on sFas levels but observed a significant increase in TNFα levels. This finding may support the hypothesis that during anti-TNFα treatment apoptosis is mediated via blocking survival signals, but the treatment does not interact with Fas and TNFR1 receptor activity [4,21].

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References

Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function
Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers in Western countries, with a median survival of 6 months and an extremely low percentage of long-term surviving patients. KRAS mutations are known to be one of the deadliest cancers in Western countries, with a median survival of 6 months and an extremely low percentage of long-term surviving patients. KRAS mutations are known to be a deadly cancer that is driven by a single activating mutation in the KRAS gene. Viale and co-workers explored the role of KRAS pathway in pancreatic cancer stem cells. Curr Opin Rheumatol 2003; 15 (3): 274-9.

Nature 2014; 514: 628
Eitan Israeli

Appendix 1. National survey of chloramphenicol use among infectious disease units in Israel

1. Does the microbiology lab in your hospital routinely assess susceptibility of clinical isolates to chloramphenicol? ☐ Yes ☐ No
1.1 If yes, what isolates are tested for chloramphenicol susceptibility?
   1.1.1 Blood ☐ Yes ☐ No
   1.1.2 Sputum ☐ Yes ☐ No
   1.1.3 CSF ☐ Yes ☐ No
   1.1.4 Wounds ☐ Yes ☐ No
   1.1.5 Abscesses ☐ Yes ☐ No
   1.1.6 Intra-abdominal samples ☐ Yes ☐ No
   1.1.7 Gynecological samples ☐ Yes ☐ No
   1.1.8 Other sample: __________ ☐ Y es ☐ No
   1.1.9 Other sample: __________ ☐ Y es ☐ No
   1.1.10 Other sample: __________ ☐ Y es ☐ No
1.2 If yes, what pathogens are tested for chloramphenicol susceptibility?
   1.2.1 Enterobacteriaceae ☐ Yes ☐ No
   1.2.2 Anaerobes ☐ Yes ☐ No
   1.2.3 Strep. Pneumoniae ☐ Yes ☐ No
   1.2.4 Staph. Aureus ☐ Yes ☐ No
   1.2.5 Other pathogen: __________ ☐ Yes ☐ No
   1.2.6 Other pathogen: __________ ☐ Yes ☐ No
   1.2.7 Other pathogen: __________ ☐ Yes ☐ No
1.3 If yes, what are the susceptibility rates to chloramphenicol in blood isolates?
   1.3.1 Not tested/not known ☐ Yes ☐ No
   1.3.2 Enterobacteriaceae Susceptibility % Year __________
   1.3.3 Anaerobes Susceptibility % Year __________
   1.3.4 Strep. pneumoniae Susceptibility % Year __________
   1.3.5 Staph. aureus Susceptibility % Year __________
   1.3.6 Other pathogen: __________ Susceptibility % Year __________
   1.3.7 Other pathogen: __________ Susceptibility % Year __________
   1.3.8 Other pathogen: __________ Susceptibility % Year __________
1.4 If yes, what are the susceptibility rates to chloramphenicol in other isolates?
   1.4.1 Not tested/ Not known/ Other culture ☐ Yes ☐ No
   1.4.2 Enterobacteriaceae Susceptibility % Year __________
   1.4.3 Anaerobes Susceptibility % Year __________
   1.4.4 Strep. pneumoniae Susceptibility % Year __________
   1.4.5 Staph. aureus Susceptibility % Year __________
   1.4.6 Other pathogen: __________ Susceptibility % Year __________
   1.4.7 Other pathogen: __________ Susceptibility % Year __________

2. Is chloramphenicol used in your hospital? ☐ Yes ☐ No
   2.1 If yes, for what indications?
      2.1.1 Aspiration pneumonia ☐ Yes ☐ No
      2.1.2 Intra-abdominal infections ☐ Yes ☐ No
      2.1.3 Other infection: __________ ☐ Yes ☐ No
      2.1.4 Other infection: __________ ☐ Yes ☐ No
3. Does the ID unit in your hospital recommend in its guidelines the use of chloramphenicol for the treatment of various infections? ☐ Yes ☐ No
   3.1 If yes, for what infections?
      3.1.1 Aspiration pneumonia ☐ Yes ☐ No
      3.1.2 Intra-abdominal infections ☐ Yes ☐ No
      3.1.3 Other infection: __________ ☐ Yes ☐ No
      3.1.4 Other infection: __________ ☐ Yes ☐ No
4. In your opinion, is chloramphenicol a drug with dangerous side effects that should be avoided in treatment of patients? ☐ Yes ☐ No
   4.1 If yes, what are the potential side effects causing you to refrain from this treatment?
      4.1.1 Aplastic anemia ☐ Yes ☐ No
      4.1.2 Optic neuritis ☐ Yes ☐ No
      4.1.3 Hematologic malignancies ☐ Yes ☐ No
      4.1.4 Hepatic toxicity ☐ Yes ☐ No
      4.1.5 Other: ___________ ☐ Yes ☐ No
      4.1.6 Other: ___________ ☐ Yes ☐ No
5. In your opinion, does the efficacy of chloramphenicol treatment for certain infections exceed the potentially dangerous side effects? ☐ Yes ☐ No
   5.1 If yes, for what infections?
      5.1.1 Aspiration pneumonia ☐ Yes ☐ No
      5.1.2 Intra-abdominal infections ☐ Yes ☐ No
      5.1.3 Other infection: ___________ ☐ Yes ☐ No
      5.1.4 Other infection: ___________ ☐ Yes ☐ No
   5.2 If no, please elaborate:

6. Do you believe that chloramphenicol has a role in treating infections in hospitalized patients in this era of increasing antibiotic resistance? ☐ Yes ☐ No
   Please elaborate:

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**Capsule**

**Hunting for the effects of huntingtin**

Huntington’s disease (HD) is associated with a mutant form of the protein huntingtin (Htt). HD-associated symptoms are alleviated by inhibition of the kinase mTOR, which activates protein synthesis when amino acids are plentiful. In mouse striatal neurons, Pryor and colleagues found that wild-type Htt stimulated amino acid-induced mTOR signaling by enhancing its interaction with an activating protein. Mutant Htt promoted this interaction even when amino acid availability was not increased. In a mouse model of HD, activating mTOR in striatal neurons accelerated the onset of symptoms.

Sci Signal 2014; 7: ra103
Eitan Israeli
as presented in our study, ranging from benign conditions to biliary cystic malformations that require early surgical intervention. The diagnosis may be challenging, and specialized imaging should be performed to define the anatomic connection between the cyst and the biliary tree and the developmental status of the gallbladder in order to differentiate those cases with attendant biliary atresia, which requires urgent surgery. Small hepatic hilar cysts, hypoplastic gallbladder and high levels of direct bilirubin are suggestive of biliary atresia.

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References

Capsule
High-fat diet mediated dysbiosis promotes intestinal carcinogenesis independently of obesity

Several features common to a Western lifestyle, including obesity and low levels of physical activity, are known risk factors for gastrointestinal cancers. There is substantial evidence suggesting that diet markedly affects the composition of the intestinal microbiota. Moreover, there is now unequivocal evidence linking dysbiosis to cancer development. However, the mechanisms by which high-fat diet (HFD)-mediated changes in the microbial community affect the severity of tumorigenesis in the gut remain to be determined. Schulz et al. demonstrate that an HFD promotes tumor progression in the small intestine of genetically susceptible, Kras<sup>G12D/0</sup> mice, independently of obesity. HFD consumption, in conjunction with Kras mutation, mediated a shift in the composition of the gut microbiota, and this shift was associated with a decrease in Paneth cell-mediated antimicrobial host defense that compromised dendritic cell recruitment and MHC class II molecule presentation in the gut-associated lymphoid tissues. When butyrate was administered to HFD-fed Kras<sup>G12D/0</sup> mice, dendritic cell recruitment in the gut-associated lymphoid tissues was normalized, and tumor progression was attenuated. Importantly, deficiency in MYD88, a signaling adaptor for pattern recognition receptors and Toll-like receptors, blocked tumor progression. The transfer of fecal samples from HFD-fed mice with intestinal tumors to healthy adult Kras<sup>G12D/0</sup> mice was sufficient to transmit disease in the absence of an HFD. Furthermore, treatment with antibiotics completely blocked HFD-induced tumor progression, suggesting that distinct shifts in the microbiota have a pivotal role in aggravating disease. Collectively, these data underscore the importance of the reciprocal interaction between host and environmental factors in selecting a microbiota that favors carcinogenesis, and they suggest that tumorigenesis is transmissible among genetically predisposed individuals.

Nature 2014; 514: 508
Eitan Israeli


Animation defines life, and the three-dimensional (3D) imaging of dynamic biological processes occurring within living specimens is essential to understand life. However, in vivo imaging, especially in 3D, involves inevitable tradeoffs of resolution, speed, and phototoxicity. Chen and team describe a microscope that can address these concerns. They used a class of non-diffracting beams, known as 2D optical lattices, which spread the excitation energy across the entire field of view while simultaneously eliminating out-of-focus excitation. Lattice light sheets increase the speed of image acquisition and reduce phototoxicity, which expands the range of biological problems that can be investigated. The authors illustrate the power of their approach using 20 distinct biological systems ranging from single-molecule binding kinetics to cell migration and division, immunology, and embryonic development.

Science 2014; 346: 10.1126/science.1257998

Eitan Israeli

Pre-Columbian mycobacterial genomes reveal seals as a source of New World human tuberculosis

Modern strains of Mycobacterium tuberculosis from the Americas are closely related to those from Europe, supporting the assumption that human tuberculosis was introduced post-contact. This notion, however, is incompatible with archaeological evidence of pre-contact tuberculosis in the New World. Comparative genomics of modern isolates suggests that M. tuberculosis attained its worldwide distribution following human dispersals out of Africa during the Pleistocene epoch, although this has yet to be confirmed with ancient calibration points. Bos et al. present three 1000 year old mycobacterial genomes from Peruvian human skeletons, revealing that a member of the M. tuberculosis complex caused human disease before contact. The ancient strains are distinct from known human-adapted forms and are most closely related to those adapted to seals and sea lions. Two independent dating approaches suggest a most recent common ancestor for the M. tuberculosis complex less than 6000 years ago, which supports a Holocene dispersal of the disease. These results implicate sea mammals as having played a role in transmitting the disease to humans across the ocean.

Nature 2014; 514: 494

Eitan Israeli

A drug fights off ravages of aging in mice

Interested in a pill to extend life span and delay the onset of age-related diseases? The answer may lie in targeting the enzyme NAD-dependent deactylase sirtuin 1 (SIRT1): Animals with enhanced activity of SIRT1 show some of these effects. To study the effects of long-term SIRT1 activity, Mercken et al. fed mice a synthetic activator of SIRT1 from 6 months of age for the rest of their (~3 year) life span. The treated mice had 5% and 10% increases in maximum and mean life span, respectively. They also resisted many problems associated with human aging. The mice had more stable blood glucose levels, better muscle endurance and balance, less fat, and suppressed inflammatory responses.

Aging Cell 2014; 10.1111/acel.12220

Eitan Israeli

From single molecules to embryos in living color

Animation defines life, and the three-dimensional (3D) imaging of dynamic biological processes occurring within living specimens is essential to understand life. However, in vivo imaging, especially in 3D, involves inevitable tradeoffs of resolution, speed, and phototoxicity. Chen and team describe a microscope that can address these concerns. They used a class of non-diffracting beams, known as 2D optical lattices, which spread the excitation energy across the entire field of view while simultaneously eliminating out-of-focus excitation. Lattice light sheets increase the speed of image acquisition and reduce phototoxicity, which expands the range of biological problems that can be investigated. The authors illustrate the power of their approach using 20 distinct biological systems ranging from single-molecule binding kinetics to cell migration and division, immunology, and embryonic development.

Science 2014; 346: 10.1126/science.1257998

Eitan Israeli
the minimum necessary, increasing the pitch to > 1, decreasing kilovoltage (especially for small-sized women), decreasing tube current, and using automated mA modulation. New-generation CT machines possess powerful reconstruction algorithms that reduce image noise, allowing reduction of the tube current or voltage required for the examination.

In our experience, radiation exposure can be reduced to as low as 1–2 mSv, especially in slender patients, without compromising image quality. We found this holds true even at relatively young gestational ages where skeletal ossification is at an early stage. This level of radiation exposure is acceptable and is equivalent to a single abdominal X-ray or 9 months exposure to natural environmental radiation.

Our study has a number of limitations, most of them inherent to the nature of the study. The series is relatively small. Moreover, since many obstetricians are not familiar with the role that helical CT can play in prenatal diagnosis of skeletal dysplasia, CT referrals for this indication are sparse and it is difficult to obtain a larger series. CT examinations were performed with various scan protocols on three different machines. The optimal protocol we suggest is suitable for new-generation CT machines that allow very low radiation exposure.

In conclusion, repeated ultrasound examinations are the primary tool for prenatal diagnosis of skeletal malformations. Helical CT with 3D reconstruction may serve as an important adjunctive to prenatal 2D and 3D ultrasound for the evaluation of possible skeletal dysplasia and may play an important role in decision making in problematic cases.

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References

Capsule
Mesenchymal-endothelial transition contributes to cardiac neovascularization
Endothelial cells contribute to a subset of cardiac fibroblasts by undergoing endothelial-to-mesenchymal transition, but whether cardiac fibroblasts can adopt an endothelial cell fate and directly contribute to neovascularization after cardiac injury is not known. Ubil et al. used genetic fate map techniques to demonstrate that cardiac fibroblasts rapidly adopt an endothelial cell-like phenotype after acute ischemic cardiac injury. Fibroblast-derived endothelial cells exhibit anatomical and functional characteristics of native endothelial cells. The authors show that the transcription factor p53 regulates such a switch in cardiac fibroblast fate. Loss of p53 in cardiac fibroblasts severely decreases the formation of fibroblast-derived endothelial cells, reduces post-infarct vascular density and worsens cardiac function. Conversely, stimulation of the p53 pathway in cardiac fibroblasts augments mesenchymal-to-endothelial transition, enhances vascularity and improves cardiac function. These observations demonstrate that mesenchymal-to-endothelial transition contributes to neovascularization of the injured heart and represents a potential therapeutic target for enhancing cardiac repair.

Nature 2014; 514: 585
Eitan Israeli
Capsule

For radiotherapy, less can be more

Radionuclides attached to antibodies have the potential to target radiation specifically to cancer cells, reducing the damage to non-cancerous cells and the side effects of radiotherapy. Clinical trials evaluating antibodies labeled with actinium-225, a radionuclide that emits high energy α-particles, are currently underway. However, the two-step method used to label antibodies with actinium-225 is inefficient and expensive. Maguire et al. describe an improved one-step method for producing stable and therapeutically active actinium-225 antibodies. They report increases in yield and specific activity of up to 10- and 30-fold, respectively. Through lowering the cost and dose required for actinium-225 targeted therapy, this method may help to expand the clinical use of actinium-225-labeled antibodies.


Eitan Israeli

Capsule

Dendritic cells control fibroblastic reticular network tension and lymph node expansion

After immunogenic challenge, infiltrating and dividing lymphocytes markedly increase lymph node cellularity, leading to organ expansion. Acton et al. report that the physical elasticity of lymph nodes is maintained in part by podoplanin (PDPN) signaling in stromal fibroblastic reticular cells (FRCs) and its modulation by CLEC-2 expressed on dendritic cells. They show in mouse cells that PDPN induces actomyosin contractility in FRCs via activation of RhoA/C and downstream Rho-associated protein kinase (ROCK). Engagement by CLEC-2 causes PDPN clustering and rapidly uncouples PDPN from RhoA/C activation, relaxing the actomyosin cytoskeleton and permitting FRC stretching. Notably, administration of CLEC-2 protein to immunized mice augments lymph node expansion. In contrast, lymph node expansion is significantly constrained in mice selectively lacking CLEC-2 expression in dendritic cells. Thus, the same dendritic cells that initiate immunity by presenting antigens to T lymphocytes also initiate remodeling of lymph nodes by delivering CLEC-2 to FRCs. CLEC-2 modulation of PDPN signaling permits FRC network stretching and allows for the rapid lymph node expansion – driven by lymphocyte influx and proliferation – that is the critical hallmark of adaptive immunity.

_Nature_ 2014; 514: 498

Eitan Israeli

“Your most unhappy customers are your greatest source of learning”

Bill Gates (born 1955), American business magnate, philanthropist, investor, computer programmer, and inventor. Gates was the co-founder of Microsoft, the world’s largest PC software company. He has pursued a number of philanthropic endeavors, donating large amounts of money to various charitable organizations and scientific research programs through the Bill & Melinda Gates Foundation.

References

Capsule

Cleavage of tau by asparagine endopeptidase mediates the neurofibrillary pathology in Alzheimer’s disease

Neurofibrillary tangles (NFTs), composed of truncated and hyperphosphorylated tau, are a common feature of numerous aging-related neurodegenerative diseases, including Alzheimer’s disease (AD). However, the molecular mechanisms mediating tau truncation and aggregation during aging remain elusive. Zhang et al. show that asparagine endopeptidase (AEP), a lysosomal cysteine proteinase, is activated during aging and proteolytically degrades tau, abolishes its microtubule assembly function, induces tau aggregation and triggers neurodegeneration. AEP is upregulated and active during aging and is activated in human AD brain and tau P301S-transgenic mice with synaptic pathology and behavioral impairments, leading to tau truncation in NFTs. Tau P301S-transgenic mice with deletion of the gene encoding AEP show substantially reduced tau hyperphosphorylation, less synapse loss and rescue of impaired hippocampal synaptic function and cognitive deficits. Mice infected with adeno-associated virus encoding an uncleavable tau mutant showed attenuated pathological and behavioral defects compared to mice injected with adeno-associated virus encoding tau P301S. Together, these observations indicate that AEP acts as a crucial mediator of tau-related clinical and neuropathological changes. Inhibition of AEP may be therapeutically useful for treating tau-mediated neurodegenerative diseases.

Nature Med 2014; 20: 1254
Eitan Israeli

Capsule

Diabetes recovery by age-dependent conversion of pancreatic δ cells into insulin producers

Total or near-total loss of insulin-producing β cells occurs in type 1 diabetes. Restoration of insulin production in type 1 diabetes is thus a major medical challenge. Chera et al. previously observed in mice in which β cells are completely ablated that the pancreas reconstitutes new insulin-producing cells in the absence of autoimmunity. The process involves the contribution of islet non-β cells; specifically, glucagon-producing α cells begin producing insulin by a process of reprogramming (transdifferentiation) without proliferation. Now the authors show the influence of age on β cell reconstitution from heterologous islet cells after near-total β cell loss in mice. The authors found that senescence does not alter α cell plasticity: α cells can reprogram to produce insulin from puberty through to adulthood, and also in aged individuals, even a long time after β cell loss. In contrast, before puberty there is no detectable α cell conversion, although β cell reconstitution after injury is more efficient, always leading to diabetes recovery. This process occurs through a newly discovered mechanism: the spontaneous en masse reprogramming of somatostatin-producing δ cells. The juveniles display ‘somatostatin-to-insulin’ δ cell conversion, involving dedifferentiation, proliferation and re-expression of islet developmental regulators. This juvenile adaptability relies, at least in part, upon the combined action of FoxO1 and downstream effectors. Restoration of insulin-producing cells from non-β cell origins is thus enabled throughout life via δ or α cell spontaneous reprogramming. A landscape with multiple intra-islet cell interconversion events is emerging, offering new perspectives for therapy.

Nature 2014; 514: 503
Eitan Israeli

“‘Respect for religion’ has become a code phrase meaning ‘fear of religion’. Religions, like all other ideas, deserve criticism, satire, and, yes, our fearless disrespect”

Salman Rushdie (b. 1947), British Indian novelist and essayist. His second novel, Midnight’s Children (1981), won the Booker Prize in 1981. Much of his fiction is set on the Indian subcontinent. He combines magical realism with historical fiction; his work is concerned with the many connections, disruptions, and migrations between Eastern and Western civilizations. His fourth novel, The Satanic Verses (1988), evoked a major controversy
Disease biomarkers: What’s the risk?

With approximately 60% of cardiac events occurring in patients of low or moderate risk, doctors need new biomarkers to accurately predict which of their patients will develop disease. Antibodies targeting the protein apolipoprotein A-1 (apoA-1), which plays a role in lipid metabolism, are one such candidate. Some of these antibodies may confer more risk than others, depending where on apoA-1 they bind. Using serum samples from cardiac patients, Teixeira et al. identified the peptides within apoA-1 where antibodies bind. These findings may point toward new therapeutic opportunities and improved biomarkers for predicting the risk of cardiovascular disease.

A dendritic cell target for immunotherapy

Cancer immunotherapies work by activating T cells to kill tumors. Antigen-presenting cells (APCs), such as dendritic cells and macrophages, activate T cells by engaging protein receptors on the T cell surface. This then tells the T cells to attack the tumors. But T cells typically cannot attack tumors because the immunosuppressive microenvironment of tumors keeps APCs from turning these signals on. Broz and fellow researchers report, however, that low numbers of dendritic cells capable of activating T cells exist in tumors in mice. T cell-mediated clearance of tumors depended on these cells.

In humans, an increased genetic signature of these cells correlated with better outcomes in a variety of tumor types.
melanoma black 45 (HMB 45). Ductal carcinoma in situ immunostaining was positive for estrogen receptor and negative for progesterone receptor. Her-2/neu immunohistochemical examination showed faint partial membrane staining in 80% of the tumor cells. The patient was referred to the oncologist for further treatment.

**COMMENT**

The patient was referred to our department with an eczematoid lesion involving the NAC. Differential diagnosis includes, by descending order, eczema, Bowen’s disease, squamous cell carcinoma, melanoma and Paget’s disease. Histological evaluation confirmed the diagnosis of Paget’s disease. Paget’s disease does not penetrate beyond the basement membrane and is therefore defined as carcinoma in situ. However, in more than 90% of cases there is ductal carcinoma in situ (DCIS) or invasive breast cancer in the underlying breast tissue [3]. In our patient the sub-areolar mass was diagnosed as DCIS compared to other reports where palpable mass usually involves invasive breast cancer [3].

Treatment consists of mastectomy and sentinel lymph node biopsy, although several cases of lumpectomy accompanied by radiation and adjuvant therapy have been reported [1]. In males, surgical choices are the same as for females, as mentioned above. In our patient, in view of his personality disorders, treatment comprised mastectomy only, with optional staged lymph node biopsy. Prognostic factors are the same as for female breast cancer and include nodal involvement and palpable mass size. The 5-year survival rate of male patients with Paget’s disease is 20–30% compared to 30–40% in females [4]. The presence of DCIS or invasive breast cancer alters the survival rate, as does palpable mass [5]. The average delay between treatment and diagnosis is 7–8 months [1], unlike the 3 months in our patient.

We wish to draw the attention of physicians caring for patients with nipple dermatitis, eczematoid or psoriatic lesions to this lethal and rare tumor.

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**References**


**Capsule**

**The dark side of protective genes**

Aberrant antibody deposits in the kidney characterize immunoglobulin A nephropathy (IgAN), a disease most prevalent in East Asians. Kiryluk et al. studied the underlying genetics of IgAN and found that variants of genes with roles in maintaining the intestinal epithelial barrier or in the immune response to mucosal pathogens conferred an elevated risk of IgAN. People living in areas with the greatest diversity of helminthes showed the highest genetic risk for developing IgAN. This intriguing correlation suggests that the high incidence of IgAN in certain regions might be a consequence of protective adaptation to mucosal pathogens.

*Nat Genet* 2014; 10.1038/ng.3118
Eitan Israeli

**Capsule**

**Nanoparticles for molecular cancer imaging**

Tiny particles can be coated with antibodies or peptides to target a molecule specific to cancer, improving diagnostic accuracy and patient stratification. Yet these decorated nanoparticles have been slow in making it to clinical trials. Phillips et al. describe the translation of ultrasmall (<10 nm) inorganic nanoparticles, called “C dots,” from animals to patients. The nanoparticles were not toxic in a small group of five patients with metastatic melanoma and were excreted intact via the kidneys and bladder. In contrast, larger or uncoated particles often get lodged in the liver. Many more studies in patients will be needed to confirm lack of toxicity and to optimize tumor targeting, but now that such ultrasmall nanoparticles can be tested in people, a new era of molecular cancer imaging has begun.

*Sci Transl Med* 2014; 6: 260ra149
Eitan Israeli

“It is not what we do, but also what we do not do, for which we are accountable”

Moliere (1622-1673), French actor and playwright considered one of the greatest masters of comedy in Western literature.