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DRUG DISCOVERY AND DEVELOPMENT EDITION

CHEMOGENICS BIOPHARMA

EXCELLENCE IN COLLABORATIVE RESEARCH RESULTING IN COMMERCIAL AND CLINICAL COMPOUNDS

FRANCIS TAVARES,
PRESIDENT AND CEO

COVER STORY

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EXCELLENCE IN COLLABORATIVE RESEARCH RESULTING IN COMMERCIAL AND CLINICAL COMPOUNDS

The art of drug discovery is continuously evolving. Due to technological advances in the field of automation, imaging, and AI, certain functions have become simpler. Despite these advancements, drug discovery remains a high-stakes endeavor, characterized by a considerable risk of failure in the preclinical phase, often due to nuanced pharmacological interactions that only become apparent during safety evaluations in animal models. Failures can also stem from poor selection of the target, compensatory mechanisms that overcome inhibitory effects of proteins, and poor choice of assay that is irrelevant to the phenotype of interest.

To tackle the many barriers encountered as compounds move from hit to lead optimization and ultimately candidate, ChemoGenics BioPharma's efforts are directed to integrate various functions in the preclinical drug discovery phase. In fact, success in this industry requires one to be a generalist and not be specialized in just one area. People often have this misconception that they can emulate somebody else's success, success is tied to what works for you as a person, in essence find a philosophy that fits you.

"In essence, its collaborators don't need external consultants to address different aspects of drug discovery as the company is well-resourced to help clients reach IND-enabling studies," says Francis Tavares, President and CEO of ChemoGenics BioPharma. "Using propriety information, we can quickly transition molecules into animal studies that we offer in-house and follow them with bioanalysis to get data turnaround in a few weeks rather than months."

Excellent Preclinical Facilities

Initially established as a service-oriented entity, ChemoGenics has set its sights on a broader vision for the future. Drawing upon its rich reservoir of knowledge and expertise in drug discovery, the company aims to transcend its role as a mere service provider. Instead, it aspires to become a pivotal partner in the pharmaceutical industry, aiding peers in the identification of molecules that substantiate biological hypotheses and propel projects toward the crucial stage of lead candidate selection. This strategic evolution underscores ChemoGenics' commitment to driving innovation and facilitating the advancement of transformative therapies within the field of drug development.

This scenario would involve utilizing ChemoGenics' excellent preclinical facilities to perform key functions, including in-house medicinal chemistry (compound design and SAR studies), evaluation of pharmacokinetic (PK) properties (in vitro and in-life), optimization of synthetic route, and synthetic scale-up of the candidate to produce 100–500 grams quantities for preclinical toxicology studies in two species.

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In some cases, ChemoGenics can get PK turnaround (in vivo and bioanalysis) in a matter of days. In its past collaborations, clients were thrilled to have a quick turnaround of data so they could make informed decisions rapidly to progress compounds toward IND-enabling studies. Some of its clients prefer to go directly into animal studies instead of doing in vitro metabolic profiling.

"We offer highly competitive ways to do the studies. Recently, we have also added cancer xenograft models in-house, since many compounds are undergoing cancer studies," says Tavares.

Developing Selective CDK4/6 Inhibitors

ChemoGenics embarked on its journey to develop selective CDK4/6 inhibitors through a collaborative research initiative underpinned by a pioneering risk-sharing approach. Entrusted with the task of formulating a composition of matter patent for the biological insights cultivated by its collaborator, the company forged a partnership to drive innovation in CDK4/6 inhibition. This collaboration exemplifies ChemoGenics' commitment to seeding strategic partnerships and leveraging collective expertise to push the boundaries of drug discovery and development. The project included developing patentable selective CDK/6 compounds, working with patent lawyers to craft enforceable patent claims with broad coverage, selecting and progressing compounds for PK, in vivo efficacy development, presenting the medicinal chemistry and PK data to investors for venture funding, and ultimately identifying candidates for safety studies and candidate selection.

During the early days, Tavares was the only chemist laying out the design and synthesis of these compounds, filing provisional composition of matter patents, until the molecules turned out to be interesting enough for additional research and funding. This was ChemoGenics' first collaborative preclinical drug discovery project, and it was an enormous undertaking that the company wanted to make successful. Dr Tavares led the success of the whole medicinal chemistry program in-house for the CDK4/6 target.

Utilizing internally developed homology models, Tavares initiated the design and synthesis of the initial set of molecules, which demonstrated potency within the range of 0.160 – 2 µM. While this early achievement was cause for excitement, it became apparent that these compounds encountered challenges with poor cell permeability.

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Undeterred, ChemoGenics swiftly addressed this issue, dedicating significant efforts to enhance the cell permeability of the compounds. Within a couple of months, significant progress was achieved in this regard.

The company succeeded in generating the first batch of approximately 40 compounds that included Trilaciclib (commercial) and Lerociclib (clinical). These compounds emerged as the most potent and selective inhibitors of CDK4/6 in the field, a testament to its dedication to pushing the boundaries of drug discovery and innovation.

Helping Reach IND Enabling Studies

The fact that ChemoGenics has achieved phenomenal success since its inception during its first five years in existence implies that it was certainly above its competition in the field. The company's offerings have continued to be of great value to vendors and collaborators.

Understanding the biology of the project and the chemistry that it needs helps greatly to speak in a common language with collaborators and understand issues to help resolve them efficiently. In addition, ChemoGenics also thoroughly understands the pharmacokinetic aspects not only in theory but also in practice. In essence, its collaborators don't need external consultants to address different aspects of drug discovery as the company is well-resourced to help clients reach IND-enabling studies.

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Offering an Edge in the Clinical Trial Phases

When Tavares started ChemoGenics, he was well trained in medicinal chemistry and was fortunate to work with some great scientists at GSK that were highly motivated and driven.

"My interest in biology was spurred by its importance to the field. Within three years of my work at GSK, I was proposing and presenting biological targets to large committee members, designing experiments for PK studies, as well as identifying the right efficacy models. In certain instances, I would collaborate with biologists to come up with appropriate experiments," says Tavares.

While modern technologies and AI tools undoubtedly enhance and expedite processes in drug discovery and development, they cannot replace the invaluable practical insights gained through decades of tackling the complex challenges inherent in this field. Additionally, and most importantly, the biggest deficit of AI is that is entirely based on positive data reported in the scientific literature, since over 95% of the negative data remains unpublished. This can produce biased conclusions and directions arising from unjudicious use of AI in drug discovery.

To the extent that state-of-the-art tools provide a competitive advantage in the marketplace, ChemoGenics believes that integrating medicinal chemistry, lead optimization, in vitro ADME, and in vivo PK in a US-located partner offers unparalleled efficiencies in terms of IP protection, costs, and turnaround times. This also facilitates fail-fast approaches and ensures the most effective resource allocation while managing multiple therapeutic projects.

With the recent introduction of ChemoGenics' in-life animal capability, the company plans to use in-house animal models to evaluate drug efficacy in cancer and arthritis. This resource will assist clients to quickly enter into the clinic in these areas.

"As we grow, we also plan to transition to a larger facility to help great ideas in biology transition into the clinic as we did with Trilaciclib and Lerociclib," says Tavares. Ph