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Integrated drug discovery fuels healthy outcomes

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guest-column-takeshi-yuraPharmaceutical and biotechnology companies reap the most benefit from their strategic collaborations, by working with suppliers whose practices aim to combine and apply the comprehensive process knowledge that have been gained during research. The integration of chemistry and biology, and other capabilities during early drug discovery, delivers significant value to any company by assembling crucial information that has the potential to shorten time-line and improve outcomes at all stages of the pipeline. Working with contract research and manufacturing organizations that support fully integrated research services, with flexible business options and broad technical expertise, provide the best path towards obtaining the ultimate goal: commercialization.

AMRI continues to ensure that customers have access to the most adept experts to address their complex challenges. Recent investments, including the addition of global medicinal and computational chemistry capabilities in India, complement the company's existing capabilities in the US and Singapore. These investments, when coupled with the relocation of custom library synthesis resources and capabilities to India (from the company's Budapest, Hungary operations), would provide additional flexibility to enhance productivity for AMRI's global drug-discovery operations.

AMRI, which is distinguished as one of the top five CROs in the area of drug discovery and development, is equipped with the experience and problem-solving knowledge that is critical to contributing to successful outcomes. This knowledge stems from the company's integrated approach to drug discovery and development, including capabilities in the areas of in vitro biology, in vitro pharmacology, DMPK, medicinal chemistry, computer-aided drug discovery (CADD), structural biology and screening of

both natural products and synthetic compound libraries. The chemistry group at AMRI applies medicinal chemistry to modify the structure of a hit compound, or series of hit compounds, in order to synthesize new molecules with the end goal of discovering compounds that are suitable for progressing into the human clinical trials phase. The biology group's capabilities, which easily integrate with its chemistry services, includes target and biomarker validation; assay development and design; in vitro pharmacology, such as potency, selectivity and mechanism-of-action studies; high-throughput screening (HTS); chemical genomics; in vitro DMPK; in vivo DMPK and in vivo pharmacology.

AMRI uses sophisticated CADD software and techniques to help identify novel hits or leads against selected therapeutic targets, as-well-as to support medicinal chemistry lead optimization programs. CADD methods increase the odds of identifying compounds with desirable characteristics, speed up the hit-to-lead process and improve the chances of propelling a compound over the many hurdles of preclinical testing.

Vast therapeutic strengths and R&D partnering

Since 2001, AMRI has been involved in 175 drug discovery projects resulting in 75 pre-clinical and clinical candidates. Working with large pharmaceutical and biotechnology companies has led AMRI to gain strength and experience across various therapeutic areas. The following case studies summarizes successful R&D applications and partnering opportunities in the therapeutic areas of anti-infectives, central nervous system (CNS) disorders, metabolic diseases, oncology and inflammation.

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In the area of anti-infectives, AMRI licensed a series of potent, small molecular antibacterial compounds with a novel mechanism of action to a large biotechnology company in January 2011. AMRI used multi-drug resistant clinical isolates to screen its own natural product libraries for samples containing antibiotics. Classical antibacterial microbiology and human cell line toxicity assays were used by AMRI to select samples for the purification and structural elucidation of active compounds. The company conducted optimizations of fermentation conditions and downstream isolation processes. AMRI designed in vivo efficacy and pharmacokinetic studies and outsourced the in-life phases to CROs with a reputation for providing high quality in vivo work among the antibacterial community. In addition, AMRI designed and conducted mechanism-of-action studies.

In the area of CNS, a large pharmaceutical company licensed an entire AMRI technology platform and in collaboration with AMRI has progressed three compounds into human clinical trials. One compound, which is designed for the treatment of major depressive disorder (MDD), is furthest along in phase II human clinical trials. During this project, AMRI's medicinal chemistry team performed lead optimization to identify potent triple reuptake inhibitors suitable for advancement to human clinical trials for treatment of MDD. The synthesis of more than 2,000 novel compounds has led to the filing of more than 10 patent applications covering composition of matter and chemical method of preparation where AMRI scientists played a major role as inventors. Lead compounds were developed and advanced that met the target product profile (TPP), which defined safe and effective lead agents for treatment of MDD. Lead compounds and preclinical development candidates demonstrated excellent pharmacokinetics / pharmacodynamics (PK/PD) and target engagement data and good safety in animal toxicology studies. In early stages, AMRI defined a lead optimization screening paradigm and TPP and identified a preclinical development candidate.

AMRI's CNS strengths are backed by a history of success regarding its former proprietary drug discovery and development activities. Within its current portfolio, several programs are available for partnering and out-licensing. Each program has a business strategy to differentiate them from the existing standard of care. AMRI's goal is to find partners with the ability to drive these programs through development and to commercial success.
For example, AMRI is seeking a partner to progress development of its 5-HT3 partial agonist program. AMRI's advanced compounds are mechanistically differentiated from existing medications targeting this receptor. AMRI has identified its first preclinical candidate, ALB-137391(a), and back-up candidates that are available for partnering.

AMRI also seeks a partner for its 5-HT6 antagonist research program targeting treatments for cognitive impairment in Alzheimer's disease, schizophrenia and orphan diseases. A leading candidate compound and multiple back-up compounds are available for advancement.

Additionally, AMRI is seeking a partner for its glycine transporter-1 (GlyT-1) inhibitor R&D program. AMRI's lead series is differentiated from advanced clinical compounds through a preferred competitive inhibition mode of action and higher potency. In preclinical studies, these compounds show excellent potency in animal efficacy models and without the side-effect profile of traditional anti-psychotic medications.

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In the area of inflammation, AMRI identified a selective glucocorticoid receptor modulator (SGRM). This program progressed to the lead optimization phase. AMRI identified compounds to selectively displace the natural ligand from the glucocorticoid receptor. The company developed cell-based assays to identify compounds that could selectively inhibit the expression of inflammatory cytokines, leaving the activities of glucocorticoid response element-mediated pathways unaltered. Portions of AMRI's small molecule and natural product sample libraries were screened for SGRMs and natural product actives were purified and their structures elucidated. Following the use of technologies, which were implemented to determine if mechanisms of action were dependent on the glucocorticoid receptor, several SGRMs were identified. This included a 450 pM natural product, non-steroidal SGRM, which had greater than 50-fold selectivity for transrepression of inflammatory cytokine expression over transactivation of glucocorticoid response element-mediated pathways. Before moving to lead optimization, the compound was purified and the structure elucidated. This compound is no longer available for licensing.

In the area of metabolic diseases, AMRI carried out a fully integrated MCH-1 antagonist drug-discovery program. The MCH-1 antagonist approach was chosen as a target for AMRI's internally funded R&D. The screening strategy, target product profile and differentiation strategy was designed and implemented by the fully integrated AMRI project team. Hits were generated through a dual approach using a screen of library compounds and through rational compound design and selection using a pharmacophore model. Lead optimization drove parameters, such as affinity, selectivity, metabolic stability and in vivo activity. An in vitro target assay was developed around AMRI proprietary radioligand, with in vitro DMPK using AMRI platforms. AMRI directed the design and the validation of in vivo efficacy/novel ex vivo receptor occupancy assays. Of the 1,000 compounds prepared during lead optimization, multiple compounds progressed into advanced in vivo candidate selection studies and ALB-127158(a) was chosen as a pre-clinical candidate. AMRI guided the completion of regulatory safety, toxicity studies and a phase I clinical trial. Overall, the study demonstrated safety/tolerability with a second translational phase I study indicating CNS penetration. AMRI then identified follow-on compounds as a back-up strategy.

AMRI is seeking a partner to progress the research and development of its MCH1 ALB-127158(a) program. The phase I study met both its primary and secondary objectives, demonstrating safety and tolerability, and multiple patent applications have been filed to protect AMRI intellectual property.
AMRI also has experience in the complex therapeutic area of oncology. For one project, a multidisciplinary team of AMRI medicinal chemists, in vitro biologists and DMPK scientists worked together to discover preclinical candidates for two protein kinase targets. AMRI's in vitro biology group developed and validated a client's two kinase assays for HTS. Follow-on activities were performed, which included the screening of AMRI's Diverse Synthetic Library Collection to generate hits; and medicinal chemistry, CADD and in vitro DMPK activities. More than 2,500 compounds were prepared in this program and more than 10 compounds have demonstrated 30% to 90% tumor growth inhibition in vivo upon intravenous dosing on a 14-day efficacy study in nude mice xenograft studies. Mouse pharmacokinetic studies have shown two compounds exhibiting greater than 50 percent oral bioavailability. Two patent applications filed with additional applications pending filing.