# 'The process by which drugs are discovered and developed will be fundamentally different in the future'

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(Medical Xpress)—Before joining Washington University in St. Louis, Michael Kinch, PhD, was managing director of the Center for Molecular Discovery at Yale University. "A few years ago, to motivate the team I gave them what's called a Big Hairy Audacious Goal (a B-HAG)," Kinch says. The B-HAG was many-headed but one of the heads was to make a collection of all FDA-approved drugs. The idea was that the collection would serve as a screening library for drug repurposing.

Kinch thought the first step—pulling a list of drugs—would be easy;

they'd go the FDA and get their list. But it turned out the FDA doesn't have a complete list. They had a running list of all prescribable drugs called the Orange Book. But "all prescribable drugs" isn't quite the same thing as all the drugs that have ever been prescribed, since there are drugs that are no longer marketed or have been withdrawn because of concerns about safety or effectiveness.

"So what we did was compile a comprehensive list of drugs approved for use in the U.S.," Kinch said. "By drugs, I mean the actual molecules that do the work, called new molecular entities (NMEs), as opposed to the fillers and the flavors. We went all the way back to morphine, first sold by Merck in Germany in 1827 and shortly thereafter in the U.S., and worked our way forward to 2013, closing the database at the end of that year.

"How many do you think there were?" he asks.

There were 1,453—only 1,453 drugs for all of the infectious diseases, cancers, cardiovascular diseases, skin conditions, neurodegenerative diseases and other ills the flesh is heir to. "I thought it was rather a small number, myself," Kinch said.

"I'm a bit of a workaholic and a dataholic," Kinch continued, "and this list of 1,400 molecules was irresistible to me because it raised so many questions. I started to ask, 'Who got the approval for the drug, and what was the fate of the company that got the approval for the drug'? 'Who did the clinical trials on the drug, who filed the first patent on the drug, who did the first publication on the drug, who discovered it in the first place'?"

Over weekends and in the evenings the list turned into a database and the database grew and grew. "I would sit on the couch at home after everything calmed down for the night and look at the data. The kids

would say, 'Oh, look, Daddy's doing drugs again.' It was the family joke."

"Finally I had this ridiculously large database of information," he said. "And I began to wonder how to mine it for publication." He sold the editor of Drug Discovery Today on a long series of peer-reviewed articles before he had even identified the topics of the articles. "It was the stupidest thing I've ever done," he said, but also accidentally brilliant, because it forced him to dig the ore out of his goldmine.

"To begin a paper, I pick a topic or a question and look at a spreadsheet to see if there is a story there," Kinch said. "And you know what, every darn time there has been a story."

The Drug Discovery Today series has already led to his participation in both New York Times articles about the pharmaceutical industry by Economic Scene columnist Eduardo Porter and in a two-part BBC Radio special about antibiotics.

Together Kinch's stories add up to one shocking revelation: the R&D infrastructure for drug development is shrinking, perhaps irreversibly, and our ability to discover and develop new medicines is being progressively dismantled.

What is to be done? Kinch has come to Washington University in St. Louis to help find an answer. He regards the clear-eyed recognition of the problem as a first, giant step toward solving it. But he also feels we have no choice but to do the hard work of defining new models for drug discovery and that the role universities play must change, and not necessarily in comfortable ways.

## Big Pharma has left the building

Over the past several decades, Kinch said, the pharmaceutical industry has managed to dismantle itself. "It's done a really efficient job of it," he said.

Starting in the mid-1970s, the industry started outsourcing the discovery of new drug targets and then the early stages of drug development. "When you compare the number of drugs that were approved to their R&D costs," Kinch said, "you see that the cost per drug was going through the roof. So they were happy to outsource research."

"As pharma pulled out, biotech pulled in," he said. That continued through the '70s and '80s, but then pharmaceutical companies began to buy out biotechnology companies. The number of biotech companies peaked in 2000, and today they are often acquired before their first product is approved.

"I used to work for a big biotech company called MedImmune that everyone thought would remain independent indefinitely. It was bought by AstraZeneca in 2007," Kinch said.

He sees two worrying trends. One is that the number of biotech companies has followed a Bell curve. "What's scary to me," he said, "is how symmetrical that curve is. There really aren't that many independent biotechs left, and there aren't that many entering the field. Where is the drug discovery and early development going to come from?" (See "The rise (and decline?) of biotechnology.")

The second worry is the rise of drug companies with limited R&D capabilities. One example is Valeant Pharmaceuticals, a Canadian company that now controls as many drugs as the more familiar Eli Lilly but has a research budget that is one percent of Eli Lilly's. The only research Valeant does is post-approval trials for the FDA or market research, Kinch said. They don't do new drug research.

"A growing number of drugs," Kinch said, "are now controlled by marketing organizations that have little or no internal drug discovery or development activities." (See "An overview of FDA-approved new molecular entities: 1827-2013.")

"We all see it coming," Kinch said. "And no one has an answer for it. The pharmaceutical industry has made rational business decisions. It is unrealistic to expect them to repopulate their labs; they're out of it and they're not going back."

Because of the shrinkage in the pharmaceutical industry, Kinch estimates that we have lost more than 75 percent of the "expertise" that supported drug discovery. By expertise he means scientists with the experience to modify chemical compounds to improve their efficacy and decrease their toxicity, the hard part of drug development.

While Kinch was at Yale he hired three computational chemists who had been laid off from Pfizer's Groton CT labs. One was teaching high school chemistry, one was a 50-something postdoctoral associate, and one was working part-time. "These are not just good people; they are world leaders in their field with decades of experience," Kinch said.

This is the hidden sting in the scorpion's tail because, once gone, there is no quick way to replace these highly skilled people. "They learn their craft through a mentoring relationship and over many years in the lab," Kinch said. "Some of what they know is written down, but most of it is passed on in the lab.

"These guys are getting ready to retire or they've retired, or given up.

"Who's going to train the next generation?" he asked. "I started my professional life as a professor and I can tell you academia doesn't do it. Is academia going to take over this role or are we going to find another

way to do it?

"I don't know how this story's going to end," he said, "but right now it's not looking like it ends well."

## Starting from scratch

"We need to recognize that this is a going to be a completely new game and that means we basically throw out all past assumptions and start from scratch," Kinch said.

Although he is still in the listening phase of his new assignment, he points out the drug landscape is very uneven these days. Pharmaceutical companies still make money in cancer drugs and drugs for "orphan" (rare) diseases such as cystic fibrosis. "Antibiotics and drugs targeting psychiatric, neurological and pain or itch are at the bottom," he said. "Few in the industry want to touch either of those two areas." (See "Trends in pharmaceutical targeting of clinical indications: 1930-2013.")

Washington University has deep expertise in the microbiome relevant to infectious diseases and in neurological diseases such as Alzheimer's, he said, so there's an opportunity there. But the model for research has to be different than it has been in the past.

University scientists are used to publication being the end-point of a project. We have to take drug candidates further than the peer-reviewed journals and find ways to ferry them across the "Valley of Death" between the university lab and the company lab, Kinch said.

"Keep in mind," he added, "that the majority of the $1.2 to $1.5 billion it takes to develop a new drug is spent on late-stage clinical trials. We shouldn't be making that kind of bet. But on the front end, you're talking millions, not billions, maybe $10 million to discover a class of drugs and

identify a lead candidate."

The market cannot be the only mechanism by which we meet the need for new drugs, Kinch said, because the common good and the stockholders' good are too often disastrously misaligned. Answers will have to come out of the interaction and coordination of the government, universities, venture capital firms and foundations, as well as the private sector.

This all sounds a bit scary, Kinch said. But remember that the research university itself dates back only to the beginning of the 19th century, and the double-blinded, placebo controlled trial only until the 1950s and 1960s. Research models are not static but rather have continually changed as new challenges have arisen.

The collapse of the pharmaceutical industry's research infrastructure is our challenge, Kinch said, and we will define the future of medicine by the way we address it.

**More information:** "An overview of FDA-approved new molecular entities: 1827-2013." Kinch MS, Haynesworth A, Kinch SL, Hoyer D. *Drug Discov Today*. 2014 Aug;19(8):1033-9. DOI: 10.1016/j.drudis.2014.03.018. Epub 2014 Mar 26.

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