



all sides as the animal the crab has its feet, whence it derives its name". Celsus (ca. 25 BC – 50 AD) translated carcinos into the Latin cancer, also meaning crab and recommended surgery as treatment. Galen (2nd century AD) disagreed with the use of surgery and recommended purgatives instead<sup>4</sup>. These recommendations largely stood for 1000 years. In the 15th, 16th and 17th centuries, it became more acceptable for doctors to dissect bodies to discover the cause of death. The German professor Wilhelm believed that breast cancer was caused by a milk clot in a mammary duct. The Dutch professor Francois de la Boa Sylvius, a follower of Descartes, believed that all disease was the outcome of chemical processes, and that acidic lymph fluid was the cause of cancer. His contemporary Nicolaes Tulp believed that cancer was a poison that slowly spreads, and concluded that it was contagious Fig 2.

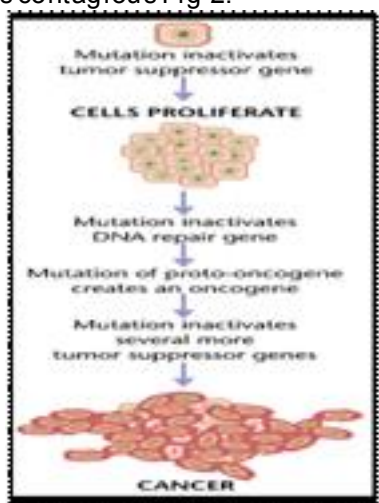


Fig.2: This is predicated pathophysiology

### Pathophysiology:

Cancers are caused by a series of mutations. Each mutation alters the behavior of the cell somewhat. Fig.3. Cancer is fundamentally a disease of failure of regulation of tissue growth. In order for a normal cell to transform into a cancer cell, the genes which regulate cell growth and differentiation must be altered. The affected genes are divided into two broad categories. Oncogenes are genes which promote cell growth and reproduction. Tumor suppressor genes are genes which inhibit cell division and survival. Malignant transformation can occur through the formation of novel oncogenes, the inappropriate over-expression of normal oncogenes, or by the under-expression or disabling of tumor suppressor genes. Typically, changes in many genes are required to transform a normal cell into a cancer cell<sup>5</sup>. Genetic changes can occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors in mitosis. More common are mutations, which are changes in the nucleotide sequence of genomic DNA. Large-scale mutations involve the deletion or gain of a

portion of a chromosome. Some environments make errors more likely to arise and propagate. Such environments can include the presence of disruptive substances called carcinogens, repeated physical injury, heat, ionizing radiation, or hypoxia<sup>6</sup>. The errors which cause cancer are self-amplifying and compounding, for example: 1. A mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly. 2. A further mutation in an oncogene might cause the cell to reproduce more rapidly and more frequently than its normal counterparts. 3. A further mutation may cause loss of a tumor suppressor gene, disrupting the apoptosis signaling pathway and resulting in the cell becoming immortal. A further mutation in signaling machinery of the cell might send error-causing signals to nearby cells.

### Cancer Therapy:

**Cancer signs and symptoms:** Symptoms of cancer metastasis depend on the location of the tumor. When cancer begins it invariably produces no symptoms with signs and symptoms only appearing as the mass continues to grow or ulcerates. The findings and result depends on the type and location of the cancer. Few symptoms are specific, with many of them also frequently occurring in individuals who have other conditions. Cancer is the new "great imitator". Thus it is not uncommon for people diagnosed with cancer to have been treated for other diseases to which it was assumed their symptoms were due.

**Local effects:** Local symptoms may occur due to the mass of the tumor or its ulceration. For example, mass effects from lung cancer can cause blockage of the bronchus resulting in cough or pneumonia; esophageal cancer can cause narrowing of the esophagus, making it difficult or painful to swallow; and colorectal may lead to narrowing or blockages in the bowel, resulting in changes in bowel habits<sup>7</sup>. Masses of breast or testicles may be easily felt. Ulceration can cause bleeding which, if it occurs in the lung, will lead to coughing up blood, in the bowel to anemia or rectal bleeding, in the bladder to blood in the urine, and in the uterus to vaginal bleeding. Although localized pain may occur in advanced cancer, the initial swelling is usually painless. Some cancers can cause buildup of fluid within the chest or abdomen.

**Systemic symptoms:** General symptoms occur due to distant effects of the cancer that are not related to direct or metastatic spread. These may include: unintentional weight loss, fever, being excessively tired, and changes to the skin. Hodgkin disease, leukemia's, and cancers of the liver or kidney can cause a persistent fever. Specific constellations of systemic symptoms, termed paraneoplastic phenomena, may occur with some

cancers<sup>8</sup>. Examples include the appearance of myasthenia in thymoma and clubbing in lung cancer.

**Metastasis:** Symptoms of metastasis are due to the spread of cancer to other locations in the body. They can include enlarged lymph nodes (which can be felt or sometimes seen under the skin and are typically hard), hepatomegaly (enlarged liver) or splenomegaly (enlarged spleen) which can be felt in the abdomen, pain or fracture of affected bones, and neurological symptoms<sup>9</sup>.

**Causes:** Cancers are primarily an environmental disease with 90–95% of cases attributed to environmental factors and 5–10% due to genetics. Environmental, as used by cancer researchers, means any cause that is not inherited genetically, not merely pollution. Common environmental factors that contribute to cancer death include tobacco (25–30%), diet and obesity infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), stress, lack of physical activity, and environmental pollutants<sup>10</sup>.

It is nearly impossible to prove what caused a cancer in any individual, because most cancers have multiple possible causes. For example, if a person who uses tobacco heavily develops lung cancer, then it was probably caused by the tobacco use, but since everyone has a small chance of developing lung cancer as a result of air pollution or radiation, then there is a small chance that the cancer developed because of air pollution or radiation.

**Chemicals:** Further information: Alcohol and cancer and Smoking and cancer GH: 1. The incidence of lung cancer is highly correlated with smoking. Cancer pathogenesis is traceable back to DNA mutations that impact cell growth and metastasis. Substances that cause DNA mutations are known as mutagens, and mutagens that cause cancers are known as carcinogens. Particular substances have been linked to specific types of cancer. Tobacco smoking is associated with many forms of cancer, and causes 90% of lung cancer.

Decades of research has demonstrated the link between tobacco use and cancer in the lung, larynx, head, neck, stomach, bladder, kidney, esophagus and pancreas. Tobacco smoke contains over fifty known carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons. Tobacco is responsible for about one in three of all cancer deaths in the developed world, and about one in five worldwide. Lung cancer death rates in the United States have mirrored smoking patterns<sup>11</sup>.

**Diet and exercise:** Diet, physical inactivity, and obesity are related to approximately 30–35% of cancer deaths. In the United States excess body

weight is associated with the development of many types of cancer and is a factor in 14–20% of all cancer deaths. Physical inactivity is believed to contribute to cancer risk not only through its effect on body weight but also through negative effects on immune and endocrine system.

**Infection:** A virus that can cause cancer is called oncovirus. These include human papillomavirus (cervical carcinoma), Epstein-Barr virus (B-cell lymph proliferative disease and nasopharyngeal carcinoma), Kaposi's sarcoma herpes virus (Kaposi's Sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma), and Human T-cell leukemia virus-1 (T-cell leukemias). Bacterial infection may also increase the risk of cancer, as seen in *Helicobacter pylori*-induced gastric carcinoma. Parasitic infections strongly associated with cancer include *Schistosoma haematobium* (squamous) and the liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis* (cholangiocarcinoma).

**Radiation:** Up to 10% of invasive cancers are related to radiation exposure, including both ionizing radiation and non-ionizing radiation. Additionally, the vast majority of non-invasive cancers are non-melanoma skin cancers caused by non-ionizing ultraviolet radiation. Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies. Clear evidence establishes ultraviolet radiation, especially the non-ionizing medium wave UVB, as the cause of most non-melanoma skin cancers, which are the most common forms of cancer in the world. Non-ionizing radio frequency radiation from mobile phones, electric power transmission, and other similar sources have been described as a possible carcinogen by the World Health Organization's International Agency for Research on Cancer.

**Heredity:** The vast majority of cancers are non-hereditary ("sporadic cancers"). Hereditary cancers are primarily caused by an inherited genetic defect. Less than 0.3% of the population is carriers of a genetic mutation which has a large effect on cancer risk and this cause less than 3–10% of all cancer.

**Physical agents:** Some substances cause cancer primarily through their physical, rather than chemical, effect on cells. A prominent example of this is prolonged exposure to asbestos, naturally occurring mineral fibers which are a major cause of mesothelioma, a type of cancer of the serous membrane<sup>12</sup>. Other substances in this category, including both naturally occurring and synthetic asbestos-like fibers such as wollastonite, attapulgite, glass wool, and rock wool, are believed to have similar effects.

**Hormones:** Some hormones play a role in the development of cancer by promoting cell proliferation. Hormones are important agents in sex-related cancers such as cancer of the breast, endometrial, prostate, ovary, and testis, and also of thyroid cancer and bone cancer. An individual's hormone levels are mostly determined genetically, so this may at least partly explain the presence of some cancers that run in families that do not seem to have any cancer-causing genes. For example, the daughters of women who have breast cancer have significantly higher levels of estrogen and progesterone than the daughters of women without breast cancer.

**Diagnosis:** Most cancers are initially recognized either because of the appearance of signs or symptoms or through screening. Neither of these led to a definitive diagnosis, which requires the examination of a tissue sample by a pathologist. People with suspected cancer are investigated with medical tests. These commonly include blood tests, X-rays, CT scans and endoscopy Fig.3.

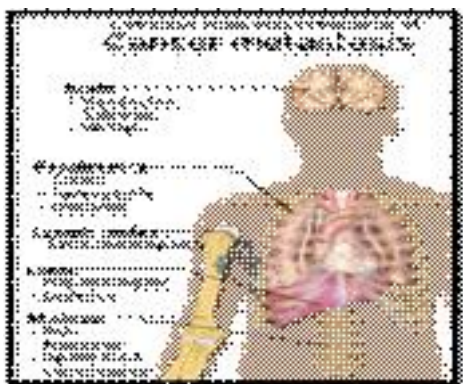


Fig:(3) This is predicated to symptoms

**Prevention:** Cancer prevention is defined as active measures to decrease the risk of cancer. The vast majority of cancer cases are due to environmental risk factors, and many, but not all, of these environmental factors are controllable lifestyle choices. Thus, cancer is considered a largely preventable disease. Greater than 30% of cancer deaths could be prevented by avoiding risk factors including: tobacco, overweight/obesity, an insufficient diet, physical inactivity, alcohol, sexually transmitted infections, and air pollution. Not all environmental causes are controllable, such as naturally occurring background radiation, and other cases of cancer are caused through hereditary genetic disorders, and thus it is not possible to prevent all cases of cancer.

**Dietary:** While many dietary recommendations have been proposed to reduce the risk of cancer, few have significant supporting scientific evidence. The primary dietary factors that increase risk are obesity and alcohol consumption; with a diet low in fruits and vegetables and high in

red meat being implicated but not confirmed. Consumption of coffee is associated with a reduced risk of liver<sup>13</sup>. Studies have linked consumption of red or processed meat to an increased risk of breast cancer, colon cancer, and pancreatic cancer, a phenomenon which could be due to the presence of carcinogens in meats cooked at high temperatures. Dietary recommendations for cancer prevention emphasize on vegetables, fruits, whole grains, and fishes and avoidance of red meat, animal fats and refined carbohydrates. However, these typically include an recommendation based on relatively limited evidence.

**Medication:** The concept that medications can be used to prevent cancer is attractive, and evidence supports their use in a few defined circumstances. In the general population NSAIDs reduce the risk of colorectal cancer however due to the cardiovascular and gastrointestinal side effects they cause overall harm when used for prevention. Aspirin has been found to reduce the risk of death from cancer by about 7% may decrease the rate of polyp formation in people with familial adenomatous polypus's however are associated with the same adverse effects as NSAIDs. Daily use of tamoxifen or raloxifene has been demonstrated to reduce the risk of developing breast cancer in high-risk women. The benefit versus harm for 5-alpha-reductase inhibitor such as finasteride is not clear<sup>14</sup>. Vitamins have not been found to be effective at preventing cancer, although low blood levels of vitamin D are correlated with increased cancer risk. Whether this relationship is causal and vitamin D supplementation is protective is not determined. Beta-carotene supplementation has been found to increase lung cancer rates in those who are high risk. Acid supplementation has not been found effective in preventing colon cancer and may increase colon polyps.

**Vaccination:** Vaccines have been developed that prevent some infection by some viruses. Human papillomavirus vaccine (Gardasil and Cervarix) decreases the risk of developing cervical cancer. The hepatitis prevents infection with hepatitis B virus and thus decreases the risk of liver cancer.

**Screening:** Unlike diagnosis efforts prompted by symptoms and medical signs, cancer screening involves efforts to detect cancer after it has formed, but before any noticeable symptoms appear. This may involve physical examination, blood or urine tests, or medical imaging. Cancer screening is currently not possible for many types of cancers, and even when tests are available. Possible harms from the screening test: for example, X-ray images involve exposure to potentially harmful radiation. The likelihood of the test correctly identifying cancer.

The likelihood of cancer being present: Screening is not normally useful for rare cancers<sup>15</sup>.

1. Possible harms from follow-up procedures.
2. Whether suitable treatment is available.
3. Whether early detection improves treatment outcomes.
4. Whether the cancer will ever need treatment.
5. Whether the test is acceptable to the people: If a screening test is too burdensome (for example, being extremely painful), then people will refuse to participate.
6. Cost of the test.

### Therapy with Novel Methods

#### Targeting HSP90 cancers with multiple receptor tyrosine kinase co activation:

**Hsp90 inhibitor:** An Hsp90 inhibitor is a substance that inhibits the activity of the Hsp90 heat shock protein. Since Hsp90 stabilizes a variety of proteins required for survival of cancer cells, these substances may have therapeutic benefit in the treatment of various types of malignancies. Furthermore a number of Hsp90 inhibitors are currently undergoing clinical trials for a variety of cancers. Hsp90 inhibitors include the natural products geldanamycin and radicicol as well as semi synthetic derivatives

**Mechanism of action:** Among heat shock proteins the focus on HSP90 has increased due to its involvement in several cellular phenomena and more importantly in disease progression. HSP90 keeps the death proteins in an apoptosis resistant state by direct association. Its wide range of functions results from the ability of HSP90 to chaperone several client proteins that play a central pathogenic role in human diseases including cancer, neurodegenerative diseases and viral infection. Geldanamycin directly binds to the ATP-binding pocket in the N-terminal domain of Hsp90 and, hence, blocks the binding of nucleotides to Hsp90. Analysis of the effects of Geldanamycin on steroid receptor activation indicates that the antibiotic blocks the chaperone cycle at the intermediate complex, preventing the release of the receptor from Hsp90 and, eventually, resulting in its degradation. Ewing's sarcoma shows several deregulated anticrime loops mediating cell survival and proliferation. So their blockade is a promising therapeutic approach<sup>16</sup>. Proteosome analysis revealed that Hsp90 is differentially expressed between ewing's sarcoma cell lines, sensitive and resistant to specific IGF1R/KIT inhibitors. Fig.4.

**Natural product inhibitors:** The current HSP90 inhibitors are developed from geldanamycin and radicicol which are the natural product inhibitors and are starting point for new approach. HSP 90 is required for ATP dependent refolding of denatured or unfolded proteins and for the conformational maturation of a subset of proteins involved in the

response of cells to extracellular signals. These include steroid receptors Raf-1, Akt, Met and Her 2. HSP90 has conserved unique pocket in N terminal region. It binds ATP & ADP and has weak ATPase activity. This suggests that site acts as nucleotide or nucleotide ratio sensor. It is observed that nucleotides adopt unique C shaped bent shape when binding to this pocket. This is particularly unusual as nucleotides never adopt shape change in high affinity ATP/ADP sites.

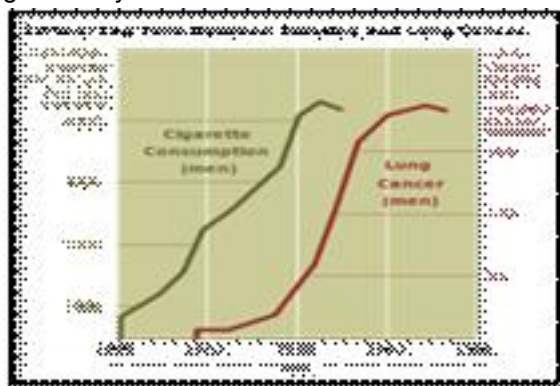


Fig.4: This is predicated chemical producing cancer

**Geldanamycin:** Derivative 17 AAG 17-N-Allylamino-17-demethoxygeldanamycin (17AAG) is the semi-synthetic derivative of natural product Geldanamycin. It is less toxic with same therapeutic potential as Geldanamycin. It is the first HSP90 inhibitor to be evaluated in clinical trials. Currently 17AAG is being evaluated as potent drug against AML. It is known that 17 AAG decreases the concentration of client proteins but it was a question of debate if 17 AAG affected the genes for client proteins or it inhibited cytosolic proteins. Gene expression profiling of human colon cancer cell lines with 17AAG proves that Hsp90 client protein genes are not affected but the client proteins like hsc, keratin 8, keratin 18, akt, c-raf1 and caveolin-1 are deregulated resulting in inhibition of signal transduction<sup>17</sup>.

**Purine scaffolding:** One of the important results obtained from the study of natural product inhibitor geldanamycin and its interaction with HSP90 is that the use of smaller molecules as inhibitors instead of complex molecules like radicicol is more efficient. Based on this information and advanced rational drug design technique, phenomenological relevant scaffolds can be constructed. Random in vitro screening of library of small purine-related molecules led to identification and screening of more than 60000 compounds that have inhibition potency. Chiosis and colleagues reported the novel class of HSP90 inhibitors using rational design. The important factors considered in this rational design are

- Key interaction between inhibitor and Asp 93/ser 52 and lys 112/lys 58 at the base and top of the pocket respectively.

- Occupancy by inhibitor of hydrophobic pocket laying midway in the binding site and constituted and is essential for affinity and selectivity .
- Molecules should have superior affinity to HSP90 as compared to natural nucleotides .
- Since many proteins depend on prune containing ligands for their function, derivatives of purine skeleton should have bioactivity, cell permeability and solubility .

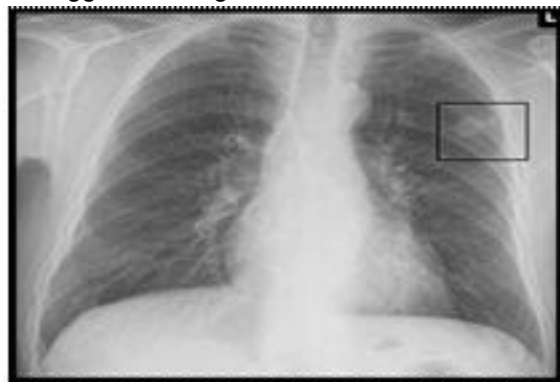
So based on these considerations and observations chiosis and colleagues theoretically designed following class of purines in which PU3 is the lead molecule.

**Gamitrinib:** Targeting networks of signaling pathways instead of single pathway is effective way for cancer treatment. Hsp90 is responsible for folding of proteins in multiple signaling networks in tumorigenesis. Mitochondrial Hsp90 is involved in complex signaling pathway that prevents initiation of induced apoptosis. Gamitrinib is a resorcinolic small molecule that specifically act on mitochondrial Hsp90. It induces a sudden loss of membrane potential which is followed by membrane rupture and initiation of apoptosis. Also gamitrinib is highly selective and does not affect normal cells.

### Mechanisms and of Molecular Marker Design Hypoxia:

**Intratumor Variability and Influence on Metastasis:** Hypoxia or oxygen deficiency is a salient feature of locally advanced solid tumors resulting from an imbalance between oxygen (O<sub>2</sub>) supply and consumption. Major causative factors of tumor hypoxia are abnormal structure and function of the micro vessels supplying the tumor, increased diffusion distances between the nutritive blood vessels and the tumor cells, and reduced O<sub>2</sub> transport capacity of the blood due to the presence of disease- or treatment-related anemia. Heterogeneities in tumor blood flow are associated with cyclic changes in pO<sub>2</sub> or cyclic hypoxia. A major difference from O<sub>2</sub> diffusion-limited or chronic hypoxia is that the tumor vasculature itself may be directly influenced by the fluctuating hypoxic environment, and the reoxygenation phases complicate the usual hypoxia-induced phenotypic pattern. Hypoxia induces a number of genes responsible for increased invasion, aggressiveness, and metastasis of tumors, including genes related with ECM interactions, migration, and proliferation. Necrosis, proliferation, and blood vessel distribution cannot predict the level or presence of hypoxia in an individual tumor. The exposure of endothelial cells to cycles of hypoxia/reoxygenation led to accumulation of HIF-1 $\alpha$  during the hypoxic periods and the phosphorylation of protein kinase B (Akt), extracellular regulated kinase (ERK) and endothelial nitric oxide synthase (eNOS) during the reoxygenation phases. Cyclic hypoxia, as reported

in many tumor types, as a unique biological challenge for endothelial cells that promotes their survival in a HIF-1 $\alpha$ -dependent manner through phenotypic alterations occurring during the reoxygenation periods. Histopathological examination of solid tumors frequently reveals pronounced tumor cell heterogeneity<sup>18</sup>, often demonstrating substantial diversity within a given tumor. The molecular mechanisms underlying the phenotypic heterogeneity are very complex with genetic, epigenetic and environmental components, such as shortage in oxygen. Hypoxic tumors appear to be poorly differentiated. Increasing evidence suggests that hypoxia has the potential to inhibit tumor cell differentiation, thus playing a direct role in the maintenance of CSCs, also blocks differentiation of mesenchymal stem/progenitor cells, a potential source of tumor-associated stromal cells. It is therefore likely that hypoxia may have a profound impact on the evolution of the tumor stromal micro environment, facilitating tumor progression. Hypoxia may help create a microenvironment enriched in poorly differentiated tumor cells and undifferentiated stromal cells. Such an undifferentiated hypoxic microenvironment may provide essential cellular interactions and environmental signals for the preferential maintenance of CSCs. Hypoxia greatly influences cellular phenotypes by altering the expression of specific genes, makes the tumors more aggressive Fig.5.



**Fig.5:** This is predicated diagnosis

**Quantum dot flux:** The molecular chaperone Hsp90 (heat shock protein 90) is a promising target in cancer therapy. Preclinical and clinical evaluations of a variety of Hsp90 inhibitors have shown anti-tumor effect as a single agent and in combination with chemotherapy. Current Hsp90 inhibitors are categorized into several classes based on distinct modes of inhibition, including (i) blockade of ATP binding, (ii) disruption of co-chaperone/Hsp90 interactions, (iii) antagonism of client/Hsp90 associations and (iv) interference with post-translational modifications of Hsp90. The different functions of Hsp90 isoforms and the form selectivity of drugs need further investigation. The correlation of cell surface Hsp90 with cancer metastasis and the emerging involvement of Hsp90 inhibition in cancer stem cells have become exciting

areas that could be exploited. Therefore, the aim of this review is (1) to summarize the up-to-date knowledge of mechanistic studies and clinical prospect of currently available Hsp90 inhibitors, (2) to enhance our perspectives for designing and discovering novel Hsp90 inhibitors, and (3) to provide an insight into less-understood potential of Hsp90 inhibition in cancer therapy<sup>19</sup>.

**Effects of decreased transmonolayer resistance:** In order to determine the effects of "leakier" tight junctions (increased tight functional conductance) on trafficking rates of quantum dots across RAECM, quantum dot flux was measured in the presence of 2mM ethylene glycol- bis ( $\beta$ -amino ethyl ether) N,N,N',N'-tetra-acetate (EGTA, Sigma) in both apical and basolateral fluids. RAECM were pretreated with EGTA for 30 minutes, followed by apical instillation of carboxylateamine, or non-modified quantum dots at a final concentration of 6.25  $\mu\text{g}/\text{mL}$  with continued presence of 2mM EGTA in both apical and basolateral fluids for 24 hours. Control monolayers were exposed apically to various quantum dots (6.25  $\mu\text{g}/\text{mL}$ ) in the absence of EGTA in the apical and basolateral fluids for 24 hours. Flux of quantum dots was assessed as described above. Bioelectric properties (i.e., transmonolayer resistance, equivalent active ion transport rate, and potential difference) of RAECM in the presence and absence of EGTA were determined over time. Effects of decreased temperature To determine the effects of energy depletion, the flux of amine-, carboxylate-, or non-modified quantum dots across RAECM was measured at 4°C (and 37°C) over 6 hours using an apical [quantum dot] of 6.25  $\mu\text{g}/\text{mL}$ . Effects of endocytosis inhibitors to explore if quantum dot translocation across RAECM involves endocytotic mechanisms, methyl- $\beta$ -cyclodextrin, chlorpromazine, and dynasore were used to disrupt lipid raft-mediated endocytosis, 30, 32, 36, 37 clathrin mediated endocytosis, 30, 38 and dynamin-dependent endocytosis (including clathrin-mediated and caveolin-mediated endocytosis). Resistance, equivalent active ion transport rate, and potential difference) of RAECM in the presence and absence of inhibitors were determined over time<sup>20</sup>.

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