collaborators may or may not reside in Texas. However, collaborators who do not reside in Texas are not eligible to receive CPRIT funds. Subcontracting and collaborating organizations may include public, not-for-profit, and for-profit entities. Such entities may be located outside of the State of Texas, but non-Texas-based organizations are not eligible to receive CPRIT funds.
 - A PI may resubmit an application that was previously not funded (see Sections 9 and 12.3.6).
 - CPRIT grants will be awarded by contract to successful applicants. Certain contractual requirements are mandated by Texas law or by administrative rules. Although applicants need not demonstrate the ability to comply with these contractual requirements at the time the application is submitted, applicants should make themselves aware of these standards before submitting a grant application. Significant issues addressed by the CPRIT contract are listed in Sections 13 and 14. All statutory provisions and relevant administrative rules can be found at www.cprit.state.tx.us.

9. RESUBMISSION POLICY

An application previously submitted to CPRIT but not funded may be resubmitted once. More than one resubmission is not permitted. This policy is in effect for all applications submitted to date. See Section 12.3.6.

10. RENEWAL POLICY

An application previously funded by CPRIT may be submitted for a competitive renewal. This policy is in effect for all awards to date. See Section 12.3.7.

11. APPLICATION REVIEW

11.1. Triage Review

To ensure the timely and thorough review of only the most innovative and cutting-edge research with the greatest potential for advancement of cancer research, all eligible new or resubmission applications will be initially evaluated by CPRIT Scientific Research and Prevention Programs committee members for scientific merit and impact. **This initial evaluation will be based on a subset of material presented in the application, namely, Abstract and Significance, Budget and Justification, and Biographical Sketches. Applications that do not sufficiently capture the reviewers' interest at this stage will not be considered for further review. Such applications will have been judged to offer only modest contributions to the field of cancer research and, therefore, will be excluded from further peer review.** The applicant will be notified of a decision to disapprove the application at the triage review stage when it is made. Because of the volume of applications to be reviewed, comments made by reviewers at this stage of initial evaluation will not be provided to applicants.

11.2. Full Peer Review

Applications that pass triage review will undergo further review using a two-stage process: (1) Full peer review, and (2) programmatic review. In the full peer review stage, applications will be evaluated by an independent scientific merit review committee using the criteria listed below. In the programmatic review stage, applications judged to be most meritorious by review committees will be evaluated and recommended for funding by the CPRIT Scientific Review Council based on comparisons with applications from all of the merit review committees and programmatic priorities.

11.2.1. Confidentiality of Review

Each stage of application review is conducted completely confidentially, and all council and committee members are required to sign nondisclosure statements regarding the contents of the applications. All council and committee members will be non-Texas residents and operate under strict conflict of interest prohibitions. Under no circumstances should institutional personnel and/or individual applicants initiate contact with any member involved in the peer review process (with the exception of members of the CPRIT Scientific Review Office), the CPRIT executive director, or any member of the CPRIT Oversight Committee regarding the status or substance of the application. Violations of this prohibition will result in the administrative

withdrawal of the application. Any communication regarding the application should be directed to the CPRIT Research HelpDesk and/or CPRIT's Scientific Review Office.

11.3. Review Criteria

Full peer review of applications will be based on primary scored criteria and secondary unscored criteria, listed below. Review committees will evaluate and score each primary criterion and subsequently assign a global score that reflects an overall assessment of the application. **The overall assessment will not be an average of the scores of individual criteria; rather, it will reflect the reviewers' overall impression of the application. Evaluation of the scientific merit of each application is within the sole discretion of the peer reviewers.**

11.3.1. Primary Criteria

Primary criteria will evaluate the scientific merit of the proposed work contained in the application. Concerns with any of these criteria potentially indicate a major flaw in the significance and/or design of the proposed study.

Significance and Impact: Will the results of this research, if successful, significantly change the research of others or the opportunities for better cancer diagnosis or treatment for patients? Is the application innovative? Does the applicant propose new paradigms or challenge existing ones? Does the project develop state-of-the-art technologies, methods, tools, or resources for cancer research or address important under- or unexplored areas? If the research project is successful, will it lead to truly substantial advances in the field rather than add modest increments of insight? Projects that modestly extend current lines of research will not be considered for this award. Projects that represent straightforward extensions of ongoing work, especially work traditionally funded by other mechanisms, will not be competitive.

Research Plan: Is the proposed work presented as a self-contained research project? Does the proposed research have a clearly defined hypothesis or goal that is supported by sufficient preliminary data and/or scientific rationale? Are the methods appropriate, and are potential experimental obstacles and unexpected results discussed?

Applicant Investigator: Does the applicant demonstrate the required creativity, expertise, experience, and accomplishments to make a significant contribution to cancer research? Applicants' credentials will be evaluated in a career stage-specific fashion. Have early career-stage investigators received excellent training, and do their accomplishments to date offer great

promise for a successful career? Has the applicant devoted a sufficient amount of his or her time (percentage effort) to this project?

Relevance: Does the proposed research have a high degree of relevance to cancer research? This will be an important criterion for evaluation of projects for CPRIT support (see Section 4).

11.3.2. Secondary Criteria

Secondary criteria contribute to the global score assigned to the application. Concerns with these criteria potentially question the feasibility of the proposed research.

Research Environment: Does the research team have the needed expertise, facilities, and resources to accomplish all aspects of the proposed research? Are the levels of effort of the key personnel appropriate? Is there evidence of institutional support of the research team and the project?

Vertebrate Animals and/or Human Subjects: If vertebrate animals and/or human subjects are included in the proposed research, certification of approval by the institutional IACUC and/or IRB, as appropriate, will be required before funding can occur.

Budget: Is the budget appropriate for the proposed work?

Duration: Is the stated duration appropriate for the proposed work?

12. SUBMISSION GUIDELINES

12.1. Online Application Receipt System

Applications will be accepted beginning at 7 a.m. Central Time on April 12, 2012 and must be submitted via the CPRIT Application Receipt System (<https://CPRITGrants.org>). **Only applications submitted at this portal will be considered eligible for evaluation.** The PI must create a user account in the system to start and submit an application. The Co-PI, if applicable, must also create a user account to participate on the application. Submission of an application is considered an acceptance of the terms and conditions of the RFA.

12.2. Submission Deadline

All applications must be submitted by 3 p.m. Central Time on May 31, 2012.

12.3. Application Components

Applicants are advised to follow all instructions to ensure accurate and complete submission of all components of the application. Submissions that are missing one or more components or do

not meet the eligibility requirements listed in Section 8 will be administratively withdrawn without review.

12.3.1. Application Signing Official (ASO)

The ASO is an individual authorized to submit an application on behalf of an organization. An ASO must be identified and assigned to the application by the PI. An application may not be submitted without ASO approval. Only the ASO is authorized to officially submit the application to CPRIT. The ASO must also create a user account in the online application receipt system.

12.3.2. Grants Contract/Office of Sponsored Projects Official

The grants contract/Office of Sponsored Projects official is the individual who will manage the grant if an award is made. This individual must be identified and assigned to the application either by the PI or by the ASO. The grants contract/Office of Sponsored Projects official must also create an ASO-type user account in the online application receipt system.

12.3.3. Abstract and Significance (5,000 characters)

Clearly explain the question or problem to be addressed and the approach to its answer or solution. The specific aims of the application must be obvious from the abstract, although they need not be restated verbatim from the Research Plan. Clearly address how the proposed project, if successful, will have a major impact on the field of cancer research or on the care of patients with cancer. Summarize how the proposed research creates new paradigms or challenges existing ones. Explain how this research plan represents a new direction for the PI. Projects that represent logical extensions of ongoing work funded from other sources will not be competitive.

Note: It is the applicant's responsibility to capture CPRIT's attention primarily with the Abstract and Significance statement alone. Therefore, applicants are advised to prepare this section wisely. Applicants should not waste this precious space by stating obvious facts (e.g., that cancer is a bad disease; that better diagnostic and therapeutic approaches are needed urgently; that the type of cancer of interest to the PI is important, vexing, or deadly; etc.). CPRIT is well aware of these facts. **Based on this statement (and the Budget and Justification and Biographical Sketches), applications that are judged to offer only modest contributions to the field of cancer research or do not sufficiently capture the reviewers' interest will be excluded from further peer review (see Section 11.1).**

12.3.4. Layperson's Summary (2,000 characters)

Provide a layperson's summary of the proposed work. Describe, in very simple, nontechnical terms, the overall goals of the proposed work, the type(s) of cancer addressed, the potential significance of the results, and the impact of the work on advancing the field of cancer research. The information provided in this summary will be made publicly available by CPRIT, particularly if the application is recommended for funding. Do not include any proprietary information in the Layperson's Summary.

12.3.5. Overall Goals and Timeline (1 page)

Outline the specific aims of the research project. Provide an outline of anticipated major milestones to be tracked. Timelines will be reviewed for reasonableness, and adherence to timelines will be a criterion for continued support of successful applications. If the application is approved for funding, this section will be included in the award contract. Applicants are advised not to include information that they consider confidential or proprietary when preparing this section.

12.3.6. Resubmission Summary (1 page)

Applicants preparing a resubmission must describe the approach to the resubmission. If a summary statement was prepared for the original application review, applicants are advised to address all noted concerns.

Note: An application previously submitted to CPRIT but not funded may be resubmitted once after careful consideration of the reasons for lack of prior success. Applications that received overall numerical scores of 5 or higher are likely to need considerable attention. Applicants may prepare a fresh Research Plan or modify the original Research Plan and mark the changes. However, all resubmitted applications should be carefully reconstructed; a simple revision of the prior application with editorial or technical changes is not sufficient, and applicants are advised not to direct reviewers to such modest changes.

12.3.7. Renewal Summary (2 pages)

Applicants preparing a renewal must describe and demonstrate that appropriate/adequate progress been made on the current funded award to warrant further funding (1 page). Publications and manuscripts in press that have resulted from work performed during the initial funded period should be listed on the second page of the renewal summary.

12.3.8. Research Plan (10 pages)

Background: Present the rationale behind the proposed project, emphasizing the pressing problem in cancer research that will be addressed.

Hypothesis and Specific Aims: Concisely state the hypothesis and/or specific aims to be tested or addressed by the research described in the application.

Research Strategy: Describe the experimental design, including methods, anticipated results, potential problems or pitfalls, and alternative approaches. Preliminary data that support the proposed hypothesis are encouraged but not required.

12.3.9. Vertebrate Animals and/or Human Subjects (1 page)

If vertebrate animals will be used, provide an outline of the appropriate protocols that will be followed. If human subjects or human biological samples will be used, provide a plan for recruitment of subjects or acquisition of samples that will meet the time constraints of this award mechanism.

12.3.10. Publications/References

Provide a concise and relevant list of publications/references cited for the application.

12.3.11. Budget and Justification

Provide a compelling justification of the budget for the entire proposed period of support, including salaries and benefits, supplies, equipment, patient care costs, animal care costs, and other expenses. Applicants are advised NOT to interpret the maximum allowable request under this award as an invitation to expand the budget to this level. Reasonable budgets clearly work in favor of the applicant. However, if there is a highly specific and defensible need to request more than \$500,000 in any year(s) of the proposed budget, include a special and clearly labeled section in the budget justification that explains the request. Poorly justified requests of this type will likely have a negative impact on the overall evaluation of the application.

In preparing the requested budget, applicants should be aware of the following:

- Equipment having a useful life of more than 1 year and an acquisition cost of \$5,000 or more per unit must be specifically approved by CPRIT. An applicant does not need to seek this approval prior to submitting the application.
- Texas law limits the amount of grant funds that may be spent on indirect costs to no more than 5 percent of the total award amount (5.263 percent of the direct costs). Guidance

regarding indirect cost recovery can be found in CPRIT's administrative rules, which are available at www.cprit.state.tx.us. So-called grants management and facilities fees (e.g., sponsored programs fees; grants and contracts fees; electricity, gas and water; custodial fees; maintenance fees; etc.) may not be requested. Applications that include such budgetary items will be rejected administratively and returned without review.

- The annual salary (also referred to as direct salary or institutional base salary) that an individual may receive under a CPRIT award for FY 2013 is \$200,000; CPRIT FY 2013 is from September 1, 2012 through August 31, 2013. Salary does not include fringe benefits and/or facilities and administrative (F&A) costs, also referred to as indirect costs. An individual's institutional base salary is the annual compensation that the applicant organization pays for an individual's appointment, whether that individual's time is spent on research, teaching, patient care, or other activities. Base salary excludes any income that an individual may be permitted to earn outside of his or her duties to the applicant organization.

12.3.12. Biographical Sketches (2 pages each)

Applicants should provide a biographical sketch that describes their education and training, professional experience, awards and honors, and publications relevant to cancer research. A biographical sketch must be provided for the PI and, if applicable, the Co-PI (as required by the online application receipt system). Up to two additional biographical sketches for key personnel may be provided. Each biographical sketch must not exceed 2 pages.

12.3.13. Current and Pending Support

Describe the funding source and duration of all current and pending support for all personnel who have included a biographical sketch with the application. For each award, provide the title, a two-line summary of the goal of the project, and, if relevant, a statement of overlap with the current application. At a minimum, Current and Pending Support of the PI and, if applicable, the Co-PI must be provided.

12.3.14. Institutional/Collaborator Support and/or Other Certification (4 pages)

Applicants may provide letters of institutional support, collaborator support, and/or other certification documentation relevant to the proposed project. A maximum of 4 pages may be provided.

12.3.15. Previous Summary Statement

If the application is being resubmitted, the summary statement of the original application review, if previously prepared, will be automatically appended to the resubmission. The applicant is not responsible for providing this document.

Applications that are missing one or more of these components, exceed the specified page, word, or budget limits, or do not meet the eligibility requirements listed above will be administratively rejected without review.

13. AWARD ADMINISTRATION

Texas law requires that CPRIT research awards be made by contract between the applicant and CPRIT. Texas law specifies several components that must be addressed by the award contract, including needed compliance and assurance documentation, budgetary review, and terms relating to intellectual property rights. These contract provisions are specified in CPRIT's administrative rules, which are available at www.cprit.state.tx.us.

All CPRIT awards will be made to institutions, not to individuals. Applicants who change their institutional affiliation during the time period of the award must submit a written request to CPRIT to transfer the award to the new institution. Transfer of awards to institutions outside of Texas is not permitted.

CPRIT requires award recipients to submit an annual progress report. These reports summarize the progress made toward the research goals and address plans for the upcoming year. In addition, fiscal reporting, human studies reporting, and vertebrate animal use reporting will be required as appropriate. Continuation of funding is contingent upon receipt of these reports. Forms and instructions will be made available at www.cprit.state.tx.us.

14. REQUIREMENT TO DEMONSTRATE AVAILABLE FUNDS

Texas law requires the CPRIT award recipient to demonstrate that it has an amount of funds equal to one-half of the CPRIT funding dedicated to the research that is the subject of the award. The demonstration of available matching funds must be made at the time the award contract is executed, not when the application is submitted.

15. CONTACT INFORMATION

15.1. HelpDesk

HelpDesk support is available for questions regarding user registration and online submission of applications. Queries submitted via e-mail will be answered within 1 business day. HelpDesk staff are not in a position to answer questions regarding scientific aspects of applications.

Dates of operation: February 16, 2012, to May 31, 2012 (excluding public holidays)

Hours of operation: Monday through Friday, 7 a.m. to 4 p.m. Central Time

Tel: 866-941-7146

E-mail: ResearchHelp@CPRITGrants.org

15.2. Scientific and Programmatic Questions

Questions regarding the CPRIT program, including questions regarding this or any other funding opportunity, should be directed to the CPRIT Scientific Review Office.

Tel: 512-305-8491

E-mail: ResearchHelp@CPRITGrants.org

Web site: www.cprit.state.tx.us

16. APPENDIX: TOPIC AREAS FOR HOFFMAN-LA ROCHE-SUPPORTED RESEARCH AWARDS

As stated in Section 6, Hoffman-La Roche has partnered with CPRIT to provide partial or complete support for research in two specific areas of cancer research. These are described below.

16.1. Factors That Influence the Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) Functional Capacity of NK Cells

ADCC is the process by which antibodies, that are bound to target cells, activate effector cells which lyse the target cells by release of lytic enzymes (e.g., perforin, granzyme B). This process is mediated through binding of the Fc portion of the antibody to the FcγRIII (CD16) on the surface of the effector cells (mostly NK cells).

The glycoengineered antibody GA201 has enhanced ADCC capacity due to an increased binding of its engineered Fc portion to FcγRIII (CD16). GA201 is an EGFR-targeted antibody that is currently tested in Phase II clinical trials.

Treatment with GA201 leads to a decrease of circulating NK cells, a diminished expression of CD16 on the surface of these cells, and a slightly impaired circulating NK cell functional capacity, as determined in both antibody dependent and independent cell killing experiments. Preliminary clinical observations suggest that those patients who maintain a higher level of circulating NK cell functionality after one or more cycles of GA201 treatment show a better response to therapy compared to those patients in whom the NK cell functionality deteriorates more strongly.

It is currently unclear which molecular factors determine whether NK cell functionality is maintained after GA201 therapy. Several activating and inhibitory receptors have been described on the surface of NK cells (e.g., NKG2D, KIR family of receptors) and their cognate ligands on target cells (e.g. MICA, HLA class I) have largely been identified. However, their contribution to initiating and maintaining ADCC capacity is still unclear. In addition, NK cell functionality is influenced by soluble factors.

Scientific questions:

1. Are there molecular characteristics of NK cells at baseline that would indicate whether NK cell function is preserved after one or more rounds of antibody-dependent cell killing?

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- a. Are there genetic host factors that would predispose individuals to preservation of or a rapid decline in NK cell functionality after ADCC?
 - b. Are there other factors at baseline that would indicate the vulnerability of NK cell function to repeated triggering of ADCC (e.g., receptor status, soluble factors)?
2. Which assay could best be used to measure NK cell functionality in the clinical setting?
 - a. Is there an assay that can detect antibody-dependent NK cell killing capacity reproducibly in preserved (optimally not cryopreserved) blood specimens?

16.2. Predicting Tumor Diffusion for Small and Large Molecules Including Complex Engineered Antibodies

The plasma concentration of a therapeutic drug is often used as a surrogate for the concentration of the drug in the tumor. However, the disorganized nature of tumor vasculature means that drugs must diffuse over considerable distances to reach all their target cells. In addition, cancer tissues, both solid tumors and leukemias, have potential to develop clinical resistance to therapeutic compounds by overexpression of efflux transporters for which therapeutic compounds with small molecular weight are substrates. Poor penetration of a drug through the extravascular compartment of a tumor is therefore likely to result in therapy failure.

It is well known that the microvascular system in many tumors is functionally inadequate. Tumors typically contain irregular, tortuous networks of leaky microvessels with heterogeneous blood flow and large intervessel distances. These features, together with the lack of functional lymphatic drainage and high interstitial pressures, make diffusion, rather than convection, the dominant mechanism of extravascular transport of drugs in tumors.

One key element of Hoffman-La Roche's PK/PD strategies to predict anticancer efficacy based on preclinical data is to estimate target occupancy or enzyme inhibition by assessing concentration of the drug inside the tumor for anticancer compounds.

To develop a model of drug distribution in tumors, information on parameters affecting extravascular transport properties of drugs (including diffusion coefficients, metabolism, and transport) is needed. One way to obtain such information is from drug transport studies using multicellular layer cultures of human tumor cells in vitro.

Such in vitro systems should allow also characterizing the diffusion/efflux rate of a test compound as well as the identification of transporters for which the drug is a substrate.

In order to understand the in vivo significance of the data generated in vitro, it is essential to apply mechanistically based models to determine the diffusion and transport parameters that control these extravascular transport properties. These parameters can then be incorporated into PK/PD models to predict anticancer efficacy.

These developments are proposed to be validated beyond the “traditional” compounds such as small molecules and monoclonal antibodies and will encompass more complex engineered antibodies that are diversifying the discovery and development pipeline. Thus, extending these methodological developments to antibody-drug conjugates (ADCs), bispecific antibodies and trifunctional antibodies, domain antibodies (DAbs), nanobodies, and fragment crystallizable (Fc)-engineered antibodies will promote the understanding of how these factors will affect the discovery and development efforts for more complex engineered antibodies.

The use of in vitro models in conjunction with mechanistically based in vitro in vivo PK/PD modeling has the potential, to reduce the number of animals required for testing of anticancer drugs because drug candidates with inadequate tumor penetration properties can be rejected on the basis of in vitro testing. Such in vitro-guided PK/PD modeling also makes it possible to identify optimal rates of diffusion versus efflux clearance rates in tissue during lead optimization of new anticancer drugs.

With the increasing ability to predict such properties from drug physicochemical parameters and from in vitro data, such modeling enhances the probability to move useful anticancer compounds into development. Using specific examples of large molecules therapeutics currently in the Hoffman-La Roche development pipeline, this project should produce data to guide clinical studies with the intention of using the clinical data to validate the methodologies and results derived from the project. This represents a true opportunity to perform translational research within the academic/industry interface.

Scientific questions:

1. Can an in vitro assay be established to allow quantification of diffusion and transport of molecules into tumor?
 - a. Can such a model be validated for both large molecules (i.e., mAbs) and small molecules?
 - b. Is there an in vitro system representing various efflux transporters, e.g., PGP and BCRP, relevant for small molecules?
 - c. Can these models be characterized for their level of transporter expression?
 - d. Which set of reference compounds, focusing mainly on passive diffusion and PGP efflux, could be included in such an evaluation?
2. Can the validity of these models be tested to predict in vivo tumor diffusion, in xenograft mice and/or in humans for a set of reference compounds?
 - a. How can in vitro determined parameters be scaled for diffusion and transport to in vivo?
 - b. Are unbound concentrations in tumors available for this validation?
 - c. How are pathophysiological parameters for various types of tumors accounted for?
 - d. What are the key pathophysiological parameters (vasculature, pressure, density, etc.) that should be taken into account?