

EMERGING COMPANY PROFILE

HERCULES' IDO ALTERNATIVE

BY STEPHEN HANSEN, ASSOCIATE EDITOR

Hercules Pharmaceuticals B.V. is developing an inhibitor of aryl hydrocarbon receptor that taps into the same pathway as IDO and TDO inhibitors but could improve upon their tolerability while delivering similar efficacy. Improved tolerability could be a benefit when used in combination with other immunotherapies.

According to CEO Bart Wuurman, aryl hydrocarbon receptor (AHR) is a key component of the tryptophan metabolism signaling pathway, which includes indoleamine 2,3-dioxygenase (INDO; IDO) and tryptophan 2,3-dioxygenase (TDO2; TDO).

In cancer, both IDO and TDO mediate tryptophan catabolism to generate kynurenine, which in turn leads to chronic activation of AHR. Activated AHR increases Treg activity in the tumor environment, suppressing the antitumor immune response.

At least eight companies are developing inhibitors of IDO or TDO, with at least five candidates in the clinic. The lead compounds are in Phase II testing and have reported encouraging early data.

In November, [Incyte Corp.](#) reported Phase I/II data for the IDO1 inhibitor epacadostat that showed a disease control rate of 74% and an objective response rate (ORR) of 53% in 19 evaluable melanoma patients who also received [Merck & Co. Inc.](#)'s anti-PD-1 mAb Keytruda pembrolizumab.

Last month, [NewLink Genetics Corp.](#) reported Phase Ib/II data from 12 evaluable metastatic pancreatic cancer patients that showed the IDO inhibitor indoximod led to an ORR of 42% when given in combination with gemcitabine and [Celgene Corp.](#)'s Abraxane nab-paclitaxel.

Epacadostat and indoximod were well tolerated, but Wuurman thinks an AHR inhibitor could be even better tolerated. The reason is that IDO and TDO are widely expressed in many healthy and malignant tissues, while AHR is 50x overexpressed in tumor cells compared with normal tissue. Wuurman said *in vitro* data have shown the more aggressive the tumor type, the higher the expression levels of AHR.

HERCULES PHARMACEUTICALS B.V.

Amsterdam, the Netherlands

Technology: Small molecule inhibitors of aryl hydrocarbon receptor (AHR)

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2013 by David Sherr and Drug Discovery Factory (DDF)

University collaborators: [Boston University](#)

Corporate partners: None

Number of employees: 3

Funds raised: None

Investors: None

CEO: Bart Wuurman

Patents: None

He noted that a better tolerability profile may be particularly important in combination studies with immunotherapy drugs that have their own significant toxicities, such as [Bristol-Myers Squibb Co.](#)'s Yervoy ipilimumab. Yervoy's label includes a black box warning for immune-mediated adverse reactions, including hepatotoxicity.

Hercules has not yet published preclinical data for its lead AHR inhibitor, CB7993113. But according to co-founder and CSO David Sherr, the compound has shown no signs of toxicity in a highly sensitive embryo zebrafish model and in mouse xenograft models of various cancer types treated with increasing doses over a six-week period.


Sherr added that data from a mouse xenograft model of oral cancer showed that 90% of animals treated with CB7993113 survived vs. only 25% of animals treated with placebo at 28 days.

"In some of these experiments we are doing xenografts of tumors where mice actually begin to gain weight toward the end as the tumor gets under control," he said.

He said additional preclinical data show that inhibiting AHR can resensitize tumors to traditional chemotherapy, block cancer cell metastasis and prevent the generation of cancer stem cells.

Hercules is funding preclinical development with €3.5 million (\$3.8 million) in European grants.

The biotech is aiming to raise at least €14 million (\$15.2 million) in a series A round to fund development through Phase IIa testing. The company expects CB7993113 to enter the clinic next year for triple-negative breast cancer, oral cancers, glioblastoma or pancreatic cancer.

Wuurman said he isn't aware of any other companies developing an AHR inhibitor. The company licensed exclusive, worldwide rights to CB7993113 from [Boston University](#), which received an equity stake in Hercules in the deal. 

COMPANIES AND INSTITUTIONS MENTIONED

Boston University, Boston, Mass.

Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.

Celgene Corp. (NASDAQ:CELG), Summit, N.J.

Hercules Pharmaceuticals B.V., Amsterdam, the Netherlands

Incyte Corp. (NASDAQ:INCY), Wilmington, Del.

Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.

NewLink Genetics Corp. (NASDAQ:NLNK), Ames, Iowa

REFERENCES

Lou, K.-J. "Much ado about TDO." *SciBX: Science-Business eXchange* (2011)

Quintana, F. and Sherr, D. "Aryl hydrocarbon receptor control of adaptive immunity." *Pharmacological Reviews* (2013)

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