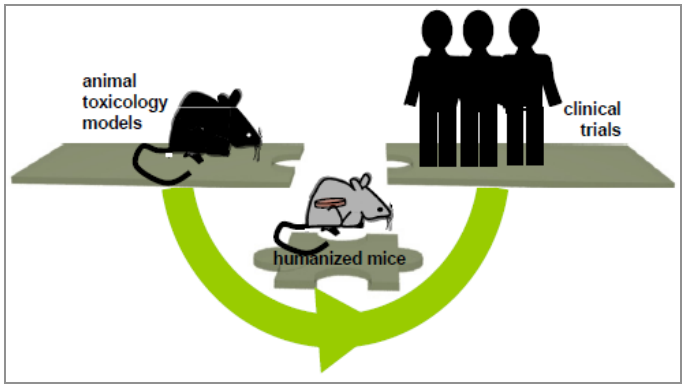
Alice A. Chen: Notable Inventions
Winner of the 2011 $30,000 Lemelson-MIT Student Prize

Humanized Mice with Tissue-Engineered Livers

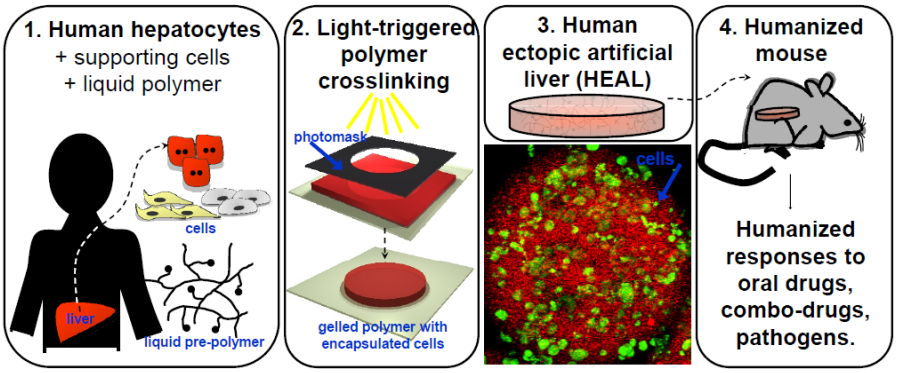
Drug development is risky, expensive and time consuming, requiring an estimated price tag of $1B and time commitment of 10 years for one drug's advance to market. Pre-clinical animal testing is an important step of this process that helps determine which drugs are safe for human clinical trials. However, because of stark differences between animal and human liver activity, pre-clinical animal screens commonly under-report human toxicities.[1] For example, over half of the drugs withdrawn from the U.S. and European markets were due to toxic effects unforeseen by pre-clinical studies.[2] Further contributing to the safety and economic burden of drug development, eight out of nine drugs fail in the clinical trial stage, often due to unpredicted human responses.



Chen's humanized mice invention aims to bridge the gap between unpredictable animal testing and human clinical trials.

Humanized mice are poised to improve the drug development pipeline, bridging the gap between animal testing and clinical trials, saving money and minimizing patient risk. However, current models to create humanized mice are limited to immune-compromised mice, which have restricted utility for research; and to mice with genetic liver injuries, which enable human cell repopulation of the mouse liver but are costly, time-consuming and difficult to predict or scale.

Applying her expertise in tissue engineering, Alice A. Chen created humanized mice with tissue-engineered human livers, which can metabolize compounds to human-specific products and predict toxic drug interactions, among other behaviors. In Chen's model, an artificial human liver is first engineered *in vitro* by combining human liver cells, supporting cells, and a liquid solution that solidifies when triggered by light. The resulting engineered human liver, patterned with light to resemble a soft contact lens, is then implanted into the abdomen of a mouse. Chen's humanized mice can be customized by donor or mouse background, allowing drugs to be tested on a large population of various "patients." In addition to reducing the cost of humanizing mice by nearly 100-fold, Chen's tissue-engineering approach also reduces the time for humanization from one month to one week, making it more suitable for large scale pharmaceutical adoption and broad research.



Multi-stage development process of humanizing mice via tissue engineering.

[1] Smith and Obach, Chem Res Toxicol 2006, 19:1570-1579
[2] Kola and Landis, Nature Reviews Drug Discovery 2004, 3: 711-715

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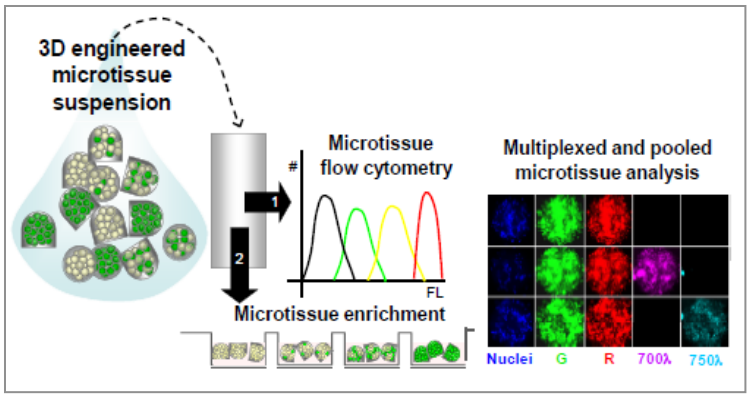
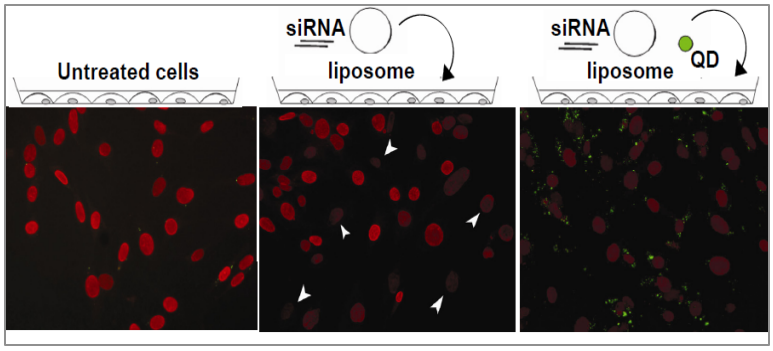
High-throughput and Multiplexed 3D Microtissue Analysis



Although 3D tissue-engineered models play a critical role in biology, drug development and regenerative therapies, the slow and limited methods used to assess biological outcomes hinder their effective development, testing and utility. Chen and colleague Greg Underhill co-invented a platform to functionally analyze large populations of miniaturized 3D engineered "microtissues" by integrating biomaterials, novel optical labeling strategies, and large-particle sorting methods. This invention changes a paradigm of tissue engineering in the same way that flow cytometry was transformative to single-cell biology. Unlike current empirical approaches to tissue engineering where there is no high throughput way of retrieving statistical data, Chen and Underhill's method allows for the assessment of microtissue functions with unprecedented flexibility – additionally reducing experimental costs and enabling 3D tissue screening for new discoveries. Featured on the cover of the October 2010 issue of *Integrative Biology*, Chen and Underhill anticipate continued enthusiasm and widespread adoption of this new invention in the cell and tissue research field.

Quantum Dots to Monitor RNAi and Improve Gene Silencing



RNA interference (RNAi) is initiated in cells by introducing a special form of RNA called small interfering RNA (siRNA). In cell biology, RNAi has become a powerful tool for "silencing" the functions of a specific gene to determine its purpose. However, gene silencing can be challenging and unpredictable if the siRNA is inconsistently delivered among cells. While attempting to use RNAi to study the roles of specific genes involved in cellular interactions, Chen needed to ensure that all cells were receiving siRNA and experiencing complete – and not partial – gene silencing. Her challenge was doing this without directly altering the siRNA molecules or the surrounding cellular environment. Chen collaborated with colleague Austin Derfus to develop a method to monitor siRNA delivery based on the electrostatic assembly of negatively charged quantum dot fluorescent probes, negatively charged siRNA, and positively charged lipid carriers, or liposomes. Cells treated with these assemblies either contained bright fluorescence and siRNA, or dim fluorescence and no siRNA, and could be separated from each other using fluorescence-activated cell sorting (FACS). Beyond enabling isolation of cells with desired gene silencing properties, the method enables long-term monitoring of siRNA delivery and trafficking in cells. It further enables multiple siRNAs to be paired with unique quantum dot tags for dual- or multi-siRNA gene silencing. From this, researchers can now isolate cells with precisely defined gene silencing properties, resulting in greater accuracy and efficiency in biology research.