CAN GRANT CONCEPT CLEARANCE RECORD
FY 2018 RESEARCH INITIATIVE — NCATS
September 2017, Concept 2

CONCEPT TITLE: Automated Synthesis Platform for Innovative Research and Execution (ASPIRE)

CONCEPT TYPE: New; developed by NCATS staff

ASSIGNED DISCUSSANTS: Palkowitz, Marks

OBJECTIVE(S): This initiative will solve longstanding, previously intractable problems in chemistry by enabling (a) synthesis of biologically relevant libraries of diverse compounds with minimal human intervention; (b) prediction of effect of synthesized chemical compounds on biological function and/or structure; (c) development of new tools and technologies to achieve fully automated synthesis (AS); and (d) systematic development of better and more effective therapies through AS.

CAN PROJECT CRITERIA:

- **Collaborative:** The proposed initiative will be highly collaborative and will engage stakeholders from government, academia, pharma industry, professional societies and scientific journals. The initiative will involve potential co-funding opportunities with other government agencies, NIH Institutes and Centers, and pharma companies.
- **Discrete and Measurable Outcomes:** The Automated Chemical Synthesis Workshop will identify challenges and opportunities in the field and engage stakeholders (view the agenda). The tools and technologies developed through this initiative will significantly increase the diversity of chemical libraries. Automated synthesis, as a tool, will be adopted widely by scientists and lead to the more rapid identification of safer and more effective compounds against a wide spectrum of previously undruggable and/or new drug targets.
- **Broad and Significant Impact:** The initiative will transform chemistry from empirical to predictive science. The initiative is directly relevant to the NCATS mission of developing innovative technologies and bringing more safe and effective treatments to more people more quickly, as well as to the NIH mission of increasing reproducibility and scientific rigor.
- **Disease Relevance:** The initiative will facilitate more efficient drug discovery/development across many disease phenotypes.

HISTORY: The generation of new chemical entities capable of modulating biological targets is fundamental to translation from biological function to drug development. A fundamental roadblock to efficient translation is the inability to predict chemicals that will modulate any desired target *ab initio* or to produce chemicals of desired structure cheaply and rapidly. After more than a century of synthetic organic chemistry and pharmacology, there is still no general understanding of the relationship of chemical space to biological space. This leaves more than 99.9 percent of theoretical biologically relevant chemical space unexplored and the process of new bioactive chemical discovery fraught with gross inefficiency wrought from intuition and empiricism. Chemistry drives pharmaceutical innovation, so expanding the druggability of the genome to test innovative therapeutic hypotheses is key for future breakthroughs.

Most fields of biology, especially genetics, have evolved from empirical to predictive sciences because of an intense focus on technology development that has produced logarithmic increases in experimental scale. Chemistry, by contrast, continues for the most part to use the empirical approaches and methods

developed a century ago. Production remains artisanal, with synthetic throughput of novel bioactive chemicals improved during the last century, but far from reaching its full potential. A convergence of technologies now provides the opportunity to break this translational bottleneck, to the benefit of science and health. Advances in chemical laboratory automation, microfluidic flow chemistry, biological high-throughput screening (HS) and machine learning are the basis of automated synthesis as the solution, which will have biological/therapeutic, chemical and technological/commercial benefits.

The envisioned Automated Synthesis Platform for Innovative Research and Execution (ASPIRE) will serve as an unprecedented portal for automated rapid testing of hypotheses regarding novel chemical scaffolds (i.e., structures that hold up or support other materials, such as drugs, crystals or proteins) designed through computational approaches to interact with specific therapeutic targets. ASPIRE will be coupled with next-generation computational systems that generate chemical predictions and will, in turn, provide automated small-scale synthesis of said compounds for immediate/in-line biological testing using existing or adopted robotic HTS and analytic systems. Results from the immediate assessment of bioactivity will in turn be fed back into the chemical prediction algorithms to enable facile improvements of the molecules, representing a feedback loop for hypothesis-building and fine-tuning.

The envisioned integration of automated chemical synthesis into the iterative paradigm of drug discovery, also coupled to companion technological advances in analytical chemistry, computational and predictive science, automated high-resolution biology, and informatics analysis, will define a new frontier for the creation of innovative therapies. The currently available automated workstations produce molecules with a very narrow range of chemical properties using known chemistries, and these platforms are expensive for most academic laboratories. The envisioned platform will have the capacity for remote worldwide access and the ability to support real-time collaborative work that will integrate efforts from diverse researchers all over the world from academia, government and industry to solve complex biomedical challenges. Through automated synthesis, the immense value of diversity of scientific expertise to solve complex problems will be brought closer to routine practice. The tools developed through this initiative will minimize the amount of time synthetic chemists spend on tedious and repetitive tasks and will provide them with more time to pursue creative endeavors. In addition, other scientists, whose primary expertise is not in chemistry and who are capable of formulating a molecular hypothesis, will be able to translate their ideas into testable compounds.

The ASPIRE initiative will facilitate the development of new medicines to treat diseases and conditions that we cannot treat now, assist with the development of personalized treatments and accelerate our entry into a future in which known medicines are produced at a cost that all can afford.

CONCEPT CLEARANCE DATE:
Sept. 7, 2017

COUNCIL RECOMMENDATION:
Council approved as recommended by staff.

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