Hot Topic:

# Rethinking Cancer Nano-Theranostics

Neel M. Bardhan & Uyanga Tsedev

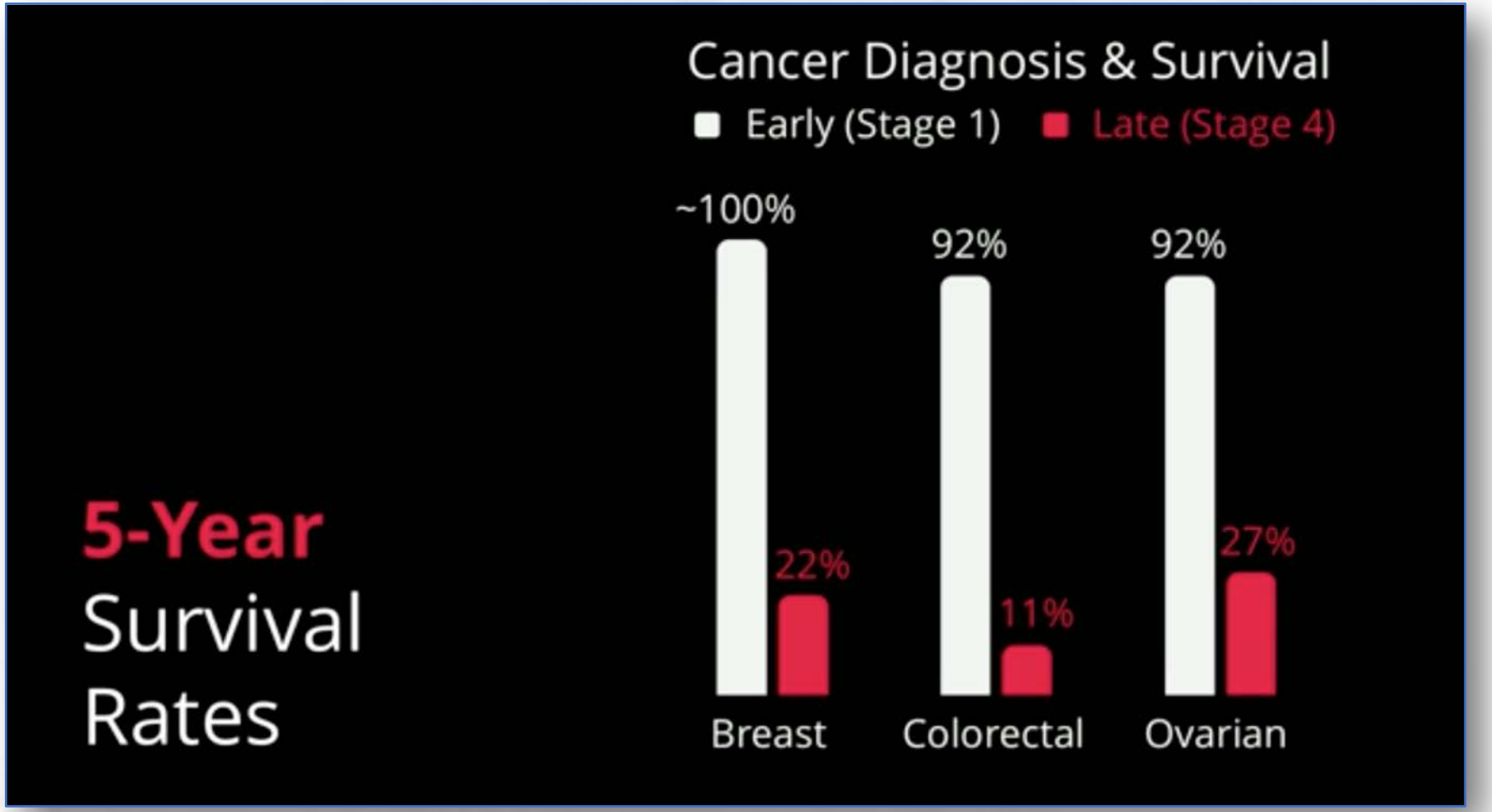
July 17, 2017

MARBLE CENTER FOR CANCER NANOMEDICINE

Small technologies, BIG impact

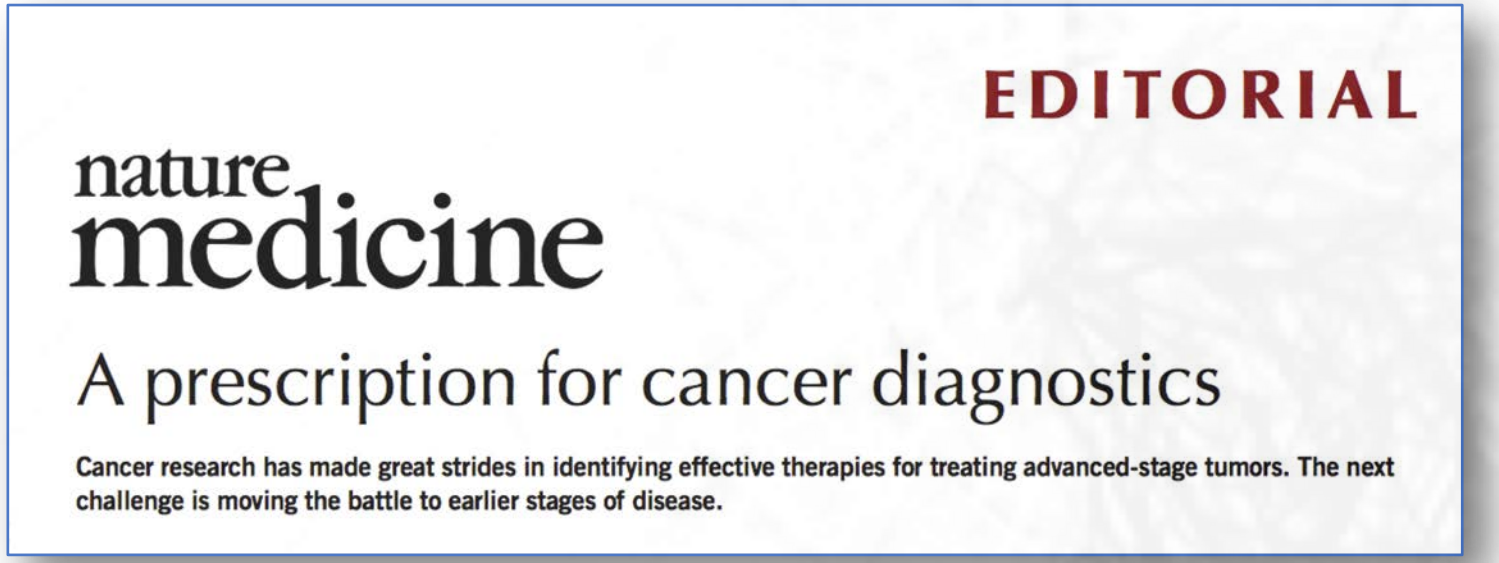
KOCH INSTITUTE for Integrative Cancer Research at MIT

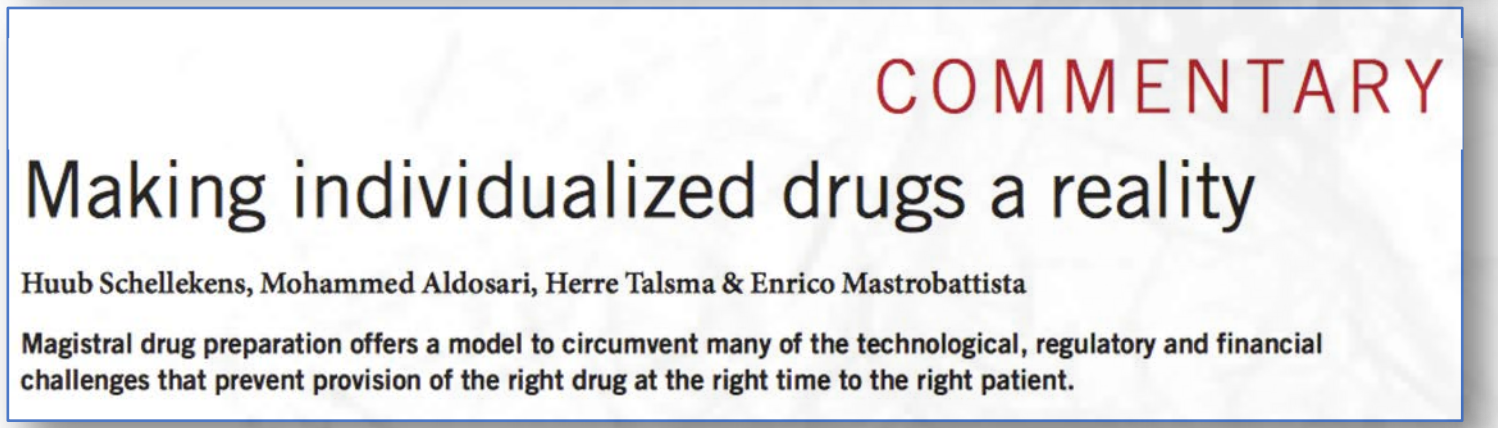
# Developing Early Warning Systems




**Source:** Smith, J. TED Talks (2017)

# Battling Cancer at Earlier Stages of the Disease



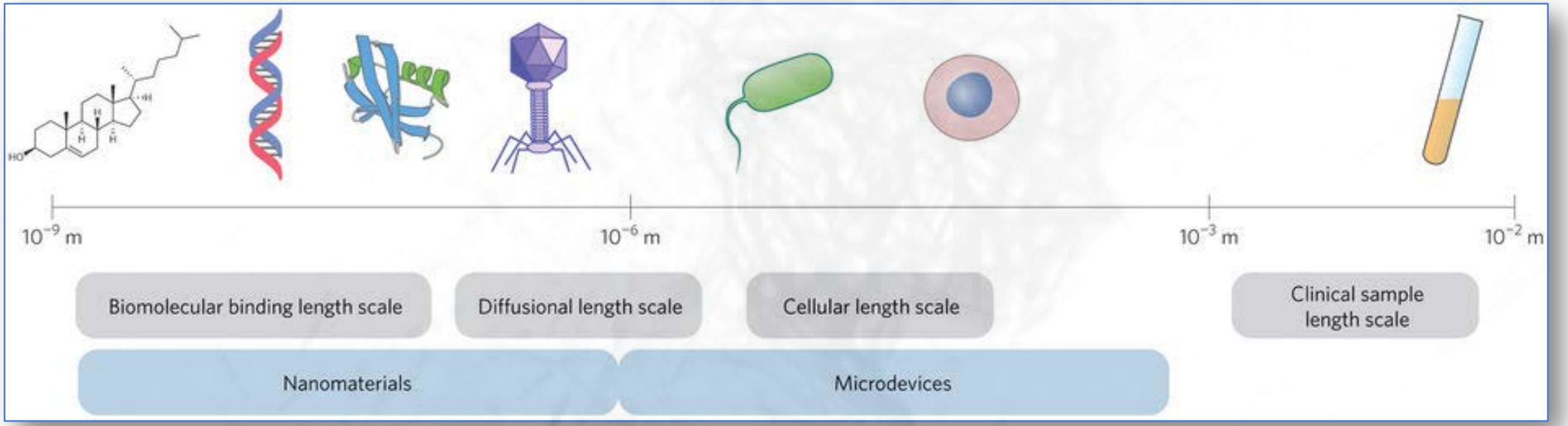

"Precision (or personalized) medicine promises to improve the efficacy and safety of pharmacotherapy for individual patients. But the truth is that precision medicine today is not tailored to individual patients; it is tailored to groups of patients. Precision drugs are tested on groups of patients that share a disease marker but other differences among patients are not taken into consideration…"

**Schellekens, et al. Nature Biotech. (2017)**

**Sources:** Editorial, Nature Medicine (2017) and Schellekens, H. et al. Nature Biotech. (2017)

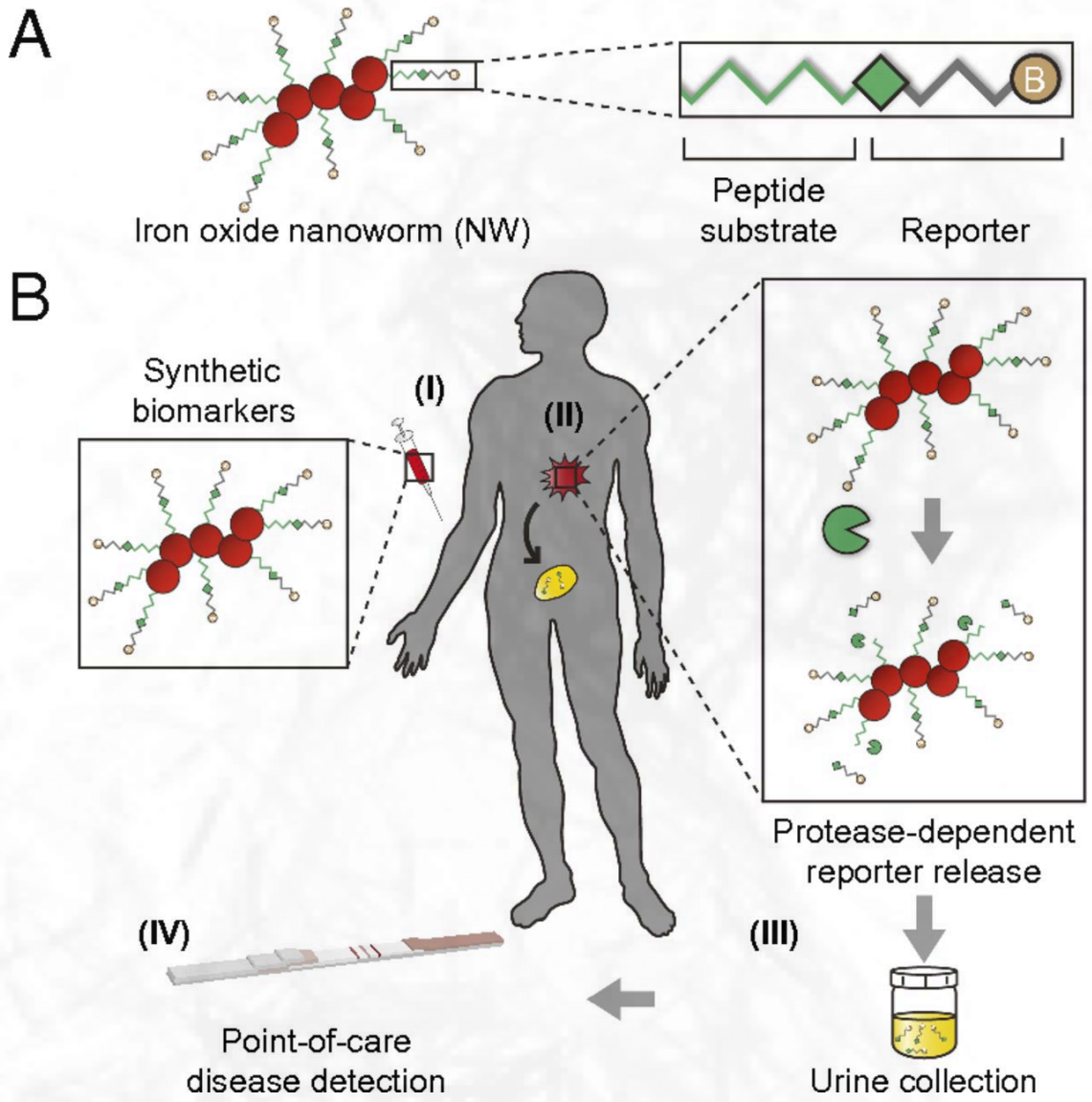
# A Matter of Resolution and Scale

Length scales of interest for biomolecular detection




**Source:** Kelley, O. S. et al. Nat. Nanotech. (2014)

# Synthetic Biomarkers




Warren, A.D., Bhatia, S.N. *et al*. PNAS (2014)

# Scaled Approaches as 'Barometers' of Tumor State

- Detection of molecular entities (nucleic acids, proteases, exosomes, etc.)
- Capturing circulating tumor cell
- Advanced imaging techniques
- Companion diagnostic
- Theranostics

# Scaled Approaches as 'Barometers' of Tumor State

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- Companion diagnostic
- (re-thinking) Theranostics

# Rethinking Cancer Nanotheranostics

REVIEWS

## Rethinking cancer nanotheranostics

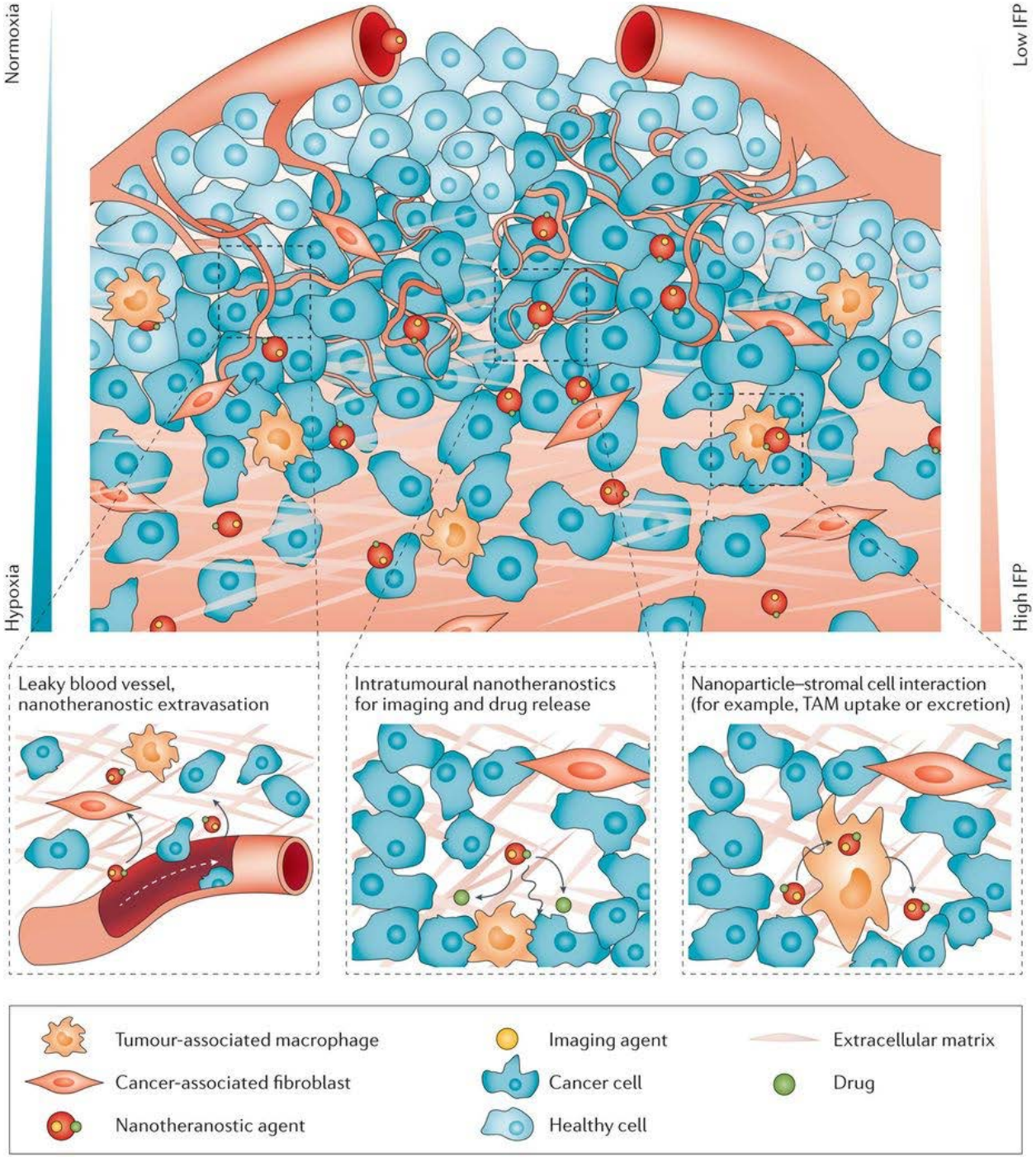
*Hongmin Chen[1–3], Weizhong Zhang[2], Guizhi Zhu[4], Jin Xie[2,3] and Xiaoyuan Chen[4]*

Abstract | Advances in nanoparticle synthesis and engineering have produced nanoscale agents affording both therapeutic and diagnostic functions that are often referred to by the portmanteau 'nanotheranostics'. The field is associated with many applications in the clinic, especially in cancer management. These include patient stratification, drug-release monitoring, imaging-guided focal therapy and post-treatment response monitoring. Recent advances in nanotheranostics have expanded this notion and enabled the characterization of individual tumours, the prediction of nanoparticle–tumour interactions, and the creation of tailor-designed nanomedicines for individualized treatment. Some of these applications require breaking the dogma that a nanotheranostic must combine both therapeutic and diagnostic agents within a single, physical entity; instead, it can be a general approach in which diagnosis and therapy are interwoven to solve clinical issues and improve treatment outcomes. In this Review, we describe the evolution and state of the art of cancer nanotheranostics, with an emphasis on clinical impact and translation.

**Source:** Chen, H. et al. Nature Reviews Materials (2017)

"Breaking the dogma that a nanotheranostic must combine both therapeutic and diagnostic agents within a single, physical entity; instead, it can be a **general approach** in which diagnosis and therapy are interwoven to solve clinical issues and improve treatment outcomes."

Shawn Chen (NIH/NIBIB)

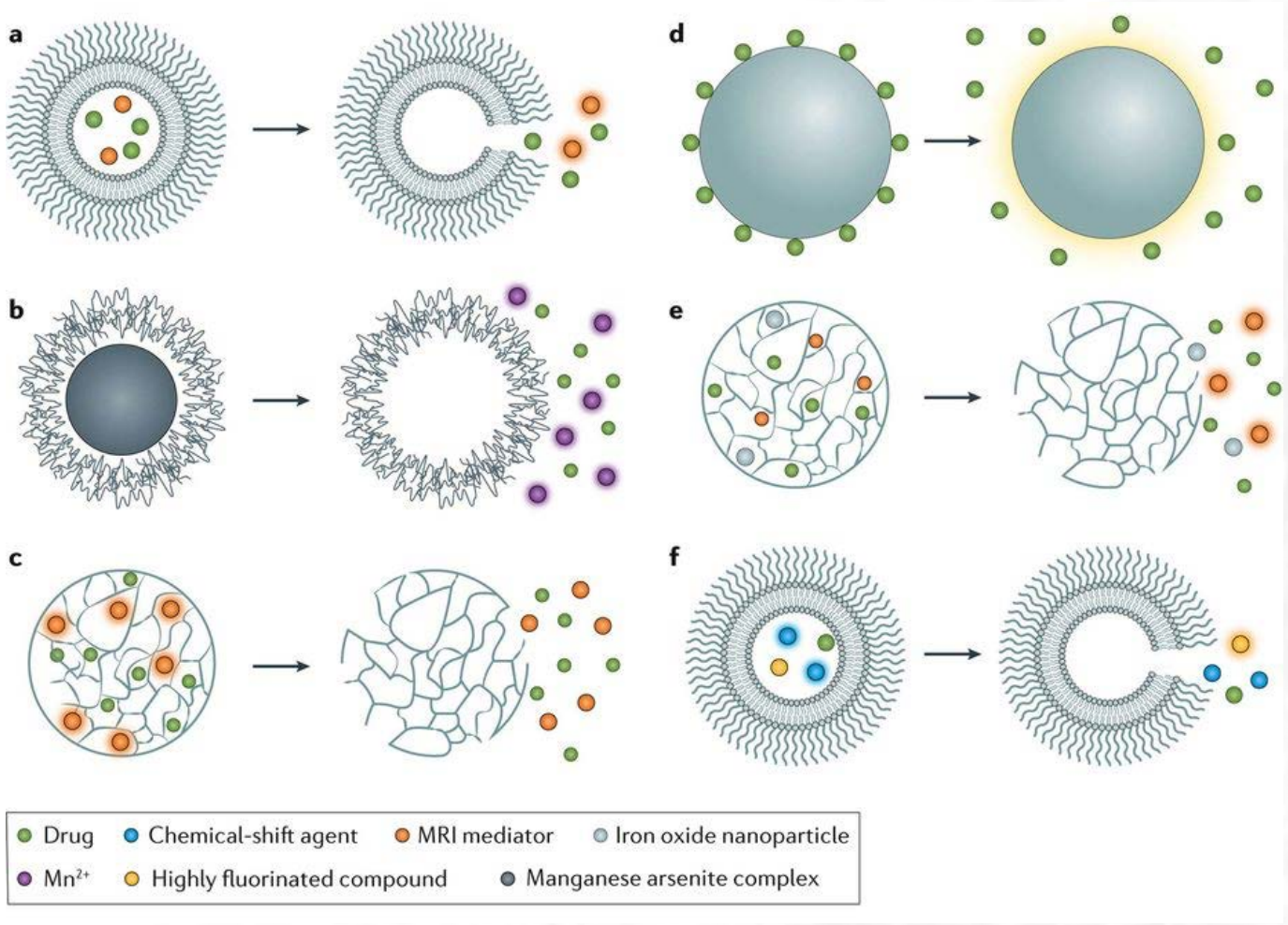



# Tumor Characteristics that Affect the Intratumoral Fates of Nanotheranostics

- Leaky/dense blood vessels
  - Variability between tumors/stages
- Dense extracellular matrix
- Increased interstitial fluid pressure
- Nonspecific uptake by stromal cells

**Source:** Chen, H. et al. Nature Reviews Materials (2017)

# Example: Monitoring Intratumoral Drug Release




a) $T_1$ MRI mediators co-released with drug molecules
b) Drug molecules are released w/ decomposition of silica shell, resulting in $T_1$ hyperintensity
c) $T_1$ mediators co-released with drug molecules from polymeric micelle
d) Drugs released from iron oxide NPs, resulting in $T_2$ hyperintensity
e) $T_1$ hyperintensity generated in magnetic resonance scans owing to deshielding
f) Signal enhancement generated in $^{1}H$ CEST magnetic resonance images; after drug release, hyperintensity results in the $^{19}F$ magnetic resonance images

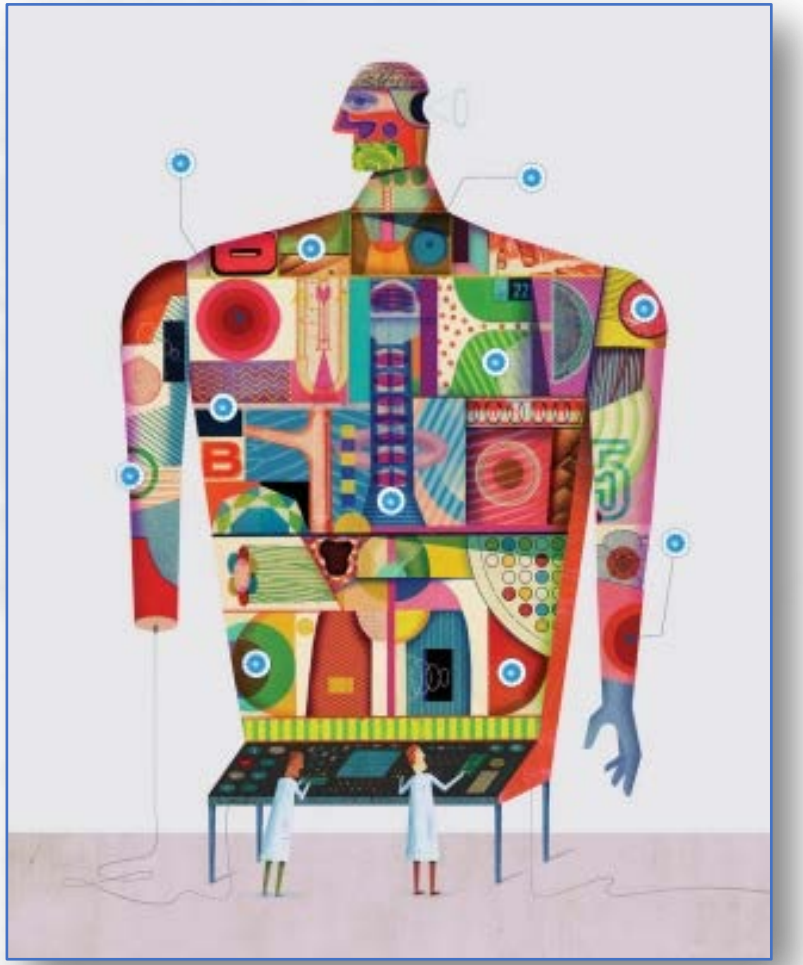
**Source:** Chen, H. et al. Nature Reviews Materials (2017)

# Re-defining Theranostics: Challenges and Opportunities

- Variation in vascular density among tumors
- Enhancing tumor uptake of nanoparticles through nanoparticle engineering and tumor microenvironment modulation
- Increasing the EPR effect for optimal tumor uptake
- Therapeutic efficacy versus systemic toxicity
- Nanotheranostics for cancer immunotherapy

# Take home

- Nanotheranostics should focus now more than ever on tumor heterogeneity and tailoring of regimens for individual patients.
- Broaden the approach to use the diagnostic arm in guiding [early] nanoparticle therapeutics.



Conger, K. Stanford Medicine Magazine (2016)

# Discussion Questions

- Question 1:

How predictive are current cancer biomarkers in enabling early diagnosis?

# Biomarkers in Cancer Diagnosis

- Ovarian Cancer: CA-125 screening
- Prostate Cancer: PSA screening
- BRCA1/ BRCA2 testing
- Glioma: "Although many candidate circulating protein biomarkers were reported, none of these have reached the required validation to be introduced for clinical practice" (Kros et al, *Neuro-Oncology 2014*)

**Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up**

Gerald L. Andriole, E. David Crawford, Robert L. Grubb III, Saundra S. Buys, David Chia, Timothy R. Church, Mona N. Fouad, Claudine Isaacs, Paul A. Kvale, Douglas J. Reding, Joel L. Weissfeld, Lance A. Yokochi, Barbara O'Brien, Lawrence R. Ragard, Jonathan D. Clapp, Joshua M. Rathmell, Thomas L. Riley, Ann W. Hsing, Grant Izmirlian, Paul F. Pinsky, Barnett S. Kramer, Anthony B. Miller, John K. Gohagan, Philip C. Prorok; for the PLCO Project Team

Manuscript received March 17, 2011; revised November 8, 2011; accepted November 9, 2011.

**Conclusions** After 13 years of follow-up, there was no evidence of a mortality benefit for organized annual screening in the PLCO trial compared with opportunistic screening, which forms part of usual care, and there was no apparent interaction with age, baseline comorbidity, or pretrial PSA testing.

J Natl Cancer Inst 2012;104:125–132

**ONLINE FIRST**

**Effect of Screening on Ovarian Cancer Mortality**

The Prostate, Lung, Colorectal and Ovari
Cancer Screening Randomized Controlle

**Conclusions** Among women in the general US population, simultaneous screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false-positive screening test result was associated with complications.

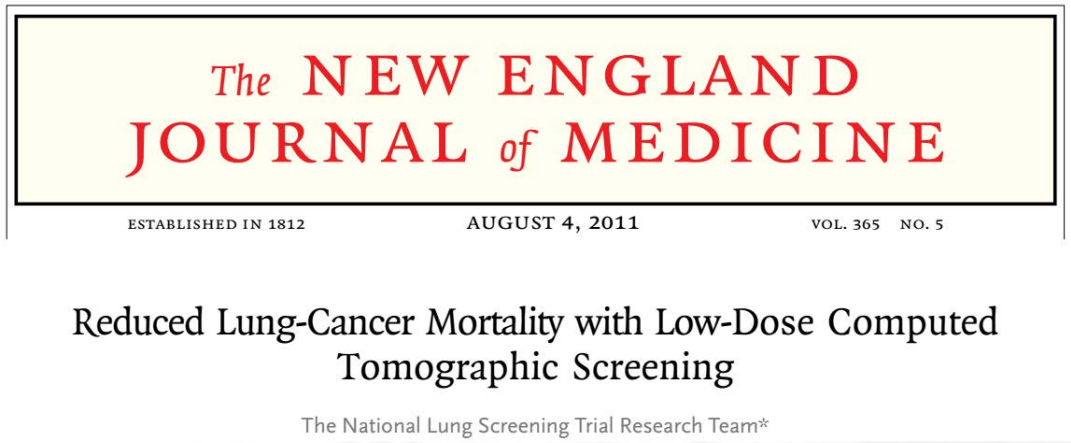
# Discussion Questions

- Question 2:

Should early cancer diagnosis be built on continuous screening/monitoring or via genetic testing (or both)?

# Continuous Monitoring Strategies

- Too expensive for regular checkups
- High rates of false positives



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

96.4% False-positive results

ELSEVIER

Journal of Clinical Neuroscience

Volume 19, Issue 3, March 2012, Pages 411-414

Clinical Study

Normal or non-diagnostic neuroimaging studies prior to the detection of malignant primary brain tumors

Paul B. Thaler [a], Jian Yi Li [b], Yakov Isakov [c], Karen S. Black [d], Michael Schulder [e], Alexis Demopoulos [f]

ELSEVIER

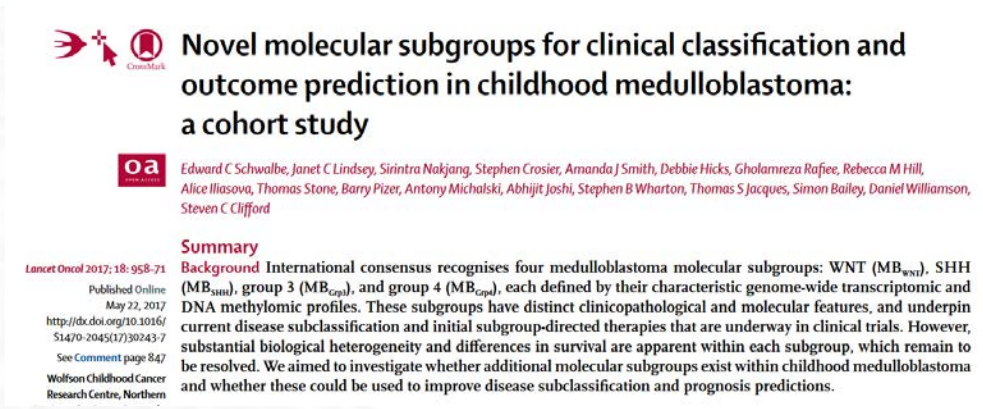
Mayo Clinic Proceedings

Volume 83, Issue 5, May 2008, Pages 563-565

COMMENTARY

Brain Magnetic Resonance Imaging Scans for Asymptomatic Patients: Role in Medical Screening

Ricardo J. Komotar MD, Robert M. Starke BS, E. Sander Connolly MD



Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: a cohort study

oa

Edward C Schwalbe, Janet C Lindsey, Sirintra Nakjang, Stephen Crosier, Amanda J Smith, Debbie Hicks, Gholamreza Rafiee, Rebecca M Hill, Alice Iliasova, Thomas Stone, Barry Pizer, Antony Michalski, Abhijit Joshi, Stephen B Wharton, Thomas S Jacques, Simon Bailey, Daniel Williamson, Steven C Clifford

Lancet Oncol 2017; 18: 958-71

Published Online May 22, 2017

http://dx.doi.org/10.1016/S1470-2045(17)30243-7

See Comment page 847

Wolfson Childhood Cancer Research Centre, Northern

Summary

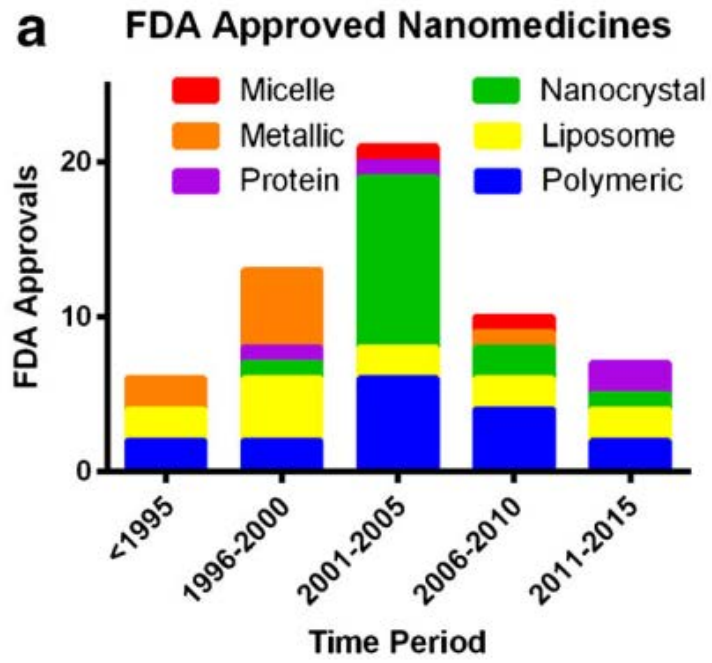
Background International consensus recognises four medulloblastoma molecular subgroups: WNT ($MB_{WNT}$), SHH ($MB_{SHH}$), group 3 ($MB_{Gp3}$), and group 4 ($MB_{Gp4}$), each defined by their characteristic genome-wide transcriptomic and DNA methylomic profiles. These subgroups have distinct clinicopathological and molecular features, and underpin current disease subclassification and initial subgroup-directed therapies that are underway in clinical trials. However, substantial biological heterogeneity and differences in survival are apparent within each subgroup, which remain to be resolved. We aimed to investigate whether additional molecular subgroups exist within childhood medulloblastoma and whether these could be used to improve disease subclassification and prognosis predictions.

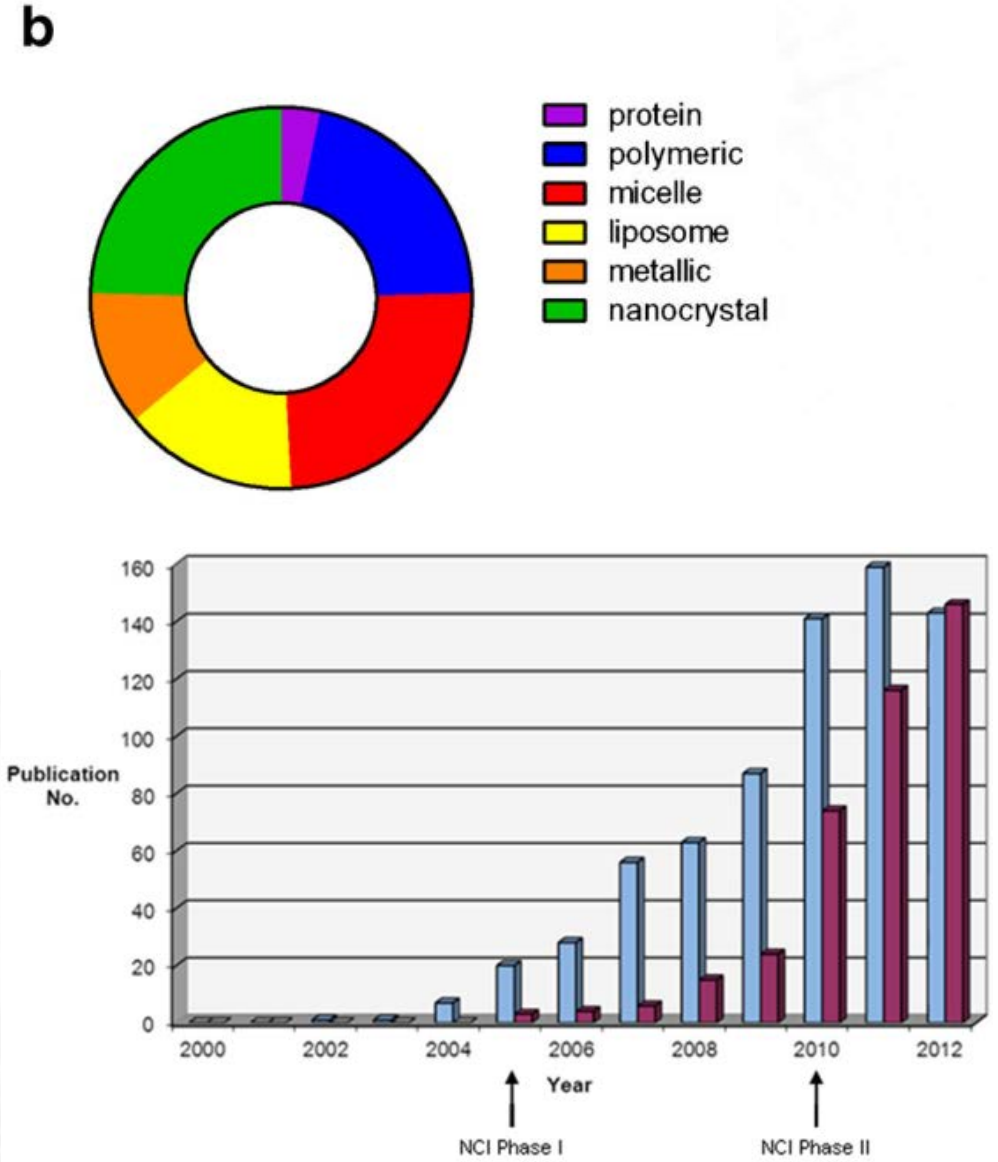
# Discussion Questions

- Question 3

Are theranostics expected to be subject to greater regulatory hurdles prior to clinical translation (compared to other nano drugs / diagnostic agents)?

# Nanomedicines in Clinical Trial




(1) Explore more effective targeted agents
(2) Take into account effective drug combinations
(3) Try these approaches at early stages of disease

**Source:** Bobo, D. et al. Pharmaceutical Research (2016)