Increasing R&D Productivity to Deliver Transformational Medicines

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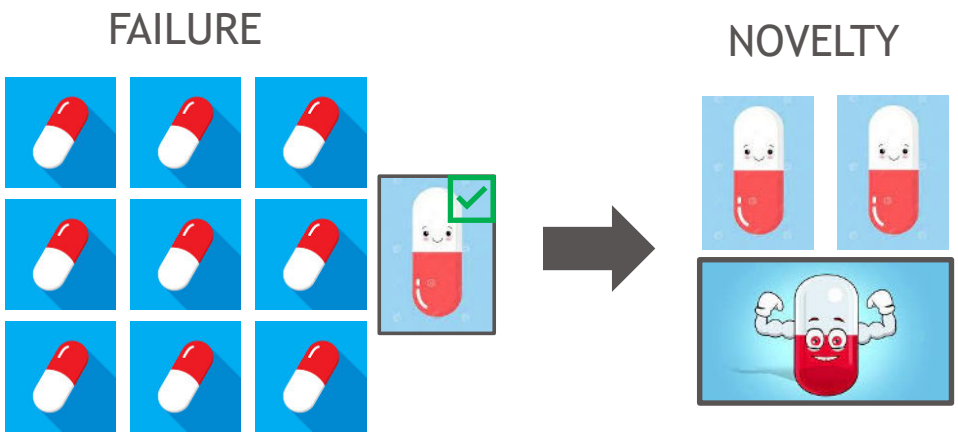
1787-US-2300697 | 09/23

Hi, I am Robert Plenge, Chief Research Officer at Bristol Myers Squibb (BMS). For my presentation today, I am going to talk to you about a favorite topic of mine – how we select targets and conduct research programs at BMS. The first half of the presentation frames the problem in a unique way. I then give an example of a program here at BMS that brings the problem and solutions to life.

But first, I am going to start with an ominous warning:

Our pharmaceutical industry has a productivity crisis.

Pharmaceutical R&D Productivity Crisis



Did you know that for every 10 new medicines that enter clinical development, only 1 will emerge as an approved therapy. Making matters worse, for every approved medicine, only 1 in 3 are truly novel and differentiate from standard of care medicines.

How can our industry not only reduce FAILURE RATES (pause) in clinical trials (pause) but also increase NOVELTY (pause) of the medicines that are approved?

I BELIEVE THERE IS A SOLUTION TO THE **FAILURE-NOVELTY PROBLEM**. AND IT CUTS RIGHT TO THE HEART OF HOW RESEARCH AND DEVELOPMENT IS DONE TODAY.

To solve the FAILURE problem, some in industry argue for a "**Ready-AIM-Fire**" approach. For those in this camp, YOU BELIEVE that clinical trial failure comes from poor planning and execution. YOUR SOLUTION is **simply better FOCUS**: **Ready**: pick the best possible target, even if using conventional methods; **Aim**: make a drug against that target; and **Fire**, conduct an operationally efficient clinical trial.

However, to solve the NOVELTY problem, others flip this paradigm and argue for a "**Ready-FIRE-Aim**" approach. For those in this camp, YOU BELIEVE that human biology is too complex and messy to figure out if a novel mechanism will be successful in a clinical trial. YOUR SOLUTION: just get into the clinic to test ideas, even if such trials require experimentation and are inefficient to conduct. To quote an MIT scientist: "*The problem with "Ready-AIM-Fire" is that if you aim first, you can't hit anything unexpected.*"

So, if we believe this framing of the problem, then we are TEMPTED to think we face a choice between two mutually exclusive possibilities: *Focus and discipline to solve the FAILURE problem vs serendipity and the unexpected to solve the NOVELTY problem.*

BUT I BELIEVE WE DON'T HAVE TO CHOOSE, AS BOTH (pause) ARE POSSIBLE – AND EVEN MORE.

Bullseye, Aim, Fire

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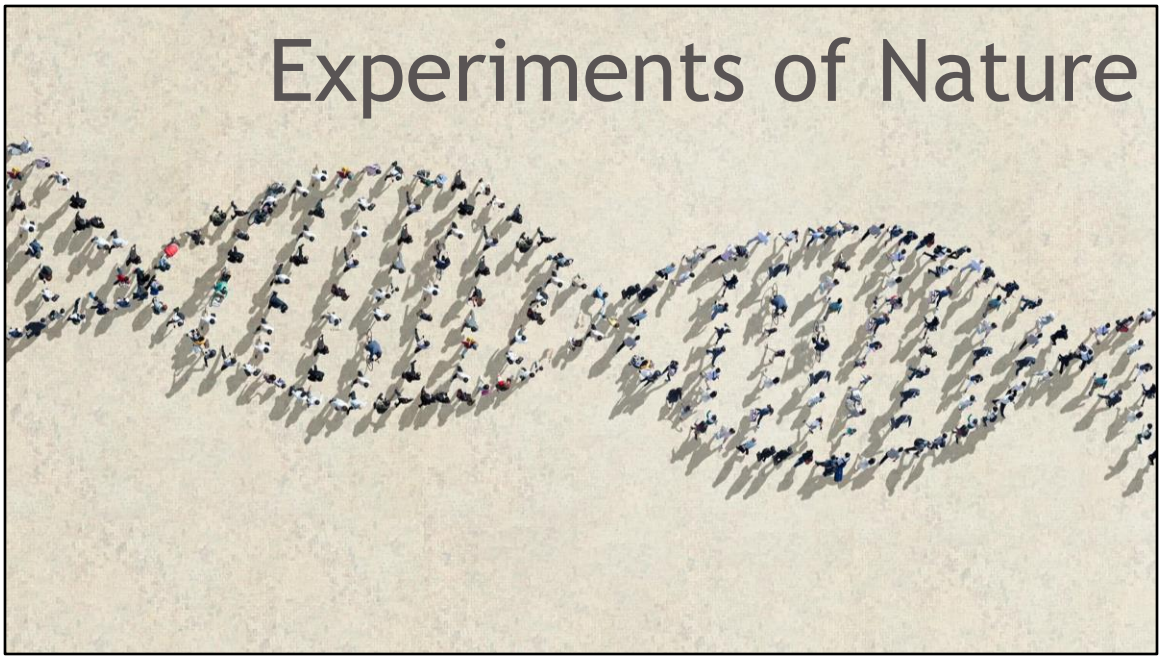
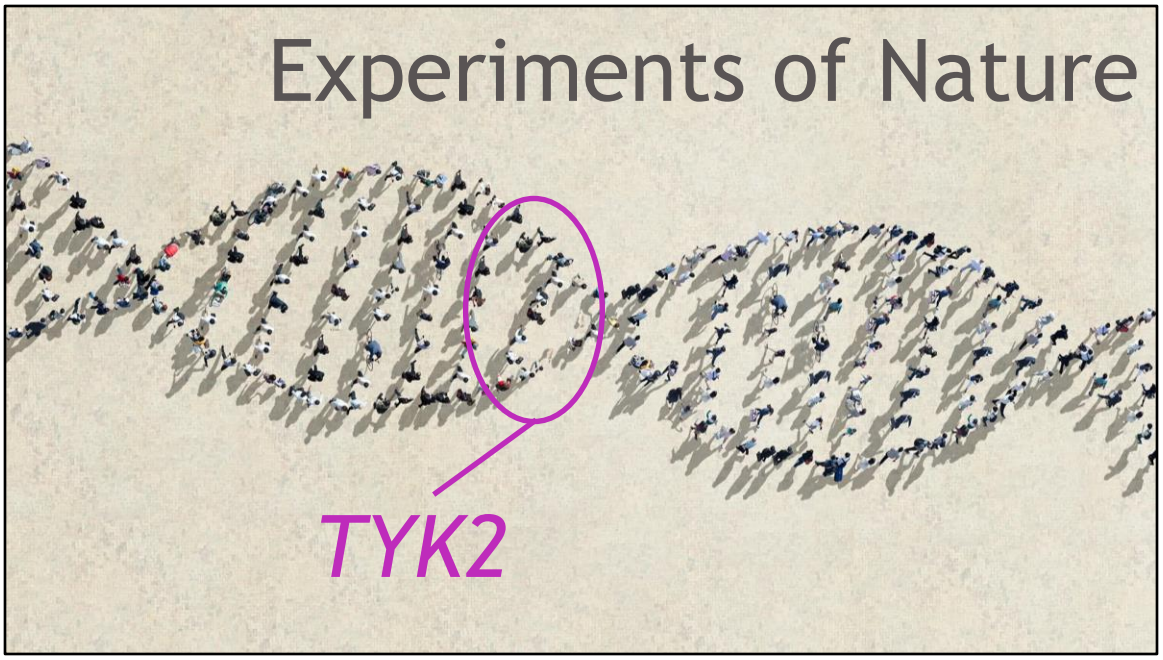
I PROPOSE A **BULLSEYE-Aim-Fire approach** , where new technologies can predict the outcome of a clinical trial even BEFORE a new target is selected. LET ME SAY THAT AGAIN: new technologies can predict the outcome of a clinical trial right at the start of a drug discovery journey. THIS GIVES US THE BULLSEYE.

HOW IS IT POSSIBLE for new technologies to predict the outcomes of a clinical trial?



Because these new technologies allow us to tap into ***experiments of nature*** to select drug targets. And these targets have BOTH increased probability of success in clinical development AND increased probability of differentiating from standard of care medicines. **SUCCESS plus NOVELTY in one package, based on letting nature do some of the work for us.**

We are increasingly seeing success for the **Bullseye-Aim-Fire** approach. This includes one example that I have been involved with for over a decade.



A bullseye target – TYK2 – was identified through an experiment of nature – human genetics, which taps into the serendipity of human evolution. The company I work for, Bristol Myers Squibb, has taken a quite a journey in working with this target through discovery, development and commercialization. But as you will hear throughout this presentation, there were SURPRISES along the way that made developing and testing a TYK2 inhibitor anything but a certainty.

Before we get to the TYK2 story, let's look a little closer at the Bullseye-Aim-Fire approach…what it means, and WHY. IT. WORKS.

Selecting a target is the very start of the drug R&D journey. If the members of our pharmaceutical industry are honest with ourselves, we would acknowledge that most targets are "meh targets". A "meh target" is basically like aiming a dart precisely where you hope it to go, but having no idea what the outcome will be. You know it could be great: if you hit your target, the center of the bullseye, you are going to get 50 points. But the outcome could just as easily be a giant disappointment: zero points – because the dart missed the board altogether. This is why we have the Failure-Novelty problem!

In contrast, a BULLSEYE TARGET is *exactly* what it sounds like. It means having *confidence that the target* will be successful in clinical development – addressing the FAILURE problem – and will also be sufficiently novel to differentiate from standard of care – addressing the NOVELTY problem. **BULLSEYE**.

Seems obvious, right? Why is it SO HARD to define a bullseye target? I believe that THE FUNDAMENTAL CHALLENGE is establishing cause-and-effect between perturbing the target with a drug and knowing the outcome of that drug perturbation on *human* physiology. This is what I refer to as **"causal human biology".**

Causal human biology

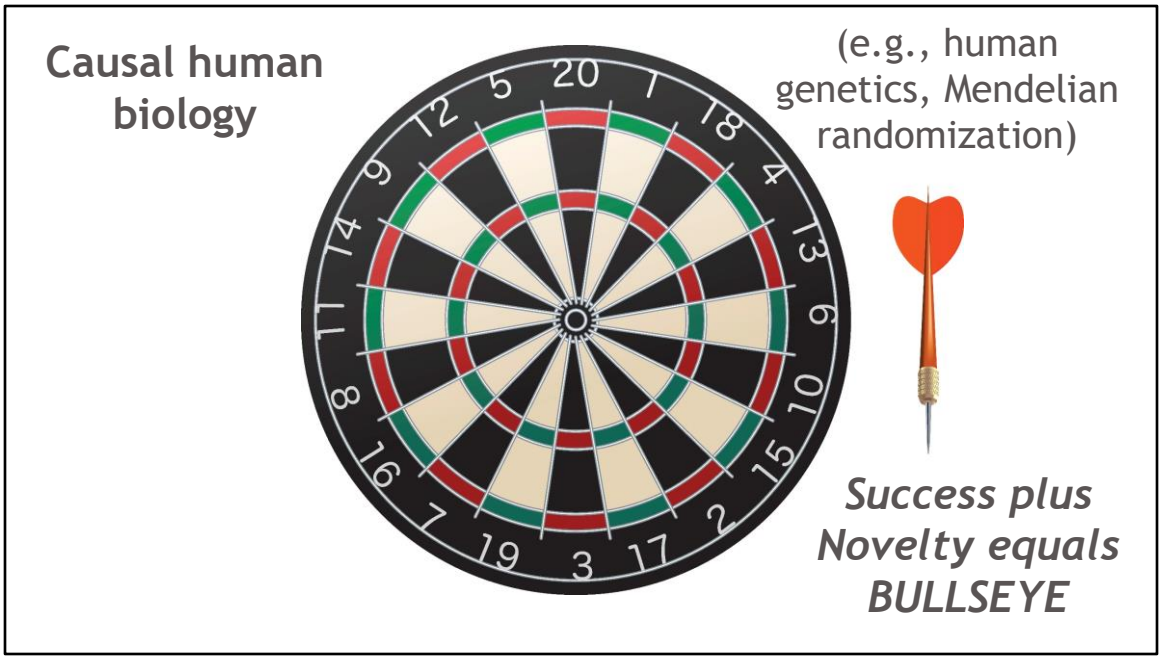
Establishing a cause-effect relationship is a more general problem in our society. Too often we think an event causes an outcome. An extreme example? Wearing my favorite sports jersey while watching a game will determine the outcome of the game itself.

In drug discovery, selecting targets based on mouse model data alone or correlative data in humans is the equivalent of wearing your favorite basketball jersey and expecting your team to win. What you need is Michael Jordan on the court – and when the Chicago Bulls win, THAT is a cause-effect relationship!

Fortunately, more tools are becoming available to establish CAUSAL HUMAN BIOLOGY. One of my favorites is **human genetics**.

Over the course of human evolution, nature has done the experiment of mutating most, if not all, of the 6 billion base pairs in our genomes. Because these mutations are inherited at birth, which is generally before a disease presents itself in a patient, a cause-effect relationship can be established.

Even more interesting is that because mutations are *randomly distributed* across people in our society, these mutations mimic a randomized control clinical trial. Indeed, there is a technique called **Mendelian randomization** designed to use human genetics to predict a cause-effect outcome in a clinical trial. **EVEN *BEFORE* (pause) A CLINICAL TRIAL IS CONDUCTED.**



That is how SUCCESS plus NOVELTY equals BULLSEYE.

What does it mean to "Aim" in drug R&D?

It means having a therapeutic modality that binds to and perturbs a target. Twenty years ago, there were relative few therapeutic modalities. For example, approximately 90% of approved medicines were small molecules pills.

Today, there multiple therapeutic modalities, with many more emerging. Because of the diversity of these therapeutic modalities, IT IS NOW POSSIBLE to manipulate drug targets in more subtle ways. IT IS POSSIBLE to degrade targets with small molecules; IT IS POSSIBLE to replace or edit defective genes; IT IS POSSIBLE to use antibodies to deliver cytotoxic payloads to kill cancer cells. It is EVEN POSSIBLE to put poop in a pill to treat deadly intestinal infections!

Because of this diversity in therapeutic modalities, it is now POSSIBLE to FIX the underlying molecular defect in a patient with a disease, as defined by causal human biology. I like to say this "*matching a therapeutic modality to a molecular mechanism of action*", or "**matching modality to mechanism**" for short.

So, what we want to do is "Aim" a therapeutic modality at a BULLSEYE target.

Of course, one must do a clinical trial to show that a medicine is safe and effective. And it is important that these trials are operationally efficient.

Remember that number…1 in 10? That for every 10 new medicines that enter clinical development, only 1 will hit the bullseye and emerge as an approved therapy?

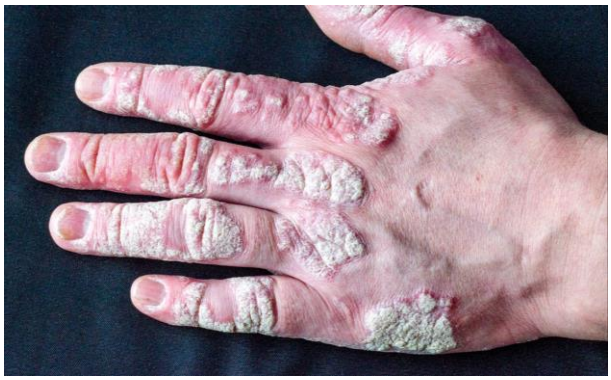
Well, if targets and therapeutic molecules are selected based on the principles of **CAUSAL HUMAN BIOLOGY** and **MATCHING MODALITY TO MECHANISM**, there are now empirical data that probability of success will more than double.

Moving from 1 in 10 to 2 in 10 may not sound like a lot, given the cost of drug R&D, doubling success rates will save BILLIONS of dollars.

To start a clinical trial is to "Fire" at a disease.

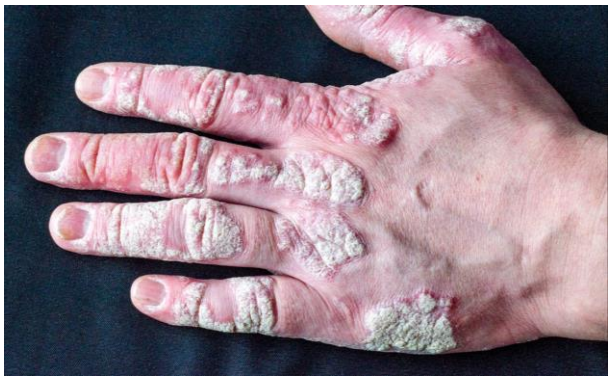
WHAT DOES THIS LOOK LIKE IN ACTION? Psoriasis and TYK2 provide a clear example.

psoriasis

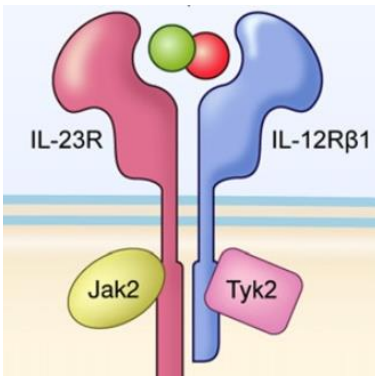


Psoriasis is a skin disease which causes discolored, itchy, and scaly skin. There are several effective treatments that can clear these skin lesions. Until last year options were extremely limited, as the most recently available oral medicine could clear 75% of skin lesions but in only about one-third of patients, according to clinical trials.

psoriasis



TYK2 signaling



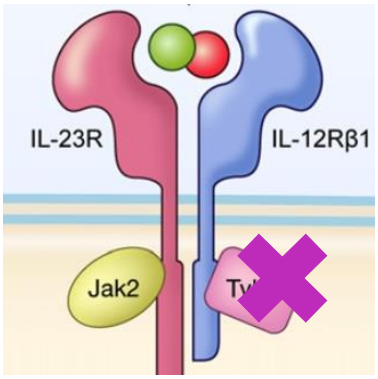
Human genetics pointed to a novel target called TYK2. TYK2 is an intracellular – inside of a cell – signaling molecule, which means it serves as a messenger to communicate a signal from outside of a cell to the molecular machinery inside of a cell.

While TYK2 itself was discovered in 1990, a causal link to human disease was not established until the early 2000's. That's when scientists identified naturally occurring mutations in TYK2 that could lead to a wide range of immune-mediated diseases. Complete loss of TYK2 caused immune deficiency. **BUT HERE WAS A FIRST SURPRISE**: partial loss-of-function seemed to **protect** from human inflammatory diseases such as psoriasis.

This led our scientists at BMS to ask:

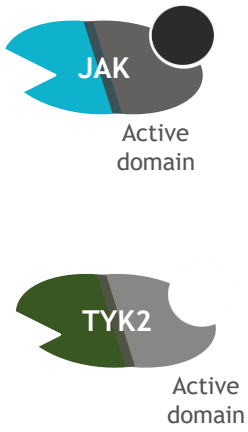
Could a drug mimic the *experiment of nature*?

TYK2 signaling



What if we could create a drug to mimic the protective loss-of-function mutations? Would such a drug RECAPITULATE nature's experiment and protect patients from developing psoriatic skin rashes?

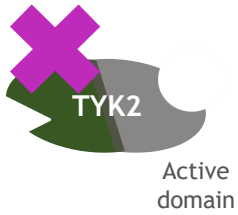
Could a drug mimic the *experiment of nature*?



This was not a straightforward task, as the ACTIVE DOMAIN of TYK2 looks a lot like the ACTIVE DOMAIN structure of a related family of molecules called JAKs. For several reasons, the team at BMS thought it was necessary to specifically inhibit TYK2 without also inhibiting JAK.

Could a drug mimic the *experiment of nature*?

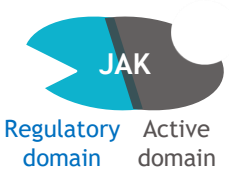
Protective loss-of-function *TYK2* mutations do not appear to effect broader system functions



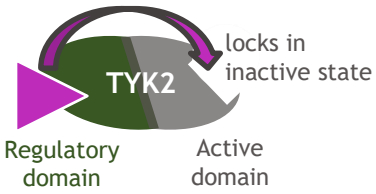
ALONG CAME ANOTHER SURPRISE, also from human genetics.
Human genetics suggested that the TYK2 kinase is not involved in broad systemic functions, such as blood cell development.

So BMS scientists were faced with a task of selectively inhibiting TYK2 without inhibiting JAKs. BMS scientists conducted a *phenotypic screen* to find such small molecules.

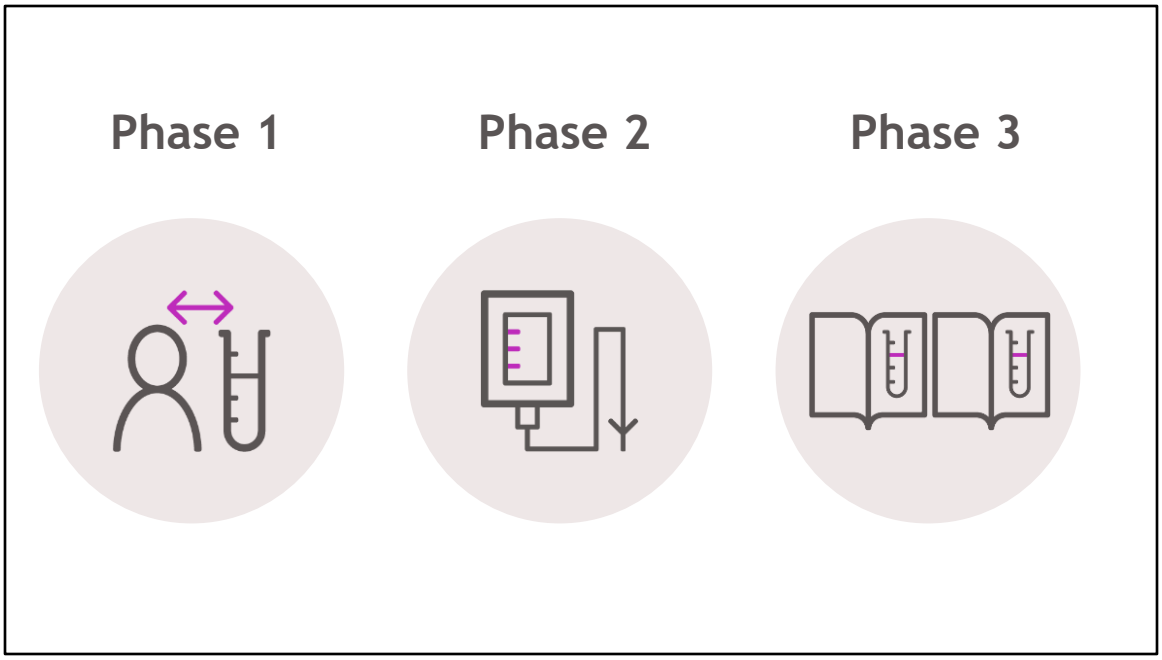
Could a drug mimic the *experiment of nature*?



TYK2 allosteric inhibitors achieve *exquisite selectivity*

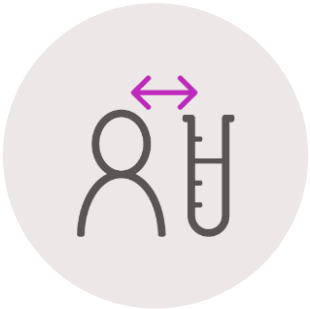


THE RESULTS WERE…A SURPRISE: a small molecule was found to bind NOT to the ACTIVE domain of TYK2, but to a domain on the other side of the molecule. The TYK2 inhibitors discovered by our BMS scientists bound to a REGULATORY DOMAIN, which locked the ACTIVE DOMAIN of TYK2 in an inactive state. This is known as an ALLOSTERIC INHIBITOR.



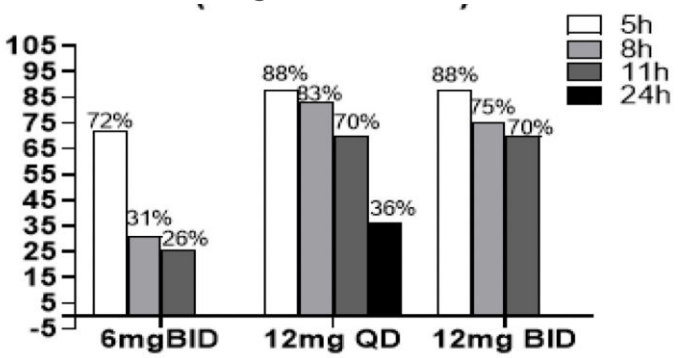
Now it was time to start clinical trials. The TYK2 program was like many clinical programs, starting first with a small Phase 1 study to determine safety and tolerability; a larger Phase 2 study to select an efficacious dose in psoriasis; and a larger yet Phase 3 study with registrational endpoints.

Phase 1



Early Clinical Development

Interferon Signature % inhibition in HV

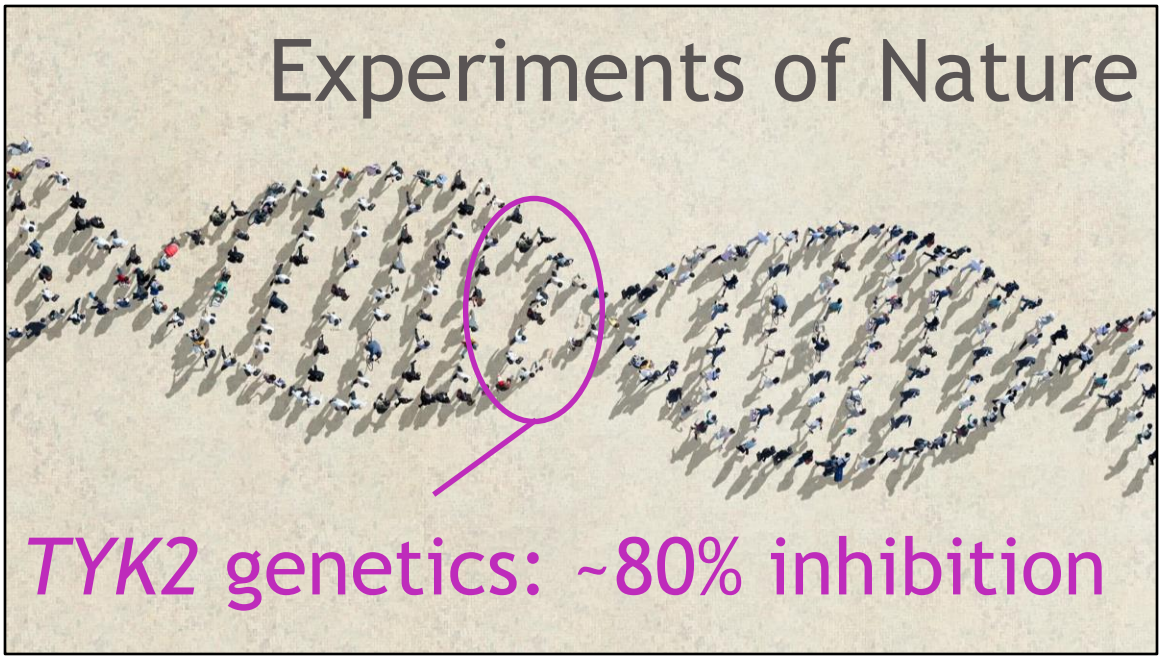


Deucravacitinib Inhibits interferon Signature in healthy subjects after IFNα-2a challenge

Clin Transl Sci. 2023 Jan; 16(1): 151–164

An interesting aspect of the TYK2 program was that the Phase 1 healthy volunteer study include a "challenge test", where healthy volunteers where given a dose of interferon to mimic the disease state in psoriasis and other autoimmune diseases such as systemic lupus erythematosus. The results, shown on this slide, demonstrated that increasing doses of our TYK2 inhibitor resulted in increasing levels of inhibition of the interferon signaling pathway. **A cause-effect relationship was definitively established.**

But to gain regulatory approval it is necessary to conduct large-scale, randomized control trials at a *very specific dose*.

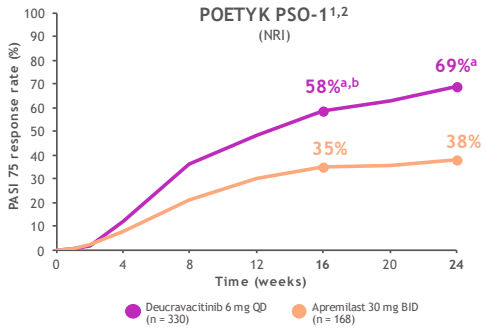


Human genetics suggested that ~80% inhibition of TYK2 would be safe and effective. **ANOTHER SURPRISE:** The dose of the medicine that was selected for Phase 3 inhibited TYK2 by… APPROXIMATELY EIGHTY PERCENT! That is, the investigational drug very closely mimicked the naturally occurring mutation.

We had our BULLSEYE. We had AIMED carefully. And now it was time to FIRE!

BMS conducted *two* large Phase 3 trials with the drug in patients with moderate to severe psoriasis. And we all held our breath for the results…

Nearly two thirds of SOTYKTU patients saw a 75% improvement in PASI score at Week 24 in a clinical trial
(secondary endpoint)



SOTYKTU: *Nearly two-thirds of patients had a PASI 75 response rate (Week 24)*

Standard of care oral medicine: *Approximately one-third of patients had a PASI 75 response rate (Week 24)*

In a second trial, POETYK PSO2, response rates were 58 percent and 38 percent for SOTYKTU vs standard of care at Week 24

SOTYKTU is approved for the treatment of adults with moderateto-severe plaque psoriasis who are candidates for systemic or phototherapy. SOTYKTU is not recommended for use in combination with other potent immunosuppressants. 25

As you can see, in one trial, the medicine had nearly TWICE the response rates vs the standard of care oral medicine care, with nearly TWO-THIRDS of patients seeing a 75% improvement in PASI score at Week 24.

In September 2022, the FDA approved the medicine, now called **SOTYKTU**, for first-line treatment of patients with moderate-to-severe psoriasis.

SOTYKTU study design, results and safety information

STUDY DESIGNS

POETYK PSO-1 (N=664) and POETYK PSO-2 (N=1020) were two, 52-week, multicenter, randomized, double-blind, placebo- and active (apremilast 30 mg twice daily)-controlled, Phase 3 studies to evaluate the safety and efficacy of SOTYKTU (6 mg once daily) in adult patients with moderate-to-severe plaque psoriasis who were eligible for systemic therapy or phototherapy. Patients had a body surface area (BSA) involvement of ≥10%, a Psoriasis Area and Severity Index (PASI) score ≥12, and a static Physician's Global Assessment (sPGA) ≥3 (moderate or severe).

Both studies assessed the responses at Week 16 compared with placebo for the two co-primary endpoints:
- The proportion of patients who achieved at least a 75% improvement in PASI scores from baseline (PASI 75)
- The proportion of patients who achieved an sPGA score of 0 (clear) or 1 (almost clear)

There were multiple ranked secondary endpoints, including:
- The proportion of patients who achieved PASI 75 at Week 16 and Week 24 vs apremilast

STUDY RESULTS

Comparison between SOTYKTU and apremilast was a secondary endpoint. Co-primary endpoints:
- PASI 75 at Week 16 for SOTYKTU vs placebo: PSO-1: 58% (193/330) vs 13% (21/166), P<0.0001; PSO-2: 53% (271/511) vs 9% (24/255), P<0.0001
- sPGA 0/1 at Week 16 for SOTYKTU vs placebo: PSO-1: 54% (178/330) vs 7% (12/166), P<0.0001; PSO-2: 50% (253/511) vs 9% (22/255), P<0.0001

Select secondary endpoints:
- PASI 75 at Week 16 for SOTYKTU vs apremilast: PSO-1: 58% (193/330) vs 35% (59/168); P<0.0001. PSO-2: 53% (271/511) vs 40% (101/254); P=0.0004

SELECT IMPORTANT SAFETY INFORMATION

In the PSO-1 and PSO-2 trials, through Week 16, the most common adverse reactions (≥1% and higher than placebo) in patients taking SOTYKTU (n=840) were upper respiratory infections (19.2%), blood creatine phosphokinase increase (2.7%), herpes simplex (2.0%), mouth ulcers (1.9%), folliculitis (1.7%), and acne (1.4%).

FOOTNOTES

BSA=body surface area; PASI=psoriasis area and severity index; PASI 75=75% reduction from baseline in PASI; PASI 90=90% reduction from baseline in PASI; PSSD=Psoriasis Symptoms and Signs Diary; sPGA=static Physician's Global Assessment; ss-PGA=scalp-specific Physician's Global Assessment; TYK2=tyrosine kinase 2.

Indication and Important Safety Information

INDICATION

SOTYKTU™ (deucravacitinib) is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Limitations of Use:
SOTYKTU is not recommended for use in combination with other potent immunosuppressants.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

SOTYKTU is contraindicated in patients with a history of hypersensitivity reaction to deucravacitinib or to any of the excipients in SOTYKTU.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions such as angioedema have been reported. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue SOTYKTU.

Infections: SOTYKTU may increase the risk of infections. Serious infections have been reported in patients with psoriasis who received SOTYKTU. The most common serious infections reported with SOTYKTU included pneumonia and COVID-19. Avoid use of SOTYKTU in patients with an active or serious infection. Consider the risks and benefits of treatment prior to initiating SOTYKTU in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- with underlying conditions that may predispose them to infection.

Please click here for the full prescribing Information for SOTYKTU, including Medication Guide.

Important Safety Information (cont'd)

Infections (cont'd):

Closely monitor patients for the development of signs and symptoms of infection during and after treatment. A patient who develops a new infection during treatment should undergo prompt and complete diagnostic testing, have appropriate antimicrobial therapy initiated and be closely monitored. Interrupt SOTYKTU™ (deucravacitinib) if a patient develops a serious infection. Do not resume SOTYKTU until the infection resolves or is adequately treated.

Viral Reactivation

Herpes virus reactivation (e.g., herpes zoster, herpes simplex) was reported in clinical trials with SOTYKTU. Through Week 16, herpes simplex infections were reported in 17 patients (6.8 per 100 person-years) treated with SOTYKTU, and 1 patient (0.8 per 100 person-years) treated with placebo. Multidermatomal herpes zoster was reported in an immunocompetent patient. During PSO-1, PSO-2, and the open-label extension trial, the majority of patients who reported events of herpes zoster while receiving SOTYKTU were under 50 years of age. The impact of SOTYKTU on chronic viral hepatitis reactivation is unknown. Consider viral hepatitis screening and monitoring for reactivation in accordance with clinical guidelines before starting and during therapy with SOTYKTU. If signs of reactivation occur, consult a hepatitis specialist. SOTYKTU is not recommended for use in patients with active hepatitis B or hepatitis C.

Please click here for the full prescribing Information for SOTYKTU, including Medication Guide.

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Important Safety Information (cont'd)

Tuberculosis (TB): In clinical trials, of 4 patients with latent TB who were treated with SOTYKTU™ (deucravacitinib) and received appropriate TB prophylaxis, no patients developed active TB (during the mean follow-up of 34 weeks). One patient, who did not have latent TB, developed active TB after receiving 54 weeks of SOTYKTU. Evaluate patients for latent and active TB infection prior to initiating treatment with SOTYKTU. Do not administer SOTYKTU to patients with active TB. Initiate treatment of latent TB prior to administering SOTYKTU. Consider anti-TB therapy prior to initiation of SOTYKTU in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during treatment.

Malignancy including Lymphomas: Malignancies, including lymphomas, were observed in clinical trials with SOTYKTU. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with SOTYKTU, particularly in patients with a known malignancy (other than a successfully treated non-melanoma skin cancer) and patients who develop a malignancy when on treatment with SOTYKTU.

Rhabdomyolysis and Elevated CPK: Treatment with SOTYKTU was associated with an increased incidence of asymptomatic creatine phosphokinase (CPK) elevation and rhabdomyolysis compared to placebo. Discontinue SOTYKTU if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Instruct patients to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Please click here for the full prescribing Information for SOTYKTU, including Medication Guide.

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Important Safety Information (cont'd)

Laboratory Abnormalities: Treatment with SOTYKTU™ (deucravacitinib) was associated with increases in triglyceride levels. Periodically evaluate serum triglycerides according to clinical guidelines during treatment. SOTYKTU treatment was associated with an increase in the incidence of liver enzyme elevation compared to placebo. Evaluate liver enzymes at baseline and thereafter in patients with known or suspected liver disease according to routine management. If treatment-related increases in liver enzymes occur and drug-induced liver injury is suspected, interrupt SOTYKTU until a diagnosis of liver injury is excluded.

Immunizations: Prior to initiating therapy with SOTYKTU, consider completion of all age-appropriate immunizations according to current immunization guidelines including prophylactic herpes zoster vaccination. Avoid use of live vaccines in patients treated with SOTYKTU. The response to live or non-live vaccines has not been evaluated.

Potential Risks Related to JAK Inhibition: It is not known whether tyrosine kinase 2 (TYK2) inhibition may be associated with the observed or potential adverse reactions of Janus Kinase (JAK) inhibition. In a large, randomized, postmarketing safety trial of a JAK inhibitor in rheumatoid arthritis (RA), patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of all-cause mortality, including sudden cardiovascular death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and malignancies (excluding non-melanoma skin cancer) were observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. SOTYKTU is not approved for use in RA.

Please click here for the full prescribing Information for SOTYKTU, including Medication Guide.

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Important Safety Information (cont'd)

Adverse Reactions

Most common adverse reactions (≥1% of patients on SOTYKTU™ (deucravacitinib) and more frequently than with placebo) include upper respiratory infections, blood creatine phosphokinase increased, herpes simplex, mouth ulcers, folliculitis and acne.

Specific Populations

Pregnancy: Available data from case reports on SOTYKTU use during pregnancy are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Report pregnancies to the Bristol Myers Squibb Company's Adverse Event reporting line at 1-800-721-5072.

Lactation: There are no data on the presence of SOTYKTU in human milk, the effects on the breastfed infant, or the effects on milk production. SOTYKTU is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SOTYKTU and any potential adverse effects on the breastfed infant from SOTYKTU or from the underlying maternal condition.

Hepatic Impairment: SOTYKTU is not recommended for use in patients with severe hepatic impairment.

SOTYKTU is available in 6 mg tablets.

Please click here for the full prescribing Information for SOTYKTU, including Medication Guide.

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So to conclude, I hope this presentation provides you with a better understanding of how we think about R&D at BMS.

BULLSEYE: selecting targets based on **causal human biology** derived from nature's experiment; TYK2 genetics as one example.

AIM: **matching a therapeutic modality to mechanism**; for TYK2, a small molecule allosteric inhibitor that recapitulates nature's *human genetic* experiment.

FIRE: Operationally efficient clinical trials, which for SOTYKTU concluded with two successful Phase 3 clinical trials, leading to an approved medicine for patients suffering from psoriasis.

Thank you.