

# LJARI: Creating Cutting-Edge Systems for Addiction Research





# LJARI: CREATING CUTTING-EDGE SYSTEMS FOR ADDICTION RESEARCH

Founded by **Catherine Rivier, Maury Cole and Bette Cessna**, **La Jolla Alcohol Research, Inc (LJARI)** is developing cutting-edge systems for researchers in the field of alcohol and drug addiction.

A glass of cold beer after a hot day of hard work. A glass of wine on your anniversary dinner. A cocktail at the beach, complete with jaunty umbrella. We drink alcohol on many occasions, for many reasons – it acts as a way to relax and a means to celebrate. A ubiquitous drink that we have enjoyed throughout history, alcohol forms an almost inseparable part of much of our culture.

Yet alcohol has a darker side – one in which the glass of beer or wine leads to another glass, and another, and so on into drunken paralysis. A side in which the feeling of celebration is replaced by the feeling of anger, where that one cocktail on holiday turns into a bottle of bourbon each night. A side where alcohol becomes a toxic friend who destroys your life and yet one whom you simply cannot live without.

Alcohol addiction is a major problem across the world, driven by the cheap cost of alcoholic drinks and the ease of obtaining them. Yet despite this, we often have difficulties saying why addiction occurs – what exactly is the difference between the dependent alcoholic and the social drinker? Where does addiction start and how does it progress? How does alcohol dependence affect our health, be it in the short term or the long term?

These questions become even more difficult to answer when we move beyond alcohol and look into the field of drug dependence. The sheer variety of drugs that are available in modern society means that researchers need to cover more ground, yet the illegal nature of the addiction means that researchers are often poorly funded. Despite this, the same questions need to be answered – where does addiction begin, how does it progress, and what are the health implications?

As with many questions about human behaviour, the answers revolve around a number of factors, from the psychological to the neurochemical. This in turn means that researchers in the field of addiction must balance many different factors when trying to identify those that have the strongest or most critical effects. This is often done through the use of animal models – most commonly the mice and rats that are used in laboratories around the world. Both species can develop alcohol or drug dependence, and both develop health issues that are analogous to human ones. For this reason, much ground-breaking work in the field of addiction has been performed with the help of animal researchers.

Mice and rats are, naturally enough, different to humans. Humans drink alcohol because they enjoy it and they enjoy the effects it brings. Rats dislike the taste of alcohol as well as the effects, which means that they will voluntarily drink it up to a certain point but no further. This aversion to alcohol means that rats are a good model for the blood-alcohol levels of short-term binge drinkers, yet cannot simulate the much greater, continuously-high levels of alcohol found in the system of a human alcoholic. Methods do exist to reach these higher blood-alcohol levels, usually by injecting or force feeding the rats with alcohol. However, these are stressful for the animals, producing a number of stress-related hormones that can interfere with the biochemical mechanisms being studied. Similarly, these methods are difficult to perform over long periods of time, making them an unreliable simulation of alcoholism.

There is thus a need for better modelling of alcoholism in animal models, and it is this need which the team at LJARI set out to fulfil.



*Self-administration controller*



## New Solutions for Addiction Research

LJARI, short for La Jolla Alcohol Research Inc, was founded in 1997 by Professor Catherine Rivier from The Salk Institute, and Maury Cole and Bette Cessna, both from The Scripps Research Institute. Their roles eventually evolved into that of Chief Science Officer and Scientific Head (Catherine Rivier), CEO and Head of Design Engineering (Maury Cole) and Director of Operations and Head of the Business Team (Bette Cessna). The company



*The single-chamber self-administration e-Vape™ vapor inhalation system*

is currently located in La Jolla, California, a beautiful region with a number of highly-reputed research institutions. 'San Diego County represents one of the top alcohol and drug dependence research areas in the country,' says Bette.

The company was founded with the intent of commercialising an alcohol vapour system that Maury Cole had developed as part of his previous work in the field. The original system, developed to assist in experiments for a large Alcohol Research Centre grant, works by vaporising ethanol and incorporating it into the airflow entering the rat cages. The rats then inhale this and it becomes rapidly incorporated into the bloodstream, leading to high blood-alcohol levels with none of the stress-related problems associated with other methods. 'Physiological relevance to humans is paramount in animal research,' explains Maury. 'The panic response and stress factors induced by handling rodents presented a huge barrier, as this panic response is not present in humans who drink alcohol.'

The company was originally funded with the help of the highly competitive Small Business Innovation Research grants – funding which was vital for the development of the commercial vapour system. With the ability

to provide specific levels of alcohol vapour to up to eight animal cages, the LJARI system offers an extremely useful level of control for researchers in the alcoholism field. In particular, the ability to set up the cages with bedding and toys meant that the rats would feel perfectly comfortable while becoming very drunk – an excellent model for the human experience.

The basic technology and available modifications (such as advanced safety features or the ability to allow rats to dose themselves) meant that the LJARI system has been widely taken up by the research field, with machines installed in laboratories across the world. In the US, the company's products are currently being used at top academic institutions and federal agencies, such as the National Institute on Drug Abuse (NIDA), the National Institute on Alcoholism and Alcohol Abuse (NIAAA), the Food and Drug Administration (FDA), Mayo Clinics, the Scripps Research Institute, the Salk Institute, Yale University and Harvard University. 'We custom build each system to order, because the combinations are so varied,' says Bette. 'Our customisation ability enables us to give investigators exactly what they need for their research.'

These products have led to a number of

ground breaking discoveries based on data gathered through the use of the LJARI machines. For example, researchers from the Scripps Institute have worked with alcohol-dependent rats who have been provided with high levels of vaporised alcohol through the use of LJARI systems. These rats were treated with a compound that led to inactivation of certain neurons within the amygdala – a part of the brain critical for memory, emotion and decision making. The researchers found that by targeting specific subsets of the amygdala, they were able to produce a long-term decrease in alcoholism in the dependent rats. This in turn suggests that the region could be targeted in the development of treatments for humans.

#### **Tools to Investigate the Dangers of E-Cigarettes**

Although the company was founded with a focus on alcohol studies, LJARI eventually branched out into several other areas of addiction research. One of these is nicotine, and in particular, the simulation of e-cigarette use. E-cigarette use is rapidly booming across the developed world, driven by increased restrictions on plain cigarettes and a corresponding belief that they are the 'healthier' alternative.





*Vapor generator with the vape tank on top*



The actual health risks are relatively unknown for e-cigarettes, as the pace of research is much slower than the pace of commercial development. 'Because of the explosive growth of e-cigarette use, the NIH, CDC, FDA and other federal and state agencies began allocating funding to e-cigarette research, as data is desperately needed for safety and regulatory policy,' says Maury. E-cigarettes rely on the production of vaporised liquid that contains nicotine, and thus were a perfect match to the systems already developed at LJARI. The new system, known as e-Vape™, allows researchers to study the long-term effects of e-cigarette fumes on animal models.

Inhalation of addictive compounds is, naturally, not limited to nicotine and tobacco. The ever-expanding legalisation of recreational marijuana means that more and more people are legally inhaling than ever

before. 'Voters have made their feelings on legalized marijuana very clear,' notes Bette, 'and most, if not all states are expected to vote for legalisation within the next decade.' This wave of legalisation is bringing new technology and venture capital into the marijuana field. One of the outcomes of this change is the development of e-cigarette cartridges which contain THC – the active compound found in marijuana. 'The resulting vapour does not have the traditional marijuana smell,' explains Bette, 'making it very easy for folks to walk down the street vaping marijuana, even in states where it has not been legalised.'

This is concerning for both regulatory and research agencies – the effects of e-cigarettes are poorly understood – the effects of vaporised cannabinoids even less so. With a strong position in simulating vaporised compounds, LJARI was thus in an excellent position to extend the capabilities of their system. A further Small Business Innovation Research grant was obtained, allowing the team at LJARI to extend the e-Vape™ system into one that can deliver marijuana, psychostimulants, opioids and various other drugs. These systems are highly sought after: 'Every time a system is built, we schedule to photograph the system so it can be added to our website,' says Maury, 'then a lab begs us to fill their order now and wait to photograph the next one! "We don't care if it's a prototype, we want it now" is not exactly a problem we will complain about!'

As a relatively new system, the majority of the publications developed using data from the e-Vape™ system have focused on establishing the ability of the system to simulate many of these drugs. For example, rats can be provided with vaporised stimulants such as methamphetamine (speed) or mephedrone, and will then show the heightened activity and movement that we associate with methamphetamine users. Similarly, the system has been shown to work with vaporised THC, with rats showing typical symptoms of intoxication such as reduced body temperatures and slower reflexes.

A more recent work conducted by NIDA showed that rats could be provided with vapour forms of the opioid Sufentanil – the strongest opioid painkiller which can currently be used by humans. The rats rapidly developed an addiction to the Sufentanil, seeking out hits when possible and showing signs of withdrawal (shaking, teeth-chattering) when denied. 'We're really excited to have such a huge range of drugs being used with our e-Vape™ system,' says Bette, 'especially given the opioid addiction crisis in the US.'

#### **Plans for the Future**

La Jolla Alcohol Research, Inc is currently going from strength to strength, developing innovative systems for researchers in the field of alcohol and drug addiction. Although the team's latest experiments have predominantly been focused on establishing the LJARI system in the field of drug-related research, follow-up studies will begin to investigate the biological and neurochemical mechanisms behind addiction, as well as the long-term health effects of these treatments. This will help scientists and doctors determine how best to treat human drug and alcohol-dependence, which in turn, will help save many from their toxic relationships.



# Meet the researcher

**Maury D Cole**  
President and CEO  
La Jolla Alcohol Research, Inc.  
La Jolla, CA  
USA

Maury Cole began his scientific career in 1985, when he worked as an animal lab technician in the Department of Animal Research at The Scripps Research Institute until 1987. While also working as a supervisor at the Agouron Institute, he simultaneously completed his degree in Biology at San Diego State University in 1989. Since the completion of his degree, he worked as a senior research associate in the Department of Neuropharmacology at The Scripps Research Institute. Maury is one of the founders and the current CEO of La Jolla Alcohol Research, Inc. With over a decade of experience in animal handling and many years working with rodent models of alcoholism, Maury was the perfect person to develop what would become the LJARI alcohol vapour system and the follow-on e-Vape™ system. With over 13 publications to his name from these systems alone, and more on the way, Maury Cole has significantly advanced the field of alcohol and drug research.

## CONTACT

**E:** mcole@ljari.com  
**T:** (+1) 619 279 7587  
**W:** <http://www.ljari.com/>

## KEY COLLABORATORS

Bette Cessna, La Jolla Alcohol Research, Inc.  
Catherine Rivier, La Jolla Alcohol Research, Inc.

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