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Innovations

Xanthus Life Sciences

Fine-Tuning Personalized Medicine

In 2001, Xanthus Life Sciences won a beauty contest of sorts. It was selected to receive $10.6 million Series A venture financing lead by Health Care Ventures and others to fully optimize its mission of creating truly personalized anticancer medicines.

Xanthus began its life as a venture out of McGill University in Montreal under the guidance of Brian Leyland-Jones, MD. When the venture community selected Xanthus to receive funding, they also selected another complementary company, Phenome Sciences, based in Massachusetts. The two were merged into the present-day 40-person Xanthus Life Sciences, headquartered in Cambridge, Massachusetts, with Leyland-Jones as CEO. Phenome founder Alfred Ajami, PhD, is now Chief Scientific Officer.

"The original Xanthus had the clinical side and Phenome had the scientific platform," says Chief Operating Officer Michael A. Boss, PhD. Leyland-Jones had been a researcher at the National Cancer Institute (NCI), Memorial-Sloan Kettering Cancer Center, and ultimately the founding chairman of oncology at McGill. "That is where he had the vision that we have to do better than one size fits all in cancer treatment," says Boss, "and Alfred had developed a broad set of scientific solutions and technology looking for a problem.

Small Molecules for Cancer

The mission at Xanthus is to develop drugs that utilize its personalized medicine technology platform, beginning in the oncology arena with drugs that have previously stalled in development elsewhere. "By optimizing the dose for each person," says Boss, "everyone receives the correct individualized dose that will achieve maximum therapeutic benefit and minimize risk of serious adverse drug events." Behind this plan is the phenotypic reality that individuals metabolize drugs at different rates and that drugs trigger unique metabolic events. From Xanthus' perspective, these metabolic profiles explain differences in therapeutic efficacy and unpredictable risks for side effects in individual patients.

"We focused on cancer in particular because it is important to bring in some new technology to make sure everyone is getting the biggest 'hit' they can take or that they are switched to other medications depending on what they are likely to respond to," says Ajami. Historically, antineoplastics have a 20% to near 100% response failure rate, and Xanthus believes it has found a way to boost the efficacy and safety of cancer drugs by determining beforehand what the appropriate dose may be for any given patient.

"When you look at the entire pie of what affects a drug's response, genotype provides only a minority of the variability in and amongst us. Also involved are physiology, metabolic, biology, and epigenomic factors such as diet, polypharmacy, and enzyme induction." –Alfred Ajami, PhD, Chief Scientific Officer, Xanthus

Test/Drug Combination

Leyland-Jones was a coprincipal investigator on the study that identified the Her2-targeting drug trastuzumab (manufactured by Genentech as Herceptin), a drug for breast cancer with efficacy in roughly 20% of all women who have the disease. Patients must be tested for the presence of HER-2/neu protein to determine if they are eligible for trastuzumab treatment. "The paradigm of a test/drug combination has now been proven and accepted with Herceptin," says Boss. But Boss adds that Xanthus' purpose differs in that their technology does not select for who should or should not be given a drug. "The idea is to be able to give it to everybody," he says. "This is very different from the traditional pharmacogenomics approach that selects which subgroup of patients should receive the drug. Instead, we are trying to figure out how to give everybody the dose that is right for them."

Ajami explains that using a specific sensor, or probe, to test biological parameters is a way to figure out your phenotype without having to do a lot of genetics or other exams. Xanthus is developing straightforward tests to determine how an individual might metabolize a known drug and also assess what the potential side effects of a molecule may be. "We have to determine who will be most susceptible to the side effects or more susceptible to the primary efficacy," says Ajami.

Ajami has spent much of his career looking at metabolic pathways searching for control points to probe with a pro-drug or a probe substance to allow him to tune in to some key transformation that would be an appraisal of the entire system. "We are now able functionally to figure out if someone is a high, low, or medium responder," says Ajami. "The implications of that is the individualized dose to be taken for maximum benefit and safety."

It does not hurt that FDA Commissioner Mark McClellan made a statement in January 2003 effectively confirming Xanthus' business model. "Certain new therapies will be developed along with tests that can identify the responding subpopulation, detect individuals who need a different dose, or find people who are prone to a certain toxic effect," said McClellan. In addition, he went on to confirm that "development of these test/therapy combinations must be facilitated because they have the

potential to maximize drug benefits while minimizing toxicity."

Functional Phenotyping

"When you look at the entire pie of what affects a drug's response, genotype provides only a minority of the variability in and amongst us," says Ajami. "Also involved are physiology, metabolic, biology, and epigenomic factors such as diet, polypharmacy, and enzyme induction." So the company is creating a biochemical equivalent of a treadmill stress test as a probing strategy to see what happens phenotypically when an individual is presented with a surrogate stand-in for the drug in question. "The beauty of the Xanthus strategy is that you do not need to understand what is going on in each of these complicated areas because what we are focusing on is an apparently simple integrated output," explains Boss.

The sensor technology delivers a simple measurement of function. "Once you know where it is you want to probe, you can find the appropriate probe through molecular informatics," explains Ajami. In the clinic, a patient would be given a metabolic sensor probe, and urine, plasma, or breath would be collected thirty minutes to several hours after ingesting the probe. The metabolized compounds are measured and analyzed to provide a metabolic profile similar to a barcode. "Individuals have different barcodes, and so clinically you would then make some judgements as to the dose of the therapeutic drug to give to end up in the same place in regard to the desired pharmacokinetic model," says Ajami.

"We have developed the probe science and are now applying it with lateral flow technology by building antibodies to each of the small molecules we are analyzing," says Ajami. Xanthus uses immunorecognition techniques to ultimately develop point-of-use devices (a reader plus a data processor) akin to devices already available for therapeutic drug monitoring using a drop of urine or blood as the analyte.

I'll Take Mine Black

Xanthus' lead drug is the well-known anticancer medicine amonafide (XLS-001) developed in the late 1980s at the NCI. But before amonafide could gain any traction at Xanthus, a metabolic probe test had to be developed to determine appropriate dosing. In this case, the probe is caffeine. "Caffeine is metabolized in a similar way to amonafide," says Ajami; both are metabolized by N-acetyl-transferase 2 (NAT2). "If you are a fast caffeine metabolizer, you are going to be a fast metabolizer of the cancer drug," according to Ajami, which will lead to side effects if the dosing is not adjusted beforehand. "You take the probe before you start therapy to figure out where you fit into a population distribution and therefore determine what is the right dose." A potential amonafide patient is given 100 mg caffeine. Urine specimens are collected and analyzed to assess the level of metabolites to determine the correct amonafide dosing. "This is the general approach we are validating in our clinical trials for all our drugs," says Ajami.

Lead Drug Candidates

Amonafide is being scrutinized in a 127-person phase IIB clinical trial for metastatic breast cancer. In patients, the drug is processed by NAT2 to an acetylated form (N-acetyl-amonafide), and both forms have anticancer properties; however, the acetylated form also has myelosuppressive side effects. "Individuals differ in their rate of NAT2 metabolism by some 200-fold," says Boss, and therefore people with high NAT2 activity may make higher amounts of the acetylated form with its unwanted myelosuppressive property.

A clinical study of the response of 73 patients to amonafide found that 18% of these individuals responded positively to the drug. Xanthus examined the NAT levels in these patients. "If you look at the group whose NAT2 levels were in the middle of the range, these women had myelosuppression but it was not too severe," says Boss. "And they also had a [positive] response rate of approximately 35% [to the drug]." The aim with amonafide at Xanthus is to find the correct individual dose—from 100–400 mg/M^2—to bring everyone into this middle range. "Rapid metabolizers start out on the lower dose, and slow metabolizers will start out on a higher dose which is about 33%–50% higher than the dose you would have received previously, when you would have been underdosed," explains Ajami.

Xanthus also plans to develop amonafide for prostate cancer treatment. Behind amonafide is C-1311, primarily for colorectal cancer, and DMPEN for brain tumors. Clinical studies have not begun with these programs.

Wide—yet Narrow—Applicability

"This approach is extendable to a large number of drugs in a variety of therapeutic areas, but not any drug, though," says Ajami. "It has to be a drug with a narrow therapeutic index where dosing is critical to avoid dangerous side effects without underdosing patients who can tolerate a larger dose." And it is no small feat to develop the probing technology for each drug, a key requirement of the Xanthus strategy. "Each probe/drug is a specific combination, and we would need to demonstrate the effectiveness of each particular combination," says Boss.

Aside from the three anticancer drugs currently in play, Xanthus is interested in collaborating with companies with drugs that may benefit from the boost this sensor/drug model may be able to provide. "Our view of development is to rejuvenate molecules that are already there from the treasure trove of the past," explains Ajami.

Chemistry & Biology **invites your comments on this topic. Please write to the editors at chembiol@cell.com.**

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