

Combining Immunotherapy with Nanoparticles for Improved Kidney Cancer Outcomes

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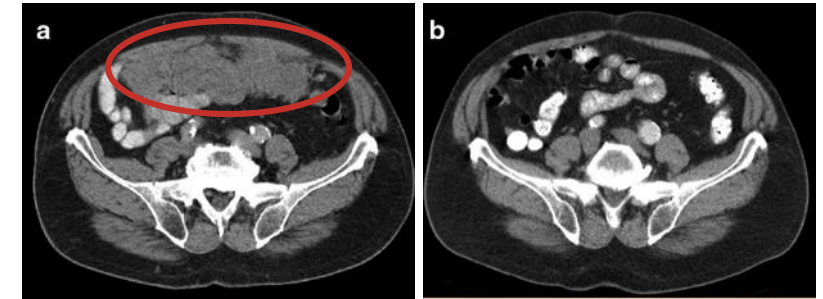
James Graham Brown Cancer Center
University of Louisville, Louisville, KY

Financial Interests: Patents (AS1411, AS1411-GNS); Qualigen, Inc. (licensee & research sponsorship)

Background: A little about me ...

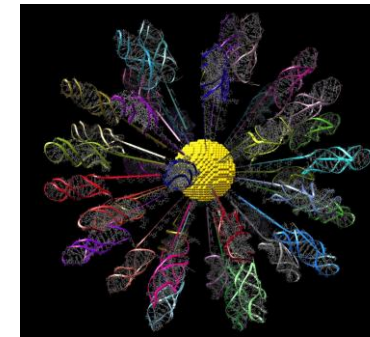
- Interested in **kidney cancer**

Discovery and development of AS1411



- Interested in **nanoparticles**

AS1411-linked gold nanospheres



- Interested in **immunotherapy**

Brown Cancer Center focus & collaborations

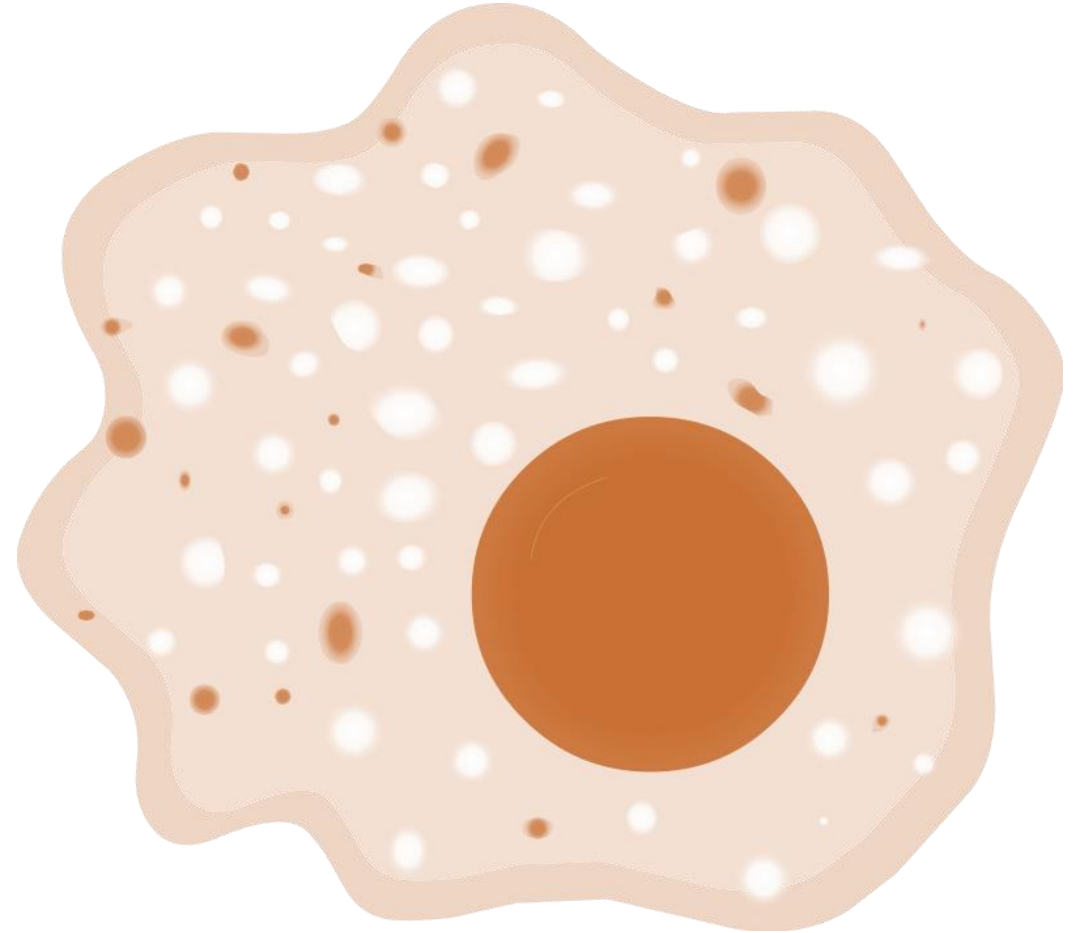


My Idea ...

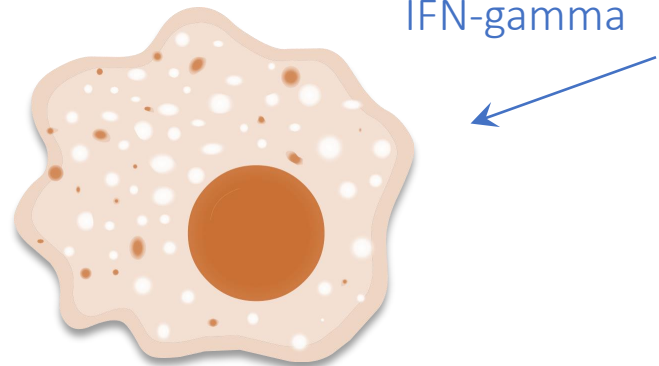


Macrophages

- They like to “eat” nanoparticles!
- Extensive accumulation in tumors (TAMs)
- TAMs correlate with clinical outcomes
- Activation/polarization (M1 or M2) ...



TAMs (tumor-associated macrophages) as Jekyll and Hyde

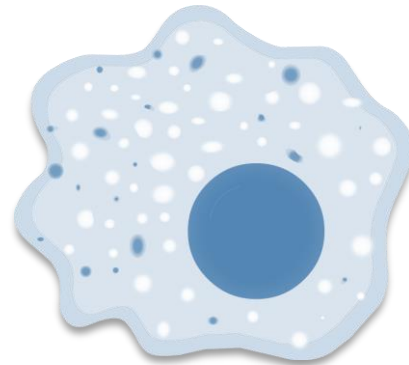


M1 phenotype

Classically activated

Anti-tumor phenotype

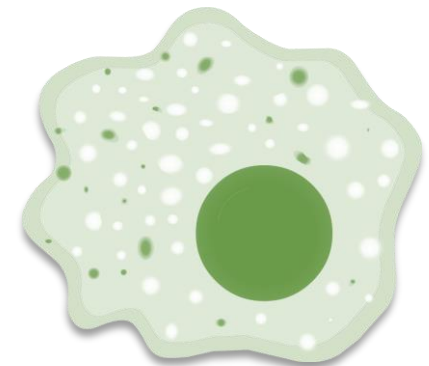
Pro-inflammatory



M0 phenotype

Undifferentiated

IL-4 + IL-10



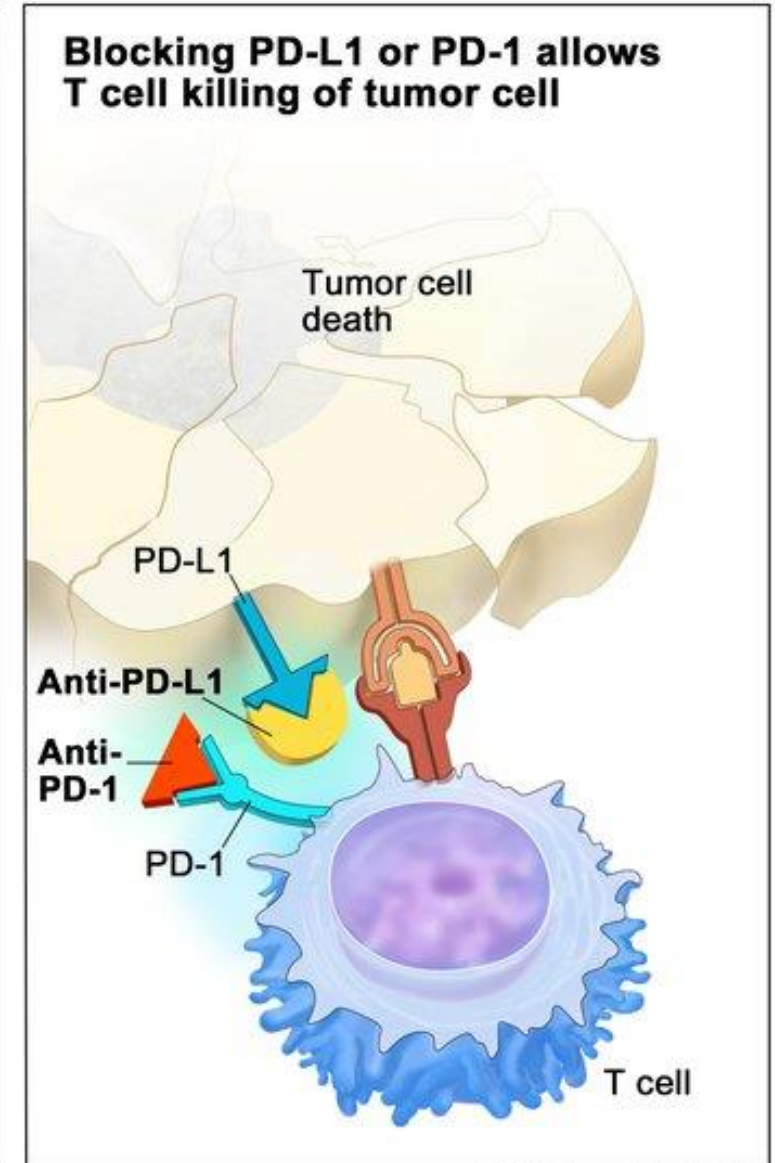
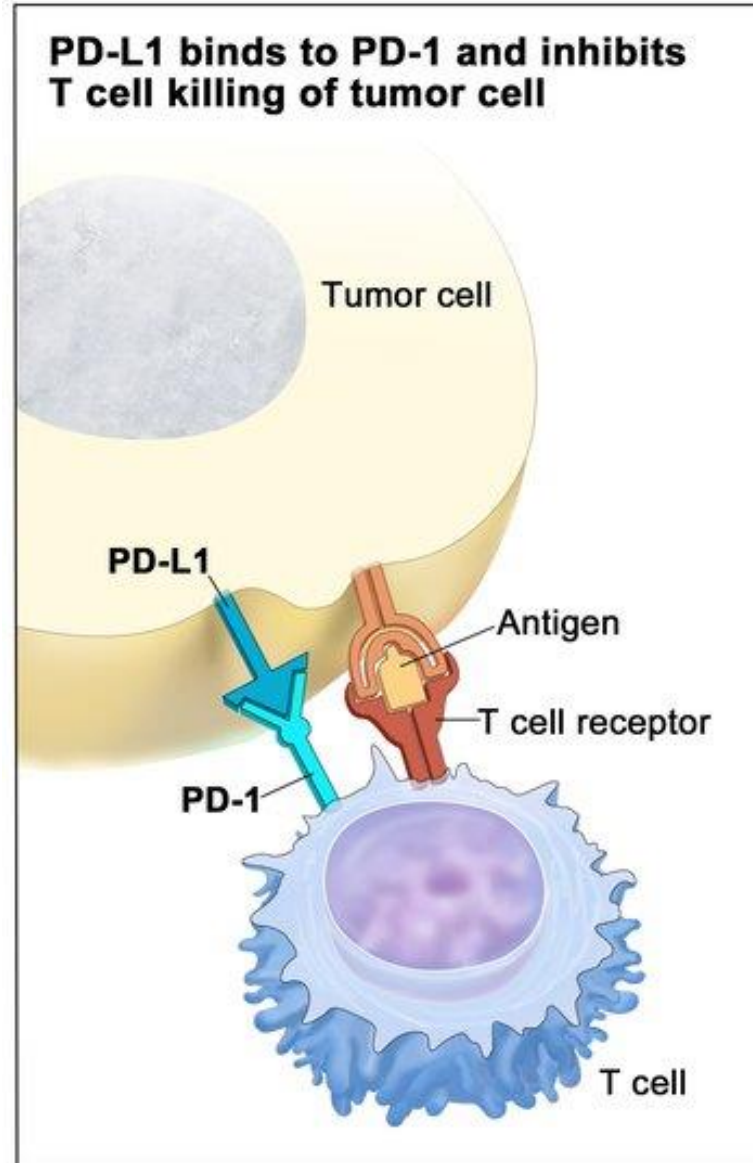
M2 phenotype

Alternatively activated

Pro-tumor phenotype

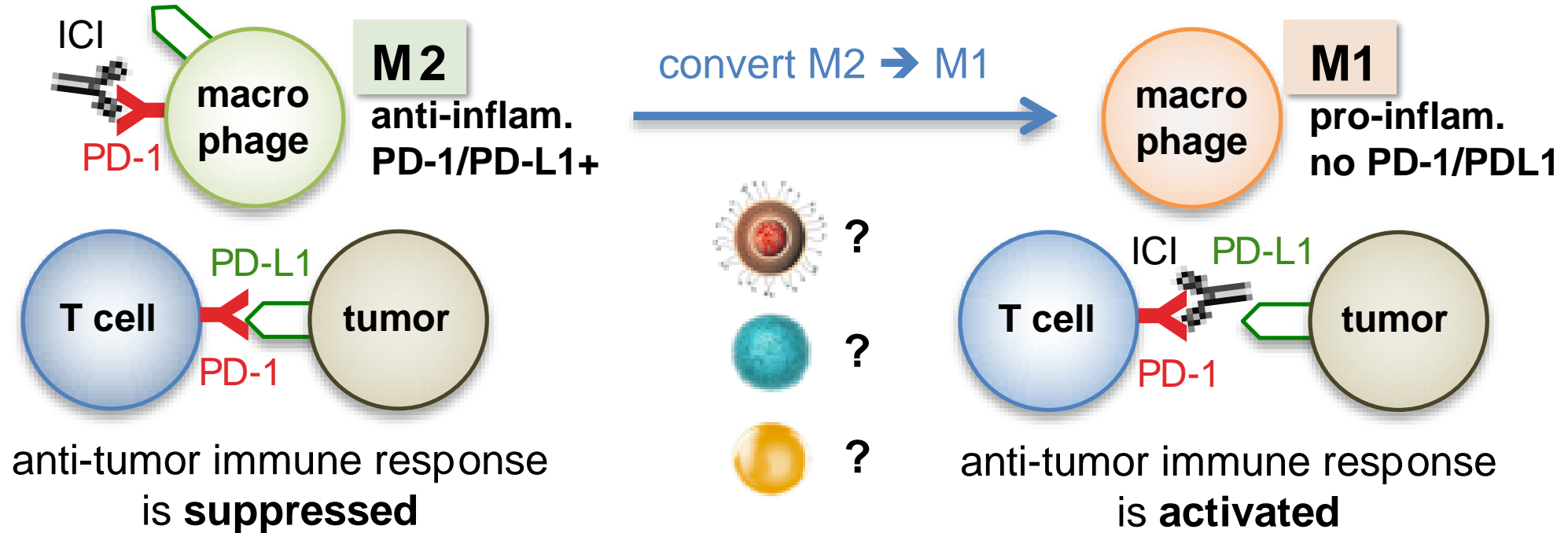
Anti-inflammatory/wound healing

TAMs and response to checkpoint inhibitors



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TAMs and response to checkpoint inhibitors



Can **FDA-approved** nanoparticles repolarize M2 macrophages to M1 and sensitize kidney cancers to checkpoint inhibitors?

TAMs and response to checkpoint inhibitors



Can FDA-approved nanoparticles repolarize M2 macrophages to M1?

Cullis J ... Bar-Sagi D. **Macropinocytosis of Nab-paclitaxel Drives Macrophage Activation in Pancreatic Cancer.** *Cancer Immunol Res.* 2017

Zanganeh S ... Daldrup-Link HE. **Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues.** *Nat Nanotechnol.* 2016

Our Ongoing Experiments

Table 1: Examples of nanoparticles in clinical use

Name	Description	Indication
ferumoxytol	iron oxide NPs	anemia
nab-paclitaxel	albumin-bound paclitaxel	NSCLC, breast cancer
depocyt	liposomal cytarabine	malignant meningitis
doxil	liposomal doxorubicin	several cancers
marqibo	liposomal vincristine	leukemias
visudyne	liposomal verteporfin	eye diseases
onivyde	liposomal irinotecan	pancreatic cancer
daunosome	liposomal daunorubicin	glioblastoma
trikor	fenofibrate nanocrystals	hyperlipidemia
rapamune	sirolimus nanocrystals	immunomodulation
opaxio	polyglutamate-bound paclitaxel	glioblastoma

Screen available nanomedicines for activity in macrophage cell line (M1/M2?)

Test selected nanomedicines in tumor-bearing mice (M1/M2?)

Test in combo with anti-PD1 in mice

Final Thoughts

- I look forward to hearing from kidney cancer experts!
 - animal models, clinical immunotherapy developments, etc.
- Recent approval of anti-PD-L1 + nab-paclitaxel in breast cancer.
 - does macrophage repolarization play a role?
- DOD “Concept Award” mechanism provides valuable opportunities.
 - thank you for supporting W81XWH-18-1-0428