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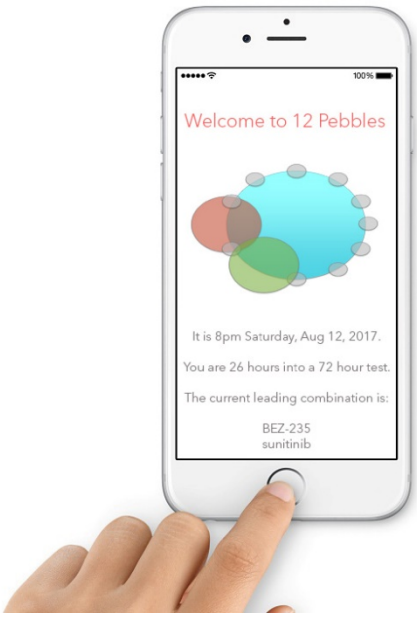
Dear Janet,

Thank you for reaching out to explore the possibility of promoting the development of therapies for DIPG at cc-TDI. We'd be grateful for support through your next event, Relay for Jack, in May.

I'd like to propose a high-risk, high-reward pilot project: Jack's 12 PEBBLES. For this research project, there is the big picture vision, and then there are the early pilot study steps towards the vision (where your funding would go).

Here is the Vision:

We and others have identified drugs effective at slowing tumor regression – these drugs do not bring about tumor shrinking; however, on an *individualized* basis, drug combination may be remarkably effective and life-extending. The choice of those 2 drugs needs to be carefully made – because drug side effects might be non-trivial. Our approach is to design a microchip implanted into the patient's tumor that directly tests which 2 drugs out of 12 will combine best to slow, stop or reverse DIPG tumor growth.



Imagine a child has 5 tiny microchips implanted in their tumor on a Friday afternoon. Each microchip is smaller than half the width of a pencil eraser. The child goes home that day. Each microchip wafer is a shaped like a circle, and from the edge of each wafer there are 12 equally-spaced drugs slow-released into the circle. DIPG cell death is recorded by impedance changes across the microchip. Each drug on the microchip creates 'ripples' of DIPG tumor cell death across the circular wafer, *like a pebble would make when dropped in a pond*. A little bit of signal processing math is applied to understand the intersecting "pond ripples" of tumor cell death across the circular wafer (where the ripple of effective DIPG cell killing of one drug meets the ripple of another effective drug). Meanwhile, the microchips communicate to the parents' iPhones for how well each drug and drug combination is working. Saturday night, a certain 2-drug combination appears optimal, but by Monday morning the definitive answer is that a different 2-drug combination is ideal. The child and parent go to the clinic on a Monday morning and show the results on their iPhone to their neuro-oncologist. The doctor says, "sounds good – let's start that today."

Here are the Pilot Study Goals:

We will design a macroscopic (quarter-sized) prototype in collaboration with a Student Capstone Team at Oregon Institute of Technology. The key milestone is to validate the measured impedance changes caused by drug-induced DIPG tumor cell death. We will compare impedance changes to definitive, established cell viability and cell death stains. The other important aspect is to develop the first set of math algorithms that 'deconvolute' the drug-related ripples of DIPG cell death across the wafer. These 2 key milestones will be accomplished in 12 months at an approximate cost of $75,000 to perform/support. Any part of this cost moves this project towards the goal line.

12 PEBBLES is a project we've been planning towards for some time, in direct response to the needs of DIPG patients. This project is made possible given the culture of our institute, strongly influenced by our Board member, Sunit Rikhi, the recently-retired vice president of the Intel Custom Foundry.

In full disclosure, the Objectives of the patent application filed September 2015 include:

- An implantable microchip device that detects tumor cell viability by conductance/impedance
- An implantable microchip device that has embedded anti-cancer therapeutic agents (i.e., drugs) arranged circumferentially
- An implantable microchip device that has embedded anti-cancer therapeutic agents arranged circumferentially for whom anti-cancer activity of these drugs can be detected by changes in conductance/impedance
- An implantable microchip device that has embedded anti-cancer therapeutic agents arranged circumferentially for whom monotherapy efficacy of anti-cancer activity of these drugs can be detected by changes in conductance/impedance on the outside periphery
- An implantable microchip device that has embedded anti-cancer therapeutic agents arranged circumferentially for whom combination efficacy of anti-cancer activity of these drugs can be detected by changes in conductance/impedance inside of the circumference
- An implantable microchip device that has embedded anti-cancer therapeutic agents for which monotherapy or combination therapy anti-tumor efficacy can be communicated to an external device by near-field communication (e.g., RFID or NFC).
- An external device that takes reading from one or more implantable devices of anti-tumor efficacy as a measure of changes over time of conductance/impedance and deconvolutes anti-tumor activity with respect not only to conductance/impedance but also drug diffusion characteristics across the microchip and across the adjoining tumor tissue.
- An algorithm running on an external device (e.g., as an App/application) that summarizes monotherapy or combination therapy efficacy in one or more sites of implanted microchips for the same patient.

Thank you for considering this proposal. We look forward to our partnership and making an impact for children and families whose lives are touched by DIPG.

Sincerely,

Charles Keller MD, Scientific Director, cc-TDI