



WAVEGUIDE

NMR IN THE PALM OF YOUR HAND
NEWNMR SESSION JUNE 30 2021

WaveGuide Agenda

- ☐ Introduction WaveGuide Team
- ☐ Nuclear Magnetic Resonance (NMR) Brief History
- ☐ Seminal work completed at Harvard University
- ☐ Commercialization of the WaveGuide μ NMR
- ☐ Applications
 - ☐ Rational Product Authentication of PD1-PDL1 Mabs
 - ☐ PD1-PDL1 Authentication
 - ☐ Vaccine Authentication

Executive summary: WaveGuide Corporation

Founded & funded: 2015

Location: Waltham, MA. USA (ISO 13485:2016)

Operating status:

- Privately held, Delaware C corporation
- Angel investors through Series-A , \$30M raised

Product & commercial status:

- Beta ready platform for field trials
- NRE projects active with customers
- Commercial launch in 2020

Patent & intellectual property portfolio:

- Two assigned patents from Harvard University that encompass the core technology that enables small, low-cost, inhomogeneous magnets to produce a handheld chemical analyzer based on NMR. Fundamentally amplifying the NMR signal-to-noise by a factor of 10,000 times.
- Additional (6) patents filed by WaveGuide Corp bolstering the core technology.
- Company know-how, nanoparticle chemistry, algorithms, calibrations, and unit-unit repeatability.

More WaveGuide online

- Interview at NYSE: <https://vimeo.com/264443486>
- LinkedIn: <http://www.linkedin.com/company/portablenmr>



HARVARD UNIVERSITY
Department of Physics



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Executive operating members of the team



Nelson K. Stacks

CEO & President

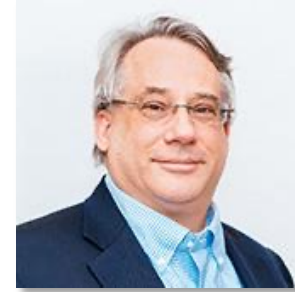
- Serial entrepreneur with broad turn-around experience in biopharma, diagnostics & medical devices
- Multiple CEO roles in successful turn-arounds
- Molecular Insight Pharmaceuticals, Tarpon Biosystems, Vascular Pathways, and Xenome
- Venture capitalist in healthcare, diagnostics, and digital comms with 3i & Oak Investment Partners
- Kauffman Fellow Class IV



Wendy Graham-Coco

Chief Operating Officer

- Pharmaceutical and biotech executive with extensive experience in drug and device development in both therapeutic and diagnostic products
- Oversees operations across clinical, regulatory, and quality systems
- Former roles with Molecular Insight Pharmaceuticals, Biostream, Inc. and the Massachusetts General Hospital



Marcus Semones Ph.D.

Co-Founder & CSO

- Entrepreneur with expertise in drug development and analytical diagnostic technologies
- Senior Investigator, GSK Pharmaceuticals
- Harvard University, Faculty Department of Chemistry



Duane Sword

Vice President, Business Development

- 25 years in photonics, imaging and portable diagnostic ventures
- Hewlett-Packard & Agilent Technologies
- Ahura Scientific, VP Product Management, Marketing & Sales portable FTIR & Raman (acquired)
- Thermo Fisher Scientific, Senior Director Global Sales portable analytical solutions
- Precise, CEO (C1-C5 hydrocarbon composition & BTU/CV) (acquired)
- Launchpad Venture Group (member)

What is NMR?

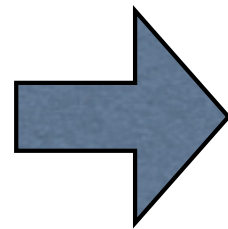
Nuclear Magnetic Resonance

- NMR spectroscopy is a laboratory based analytical chemistry technique used in quality control and research for determining the content and purity of a sample as well as its molecular structure.
- The Purcell group at [Harvard University](#) and the Bloch group at Stanford University independently developed NMR spectroscopy in the late 1940s. Edward Purcell and Felix Bloch shared the 1952 Nobel Physics Prize for demonstrating NMR in condensed matter: water and paraffin (Isidor Isaac Rabi presented with the 1944 Nobel Prize for the discovery of the technique).



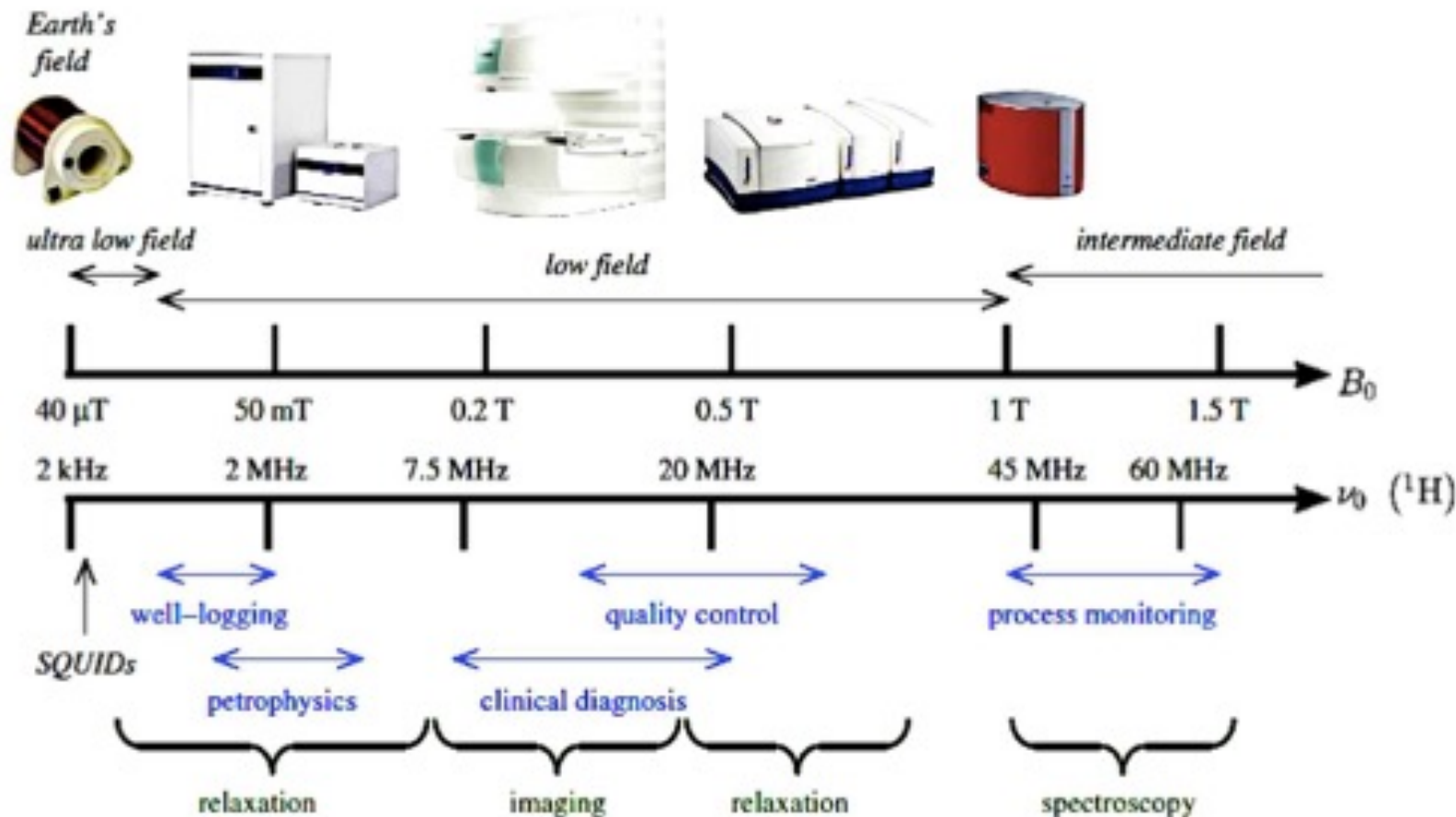
The First Commercial NMR, The HR-30, was sold in 1952 by Varian Associates to Humble Oil Company. This 30 MHz water-cooled electromagnet spectrometer weighed over two tons and had sufficient field homogeneity to resolve the chemical shifts of the three groups of protons in ethanol.

Why Miniaturize NMR Instruments?



Technology's Value Increases as it Migrates from Stationary to Mobile Formats

Commercial Low Field TD-NMR Instruments

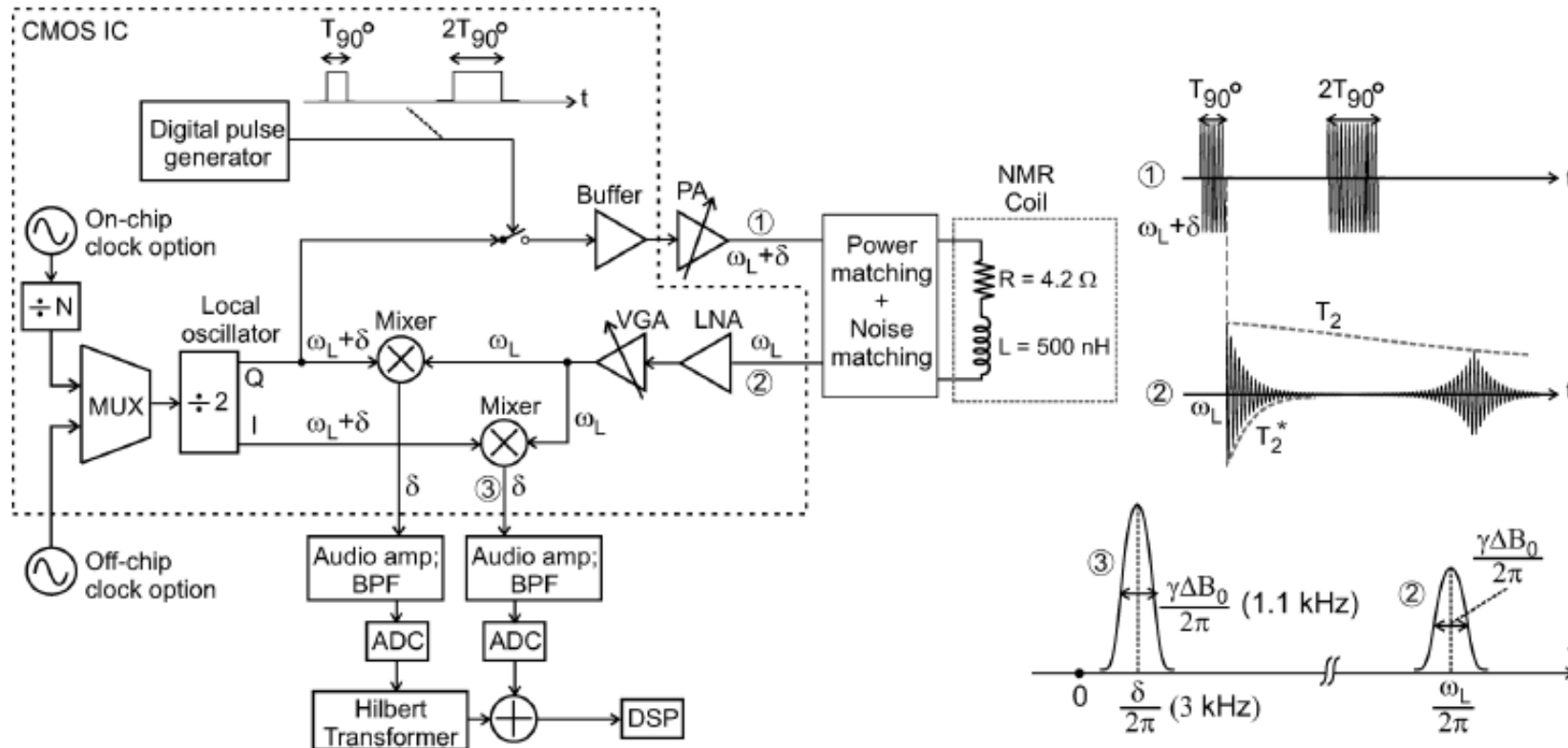


- Contemporary Low Field TD-NMRs are \$80k to \$200k
- Permanently fixtured systems in a laboratory as these devices require significant temperature stabilization
- Expensive and sophisticated and requires a PhD/ Masters to use
- Wide range of applications in different fields of use

Can you take the PhD / Masters personnel out of the workflow??

NMR – New Technology 60 Years After The Invention

Core Technology: Harvard's Discovery

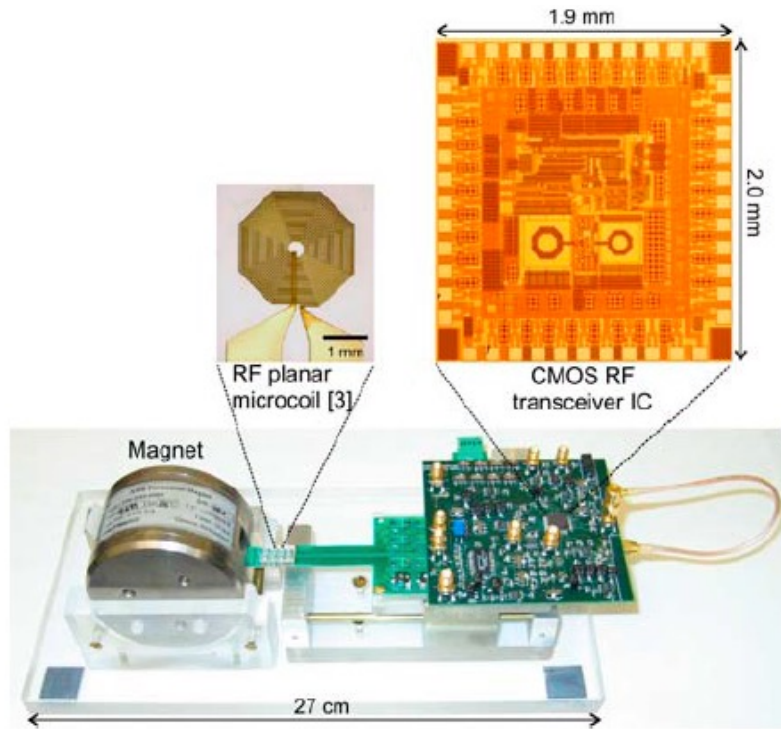


A 50 Ω matching with abundantly available 50 Ω off-the-shelf LNAs has been the dominant choice for the LNA-coil connection in all NMR's commercialized

Harvard switched to power matching and noise matching at the Larmor frequency and integrated on a CMOS

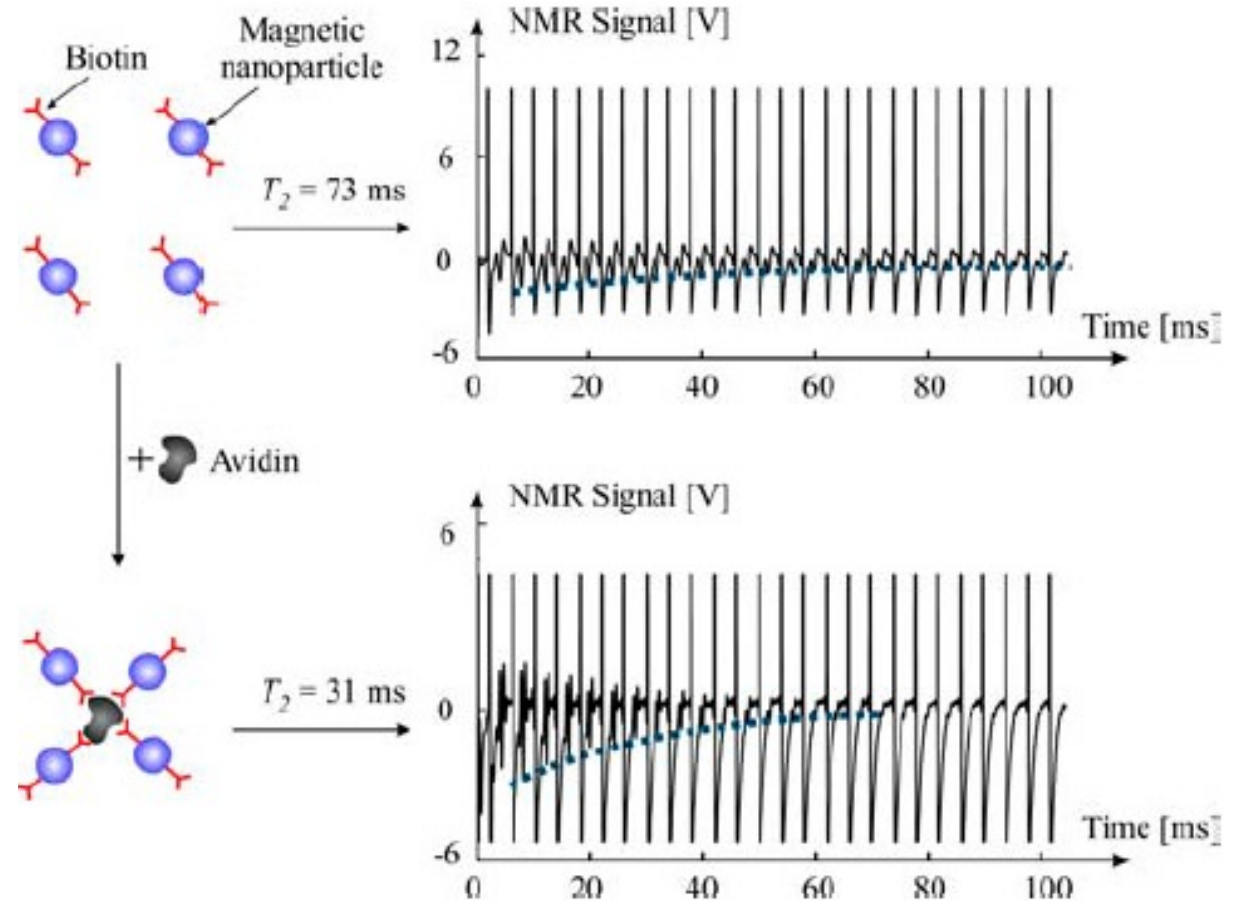
Professor Donhee Ham and Graduate Student Nan Sun
EEE J. Solid-State Circuits **44**, 1629 (2009)

NMR Discovery at Harvard 1st CMOS



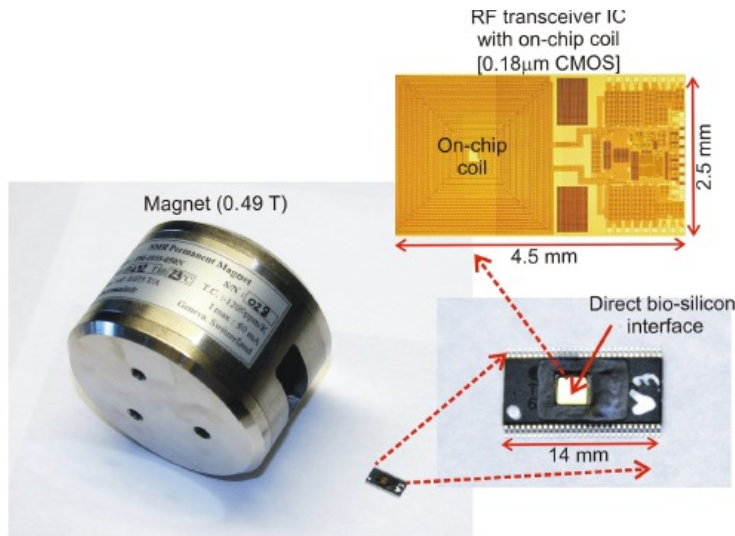
Partially integrated (LNA VGA)
 $Q=16$ for Planar Coil
 $Q=200$ for Solenoid Coil

EEE J. Solid-State Circuits **44**, 1629 (2009)



T_2 Measurement in Water Detection of Avidin
 Planar Coil 20 fmol sensitivity

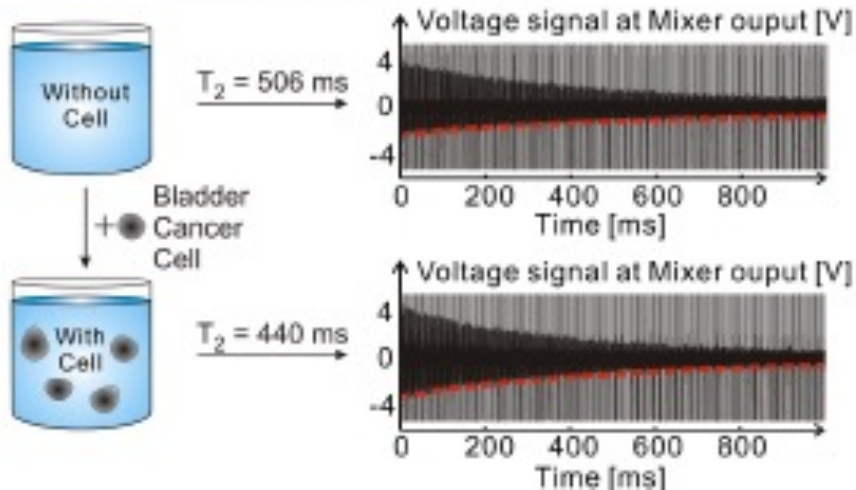
NMR Discovery at Harvard 2nd CMOS



***Coil on Chip & Solenoid
Fully Integrated (LNA VGA
PA)***

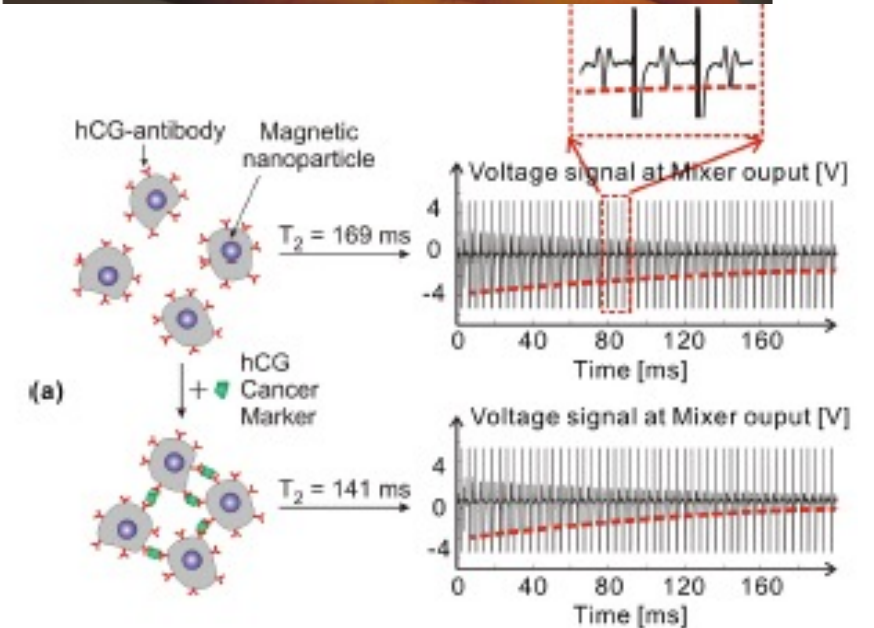
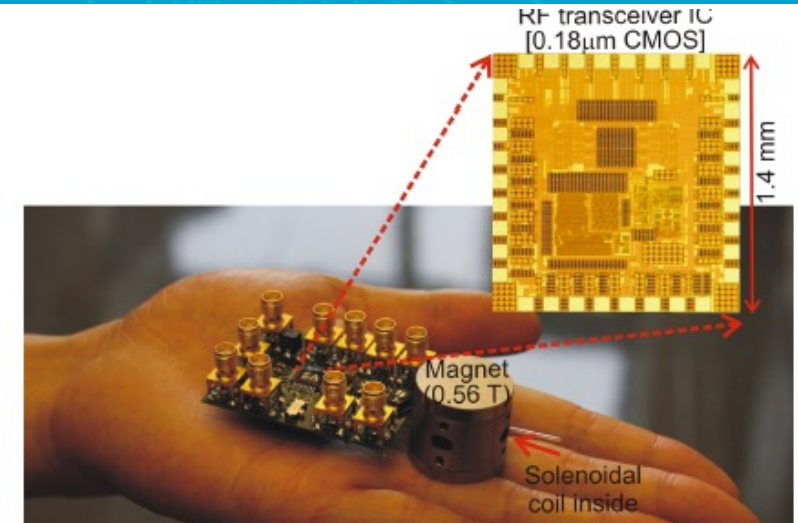
1-Chip NMR system (Lab-on-a-chip)

- Direct interface between bio-sample and IC
- Disposable sensor probe with on-chip coil

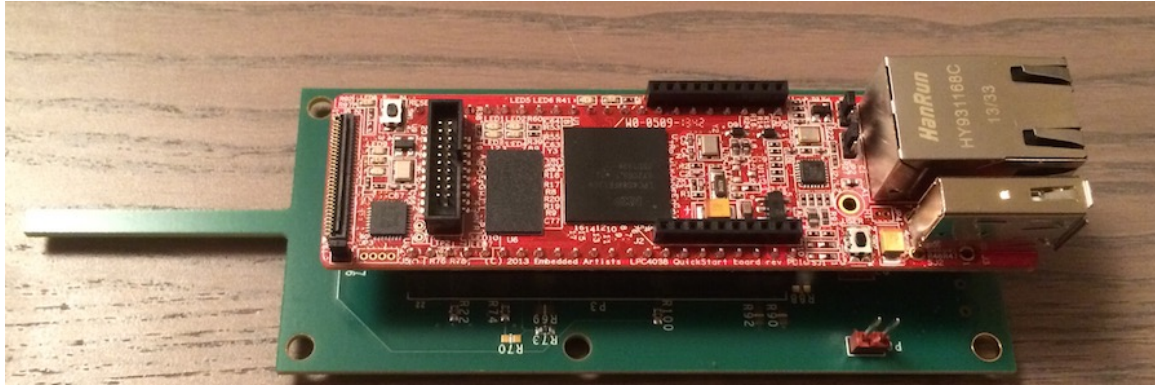


EEE J. Solid-State Circuits **46**, 342 (2011)

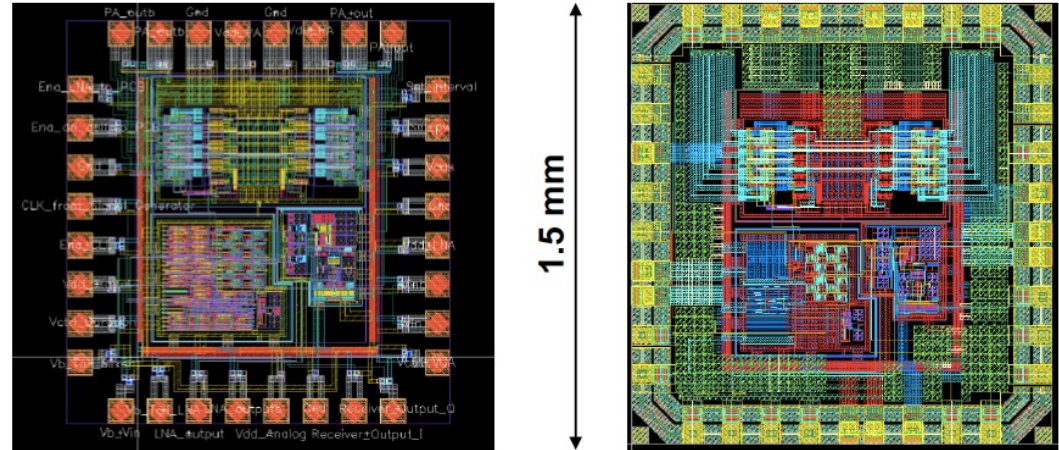
***MNP Binding assay for
biosensing applications***



Commercialization of Harvard's CMOS Technology



ADI re-designed PCB board to incorporate all components to execute experiments (PC driven)



HU

ADI



ADI fixed critical bugs in HU CMOS chip design to reproduce their results

ESD structures on Harvard chip were just diodes for all pins (analog and digital signals and power). Used ADI silicon proven I/Os

WaveGuide secured an early partnership with Analog Devices (ADI) to evaluate and reproduce Harvard CMOS technology before infusion of capital

Commercialization of Harvard's CMOS Technology at WG

WG1000 NMR transceiver ASIC

TSMC 0.18um RF CMOS process

48-pin QFN 7x7mm package with exposed paddle (2mm x 2mm die size)

Supports permanent magnets from 0.25T to 1.5T (10-64MHz)

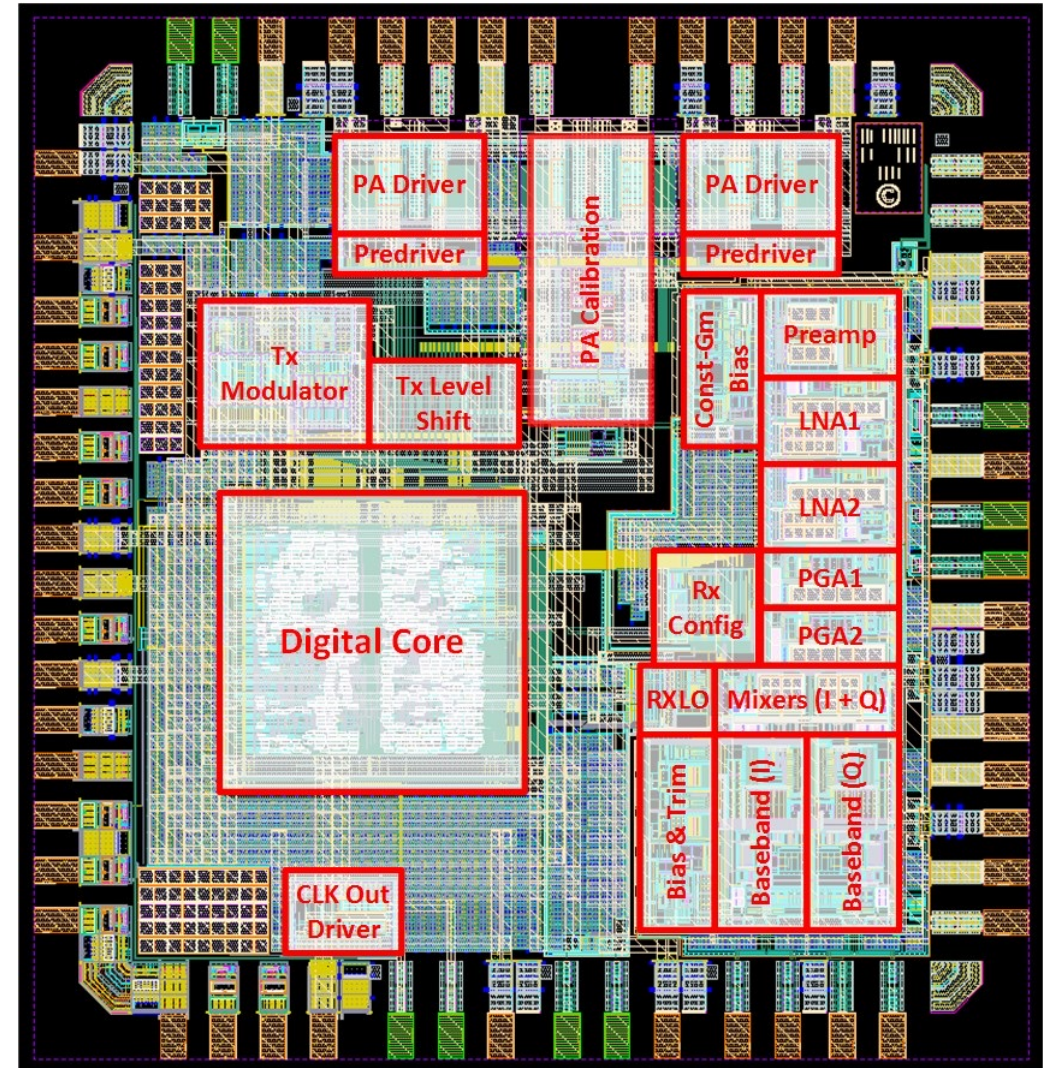
Temperature Range: 0 to 85°C

Input Sensitivity = -107dBm

Gain Temp-Co < 300ppm/°C

Digitally programmable linear in dB PGA

PA Max Output Power ~100mW



Why Miniaturize Instruments: Applications?



Laboratory Raman spectrometer in the 1980s for chemical characterization



Portable Raman for in-situ explosives identification



LAB scale High Field NMR spectrometers
(\$1M - \$15M machines)



Highly configurable benchtop NMR platforms
(\$100k - \$500k)
Optimized for the PhD
\$200M market today

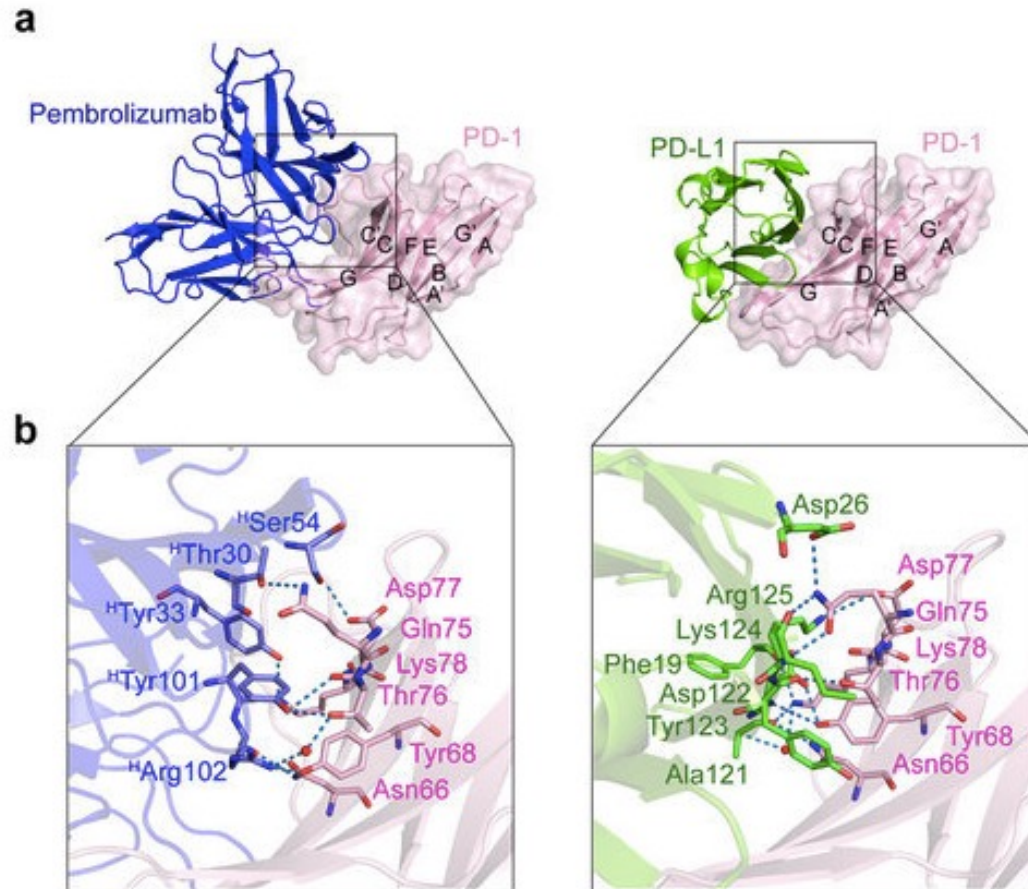


WaveGuide Formula
(\$7.5k plus per-cartridge model)
In-situ screening with predefined methods
“PhD inside”

- 2006 a breakthrough with portable optical spectroscopy for in-situ chemical analysis by Ahura Scientific (acquired by Thermo Fisher Scientific for ~\$200M in 2010) with Raman & FTIR.
- 2020, WaveGuide unveils the world's first portable battery-operated NMR for rapid screening and diagnostics.

Technology's Value Increases as it Migrates from Stationary to Mobile Formats

Analysis of Exchangeable OH and NH Protons in the PD1 PD-L1 Family of Proteins

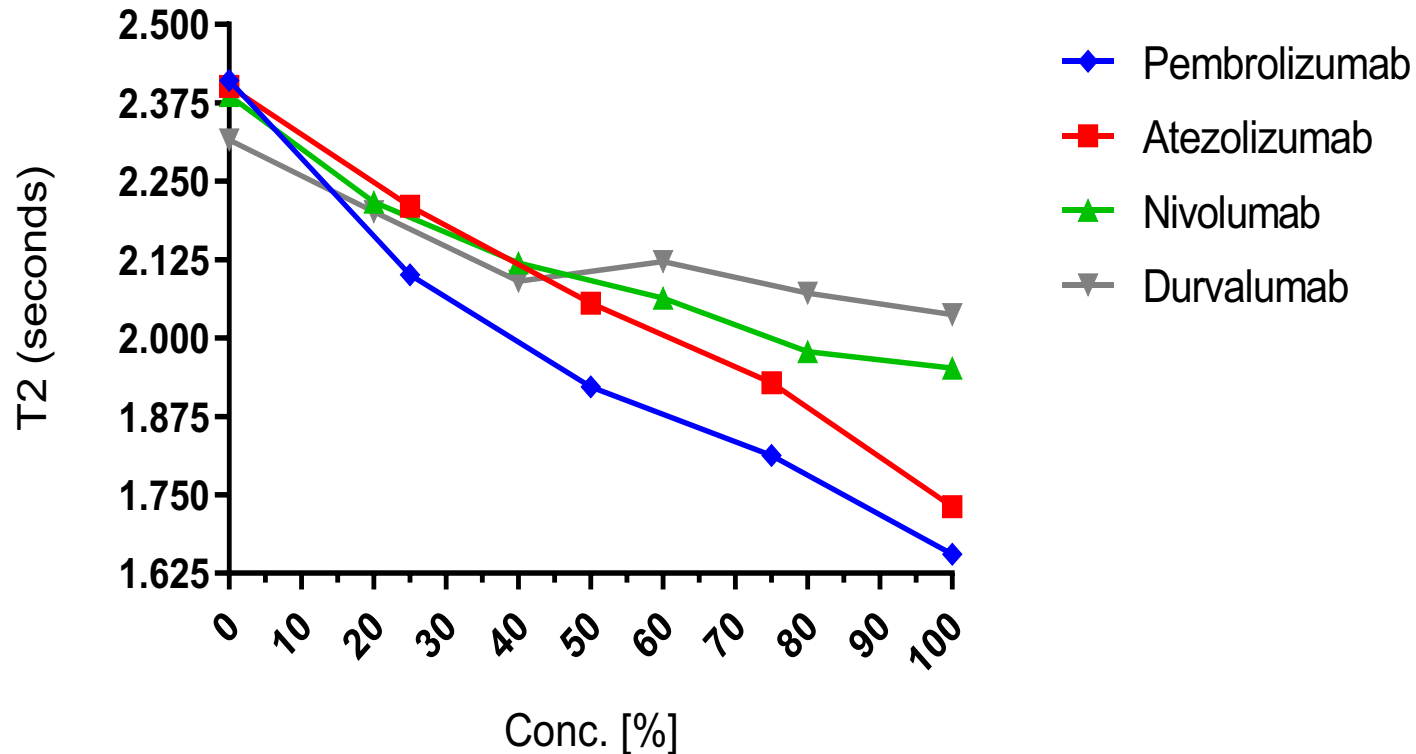


- ❑ A. Structure of the pembrolizumab/PD-1 complex and comparison with the PD-L1/PD-1 complex.
- ❑ B. Close-up views of interfaces shows residues involved in hydrogen bonds (blue dashes) are shown with water molecules in red
- ❑ WaveGuide Proof of Concept Study: Analysis of native PD-1 and PD-L1 family of inhibitors to examine the effect of exchangeable OH and NH protons on relaxation in water
- ❑ Each structure predicted to have unique T2 relaxation profile

Shoichiro Horita, Yayoi Nomura, Yumi Sato, Tatsuro Shimamura, So Iwata & Norimichi Nomura Scientific Reports Volume 6, Article Number: 35297 (2016)

Proof of Concept Analysis of PD-1 and PD-L1 Inhibitors

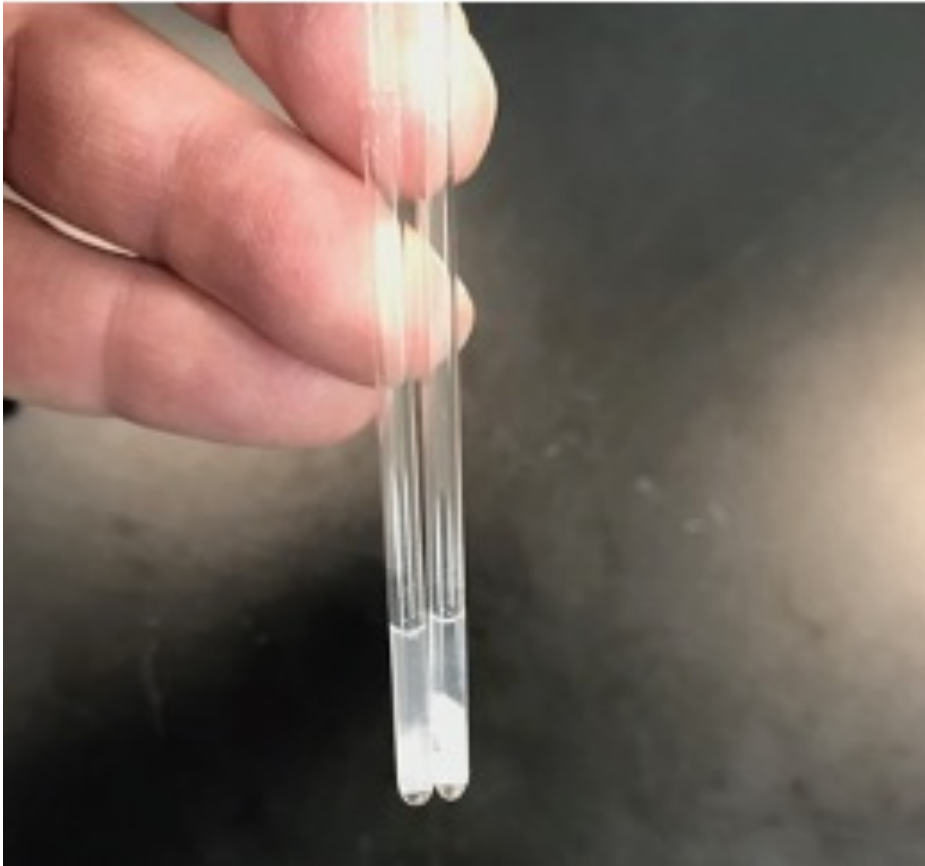
Feasibility study: analysis of native immuno-oncology agents PD-1 and PD-L1



- ☐ The plot on the left shows the measured T2 relaxation values of four different monoclonal antibodies used in cancer immunotherapy
- ☐ Each of the APIs have a unique T2 value even at the same effective protein concentration (100%)
- ☐ Each API was diluted from original concentration (100%) in either 20% or 25% decrement
- ☐ Quantitative analysis method
- ☐ These results suggested that this novel TD-NMR technique can distinguish biosimilars in the PD-1 and PD-L1 family

Proof of Concept Analysis of PD-1 and PD-L1 Inhibitors

Feasibility study: Aggregation analysis of native immuno-oncology agent PD-1



- ☐ Is it possible to detect a conformational change of the native pembrolizumab protein by adding stress?
- ☐ Heat aggregation study showed that upon heat the native pembrolizumab MAb aggregated and a white ppt appearing
- ☐ A significant change in the T2 relaxation decay occurred from the from the baseline of 1.38 sec to 1.98 sec (9.97 mg/mL)

Looking for Partners to Explore Applications

Proof of Concept Analysis of PD-1 and PD-L1 Inhibitors

Feasibility study: Analysis of final formulation of PD1 / PD-L1 inhibitors

Atezolizumab Each 20 mL vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8

Pembrolizumab Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP

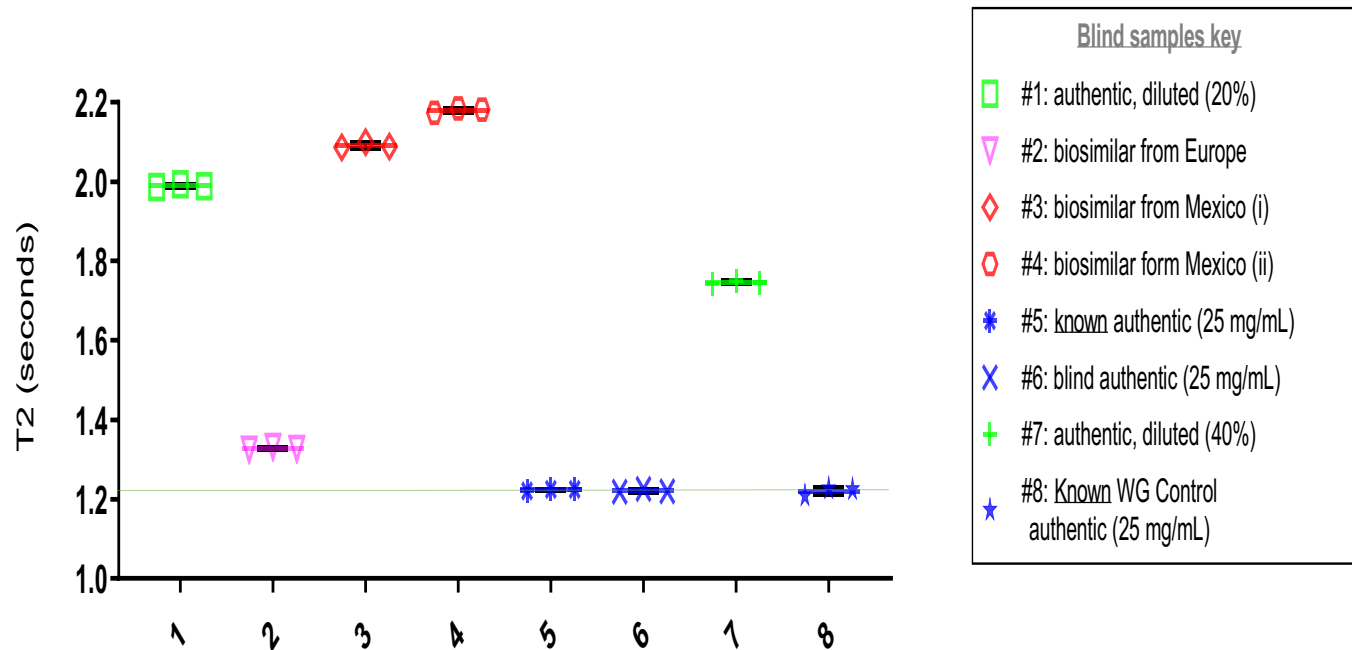
Nivolumab Each mL of solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6

Durvalumab Each mL contains durvalumab 500 mg , 50 mg, L-histidine (2 mg), L-histidine hydrochloride monohydrate (2.7 mg), α,α -trehalose dihydrate (104 mg), Polysorbate 80 (0.2 mg), and Water for Injection, USP.

- ☐ Complex formulations of final drug substance
- ☐ Optical analysis techniques will have issues with the color and excipients contained in the final formulation
- ☐ [Proof of concept study conducted to analyze final formulation comparing manufacturing lots and counterfeits](#)

Pharmaceutical Products Authentication: Oncology Treatment

Proof of Concept study: blind analysis of final formulation and authentic anti-cancer drug



- ❑ A fully developed and formulated drug #8 was analyzed from several manufacturing lots to set the T2 relaxation decay time baseline
- ❑ The authentic product (change in T2 from baseline #8 studies) was tested against blinded samples (#1-7)
- ❑ Blinded samples #5 and #6 have nearly indistinguishable T2 values from known #8 as expected they are both known authentic product at 25 mg/mL
- ❑ Samples #2 #3 and #4 are known counterfeit biosimilars and were easily distinguishable from the authentic product #8 T2 relaxation decay time profile

Formulations of Multivalent Vaccines on the Market

TWINRIX 1-mL dose of vaccine contains 720 ELISA Units of inactivated hepatitis A virus and 20 mcg of recombinant HBsAg protein

One dose of vaccine also contains 0.45 mg of aluminum in the form of aluminum phosphate and aluminum hydroxide as adjuvants, amino acids, sodium chloride, phosphate buffer, polysorbate 20, and Water for Injection.

Prevnar 13, Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)

Each 0.5 mL dose of the vaccine is formulated to contain approximately 2.2 µg of each of Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides, 4.4 µg of 6B saccharides, 34 µg CRM197 carrier protein, 100 µg polysorbate 80, 295 µg succinate buffer and 125 µg aluminum as aluminum phosphate adjuvant

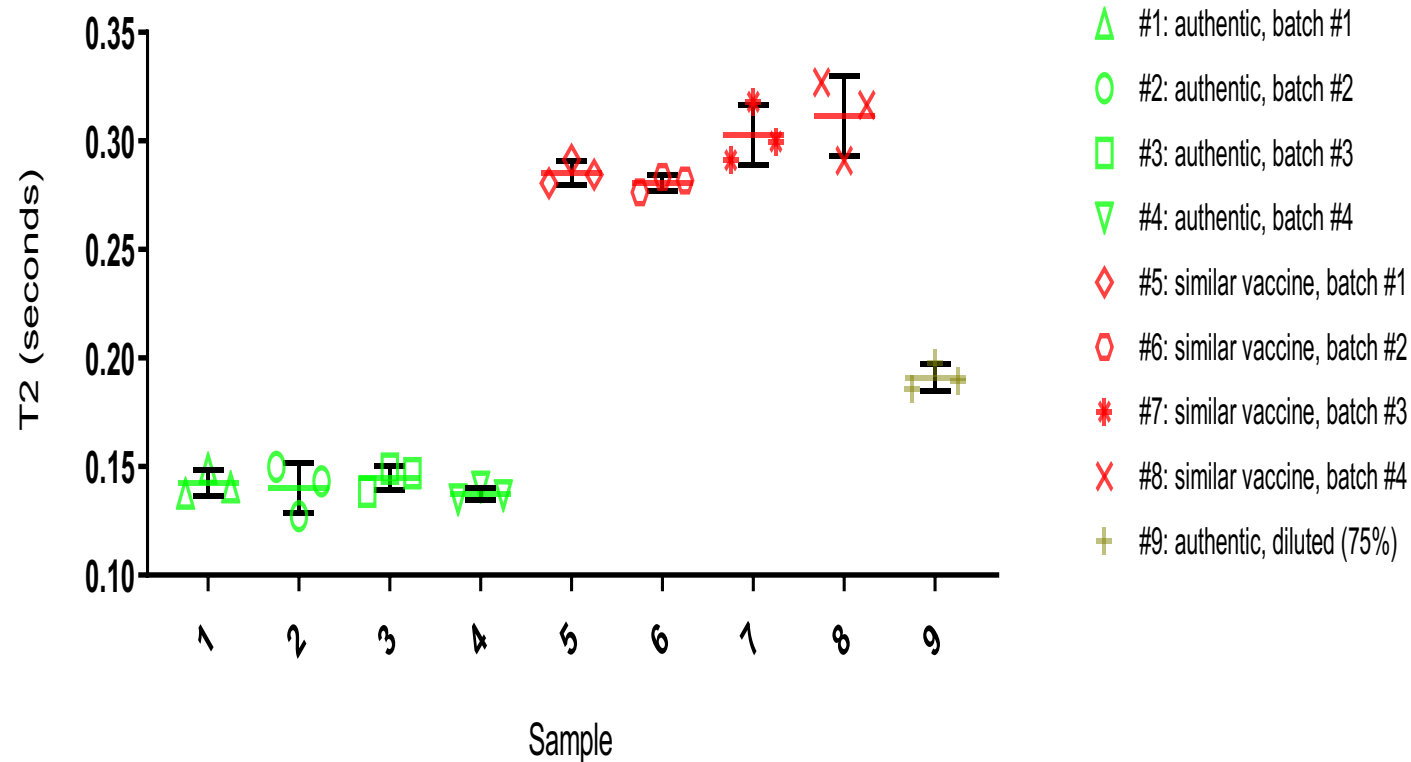
PedvaxHIB®

Each 0.5 mL dose of Liquid PedvaxHIB is a sterile product formulated to contain: 7.5 mcg of Haemophilus b PRP, 125 mcg of Neisseria meningitidis OMPC and 225mcg of aluminum as amorphous aluminum hydroxyphosphate sulfate in 0.9% sodium chloride and is a slightly opaque white suspension.

- ☐ Complex formulations of final vaccines as Aluminum adjuvant suspensions
- ☐ Must re-suspend the vaccine before delivery to patient into uniform hazy white suspension
- ☐ Extremely low concentration of virus / proteins in the vaccine “soup”
- ☐ Optical analysis techniques will have issues with the cloudy Aluminum adjuvant suspension
- ☐ [Proof of concept study conducted to analyze final formulation of vaccines comparing manufacturing lots and counterfeits](#)

Pharmaceutical Products Authentication: Multivalent Vaccine

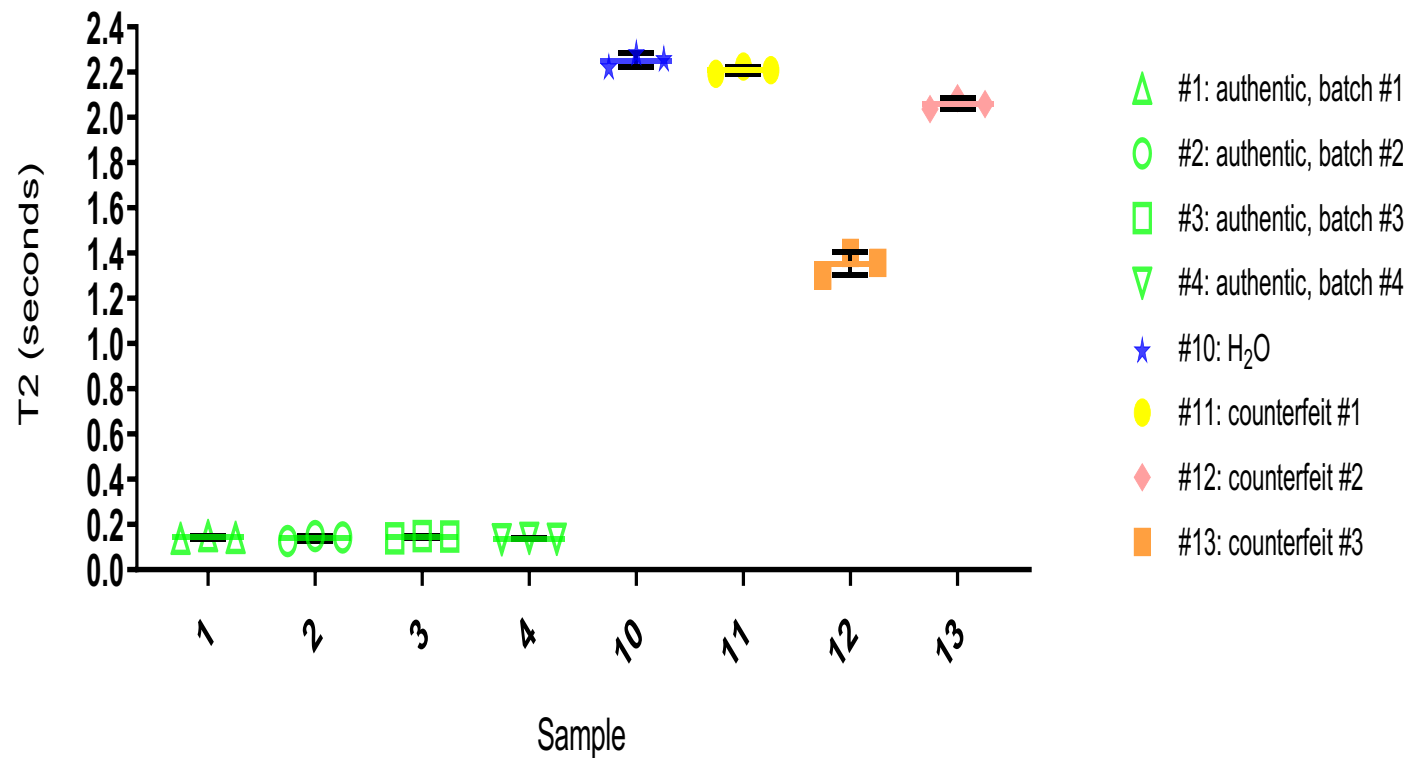
Method development for the authentication of multivalent vaccine



- An authentic multivalent vaccine was analyzed against a similar vaccine product, diluted and counterfeit samples
- The plot on the left shows the measured T2 values for the authentic vaccine, a similar vaccine, and a dilution of the authentic vaccine
- The authentic multivalent vaccine was tested across four different batches and the results were very consistent
- The authentic multivalent vaccine was clearly distinguishable from diluted, biosimilar, or counterfeit products

Pharmaceutical Products Authentication: Multivalent Vaccine

Method development for the authentication of multivalent vaccine



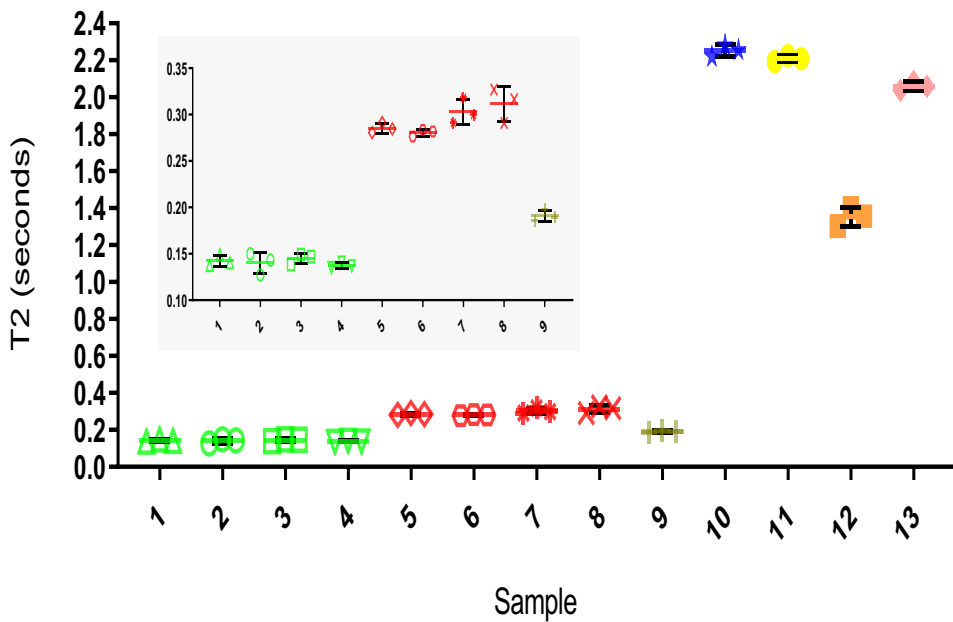
- ☐ An authentic multivalent vaccine was analyzed against a similar vaccine product, diluted and counterfeit samples
- ☐ The plot on the left shows the measured T2 values for the authentic vaccine, a molecular biology grade water sample, and three counterfeit products from the foreign market
- ☐ The authentic multivalent vaccine was tested across four different batches and the results were very consistent
- ☐ The authentic multivalent vaccine was clearly distinguishable from diluted, biosimilar, or counterfeit products

Pharmaceutical Products Authentication: HPV Vaccine

Method development for the authentication of multivalent vaccine

- Waveguide developed a robust authentication method for the authentication/identification of vaccine
- An authentic vaccine was analyzed against a similar vaccine product, diluted and counterfeit samples

Authentication of HPV vaccine



- The plot on the left shows the measured T_2 values for each sample
- The authentic vaccine was tested across four different batches and the results were very consistent
- The vaccine was clearly distinguishable from diluted, similar, or counterfeit products

15 Unique vaccines tested to date

WaveGuide self-contained μ NMR instrument



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