Finding new purposes for established or abandoned therapeutics

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It's a wonder new medications are ever developed at all. Taking a new drug from promising molecule to marketable product can cost upwards of a billion dollars and take a decade or more to move from clinical trials to approval. Oh, and the overall failure rate hovers near 95%.

Not surprisingly, the drug industry has become interested in repurposing drugs, which involves testing a medication for a therapeutic use different from its original intended use. These can be drugs already on the market, or those that didn't pan out for their original intended use.

Repurposing an existing drug can save developers years of time and almost 40% of the cost of bringing a drug to market by eliminating the need for additional toxicological and pharmacokinetic assessments. "The amount needed to bring these drugs to market is often less, which is why smaller companies are interested: some of the risk has been taken out of the equation," says Cliff Michaels, senior licensing associate with Emory's Office of Technology Transfer.

Well-known repositioned drug success stories include:

- Rogaine, the hair regrowth treatment, which was developed from the oral blood pressure medication minoxidil after researchers noticed that hair growth was a common side effect.
- Thalidomide, which was taken off the market in 1961 after being discovered to cause severe birth defects, but approved again by the FDA in 1998 for use in leprosy and again in 2006 for

multiple myeloma
- Viagra, which was developed to treat pulmonary arterial hypertension before gaining approval in 1998 to treat erectile dysfunction.

As the cost to develop drugs continued to go up, there is also an increased interest among the public and federal government to make the most of drugs that have already been approved. The NIH's Chemical Genomics Center recently opened its Pharmaceutical Collection database for public screening of nearly 27,000 active pharmaceutical ingredients, including 2,750 approved small-molecule drugs and all compounds registered for human clinical trials.

NIH Director Francis Collins said the agency would be leading a "comprehensive effort to identify appropriate abandoned compounds, establish master agreements, match partners, make data resources available, and provide a central access point to relevant resources and expertise."

Emory's OTT already has several repurposed drug candidates in development to treat conditions from post-traumatic stress disorder (PTSD) to hypersomnia to ischemic stroke.

Flumazenil was developed for overdoses of benzodiazepine sedative hypnotics, but was found by sleep researchers in the School of Medicine David Rye, MD, PhD, and Andrew Jenkins to be useful for patients with hypersomnia. In some patients, this excessive sleepiness was found, through spinal taps, to be associated with excess of an endogenous activity that mimics the actions of benzodiazepines. Flumazenil reformulated as a lozenge or transdermal cream restores vigilance in many of these patients who are otherwise refractory to traditional wake-promoting agents including psychostimulants.

Rapamycin originally developed as an antifungal agent, was discovered to have potent immunosuppressive and anti-inflammatory properties and has been used to prevent rejection of transplanted organs. School of Medicine researchers Christian Larsen, MD, PhD, Rafi Ahmed, PhD, and colleagues at the Emory transplant and vaccine centers found that the drug could also boost T cell immunity from immunizations. With proper timing and dosing, Ahmed discovered that this therapeutic given with vaccinations results in an increase in high-quality memory T cells that respond to future pathogen challenges more efficiently than untreated controls. There are also potential applications for chronic infections and benign and malignant tumors.

Osanetant was first tested to treat schizophrenia but did not show a clear advantage over traditional treatments and was abandoned. Yerkes National Primate Research Center scientists Kerry Ressler, MD, PhD, Raül Andero Galí, and Brian Dias, however, discovered that osanetant made memories of frightening events less durable in mice, due to blocking the "Tac2 gene" pathway involved in fear learning and the consolidation of fear memories. The drug may prove to be therapeutic for people with anxiety or fear disorders, such as post-traumatic stress disorder (PTSD).

A combination of rapamycin and the drug imatinib (Gleevec), used in the treatment of chronic myeloid leukemia, was found by researcher Jack Arbiser, MD, PhD, in dermatology, to be highly effective in decreasing tumors in mouse models of tuberous sclerosis (TS), a genetic disorder that causes non-malignant tumors to form in many different organs, primarily the brain, eyes, heart, kidney, skin, and lungs. The combination was found to be far better in preventing tumor growth than either drug alone.

TAK-242 a Japanese drug that was originally developed to treat sepsis, went through safety trials but didn't show efficacy. But researchers Fang

Hua, MD, PhD (who has since left Emory), Donald Stein, PhD, and Iqbal Sayeed, PhD, from emergency medicine, found that TAK-242 could be used as a non-surgical treatment of ischemic stroke, by blocking inflammatory signaling. Because inflammatory response in brain tissue after the stroke can significantly contribute to brain injury, inhibitors or blockades of this response could lessen the long-term adverse effects.

Metformin which is used to treat type 2 diabetes, may be effective in treating nephrogenic diabetes insipidus, found researcher Jeff Sands, MD, in nephrology. People with this rare condition can not regulate the water in their body vs. the urine they excrete. Sands, chair of nephrology, says these individuals can produce gallons of urine a day, which makes life difficult during the day but is even harder to manage at night. Children with this genetic condition can make almost a liter of urine an hour, and their parents have to make sure they also drink at least that much to rehydrate. This same condition can be a side effect of chronic lithium use, so is seen in adults being treated for bipolar disorder. So far, the drug has proven effective in improving the condition in mice. Larry Greenbaum, MD, PhD, of pediatric neurology, is doing a pilot study to see if what has been observed in animals can be duplicated in humans. "Even if we just reduce the urine output to two to five liters a day, we've significantly improved someon"s quality of life," Sands says.

"Emory has a diverse portfolio of technologies across the bio/medical spectrum, including repurposed therapeutics," says OTT Executive Director Todd Sherer. "We understand that our partners have different needs and we work with them to find the best fit."

Provided by Emory University