**31 – Informations BBS Juillet 2011. Résumé par F.Lestel d’articles parus sur Internet**

*Comme toujours, sous réserve d’éventuelles erreurs de l’article originel ou de la traduction*

**1**) **Un dispositif pour repérer des médicaments déjà autorisés susceptibles d’avoir une indication pour des maladies rares (source Orphanet)**

Le National Institute of Health (NIH) aux Etats-Unis a annoncé dans un communiqué de presse le lancement d’un processus de criblage de médicaments autorisés dans le but de déterminer s’ils peuvent avoir une utilité clinique pour les maladies rares et négligées. Une liste de médicaments à soumettre au processus a été établie à partir d’informations issues d’une exploration de la collection pharmaceutique du NCGC ([NPC](http://tripod.nih.gov/npc/)).

Un article paru dans le numéro de Science Translational Medicine du 27 avril 2011 définit les trois principales fonctions de la NPC :

* réorienter les médicaments pour le traitement des maladies rares et négligées ;
* affiner la compréhension de la toxicologie des médicaments ;
* améliorer la prévisibilité des principes généraux par lesquels de petites molécules interagissent avec leurs cibles biologiques.

L’article décrit la complexité sémantique et lexicale de la NPC ainsi que les incohérences constatées dans le sens de termes tels que « entité moléculaire », « ingrédient pharmaceutique actif » et « produit médicamenteux ».

La NPC est décrite comme un « outil collaboratif » dont le but est de permettre à la communauté, y compris les fondations, l’industrie et les chercheurs universitaires, d’« utiliser tout le potentiel de ces médicaments pour la santé humaine, face aux nombreuses maladies destructrices et incurables pour lesquelles il y a un besoin urgent en thérapie ». Le navigateur NPC permet aux utilisateurs de rechercher les médicaments par nom, structure chimique et état d’approbation. Les groupes désireux de créer leur propre liste peuvent « se servir des informations du fournisseur et du catalogue disponibles sur le navigateur ». « Le but est de collecter tous les 7500 composés qui ont été testés sur l’homme et qui présentent un potentiel de développement de traitements pour les maladies rares et négligées. »

**2) Amaurose Congénitale de Leber, le cortex visuel répond à une récupération de la fonction rétinienne due à une thérapie génique (source Orphanet) :**

La capacité du cortex visuel à répondre à la récupération de la fonction rétinienne après une longue période de privation sensorielle n’était pas connue. Dans cette publication, [Ashtari et coll.](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=21606598) présentent des résultats d’IRM fonctionnelle chez 3 patients atteints d’une amaurose congénitale de Leber due à une mutation du gène *RPE65* (LCA2) qui avaient été traités par thérapie génique deux ans auparavant. Ces patients avaient reçu une injection subrétinienne unilatérale d’un vecteur viral adéno-associé porteur d’ADN complémentaire de *RPE65* à l’âge de 8 ans, 9 ans ou 35 ans. Les données suggèrent que malgré une longue période passée avec un handicap visuel sévère, ces patients ont des voies optiques intactes, qui répondent au traitement, et que la thérapie génique produit non seulement une amélioration durable de la vision mais aussi une augmentation de la sensibilité aux contrastes.

*Journal of Clinical Investigation ; 121(6):2160-8 ; 1er juin 2011*

3) la conférence DeViNT (Déficients Visuels & Nouvelles Technologies)

a eu lieu le jeudi 26 Mai 2011 à Sophia-Antipolis (Alpes Maritimes), elle a rassemblé 300 personnes ; les résumés des auteurs (en français et anglais), ainsi que le compte rendu en français se trouvent sous : <http://devint.polytech.unice.fr/index.html>

Le site sera mis à jour quand les auteurs auront donné une copie de leur présentation.

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**31 – Information BBS July 2011. Summary by F.Lestel of articles from Internet**

*As usual, without guarantee of possible mistakes in the original article or in the translation.*

**1) NIH researchers create comprehensive collection of approved drugs to identify new therapies for rare and neglected diseases (press release from NIH)**

Researchers have begun screening the first definitive collection of thousands of approved drugs for clinical use against rare and neglected diseases. They are hunting for additional uses of the drugs hoping to find off-label therapies, for some of the 6,000 rare diseases that afflict 25 million Americans. The effort is coordinated by the National Institutes of Health’s Chemical Genomics Center (NCGC).

"This is a critical step to explore the full potential of these drugs for new applications," said NIH Director Francis S. Collins, M.D., Ph.D. "The hope is that this process may identify some potential new treatments for rare and neglected diseases."

The researchers assembled the collection of approved drugs for screening based on information from the NCGC Pharmaceutical Collection browser at <http://tripod.nih.gov/npc>. This publicly available, Web-based application described in a paper appearing in the April 27 issue of Science Translational Medicine, provides complete information on the nearly 27,000 active pharmaceutical ingredients including 2,750 small molecule drugs that have been approved by regulatory agencies from the United States, Canada, Europe and Japan, as well as all compounds that have been registered for human clinical trials.

“In order to launch a systematic repurposing effort using NCGC’s drug screening technologies, we needed access to a comprehensive collection of clinically approved drugs,” said Christopher P. Austin, M.D., director of NCGC, which is currently administered by the National Human Genome Research Institute (NHGRI). “Our team took on the monumental task of assembling this collection, making it publicly available and creating a world class resource.”

The NCGC Pharmaceutical Collection (NPC) browser provides users with the ability to explore drugs by name, chemical structure, approval status and indication. Groups interested in developing their own screening collections can leverage the supplier and catalog information provided in the browser. The browser, which is an ongoing effort, also includes entries on investigational drugs. The ultimate goal is to collect all of the more than 7,500 compounds that have been tested in man and which present potential jump-start development of treatments for rare and neglected diseases.

The current focus is on collaborating with disease foundations, industry, and academic investigators with disease-relevant assays to screen against the approved drug collection acquired by NCGC. Any new therapeutic use of an approved drug would require additional studies including clinical trials in that disease, approved by the U.S. Food and Drug Administration. Given the cost and limited quantities of the drugs in the collection, each partnership to screen the NPC will be evaluated based on the quality of each disease-related assay and its scientific merit.

Creating a new drug is expensive. Recouping the investment can be difficult for rare diseases, due to the small number of patients with the disease or, in the case of tropical neglected diseases, the limited ability of patients to pay for treatments. Today, therapies are available for less than 300 rare diseases.

Drugs that receive regulatory approval have been demonstrated to be reasonably safe and effective in the treatment of a specific disease or condition. When such drugs are used in large populations, new benefits or adverse effects can be discovered. Subsequently, the use of approved drugs can be expanded beyond what a drug was originally approved for to treat other health conditions.

Thalidomide is an example of repurposing a drug with serious adverse effects in one condition to treat another disease, according to the authors. In the 1950s, it was used as a sedative and as a treatment for morning sickness during pregnancy. It was later withdrawn because it was found to cause severe birth defects. Thalidomide was then repurposed for use against leprosy, an infectious disease causing skin lesions and multiple myeloma, a cancer of plasma cells, which are a type of white blood cell present in bone marrow.

Based on the drug's new application, the U.S. Food and Drug Administration approved thalidomide for the treatment of leprosy in 1998 and for multiple myeloma patients in 2006.

More recently, a team of NHGRI researchers used a similar approach, examining patient blood samples to see what gene and protein networks were active in a syndrome called periodic childhood fever associated with aphthous stomatitis, pharyngitis and cervical adenitis — or PFAPA. PFAPA causes monthly flare-ups of fever, accompanied by sore throat, swollen glands and mouth lesions.

The researchers detected overactive genes in the patient's immune response, including interleukin-1, a molecule that is important in triggering fever and inflammation. From these data, the researchers hypothesized that anakinra, a drug that prevents interleukin-1 from binding to its receptor, could be therapeutic. They injected anakinra into five children on the second day of their PFAPA fevers and [all showed a reduction in fever and inflammatory symptoms within hours](http://www.genome.gov/27544064).

Another approach that does not require a complete knowledge of a disease or drug mechanism uses high-throughput drug screening technologies that screen drugs for biological activity in cell-based models of disease. Drugs that record an activity are known as hits and can be further studied for their therapeutic potential by researchers in animal models of the disease and eventually in human clinical trials.

NCGC already has screened the approved drug collection against more than 200 cell-based models of disease. In every screen, NCGC characterizes the pharmacology of each compound over a wide range of concentrations using its signature quantitative high-throughput screening approach. All of the data from NCGC screens will be published and made publicly available.

In addition to repurposing drugs, the NCGC plans to screen the collection as part of the [Tox21 initiative](http://www.genome.gov/27543708) to better predict and model adverse effects associated with approved drugs. Drug toxicity is one of the primary reasons that approved drugs are removed from the marketplace and the ability to predict toxicity would dramatically improve the efficiency of drug development.

**2) The human visual cortex responds to gene therapy-mediated recovery of retinal function.***The Journal of clinical investigation 2011;121(6):2160-8.*

Leber congenital amaurosis (LCA) is a rare degenerative eye disease, linked to mutations in at least 14 genes. A recent gene therapy trial in patients with LCA2, who have mutations in RPE65, demonstrated that subretinal injection of an adeno-associated virus (AAV) carrying the normal cDNA of that gene (AAV2-hRPE65v2) could markedly improve vision. However, it remains unclear how the visual cortex responds to recovery of retinal function after prolonged sensory deprivation. Here, 3 of the gene therapy trial subjects, treated at ages 8, 9, and 35 years, underwent functional MRI within 2 years of unilateral injection of AAV2-hRPE65v2. All subjects showed increased cortical activation in response to high- and medium-contrast stimuli after exposure to the treated compared with the untreated eye. Furthermore, we observed a correlation between the visual field maps and the distribution of cortical activations for the treated eyes. These data suggest that despite severe and long-term visual impairment, treated LCA2 patients have intact and responsive visual pathways. In addition, these data suggest that gene therapy resulted in not only sustained and improved visual ability, but also enhanced contrast sensitivity.

3) The DEViNT conference took place on Thursday 26 May 2011 in Sophia-Antipolis (French Silicon Valley, in-between Cannes and Nice), with 300 participants.

DeViNT is a French acronym which means « New Technologies for Visually Impaired ». The main language is French, with some English speakers with real time translation.

Authors summaries can be found (in both French and English) on :

<http://devint.polytech.unice.fr/index.html>