BIOCENTURY
Innovations
FROM IDEA TO IND

REPRINT FROM AUGUST 2, 2018

TOOLS & TECHNIQUES

MODEL FIRSTS

By Karen Tkach Tuzman, Associate Editor

By combining disparate data into coherent mechanistic models, quantitative systems pharmacology is becoming a key tool for picking the right dose for first-in-human trials and other early make-or-break decisions. Advocates see it as part of an expanding toolbox of models that can yield better safety and efficacy predictions from preclinical data, and want regulators to include it in their guidances.

Moreover, they argue the disastrous outcome of the 2016 Phase I BIA 10-2474 trial could have been avoided if published QSP studies on parallel compounds had been taken into account.

QSP can enable companies to turn data into actionable decisions by translating biological mechanisms and lab measurements into mathematical equations and computational simulations. The models go beyond standard allometric scaling from finite animal data, to incorporate mechanistic information about what cellular compartments a molecule acts in, and how fast it is both produced and degraded, for example.

"The decisions in drug companies we have to make at a high level are — 'should we keep this program going forward' and 'what are the risks that we're going to encounter with it?'" said Vikram Sinha, Associate VP of Quantitative Sciences at the Merck Research Laboratories unit of Merck & Co. Inc. "That's where these models are becoming more and more influential, because this is the only way that we can integrate all this information."

Certara L.P. believes QSP can provide critical guidance for making decisions on first-in-human dosing, where mistakes can be costly. The company develops software for model-informed drug development and other forms of pharmacology and PK/PD modeling.

In 2014, Certara researchers published a QSP model suggesting the therapeutic efficacy of FAAH inhibitors would reach a maximum at doses of 3 mg. That's well below the daily 50 mg dose of Bial-Portela & Ca. S.A.'s FAAH inhibitor BIA 10-2474 that induced neurological toxicity in healthy volunteers in the 2016 Phase I trial, leaving one brain dead and hospitalizing five others. Bial-Portela did not respond to requests for an interview.

"Our QSP model predicted that at relatively low dose levels you will saturate the FAAH enzyme with your compounds, but that doesn't necessarily lead to any increased desired pharmacology," said Piet van der Graaf, Certara's VP of QSP.

In a June letter to the editor of *Clinical Pharmacology & Therapeutics*, Certara argued EMA's 2017 first-in-human guidelines, published in response to the BIA 10-2474 incident, failed to address the potential of QSP models to make dose selection safer. EMA responded that it "encouraged" and "supported" the use of mechanistic models, while noting it would question models with insufficient validation, particularly those recommending higher doses than standard preclinical approaches. The agency said it would consider including guidelines on QSP in future documents.

Sinha said that while FDA and EMA guidelines have made choosing a starting dose fairly straightforward, QSP models still have a lot to offer as they can address the more complicated question of how far to escalate dosing to capture desired pharmacology. "QSP actually becomes important in trying to say, how are we going to dose escalate, and how best should we be designing this to actually understand the dose-response relationship?"

Applied BioMath LLC CSO Joshua Apgar told BioCentury QSP counters the conventional thinking that "if it's tolerated, higher must be better."

"QSP models provide a valuable tool to say, what's the highest dose that has a rational basis for being maximally efficacious?"

Apgar said Applied BioMath's QSP partnerships with drug developers "almost always" include first-in-human dose projection. "I think that's because this is one of those critical pieces where a model can really build a picture in a way that no individual data set can," he said.

MAKING EQUATIONS

According to van der Graaf, the QSP field launched in 2011 with the publication of a white paper summarizing a series of NIH workshops on the topic. The workshops brought together academic systems biologists, who built detailed models of biological mechanisms from the "bottom-up," and pharma PK/PD modelers, who built "top-down" minimal models based on preclinical and clinical observations.

QSP models "sit somewhere in between these two," said van der Graaf.

"They are definitely biologically plausible, and contain much more detail than a typical pharmacostatistical model, but

METAMORWORKS/ISTOCK/GETTY IMAGES

they don't necessarily need to include the level of detail that a typical systems biology model would need," he said. "For example, we're only interested in a timescale of days and weeks, not seconds."

The approach builds on physiologically-based pharmacokinetic (PBPK) modeling, which represents biochemical interactions — such as the binding of a receptor to a ligand — as a set of mass balance equations. The equations are fed a set of starting parameters, and the simulation is run over a defined duration of time.

But while PBPK models depict ADME processes, QSP models add in biological pathways that are relevant for disease modification, according to van der Graaf.

Applied BioMath President and CEO John Burke said the "canned" PK/PD models used for the last 30 years, which employ allometric scaling to select doses by extrapolating a compound's effects from animals to humans, have been fairly good for small molecule drug development, but are running into limitations more frequently with newer modalities.

"It's much better for small molecules than for biologics, or cell therapies, or RNAi, or gene therapy, because of the timescale," Burke said. "The more complex the biology, the more complex the drug and the longer timescale between dosing," the greater the need is to lean on mechanistic modeling approaches.

Apgar said QSP models have also gained importance as drug development increasingly focuses on how specific targets behave in their native context of human cells and physiology, which can be misrepresented by rodent, monkey and human cell culture experiments in isolation.

"If a drug has really broad pharmacology that's not that species-specific or target-specific, then in a counter-intuitive way, it can be easier to do non-clinical safety evaluations because you get the whole pharmacology in these animals," he said.

For targeted therapies that may act differently in different model systems, the power of QSP is that "we can get a little bit of information from each of these different contexts, and then the model stitches it together into a single picture," said Apgar.

For example, a QSP model could combine protein expression measurements from experiments in patient-derived cells with tissue-specific enzymatic Km values from literature experiments in rats.

Merck's Sinha agreed, adding that the models can incorporate clinical data as well. "The strength of the QSP model is the ability to leverage all the data we have across clinical trials, and other preclinical studies that have been published," in addition to data from an in-house preclinical program, he said.

QSP practitioners iteratively hone a model's predictive power by updating its equations and parameters with new data, then comparing the simulations to known results. "We try to get to a point where we feel it is a clear and accurate representation of the mechanism," Sinha said.

The model building process often helps companies prioritize experiments. "We say, what experiment can you do preclinically that can help bring us more understanding mechanistically to the human dose predictions," said Burke.

That doesn't necessarily mean collecting more data than usual, said Sinha. "You're designing your experiments differently to give us more precise estimates of certain parameters," which

could include adding more doses, or capturing measurements on a relevant time scale.

QUANTS AGAINST CATASTROPHE

In the 2014 paper, van der Graaf and colleagues modeled the pharmacology of Pfizer Inc.'s FAAH inhibitor PF-04457845, and identified gaps in the field's understanding of the pathway that could explain the compound's failure in Phase II testing for osteoarthritic pain (see "Figure: Picturing Pathways").

Pfizer stopped development of PF-04457845 for pain in 2010, but launched a Phase II study in 2015 to test the compound in post-traumatic stress disorder (PTSD). The compound was acquired by Pfizer spinout SpringWorks Therapeutics LLC last year.

In hindsight, the model's conclusions also could have provided warning that Bial-Portela's 50 mg daily dosing of BIA 10-2474 was well beyond what was needed to saturate the target pharmacology.

On a physiological level, Certara's model quantified FAAH-mediated degradation of AEA — a fatty acid neurotransmitter agonist of the cannabinoid receptor CB1 — and three other related fatty acid ligands, the synthesis rates of all four ligands, and their transit between different tissue compartments. The model also included parameters describing PF-04457845's distribution throughout the body, and its inhibition of FAAH.

PICTURING PATHWAYS

In 2014, researchers from **Certara L.P.** and **Pfizer Inc.** developed a quantitative systems pharmacology (QSP) model of how Pfizer's **FAAH** inhibitor **PF-04457845** acts in the body. The compound was designed to prevent FAAH-mediated degradation of the endocannabinoid **AEA**; higher AEA levels would increase AEA binding to the cannabinoid receptor **CB1**, which activates cellular signals that suppress pain. In 2010, the compound failed in Phase II testing for osteoarthritic pain.

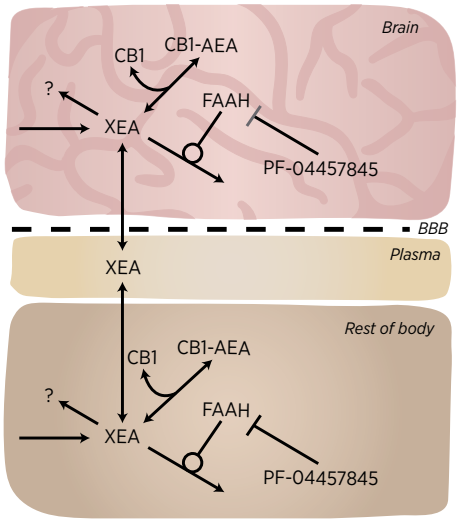
The QSP model used mass action equations to describe biochemical interactions between the compound and the FAAH pathway at the tissue and cellular levels, and incorporated parameters based on clinical trial data and preclinical experiments.

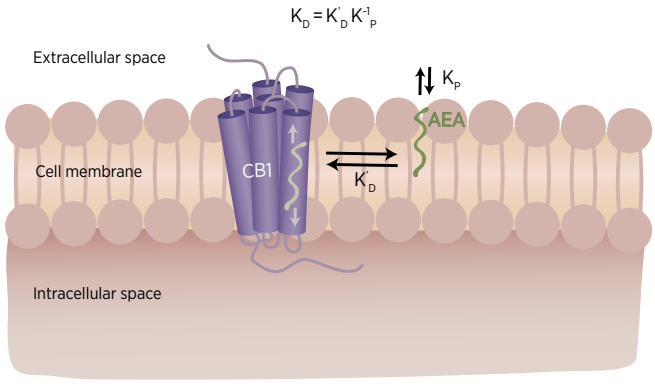
Left. At the tissue level, the model described PF-04457845 inhibition of FAAH in the brain and the rest of the body. It also described the brain, body and plasma distribution of AEA and three other related fatty amides, referred to in aggregate as **XEA**.

The model included four mechanisms that decreased XEA levels (**arrows away from XEA**) — transit out of tissues, AEA binding to CB1 to form the **CB1-AEA** complex, FAAH-mediated XEA degradation (**loop shape**) and an FAAH-independent mechanism of XEA clearance (**question mark**) — and three mechanisms that increased XEA levels (**arrows toward XEA**) — transit into tissues, dissociation of the CB1-AEA complex, and biosynthesis.

Right. At the cellular level, the model captured AEA partitioning of the cell membrane, its lateral diffusion within the membrane, and its binding interaction with CB1. The overall dissociation constant of the CB1-AEA interaction, $\mathbf{K}_D$, was approximated as the product of the dissociation constant for CB1 and AEA binding, $\mathbf{K'}_{D'}$ and the inverse of AEA's membrane partition coefficient, $\mathbf{K}^{-1}_{P}$. *Source: CPT: Pharmacometrics Systems Pharmacology (2014) 3, e91; doi:10.1038/psp.2013.72*

CB1 (CNR1) - Cannabinoid receptor 1; FAAH - Fatty acid amide hydrolase





On a cellular level, the model captured AEA entry into cell membranes, where it binds the receptor CB1 and induces cellular responses that suppress pain. PF-04457845 was intended to relieve pain by inhibiting FAAH-mediated degradation of AEA, thereby increasing AEA's occupancy of CB1.

Through the QSP model, the authors deduced that there must be FAAH-independent mechanisms of AEA degradation, and hypothesized this redundancy could explain PF-04457845's limited therapeutic effects.

> "QSP actually becomes important in trying to say, how are we going to dose escalate, and how best should we be designing this to actually understand the dose-response relationship?"
>
> Joshua Apgar, Applied BioMath

The model also predicted single doses of PF-04457845 would saturate at about 25% CB1 receptor occupancy; increasing the dose from 3 mg to 40 mg did not increase receptor occupancy, although it did extend the time spent at peak receptor occupancy from one to several days (see "Figure: Topping Off").

"If you've saturated your pharmacology, there's no real scientific rationale to keep escalating the dose higher," said van der Graaf. "What we think happened in the Bial trial was that they kept escalating the dose to a point where they started to engage other targets."

A proteomics study published in *Science* last year confirmed that BIA 10-2474 inhibits several other lipases in addition to FAAH.

In addition, a 2016 Temporary Specialist Scientific Committee (TSSC) report concluded BIA 10-2474 "achieved FAAH inhibition" in humans at a dose of 1.25 mg, with FAAH inhibition "almost complete" at a dose of 5 mg.

The BIA 10-2474 ordeal prompted EMA to update its 2007 first-in-human dosing guidelines, which were published in response to a 2006 incident in which six healthy volunteers were hospitalized after receiving TeGenero Immuno Therapeutics AG's CD28 agonist TGN1412 (see "TGN1412: The Next Generation").

In the BIA 10-2474 and TGN1412 incidents, sponsors set their maximum doses at 1/400 and 1/500 of the no observable adverse effect level (NOAEL) in animals, respectively. But retrospective studies showed both compounds had very different pharmacology in animal models than in humans, invalidating the extrapolation approach.

EMA's 2007 guidelines recommended basing doses for first-in-human trials off of the minimal anticipated biological effect level (MABEL), instead of the NOAEL, for compounds considered risky according to established criteria. MABEL calculations incorporate target binding, receptor occupancy and dose-response studies in human cells and relevant *in vivo* animal models.

The retrospective TSSC report determined that because BIA 10-2474 did not have a risk profile that would have flagged it for MABEL studies, its use of NOAEL was justified under the 2007 guidelines.

The updated 2017 guidelines now specify that NOAEL calculations can serve as a starting point for determining safety, but sponsors should also use preclinical data, particularly data from human cells and tissues, to calculate the MABEL and estimate the pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans.

According to the document, sponsors should also consider possible differences in sensitivity between model animals and humans, and "whenever possible," integrate relevant data into models to help determine MABEL, PAD and ATD.

"I think the EMA guidelines are pretty clear that they now expect a scientific underpinning of the dose range," said van der Graaf.

SIM CITY

Merck's Sinha said there are still skeptics who won't believe any model predictions until they see human data, but there is "a very large majority in the industry who are utilizing such systems more and more."

He said Merck incorporates people with QSP experience into each of its therapeutic areas. "QSP is now part of the thinking, versus just someone working in isolation developing the model."

Burke said Applied BioMath only works on projects where it believes QSP will be helpful, and is "very careful not to overpromise."

"In a field as regulated as ours, with a greater than 90% fail rate, if we come in and don't deliver, it will be too easy to blame math, and not the target itself or other problems," he said.

Apgar said the goal is to supplement, not replace, traditional methods for first-in-human dose projection.

"The traditional methods have the advantage that they don't rely on our mechanistic understanding, which may be incomplete; they're very empirical, so in some ways they can be more robust," said Apgar. "We'll provide those estimates next to the QSP estimates, and try to put all of that information in context."

Revitope Oncology Inc. CSO Werner Meier said QSP models can help companies spell out the rationale behind their proposed dose range. "It will help regulators understand your thinking, and why you're thinking it."

Last month, Revitope and Applied BioMath announced a collaboration to optimize the PK/PD of Revitope's bispecific T Cell Engaging Antibody Circuits (TEAC) using mechanistic modeling. The collaboration's second stage will involve using QSP to home in on a first-in-human dose range.

Certara aims to foster trust in QSP approaches by developing disease-specific models via precompetitive consortia; the company has spearheaded one on PBPK, and another on immuno-oncology (see "Model Combination").

By working with multiple companies, and potentially regulators in the future, Certara hopes to "build consensus models that people know, trust and understand," van der Graaf said.

Applied BioMath's Apgar thinks the advancement of high-performance computing and the routinization of precision measurement technologies like Biacore assays have "opened up a lot of spaces" for QSP, and that the major bottleneck now is understanding the biology.

Certara is expanding its QSP toolbox through a partnership with an undisclosed organ-on-a-chip developer, and a collaboration between its QSP modelers and internal experts in clinical trial meta-analysis to develop models that connect biological mechanisms to clinical endpoints.

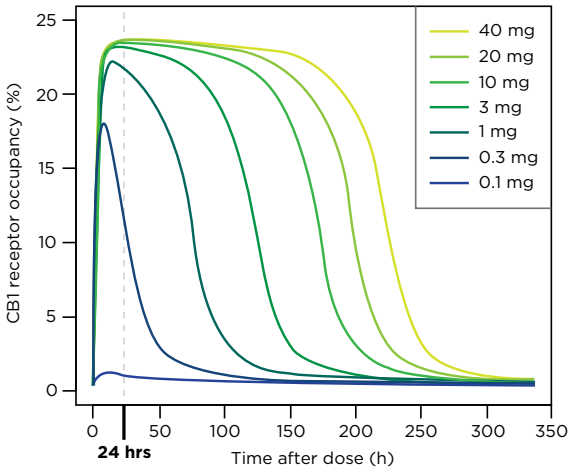
TOPPING OFF

Researchers from **Certara L.P.** and **Pfizer Inc.** used QSP modeling of FAAH inhibitor PF-04457845 to predict how single doses of the compound would affect CB1 receptor occupancy by its endogenous ligand, the endocannabinoid AEA. AEA is normally degraded by FAAH. AEA binding to CB1 activates cellular signaling pathways that suppress pain.The model used mass action equations and experimentally-derived parameters to describe the effects of single doses of PF-04457845 on FAAH, AEA and CB1 (see "Figure: Picturing Pathways").

According to the model, PF-04457845 reaches its maximum effect at less than 25% CB1 receptor occupancy. That maximum was achieved with a 3 mg dose of PF-04457845 within about 24 hours. Raising the dose to 40 mg did not increase receptor occupancy, though it extended the time spent close to peak receptor occupancy on the order of days. According to Certara, there is no rationale to escalate the dose of an FAAH inhibitor to treat pain after CB1 receptor occupancy achieves the maximal effect.

In a 2016 Phase I trial, Bial-Portela & Ca. S.A. treated patients daily with 50 mg doses of its FAAH inhibitor BIA 10-2474. One patient was left brain dead, and another five were hospitalized with neurological toxicity. A subsequent report by a Temporary Specialist Scientific Committee (TSSC) said BIA 10-2474 achieved FAAH inhibition at a dose of 1.25 mg, and nearly saturated FAAH inhibition at a dose of 5 mg. *Source: CPT: Pharmacometrics Systems Pharmacology (2014) 3, e91; doi:10.1038/psp.2013.72*

CB1 (CNR1) - Cannabinoid receptor 1; FAAH - Fatty acid amide hydrolase



He thinks "artificial intelligence will no doubt start to play a role" in QSP, but that its first applications will be to help interpret the results of model simulations. "Automatic model building would be fantastic, but I think we're still quite a way off from that future."

COMPANIES AND INSTITUTIONS MENTIONED

Applied BioMath LLC, Lincoln, Mass.
Bial-Portela & Ca. S.A., Mamede do Coronado, Portugal
Certara L.P., Princeton, N.J.
European Medicines Agency (EMA), London, U.K.
Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
National Institutes of Health (NIH), Bethesda, Md.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Revitope Oncology Inc., San Francisco, Calif.
SpringWorks Therapeutics LLC, New York, N.Y.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

TARGETS

CB1 (CNR1) - Cannabinoid receptor 1
FAAH - Fatty acid amide hydrolase

BIOCENTURY INC.

NEWSROOM
pressreleases@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM
+44 (0)1865-512184; Fax: +1 650-595-5589

