

Pathways to success: finding single drugs to treat multiple diseases

All biological processes have backup strategies. So do most diseases. This makes drug discovery complex and challenging.

Signaling pathways are a cell's mode of communication – interference with or damage to certain aspects of a pathway may result in disease. By understanding how to alter the function of a pathway, researchers can determine its influence on a particular disease. Mapping out the details of a signaling pathway allows researchers to determine the most appropriate target (molecule in the pathway) for a drug. Due to the complexity of a signaling pathway, one pathway and sometimes one target may be the source of multiple diseases. With a focus on bringing medicines rapidly to the clinic, a “more is indeed more” philosophy about knowledge of the pathways of a disease holds true: The more information uncovered about the molecular mechanisms of a disease, the more specific the design of a drug and the more accurate its potential to address the cause of a disease. In fact, if designed correctly, a single drug may have the enormous ca-

capacity of treating more than one disease with related molecular mechanisms.

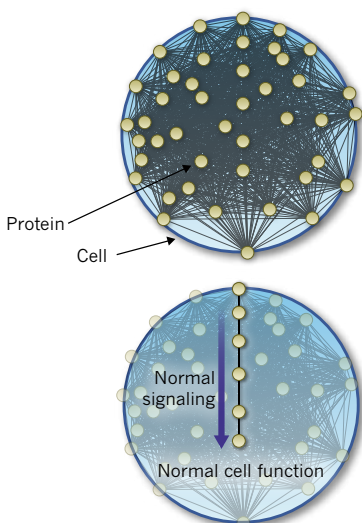
Review of Proof-of-Concept (PoC) clinical trials

At the Novartis Institutes for BioMedical Research (NIBR), the primary objective of a PoC study is to test hypotheses of how a drug may work in the body and to expedite the generation of clinical evidence regarding patient benefit. A PoC trial is ideally conducted in a molecularly/genetically well-defined patient population, providing insight into whether the compound is reaching the pathway at the therapeutic dose level, and achieving therapeutic benefit at minimum toxicity. This is in contrast to traditional Phase I and early Phase II clinical trials, which are conducted in healthy volunteers and general disease patient populations to assess toxicity, tolerability and efficacy.

Selected 2010 PoCs described below demonstrate NIBR's strength in innovation and discovery as these PoCs have been accomplished with first-in-class drugs targeting oncogenic PI3K pathway and the molecular cause of Fragile X Syndrome, illustrating the potential benefit of targeted anticancer treatment and demonstrating the importance of epigenetic markers of drug efficacy.

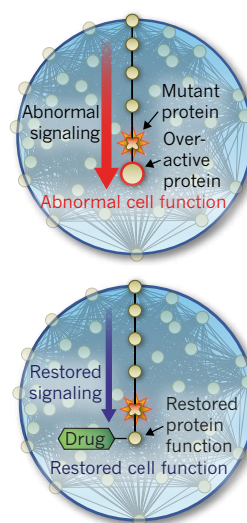
Our twelve positive PoCs in 2010 were contributed from the following disease areas:

- Oncology
- Cardiovascular and Metabolism
- Autoimmunity, Transplantation and Inflammation
- Typhoid Fever
- Neuroscience
- Musculoskeletal
- Gastrointestinal



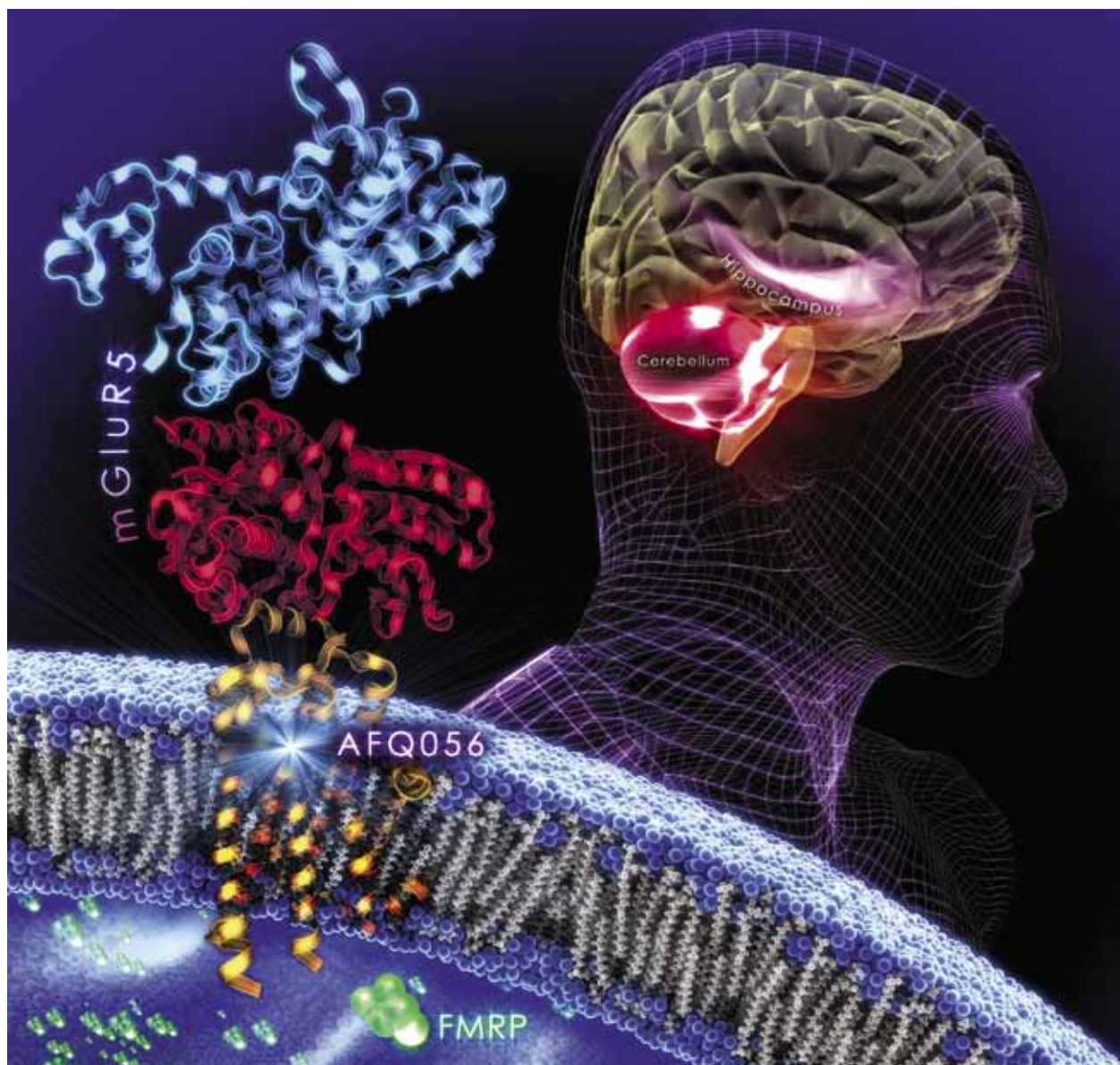
1. The NIBR are studying complex protein networks known as molecular signaling pathways inside of human cells. These proteins are generated from our DNA.

2. Molecular pathways are highly controlled and interconnected signal-relay systems, similar to communication networks, and are responsible for normal cell function.



3. When a protein in a pathway does not function properly, the result can be abnormal signaling and disease. Excessive cell growth in cancer is often the consequence of mutant proteins and a loss of pathway control.

4. Discovering which protein to treat in a pathway is known as finding a drug target. By determining the right targets, Novartis hopes to create medicines that will restore pathway function and treat a variety of diseases.



AFQ056 in Fragile X Syndrome.

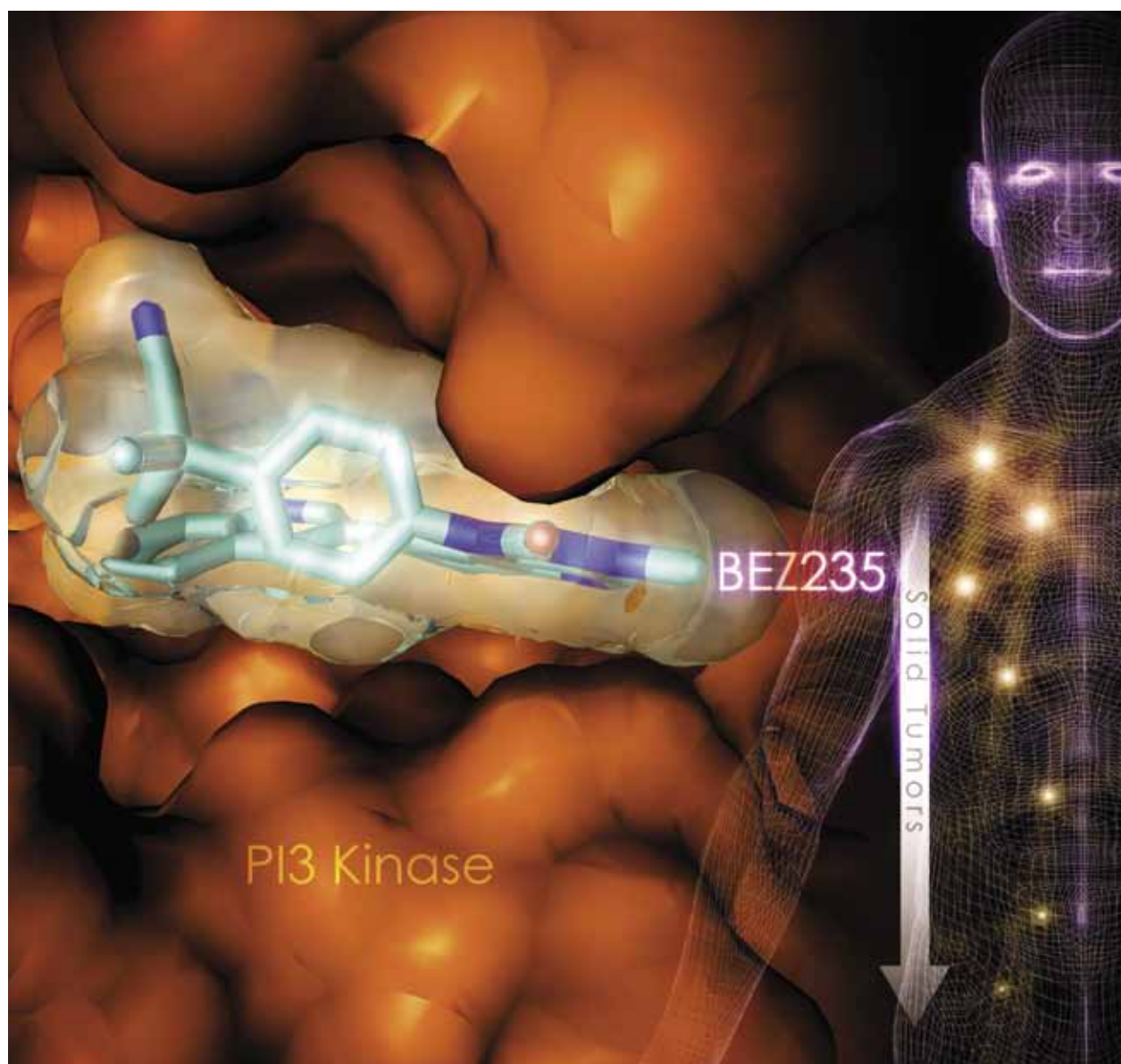
January 2010: AFQ056 in Fragile X

Fragile X Syndrome is the most common genetic cause of mental impairment. This inherited disease is caused by a mutation in a single gene: the expansion of a CGG repeat in the promoter region of the FMR1 (Fragile X Mental Retardation) gene located on the X chromosome. Patients are termed “fully mutated” if they carry 200 or more of these repeats, resulting in a loss of FMRP (Fragile X Mental Retardation Protein). Protein synthesis at the synapse, and thus, many aspects of normal brain function, is stimulated by mGluR5 (metabotropic receptor subtype 5); FMRP usually inhibits this process. The absence of FMRP leads to an increase of mGluR5-mediated protein production and symptoms associated with Fragile X.

AFQ056 is an mGluR5 antagonist. It reached PoC in 2009, and initial results from the clinical

trial were not significant. “When we received the first analysis of the trial, we were incredibly disappointed,” says Baltazar Gomez Mancilla, Executive Director Neuroscience Translational Medicine, who led the PoC team. However, further investigation by Gomez Mancilla and his team using specific biomarkers resulted in an unexpected discovery: In patients with full mutation, only a subset was fully methylated (addition of methyl groups to the DNA). This process, called epigenetic modification, means that the DNA sequence is not altered; rather, changes in DNA methylation or modifications of DNA-binding proteins can cause disease. This sub-population of Fragile X patients with fully mutated, fully methylated FMR1 showed positive improvements upon administration of AFQ056. Patients with a partially methylated FRM1 gene did not respond significantly.

If safety and efficacy is proven through clinical studies, AFQ056 will be the first drug to address the underlying molecular mechanism of Fragile X, rather than the symptoms. It is also the first drug to rely upon epigenetic markers in order to accurately assess drug response. With these specific epigenetic biomarkers, researchers can now predict, with a high level of accuracy, an individual patient’s response to the treatment. The AFQ056 program for Fragile X has now progressed to late-stage development.



BEZ235 in solid tumors.

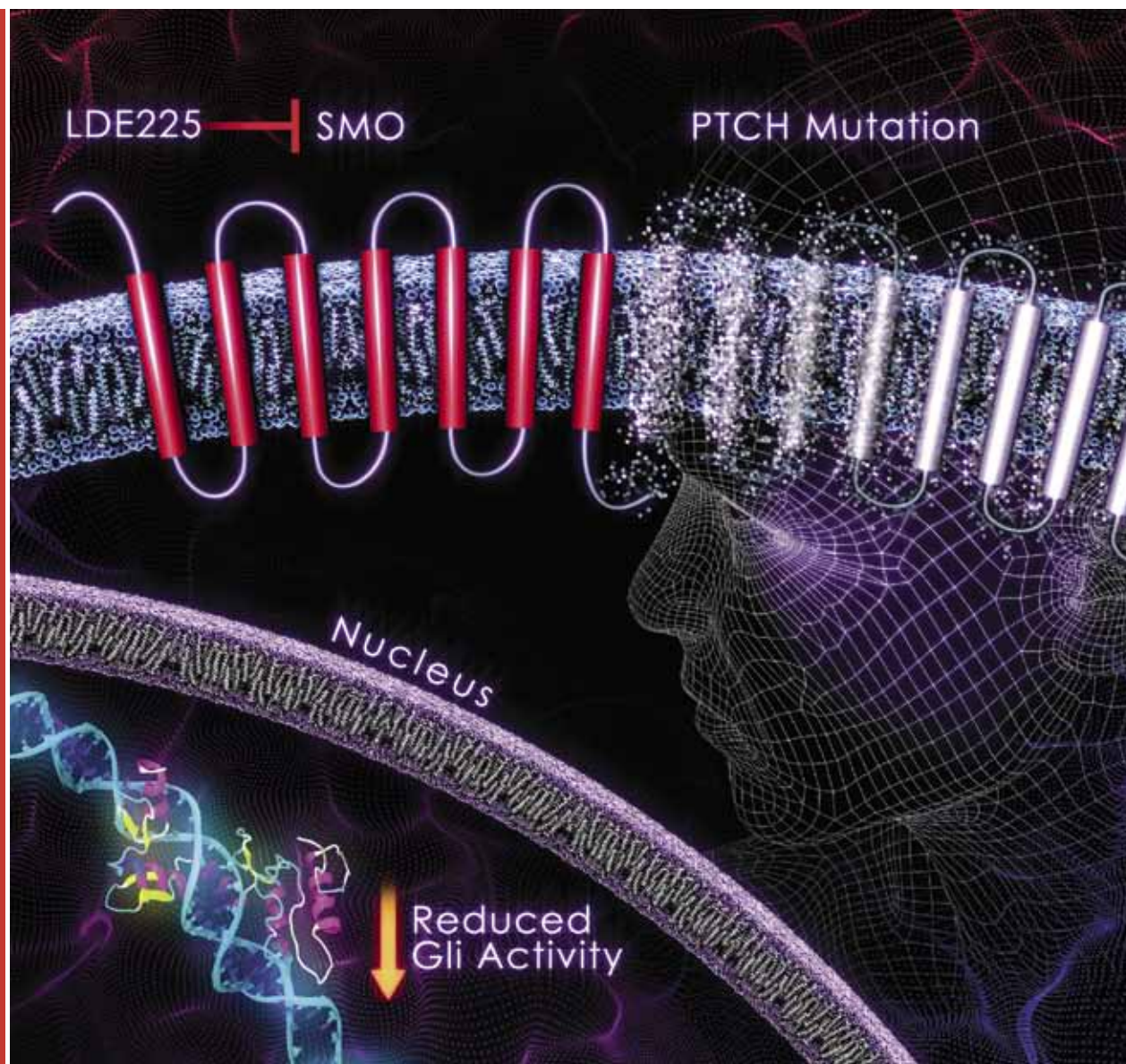
May 2010: BEZ235 in solid tumors

The complex PI3K/AKT/mTOR pathway is a key regulator of cell proliferation. When mutated, the pathway is always active, leading to tumor cell proliferation and survival. Blocking this pathway could result in preventing tumors from growing. "A hallmark of cancer is diversity and heterogeneity," states Wolfgang Hackl, Global Head of Strategic Clinical Planning. Thus, it is important to tailor and personalize cancer treatment.

Yet Michel-Sauveur Maira, Director in NIBR Oncology, and his team have now demonstrated inhibition at two locations in the pathway (PI3K and mTor) by one drug, BEZ235. "It's exciting to be able to positively contribute to the broad portfolio of the Oncology department," says a modest Frederick Stauffer, Senior Scientist, one of the chemists who synthesized the compound.

We are continuing to investigate this drug in our clinical studies.

BEZ235 is a dual selective inhibitor which, according to Hackl, "provides us with an opportunity to tailor this treatment to the needs of specific individuals." BEZ235 is being investigated as a PI3K inhibitor for patients with advanced solid tumors. This drug is now being tested in Phase II clinical trials for other indications such as breast cancer and endometrial carcinoma, as a single-agent treatment as well as in combination with other anti-cancer drugs.



LDE225 in solid tumors.

October 2010: LDE225 in solid tumors

The Hedgehog (Hh) pathway is an essential regulator for many processes in the developing embryo and is involved in the maintenance and regeneration of adult tissues. It is also implicated in a variety of cancers, such as medulloblastoma (MB), basal cell carcinoma (BCC), pancreatic cancer, breast cancer and others.

The Hh pathway, named for the Hedgehog protein (ligand) that activates it, involves two key proteins, Patched (Ptch) and Smoothed (Smo). In a cell's normal resting state, the activity of Smo is blocked by Ptch, the Hh-ligand-specific cell surface receptor. In a disease context, however, mutations of Ptch and/or Smo can lead to continuous activation of the Hh pathway, resulting in the growth and survival of cancer cells. These mutations have been found in BCCs and MBs, in particular. In other cancers,

the activation of the Hh pathway occurs via binding of the Hh ligand to Ptch inducing abnormal growth of the cancer cells. Understanding the intricacies of the Hh pathway has enabled NIBR researchers to successfully develop LDE225, an inhibitor of Smo.

LDE225 entered in the clinic in early 2009 with a Phase I clinical trial that included all advanced solid tumors. LDE225 reached PoC at the end of October 2010, and "the results potentially showed antitumor activity in BCC and MB patients with evidence of activation of the Hh pathway in their tumors," noted Dereck Amakye, Novartis Oncology Senior Director and clinical program leader. "The antitumor activity was associated with inhibition of downstream targets of the Hh pathway."

Silvia Buonamici, Project Research Leader in NIBR Oncology Pharmacology, attributes the

huge success of LDE225 to the multidisciplinary teams at Novartis as well as the many academic laboratories around the world with whom they collaborate. "Our collaborators provide important information to advance our understanding of the Hh pathway," says Buonamici, "and together with the strong diverse research and clinical teams at NIBR, we were able to determine the best way to approach the development of this drug." LDE225 is currently in ongoing clinical trials, while researchers at NIBR continue to dissect the role of the Hh pathway in other tumors where mutations of Ptch/Smo have not been identified, in an effort to determine how to overcome resistance to the drug and to expand its potential clinical application. so