Telocyte Newsletter
Q2 2018

Alzheimer's disease has been with human beings as long as we've been human. Few of us grew old enough to suffer from "senile dementia"; many of us died as children, during childbirth, or from trauma, infection, and the host of diseases that we are still prey to. And yet, some of us, even thousands of years ago, succumbed to Alzheimer's.

Alzheimer's disease was first named more than a century ago. Essentially, it's been around as "Alzheimer's disease" for about as long as modern medicine began to become modern. We knew about the "shrunken brain", the amyloid plaques, the dying neurons, and even the tau tangles for a century or so. And yet, modern medicine or not, we succumbed to dementia.

Alzheimer's disease trials, more than 400 of them, even if we only count those registered on the clinical trials website, have been trying to prevent, cure, or stop the disease for several decades. More recently, those trials have moved toward the more fatalistic goal of merely hoping to slow it down, and even then, only statistically. And yet, even after hundreds of trials, we succumb to Alzheimer's.

Alzheimer's disease as caused by cell aging, was first suggested twenty years ago and that same paper suggested that we might be able to use cell aging as a therapeutic target. That notion, that cell aging not only caused Alzheimer's disease and a host of other age-related diseases but could be an effective point of intervention was consistent with everything we know about Alzheimer's disease, everything we know about those failed clinical trials – and why they failed, and everything we know about human aging itself. And yet, even after twenty years, we succumb to Alzheimer's.

Alzheimer's disease became the target for our human trials two years ago. We have put our time, our resources, and our very lives into moving ahead, into getting to human trials, into finding a way to save human lives. We have flown around the world, we have spoken at conferences, we have met with investors. We have found others to join us, we have designed protocols, we have niggled over the best way to deliver a cure in real, suffering human patients whose souls are day-by-day disappearing to Alzheimer's disease. And yet, even after two years, the people we most want to help still we succumb to Alzheimer's.

Alzheimer's disease is hard for most people to understand. Researchers, clinicians, investors, regulatory agencies all struggle to understand the disease. Most people, once they overcome their assumptions and look carefully at the disease with a fresh eye, realize that we not only have the ability to understand Alzheimer's, we have the ability to cure it. To cure it takes several things. It requires that we understand the disease itself and that we have the right tools to fix the fundamental problem: the changes in gene expression that drive all of the other findings that we mistake for the disease itself are no more than symptoms and outcomes, rather than the cause. It also takes the ability to move from merely having the understanding and the tools to the clinic itself. We now have the understanding and the tools. We need only move to the clinic.

To get there, requires very little else. We need the funding and we need regulatory approval. We are on the edge of both as we quiver on the brink of a cure for Alzheimer's. And yet, even now, those we could cure still succumb to Alzheimer's.

We need to finish a job that began when we first became human.

Where we stand and where we are going

As we finish the first quarter of 2018, we are confident that we can not only prevent and cure Alzheimer's disease – and other age-related dementias – but most other age-related diseases. We are still scheduled to begin our human trials next year and we are putting together our formal application for the FDA. In chemistry, one talks about "rate-limiting steps" in any process: those steps that are the funnel, the slowest process, the narrowest point in the path forward. We have three rate-limiting steps: investors, our production schedule, and the FDA. At the moment, our major concern is funding. While we have several interested global investment groups, interest is not sufficient: we need funds to move to human trials. Production of our gene therapy agents lies in the hands of the vendors. Given the current interest in AAV gene therapy and the time it takes to produce high-quality gene therapy vectors, the vendor's ability to provide GMP quality agents adds to the time to human trials. Finally, the FDA will determine when we can finish our animal toxicity study and when we can begin our human trial.

The sooner we finalize funding, the sooner we can move ahead.

Meet our Scientific Advisory Board:

Last quarter, we featured Brian Kaspar, one of our two world-renown specialists in gene therapy. We'd now like to introduce you to the other one: Mimoun Azzouz,

Professor Mimoun Azzouz, formerly Director of Neurobiology at Oxford BioMedica, is currently Chair of Translational Neuroscience at the University of Sheffield. Azzouz is also Deputy Head of Neurology Unit and Director of Research & Innovation at the Neuroscience Department. His translational research productivity is characterised by publications in top ranking scientific journals, including *Nature*, *Nature Medicine*, *Nature Neuroscience*, and *STM*. Several inventions emerged from his research. One of his major achievements is his involvement in a gene therapy approach designed to achieve dopamine replacement in models of Parkinson's disease. This strategy has yielded significant translational impact having entered into phase I/II human clinical

trials since 2008. He is currently driving 2 clinical development programs through regulatory tox, GMP clinical manufacturing and regulatory bodies. He recently won top level EU *ad hominem* prestigious ERC Advanced Investigator (2011) and ERC Proof-of-Concept (2017) Awards. These awards are acknowledging his pre-eminence in European biomedical research. He is/has been advisor for companies and academic institutions. He is currently a member of scientific Panels/Boards for various funding bodies such as the Medical Research Council (DPFS MRC, UK), the French Muscular Dystrophy Association (AFM), the Health Research Board (HRB) of Ireland and the Neuroscience Panel, Germany. He has been recently named as Board member of the British Society for Gene and Cell Therapy.