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Synopsis

DRUG REPURPOSING FOR RARE DISEASES

THE CURE FOR THE 21ST CENTURY

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AN OPPORTUNITY: OLD DRUGS FOR RARE DISEASES

Rare diseases each, by definition, affect only a handful of people. However, there are more than 7,000 different types and together they affect roughly 10% of the global population. Nevertheless, only 5% of all rare disease currently have some sort of treatment available.

There are many difficulties in researching therapies for rare diseases. Firstly, studies tend to focus on common diseases, which have a broader margin of action and larger profit margin. And, secondly, the studies are more complicated due to the scarcity of patients on which to test new drugs.

One strategy to improve this situation is called “**drug repurposing**”, or **repositioning drugs already approved for other indications**. The advantages are clear: cumulative knowledge about these drugs shortens timelines while also cutting down on the investment needed. Nevertheless, this strategy has its own hurdles and difficulties.

To discuss the new advances in drug repurposing for rare diseases, the problems and proposed solutions, several top international experts met on 17 and 18 November 2016 for the debate ‘[Drug Repurposing for Rare Diseases. The Cure for the 21st Century](#)’, organized by [B-Debate](#) –and initiative of [Biocat](#) and the “[la Caixa](#)” [Foundation](#) to promote scientific debate– with the [Barcelona Science Park \(PCB\)](#) and [Hospital Sant Joan de Déu \(HSJD\)](#).

CONCLUSIONS

- Over 90% of rare diseases have no treatment. In part, this is due to lack of interest but also because of the difficulty of doing research with so few patients.
- Drug repurposing, or repositioning drugs already approved to treat other diseases, cuts the investment and time needed for development.
- Networks seem to be key for pooling information and patients, which in the case of these diseases can be spread out and not interconnected.
- There are several examples of repurposed drugs and many are in the clinical trial phase. The final price of the new indication is a source of controversy, as it is often much higher than the original price.

1. THE DATA, THE PROBLEM, THE OPPORTUNITIES

In Europe, a rare disease is one that affects no more than one in 2,000 people. Despite the low percentage (0.05%), there are roughly 7,000 identified rare diseases and, together, they affect between 6% and 8% of the global population. The problem is even more significant taking into account the data shared by [Noel Southall](#) of the United States National Institutes of Health (NIH): **"50% of those affected are children and 30% of them die before the age of 5. And more than 90% of these diseases have no approved treatment."**

Drug development is a complicated and often frustrating process. For [Pierre Meulien](#), executive director of the [Innovative Medicines Initiative](#) (IMI), "It is probably the least efficient process of any sort of industry." Southall also shared data on the development chain: of ten thousand drugs involved in laboratory research targeting any one disease, only 250 go on to the preclinical phase. Out of these, only 5 will be tested in clinical trials and only one will gain regulatory approval.

Research into treatments for rare diseases is even more difficult, as there are so few patients with each condition. On one hand, **companies tend to be less interested because their anticipated profits are lower.** And even though measures incentivizing this work have "[encouraged](#)" companies, the flipside of the situation is that the drugs are normally quite expensive. On the other hand, **the lack of patients makes it more complicated to study and conduct representative clinical trials.**

A new concept has opened an encouraging new door: **drug repurposing.** This consists in "recycling" drugs approved for one disease that, given their characteristics (or even their side effects), may benefit another. For [Bruce Bloom](#), president of [Cures Within Reach](#), this approach may work with any disease, "even *ours*, those that have traditionally been *neglected*."

The advantages are undeniable. Cumulative knowledge on the safety and behavior of these drugs massively cuts down of the time and money required. In fact, **the 15 years it takes, on average, to develop a drug could be cut down to just three.**

However, there are obstacles in this path as well. For example, the hurdles put up by pharmaceutical companies. "Imagine a drug approved to treat diabetes is given to children and there is some sort of problem," said Bloom. Their objection "is understandable. But we can use generics."

To combat the hurdle of atomization, that the scarce number of patients are very spread out, there are networks. Pierre Meulien wondered why there isn't a joint international

project in health like the CERN for physics. Given their characteristics and needs, **“rare diseases could be an opportunity, a great unifier.”**

These networks mean forging bonds, between people and data, and the role of patients seems to be key.

2. NETWORKS: TOWARDS PATIENTS, WITH PATIENTS

“We’re facing a new era. In ten years, social media like Facebook and Twitter have connected and empowered patients like never before imagined.” This is the opinion of [Tim Guilliams](#), CEO of [Healx](#), an initiative that helps researchers, foundations and patients with rare diseases identify drugs that could work to treat them. And he doesn’t hesitate to bring up [John Crowley](#), a lawyer with two children with [Pompe disease](#), a rare disease that had no treatment at the time and can be mortal. For Crowley, **“It is impossible to develop drugs for these diseases without a group of patients.”** He co-founded a small company called Novazyme, which quickly grew and discovered a treatment that partially curbs the progression of the disease.

Networks allow data to be shared and put researchers and patients in contact. This has led to websites like [Orphanet](#) and international platforms to manage scientific projects, like [E-Rare](#). Others focus specifically on drug repurposing, like [Cures Within Reach](#). And there are more that work to connect and group together patients, such as the [Rare Commons](#) initiative at Hospital Sant Joan de Déu in Barcelona. “Many childhood diseases can be considered rare,” explained [Ainhoa Andueza](#), project manager in the Clinical Research Unit. **Drug repurposing can be a way to improve on the options available for these kids, and the website is one way to channel it.** The example Andueza gave was a pilot study for a rare disease called [Lowe syndrome](#). Before the study, there were only two patients registered in the Spanish healthcare system’s database. After launching the study and announcing it on Rare Commons, they are now working with 24 Spanish families and 41 from other countries. Plus, “It has helped generate and share knowledge on the disease, while connecting doctors interested in it who were more isolated before.”

3. Success stories and hope for repurposing

Some of the most noteworthy successes in drug repurposing haven’t been for rare diseases. The most well-known may be **Viagra** being used for erectile dysfunction.

Created to treat angina, one of its side effects was that it caused erections. In this end, this became the main indication for the drug.

For minorities diseases, there are some drugs that have already been approved. **Thalidomide**, created to alleviate morning sickness, had to be banned because it caused serious malformations. Nevertheless, now it is used to treat leprosy, an infectious disease that is rare in western countries. And canakinumab, a drug originally used to treat rheumatoid arthritis that was also approved as a therapy for Muckle-Wells syndrome, a rare genetic disease.

Jordi Quintana, director of Business Development at the Barcelona Science Park (PCB) and one of the scientific leaders of this B-Debate, said that even though **“repurposed drugs, in general, won’t be a cure,” we have to take into account that “they can alleviate diseases that in many cases are deadly.”** In addition to drugs already approved for other uses, there are many classified as *off-target*. This is a shortcut that allows drugs to be used, without large-scale clinical trials, as long as there aren’t any other alternatives, as is the case with many rare diseases. Others are currently undergoing clinical trials. Following are some examples.

Bruce Bloom discussed the case of **sirolimus**, a drug used to prevent transplant rejection that can now be used for autoimmune lymphoproliferative syndrome, a very serious and rare congenital disease. Raúl Insa, CEO of a start-up specializing in drug repurposing - SOM Biotech, shared the advances towards using a drug meant for Parkinson to **treat a type of amyloidosis**, a rare disease that causes proteins to aggregate and damage the nerves and heart. And Noël Raynal, professor at the University of Montreal, explained how they **trawl the effects of more than a thousand approved drugs to research new applications**. One of them is **proscillaridin**, a drug to treat arrhythmia that can help low-frequency childhood tumors.

Jordi Mestres, group leader at the Hospital del Mar Medical Research Institute (IMIM), spoke about mechanisms. **Drugs may seem selective, but they are far from it.** “More than half of all drugs each interact with at least five proteins,” he explained. This promiscuity leads to opportunities as well as dangers. It allows us to expand the drug’s applications, but can also have side effects when the indications and doses are changed.

There are also other ways to focus the work. For example, **repurposing not a specific drug but its mechanism of action**. If a drug is found to be beneficial but not effective enough, scientists research its mechanism and seek out other molecules that do a better job. This topic was discussed by Marc Martinell, CEO of Mynorix Therapeutics, a company that specializes in research into rare metabolic diseases. One of them, now in clinical trials, is a drug based on one for diabetes, a PPAR gamma receptor agonist, which

may be useful in treating **adrenoleukodystrophy**, a metabolic disease that causes serious damage to the nervous system.

In this joint effort to get drugs to patients, **all of the stakeholders seem to play an essential role**. Also in the final stage, commercialization. EURORDIS Therapeutic Development Director **Virginie Hivert** shared her concerns about the fact that repurposing doesn't necessarily mean more advantageous prices. "It's a controversial issue," recognized Quintana and **Francesc Palau**, director of the Department of Genetic Medicine and the **Pediatric Institute for Rare Diseases** (IPER) at Hospital Sant Joan de Déu in Barcelona and joint scientific leader of this B-Debate. "Companies reason that, even though it is a repurposed drug and therefore the investment is lower, rare diseases affect fewer patients, which could justify the increase in price." Although the data and examples vary, and some drugs have hardly changed in price after being repurposed, **a study in Belgium** observed that, on average, hospitals paid twenty times more for the new use. In some cases, for the same dose and route of administration, the cost was up to 200 times higher.