評価委員による評価 / Reviews by Advisors

有賀 克彦 博士　物質・材料研究機構 世界トップレベル研究拠点形成プログラム 国際ナノアーキテクトニクス研究拠点 主任研究者
Dr. Katsuhiko Ariga, the National Institute for Materials Science

齋藤 烈 教授　日本大学工学部次世代工学技術研究センター長，京都大学名誉教授
Prof. Isao Saito, Nihon University

末宗 幾夫 教授　北海道大学 電子科学研究所
Prof. Ikuo Suemune, Hokkaido University

Prof. Allan Balmain　UCSF Helen Diller Family Comprehensive Cancer Center and Department of Biochemistry & Biophysics

N 研究プロジェクト「ナノ物質を基盤とする光・量子技術の極限追求」は大変希望に満ちた出発をしたという印象を持った。ナノ物質・ナノ技術を機軸としながら、必ずしも基礎研究に終始することなく、情報・エネルギー・医療といった社会的要請の高いアウトプットが目標にすえられている。これらの計画が、絵空事でないことは、Nature をはじめとする著名誌に多くの論文発表を既になしていることからも伺える。このような点から、次年度以降のさらなる発展を期待したい。

今後のプロジェクト発展のために以下の二つの課題が達成されるとよりいいと思われる。

１）ナノ物質あるいは、情報・エネルギー・医療といった目標は多くの研究プロジェクトが抱える課題である。是非、N 研究プロジェクトの独自性が色濃く表れる特異的な研究成果を出してほしい。

２）既に学会で活躍が認められている若手研究者ということではなく、無名の若手からスーパースターが生まれるような実例がいくつかあると大変いいと思われる。

上記の課題解決は必ずしも容易ではないが、この１年間の活動の充実ぶりを見ると決して不可能な達成目標ではないと考えている。

物質・材料研究機構
世界トップレベル研究拠点形成プログラム
国際ナノアーキテクトニクス研究拠点
主任研究者

有賀克彦

日本大学学術研究戦略プロジェクト評価

外部評価アドバイザー　日大工学部次世代工学技術研究センター長　齋藤　烈
京都大学名誉教授

研究プロジェクト全般について

日本大学初の大型研究プロジェクトである *N.* 研究プロジェクトが発足して１年になるが、その研究成果は１年目にしては上出来で、十分期待に応えられそうな状況にある。研究代表者の努力に負うところが大きい。

高く評価される点

1. 年間８回にも及ぶ班会議、フォーラム、セミナで研究者間の交流をはかっていること。特に、若手に研究発表を積極的にやらせている点。
2. 各班で達成すべき目標を設定している点は高く評価
   (最初に高い具体的な目標を設定するとことは大変勇気の要ることで、
   国プロでも設定目標を達成できたケースは少ないのが実情である)
3. 学内新聞など広報活動を広くおこなっていること。

改善すべきあるあいは考慮すべき点

1. 研究評価で最も重要なことは、投資研究費用 *vs* 効果（研究投資効果）の判定であるが、それを判定する資料が報告書には欠けている。
   即ち、　１）年間どれくらいの費用を使い，２）誰がどれだけの論文（2009年）をだしたか（全ての論文リストを著者毎にまとめる，国内外での学会などでの招待講演のリスト、特許の具体的なリスト）　３）３０人の研究者が過去１年間に、どれだけ科研費または学外の他の競争的資金に応募したか（全ての申請項目）、および実際に獲得した金額をリストにする。
2. 研究分野が広すぎて代表者が全てカバーできないのは当然で、３班の班長に責任と権限を大幅に委譲してはどうか。
3. 外国人のアドバイザーのために英文でも報告書を書いているようであるが、世話人は手間が大変だと思うので、外国人のアドバイザーを外すか最終報告でまとめてコメントをもらってはどうか。
4. 全体として，受賞（若手のポスター賞など）が少ない気がするが、指導者は積極的に若手に賞を取らせるよう指導すべきで、それが本プロジェクトの主眼である若手研究者の育成につながるはず。

医療班の評価

学術フロンチアのメンバーでもあるので、ここでの論評は控えたい。

エネルギー、ナノ物質班の評価

色素増感太陽エネルギーや水の光分解で顕著な成果が出ている。学外、国外に積極的にアピールする努力をしてもらいたい。

日本大学Ｎ研究プロジェクト「ナノ物質を基盤とする光・量子技術の極限追求」
平成２１年度報告書に寄せて

外部評価委員
北海道大学　電子科学研究所
末宗　幾夫

日本大学では健やかな未来を実現するための課題として、人間の健康、エネルギーと環境、情報化がキーとなる問題であると捉え、これを特にエネルギーや情報を運ぶ「光」とナノ物質との相互作用に基づく最先端技術に焦点を当て、ナノ科学、ナノ技術を基盤とする医療分野、エネルギー分野、情報分野の専門家が連携してこれらの課題を解決するための応用技術の開発を目指しておられます。

それぞれの研究項目ごとに具体的な達成目標を数値で示し計画を立案されている指針は高く評価されます。また初年度からすでに情報分野の超高速記録、医療分野の遺伝子ネットワーク解析に関連する顕著な成果が有力な学術誌に出版されるなどの成果があがっているようで今後がさらに期待されます。また各研究チームそれぞれ査読論文への成果公表、国際会議での成果発表など、充分な成果が得られていると判断されます。

各研究チームごとの研究だけではなく、学部横断的な共同研究が具体的に進みつつあり、高く評価されます。特にこのようなプロジェクトのもたらす学部の垣根を越えた共同研究は、大学の持つ総合的な研究能力を大きく引き出す可能性があり、今後さらに進展させて行かれることを望みます。また若手人材の育成は将来の我が国の科学技術を発展させるためには欠かせない項目であり、今後とも人材育成とその効果の検証を進めて行かれるように望みます。

私は特に情報関連分野を担当しておりますので、以下各項目の研究内容について述べさせていただきます。

円偏光レーザパルスで磁気情報の記録と読み出しを30ps以内で行うことができたということですが、これは現在の磁気記録に比べれば圧倒的に速い記録速度であり、今後情報記録分野での大いなる進展が期待されます。

量子情報分野では、量子もつれを使った量子情報伝送、ならびに量子情報システム応用の鍵を握る単一光子検出器の性能向上が中心的な課題となっています。これに対して量子もつれの光ファイバー伝送による劣化の評価を進め、ル

ビジウム原子で安定化させた偏光量子もつれ光子対光源の開発を進めるなど、今後が期待されます。一般に光通信波長帯の 1550nm ではシリコン検出器が使える可視波長域に比べて光子検出器の量子効率がかなり低下してしまいますが、誘電体反射ミラーなどを駆使し、量子効率 82%の高い検出効率を持つ光子数識別器が初年度に開発されたことはすばらしい成果であり、今後の量子情報応用が期待されます。また光導波路などの微細加工も進んでおり、量子情報応用に向けた光集積回路へと展開するポテンシャルが感じられます。

UCSF Helen Diller Family
Comprehensive
Cancer Center

Allan Balmain, PhD, FRSE
Professor

UCSF Helen Diller Family
Comprehensive Cancer
Center and Department of
Biochemistry & Biophysics

Barbara Bass Bakar
Distinguished Professor of
Cancer Genetics

1450 Third Street,
Campus Mail Code 0128
Helen Diller Family Cancer
Research Building, HD-377
San Francisco, CA
94158-9001
USA

415-502-4192 (phone)
415-502-3179 (fax)
abalmain@cc.ucsf.edu

External review board comments
Nihon University Strategic Projects for Academic Research
Nanotechnology Excellence, Nihon University - Nanomaterial-based Photonic, Quantum and Bio Technologies –

Reviewer for Bio Technologies Allan Balmain

DESCRIPTION (provided by applicant):

The major purpose of this proposal is to establish a novel designable multi-targeted approach in a tumor-specific manner by means of pre-transcriptional targets, such as the double-stranded genomic DNA using nucleic acid binding chemicals. The object of this research is, therefore, to develop and evaluate a novel target DNA recognition approach using Pyrrole-Imidazole (PI) polyamide molecules or its conjugates for safe administration, diagnosis and therapy in cancer patients. In the last two years discovery phase and drug candidate development have been successfully established by this project. Four sub projects were proposed by the Bio Technologies Group, which are:

1. Development of Molecules for Cancer Diagnosis and Therapy,
2. DNA Binding Molecules for Amplified Oncogene Detection and Silencing,
3. Development of a Novel Radiation Dynamic Therapy against Cancer Cells in Internal Organs, and
4. Peptide Nucleic Acid Molecules for Over-expressed Genes for Disease Diagnosis and Therapy.

CRITIQUE

Significance: It is well recognized that nucleotide recognition approaches are one of the most promising "next generation" therapeutic approaches for human disease. Many laboratories and funding agencies have invested heavily in this field, field especially in applications of siRNA technologies. Nucleotide recognition approaches have the unique property of targeting the source of the information that drives cancer cells, which is encoded in the DNA sequence. Initially this project seeks to identify the complex genetic and epigenetic components that drive tumor development, to ultimately identify the genetic causes of tumorigenesis. This is done primarily by exploiting mouse genetics to develop models of cancer that closely mimic the processes that cause cancer in human populations. The goal is to identify genetic targets in mouse models that will provide novel routes to therapeutic approaches in humans. The research team has developed intriguing nano-technological approaches, which emphasize the team's ability to develop unique diagnostic and therapeutic approaches for complex diseases, such as cancer. For instance their use of pyrrole-imidazole polyamide based drug candidate molecules is an interesting approach that may lead to the anticancer drugs and provide a viable altemative to more widely studies approaches such as those based on small interfering RNAs (siRNAs). Those

molecules may also have applications in cancer diagnosis, when targeting cancer-specific genetic events such as gene amplifications. In addition to these specific targeted approaches, the team has also developed a novel radiation mediated photo dynamic therapy (PDT) approach to cancer treatment. Although the unique mixture of scientists and clinicians in the team has allowed them to pursue these multiple strategies and make considerable progress, the team may need to develop a more focused approach concentrated on the most promising strategy, in the subsequent years of this funded project. Because each project needs a substantial amount of effort, the team would be well advised to invest their efforts in one of the most feasible approaches.

Approach: This is a competing continuation report from productive investigators. During the previous funding period of two years, the applicants made significant progress toward completion of all of the specific sub-projects.
More than10 peer-reviewed publications from the PI and hundreds from collaborators are cited as having been funded wholly or partly by this grant within a relatively short period. Many are highly collaborative, multi-author endeavors; thus, it is difficult to ascertain what the actual contributions were and how they directly related to the original publications. Nonetheless, this level of productivity is extremely impressive.

The goals of this continuation report involve focusing on therapeutic target discovery using mouse carcinogenesis models, pharmacokinetics of PI polyamides, development of preclinical drug candidates and assessment of parametric X-ray for radiation induced PDT for cancers in internal organs. In general, the application is primarily a technological tour de force to identify anti-cancer drug candidates. The PI has proposed to utilize a genome-wide genetic and epigenetic search in conjunction with multi-phenotypic detection in a mouse model of human cancer. The orthologous regions of the human genome were analyzed for identification of human cancer related genes. This is a densely written proposal, that is difficult to follow. The presentation also includes several peripheral issues which, while interesting, are not clearly connected with the main themes of this proposal. Nonetheless, the research directions are important, cleverly designed and appropriately resourced. The greatest concerns, and questions that should be addressed, are: (1) Is the scope of the project too excessive for a 5-yr proposal? (2) How consistent will therapeutic effect of PI polyamides be? (3) Why drop the already-identified (and sometimes successful) drug development approaches in favor of nucleotide binding approaches? For the first, the PI has carefully outlined the costs of the analyses within the proposal, but the "bottom line" is not readily apparent. In short, the costs in terms of personnel, assay costs, chemical synthesis and animal husbandry would seem to exceed the time and budget proposed. With regard to consistency of the polyamide therapeutic effects in rodents, the theoretical considerations would seem to support the proposal; however, subtle changes in species could profoundly affect the parameters of therapeutic and/or adverse effects of PI polyamides. While the proposal is carefully presented, more detailed explanations for how the PI polyamide will be able to become localized in certain tissues, remain sufficiently stable to get into the nucleus, and then to target specific DNA sequences, would be required to assure that 'trivial' parameters are not responsible for increased variance or false negative/positive findings in animal models. The proposal to evaluate the parametric X-rays for PDT raises some substantial concerns. This description is not all inclusive, but meant to provide some feedback to justify the scoring. The results of *in vitro* treatment of human cancer cell cultures with parametric X-rays are promising and led to cell growth inhibition in at least two cancer cell lines, but the approach raises some significant concerns. Non tumorous cellular behavior upon exposure to parametric X-rays is not described. Why ionizing radiation, which includes substantial amount of 33.4Kev X-rays, may not show this effect using clinically used PDT drugs or X-ray sensitive chemical conjugates. It is not clear why parameric X-rays show such effects

while ionizing radiation does not. Consistency using more in vitro analysis and in vivo tumor model studies compared with ionizing radiation would show its application more appropriately. The analysis of PNAs is appropriate. However, important details regarding which type of PNA used for RNA recognition will be needed.

PI acknowledges that the team may have to "identify new key cancer regulators" to identify novel targets for cancer therapy. This may be correct, but is rather open-ended and lacks important details regarding molecules and prioritization. The PI polyamide study is an impressive and highly challenging study, with a good probability of providing a drug for anticancer therapy. There are many challenging problems that need to be solved. The possible adverse effects on the human body have not been studied at all. Chemical delivery to tissue, cell type and nuclear localization is unclear. We also need an improved understanding of tissue distribution, stability, metabolism and excretion of PI polyamides.

Nonetheless, the research proposed by Dr. Nagase and colleagues in this continuation report is extremely exciting and should be funded in full by the appropriate organization.

Investigators: Dr. Nagase (15% effort) received his MD (1987) and PhD (1999) degrees from Kumamoto University in Japan. He has experience in academia and industry before joining the Nihon University, where he holds full professor with the rank of Associate Professor at Roswell Park Cancer Institute and SUNY-Buffalo. He has been involved in several large research efforts, among which are included the analysis of the involvement of the Adenomatous Polyposis Coli (APC) gene, Aurora-A and trefoil factor 3 in cancer development. He will be assisted by an assistant professor, 3 trainees, 9 PhD candidates and three technicians. Dr. Nagase has initiated collaborations with 8 researchers in Nihon University including Drs. Motoichiro Takahashi, Satoru Takahashi, Yoshiaki Matsumoto, Tsugumichi Koshinaga, Noboru Fukuda and Koichiro Kano. Their involvement amplifies the likelihood of obtaining useful results.

Environment: The facilities at Nihon University School of Medicine, Research Cancer are excellent, especially for performing the types of experiments proposed in this proposal. All of the key molecular genetic assays and preclinical experimental approaches are available.

Innovation: Complex phenotypes involving contributions from multiple genes in cancer development are not a newly described area of research, but they are not widely studied for therapeutic targets because of the complexity. Dr. Nagase has proposed a clever twist on the 'standard' molecular target therapy by incorporating targets of key regulators for cancer treatment. Again, this avenue of study is not common, but critically important. Research involved in the designable molecule of PI polyamide is intriguing. This study also has the potential to lead to a new paradigm for drug discovery.

Protection of Human Subjects from Research Risks: The application refers to data exchange and analysis of human samples at other institutions. IRB approval from his institution and institutions for the collaborators are appropriately obtained.

Inclusion of Women Plan: Not applicable.
Inclusion of Minorities Plan: Not applicable.
Inclusion of Children Plan: Not applicable.
Vertebrate Animals: Acceptable, all 5 points are covered.
Biohazards: No concerns.
Model organism sharing plan: Acceptable
DATA SHARING PLAN: Acceptable.

Overall Evaluation: This is a competing continuation report from a productive, highly collaborative investigator. The application is densely written and challenging to follow, but the nature of the proposed studies - to evaluate in a genome-wide manner the key genetic and epigenetic targets that are correlated with multi-stage carcinogenesis model - are potentially extremely informative and may provide unique information on DNA targets. Two issues may need to be addressed in the next funding period: the consistency and magnitude of the therapeutic effect of radiation induced PDT and PI treatments may not be sufficiently high to interpret the data obtained; and previously identified drug targets may not be sufficiently specific to justify studying in detail. In addition, translation of the findings to human application may be challenging. The PI polyamide as a candidate drug is an outstanding, if challenging, research area. The proposed project is well organized as a result of the PI's experience and deep understanding of drug discovery, and the excellent team of collaborators assembled.

Budget: The budget of next year period with continuation plan of three more years is requested; however, there are concerns that the budget may not be adequate to accomplish the proposed studies.

Please feel free to contact me if there are any additional questions regarding this proposal.

Allan Balmain, PhD, FRSE