外部評価委員による評価 / Reviews by the Advisors

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General comments on Medical Group. The Directors and PIs of the Academic Frontiers Program deserve to be commended on their accomplishments over the past 5 years. They have tackled a wide range of important problems with the goal of improving human health, and in particular of making an impact on the high mortality due to cancer in the human population. There is clear evidence of high productivity with a large series of papers and patents emerging from the program. Some of the approaches adopted by the Medical Group are high risk, as is completely appropriate for an ambitious program of this kind. In particular, much has been investigated in the development of PI Polyamide drugs for the specific targeting of cancers and other diseases. At the beginning of this program this reviewer had major doubts as to the likelihood of success using these DNA intercalating drugs, mainly due to difficulties in attaining the required specificity and potency for in vivo application. Dr. Nagase and colleagues have persevered with this approach, and now have both in vitro and in vivo proof of principle that the approach can work. With continued progress and funding of this research, it has the promise to revolutionize the treatment of cancer. One of the major difficulties in present approaches to cancer is that many of the genes known to be involved in tumor development are not “druggable”, ie they are not amenable to high throughput screens for small molecule inhibitors. This class of genes includes transcription factors and protein involved in protein-protein interactions for which no clear interacting pocket can be identified. The PI Polyamide approach is independent of the biochemical activity of the particular protein targets, opening up a much wider range of targets for inhibition in tumor cells. A particular advantage of the strategy the group has developed is the possibility for simultaneous targeting of multiple transcription factor binding sites, either in the same gene or in genes that are likely to have synergistic activity. The latter approach will benefit from novel approaches to network interactions based on proteomic or gene expression network analyses of normal and tumor cells. It is already clear that the targeting of any single molecule in cancers will not lead to complete remissions or cures, because of the inherent plasticity of tumor cells. Approaches will have to be developed that involve either simultaneous or sequential targeting of genes that work in these network in order to avoid the obligator rewiring that will undoubtedly take place when single targets are inhibited. The Medical Group is well placed to take advantage of these new approaches to combinatorial target identification.

Advances in 2011. The program presented at the 2011 meeting described advances made during the previous year. These included the further development and characterization of PI Polyamides targeting the Tgfb pathway, as well as further studies on N-Myc,and metalloproteases (MMP9). Candidate drugs have also been synthesized for an impressive array of additional potential targets. They have also made considerable advances in coupling of existing drugs , eg SAHA which is begin used as an HDAC inhibitor, to PI polyamides for targeting specific subsets of genes for reactivation in cancers (e.g. Cdkn2a / p16). These studies are very promising, and preliminary proof of principle data were presented. However further experiments will be required to demonstrate specificity, and in particular to demonstrate in vivo activity of SAHA coupled to the PI polyamides. Data were also presented on the development of photodynamic therapy using Iodine conjugated to porphyrins. These are also promising but further evidence for in vivo efficacy will be required if these are to be developed into clinical candidate drugs.

Recommendations. A continuing theme in the studies of PI polyimides was the requirement to continue to pursue proof of specificity. The molecules readily enter into cells, but have a wide range of binding sites throughout the genome, in spite of targeting to specific (but short)　sequences. Nevertheless, they have evidence that the specific genes targeted are among those that are clearly inhibited by treatment. What is lacking is a clear assessment of the extent of non-target effects. It would therefore be recommended that they carry out detailed transcriptional profiling of cells treated with candidate drugs, as well as CHIP-Seq to demonstrate alteration in the binding of the specific transcription factors to their cognate binding sites in the genome.

In my view, it would be advisable to focus on drug targets for which the small molecule approach will not work, eg for transcription factors or important proteins involved in protein-protein interactions but for which

there is no obvious targetable enzyme activity. Examples are Myc (for which the group already has a program in place) as well as some of the other transcription factors involved in growth and tumor dissemination. I was less enthusiastic about the likelihood of obtaining funding to pursue targets for which the Pharmaceutical industry already has small molecule drugs, and that are already well advanced in the clinic. Examples of these include TGFB inhibitors and MMP inhibitors. While the studies on these PI Polyamides have provided important evidence that the overall approach works, a more focused approach on transcription factors would attract stronger interest from the Pharmaceutical industry and potential investors.

Overall, the program has made some excellent progress and I hope that the investigators will be able to obtain the substantial funding required to enable this very promising program to continue over the next few years.

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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」は各課題において順調に成果が得られている。特に、情報分野において世界トップレベルの研究成果が得られていること、超分子機能において分子運動を評価するなど最先端の成果が得られている点などが特筆される。特段問題はないが、下記の点についてあえてコメントしたい。

１）共同研究への取り組みは活発であるが、プロジェクトとしてそれらが全体的・有機的にどうつながっているかが、やや見えにくい。全体像を示すようなスキームとそれを実践した具体例の例示が望ましい。

２）上述の情報分野の成果のように世界標準に対してどのような成果が得られているかというような表現の研究成果発表がもう少しあってもいいと考える。プロジェクトの世界レベルでの立ち位置を示すことが、プロジェクトの価値をよりわかりやすく示すことになると思われる。

３）松下氏の「研究者ノート」の連載など、アウトリーチ活動を示す成果も見られる。研究主体の若手のプロジェクトであるので、アウトリーチ活動に縛られる必要はないが、現存するものをもっと積極的にアピールして、一般社会の貢献をわかりやすく示すといいものと思われる。アウトリーチ活動は今後外部評価で重要視されるものと予想される。

４）若手中心の萌芽的・挑戦的な研究のアッセンブリーであるので、ロードマップのようなものはあまり必要ないと考える。仮に、外部からロードマップ作成のような指摘があっても、それに惑わされるべきではない。

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研究プロジェクト全般についての評価．昨年度指摘した改善すべき点が本年度では改良され、全体とて順調に推移している。その第１点は、若手研究者の育成に関して、若手対象の賞（ポスター賞、奨励賞など）をとらせるなどしてエンカレッジする点であったが、今年度は６件の受賞があり成果が出ている。第２点は、メンバーによる科研費などの外部資金獲得を増やす事であったが、今年度は３１件の外部資金獲得があり、外部大型プロジェクト獲得にも繋がる成果もでているので大成功といえるのではないか。論文９０報、特許６件も研究業績として及第点である。第３点は広報活動であるが、日大新聞の未来創造の連載記事は白眉であり、これまで日大新聞はスポーツ、本部記事、芸能記事などにかたよっていたが、この種のサイエンスの連載記事を入れたのは大きな進歩であり、日大の品位向上にも大いに役立ち、大きな成果といえる。

昨年９月の N.研究プロジェクトシンポジュウム「羽ばたけ N.若手研究者」に出席して全講演、ポスターを見て、討論にも参加したが、全て英語で行われ、内容もレベルが高くこれだけ多くの若手研究者が日大に育っているのかと感心した。外部からの招待講演者よりもレベルの高いものもいくつかあった。

学部間、学科間の共同研究も増えており共著論文（１４報）も増えているのも本プロジェクトの本来の目的が着々と達成されつつある事の証で、研究代表者の労を多とすべきである。全日大人の研究のモチベーションを上げるためにも、日大全体の教育研究水準のレベルアップのためにも、N.プロジェクトを今後継続して支援することは極めて重要である。

改善すべき点およびコメント

① 優秀な主力班員２名（永瀬、松下班員）が外部に引き抜かれ、その後も共同研究者として継続して *N.*研究に入っていただいているのは有り難い事であるが、代わりの優秀な若手研究者をいれるべきである。

② 論文数は多いが、一流海外雑誌の論文が少ないのが気になる。

③ 毎年一つぐらいは各班からメダマとなる成果を出して欲しい。そうでないと、毎年同じような成果報告となってしまう。

④ 本プロジェクトのシンポジュウムやポスター発表を、大学院 DC 学生の必須の授業演習科目に入れたらどうか。DC 学生にとっては、*N.*に入っていようがいまいが、大いに刺激になるはずで、その教育効果も大きい。