agenusnews

Innovation Is Key To Outpacing Obsolescence

Having established clinical activity of our anti-PD-1 and anti-CTLA-4 programs, our scientists are sprinting to discover curative combinations. Agenus discovery platforms have delivered 5 INDs in 2016-17 and 3 more so far this year. We are also on track to file 3 additional INDs by year end and 2 more in 1H 2019. This would make a total of 13 INDs in ~3 years, an I-O industry record. To learn HOW, check out Issue 4.

Our discovery engines, along with our clinical, biological and technical expertise, helps us discover and develop optimal drug candidates. Our translational science helps us identify which patients are not likely to respond to today's drugs. In this issue, we highlight how our ability to innovate is expected to deliver transformative immunotherapy to patients unresponsive to today's treatments.

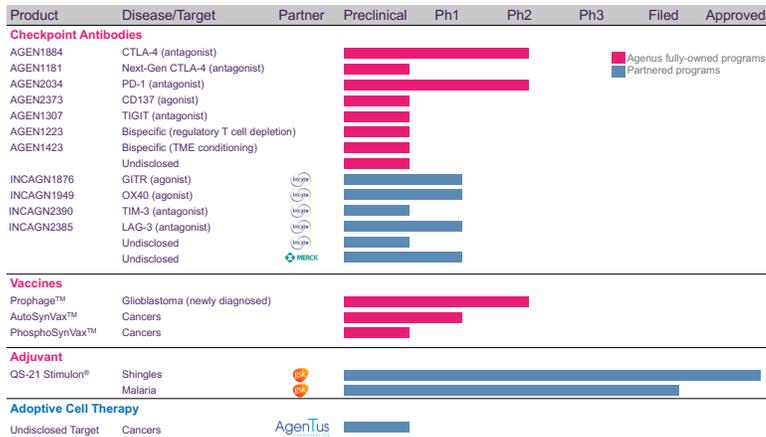## OUR Next-Gen I-O Antibodies Drive Enhanced Functionality

Old dog, new tricks

Artwork by Jeremy Waight, Agenus Principal Scientist

Agenus is pushing the boundaries of cancer immunotherapy. Our first generation anti-CTLA-4 (AGEN1884) and anti-PD-1 (AGEN2034) antibodies have generated impressive clinical responses BUT our next-generation antibodies are designed to generate responses in wider numbers of patients. They feature unprecedented antitumor functions in experimental models. While it is well established that anti-CTLA-4 antibodies block co-inhibitory receptors on immune cells, Agenus scientists have discovered a new mechanism of action in which a specialized domain of the antibody engages with receptors on other immune cells to significantly bolster antitumor immunity. This new insight has enabled Agenus to engineer a next-generation anti-CTLA-4 antibody (AGEN1181) with enhanced tumor fighting abilities. Going beyond anti-CTLA4, Agenus scientists have employed this novel discovery to develop a pipeline of next-generation antibodies. Thus, by unlocking new biological mechanisms of well-established immuno-oncology targets, Agenus has created a diverse set of best-in-class antibodies.

OUR Rationally Designed Pipeline Enables Transformative Combinations

Product	Disease/Target	Partner	Preclinical	Ph1	Ph2	Ph3	Filed	Approved
Checkpoint Antibodies								
AGEN1884	CTLA-4 (antagonist)							
AGEN1181	Next-Gen CTLA-4 (antagonist)							
AGEN2034	PD-1 (antagonist)							
AGEN2373	CD137 (agonist)							
AGEN1307	TIGIT (antagonist)							
AGEN1223	Bispecific (regulatory T cell depletion)							
AGEN1423	Bispecific (TME conditioning)							
	Undisclosed							
INCAGN1876	GITR (agonist)	Incyte						
INCAGN1949	OX40 (agonist)	Incyte						
INCAGN2390	TIM-3 (antagonist)	Incyte						
INCAGN2385	LAG-3 (antagonist)	Incyte						
	Undisclosed	Incyte						
	Undisclosed	MERCK						
Vaccines								
Prophage™	Glioblastoma (newly diagnosed)							
AutoSynVax™	Cancers							
PhosphoSynVax™	Cancers							
Adjuvant								
QS-21 Stimulon®	Shingles	GSK						
	Malaria	GSK						
Adoptive Cell Therapy								
Undisclosed Target	Cancers	AgenTus						

■ Agenus fully-owned programs
■ Partnered programs

Notes: AGEN1884 and AGEN2034 are being evaluated in 2L cervical cancer and undisclosed tumors
Recepta Biopharma S.A. has exclusive rights to AGEN1884 and AGEN2034 in Brazil and five other South American countries

See Agenus' Diverse Pipeline [here](#).

Agenus' industry-leading immunotherapy pipeline features vaccines, adjuvants, immunomodulatory and tumor microenvironment modifying antibodies. The strength of our pipeline, which includes first-in-class / best-in-class assets and our ability to devise custom combination therapies from our own pipeline, is expected to drive our ability to meet individual patients' needs.

Recognizing the complexity of the tumor-immune microenvironment, Agenus scientists have leveraged our innovative internal discovery and translational platforms and powerful algorithms to develop a toolkit of molecules that are intended to address key aspects of antitumor immunity. This involves bolstering immune response and recharging exhausted immune cells. For example, our cancer vaccines educate a patient's immune system to fight tumor cells, but the benefit doesn't end there. Once patients mount an antitumor response, it is further enabled by other molecules in our toolkit, including foundational antibodies targeting PD-1 (AGEN2034) and CTLA-4 (AGEN1884).

To further improve patient response rates, Agenus scientists are developing first-in-class and best-in-class therapies intended to address mechanisms of immune evasion and therapeutic resistance. These include "multi-specific" antibodies that are designed to condition the tumor microenvironment and augment the activity of immune cells. We are on track to file INDs on two of these novel assets by end of 2018. With this diverse pipeline, Agenus is uniquely positioned to potentially deliver combination therapies that will enhance response rates and treat patients who are unresponsive to current immunotherapies.

OUR Algorithms Help Us Discover New Targets and Optimize Clinical Development

The landscape of immuno-oncology is rapidly evolving. First generation agents are maturing. BUT Agenus' next wave of immunotherapy targets and agents have the potential to substantially expand the population of patients who can benefit. Our innovative discovery platforms leverage advanced gene editing, sequencing, and single cell technologies to define novel pathways that can be targeted to boost antitumor immunity. These platforms are delivering thousands upon thousands of data points, which are fed into sophisticated algorithms to model complex phenotypes of T cells in the tumor microenvironment. These models help us predict potential responses to new treatments and define biomarker signatures, which we expect to lead to safer and more informative clinical trials. Ultimately, the data we collect from clinical trials will be fed back into our algorithms, which should strengthen our predictive models and lead to optimized patient outcomes over time.

The Agenus Innovation Engine is organized to use cutting-edge technology and data mining to understand patient to patient differences, tumor heterogeneity, and the immune system. We recognize that many tumors have escape mechanisms to evade current therapies. We have identified targets intended to prevent escape. We continue to design, optimize and manufacture mono- and bi-specific antibodies and vaccines against these targets that we are advancing into clinical trials as monotherapies and in combination with our pipeline of drugs.