



**One-two Punch to Deadly
Pancreatic Cancer: Targeted
Therapy with Mab AR9.6 and
Rapamycin Analogue ACP 2127**

AmrutBio

Jan 2016

AmrutBio Overview

- A subsidiary of Quest PharmaTech, a publicly traded (QPT-TSXV), Canadian pharmaceutical company
- Lead product (Mab AR9.6) under development is for a novel target for cancer therapy discovered at University of Nebraska Medical Center; **Target: truncated O-glycans on MUC16**
- Second product (ACP2127) under development is for a well established target for cancer treatment; **Target: CDK/mTOR**

AmrutBio Overview Continued

- Combinatorial approach for optimal efficacy
- Diversified Product Pipeline with two proprietary technologies
- Experienced management and scientific team
- Access to academic and clinical expertise
- Funding required for product development and clinical trials

Management and Scientific Team

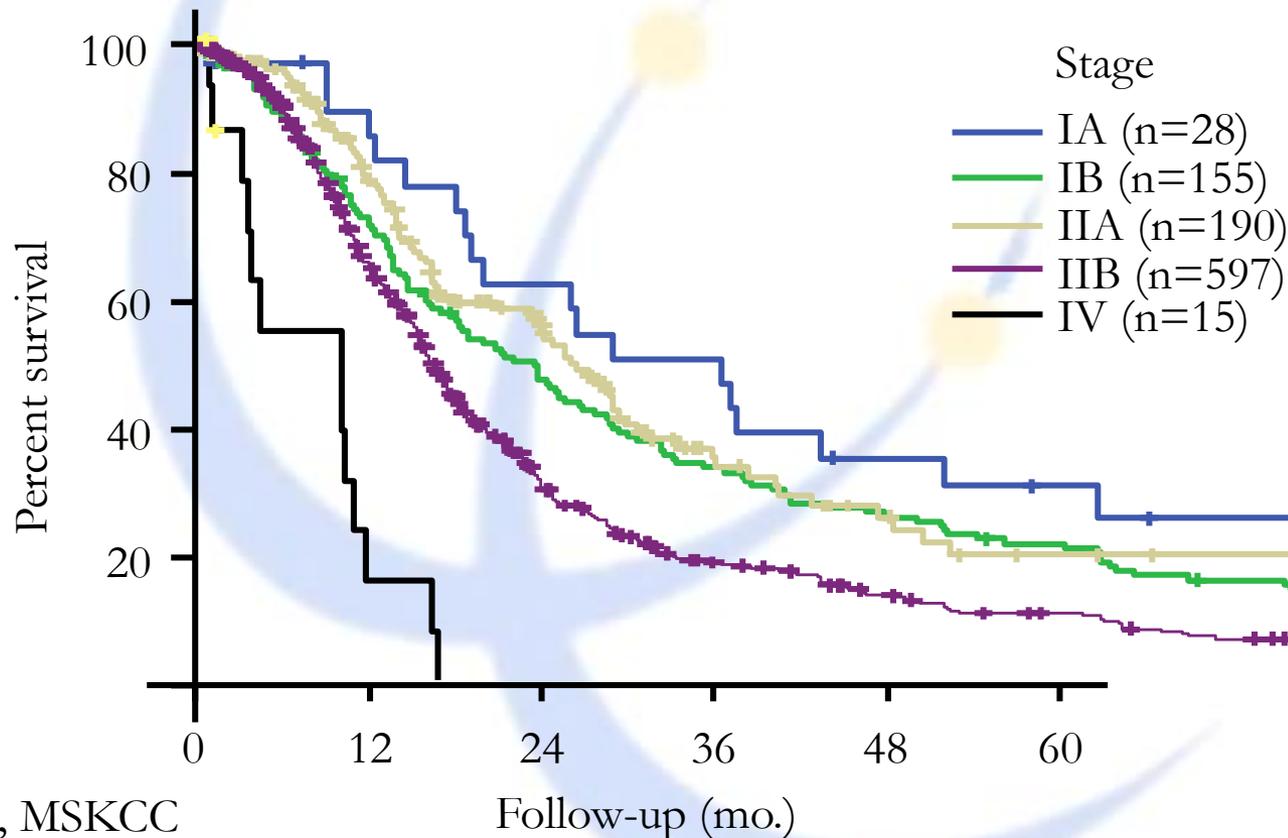
- **Madi R. Madiyalakan Ph.D**, Successful public company CEO, 25 + years Oncology experience
- **Tony Hollingsworth Ph.D**, Chief Scientific Officer, Professor, UNMC
- Selvaraj Naicker Ph.D, Chief Chemist
- **Prakash Radhakrishnan Ph.D**, Director of R & D, Research Assistant Professor, UNMC
- **Chris Nicodemus M.D.. FACP**, Chief Medical Officer, President, AIT Strategies
- **Pierre Vermette CA**, CFO, 20 + years experience - Regulatory and Corporate Finance

Company Directors

- Lorne Meikle, B.Econ
- Ian McConnan, FCA
- Eric Shi, Ph.D.
- Shawn Lu, MBA
- Madi Madiyalakan, Ph.D.

Pancreatic cancer: A problem

Overall survival for resected patients with pancreatic cancer
(MSKCC surgical database: 1983 – 2005, n =985) (PDA has a five year
Survival of only ~6% - Saif, 2013)



First Punch: Mab AR9.6

Binds to truncated O-glycans on MUC16 mucin (PCT patent pending)

Mucins are expressed by most adenocarcinomas

Biomarkers CA19-9 and CA125 are mucins

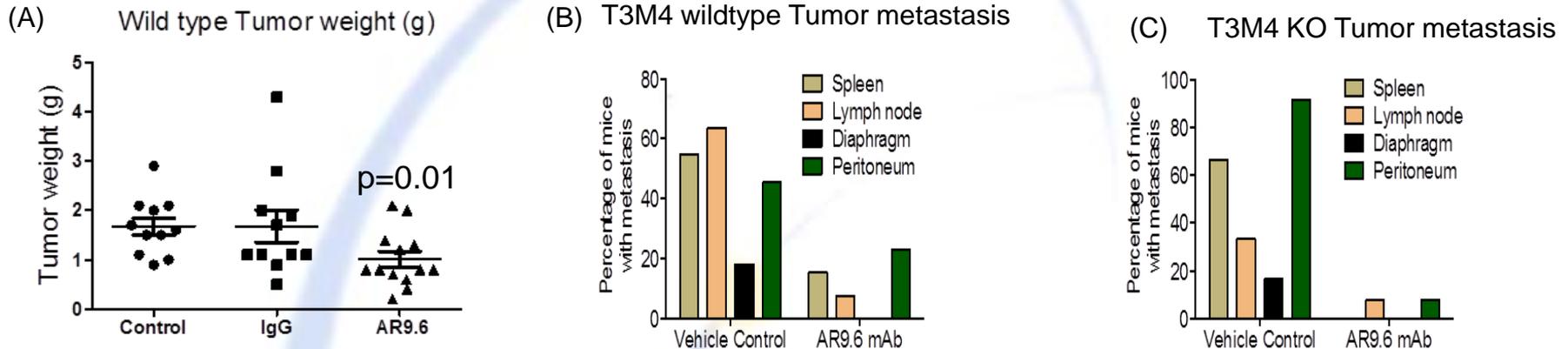
Most other longstanding biomarkers for cancer (CEA, AFP, others) are glycoproteins

Pathologists consider mucin expression to be a sign of a “bad” tumor

Aberrant glycoforms of MUC16 create biologically active compounds that contribute to tumor aggressiveness

- ❑ MUC16 is a membrane bound, heavily glycosylated cell surface glycoprotein, expressed in certain normal cells; however, its expression is often upregulated in malignant tumors that also produce circulating soluble forms of MUC16.
- ❑ Aberrant expression of membrane mucin MUC16 is associated with tumor progression and metastasis of ovarian and pancreatic and liver cancer.
- ❑ The oncogenic interaction between MUC16 and mesothelin (tumor differentiation factor) increases invasive properties of pancreatic cancer cells.
- ❑ A recent study also showed that overexpression MUC16 increases breast cancer cell proliferation via stimulation of Janus Kinase 2 (JAK2).
- ❑ Truncated O-glycans on MUC16 facilitate interaction between these glycoprotein and HER2 receptors and activate downstream p13/Akt oncogenic signaling cascade.
- ❑ These reports strongly suggest that MUC16 plays a major role in tumor progression and metastasis through interaction with oncogenic modulators.
- ❑ Treatment of cancer cells with Mab AR9.6 significantly reduced the phosphorylation of Akt and FAK compared to control antibody.

Mab AR9.6 Treatment: T3M4 Cells tumor growth and metastasis



We examined the *in vivo* therapeutic efficacy of AR9.6 mAb in an orthotopic pancreas tumor model system. T3M4 wildtype and SC cells tumor bearing animals (n=15/group) were randomized to receive treatment with PBS (control), IgG (500 μ g; Isotype control) and AR9.6 mAb (500 μ g) i.p for four times with a four days interval.

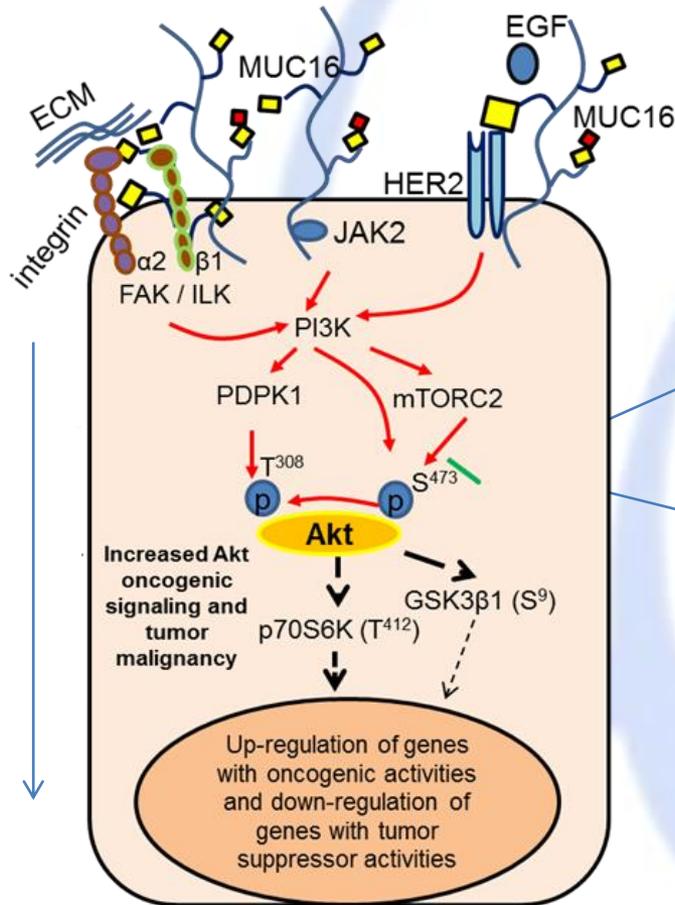
Treatment of T3M4 wildtype tumor bearing animals with AR9.6 mAb showed a significantly reduced tumor growth (by tumor weight (g)) (p=0.01) (A) and metastases to spleen (15.34%, p=0.04), lymph nodes (7.69%, p=0.003) and no metastasis to diaphragm as compared to vehicle control treatment (B).

Treatment of T3M4 SC tumor bearing animals with AR9.6 mAb showed a significantly reduced tumor metastasis to peritoneum (p<0.0001), no metastasis to spleen and diaphragm (p<0.0001) as compared to vehicle control treated animals (C). There were no detectable changes in tumor growth of T3M4 SC tumor bearing animals with different treatment conditions (data not shown).

In summary, our data show that AR9.6 mAb treatments significantly reduced cell proliferation, *in vivo* tumor growth and metastasis.

Central Hypothesis

We hypothesize that differential glycosylation of MUC16 creates novel ligands for growth factor receptors and integrin complexes, and their interactions facilitate constitutive activation of autocrine and paracrine oncogenic cell signaling pathways, which results in enhanced malignant properties of pancreatic cancer cells or paracrine effects at distant sites.



Secreted Tn-MUC16:
Paracrine signaling
Tumor microenvironment
and distant organ sites
(metastatic and non-
metastatic).

**Confirmation and
validation of oncogenic
functions of Tn-MUC16:**
KPC/Cosmc KO/Muc16 KO
mouse model.

Summary

- ❑ Our results demonstrate that aberrant expression of Tn/STn epitopes on the MUC16/CA125 mucin glycoproteins expose EGF-like and other regions of the protein cores that bind to growth factor receptors (ErbB2), and integrin ($\alpha 2\beta 1$) complexes, which induce activation of oncogenic signaling cascades through Akt and FAK, and in turn increase the malignant potential of pancreatic cancer cells.
- ❑ Treatment of cancer cells with monoclonal antibody AR9.6 block these oncogenic signaling cascades and inhibit *in vivo* tumor growth and metastasis.
- ❑ Akt pathway can also be regulated by Cyclin Dependent Kinases and/or mTOR Inhibitors (second punch)

Cyclin Dependent Kinases (CDK)

- Play a crucial role in the processes of transcription, mRNA processing and cellular differentiation
- can be targeted in order to prevent proliferation of cancer cells
- Inhibition of these kinases has shown induction of apoptosis especially in cancer cells

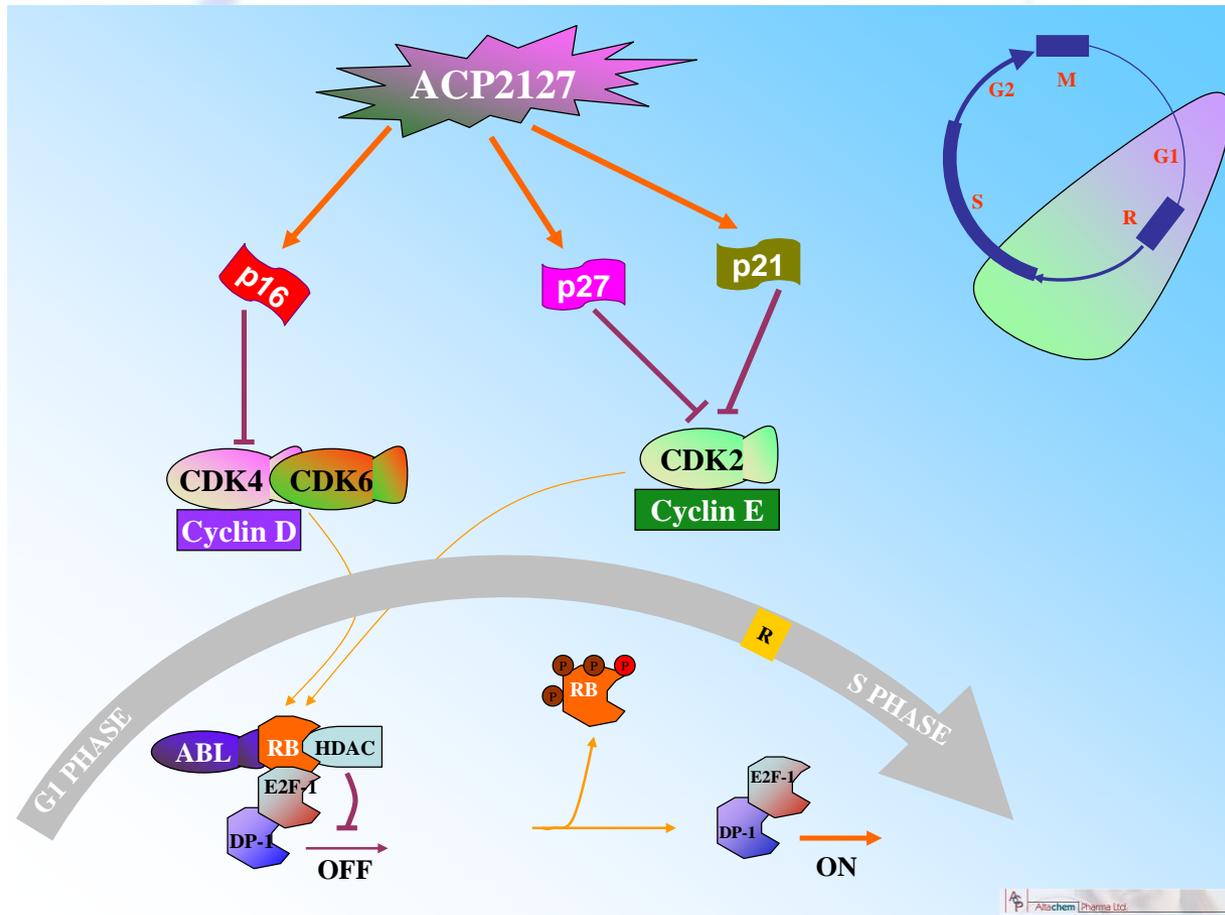
mTOR Pathway (2nd Control)

- The mammalian TOR (mTOR) pathway is a key regulator of cell growth and proliferation
- increasing evidence suggests that its deregulation is associated with human diseases, including cancer and diabetes
- mTOR exists in two multiprotein complexes mTORC1 and mTORC2
- mTORC1 is regulated by numerous signaling pathways, including the PI3K/Akt pathway
- A number of feedback control system in place

ACP2127

- ACP 2127 is a novel immunomodulator with anti-cancer properties targeted to inhibit CDK functionality and prevent the growth of cancer cells.
- More than 40 compounds were synthesized and screened against various human cancer cell line and 3 drug candidates have been selected for further development.

ACP2127 Cell Cycle Inhibition



ACP2127

- Inhibition of growth of various cancer cell-lines.
- Cell-cycle analysis using western blot of various cancer cell lysates confirms G1-S block and apoptosis.
- Induces cancer cells apoptosis at low concentration (50 μ M)
- Inhibition of the mTOR PI3K-AKT pathway

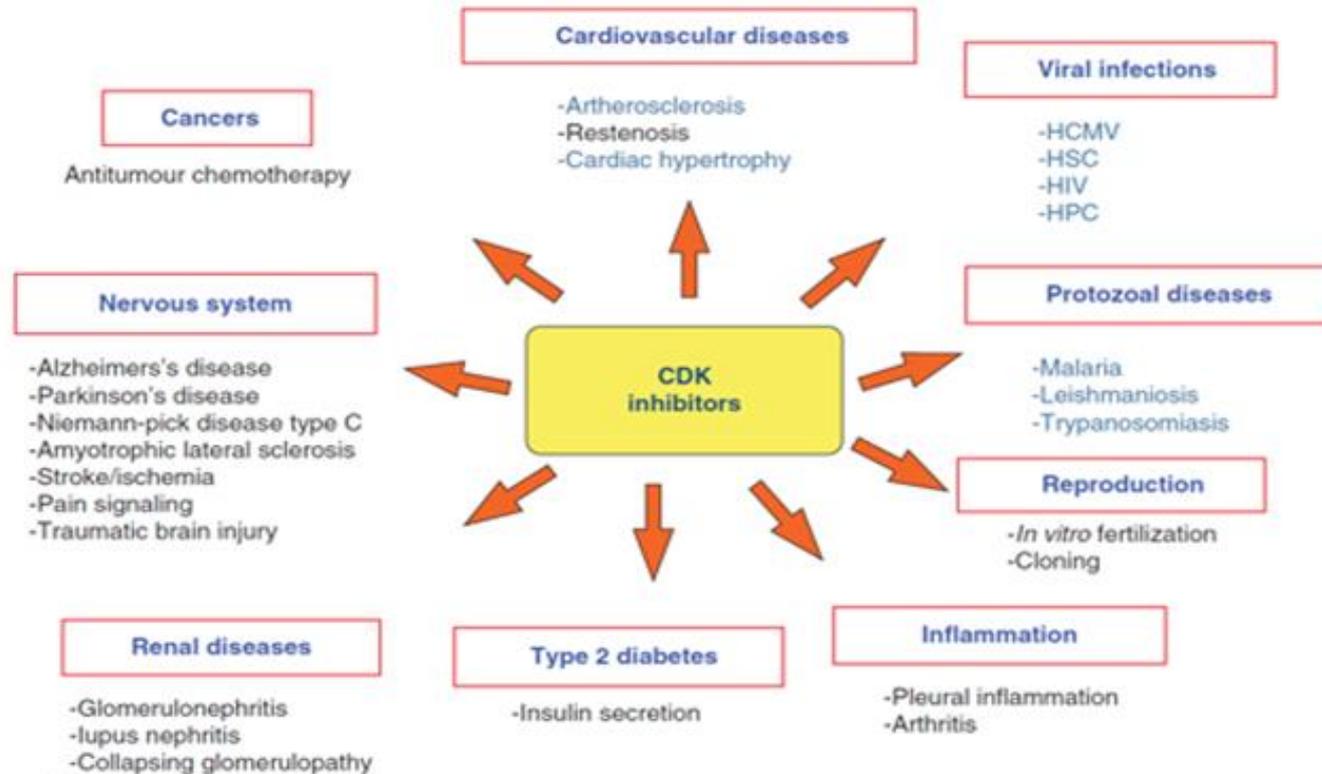
ACP2127

Dual Cell Cycle CDK and mTor Inhibitor

- Multi-functional potential irreversible inhibitor combining the effect of CDK inhibitor p21 and also through additionally inhibiting mTOR in the PI3K-AKT Pathway
- Dual target activity enhance efficacy
- Effective Cancer targets: Pancreatic, colon, leukemia, ovarian and breast
- US Patent Issued:
 - US 7659244 “Rapamycin peptides conjugates: synthesis and uses thereof”

Applications for ACP2127

Therapeutic potential of CDK inhibitors



Competitions (CDK Inhibitors)

Name of Drug	Indications	Status
Dinaciclib (SCH727965)	Breast, NSCLC, chronic Lymphocytic Leukemia refractory chronic lymphocytic leukemia refractory chronic lymphocytic leukemia	Phase 3 study in CLL initiated in 2012
Palbociclib (PD-0332991)	Breast Cancer	Phase II trial completed
LY2835219	Mantle cell lymphoma, NSCLC, and breast cancer.	Phase I
Flavopiridol (Alvocidib)	Acute myelogenous leukemia, chronic lymphocytic leukemia, NSCLC	Development discontinued by Sanofi in 2010
Indisulam (E7070)	Colorectal, breast, gastric cancer, renal cell carcinoma	Completed Phase II study
Seliciclib (CYC202)	chronic lymphocytic leukemia, mantle cell lymphoma, and multiple myeloma, NSCLC	Phase II studies ongoing

Competition (mTor Inhibitors)

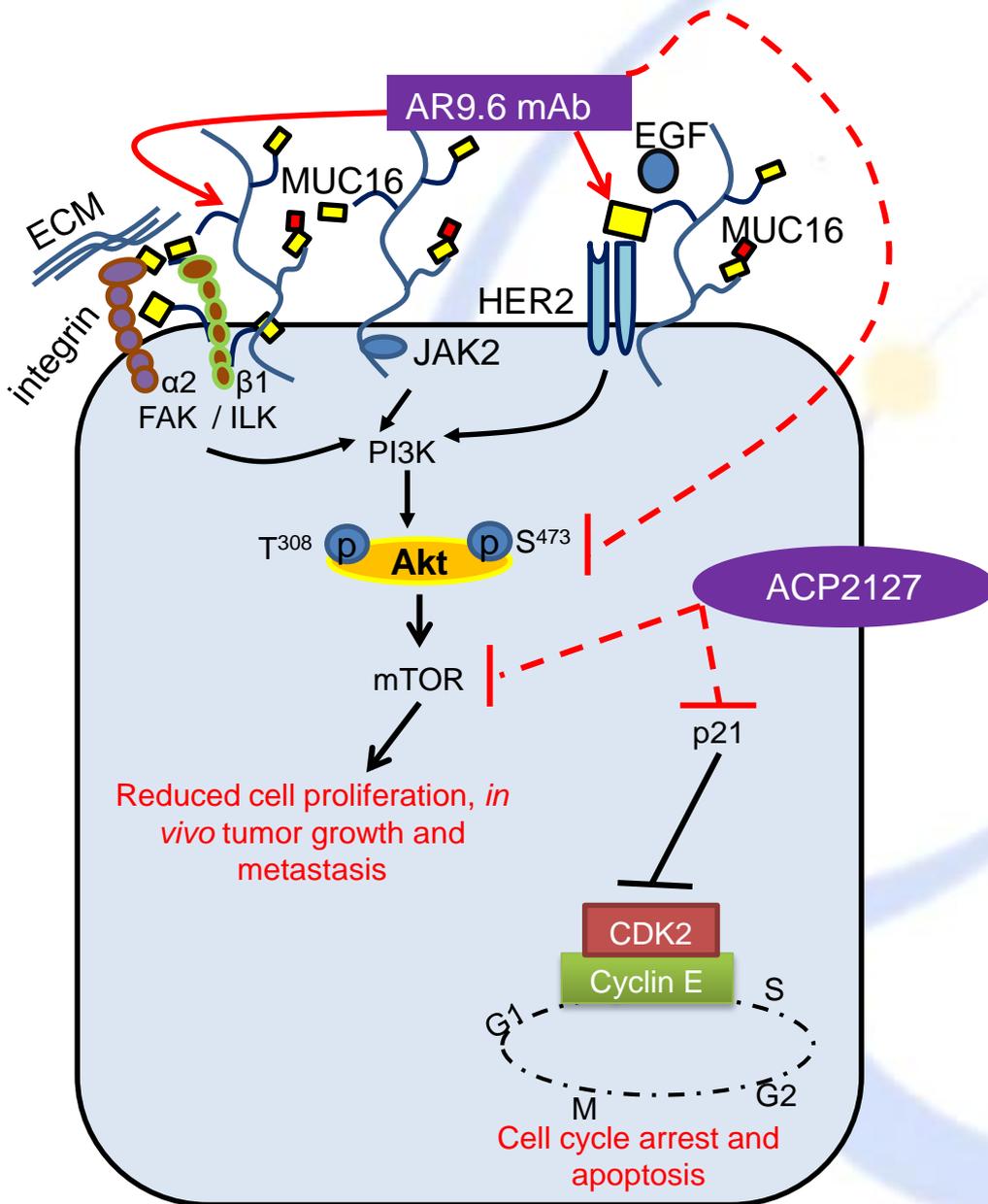
Name of Drug	Indications	Status
TORISEL (Temsirolimus, CCI-779)	Renal cell carcinoma, glioblastoma multiforme, lymphoma, breast and lung cancer	Approved for treatment of advanced renal cell carcinoma in 2007
Afinitor (Everolimus, RAD-001)	Kidney cancer, breast cancer, gastric cancer , hepatocellular carcinoma and lymphoma	Approved for Advanced kidney cancer, Progressive or metastatic pancreatic neuroendocrine tumors not surgically removable, Breast cancer in post-menopausal women with advanced hormone-receptor positive, HER2-negative type cancer, in conjunction with exemestane .
Ridaforolimus (AP23573)	Breast, prostate cancer, sarcoma, and endometrial carcinoma	NDA was not approved by FDA in 2012 for maintenance treatment of metastatic soft tissue or bone sarcoma

Competitive Advantage of ACP2127

ACP2127 is the only drug candidate in development that targets simultaneously two cell cycle regulatory checkpoints for optimal efficacy

- p21 through CDK inhibition
- p13k/AKT through mTOR inhibition

Summary



Treatment of cancer cells with AR9.6mAb binds to MUC16 and blocks the activation of growth factor receptors and thereby inhibit phosphorylation of Akt, which leads to reduced cell proliferation, in vivo tumor growth and metastasis.

Treatment of cancer cells with ACP2127 inhibits the activation of Akt downstream target mTOR, and p21, leads to reduced cell proliferation, cell cycle arrest and apoptosis.