Title
Molecular Recognition of Protein Nanofibers as a Basis for Prior Disease Diagnostics:

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LBNL Report Number_____

1. Parties: Novartis Vaccines & Diagnostics, Inc.

2. Title of the Project: "Molecular Recognition of Protein Nanofibers as a Basis for Prior Disease Diagnostics"

3. Summary of the specific research and project accomplishments:
(Were the goals of the CRADA achieved? Include relevant information but do not include proprietary or protected CRADA information.)

   The goals of this project were achieved. The project was able to develop new regents for the detection of mis-folded proteins in blood samples. Several new compounds were identified, and a synthesis and screening method was developed to facilitate the discovery of new diagnostic reagents.

4. Deliverables:

Deliverable Achieved	Party (LBNL, Participant, Both)	Delivered to Other Party?
Discovery of peptoids capable of misfolded protein detection	Both	Yes
Development of synthesis and screening platform	Both	Yes

5. Identify publications or presentations at conferences directly related to the CRADA?

   A Universal Method for Detection of Amyloidogenic Misfolded Proteins. Yam, A.Y.; Wang, X.; Gao, C.; Connolly, M.D.; Zuckermann, R.N.; Bleua, T.; Halla, J.; Fedynyshyn, J.; Allauzen, S.; Peretz, D.; Salisbury, C.M., *Biochem.,* **50,** 4322-4329 (20 11).

   AB40 Oligomers Identified as a **Potential Biomarker for the Diagnosis of Alzheimer's Disease.** Gao, C.M.; Yam, A.Y.; Wang, X.; Magdangal, E.; Salisbury, C.; Peretz, D.; Zuckermann, R.N.; Connolly, M.D.; Hansson, O.; Minthon. L.; Zetterberg, H.; Blennow, K.; Fedynyshyn, J.P.; Allauzen, S., *PLoS ONE,* **5,** el5725 (20 l 0).

6. List of Subject Inventions and software developed under the CRADA:
(Please provide identifying numbers or other information.)

7. A final abstract suitable for public release:
(Very brief description of the project and accomplishments without inclusion of any proprietary information or protected CRADA information.)

Alzheimer's disease is the most common form of dementia, currently affecting more than 35 million people worldwide. Although many genetic and hereditary factors are thought to contribute to the telltale deterioration of memory and cognitive functions resulting from Alzheimer's, a central aspect to this disease is an accumulation of misfolded proteins in the brain.

Now, scientists at Berkeley Lab have engineered a universal, highly sensitive technique for detecting misfolded proteins in biological fluids. This groundbreaking nanoscience capability could help pinpoint Alzheimer's in its early stages and enable researchers to discover new therapies for this devastating disease.

When a protein doesn 't fold into its normal shape, it also doesn 't perform its normal functions. This disruption in behavior could lead to proteins that aggregate into plaques or deposits and become toxic to cells. In Alzheimer's disease, aggregates of a protein called beta-amyloid form in the central nervous system, causing damage to cells in the brain and triggering dementia.

An analytical capability for measuring tiny clusters of these proteins- before irreversible damage occurs-would be a powerful tool in the early detection of Alzheimer's and other misfolded protein diseases. However, despite significant research efforts, there are currently no diagnostic tools available to selectively detect small-scale aggregates of misfolded proteins in biological fluids , such as blood or spinal fluid.

"This collaboration illustrates how a biomedical problem can also be a nanoscience problem, in which a chemical reagent is needed to recognize partially aggregated proteins," said Ron Zuckermann, Director of the Biological Nanostructures Facility at the Molecular Foundry, a nanoscience user facility at Berkeley Lab. "We were faced with the challenge of synthesizing a material that's capable of specifically detecting this aggregated protein and not any of the other proteins in the blood."

Using the Foundry' s state-of-the-art robotic synthesis capabilities, the team prepared a panel of peptoids designed to capture a misfolded prion protein, an abnormal, infectious form of a cellular protein found in the brain. By attaching these peptoids to tiny magnetic beads, the team could then use a magnet to isolate misfolded proteins directly from blood samples. The most selective and sensitive of these peptoids, coined aggregate-specific reagent, or ASRI, could capture not only the prion

aggregates, but aggregates associated with Alzheimer's disease as well.

"Our study shows how basic research capabilities can be translated into a practical application," said Zuckermann. "The potential for this tool to serve as a diagnostic in other misfolded protein diseases, such as Parkinson 's and Type II diabetes, is wide open, and I'm excited to continue this collaboration."

This research is reported in a paper titled, "A universal method for detection of amyloidogenic misfolded proteins," appearing in the journal Biochemistry and available in Biochemistry online. Co-authoring the paper with Zuckermann were Cleo Salisbury, Xuemei Wang, Carol Gao, Michael Connolly, Thieu Bleu, John Hall, Joseph Fedynyshyn, Sophie Allauzen and David Peretz.

Portions of this work were supported by DOE's Office of Science.

8. Benefits to DOE, LBNL, Participant and/or the U.S. economy.

This project is directed toward the development of a diagnostic test that will be used to screen blood and/or people/animals for the presence of prion disease agents. This would be of great benefit to society in general as well as to Novartis Corp. This research also takes advantage of LBNL's knowledge and technology and thus will further develop our technology base. Specifically, we will have the opportunity to work with experts on the molecular recognition of protein nanofibers, which is an important problem in a wide variety of diseases. This knowledge should help us in developing techniques that will be useful in other areas of nanoscience as well.

9. Financial Contributions to the CRADA:

DOE Funding to LBNL	$0
Participant Funding to LBNL	$668,760
Participant In-Kind Contribution Value	$1,435,208
Total of all Contributions	$2,103,968

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