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Synthetic Biology for Improved Personalized Medicine

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ABSTRACT

Tools to re-sequence the genomes of individual patients having well described medical histories is the first step required to connect genetic information to diagnosis, prognosis, and treatment. There is little doubt that in the future, genomics will influence the choice of therapies for individual patients based on their specific genetic inheritance, as well as the genetic defects that led to disease. Cost is the principle obstacle preventing the realization of this vision. Unless the interesting parts of a patient genome can be re-sequenced for less than $10,000 (as opposed to $100,000 or more), it will be difficult to start the discovery process that will enable this vision. While instrumentation and biology are important to reducing costs, the key element to cost-effective personalized genomic sequencing will be new chemical reagents that deliver capabilities that are not available from standard DNA. Scientists at the Foundation for Applied Molecular Evolution and the Westheimer Institute have developed several of these, which will be the topic of this talk..

INTRODUCTION

While we are more similar than we are different, individual humans differ at their genetic level in ways that change what diseases we get, how we react to various disease treatments, and how our physician should proceed to maximally improve our personal welfare. Further, current clinical practice, especially for geriatric patients, administers an endless series of tests involving repeated visits to the clinic to identify diseases from often non-descript symptoms. A rapid genomic and inexpensive testing technology to shorten the diagnostic ordeal is essential to the future of medicine and, in particular, containing its costs. The issue of cost is especially important. If we can sequence the interesting portions of the human genome (in particular, the non-repeating regions) for less than ca. $10,000, it should be possible to enable a cycle in genomic research, where the genomes of individuals are determined, their medical histories are closely followed, and a database of information is assembled that empirically connects genome to disease, health, and treatment.

RESULTS AND DISCUSSION

Scientists at the Foundation for Applied Molecular Evolution and the Westheimer Institute have developed a series of reagents that permit low-cost individual genotyping and sequencing. The first is an Artificially

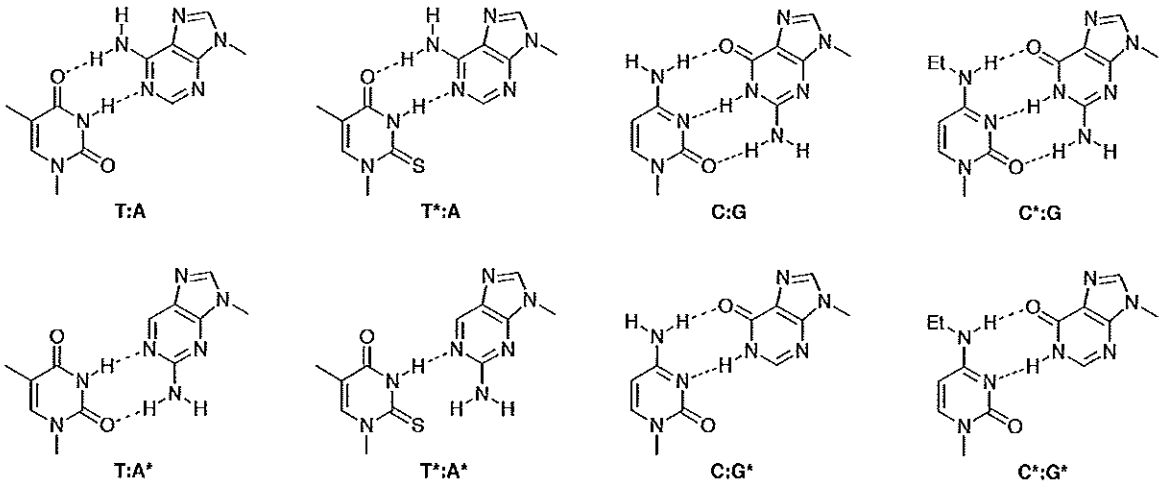

Fig. 1 Base pairing motifs of natural:natural SAMRS:natural and SAMRS:SAMRS.

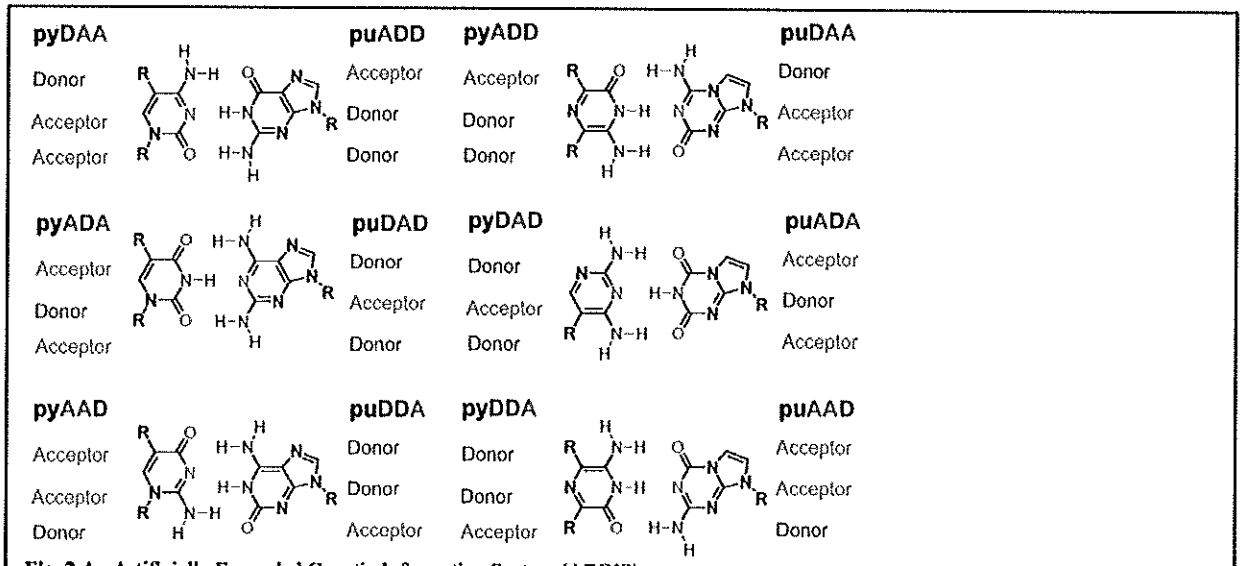

Fig. 2 An Artificially Expanded Genetic Information System (AEGIS)

Expanded Genetic Information System (AEGIS) (Fig. 2) which allows rule-based molecular recognition without interference from genomic complexity in a sample. Today, AEGIS improves the health of some 400,000 patients infected with HIV, hepatitis B and hepatitis C infections annually.[1] It also improves binning of genome elements, avoiding the need for polonies and other single molecule detection schemes.

Next, FfAME and Westheimer scientists, who invented dynamic combinatorial chemistry in the past, have applied this technology in a SNAP2 architecture to generate priming with the specificity of a 16mer must the mismatch discrimination of an 8mer.[2] This permits highly specific priming, potentially in complex mixtures.

The third is a self-avoiding molecular recognition system (SAMRS), shown in Fig. 1. Each SAMRS species (A*, T*, G* and C*) is designed to bind to a natural complement (T, A, C and G) more tightly than a corresponding SAMRS complement (T*, A*, C* and G*) respectively. This permits highly multiplexed priming.

The fourth is a 3'-O blocking group that, when appended to a triphosphate, allows a single triphosphate to be accepted by polymerases, but not a second. The terminator is, however, reversible, as the 3'-O blocking grou can be removed in just seconds, to allow primer extension to continue. This permits highly parallel sequencing-during-synthesis.

The fifth reagent-based solution to genomics developed at the FfAME and the Westheimer Institute is an architecture that removes from a complex biological mixture only those components that are different in sequence from the analogous sequences in a reference genome. These differences can be delivered for sequencing, focusing only on what is unique in the personal genome.

CONCLUSION

We report a series of reagent-based solutions to problems in genomics. These can be applied to virtually any platform, including single molecule sequencing, nanopore sequencing, two dimensional array sequencing, and polony sequencing. In combination, they should push the price of personalized genomics to the level where individuals will be able to have their own genome sequenced. The FfAME will soon offer individual genome sequencing services at such reasonable prices.

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