

DRUG DISCOVERY AND DEVELOPMENT ALLIANCES IN INDIA – UPDATE ON RECENT OUT-LICENSING DEALS

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OUT-LICENSING - A CRITICAL COMPONENT IN INDIAN DRUG DISCOVERY

In 1997, Dr Reddy's Laboratories (DRL) was the first Indian company to out-license a molecule, Balaglitazone or DRF 2593, a partial PPAR γ agonist for the treatment of diabetes, to a Western pharmaceutical company (Novo Nordisk). More DRL deals followed in the area of diabetes, including on Ragaglitazar or DRF 2725, a dual-acting a PPAR α/γ agonist (also Novo Nordisk, 1998), and DRF 4158, another PPAR α/γ agonist (Novartis, 2000), or in oncology with DRF 1042, a topoisomerase-I inhibitor for the treatment of solid tumors (ClinTec, 2006).

Other Indian pharmaceutical and biotechnology companies adopted the same business strategy, such as Ranbaxy (Parvosin or RBx 2258, an alpha-1 adrenoceptor antagonist to treat benign prostatic hyperplasia, licensed to Schwarz Pharma in 2002), Torrent Pharmaceuticals (TRC-4186, an AGE-breaker for the treatment of diabetes related cardiovascular complications, licensed to Novartis in 2002). Glenmark in particular, has been very successful in licensing out preclinical drug candidates such as Oglemilast or GRC 3886, a PDE-4 inhibitor for the treatment of asthma and COPD (Forest Laboratories in 2004, and Teijin Pharma in 2005), Melogliptin or GRC 8200, a DPPIV inhibitor, for diabetes (Merck and Co., 2006), GRC 6211, a TRPV1 antagonist to treat pain and migraine (Lilly, 2007), or GRC 15300, a TRPV3 antagonist for osteoarthritic pain (Sanofi, 2009). In 2013, the company claimed to have received more than 200 M US \$ as upfront or milestone payments from its various partners. Other Indian companies, including Orchid, Panacea Biotec or Piramal, have tried in the past to find partners for their preclinical and clinical development compounds.

The major reason for this is that the full clinical development of a molecule is a long, high-risk and expensive process, which most Indian companies were not able, or were not ready to engage in, even though the larger ones made efforts to advance their molecules in-house as far up into clinical trials as possible, in order to add value to the compounds, and to benefit from higher fees on later deals.

A notable exception to this strategy has been Zydus Cadila, with the in-house discovery, development, and launch in 2013 of Saroglitazar, a PPAR α/γ agonist for the treatment of



dyslipidemia, the first compound ever to be discovered and developed by an Indian company. More recently, Aurigene, a company that has so far been very successful in partnering research programs with Western pharma companies in the areas of oncology and inflammation, announced plans to develop and sell its own anti-infective drug, with a first compound scheduled to enter clinical trials later this year.

RECENT EXAMPLES OF LICENSING DEALS WITH INDIAN BIOTECH COMPANIES

Out-licensing remains however essential to the business model of most Indian pharma and biotech companies, and several of them have been quite successful recently in attracting partners, as shown by deals announced over the past 18 months (Table).

Table: Major licensing deals announced between early 2014 and mid-2015

Pharma company	Indian partner	Year	Therapeutic area - mode of action
Hoffmann-La Roche	Curadev	2015	Cancer - IDO1 and TDO inhibition
Curis	Aurigene	2015	Cancer – PD-L1 and IRAK4 antagonism (small molecules)
TG Therapeutics	Rhizen Pharmaceuticals	2014	Cancer – PI3K inhibition
Orion Pharma	Aurigene	2014	Cancer – BET Bromodomain inhibition
Boehringer Ingelheim	Connexios	2014	Diabetes – AMPK activation
Pierre Fabre	Aurigene	2014	Cancer – PD-L1 antagonism (peptide)

Even though the full details are not disclosed in most cases, the following excerpts taken from press releases illustrate the scope of the deals:

1. Hoffmann-La Roche partners with Curadev Pharma Ltd. for IDO1 and TDO inhibitors (April 20, 2015)

Curadev Pharma Pvt Ltd., founded in 2010 and headquartered in New Delhi, announced that it has entered into a research collaboration and exclusive license agreement with Roche for the development and commercialization of IDO1 and TDO inhibitors to treat cancer. The agreement covers the development of CRD1152, the lead preclinical immune tolerance



inhibitor and a research collaboration with Roche's research and early development organization to further explore the IDO and TDO pathways.

IDO1 (indoleamine-2,3-dioxygenase-1) and TDO (tryptophan-2,3-dioxygenase) are enzymes that mediate cancer-induced immune suppression. This mechanism is exploited by tumor cells as well as certain type of immune cells, limiting the anti-tumor immune response. Dual inhibition of the IDO1 and TDO pathways promises to maintain the immune response, prevent local tumor immune escape and potentially avoid resistance to other immunotherapies when used in combination, and could lead to new treatment options for cancer patients. Curadev's preclinical lead-compound, a small-molecule that shows potent inhibition of the two rate-limiting enzymes in the tryptophan to kynurenine metabolic pathways, has the potential for mono therapy as well as combination with Roche's broad oncology pipeline and portfolio.

Under the terms of agreement, which includes a research collaboration with Roche's research and early development organization, Curadev will receive an upfront payment of \$25 million and will be eligible to receive up to \$530 million in milestone payments, as well as escalating royalties potentially reaching double digits for the first product from the collaboration developed and commercialized by Roche. Curadev is also eligible for milestones and royalties on any additional products resulting from the research collaboration.

For the full press release: <http://www.prnewswire.com/news-releases/curadev-announces-research-collaboration-and-licensing-agreement-to-develop-cancer-immunotherapeutic-500630711.html>

2. Curis, Inc. partners with Aurigene for Small Molecule Antagonists for Immuno-Oncology and Precision Oncology Targets (January 21, 2015)

Aurigene Discovery Technologies Limited, established in 2002 as a subsidiary of Dr. Reddy's Laboratories Ltd, and based in Bangalore, is a specialized, discovery stage biotechnology company developing novel therapies to treat cancer and inflammatory diseases. The company, which currently employs over 500 scientists, has a track record of collaborations with 6 of the top 10 pharma companies.

On January 21, 2015, Curis Inc., a biotechnology company based in Lexington, Massachusetts (USA), and focused on the development and commercialization of innovative drug candidates for the treatment of human cancers, and Aurigene announced a collaboration, license and option agreement to discover, develop and commercialize small molecule antagonists for immuno-oncology and precision oncology targets.

Aurigene has the responsibility for conducting all discovery and preclinical activities, including IND-enabling studies and providing Phase 1 clinical trial supply, and Curis has the responsibility for all clinical development, regulatory and commercialization efforts worldwide,



excluding India and Russia, for each program for which it exercises an option to obtain a license.

The agreement provides Curis with the option to exclusively license Aurigene's orally-available small molecule antagonist of programmed death ligand-1 (PD-L1) in the immuno-oncology field and an orally-available small molecule inhibitor of Interleukin-1 receptor-associated kinase 4 (IRAK4) in the precision oncology field. Curis expects to exercise its option to obtain exclusive licenses to both programs and file IND applications for a development candidate from each in 2015.

Addressing immune checkpoint pathways is a well validated strategy to treat human cancers and the ability to target PD-1/PD-L1 and other immune checkpoints with orally available small molecule drugs has the potential to be a distinct and major advancement for patients. Recent studies have also shown that alterations of the MYD88 gene lead to dysregulation of its downstream target IRAK4 in a number of hematologic malignancies, including Waldenström's Macroglobulinemia and a subset of diffuse large B-cell lymphomas, making IRAK4 an attractive target for the treatment of these cancers.

In connection with the transaction, Curis has issued to Aurigene approximately 17.1 million shares of its common stock, or 19.9% of its outstanding common stock immediately prior to the transaction, in partial consideration for the rights granted to Curis under the collaboration agreement. The shares issued to Aurigene are subject to a lock-up agreement until January 18, 2017, with a portion of the shares being released from the lock-up in four equal bi-annual installments between now and that date.

The agreement provides that the parties will collaborate exclusively in immuno-oncology for an initial period of approximately two years, with the option for Curis to extend the broad immuno-oncology exclusivity.

In addition Curis has agreed to make milestone payments of up to \$205 million for up to four programs, and up to \$140.5 million per additional program, plus specified approval milestone payments for additional indications, if any. Curis has also agreed to pay Aurigene royalties on any net sales ranging from high single digits to 10% in territories where it successfully commercializes products and will also share in amounts that it receives from sublicensees, depending upon the stage of development of the respective molecule.

For the full press release: <http://investors.curis.com/releasedetail.cfm?ReleaseID=892180>

3. TG Therapeutics exercises license option for Rhizen Pharmaceuticals' PI3K-Delta Inhibitor (September 23, 2014)

TG Therapeutics, Inc., a clinical-stage biopharmaceutical company focused on the acquisition, development and commercialization of novel treatments for cancer and autoimmune diseases, announced that it has exercised its option to license the global rights to TGR-1202, a PI3K-delta inhibitor from Rhizen Pharmaceuticals. TG Therapeutics and



Rhizen have to date been jointly developing TGR-1202 in a 50:50 joint venture. Given the successful development of TGR-1202, Rhizen's lead compound initially called RP-5264 and discovered in collaboration with Incozen in Hyderabad, TG Therapeutics elected an early exercise of TG Therapeutics license option. The development of TGR-1202 has progressed very rapidly, having entered the clinic less than two years ago and now being prepared for Phase 3 clinical trials.

In exchange for the global license, Rhizen received a one-time, upfront cash payment of \$4.0 million and approximately 370,000 shares of TG Therapeutics' common stock. TG Therapeutics received exclusive worldwide rights, excluding India, for the development and commercialization of TGR-1202 for all indications. Rhizen will be eligible to receive regulatory filing, approval and sales based milestones in the aggregate of up to \$240 million, and tiered royalties based on net sales.

To access the full press release:

<http://ir.tgtherapeutics.com/releasedetail.cfm?ReleaseID=872084>

Note: Rhizen Pharmaceuticals is a biotechnology company with Indian founders, headquartered in Switzerland, which develops novel treatments for oncology and inflammation discovered in collaboration with Incozen Therapeutics, a research stage company based in Hyderabad.

4. Orion Corporation and Aurigene announce research, collaboration and option agreement for rights to Aurigene's epigenetics program (June 24, 2014)

Orion Corporation, a Finnish pharmaceuticals company and Aurigene have entered into an option and research & collaboration agreement for rights to Aurigene's Pan BET and Selective BET Bromodomain inhibitors program.

Under the terms of the Option Agreement, Aurigene will receive an upfront payment from Orion, followed by a licensing fee, milestones and royalties upon exercising the option at the Candidate selection stage for the BET inhibitors. Orion will collaborate with Aurigene and fund the selective BET program at Aurigene, with Aurigene being eligible for development phase milestones and royalties. Aurigene and Orion have worked together in a number of programs over the past several years, with some of our early collaborations having reached the clinical development phase recently.

Aurigene has been working in the Bromodomain space, for development of pan-BET and selective BET therapeutics, since early 2012. Aurigene's BET inhibitors, developed from a novel chemotype, have demonstrated a unique binding mode leading to a differentiated pharmacological profile that may offer a superior therapeutic window. Selective BET inhibitors under development at Aurigene will be profiled extensively in oncology and other potential indications.



For the full press release: <http://aurigene.com/news/aurigene-and-orion-corporation-announce-research-collaboration-and-option-agreement-for-rights-to-aurigenes-epigenetics-program-for-pan-bet-and-selective-bet-bromodomain-inhibitors/>

5. Boehringer Ingelheim and Connexios Life Sciences enter agreement for novel AMPK activators (May 6, 2014)

Connexios Life Sciences, a Bangalore based biotechnology company, and Boehringer Ingelheim enter an exclusive global research collaboration agreement for AMPK agonists for the treatment of patients with Type 2 Diabetes. As part of the agreement, Boehringer Ingelheim obtains global rights to CNX-012, Connexios Life Sciences' program on AMPK activators. The program includes CNX-012-570 and other compounds in early pre-clinical development. Boehringer Ingelheim will be responsible for all further development and commercialization of the candidates from the AMPK program. Further terms and financial details were not disclosed.

CNX-012-570 is the lead candidate from the Connexios program of AMPK activators that directly activate specific isoforms of the protein, designed and selected to bring about a robust impact on the cellular energetics and redox balance across key cell types and tissues. Connexios has shown beneficial outcomes from target modulation across the liver, muscle, adipose and other relevant tissues in preclinical studies across several animal models of disease. The CNX-012 program comprises several CNX-012-570 analogs which cover a wide chemistry and patent space.

To access the full press release: http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2014/06_may_2014_connexios.html#

6. Pierre Fabre Medicaments and Aurigene enter a licensing agreement in immunology (February 12, 2014)

Aurigene and Pierre Fabre entered a collaborative license, development and commercialization agreement granting Pierre Fabre global worldwide rights, excluding India, to a new immune checkpoint modulator, AUNP-12 targeting the PD-1 pathway. With this agreement, Pierre Fabre are reinforcing their oncology portfolio which already enjoys a combination of chemotherapies, monoclonal antibodies and immuno-conjugates assets at various development phases.

AUNP-12 offers a breakthrough mechanism of action in the PD-1 pathway compared to other molecules currently in development in the highly promising immune therapy cancer space. AUNP-12 is the only peptide therapeutic in this pathway and could offer more effective and safer combination opportunities with emerging and established treatment regimens.



Under the terms of this agreement, Aurigene will receive an upfront payment from Pierre Fabre. Aurigene will also receive additional milestone payments based upon the continued development, regulatory progresses and commercialization of AUNP-12.

For the full press release: <http://www.pierre-fabre.com/en/news/immuno-oncology-licensing-agreement-between-aurigene-and-pierre-fabre-pharmaceuticals>

For an earlier analysis of patents and chemical structures related to AUNP-12, including peptidomimetics and other small molecules:

http://www.differding.com/data/AUNP_12_A_novel_peptide_therapeutic_targeting_PD_1_immune_checkpoint_pathway_for_cancer_immunotherapy.pdf

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More details on this report, and on drug discovery and development in India in general are available from:

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