RITUXIMAB IN MYOCARDIAL INFARCTION/ATHEROSCLEROSIS

Information memorandum

GENERAL PRODUCT OVERVIEW

Generalities

Generalities

Generic names	Rituximab
Therapeutic class	L01XC Monoclonal antibodies
Mechanism of action	Cytotoxic To Cells Expressing B Lymphocyte Antigen CD20
Indications	Myocardial Infarction, Ischemic Heart Disease, Atherosclerosis

Key Characteristics

Presentation	Solution
Mode of Administration	Intravenous
Total duration of treatment	Single injection
Posology	1g

PATENT PROTECTION

Claims allowing a large market opportunity

WO2010079161A1 :
A B CELL DEPLETING AGENT FOR THE TREATMENT OF ATHEROSCLEROSIS

Mechanism of action	• After acute myocardial infarction in mice, mature B lymphocytes selectively produce Ccl7 and induce Ly6Chi monocyte mobilization and recruitment to the heart, leading to enhanced tissue injury and deterioration of myocardial function • Genetic (Baff receptor deficiency) or antibody-mediated (CD20- or Baff-specific antibody) depletion of mature B lymphocytes impeded Ccl7 production and monocyte mobilization, limited myocardial injury and improved heart function
Claims	• A B cell depleting agent for use: ➢ in the treatment or prevention of atherosclerosis ➢ in treatment or prevention of a vascular or coronary disorder
Protection	• US, EU & Japan

B lymphocytes trigger monocyte mobilization and impair heart function after acute myocardial infarction. Zouggari Y et al., Nat Med, 2013

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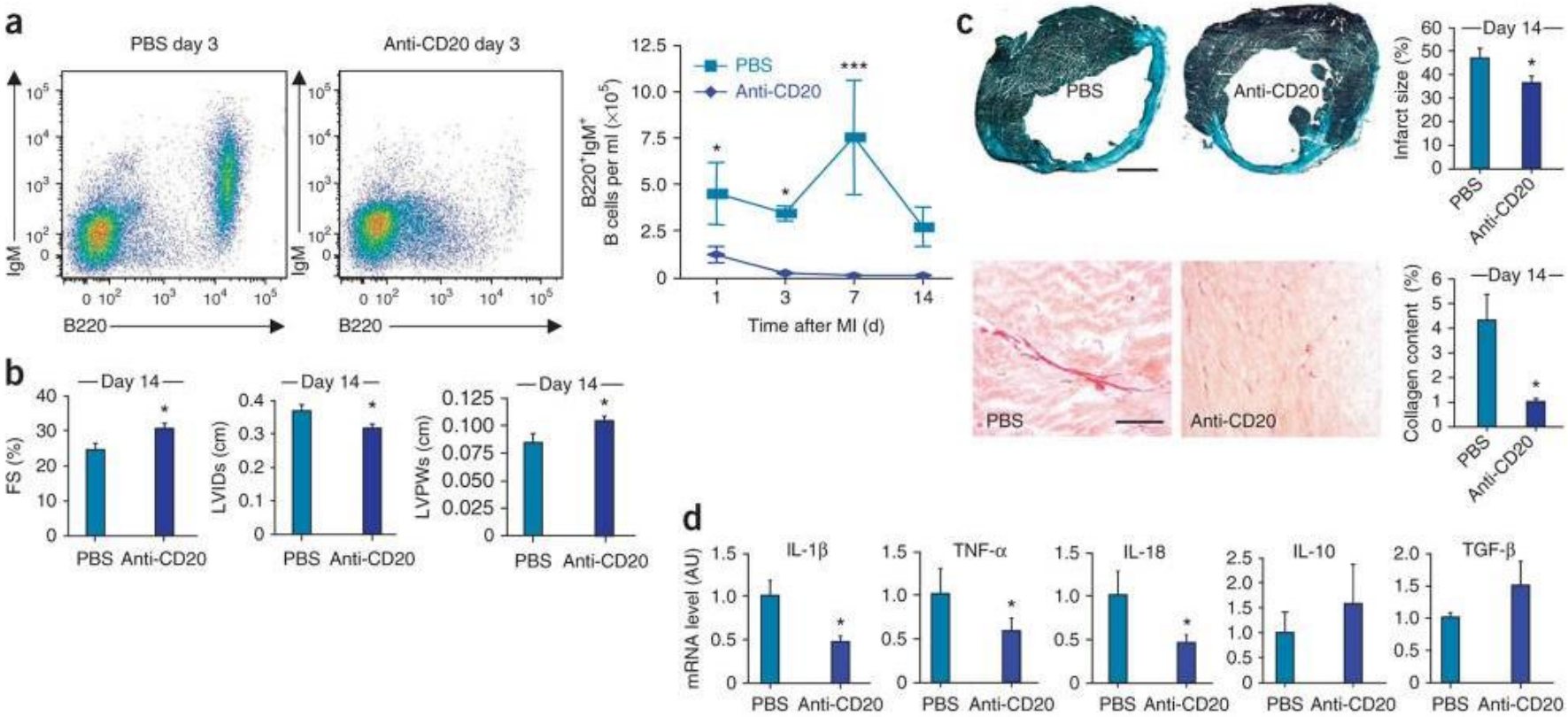
PROOF OF CONCEPT (1/2)

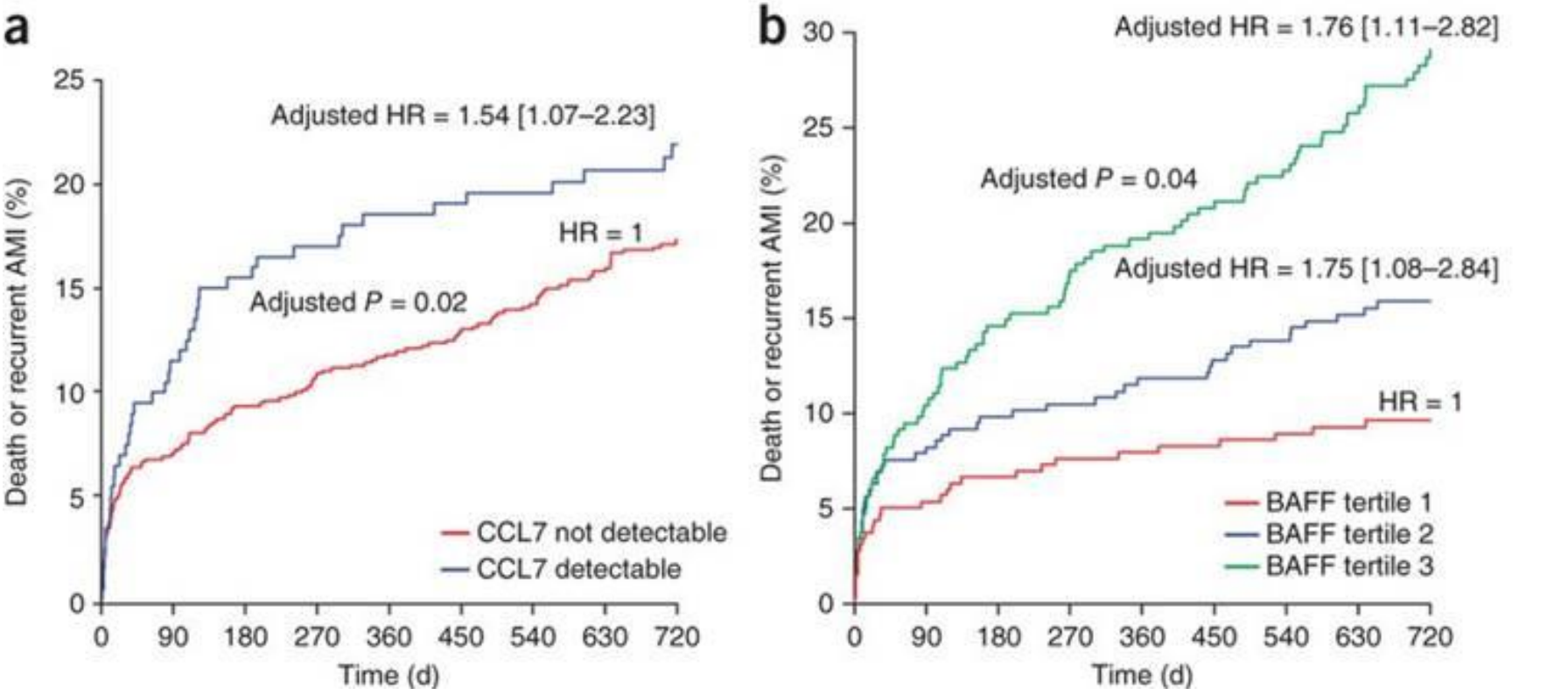
The B cell–depleting CD20 mAb reduces infarct size, improves heart function and limits myocardial inflammation



(a) Representative examples (left) and quantitative analysis (right) of B220hi IgM+ B cell staining in the blood of C57BL/6J mice treated with or without the CD20 mAb (anti-CD20) (n = 12–15 mice per group); ***P < 0.001. MI, myocardial infarction. (b) Echocardiographic analysis after anti-CD20 therapy. Left ventricular fractional shortening (FS), left ventricular internal diameter at end systole (LVIDs) and left ventricular posterior wall thickness at end systole (LVPWs) were measured at day 14 after myocardial infarction; *P < 0.05. (c) Representative photomicrographs (left) and quantitative analysis (right) of infarct size and myocardial fibrosis evaluation evaluated by Masson trichrome (top) and Sirius red (bottom) staining, respectively, measured at day 14 after myocardial infarction. Data are representative of 10–14 mice per group in three independent experiments. Scale bars: top, 1 mm; bottom,100 µm. (d) mRNA levels of the proinflammatory cytokines IL-1β, TNF-α and IL-18 and the anti-inflammatory cytokines IL-10 and TGF-β within the injured myocardium on day 14 after myocardial infarction (n = 8–12 mice per group). AU, arbitrary units. Mean values ± s.e.m. are represented. *P < 0.05 versus PBS.

PROOF OF CONCEPT (2/2)

Circulating levels of CCL7 and BAFF during the acute phase of myocardial infarction are associated with cardiovascular outcomes.



(a,b) The probability of outcome events (death or recurrent myocardial infarction) as a function of baseline circulating CCL7 (a) or BAFF (b) levels in patients with acute myocardial infarction (AMI). HR, hazard ratio.

CLINICAL DATA

Phase 1 shown no adverse effects in patients (not published yet)

	Phase 1/2	Phase 2
Official tittle	Rituximab in Patients With Acute ST-elevation Myocardial Infarction Study	/
Status	Active, not recruiting (Study Completion Date: September 1, 2019)	Planned to 2020
Treatment	Single dose of Rituximab given intravenously within 48hours of myocardial infarction	Single dose of Rituximab given intravenously
Condition or disease	Ischemic Heart Disease / Myocardial Infarction / Inflammation	Myocardial Infarction
Estimated Enrollment	24 participants	360 participants
Intervention model	Single Group Assignment, Open label	Randomised, double-bind, placebo controlled, parallel group
Description	Unblinded interventional dose escalation study	/

https://clinicaltrials.gov/ct2/show/NCT03072199?term=rituximab&cond=Myocardial+Infarction&rank=1

CARDIOVASCULAR MARKET

"Cardiovascular diseases (CVDs) are the number 1 cause of death globally: more people die annually from CVDs than from any other cause" [1]

Cardiovascular disease is responsible about 1 of every 3 deaths in the US.

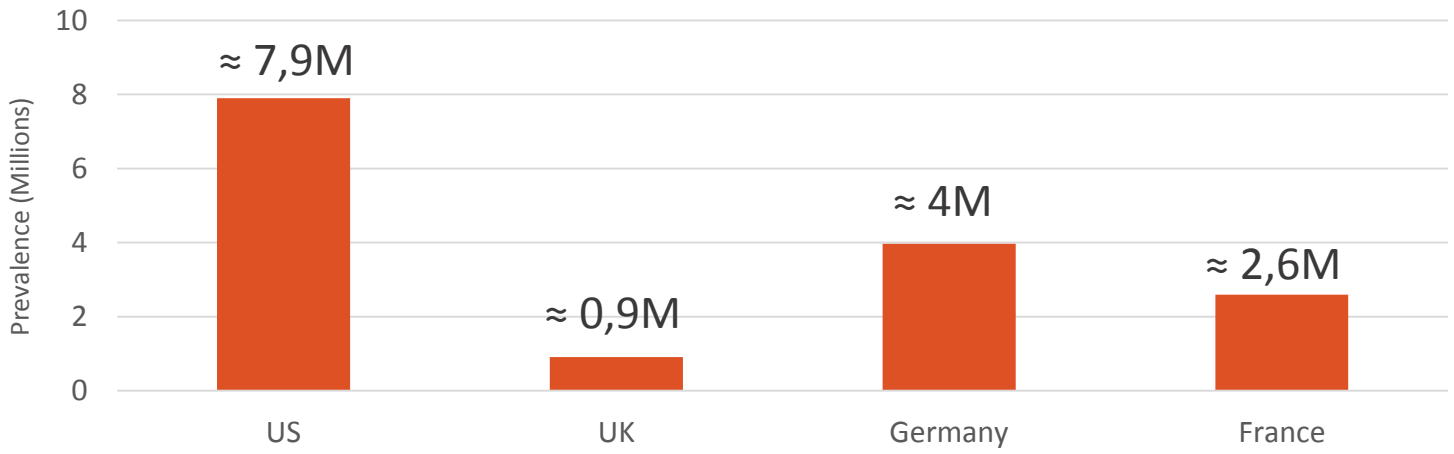
Atherosclerosis

- **Atherosclerosis** is characterized by the accumulation of lipids and fibrous elements in the large arteries and **the most common** cause of Coronary Heart Disease (CHD).
- Between 2013 and 2030, **medical costs** of CHD are projected **to increase by about 100 percent** [2].

Myocardial Infarction (MI)

- MI is defined pathologically as **myocardial cell death** due to prolonged ischemia[2].
- The overall prevalence for MI in the US is about **7.9 million**, or 3 percent, in **US adults** [3].
- In the US, the mean cost of acute MI is **$24,695** per patient per year [4].

Myocardial Infarction Prevalence



[1] *World Health Organization*, Cardiovascular diseases Fact sheets, 17 May 2017
[2] *European Heart Journal*, Volume 40, Issue 3, 14 January 2019, Pages 237–269
[3] *American Heart Assoication*, Heart Disease and Stroke Statistics 2018 At-a-Glance
[4] *ClinicoEconomics and Outcomes Research,* Patient-level costs of major cardiovascular conditions: a review of the international literature, 21 September 2016

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CLINICAL AND SCIENTIFIC TEAM

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- Associated Professor Intensive Unit Care, Paris, Public Hospitals

Paris Cardiovascular research Center PARCC H E G P

Paris Cardiovascular Research Center (PARCC):

- Created by INSERM and Paris-Descartes University at the Georges-Pompidou Hospital (HEGP)
- Brings together 14 research teams in the field of cardiology
- Translational research in close connection with clinical laboratories and departments of HEGP

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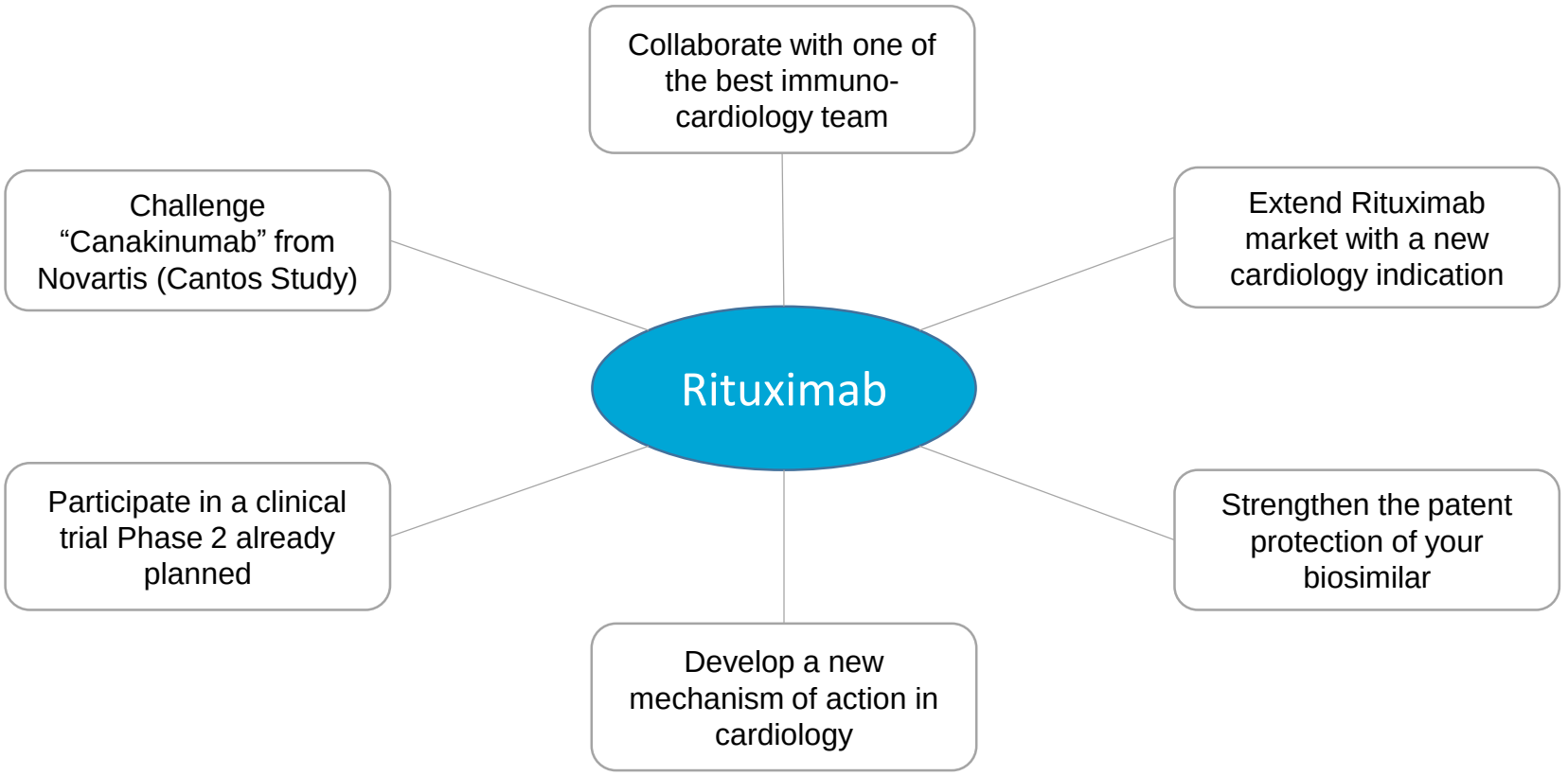
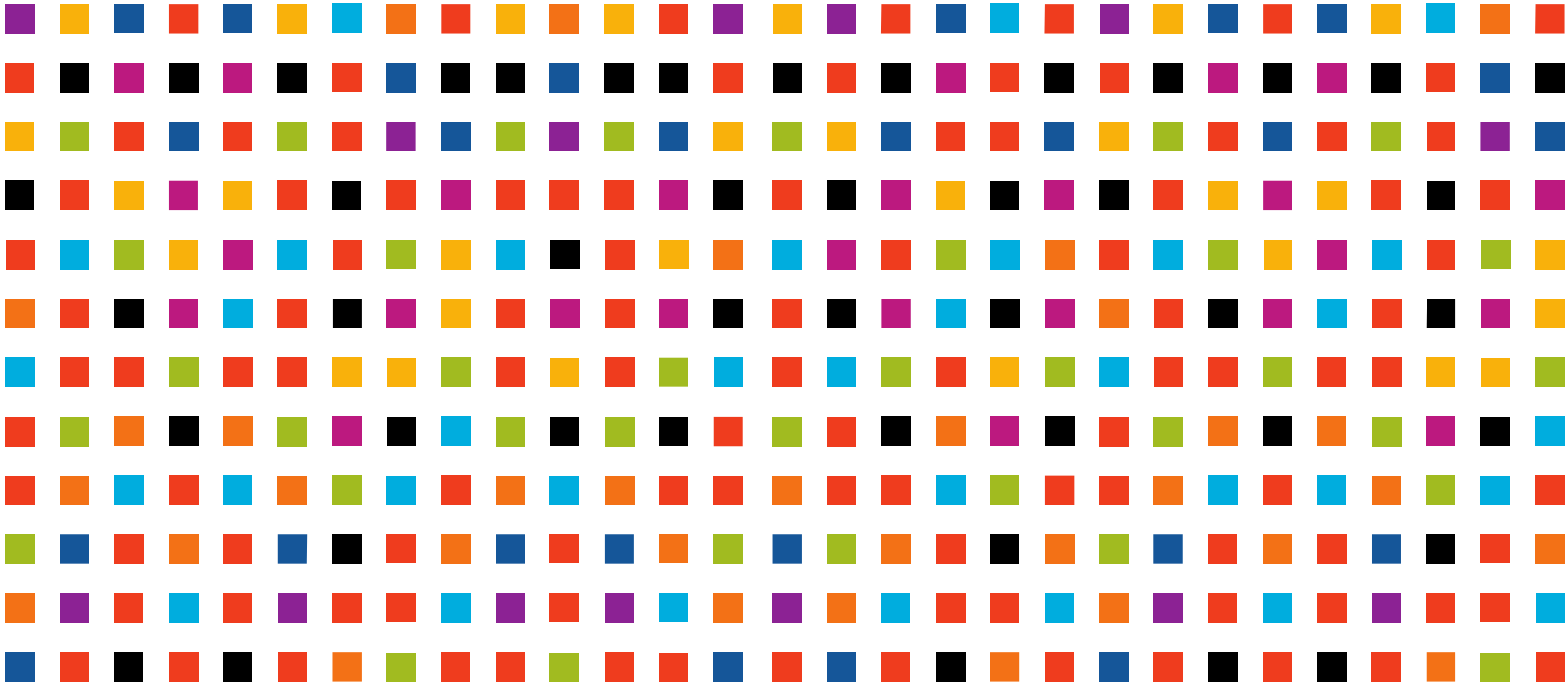
BUSINESS OPPORTUNITY

Immuno-Cardiology: the next generation of cardiovascular treatment.





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