Latest advances in drug repurposing for Cystic Fibrosis lung infections

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This manuscript highlights the importance of a new strategy put in place for fighting lung infections in Cystic Fibrosis: the repurposing of drugs already available on the market. This approach is attracting the scientific community’s attention and has already provided evidence that there are hidden therapies within the set of drugs approved for chemical use.

Keywords: cystic fibrosis, drug repurposing, lung infection

Cystic Fibrosis (CF) is a very serious genetic pathology due to the dysfunctional behavior of the Cystic Fibrosis Transmembraner Regulator (CFTR), a membrane protein that is responsible for the transportation of chloride (Fig. 1). Defective protein functions are due either to the quantity of the functional CFTR that reaches the membrane or the compromised functionality of the protein. One of the main consequences of the disrupted regulation of chloride ion density is the recurrence and severity of lung infections in CF patients, in which Pseudomonas aeruginosa infections determine loss of lung function. In fact, mucus keeps building up in the lungs because the interchange of chloride and sodium is not working properly thus not creating a suitable environment for the cilia to control the flow.

Basic research has been seeking new active molecules against CF lung infections for a number of years. However, the process that leads a promising molecule to become an available antibiotic is long and the pipeline is lacking of new discoveries. Therefore, identifying the anti-Pseudomonas aeruginosa activity of currently available drugs would reduce both the costs and research efforts necessary to bring new compounds to the clinic.

Figure 1 Membrane localization and function of the CFTR chloride transporter. Dysfunctional behaviors of CFTR lead to all CF-correlated pathologies and recurrent infections by P. aeruginosa (the figure was created thanks to the Vertex Application CF geneE ). There can be 1,800 different kinds of CFTR mutations (1). Well known defective behaviors are due to narrow ion channels, improper gating, splicing, folding or trafficking errors, or premature stop codon mutations.

Moreover, antibiotics generally target certain vital functions of bacteria, but the development of resistance is limiting their use. An alternative approach would involve antimicrobial substances that inhibit bacterial virulence, disarming instead of killing the pathogen.

As a consequence, a new strategy has recently gained the attention of the CF
community: the repurposing of drugs already available on the market. This approach provides evidence that there are still hidden therapies within the set of drugs already approved for chemical use. It is a strategy that has already been applied to CF (2), as recently acknowledged by a Faculty of 1000 Member, who wrote (3): "Two emerging strategies for drug discovery, antivirulence targeting and drug repositioning, are used together to generate a promising drug lead for a morbid and highly resistant pathogen. The article [ (2)] confirms the promise of new strategies for treating infection, which have not been subject to the same selective pressure as traditional antibiotics”.

In their paper, Imperi and coworkers (2), identified seven promising compounds through a method named SOSA (Selective Optimization of Side Activities of Drug Molecules), which consists of a limited number of already available and diverse drugs being tested on the target (4). Among those molecules (4 antibiotics, disinfectant, a chemotherapy, a pesticide), the authors restricted their attention to niclosamide, which is on the market as an anthelmintic drug to treat intestinal infections. They showed that niclosamide strongly inhibits the *P. aeruginosa* Quorum Sensing response both *in vitro* and in an insect model of acute infection.

Through the same approach, Imperi and colleagues (5) also reported on the repurposing of the antimycotic drug flucytosine (an antifungal drug already used in humans) for suppression of *P. aeruginosa* pathogenicity. *P. aeruginosa* produces an important siderphore (from Greek: iron carrier) called pyoverdine (a green-fluorescent molecule). The pyoverdine is the iron carrier in infections by *P. aeruginosa* and biofilm formation, and is a signal molecule that controls the expression of virulent genes. This work applied repurposing to identify an antivirulence drug to be used against *P. aeruginosa*. The authors screened a commercial library of 1,120 chemical compounds with known biological activities selected for their high chemical and pharmacological diversity and safety in humans (Prestwick Chemicals), and identified a promising US Food and Drug Administration approved compound, flucytosine, as effective in suppressing the virulence of *P. aeruginosa* both in vitro and in a CF mouse model of lung infection. They demonstrated that flucytosine inhibits the production of the critical virulence factor pyoverdine.

Encouraging drug repurposing and finding new ways of screening potentially suitable compounds can be a challenge. In a recent publication Gramatica et al. (6) suggest a dry-lab and completely new methodology for identifying candidate molecules for drug repositioning. They propose a computational approach, in which proper graph representation – the knowledge graph - and path analysis are shown to provide evidence on whether or not an available peptide could be used to treat different pathologies. This methodology that has two different aspects: on one side the development of a “semantic analysis” through the use of the computational linguistics (an inter-disciplinary approach that encompasses computer science and natural language expertise) to target the problem, on the other side the exploitation of the graph theory with particular attention to the stochastic processes that are guided by random variables and analyzed through probability distributions. This methodology works essentially by measuring the number of "degrees of separation" between a potential drug candidate and a disease through analyzing the content of 3 million PubMed abstracts. Large numbers of, or very close
connections between, two ideas indicate a potential therapeutic effect. For example, aspirin is associated with inflammation, which is in turn associated with cancer. This would be a link between aspirin and cancer. In their paper (6) they show examples of rationales produced by their approach with regard to the granulomatous disease sarcoidosis and its pulmonary pathology, and Imatinib, which is a targeted-therapy agent against cancer cells, well known for its pro-apoptotic action. The authors conclude this methodology can find many applications in clinical science, and is useful for the specific clinical case they analyzed. However, it is reasonable thinking that further examples would be needed to confirm the reproducibility of this computational and probabilistic approach.

With regard to CF research, one of the main problems is represented by the availability of suitable models and samples of lung infections, for either in vitro or in vivo experiments. CF mice models that developed lung infection by *P. aeruginosa* are mostly desirable for in vivo analysis and they are frequently used, but not always easily available. The method delineated by Gramatica and coworkers (6) would allow to perform a “pre-screening” of all possible compounds and reduce the number of experiments and the time necessary to determine which approved compounds may be useful to treat CF patients.

References


